WORKING PAPER 48

Governing new global healthcare markets: the case of stem cell treatments

Rising Powers Research

funded by the

Economic and Social Research Council (UK ESRC)

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May 2015

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Introduction

Health consumers regularly purchase treatment through a global healthcare market with the capacity to deliver both established and new forms of therapy. One new and rapidly developing market is that of stem cell therapies where intervention occurs to replace or regenerate human cells, tissue or organs in order to restore or establish normal function. Innovative treatments are available for a wide range of conditions including spinal-cord injury, muscular dystrophy, optic nerve hypoplasia (ONH), septo-optic dysplasia (SOD), Lyme Disease, diabetes, ataxia, cerebral palsy and Parkinson's with a potential market value projected to rise from $26 billion in 2011 to $119 billion in 2018[i]. Hundreds of clinics worldwide are treating thousands of patients (Table 1).

The major political difficulty confronting the governance of this global innovation market is that the majority of the supply is from providers utilizing practice-based models of biomedical innovation whilst only a very small supply has been generated by the orthodox science-based model of innovation. To date, much of the analysis of the governance problem has adopted a supply side perspective informed by the values of the orthodox model, arguing that national and transnational regulation has failed to impose what are regarded as appropriate standards on the 'illicit' supply of stem cell therapies. The practice based model of stem cell innovation used by stem cell clinics is condemned as unproven, unsafe and illegitimate by supporters of the orthodox science based model of stem cell innovation and consumers who purchase such stem cell therapy products are dismissed as ill-informed 'stem cell tourists'[ii]. International scientific organisations such as the International Society for Stem Cell Research (ISSCR) warn strongly against consumer use of the clinics[iii], states with an established tradition of regulation in orthodox biomedical innovation look to tighten their rules to prevent or restrict their operation[iv], and bioethicists discuss how better to protect what are assumed to be vulnerable health consumers from exploitation by what are assumed to be mercenary clinicians[v].

In contrast, this paper presents a political economic analysis with a strong demand side perspective, arguing that the issue of what is termed 'stem cell tourism' is embedded in the demand-supply relationship of the health consumer market and its mediation by different models of stem cell innovation governance. Given the nature of the market dynamic, policy recommendations on the governance of stem cell innovation that neglect this perspective are unlikely to be productive. The paper begins with the challenges posed by the rise of the global health consumer. What is the nature of the economic and political demands by health consumers on the global health care market, how do the two types of demands interact, and what are their implications for the emergence of new health treatments? Second, it examines the engagement between these demands and different models of stem cell innovation governance. In what ways do innovation models mediate between consumer demand and the emerging health care supply? What are the implications of this mediation for the competitive position of a particular model in the global stem cell therapy market? Third, it relates the operation of this market dynamic to the existing structures of national and transnational governance in stem cell innovation. What synergies and dissonances are thus revealed in the interaction of market dynamic and governance form?

Global health consumers: economic and political demand

In large part, consumer demand for established and new forms of health care has traditionally been mediated through the role of the doctor acting to define demand in terms of 'clinical need'. In economic terms, an 'agency relationship' between professional and consumer

characterised by an asymmetry of information between a principal (an uninformed player) and an agent (an informed player) who acts on behalf of the principal[vi]. The distinctive and important dimension in health care is that the consumers' agents (the doctors) are also the suppliers of health care. As a consequence, and unlike other market situations, the utility functions of doctor and patient are no longer independent but interdependent: the provider has interests which are partly congruent and partly in conflict with those of the consumer.The control of this inherent instability in the traditional model of the consumer-doctor relationship is dependent upon, firstly, the maintenance of public trust in medical expertise as the only valid source of knowledge in the doctor-patient encounter and, secondly, regulation of consumer access to alternative sources of information. If both these conditions are fulfilled then the operation of a health care market where consumer and provider power are more evenly balanced is prevented and medical hegemony maintained.

The rise of health consumerism to challenge the traditional model has taken a number of economic forms ranging from global access to common and standardised modes of orthodox treatment, through the expansion of demand for complementary and alternative medicine (CAM), to the 'direct to consumer' (DTC) internet-based market trading in pharmaceuticals and the new technologies of genetic testing. Common to all is a re-assessment of the consumer-doctor relationship which, Haug and Levin argue:

> 'focuses on the purchaser's (patient's) rights and the seller's (physician's) obligations, rather than on the physician's rights (to direct) and the patient's obligations (to follow directions)….In a consumer relationship, the seller has no particular authority; if anything, legitimated power rests in the buyer who can make the decision to buy or not to buy as he or she sees fit'[vii].

Accompanying this position may be the assumption that 'consumerism implies the buyer's challenge of the seller's claims….an approach of doubt and caution, rather than faith and trust, in any transaction including the medical'[viii]. The implications of this shift for the nature and governance of the patient-doctor relationship are considerable. Effectively the market acts to increase the sensitivity of doctors to patient needs and to the information that patients bring to the patient-doctor transaction. In so doing, it brings to the fore the importance of the core medical value of the patient interest; a value which, as we shall see in the case of innovative treatments, may be challenged by the scientific interest of creating generalizable knowledge. The role of patient as consumer thus acts to emphasise the importance of the protection of the patient in the governance of the patient-doctor relationship.
At the global level, the expression of the consumerist ethos in health care has benefitted from the liberalising effects of the free movement of goods and services promoted under the auspices of the World Trade Organization and its General Agreement on Trade in Services[ix]. Supported by an enabling infrastructure of affordable travel, facilitating agencies, internet based advertising and information and investment by governments keen to access foreign revenue, the global market for orthodox health care has expanded rapidly with new suppliers particularly in emerging economies such as India, China and Singapore. Available treatments span the full range of medical services but most commonly include dental care, cosmetic surgery, elective surgery, and fertility treatment[x]. Figures on the market size range from approximately 8 million cross-border patients generating a market value of USD 24-40 billion per year[xi] to a market size of USD 60 billion and upwards[xii].

Similarly in CAM, the evidence is of increasing numbers of active health consumers prepared to purchase the service they want at a personal cost to themselves rather than rely exclusively

on the advice of doctors and conventional treatment provided through state or insurance funded systems of reimbursement.In the UK, in 2005 the Health Survey of England reported a 26 per cent prevalence of CAM use in the last 12 months. Internationally the figure is higher with 12 month prevalence of CAM use reported as 62%, 69% and 76% in the Germany, Australia and Japan[xiii]. In the United States, Eisenberg *et al* found that between 1990 and 1997 the total visits to alternative medical practitioners (defined as a specific list of 16 therapies) had increased by 47 per cent from 427 million to 629 million, thereby exceeding total visits to all US primary care physicians[xiv]. More recent data confirms that the trend has continued. The 2007 National Health Interview Survey reported that 38 per cent of American adults had used some type of CAM during the prior 12 months with an out of pocket expenditure of $33.9 billion[xv].

With health consumers providing strong indicators of their willingness to exercise their demand in the market of non-conventional health care independently of the clinical judgement of doctors, the suppliers of conventional drugs and therapies recognised the market opportunity this represents by developing their own direct-to-consumer (DTC) approach[xvi]. In bypassing the information gatekeeping role of the doctor, it is in the interest of industry to encourage demand from the consumer as well as from the professional. And with consumers increasingly using the internet not only to access health information but also to inform their health care decisions, the means to achieve this are readily available[xvii]. In the US, the regulatory changes introduced by the FDA in 1997 and 1999 allowing DTC advertising resulted in an increase of spending on such advertising from $150 million in 1993 to $4.24 billion in 2005 with the consequent impact on demand producing an estimated 18 per cent increase in drug expenditures[xviii]. More recently, DTC advertising has been used to promote a small industry of genetic testing, largely independent of any regulatory control, where consumers can access genetic information about themselves to predict, diagnose or guide treatment on genetically-related diseases. Much of the consumer demand in this field, particularly in the sub-sector of pharmacogenomics, is well ahead of the ability of conventional medicine to provide an appropriate supply[xix].

The increased economic activity of health consumers through markets that operate independently of the traditional demand-control function of the medical profession has been matched by a rise in the number and variety of groups representing their interests. Economic and political demand have expanded together. Traditionally, disease-based patient organisations acted as adjuncts to the medical science project, helping to gather resources in support of that project through fundraising and, where providing advice to patients, acting within the medical definition of patient need[xx]. However,in the last two decades Europe and the US have witnessed both a rapid increase in the number of health consumer groups and a broadening of their functions to include service user groups (eg Survivors Speak Out, Mindlink), condition-related groups (eg National Schizophrenic Fellowship, Manic Depression Fellowship, Depression Alliance) and advocacy groups (eg UK Advocacy Network)[xxi]. No longer working within the orthodox medical paradigm where the assumptions of physician knowledge and authority dominate, the new breed of health consumer groups are prepared to challenge the implications of those assumptions for the operation of the health care market by promoting their own distinct definition of patient demand.

The engagement between the economic and political demands of health consumers is influenced, and in some cases stimulated, by the maturity of the sector of the market they inhabit. In the case of established health care treatments, CAM, and DTC products such as

pharmacogenomics, the global supply can easily meet the consumer demand. In the case of new and emerging therapies, there are increasingly examples of a mismatch between what health consumers, on the one hand, and scientists and clinicians, on the other, deem a timely and legitimate supply. As the health consumer economic demand is thus frustrated, so it translates into both a continuing global search for new sources of treatment and a political demand for change in the way in which the new supply is generated through biomedical innovation. Perhaps the most celebrated example of this is the case of HIV/AIDS where the politicisation of health consumer demand through patient organisations, lobbying and the media caused a radical reassessment of both the role of patients in the biomedical innovation process, particularly with regard to access to clinical trials, and the values that should govern that process[xxii]. Other consumer groups who have questioned, and in some cases rejected, the accepted right of medical science to be the sole arbiter of the patient contribution to innovations in their own treatment include women, disability groups, and those with neuromuscular disease[xxiii]. The model of patient driven research is becoming a public reality.[xxiv] So although the orthodox model by which new health therapies are researched and developed remains politically intact, precedents have been established for its underlying values and legitimacy to be challenged and changes proposed[xxv].

Turning now to the stem cell therapy market, we encounter a consumer demand expressed across the considerable range of diseases mentioned earlier, constantly encouraged by a stem cell science optimistic of many and various health benefits, to a degree that has been described as amounting to 'promissory politics'[xxvi]. The 'hype and hope' of the stem cell science narrative, aided and abetted by a media diligently pursuing its customary quest for new cures, has fostered large consumer expectations[xxvii]. Online sources, including the websites of private companies, patient blogs, and internet articles provide the main basis for health consumer choice[xxviii]. Suppliers see no reason for denting consumer expectations and demand is enhanced by their provision of consumer information which, like the information from stem cell science itself, is unremittingly positive, claiming that the therapies offered provide a safe and efficient treatment for diseases that orthodox Western medicine regards as incurable or difficult to treat[xxix]. In this sense, consumer information from suppliers continues to be asymmetric, reinforcing the promises of stem cell science[xxx].

In addition, an important characteristic of global health consumer demand for stem cell therapies is that it is a product not only of the 'pull' factors generated by such 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. 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 rationality and values. Such a subjective rationality may be at odds with that of the external observer, be they scientist, bioethicist or policy maker, and generate a robust demand with limited responsiveness to negative information about stem cell therapies and a high tolerance of health risk[xxxi]. It cannot be assumed that such a consumer demand will behave in a manner consistent with the values of orthodox models of biomedical innovation. It may display its own logic, dynamic and direction requiring a shorter timescale in the delivery of new treatments and access to innovation models with the capacity to respond accordingly.

As is the case with other sectors of the health care market such as HIV/AIDS, the collision between the economic demand for stem cell therapies and the very limited supply available within the jurisdiction of many Western states may metamorphose into political demands for change in the governance of stem cell innovation to enable the earlier delivery of new

treatments. Thus, in the US, an internet driven consumer demand for stem cell therapies has fuelled a continuing conflict between the Federal Drugs Agency (FDA) which has responsibility for stem cell therapies (classifying them as biologic drugs) and Celltex Therapeutics regarding the legality of its treatments. The resulting 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 to its governance, combined to politicize the stem cell therapy market in very visible fashion[xxxii]. As a result, new rules were introduced by the Texas Medical Board to 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[xxxiii]. A second example is Italy where in May 2013 protests by patient groups led the Italian Parliament to introduce legal changes to allow experimental stem cell therapies by the Stamina Foundation on 32 terminally ill patients to proceed despite strong opposition from national and transnational scientific organisations[xxxiv]. The resolution of the political conflict remains uncertain following a subsequent report from an expert panel of leading scientists appointed by the Italian Minister of Health which concluded that the therapies lacked any scientific foundation[xxxv]. Nonetheless, regardless of the outcome, stem cell therapy consumers in Italy have made their political mark in the debate about how stem cell innovation should be constructed.

Innovation model and stem cell therapy supply

The economic and political demand for new stem cell therapies engages with a global supply that varies in terms of both timing and quantity in accordance with the innovation governance model employed. Although the data on the global stem cell therapy market is scanty, it consistently points towards a supply side largely based in the emerging economies, plus Japan, with a very limited presence in Western states (Table 1).

Table 1[xxxvi]

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

The reasons for this imbalance are not hard to find. Stem cell innovation in the West is dominated by Stem Cell Innovation Model I – Scientific Innovation (Table 2) where, following the orthodox drug development model, 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 and delay or abandonment of the innovation entirely[xxxvii]. Given the high demand for stem cell therapies, the time and cost

of product development required by this model puts it at a clear market disadvantage with therapies typically taking 12-15 years and approximately €1 billion to develop – a difficult business model to sustain[xxxviii]. As a result, there are only seven approved stem cell therapies generated by this model in the global market[xxxix] (Table 6).

Table 2

Stem Cell Innovation Model I – Scientific Innovation

The mismatch between demand and supply that characterises the operation of Model I has encouraged the emergence of alternative models 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, which allow regulated clinician discretion in the provision of therapies that are not approved through the ATMP Regulation procedures themselves[xl]. 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 an example of *medical innovation*,

where the goal is the benefit of the individual patient, as distinct from *scientific innovation* which characterises Model I, where the goal is scientifically generalizable results[xli]. 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'[xlii]. It must be scientifically based and safe but does not include clinical trials and the therapy remains unproven.

Such medical innovation is regarded as a form of practice, not research, and therefore its governance falls within the normal regulation of the professional standards of medical practice by licensing bodies and medical malpractice laws and not within the purview of science[xliii].

The implementation in EU Member States of Stem Cell 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 pursued by Model I. 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[xliv] – 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 thus creating a more heterogeneous supply. 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 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 operate in the governance jurisdictions of emerging economies such as those of China and India which allow them to respond more readily 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. NutechMediworld, Xcell, Celltex and Unique Cell Treatment Clinic). In contrast, Model IV 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 dealing with safety and efficacy 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)[xlv]. For example, using Model IV, 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[xlvi].

Market dynamic and 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 governance with widely differing levels of responsiveness to health consumer demand. To explicate the political economy of the engagement between this market dynamic and the governance of stem cell innovation, we can combine innovation models and governance jurisdictions to identify eight types of'governance domains' within which can be placed examples of stem cell therapy suppliers. The structural complexity of the governance of the global stem cell market thus becomes manifest, 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 IV Medical and Scientific Innovation*
Single national jurisdiction	*US FDA Approved* Duke University School of Medicine (Ducord) New York Blood Center (Hemacord) *Australia TGA* Approved: Mesoblas (MPC) *Korea KFDA Approved* FCB-Pharmicell (Hearticellgram-AMI) Medipost (Cartistem) Anterogen (Cuepistem)		NutechMediworld Bioengineering corporation Wu Stem Cells Medical Centre Unique Cell Treatment Clinic Spectrum Cell Clinic	Chaitanya Stem Cell Therapy Centre Zhongyuan Union Stem Cell
Multiple national jurisdictions	*Health Canada Approved* Osiris (Prochymal) *New Zealand Medsafe*: Osiris (Prochymal)		Cells4Health (Xcell) Celltex Therapeutics Shinjuku Clinic Hakatain Nuchi-In Centre for Regenerative Medicine	BeikeBiotechnology RNL Bio

Note: 'Stem cell therapies' are defined as treatments derived from the manipulation of stem cells. Such treatments may be delivered by drug or surgical interventions and their precise governance route to approval will vary accordingly.

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 US based company, has received licenses from Health Canada and Medsafe (New Zealand) for its allogeneic stem

cell drug-Prochymal® for the treatment of GvHD in children. By definition, stem cell therapy provision through Model II is supplied by the clinician working within the jurisdiction of a single EU Member State and therefore no companies exist in this category. Models III and IV contain examples of companies operating within single and multiple national jurisdictions. Thus, 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,and a tribute to the hegemony of Model I values, 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, the discourse neglects, and in some cases ignores, the role of medical innovation in 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 stem cell 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 growing their capacity for innovation in the life sciences.

In practice this means that although regulation in the BRICS (Brazil, Russia, India, China, and South Africa) reflective of Model I assumptions is often formally present, its implementation is limited by a number of factors[xlvii]. 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 and Russia but the linguistic limitations are clearly present[xlviii]. In India's *Guidelines for stem cell research (Draft)* there is extensive guidance on 'clinical research' and 'clinical trials' but the term 'clinical experimentation' does not occur[xlix]. The confusion created by an absence of conceptual harmonization of the components of Model I across national jurisdictions is compounded by variations in both the statutory basis of regulation and its effective translation through a dedicated bureaucracy. For example, although in China guidance on stem cell innovation 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.

Transnational governance and consumer choice

The prevalence of Model I scientific innovation assumptions in national governance discussions and the corresponding neglect of the three medical innovation models is reflected at the transnational governance level where there is a preponderance of guidance on the governance of the basic and pre-clinical stages of stem cell 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[l]. 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'[li]. 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.

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'[lii]. Taking a broader view of stem cell innovation, one that is inclusive of the demand side of the stem cell therapy market, the ISCT 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'[liii]. Here, for the first time, we see the primacy of the health consumer in the formulation of stem cell innovation governance. Its conceptual impact is significant: once consumer demand is accepted as an important 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.'[liv]. For governance, the implication is that both medical innovation and the facilitation of consumer choice become an integral part of stem cell innovation and a new dimension of consumer oriented rules has to be considered.

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 global stem cell therapy 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'.

The potential exists for both public and private governance to make a contribution to the supply of relevant information to consumers of novel stem cell therapies in a manner comparable to the demand side governance available in the global market of established health care treatments. There is a global standard setting and monitoring market of governance relevant to the cell therapy field, one keen to sell its products to stem cell clinics which need to bolster their clinical respectability in the eyes of potential clients. In terms of quality of process and safety, an existing market of standardised measures (eg Good Clinnical Practice, Good Manufacturing Practice, Good Laboratory Practice, Good Clinical Practice) is provided by national, international and private organisations (eg US Food and Drugs Administrarion, UK Medicines and Healthcare Products Regulatory Agency, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, World Health Organisation) which some clinics already claim to access. More specifically, the International Cellular Medicine Society (ICMS) has produced guidelines for best practice in cell based medicines and has recently formed an alliance with the American Association of Blood Banks (AABB) for the production of a global accreditation programme for stem cell clinics[lv] (AABB, 2013). Thus, for example, the Chinese firm Beike Biotechnology has AABB accreditation for its somatic cell facilities and cord blood bank. If health consumers are to make an informed choice about the safety of the stem cell therapy product they are considering purchasing then clearly they should be aware of the importance of these standards indicators. Equally, in terms of efficacy, although stem cell clinics do not publish systematic data on the results of their interventions there is no reason why consumers should not provide evidence of their experiences through patient-centred websites as is customary practice in the wider health care market[lvi] (Herrick, 2007: 16).

Conclusions

The orthodox model of stem cell innovation is characterized by a supply side focused mode of governance where regulation addresses the rules and values that should govern the operation of the science and its engagement with the patient. The market and consumer demand are not present in this governance model except to the extent that it is assumed they will welcome the eventual product. As a hegemonic form, the model maintains its political dominance and the political economy of stem cell innovation its stability so long as consumers accept that it is the only legitimate way of producing new stem cell products and no alternative models emerge to challenge that belief. When those conditions no longer pertain, a fresh dynamic is created and the political economy of innovation begins to take new directions. As it does so it is fuelled by a growing tide of health consumerism accustomed to making choices not only about the health products purchased but also about the way in which those products are created and delivered.

In this context, the economic and political significance of the four models of stem cell innovation governance is that they mediate between the consumer demand for, and clinical supply of, stem cell therapies. Health consumer demand for stem cell therapies highlights the divisions between science based and clinician based models of innovation through 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 the assiduous propagation of the values and rules of their governance model at national and

transnational levels of governance, emphasising the exceptional nature of any medical innovation provision. This, in turn, has provoked a political reaction from health consumers against the reiteration of the lengthy timescale of the scientific innovation model and demands for changes in the modes of innovation governance.

The continuing iteration between health consumer demand, changing models of innovation governance and clinical supply constitutes the dynamic of the political economy of stem cell innovation to which governance must respond if it is to remain relevant. At present it remains a political economy still dominated by the governance hegemony of Model I values and the exclusive assumptions this model embodies regarding the very limited acceptability of medical innovation. As yet, the economic and political issues posed by Models II, III and IV have not carried sufficient weight to challenge explicitly this hegemony at national and transnational levels in order to allow open discussion of either more sophisticated modes of supply side medical innovation governance or very basic demand side governance. Instead, the models have operated in Western jurisdictions where they are marginalised and those of the emerging economies where they are tolerated or ignored. However, it is likely that as consumer choice becomes a more legitimate component of the debate about stem cell innovation governance, it will lead to an assessment of the appropriateness of models of scientific and medical innovation governance in terms not only of their scientific integrity but also their ability to respond to health consumer demand. The more that consumer demand is accorded an explicit role in discussions about innovation governance, the more likely it is that medical innovation will become an accepted feature of the governance agenda.

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