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IN SEARCH OF TRANSLATIONAL RESEARCH

Report on the Development and Current Understanding of a New Terminology in Medical Research and Practice

BERLIN INSTITUTE OF HEALTH
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Report on the Development and Current Understanding of a New Terminology in Medical Research and Practice

Institute for Research Information und Quality Assurance (iFQ)

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EXECUTIVE SUMMARY

Translational Research (TR) has become an intensely debated subject in biomedicine. The promise of a "translational turn" has raised high expectations, despite the fact that a widely shared definition of what TR is or should be is still missing. However, the multiple meanings that currently exist have been instrumental in establishing the concept of TR and its importance.

- The idea of TR has its roots in nursing in the 1970s. It has experienced a resurgence with increased attention since the 1990s in the context of (bio-)medical research and evidence-based medicine (EBM) (section 1.1).
- Expectations are high as TR is supposed to overcome the valley of death and reduce waste in (bio-)medical research (section 1.2).
- TR is not a mere hype. The number of TR-related publications shows no signs of decline and a stable array of core journals and organizations has been established (section 1.6).
- TR is not clearly defined. Multiple stakeholders are currently discussing its meaning, relating it to multiple problems and possible solutions (section 1.2).
    - Besides the narrower context of quality and efficiency in scientific research, the meaning and importance of TR extend into the domains of policy, education, ethics, economics, and organizational design (sections 1.3 & 1.4).
    - Definitions of TR show some common features. First, they identify the problem either as waste in research or the valley of death. Second, they draw on one or more of the six domains (scientific, economic, moral-ethical, political, educational, organizational) to describe and analyze the problem. And, third, they propose solutions to overcome either the innovation or the implementation gap (section 1.3).
    - There is no dominant way of "doing" TR. There are multiple and competing ideas on how TR can be organized (section 2.1).
    - Different models describe how research is transferred into innovation; they vary in their characterization and enumeration of translational phases. Some highlight a linear phase-oriented view of knowledge transfer, while others take a more evolutionary stance emphasizing multidirectionality and feedback loops (section 2.1).
- TR is an important policy issue. Professional associations, research funding organizations, and ministries in Western European and North American countries engage in propagating the concept and providing funding for research dedicated to TR (section 1.5.).
    - In policy, TR is framed either as an organizational or a professional "crisis" with the US as a global leader in propagating TR and providing a context in which new organizations emerge (sections 1.5 & 2.2).

The publication landscape has been dominated since the mid-1990s by US organizations. In recent years European organizations have increasingly joined the field, leading to a shift in geographical structures of cooperation. Germany is among the most active nations in this context.

- The TR landscape in Germany centers around large university hospitals, but is still highly dynamic. Many new entrants have just recently started publishing TR-related scientific articles, among them smaller hospitals and industry actors (section 3.1).
- Geographical distance is relevant for the choice of cooperation partners within Germany. Distance becomes less important, however, with the increasing reputation of an organization (section 3.1).
- The number of joint publications from different organizations has increased rapidly dur-ing the past decade, resulting in a highly cooperative network within Germany (section 3.1).

INTRODUCTION

In the context of recent debates about medical innovation, Translational Research (TR) has become a major and widely acknowledged approach. The aim of TR is to support an efficient translation "from bench to bedside" and "from bedside to bench", hence from laboratory basic research into clinical therapies and vice versa. However, organizational processes that link researchers and clinicians seem to be especially contested. Up until now, no dominant model has evolved to address these problems. A clear conceptual framework is also missing. Rather, a number of approaches and concepts are currently promoted by various stakeholders that highlight different aspects of TR. Professional and public discourse on the subject now reaches well beyond the realm of medicine. The debate presents a thicket of issues – political, economic, moral-ethical, or organizational in nature – that may influence the successful implementation of TR. But what is actually meant by TR? Which core processes, structures, and goals are addressed? How can these processes be treated as means for organization building and quality assurance?

The overall goal of this report is to disentangle the concept TR on different levels and to provide a starting point for further activities related to the successful implementation of TR. In this context, the present study aims at reconstructing how TR concepts are understood and organized. The report therefore provides an overview of the meanings and dimensions of TR as a concept. Furthermore, it depicts the research landscape and highlights some of the leading organizations in the US while also portraying the networked landscape of research organizations in Germany. This helps to establish a context for implementation suggestions at both the international and the national level.

The report is structured as follows: The first part (chapter 1), "How to understand Translational Research?" provides an overview of the emergence and use of the concept. By asking "What does TR mean?" we discuss current literature and provide a systematic analysis of problems and issues addressed by TR. The review of literature[1] includes, on the one hand, literature that propagates TR as a possible solution. On the other hand, it also acknowledges problems in the realization of TR and therefore engages in the search for its adequate operationalization and application. We analyze this literature to identify dimensions of TR. Our analysis suggests that scientific, economic, moral-ethical, organizational, and political issues are important dimensions for the debate surrounding TR. Due to its importance for structuring the discourse in TR, we will particularly highlight how TR is tackled as a policy issue, thus addressing its policy dimension. The qualitative analysis of "How to understand Translational Research" is complemented by a bibliometric analysis of the semantics of TR. The results of our analyses show that the dimensions identified by the qualitative analysis are also present on a large scale, i.e. in the scientific literature on TR as a whole.

In the second part (chapter 2), we focus on the organizational dimension of the TR concept and ask: "How to organize Translational Research?" We present and discuss current understandings of phases and organizational processes in TR that are highlighted in the literature. Here we can find two tendencies that have developed over time: (1) an ongoing expansion of the TR process to encompass more and more aspects, particularly in the context of clinical practice and public health, and (2) a subsequent increase in the conceptualization of translational phases (T) within the proposed process models. In order to come to terms with the ways in which these characterizations can be found in research organizations, we present some of the leading research organizations in the US, where the establishment of TR can be considered most advanced.

In the third part (chapter 3), we return to the German context. This will be done by presenting findings from a bibliometric analysis of how the organizational landscape surrounding TR has evolved in Germany and which types of organizations can be considered most dynamic according to publication figures. In the last section, we specifically focus on collaborative networks that can be traced by a co-authorship analysis in Web of Science.

The report concludes with a synthesis of findings and implications for further research.

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[1] *We rely mostly on literature that addresses the question of translation as a new approach to medical research in general terms instead of focusing on a particular branch of medical research.*

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1 HOW TO UNDERSTAND TRANSLATIONAL RESEARCH?

The goal of this chapter is to provide an overview of how TR is framed and defined by different stakeholders both within and outside the domain of medical experts. Understanding the term is crucial in order to provide a basis for the assessment of different models of TR that aim either at examining the topic in different research contexts or at supporting its implementation in practice. Since the term can be considered a rather fuzzy concept, it is difficult to give a clear-cut definition. However, we claim that this fuzziness also has advantages that allow different stakeholders to address specific issues or problems that need to be overcome. In this chapter, we therefore intend to reconstruct these different meanings in order to understand which issues can be addressed by which meanings and how they refer to different socio-economic dimensions such as the scientific, moral-ethical, organizational, and/or political dimension. These dimensions of the concept have to be related to the specific socio-historical context in which TR claims a presence, thus helping to explain its emergence and its diffusion.

The chapter is structured as follows: At the beginning, we provide a brief historical sketch of the term TR and locate the origin of the debate and its re-emergence in different contexts (section 1.1). We then focus on reconstructing different meanings of the term in the realms of medicine and the social sciences (section 1.2). This serves as a basis for understanding different problems and issues related to TR. In section 1.3, we dimensionalize the concept according to these different issues that constitute the semantic field of TR to illustrate and understand available means of framing TR. In order to explain which framing of the problem becomes dominant, we analyze the policy context of TR (section 1.5). This analysis offers insights into how different stakeholders position themselves in the debate and why, as well as which lines of research are supported and undertaken by funding agencies and political authorities. This view of TR and its dominant frames is complemented by a bibliometric analysis (section 1.4) of the semantic field according to the issues introduced in section 1.3. We find that the dimensions identified in section 1.3 can be mirrored in the keywords of TR-related publications. Finally, we deepen the bibliometric analysis by tracking how the concept has diffused within the academic realm. This is necessary in order to understand whether the topic has gained adequate significance among the scientific community and how TR-related publications have developed. We find that TR can be considered a highly dynamic issue currently experiencing a boom in the scientific field. This analysis allows us to validate the preceding sections tracing the origin, re-emergence and the diffusion of the TR concept.

1.1 Translational Research: Its history in a nutshell

In biomedicine, the term "Translational Research" means different things to different people (Marincola 2003), yet it is an important issue for a multitude of stakeholders. As *Nature* journalist Declan Butler put it: "Ask ten people what translational research means and you're likely to get ten different answers" (Butler 2008; Opsahl et al. 2010). Despite this variety of definitions, we can at least state that the term TR (also known as Translational Medicine or Translational Science) addresses the reshaping of processes by translating the results of basic medical research into clinical practice, clinical techniques, and drugs; in other words, it is a translation from the lab bench to the patient's bedside (Marincola 2003; Ma et al. 2014; van der Laan & Boenink 2012; Zerhouni 2005a).

Origin of TR in implementation research

Nursing science – as a part of implementation science – (re)evaluates how new knowledge can be translated to the care of various communities and populations. Chesla (2008) points out that nursing developed its own definition of TR. She recurs to a definition from the US conference "Advancing Quality Care through Translation Research" published by Titler (2004). There, TR was defined as "the scientific investigation of methods, interventions, and variables that influence adoption of evidence-based practices (EBPs) by individuals and organizations to improve clinical and operational decision making in health care" (Titler 2004). The origin of the term TR in the area of implementation research dates back to 1979. In her analysis Pamela Mitchell finds that TR has been a central issue in nursing research since the inception of this field (Mitchell 2004; Chesla 2008). To underpin her argument, Mitchell refers to an early publication by Jean Johnson entitled "Translating Research into Practice" (Johnson 1979). Mitchell also finds that the term "translation", which dominated in the field of nursing in the 1970s, "morphed into research utilization in the 1980s and into evidence-based practice in the 1990s, with some re-acquaintance with translation again in the first years of the 21st century" (Mitchell 2004).

Re-emergence of TR in (bio-)medical and (pre-)clinical research

The origin of the TR discourse in the biomedical domain can be traced to the debate on problems in biomedical research and clinical practice in the 1990s. A sizeable increase in NIH funds between 1993 and 2001 (from $13.6 billion to over $27 billion) led to expectations concerning practical returns on investments (Kraft 2013) which could not be met (Pisano 2006). This was accompanied by the realization that increased investments – for example in the human genome platforms – were not leading to major innovations in clinical practice by themselves. At the same time, serious deficits in the pharmaceutical industry (Vignola-Gagné 2014) came under scrutiny. The number of new drugs launched by pharmaceutical companies had been steadily decreasing since the 1970s. Alison Kraft, a science historian, finds that "the[se] escalating costs of drug innovation were interpreted by many as evidence that the industry was facing an acute 'productivity crisis'" (Kraft 2013). This controversy about the "productivity crisis" is reflected in the increasing emergence of TR-related publications between 1994 and 2013 (see Fig. 3 in section 1.6). In a way, the 1990s can be seen as the starting point for the "translational turn" in the field of bio-medical research, a development which calls for a "closer and effective relation in order […] to improve the efficiency of the (biomedical) innovation process" (Kraft 2013). The emergence of these narratives of "crisis" made TR a central topic in biomedical agenda setting (Vignola-Gagné 2014).

Emergence of TR in different countries

TR has emerged as a specific term and phenomenon in various countries all over the world. We observe that TR is regarded as an important policy issue: Various funding measures and programs have been established, especially in North America and Western Europe. In these measures, TR was framed as a means to overcome current obstacles in biomedical research. The British Medical Research Council (MRC), for example, set up a TR strategy and framed TR as "the principle of turning fundamental discoveries into improvements in human health and economic benefit" (Medical Research Council 2014). The MRC's translational strategy aims "to drive innovation, speed up the transfer of the best ideas into new interventions, and improve the return on investment in fundamental research" (Medical Research Council 2014). The Netherlands Advisory Council on Health Research (in Dutch: De Raad voor Gezondheidsonderzoek (RGO)) published a 2007 report in which it mapped the strengths and weaknesses of TR processes in the Dutch research system (RGO 2007; van der Laan & Boenink 2012). The RGO thereby describes TR as "a phase in the knowledge chain. It comprises all steps from the identification of possible leads (in patients or patient material) for diagnostics, prevention or treatment, up [to] and including early application in clinical practice. Research questions may originate from clinical practice as well as from the laboratory" (RGO 2007). And in 2010 the Federal Ministry of Education and Research in Germany (in German: Bundesministerium für Bildung und Forschung (BMBF)) announced plans to launch the German Cancer Consortium (in German: Deutsches Konsortium für Translationale Krebsforschung (DKFZ)), claiming that to realize Translational Research potential "a close collaboration between cancer researchers and clinicians" was needed. TR was hailed as a "milestone for cancer research and cancer medicine" (BMBF 2010a).

Thus, in its short history, we can see that TR has been pursued as a means to overcome current problems in research and practice which qualifies its treatment as both a policy matter and a scientific issue. Attempts and initiatives to fund and institutionalize TR in different settings and countries therefore provide evidence that TR can be considered a recognized concept in this realm. Nevertheless, the reasoning and rationale behind the implementation of TR vary considerably among countries (Ma et al. 2014), although the literature attempts to define the term in various fields (Rubio et al. 2010; Ma et al. 2014). So what does TR really mean? It seems that a unifying conceptual basis for governance and research cannot be provided. Hence, in the following section we attempt to reconstruct the development of TR based on available research literature as well as a bibliometric analysis.

1.2 Terminology: What does Translational Research mean?

After a brief foray into the history of the TR debate, we are confronted with a variety of definitions. The goal of this section is to structure the different TR terminologies and provide a review of current literature by discussing the meaning and practice of TR in the field of medical research.

In 2012, PubMed introduced "translational medical research" as a medical subject heading (MeSH) that is defined as "[t]he application of discoveries generated by laboratory research and preclinical studies to the development of clinical trials and studies in humans. A second area of translational research concerns enhancing the adoption of best practices" (NCBI 2012). This preliminary definition indicates that translation takes place within two main areas in which translational medical research (TR)[2] is discussed as a major issue: (1) the area of (bio-)medical and (pre-)clinical research and (2) the area of implementation research. The first area deals with the question of how new medical knowledge is produced. The second area focuses on questions of how this new knowledge can be implemented.

Yet, in the area of implementation research we find that – alongside TR – other terminology is also in place. Problems in translating knowledge into everyday clinical routines are addressed through **knowledge translation**. The Canadian Institutes of Health Research (CIHR) have supported this concept in the form of a knowledge translation strategy provided for in knowledge translation funding programs (CIHR 2015).

Graham et al. supply an overview of different terminology ranging from knowledge exchange, knowledge transfer, and knowledge dissemination to knowledge translation (Graham et al. 2006). In addition, they propose a **knowledge-to-action (KTA)** framework that has become the model promoted by the CIHR and has since then inspired various studies addressing translation problems in implementation research (Field et al. 2014; Heyland et al. 2010; Campbell 2010; Petzold et al. 2010). KTA is conceptualized as encompassing two stages: knowledge creation and an action cycle. Greater attention is directed towards the action cycle, however, in other words, how newly produced knowledge can be implemented (Field et al. 2014).

Another concept that has developed in the context of implementation research is **translating research into practice (TRIP)**, which focuses on how to employ evidence-based practice (EBP). TRIP was backed by grants from the US Agency for Healthcare Research and Quality (AHRQ). This agency was established to "support research that develops the scientific base for US health care and health care delivery, determine best practices to improve health care quality, increase access to care, foster appropriate use of services, and reduce unnecessary expenditures" (Kirchhoff 2004). TRIP thus puts a strong emphasis on aspects of efficacy and efficiency.

However, despite existing terminologies, both areas, i.e. the production of new medical knowledge and its implementation, are often not defined in a clear-cut way. They can be further differentiated into a variety of subareas, leading to a highly fragmented field to which the term "translation" is applied (see chapter 2). The heterogeneous landscape of TR concepts is reflected in the diverse literature on what translation is and how it should be organized[3]. However, among these publications only a few articles address the rise of TR, its surprisingly vague definition, and related issues involving its enactment. Mittra & Milne (2013) as well as Mittra (2013) are among the few exceptions. While they argue that the use of "translational medicine"[4] is quite fuzzy, they do show that the term is based on a number of shared assumptions about the nature of innovation processes in medical research and development (R&D). In his analysis of these shared assumptions, Mittra (2013) is able to demonstrate that the narrative of the "'broken middle' of the health innovation pathway" is the predominant account of ongoing problems. This narrative suggests a productivity crisis that is caused by a disconnect between basic research and the application of its results, particularly in clinical phase II studies. This "broken middle" account of medical innovation has triggered the rise of TR as a viable solution. Investigating personal narratives of practitioners from different sites within medical research and practice as well as narratives from industry and policy stakeholders regarding TR as an adequate solution to this similarly perceived problem, Mittra finds two distinct ways of defining TR: (1) Some practitioners have an unidirectional perspective on TR with a focus on life sciences where biomarkers, for example, are regarded as the promising

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[2] In the following, translational medical research (TR) will be used as the umbrella term due to its status as a PubMed MeSH (medical subject heading).

[3] Most of this literature refers to a particular research area such as cancer research.

[4] The authors do not explain their choice of the term "translational medicine". Mittra (2013) does, however, present the perspective of one of his interview respondents who interprets TM as "a subset of research focused on what has traditionally been called 'experimental medicine'" (p.111). TR is thus not regarded as an "area of science, but [as] a process of bi-directional knowledge flow from fundamental research to application and back again" (ibid.).

basis for TR (Mittra 2013). (2) Others refer to a broader definition of TR as a two-way interactive process that goes beyond clinical research and also encompasses knowledge received in the day-to-day treatment of patients and subsequently looped back into the basic research process. TR is thus regarded as providing a "feedback loop from bench to bedside" that grants "multidirectional integration of basic research, patient-oriented research, and population-based research with the long-term objective to improve public health" (ibid.: 113)[5]. However, Mittra claims that these approaches are – though now labeled TM – nothing new. He argues that medical research has always been a joint venture of basic and applied researchers – if it is even possible to treat basic and applied research as two distinct categories at all. Mittra furthermore asserts that medical research has always been organized not as a linear sequence but rather as an oscillating, back-and-forth process of knowledge production (ibid.: 106). Yet, he finds that practitioners are fully aware of this situation which he describes as "old wine in new bottles". They are, however, convinced that this new attention to the problem of how to fix the "broken middle of health R&D" (ibid.: 114) stemming from the new buzzword "TM" is important and necessary because it promotes commitment on the part of policy makers and indirectly supports efforts to discover new therapy strategies such as biomarkers. The relevance of TM as a shared yet fuzzy concept extends beyond the mere medical realm. It also provides a locus to organize discourse with other societal stakeholders (see section 1.3).

Another exception in researching the fuzzy, yet prominent concept of TR can be found in the work of van der Laan and Boenink (2012). The two authors locate the initial cause for this development in an increasing public distrust in the effectiveness of highly subsidized biomedical research (van der Laan & Boenink 2012). In order to shed light on the subsequent rise of TR and its tenacious ambiguity, they suggest an analysis of TR along three dimensions: "(1) the construction of the 'translational gap'; (2) the model of the translational process; and (3) the cause of the perceived translational gap" (van der Laan & Boenink 2012). Like Mittra (2013), they find that the translational gap diagnosed in recent literature is defined in either narrow or broad terms. The narrow perspective on TR locates the translational gap "between basic science on the one hand and pre-clinical work, knowledge of the human body or medical application on the other" (ibid.: 6). The broader perspective reaches beyond initial knowledge production to include "clinical practice or the actual health condition of individuals and populations" (ibid.). Models of the translational process that van der Laan and Boenink find are based on unidirectional, bi-directional, or even multidirectional and iterative conceptualizations of TR's temporal progression. While the unidirectional understanding of TR suggests a linear model of innovation, the latter two conceptualizations also integrate feedback from practitioners and even patients as relevant to a thoroughly functioning translation process. The authors, furthermore, find that the causes of the translational gap are discussed as being either external or internal to the realm of actors participating in the process. External causes can refer to a "lack of funds for expensive clinical trials, lack of communication between lab researchers and clinicians, or strict regulation for research with human subjects" (ibid.: 11). But also a "lack of professional awareness of the state of the art of biomedical sciences" and "the general lack of interest of medical journals for negative results" (ibid.) are mentioned as external causes of the translational gap. Internal causes, on the other hand, are identified as inherent to the research process as such. In vitro and animal models are called into question as to the adequacy of their results and whether they allow for a translation to human patient settings. They also find that randomized clinical trials are discussed as producing artificial results that are not applicable to a wider group of more diverse patients. Yet, in sum, the authors conclude that the current discussion in medical research focuses pre-dominantly on a narrow and unidirectional understanding of TR that locates the causes for the translational gap outside of medical research. As a consequence, the solutions that are currently proposed and the money that is spent mainly address TR as being located exclusively between pre-clinical research and phase I or II clinical trials (ibid.: 14).

From his research on argumentative practices in biomedical research policy, Vignola-Gagné (2013; 2014) supplies findings that point in a similar direction. He finds that "[b]iomedical investigators themselves are still arguing as to whether TR is a distinct area of experimental practice, a specific model for organising biomedical innovation, or just what else it might exactly be" (Vignola-Gagné 2014). He ascribes the rise of TR to an "intensive advocacy of a multitude of dispersed policy-makers,

[5] *This differentiation interestingly captures a dichotomy found in innovation research, namely the difference between linear and non-linear models of innovation processes. While the former are largely orientied towards phases and feature a clear-cut directionality from discovery (basic research) towards diffusion (innovation), the latter models highlight the evolutionary character of innovation processes.*

local academic administrators and biomedical leaders" (ibid.). As with Mittra & Milne (2013), Mittra (2013), and van der Laan and Boenink (2012), Vignola-Gagné also locates the crucial problem addressed through TR in a perceived crisis of innovation in biomedical research that prevails despite sizeable public investments. He states that the successful rise of TR rests on "its availability as a rhetorical base for arguing about a variety of propositions and projects to reform current practices in biomedical innovation" (ibid.). However, he does not only point to the same narrative or rhetoric espoused by the other authors as the trigger for TR. Starting from the observation that "efforts to bring research groups engaged in the laboratory and clinical parts of biomedical innovation closer together; interventions to institutionalize new interdisciplinary career paths; or the development of academic research capacities and experimental methods for studying and improving the process of therapy research itself" (ibid.: 96) are discussed as possible solutions, he moreover finds that "there is much less agreement on which specific assemblages of experimental, institutional and epistemic practices are to be deployed" (ibid.). In other words, the measures required to improve (bio-)medical research are not at all clear. Vignola-Gagné demonstrates that in this situation, a coalition of clinician-scientists has stepped in to foster the narrative of the innovation crisis and suggest their own role as crucial to its solution (ibid.). These clinician-scientists regard themselves as working at the interstices of bench and bedside and see their position threatened by the increasing gap between basic research and clinical practice. Therefore, they engage in the discussion about the crisis of innovation in (bio-)medical research and push for the rise of TR in order to strengthen their own position. Their efforts furthermore add to the awareness that the medical practice aspect, including dedication to patients, is also an important part of TR (ibid.: 103).

This brief review of (social sciences) literature already provides some insights into ongoing discussions about the meaning and the practice of TR in the field of medical research. "Translational research", "translational medicine", "translational science" and "knowledge translation"[6,7] – although these terms phrase "translation" in slightly different ways, they all address questions related to the problem of how medical knowledge can be usefully applied in a site of action that differs from its origin. These different terminologies also hint at the main problems related to the question of "translation" and the answers that have been provided so far: (1) It is still difficult to describe, define, and pin down the exact meaning of translation in medical research. (2) It is thus unclear how to operationalize the translation process (see chapter 2). Although "translational research/medicine/science" is framed and often treated as a specific type of research, it is rather difficult to sketch out a clear-cut definition that corresponds with specific practices. Instead, we find a multitude of problems and goals which are addressed by referring to "translation".

Yet, the (medical) research literature that directly seeks to provide an applicable conceptualization of TR encompasses a far broader scope of problems. In the following, we will thus dig deeper into TR in order to provide a systematic account of the range and types of problems it emphasizes. We will give an overview of the literature[8] that propagates TR as a possible solution while simultaneously acknowledging difficulties in its realization and therefore engaging in the search for its adequate operationalization and application. We will delineate the various different problems TR seeks to address and highlight the dimensions of TR that thereby become visible. In chapter 2, we will furthermore shed light on the different conceptualizations of the TR process that follow from the varying dimensions of problems addressed.

1.3 Dimensions of Translational Research

To understand the full scope of meanings attributed to TR it is necessary to analyze which dimensions TR seeks to address to overcome the lack of knowledge transfer in medicine. Two cross-cutting dimensions can be gleaned from relevant literature: (1) *waste in (bio-)medical research* (Chalmers et al. 2014; Glasziou et al. 2014; Ioannidis et al. 2014; Macleod et al. 2014; Ioannidis John P. A., Oliver, Sander et al. 2014) and (2) the so-called *valley of death* (Butler 2008). While the discussion on waste in *(bio-)medical research* can be pinned down to problems in the scientific production of new medical

[6] *In the following, we will use the term Translational Research as synonym for other terms such as TM or TS.*
[7] *These terms are all listed as entry terms in PubMed for the MeSH "translational medical research".*
[8] *We rely mostly on literature that does not focus exclusively on a particular branch of medical research but addresses the question of translation as a new approach to medical research in general terms.*

knowledge at the laboratory bench or in clinical research, the *valley of death* terminology is not as clearly applied to one particular area. Instead, it is discussed by referring to different dimensions within the context of medical research and practice. Thus, beneath these two overarching problems we can find multiple dimensions that are addressed by and thus contribute to different conceptualizations of TR, which are also, however, interlinked.

Mittra and Milne identify three "needs" or "drivers" that foster the rise of TR as a magic bullet. (1) As "scientific needs/drivers" they see the "widening gulf between scientific researchers and clinicians" (Mittra & Milne 2013) despite the growing complexity of research technologies, and thus identify a need for more interdisciplinary research. (2) They regard "the gap between drug discovery and development" (ibid.: 8) as the "commercial need/driver" for TR. It is argued that "questions related to how their drugs actually work in humans" need to be answered faster and "go/no-go decisions on product candidates" (ibid.) need to be made earlier in order to reduce attrition rates in phase II studies and thus the costs for the pharmaceutical industry. (3) With "social/regulatory drivers" (ibid.: 10), Mittra and Milne address the concerns of politicians and the public. Both are concerned with the costs and safety and therefore the efficacy of new therapeutic products. Here, TR is seen as more effective in meeting the high regulatory safety standards while at the same time reducing costs. Building on this differentiation by Mittra and Milne but also drawing on the pertinent literature on TR, we find six dimensions that are discussed in the context of TR.

Regarding the **scientific dimension**, it is not only the widening gulf between different sites of research, namely between basic, pre-clinical, and clinical research, which matters. The recent discussion in *The Lancet* (Chalmers et al. 2014; Macleod et al. 2014; Ioannidis et al. 2014; Glasziou et al. 2014) has also demonstrated that the production of *waste in (bio-)medical research* relates to other aspects in biomedical knowledge production. Back in the 1990s, Altman already criticized "the scandal of poor medical research" as such (Altman 1994). He identified unsuitable incentives within the scientific community as the cause. He predicted that the pressure to "publish or perish" would lead to increased misconduct in scientific research that would go hand in hand with a lack of methodological skills. Since then, these claims have been repeated in various contexts and ways. Chalmers and Glasziou calculate that about 85% of research investments, i.e. $200 billion for 2010, have been "wasted" in badly performed basic and pre-clinical research. Clinical trial designs also show serious deficits (Chalmers & Glasziou 2009).

In addition to the scientific dimension and its diagnosis of *waste in (bio-)medical research*, there are other dimensions that relate to the diagnosis of a *valley of death* (Butler 2008). The **economic dimension** has already been referenced here in our discussion of Mittra's (2013) analysis of the "broken middle" narrative and Mittra and Milne's commercial needs and drivers. Khanna provides a suitable example of this dimension because he points to "low productivity, rising R&D costs, dissipating proprietary products and dwindling pipelines" (Khanna 2012) as challenges for the pharmaceutical industry. In addition to the "broken middle" narrative, Contopoulos-Ioannidis et al. demonstrate that it also takes a very long time from the first mention of positive outcomes in basic research to testing in clinical trials and finally the translation into therapy (Contopoulos-Ioannidis et al. 2008). Both the "broken middle" and the application lag produce high economic costs.

The **moral-ethical dimension** focuses on the lack of implementation when translation fails to occur, resulting in a shortage of effective therapies. This, it is argued, costs patients' lives since promising treatments get "buried" – metaphorically speaking – in the *valley of death* (Butler 2008). The relevance of this dimension has been strengthened in particular by researchers and practitioners who focus on the bedside perspective, i.e. the treatment of the individual patient. In the first editorial of the *Journal of Translational Medicine*, Marincola underlined that "the scientific process is meant, after all, to alleviate human misery and this ultimate goal could be facilitated by connecting basic scientists with the reality of human disease" (Marincola 2003). The moral-ethical argument thus serves to demonstrate the importance of understanding TR as a multidirectional enterprise, addressing efforts to move more effectively from bedside to bench and vice versa. It furthermore highlights the importance that is attributed to the development of evidence-based guidelines as another area of the TR process. The discussion on evidence-based guidelines already started in the 1990s when evidence-based medicine became an increasingly popular issue (Davis & Taylor-Vaisey 1997; Grol & Grimshaw 1999). Evidence-based practice also appears in the context of TR (Pearson et al. 2012).

The question of guidelines and their implementation refers to another dimension that Mittra and Milne (2013) have addressed as the regulatory dimension without, however, discussing this particular issue. The regulatory or – in more encompassing terms – the **policy dimension** is another important aspect of TR. It addresses TR as a means to fund and allocate resources for research, to determine how research in this field is regulated, and how processes are monitored and evaluated. The policy dimension is not only important to regulate how new knowledge is translated into evidence-based guidelines (in particular via meta-reviews provided by the Cochrane Collaboration (Sackett et al. 1996; Chalmers & Haynes 1994)) and how these guidelines are applied. Knoepfler (2014) further hints at regulations through national (US) policies by adding the Federal Drug Administration (FDA) to the familiar "bench to bedside" metaphor. He thereby points to regulatory policies as a further intermediary step within the TR process that has to be understood as proceeding "from bench to FDA to bedside" (Knoepfler 2014). Mankoff et al. (2004) also emphasize policy regulation. They argue that such regulations pose a critical obstacle to translating bench research into clinical trials which they problematize as particularly obstructive to academic research:

> *"While biopharmaceutical companies employ contractors or staff to address and meet regulatory requirements as required by regulations and the law, many academic institutions do not provide appropriate regulatory support" (Mankoff et al. 2004).*

The same problem holds true for supporting grants. Mankoff et al. (2004) claim that "[m]ost translational research is supported by grants; however, few provide funding for regulatory staff or consultation" (ibid.). Due to its influence on the diffusion and framing of the concept, funding initiatives and measures shape the development of a research field, especially in its initial phases. Since TR has been widely acknowledged by policy makers, as we have already shown in section 1.1, we will focus on this dimension in more detail, analyzing policy discourse by investigating position papers and funding programs (see section 1.5).

Besides funding measures, evidence-based guidelines, and regulation through laws and drug administration agencies, another problem that is also connected to the scientific dimension appears to be crucial for crossing the *valley of death*: the problem of data transparency. Researchers as well as practitioners claim that data transparency needs to become a major concern for regulatory efforts[9]. To replicate studies and their results and to check the conclusions that have led to the approval of new therapies and their implementation in practice, all clinical trials would need to be registered and their data made accessible (Chalmers et al. 2013). Other suggestions include motivating journals to change their publication policies and publish negative study results as well, because these insights hold important implications for further research (Dirnagl & Lauritzen 2010). TR is thus seen as being obstructed by a lack of adequate policies and regulations on various levels from research and industry to politics.

One dimension not addressed by Mittra and Milne (2013) but nonetheless important to many researchers and practitioners is education. Reducing *waste in (bio-)medical research* as well as crossing the *valley of death* are regarded as matters that require better education (Rubio et al. 2010) and thus as a better trained workforce, in particular, of clinicians and physician-scientists who work at the interstices of medical research and practice (Cohen & Siegel 2005; Sung et al. 2003; Roth et al. 2011). TR thus has a strong **educational dimension**. Consequently, educational issues have become part of the application procedure for the Clinical and Translational Science Awards (CTSA), a funding instrument that has been crucial for the establishment of TR in the US[10]. In their assessment of the 12 initial CTSA awardees, Heller and Melo-Martín (2009) identify several fundamental barriers. Among them are a lack of "qualified clinical and translational investigators" and of "sufficient mentoring" as well as a problematic academic reward system and career disincentives (Heller & Melo-Martín 2009). Heller and Melo-Martín provide some examples of how the CTSA awardees have addressed this problem (ibid.: 427). The implementation of Master's and PhD programs as well as mentoring for postdoctoral physicians are two central aspects

[9] *See the AllTrials campaign, www.alltrials.net.*

[10] *See sections 1.5. and 2.2. for a discussion of the effects of funding programs on the institutionalization of TR in the US.*

of the proposed solutions to enhance the conditions for TR. Vignola-Gagné conducted a comparative analysis of the role of clinician-scientists in the rise of TR in the United States and in Germany. In the case of Germany, he also points to policy recommendations that criticize a lack of research training in German medical education (Vignola-Gagné 2014). In response to this critique, Master's programs were established such as the Master of Science in Clinical Research and Translational Medicine at Leipzig University, as well as doctoral programs like the International Research Training Group for Myology Berlin/Paris (MyoGrad), the International Research Graduate School for Translational Biomedicine (FIRST) at Frankfurt University, or the Doctoral Program on Translational Medicine at TUM Medical Graduate Center. Medical education in the context of TR still remains a current topic (Wissenschaftsrat 2014).

Heller and Melo-Martín (2009) also mention a further dimension that sheds light on the formal organization of TR. Problems concerning a "fragmented infrastructure", a "[l]ack of systematic implementation of interdisciplinary centers", a "[l]ack of communication, coordination, and connection between basic scientist and clinical investigator", the "[d]epartment-based budgeting structure of universities", and "[d]ifferent departmental policies and procedures" (Heller & Melo-Martín 2009) indicate that there is also an **organizational dimension** that is central to TR. How and where research is organized by whom and within which formal organizational structures is deemed relevant for the successful performance of TR. Heller and Melo-Martín summarize some of the strategies proposed by universities such as Duke University, Yale University, or the Oregon Health and Science University that address these organizational aspects (ibid.: 427–429). However, they note that these solutions vary distinctly according to the various institutional settings in which TR takes place. Although similar problems are mentioned in the literature, CTSA applicants propose varying solutions which range from establishing an "[e]lectronic research resource inventory to track clinical and basic research" to strengthening the "[p]rimary role of (…) deputy directors to proactively assemble and facilitate new teams of basic and clinical researchers around breakthrough translational foci" (ibid.: 429). It is therefore justified to assume that scientific infrastructure can be related to problems in the organizational dimension: Scientific infrastructure plays a crucial role in implementing TR in current practices. In the next report, we will investigate precisely these organizational dimensions of the TR domain.

There are, however, further organizational problems addressed in the literature on TR that are not related to the research on new medical knowledge but point instead to the level of knowledge implementation. Once new medical findings have been translated into evidence-based practice (EBP), the next question is how this EBP can be translated into the everyday routines of physicians and nurses. Stetler (2003) discusses an organizational perspective on the translation of EBP into day-to-day clinical care. Drawing on current research on knowledge implementation she highlights that organizational aspects play a decisive role. She furthermore develops a comprehensive framework in which she addresses "[l]eadership support", the "[c]apacity to engage in EBP", and an "[i]nfrastructure to support and maintain an EBP culture and related activities" (Stetler 2003) as means for facilitating a better organization of translation processes.

Attempts to reduce *waste in (bio-)medical research* and to cross the *valley of death* are thus operationalized in six different dimensions that address scientific, economic, moral-ethical, policy, educational, and organizational aspects of TR. These two central problems provide an idea of the multiple facets addressed through demands to support, improve, and foster TR. They have triggered its rise and receive increasing attention in turn. By the same token, as their multiple dimensions address different issues within medical and implementation research there are obviously also different ways of conceptualizing the TR process.

The literature discussed in the terminology section (1.2) mainly focuses on the distinction between a narrow and a broader definition of the TR process. This differentiation refers to the directionality of the TR process, understood either as a linear innovation pathway that progresses from basic to clinical research or instead as a multidirectional research process with an even broader scope that also seeks to translate patients' experiences or public health insights back into basic or clinical research. For all that, the problems of waste in (bio-)medical research and the valley of death and their underlying six dimensions show that it is not only the direction of the TR process that matters. These six dimensions, moreover, raise the question of where TR actually takes place within an organization. In order to find answers, the various issues related to these six dimensions can be summarized as two distinct perspectives on the TR process: A TR process is initiated in order to address either (1) an innovation gap or (2) an implementation gap.

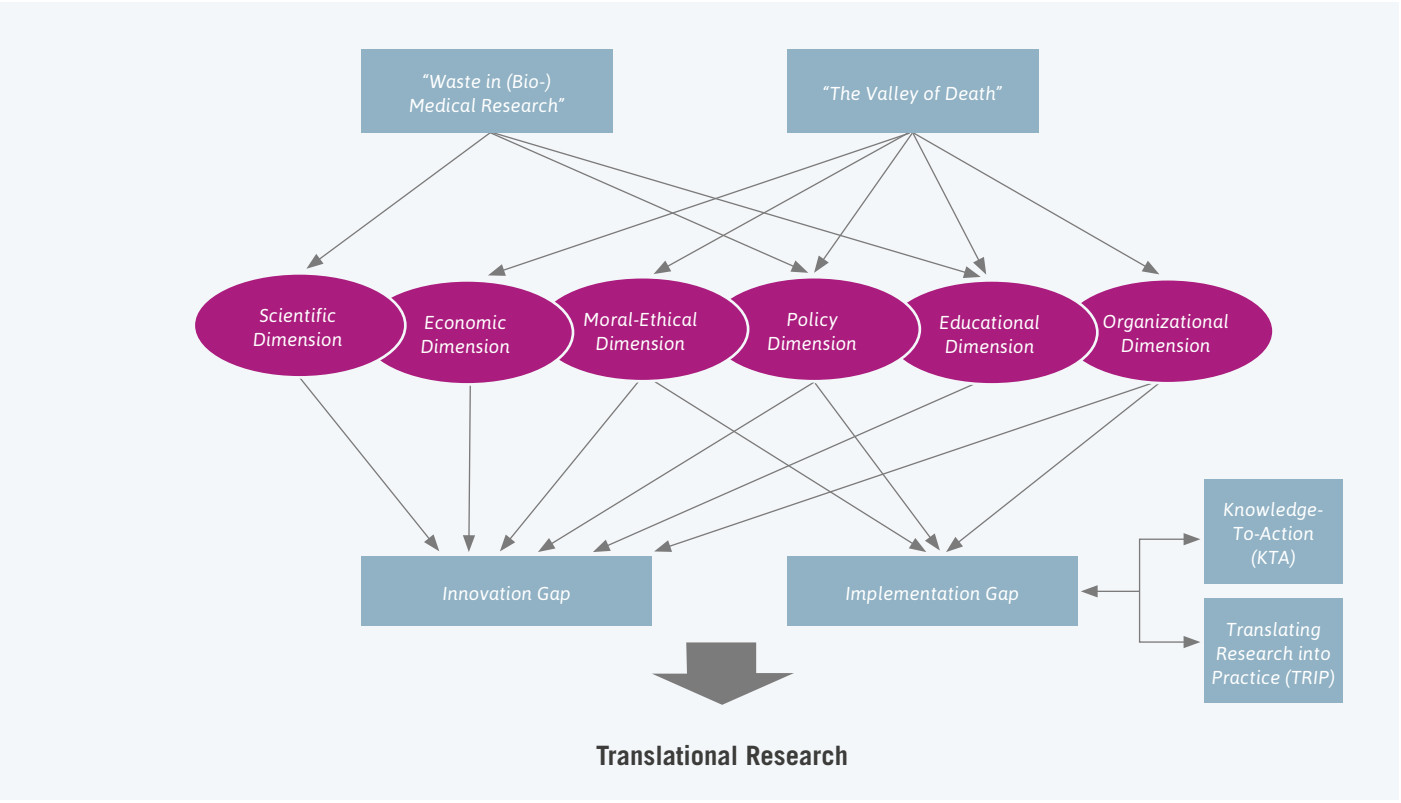

Figure 1: Dimensions of TR

The *innovation gap* is diagnosed at the production site of new medical knowledge, i.e. the laboratory bench and clinical trials. The *implementation gap* addresses the question of how new knowledge can be implemented to actually arrive at the patient's bedside and contribute to better public health care in general. These two gaps have also been emphasized by the Clinical Research Roundtable of the Institute of Medicine (IOM) that identifies "2 major obstacles, or translational blocks: impeding the translation of basic science discoveries into clinical studies and of clinical studies into medical practice and health decision making in systems of care" (Sung et al. 2003).

While the perspective on medical knowledge production and the innovation gap restricts the metaphor "from bench to bedside" to a translation process from basic and pre-clinical research to clinical trials, the knowledge implementation gap perspective figuratively sits at the patients' bedside and asks how new medical knowledge can finally make its way into everyday clinical practice. The "laboratory" for the latter line of research therefore extends to "the community and ambulatory care settings, where population-based interventions and practice-based research networks bring the results of (…) [medical] research to the public" (Woolf 2008). We are confronted with different understandings of where the "bench" ends and the "bedside" actually begins: At the stage of clinical trials? Or not until the implementation of results into medical practice? How and where this demarcation is drawn can have effects on the transfer of knowledge.

To summarize, the framing of these processes appears to be a highly political issue, contested by various groups but also pursued by political attempts and initiatives that take up the different notions of "innovation gap" and "implementation gap" and refer to them as a distinct set of either organizational or professional problems. Casting a political label on these problems obscures how they are actually reflected in the scientific literature. Can a conceptual analysis of the identified dimensions help interpret the structure of topics associated with TR in science? In the following, we provide an initial overview of the semantic field[11] by conducting a bibliometric analysis of the keywords used in documents related to TR.

[11] *A semantic field is a set of words grouped semantically (by meaning) http://en.wikipedia.org/wiki/Semantic_field*

1.4 Translational Research from a bibliometric view

In this section, we will complement our terminology analysis above with a bibliometric view. Bibliometric analyses can function as a steering instrument in the analysis of the cognitive structure of a research field: They can validate examinations of terminology but at the same time pose interesting new questions by focusing on stabilized or contested semantic structures.

In order to achieve an overview of the topics that are related to TR in the scientific literature, a semantic analysis was conducted using the titles, abstracts, and author keywords in the corpus of scientific articles extracted from the Science Citation Index (SCI) published from 2010 onwards. Based on the raw text data, n-grams[12] were extracted up to three consecutive terms. These terms were analyzed according to how the terms were used in conjunction with each other using a clustering algorithm (see Fig. 2).

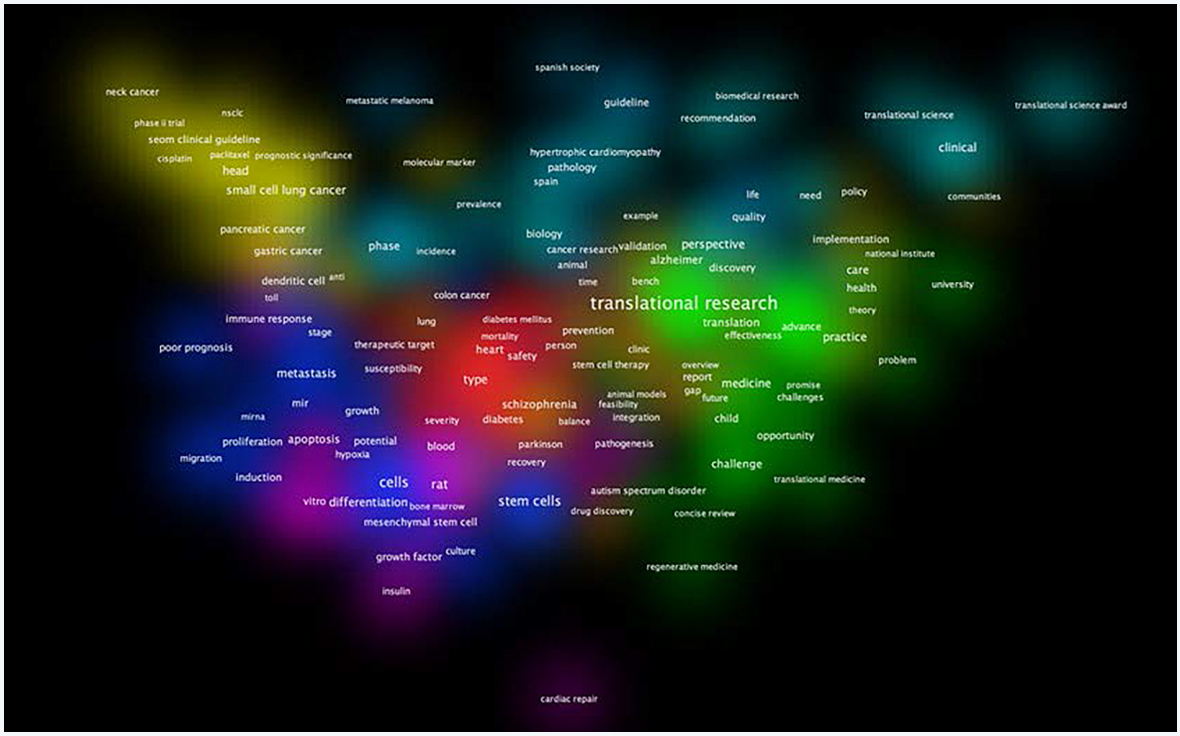

Figure 2: Overview of the semantic field in TR

Results of this analysis can be directly related to the examination of terminology in sections 1.2 and 1.3. In the following, we will present which groups of keywords dominate in the scientific literature that can be traced either to the content or field of activity where research is conducted. In terms of content, this can include, for example, treating major diseases or the aforementioned organizational, economic, or moral-ethical dimensions. Regarding the field of activity that is represented, we can assume that policy activities such as funding measures related to a specific disease may influence the structure of the topics in a direct way. Other socio-economic keywords could also be partially influenced by these measures.

Regarding the scientific dimension, the results show that the field of TR is dominated by cancer research, heart disease, stem cell research, blood-related diseases and research on mental illness. This shows that TR can be traced in significant

[12] *See the Methodological Appendix for details.*

ways to the treatment of major diseases. The fact that "cancer research" is located at the center of the field can be also interpreted as a potential impact of the initial funding programs for TR related to cancer research, especially in the US by the NCI (see section 1.5).

We also find topics within the semantic field closely related to the dimensions identified in the previous section. For example, topics such as "practice", "implementation", "validation", "prevention", or "feasibility" can be related to the moral-ethical dimension of TR triggered by a lack of translation. Moreover, we find that among these most dominant keywords, other aspects of TR are covered which are mostly oriented towards the socio-economic implications of TR, such as "effectiveness", "policy", "gap", "challenge", "opportunity", or "future". These keywords indicate that dominant framings in the scientific debate refer to TR as a means to overcome certain societal problems, a finding which can easily be linked to the policy dimension of TR mentioned in section 1.3. Finally, we find terms with ties to specific TR-related problems that are less medical in nature but aim at solving organizational issues in TR such as "quality", "guidelines", and "recommendations". This can be connected to the organizational dimension stated in section 1.3 and can also link TR to the evidence-based medicine (EBM) literature. In total, we can argue that the field of TR is currently, at least on an abstract level, embedded in a distinct set of medical fields of activity with a focus on issues of organizing and implementing these activities. Furthermore, we find that certain aspects relating to the actual practice and challenges of TR are covered. It can be assumed that there still is a substantial amount of discourse among practitioners related to the procedural, social, economic, and policy aspects of TR. Especially the existence of debate suggests that the field of TR has not yet reached a state of closure in terms of discourse, nor has it achieved stability in practice; procedural challenges still remain unsolved. This lack of closure could also suggest that currently no distinct shared patterns of practice exist between the organizations. Therefore, a more in-depth analysis of arrangements and current modes and practices of TR within selected organizations could provide valuable insights into TR-related procedures and shape organizational strategies towards its implementation.

At this point, we have outlined different dimensions of issues and problems related to TR and how they are mirrored in the scientific field. To further contextualize our findings it is important to understand which problem frame became dominant and why by relating this explanation to specific organizational or professional problems of the scientific and the medical field. Consequently, our analysis of the semantic field has to be supplemented by an analysis of the associated policy context. Such an analysis is important since the emergence of dominant political positions and frames in the policy discourse also relates to funding programs and measures that influence the direction of research and the establishment of new organizations. New organizations or transformations of existing organizations also have an impact on policy frames in the institutionalization process of TR[13].

1.5 Translational Research as a policy issue

In order to understand the dominant framings in TR it is useful to analyze the policy discourse organized around and dedicated to TM and TR. Given TR's widely acknowledged goal of strengthening ties "from bedside to bench" (Broder & Gushing 1993), it might be assumed that this concept is an important policy issue in science and technology policy making. In this perspective, policy is the framing of goals and rationales, the processes in which "priorities and courses of action [are] debated" (Vignola-Gagné 2014). More specifically, policy in the science and technology field means financial, discursive, and managerial practices that can but do not need to be restricted to "the traditional sites of public deliberation" (Hajer 1993, 2008). These processes in policy discourses are important in a research context in which newly established research institutes and organizations are affected by and relate themselves to debates about societal usefulness and are financially dependent on targeted public funding programs. Although it is reasonable to assume that science policy documents "reveal more about ideals than about actual activities in TR" (van der Laan & Boenink 2012), these documents reflect relevant actor positions which in turn structure the debate in TR. For this report, we cannot provide a complete picture of the emergent policy discourse. We restrict the analysis of the science policy discourse to major documents from two types of sources

[13] *See section 2.2. for an analysis of US research organizations that relate themselves to the dominant framings of research funding programs.*

which are both conceptually and empirically well established in the field of science and technology studies (STS): policy papers and funding programs. In both cases we concentrate on the most important documents and funding schemes in Europe and the US.

1.5.1 Policy papers dealing with TR

The first source for identifying policy issues and positions in a policy discourse are policy papers. Policy papers can be produced by a variety of actors ranging from parliamentary advisory boards, roadmap committees, and PR agencies of professional organizations, and can be regarded as an interesting source for an analysis of issue framing and various stakeholder interests in the field. In the case of TR, policy issues have been raised by a diverse set of actors; TR has not always been the exclusive or explicit focus. Because of its connections to biomedical genetic testing and clinical analysis, the concept of "individualized medicine" (IM) also labeled "personalized medicine" (PM) gains particular importance. The problem which connects TR and personalized medicine is the need for patient identification – for instance by biomarkers and genetic profiling: "if biomarker and clinical criteria of disparate quality are used for decision making and translated into multi-modal therapy concepts (…) then the resulting complexity cannot be tackled in clinical practice. It can only be used for patient-centered care if the findings are clinically validated in huge populations by performing translational research (…)" (Hüsing et al. 2008). Therefore PM becomes a resource for the diffusion of the concept of TR and efforts to increase this type of research across the health system (Abrahams & Silver 2010), involving clinical researchers but also health care funds and leading to the claim that research needs to be performed in a more integrated way in order to achieve the goal of effective patient-oriented research (Hüsing et al. 2008). Until now, we have found policy papers dealing with both concepts mainly in the UK, but we assume that PM could become an important issue which could be analyzed in more detail.

In the US, TR was first raised as policy issue by professional communities which perceived their academic status as declining (Ahrens 1992). In this context, the framing of translational research is adopted as a solution to the diminishing public awareness of and shrinking career options for physician scientists (Nathan 2002). These communities are addressed as the main personnel resource for TR (National Cancer Institute 2007). The recent name change of a professional organization shows the concept's attractiveness for framing their claims:

> *"There are new challenges facing our society (ie, declining membership), and academic researchers as a whole (ie, declining sources of funding). Physician-scientists in particular are pulled between their desire to discover new knowledge and the desire of their institutions to have them provide more reimbursable clinical care. These challenges prompted us to embark on a strategic initiative last year that, more than anything else evoked an introspective and deliberate self-evaluation and precise definition of our core purpose and values. (…) However, there will be a greater emphasis overall on clinical and translational research, which should provide an incentive for clinical faculty members and PhD scientists engaged in translational research to affiliate with the society. In this way, the society will become more inclusive, which also paves the way for enhancing partnerships with other regional societies and the pharmaceutical industry" (Weintraub & Metcalf 2013).*

In the literature, it has been argued that the group of physician-scientists gains the greatest reputational benefit out of the dissemination of "translational research" (Vignola-Gagné 2014). This professional community therefore emphasizes the need to strengthen the institutions of their respective profession since the "actual products of much TR, conducting clinical trials or doing drug screening are often not valued by peers in the same way that scientific publications are" (Vignola-Gagné 2014). It is widely held that advances in biomedical research are not effectively translated because of missing incentives and inadequate skill sets within a particular research community (van der Laan & Boenink 2012). In Europe, the situation of the professional communities differs from that of their North American counterparts, since the status of the former communities in mediators between scientific and medical interests does seem to be questioned. Rather, the medical profession nudges its community members towards increasingly academic standards to improve its reputation. As an exemplary document, the annual policy paper of the Swiss Academy of Medical Sciences (Swiss Association of Medical Sciences 2011) shows that

the concept of TR is introduced in the context of re-emphasizing the status of medicine as a science (Swiss Association of Medical Sciences 2011). The narrative of crisis has been taken up and framed as the community's lack of capacity for translational research. Thus, translational practice should not be understood as opposed to biomedical science (Vignola-Gagné 2014) but should become more scientific itself. Educational initiatives are recommended as a means of shifting epistemic practices in medicine towards more academic parameters.

Policy papers have been also published by research organizations that do what could be labeled "translational research". In the US, the National Cancer Research Institutes (NCI) are key actors in performing TR. Founded in 1971, NCI is the oldest institute of NIH and the progenitor of many biomedical research programs funded by the federal government (Kalberer 1975). A report to the NCI Advisory board provides insights into the relation of that research organization to the TR concept:

> *"National Cancer Institute (NCI)-Designated Cancer Centers (…) play a fundamental role in the nation's cancer research agenda. These centers are unique entities where discovery, development, and delivery come together to make progress in the alleviation of the burden of cancer. As such, they are a model of TR, unparalleled by any other national effort in any disease area. In an embattled health care system, the NCI Cancer Centers Program provides the nation with an extraordinary opportunity to address one set of diseases in a comprehensive manner, relying on the best science, clinicians, community networks, and patient groups to improve the quality of care" (National Cancer Institute 2003).*

Cancer research appeared to play a dominant role for the early use and framing of the TR concept. It was only in the late 1990s that TR moved to other fields in biomedicine with the establishment of new research centers (van der Laan & Boenink 2012).

In Europe, strategic research in biomedical fields is performed in dedicated extra-university research organizations. Particularly in the German research system, big science is conducted in large facilities without many links to clinical research (Deutsche Forschungsgemeinschaft 1999). Scientific research is steered by specific organizations that differ in important aspects such as incentives, external publics, and dependence on basic funding. One of these large research organizations in Germany conducting what can be called "big science" is the Helmholtz Association which is involved in grand research programs in different fields, for example disease prevention and treatment. In 2011, the Helmholtz Association published a position paper on the Horizon 2020 Framework Programme for Research and Innovation on Health, Demographic Change and Wellbeing[14] claiming their strategic position in the European TR landscape. TR appears several times in the position paper as a strategic goal which should be pursued within the construction of the research framework program:

> *"Translational research is needed to accelerate the transfer of research results into clinical therapies for the benefit of the patient and to realize the potential arising out of fundamental research through the development of clinical applications. Innovative medicine requires a long-term commitment of public fundamental research, market analyses, preclinical research, including research on animals, studies involving clinical partners and a long-term focus on attracting and integrating the pharmaceutical and medical devices industries in order to achieve the commercialization of results" (Helmholtz Association of German Research Centres 2011).*

This statement provides insights into how the concept of TR can be associated with the goals of a specific organizational model of research. One important organizational feature of research that can be influenced by means of organization is the temporal structure of research, i.e. whether research is conducted in short-term projects or in long-term programs. In this particular case, TR is framed as a means to support the idea of mission-based research funding which can only be pursued

[14] *http://ec.europa.eu/programmes/horizon2020/en/h2020-section/health-demographic-change-and-wellbeing*

in long-term programs. The policy paper justifies this long-term dedication of public money based on the societal value of the issues investigated. According to the self-characterization of the organization, Helmholtz aims at "solving grand challenges which face society, science and industry by performing toprate research in strategic programs in the fields of Aeronautics, Space and Transport, Earth and Environment, Energy, Health, Key Technologies as well as the Structure of Matter"[15]. Thus, the organization raises hopes of contributing to specific problems or "grand challenges" faced by society as a whole. The grand challenges debate is well established in the European research policy community and can also be interpreted as a frame for collective societal expectations (Konrad 2001, 2006) towards science. By referring to this debate, the paper provides a legitimation for both the specific organizational model in which research is performed (long-term programs) and for TR as a particular topic in that context. Therefore, the notion of TR is placed within a narrative of need for this particular approach to research and clinical practice in order to achieve desired societal goals. But while the rationale for supporting the goal and the type of funding that is associated with it are expressed, the position paper contains no policy options or ideas for implementation. Instead, pharmaceutical industries and producers of medical devices are addressed as potential partners for the commercialization of results, a perspective which dominates the policy documents in this particular policy field.

1.5.2 Funding programs dealing with TR

The second major source for an analysis of TR/TM as a policy issue are funding programs. Research funding programs are major instruments that can be wielded to steer research goals and programs in science or to change the direction of research (Rip 1994; Braun 1998). Broadly speaking, two types of funding agencies can be distinguished on this intermediary level: On the one hand so-called "mission agencies" fund a specific objective, for instance fostering research to fight disease as major goal of the National Institutes of Health (NIH 2015a). Similar German counterparts include Federal Ministry of Research and Education programs that are dedicated to health research. On the other hand, "general purpose agencies" are more oriented towards the disciplinary structure of science (e.g. the NSF or DFG in Germany) (Braun 1998). As general purpose agency, the NSF was founded to fund basic research without any specific mission (Braun 1997). In Germany, this position is represented by the German Research Foundation (DFG). One of the first funding programs in the US in which research was oriented towards an exchange between basic and clinical science was the "Specialized Program of Research Excellence" (SPORE), mainly connected with cancer research and founded by the National Cancer Institute (NCI). With the goal of more effectively fighting cancer and thus addressing a major societal concern, it can be labeled strategic, as it widens the scope of potential funding recipients of the National Cancer Institute. Its major addressees were scientists in the biomedical field (Vignola-Gagné 2014). The program explicitly focused on translating these findings, however, which were perceived to be the main justification for the funding of bigger centers for cancer research:

> *"Justification for the Cancer Centers Program has been based on the presumption that clinical progress can only be made by teams of clinicians, clinical investigators, and basic scientists working together to translate information gained at the cellular and molecular level into new therapeutics and diagnostics" (National Cancer Institute 2003).*

The research program had a huge impact on the scientific community, particularly in diffusing the term TR (van der Laan & Boenink 2012).

In the 1990s, the NIH as the main mission-based funding agency in the US dedicated to biomedical research took the initiative in actively promoting the concept of TR (Vignola-Gagné 2014). At this time, research dedicated to biomarkers diffused from the cancer research community to other research communities, which led to a diffusion of TR. One of the most important documents in the policy discourse is Zerhouni's NIH Roadmap published in 2003

[15] *wwww.helmholtz.de/en/about_us/mission/*
With more than 36,000 scientists and technicians employed in large facilities and conducting long-term research programs, the organization is usually associated with what Derek de Solla Price calls "big science."

(Zerhouni 2003) by Elias Zerhouni, the director of the NIH between 2002 and 2008. It focused particularly on the recent biomedical challenges and aimed at increasing interdisciplinary cooperation. By framing these challenges as a "crisis", TR was presented as a "new vision" for the research landscape where strengthened clinical research seemed to be the solution. Therefore, "re-engineering clinical research" was one of the main objectives of the policy paper.

> *"Although biomedical research has succeeded in converting many lethal diseases into chronic, treatable conditions, continued success requires that the United States recast its entire system of clinical research. Over the years, clinical research has become more difficult to conduct. However, exciting basic science discoveries demand that clinical research continue and even expand, while striving to improve efficiency and better inform basic science. This is undoubtedly the most difficult but most important challenge identified by the NIH roadmap process" (Zerhouni 2003).*

The intended goal of that program was to announce funding that would contribute to the organizational management of clinical research and lead to what Zerhouni called "regional translational research centers". At that stage, TR was mainly framed as an issue of the quality of clinical research. In 2005, Zerhouni explained which problems he estimated to be most important: "Clinical research was increasingly less attractive to new investigators and clinical researchers were moving away from patient-oriented research" (Zerhouni 2005a). Furthermore, neither a solid epistemic basis nor the required tools were available for conducting methodological research (ibid.). Thus, the perceived gap was attributed more to the profession of clinical researchers than to the organizational arrangement. As a consequence, the Clinical and Translational Science Awards (CTSAs)[16] had been introduced in 2006 as a major funding program to tackle these problems. Today, the CTSA can be considered one of the most important funding programs for the establishment of TR as a topic. This program focuses specifically on enhancing career paths and enabling research tracks in these fields[17]. More than 60 projects have been funded by the NIH and led, in a number of cases, to the emergence of research units specifically dedicated to TR. In 2013, this funding program was evaluated by the Institute of Medicine (IOM), which led to a reinforcement of the established units. The funding schemes now aim at constructing funding curricula in order to sustain these first attempts, meaning the creation of specific educational initiatives for collaborative teaching. "CTSA programs should foster training in rigorous research methodology that would help promote best practices among the next generation of researchers for minimizing bias in experimental design and reporting" (National Institute of Health 2014). Despite these proclamations of support, researchers continuously criticize the NIH for focusing too much on dissemination and too little on clinical research funding (Woolf 2008).

Nevertheless, the NIH's priority program has influenced the narratives of research funding agencies in North America and Western Europe. In Canada, the government founded the Canadian Institutes of Health Research (CIHR) in 2000 with the goal of improving knowledge transfer from research settings to applications (Ellis 2014). In contrast to the US, the program not only focused on transferring research results from the lab to the clinic but also on local health services and patient-oriented research. Thus, the Canadian government introduced a new concept which it labeled "knowledge translation" (Tetroe et al. 2008). The authors claim that this perspective goes beyond TR since "translational research is about finding solutions to clinical problems" but "stops short of widespread dissemination of the clinical application once it has been proved beneficial by clinical research" (ibid.: 2). The funding system is viewed as far more holistic than its US counterpart. It also focuses, for instance, on the establishment of synthesis reports in order to obtain a knowledge base in which research results can be contextualized (ibid: 3). This goal was implemented with the institutionalization of the Cochrane Collaboration which specifically funds research "synthesis" reports or systematic reviews (ibid.: 6).

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[16] *The goal of the CTSA program was the improvement of "(1) the national capability for clinical and translational research, (2) the training and career development of clinical and translational scientists, (3) consortium-wide institutional and scientific collaborations, (4) the health of our communities and the nation through the conduct of clinical and translational research, and (5) T1 translational research" (Reis et al. 2010: 7).*

[17] *See 2.2. for an qualitative analysis of some of these organizations that have been funded by CTSA.*

European efforts have focused on research infrastructure and regulatory affairs for TR, mainly through a program called EATRIS. The primary goal is to enhance and ensure research quality in TR[18]. Until now, the EATRIS program has not been integrated in a Pan European agenda but is mainly driven by country-specific agencies[19]. Efforts for strategically framing and implementing TR research funds were particularly strong in the UK as the Medical Research Council (MRC) launched its program entitled "Translational Research Strategy". Since then TR has evolved as an important part of MRC's strategic program, that is, making "translational research a key part of core business, including the establishment of dedicated funding schemes to support this research" (Medical Research Council 2014). In the strategic program of the MRC, TR is now associated with almost all stages of MRC funding. Its major goal is to "target funding towards translational projects that require an interdisciplinary approach and a critical mass of researchers to get therapies to the point of clinical testing" (Medical Research Council 2014). To achieve the goals attributed to TR, the MRC aims at enhancing partnerships between research institutions (Medical Research Council 2014), orienting researchers towards TR (Medical Research Council 2014), and strengthening transfer activities in health research (Medical Research Council 2014). The MRC also institutionalized the Translational Research Group as a support organization for TR across all levels that develops and monitors funding schemes in TR[20]. In the MRC report, the framing of a professional or institutional crisis is no longer prevalent. Instead, new policy framings emerge. A specific connection that is more important than in other reports is the relation between TR and personalized medicine (PM). From the latter perspective, TR should be set up in a context that facilitates patient categorization and analysis. Accordingly, goals can be achieved by producing more efficient and effective biomarkers that enable faster drug development. In the social science literature, such political attempts to exploit the economic resources of the health care sector are labeled the "biomedicalization" of policy and society (Clarke et al. 2003). TR in this context cannot be related to the problems associated with the *valley of death* or the reduction of *waste in (bio-)medical research* but to the notion of an "innovation resource", making the health care sector itself a resource for exploitation. According to the MRC documents, TR has become a means to achieve integrated evidence-based medicine and policy making in the health care sector as a whole (Medical Research Council 2014).

In Germany, the crisis of clinical research (Deutsche Forschungsgemeinschaft 1999) has been recognized and tackled by a number of different programs with the objective of enhancing the perspectives of clinical care and research in university hospitals, which are generally faced with heterogeneous demands (Hicks & Katz 1996). "Integrated clinical research and care centers" (Hüsing et al. 2008) were therefore funded in order to combine basic research and patient-oriented research. Between 2008 and 2015, more than €190 million had been invested in this particular funding scheme[21]. Other funding schemes were designed to specifically advance competencies in clinical research and clinical studies by enhancing the methodological skills of students and researchers to perform clinical research. In recent years, the BMBF focused on more institutionalized forms of funding which aimed to create shorter paths between different areas of clinical and pre-clinical research (BMBF 2010a)[22]. In organizational terms, these "translational clinical treatment centers" were based at the Institutes of the Helmholtz Association, which were closely linked to research areas involving major diseases such as cancer (German Cancer Research Center (in German: Deutsches Krebsforschungszentrum (DKFZ)) and University Clinic Heidelberg), respiratory disease (Munich), and heart disease (Berlin) – as a cooperation between the Charité and Max Delbrück Centre for Molecular Medicine [23, 24].

The most important funding initiative was introduced by the German federal government through its ministry. In 2010, the Federal Ministry of Research and Education founded the Health Research Framework Program with the foundation of six "Health Research Centres". The main challenge which the program sought to address was demographic change, which

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[18] *www.eatris.eu/services/core_process.html*

[19] *The second report will focus more specifically on EATRIS core processes dealing with research quality in TR.*

[20] *www.mrc.ac.uk/about/strategy-board-overview-groups/translational-research-group/*

[21] *www.gesundheitsforschung-bmbf.de/de/2067.php*

[22] *www.bmbf.de/de/16551.php*

[23] *www.dkfz.de/de/presse/pressemitteilungen/2011/dkfz-pm-11-24-Gemeinsam-gegen-KrebsDeutsches-Konsortium-fuer-Translationale-Krebsforschung-geht-an-den-Start.php*

[24] *cccc.charite.de/forschung/translationale_forschung/*

poses enormous problems for the country, particularly due to the diseases modern civilizations suffer most – the major diseases. A second reason for launching the program was identified as enhancing the speed and effectiveness of basic research to standardize medical care (BMBF 2010b). The research program was designed to last eight years with different funding schemes for constructing infrastructures and focusing on major diseases in the core institutions and beyond. Contrary to the framing of the problem in the US, the term "translational research" was used to describe organizational problems experienced by the clinical research institutes in their collaboration with external partners (BMBF 2010b). Problems involving insufficient translation of knowledge to therapies were hence framed as systemic problems of the German science system (Loos et al. 2014). Consequently, the instruments to overcome these problems were also defined as organizational (BMBF 2010b), addressing the tiered structures of the research system:

> *"In an approach that overcomes the previous limitations of the German science system, these Centres are focused on six different major diseases and bring together the best research groups from university medicine and non-university research institutions. Further structural measures will improve working conditions and opportunities for young scientists and will strengthen clinical research" (BMBF 2010b).*

This perspective had also been strengthened in a report to the German Expert Commission for Research and Innovation (EFI). The report recommended the implementation of measures to establish ties between university hospital research and extra-university research organizations such as the Helmholtz Association, while conserving traditional distinctions of both organizational forms (EFI 2010; Loos et al. 2014). Taken together, the foundation of the Health Research Centres, financed by the Federal State and the Competence Network, is by far the most influential part of the funding initiative in Germany. Soon after its publication, the program received widespread attention (Abbott 2010), although it appeared as a relative latecomer compared to its counterparts in Canada, the US, the Netherlands, or the UK. The evolution of the policy discourse and funding policies in Germany show that the problem of TR was therefore mainly tackled as an organizational problem and, to a lesser extent, as a professional problem.

Two types of sources were used to analyze policy issues – funding schemes and policy papers. Policy papers provide insights into how a semantic field might be structured by the interests and narratives of different groups and societal actors. Funding schemes specifically illustrate incentive structures and governance modes in the research system (Jansen 2007). By analytically distinguishing between both types of sources, we observed that problem framings and funding incentives differ largely in the countries that introduced TR. We can also see differences regarding chronological development: Policy papers from academic professions were important in the starting phase of TR (Vignola-Gagné 2014) while funding measures and the strategic plans of research councils seem to dominate in more recent years.

Analyzing the first source – policy papers – we found a large variety of actors and institutions dealing with TR. Regarding the distribution of actors and organizations that participated in the debate in the different countries, we could observe that in Europe political actors dominate while in the US the policy paper landscape seems to be more diverse (Vignola-Gagné 2014). The framing of TR also differs in the respective countries. All countries adopted the narrative of crisis, but attributed it to rather different sources ranging from the capacity of clinical research to the organizational features of the research system. We could therefore observe that the recommendations to overcome obstacles in TR differ depending on whether the primary addressee is the medical profession or their organization. For instance, in Germany, the gap between lab and clinical research is often framed as a systemic problem of the highly tiered German research system (Jansen 2007, 1995), which could potentially be solved by founding new organizational configurations responsible for bridging this gap (Loos et al. 2014). On the contrary, in the US, TR is framed as a professional problem which should therefore be engaged with by professional actors.

These differences in framing TR as a problem in the different countries also had effects on the funding schemes which were analyzed. Particularly in Germany we found evidence of funding new organizational configurations as a primary approach (BMBF 2010a; 2010b), while in the US, project funding seems to be more important for the diffusion of the concept. Such

funding programs in the US initially had an influence on the research community; the SPORE program, for instance, proved very influential for taking up the concept of TR (van der Laan & Boenink 2012). Regarding the type of organizational actors that actively fund research (Braun 1998), we can mainly observe funding by mission agencies both in the US and in Europe. TR is tackled by strategic programs or dedicated mission agencies such as the NIH in the US, the MRC in Britain, or the BMBF Health Research Framework in Germany. These findings seem to indicate that TM is very close to the political sphere where societal problems are addressed in strategic and comprehensive measures (Roco 2003). Hence, TR is often framed in the context of societal challenges (Bhan et al. 2007; Porcar et al. 2011).

To wrap up, policy initiatives can be considered influential for both the evolution of TR as a concept and the framing of the debate (Zerhouni 2005b). However, by introducing financial measures and institutional funding, these activities can also have an impact on the cognitive structure of a research field. Thus, it is reasonable to assume that the funding measures and initiatives are represented in the semantic field. We have already presented preliminary findings from the bibliometric analysis that indicate how policy issues are reflected in the scientific literature (see section 1.4.). Some of the keywords used in the publications related to TR may be influenced by funding measures dedicated to a specific field of research (e.g. cancer research) or to policy framings that perceive certain practices in biomedical research as problems that ought to be overcome and pose "challenges" or "opportunities" for the development of methodologies and guidelines. What is unclear up to now is whether the scientific literature on TR only reflects the term's current and potentially short-lived hype due to the introduction of funding measures or whether TR itself has become institutionalized as a dedicated field of scientific inquiry. Thus, in the next section, we analyze the institutionalization of TR from a bibliometric view in order to understand the scientific status of the field.

1.6 Origin of Translational Research from a bibliometric view

From a bibliometric perspective, the first step towards understanding the dynamics of TR is to understand the structure of outputs in terms of scientific articles produced and of the specificity of channels for codified knowledge transfer, i.e. the structure of the journal landscape that represents TR. The reasoning behind this sort of analysis is to determine whether a topic has gained enough significance among the scientific community. This, in turn, is reflected in both an increase in the production of new knowledge captured in scientific articles and in the institutionalization of the topic that leads to an emergence of specialized journals. This perspective poses an analytical challenge, namely the demarcation and identification of TR as a focus of a paper and as the main focus of a journal. Unlike analyses based on specific and clearly discernable disciplinary foci, we are confronted with a cross-cutting perspective (see section 1.4) relating to numerous different objects of research. We can therefore only identify papers that can be directly related to TR, either through the occurrence of specific keywords in titles, abstracts, or author keywords, or through their publication in specialized journals that are clearly dedicated to TR. If neither is the case, i.e. if papers result from TR but fail to make this connection discernible, we are unable to identify them.

The bibliometric analysis of the global output of scientific articles relating to TR reveals that the topic can be traced back to a journal paper from 1994 entitled "New Avenues of Translational Research in Leukemia and Lymphoma – Outgrowth of a Leukemia-Society-of-America National-Cancer-Institute Workshop" published by a research team from Boston University (see Fig. 3). Given the centrality and dominance of cancer research for the TR discourse and the fact that substantial funding measures addressing TR had been initiated by the National Institute for Cancer Research in the US, it is not surprising that the first paper originated from this particular field of research. The early period of TR, spanning from the mid-1990s to the early 2000s, shows little publication activity. Most of the papers in that period have their origins in the US. From mid-2002, a significant increase in publication activity can be observed with an almost exponential growth. The curve representing the total output of scientific publications related to TR represents a rather typical shape for an emergent and sustainable trend. In the past, similar developments have been observed for nanotechnology or biotechnology. Current data does not show any signs of a decline in publication activity regarding TR.

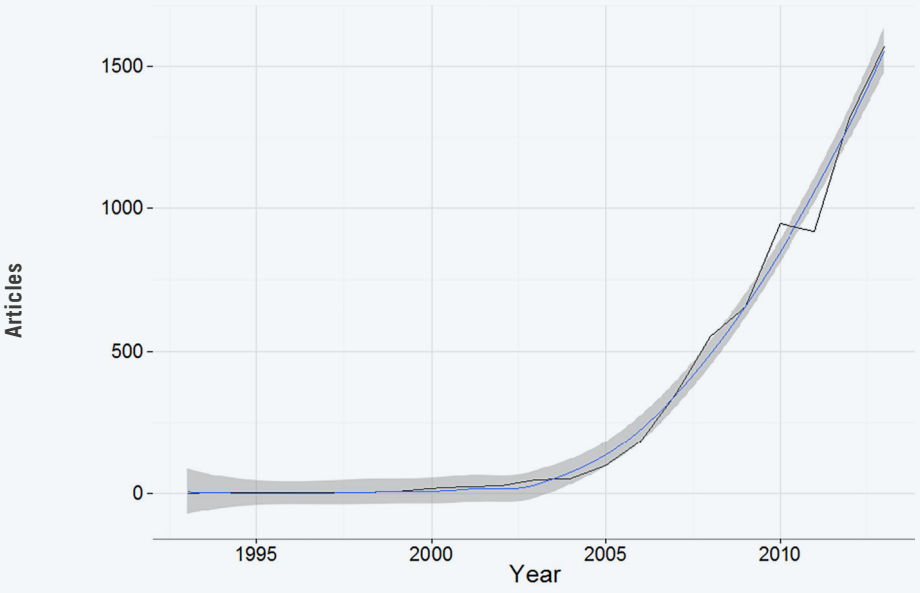

Figure 3: Number of TR-related articles in scientific journals, 1994–2013

Besides the absolute number of scientific articles, an analysis of scientific journals can also yield interesting results by revealing how articles spread within the scientific community. The underlying questions to address are: (1) How does the topic of TR enter into an established journal landscape? (2) What effect does TR have in shaping the journal landscape over time?

This analysis therefore highlights the dynamics of scientific knowledge production as well as the concentration, stabilization, and structuration of the scientific community around the topic of TR. The reason for this type of analysis lies in the fact that the evolutionary dynamics of a scientific topic can follow a multitude of different paths. These paths can appear, on the one hand, as rather immanent and integrative paths, in which TR does not lead to more differentiation in medical research or practice in the established domain from which it emerged. Or they may appear as radical paths, even paradigmatic and revolutionary, that could in the long run potentially overthrow established modes of scientific inquiry or even, taken to the extreme, create a new discipline over time. It is difficult to disentangle these paths from a mere quantitative perspective, as these potential developments also involve changes in practices that cannot be captured by merely codifying and quantifying the output of scientific knowledge. Bibliometric analyses can, however, provide a good starting point by which to judge the importance a scientific community ascribes to a topic, as well as to understand how it is distinguished from other established topics.

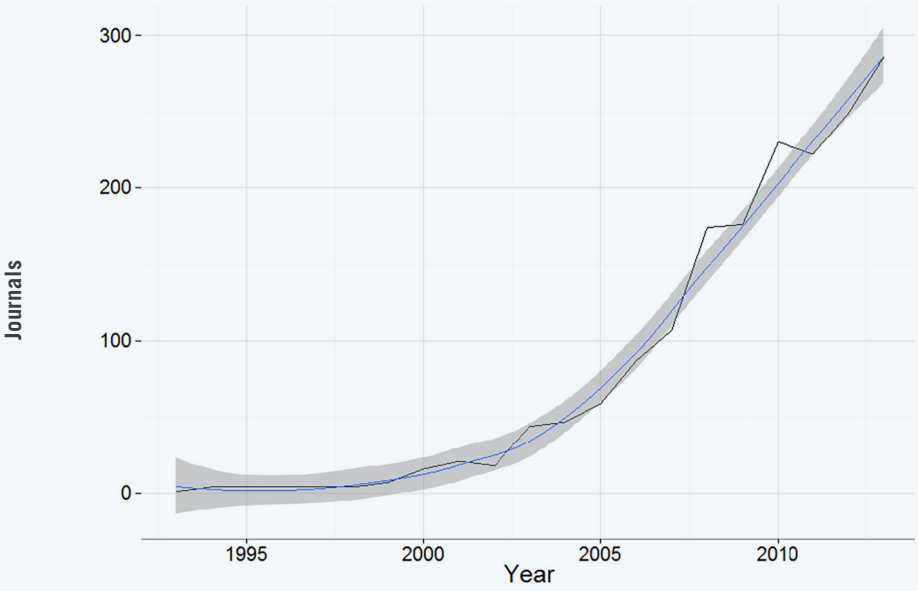

Figure 4: Number of journals publishing articles relevant to TR, 1994–2013

A first step towards this type of analysis is to assess the spread of articles within the journal landscape, i.e. how widely the body of knowledge for a scientific topic is distributed. Similar to the substantial increase in the volume of articles observable in Figure 3, the number of journals publishing articles relating to TR has increased over time (see Fig. 4). For 2013, we find a total of 286 journals hosting 1568 articles related to TR. The topic's significance therefore seems to have increased substantially for a wide array of journals.

The absolute number of journals publishing articles related to TR only provides a rough overview of how much the idea of TR has spread within the scientific community. A more developed analysis must account for further aspects, such as a clear demarcation of TR as a separate topic, as well as the existence of a critical mass of scholars and new knowledge related to TR. The result of a positive interaction between both effects, i.e. the demarcation of TR as a separate topic and a critical mass of scholars, should lead to an increased stabilization of publishing activities over time. In simple terms: A nucleus of journals specifically dedicated to TR emerges.

To determine whether this is the case, we need to conduct a more advanced analysis which allows us to identify how the increase in articles is concentrated among these journals, thereby providing evidence for (or against) a consolidation of TR. One relevant method is based on the concept of entropy. Entropy, as it is employed in information theory, has been established as an indicator by Shannon and Weaver (Shannon & Weaver 1949) and adapted to the analysis of technological change by Grupp (Grupp 1997). Basically, entropy allows us to analyze the distribution of a given population of objects. In our case, the entropy measure relates to the distribution of number of articles across journals, i.e. how many articles are published in the journals observed for a given year. Formulated in mathematical terms, we can express entropy in our case as

$$ETMF = -\Sigma\ pjTMF\ ln\ pjTMF$$

where E_{TMF} denotes the journal entropy of the field TMF and pj_{TMF} is the number of articles related to TMF published in journal j, where

$$\Sigma pjTMF = 1.$$

An increase in entropy denotes an increase in diversity of the journal landscape related to TMF. In turn, a decline in entropy denotes a focusing of the journal landscape related to TR.

Figure 5: Entropy of journal landscape relating to TR, 1995–2013

The early period of TR is characterized by a strong increase in entropy up to the year 2003 (see Fig. 5). This is not surprising as the publication volume during this early period is rather low and publications are spread rather unsystematically among different journals. Interestingly, the entropy values stabilize around the same time that we observe a strong increase in publication activities (see Fig. 3). This implies a consolidation in the journal landscape. Taking into account the results relating to the number of journals, this seems counter-intuitive at first, as the number of journals covering TR also shows a strong increase during the mid-to late 2000s (see Fig. 4).

Based on the above results, we can supply the following interpretation: The topic of TR has experienced a strong increase in relevance as indicated by an increase in publication activities. Despite the growing number of journals featuring TR-related articles, we can identify a plateau in journal entropy. This implies that the topic of TR has stabilized with a consolidated core set of journals. This stabilization is offset by a steady increase in journals at the periphery of the topic of TR. The consolidation of the topic TR can also be observed in the most relevant journals for the year 2013 (see Table 1). In total, 76% of all scientific papers related to TR published in 2013 are captured in these ten most important journals.

After having described the emergence of TR, we can conclude that although TR has stabilized as a major topic with a core set of journals, the field has still not reached a closure, so that practical and procedural challenges – as suggested in the semantic analysis (see section 1.4) – remain unsolved. For a more in-depth view on TR, in the following chapter we will provide some insights into how TR can be organized by focusing on the scientific literature in section 2.1 and on the organizational self-characterizations in section 2.2.

Table 1: Ten most important TR journals in 2013

RANK	TITLE OF JOURNAL	NUMBER OF ARTICLES	% OF ARTICLES TO TOTAL	% OF ARTICLES TO TOTAL (CUMULATED)
1	J of translational medicine	284	18	18
2	Science translational medicine	200	13	31
3	Clinical & translational oncology	143	9	40
4	Translational psychiatry	116	7	47
5	J of cardiovascular translational research	92	6	53
6	Stem cells translational medicine	88	6	59
7	Translational oncology	80	5	64
8	CTS-clinical and translational science	60	4	68
9	Translational stroke research	58	4	72
10	Translational research	56	4	76

2 HOW TO ORGANIZE TRANSLATIONAL RESEARCH?

In chapter 1 we aimed to provide a deeper understanding of the different facets of the TR concept. We also looked at how the scientific community ascribes relevance to TR by analyzing the output and structure of scientific publications related to TR. The findings show that the scientific literature and the political debates related to TR include multiple issues of several dimensions with relevance beyond the medical profession. These issues highlight economic expectations towards TR that have been interpreted as the economic dimension. The moral-ethical dimension relates TR to the needs of the patients. In the political dimension, we highlighted different framings of how current problems in biomedical research can be overcome. In our analysis of policy papers and funding measures, we found that the educational dimension, that is, educating the next generation of TR researchers, to be the most important. In addition to these dimensions, we identified the organizational dimension, which describes how TR is embedded into the organizational design and processes of performing TR.

The goal of this chapter is to elaborate on these findings by collecting and analyzing publicly available material about "blueprints" employed for putting TR into practice. The first main focus in this chapter is on which processes and procedures are currently perceived by different stakeholders to either describe or prescribe fundamental procedural aspects of TR. Understandings of such condensed notions as to how TR "works" or "should work" can have a strong influence on the performance of TR in practice. This happens, for example, through frames prescribing how knowledge should be transferred, how different actor groups should interact at certain points in time, or by generally shaping expectations regarding the responsibilities of the involved actor groups towards themselves and others. The second focus of this chapter relates to the organizational designs and settings of a selected set of organizations in the US. The overview we can provide is limited to publicly available information, a fact that has to be taken into account. Such information may have been produced with a specific purpose in mind, e.g. to attract funding or to establish a certain public image of an organization. Therefore, the answers and insights we can provide are limited and should not be confused with the results that can be obtained by careful onsite organizational analyses, case studies, or quantitative surveys.

2.1 Phases of Translational Research: From phase 0 to phase 4

In conceptual terms, moving from TR's meaning to how it is organized is no big leap. However, as there is no clear-cut definition of TR, the question of its organization can illicit a number of answers. We can find two basic tendencies that have developed over time: (1) an ongoing expansion of the TR process to encompass more and more aspects, particularly in the context of clinical practice and public health, and (2) a subsequent increase in the number of translational phases (T) within the proposed process models.

At the beginning of discussions about the TR process, we find claims that emphasize a multidirectional understanding (Marincola 2003) and address TR as an interdisciplinary approach that connects different research areas, as stated by the director of the National Institutes of Health (NIH), Elias Zerhouni (2002–2008), at the initiation of the NIH Roadmap for Medical Research (Zerhouni 2003). This roadmap comprised explicit efforts for a "reengineering of the national clinical research enterprise" (Zerhouni 2005b) to develop more joint research enterprises between biomedical researchers and physicians.

The Clinical Research Roundtable of the Institute of Medicine (IOM) has delineated two translational blocks that have often been referred to as T1 and T2. T1 is defined as "the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans" (Sung et al. 2003). T2 addresses "the translation of results from clinical studies into everyday clinical practice and health decision making" (ibid.).

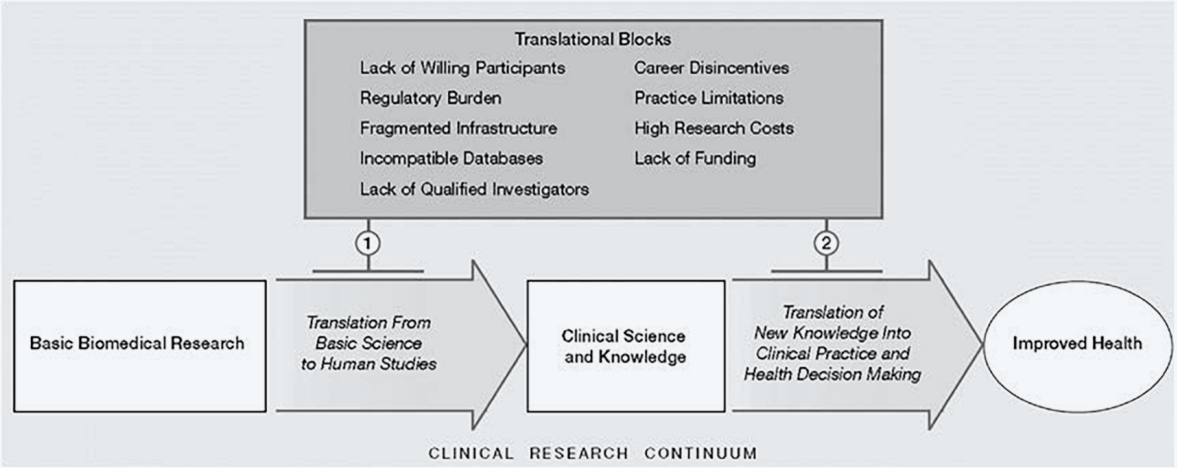

Figure 6: TR process model with two translational phases in Sung et al. (2003)

Woolf, however, notes that "[r]eferring to T1 and T2 by the same name – translational research – has become a source of some confusion" (Woolf 2008) because T1 and T2 are "alike in name only" (ibid.) but require different personnel and research competencies. He furthermore criticizes that although both phases are regarded as important (also by the NIH Roadmap), T2 research still lacks funding comparable to that spent on T1 research.

Woolf also points to studies that add a third phase to the TR process. T3 can be found in process models by Westfall et al. (2007), Dougherty & Conway (2010), Rubio et al. (2010), and Drolet & Lorenzi (2011). The least differentiated model is from the Evaluation Committee of the Association for Clinical Research Training (Rubio et al. 2010). However, the model clearly emphasizes that it seeks to connect three different research sites that, in the committee's opinion, all need to be integrated into a coherent TR process model. These three research sites are basic biomedical research, patient-oriented research, and population-based research. For TR, T1 research includes "drug development, pharmacogenomics, and some studies of disease mechanisms and research into new areas such as genetics, genomics, and proteomics", T2 includes "clinical epidemiology, health services (outcomes) research, and the newly developing methodology of community-based participatory research", and T3 includes "emerging disciplines such as molecular and genetic epidemiology" (ibid.: 5). The model notably integrates feedback from population-based research to the laboratory as a distinct phase (T3). T3 highlights "how research in populations informs hypotheses that can be tested in basic science laboratories and how biomarkers in animal models can translate into population-based screening tools" (ibid.). It is thus the only process model that regards this feedback loop as a proper and separate translational phase. The authors' understanding of T1 to T3, however, rather resembles a description of the different research areas between which translation is supposed to take place. How translation actually occurs in each of the mentioned T phases is not further elaborated.

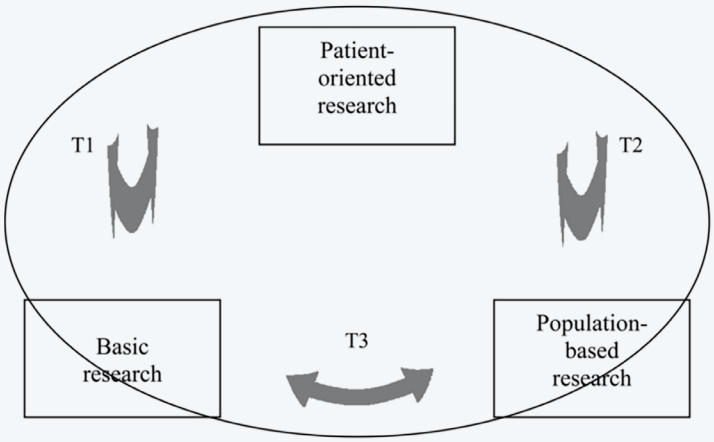

Figure 7: TR process model with three translational phases in Rubio et al. (2010)

In contrast to this all-encompassing idea of TR, Drolet & Lorenzi (2011) put their emphasis on the clinical research process. Their "zone of translation" starts with the translation of basic research (itself not part of this zone) into "proposed human application". T2 comprises "safety and efficacy research" and translates results from "proposed human application" into "proven clinical application". T3 consists of research on implementation and adoption in clinical practice (again not actually included in the TR process). Further practice-based research with an impact on public health is not part of the authors' translational concept. It is nonetheless mentioned and furthermore understood as providing input for each step and translational phase throughout the entire TR process. This is why Drolet and Lorenzi speak of a "biomedical research translation continuum". Even though they are a bit clearer in what should be considered TR in the different phases, they nonetheless point to the fact that what actually happens in the translational phases is still black-boxed and thus not entirely understood (Drolet & Lorenzi 2011).

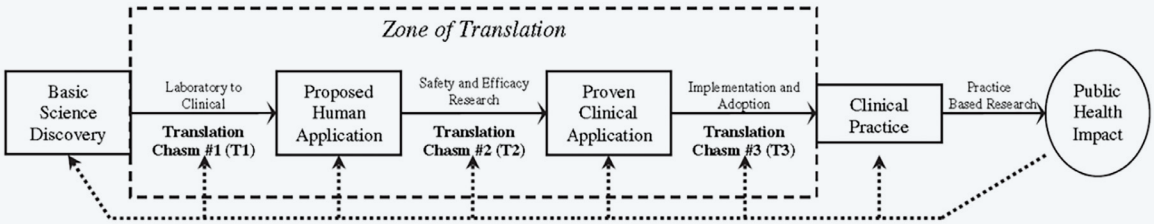

Figure 8: TR process model with three translational phases in Drolet & Lorenzi (2011)

Westfall et al. (2007) refer to the NIH understanding of T1 and T2 that distinguishes between the "translation of basic science laboratory work in animals into an understanding of basic human medical chemistry and physiology and [the] translation of basic human chemistry and physiology into improved diagnostic tests, medicines, and treatments for use in clinical practice" (Westfall et al. 2007). Yet, the authors propose an expansion of T2 into (1) the translation to patients through the development of evidence-based guidelines and (2) the translation of these guidelines into everyday clinical care through their dissemination and implementation. Westfall et al. state that "[t]his additional laboratory and third translational step seeks to solve the problems encountered by primary care physicians as they attempt to incorporate new discoveries into clinical practice" (ibid.: 404). In contrast to the model proposed by Drolet & Lorenzi (2011), they include practice-based research in their model and conceptualize it as a pivotal but currently neglected research perspective. Westfall et al. are furthermore more explicit in describing what happens in the translational phases. They do so by aligning the translation

process with the phases of clinical trials and also combining practice-based research with long-term observational studies including phase III and IV clinical trials. In addition to this TR process model, the authors propose paying greater attention to "community-based participatory research, public health research, and health policy analysis" (ibid.: 405).

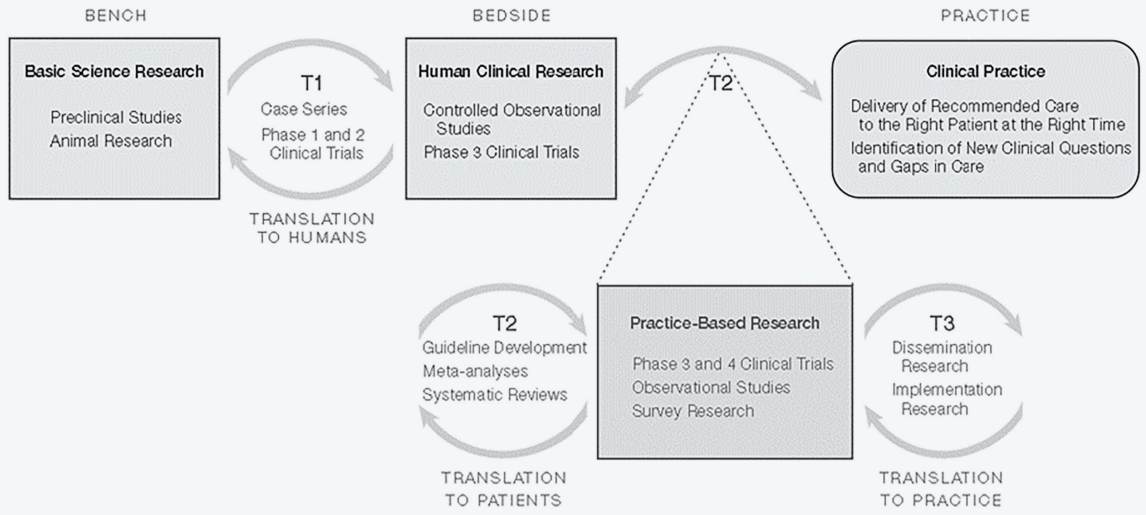

Figure 9: TR process model with three translational phases in Westfall et al. (2007)

Dougherty and Conway (2010) provide another TR process model that has been prominently cited (Ma et al. 2014). In their model, they distinguish between "clinical efficacy" and "clinical effectiveness" that need to be analyzed in T1 and T2 once a biomedical product has been developed. As with Westfall et al., T3 addresses the dissemination and widespread implementation of a therapeutic product. Dougherty and Conway also consider a feedback loop that transfers results from the measurement of health care quality and costs back to basic biomedical research. Such feedback loops are also conceptualized throughout the entire TR process. They therefore follow a predominantly economic perspective on TR, one that pays particular attention to measuring and accounting for health care quality and its costs. The perspective highlights that such "[m]easures enable key health care stakeholders to assess progress continuously, hold the health care system accountable, identify areas for improvement, and facilitate market-driven approaches to health care" (Dougherty & Conway 2010).

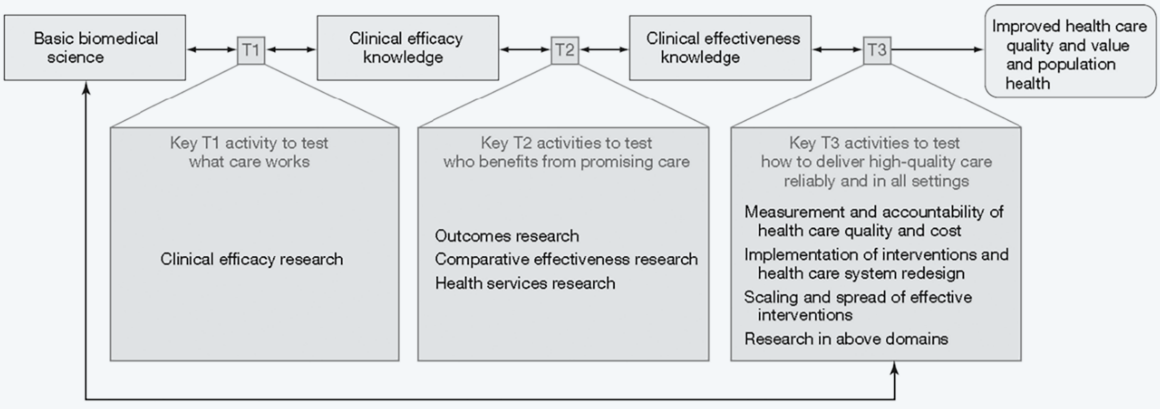

Figure 10: TR process model with three translational phases in Dougherty & Conway (2010)

Moreover, there are already TR process models that distinguish four translational phases. Khoury et al. (2007) propose four translational phases that cover the full scope of medical and implementation research from the laboratory to population health. Examining the case of human genome epidemiology, they furthermore give an ideal example for each translational phase between the different research areas. T1 and T2 are associated with the clinical trial phases from I to IV as well as with research that is focused on complying with the ACCE criteria of analytic validity, clinical validity, clinical utility, and satisfying key points related to ethical, legal, and social issues. T3 is composed of dissemination, implementation, and diffusion research, and T4 addresses outcomes research (ibid.: 668). In each of these phases, Khoury et al. clearly describe what these TR practices encompass in the case of human genome epidemiology. Similar to the aforementioned TR process models, this model is also understood as a continuum where each phase can also provide insights for the next phase(s).

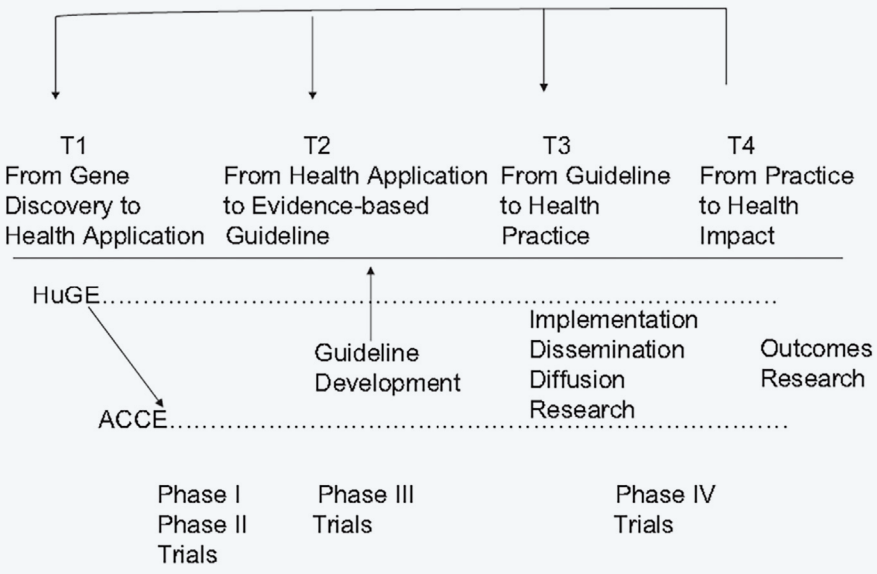

Figure 11: TR process model with three translational phases in Khoury et al. (2007) [25]

Trochim et al. (2011), Rajan et al. (2012), and Ma et al. (2014) have reviewed these (and other) TR process models. While Ma et al. provide only a temporal overview that includes short descriptions of the respective models (Ma et al. 2014), Trochim et al. and Rajan et al. aim at finding an appropriate model for assessing TR. They are looking for an evaluation tool to assess TR processes in order to reduce time required for the development of new therapies. Trochim et al. furthermore seek to assess how "the rate and volume of translation" can be increased (Trochim et al. 2011).

However, Trochim et al. do not develop their own concept of the TR process. Instead, they develop an assessment tool they call "the process marker model" (Trochim et al. 2011), which is applicable "regardless of the number or type of 'T' phases in use" (ibid.: 158). This model seeks to identify "a set of observable points in the process that can be operationally defined and measured, in order to enable evaluation of the duration of segments of the research-practice continuum" (ibid.). Although this model does not provide us with a conceptualization of what TR actually is, it might still be helpful for analyzing ongoing research processes that claim to be TR and thus for shedding some light into the black box (Drolet & Lorenzi 2011).

[25] *HuGE = human genome epidemiology (Khoury et al. 2007: 667).*

Rajan et al. also seek an assessment tool that could help evaluate the performance of cancer research centers (Rajan et al. 2012). They start by reviewing current TR process models, although they are actually searching for assessment strategies. Among the process models they review is the aforementioned study by Trochim et al. (2011), whose process marker model Rajan et al. seem to find most convincing. Other evaluation tools that they consider helpful for their purposes are the Lean and Six Sigma business management strategies proposed by Schweikhart & Dembe (2009) for assessing TR. It must be noted that the Lean and Six Sigma model also fails to provide a conceptualization of the TR process, but it does supply tools to illuminate the micro processes that take place in the everyday research process. Similar to the process marker model, it could thus help to develop a better understanding of TR practices. However, both assessment tools exhibit a strong focus on hurdles and obstacles to a more efficient research process. The question of how to foster better translation is not addressed, as both tools fail to offer an understanding of what TR actually entails.

Organizations such as the Duke Translational Medicine Institute or the Harvard Clinical and Translational Science Center develop their own understanding of the TR process, which they seek to follow in their particular TR programs. The TR process model referred to by the Duke Translational Medicine Institute comprises medical research and its implementation in clinical practice. It furthermore includes community assessment, care delivery, and health services research as aspects of TR. In addition, this model links research that has been done so far in separate arenas to organizational units within the Duke Translational Medical Institute (see section 2.2).

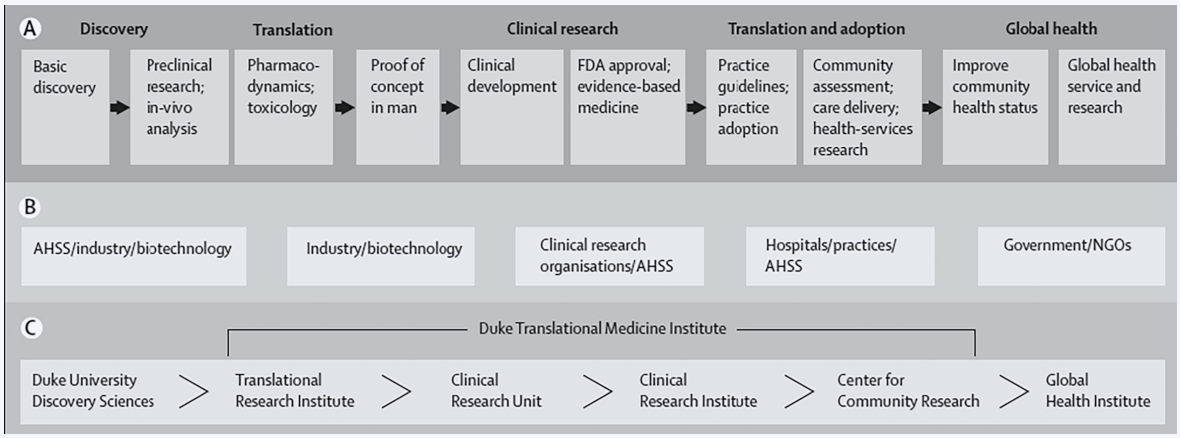

Figure 12: Duke Medicine Model for Translation in Dzau et al. (2010)

The Harvard Clinical and Translational Science Center provides a short video clip (see Fig. 13) on their understanding of TR. They define four phases that are shown in parallel with clinical trial phases and that extend from first-in-human clinical trials to research on global public health (T4). The model also defines T0 as a fifth phase that is understood as the development of animal models preceding clinical trials (T1). T2 and T3 comprise the development of guidelines (T2) and an assessment of the costs and effectiveness of a new therapy (T3).

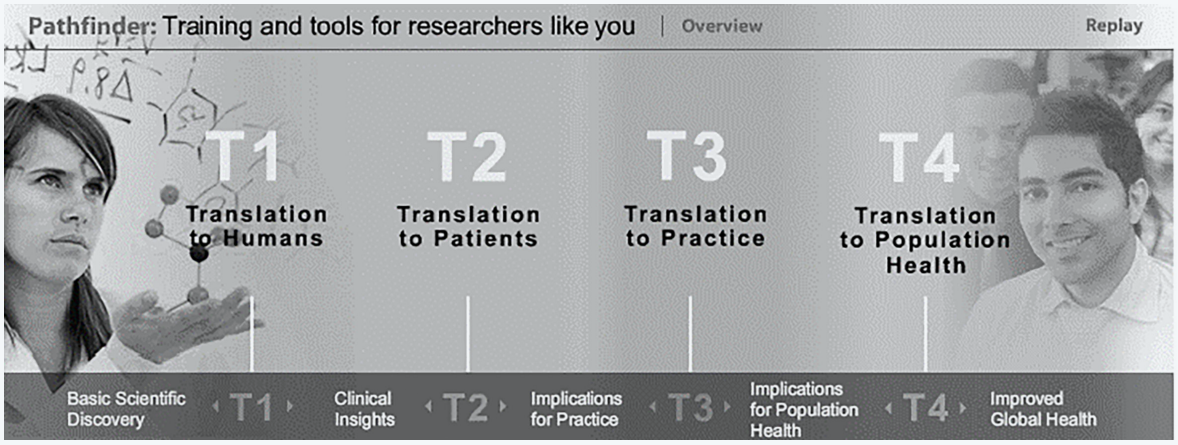

Figure 13: Harvard Clinical and Translational Science Center TR process model [26]

This brief analysis of current TR process models demonstrates that these models vary according to the respective perception of TR. As there is still no commonly shared definition of TR, multiple TR process models can be found as well. These process models not only vary in the different research areas they comprise (basic research, pre-clinical research, clinical research, meta-reviews for evidence-based guidelines, clinical practice research, patient-oriented research, population-centered research), but also in their understanding of what they actually address. Some models focus on the research areas rather than on the actual TR practices. This indicates – although researchers and practitioners claim already to practice TR – that ideas about what TR should comprise and what it actually is still remain a black box "in which activities of translation remain vague"(Drolet & Lorenzi 2011).

2.2 Translational Research organizations and organizational procedures in the United States

2.2.1 Translational Research organizations: A qualitative perspective

In a previous section (see section 1.5), we examined the impact of policy issues – in our case through policy papers and funding programs. These issues frame goals and rationales and help set priorities in an emerging field like TR. The National Institutes of Health (NIH) could be identified as one of the main mission funding agencies in the US. Furthermore, the NIH program influenced research funding programs in other countries, for example in Western Europe. Hence, we focus our qualitative research towards international organizational procedures in institutions funded by the NIH's National Center for Advancing Translational Science (NCATS). Before describing the organizations we have selected, we will start with a short description of the organizational design of the NIH system.

As a part of the US Department of Health and Human Services, the NIH is the national medical research agency of the United States. The NIH has a total annual budget of around $30.1 billion and cooperates with over 2500 offsite research institutes and universities. It consists of 27 intramural institutes and centers (see Table 6 in Appendix), each with their own research agenda and programs, but all subject to centralized leadership (see Fig. 14).

In 2006, the NIH launched the Clinical & Translational Science Award (CTSA) program to accelerate the implementation of TMR. The defined goal was to develop new treatments more efficiently and to deliver them more quickly to patients (NIH

[26] *Source: catalyst.harvard.edu/pathfinder/t1detail.html*

2015c). Today, the CTSA program supports about 60 academic research institutes (consortium) with financial funding, management, and resources such as technologies and data. Initially governed by principle investigators of the CTSA sites and NIH representatives, the area of accountability was delegated to the newest NIH site in 2012, the National Center for Advancing Translational Science (NCATS). As the research areas of the supported institutions exhibit considerable breadth, the NCATS does not focus on a particular disease or basic science but serves "as an adaptor to enable other parts of the research system to work more effectively. NCATS complements other ICs [Institutes and Centers of the NIH], the private sector and the nonprofit community (NIH 2015b). The mission of the NCATS at NIH is to "catalyse the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions" (NIH 2015d). The NCATS will be funded with a total of $657,471 million in 2015.

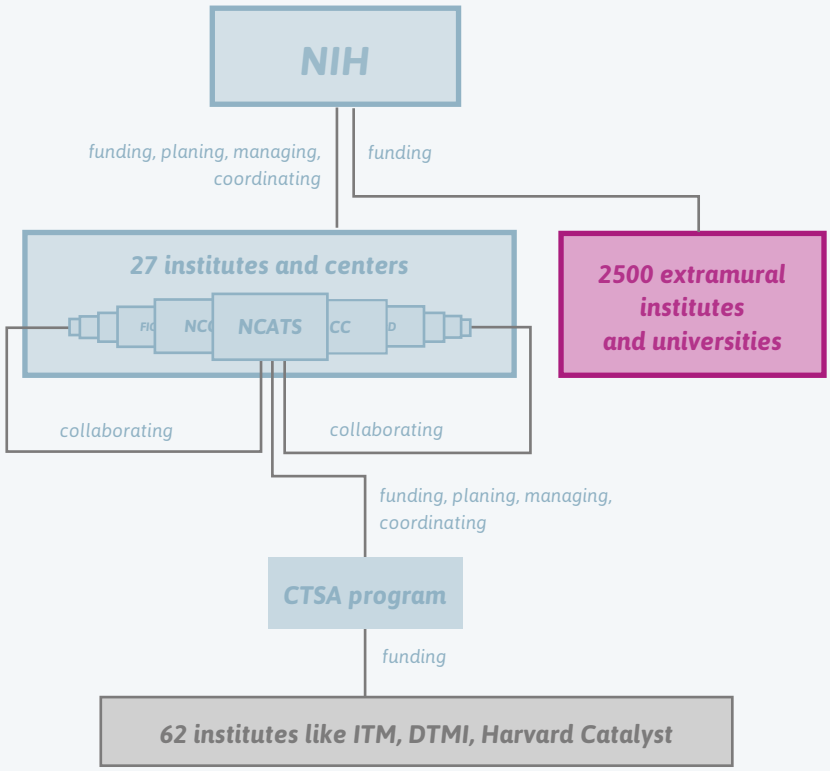

Figure 14: Organization of NIH, CTSA, and NCATS

Table 2: Most active institutions in publishing TR-related papers

RANK	UNIVERSITY	NO.
1	HARVARD	302
2	UNIVERSITY PENN	162
3	UNIVERSITY MICHIGAN	160
4	STANFORD	152
5	UNIVERSITY PITTSBURGH	141
6	UNIVERSITY CALIFORNIA SAN FRANCISCO	134
7	JOHNS HOPKINS UNIVERSITY	127
8	UNIVERSITY MINNESOTA	127
9	UNIVERSITY WASHINGTON	127
10	DUKE UNIVERSITY	114
11	NCI	113
12	MAYO CLIN	111
13	UNIVERSITY CALIFORNIA LOS ANGELES	105
14	NIH	104
15	YALE UNIVERSITY	102
16	COLUMBIA UNIVERSITY	97
17	UNIVERSITY CALIFORNIA SAN DIEGO	97
18	WASHINGTON UNIVERSITY	88
19	UNIVERSITY CHICAGO	81
20	VANDERBILT UNIVERSITY	80

Organizational procedures of Havard Catalyst, DTMI, and ITM

In the following, we will present some of the leading research organizations in the field of TR which are active in promoting the concept. Our aim is to analyze not only how these institutions position themselves with respect to TR but also the ways in which TR was implemented organizationally at these institutes according to institutional self-characterizations and organizational charts. We will focus on institutes in the US since the above-mentioned funding initiatives and policy activities have led to established institutional structures and research groups there that are highly active in TR and can therefore be perceived as leading organizations in the field. The following institutions were identified based on (1) a screening of influential papers and a (2) bibliometric ranking of the most active institutions in publishing TR-related papers (see Table 2). During our inquiry we found some sites in the field of TR to be good starting points to gain insights into organizational structures and practices, but we needed to restrict our analysis to a few institutions.

Harvard Catalyst – the Harvard Clinical and Translational Science Center

Harvard Catalyst, the Harvard Clinical and Translational Science Center, was founded to improve human health through clinical research and TR. The name Harvard Catalyst reveals its primary focus on accelerating networking and collaboration between scientific institutions and health care actors. As a shared enterprise of Harvard University, the Harvard Catalyst facilitates collaboration by providing tools, training, and technologies to all Harvard faculty members and trainees and external actors. Since its establishment in 2008, it was funded by the NIH CTSA program on a five-year basis with $117.5 million, which was renewed in 2013. According to its self-characterization, the Harvard Catalyst perceives its role as mediating and allocating the academic and medical science resources of existing institutions at Harvard University in order to focus and strengthen the capabilities of the research institutes.

> *"Harvard Catalyst works with Harvard schools and the academic healthcare centers (hospitals) to build and grow an environment where discoveries are rapidly and efficiently translated to improve human health" (Harvard Catalyst 2015).*

Furthermore, the Harvard Catalyst provides funding and multiple education and training programs. Part of this training program is a specific Master's program in "Clinical and Translational Investigation" tailored to medical graduates.

Duke Translational Medicine Institute (DTMI)

The Duke Translational Medicine Institute (DTMI) of Duke University aspires to improve individual and population health through clinical research and TR. Formed in 2006, it was one of the first institutes to receive the Clinical and Translational Science Awards (CTSA) from the NIH. In 2013, the NIH renewed this funding award with a total of $47 million over five years. The DTMI organizational structure combines diverse institutes and centers which provide expertise in fields from translational to community research (see Fig. 15). With its organizational structure, it bridges the gap between new discoveries in science and global health. Global health is to be understood as an attempt to improve health beyond national borders and to establish equity of care through research, education, and application (Koplan et al. 2009), all of which are represented by the Duke Global Health Institute.

To achieve these goals, the DTMI aims to create synergies between science and the health care system by resolving financial and practical obstacles focusing on implementing new health care innovations. It therefore intends to provide resources, expertise, and information and further enhance networking and collaboration between multidisciplinary investigators and industrial project management (DTMI 2015b).

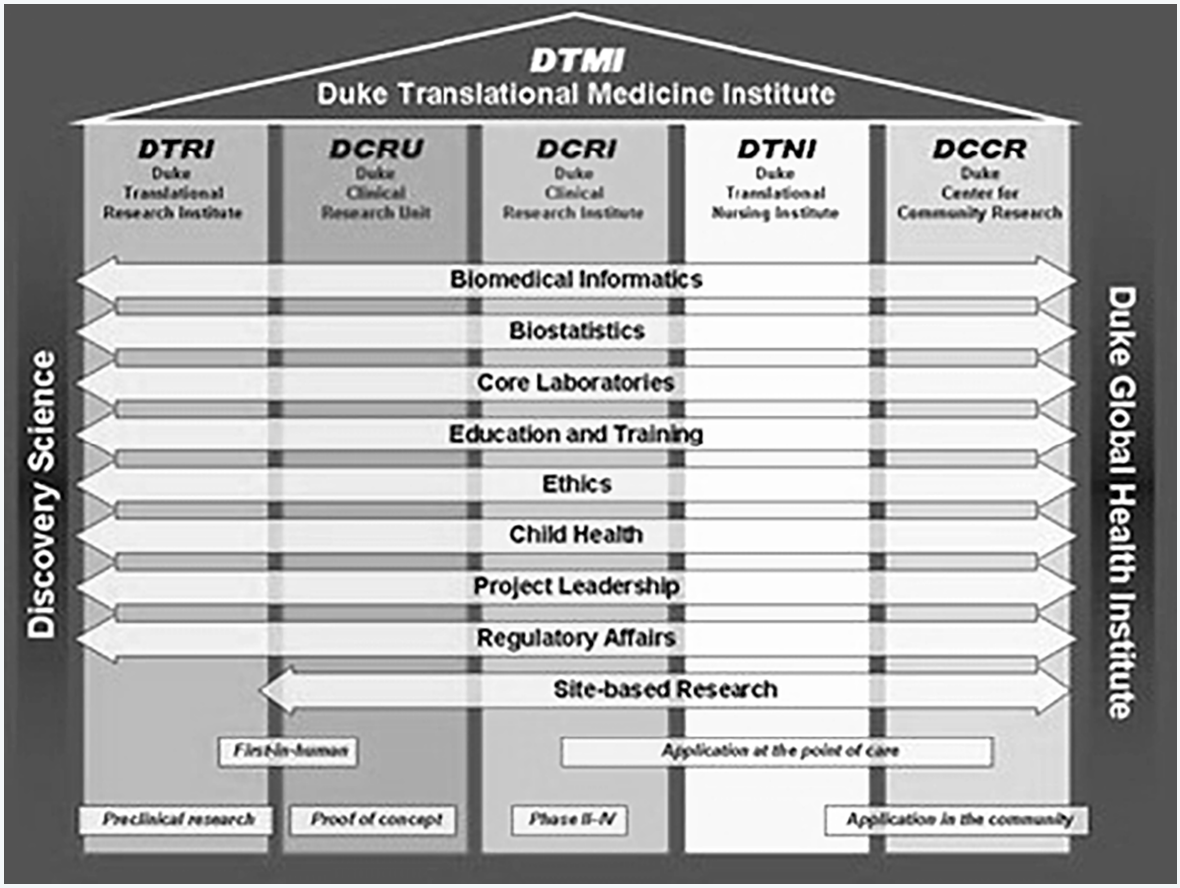

Figure 15: Duke Translational Medicine Institute (DTMI 2015a)

Institute for Translational Medicine (ITM) Chicago

The University of Chicago's Institute for Translational Medicine (ITM) focuses on accelerating the transformation of laboratory research into daily use by health care practitioners and other community health actors. The ITM is one of 61 institutions which are funded by the NIH's National Center for Advancing Translational Sciences (NCATS), which claims to advance innovative medicine. Since its foundation in 2007, the ITM has invested almost $50 million in its own research infrastructure and $9 million in research funding. The organizational structure is one of several clusters which account for clinical trials or community engagement, for instance (see Fig. 16). All clusters and their operating workgroups are encompassed by an educational cluster that provides training opportunities and programs from the academic Committee on Translational Science. As part of the University of Chicago, there are several research facilities on the campus which are dedicated to the ITM. It also collaborates with other national institutes (networking, laboratories, and universities).

The above-mentioned programmatic goals are incorporated in the institute's organizational practice to promote researchers by funding studies, establishing educational programs, and building resources and tools. Furthermore, it connects researchers with community organizations. The ITM describes its own main goal as follows: "(…) to train scientists and healthcare providers at the University of Chicago and in our community to determine the molecular, genetic, pathophysiologic, and social determinants of disease and disease predisposition in individuals" (ITM 2014b). This goal is to be understood nationwide, but the institute also explicitly intends to target medically underserved parts of the population in the Chicago area.

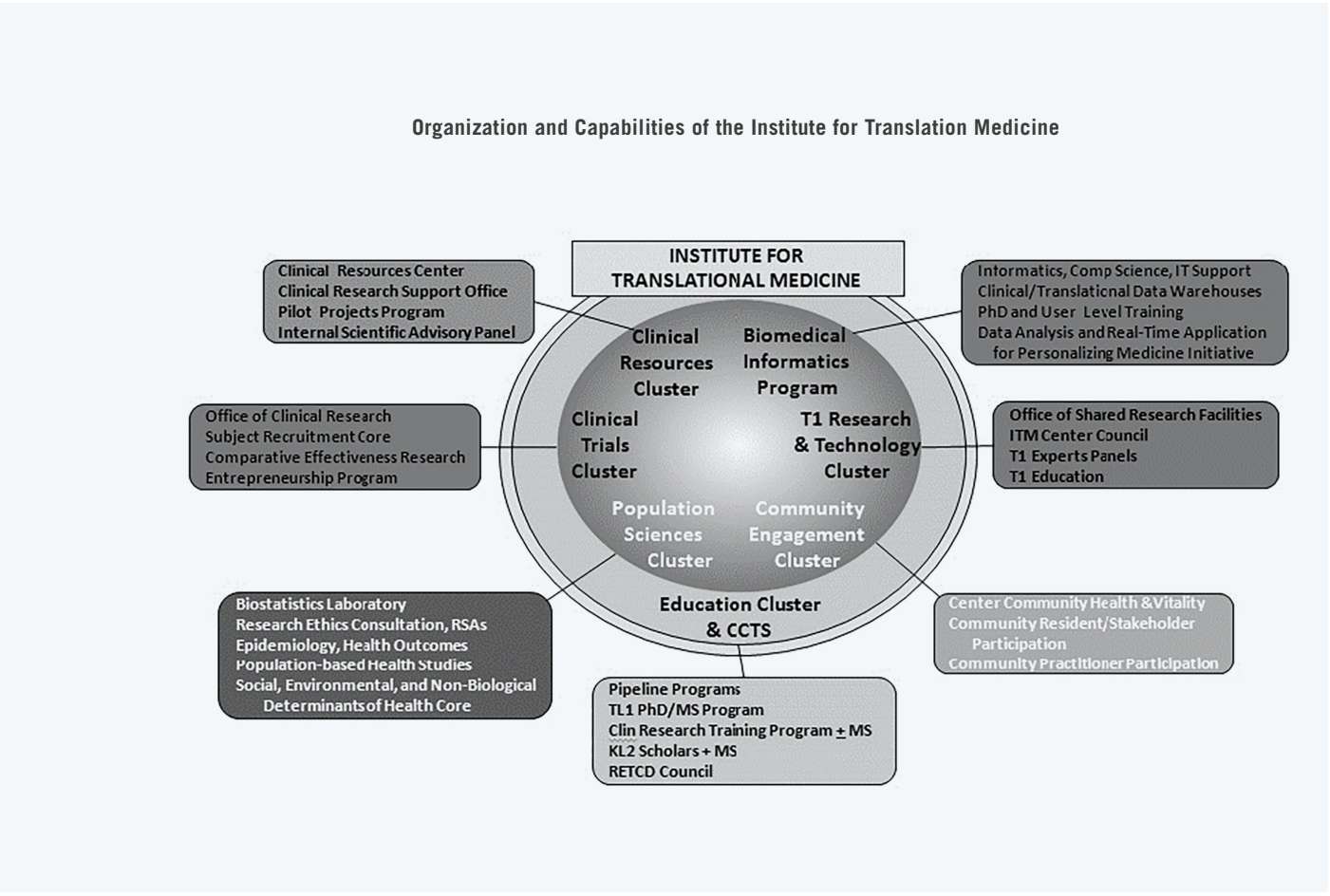

Figure 16: Organization and capabilities of the Institute for Translational Medicine in Chicago (ITM 2014a)

2.2.2 Insights into the US organizational landscape: Summary of findings

Despite the diverse understandings of translational processes in section 2.1 and differences in publishing activities, the qualitative results exhibit some similarities in the organizational practices of all three institutes. One can summarize these findings in three organizational domains which consist of **collaboration and networking**, **training and education**, and **resource provision**. The first domain addresses the joining of intramural university actors as well as extramural institutes and organizations. The second domain aims at the qualification of junior scientific staff as well as graduates and postgraduates. The third domain consists of several types of resources needed to support and catalyze scientific output like technologies, data, or financial aid.

3.0 CURRENT STATE OF TRANSLATIONAL RESEARCH IN GERMANY: RESULTS FROM A BIBLIOMETRIC ANALYSIS

In the preceding chapters, we provided evidence for the emergence and diffusion of the TR concept, both at the publication landscape and the organizational level. We have shown that major research institutes in the US that relate to TR or even characterize it as their main mission have been established or transformed. Now, we will turn to Germany. We will therefore once again rely on a bibliometric analysis focusing on the organizational landscape.

The analysis in section 1.6 has shown a vast increase in publications on the topic of TR at the global level. Even though this information is valuable in its own right, a more in-depth understanding at the organizational level can help to understand the evolution of TR in Germany[27].

3.1 Organizations entering the field of TR

In order to understand the dynamics of TR from an organizational perspective, we conducted an analysis that highlights new entrants to TR for Germany (see Fig. 17).

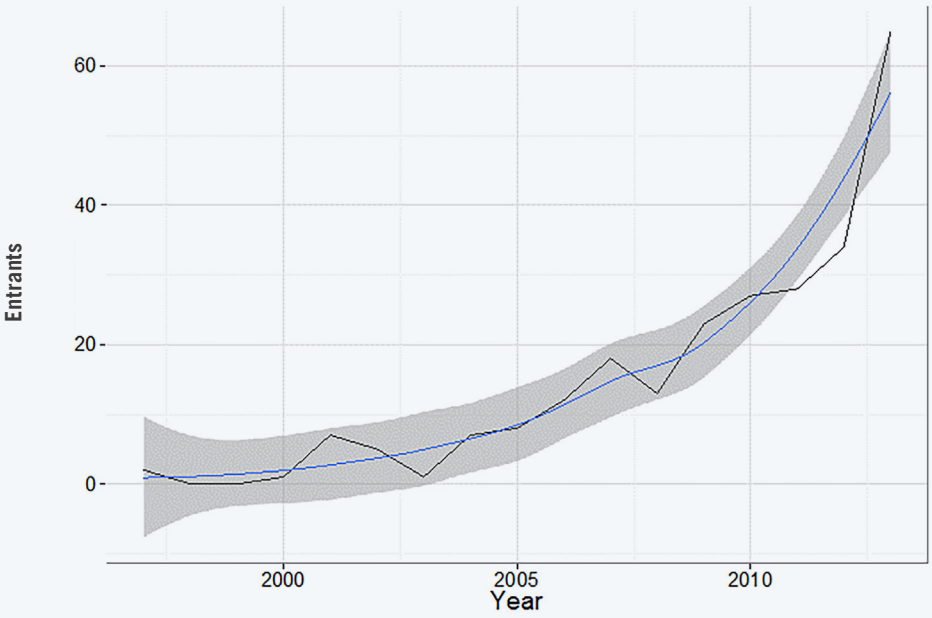

Figure 17: Number of new entrants to TR for Germany, 1997–2013

The results show that there is still a substantial number of new German organizations starting to engage with the topic of TR. Especially after 2011, we find a strong increase in new entrants, suggesting that the community around TR has not reached a state of saturation.

[27] *The analysis of bibliometric data on an organizational level requires substantial data cleaning due to the fact that authors are rarely consistent in how they handle affiliations in publications. We therefore have to focus this type of analysis on Germany, as validated cleaning procedures are available for our data in this case.*

In order to understand which type of organizations started engaging in TR during recent years, we drew a random sample of the new entrants (see Table 3). The sample shows some interesting results, which were also validated with the whole data set. In total, we determined the following: There has been a surge in pharmaceutical companies in recent years. We also found that Max-Planck Institutes, which are almost exclusively oriented towards basic research, started to engage in TR at a rather late stage after 2010. Finally, we determined that smaller hospitals have started to engage in TR, which suggests that the topic is reaching a stage of diffusion that is not limited to the dominant academic players with ties to university hospitals. Furthermore, this might be a sign of saturation as most possible organizations have already entered the field.

Table 3: Sample of German organizations joining TR in 2013

Organizations joining in 2013 (sample)
UNIV BREMEN
MAX PLANCK INST MOL CELL BIOL & GENET
EPIONTIS GMBH
PFIZER DEUTSCH GMBH
EVANGEL KRANKENHAUS KALK
LUKASKRANKENHAUS NEUSS
GEMEINSCHAFTSPRAXIS HAMATOL & ONKOL
XVIR THERAPEUT GMBH
INST MED DOCUMENTAT & INFORMAT DIMD
SANOFI R&D DIABET DIV

On their own, the results are not sufficient to draw overarching conclusions about the causes behind these developments. They do, however, allow for interesting qualitative propositions to be tested in subsequent research. One proposition relates to the recent interest of companies in TR. This could be due to the fact that companies perceive an increased economic benefit from TR in terms of drug development or establishing new products and services based on TR in general. The second proposition relates to the interaction between pure basic research and economic expectations towards TR. To understand the development of TR it would be interesting to assess if TR has a stronger foothold in applied research than expected and the interest from players in basic research and economic implications of companies is indeed a recent development. A qualitative analysis validating the bibliometric results and enriching them through qualitative research results should lead to a better understanding of TR and also shed some light on motives for cooperation as well as strategies followed by the organizations involved.

3.2 Organizations and cooperation structures

In the following, we will analyze the structure of TR from an actor perspective, primarily focusing on the development of cooperation structures in Germany. In order to analyze the cooperation structures we used the data collected in our corpus to analyze co-publications at the organizational level. To highlight the evolution of the field, we chose three time frames, each comprising two years. As the volume of publications from German authors is rather low in the early phases of TR up to the mid-2000s, we chose to analyze the structures from 2003 onwards. Due to the fact that we have no consolidated address data for non-German organizations, we only used the German address data in our corpus. This implies that the publications used in our analysis also involve international organizations. The visualization of the network structures is limited to German organizations.

For the period from 2003 to 2005, we find very little cooperation activity manifested in the co-publication structures (see Fig. 18).

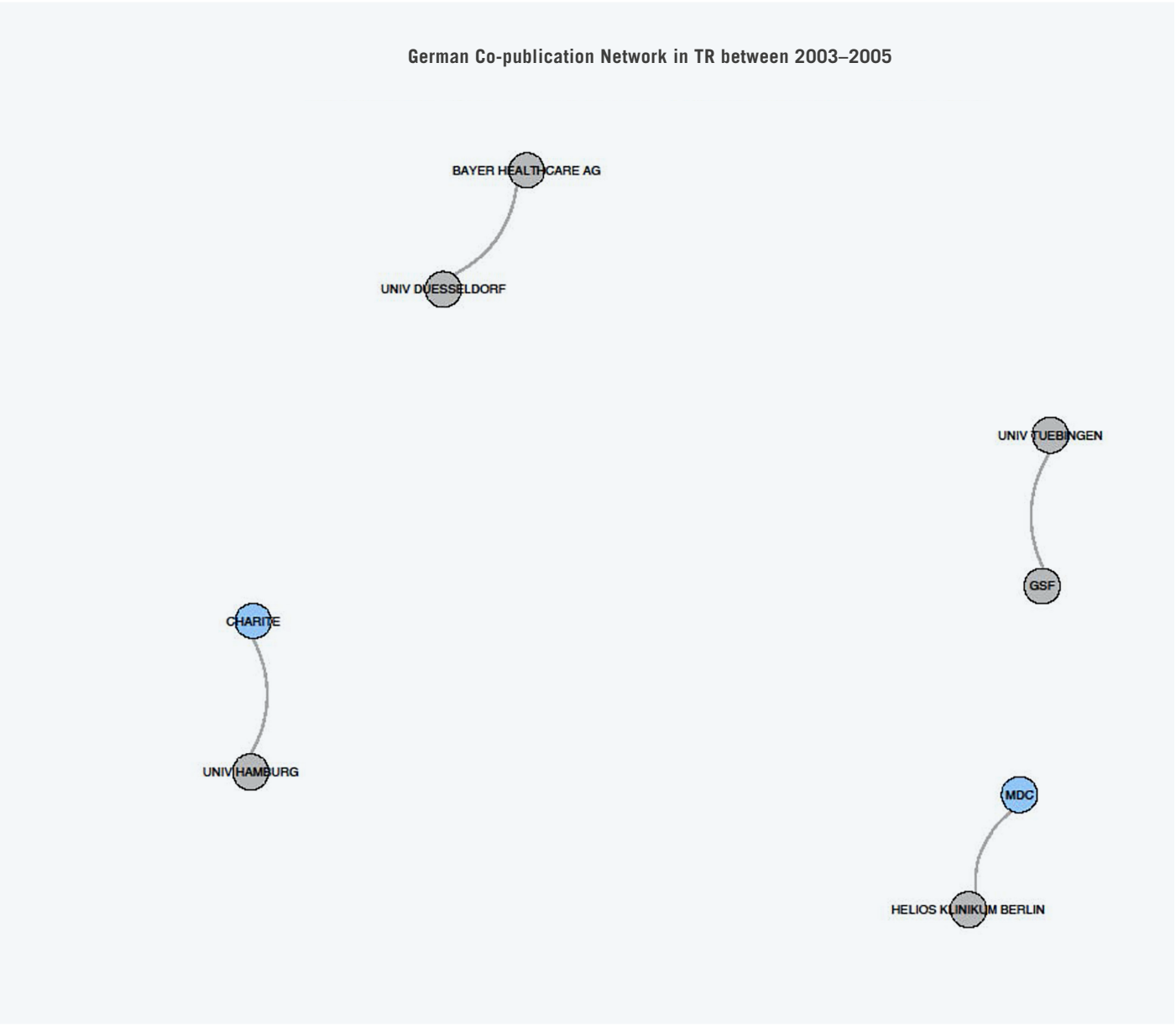

Figure 18: Co-publication structure of German TR-related publications, 2003–2005

Figure 19 shows the results of our co-publication analysis for the period from 2008 to 2010. We can find a clear increase in cooperation activities during these years. This is in part due to an increase in the absolute volume of publication activities (see Fig. 3). We also find that the network already features a number of hubs that are more actively involved in cooperation activities. In this period, the University of Erlangen features the most co-publications with other organizations. The second most collaborative organization is the Charité. Other highly collaborative organizations are the two major universities in Munich (LMU and TUM), the University of Heidelberg, University of Münster, and University of Jena.

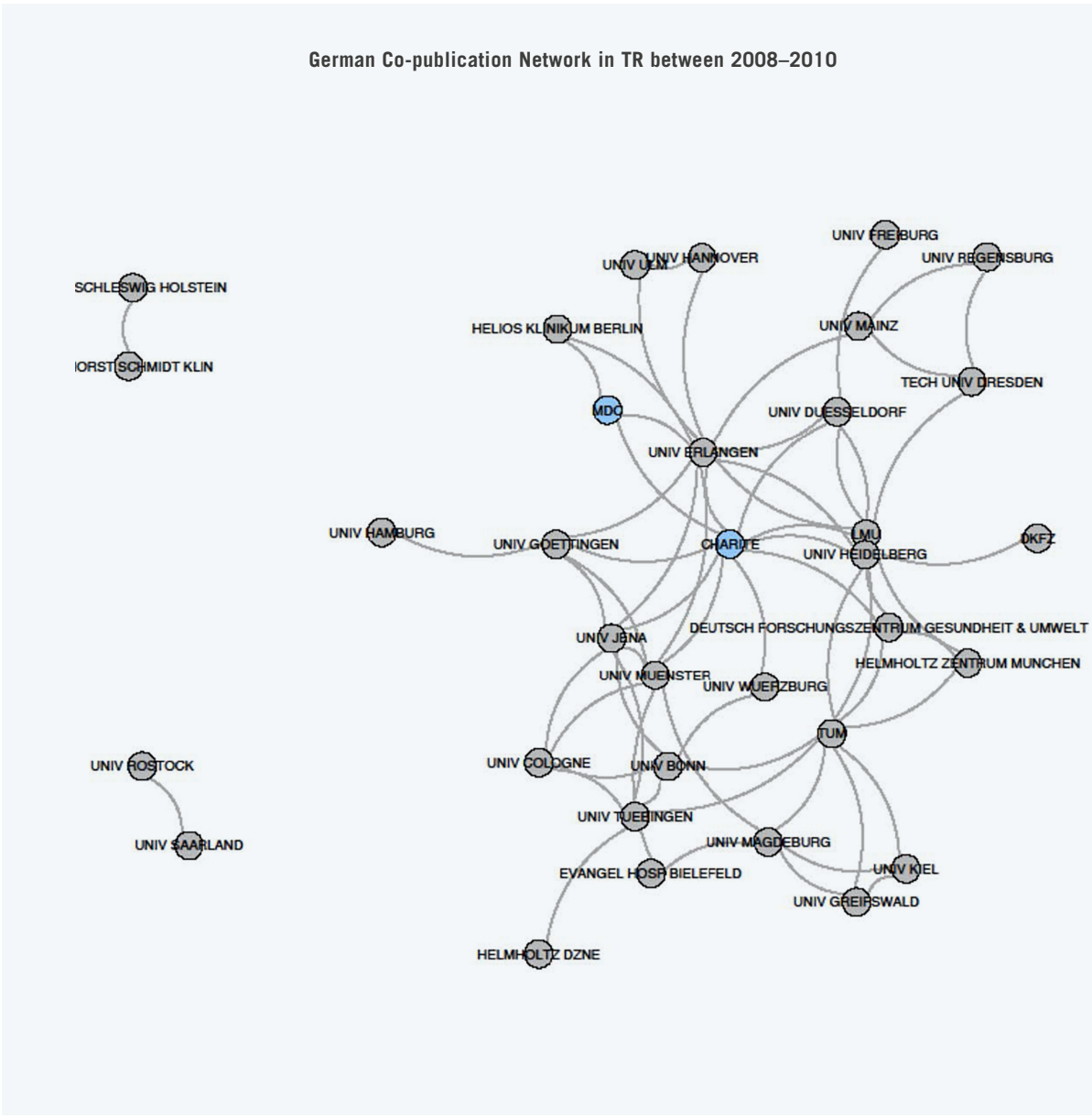

Figure 19: Co-publication structure of German TR-related publications, 2008–2010

The cooperation structures in our case are not random, but can be mathematically decomposed into clusters (see Fig. 20). The results show that cooperation in TR is often organized around localized activities, with closely colocated organizations also being more actively involved in cooperation activities leading to publications. Yet, we find that highly active organizations such as the Charité, LMU, and TUM are also involved in collaborative activities that break with this localized pattern, i.e. they cooperate with other organizations not located in their direct geographical vicinity. These results challenge the implicit assumption that colocation of facilities is an explicit precondition for research activities in TR. Cooperation and the transfer of knowledge between geographically distinct organizations as well as the conditions under which these interactions occur should be analyzed in more detail using both large-scale surveys of authors and practitioners and in-depth qualitative case studies[28].

[28] *How geography and knowledge transfer interact becomes even more striking when taking into account international co-publication activities. Based on our data we can determine that since 2009 approximately 30% of all publications involving German authors have been conducted in cooperation with authors from the United States of America.*

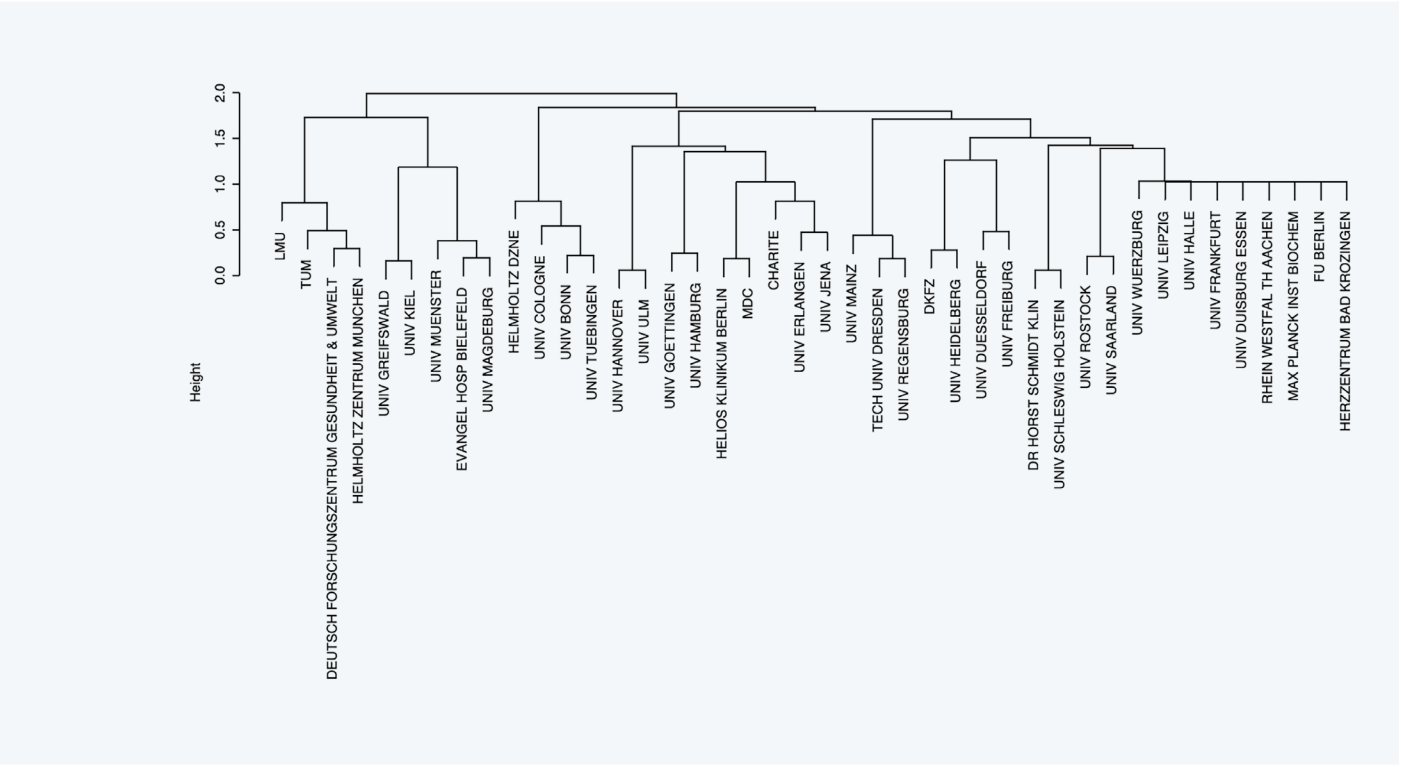

Figure 20: Cluster analysis of co-publication activities, 2008–2010

For the most recent period from 2012 to the first half of 2014, we find an even stronger increase in cooperation activities compared to earlier periods, which again is due in part to an increased publication volume by authors from German organizations (see Fig. 21). The network visualization suggests that recent co-publication activities have led to a strongly integrated German research field in TR comprising a core set of actors as well as a number of less strongly connected organizations.

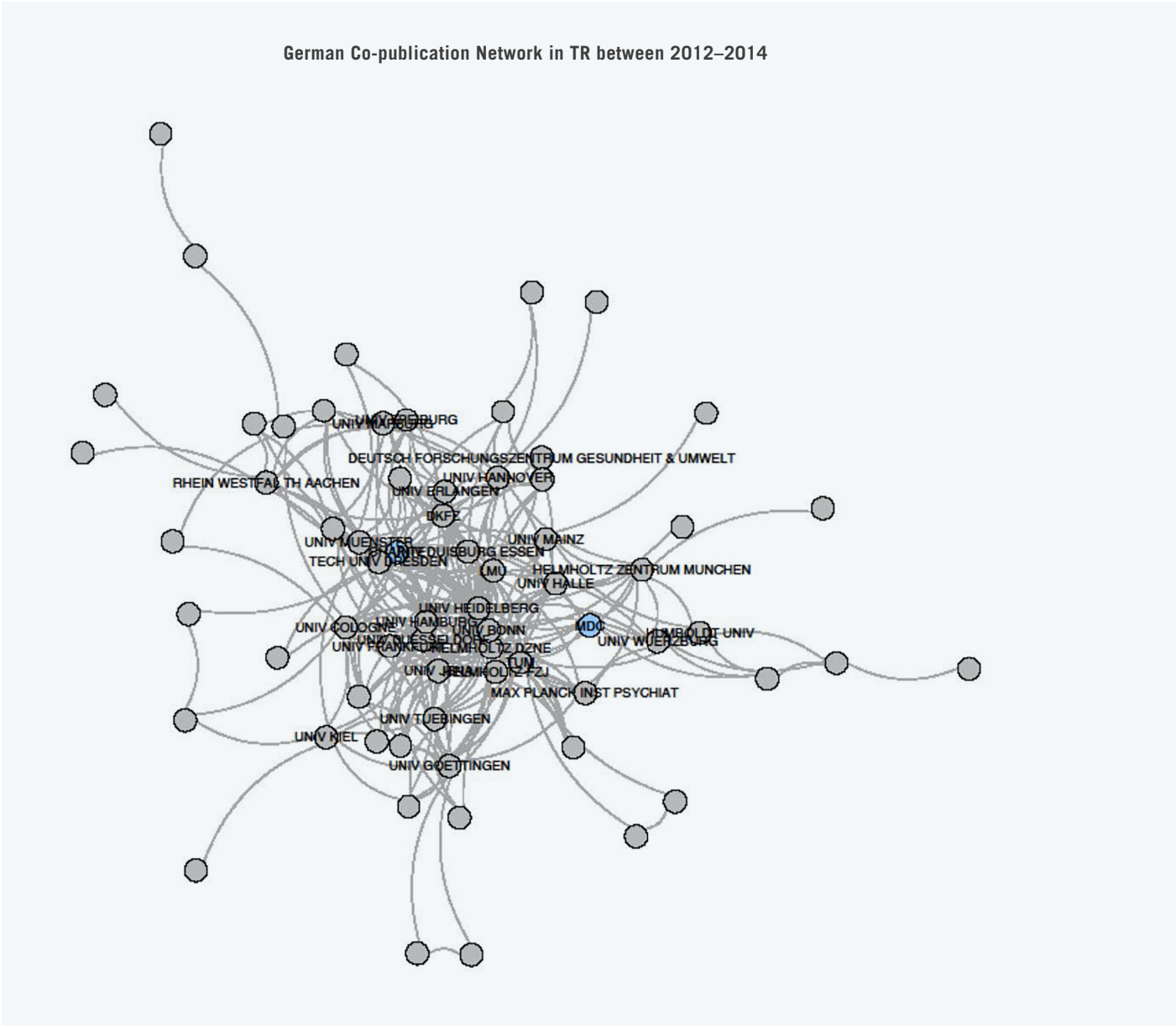

Figure 21: Co-publication structure of German TR-related publications, 2012–2014

The most recent German research landscape based on co-publication activities in TR can be roughly divided into four organizational clusters (see Fig. 22). Interestingly, in this time period geographical co-location seems to play an even less important role in the choice of cooperation partners compared to the period from 2008 to 2010. This observation mostly holds true for players that are strongly connected and that were active in previous periods. Organizations that were not active in previous periods show a stronger tendency to seek nearby cooperation partners. The reason for this pattern might be found in an increased specialization of the field as such, which should also have an impact on the choice of partners, or it could be due to an evolutionary momentum in the choice of cooperation partners. These organizations generally tend to expand their research network over time and develop cooperation strategies that are less oriented towards the co-location of cooperation partners. Either of these propositions is plausible and will be analyzed qualitatively in later stages of the project. The analysis will include questions such as: Which motives are prevalent in the choice of cooperation partners? Which types of knowledge are transferred among cooperation partners? Does knowledge sharing also involve the sharing of procedures and practices of TR-related research and of how TR-related results are implemented?

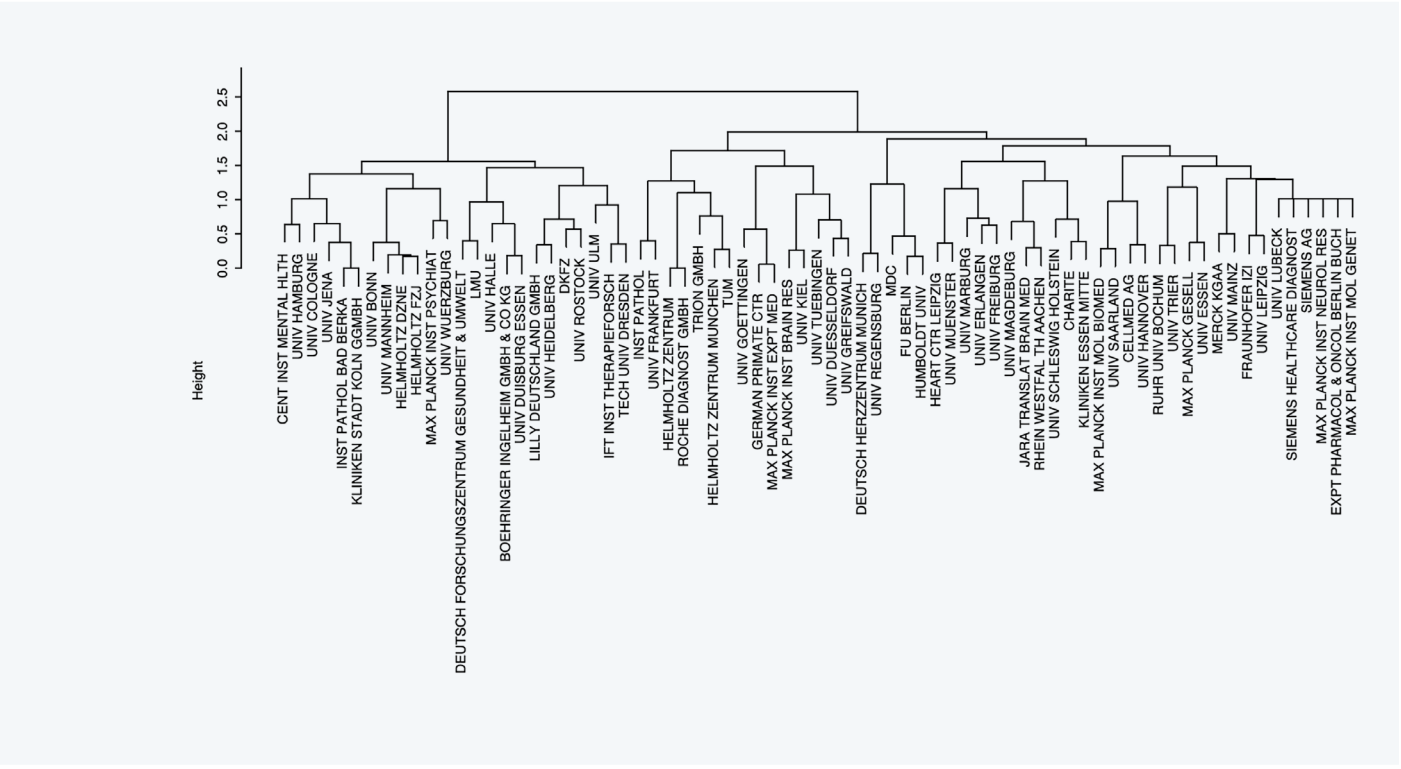

Figure 22: Cluster analysis of co-publication activities, 2012–2014

Besides the analysis of the evolution of the German TR research network, we can also apply selected network metrics related to the network position of the involved organizations for a more indepth analysis. These measures can be used to identify specific traits of each organization involved in cooperation activities, such as the extent of cooperation activities (degree)[29], but also related to their position as boundary spanners, i.e. the tendency of organizations to connect disparate communities in a network (betweenness)[30], and an implicit measure of how "prestigious" organizations in the network are for others (authority)[31].

The results show overlaps among high-scoring organizations based on the three selected measures. Interestingly, the University of Hannover and the University of Göttingen show high "betweenness" values, despite their lower rankings in the other network metrics. This is mostly due to the fact that these two organizations connect larger, less connected subsets of the German community, especially organizations situated in the southern and the eastern parts of Germany. Organizations scoring high in all three metrics are the Munich universities (TUM and LMU) as well as the Charité and the University of Heidelberg. This result also reflects the findings from 2008 onwards from our explorative analyses of network structures. The reason for these outcomes could be attributed to at least two possible causes. One proposition could be that early entrants to the field of TR have a distinct lead-time advantage over later entrants. This leadtime advantage might result in more developed practices in TR as well as a more prominent image as a leader in TR, which in turn attracts cooperation partners. Another plausible proposition could be that the overall prestige of the organizations spills over onto the TR-related activities due to a "halo effect," i.e. the overall prestige of an organization and its prestige in TR are positively correlated. Both propositions are not disjunctive and it might well be the case that both effects interact to further increase the relative position in the network of organizations engaged in TR.

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[29] *It should be taken into account that under certain conditions betweenness and degree measures can be positively correlated in complex networks (Lee 2006).*

[30] *In this study we used a generalized betweenness algorithm, which can also be applied to weighted network data as introduced by Brandes (2001) and further developed by Opsahl et al. (2010).*

[31] *The authority measure captures the idea of prestige from two perspectives. High authority scores are attributed to nodes linked to densely connected nodes while also being densely connected themselves.*

In further research, both effects will be taken into account to increase our understanding of how an organization can achieve a position as a prominent cooperation partner in TR and how strategies could be developed to attain such a position.

Table 4: Ranking of German research organizations active in TR according to selected network metrics, 2003–2014

	Degree		Betweenness		Authority
CHARITÉ	72	UNIV HANNOVER	0.104	UNIV HEIDELBERG	1.000
UNIV HEIDELBERG	70	UNIV GOETTINGEN	0.078	LMU	0.672
UNIV BONN	58	CHARITÉ	0.074	CHARITÉ	0.652
LMU	56	UNIV COLOGNE	0.067	UNIV BONN	0.406
TUM	54	UNIV HEIDELBERG	0.064	TUM	0.290
TECH UNIV DRESDEN	46	UNIV MAINZ	0.059	UNIV HAMBURG	0.199
UNIV GOETTINGEN	46	TUM	0.058	DKFZ	0.188
UNIV HAMBURG	46	TECH UNIV DRESDEN	0.042	TECH UNIV DRESDEN	0.161
UNIV HANNOVER	42	UNIV ESSEN	0.041	UNIV DUESSELDORF	0.134
UNIV MUENSTER	42	UNIV DUESSELDORF	0.040	HELMHOLTZ ZENTRUM MUNCHEN	0.126

4 SUMMARY, CONCLUSION, AND OUTLOOK

Understanding the **multiple meanings of the term Translational Reseach** is a crucial basis to assess different models of TR that focus either on examining the topic in different research contexts or supporting its implementation in practice. We found that it is challenging to describe, define, and pin down the exact meaning of "translation" in medical research, a finding which has consequences for the organization of the translation process. Although "translational research/medicine/science" is framed and often treated as a specific type of research, we could not locate a current common understanding that corresponds with specific practices. What we found instead was a multitude of problems and goals that are addressed by referring to "translation". Given this state of affairs, we derived dimensions related to TR either from a social science or medical perspective. We found **scientific, economic, organizational, moral-ethical, educational as well as policy dimensions to be important in framing the debate** (section 1.3). Most understandings of TR relate one or more of these dimensions, on the one hand, to the well-established problems of *waste in research or the valley of death* or, on the other hand, to solutions to overcome either an innovation gap or an implementation gap. To explain which framing is dominant, we analyzed the policy context of TR (section 1.4). We found that narratives of professional or organizational crisis frame the discourse in the policy field and influence the direction of research by establishing funding programs that steer TR toward becoming a dedicated scientific enterprise. Up to now, the US dominates the policy field by providing a context that has led to the emergence of major scientific players. We supplemented our analysis of the dimensions in the research literature and the framing of the debate in the policy discourse by a bibliometric analysis of the keywords used in the scientific literature. We found that the identified dimensions of the concept can be mirrored, and thus validated, in the keywords of TR-related publications. It is reasonable to assume, furthermore, that funding programs impact the scientific community – especially in cancer research. In order to understand the dynamics of TR, we ran a quantitative analysis of the development of the TR discourse in the scientific literature. We found that TR-related scientific literature is highly dynamic and has reached a level of consolidation with the establishment of core journals. Therefore it is reasonable to assume that **TR is a highly diverse but established scientific topic**.

We found no dominant way of "doing" translational research. Today, there are **multiple and competing ideas about how TR processes and organizations can be organized** (section 2.1). Process models vary according to the respective perception, i.e. definition, of TR. Multiple TR process models are prevalent. These models not only vary according to different research contexts (basic research, preclinical research, clinical research, meta reviews for evidence-based guidelines, clinical practice research, patient-oriented research, population-centered research), but also according to the goals they address. We could also find that process models related to TR have different views on how research is transferred into innovation. Some highlight a linear phase-oriented view of knowledge transfer, while others take a more evolutionary stance. In section 2.2, we analyzed major scientific organizations that are highly active in the scientific discourse concerning TR. Because of the specific policy context in which these organizations are embedded, we focused particularly on the US. Despite the diverging understandings of translational processes and the differences in publishing activities, the results of our qualitative analysis exhibit three fields of similarities in the organizational procedures. These can be summarized as three organizational domains which consist of **collaboration and networking**, of **training and education**, and of **resource provision**. The first domain addresses joining of intramural university actors as well as extramural institutes and organizations. The second domain addresses the qualification of junior scientific staff as well as graduates and postgraduates. The third domain contains several types of resources needed to support and catalyze scientific output like technologies, data, or financial aid.

Bibliometric analyses revealed that the topic of TR increased substantially in relevance during the last decade. We found a strong increase in global publication output as well as an increase in the number of journals that publish TR-related scientific papers. At the same time, we could observe effects of **consolidation in the research landscape organized around a set of core journals** related to TR. For the German landscape, we found an increase in cooperation activities, with the Charité, LMU, and TUM among the most prominent German cooperation partners. We also found a substantial increase in new entrants to the TR publication landscape, which notably consist of smaller hospitals as well as industry players. Furthermore, the analysis of cooperation structures showed that distance seems to play a role in choosing cooperation partners. Yet, the effect of distance as a promoting factor in the choice of cooperation partners declines with the increasing prominence of an organization.

Outlook: Next steps and further research questions

This report raises multiple questions on how TR is organized that can serve as a basis for further research. Given the diverging organizational models in TR, especially regarding how research is transferred into innovation, two questions take center stage. First: What solutions for establishing, organizing, and evaluating TR are employed by different organizations? Based on the current report, it will be important to relate these solutions to the definitions of TR in the individual cases. Second: What can be learned from the field of innovation studies with respect to organizing TR processes? We suspect that the general literature on models of innovation can provide important cues and ideas for research managers in translational research organizations. As the clinician-scientist is identified as a key actor in the TR literature, the question will be raised as to whether this role can be expected to integrate the different organizational tasks and identities. Since the TR literature also stresses novel practices and technologies not primarily related to the clinician-scientist, e.g. scientific infrastructure systems, their importance will also be assessed.

In short, further research should focus on organizational structures and practices found in major research institutions dedicated to TR. Furthermore, the ways in which these institutions fund and promote TR by establishing incentives and evaluation structures should be analyzed. The role of technical systems and infrastructure for TR will be relevant.

Further research should focus on the development of TR. The socio-political context in Germany should be monitored and analyzed as the possibilities and restrictions for TR depend on the way TR is defined in these circles. Given the importance of the policy discourse for the emergence of the institutions in the US, the following questions seem relevant: Which strategies and chances exist for shaping or adapting the discourse about TR in different domains? How can other topics that relate to TR such as personalized medicine or evidence-based medicine be integrated? These questions relate to the interests and framings of different actors active in the field in the context of a changing science policy interface in Germany.

Moreover, understandings of TR and its consequences for the formal organization of TR should be analyzed. Different organizational profiles – as a specific characteristic of the German research system – may result in different expectations as to how TR should be implemented. We therefore propose analyses that will generate data on how various key actors understand TR and how these understandings are interrelated. Hence, further research should focus on how organizational structures and everyday research practices fit with the prevalent understanding of TR.

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6 APPENDIX

Bibliometric Data

The bibliometric analyses in this report are based on a corpus of journals published in the Science Citation Index Expanded (SCIE) and the Social Science Citation Index (SSCI) produced and hosted by Thomson Reuters. Both the SCIE and the SSCI are among the most widely used databases for bibliometric analyses. The SCIE covers publications in scientific journals from all fields of science. The SSCI covers social science publications. Both data sources do not contain all available journals in a scientific field. Rather, journals are included based on an evaluation comprising quantitative aspects related to citation counts of journals and other quality assessment factors.

The identification of TR-related publications represents a challenge, as only such publications can be accounted for that are either published in a specialized journal relating to the topic of TR or that can be identified using keyword-based searches for specific text elements in the respective database. Approaches that combine journal lists and keyword searches have also been used in previous bibliometric studies focusing on the development of TR based on publication data, such as Ma et al. (2014) or van der Laan and Boenink (2012). These types of approaches come with a clear caveat: When publications are neither published in highly specialized TR journals nor retrievable using keyword searches, they cannot be identified in practice and are therefore not part of the corpus used in this study.

In order to compile our publication corpus, we employed a multi-step approach. In a first step, we selected a list of journals with a clear focus on TR from the complete set of journals contained in the SCIE and SSCI. This list includes the following journals:

- STEM CELLS TRANSLATIONAL MEDICINE
- SCIENCE TRANSLATIONAL MEDICINE
- CTS CLINICAL AND TRANSLATIONAL
- SCIENCE TRANSLATIONAL
- RESEARCH JOURNAL OF TRANSLATIONAL MEDICINE
- TRANSLATIONAL PSYCHIATRY CLINICAL & TRANSLATIONAL
- ONCOLOGY JOURNAL OF CARDIOVASCULAR TRANSLATIONAL
- RESEARCH PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE
- TRANSLATIONAL NEUROSCIENCE
- TRANSLATIONAL ONCOLOGY
- TRANSLATIONAL STROKE RESEARCH

In a second step, we developed an initial set of keywords based on the qualitative assessment of the current literature, including publications but also policy-related documents and gray literature.

In a third step, we used a combined database query to extract scientific articles published in the core journal set compiled in step 1 and retrieved using initial keywords identified in step 2 to build a preliminary corpus of journal publications.

In a fourth step, we performed an n-gram analysis of the titles and abstracts in the preliminary corpus with a maximum of four words appearing in succession to find further keywords. We conducted a parallel qualitative analysis of a sample of abstracts and titles. Keywords were chosen according to their specificity to the field of TR. Keywords that were not specific enough to delineate the topic of TR were excluded. In order to attain better coverage, keywords were truncated and the impact of truncation tested using database queries. The final list after processing comprised the following keywords: “translational res* OR translational medic* OR translational science* OR Investigator initiated trial OR bench to bedside OR bedside to bench OR bench-to-bedside or bedside-to-bench OR (translat* AND clinical trial*) OR t-phases OR knowledge translat* OR clinical translat* OR (translat* AND (study or studie*)”. Additionally, the keyword “knowledge translat*” was included while also limiting the search to medical journals.

In a fifth step, a statistical analysis of journal titles was conducted based on the preliminary journal set to identify further journals that explicitly feature only TR-related titles. As a result, no further journal explicitly related to TR could be identified.

The sixth and final step used the refined keyword list from step 4 and the journal list from step 1 which were combined to produce the final corpus. This final corpus consists of a total of 8133 scientific articles and furnishes the basis for all bibliometric analyses conducted in this study.

NIH Institutes and Centers

Table 5: NIH Institutes and Centers

	NIH Institutes and Centers	Year of Est.
Institutes	National Cancer Institute (NCI)	1937
	National Eye Institute (NEI)	1968
	National Heart, Lung, and Blood Institute (NHLBI)	1948
	National Human Genome Research Institute (NHGRI)	1989
	National Institute on Aging (NIA)	1974
	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	1970
	National Institute of Allergy and Infectious Diseases (NIAID)	1948
	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)	1986
	National Institute of Biomedical Imaging and Bioengineering (NIBIB)	2000
	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	1962
	National Institute on Deafness and Other Communication Disorders (NIDCD)	1988
	National Institute of Dental and Craniofacial Research (NIDCR)	1948
	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	1950
	National Institute on Drug Abuse (NIDA)	1974
	National Institute of Environmental Health Sciences (NIEHS)	1969
	National Institute of General Medical Sciences (NIGMS)	1962
	National Institute of Mental Health (NIMH)	1949
	National Institute on Minority Health and Health Disparities (NIMHD)	1993
	National Institute of Neurological Disorders and Stroke (NINDS)	1950
	National Institute of Nursing Research (NINR)	1986
Centers	National Library of Medicine (NLM)	1956
	Center for Information Technology (CIT)	1964
	Center for Scientific Review (CSR)	1946
	Fogarty International Center (FIC)	1968
	National Center for Complementary and Integrative Health (NCCIH)	1999
	National Center for Advancing Translational Sciences (NCATS)	2011
	NIH Clinical Center (CC)	1953

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