Cell Stem Cell
Commentary

Harnessing Stem Cells for Health Needs in India

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While industrialized countries' stem cell research will be transferable to the developing world, research conducted by developing countries offers the potential to target innovation to local context, make treatments more affordable, and aid in economic development. India demonstrates that stem cell research and development (R&D) is not confined to industrialized countries and has begun to harness stem cells to address its own health needs.

An epidemiological transition is occurring in developing countries. Once thought of as "Western diseases," the prevalence of noncommunicable diseases such as diabetes, cardiovascular disease, and cancer are rapidly increasing in low and middle income countries. While still an emerging field of medicine, stem cell R&D has the potential to help developing countries treat increasing noncommunicable disease rates. Until recently, stem cell research has been concentrated in relatively few countries, largely the most affluent and technologically advanced. Several developing countries, however, now actively participate in the stem cell field, producing new knowledge and promising clinical trials. Our previous work supports the belief that regenerative medicine, a field in which stem cells act as key building blocks, could help address developing countries' health needs and identifies three top regenerative medicine applications for the developing world: novel methods of insulin replacement and pancreatic islet regeneration for diabetes, autologous cells for the regeneration of heart muscle, and immune system enhancement and novel vaccination strategies (Greenwood et al., 2006). Certainly the health needs of the developing world are great: for example, 80% of chronic disease deaths occur there, according to a 2005 World Health Organization report, and this rate is expected to rise in the coming years (Boutayeb and Boutayeb, 2005). While stem cell research conducted in industrialized countries will, in many cases, be transferable to the developing world, research in the developing world tailors innovation based on the local context in order to make treatments more affordable and contributes toward the economic development of these countries. This targeting approach is especially relevant in emerging economies like India and China that have the potential to conduct their own stem cell research and therapy development. To better understand the potential developing countries have for building their own stem cell R&D capacity, we present here the case of stem cell R&D in India, based in part on interviews with 38 Indian experts on stem cell research and therapies from research institutes, hospitals, private firms, universities, and government agencies (see Table S1 and the Supplemental Data, available online, for details on methodology).

India is one of few developing countries to have begun work on novel stem cell technologies and therapies. We believe that India has strengths in stem cell research geared toward developing applications to meet its health needs and budget; it also has the potential to make important global contributions to this emerging field. The experience in India shows how the developing world can harness the potential of stem cell research and make an active contribution to the development of this field.

Current State of Stem Cell Research in India

Indian authors have, in recent years, sharply increased their publications in stem cell research in international peer-reviewed journals. At the beginning of the new millennium, Indians authored hardly any stem cell publications, but by 2007 they were authoring around 100 stem cell papers a year listed in the Web of Science alone. Indians have also started to develop 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 derived by the Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), in Bengaluru, are now accepted for deposition and 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 on an ISCI project. Alka Sharma, principal scientific officer of India's Department of Biotechnology (DBT), believes there are more than 30 research institutes, hospitals, and firms involved in stem cell research in India (Sharma, 2006). 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 (see Figure 1 for geographic locations). Their activities are varied and include basic research, clinical trials, treatments, and service provision.

Research Institutes

Public research institutes are the largest group active in stem cell research within India. Some institutes focus primarily on basic research. JNCASR, for example, studies ESC differentiation into cardiovascular cells. Other institutes balance basic research with applied activities such as animal modeling, clinical trials, or pilot treatments. NCCS has conducted animal and preclinical analyses of bone marrow stem cell injections for pancreatic regeneration. Research efforts from this institute succeeded in rescuing mice with experimentally induced diabetes after a 30 day follow up (Banerjee et al., 2005), and scientists at NCCS hope to extend this work to an autologous clinical trial in human

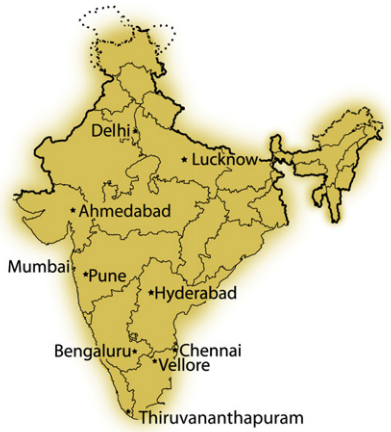

Figure 1. Locations of Main Stem Cell Activities in India

diabetic patients. The institute is working to establish a team of clinicians, scientists, and patients to act as a platform for the trial, a process they estimate will take 3–4 years. Others, 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.

Hospitals and Clinics

Unlike India's biotechnology sector as a whole (Frew et al., 2007), few Indian companies are involved in stem cell research. Instead, Indian hospitals and clinics are key players. India's large research-intensive hospitals, such as AIIMS, conduct basic and applied research and have clinical trial and pilot treatment capabilities. This combination of resources creates a bridge between research and therapy and makes hospitals pivotal for Indian stem cell innovation. AIIMS works on a wide spectrum of clinical applications in cardiology, ophthalmology, neurology, and hematology and also carries out basic research on, for example, stem cells and biopolymers aimed at treatments for orthopedic, ocular, and skin diseases. Christian Medical College and Hospital (CMC) in Vellore is founding a center for stem cell research in collaboration with DBT to promote translational research with stem cells. Sankara Nethralaya, an eye hospital based in Chennai, has similarly built a research building to house the Kamalnayan Bajaj Institute of Research in Vision and Ophthalmology. Opening in September 2008, stem cell research will be a key focus of this new building, with projects covering diverse areas such as corneal stem cells, cancer stem cells, and the use of stem cells in tissue engineering. Stempeutics, in Bengaluru, is the research arm of Manipal Education and Medical Group (MEMG). Its efforts are designed to divide resources between basic and clinical research. Employing both scientists and clinicians, Stempeutics sees itself as a bridge between the two groups. Areas of basic research include mesenchymal stem cells, cancer biology, and cardiovascular research, while clinical trials are underway for myocardial infarction, critical limb ischemia, cerebral stroke, and multiple sclerosis. Stempeutics has also recently established an R&D lab in Malaysia, joining hands with one of Malaysia's largest healthcare groups, KPJ Healthcare Berhad. Many hospitals have conducted pilot treatments in areas such as cardiac, spinal, and ocular regeneration. AIIMS has been involved in a variety of stem cell pilot therapies for disorders ranging from liver cirrhosis (Sharma et al., 2006) to nonischemic dilated cardiomyopathy (Narang et al., 2006).

The best example of a homegrown Indian stem cell treatment that addresses local health needs is the ocular surface reconstruction method developed at L.V. Prasad Eye Institute (LVPEI), a nonprofit hospital in Hyderabad. LVPEI clinicians saw patients suffering from severe ocular surface disease that they were unable to treat with traditional corneal transplantation methods. Many of these injuries affected children under 15 and were often caused by chemical burns from accidental exposure to materials frequently used in Indian homes. Lime, which is a highly alkaline substance and a key ingredient in paan (a popular Indian stimulant and digestive), was the leading cause of chemical burns (Fatima et al., 2007). In reaction to patient need, LVPEI scientists and clinicians explored potential stem cell-based treatments and ultimately developed a time- and cost-effective ocular surface reconstruction method. Still an "extended clinical trial," LVPEI has performed the treatment on more than 500 patients with a success rate of 70% (Sangwan et al., 2003, 2005). LVPEI offers this treatment irrespective of income and is supported by DBT, the government of India, the Hyderabad Eye Reserach Foundation, and the Champalimaud Foundation. To date, at least half the patients treated have been nonpaying.

Companies

Most Indian companies that can be classified as working within the field of stem cells are primarily involved in umbilical cord blood banking, an established practice that provides the industry with a commercial base. Some of these companies are beginning to develop stem cell-based treatments as well, 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 also have international links. LifeCell is planning to expand into the Middle East and South Asia and has a technology licensing agreement with the firm Cryo-Cell International, a company from the United States. LifeCell has also opened a stem cell therapy facility at Sri Ramachandra Medical College and Research Institute, in Chennai. 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).

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 hemisphere but common in India. It represents up to 45%–63% of peripheral arterial disease cases in India but only 0.5%–5.6% in Western Europe (Olin, 2000). 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.

Finally, 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, due to several perceived advantages in conducting applied research within India. These 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; the fact that Indian scientists speak English, allowing for article submission for English journals; 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 collaborating with health care delivery systems. Collaboration with Japan is high. NCRM has signed a research memorandum of understanding with Yamanashi University, has started a nanobiomaterial-based cell culture with the Kawamura Institute of Chemical Research, and is collaborating with Yamaguchi University on hematopoietic stem cell research.

Universities

Few Indian universities appear active in stem cell research at this time. The main exception is 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 also involved in education. Both CMC and AIIMS are teaching hospitals that provide postgraduate degrees. Many of India's research institutes are colocated with a university and informally train students within their research labs.

Government Support

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 and is identified as a strategic biotechnology area in the DBT's 2007 Biotechnology Strategy (available online). Four government departments are key supporters of stem cell R&D: DBT, the Indian Council for Medical Research (ICMR), the Department of Science and Technology, and the Council of Scientific and Industrial Research. Stem cell R&D promotion is driven largely by the DBT Stem Cell Taskforce and by ICMR through its affiliated institutes and regulatory capacity. DBT provides direct funding to targeted initiatives in this field and supports both infrastructure building and operational activities such as clinical trials. It has begun to support large-scale strategic programs, such as a phase III multicenter trial using bone marrow cells to treat myocardial infarctions, and sponsors stem cell research centers like the Centre for Stem Cell Research (CMC, in Vellore) and a soon-to-be-established stem cell research center in Bengaluru, the Institute for Stem Cells and Regenerative Medicines. As has been shown elsewhere for the case of health biotechnology (Thorsteinsdóttir et al., 2004), government support is often key to capability building within emerging economies.

Building Stem Cell R&D on India's Strengths

India's capacity to participate in a cutting-edge field such as stem cell research is, in part, built on skills and infrastructure previously developed by the nation's pharmaceutical and biotechnology sectors (Kumar et al., 2004). One such skill is the proven ability of Indian firms to develop process innovations in order to lower prices (Frew et al., 2007). Innovations that lower process costs have already occurred in the stem cell field. Researchers do not necessarily copy blindly the techniques used in developed countries but create their own cost-efficient cell and tissue culturing and storage techniques that use fewer disposable devices. Indian companies have also begun to produce materials, such as growth factors, that are needed in stem cell research at significantly lower rates.

In addition, 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-naive 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 NCMR.

The cultural acceptability of stem cell therapies will help India further develop this sector. Unlike the public controversies that surround ESC research in many other nations, there has been no strong public objection to ESC research in India. Some themes in Hindu mythology might help increase Indian acceptance of embryonic research practices such as cell or tissue cloning. For example, in one Indian myth, King Dhritarashtra creates 100 sons by dividing a fetus into 100 different parts and growing each in a pot, in effect through cloning. There is also a potential complementarity between India's traditional medicine system, Ayurveda, and stem cell therapy. Researchers currently complement stem cell therapies with Ayurvedic principles of purging and rejuvenating the body in conjunction with modern stem cell leukemia treatments. Further synergies could develop between stem cell therapies and Ayurveda in order to advance the national experience in this field, as well as giving such therapies a distinctively Indian twist.

Overcoming India's Stem Cell R&D Challenges

Promoting Linkages

As a translational research field, stem cell development requires a high degree of linkage between basic and clinical expertise. India's most successful research institutes and hospitals, such as AIIMS and LVPEI, are those that integrate the efforts of basic scientists with clinicians. Unfortunately, this integration has historically been weak at most research sites elsewhere in India. Increasing coherence and connectivity between these different sectors is the cornerstone of India's new biotechnology strategy (DBT Strategy, 2007), and 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 center 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 institutional initiative aiming to increase clinician/scientist interaction.

The DBT is promoting improved integration with its stem cell cluster initiative, which encourages publicly and privately funded stem cell research groups to share ideas, facilities, and research. Four clusters are already established: around the CMC in Vellore, the NCCS in Pune, in Bengaluru, and in Hyderabad. The project is expected to expand and promote an additional cluster in Delhi (see the DBT strategy report, available online). The DBT also supports India's Stem Cell Research Forum in partnership with Stempeutics, 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, such as the stem cell institute it is building in Bengaluru, which will be designed with a strong bias for integrating science and translation and for producing personnel skilled to carry out entrepreneurial activities.

Strengthening Training

For India to increase its stem cell research capacity, it will need to strengthen the quality of its current scientific education. The DBT is helping Indian scientists gain expertise abroad by offering overseas stem cell fellowships and travel bursaries for conferences. Research institutes are increasing their involvement in training through postgraduate supervision and by coordinating workshops, such as the stem cell training workshops currently run by JNCASR in partnership with the NCBS, both in Bengaluru. Universities are also becoming more involved in stem cell training programs, such as Manipal University's efforts to establish an Institute of Regenerative Medicine with a related graduate program in the summer of 2007. NCMR, in collaboration with Acharya Nagarjuna University (in Chennai), launched a stem cell PhD program in April 2008. The program will be focused on bringing clinicians together with scientists. Indians can also strengthen their capacity for stem cell research by attracting Indian experts who are currently active in this field in developed countries. Members of the Indian scientific diaspora (expatriates working in industrially developed countries) have begun to return to India in greater numbers, encouraged by economic prosperity and active recruitment initiatives from firms and research institutes. More proactive strategies could strengthen this flow of returning scientists, with targeted efforts designed to attract expatriate experts in stem cell research.

Increasing Public Awareness

While Indians who have heard of stem cell research and therapies are generally supportive, this field is still relatively unknown to the general public, except to a small subpopulation of educated urbanites. There is some risk that this lack of broad understanding may lead to uninformed mistrust of the field, particularly if scandals or slow results help to destroy public support and lead Indians to mobilize against new stem cell therapies. This mobilization against new technologies has already occurred in India with the introduction of genetically modified cotton (Padma, 2006). While this risk is not unique to India, it is particularly challenging to educate the extensive Indian population about stem cells, due to the logistical difficulty of communicating the details of scientific advances to a vast population with typically low levels of general education. Another risk that is not specific to India, but that might be unusually challenging to overcome in this country, is that expectations for stem cell-based therapies may be overly inflated to the ultimate detriment of the field. There is considerable potential for the exploitation of patients who see stem cell therapy as a "magic bullet" to solve their health needs. This exploitation has already been described in anecdotes of Indian clinics offering stem cell therapies without a strong scientific basis or proper safety and efficacy tests. Public education about the current and future potential of stem cell therapies should decrease uninformed mistrust of stem cell therapies and reduce the potential for patient exploitation. As in most countries, there is as yet no public initiative in India aimed at stem cell education, something that the Indian government should take steps to change.

Developing the Regulatory Framework

Until recently, India lacked comprehensive stem cell research and therapy guidelines, an omission that compounded the potential for patient exploitation. Uncertainty over which stem cell scientific research areas could ultimately be seen as legally and ethically acceptable also discouraged cautious researchers from entering the field. To address this barrier, ICMR led the development of stem cell research and therapy guidelines (see ICMR National Guidelines) with the participation of DBT and others. Newly finalized, the guidelines are relatively permissive, allowing 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 create two levels of stem cell research review and monitoring: a National Apex Committee for Stem Cell Research and Therapy as well as institutional committees. Depending on the research topic, projects will be approved nationally or institutionally; research will be 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. Regarding hESC research, one study surveyed 50 countries and found that hESC research was allowed under strict conditions in 23 countries and banned in five, while the rest had no explicit policy (Isasi and Knoppers, 2006). The new Indian guidelines are not legally binding; however, many Indians remain optimistic that their existence will encourage researchers to begin working in the area of stem cells while simultaneously stopping unethical R&D. It's unclear how successful the guidelines' implementation will be. India has a poor track record at monitoring IVF clinics and enforcing its guidelines for biomedical research using human subjects (Salter et al., 2007). 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.

Concluding Thoughts

Much of the interest in stem cell research and therapies in India appears focused on patient need, particularly the growing national burden of chronic diseases such as diabetes 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. As the LVPEI ocular surface reconstruction work illustrates, affordable stem cell-based treatments can be developed. It may be that stem cell therapies developed in India would cost less than treatments developed in industrialized countries due to India's low R&D cost and process engineering advantages. Moreover, because stem cell therapies can potentially be applied to cure chronic diseases such as diabetes that require lifelong treatment, the cost of a stem cell therapy may be less than cumulative conventional treatment costs, at least in some cases. However, the initial costs of most stem cell treatments will likely be high. 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). Many Indians cannot afford even basic health care, and relatively established stem cell treatments such as bone marrow transplants are beyond the budget of a significant number of the Indian population that can pay for standard care (Kanga et al., 2007). Several hospitals in India do charity work or charge based on patient income. This approach will likely provide a means to bring stem cell therapies to the Indian population, but not at a meaningful scale. As the technology matures, treatments may become more affordable. Only time will tell whether stem cell therapies, as they develop, will become a widely available treatment option for India's poor.

As India's capacity in stem cell research continues to develop, it can draw upon the nation's numerous strengths to actively expand its involvement in this field. Based on its track record in information technologies and biotechnology, it is likely that India will be successful in building its capacity for implementing stem cell therapies. To address current barriers to 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. 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. As Professor D. Balasubramanian, director of research at the LVPEI, questioned: "So, how many years are we behind? Five years behind? Four years behind? Why can't we catch up?" 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.

SUPPLEMENTAL DATA

The Supplemental Data include supplemental text and one table and can be found with this article online at http://www.cellstemcell.com/cgi/content/full/3/1/11/DC1/.

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