

# Repairing the 'Broken Middle' of the Health Innovation Pathway: Exploring Diverse Practitioner Perspectives on the Emergence and Role of 'Translational Medicine'

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The emergence of Translational Medicine (TM) as a potential solution to health innovation challenges has gained currency in scientific, clinical and policy discourses. Using interview data from key professionals involved in TM, this article explores diverse practitioner definitions and the multiple meanings ascribed to TM in the context of a purportedly broken R&D system and promissory visions and expectations built around new life science. It also begins to address some of the transformative impacts of TM on the broader institutional landscape for life science innovation, particularly the changes in traditional institutional boundaries. I conclude that in light of the multiple framings of TM, it might best be conceived as an institutional mechanism or process for co-ordinating multiple actors and complex activities in the new collaborative research and development contexts now demanded of the life sciences.

*Keywords:* Translational Medicine, R&D, innovation

## **Introduction**

Over the past 15-20 years Translational Medicine (TM) has become an omnipresent concept in the healthcare and life science sectors. It is employed as a broad, often ambiguous, metaphor to describe new ways of organising and funding R&D activities in the biosciences, with clinical application the primary goal. It is also used as a term that encompasses more tangible new technologies and approaches to drug development and clinical practice, such

as biomarkers and associated diagnostic testing. TM is presented as a new solution to what is perceived to be a growing problem in health innovation: namely a widening gulf between basic science in the laboratory and its successful application in the clinic.

The impetus for TM's arrival and subsequent entrenchment in science, policy and clinical discourses (FDA, 2006; MRC, 2008; Cooksey, 2006), appears to be the continuing problem that insufficient novel therapies successfully transition from the lab to the clinic. What we might call the 'broken

middle' of therapeutic R&D has emerged as a powerful problem narrative that the pharmaceutical industry, in particular, believes is rooted in the complexity, risk and uncertainty of phase 2 clinical studies. This compounds a number of 21<sup>st</sup> century global health challenges (Tait et al., 2008), including industry's continuing productivity crisis and perception of innovation deficit (Mittra, 2008). The response has been unprecedented investment from both commercial and public sectors in various 'translational activities' (individual projects, funding mechanisms, and new R&D units/collaborative partnerships). Firms respond to the problem of mature product pipelines (Mittra et al., 2011) and an unsustainably high attrition rate of therapies in phase 2; while the public sector appears to push an expansive, downstream R&D agenda in biomedical sciences to deliver sustainable solutions for various public health challenges (BMJ, 2008).

The central aim of this article is to explore different practitioner perspectives on the nature, role and value of TM in the context of these perceived challenges of the health innovation system, and consider some of the implications for the organisation of health R&D. How are diverse practitioner narratives being mobilised to frame 'the problem' of a broken health innovation pathway; what assumptions do these narratives make about the relationship between basic and applied science; and how has TM emerged as a potential panacea? While the primary focus is on the UK, where most of the primary data was collected, relevant developments in the United States are also considered, particularly the institutional and policy context of funding new translational initiatives.

Theoretically, the paper draws on the literature of hopes and expectations and the ways in which these shape and mobilise various resources in translational life

science R&D (Borup et al., 2006, Martin et al., 2008), as well as a broad critical literature that has dealt with the changing relationship between basic and applied science, the limitations of the conventional linear or pathway model of innovation, and notional ideas of value in life science (Stokes, 1997; Tait & Williams, 1999; Williams, 2006; Birch, 2012). These approaches are used initially to frame the 'broken middle' narrative and critically assess subsequent arguments that are strategically co-opted by different actors and institutions to justify the need for new translational processes and activities. At the end of the article, I will draw some conclusions about the broader impacts of this expansive and often opaque TM agenda on the organisational and institutional landscape for health R&D. Although the data reveal that the definition of TM is not unitary, and as a concept may often be chaotic and ephemeral, I conclude that it appears to be engendering real and potentially indelible changes in biomedicine and therefore should not simply be dismissed as mere hype.

Empirically, the paper draws on the author's data from 20 in-depth semi-structured interviews conducted with senior academic life scientists, academic clinicians, NHS directors, and representatives from the pharmaceutical industry and the policy/regulatory community. Many respondents had dual roles and had worked in different sectors. Most were either actively involved in projects or collaborative partnerships labelled as TM, or had clear professional interests at the interface between the laboratory and the clinic. 16 interviewees were based in the UK, while 4 were from outside the UK, including the Netherlands (1 interview) and the United States (3 interviews). The UK-based interviews tended to focus on specific TM initiatives in the UK, whilst the US-based interviews tended to focus on more general issues

relevant to TM in both national and global contexts. Although not a fully representative sample, which was never the aim of the project for which the data was collected, the interviews provide rich accounts of the salient features of TM; its various drivers, definitions and meanings; and the enduring impact on biomedical research in a number of different research and clinical contexts. Furthermore, relevant policy documents and grey literature from the UK and United States are used to reveal some of the broader sectoral interests and values that circulate around TM.

The article is structured as follows. The first section critically explores the notion of a 'broken middle' in health innovation, which foregrounds the emergence of TM and its subsequent framings in different professional and institutional contexts. This section will highlight the different drivers of TM and consider the broken middle of R&D, and its assumptions about the linear model of innovation and relationship between basic and applied science, as a recurrent 'problem narrative' that presupposes TM as a viable solution.

Next, interview data are used to explore practitioners' discursive narratives for framing TM and its practical and conceptual boundaries. What do key actors consider the most salient features of TM and what are their long-term hopes and expectations for the field? This section will identify both narrow and broad definitional frameworks for TM. The centrality of 'biomarkers' in contemporary discussions about the potential value of TM will then be explored. The ways in which practitioner narratives become structured around the value, benefit and limitations of trying to reconfigure the R&D pathway according to 'translational' principles will become evident in this section.

In the conclusion, I will reflect on some of the broader organisational and

institutional changes engendered by TM and the multiple meanings different actors and institutions have ascribed to it. Ultimately, TM will be presented as an institutional mechanism for coordinating multiple professions, knowledge domains and economic/scientific activities within new organisational contexts; a kind of 'social technology' in Nelson and Sampat's terminology (Nelson & Sampat, 2001).

### **The 'Broken Middle of R&D' Narrative and its Role in Shaping the Translational Medicine Agenda**

The emergence of TM in the mid 1990s as a set of diverse strategic initiatives to facilitate health innovation was engendered by growing concern that despite unprecedented investment in life sciences, coupled with the growth of scientific knowledge around the cellular and physiological mechanisms of disease, many promising therapeutic products in early stage drug development fail to make it to market. Furthermore, few new therapies that do make it through the regulatory system become widely adopted as the clinical standard (Milne, 2009). There is a prevalent belief that healthcare innovation is stymied by a constellation of scientific, clinical, social, policy and regulatory challenges. An increasingly powerful and pervasive rhetoric in industry and policy circles is that between discovery and the clinic (specifically phase 2 R&D) many drugs fall into what some have labelled 'the valley of death,' characterised by a chronic disconnect between the knowledge, findings and expertise of research scientists in the lab and those of clinicians at the bedside (Nature, 2008). This problem, which presupposes a particular view of the historical relationship between bench and bedside and the very structure of the innovation pathway, has shaped certain expectations and hopes around TM.

***The Basic/Applied Science Distinction and Assumptions about the Conventional Health Innovation Pathway Model***

Kraft (2013) argues that the ostensibly tenuous relationship between lab and clinic has long been viewed by policymakers as a barrier to therapeutic innovation and has become a key target for new interventionist strategies from all sectors involved in health innovation. Both industry and the public sector are embracing the philosophy and promissory visions of TM as a central strategy for driving improvement of the health innovation cycle, which is considered to be fundamentally broken (Mitra & Milne, 2013). However, a more sceptical literature has begun to question the novelty and underlying assumptions of TM and the purported notions of value and benefit that resonate within an expectant biomedical research and clinical community (Birch, 2012; Birch & Tyfield, 2012; Martin et al., 2008).

Furthermore, questions must be asked about the implicit assumption of a fixed and linear health innovation pathway, and the conventional distinction between basic and applied research, which is couched within the rhetoric of a broken middle of R&D and the concept of 'translation' itself. The hopes and expectations that have been built around new life science and TM approaches, which are driving the organisation and management of institutional resources, may be based on unrealistic or untested assumptions both about the science and technology and the nature of R&D (Terwilliger & Goring, 2009).

Stokes (1997) nicely critiqued the traditional linear model of innovation, and the conventional distinction made between basic and applied research, by looking at a number of historical examples, such as Pasteur's work in microbiology, which was simultaneously basic and applied research. There is also growing evidence to suggest

that the past portrayal of therapeutic R&D as linear and one directional, in contrast to the now more dynamic and novel TM approach, never reflected realities on the ground. For instance, Martin et al. (2008) have noted that historically the application of basic science never was the caricatured one-directional process often presented. The authors cite Lowry's account of cancer therapies using interleukin 11, which required significant contributions from both clinicians and patients (Lowry, 1997). Another example is Banting and Macleod's 1922 discovery of insulin as a treatment for diabetes, which moved back-and-forth from animal models to first-in-man studies and involved many of the interdisciplinary and cross-sector collaborations that are often heralded as the cornerstone of TM. Furthermore, the very notion that a problem exists at the lab-clinic interface was recognised in the early 1970s, as Woolf (1974) noted in a *New England Journal of Medicine* editorial in 1974. The leitmotif of linearity in retrospective accounts of applied basic science does not seem to correspond to scientific practice, which begs the question of what is new in contemporary attempts to reconfigure or fix the lab-clinic interface.

Although health innovation is not the crude linear process that is often portrayed, as the basic and applied sciences are not temporally and spatially distinct as often assumed, the linear model is still routinely used to frame biomedical R&D. The linear stages of therapeutic R&D are perhaps more a representational artefact of the regulatory regime, which demands the presentation of research in distinct, sequential phases. This elides the parallel processes and heterogeneous actors and innovation networks that actually shape R&D, as described in detail by Hara (Hara, 2003). The concept of linearity, which is easily reified through casual rhetoric of translational gaps in drug 'pipelines', therefore continues

to drive much R&D policy and management (Tait & Williams, 1999; Williams, 2006). An alternative to viewing innovation in these crude linear terms is to consider broader innovation value systems and the various feedback loops and contingencies that shape and influence individual value chains, as discussed recently by the author and others in Mastroeni et al. (2012). One interview respondent from the policy community captured this problem with the linear model when he stated:

I think one of the challenges in this whole area is that the linear model of drug development is overly simplistic and, whilst it had enormous strengths in persuading those in the Treasury as to where the gaps might be, in the real world scientific discovery or even therapeutic development is in no way as simple as that (POL1).

This tension between linear models of innovation, bench to bedside relations and the novelty of TM will become more apparent later when practitioner narratives on the role and scope of TM are explored. For now, I simply emphasise that discussions about basic and applied research; assumptions of linearity in R&D, and expectations that ‘translation’ might fix the problem of the broken middle are closely connected and foreground the many different framings of TM as well as the institutional and organisational practices of those sectors involved in biomedical innovation.

### **The Foundations of the ‘Broken Middle’ Narrative**

Arguments claiming there are translational gaps in the health innovation system tend to focus on specific hurdles and constraints along the conventionally understood ‘bench-to-bedside continuum’, which

makes it easy to slip into the casual rhetoric of a broken middle that can in principle be fixed by TM. Hurdles that are routinely highlighted include not only cultural, institutional and economic barriers that can inhibit successful translation of discovery science into viable clinical products, but also more tangible challenges facing drug developers. These include lack of sufficient efficacy and safety in phase 2 clinical studies, onerous and costly regulatory systems; rising R&D costs, patent expiry on blockbuster drugs with few products to replace them; and the organisational challenge of moving from small-molecule to life science-based R&D (Mittra, 2007).

Mature product pipelines and the difficulty of identifying viable business models for novel life science therapies appear to be contributing to industry’s growing anxiety about R&D and long-term sustainability of blockbuster drug development. Although there is debate about the nature and extent of ‘innovation deficit’ in the pharmaceutical industry - some authors ask if declining innovation is actually a myth (Schmid & Smith, 2005), and others maintain that reduction in R&D productivity is the result of a concentration of R&D efforts in high risk research for unmet medical need, rather than a lack of innovation (Pamolli, 2011) - there is little doubt that companies believe that they are no longer producing sufficient high-value therapies to sustain growth. Furthermore, ‘productivity’ from in-house R&D is evidently falling according to the bibliometric analysis conducted by Rafols et al. (2012). The so called genomics revolution has also yet to prove the panacea for industry woes and bring about a truly revolutionary era of biotechnology-based therapeutics (Kraft, 2004; Hopkins et al., 2007). Data reveal that the number of new drug approvals has continued to decline since the mid-1990s, despite increasing

year-on-year investment in R&D (Kaitin, 2010). Additionally, less than 25% of promising biomedical discoveries result in published clinical trials and less than 10% become established in clinical practice within twenty years (Drolet & Lorenzi, 2010). Many stakeholders consider there to be a fundamental problem with the prevailing blockbuster model of drug development. An industry respondent, for example, stated:

...there isn't a good business model for the current paradigm [blockbuster drug discovery and marketing to large, undifferentiated patient populations] ... people who think there will be pharmaceutical companies in 10 years' time doing what they do today I believe are seriously mistaken, and you can see that the stock markets to a large degree agree with that position ... individual companies with other areas of commercial activity are also reducing their investment in pharmaceuticals ... I don't think there is a [shared] business model of how we're doing things along the whole R&D pathway ... we need to understand mechanisms, we need to understand the patients that we give our products to, and only then can we create any kind of product. (IND3)

The notion of a broken drug innovation system has also been discussed in a number of reports by scientific organisations (AMS, 2011; Cooksey, 2006), regulatory agencies (FDA, 2006) and funders of medical research (MRC, 2008; NIH, 2010; NIH, 2011), which reflects the diverse set of interests and systemic issues at stake, so this should not be considered merely a concern of the multinational pharmaceutical industry. All tend to agree that there are entrenched problems in the middle stages of R&D requiring support for greater 'translational activities' and

the development and uptake of new tools to enhance drug discovery, development and regulatory processes. A key issue identified in these reports, and a canonical theme in much of the TM literature, is the identification and validation of 'biomarkers' to facilitate drug development and delivery, which will be discussed in more detail later. Central to many of these discourses are imagined futures in which the exploitation of technologies within a new TM framework contributes to solving the current challenge of a broken R&D system and brings benefit to industry, patients and broader society in terms of improved therapies and economic return on innovation. Indeed, there are a number of drivers and strategic priorities for TM being put into practice by different constituencies, each with their own expectations and notional ideas of value and benefit. These should not, as many authors have argued, be simply discounted as hype (Morrison & Cornips, 2012; Brown et al., 2000).

### **Industry, Academic and Policy Drivers and Expectations for TM**

As both a general overarching philosophy and set of concrete practical activities, TM has acquired increasing status in academic medicine, the biopharmaceutical industries and policy/regulatory communities to capitalise on life science investments; contribute to what is now considered a growing knowledge-based bioeconomy (OECD, 2009); and provide tangible benefits in terms of safe and effective therapies for unmet medical need. Casting a more critical gaze on such narratives, we can observe different notions of present and future value being mobilised across nuanced scientific, clinical, commercial and political landscapes. To be sure, despite enormous investment in resource, infrastructure and training; there is, as we shall see in the next

section, little consensus on the definitional and conceptual boundaries of TM; its scale, scope and role in clinical practice; and what it can realistically deliver. This is partly a result of different TM practitioners using the term in a variety of institutional and professional contexts, such that a simple, unified vision of its key aims, objectives and ultimate goals is yet to emerge. Lack of consensus may become a problem if incompatible visions and expectations (Borup et al., 2006), based on unrealistic assumptions about bench to bedside research, become entangled within emerging institutional and organisational structures. It is also important to reiterate that many of the practices underpinning TM are not new, but simply a recasting of conventional historical practices, as the examples provided earlier testify. But there are essentially three key constituencies pushing a broad TM agenda.

For the biopharmaceutical industry concerned about phase 2 attrition rates, TM has acquired several meanings and driven a range of organisational and management strategies. There are now TM units within most major pharmaceutical firms. In some, TM groups facilitate direct connection between basic research and patient care to address key questions about how therapies will work in the clinical setting. This is the 'patient-centred approach' and includes attempts to perform first-in-human studies much earlier in the development process, as described by Milne (2013). Firms have also tried to bridge the gap between late discovery and early clinical development to de-risk candidate selection and improve decision-making on what products to take forward into clinical trials. TM units have also served as conduits for accessing external knowledge, technologies and expertise through collaborations (Mittra, 2007). Industry is essentially experimenting with various TM initiatives to improve the *business* of drug development, and respond

to the pressures being placed on blockbuster drug discovery.

Academic science and clinical medicine are driving the TM approach ostensibly to exploit the range of new technologies emerging from life sciences and encourage communication and sharing of knowledge and expertise between the bench and the bedside, which are considered to have become too intuitively and culturally distinct. Many scientists and clinicians believe a gulf has emerged as a consequence of increasing specialisation on both sides, so TM is embraced as a mechanism to better coordinate and integrate research and clinical activities. The resurgent interest in the role of the 'clinician-scientist' (a professional equally adept at working in the lab or the clinic) is indicative of this broader concern about the lab/clinic interface (Wilson-Kovacs & Hauskeller, 2012). The academic and clinical sectors have built hopes and expectations around a particular vision of TM that they hope will help improve understanding of key mechanisms of disease and diagnostic procedures. This contrasts with the more narrowly focused commercial expectations of industry. A senior academic clinician that was interviewed described the academic drivers and interests in terms of 'practical problem-solving driven by scientific curiosity' (SC2).

Finally, there are complex assemblages of social, regulatory and policy drivers of TM centred on the safety and cost-effectiveness of new drugs. TM is promoted by the policy community as a means to (1) facilitate innovation of novel therapies and improve standards of safety and efficacy, for instance through the use of biomarkers and new diagnostic testing; (2) improve the design and execution of clinical trials by utilising improved preclinical knowledge; and (3) contribute to the growing bioeconomy through investment in new innovative technologies and therapies. Consequently,

there has been substantial government and charitable investment in translational R&D in universities and other public sector organisations; particularly from the MRC in the UK and the National Institutes of Health (NIH) in the United States. The NIH's \$575m investment in the National Center for Advancing Translational Sciences (NCATS), with a remit to catalyze innovations in translational science to improve innovation in drugs, diagnostics and devices, is indicative of the science and policy community's growing commitment to the field (NIH, 2011). Indeed, one could argue more cynically that TM was pushed by the policy community as a means to channel public funds to downstream drug development processes without having to explicitly state as such, which would not be politically expedient.

That there have been different imperatives driving TM and strategies for implementing it, reflects both the range of different sectors' needs and expectations, as well as their understanding and framing of the core problem. Nevertheless, there appears to be consensus that a systemic problem exists in the middle stages of health R&D that requires new approaches in terms of science, technology, infrastructure and organisation. Indeed, a basic lexicon for TM has emerged, with the latest model expounding 3 distinct phases of translation. **T1** refers to the translation of basic science into clinical efficacy and is focused on the early stages of drug discovery and preclinical testing. **T2** refers to efficacy translated to clinical effectiveness, and focuses on the middle stages of R&D. **T3** refers to effectiveness translated to health care delivery, so is very much rooted in late stage development (Dougherty & Conway, 2008). Drolet and Lorenzi (2010) take this approach further by distinguishing a 'zone of translation' that is an intermediary

between basic science and accepted clinical practice/overall societal health impact. For these authors, T1-T3 represents particular 'chasms' in research progression along the bench-to-bedside continuum and translational research refers to those specific activities aimed at bridging the chasms. Although this is quite a linear description of TM, it highlights some of the different sites and interstices of knowledge where practitioners believe better translational is required. It is with this general TM framework in mind, and understanding of what is driving the approach, that we can begin to explore practitioner narratives in more detail.

### **Practitioner Narratives and the Different 'Framings of Translational Medicine**

In this section, I analyse the underlying definitions and framings of TM from the perspective of different TM practitioners, before exploring a specific and crucial focus of TM, namely the identification and use of biomarkers. The value currently ascribed to biomarkers, and high expectations about their role in mitigating phase 2 attrition rates, further highlights the power of the broken middle argument.

The definition of TM and its conceptual and practical boundaries is a topic of much debate within biomedical science and policy communities. The T1-T3 model simplifies quite complex and diverse beliefs and understandings of the R&D challenge and appropriate scientific, clinical, regulatory, social and institutional responses. On definitions and boundaries, a number of views emerge from the scientific literature and interview accounts of key professionals, which map on to one or more aspects of the T1-T3 model. Definitions range from the specific to the general and



can cover 'organisational processes' as well as 'scientific application'. One interview respondent (head of the translational department of a major funding agency) argued that for his organisation, translational *research* is not area of science, but a process of bi-directional knowledge flow from fundamental research to application and back again. Note here again the implicit assumption of a distinction between basic and applied science that are temporally separate. Translational *medicine*, in contrast, is a sub-set of research focused on what has traditionally been called 'experimental medicine'. It is interesting to note that the definition of experimental medicine, like TM, is also open to some debate. Some believe it should encompass epidemiology, whilst others think it should be limited to small patient studies, according to this respondent. Nevertheless, terms are used interchangeably by practitioners of TM and different framings may cover organisational or institutional processes as well as specific applications of science and technology.

### ***Narrow Definitions/Framings of TM***

Narrow framings of TM tend to emphasise the concept of 'applied basic science' and are often life science-focused. For example, TM has been described as a process for determining treatment based on molecular biological characteristics (Saijo, 2002) or as the 'translation of genomic and functional biology discoveries into clinical practice' (Niederhuber, 2010: 1088). A common trend has been to reduce TM to a discrete set of genomics-based techniques and applications that can serve as a conduit for integrating different types of knowledge and expertise at both the bench and the bedside. One senior academic interview respondent stated: 'I think that the definition currently of translational medicine is probably DNA-based or protein-based type of biomarker

studies.' (SA7). Another senior academic emphasised the benefits of this narrow and clearly delineated definition when he stated:

I think in many ways translational medicine is a very murky term ... I think that a narrower definition gives some clear goals and directives and ways of unifying the academic and industrial community in partnership (SA5).

Here, the importance of clearly defined outcomes from academic-industry collaborations is presented as a key feature in scoping the boundaries of TM, which is very much an output or goal-oriented view of TM.

There also appear to be some sector-specific framings, with the pharmaceutical industry very much reducing TM to the process of commercial drug development. An interview respondent that heads a commercial clinical trial company gave the following account, which is very much rooted in a commercial bench-to-bedside notion of TM.

What we're looking at is taking something that perhaps is defined at bench level in terms of a particular drug or something that targets a particular site and then that is developed through a whole range of processes to the point where it can be accepted as a potential drug target to work on through a pharmaceutical company, and then eventually into the clinical side. So the way that we would define TM is taking something that is very much research-oriented and translating that into a commercial product. (IND4)

Similarly, another industry respondent stated that TM was simply:

Translating experimental findings in the laboratory through to clinical findings in the hospital setting ... we're trying to develop drugs to treat established diseases and we need to predict what might happen in the clinic (IND1).

Responses from industry suggest it adopts a process-driven approach to TM with a clear commercial focus on improving efficiency of R&D and reducing phase 2 attrition. This narrative is rooted in the notion of a bench-to-bedside continuum, and assumes that in the middle stages of a sequential R&D process there is a fundamental problem that needs to be fixed.

In contrast to this commercial view of translation, the clinicians framed TM predominantly in terms of using life science technologies to improve diagnosis and categorisation of disease. One senior clinical psychiatrist stated:

The studies we have done to identify genes in schizophrenia, bipolar disorder and depression can all be considered highly translational because they are aimed at identifying sub-populations of psychiatric diagnoses to improve treatment studies ... Our [current] diagnostic categories don't have any real biological validity. If genetic studies lead to clearer diagnoses in psychiatry this will translate into better treatment studies. (SC1)

This account presents TM as invaluable for exploiting life science tools and technologies to better categorise clinical disorders and ultimately improve patient treatment, which was a recurrent theme in the accounts of both academic scientists and clinicians.

These narrow framings of TM prioritise the science, technology and clinical processes of TM, rather than the broader institutional

and system-level dynamics that are perhaps more relevant to implementation and exploitation of new organisational models. They also appear to reify the bench-to-bedside continuum (with the conventional demarcation of basic and applied research), in the spirit of the T1-T3 model. There is little or no emphasis on feedback loops from the clinic to the lab, or the parallel processes that can often be temporally and spatially disjointed in modern health innovation.

### ***Broader Framings and Emphasis on the "Bench-to-Bedside and Back Again" Process***

Some authors consider the one directional bench-to-bedside approach to TM outdated and unhelpful. Instead, they define TM as a two-way iterative process from bench-to-bedside and back again, with knowledge, information and expertise continually shared between clinicians and lab scientists so that patient data can explicitly inform basic science (Ledford, 2008; Soderquest & Lord, 2010). Mankoff et al. (2004) have argued that the uni-directional definition fails because animal and other experimental models are not truly representative of human pathology. Many interview respondents countenanced the view that a feedback loop from bedside to bench is crucial. An industry respondent stated:

First of all it goes both ways, because a lot of the stuff that we have discovered from doing this in humans [treating with experimental drug] was then translated back into the lab. It's not uni-directional. (IND5)

Similarly, a respondent from the policy community argued that this way of framing TM takes us away from crude, linear accounts of R&D. He stated:

The translational medicine element that I think is really beneficial is the fact that, rather than it being a linear process, there is this two-way feedback ... the science is definitely being influenced by patient accessibility in application. (POL4)

Rubio et al. (2010) have developed a broad working definition of TM, which emphasises multidirectional integration of basic research, patient-oriented research, and population-based research with the long-term objective to improve public health. For these authors, population-based research includes studies involving epidemiology, as well as social and behavioural sciences, public health equality evaluation and cost-efficiency. The US NIH (National Institutes of Health, 2010) considers research that facilitates the use of best practice healthcare within the community and ensures cost-effective treatment of disease an important component of TM, which goes slightly beyond the T3 phase of translation. Here, we are beginning to get towards a fuller and more systemic account of translation. As one academic scientist stated:

My understanding of translational medicine is converting fundamental biomedical discoveries into practical solutions for health problems. Mostly it's in the form of drugs, but it's also in terms of policy and other things. So, the discovery that smoking is bad for your health was a major translational achievement where somebody's fundamental epidemiological studies followed up by some animal experimental studies clearly indicated that smoking was bad for your health, and was perhaps the major component of lung cancer. And that's been reinforced over the years and given rise to policy change, which has given rise to measurable ben-

efit. That's an example of translation in the policy field. (SA6)

This account exemplifies the broader institutional policy dimension and presents TM as about much more than the conventional drug development pipeline model.

This range of views suggests that TM should be characterised as a general organising principle, or 'social technology' in Nelson and Sampat's terminology, to drive the development of new scientific methods and technologies, innovation strategies and collaborative institutional arrangements to better bridge or integrate basic and clinical science and facilitate knowledge and information transfer from bench to bedside and, crucially, *back again*. However, even if we consider TM in this broadest sense, the question still arises as to whether there is anything novel in the current practices based on the 'bench-to-bedside and back again' philosophy, and whether the very distinctions made between basic and applied phases of R&D adequately reflect the messy realities of contemporary life science innovation and the challenges that lie therein.

### ***The 'Novelty' of TM Practices in the Context of the Bench to Bedside 'Problem'***

As was discussed earlier, the conventional view of basic and applied science, and the caricatured accounts of bench-to-bedside relations that are used to present TM as novel and cutting edge, are largely based on a misrepresentation of the history of clinical medicine and the professional and institutional boundaries between laboratory and clinic, as a number of authors have nicely illustrated (Hoonard, 2009; Martin et al., 2008; Stokes, 1997; Sturdy 2012). Sturdy, for example, argues that the tensions and conflicts between clinicians and bench scientists are often overstated

in historical accounts, which implies that the problem of a broken middle has also perhaps been overstated, or provided only a partial account of the health innovation challenge. Indeed, many of the barriers to successful health innovation, particularly in the context of novel life science innovation, are broad and systemic, such as the impact of regulation, markets and clinical uptake on innovation strategies (Tait, 2007, Mittra, 2008; Mastroeni et al., 2012). From this perspective, a TM approach focused only on a particular set of technology and knowledge integration problems in the middle stages of the drug pipeline will not be sufficient.

Similarly, Martin et al. (2008) draw on the concept of 'communities of promise' to help us think more critically about the supposed new configurations between basic research and the clinic that coalesce around particular socio-technical objects. Using stem cells as a case study, the authors point to the ways in which narratives are often structured around expectations about how clinical developments emerge and idealised assumptions about the distinctive roles of basic science, clinical science and the commercial sector. The discourse of 'translation,' according to the authors, has thrown into sharp relief the 'more complex and dynamic relationship between the spaces and communities of science and application in the clinic' (Martin et al., 2008: 30).

Interestingly, a number of interview respondents also had quite a critical and nuanced view of the putative novelty of TM. For example, most respondents agreed there has been a re-branding of conventional scientific and clinical practice in the drive to secure research funding from a policy community that has become enamoured by the rhetoric of 'translation,' or has at least been using it to justify public investment in drug development. Some respondents expressed concern that TM

is defined so broadly that it can essentially cover anything that is broadly applied basic science. A respondent from the NHS, for example, stated: 'They're buzz words; I used to call it applied research' (NHS 1). A senior academic scientist stated:

I'm not so sure it's novel because there have always been people pursuing translational research. Really what it's reflective of is an effort to brand something and use that brand to catalyse the movement of discoveries of basic research into clinical practice. (SA4)

Other respondents also emphasised that although the concept itself was not necessarily describing anything radically novel, it still had an important function in alerting the biomedical community to the significance of the R&D challenge and the need to think of new ways to resolve them at the scientific, clinical, technological and policy levels. It is important to note here that those who see TM as a re-branding exercise do not deny that the conventional innovation pathway is broken and needs fixing in some fundamental sense.

So, despite competing views about the role and scope of TM, and the fact that many of the practices underpinning TM are not novel in and of themselves, there has clearly been growing interest in efforts to influence bedside-to-bench relations and much institutional resource and infrastructure (both public and commercial) dedicated to fixing what is considered to be a broken middle of health R&D. In recent years, biomarkers have become an emblematic feature of this TM agenda and are generating powerful promissory discourses. I will now critically explore the nature and growing role of biomarkers and the underlying assumptions made about the current innovation pathway model.

## The Promissory Role of Biomarkers as a Translational Technology

A biomarker is any objective, measurable indicator of a biological state or process. The value of a biomarker is linked to its ability to facilitate understanding of disease mechanisms/pathways or therapeutic safety and efficacy. Some conventional biomarkers are relatively simple and well established within the clinic, such as cholesterol as a biomarker for risk of coronary heart disease, or blood pressure as a biomarker for hypertension, but a number of novel molecular biomarkers have been identified since the mapping of the Human Genome. Although there has been a focus on complex molecular or biochemical biomarkers, there has also been significant innovation in non-invasive imaging biomarkers, such as anatomical and functional imaging (Weber, 2006). Many different kinds of biomarkers are now being identified, and translational studies are trying to validate new biomarkers to improve knowledge and understanding of disease, clinical decision-making and drug development processes.

Biomarkers have become a central theme in discussions about the role and long-term value of TM. They are treated as almost synonymous with TM as they are considered relevant both to industry attempts to reduce phase 2 attrition rates and academics and clinicians hoping to improve understanding of disease mechanisms and patient outcomes. Biomarkers with associated diagnostic tests are also crucial to the development of stratified medicine, which is currently high on the agenda of both commercial pharmaceutical companies and healthcare providers as a way of targeting therapies more effectively (Mittra & Tait, 2012). Furthermore, some practitioners believe that biomarkers provide concrete foci for cross-sector and interdisciplinary TM collaborations, which are perhaps easier

to manage than projects built around more ephemeral and vague areas of translational science, a view supported in the following account from a clinician:

I think it's [biomarkers] a critical area certainly, and it's one that universities and medical schools can get engaged with relatively simply. Whereas the late-phase clinical trials are much more difficult for us to be engaged in. (SC2)

In general, the senior academic scientists were optimistic about the potential role and significance of biomarkers. In some accounts, biomarkers were implicitly framed as a progressive innovation that will come to replace many of the conventional clinical practices currently relied upon, as the following response nicely illustrates.

Molecular biomarkers will replace a lot of conventional diagnostic tests, inevitably. Cancer at the moment is still defined, subdivided and graded by pathologists looking down microscopes ... all of this diagnosis has to change in the next 20 years; it's still arcane. (SA7)

Here, biomarkers are imbued with a great deal of promissory clinical value that will enable scientists and clinicians to replace the old, subjective and imprecise methods of the pre-genomic era. Another interview respondent, from a funding agency, countenanced this view when he talked about biomarkers being of particular value to the field of psychiatry. He argued that current diagnostic methods for psychiatric disorders are inadequate, because there is often a constellation of complex symptoms and the diagnostic categories are largely based on subjective judgements. Here, molecular biomarkers are considered to provide a more robust and objective measurement of disease state.

In contrast to scientists and clinicians' primary interest in biomarkers as a means to improve classification and diagnosis of disease, industry's interest lies in their potential to identify safety or efficacy issues in the middle stages of R&D such that cost-of-failure in phase 2 and phase 3 clinical trials can be reduced. Here, the value of biomarkers is inextricably linked to the notion of a broken middle of R&D. This industry narrative provides a more pragmatic and tightly defined role for biomarkers, and has recently been used to justify industry participation and growing investment in various pre-competitive biomarker partnerships and consortia, including in the United States a major public-private Biomarkers Consortium, which is managed by the Foundation for the NIH (<http://www.biomarkersconsortium.org/>).

There is additional interest in the potential for biomarker data to be used in regulatory decision-making, both to provide surrogate-endpoints for clinical trials and to select patients for clinical studies. This particular application is not being driven solely by the pharmaceutical industry. Regulators, such as the FDA, have outlined a commitment to the identification and validation of biomarkers and innovative clinical trial design to drive forward pharmaceutical innovation (FDA, 2006), and similar approaches are being considered by the European Medicines Agency (EMA). The FDA has also established an initiative to facilitate the development of biomarkers and ensure that regulations for the associated diagnostic tests are fit for purpose (FDA, 2011), which is indicative of regulators' growing expectations for the technology.

While it is clear that biomarkers are being embraced by a number of diverse actors and organisations involved in biomedical research and innovation, it is important to

subject these promissory narratives and expectations to critical analysis, and also consider the assumptions that this focus on biomarkers makes about the nature of the health innovation pathway.

#### ***Limitations of Biomarkers and Underlying Assumptions about the Broken Innovation Pathway Model***

The broken middle of health R&D is a powerful narrative that has driven TM strategies within industry, academia and the policy community. Biomarkers, I argue, have become a central focus in discussions about TM and have generated high expectations and future-oriented visions of a biomarker led diagnostic and drug discovery platform that will solve a number of R&D challenges.

However, we must consider whether translational activities such as biomarker discovery and validation are based on untested and perhaps unrealistic assumptions about the transformative impact they are likely to have on the development of diagnostics and therapies in the short-term. Some interview respondents cautioned against fetishising biomarkers as a panacea for the broken innovation system. One academic scientist, specialising in haematology, described how biomarkers for indicating the fragility of plaque are considered the 'Holy Grail' within his field. Basically, scientists want to understand when plaque is about to rupture and have developed a number of techniques to try and identify this in real time. He claimed that scientists have tried to measure markers in the blood stream, such as metalloproteinases that are shed from the plaque. They have also used imaging techniques to visualise the plaque and see if it 'lights up' with a PET (Positron Emission Tomography) ligand, which would be indicative of very active plaque and a potential target for a therapy. However, the respondent added the following crucial caveat:

These approaches sound quite mature and well thought out but what they don't address is the fact that there are hundreds of plaques in the average vasculature, and some of them are vulnerable and some of them not, and what you see really is an aggregation of all these things, and if you were trying to find the plaque that killed you, you'd be on a hiding to nothing. So it's helpful, but not as helpful as people would try to make out. (SA2)

Incomplete knowledge about biomarkers, and a tendency to grant them special status in clinical decision-making and/or commercial drug development programmes, can also lead to false conclusions about process and outcomes. The respondent continued to state:

Let me give you the example of oestrogen. If you give it as hormone replacement therapy [trials have shown] it lowered LDL cholesterol, it raised HDL cholesterol, it did a host of other things in the artery wall that you would have said, right, this is absolutely cast-iron, we're ok here, we'll get benefit ... At the end of the day, oestrogen caused more heart disease, and the biomarkers would have driven this in entirely the wrong direction ... I think we're decades away from having enough biomarkers to understand the entirety of the process, and then aggregating them is very difficult. (SA2)

These accounts run counter to the more optimistic and transformative views of the use of biomarkers in drug development and diagnosis. The underlying complexity of disease processes and treatment effects, from this more sceptical perspective, renders biomarker studies so far insufficient as a replacement for conventional

clinical studies and outcome measures. The promissory and sanguine vision of a biomarker-led drug development and therapy paradigm is therefore very much a projected future; one that must overcome current technological reality and clinical complexity. This has implications for their more general and extended use in regulatory decision-making for clinical trials and clinical practice, which continues to be anchored to the conservative and cautious 'big pharma model' of drug development (Tait, 2007).

In their paper on gene mapping, Terwilliger and Goring (2009) provide a compelling argument that many future strategies around genomics have been made on unrealistic and untested assumptions about what the technology can realistically deliver. This argument would seem to apply equally to biomarkers and perhaps TM more generally. The diverse, and sometimes contradictory, views of interview respondents about the benefits and limitations of biomarkers would suggest that these technologies may work in some fields but not necessarily others. For example, biomarkers might facilitate better characterisation, diagnosis and treatment of certain cancers, but may not be so helpful in other areas (diabetes for instance), where there might be 30 known markers that only slightly raise the risk level. In the latter case, we must question the real underlying power of this new technological tool.

So, while biomarkers do promise a number of solutions to the purportedly broken conventional model of drug innovation, there is a clear danger in fetishising one technological solution and ignoring broader systemic challenges and constraints. Furthermore, this focus on biomarkers, which from an industry perspective is very much rooted in concerns about phase 2 attrition rates, does tend to assume a particular innovation pathway

model for drug development, with a chasm between basic and applied research being responsible for a lack of successful translation from bench to bedside. TM then emerges as the most obvious solution. However, as we have seen, the broken middle of R&D narrative is far more complex and contested, and the distinction between basic and applied research, or lab and clinic, is not as straightforward as is often presented.

### Conclusions

The data I have presented in this paper suggests that TM is more than a discrete set of technological instruments and mechanisms for exploiting the life sciences for therapeutic benefit, and it is based on a number of shared assumptions about the nature of R&D and the current challenges of drug development, particularly phase 2 attrition and a gap between the lab and the clinic. Conceptually, I have drawn on a broad literature around hopes and expectations, as well as some critical approaches to the linear model of R&D and conventional distinctions between basic and applied research, to analyse diverse practitioner accounts centred on definitional frameworks, drivers and the general framing of TM. The data reveal the complex and relatively fluid definitional and conceptual boundaries that are employed by different professionals as they envision various objectives and outputs for the field. Driving these discursive narratives has been a particular set of perceived health innovation challenges, which I have referred to as the 'broken middle' of health R&D. This problem narrative has, I have shown, presupposed a particular role and scope for TM – the centrality of biomarkers providing one key illustrative example.

What has been demonstrated is that TM remains a relatively vague and ambiguous

term, as different practitioners delineate its role, scope and long-term value in a variety of different ways. However, they all have in common a presumption that there is a problem in the successful transition of new technologies and therapies from the laboratory bench to the patient at the bedside and that a range of more translational activities will be critical to solving the innovation challenge. In this article I have taken a critical approach to both the conventional view of the 'broken middle' narrative and the notion that TM is a novel approach that truly transforms bench to bedside relations in ways that are historically unique. This, I suggest, is an untenable position and places far too high an expectation on TM.

Instead, it is worth considering TM as both a general philosophy for 'doing applied science' in the context of new life science, and a diverse set of scientific and clinical activities orchestrated within new institutional settings and configurations. Indeed, despite TM being a rather murky and messy term, it has engendered tangible new opportunities and strategies for therapy development. This can be seen in the very real policy commitment to building new resource and infrastructure in the spirit of TM. Substantive cross-sector collaborations, particularly between academia and the pharmaceutical industry, have been brought about as a result of this emerging TM agenda. There has also been an increasing role of public sector finance and expertise in downstream drug development in both the UK and globally. There are many examples of such initiatives. In the Netherlands, there has been the Center for Translational Molecular Medicine (CTMM), which involves multiple public sector and commercial research and clinical organisations collaborating to develop technologies and tools for personalized medicine (<http://www.ctmm>).



nl/pro1/general/home.asp). In the United States, there is the heavily resourced NCATS initiative and the Biomarkers Consortium, which was discussed earlier. The UK Medical Research Council's (MRC) launch of six translational medicine centres with funding of £15.5m in 2007, which were tasked with developing programmes with clear milestones to 'overcome existing gaps or hurdles in translational science' (MRC, 2007), is also indicative of this broad policy drive to invest in new kinds of approaches to biomedical research and therapy development. These are just a few of the many hundreds of TM-inspired organisational changes that are arguably re-shaping the therapeutic R&D landscape, and reveal the transformative impact of the TM philosophy on institutional and organisational practices. This of course raises important issues around institutional constraints and the management of different expectations about value and benefit, which is beyond the scope of this paper.

Nevertheless, TM's key feature and enduring legacy might in the end be the reshaping of conventional approaches to the development and delivery of health innovation through a variety of changes in institutional and organisational practices. Indeed, it might be useful to consider TM as a new organising principle for health R&D, rather than something more bounded and tangible. If we accept this broad definition of TM as a kind of 'social technology', discussions about what TM is and what it can realistically deliver becomes less important than the question of how this amorphous concept is actively

reshaping health innovation systems and the conventional everyday practices therein. This is not to deny that there are many challenges ahead. There are policy challenges in terms of deriving long term health impacts as well as economic impact, which will take time to emerge. It is therefore important that consideration is given to the systemic features of TM and that attempts to institutionalise it in ways that will improve health innovation recognise relevant linkages (both enablers and constraints) along various health, innovation and policy/regulatory pathways. This requires an acceptance that the challenges facing life science-based therapeutic innovation have a broader systemic origin than those captured by the crude broken middle narrative and its assumption of linearity. Furthermore, expectations must be based on testable criteria and more robust evidence. This requires a means of better aligning the broader promissory futures expressed by certain TM advocates with the far more narrow goals of industry.

### **Acknowledgements**

I would like to thank the Economic and Social Research Council (ESRC) and the Innogen Institute for providing funding for the research on which this article is based. I would also like to thank my colleagues Prof. David Wield, Dr. Steve Sturdy & Dr. Sarah Parry for their extremely helpful comments on early drafts of this article. Finally, I would like to thank the external referees for their constructive assessment of the article and helpful suggestions for improvement.

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