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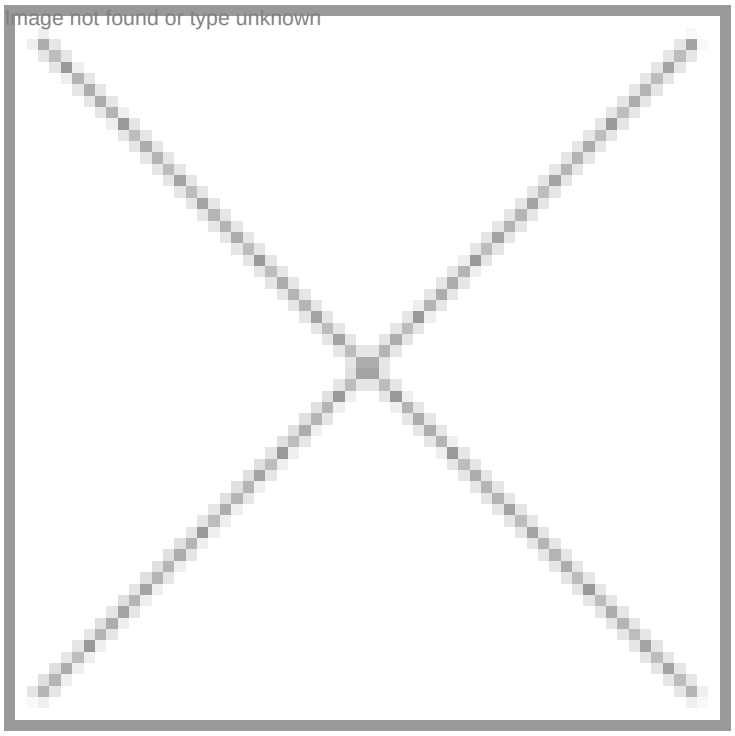
Australia takes lead, again

14 October 2008 | News



Australia takes lead, again

In a first-of-its-kind of decision Australian medical regulator National Health and Medical Research Council (NHMRC) has issued license to a Sydney firm to create cloned human embryo to obtain embryonic stem cells. Sydney IVF, which received the government permission, has about 7,200 human eggs ready for research and has been given license to do only therapeutic cloning.

The regulator said that if the Sydney based invitro-fertilization company is successful in its endeavor, it will be the world's first.

This is the first time Australia has granted permission to research on embryonic stem cells although Australia has been a pioneer on research on adult stem cells.

In fact, Australia has been at the cutting edge of stem cell research since long. Australian government has two laws that regulate the stem cell research-The Prohibition of Human Cloning for Research Act 2002, which draws the fundamental lines as to what is allowed and what is not; and The Research Involving Human Embryos Act 2002, which sets out guidelines for research involving the activities that are allowed. The net effect of this approach is that Australia has chosen not to regulate basic research using human embryonic stem cell lines, but instead regulate activities associated with their creation.

The country has an envious position in stem cells business not only because it has some of the best centers and labs for research but also because it has some of the best talents and pioneering companies.

"Australian scientists are at the forefront of stem cell research and in fact have been there for many years," says Prof. Silviu Itescu, Executive Director at Mesoblast. A well-known Australian stem cell company Mesoblast is publicly listed and for the last three-and-a-half years has been commercializing technologies developed by world leading Australian researchers from the Hanson Institute from Australia.

Australia, unlike some other countries in the region such as China and Singapore that depends on Western trained and returned scientists to do bulk of stem cell research, doesn't have to depend on overseas scientists. It has all the talent within the country and in fact has seen its scientists working and heading some other international research institutes across the globe. India, Taiwan, Japan and to a larger extent south Korea, in this case, have a strong line up of stem cell researchers that are domestically trained and with the available local talent, are doing some amazing work.

A look at Mesoblast reveals how its researchers have progressed in this domain. In late August 2008, scientists at Mesoblast launched an off-the-shelf cell therapy product that was found to be effective for interbody fusion of the cervical spine in the neck. And in the same month, Mesoblast's researchers reported that their adult stem cell product regenerated and regrew damaged knee cartilage in post-menopausal osteoarthritis.

Apart from the open and exciting stem cell research culture in the country, Australia's pre-eminent position in the stem cell business comes from the fact that government backing for the industry is very active although funding is quite modest when compared to other Asian countries. "I think the Australian government has been funding stem cell research because of the belief that academic and industrial partnership will bring more benefit to the Australian companies and research centers," says Prof. Itescu. "I think that the institutional investor support has been tremendous. Although the funding from federal government can increase and match if not exceed the funding that governments in other Asian countries provide. "

The National Health and Medical Research Council (NHMRC) provides funding for stem cell research, so do the various state governments. In 2007, NHMRC's total funding for all types of stem cell research, including animal, human adult and human embryonic stem cell research, was somewhere around A$50 million. Of that, a small proportion was specifically for human embryonic stem cell research, states an official Australian Government note.

In the neighboring New Zealand, the government does not have a policy in place for stem cell research. The country's strengths lie in somatic nuclear transfer (SCNT) and the production of cloned and genetically modified farm animals and in basic stem cell biology research. The funding in New Zealand is very limited, both from governmental and private sources and New Zealand researchers therefore can't compete in the main fields with the big players, but they are thriving in niches and through overseas collaborations using unique expertise and resources.

In New Zealand, most of the research in stem cells is undertaken by the Ministry of Research, Science and Technology (MoRST). There are also a number of other government agencies that have progressed work in the stem cell domain and some private companies that too are researching on stem cells. Companies such as AgResearch and Industrial Research have stem cell programs of potential commercial value for agricultural and industrial applications.

Living Cell Technologies (LCT) is one of the few companies here researching on stem cells. Dr Paul Tan, CEO of LCT informs that the company is researching the presence, proliferation and ability to differentiate into islet beta cells of pancreatic progenitors in their microencapsulated porcine islets. This could be a vital factor for the function and longevity of the DiabeCell product.

"We are further currently researching the effects of our preclinical microencapsulated porcine choroid plexus cell product (neurotrophin producing cells) for the treatment of neurological diseases on neural stem cells as a possible mechanism of action for the beneficial effects we have observed in animal models of Stroke, Huntington's and Parkinson's disease," says Dr Tan. "LCT is a world leader in the use of encapsulated porcine derived neonatal islet implants. A prototype product of implanted encapsulted islets remained viable and producing insulin in a patient after 10 years. Further, the positive results from the ongoing clinical trial led to international media interest and recognition. LCT is the first company to have the capability to conduct human clinical trials under present regulatory guidelines."

The company is developing a product comprising encapsulated neurotrophin producing cells that can be implanted to recruit endogenous progenitor cells in the brain to the site of injury or disease and thereby repair or regenerate brain tissue.

"This year we drew up a memorandum of understanding with an international stem cell company to develop LCT technology for non-therapeutic and therapeutic use with their of stem cell technologies," says Dr Tan.

Further, LCT entered into collaboration with a University in Germany to use LCT's proprietary technology to stimulate neural crest stem cells with the aim to treat Hirschsprung's disease, a congenital colon motility disorder. This project is receiving joint financial support from New Zealand and German government grants.

Then there is, Prof Richard Faull who is conducting world leading basic research on human neural stem cell biology at the University of Auckland. This work provides the basis for LCT's approach in the use of implants of encapsulated neurotrophin producing cells for the recruitment of natural progenitor cells for brain repair and regeneration.

AgResearch has a worldwide reputation in cloning of farm animals, nuclear reprogramming and the derivation of ruminant species embryonic-like stem cells. Further their research into tissue regeneration by deer anthler stem cells holds great promise. Industrial Research recently entered into a commercial collaboration with Singapore to test the utility of purified glycocompounds in stem cell culture.

Although New Zealand has had its fair success in the stem cell business, Dr Tan believes New Zealand cannot catch up with the rest of the world. "New Zealand cannot catch-up with the US, Europe, Australia and Asia in human embryonic stem cell research. There are, however, good opportunities that New Zealand will become a recognized, innovative force in tissue stem cell and tissue engineering therapeutics," he says.

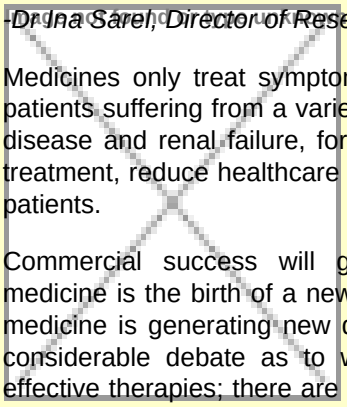
Coming to the rest of Asia. India has no clear policy regulating stem cell research but the country has its fair share of research going on-though blazing success stories from India are yet to come by. Also, the Indian regulations are by far more relaxed and quite supportive than some other countries in the region. "However, there is a need for regulation of individual investigator (doctor) initiated cell based therapies, as these tend to be conducted in variance with international standards of clinical trials and cell processing and the imponderables on safety and efficacy are not scientifically addressed," says K V Subramaniam, President and CEO, Reliance Life Sciences, a Mumbai-India based stem cell research and biopharmaceuticals company.

Subramaniam says if India has to grow as a top stem cell research hub, regulators would have to ensure that the:

- Conduct of research in stem cells consistent with ICMR and DBT guidelines.
- Allogenic clinical trials are conducted based on approvals of Drug Controller General of India.
- Efficacy of stem cell therapies are based on clinical data generated through trials conducted as per ICH-GCP guidelines, which are accepted by the international community.
- Processing of stem cells for clinical trials and commercial therapies are carried out in a cGMP environment, approved by FDA.

In India several scientific departments and institutions of the government, such as Department of Biotechnology, Department of Science and Technology, Indian Council of Medical Research and Council for Scientific and Industrial Research are promoting stem cell research. The priority areas of research have been identified through discussions at various forums on basic and applied sciences. Among the various programs being supported in embryonic and adult stem cells research are: establishment of hESC lines, use of limbal stem cells for repair of ocular surface disorders, isolation; purification and characterization of hematopoietic, mesenchymal cells among others.

Embryonic stem cells years away from therapy



-Dr Ina Sarel, Director of Research and Development, Theravitae, Israel

Medicines only treat symptoms, not diseases. Repair stem cell therapy offers a real solution to patients suffering from a variety of diseases. It can be applied to cardiac disorders, nervous system disease and renal failure, for example. Stem cell research has the potential to transform disease treatment, reduce healthcare costs to society and enhance quantity and quality of life for millions of patients.

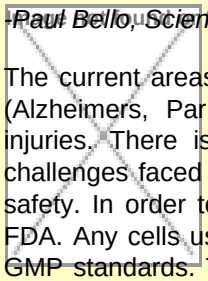
Commercial success will generate significant business opportunities. Literally, regenerative medicine is the birth of a new sector of healthcare. Just like the dawn of the Internet, regenerative medicine is generating new directions for industry, innovation and product development. There is considerable debate as to which type of stem cells-embryonic or adult-will produce the most effective therapies; there are advantages and drawbacks to each. However, the safety and efficacy data of adult stem cell treatments is published with increasing frequency whereas embryonic stem cells are several years away from being used as a therapy. At TheraVitae we derive adult stem cells from a patient's blood; our technology improves heart function and blood flow to limbs that would otherwise be amputated.

In Israel, the Israel Stem Cell Therapy Consortium, a group of medical companies and academic research facilities, was created to coordinate the efforts of local companies, scientists, and hospital research centers to develop generic technologies for stem cell therapy. The Consortium had been awarded a government grant of $15-20 million to develop the tools and techniques for widespread development of stem cell-based therapies.

Reliance Life Sciences is developing a wide range of novel research-led, autologous and allogenic cell therapies and tissue-engineered products to get into regenerative medicines business. Under the "regenerative medicine initiative", the company has divided several groups who work in areas such as embryonic stem cells, ocular stem cells, haematopoietic stem cells and skin and tissue engineering. Cell-based therapies from Reliance Life Sciences aim to meet unmet patient needs in the areas of cardiac disorders, neural degeneration, spinal cord injury, metabolic disorders, ophthalmic diseases, hematological diseases, oncological diseases, burns and wound management, diabetic and venous ulcers, skin pigmentation disorders, orthopaedic and cartilage disorders.

One of the newest companies in stem cell research in India is Stempeutics Research, a Bangalore-based company focused on research, therapeutics and therapy in the field of regenerative medicine.

The key challenges are all linked to safety



-Paul Bello, Scientific Program Manager, Stem Cell Sciences, Australia

The current areas in which stem cell therapy research is most active are: neurology (Alzheimers, Parkinsons diseases), diabetes, cardiac conditions and spinal cord injuries. There is also considerable research being done on iPS cells. The key challenges faced by any firm working in the stem cell therapy space are all linked to safety. In order to take such therapies to market, they need to be accepted by the FDA. Any cells used in therapy must be robust, consistent and efficiently scalable to GMP standards. This is one of the areas that SCS is involved in. Scalability of cells involves the culture of pure cell populations in suitable growth media, which is serum-free. Animal product-free reagents are also desirable for any potential therapeutic applications. SCS provides such media under its CultiCell brand.

B N Manohar, President of Stempeutics told BioSpectrum that since its inception two years ago, Stempeutics has focused on two major types of stem cells-Adult Stem Cells and Mesenchymal Stem Cells while also focusing on human embryonic stem cells. It has developed cell characterization for purity and identity by flow cytometry, functional assay for multipotency, process validation for manufacturing, large scale cGMP complaint up-scaling of mesochymal stem cells and quality control testing and quality assurance.

Stempeutics has established cell and tissue manipulation facilities at Bangalore, Manipal (India) and Kuala Lumpur in Malaysia. "India has massive potential for stem cell research as there is a very good environment and we have things going for us," says Dr Manohar.

Stempeutics' research is into embryonic stem cells, stem cell niches, self-renewal and signaling pathways, cancer stem cells, mesenchymal stem cell biology, differentiation and transcriptional determination, diabetes, cardiovascular, neuro-regenerative potential of adult stem cells, ocular stem cells, and dental stem cells.

The island nation of Taiwan has a pro-stem cell policy that has made the country a place of choice for stem cell research.

Dr Oscar Lee, who is with Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, Taipei and Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei has been a foremost stem cell researcher in Taiwan.

He says just like other Asia Pacific countries such as Singapore, Hong Kong, and even Mainland China, the Taiwan government is putting a lot of emphasis on the development of the stem cell industry.

"The government is pouring in considerable resources in setting up and helping stem cell industries," says Dr Lee.

There are about 100-200 stem cell startups in Taiwan and this number is quite huge considering the country has a population of just 23 million. Both domestic and international VCs are quite active in Taiwan offering to fund anyone that comes up with an interesting project. Dr Lee predicts that in 20-30 years Taiwan will be one of the most active countries in stem cell research and the country to watch out for.

Taiwan has a lot going for it in the stem cell business. The country is also benefiting from its researchers returning to work in the country after retiring as professors and professionals in top Western universities and top stem cell research labs across the world.

Taiwan researchers, informs Dr Lee, are working on usage of stem cells to treat liver and cardiac diseases, gastroenterology, regrowing of limbs and even human embryonic stem cells.

The major research theme of Dr Lee's lab is plasticity and application of mesenchymal stem cells. Being an orthopedic surgeon as well as a stem cell scientist, Dr Lee says he is particularly interested in developing new application of mesenchymal stem cells to treat orthopedic problems.

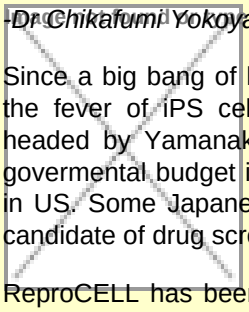
His lab at National Yang-Ming University in Taiwan has successfully isolated mesenchymal stem cells from human term umbilical cord blood.

In addition, he says his research team has demonstrated the differentiation potential of mesenchymal stem cells into hepatocytes in vitro. The team also worked on an animal model of in utero transplantation of human mesenchymal stem cells into mice to investigate in their vivo differentiation potentials.

"We have demonstrated that human bone marrow-derived mesenchymal stem cells are able to differentiate into progenies originated from all three germ layers in vivo," Dr Lee says.

The team also investigated the growth and differentiation of mesenchymal stem cells on Type 1 collagen nanofibers. "We have also looked into the possibility of incorporating gene therapy with stem cells to further enhance bone formation and found that concomitant overexpression of Cbfb and Cbfa-1 can efficiently enhance osteogenic differentiation of MSCs," Dr Lee adds.

The combination of non-therapeutic businesses and R&D of cell therapy is good business model



-Dr Chikafumi Yokoyaama, CEO, ReproCELL, Japan

Since a big bang of human iPS cells by Prof. Shinya Yamanaka, Japan has been in the fever of iPS cells, which is supported by Japanese government. iPS center, headed by Yamanaka, was established in Kyoto and a relatively large amount of govermental budget is prepared for iPS cell research, although it is far less than that in US. Some Japanese pharamaceutical companies are interested in iPS cells as a candidate of drug screening and development tool, but not yet in cell therapy.

ReproCELL has been focused on the drug screening and development applications by using ES and iPS cells. Our first business target is a cardiotoxicity test service, QT prolongation, by using monkey ES cell derived beating cardiomyocyte. It is now on sale. Now, we are developing the same QT prolongation system by using human iPS cells instead of monkey ES cells as our second new service that will be launched in the spring of 2009.

I think that the fund raising is one of the most severe challenges for stem cell therapy. Since, it is difficult to estimate the money and time needed to reach the goals through clinical trials, most hesitate to invest money. If a company such as Geron, move forward to clinical trial of ES cell cell therapy, some investors may change their opinions.

I think the most important thing for stem cell companies is to start some business in non-cell therapy field as soon as possible. Most of stem cell companies had the same business model as the drug development type biotechnology company. However, it is difficult to estimate the amount of money invested in cell therapy business. It is quite different from the drug development business. I think the combination of earning money in non-therapeutic business and doing R&D of cell therapy is reasonable to overcome the financial issue in the current situation.

In ReproCELL, three years ago we started some non-therapeutic businesses including human ES cell medium, stem cell related antibodies, clinical diagnostics related to transplantation, and recently have launched the QT prolongation assay service. In parallel, we have been continuing a research of cell therapy "Ex-vivo expansion of hematopoietic stem cell by a low molecular compound". Some stem cell companies have excellent technology especially in cell culture and differentiation that must become seeds of businesses. Stem cell business is not only a cell therapy but also research reagent, drug screening tool, and order-made medicine.

In addition, these non-therapeutic businesses should have a synergy effect on cell therapy. In our case, we have been developing the differentiation technology from ES cell to cardiomyocyte for QT prolongation business. However, if the differentiation technology is brushed up further, it could be applied for cell therapy in the future. I think the appropriate business model is the key for success in stem cell business.

Partnerships

Historically Asian research institutes have sought partnerships and collaborations with North American or European institutes or companies because West gives what Asians need-vast experience and in turn West gains from generous fundings and strong support of both the government and people in Asia and this makes job easier for both Western and Asian researchers.

India's Stempeutics has tied up with hospitals in Malaysia where it has a research center. Stempeutic's partnership with Manipal Hospital in Bangalore and a few other hospitals in both India and Malaysia have been successful and now the company is seeking partnerships from other hospitals in the Asia Pacific region.

Meanwhile, flushed with recent successes, Prof. Silviu Itescu says Mesoblast is in the process of finalizing commercial

partnerships both in the US and in Asia Pacific. Mesoblast's sister company in the US Angioblast has partnership with several companies in the cardiovascular space. "It is looking to expanding that partnership and bringing more partnership to the table," says Itescu.

Taiwan's Dr Lee says his research lab has tie ups with various research centers around the world, most importantly with Kings' College in London.

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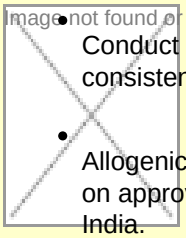

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Narayan Kulkarni & Sanjeev Jain