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The social management of biomedical novelty: Facilitating translation in regenerative medicine

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ABSTRACT

Regenerative medicine (RM) is championed as a potential source of curative treatments for a variety of illnesses, and as a generator of economic wealth and prosperity. Alongside this optimism, however, is a sense of concern that the translation of basic science into useful RM therapies will be laboriously slow due to a range of challenges relating to live tissue handling and manufacturing, regulation, reimbursement and commissioning, and clinical adoption. This paper explores the attempts of stakeholders to overcome these innovation challenges and thus facilitate the emergence of useful RM therapies. The paper uses the notion of innovation niches as an analytical frame. Innovation niches are collectively constructed socio-technical spaces in which a novel technology can be tested and further developed, with the intention of enabling wider adoption. Drawing on primary and secondary data, we explore the motivation for, and the attempted construction of, niches in three domains which are central to the adoption of innovative technologies: the regulatory, the health economic, and the clinical. We illustrate that these niches are collectively constructed via both formal and informal initiatives, and we argue that they reflect wider socio-political trends in the social management of biomedical novelty.

1. Introduction

An oft-quoted description of RM defines it as that which "replaces or regenerates human cells, tissues and organs, to restore or establish normal function" (Mason and Dunnill, 2008, 4). Many RM therapies will involve the use of live cells and tissues to repair damaged or diseased tissue, and are thus considered radically distinct from drugs and therapeutic medical devices. Examples include: generating retinal epithelial tissue from human embryonic stem cells (hESC) to treat forms of visual impairment (Ramsden et al., 2013); using bone marrow-derived cells for the treatment of autoimmune conditions (Ringden and Keating, 2011), and engineering tracheas comprising a donor-derived scaffold 'seeded' with a patient's own cells (Elliott et al., 2012). 'Regenerative medicine' is also applied to therapeutic developments with a history that predates the term, including gene therapy and bone-marrow transplantation. Despite its apparent distinctiveness, the boundaries of 'RM' are not necessarily well-defined and they have been somewhat mutable (Webster, 2013).

As with many biomedical developments, high expectation surrounds RM. The field has been animated by promissory future-orientated statements about its considerable clinical and economic value. RM has the potential, it is stated, to deliver curative treatments for a range of diseases, including diabetes, neurological conditions, and heart disease, (Department for Business Innovation and Skills, 2011), and will thus "revolutionise patient care in the 21st century" (TSB UK Research Councils., 2012, 2). For proponents, this clinical value also holds considerable economic value. RM has been named by the UK government, for example, as one of 'Eight Great Technologies' that will drive innovation and propel the UK's growth, and in which the UK can become a global leader (Willetts, 2013).

Alongside this high-expectation is a prevalent discourse of concern. This is that scientific advancements will fail to translate into useful RM therapies, or that the rate of translation will be laboriously slow, due to its novelty and apparent incommensurability with existing biomedical and health delivery infrastructures. Healthcare systems and infrastructure, as well as regulatory systems, have emerged to accommodate conventional therapies based on drugs and devices, and may then be poorly suited to the governance and delivery of RM (Tait, 2007). Various initiatives have set about identifying perceived and linked translational challenges,

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including: safety concerns over the instability of live cells and tissues and their potential to become tumorous; logistical and manufacturing difficulties, particularly a stable scale-up of cell and tissue production; the regulatory burden; the potentially high up-front costs of RM products and procedures; and the difficulty of integrating RM therapies into existing workflows in clinical settings (Regenerative Medicine Expert Group, 2015) [hereafter RMEG]. Collectively, such challenges are said to generate levels of risk and uncertainty that deter investors, particularly venture capital and large industry (Omidvar et al., 2014). Developments within the RM field, then, are particularly susceptible to the so-called 'valley of death' (Department for Business Innovation and Skills, 2011); the perceived gap between initial invention and 'successful' technology that 'translational' activity is supposed to bridge.

The translational challenge has figured prominently in debate (Regenerative Medicine Expert Group, 2015, House of Lords Science and Technology Committee, 2013, UK Research Councils., 2012), and regional and national agencies, such as the California Institute for Regenerative Medicine (CIRM) in the US and the Cell Therapy Catapult in the UK (Thompson and Foster, 2013), have been established to support research, build new infrastructure and expertise, and to foster commercialisation. Similarly, the UK's Regenerative Medicine Platform has been established to address key safety, manufacturing and delivery concerns within the field.

The field of RM, then, is characterised by a concurrent assembling of new directions in biomedical research, and new socio-technical networks tasked with delineating, managing and routinizing these emerging forms of life. These assemblages are being driven by promissory future-oriented visions (Morrison, 2012), and involve the coordinating of heterogeneous agents (ie, clinicians, scientists, patients, commercial and not-for-profit enterprises) with potentially convergent worldviews and interests. The field, in other words, constitutes a form of collective organising and social change, propelled by the promise of a future of greater "health and wealth" (NHS, 2011). It is for this reason that the field of RM provides a rich area for inquiry for the social scientist. It is a field in which jostling entities – whether they be small *bioobjects* (Vermeulen et al., 2012), or large institutions – are being enacted into existence, delineated, and assigned roles which are taken-up, challenged and renegotiated. It is, in other words, a field that is rich with 'matters of concern' (Latour, 2005) which, once addressed, may become 'going concerns' (Rip and Joly, 2012) and so normalised in clinical practice (May, 2013). Thus, RM provides an opportunity to examine a key problematic in the social sciences: how is it that socio-technical change occurs, and how it is that perceived socio-technical novelty is routinized and normalised. In this paper, we explore some of the innovation challenges posed by the field of regenerative medicine, and we examine attempts to manage and harness its biomedical novelty, specifically within three domains: the regulatory sphere, the health economic sphere, and the clinical development sphere.

2. Novelty and its management

Regenerative medicine is among several fields within the biosciences that have been characterised as novel and transformative, both in terms of how biological forms of life are manipulated, engineered and understood (Metzler and Webster, 2011), and the new challenges they pose for regulatory agencies and wider society (van Est and Stemerding, 2012). For example synthetic biology (Calvert, 2013), bio-nanotechnology (Swierstra and Rip, 2007; Boenink et al., 2010), and the neurosciences (Rose and Abi-Rached, 2013), are constituted by the emergence of what has been described as transformative biomedical platforms (Keating and Cambrosio, 2003), implicated in generating novel entities that may challenge the very notion of 'human' (Bateman et al., 2015).

This paper adopts the position that novelty and its transformative character are, however, neither self-evident nor intrinsic to specific technological developments. What counts as being "novel" is dependent on a range of socio-technical processes associated with how perceived novelty is mobilised, embraced, valued or discounted, and managed. This is true within the lab, the regulatory universe, the intellectual property domain, and in any commercial product for markets (Dussauge et al., 2015; Packer and Webster, 1996). Novelty in this sense is both a claimed social and technical attribute (Barry, 2001), and in that sense its meaning and boundaries are never self-evident but are, rather, subject to negotiation by actors. Developments within the biosciences may be positioned by actors as being simply a valuable extension of existing practices (and so iterative and non-radical): this is often associated with the incremental innovation associated with surgery (Riskin et al., 2006). In other settings, techniques that are positioned as assisting conventional practices can *also* be seen as radical. This is true, for example, in the field of IVF where supernumerary embryos provide the basis for a reproductive socio-technology that both extends and opens up opportunities for two divergent activities: the reproduction of children and, via the production of embryonic stem cells, regenerative medicine (Webster, 2007).

Two notable developments in regenerative medicine associated with claims to novelty were the identification and isolation of human embryonic stem cells (hESC) at the University of Wisconsin-Madison in 1998, and the creation at the University of Kyoto in 2007 of 'induced pluripotent stem cells' (iPS), which are reprogrammed from adult human cells and have the biological potential of hESC. More generally it is the use and manipulation of live tissues and cells that are considered to be the basis for the 'novel' and 'transformative' nature of RM, and extracting, purifying handling, and storing live tissue is a difficult task, as is manipulating it to become a differentiated cell and then scaling up that cell without loss of functionality. This has raised questions about how quality control, potency and release assays are to be developed and validated (Ali et al., 2014), the ways in which clinical trials are designed (Mittra et al., 2015; Webster et al., 2011) and how cell therapies are to be classified in regulatory terms (as a medicine or a device; see (Faulkner, 2012b). Coping with material variability and instability has become a core 'matter of concern' in the field.

Here, we use the notion of innovation niches (Schot and Geels (2007) as a conceptual tool to explore novelty and transformation as it relates to RM. Schot and Geels note that some innovations are perceived to be so novel that they are regarded by their developers as incommensurable with the existing socio-technical infrastructure (or what they call *sociotechnical regimes*). The success of such innovations requires the construction of a protected socio-technical space – what can be called a "technological niche" – that will provide a 'seed-bed' in which the innovation can be nurtured, tested and further developed. Depending on the perceived desirability of the innovation and the success in enrolling others into the development, the niche may eventually be expanded to the point where it becomes a new socio-technical regime, perhaps supplanting earlier socio-technical regimes. It is in this way that an innovation can become widespread, routinized, and thus *transformative*. Niches are actively constructed by various actors and thus reflect diverse interests and the social and political contexts within which they are constructed and negotiated. Hence, we use the notion of 'innovation niche' as a conceptual tool to refer to socio-technical spaces that could, 'on the ground', be highly variable in form. It is important to note that while innovation niches are designed to enable developments that are seen as novel and require