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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

special handling – and in contexts where the notion of 'the novel' has itself been strategically mobilised by actors (see Pickersgill's [2013] discussion on neuroscience) – not all actors will necessarily agree on *how* novel such developments are.

National healthcare systems (and international regulation) engender and reproduce a dominant *socio-technical regime* which shapes the development, evaluation, adoption and implementation of most new therapeutics, principally relating to new drugs and medical devices. As we will see, commentators and investigators working within the field believe that RM is poorly served – indeed inhibited – by this socio-technical regime. Initiatives have thus been launched to actively support the emergence of RM. Drawing on interview and secondary data, we will explore some of these initiatives - which can be said to constitute the formation of *innovation niches* - in three areas: the regulatory, health economic, and clinical development domains.

These three areas play a central role in the translation process. Each carries both macro and micro dimensions – reflected at the macro level in formal oversight, evaluation and implementation requirements as well as how, at a local level these are expressed within more informal, everyday contexts. In effect they act to make an innovation *workable* within specific contexts and so help to normalise it (May, 2013). Ethical considerations are also important in the biomedical context (Salter and Salter, 2013) and are encompassed here by the 'regulatory' domain, though our data and discussion do not deal with this explicitly in this paper.

3. Methods

The paper draws upon data from the ESRC-funded REGenableMED collaborative research project which explores the social dynamics of innovation within the RM field, with a particular focus on *institutional readiness*: how it is that elements of the healthcare system might enable the workability of RM. We draw on 40 interviews with individuals working within the field from across the UK in different institutional settings, including research labs, teaching hospitals, companies, patient and professional bodies and government agencies. Our respondents included clinicians developing RM products and procedures that are in, or are about to begin, clinical trials. Specifically, we sought to include therapeutic developments that had been identified by stakeholders as 'pioneering' or 'path-breaking' within the field of RM. Our projet advisory group, which includes patient advocacy representatives, commercial representatives, and representatives from the public sector, helped to identify these developments and appropriate participants. Other participants included scientists working within academic networks tasked with identifying and overcoming technical, manufacturing and safety translational challenges; patient association representatives and members of trade and professional organisations with involvement in RM; representatives from regulatory agencies and other national health governance organisations; and representatives from companies with an interest in RM. Interviews have been transcribed and subjected to thematic analysis using NVivo 10 software. Interview data are supplemented by RM secondary data: publicly-available committee reports and meeting minutes, company annual reports, and media coverage. In addition, one of the authors is a member of the Regenerative Medicine Expert Group and so was party to discussion therein, though material used here is in the public domain. Thematic analysis of the dataset was by guided by the 'innovation niches' concept, which was used as sensitising tool while analysing the data. We thus sought to note: how RM is framed by participants; their perceptions of its innovative form in relation to existing therapies, their perceptions of the arrangements which either hinder or enable innovation, and their involvement in attempts to facilitate innovation. We also noted and analysed their general impressions and perceptions of RM and how it relates to other field of biomedicine. Ethics approval for this data collection was obtained from the appropriate institutional ethics review board, and informed consent was obtained from all participants.

4. Findings: the construction of socio-technical niches

There is considerable variation amongst the potential products and procedures that are defined as being 'regenerative medicine', and participants we spoke to indicated that the specific translational challenges encountered in each therapeutic area would vary. Participants, however, also made reference to some general translational challenges that affect the field as a whole. Generally participants felt that while basic science was well-supported in the UK, the current environment was not conducive to RM translation:

I think it's been enabling for basic scientists but not for clinicians … It is [enabling] if you're a molecular biologist but if you're a person who is truly translational, no. (CEO)

There's a reasonably good infrastructure and funding to take things through basic science at universities but there's a translational hiatus because the costs are high, then a disinterest once you get pretty close. (Surgeon1)

More importantly, respondents regarded regenerative medicine as being sufficiently distinct, in terms of biological structure and complexity, that it warranted new translational 'pathways'. Here a small RM company CEO believes that the novelty of RM as a technology meant firms are reluctant to invest and clinical commissioning managers are reluctant to reimburse (and, implicitly, regulators to approve):

Not a single one was willing to invest at that point because no one had done it before. There wasn't a pathway … the technology hadn't been demonstrated anywhere … (CEO)

These comments reflect the general sentiments expressed in many of the official reports: that the current healthcare system is poorly suited to accommodating RM (House of Lords Science and Technology Committee, 2013, UK Research Councils, 2012, Department for Business Innovation and Skills, 2011). It is this framing of RM (as complex and novel) and the healthcare system (as not 'enabling' of RM) that has been mobilised to justify and prompt initiatives that provide a more enabling environment. In what follows, we explore this delineation of novelty in more detail as it relates to the creation of three niches, and we provide a description of the steps that have been taken in each of these areas to support RM. In each area we focus on the construction of the niche domain, its relation to existing structures, its formal and more local dimensions and the negotiations surrounding it.

4.1. The regulatory niche

A major translational challenge, according to commentators, is the existing regulatory regime which has largely emerged to accommodate and govern drugs and devices. In this section we explore the attempts to construct a regulatory niche for RM products and procedures. We will see that the construction of this niche is characterised by formal initiatives, such as the establishment of the Advanced Therapy Medicinal Products (ATMP) framework, and more-informal processes 'on the ground' that include a pragmatic negotiation between clinicians and regulators. These initiatives entail the formation of unique standards, codes and procedures intended to allay safety and efficacy concerns and to provide a coherent and 'enabling' regulatory environment for RM investigators.

In 2007 EU institutions ratified the ATMP regulatory framework (European Parliamant and Council of the European Union, 2007). It

represents an important regulatory response to the perceived novelty of developments within RM (Faulkner, 2012a), and the most notable attempt to mitigate concerns about safety and quality. The framework itself reflects how key policy-making stakeholders have apprehended the field of RM, and it reveals how they anticipate its future development. The collective effort that led to the framework, and the implications of the framework have been discussed in detail elsewhere (see Faulkner, 2012a), but it is worth highlighting some of its key features. It introduced, for example, a central marketing authorisation procedure, in which prospective therapies would be assessed (having undergone clinical studies), by the specially-created multidisciplinary Committee for Advanced Therapies (CAT). It also introduced post-market surveillance rules so that the longer-term safety of products can be assessed, and it stipulated a 30-year traceability requirement as a way of mitigating safety concerns (Faulkner, 2012a). Additionally, the regulation has meant that the manufacturing of RM products has to take place in carefully controlled clean spaces: facilities licensed as being of clinical Good Manufacturing Practice (GMP) grade. In an attempt to lessen the financial burden of obtaining central marketing authorisation, the regulation also introduced a substantial licence fee waiver for small companies, reflecting a key concern that was voiced during deliberations over the framework, that any such regulation should not unduly hinder innovation. Indeed, the EU-wide Regulation is framed as replacing divergent national approaches to governing RM, "which hampered growth of this emerging industry" and "hindered patients access to products". The Regulation, in contrast, was designed to "facilitate access to the EU market and to foster the competitiveness of European Companies in the field" (Director-General for Health and Food Safety, 2015). The framework represents the establishment of specifically-designed regulatory niche, which has the effect of confirming RM as 'distinct' from other, more conventional areas of medicine, yet at the same time seeking to manage and normalise its biomedical novelty.

At the same time, this component of the niche sits within and builds upon an existing regulatory regime to which RM developers must also respond. Depending on the source and nature of cells or tissues used, the nature of other components, and the stage of translational development, RM products and procedures within the UK may also be subject to governance by the Human Fertilisation & Embryology Authority (HFEA), the Human Tissues Authority (HTA), and the Medicines and Healthcare products Regulatory Agency (MHRA, which also implements the ATMP framework within the UK). Navigating a route through these authorities has been identified as a considerable challenge by advocates of RM. The House of Lords Science and Technology Committee's influential Report (2013) on RM in the UK notes that RM stakeholders felt that the regulatory environment was "labyrinthine and off-putting for overseas investigators, whilst demoralising for home investigators" (2013, 38), and it suggested, therefore, that a regulatory advice service be established. Consequently, a "one stop shop" regulatory advice service spanning the HFEA, HTA and MHRA has been established, specifically for regenerative medicine. It is claimed that bringing together the relevant regulatory bodies into a single access point will "smooth the translational pathway for all those UK workers engaged in regenerative medicine" (MHRA, 2014). Here we see an attempt to align new and existing regulatory components.

In addition to these formal top-down regulatory initiatives, more localised processes across the science base are contributing to the construction of a regulatory niche for RM. Regulatory provisions such as the ATMP framework aim to ensure that clinical trial participants are not subjected to unnecessary levels of risk, and that only those therapies that meet minimum safety and efficacy requirements will be offered to patients on a routine basis. Yet, according to respondents, precisely how safety and efficacy should be assessed is not clear, and the guidelines used for drugs and devices may not – depending on the nature of the therapy, be appropriate. Cells and tissues within RM are perceived to be more "complex" than drugs and devices, and this creates particular challenges:

> The real obstacle is that as cell therapy is a complex product it can never ever be analysed to the degree that even a biopharmaceutical can … (Surgeon1)

And clinical trials conventions are equally problematic:

> One of the biggest things is the standard deviations. So, if you're going to produce a drug, you would expect that you're going to be giving exactly the same formulation, exactly the same dose, exactly the same quality control every single time you give it. But cells have such variability that you simply can't do that. You're, therefore, looking at maybe 20 percent variation in certain quality control parameters, far, far greater than you would in any other medicinal products. (Cell scientist1)

This is, according to respondents, particularly problematic in regards to therapies that use cells or tissues derived from pluripotent cells. Any residing 'pluripotent potential' may manifest in the form of tumours:

> If you start with an already differentiated cell, 'purity' is not an issue (since the characterisation/stability etc. has been done/secured); the main issue is efficacy. If you start with a pluripotent cell, you need 100% purity in the assay to avoid tumorigenicity'. (Cell scientist1)

Respondents argued it was therefore necessary to develop new standards that could be used to assess quality and safety, based on standardised assays and the identification of appropriate biomarkers, phenotypical traits that are easily detectable, and indicative of the cell or tissue's safety and efficacy:

> 'MHRA's traditions have been based on purity of a drug/compound – 99% pure … But with a cell (an MSC) can't make the same statement (cant 'purify' in the same way) so we rely heavily on being able to show that you have key biomarkers that show safety and efficacy. (Cell scientist1)

It is these concerns that prompted the formation of a 'safety and efficacy' hub as part of the UKRMP, the official aim of which is to "provide clearer understandings of the potential hazards with [RM technologies] and to develop new methodologies to assess their risk". As with all the UKRMP hubs, the safety and efficacy hub employs a multi-centred, multidisciplinary methodology, bringing together expertise from several key disciplines. It represents an attempt to create a novel biomedical platform: a particular set of standards, tools and protocols that can facilitate translation.

Finally, in the process of designing clinical trials, the clinicians we spoke to have also been attempting to formulate standards for assessing safety and efficacy for specific RM therapies. This has involved negotiations with MHRA officials who, they say, initially had very little understanding of how the quality of RM products and the safety of RM therapies should be assessed. This 'matter of concern' was yet to be properly articulated on both sides: as one biomedical scientist said,

> How do I get to understand what it is that you [the MHRA] need if I don't know what questions I need to ask of you? (CEO)

And similar comments were:

> I felt great sympathy for them because they are, like everybody else, understaffed and they don't have anybody there who has any previous experience because these are completely new, in a sense, to this [product]. (Surgeon2)

> You go back when you start some years ago, the knowledge about regulation was very limited from both ways … even the regulators themselves they didn't know exactly what to do. (Surgeon3)

> So, we've had to have more meetings with MHRA than you might normally think and they have had to learn on the job as well. (Surgeon2)

Through iterative negotiation, these clinicians are formulating quality and safety standards that, while not ideal, are satisfactory for the MHRA, especially when there is considerable clinical need for the procedure:

> Yes, definitely but it's almost as though, when we have the meetings, [the MHRA] are saying to us, "Well, what's the best you can …" And there's something about these patient groups being particularly in need, being orphan[1] and particularly ill in that sense. So that, I would guess, feeds into the MHRA's feelings on this. (Surgeon2)

Thus, for some therapeutic developments, particularly in those clinician-led projects that are more advanced along the translational pipeline, quality control and safety protocols are being developed via pragmatic negotiation between clinicians and regulators. The approach here is to generate some of the standards by which subsequent RM products and procedures that are deemed similar will be judged.

In effect, a regulatory niche for nascent RM therapies is being collectively constructed in a variety of formal and informal ways. Some aspects of the niche, such as the MHRA regulatory advice service, build upon existing regulatory provisions and articulate with more formal initiatives, such as the ATMP framework, and other aspects are established through pragmatic negotiation at the local level.

4.2. The health economics niche

Another translational challenge for any innovative biomedical therapy relates to reimbursement and commissioning. In many countries the decision to commission a therapy depends heavily on the results of a formal technology appraisal which determines whether it is clinically and cost effective, and thus whether it should replace or complement existing services. In the UK this is undertaken by the National Institute for Health and Care Excellence (NICE) and it involves a Quality Adjusted Life Year (QALY)-based cost-utility analysis: the cost of the therapy is compared to that of the existing standard of care, relative to the added clinical benefit (measured in terms of QALYs). Those therapies that are accompanied by robust and comprehensive data on cost and clinical benefit are more likely to receive a favourable technology appraisal, important for their marketability. Our respondents felt that such a system is not well suited to RM products and procedures, and may then place them at a disadvantage.

A common point made by respondents was that RM products and procedures would likely, at least initially, have a high upfront cost (due to the investment required to produce and support them). While in the longer term they may bring about cost savings, this high-upfront cost would disadvantage them under the current appraisal system used by NICE, which reflected the reimbursement structure of the healthcare system more generally. As a director of an RM centre stated:

> The bad thing about the UK is NICE … Because cell therapies are almost certain to cost almost as much as biologics and biologics are very expensive. The reimbursement system at the moment …, isn't very good. … Paying a lot of money this year to save an awful lot of money down the line - the government as you know can't do that … So that's an obstacle. (Cell scientist2)

Another issue relates to the requirement for robust and comprehensive data necessary for a technology appraisal. Participants noted that the data required was not the same as that which would be submitted as part of a central marketing authorisation. This meant that two 'streams' of data need to be collected during clinical studies, which was a major hurdle for the small enterprises that typify the RM commercial landscape. This issue is complicated by some ambiguity over the type of data that are required, and the alleged lack of guidance from NICE. These issues are illustrated in an extract from an interview with a CEO of a small company developing an RM product:

> But some of the comments that I heard from NICE recently at [a talk] sent shivers down my spine … [they] pretty much dismissed data that was presented to them … It was data the MHRA wanted or the EMA wanted or the FDA wanted so it got the product approval to market but NICE essentially said, "We don't care about any of that. It's not in the right format, it's not addressing things we need to know about"; yet they wouldn't necessarily say what those things are and the [NICE rep] bluntly said, "We'll answer a direct question but we won't give you guidance" … we've got enough on our hands both financially and logistically and have more kinds of ways to navigate the regulatory pathway. Then to have a parallel pathway that may require a completely different set of clinical data; we just can't afford to do two sets of clinical work. I don't know how we get that feedback early enough so we can design our clinical data to feed both streams. (CEO)

These points have also been raised in several reports exploring translational challenges in RM (House of Lords Science and Technology Committee (2013)), which have noted that investigators may be unable to meet the requirements for robust and comprehensive economic and clinical effectiveness data. The difficulty here is that such data can only be generated if the therapy is being regularly used; yet without such data, it is unlikely to be adopted into routine therapy. In response to these challenges, the House of Lords Science and Technology Committee report concluded that the NICE methodology is inappropriate for appraising RM therapies (2013).

As we saw in regard to regulation, creating a niche to address these challenges has meant engaging with and building upon *existing* provisions. One such provision is the 'risk-sharing' model where the initial financial risk of introducing a new therapy into the healthcare system is shared between industry, the government,

[1] Products with an 'orphan' designation are targeted at rare, life threatening illnesses for which there is no alternative treatment.

and the NHS. The RMEG argued that this should be used for RM. It was also thought that the current 'commissioning through evaluation' scheme, in which the NHS sets aside funds for trialling a therapy in a clinical setting, might be appropriate. The RMEG has also recommended that NICE establishes a scientific advice service specifically for the SMEs involved in RM development.

However, none of these spaces deals directly with the key issue of QALYs and the evidence that is needed to make robust cost-effectiveness calculations. The RMEG has therefore seen the need to take a further and more radical step in creating an appropriately framed health economics niche for RM by commissioning a 'mock appraisal' of a cell therapy that could assess whether, and if so in what way, existing NICE methodology needs to be changed to accommodate the particular characteristics of RM. It also stated that the agency should ' … seriously consider developing a methods and process manual for regenerative medicine or incorporate into existing documentation' (RMEG Minutes, Sept 2014). A mock appraisal was subsequently approved, but this raised an additional dilemma: what specific therapy could be used as an exemplar for RM? What characteristics, in other words, would constitute an RM exemplar, and could this be used to adequately test the existing socio-technical regime? There was considerable discussion and negotiation over this in the RMEG. The eventual choice was to use T-Cell therapy used in oncology, but the Minutes of the RMEG discussion reflect the lack of complete consensus:

> 'a number of voices indicating that an oncology cell therapy was not a good example. A better and more relevant example would be a true regenerative medicine therapeutic for the treatment of a chronic degenerative disease, particularly one that affected the older population' (Ibid).

At the time of writing the appraisal remains incomplete, but this debate over the exemplars highlights how defining a product is key to defining an innovation niche. When the results of the review are published (in spring 2016) we are likely to see further negotiation over the results, and how they impinge on the formal processes of appraisal adopted by NICE.

4.3. The clinical development niche

A third key challenge for an innovative therapy is how it can be adopted and implemented in existing clinical practice (Ulucanlar et al., 2013). The technical and logistical infrastructure, payment systems, and staff training in clinical centres have been closely associated with drug and device-based therapies. Such centres may therefore lack the capacity and competency to implement new RM therapies that, due to the live and complex nature of their constituent cells and tissue, will require bespoke logistical systems for the sourcing and movement of cells, and specially-trained staff. An 'enabling' clinical niche has been built in several ways.

First, respondents spoke about ways in which they could mobilise aspects of the current clinical infrastructure, both in terms of particular technical and related regulatory assets. A key resource has been the NHS Blood and Transplant (NHSBT) service. Within the NHS, NHSBT centres are largely responsible for collecting and distributing products for transfusion or transplantation (including bone-marrow transplantation), and thus have extensive experience in handling live tissue, logistics, and managing the associated regulatory hurdles. For several of our respondents involved in the development of a tissue-engineered product, the NHSBT was key to their RM project. This particular product had been implanted in several 'compassionate use' cases, and is currently undergoing phase I/II clinical trials.

> We can't afford to buy and build facilities so we're using the facilities at the NHSBT who have got state of the art facilities to do [product constituent] processing … So we're using essentially those guys as contract facilitators. (CEO)

> They're an existing resource and they have been involved in tissue procurement from human sources for a long, long time … they have particular expertise that we've been able to leverage on. So they're sourcing the [product] for us … [They have been] delivering routine cell therapies for haematological diseases. So we're able to use that kind of expertise of how to deliver cells or cellularised products, in this case, to GMP standards and that's been utterly crucial in making this a goer, really. (Surgeon2)

As this respondent notes, a key aspect of NHSBT is their capacity to produce products within facilities that meet rigid GMP standards - a requirement for all ATMP products intended for clinical use.

Another way in which existing structures have been important has been the role of research-intensive NHS Trusts which have infrastructural elements that are orientated towards innovation: respondents report on how the Trusts had facilitated their RM projects. As one observed:

> We've got this very nice and well understood relationship with the Trust which is where [the project has] got a clinical component … it's got a research component - that's what we're good at [and] when we put them together - So it works very well and it's an interesting model actually to look at … I don't think anybody is as fortunate as us in having such a good clinical environment behind the medical school.

Due to its geographical position within the UK, this particular Trust provides a range of specialist clinical services, including bone-marrow transplantation services. It operates a GMP facility and has expertise in handling and manufacturing blood and tissue products.

> Because [location] is remote from other places, it does all the specialities … in fact the cell manufacturing facility is run by the Trust … it's that understanding of the regulatory requirements, it's also that we built a manufacturing centre.… so we've got a good number of clinical trials in stem cells.

Indeed, respondents at other research-intensive trusts involved in RM clinical trials mentioned the importance of having easy access to established cell-manufacturing facilities, and in particular, close alliances between cell-scientists within those facilities and clinicians:

> Then at the [hospital] is [cell scientists]. He's a world leader in cell therapy manufacture. He's involved in lots of different projects with different companies, has a great facility for GMP manufacture of cell products … he's well placed from a regulatory perspective, as well, to guide us. (CEO)

> I've worked with [cell scientist] who's very senior and well respected researcher in stem cells and together we've looked at combining developments in both clinic and laboratory technique at the same time. And we … run the clinical development of delivery, the surgery, the patients, everything at the same time as developing the cells we were going to transplant so that it would be a shorter timeframe, that's the gist of the project. (Surgeon1)

Respondents mentioned other features of the existing system

that have helped them deliver RM products or procedures to patients. These included supportive ethics committees, competent clinical trial units, and clinicians with the time and expertise to manage the onerous regulatory requirements. In effect, these Trusts constitute a clinical niche not found across the NHS for developing RM products and procedures. They are enabling the collection of safety and efficacy data, but importantly, they also provide an opportunity for investigators to develop and test some of the supporting socio-technical infrastructure that would be required if the therapy were to be offered routinely, infrastructure that relates to, for example, logistics and therapy administration, clinical outcome data collection, and personnel skill.

Indeed, the importance of these clinical contexts to the eventual embedding of RM in the healthcare system has been recognised in the RMEG's report (2015). The report suggests that such centres, which have 'experience in the development of regenerative medicines' should become the basis of Cell Therapy Centres of Excellence. Investment, specialist resources and skills, the report suggests, should be further consolidated around such centres to create a coordinated network supporting further RM research and the routine treatment of patients. The report recommends that various bodies (the Department of Health, BIS, NHS England, and the Cell Therapy Catapult) be involved in the process of identifying such centres and examining how they can best be coordinated and consolidated. Here we see the way in which a bottom-up innovation process in particular clinical contexts leads to moves towards a more formalised clinical niche for emergent RM therapies.

5. Discussion: enabling novelty in RM

The formulation of the three niches involves the creation of sites which, it is hoped, will provide an innovation space for RM. As we have seen, this entails engaging with, and where possible, mobilising, the existing sociotechnical infrastructure. In addition, the niche-constructing initiatives have a recursive relationship, inasmuch as stakeholders are aware that a niche in any one of the three domains will only be effective if it makes wider sense. As was noted by the RMEG:

> 'even where [RM] products were in truth clinically effective, this may not be known with a high level of certainty at the time an ATMP first comes to market. Exploring the impact of a limited evidence base on the NICE appraisal should be a major consideration of this study.'

ATMP regulatory provisions, NICE economic appraisal, and clinical considerations, as the extract suggests, need be considered as inter-related. A consequence of this is that a range of actors spanning various domains are involved in the formatulation of niches, and boundaries are not clear-cut. Indeed, the boundaries of each niche can be defined in formal terms – such as a regulatory change (the ATMP provisions) – or informally, such as in emergent centres of collaboration within specific Trusts.

Some features of emerging niches, particularly formal aspects, may be more obdurate than others and have widespread effects. The ATMP framework, which stipulates that those RM products and procedures classified as 'ATMP' must be manufactured according to GMP standards, is an example of this: as we have seen the niche-forming activities in the clinical domain has involved mobilising the GMP facilities of the NHSBT infrastructure.

The niches make an important contribution to socio-technical change by opening up specific spaces where negotiation of the potential role and value of RM is enabled and where resources – regulatory, economic and clinical organisational – are mobilised. Together these three niches are helping to manage the novelty and 'matters of concern' posed by RM. These concerns derive from the bio-social problem of deriving, handling, stabilising and deploying live tissue which has been manipulated and, thereby, is not, in regulatory terms 'viable in nature'. Making it viable in healthcare systems requires considerable work. The niches explored here provide some of the key spaces that help to coordinate efforts to establish a broader socio-technical infrastructure for RM and make the eventual routinisation of the RM field more possible. Without them, it is likely that RM would remain a marginal and clinically very limited field. They are part of what in STS and innovation studies can be seen as the co-production of technologies and (clinical) markets (Coombs et al., 2003). However, the construction of niches can be a difficult and contentious process. For example, although the ATMP framework was positioned by proponents as a means to support RM, some investigators within the field have found it onerous: one responded described it as committing a 'category mistake', by defining cell therapy as a medicine rather than a device (which has less onerous regulation). Similarly, NICE's mock appraisal is based on an exemplar that may be far from generalisable. In both cases we see that the development of niches poses epistemic 'matters of concern' for some of the actors involved.

The construction of the niches reflect broader socio-political trends in the management of biomedical novelty; trends that may be opening-up current delivery and governance systems (the current *regime*) to regenerative medicine. These include a movement towards reconceptualising regulatory bodies as facilitators of innovation, rather than as simply mechanisms to protect the public from unsafe or ineffective interventions. This movement can be seen as what some authors have referred to as a 'proactionary approach' (Fuller and Lipińska, 2014) to regulation in which calculated risk-taking is seen as central to innovation (Mittra, 2016). This has been noted, for example, in the FDA's response to pharmacogenetics (Hogarth, 2015), and in more general calls for 'smart regulation' for speedier product approval processes, such as via progressive licensing/adaptive licensing arrangements. Such initiatives may be co-opted and mobilised in the development of RM innovation niches, and they may subsequently constitute a broader change in the 'socio-technical regime' (Geels, 2004). In regard to pharmaceuticals, commentators have argued that this reconfiguration of regulation is indicative of the increasing influence of commercial interests, particularly big pharma, in agenda setting for policy (Davis and Abraham, 2013). What we are seeing currently in regenerative medicine, however, is that the emerging regulatory niche is a consequence of a variety of initiatives each involving various interests. Key aspects of the emerging regulatory niche, for example, are the consequence of pragmatic negotiation between clinicians and UK regulators.

Another broader socio-political trend reflected in the initiatives to facilitate regenerative medicine is the instrumentalisation of the healthcare system as a machine for innovation and of wealth generation. In the UK, this is reflected in the emerging discourse on 'health and wealth' that surrounds the NHS (c.f. DOH, 2011). It can also be seen in initiatives such as the combining of patient DNA records in the government led '100,000 Genomes' project (Davis and Bale, 2014), and indeed the Health & Social Care Act 2012 which has designated research and innovation as key responsibilities for the NHS (2011). The formal recognition of some clinical sites as Centres of Stem Cell Excellence, for example, can be seen as a reflection of this trend.

6. Conclusion

The paper has argued that the three niches – of general importance to all emerging technologies - reflect specific socio-

technical spaces through which the stabilisation and management of regenerative medicine is made possible. They have emerged in response to perceived innovation challenges relating to the myriad of relevant regulatory tools, uncertainties about how to implement such tools, the potential high costs of emerging therapies, and logistical and delivery infrastructures within the clinic. These niches may serve to take RM beyond the restricted domain of clinician-dependent individual therapies (in which clinician may deploy cell therapies on a compassionate use basis for individual patients) and, in principle open up the possibility of a scaled-up RM field that becomes a 'going concern'. We have shown how within each niche we found processes relating to its creation, its articulation with existing structures, the role of both formal and more informal practices, and sites for negotiation among different parties. We expect that developments elsewhere – such in synthetic biology or neuroscience – could usefully be interrogated in a similar way by social science seeking to make sense of emerging medicine. Moreover, such work could help shape policy by showing how niche formation occurs and how formal policy-driven and informal processes might be optimally aligned.

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