Translational research: entrepreneurship, advocacy and programmatic work in the governance of biomedical innovation

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Preprint / Preprint
Sammelwerksbeitrag / collection article

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7.1 INTRODUCTION

A number of conceptual and disciplinary splits reduce the analytical power of STI policy and systems analyses. Most notably, STI policy analyses have tended to frame these processes as out of their boundaries, despite the recognition that debate or bargaining as processes shape policy instruments and their targets in a world of constrained resources (Holzinger, 2004; Saretzki, 2009), making the formulation and implementation of policy instruments an inherently political matter (Meadowcroft, 2009; Biegelbauer and Hansen, 2011; Geels and Verhees, 2011). Yet, several decades of policy analysis provide ample proof that only in the rarest of cases do policy interventions come out of the blue. Normally they are the result of struggles for power, the ambition to be represented, to have one's interests included, to learn from experience, to win an argument, to see a set of ideas vested with the power to explain, and the like (for example Truman, 1956; Lasswell, 1970; Hall, 1993; Sabatier and Jenkins-Smith, 1993; Gottweis, 1998; Parsons, 2003).

Therefore power struggles are not the only highly political element in policy-making. Bargaining, entrepreneurship and advocacy may be required even for the continued maintenance and performance of innovation systems**.** Complementarities need to be activated and reactivated. Interdependencies between areas of expertise and between organizations often 'fall out' and become dysfunctional. Here, we will show that governance is not only about the creation of legitimacy towards a broad public for the 'reception of technology', but also the building of

legitimacy within a network to build support for the 'reception' of an organizational form. Indeed, governance does not end at the doorstep of an organization; rather, the term has an inside and an outside quality. We are interested in both, the governance of change on the level of policies, and on the level of organizations, their structures, norms and values (Hall and Taylor, 1996; Peters, 1999; Hollingsworth, 2000).

Initiative, entrepreneurship and advocacy are constantly required at the organizational level to ensure collaboration and coordination. In these contexts of high ambivalence, entrepreneurial activity is also required to negotiate which policy instruments will be marshalled in the specific context, and how. An important condition to achieve successful advocacy by entrepreneurs are sets of policy rationales and/or programmatic statements that clarify targets and tactics for collective action. STI policies in implementation are confronted with a policy field in which varying sets of skilled actors are making them part of their opportunity structures when they try, for example, to raise funds for new projects or institutions. This is the case for 'hard', that is, regulatory and distributive, and 'soft', that is, information delivery and community formation measures, both of which are subject to interpretation by various actors. In the process, new rationales, scientific concepts and programmatic frameworks are utilized as framings: opportunistically, in order to gain funding; as sense-making tools, in order to interpret social problems and environments; but also instrumentally, as mechanisms to coordinate and channel the efforts of the range of actors brought together by advocacy efforts.

In short, Chapter 7 focuses on change in some of the experimental and organizational practices that are central components of socio-technical systems. It uses novel observations drawn from case studies of biomedical innovation systems reform to trace the role of selected parameters in this process of transforming existing practices. Specifically, we look at the role of (1) programmatic statements; (2) their advocacy by entrepreneurs and (3) their interplay with existing and new policy instruments, in explaining the governance of socio-technical change. This analytical strategy could have explanatory power in other cases of socio-technical change where policy design and implementation define parameters of the process.

The three case studies each revolve around efforts in the implementation of translational research (TR) programmes in biomedical RTD sites located in Austria and Germany. TR can be defined as a policy rationale (Braun, 2005) that first problematizes current practices in biomedical

practices, offering a distinct diagnostic of well-discussed 'crisis situations' in biomedical innovation systems. These innovation crises include:

(1) public disappointment with the outcomes for patients of big science projects such as the Human Genome Project;
(2) a perceived widening gap between the practice of academic medicine and the advances of molecular biology and
(3) decreased RTD productivity in the pharmaceutical industry which has led to the loss of thousands of RTD jobs (Kraft, 2013; Vignola-Gagné, 2014).

Second, TR advocates championing a specific set of scientific approaches, organizational arrangements and policy packages as the way out of these problems. The most prominent interventions on biomedical innovation systems and attendant policies that are advocated through TR include:

- Closer integration of clinical experience with cutting-edge laboratory experimentation (including sequencing technologies and biomarker discovery experiments), notably through forms of 'patient-oriented research' and the development of experimental routines within clinical trials.
- Investment of research monies and scientific work capacity in 'gap areas', such as clinical pharmacology and drug development as a scientific/engineering problem.
- Redistributed and new professional roles across the continuum of labour in biomedical innovation, including greater leadership from clinician-scientists.
- Greater coordination and orientation of innovation projects, to increase efficiency and reduce trial-and-error in intervention development.

As the dimensions above make clear, much of the TR rationale is aimed explicitly at change in the governance of biomedical innovation systems rather than techno–scientific change alone. Nevertheless, the TR rationale is entangled with broad developments brought on by genomic sequencing technologies, continuing reform of clinical research, past achievements and desired futures. Prior to the establishment of the initiatives studied in Chapter 7, TR had been used since the 1990s, in the US most notably, to justify and orient policy-driven efforts targeting the dimensions mentioned above. The TR rationale attempts to harness and orient change in

biomedical innovation systems brought on by advances in genomics towards a specific set of outcomes, both techno-scientific and governmental.

The three cases of implementation of TR rationales into regional STI policies that will be studied below highlight the importance of the interplay between scientific entrepreneurs and explicit programmes of change in reforming experimental and organizational practices in biomedical innovation. Entrepreneurs and advocates of TR negotiate the formulation and implementation of pre-existing policy instruments to build their networks, draw on higher-level debates about the legitimacy of biomedical innovation to frame their action and shape the role of other actors. These findings are relevant for the pillars of theory building introduced by Borrás and Edler (2014), highlighting how advocacy, entrepreneurship and governance processes around the design and implementation of policy instruments (pillar 2) are themselves entangled with structures of opportunity (pillar 1) and in processes of legitimacy building (pillar 3).

Detailing our understanding of how: (1) policy rationales and programmes of socio-technical change; (2) advocacy works to enrol allies for these programmes and (3) entrepreneurs interact to produce change in experimental and organizational practices through TR initiatives studied here, raises the following research questions:

- How is a global rationale such as TR made use of in locales far removed from its origins in Austria and Germany?
- How are programmatic statements, concepts and assumptions about current crises and benefits of the TR-model used to shape or drive socio-technical change, and to shape or drive change in related governance arrangements?
- How do entrepreneurs engage in advocacy activities and deploy programmatic statements in their innovation practices, and how do these interact with policy instruments already deployed in the field?

The rest of Chapter 7 will be structured as follows: Section 7.2 reviews previous efforts to use policy rationales, programmatic statements and the role of entrepreneurs as analytical units in order to explain change in socio-technical systems and their governance. Section 7.2 highlights especially the potential contribution of the two categories ‘entrepreneur’ and ‘advocacy work’ to this research agenda. Section 7.3 provides a brief overview of our data collection and analytical strategies. Section 7.4 presents and analyses our empirical material, starting with a review of the emergence and evolution of TR rationales in the USA, and later

internationally (section 7.4.1). This step is essential for understanding the interventions advocated by the entrepreneurs in our case studies. Subsection 7.4.2 details case study material, with observations structured along the three pillars by Edler and Borrás (2014). The presentation of the policy instruments deployed in each initiative is successively contextualized with a view to the entrepreneurial (section 7.4.2.3 – pillar opportunity structures and capable agents) and advocacy work (section 7.4.2.4 – pillar legitimacy) that has aligned and framed them. Section 7.5 concludes with a discussion of the findings, detailing the crucial role of entrepreneurs and their advocacy of TR programmes in producing change in socio-technical systems and their governance mechanisms.

7.2 LITERATURE REVIEW: RATIONALES, PROGRAMMATIC STATEMENTS AND ENTREPRENEURS

To understand the role of policy rationales and programmes in managing change in socio-technical systems, one can follow along the lines of work that aims to combine traditions of analysis in the economics of innovation and in the politics of policy (to use the terms of Jacobsson and Lauber, 2006). One approach employed in this strand of works has been to identify 'technology-specific coalitions' that 'engage in wider political debates in order to gain influence over institutions and secure institutional alignment' (Jacobsson and Lauber, 2006, p. 259). While Geels and Verhees (2011) have also studied the role of coalitions, cognitive frames and discourses in innovation systems and policy, they have yet to look in detail at how these processes reorganize systems of knowledge production, for example at the level of mundane experimental and institutional practice. Hillman et al. (2011) have provided STI policy and systems analysts with typologies of parameters for modelling the steering action of governance arrangements on innovation systems. Governance in innovation systems may include regulatory, market, cognitive and normative mechanisms. These authors rightly point out the unique role of public or governmental policy-makers in shaping and performing the governance of innovation systems. Nevertheless, the current chapter should make it clearer that while governmental actors may be obligatory passage points in governance processes, they are not the critical source of agency for change.

Elsewhere, scholars have combined the analysis of 'traditional STI' policy instruments and of 'modes/strategies of governance' by deploying

a more dynamic approach to system building and resource utilization. They have looked at the formation of networks to establish shared resources, including reputational capital, standardization authorities or financial resources (Musiolik et al., 2012). An important finding has been that the system building process is partly determined by the type of networks that lead these efforts and the resources they have access to. This opens a path to further analyses of how policy instruments are actively elaborated and operationalized within the mundane practices of innovation, notably by highly entrepreneurial local actors.

Entrepreneurs have been the subject of a long-standing line of work in economics. These studies have emphasized the role of individuals in organizing or catalysing institutional change, taking risks and building alliances for achieving their aims (Bergeron et al., 2013). The concept has now been integrated across the social sciences, and the policy entrepreneur or change entrepreneur has emerged as a useful analytical unit to understand policy change. Interesting findings from the attendant literature have highlighted how entrepreneurs realize their interests by transforming the social space and institutional arrangements they evolve in, rather than reproducing them; how they create and frame collective crises and direct attention towards specific resources to solve them; and how they play on the fragmentation of social systems and boundaries or differences between groups and institutions to generate innovation and/or benefit (Bergeron et al., 2013; Castel and Friedberg, 2010).

Authors have also highlighted the interaction between entrepreneurs and policy rationales or programmes in pushing governance change. Hassenteufel et al emphasize the determination of 'programmatic actors' on the content of policy change, on the legitimization of some programmatic statements and the marginalizing of others. 'By selecting, translating, recombining, and, most important, imposing ideas, they fulfil a genuinely creative and constructive role' (Hassenteufel et al., 2008, p. 529). Programmatic statements are an essential component of policy change, since crises and external destabilizations on policy processes do not alone determine solutions.

These findings are in line with the original formulation of the advocacy-coalition framework (ACF), formulated by Paul Sabatier and Hank Jenkins-Smith, who state that policy change is mainly induced by external effects such as economic crises or natural disasters, rather than by policy entrepreneurs. Indeed, the ACF has been less interested in the role of entrepreneurs, but more focused on the level of a policy subsystem and the advocacy coalitions, which are seen as the main constituent of policy fields. In the ACF, policy advocates are the prime

movers of advocacy coalitions, being linked by shared policy beliefs and interests (Sabatier and Jenkins-Smith, 1993; Sabatier, 1998).

Hassenteufel and colleagues oppose programmatic actors compared to policy entrepreneurs in that the latter are seen mostly as brokers and packagers but not creators. Such a strict delineation between the two categories is questionable, however. Indeed, transfer and brokering rarely leaves policy content intact. Clavier (2010) has shown the importance of the self-initiative of local entrepreneurs in diffusing and implementing public health and health care policies elaborated by the World Health Organization. Much like TR rationales and other scientific programmes, WHO policies are proposed interventions that are not intrinsically backed with financial or regulatory obligation. Their careers rest on persuasion, marketing and advocacy. Clavier's examples provide a clear view of the crucial role played by the combination of broadly circulated programmes and policy rationale, as well as appropriation by local entrepreneurs for enacting local change of practices and institutional arrangements.

Similarly, Peter Biegelbauer finds that in Austrian RTD policy-making, major programmes usually are the result of policy entrepreneurs' actions with entrepreneurs in most cases (also) playing an important part in the creation and (re)combination of policy ideas (2007, 2013b).

In the science, technology and society (STS) literature, forms of advocacy have been captured in actor-network theory analyses of the construction of innovation networks. Especially, a recent iteration of the theory has drawn attention to the future-oriented work that is performed to justify and, indeed, advocate for certain technological options rather than others (van Lente and Rip, 1998; Hedgecoe and Martin, 2003). Advocacy through raising technological expectations is here considered a crucial strategy for building new networks of actors and artefacts, and thus conducting socio-technical change. Arguments and rationales about preferred courses for collective action have also been shown to be an important component of the implementation and effectiveness of policy formulated by governmental agencies (Borrás and Radaelli, 2011).

7.3 RESEARCH STRATEGY

A critical mass of attention has recently been afforded to TR rationales within the biomedical innovation community, with a number of initiatives being put into place internationally (Shahzad et al., 2011; von Roth et al., 2011). Here, we mobilize case studies of TR-related entrepreneurship in three initiatives established in Austria and Germany. The selected initiatives have been launched in the last ten years and have been explicitly

construed by their promoters as being focused on TR. The initiatives offer a degree of diversity and contrasting experiences to allow for in-depth comparison. Taken as an ensemble, the initiatives should constitute a broadly typical panel of cases. In a first case study (TRAIN), a core group of entrepreneurs very actively advocate for the TR model to reform regional innovation practices. Based on their work, new mechanisms of coordination, for what were previously dispersed and discrete experimental projects, are being put into place and renewed legitimacy is offered to RTD activities. In a second case study (ASC), technological change is emphasized, with the other dimensions only marginally present. The absence of a core single or group of entrepreneurs is noticeable here, and both advocacy activities and uptake of the rationale appear to be low. Use of TR was of a highly instrumental character. The third initiative (OncoTyrol) offers a middle case in that it is characterized by a strong group of entrepreneurs, but with less pronounced advocacy work. Financial resources are used as driver of change, more so than programmatic statements, although change is aimed in part at the implementation of the TR model presented above. TR rationales thus have more of a guiding role, but are also crucial to legitimize the strongly centralized and top-down mode of coordination encountered in this consortium.

For each case study, semi-directed interviews were conducted with coordinators, administrators, research leaders and policy-makers, who had been identified as playing a central role in the establishment and maintenance of the respective initiative (six interviews for the TRAIN case study; seven for the OncoTyrol case study; 11 for the Anna-Spiegel-Center case study). Interviews and relevant documents were coded and analysed following an analytical grid that aimed to capture the diachronic development of the initiatives, who was involved and how, the relations to the international policy discussion, coordination issues, governmental support and the features of the experimental practices deployed locally.

Lastly, this discrete investigation into TR initiatives was part of a broader research programme concerned with understanding the origins and implications of TR as a 'reform movement' in contemporary biomedical innovation. Even if they do not form the focus of analysis here, our reflections on this topic have also drawn from 39 further interviews conducted in Germany, EU-networks and the USA, as well as a document analysis of governmental white papers and approximately 200 editorials, commentaries and reviews about TR, that are published in peer- reviewed biomedical journals.

7.4 RESULTS

TR is a policy rationale that appeared in the early 1990s. More specifically, it advocates for certain institutional and experimental reforms as privileged means to solve a number of crises that have shaken biomedical innovation systems since the 1970s (Vignola-Gagné and Biegelbauer, 2013).

7.4.1 Translational Research: Scope and Novelty

Section 7.4.1 looks at these constitutive crises and the kind of structural changes in biomedical innovation that TR advocates aim for.

In the 1970s, the character of biomedical research was irrevocably changed by the steady expansion of molecular biology approaches in the field. Whereas the period immediately after World War 2 until the 1960s saw a 'golden-age' of research performed by medical doctors in close proximity to clinical contexts and practices, a paradigm retrospectively dubbed 'patient-oriented research' (Swazey and Fox, 2004), the new approach emphasized the control and replicability of laboratory systems and modelling. Molecular biologists were slowly filling an increasing number of research positions at academic medical centres and university clinics, and also started to systematically outperform medical doctors in obtaining National Institutes of Health research funding. Starting in the late 1970s, but lasting up to now, a number of biomedical policy actors and academic medicine leaders started to problematize the situation of these clinician-scientists (for primary literature see: Wyngaarden, 1979; Nathan, 2002; for secondary analysis see: Wilson-Kovacs and Hauskeller, 2012; Vignola-Gagné, 2014). They argued that these professionals possessed a unique dual expertise in both clinical care and clinical or laboratory research, and were thus privileged drivers of biomedical innovation with relevance to patients. Yet, the increasing sophistication of molecular biology made them experience an increasing 'gap' between both areas of practice, and increased public support was necessary to enable these clinician-scientists to be competitive again in funding calls. In 1991, with the establishment of a number of specialized centres for clinical oncology research by the National Cancer Institute in the USA, the notion of TR was first introduced and was immediately associated with ongoing policy discussions about the future of clinician-scientists (Cancer Letter, 1991). Major TR initiatives that came later also planned support for clinician-scientists (for primary literature see: Zerhouni, 2005; Borstein and Licinio, 2011; for secondary analysis see: Vignola-Gagné, 2014).

The perception of a gap or disconnection between molecular biology-driven biomedical research and clinical application gained much broader currency in the early 2000s, in the immediate aftermath of the international Human Genome Project. This big science project of unprecedented scope in biology and medicine raised high expectations of short- and mid-term contributions to clinical innovation, which were however followed by a cycle of disappointment (for primary literature see: Anonymous, 2011; Lander, 2011; for secondary analysis see: Martin et al., 2009; Hogarth et al., 2012). Advocates have positioned TR as the approach that would make genomics and related technological platforms relevant to the clinic (Collins, 2011). This involves, most notably, modernising clinical research networks so as to make genetic sequencing an integral part of clinical testing and the development of new interventions, or expanding experimental platforms such as biobanks, which can generate therapeutic hypotheses by directly using human tissues instead of model systems.

The latest, but possibly the most urgent, series of developments to have shaped the trajectory of TR concepts has been the increased perception of a situation crisis in the pharmaceutical industry. With its 2004 report *Innovation/Stagnation,* the US Food and Drug Administration brought the existence of data indicating stagnating productivity in the pharmaceutical industry in terms of new innovative drugs, despite increasing investments, to the attention of a broad audience (Food and Drug Administration, 2004). Although the data and interpretations have been subjected to discussion, by the late 2000s, events seemed to confirm the diagnosis. Large pharmaceutical companies have recently slashed thousands of RTD jobs as their recently off-patent portfolio 'blockbuster' drugs, selling for billions annually, had failed to be replaced by new ones (Milne, 2009). In prevision or in reaction to this situation, a number of biomedical leaders and academic administrations had advocated the establishment of 'academic drug pipelines', hence providing for unprecedented forms of development research, divisions of labour and industrial RTD equipment within the public research systems (Tralau-Stewart et al., 2009; Becker and van Dongen, 2011).

TR as policy rationale thus emerged as a response to these three interconnected series of developments. Although the TR rationale repeats many themes and proposals commonly voiced by reformers of biomedical innovation since the 1970s (Vignola-Gagné, 2014), the programme has received unprecedented levels of commitment. It is now backed by major research funds, training programs and institutes (Zerhouni, 2005; Collins, 2011; Shahzad et al., 2011; von Roth et al., 2011).

7.4.2 Case Study Results

Section 7.4.2 presents the results of our case studies of TR initiatives. For each case, the relevant policy instruments are described. It is then shown how these instruments were introduced and put into operation by local entrepreneurs, simultaneously, as they advocated for the adoption of the TR model.

Based on interviews and literature studies described above, Table 7.1 below uses the four dimensions of socio-technical change advocated by TR programmes (see section 7.1) to summarize the technological and organizational changes that have taken place at the sites of each of our three case studies.

Table 7.1 Forms and depth of socio-technical change brought by TR initiatives in three regional biomedical innovation systems

	ASC	OncoTyrol	TRAIN
Lab – clinic integration	++	+	+
Investment in gap areas	++	++	++
New division of labour	–	+	++
Enhanced coordination	–	++	+

7.4.2.1 Description of cases

The three cases studies from the Anna Spiegel Centre, OncoTyrol and the Translational Research Alliance in Lower-Saxony are described below.

7.4.2.1.1 Anna Spiegel Center for Translational Research The Anna Spiegel Center (ASC) is a research building situated at the Medical University of Vienna (MUV), as part of the General Hospital of Vienna (AKH). It has specifically been labelled as a translational centre and was built with the intention to create more lab-space and to centralize 'Core Facilities' – high-tech to support basic research at the AKH/MUV. Opened in 2010, the centre is an example of a highly modern research institute composed of relatively independent teams that were previously situated in a more clinical environment at the main buildings of the MUV.

The ASC consists of six research departments (surgery, dermatology, cardiology, paediatrics, oncology and haematology), which comprise a varying number of research and/or lab-groups. The official mission of the

centre is to conduct clinically-driven research using the latest techniques biomedical research has to offer. The chemists and biologists at the ASC work closely together with the physicians at the clinic located at the main building of the AKH/MUV. Their research projects are based on clinical considerations/observations, and they try to translate their new findings (new diagnostics, bio-markers) immediately to the clinic. Accordingly, the scientific practices are translational in a bi-directional manner since both areas – the lab and the clinic – need each other's expertise and knowledge. Moreover, this close relationship is based on 'material exchange', as the basic researchers need, for example, tissue samples from patients or bio-banks.

The ASC does not have a director or management team of its own. The ASC staff have a very heterodox understanding of TR notions, ranging from an economic conception to a more clinically oriented definition.

7.4.2.1.2 OncoTyrol OncoTyrol comprises a regional cluster of 22 research groups located in universities, research institutes and companies, specialising in applied research in the growing field of personalized cancer medicine in the area of Innsbruck. OncoTyrol operates as a GmbH (limited liability company). The consortium is led by the board of shareholders (56 per cent universities; 21 per cent Hospital Holding; 23 per cent Province of the Tyrol), and decisions are implemented by the management in Innsbruck. Currently, OncoTyrol is employing about 90 scientists and providing facilities for the research teams (for example, offices for HTA-research, lab-space in a special building, facilities for bio-informatics).

The research teams are expected to produce patents, licences or products in cooperation with industrial partners. Part of the IPR from the funded projects is retained by the OncoTyrol management – a situation which prompts the consortium administrators' hope that it will become self–sufficient in the future, without a need for additional public funding. In terms of the sheer amount of industrial partners involved, OncoTyrol is an atypical TR initiative. Although some industrial members act more as *mécènes*, providing funding in the background in the hope of the development of eventual products, other projects have called for joint and sustained collaborations.

As a consortium with its own dedicated project funding mechanism, OncoTyrol features a unique structure within the networks and initiatives we have studied. Whereas in TRAIN, funding is mostly provided for building and equipment infrastructure, in OncoTyrol, funding is given to projects directly (including personnel costs). The OncoTyrol administration can decide (and has been known) to withdraw membership and

funding from project teams that are not committed enough towards clinical and/or commercial aims.

7.4.2.1.3 Translational Research Alliance in Lower Saxony The Translational Research Alliance in Lower–Saxony (TRAIN), a state in the Centre–North of Germany, is an initiative explicitly dedicated to developing new drug compounds that are typically brought forward by pharmaceutical corporations. TRAIN regroups seven main institutional partners, all of which directly take part in various tasks and work packages of the collaboration's projects. The institutes are located in relative proximity in the two largest cities of the region. Their founding members include universities, public research institutes and a medical school. A number of joint ventures between partner institutes have significantly extended the local expertise in drug development. Further, the consortium includes a firm specialized in managing life science projects (VPM).

Based on the capacities that are being regrouped, the TRAIN management claims that within the TRAIN partnership it is possible to go from pathophysiological hypothesis to lead compound to early phase II clinical trials (that is, clinical development with tests on human subjects to measure safety and administration modalities, thus requiring a comparatively complex infrastructure). This claim positions the consortium as a structure of unique breadth and complexity in Germany and at the European level.

7.4.2.2 Pillar 2: policy instruments

As discussed in Section 7.1, a number of different policy instruments have been advocated in the literature to realize the TR programme (Vignola-Gagné and Biegelbauer, 2013; Vignola-Gagné et al., 2013). Reformulated in the language of STI policy analysis, these instruments most importantly include:

- measures of organization building in the sense of creating the infrastructure for TR;
- funding programmes fostering TR, but also general research funding programmes;
- the professionalization of education such as support for clinician-scientists with degrees in both medicine and natural sciences;
- efforts of governance coordination in which either various governance initiatives are coordinated and/or in which actors are brought together in order to exchange information.

In all three case studies, measures of organization building and general funding programmes proved to be most central. In the case of the ASC, the funds that had been earmarked for the completion of the General Hospital (AKH) were used for a building for two research institutions, the Anna-Spiegel-Centre (ASC) and the Research Center for Molecular Medicine (CeMM). The cost of 41 million Euro for the building was shared between the city of Vienna and the Austrian Ministry for Science and Research. Research at the ASC is supported by standard principal investigator grants or project funding from thematic programmes (from the Austrian Science Fund (FWF)'s general competitions, 'Translational Research' and 'Clinical Research' (both FWF), 'Patients in Focus' (Centre for Innovation and Technology of Vienna, ZIT) and the life science programmes of the Vienna Science and Technology Fund (WWTF)).

OncoTyrol was mostly funded by the Austrian COMET programme (Competence Centres for Excellent Technologies; Biegelbauer, 2007), a multi-actor, multi-purpose competence centre programme, aiming at linking actors in science and industry by realising cooperative research initiatives co-funded by federal and state (Länder) levels, companies and research institutions. When its predecessor Kplus was set up in 1998, it was arguably the most complex RTI policy instrument in Austria and in 2013 it remains to be one of the most important RTI funding instruments in the country (Biegelbauer, 2013b). In addition to COMET funding (from 2008–2012, approximately 18 million Euro came from the federal level, 6 million from the state of Tyrol, 23 million from industry and 1 million from academia), additional support stems from a variety of research funding programmes. Broadly**,** the OncoTyrol consortium can be said to have been assembled by the combination of policy instruments commonly used in the last 20 years to foster commercially-oriented STI activities: centres of excellence with a high level of participation from industrial partners; the availability of venture or seed capital; and high interdisciplinarity. Nonetheless, the specific configuration of expertise and disciplines present within the consortium, especially its emphasis on fostering clinically-informed laboratory research, is aligned with TR rationales.

TRAIN institutionalizes previously dispersed regional expertise in drug development in a clear model, through regional coordination and cooperation, and a consensual division of labour between local actors. This policy plan was jointly developed by local leaders of relevant institutions and the Lower Saxony Ministry of Science and Culture. The model makes direct reference to the rationale of academic pipelines (see section 7.4.1), thus providing 'blueprints' for local TR projects, including

model collaborations. The central office of the initiative (staffed by one part-time administrator), together with the life sciences project management firm VPM, encouraged active participation of research teams that are affiliated with consortium member institutions. The business managers and coordinators were central agents for transforming research projects of autonomous teams into complex TR projects with centralized coordination and strategic commercial planning. The consortium model also assigned specific tasks to different expert groups within the consortium. The infrastructure building activities that have taken place there since 2007, especially multiple joint ventures, have helped to establish the consortium collaboration blueprint more readily. A first wave of such joint ventures was initially funded by the local Lower Saxony Ministry of Science and Culture (at the level of slightly under 30 million Euro). With this initial funding secured and the overarching concept established, members of the consortium have also been able to secure infrastructure funding for other joint institutions from the German federal programme for university infrastructure building, the *Forschungsbau* programme.

Despite the focus on infrastructure funding up to now, business managers and coordinators at the consortium central office can also assist member teams with obtaining grants or venture capital to finance actual experimental work. A drug development project related to the consortium benefitted, for example, from funding from the German federal Bio-Profile programme, which offers proof-of-concept funding for exploratory development work in the life sciences conducted in biotechnology firms or academic settings. Drawing on this funding, and directed by principle of the 'academic pipeline', the TRAIN consortium has thus focused on the development of the large-scale equipment used in industrial drug development, including natural substance libraries and a chemical screening facility.

OncoTyrol is an interesting case here as the COMET funding programme allows funding of research groups and facilities alike and thus offers OncoTyrol's management some flexibility. Yet COMET funding is tied to a number of conditions, most importantly science-industry cooperation. In order to provide the management with the structures necessary for coordinating competence centres with a large number of actors with diverse multi-disciplinary commercial and non-commercial background, COMET centres are set up with a clear hierarchical structure (Biegelbauer, 2007). OncoTyrol features a network structure combined with a strong hierarchical component, while ASC and TRAIN are less hierarchical. Leadership in ASC is externalized in the form of the management of the AKH/MUV. TRAIN's strongest management structure is the cluster formed by a steering committee in

which representatives of the six founding partner institutions are co-located with the consortium administration office.

7.4.2.3 Pillar 1: opportunity structures and capable agents

The cases of TR collaborations we studied have highlighted the central role of a few academic leaders in implementing local iterations of the proposals made in the international policy discussion. They show how the emerging policy rationale, and its specific repertoire of problems and solutions, was used by these entrepreneurs to reframe collective interpretations of the biomedical innovation process shared by local actors, and of their preferred policy instruments.

Within TRAIN, understandings of TR have been most thoroughly shaped by the sub-rationale of crisis in innovation productivity in the pharmaceutical industry. The consortium leaders are also very clear about the origins of this initiative as a response to the pharmaceutical innovation crisis. The uptake of the consortium model has been actively advocated among the member institutions by information sessions or 'internal PR'. In their presentations, consortium coordinators directly refer to the models recently expounded by Francis Collins, the current director of the US National Institutes of Health (NIH), who has called for universities and public institutions to take on some of the scientific risk associated with drug development and increase collaboration with the pharmaceutical industry. The explicit goal of these information activities is to promote the TR model of biomedical innovation locally among research teams and other relevant actors, some of them being core funders at the regional and federal level. Establishing the TRAIN consortium has thus called for action on local work programmes, problematizing capacities for biomedical innovation and presenting the TR model as the preferred solution. Nonetheless, consortium leaders also worked at the level of resources and incentives, offering expertise to potential partners with regard to business management, patent portfolio development or networking with venture capital. The TRAIN entrepreneurs aligned governmental funding schemes and other policy instruments with the demands of local projects to realize a coherent TR network that is in accordance with current rationales about biomedical innovation.

OncoTyrol's origins lie in the strong departments for clinical oncology at the Medical University Innsbruck and related biological research centres. In 2002, this collective of excellent scientists already present in Innsbruck was consolidated into a better network by a prime mover with a background both in science and industry. Notably problematic at that point was a perceived financing gap for proof-of-concept studies, which

meant that promising therapeutic intervention candidates, who had been developed locally, were 'lost' to industry instead of being led through early clinical development within Medical School.

The opportunity to establish an excellence centre for oncology arose when COMET calls for application were issued. Similar to TRAIN, the founders of OncoTyrol seized the increasing difficulties within the pharmaceutical industry as an opportunity to elaborate a centre of excellence model centred around 'open innovation' (they made an explicit reference to the work of Henry Chesbrough), with strong networks of collaboration between the Medical University and industry partners. This way, tentative TR projects would obtain proof-of-concept funding and access to industry-specific competences and infrastructures while retaining more control over product development than was previously possible.

With the excellence centre approved and in place, the coordination of participating TR projects changed dramatically. The consortium directly employs more than 80 administrative and technical staff, and participating research teams obtain most of their project funding and even salaries through the OncoTyrol administration. Continued availability of this funding is subject to successful progress in TR terms, and in terms of clinical and commercial relevance. COMET funding, which itself was marshalled by a few entrepreneurs that identified a unique support opportunity and made use of the international rationale of TR to advocate their vision, thus durably altered the structures of opportunity for regional biomedical actors as well as their understanding of TR. While the compliance of participating research teams with the TR model does not rest on its advocacy by the entrepreneurs alone (as it does in TRAIN), the OncoTyrol leadership nonetheless has made use of its programmatic statements in preparing future expansions of the consortium (including a move towards financial self-sufficiency).

In the case of ASC, several scientific entrepreneurs came to the conclusion that lab space was too limited in the Medical University Vienna and therefore infrastructure building was the only possible solution to the problem. In lengthy negotiations with the City of Vienna and the Austrian Ministry for Science it became clear that a new building would become more feasible when sharing space with a second institution. This turned out to be CEMM, which was at this time rapidly expanding and therefore also looking for a new building.

Labelling the building with TR coincided with the fact that different elements of the TR metaphor had already taken root in Austrian RTI policy discussions, leading to the first TR funding programmes at the time. Policymakers therefore were receptive to the programme of TR,

with its affinities for their own commitment towards the renewal of medical schools. However, once they had successfully marshalled funds for their infrastructure and equipment project, the entrepreneurs however did not push through with the organizational interventions advocated in international TR programmes.

7.4.2.4 Pillar 3: questions of legitimacy

To a certain extent, we can reduce the question of opportunity structures surrounding TR to the issue of legitimacy in biomedical innovation systems. The opportunity for TR consortium building appears to have been thoroughly shaped by global policy discussions about how best to conduct biomedical innovation so as to ensure its continued relevance in the eyes of a broad civil constituency, as well as its 'value for money' (in the sense of Braun, 2005; see also Leonelli and Sunder Rajan, 2013; Maeinschein et al., 2008).

Despite this potential for making TR a vehicle for extended civil participation in RTD systems, our results show that this has not been the case in Austria and Germany. The consortia we studied had no mechanism to ensure patient or citizen input into decision-making. Interview respondents sometimes considered the market's demand for given health products, or that clinicians' experiences with patients provided the best means to capture patient or end user preferences, with even patient representatives being sceptical about the possibility of co-decision making regarding TR on grounds of the involved issues' complexity.

This does not mean that legitimacy is not an important dimension in order to make sense of the changes brought about by TR in biomedical innovation systems. Indeed, 'internal' or intra-network legitimacy, as a resource that can be deployed to ensure coordination and collaboration within the narrowly defined communities of innovation studied here was a central concern of the consortia. This can be most clearly witnessed in the case of TRAIN, where, as discussed above, the actual realization and performance of the consortium model depended on well-coordinated collaboration of a number of research teams with broadly different disciplinary and organizational missions and demands to answer to. Establishing participation in TRAIN as a new and distinct goal for each of these teams thus entails building legitimacy for the project that answers to the necessarily particularistic (with respect to the consortium's goals) agendas of these groups of experts.

While within OncoTyrol, the broader discussion of crisis in biomedical innovation played some role in its overall set-up and direction of the consortium, it was less prominent and somewhat less operationalized in the case of TRAIN. Indeed, because of direct management of research

funding by the central administration, it seemed that the official narrative was not being extensively used in daily practice. Nevertheless, legitimate participation of research teams within the OncoTyrol structure depended on their compliance with collaboration and experimental practices in line with those advocated in TR rationales.

In the case of the ASC, TR had little effect on intra-network legitimacy. Since the legitimacy of the organization rests on a strong scientific rationale, it is well aligned with the mind-set of scientists and medical doctors working there. The internal governance schemes of ASC are very much driven by the experienced principal investigators leading small research groups, who coordinate loosely and without much internal differentiation. The framework of the organization is predefined by the MUV's rectorate, which conceives of the ASC as an institution for scientific excellence, where only the best research groups of the MUV should work. Accordingly, these groups were chosen by MUV in a selection procedure based on scientific output criteria only. 'Intra-network legitimacy' is of course interconnected with 'extra-network legitimacy'. The TRAIN leaders advocate to local partners the model proposed with their consortium by framing the current biomedical innovation policy landscape as threatened by a crisis with far-reaching consequences. Consortium leaders thus readily draw on debates around the legitimacy of the biomedical innovation enterprise and its relevance to civil society to justify their agendas.

Interestingly, consortium collaborators sometimes appeared to be 'phantom allies', that is partners more on paper than in practice, yet useful in order to keep current core collaborations going with the prospect of future collaborations around commercial development, for example. These phantom allies (most notably industry and patients) imbued the work blueprint provided by the consortium with legitimacy, and thus provided consortium leaders with resources to align academic members and ensure effective coordination of their work within the division of labour planned by the model. In other words, the 'presence' of these phantom allies had essentially boosted the legitimacy to alter local interpretative frameworks related to the biomedical innovation process and to marshal support from a number of policy instruments.

The ASC, for its part, consolidated an orientation towards laboratory-based research on human material that was already present at the MUV. As such, it provides a case of TR as a transformative notion being used in a non-transformative manner and to extend previously existing practices. Nevertheless the external legitimacy of ASC secured funding for infrastructure which was justified by a broader importance beyond ASC. This utilization of TR as a legitimising metaphor includes the instrumental

usage of firms, which are again being used as 'phantom allies' and which in the actual daily practices of the organization until now have played a rather small role – something which may or may not change with an increasing age of the still young institution. Firms, however, were not the only 'phantom allies' – patients also tended to slip out of the roles assigned by programmatic statements. In the actual daily routines of ASC personnel, patient participation in the research process was mostly limited to tissue donation.

7.5 DISCUSSION

The material and analysis presented above provided multiple points of support for our argument that traditional STI policy analysis can benefit from closer attention to programmatic statements and their deployment in advocacy practices by change–bearing entrepreneurs.

To demonstrate this, we have drawn support from empirical cases showing how a set of socio–technical changes – that is, the closer integration of clinical experience with laboratory experimentation, investment in gap areas, new professional roles and greater coordination of projects – in some biomedical innovation systems has been recently affected by the emergence of a new policy rationale called TR. At the international level, this emergence has notably been fostered by parallel interventions and advocacy from academic leaders, academic administrations and STI policy–makers. Yet, this new policy rationale does not map out directly into a specific set of policy instruments that could be used to deploy or implement its proposals, at least not in Germany and Austria, where the networks we studied are located. We are not presented with a 'linear model of policy formulation and implementation', where one issue would be linked with one set of policy instruments, which in turn would translate to one defined set of behavioural and organizational impacts in innovation systems.

Instead, multiple issues and policy instruments co-exist in various relations, and 'impact' in innovation systems may well be achieved by new alignments of actors to long-existing instruments. Indeed, in our case studies, local entrepreneurs made opportunistic use of various pre-existing instruments. These instruments were useful for building an innovation network modelled after TR programmes, helping to enrol local allies to take on parts of the necessary labour. As such, local implementations and deployment of existing policy instruments were inflected and performed through governance processes such as the reframing of legitimate experimental practices affected by advocacy of

TR notions. New policy instruments put into place for the networks (mostly infrastructure funding) were sometimes also a consequence of previous advocacy. Furthermore, advocacy work was greatly aided by previous network building efforts. That is, building a successful collaboration to engage in multidisciplinary TR projects itself functioned as a powerful argument to enrol further allies.

Sometimes, this also meant that advocacy was constantly required to hold the emerging system together. Even in the case of the TRAIN consortium, which can be characterized as one whole and well planned policy instrument, implementation and collaboration of local actors has to be constantly maintained. Different local actors had different interpretations of the challenges facing biomedical innovation and might not join the TRAIN way of doing things.

Here, changes in programmatic orientation and deployment of classical STI policy instruments seamlessly rubbed shoulders with one another and even fed on each other. Local entrepreneurs drove these changes, supporting their contentions and actions on higher-order policy narratives made culturally available in biomedical policy networks.

In the OncoTyrol case, instead, the availability of locally yet centrally managed research money made use of programmatic TR statements with a coordinative intent less salient. That is, here the potency of a classical STI policy instrument (a centre of excellence) enabled the consortium management to ensure better, more direct coordination of the research teams. The formal programme of TR gave legitimacy and justification to an organizational model that was quite different from what participating researchers had been accustomed to in a purely academic context.

TR was used in an even more metaphoric way with ASC, where it was used as a recognizable symbol to link the idea of creating a new centre of excellence for biomedical research to pre-existing discussions on deficiencies in the cooperation between basic science and clinical application of research findings. Moreover, central management functions remained with the AKH/MUV, which is another factor that worked against the emergence of strong entrepreneurial and advocacy activities around the TR programme in the ASC case.

In TRAIN and OncoTyrol TR was systematically interpreted in a strong alignment towards industry collaboration. Yet, efforts by the consortium leadership to realize this seem to have fallen a bit short of the rhetoric of ‘close integration’. Instead, industry partners in TRAIN, OncoTyrol, but also the ASC, often appeared as ‘phantom allies’ whose participation was an important signifier of success, but who ultimately made modest contributions to actual experimental activities. Similarly, patient orientation is generally considered a modus operandi of TR, also

repeated in presentations of TRAIN, OncoTyrol and ASC, yet actual involvement was nowhere to be found.

Jacobsson and Lauber (2006) highlighted the role that advocacy coalitions can play in STI policy, especially in building legitimacy for given projects or programmes and aligning institutions around the corresponding goals. In other words, much like us, they find that legitimacy is a central component of innovation systems and the policies that target them. Nonetheless, these authors concentrated on high-order changes in rationale and corresponding legislative pressure as a main driver of STI policy change. What we have seen here is that legitimacy building through the formulation and advocacy of programmes is also an essential factor in the implementation of policy instruments. Deliberations about common goals, programmes or rationales can take place at the 'grassroots' level of innovation systems, especially through the work of entrepreneurs, as much as it does in parliaments and the offices of civil servants. Additionally, in the cases examined here, existing policy instruments were re-aligned and given new impacts through their use within new networks dedicated to TR. We should therefore not posit that new programmes and rationales act on the governance of STI activities only in the formulation phase of policy instruments, but that they are central determinants of policy transfer and implementation as well.

ACKNOWLEDGEMENTS

The empirical research for this paper was carried out as part of the international ELSA-GEN project 'Translational Research in Genomic Medicine: institutional and social aspects', which was active from 2010 to 2013. The Austrian research team has been financed through the GEN-AU scheme by the Austrian Research Agency (FFG) and the Austrian Federal Ministry for Science and Research (BMWF) and the German team received money from the German science ministry (BMBF) through the project management centre of the German Aerospace Centre (DLR). Etienne Vignola-Gagné was also supported by a Doctoral Fellowship of the Social Science and Humanities Research Council of Canada (grant number 752-2010-0667).

We wish to thank Susanna Borrás, Jakob Edler and all the other participants to the Jean-Monnet Conference.

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Interviews

TRAIN case study

TRAIN Interview #1A: Staff, Twincore, Hannover; Interview in Hannover on 29 October 2010.
TRAIN Interview #1B: Staff, Twincore, Hannover; Interview in Hannover on 10 January 2012.
TRAIN Interview #2: Staff, VPM GmbH, Hannover; Interview in Hannover on 13 December 2011.
TRAIN Interview #3: Professor, Eberhard Karls University Clinic Tübingen; Interview in Tübingen on 19 December 2011.
TRAIN Interview #4: Staff, Twincore, Hannover; Interview in Hannover on 10 January 2012.
TRAIN Interview #5: Scientific Coordinator, Helmholtz Center for Infection Research, Braunschweig; Telephone interview on 18 January 2012.
TRAIN Interview #6: Staff, Niedersächsisches Ministerium für Wissenschaft und Kultur Hannover; Telephone interview on 9 March 2012.

Anna–Spiegel–Center Case study

ASC Interview #1: Head of a research group, Professor; only located at the ASC; Interview in Vienna on 9 December 2011.
ASC Interview #2: Head of a research group; trained as biologist; Ao. Professor; only located at the ASC; Interview in Vienna on 19 December 2011.
ASC Interview #3: PhD–student; trained in molecular biology with specialization on genetics and biomedicine; in her second year; located in the research group of #1; mainly located at the ASC; Interview in Vienna on 19 December 2011.
ASC Interview #4: Head of a research group, trained as biologist, Ao. Professor; only located at the ASC; Interview in Vienna on 4 January 2012.

ASC Interview #5: Assistant head of a clinical department, Professor; responsible for a small lab team, but mainly located at the clinic; Interview in Vienna on 16 January 2012.
ASC Interview #6: Research direction at the MUV, head of department and Professor; located at the main building of the MUV/AKH; Interview in Vienna on 17 January 2012.
ASC Interview #7: Head of a research group, trained as chemist (PhD); Interview in Vienna on 20 January 2012.
ASC Interview #8: Direction, laboratory of the university clinic, located at main building; Interview in Vienna on 2 April 2012.
ASC Interview #9: Joint Interview with one chemist, responsible for a core facility, and one principal investigator; Interview in Vienna on 16 December 2012.
ASC Interview #10: Interview with administrative staff of the MUV; Interview in Vienna on 8 May 2012.
ASC Interview #11: Administrative staff, university clinic; Written answer to the interview questionnaire provided on 18 May 2012.

OncoTyrol case study

OncoTyrol Interview #1: Joint Interview with two principal investigators, Medical University of Innsbruck; Interview conducted in Innsbruck on 13 February 2012.
OncoTyrol Interview #2: Industry partner, Innsbruck; Telephone interview conducted on 23 March 2012
OncoTyrol Interview #3: Joint interview with two administration staff, OncoTyrol Management; Interview conducted in Innsbruck on 21 February 2012.
OncoTyrol Interview #4: Research direction staff, OncoTyrol Office and Professor, Medical University of Innsbruck: Interview conducted in Innsbruck on 22 February 2012.
OncoTyrol Interview #5: Industry Partner, Vienna; Interview conducted in Vienna in 19 March 2012.
OncoTyrol Interview #6: Industry Partner, Zürich; Telephone interview conducted on 21 March 2012.