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A Shot In The Dark

STEM CELL THERAPY IS BIG BUSINESS IN INDIA. BUT DOES THE HYPE STEM FROM SCIENCE OR FAITH? by Noemie Bisserbe



Dr Geeta Shroff and her patient Ajit Jogi (former chief minister of Chhattisgarh) The paralysed politician has opted for the controversial stem cell therapy, hoping it will help him lead a normal life again



IN NEW DELHI'S CROWDED Green Park Extension area, Nu Tech Nursing Home hardly looks like the kind of place where cutting edge, next generation medicine and research is being practised. The nursing home is housed in a small, non-descript, glass-fronted building just off the main market area. It has no board or sign to identify it; only a small cardboard placard placed next to the entrance. The one thing unusual about the building compared with its neighbours is a small metal platform outside the entrance that can be raised — a sort of open air elevator. This is used to help disabled patients who cannot negotiate the stairs at the entrance.

This is Dr Geeta Shroff's clinic. And this is where Ajit Jogi, former chief minister of Chhattisgarh, has come for a controversial embryonic stem cell therapy, which, he hopes, will allow him to lead a normal life once again. At the peak of his career 10 years ago, Jogi's life came crashing down after a road accident injured his spine, leaving him completely paralysed.

Jogi has tried everything — conventional treatment, surgery, physiotherapy, alternative medicine — and nothing has worked yet. Doctors said that Jogi would never walk again.

And that is what brought him to Shroff's clinic five years ago, says Jogi. He knows that what Shroff practises is untried and untested. Jogi knows that it is not regulated by any Indian

medical or drug regulator. He also knows that there are dangers — including the chance of developing cysts. He also knows that there is a very high chance that the treatment will do him no good whatsoever. But, as he says, "At my age (he is 64), I do not have much time. I cannot wait until a foolproof system is in place."

So far, Jogi says, the five years of treatment seems to be working a bit. He can sit up for brief periods without a back rest. And he can also pick up small things with his hands. He can sign once again. Whether that is due to the stem cells injected in his spine or something else — placebo effect, intensive physiotherapy regimen or even conventional medicine — is open to question. As far as Jogi is concerned, he can hope once again to lead a normal life.

Shroff, who is actually an infertility specialist, gets a lot of patients such as Jogi — people who have been given up as hopeless cases by conventional doctors and medicine. Many of them fly down from the US and from Europe after they have done the rounds of hospitals there. They raise money, and are prepared to spend in thousands of dollars for some sort of a cure.

So far, Shroff claims, she has treated 700 patients, and they have all shown improvement. Not all her patients go back satisfied. "Because all of them are terminal, any positive response or even stability in their condition is for me a success," she says. "But the patient's perception of success may be different."

Nu Tech nursing home is not the only institution in India offering hope and stem cell therapy to terminal patients. Go looking for stem cell cures, and you will come across dozens of

CLINICS offering stem cell treatment in India

Nu Tech, Delhi: Treats spinal injuries, lyme disease, osteoarthritis

International Stemcell Services, Bangalore: Treats spinal injuries, diabetes, osteoarthritis, liver cirrhosis, cancer

Life Line International, Chennai: Treats spinal cord injury

LV Prasad Eye Institute, Hyderabad: Treats eye disorders and autoimmune diseases

Medanta Medicity, Gurgaon: Treats patients recovering from a heart attack

Nichi-In Centre for Regenerative Medicine, Chennai: Treats ulcers, heart disease, spinal injury, liver cirrhosis, oral submucosal fibrosis

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THE PIONEER: Satish Totey kicked off stem cell programmes at RLS and Stempeutics before founding ANSA

institutions — ranging from big, government and corporate hospitals to small, hole-in-the-wall outfits ready to offer you their services. Some of the big-name hospitals do not offer stem cell therapy directly — but individual doctors and consultants do so unofficially.

Renowned cardiac surgeon Dr Naresh Trehan offers stem cell therapy to a limited number of heart patients in his Gurgaon based medcity, Medanta. Other hospitals — Apollo Hospitals for example — are conducting clinical trials, in which patients can enroll, after they have been checked for suitability and warned of the dangers. There are many others who simply go ahead and offer therapy.

In Bangalore, International Stemcell Services (ISSL) claims to provide stem cell-based therapies for conditions ranging from cancer to diabetes and spinal cord injury. Unlike Nu Tech, it does not use embryonic stem cells, but stem cells derived from the patient's own bone marrow. (This method is somewhat safer, as we shall see shortly.)

Similarly, in Chennai, the Nichi-In Centre for Regenerative Medicine, an Indo-Japanese joint venture operating out of the Vijaya Healthcare premises in Vadapalani, and Life Line International treat patients using adult stem cells. These are only some of the more prominent names — there are literally hundreds of others across India.

The Science, The Promise And The Dangers To understand why so many people are desperate to try out stem cell therapies — and why it is becoming a big business opportunity in India, you need to understand a little bit of the science as well as the economics of stem cell treatment.

In our bodies, most of the cells are highly specialised and cannot be interchanged. A nerve cell, for example, will be completely different from a heart muscle cell, which will be different from a liver cell. Also, these cells, once damaged, cannot easily be regrown or regenerated. This means, once you have damaged your, say, liver or heart muscles, you will have to pretty well live with that damage.

In the simplest terms, stem cells are those that have the ability to grow into other kinds of cells. There are essentially two kinds of stem cells: embryonic and adult. Embryonic stem cells — derived from 3-5-day-old embryos as the name suggests — are the most malleable. They can pretty well turn into almost any kind of specialised cell under the right conditions. Adult stem cells — derived from adult organs or tissues — are somewhat less versatile, but scientists have found out that some of them, known as mesenchymal adult stem cells, can also give rise to a variety of cells: bone cells, cartilage cells, fat cells and stromal cells.

Stem cell research offers extraordinary hope to cure diseases that are considered incurable today. For example, once you have had a heart attack and have damaged your heart muscles, there is not much that any current medicine or treatment can offer in terms of regenerating the damaged muscles. But, at least theoretically, stem cells can be used to regenerate new heart muscles that will take the place of your damaged ones. Similarly, stem cells offer hope to patients who have damaged their nervous system, liver, and so on.

The problem is that stem cell research is still at a very early stage across the world today. Until recently, embryonic stem cells were generally considered more promising albeit associated to more risks — you never know what it will become in your body, and no one knows quite what makes them decide which kind of cells to turn into. Now most of the research is actually focused on mesenchymal stem cells that are somewhat less dangerous because they are less likely to lead to development of cysts, and yet are fairly versatile.

In developed countries — in the US and in Europe — stem cell research is tightly regulated and monitored. There are protocols to be followed. No stem cell treatment has been approved for commercial use — no matter how hopeless patients are.

In India, on the other hand, there is a regulatory vacuum as far as stem cell research and therapy is concerned. And that allows hospitals and clinics to offer stem cell therapy with impunity. It is a lucrative business, at least for some. While the clinical trials in the bigger

hospitals cost no money to the patients, the smaller clinics often charge tens of thousands of dollars, with little overheads or specialised equipment. Nu Tech, for example, charges \$15,000 for one round of stem cell therapy. But many patients require at least three rounds, and they end up spending \$45,000 (Rs 21 lakh) for the full treatment.

The lack of regulation does not discriminate between the good and the bad, the unorganised and the organised players. Which is why the bigger players — Reliance Life Sciences (RLS) or Stempeutics, for instance — who are conducting large-scale research and sinking in money think that this sort of proliferation of clinics will create problems for them. It requires only one bad clinic and a few disgruntled patients to bring bad publicity to the country's genuine stem cell research, they say.

The Regulatory Vacuum

They have reasons to worry. The complete absence of regulation has allowed institutions offering stem cell therapy to proliferate. While the Indian Council of Medical Research (ICMR), at the request of the central government, designed some guidelines for stem cell research back in 2007, the latter have not been made mandatory. The ICMR has no real powers to enforce them. "We are an advisory board; our job is to think and plan, we don't have the power to monitor," says Dr V.M. Katoch, director general of ICMR.

As a result, clinics just claim that they follow the ICMR guidelines without having to provide any proof that they in fact do so. "Many clinics say they follow our guidelines and use our brand name to gain patients' confidence. But we do not recognise or endorse," says Katoch.

Shroff, for instance, claims that all cases are documented and the reports were sent to ICMR. But officials claim otherwise. "We receive one A4-size page that just states the patient's condition and the date of injections. This is not what we need," says a senior scientist. None of these cases could help medical research going forward.

Actually, when ICMR scientists came to visit Shroff's lab, they were turned away. "For all we know, she could be injecting apple juice," says a scientist at ICMR. Shroff claims she did not let them in because they had come with a "competitor". However, when this reporter asked to visit the lab, Shroff also refused. In fact, she even declined to disclose its location in Delhi, while her staff claimed ignorance.

Similarly, in Bangalore, ISSL, which works with stem cells extracted from patients' own

bone marrow, says it follows the ICMR guidelines. Senior officials at ICMR claim complete ignorance about ISSL's treatment protocols or reporting systems.

Private life science companies such as Stempeutics, a stem cell research company affiliated to the Bangalore-based Manipal group, and Mumbai-headquartered RLS have taken more pro-active steps.

Stempeutics has approached the Drug Controller General of India (DCGI), headed by Dr Surinder Singh, to get approval for the several clinical trials the company is conducting. Technically, the DCGI does not have the authority to do so, as the Drugs and Cosmetics Act does not cover stem cell treatment. But for lack of a better option Stempeutics approached the DCGI's office, to give some credibility to its research.

"There is still a question mark on whether the

THE STEM CELL PRIMER A few essentials explained

What is a stem cell?

A stem cell has the ability to grow into other kinds of cell. In many tissues, stem cells serve as an internal repair system, dividing essentially without limit to replenish other cells. Scientists primarily work with two kinds of stem cells:

Embryonic stem cells: In 3-5-day-old embryos, the inner cells can give rise to the entire body of the organism, including many specialised cell types and organs such as the heart, lung and skin

Adult stem cells: They can be found in many organs and tissues (brain, bone marrow, blood vessels, skin, teeth, heart, gut, liver, etc.). Unlike embryonic stem cells, adult stem cells can't become any type of cell. They can divide and create another stem cell like itself. But mesenchymal stem cells in the bone marrow and in the umbilical cord can give rise to a variety of cells: bone cells, cartilage cells, fat cells and stromal cells, among others

Their use: Given their remarkable regenerative abilities, stem cell research could help treat diseases like Alzheimer's, Parkinson's, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis

Keywords:

AUTOLOGOUS: Transplant in which the patient's own cells are used.

ALLOGENEIC: Transplant where cells come from another person.

CELL-BASED THERAPIES: Treatment in which stem cells are induced to differentiate into the specific cell required to repair damaged tissue.

CELL CULTURE: Growth of cells in vitro for experimental research

DIFFERENTIATION: The process whereby an unspecialised embryonic cell acquires the features of a specialised cell such as a heart, liver or muscle cell

EMBRYONIC STEM CELL LINE: Stem cells cultured under artificial conditions that allow them to divide without developing into a different type of cell



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Stem cell research IN INDIA

Company

STEMPEUTICS

Products for:

- Heart attack*
- Chronic wound*
- Chronic obstructive pulmonary disease
- Dilated cardiomyopathy
- Liver cirrhosis
- Osteoarthritis
- Diabetes type 2
- Cerebral stroke*

Company

ANSA

Product for:

- Parkinson's disease*

*in phase I/II; others are in phase II. All approved by DCGI. Approval pending for large-scale trials.

IN THE US

Company

OSIRIS THERAPEUTICS

Product name: Prochymal

Being developed for:

- Steroid refractory acute GvHD*
- Newly diagnosed acute GvHD*
- Crohn's disease*
- Diabetes type 1
- Cardiac

Company

MESOPLAST

Product for:

- Cardiac

Prochymal has both an orphan drug and fast-track status with the USFDA for GvHD and Crohn's disease. GvHD or Graft versus Host Disease occurs when immunologically competent cells are introduced into an immuno-incompetent host. Crohn's disease is an inflammatory disease of the intestines. *Expected to get USFDA approval soon; in phase III trials. Others are in phase II. All the products, both in India and the US, are allogeneic. Source: BW research; More details at www.businessworld.in

DCGI actually has the competence and expertise to approve stem cell products," admits B.N. Manohar, Stempeutics' CEO.

When this reporter contacted the DCGI's office in New Delhi, she was told that Surinder Singh was no longer permitted to speak with the media. However, according to Katoch, a new committee, which will approve stem cell products, is being set up, under the DCGI. For now, the DCGI is sending the applications to the ICMR, which gives recommendations.

Scientists also complain that ICMR's guidelines are too vague. "Of the 12 pages in the report, 10 are on the definition of stem cells and barely one actually tells you how trials should be conducted," says Satish Totey, co-founder of stem cell research company Advanced Neuro-Science Allies (ANSA) and a prominent stem cell scientist in India. Totey kicked off stem cell research programmes at RLS and Stempeutics, before founding ANSA.

There is also a lot of confusion about what norms companies should follow according to the type of treatment they offer. Treating a patient with stem cells derived from his own bone marrow or blood, is very different from treating him with stem cells from a donor. It involves different risks such as transplant rejection. When a patient's own stem cells are used, it is termed an autologous therapy, while when a cell culture from a donor is used to treat a patient, it is referred to as allogeneic therapy.

Allogeneic stem cell treatments could be bought off the shelf much like a drug. On the other hand, autologous therapies would be a service provided by a hospital. But how should hospitals be regulated?

"How much could hospitals manipulate the stem cells before re-injecting them?" asks Manohar. "Even for autologous treatments, cells have to be cultured." Stempeutics is currently working on new guidelines with the DCGI, which they hope will help the industry take shape.

Dr Katoch says that some of the vacuum will be filled once the National Biotechnology Regulatory Authority Bill is passed — the bill should be put before the Parliament this year. "It is a temporary situation." However, the Biotech bill would at best cover allogeneic treatments.

Research In the US And In India

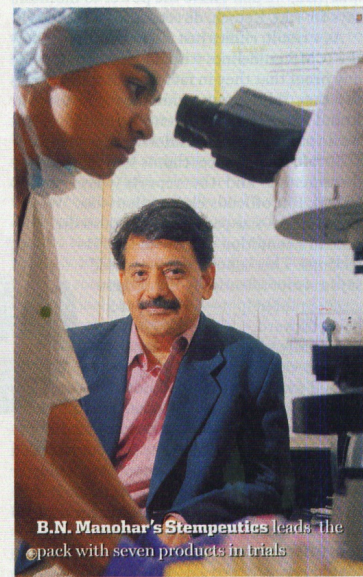
The Bush administration used to frown upon embryonic stem cell research but after Barack Obama took charge, things changed. All research on stem cells — whether using embryonic or adult stem cells — are under the purview of the Food and Drug Administration (FDA) in the US. And are tightly monitored.

The FDA had okayed a clinical trial with embryonic stem cells to California-based pharma giant Geron, which is planning to create a therapy for spinal cord injuries. The FDA withdrew its approval in September 2009 after animal tests revealed small cysts.

Meanwhile, other researches are carrying on. US-based Osiris Therapeutics has one product in phase III (the final stage of clinical trials before approval by FDA), Prochymal, which is likely to hit the market in the next few months. Prochymal, in development for multiple indications, the most advanced being graft versus host disease (GvHD) and Crohn disease, would be the first FDA approved stem cell treatment.

In India too, RLS, Stempeutics and ANSA are conducting clinical trials for various therapies. ANSA has conducted limited safety trials for an adult stem cell treatment for Parkinson's patients and is about to initiate large-scale studies. Stempeutics currently has seven allogeneic therapies under clinical trials (all approved by the DCGI) for conditions ranging from heart disease, ulcers to chronic obstructive pulmonary disease. "Allogeneic treatment is more scalable as a business," explains Manohar. They can also be patented. "And our aim is to make big money."

Last April, Stempeutics completed phase I/II of clinical trials for a treatment for non-



B.N. Manohar's Stempeutics leads the pack with seven products in trials

healing diabetic ulcers, and has already tied up with Mumbai-based drug major Cipla to market the product in India. Cipla has agreed to invest Rs 50 crore to fund further clinical trials, and may invest more going forward, according to Cipla's medical director Jaideep Gogtay. "Cipla has adopted a wait-and-watch approach when it comes to new drug discovery but we believe there's great potential in stem cells," says Gogtay.

So far, in India, only RLS has received marketing approval from the DCGI for two autologous stem cell based therapies: Relinath, for chronic inflammatory eye disease, and CardioRel for heart attack. However, they have gained little traction. "There is still a lot we do not understand about stem cells. The route through which they should be injected is not well understood either," says Dr Ashok Seth, cardio-vascular surgeon and chief cardiologist at New Delhi's Escorts Heart Institute and Research Centre.

The commercial viability of these products still remains uncertain — these treatments are not products as such, since the stem cells have to be taken from the patient. In the US, some companies have developed medical devices used to deliver autologous therapies that can be patented and sold to hospitals.

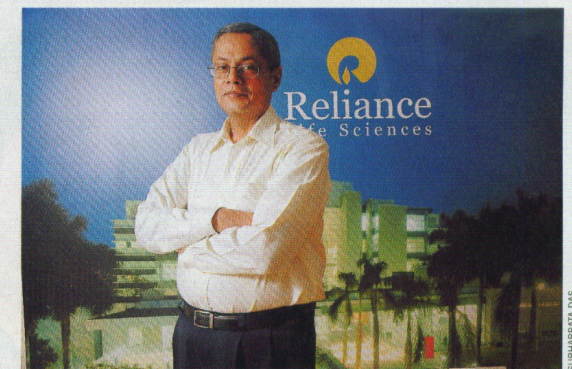
"The holy grail is to take these therapies into allogeneic mode," says K.V. Subramaniam, president and CEO of RLS. "But we still need to work on immunology." Though it is still at a fairly early stage, the company also runs an embryonic stem cell research programme.

Meanwhile...

Even as firms such as RLS, Stempeutics and ANSA pour big money into stem cell research in the hope of creating blockbuster drugs or therapies, thousands of patients from India and abroad continue to flock to hospitals and nursing homes looking for an immediate cure.

In Bangalore, S.G.A Rao, ISSI's chairman, says he gets a dozen patients per month. As he does not run a proper hospital himself, most of his patients are treated at a somewhat run-down government hospital, Saint Theresa's hospital on Dr Rajkumar Road.

Rao claims that he has had amazing success stories from his treatment protocols. "A few months ago, we had a patient from the US, an athlete. Both his knees were gone," says Rao. The athlete was apparently walking by the time he left the clinic. Rao says he charges patients Rs 20,000-25,000 (in addition to hospital charges). "Since we are not supported by the government, we need to get money from somewhere," he says apologetically.



CELLS OF HOPE: K.V. Subramaniam, president and CEO of Reliance Life Sciences, says the holy grail is to take the therapies into allogeneic mode

In Chennai, Nichi-In paints a more realistic picture: up to 10 per cent of the spinal cord injury patients have shown good results. In cardiology, 40 per cent of patients have shown improvement and 35 per cent of liver cirrhosis patients felt better.

Meanwhile, back at Nu Tech, we meet at least one patient who says Shroff is a miracle worker. Monica Goulette, a 15-year-old girl from California, who came with her mother Tracy and aunt, Hope Gelbach, is leaving today, after three months at the clinic. "Doctors here have been so kind and compassionate," explains Tracy. "This place offers hope and there is nothing like that." Goulette fell sick four years ago. She was later diagnosed with Lyme disease, a tick-borne infectious disease that spreads throughout the body — skin, heart, joints and nervous system.

But Goulette deteriorated to the point where she started losing some motor skills. She finally ended up in a wheelchair and doctors in the US gave up all hope of her ever recovering. A few months ago, she took the flight to India. "We had nothing to lose, and nowhere else to go," says Tracy. The first round of treatment saw Goulette regain her ability to walk, though she continues to suffer from all sorts of other problems, including the inability to experience sensations. This second trip has not been too successful, but Goulette and Tracy are not complaining.

It is patients such as Goulette who are giving rise to India's stem cell therapy boom. Whether it is based on actual science or faith, is still not clear. But until India brings in some regulation in this new field of medicine, it will remain nothing more than a shot in the dark.

With inputs from Lalitha Sridhar
noemie.bisserbe@abp.in