advancements in stem cell research : an Indian perspective-II

Stem cell research has stolen the limelight in the past decade and created a lot of hype and hope. Notwithstanding all the hype, development in stem cells have come a long way. Stem cell research in India is at par with the developed nations in the global arena.

A decade of progress

There has been a quantum leap in stem cell-related publications in international peer-reviewed journals by Indian authors. By 2007, there were around 100 papers a year listed in the Web of Science alone, in stark contrast to the almost nought at the start of the decade. According to Dr. Alka Sharma, Joint Director, DBT, there are more than 30 research Institutes, hospitals and firms involved in stem cell research in India. The recent acceptance, by the U.K. Stem Cell Bank, of two sibling HES cell lines(BJN-hem19 & 20) developed by Dr. Inamdar's team at JNCASR/NCBS stands testimony to these claims.

Government's initiatives

The zeal exuded by the Government of India has led to the prompt identification of stem cells as a niche area requiring intense focus. Its translation in real-time is evidenced by its ever-increasing patronage in the form of grants towards infrastructure development and operational activities. The Stem Cell Task Force(SCTF), constituted in 2003 was enthrusted with the responsibility of evaluating project proposals, pushing the formulation of protocols, monitoring and evaluating results. There was a proposal for "stem cell priority fund" with possibilities of including ICMR, DST and DRDO.

R&D in India

Major funding agencies in stem cells are: DBT, ICMR, DST and CSIR. Excellent groundwork is being carried out at research institutes under the purview of these bodies. NCCS, Pune, has an impressive portfolio of scientists which included Dr. Bhonde who tested stem cells potential to transdifferentiate into pancreatic islets. Young scientists who have carved their niche include V. Kale setting out to explore the HSC signalling pathways, N. Lenka working on ESCs to produce neural cells. A. Hardikar is attempting to regenerate islet cells in order to understand the differentiation potential of pancreatic progenitor cells. Dr. Bapat has provided the evidence of stem cell dysfunction as the cause of human ovarian cancer, paving way for further investments. At NBRC, Ellora and Shyamala Mani are steering their efforts towards deriving neural cells from adult and embryonic stem cells respectively. Pankaj Seth and Ranjit Giri have adopted stem cells as a model to study virus-induced neuro-degeneration and Alzheimer's disease. Dr. Asok Mukopadhyay of NII working on cancer stem cells, HSCs has been and has successfully transdifferentiated HSCs into hepatocytes. Dr. Subeer Majmudar of the same institute has his expertise on testicular stem cells.

Dr. Deepa Bhartiya of NIRRH has succeeded in deriving and characterising two genetically unique hES cell lines on in-house derived human feeders. Umbilical cord-derived mesenchymal stem cells have been differentiated into cardiomyocytes by Dr. Winston Pereira of NIIH. Prof. P. Seshagiri of IISc seeks to decipher cell lineage specification using ESCs while Annapoorni Rangarajan is focusing unravel the mechanism of carcinogenesis using cancer stem cells. Dr. Panicker of NCBS is probing the effects of the neurotransmitter serotonin on neural stem cells and ESCs. At CCMB, Dr. Jyotsna Dhawan's team is trying to obtain myocytes. Dr. Shobha Tole employs genetically engineered ESCs to expound the intricacies of brain development at TIFR, Mumbai.

Combining these efforts, Dr. Vijayalakshmi Venkateshan, at NIN, is engaged in differentiating adult stem cells into insulin-producing cells. AIIMS has pioneered a number of pilot studies across a wide spectrum of clinical diseases even though this attracted widespread criticism in the press. Now that major clinical trials are underway, Dr. Sujata Mohanty is planning to boost work on basic stem cell biology. The stem cell facility at PGI, Chandigarh is also supported by DBT. Dr. Akshay Anand's lab at PGI combines the clinical expertise of Dr. Prabhakar. This lab focuses on the protective role of stem cells in retinal degeneration and stroke. It serves to provide an immediate bridging effect between basic and clinical research. Dr. KK Talwar, Dr. Bhansali and Dr. Sen are spearheading the other clinical trials at PGI. Concurrent work is also being done in the fields of tissue engineering and nano technologies employing stem cells at CLRI, Chennai and Sri Chitra Tirunal Institute, Trivandrum. Any benchwork should aim for its integration with potential clinical application. In order to achieve tangible benefits, collateral and multidisciplinary approach should be favoured over the existing tangential ones. Towards this end, Centre for Excellence in Stem Cells was set up in CMC Vellore in 2007 under the aegis of DBT. The dedicated efforts of Dr. Alok Srivastava's team has attained fruition with their breakthrough in the realm of iPs cells. This center is part of the "Stem Cell Cluster" which includes IISc, NCBS and Manipal Hospital, Bangalore.

Private Players

The research prowess of the private sector has been equally impressive. Their effort was led by Reliance Life Sciences (RLS) with their landmark achievement of hES cell lines were the first from India to be accepted and listed in the UK Stem cell registry. There are a number of private players who have set up cord blood banks. These include RLS (Mumbai), Life Cell (Chennai), Advanced Cell Therapeutics, CryoCell to name a few. NIRM, Chennai has set up a Corneal Endothelial Stem Cell Bank (CESBANK). Corneal limbal stem cells have been developed at the L V Prasad Eye Institute (LVPEI) under the leadership of Dr. Geeta Vemuganti alongwith Dr. Virendar Sangwan. Sankara Netralaya has set up an exclusive centre for stem cell research in 2008-Kamlnayan Najaj Institute of Research in Vision and Ophthalmology. Stempeutics is conducting clinical trials on chronic limb ischemia and acute myocardial infarction in the pipeline, in collaboration with Manipal Hospital, Bangalore.

Need for caution

The scientific community was recently

confronted with the shameful fallout of Woo Suk Hwang, which included the ethical breach in the collection of human oocytes. The South Korean National Bioethics Committee reported that 16% of donors suffered adverse effects from the procedure and required in-hospital treatment. The penchant for innovation had, ironically, given way to the idiosyncrasies of human nature and folly. This scandal called into question the legitimacy of hES cell research.

Regulation : A political responsibility

India is a significant contributor to the global market for stem cells and is growing at a rate of 15% according to Dr. Satish Totey. With such a tremendous growth potential, the need for stringent regulations is widely felt. This has been aptly summarised by Prof. M.K. Bhan of DBT when he announced the setting up of "Institute for Stem cells and Regenerative Medicine" in Bangalore saying, "we have a broad strategy to recognise the biology of stem cells and create practical accessible therapies. The way we see it in India is that while promoting science and technology strongly, we want to follow world-class standards of ethics, regulation and engage the civic society in terms of getting their consensus."

Realising the complicated ethical, social and legal issues involved in this field, ICMR took up the reins and laid down the "National Guidelines of Stem Cell Research and Therapy 2006". One of its salient features of the report is the classification of stem cell research under permissible, restricted and prohibited categories. The research pertaining to adult and umbilical cord blood stem cells would be classified as permissible. It would require approval from Institutional committee. However, embryonic stem cells research falls under restricted category. It can be carried out with the approval of Institutional Committees and National Apex Committee. Research pertaining to reproductive cloning, introducing animal embryos in human, etc. has been categorized as prohibited.

A distinction has been made between establishing embryonic stem cell lines from spare embryos and embryos specifically made for the purpose, including both *in vitro* fertilization and somatic cell nuclear transfer techniques. The former is placed in the permissive category provided spare embryos are obtained in an ethically acceptable manner while the latter is restricted in its category to require specific scientific justification and proof of technical competence of the investigator. It has been done to dissuade frivolous creation of embryos for establishment of hES cell lines.

It has also set standards for the collection, processing and storage of cells intended for clinical use. All cord blood banks would have to be registered with the Drug Controller-General of India (DCGI). The NAC-SCRT(National Apex Committee-Stem Cell Research Therapy) and IC-SCRT (Institutional Committee-Stem Cell Research Therapy) have been constituted as a separate body to address the regulatory issues. The National Apex Committee shall serve to register all the stem cell research centers, available stem cell lines in India, including the newly developed ones, and ongoing clinical stem cell trials in the country. It will also receive periodic reports from the Institutional SCRTs and provide the status of SCRT from time to time. The National Bioethics Committee has prepared the consent protocol for tissue collection for human stem cell research. Thus, the Indian Government is playing a proactive role in guarding research ethics unlike the "growth-first policy" of South Korea which recklessly dashed ahead only to crash in the pursuit of its national motto, "Nation building with science and technology".

US' new policy : Implications for India

Obama's nod to give ESC research its long-due fillip has infused palpable enthusiasm among healthcare professionals. The prospects of the increase in outsourcing of stem cell-related clinical trials to India, may both address or sabotage the unmet health needs and versatile biodiversity of our population. "The development in US would help attract collaborative work and access to an expanded scientific knowledge base" says KV Subramaniam of RLS.

Business potential and India's stand

" The stem cell therapy market is expected to touch $96 billion by 2010. In all probability, a $10-billion business opportunity in the therapies segment would come India's way in the next couple of years. Another $3-4 billion in expected in the research segment during the same period" says Abhaya of Life Cell. Cryo-Save has invested $1.6 million in stem cell banking in India. Its Scientific Director, Prof. Colin McGuckin opines that "Public-Private Partnership"(PPP) is the key to surge ahead.

Strengthening the triad of government's commitment, PPP and well-trained scientific base is needed to foster India's leadership in the field of stem cells. DBT's Biotechnology Strategy 2007 assures the same. 30% of DBT's budget is to be allocated for PPP. It has come up with SBIR (Small Business Innovation research Industry) scheme under the umbrella of BIPPP (Biotechnology Industry Public-Private Partnership). This allows the industry partner to retain the IP with payment of appropriate royalty to the contributing public sector scientists, thereby paving the way for global competitiveness.

Initiatives to expand and enrich human resources have been envisaged. Innovation systems, a network of institutions, that aim to weave new knowledge into the existing tapestry, aid in its inter-disciplinary diffusion and create high-quality translational workforce are the need of the hour. Seamless flow of ideas and flexible multidirectional streaming of knowledge should form the core of this model. The "city clusters" are being promoted to moot this principle, share information, discuss emerging policy issues, explore collaboration with clinicians and to establish virtual network of these centres. The "Stem Cell research forum of India"(SCFRI) offers a good vantage point.

Horizontal transfer of knowledge has been facilitated to a great extent across the country-Symposia on stem cells at Agharkar research Institute Pune, CCMB Hyderabad, International Stem Cell Summit at IIT Madras, ICMR's 4th MDC on Stem Cell Research and Therapy- are a few examples. A training course is being implemented at NCBS/JNCASR to train young minds in adult and embryonic stem cells. MIRM (Manipal Institute of

Regenerative Medicine) Bangalore has started an exclusive regenerative medicine post-graduate program. Clinical research workshops are organised by DBT to update clinicians on laboratory developments.

Harnessing the full potential of talent is possible only with pragmatic measures and not by merely propagating utopian ideas. The Wellcome Trust/DBT partnership-a £160 million funding- is an effort to allure the sea turtles, who are holding back a shell-house of scientific talent and international credibility, to Indian shores. A $11.5 million Indo-Australian joint fund has been supporting public and private sector researchers since 2006 in Biotech areas including stem cells.

Conclusion

Science in India has grown with strong roots under the stalwartship of Nehru who believed, "the future belongs to science and those who make friends with science". With the resources in hand, we need to encourage lifescience leadership as much as science entrepreneurship, particularly in medical institutions, with the aim of prioritising and streamlining strategies to address local unmet health needs and achieve regional aspirations of self-reliance.

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