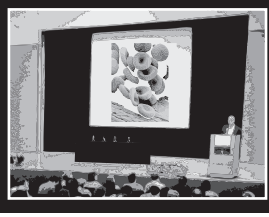

Conference Scene

Trends in the stem cells marketplace – report from Select Biosciences Stem Cells 2012 Conference

Select Biosciences Stem Cells 2012 Conference
San Diego, CA, USA, 2–3 February 2012

Select Biosciences hosted a three-track conference in San Diego (CA, USA) focusing on stem cells, circulating tumor cells and cell culture. In this article, I present a snapshot of selected presentations from the Stem Cells conference track and frame them in the big picture of the trajectory of this field and expectations for the coming years. This conference track focused on three themes: cellular therapy translational development and clinical trials in this space; biobanking; and stem cells in research, drug discovery and development. Even though all of the above segments of the stem cells marketplace are undergoing vigorous growth and expansion, perhaps the most vigorous growth exists in the translational research space, wherein various adult stem cell populations are being developed to address different important disease classes such as cardiovascular disease, CNS diseases, diabetes, HIV and various types of cancer, as well as macular degeneration and other disorders. This segment of the conference will be a key subject of this article.

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Cellular therapy translational development

Alan Trounson, California Institute of Regenerative Medicine (CIRM), presented a conference keynote entitled 'Companies in Translation with CIRM'. The goal of CIRM, which is financed by the State of California with US$3 billion, is to fund stem cell research that has a chance of moving through the preclinical stage into early clinical trials and will subsequently be partnered out to companies in this space. As of September 2011, CIRM has made awards (grants and loans) of $1.35 billion. According to Trounson, "Translation to the clinic is a challenging process that demands a team approach." Therefore, CIRM's funding is leveraged by biotechnology/pharmaceutical company cofunding, and this enables the research to be application-focused as well as targeted towards quickly being driven into clinical trials. The importance of engaging biotechnology and pharmaceutical companies early is for the following:

- Cofunding early clinical trials;
- Funding for expensive Phase III trials since CIRM will not be funding Phase III trials, financing from the industry community is critical;
- Expertise in clinical trial design, the regulatory landscape, manufacturing and reimbursement.

This strategic funding has so far led to 44 research projects in progress worth $360 million towards therapies for 26 diseases; this is the current report card for CIRM. CIRM is focused on translational and clinical programs for the following therapeutic classes using adult stem cells:

- Heart repair/cardiovascular disease
- HIV/AIDS
- Cancer

Using pluripotent stem cells, CIRM is focused on the following therapeutic classes:

- Stroke
- Type 1 diabetes
- Amyotrophic lateral sclerosis
- Macular degeneration

In summary, government and nontraditional sources of funding are important in emerging spaces such as stem cells in a difficult economic climate, and the goal of CIRM is to create a lasting footprint via financing of 12 state-of-the-art institutions and an induced pluripotent stem cell (iPSC) bank, as well as awarding large multidisciplinary grants and engaging with industry partners.

Hans Keirstead, University of California at Irvine (CA, USA), presented a keynote entitled 'Stem Cell-based Treatments for Clinical Application'. In this presentation, the focus was on the clinical parameters involved in the development of cellular therapies.As an example, Keirstead focused on spinal cord injury (SCI). The

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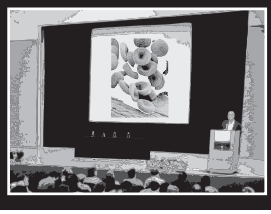
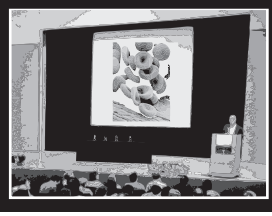


four pillars of a successful clinical trial are as follows: drug production, preclinical efficacy, preclinical safety and clinical synopsis. In the subacute SCI space, Keirstead worked with Geron Corporation (CA, USA) to develop differentiation protocols for the production of high-purity oligodendrocyte precursor preparations (hOPCs) from human embryonic stem cells. The cells were prepared under cGMP conditions to be used for transplantation for thoracic SCIs. Conditioned media from hOPC preparations induced axon branching *in vitro*, as well as neuronal survival *in vitro*, suggesting a mode of action of these cells *in vivo* via secretion of growth factors and other cytokines *in situ* at the site of injury. In preclinical studies, transplantation of hOPCs into cervical SCI animal models demonstrated that the cells survived *in situ*, tissue was spared and there was demonstrable functional recovery. Indeed, the number of axons was much higher in transplanted animals as compared with controls, and these observations led to the filing of the investigational new drug by Geron Corporation with the US FDA to commence a Phase I trial of hOPCs in SCI patients. In the first cohort of patients in this Phase I clinical trial, safety was demonstrated, and since the FDA imposed a strict regulation of this trial due to the origin of the hOPCs being human embryonic stem cells, they required a 15-year patient follow-up. With stringent inclusion criteria for this clinical trial, very few patients were capable of fitting these criteria, and the difficult recruitment and cost of this trial became a factor in Geron's decision to drop their stem cell program. These data are consistent with the need to choose therapeutic areas in the stem cell space with sustainable growing market opportunity and standards of care that are sufficiently low, wherein stem cell therapy can make a measurable impact both on the quality of life of the patients and in economic terms.

Casey Case, SanBio (CA, USA), presented a talk entitled 'Gene-Modified MSCs for Stable Stroke: Pre-Clinical and Early Clinical Development'. SanBio is developing gene-modified mesenchymal stem cells (MSCs) for stable stroke patients. The cells are bone marrow-derived MSCs that have been transfected with the *Notch* gene and are delivered via stereotactic surgery into the peri-infarct area of the brain. Case stated that from 120 ml of bone marrow, approximately 1000 doses of cryopreserved finished product are generated. In terms of the mechanism of action *in vivo*, the cells function via a combination of trophic factor secretion, extracellular matrix generation and blocking inflammatory effects. Indeed, *in vitro* experiments have shown that these transfected MSCs secreted growth factors that support primary neurons. SanBio is currently running a Phase I clinical trial utilizing these cells in an 18-patient stroke trial focusing primarily on safety of the cells, but also as a secondary end point, focusing on the clinical efficacy of these cells as assessed by functional improvement of the patients.

Robert Deans, Athersys (OH, USA), presented a talk entitled 'Adherent Adult Stem Cell Therapy for Ischemic Injury in the Heart and Brain'. Athersys is championing the development of bone marrow-derived adult stem cells termed MultiStem™ as a means for mediating cellular therapy in acute myocardial infarction (AMI) model systems. In pig AMI model systems, MultiStem has been shown to increase ejection fraction and reduce scar size. Currently, Athersys is conducting clinical trials to demonstrate the safety and efficacy of MultiStem delivered via a catheter *in situ* to the areas of the infarcted heart in AMI.

Alain Chapel, 'Prolifération et Différentiation des cellules souches' at the Centre de Recherches Paris Saint-Antoine (France), presented a talk entitled 'Stem Cell Therapy for the Treatment of Radiation-induced Normal Tissue Damage'. The focus of this talk was on the use of adult stem cells for radiological burns, which have an unpredictable evolution with successive inflammatory waves. These researchers established a proof-of-concept demonstration of the therapeutic efficacy of MSCs in treating radiological burn patients. MSCs migrate to the damaged tissues following a severe multiorgan injury such as a radiological burn. Human MSCs are preferentially found in areas of the body that have received the highest irradiation dose. Local irradiation induces not only homing of human MSCs at exposed sites, but also promotes their widespread



engraftment to multiple organs. MSCs circulate around and integrate into tissues. Chapel also presented data showing successful treatment of accidental radiation burns by local administration of autologous MSCs combined with an autologous epidermal graft. According to Chapel, this is the first therapeutic approach for radiological burns in humans using MSCs. MSCs also induce structural and functional regeneration of the small intestine after irradiation and were shown to enhance the proliferating process of intestinal stem cells, most probably via a paracrine effect *in situ*. Taken together, these data reinforce the high regenerative potential of MSCs in a number of different therapeutic classes.

Stem cells in research, drug discovery & development

Robert Halliwell, University of the Pacific (CA, USA), presented a talk entitled 'Neurophysiological Studies of Ion Channels and Receptors Expressed in Neurons Derived from Stem Cells'. This research group is focusing on human embryonal carcinoma (EC)-derived stem cells as a model system, since these cells are pluripotent with an enhanced ability to form neurons and glial-like cells. Retinoic acid induces the differentiation of these ECs into neurons. Halliwell and colleagues utilized human ECs for toxicity screening assays utilizing patch-clamp recordings from cells. They demonstrated the presence of voltage-activated currents in human stem cell-derived neurons and showed that both sodium and potassium channels are expressed by stem cell-derived neurons. Furthermore, these researchers showed that ligand-gated ion channels are expressed by these EC-derived neurons. GABA induces concentration-dependent chloride currents in human EC-derived neurons. Also, glutamate (which represents a cation channel) elicits currents in neurons derived from human ECs. Current work is focused on the evaluation of human EC-derived neurons as a model system for evaluating the neurotoxicity of drug-like compounds.

Paul Burridge, Stanford University School of Medicine (CA, USA), presented a talk entitled 'Efficient Cardiac Differentiation of Human Induced Pluripotent Stem Cells: Development of Tools for Cardiotoxicity Testing'. These researchers generated integration-free iPSCs using an episonal method. In this manner, they reprogrammed $CD34^+$ hematopoietic progenitors to iPSCs and subsequently converted these iPSCs into cardiomyocytes, which have the ability to beat in culture, demonstrate electrophysiological responses and exhibit drug responsiveness.

Steven Sheridan, Massachusetts General Hospital/Harvard Medical School (MA, USA), presented a talk entitled 'Epigenetic Characterization of the *FMR1* Gene and Aberrant Neurodevelopment in Human

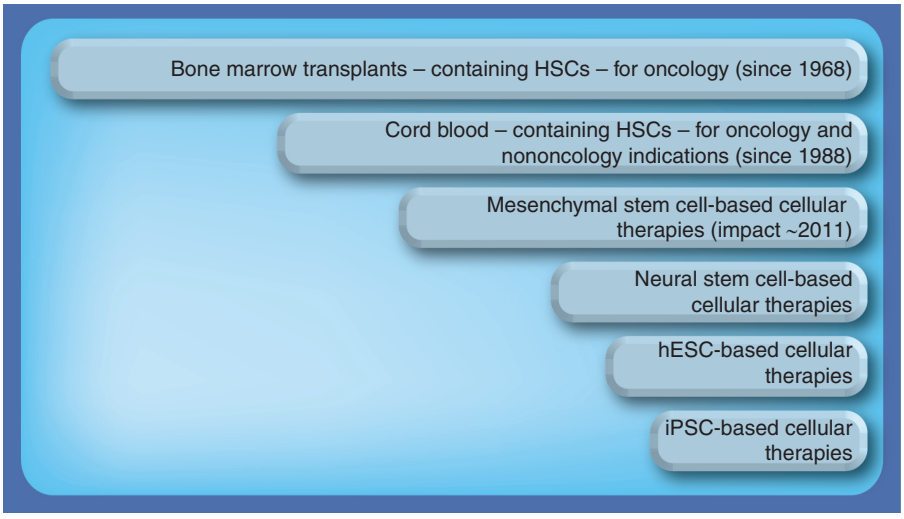
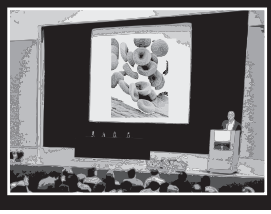


Figure 1. The waves of cellular therapy over more than 40 years. This continuum frames the broader cellular therapy-based marketplace.
hESC: Human embryonic stem cell; HSC: Hematopoietic stem cell; iPSC: Induced pluripotent stem cell.



Induced Pluripotent Stem Cell Models of Fragile X Syndrome'. Sheridan utilized iPSC methodology to model the fragile X syndrome. Specifically, these researchers generated iPSC models of fragile X syndrome, isolated self-renewing CNS neural progenitor cells from iPSCs and demonstrated aberrant neural differentiation from fragile X syndrome iPSC-derived neural progenitor cells. In summary, stem cells provide a way to link basic research on brain plasticity to the clinical setting.

Summary & future perspective

This conference focused on cutting-edge topics in the stem cell space, spanning basic research through to translational research and clinical development. The research efforts in the stem cell field are expanding and a number of clinical trials are being conducted, focusing primarily on adult stem cells in a variety of therapeutic areas. We expect that these trials will yield approved products to be launched into the marketplace over the course of this decade.

Cellular therapy is not new, it has more than a 40-year operating history, starting with bone marrow transplantation for hematological diseases. The 'current wave' of cellular therapy (as shown in Figure 1) is the development of new types of stem cells in a broad array of disease classes that can be addressed using cell-based approaches, thereby enabling the full potential of regenerative medicine to be realized.

Financial & competing interests disclosure

E Razvi works with a number of companies commercializing technologies for stem cell research, and also produces market analysis reports on stem cells and other topic areas in addition to conducting market research and custom consulting for companies worldwide. ***The author has no other relevant affiliations*** *or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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