stem cell entrepreneurship-trends and advances-II

Stem cell research market in the world has grown exponentially over the last decade and in India the total investment is estimated to be about \$540 million in 2010 with an annual growth rate of 15%.¹ From just a few Institutes in India two years back, today over 30 institutions are involved in stem cell research with the Indian government investing around \$8 million dollars in just the last two years. What is the ultimate goal of Stem Cell research? Today, the ultimate aim of scientists is to be able to build tissues or organs that can replace injured or diseased tissues in the human body. This concept which gives rise to the generation of mature tissues has made adult stem cells the focus of intense research, designed to treat a variety of human diseases. In the clinical scenario, stem cells are expected to be transplanted into the damaged area and then grow to a new, healthy tissue. Considering the immense interest worldwide, it comes as no surprise that the global market for stem cell therapy is around \$20 billion in 2010, as per a Frost & Sullivan study. There are almost 180 prominent companies working on stem cell research in the world, majority of which are based in the US, followed by the EU, Israel, Thailand, Canada, and Australia. India and China are poised to play a key role in the scientific, clinical and commercial development of stem cell research. The high patient demand, vibrant pharmaceutical or biotechnological companies, a large intellectual pool of scientific talent and a mature information technology industry have together converted this sub-continent into a big platform for research and clinical translation. The early starters include National Centre For Cell Sciences (Pune), the Indian Institute of Sciences (Bangalore), Post Graduate Institute of Medical Education Research (PGI) and All India Institute of Medical Sciences (AIIMS) with central focus on adult stem cells and cord derived stem cells.

Focus on India and China in Stem Cell Research

In Western countries, it is the Church that raised an objection to stem cell research, with its stance against abortion. According to some critics, which also included former US President George W Bush, stem cells are mostly derived from embryos that have the potential to create life, hence any research involving such stem cells is akin to murder. As a result, research was slow

and funding difficult to come. During this era, research focus moved out of the US and experts believed that such barriers added a distinct advantage to countries like India, which with a large pool of scientific talent capitalized the field without such opposition. Secondly, a significant local interest of Physicians in the clinical application of stem cells in areas such as ophthalmology, cardiology, diabetes, and spinal cord repair prompted research in this direction. Therefore, the market in India, China and Singapore showed an upward trend with India boasting of \$540 million, Taiwan-\$320 million, Thailand-\$230 million, Malaysia-\$157 million and Singapore-\$100 million investments in the field. One of the dominant factors responsible for several clinical trials in India is the lackadaisical approach towards framing strict regulations. The draft guidelines for stem cell research have recently been formulated jointly by the Department of Biotechnology under Ministry of Science and Indian Council for Medical Research (ICMR), New Delhi and these are likely to be revised further. Experts have unanimously voiced a proposal to have a National Apex Committee (NAC), as mentioned in the ICMR guidelines which has recently been formed under chairmanship of Alok Srivastava in order to regulate the stem cell research and therapy. Several companies are waiting to conduct clinical trials on subjects and with proper regulations in place, the onus of monitoring stem cell research now rests with NAC. Another aspect that makes India a potential hub for stem cell transplants is the low cost of the treatment. Some estimates project the treatments consisting of peripheral blood mononuclear therapy to be close to \$34,000 in Bangkok in contrast to \$5,000 in India with comparable standards of health management. However, concerns are being raised over the possibility that stem cell research in India may leave Indian Physicians virtually free to conduct stem cell trials without following established scientific principles and medical ethics. Apart from the Government, some research organizations representing the industry are also involved in stem cell research. Reliance Life Sciences has characterized 10 stem cell lines including two neural SC lines, dopamine producing neurons and progenitors for stroke patients. Another

Hyderabad-based lab, the Center for Cellular and Molecular Biology (CCMB), is attempting to grow transplantable corneas *in vitro* from limbal stem cells. LV Prasad Research Institute and CCMB are two of about 15 laboratories across India engaged in stem cell application. Many of these are moving from animal to human studies.

Current status of Stem Cell Research in India

Research in Indian Institutes has sharply increased in the field of stem cell research and this has led to an increase in the publications on stem cell research in international peer-reviewed journals. At the beginning of the new millennium, Indians authored very few stem cell publications, but by 2007, these publications crossed the 100 mark per year. This included development of stem cell lines, including at least three human embryonic stem cell (hESC) lines to date (see UK Stem Cell Bank and National Institutes of Health (NIH) Human Embryonic Stem Cell Registry). Two hESC lines were derived at Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru and are now accepted for distribution by the UK Stem Cell Bank (see the UK Stem Cell Bank website). The cell lines, derived from low-quality embryos discarded post-IVF procedures, will be part of the International Stem Cell Initiative 2 (ISCI2) project to identify the common genetic changes that occur in hESC lines on prolonged culture. This will be the first time that India is represented at ISCI project. According to Alka Sharma, principal scientific officer of India's Department of Biotechnology (DBT), there are more than 30 research institutes, hospitals, and firms involved in stem cell research in India.² These sites include large public hospitals such as the All India Institute of Medical Sciences (AIIMS), in Delhi; dedicated private companies such as LifeCell, in Chennai; and research institutes such as the National Centre for Cell Sciences (NCCS), in Pune. Their activities are varied and include basic research and clinical trials.

Public-Private Partnership in the propagation of stem cell research

Much of India's focus on Stem Cell Research has come from Public research institutes that conduct basic research

with applied activities such as animal modeling, clinical trials, or pilot studies. A close coordination is essential with a team of clinicians, scientists, and patients in order to conduct a clinical trial, a process they estimate will take 3–4 years. Institutes such as the Central Leather Research Institute (CLRI), hope to transfer their current stem cell research to the private sector. CLRI is currently focused on engineering tissue by seeding scaffolds with stem cells. Their general business model is to conduct the basic research and find a private partner for further development. This is a model they have successfully applied in the past, as illustrated in their transfer of collagen sheet wound dressing technology to a local company, Eucare Pharmaceutical Pvt. Ltd. (Chennai), for production.

Private companies in the field of stem cells

Most Indian companies that can be classified as working in the field of stem cells are primarily involved in umbilical cord blood banking, an established business that provides the industry with a commercial base. Some of these companies are beginning to develop stem cell-based treatments often linked to Indian health needs. The Indian firms LifeCell (in Chennai), CryoStemCell (in Bengaluru), and Reliance Life Sciences (in Mumbai) have all established umbilical cord blood banking facilities. Many of these firms have technological tieups with established Cord Blood Stem Cell banks overseas. The potential to collect umbilical cord samples from India's large and ethnically diverse population recently led to the establishment of a joint venture, StemCyte India Therapeutics, between another firm from the United States, StemCyte, and India's Apollo Hospitals network and Cadila Pharmaceuticals (Ahmedabad). Most of the private entrepreneurship endeavours are limited to the private banking, however, public banking facilities are almost absent and have the potential to be well patronized by the medical fraternity due to the requirement for HLA matched recipients. However, statistics have shown that an excess of 10,000 umbilical cord blood units are required to get the highest probability of a match.

There are a few private entrepreneurs involved in stem cell therapy in the country. They involve LifeCell which has opened a stem cell therapy facility at Sri Ramachandra medical college and research Insti-

tute, in Chennai. Some Indian companies have also begun to develop treatments for various diseases. CryoStemCell, in partnership with Sri Bhagwan Mahaveer Jain Hospital (in Bengaluru), conducted a pilot stem cell treatment for Buerger's disease, a severe form of peripheral vascular disease, which is relatively rare in the Western world but common in India. It represents up to 45%–63% of peripheral arterial disease cases in India in contrast to 0.5%–5.6% in Western Europe. Buerger's disease causes inflammation of limb arteries, often leading to amputation and incapacitation of Indian farmers. If successful, CryoStemCell's pilot therapy has the potential to address a very real health need in India. Reliance Life Sciences is also involved in treatment development and is investing in an animal facility to conduct toxicology and preclinical efficacy studies for cell-based therapies. Nich-In Centre for Regenerative Medicine (NCRM), in Chennai, is not involved in umbilical cord banking but is instead focused on treatment development within India. NCRM was started by a group of scientists at Waseda University in Japan, including one Indian expatriate. A research lab was established in Chennai in September 2005. The perceived advantages included India's large population and vast spectrum of diseases on which research might be conducted; the substantially lower price of conducting research in India as opposed to Japan and finally, the shorter timelines for gaining approval to conduct applied research in India as opposed to Japan. The NCRM business model is to employ both scientists and clinicians in developing technology while coordinating with health care delivery systems. NCRM has signed a research memorandum of understanding with Yamanashi University in Japan and has started a nano-biomaterial-based cell culture with the Kawamura Institute of Chemical Research, actively collaborating with Yamaguchi University on hematopoietic stem cell research.

Finally, a number of Companies in the form of private entrepreneurs are planning to set up base in India in the near future. One such company is Unistem BioSciences Pvt Ltd which is a subsidiary group company of Beike Biotech Pvt Ltd, Shenzhen, China which is setting up base in Gurgaon, Haryana with a world class infrastructure, aspiring to be one of the biggest player in Stem Cell Industry that deals with private banking for umbilical

cord blood and public banking for the Cord tissue. It plans to conduct experimental therapy using stem cells as part of the endeavor to take stem cell therapy to the masses.

University and Training Institutes

A few Indian Universities appear very active in stem cell research. The University of Delhi, which, together with the Indian Institute of Nuclear Medicine and Allied Sciences, is examining basic mechanisms of stem cell function. However, many of the hospitals, firms and research institutes active in stem cell R&D are involved in education. Both Christian Medical College, Vellore (CMC) and AIIMS are teaching hospitals that provide postgraduate degrees and are active in stem cell research.

Lack of partnership between private companies and teaching Institutes including medical colleges

The success of medical research includes active participation of medical Institutes due to the impending clinical application involved but so far there is a lack of interest among the private companies to tie up with these Institutes either due to reluctance of these institutions or the lack of trust among the two which will not be healthy for advancement of stem cell translation. These institutes lack focus on basic research as they focus more on the teaching curriculum. However, courses are offered by some universities where the trainees get exposure in the Industry set up for a period not exceeding more than 6 months. Even though the Govt of India has approved science entrepreneurship scheme by which the faculty of all the medical institutions are insulated by the conduct rules, no medical institute in the country¹ has pushed the scheme. Most of the partnerships revolve around outsourced clinical trials that do not engage or reward the intellectual input of faculty of these Institutes. At a time when the Institutes in the world are gearing up to acquire stem cell leadership in the world, medical institutions should not be left behind in participating in the PPP model aggressively promoted by the Govt.

Building stem cell R&D on India's strengths

India has the capacity to participate in a cutting-edge stem cell research due to the strong prevalence of pharmaceutical and biotechnology sectors.³ Innovations that lower process costs have already

occurred in the stem cell field. Researchers aim to create their own cost-efficient cell and tissue culturing and storage techniques that can bring down the cost for the Indian consumer.⁴ Additionally, India's pharmaceutical and biotechnology sectors have helped India develop an expertise in conducting clinical trials. Bolstering this expertise, India's large, diverse, and treatment-naïve population provides a valuable resource for clinical trials, especially for rare diseases where the Indian population could provide sufficient patients for trial groups. As a result, India has great potential to act as a clinical trial destination of choice for stem cell therapies. This could help India develop and test stem cell therapies for a variety of diseases. This strength is likely to encourage more international ties and joint ventures, a trend already exemplified in the collaborations of United States/Indian firm StemCyte India Therapeutics and the Japanese/Indian venture NICRM in Chennai. However, this should not be done at the cost of developing own innovation systems and discoveries which will invariably come from investments in basic research.

Government support for R&D activities in India

The Indian government has been a key factor in encouraging stem cell R&D activity and growth. Stem cell engineering is seen as an important area for the government initiative in promoting stem cell research through federal funding. Four government agencies are key supporters of stem cell R&D: DBT, ICMR, DST and CSIR. Stem cell R&D promotion is driven largely by the DBT Stem Cell Taskforce and by ICMR through its affiliated institutes. DBT provides direct funding to targeted initiatives in this field and supports both infrastructure and operational activities such as clinical trials in research centers like the Centre for Stem Cell Research (in CMC, Vellore). It has been shown by Thorsteinsdóttir *et al.*,⁵ that government support is often crucial to capability building within emerging economies.

Overcoming India's stem cell R&D challenges by promoting linkages through Valliathan's committee recommendations

As a translational field, stem cell development requires a high degree of linkage between basic and clinical expertise. India's most prestigious medical institutes and hospitals, such as AIIMS, PGI and LVPEI, are those that integrate the efforts of ba-

sic scientists with clinicians. Unfortunately, this integration has historically been weak at most such sites in India. Increasing coherence and connectivity between these different sectors is the cornerstone of India's new medical biotechnology strategy. Specific institutions, as well as the government, have initiated steps to promote interactions between basic and clinical stem cell researchers. The construction of a joint research centre between the academic Centre for Cellular and Molecular Biology and the hospital-based Nizam Institute of Medical Sciences, both in Hyderabad, is an example of an Indian initiative aiming to increase clinician/scientist interaction. To address current barriers in this sector, India needs to further increase integration between researchers and clinicians, foster high-quality education and training, increase public awareness, and secure adherence to its new stem cell regulatory framework. In this regard the Prime Minister of India had constituted Valliathan committee for AIIMS & PGI which awaits implementation. India must also build on its current strengths by leveraging the vast and diverse population, government resources, and past entrepreneurial experience in clinical trials and treatment development. By taking additional steps in this direction, India will not only be successful in harnessing stem cells to improve the health of its population but is likely to become one of the main contributors to this emerging field.

The DBT is promoting an initiative which encourages publicly and privately funded stem cell research groups to share ideas, facilities, and research. These initiatives have been established at CMC in Vellore, and NCCS in Pune. The project is expected to be extended to Delhi. The DBT also supports India's Stem Cell Research Forum in partnership with Stempeutics (in Bengaluru), which encourages knowledge flow and linkages by acting as a platform for Indian scientists to discuss ideas and network with one another. The DBT is also planning to establish a new breed of institutions one of which is the Stem Cell Institute in Bengaluru which is being designed with a strong bias for integrating science and translation and for producing personnel skilled to carry out entrepreneurial activities. India's current and future successes within stem cell R&D provide an example for other developing countries and demonstrate that cutting edge science can be applied successfully to improve health in the developing world. The situation in

India also conveys to the rest of the world that the innovation landscape is changing and that the contributions made by emerging economies to the stem cell field must not be ignored or overlooked.

Increasing public awareness

While Indians who have heard of stem cell research and therapies are generally supportive even if this field is still relatively unknown to the general public. There is some understanding that this may lead to uninformed mistrust of the field, particularly if scandals or slow results help to destroy public support and lead people to be mobilized against new stem cell therapies. It is particularly challenging to educate the extensive Indian population about stem cells due to the difficulties of communicating the details of scientific advances to a vast population with typically low levels of general education. Journals and academies can play a vital role in dissemination of balanced information. Patient exploitation could be rampant with a false hope that immediate cure is at hand without a strong scientific basis or proper safety and efficacy data. Thus, public education may reduce the potential for patient exploitation which is an initiative that the Indian Government alongwith NGOs must take.

Developing the regulatory framework

Until recently, India lacked comprehensive stem cell research and therapy guidelines, an omission that compounded the potential for patient exploitation. To address this shortcoming, ICMR led the development of stem cell research and therapy guidelines with the participation of DBT and others. The draft guidelines allowed hESC and adult stem cell research and cell line development under close monitoring. Experimental treatments, embryo creation for research, and chimera studies are permissible subject to approval. The guidelines are categorized into permissive, restricted, and prohibitive areas for research, and all projects will have to register nationally. India's guidelines are relatively permissive when compared to other countries. Isasi and Knopper, have reported in a survey of 50 countries that hESC research was allowed under strict conditions in 23 countries and banned in five, while the rest had no explicit policy.⁶ It is unclear how successful the guidelines' implementation will be given the poor track record in India at monitoring IVF clinics. The new Indian guidelines,

though not legally binding, may encourage researchers to begin working in the area of stem cells while simultaneously stopping unregulated R&D. With hospitals and clinics already initiating stem cell-based trials and experimental procedures, the Indian government needs to proactively enforce its new guidelines. If it fails to do so, a poor stem cell regulatory framework may become a significant hindrance to the field's development, particularly as related to international collaborations and commercial links.

Conclusions

Much of the interest in stem cell research and therapies in India appears focused on patient's needs, particularly the growing national burden of chronic diseases such as diabetes, stroke and myocardial infarction, for which stem cell therapies may offer promising solutions. While stem cell therapies do have the potential to address India's health needs, it remains unclear if these treatments will be accessible to most Indians. In the clinical scenario, the initial costs of most stem cell treatments will likely be high but these therapies may in some cases cost less than the total cumulative cost. Stem Cell Entrepreneurship in India

will be of great advantage as therapies generated in India would cost less than treatments developed in industrialized countries due to India's low R&D cost and process engineering advantages. The Science entrepreneurship either around an individual scientist or Public Private Partnership model assumes significance as health insurance remains limited in India, and private households account for more than 80% of total health spending in the nation (National Commission on Macroeconomics and Health). It may also be seen that many Indians cannot afford even basic health care, and as reported by Kanga *et al.*, recently established stem cell treatments such as bone marrow transplants are beyond the budget of an average Indian.⁷ As the technology matures, treatments may become more affordable and a collective effort of the private entrepreneurship and the government will hasten the initiative in this regard. Only time will tell whether stem cell therapies, as they develop, will become a widely available treatment option for Indians.

Web Resources

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