Stem cell therapies to hit market soon

Going by the research and commercialization efforts underway in the industry, it won't be long before stem cell therapy would be commonplace. The next 10 years will see a number of initiatives in that direction. The first products in the cardiovascular, diabetes, neurological, and tissue and organ stem cell therapy are expected to enter the market between 2009 and 2013

- *Earlier this year, in a hospital in Bangkok, the life of a two-year-old baby was saved when the pediatrician decided to use stem cells. The baby was suffering from a fatal disorder of the immune system known as bubble-boy disease and lived because of a transplant of umbilical cord blood.*
- *In May, this year, India-based Manipal Hospital announced a major breakthrough in the treatment of Parkinson's disease using stem cell therapy. It presented the case of Andrew Kisana, a US national. The doctors at the hospital said that the patient's bone marrow was harvested at the regenerative medicine department and the mesenchymal stem cells were injected into the part of the brain, which was affected because of Parkinson's disease. Kisana received three injections. This was the first time such a major effort was attempted in India for treatment of Parkinson's disease. Kisana was suffering from the degenerating disorder for 15 years. After undergoing intensive drug therapy, lesion and deep brain stimulation (DBS), he had come to Manipal Hospital.*

IN 2007, the US stem cell therapies market earned over $25 million in revenues, reports a Millennium Research Group (MRG) study. This revenue came from only two orthopedic products available in the US—Osiris Therapeutics' Osteocel and Blackstone Medical's Trinity. It is expected that, in addition to these two products, the entry of other products will open up the stem cell therapies market globally, not just in the US. A number of companies such as Aastrom Biosciences, Advanced Cell Technologies, Arteriocyte, Blackstone Medical, Cytori Therapeutics, Geron, Harvest Technologies, International Stem Cell Corporation, Stem Cell Sciences, Mesoblast, Cytometrix and Osiris Therapeutics are working on the applications of stem cell therapies.

However, the development of the market for stem cell therapies is primarily dependent on the success of clinical trials, regulatory approval, and public acceptance. The first products in the cardiovascular, diabetes, neurological, and tissue and organ stem cell therapy are expected to enter the market between 2009 and 2013. The MRG report forecasted that by 2017 about 90 products are likely to be available in the market.

The prevalence of potentially treatable disorders, unmet medical needs, rising health care costs, growth in the ageing population, and the success of the first stem cell therapy products are driving this market upward through 2017. The market has everything going its way. However, the success of the stem cell therapies will depend on the political and public support, reports MRG.

In the ensuing pages *BioSpectrum* brings you a ringside view of the developments in the stem cell industry:

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The cutting-edge research

IF ONE were to start compiling who's who of stem cell research the list would indeed be long. Considering the successes in animal studies and applications of stem cells many organizations, companies and institutes are undertaking research on stem cell therapies. Some of them are working on clinical studies for diseases such as Spinal Cord injury, Parkinson's Diseases, Muscular Dystrophy, Diabetes and Ischemic Heart Disease. There are over 600 stem cell trials currently listed on *www.clinicaltrials.gov*. And according to industry estimates, across the globe over 9,000 stem cell transplantations are conducted every year.

The human stem cell research has enormous potential for contributing to the understanding of human biology. Although it is not possible to predict the outcomes from the basic research studies, it offers real possibility for treatments and ultimately for cures for many diseases for which adequate therapies do not exist. There already exists evidence from animal studies that stem cells can be made to differentiate into cells of choice and that these cells will act appropriately in their transplanted environment.

Across the globe companies such as Aastrom Biosciences, Advanced Cell Technologies, Arteriocyte, Blackstone Medical, Cytori Therapeutics, Curis, Insception, Macropore, Geron, Harvest Technologies, International Stem Cell Corporation, Stem Cell Sciences, Stem Cell Technologies, Stem Cell Therapeutics, StemCells, Mesoblast, Cytometrix, Reneuron, CyGenics, Osiris Therapeutics and ViaCell are working on stem cell therapies. But so far only a few companies have been able to develop therapies that actually reached the clinical stage, while others are still making efforts to arrive at suitable therapies. Let's look at what these stem cell research companies have been doing.

US-based **Osiris Therapeutics**, has been developing cellular therapies based on stem cells isolated from readily available adult bone marrow. These stem cells offer the opportunity to provide revolutionary treatments for many disease conditions. Currently, it has three product candidates in clinical trials. Prochymal is now enrolling patients in two phase III clinical trials. The first trial is evaluating the use of Prochymal to treat Graft versus Host Disease (GVHD), a life threatening disease afflicting patients who have received a bone marrow transplant. The second trial is evaluating Prochymal for the treatment of Crohn's disease, a painful, disabling bowel disease that often leads to surgery. Provacel, a formulation of stem cells to repair damaged heart tissue following heart attack, completed enrolment of a phase I clinical trial. Osiris has also completed enrolment of a phase I/II study for its third product candidate—Chondrogen, an injection of stem cells formulated to repair damaged tissue in the knee joint and prevent the progression of arthritis.

US-based **Blackstone Medical** is dedicated to advancing techniques in the treatment of the human spine by identifying solutions with the spine surgeon and together creating pathways for innovative products. Through a partnership with Osiris Therapeutics, it distributes Trinity, a surgery-ready, first-of-its-kind bone graft product containing viable adult stem cells. Trinity is unique in the field of biologics because it provides all three bone growth properties: osteoconductivity, osteoinductivity and osteogenesis and is free of donor matching or recipient immune expression concerns. It is also a safe alternative to autograft harvesting because it eliminates patient discomfort and the risk of inherent complication as well as reducing procedure time.

Geron Corporation from the US has demonstrated that human embry-

Some cell-based products in trials or on sale

Company	Cell type	Indication	Development stage
Aastrom	Stem cells (bm)	Ischemia Bone fracture	Phase I Phase II
Bioheart	Myoblasts	Heart attack/ failure	Phase I/II
Proneuron	Macrophages	Spinal repair	Phase II (recruitment suspended)
Genzyme	Chondrocytes	Cartilage	Market
NeuroGeneration	DA neurons from neural stem cells	Parkinson's	Phase I/II (clinical hold
Organogenesis	Fibroblasts keratinocytes	Chronic wounds	Market
Osiris	Stem cells (msc)	GVHD Meniscus repair heart failure	Phase III Phase I/II (failed) Phase I/II
Stem cells Inc	Stem cell (neural)	Batten's	Phase I/II

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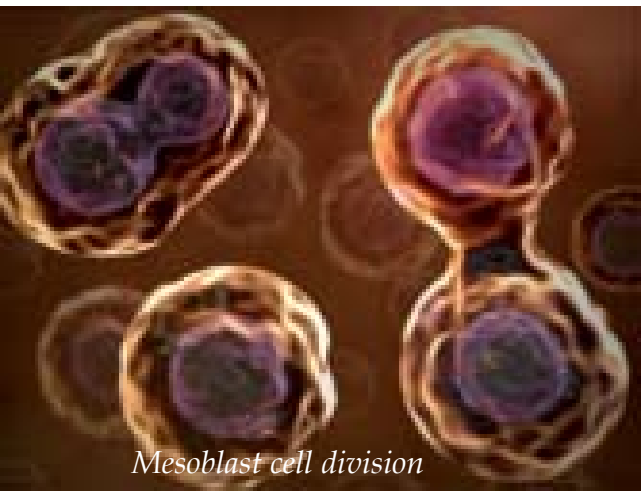
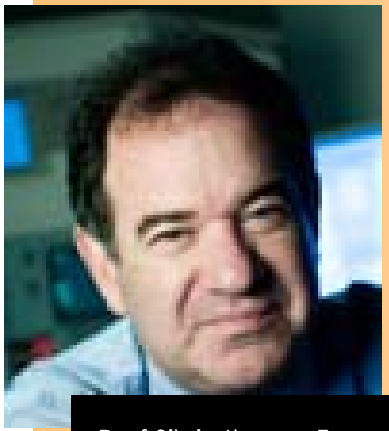

Mesoblast cell division

planted four days after infarction, and echocardiographic and MRI evidence of significant improvement in cardiac structure and contractile function.

Commercializing a unique population of adult stem cells for orthopaedic applications, Australia-based **Mesoblast** is conducting a phase 1b clinical trial at The Royal Melbourne Hospital in patients suffering from non-healing, long bone fractures. Interim results indicated strong bone regeneration and fracture union in every one of the first five patients implanted with Mesoblast's proprietary cells. The success of the stem cell therapy in these patients eliminated the need for a second operation to harvest bone from their hips. There have been no reported cell-related adverse events. The success of this trial will lead to Mesoblast developing a proprietary stem cell product for repair of long bone fractures.

onic stem cell (hESC)-derived cardiomyocytes improve heart function when transplanted after a myocardial infarction. This study is the first to document the potential clinical utility of regenerating damaged heart muscle by injecting hESC-derived cardiomyocytes directly into the site of the infarct. In addition, the research confirms the effectiveness of a scalable production system that enables Geron to manufacture the cardiomyocytes for use in ongoing large animal studies and, ultimately, testing in humans. The study describes the feeder- and serum-free, scalable production of hESC-derived cardiomyocytes, their survival in the infarct zone of rats when transMNC biotech major **Stem Cell Sciences** focused on technologies to grow, differentiate, and purify embryonic and neural stem cells has a portfolio of patents and patent applications in both adult and embryonic stem cell fields. These include technologies to permit the generation of highly purified stem cells and their differentiated progeny for use in genetic, pharmacological and toxicological screens. Moreover, these technologies can be utilized to provide pure populations of appropriate cell types for transplantation therapies. It has an exclusive in-licensing of a technology, which is expected to significantly accelerate the application of human embryonic stem cells in both research and cell-based therapies. This discovery overcomes the key challenge in the effective scale-up of stem cell technologies—cell death. The discovery, made by Prof Yoshiki Sasai's team at The Institute of Physical and Chemical Research of the RIKEN Centre for Developmental Biology (Kobe, Japan), uses a class of compounds known as ROCK (Rho-associated kinase) inhibitors to block the onset of stem cell death when the clusters of growing cells are dissociated for transfer and scale-up. This discovery was effective on all human embryonic stem cell lines tested. The discovery represents a world's first in terms of stem cell technology. Stem Cell Sciences has secured exclusive


Prof Siloiu Itescu, Founder & Chief Scientific Advisor, Mesoblast, Australia

Q How is Mesoblast capitalizing on its research in the market?

Both Mesoblast and Angioblast are confident that the preclinical success of the shared allogeneic MPC platform technology will be translated into commercial success by developing off-the-shelf products that will be highly effective in large, pivotal clinical trials. Both Mesoblast and Angioblast are making significant progress in commercializing the technology and are well-positioned to capitalize on the leading edge, shared platform technology, and are supported by robust patent protection, good management and corporate governance, sufficient funds, and solid communication capabilities. Both companies have now progressed to the stage of mature clinical stage commercial development. By the middle of 2008, it is anticipated that a total of five phase 2 clinical trial IND submissions for orthopaedic and cardiovascular indications will have been filed, and that at least two phase 2 trials will be significantly advanced with a further three commencing. These characteristics underpin the emergence of Mesoblast and Angioblast as global leaders in the exciting field of regenerative medicine.

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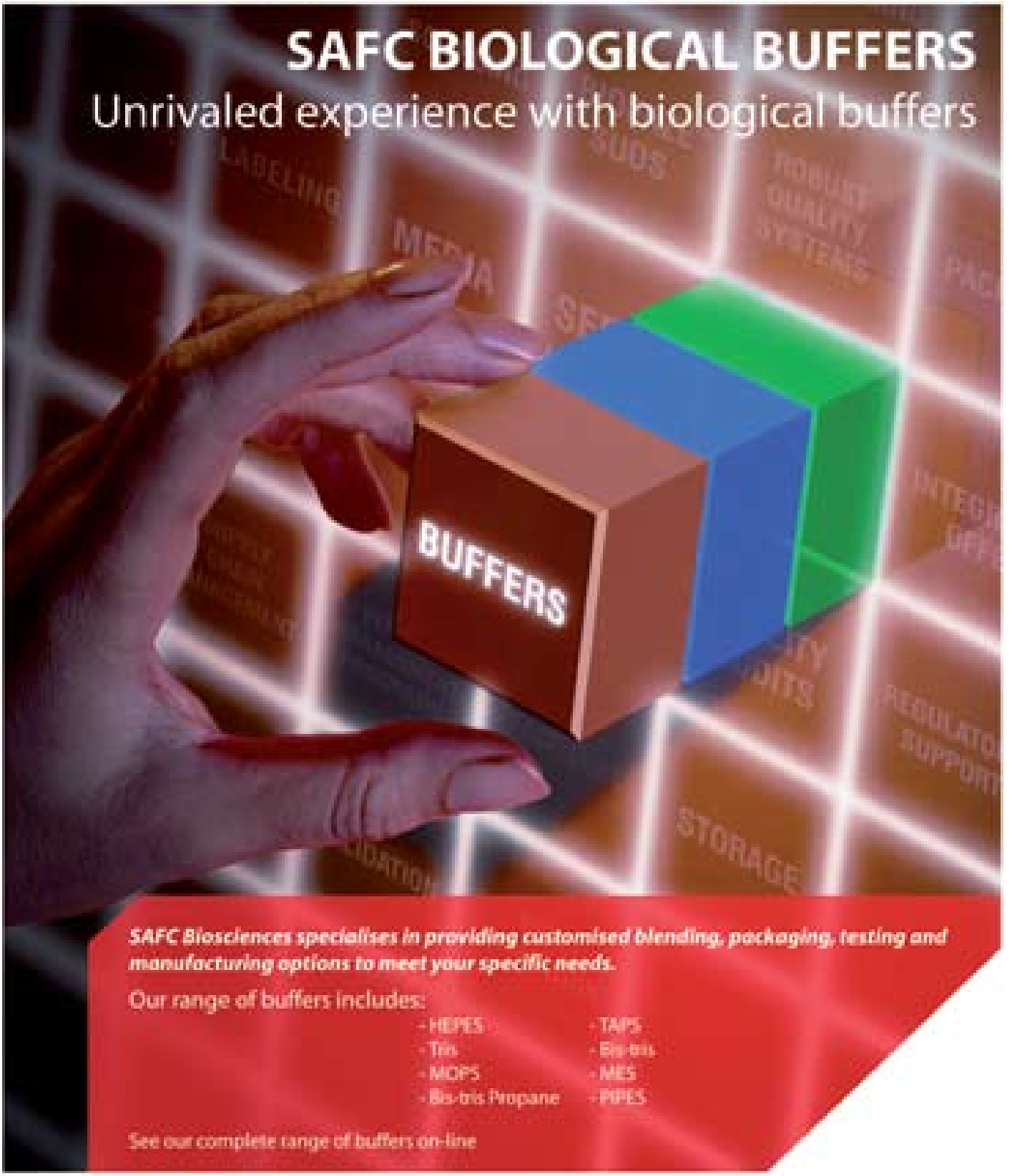

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Singapore-based **Stem Cell Technologies** is focusing on human adult progenitor cells derived from adipose tissue. Its team has optimized the isolation protocols for maximising the yield of Adipose Derived Adult Progenitor (ADAP) cells. It is in the process of charactering these cells as well as differentiating them along the various lineage pathways.

US-based **Cytomatrix** is a development stage biotechnology company focused on researching, developing and commercializing new therapeutics based on the use of cells to help treat diseases. It develops high value production devices. Its core technology is a unique cell growth technology termed "The Cytomatrix" that enables cells to grow in three dimensions. Its initial focus is on diseases in which hematopoietic (blood) cells such as stem cells and lymphocytes play a role. Made from inert materials through a sophisticated manufacturing process, the Cytomatrix provides an ideal environment for growing cells outside the body and for subsequent implantation into the body.

Australia-based adult stem cell research company, **CyGenics** is involved in developing new stem cell-based medical therapies. It is involved in the production of human T cells, a critical component of the immune system. The human T cell has implications in treatments for cancers, immune disorders, viral or bacterial infections and other conditions that are proving drug resistant. CyGenics is making efforts to develop stem cell-based treatments for wider range of medical conditions.

Dr Samuel JK Abraham, Nichi-In Center for Regenerative Medicine, Japan

Q ***What are the latest applications of stem cells?***

Currently, stem cell applications in clinical studies are undertaken in several institutes all over the world for diseases such as Spinal Cord injury, Parkinson's Diseases, Muscular Dystrophy, Diabetes and Ischemic Heart Disease. The source of the stem cells used is often different in each institute. As far as Nich-In Center for Regenerative Medicine (NCRM) is concerned, though we are doing research on stem cells from various sources (Adult stem cells from Cornea, Liver, Bone Marrow, Peripheral Blood, Umbilical cord, Foetal stem cells, Embryonic stem cells of animal origin) our clinical studies use only adult bone marrow stem cells of Autologous origin. At the moment, we are not using Mesenchyma stem cells, which are sub group of bone marrow stem cells, as they need to be grown in the laboratory using animal serum.

Q ***What is the future of regenerative therapy?***

It is very promising and has a huge potential in various diseases for which no cure is available for the patient at the moment in allopathy or other alternate systems of medicine. The regenerative capabilities of cells is very little understood, and if we can explore the same thoroughly I guess the even the basic approach to prevention or cure of several diseases would be different. There is no doubt that in another decade a fully-evolved and equipped department of regenerative medicine is going to become an indispensable part of any and every health care set up.

Q ***Please elaborate on the breakthrough at the Institute in treating liver cirrhosis with stem cells.***

The credit goes to Dr Isao Sakaida and his team who have first proven in animal models that the Autologous bone marrow stem cells work in them when liver injury is induced and also that the same works in human clinical trials. The procedure we follow is as per their methodology and know-how that has been tried in close to 11 patients among which several of them show very good improvements in their biochemical parameters. We are waiting for a six-month follow up to be published.

Next Issue

November 2007

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- **Vietnam: An emerging market for life sciences**
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Overcoming funding issues

RESEARCH on stem cells has been taking place for decades but so far no therapeutic products have seen the light. So to continue to carry out research on stem cells the companies need financial support. Researchers say that it will take few more years to launch successful therapeutic products based on stem cells. Due to lack of flow of funds the companies are finding it difficult to continue research on stem cells and are deciding to close down their research activities.

In Asia's biomedical research hub, Singapore, two companies focused on stem cell research have closed their operations in the last couple of months. ViaCells, a US based company closed its stem cell research initiative in Singapore due to lack of flow of funds from the funding agency. According to market reports, ViaCell failed to comply with the objectives set by the funding agency. Similarly, ES Cell International has decided to shift its focus from research to commer-

Dr Ramananda S Nadig, former COO, Stempeutics Research, India

Q ***What are the latest significant developments in stem cell research?***

The most significant breakthrough in stem cell research, as of now, is the fact that we have understood the phenomenal potential of adult mesenchymal stem cell use in various indications. The initial response is very encouraging and the subjective improvements seen in our patients will have to stand the scientific scrutiny of well-planned proof of concept studies before stem cells are accepted by physicians practicing evidence-based medicine.

The latest developments in stem cell research is the fact that the US FDA has accorded a fast track approval for Osiris, a US-based company, to conduct a phase III study of the use of mesenchymal stem cells in graft versus host disease. Based on the results of this study, there is every likelihood that Osiris would be permitted to market these MSCs. The fact that the US FDA has accorded this status to MSCs is significant and will probably pave the way for many other drug authorities to consider permitting such trials.

Q ***What are the bottlenecks in commercialization of stem cells?***

As of now the bottleneck for commercialization of stem cells in India is the lack of clear guidelines either from the DCGI or the ICMR. While everyone is going gaga about stem cells, there is no clear appreciation of stem cells as a new biological entity, clarity on pre-clinical animal testing requirement, need for a phase I study in humans and a blue print on how to get them to the market. Adult stem cells are being used in bone marrow transplants without a clear okay for various indications.


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cialization of its human cell lines. To overcome the lack of funding companies are taking other routes. Companies like Stem Cell Sciences and CyGenics have adopted a balanced approach.

Let's look at the model adopted by **Stem Cell Sciences**. It has adopted a balanced approach that has proved to be durable over time and it has the support of its investor base through listings in both the UK and Australia to support its developments going forward. The company is aware of the current issues related to funding (real or perceived in the marketplace), and continues to develop its hybrid business model of revenue-based business units combined with investment and partnering associated with higher value future outcomes. To date, Stem Cell Sciences has raised capital through private investment (but not VCs), listing on UK stock exchange (AIM—2005) and Australia stock exchange (ASX—2007). Funds were also generated through revenues from sales and licensing, plus substantial grant funded collaborative programs especially through the European Union.

Stem Cell Sciences' growing revenue streams and established network of academic centers in the stem cell field provide strong foundation and pipeline of new research products and clinical development opportunities. Income from its three research business units and participation in multiple government-funded research consortia help offset its costs and risks in the development of its long-term objectives in cell-based therapies. Its income is sourced from its three revenue generating business units including its cell culture media business SC Proven, technology licensing undertaken by the SC Licensing business unit, and the recently established custom engineering and stem cell supply

Dr Sohail Ahmed, Principal Investigator, Center for Molecular Medicine, Singapore

Q ***How far do you think we are from commercialization of human embryonic stem cells?***

Commercialization of human embryonic stem cells research initiatives is all hype. It is still in development phase. It takes at least 15-20 years to develop a product from embryonic stem cells.

Q ***According to you what are the barriers in collaboration between industry and academia?***

There is conflict of interests between the industry people and the academicians. Academicians are more inclined towards science and biology. In industry, the focus will always be on commercialization of the research initiatives. However, it will be good if both work together.

In Singapore we (who are actively involved in the stem cell research) started Stem Cell Club, a voluntary organization wherein seminars, workshops are conducted for the benefit of stem cell researchers and general public. There will be regular lecture programs from the experts. Now, we are planning to set up a Stem Cell Society. The aim of this Society is to do things in a professional way. I think this Society might play a key role in bringing academicians and industry players on a single platform.

Q ***How do you see the stem cell research initiatives in Asia Pacific countries?***

I have been to Malaysia, Indonesia and Thailand. Considering the hype in the market, few researchers are working on stem cells with the help of venture capitalists in Malaysia and Indonesia. But the infrastructure is not up to the international standards. However, Thailand has better facilities compared to other countries.

SC Services business unit. Stem Cell Sciences' fourth business unit, SC Therapies, is not currently revenue generating, though it has recovered some costs of intellectual property protection and mitigated some similar future costs through the cross-licensing agreement entered into with its affiliate company in Japan, SCS KK.

Australia-based **CyGenics**, a healthcare company focused on tissue and cord blood banking, owns and operates the largest network of private cord blood banks in the Asia Pacific region. It has a portfolio of stem cell technology related investments. Listed in Australian stock exchange it holds patents in the field of stem cell expansion and differentiation.

Mr Steven Fang, CEO of **CordLife**, which acquired Cytomatrix in 2003, said, "This year we have spun off our research arm Cytomatrix into a separate entity, by diluting our stake to 41 percent. By doing this, we have added two more promoters and brought in more technologies, which were patented by our partners. This will help the company to build stronger platform to build on technologies. In the restructuring process the Chief Operating Officer became the Chief Executive Officer. This restructuring will help generate more research grants to drive research activities. Now, it is an Australia-based research company. Cytomatrix generates funds to carry out research activities in the form of research grants by entering into tie-up with universities and raises funds from high net worth individuals, financial institutions and the market."

Mr Fang further added, "CordLife is a provider of raw materials and Cytomatrix is a provider of technologies. Together we can develop useful therapies. Each is specialized in its core area. CordLife is specialized in building network for creating volume of raw materials for future therapies, and Cytomatrix on its own undertakes the development of the technologies. Each will work with each other or without each other. So, it is not mutually exclusive."

Except a few successful companies like Stem Cell Sciences and Cytomatrix most of the companies are still struggling to generate revenue to run the operations

Except a few successful companies like Stem Cell Sciences and Cytomatrix most of the companies are still struggling to generate revenue to run the operations. At the same time issues like ethics, complex nature of research, public acceptance and long gestation time-period will continue to prolong the success timeline of the research initiatives in stem cells. The companies, doing basic research have to look for government support as financial institutions and venture capitalists are still not showing confidence in the success of stem cell research outcomes.

Commenting on the potential opportunities for stem cell companies, Dr Sohail Ahmed, Principal Investigator, Centre for Molecular Medicine in Singapore, said, "Drug toxicology study, diagnostic testing and developing cell lines offer lot of potential for stem cell research companies. They can look at these areas as opportunities. At present, the cell lines for research activities are available at $5000-$6000 for one-off sale."

Realizing the potential health benefits of stem cell technology will require a large and sustained investment in research. The government is the only source for such an infusion of funds. In an effort to woo researchers and investors, Mr Rod Blagojevich the Governor of Illinois, USA recently signed a bill that allows public funding of research on all types of stem cells, including controversial embryonic stem cells. If other governments, too, have same views on stem cells research then companies doing research can receive government funds to continue their research activities and we can expect faster progress.

Narayan Kulkarni
(Inputs: Hasthana Rajappa) BS