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Dissertation

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Gaps, Pitfalls and the Valley of Death:

Translational research and the reform of biomedical innovation

Verfasser

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List of abbreviations

AAMC - Association of American Medical Colleges

BfArM - Federal Institute for Drugs and Medical Devices

BMBF – Bundesministerium für Bildung und Forschung

CRO - contract research organisation

CTSA - Clinical and Translational Science Awards

DFG – German Science Foundation

EATRIS - European Infrastructure for Translational Medicine

FDA – Food and Drug Administration

FWF - Austrian Science Fund

GCP – good clinical practice

GCRC - General Clinical Research Center

GLP – good laboratory practice

GMP - good manufacturing practice

HGP – Human Genome Project

HZI - Helmholtz Institute for Infection Research

IOM – Institute of Medicine

IRB – institutional review board

ITEM - Fraunhofer Institute for Toxicology and Experimental Medicine

LUH - Leibniz University Hannover

MHH - Hannover Medical School

MSTP - Medical Scientist Training Program

NCATS - National Center for Advancing Translational Sciences

NHGRI - National Human Genome Research Institute

NCE – new chemical entity

NCI – National Cancer Institute

NCRR - National Center for Research Resources

NIH – National Institutes of Health

RFA – request for applications

RTD – research and technology development

SOP – standard operating procedures

SPORE - Specialized Programs of Research Excellence (NCI)

STS - science and technology studies

STI – science, technology and innovation

TiHo - University of Veterinary Medicine Hannover

TMAT – translational medicine and therapeutics

TR – translational research, translational medicine, translational science

TRAIN - Translational Research Alliance in Lower-Saxony

TRWG - Translational Research Working Group (NCI)

TU BS - Technische Universität Carolo-Wilhelmina zu Braunschweig

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1 A new priority in biomedical policy

In late 2010 and early 2011, the news and commentaries pages of scientific journals such as *Nature* and *Science* came to be regularly concerned with the new project of Francis S. Collins, former leader of US Human Genome Project efforts and current National Institutes of Health director. Collins was investing major energies and resources from the Director's office into the creation of a new federal Institute of Health, which would become the National Center for Advancing Translational Sciences (NCATS - Collins 2011; Harris 2011; Wadman 2010). All actors in the US biomedical community did not welcome the creation of this new Institute. The amplitude of resources engaged in the initiative (500 M US $ a year) made sure it attracted attention. The necessity to dismantle an existing Institute of Health to create a new one also implied that institutional routines and the jurisdictions of established group would have to be change, unlikely without some resistance. Thirdly, the new institute's raison d'être would be to act as the catalyst of major efforts for developing innovation platforms from recent advances in molecular biology and experimental approaches based on the sequencing technologies that were the focus of the Human Genome Project (HGP). This project and the efforts had boosted the development of these sequencing technologies, but it was felt that specific investment had to be done to make their creative potential available to innovation activities that could actually result in new health interventions. The NCATS would help develop such innovation platforms, with a major aim to create medicinal prototypes that could be transferred to a pharmaceutical industry that was increasingly perceived as loosing its innovativeness. Yet, these goals did not sit well with some biomedical researchers, who saw this as thinly veiled manoeuvre to use public money to "bail out" an arrogant and reckless pharmaceutical industry (Avorn and Kesselheim 2011; MacIlwain 2011).

The perils of ineffective innovation that commentators have evoked in these discussions are closely tied to the shape and institutional structure of the biomedical innovation enterprise, as much as they are to the current state of experimental approaches in the field. These issues are being actively solidified as pressing shared problems in the collective imagination of biomedical communities with metaphors of "gaps", "cliffs", "pitfalls", "bottlenecks" or even the "Valley of Death", rhetorical practices that solicit adhesion to an agenda by emphasizing the threat of a purported alternative. A "gap between scientific opportunity and medical advance" (Coller 2009), "leadership gaps" (IOM 2009) or "patent cliffs" (Becker and Dongen 2011; Christel 2010) are recurrently observed by commentators of the biomedical innovation enterprise.

NCATS aims to directly tackle some of these perils in biomedical innovation. The very name of this new institute makes direct reference to a set of concepts often presented as the "bridge" that will allow us to cross these gaps and cliffs, but whose short history has nonetheless repeatedly been associated with controversy and argument in biomedical communities: translational science, translational research and translational medicine (I will abbreviate to TR from now on).

TR has become a *bona fide* trope in current biomedicine and associated circles of policy-making, the latter understood in the broadest sense as whichever collective means are used to set orientations and priorities for individual and coordinated practices within groups and communities. The NCATS provides a salient case from the large sample of worldwide, well-funded initiatives recently put into place to support TR (Borstein and Licinio 2011; Kupferschmidt 2011; NCI 2007; Shahzad et al. 2011; von Roth et al. 2011; Vignola-Gagné et al 2013; Zerhouni 2005). Institutional interventions or rhetorical calls made to support TR tend to be controversial, because they very often contain a strong programmatic component. Adopting TR priorities seems to entail closing off other potential goals and models of collective work in biomedical innovation. To convince their audiences of the soundness of their specific approach, TR advocates are prone to frame the issue as being of wide collective relevance, to be of immediate relevance to the aspirations and experiences of citizens and patients, as well as biomedical experts. In discussing the need for greater support for TR in the biomedical research field, the recent *Strategy for Patient-Oriented Research* of the Canadian Institutes of Health Research eloquently talks about an "increasing impatience among clinicians, policy makers and patients with the pace at which scientific discovery is resulting in new products or interventions" (CIHR 2011: 2). When the European Medical Research Councils switch their official policy to accommodate a growing priority given to TR, they justify this change by invoking "… a moral and ethical duty to bring new knowledge generated by biomedical research as rapidly as possible to patients in the form of new drugs, procedures and technologies" (European Medical Research Councils 2011, p. 48). For the American think thank FasterCures, who has produce a number of position papers about the urgency of giving TR greater priority in biomedical policy, current failures in make use of biomedical research findings to achieve crucial advances in therapeutic practice is a source of outrage. Drawing on the universal experience of living through disease, FasterCures contends that "[w]e'll all be patients at some point. We have to act now and act smartly - because patients are dying every day waiting for treatments and cures." (FasterCures 2013).

Such emotionally charged argumentative interventions about biomedical innovation are not new to scholars concerned with technoscientific-mediated medical practices such as abortion, pre-implementation diagnostic or stem cell therapies (Gottweis, Salter and

Waldby 2009; Metzler 2007). They are, however, much more seldom to be witnessed in discussions on the workings of biomedical innovation, which tend to be framed in the impersonal and systemic style of argumentation of public administrators. The rise of TR seems to be associated with a change in the register of arguments used to talk about things such as biomedical innovation policy, technology transfer or biotechnology entrepreneurship. This change impacts arguments made both by biomedical researchers talking about their own work, but also the arguments that social scientists need to make with respect to the inner workings of biomedical innovation, and of its relevance to contemporary technoscientific lives.

There are other aspects of the phenomenon of TR that are puzzling in the light of established findings from social studies of biomedicine and innovation studies. To point out just one for now, how can the notions of TR inspire such dedication and attention from biomedical actors themselves, when the search for relevance and entrepreneurship have been hallmarks of academic science since the 1980s, especially in the life sciences (Corolleur, Carrere and Mangematin 2004; Ebers and Powell 2007; Göransson and Palsson 2011; Grimaldi et al. 2011)? Innovation studies has often place the locus of innovation in biomedicine in biotechnology entrepreneurship, is the model changing? Was the model wrong all along? What are the consequences for the governance of biomedicine? Does TR extends, displaces and/or undermines previous repertoires of expectations, hopes and promises of revolutionary therapeutic breakthroughs that had been articulated by researchers, industry, policy-makers and the (Hedgecoe and Martin 2003; Kitzinger 2008; Martin et al 2009; Tutton 2012)?

1.1 Translational research: discipline, experimental practice or political agenda?

The way TR initiatives and the shared research programmes they are associated with are presented in public discourse about biomedical innovation, one might think that TR denotes a specific area of biomedical research, with its own privileged objects of inquiries, an emerging body of theories about human (patho)physiology and the ways to intervene in it, and specific methodological approaches and experimental systems. This impression however will quickly fade away if one does a more systematic inquiry into the actual research projects and experimental practices that biomedical researchers present as instances of TR. Although TR has a deeper historical association with the oncology field, where it tends to be associated with a specific set of experimental practices (see Keating and Cambrosio 2012; TRWG 2007), the notion is now used to denote projects in all areas of biomedical activity or beyond in the allied health sciences (including psychology, public health, or social work). In Austria, the term if used by a major science funding body (the Austrian Science Fund - FWF) for a programme that offers seed money to investigators engaged in early development work of a new inter-

vention that could stem from previous findings, irrelevant of the field of research, be it biomedicine, solar cells engineering or organisational psychology. The programme aims to encourage technology transfer, a notion that is not quite as new and glittering as TR, although it did seem to enjoy similar policy attention in the 1990s.

In fact, what one would find is that biomedical researchers writing about TR (and there are lots of them, see section 4) mostly address argue about how their colleagues, their purported community, could change the organisation and institutional frames of their research activities. Although TR sounds like a specific type of research, here we find that doing TR is mostly about doing mundane immunology or oncology in a slightly different way: with intentions that veer more towards the development a new clinical intervention rather than only the publication of articles in the specialised literature, and consequently with an organisational set-up that might include specialised large-scale equipment with uses that typically tend towards the industrial than the academic. It is not however that TR is purely an organisational phenomenon. As authors in the field of science and technology and studies (STS) have repeatedly shown, technological, scientific and organisational innovations are usually highly interdependent (Golinski 2005; Kohli-Laven et al 2011; Latour 1987; Löwy 1996; Marks 1997).

Technology transfer might be a good way to gain some conceptual grasp on the activities labelled as TR. TR is about the hypothesis that fundamental research in biomedicine is producing a lot of findings and experimental technologies that could be marshalled to improve patient's predicament, but that there is an important lag between fundamental advances and clinical innovation. The potential for intervention does not seem to match the fundamental advances. In the 1980s and 1990s, as the biotechnology industry was emerging and increasingly perceived as a sector of crucial importance to post-industrial economies, technology transfer offices were set up in most universities with the similar rationale that advances in molecular biology (among others) were providing new opportunities to turn academic knowledge into medical, commercial and/or societal returns. Technology transfer was more of an administrative rationale that is now well assimilated by university administrations and policy-makers. Molecular biologists themselves have in the meantime assimilated these demands to go to the local technology transfer office when they think they might have something to patent. TR, on the other hand, would appear to stir deep commitment (and sometimes revulsion) from certain parts of the biomedical community. Some commentators now fashion themselves as 'translational investigators' and enjoin their colleagues to adopt a new vision for the biomedical enterprise (Coller 2008; Zerhouni 2005). Although technology transfer has been an important component in visions of academic entrepreneurship in the near-future knowledge economy, it has never provided the kind of adhesions and conversations that can be observed for TR.

Indeed, as I will contend in this document, a historically unique conjuncture has lead to the emergence of TR as a matter of great urgency in current biomedical policy (policy understood broadly here, to include for example bottom-up collective deliberation on shared priorities and legitimate approaches to research for example; collective processes of coordination). This conjuncture has both important discursive and practice components. The strategic diagnosis and framing of a string of crises in biomedical innovation has contributed to the construction of an overwhelming/ominous sense of urgency, and proposed TR as a cross-cutting socio-technical agenda of reform. I will briefly examine the contours of this argumentative work in the next subsection.

1.2 Crises in biomedical innovation

Recently, we have been told that the pharmaceutical industry was in state of deep crisis, and that thousands of enviable RTD jobs were being slashed as the top firms in the sector concentrate on their winning assets in marketing, regulatory approval and commercialisation (Cressey 2011; Holmes 2012). Commentators have talked of the imminent 'patent cliff' where an unprecedented constellation of brand drugs falling off patents will drastically reduce profits in the sector (Khanna 2012).

Earlier, a widespread sense of anxiety or disappointment seemed to have mixed a sense of achievement as the Human Genome Project (HGP) neared its completion. The technologies promised to arise from the HGP by commentators included, as early as the mid 1990s: „therapeutic proteins, medical diagnostics, gene therapy, targeted molecules, small molecule therapeutics, DNA sequencing, bioinformatics, functional genomics" (Hedgecoe 2003, p.522 citing McKowen and Sarin 1997). Yet geneticists and bioinformaticians seem to increasingly find that their achievements only reveal small fractions of the human (patho)physiology knowledge that was to make these new therapies possible. As of 2012, many commentators were more sceptical than ever concerning a future genomics-driven revolution in clinical care, even as they spurred on further basic work to understand physiology and pathology (Anonymous 2012; Hoelder et al. 2012; Janssens and van Duijn 2010; Lander 2011; Swinney and Anthony 2011;). Despite the resignation of some, however, most biomedical leaders and policy-makers considered that the –omics platforms offered unprecedented opportunities for intervention on humans, and that a "gap" just needed to be "bridged" with the clinic to allow for the technological revolution to finally flow unobstructed into the clinics.

In fact, the intuition that advances in molecular biology should lead to clinical improvements in a relatively forward and diligent manner, but that somehow this was not happening in practice, was already spreading in the 1970s. At that time, commentators at medical schools started to notice the relative marginalisation of academic physicians

from biomedical research. These so-called clinician-scientists had been at the forefront of a “Golden Age” of interlinked advances in both understanding of (patho)physiology and therapeutic modalities in the afterward period, yet they were increasingly displaced by biologists dedicated to laboratory research even within research positions at medical schools (Swazey and Fox 2004). This displacement, others argued, reflected the marginalisation not of a specific group of investigators, but rather of a specific approach to medical experimentation, retrospectively called “patient-oriented research” (Ahrens 1992). This research, based on clinical observation and what limited experiments could be performed in patients, could not compete so easily with the modelling methods allowing molecular-level understanding of cell and other processes, and might have been gradually shut off the most important venues for building reputation in the biomedical field.

This series of three crises in the imagined “biomedical innovation enterprise” (indeed, such crises make most sense at the collective level, if one imagines the sum of all individual experimental projects and the investigators they come with, projects the existence of a web of collaborations to tie them all together and then examines the output of this “enterprise”) have had, recently at least, a single solution: the collective construction and acknowledgement of a field of activity called translational research.

This will be the an important basis of my argument here: TR is defined crucially by the problems of collective prioritization and ordering of experimental and institutional practices, orderings that are made uncertain by the “public controversy” such as the crises mention above (Gottweis 1998). I will show in more detail below how the gradual intensification of perceptions of crisis in biomedical innovation have lead to major public efforts to support something as ill-defined as TR (indeed at a time where, one would think, funding agencies and policy makers would have great pressure to have very clearly defined agendas for intervention and of the means through which outputs for patients and citizens is to be obtained).

In many ways, these three major problematisations have built upon one another in shaping a collective policy space for TR. The catchphrase that has become emblematic of the TR “ethos” (to make reference the analysis of Maienschein et al 2008), “from bench to bedside” is a common thread to all three narratives (patient-oriented research advocates might be more inclined to talk of “bedside to bench and back” however). However, here, I will also show at which point the three narratives chafe and sometimes outright conflict with one another. In fact, one of my hopes here is to be able to convince the reader that there are multiple ethoses of TR, and to not dismiss the multiplicity of practice surrounding this new notion as an epiphenomenon to some deeper structure or ontology.

1.3 Social studies of translational research

Few analyses have been published specifically on TR as an emerging programme in biomedicine, with a certain degree of distinctiveness from baseline understandings of technology transfer or applied research. Of course, this is not to imply that there are not a great number of studies from STS, sociology of science, or innovation studies that can bear on our analyses. Scholars have discussed abundantly the articulation between medicine and biology, contemporary pressures to achieve commercial and societal value from fundamental research, or how biomedical innovation reshapes power and subjectivities in post-industrial societies. The dearth of social science literature specifically about TR is, however, in sharp contrast with reviews, commentaries and editorials on the phenomenon, authored by members of the biomedical professions, which are abundant.

Within the sample of social science literature that has directly addressed TR, a first ensemble of work has aimed to provide detailed, often ethnographic accounts of the type of experimental and, to a lesser extent, institutional practices that concretely perform the TR agenda, or related ideas such as the process of innovation "between bench and bedside".

Löwy (1996) has conducted an ethnography of the interactions between clinical and basic research teams in the course of developing potentially groundbreaking immunological interventions, touching on many of the issues that would later become core themes in discussions of the biomedical community about TR. Keating and Cambrosio (2003) have provided an interesting conceptual framework for analysing the increasing integration of laboratory and clinical approaches, of biology and medicine, in modern biomedicine, based around the concept of 'biomedical platforms' that cut across organisational and professional boundaries. Following these authors' argument, which states that medical practice and research into human biology are now deeply interdependent activities, the divides between 'bench and bedside' diagnosed by many TR advocates would appear to be a comparatively minor point of resistance within an otherwise broadly realised convergence. In their latest work, Keating and Cambrosio (2012) contend that even as medical and biological research practices are increasingly interdependent, there is an increased perception within the biomedical community that *therapy* and *research* are becoming independent practices. TR emerges as a reaction to this drift, a set of initiatives trying to recapture earlier successes in having both repertoires of practice build on one another.

Lander and Atkinson-Grosjean (2011), defending the concept of the hospital and clinic as 'hidden research system', argue that recent biomedical policy has overemphasised

cooperation between industry and university in seeking to foster the development of new health interventions. They draw on a detailed ethnography of the mundane experimental and institutional practices deployed in the development of a diagnostic test, practices that cut across a number of disciplines and organisations. Webster, Haddad and Waldby (2011) have shown how, in the current field of stem cell therapeutics development, a 'pharmaceutical model' of innovation co-exists with a 'medical innovation' model based on more restricted and clinically-based networks of research and technology development (RTD) work. Also working on the field of stem cells, Martin, Brown and Kraft (2008) contend that the relation between clinical and laboratory-based sites of biomedical knowledge production have indeed seen much variation over the last 60 years, but that current implementations of TR are very much laboratory-centred and follow a science-push model (Biegelbauer 2000), relegating clinical experimental systems to subordinated instruments of evidence generation. Yet, the development of new therapeutics and innovative health interventions is often associated with the emergence of specific innovations and know-how in networks accomplishing clinical research (Keating and Cambrosio 2012), and it is now increasingly untenable to consider these areas of the biomedical enterprise as rote screening of fully formed products waiting for regulatory approval (Nightingale and Martin 2004).

Wainwright and colleagues (Wainwright et al 2009; Wainwright, Michael and Williams 2008) have published a number of studies that capture the interactions and negotiations for authority taking place between the different disciplinary and institutional cultures involved in the development of stem cell therapeutics. These authors use the theory of action, habitus and field from Pierre Bourdieu to analyse how the construction of knowledge, experimental platforms and institutional settings for TR initiatives are determined by struggles for setting collective definitions of legitimate TR practices. Wilson-Kovacs and Hauskeller (2012) study the claims of clinician-scientists as a specific professional group vying to establish themselves as the privileged 'translational investigators' within an arena of contesting disciplinary stakes over TR, hoping to make of their individual multidisciplinary competences in both laboratory research and clinical care a recognised principle of authority in the field. Morgan et al (2011) have shown how policy initiatives aiming to support TR activities in academia such as a translational cluster they studied are likely to run into these competing disciplinary claims over the best way to conduct these efforts. The clinical and industrial requirements often deployed in TR projects may be problematic to assert in contexts were the pursuit of experimental biology for its own sake may constitute the dominant frame for evaluating the worth of given research practices.

More recently, a few authors have aimed to address the breadth of TR as a deep trend restructuring biomedical innovation, moving beyond the realm of local case studies.

Van der Laan and Beonink (2013) have recently provided an extensive review of the ways in which concepts of TR have been used in the specialised biomedical literature. They find a broad variety of grievances, from purely technical issues and failings in contemporary experimental approaches to demands aimed more at the institutional structure of biomedicine, to which TR should provide solutions to. Nonetheless, they are able to reduce the messiness of TR and circumscribe recurring categories that provide more central repertoires of interpretation within a broader proliferation of meanings.

The contributions included in a recent collection edited by James Mittra and Christopher-Paul Milne and dedicated to the topic of TR also provide an ordering exercise that allows to reduce the complexity of this phenomenon by delineating central historical trends within current biomedical innovation systems (Kraft 2013; Mittra 2013; Mittra and Milne 2013). In the introductory essay, the authors clearly contend that the emergence TR is not mere rhetoric but offers a unique opportunity to durably solve some of biomedical innovation systems' long recurring problems. They consider efforts to maintain a tighter feedback loop between clinical medicine and bench science as the mark of a new set of practices and positive advance on previous innovation approaches (Mittra and Milne 2013).

Mittra (2013) thoroughly examines the trajectory of a single industry and, to a lesser extent, government-driven public-private TR collaboration in Scotland. His contribution provide details about the kind of collaborative network approaches now often deployed by the pharmaceutical industry to access key academic knowledge from laboratory and clinical studies, especially those conducted with human tissues. The case of the Translational Medicine Research Collaboration illustrates well the kind of challenges faced by TR initiatives, where conflicting priorities and organisational routines may sap otherwise well-planned, encompassing collaborations. It also contends for a need of innovation in the regulatory system itself as a requisite of success in the TR enterprise.

Alison Kraft (2013), in her contribution to the collection, adopts an approach and sets of observations about TR that very much overlap with my own work here. She also situates the construction of TR as a collective priority imbued with much urgency within a particular policy plane where a number of crises converged and were articulated together. My own findings here should substantiate and expand on her findings. Additionally, my focus on policy narratives as drivers of socio-technical change will bring into greater relief the struggles for the governance of biomedical innovation in which TR has become entangled.

Taking a broader view, Mittra and colleagues (Wield et al 2013) have highlighted the impact of TR agendas across a number of large-scale public-private RTD collaborations as well as in a number of pharmaceutical companies. In their findings, uptake of TR is predicated on the promises of better integration of the technologies emerging in the wake of the "new biology" with the knowledge and expertise specific to clinical contexts, but also in as a mean to increase the financial robustness of pharmaceutical innovation. They contextualise TR within an emerging bioeconomy that privileges interdisciplinary and 'open' routes of innovation, including increase participation from 'users' such as patients in biomedicine.

Fischer (2012) uses the case of TR, and with extensive experience of a specific investigator particularly, to tease out the properties of emergent forms of life assembled through contemporary biomedical and biotechnology research, in their entanglements with the conditions of late capitalism.

Leonelli and Sunder Rajan propose that TR be understood within the "increased capitalization and globalization of the life sciences" (Leonelli and Sunder Rajan 2013, p.3). They contend that the case of TR illustrate the growing importance of producing knowledge that is in movement, that is, knowledge with a high mobility between different „laboratories, communities, nation-states and disciplines" as part of „data journeys" (Leonelli and Sunder Rajan 2013, p.12). Mobility, in itself, would also act as an eminently tractable „output" of more fundamental research supported by public money, making of TR one tactical manoeuvre to enhance the accountability of the biomedical research enterprise. TR thus appears to extend the grasp of regimes of accountability in research and higher education, reconfiguring the production of knowledge so that its public value can be always more readily demonstrated (Braun 2005; Felt and Stöckelová 2009; Maasen and Lieven 2006; Power 2007; Weingart 2005).

Maienschein et al (2008) have taken a more explicitly critical stance over the broad movement towards TR in recent biomedical policy. They warn against the potential dangers of prioritising TR excessively, which may distort the long-term viability of the biomedical research enterprise by draining resources away from the basic research that might form the basis of future TR. Clearer demands and expectations would help ensure that the goals of basic and translational research projects are not confused and that adequate institutional space is provided for each investigational area to prosper. To this critical approach, one could add recent studies of the biotechnology sector that have questioned the wisdom of massive public support for an industry that has yet, after 25 years of activity, to be profitable (Pisano 2006; Mirowski 2011), or that dispute the wisdom of making promises of short-term clinical innovation as a mean to justify large-scale investments in biomedical research (Nightingale and Martin 2004; Martin et

al 2009). van der Laan and Boenink (2013), reflecting on the results already presented above, contended that dominant understandings of TR do not appear to propose radically new solutions to the problems they should solve, notably because they remained within the confines of the limited understanding of linear models of innovation (see also Martin, Brown and Kraft 2008, for similar conclusions). Elsewhere, however, an attempt at evaluating the consequences of TR initiatives on the degree of societal relevance of life sciences research have found a positive effect of these new modes of innovation, although using broader understandings of relevance then those usually emphasized in the biomedical and policy literature (van der Weijden, Verbree and van den Besselaar 2012).

Despite the path-breaking analyses of authors such Löwy, Keating and Cambrosio or Lander and Atkinson-Grosjean, we still know little about the mundane practices of TR (Maeinschein et al 2008). Indeed,

> "While there is a plethora of ethnographies that focus on either the laboratory or the clinic, few social research studies have examined both the bench [the laboratory] and the bedside [the clinic]... [Even t]hese studies do not, however, focus specifically on the interactions between bench and bedside" (Wainwright et al. 2009: 44).

Hogarth, Hopkins and Faulkner have similarly contended that (2012: 122): "Despite the priority given to translational research there is relatively little detailed empirical social science work that has critically analyzed the dynamics of knowledge translation in this domain". The recent achievements examined above only highlight further gaps in our knowledge about the implications of these new TR notions for the conduct of biomedical innovation and for our technoscientific lives. There is thus, more than ever, a need to further develop a "social science of translational research" (Wainwright et al 2009).

Moreover, what is still missing about much of the work summarized above is an adequate conceptualisation of the 'very idea of TR'. Much of the work cited above utilise TR as a shorthand to signify biomedical innovation work with laboratory and clinical components and then go on to analyses the dynamics of interdisciplinary or translation work in specific local instances. Yet, I would argue that what is so interesting about TR is the widespread use of this notion with a programmatic intent, argumentative practices that hint at deeper struggles within the biomedical field. The emergence of TR when perfectly acceptable synonyms are already available to describe processes of technology transfer or clinical innovation hints at epistemic, institutional and material turmoil below the rhetorical surface.

1.4 TR as reform

TR is a label or notion that brings together researchers and other actors from the biomedical field that share certain interpretations of what is in need of collective attention and improvement in their domain of practice, and what are the best epistemic, institutional and material means to achieve these aims. With this basic understanding of TR, I will propose here to make use here of contentions that changes in the socio-technical makeup of scientific fields are the often the results of "scientific and intellectual movements" (Frickel and Gross 2005). Such reform movements in the scientific field typically seek to legitimate new or peripheral experimental or institutional practices in the face of more established disciplinary customs. Emerging research programmes "are fundamentally political outcomes, the result of struggles for resources, identities, and status" (Jacobs and Frickel 2009, p. 57). New socio-technical practices of scientific research innovation, if successfully established, are likely to reduce the collective authority of the privileged programmes of dominant groups of researchers (Bourdieu 1976). Indeed, what is so often at stake in discussions about TR, as will be shown later, is the legitimation of a space of inquiry that is traditionally less prestigious then laboratory-based investigations in (patho)physiology, cast aside as unexciting "applied research". Changing this reputational frame would bolster the domain of practice labelled as TR, and in turn allow to solve some of the pressing problems of innovation productivity sketched above.

1.5 Reform as discursive change: argumentative policy analysis

Molyneux-Hodgson and Meyer (2009) contend that one can fruitfully study the emergence of scientific communities by looking at the spaces where these groups are constructed and articulated, which include funding proposals, or policy documents. Indeed, researchers and technologists are constantly arguing about the virtues and benefits of their intellectual agendas, for the advancement of knowledge but also the progress of society at large. Biomedical research actors, to obtain funding, need to have their findings read and to convince colleagues to engage in collaborate with them. As such, they are constantly engaging in programmatic work that projects future visions of what scientific research and biomedical innovation systems should be like in coming years, to better tackle knowledge puzzles and societal needs. Research practice is "thoroughly suffused" with evaluations by peers (Laudel and Gläser 2011), so that these programmatic efforts can be considered to take up a sizable portion of their work to advance researchers' intellectual and institutional agendas.

In short, the programmatic work of researchers and technologists aims to convince colleagues to provide them with the resources they need to carry their projects (Latour

and Woolgar 1986), but it also increases their credibility and authority in the field (Bourdieu 1976) and allows to mobilize allies with which to extend the agenda (Brown, Rappert and Webster 2000; Hedgecoe 2003; van Lente and Rip 1998). As such, we can consider this programmatic work as a form of highly distributed, bottom-up form of policy-making. These processes of policy-making are co-extensive with the work of governmental agencies such as funding councils, yet they do not always coincide (Braun 1998). Tension between grassroots demands in scientific fields and state bodies' intentions may also result in a variety of strategies on the part of researchers to obtain public support while evading the specific demands that such assistance come be assorted with (Laudel 2006; Power 2007). The making of science, technology and innovation (STI) policy can be a cause of potential struggles, although their effective empirical realisation should by no means be taken for granted (Cambrosio, Limoges and Pronovost 1991).

On the political science side, in the last 25 years, a more interpretativist strand of policy sciences has emerged with an interest for examining the ways that arguments, rhetoric and narratives frame the performance of state policy-making (Fischer 2003). The broad construction of policy narratives through discursive activism is recognised as playing crucial roles in the formulation and implementation of policy, along or sometimes against the more traditionally economic or political calculi that, we tend to consider, characterise the activity of civil servants and politicians. Argumentative policy analysis

> "…embraces and understanding of human action as intermediated and embedded in symbolically rich social and cultural contexts… Recognizing that the policy process is constituted by and mediated through communicative practices, the argumentative turn therefore attempts to understand both the process of policy making and the analytical activities of policy inquiry on their own terms… This requires close attention to the social construction of the normative – often conflicting – policy frames of those who struggle over power and policy" (Fischer and Gottweis 2012, p. 2-3).

I contend that argumentative policy analysis can be very illuminating of the TR case. Argumentative policy analysis is especially well suited for tracking argumentative practices that impact policy-making and implementation but that take place outside the traditional sites of political deliberation. These practices may include the articulation and dissemination of certain story-lines about what current urgent societal problems are and how to best answer them, as formulated by actors such as the popular press, expert committees or social movements (Hajer 1995; Gottweis 1998). In this way, it is possible to trace the influence of a broad spectrum of practices on the parameters that govern the legitimate formulation of policy issues and policy instruments. I contend that TR is primarily a set of programmatic statements aimed at an audience of biomedical experts, in a professional domain where 'command and control' styles of governance

are not prevalent. Biomedical innovation systems can be characterised as instances of communities where a form of "network governance" (Torfing 2005) prevails, with a high autonomy afforded to individual actors. Spaces of collective deliberation may be the main sites open for TR advocates to "implement" collective reform, and thus effect change in governance (who sets collective priorities for research, how are different form of knowledge and experimental practice ordered, which networks are in place to carry complex, interdisciplinary projects).

1.6 Arguments

I have already made references to some of the arguments that have structured my work and will structure the account continued within these pages. For the sake of clarity, I will repeat them here in concise, logical order.

Argument 1. There has been mounting perception of crisis in the area of biomedical innovation in the last 20 years, with policy-makers, academic administrations and research leaders calling for new collective models of collective action to reform the application of fundamental biological knowledge to clinical intervention; accomplishments such as the completion of the Human Genome Project appear to have compounded rather than mitigated the crisis, since impatience stems notably from the perception that major achievements in "basic research" are increasingly irrelevant to clinical innovation.

Argument 2. Emerging as a proposed solution to these innovation crises, a broad reform movement has been coalescing under the label of "translational research", "translational medicine" or "translational science".

Argument 3. The TR reform movement is succeeding in inducing change in practices of biomedical innovation through a number of argumentative interventions:

a. By formulating problematisations of current biomedical innovation crises around specific and well delineated issues.

b. By constructing dominant shared understandings within the biomedical field of which models of collective action will best address the crisis: that is, convincingly offering certain research programmes and institution-building agendas as the best means to overcome innovation crises.

Problematizations and models of collective action can be regrouped in three dominant policy narratives of TR as reform:

- Focus on the renewal of clinician-scientists as a privileged class of investigators to individually incorporate both laboratory- and clinic-based practice; this implies

the deployment institutional support to clinician-scientists, of new practices of patient-oriented research and renewed attention on academic medicine and hospital contexts as sites of clinical innovation;

- Focus on continued effort in the development of post-genomic sequencing platforms for clinical contexts, with the argument that these experimental tools are the best means to obtain deep mechanistic (patho)physiological understanding that is necessary to drive clinical innovation; this implies the expansion of socio-technical systems surrounding biomarker research using tissue repositories, for example.

- Focus on the development of drug development capacities within academic settings as a mean to take over RTD efforts from the pharmaceutical industry; this implies the implementation of large-scale, quasi-industrial RTD instruments and divisions of labour within academia, in a way that is completely novel for this specific context.

Argument 4. Changes in experimental and institutional practices effected through TR-driven argumentative practices are leading to new regimes of governance in biomedical innovation systems.

These are statements I would like to submit to the consideration of these scholars concerned with the social studies of translational research. As I have already mentioned, these have been crafted with a goal to account for the interdependence between local experimental practice and institutional form, on the one hand, and argumentative practices situated within the specific collective spaces for coordination and governance characteristic of technoscientific systems. These arguments should carry with them and assert my contention that our conceptualisations of TR are most fruitful when they account for this interdependence in explaining socio-technical change within biomedical systems of innovation.

1.7 What comes next

In chapter 2, I will elaborate on the argumentative policy analysis and STS scholarships I have tapped into in trying to make sense of the phenomenon on TR. I will examine recent achievements from the former tradition, and show how they are especially well suited to conceptualise forms and processes of governance within research communities.

Chapter 3 starts my analytical engagement with the empirical material I collected by examining three specific TR projects I have encountered over the course of my fieldwork. The aim here is to provide a thicker description of the mundane conduct of actual TR efforts (rather than the abstract models and idealised projects so often described in the programmatic literature). Some of the characteristics of the projects identified here will be relevant for understanding later arguments made throughout the document.

Chapter 4 details the origin of the three main policy narratives that I contend form the dominant interpretative grids with which biomedical actors engage with TR. This analysis will be based on the documentary record of specialised periodicals and governmental policy formulations. Focus here will be on tracing the argumentative practices through which a notion such as TR was called into existence, and the kind of models they each put forward.

Chapter 5 takes the three narratives of TR elaborated in chapter 4 and uses interview material and analyses of specific TR initiatives to substantiate our claims about the grasp/power of these three narratives, as well as the way they are reshaping institutional, epistemic and material practices in biomedicine. Here, we follow reformers as the policy narratives of TR are being ‘implemented’ and deployed concretely within new initiatives established to foster clinical innovation.

While chapters 3 to 5 were centrally concerned with the presentation and processing of the empirical material I have collected, the remaining chapters build on these findings to refine my analytical statements. Chapter 6 examines the ways that the three narratives build upon each other or enter into tension with one another in specific case studies. It provides additional insight into how TR advocates make use of the policy narratives to orient their mundane practices and coordinate them with those of others. Chapter 7 re-examines our main arguments and summarize the empirical support for each. It also highlights further analytical implications of these arguments for social studies of biomedicine and innovation studies. Finally, chapter 8 concludes by offering a number of lessons for current biomedical policy that can be drawn based from the study of the TR case.

2 Argumentation and governance in biomedical innovation systems

To gain conceptual thrust on the multitude of narratives and institutional practices entangled with notions of TR, I will deploy an analytical toolbox that draws on argumentative and interpretative strands in the policy sciences, as well as STS and innovation studies work that deal with the governance of innovation systems and the role of STI policies in these processes. The theory synthesis work conducted in the following pages should put in greater light the potential benefits to STI policy studies of having more regular attention to argumentative and interpretative processes.

2.1 Argumentative policy analysis

Aarden (2009, p.116) reports, in what can be a useful example for us here, on how the UK' National Health Service framed the issue of familial hypercholesterolemia as an important health problem, supporting developments for genetic and phenotypic testing and funding further research. These measures lead to a specific definition of the familial hypercholesterolemia problem in the UK, together with the establishment of specific institutional set-ups for research and testing provisions. This is in contrast with the situation in Germany, where the state most notably classified familial hypercholesterolemia as just one risk factor among others for cardiovascular diseases. The discursive and conceptual work of British and German health services, such as the official classification and ordering of a health condition, had major impacts on the shape of clinical care infrastructure for cardiovascular diseases in both countries. The following subsections detail recent work the policy sciences that help us track how narrative framing of collective issues can effect socio-technical change.

2.1.1 Discourse and socio-technical change

The example above attests to the power that culturally crosscutting discourses, interpretations and meanings have over the shape of public policy. A still young strand of analysis in the subfield of policy sciences has been preoccupied with sharpening our comprehension of how discursive developments and struggles play into empirical, mundane practices of policy-making. This scholarship has drawn from Foucaldian discourse theory (Laclau and Mouffe 1985), interpretativist approaches (Yanow 1999) or studies of argumentation and persuasion (Majone 1989) to foreground collective, historical constructions of shared categories in trying to gain conceptual grasp on social transactions.

As such, Foucaldian discourse theory offered an "analytical perspective which focused on the rules and meanings that condition the construction of social, political, and cultural identity" (Torfing 2005, p.1). Its import for political scientists interested in discourse

has been to offer means to "pay attention to new issues such as knowledge paradigms, identity formation, and the discursive construction of sedimented norms, values and symbols" (Torfing 2005, p.4). This can be translated into a sustained interest in how meaning is created, communicated and understood in social practices and texts (Gottweis 1998). Discourse theory follows in the Kantian tradition of examining how pre-given categories affect perception and experience of empirical phenomena, how structures allow agency in a certain spectrum of possibilities. Yet, these conditions of possibility are subject to struggle and social conflicts, as well as historical transformation (Torfing 2005). Meanings orient the actions of actors, and therefore tend to become privileged sites for conflicts and negotiations.

The rather recent development of argumentative or interpretative policy analysis can be seen as one strand in a broad tradition of discourse analysis within social science research. Brief examination of the arguments made in this tradition can help to better understand the role of meanings and narratives in socio-technical change.

Post-structuralist works, shaped as they were by the Saussurian heritage, offered somewhat different readings of such theses. A less followed route in discourse analysis might have concentrated on the work of Bourdieu, and focus on symbolic struggles as processes for the imposition of specific meanings or perspectives. In other words, these are the processes by which agents or institutions – consciously or not – try to impose their vision of the world, as well as the categories they use to understand it, upon other agents. Bourdieu's would also emphasize how these discursive practices are seldom rational or explicitly formulated strategies, being rather habitual, implicit and co-extensive to practices that have seemingly other ends (economic or cultural, notably). Thus, for Bourdieu

> "Political action [. . .] aims at producing and imposing representations (mental, verbal, graphical, or theatrical) of the social world which are able to influence this world by influencing the representation actors have of it" (Bourdieu 1982, p. 149 – translation in Contandriopoulous, Denis and Langley 2004; p. 1575)

Coming rather from the tradition of intellectual history, Skinner (2002) proposes being interested with "ideological innovations", whose introduction of new concepts, or new uses for conducts, which replace certain meanings of context at a certain time with other meanings, often for strategic purposes. Innovators will try to show that terms used to describe morally admirable things or conducts can be applied to their own practices as well, even if these practices may have been framed as interested or distasteful up to that point. At the same time, new meanings or new rhetorical uses of

concept can be seen as reflective of broader changes within society, following negotiations and conflicts between specific groups notably:

> "The surest sign that a group or society has entered into the self-conscious possession of a new concept is that a corresponding vocabulary will be developed, a vocabulary which can then be used to pick out and discuss the concept in question with consistency" (Skinner 2002, p. 160).

Skinner notably is particularly sensible to the context in which historical texts have been written, and build on Austin's concept of speech acts to assess what particular texts, discourses or documents are meant to perform by their author or users. Understanding, in Skinner's example, that Descartes was addressing new forms of scepticism with is Meditations allows us to interpret texts in new light, as well as to posit their potential effects (Skinner 2002, p. 83): "The only histories of ideas to be written are histories of their uses in argument". Social vocabulary and social practices are constituted thought one another, and this co-production is itself co-extensive with the contentions of many social groups for legitimacy and authority.

STS authors have also made use of interpretative and narrative approaches to understand how ordering processes in technoscience and civil society tend to draw on one another. Jasanoff's comparative approach to STS work stresses the interpretative, because, in her view, the meanings that are attributed to emerging technologies (and, we could add, sciences and styles of doing science), cannot obtain from direct interventions from leaders or policy-makers, nor strictly from regulatory provisions or specificities of particular markets. Drawing on Erving Goffman's work, Jasanoff talk of the ways scientific developments are framed by collectives, who make sense of these developments through story-telling and by situating the stories of these developments within their broader narratives and discourses.

> "Just as any culture has established folkways that give meanings to its social interactions, so I suggest that modern technoscientific cultures have developed tacit knowledge-ways through which they assess the rationality and robustness of claims they seek to order their lives: demonstrations or arguments that fail to meet these tests may be dismissed as illegitimate or irrational. These collective knowledge-ways constitute a culture's civic epistemology; they are distinctive, systematic, often institutionalized, and articulated through practice rather than formal rules." (Jasanoff 2004, p. 255).

Civic epistemology refers, in Jasanoff's approach, to the local cultural composition (of meanings, dominant discourses, ways of seeing the world) through which scientific events and technologies are processed. These indicate the way that collectives, coalitions of citizens, politicians, scientists, industrialists have of building stabilised knowledge, and the criteria that these collective have when it comes to counting knowledge

as reliable or valid. This is thus to say, that interpretative and argumentative processes are also central here to understanding socio-technical change, identities or authority and power, even as this argumentative work is constantly stabilised and performed through mundane practice.

2.1.2 Policy narratives and argumentation

It might seem contradictory to argue that narrative structures act as tools to reduce the complexity of the world, when discourse is often associated with empty rhetoric, fad or utter fluidity. Yet, it is exactly the fact that texts, narratives, arguments can be interpreted in a multiplicity of contexts and their plasticity that provides them with a crucial capacity to order the socio-technical world (Hajer 1995). Indeed, in the research of Hajer (1995), proponents of the specific discourse of ecological modernization could draw on the authority of arguments provided by collection of texts as varied as cybernetics research, essays such as *Small is Beautiful*, or increasingly apocalyptic visions of the human future provided in the media. These highly heterogeneous settings and contents nonetheless came to be associated, connected and ordered through relatively simple story-lines.

One important means for actors to organise meanings and provide the ideological map mentioned above, in policy-making as much as in all areas of human activity, is through narratives that order, provide causal explanations and articulate deeper social and political dispositions into cognitive content. Narratives provide these meanings and representations by offering a story as an ordered representation of how times, places and characters interact, and thus an ideal configuration of actors and their practices in the field. (Meta)Narratives end constituting elements in the "available repertoire of political visions and identifications in one's social situation" (Gottweis 1998, p.34). But these discourses cannot be freely used by any actor, and existing narratives condition which parts of the repertoire may be used by whom with authority. Finally, narratives are always changing, as they interact with one another, are used in social struggles and are imbued with different meanings as part of this, and as practices change.

What is a policy narrative then? A narrative is a construction of various categories, evidence, metaphors and other elements that enable us to make sense of the world into a structured story, which may rely on conventional plots for example, to provide a reasonable conclusion about what has happened or will happen, given certain conditions (Fischer 2003). Narratives, whether in analytical, ordinary or literary text or discourse, reduce the complexity of the world by identifying crucial problems, and orienting action along a few preferred solutions. Shared story lines form conceptual repertoires, which justify and frame local practices, notably those that participate in policy formulation,

implementation and evaluation. Policy narratives more specifically create ordered meanings and representations of events, articulating interventions and shaping policies, providing legitimacy or providing arbitrage for conflicts:

> "Narratives also interconnect the various sites of a regime of governability, such as laboratories, scientific journals, and research ministries. In other words, they function as 'networks of meaning', establishing relationships among a variety of entities. They problematize, enroll, and mobilize persons, procedures, artifacts, and representations in the pursuit of a particular policy goal" (Gottweis 1998, p.32).

The quote above highlights the issue of problematisation as one of the important processes through which policy narratives effect change. Indeed, here I will afford a central role to processes of problematisation as one of the two major moments in the life cycles of policy narratives. I follow in the footsteps of Hajer in contending that:

> "[p]olicy-making is in fact to be analysed as the creation of problems, that is to say, policy-making can be analysed as a set of practices that are meant to process fragmented and contradictory statements to be able to create the sort of problems that institutions can handle and for which solutions can be found. Hence policies are not only devised to solve problems, problems also have to be devised to be able to create policies" (Hajer 1995, p. 15).

Positing or diagnosing the existence of a problem of pressing urgency and deep consequences for communities is a powerful rhetorical mean to draw collective attention and resources to specific sites, objects and practices. When actors in policy networks propose given **problematisations**, they reduce complexity by actively favouring certain sites and behaviours, while leaving beside issues that may be of importance to other actors (Howarth and Griggs 2012). Problematisations can also act to ascribe responsibilities, blame or trust to various actors involve in a policy issue (Fischer 2003). As such, collective problematisations are actively shaped by policy actors, as struggles over the definition of problems have outcomes for the implementation and life cycles of policies and how they impact collective life.

A second moment of policy narratives proposes representations of what future collective action would have to look like in order to achieve a certain policy goal. These **models of collective action** provide more detailed arguments about which actors, practices, institutions and/or policy endpoints need to be privilege in order to achieve a broader policy outcome and closure of the associated problematisations. Schmidt (2012) has thus highlighted how policy narratives may play 'coordinative' and 'communicative' functions. The first acts to bring together "epistemic communities, advocacy coalitions and discourse coalitions" (Fischer 2003, p.31) around policy goals, while the communication function deals with generating legitimacy in a broader, perhaps more

external audience of the closer policy network. Such coordinative and communicative functions could be classified, in my own framework, as some of the components of a models of collective action advocated through policy narratives.

At a given point, different policy narratives, different problems and associated models of collective action are likely to be available to policy actors engaged in making sense of the complexity before them, be they state policy-makers or the individual researcher. Scholars from the argumentative and interpretative policy analysis strand also provide some indication as to what may make one narrative more successful or convincing then the other. Fischer has argued that argumentative practices in policy-making can be adequately framed as an instance of practical reasoning, as the concept has been developed by Stephen Toulmin (Fischer 2007). Fischer identifies four discourses (technical analytical discourse, contextual, systems, ideological) that a practical reason or argumentation in defending or proposing a particular policy programme may answer to or make sense towards (provide reasons to), in order to be accepted as good argument regarding past or future policies.

Many authors have instead resorted to a conception of hegemony inspired by the work of Gramsci to explain the grasp of certain policy narratives. Hegemony, defined as a discursive project that manages to articulate and structure large segments of society's manifold other discursive projects under its fold. Hegemony thus represents the dominant core of meaning and practices structuring further social meanings, identities, interpretations, narratives, institutions, or representations in a certain field. Borrowing from a different conceptual idiom, a hegemonic metanarrative acts as the obligatory passage point (Callon 1986) for formulating legitimate lower-order narratives. "Articulations that manage to provide a credible principle upon which to read past, present and future events, and capture people's hearts and minds, become hegemonic" (Torfing 2005, p.15). Gottweis also emphasizes this brokering function of narratives that achieve hegemonic status:

> "Ultimately, what is of importance in policymaking is the intermediation between policy narrative, discursive constellation (or discursive economy), and discursive context. The success of policymaking depends as much on the inscription of a policy narrative into the given discursive constellations as on its ability to mediate between competing codes by which economic, scientific, or political reality (context) is assigned meanings" (Gottweis 1998, p.37)."

Hegemony for Hajer has two dimensions: discourse structuration and discourse institutionalisation. The first refer to the process by which actors have to draw on a discourse to be able to act with credibility in a certain context; the second when modalities proper

to this form of discourse are effectively put into place concretely into policies (Hajer 1995).

Discourse coalitions

Identifying **discourse coalitions** allows the analyst to capture the social negotiations that are co-extensive to the performance of argumentative practices. “A discourse coalition is the ensemble of a set of story lines, the actors that utters these story lines, and the practices that conform to these story lines, all organized around a discourse” (Hajer 1993: 47). Discourse coalitions aim to convince or even force central policy actors to adopt the terms of their story-line to formulate and address policy problems, steering institutional practices in this process. Discourse coalitions are not formally organised as some advocacy or lobbying coalitions can be. Rather, the concept aims to capture the type of institutional change that can take place when dispersed actors from a variety of backgrounds advocate or adopt a specific set of interpretations of a policy problem and preferred solutions to it. The force of certain arguments, evidence or story-lines and of the coalitions uttering them can be such, that it becomes difficult or illegitimate to frame a problem from a different perspective. Additionally, in discourse coalitions, story lines about policy are constitutive of actors’ perceptions of their own interests and priorities, whereas advocacy coalitions typically are the vehicles that different groups use to defend pre-existing interests (Hajer 1995).

However, one cannot always or even often identify well-delineated discourse coalitions, with a clear identity for its members. Instead, these should be seen as shifting, and Hajer tells us that there is a varied set of actions which reproduce these narratives and discourses. Discourse coalitions are composed of actors that are not necessarily in close contact, or that are closely coordinated, but rather they draw from the same repertoire of story-lines in defending and advocating their positions. Each can interpret and deploy these story-lines differently, but the recurring use of the story-lines in themselves reinforces their stability, even as they are being stretched in their use in various political contexts. Coalitions can thus include actors such as science journalists which might not be directly involved in the policy process. The more different actors can refer to a specific discursive frame to formulate their claims, the more hegemonic the frame is.

The use of arguments and narratives in discursive struggles tries to position actors in specific ways. Also, the ordering of society through rules and conventions are constantly being reproduced through speech acts (Hajer 1995). This means, notably, that interests are not essentialist features of actors, but rather are constructed through interactions, arguments and narratives. This means that change in dominant dis-

courses may allow for new coalitions and alliances to be formed. Additionally, the groups which end up having the most influence on the authoritative or legitimate definition of the policy problems might change over time, even as the science policy is 'implemented' (Fischer 003).

Argumentative practices

Argumentative practices, then, are the acts of communication through which discourse coalitions or individual actors will propose and diffuse policy narratives. Specifically in fields such as biomedicine and STI sectors, Hedgecoe (2003) has shown how certain categories of peer-reviewed publications, such as editorials and reviews, are often used to make claims about priorities for collective policy and the coordination of individual experimental practices. More broadly, Whitley highlights how collective appropriation and use of experimental results are crucial attempts at coordinating research procedures and strategies. The formal public communication system:

> "both connects research results from different production sites concerned with common problems and provides the arena for conflicts over reputations and interpretations. It is the major agency of social control of competence standards and work process as well as being the locus of negotiations over intellectual goals and priorities" (Whitley 2000, p. 33-34).

Researchers thus commonly engage in argumentative practices that shape local and state policies relevant to their activities. Argumentative policy analysis thus seems ideally positioned to capture how bottom-up movements taking place within scientific communities can lead to change in STI policy. Research programmes elaborated through discussions at conferences and in editorials are just as likely to have coordinative and steering effects on scientific communities as formal white papers or other state-based policy instruments. This is not to say that regulatory developments or laws that frame the daily functioning of scientific institutions are not important effectors of change in STI activities. Rather, I wish to highlight the importance of also capturing dispersed and de-centralised argumentative practices for understanding STI policy-making processes. Such dispersed argumentative practices should be considered alongside better-studied deliberative activities such as those witnessed in official consultation exercises and those other hybrid fora often convened with the explicit intention of broadening participation in the governance of STI systems.

2.2 The governance of biomedical innovation

The scientific field has historically been portrayed as a model of democratic governance. If governance is meant to denote contemporary arrangements with highly dispersed legitimacy to participate in collectively recognized forum of policy-making, then

scientific fields may be seen as long forerunners of this development. Indeed, central processes of coordination and authority building in scientific fields are generally considered to be highly accessible to members of the field and to be non-hierarchical (Whitley 2000), although there is considerable variation between fields or even subspecialties or domains (Atkinson-Grosjean and Fairley 2009). At the very least, some researchers and scientists themselves have been historically keen to emphasize how legitimacy in their professional field is established in opposition to "worldly politics" through public displays of work diligence. In this narrative, deference to evidence and observations was due for being objects explicitly represented as being outside subjectivity, interest and politics. Historically, researchers have "linked objective representation with a capacity for discipline and self-restraint… The observer was expected to practice a heroic ascetism, laboriously attained, in order to keep at bay the temptations of subjective judgement" (Golinksi 2005, p. 153).

This formal ethos (to use the words of its most famous apologist, sociologist Robert K. Merton) has been co-extensive with the de-centralized governance and high levels of autonomy that can be observed in scientific communities. Narrow attention towards objects that are collectively recognized as instances of objective facts should, in principle, place the impetus for individual and coordinated action within a few institutional sites highly specific to the scientific field and concerned exclusively with the production of formal knowledge. Indeed, "research is valued to the extent that it affects, influences, and is essential for others' work to be successfully accomplished" (Whitley 2000, p. 12). It is through collective appropriation and use of previous results that the crucial attempts at coordinating research procedures and strategies are made. As already mentioned above, the formal system of specialized scientific periodicals can thus be seen as important nodes in organizing a highly distributed form of collective governance in scientific fields.

Just as researchers are used to arguing about competing interpretations and hypotheses, so do they also commonly argue about to work together and which institutions should shape their fields of practice, often within the same text. In fact, the morphology of governance structures and routines in scientific fields comes uncannily close to those arrangements that are now commonly called "network governance" in political sciences. Jacob Torfing provides a definition of network governance that makes the similarities clear:

> „[network governance is a] relatively stable, horizontal articulation of interdependent, but operationally autonomous actors who interact through negotiations that take place within a relatively institutionalized community which is self-regulating within limits sets by external agencies and contributes to the production of public purpose." (Torfing 2007, p. 5).

The characterisation of scientific fields as self-governed is still a dominant public representation, one that is readily used in the argumentative practices of researchers and science policy-makers. Social science scholarship, especially in the STS tradition, has shown how these representations have been used as rhetorical weapons to conceal alternative power orderings (Bourdieu 1975; Barnes and Dolby 1970). Scientific authority and power between researchers is constructed in the interplay of "technical interests", with convincing research programmes and creative experimental platforms offering their originators and gatekeepers with privileged positions to accumulate resources and direct the actions of others in the field. From a broader perspective, STS scholarship has also shown that 'societal' and 'scientific' orders tend to evolve together (Shapin and Schaffer 1985; Jasanoff 2004b; Nowotny, Scott and Gibbons 2001; Smith and Wise 1989). For example, Maasen and Lieven (2006) have shown that discourses of accountability and enterprising selves are having an impact on the conduct of contemporary researchers, and are thus reshaping practices and systems of knowledge production. From a different perspective, authors have also shown how scientific fields are increasingly amenable to qualified steering by governmental policy-makers (Guston 2000). The next subsection will examine how contemporary state STI policy-making can be expected to shape the experimental and institutional practices of researchers and associated actors.

2.2.1 Coordinating science and technology

The intensive participation of policy-makers in promoting TR is a case in point to show that the relative self-government of biomedical research (and scientific research more broadly) is nonetheless in constant interchange with civil society. STI policy-makers, although they may be initially drawn from the ranks of scientists themselves, also have their own agendas and imperatives (Braun 1998) and have been increasingly concerned since the 1980s with enforcing baseline demands of public utility from fundamental research (Guston 2000; Power 2007).

Typical policy mechanisms used to orient or catalyze certain technoscientific developments include Infrastructural investments, mission-specific or earmarked grants, and RTD tax breaks. Lepori (2011) identifies as ‚coordination' modes different institutional settings for conducting science and attributing research funding, discerning five ideal types: project funding (principal investigator type) as market mechanism; core funding to higher education institutions as non-competitive but hierarchical coordination; networks and consortia that allow broad participation including from end users; central planning effected through hierarchical public research institutions; and core funding to public laboratories which reduces accountability but allows integrated overview of research projects at the level of single investigators. For Hessels, van Lente and Smits

(2009) policy may steer research towards more societal relevance by intervening in the credibility cycle. Organisational devices such as earmarked funding, foresights activities, minute university management and performance assessments were used in Dutch chemistry departments for example to develop incentives for doing applied research.

A central to STI policy-makers is to ensure that actors in innovation systems engage in the collaborative work necessary to the production of commercial and civic value, a task that is not trivial considering the relative autonomy of those whose involvement is required. Typical state coordination of scientific activities can be usefully said to revolve around five general objectives for policy coordination (Braun 2008, p.230 based on Painter 1981):

1. "Avoidance, or at least minimization, of duplication and overlap.
2. Avoidance of policy inconsistencies.
3. Minimisation of conflict, both bureaucratic and political.
4. Quest for coherence and cohesion and an agreed ordering of priorities.
5. Promotion of a comprehensive or 'whole government' perspective against the constant advocacy of narrow, particularistic or sectoral perspectives."

My baseline assumption here is that these attempts at coordination are crucially shaped by the kind of argumentative practices such as those discussed in subsection 2.1, more so in my view then the traditional steering instruments discussed above. For example, operations with an important discursive component such as doing boundary work have been shown to be central to implementation of STI policy:

> "Both Shapin (1992) and Halffman (2003) have drawn attention to the dual nature of boundary work: not only demarcating scientific research and policy, but also coordinating their mutual relations. Fields are demarcated so that their relations can be coordinated in specific ways, and the coordination of their mutual relations will always also contain a specific demarcation of their roles or tasks. Boundary work can produce various configurations of science-policy relations..." (Scholten 2009, p. 562).

Based on these previous findings, I will consider here that the kind of STI policy-making that is relevant to the TR case is much more of a strategic (in the sense of Braun 2008), future-oriented nature than it is concerned with elaborating classical mechanisms of support for technoscientific activity. Furthermore, I will open the definition of STI policy-making to include collective processes of deliberation conducted by researchers themselves. The next subsections will explore this conceptualization of STI policy-making as an extension of the network governance in scientific fields, as an exercise of framing and generating practices discursively within policy narratives that problematise collective action and shared futures.

2.2.2 Experiment and argument

In Latour and Woolgar's notorious circle of credibility, arguments are an important output of previous scientific work, and input for further scientific work (Latour and Woolgar 1986). This representation makes clear that scientific arguments, when convincing and conducive to further experiments, can act as resources to make reputational gains, or to obtain further funding, collaborations and research infrastructure. A small group of STS scholars have deepened our understanding of how arguments about the workings of natural phenomena, or more explicitly programmatic statements about scientific priorities, tend to have implications for the ordering of social communities. These communities may include a broad delineation of civil and state society (Shapin and Schaffer 1985), or more "secluded" scientific collectives (to use the expression of Callon, Lascoumes and Barthe 2011). A strong version of this claim could be formulated so:

> "... knowledge is always underdetermined, in the sense that, faced with choices, researchers tend to adopt interpretations, theories, or lines of research that enable them to monopolize areas of investigation, dismiss the work of competitors, or answer to the social demands of a particular class (such as the state, a political party, or a church)" (Gottweis 1998, p.29).

Given our purposes here, it is unlikely to that we find any entanglements between TR and political parties or religious organisations, but this quote nevertheless make clear the point that scientific claims can have a strategic component and work to reshape the governance of research fields.

A certain number of previous studies have considered how the media and processes of communicating scientific findings are determinants that shape research work. Although these studies may devote more attention to literary processes rather than sociotechnical change, they also conclude that argumentation about nature (such as human (patho)physiology) can be an argument about social orders: "language is not simply a transparent medium of communication, but a shaper (perhaps a realizer) of thought and an embodiment of social relations" (Dear 1991, p.3-4). Dear and colleagues thus argue that literary genres play a role in "perpetuating, changing or subverting scientific research programs", in "defining disciplinary boundaries" (and doing boundary-making one could add), that scientific texts embody "the cognitive assumptions or social structure of the sciences to which they belong", and that literary forms can indeed "direct" the epistemic content of sciences (Dear 1991, p.5).

A more recent strand of scholarship has been concerned with detailing the role of argumentative practices in the elaboration of the technoscientific visions of the future that often act as crucial points of reference for coordinating collective work around emerging technologies and systems of innovation. Articulating visions of a bright technologi-

cal future, or telling a story of genius and entrepreneurship that leads to cures for patients and economic development are typical instances of building expectations. Such visions achieve many goals. When claims are made about what should be done in the present, actors will typically draw on the future and the past to make their point more forceful, and denote its interest to others:

> Indeed, one of the striking things about technological futures is that they often appear in the imperative mode. That is, once defined as promise, action is required. Statements about future technological performance are not received as factual descriptions to be verified or falsified in due course. Instead, they mobilise attention, guide efforts and legitimate actions. Technological futures, are then forceful and render technological developments a specific dynamic. (van Lente 2000, p. 43).

Building expectations thus allows to enrol actors around a specific vision or model, and thus to mobilize and coordinate different groups around it. In effect, vision-building that is successful establishes a dominant representation of how actors should orient their activities, what constitute valuable goals, and which institutional forms are appropriate. Telling the story of TR in journal review sections can allow, for example, to enrol external allies, but also to mutually build expectations and commitments with the community (Deuten and Rip 2000).

van Lente contends that to construct these promises and expectations, actors will typically draw on the discursive resources (the “terms” and “arguments” of “well established vocabularies”) offered by broader metadiscourses about social change and technological development (van Lente 2000, p.43). Much like in the strands of discourse analysis explored in section 2.1, the analysis of expectations shows that the construction of promises is successful when the adoption of these promises simultaneously leads to implications for conduct and action. Deuten and Rip talk of narrative infrastructures to capture the structural effects of discourse, and talk about how narratives that are especially well interconnected to other narratives and practices come to be stabilised. Narrative infrastructures also have a steering effect on actors by providing them with roles in a specific script, which they might try to fulfil as a mean to increase their legitimacy. Yet, one must also remember that expectations “mean different things to different groups” (Hedgecoe 2004, p.27) – roles have to be stabilized and are likely to come under renewed negotiation as new claims come to be articulated in time.

Hedgecoe shows how names and labels can play an important role in securing legitimacy and support for emerging areas, holding a rhetoric function which can delineate a protected space for certain activities, especially if public funding is also provided. Examining developments at the juncture of genomics and pharmacology, he considers how the term “pharmacogenomics”, which appeared in the early 90s, advantageously

came to replace “pharmacogenetics”, allowing for a number of institutional changes to be made in the meantime, notably by enrolling support and resources. Hedgecoe thus contends that “[t]he names we use to label particular disciplines have a role in structuring them, and this in turn affects the uptake of particular technologies” (Hedgecoe 2003, p. 515). One example of this structuring effect could be observed in how pharmacologists were involved in the construction of pharmacogenomics. This professional group tried to bolster their legitimacy, at a time where their role in increasingly uncertain, by associating themselves (and trying to make themselves central) to this new biomedical enterprise.

Drawing on Myers (1990), Hedgecoe has also been able to trace how scientific arguments as made in specialized periodicals could have a performative charge with an aim to re-organise socio-technical systems. He contends that reviews and commentaries are the sites of some of the most central work to construct futures and promises in the scientific field, publications that actively enrol previous findings to create a narrative (with problems, causes and plot development) about the (potential) development of a research field or object. Publications in scientific journals allowed companies interested in the area to shape regulatory structures as well potential markets. The second important point from Hedgecoe (2003) is that articles on pharmacogenomics indeed tend to appear more in reviews or commentaries than research articles, that is categories of publications where previous results are discussed rather than were new findings are presented. Hedgecoe thus contends that pharmacogenomics and pharmacogenetics are terms under negotiation, and that stabilizing a certain meaning would construct the terms as resources more likely to be legitimately mobilized in certain socio-technical systems than others.

The studies mentioned above, especially those from the sociology of expectations, come very close in analytical focus and findings to the concerns of argumentative policy analysis. My intention here is to fully integrate these two strands of scholarship. If one considers the building of research and innovation networks a form of policy-making, then the constitution of expectations and futures are processes that are part of a larger ensemble of argumentative practices commonly engaged in by researchers and technologists.

2.2.3 Reform movements and change in STI governance

An important pattern of experimental and institutional change in the last century of biology and medicine has come in the form of reform movements that have recurrently aimed to re-calibrate the interdependencies between the two domains of practice (Kohler 2008; Lenoir 1997; Marks 1997). I suggest that TR might usefully be con-

sidered as a specific instance of such reform movements, and that the elaboration and reproduction of policy narratives may be considered as a crucial activity that these movements engage in.

Frickel has characterised the emergence of many new research programmes as instances of “scientific and intellectual movements”. Emerging, interdisciplinary or radically unique research programmes typically threaten to destabilise established jurisdictions over academic and scientific “resources, identities, and status” (Jacobs and Frickel 2009, p. 57). Where different research communities are staking a certain scientific domain as their own, discursive struggle will take place concerning the legitimate language to be used for elaborating epistemic content, such as describing new phenomena (Golinski 1985). Because of this, advocates of the approach may tend to informally organise in movements that seek to legitimate new or peripheral experimental or institutional practices in the face of established disciplinary customs. As the introduction has already made clear, TR notions are contentious in current biomedicine, and disciplinary conflicts around TR projects would here be recast as “collective efforts to pursue research programmes or projects for thought in the face of resistance from others in the scientific or intellectual community...” (Frickel and Gross 2005, p. 206). The goal of these efforts is to establish the experimental and research programme advocated as at least one among many valid order of evaluation with which to assign collective value and legitimacy to scientific practice (Lamont 2012). I would argue that this category of reform movement is especially appropriate to analytically delineate the loose confederations of biomedical actors that articulate policy narratives about TR. Collectives that fashion themselves as reform movements may also use the label to anchor claims and expectations as they have been examined in section 2.2.3. Claims made by scientific reform movements might typically centre on collective recognition of the research programme as a fully-fledge discipline or subspecialty (Lenoir 1997). These organisational units afford distinctively potent institutional resources to its members, bringing us back again to the idea that scientific arguments and research programmes carry with them performative proposals for certain academic and societal orders:

> “I suggest that work on the research front and discipline formation be treated as interrelated, not as cause and effect but as mutual resource. Within the spectrum of self-proclaimed discipline builders, some use the organizational power of their own scientific work as an ideological resource dominating the research field, a reductionist strategy of legitimation aimed at imposing a definition of science” (Lenoir 1997, p. 53).

A recent example of this contention is provided by Molyneux-Hodgson and Meyer (2009). These authors have studied the emergence of scientific communities such as

the one that has sprung up around the notions of synthetic biology. They track this emergence by looking at the spaces where these groups are constructed and articulated, which include funding proposals, or policy documents. In other words, these are documents that act as argumentative practices, when they are assembled or distributed, promoting policy narratives that place the reform movement as a crucial component of social and technical change. Morrison (2012) has also shown how the establishment of specialised communities in the life sciences, such as those around regenerative medicine and tissue engineering, has been effected notably through the type of promissory processes studied by the sociology of expectations. This shows the interest of studying informal activist networks within scientific fields as movements that effect reform by engaging in argumentative practices of policy-making and expectation building.

More broadly, this shows the potential of studying argumentative practices as privileged sites for the valuation and construction legitimacy for STI policies, broadly understood as collective repertoires of coordination, towards an audience of peers and potential practitioners. In this, we can mitigate a widespread tendency to see STI rhetoric and argumentative practices as solely aimed at "publics" of users, patients and citizens (an inadvertent consequence of models of innovation systems such as those deployed by Geels and Veerhees 2011; Wieczorek and Hekkert 2012).

2.2.4 Co-producing new (patho)physiological knowledge and new biomedical institutions

The analytical toolbox developed here has broad affinities with the "idiom of co-production" which has run through STS studies since the 1980s and has been recently formalized by Sheila Jasanoff (Shapin and Schaffer 1985; Latour 1987; Jasanoff 2004b). The co-production approach invites social scientists to consider both social determinations on scientific knowledge, and technological and epistemic determinations on social practices, without according primacy to one or the other. It hopes to allow the unpacking of complex and intertwined phenomena by this continuous movement to in fro between science and society, and the consideration of how they each underwrite one another (Jasanoff 2004a; Jasanoff 2004b).

Scientific knowledge, for the co-production idiom, is tightly inter-connected with those elements that social scientists include in the term "social": "practices, identities, norms, conventions, discourses, instruments and institutions", (Jasanoff, 2004, p. 3) as well as representations: "nothing significant happens in science without concurrent adjustments in society, politics or culture; similarly, intransigent social problems seldom yield to resolution without changes in existing structures of knowledge" (Jasanoff 2004b, p.21). Most importantly, the co-production idiom emphases how no conceptual cate-

gory of the social world can be used as an explanatory or determining variable (examples given include “power”, “state” or “gender”) without being put into context itself, and produced and enacted together with scientific knowledge.

This is to say, then, that we can expect proponents of TR agenda to make claims that stand to reshape both the kind of science that biomedical research mainly concerns itself with, but also the organisational and material conditions under which this work is conducted, even when they do not explicitly have this aim.

2.3 Summary: analytical toolbox

It is precisely because the scientific field is a prime example of ‘network governance’, where there is an explicit attempt to quell the establish of any formal hierarchy within its domain, that the study of steering and coordination of scientific practices seems so promising from the angle of the study of narratives, and how they shape the ‘conduct of conduct’ (Dardot and Laval 2010; Maasen and Lieven 2006). If one can account for the genealogy of scientific discourses that provide meaning to innovation practices, then one can perhaps understand in which context individual scientists are attracted to certain research objects, experimental platforms and/or institutional framings of their activities more than others.

I made mention in the introduction to the contention that STS scholars need to track scientists’ policy activism beyond official fora of deliberation organized by state policy-makers if it is to understand governance processes in scientific communities. Following up on this, I discussed how practices of collective argumentation and deliberation about future STI policy could be observed in sites such as scientific periodicals, institution building or the academic department meeting. In the sequences of cross-referenced editorials, policy or advocacy documents and new funding interventions, one can trace the deliberation of biomedical researchers concerning what kind of experimental practices and organizational routines will act as future best practices, against which the worth of community members’ activities and claims are appraised. TR has appeared and proliferated in this space of highly distributed policy-making, and need to be understood in this context.

Especially, the pages that follow will make extensive use of the analytical unit of **policy narratives** and its components of **problematisation** and **models of collective action** for understanding the emergence of TR as a major priority in contemporary biomedical policy (see subsection 2.1.2). These tools will also allow to track the impacts of TR as a repertoire which provides legitimacy to a range of new experimental and institutional practices. Furthermore, the conceptualisation of TR as a broad **reform movement** (subsection 2.2.3) formed of interdependent but distinct and sometimes competing

discourse coalitions (subsection 2.1.2) will provide greater understanding into current struggles for legitimacy and resources that structure biomedical innovation systems. Finally, I will make use of a baseline typology of governance processes in biomedical innovation to highlight how the associated socio-technical systems are changing in the wake of this reform movement, along the following dimensions (see the introduction to section 2.2, and subsection 2.2.1):

1) the dominant experimental approaches and the type of knowledge that counts as legitimate and authoritative within the system;
2) the dominant organisational and institutional forms for the socio-technical networks producing knowledge and innovation, including the professional groups that are awarded leading or brokering responsibilities;
3) the privileged means of coordinating autonomous actor and ensure the collective production of clinical and/or commercial utility, within the system.

Finally, my analytical toolbox will also carry over some of the findings of previous work on TR presented in chapter 1. I will try to frame the relations between biology and medicine that are a central concern of translational research within broader alignments of these two domains of practice since World War II, following the advice of Keating and Cambrosio (2003). Especially, I will draw on the notion of "alignment" to foster "understanding the interactions between fundamental and clinical research in terms of other than subordination or application" (Keating and Cambrosio 2004, p. 368). My use of the notion of "reform movement" also stems from a concerned shared with previous studies to account for those situations where local tensions and struggles for authority may be co-extensive to broader re-alignments between domains of expertise (Martin, Brown and Kraft 2008; Morgan et al 2011; Wainwright et al 2009). A heightened attention to practices of audit and accountability will also be retained from Leonelli and Sunder Rajan (2013).

2.3 Methods

The following lines detail how the analytical approach presented above has been carried into the data collection and analysis components of my research strategy.

2.3.1 Spatial contexts

Insofar as its major proposals for organising biomedical innovation have been made in the peer-reviewed literature, TR can be said to have achieved an international scope. Discussions about the issues of clinician-scientists now use cross-countries comparisons, for example (Shahzad et al 2011; von Roth et al 2011). I have thus deployed a broad scope when trying to capture the genealogy of policy narratives of TR.

Nonetheless, implementations of the proposals found in the literature necessarily take place within national systems of innovation and traditions of policy-making, and thus a certain degree of institutional path dependency. Collection of empirical material regarding socio-technical change supported by TR policy narratives has therefore been restricted to two specific national contexts, with one instance of a pan-EU network with strong ties to German institutions. The USA was selected because of the historical importance of its research elites and policy-makers in spearheading the emergence of TR as a central theme of biomedical policy internationally. Germany offers a potential empirical counterpoint to the US example. German academic institutions are often more isolated from contexts of application then in the USA.

2.3.2 Data collection

An analysis of initiatives and policies dealing with TR in Germany and the USA was conducted between September 2010 and April 2012. Data collection focused firstly on documents such as governmental white papers or guidelines of research funding institutions– documents that count as central argumentative practices in constituting and maintaining policy narratives. Additionally, more than 100 editorials, reviews and commentaries about TR were analysed.

Secondly, a number of semi-structured interviews were conducted with participants and leaders in TR projects, initiatives or policies. Interviews were consequently conducted with policy-makers, investigators (from a variety of disciplinary backgrounds) and coordinators or managers of TR projects. The approach used to construct this sample was to build a panel of informants made of actors in the biomedical field that could acted as witnessed to the emergence of the concept, members of the “loose collective” that is the TR movement (Weiss 1995, p. 18 and 19). The respondents chosen for the interviews were included because they possessed insider’s knowledge, experience and interpretations of their field, which could not be accessed through documents or other codified means (Weiss 1995). Selection of informants was based, in a first time, on publications of their views in specialised periodicals. This was complemented with snowball sampling. Addition to the panel of informants was stopped once data saturation had been reached. The selection was also made with a view to provide contrasts in the background and potential views of respondents: defenders of a TR movement were mainly interviewed, but also commentators with a more sceptical stance.

Exploratory telephone interviews were conducted in the summer of 2009 with a number of US-based prominent advocates of TR (11 interviews). The aim here was to test questions, clarify the frame of the dissertation, generate and falsify early hypotheses (Weiss 1995). Despite commonly voiced reserves against the purported lower quality of

telephone interviews, I have obtained some of my richest empirical material from these interviews, and have found that “evidence-rich” and “evidence-poor” interviews were equally distributed among telephone and face-to-face interviews. The second round of interviews (34 further interviews) were mostly conducted face-to-face, but some respondents insisted that interviews be conducted over the telephone rather than in person (4 out of these 34 interviews from the second round). In these cases, I have acceded to their demands. 19 respondents were affiliated with US institutions, 17 with German institutions and 9 were located in further EU countries or within EU-level agencies.

The interview guides used at various stages of our study are provided in Annex B. Informed consent was sought and obtained from all respondents, along the guidelines of the Social Sciences and Humanities Research Council of Canada.

2.3.3 Analysis

I can distinguish two analytical moments in the broader process of engaging with the empirical material collected and working to make sense of the material in light of argumentative policy analysis and STS approaches.

A first moment aimed to order the empirical material and identify analytical categories around recurring themes in the material. In this session of analysis, I could allow my three policy narratives to emerge from the data. This reflection work was concretely supported through desk research and an extensive literature review of policy documents and articles in the biomedical periodicals on TR, as well as using material from the preliminary interviews.

In a second moment, the complete empirical material was analysed or re-analysed using crosscutting coding categories derived from my identification of the three policy narratives. Coding here was aided by the social science analysis software ATLAS.ti. The analytical grid that underpinned these efforts included some of the following analytical dimensions (Fischer 2003):

- Contextualising social acts (including arguments made in oral or textual forms);
- Making explicit the meaning and intentions co-extensive to these actions;
- Identifying the communities involved in these acts;
- Delineating the narratives being constructed and delivered, and their relation to broader discourses;
- Identifying points of contention between various communities and narratives;

Coding and analysis also aimed to capture the historical development of a discussion on TR in biomedical policy networks, organisational shaping and coordination issues in

TR projects, or practices of boundary-making (Lamont 2009) in defining what constitutes ‘good’ and ‘bad’ TR. Utterances in interviews could thus be directed at a rival from a different discipline, or a collaborator with which there is a difference in views, offering ‘real-time’ instances of argumentative practice. This position is also congruent with certain hermeneutic strategies which see actors as giving meaning to their practices within a frame of life-long discussion and argument with friends, family, rivals or colleagues (Taylor 1989).

Because interview respondents could offer only limited insight into the historical development of TR concepts, even as many had played notable roles in these developments, triangulation of interview material with documentary evidence was also sought as often as possible.

3 TR as it happens in clinic and laboratory

Before going into the crux of my argument about the origins and current grasp of policy narratives of TR, it will be useful to examine actual projects fashioned by their leaders as examples of TR. This should allow the reader to better relate the discussions and arguments that come later to the experimental and institutional practices they problematise. This section also provides the occasion to examine such projects one at the time, as they unfold in time. Later sections will forego this full diachronic perspective for the sake of analytical clarity.

In keeping with my engagements to the respondents and the ethical guidelines of the funders of this research, I have narrated the two cases in a manner that protects as much as possible the anonymity of those involved.

3.1 A natural compound against cancer

Natural compound A is a naturally-occurring compound that, at the time of writing these lines, is hoped to offer an improved treatment over existing therapeutic modalities for certain forms of cancer. *Natural compound A* is expected to enter clinical testing in the coming months, and a small team of investigators and contract research organisations are currently hard at work to obtain the evidence that would allow it to move towards clinical development.

The *natural compound A* project is the work of a clinician-scientist working at the Hannover Medical School. In 2001, respondent DE TRAIN 5, together with his post-doc and colleagues from a number of other institutions publish in *Nature* an article presenting results from mouse knock-in models that show how a *protein B* inhibits cell division. When levels of the protein are low, abnormally high cell division can occur, indicating a potential role of the protein in (controlling) cancer cell proliferation. Interestingly, experimenting on the mouse models around the *protein B* leads to the discovery of a molecular pathway that regulates the expression of the protein, suggesting a potential therapeutic modality.

In the wake of this article, respondent DE TRAIN 5 starts to feel that he may want to make these basic (patho)physiology results relevant for his own clinical work. He cares for cancer patients on a daily basis, but his laboratory research had been relatively distant from these concerns up to that point. Around 2005 he contacts the head of the natural compounds library and its chemical biology unit at the Helmholtz Institute for Infection Research (HZI) in Braunschweig, Germany - respondent DE TRAIN 2. The German National Genome Consortium had made used of the natural compounds library, and respondent DE TRAIN 2 believed that respondent DE TRAIN 5 approached

him after having heard of the initiative through the consortium. Plans for a collaboration coalesced around the hope that a compound from the HZI's library would have an effect on the regulatory pathway for *protein B* prompting an increase in its production and helping to stabilize or perhaps even reverse cancer cell proliferation. Respondent DE TRAIN 2 and his team assayed natural compounds from their library against the protein isolated by respondent DE TRAIN 5. This lead to a few "hits" in the jargon of the field, that is, compounds that could be considered candidates of medicinal agents by acting on the *protein B* pathway. The most interesting of these hits was obtained with *natural compound A*. The compound showed a moderate reaction, but most importantly, was associated with only mild known side effects in humans. Comparatively, the pharmacological literature indicated that other compounds with a stronger reaction also had stronger side effects. Further testing was made with *natural compound A*, using animal models and cancer cell cultures, also showing promising results. With Hannover and Braunschweig located at about 70 kilometres apart from one another within the German state of Lower Saxony, a regional collaboration was thus being put into place through the work on *natural compound A* and *protein B*.

Respondents DE TRAIN 5 and DE TRAIN 2 then approached another chemist, this one located at the department of chemistry of the Leibniz University in Hannover (LUH). This chemist had particular expertise in assembling synthetic variations of known compounds, finding new molecular configuration of these agents that achieved specific physiological effects in animal models and eventually in humans. This chemist was interested by the possibility to extend his expertise to natural compounds and the possibility to engage in the development work for an actual therapeutic agent, "almost like a pharmaceutical company" (respondent DE TRAIN 2). His role thus become to try and derive variations of *natural compound A* that might either offer more efficacy for a comparable toxicity on the human body, or less toxicity. Other collaborators from a structural biology department at the European Molecular Biology Laboratory in Heidelberg also participated in these efforts to develop derivatives.

At that points, patents were filled both for the use of *natural compound A* in the treatment of cancer and for the chemistry methods used to synthesize derivatives. New derivatives were still produced after the patents were filled, and the research teams in the collaboration tested those gradually through their cell assays.

In 2008, together with his collaborators, respondent DE TRAIN 5 brought together all of these results in paper for the journal *Cancer Cell*. The paper presents and analyses the results from one chemical assay experiment, five animal model experiments and 17 cell culture experiments to support its hypothesis of a therapeutic effect of *natural compound A* and related compounds through action on the *protein B* translation pathway.

The publication of the *Cancer Cell* article and the filling of patents were first steps towards the entry of the project into product development. The step was fully taken when the three main investigators met with German regulatory authorities from the BfArM agency (Federal Institute for Drugs and Medical Devices). In this meeting, BfArM could access the data that had been produced so far to provide a preliminary list of regulation-compliant experiments that might eventually allow a *natural compound A* agent to enter the market as a certified anti-cancer drug.

Conducting experiments on an experimental agent with the view of obtaining regulatory market approval requires a number of repetitive and costly operations. The compounds used in these tests would need to be manufactured in specialized facilities that respect Good Manufacturing Practice (GMP) guidelines, as they are outlined in European directives. GMP guidelines ensure that every dose of drug produced is chemically stable and that its composition is in accordance with pre-determined parameters. Testing on cell cultures and animal models, which will provide the evidence concerning the efficacy and safety of *natural compound A* that is necessary to move to human studies, will need to be following Good Laboratory Practice (GLP) guidelines. These guidelines outline methods to standardize experimental manipulations, ensuring that results produced by these assays are statistically robust and replicable.

The experimental equipment necessary to these manipulations is not often found in the possession of academic research groups, and is too costly to justify acquisition for a single development project. As such, respondent DE TRAIN 5 decided that these experiments should best be conducted by contract research organisations (CRO). CROs have most often been understood to be outsourcing firms that assist large pharmaceutical companies in the conduct of clinical research. As recent ethnographies have shown, however, CROs can provide services for all types of biomedical experiments, both to academic as well as industry customers (Fisher 2009). Funding for having these experiments performed by CROs is also problematic, however. The regulatory experiments now needed to proceed with the development of natural compound anti-cancer agent could not be financed through the typical principal investigator grants that support much of the science base around the world. These regulatory experiments cannot be used to formulate ingenious hypotheses and write high-impact articles that many scientists aim to produce, thus eliminating any possibility of getting support from the German Science Foundation (DFG) for example. Rather, DE TRAIN 5 has to look for funding through programmes that are earmarked for supporting technology transfer or biotechnology development.

Respondent DE TRAIN 5 managed to obtain one million euro from the BioProfile programme of the German Federal Ministry of Education and Research (BMBF) to do this

regulatory, pre-clinical testing of a derivative of *natural compound A*. This led to a contract with a first CRO, but this arrangement is discontinued prematurely when the associates became unsatisfied by the quality of the manipulations performed by the company.

Help after this setback came when respondent DE TRAIN 5 met the CEO of a local clinical research unit. This professor at the MHH also had experience in the formation of new biotechnology and in the organisation of clinical trials, as well as with regulatory matters. He and the clinical research unit now offered consultancy services investigators like respondent DE TRAIN 5 who were interested in the development of new biomedical products. So the group of now four associates set out to find another CRO. This was constrained by the fact that BMBF wants the money from its grants to be invested in Germany, and it became clear that some CROs would themselves subcontract research elsewhere.

A second try with another CRO again lead to setbacks, when this company used the knowledge they gained on the *natural compound A* class of compounds to elaborate new chemical tests and to fill patents for related agents. Such a situation would have reduced the breath of the monopoly afforded by the project team's own patents and thus could not be tolerated.

A renewal of the BioProfile grant allowed to follow up on first results with further testing of toxicology, pharmacokinetics, and excretion. A third CRO was given the contract to conduct these experiments. The exact requirements were set out through a second meeting with the BfArM. CRO #2 was set to provide first results of dose-rate testing in March 2012. Meanwhile, the LUB team started working on synthesizing smaller components of the compound (there are three) while CRO #3 synthesizes the whole molecules in their GMP facilities, and CRO #2 does the toxicology.

The second meeting with BfArM representatives also raised the possibility that a second round of animal model experiments be required, this time with dogs. There were only few instances of side effects in mouse models in the first series of experiments. This is not a comforting result, as one might expect, but rather raises doubts as to whether the model organism chosen was appropriate to establish the toxicological profile of this specific drug. If the second animal model results are good, then it will be time to move to first-in-humans trials. Exceptionally (for a cancer drug), this would start with healthy subjects, again because toxicological data had been puzzling up to that point.

Before this happens, however, the project will new more money, as current grants cover expenses that run only until the end of the toxicology experiments in mouse. To muster this new money, the associates are thinking about a new BMBF programme

called Spinnovator. This would involve the creation of specialized biotechnology start-up firm to carry the project. Respondent DE TRAIN 5 shared in discussion that he had been thinking doing exactly this at any rate, at least as a mean to “store” the knowledge and experiences he and other members of the team had meanwhile acquired in product development. This would also allow to explore new streams of funding, notably those made available by venture capital firms.

3.2 Oncogene/tumour suppressor gene research at a SPORE

In the course of my fieldwork in the USA, I also interviewed an investigator at one of the country’s Specialized Programs of Research Excellence (SPORE) centres, which have played an important historical role in spearheading efforts to establish something close to an institutional specialization in TR. This person provided a perfectly coherent narrative of his own research journeys and experiences with translational research. This subsection will be based mostly around his narrative, not so much as a convenient way to make use of this empirical material, but because the internal coherence of this story allows us to better point out what will later be important aspects of the TR enterprise, and, indeed, their entanglements.

> A: [S]everal of the things that we are working on actually were, in the laboratory, were based on specific patients, things that we saw in the clinic and then we took that patient’s tumour, studied it in the lab and then found different things. And then several of the projects in the SPORE and then took those findings from the lab and then brought them back into clinical trials in the patients. So that is exactly what the program is designed to do (US investigator 7).

This first fragment of US investigator 7’s story provides insight into an important contention of many TR advocates. This contention, is that clinical innovation will be spurred if the experiences and expertise acquire in clinical care of patients are ‘brought back’ to laboratory investigations. Some employ the expression of “bedside to bench and back” to designate this hypothesis (von Roth et al 2011). While this appears like a sensible proposition, the authors contending this in the primary literature on TR are not very explicit about the precise intellectual, experimental, institutional or material practices and processes which are solicited in such exchanges. This part of US investigator 7’s story provides a first indication. Regular contact with patients simply provides a thick stream of empirical evidence and observations that can be used to formulate new hypotheses. Most interestingly, predictions made from laboratory experimentation (most likely on animal models, cultivated populations of human cells, or collections of human tissue bio-specimen) can be tested against the lived experience of patients. Interesting empirical cases may open the way to new or modified hypotheses regarding specific pathological or physiological mechanisms of the human body.

> „[O]ne of the projects involves a gene called [*Gene A*]. So this all was based on a patient in the clinic, where we had, we had a patient in the clinic who had a tumour in their chest. And we thought at first that it was a type of cancer called a lymphoma. And in lymphoma you normally do chromosome analysis. Because there are certain chromosome abnormalities that you treat differently in lymphomas. But in lung cancer, you generally don't do it. So they initially thought that this person had a lymphoma, so they did a chromosome analysis. But it turned out this person had lung cancer. But then they looked at the chromosome analysis and then they found that this person had, what we call a translocation where one piece of a chromosome was stuck on another. And the rest of the chromosome was pretty normal. So that was quite unusual, and this was a patient who had no smoking history either. So that's a little unusual among lung cancer too. So I thought, well this chromosome translocation may, in other diseases, chromosome translocation often identify important genes. Because what happens is, a gene from one chromosome gets tacked on to an expression system from another chromosome, so it get turned on when it's not supposed to be turned on because of the cancer. So what I did is I took the cells from this patient, grew them up in the laboratory and then you could still see this chromosome translocation. I had one of the clinical fellows in my lab, I told her 'why don't you just figure out what genes are at this translocation breakpoint', which she did. It turned out that it's the gene called [*Gene A*]. And [*Gene A*] was massively over expressed in this type of cancer. In this patient's cancer, and that had never been reported before. And [*Gene A*] is a very, is a gene that is very important in development, who has been found in drosophila as regulating the differentiation of cells from primitive cells to adult cells. So it made some sense that cancer cells that might active the pathway would block the differentiation to keep them more primitive than rather in a differentiated state. So then we looked and saw that many lung cancers over express this gene, and we developed antibodies that targeted this gene, and we developed drugs that targeted this, and we showed that if you block this, the cancer shrinks. And so we initiated a clinical trial, looking at drugs that block the target that we discovered in the patient, and characterized in the laboratory. And we did developed new antibodies and new drugs in the lab that are now moving, some of them are in patients, some of them are being developed for patients".

This fragment provides further clarification of the type of intellectual and experimental operations that lead to the formulation of a specific therapeutic hypothesis. The investigations were kick-started by treatment of a 34-year old woman with no history of cancer in her family and no smoking history. The tumour was subjected to a number of tests. Classical genetic mapping techniques were used, and through further tinkering and trial and error, the team could eliminate a number of potential hypotheses that may help characterise the specific make-up of both the cancer patient and her tumour. They eventually contended that a chromosome translocation and the expression of *Gene A* could explain the apparition of cancer in this specific patient.

Combined use of known anti-cancer biologics and drugs notably allowed US investigator 7 and his team to use these agents as experimental tools to learn about the properties of the non-small lung cancer tumours they studied. They used the agents to modulate the expression of *Gene A*, finding that its tumour growth inhibition effects were linked to the expression of a specific protein. Much as in the case of *natural compound A,* here again this opened the way towards the development of a therapeutic modality, but also further investigations into the pathology of cancer.

> But now it's come back to the laboratory because this gene was found to be important in cancer stem cells. Have you ever heard that hypothesis? There is a hypothesis that all of the cells in a cancer are not equivalent, but some of them are not [carcinogenic], they don't [belong to] the subpopulation in here that are the cancer stem cells that really cause the metastases and the [growth] of the cancer. Well it turns out that if you separate out those cells from the cancer you have what for a gene that is most highly expressed, *Gene A*. Exactly the one that we've already been studying. And if you block *Gene A*, it selectively affects those stem cells. So we made the loop back into patients and all, but now we're finding that in those tumours, in the laboratory, it targets this specific subset of cells. Now then we have, we say 'well, maybe it would be useful in a different type of clinical trials designed to look at inhibiting specifically cancer stem cells'. So now we've got a combination of two different drugs, one that targets the non stem cells and one that targets the stem cells, to see if they have an improved effect. This whole pathway goes round and round in the clinic to the lab to the clinic to lab. And so I think that is a good example of this translational research. And we have other examples of patients that responded unusually well to drugs, we get their tumour back in the lab and you sequence the genes, you find out why this patient's tumour responded real well. Then you can design clinical trials selecting patients for their genes or their protein markers. We even have one test that is commercialised, that we developed in this SPORE. It is a protein analysis that predicts benefit from a particular drug, and this has now been taken over by a company and being sold on the market. So this is I think another example of a success of the program. That's the kind of things that we are doing.

This story-line resonates with a number of themes that are central to policy narratives on TR. This is especially interesting considering how little I had intervened at that point of the interview. Most important is perhaps the image of the bridge and bi-directional exchanges between clinical and laboratory contexts. This example also highlights some of the uses that are being made of experimental platforms based on technologies that allow the rapid sequencing of human genetic material, also called genomics. Associated approaches focus for example on the protein coded for and expressed by human genetic information, which can also be sequenced using related technologies for research purposes, and are called proteomics. Sequencing technology finds a number of applications at other levels of human biological and pathological processes, and we

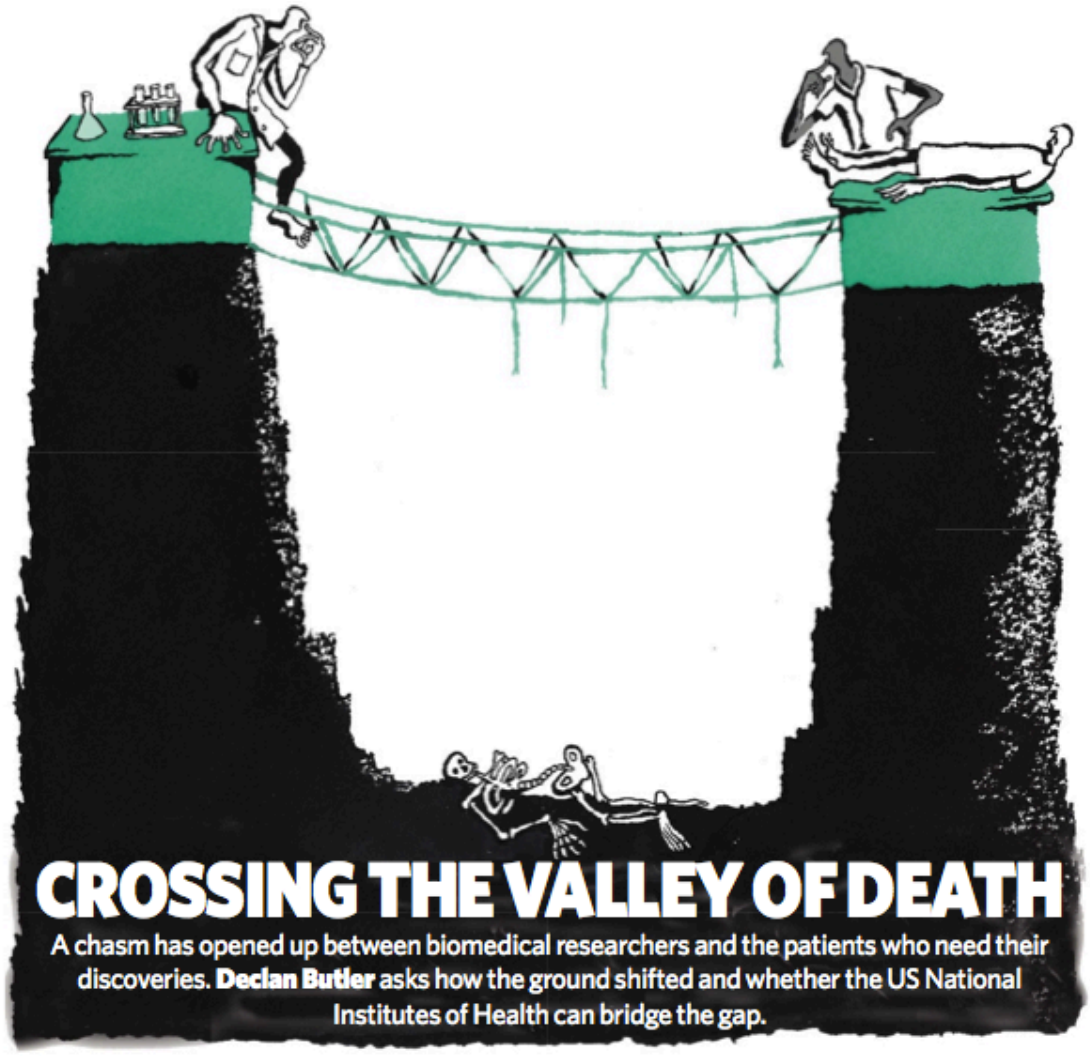
might take up here the commonly used concept of “omics” in reference to these approaches.

In it also interesting here that a policy-maker-lead funding programme for translational research such as the SPORE programme would require a 5 years horizon for human relevance. A predictable reaction to such a proposal might have been scepticism. Indeed, one might think that a research team dedicated to clinical development of new heath interventions may “run out of ideas” without having access to its own basic research findings. According to this specific representation of biomedical innovation, the actors responsible for developing new health interventions would be senior investigators drawing on a broad experience and knowledge pool concerning a very narrow area of research. In these cases (because the representation is actually based on the lived experiences of some investigators), a translational project is a once in a lifetime opportunity. US Investigator 7’s experience is a direct counter-example of this. Here, we see the deployment of an almost curiosity-driven, yet clinically-grounded experimental research system. It draws on basic science (as well illustrated by the impulse that the cancer stem cell hypothesis provided), but it is not science for science’s sake only.

3.3 Some lessons

The close examination of projects conducted above aimed to provide the reader with a sense of the mundane experimental and institutional practices of biomedical researchers engaged in projects that have been labelled as instances of TR. These projects also allowed to introduce a number of epistemic, material and institutional entities that will make regular appearances in the pages that follow. Based on these cases, it is also possible to already make a number of analytical points that it will be useful to keep in mind as this text explores the genealogy of TR agendas and their practical deployment in recent biomedical initiatives.

Figure 1: Crossing the Valley of Death



Source: Butler 2008, p. 840; used with permission from the Nature Publishing Group.

First, I would like to try and explain the relevance of the two local cases above for understanding the issues at play around TR by bringing in a figure used in a *Nature* inquiry about the phenomenon of TR in recent biomedical policy. In this journalistic piece, the author, just like I do, contends that TR is being pushed as a solution to a number of crises. The most ominous crisis concerns an apparently increasing disconnect between laboratory discovery work and the clinical contexts where fundamental could potentially be marshalled to help patients. The author put it this way:

> Over the past 30 or so years, the ecosystems of basic and clinical research have diverged. The pharmaceutical industry, which for many years was expected to carry discoveries across the divide, is now hard pushed to do so. The abyss left behind is sometimes labelled the 'valley of death' — and nei-

> ther basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there (Butler 2008, p. 840).

The cases examined above were both about research teams that had dared to venture in the valley of death. In the *natural compound A* case, the prime mover for the TR project had been active on both the discovery laboratory and clinical medicine worlds, but decide to attempt and bring them together by developing a new therapeutic based on his fundamental research and bringing it towards clinical development. In the SPORE case, the principal investigator actually seemed to make his home in the valley of death, making use of laboratory and clinical infrastructures and knowledge as opportunity dictated to solve problems that gradually emerge in both fundamental research and clinical practice. These two cases are respectively exemplars of the oft touted "bench to bedside" and "bedside to bench and back" metaphors, which aim to provide shared representations of the innovation process that can allow greater collective coordination and the elaboration of common research programmes and policies. Yet, the difference in routines and organizational structure that characterize each example are sufficient to associate them with distinct models for conducting clinical innovation.

This multiplicity of innovation models labelled as instances of TR indexes the degree of dispersion of TR concepts, which have moved from specific socio-technical contexts in oncology (see Keating and Cambrosio 2012 - indeed exemplified by the research done in SPOREs) to denote broad claims and grievances about the clinical innovation process. As I have already mentioned in chapter 1 and 2, the difference between these models can be traced back to the cultural availability in biomedicine of different and competing policy narratives about TR. The next chapters will detail how these different narratives construct dominant collective understandings of important issues to be addressed by TR projects and initiatives, and which interventions are to be privileged in targeting them.

As the *natural compound A* project especially made clear, clinical innovation processes and specific TR projects take place in contexts of increasing interdisciplinary and interorganisational collaboration, where the vagaries of funding and regulatory agencies are as likely to shape the next experiment as scientific imperatives are. The restructuration and diversification of the pharmaceutical and health industries since the 1980s also plays a part there, with the protein's story becoming entangled and for a moment derailed by the pretensions of an overseas CRO.

Finally, these two cases have allowed the introduction of a number of concepts and entities that will be recurring presences as we follow the fortunes of narratives of TR across a variety of locales. It will be useful to define a pair of these now.

Both the SPORE and *natural compound A* projects examined above constitute engagements in a practice I call **clinical innovation**. Clinical innovation consists in the production of new or improved health interventions for human patients. Within the current text, I will focus on practices of clinical innovation that marshal experimental knowledge, often biological or pathological obtained in the laboratory, to achieve their aims. Nonetheless, clinical innovation might just as well be achieved through organizational improvements in the management of disease, for example.

I consider **biomedical innovation** to be a broader category than clinical innovation. Its outcomes are necessarily the achievement of experimental research. It includes those clinical innovations achieved with the concourse of experimental approaches, but it might also include technological advances in bioinformatics for example that do not have a direct clinical application. Many authors have contended, notably, that biotechnological methods that emerged in the mid 70s onwards yielded mostly process innovations that could be used to improve productivity of research and production in both academia and industry. An example of this are the technological advancements that have allowed faster sequencing of hereditary material. They have had immediate research applications in the life sciences, and thus constitute a form of innovation. Yet, clinical application is only realized if technological advance is coupled with further advances in (patho)physiological knowledge, as well as product development. Within the current work, then, clinical innovation will be used mainly as a subset of biomedical innovation.

4 Translational research as policy narrative

Chapter 3 provided a snapshot into the life of specific research and/or development projects I encountered and that were explicitly labelled and advertised as instances of TR. The presentation of these projects hopefully allowed the reader to obtain some sense for the kind of experimental and institutional practices that are deployed laboratories and clinics to realise the agendas of TR. Yet, at this point, it is necessary to go back and to better define what are exactly the agendas of TR. Indeed, as the following lines will show, while it is possible to understand TR as a distinct area of investigations made possible by specific advances in post-genomic experimental platforms, I contend that the crucial dimension about TR is its proliferation as a notion for organising policy discourse and collective priorities in biomedicine. This section will thus focus on the way experiences and practices from the laboratory and the clinic have been problematised and re-framed by their circulation in sites such as specialized periodicals or expert committees with a policy-making remit.

Here, I will present findings from an analysis that has allowed me to delineate the contours of three dominant, mutually reinforcing but historically sequenced policy narratives of TR. For each, I highlight problems and the collective models of reform that have been put forward as privileged solutions in each story-line. In doing this work, I will show that proposed means to align discovery laboratories and clinics have evolved substantially over the last 30 years. Leonelli and Sunder Rajan (2013) contend that conceptual grasp on TR is best obtained without trying to sift through within the multitudes of meanings and practices that are entangled with the labels of TR. In contrast, my own analysis is underpinned by the possibility to identify some order in this discursive proliferation and dispersion, that there are dominant discursive repertoires and meanings of TR that shape the use of the concepts and the framing of biomedical innovation practice.

Subsections 4.1, 4.2 and 4.3 each traces the assemblage of one of these three policy narratives. These policy narratives each revolve around one of the ‘crises’ in biomedical innovation I have identified in section 1.2. To accomplish this, I will marshal evidence from the documentary record of specialized periodical articles and commentaries as well as policy documents. This will allow to trace the historical evolution of problematisations and proposals for reform associated with TR. But first, the following pages provide a basic empirical portrait of the trajectory of notions of TR in contemporary biomedical discourse.

The dispersion of TR concepts and practices

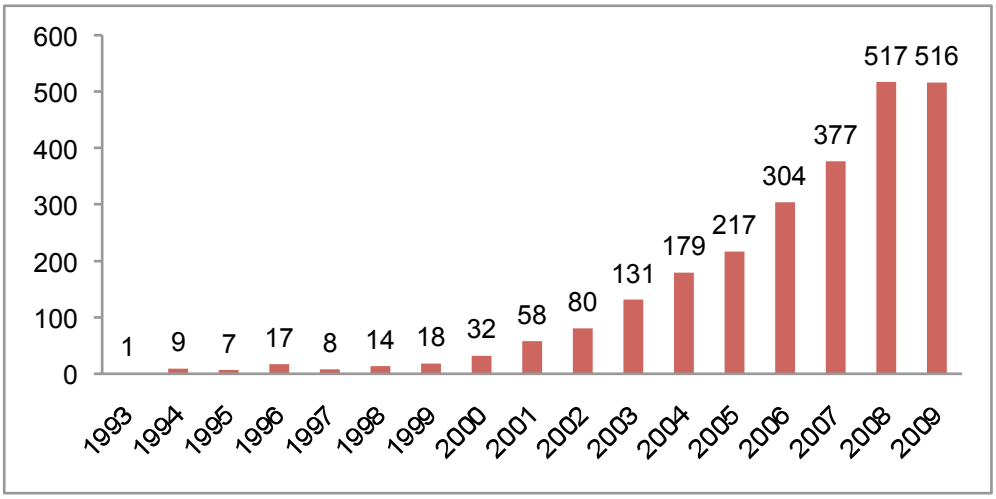
A characteristic of TR notions that has provoked some of the strongest reactions from commentators in both the biomedical and social sciences has been their broad dispersion and their seemingly endless flexibility (Drolet and Lorenzi 2011; Woolf 2008; van der Laan and Boenink 2013). The concepts of TR have a clear origin in the field of oncology to denote a specific area of experimental practice that emerged with large-scale analysis of tumour tissue and new clinical trial designs necessitated by the development of targeted therapies (see section 3 and 4.2; also Keating and Cambrosio 2012). Yet, the transformative potential and centrality of TR notions in current biomedicine seem determined specifically by their success and usage across a broad cross-section of disciplines, institutions and contexts. The proliferation of TR concepts has thus brought them to be used to describe experimental or development projects in diverse areas such as behavior analysis and experimental pathopsychology (Lerman 2003), dentistry (Chiappeli and Prolo 2003; Forysth and Zvolensky 2001), or to community-based participatory health research (Hebert et al. 2009). Other TR advocates even defend the idea that the social sciences can contribute to the reform of biomedical innovation:

> "Translational medicine is the 21st Century progression of evidence-based medicine, bringing with it an emphasis on an evidentiary process for decision-making in healthcare practices based on translational research. In a philosophical sea change, TM brought with it an appreciation of the need to integrate research inputs from the basic sciences, social sciences and political sciences to optimize patient and preventive care measures". (Milne 2009, p.544).

Even within the concise space offered by the quote above, the reader can obtain a sense of the wide-ranging ambitions that advocates of the TR approach have built in recent years. Here, the author links the discussion about TR to the evidence-based medicine movement, a major source of change in the practice of clinical medicine in recent years (Timmermans and Berg 2003). Not afraid to set up expectations, the author also characterises TR as a "philosophical sea change" for biomedicine.

The ambition and enthusiasm of individual advocates of the TR agenda seems to have been impressive to their peers, because in the year 2000s, about 10 years after the concept first emerged, proposals on how to organise a reform of biomedical innovation bearing the label of TR became especially abundant. Figure 2 below shows the emergence of TR concepts in peer-reviewed biomedical publications in the last decade and a half, providing an indication of the intensity of use and discussion of TR concepts.

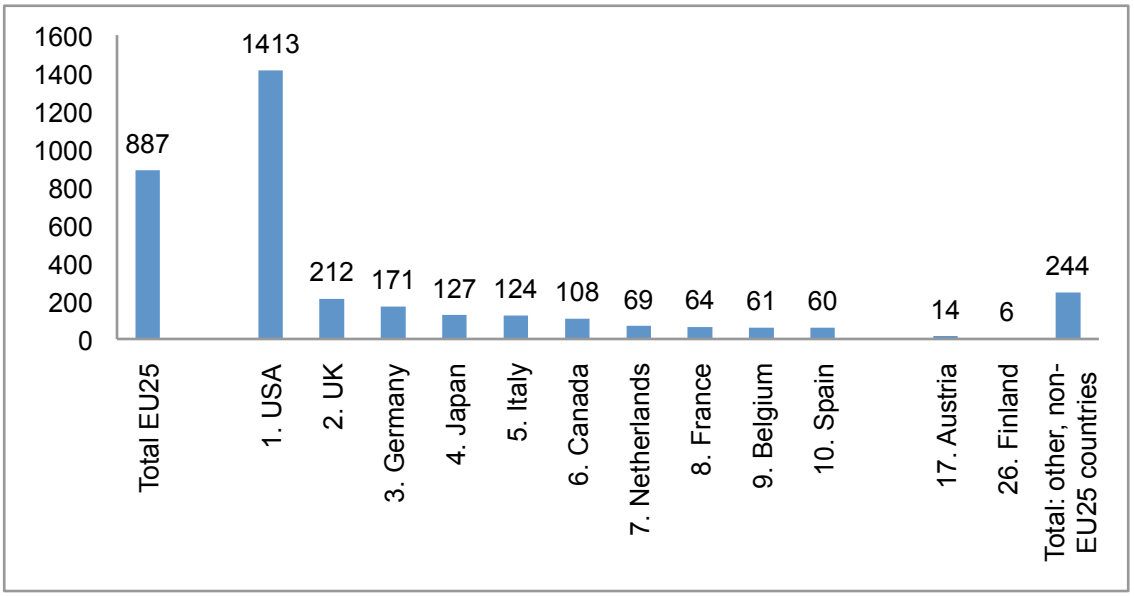
Figure 2: Annual counts of articles in peer-reviewed journals with the terms 'translational research' or 'translational medicine' in their title, keywords or abstract, 1993-2009.



The figure shows the exponential growth in usage of the concepts of TR since 1993, with a clear acceleration of this trend starting in 2000. What is perhaps most important to retain from this material is that the amplitude of current TR discussions indexes the stakes of defining TR for biomedical actors. True enough, many biomedical researchers have stepped up to denounce the fad and phraseology of surrounding TR. More uncompromising commentators have also critiqued TR as a political manoeuvre to establish protected jurisdictions for restricted groups of experts within the biomedical landscape. These authors advocate a return to a more 'authentic' vision of the researcher as driven by curiosity and creativity, and collective acceptation to what they perceive as the fact that biomedical innovation would mostly 'spill-out' from these efforts (Levine 2007; Weissmann 2005). Nonetheless, these diatribes are usually preludes to the presentation of another model for fostering biomedical innovation (Wehling 2008; Mullane and Williams 2012). Even when humility and level-headedness and a return to scientific basics is advocated, the political is not completely evacuated from the science, as even these calls put forward specific models of collective work.

Despite the current import of TR notions in a variety of institutional and national contexts, it is also important to take note of the initial elaboration of the concepts within specific oncology research networks situated for the most part in the USA. Indeed, even today, as Figure 3 shows, the majority of publications that make use of the expressions "translational research" and "translational medicine" were authored or co-authored with at least one researcher with an affiliation in the USA.

Figure 3: Distribution of 2,779 country occurrences in the affiliations for authors of 2,312 articles on 'translational research' or 'translational medicine' published between 1993- 2009



This bibliometric data above indicates the need to understand the American context for the usage of TR concepts to make sense of international developments in the practice of TR. The SPORE programme by the National Cancer Institute (NCI), established in 1992, was the first funding initiative explicitly making use of the expression "translational research" (see section 4.2; 5.1; 5.2; Osborne and Chamness 1994). This programme aimed at supporting translation by providing infrastructure funding to cancer research centres meeting certain requirements, such as proximity between laboratory units and clinical research units, training components, and encouraging consortium-like networks. In fact, the first few articles published on TR in 1993 and 1994 often referred to the work done at SPORE centres. Over the years, however, the terms became much more commonly used, firstly in the USA, and then only in the variegated contexts mentioned above. As examples commented later in section 5.1 will show, at least part of the problematisations that were first made in the US context seem to have been carried over intact into these various arenas.

4.1 The plights of clinician-scientists and patient-oriented research

Medical doctors (also referred to as clinicians or physicians) affiliated with academic health centres, medical schools and/or university clinics in either the USA or Germany, notably, have traditionally been asked to fulfil three roles: teaching medical trainees, the direct provision of clinical care to patients, and conducting research. With the expansion of both biomedical research and clinical care systems, however, commentators have argued that many academic medical doctors have been increasingly focusing solely on teaching and clinical services. A subset of academic physicians who have been particularly successful at combining clinical care and research activities have thus come to define themselves as a particular class of "clinician-scientists" since the mid 1970s. This section examines how clinician-scientists have problematised local issues with their own work conditions and actively cast them into the broader problem of making the translational research enterprise a success. In doing so, they have succeeded in articulating and stabilizing a policy narrative about 'the plight of clinician-scientists', to borrow a phrase I found in an article about the issue (Gershon 1999), and the promises that a return to what they call "patient-oriented research" (Swazey and Fox 2004) might hold for the future of clinical innovation.

This section follows influential early articulations of the policy narrative about a plight of clinician-scientists. The arguments extracted from this literature and presented here were authored by clinician-scientists themselves and should thus be considered as primary material detailing the substantial content and material deployment of their argumentative practices. The mundane issues they discussed can be expected to form the basis for the problematisation, learning and evaluation processes that are constitutive of policy change. In doing so, I aim to realise calls to investigate policy-making ethnographically, as it unfolds in interactions between local and national scales of governance (Jenkins 2007).

A brief note needs to be made before going forward. It is important to mention here how clinical research in the 1980s until into the 1990s was defined not strictly as the conduct of clinical trials, but also included experiments with human tissues or even animal models that are currently associated with TR, or more classically, experimental medicine (see for example the definitions provided by Ahrens 1992). Our current understanding of what the area of clinical research covers seems to have shifted away from experimental medicine to encompass only those areas linked to the conduct of clinical trials. Yet, current advocacy for greater integration between "bedside and bench" seems to owe much to these early ideas of an area of research known as "pa-

tient-oriented research" with a close interdependency between early clinical research and laboratory investigations based on clinical observations.

4.1.1 USA: Early problematisations

Since the late 1970s, observations and arguments have accrued showing how US-based clinician-scientists have gone from acting as major players in biomedical innovation to being increasingly confined to either clinical care or research. James Wyngaarden, at the time the director of the National Institutes of Health (NIH) and himself a clinician-scientist, published in 1979 an article that qualified the condition of the professional group as that of an 'endangered species'. Wyngaarden provided results of Principal Investigator Grant competitions at the agency showing a trend of diminishing participation from MDs and MD-PhDs (the usual qualifications of clinician-scientists), this space being taken up by holders of PhDs (typically biologists).

The data by James Wyngaarden and associates at the NIH showed how the number of clinicians in research training programmes had went down from 4100 in 1969 to 1,790 in 1977. In parallel, the pool of postdoctoral researchers supported by NIH grants was increasingly composed of scientists with a PhD qualification only, as compared to scientists with an MD or MD-PhD. Indeed, MDs composed 46% of the pool in 1968, but only 20% in 1977 (Forrest 1980). Data also showed that established academic clinicians were less likely than before to engage in research or describe research as their primary activity. Surveys showed that 15441 academic clinicians declared research as their primary activity in 1968, compared to 7944 in 1975 (commentators contended that the total number of clinicians employed by medical schools over the period had assuredly increased). NIH grants were handed out in 44% of cases to researchers with at least an MD qualification in 1966, but only in 23% of cases in 1978 (Forrest 1980). Because data showed at this point that the success rates of those MDs that applied for NIH funding remained constant, the previous numbers implied that a decreasing number of MDs were asking for NIH funding at all.

In June of 1979, the Association of American Medical Colleges (AAMC), acting on the growing observations of attrition in the pool of clinician-scientists, formed the Ad Hoc Committee on Clinical Research Training. The Committee mostly collected and processed available evidence to issue policy recommendations, but it also conducted a number of additional surveys with its members to complete the evidence available (Thier et al 1980; Bickel et al 1981).

The Ad Hoc Committee mobilized a variegated ensemble of issues in trying to find the causes of decline in the clinician-scientist specialization (Thier et al 1980). It mentioned public support shifting away from biomedical research careers towards clinical care

careers. It showed that medical students had declining interest in clinical research, especially given the level of debts they had typically amassed after completing the medical curricula; that the number of fully-fledged physicians enrolling in further training in research (through a PhD programme most notably) was also diminishing, with the hypothesis that increasing salaries for physicians focusing on clinical care was acting as a disincentive; it also made use of the data of Wyngaarden showing that a relatively stable pool of physicians were less and less involved in research projects. The Committee contended that clinical incomes were soaring while generating steady streams of research funding was made more difficult by heightened competition at the NIH. The later situation was compounded by the expansion of federally supported PhD programmes in biomedical research that had created a pool of highly specialized biologists which might be deemed more susceptible to fill in research positions at medical schools by these institutions' administrations. Despite the availability of a pool this highly specialized PhD holders, the report argued that:

> "The physician investigator possesses unique capabilities and perspectives that form the bridge between the research lab and the bedside. On one hand, the physician's knowledge of human disease is essential in focusing research ideas and maintaining the link between research and the treatment of patients. The MD possesses the clinical insight to transfer knowledge gained through research to the patient. Conversely, many research ideas are sparked by a physician who encounters a particular patient care problem and transfer ideas about the problem back to the research laboratory. Without the physician investigator in the cross-over role, the separation between basic science and clinical science departments would be exacerbated; neither group will function optimally in isolation from the other (Thier et al 1980, p. 87).

Based on these observations and interpretations, the AAMC made a number of recommendations. Proposals included detailed programmes of data collection and research concerning the economic and educational aspects of clinician-scientist training, pleas to have medical schools extend their support for these careers and earlier and more systematic exposure of medical trainees to research, and demands for increased federal support. Bickel and colleagues concentrate on the expansion of resources to the Medical Scientist Training Program (MSTP) as the best mean to ensure the longevity of clinician-scientists in the USA. This programme had been established as early as 1964 by the National Institute of General Medical Sciences to support exactly the kind of training trajectories that lead to clinician-scientist careers.

Drawing on data collected by the Ad Hoc Committee on Clinical Research Training, these authors supported their arguments by showing that there was a much higher rate of attrition in groups of MDs pursuing PhDs without federal support than for those groups of MDs completing PhDs and supported by the MSTP. The Committee also

argued that private industry should participate in these efforts to provide long-term help for the profession, given how they were felt to have benefitted from this specialized source of human capital.

It is also interesting to note in the quote above expressions that are very close to those that TR advocates still used today to diagnose gaps between laboratory modelling and capacities for clinical intervention. The relevance of these arguments at this point of biomedical history are also made clear by another quote taken from the AAMC Committee's publications:

> "Most people would agree that the great successes of American medicine since World War II are due to the coupling of unparalleled advances in basic research with the clinical practice of medicine. This translation of research discoveries to the care of patients has depended on the availability of a sizable cadre of bright, young physicians with excellent training in biomedical research… Only a constant influx of bright and dedicated M.D.-investigators can ensure the continued development and transfer of scientific knowledge to clinical practice and the necessary clinical trials to assess the value and effectiveness of drugs, devices, and diagnostic regimens in human beings (Bickel et al 1981, p. 1265).

Committee members Bickel and colleagues here provide a clear argument for treating clinician-scientists as obligatory passage points in collective representations of how innovation moves from basic research to clinical care.

Over the same time period, other advisory bodies contributed their counsel on the topic, with the National Research Council arguing that 3,660 new clinician-scientists should be trained every year in the US in 1981 and after (Forrest 1980). By 1983, the Institute of Medicine (IOM) had published data that showed that MDs not only formed a diminishing proportion of the pool submitting grants to the NIH, as Wyngaarden had already noticed, but that MDs had comparatively less chances of being awarded a grant then PhDs (IOM 1983). This report also mentioned that PhD holders were increasingly tasked with the conduct of research in the clinical departments of medical schools (such as internal medicine, pathology or anaesthesiology).

The team behind the IOM reports was itself an important promoter for clinician-scientist careers, and readily advocated increased governmental support and protected training programmes as a mean to foster the profession. "This emphasis derives from the M.D.s irreplaceable role in bringing clinical insights to bear in the laboratory and in translating basic observation into clinical practice" (IOM 1983, p. 33). The IOM team's position makes it quite apparent that at this time already, a basic representation of biomedical innovation placed the impetus for this process in hypotheses obtained from laboratory experiments with animals or cell cultures. Clinician-scientists would be ne-

cessary to make sure that knowledge generated in the laboratory could be carried over and adapted to the clinical context.

From these initial reports, clinician-scientists started sharing personal experiences and results of more systematic investigations, identifying a number of obstacles they collectively face. Peer-reviewed medical publications such as the *Journal of the American Medical Association, New England Journal of Medicine* or *Clinical Research* and later *Academic Medicine*, but also generalist journals such as *Nature* or *Science*, became important venues for publishing such reflections on the status of US clinician-scientists. These argumentative practices about training and funding statistics allowed to trace the contours of a problematisation of the institutional conditions for the work of clinician-scientists, that indeed emerge as a distinct class of biomedical investigators through this very process. The story-line that was being stabilized as a result of this discursive work by NIH policy-makers, academic medicine elites and other commentators made the 'professional well-being' of clinician-scientists an essential determinant of the success of future clinical innovation initiatives.

1980s: From public narrative to personal narrative

With the contours of the problem established by the NIH, AAMC and IOM task forces and committees, a number of authors went on to further distinguish the specific causes of decline in the numbers of clinician-scientists, or consider specific aspect of the issue. The initial observations made at the end of the 1970s were given multiple leases on life and re-used to feed into discussions that seemingly reproduce those that had already taken place earlier (Healy 1988), although sometimes they were transposed to other national contexts such as the UK (Smith 1988). Generally, in the second half of the 1980s, a large number of dispersed clinician-scientists seemingly relied on the repertoire of the policy narrative of a plight of clinician-scientists to make sense of their own struggles. Activity by federal or professional bodies had diminished after the initial spurt of interest, the fleshing out of the storyline came more from these individual clinician-scientists sharing their personal experiences rather than policy-level activity. Advocates of the policy narrative also shared experiences about mechanisms they had put into place at their local medical schools to support clinician-scientists. These articles reported on new training programmes put into place following the various recommendations detailed above (Levey, Lehotay and Dugas 1981).

Whereas focus of discussions on the causes in the decline of clinician-scientists had often focused on questions of institutional support and academic prestige, some commentators framed the plight of the clinician-scientists in a much broader societal parameter. Writing in 1985, radiologist Bruce J. Hillman contended that the profession

had been hit in the 1970s by the Nixon's administration cut into support programmes that were deemed to be contrary to the spirit of unsubsidized free enterprise. Hillman contended that PhDs would commend comparatively lower salaries for positions in research while reaching higher levels of specialisation than MDs, particularly with the evolution of research instrumentation. Furthermore, Hillman reasoned that public disillusionment with the capacity of major scientific breakthroughs in the 1950s and 1960s to lead to new clinical innovations influenced young physicians to look for "community-based clinical careers", and "many schools decreased the time traditionally allotted to laboratory experiences in favour of courses on such subjects as community health, sexual awareness, and cost containment" (Hillman 1983, p. 768). Yet, he also makes mention of the problems commonly problematised by his peers, including debt or conflicting demands. He focuses for example on IOM report data showing that PhD holders employed by medical schools tend to be both younger and of lower academic rank than MDs, but at the same time possess more research experience. MDs are thus, for Hillman, bound to be disfavoured in employment decisions. Hillman advocated continued and intensified institutionalization of dedicated MD-PhD programmes as a privileged mean to support clinician-scientist careers, as well as more systematic organizations of mentoring activities on the part of senior clinician-scientists.

Other commentators preferred instead to draw on the narrative of medicine as an embodied art and frame the situation of clinician-scientists within a context of rapidly changing technoscientific infrastructure and instrumentation for the conduct of medicine. These arguments often drew on what might call the "grand tradition of the history of medicine" and lessons from the work of figures such as James Lind or William Osler (Warren 1983). Also relevant to that specific furrow of argumentation were interventions that marshalled C.P. Snow and his characterization of a divide between the two cultures of science and the arts to call for closer cohabitation between laboratory- and clinic-based teams (Haber 1985). Advances in molecular biology were felt to be associated with increasing complexity and division of labour within biomedical research, a situation that would tend to slowly displace clinician-scientists away from the locus of this work, given the dedication it requires:

> "Already, the techniques of molecular biology dominate research in genetics and constitute the most active frontier of cancer research, are of much importance in virology and immunology, and are fast becoming so in hematology and endocrinology and even in the neurosciences. But molecular biology is becoming harder and harder to perform on a part-time basis because it is too complex, competitive, and quickly evolving" (Littlefield 1986, p. 786).

Pushing the logic of marginalization of the art of medicine under the expansion of molecular biology further, certain commentators engaged in boundary-making to distin-

guish between clinician-scientists that simply exercise laboratory research and patient care in parallel, and those that strive to closely integrate both areas together. In opposition to previous arguments, these commentators emphasized that the safeguarding of MD-PhDs were no guarantee that something such as 'patient-oriented research' revolving around the messy world of real-life humans was preserved at a time where the successes of molecular biology rested mostly on animal and in vitro modelling:

> At least one objective of the MD-PhD programs should be to produce young men and women who will apply basic science to the problems of human disease. To a certain extent we are missing that target. I am afraid that on the average the MD-PhD group tends to be a small elite group, heavily trained in the basic sciences who follow role models who are themselves basic scientists. The preceptors believe all the action is at the molecular level and that a clinical investigator must be a molecular biologist first. These young people may not have enough experience with clinical medicine to be able to deal with human disease and therefore, they stick with what is familiar, namely, basic science. The MD-PhDs student may become over-trained in basic science and under-trained in clinical medicine. Others have spoken about the promise of molecular biology applied to human disease and I agree that prospects are bright, but this is not enough. We need people who start with a clinical problem and seek a solution using any of a number of tools (Ross 1985, p. 107).

Accommodating molecular biology with medicine thus already posed institutional as well as personal challenges, and more than just a matter of exporting routines and platforms from the laboratory to the clinic. Instead, Ross seems to argue that molecular biology needs to be accommodated to the realities of the clinic, and not the other way around. What the arguments in this quote do is re-open the possibility of forms of clinical innovation that do not start from an experimental result obtained in the animal model or cell culture laboratory. Instead, with appropriate support, clinical contexts could provide the material to come up with novel therapeutic hypotheses for example.

To put his contentions into practice, Ross argues that General Clinical Research Centers (GCRC), created by the NIH in the 1960s to provide institutional homes for expertise in clinical research, could extend their mission to the training of clinician-scientists that 'truly' engage in patient-oriented research. NIH will indeed pick up on this idea, but most interesting for our purposes is how it also seemed to have been carried over, albeit much later, into a central intervention for TR, the Clinical and Translational Science Awards (see section 5.1 and 5.2).

4.1.2 The 1990s

With the passage of the next decade, studies of the plight of clinician-scientists continued to gain traction, although the basic arguments and observations invoked tended

to remain substantively the same, with updates to account for minor evolutions. The contentions of clinician-scientists were also vindicated by major policy interventions that aimed to support TR orientations explicitly by supporting related career paths (including the National Cancer Institute SPOREs, a policy intervention examined in details in section 4.1, and other interventions briefly described below).

Emil J. Freireich, a central figure of the development of the large-scale enterprise of anti-cancer agent clinical research in the USA (Keating and Cambrosio 2012), refined the argument to find specific parameters to this situation of decline in clinical oncology (Freireich 1991). Freireich, like the other advocates whose position has been examined above, also held that the clinician-scientist is "the exclusive individual for conducting research that specifically bridges the gap between the laboratory and the clinic" (Freireich 1991, p. 831). He used results of a survey he conducted at 20 training programmes in oncology to show the relevance of problems such as peer review reluctance towards clinical research and associated problems of academic status, the tendency to focus on clinical care as a mean to generate revenues and the financial burdens placed on trainees in the field of oncology. Most interestingly, he characterises participation in the protocol-driven, cooperative group studies he himself played such a great part in establishing as a potential source of insatisfaction or insecurity for trainees. This would be the case given the exacting work required for the trials and the impersonal hierarchies they would often be associated with.

MD-PhD Joseph B Martin warned in 1990 of the dangers that a shortage of clinician-scientists would pose for the transformation of advances in basic biology into clinical applications. Martin argued that

> "In the 1990s, the opportunities in biomedical research place us on the threshold of a new era. Revolutionary advances in genetics at the molecular level, originally worked out in simple bacteria and their viruses, have now engendered powerful new technologies that make possible the study of virtually any biological system… The opportunity is the prospect of unparalleled progress in understanding human diseases at a molecular level and in developing novel strategies for their prevention and treatment. The problem is that too few people are being adequately trained to carry out the advances that appear before us" (Martin 1990, p. 123).
>
> We expect that physicians perceive a broader picture of the importance of biological research for patient treatment. We would also agree that the more deeply immerse in the primary literature surrounding basic biological discoveries, the more likely is research directed by physician-scientists to lead to fundamental discoveries that will further our understanding of disease processes. Furthermore, I suspect that most of us would agree that early participation in research is desirable, and that freedom from other responsibilities during the research training period is advantageous to suc-

> cess. Adequate protection of time during the early development of independent research is also essential" (Martin 1990, p. 124).

In the rest of the article, Martin notably reported results of a survey with the administration of MD-PhDs programmes at eight US medical schools, arguing that such programmes, formally established and supported by the NIH in the 1960s, were the most likely to systematically train individuals interested in clinician-scientist careers. Martin emphasized the success of these programmes up to the point of his evaluation. Yet, he also mentioned room for improvement in support for developing research programmes that may lead to the first writing of a clinician-scientist's demand for principal investigator grants. He also provided reports of a small in-house survey at his faculty showing that colleagues and medical students readily associated indebtness, reducing research funding in an increasingly competitive environment and lack of positions to clinician-scientists careers. Martin concludes his article by examining dedicated training or support programmes such as the "NIH Physician-Scientist Training Awards" or the "UCSF Medicine Molecular Training Program", arguing that these should be exemplars followed by medical schools elsewhere in the country to boost nation-wide efforts to help the profession. In essence, Martin does not bring any new arguments in his analysis of the clinician-scientist issue, but it is interesting to note how the passage of time offers the opportunity for renewed urgency, as if the assumption was that basic knowledge keeps on accumulating, yet nothing too concrete is being done about this. His formulation of the issues at may even play indicate a relative stabilization of the policy narrative at this stage already, with clear and consensual problematic and proposals for reform. Martin's argumentative intervention also makes it clear that absolute novelty is not necessary to the dispersion and reproduction of policy narratives, if they still speak to institutional or cultural conditions

The Crisis in Clinical Research

In 1992, a retired professor from the Rockefeller University, Edward H. Ahrens, published *The Crisis in Clinical Research.* This book-length essay problematised the professional status of clinician-scientists, in an era when "integrative patient-oriented research" was being increasingly marginalised by "reductionist molecular biology" (Ahrens 1992, p.48). In this, Ahrens crystallized the argument presented above and that aimed to show that MDs doing research and MD-PhDs were a good class of investigators to encourage what was at that point starting to be called TR. Nonetheless, many of these investigators were still not engaged in exactly the kind of clinical research that was felt would most likely result in "patient-oriented research".

> "In the last three decades, the focus of clinical investigators has shifted dramatically from integrative to reductionist research. This is due largerly to a fascination with the power of the new reductionist technologies of molecu-

> lar biology to reach new insights at the molecular level and to do so rapidly. POR [patient-oriented research], on the other hand, is the most time-consuming form of clinical research, the most difficult, and the slowest. Thus, as physician-scientists have found themselves increasingly constrained in finding time for research, they have turned from POR to the reductionist modes of research" (Ahrens 1992, p. 48).

To arrive to such conclusions, Ahrens relied on surveys with medical schools that used a very fine granularity of clinical research categories. These categories included mechanistic studies of human disease conducted exclusively with patients or volunteers, studies of management of disease, "In Vitro Studies on Materials of Human Origin" or studies with animal models of human (patho)physiology (Ahrens 1992, p. 41). He was subsequently able to find out, for example, that only a few NIH grants awarded to investigators affiliated to medical schools were used for mechanistic studies of human disease conducted in human systems, the category that he considered to be the apex of exemplary clinical research. Ahrens thus problematised the utility of the MSTP, which at that time had been provided with 4000 million US$ since its establishment in 1963 and supported the training about 2000 MD-PhDs over this period. No extensive evaluation of the programme had been made, and it was not possible to say whether the MD-PhDs supported had oriented their career towards basic science, clinical care or patient-oriented research. Ahrens himself contends, based on a small survey he conducted with 82 graduates from dual MD-PhD programmes, that 71 were engaged in non-clinical research and that only two conducted the basic patient-oriented research he himself found so important. This was all highly problematic, for Ahrens, because sustained engagement in clinical innovation that impacted patients' quality of life could simply not be expected from advances in molecular biology on their own:

> "Animal models can never tell us the whole story, predicting human medical problems in the future is highly uncertain, and there are no road maps that can lead the investigator in a well-defined way from the 30 billion base pairs of the human genome to an understanding of the complexities characteristic of human function and behavior (Ahrens 1992, p.179):

For Ahrens, as for Ross whose argument was examined above, the promises of molecular biology in offering unprecedented means of understanding human systems, and especially the extant of the laboratory control it afforded to investigators, threatened to disproportionally divert collective attention towards narrow subsets of problems. To nurture patient-oriented research with a focus on mechanistic understanding of (patho)physiology, Ahrens pleaded for both MDs and PhDs to form partnerships to train future generations of biomedical researchers that would focus on this area of research. Also, Ahrens argued for the production of "integrative physician-scientists", trained through "*post-post*graduate" opportunities addressed at those individuals having already completed a dual MD-PhD programme. Additionally, the continued existence of a

pool MD-PhDs themselves had, in Ahrens' view, to be ensured through special grants that could act as "bribes to lure research-minded candidates away from what they would otherwise be forced by economic and employment circumstances to do" (Ahrens 1992, p. 181).

The position of Ahrens highlights the tension between molecular biology approaches and the tradition of clinical medicine from which clinician-scientists have often drawn from to build their professional identity. Ahrens seems to present the possibility that TR be accomplished in other manners than by translating science to the clinic, but rather by engaging in a sort of experimental medicine that draws from formal basic research findings published in periodicals but that follows its own institutional rhythms and evaluations. With this, Ahrens also indicates the potential that academic experimental medicine may be a different beast than the modelling of laboratory biology. TR might then be envisioned as a response to molecular biology and genomics, one where the clinical expertise of physicians and physicians-scientists might not be soluble with the demands of mechanistic laboratory modelling practices.

More importantly, Ahrens produced a work that informed the argumentative practices of a new wave of clinician-scientists, in much the same way the article by Wyngaarden did previously. It consolidated an argumentative repertoire for justifying investigations that might not be considered as cutting edge science under the molecular biology paradigm, but that its advocates may consider to be more relevant to clinical innovation (for examples of later usage of this repertoire see Marincola 2012; Witte 2011). Nonetheless, this repertoire seems to have had only restricted uptake by other advocates of TR. Not so many subsequent commentators seem to have picked up the crux of Ahrens's argument about basic patient-oriented research as a specific conceptual and methodological approach, and the fact that clinician-scientists could be the protectors of this threatened form of research. Indeed, clinician-scientists have often been arguing since that they are the gatekeepers to the transformation from genomic biology to genomic medicine (Nathan and Varmus 2000), rather than for the renewal of any sort of patient-oriented research.

NIH stirs again

As was already seen above, the second half of the 1980s and the early 1990s did not see major activity from policy-makers and relevant advisory or professional bodies on the matter of clinician-scientists. Perhaps in the wake of Ahrens' fiery contribution to the policy narrative, however, this begins to change in the mid 1990s. In 1994, the Institute of Medicine thus published a complete report dedicated to the issue of clinician-scientists engaged in "patient-oriented clinical research" (IOM 1994). It firstly recon-

ducted the validity of the major findings that had been reported in the preceding 15 years:

> The current level of training and support for health professionals in clinical research is fragmented, frequently undervalued, and potentially underfunded. This is especially true for those concerned with human research, that is, research focused on the human subject. (IOM 1994, p. 4)

Doing it own inquiries, the committee behind the report estimated that only 10% of NIH principal-investigators grants (R01 grants) were awarded in 1991 for projects that revolved around research in human or with human material. The committee generally considered that clinician-scientists would be crucial resources in translating the findings of molecular biology into clinical innovations. In turn, it argued that the success of these translation efforts was essential in a context of increasing societal pressure to derive value from the opportunities created by advances in molecular biology. As such, it recommended that increased resources be committed to NIH mechanisms such as First Investigator Research Support and Transition awards and other training initiatives, or for the GCRC. It also called for medical schools to review curricula and evaluation procedures for clinician-scientists, so as to allow measurements that account for their specificity and provide protected time for research, for example.

In the wake of the IOM report, Harold E. Varmus, then director of the NIH, established in 1995 a Director's Panel on Clinical Research to evaluate the situation pertaining to clinician-scientist careers (further analysis on this committee’s impacts is provided in section 5.1). The report of the Panel made clear reference to the work by Wyngaarden and Ahrens. It drew on the parameters provided in these works to problematise the professional situation of clinician-scientists as an obstacle in ensuring the success of efforts in the TR enterprise. It essentially then certified the validity of the issues already identified in past works (debt, obstacles to training and mentoring, difficulty to compete for funding, professional pressures related to clinical care work). It also made use of many of the recommendations previously made in the Institute of Medicine and Ahrens reports, notably those concerning the expansion of the mission of GCRCs, the creation of mechanisms to reduce trainees’ debt or the creation of special sections in grant proposal review committees mandated to evaluate patient-oriented research specifically.

Despite efforts that have been implemented in the wake of these discussions, commentators were still arguing that the situation of clinician-scientists was worsening at the turn of the millennium (Thompson and Moskowitz 1997; Nathan 2002). David G. Nathan, who had lead the Director's Panel on Clinical Research, reflected in a 2002 article on the impacts of these activities. He noted how NIH had indeed acted on recommendations to increase training opportunities, to expand GCRC budgets, to provide

specific grants for young clinician-scientists and to create special sections in grant competitions. Nonetheless, he argued that change was still needed, not so much at the level of the NIH and other federal agencies as in the way the community of biomedical investigators were handling collective priorities and assigning legitimacy to certain areas of research. Nathan contended that patient-oriented and clinical research were still disincentived by academic reputational practices that emphasized individual creativity projects rather than team-based efforts, and by the long-standing problem of the burden of clinical care work assigned to clinician-scientists.

4.1.3 Germany

The sections above had traced the rapid stabilisation of a policy narrative about the plight of American clinician-scientists in the late 1970s, with consolidation and extension in the 1980s and 1990s. The situation of academic medicine in Germany over that period offers an interesting contrast. The documentary record formed of German medical periodicals does not make extensive mention of issues in the training and maintenance of a specific cadre of professionals situated at the interface of clinical care and research. Certainly, this body of literature hasn't been made as accessible to current digitized modes of data accession. However, my investigations do seem to indicate that the theme of clinician-scientists has been for along time much less of a concern in Germany than it has been in the USA. More convincingly for our purposes, the recent development of a local articulation of the clinician-scientist policy narrative seems to draw directly on arguments made in the US context, rather than refer to a local repertoire of experiences and interpretations (as will be seen in section 5.1).

The reference of contemporary German advocates of TR to the US discussion about clinician-scientists is nonetheless peculiar in that it ignores a local strand of argumentation that is of high relevance to this discussion. Indeed, funding and advisory agencies such as the German Research Foundation (Deutsche Forschungsgemeinschaft – DFG) and the Council of Science and Humanities (Wissenschaftsrat) have issued reports since the 1980s decrying a perceived poor state of clinical research and experimental medicine in Germany (Wissenschaftrat 1986; DFG 1999; Wissenschaftrat 2004). These documents have argued that research activities are increasingly marginalised in German academic medicine. Whereas all clinicians affiliated with university clinics in Germany are expected to engage in research beside clinical care, in practice, these documents have argued, those that do engage in high-level research are a minority. And this has to change, for reasons similar to those already used in the US context, it has been argued throughout these critiques.

Earlier, concern actually seemed to be oriented more towards the construction of dedicated infrastructure for medical research that would enable “clinical theoricists” to free themselves from the constrains of clinical contexts and establish deeper connections to their peers from the natural sciences. Indeed, in a 1968 series of recommendations, the Wissenschaftsrat commented that major concern for medical research was more on the plane of “fundamental… problem-oriented research” then “clinic-near… patient-oriented research” (Wissenschaftsrat 1968, p. 67). The report generally recommended the expansion of personnel and positions for both clinical practice and research as well as pre-clinical research at a time of generally increasing need.

In 1980, the DFG published a report highlighting the specificities of clinical research, challenges to its conduct at a time when molecular biology is reshuffling methods of accessing human (patho)physiological information, and recommendations for the improvement of the speciality in Germany (Gerok 1980). The author of the report, Wolfgang Gerok, a Professor of internal medicine at the Albert-Ludwigs-Universität Freiburg and director of its university clinic, offers a problematisation that is similar to the one being assembled in parallel in the USA: clinician trainees find themselves early with a choice of concentrating solely on medical practice, which is a demanding path in its own right, or adding research training to their personal curriculum, with the added demands this entails. Even for those trainees interested in research, “theoretical medical” laboratory-based projects are more likely to provide quicker results with less demanding work than clinical research. Low numbers of trainees are compounded by lacking institutional support from academic medical centres overloaded with clinical care tasks, lacking funding and the expansion of natural science positions at academic medical centres, at the cost of traditional medical positions.

The problematisation of clinical research and clinician-scientists that the Gerok report introduced in the German context was pursued by a number of reports from the DFG and Wissenschaftrat. The Wissenschafsrat’s report of 1986 already notes how scientifically-inclined medical doctor are not presented with any credible career paths that does not include a primary concern for clinical tasks. Pursuing a Habilitation (an advanced degree given to PhD holders that certifies an academician’s research capacities and capacity to hold a professoral chair) won’t discount clinicians from care duties. At the graduate level, the quality of medical doctoral dissertations would not reach the level of those in the natural sciences. Indeed, in Germany, physicians can obtain a doctoral certification specifically tailored to the profession (Dr. med), but the Wissenschafsrat considered that the quality of the graduates would not compare to those coming out of MD-PhD training in the USA or the UK. Also, the agency decried the comparatively small space given to scientific training in medical students’ curricula, despite

the increasing number of clinical interventions coming from immunology, biochemistry, biophysics and other natural sciences (Wissenschaftsrat 1986).

Broader institutional configurations at German medical schools were also obstacles to the conduct of clinical research by clinician-scientists in Germany. In terms of university clinic infrastructures, even when clinics integrating locations that allowed for links between clinical care and experimental medical work at the end of the 60s, the Wissenschaftsrat commented that the higher number of German clinics were organised in distinct pavilions belonging to distinct specialties, which were not an optimal configuration for clinical research.

Finally, possibility for funding clinical trials and research at the interface of laboratory and clinic were also deemed lacking, although positive developments were also noted. The Wissenschaftsrat thus approved of actions by the DFG to provide funding for clinical studies. This support was made available in a number of fashions: 1) traditional principal-investigator grants for clinical investigators, 2) multicentre clinical trials; 3) support for 32 multidisciplinary research groups mixing clinical with experimental medical and natural science teams. This intervention, together with the Max Planck Association's efforts to establish a network of research teams at university clinics, were cited as exemplars to be followed by broader public interventions following in these footsteps (Wissenschaftsrat 1986; Wissenschaftsrat 1987).

The DFG's 1999 report repeats much of the Wissenschaftsrat's earlier contentions regarding the possibility to conduct clinical research at German medical schools: 1) laboratory and clinic beds are rarely dedicated to it; 2) competencies for leading efforts in the area are distributed across departments; 3) financial and other resources for clinical care and for clinical research are rarely made independent and thus the former tends to impinge on the later; 4) there are too few clear and established training trajectories for medical students wishing to develop into clinical investigators, and 5) there are too few attractive positions in medical schools for clinical investigators (DFG 1999). The DFG even goes so far as to characterise a part of the research done in medical faculties as *pro forma,* that is, performed to cater to evaluation or career demands but being of little intrinsic scientific value.

Examples of structural obstacles to patient-oriented research mentioned by the DFG include the lack of training for clinical trial principal investigators as well as study nurses; the lack of a single department or unit specialising on clinical research; the separation between ambulatory and stationary care, which make enrolling ambulatory patients, an important source of participants in phase III and IV studies, difficult; and a

lack of motivation and concerted efforts from political, regulatory, insurance, industrial and research actors to participate in clinical research efforts.

The Wissenschaftsrat's 2004 report on research and training infrastructures in academic medicine continues in much the same argumentative furrow as its previous works and that of the DFG. The report re-emphasized the need for separate finances between research, teaching and clinical care, advocated the use of departments as flexible organisation units allowing transdiciplinary and inter-institutional research, as well as advocated for more scientific education for medical students (Wissenschaftsrat 2004). The propositions put forward by the Wissenschafrat thus again made clear the concern to provide university clinicians with the optimal institutional configurations to be able to engage in research projects.

In summary, German advisory bodies have been concerned with much of the same issues that have constituted the discussion about clinician-scientists and patient-oriented research in the USA. Most notably, even if clinicians in Germany do not work strictly on the same fee-for-service model as that of the USA, clinical care has also been perceived to takes up always more resources that are otherwise earmarked for research. As such, German advocates of TR will readily draw on the idea that a dedicated class of clinician-scientists need to be fostered in the country to implement the agenda, even if they seem to have drawn more from the US argumentative repertoire than the work of the Wissenschafsrat or the DFG (see section 5.1).

4.1.4 Continued plight, 2009 and after

Despite the proliferation of initiatives and funding aimed at building TR in recent years, at the time of writing these lines, the policy narrative about a plight of clinician-scientists and the potential consequences of this situation on the capacity of TR initiatives to deliver clinical innovations had not subsidized at all. On the contrary, a great portion of the large number of editorials and reviews in specialized periodicals as well as policy documents about TR made mention of the clinician-scientist theme as one component of their proposals or wishes for implementation the agenda. A recent article in the central journal *Academic Medicine* was thus titled "Transforming Science Into Medicine: How Clinician–Scientists Can Build Bridges Across Research's 'Valley of Death' " (Roberts et al 2012), linking the issue of clinician-scientists to a metaphor (the valley of death) that is more readily associated with the crisis in the pharmaceutical industry. Whereas the traditional journals associated with academic medicine had first housed these discussions, new journals established by US researchers to tap into the growing popularity of TR concepts also provided contemporary outlets for discussions about the plight of clinician-scientists (Feldman 2009; Laurence 2008; Mankoff et al. 2004).

These new periodicals included the *Journal of Translational Medicine* (established in 2003), *Translational Research* (2006), *Clinical and Translational Research* (2008) or *Science Translational Medicine* (2009).

Books and other studies presented as the continuation of the work of Wyngaarden or Ahrens were published by clinician-scientists, with a recent example being *The Vanishing Physician-Scientist?*, edited by Andrew I. Schafer, an MD from the Weill Cornell Medical College (Schafer 2009). Contributions engage the issues that had already been covered above and provide various statistical analyses to examine the contemporary situation of clinician-scientists. Other contributions in the book, however, also branch out to address topics such as the specific issues encountered by women as clinician-scientists or by members of "generation x and the millenials", who would have different priorities in conciliating work and family life then their predecessors.

With the success of the TR movement and the extension of its agenda to a number of other issues in biomedical innovation, the tasks and professional identity clinician-scientists are also being redefined. An indication of this change is given in recent interventions that describe the tasks of the modern "clinical/translational research" as follows:

> • "Core professional functions: Conducting research to ultimately enhance the health of the individual, the community, the nation, and the world
> • Intellectual orientation: Creative and disciplined thinking
> • Technical skill: Systematic, objective investigations
> • Management skills: Organization, maintenance, and efficiency of research efforts
> • Values and integrity: Scholarly processes that adhere to the highest standards of ethical conduct
> • Understanding interdisciplinary perspectives: Collaboration and integration across silos of investigative activity" (Pincus 2009, p. 412).

This list of potential attributes of the translational investigator is provided in response to a review that had found lack in leadership and incentives at Clinical and Translational Science Awards centers (CTSA) that would ensure that affiliated basic researchers would contribute to TR projects (Heller and de Melo-Martin 2009). CTSAs are a major current initiative to support TR established by the NIH in 2006. Pincus wants to make a clear case that fostering the development of a cadre of translational investigators, as CTSAs aim to do, should solve problems in the coordination and stewardship of TR projects through the various phases and expertise areas that need to be navigated. His intervention also makes clear recent evolutions in the understanding of clinician-scientists' role in the TR enterprise. First is the proposition that clinician-scientists are being redefined as translational investigators. This group of professionals will not strictly include only medical doctors engaged in research or that have completed a re-

search PhD, but that may also make place for biologists conducting research that is very close to clinical development and for other types of professionals that may act as interdisciplinary brokers (Calvert 2010). A second innovation is linked with claims that translational investigators have specific management skills that are also absent from the toolbox of most basic researchers (see section 5.1.1).

4.1.5 Golden Age lost: further analytical considerations

Keating and Cambrosio (2012) make a link between the emergence of notions of TR with a longing for a lost "mythical" (in the sense of Barthes) time of interdependency of (patho)physiological research and therapeutic research. Swazey and Fox (2004) talk of the period starting with the end of WWII until the molecular biology wave of the 1970s as that of the "golden age of patient-oriented research". The policy narrative of the plight of clinician-scientists seems to feed off of this culturally broadly available script of a "paradise lost" in arguing that the clinical innovation enterprise would be improved if some of the features of this old system could be safeguarded or reintroduced in contemporary biomedicine. This circumscribed bout of nostalgia can even be replaced within a more fundamental discourse about the role of clinical data in the construction of hypotheses on human (patho)physiology. Foucault had already noticed a tendency by medical scientists to bolster their status by ascribing a unique epistemic quality to the clinical knowledge they produce:

> **"**Medicine has tended since the eighteenth century, to recount its own history as if the patient's bedside had always been a place of constant, stable experience, in contrast to theories and systems, which had been in perpetual change and masked beneath their speculation the purity of clinical evidence" birth of the clinic" (Foucault 1963 cited in Diedrich 2010, p. 143)

Indeed, it seems we cannot fully understand the advocacy of clinician-scientists only as the punctual claims of a small group of investigators trying to defend their interests and professional jurisdiction. Instead, clinician-scientists were the central epistemic authorities within a specific socio-technical system that became marginalized (but by not means went away) in the 1970s, as molecular biology became the central source of scientific authority in biomedical research.

Starting with this rich discursive reservoir, a core group of clinician-scientists and associated policy-makers have been able to create a powerful policy narrative by foregrounding the potential of the personal capacities in their group for the TR enterprise. They have problematised the conditions and institutional support for their work as elements that could endanger not just the survival of their professional jurisdiction, but also the success of the clinical innovation (and later) TR enterprise as a whole. The discourse coalition formed around this issue thus quite simply proposes to reinforce

funding and training opportunities for clinician-scientists, as a privileged mean to support TR. One of the successes of the policy narrative will also be made clear later on, as I show how the discourse coalition articulating this storyline evolved to include a number of different actors that also believed clinician-scientists had a special role in TR. It is also interesting to note how the personal process of separation or fracture between formal knowledge and medical practice, as experienced by clinician-scientists in the 1970s, seemed to have shaped the central theme of a gap "between bench and bedside" that TR would address. In arguing about the plight of clinician-scientists and showing that these personal experiences had system-wide consequences, advocates of the narrative elaborated a coherent problematisation of an explosion of knowledge in molecular biology that would not be simultaneously followed by corresponding advances in clinical innovation. This problematisation forms a core idea of the broad TR discursive repertoire, one that has been reused in a variety of arguments, even as these had no relation to the plight of clinician-scientists.

Much like the discussions around the status of clinician-scientists predate the emergence of the notion of TR, there are also precedents for the former movement itself. Dominique A. Tobbell has shown that the creation of a subfield of clinical pharmacology in the American academic medical landscape of the 1950s and 1960s has been an arduous endeavour, made possible by the alliance of medical schools and large pharmaceutical companies (Tobbell 2012). Clinical pharmacologists, who are today considered central actors in the TR movement (FDA 2004; DE investigator 6; US investigator 8), faced professional and legitimacy challenges that anticipated the obstacles of all clinician-scientists later on. Having no dedicated patients themselves but being issued mostly referrals from frontline physicians, salaries were accordingly lower. To counterbalance these economic forces, proponents of clinical pharmacology went about raising the prestige of the specialization, institutionalizing training programme and advocating for increase NIH support. They even proposed an Institute of Clinical Pharmacology as a fully-fledged national institute of health (this proposition might well be considered to have been partly realized now within the NCATS). Tobbell's analysis shows the central role that alliances with industry and certain policy makers have played in raising the profile of the specialization. Further work would be necessary to substantiate such an hypothesis, but the narrative of plight of clinician-scientists is perhaps related to this early problematisation of activities that are now considered central to the TR agenda.

From the broader STS perspective, the case of clinician-scientists also offers an interesting empirical counterpoint to certain studies of interdisciplinarity and of the institutional trajectories of research communities. Calvert (2010) has already emphasized the importance that individuals personally embodying the integration of multiple areas of expertise can play in the formation of contemporary interdisciplines in the life sciences.

The case of the clinician-scientists opens the empirical possibility of the individual components of interdisciplines may actually drift away from one another, in contrast to the dominant policy discourse (and sometimes social science discourse) that posits ever increasing interdisciplinarity across the sciences.

4.2 The emergence of sequencing-driven experimental medicine

This section will show how the development of high-throughput, bioinformatics and eventually post-genomic capacities starting in the 1980s and crystallized by the completion of the HGP draft in 2000 and final version in 2004 offered a new discursive repertoire for representing and understanding the relations between biomedical research and therapeutic and diagnostic research. The development over this period of sequencing technologies that enabled experimentation with samples from human subjects, such as tumour tissue typing, enabled collective representations of laboratory-like experimentation close to clinical contexts. This, at a time when experimentation on human systems or material had been increasingly restricted within the confines of classical clinical genetic analysis or strictly regimented clinical research, the later often being oriented towards regulatory and commercial rather than epistemic demands. This chapter will thus examine how biomedical actors from the late 1980s to the mid 2000s have interpreted and analysed developments in sequencing technology over that period, and the kinds of calls for collective action and programmes of research they have elaborated based on these developments. In doing so, I will sketch the contours of a major policy narrative that has defined the agenda of TR and the orientations of biomedical elites and associated policy-makers.

4.2.1 Aligning clinic and laboratory through tissue typing

As the previous section (4.1) has shown, already in the 1970s, a collective belief was well entrenched in biomedical community concerning how major advances in molecular biology ought to be followed by associated changes in the new health interventions produced by clinical innovation projects. During the late 1980s and early 1990s, talk of an endeavour such as a projected HGP was fuelled by promises of decisive advances in research technologies, advances that would also be taken over into the clinical context to change treatment for both rare hereditary diseases, but also common conditions such as diabetes and cancer (Howard Hughes Medical Institute 1991).

Advances in genomic sequencing and increased understanding of the role of specific genes in disease processes was also hoped to provide the pharmaceutical industry with new proteins that may be used as therapeutic agents. An annual report from the pharmaceutical multinational SmithKline Beecham PLC from 1994 predicted a bright and very near future for the industry based on contemporary advances in molecular biology and genomics:

> Before new technologies made genomics possible at the beginning of this decade geneticists found genes by stalking rare mutations … the hunt for a single gene could take decades. Now sophisticated high-speed sequencing

> strategies pioneered by SB's collaborators generate sequences from more than twenty thousand genes per year… each new gene is potentially to key to a treatment – and a new product (SmithKline Beechman PLC 1994, p 5; cited in Martin et al 2009, p. 146).

Post-genomic experimental platforms and genetic engineering also provided the opportunity to create whole new categories of therapeutic interventions, such as gene therapy (the replacement of a "defective gene" with the correct gene in patients' genome). Jürgen Drews, then president of international R&D at Hoffmann-La Roche, commented on advances in genomics and the potential of gene therapy in 1993:

> "Right now, it is difficult to decide whether gene therapy will become an industry of its own or eventually be incorporated in the traditional pharmaceutical industry. In any case, it will be the most rigorous expression of new thinking in medicine, an informational paradigm that will otherwise tend to emphasize diagnosis and prevention. Taking a radical view, one could assume that gene therapy will eventually make many forms of drug therapy obsolete" (Drews 1993, p. S20).

Drews thus contended that a major new stream of "therapies based in the synthesis of small molecules and on the identification of new disease genes involved in major multifactorial diseases" would be entering clinical development in 1999. The year 2003 would mark the start of a steady stream of regulatory approval of such agents (Drews 1995, p. 191).

More so than in the context of the early HGP, I find the first arguments for the establishment of something resembling the concerted translation of sequencing technologies towards clinical research contexts in the field of clinical oncology. More precisely, the very first instance I could find of the use of the expression "translational research" can be located back to the initial request for applications (RFA) for a new type of research centres that the US National Cancer Institute (NCI) started to fund in 1991. The RFA was published in the "trade journal" of American oncologists, *The Cancer Letter*, and sets out a clear research programme out of the need to development clinical interventions from advances in molecular biology (see especially the last lines of the quote about this last point):

> Since 1980, breast cancer incidence has increased dramatically in both pre- and postmenopausal women at a rate approximately 2 percent per year. During this time, the scientific information base for breast cancer has expanded significantly; however, application of this scientific base to clinical and preventive activities has not been commensurate with this expansion. There is thus a need to encourage translational research that would require interdependence between basic and clinical investigators in both the planning and implementation of research and would emphasize clinical application of basic research findings with patients and populations. There exists significant scientific and clinical expertise in breast cancer in NCI desig-

> nated cancer centers and other institutions throughout the country. A concerted effort to mobilize this expertise through SPORES can accelerate advances in the management and ultimately prevention of this disease. The recent NCI sponsored workshop "Emerging Concepts and Strategies in Breast Cancer" indicated a number of areas where such interdisciplinary applications could prove fruitful. Experts from many disciplines addressed growth factors, oncogenes and suppressor genes, new technologies relevant to the field and resistance to drugs and hormones (*The Cancer Letter* 1991, p.2).

This quote is taken from the very first phrases of the request for applications for breast cancer SPOREs, and it is striking to read the framing of the problem that is being done there. In the first sentence, it is made clear that breast cancer is a societal problem of growing acuity. In the second sentence, this growing acuity is made troubling or even revolting by the observation that in parallel to this worsening conjuncture, advances in understanding of breast cancer are proceeding at an unprecedented pace. This representation of urgency and wasted opportunities is a recurring theme in utterances about TR, and were already present in the policy narrative about the plight of clinician-scientists and patient-oriented research, but it seems to reach its apex in discussions about the prospects of genomics-based and other sequencing platforms (later proteomics, metabolomics and so forth).

The quote above makes an explicit problematisation out of the inability of advances in molecular biology to bring about decisive new tools for the clinical treatment of cancer. Through the kind of experimental practices and research problems it aims to support, the new NCI initiative participates in more implicit process for defining the novel efforts that may be necessary to actively effect the alignment of sequencing technologies and clinical innovation. Most centrally, approaches that used sequencing developments to work with human tissue on a large scale basis seemed poised to have more direct impact on clinical innovation than work with animal or cell models. Such an argument can be seen, for example in a testimony made before the President's Cancer Panel Special Commission on Breast Cancer in July 1992:

> The program we are going to talk about is a program looking at a gene called HER2/neu and the HER-2/neu gene is a gene that was identified in the mid-1980s that is a growth factor receptor receiving signals from the outside of the cell that tells the cell to grow. And, basically, the program that we designed was based on a program that started in about 1982 at UCLA [University of California in Los Angeles], where we took actual tumor tissue from patients, in this case breast tumor tissue, when it was removed for therapeutic purposes, and began to analyze tissue at a molecular level to develop questions. So the problem was based on a clinical problem, that of breast cancer and a hetereogeneitive breast cancer and why it behaves differently in various patients. It was based on utilizing clinical material. We approached the clinical problem with modem basic science technology.

> **With the sort of explosion in new biology, there is now technology available to use actual, not cell lines or model systems, but real clinical material to begin to ask questions.** Generate new information to address the basic science questions regarding the biology of the disease and the use of newly generated data to design newer therapeutic approaches in various models. In other words, construct our models after the fact, after we know what may be going on, or we think we know what might be going on in some of the human tissues, and then develop and test new clinical approaches. Basically, again, I want to present this as a paradigm, and this is one example of how it can be done (NCI 1992, p. 50; my emphasis).

This testimony was delivered by Dennis Slamon, an MD-PhD who is today still working on breast cancer at the University of California and Los Angeles, and would eventually go on to lead a translational research programme at the Jonsson Comprehensive Cancer Center there. Further on in this workshop, Dr. Slamon goes on to describe the various experimental manipulations that were conducted with breast cancer tumour tissue. Immortalized cell lines were elaborated from this tissue material, and eventually, Dr. Slamon and his team were able to develop antibodies as a potential therapeutic modality to act on the HER-2/neu gene and its role as a tumour growth factor. What is especially interesting here is the idea that it is the advances in molecular biology and genetic sequencing that are allowing new means to conduct *experimental medicine*, by the virtue of working directing on human material rather than engaging in modelling experiments. This also called for a different organization of clinical innovation, activities, where clinicians and laboratory-based researchers could work more closely together. Dr. Slamon considered that this was a clear break with previous models where clinical innovation was in fact more likely to originate at a distance from clinical realities, within the controlled settings of the laboratory. This break is enabled notably by new types of centres supported by the NCI, the SPORE:

> Now, that is no testimony to our ingenious approach but is, I think, a real testimony to the ability, when clinical researchers and basic science researchers collaborate closely using the technologies and the questions that are available to both, to try to make something happen. I think that is the real strength of what we have been able to do at UCLA. I think that this is a paradigm that is being carefully fostered by the NCI in some of its recent initiatives. Notably, the SPORE initiative, which is directly aimed at translating basic science observations into clinically relevant new trials and at taking clinical problems and asking about their nature at the basic science level. (NCI 1992, p.56)

SPOREs, as an early policy intervention aimed at stabilizing an epistemic and institutional space known as TR, were important exemplars to be used in story lines about how the genomics revolution would re-configuration processes of clinical innovation. Section 5.1 and 5.2 provides a more detailed analysis of how SPOREs institutionalized

the narrative of sequencing-driven experimental medicine (as well as that of the plight of clinician-scientists and patient-oriented research).

The growing research possibilities offering by large-scale sequencing of tumour tissues can also be observed in the epistemic trajectories of individual oncologists. The trajectory of one of the first authors to make explicit use of the concepts of TR, C. Kent Osborne from the University of Texas and then Baylor College of Medicine SPOREs, provides such an instance. Dr. Osborne's earlier research from the end of the 1970s until the late 1980s was mainly conducted using in vitro cultures of breast cancer cells as well as animal models (Arteaga et al 1988; Osborne, Boldt and Estrada 1984; Osborne, Hobbs and Clark 1985). With the turn of the decade, however, his research increasingly draws on a third methodological stream. Namely, this stream consists of the sequencing of large-scale collection of tumour tissues, with an aim to elucidate the pathophsyiology of "oncogenes" such as p53 (genes that play a role in the growth and regulation of cancer cells) and the downstream hormones and growth factors they regulate (Allred et al 1992; Allred et al 1993; Osborne and Arteaga 1990).

Other commentators elsewhere also argued for similar partnerships between the fundamental and the clinical laboratories. Emerging technologies often allowed to make a statistical association between a certain gene mutation and a disease, but the mechanistic understanding of the aetiology of the disease often remained obscured, and complex, difficult work in its own right. Advances in sequencing technologies were thus hoped to prompt biologists and physicians to come together in trying to make basic science investigations relevant to clinical innovation (Lamm 1992).

4.2.2 Tacking stock of the mapping

The publication of a working draft of the HGP in 2001 and even more so with the complete version of the mapping in 2004 seemed to have decisively intensified excitement for TR (a 2005 editorial in *Nature Reviews Drug Discovery* mentioned "all the hype surrounding translational research" – Nature Editorial 2005, p. 613). This section will focus on editorial material published in specialized periodicals between 2000 and 2007. This material shows how a policy narrative of TR pertaining to the development of post-genomic platforms in clinical contexts became a major force for providing collective direction and research programmes in the biomedical field at that point. Earlier efforts at using human tissue typing, such as those in oncology discussed above, became pioneering studies in a whole area of research using high-throughput post-genomic platforms at the interface between the experimental molecular biology laboratory and clinical care and clinical research.

An agenda for TR focused on the clinical development of post-genomic platforms was most powerfully advocated by the leaders of the HGP themselves, Francis S. Collins, Eric Green and other high-ranking scientists at the National Human Genome Research Institute (NHGRI; Collins et al 2003). In an article titled “Vision for the future of genomics research” and published in *Nature* in April 2003, these leaders set out a comprehensive research programme for ensuring that the HGP as a scientific accomplishment would be marshalled to lead to further advances in biology, medicine and society more broadly.

This agenda certainly put forward the activities of the NHGRI, and as such, can be considered to make explicit the implementation strategies for the fully formed policy narrative of genomic medicine. At the same time, however, these activities are also presented as exemplars for research teams everywhere to follow. The document clearly aims to propose collective goals for the biomedical community and provide powerful rationales for supporting these aims.

In their priorities for TR, Collins and colleagues focus on clinical innovation projects that can readily draw on the tools that have been developed as part of the HGP: high-throughput sequencing and bioinformatics analysis, most notably. In the section of the document concerned with the “translation of genomics to health”, heavy emphasis is put on determining the contribution of genetic factors to disease aetiology and its course in human physiology. Mention is also made of the possibility to generate drug targets and draw on post-genomics platforms to help devise new therapeutics, but the focus here is certainly more on the side of prediction and diagnostic.

4.2.3 Reaching a threshold?

The arguments reported on in the previous section called for even greater attention to be devoted to genetic entities to explain human disease. In the wake of this intensified articulation of collective policy and research goals surrounding the completion of the HGP, commentators posited that the brute existence of this great deal of new knowledge in the genetics of human (patho)physiology could only lead to translational developments. While the literature advocating for these interpretations seldom back them with extensive analysis, the influence of these arguments has nonetheless been considerable. A year before the publication of the final version of the sequence produced by the HGP, a life sciences consultant thus explained in the following terms what he envisioned the near future of biomedical research to be:

> The emerging interest in translational activities is not surprising, given the success of the Human Genome Project (HGP)... In the wake of the HGP, it is evident that the time required for completion of what until recently were considered heroic projects (e.g., positional cloning, genome sequencing,

> etc.) has been substantially shortened and that an increasing number of the traditional tasks of molecular genetics have become trivialized... Another driver for translational research is the acknowledgement that the essential component of the funding thesis for the HGP has been the promise of its direct and tangible impact on human health, and it logically follows that promoting such activities should lend additional credibility to the ongoing effort (Duyk 2003, p. 603).

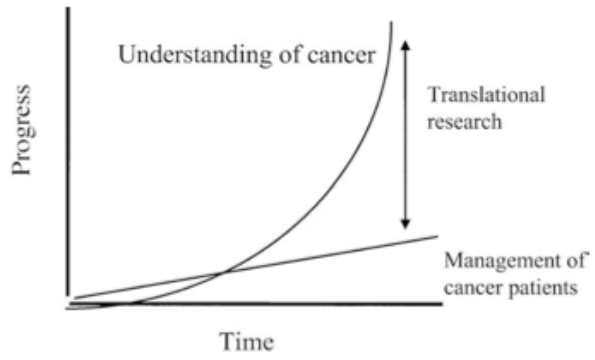
The first part of the quote above usefully provides some details as to what kind of experimental or organisational practices it is that the HGP results allow, and that have the potential for drastic changes in how clinical innovation takes place. Here, it is the development and automation of experimental technologies that promises to help reduce the complexity of human (patho)physiology by providing the possibility to greatly increase the amount of information generated by a given experimental protocol. Here one then finds a belief of clear "technological breakthrough" that, if diffused, would allow investigators everywhere to engage in what would previously have been long-winded TR projects. The second part of the quote reminds us that technological and scientific claims leave traces behind them. Biomedical researchers may indeed have felt a responsibility to try and make good on the promises of clinical innovation made as part of the HGP. This sense of responsibility may also be felt in calls made in the literature to increase accountability through greater collective control over the conduct of TR projects, although this particular point will be examined in greater detail below in subsections 4.2.7 and 5.2.

Coming back to our main concern, the claim that the completion of the HGP inaugurates a new era of clinical innovation-oriented work in the biomedical field is widespread in the documentary record on TR. Some emphasize the "maturity of basic science" (Ioannidis 2004), implying that biomedical innovation work was difficult and necessarily of a trial-and-error character in previous times when fundamental work could only provide limited guidance to developers of new interventions. With the advances in molecular biology, however, development work is then bound to proceed more rationally. Elsewhere, we learn that „[t]ranslational research embracing a continuum of investigative approaches will probably expand very rapidly as a result of the overwhelming amount of information generated by the human genome program" (Schwartz and Vilquin 2003, p. 493). Others authors characterize current medicine as „post-genomic, translational" (Stratakis 2005, p. 38) making practices of TR appear to derive entirely from genomic advances, instead of drawing on longer-running traditions of "patient-oriented research" that the narrative presented in section 4.1 instead foregrounded.

4.2.4 The HGP as stepping stone rather than peak

Of course, repeated claims that exponential advances in molecular biology must lead to corresponding changes in clinical innovation can also lead to more acute problematisation rather than clearer ground for collective action. Indeed, if a common reason for arguing about the need for a domain of practice such as TR is the perception of a gap between the production of formal knowledge and outputs in terms of clinical innovations, then an achievement such as the HGP might have drastically increased the gap rather than contribute to its closure. Already in 2001, as the HGP was nearing completion, commentators were noticing how biological knowledge had advanced exponentially while clinical management improved in a linear manner (Bast, Mills and Young 2001). Figure 4 below provides an elegantly simple, and thus striking example, of these interpretations:

Figure 4: The translational gap



Source: Bast, Mills and Young 2001, p.565; used with permission from Elsevier Paris

As the years went it, a multitude of authors seemed to become aware of the potential strain on current research agendas that the inability to fulfil in the short term past promises regarding the clinical potential of sequencing platforms. Accounting for these unpredicted difficulties, commentators positioned TR as the very domain of practice concerned with making sequencing technologies relevant to clinical contexts:

> Advances in 'omics' technologies (genomics, transcriptomics, proteomics and metabonomics) were touted as having the potential to revolutionize our approach to disease diagnosis, prognostication and development of novel therapeutics. However, the promise of rapid advances in medicine 'from the lab bench to the bedside' has not manifested as of yet. Indeed it appears that the translational application of genomic-based research have preceded the development of (*i*) a conceptual framework for disease understanding, (*ii*) effective tools that can exploit the vast amounts of data derived from these efforts and (*iii*) a process to systematically move the products of

> basic research towards standardized, reproducible, clinical diagnostic tools (Billelo 2007, p. 133).

One can thus identify another group of authors who hold that evolution in understanding of the molecular basis of diseases has generally not been followed by major changes in clinical practice (De Noo, Liefers and Tollenaar 2005). Yet, these commentators do not use this argument to discredit TR efforts revolving around the possible use of sequencing technologies in clinical innovation. Instead, they discredit previous efforts as purely "technology-driven", but leave space open for the possibility of more TR-inflected sequencing efforts. Here, the answer is then that more of the same is needed to finally reach the goal, with amendments to take into accounts the specificities of the clinical context. A coalition can be seen to be constituted around models of reform that advocate the recognition of a specific and pivotal domain of practice in the expansion of sequencing platforms to areas traditionally designated as "patient-oriented research" or "experimental medicine".

To accomplish these goals, institution building and special training programmes may be required: „[t]o educate the leaders of a new era in which basic science discoveries will be increasingly converted into useful products, we need to expand curricula and programmes around an expanded context of what is becoming known as ‘‘translational research" (Schuster 2007, p. 155). TR is presented in this article as a kind of engineering science that draws from the pool of basic knowledge created by molecular biology to come up with a series of prototypes of health interventions. The second task of TR efforts is to select and develop those prototypes with the most potential to become fully-fledged clinical innovations, in an efficient manner (Sultana, Roblin and O'Connell 2007, p. 419):

> "For translational research to be successful, a two-way dialogue between scientists and clinicians is necessary, to foster cooperation towards common goals and the setting of complementary strategies, whereby work in one area informs efforts in the other. Translational research enables researchers to capitalize on recent technological breakthroughs and advances in basic sciences, such as the mapping of the human genome, the availability of techniques such as proteomics and metabolomics that enable the detection of small changes in tissue composition, and improvements in imaging platforms that enable a better understanding of the functional changes in normal and disease states. This greater understanding, in turn, facilitates the identification of new targets and the development of linked animal models and clinical biomarkers that can be used to increase confidence in rationale in the preclinical and early development stages. This is particularly relevant with unprecedented drug targets; discarding ineffective mechanisms early on enables more efficient use of resources and better-focussed efforts on targets that are more likely to deliver effective medicines".

Sultana and colleagues provide a concise snapshot of the kind of toolbox on which post-genomic TR can rely on to accomplish its mission. Techniques in imaging (obtaining visual readouts of (patho)physiological mechanisms in the human body using radioactive grafts to chemical or physiological substances) and biomarker deployment are felt to offer ever finer readouts of drug action in the human body, consequently allowing the development of correspondingly sophisticated interventions. These sophisticated interventions include targeted agents that are developed with the full knowledge and supporting evidence of how their action of a (patho)physiological pathway the mechanism through which therapeutic effect is achieved (Yap et al 2010). As the quote also makes clear, this TR toolbox is ideally operated in cooperation between fundamental biologists and clinicians, although here no elaborate rationale is given for this partnership, of the type that might have been found in the policy narrative of the plight of clinician-scientists. Sultana and colleagues were members of the 'Global Research and Development' unit at the Pfizer laboratories in Sandwich in the UK at the time they wrote this particular article. Sequencing-driven experimental medicine approaches also can consequently be seen to reshape research strategies in the industrial as much as in the academic sector.

4.2.5 An alliance between sequencing and clinical research

The contention that the establishment of a domain of practice that combined the best of the sequencing technologies and of clinical research and experimental medicine was given major endorsement in official NIH policy at the beginning of the 2000s. The NIH elaborated and presented in 2003 a Roadmap that highlighted its preferred approaches to the collective appropriation of sequencing technologies for clinical innovation purposes (Zerhouni 2003). This exercise offers an interesting contrast to the vision elaborated by Francis S. Collins and colleagues at almost the same time. It provides space for the establishment of TR as an approach that draws on the sequencing technologies but becomes a relatively autonomous area of investigation with its own history, rather than making it purely an extension of the bioinformatics-driven genomic paradigm and the tradition of clinical genetics and cytogenetics that came before it. Elias Zerhouni, then new NIH director, establishes a TR agenda for his institution in the following words:

> Although the sequencing of the human genome presents vast opportunities for researchers, it also creates a series of challenges that will redefine the ways that medical research is conducted and, ultimately, how research leads to improvements in health… Solving the puzzle of complex diseases, from obesity to cancer, will require a holistic understanding of the interplay between factors such as genetics, diet, infectious agents, environment, behavior, and social structures. To devise and use the state-of-the-art technologies developed from the roadmap effort, we will need the expertise of

> nontraditional teams of biological scientists, engineers, mathematicians, physical scientists, computer scientists, and others. (Zerhouni 2003, p. 63 and 64).

Zerhouni makes a clear connection between advances in molecular biology and genomic sequencing more specifically, and the necessity to establish new tools and experimental platforms to be able to make use of these achievements in the specific context of clinical innovation. The composition of translational teams that Zerhouni envisions illustrate the belief that the common TR projects will have to deal with a high level of complexity that it will only be able to tackle in a "holistic" manner – thus also justifying intensive efforts to engage in institution building at this site of biomedical experimentation. Indeed, the argument here seems to be that TR is increasingly proving to be a complex scientific project in its own right. TR can no longer be appropriately supported "by proxy", through support to fundamental research, on the one side, and to clinical research, on the other side. We collectively have to boost investments in the " broken middle of the pipeline" (Mittra 2012), or so the argument went, if we want sequencing technologies to be relevant for clinical innovation. In this sense, then, it became a common figure that there were strong peaks of activity in fundamental research, on one site, and in late clinical research and clinical care, on the other hand, but that intensified biomedical innovation would necessitate a strong connection – a "bridge" – between those two sites, as a fully fledged area of inquiry.

These arguments were also clearly to seen in the formal consultation processes that have lead to the formulation of the NIH Roadmap. In advocating for the establishment of TR as "middle field" of experimental work, a joint group of five health policy organisations forcefully make the case that improvements in clinical research infrastructure and organisation is necessary to marshal the possibilities of post-genomic platforms:

> "The importance of clinical research in translating the vast knowledge emanating from basic science efforts, such as the Human Genome Project, cannot be overstated. As the result of a wide spectrum of developments in the biomedical sciences, extensive research can now be done on the pathogenesis and (patho)physiology of human disease. In addition, new developments in imaging provide novel approaches to understanding the health and disease states in humans. As described in Chapter 3, the challenge for clinical research is that most common diseases are complex, multietiologic disorders in which a multiplicity of genetic and other factors interact with each other. As a result, clinical research is faced with the complex challenge of identifying the resources, intellectual capital, and large cohorts of patients with appropriate phenotypes for studies. It will take a revitalized investment in clinical research, including many large-scale trials, to figure out how to tie together all the factors that contribute to particular diseases" (Committee on the Organizational Structure of the National Institutes of Health et al 2003, p.74).

For certain TR advocates, these efforts should be organised within a distinct discipline that bring clinicians and biologists together, with an associated re-organisation of academic departments and research facilities to allow this (Pober, Neuhauser and Pober 2001). Likewise, Duyk contends that the main obstacle to success in TR is failings in efforts to provide "clear chains of causality that would effectively link genetics to physiology" (Duyk 2003, p. 604). Genetics and physiology need to be reconciled to come up with a predictable translational research model. This means, for Duyk, moving collective attention (and the consequent attribution of prestige) away from solely reductionist investigations into molecular mechanisms to obtain more "systematic and comprehensive" mechanistic understandings of the action of drugs in human systems for example (Duyk 2003, p. 604):

> "Research in human subjects remains the cornerstone of our efforts to link genetics to physiology. We need to invest in clinical researchers and clinical research centers in order to both drive and support translational research... Like physiological and pharmacological research, experimental medicine efforts have lagged in investment and prominence during the emergence of molecular genetics and genomics, and this is another trend that needs to be reversed" (Duyk 2003, p. 604).

The research programme that has been articulated in the narrative of sequencing-driven experimental medicine also calls for new practices of clinical research. Clinical development of targeted agents or the discovery and validation of new biomarkers calls for new or modified designs of clinical trials. Clinical studies may also increasingly make place for close collaborations with laboratory-based teams so as to elucidate questions that may appear as part of a clinical investigation (Lacombe, Passioukov and Hill 2003; Lehmann et al 2003; Rüegg et al 2003). Such "investigator-initiated clinical trails [sic] with appended mechanistic basic science studies" were susceptible to increase the legibility of clinical spaces to rationalistic inference at the molecular level (Sartor 2003, p. 1178). The coalescing alliance between the sequencing agenda and clinical research led to novel developments within this socio-technical system, such as new professional trajectories for "[la]boratory investigators complementary to clinical investigators" (Lacombe, Passioukov and Hill 2003, p. 308). More recently, new developments in "biology-led clinical trials" re-shuffle the roles and alignment of clinical practice and laboratory investigation in early studies with human subjects, transforming them into complex experimental platforms (Hoelder, Clarke and Workman 2012).

4.2.6 Troubled anniversaries

At the time of writing these lines, arguments calling for intensified efforts to extract value from the mass of sequencing data and high-throughput technologies available were given additional urgency when the term of validity for the promises made around

the HGP very publicly came to expiration with the 10th anniversary of the completion of the first sequence draft. Indeed, since speed and automation in laboratory procedures were touted as one, if not the major achievement of the HGP (following Fortun 1999), it might be legitimate to ask why the development of clinical innovations that draw on the post-genomic platforms is going so slowly. This is not only a question that critical social scientists are susceptible to ask, but rather something that a broad stratum of actors related to biomedical field seems concerned with. A 2010 article from the *New York Times* noted the 10th anniversary of the first draft with an article whose title transmitted a clear feeling of pique in the broad community of biomedical innovation observators: „A Decade Later, Genetic Map Yields Few New Cures - The primary goal of the $3 billion Human Genome Project — to ferret out the genetic roots of common diseases and generate treatments — remains largely elusive".

While there may be renewed (or simply ever mounting) urgency of bringing clinical value out of genomic advances, proposals for reform or collective actions do not seem to have changed drastically in the last few years from those already explored above. Yet, it is not useless to look at recent iterations of the policy narratives, as prominent advocates are even more strikingly clear about how they envision sequencing technologies to contribute to human health, no doubt against a background of fragilized support for the approach.

The journal *Nature* thus published a series of reviews and commentaries by US leaders of HGP and post-genomic initiatives to commemorate the 10-year anniversary in February 2011. Eric S. Lander from the joint MIT and Harvard Broad Institute, an outspoken leader and advocate of genomics agenda, made a thinly veiled reference to the *New York Times* story mentioned above as a departure point for what he presents as a more level-headed assessment of the impacts of sequencing technologies over the last 10 years. Mostly, Lander supports his argument about the positive impact of these efforts by invoking the gains in automation and "experimental productivity" provided by sequencing technologies. He provides figure to show how little was known on a number of monogenic and multifactorial diseases in the 1990s. Post-genomic sequencing technologies had allowed to identify more than 2,850 disease genes for monogenic conditions (compared to the 100 known at the time of the HGP launch). Similarly, about 1,100 loci for 165 genetic traits involved in common diseases had been identified mostly since 2007, when little was known at all in this regard previously. Moreover, Lander repeated the argument that sequencing technologies had allowed a qualitative jump in biomedical experiment by moving away from "guesswork about the underlying chemistry" (Lander 2011, p. 191) to an approach increasingly based on knowledge of (patho)physiological mechanisms. Taking cancer as an example, he maintained that a

continued agenda of detailed, systematic sequencing would provide the best route to clinical innovation:

> To guide therapeutics, we must develop over the next decade a comprehensive catalogue of all genes that are significant targets of somatic alteration in all human cancer types, all animal models and all cancer cell lines.
>
> The patterns of mutated genes will: (1) define direct drug targets in some cases; (2) identify cellular pathways and synthetic lethal interactors to target in others; (3) direct the creation of animal models; (4) allow chemical screening against cancer cells with defined molecular mechanisms; and (5) guide the design of human clinical trials (Lander 2011, p. 194).

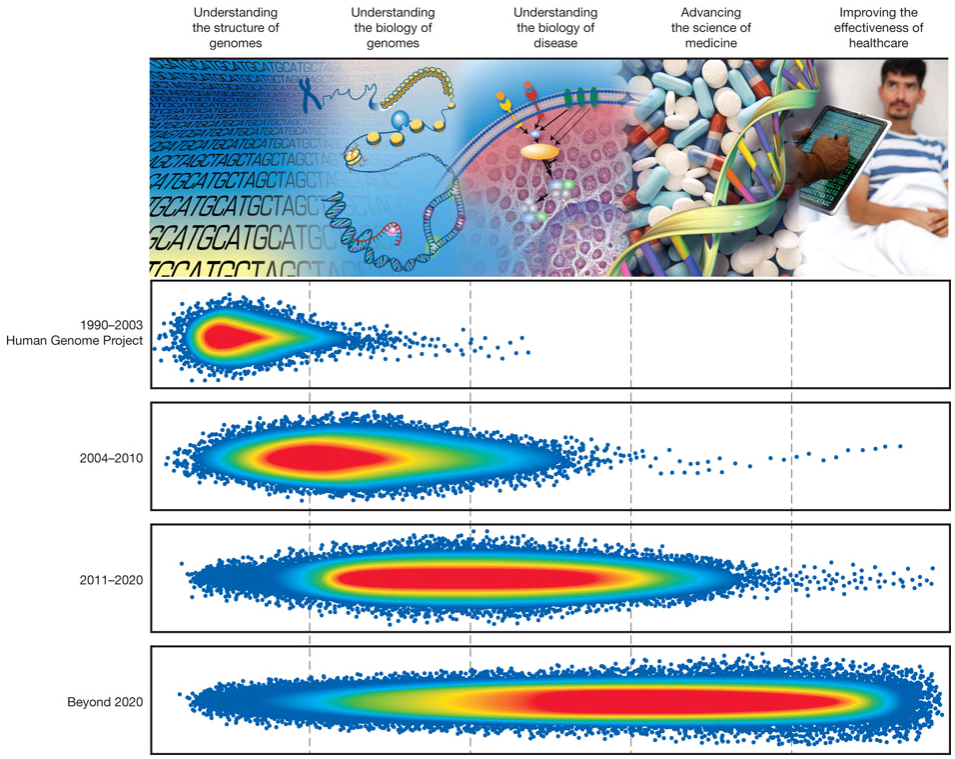
The argument here is eerily close to the one previously employed to justify the launch of the HGP: an extensive catalogue of genetic mechanisms as the obligatory passage point for any efforts at rational therapeutic research.

Another article published in the same *Nature* series aims for "[c]harting a course for genomic medicine from base pairs to bedside" (Green et al 2011). One can notice first how the formulation of the title picks up on the most common trope of TR narratives. The article then goes on to predict some ways genomic knowledge will impact clinical practice, including stratification in clinical trials, pharmacogenomics, and so forth. The graphic below shows the various stages of this process of genomic extension into clinical settings, as it was presented in this article. If anyone still had expectations of short terms benefits for medicine based on advances in sequencing platforms in the wake of the HGP, then this figure, authored by leading voices in the field, might be set to change their tune. "[I]mproving the effectiveness of healthcare" is instead recast as a long-term, sometime "beyond 2020" goal.

Other commentators simply held that post-genomics sequencing platforms did not, in of themselves, provide direct ways towards clinical innovation. Instead, they automated a certain number of operations, but the central problem of explaining (patho)physiological mechanisms remained important. According to David Baltimore, a 1975 Nobel laureate and a professor at the California Institute of Technology:

> „The major challenges to translating genomics into medicine are to figure out which genes are important in which diseases and why. There are countless efforts going on worldwide to associate particular genes with particular diseases where the underlying cause of those diseases is not clear. … That is going slowly because we're finding too many genes — many diseases are associated with 20, 30, or 40 genes — and that makes it difficult to know how to focus therapeutic development" (cited in Dublin 2010).

Figure 5: "Schematic representation of accomplishments across five domains of genomics research"



Source: Green et al 2011; Reprinted with permission from the Nature Publishing Group

Mechanistic understanding of human physiology and pathology are thus proving to be slippery goals. Indeed, in 1996, then Hoffmann-LaRoche director of global R-D Jürgen Drews reported estimates by a colleague that complex disease phenotypes could typically traced back to the risk contributions of between 5 and 10 genes (in addition to environmental contributions – Drews 1996). The discrepancy between the figures invoked in the 1990s and invoked at the beginning of the 2010s is far from trivial. It seems here that technology and the complexity of the human body have caught up to the hopes and rhetoric of the promoters of genomics approaches, necessitating constant management of hype and promises to rescue a deeper foundation of hope (Kitzinger 2008; Van Lente, Spitters and Peine 2013). In turn, this need for sustained management of collective hype and hope would also bring incremental modifications and amendments to the problematisation of post-genomic platforms' contribution to clinical innovation.

4.2.7 Auditing the gold rush

The subsections above have explored arguments that technology-driven efforts were the best means to achieve translational output. My empirical material shows that there

is another strand of discourse that should be related to this policy narrative, while focusing much more on organisational and indeed governance parameters of innovation. Indeed, in this specific constellation of the policy narrative of sequencing-driven experimental medicine, the kind of mechanistic understanding made possible by advances in molecular biology now offer unique tools for the coordination and management of translation projects.

A widely discussed effort in this respect has been the model developed by Muin Khoury of the Public Health Genomics unit at the US Centers for Disease Control and Prevention (Khoury et al 2007). Khoury and colleagues have conceptualized the translation process for sequencing-based diagnostic and predictive tools as a continuum that can be roughly disaggregated into four steps of development. In each of these steps, certain types of evidence about a given genotype-phenotype association should be generated so that its scientific validity and clinical appropriateness can be publicly validated and recognized. While the first steps revolve more around formal laboratory-generated knowledge, the later steps aim to take into account methods of delivery and diffusion of information about a specific intervention can shape its effectiveness in clinical contexts (see table 1 below). Based on this typology, the authors estimated that only 3% of research produced in genomic medicine could be classified as belonging to the later steps of the continuum.

Table 1: "The continuum of translation research in human genetics"

Table 1
The continuum of translation research in human genetics: types of research and examples

Translation research phase	Notation	Types of research	Examples
T1	Discovery to candidate health application	Phases I and II clinical trials; observational studies	Is there an association between *BRCA* mutations and breast cancer?
T2	Health application to evidence-based practice guidelines	Phase III clinical trials; observational studies; evidence synthesis and guidelines development	What is the positive predictive value of *BRCA* mutations in at-risk women?
T3	Practice guidelines to health practice	Dissemination research; implementation research; diffusion research Phase IV clinical trials	What proportion of women who meet the family history criteria are tested for *BRCA* and what are the barriers to testing?
T4	Practice to population health impact	Outcomes research (includes many disciplines); population monitoring of morbidity, mortality, benefits, and risks	Does *BRCA* testing in asymptomatic women reduce breast cancer incidence or improve outcomes?

Source: Khoury et al 2007, p. 666; Used with permission from Nature Publishing Group.

Khoury et al's proposal contains an organisational claim in that it calls for tighter a coordination between post-genomics researchers, one that would ensure that collective labour is more equally divided between different phases of the TR process. But there is more. The organisational claims mentioned above are steered and defined by the contention that only a fraction of research efforts are dedicated to crucial phases in "late

translation". Organisational reform is here crucially framed within logics of accountability and public evaluation of the relevance of research for civil society. I will briefly consider in the conclusion of this section how such argumentative practices relate to the broader expansion of regimes of accountability in contemporary societies. It is however useful to already take notice of the emergence of these novel practices at the intersection of narratives on the role of the sequencing enterprise in biomedicine, and proposals to steer research towards clinical relevance through the use of managerial tools and routines that increase the legibility (in the sense of Scott 1998) of individual project management to collective scrutiny. Further examples studied below will also show that the same planning schemes are made available and fashioned in the scientific literature as "self-help instruments", tools that the individual researcher might want to actively deploy in her experimental practice to increase its translational soundness and make an effective use of the public funding she draws on. In an interesting turn of events, models such as those by Khoury et al are now being systematically reviewed for potential usage in performance assessment exercises of individual cancer centres, for example (Rajan et al 2012).

Other translational accountability and evaluation tools have been elaborated with an even more explicit aim of tightly monitoring the evolution of TR projects. Martin Wehling, a professor of clinical pharmacology at the University of Heidelberg with past experience as director of discovery medicine at AstraZeneca, has thus been advocating the use of a "translatability scoring scheme" he has elaborated. One goal here is to reduce false starts and help decision making in TR projects. His ambitions would make the algorithm he developed a widely used tools in most TR projects:

> "Translational assessment of drug, device or diagnostic projects needs to be done from the start. It is therefore recommended to establish a translational medicine plan when a novel target is initially discussed, which details all the steps that are necessary for its development from early to late (clinical) stages... This certainly applies to commercial ventures, but should arguably also become a feature of academic biomedical research; for example, forming an essential part of funding applications in the public domain" (Wehling 2009a, p. 542).

The tool itself asks of its user to consider a variety of evidence sources that are relevant to the TR project itself to come up with a composite, predicative indicator of future success of a candidate drug. Evidence to be marshalled include that from animal models, tissue typing or clinical trials, as well as evidence of what we could call "managerial readiness" – that is, the sponsor for the intervention has adequately planned for biomarkers that may help validate his therapeutic hypothesis (see Table 2 below). With the scoring scheme found to have good retrospective success in determining failure or success of a number of drugs, Wehling highlights the desirability of a prospective exer-

cise potentially lead by a pre-competitive consortium of public and private actors (Wendler and Wehling 2012).

Table 2: "Proposal for scoring the translatability of an early drug project"

Table 1 | **Proposal for scoring the translatability of an early drug project***

Aspect	Weight (W: %)‡	Score§ (S: 1–5)	∑ (S xW/ 100)§	Typical features for weak score (1)	Typical features for strong score (5)
Starting evidence					
In vitro data, including animal genetics	2	5	0.1	Recently discovered, unconfirmed target; no genetic data	Well-studied target including *in vitro* genetic data
In vivo data, including animal genetics (for example, knockout models)	3	5	0.15	Physiological relevance unclear; no genetic manipulation or negative results	Physiological relevance uncovered; genetics manipulated, with supportive results
Animal disease models	3	5	0.15	No or weak animal models for human disease, as in many aspects of psychiatry, for example	Good animal model for human disease, for example, hypertensive rats
Data from multiple species	3	5	0.15	Only one species	3 or more species including primates; data fully consistent with each other
Human evidence					
Genetics	5	1	0.05	No genetic or epidemiological evidence of relevance	Strong evidence, especially for monogenetic disease and related targeting
Model compounds	13	5	0.65	No model compounds	Same target successfully treated in humans by congener or model compound
Clinical trials	13	4	0.52	No clinical trials so far	Strong, consistent evidence from clinical trials (for clinical development assessment)
Biomarkers for efficacy and safety prediction					
Biomarker grading	24	5	1.2	Biomarker distant to disease or no biomarker (see REF. 20 for details)	Biomarker is, or is almost, a surrogate end point (see REF. 20 for details)
Biomarker development	13	4	0.52	No development	Development started; high likelihood from existing data that biomarker grading will be improved
Proof-of-mechanism, proof-of-principle and proof-of-concept testing					
Biomarker strategy	5	5	0.25	Biomarker strategy does not reach beyond current stage of development — for example, human biomarkers are as yet unknown	Biomarker strategy covers all major aspects of even distant (clinical) development
Surrogate or end point strategy	8	4	0.32	No surrogates; end points require year-long megatrials in the disease area	Clear and accepted surrogates for end point studies (for example, low density lipoprotein–cholesterol levels for statins), or end points are easy to obtain in the disease area
Personalized medicine aspects					
Disease sub-classification and responder concentration	3	1	0.03	'Drug for all': no disease subclassification for responder concentration achieved	Predictors of clinical success are known, and responders concentrated
Pharmacogenetics	5	1	0.05	Impact of genetic variation on drug action and metabolism are unknown	Impact of genetic variation on drug action and metabolism are known and reflected in administration rules — for example, dosing
Sum	100		4.14		

*The individual scores are chosen between 1 and 5 and multiplied by the percent weight factors. Extreme scores (1 and 5) are described in the columns at the right. Any sum score above 4 is indicative of fair to good translatability. If no data are available, no score will be given in this line. 'Stoppers' (such as no or very weak evidence for animal effects) will be rated 0 and render the project 'untranslatable'. ‡Weight factors are independent of the compound in the test run. §Values reflect the author's assessment of a selected existing compound, and are included purely for illustrative purposes; the score of 4.14 indicates fair to good translatability.

Source: Wehling 2009a, p. 543; Used with permission from the Nature Publishing Group.

What this modelling tool substantiates is the co-production of biomarker development practices and collective frames for evaluating scientific uncertainty and commercial risk in biomedicine. Biomarkers are centrally important on an economic plane, because "[b]ased on biomarkers, pharmaceutical R&D has to take decisions worth 100-300 mil-

lion USD if e.g. investment in major phase III clinical trials has to be cleared" (Wehling 2009b, p. 6). Wehling also makes use of the argument for a need to increase the societal legitimacy of biomedical research, making it an impetus for the elaboration of these new accountability practices. In a colourful way, the clinical pharmacologist mentions how:

> "taxpayers might not tolerate expenditures of billions of dollars or Euros without measurable treatment improvement, especially in the light of surging public deficits… if biomedical research does not improve its utility and create an impressive track record of substantial innovations, biomedical research will be marginalised in competition for scarce resources, as climate changes, or energy shortages, create tremendous challenges to humankind" (Wehling 2011, p. 1077).

Wehling's interventions make it very clear to which extent some of the tools of "translational science" are being produced as solutions that simultaneously address the problem of ordering post-genomic scientific knowledge and the problem of ensuring the orderly and accountable use of increasingly contested collective resources (to use the phrase of Shapin and Schaeffer 1985).

Modern biology in its molecular instantiations has been characterized as particularly individualistic (Knorr-Cetina 1999), and it is because this state of things would hinder TR efforts that other commentators have advocated greater coordination of biomedical efforts and central leadership as the best mean to bring about increased innovation productivity in biomedicine. In its more simple form, this argument leads to demands for more interdiscipinarity in the vein already defended by Elias Zerhouni, and greater orientation towards clinical output. An example of this can be found in George Poste's recent grievances that biomarker research be more centrally coordinated and evaluated in a recent *Nature* piece. Poste is a leader of a large initiative for synthetic biology and sensor development at Arizona State University also involved in a molecular diagnostics company. He estimated that about 150,000 papers had been published proposing potential biomarkers, but that only 100 validated biomarkers were routinely used in clinical settings. The commentator portrayed biomarker research to be performed mostly at investigator-centred labs, with few resources and little multidisciplinarity. Instead, collaborative models should be used, involve multiple disciplines and institutions, we are told, a "coordinated systems-based approach" (Poste 2011, p. 156). One proposed way of achieving this is for funding agencies to actually demand that translational measures be devised when supporting biomarker-related projects.

4.2.8 Discussion

The potential of sequencing platforms in terms of reforming clinical research and directly contributing to clinical innovation activities has been argued along a number of

lines. First, work in classifying and characterizing tumour specimen in oncology using sequencing methods to process large collections of these tissues opened the possibility for new experimental approaches dealing with human material rather than cell cultures or animal models. In a second moment, as work surrounding the HGP, and later post-genomic sequencing platforms, pushed forward, proposals for collective action were also articulated around the perceived potential of sequencing platforms as process innovations in the clinical research sector. In parallel to this, sequencing technologies were argued to be central component in envisioned future interventions such as pharmacogenetics or predictive and susceptibility testing.

What kind of discourse coalition would participate in the articulation and reproduction of this policy narrative? As can be attested by the success of molecular biology and genomics tools in contemporary biology and biomedical research, a vast number of investigators make theirs the basic premise that these approaches are the best means to achieve deep understanding of (patho)physiology. Here then, there is much less of a clear pattern in terms of professional, disciplinary or organisational affiliation that may help explain individual association with the narrative. It is possible, however, to say that the leaders of large-scale sequencing initiatives have been particularly active in setting up collective priorities and agendas. These leaders have tended to be very close to the technology development end of the field.

In the case of the two other policy narratives of TR that are our focus here, their emergence can be clearly traced back to foundational argumentative interventions that established the parameters of a durable problematisation of the biomedical innovation process. Interestingly enough, the policy narrative of sequencing-driven experimental medicine initially emerged more on the strength of its model for collective action rather than any particular reading of an urgent set of issues. It seems that the technological promises that would follow from concerted action on the development of sequencing platforms opened up their own horizon of desirable collective outcomes, addressing only in the most general way crosscutting problems in the application of biomedical research to clinical intervention. Even more interestingly, however, this initial model of collective action did give way to more defined problematisations as the 1990s and especially 2000s went by. By the mid 2000s, there was general consensus that sequencing-driven systems for TR would need to be achieved through major further experimental and institutional efforts. This renewed problematisation did not necessarily lead to a new model of collective action. As shown above, instead, minor amendments were made to the agenda, but the central directive remained that more sequencing would eventually lead to a threshold in mechanistic understanding of (patho)physiology, in turn allowing for game-changing rationalistic approaches to clinical innovation.

This interesting temporal turn in the parameters of the policy narrative can perhaps be framed against the logics of speed, whose prevalence in the genomics field Michael Fortun has previously highlighted. Could it be that the claims related to the achievement of exceptional speed within sequencing projects might have also been transferred to contexts of evaluations of their clinical outputs? In other words, expectations of speed in terms of technological automation, and thus as a process innovation, might have unintentionally contributed to building expectations of speedy impacts on clinical innovation activities. Because of this, it might have become necessary, through the argumentative practices detailed above, to re-calibrate the parameters of the problematisation, and engage in the management of both hype and disappointments produced by previous expectations (Kitzinger 2008; van Lente, Spitters and Peine 2013).

Another recurring argument I have come across in reviewing the empirical material presented above concerns the capacity of sequencing platforms to allow for a special kind of deeply mechanistic rationality about (patho)physiological knowledge. Throughout the sample of documents consulted, a central contention has been that a qualitative threshold would be reached through the quantitative exploits of sequencing technologies. This assumption then informed other plans for desire reforms to institutional and experimental practices of clinical innovation. Of all three dominant policy narratives I have identified, sequencing-driven experimental medicine is the one best positioned to legitimately associate itself a form of mechanistic rationality. By presenting it as the current cutting edge of molecular biology approaches, which themselves have historically emerged from the migration of physicists to the life sciences (Strasser 2002: Abir-Am 1982), advocates of the sequencing-driven experimental medicine narrative can wrap their contentions and benefit from what one might call ‘spill-over authority’ from these forms of knowledge.

Finally, another point of interest that has emerged here is how the central concern for fostering rationalistic clinical innovation routines through sequencing platforms has intriguingly mixed with arguments about the rational organisation of the enterprise of innovation itself, and the use of auditized evaluation practices (in the sense of Power 2007) to achieve this goal (section 4.2.7). I will discuss at later stages the implications of this development. Its consideration already helps to delineates the precarious space that advocates of the sequencing-driven experimental medicine narrative try to carve out for themselves: highly dependent on epistemic content and technological input from fundamental bioinformatics and –omic sciences, yet hopefully distinct in having its own research programmes and collective criteria for evaluating what constitutes legitimate scientific activity.

4.3 Crisis in the pharmaceutical industry and the emergence of academic drug pipelines

This section examines a strand of arguments that have evolved into the third major policy narrative of TR I have identified. This particular narrative first offers a problematisation of a perceived state of crisis in the pharmaceutical industry specifically. Industry analysts, including consultant and journalists, have drawn on data of profitability and costs of innovation in the pharmaceutical sector since the early 2000s to increasingly advertise an analysis that top firms were heading towards an acute crisis. This crisis would threaten thousands of RTD jobs and the development systems on which current expectations of future therapeutic benefit are built on. To put it simply here, data have been marshalled showing how the cost of developing new drugs is rising exponentially for pharmaceutical companies, at the same time as 1) the rate of new innovative agents being discovered and commercialised is stable or decreasing and 2) a number of blockbuster drugs providing firms with millions of dollars in revenues are due to fall off patent, and are not expected to be replaced by new blockbusters.

With an aim to address this issue, filling gaps in the biomedical innovation system and opening new opportunities for academic health research centres, some TR advocates have argued that this situation of crisis has to be met with intensified therapeutics discovery and development efforts in public research institutions. Offering a slightly different spin on TR centres, “Academic drug discovery units” and “academic pipelines” are being presented as privileged solutions to the problem of the pharmaceutical crisis. But developing these centres is not trivial, as it might imply the implementation of large-scale equipment, as well as collaboration and management methods previously thought reserved to the private sector and antagonistic to academia.

4.3.1 Pricing controversies and innovation deficits: a long history of pharmaceutical industry woes

I situate the important shift in discourse on pharmaceutical innovation towards the themes of crisis and the need for academic drug development around 2002-2004. Yet, it is also important to frame these discursive developments in relation to a more ancient repertoire of contentions about the exceptional situation of the pharmaceutical industry in post-industrial economies.

Dominique Tobbell (2012) has shown in *Pills, Power, and Policy* that the pharmaceutical industry has long argued that it is in an exceptional position of economic risk due to the high uncertainty and lost investments associated with drug RTD. This claim has been used as a rationale justifying various privileges the industry has traditionally en-

joyed, notably in terms of intellectual property rights, to audiences of patients, consumers, pharmacists, health policy makers, medical schools and elected representatives. In the story traced by Tobbell, it is the issue of pricing that gives rise to a clash between partisans of containing the pricing of innovative drugs for patients and consumers, on the one side, and an alliance of pharmaceutical firms and academic physicians with interest in protecting or increasing private and public funding in RTD activities, on the other side. What Tobbell shows is that the pharmaceutical industry was already arguing in the 1950s and 1960s that its business was tied to an exceptional amount of financial risk through RTD projects. Industry representatives and academic medicine leaders were able to successfully argue to successions of Congress-mandated committees in the USA that restricted pricing of medications would damper the innovation capacity of pharmas, and put the whole nation in jeopardy in the scientific race against the Soviet Union. Scientific uncertainty and its impact on commercial risk and innovation productivity have thus long been central arguments used by the pharmaceutical industry to ground its demands and grievances (see Pisano 2006 for a more detailed analysis of current discussions).

Various iterations of these arguments can be observed since the period analysed by Tobbell. More recently, Jürgen Drews, the Hoffmann-La Roche RTD leader and commentator already introduced in section 4.2, started discussing an “innovation deficit” in various biomedical and pharmaceutical trade journals in 1996 and onwards. He mentioned the issue of an “NCE gap” (NCE standing for new chemical entity) in a *Nature Biotechnology* article of 1996. There, he made the observation that in order for the industry to maintain its previous growth rate of 10% per year, the top 50 firms in the sector needed to collectively produce 42 NCE per years. Yet, Drews estimated that only 10 NCE would be produced annually in incoming years by these firms, and that NCE candidates provided by the biotechnology industry would not allow the figure to rise to 42. As such, this data provided indications that the “the growth expectations of the industry” would possibly not be met in the near future (Drews 1998). A later study of NCEs produced by the industry in 1996, 1997, and 1998 confirmed that the annual production of the top 50 pharmaceutical firms was less than 1 NCE per year, while showing that the biotech industry’s contribution of leads had been more modest than expected. Most importantly for what was to come, however, was a small paragraph that noted how RTD expenditures in the industry had started to grow over between 1988 and 1998, passing from an estimate of 15 to 20 billion US $ to 27 billion US $. Drews calculated that this brought the cost of developing NCE to 750 million US$ each (Drews 1998). Although Drews did not develop an elaborate argument based on these figures, and the RTD director’s interventions between 1996 and the early 2000s were mostly concerned with prospects of reduced profits for the industry. Yet, the observations he

made provided early building blocks for a policy narrative that would articulate diminishing innovation outputs in parallel to increasing RTD expenditures as the causes of a crisis in pharmaceutical productivity. When this problematisation stabilised, TR became a core concept to argue about collective solutions to the crisis.

Part of the concerns at that point in fact relate to developments in the area of sequencing technologies. There was some fear that the integration of the post-genomic experimental platforms as drug discovery tools may not run smoothly, and that the sector might have to suffer through a transition period as more established sources of innovations simultaneously dried up (Tollman et al 2001). Elsewhere, a 2002 study by Pfizer bioinformaticians concluded with the prediction that the genome mappings would not fundamentally alter the landscape of small molecule drug discovery, mostly because the new drug target provided by these tools would not easily conform to existing socio-technical routines of drug development and delivery in actual health care settings. As such, the authors concluded that "to exploit the opportunity of the druggable genome in a cost-effective manner, the next round of innovation for the pharmaceutical industry lies not necessarily just in the science, but also in the business models" (Hopkins and Groom 2002, p. 730). This idea that restructuration of the industry would be necessary to tap into the post-genomic platforms received support through a number of venues (Tollman et al 2001: Schmid and Smith 2005). As such, the specific reception of the narrative of sequencing-driven experimental medicine in the pharmaceutical industry was partly reshaped to account for specific concerns regarding business calculus and the specificities of incumbent experimental platforms that were mostly based on medicinal chemistry.

4.3.2 The cost of a drug

In 2002, *New York Times* journalist Andrew Pollack titled an article with the contention that "Despite Billions for Discoveries, Pipeline of Drugs Is Far From Full" (Pollack 2002). Pollack drew from yet unpublished figures from the Tuft Centre for the Study of Drug Development to show that the price of developing one single drug had more than doubled since between 1991 and 2003. Pollack also argued that advances in the HGP and in molecular biology, as well as in combinatorial chemistry, the toolbox of modern chemical approaches used to design and optimise therapeutic agents, had raised expectations which had yet to be met by pharmaceutical innovation output. It is worth to provide a lengthy quote from this article here:

> This should be the golden age for pharmaceutical scientists. The deciphering of the human genome is laying bare the blueprint of human life. Medical research has increased understanding of disease. Robots and computers are turning drug discovery from a mixing of chemicals in a test tube to an industrialized, automated process.

> Yet if industrialization normally means higher speed and lower costs, the pharmaceutical industry has been experiencing the opposite -- a "clear fall in productivity," according to Dr. Frank L. Douglas, the chief scientific officer of Aventis. Instead of narrowing the list of compounds that might be useful in drugs, automation has broadened it -- greatly increasing the number of formulas tested without yet delivering commensurate growth in safe and effective drugs. The industry's output of new drugs has risen only modestly in the last two decades despite a more than sixfold increase, after adjusting for inflation, in research and development spending, to more than $30 billion annually. In the last few years, the output has actually declined...
>
> The perceived paucity of new drugs in company pipelines has become a preoccupation of the industry and of Wall Street. Bristol-Myers Squibb, Merck and other drug makers have said earnings will be lower than expected this year, in part because there are not enough new products to offset declining sales of old ones that lose patent protection and face competition from generic versions...
>
> With drugs not coming fast enough to sustain the double-digit growth in earnings and revenue that Wall Street has come to expect, more companies might merge, to bolster earnings through reduced costs, analysts say (Pollack 2002, p. C1).

A number of major observations usually brought together to diagnose a crisis in pharmaceutical innovation productivity are all mentioned in these few lines. This quote shows that there were already concerns at that time concerning the renewal of revenue-rich patented drugs. The last part of the quote again shows, however, that there is no prospect yet of a crisis that might dramatically downsize pharma innovation activities, but that the concern is rather with maintaining “double-digit growth in earnings and revenue” to please investors.

Part of the data that Pollack based his assessment on was later published in an article in the *Journal of Health Economics.* There, members of the Tuft Centre for the Study of Drug Development provided an elaborate quantitative study to come up with a simple figure. The authors had estimated the cost of developing a new drug, including costs engaged in failures for other drug, at 231 million US $ in 1987, in an earlier study (DiMasi et al 1991). In 2000, the costs had risen to 802 million US $ (in dollars respective to each year - DiMasi, Hansen and Grabowski 2003).

In their paper, DiMasi, Hansen and Grabowski are careful not to draw too many conclusions from these figures. They discuss broader development in the pharmaceutical sector only minimally. The paper is argued to be relevant to discussions on cost containment of health expenditures, thus making a clear connection to the kind of debates that Tobbell and all referred to. Also, even at that point, there had been criticism of the methodology used by the authors, which relied on self-reported figures provided by

pharmaceutical firms obtained through a survey (Pollock 2002; see also Light and Warburton 2011 for a critical review of the debates surrounding these figures).

Yet, the findings by DiMasi and colleagues crucially shifted the arguments being made about potential pharmaceutical industry issues. Other commentators picked up the figure of drug development costs and quickly argued that industry might be in big trouble. The paper became very highly cited very rapidly. In December 2012, when I checked the figures in Scopus, the 1996 and 1998 papers by Drews on the "innovation deficit" had been cited 40 and 31 times each, respectively (Drews and Ryser 1996; Drews 1998). In contrast, the DiMasi, Hansen and Grabowski paper had been cited 1287 times, 109 times alone in 2003 and 2004.

Thus, in 2004, commentators could diagnose an emerging crisis in the pharmaceutical crisis. A paper bent on refuting the existence of a crisis nonetheless provides useful insight into the character of the discussion being held at the time:

> By some accounts, the pharmaceutical industry is facing a productivity crisis. Notwithstanding extraordinary scientific achievements such as completing the sequencing of the human genome, the rate at which the industry generates new products appears to be shrinking. In 2002 the U.S. Food and Drug Administration (FDA) approved only seventeen new molecular entities (NMEs) for sale in the United States—a disappointing fraction of the fifteen-year high of fifty-six NMEs approved in 1996 and the lowest since 1983. Alarmingly, this decline occurred despite a doubling of research and development (R&D) spending by U.S.-based pharmaceutical companies between 1995 and 2002 (Exhibit 1). The same pattern is apparent in worldwide statistics, where the annual number of new active substances approved in major markets fell by 50 percent during the 1990s, while private-sector pharmaceutical R&D spending tripled. These numbers have prompted headlines about 'dry,' 'weak,' or 'strangled' pipelines and claims that 'Big Pharma's business model is bankrupt.' (Cockburn 2004, p. 10).

Indeed, the 2002 *New York Times* article was followed by similar features in *The Economist* (The Economist 2004), where reference to the Tuft centres numbers and to Jürgen Drews' work were made, or in *The Wall Street Journal* (Landers 2004). Based on these interpretations, a number of authors observed or advocated an increased role for academia in biomedical innovation, making direct reference to the article by DiMasi and colleagues to diagnose a stepback of industry from early drug discovery and development (Cockburn 2004; Mehta 2004; Tralau-Stewart et al 2009; Silber 2010; Verkman 2004). These results were also used to problematise the role that pharmaceutical innovation plays in health care for example (Riggs 2004).

Elsewhere, however, these claims of drastic changes were tempered by other analyses conducted by industry insiders. These showed how outputs in terms of new innovative

therapeutics was higher between 1995 and 2005 than at any point in the history of pharmaceutical innovation (Schmid and Smith 2005), that increasing RTD costs reflect a transition period that will open a period of renewed productivity (Schmid and Smith 2006), or that profits were being cut by cost containment practices and burgeoning marketing expenses rather than any sort of innovation deficit (McKinnon et al 2004). This dispute around claims is reminiscent of what Hedgecoe (2003) could observe in the field of pharmacogenetics. There, the main academic and industry researchers responsible in active proselytizing for the establishment and investment in this subspecialty often turned out to be located outside of the core group of experts that might have been thought most legitimately placed to deliberate on these matters. Similarly, in our case, experts and executives from big pharmaceutical companies turned out to have initially nuanced arguments about the empirical possibility of an innovation crisis in their sector. The consequence of such an observation would be to look for the initial policy entrepreneurs fuelling the narrative of pharmaceutical crisis outside the industry itself.

4.3.3 Innovation / Stagnation

With its 2004 report *Innovation / Stagnation*, the US Food and Drug Administration (FDA) provided powerful institutional endorsement to the idea that there was something wrong with the innovation activities of the pharmaceutical industry (FDA 2004). The report's authors drew on FDA data to show stagnation in the number of biologicals and drugs being submitted to the agency, and brought in the figures of increasing investment by the Tuft centre to posit low productivity in medical product development.

The FDA then argued that emerging initiatives aiming to foster TR were ideally positioned to engage in a science of the drug development itself that would be able to substantially improve prospects of extracting value from formal biological knowledge:

> In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs (FDA 2004, p. ii).

From this quote, two points can be made. At the time where major TR initiatives were being devised, the FDA was constructing a powerful (and influential, it will be seen) narrative about the neglect of applied biomedical sciences. This has taken the form, most notably, of a neglect of methodological issues in drug development, and what

seems to be needed is no less than a science of drug development. The tools of this science of drug development, for the FDA, include animal and in-silico predictive models, biomarkers and "new clinical evaluation techniques" (FDA 2004, p. ii). The FDA also considers that current understandings from physiology and (patho)physiology are reductionist, which we can understand as meaning that they owe much to molecular biology, which means that there is a gap in more systematic understanding of organs, or cells, or the (patho)physiology of diseases taken as a whole. 'Bridging the laboratory and the whole organism' (FDA 2004, p.11) means either developing systems biology approaches, heavily reliant on in-silico models and thus bioinformatics, but also 're-building' physiology, pharmacology and clinical pharmacology, in a way the disciplinary forerunners to TR (see section 4.1). Other recommendations to the biomedical community include increasing the frequency at which exploratory, 'proof-of-concept' trials in humans are conducted, or the need to foster public-private partnerships. All in all, the report proposes an elaborate agenda for (mostly) academia to engage and re-engage more closely in drug development and develop meaningful ways to assist industry in biomedical innovation, aside from the generation of fundamental insights into (patho)physiology which it had always made available.

The *Innovation / Stagnation* report also illuminates the junctures between the policy narrative of pharmaceutical crisis and that of sequencing-driven experimental medicine. There is no doubt that the HGP has cast a long shadow on prospects for pharmaceutical innovation. The following quote makes this very clear:

> "The sequencing of the human genome four years ago raised widespread hope for a new era in the prevention and treatment of disease created by the ongoing investment in biomedical research… But that new era has not yet arrived. Instead, 2000 marked the start of a slowdown in new drug and biologic submissions to regulatory agencies worldwide... The submission of innovative medical device applications has also slowed recently. This means fewer new products can be approved and made available to patients. At a time when basic biomedical knowledge is increasing exponentially, the gap between bench discovery and bedside application appears to be expanding. There is great concern about the ability to bring the hoped-for outcomes of basic research advances — much awaited new treatments — to patients. There is concern that hoped-for advances in medicine and new treatments for diseases may never materialize" (FDA 2004, p. 3).

Yet, what is interesting here is in fact that the FDA details the failures in the sequencing programme as the background *against which* to present its own propositions for reform in the biomedical innovation enterprise. While the FDA acknowledges the potential of the post-genomic platforms for generating new intervention hypotheses, it contends that crucial priority is also to be afforded to the drug development as a scientific object in its own right. In fact, as we have seen above, the *Critical Path* report contained little

proposals for addressing the adjustment of post-genomic platforms specifically to clinical contexts. This founding argumentative act thus positioned the policy narrative of pharmaceutical crisis as simultaneously related but autonomous repertoire for understanding clinical innovation.

4.3.4 A patent cliff

In February 2011, Pfizer announced that it was cutting thousands of jobs and reducing its R&D expenditures by about a billion US$, in response to the imminent "patent cliff", closing whole research facilities. This follows similar interventions by GlaxoSmithKline, notably, which made public its intentions at that point to concentrate on marketing and commercialization, while mostly outsourcing its R&D activities (Cressey 2011). Pfizer, for its part, is predicted to lose two-third of sales to competition from generics in 2014, with the loss of sales of its drug Lipitor, a cholesterol lowering statin that had generated most of the company revenues in the last few years and, poised to hit the most. The loss of patent on Lipitor in November 2011 would mean the loss of a US$ 10 billion revenue stream to the company, and the passing off of patents on 9 other megablockbusters in 2011 alone would bring the combined annual sales loss to US$ 50 billion for the Pharma industry (Wilson 2011). Morgan Stanley has thus downgraded the credit rating for the whole group of big Pharmas in Europe (AstraZeneca, Bayer, GlaxoSmithKline, Novartis, Novo Nordisk and Roche), with a report on this called "An Avalanche of Risk? Downgrading to Cautious" (Wilson 2011). Reports were also made of cuts of 61,000 jobs in 2009 and 53,000 jobs in 2010 in the sector. In a *New York Times* article on the topic (and titled : "Drug Firms Face Billions in Losses in '11 as Patents End"), a researcher at the Tufts University's Center for the Study of Drug Development is thus mentioned as proffering the following analysis:

> "This is panic time, this is truly panic time for the industry... I don't think there's a company out there that doesn't realize they don't have enough products in the pipeline or the portfolio, don't have enough revenue to sustain their research and development" (Wilson 2011, p. A1).

Even if the falling off patent of blockbusters was already mention in Pollock's 2002 *New York Times* reportage as a important factor that might threaten the pharma industry, this danger seemed to have intensified in late 2009 and after, as the number of drugs falling off patent reached a critical point never met previously. A Lancet reportage from 2012 was titled "Skies darkens over drug company". Job cuts from pharma giants such as Merck and Pfizer were reported, pressures from governments engaged in cost containment but especially the reality and already observed impacts of the patent cliff (Holmes 2012).

As an antidote to this situation, the *Lancet* inquiry piece noted an increasing trend from industry to rely on outsourcing and joint partnerships with the biotech sector and academic research teams as a source of drug candidates. This last point is indeed a central contention of this section: the problem delineated by the policy narrative of crisis in pharmaceutical innovation is argued to be best solved by the expansion of "academic drug pipelines". This next section details these claims.

4.3.5 The search for new models: academic pipelines

Mehta reported in 2004 on a rising trend to create academic centres dedicated to drug development with the emergence of the TR agenda in the USA. Mehta attributes this newfound willingness of academia to take on development projects with intrinsically less scientific prestige and with high financial risks to a perception of increased opportunities for financial rewards. In a time when the pharmaceutical industry would be increasingly concentrating on late clinical research and registration and commercialisation/marketing as a mean to diminish its engagement in risky RTD projects, public institutes extend their ativities. In other words, some TR advocates were arguing at that point in time that there was a mission for TR to take over some of the discovery and early development work that an ailing industry was leaving behind.

Mehta provides a list of forerunners that implemented this approach at a time even when there was no clear problematisation of a crisis in pharmaceutical innovation productivity can be observe. The list provided includes the following programmes and initiatives such as:

- University of Pittsburgh's Drug Development Program (1995)
- University of Texas Southwestern Medical Center's Center for Biomedical Inventions (1997)
- Georgia State University's CollabTech (1999)
- The State University of New York, Buffalo's Center for Drug Discovery and Experimental Therapeutics (2000)
- Harvard University's Laboratory for Drug Discovery (2001)
- PharmaStart: partnership Stanford University, SRI International, University of California San Diego and San Francisco, and the Institute for Quantitative Biomedical Research (2003).

Commenting on the structure and orientation of these new centers, Mehta mentions how:

> "These centers focus on translational research or on discovering new chemical compounds using industrial techniques and tools, such as high-throughput screening and computational chemistry. Although most of the centers were founded with a mission to target specialized diseases that might be too small a market for pharma companies, these centers' capabilities are clearly industrial and commercial in nature" (Mehta 2004, p. 22).

What is important here is that the TR initiatives informed by the policy narrative of crisis in pharmaceutical productivity adopt experimental platforms and the type of equipment that was previously thought to be the remit of the pharmaceutical industry only. Operating these platforms demand resources that will not lead to the highly creative research publishable in high-impact journals that would be expected in academic settings (Geddes 2005). Moreover, many of my interview respondents for example have contended that the actual work of compound discovery and optimisation was ideally performed by industry who had a long experience in the area and which could afford to employ the large teams of chemists and laboratory technicians necessary to the conduct of this development work. Despite these reservations, Mehta reports that by engaging in these experimental steps, academic centres hope to apply for stronger patents then is usual for cases of technology transfer, thus allowing greater financial rewards if a drug candidate can make it to the market.

As perceptions of an innovation crisis were substantiated by events such as ever declining revenues and the series of job cuts starting in 2009, the proposal to develop academic drug pipelines gained steam. Although commentators highlighted the scientific and commercial opportunities for academic teams that moving deeper into drug development might entail, others contended that the continued maintenance of the pharmaceutical innovation system required greater participation from these teams. The increasing commercial risks of drug development was perceived to lead the industry away from early RTD projects to concentrate on the late phases of clinical research and marketing and commercialisation operations. Continued pharmaceutical innovation thus increasingly depended on the drug discovery projects of academic teams. In other words, changes in pharmaceutical business models had to be followed by corresponding changes in academic innovation activities. An example of how advocates of academic pipelines have problematised the woes of the pharmaceutical industry and simultaneously framed the collective need for new innovation models in public institutions is provided in a recent intervention in the journal *Science Translational Medicine:*

> "Recently, because of a dearth of research innovation and high-quality experimental candidates from discovery research pipelines, the strategy at most established pharmaceutical and biotechnology companies has changed. Now the aim is to create and sustain research innovation by increasing collaboration with academic labs and institutes and startup companies. Most companies are now focused on licensing new drug targets,

> assays and screening methods, and preclinical and clinical drug candidates, especially those at later stages of development" (Silber 2010, p. 3).

Areas of expertise where academic teams are likely to be able to make significant contributions include the screening of the sort of small molecules that have overwhelmingly comprised therapeutic agents by using biochemical or cell assays; creating libraries of chemical and biological substances that could become potential drug candidates; or obtaining deep understanding of the mechanisms through which drugs enter the body, reach their targets, act on disease mechanisms, and cause secondary effects such as liver toxicity; select those drug candidates with the most potential of efficacy and safety in humans based on pre-clinical evidence; and conduct early clinical trials (Silber 2010). Elsewhere, the leaders of an "academic drug discovery unit" at the Imperial College London also advocated for the concept based on their own experience. They highlight the intellectual and scientific richness of academic environments and the possibilities they may offer fore more thorough investigations than in the sharply constrained environment of pharmaceutical RTD:

> "The number of examples of academic drug discovery units based within universities is growing, as is the range of capabilities and activities they undertake, from target validation through to candidate approval... In general, these units are focused around a scaled-down pharma model comprising most of the functions required for small molecule drug discovery—including synthetic chemistry, high-throughput screening, absorption, distribution and metabolism analysis" (Tralau-Stewart et al 2009, p. 99).

> There are many hypotheses for declining attrition and suggestions for crucial factors to consider. Academia is ideally placed to consider these hypotheses and develop solutions. In particular, academic–industry partnerships are well placed to develop co-ordinated approaches to target validation and disease linkage in man. Universities with allied clinical facilities are uniquely situated to directly relate projects and targets to clinical questions (for example, identify targets by patient observation, validate these in human systems and identify phenotypic biomarkers) at all stages of what should be an iterative rather than a single linear process to the clinic" (Tralau-Stewart et al 2009, p. 100).

Interestingly enough, Eric Lander's previously examined programme for the sequencing domain in biomedical research (see section 4.2) also included a call to develop academic pipelines. He considered there that advances in sequencing technologies would participate in the expansion of academic pipelines and be an important component in solving the pharmaceutical innovation crisis: "Academia must become a hotbed for heterodox approaches that combine creativity and scale, exploit genomic approaches and targets, and empower a new generation of scientists" (Lander 2011, p. 196).

Other germane models for improving pharmaceutical innovation draw more on ideas of pre-competitive collaboration or open innovation between a number of partners, most often including a mix of pharmaceutical and university organisations (Munos and Chin 2009). Networked big-science projects can offer a mean for academia to enter downstream RTD while offering an amount of uncertainty that is acceptable for an institution not expected to take much commercial risk at all (Pisano 2006). For the pharmaceutical industry, shared infrastructures and consortia might allow to tackle the high complexity of turning genomic knowledge into clinical interventions:

> "Ultimately, sharing should bring about an efficient division of labor in which companies collaborate and share the cost of advancing foundational knowledge, such as identifying single-nucleotide polymorphisms (SNPs) and other biomarkers; developing disease-state models; elucidating pathways in complex diseases; and bringing to maturity sciences and technologies such as translational medicine, epigenomics, and stem cell biology. Companies can then focus the bulk of their resources on areas that are likely to yield new treatments, such as designing small molecules that effectively modulate the specific targets and pathways, with distinctive clinical benefits over the current standard of care" (Munos and Chin 2009, p. 2).

The material examined in this subsection add further support to my contention that academic extension into quasi-industrial drug development projects is a central development to understand current TR agendas. It also shows how these new local institutional configurations are to be aligned with large-scale networks of collaborations that are no less novel in their own right. The next section details this.

4.3.6 Academic but managed pharmaceutical innovation

The contention of Munos and Chin reported above makes clear a belief within the biomedical field that the pharmaceutical industry has grown conservative over the years and that it has concentrated on incremental management innovations and new agents that offer marginal but safe therapeutic gains, but that consequently require more and more complex clinical trials to offer statistical proof of their efficacy. To counter the situation, the pharmaceutical industry should get back into risky but innovation research, establishing sharing and collaboration practices within the sector, with academia and even with regulatory partners to reduce commercial stakes. These arrangements would allow deeper understandings of (patho)physiology and aetiology, notably by drawing on academic expertise to develop better animal models at the preclinical stage (by having done previous characterisations of human tissues) or mobilizing post-genomic technologies (Lockhart and Walther 2009; Nature Editorial 2005). Indeed, in a way, it should be noted that the translational research programme put forward by industry commentators as a mean to get out of the innovation crisis tends to overlap with the language of the genomic medicine narrative. Here also, biomarkers

are hoped to increase the 'rationality' of drug development and thus reduce attrition and commercial risk, as is made clear in the following quote about the mission and nature of TR:

> "The rate of novel medical entities being approved by regulatory agencies in the last decade has been stagnating. To offset this trend, pharmaceutical companies faced with major patent expirations and late-stage failures leading to a loss of revenue, have been searching for ways to enhance the efficiency and success of drug discovery and development. This need has spawned the advent of translational medicine, a research discipline aimed at improving the congruency between preclinical and clinical drug development to reduce attritions rates. Translational medicine seeks to improve the predictability of drug efficacy and safety, to enhance cost-effective decision-making and to optimize the design of clinical programs. The discovery, development and implementation of biomarkers are essential to this effort. Incorporation of biomarkers into all phases of preclinical and clinical development to impact go/no go decisions is at the core of the translational medicine philosophy" (Johnston, Su and Alesci 2009, p. 1650).

What is especially interesting about this fragment of commentary is how it encapsulates within its length the argumentative link between the problematisation of a crisis in pharmaceutical innovation and TR as a solution to it. In this case, one can also see how the use of biomarkers as dual tools for (patho)physiological understanding and commercial decision-making may also be advocated within the policy narrative of academic pipelines. Yet, I would contend that organisational claims within this narrative have a distinct character from those centred on practices of accountability in the sequencing-driven understanding of TR. Instead, TR advocates arguing about academic pipelines and the pharmaceutical innovation crisis tend to focus on the use of business management methods and collective coordination issues, rather than the need for increased control of the scientific soundness of translational hypotheses and projects.

Indeed, setting up academic drug discovery units and large-scale collaborations require institutional changes beyond those called for by new experimental infrastructures. Adopting the experimental platforms of the industry might also imply adopting associated management practices and divisions of labour, to be able to coordinate and direct complex, interdisciplinary and long-term research projects:

> "Good project management brings order to complex and numerous tasks, such as providing work breakdown structures, managing external relationships, making project progression decisions, and keeping the overall work on track (to ensure timely publication for the academic contingent and hitting the milestones for the industry side). Project managers provide the tools to accurately capture data and information acquired during the course of the work, organise the necessary meetings among team members and stakeholders, maintain all records, and organise relevant team training. All of these activities are essential when working with a team of people from

> different disciplines and cultures who may have very specific backgrounds and skills and who do not otherwise work in tight project team environments. This type of approach to project management in medical research generally is quite foreign to most academic researchers, but it is essential for translational research to be successful" (Venters 2010, p.16)

What is interesting here is also the theme of 'orderly translation'. The need for increased coordination of a variety of teams or expertises takes the form of more classically organisational methods, whereas the schemes examined previously (see section 4.2) where still concerned with the management of experimental programmes. The author also implies that these kinds of tightly managed teams are not congenial to the academic environment. Again, it seems that incumbent practices in academic biology are perceived as obstacles to the establishment of new TR institutions with specific research programmes. In a *Nature* editorial*,* the lack of adequate incentives to the kind of work that would be performed by academic drug discovery units is presented as a major bottleneck. Ideally, the editorial explains, academic biomedical centres would be the home of large, mixed teams of experts dedicated to taking findings from local laboratory-based colleagues and developing clinical innovations based on them. These teams would thus not have long-term research projects of their own, but would possess expertise in "all aspects of clinical research, including medicine, pharmacology, toxicology, intellectual property, manufacturing, clinical trial design and regulation". But for such a model to be viable, it must be so that "all the team members are rewarded in terms of pay and promotion just as richly as if they had produced a string of publications" (Nature editorial 2008, p. 823). The establishment of academic drug discovery units as a solution to the innovation crisis is thus itself contingent on further efforts to raise legitimacy and acceptance within academic biomedicine for the new TR practices.

4.3.7 Fostering heterogeneous and orderly translation

In my empirical research, I have stumbled upon an interesting, hybrid repertoire of argumentation that simultaneously problematises failing productivity in the later stages of both sequencing-driven and pharmaceutical clinical innovation, but that clearly foregrounds organisational change as the preferred proposal for collective reform. A central concern becomes the question of stewardship, that is, ensuring the coordination of the complementary yet often disparate areas of expertise that need to come together in TR projects to move with a consistency a clinical product candidate towards regulatory testing and commercialisation. Advocates of this hybrid repertoire focus on the alignment of incentives and the establishment of new types of leaders in TR collaborations, bringing in patient organisations for example, and thus taking out the pipelines of clinical innovation not only in academia, but into fully heterogeneous settings (to use the formulation of Kaplan and Murray 2010).

A radical use of this line of argumentation elaborated by the American think tank FasterCures. The non-profit organisation aims to shape the USA's biomedical policy and institutional landscape to accelerate clinical innovation. In a series of guides and position papers it published on how to conduct TR, it makes it quite clear that the obstacles barring the flow of innovation from the fundamental pool of knowledge to the 'floodplains of the clinic' are these systems disincentives which leave important discoveries to gather dust in the formal publication system or in the heads of academic investigators:

> "Every day we see stories in the media about the latest medical 'breakthroughs' that could lead to cures for dreaded diseases.
>
> And yet, over the years, many breakthroughs like these have yet to bear fruit for patients. Why? Perhaps the media over-hype early discoveries. After all, science is complex and unpredictable. We have to first fail – numerous times – before we succeed, but we tend not to hear about the failures. No one gets rewarded for failure.
>
> The fact is that many basic discoveries barely get to start the journey down the therapeutic development pipeline. Fascinating observations and creative insights often get lost in translation because they lack funding, incentives, and technical expertise to advance any further. They get stuck in an ever-widening gap in funding and support for the kind of research that moves basic science down the path toward treatments. That gap has come to be called by many the 'Valley of Death.' (Faster Cures, undated A; p. 3).

It is highly intriguing to see how the think tank first acknowledges the possibility that the formal knowledge produced by molecular biology may not be realistically relevant to clinical innovation. In other words, that hopes to draw on this body of knowledge to devise new health interventions would be no more than hype. The quote shows how the organisation dodges this potential counter-argument, indeed making use of it to augment the rhetorical power of its own argument of indignation about how it is really institutional failings that block clinical innovation.

FasterCures then goes on to support its contentions by providing statistics on new therapeutics development at the NIH and in the pharmaceutical industry. FasterCures explain that new means of coordination and leadership are needed to make sure that value is appropriately extracted from the 'fascinating observations and creative insights'. In another document, the think tank reports on the comments of a participant at a 'leadership forum' it organised to support its contentions that greater coordination and direction might be needed in academic biomedicine to make TR a reality: "What the Valley of Death needs is more cattle herders who know where the water is – or how to get the cows to the water" (Faster Cures undated B, p. 10). The implication here is that the vast crowd of biomedical actors are like clueless cattle subject to mass movements

and more likely to follow one another than to rise above the herd to get a broader vision. It is not clear here who the cattle herders should be – the think tank's document mentions a bit further that even biotech and pharma companies may have decision-making processes that are not optimally "rational or evidence-driven" - "some times because people are intellectually or financially wedded to their success, or because the company has a narrow or limited view of the field of research (FasterCures undated B, p. 10). FasterCures seems to suggest that "venture philanthropy" firms grounded by patient advocacy foundations could be the type of leaders that catalyze and channel the powerful but ultimately entropic forces of public and even private biomedical innovation. They provide the example of Fast Forward, a firm founded by the National Multiple Sclerosis Society in the USA, and which offers venture capital, technology transfer and networking services in this disease field. Through this agency, the non-profit foundation could act as an "innovation scout" and set up funding alliance together with a Merck subsidiary to set up academic-industry joint TR projects with a variety of university partners.

FasterCures more generally discusses plans for increasing the efficiency and decreasing the costs for patients of lost technoscientific opportunities. The idea that biomedical innovation can be organised as a coherent or unified "enterprise" betrays a desire for increased coordination, perhaps through more centralized control. Recurrent use of the concept of "enterprise" shows adherence to the hypothesis that a corporation is in better position to make difficult decisions, to trim off inefficient projects (and personnel). Indeed, interview respondents from academia I spoke to (to anticipate somehow on the next sections) often mentioned the important role of the pharmaceutical industry in TR projects, with its profit orientation allowing it to make cold-blooded "go or no-go" decisions, or to expedite experimental work by narrowing only on those steps that are crucial to product approval (Geddes 2005). This is something that would be seen as desirable in academic biomedicine also. Elsewhere, other patient organisations also lament a situation where "there is no one paid to spend 100 percent of his or her time following a problem from start to finish. This creates a leadership gap…" (IOM 2009, p.23). The solution for many patient groups seems to be to step in as a "focal point for the research… Increasingly, voluntary health organizations are doing more than just writing checks… [They are b]ecoming more involved and actively leading the scientific process…" ((IOM 2009, p.23).

The rationale here is of course that patient groups are privileged coordinators since their motivation should be patient improvement above considerations of profit and scientific prestige. Indeed, as one cystic fibrosis research notes:

> "Perhaps the single most important lesson from the recent history of drug development in CF is that a charity can make an enormous contribution not

> only by funding the trials but by coordinating academics, clinicians and clinical trial centres in a way that would normally be done by a drug company. Where there is no profit, altruism must take over" (Geddes 2005, p. 261).

What this quote makes clear is the prevalence of a certain belief in the broader biomedical community that the achievements of sequencing systems need to be complemented by efforts that are free from the demands of scientific excellence if translation is to happen in this domain. The socio-technical systems that have allowed commendable achievements in mechanistic understanding of (patho)physiology are intrinsically ill suited to ensure the coordination and stewardship of TR projects. As such, the efforts of TR advocates should aim to establish a parallel and interdependent innovation system than can fulfil these functions. We can conclude this section by noting how coordination and stewardship have been central concerns of TR discussion for a long time. The following quote is taken from a text written by a former NIH director in 1975, and one of the first usage of the idea of "translation gap" I could find. The original document was not cited in the literature on TR that emerged years after, so its argumentative value is limited, yet it uncannily illustrates the enduring centrality of this concern for the clinical innovation enterprise:

> The need for closing the translation gap that exists between biomedical research and the effective application of its discoveries is a major issue requiring the attention of the National Institutes of Health. An element of urgency is derived from a national determination, largely Government directed, to increase the cost-effectiveness and efficacy of health care. The importance of clinical trials to NIH is several fold. They provoke a reaffirmation of the necessity of the union of biological and medical research, while simultaneously they raise a question of how far the Agency's resources can be deployed in matters of medical practice before its principal mission of discovery is imperiled. Thus, they are one element in the complex question of where the appropriate boundaries of NIH activities lie. Clinical trials also force us to consider how well we understand the apparatus that is supposed to provide for **orderly translation of discoveries into the substance of medical care**. The processes of validation and continuing reevaluation do not always operate smoothly or even serially. The loose confederation of diverse talents and interests involved need better articulation. Perhaps the essential first step is the more formal recognition of collective responsibility for any gaps in translation that persist (Fredrickson 1975, p. 9-10; my emphasis).

This quote handily illustrates the connections between public expectations about biomedical research, the relations of biology and medicine and collective processes for negotiation divisions of labour and project stewardship. "Orderly translation" and coordination of efforts also appears as a central concern in this early problematisation of a TR agenda, and one that remains at the core of current struggles.

4.3.8 Discussion

This subsection has examined how long-standing claims about commercial risk in pharmaceutical innovation have been transformed into a narrative of crisis in the first half of the 2000s decade. Commentators of the performance of the pharmaceutical industry and of biomedical innovation systems more broadly, marshalling evidence of increasing costs, decreasing productivity and, later on, a unique conjuncture in the major players' patent portfolios. At the same time as this problematisation was being articulated, TR was emerging as a stable and coherent agenda of reform in the biomedical field. Quickly, then, advocates started arguing that a projected domain of TR, if it was well supported, would offer the solution to the crisis at hand. More specifically, these advocates have made proposals to implement TR agendas by establishing quasi-industrial drug development infrastructures within academic institutions and consortia. Areas of experimental and development practice such as large-scale compound screening, chemical optimization of new drugs, or the conduct of pre-clinical and clinical experiments with a clear regulatory purpose have been advocated as part of this policy narrative. It is not just the type of experiments to be conducted in these initiatives that are "borrowed" from the pharmaceutical industry. Expounders of the approach have also highlighted the need for the kind of division and labour and perhaps more centralized coordination of what are often complex projects necessitating contributions from a variety of expertise groups. These infrastructures and models of collective work are by no means common practice in current academic biomedicine, but advocates favouring this interpretation of TR have been especially outspoken in recent years, and have made great use of the effect of urgency created by the situation in the pharmaceutical industry. Argumentative activism here seems especially concerned with providing legitimacy for experimental and development practices that are not normally considered within the remit of academic excellence (see Fischer 2012 for reports of similar testimonies).

The development of these large-scale, quasi-industrial academic pipelines should perhaps be contextualised within the greater history of "big biology" and "big medicine". Löwy (1996) has already shown how the clinical research enterprise, following WWII, gradually expanded into a sort of "big medicine", with its emphasis on multi-centric trials, notably, calling for novel organisational practices. More recently, parts of biology and the life sciences at large (Vermeulen and Penders 2010) would also have evolved into models of 'networked big biology' (Vermeulen 2009), with a large number of geographically dispersed research teams working in a highly coordinated manner around nodes of large, core equipment. These studies bring to light a number of characteristics of recent large-scale collaborations in the life sciences and in medicine, which are relevant for the case at hand. Most important is perhaps the insight that emerging large-

scale research programmes in the post-genomic framework of biomedicine should concurrently re-align exchanges between disciplines and organisational locations, the conditions of access to increasingly complex and costly research equipment and biomedical platforms, as well as the division of labour within and between participating research teams. The movement for the establishment of academic drug pipelines on first view certainly seems to participate of these developments, with its priority on industrial infrastructure and development equipment, and the attention given to questions of business strategy and efficient alignment of involved research teams.

Surprisingly enough, as the material above has shown, the initial instigators of a policy narrative of pharmaceutical do not appear to be directly affiliated with the pharmaceutical industry. Interventions from industry members reported above showed an initial desire to calm the field and situate doubts concerning innovation capacities as discrete moments within more complex structural cycles. Initially, it was rather journalists, consultants and financiers that might have been alarmed about the prospects of the industry. Academic administrations with a pronounced entrepreneurial bent and associated local research leaders have also made use of the policy narrative to justify the establishment of academic pipelines, with the expectation that future partnerships with an increasingly outsourcing pharmaceutical industry would bring in big rewards. At that point the FDA provided the crucial catalyser for the establishment of this policy narrative, using the problematic it so formulated as a rationale for launching into a broad attempt to re-position itself in the post-genomic innovation landscape and cultivate a related and new potential space of jurisdiction (Hogarth and Martin 2012). With the end of the 2000s, massive job cuts in the RTD departments of the pharmaceutical industry provided great fuel to the narrative.

5 Incorporations, implementations and institutionalizations

Hajer (2005) has argued for the importance of differentiating between the *sites* where discourses and policy narratives are articulated and performed. Chapter 4 traced the origins of TR back to a series of sometimes distinct, sometimes interlocking and overlapping policy narratives. To do so, it focused on sites for the formulation of problems and proposals for collective models of action in biomedicine, including the editorial and commentary pages of specialized periodicals as well as public policy documents. This section instead examines the trajectories of the three policy narratives in a broader community of biomedical researchers, administrators, consultants, or pharmaceutical and biotechnology firms. It thus concerns itself with the articulation of policy narratives of TR in local (as opposed to collective) sites of biomedical experimentation and clinical innovation. The sections contained in the present chapter interrogate advocates and TR initiatives to trace how the recent emergence of TR policy narratives has changed experimental, organisational and coordination practices in biomedical innovation system. In other words, the empirical material contained here provides central substantiation of my argument that TR is poised to destabilise established regimes of governance in biomedical innovation. Hopefully, the separation of the argumentative structure of this thesis between the formulation of policy narratives and their implementations allows to us to better consider how policy narratives are re-aligning and re-shuffling biomedical innovation systems. This section starts with the baseline assumption that these policy narratives had been relatively stabilized and were culturally available in biomedicine by 2009 and that examining the views and experiences of current advocates of TR can help us understand the changes that the TR movement is bringing to the practice and the organisation of clinical innovation.

I have thus organised my account along a distinction between sites of formulation and sites of implementation in the trajectories of the policy narratives of TR. Nonetheless, my goal is not to establish a strong distinction between realms of discourse and realms of practice and see how one might influence the other, but rather to show how the construction of policy narratives of TR and the establishment of TR initiatives have been interdependent. Policy narratives of TR have reshaped individual and institutional practices of biomedical innovation, while innovations and issues with the practice of clinical innovation and the vagaries of institutional innovation have contributed to the advancement of policy narratives. Nonetheless, the separation of the empirical material between chapter 4 and 5 allows a clearer readout of the journeys of TR narratives as they moved proliferated from core groups of advocates towards broader articulation in biomedical communities.

I have named this ensemble of sections “incorporations” to denote the process by which the policy narratives have been added and integrated to the interpretative repertoire of individual TR advocates I have met with, and “implementations and institutionalizations” to label changes at the collective level effected with the help of these narratives.

Here again, the empirical material has been organised around each of the three policy narratives delineated in chapter 4. Section 5.1 will analyze the implementations and incorporations of the “clinician-scientist” policy narrative, section 5.2 those of the “sequencing-driven experimental medicine” narrative and section 5.2 that of the “pharmaceutical crisis and academic pipelines” narrative. In each section, I will first make use of the interview material I have collected. Of course, given how my selection of interview respondents explicitly sought out supporters of TR agendas, this data cannot be read as a survey the degree of general uptake of TR in the biomedical field. Rather, this material should provide detail into how the policy narratives of TR have become entangled (or not) in the mundane experimental practices and interpretative repertoires of biomedical actors. In a second time, each section will focus on a selected number of initiatives that are particularly illustrative of the kind of experimental and institutional realignments that have taken place in the wake of the TR movement.

5.1 Addressing the plight of clinician-scientists and patient-oriented research

Towards the end of the US and German subsection above, material was presented that showed how local observations about the shared mundane problems of a group of health professionals were transformed into a set of issues with national importance and specific policy solutions to create public good. A coherent policy narrative about the plight of clinician-scientists had been stabilised by this insistent argumentative activity. The issues that were argued to be cause for collective concern within the biomedical research field included:

- **The diminishing number of academic physicians that participated in research simultaneously to their clinical care and teaching duties;**
- **Diminishing incentives for new medical trainees to pursue clinician-scientists careers;**
- **The marginalisation of "patient-oriented research" in funding opportunities and the central representation of prestigious biomedical research.**

Reversing these trends called, in the view of these TR advocates, for countering the disincentives that clinician-scientists and patient-oriented research face. This implied:

- **Increased support for training and career trajectories for clinician-scientists;**
- **Increased funding and support more generally for patient-oriented research projects.**

These demands have been broadly acknowledged in recent TR initiatives, although, as the end of this section shows, this policy narrative seems to be the least well implemented of our three modalities, owing perhaps to the necessarily particularistic nature of its claims.

5.1.1 Incorporations: TR advocates' views of the plight of clinician-scientists

I want to start this survey of my interview material by providing a rough measurement of how widespread recognition and articulation of the policy narrative of a plight of clinician-scientists is in my sample of respondents. This narrative deals, after all, with the particularistic concerns of a group of professionals that cannot necessarily speak for all TR advocates. In some instances, however, respondents have explicitly defined themselves as clinician-scientists without prompting from my part (DE investigator 1; DE investigator 2). These respondents have framed their interventions and practices to

build TR projects and institutions as building on their experience in working both within the clinic and the laboratory (US Investigator 13).

These clinician-scientists, but also other proponents of TR with different professional backgrounds, readily reproduced the arguments from the narrative of the plight of clinician-scientists and contended that the profession was a crucial component of TR projects. The quotes below show the prevalence of the articulation of a model for collective action centred on clinician-scientists as privileged experimenters and stewards for TR projects.

The first quote comes from an interview with a clinician-scientist with an extensive career in the pharmaceutical industry. Here, he relates not what he himself considers to be the role of clinician-scientists in the enterprise, but how in the pharmaceutical industry, with the rise of a new wave of experimental platforms stemming from recent advances in molecular biology, collective belief in the usefulness of the clinical gaze for innovation projects came to rise:

> "So the novelty was to have on the discovery side, pre-clinical side, to have physicians. Usually physicians only became involved in clinical drug development, after you put it in man. The novelty here, was helping pick the targets, helping plan in advance for that. And at that time, it was sort of a vague idea that it was sort of a good thing to do, starting with notions of personalised medicine, of somehow having designer drugs based on a particular defect" (US investigator 9).

A German clinician-scientist instead explained how he had established central roles for himself and his peers in the TR projects he had set up. He is quite clear about his belief that TR is an inter-disciplinary effort that will necessarily involve a variety of expertise. But he simultaneously argue that clinician-clinician-scientists may be the one type of professionals where collective attention might be especially needed, because of a scarcity not encountered for the other groups:

> "But translational research means to have the application component in it, and therefore TR is in most instances carried off by teams which are involved with different qualifications. So there are clinician-scientists, like myself, who can work in both sides, but only to some degree. There must be also, for example I wouldn't cover the basic science component, I really do the interface between pre-clinical research and clinical research. That is my position and I treat clinical patients, very clearly, but I do not treat all clinical patients, because of the need to focus. So a translational team needs clinicians, needs clinician-scientists, and needs basic scientists if it's a really good translation team... I really think TR needs clinician-scientists, and that's a big problem in Germany because there are not too many" (DE investigator 1).

Coming from a coordinator and an administrator of a TR service unit rather than an investigator, the next quote provides further illustration of the grounds on which the claims of clinician-scientists towards "translational expertise" seem to rest. This coordinator at a French institution explained why a special emphasis had recently been but on training and hiring clinician-scientists in his unit:

> "It is true that we have a tendency to think that what is happening the most is a fundamental discovery that is going towards the clinic. But more and more, because medical doctors are intelligent and they think like researchers, it's really that they think like researchers, well they can see in their trials what is it that could become important to adapt the treatment. And there I think, that is why the training of medical doctors to research is crucial. They see the things. And to have the depth, to have the good idea before the patients, it won't be researchers since they don't see patients. And medical doctors cannot see it because they don't think as researchers. That's the philosophy that we are looking for" (EU coordinator 4).

For this coordinator, personal proximity to both laboratory- and clinic-based sites of evidence production allowed clinician-scientists to engage in unique processes of triangulation (in the sense of Sturdy 2007) for the generation of hypotheses about (patho)physiology. This made clinician-scientists crucial investigators for TR projects.

If the quotes above have shown adhesion to a collective goal in the establishment of TR projects around the unique expertise of clinician-scientists, respondents also made use of the problematisation that clinician-scientists were too scarce a resource in current biomedical innovation systems. Indeed, interview partners also recounted how problems in training and maintaining a sizable pool of clinician-scientists were creating bottlenecks for the realisation of the TR agenda:

> "And there are, or the manpower problem, which I mentioned before, in toxicology, is ten times worse in efficacy translation. We have almost no chairs for toxicology at the universities, I think in Germany there are 2 left. In 37 medical faculties... It used to be one per faculty. And in industry they have the biggest problems to find toxicologists, especially those with some clinical background. They sometimes find some biologists to, who understand the Ames test and some other in-vitro stuff, but if it comes to clinical, they have no idea. And these clinical… I call them translational toxicologists, because the biggest obstacle, [they are the bottleneck], they are the biggest obstacle" (DE investigator 6).

My interview material thus shows clear adoption of the argumentative repertoire associated with the narrative of plight of clinician-scientists in a subset of our interview respondents. This applies to both the problematisation in terms of a perceived lack of institutional support for clinician-scientists, and the associated programme of reform to establish increased support for the professional group. The next subsections will pro-

vide further details on the problematisations and models of collective action revolving around clinician-scientists that my respondents expounded.

A professional identity in the interstices

In 1959, C.P. Snow, a British chemist, civil servant and novelist, delivered a now famous lecture, later published in book form, that identified the inflexible boundary between the natural sciences and the humanities as a major source of systemic, one might say wicked problems (see Ferlie et al 2011) in western societies (Snow 1959). Advocates of TR have often made reference to Snow's argument in interpreting the issue of a gap between biomedical laboratory investigations and clinical practice and research (see also Wainwright et al 2009). Respondents shared experiences that recalled C.P. Snow's "two cultures" argument. The related argument from TR advocates is not so much about individual capacities to develop expertise in two complex field of practice as about questions of identity and belonging in professional jurisdictions that otherwise build their distinctiveness in opposition to one another. That is, professional and disciplinary boundaries between biology and medicine are likely to be called upon and performed in the presence of clinician-scientists, and their ability to form collaborations or be granted legitimacy adversely affected by this. The following quote from an investigator at a CTSA illustrates how not fitting in either the world of either laboratory research or institutionalised forms of clinical research informed the need to establish a new identity, one that was distinct from either realities and that, I was told, formed the foundations for current discussions of TR:

> "... it was experimentation that was basic on the one hand, clinical on the other hand, that went back and forth between the clinical and the science arena, and then went out into the community as an actual advancement in patient diagnosis and patient care. But we didn't have a name for it. So people who did it, sort of sat in this quasi-position, were they clinical investigators or basic investigators? How did you group them? They weren't accepted by the basic scientists because their work was maybe not as basic, and they often weren't accepted by the clinical investigators because they weren't doing these huge multi-centre clinical trials and they sort of sat in this in-between arena. And then in the late 60s, or early 70s this term "bench to bedside" was coined which was this notion that there was this group of scientists, clinician-investigators who constantly bridged the bench and the bedside and went back and forth between the two" (US Investigator 13).

Another example is provided by a French coordinator at a large-scale clinical trial network. This intervention particularly marks the importance played by unequal financial

rewards in setting the terms on which two professional groups come in contact with one another:

> "The problem is mostly that cultures are not very permeable. It has evolved a lot, I am myself older and I have suffered quite a lot from this deficiency in continuity between laboratory work, research work, and the work at the clinic. At the clinic, I was told "you are the guy who works with rats", and in the laboratory I was told "you are a medical doctor" etc. So from both sides I was a bit rejected because it is a question of culture, of communities that don't talk too much with one another, because their careers are very different, because their salaries are very different. Medical doctors are paid better than researchers, as a consequence researchers... we lose a bit of consideration from researchers because they consider that we are not better but that we are paid more. A number of things lead to these two worlds rubbing shoulders with one another but speaking little with one another. Finding oneself in the middle is not a comfortable situation, I think it is changing but I'm not sure that it is completely... "(EU coordinator 1).

A quote from an interview with a respondent with a varied career in both academic medicine and later industry confirms the prevalence of these representations of identity, and reflections on the constitutive power of work routines and epistemic dispositions that uncannily remind Bourdieu's understanding of *habitus*:

> "Now physicians, specifically, and again it may or may not be important, medicine is very different from PhDs, even though we have academic pretensions, medicine is basically a trade school. Like learning to be a carpenter or learning to be a plumber or an electrician. Very very practical skills, you go in and you have to operate, you have to see clients. You have to know enough science and so on, to make sure you are acting correctly but essentially a patient comes to you for a 30 minute interview. If you are a scientist, you have the options as well this is a very complex problem and interesting problem… And essentially, most of the time, one of the tensions between the physicians and the scientists is if you function that way as a scientist, you would not be a very good scientist. Science depends on rigour. You don't say anything until you gathered the data correctly, analysed it and you have enough there to make a statement" (US investigator 9).

Again, the quote above shows how personal experiences in biomedical innovation systems are shaped by the typical mundane practices of these differing professional cultures, and how prospects for collaborative research projects are felt to be conditioned or constrained by these routines. The next subsection also show how these patterned practices become entangled in academic reward systems.

Reputational bottlenecks

Interview respondents have reported on a number of issues they face in their personal intellectual and professional development, and that correspond to the paradigmatic cases already identified in the literature examined in section 4.1. These include: pres-

sure from departments for clinicians to generate revenues through patient consultations at the cost of research time; lengthening clinical training programmes which leave less time for research training and puts a heavy toll on personal finances; inadequate infrastructure for clinical research; and loss of role models (US investigator 13). The experiences of interview respondents illustrate the kinds of contradictory obligations made by the clinician-scientists' tasks, as well as the shear strain they induce on their personal lives (US investigator 4; US investigator 7; US investigator 8). In such a context, staying competitive to obtain even the most basic of research funding is perceived by clinician-scientists as an important challenge, as this leader of a successful federally-funded TR unit explains:

> "Because there is less money available in the pie, and the clinicians are being forced to spend a lot of time to see patients to generate their salaries. While at the same time trying to get grant funding to generate their salary. A pure PhD would not have to do any time in the clinic so they have a 100% of their time working in the lab and doing the research component whereas the clinician-scientist has to spend a certain amount of his time seeing patients and so it's sort of a disadvantage when competing with the 100% scientist" (US investigator 6).

Obtaining recognition for TR work also poses a number of issues. The actual products of much TR, conducting clinical trials or doing drug screening, are often not valued by peers the way scientific publications are (US investigator 10). The ideal form of TR conducted by clinician-scientists is team-based, but reputational credit tends to be attributed to a few individuals only, such as first and senior authors on a publication (US investigator 4). For one respondent, recent policy emphasis on TR had showed just how this type of investigations had become marginalized in the perception of their peers:

> "The people that are doing basic science, they are threatened. Because they had a monopoly on NIH money. So they could go to the NIH and show very mechanistic research, very highly controlled, precisely controlled laboratory benchtop research and reviewers liked that. Translational research is messy. It'll never look as good, you can't control things very well. And you have to make a lot of compromises because it's human subjects. So it's much harder to get mechanistic and have proper controls and so forth. But no one can deny that you need to do it. So by giving it a name, and by saying we're not translating, and everyone agrees, we're not translating, especially T2, that then all of a sudden, systems have to change so that we are. So I agree with them, it's a political move, but it's a political move so that science can be more appropriately evaluated for improving human health" (US investigator 1).

This quotation also highlights how the plight of clinician-scientists has been entangled with (or helped co-produce) the notion of TR. Here, the respondent makes it very clear

that the notions of TR are contested territory, but that advocating the concept allows for clinician-scientists to make systems of clinical innovation inch closer to the kind of experimental and institutional practices to which they are best adapted to contribute.

Although family and work conciliation are important topics being discussed throughout society, within the specific context of the biomedical field, clinician-scientists were felt to be particularly at a disadvantaged when it came to rewards in private life.

> "But I think another problem and this is harder to address and a lot of it is just going to be kind of money and standard of living, is that there is a lot of people that have the aptitude to be a basic scientist or a clinician or to combine the two, but you also you just don't need the aptitude, much more important is the attitude. Because the lifestyle of someone who is going to be both in the science lab and seeing patients and probably also teaching medical students, the overall the salaries are lower, your hours are longer, because sometimes you are in the lab, you basically it's not a 8 to 6 job in a lab, things happen over the weekend and you need to be there. It's a very reasonable life I feel as a professor, but when I was a post-doctoral fellow, and a clinical fellow and a young assistant professor and so forth, I mean in the lab seven days a week. All the time, I would be silly not to be, and anyone who was serious about it had to be. And that's not necessarily what people want to do" (US investigator 4).

The response from one policy-maker who had trained as an MD and then completed a PhD in the USA makes it clear that what is a stake here is not solely conditions of material existence, but also questions of social prestige, which are associated with rewards:

> "So if you don't miss just one year of this continuum, when you just finished, your studies, you are about 35-36, obviously those that are brave enough to also do a PhD may finish at about age 40. Then you start having a job. The requirements are also very difficult. Of if you are in a residency program, you maybe on call 24 hours out of 36. Which means that you have to sacrifice on your family life and your personal life a lot. And at the end, when you come out of all this tribulations, your salary is not very big. When I finished my PhD and I was a postdoctoral fellow, in the United States, I had a salary that was the equivalent of that of the janitor of the department" (EU policy-maker 1).

Much like their American counterparts, interviewed German clinicians-scientists discussed the difficulties they encountered in getting appropriate rewards for their TR work. Respondents mentioned how typical TR projects will only lead to only one or two publications, with a multitude of co-authors, over a period of two or three years, putting them at a clear disadvantage in competitions for promotion comparatively to their colleagues working with animal models notably (DE investigator 1; DE investigator 3; DE investigator 4; DE investigator 5; DE investigator 6). A coordinator at a clinical trial unit in a German university clinic drew the following picture of career perspectives for clin-

icians interested in focusing on clinical research. Although she mentioned a positive change in institutional support at her own institution, the issues that these new initiatives aim to address belong very much to the narrative of plight:

> "Like I said before, it's not attractive, in Germany it's not attractive. It takes time, and there's not enough money. You don't really have the time to do it, it's easier to say 'I want six months in the lab' and start doing some research than saying 'I want six months for doing clinical trials', they think you can do this by [incomprehensible] in the basement. A weekend thing. It's not structured the way it is in other countries, where you have clinical research really as a tenure track. But that's changed as well, here with the CCI, Centre for Chronic Immune Deficiency, they were asked by the funders to do such things like you can start a career here, you do clinical trials and in the end you are a professor. In the CCCF as well, in the Cancer Comprehensive Centre, they are obliged to find a way that you can build your career not only on the back on basic research but of clinical research as well" (DE coordinator 2).

German respondents also mentioned the pervasiveness of a tension between clinical care work and the demands of research. Even if in Germany, unlike in the USA, revenue for medical schools might not be generated on the basis of clinical service provided, medical doctors are still evolving in a context of high pressure to contribute to the performance of public health systems and the reaching of administrative targets:

> "It might be that there are rich universities that do not control what their clinicians do, but I can tell you that this University, the administration is controlling, they know exactly how many patients this doctor is treating a day. So that would allow only to do research basically at nights and at weekends. And so, I think we have a problem not having created scientist-clinician positions" (DE investigator 1).

As this last quote and other empirical material collected here shows, TR advocates we spoke to, especially but not exclusively those that were themselves clinician-scientists, appeared to have participated in the articulation and reproduction of the plight narrative.

Patient-oriented research as "applied science"

In German respondent's accounts, institutional tension seems not only induced by the sheer magnitude of the task of integrating two demanding professional agendas within one individual's daily work routine. Rather, obstacles are also constituted from the increasing technical and organisational complexity of TR as a recognised scientific domain, and for which clinician-scientists are posed to play central coordinative functions given their specific interdisciplinary background. Indeed, because of the regulatory burden now associated with all forms of clinical trials, even those early studies with a few human subject are subjected to regulatory demands that are similar to those normally

faced by industry. This includes the respect of good clinical practice (GCP) in the management of research beds and clinical care within the trial, GLPs in making laboratory analyses of the results and GMPs in the making of candidate therapeutics with standardised pharmacological qualities. In other words, engaging in patient-oriented research today requires a quasi-industrial infrastructure within academic clinics, although of a smaller order of magnitude I would argue than the networks and collaborations found in "academic pipelines" (sections 4.3 and 5.3).

Although academic biomedical communities have often been, historically, loosely associated, dispersed and highly autonomous (Whitley 2000), technology development that requires close integration of different groups might have to rely on more formalised hierarchies and dedicated classes of managers to provide coordination. A German clinician-scientist thus contrasted the strategic requirements of a TR project to the freedom accessible, in his view, to laboratory-based molecular biologists or basic researchers:

> "And it's much more strategic than individual creativity research, you need a much more strategic component. You need to have plans, short-term plans, you need to have milestones, you have to control these milestones, you have to change your overall strategy if it turns out that in one of the research groups there are results that are not allowing anymore to have the long-term strategy for the whole thing" (DE investigator 1).

For this respondent, rewards for the average biomedical research usually lay in unexpected but highly interesting experimental results that open possibilities for new research questions and experiments. Generating unexpected hypotheses and testing models are the most interesting result of this widespread model of biological investigation. There is no place to pursue side projects and emerging experimental insights, however, in most translational projects – focus has to be on a set of development practices that are time- and resource-consuming in their own right. This aspect of clinician-scientists' specific ethos is particularly important in the context of large-scale TR collaborations examined in sections 4.3 and 5.3. These shared concerns indeed allow to identify an overlapping discursive space between the policy narrative of the plight of clinician-scientists and that of academic drug pipelines.

Perceptions of comparatively narrow intellectual interests in TR were reinforced by the need to develop standard operating procedures (SOP) for work involving multiple centres, a clearer division of labour and the regulatory requirements to respect GMPs and GCPs. TR projects seek to achieve "uniformity and reproducibility and stability and process" (DE investigator 4). Respondents believed that to most biomedical research groups, TR work would be 'boring' and 'repetitive', something most reserved for biotechnology and pharmaceutical companies. "TR isn't done by geniuses" (DE coordinator 1), told us one respondent in this respect. For German clinician-scientists, the bio-

medical research community was predominantly composed of researchers interested in "ingenious" or "elegant" laboratory work. This implies that obtaining the recognition necessary for project grants, career promotions or high-impact publications is made distinctively harder on the basis of the experimental practices privileged in TR projects (DE coordinator 1; DE investigator 1).

Distributing value and virtue

Although the material reviewed above might be taken to indicate that clinician-scientists feel marginalised and undervalued in current biomedical research, many respondents instead characterised their commitment to patient-oriented research despite adversity as something commendable. The recent focus on TR might just then bring deserved recognition to an activity that has too long been pushed aside by collective concerns for a well-oiled loop of intellectual, career and reputational opportunities revolving around creativity-driven molecular biology. Ingenious basic research may be of greater repute, but the boring and repetitive TR projects are in fact what will have a greater impact on patients and communities:

> "And translational research is much more time consuming before you have results than if you do, let's say, basic physics or basic biology. So if your major aim as a scientist is to have many very high-ranging, so-called high-ranking publications, than TR is not to that [incomprehensible]. But for the patients and for society, translational research is of enormous importance" (DE investigator 1).

The respondent above went on to distinguish TR from "individual creativity research" (see also section 5.3 for a related discussion), providing more precise insight into what he considered research not to be amenable to bear the TR label. With these kinds of claims, clinician-scientists seem to engage in processes of boundary-making, using arguments to delineate between an "us" and "them" and constructing authority by foregrounding exclusive qualities of a group (Gieryn 1999; Gottweis 1998). Here, clinician-scientists are drawing a boundary between experimental practices in biomedicine that are associated with research excellence but that they argue cannot be associated with clinical relevance, and practices that are "truly" geared towards clinical utility. This point was made even more forcefully by a respondent, whom we have seen above generally believes that the training and support of clinician-scientists is a central measure for the development of TR, but who nonetheless distinguished between "authentic" patient-oriented researchers and clinician-scientists that engage in both clinical work and research without having a close integration of the two spheres:

> "Well these people do know how to do research, and become doctors as well. They are not specifically trained for translational science. When I was young, we had these medical doctors, who did either a full thesis or habili-

> tation, some basic work. In the basement of their clinics. And they are now called MD-PhDs, because they are taught how to do the phase I, you know, whatever. Growth, cell cultures. But the translational aspects are not taught, there are no teachers for that. So they become good researchers at the basic level, and don't loose their licence to treat patients, that's what the major outcome is. So many of them, I have no statistics at hand, but many of them decide to stay in the basic science environment" (DE investigator 6).

Clinician-scientists are also quick to make distinctions between themselves and other groups of brokers that might have gotten until recently most of the attention in policy discussion about translation and clinical innovation. The dominant model of translation since the 80s, that of academic entrepreneurship (the creation of biotechnology spin-offs from molecular biology laboratories) and technology transfer, is discarded by some respondents as insufficient for current problems:

> "So these technology transfer themselves would be one of 50 components in a translational network, which you need, you need attorneys, you need patent protection for sure. But they need to be embedded in a living organism with some strategies, forward strategies. And nowadays it seems that they [the technology transfer offices] are the only ones to be able to promote the [translational] projects which is a non-sense" (DE investigator 6).

The quotes above illustrate how the complexity of the TR enterprise seems to have been inappropriately managed by initiatives for technology transfer and through biotechnology firm formation as translational mechanism (see Pisano, 2006). In contrast to these brokering and management mechanisms, clinician-scientists can add to their organisational capacities a certain level of technical proficiency in the technoscientific areas to be integrated, and a motivation for patient-oriented research. These characteristics of clinician-scientists would further cement their claims as authoritative coordinators.

Successes beyond academic medicine

The interview material interestingly illustrates the traction of the policy narrative about the plight of clinician-scientists beyond both this group and policy-makers in the German context. A coordinator of TR initiatives within a major German biomedical centre explained that clinicians-scientists and clinicians were, in her experience, key participants in networks she worked with (DE coordinator 1). In her view, the clinical observations made by clinician-scientists allowed more probing appraisals of how early concepts for therapy might or not be efficacious and safe in the clinical context. A biologist at another centre had developed therapy research programmes that were increasingly closer to clinical development. Through her work in a ‚clinical cooperation group' that brings laboratory and clinical professionals together, she had been able to appreciate

both the unique and necessary contributions made by clinician-scientists and the difficulties of obtaining necessary institutional support and rewards for engaging in clinical development (DE investigator 4). Assertions for increased professional support for clinician-scientists were also uttered by other managers and coordinators of TR partnerships (DE coordinator 2; DE coordinator 4), as were more general perceptions that clinician-scientists made unique contributions to these initiatives (DE coordinator 3; DE investigator 7).

5.1.2 Institutionalisations: USA

In parallel to contemporary discussions about clinician-scientists' functions in the biomedical enterprise, the early 90s saw the emergence of funding mechanisms explicitly concerned with supporting a family of investigations that might be defined as 'translational research', 'translational medicine' or 'translational science'. The very first of them was the National Cancer Institutes' SPORE, which aimed to support research units that combined clinical and laboratory-based expertises in projects that promised to have relevance for human physiology or even clinical intervention within short time frames. In a document of the National Cancer Advisory Board taking stock of the first decade of activity of these centres, the support of clinician-scientists is shown to have been a privileged tool to achieve its objectives:

> "The numbers of physicians willing or able to spend the time needed to learn, develop, and sustain a career as a clinician who sees a substantial number of patients and who also participates in clinical trials and translational research has suffered a steady decline. These clinician-investigators will be viewed as a critical resource in a cancer center and will be supported through the P30 mechanism for their research time" (National Cancer Advisory Board 2003, p. 30).

My interviews with researchers involved with the SPORE programme also substantiated the claim that this mechanism had played a role in renewing training and institutional support for the clinician-scientist profession in the field of cancer. One of them explained how SPOREs were providing exactly the kind of research funding incentives and protected time for research that I have shown had been advocated for, starting in the 1970s-1980s with talk on clinician-scientists and patient-oriented research as 'endangered species':

> "And so what the SPORE grant Career Development Award are designed to do is to take, yeah, promising young people and give them some money to start their research program focusing on, in my case, lung cancer translational research. So you'll take somebody who may have ended up working on fruit flies, instead you start off their career in lung cancer translational research. And you give them a significant amount of money for a couple of years, and it means a lot to a young person who might have

> trouble getting grant support, and once they start getting connected in their field, and they get data in that field, they are more likely to continue in lung cancer research for example. So I think that's really important" (US investigator 7).
>
> "Q: There has been a discussion a little bit about clinician-scientists as 'endangered species'.
>
> A: Well there are not many people who see patients, have private patients, and have big research programmes too. Pretty uncommon. But I've been in practice twenty years now, and I've been able to keep that, you know see patients and have a lab at the same time.
>
> Q: So is the SPORE programme supporting these kinds of…
>
> A: Oh yeah, that's exactly what they are looking for.
>
> Q: So there is some protected time? So the people who will be here …
>
> A: Yeah I only see patient, like I said, I'm supposed to see them one day a week. Where a typical full-time clinician here will see patients everyday, three or four days a week. So they, the SPOREs pay some of my salary, then the university says its OK for me not to see patients everyday" (US investigator 7).

What is also of interest in my discussion with this SPORE investigator was the belief he professed that this mechanism provided tailored institutional homes for the experimental practices favoured by clinician-scientists involved in patient-oriented research.

> "There is value to all different kinds of research, from very basic research to clinical trials. But as somebody who spent time in the lab, getting a PhD and time in the hospital getting an MD, I think my opinion is, that my own skills set is best utilised in a translational research programme. And the SPOREs are the best way to fund the translational research programme in my opinion. So someone who came through as a basic PhD scientist probably wouldn't be interested in the SPORE mechanism like I was. But it's just my own personal desire to do this kind of translation. And to see direct human evidence that we are making a difference in patients" (US investigator 7).

As already indicated in section 4.2, the establishment of the SPORE centres was grounded on the assumption that emerging experimental platforms revolving around large-scale sequencing of tumour tissue allowed new ways to align clinical empirical material with the experimental arsenal of molecular biology. Within the SPOREs, the emerging policy narrative of genomic medicine and the slightly older narrative of clinician-scientists found complementarities and points of shared concern, as one investigator I interviewed made clear:

> "Q: Do you think that you need this kind of clinicians' or medicine' point of view to really capture what is in these biobanks, or could this eventually be

> used by basic scientists. Or it needs to have this interaction between the two.
>
> A: Got to have the interaction. The basic scientists would be able to say, if you gave him a 100 tumours, he could measure his gene. But he doesn't have the experience or knowledge to then ask the second question and that is, what does it mean, and the tumour, and they don't understand what the question might mean, so you need an expert in breast cancer as an example, a clinician who is an expert in breast cancer to be able to study the findings, to make any clinical sense out of it. So it really requires a close collaboration. You either have to be as I said a clinician-scientist, where you can do both, or if you are a basic scientist, you need to work closely with a clinician" (US investigator 6).

With the establishment of the SPOREs in the early 90s and the expansion of this network throughout the decade, clinician-scientists could thus count with a first major policy success. In the mid 90s, NIH leadership picked up on the ongoing discussions generated by Ahrens' work, as well as a report by the Institute of Medicine of the National Academies of Sciences (1994), and formed a Director's Panel on Clinical Research in 1995. Professional conditions for clinician-scientists engaged in clinical research were a central issue examined by this committee and addressed in its recommendations (Thompson and Moskowitz 1997; Nathan 2002). NIH funding was notably set aside to relieve new clinical investigators from some of their training debts. Interestingly, the pull of the policy narrative was strong enough to draw a contribution to the panel from the Federation of American Societies of Experimental Biology, whose membership includes a large portion of laboratory biologists with no link to clinical practice. This panel nonetheless failed to have major impact on the dimensions that most count for clinician-scientists, at least from the viewpoint of its director (Nathan 2002). A bill introduced in Congress to provide additional earmarked funds for clinical research, the Clinical Research Enhancement Act of 1996, also failed to be adopted (Thompson and Moskowitz 1997).

Later on, as the support for TR became priority at increasingly higher level US of biomedical policy-making, the issue of clinician-scientists' professional conditions again captured more attention. In 2003, the then new director of the NIH, Elias Zerhouni, unveiled a „NIH Roadmap". This strategy aimed to stake stock of recent technoscientific advances spearheaded notably by the Human Genome Project, and of a new institutional situation following the doubling of the agency's budget between 1998 and 2003. Although it did not target clinician-scientists specifically, it announced the intention to support the training of an interdisciplinary workforce (Zerhouni 2003). Analysing retrospectively the developments that had led to the establishment of this roadmap, Zerhouni made his concerns for clinician-scientists clearer:

> “we heard resounding concern from basic, translational, and clinical researchers alike that their interactions were becoming more remote and difficult, that clinical research was increasingly less attractive to new investigators, and that clinician–scientists were moving away from patient-oriented research" (Zerhouni 2005, p. 1621).

In building this agenda, Zerhouni could draw from arguments articulated from a reflection exercise on the organisational challenges facing the NIH after increased financial commitment from the federal government and at a time of perceived upheaval brought about a changing experimental landscape. More specifically, these arguments emphasized the role of clinician-scientists in configuring the post-genomic experimental platforms to the demands of clinical innovation.

> „The length of training required, the expense and time involved, and the complex regulatory environment of clinical research have depleted the ranks of those willing to engage in clinical research, and many feel that this trend contributes to the inability to translate basic research findings into improved health. To ensure the success of the clinical research system, there must be a cadre of highly trained clinical investigators for several reasons: to discern the questions to be asked; to ensure that studies are conducted with the highest quality standards; and to ensure that there are trained clinical investigators in all medical specialties enrolling patients in trials. As basic science discoveries outstrip clinical capabilities to apply them, the lag in translating clinical research to practice will continue to lengthen. This can only be addressed by providing coordinated support for stable and rigorous academic training programs, recruiting physicians to become scientists or continue their professional development through mid-career research training, and ensuring that funds are available for clinical research proposals that seek to address significant problems in the diagnosis and treatment of human disease. For these reasons, it is critical that NIH concentrate its efforts to make the most effective use of what is already a sizeable investment.“ (Committee on the Organizational Structure of the National Institutes of Health et al 2003, p.76-77).

The former leaders of the Director’s Panel on Clinical Research put it in a more concise matter, decrying continued lack of attention to the issue even in the wake of this committee’s interventions:

> „We simply cannot deliver the enormous promise of the genetics revolution without close attention to careers in clinical research“ (Nathan and Varmus 2000, p. 1204).

Putting these claims to work, in 2005 Elias Zerhouni extended the agenda set out by the NIH Roadmap by initiating a “New Vision” for “Translational and Clinical Science”. The main component of this vision has been the establishment of sixty Clinical and Translational Science Award (CTSA) in American academic medical centres, between 2006 and 2010. Here again, the support and training of clinician-scientists, but also

"translational investigators" more broadly, is a central concern of the strategy. Indeed, the maintenance of specialised training programmes and "well-recognized career pathways" are necessary components of academic medical centres applying for a CTSA grant. CTSAs were thus expected to provide "homes" for clinical and translational science as an "emerging discipline" (Zerhouni 2005, p. 1622).

Clinician-scientists themselves have mostly responded positively to the institution of the SPOREs and then the CTSAs, sometimes seeing as a vindication of their claims and efforts (US investigator 1; US investigator 4; US investigator 7; US investigator 8).

> "... the CTSAs, it was a great vision by doctor Zerhouni, the head of the NIH at that time... to enhanc[e] the translation of T1 translation of basic discoveries into clinically relevant findings, to enhance the education of new clinical researchers so that we didn't loose altogether that population of people that were increasingly and still are motivated to go into clinical practice and not into clinical research. So the vision, is a wonderful vision, it's exactly what we thought was necessary… The one thing I would close with is, the reason I became the PI of our CTSA was because of my own personal translational. You know, I think if you look at the people who are CTSA directors across the country, they personally have experienced the pleasure and the satisfaction of being in translational science. Most of us, who are CTSA directors, have been moving back and forth between clinical - basic, clinical -basic for most of our careers. And so it made sense that we would lead this programme because we are the ones that have done that for our own careers. And if we could help young investigators do that for their own career that would be the best possible end of our own careers. I think all of us have that motivation" (US investigator 13).

The quote above is taken from an interview with the director of a CTSA, and he went on to further explain that he thought this initiative allowed clinician-scientists to have a real institutional home. This increased support made the specific competences of clinician-scientists, that is, the individual confrontation of clinical observation and laboratory savvy, more readily accessible:

> "But reminding, particularly young investigators today that their clinical observations are crucial in terms of deciding what things really need to be looked at translationally in the lab, in order to understand them. Without that, you've got you know a huge area of almost unlimited scientific inquiry, which may not be directed at the most important questions. Clinically. I am the last one to say that pure science for the sake of pure science isn't useful, it's extremely useful, it's our database of knowledge. But if one wants to talk about true translational research, I think that to be most productive - and of course that's what the NIH and people who are demanding that science show more productivity in terms of new drugs and new treatments - if we want to be the most productive, then the questions have to be focused questions. And the questions can be focused mostly by clinical observations of what we don't understand and what would make a difference in

> terms of understanding human disease in patient care" (US investigator 13).

Another CTSA investigator could see a clear impact of the initiative for bringing clinician-scientists back into the core of biomedical research, after a long period of hardship. This investigator was quite adamant that the major factor that had contributed to constriction of the clinician-scientist pool had been reputation and the lack of legitimacy collectively attributed to patient-oriented research:

> "Again to come back to the political issue around TR, physicians are uniquely situated to perform TR. As the funding, as the recognition becomes more focused and funding this activity has to be present and recurrent, than you will see a return of physician-scientists to the research table. For a while there, it was looking pretty bleak. It was looking like you could never get funding from the NIH for this kind of work" (US investigator 1).

Some clinician-scientists however are also quick to point out that the battle is not over (US investigator 8). The CTSA programme "augurs well for the future of the physician-scientist, but it will require broad commitment..." (Coller 2009: 68-69). Yet it seems that this commitment, if it implies a broad base of actors also taking risks and making deep institutional changes, has not come to pass. Indeed, one of the most ambitious objectives of the CTSA strategy, one that would have encouraged the creation of departments with distinct training and career paths for clinician-scientists did not succeed, mostly due to the persistence of the institutional obstacles such as insufficient capacity to generate clinical earnings long problematised by the policy narrative. As one civil servant working with this mechanism explained:

> "I think that what Dr. Zerhouni felt was that you needed a lot of skill to be able to do clinical research well. And that that should be recognised. And that maybe when there were higher degrees in clinical research, then universities would see the value of having a department of clinical research. It would ensure that clinical research was not done on a sort of small scale, but on a large and highly professional scale. At the moment, well let me change that a little bit, the original request for applications indicated that applicants could propose either a center or a department, one institute within their organisation. So you know if you were the University of California in San Francisco, you could say OK my CTSA will be a department, it will therefore have academic positions within that department that will carry with them a promotion structure, a tenure structure etc etc. Now for the most part, that hasn't happened and almost all of the awardees have actually chosen to have institutes. That's because they haven't wanted to commit themselves to a career structure. You see as soon as you got a career structure, then you have to have a way of paying salaries. And most physicians in this country, or most researchers still get their clinical income from practising within a faculty… And bill within the faculty... so mostly it's the traditional academic department that form the sort of billing structure also

> for an academic institution that allows it to be financially viable" (US policy maker 1).

Despite this setback, the material previewed above has shown a sure impact of the policy narrative of a plight of clinician-scientists within major initiatives for TR established in the USA. This success was also readily exportable abroad, as the next subsection will demonstrate.

5.1.3 Institutionalisations: Germany

German clinician-scientists have recently also taken to editorials and commentaries in a bid to imbue the practices of TR appear with more epistemic authority. In an article for *Nature Biotechnology,* Berlin-based investigator Georg N. Duda (and international co-authors) define the challenge for 'clinical scientists' as an ever growing gap between the advancement of formal knowledge in the life sciences and the capacity of physicians to integrate these into practice, or therapeutic or diagnostic research (von Roth et al. 2011). To address these problems, these authors propose more widespread establishment of training programmes for clinical scientists, and provide as examples the programmes they have themselves put into place in their respective institutions, including at the Berlin-Brandenburg School for Regenerative Therapies. The rationale for founding such a programme and, perhaps more importantly, present it as an example to follow for those interested in strengthening TR, is that:

> "[a]fter all, issues for basic research arise and have to be solved at the patient's bedside or operation room. This point illustrates the need to rethink current medical education strategy toward a realistic 'bed to bench to bed' concept to regain ground for the medical practitioner as a researcher" (von Roth et al. 2011: 1146).

Elsewhere in this commentary, the authors warn against a drift in biomedical research to value 'science for science's sake' over work leading to clinically useful innovations. Another German commentator provides an even clearer proposal to reform institutional policies within academic medical centres. Here, they closely link together issues of dominant models of doing science, the professional condition of the clinician-scientist and the success of the TR enterprise:

> "The key battlefront of translational research is the issue of career advancement... Implementing new ways to evaluate translational researchers and establishing a clear career structure for young academics interested in this path will go a long way toward counteracting the perennial decline in the number of physician-scientists, the ones who are best positioned to bridge the gap between bench and bedside" (Borstein and Licinio 2011: 1568).

Borstein and Licinio are outspoken in their desire to create a global class of 'translational physician scientist' to lead and organise the TR enterprise. The commentaries by Duda and Borstein show how the day-to-day issues of clinician-scientists have been mobilized in the process of policy formulation. Clinician-scientists training programmes such as those presented in the article should not only replenish the effectives of the profession, but also afford legitimacy to TR in the face of dominant models of biomedical research centred on more abstract elucidation of human (patho)physiological mechanisms.

Recent health and biomedical innovation policies from the Federal government of Germany, whose elaboration have been lead mostly from the Ministry of Education and Research (BMBF), have addressed the issue of research conducted by clinicians along the lines first elaborated by the Wissenschaftsrat. Picking up on the problematic elaborated by clinician-scientists, the BMBF's recent *Health Research Framework Programme* reiterates the need for better opportunities for scientific training and to conduct translational research within the network of German academic medicine centres:

> "medical training at German universities is oriented towards practical medical work and includes hardly any training for scientific work. The increasing importance of patient-oriented research should not be allowed to further increase the workload on dedicated young scientists. Research should not be relegated to "spare time", but should instead be regarded as one of the duties of a medical professional and should be accorded corresponding status" (BMBF 2010: 16).

Measures taken by the federal government to change the situation described in the quote include training programmes that were instituted as part of the establishment of specialised networks and centres for clinical research and translational research, as well as through funding mechanisms for junior professorships, notably. The DFG has also set aside funding so that clinician-scientists can be replaced by other physicians for the portion of their time dedicated to research (Bossé, Milger and Morty 2011). The main mechanism put forward by the BMBF to promote TR has been the creation of six German Health Research Centres. These centres are expected to "lead the way in creating framework conditions and structures that are tailored for research and to foster the development of young professionals" (BMBF 2010: 16). These German Health Research Centres are consortia of university clinics each linked to a core Helmholtz Institute (publicly-financed research centres with a mission to pursue long-term goals in areas of research that require heavier investments). The National Centres' aim is very clearly to accelerate the transfer of laboratory discoveries to clinical innovation. The role given to academic medicine in these consortium simultaneously frames clinician-scientists as essential components of this innovation model. A self-described clinician-scientist thus considered that German policy-makers had in fact taken up a leading role

in strengthening TR in the country in the second half of the last decade (DE-Investigtor-1). This respondent went on to explain that the research partnership he led had been able to establish new and specific salary structures that allowed to employ clinician-scientists with protected time for research. This institutional innovation had been made possible by the specific provisions of the Cluster of excellence programme of the federal government.

Aside from these activities conducted by state policy-makers, the German policy narrative about a plight of clinician-scientists seems to have been given impulse most decisively through reforms at single institutions. Throughout Germany, new centres and training programmes have been instituted in recent year with the aim to support TR research programmes. The International Research Graduate School for Translational Biomedicine (FIRST) at the Goethe University of Frankfurt has started to offer a PhD curriculum with a heavy focus on drug development, including experimental approaches but also regulatory affairs and strategic planning. A number of medical faculties and their associated biomedical research centres have opted instead to create Master's level programmes in TR. These programmes target biologists as well as pharmacologists and medical doctors. These include the Munich M^4 Leading-Edge Cluster's Master of Science Translational Medicine; the University of Heidelberg's Master of Science in Translational Medical Research or the University of Leipzig Centre for Clinical Trials' Master of Science Clinical Research and Translational Medicine. Interestingly, an early attempt (1997) to establish a network of MD-PhD training programmes modelled after US curricula in German medical schools had however failed to attract sizable cohorts of students, possibly because of the enduring lack of career incentives for clinician-scientists in the experience of one of its initiators (DE investigator 3). Elsewhere, however, the prime mover behind the ongoing construction and establishment of a new Translational Research Center affiliated to a medical school explained in an interview how the very architecture of this new building was being thought out to help clinician-scientists like himself manage their dual duties in the laboratory and the clinic:

> "I do believe however that we need and will also in the future need the types of clinician-scientists who are involved in patient care, who have gone to medical school, are qualified to treat patients, see the diseases, have a qualification to treat diseases and yet at the same time, have gone through a training programme in biomedical sciences and use these expertise, both areas, to work in a specific field. It is equally important, so we get basic scientists involved in questions of biomedical research. But there is no way, as I see it, as an MD to outsource medical research to basic scientists only. So, I think we need those people and not everybody working in the field must have this dual experience, but a significant group of people should have it. And with other challenges that we face, time demands, bureau-

> cratic time restrictions, you name it, I think it's essential for the universities, and university hospitals, to try to establish an optimal infrastructure that makes it as easy as possible, it still remains difficult, but as easy as possible to achieve this. And these are to some extent trivial things, to some extent more costly things. And this is exactly what we are trying to address. So the trivial things start with having the buildings close to where patient care takes place, yeah, so you can actually walk over and don't have to change your location and don't loose too much time in going to your second workplace… Biomedical research is a professional task and you can't perform a professional task after six, after long working days. This doesn't mean that we don't have the double load, on our shoulders but we have to organise it in a way that they can somehow cope with it. And this implies that they need protected time to focus on their projects only, they need, if you want, also protected time to do clinical work only. And then there needs to be time periods where they find a way to combine both, but with the reduced clinical load. And this is what we are trying to organise, and we are certainly not planning for buildings where nothing happens until 6 pm in the evening. And then subsequently you will try to achieve something. It doesn't work" (DE investigator 2).

The quote above provides another clear empirical instance to show how the policy narrative of a plight of clinician-scientists has contributed to the shaping of recent TR initiatives. The quote simultaneously provides a delineation of the group to be properly understood as clinician-scientists, a description of some of the institutional obstacles they face and concrete propositions for reform being deployed to address these issues. Although in Germany the contours of the issue about clinician-scientists have been quite different then in those of the US case, notably due to differences in the shape of academic medicine in each country, recent initiatives have seen very similar measures being put into place to those witnessed in the USA. This might in fact come in the wake of the increased visibility afforded to the US problematisation of the clinician-scientist issue in the wake of the emergence of TR as a major international policy issue.

5.1.4: The expansion of the translational investigators profession beyond clinician-scientists

The success of the policy narrative of the plight of clinician-scientists seems to be such, that the expansion of the narrative may in fact durably alter its core proposition. Indeed, if an all around advocate of TR such as Barry Coller could recently argue for the creation of a cadre of "translational investigators" taken from the pool of clinician-scientists (Coller 2008), many others now claim that these investigators will be composed of individuals with a much wider collection of backgrounds. The 2010 report that laid the groundwork for the establishment of the NCTAS (see section 5.3) thus emphasized a conception of TR training that was more in line with the one previously advocated by the FDA and revolving around clinical pharmacology and therapeutic development:

> "NIH should work to increase the quality and number of individuals conducting TMAT research. Activities should include developing clear career tracks for TMAT research, including clinical pharmacology. The agency also should assist in training grants for translational research education (including bioinformatics, systems biology, biomarker development, and cross-sector training (including FDA and pharma)), developing programs for navigating regulatory pathways, and establishing curricula in regulatory science" (NIH 2010, p. 12).

The definition of TR training offered in the Translational Medicine and Therapeutics (TMAT) Committee doesn't make any mention of a specific status for clinical expertise. This situation seems indeed to be in line with a re-calibrated focus on sequencing-driven experimental medicine and academic pipelines policy narratives that has taken place with NIH discourse on TR with the arrival of Francis Collins at the helm of the organisation.

In contrast, interview respondents emphasized the continued relevance of brokering collaborations between the clinic and the research laboratory as a professional expertise to elaborate for TR, but that clinician-scientists were not necessarily the only professionals able to achieve this. A pair of respondents argued that there is no single career trajectory that touch on all the important bases in TR, and that a deeper sort of disposition was of greater importance than any formal training:

> "More importantly even then that the degree, whether you got a PhD or an MD is what the person [does] and I think that's what's [important]. If the focus of the person, whether he' an MD or PhD is human disease, not the molecules, but essentially the centre of gravity is what happens in a human disease, I think that's the most important thing" (US investigator 9).

> "I think it works in all different ways. I don't think there is one single paradigm, in different situations it is gonna work in different ways. In my case, I can take something that I've seen in my clinic and I can go to my own laboratory. If its still a hypothesis. If I didn't have basic science training, didn't have a laboratory, then I would need to seek somebody to test what I wanted to test. I think different people are gonna do it differently" (US investigator 3).

The last quote indicates how individual interdisciplinarity (Calvert 2010) and interdisciplinarity achieved through collaboration can also be perceived as alternatives of equal value to these TR advocates. Nonetheless, these respondents had also at other points of the interviews contended that clinical contexts provided unique sources of data for biomedical innovation, and that physicians were thus the bearers of greatly important knowledge. As such, these interpretations highlight the evolution of a policy narrative of patient-oriented knowledge to gradually encompass a broader variety of health researchers with a footing in the clinic, but that do not follow closely the specific trajectories of MD-PhDs. This gradual differentiation could be shaped after the evolution of TR

efforts towards large-scale collaborative efforts (see section 4.3 and 5.3). This point was made especially clear in the discourse of a researcher who had participated the elaboration of a US federal agency's recent instruments to support TR. The policy-making committee she had been a part of had made a conscious decision to move away from the issue of clinician-scientists to emphasize intensified collaboration instead:

> "So one of our initiatives was to think about how are we going to get the workforce that we need in TR. And I lead that, it was one of the subgroups that I lead, but they kept on coming back to 'we need to train more MD-PhDs.' And I disagreed. I don't think that's the solution. I think having more MD-PhDs might, it helps, those are in general the ones doing that kind of research, although not always. In fact, we decided that just because you have an MD-PhD doesn't mean that you are gonna be good at TR. Or you're gonna want to be TR. That it really turned out, say a personality flaw or I don't know, there are some people who are just driven to do this, and are just going to make it work. And I don't think you can train that. I guess what I meant to say was that, we will never be able to, regardless of how much money or effort we put into more MD-PhDs, I'm not sure that's ever be enough to solve the problem. So we never did really come up with a solution, other than, and the committee agreed, we agreed, even though everybody wants to go down that path, that's not what we are going to endorse. What we really need to endorse is to make these teams function. Ways to make people who have expertise in animal models and people who have expertise in human biomarkers and people who have expertise in IGF [insuline-like growth factor] receptor pathway and people who have expertise in GMP manufacturing, we need all those different people to work together. That's what we need, we should not be thinking about training one person to do all those things because that's too many things, and that's wasted" (US investigator 11).

Despite a rejection of the clinician-scientists model in this particular policy-making instance, this interview fragment nonetheless provides indirect but strong evidence of the prevalence of the policy narrative of a plight of clinician-scientists in the US biomedical innovation system. Indeed, there would not be a need to argue *against* the model if it had only offered a peripheral interpretation of the TR problematic so far.

5.1.5 Discussion

The empirical material presented in this section has allowed us to follow the institutional trajectory of a policy narrative about the plight of clinician-scientists in the USA and in Germany. In the USA, an initial period of observation and discussion in specialised literature can be observed (from the 1979 Wyngaarden editorial to the early 90s). This is then followed by intensifying advocacy from clinician-scientists themselves strengthened by parallel, gradual adoption from policy-makers. The SPOREs provided an early policy exemplar in a specific field (oncology) that, combined with further argu-

mentative activity from an increasingly larger part of the US biomedical community, led to broad-reaching intervention in the form of the NIH Roadmap and CTSAs. In contrast, in Germany, a long standing discussion led by public advisory bodies about the quality of research performed in the national medical schools provided an early problematisation of the status of the clinician-scientist. This early delineation of the issue, however, seemed for an extended period to have had minimal impact on policy. By the second half of the 2000s, however, a few well-advertised initiatives dedicated to TR and with a support component for clinician-scientists had been established. In parallel, policy-makers followed suit and adopted the narrative about clinician-scientists as one element within a broader strategy to support TR, actually becoming central members of the discourse coalition according to certain respondents. With the beginning of the following decade, a restricted circle of German policy-makers and leaders of TR initiatives seemed to have established a stable coalition, one who perceived as its audience a silent mass of academic clinicians who were deemed to be involved too seldom in STI activities.

By the time of writing these lines, the issues confronted by clinician-scientists in their daily practices had been successfully articulated in a policy narrative. Through this narrative, it had been possible to enrol a constellation of actors around the specific institutional reforms proposed as best solutions to the issue at hand. The articulation of this policy narrative was effected through a mixture of argumentative practices, including the publication of editorial and commentaries, setting federal policies in white papers, or building new centres and institutes. These argumentative practices provided the mean to engage in the collective coordination and negotiation over intellectual goals and scientific priorities. Policy-makers and clinician-scientists themselves have alternatively taken the lead in these argumentative practices. The fact that policy-makers themselves had been active in reproducing and elaborating on the policy narrative with their own propositions for collective action supports their categorization as full members of the discourse coalition. Other actors of the biomedical field with backgrounds in laboratory biology or project management made reference to the plight of clinician-scientists in making sense of current issues in TR, thus further supporting to need to talk about a discourse coalition in this case.

What might explain differentiated outcomes of argumentative practices about the professional status of clinician-scientists on policy-making for biomedical research in the USA and in Germany? Even if by the second half of the 2000s the general TR narrative had become a global policy theme, it has historically emerged in the USA and was initially concerned with reform of institutions specific to this country (and the TR movement seem to fit nicely in the historical series of reform in the US academic medicine sector studied by Kohler 2008; Marks 1997; or Tobbell 2012). The German biomedical

leaders and academic administrations that spearheaded the establishment of specialised programmes and the use of a policy narrative about clinician-scientists as privileged translational investigators often made so in explicit reference to the US model (Borstein and Licinio 2011; DE investigator 1; DE investigator 2; DE investigator 5; DE investigator 6). German policy-makers seem to have readily adopted the TR policy narrative only as it was becoming a global narrative. This perhaps indicates a greater argumentative authority afforded to overseas initiatives compared to those of a restricted group of local biomedical leaders. It may also be that the policy narrative about clinician-scientists gained in urgency once it had been stabilised as one component within broader TR discussions about crisis in the pharmaceutical industry or failed promises of clinical innovation from the genomic technoscientific programme.

Additionally, the receptivity of policy-makers to what might otherwise appear as particularistic support for a circumscribed group of actors has perhaps to do with the logic of professionalism and its historical role in expanding the capacities of the state. In their own ethnographic account of the struggles of clinician-scientists in the UK and in Germany, Wilson-Kovacs and Hauskeller (2012) highlight the continuity of their advocacy work with that of other professional groups struggling to establish exclusive jurisdiction over a given form of practice. Fourcade (2010) has recently shown how research programmes in field of economics in France, the UK and the USA had been intertwined with the specific forms that professional institutionalisation had taken in each case. Most importantly, professional claims to expertise had evolved conjointly with the specific exigencies of statecraft, and the implementation of given policy objectives could be delegated or helped by mobilizing the capacities of specific professional group. Taking stock of these findings, we could consider that clinician-scientists' models of successful TR play especially well into the current concerns of biomedical policy-makers to make their investments more tangible to patients and citizens. The support of certain professional groups may be a privileged instrument in the implementation of state STI policy, offering a tractable locus of entrepreneurial activity and authority whereas other models of TR might make it seem more intractable by increasing complexity and dividing responsibility between a number of actors. So that it to say, arguments such as those made by clinician-scientists may obtain purchase for policy-makers that can frame a potential intervention from their part as an extension of this traditional mechanism of delegation of policy implementation to structured professional groups.

In another way, clinician-scientists could also obtain the support of a variety of other health professionals by playing with perceptions of benefits and costs, as these have been conceptualised by Baumgartner and Jones (1993 – see also McBeth et al 2007). Construction of costs and benefits can allow a narrative to reach a broader audience, by highlighting how benefits from a particular course of action are to be expected from

a wide constituency, and cost be born out by a few groups. In this case, clinician-scientists may just have been arguing that they have been bearing the bulk of the costs of doing TR, and that with increased resources made available to them, collective benefits might be even more widely distributed.

5.2 Implementing sequencing-driven experimental medicine

Section 4.2 above already introduced how a policy narrative of sequencing-driven experimental medicine came to be formulated around the new articulation of laboratory experimentation and intervention in human (patho)physiology that the genomic and post-genomic platforms enabled. Briefly, advocates of the policy narrative of sequencing-driven experimental medicine contend that major issues in current approaches to clinical innovation are:

- **Molecular biology and –omics platforms are generating great amounts of data and technologies possibilities that could be, but are not currently being fully used to fuel clinical innovation;**
- **The completion of the HGP ushers a new era in biomedical research – TR denotes corresponding changes in the way clinical innovation is performed in this new era, but changes still have to be performed if this era is to be brought about.**

Based on this problematisation, the policy narrative proposes that biomedical researchers, policy makers and other associated actors orient their action towards the following priorities:

- **Further developing sequencing technologies / bioinformatic-driven research specifically as a mean to elaborate new health interventions;**
- **Extending the mechanistic rationality associated with molecular biology towards the clinic;**
- **The use of specific accountability and decision-making tools that combine experimental evidence with management techniques into novel assemblages for risk control.**

The interview material and cases reviewed below further substantiate the centrality of these solutions in major initiatives to support TR put into place in the USA. The policy narrative of sequencing-driven experimental medicine has seen widespread uptake of its arguments, as will be evident in the material examined below.

5.2.1 TR advocates and the policy narrative sequencing-driven experimental medicine narrative

Starting with the interview material, we find that the model of biomedical innovation proposed in the sequencing-driven experimental medicine narrative is dominant in the variety of geographical locales and institutional forms to which the respondents I talked

to belonged. The cultural availability of this narrative seems greater than the two other policy narratives I have identified in my work, and certainly of other less common understandings of TR. As such, a broad stratum of biomedical actors frames their daily experimental practices and the TR initiatives deploying the argumentative repertoire of the sequencing-driven experimental medicine policy narrative.

A turning point in mechanistic understanding of human (patho)physiology

The second half of the 20th century has seen the production of a great deal of formal knowledge shedding insight into the workings of both human physiology and disease pathology. Nonetheless, the development of new health interventions has historically often relied on limited knowledge of expected action of these interventions on disease, complemented with an even great amount of empirical exploration and trial-and-error (Adam 2005; Pisano 2006). The emergence of genetics and a range of associated technologies have been argued to allow for the study of action of drugs directly, to open the black box of the body. This increases hope that therapeutic discovery systems are inching ever closer to "rationalist design" and away from empirical, trial-and-error approaches. By 2009 and later, it was an accepted conclusion, repeatedly discussed in central scientific periodicals, that the post-genomic research platforms developed in the last 20 years had dramatically changed the way to design and conduct biomedical experiments, although work was still needed to adapt these instruments to the specific demands of clinical innovation projects (see section 4.2.6).

These assumptions were widely shared by the TR advocates I interviewed. Respondents contended that the projects their work engaged in at the moment of the interview were made possible and were given a specific connection to clinical matters by the availability of post-genomic platforms. Many respondents expressed the opinion that a threshold in ways of obtaining insight into the mechanistic foundations of disease processes (hence the title of this section) had been reached in recent years, allowing rational therapeutic research and thus justifying a massive move towards TR. A number of respondents (EU policy maker 1) also made reference to the availability of post-genomic platforms as a major rationale for initiating new TR projects:

> "The interest for TR comes now that we have the capacities and knowledge of molecular biology, the capabilities for sequencing are there, it's possible now to understand the pathways more precisely and develop rational interventions from that" (EU coordinator 2+3).

While the quote above is taken from an interview with two coordinators working at a major hub for the coordination of multi-centric oncology drug trials, the quote below comes from a researcher with the traditional background in genetics. He highlights how it is advances in automation and granularity of sequencing that now allows to obtain in

a much more efficient manner detailed information from a given amount of hereditary material collected:

> "I think we are in a very exciting time, because, with the whole genome sequence being done, and all the investment that have been placed later, in high-throughput technology… Because for the first time, with all the DNA sequence capacities, we will be able to actually decipher the causes of diseases, by just looking at the segregation of defective genes in one family. We needed often much more families to do that" (EU investigator 3).

An investigator and administrator at a major German cancer research institution thus explained how he perceived a clear logical progression in the orientations of collective research programmes

> "I think the sort of interesting aspect is that of course for a long time, translation appeared to be quite remote. Because in order to be successful in translational research, you must first understand basic mechanisms of cancer development, for instance. And it has taken us many decades, to develop a basic understanding of important courses, mechanisms, pathways of cancer development. And once these have been, or are unravelled, then you have targets to interfere. Molecules to develop specific inhibitors against, novel assays for the diagnosis of cancer, novel machines for a diagnosis or treatment, I think particularly during the last 15 or 20 years, this is becoming increasingly possible, and this is probably why the term translational research has emerged so strongly… I think there has been a major shift in sort of strategies for well, translational or clinical research. Until the 80s probably, many of the developments in the pharmaceutical area for instance were really screening-driven, the companies had [assembled] large libraries of compounds, hoping that by change, they may come up with an interesting candidate who is active against cancer growth or other diseases...
>
> With all this excitement, of course, there is another level motivation. Sort of exploit it, to join forces, to come together between research and medicine, for instance" (DE investigator 7).

In the interview fragment presented above, the claim of an unprecedented accumulation of knowledge directly structures experimental possibilities for a short-term future. The development of TR is an expression of this more rationalistic present. This perception was often expressed in a distinction between empirical therapeutic research and rationalistic agent development. The first mode of biomedical innovation would refer to a large number of past cases where therapeutics were developed based on a clinical observation, the elaboration of a thin hypothesis (in the retrospective view of my respondents at least) and trial-and-error testing of different compounds until some therapeutic effect could be observed. On the other hand, rationalistic drug design would allow the development of therapeutic hypotheses deductively, from reliable findings on

(patho)physiology. A European geneticist provided an articulation of how the empirical mode of clinical innovation had dominated the history of biomedicine:

> "But if you look at the last 150 years of clinical medicine, then I think that the times that a therapy was developed on a rational basis because we knew what was wrong is largely exceeded by the times that the therapy was just developed by accident. Because some things, some treatment worked. And actually, I think 9 out of 10 drugs that are on the market today, have not been developed based on the mechanism of the disease" (EU investigator 3).

Of course, the claim made in the quote above was used to pave the way for a stronger claim that current methods would drastically change our modes of clinical innovation.

Aligning the clinic to post-genomic experimental platforms

Even if genomics and post-genomic experimental platforms were being argued by respondents to be the privileged vehicles for establishing rationalistic practices of clinical innovation in biomedicine, few contended that past achievement in this technology area were enough to secure a more translational future. Instead, they argue that sequencing-driven experimental medicine will be made a reality if the successful basis of genomics research can be given a slightly more translational orientation.

A main contention of many respondents concerning the means to make sequencing-driven experimental medicine a reality was thus quite simply to have more interdisciplinary work involving both laboratory researchers with access to post-genomic platforms, on the one hand, and more researchers with a good grasp of clinical realities, on the other hand. Deeper mechanistic understanding of (patho)physiological processes had been obtained by post-genomic platforms, but the input of clinical teams on the messy world of real human patients was now necessary to complete the puzzle. Although the proposition sounds almost trivial, this particular component of the policy narrative of sequencing-driven experimental medicine had been widely uttered in my sample of respondents.

A coordinator at a German institution with a number of TR initiatives contended that "the Human Genome Project provided a huge amounts of hints, but that the lab is not sufficient to get answers. You need patients and you need reality". Obtaining observations and evidence from the clinic is a necessity to realize the hopes that HGP and that the Gleevec story (a hugely successful cancer drug) have generated in terms of clinical innovation (DE coordinator 1). Elsewhere, the leader of a German TR centre contended that it was the advances in molecular biology and the –omics platform that both created perceptions of unacceptable delay in clinical innovation, but also the possibili-

ties to bridge the gap between laboratory and clinic so as to allow simultaneous reduction of this delay:

> "… I think there is also increasing awareness of the discordance between the increase in knowledge in basic science, and the potential to actually apply this knowledge in patient care. So as this gap is being realised more and more. And finally the progress that is being made in the methodology and in basic science offers increasing opportunities to bridge the gap. When you think about genomics and concepts of individualised medicine, this is something that was simply not available 10 or 15 years ago. And the worlds of animal models, animal experiments and patient care were very distant. But now, I think moving one direction from bench, from bedside to bench, animal cage to bench, and the other way around, becomes more and more reality, and something that can be achieved, and this is why, I mean, I think we need to refocus things a little bit, and also improve the infrastructure to make this possible a little bit" (DE investigator 2).

For a US CTSA investigator, the amount of attention afforded in the biomedical community to the post-genomic platforms somehow allowed this area of expertise to close on itself. This situation had been especially supported by the amount of collective attraction that had been afforded to technology development. While this investigator himself was convinced of the necessity to use cutting edge tools for –omics profiling notably, he also maintained that there was now a need to "be switching back and forth between model systems and humans" (US investigator 8). An industry RTD scientist located in a biopharmaceutical firm illustrated this problem of self-containment with a very fertile metaphor. It is worth to cite him at length here:

> "I often feel that trying to be a drug discoverer in industry, where all you are limited to is some in vitro cells-based assays and some animal models, it's a bit like being a detective on a murder. Except you're not allowed to go to the crime scene. See? Okay. And that's what it is, you go to a different crime scene. Because it's more convenient. But you are still not studying the disease directly, and for me that is the real challenge to industry. And when we achieve that level of understanding, that should be able to position our drugs, to discover our drugs in the first place but to also be able to position them in the right diseases as well. So that's the challenge that we're facing in translational research, and we are trying to put that right. And it isn't also just about studying patients samples, actually doing experimental studies with patients in real time. So short pilot studies, looking for certain readouts, they are very important and very useful too. Investigating how your drug actually works in patients, once you know it failed, is very important. And the information gained in those clinical trials studies need to be feed back into research to help them understand what to do better or differently the next time. And that learn-confirm cycle between clinical and discovery, isn't as good as it needs to be. And that's an industry problem that we need to improve on" (EU investigator 4).

This respondent makes it clear that the hurtful segregation between laboratory modelling and clinical contexts results in part from institutional boundaries proper to the pharmaceutical industry. Industry normally conducts its clinical research by outsourcing projects to academic centres or contract research organisations, where studies will be structured strictly to answer regulatory requirements. Access to human tissue material, to allow the type of investigations conducted for example at SPOREs, is especially problematic for industry. Biospecimen are usually collected in university clinics, where consent procedures do not allow their access by non-academic third parties. This was one major reason for this firm to be engaged in the pan-European Innovative Medicines Initiative (IMI), as it provided opportunities to collaborate with academic teams with extensive collections of human tissues. Despite the specific situation of biopharmaceutical firms, the validity of this reasoning extends to academic –omics research. Indeed, this argument also echoes the criticism of technology-focused work or in the discourse of somebody such as Francesco Marincola, editor of the *Journal of Translational Medicine* (Marincola 2011). This contention that incentive structures in biomedicine might systematically divert investigators from the research objects and approaches that are most likely to yield important findings for TR projects resonates with similar arguments made around the patient-oriented research discussion, notably.

Stratification in research and biomarkers

In trying to extend the reach of post-genomic platforms towards the clinic and therefore increasing mechanistic understanding of patient (patho)physiology, a number of experimental approaches seem to be privileged as means to extend or complement post-genomic platforms. This and following subsections will detail respondent's belief about how these approaches can better align the clinic to post-genomic platforms.

A majority of respondents referred in one way or another to emerging approaches that focus on pathological and/or physiological characteristics of specific subsets of patients as a mean to conduct mechanism discovery and therapeutic research. The contention here is that a productive approach to develop new health interventions is to focus on these strata of patients, with the increasing realization for example that breast cancer may be an umbrella category that can be declined in various subtypes of cancer. This is expressed by one principal investigator, leader of a TR initiative within a German medical school:

> "That means that we have on the one hand, we know that cancer, even if it is exactly the same cancer, is very different in different patients. And so there is a huge heterogeneity response of cancer to given therapies. And the future will be that cancer therapy will be much more personalised, or individualised, then currently. Currently we have relatively wide strata, which are fine, and help a lot compared to let's say 20 or 30 years ago, but new

> molecular biology methodology gives us options to more and more understand why a given patient and a given tumour is resistant… to a specific treatment. And the future of cancer treatment will be to utilise this knowledge more and more and getting to much more tailored therapies than today" (DE investigator 1).

Stratification in biomedical research broadly participates in the search for detailed understanding of (patho)physiological mechanisms. Identifying biomarkers, which are biological entities that can be measured and allow to monitor activity in a variety of pathological or physiological contexts (Hoelder, Clarke and Workman 2012), allows to classify patients and/or research subjects in specific strata (it is important to note, however, that not all biomarkers are used only in a context of stratification). The use of biomarkers should allow to obtain more detailed information about the potential activity of experimental agents in human subjects than previous readouts allowed. This in turn allows faster generation of evidence from clinical research, evidence that can be more readily triangulated with the findings of modelling laboratories. For example, "translational biomarkers" are used in both animal models and human subjects, potentially providing early indications of whether pre-clinical results will apply to human physiology (Biomarker Commons 2012). As one coordinator at a pan-European TR network explained:

> "You can do the same with patients, so you don't have to wait until you can see something, you can immediately see the metabolism changes. And you kind of develop the traces for the right process in the body, you can see very early on this work or this doesn't work. And this for example is very important at the moment for TR, and they can do that. So this is something where we feel, this is just a helpful thing in TR, biomarker is another one. Which works more or less in the same way, that you just look at certain things, and often it's more on the genomics, metabolomics, proteomics, so you measure the, there are proteins that are generated and from the proteins you can measure, conclude what is happening in the body. And know this works or this didn't work. Or you can find people with a certain genomic profile and you realise for a certain genomic profile, that drug works and the other one doesn't. And then you can do a more individualised medicine. And all this is part of TR, really understanding the kind of, the target where do I want to achieve something, what is the means to do that, like a compound, what should that compound look like, and what are the effects in the clinic" (DE coordinator 5).

The quote above also contains references to one prominent set of claims about the way that post-genomic platforms and biomarkers would be harnessed for clinical innovation, that is the development of the area of pharmacogenetics (EU coordinator 1). Others have already analysed the developments about this area of genomics research (Hedgecoe 2003), so I will not dwell much on this topic here, but it is important to note how these claims participate the policy narrative of sequencing-driven experimental

medicine. A major finding of pharmacogenetics research has notably been that many drugs were influenced by the genetic make-up of patients to which they are administered. For example, a given cancer drug will only show activity in patients with a certain allele of a gene that codes for processes that deal with the absorption of the agent. The genomic studies linked to these cancer drugs thus appeared to increased the rationality of treatment by offering mechanistic explanation of therapeutic action and associated consequences for clinical management.

The two quotes below also makes clear the important link that exists between, on the one hand, efforts to develop technical solutions to obtain more complete understanding of discrete (patho)physiological mechanisms in humans and more detailed readouts of drug action, and, on the other hand, the use of that information for taking managerial decisions about development projects. This theme was already touched upon in section 4.2.7 and will also be developed upon below.

> "The next stage of TR will really try to use these biomarkers or diagnostic tests to identify the patient stratification that you are deliberately going to target your drug against. In the past, we've taken drugs into [incomprehensible] and then look after, which patients did it work best in. That's a very expensive way of doing things, and you also get a lot of noise so the data is difficult to interpret. If we have biomarkers that select a certain patient subset within a population and we believe that our pathway or target is particularly preeminent in those patients, then if we can pick these patients out and give them drugs then we should see a better effect in our phase 2. It's trying to get rid of that early attrition, and edge your bets, put your drugs in the most responsive population you can" (EU investigator 4).

> "But I think more important is at a much later stage, because I think we already mentioned personalised medicine, and very early on these days you have to take into account the stratification of your later patient population, therefore really for which patients does this drug make sense. So from maybe, certainly from certain pre-clinical studies on or certainly from a phase I on you will do accompanying genomic testing on the patients to be later able to say this didn't work on a certain subset of patients, to be able to say why. It's more and more important I think to make the drugs more efficient because it's scary if you look currently at common drugs across various indications, how little efficacy there is actually because patients just don't react to it" (DE TRAIN 3).

TR leaders in Europe and in the USA have thus adopted biomarker and stratification approaches as central instrument in the toolbox that should make the clinical innovation process more rationalistic and amenable to innovation practices. As the material presented here has show, biomarker are also mobilized in efforts to mitigate the deep uncertainties associated with biomedical hypotheses (Pisano 2006). They consequently also participate to proposed solutions for problems of profitability and productivity in the pharmaceutical industry.

Imaging

Some respondents highlighted specifically the experimental potential of modern imaging in increasing the "rationality" or "mechanistic" character of contemporary therapeutic research (DE investigator 5; DE coordinator 5). These techniques allow for example to attach radioactive nano-particules to drug molecules. The radiation traces can be followed using x-ray or other imaging techniques. This then offers a visual representation of the movements of drug molecules in the body. If a drug doesn't reach the organ or tissues its sponsors have intended it to target, then there is possibly something wrong with the therapeutic hypothesis that underpins the develop of the compound or with its chemical formulation. Although medical imaging has a long tradition, which originates in medical engineering (see Blume 1992), some of these technologies have now become closely associated with post-genomic experimental platforms.

In this way, the emphasis on imaging biomarkers expresses concerns for obtaining sophisticated readouts of discrete stages in drug action, instead of more general modelling of disease and health before and after treatment. This also participates in the global trend towards mechanistic understanding of (patho)physiology, as well as the search for means to make human systems accessible to biomedical experiment within the strict constraints of ethical and regulatory framing. The value of these readouts is put in blunt terms by an American clinician-scientist with a long career in both academia and industry behind him:

> "First of all, does the drug get to the brain? Believe or not, there are examples, by very famous drug companies, who had a lot of money investigating anti-depressants or anti-psychotic drugs, and in retrospect, you found out that why you just lost 309 million $ of your development programme is because the drug never got into the brain. And this sounds like a joke, but it's true. Unless you have some way of measuring, you can't be certain what it does" (US investigator 9).

Much like the quotes about biomarker and stratification, here the possibility to closely monitor (patho)physiological mechanisms is shown to have deep resonances for issues of commercial risk and project management. Another respondent focuses more on the potential of imaging to contribute to the development of experimental strategies that allow early clinical research to loop back and contribute to pre-clinical development:

> "The genes, they are all very helpful, but they are only giving you parts of the picture, you need to know how these gene products actually interact in real life in real time in the tissues and cells that your are studying. And this is why I returned to the access to human tissues, and also early experimental medicine studies in patients, bringing to bear some of the technologies that we will perhaps use in research like imaging techniques or molecular labelling techniques so we can track things in the body, in real time"

(EU investigator 4).

This quote also already highlights a theme which will be explored a bit later below: the fact that post-genomic platforms first emerged from a concern for understanding genomics and genes, but that a more deeply mechanistic approach would study genes as one component of broader pathological and/or physiological processes. Thus, part of the TR movement participates in and draws its substance from functional genomics and studies of biological mechanisms as only a temporary step towards detailed analysis of clinical situations.

A unique toolbox?

An underlying thread in the evidence provided so far in this chapter appears to be that a new, specialized and separate area of investigation and expertise is emerging around the translation of post-genomic experimental platforms into the tools of sequencing-driven experimental medicine. Certainly, this area of expertise emerges from the advances of molecular biology (in line with the main contention of this chapter), but claims are now that it should develop into an autonomous area of research.

Nicely rehearsing some of the central arguments of this chapter, the quote from a US consultant with an industry and academic past shows how the emergence of TR has been entangled with negotiations to establish a specific toolbox of experimental approaches that did not fit neatly in either the molecular biology or clinical research traditions, but that nonetheless drew from both:

> "However the general notion of how can you better translate into the clinic from pre-clinical studies if you expanded the array of testing techniques beyond genetics to things like imaging, to things like more detailed pharmacology, then it became clear that there was a lot of useful things to do. And there was a very nice expression, which never caught on but I thought it was very good, Tachi Yamada, who was made head of R-D at SmithKline Beecham, coined the expression 'discovery lab in human'. Can we use the same sort of scientific approach that we use in pre-clinical species in investigating new drugs in human beings? And I thought that was a very good notion. So we changed the name, we changed our focus a little bit, but the same idea, 'discovery lab in human'. So we went from being called investigational medicine, then it was called discovery medicine and finally the name that stuck, and has been adopted by the whole industry, is translational medicine" (US investigator 9).

Respondents have argued that TR could form its own discipline by integrating but redirecting established and relevant expertise from both the molecular biology laboratories and the more research-oriented parts of academic clinics. One respondent mentioned the desire to have a field such as "systems pharmacology" put into place, with the goal of integrating the latest advances in molecular biology (systems biology in this

case) to broad-ranging investigations of the action of drugs in the human body. At present, the creation of such a field would be hampered, however, by regulatory agencies:

> "The regulatory agencies have a big role to play and currently the rules of the game are, if I'm developing a drug for let's say rheumatology, I am highly incentived not to do any studies before my drug is approved, that are related to any other aspects of drug action then is ultimately [incomprehensible on recording] in rheumatology. Because, if I start looking at central functions, this is just an opportunity to get bad news. I have to report to the FDA everything. So what the regulatory agencies need to do is create a safe haven, for so-called systems pharmacology. They need to incent companies to pursue all aspects of drug action, from the earliest stage…" (US investigator 8)

Although the debate about the effect of current patient protection regulations is beyond the scope of the present work, it is interesting to note the proposals for institutional reform that the idea of increased mechanistic investigations in humans lead to. What this quotes make clear is the advocate's contention that institutional reform is a necessary component to achieve high level mechanistic biomedical science.

What is emerging from all these respondents' reflections about how best to conduct TR is the need for a type of interdiscipline with its own resources and institutional resources. This professional grouping should allow closer exchanges between the variety of expertise that are called upon in the development of new health interventions:

> "To integrate the different disciplines and not do one after the other, but have interdisciplinary teams from the very beginning, to make sure you know you don't end up here and find out, "oh that… it doesn't work here". Like "I should have been involved from the very beginning". This is why ideally the, to run the project the competences, the components, the bricks and the brains should be more or less close together" (DE coordinator 5).

The quote above shows attempts to engage in boundary-making to delineate groups that engage in "true TR" and groups that might be using the label more strategically while still engaging in experimental and institutional practices more germane to molecular biology. Discursive practices of boundary–making can often be effected in attempts to establish new fields of research activity (Gieryn 1999), and our material shows a desire from TR advocates to set space for a relatively autonomous area for TR.

Many other respondents also mentioned the importance of having close and intensive contacts between clinicians and biologists in early development an intervention prototype, as a mean to control for common mistakes that non-experts might do and that would bring devastating blows to the resources a typical project (US investigator 4; US

investigator 13), a theme that will be further developed below. There was also evidence that interdisciplinarity is problematic in industry as much as in academic contexts, that teams tend to form silos and that integration across silos remains problematic (EU investigator 4).

Other respondents took the proposition of making TR a discipline of its own much further, dedicating major part of their work to the elaboration of a sort of 'science of biomedical innovation". This was the case of a German pharmacologist, who explained, as I was puzzled by his answers concerning what type of actual TR projects he was involved, that:

> "What I'm doing, I try to further the idea that we need a new science. And what are the toolboxes, what are the algorithms. So I'm not doing a lot of thinking and writing, rather than doing experiments. I still run a lab on these non-genomic steroid actions where I started off some 35 years ago, but now I'm more into the theoretics and I give lectures across the world" (DE investigator 6).

The work of this respondent had involved writing articles and books about how to plan and conduct TR projects, and how to decide which research findings or hypotheses were worth pursuing with development efforts. The "toolboxes and algorithms" mentioned in the quote include a mix of biomedical entities such as biomarkers and management techniques used to calculate risk and design detailed "business plans" for health interventions prototypes. This professor saw his task as particularly crucial considering the successes of notions of TR in biomedical policy, which he contended had not been matched by decisive changes in the actual experimental approaches of his colleagues:

> "I would say, in parallel, if you count the number of chairs for translational something, whether it's translational cardiology or neurology, this word, in scientific terms, has been spreading out excessively. In most cases it doesn't mean anything. It's just someone who does some basic work in the bottom of a clinic. That's not translational science. They have rats in the bottom of the clinic and they [words inaudible in the recording] in another clinic. So the true transmission process, translational process needs to be established" (DE investigator 6).

Again, this quote provides a clear instance of boundary-making with the aim of legitimating a set of novel experimental and institutional practices entangled with the notions of TR against what is perceived as incumbent practices in the biomedical field. This boundary making activity and the argument that TR can form an autonomous and fully-fledged specialty within biomedical research, in my view, comes from the success of the policy narrative of sequencing-driven experimental medicine rather than being a reaction against it. Even when this last respondent is careful to distinguish between

researchers that truly engage with clinical realities and those that do “some basic work in the bottom of a clinic”, his own efforts to establish a translational toolbox are fundamentally based on molecular biology experimental approaches.

Experimental accountability and self-control

As was seen above, there was a widely shared belief by interview respondents that advances in molecular biology and –omics platforms allowed increased possibilities for the average biomedical scientist to engage in clinical innovation projects (US policy-maker 1). One respondent tellingly explained how the average researchers had found out at once that they could be closer to contributing to clinical innovation then they thought:

> “And I think that little by little, with the discoveries that are being done and that are starting to advance treatments in oncology, notably with the first targeted therapies, derived antibodies, specific kinase inhibitors, the gleevecs that treat untreatable patients, we are saying ‘Well now there is something we can do. Us researchers, we are working on kinase inhibitors, and we are discovering that in working on this we can create therapeutics’” (EU coordinator 4).

Nonetheless, given increasing financial risks involved in leading TR projects until clinical development and commercialization or alliance with a big pharmaceutical, many respondents contended that some form of control or evaluation was needed to determine which of these projects would be worth the risk and which would not. It is exactly the widespread feeling that therapeutic research is in reach that have prompted these respondents to define TR as a kind of regulatory science or coordination framework that ensure some level of control when there might be too widespread attempts at clinical development. With the collective pressures on the biomedical field in the wake of the HGP and other large-scale public science investments, there seems to be a belief that translation has to be done in an efficient and convincing matter, without “waste” of resources. As I have already mentioned in section 4.2.7, the narrative about lost opportunities to extract clinical value from the genomic sciences has sometimes lead to claims that greater collective control needed to be exerted in deciding which research projects were worthy of TR leaders’ attention and which not. Many respondents touched on these themes during interviews.

Stories of wasted opportunities and disastrous failures in biomedical innovation where often mustered by respondents to illustrate the need for tighter collective control and professionalization of the conduct of translational research.

> “The way I look at that is that, a lot of clinical studies have been unsuccessful because they have not effectively linked the bench and the bedside... Because translational medicine would suggest that you get a real funda-

> mental understanding of how, what the biology of the target proteins were, how perturbation of the proteins influence the phenotype in transgenic models or just rodent models. Then, when you've seen changes there, then move to the clinic. But instead, he had a drug, they showed that the drug worked and jumped right into the clinical trials with a… just an early formulated hypothesis and no science to support it. And that's where we are all starting to say, well this clinical trial or that clinical trial would have had a different outcome if it had been undertaken in the context of translational…" (US investigator 3).

We can follow-up on this problematisation of collective "un-ruliness" by a similar point made by another researcher. This second respondent brings out the need to attend individual scientists more, and make colleagues realize that if the revolution in molecular biology provided many opportunities for the average researcher to engage in TR, this also means that appropriate efforts at validating hypotheses have to be made. Here, the themes of waste and irresponsible use of–omics platforms is even stronger:

> "So I'm gonna spend the next 10 years with a mice model to see that if you put the protein [incomprehensible word] and then you're gonna block it, you're gonna cure cancer? That doesn't work. And it doesn't work, because the guy forgets well there are 4,000 proteins that are over-expressed in cancer, that's not the only one. It's a totally different problem... So this to me is the intellectual problem with translational medicine, of course there are many other issues. But I think one of the biggest one is really the wasting time. I think that's a problem of the translational medicine people in [incomprehensible word] I mean they want to do it, but they are not gonna do it, they are gonna do, won't do clinical studies or anything because it's costly, getting samples to study what happened in the patients, it's costly, it's time-consuming, it's difficult to establish. So forget about them, you do the usual phase III and you see if the patients survive or not. Which really is what most of the times happens, and then you waste all the time and the money, a billion dollars, and you still haven't learned anything" (US investigator 10).

These quotes from American clinician-scientists at public research institutes makes clear the interdependencies between a number of trends in biomedical research which are now finding their expression in the TR movement. Here, we can observe an overarching concern for making sure that the TR label and associated financial support is provided only to certified hypotheses. In this respond's understanding, an inordinate number of RTD projects are based on faulty premises, on hypotheses that are not robust enough to justify RTD activities. For this respondent, the representation of excellence revolving around ingenuity and creativity in the life sciences, and the economic rewards that have been awarded to star scientists (even those with wanting economic or managerial credentials) had contributed to this proliferation of RTD projects. By bringing robust clinical experimentation back into the discovery process, a more discriminating filter for new therapeutic hypotheses could be elaborated. TR is thus associ-

ated with more self-control from scientists, and the idea that better collective management of funding resources and experimental efforts are needed to repair the reputation of the biomedical sciences. Another respondent provided answers that support this interpretation, although in this case it applies to the pharmaceutical industry. It is worthwhile to quote from his interview at length:

> "Again, it's the same genetic revolution that got me involved in this business at all, I didn't realise it at the time, but I realised that the dramatic change that happened in the industry around this time of sequencing of the human genome. It went from a very practical empirical choice of targets, to a very theoretical one. What do I mean by this? Before this current era, where did our most biomedicines come from? They came from, for example, herbal products, that over millennia people had discovered that opium poppy is good for pain, that foxglove is useful for congestive heart failure, willow bark is good for fever - aspirin - the point is, you already knew something in this mixture works for particular human diseases or conditions. The enterprise wasn't in particular about if it works, but what are the active principles, how can we purify it, how can we make it longer half-life, less toxic side effects, but you already knew that it worked. Now we switched to target-based drug discovery, which is what this genetic revolution brought us. And this now becomes very theoretical. Somebody checks a gene database, say 'oh! This looks like it codes for a potassium channel', some similarities, and then you do distribution studies and 'oh! This potassium channel is in the dorsal root ganglia channel'. And there's a theory 'Well, it must involve nerve conduction in these cells, maybe it will be good for pain'. Very very theoretical, and you do not find out if that hypothesis is correct until 10, 12 years, 30, 40, 50 million dollars later, if this hypothesis is correct! That's traditionally in the phase II studies, and by that time you've already invested almost 10 years, maybe a little less, certainly invested tens of millions of dollars. And guess what? Most of the hypotheses have turned out to be incorrect. So again, you went from a very practical approach 'how can we make it better' to 'gee I wonder if this will work'. That's why we need translational medicine... In the industrial enterprise, how can we help our company decide quickly and efficiently if that initial hypothesis is correct, or if it was a nice idea, but it doesn't work. Before you spend a whole lot more money on other developmental trials" (US investigator 9).

The last part of this quote nicely ties into the policy narrative of pharmaceutical crisis, yet for the purposes of this section, it is also interesting to note how the same revolution in research methods that allowed to moved beyond empiricism and the trial-and-error approach of early times is here made to carry its own set of risks. In fact, what this respondent shows, is that the location of empiricism and rationalism have been displaced with rational drug development, but trial-and-error has not been reduced. Trial-and-error has been displaced to clinical research, with clinical studies now becoming tools of validation whereas they might early have been used to calibrate an intervention with proven action for a given therapeutic hypothesis. So in this sense, TR becomes a tool to gather early evidence of the clinical validity of hypotheses and, espe-

cially, trim out those hypotheses and projects with a higher chance of failure. Drawing on the toolboxes and algorithms mentioned in the subsection above, TR should provide, in this set of proposals at least, a recognized locus of expertise in coordinating and controlling clinical innovation projects, with all the consequences in division of labour and hierarchies of that centralized expertise entails (Shrum, Genuth and Chompalov 2007).

In a way, what the respondents quoted in this subsection call for is increased self-control, discipline and humility from their peers. In this interpretative repertoire, TR does not stand for a savage and uncoordinated push of early technologies towards clinical application (Balaram 2009; Maienschein et al 2008). On the opposite, successfully establishing TR capacities means implementing stringent collective means of evaluating the robustness therapeutic hypotheses that are candidate for translation work and conducting this work in an orderly manner. Apparently purely experimental constructs such as biomarkers and imaging technologies also participate in the exercises through which risk or robustness is assigned to certain hypotheses.

5.2.2 Traces of a policy narratives of sequencing-driven experimental medicine in recent TR initiatives

As was seen above, the events surrounding the establishment, maintenance and completion of the HGP and its branching out into the post-genomic platforms (-omics and bioinformatics, systems biology, synthetic biology, advanced therapeutic gene and tissue engineering) have created powerful rationales for engaging in a number of new or renewed socio-technical practices directly spinout out of these technological developments. The following lines examine how some of the proposals have put into practice in central TR initiatives.

SPOREs

SPORE were founded in 1991 by the US National Cancer Institute with a goal to “promote interdisciplinary research and to speed the bi-directional exchange between basic and clinical science to move basic research findings from the laboratory to applied settings involving patients and populations” (National Cancer Advisory Board, 2003, p. 3 – notice how the idea of bi-directionality is present at the founding moment of TR). To do so, they support both infrastructure development at the selected institutions, but also provide direct funding to support investigations that participate in clinical innovation. In 2011, there were 68 SPOREs, which accounted for 2,6% of the total research budget of the NCI with a bit less than 134 million dollars being awarded in total (NCI 2011)

SPOREs are awarded to centres with a clear programme and capacity to take findings from basic research closer to clinically valid interventions, or to take observations from the clinic or population studies back into the laboratory and investigate its implications. The goal of the programme is to support centres to "conduct research that will have the most immediate impact possible on reducing the incidence and mortality of human cancer" (National Cancer Advisory Board, 2003, p. 11). To be able to obtain such an award, applying centres must maintain repositories of tumour specimen, to foster collaborations between clinicians and laboratory scientists, both in-house and externally; to collaborative with other SPORE centres in setting research orientations: to have at least four experienced principal investigators leading projects; and to have capabilities in population-based studies of early cancer detection (National Cancer Advisory Board, 2003). SPORE programmes were also felt to be some of the privileged sites for early introduction of genomic sequencing technologies and bioinformatics more broadly, though tissue-typing activities.

NCI civil servants work together with prospective medical centres and their principal investigators to make sure that proposals made to the programme's calls are "translational enough" (US policy-maker 2). This often means making concrete plans for clinical trials when only pre-clinical studies were included. Indeed, SPOREs have a mandate to support research that is relevant for humans within five years. Accordingly, the work primarily done at SPOREs then, according to a programme manager, is mostly biomarker studies that use human tissues. Thus a requirement provided in the original call for application thus mentions how "research projects must be headed by independent investigators and oriented toward translational research activities using human materials and human subjects which address new, innovative possibilities in breast cancer research" (*The Cancer Letter* 1991, p.3). One case examined in Section 3 provided a snapshot of the kind of work with human tissue and clinical trials being conducted in SPOREs. One SPORE investigator I interviewed considered that this specific research orientation fostered by the NCI support mechanism had real consequences on the type of projects emerging with the centres:

> "So there is a lot of unique things about SPOREs, I mean one of them is the translational focus. And that is that you take things from laboratory observations, to make a difference in patients within 5 years. You know, they have that as a mandate, in the SPORE programme. I think that that's unique, I don't think they have any other granting programmes that makes that. So that defines the kind of things you work on, you can't do a project that is simply in bacteria, you know and then expect in 5 years to be making a difference in patient. So that defines the kind of projects... But several of the things that we are working on actually were, in the laboratory, were based on specific patients, things that we saw in the clinic and then we took that patient's tumour, studied it in the lab and then found different things.

> And then several of the projects in the SPORE and then took those findings from the lab and then brought them back into clinical trials in the patients. So that is exactly what the programme is designed to do. And so we have good examples of having accomplished that" (US investigator 7).

The specific environment that SPORE supports was also mentioned by another investigator at another centre, showing how this orientation goes beyond joint projects to frame even the individual projects of basic scientists normally removed from clinical realities:

> "We've always had a mixture in our department or in our breast centre where we had some clinicians, some basic scientists, and some clinician-scientists, just the exposure of clinicians to basic scientists and vice versa tends to generate a theme of TR. Some of our basic researchers, instead of being where they were, they could have just been just basic researchers. Now they tend to orient their basic research around a clinical issue" (US investigator 6).

20 years after the appearance of first hopes for engaging experimental medicine in a new manner through sequencing technologies, the current pool of SPOREs (that went from an initial number of 4 to 63 now) seems to have borne out the promises of sequencing technologies for enabling experimental programmes that draw heavily from clinical material. References to the SPORE as exemplary TR initative have been made in other important policy formulations for TR, including the FDA's *Innovation / Stagnation* report Indeed, in a 2003 review of the mechanism, the National Cancer Advisory Board, which counsels the US president on cancer research, noted the impact of the initiative on the oncology landscape:

> "The success of the SPORE P50 mechanism has been to legitimize, popularize and advance translational cancer research. The program has galvanized the formation of basic/clinical teams focused on particular disease sites at many institutions, resulting in novel and effective approaches to cancer prevention, diagnosis, and treatment, and producing better understanding of the biology of cancer from different sites at the clinical, cellular and molecular levels…" (National Cancer Advisory Board, 2003, p.11).

This quotation is also remarkable for showing biomedical actors' own contentions that the kind of research understood as TR was in need of legitimation. A SPORE investigator, who was also a pioneer in establishing repositories banks of tumour biospecimen and conducting tissue typing, mentioned how the mechanism had allowed institutionalization and recognition for this specific approach (US investigator 6). A programme manager also mentioned how SPORE was the first NCI initiative that tried to provide "specific evaluations" for TR projects, at a time when they had been in competition with hypothesis-driven research done in animal models for example (US policy-maker 2). This evaluation mechanism, already in 1992, addressed issues of legitimacy and peer

recognition that were still relevant in discussions about TR models 20 years onwards. SPORE investigators may have been early pioneers of the biobanking field.

Clinical and Translational Science Awards

The Clinical and Translational Science Awards (CTSA) launched in 2005 with an aim to fund 60 academic medical centres by 2012 (from a total pool of 144 members of the America Association of Medical Colleges), for a total investment of 500 M$ per year. The initiative is associated with a clear volition to engage in discipline-building, with then NIH director Elias Zerhouni using the intervention as a call to establish TR as a recognized domain of biomedical research in its own right:

> "The CTSAs will advance the assembly of institutional academic "homes" that can provide integrated intellectual and physical resources for the conduct of original clinical and translational science. We anticipate that the creative installation and development of these environments will, over time, enhance the theoretical underpinnings of the discipline, provide much-needed educational programs, contribute to the growth of well-structured and well-recognized career pathways, and provide a research environment that is more nimble, conducive to, and responsive to the demands of modern translational and clinical research" (Zerhouni 2005, p. 1622).

CTSA efforts at institution building for TR were crucially framed by the context of US biomedical research in the mid 2000s, with the completion of the HGP having just been achieved and expectations of clinical outputs compounded by budget increases at the NIH. Indeed, the CTSAs seem to provide institutional form to the claim that the alignment of clinical research with sequencing platforms is the best programme to achieve boosted clinical innovation productive. Very clear evidence of this was provided in another of Elias Zerhouni's statements about the goals of the CTSA initiative. The following text fragment clearly shows the workings of this rationale, but also how makes clear some of the argumentative work through which it is imbued with an effect of urgency: it is being actively entangled with the issue of demonstrating responsible use of the public resources being made available to the field:

> "The groundwork for the development of the CTSA program has been formed through the doubling of the NIH budget. An example of the explosion in genetic information and technology is the International HapMap Project, led by the NIH, which was completed in 2005. This project showed the power and the relatively low cost of using selected single nucleotide polymorphisms (SNPs) to study human haplotypes. These new findings can be applied to the study of large populations and will have immense benefit in clinical trials and studies that are storing DNA samples. Activities in genomics, as well as in development of new molecular entities for treatment of diseases, can be undertaken as partnerships with industry through well- defined agreements. **The CTSAs can ensure that, through their degree-granting programs, researchers will have the training to work in**

> **multidisciplinary teams that can use the new tools in genomics and proteomics as they design their clinical studies and trials**" (Zerhouni and Alving 2006, p. 4; my emphasis).

Most interestingly, CTSAs funds are awarded only to academic medical centres having very specific requirements in terms of experimental and clinical capacity. This includes having strong basic science and clinical research departments, a nursing sciences centre, a training component for junior investigators, community outreach initiatives, and a support infrastructure offering services with respect to FDA regulations, intellectual property right, institutional review board (IRB) approval, or coordination of clinical trials. The centres should be connected within networks that include industry and community groups, and the CTSA award is also wanted as a mean to increase public awareness and trust for clinical research (Zerhouni and Alving 2006). Funding awarded for individual CTSAs ranges from 4 to 22 million dollars a year (US policy-maker 1).

The CTSAs was only the second major NIH initiative to bear the TR label after the SPOREs, yet it did not carry over the relatively narrow experimental programme of the NCI initiative (revolving around early clinical trials and tissue typing studies). In fact, the main aim of the mechanism seem to legitimatize TR as a broad research programme that mobilizes multiple disciplines, medical specialities and organisations in a varieties of pathways to conduct patient-oriented research. Even with the explicit focus towards T1 activities (laboratory manipulations and early clinical research), some CTSAs have been established with a clear focus towards public health and health systems research, notably. This is partly explained by the origins of the mechanism in an earlier NIH funding mechanism, GCRCs. GCRCs were a network of core platforms for clinical trials located in American Medical School hospitals since the 1960s. The CTSAs replace these centres (although attribution was competitive and not all institutions with a GCRC obtained a CTSA), thus conserving a strong orientation towards support for clinical research, but also considerably expanding their remit (Califf and Berglund 2009). Nonetheless, developing clinical sequencing capacity remains a central, transversal concern in all CTSAs, necessarily leading to interesting combinations in those centres more aligned with areas such as public health or nursing.

Examining the details of the initiative, it is possible to see how a policy intervention whose immediate targets are often towards the side of clinical research can participate to the realization of the sequencing-driven experimental medicine agenda. CTSAs notably aim to provide interoperable bioinformatics and biobanking nodes accessible throughout the consortium of institutions, thus broadly allowing the expansion of the tissue typing studies that are at the centre of genomics's claim to relevance for the clinic.

On the side of clinical research, the CTSA provides support to revitalize and expands centralised infrastructures in academic health centres that can tackle issues that GCRC struggled to address, such as increased regulatory burdens for the conduct of trials, or growing difficulties in enrolling patients in clinical trials, especially those belonging to minority groups (Heller and Melo-Martin 2009). It also aims to strengthen clinical research management systems with continuous quality improvement principles, create complimentary loci of expertise at different CTSAs to obtain a „clinical trial network of networks“, or to develop a national phenotyping system with standards and shared informatics solutions and which will contribute to human tissue typing studies and clinical studies (Reis et al 2010, p. 465).

The other major component of the CTSAs lies in improving capacities for coordination across departments and disciplines that may have to come together for TR projects that are to be initiated within academic health centres. It also aims to increase the stewardship of projects by enabling principal investigators with intervention hypotheses to easily call upon these collaborations and to access centralized services for dealing with complex issues such as regulation of commercial planning.

As such, communication and exchanges between clinic and laboratory are expected to take place not only within the confines of single medical schools, but also across the whole CTSA consortium. With IT infrastructure aiding, resources for a “national resource inventory, research networking, and data sharing” are expected to provide teams in CTSAs access to the best expertise in complimentary areas of investigation available across the whole consortium (Califf and Berglund 2010, p. 459). In fact, the “CTSA should serve as a federated network to conduct multisite clinical and translational research studies to optimize the efficiency of core facilities, to develop research tools, and to engage common stakeholders (e.g., lay community, industry)” (Reis et al. 2010, p. 464).

Stewardship of more upstream projects within local institution is accomplished differently in each CTSA, but in many cases, principal investigators directing the local awarded centre have been provided with high-level administrative powers within the medical faculty (Heller and Melo-Martin 2009). Such organisational measures can aim to facilitate the generation of intervention hypotheses and product candidates at the preclinical level, as explained by one CTSA director:

> “And the dean basically changed, is changing the structure of the institution from one that is department-driven, so you have a department of medicine, a department of paediatrics, department of anastheology into institutes, whereby someone like me who is a pediatric allergist and immunologist, interested in immunology, I have much more in common with immunologists then I do with somebody doing paediatric cardiology. Rather than having all

> these disparate areas, I interact with this immunology group, in both in medicine, the transplant people, the cancer people, because we're all interested in some of the basic underlying mechanisms. And so by organising that way, you are getting people of similar interest who can interact together in a more effective way, and you know, you're not blocked by this departmental issue" (US investigator 12).

Although the problem-oriented approach to setting up organisational divisions described here in universities is not entirely novel, it is certainly interesting to see such an approach implemented around specific mechanisms or ensemble of mechanisms. This highlights the grasp of mechanistic rationalism at the organisational level, in addition to its central position in the design of experiments already covered earlier in this section.

Elsewhere, it was the eventual movement of intervention candidates towards clinical development that were targeted for major CTSA efforts. Additional mechanisms such as earmarked funding for pilot and „proof-of-concept" studies bringing together teams from both the laboratory and clinical backgrounds provided incentives for increased exchanges. For example, the Vanderbilt Medical School launched in 2007 "Clinical and Translational Research Studios". This mechanism allows investigators to organise meetings to discuss hypotheses or projects proposals, with a dedicated coordinator finding experts across various areas of practice relevant to the proposal to participate to the discussion (Byrne et al 2012). The following two quotes come from interviews with directors of CTSAs both highlight the concern to make resources and collaboration partners readily available to biologists and laboratory-based investigators, so that promising research can be quickly transformed into development projects.

> "It's not typical for someone with a PhD in biochemistry, biology, chemistry, physics or biophysics to just hold and drop what they are doing and become an MD, but it is becoming crucial, and another reason why these CTSA exist, if a basic scientist makes a finding and that person thinks that the thing has some sort of application for clinical medicine, reads enough to know that it should, and then what does that person do? That's what the CTSA is supposed to enable, that they want close collaboration between the clinician and the scientist so that it's not that the basic scientist is just going to turn into a clinician it's that basic scientists need to know what a clinician need, what is a clinician looking for in terms of testing findings that might help the clinician say this is a person I want to collaborate with, to suggest maybe another disease, blood samples from another type of patient then that the basic scientist had looked at" (US investigator 4).

> "What we try to do is match up basic scientists with investigators who are willing to take that step, you know to get it into humans. So we look for ideas that are out there, we look for doctors who pick that up and match them up. The basic scientists here complain that they have lots of ideas but they can't get the clinicians interested. And I'm thinking that's really weird, I can't imagine that's true. But what it probably really means is that they don't know who to go talk to about their ideas" (US investigator 1)

These initiatives also appear to be reaching their objectives. A 2011 survey of CTSAs showed developing (although by no mean extensive) central capacities in these institutions to help investigators design and initiative their own clinical trials, so called investigator-initiated clinical research (Berro et al 2011). Traditionally, much clinical research at medical schools is initiated by the private industry or by government agencies, and academic teams may or may not be working in collaboration with these sponsors. Data on investigator-initiated clinical research is a sure sign of TR activity at an institution, since it implies that a local investigator is initiating a clinical research project to develop a health intervention that she or another colleague have themselves elaborated, rather than being studies sponsored by external pharmaceutical companies, for example.

The CTSA competition and the broader NIH policy it articulated announced a shift in the role ascribed by the federal agency in the biomedical innovation enterprise to American academic health centres. Academic health centres up to that point had been able to run a patchwork of patient-oriented research, clinical research (often for pharmaceutical sponsors) and laboratory-based projects rather separately, based on the initiatives of its pool of investigators. The new imperative was then to have much tighter interaction between the proponents and developers of post-genomic platforms with teams engaged in clinical care and clinical research. Yet, impetus for these collaborations was predicted to come mostly from pre-clinical side advances. What is apparent in these observations is how the sequencing-driven experimental medicine also incorporates the idea of closer integration “between bench and bedside”, but how the locus for the generation of intervention hypotheses systematically tends to be attributed to laboratory-based scientists, with all the implications of such a model on the shape of formal coordination an stewardship measures put into place. This is in sharp contrast with patient-oriented research narratives, for example, where the explosion of knowledge brought about by molecular biology is framed much more modestly as offering an improved toolbox to investigate questions that can only be generated by clinical practice.

National Center for Advancing Translational Sciences

In December 2010, Francis Collins, who had succeeded to Elias Zerhouni as director of the NIH, announced his continuation of his predecessor’s priority on TR by the reorganisation of relevant activities at the NIH around a new Institute of Health, the National Center for Advancing Translational Sciences (NCATS – Wadman 2010; Harris 2011). The CTSAs, as well as a number of other programmes concerned with fostering therapeutic and TR research with the NIH, were to be moved to the new Institute. The Institute that previously housed the CTSAs, the National Center for Research Resources (NCRR), was to be dismantled, and its surviving programmes not relevant to

TR moved to the NIH Director's Office. On December 23, 2011, NCATS was officially established. Its director, Dr. Christopher P Austin, had worked as advisor for TR matters at the National Human Genome Research Institute, notably, and was previously employed by Merck where he concentrated his efforts on "genome-based discovery of novel targets and drugs" (NCATS 2012).

In establishing NCATS, Collins accessed to the demands of the NIH Scientific Management Review Board responsible for elaborating a *Report on Translational Medicine and Therapeutics* earlier that year. This committee had argued for the establishment of a new institute dedicated to TR within the NIH based on observations of a unique situation in biomedical innovation systems, one that it described in the following terms:

> "Developing new therapeutics for human disease is an inherently risky, complex, and challenging process. The outcome is often disappointing; 95 percent of candidate drugs prove ineffective. Biotechnology and pharmaceutical companies face myriad challenges in their efforts to develop new molecular entities and resources for research and development are shrinking. Moreover, patent expirations and an increasingly cost-constrained healthcare system will result in further revenue losses for these industries.
>
> Paradoxically, advances in genomics and molecular biology have generated unprecedented numbers of new molecular targets for developing potential therapeutics. Moreover, academic investigators, in large part with support from NIH, now have access to resources (e.g., technologies, services) that enable them to participate in translational medicine and therapeutics development in ways that were not previously possible. As the current landscape of translational medicine continues to evolve, a new model for therapeutics discovery should be employed to accelerate, improve, and streamline efforts in this arena" (NIH 2010, p. 3).

The first paragraph describes elements of a perceived crisis in the pharmaceutical industry. This is in fact the focus of what I consider to be a different policy narrative (examined in sections 4.3 and 5.3), but I have left it here to highlight the interrelations between these different narratives (a point I itself explore in chapter 6). The second paragraph clearly highlights the framing of the future NCATS as a mechanism to increase the availability of post-genomic platforms for TR projects. Indeed, the text gives off the impression that technological development itself is pushing biomedical researchers to consider getting involved into TR. An additional quote from the *Report on Translational Medicine and Therapeutics* substantiates this interpretation that for the authors of this document, the development of post-genomic platforms is a cause for increased orientation of academic researchers towards TR work:

> "Recent scientific discoveries and technological innovations have provided an unprecedented window of opportunity for accelerating the development of new therapeutics. For example, the discovery of the molecular basis of hundreds of diseases has generated a substantial inventory of potential

> new therapeutic targets. Academic investigators are playing a growing role in identifying lead compounds for pre-clinical testing and, in some cases, clinical trials, as they now have access to resources enabling the conversion of fundamental observations regarding disease into assays for screening hundreds of thousands of compounds to identify promising leads for further development. NIH should capitalize upon these scientific advances to streamline the process for therapeutics development and advance the translation of basic discoveries into new diagnostics, treatments, and cures" (NIH 2010, p. 7).

If the documentary material presented above shows the grasp of a policy narrative of sequencing-driven experimental medicine within the NIH and associated biomedical leaders, the concrete mechanisms housed within the NCATS confirm a strong orientation towards "rationalist" intervention development strategies based on post-genomic platforms. Central programmes of the NCATS can be considered to make intensive use of post-genomic platforms, including "Assay development and High Throughput Screening", "Molecular Libraries Probe Production Center", "NIH Chemical Genomics Center", "RNAi", "Identifying and Validating Drug Targets". The *Division of clinical innovation* is largely composed of the CTSA programme, which itself is not focused solely on clinical research, while the *Division of pre-clinical innovation* has a variety of mechanisms. As such, one can see a strong focus on post-genomic platforms here.

Francis Collins, in presenting the experimental strategies that would be privileged at the centre, very much seems to carry over the agenda he advocated for at the time of the completion of the detailed draft of the HGP (Collins et al 2003; Collins 2011). Areas of specialization for the NCATS include:

> "Data-intensive strategies – from GWAS analyses, to deep sequencing of the genomes of individuals with exceptional phenotypes, to studies of epigenomic regulation of gene expression, to more comprehensive methods to assess proteomes, metabolomes, and cellular pathways – have exposed many new potential avenues for clinical intervention" (Collins 2011, p.2).

Collins here draws upon the best that the frontier of post-genomic tool development has to offer and frames these developments as translational opportunities with direct potential for clinical care. Offering clear support my assertion that TR is understood by this specific discourse coalition as the embedding of post-genomic platforms and clinical experimentation in a tight feedback loop, Collins himself makes a clear connection between the TR enterprise in 2011 and the beginnings of the HGP in 1990:

> "Although the parallels are not precise, the field of translational science today faces some challenges that are similar to those of the genomics field in 1990. For example, little focused effort has been devoted to the translational process itself as a scientific problem amenable to innovation. As was the case with genomics, translational science needs to shift from a series of

> one-off solutions toward a more comprehensive approach" (Collins 2011, p. 2).

Other important areas of future work for the NCATS do include the more traditional expertise of pharmaceutical RTD, including medicinal chemistry, chemical informatics and bioinformatics, toxicology and clinical trial design. But even those areas are re-shaped, in Collins' vision, by recent policy emphasis on biomarker development and the data-driven approaches described above. The initiative marks renewed investment in the post-genomic platforms as a symbol of future medical revolution.

Institutional practices of accountability within TR initiatives

Subsections 5.2.1 and section 4.2 have shown how a particular theme of accountability has developed at the intersection between the problematisation of a perceived lack of tangible outputs and outcomes of the post-genomic platforms, on the one hand, and broadly available discourses of audit and performance evaluation in western societies (Leonelli and Sunder Rajan 2013; Power 2003a; Power 2007), on the other hand. In this subsection, I am able to show how this increased emphasis on accountability is transported in the actual experimental and organisational practices of new initiatives.

One of the most interesting mechanisms elaborated by TR advocates as a mean to increase the coordination and efficiency of the clinical innovation enterprise has been a series of "developmental pathways to clinical goals" elaborated by the NCI's Translational Research Working Group (TRWG - TRWG 2007). These process diagrams (see Figures 6 and 7) aim to provide a concise and simplified representation of the innovation process for various classes of interventions and diagnostics in oncology. They highlight decision points and dependencies, feedback loops and iterative components of the various activities involved. These figures were published in a series of articles for the journal *Clinical Cancer Research*. The aim, then, has increasingly been to try and elaborate collective mechanisms or blueprints that individual investigators interested in starting TR projects may use to get a better grasp of what is involved, what to plan for and avoid costly and ill-placed development efforts.

Indeed, the first three boxes in the "generic development pathway" aim solely at evaluating whether investment in a given interventional hypothesis will be worth the TR efforts and whether there is good reason to believe they will lead to substantial benefits to patients. An investigator I interviewed and who participated in elaborating these pathways justified their creation and diffusion through her own difficult experience starting a TR project based on laboratory findings. She reflected that she would have done things differently if she would have been more prepared for what this TR work exactly involved and could have made keener decisions, both in terms of management and

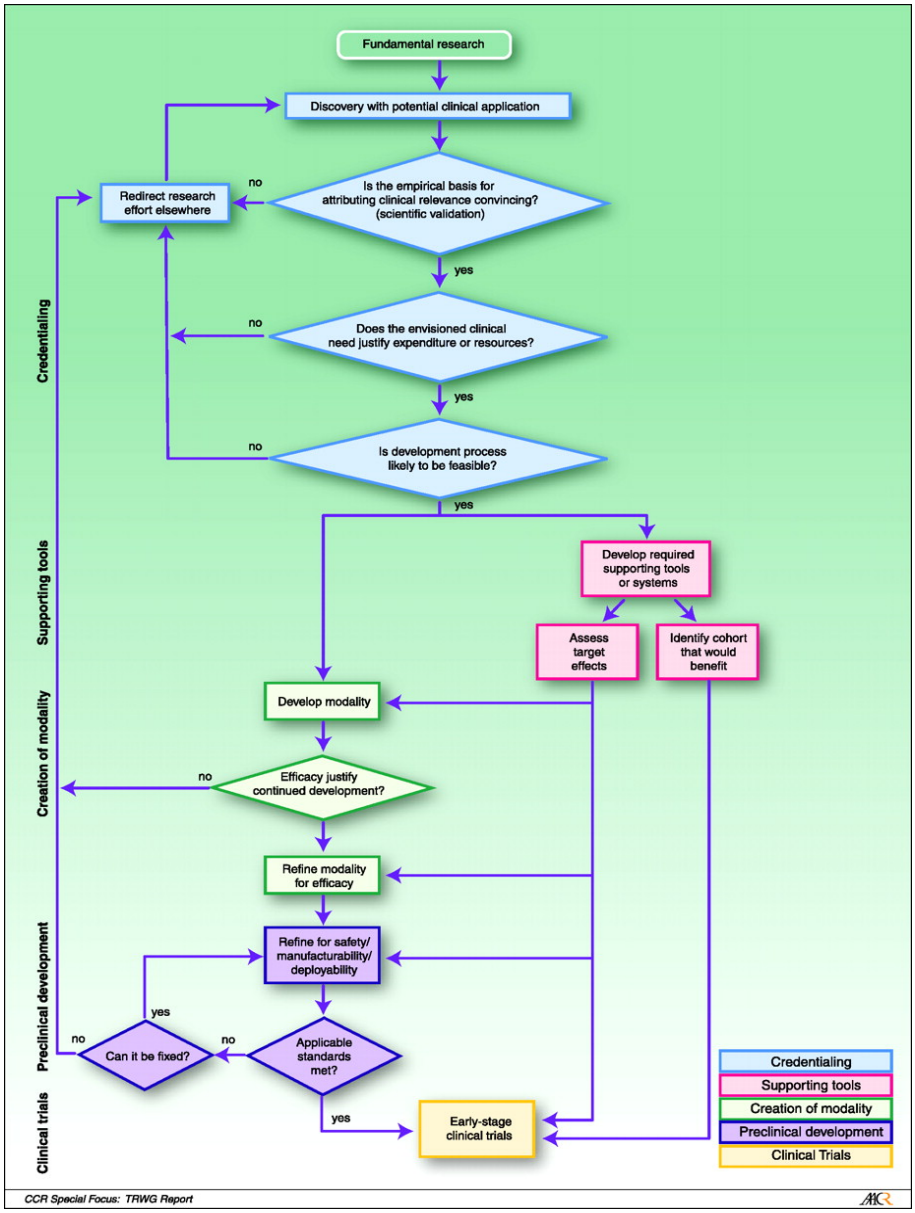
experiments. She talked about this experience as a once in a lifetime opportunity, because of the high financial and personal stakes involved, and the disappointment at not having been able to make more of it. She then explained that the widespread belief that recent advances in the post-genomic platforms enabled the average investigator to engage in product development or clinical innovation needed to be tempered with a selection and stewardship process, so as to make sure that TR efforts would have appreciable success rates and not be associated with squandered opportunities:

> "So basic science has exploded, there are incredible opportunities, but the process of actually doing it is different then the discovery process. And a lot of us are not trained in that. And we are not, we are going to get lost in this pathway, unless somebody helps us. And so I'm convinced that you do not manage basic research, but you have to manage translational research. So one of our initiatives was this project management, you know, borrowing from industry... Now people don't want to hear that. And the reason you get resistance to this, is that everybody who comes from this end thinks their, if their findings, if their discoveries isn't translated, it's because somebody else didn't help them do it. You know, it's the sense that what they found has got to be important. I think one of the realities, and the hard things of this, is that as a nation we need to look at it as what are the best things. You know, you stack the deck in your favour. You give resources to the things that have the most potential, but if they don't work, you drop them" (US investigator 11).

The developmental pathways are tools that can help the individual biomedical scientist level-headedly appraise the TR potential of their work. This respondent contends that such tools are necessary to help biomedical researchers ensure the robustness of their TR projects in terms of public benefit and efficiency.

The claim here is that increased accountability and coordination would allow biomedical researchers to fulfil the duty not to miss out on those exceptional opportunities for clinical innovation, while also safeguarding contested collective resources set aside for TR by avoiding. It is important to highlight this last point, the belief that there is intense public scrutiny of biomedical research, and that the TR enterprise will only be afforded continued legitimacy if it can draw from the creativity of the fundamental biomedical researcher while being able to keep her or his traditional autonomy in check. The work of the TRWG has had pretty wide influence in the biomedical field, and my interviews have allowed me to collect evidence of that influence both elsewhere within the NCI (US policy-maker 2) and outside of it, as far as Europe (EU coordinator 4).

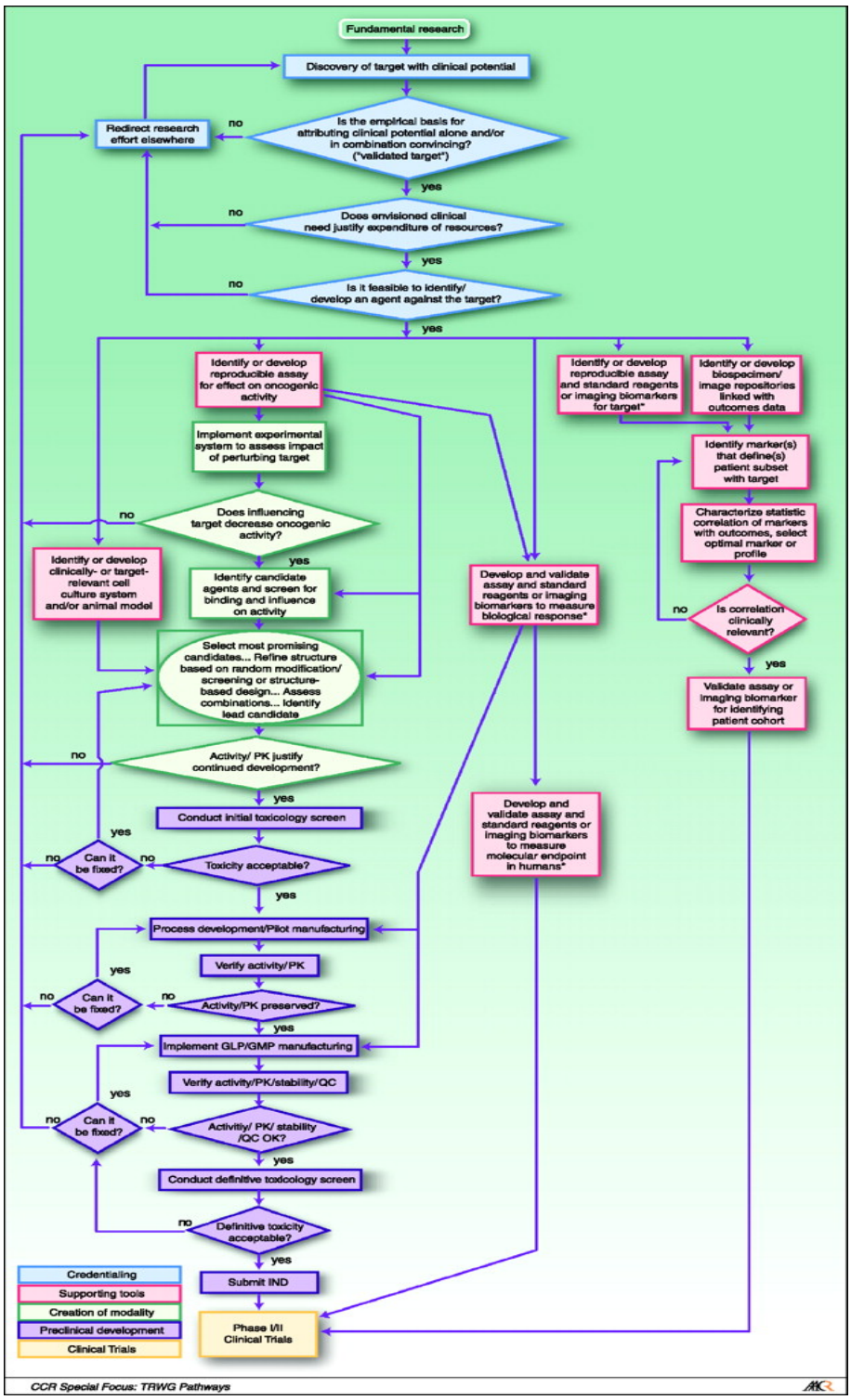
Figure 6: TRWG's Generic Developmental Pathway



"Generic Developmental Pathway. The generic TRWG pathway is depicted as a flowchart, a schematic process representation widely used in engineering. Rounded rectangle at the top, origin of the process. Square-cornered rectangles, activity steps. Diamonds, conditional tests or decision steps. Unidirectional arrows, direction of the activity sequence, and the direction of transfer of supporting tools from their parallel development paths to the main path of modality development. The initial steps of the pathway (blue) are required to proceed through the pathway, with the blue diamonds representing the credentialing steps of scientific validation, clinical need, and feasibility. Subsequent steps include the development of supporting tools (red), the creation of the modality (green), preclinical development (purple), and early stage clinical trials (yellow)" (Hawk et al. 2008, p. 5668).

Source: Hawk et al. 2008, p. 5668 ; Used with permission from the American Association for Cancer Research

Figure 7: TRWG's Agents Developmental Pathway



"Agents Developmental Pathway. The Pathway is depicted as a flowchart, a schematic process representation widely used in engineering. Top, origin of the process (rounded rectangle), activity steps (square-cornered rectangles), and conditional tests or decision steps (diamonds). Unidirectional arrows: direction

of the activity sequence, and the direction of transfer of supporting tools from their parallel development paths to the main path of modality development. Bidirectional arrows: co-development or concurrent, interactive refinement. Rectangle with inset oval: an iterative refinement process (used to conserve space). The initial steps (blue) are required to proceed through the Pathway, with the credentialing steps of scientific validation, clinical need, and feasibility (blue diamonds). The Pathway includes three parallel paths, representing the development of the modality itself (green) as well as the development of two different classes of supporting tools (red): tools for characterizing and evaluating the effects of modality, and tools for defining the cohort for which the modality is appropriate. Parallel paths have been made explicit to acknowledge that some of the required tools may not exist and their parallel or co-development will be a prerequisite for the viability of the new modality. Some of the supporting tools are assessment modalities represented by either the Biospecimen-based or Imaging-based Assessment Modality Pathways. Subsequent steps include preclinical development (purple) and early stage clinical trials (yellow). For each activity, decision point, parallel path, or feedback loop, it is understood that there are many more variations which can occur, and that not all steps may occur in each instance. The Pathway does not address the ways in which insights gained from late-stage clinical trials can influence the development process. Agent interventions may be used for treatment or for primary, secondary, or tertiary prevention. The Pathways are conceived not as comprehensive descriptions of the corresponding real-world processes but as tools designed to serve specific purposes, including research program and project management, coordination of research efforts, and professional and lay education and communication" (Schilsky et al. 2008, p. 5689).

Source: Schilsky et al. 2008, p. 5688; Used with permission from the American Association for Cancer Research

Of course, it is not every respondent who was very receptive to the idea that TR needed to be a highly managed science. Others explicitly took stance against the idea that increased use of management and accountability techniques could foster well-ordered translational efforts. One respondent mentioned how the creativity-driven science attitude decried by other TR advocates as inadequate to the development projects was the only potential source of TR efforts:

> "And in fact, the real science happens when you get a robust signal that you don't understand. Because if you only get robust signals that you had expected, this is all nice and well, but it's only the surface of science. The advances come when you get a signal that you don't understand, which is very reproducible. And so those things are the things that you have to stay aware of, because they are going to lead you to new insights. And the new insights are going to be translational opportunities that you didn't have before. And so, while we are always being yield at by funders that we are doing two things that we promised not to do, and that is, 1) not doing what we told them and B) doing something else which was goddamn more interesting either. But this is how it goes. That's the fabric of science. And if people want to modify the fabric of science, they, well it's all nice and well but they just have no clue what they are doing. They only frustrate the advancement, because it has never been that you can sort of sit down and predict what you are going to do" (EU investigator 3).

This last quote reminds one that even if the use of novel accountability techniques in TR initiatives can be framed within a strong metanarrative that shapes most post-industrial societies, the extension of this practices could find resistance in the equally strong narratives of creativity and invention that are still highly prevalent even in "applied" fields of research (see for a related discussion Hessels and van Lente 2011).

5.2.3 Discussion

The subsections above have examined the widely held belief in the TR advocates and policy-makers I interviewed that advances in molecular biology and post-genomic experimental platforms provided foundations for a new regime of biomedical innovation. Nonetheless, a contention that emerged strongly from this material is that TR was made possible, but is not brought out fully formed by the genomics revolution. Only further efforts and institutional and experimental reform can ensure the translation of the genomic sciences into clinical innovations. Key sites for performing this reform include projects for the development of experimental techniques such as imaging or biomarker discovery and validation, which were felt to provide an increase in the mechanistic rationality of the clinical innovation process.

This chapter should have provided the reader with a sense for the very broad uptake that the genomic-driven agenda of TR has seen within the population of reformers, while also highlighting the somewhat restricted scope of measures that this vision puts forward. The sequencing-driven experimental medicine policy narrative privileges a kind of technology push, linear model of innovation, where breakthrough in sequencing technologies ("the 1,000$ genome") or in advanced modalities of genetic engineering (stem cell, cell-based or gene transfer therapies) are expected to open up the field of translational possibilities. The development of biobanks and their integration in TR initiatives such as SPOREs has shown that experimentation with humans (or human material at least) could be aligned to the parameters and demands of sequencing technologies. Initiatives regrouped under the CTSA and NCATS umbrella in the USA have shown how post-genomic platforms could be made to reshape a variety of clinical innovation strategies, including traditional drug chemical synthesizing or the conduct of clinical research.

The empirical material provided here substantiates the claim that the discourse coalition that is co-extensive to the policy narrative of sequencing-driven experimental medicine is the broadest of the three we examine here. Given the high intensity of promise-making and building of expectations that have surrounded the HGP and the development of related bioinformatics and post-genomic platforms, as well as the penetration of these tools as experimental platforms in all areas of the life sciences, most biomedical investigators are likely to take up large parts of this discursive repertoire in framing their own work. This was illustrated by the interview material, which substantiated the existence of a widespread belief that post-genomic platforms would profoundly alter our capacities for clinical interventions, provided current efforts are sustained.

Nonetheless, this does not mean that broad adherence to the sequencing-driven experimental medicine narrative leads to a homogenous discourse coalition. Fortun has show that the search for speed in sequencing genetic information has structured and crystallized hierarchies between contributors to the HGP (Fortun 1999). Similarly, bioinformaticians and those biologists that are at the centre of post-genomic technology development can be expected to have a more central function in articulating the narrative then researchers that simply use the tools as a mean to answer discipline-relevant questions.

5.3 Institutionalisations of the pharmaceutical crisis narrative

As section 4.3 showed, the TR policy narrative of more recent origin seems also to be the one that had achieved the greatest shared sense of urgency in the biomedical community by 2013. Indeed, a broad coalition of commentators that extends to daily press journalists and consultancies have been eager to point out that:

- **Data show an increasingly high R&D costs for developing a new drug in the pharmaceutical industry;**
- **The number of innovation new drugs approved by regulatory authorities is stagnating or going down;**
- **A series of profitable blockbuster drugs are falling off patent protection, and have not been replaced by new therapeutics with similar profit-making potential;**
- **In the late 2000s and early 2010s, the pharmaceutical industry started to massively cut in R&D capacities and lying off thousands of employees.**

Although some in the pharmaceutical industry have put their hopes on the incremental productivity of post-genomic platforms within the pharmaceutical setting, a number of TR advocates have rather contended for the following solutions to the crisis:

- **The creation of academic therapeutics discovery centres, or "academic pipelines", that tackle development work previously done in the pharmaceutical industry;**
- **The expansion of large-scale, inter-organisational collaborative work as a mean to develop biomedical knowledge shaped by input from a broader constituency of actors;**
- **The expansion of centralized or highly coordinated divisions of labour in innovation partnerships, with a goal to increase stewardship.**

This section explores how these proposals have been put into practice within TR initiatives.

5.3.1 Articulation of the pharmaceutical innovation crisis in respondents' discourse

A great number of interviewees I discussed with made reference to the crisis in pharmaceutical innovation or to the 'patent cliff' in justifying their own TR initiatives (DE coordinator 1; DE coordinator 2; DE investigator 6; DE TRAIN 3). Interviews did not reveal substantial new arguments than those already available from the literature, but it is

perhaps interesting to note in passing however the level of urgency with which certain respondents imbued the situation:

> "Not a couple of years, starting next year, three more years, and then we will have lost 150 billion dollars in turnover in the [word incomprehensible on recording]. You know what that means? That is more than two or three of the largest companies have as a turnover, of course it is spread out among all of them, but there will be substantial cuts in the industrial domain. And without that, the public domain will have to cover all those things I mentioned earlier, and you don't have to be a prophet to understand that the public domain doesn't have the money to spend into the gaps which come up from the industry!" (DE investigator 6).

For this particular respondent, involvement of universities and public institution in downstream therapeutic development appeared to be more of the last ditch solution than the opportunity that others have argued (see section 4.3). What is important to retain here is the framing of the issue as a potentially backbreaking situation for biomedical innovation, especially for capacity in the pharmaceutical industry. This researcher's own work now revolved around trying to find management-level solutions to the problems brought about the patent cliff.

Yet, all respondents did not share this pessimism. An investigator at a CTSA saw the trend of academic outsourcing in a more positive light, but also emphasizing the kind of infrastructural and experimental commitments that universities interested in benefiting from these opportunities have to make:

> "One of the things that is happening in the US, and I don't know if, it's probably going to happen worldwide if it hasn't already, it's a lot of these big pharmaceutical companies are cutting way back on their own research and development. And they are really partnering with universities, but they want to see things that are far enough along that there is reason to take it to a phase III. You know they are not so interested if it's only at the pre-clinical stage. And so that's why it's gonna be really necessary to have these kinds of programmes where we can, you know get through that phase I and phase II you know to interest companies in some of these novel approaches" (US investigator 12)

The novelty and distinctiveness of academic therapeutics development units as an innovation model seems to be put into further relief by the belief of many respondents that tasks such as compound screening, GMP manufacturing and GLP testing in animal models are actually better be left to industry (DE investigator 6; US investigator 7; US policy-maker 1). This sentiment was also echoed by the coordinator of a French TR unit, who reported instances of local researchers bring too eager to take up the work typically conducted by industry, without fully realizing the financial and productive resources these steps would require:

> "So I think within the pipeline, within the life of a project, the moment where industry should become an integral part of the project. So partnership with industry is very important. Industry has understood it, but I am not sure that researchers have understood it. They stay very, it is changing, I personally come from the industrial world, I am still shocked by [incomprehensible word on recording]. When I hear in Curie somebody who has a target, who does a screening, a compound library… I say, 'I don't put a single euro into this'. He says 'Why?'. I say 'It is quite simple, you are going to do a screening, you are going to spend 50000 Euro. After that you will find, because you *will* find targets, molecules, which work in your… In the jargon, you need at minimum of ten chemists for each chemistry series. You have a chemist?'. 'No, I have 10% of a chemist'. 'But I can have this done in India, I send this to India, they do all my molecules'. I say 'OK, good, go for it. You start already with 50000 Indian rupees, they are very good in chemistry, I'm not saying otherwise, but you have to them tell what you want synthesized. They are not going to tell you what to synthesize. Afterwards, you'll have to test it again. And so when you discover all the people necessary, and the time you are going to lose, I tell you, either your target was bad, and you will lose money, either your target was good, and patients will pay the price. Because you'll never complete this project'. So I think it is very important, I say this openly, there are people who don't think like this, I think it is central in translational research, quickly, at which moment precisely we can see afterwards, but that industry does its job. Because they make it so that things work fast, because they have a clear goal, and it is making profit. When you want to make money, and *they* depend on that, you go fast. And they are efficient. Researchers aren't efficient for this part" (EU coordinator 4).

There are a number of interesting issues being raised here. First is a related argument to the claims (already mentioned in sections 4.2 and 5.2) that the expansion of TR discourses has created excessive expectations that the average biomedical scientist is able to engage in downstream development projects. Increasing the attention of this group of people towards TR opportunities is important, but they should not think they can proceed with the same organisational routines that they used within the confines of their typical principal investigator laboratory. Some level of collective coordination or control over the initiation of TR projects is necessary for this respondent. So this respondent supports partnering with specialized expertise when it comes to pre-clinical and clinical intervention development, and his own TR unit does supply some of that expertise to local researcher. Here again, as already noticed in the narrative of genomic medicine, there is also the idea that there is a sort of collective responsibility and accountability for the use biomedical funding, on the one hand, and for making sure that useful findings are marshalled for clinical innovations. The deployment of academic pipelines with business management approaches to coordinating TR would also participate to this cross-cutting imperative towards accountability, and the search for increased efficiency in the extraction of value out of biomedical knowledge.

Industrial work in academia: "The damn thing simply won't dissolve in water"

Respondents have provided a number of examples of practices they are engaged in through TR projects and which substantiate my contention that the TR policy narrative of pharmaceutical crisis is pushing the creation of academic pipelines. Some respondents emphasized the complexity of development projects and the multiplicity of expertise that had to be put into place in their institutions:

> "I think the special thing with translational research is the fact that it's interdisciplinary or multidisciplinary, so you bring together many different aspects. I mean you can probably see that a little bit reflected in what I mentioned before, but training in biology, have some understanding of the physical design, to allow you to design experiments and studies appropriately, understanding of the clinical aspects, so how would that actually translate into something, how to embedded it into clinical processes and procedures, also other more practical aspects, you have to consider as well, for example if you want to collect samples to do a research study, you have a practical aspect, how are you going to collect these samples, how are they going to be stored, and maintained in an appropriate quality, in a way to allow you to conduct your experiments, so maybe some more logistical project management aspects there as well, you also have to consider regulatory aspects, consent of the patient of course for participating in that kind of research, and one of the major functions that we perform in the TR unit here is to interact with the many different expertises here at the headquarters. For example we have a regulatory affairs group, we have a project management department, we have statistical expertise so one of the key functions that we do, is to integrate these expertises and bring together these expertises in a coordinated fashion but also with the expertise coming at the right moment in the project development. And with a, I would say, quite a strong bend towards quality assurance" (EU coordinator 2 + 3).

The quote above comes from two respondents affiliated with a pan-European organising large-scale clinical trials. Here, it is possible to see a concern normally associated with large-scale collaborations for a rational division of labour and efficient stewardship of projects, as already explored in section 4.3. This complexity is compounded by the necessity, in order to respect EU and national regulations, to conduct these experiments according to a set of standards such as GLP and GMP and GCP. TR projects of the sort should also be conducted using SOPs if the findings to be obtained are to be considered reliable by a potential big pharma partner for example (DE investigator 5). The setting up of infrastructure and equipment to be able to able to perform GLP and GMP compliant are costly, and their maintenance demands teams of technicians of their own. Moving from laboratory explorations and 'hypothesis-driven research' to this mode of technoscientific work can be daunting:

> "We start here, with, working with cells, small cultures, doing little scale experiments and doctoral or post-doc or diploma students look at 5 or 10 dif-

> ferent aspects, and we pool all of that data. And then we think 'OK we have a procedure, or we have a good vaccine concept', then we have to take that from that small, rather unstructured discovery process in the hands of multiple people and put that in the hands of a team that is really strict and they pick that process and put it into a form where every component of it is controlled, defined and proven to be usable in patients. And that's called good manufacturing process, development, and that's a big step to go from, you know what we developed in the laboratory to having that or work in large scale" (DE investigator 4).

This respondent provided more precise figures into the kind of efforts necessitated for running the TR platforms at her institution:

> "The second major hurdle is the European regulations for GMP. In the States, you have to apply full GMP only in phase III. And here we have to apply that to phase I. So everybody who wants to do a phase I trial has to have access to a GMP facility, costs a least 5 million Euro to build one. Costs about half a million Euro a year to do the running. You have to have dedicated staff. You have to prepare documentation for such a facility or for any procedure, running it. We're in the phase of that, we are preparing documents, one post-doc, two years, writing one set of documents. It probably costed 300,000 Euro to get all of that documentation put together and then follow it through in a clinical trial. And then you see if you grant, you have to be lucky to get into a programme where you get a grant that will cover that. And they are rare, they are really rare" (DE investigator 4).

I do want to discuss the validity of EU clinical trial directives in using this quote, but rather emphasize the demands that need to be met in order to conduct TR projects within academic institutions. Funding becomes a problem with these kinds of investments, especially considering that this is not the kind of typical principal-investigator research that will results in multiple publications where the name of the funding agency is mentioned (DE investigator 4). Indeed, much like in the policy narrative on patient-oriented research, proponents of academic drug discovery units contend that establishing (their version of) TR is problematic because it does not fit within the traditional cannons of research excellence. In both cases, this difficulty stems from experimentation that is close to human systems. But whereas in the patient-oriented research the keyword seems to be "messy", that is, it is difficult to adequately control experiments, observations or data collection with humans to come up with convincing hypotheses, the keyword with the pharmaceutical innovation crisis narrative seems to be "rote and boring". As was already alluded to in section 5.1, the kind of industrial work involved in developing new therapeutic modalities is repetitive and boring by academic standards, and might involve a lot of trial and error about what might appear like trivial problems. Specific steps of clinical innovation such as calibrating chemical design or properties of absorption in human bodies are unlikely to lead to any publications at all (DE coordinator 1). Fischer, reporting on his conversations with a TR advocate from Harvard Medi-

cal School, has written about how quarrels about apparently insignificant matters such as temperature room at government research facilities can create fatal obstacles to TR projects (Fischer 2012). One of my respondents raised the same point in commenting the impact he felt the establishment of the NCATS might have on the US TR landscape.

> "The difficulty is, and what they are trying to solve is, it's one thing to have a good idea, both scientifically and ethically, and another thing to have the practical experience how to convert from a good idea into a practical drug. And so one of the things Francis and other people at the Gates foundation are trying to do is to say 'well how we can supply not just the money, but also the expertise to deal with the largely, quite frankly, boring details of going from a great scientific idea, great understanding of disease to a practical solution'. Because most of drug development is not very sexy. It's not very intellectually stimulating. The damn thing simply won't dissolve in water. Or you take the thing, it gets urinated out three minutes after you take it. Or it goes to the liver and causes damage there and stuff like that. There are ways of dealing with this, and essentially, expertise for dealing with these boring bits. But you and I are talking now about the biologist's point of view" (US investigator 9).

What this quote makes clear is that important policy interventions (and I would extent and add argumentative practices) for TR have targeted perceived disincentives to the performance of development work in academia. In this case, the respondent mentions funding and expertise as important resources to have access to. Anxiety about the availability of these resources for TR projects would be well founded since the NIH has a clear mission to fund cutting edge basic research, but not large teams of technicians and development staff in academic institutions. As such, establishing TR as a visible policy priority also participates in the mitigation of disincentives in terms of symbolic capital and prestige (which are also interconnected to funding matters).

New management practices

The very presence of dedicated coordinators in TR initiatives indicates the importance afforded to novel management practices (DE coordinator 1; DE coordinator 2; DE coordinator 3; EU coordinator 1; EU coordinator 4). All of these coordinators engage in various communication and management practices (such as organising meetings and public relations activities which are sometimes more oriented towards in-house partners than any 'outside public') to bring together parties that might have complimentary expertise and to make sure that TR projects go forward. They manage the complexity of dealing with technology transfer offices, regulatory instances, venture capitalists, industrial partners and so forth (DE coordinator 1):

> "…the innovation office people say 'well we got someone interested in a phase 1 trial, something we can bring to a phase I trial, OK this is the tech-

> nician you should talk to because she is the one in prostate cancer, and this is the statistician you should talk to, and this is the pharma-tox person you should talk to'. And then bring that together, so it's all communication" (DE coordinator 3).

On one side, the quote above shows how intensive communication can be necessary within a single institution to take a finding and build a collaboration that combines the expertise to engage in the development of a related intervention. On the other side, these initial efforts in stewardship do not guarantee that collaborative work will proceed smoothly. Many respondents thus emphasized the distinctiveness of TR projects when it came to project management. The following quote contains fragments already shown in section 5.1, where it was useful for showing the purported role of clinician-scientists as ideal coordinators of large-scale TR projects. Here, I present these fragments in their broader context, to highlight the kind of organisational innovations required to academia for it to accommodate therapeutics pipelines:

> "You need a single person to plan the whole process, you cannot go into details in all processes, but you need a [incomprehensible word on recording] who knows what a translational chain means. Then you need a structure to bring together, you perhaps, frequent conferences with different people in the steps in the chain. So that is all a completely different research environment than what you usually find with the one or two men lab. And so you need to accommodate those structures otherwise you will fail. And it's much more strategic than individual creativity research, you need a much more strategic component. You need to have plans, short-term plans, you need to have milestones, you have to control these milestones, you have to change your overall strategy if it turns out that in one of the research groups there are results that are not allowing anymore to have the long-term strategy for the whole thing. So you need to have the communication channels that you find out that this is happening. And this is not what is happening in academic laboratories. Now more and more, but that is what translation really need. And you need people who are educated in that kind of translational research" (DE investigator 1).

This particular respondent provide further details into the kind of work routines that had to be put into place within the collaborations that he leads:

> "…basically we meet every couple of weeks and check that all researchers are working on this project, are still completely aligned to the long-term aims [incomprehensible word]. Because such a long term project, could also easily lead to a situation where people leave the main track and do something which might be scientifically very interesting in terms of basic research, but have no connection at all to the direction we want to go. So TR needs organisation principles which are not necessarily that of an individual researcher, it needs a much more strategic approach. And also some controlling. And that's different to what an individual scientist would do in a laboratory" (DE investigator 1).

What appears strongly in the last quote is again the theme that biomedical researchers would not be inclined to restrict their curiosity and see through the completion of a single large-scale project. This has to be understood against the background that most researchers might expect their most enduring work (intellectually, at least) to have come from 'unexpected' but 'game changing' results (EU investigator 3). Instead here, a certain 'self control' is expected. Looking for creativity and distinction would still be very much ingrained in the professional and intellectual dispositions of biomedical researchers, creating tensions in TR projects:

> "In other words, these people have to be willing to work really work under SOP conditions, not vary the experiment everyday. Not changed something. They have to be looking for uniformity and reproducibility and stability and process. And that's a different mentality then here. You can't very easily transfer someone here even though he had developed a great idea, it's too boring. And this is a different type, it's a different team that you need. When you are trying to bring these two together, there can be frustration. Because this one will say I've got this process developed and this one says 'oh! I discovered this, and we should really do this. We should add this.' And at a certain point you have to say, this is finished, and now we are doing this. And then you get down the line in this, and you really discover something great there, but you can't start all over. Otherwise you'll never get this into the clinic" (DE investigator 4).

Again the teamwork and division of labour involved in academic pipelines pose problems when it comes to publications and assignment of credit and reputation. Who should be first author and senior author, and why would the guys who did the chemistry have less chances at obtaining these positions then the clinicians or molecular biologists who came up with the initial hypothesis? My respondents referred to this common problematisation in the TR movement to make sense of this obstacle to the expansion of academic pipelines within their local institutions.

5.3.2 Implementations and Institutionalisations

Again for the policy narrative of pharmaceutical crisis and academic drug pipelines, I will examine a number of recent TR initiatives to track how this argument repertoire has been deployed at a local level within circumscribed reform efforts at biomedical research institutions. The initiatives chosen include a regional consortium in northern Germany, a EU-funded European research infrastructure network and the latest major intervention of the NIH directed towards TR.

TRAIN

I have conducted a number of interviewees with researchers and coordinators affiliated with the Translational Research Alliance in Lower-Saxony (TRAIN; Lower-Saxony is a

state in the Centre-North of Germany). In my research, this is one of the closest example to the concept of a fully-fledged “academic drug pipeline” I have encountered. The initiative, a regional partnership of publication research institutions, explicitly positions itself as concerned with using local knowledge for developing new drugs and therapeutics for future big pharma partners.

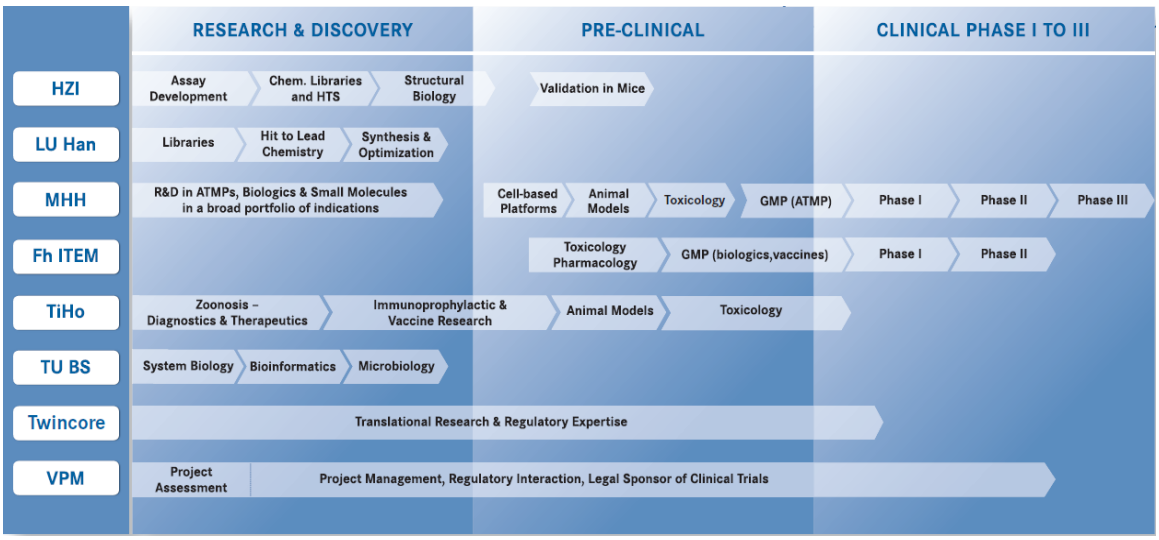
TRAIN regroups seven partners that are all available to take part in various tasks and work packages of projects sponsored by the consortium. These institutes are located in relative proximity within the two largest cities of the Lower Saxony region. Founding members of the consortium are the Gottfried Wilhelm Leibnitz Universität Hannover (LUH), the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), the Hannover Medical School (MHH), the Helmholtz Centre for Infection Research (HZI), the Technische Universität Carolo-Wilhelmina zu Braunschweig (TU BS) and the University of Veterinary Medicine Hannover (TiHo). An additional member of the consortium is the life sciences project management firm VPM. These founding members have additionally launched a number of joint ventures that act as further members of the consortium, including: Twincore, which brings together researchers from the Helmholtz Centre for Infection Research with large laboratory equipment for analyzing pharmaceutically-active substances with clinicians and laboratory scientists with a clinical background from the nearby Hannover Medical School; the Centre for Biomolecular Drug Research, a screening and drug development facility; and the forthcoming Clinical Research Center, linking capacities for early clinical trials to pre-clinical laboratory facilities. Also forthcoming is a *Zentrum für Pharmaverfahrenstechnik* (roughly translated as Centre for Pharmaceutical Process Engineering), which will take the pharmaceutical innovation process itself as an object of inquiry. The consortium also includes a firm specialised in managing life science projects. Through its members institutions, the consortium has access to a number of research teams working on the development of pre-clinical therapeutic hypotheses and interventions, using classical systems such as animal models, cell cultures and tissue collections. However, the consortium also has access to banks of natural compounds (HZI), mass compound screening equipment and expertise (HZI, Centre for Biomolecular Drug Research and Centre for Pharmaceutical Process Engineering), pharmacology and toxicology expertise (ITEM), skills in experimental medicine and clinical research (MHH and ITEM), facilities for the regulatory-compliant production and testing of new compounds (Centre for Biomolecular Drug Research, ITEM), as well as access to competences in strategic planning and coordination (VPM).

TRAIN thus closely resembles the prototypical TR consortium envisioned in TR models. It brings together a number of different but physically close centres of expertises with the hope that their capacities can combine and complement each other. Coordi-

nated common work would allow advanced clinical development of new therapeutics within the public academic sector. Promoters of the consortium contend that the crisis in the pharmaceutical industry will vindicate their model, as firms in the sector would increasingly seek to "outsource" their RTD activities by tapping into academic development projects notably (DE TRAIN 3). TRAIN also has strong clinical development components through the Hannover Medical School and the Fraunhofer Institute for Toxicology and Experimental Medicine (which both have clinical bed reserved for clinical studies, and with the first one having access to patient through its university clinic), although impetus for new project development does seem poised to originate more in individual laboratory projects rather than from clinical care and experimentation.

Based on the capacities that are being regrouped here, the TRAIN management claims that it is possible to go from (patho)physiological hypothesis to lead compound to early phase II trials entirely within the TRAIN partnership, and without additional ad hoc partnership until an alliance with a pharmaceutical for regulatory approval and commercialisation. Figures 8 and 9 below can help the reader to understand the development pathways for TR projects as the consortium leadership envisions them.

Figure 8: Institutional contributions to the TR development chain, TRAIN consortium



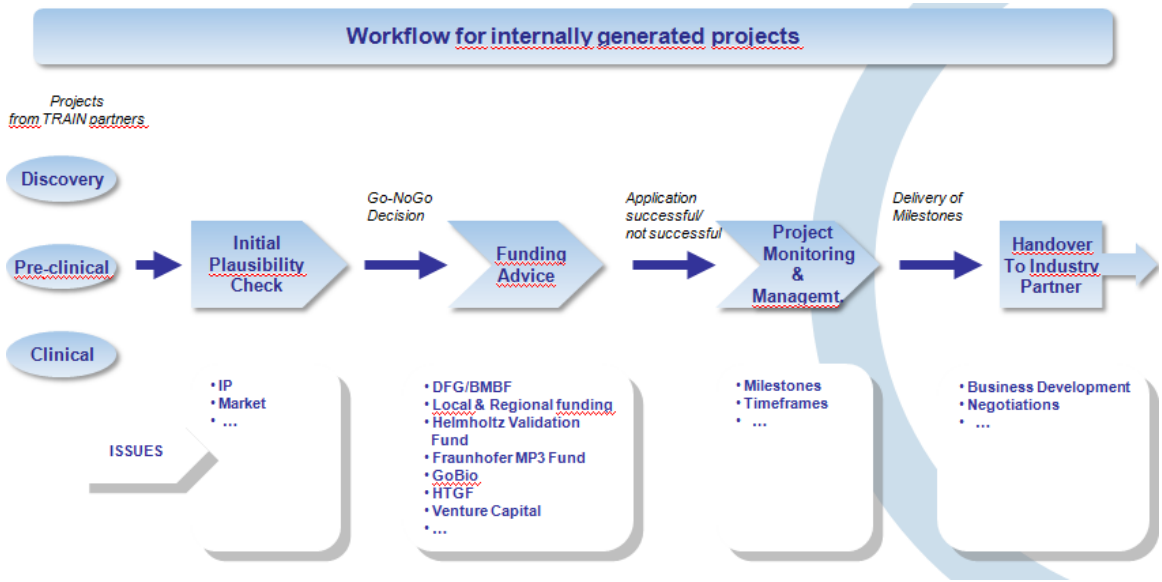
Source: Dr. Marc Hentz, Translational Alliance in Lower Saxony. Used with permission.

The left column in the figure, titled 'research & discovery', indicates the source of hypotheses and laboratory findings that are expected to provide the foundations of TR projects at the consortium. The work of existing research teams on animal models, in vitro cell cultures or human tissue collections, using specific approaches such as systems biology (at a new joint TU BS and HZI centre dedicated to the topic), is expected

to generate a number of ‘translatable’ findings and therapeutic hypotheses at the HZI, MHH, TiHo, TU BS and Twincore. These projects will be identified by the TRAIN consortium leadership, through internal public relations activities and through the work of the consortium steering committee, which includes the directors of the participating institutions. From there on, a selection process is made to come up with a subset of the most promising projects. The investigators behind these projects will be proposed to enter in collaboration with the consortium, with promises that the structure can help them obtain further funding for development work and to access other centres of expertise within TRAIN. For example, an investigator from the MHH with an interesting protein that could act as a target for therapeutic intervention in cancer would then be directed towards the LUH and the HZI. There, chemists will use libraries of compounds to find substances that may act on this protein. Chemists will then work to duplicate and optimize the compound. Teams at the MHH or ITEM would then be able to do the first regulatory testing of the candidate agent in animals, using the GMP and GLP already mentioned above. In the same institution, first in human trials would also be conducted if initial results in animals were promising. Clinicians from the MHH are recognized as a privileged source of expertise into the clinical contexts in which therapeutic innovation ultimately has to be realized (Interview Case Study 1 #1, 3 and 4).

All the while, coordinators at VPM and at the consortium office can provide the sponsoring investigator with counsel concerning project management, market prospects for the new intervention, patenting and so forth. As Figure 9 below shows, these management and coordination experts use a variety of tools to make sure that projects will adequately answer demands from regulatory authorities and eventual industrial partners in the future. This includes making a “red flag analysis” that allows the calculation of projected commercial risks and benefits based on patent landscape assessments, analysis of market demand, or making use of Eliyahu M. Goldratt’s theory of constraints (Goldratt 1984) to model and manage interdependent work packages in TR projects. These coordinators also make sure to establish contact with regulatory authorities early on, so as to establish clearly a list of those experiments that will be crucial for regulatory approval. The goal is to avoid any experimental work that would be superfluous for approval and thus might unduly lengthen the project. In turn, this makes TR projects more attractive to potential pharmaceutical investors and buyers.

Figure 9: TRAIN "[w]orkflow for internally generated projects"



Source: Dr. Marc Hentz, Translational Alliance in Lower Saxony. Used with permission.

The consortium thus appears as a TR structure of unique breadth and complexity in Germany and even at the European level. The consortium is linked to the Pan-European Infrastructure for Translational Medicine (EATRIS) consortium, also concerned with fostering TR projects, as well as the German Centres for Health Research (see below). The concept of academic drug discovery unit is here implemented in an extensive matter. The consortium leaders are also very clear about the origins of this initiative as a response to the pharmaceutical innovation crisis. In PowerPoint presentations, consortium coordinators make direct citations to the models recently expounded by Francis Collins, notably:

> "A new paradigm in publicly funded health care is needed … We must take out some of the inherent risk for Pharma ……Not trying this is simply not an option." (Francis Collins as cited in Hentz 2012).

To a great extent, the policy narrative of academic pipelines is deployed locally by consortium leaders to convince research teams at member institutions to join their model of doing TR. Given that, unlike other TR initiatives, TRAIN did not have its own funding for in-house projects, the use of the pharmaceutical crisis policy argument had to be marshalled in establishing the consortium, but its maintenance and the performance of its vision was also dependent on the uptake of the narrative by local teams. In this way, here, the policy narrative of pharmaceutical crisis very much acted as form of "coordinative discourse" (Schmidt 2012), assigning roles and tasks to specific constituents to the imagined TRAIN community. Narrative of academic pipelines is used to bind together a number of sites dispersed within the six members institutions into experi-

mental platforms for TR. These platforms provide 'blueprints' for TR projects, that is, development pathways that are already constituted in 'model collaborations'. The TRAIN TR development chain will only become a reality if it is performed by a broad coalition of actors at the Hannover and Braunschweig institutions. In others words, the development chain and table of roles presented in Figures 8 and 9 will only *become* an accurate representation of the practices effected by members if the TRAIN management is successful in making research team members at participating institutions accept the roles that is ascribed to them in these figures. This case provides a clear example of the performative power of emblems and representations of models of innovation such as "development chains"

Godin (2006) has explored how the linear model of innovation has been maintained as a dominant representation of technoscientific innovation processes despite widespread contestation of its premises. I believe that the development chains used in the TRAIN consortium should not be associated with the more simplistic usage of the linear model of innovation, but nonetheless, one can see how such simplifying models derive some of their social efficacy. Godin concludes that policy-makers have especially stood to benefit in their efforts of statecraft from reproducing the model. Here we have empirical substance to show how such models of innovation are widely used to do exactly what policy narratives and story-lines are also useful for - assign others to specific functions, provide performative visions of the future, and so forth – at the local level, in a network where state policy-makers are peripheral actors at best.

EATRIS

The TRAIN consortium itself is linked to a pan-European consortium, EATRIS, through the participation of the HZI. Indeed, former HZI head Rudi Balling also used to head the EATRIS consortium, perhaps explaining a certain similarity between the two initiatives (Balling, incidentally also used to be a leading head in the German national Genome Project). Indeed, EATRIS similarly aims to provide an integrated chain of product development, although the individual nodes in this network are dispersed throughout Europe rather than being concentrated in a specific region. EATRIS thus aspires to be a shared core facility (Vermeulen 2009) at the European level, whose services are available to all researchers within the Union, provided they are willing to share some of the potential returns with the network. Members of the consortium, however, are not brought together by complimentary in terms of division of labour with sequential use of different experimental or development platforms over an innovation cycle, but rather along different disease areas. Each member centre is expected to be self-reliant for a certain number of distinct development phases, with other consortium partners offering a restricted amount of collaborations and the consortium office offering centralized ser-

vices in terms of management and coordination. The HZI and the associated TRAIN consortium takes care of infectious diseases projects within EATRIS, whereas the German Cancer Research Center in Heidelberg offer TR services for cancer, for example. This ambition of using EATRIS to create integrated TR pathways across a number of indications is made clear in a periodical article published by members of the consortium:

> "To build an EATRIS Centre, leading European research institutions dedicate part of their research and development capacities to EATRIS. Clinics and research centres integrate their working procedures for translational research and development to create "virtual centres" covering the entire product development chain up to the clinic.
>
> The goal is to have all necessary disciplines (basic and clinical research) close together as a strong innovation core. The EATRIS translational research infrastructure will overcome fragmentation by establishing multidisciplinary teams to accompany the projects run within EATRIS. These teams bring together from the outset all clinical, scientific, regulatory and product development aspects needed over the course of the project. This helps to ensure that all steps and potential issues during the development process are considered from the start. Meticulous quality control and continuous advancement of facilities will ensure the necessary performance needed for translation and successful transfer of EATRIS developmental candidate to industry" (Becker and Dongen 2011, p. 234).

This quote highlights how the specific mix and configuration of disciplines and experimental platforms linked together through the consortium has been thought out explicitly to instantiate the concept of an integrated product development pathway. The necessity of collaboration for successful TR in academic institutions is also explained by another researcher at an institution participating in EATRIS:

> "Well I mean the basic idea of the EATRIS project was that in order to be successful in translational research, you need a lot of expertise and know-how, translating research is different from basic research. You need to invest quite heavily into infrastructures, production of compounds, screening technologies, pre-clinical testing of devices, or of molecules and compounds. And for a single institution, in the public sort of sector, it's often difficult or impossible to sort of establish the entire infrastructure and pipeline which would be required to move a test reagent or a molecule from the laboratory into clinical applications. One of the ideas of EATRIS is, that by joining forces between some of the leading European institutions in translational biomedical research, and by jointly exploiting our complementary infrastructure, we may all benefit in the end" (DE investigator 7).

The consortium uses experimental and development platforms such as molecular imaging and biomarker research to engage in therapeutic development, including in the area of advanced medicinal therapy products (which include stem cell and gene

therapy interventions notably). Another distinctive characteristic of the consortium is its access to extensive libraries of compound that can be used to find potential therapeutic candidates that can intervene in mechanisms of disease identified in previous research. These libraries, we are told, are not of a level comparable to those found in the pharmaceutical and biotechnology sectors, but they are nonetheless quite unique for an academic environment. Similarly, large biobanks were being put into place with an aim to allow tissue typing to generate and validate intervention hypotheses. GOP, GLP and GCP facilities were also being implemented. As we have already showed, these are the kinds of platforms and infrastructures typically implemented in "academic pipeline" initiatives.

As in other initiatives aimed to deploy therapeutic development projects in academia, project management was presented as a dimension necessitating sustained attention. A coordinator at the consortium I spoke to felt that regulatory and management aspects were often left aside in all the talk of bringing the clinic and the laboratory together:

> "Well for me TR is kind of the both bench to bedside and bedside to bench. So you need to connect the basic research to the clinic, and you need to connect all the pillars in-between. Because I think that it's not enough that just the clinic and basic researchers talk to each other, between that, there is a big gap of regulatory requirements for example, where I feel neither the clinicians nor the researchers understand about. There is a lot about project management as well" (DE coordinator 5).

This quote also makes clear the plasticity of the concept of "gap" within the discursive field of TR, which might be usefully considered as an emblem (Hajer 1995) or empty signifier (Gottweis 1998). What this respondent is doing is arguing that the widely recognized gap between bench and bedside is itself problematic, that it leaves key issues aside, and that the solutions proposed in the academic pipelines narrative are more likely to realize the promise of TR.

Finally, at the time I spoke to a member of the consortium, she mentioned the possibility that a dedicated funding mechanism be put made available to members, to avoid having to rely on venture or public funding in the early phases of promising projects. The proposition was to find some starting monies to create a fund that would invest money on financial markets to generate a pool of funding that could then be used for EATRIS products. This idea was not on the way of realization at the time of the interview, but it illustrates the kind of ambitions that can be associated with large-scale TR. An in-house venture capital fund is certainly something that is not widespread in the European academic sector. As our respondent from EATRIS makes clear, this also links in to management practices as a mean to increase efficiency:

> "It's a board of experts in which the people who pay into the fund accept as the board that can release the funds. So that means, if that board says it's OK, we know we've got the money to run the project. It cannot be once you've decided to accept the project to run it in EATRIS, and then go around knocking doors and "now we need funding". It just doesn't work. We need to be quick. TR is a lot about speed as well" (DE coordinator 5).

Here the dimension of speed does not have the same character as the speed of –omics platforms, but it rather refers to the requirements of pharmaceutical markets. A project manager within the TRAIN consortium explained how every delay encountered in biomedical product development can have consequences on the ability to strike a deal with a large pharmaceutical for commercialization. Patents have a life cycle of about 20 years, depending on the jurisdiction where they are in force. Since patents are applied for relatively early in the development of a new product, the final cycle of commercialisation of a pharmaceutical product might take place under patent protection for only a few years. Given the giant sales of blockbusters, the respondent explained, an additional week or month on the market under patent protection might mean millions of Euros or dollars worth of revenues, and might tilt the balance as to whether a new product recoups its development costs or not (DE TRAIN 1). To safeguard the commercial value of candidate interventions, it was similarly important to use management techniques such as SOPs that ensured data produced to comfort a therapeutic hypothesis would be receivable by regulatory authorities. SOPs also make data interoperable between various EATRIS nodes as well as when transferred over to industry partners. All of these organisational and material practices appear to be constituted and performed in close feedback loop with the argumentative practices related to the pharmaceutical crisis policy narrative.

NCATS

Section 5.2 has already provided basic information about the structure and orientation of the newest US National Institute of Health, the NCATS. It should also have been clear already at that point, that the initiative's mobilization of the post-genomic sequencing platforms is strongly shaped by the demands of drug and other therapeutics development. Indeed, the case of the NCATS provides indication of the meteoric rise of the pharmaceutical crisis narrative, which can be perceived here as even re-shuffling the contours of the genomic medicine narrative. Since NCATS was still an initiative in building at the moment of writing these lines, extensive details about the institutional context and experimental practices regrouped under its umbrella have yet to emerge. Nonetheless, NIH director Francis S. Collins has widely advertised and defended the initiative, and a look at his arguments provides further insight into the current thrust of the narrative. An extensive quotation taken from an interview conducted shortly after

the initial public announcement of the new institute provides insight into the problematisations and models of collective actions that have underpinned this major policy intervention:

> "We have seen a deluge of new discoveries in the last few years on the molecular basis of disease. This is true for rare diseases, common diseases and neglected diseases, and allows us to feed new ideas into the therapeutic pipeline. That's the good news. But there is bad news too. Despite increasing investments by the private sector, there has been a downturn in the number of approved new molecular entities over the last few years. Also, drug development research remains very expensive and the failure rate is extremely high.
>
> Perhaps in part responding to these factors, and to the downturn in the economy, pharmaceutical companies have cut back their investments in research and development. We can't count on the biotech community to step in and fill that void either, because they are hurting from an absence of long-term venture capital support. So, we have this paradox: we have a great opportunity to develop truly new therapeutic approaches, but are undergoing a real constriction of the pipeline. One solution is to come up with a non-traditional way of fostering drug development — through increased NIH involvement" (Mullard 2011, p.14).

The first part of the quotation corresponds to the setting of the problem. Collins uses the premises of unprecedented advances in molecular biology, quite possibly a common thread in all TR narratives, to highlight the urgency of the pharmaceutical crisis. The pharmaceutical crisis is not necessarily to be considered a consequence of troubles in mobilizing molecular biology for clinical innovation, since reports have long said that genomics would not necessarily have a great impact on drug discovery, the main business of pharmaceutical companies, but rather that it would create different sets of therapeutic opportunities (Drews 1993; Tollman et al 2001). Nonetheless, Collins makes a clear link between the two issues, and ends these two paragraphs with the proposal for a collective solution: increased involvement of the NIH in the drug discovery and development area. In the part of the interview that immediately follows, Collins highlight an agenda that is very much in the mould of the academic pipelines model:

> "I like to think of this in a broad sense of "what kind of paradigm can we initiate and expand between academic researchers and the private sector to move the therapeutic agenda forward?" Academic investigators have always played some role in drug development, but usually in the earliest stages of target identification. If we want to see those targets exploited — recognizing that many of them are not initially attractive economically because of their uncertain druggability or perhaps relevance for only a rare disease — then academic investigators need to have the tools to push discovery efforts forward themselves.

> By having the NIH more engaged in the pipeline, we can also ask whether we can improve the success rates of drug development. Pharmaceutical companies have been making drugs for a long time, and have created some great products, but there's been less consideration of the whole drug development pipeline itself as a scientific problem. We need to re-engineer the process, with a lot more focus on the front end..." (Mullard 2011, p.14).

The second part of the quotation above seems to take its cues straight from the FDA 2004 *Critical Path* report. The details of the solution proposed by Collins and provided in this second part of the quote clearly aim to legitimate not only the expense of public funds for this initiative, but also to encourage individual scientists to pick up the whole drug development pipeline itself as a scientific problem. The proposal here is to have a broad number of academic investigators move into areas of drug development when very few of them have been active there before. The NCATS thus aims to provide centralized, core facilities that these investigators can gain access to when they are interested in orienting their research programmes towards these goals. In this case again, the idea of linking together distinct experimental or development platforms into integrated development pathways is mentioned, when Collins explains how the NIH can take up some of the activities previously thought reserved to the pharmaceutical industry:

> "We have several different programmes that we are working to fit together. We have four NIH-funded facilities that collectively have the capacity of a midsized pharmaceutical company to do high-throughput screening, assay development and medicinal chemistry. In the preclinical space — moving promising compounds through the expensive and risky 'valley of death' — Therapeutics for Rare and Neglected Diseases (TRND) supports projects that would not be of interest to commercial players because of modest market sizes... " (Mullard 2011, p.14).

The quote above makes use of the "valley of death" theme that has already been ubiquitous in discussing productivity problems in the pharmaceutical and biotechnology industries, further indicating the kinship of this argumentative intervention to narratives of crisis in these sectors. We are also given a clear indication that the goal of academic pipelines is to emulate the work of pharmaceutical companies. NCATS has access to high-throughput screening and chemistry optimization on compounds through its Molecular Libraries Program and the NIH Chemical Genomics Center, notably. It has access to GMP production and GLP regulatory testing on animal through the Rapid Access to Interventional Development (RAID) Program. It also has is own hospital dedicated to clinical research (NIH 2010).

Another programme of the NCATS (Discovering New Therapeutic Uses for Existing Molecules) establishes collaboration with the pharmaceutical industry and public sector scientists to make compounds that failed development in private firms available for

further testing. Experiments with these agents might open possibilities for their application to other medical indications than those initially planned, or the demonstration of proof of efficacy or safety in a stratum of patients more specific than thought (those with a given gene mutation/allele, for example). This, again, is work that is far off from the core NIH mission of fundamental, principal-investigator based and hypothesis-driven research.

Given the location of the NIH within the American institutional space, the NCATS has been criticized for not only engaging in development work that does not belong in academia, but also for gambling public money on projects with inherently high uncertainty (Avorn and Kesselheim 2011). To these critics, Collins has responded that the intention with the NCATS is to "de-risk projects that might otherwise be seen as economically unattractive" and then to hand over the projects to industry partners as soon as it makes sense (Mullard 2011, p.14). Shared intellectual property rights would ensure that the public investment would be paid back. Interestingly, what comes off of this discussion is that, whereas other advocates of TR have justified models of academic pipelines as offering new opportunities for the development of academic institutions, here we come back to the argument that there will be system failure in the entire biomedical enterprise if the pharmaceutical industry is not "saved".

5.3.3 Discussion

Through their complex division of labour, the type of experimental infrastructure they mobilize and the advanced management techniques they deploy, initiatives such as TRAIN, EATRIS or NCATS testify to the grasp of a narrative of pharmaceutical crisis and need for academic pipelines in current TR-building efforts. Problematisations and representations such as the "patent cliff", the "valley of death" and other types of gaps were recurrently made use of in the material collected with leading TR advocates. The use of these signifiers index the pervasiveness in the biomedical field of a belief that the pharmaceutical industry is contracting its early R&D activities, and that there is either a beneficial opportunity or an obligation to have academia take over some of this work. Whichever their exact motivations, a number of TR advocates have been able to tap into the sense of impeding catastrophe to mobilize allies in significant reform efforts, decidedly reshuffling traditional definitions of academic biomedical work to include on an unprecedented scale quasi-industrial practices within their remit. These quasi-industrial development practices include conducting regulatory compliant preclinical assays in animal models and in vitro cell cultures to produce data that can be used by competent authorities in reviewing the marketing authorization demand of the eventual product. Doing these studies is costly and time-consuming work, requiring specialized facilities, equipment and teams that do not dedicate their time to either "cu-

riosity-driven research", teaching or patient care (in the case of academic medical centres). Burdens to deploy regulatory compliant assays and facilities required in clinical research, including early trials with a restricted number of healthy volunteers, have also been extended in Europe in the 2000s, notably. Consequently, those academic TR centres expanding their activities into outright RTD have been making major investments in infrastructure and personnel for large-scale applied research projects. Often, collaborative models have been promoted as a way to pool capacities distributed across several academic and/or private partners, in an effort to form a complete 'value chain' at the level of the whole consortium.

The problem of pharmaceutical RTD productivity has been articulated by a broad coalition of industry, public and academic actors of advanced economies, not least of which has been a regulatory agency itself, the FDA. Interestingly enough, however, the actors pushing for 'academic pipelines' models of TR are not necessarily in the pharmaceutical industry itself, as I already mentioned in summary to section 4.3. Rather, they might be entrepreneurial public sector advocates of TR with a desire to expand the remit of their institution or to increase their own affluence by providing exemplary tools for an anticipated change of regime in biomedical innovation. This group of academic administrators and coordinators, as well as a few associated research leaders, seem to form the core advocates of this policy narrative.

The problematic of pharmaceutical innovation has been the object of sustained critical attention from social scientists. Light and Warburton (2011) contend that the groups of consultants, research teams, policy-makers and journalists who expound the interpretation of a crisis of innovation in the pharmaceutical industry have vested interests in doing so. Tobbell (2012) has shown that the industry has a long history of foregrounding risks in the innovation process to secure commercial privileges enforced through state regulation. Recently collected empirical evidence shows that big pharma is indeed moving away from RTD (Rafols et al forthcoming), although this does not provide any indication as to whether this is part of an active strategy of outsourcing or the consequences of an actual crisis in innovation. The research presented here does not allow me to take part in this debate, but it does highlight how, whether or not we have convincing reasons evoke a situation of crisis in the pharmaceutical industry, convincing problematization of a situation of crisis currently acts to durably reshape systems of biomedical innovation.

6 Argumentation, practice and legitimacy

Chapters 4 and 5 have been structured around the central argument that the proliferation of TR initiatives and discourse has been gradually effected through different discursive formations, namely three dominant policy narratives. I made note of empirical observations that seemed to indicate sites and moments where distinct TR narratives were converging, and where narratives have taken up specific arguments from a previous articulation and incorporated it *tel quel*. My analysis of the empirical material also indicated how certain TR initiatives had been informed by more than one of the three narratives. Yet, I have also pointed out some instances where there might be conflicts or tensions between policy narratives of TR.

How should we make sense of this argumentative flexibility? Can arguments for TR be used against one another in one context, but then in solidarity with one another in the next, without the risk of delegitimizing them and their proponents? In which situations and by whom are the policy narratives of TR likely to be combined, or construed in opposition to one another? Finally, how do these policy narratives stand in relation to other important policy narratives about biomedical innovation systems?

Much argumentative policy analysis literature has adopted a view of widespread discursive competition based on Laclau and Mouffe's elaboration of the concept of hegemony and its conjunction to Foucaldian discourse analysis (Laclau and Mouffe 1985). These studies have put their conceptual tools to work in empirical studies by showing how hegemonic blocs can be formed, crucially shaping attempts at policy formulation through a dominant repertoire of meanings and problematisations. In this instance, there is an underlying assumption that policy narratives compete with one another to achieve hegemonic position. Competition between narratives, and the policy solutions they each offer, follows to a certain extent the model of competition between interest groups/coalitions, where one group stands to have privileges enshrined by adoption of their story-lines by policy-makers. Ascui and Lovell (2012) for example link the recent annexation of carbon accounting schemes to the professional jurisdiction of accountants to the ability of these groups to convincingly frame the issue at play in relation to their specific competences. Here, there can be a tendency to have a binary understanding of policy narratives on the basis of the dominant narrative, counter-narrative logic, or to have a sequential view of the formation of dominant policy narratives. From the STS perspective, Calvert and Fujimura (2011) have recently written of "duelling discourses" in the emergence of systems biology, each foregrounding different research objects, experimental platforms and professional identities. This work ap-

pears very much to be in the mould described above, although it does not draw on the strand of discourse analysis described above.

As chapters 4 and 5 have shown, even focusing on just the three dominant narratives of TR shows a complex landscape of long-lasting and intertwining narratives. These narratives are sometimes in competition with one another but, they can also form combined repertoires within single argumentative interventions. As such, I wanted to take some lines here to explore the discursive dynamics of TR taken as a whole, and notably to consider what happens in the spaces where multiple policy narratives of TR evolve. Additionally, my characterisation of TR as the label of a reform movement in biomedical innovation systems can only be sustained with a better understanding of which argumentative content can bring a broad basis of advocates together, and those that are patterned on a separation between smaller groups.

6.1 Tensions and competitions between narratives

In the TR case, it appears that sizable attention by state policy-makers and biomedical leaders is afforded, at a given time, to either one or two of the dominant policy narratives identified. The narratives that are privileged also change over time. That is, the policy narratives available at a given point tend to favour different, and to a certain extent mutually exclusive socio-technical systems of innovation.

For example, under the current leadership of Francis Collins, the NIH strategy for TR has intensified the emphasis of its argumentative interventions towards issues in the development work for the so-called –omics experimental platforms for drug discovery (Collins 2011). The main instruments in Collins' new TR policy are poised to direct NIH efforts towards the production of therapeutic candidates that can be transferred to industry partners. This responds to the mounting perceptions of an intensifying crisis in pharmaceutical productivity previously explored. NIH Leadership under Elias Zerhouni had instead put much more emphasis on academic medicine and even patient-oriented research, with associated support for clinician-scientists. Collins' vision for TR does not include these sites and actors. They will certainly retain their role in biomedical innovation systems, but their grievances might not be afforded the kind of legitimacy that being at the centre of policy attention would offer.

The same finding can be drawn from observations at the local level, within specific TR initiatives. For example, I have already mentioned how the existence of the TRAIN consortium had to be maintained and re-asserted by the work of its coordinators. These coordinators had to bring together research teams around common TRAIN-specific goals, when they might have as many or more incentives to pursue existing projects independently. I mentioned how the coordinators there had made great use of

the policy narrative of pharmaceutical crisis, with direct references to policy formulations by Francis Collins and the FDA for example, to foster local collaborations and coordination of TR activities. Here, a local iteration of the policy narrative of academic pipelines had to compete with more entrenched interpretations of legitimate research practice.

Based on this understanding of TR practice, these coordinators elaborated and implemented an elaborate scheme to guide and manage local TR collaborations. This scheme informed coordination work through tools such as early evaluation of market and regulatory demands. For example, the collection of data on medical needs, meetings with competent authorities that approve new medical products and the assessment of freedom to operate on a given set of patents surrounding a potential candidate provided precise plans of work to be performed and expertise to be mobilized in developing a new health intervention. Adequate responses to regulatory and market demands were deemed to be the most important components of successful TR, because health interventions can only reach patients if they are potentially profitable to a pharmaceutical company that can commercialize them. As one respondent mentioned in an interview, for blockbuster therapeutic products for example, a difference of days or weeks in patent protection once approval and commercialization has been achieved can be worth millions of euros in profits – good timing is thus of paramount importance to make a new intervention attractive to industry and consequently achieve commercialisation (DE TRAIN 1).

The experimental and institutional capacities in place at TRAIN have thus been crucially shaped by the policy narrative of pharmaceutical crisis. Nonetheless, outside the core consortium leaders, other experimental and institutional practices may have been emphasized by actors with different understandings of TR. In the academic institutions that were members of the consortium, the narrative of pharmaceutical crisis is not necessarily as readily taken up as one might expect. The TR project on *natural compound A* presented in Chapter 3 is readily given as a prototype of the kind of collaborations that can be established within the TRAIN consortium, yet its prime movers have not been closely associated with it. Rather, respondent DE TRAIN 5 and his associates first went their own way (starting at a time, it is true, where TRAIN was not yet into place) and opted to take care of strategic planning themselves, enlisting contract research organisations for experimental and regulatory steps they could not cover. At a later date, when negative experiences made respondent DE TRAIN 5 change his mind and seek out the help of ‘professional coordinators’, he again opted out of the consortium and went instead to a local coordination centre. In part, as it appeared to me in conversation with respondent DE TRAIN 5, this could be attributed to a perception of his own expertise and capacities that recalled the kind of claims made in the policy

narrative of the plight of clinician-scientists. DE TRAIN 5 was quite convinced that clinician-scientists possessed unique capacities to be leaders of TR projects, along the lines provided in the public narrative (see section 4.1 and 5.1). As such, he had considered that he would be best positioned to take crucial decisions surrounding the *natural compound A* project. He also subscribed to the view that opportunities for academic biomedicine were especially salient now with the withdrawal of the pharmaceutical industry for R&D work, but he offered quite a different model of how to best bring TR projects to term then the one put forward in the consortium.

The policy makers and funders that had generously supported the establishment of the TRAIN consortium used yet another logic to assess whether the initiative would be successful. For regional government funders, commercial or clinical outputs were only secondary to goals such as fostering the extension of local research infrastructure, supporting PhD student theses, helping the generation of formal publications and supporting local researchers into channeling more funding from federal and international sources into local institutions. The Lower Saxony funders simply did not make use of any of the repertoires offered by TR policy narratives to make sense of what was taking place within TRAIN, but rather referred to the well-established categories of scientific excellence.

I have also noted above other examples of tensions of competition between narratives, such as Ahrens' defence of patient-oriented research against "reductionist molecular biology" (see section 4.3).

Each policy narrative singles out specific epistemic, institutional or material sites for collective social action. Policy narratives each focus on a narrow spectrum of models as privileged means to solve these problems. As such, each narrative tends to foreground practices, policy interventions and specific group of actors as catalysts or leaders of the collective models they put forward. This can create concrete tensions or even struggles between policy narratives and the discourse coalitions that articulate and maintain them, especially if resources to effect experimental and/or institutional reform are scarce and making priorities means selecting out other interventions. From another perspective, van Lente and Bakker (2010) highlight the empirical possibility that the framing of a situation of competition between different future technologies may itself be an achievement of argumentative practice. Talking of competition allows one to distinguish a given model or technological option as superior to other potential futures, providing additional argumentative power to a given policy narrative. In this way, there can be hope for one set of promises to realise because other options are framed as present or future disappointments (van Lente, Spitters and Peine 2013).

6.2 Aligning policy narratives

There are many instances in the empirical material considered here where specific argumentative interventions by TR advocates drew from the discursive repertoires of multiple policy narratives. For example, the *Science* editorial by Duyk (2003) predicts the expansion of academic drug development capacities by harnessing post-genomic platforms, but also through broader support for clinician-scientists as privilege participants in these initiatives and a return towards experimental medicine (to which he gives a meaning that is close to that of patient-oriented medicine). Borstein and Licinio (2012) can also touch on all three agendas in their apology of TR. In section 5, I have also mentioned the same initiatives to substantiate my claims about the grasp of several policy narratives. The goals and means of NCATS are clearly indebted to the pharmaceutical crisis narrative, but they also extend Francis Collins' long-standing articulation of the sequencing-driven experimental medicine narrative. The SPOREs were established when the tissue typing approaches central to the genomic medicine narrative started to allow for talk of clinic-near molecular biology, but the support of clinician-scientists was also mobilized to achieve support for the specific agenda of TR elaborated in this instance.

The combination of narratives in single argumentative interventions need not be seen as an indication that I am straining the data. Rather, Ney has shown in his own analysis of policy narratives about global health and equality that few policy documents and position papers tend to be "pure" and belong solely to a single narrative (Ney 2012). Warner and van Buuren (2011) report instances of actors elaborating their own personal narratives by selecting and "cherry-picking" individual components from each of three official narratives available to interpret the status of flood-prone rivers in the Netherlands.

A first point here may be that frictions between narratives may be most apparent when advocates are engaged in argumentative practices that are addressed at their research colleagues and at high-level policy-makers. These audiences readily afford a baseline legitimacy to the notions of TR. When addressing a broader audience, however, it might be more likely that advocates draw from the problematisations of all narratives to drive the sense of urgency and attention broadly afforded to TR topics. The boundaries between narratives are also likely to blur if the very notion of TR in itself is being put on trial, as when commentators advocate altogether different models of biomedical innovation or decry the concept as "empty phraseology", "fad" or "political rhetoric" (see for examples of such critiques: Mullane and Williams 2012; Weissmann 2005; for the rebuttals by TR advocates : Laurence 2006 ; Wehling 2008). This selective flexibility in

sequential adherences and disavowals from TR agendas by individual researchers was also noted by Wainwright et al (2009, p. 47), who observed that:

> "What emerges is a complex tapestry of discourse in which social and technical expectations interdigitate as scientists attempt, on the one hand, to 'withdraw' from, or be critical about, approaches to translational research, and on the other, to promote the process of translational research in order to allow at least some versions of what counts as translational research to flourish in the future"

A second analytical consideration is that temporality appears to be an important dimension to understand the sequential, and to a certain point interdependent emergence of the three dominant TR policy narratives. The narrative of the plight of clinician-scientists appeared in the collective consciousness of biomedicine in 1979, with the publication of the famous paper on the profession as "endangered species" by James Wyngaarden. I would situate the emergence of a policy narrative of TR problematising the usage of sequencing technologies for clinical innovation with the NCI RFA for the SPOREs in 1991. And the articulation of TR agenda to older discussions of innovation productivity and commercial risk in the pharmaceutical industry was decidedly effected through the FDA's *Innovation / Stagnation* report of 2004. We are thus in the presence of three temporally intercalated narratives. Competition within the reform movement of TR is then by necessity a rather recent phenomenon, one that can only have been accentuated by the recent effervescence surrounding the notion of TR. My empirical investigation into how the policy narratives have been incorporated in some biomedical investigators' or groups' of investigators experimental and institutional practices necessarily reflects this recent proliferation of meanings and the frictions and struggles that can result from it.

Yet, comparison of older and newer reviews or commentaries about TR, as well as interventions aligned with different policy narratives, shows that there are genealogical ties between the policy narratives. As already mentioned in section 4.1.5, the narrative of patient-oriented research provided important arguments that were built upon and inflected by the historically subsequent policy narratives. The personal dislocation of molecular biology and clinical practice experienced by clinician-scientists in the 1970s appears to have provided a powerful origin story or metaphor of increasing gap between laboratory and clinic. The basic principle of this metaphor seems to have been carried over up to the very recent narrative of pharmaceutical crisis.

Indeed, it very appropriate to consider metaphors at this point of the discussion, since empty signifiers and what Hajer (2005) calls "emblems" seem to have crucial roles in sealing the joints between the three policy narratives in cases where they are aligned together by TR advocates. Expressions such as "translational research" and "transla-

tional medicine" themselves, but also "benchside to bed", "benchside to bed and back", the "Valley of Death" are useful to provide a widely accepted baseline problematisation of the exchanges between laboratory-based formal knowledge production and clinical practice and research in biomedicine. Less precisely defined expressions such "gaps", "bottlenecks" or "pitfalls" are widely used in science, technology and innovation policy and indeed in common and language, but their recurring use in discussing TR seems to be associated with the same functions as for those emblematic expressions mentioned above. The sections above have provided some examples of the types of visual representations that are commonly used as emblems of the broad problematisation of TR in the biomedical community. Use of these emblems may allow to curtail detailing specific models of collective intervention to focus on cross-cutting issues against proponents of academia concerned solely with basic science, for example (as in the case of Weissmann 2005). These emblems or empty signifiers might even have acted as the stable nodal points (Laclau and Mouffe 1985) that have ensured the transfer of those meanings that have stayed constant from one policy narrative to others.

The variety of issues that have been recognised to participate to the problematic of TR certainly contribute to its success, as it can be measured by its articulations by a wide constituency and uses as solution to problems in a variety of contexts. Central TR advocates must thus simultaneously strive to retain a broad definition of TR in some venues and contexts, so as to gather as broad a support as possible for their agenda, and to push for a narrow definition of TR in other contexts, so as to frame their specific resources and assets as crucial elements in collective models of the innovation process.

Alignment of the policy narratives of TR may be aided by the fact that they each put emphasis on different sites of interventions: "sequencing-driven experimental medicine" on pre-clinical research and technology development, "academic pipelines" on chemistry and drug development infrastructure and strategic project management, patient-oriented research on a specific profession and style of practice (to use the term of Keating and Cambrosio 2012). Potential tensions due to scarce collective resources available to conduct a restricted number of reform agendas may thus be mitigated because they are not mutually exclusive in principle.

Finally, some of the claims and grievances of TR advocates seem to be shared in all three argumentative repertoires. This is the case for the demand that typical TR work be more adequately rewarded in academic contexts. As seen in sections 5.1, and 5.3, TR advocates often contend that their experimental and development work cannot be readily marshalled in "hypothesis-driven" and creative mechanistic work with appropriate controls that, so they perceive, high-impact biomedical or scientific periodicals fa-

vour. This is true for practices in patient-oriented research, drug development and some domains of sequencing-driven work. More deeply, this set of grievances seems to signpost the fault line between TR and the metanarrative of mechanistic understanding that informs modern conceptions of legitimate scientific investigation and the production of objective knowledge.

6.3 Hegemonic formations?

Now that the details of the solidarities and clashes between the three dominant policy narratives of TR have been examined, is it possible to say that one of them has decidedly capture policy attention in the biomedical field? In other words, has any of these narratives achieved a position of hegemony, whether in the biomedical field as a whole or in the subset of deliberation concerned with the relevance of research and the production of clinical and commercial value? Some STS studies have in fact criticized TR agendas for promoting and reinforcing hegemonic public representations of the process of biomedical innovation as instances of the 'technology push', 'breakthrough'-oriented linear model of innovation (Martin, Brown and Kraft 2008; van der Laan and Boenink 2013), instead of proposing alternative and perhaps more practice-true modes of conceptualizing science-driven advances in health care.

I believe the authors of these studies are right in pointing out that if any circumstances allow us to apply the concept of hegemony to the TR case, these are related to the still widespread belief that it is intensified or continued efforts in "basic" or "upstream" technology development and curiosity-driven research that can solve the perceived disconnect between high rates of formal knowledge generation and comparatively low rates of clinical innovation. My belief is informed by recurring statements in my empirical material to the effect that "TR should not take resources away from basic biomedical research".

Indeed, a majority of interview respondents were very careful to highlight their conviction that advocacy of TR agendas in fact did not implicate any proposals to reduce the policy attention and collective efforts devoted to "basic science". Such a stance was not completely surprising coming from respondents affiliated with institutions that had strong fundamental research programmes, and who were most likely to articulate the sequencing-driven narrative of TR (EU policy-maker 1; EU investigator 3). These respondents often contended that curiosity-driven research was an essential component of the broader TR enterprise, in terms often close to those used by the German leader of an oncology research centre:

> "I think successful translational research, and this is sometimes forgotten, will always rely on excellent basic research. This sounds trivial, but it's very important to remember. Without highly innovative basic research, there is

> not much to translate. So it would be totally contra-productive if somebody would propose to shift some of the funds, which we have been investing into basic funding so far, into these wonderful new fields of translation. This would never work" (DE investigator 7).

Even within official discourse, such as in the 1995 NIH Panel created to look specifically at the state of clinical research and clinician-scientists, commitment to basic research appears to be a case of *sine qua non*. Here, explicit resignation or approval is made to the effect that any reflections about how to improve the clinical research enterprise are legitimately constrained by the concentration of resources towards fundamental research:

> "It would have been impossible to suggest a decrease in the basic biomedical science budget of the NIH to support clinical research because new ideas in clinical research demand a vibrant and productive basic science program. In fact, biomedical research is a hugely successful aspect of American society and doing more of it, including both basic and clinical research, is both a rational goal and expected by the American public" (NIH 1997, p.6).

But similar defences of the necessity of basic research by publicly vocal advocates of the TR enterprise were indeed surprising to me (DE investigator 1; DE coordinator 2; EU coordinator 4). This included, notably, a top investigator at a CTSA and vocal TR defender:

> "I think here, there are these sorts of pressures, but there are still a pretty vocal community, and I would count myself among them, that says that a cardinal mission of the NIH is to support the most fundamental research, biomedical research. And if they don't do it, we're lost. And to have a translational endeavour you know as part of that is fine, because what you really are doing is awakening people to the translational possibilities of what they do. You are creating infrastructure to allow them to do this. But it would be a terrible mistake to force them to do it. The great thing about science is because the unexpected happens. So I'm a big advocate for the NIH to invest into basic science being sustained and expanded" (US investigator 8).

Such TR advocates themselves are obviously struggling to frame their work and the sense they ascribe to it within the greater biomedical enterprise of obtaining comprehensive, detailed mechanistic knowledge of human (patho)physiology (in the sense explored by Fortun 2008). When I asked TR apologists about what is it exactly that fundamental advances, notably in sequencing technologies, allowed for clinical innovation practices and that was not available 10 or 20 years ago, it was very hard to get a straight, concrete answer, but belief in a recent revolution strongly came through (DE investigator 1; DE investigator 7). Clinician-scientists and apologists of patient-oriented research have been some of the most critical commentators of a situation where molecular biology and genomics technology development might have become autono-

mous ends of their own in biomedicine, rather than instruments to improve health. Nonetheless, Donald S. Fredrickson, the former NIH director, participating in the workshop organised by Swazey and Fox on "the golden-age of patient-oriented research", mentioned how molecular biology was "not this bully that has overrun us [academic clinician-scientists doing patient-oriented research] like the Visigoths" (Swazey and Fox 2004, p. 502).

This strong support for basic research could be associated most readily to the sequencing-driven experimental medicine policy narrative, in that it is the narrative that can readily claim to be associated with mechanistic experimentation. Perhaps because of this thick entanglement between the sequencing-driven experimental medicine narrative and the broader discourse of mechanistic understanding in the life sciences, this narrative may be the most likely candidate to having achieved hegemonic position in collective representations of TR. The dominant representation of TR seems to be that of the molecular biologist (in all of its empirical iterations) as principal investigator that can take the results of breakthrough work with post-genomic platforms to clinical innovation with the help of academic core TR services that act as in-house, public-to-public outsourcing resources (as opposed to public-to-private or private-to-private). This is in contrast to the patient-oriented research narrative, which may locate an important locus of clinical innovation in clinical observation and practice. It is also in contrast with the academic pipelines narrative, which put forwards complex interdisciplinary teams with coordinative leadership being more in the hands of business strategists. In the settings advocated through these narratives, we are likely to have a bit less of the "unexpected happen", and to have people dedicated ("forced") to do TR, to take the terms provided in the quote above.

Despite this situation, a few respondents held that TR had to be expanded at the costs of basic science. Interestingly here, we have already alluded to how reference to a metanarrative of "public accountability towards societal relevance" might have been used by TR advocates to increase collective control over TR projects (see sections 4.2.7, and 5.2.1). Some interview respondents also considered that TR as an independent domain of practice would not be afforded sustained legitimacy unless some resources were taken away from fundamental research:

> "So money needs to be focused there. If you just give more money to the NIH, you won't get this kind of research done. Because of what I said before, the basic scientist will insists that its not basic discovery, its not science, blah blah blah, and all of that is true, but that doesn't mean that it isn't needed. You need the answers to these questions. And I would argue that there is a science in it, its just not the basic kind of science" (US investigator 1).

For these respondents, the more ominous risk is not that highly creative molecular biologists be forced to engage in TR projects when their abilities are best used at fundamental research. Instead, the danger would be that many trainees that would readily become “translational investigators” (to use the words of Coller 2009) are turned away from the domain through lack of recognition and incentive, or that too many TR projects are initiated by “basic researchers” that are excessively confident in their hypotheses. I will highlight the implications of this situation of hegemony of the sequencing-driven experimental medicine narrative over current understandings of TR in chapter 8.

7 Policy narratives and emerging regimes of governance

The current study has taken to heart the call to establish and expand a "social science of translational research" made by Steven Wainwright and colleagues (2009; p. 43). A baseline assumption I have followed here is that an important stepping stone for further efforts would be a greater comprehension of how "the very idea" of TR emerged. Also useful would be insights into how preference for specific languages of TR might harden preferences for certain socio-technical systems and innovation models, as Maienschein et al (2008) already suspected.

This section is the place to have a more systematic look back at the main arguments posited at the beginning of this work, and evaluate how the empirical material I have surveyed substantiate and illuminate these propositions. I will also make clear how my arguments and data can contribute to the emerging debates about the importance of TR for understanding contemporary biomedical innovation and its implications for definitions of health and collective priorities in our societies. In the lines below, I will recall each of my research questions and evaluate which answers were obtained from the analysis performed above.

7.1 There has been mounting perception of crisis in the area of biomedical innovation in the last 20 years, with policy-makers, academic administrations and research leaders calling for new collective models of collective action to reform the application of fundamental biological knowledge to clinical intervention; accomplishments such as the completion of the Human Genome Project appear to have compounded rather than mitigated the crisis, since impatience stems notably from the perception that major achievements in "basic research" are increasingly irrelevant to clinical innovation.

Chapters 4 and 5 have shown a range of mundane and extraordinary argumentative and institutional practices since 1990 and beyond that have worked to produce widespread sentiment of crisis concerning the capacity of biomedical research systems to regularly yield findings amenable to clinical innovation. Individual biomedical researchers, policy makers and other relevant actors have taken their personal grievances concerning the practice and organisation of clinical innovation and carefully formulated them in programmatic statements with a systemic scope. Use of arguments about crisis is also deeply interdependent with the advocacy for particular representations of collective work. Indeed, the prevalence of problematisations in terms of "crisis", "gaps", "bottlenecks", "valleys of death" or "(patent) cliffs" could perhaps be considered to be partly determined by a desire of TR advocates to provide legitimacy to alternative modes of experimentation, career development or inter-disciplinary and inter-

organisational collaborations, irrelevant of the state of biomedical innovation as such. In any case, the analysis conducted here has made visible the argumentative work necessary to create TR as a widely recognised issue in the biomedical field. Specific events, or transformations in the local and system conditions for biomedical innovation brought about experimental and institutional practice in itself, were crucially mediated for interpretation by dominant definitions of TR issues. In this sense, the content of TR problematisations have been arbitrary, in so far as they can never be the unmediated expressions of "objective system failures" in collective projects of biomedical innovation. No TR model can provide global benefit to citizens and society – all proposals are particularistic to a degree.

Chapter 4, particularly, has shown the discursive processes through which the very problem of an ominous and compelling crisis in science-driven biomedical innovation has been gradually assembled together from disparate and particularistic grievances and demands. TR as a relatively coherent and stabilised programme of experimental and institutional reform really only took off in the middle of the 2000s decade, as a number of crises were aligning with one another and TR emerged as a plausible solution to the three of them. Yet, the individual crises have histories that precede the very emergence of TR concepts by quite some time. As shown in chapter 4.1, clinician-scientists in the 70s were already arguing that there was an "explosion" of formal, laboratory-driven knowledge production with the expansion of molecular biology in biomedical research. As a consequence of this trend, they could perceived a novel disconnect between processes of clinical innovation and formal knowledge generation, a disconnect they could partly experience themselves as their capacity to individually integrate both areas of expertise came under pressure by the expansion and increasing sophistication of molecular biology methods. Similarly, section 4.3 mentioned long-standing concerns with the innovation productivity of the pharmaceutical industry. Yet, in the unprecedented conjuncture also brought about the apparent "exhaustion" of traditional small molecule libraries for identifying new drug candidates and the perception of an unrealised potential for dramatic make-over if omics sequencing technologies could be properly tapped into, TR emerged as an urgent necessity to help the ailing sector.

7.2 Emerging as an proposed solution to these innovation crises, a broad reform movement has been coalescing under the label of "translational research" or "translational medicine"

As the lines above have shown, a unique constellation of problematisations could provide the crucial impulse for the launch of TR concepts as a baseline response to crisis in biomedical innovation. Yet, in the specific contours of the solutions put forward be-

tween different policy narratives, there is competition and struggle between lower level of aggregation of TR advocates, or discourse coalitions. Chapter 6 has already explore this in greater details, but did not comment on how the concept of “reform movement” fits in within our argumentative approach and the units of policy narrative and discourse coalitions.

At its simplest, the reform movement of TR can be considered as composed of the sum of all actors uttering or reproducing narratives of TR, including the three dominant policy narratives that have been on focus here but also the multitude of other meanings the terms have been associated with. In this sense then, using this concept allows to capture the argumentative repertoire shared by all three policy narratives. This repertoire, I would argue based on the data presented previously, tends to hinge on metanarratives of epistemic authority through mechanistic understanding and public accountability, notably. The use of the concept of “reform movement” thus allows to adequately conceptualise those situations where various policy narratives of TR can be presented as a unity, and where the baseline narrative of TR is to be advocated for against completely different models of biomedical innovation (see section 6.2).

Talking about a reform movement also contextualises TR within a series of previous realignments (to use the language of Keating and Cambrosio 2003) between biology and medicine, between laboratory- and clinic-driven research, between mechanistic and therapeutic research. The works of Harry Marks, Robert Kohler, or Timothy Lenoir have shown how past reformers of biomedicine have built alliances and stimulated broad deliberations and bargaining about the ways biological and medical knowledge production ought to be related. Replacing TR in this longer history suggests that the alignment of biology and medicine since WWII observed by Keating and Cambrosio was but one specific empirical modality, and that alternative regimes of innovation, such as the one emerging under the label of TR, might propose differing alignments between the two fields.

Moving closer back to Frickel and Gross’ (2005) original work on intellectual and scientific movements, one is also brought back to the central idea there that movements are about power, as well as challenges to dominant regimes of governance. If regimes of governance in biomedical innovation and research are understood as being coextensive with dominant experimental approaches, institutional morphologies and privileged means of coordination and collaboration, then changes to these practices and equipments also bring in questions of collective authority. Then we can also ask which practices, institutions and collectives stand to lose or gain in prominence from the proliferation of TR discourse. Especially, *against* what is TR a reform exactly? What is the incumbent power that TR reformers try to destabilize?

Indeed, a crosscutting concern throughout all three policy narratives of TR examined here has been with issues of what has alternatively been called reputational structures (Whitley 2000), cycles of credibility (Latour and Woolgar 1986) or the accumulation of symbolic capital (Bourdieu 1975). Some of the policy grievances recorded throughout chapter 5 have to do with the fact TR practices and their outputs are not readily convertible into the matters that make academic careers turn: intellectual recognition and influence on peer's experimental practices; access to human, infrastructural and institutional resources. The whole policy narrative of the plight of clinician-scientists hinges on this struggle for defining what counts as highly authoritative biomedical research work. In other words, it is a struggle about scientific hegemony, with all of the experimental and institutional ramifications just mentioned.

7.3 The TR reform movement is succeeding in inducing change in practices of biomedical innovation through a number of argumentative interventions:

> **By formulating policy narratives that problematise the biomedical innovation crises around specific and well delineated issues.**
>
> **Constructing dominant shared understandings within the biomedical field of which models of collective action will best address the crisis: that is, convincingly offering certain research programmes and institution-building agendas as the best means to overcome innovation crises.**

This argument has been the central organising principle of this work. Chapter 4 has operationalised the first part of this argument, chapter 5 the second. Chapter 6 has already appraised in greater detail the validity of applying the concepts of "problematisations" and "models of collective action" to the case.

Perhaps one further precision is warranted before moving on to the next argument. We can legitimately talk of policy narratives here not only because the argumentative interventions studied above have a policy-like effect or attempt to coordinate and orient dispersed individual behaviour in the field, but also because, in all three cases, state policy-makers have played important role in their formulation and institutionalisation. The very first initiative to make use of the TR label, the SPOREs, from the start aimed to provide an institutional home for a domain of TR by supporting the training and career of clinician-scientists. It also made the establishment of biospecimen repositories for large-scale sequencing studies of tumour tissue a pre-condition for centres applying to its specific funding scheme. As such, policy-makers have not been "institutionalisers" of agendas that arrived fully formed from the community of biomedical researchers, but were co-producers of these programmes. The policy narrative of sequencing-driven experimental medicine was articulated in the start by a smaller group of investigators

and policy-makers mostly situated in the field of oncology. As the HGP, notably, progressed, this argumentative repertoire became incorporated by a broader constituency of policy-makers and researchers associated with other disciplines or domains of expertise, as well as actors from other sectors of the biomedical innovation system. A similar pattern can be witnessed with the policy narrative of pharmaceutical crisis and academic pipelines. The FDA played a crucial role in setting the contours and the basic parameters of the problematisation of an innovation crisis in the pharmaceutical industry with its 2004 *Innovation / Stagnation* report.

Chapter 4 has sketched the genealogy of dominant policy narratives of TR, using the traces I found in public fora for collective deliberation and policy-making in the biomedical field. Chapter 5, then, has made especially clear the direct retroaction between both collective and local levels of coordination and policy-making. The empirical material collected there has shown how programmatic proposals for collective agendas were often constructed from local experiences at specific institutions that were argued as "best practices"'. On the other hand, new institutions and initiatives were also presented as directly inspired by previous best practices and experiences of other colleagues, while also

The case of TRAIN (section 5.3) is especially useful here. There, the policy narrative of pharmaceutical crisis and academic pipelines has provided the privileged repertoire to envision a new large-scale initiative for TR and to enrol and coordinate regional actors in this collaboration. Explicit mention of the traditional arguments made to diagnose a crisis in pharmaceutical industry innovation was made to rearrange local coordination routines. The intensive and visible institution-building work in this regional collaboration was held together as a coherent vision through the use of this narrative. Given the absence of earmarked funding that might have been controlled by the consortium to finance local TR projects, and the relatively modest incentives in place to make local teams bring their candidates to the collaboration, argumentative practices where the central means in place to implement the TR agenda. As was seen in section 5.3, there was also an instance of local actors making reference to competing policy narratives and deciding to conduct their TR projects outside the consortium.

This highlights, in my mind, the need of tracing the impacts of TR at both the local and policy-level, between effected practice and discourse about experimental and institutional practice. A number of previous studies on TR have used ethnographic approaches to explore the type of challenges faced in the intensively multi-disciplinary and multi-organisational projects typically labelled as TR (Fischer 2012; Lander and Atkinson-Grosjean 2011; Martin, Kraft and Brown 2008; Morgan et al 2011; Wainwright et al 2009; Wilson-Kovacs and Hauskeller 2012). Here, I have been able to show how

these mundane challenges in practising TR and setting up TR institutions have been entangled with much broader changes in biomedical policy. The emergence of TR as a programme of research and institutional reform in the biomedical field re-shuffles both local experimental practices and collective understandings of what authoritative biomedical research is. Understanding the impacts of this new priority in biomedical policy thus seems to call for robust investigations of its articulation at policy-level as well as local-level sites of practice.

7.4 Changes in experimental and institutional practices effected through TR-driven change are leading to new regimes of governance in biomedical innovation systems

In section 2.2, I made clear the dimensions that I considered to be central to the governance of biomedical innovation. These dimensions include: 1) dominant experimental approaches and the type of knowledge that counts as legitimate and authoritative; 2) dominant organisational and institutional forms for the socio-technical networks producing knowledge and innovation, including the professional groups that are awarded leading or brokering responsibilities; 3) privileged means of coordinating autonomous actor and ensure the collective production of clinical and/or commercial utility. Section 5, most specifically, has detailed how policy narratives of TR are indeed marshalled in a number of recent reform efforts in the biomedical field (SPOREs, CTSAs, NCATS or TRAIN), with consequences for the governance of biomedical innovation along its three dimensions. Each of the policy narratives of TR focused on different issues where change is to be effected.

> **Focus on the renewal of clinician-scientists as a privileged class of investigators to individually incorporate both laboratory- and clinic-based practice; this implies the deployment institutional support to clinician-scientists, of new practices of patient-oriented research and renewed attention on academic medicine and hospital contexts as sites of clinical innovation;**

Sections 4.1 and 5.1 have shown how clinician-scientists have been quite convincingly argued to form privileged leaders and coordinators of translational efforts. The organisational ramifications of their expertise and their research networks based in academic medicine institutions is co-extensive to the defence of “patient-oriented research” as an approach to clinical innovation.

> **Focus on continued effort in the development of post-genomic sequencing platforms for clinical contexts, with the argument that these experimental tools are the best means to obtain deep mechanistic**

(patho)physiological understanding that is necessary to drive clinical innovation; this implies the expansion of socio-technical systems surrounding biomarker research using tissue repositories, for example.

Sections 4.2 and 5.2 have detailed a policy narrative that proposes a regime of governance for clinical innovation that centres around the exceptional explanatory power of genetic sequencing technologies and their potential contributions to mechanistic understanding of human (patho)physiology. Privileged institutions in this projected regime of governance are aligned with the demands of high sequencing capacity, including clinical settings. Coordination is a more marginal function here, with clear "breakthroughs" considered to offer explicit rationale for collective work, aided by peripheral networks of technology transfer offices and industry partners.

Focus on the development of drug development capacities within academic settings as a mean to take over RTD efforts from the pharmaceutical industry; this implies the implementation of large-scale, quasi-industrial RTD instruments and divisions of labour within academia, in a way that is completely novel for this specific context.

The regime of governance advocated in the last policy narrative was sketched in the initiatives and arguments examined in sections 4.3 and 5.3. There it was shown that this version of TR emphasizes a hybrid pharmaceutical-academic approach to clinical innovation (not unlike the innovation systems studied by Webster, Haddad and Waldby 2011). In stark opposition to the previous narrative, here coordination is a central function, and the socio-technical networks advocated in this case bring with them well-defined divisions of labour and other organisational routines characteristic of large-scale collaborations (Vermeulen 2009).

7.4.1 Precising the regime shift

By its nature, the empirical material collected and presented here does not allow me to make a systematic comparative analysis of biomedical innovation systems "before" and "after" the emergence of TR as a central policy narrative. Yet, my review of central TR initiatives and the discriminating use of persona recollections by interview respondents certainly captures organisational, technical or material changes at a number of important nodes in biomedical innovation systems. Additionally, one specific regime of governance in biomedical innovation systems has been the subject of sustained attention from both policy-makers and social scientists associated with the innovation studies tradition. Because of the availability of data and findings in the specialised literature, it is possible to briefly sketch a comparison with the regime I have labelled as "biotechnology entrepreneurship". Engaging in this exercise will provide a clearer view of the

changes brought by TR policy narratives on the mundane institutional and experimental practices of biomedical researchers. Additionally, the biotechnology entrepreneurship model has arguably been the dominant interpretation of governance in biomedical innovation policy until recently (Lander and Atkinson-Grosjean 2011; Martin et al. 2009; Pisano 2006).

Table 3 below summarizes the innovations brought about TR proposals in contrast to the biotechnology entrepreneurship model, while the following lines detail the comparative exercise.

Table 3: Comparison, biotechnology entrepreneurship and TR regimes of biomedical and clinical innovation

Regime of biomedical innovation	Dominant experimental approaches	Dominant organisational forms	Coordination structures and routines
Biotechnology Entrepreneurship	° Locus of hypothesis generation in laboratory (cell culture and animal models); ° Clinic as validation engine.	° Spin-off companies; ° CROs; ° Star scientist.	° Technology transfer offices; ° Early industry-academia partnership with intercallated division of labor.
Clinician-scientists and patient-oriented research	° Patient-oriented research.	° University clinics and academic medicine as institutional locus.	° Clinician-scientists as interdisciplinary brokers.
Sequencing-driven experimental medicine	° Sequencing platforms.	° Biobanks; ° Bioinfornatics lab; ° Aligned clinics.	° Ad hoc, breakthrough; ° Biotechnology regime facilitators; ° Epistemic-accountability entities (biomarkers).
Pharmaceutical crisis and academic pipelines	° Focus on chemical drug development rationality.	° Academic drug development units.	° Demands of pharma. industry and regulatory authorities; ° Business managers and coordinators.

Dominant experimental approaches

Many representations of biomedical innovation have had a tendency to treat clinical research as simply a means to validate therapeutic hypotheses that originate in laboratory experiments using animal models or cell cultures (Nightingale and Martin 2004; Keating and Cambrosio 2012). The discourse of biotechnology entrepreneurship has compounded this, with the locus of generation of new therapeutic hypotheses being placed on "star" molecular biologists able to singlehandedly align clinical and financial capacities with the demands of their "breakthroughs" (Corolleur, Carrere and Mangematin 2004; Zucker and Darby 1996). Here, clinical research might be reduced to a knowledge-poor testing procedure that can be outsourced to contract research organisations, notably (Niosi and Bas 2003; Fisher 2009).

In section 6.4, I argued that the dominant policy narrative of TR, "sequencing-driven experimental medicine", still places the locus of clinical innovation in the molecular biology lab, and puts forward a technology push, rather linear representation of the RTD process. To a limited degree, this policy narrative does indeed extend the model of biotechnology entrepreneurship, and this version of TR seems to have attracted the most attention.

Nonetheless, even the sequencing-driven experimental medicine narrative, one can witness greater attention being brought to a more systemic comprehension of clinical innovation processes. This is even more so the case in the other central policy narratives of TR. Proponents of TR models maintain that biomedical innovation should make a central place to experimental practices conducted in clinical contexts. Instead, TR advocates maintain that clinical research and clinical care are practices productive of experimental knowledge in their own right, that they are an important source of hypotheses and data, and that they need to be but at the foreground of biomedical innovation to improve productivity. The experimental fecundity of clinical research is argued to be especially well visible in areas such as therapeutic research into targeted anti-cancer agents. There, new developments in "biology-led clinical trials", for example, transform early clinical studies into complex experimental platforms that combine simultaneous and interdependent clinical and laboratory areas.

There is a second aspect to the arguments about the experimental platforms and research practices that are most conducive to TR. Advocates of the approach have often contended that TR projects are best conducted by large-scale inter-disciplinary and inter-organisational collaborations. The development of complex new health interventions (such as small molecule drugs and biologics, advanced therapy medicinal products such as stem-cell treatments, diagnostics based on gene or genome-wide se-

quencing technologies) necessitate the successful combination of a variety of competences, experimental equipments and institutional routines, in addition to close interactions between laboratory and clinic. Expertise in animal models; in vitro cell cultures; typing of tissue samples, pharmaceutical chemistry in all of its ramifications, including mass screening of compound libraries; and medical imaging are all mobilized in the development of a new drug, for example. While these domains of expertise have been established for a long time, they have often been distributed across academic departments or organisations. TR models aim to more closely integrate these domains of expertise within single experimental projects.

Dominant institutional and organisational forms

The biotechnology entrepreneurship regime has been characterised by the promotion of academic entrepreneurship for the creation of specialized biotechnology firms that can engage in RTD work (Corolleur, Carrere and Mangematin 2004; Ebers and Powell 2007; Grimaldi et al. 2011). These specialised biotechnology firms were to be embedded within mixed research networks including both academic research centres and pharmaceutical organisations, as well as venture capital firms (Stuart, Ozdemir and Ding 2007).

With TR, academic contexts come back to the centre of attention. Analysts of biomedical policy themselves have indeed commented that hospitals and clinics had been "hidden innovation systems", because these sites of knowledge production have often been left out of the dominant representations of innovation in the field (Lander and Atkinson-Grosjean 2011). Academic medicine centres and university clinics have been argued to form the central institutions in TR initiatives. Many of the experiments and development work conducted in TR projects have to comply with strict regulatory standards, or necessitate costly investments in specialised equipment not commonly found in academic institutions. While these experimental approaches are commonly combined by the pharmaceutical industry, similar efforts in an academic environment are mostly novel, especially when it comes to establishing large-scale drug development equipment in this environment. In other initiatives, the demands introduced by projects such as extensive repositories of bio-specimen are also reconfiguring the clinic in novel ways.

The large and complex projects of the TR enterprise necessitate more management and coordination than what is typical for academic research networks. Consensus and a sophisticated division of labour are necessary to diligently work on one single development project. This was true of biomedical innovation before, but it is even more so in public TR networks, where individual members of the consortium are likely to find

greater academic recognition by engaging in curiosity-driven projects then engaging in the development work required by the consortium. Strategic planning may be required to make sure that the multiple actors composing biomedical innovation systems collectively carry over new knowledge and technologies to development phases, even when the principal investigators responsible for these advances are not interested in this work. To ensure a high level of coordination in TR initiatives, commentators have devised elaborated project planning methods (Wehling 2010; Hoelder, Clarke and Workman 2012). There has also been a proliferation of models and representations of the innovation process that assign roles and functions to various groups of academic professionals, essentially creating plans for sophisticated divisions of translational labour.

Privileged means of coordination

The alignment and smooth collaboration of the areas of expertise required in biomedical innovation is effected in the biotechnology entrepreneurship model through a strong emphasis on commercial incentives. Division of labour and centralised coordination can be achieved on an industrial basis within the confines of specialised biotechnology firms. The promotion of technology transfer activities, often through the creation of dedicated offices in universities, ensures the creation of these spin-off companies, facilitating patent filing or cooperative research with industry (Colyvas 2007; Trippl and Tödtling 2008).

In TR, instead, other means of coordination are often foregrounded, even if the creation of specialised biotechnology firms is not strictly excluded from TR models. Coordination can be ensured by interdisciplinary brokers, single individuals that can legitimately engage in the practices of multiple scientific disciplines or organisations, and assist colleagues belonging to one of these social groups to exchange with members of the other (Calvert 2010). New professional inter-disciplinary identities, institutionalized through dedicated training programmes, can help to stabilize emerging fields of research and the networks that enact them. Given the high inter-disciplinary and inter-organisational character of TR, it should come as no surprise that the emergence of this policy narrative has been accompanied by claims of professional jurisdiction. Particularly, clinician-scientists have claimed a privileged expertise in coordinating and leading TR projects, resting on their dual expertise in both experimental and clinical care practices. The potential authority of this interdisciplinary human capital is compounded by the reunion within single TR projects of actors with a variety of backgrounds, each bringing different frameworks for experimental practice and for evaluating what counts as “good translational research”. It can thus be expected that other types of interdisciplinary brokers, beside from clinician-scientists can also be encountered in actual academic TR projects (see also Ferlie et al 2011; Morgan et al 2011).

Indeed, there has been mounting argumentation that a new group of professionals are needed to lead TR projects, individuals that have fewer capacities for creativity and curiosity then for the management and coordination of large teams. Chapter 5 has shown a proliferation of research coordinators and business managers within academic TR initiatives. These professionals are dedicated to ensuring stewardship of TR projects, ensuring smooth collaboration across disciplines and organisations, and streamlining the development process so that it is aligned to the demands of regulatory agencies and future pharmaceutical partners. Even patient organisations or charities have felt that they might have to fill such coordination roles, as could be seen in section 4.2.

7.4.2 Inclusive or exclusive new regimes of governance?

Before concluding the analytical component of this dissertation, I want to indulge in a slight tangent to reflect on a recent and highly interesting development taking place around TR. These developments show the potential to change again in the near future the governance of clinical innovation. Although I have used the term governance to denote how deliberation and policy-making in biomedical innovation is often a process that is highly distributed among a variety of relevant actors, many authors talk of the governance of technoscience in discussing its reception and appropriation within 'lay' publics of citizens, patients, or other groups commonly formed of "non-experts". Where are these groups in this account of the emergence and institutionalisation of TR agendas? Have they played no part in the success of the TR notions?

Not quite. I have already mentioned in section XZY the advocacy work of the think tank FasterCures, which has done active promotion of the TR agenda taken as a whole. There are other similar examples of lay groups articulating the various policy narratives of TR in sites such as periodical commentaries or consultations organised by governmental policy makers (IOM 2009; Terry et al 2007). Central initiatives to the stabilization of TR narratives and as a domain of practices such as SPOREs and CTSAs have also been required by their funders to make use of mechanisms that enhance patient and citizen participation in local decision-making (Fagnan et al 2010; Pediatric Brain Tumour Foundation 2013). Such a demand for increased patient or citizen participation in decision-making is much more likely to appear in implementation or health systems research, but I have yet to witness it in core documents on discourses on TR. It is quite puzzling to consider advocacy for "patient-oriented" TR can make the economy of arguments for a greater dialogue between patients and innovators.

An another important point to make here however is that if they have not been so much involved in actual TR projects as one might expect, the "average patient" or "average citizen" is regularly construed as the audience, client or patron of biomedical innova-

tion, and one that is actively demanding more output from established systems. This can be witnessed for example in the Canadian Institutes of Health Research's *Strategy for Patient-Oriented Research* quoted in the introductory chapter. This can be observed also in a number of interview fragments where respondents have mentioned a feeling of responsibility for making good on the tax money that constitute their funding (DE investigator 6; US investigator 4; US investigator 11). Should we then look for the rise of TR as a subordinated phenomenon to a deeper metanarrative promoting "applied research" and clinical and commercial relevance in biomedical research as a mean to increase public accountability?

I feel that most of the discourse on TR is actually directed at an audience of researchers and policy-makers. I do not see the legitimacy of biomedical research in the eyes of broader publics to be the crucial object of TR. I have had the occasion to discuss this issue in some interviews with TR advocates, and some respondents considered that clinicians' experiences or indicators of market demand were entirely appropriate indexes of patients' preferences (DE TRAIN 1).

Considering these two points, I would contend that the new regime of governance brought about by TR in some sites of biomedical research do not owe much to attempts to bring biomedical innovation in dialogue with patients, citizens and other lay publics. In fact, in those instances where patient groups engage in discussions and advocacy about TR, they may reinforce and reproduce the dominant policy narratives analyzed here instead of offering counter- or alternative interpretations.

This could be changing, as I write these lines. Given the timeframe of my research, I have been unable to adequately capture some of the most recent developments surrounding TR and where patient groups, for example are a driving force of change. The community engagement agenda at the CTSAs seem to be expanding (Fagan et al 2010; Tendulkar et al 2011; Melvin et al 2013), but most importantly, some patient groups are establishing their own research and/or development centres to "some of the "translation gaps" they have identified (Kaye et al 2012; Kling 2012; Lloyd, White and Chalmers 2012).

7.4.3 Accountability practices and regimes of biomedical innovation

Despite a deficit of substantial involvement of users and patients in the dominant policy narratives I have analysed here, the figure of 'the public' still looms large over TR, especially when it comes to demonstrating relevance and 'value for money'. As subsections 4.2 and 5.2 particularly have shown, the discourse of interview respondents and printer commentaries of other TR advocates afforded much space for themes of responsibility and accountability, especially in the use of public research monies. Leonelli

and Sunder Rajan (2013) contend that this development index a central innovation of TR agendas over previous regimes of governance in biomedical RTD, especially with respect to the production of publicly legible commercial and clinical value.

The original research framework on the “audit explosion” in post-industrial societies accorded much importance to financial auditing and practices for verifying the veracity of public information provided by firms and administrations (Power 2003b). This is less relevant for us here, rather than the analysis also made in these studies of the expansion of “good management practice” (Power 2003b, p. 387). Audit in biomedical innovation is certainly less about financial verification then transparent and accountable decision-making in terms of near-future experimental and organisational projects. More cogent to the subject matters here are observations from this scholarship regarding how audit processes can become agents of reform in organisations or communities that need to be made auditable. Specifically, the expansion of accountability practices within a community often finds crucial thrust at the level of the standardization of procedures for self-observation and the establishment of provisions for the “control of control” (Power 2003a, p. 189). In its stronger manifestations, this can lead to a form of “enforced self-regulation” (Power 2003a, p. 189 citing Ayres and Braithwaite 1992). Indeed, in a more recent development, Power has contended that even current peer review procedures may for example reinforce use of publication performance indicators as a gold standard for evaluating research excellence, thus provoking massive pressure towards self-regulation and alignment of scientists’ practices towards these metrics (Power 2007).

These latter considerations bring us very close to the kind of practices examined in section 4.2.7 and 5.2.7. Here, the instruments elaborated to take decisions about the translability of biomedical projects are very much presented as optional self-help guides, whose broad use would however help to bolster the credibility of the TR enterprise by diminishing failures and associated financial losses. The TR experts who elaborate these instruments might position themselves as quasi-auditors. Their success of course depend on uptake of these instruments since, through audit exercises, the “legitimacy of both auditor and auditee are co-produced” (Power 2003b, p. 380).

On the other hand, the kind of elaborate business strategies and coordination apparatus being developed in academic pipelines (sections 4.3 and 5.3) participate more in the broader trend of good management practice also delineated by Power. The goal here is again to contain financial risks associated with academic development work, but the focus here is much more on direct management of investigators and their projects, rather than self-regulation. Finally, as already briefly sketched above, clinician-

scientists have already been centrally involved in the politics of evaluation and management of TR.

What emerges from these observations and contentions is how different clusters of accountability practices might be co-extensive to each policy narrative. With the rise of regimes of governance in biomedical innovation revolving around TR, dominant schemes of evaluation and audit might also be destabilized. We are likely to witness a contest between these different agendas of accountability and for the determination of the "relevant policy language of… evaluation" (Power 2003a, p. 192). Leonelli and Sunder Rajan (2013) consider that TR participates in the expansionism of accountability by foregrounding means to extract commercial and clinical value from fundamental research. In chapter 8 I will provide some arguments for why I think this may not be necessarily the case, but the analysis made here also already points out how different forms of accountability may be in competition here.

7.5 Conclusions: the value(s) of arguments

To conclude, I would like to highlight the relevance of the analytical exercise conducted here for the broader community of scholars interested in STI policy-making. While discursive, argumentative and interpretative approaches have well-established traditions in political science and STS, they are much less often deployed when it comes to studying the formulations and implementation of innovation policies.

Yet, I would contend that argumentative policy analysis can help us better contextualise STI policies within the domain of general politics, with its negotiation and bargaining processes. Major strands of scholarship in the area of STI policy studies have concentrated on identifying the determinants, functions or institutional composition of high performing innovation systems. An assumption of these studies seems to have been that state agencies can eventually steer the actors and institutions under their jurisdiction to conform to the ideal system identified through by STI policy analysts. In this tradition, coalitional politics and argumentative activities are likely to be categorised as precisely the kind of particularistic and conflict-inducing practices that innovation policy scholarship and state actors should aim to overcome in efforts to ensure the "political coordination of knowledge and innovation policies" (Braun 2008). Such a framework thus *intentionally* leaves processes of advocacy by groups of researchers as unproblematised, even has recent models have sought to integrate coalition-building with users or consumers of new STI has an important condition of success for STI policies (Wieczorek and Hekkert 2012). Yet, in earlier work, Braun (1998) had considered how funding agency managers might ally with specific groups of researchers to steer and select scientific orientations through peer review, leading to negotiations in cooper-

ation. He had also raised the possibility that funding agencies be captured by particular groups of researchers. It would seem crucial to better understand the factors and processes that can lead to such situations, instead of dismissing them as instances of deviant behaviour.

I contend that research communities play an active role in STI policy formulation exactly through the kind of communicative practices tracked by argumentative policy analysis. In some instances, coordination achieved in local communities of researchers through deliberative practices are potentially more powerful mechanisms of steering then typical STI policy instruments such as tax breaks, start-up incubators and technology transfer offices or earmarked funding programmes.

Of course, many studies have examined how consumers, technology users, citizens and stakeholder groups participate in shaping both the content and direction of STI itself, and STI policies. These studies have concentrated on hybrid agora and fora (Nowotny, Scott and Gibbons 2001), including boundary organisation such as funding agencies (Braun 1998) or scientific advisory committees (Scholten 2009), and novel policy networks (Crompton 2007; Lyall 2007; Klerkx and Leeuwis 2008) as privileged sites to capture how these interactions take place. They have also sometimes indicated how STI policy is increasingly formulated by competing coalitions that involve both scientific and lay, state and non-state actors. Nonetheless, I would contend that many of these studies have drawn on empirical cases where policy-makers had set-up specific mechanisms with the explicit intention to allow stakeholders to interact with civil servants and researchers and participate in STI policies and research programmes formulation. Here, I follow the call by Michael and Irwin (2003), made in a slightly different context but still relevant for us, to try and refocus our attention away from these official channels for deliberating STI. Here, I hope to have shown that STI policy-making can be crucially framed by advocacy activities that are much less centralised and organised then those examined in the literature mentioned above. With the tools of argumentative policy analysis, social science scholars should be in a better position to trace the process of STI policy formulation and implementation as it develops through both state-level and local sites (laboratories, disciplinary conferences and journals).

8 Policy lessons

Can we find a definition and model of TR that is precise enough to encourage pragmatic improvements to clinical innovation, while being inclusive enough to speak to the highly variegated situations that biomedical and health researchers and professionals find themselves in. Should all biomedical researchers aim to engage in TR work, or should we rather support intensified specialization by a small group of investigators? Is more fundamental research into human pathology and physiology needed to foster clinical innovation based on the –omics platforms, or should we speed up the deployment of "application strategies"? These are the kind of questions that TR advocates and commentators of biomedical research policy commonly ask themselves, and for which the policy narratives typically aim to provide answers.

Until now, I have sought to provide purely analytical insights into the emergence of TR notions, and how the associated policy narratives might be seen to provoke and steer change in systems of biomedical innovation. With this concluding section, I will instead enter the fray and provide some of my own answers to the questions above, hoping to provide advocates and leaders of TR projects as well as biomedical policy makers with new conceptual tools to tackle TR problems.

Below, I make seven statements aimed at improving our common policies about how to go about with TR and clinical innovation more broadly. My general approach here is not to provide those that engage in TR with detailed tools to organise their activities. These claims somewhat trump some widespread interpretations of the issues TR is about. Consequently, they aim to open up the spectrum of solutions and problematisations that we might legitimately associated with TR, pointing the way towards alternative avenues of reflection, and perhaps even defusing some commonly perceived threats.

8.1 It is not useful to determine whether we are, or not, in unique historical conjuncture of basic knowledge explosion that in itself singlehandedly justifies TR efforts

Section 6.3 sketched along which lines an hegemonic narrative of scientific authority might be delineated in current biomedicine, and how it might structure the argumentative practices effected and policy narratives articulated by differentiated groups of TR advocates. Specifically, I contended that the narrative of mechanistic (patho)physiological knowledge and its associations with rationalistic therapeutic research provided baselines for both dominant forms of knowledge production in biomedicine and collective representations of clinical innovation processes. Although I haven't been able yet to research this in a more detailed matter, the narrative of

mechanistic rationality seem to be co-extensive with a highly prevalent belief that the extension of molecular biology approaches in biomedicine would have lead to an "explosion of knowledge" since the 1970s. My empirical material demonstrates the extent to which this belief is shared by current TR advocates, but also how important it has been in the emergence of notions of TR.

Based on this, the first lesson for future policy I would draw from the analysis conducted here is to be more levelheaded when it comes to expectations of clinical application when it comes to molecular biology advances. It is perhaps necessary here to take the historical long view, and remember that basic advances always take a long time to provide material for applied innovation (Martin et al 2009).

Section 6.3 showed empirical material that may support this hypothesis of a hegemonic grasp of mechanistic rationalities in biomedicine even for advocates that aimed to engage in a completely different type of experimental and epistemic practice. Throughout my work, I have found multiple pieces of evidence indicating that we should indeed be very careful about thinking that the process of scientific discovery and application to problem contexts in biomedicine should be any different now, with the advances in molecular biology and genomics more specifically, than it has been in the past, with all of its empiricism, trial-and-error and long development times. It is still unclear which threshold is being reached that *now* allows rationalism and predictability to replace empiricism in health intervention development. Such promises have been repeatedly made before. Consider the quote below taken from a reflection on the "Changes, Problems and Opportunities" facing the area of pharmaceutical chemistry in 1980:

> "Dissatisfaction with empirical methods, high expectations of the public, poorly harmonized international regulations, and rising costs have induced pharmaceutical research to search for new approaches. As a consequence, the medicinal chemist's professional activity is in a state of change. His synthetic strategy is being increasingly influenced by the reasoning of molecular biology" (König 1980, p. 749).

König's assessment of the basic challenges facing pharmaceutical innovation in 1980 are surreally similar to those that can still be found today. Indeed, in his assessment of the successes and challenges of the biotechnology at the mid 2000s, Michael Pisano stressed how there has been a long history of supposedly revolutionary approaches to drug development that have then been integrated as incremental innovations to the process (Pisano 2006):

> " Many predicted that new methods of making drugs based on genetic engineering would replace traditional "old" medicinal chemistry. This has not happened; moreover, it now turns out that medicinal chemistry and genetic engineering are complementary. This pattern has repeated itself over the subsequent thirty years, with the emergence of rational drug design, com-

> binatorial chemistry, and high throughput screening; then genomics, proteomics, and more recently, systems biology and RNA interference. Each new approach emerges from science and initial expectations (and hype) are that this one is "the real deal" and will dominate. But there has been little replacement of old with new. Instead, the new technologies, as well as the even newer ones, coexist with the old. Furthermore, it appears that they do not operate independently; rather, they are often highly complementary" (Pisano 2006, p. 71).

Claims of new, revolutionary rationalism that could feed an exceptional wave of TR efforts are often supported by mentioning the developing field of biomarkers discovery and development. Yet, so far, biomarkers have not been integrated in daily clinical practice or drug discovery in a field such as oncology (Keating and Cambrosio 2012). What is more, biomarkers can be validated using statistical and probabilistic approaches that leave specific mechanisms unexplained (Metzler 2010), thereby not increasing mechanistic understanding of (patho)physiology in the sense commonly understood when actors defend the idea that current biomedicine has reached a point of rupture with past experimental approaches. Indeed, even Francis Collins recently argued that:

> "**Genome-wide association studies (GWAS) assume no knowledge of disease pathogenesis** and provide a comprehensive approach to the discovery of common genetic risk factors. Many known drug targets and associated pathways appear on the list of GWAS hits for common diseases, suggesting that other GWAS hits likely represent "druggable" targets worthy of further investigation" (Collins 2011, p. 1; my emphasis).

As such, even in the core group of promoters of sequencing-driven experimental medicine, it is not self-evident that –omics platform increases mechanistic understanding of (patho)physiology.

Looking more on the side of drug development, rationalistic therapy research appears in fact to be more of a well-established approach running out of steam than the latest achievement of science. A first form of biology-intensive rational design approach to drug to discovery and development had also emerged in the 1970s, even before the appearance of biotechnology (Martin et al 2009; see also Adam 2005). This heuristic centred on the "'structural properties of drug-target interactions to guide screening" (Martin et al 2009, p. 151), so it is a different beast than the kind of mechanistic understanding currently discussed by TR advocates. Yet, this broader historical perspective suggests that current mechanistic understandings are not unprecedented achievements, and that previous gains in this area have not prevented current problems in innovation productivity.

It is perhaps necessary to unpack the idea of an explosion of knowledge from molecular biology and the omics subspecialties more specifically. Certainly, work in the sociology of expectations has started to do this, but this scholarship also needs to integrate more historical material to tackle this question. Does this knowledge really provide a unique conjuncture for clinical innovation, one that is in clear fracture with what came previously? Or do factors such as the expansion of online publishing and bibliometric evaluation, which in turn push for increased publications by given researchers for given periods of time, also play a role in our appraisals of the basis of knowledge available[1]? It might be troubling that the expansion of certain practices of accountability oriented towards traditional research excellence might have contributed to the inflation of expectations regarding the clinical application of recent achievements in molecular biology.

Similar collective unpacking might also be relevant for other policy narratives of TR. Looking at the policy narrative of pharmaceutical crisis, Martin et al (2009) make the important point that the blockbuster model of pharmaceutical business really only emerged over the 1980s. This means that the endangered business model which TR should save or provide a revolutionary alternative to was itself more of a temporary phase in the longer history of pharmaceutical innovation, rather than core dimension of this system. Especially, the pronounced dedication of expenses to marketing and RTD which we now readily associated to the pharmaceutical industry appear to be characteristic of this historical phase of the pharmaceutical industry. The sense of urgency that we afford to the current “pharmaceutical crisis” might be mitigated by conscience of this ever-changing character of pharmaceutical innovation. Other social scientists have also provided evidence that support the dismissal of narratives of crises in pharmaceutical innovation (Light and Warburton 2011) or in the support for clinician-scientists (Lander, Hanley and Atkinson-Grosjean 2010). In the first case, the authors are quite clear that argumentation in terms of crisis is a rhetorical strategy used to advance the particularistic agendas of given interest groups. Scholarship in the sociology of expectations has shown some amount of rhetoric is constitutive of change in socio-technical systems of innovation. Consequently, my claim here would not be to abandon wholesale these narratives, but rather to engage critically with them and try to determine where they usefully highlight issues for collective attention, and where do particularistic claims take over.

Following the observations of Wainwright et al (2009), we should also be sensitive to the broad spectrum of performative effects brought about by TR problematisations. Problematisation of given issues may also participate to their toleration. These authors

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[1] I owe this idea to Prof. Ulrike Felt

highlight the risk that arguments about the "two cultures" of medicine and biology I already discussed (see section 5.1) may be used not to validate attempts at institutional reform, but rather to do the exact opposite and justify the continued existence of "gaps":

> "Such accounts are performative, serving to enact the (im)possibility of collaboration grounded in institutional differentiation. If medical schools are presented as more hierarchical and practice-oriented, and research communities as more meritocratic and theory-oriented, the expectations of collaboration become diluted (though there is also a mutual capacity for collaboration)" (Wainwright et al 2009, p. 48).

This insight highlights the potential for unintended deployments of argumentative repertoires linked to reform narratives, in this case with an effect that transforms a plea for change into a justification for the *status quo*. It also points towards a need for collective unpacking exercises that can help dissipate both exaggerated interpretations of crisis, but also unwarranted complacencies.

8.2 We might want to reduce some "gaps" in the biomedical innovation systems, but also preserve or even reinforce others

Even if we recognize that we are not situated at a unique conjuncture of revolution in terms of "extractable value" in biomedical research, this does not mean that we should not step up efforts in TR. On the contrary, we are indeed in a unique conjuncture where our models have to be rethought to keep clinical innovation advances going. It is just that we should not count on a projected basic science revolution to provide the impulse for this to happen. Instead, I argue that the current conjuncture supports a strong case for establishing TR as an engineering type of "discipline" or area of biomedical practice. It would make it own use of formal (patho)physiological knowledge where appropriate, but mostly would be concerned with developing its own strong experimental and development programme. This is in line with a long tradition in the history of technology that has shown how "applied research" has historically been conducted as a self-contained experimental programme that can successfully run in relative isolation from basic science activities. As STS authors have shown (Carrier 2010; Lenoir 1997; Rosenberg and Nelson 1994), innovations with broad societal uptake are quite often the results of a type of engineering experimentation that takes what it needs from the formal knowledge and more theoretical knowledge available. Keating and Cambrosio (2012) have shown how the development of a specific expertise in clinical research, distinct from pre-clinical laboratory research and with its own exigencies and dynamics, was crucial to the success of the enterprise.

I share the fear of many TR advocates that the greatest risk right now is not that a large constituency of creativity-driven researchers be “forced” to engage in application work, but rather that there is a large number of trainees and researchers that would like to engage in TR but that are “forced” to do creativity-driven research by incentive structures in biomedical research. Additionally, I am critical of much TR discourse that seems to assume that the only way to improve innovation productivity rates is to more systematically extract value from a purported goldmine of genomic information. My suggestion is that it is perhaps necessary to distinguish more often between “developing applied science” and “putting existing science into application” (to paraphrase Carrier 2010). Perhaps we should let go of the urgency of “applying the science” of the HGP/the post-genomic platforms and concentrate instead on developing TR as an “applied science” of clinical innovation or experimental medicine. Post-genomic science should continue to develop at its own pace, without the pressure for immediate translation, while translation should proceed without being burdened by the task of aligning post-genomic platforms to clinical contexts, if other avenues of research may prove more rewarding in the short term.

Additionally, the formal knowledge of molecular biology somehow needs to be made available to clinical innovation without having to simultaneously take up the whole socio-technical regime it is co-extensive with. Many TR advocates feel that advanced molecular biology tools are of great help, but they do not necessarily want to take up the research programmes of molecular biologists nor be evaluated for career advancements as they are. This situation highlights a darker side of the co-production of science and society: it would seem more beneficial here if post-genomic experimental systems could be dis-embedded from some of the thick networks of institutional practices they have been co-extensive with, so far.

But don’t recent TR initiatives aim to achieve exactly this? On paper, yes, although I fear that concretely the more ambitious objectives are not being realized. As we have seen, the envisioned CTSA departmental structure, which would have provided an institutional home for “TR engineering” did not come to be widely adopted. In Germany, an initiative such as the National Centres for Health Research certainly seems to be driven by the logic that the alignment of university clinics with traditional centres of preclinical research excellence allows breakthroughs produced in the latter sites to flow more easily towards application. Yet, it remains unclear how proximity of clinic and laboratory allows for deep exchanges between those sites of knowledge production.

Achieving the institutional establishment of TR as an “engineering discipline” also involves solving other problems that have not been adequately addressed in recent reform work. For example, questions of stewardship and intellectual property might prove

problematic. The engineering teams that might become the coordinators of TR projects and institutions might need the cooperation and tacit knowledge possessed by laboratory investigators. Can the latter be convinced to contribute to clinical innovation projects as subordinated partners rather than driving forces? How can they be adequately rewarded within a reputational system based on creativity-driven publication practices?

This is to say, there should be a clearer division of labour between discovery and translation practices in biomedical innovation systems, even as intermingling and networking across disciplines and organisations need to be intensified. As we have seen here, a central assumption of TR and the biotechnology entrepreneurship model before was that any molecular biologist or biomedical research can transform her or his research into clinical innovation. This logic needs to be topped on its head, since it is producing massive expectations and massive push on TR resources to sift through a high number of therapeutic or health intervention hypotheses. Instead, the push on basic researchers to try and develop clinical innovations should be all but removed. The locus of coordination should be in the hand of the TR area, and new projects should be initiated by TR leaders, approaching laboratory researchers as fits their purposes. In fact, it seems like *widening the gap* between the *institutional practices* of laboratory and clinic is what is needed here! (see also Maienschein et al 2008). Yet, gaps between mechanistic molecular knowledge and clinical experience need to be reduced.

Safeguarding a certain level of autonomy between TR and curiosity-driven biomedical research can also protect the latter. Maienschein et al (2008) have raised the possibility that widespread adoption of the baseline imperative and “ethos” of TR might drive the development of scientifically ethically dubious areas of research as the push towards clinical applications becomes ominous. Such a situation could be observed in the field of stem cells research notably. Recognizing the necessity of both TR and curiosity-driven research as separate but interdependent enterprises might mitigate such risks.

8.3 We need recalibrated critiques of the linear model of innovation

The previous policy lesson seem to run counter to a finding that is central to STS scholarship: the idea that STI policy-makers and researchers themselves often overtly and performatively simplify the innovation process into a “linear model of innovation”, with negative consequences for the actual practice of innovation and its organisation (Godin 2006; Martin, Brown and Kraft 2008; van der Laan and Boenink 2013).

The first point to make here it is that we should not take an essentialist position and make the linear model of innovation an absolute impossibility. Rather, the linear model might is an analytical modality among others that might useful describe certain socio-technical systems of innovation empirically occurring, albeit certainly much less often

than is contended in much STI policy commentary and making (Balconi, Brusoni and Orsenigo 2010). Most prominently within the context of TR, linearity is actively sought and performed by health innovation regulatory systems and the pharmaceutical industry in search legible evidence of progress in product development.

We need to be critical of iterations of TR narratives that narrow the discussion by using the linear model of innovation to gloss on central experimental and institutional uncertainties of the innovation process, as other social science scholars of TR have warned (Martin, Brown and Kraft 2008; Maienschein et al 2008; van der Laan and Boenink 2013). Yet, I think that it is also very important that social scientists do not reinforce the power of "trickle down" representations of the application of formal knowledge in arguing that there are no absolute epistemic boundaries between applied and basic research. There may not be epistemology police-women and -men that do the rounds to make sure that engineers do not contribute to the advancement of basic knowledge, and researchers working with animal models and in vitro cell cultures can certainly make discoveries that will end up of crucial importance to the development of new therapeutic modalities. But doing the actual work of clinical innovation quite simply implies engaging in specific development practices, as well as using experimental equipments that are thoroughly shaped by constraints put forward by health regulatory agencies. The vast majority of biomedical researchers do not engage in these practices. Too often, when social scientists aim to make the boundaries between applied and basic science appear blurry or completely arbitrary, the effect is that support for fundamental research is seen to automatically contribute to innovation activities. This is not the case, as TR advocates have repeatedly told us. STS scholarship, even with its tradition of attention to the mundane practices of technoscience, sometimes seems to gloss over the respective specificities of development and research practices. This is often the case when traditional grievances against the linear model of innovation are made. We need to qualify these charges by taking into account the point previously made that technological advance can proceed without "highbrow fundamental research" (Carrier 2010), and that, in the biomedical field, clinical research in all of its ramification is a domain rich in knowledge, evidence and prospective hypotheses about human (patho)physiology (Nightingale and Martin 2004; Keating and Cambrosio 2012). These domains of practice show high levels of complexity and are thus perhaps deserving of more academic prestige than they are too often still afforded.

8.4 We should emphasize the complex, necessarily collective character of TR

Following up on the thread of the previous policy lesson, there is undeniably much complexity to be witnessed in some aspects of the TR enterprise. I believe that those advocates arguing that the complexity of average TR projects calls for dedicated and

stable institutional and experimental resources are right on a number of points. Indeed, a consequence of having the dedicated cadre of “TR engineers” I argued for in statement 8.2 would be to create collective standards for the evaluation of new TR projects and therapeutic hypotheses.

I believe that it is important to highlight how highly successful clinical innovation enterprises, such as the anti-cancer agent development enterprise lead by the NCI cooperative clinical groups studied by Keating and Cambrosio (2012), were highly sophisticated enterprises. There, one could witness clear a division of labour within a complex multiplicity of actors centrally coordinated by the NCI. Academic and industry labs were providing new chemical compounds as potential ant-cancer agents, clinical cooperation groups supported by biostatisticians elaborated and performed the trials to test those agents, academic laboratory researchers simultaneously elucidated disease mechanisms, and coordinators made sure that the most promising agents moved back to industry for further development.

Despite the success of the NCI and the clinical cooperation groups, innovation studies and STI policy-makers alike have tended to ignore this or similar cases in their search for “best practices”. Lander and Atkinson-Grosjean (2011) have already shown how policy visions of clinical innovation have been cantered on a few vehicles and systems such as biotechnology entrepreneurship. They have often left important or potentially important sites of innovation such as hospitals, leaving them as a shadow, “hidden research system” (see also Hopkins 2006). Indeed, these authors contend that following this analytical bias from STI policy-makers and their allies from the field of innovation studies, “the majority of innovation policy initiatives focus on the commercial sector, often equating innovation policies with employment and competitive-ness initiatives” (Lander and Atkinson-Grosjean 2011, p. 542). A consequence of this is that, since the 1980s a dominant representation of innovation in some biomedical policy circles has argued that “star scientists” and individual investigators are the locus of new health interventions (Zucker, Darby and Armstrong 2002). Martin et al contend that the advent of genomics has encouraged scientists in the pharmaceutical industry to “take a higher risk approach by discovering and validating entirely new targets” (2009, p. 154). The flipside of this newfound freedom has been that development work on these new targets, whose discovery was allowed by omics platforms, could not benefit from the deep archives of (patho)physiological knowledge that academic research had often created for earlier classes of pharmaceutical targets. This has exacerbated RTD costs in the pharmaceutical industry. In my own research, I have often encountered the argument that the TR conjuncture allows single investigators to enter processes of therapeutic modality development. The model here still seems to be crucially informed by biotechnology entrepreneurship, which many social scientists decried had definite elements of

financial speculation. The TR movement should not be used to promote widespread uptake of clinical innovation as a goal, but rather to increase institutionalization and collective coordination of individual projects.

8.5 TR can become a force for a different alignment of academic biomedicine with clinical and commercial contexts

There is a wide set of STS scholars that hold that academic biomedicine has been thoroughly reshaped by demands for commercial relevance and the encroaching of neo-liberalism within universities (Radder 2010; Mirowski 2011).

> "More than ever before, the legitimacy of the life sciences now rests on claims to produce health... The bioscience community now runs the risk that merely producing truth will be insufficient to move the venture capitalists, patent offices, and science writers on whom the biosciences are increasingly dependent for their new found wealth" (Rabinow 1996, p. 137).

The observation in the quote above was made more than 15 years ago, just as the movement to establish TR was emerging and taking speed. Does the TR phenomenon vindicate or contradict Rabinow's claim? If we look at some recent writings on the topic of TR, we might want to locate this phenomenon as one further increment in the trajectory of commodification of the life sciences:

> "Today, under changed government-industry-academic relations, in a post-Bayh-Dole Act, post-Chakrabarty Supreme Court decision, and post-venture capital era, the emphasis is on ensuring that basic science always keeps an eye on medical therapies to relieve patient suffering and create value" (Fischer 2012, p. 415).

One could believe that TR emerged when "venture capitalists, patent offices, and science writers", publics and policy makers one might also add, started to ask for actual clinical innovations from biomedical research and not just promises or great publication records. Leonelli and Sunder Rajan talk of an imperative to "extract value" out of the archive of knowledge created by the molecular biology and genomics projects. This would be reinforced by current tendencies to ask for readily legible or tractable returns on collective investments in our "audit societies" (Leonelli and Sunder Rajan 2013). Such interpretations would be supported by developments in the area of advanced therapy medicinal products. There, commentators have for example spoken of a context of „hyper-translation" (Balaram 2009) that has lead to the tragic death of a clinical trial participant in the case of gene therapy. What does the intense mobilization of biomedical actors around questions of "translational" and "patient-oriented research" and explored in sections 4 to 6 sit with Rabinow's claim? In other words, does the TR case support that interpretation that biomedicine is now primarily concerned in practice with the production of clinical and commercial value to maintain its legitimacy? Might TR

exacerbate the dangers of a bias towards commercial utility in biomedical research, with potential deleterious impacts on both A) the capacities to produce high quality future (patho)physiological knowledge and B) the safeguarding of patient and citizen interests versus the powerful priorities of research, industry and political elites (Avorn and Kesselheim 2011; Mirowski 2011; Maienschein et al 2008)?

As we have seen, TR advocates themselves are overwhelmingly of the opinion that science for science's sake has remained the dominant goal of the biomedical enterprise, and at the same time that this orientation indeed needs to be safeguarded while simultaneously supporting the extension of capacities in translation. We have seen above that many TR advocates contended that their choice of intellectual and professional focus did not sit well with established practices and routines in the biomedical field. Many respondents portrayed themselves and colleagues in sometimes quasi-heroic overtones, mentioning how they had chosen the path with the lower economic and prestige rewards but with an intrinsic deontological satisfaction, the conviction that is one is contributing to the improvement of patients' well being. If we believe this subset of interview respondents and the authors of many commentaries and editorials, more support would indeed be needed for TR, and this area of practice would still form a marginal part of the *academic* biomedical enterprise. Previous efforts at establishing technology transfer offices and encouraging patenting, biotechnology entrepreneurship and industry-academia partnerships would have to be interpreted as the first steps in a long series of interventions needed to step up academic translation, rather than definitive measures to solve the major "gaps" in the process (DE Investigator 6; DE TRAIN 3).

This claim of TR advocates about the significance of their own actions is not unsupported by social studies of science and technology. Scholars have recently contended that there is a tension between findings from social science analysis that emphasize the drive towards relevance, particularly of a commercial kind, in current STI policy-making, on the one hand, and critics of the extension of practices of accountability revolving around indicators of research excellence, on the other hand (Hessels and van Lente 2011). In other words, the drive towards the commercialization of STI has to be contained or mitigated by a trend such as reinforced support for traditional research excellence through extended use of knowledge productivity indicators.

A crucial observation for this discussion was recently made by Philip Mirowski in his recent work *Science-Mart.* There, he contends that the expansion of the biotechnology industry formed of university spin-offs (in a sector at the time dominated by large multinational pharmaceutical firms) coincided with the promulgation of special rules at the NASDAQ that allowed listing of companies that report not profits, but have tangible

assets such as IP portfolios (Mirowski 2011). This new ruling allowed firms to obtain public money through the financial sector based on their patent portfolio alone, with no obligations to generate profits. Life sciences research readily leads to patents, which are however rarely associated directly to a new clinical innovation. For Mirowski, these new rules allowed the development of a whole sector that could attract investments and glamour through creativity-driven research practices and promises of future therapies, and that mostly lived off venture capital, Wall Street speculation and public technology transfer support mechanisms. This augmented the status and wealth of those life science researchers that could successfully double as entrepreneurs, and these individual quite often happened to be the "star scientists" previously mentioned. Rabinow made a similar observation when he had noted how symbolic capital in the life sciences could be so readily be converted into commercial opportunity (Rabinow 1996). Mirowski holds that very few actual products brought profits that were worth the investments. The biotechnology industry's contributions might have often been in terms of research instruments and improvements in discovery and development processes.

Now, the biotechnology sector does not represent the whole of the biomedical research enterprise, and Mirowski's argument is not that there has not been any major therapeutic development since the 1980s. The point I want to make here is that successful biomedical researchers seemed to have been collectively ascribed high capacities for clinical innovation, but many of them might not have had real competence to exploit resources entrusted to them as a consequence of this collective interpretation. Areas of biomedical research that can be considered highly "commodified" might have ironically been also the most removed from immediate prospects of clinical or even commercial utility. It might even be that the expansion of academic entrepreneurship and industry-university relations solidified the position of creativity-driven, laboratory-based biomedical research as the exemplary model of research practice in the field, consequently *reducing* capacities to conduct successful TR projects.

The alignment of the pharmaceutical industry and academic biomedicine is a central concern of TR discourse. Yet, if we believe the arguments of some TR advocates, this alignment could be recalibrated through the expansion of TR, in a matter that allows pragmatic focus on the experimental and institutional practices that hold most certified potential for short-term patient benefit, instead of supporting a form of commercial yet still fundamental science.

8.6 Do not pin down TR too fast

The various policy lessons stated above can all be said to be variations of a single theme: while TR is still coalescing and the suggest of intense negotiation, it is best to

open up the field of discussion even more, rather than narrowing as many advocates wish. We should welcome the broader proliferation of definitions and phraseologies of TR. Empty rhetoric also participates in social change. Advocacy about TR is just starting to scratch the broader issues understood as "late translation" (NCI 2007; Woolf 2008), including patient and community involvement or global health, and these urgently need to be discussed.

As could be seen in chapters 4 and 5, the three dominant policy narratives of TR between 1990 and 2010 have not systematically problematised these issues in "late translation". Policy narratives always have their blind spots, in part because policy narratives obtain some of their efficacy precisely by "organising out" of politics some issues "organized into politics while others are organized out" (to paraphrase Ney 2012, citing Schattschneider 1960). Following the institutionalisation of certain policy narratives can also us to better delineate blind spots in collective understandings of a problem and to open the way for critique and the formulation of alternative narratives (Ney 2012). The "genealogical accounting of a problem and its ensuing identity lays bare excluded possibilities that can, in turn, form the basis for alternative problematisations and projects" (Howarth and Griggs 2012, p. 326). The current work should have made an appreciable contribution to the first step mentioned in the last sentence, but much work remains to address the second one. Which alternative projects can we envision and bring about for TR?

Maienschein and colleagues (2008) emphasize the need for broad deliberations about the priorities that underpin current TR initiatives, and those that should underpin future interventions. Indeed, these authors contend that there is an ethical peril surrounding a current situation where the imperative towards TR would have been adopted wholesale by great parts of the biomedical community. The TR imperative itself would have occulted any possibilities for an open dialogue or negotiation about priorities and what counts as results for patients and citizens:

> The problem with the translational ethos is not translation as such, but rather the nature of the source language and certain presumptions about outcomes. We all want results from our science, but too many questions – what will count as results, who will certify these, and who is left out as a result of the choices – remain wide open. It should be simultaneously possible to protect the integrity of the source language, generate new understanding through "translation," and negotiate frankly and responsibly about the desirability of particular outcomes (Maienschein et al 2008, p. 50).

Maienschein et al's argument, similarly with my own contentions here, is that the social and cultural meanings of TR need to be better unpacked and put on trial. Elsewhere, Lander and Atkinson-Grosjean have made a useful contribution in highlighting the po-

tential benefits of TR projects not only in terms of clinical and commercial utility, but also civic utility. Clinical utility is sought by doing “patient-oriented” laboratory or clinical research that may provide new interventions for improving the care of patients. Commercial utility is realized when biomedical innovation leads to revenues for sponsors of these new interventions (whether they be public or private organisations), in turn generating employment and institutional development, fuelling the bio- or health-economy sector promoted by many governments. Finally, civic utility can be said to have been attained in research that leads to new knowledge that enables prevention and healthy living, exemplified perhaps best by public health guidelines. One could also consider, however, that civic utility is achieved through the formation of communities (such as patient groups) or when research efforts empower individuals by providing them with knowledge of their biological makeup, which they can then use in their daily negotiations with health, disease, and identity (Parthasarathy 2007). In a similar spirit, a colleague also suggested that the phenomenon of “DIY biology” (the label describing the trend of amateurs conducting “do-it-yourself” life sciences experiments in their garages, or so goes the trope) might be fruitfully considered as a case of translation[2]. Attempts at DIY biomedicine are likely to run into trouble with regulatory authorities sooner than later, but the point here is to disrupt routine assignation of legitimacy to narrow understandings of experiment, development and their public utility. The dominant narratives of TR have left very little space for discussing such proposals, or even more mainstream understandings of civic utility, instead focusing clearly on clinical and commercial utility. On a more sobering note, social scholars of TR might however do well to prepare for the eventuality that opening the base of actors that participate in the governance of TR projects might in fact reinforce the discursive grasp of the dominant policy narratives of TR. Indeed, as section 7.4.2 has briefly mentioned, recent TR initiatives recently piloted by patient organisation have often concentrated on therapeutic research in the narrowest sense. Broadly opening up the arena of deliberation will not necessarily lead to alternative problematisations of the issues at hand.

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[2] This idea is owed to Prof. Brian Rappert.

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Annex A: List of interview partners

Germany

DE Investigator 1
Department of Radiation Oncology
University Clinic of the Technische Universität Dresden
Dresden
Interview conducted at the University Clinic of the Technische Universität Dresden on December 3, 2010

DE Investigator 2
Tranlational Research Center
University Clinic Erlangen
Erlangen
Telephone interview conducted on March 18, 2011

DE Investigator 3
Institute of Virology and Immunobiology
University Clinic Würzburg
Würzburg
Telephone interview conducted on January 12, 2011

DE Investigator 4
Institut für Molekulare Immunologie, Helmholtz Zentrum München
Clinical Cooperation Group – Immune Monitoring
München
Interview conducted at the Institut für Molekulare Immunologie on March 28, 2011

DE Investigator 5
Clinical Research Unit
Department of Obstetrics and Gynecology
Klinikum rechts der Isar, Technische Universität München
München
Interview conducted at the Klinikum rechts der Isar on February 22, 2011

DE Investigator 6
Department of Clinical Pharmacology
University of Heidelberg, Medical Faculty Mannheim
Mannheim
Interview conducted at the Department of Clinical Pharmacology on December 20, 2010

DE Investigator 7
German Consortium for Translational Cancer Research
German National Cancer Institute
Heidelberg
Interview conducted at the German National Cancer Institute on January 11, 2011

DE Industry 1 and 2
Association of Research-Based Pharmaceutical Companies
Berlin
Interview conducted at the Association of Research-Based Pharmaceutical Companies office on January 5, 2011

DE Coordinator 1
Translational Project Development
Helmholtz Zentrum München - German Research Center for Environmental Health
München
Interview conducted at the Helmholtz Zentrum München on March 28, 2011

DE Coordinator 2
Studienzentrum
University Clinic Freiburg
Freiburg
Interview conducted at the University Clinic Freiburg on May 25, 2011

DE Coordinator 4
Medical Clinic and Polyclinic III and Center for Inner Medicine
University Clinic of the Technische Universität Dresden
Dresden
Interview conducted at the University Clinic of the Technische Universität Dresden on December 3, 2010

DE Coordinator 5
European Advanced Translational Research Infrastructure in Medicine
Helmholtz Association
Bruxelles, Belgium
Interview conducted at Helmholtz Association offices on December 20, 2010

DE TRAIN 1
Coordinator
VPM GmbH
Hannover
Interview conducted at the VPM office on December 13, 2011

DE TRAIN 2
Investigator
Department of Internal Medicine I
Eberhard Karls University Clinic Tübingen
Tübingen
Interview conducted at the Eberhard Karls University Clinic on December 19, 2011

DE TRAIN 3
Coordinator
Alliance for Translational Research in Lower Saxony
Twincore
Hannover
Interviews conducted at Twincore on October 29, 2010 and on January 10, 2012

DE TRAIN 4
Investigator
Twincore
Hannover
Interviews conducted at Twincore on January 10, 2012

DE TRAIN 5
Investigator
Helmholtz Center for Infection Research
Braunschweig
Telephone interview conducted on January 18, 2012

DE TRAIN 6
Lower Saxony Ministry for Science and Culture
Telephone interview conducted on March 9, 2012

EU-supported networks and other European initiatives

EU Investigator 1 and 2
Innsbruck Medical University
OncoTyrol Consortium
Innsbruck, Austria
Interview conducted at the Innsbruck Medical University on February 13, 2012.

EU Investigator 3
Centre for Medical Systems Biology
Leiden University Medical Centre
Leiden, Netherlands
Telephone interview conducted on November 10, 2010

EU Investigator 4
Senior Director Immunology Strategy
UCB
Slough, UK
Interview conducted at UCB on November 30, 2010

EU Investigator 5
Department of Biomedicine
University Hospital Basel
Basel, Switzerland
Telephone interview conducted on December 6, 2010

EU Coordinator 1
European Clinical Infrastructure Network
INSERM
Paris
Interview conducted at INSERM on November 4, 2010

EU Coordinator 2 and 3
European Organisation for Research and Treatment of Cancer (EORTC)

Bruxelles, Belgium
Interview conducted at the EORTC on December 17, 2010

EU Coordinator 4
Translational Research Department
Institut Curie
Paris, France
Interview conducted at the Institut Curie on January 26, 2010

EU Policy-maker 1
Health Directorate
Directorate General Research
European Commission
Bruxelles, Belgium
Interview conducted at DG Research on November 9, 2010

EU Policy-Maker 2
Independent policy and pharmaceutical industry consultant
Vienna, Austria
Interview conducted at the respondent's office on March 2, 2010

USA

US Investigator 1
Vanderbilt Institute for Clinical and Translational Research
Vanderbilt University
Nashville
Telephone interview conducted on July 29, 2009.

US Investigator 2
Genomics & Public Health Program
Department of Human Genetics
Emory University
Decatur
Telephone interview conducted on July 22, 2009.

US Investigator 3
Department of Medicine
Thomas Jefferson University
Philadelphia
Telephone interview conducted on August 12, 2009.

US Investigator 4
Division of Hematology-Oncology
Weill Cornell Medical College
New York
Telephone interview conducted on July 20, 2009

US Investigator 5
VA Greater Los Angeles Healthcare System

Los Angeles
Telephone interview conducted on August 12, 2009

US Investigator 6
Baylor Cancer Center
Houston
Telephone interview conducted on July 28, 2009

US Investigator 7
Vanderbilt Ingram Cancer Center
Vanderbilt University
Nashville
Interview conducted at Vanderbilt University on April 15, 2011

US Investigator 8
Department of Pharmacology
Institute for Translational Medicine and Therapeutics
Translational Research Center
University of Pennsylvania
Philadelphia
Interview conducted at the Translational Research Center on April 13, 2011

US Investigator 9
Consultant and former
Devon, PA
Interview conducted at the respondent's home on April 13, 2011

US Investigator 10
Department of Transfusion Medicine
National Institutes of Health
Bethesda
Interview conducted on the NIH campus on April 5th, 2011

US Investigator 11
Department of Cancer Biology
Vanderbilt University
Nashville
Interview conducted at Vanderbilt University on April 15, 2011

US Investigator 12
Hugh Sampson, M.D.
Mount Sinai Institutes for Clinical and Translational Sciences
Mount Sinai School of Medicine
New York
Interview conducted at the Mount Sinai School of Medicine on April 6th, 2011

US Investigator 13
Georgetown-Howard Universities Center for Clinical and Translational Science
Georgetown University
Washington DC
Interview conducted at Georgetown University on April 18, 2011

US Policy-Maker 1
Division for Clinical Research Resources
National Center for Research Resources
National Institutes of Health
Washington DC
Telephone interview conducted on August 13, 2009
Second interview on NIH premises on April 11th, 2011

US Policy-Maker 2
Translational Research Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Rockville, MD
Telephone interview conducted on September 13, 2009.

US Policy-Maker 3
Office of Public Health Genomics,
Centers for Disease Control and Prevention
Atlanta
Telephone interview conducted on July 16, 2009.

US Patient Organisation 1
Fast Foward LLC.
New York
Telephone interview conducted on August 10, 2009.

US Patient Organisation 2
Genetic Alliance
Washington DC
Telephone interview conducted on July 27, 2009.

Annex B: Sample interview guide

TriGEN SP5 interview guide for 'clinicians and researchers' (broadly understood)

Translational activities = TA

1. Please describe your past and present professional activities as well as your involvement in the area of TA more specifically.

2. What are TA for you?

3. Please describe your organisation's involvement in TA

4. I would now ask you to choose one area of TA where you or your organisation is involved, and describe to me, in details, in what consists the TA work that is accomplished there as well as the people involved.

- Does thinking and acting within a TA framework bring something different to clinical investigation, laboratory work or clinical management research?
- How is this expressed in routine activities?
- What are the results or expected results of this project/activities in this area? Was part of it uniquely translational?
- Is TA differently organised from commercial pharma R&D, i.e. done in biotechs, or work in academic medicine?

5. What would you say is the state of TA (or biomedicine, or your specialty, or clinical research, or pharmaceutical R&D, or clinical management practices) in Europe, and in your country? Who is setting the agenda for TA in Europe and your country?

6. Why is there interest in translational activities now, and not 10 or 20 years ago (what's different here then work on technology transfer, or in clinical research, or clinical management)?

7. What are, according to you, the main challenges and threats to the success of translational initiatives at present and in years to come?

8. Is there a role for regulation by the state or professional associations, and of health policy makers in translation and funding activities? If yes, which one? Have you benefitted from help specifically to conduct your TR activities from various public bodies?

Annex C: Abstract in English

Recently, biomedical innovation leaders have advocated closer alignment of clinical and research under the rubric of “translational research” (TR). Translational research has emerged as a major priority of biomedical innovation policy in a number of countries in the last 10 years, backed by substantial resources.

Despite the ubiquity of their usage in the biomedical field, little critical knowledge is currently available about the origins of the notions of translational research and their implications for biomedical innovation practice. In this work, I will propose to unpack the phenomenon of translational research by combining insights from argumentative policy analysis; science, technology and innovation policy studies; and science and technology studies work on scientific movements and the sociology of expectations. It elaborates and further formalises approaches for processing the deliberative and argumentative practices that are co-extensive to collective processes of knowledge production in research fields and institutions.

I explore how TR advocates have problematised socio-technical developments in the biomedical research field of the last 40 years as instances of crises demanding urgent collective intervention. Engaging in a range of argumentative practices (co-extensively with institutional and material practices), proponents have been able to use the perceptions of crises to channel policy and common resources in the field towards specific arrangements of preferred research priorities, experimental platforms and institutional set-ups. Policy narratives emerges from the empirical material as a powerful conceptual unit to delineate aligned and competing ensembles of arguments and associated reform practices.

I conclude by discussing some of the shortcomings of the models of biomedical innovation advocated through translational narratives, but also a few shortcomings of current assumptions science and technology studies and innovation studies made salient by this specific empirical case.

Annex D: Abstract in German

In den letzten zehn Jahren, gab es eine Vielzahl von Plädoyers für eine stärkere Verbindung der biologischen Grundlagenforschung mit der klinischen Praxis. Subsummiert unter dem Begriff der „Translationalen Forschung“ (TF), hat eben diese Forschung in vielen Ländern an Priorität gewonnen. Diese wird in mehreren Ländern durch substantielle Ressourcen gefördert.

Der Begriff der Translationalen Forschung ist im biomedizinischen Feld allgegenwärtig. Dennoch gibt es wenige analytische oder kritische Arbeiten, die sich mit dem Ursprung dieses Begriffs und deren Auswirkungen auf die biomedizinische Innovationspraxis beschäftigen. In dieser Arbeit untersuche ich das Phänomen der Translationalen Forschung mit der Hilfe eines theoretischen Ansatzes, der sich auf die „Argumentative Policy Analyse“, die „Science, Technology and Innovation Policy Studies”, und auf Ergebnisse der Wissenschaftsforschung über wissenschaftliche Bewegungen und die “Sociology of Expectations” stützt. Dabei erarbeitet und formalisiert diese Arbeit Methoden, in deren Zentrum die Analyse von argumentativen Praktiken steht. Diese werden als co-extensiv zu kollektiven Prozessen von Wissensproduktion in Forschungsfeldern und Institutionen gesehen.

Ich beschreibe wie TR Befürworter/innen sozio-technische Entwicklungen im biomedizinischen Forschungsfeld der letzten 40 Jahre als „Krisenmomente“ problematisiert haben, die kollektive Interventionen notwendig machen. Die Befürworter/innen beschäftigen sich mit einer Reihe von argumentativen Praktiken (co-extensiv zu institutionellen und materiellen Praktiken) und nutzen dabei die Wahrnehmung von Krisen erfolgreich, um Politik und kollektive Ressourcen für spezifische Forschungsprioritäten, experimentelle Systeme und institutionelle Konfigurationen zu gewinnen. “Policy narratives” dienen in diesem Kontext als konzeptuelle Einheiten, die alliierte und konkurrierende argumentativen Praktiken und assoziierte reformelle Praktiken einzuordnen helfen.

Im abschließenden Kapitel der Arbeit diskutiere ich die Schwachstellen biomedizinischer Innovationsmodelle, die durch solche translationale Erzählungen ermöglicht wurden, und diskutiere Leerstellen in den Feldern der Wissenschafts- und Technologiestudien und Innovationsstudien, die sich aus dieser spezifischen empirischen Studie ergeben.

Special thanks are due to Ingrid Metzler and Sarah Schmitz for help with the translation of the abstract to German.

Annex E: Author's curriculum vitae

Current Affiliation

Since October 2009
Doctoral student (Doctor of social science, specialisation in political science)
Department of Political Science, University of Vienna
Vienna, Austria
Thesis Supervisor: Prof. Dr. Herbert Gottweis.

Education

September 2005 – December 2008
M.Sc. Urban studies. Institut national de la recherche scientifique – Urbanisation, culture et société (INRS-UCS).
Montréal, Canada.
Thesis Supervisor : Prof. Dr. Michel Trépanier

September 2002 – April 2005
B.A. Science, Technology and Society (STS). Université du Québec à Montréal (UQAM).
Montréal, Canada.

Other Relevant Experiences

February 2008 – February 2013
Doctoral researcher
Competence Centre New Technology
Fraunhofer Institute Systems and Innovation Research (Fraunhofer ISI)
Karlsruhe, Germany

September 2007 – December 2007
Research Assistant
Canada Research Chair in the History and Sociology of Science

September 2006 – September 2007
President, Federation of the INRS students
President, Student association of the INRS-UCS
November 2005 – November 2006
Member of the organization comity – First congress of the INRS students

January 2004 – December 2005
Research Assistant
Science-Metrix Inc. (www.science-metrix.com/)

Project Fundings and Awards

February 2009 – January 2013
Research grant for the Tri-Gen project (Translational research in genomic medicine: Institutional and social aspects – nearly 500,000 € to five institutions)
German Federal Ministry of Education and Research, Austrian Ministry of Science and Research, Academy of Finland (see http://trigen.isi-projekte.de and www.elsagen.at/)
Project coordinator was Bärbel Hüsing (Fraunhofer ISI).

June 2010 – May 2013
Canada Graduate Scholarships Program: Doctoral Award (60,000$)
Social Sciences and Humanities Research Council of Canada (SSHRC)

September 2006- August 2007
Research Master's Scholarship (*Bourse de maîtrise en recherche*) **(15,000$)**
Fonds québécois de la recherche sur la société et la culture (FQRSC)

September 2005 – August 2006
Canada Graduate Scholarships Program: Master's Award (17,500$)
Social Sciences and Humanities Research Council of Canada (SSHRC)
Publications and conference presentations

Articles in peer-reviewed journals

Vignola-Gagné E. 2013. Argumentative practices in science, technology and innovation policy: the case of clinician-scientists and translational research. *Science and Public Policy.* Accepted, forthcoming.

Vignola-Gagné E, Rantanen E, Lehner D and Hüsing B. 2013. Translational research policies: disruptions and continuities in biomedical innovation systems in Austria, Finland and Germany. *Journal of Community Genetics.* 4(2): 189-201.

Larivière V, **Vignola-Gagné E**, Villeneuve C, Gélinas P and Gingras Y. 2011. Sex differences in research funding, productivity and impact: an analysis of Québec university professors. *Scientometrics.* 87: 483-498.

Gaisser S, **Vignola-Gagné E**, Hüsing B, Enzing C and Van der Valk T. 2009. EU policies in personalized-medicine-related technologies**.** *Journal of Personalized Medicine.* 6(1): 93-102.

Archambault É, Côté G, Gingras Y, Larivière V and **Vignola-Gagné E**. 2006. Benchmarking Scientific Ouput in the Social Sciences and Humanities: The Limits of Existing Databases. *Scientometrics*. 68(3): 329-342.

Archambault É, Gingras Y, Larivière V and **Vignola-Gagné E**. 2006. The Place of Serials in Referencing Practices: Comparing Natural Sciences and Engineering With Social Sciences and Humanities. *Journal of the American society for information science and technology*. 57(8): 997-1004.

Other publications

Vignola-Gagné E and Biegelbauer P. 2013. Translational Research. In *Springer Encyclopedia of Creativity, Invention, Innovation, and Entrepreneurship*. E.G. Carayannis (ed.). Heidelberg : Springer.

Reiss T and **Vignola-Gagné E**. 2013. *Thematische Schwerpunktbildung in den Life Sciences durch system-immanente Prozesse* [*Intellectual trajectories in the Life Sciences as « system-immanent » processes]*. Karlsruhe: Fraunhofer Institute for Systems and Innovation Research ISI. Report commissioned by the German Federal Ministry of Education and Research, Berlin, Germany.

Reiss T, **Vignola-Gagné E**, Kukk P, Glänzel W and Thijs B. 2013. ERACEP – Emerging Research Areas and their Coverage by ERC-supported Projects. Karlsruhe: Fraunhofer Institute for Systems and Innovation Research ISI and Leuven : Katholieke Universiteit Leuven. Report commissioned by the European Research Council, Brussels, Belgium.

Hogarth S, Hopkins M, Rodriguez V, Enzing C, Gaisser S and **Vignola-Gagné E**. 2009. *The role of patents in the development and clinical use of genetic tests. Case studies on the role of IP in the development and clinical use of genetic tests for Factor V Leiden, TPMT and HPV in the USA and EU*. Report commissioned by the European Commission Joint Research Centre Institute for Prospective Technological Studies, Seville, Spain.

Enzing C, Van der Valk T, Gaisser S, **Vignola-Gagné E**, Paci D and Ibarreta D. 2009. *Genomics knowledge for future health services*. Report commissioned by the European Commission Joint Research Centre Institute for Prospective Technological Studies, Seville, Spain.

Vignola-Gagné E**.** 2009**.** *Québec policies on biotechnologies from 1982 until today: innovation and spatial dynamics (Les politiques québécoises en matière de biotechnologies de 1982 à aujourd'hui : innovation et dynamiques spatiales*). Montréal : Institut national de la recherche scientifique – Urbanisation, culture et société. Master's thesis.

Archambault É, **Vignola-Gagné E** and Bouffard D. 2005. *Towards a Canadian Biotechnology Innovation Scoreboard.* Montréal : Science-Metrix Inc. Commissioned by Industry Canada, Life Sciences Branch, Ottawa, Canada.

Archambault É and **Vignola-Gagné E**. 2004. The Use of Bibliometrics in the Social Sciences and Humanities. Montréal : Science-Metrix Inc. Commissioned by the Social Sciences and Humanities Research Council, Ottawa, Canada.

Archambault É, Bertrand F, Côté G, Craig-Dupont O, Larivière V and **Vignola-Gagné E**. 2004. Towards a Canadian R&D Strategy for Bioproducts and Bioprocesses. Montréal : Science-Metrix Inc. Commissioned by the National Research Council of Canada (NRC), Ottawa, Canada.

Conference presentations

Vignola-Gagné E. 2013. Expertise differentials within research communities: the conflict over translational medicine and biomedical policy. Presentation at the 8th International Interpretive Policy Analysis Conference, 3 – 5 July 2013, Vienna, Austria.

Biegelbauer P, Lehner D and **Vignola-Gagné E**. 2013. The Difficulty of the Plains: Coordinating Translational Research. "Alles eine Frage der Koordination? Policy-Making in Mehrebenensystemen" Jahrestatgung der Sektion Policy-Analyse und Verwaltungswissenschaft der Deutschen Vereinigung für Politische Wissenschaft am 1 und 2 März 2013 an der Otto-Friedrich-Universität Bamberg, Bamberg, Germany.

Vignola-Gagné E. 2012. *Translational research: history, dominant practices and current provisions for patient involvement*. Invited presentation for the workshop "Values in translational research: Exploring the role of patient involvement as a way to enhance ethical reflection". University of Twente, Netherlands, November 22-23, 2012.

Vignola-Gagné E. 2012. *Smoke screens and sacred fires: Translational research and grand challenges in European biomedicine*. Presentation at the Eu-SPRI Conference "Towards Transformative Governance? Responses to mission-oriented innovation policy paradigms". Karlsruhe, Germany, June 12-13, 2012

Vignola-Gagné E. and Biegelbauer P. 2012. *Translational research: A new form of governance for genomic medicine?* Presentation at the ESRC Genomics Network Conference 2012 - Genomics in Society: Facts, Fictions and Cultures, London, 23 & 24 April 2012.

Biegelbauer P, Lehner D and **Vignola-Gagné E**. 2012. *Translational Research and The Governance of The Emerging Genomic Medicine*. Presentation at the Jean Monnet Conference „The Governance of Innovation and Socio-Technical Systems in Europe: New Trends, New Challenges". Copenhagen Business School, Denmark, March 1, 2012.

Lehner D., Rantanen E. and **Vignola-Gagné E.** 2011. *'Therapeutic eagerness': clinician-scientists and the politics of large-scale translational research*. Presentation at the Annual Meeting of the Society for Social Studies of Science (4S), Session "Collaborations across health research and care, November 2-5 2011, Cleveland, USA.

Vignola-Gagné E. 2009. *Translational research as an emerging practice in biomedicine: entrenching biology's hold in the clinic*? Presentation at Tagung „Biomedizin – Gesellschaftliche Deutung und soziale Praxis", 14-16 October 2009, Schwerte, Germany.