



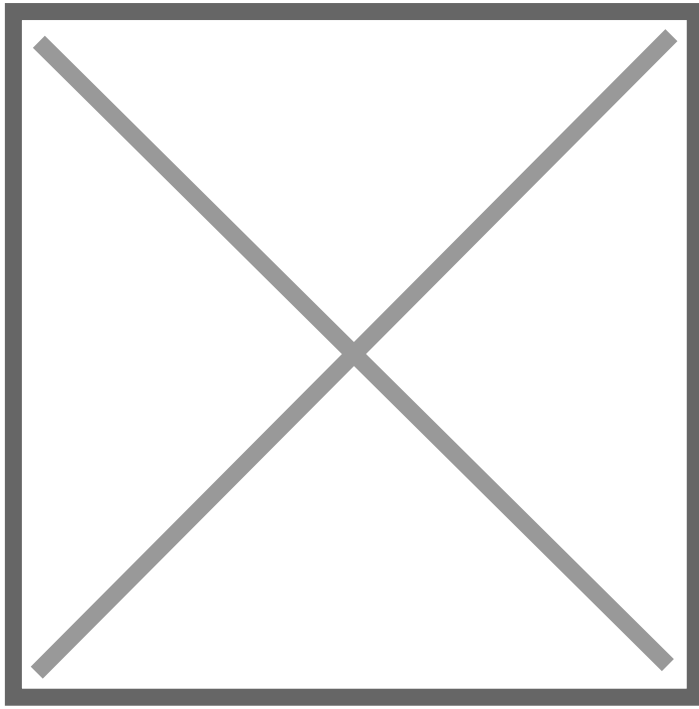
BioSpect

the business of Bio

24 years of leveraging the business of Bio
www.biospectrumindia.com

The promise of stem cell technology in India

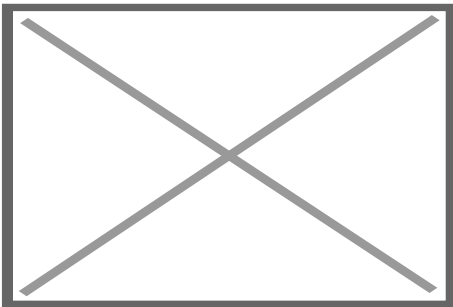
09 February 2006 | News



The promise of stem cell technology in India

India is relatively a new player in the stem cell arena. Nevertheless, stem cell researchers have already achieved some encouraging results. The right policies, public-private partnership, funding and an increasing scientific base will contribute towards strengthening India's global position over the coming years.

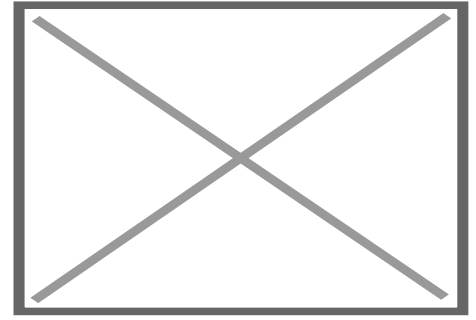
Stem cell research is under the arc lights once again. The fabricated work of the South Korean scientist Hwang Woo Suk on cloned human embryos and stem cells has focused the attention of the global scientific fraternity on this nascent, sensitive yet innately potential arena.



Scientists are realizing that research in the stem cell segment is a long drawn process especially in the wake of political, ethical and public pressure prevailing in some countries. But the promise of the technology is immense. It could pave the way for therapies of hard-to-cure diseases like diabetes and Parkinson's. Scientists hope to use stem cells as replacement parts for failing organs, as they have the potential to mature into almost any cell in the human body.

India is one of the few countries where the government is largely supportive of research in this segment. Apart from a few private initiatives in the country, most of the efforts have been state sponsored. About Rs 8 crore have been spent on stem cell research in India in the last two years. The Department of Biotechnology (DBT) under the Ministry of Science & Technology is the nodal funding agency for supporting the stem cell R&D program.

To date, more than 30 programs have been identified by DBT and supported for stem cell research that include establishment of human cell lines, limbal stem cells, haematopoietic stem cells, neural stem cells, liver stem cells, cardiac stem cells, human corneal stem cells, and stem cell preservation. Presently India has very little research work going on in human or animal embryo cloning.

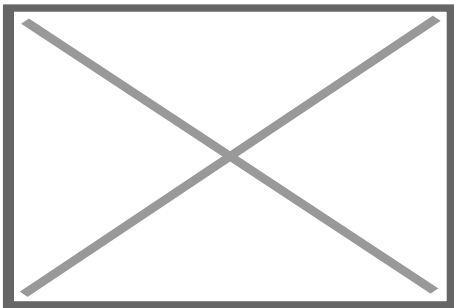


According to Prof G Padmanabhan, distinguished biotechnologist and honorary professor, IISc, Bangalore, "Stem cell therapy is a global business opportunity for India. The country can very well exploit adult stem cell therapy using cord blood cells and mesenchymal stem cells from the bone marrow. But there is a need for appropriate clinical trials even for autologous use".

Centers with ongoing programs

India is relatively a new player in this area. Nevertheless, stem cell researchers have already achieved some encouraging results such as the use of limbal stem cells from the eye to treat damaged corneas at LV Prasad Eye Institute in Hyderabad. Currently, several major institutes in India are engaged in stem cell research with most focusing on using stem cells to regenerate nerve, heart and adult muscle cells, and repair damaged bone tissue like the LV Prasad Eye Institute, Hyderabad, Christian Medical College, Vellore, National Brain Research Centre, Delhi and National Centre for Biological Sciences, Bangalore.

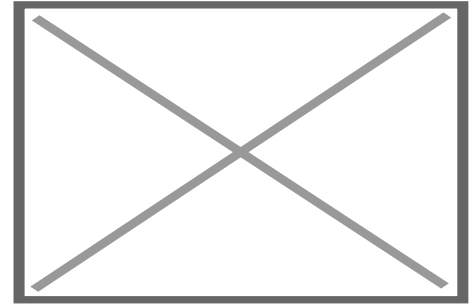
At LV Prasad Eye Institute, under a DBT supported project, scientists have been able to generate a 1-2 cell layered epithelium from the limbal tissue without the use of a feeder-cell layer and air-water interphase. About 20 patients diagnosed with limbal stem cell deficiency have been recruited for cultured limbal stem cell transplantation. Results showed complete re-epithelialization of ocular surface in 2-6 weeks time. The group has also successfully cultured limbal stem cells on human amniotic membrane for limbal stem cell transplantation.



Technology has been established at Christian Medical College, Vellore for the first time for clinical hematopoietic stem cell transplantation. This facility allows haplo-identical stem cell transplantation to be conducted for those patients with incurable hematological malignancies or genetic disorders. This technology is also being made available to other centers in India for application in their own places.

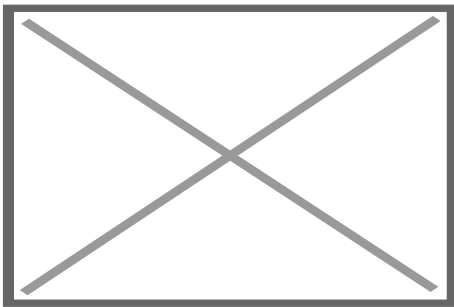
Under the DBT supported project on liver stem cells at Centre for Liver Research Diagnostics (CLRD) and Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad, hepatic progenitors have been isolated from human fetal hepatocyte using CD34+ marker and have been characterized morphologically and biochemically using liver specific markers.

The All India Institute of Medical Sciences (AIIMS) has successfully given stem cell treatment by 'injection method' to its cardiac patients. The institute conducted the study under the leadership of P Venugopal, a renowned heart surgeon and AIIMS, director, from February 2003 to January 2005, where 35 cardiac patients were given stem cell therapy and were monitored at six, 12, and 18-month intervals. All the patients were at a stage when their hearts were beyond bypass surgery and transplant was the only solution. After six months of treatment, 56 percent of the dead tissue area injected with stem cells showed improvement while after eighteen months, the improvement spread to about 64 percent of the necrotic area. These stem cells, derived from the patient or donors, act as repair agents within the body, multiplying continuously to replenish other cells. AIIMS has now been notified as India's nodal centre for conducting and coordinating stem cell research.



Commenting about these developments and the current Korean stem cell controversy, Prof D Balasubramanian, director, LV Prasad Eye Institute and chair, DBT Task Force on Stem Cell Research said, "First, there is very little human embryonic stem cell applications done in the country. Much of the work has been on adult stem cells - such as of the eye and from bone marrow. The limbal stem cell applications have now been followed through for four years, and have also been done in several centers, so that the corneal surface reconstruction using limbal cells is now rigorous and acceptable from the scientific, ethical and clinical angles. The work by Dr Venugopal and colleagues at AIIMS is also good, since such work has been done elsewhere in the world before they did it, and they have learnt from earlier experience".

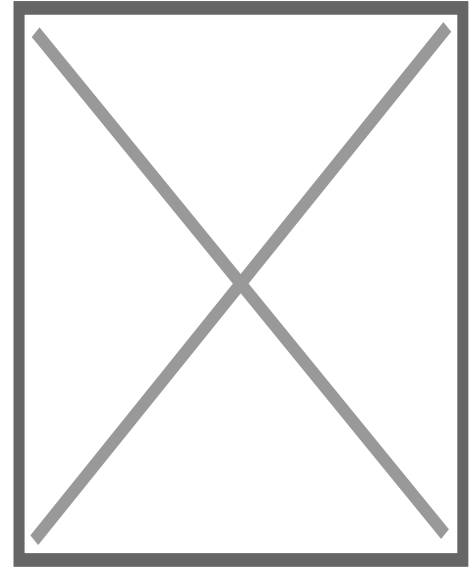
Presently the DBT has envisaged big plans for creating infrastructure in the stem cell research arena. Dr MK Bhan, secretary, DBT, said, "The department has mooted plans to create a stem cell center at CMC Vellore with a funding of Rs 19 crore. This will be under a novel scheme of Centers of Excellence (CoE), which is quite different from what has existed in the past". Elaborating further about the CoE concept, Dr Bhan said, "These centers will be around gifted individuals where the new faculty positions would be mentored by this leader. Creating such CoEs will help create focus in research, introduce a larger element of teamwork and achieve a new measure of independence by locating the centers outside the department. We will be increasing the scientific oversight by putting in a scientific advisory committee apparatus to oversee these centers".



Private initiatives

In the private sector, Reliance Life Sciences (RLS) backed by the industry major Reliance Ltd has taken the lead. It ranks third among the top 10 institutes worldwide working on stem cells, as stated in an NIH report. The center was set up with an investment of \$5 million in the cell biology facility in 2001. In the same year the embryonic stem cell work started as per the guidelines of the Indian Council of Medical Research and the National Institutes of Health, USA. The embryonic stem cell group is also focusing on basic research such as gene discovery, drug discovery and establishment of several transformed cell lines. The RLS's cell biology research activities are being carried out at Sir Harkishandas Nurrotumdas Hospital in Mumbai and Reliance had pumped in Rs 100 crore for its upgradation in 1997. Presently the RLS has created a comprehensive genetic center as part of its cell biology group. The Reliance Group will be investing about \$25 million in cell biology research that focuses on stem cells and tissue engineering. This covers embryonic stem cells, haematopoietic stem cells, skin cells, tissue engineering, genetics and molecular diagnostics.

Another player in this arena is Manipal AcuNova, a collaborative venture between Manipal Education and Medical Group International India and AcuNova Life Sciences. Elaborating on its plans in this arena, DA Prasanna, vice chairman and managing director, Manipal AcuNova, said, "Stem cell activity has been conceived as part of Manipal AcuNova. Like the KMC life sciences center labs, we also have a stem cell lab for promoting discovery research and we intend doing that when our stem cell lab is ready. This lab is undergoing stabilization and is in Bangalore (Manipal Hospital) because this lab requires working closely with specialized doctors and in a cluster-like environment. We work close with NCBS and JNC. This stem cell unit is funded by DBT and other agencies".



City cluster programs

With a focus to expand the area of stem cell research for advantage for clinical applications in the country, the DBT is making efforts to promote city clusters programs at Delhi, Vellore, Hyderabad, Pune and Bangalore through an active and enhanced interaction and collaboration between basic researchers and clinicians. Significantly, a number of competent researchers and clinicians are already involved in stem cell research at these places. The aim of the clusters is to share information, explore collaboration with clinicians and discuss emerging policy issues. The department is also exploring a virtual network of these centers.

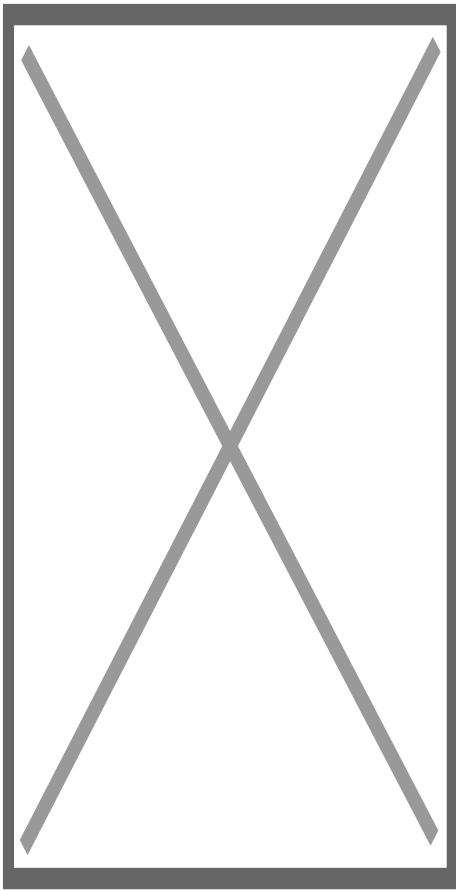
"In Bangalore we are promoting a partnership between National Centre for Biological Studies (NCBS) and CMC Vellore. The idea is to strengthen CMC Vellore as a molecular medicine, translational and clinical research centre. We are likely to create a stem cell center there soon and then we would also like to set up a molecular medicine unit there. The stem cell cluster at Bangalore will consist of the Indian Institute of Science (IISc), NCBS, Manipal Hospital, CMC Vellore and one local company whom we are going to support for production. The missing piece here has been the company and now we have located and spoken to the company", shared Dr Bhan.

"In Hyderabad we are trying to create another stem cell cluster. Both the stem cell clusters in Hyderabad and Bangalore would find their own niches. For example, one could specialize in mesenchymal stem cell research, while the other would be doing embryonic stem cell long sighted research. So they may have different niches, organs may be different, in one place they may be doing adult cell research and in another place they are specializing in neurological applications," he clarified, when queried about the necessity of creating similar facilities in multi cities. Presently the formulation of city clusters at other places in the country is under process.

During 2004-05, DBT organized a meeting of stem cell cluster at Hyderabad and a network program was prepared for use of stem cells for therapeutic purposes in areas of ophthalmology, cardiology, diabetes and spinal cord injuries. Focused and targeted programs are being initiated on human stem cell research with the clinicians such as plastic surgeons, cardiologists, neurosurgeons, orthopaedicians and others after ascertaining their requirements for stem cell therapy.

A proposal for program support on stem cell in the areas of haematology, cardiology, nephrology, neurological and gastrointestinal science is under consideration for implementation. The first component of this program involves isolation and expansion of Mesenchymal Stem Cells (MSC) that may be used for in vitro expansion, for tissue engineering / tissue repair and as immunomodulators. The expanded MSC would be used for other four projects of the program by cardiologists, nephrologists, neurologists and for gastrointestinal disease (inflammatory bowel disease).

Stem cell research strategy



Recently the DBT has evolved a strategy for stem cell research for the country. "We have been able to put a stem cell strategy in place in which both the academia and industry have a role" remarked Dr Bhan. This is considered a significant achievement in the stem cell segment. The main features of strategy are: Research will be promoted for therapeutic applications using adult and embryonic stem cells as well as other more readily available sources such as bone marrow, peripheral blood and umbilical cord blood cells; focus will be on basic research and study of factors that generate stem cells and how stem cells can be stopped from proliferation; study of stem cell biology will also form an important aspect; emphasis will also be on the study of expansion of haematopoietic stem cells without differentiation and gene transduction, gene regulation and plasticity of stem cells; establishing COE will increase productivity in stem cell research in the country. In this regard, interdisciplinary proposals are being developed with the involvement of basic researchers, clinicians and industry.

Ethical guidelines

The entire area of stem cell research faces ethical and moral dilemma as the rules on what is "ethically correct" varies from one country to the other. The recent Korean stem cell controversy had opened the Pandora's box and revived the debate on this subject. In India there are ethical guidelines on stem cell research, which permit work on therapeutic cloning and are against human reproductive cloning. The relevant regulatory bodies, Indian Council for Medical Research (ICMR) and Department of Biotechnology (DBT) are currently working on these existing guidelines to make it more adaptable for research and use in clinical practice particularly in ophthalmology, cardiology and spinal cord repair.

Lucid regulations are considered the need of the hour as Prof K Kannan, founder dean, School of Biotechnology, Guru Gobind Singh Indraprastha University, New Delhi stated, "In India also, a lot of people are under pressure to produce results in this area. They want to go to the clinical trials immediately. People are giving results, which suit them without providing a clear proof. I believe that stem cells are still in the research phase. The regulatory agencies should check whether the claimed benefits are actually due to stem cells or not as there is still no clarity on their mode of action".

"In India just like there is a regulatory body monitoring the drug trials, there should be a body looking after the stem cell trials - where data is submitted and a proper protocol and procedure is maintained just like that in drug trials. The need of the hour is to develop an international homogenized protocol in this area", he added.

Elaborating on the current status of stem cell regulations in the country, Prof D Balasubramanian, who is chairing the DBT Task Force on Stem Cell Research, said, "The DBT and ICMR have got together and come out with a common set of

guidelines and rules, which will be open for public debate and adoption in the next a few months. All institutions doing such work have, in place, the appropriate mandatory ethics committees and institutional review boards, consisting of external experts from science, medicine, ethics, law and sociology. Clinical research workshops to enable clinicians learn the rules of the technology and its applications, are being conducted across the country by the DBT. I think India, in having gone a bit slow and deliberate in the applications of stem cell methods, has done so wisely".

Presently a draft policy for stem cell research is under consideration. According to the policy, stem cell research should be promoted in the country in the view of its potential for clinical use. Research based on stem cells derived from adults, bone marrow or foetal cord blood may be undertaken after obtaining appropriate informed consent and with adequate safety measures. For embryonic stem cell research, embryos should not be generated for the sole purpose of obtaining stem cells. Only surplus, spare or supernumerary embryos can be used after obtaining informed consent of both spouses. Such collection of embryos should be done only from registered Assisted Reproductive Technique (ART) clinics. To safeguard national interests, it is also perceived that all human genetic research, stem cell research and stem cell research involving international collaboration must be undertaken after formal clearance of the national government. Consent form for use in collection of tissue to be used in human stem cell research has also been prepared by the National Bioethics Committee. A National Task Force for Stem Cell Research has been established to help develop and facilitate co-ordination.

To be competitive within the Asia-Pacific region, the Indian government needs to have a clearly defined set of regulations for stem cell research. Though embryonic stem cell therapy in India is still quite far off, adult stem cell research will reach clinical stages soon. Government commitment, increasing public and private funding and the increasing and well-trained science base in India should all contribute to India's global position strengthening over the coming years.

Rolly Dureha with inputs from Narayan Kulkarni

Cord blood banking guidelines for India soon

India is being sought after for not only its clinical/research expertise but also as a bank of stem cell lines.

The forthcoming stem cell policy of the Indian Council for Medical Research (ICMR) and the Department of Biotechnology (DBT) will also contain guidelines on umbilical cord blood banking facilities. This is in response to the increasing demand for setting umbilical cord blood banks in India. The cord blood cells can be harvested to cure a gamut of malignancies like leukaemia, Hodgkin's disease, different types of anaemia and inherited metabolic disorders.

The guidelines will be drafted in consultation with Chennai-based Asia Cryo Cell Private Ltd, whose Lifecell, a joint venture between Asia Cryo Cell and Florida based Cryo-Cell International (CCI), is deemed as the first private stem cell bank in India, and Mumbai-based Reliance Life Sciences. The government had approached both the private bodies for their suggestions some time back. The cord blood banking guidelines would be of international standards and would have specifications for requirements like space, equipment, lab expertise, approval from patient and protocol.

India is viewed as an attractive cord blood banking destination because of its largest birth count in the world and its one-billion plus population is genetically diverse enough to match the genetic characteristics of people worldwide. The cord blood is a rich source of stem cells which having the potential to cure serious ailments. The cord stem cell banks process leftover umbilical cord blood from the placenta and umbilical cord after the baby is delivered, and preserves by freezing them in liquid nitrogen at a temperature of -195 degrees celsius. Umbilical cord blood banks can be divided into two categories: private and public. In private banks, one can keep the umbilical cord for two decades, which can be claimed by the family or the patient.

Realizing its vast potential, both the public and private groups have been looking at this area with interest. The first cord blood repository in India was established by Reliance Life Sciences (RLS). The company is in the process of setting up its Cord Blood Repository (CBR) and plans to grow the repository to around 30,000 units over the next two-three years. The CBR is part of the cell biology group and has to date, collected, tested and stored the cord blood. RLS is expected to complete the HLA (Human Leukocyte Antigen) typing of the blood in the coming future, which would be followed by animal testing and matching of donor-receiver. The company is then aiming at scaling up its operations - the critical mass being 10,000 stem cell units before the company can join a global network of cord blood repositories.

The first strictly private cord blood bank in India is Asia Cryo-Cell Pvt Ltd (ACCPL), an affiliate of the American bank Cryo-Cell International based in Chennai, which began operations in late 2004.

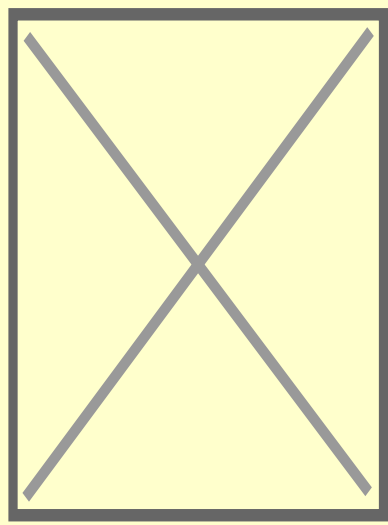
In addition, cord blood and bone marrow transplantation has been carried out at leading Indian medical centers for the last 20 years: All India Institute of Medical Sciences (AIIMS), New Delhi; KEM Hospital, Mumbai; Christian Medical College (CMC), Vellore and Indian Institute of Haematology, Mumbai, although these still do not have a dedicated cord blood centre or bank. Recently the Apollo Group of Hospitals has signed a memorandum of understanding (MoU) with the blood bank Histostem Inc

to offer stem cell therapy to patients from South Asia. As part of the deal, Histostem India will train doctors and nurses at Apollo for stem cell treatment protocols and develop new treatment protocols with relevant regulatory approval.

Meanwhile, a government-sponsored program of public banks was announced in July 2005. The Maharashtra government signed a deal with Histostem to set up a national cord blood bank in Mumbai, with additional centres planned for Delhi, Chennai and Kolkata. The company will be investing close to \$20 million to create the facility. Ultimately, these centres will offer regenerative stem cell therapies for spinal cord injuries, brain strokes, diabetes and bone cancer.

Looking at increasing number and activity of players in the cord blood banking arena, it is essential to spell out the guidelines clearly for this niche segment.

Rolly Dureha



Dr Hwang: In the eye of a storm

Stem cell controversy tempers hope of patients and researchers

Fraudulent research claims have effaced the fledgling stem cell arena

After a month of controversy, claims and counter claims it has now been conclusively established that Prof Hwang Woo Suk's work on cloned human embryos and stem cells was fabricated.

Seoul National University's (SNU) investigative panel confirmed that Hwang had fabricated data in the article published in Science last year in which he claimed to have produced 11 stem cell lines genetically tailored to patients. The panel has also reported that the scientist's landmark claim of cloning a human embryo and extracting stem cells from it was also a fake.

When this study was published in Journal Science in 2004 it was hailed as a path breaking achievement and brought Hwang instant limelight. Now the SNU investigative panel report has stated that there was a high possibility it could have merely been a mutated egg, which could appear to have similar qualities of an embryo.

In its final report, the university investigating panel said that Hwang and his research team "did not have any proof to show that cloned embryonic stem cells were ever created."

These revelations have stunned the entire scientific community and are a big setback to the research efforts in the stem cell arena. Commenting on this development, Dr K Vijay Raghavan, director of Bangalore-based National Centre for Biological studies (NCBS), one of India's leading basic sciences research centre, which is also involved in stem cell research, said, "The Korean fraud is a major setback for research-not only for stem cells, but research of all kinds. Research in emerging areas is always difficult and any success is welcomed as path breaking and as something to emulate. Thus several groups worldwide were inspired by the Korean experiments and have tried to reproduce them and have wasted valuable time and effort."

Indeed, the hopes of patients as well as researchers were buoyed by Hwang's claims but now realizing that cloned stem cells are a long way off, the euphoria created is slowing subsiding.

Prof D Balasubramanian, director - research, LV Prasad Eye Institute and chairman, Department of Biotechnology (DBT) Task Force on Stem Cell Research, said, "The work by Hwang Woo-Suk has been rightly criticized from two angles. One is the

ethical aspect, where he had forced his coworker to give him her cells. Also, it is not clear how many he had taken and how many he used. Second is the reproducibility of his work. One might have read the warning statement in a recent issue of Science by Dr Ian Wilmut (the creator of Dolly) about the necessity of work of this kind to be repeated and verified independently in another lab. This was not done."

But the person in the center of the controversy, Hwang, still maintains that he has the technology to use cloning to create human embryonic stem cells genetically matched to patients and claims that he could do so in six months if he had access to enough human eggs. Hwang's claims had vaulted him on the international center stage as his studies could pave the way for future development of therapies for hard-to-cure diseases.

In fact, stem cells have the potential to mature into every cell in the human body. Scientists hope to use stem cells as replacement parts for failing organs and to treat diabetes, Parkinson's and other diseases. Researchers want to harvest stem cells by cloning the DNA of sick people, so they could turn the cells into tissue that genetically matches a patient. That way, the patient wouldn't have to take the anti-rejection drugs used in organ transplants today. Hence any research development in this arena brings a flicker of hope for such patients.

Pointing out its impact on the scientific research especially in the Asian region, Prof K Kannan, founder dean, School of Biotechnology, Guru Gobind Singh Indraprastha University, New Delhi, said, "The biggest fallout of this entire episode is the belief that Asian science is going down. This is a big damage to the credibility of scientific research in the Asian region, especially now, when research in this region is actually picking up. This is a sad episode of cheating in the history of science. Now the regulations for accepting research results will be further tightened."

But the question remains why did a senior scientist perpetuate such a big fraud? Did he see this as an easy chance to get fame in a nascent upcoming arena? Where his work would be one of its kind and difficult to validate? Probably! "The scientific community, including the journal needs to share some of this blame, since on a fast-moving topic, with great clinical promise, the need to be the first to publish, and the need to be the first journal to publish the work had become more pressing than scientific rigour and upholding standards of ethics", said Dr Balasubramanian.

The Journal Science has since stated that it will formally retract Hwang's two studies and is now considering how to improve safeguards against scientific fraud.

"Frauds in any area are a setback to science. In this case it points to the fact, once again, that no matter how fashionable an area one should not be trapped by the pressures of this fashion. There is no moving away from careful and honest science", opined Prof Vijay Raghavan. "Actually there is a lot of hype created around stem cells and it is being touted as a panacea for all diseases, which is not correct", added Prof Kannan.

And what will be the impact of one of the biggest scientific frauds of the century on the future of stem cell research? Not much in the long run, say experts. "In the long run this incident will not have a mark and is a temporary passing phase. This is an isolated case, generally scientists do follow ethical guidelines and claim only for what they have solid proof", said Dr Ashok Mukhopadhyay, a senior scientist working in the stem cell arena at the National Institute of Immunology (NII).

"I do not think this would affect the progress of embryonic stem cell research per se, though it will slow it down a bit, and certainly sober up all scientists and journal editors. How does this affect the suffering patients? This is a sad question, since the hope built up by Hwang and by the South Korean research agencies will now be tempered, and patients will have to wait longer. This may be actually for the good, in one sense", commented Dr Balasubramanian.

Rolly Dureha