The political economy of the global stem cell therapy market

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Introduction

Innovation in the life sciences in general and stem cell science in particular is driven by an interlinked set of global markets with many and various governance arrangement at national and transnational levels. Predominant among these markets are research funding, scientific labour, research materials, clinical labour (subjects for clinical experimentation and clinical trials), venture capital, patenting and, last but not least, health consumers. It is the operation of the latter market which, in the case of stem cell science, has provoked controversy across the globe in countries such as South Korea, Thailand, China, India, the US, Japan and Italy as the demand from health consumers for treatment of diseases as diverse as spinal cord injury, neuro degenerative disorders, diabetes mellitus, heart disease and Lyme Disease has collided with the capacity of medical science to deliver innovative stem cell therapies. Much of the commentary has approached the issue from a supply side perspective, demonstrating the extent to which national and transnational regulation fails to impose what are regarded as appropriate standards on the supply of stem cell therapies (see e.g. [1, 2]). In contrast, this paper presents a political economic analysis with a strong demand side perspective, arguing that the problem of what is termed 'stem cell tourism' is embedded in the demand-supply relationship of the health consumer market and its engagement with several models of stem cell therapy innovation. Different models mediate between the demand and the supply of stem cell therapies in different ways, producing a heavily segmented global market where a single approach to regulation cannot hope to be effective.

Nature of the stem cell therapy market

Until recently, stem cell science was regarded as having an uncertain future where the commercialization of stem cell therapies was problematic. Although that view still holds sway in some, largely Western, official circles, the reality is different. There exists a vibrant global stem cell therapy market where the expansion of both demand and supply shows no sign of slowing. Thousands of health consumers are being treated by hundreds of suppliers with China, India, Russia and Japan occupying a particularly prominent position in the market (Table 1). What has preoccupied commentators is that the majority of the market operates within and across national jurisdictions with what are judged to be ineffective regulatory regimes and largely avoids contact with jurisdictions that rigorously implement the orthodox regulatory frameworks typical of innovation in Western biomedicine. The ability of both health consumers and stem cell therapy providers to move easily across regulatory jurisdictions creates a market dynamic that has thus far outpaced national governance

attempts to define its character and growth. What is the nature of this market dynamic and how do different types of stem cell innovation contribute to its operation?

Table 1

The size of the stem cell therapy market in selected countries

Country	Number of Clinics	Number of patients
China	>300	>30,000
India	>45-50	>10,000
Russia	>100	>20,000
Japan	>20	>10,000

Data sources:
China: China MOH, quoted by Sina [101].
India: Estimate calculated from data [2, 3, 4, 102, 103]
Russia: [1]
Japan: [104] and [105]

The demand side

No-one should be surprised by the rapid growth in health consumer demand for stem cell therapies. Over the past decade, stem cell science has constantly encouraged the public to expect many and various health benefits from the large scale investment in this area of biomedicine. Health consumer demand has been stimulated and maintained through a flow of positive media stories. What has been termed the 'promissory politics' of stem cell science and the accompanying possibility of public frustration at the non-delivery of results is well documented [5]. But in addition to expressing frustration at the gap between the promise of stem cell science and the reality of the very limited supply provided through the conventional Western scientific model of stem cell innovation, health consumers have chosen to create their own reality by pursuing the many stem cell therapies that are produced outside that model. As a result, the science induced demand for stem cell therapies has stimulated a global supply of what the Western model regards as 'illicit' therapies. Equally importantly, the economic demand for the rapid delivery of the stem cell promise has generated a political demand for the adaptation of Western stem cell innovation governance in ways that would enable earlier delivery of the stem cell product to occur. In common with other examples of patient demands for more rapid innovation in the treatments for AIDS and breast cancer [6], economics and politics have gone hand in hand with some health consumers in the West demanding change in the established systems of innovation regulation in the face of strong

opposition from national and transnational scientific organisations, most recently in Italy where in May 2013 following protests by patient groups the Italian Parliament introduced legal changes to allow experimental stem cell therapies on 32 terminally ill patients to proceed [7, 106, 107]. The combination of increasing economic and political demand for stem cell therapies, on the one hand, and their limited supply in the jurisdictions of Western states, on the other, has politicized the global stem cell therapy market.

Demand is further facilitated by consumer information from suppliers that, like the information from stem cell science itself, is unremittingly positive. In this sense, consumer information continues to be asymmetric, reinforcing the promises of stem cell science [8, 9]. Online sources, including the websites of private companies, patient blogs, and internet articles provide the main basis for health consumer choice [10]. The majority of online evidence from stem cell therapy suppliers claims that their therapies offer a safe and efficient treatment for diseases that orthodox Western medicine regards as incurable or difficult to treat. This evidence may be supported by reassuring information regarding the certification of the business (eg GMP and ISO 9001), the holding of patents, the registered clinical trials for other conditions, and the professionals on company advisory boards [1]. In some cases, the information provided about the innovation process supporting the therapy blurs the boundaries between the stages of clinical experimentation, clinical trial and clinical application through the use of such terms as 'experimental clinical application' and the 'clinical use of stem cell therapy' and by displacing the term 'approved clinical *trial*' by 'approved clinical *application*' or 'approved experimentation for clinical *application*' [11].

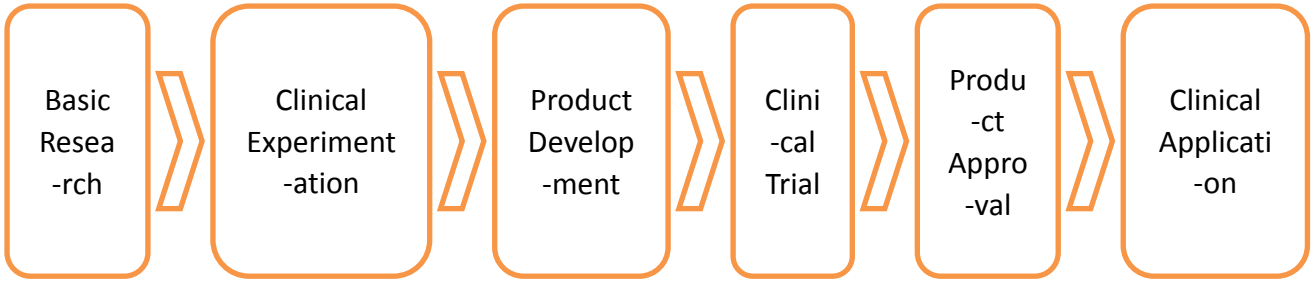
Global health consumer demand for stem cell therapies is a product not only of the 'pull' factors generated by positive information but also of the 'push' factors created by the engagement between a consumer's health status and the domestically available health care supply. In their discussion of the motivations of stem cell therapy consumers based on data gathered from open online disease-specific patient advocacy group forums, online forums responsive to news items about stem cell treatments, and closed online patient discussion groups for incurable conditions, Cohen and Cohen point out that the consumers who 'acknowledge that they are "desperate" appear to be knowledgeable about the dearth of evidence supporting certain stem cell treatments provided abroad and yet elect to receive them because they lack alternatives at home' [12, 13]. The constraints imposed by a particular disease condition, the proximity of pain and/or death, and the limits of local treatment serve to structure a calculation of risks and benefits with its own internalist rationality. Such a subjective rationality may be at odds with the rationality of the external observer, be they scientist, bioethicist or policy maker, and generate a demand with limited responsiveness to negative information about stem cell therapies.

The supply side

The global supply of the stem cell therapies available to health consumers varies in accordance with the stem cell innovation model employed to produce the stem cell therapy product. In the Scientific Innovation Model I (Table 2), the product does not reach the market until it has passed through the five stages of basic research, clinical experimentation, product development, clinical trial and product approval. Broadly speaking, the clinical application may be standardized products from a single stem cell line (allogeneic use) or standardized medical practices or procedures based on autologous stem cell use. Frequently, the simple linear flow of innovation is interrupted and rendered cyclical by the results of clinical trials which may require a return to the clinical experimentation stage or abandonment of the innovation [14].

Table 2

Stem Cell Innovation Model I – Scientific Innovation



Given the high demand for stem cell therapies, the clear market disadvantage of this model is the time and cost of product development. Including preclinical and clinical safety and efficacy testing, therapies can typically take 12-15 years and approximately €1 billion to develop – a difficult business model to sustain [15]. There are only eight approved stem cell therapies generated by this model in the global market (Table 6). Unsurprisingly, therefore, alternative models have emerged which seek to meet the demand at an earlier point in the stem cell innovation process: Model II - Medical Innovation (Western), Model III - Medical Innovation (Non-Western), and Model IV - Medical Innovation and Scientific Innovation (Tables 3, 4 and 5).

Table 3

Stem Cell Innovation Model II - Medical Innovation (Western)

Stem Cell Innovation Model II is largely based on the use of the Hospital Exemption within the EU's Advanced Medicinal Therapy Products (AMTP) Regulation 1394/2007 and other national provisions, such as the UK's 'Specials' scheme operating under an exemption under Article 5(1) of Directive 2001/83/EC and the recent legal provision by the Italian Parliament quoted earlier, which allow regulated clinician discretion in the provision of therapies that are not approved through the ATMP Regulation procedures themselves [16]. These procedures require the market authorization of ATMPs to be granted by the European Commission following assessment by the European Medicines Agency (EMA). However, as stated in Preamble 6 of the Regulation, in order to provide patients with the possibility of benefiting from a custom-made, innovative, individual treatment in the absence of valid therapeutic alternatives (i.e. respond to health consumer demand), Article 28 provides an exemption from central authorization for ATMPs that are prepared on a non-routine basis and used in a hospital within the same Member State for an individual patient in accordance with a medical prescription by a clinician (Hospital Exemption). Rooted in the professional space of the hospital clinician as opposed to that of the medical scientist, Model II is primarily legitimised through the authority of the clinician as caring professional rather than the authority of the biomedical scientific method within the innovation process, though the latter still has some part to play. As such it constitutes *medical innovation*, where the goal is the benefit of the individual patient, as distinct from *scientific innovation*, where the goal is scientifically generalizable results [17]. Thus defined, 'Medical innovation in cellular therapy may be viewed as the ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine'[18]. As the Belmont Report observes, although such a procedure may be experimental: 'When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research.' [108]. As innovative practice, rather than research, medical innovation must nonetheless be based on a scientific rationale and be safe. But the model does not include clinical trials and the efficacy of the therapy is not proven.

Its lack of visibility has led to it being described by some researchers as the 'hidden innovation system' where hospital based clinical development takes place outwith the normal structures of research governance [19, 20]. In the case of stem cell therapies, a unique

example of medical innovation being 'scaled up' through this system from the level of the individual clinician-patient interaction to the level of systematic population provision is the use of haemotopoietic stem cells (HSCs) in the treatment of blood cancers. Here treatment is overseen by the NHS Blood and Transplant (NHSBT) Special Health Authority working through a national network of over 20 specialist laboratories providing stem cell transplantation services [109]. Clinician led innovation within the hospital environment occurred over a period of four decades, characterised by non-linear development with regular recycling of procedures through the clinic and laboratory, before its position was formalised in 2005 within the NHSBT [21, 22]. No other type of stem cell therapy has achieved this degree of support for medical innovation from a public health service.

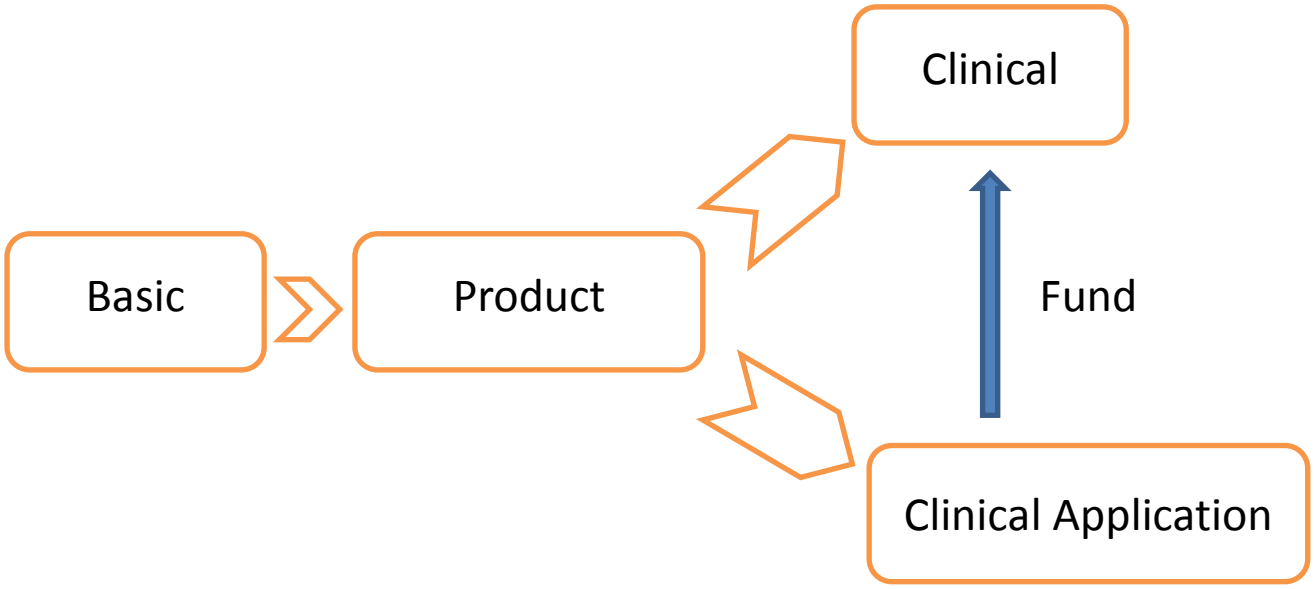
Nonetheless, the implementation in EU Member States of Medical Innovation Model II through the Hospital Exemption has created the opportunity for a legal market of authorised stem cell therapy products to emerge within the province of the clinical professional which parallels, and to an extent competes with, that of the ATMP centrally approved therapies market. As of October 2012, six EU Member States had authorised approximately 40 products under the Hospital Exemption provision and the UK 18 products under its 'Specials' scheme, though it is not known what proportion of these products were specifically stem cell therapies [110]. The effect of the procedural and legitimating shift initiated by Innovation Model II is that, through the use of what are intended as exceptional regulatory provisions, health consumer demand is met at an earlier stage in the innovation process than would otherwise be the case. The timing of the supply to the health consumer is brought forward. As the Alliance of Advanced Therapies points out, the emergence of this parallel supply may limit the market size and potential return on investment for future, centrally approved stem cell products [15] – with a possible negative impact on the economic viability of Scientific Innovation Model I. Effectively the two models are competing for position in a common global market. And they are not alone.

Table 4

Stem Cell Innovation Model III - Medical Innovation (Non-Western)

Table 5

Stem Cell Innovation Model IV - Medical Innovation and Scientific Innovation



In common with the Model II, Models III and IV provide innovative stem cell therapies in the hospital setting and use the authority of the clinician to legitimate their approach to innovation (Tables 4 and 5). Both therefore fall within the category of medical innovation. However, whereas Model II supplies therapies for single or small groups of patients in what is presented, at least in the case of the Hospital Exemption, as a non-routine exercise, both Models III and IV respond more readily and more comprehensively to health consumer demand and routinely provide therapies for large populations of patients. Models III and IV also share the characteristic that the clinical application of the therapy *is* the product: in the case of Model III clinical experimentation is a small or non-existent component of the engagement with the health consumer (see e.g. Nutech Mediworld, Xcell, Celltex and Unique Cell Treatment Clinic). In contrast, Model III combines elements of medical innovation and scientific innovation in a single business model. Here, some of the profits from stem cell medical innovation are re-invested in the funding of the registered clinical trials required for stem cell scientific innovation, but with regard to different diseases to those addressed by the treatment available through the medical innovation activity (e.g. Beike Biotechnology, RNL Bio, Chaitanya Stem Cell Therapy Centre) [1]. For example, through the medical innovation model Beike Biotechnology offers treatment for chronic and incurable neurodegenerative conditions such as brain injury and Parkinson's and in the last three years has registered nine self-funded registered clinical trials for diabetes, lupus nephritis, autism,

premature ovarian failure, Duchenne muscular dystrophy, progressive multiple sclerosis, liver cirrhosis, hereditary ataxia and burns [111]. A similar business model is used by Korean based RNL Bio which provides 'innovative medical technologies' for the treatment of Alzheimer's and Parkinson's in its China based clinics and has eight clinical trials registered in Korea for Buerger's disease, spinal cord injury (two trials), degenerative arthritis, vascular necrosis of the femoral head, progressive hemifacial atrophy, critical limb ischemia and lumbar intervertebral disc degeneration and one in the US for its adipose-derived stem cell product [111, 112]. In an extension of this model, Beike Biotechnology has combined its market generated finance with public funding from the Chinese Academy of Sciences for the establishment of the Beike Stem Cell Bank in support of its scientific research [113].

The national governance of stem cell innovation

The global market in stem cell therapies is driven by an intense, and apparently unlimited, demand for cures and treatments serviced by a supply chain that is the product of four different models of stem cell innovation with widely differing levels of responsiveness to health consumer demand. If we overlay this analysis with that of single or multiple sites of national regulatory jurisdiction and provide examples of the suppliers located in the resulting 'governance domains', the structural complexity of the governance of the global stem cell market becomes apparent, as does the difficulty of intervention faced by states and transnational organisations (Table 6).

Table 6

Jurisdiction and innovation model: governance domains of stem cell therapy provision

		Stem cell innovation model		
Jurisdiction	*Model I Scientific Innovation*	*Model II Medical Innovation (Western)*	*Model III Medical Innovation (Non-Western)*	*Model III Medical and Scientific Innovation*
Single national jurisdiction	*EU EMA Approved* TiGenix (ChondroCelect) *US FDA Approved* Duke University School of Medicine (Ducord) New York Blood Center (Hemacord)		Nutech Mediworld Bioengineering corporation Wu Stem Cells Medical Centre Unique Cell Treatment Clinic Spectrum Cell Clinic	Chaitanya Stem Cell Therapy Centre Zhongyuan Union Stem Cell

	Australia TGA Approved: Mesoblas (MPC) *Korea KFDA Approved* FCB-Pharmicell (Hearticellgram-AMI) Medipost (Cartistem) Anterogen (Cuepistem)			
Multiple national jurisdictions	*US FDA Approved:* Osiris (Prochymal) *Health Canada Approved* Osiris (Prochymal) *New Zealand Medsafe*: Osiris (Prochymal)		Cells4Health (Xcell) Celltex Therapeutics Shinjuku Clinic Hakatain Nuchi-In Centre for Regenerative Medicine	Beike Biotechnology RNL Bio

For the most part, once a company using Model I has gained market approval in one national jurisdiction, it then pursues licenses in others. For example, Osiris, a Canadian company, has received licenses from FDA, Medsafe (New Zealand) and Health Canada for its allogeneic stem cell drug-Prochymal®. By definition, stem cell therapy provision through the Model II is supplied by the clinician, rather than a company, who is obliged to work within the jurisdiction of a single EU Member State. Models III and IV contain examples of companies operating within single and multiple national jurisdictions. In the case of Model III, Nutech Mediworld successfully accesses the global market demand for stem cell therapies working solely within India's jurisdiction whilst the US based company Celltex has clinics in Mexico. Likewise, in the case of Model IV, Zhongyuan Union Stem Cell operates purely within the China jurisdiction whilst China-based Beike Biotechnology recruits foreign patients through local branches in the Czech Republic, Thailand, India and the US, has a clinic in Romania and cooperative arrangements with hospitals in India, Thailand, and the Philippines.

It is an interesting paradox that although the vast majority of the stem cell therapy market activity is in the domain of medical innovation (Models II, III and IV), the vast majority of the official policy discourse and public commentary focuses on the domain of scientific innovation (Model I): in other words, it neglects, and in some cases ignores, the political economy of the market outlined in Table 6. Hence, the regulatory debate has largely focused on the scientific innovation stages of clinical experimentation and clinical trials of Model I,

stages which are absent from the medical innovation models. Whilst the long history of this model of biomedical innovation in North America, Europe and Japan has produced governance arrangements that address these innovation components in considerable detail, governance is less developed in states such as the emerging economies which are still developing their capacity for innovation in the life sciences. Although in the BRICS (Brazil, Russia, India, China, and South Africa) the regulation of stem cell innovation is often formally present and reflective of the Model I principles, its effective implementation is limited by a number of factors [4, 13]. An initial problem is that language may impose a constraint on the translation of Western governance concepts into appropriate policy measures in a non-Western setting. Thus, for example, 'clinical experimentation' and 'clinical trial' are the same word in Chinese (临床试验) and Russian (клинические исследования). This has not prevented guidance being produced in both China [114] and Russia [115] but the linguistic limitations are clearly present – particularly when, as mentioned earlier, confronted by the tendency of suppliers to invent new terms such as 'clinical experimental application' to further muddy the conceptual waters. A related issue is present in India's *Guidelines for stem cell research (Draft)* where there is extensive guidance on clinical research and clinical trials but the term 'clinical experimentation' does not occur [116].

The confusion created by an absence of conceptual harmonization across national jurisdictions of the components of scientific stem cell innovation is compounded by variations in both the statutory basis of regulation and its effective translation through a dedicated bureaucracy. In this respect, we have already seen how the variable implementation of the EU's Hospital Exemption has implications for the viability of Model I. Likewise, although in China the regulation of stem cell therapies guidance is linked to the Drug Administration Law, the Medical Practitioner Law and the Administrative Regulations on Medical Institutions and in India to Schedule Y of the Drugs and Cosmetics Act, this legal authority as yet lacks the appropriate bureaucratic vehicle for effective implementation. At the same time, in China there is an abundance of governance space within which medical innovation occurs through the clinician-led professional authority of Models III and IV, subject largely to local self-regulatory imperatives. This stands in sharp contrast to medical innovation in Model II where the safety and quality of the stem cell therapy, if not its effectiveness, may, depending on the EU Member State, be situated within a specific set of regulations that constrain the freedom of the clinician. (Thus in the UK a hospital exemption requires approval from the MHRA, materials preparation under HTA license, and product manufacturing under a manufacturer's license from the MHRA. In addition, the product must comply with the principles of EU Good Manufacturing Practice (GMP), may need to be accompanied by a risk management plan, with adverse reactions to be submitted by medical practitioners to the MRHA, and traceability guaranteed according to Article 15 of the ATMP

Regulation, Tissues and Cells Directive (2004/23/EC) and the Blood Directive (2002/98/EC).)

Even in states with an established tradition of governance in Model I, the strength of health consumer demand coupled with the agility of companies operating with Models III and IV to create supply opportunities poses challenges to the policing of jurisdictions. Thus, in the US, there has been a running battle between the FDA which has responsibility for stem cell therapies (classifying them as biologic drugs) and companies such as Celltex Therapeutics. There, internet driven patient demand for stem cell therapies (one of whom was the Texas governor Rick Perry), tensions between state and federal level regulation of the field, and debate within the medical profession about the appropriate contribution to be made by self-regulation, have combined to politicize the stem cell therapy market in very visible fashion [23, 24, 25]. As a result, new rules were introduced by the Texas Medical Board which allow doctors to perform unproven stem cell procedures in the course of their research provided this takes place on the basis of informed consent and the approval of an Institutional Review Board: a combined form of scientific and medical innovation [117]. Meanwhile, in Australia, Model II is allowed alongside the rigorously regulated Model I: provided an unproven stem cell treatment is offered by a registered Australian doctor, is using the patient's own cells and is a one-patient treatment it does not fall within the remit of the Therapeutic Goods Administration (TGA – the Australian regulator of all medical devices, drugs and biological) [118].

A similar division in a single jurisdiction between the scientific innovation of Model I and the medical innovation of Model III is present in Japan where the supply side response to domestic demand for stem cell therapies, on the one hand, and foreign demand, on the other, is quite different. Until recently, in addition to following the 2006 *Guidelines on clinical research using human stem* cells, firms developing cell- or tissue-based products were required to conduct extra safety tests to gain permission to pursue clinical trials, with few passing this stage. Although this has been ameliorated by the introduction of an alternative and more accessible consultative procedure in 2011, the innovative hurdles to be overcome remain daunting [26]. However, the legal force of these arrangements is applied through the country's national insurance system so that doctors stand to lose their license if they use unproven therapies on Japanese citizens. This legal sanction does not apply to doctors treating foreign health consumers outside the national insurance system and it is in response to the demand from these, largely South Korean, consumers that Japan's flourishing stem cell therapy clinics have provided a supply of clinician-led medical innovation products [105].

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The transnational governance of stem cell innovation

The prevalence of Scientific Innovation Model I assumptions in national governance discussions and the corresponding neglect of the three medical innovation models is apparent also at the transnational governance level where there is a preponderance of guidance on the governance of the basic and pre-clinical stages of innovation. Underpinned by the work of the UK Stem Cell Bank, the International Stem Cell Forum (ISCF) and the International Society for Stem Cell Research (ISSCR) and supported by national research funding agencies, an international infrastructure for the governance of the basic stem cell science developed dealing with both technical and ethical issues of standardization [27, 28]. As a vehicle for scientific research, it has provided research funders with a secure locale for potential projects where national differences can be controlled. Hence, in 2012 the UK Medical Research Council (MRC) and the National Natural Science Foundation of China (NNSF) launched the one-year funding scheme 'UK-China Stem Cell Partnership Development Initiative' and this has been followed by the current joint call 'UK-China Stem Cell Research Collaboration' by the two partners– both initiatives are for basic and pre-clinical research only [119]. From the perspective of this governance infrastructure, it is then quite natural that guidance dealing with the process of innovation beyond the stages of basic and pre-clinical research should approach the task with Model I scientific innovation assumptions firmly in mind: as do the ISSCR's *Guidelines for the clinical translation of stem cells*. Here the view of medical innovation is that it should be used 'only in exceptional circumstances' with seriously ill patients because such innovation is not driven by the principles of the scientific method. Rather, the ISSCR states, 'the main goal of innovative care is to improve an individual patient's condition' - unlike clinical research which 'aims to produce generalizable knowledge about new cellular or drug treatments, or new approaches to surgery' [120]. The former value, the ISSCR implies, is of a lower status and significance than the latter, thus justifying the allocation of a marginal position to medical innovation.

However, in contrast to this, the International Society for Cellular Therapy (ISCT) maintains that medical innovation has an equal status with the science led innovation of Model I and that 'There is a place for both paradigms in the cell therapy global community' [18]. Taking a broader view of biomedical innovation, one that is inclusive of the demand side of the stem cell therapy market, the ISSCT argues that patients and their families or partners 'should have the right to seek treatment for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patient' [18]. So here we see the primacy of the health consumer in the formulation of the stem cell innovation model. Once consumer demand is accepted as a significant value in the construction of the model, it leads to an analysis of the supply side where scientific innovation and medical innovation are given equal weight and both assessed in terms not only of their scientific integrity but also their ability to respond to health consumer demand. As the ISCT puts it, 'Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell

therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed.' [18] For governance, the implication is that both medical innovation and the facilitation of consumer choice become an integral part of stem cell innovation. In practice,

> 'Patients therefore need to be equipped to understand the difference between (a) formal clinical trials and the innovative practice of medicine (where their rights are protected and risks are communicated) and (b) fraudulent cell therapy practice (where there are no protections, no demonstration of competency and misinformation is the rule). In practice, a continuum exists between these two extremes, with varying levels of scientific diligence.' [18]

As a demand side governance exercise, the provision of expert information which will enable potential health consumers to make an informed judgement on the risks and benefits of a stem cell therapy, be this science or clinician based innovation, remains a very minor governance component in the operation of the market - dominated as it is by supply side governance debates. The ISSCR has produced its *Patient handbook on stem cell therapies* and the Australian Stem Cells Foundation its *Australian Stem Cell Handbook.* However, the guidance is general rather than disease specific, structured according to the scientific innovation tenets of Model I, with medical innovation presented as an option which is only to be used as a 'one off' and 'under exceptional circumstances' [118].

In an attempt to explore further the demand side perspective in this matter in terms of whether patient organisations had a view of what information health consumers may require in order to make their choices, we conducted an internet based survey of 37 UK based patient organisations with a disease focus where stem cell therapy may be relevant. In each case the organisation's website was searched using the terms 'stem cell' and 'cell therapy' to determine: (a) whether stem cell therapy was deemed relevant to an organization and (b) if yes, which model of stem cell innovation was dominant in the information currently provided for patients (Table 7).

Table 7

Patient organisations and stem cell innovation model

Patient Organisation	No Interest in Stem Cell Therapy	Type of Stem Cell Innovation Model	
		Model I Scientific Innovation	Models I, II and III Medical Innovation
Rare Disease UK	X		

The Patients Association UK	X		
Brain and Spine Foundation		X	
British Lung Foundation		X	
Alzheimer Society		X*	
Amyotrophic Lateral Sclerosis		X*	
National Autism Society		X	
Autism Independent UK	X		
Ambitious about Autism	X		
Brain Injury UK		X	
The Cardiomyopathy Association		X	
British Heart Foundation		X*	
Heart UK	X		
Children with Crohns and Colitus	X		
Crohn's and Colitis UK		X*	
Cystic Fibrosis Trust	X		
Diabetes UK		X*	
Epilepsy Action		X	
Guillain-Barre Syndrome Support Groups	X		
Lymphoma Association		X**	
Leukaemia Care		X**	
Leukaemia and Lymphoma Research		X**	
Myeloma UK		X**	
Huntington's Disease Association		X	
Multiple Sclerosis UK		X	X
Multiple Sclerosis Trust		X*	
Multiple Sclerosis International Federation		X	
Multiple Sclerosis Society		X*	
Muscular Dystrophy Campaign		X*	
Arthritis Research UK		X	
Parkinson's UK		X*	
The Circulation Foundation	X		
Association for Spina Bifida and Hydrocephalus	X		
Scottish Spina Bifida Association	X		
Spinal Muscular Atrophy	X		

Note: *patient organisation also funds stem cell research; ** stem cell treatment for these conditions is provided under the auspices of the NHS Blood and Transplant Special Health Authority [121]

Of the 35 organisation websites surveyed, 34% (12) expressed no interest in stem cell therapies. Of the 66% providing information on stem cell therapies, all did so using the precepts of Model I, stating that 'research into stem cell treatments is only in its initial stages'[122], lacks appropriate measures of safety and efficacy, with a timescale of 'at least 5 to 10 years before clinical trials using stem cell therapy will be considered' [123], and that patients should avoid unproven treatments [124, 125, 126]. Only one organisation, MS-UK, expressed dissatisfaction with the timescale of Model I, presenting members' reports in support of Models II, III and IV citing improvements through stem cell treatments conducted in the UK NHS, the United States, and Mexico [127, 128, 129]. Clearly UK patient

organisations do not share the views of the health consumers accessing the stem cell therapy market.

Conclusions

In its 2013 report *Regenerative Medicine*, the House of Lords Science and Technology Committee observes that 'Regenerative medicine is a global market and, to attract investment and ensure the rapid development of the field, there is a need for greater harmonisation of regulatory standards and requirements across the world.' It therefore recommends: 'To realise the full potential of this global industry, and to ensure that the UK is an attractive location for regenerative medicine companies to invest in and to undertake their clinical trials in, the UK Government must take the lead in promoting harmonisation of regulatory requirements.' [29] Whilst this is an admirable goal, to be effective it has to be related to an understanding of the several innovation models that currently drive the global stem cell therapy market. What rules are being harmonized to facilitate the operation of which model? If the relationship between innovation model, demand and supply is ignored in the formation of regulatory policy, the evidence of this paper is that the market will continue to operate regardless of the good intentions of policy makers.

The economic and political significance of the different innovation models is that they mediate between the consumer demand for, and clinical supply of, stem cell therapies. In so doing, health consumer demand for stem cell therapies highlights the divisions between science based and clinician based models of innovation though its insistence that timescale is a significant, and in some cases a dominant, component of the consumer decision. As a result of this temporal component of demand, the more responsive medical innovation models have provided the majority of the global stem cell therapy supply, thus questioning the economic viability of Model I. In reply, the proponents of the latter model have sought to exclude, or severely limit, the medical innovation supply through increased propagation of the values and rules of their model at national and transnational levels, emphasising the exceptional nature of any medical innovation provision. This, in turn, has provoked a political reaction from health consumers, as in the Italian case, against the reiteration of the lengthy timescale of the scientific innovation model.

Other disciplines have recognised that science based innovation involving a necessary clinical trials stage is not the only available model of innovation. For example, in the last 40 years, only 10 to 20 per cent of surgical techniques were developed through a clinical trials process with specialities such as cardiac transplant and laparoscopic surgery emerging entirely without clinical trials [17]. The recognition that 'innovative practice' (medical

innovation) has a parallel validity with formal research as a vehicle for introducing new forms of treatment is reflected in the particular guidance that has developed to support it (see e.g. [30, 130]).

However, for the most part, the governance response to the global phenomenon of a supply chain of stem cell therapies based on medical innovation has been configured within the structures of research governance. This is unfortunate, for two reasons. First, from the Belmont Report onwards, all are agreed that medical innovation is an extension of practice, not a form of research (though it may, and some would argue should, lead to research as a form of validation). Second, as a form of practice, medical innovation is driven by the ethics of patient care, not the ethics of research and its search for generalizable knowledge about new cellular or drug treatments, or new approaches to surgery. Given the consequent differences and tensions between the conduct of innovation in practice and research based professional cultures, it would seem sensible for medical innovation to have its own governance arrangements, even if these overlapped with those of research at particular points.

On the demand side, governance measures to facilitate informed health consumer choice require the development of an infrastructure which, largely as a result of the supply side focused governance debate, is almost entirely absent. Network partnerships between those with the relevant scientific and regulatory expertise (eg ISSCR, ISCT, AAT, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH)) and patient advocacy organisations with consumer legitimacy could produce and disseminate via the internet materials and guidance geared to the diseased based demand for specific treatments). Feedback from consumers, positive and negative, could be integrated with this web-based resource. Whilst, as Mason and Manzotti observe, 'the overarching principle must be that the potential benefit for the patient justifies the potential risk including taking into account the likelihood of harm of stem cell tourism, be it physical, psychological or financial'[31], the decision regarding the risk-benefit relationship should be made by the consumer because it will always be subjective and informed by personal circumstances. To ignore the health consumer dimension as a necessary field of governance is to ignore the political and economic reality of the stem cell therapy market and the fact that it is here to stay.

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