Medicine's new frontier

Like so many other medical innovations, stem cell technology will perhaps need another two decades to become mainstream therapy

From time immemorial, the accepted wisdom is that whenever any part of the human body is destroyed by disease, it is lost forever. Whether it is heart muscle killed in a heart attack, a liver shrunk by alcohol-induced cirrhosis, or lungs ravaged because of tuberculosis, whatever tissue dies, stays dead. But now scientists across the world are attempting to use stem cell technology to turn this doctrine on its head, and enable dead tissue to literally grow back.

Stem cells are primitive cells found in the human body, which can be induced to develop into various specialised cells to replace the dead tissue. At present, medical scientists have been able to make it work in only a few groups of diseases, such as blood cancer, eye injuries, apart from bone and joint problems. While the number of people in this country to actually benefit from the technique is still relatively small – a few hundred, rather than many thousands, the heartening thing is that it is now available to people from different segments of society.

The days of anecdotal evidence about an Ajit Jogi (ex-chief minister of Chhattisgarh) recovering from paralysis or model-turned-actress Lisa Ray being cured of blood cancer are now behind us. Instead we see media reports every now and then about a retired IAS officer who had suffered a heart attack, a factory worker who lost his eye in an accident, or a truck driver in Chennai who developed cirrhosis of the liver.

An important reason why middle class people can afford stem cell therapy is that quite a lot of research is going on in publicly funded institutions – both hospitals, such as All India Institute of Medical Sciences in New Delhi, and research organisations funded by the Department of Biotechnology (DBT), Government of India and the Indian Council of Medical Research (ICMR).

Subramaniam: leading from the front

One part of this research involves work inside the cell biology laboratories, where stem cells of various kinds are grown, maintained and studied in great detail. Another part is conducted in government-run hospitals, where people from various segments of society are actually administered the treatments and the results obtained are recorded. While the people who are offered these therapies are selected carefully, according to scientific principles, the patient does not have to bear the expenses of the treatment.

Government support

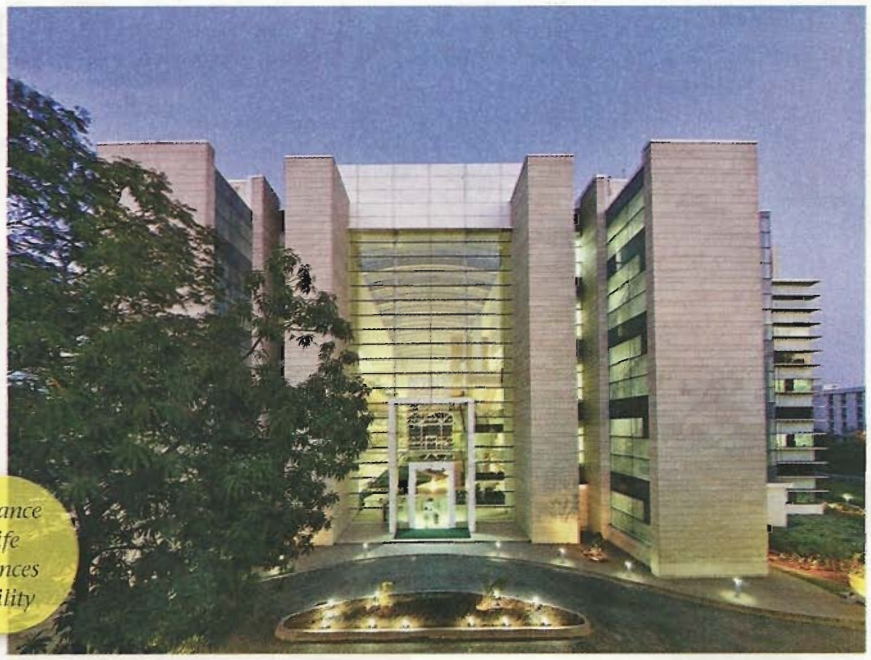
An important initiative of the DBT is the setting up of the Institute of Stem Cell Biology and Regenerative Medicine (INSTEM) in Bangalore, a couple of years ago. Not only does INSTEM carry out cutting edge research in stem cell biology and other related subjects but also runs training courses for students at every level, from undergraduates to post-doctoral fellows. In addition, the DBT has provided grants worth a total of ₹100 crore for 18 research projects in institutions located in different parts of the country. It has also formed a task force whose members include eminent scientists such as Dr G.C. Mishra, director of the National Centre for Cell Sciences, Pune, and Dr M. Radhakrishna Pillai, director, Rajiv Gandhi Centre for Biotechnology.

Likewise, the ICMR not only provides grants and scholarships to research institutions all over the country but also assists the DCGI (Drug Controller General of India) in deciding whether or not to approve proposals for clinical trials on stem cell-based products and therapies. In addition, the ICMR has come out with a set of guidelines within which stem cell research is supposed to be conducted in the country.

The private sector, too, is not far behind. Among the most advanced is the Mumbai-based Reliance Life Sciences, *(www.rellife.com)*, which has a significant commitment to developing stem cell therapies, right from research, cell processing facilities, clinical research to clinical applications.

"Through its public cord blood repository, our company has made available, several stem cell units for transplantation in patients suffering from thalassemia and leukaemia (blood cancer). About one third of transplants in each category have been successful. In addition, Reliance Life Sciences has been offering stem cell therapies for treating limbal disorders in the eye and they have shown to benefit about two-thirds of patients treated in the form of improvement in visual activity," says K.V. Subramaniam, president, Reliance Life Sciences.

Besides, companies like the Bangalore-based Stempeutics are conducting clinical trials on a wide variety of medical conditions, testing the efficacy of stem cells in much the same way as pharmaceutical companies across the world would test a newly discovered medicine. In January this year, Stempeutics got permission from the DCGI for carrying out clinical trials on Stempeucel, their brand of stem cells, on four debilitating disease – age-related arthritis, diabetes,



Reliance Life Sciences facility

cirrhosis of the liver and chronic obstructive lung disease. Earlier the company has received approval from the DCGI for Phase I/II clinical trial for acute myocardial infarction (heart attack) and critical limb ischemia (loss of blood supply to lower limbs, seen in advanced cases of diabetes) in March 2009. Based on the successful outcome of clinical studies, Stempeutics plans to introduce the first stem cell based 'drug' – available off the shelf by end-2013.

Since Stempeutics is a part of the Manipal group of companies that also includes the Manipal Hospitals in Karnataka, it has an obvious advantage, when it comes to conducting the clinical trials. Further it has formed a collaboration with pharmaceutical giant, Cipla, as a result of which the latter has made an investment of ₹50 crore in Stempeutics.

Continuing research

"While Cipla brings in the knowledge and experience of drug development and market access, Stempeutics brings in the capabilities of bringing stem cell based therapeutic products. It brings in the technical & research expertise of isolation, characterisation and up-scaling of adult mesenchymal stem cells from bone marrow for therapeutic applications," said a joint statement issued by the two companies, when the agreement was signed.

"Stem cells work best in blood-related disorders, because the cells are obtained from bone marrow in a lot of cases, and these cells are already tuned to creating new blood cells throughout adult life," says Satyen Sanghavi, chief scientific officer, Regenerative Medical Services (RMS), which has been involved in stem cell research since 2005. Subramaniam however points out that stem cells drawn from bone marrow are also being tested for effectiveness in treating

How stem cells work

A stem cell therapy is a treatment that uses stem cells, or cells that come from stem cells, to replace or to repair a patient's cells or tissues that are damaged. The stem cells might be put into the blood, or transplanted into the damaged tissue directly, or even recruited from the patient's own tissues for self-repair.

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialised cells capable of renewing themselves, sometimes after long periods of inactivity. Second, under certain experimental conditions, they can be induced to become tissue- or organ-specific cells with specialised functions.

One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialised functions. For example, a stem cell cannot work with its neighbours to pump blood through the body (like a heart muscle cell), and it cannot carry oxygen molecules through the bloodstream (like a red blood cell). However, unspecialised stem cells can give rise to specialised cells, including heart muscle cells, blood cells, or nerve cells.

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: embryonic stem cell (collected at the time of birth) and non-embryonic or 'adult' stem cells (found in some tissues like bone marrow and dental pulp). In India, these are the two varieties available. However the Indian rules permit the use of embryonic stem cells only for research, and not for treatment of patients. Yet several stem cell banking companies are storing the cells for a fee, while anticipating that it may be allowed in future.

(Adapted from a primer published in 2009 by National Institutes of Health, USA)

RMS research facility building

peripheral vascular disease, myocardial infarction, and cartilage replacement in traumatic osteoarthritis.

In fact, Indian scientists have made the maximum progress in treatment of bone and joint disorders including age-related arthritis. For the past several years, RMS has been working with a steadily increasing number of orthopaedic surgeons in Mumbai, Delhi, Ahmedabad, Kochi, Coimbatore and other places.

Gratifying results

"Stem cell therapy can be used to regenerate bone, cartilage, meniscus, intervertebral disk, tendon, and ligament. We have used stem cells for bone and cartilage regeneration in conditions like avascular necrosis, non-union or delayed union of bones (following a fracture), regeneration of bone lost due to accidental injury, and regeneration of bone following surgery for bone cancer," says David Rajan, Ortho-One Hospital, Coimbatore.

While the Coimbatore hospital gets to treat about five cases per year, Jacob Varghese at Lakeshore Hospital, Kochi, has treated about 100 patients till now, of which only one has been in the last 18 months. But in the people who have received stem cell therapy, the results are extremely gratifying. "One needs to wait about six weeks between harvest of cells and implantation. The patient can bear the full weight of his body within three months and can return to active sports in six months," says Varghese.

"These procedures take place in two steps – in the first stage, the patients own cells are harvested, which takes 10-15 minutes and these cells are grown in a laboratory for about 3-4 weeks. In the second step, these cells are implanted into the damaged area. The patient has to undergo a rehabilitation process for about 4-6 months, after which he will be able to return to his normal active life within 6-8 months," explains Nilesh Shah, an orthopaedic surgeon in Ahmedabad, who works closely with RMS.

Sanghavi: banking the cells

Autologous Chondrocyte Implantation (ACI) and Autologous Bone Implantation (ABI), techniques in which the patient's own cells (drawn from the healthy limbs) are implanted into the diseased area, was used in 300 patients across India during the past two years and the success rate was an astounding 97 per cent!

The success rate would be much more modest if the cells were drawn from another person, instead of the patient himself. This is because whenever cells from another person are inserted into a patient's body, the latter views them as 'foreign bodies', and this triggers off the patient's natural defence mechanism. The newly inserted cells are therefore rejected and then destroyed by the patient's defences, and the entire transplant procedure is a complete failure.

There are two ways to prevent rejection of the stem cells. One is to use an extensive array of tests to ensure that the tissue of the donor and recipient are matched as closely as possible. This is similar to the procedure used routinely in organ transplant cases. The other is to store the stem cells of a new born baby, so that they can be implanted in the same person later in life. This technique, known as stem cell banking, is an excellent way of avoiding rejection problems, because the tissue is not really 'foreign'. In the past few years, many people from the upper middle and middle class have opted for this, and for a few companies, such as RMS in Mumbai and Life Cell in Chennai, it is an attractive business model.

"About 75,000 people in India have chosen to store the stem cells of their new born babies with stem cell banking companies," says Sanghavi of RMS. The process begins with an agreement between the stem cell company and the parents of a new born child under which the cells are

What patients should know

The range of diseases for which there are proven treatments based on stem cells is still extremely small. Disorders of the blood and immune system and acquired loss of bone marrow function can, in some cases, be treated effectively with blood stem cell transplantation. Most stem cell treatments are still experimental. This means that it has not yet been shown that this treatment is safe or that it will work.

For most diseases, it is still being determined which cells will work best to repair a particular damaged or diseased tissue, and how to get those cells to the right place in the body.

Furthermore, side-effects and long-term safety must be determined, since transplanted cells may remain for many years in patients' bodies. Therefore, careful monitoring and extended follow-up of patients who receive stem cell treatments is extremely important.

If you are considering stem cell therapy, you need to be sure that there is good scientific evidence that the treatment is safe and effective, and that your rights as a patient are being respected. One of the most important is to ensure that the treatment providers have the approval from a national or regional regulatory agency, such as the DCGI, the US FDA, etc for the safe conduct of clinical trials or medical use of a product for this disease.

Conversely, there are certain red flags that should alert you about improper or unproven therapies. Among these are: claims based on patient testimonials, multiple diseases treated with the same cells, unclear documentation of the source of the cells or how the treatment will be done, claims there is no risk, and finally exorbitant cost of treatment or hidden costs.

You should ask a lot of questions about the treatment being offered and to seek second opinions from independent qualified doctors. Your doctor should be supportive and help in the process of obtaining a second opinion. Medical records, research protocols, treatment protocols (where not well-established), and informed consent documents should be supplied to the person giving a second opinion.

(Adapted from a handbook produced in 2008 by the International Society for Stem Cell Research)

collected at the time of birth and stored for a period of 21 years. The charges that the parents have to pay varies with the company concerned but generally within a range of ₹60,000 to ₹1.5 lakh, and the agreement can be renewed or terminated at the end of 21 years. Several companies including RMS and Stemade Biotech, also Mumbai-based, have an instalment facility as well.

"We have made arrangements to store the stem cells of my son," says Pallavi Deshmukh, head of corporate communications, SKF India. She and her husband had planned the move well in advance through an agreement with Life Cell after they read about it in a magazine. This process also began with celebrities like actress Raveena Tandon a few years ago, but has now become very popular among professionals and educated people.

Dr David Rajan, Coimbatore, examines a young patient

Long journey

While most stem cell companies work with cells taken from the umbilical cord (the organ that connects the unborn baby to its mother, until the baby is born) or with adult stem cells drawn from bone marrow, Stemade Biotech, the newest kid on the block, prefers to concentrate on stem cells present in dental pulp.

"The most important use of these cells is likely to be in regeneration of the jaw bone lost due to cancer or an accident injury," says Stemade co-founder Shailesh Gadre, who quit as managing director ORG-IMS about 18 months ago. He said early experiments to regenerate bone tissue from dental stem cells have proved successful but the technique would probably come into India after another two years.

Like so many other medical innovations, stem cell technology will perhaps need another two decades to become mainstream therapy, alongside minimally invasive (key-hole) surgery, targeted medicines for cancer, and electronics-based artificial limbs. Even in India, surgeons first began using angioplasty in 1987 and key-hole surgery in the early 1990s. Today both these techniques are widely practised, even in small and medium hospitals, both in the metros and the Tier-II cities. There are many such examples hidden in the annals of global medicine journals, and there is no reason why stem cells should not have a similar bright future.

• SUMIT GHOSHAL