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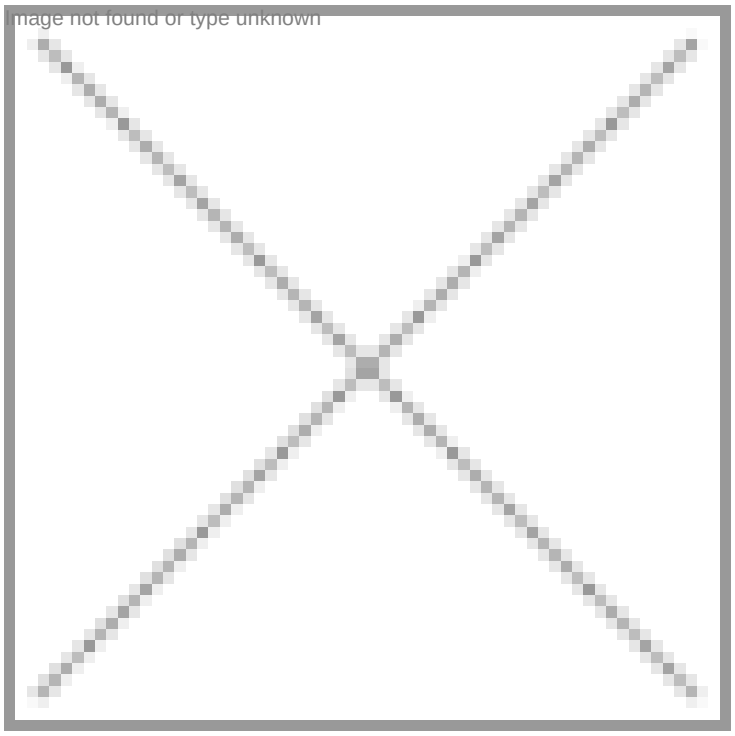

Paving way to commercialization of Mesenchymal Stem Cells

The business model of "Off-the-Shelf" products in the stem cells arena is slowly but steadily unfurling.

Dr Jyoti Kode
Dr Kode is Scientific Officer "E" at Chiplunkar Lab, Advanced Centre for Treatment, Research & Education in Cancer, Tata Memorial Centre, Navi Mumbai. Being immunologist and biotechnologist, she keeps herself updated with stem cell market trend and commercialization of cell-based products. She can be reached at jkode@actrec.gov.in

Various in vitro studies and studies in animal models have undermined the feasibility of transplanting Mesenchymal Stem Cells (MSC). Over a decade ago, Haynesworth et al successfully isolated, expanded human MSC and demonstrated a reliable in vivo bone-forming assay. Next step was to evaluate the safety, feasibility, and efficacy of transplanting "off-the-shelf" MSC for clinical trials. In vivo models have demonstrated that MSC can engraft into organs like liver, bone, lung and kidney. In a canine model, transplantation of autologous MSC with partially demineralized bone matrix restored bone defects and enhanced bone growth in non-weight-bearing gap. This combination provided an option for reconstructing bone defect while performing a cementless revision arthroplasty. These properties have led to the suggestion that MSC may have a role in tissue repair and regeneration.

Major setbacks

Some guidelines in the widespread clinical exploitation of MSC are being formulated by ISCT. One major problem is the lack of a commercial Good Manufacturing Practice licensed MSC product. There are no generally accepted assays of the potency of MSC, and the optimal route of MSC delivery must be defined for individual indications. The best MSC source, its purity and the optimal dose remain to be specified. Purity, also defined as the identification and presence of "contaminating" cell populations, is critical because the degree of contamination may affect both the biological effects observed as well as the potential side effects. Quantification of all of these factors will be required to obtain a reproducible and consistent cell preparation that could potentially be used in clinical studies. Safety issues are a concern, although injection of syngeneic, allogeneic and xenogeneic MSC into immunocompetent mice is tolerated without apparent side effects. Despite the heterogeneous nature of stromal progenitor cell populations, a consensus concerning the definition of MSC and Good Manufacturing Practice protocols are evolving.

Stem cell market

This is the dynamic area of biotechnology that is experiencing significant growth after monoclonal antibody therapeutics market. Investors are bullish on stem cell products that have application in treatment of diseases that cannot be cured by non-cell products. Adult stem cells market is the largest tapped market while cord blood and embryonic stem cell markets, though with huge market potential, are still in infancy stages. The US is the leader followed by the European and Asia-Pacific regions. With government regulations being amended in several countries, stem cell research is expected to pick up pace rapidly in the next few years. India is expected to have a market share of about $540 million with an annual growth rate of 15 percent. There are about 180 stem cell companies in the world. The market potential of this technology is so huge that revenues may be in excess of $10 billion by 2013 (www.StemCells.Net). The potential of stem cell research â€“ both medically and economically, is leading to huge investments by biotechnology companies, pharmaceutical companies and governments too.

Commercialization

Various biotechnological companies have developed patented formulations of adult stem cells and evaluated safety in Phase II/III clinical trials for treatment of acute GvHD, Crohn's disease, Type I diabetes, cardiac failure, long bone defect, non-healing wounds/burns etc. Their focus is to progress through clinical trials and international regulatory processes necessary to commercialize the technology in as short a timeframe as possible.

Osiris Thearpeutics Inc., Columbia, MD, USA (www.osiris.com) has developed "Prochymal" for treatment of patients with cardiac dysfunction, acute GvHD, Crohn's disease and Type I Diabetes. Osiris recently received contract by defense department, worth $224.7 million for development of Prochymal for treatment of Acute Radiation Syndrome.

Mesoblast (www.mesoblast.com) is an Australian biotechnology company committed to the development of novel treatments for orthopedic conditions. Mesoblast's high margin business model, allogeneic or "off-the-shelf", products is to develop clinical products using allogeneic or "off the shelf" adult stem cells. Consequently, Mesoblast's cells obtained from a single donor can be used to treat thousands of unrelated patients. This results in an efficient, highly reproducible product, with low manufacturing costs that can generate high margins akin to pharmaceutical sales. Equally as important, such "off-the-shelf" products will be available at hospitals for immediate use by orthopedic surgeons when the acute trauma or other injury needs rapid treatment.

Mesenchymal stem cells (MSC) are unspecialized cells that lack tissue specific characteristics and can maintain their undifferentiated phenotype. Minimal criteria for defining multipotent MSC, according to the International Society for Cellular Therapy (ISCT) are the ability to regenerate and differentiate into tissues of mesodermal origin (osteocytes, adipocytes and chondrocytes), and the absence of expression of haemopoietic molecules CD34 and CD45. Mesenchymal stem cells characteristically express SH2 (CD105) and SH4 (CD73) and Thy-1 (CD90) antigens. MSC can be derived from bone marrow, bone, fat and placenta. They can be easily isolated in culture and have high "ex-vivo" expansion ability. Therapeutically MSC are attractive because they do not require matching with recipients. They lack HLA-DR molecules, which make them immune-evasive, and moreover they are known to suppress innate and adaptive immune response. MSC have elicited a great clinical interest in form of allogeneic or "Off-The-Shelf" product or "universal donor cells", particularly in the areas of regenerative medicine and induction of tolerance in allogeneic transplantation.

Mesoblast Inc. has invested up to $17 million into US-based sister company Angioblast Systems Inc., NY, USA (www.angioblast.com). In alliance with Abbott, a global healthcare company (ww.abbott.com, investment of $5 million), Angioblast has entered into development and commercialization of catheter-based therapy of heart failure.

Harvest Technologies Corp. has announced BMAC System to treat patients with non-reconstructable critical limb ischemia at Shri Ramachandra Medical Center, a Harvard Medical international-associated institution based in Chennai, India (www.harvest-tech.com). Harvest's BMAC System is a device to harvest, process and deliver patient's own bone marrow stem cells all in the same procedure. The study is designed to treat patients suffering from advanced thromboangitis obliterans, commonly referred to as Buerger's Disease. The early clinical results have looked extremely promising. Gary Tureski, president of Harvest Technologies said. "When this study's data is combined with data from our ongoing multi-center FDA study in the US, these results will offer us the opportunity to demonstrate the potential for BMAC to be an effective treatment for Critical Limb Ischemia regardless of the underlying cause."

In flow with innovations in the anti-aging market, British biotechnology company Intercytex has announced the release of an injectable filler that is said to improve facial wrinkles. Intercytex has also recently created waves with the creation of artificial human skin ICX-SKN. The off-the-shelf skin replacement product is said to be revolutionary for patients affected by burns and skin damage, with the cosmetic implications beneficial for consumers who wish to avoid the painful process of skin grafts.

Cytori Therapeutics, San Diego, CA, USA (www.cytoritx.com) has successfully commenced marketing of Celution 800 system which provides patient's own adipose-derived tissue derived stem cells at the bedside. These cells are easier to extract compared to drilling hole for bone marrow. Moreover, the Celution System is a closed device that circumvents the need for GMP-clean room for cellular expansion/ manipulation and allows easy purification of stem cells at the point-of-care. The devices are now being sold into the growing international reconstructive surgery market for so-called cell-enhanced reconstruction. This product received distinct awards of year 2008 from two top-most organizations recognizing high potential of Celution 800 platform to dominate practice of regenerative medicine.

CJ CheilJedang (www.CJ.net), a healthcare company from South Korea has invested up to US$ 2.5 million in Neuralstem, Rockville, MD, USA (www.neuralstem.com) for commercializing stem cell products & technology.

Organogenesis Inc., Canton, MA, USA (www.organogenesis.com), with revenues of $55 million in 2007, is focused on skin regenerative medicine products. Its signature product "Apligraf" is used to treat patients with diabetic foot ulcers and venous leg ulcers.

Software companies too are exploiting market opportunities in stem cell therapeutics field by building software that help to ensure quality, regulatory compliance standards are met and integrated with established procedural protocols, monitoring manufacturing processes and documenting lot-to-lot traceability. The software StemLab also provides all the tools needed to comply with GMP and regulatory requirements for documentation of identity, purity and potency of products (www.stemsoft.com). This software is introduced to meet the need of researchers and clinicians involved in stem-cell based processing, manipulation & therapies.

Stem Cell Bioprocessing is being developed in the UK in partnership with system engineer, expert on bioreactors and cell encapsulation technologies for the successful transfer of laboratory-based practice of stem cells and tissue culture to the

clinic as therapeutics, through the application of engineering principles and practices. It aims to have products which are cost effective, rapid in outcome, robust, reliable and reproducible.

Based on studies conducted to date, the adult stem cell therapies provide a safer approach at curing and treating neurodegenerative diseases, cardiac failures, burns, bone defects, etc. than competitive therapies that rely on embryonic stem cells. This approach to stem cell therapeutics, using adult stem cells, eliminates the additional risk factor of teratoma formation that embryonic stem cell treatments face. It is expected that this will pave way to faster commercialization of MSC-based products than competitor stem cell products such as ES or iPS cells.

Co-author: Shayanti Mukherjee
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