A new era of stem cell research

The DCGI's clinical trial approval to Stempeutics for stem cell therapy is a milestone for regenerative medicine; the approval potentially opens the door for clinical testing of more stem-cell derived cell therapies.

In a move signaling the beginning of a new era of stem cell research, the Drug Controller General of India (DCGI) has given its nod to a proposal on stem cell-based research for human clinical trials in patients with cardiovascular diseases to be conducted by Stempeutics Research, a Bangalore-based stem cell company from the Manipal Education and Medical Group. Stempeutics will conduct study on patients with acute myocardial infarction (AMI) and critical limb ischemia (CLI), the company had applied for the DCGI clearance about 18 months back. According to the company sources, the Government of India had directed the Indian Council for Medical Research (ICMR) to constitute an expert committee on stem cell research and therapy to examine the proposal and the committee that was set up accepted the study as phase-I/II clinical trials. The ICMR and the DCGI have already approved the protocols from the company. BN Manohar, president, Stempeutics Research, Bangalore, said, “We are the first company to get DCGI clearance to start human clinical trial of stem cell-based drug. Based on the results of the clinical studies, Stempeutics plans to introduce the first stem cell-based drug available off-the-shelf in India by the end of 2011.” The Investigational New Drug (IND) is based on allogeneic ex-vivo cultured bone marrow derived mesenchymal stem cells'. After proper due diligence done by the regulatory bodies including ICMR, Stempeutics got DCGI approval for phase-I/phase-II randomized, double blind, multicentric and placebo-controlled clinical trials. “Stempeutics' goal is to bring out stem cell-based drugs in the near future using bone marrow-derived mesenchymal stem cells. Towards this goal, we have submitted proposals for conducting large scale clinical trials of its IND application for treating AMI and CLI patients to DCGI,” added Manohar.

In one of its most recent developments, Reliance Life Sciences, a yet another company working successfully towards regenerative medicine launched the first commercially available autologous limbal stem cell therapy in India, ReliNethra, to benefit Indian patients who suffer from unilateral corneal blindness. Reliance Life Sciences has also completed clinical trials after regulatory approvals, using mesenchymal stem cells derived from the patient's own bone marrow for myocardial infarction. The company is carrying out clinical trials for application of stem cell-based therapies for stable vitiligo, non-healing diabetic ulcers, Parkinson's disease and spinal cord injury. Reliance Life Sciences has also developed embryo toxicity services as a tool for drug development to benefit organizations developing new molecules.

Reliance Life Sciences has developed several mesenchymal stem cells from different sources and CD34 cells from cord blood, which are available to researchers. Embryonic stem cell lines from Reliance Life Sciences are available from the National Center for Cell Science (NCCS), Pune, for research purposes.

The year 2009 has been an exciting year for stem cell research. Early this year, US President Barack Obama reversed restrictions that former President George W Bush imposed on federal funding for stem cells in 2001. And in an encouraging move the Food and Drug Administration (FDA) has approved the first-ever clinical trial of stem cell therapy on human subjects. The trial, funded by the biotech company Geron, will test a procedure to repair spinal cord damage. The therapy involves the injection of precursor cells into the spine, where the cells will then differentiate into oligodendrocytes, the cells type that sheathes and protects the nerves of the spinal cord. As a phase-I trial, Geron's test will only examine the safety of the therapy, not the actual effectiveness.

Dr Samuel JK Abraham, faculty of medicine, Department of Surgery, Yamanashi University and director of Nichi-In Centre for Regenerative Medicine (NCRM), Chennai, said, “The approval from DCGI is a good step forward. But, while considering the recent incidences of donor stem cell tumor in a patient treated with allogeneic neural stem cells and the tumor development in an Israeli patient treated in Russia with stem cells, we need to take lot of precautions while using allogeneic applications.

“Having a single window organization like NAC-SCRT for all cell- based therapy approval would be ideal as stem cells or cells are a lot different from a drug and are rapidly changing science needs. A dynamic team, which keeps itself updated on the developments in the field, to ensure that the approvals given in India are scientifically of international standard. NCRM has initiated discussion with an institute in the US, for taking its inventions and developments in cornea for a clinical trial followed by an application through USFDA and a collaboration in that regard will be signed within this year,” added Dr Samuel JK Abraham.

While the FDA approval is an encouraging step towards the development of stem cell science, the allied developments could pave the way for more clinical trials on stem cell therapies to cure several other diseases.

Activities at Stempeutics

Overall Stempeutics is working on eight products covering various diseases. These eight products cover cardiovascular (AMI, CLI and DCM), orthopedics (osteoarthritis), respiratory (COPD), endocrinology (diabetes), central nervous system (cerebral stroke), and gastroenterology (liver cirrhosis) diseases for which there are no effective treatment available. Each product is at various stages of development.

“While all the products are very important, we took AMI and CLI on priority basis because of the availability of more research data on AMI and CLI (regeneration of dead myocardial tissue, improvement in LVEF etc.), results shown at in-vitro research work and in pilot studies at Stempeutics, and cardiovascular diseases which will be the numero uno killer disease by 2020 according to WHO,” shared Manohar.

Stem cell business is an extraordinary area which requires heavy investment for creating a world class lab for stem cell production, R&D, animal studies, and clinical trials. Stempeutics has already invested Rs 45 crore on stem cell and clinical research programs and planning to spend another Rs 70 crore in the next few years on clinical trials and pilot studies.

Stempeutics has already started the AMI and CLI clinical trials. As these clinical trials being conducted at four different hospitals in India, phase-I/phase-II trials are expected to be over by

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March 2010 and phase-III by March 2011. Based on the results of those clinical trials the company expects to bring out the first stem cell-based drug in the Indian market by the end of 2011 or early 2012.

Manipal Hospital has tied up with Stempeutics Research for promoting stem cell clinical research and pilot studies. The treatment of patients will happen at Manipal Hospital and it's role includes – taking approval of stem cell pilot study from Hospital Ethics Committee and Hospital Stem Cell Committee as per the ICMR guidelines, patient evaluation and selection as per clinical protocol, obtaining written informed consent from the patient, conducting screening tests and if found suitable performing the actual pilot study in compliance with ICH-GCP guidelines.

Focus areas

While the initial foray of Stempeutics is in bone marrow derived mesenchymal stem cells, the company has been investing heavily on its R&D to bring out some innovative products, like tailor-made progenitor cells, in the near future based on adult stem cells. Stempeutics focuses on alternate sources like Wharton's jelly and adipose tissue for mesenchymal stem cells and invests money on its long term goal of leveraging human embryonic stem cells for therapeutics purpose. To achieve this goal, Stempeutics eyes on deriving human embryonic stem cells lines. Also Stempeutics is focusing on establishing a stem cell platform for drug screening and toxicity studies for the pharma companies.

“Stempeutics' goal is to bring safe, effective and affordable stem cell-based drugs in the near future for curing diseases. We want to become an undisputed leader in the stem cell area in this part of the world,” expressed Manohar. While Stempeutics had limited its operations in Bangalore, Manipal and Malaysia, and it has plans to expand itself to the Middle East and Sri Lanka this year. Stempeutics has outsourced AMI and CLI clinical trials to Ecron-Acunova, the company will also partner with other good CRO companies for doing clinical trials of other diseases.

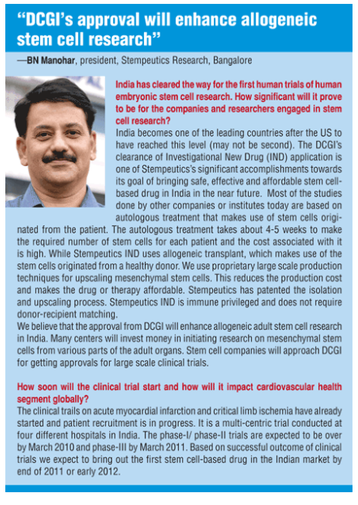
Disease impact: AMI and CLI

The study conducted by Global Burden of Diseases (GBD) reveals that the estimated mortality from coronary heart disease (CHD) in India at 16 lakh in the year 2000. Extrapolation of these numbers estimates the burden of CHD in India to be more than 320 lakh patients. Hospital statistics reveal that 20-25 percent of all medical admissions are due to CHD. The admissions due to acute myocardial infarction (AMI) are increasing in India. It has been predicted that by 2020 there would be a 111 percent increase in cardiovascular deaths in India. This increase is much more than 77 percent in China, 106 percent in other Asian countries and 15 percent in economically developed countries.

The standard protocols of care for AMI usually includes immediate perfusion, optimal pain relief, oxygen, aspirin, anti coagulants, β-blockers, nitrates and ACE inhibitors. The management of cardiac risk factor such as tobacco use, hypertension, lipid levels, diabetes, weight control and regular exercise all work to reduce further atherosclerotic events. Despite these effort AMI is still the leading cause of congestive heart failure and death in developed and developing countries. A therapy that could improve the myocardial remodelling process and reduce the incidence or severity of congestive cardiac failure (CCF) following AMI would provide a significant impact in this area of unmet medical need globally. Use of stem cells is a novel treatment modality and the successful outcome of clinical trials conducted by Stempeutics will certainly have a huge impact in India and worldwide.

Incidence of critical limb ischemia (CLI) is estimated to be approximately 50 to 100 patients per lakh per year and 10-40 percent of them are at the risk of primary amputation. Peripheral vascular disease of the lower extremities comprise a clinical spectrum that extends from asymptomatic patients to patients with chronic CLI that might result in amputation and limb loss. Narrowed vessels that cannot supply sufficient blood flow to exercising leg muscles may cause claudication, which is brought on by exercise and relieved by rest. As vessel narrowing increases, critical limb ischemia can develop when the blood flow does not meet the metabolic demands of tissue at rest.

Critical limb ischemia is a persistent and relentless problem arising as a result of atherosclerosis or vasculitis in leg arteries which severely impairs the patient functional status and quality of life, and is associated with an increased cardiovascular mortality and morbidity. Prognosis of chronic CLI is poor and no effective treatments have been established in patients who are not amenable for the traditional revascularization therapies such as angioplasty and bypass procedures due to the inappropriate anatomy of the leg arteries or frequent reocclusion following revascularization. Therefore, it is necessary to establish novel revascularization treatment to improve the prognosis in these no-option patients globally. It was this clinical need, coupled with the advances in the understanding of angiogenesis that has led to efforts using stem cells as a novel treatment modality. Successful outcome of clinical trials conducted by Stempeutics will have huge impact in India and worldwide.



“DCGI's approval will enhance allogeneic stem cell research”

—**BN Manohar**, president, Stempeutics Research, Bangalore

India has cleared the way for the first human trials of human embryonic stem cell research. How significant will it prove to be for the companies and researchers engaged in stem cell research?

India becomes one of the leading countries after the US to have reached this level (may not be second). The DCGI's clearance of Investigational New Drug (IND) application is one of Stempeutics's significant accomplishments towards its goal of bringing safe, effective and affordable stem cell-based drug in India in the near future. Most of the studies done by other companies or institutes today are based on autologous treatment that makes use of stem cells originated from the patient. The autologous treatment takes about 4-5 weeks to make the required number of stem cells for each patient and the cost associated with it is high. While Stempeutics IND uses allogeneic transplant, which makes use of the stem cells originated from a healthy donor. We use proprietary large scale production techniques for upscaling mesenchymal stem cells. This reduces the production cost and makes the drug or therapy affordable. Stempeutics has patented the isolation and upscaling process. Stempeutics IND is immune privileged and does not require donor-recipient matching.

We believe that the approval from DCGI will enhance allogeneic adult stem cell research in India. Many centers will invest money in initiating research on mesenchymal stem cells from various parts of the adult organs. Stem cell companies will approach DCGI for getting approvals for large scale clinical trials.

How soon will the clinical trial start and how will it impact cardiovascular health segment globally?

The clinical trails on acute myocardial infarction and critical limb ischemia have already started and patient recruitment is in progress. It is a multi-centric trial conducted at four different hospitals in India. The phase-I/ phase-II trials are expected to be over by March 2010 and phase-III by March 2011. Based on successful outcome of clinical trials we expect to bring out the first stem cell-based drug in the Indian market by end of 2011 or early 2012.

“Approval for clinical trials is an encouraging development”

—KV Subramaniam, president and CEO, Reliance Life Sciences, Mumbai

What significant impact does DCGI's approval for human clinical trial for stem cell research will provide for Indian stem cell companies?

For organizations such as Reliance Life Sciences, pursuing research in stem cells, consistent with ICMR and DBT guidelines, the DCGI's approval for human clinical trials has been a shot in the arm. This will help ensure that efficacy of stem cell therapies are based on clinical data generated through trials conducted as per ICH-GCP guidelines, which will be accepted by the international community. Reliance Life Sciences is working towards bringing several cell-based therapies to the market and obtaining DCGI approval for conducting clinical trials has been an encouraging development. Reliance Life Sciences had received approval to conduct clinical trials for stem cell applications for myocardial infarction, conjunctival deficiency, neural disorders and pigmentation disorders.

Will the DCGI approval paves the way for new technologies in stem cell therapy?

Regulatory clarity always helps the researcher to take a product to the bedside through a well-defined route.

What do you think will be the next step of approvals by the DCGI in stem cell research?

The way forward would be the development of a well-defined pathway for stem cell therapies in India, with a defined timeline. This will in turn lead DCGI to clearly spell out expectations from researchers, helping the development of a regulatory mechanism to foster stem cell research and development work in the country, be it institutional or individual initiated.

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