

## Bionetworking and strategic linking between India and Japan: how clinical stem cell intervention continues despite new regulatory guidelines

Article (Accepted Version)

Patra, Prasanna Kumar and Sleeboom-Faulkner, Margaret (2017) Bionetworking and strategic linking between India and Japan: how clinical stem cell intervention continues despite new regulatory guidelines. East Asian Science, Technology and Society: An International Journal. ISSN 1875-2160

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## **Bionetworking and Strategic Linking between India and Japan: How clinical stem cell intervention continues despite new regulatory guidelines**

Received: 19 August 2016 / Accepted: 20 March 2017

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### **Abstract**

Based on a case study of a clinical stem cell intervention (CSCI) centre in Chennai in India, this paper explores distinct entrepreneurial strategies for the promotion of unrecognized clinical stem cell application in India. It shows that the Centre - an Indo-Japanese joint-venture – is able to promote the CSCI due to its central position in a network relationship, its possession of specialized skills and knowledge, and because of its ability to maneuver, identify and utilize the latent value of other actors in the network. We have deliberated on the developmental history of the making and remaking of regulation, and the shift in the way clinical stem cell application providers' function – from institutional embedment to strategic linking through collaborative networks. We ask why and how unauthorized clinical applications are sustained and promoted in India. We conclude that this is possible as a result of a number of factors: jurisdictional ambiguity, institutional inability, issues concerning the legally enforceability of the relevant guidelines, the complexity of the collaborative-network structure that facilitates the circumvention of the regulation, and the non-functioning of apex level committees.

**Key words:** Bionetworking, Strategic Linking, India, Japan, Clinical stem cell intervention

### **Introduction**

Over one and half decades, notwithstanding its modest global standing in science and technology innovation, India has emerged as a major player in the stem cell sector expressed in research activities, including the creation of embryonic stem cell lines, a steady flow of patients in search of stem cell treatment, an increasing number of clinics and hospitals, and

the publication of scientific papers (Inamdar et. al. 2009; Sharma 2009; Patra & Sleeboom-Faulkner 2010; Tiwari and Desai 2011; Bharadwaj 2012; Tiwari & Raman 2014). Both government and private institutions and industries have invested heavily in stem cell research, its clinical application and the production of cell-based therapeutic products (Sharma 2006; Bharadwaj 2014). While these efforts are highlighted nationally and internationally (Salter 2008; Lander et.al. 2008, Tiwari & Raman 2014), significant concerns have been raised since the early 2000s over unproven stem cell treatments being offered at government and private clinics, hospitals and companies with apparently little regulatory oversight (Jayaraman 2005; Srinivasan 2006; Pandya 2008; Patra & Sleeboom-Faulkner 2009, 2011; Tiwari & Raman 2014). These therapies are understood to be lacking in preclinical evidence of their efficacy and safety (Cohen &Cohen 2010). Companies and institutions providing stem cell intervention offer very little or no information about the terms of reference on the medical conditions that necessitated the intake of patients, the scope of pre-clinical studies, whether informed consent has been provided by the patients and whether these treatments have duly been approved by an authorized regulatory body (Cohen &Cohen 2010; Sleeboom-Faulkner 2010; Tiwari & Raman 2014).

In 2002, the Indian Council of Medical Research (ICMR), institutionally located under the health ministry, announced a policy that permitted therapeutic cloning and encouraged stem cell research. But, the previous year the Department of Biotechnology (DBT), under the science ministry, had also issued guidelines, and some clinics had exploited the difference between the two sets of guidelines, starting clinical treatments (Jayaraman 2005).

Subsequently, with an increasing number of funding applications to the ICMR and the DBT, media reporting of unethical practices in biomedical research, and India's growing thrust on stem cell research, the DBT and ICMR in 2005 decided to jointly devise guidelines, which were released as the Guidelines for Stem Cell Research and Therapy in November 2007 (DBT-ICMR 2007). The guidelines permit research pertaining to adult and umbilical cord blood stem cells if approved by Institutional Ethics Committees.

One would have expected that with the introduction of the 2007 guidelines, the provision of what were regarded as 'unrecognized' stem cell intervention to be unavailable. The guidelines did have some influence over government-funded hospitals (e.g. AIIMS, New Delhi) as adherence to guidelines was linked to funding from the central ministries (Tiwari &

Raman 2014, Tiwari & Desai 2011, Patra & Sleeboom-Faulkner 2011). However, guidelines had little impact on private clinics, hospitals and companies, which constituted a large part of stem cell related activities in India. Reports about the availability of unrecognized stem cell intervention at increasing numbers of private clinics, hospitals and companies surfaced in media reports, internet blogs, science magazines and medical ethics journals (Kahn 2007; Pandya 2008; Salter 2008; Bharadwaj and Glasner 2009; Khullar 2009; Patra & Sleeboom-Faulkner 2009; Cohen and Cohen 2010; Dhar 2010; Jain 2010). Some critics argued that the 2007 guidelines lacked legislative force (Pandya 2008, Patra & Sleeboom-Faulkner 2011, Tiwari and Raman 2014).

The cumulative consequence of these reports, coupled with the aim to project India as a responsible player in global stem cell science, forced the policy and regulatory bodies in India, such as the Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) to revise the regulatory guidelines formulated in 2007. Starting in 2010, the revised stem cell guidelines were prepared in December 2013. After several rounds of public consultations in different parts of the country and deliberations by expert committees, the revised ‘Guidelines for Stem Cell Research’ (2013) was published. The new guidelines omitted the term ‘stem cell therapy’ from its title page, and announced a stricter oversight through a more active National Apex Committee (NAC) (Gupta & Gandhi 2014). In its Foreword, the document declared that the revised guidelines would “reflect new scientific and clinical findings that have significantly changed the scope of stem cell research and possible translation”. While discussing the changes in the mechanism for oversight, it said “an additional layer of oversight, besides the Institutional Ethics Committee (IEC), in the form of Institutional Committee for Stem Cell Research (IC-SCR) and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been introduced. This mechanism of additional review has been accepted by the scientific community in the country and the required NAC-SCRT has become operational. The role and functioning of these committees is being streamlined” (ICMR-DBT 2013). This meant that no stem cell intervention would be considered for certification; only clinical stem cell trials. The refusal to address “stem cell therapy” in the regulation thus marginalized the lion share of India’s providers of stem cell intervention.

The above discussion describes the linear development of stem cell guidelines in India. What we have found, however, is that while the development of guidelines as a response to controversy seemed to be straightforward, the question of jurisdictional authority over their

implementation has been more complicated (Tiwari & Raman 2014). The question arises here, whether this jurisdictional authority or lack of it has been the reason for the unceasing availability of unproven stem cell treatment at an increasing number of private clinics, hospitals and companies at many locations in India. It is important to note here that neither the ICMR nor the DBT has a legislative remit over medical research in India. The ICMR is the apex body in India for the formulation, coordination and promotion of biomedical research, and DBT is a department under the Ministry of Science and Technology responsible for administrating development and commercialization in the field of modern biology and biotechnology in India. None of them have a remit over the activities taking place outside government-funded R&D (research and development) programs.

The Drug Controller General India (DCGI) under the gamut of the Central Drug Standard Organization (CDSCO) is responsible for the regulatory control over the import of drugs and the approval of new drugs and clinical trials. It is frequently characterized as the “Indian FDA” and it would have been the obvious candidate to extend its remit to stem cells. In the early days, it appeared that the DCGI was uncertain about the reach of its powers which may be due to the fact that it is only nominally similar to the FDA, with a remit primarily related to drug approvals (SundarRajan 2007). In their study, Tiwari and Raman (2014) held that the DCGI had no experts of its own who were able to evaluate stem cell proposals, and suggested that ‘a fundamental jurisdictional ambiguity with even the relevant agency unsure of what falls under its regulatory scope’.

In brief, the linear trajectory of development of stem cell guidelines in India was an outcome of attempts to better govern the reported malpractices on one hand and to make India ready for the global stage as a competitive and collaborative partner in new biotechnologies, on the other. India has definitely moved in a direction, from a ‘governance vacuum’ to a ‘thick regulatory framework’. The growing availability of unapproved stem cell intervention mainly at private clinics, corporate hospitals and companies attests to the fact that implementation of these guidelines on the ground is feeble. It would be easy to explain this as ‘institutional failure’ or ‘institutional ambiguity’ as demonstrated in the case of the non-functionality on the part of NAC-SCRT oversight, and the uncertainty of the DCGI and about its own regulatory scope and role.

As the discussion above indicates, social science literature has tried to explain why unrecognized stem cell interventions (USCI) are provided in India since guidelines were put

in place in 2007, and some do this in relation to the existence of a bioethical or governance vacuum (Salter 2008; Sleeboom-Faulkner 2010; Cohen & Cohen 2010), institutional embedding (Patra & Sleeboom-Faulkner 2011) and jurisdictional ambiguity (Tiwari & Raman 2014), while others highlight making profit, acquiring glory, advancing experimental medicine (Kiatpongsan & Sipp, 2008), and ‘filling the gap’ between demand for health-care and supply of treatment. While understanding why provision is continued, it is important that social scientists examine how stem cell intervention activities continue to be carried out in India. Knowing how providers operate requires knowledge that pertains to institutional arrangements and strategies to circumvent regulatory safety nets. This we attempt to explain through the notion of ‘bionetworking’, which refers to social entrepreneurial network activities involving biomedical research and healthcare institution that respond to the health needs of the patients commercial demands of therapy providers (Patra & Sleeboom-Faulkner 2009). A bionetwork consists of a plurality of actors engaged in ‘biotechnical ventures’ (Waldby & Mitchell, 2007) working across geographical spaces, regulatory regimes and social institutions. It relates to the entrepreneurial aspects of biomedicine, and the strategic use of the differences and similarities in the provision of healthcare, levels of wealth, standards of scientific development, research regulatory regimes and their implementation and relative values of collaborators involved (Sleeboom-Faulkner 2016, Patra & Sleeboom-Faulkner 2011).

In this article, then, we are more concerned about the strategies of these institutions (the how) adopted to continue the provision of stem cell intervention. This approach explicates the institutional arrangements and attitudes/approaches to stem cell regulation. It may also shed light on a related, yet, hypothetical question. If ethical oversight is tightened and soft guidelines become hard-law with punitive powers, can we expect the demise of unapproved stem cell intervention in India? The implementation of Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) Act (1994), an Act of the Parliament of India enacted to stop female feticides and to arrest the declining sex ratio in India shows that ‘hard law’ is not necessarily effective. Two decades after the enactment of the PCPNDT Act, the law cannot control all clinics that use ultrasound for sex determination and a host of other purposes, including detection of genetic abnormalities in the foetus (Garg and Nath, 2008; Bhalla 2015).

Without going into great detail about why unapproved stem cell interventions are available in India, we will, discuss how some private clinics, corporate hospitals and companies promote and continue practicing such treatments. What we suggest is that the changing regulatory

situation in India is commensurate with a shift in the structural form of arrangements promoted by treatment providers themselves. As will become clear we see a shift in the institutional embedding (Patra & Sleeboom-Faulkner 2010, 2013) of various kinds of practitioners (e.g. public, private and independent), and an increase in collaborative networks between actors with diverse intent and expertise. As discusses below, these activities encompass interactions with a wide variety of stakeholders and institutions, ranging from political agencies, to corporate sponsors and subsidiary companies, to patient groups, local hospitals, universities, and the media (Sleeboom-Faulkner 2014).

## **Methodology**

This article is based on data gathered through both primary and secondary sources. Empirical data were collected by both authors over 10 months from 2010 to 2014. In 2010–11, the first author carried out the fieldwork in India for 3 months and the second author in Japan for 3 months. In 2013–14, the first author carried out the fieldwork for 4 months, between September 2013 and January 2014. We have visited multiple sites across India and some in Japan that include: 4 stem cell companies, 5 stem cell research institutes, and 8 hospitals and clinics where we interviewed patients/care givers (12), medical doctors (7), stem cell researcher (14), scientists (7), treatment providers (6), bioethicist (5), institutional review board members (3), venture capitalist (5), and patient organizations (3). The institutes, centers, stem cell banks and hospitals visited include the Nichi-In Centre for Regenerative Medicine (NCRM), Jeevan Stem Cell Bank, and Lifelong Institute for Regenerative Medicine (LIRM) in Chennai, Stempeutics Research Pvt. Ltd., International Stem Cell Services Limited (ISSL), Manipal Institute for Regenerative Medicine (MIRM) in Bangalore, ReeLabs and NeuroGen in Mumbai, Chaitanya Stem Cell Centre and LifeCell in Pune, CryoBank in Gurgaon, Indian Institute of Medical Research, Udaan Centre and All India Institute for Medical Sciences (AIIMS) in New Delhi, Tran-Scell Biologics Ltd in Hyderabad and Kalinga Institute for Industrial Technology (KIIT) in Bhubaneswar in India. In Japan, besides interviews with key persons in IJRM, secondary source materials were collected, including materials from web pages of the above-mentioned institutes, newspaper articles, conference materials, official documents related to stem cell research and healthcare governance published by government bodies and articles and research papers published in national and international journals on stem cell in India. We use pseudonyms for the names of interviewees, and for institutions,

hospitals and clinics, when requests were made. However, the names of individuals or centres were used where they were already used in media reports or were quoted in secondary sources.

### **The shift in provision of unapproved stem cell application provided by clinics in India: from specific institutional embedding to network-based collaboration**

As elaborated above, over the last 15 years there have been changes in the regulatory frameworks, healthcare policy, and techno-science practices regarding regenerative medicine, in India. In the initial phase (2005 - 2010), unapproved stem cell applications providers operating in private, public, and independent sectors formed diverse institutional contexts for the promotion of stem cell research and patient recruitment. State-of-the-art physical infrastructure and cutting-edge medical technology required heavy private investments, which were set off by high profits from high user fees, affordable to only a few Indian patients and a growing number of foreign patients. Competition to attract potential patient groups and a solitary focus on clinical application did not inspire private practitioners to look for large-scale collaborative networks.

After 2010, attempts to revise regulatory frameworks at the national level, new developments in the field of stem cell science and the government's emphasis on public-private partnership (PPP) in biotechnology encouraged actors such as stem cell scientists, companies, medical doctors, patients and their caregivers to come together to collectively address emerging challenges. For example, the growing interest in iPS cells, encouraging breakthroughs in preclinical studies using mesenchymal stem cells and Wharton jelly, and the popularization of umbilical cord blood and tissue banking necessitated multi-center and multi-actor collaborations. The DBT, in 2012, set up a 'not-for-profit-company' called Biotechnology Industry Research Assistance Council (BIRAC) as an interface agency, serving as a single window for the emerging biotech industry (DBT webpage 2014). These factors have encouraged actors such as stem cell research institutes, corporate hospitals and doctors to collaborate and create platforms to capitalize on relative expertise. Public and private centers and individual practitioners that had traditionally operated through their respective institutional embedding had either to create such collaborative platforms or to close their practice. Here, briefly, we present the contexts and motivation of scientists based in the public, private and independent sectors had for providing therapy, and how they have



changed their set-ups over the last decade. We do this by giving one example from each category.

Public sector: Public sector healthcare institutions involved in stem cell research and treatment receive their funding from the state. These institutions have traditionally regarded stem cell provision as a high-end healthcare service with humanitarian value that has the potential to transform the economic and health care needs of the nation. They by and large adhered to the official policies and guidelines formulated by the state and were relatively cautious and conservative with regards to scientific innovation. Compared to private-sector centers, public institutions and centers were also slow to enter into collaborative research and development activities across local and global spheres. We exemplify this using the case of the All India Institute of Medical Sciences (AIIMS), which is a premier medical institution in India, based in New Delhi. It receives substantial public funding and is in the forefront of medical research, including stem cell science. In the early 2000s, AIIMS claimed to have providing controversial experimental stem cell therapy, which was reported in 2005 in a leading English daily *The Times of India*, where the then director of AIIMS, Dr. P. Venugopal reported as saying:

[We are] finally in a position to report the results of our work. Starting in February 2003, 35 patients with end-stage cardiac disease had been given stem cell treatment through a technique developed at the institute. They had been monitored over six-month intervals and the majority had improved (Srinivasan 2006).

This ESCT took place during a time when the first ICMR–DBT guidelines on stem cell research and treatment were in preparation. Vasantha Muthuswamy, who was then in-charge of developing ICMR ethical guidelines for stem cell research and therapy, expressed her helplessness, saying, “we are only a block away from AIIMS and we did not know this was happening there” (cited in Jayaraman 2005). Eventually, AIIMS stopped a multi-centric stem cell trial project, ‘due to lack of desired result’ and a report published in 2011 highlighted how NAC (the national apex committee) was critical of Drug Controller General of India’s (DCGI) approval of a joint clinical trial proposed by AIIMS in collaboration with a private company, Stempeutics Research Private Limited (Singh 2011). By contrast, AIIMS currently has a dedicated stem cell research facility for basic stem cell research and therapy provisions limited only to randomized clinical trials. This reflects how AIIMS, a leading public hospital

and medical institute in India, had to change its position and activities relating to stem cell research and treatment owing to regulatory and policy changes.

Private sector: The private sector represents a myriad of healthcare institutions that receive funding supports from varied sources such as private firms, pharmaceutical companies and venture capital companies. The infrastructural facilities related to private sector stem cell research and therapy provision developed rapidly in India and many private sector hospitals have opened stem cell research wings that serve as a cover for commercial therapeutic service or are linked with larger client networks (Patra & Sleeboom-Faulkner 2009). Others have developed facilities in anticipation of a growing flow of hopeful patients from the West in search of therapies that are not ‘standard’ in their own country. They also targeted the upper-class wealthy patient group in India, which was rapidly growing. The driving forces behind the private sector’s heavy investment in stem cell research and therapy enterprise are manifold. Apart from profit-making, the aspiration to play a leadership role in the cutting-edge technology in India through large-scale collaborative research and development across locations plays an important role, and makes use of emerging patient flows in search of experimental stem cell therapy. The tale of Stemtech Research Private Limited (pseudonym), a stem cell-based product development company based in Bangalore, is a case in point that explicates how a private sector company transformed itself in last decade. In its initial period of existence, between 2006 and 2008, it mainly provided stem cell treatment for spinal cord injury and some neurological disorders. It was involved in cleaning, processing, and expanding the stem cells at its own laboratory facility in Bangalore and worked closely with a hospital group and a few corporate hospitals in and around the city for patient recruitment and clinical translation. But, post-2008, due to the changing regulatory scenario in India and Stemtech’s own decision to focus more on research and product development, it stopped providing ESCT. It took proactive steps to work closely with a sister institute called Nagpal Institute of Regenerative Medicine (NIRM) to create human resources, organize funding through a joint venture with a major Indian pharmaceutical company, collaborate with contract research organizations (CROs) for clinical trials and with an engineering company for stem cell-based medical device product development. It also cultivated formal and informal understandings with top-notch research institutes for the exchange of knowledge, technology, and biomaterials. It was successful in getting public funding for basic research, such as from DBT through the Small Business Innovation Research Initiative for Public

Private Partnership (SIBRI) and Biotechnology Industry Research Assistance Council (BIRAC) programs. Stemtech has an overseas branch in Malaysia where it is working with private and public institutions for stem cell research. From a relatively independent and self-reliant company in 2006-08, it has changed into a diversified and collaborative network.

Independent sector: Practitioners providing experimental stem cell therapies on an individual basis, and outside the purview of both public and private sectors view regenerative medicine as an opportunity for earning money, experience, and fame. They targeted a growing number of middle-class patients searching for better health care outside of the public health care system. Due to fear of reputational risk, threat to monopoly over technological know-how, and apprehensive of regulatory oversight, independent practitioners were operating within a limited scope. They were particularly averse to collaborative exercises. These different institutional sectors had developed varying strategies of dealing with ESCTs, which had generated new discursive dialects of bioethics (Patra & Sleeboom-Faulkner 2009). Dr. Prakash (pseudonym) is a case in point. Dr. Prakash is a medical doctor and biochemistry expert based at a leading publicly funded medical-college-cum-hospital in the city of Cuttack in Odisha State. Dr. Prakash claims to provide stem cell treatment using autologous bone marrow for medical conditions such as diabetic foot ulcer and Duchenne's muscular dystrophy (DMD). Dr. Prakash has set up a private clinic for providing stem cell treatment, after the local Institutional Review Board of the public sector medical-college-cum-hospital to which he is affiliated did not grant him permission for clinical application. The college did, however, approve of him carrying out laboratory research on stem cells. Dr. Prakash explains:

Since ours is a government hospital, the committee is very strict about implementation of ICMR guidelines. They cannot approve my study for clinical trials within this hospital, even though they know that what I am doing is medically and ethically correct. But they are waiting for other front-line hospitals like AIIMS to practice these therapies first. Perhaps then they will say yes. Once it is practiced at a big place, then they will have no problem in approving me. This made me provide this treatment out of this medical college purview (Interview, Dr. Prakash, 17.03.2009).

Thus, due to the government hospital's requirement to follow ICMR guidelines, Dr. Prakash decided to offer stem cell treatment independently in a private clinic. Although not

particularly lucrative, the practice becomes a testing ground for the research he does at the college. This was the situation prior to 2008. Dr. Prakash still continues his practice outside of the public hospital. Recently, Dr. Prakash was invited to a discussion platform to explore the possibilities for setting up a joint venture with Pluri-Scell Biologics – a Hyderabad based stem cell bank and processing center, JIIT University's Biotechnology Department, and Mangala Institute of Medical Sciences (MIMS) hospital in Bhubaneswar. The negotiation discussed the use of the expertise of Dr. Prakash to attract patients from his medical college and MIMS hospital as potential clients for stem cell treatment (Interview 1<sup>st</sup> author, 23.11.2013). This reflects the scope for individual actors to create new possibilities by combining resources from various origins.

These three cases highlight the influence of changing national regulatory guidelines on the functioning of actors and institutions based in varied institutional set-ups. The private company, Stemtech, displays maximum flexibility in its ability to change its mode of operation, and it has created strategic links for dealing with challenges in the spheres of regulatory capacity building, technological innovation, and resource generation. AIIMS, a publicly funded institution, demonstrate a sense of restraint regarding stem cell experimentation, with limited scope for collaborative activities. Individual practitioners, such as Dr. Prakash, have the leeway to focus on both consolidating experimental operations and exploring the possibility of collaboration with larger networks.

The following is a case study of a center named IJRM, the focus of this paper, which elucidates the shift in the provision of clinical stem cell intervention in India from embedment in particular (private, public, independent) institutions to collaborative enterprises. It is important to emphasize here that it is not our intention to portray this case study as representative for the state of affairs of stem cell research and clinical intervention in India. Nevertheless, IJRM in India, as we shall see, has an important exemplary function as one of the leading centers in India in stem cell research and treatment, explicates strategic maneuvering skills through a globalised bionetwork. It negotiates regulatory requirements in various geographies on the one hand, and encourages the expansion of therapy business through diversification, decentralization and network-building by using strategic linking, on the other.

### **The India-Japan Centre for Regenerative Medicine – a case of bionetworking**

The case of India-Japan Centre for Regenerative Medicine (IJRM), an Indo-Japanese joint venture based in Chennai, reflects India's regulatory transition. It also exemplifies the shift from institutional embedding to an entrepreneurial network based collaborative structure that conditions the abilities of stakeholders to sustain their work successfully and promote experimental therapy. IJRM shows how central to strategic linking and value realization in biomedical science are the ways in which exchanges are positioned in strategic networks shaped through socio-economic, political-legal and cultural factors, or 'bionetworking' (Patra & Sleeboom-Faulkner 2009, Sleeboom-Faulkner 2011), also involving a myriad of non-scientific activities, including networking, lobbying, managing, trading, and collaborative to produce science. These activities encompass interactions with a wide variety of stakeholders and institutions, ranging from political agencies, corporate sponsors and subsidiary companies to patient groups, local hospitals, universities and the media (Sleeboom-Faulkner 2016). IJRM's centrality in a collaborative network structure exhibits its capacity for maneuvering across local and national boundaries, understanding the increased complexity of clinical stem cell intervention in India.

IJRM carries out research, training, and clinical applications-protocol development in regenerative medicine, with an emphasis on stem cells, progenitor cells, and autologous adult cells with regenerative capability. IJRM claims to possess the technology for the processing, expansion, and preservation of clinical grade stem cells, precursor cells as well as mature cells (IJRM webpage 2014). Initiated in 2004, IJRM in one decade has gradually moved from a relatively secluded and small-scale entity to a medium-sized registered joint venture company with a well-connected network structure linking multiple partners in the promotion of stem cell treatment in India. IJRM, being a center involved in cutting-edge science, has signed academic and research collaborations with universities and research institutes in India to promote basic research or academic training in stem cell science. In India, it has signed a memorandum of understanding (MoU) with two universities in Andhra Pradesh for stem cell research. It has also started a web-based training program in regenerative medicine in collaboration with the TPRM (Training Programme in Regenerative Medicine) affiliated to a university in Canada. These kinds of collaborative academic links provide recognition and academic exposure, and help maintain global linkages through faculty exchanges and work exposure of young researchers at IJRM. The collaborating centers in India, in turn, get access to advanced stem cell technology developed in Japan, which enables them to work with 'world-class' scientists. The vice-chancellor of a collaborating university in India, in a

workshop organized by IJRM, stated that their collaboration is not only promoting research in the advanced life sciences, but also aims to yield solutions to the emerging health needs of the people of India:

We are proud of our tie-up with IJRM that provides us with a direct link to advanced life science laboratories in Japan. The PPP-mode (public-private partnership) is going to define the future. It is the mutual trust, sharing and benefit that are going to take us further. It is going to be driven by knowledge and technology. We cannot limit our objectives merely to academic links, it has to go further and be meaningful for human welfare and useful to many people who are suffering from innumerable number of diseases... We see this endeavor as a need-based and practical one (Presentation IJRM workshop, Chennai, November 19, 2013).

This statement suggests the various motivations of actors in the collaborative network. Collaborators utilize the relative value and different expertise held by each of them, while pursuing their own ends. The main mechanism of steering the network lies in the relative centrality of a hub.

#### ***‘Relative centrality’ and ‘strategic linking’***

The IJRM promotes clinical stem cell interventions through its central position in a network relationship, the possession of specialized skills and knowledge, and the ability to identify and utilize the value of actors in the network. Characterizations of such managerial relations can be found in business studies using various models, including, the ‘hub-and-spoke model’ and ‘business cluster.’ Hubs are described as special nodes located in the network in such a way as to facilitate connectivity between interacting places, and they are considered as a catalyst for agglomeration and scale economies (O’Kelly 1998); business clusters are described as geographic concentrations of interconnected actors in a particular field, who compete but also cooperate (Porter 2000). We argue that these models are inadequate to explicate the dynamic relationships between actor-stakeholders in promoting clinical stem cell interventions. Important to the development of network relations between actors is not just their interdependency and relative positioning, but also the modes of strategic linking and exposure (Sleeboom-Faulkner & Patra 2011) as played out by the centrally positioned main actor.

The actors' differential positioning within the dynamic of a stem cell network has important impact on the flow of resources in terms of knowledge, capacity, technology and services. One critical factor in network positioning is 'relative centrality,' denoting the crucial role that one of the actors in the network plays in uniting and mobilizing other actors in the network. This centrally positioned actor's role is akin to a 'hub.' The hub, as the lead actor, has the ability to access, apply, appropriate, and control the resources of a network through direct as well as indirect links. Another critical factor is 'diversity.' The hub, by virtue of its central positioning and ability to maneuver, can tap the differential value or resources of the specific actors in the network. Presumed mutual benefit for all participating actor-stakeholders contributes to the stability and growth of the enterprise. A third aspect is the 'relationality' of the network. Minor actors (or 'spokes') can only be part of the network if they are hubs (lead actor) in their own networks.

Crucial, however, is the way in which a distinct transnational network employs strategic linking and scaling tactics to pursue business success by means of 'relative centrality,' which is composed of three components: goal setting, strategic exposure, and the strategic linking of meaningful spaces. We explain how this network structure based on the notion of 'centrality' works by strategically linking and exposing the activities of certain actors when opportune.

### **Strategic linking through goal setting**

The hub mobilizes and steers the expertise and talents of participating actors to achieve specific goals in the field of ESCT. Since 2005, IJRM has spread its activities in length and breadth and it has entered into mutual understandings with a broad spectrum of actors across local, national, and global boundaries. By virtue of its position in the network and ability to make use of the relative strengths of each actor, IJRM is adept at streamlining its diverse motivations towards an anticipated aim. For example, it has close collaborative research links with university hospitals, companies, and funding bodies in Japan, India, Malaysia, and elsewhere in the world. IJRM's link with Japanese companies and institutes help it to receive wider acceptance and reputation in India, while ensuring a steady flow of innovative technology, research training, and funding for research and development in India. The collaborating companies and institutes of Japan, in turn, gain access to a wider patient population, revenue through technology transfer, and well-trained inexpensive expertise. A research scientist attached to IJRM explained the company strategy:

Ours is a unique centre. Here you find all stem cell solutions under one roof. With our collaborative links with Japanese universities and companies, we manage to get access to world-class technology and knowledge. Then we have entered into Memorandum of Understandings with universities in Canada and India for higher research and training in stem cell science. We are the first institute in India to start providing Autologous NK cell-based immune cell therapy for cancer, and it provides a platform for collaboration between like-minded scientists and clinicians in all specialties of medicine where there is a potential for regenerative medicine-based solutions. We also collaborate with cord blood banks. It is a center for complete solution (Interview, Dr. DS, Chennai, October 21, 2013).

The IJRM has recently entered into collaboration with the well-known private sector chain Apex Specialty Hospital in Chennai for the provision of Natural Killer (NK) cell-based autologous immune enhancement therapy (AIET). AIET is used to treat patients with acute lymphoblastic leukemia, a kind of blood cancer (IJRM webpage, 2014). IJRM provides technological support in the form of immune cell therapy, while Apex provides medical facilities and patient care. IJRM, in fact, has collaborations with over 60 small- to medium-level clinics and hospitals, to which it provides stem cell-based technological services, including cell processing and cell expansion, and where the hospitals deliver the treatment.

Some of the actors, especially those involved in stem cell research and clinical applications, emphasize the importance of the publication of their study results, as it provides the enterprise with legitimacy. Thus, to legitimize its practices and to promote its name, IJRM has been publishing a journal called the Journal of Stem Cell Research and Therapy since 2009. Although it is not peer reviewed, it provides the scope and opportunity for researchers at IJRM and its collaborating partners to showcase a selection of their studies and clinical data. A clinician collaborating with IJRM to research and clinically apply corneal limbal stem cells explains the importance of publishing:

My association with IJRM not only helps me to work in a high-throughput scientific area of stem cells, but also gives me a chance to showcase my research in a reputed science journal. This is crucial. It helps in getting academic acceptance (Interview, CS-3, November 23, 2013).



The strategic linking of clinics, companies and researchers that have access to new cell technologies and biomaterials facilitates the creation a platform for the promotion of experimental stem cell therapy, showcasing research through publications and putting compelling case histories of patients on websites. In practice, it is impossible to draw a line between the fundamental research, clinical translation, and entrepreneurial activities of the network (Sleeboom-Faulkner 2016).

### **Strategic exposure**

The entrepreneurial stem cell network enterprise strategically exposes certain aspects of its collaborative network and activities more than others. Thus, IJRM as a hub has the overview and therefore the unique capacity to recognize the specific values of the diverse actors in the network. It creates a situation of dependency and mutuality by enhancing their competencies and by helping them to channel their potential towards the goal of promoting the stem cell treatment enterprise. The hub, in this case IJRM, can skillfully manipulate, mobilize, and make use of the resources that lie within the reach of other participating actors in the network. In doing so, it may decide to display the potentials and value of specific actors required in a specific context of entrepreneurial negotiation, scientific venture, and ethical consultation. It becomes the prerogative of the principal actor, based in the hub, to decide which aspects of a collaborating partner's expertise can be made visible to an interested client and which not. As a research scientist working for IJRM explained:

Specialized hospitals in Chennai have a good reputation in India for providing world-class treatment options for reasonably low prices compared to other cities in India. There are many who want to provide the best therapeutic options to their needy patients. It is their objective. We just help them in achieving that with the best technology and know-how that we have. We provide them with processed and expanded cells as per their requirement, for experimental use. It is a mutually beneficial thing (Interview, RS-3, November 23, 2013).

The research scientist recognizes the important value that local clinics hold for the enterprise, but this recognition is not openly expressed. When asked why IJRM does not showcase the role of the local clinics or hospitals on the website, the scientist said:

We don't need to tell everyone which clinic or hospital is our local collaborator. It is perhaps not necessary for everyone to know. Ultimately, the patient who would receive the treatment will come to know when he contacts us with detailed medical documents (Interview, RS-3, November 24, 2013).

Although the principal actor, based in the hub, recognizes the potential and relative value of minor actors, it conceals their identities from outsiders and, at times, it may overplay the role of specific minor actor to achieve a specific goal. A well-known neurosurgeon, who owns a local clinic in Chennai, has close links with IJRM. Several times he has processed stem cells for the therapeutic use of patients suffering from neurological problem. He explained how he became part of the network:

(R)ather, I was discovered by IJRM (laughing). When they came to know about my reputation as a good surgeon in the area, they wanted to tie up with me for the promotion of their stem cell service products. I was also looking for avenues for this wonderful thing around stem cell treatment. I got impressed with their claims, their links with Japanese professors and researcher. I got excited. It was like we were made for each other. This technology that we are using is very unique and the Japanese company has exclusive rights over it. This has a good psychological impact on our patients' mind (Interview, C-2, November 21, 2013).

These interviews reflect how the entrepreneurial network built to promote clinical stem cell interventions in India adopt a split strategy in which there is a task division between actors: actors engaged in basic research, and actors engaged in translational research, whose innovative and sought-after field involves practices that are ethically challenging.

### **The strategic linking of geographical spaces and meaning**

This section explores the entrepreneurial logics shaped by techno-business practices, institutional forces, and material complexities through which actors negotiate scaled spaces at a local, national and global level. (Patra & Sleeboom-Faulkner 2011) have showed how the leader of a stem cell hub skillfully taps unauthorized resources by licensing innovative Japanese technologies to hospitals in India. He thus capitalizes on the need of Japanese research centers to experiment with their technologies on patients who are more easily made

available in India. We speak of spaces, as the geographical spaces in themselves provide a functional source of meaning in entrepreneurial networks. Examples are the clean and high-tech images of Japanese technology used when branding products, transferring technology, recruiting patients, and negotiating regulation.

The IJRM has strategic links in Chennai city with hospitals, such as Deepam Hospital, Shrushti Hospital and Sankar Nethralay and, formerly, with Lifelong Hospital. IJRM conducts research on corneal lymbal stem cells, corneal endothelial precursors, hepatic progenitors, chondrocytes and hematopoietic stem cells. It provides autologous bone marrow stem cell processing services, and claims to offer treatment for various illnesses. The official web page of IJRM explicitly declares that its stem cell treatment and other therapy services are based on advanced Japanese technology:

One of our core strengths has been the possession of technology (both materials and methodologies) for processing, expanding, and preservation of clinically usable stem cells, precursor cells, as well as mature cells. We have a unique advantage of having biomaterial and nanotechnology-based (without animal protein contamination) stem cell processing and expansion technology through our collaboration with Japanese institutes.

With its claim of having exclusive access to advanced Japanese technology for cell processing and expansion, it attracts physicians, usually based in small- to medium-level private hospitals. A senior physician-cum-scientist at IJRM explained:

We have collaborative works with around 40 hospitals in India, especially in southern India and about 15 to 20 in Chennai city. It is not a very strong link; they take our support when they have a need and that is good for us. We want our resources to have wider use and more people to benefit. We want to expand. It is all mutual (Interview Dr. DS, November 28, 2013).

Collaborative networks with such hospitals provide a pool of specialist physicians who can recruit patients to their clinics. IJRM's web page mentions only a few of such collaborations and describes therapeutic support other than stem cells, such as immunotherapy for cancer. It asks potential clients to send email enquiries about specific stem cell treatment centers. Mr. SR, who is presently working as the Marketing Head at Lifelong Hospital, a former

collaborating partner of IJRM (2006 -08) and provider of adult autologous stem cell therapy for several disease conditions including spinal cord injury, reflected on IJRM's networks:

There is a Japanese mind behind what you see at IJRM. Without Japanese investment and advanced technology, it cannot do anything - Just imagine the situation where you have links with 60-70 hospitals across the region and you get at least 3 or 4 patients from each hospital every year. It is a huge number. You give incentives to the doctor or clinic that introduces a patient to you or you charge than for providing stem cell processing and expansion services. You know how expensive these services are. And very intelligently Dr. SA has combined immunotherapy with stem cell treatment services. It highlights the collaborations that it has with institutes in Canada and Japan. It also boasts its links with universities outside Chennai. This is a very good business model (Interview, Mr. SR, Business Head, Lifelong Hospital, Chennai, November 30, 2013).

A Chennai-based clinician, who regularly works with IJRM in providing autologous stem cell therapy for critical limb ischemia, spinal cord injury, and ischemic heart disease, viewed the collaboration as a mutually beneficial exercise:

Ours is a small, specialized facility, but we are very proud to be working closely with IJRM. They have all the modern technological facilities from Japan, which would be otherwise difficult for us to get here. It is resource-intensive. But they also benefit from easy patient access, from the medical data that is generated through these therapies. The patients get an alternative therapy without which their life conditions would have been very different. I think it's a win-win situation for all (Interview, Dr. PA, Chennai, November 30, 2013)

The interviews show actor assessment of their collaborative partners and the rationale behind their motivation to join the network. Their assessments evaluate geographical spaces similarly in terms of high-tech level, prestige, and opportunity.

## **Discussion**

We now have come to the point at which we can explain how stem cell experimentation and treatment continue to thrive in India despite the introduction of relatively stringent guidelines for stem cell research in December 2013. In this article, we have deliberated on the developmental history of the making and remaking of guidelines, the shift in treatment provision – from institutional embedment to collaborative networks, and strategic linking and exposure in collaborative network. Several issues that emerged need to be highlighted.

First, the IC-SCR and NAC-SCRT are not functioning: the ICMR-DBT (2007) guidelines stated that:

All stem cell therapy other than BMT (for accepted indications) shall be treated as experimental. It should be conducted only as clinical trial after approval of the IC-SCRT/IEC and DCGI (for marketable products). All experimental trials shall be registered with the NAC-SCRT (ICMR-DBT 2007, pp. 11-12).

Many practitioners still continue to provide clinical interventions by taking the term ‘treated as experimental’ to be a tacit endorsement for practicing and promoting unproven stem cell therapy. The revised guidelines (2013) state that:

Clinical trials using cells derived from the differentiation of human ES or iPS cells, or any stem cell after major manipulation (as defined under Clause 6.1.6.3) shall require approval of the DCGI after obtaining approval from National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) through Institutional Committee for Stem Cell Research (IC-SCR) and Institutional Ethics Committee (IEC) (ICMR-DBT 2013, pp.9).

Some providers nevertheless refer to the Helsinki Declaration that places emphasis on the ‘physician’s judgment’ and compassionate ground (WMA 2008; Chen et al. 2014). The main issue is that the NAC-SCRT and IEC committees ‘either do not exist’ or are ‘not in operation’, as a provider (TP-3) emphasized, where he said;-

The guidelines talk about so many things. They have been saying this for so many years. Can you ask them where is their committee, where are their members, why do they sit on the applications we send and take no action. Bet me either they do not exist or they are not in operation.

This criticism suggests that there is institutional incompetency regarding the organizational capacity of the regulatory agencies, calling into question the reliability of the regulators.

Second, as highlighted by Tiwari & Raman (2014), there is an issue of ambiguity as to which agency to approach in cases of medical malpractice, patient safety, forgery, false claims and the ethical conduct of clinical trials. It is important to mention that neither the ICMR nor the DBT has a legislative remit over medical research. The Drug Controller General India (DCGI) under the gamut of Central Drug Standard Organization (CDSCO), which is responsible for regulatory control over the import of drugs, the approval of new drugs and clinical trials, does not have sufficient expert capacity to evaluate stem cell proposals. The Medical Council of India (MCI) only has statutory authority to deregister a practitioner. In this regard, a policy maker (PM-2) suggested that, “in extreme circumstances, in case of any harm to a patient or in case of medical malpractice, the patient needs to lodge a complaint” (personal interview, 11.5.2014). But in case of clandestine stem cell enterprises, patients are not in a position to lodge a complaint.

Third, the guidelines are not legally enforceable: An important development took place when the Ministry of Health and Family Welfare established a high-powered committee in June 2013 to suggest a road map for the regulation of stem cell- and other cell-based therapies practiced in India. The committee drafted the Guidance Document for Regulatory Approvals of Stem Cells and Cell based Products (SCCP) in December 2013. The Document is now available in the public domain and is open for public discussion. The rules and regulations in this Guidance Document apply to all organizations such as hospitals, private clinics, institutes, universities, tissue banks, and companies that wish to obtain a license for the use of SCCPs for therapeutic purposes in India. Failure to comply with the conditions of this document or using SCCPs without a CDSCO/DCG (I) license is penalized in agreement with the Drugs and Cosmetics Rules (CDSCO 2013). But until parliament promulgates an appropriate Act (hard law) enforcement with legal authority remains problematic. From the mid-2000s onwards, social-science studies as well as Indian stem cell observers have argued that the governance vacuum in India was a result of the lack of statutory regulation of stem cell

activities (Salter 2008, Patra & Sleeboom-Faulkner 2011, Tiwari and Raman 2014). The statutory gap in Indian stem cell governance was addressed with changes announced in 2014 to the DCGI's legal remit and a revised set of guidelines produced by the ICMR-DBT guidelines. However, doubts still remain not only about the enactment of the new law-in-practice but also about the blurred difference between guidelines and regulations that prevails in the field of stem cell research and therapy in India. The ICMR-DBT stem cell research guidelines mainly seem to assist with providing ways of complying with the legislations.

Fourth, the complexity of the collaborative-network structure makes it easy to circumvent the regulation. As clearly demonstrated through the case study of IJRM, the complex collaborative network structure emerging through the 'hub-spoke' kind of reciprocal relationships makes it difficult to monitor or regulate the field; most of actors and practitioners involved are not registered to any agency. As elaborated in earlier section, IJRM's central position and the vertical and horizontal network relationship with actor-stakeholders has important impact on the flow of resources in terms of knowledge, capacity, technology and resources. These networks are based on strategic linking and scaling tactics with three well-crafted components: one, strategic linking through goal-setting, where the 'hub' mobilizes and steers the expertise and talents of participating actors to achieve specific goals; two, strategic exposure, whereby certain aspects of collaborative network activities are exposed more than others; and, three, the strategic linking of geographical spaces, whereby actors negotiate scaled spaces at a local, national and global levels. The multiplicity of actors involved, the complexities of their relative importance to the network and diversities of their locations is an indication that this collaborative network-structure will not only survive and thrive but can skillfully circumvent the regulatory provisions, which in India, as of now, is designed to comply with guidelines.

Fifth, there are alternative cell therapies available that provides safe coverage to unproven stem cell treatments. As a result of the 2013 regulation, companies have started to emphasize the provision of 'alternative cell therapies' over 'stem cell therapy,' which have not undergone clinical trials either. For instance, IJRM claimed that "more than 23 types of cancer have been treated using AIET without any adverse reactions and there are hundreds of clinical studies" (IJRM webpage 2014). It claims that the Bioteknika Institute in Japan (pseudonym) had started AIET in the year 2000 and has provided treatment to more than 10,000 patients to date with no adverse reactions, as with other conventional treatments (IJRM webpage 2014). Further, clinical stem cell intervention is made available through the

approved randomized clinical trials route when in collaboration with a foreign company. Dr. Bhaskar, Clinical Manager of a multinational clinical research organization (CRO) based in Bangalore, explained that:

There are many stem cell companies, both from India and abroad for whom our CRO is carrying out clinical trials, especially for mesenchymal stem cell-based products and autologous SCT-based indications. There are around 5 or 6 disease conditions for which they recruit 20 to 50 patients each per study. These studies are multi-centric and our CRO has networks across several states in India to provide the required number of patients and volunteers as per the required exclusion-inclusion criteria (Interview, Bhaskar, 03.06.2014).

With the increasing number of companies and institutes investing in stem cell research and product development for an increasing number of indications for clinical trials, there is scope for wide recruitment. Apart from the instances of these two sets of provision of alternative therapies i.e. AIET and randomized clinical trials, other services, such as tertiary care under medical tourism, especially to offshore patients, also provide safe coverage of unproven stem cell. Medical travel to corporate hospitals in India takes place for an array of medical conditions such as kidney transplantation, assisted reproductive technologies, and cardiac surgery. These travels are driven by patients who aim to avoid treatment delays, and to obtain relatively affordable access to healthcare (Turner 2007). Corporate hospitals that provide tertiary care have skillfully tapped into pools of foreign patients, non-resident Indian patients and wealthy Indian patients for experimental stem cell therapy. Many of them have combined stem cell therapy provisions as an auxiliary unit to their super-specialty healthcare service platter. A physician who was earlier associated with IJRM and now is in-charge of stem cell facility at the Globus Hospital (pseudonym) in Chennai said the following about how stem cell therapy is offered as a coverage;

We are a super-specialty corporate hospital. We need to very well understand the health needs of the high-end patients that come to us for treatment for different kinds of disease profiles. We decided to keep stem cell therapy as a service in our service platter. Initially, it was not our main focus. But, now patients visiting for treatment of a particular condition may like to use stem cell as an option.... treatment of peptic foot ulcer is one condition that we are good at.

With the burgeoning growth of corporate hospitals in metro cities in India, such practices either alongside alternative therapy or as an additional therapy, the provision of experimental stem cell therapy may increase.



## **Conclusion**

In this article we have illustrated how within a decade the organization of clinical stem cell interventions in India has been altered from being embedded in specific private, public, or independent institutions to being provided through complex entrepreneurial networks. The latter involves strategic linkage created by entrepreneurs with global technology and managerial skills of public and private organizations, including universities, hospitals, high-tech companies, and other companies. This organizational trend was brought about by national-level attempts to regulate stem cell therapy and research, government policy of investment into the formation of public-private partnerships, and by developments in science itself that required an increasing variety of scarce material and intellectual resources. Using the example of IJRM, we illustrated the ways in which a distinct transnational network employs forms of strategic linking to pursue business success by means of their relative centrality in stem cell networks. And, finally, we showed how the provision of clinical stem cell intervention has continued despite the ‘thicker’ regulatory measures of December 2013. We found that it is actually the increasing complexity of the regulation, and a lack of resources to implement them, in combination with an organizational increase in complexity in the provision of clinical interventions that have enabled this continuation. We conclude that, rather than good ethical practice or scientific proof, in practice, it is the institutional sophistication and available regulatory mechanisms and resources that condition the ways in which industry caters for patient demand for USCT. The extent to which this is or is not in the interest of various kinds of patients/clients is another question in need of research and reflection.

## **Acknowledgement**

We are grateful for comments on this paper by the anonymous reviewers. This article has benefited from research support provided by the European Research Council (ERC: 283219) and the Economic and Social Science Research Council ESRC: ES/I018107/1). Due to ethical concerns, supporting data cannot be made openly available.

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