Industry Update

Latest developments in stem cell research and regenerative medicine

Latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from nonacademic institutions from 1 November 2011 until 31 December 2011.

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Business Development

■ Collaborations, partnerships & alliances

Codevelopment agreement:

Ikotech, Techshot & University of Pittsburgh

The US Army Medical Research and Materiel Command (<https://mrmc-www.army.mil>) selected the companies Ikotech LLC (www.ikotech.com) and Techshot, Inc. (www.techshot.com), both based in IN, USA, for a US\$730,000 contract to develop technology that improves the collection of stem cells from adult adipose tissue. Ikotech is working to adapt Quadrasep™, their high-throughput multi-parameter magnetic cell-sorting instrument designed for clinical-grade cell sorting, for this application. Quadrasep will allow users to isolate specific subsets of stem cells in collected adipose tissue samples. Improved selectivity in stem cells will hopefully improve the outcomes for patients because existing methods are limited in their ability to purify cells. Ikotech will oversee adaptation and commercialization of the Quadrasep technology for this new application. Techshot will design and build the new equipment, which will be tested by researchers in the Adipose Stem Cell Center at the University of Pittsburgh's McGowan Institute for Regenerative Medicine (www.mirm.pitt.edu/ascc).

Collaborative agreement:

GE Healthcare & University of California San Francisco

GE Healthcare (www.gehealthcare.com) and University of California San Francisco, CA, USA (www.ucsf.edu) have begun a

unique 3-year collaboration to screen for chemical compounds that can be added to the stem cells and progenitor cells in cord blood to increase their population. The US\$841,000 project is funded by a Discovery Grant awarded by the University of California's Office of the President, along with matching funds from GE Healthcare.

Collaborative agreement: VistaGen & University Health Network

VistaGen Therapeutics, Inc., CA, USA (www.vistagen.com) and the University Health Network (UHN), ON, Canada (www.uhn.ca) have expanded and extended their existing collaborative pluripotent stem cell research and development program through to September 2017. In 2007, VistaGen and UHN agreed to combine UHN's human pluripotent stem cell biology expertise with VistaGen's proprietary Human Clinical Trials in a Test Tube™ stem cell technology platform. The platform delivers clinically relevant indications of how humans will respond to new drug candidates early in the drug development process. The amended UHN agreement includes five key programs that will further support VistaGen's core drug rescue initiatives and potential cell therapy applications. Research conducted at UHN and VistaGen laboratories will include the development of stem cell-based drug discovery and drug rescue technologies, using mature cardiac, liver, pancreatic β -islet, blood and cartilage cells. The program will also focus on large-scale production of these cell types, each derived from human induced pluripotent stem (iPS) cells,

which are potentially suitable for *in vivo* transplantation studies and cell therapy applications. Additionally, VistaGen and UHN scientists plan to further enhance current methods used to produce cell types derived from both human embryonic stem (hES) cells and iPS cells. The research alliance also aims to establish preclinical proof-of-concept for the use of iPS cell-derived articular chondrocytes for cell therapy repair and regeneration of autologous cartilage, as well as the use of iPS cell-derived precursor cells to produce lymphocytes, granulocytic cells, red blood cells and blood platelets.

■ Launching new projects, products & services

RNL & Yanda

RNL BIO (www.rnl.co.kr), a South Korean adult stem cell firm, has opened the Stem Cell Medical Center in Yanda International Medical Research Institute (www.yandaco.com/en/1), Beijing, China. The facility occupies 3865 m² and has a capacity to store stem cells from 20,000 patients. RNL will be responsible for stem cell storage in the current GMP facility and management of medical treatment, whereas Yanda Group will be administering clinical research and treatment of patients.

■ Achievements

Cryo-Save

The Netherlands-based stem cell bank Cryo-Save (www.cryo-save.com) announced the storage of its 200,000th sample.

National Marrow Donor Program

The National Marrow Donor Program, MN, USA (<http://marrow.org>), which facilitated its first marrow transplant between an unrelated donor and patient 25 years ago, marked a major milestone by facilitating its 50,000th transplant. The Program operates the Be The Match Registry®, the world's largest and most diverse registry of potential marrow donors and umbilical cord blood units, serving patients with life-threatening diseases, such as leukemia and lymphoma.

The nonprofit organization matches patients with donors, educates healthcare professionals and conducts research.

Roslin Cells

Roslin Cells, Ltd., UK (www.roslinecells.com) has moved to the new Scottish Centre for Regenerative Medicine at Edinburgh BioQuarter (www.edinburghbioquarter.com). This is a major watershed in the company's development, enabling it to colocate with the University of Edinburgh's Medical Research Council (MRC) Centre for Regenerative Medicine (www.crm.ed.ac.uk) and to operate its 1000 m² current GMP cell-processing facility in conjunction with the Scottish National Blood Transfusion Service (www.scotblood.co.uk).

The GMP facility is state of the art for cell therapy manufacture in Europe. With seven clean rooms as well as associated quality-control laboratories, it will enable Roslin Cells to play a leading role in the translation of stem cell biology to new cellular therapies. In the coming months, the company's development program will expand rapidly to encompass the wide variety of cell types being used in cell therapy and to build on the company's collaborations with the UK science base and, in particular, the research underway at the MRC Centre for Regenerative Medicine.

■ Advancements

Lentigen & University Hospital Case Medical Center

University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, OH, USA (www.uhhospitals.org) and Lentigen, Corp., MD, USA (www.lentigen.com) initiated a novel Phase I clinical trial of Lentigen's LG631 gene therapy for the protection of hematopoietic stem cells from the dose-limiting toxicity of chemotherapy with Temodar® (www.temodar.com; www.rxlist.com/temodar-drug.htm). Approximately 17,000 Americans are diagnosed with glioblastoma every year and only 2% survive longer than 5 years, even with aggressive treatment. Glioblastoma multiforme treatment generally begins with a surgical resection, followed by radiation therapy and then

chemotherapy to destroy any remaining cancer cells. Temodar (temozolomide) is a standard treatment of glioblastoma, but dose-limiting bone marrow toxicity often accompanies such therapy. In this first-of-its-kind study, researchers are investigating if LG631 can potentially improve the tolerance and effectiveness of chemotherapy for glioblastoma multiforme by preventing damage to bone marrow. The study will evaluate the safety of this treatment and its potential to enhance current glioblastoma multiforme treatments. For this study, hematopoietic stem cells will be isolated from participating patients, transduced with LG631 (an altered DNA-repair human *MGMT* gene) to make them resistant to Temodar, and then infused back into the patient. The lentiviral vector LG631, specially designed by Lentigen, will be used to deliver the gene specifically to bone marrow stem cells that are susceptible to damage by drugs commonly used to treat cancer, thereby enabling patients to receive higher doses of Temodar with fewer severe side effects.

ReproCell

ReproCell, Japan (www.reprocell.net) negotiated worldwide rights to commercialize a human iPS cell-derived hepatocyte drug-screening technology developed by the firm in collaboration with Japan's National Institute of Biomedical Innovation (www.nibio.go.jp). The organizations have been working together since the beginning of the year to establish an *in vitro* screening platform for hepatic toxicity and liver metabolism that uses iPS cell-derived hepatocytes. ReproCell says the collaboration has led to the development of hepatocytes that express primary liver cell levels of active metabolizing enzymes. The firm is currently evaluating the system in partnership with pharmaceutical companies and expects to launch the platform commercially during the second quarter 2012.

RIKEN

A clinical study into the use of laboratory-grown retina cells to treat age-related macular degeneration has been slated for fiscal year 2013, Japanese news agency Kyodo reported. The project might be

the world's first to use iPS cells for the treatment of human diseases. The Center for Developmental Biology of RIKEN (www.cdb.riken.jp/en/index.html) will report its plan to the health ministry in fiscal year 2012. The study will initially

target several patients with the eye disease whose vision cannot be sufficiently restored through existing medication. It will then be expanded to include earlier-stage patients provided the safety of the iPS cell treatment can be determined.

Clinical Trials

■ Pluristem

Pluristem Therapeutics, Inc., Israel (www.pluristem.com) announced positive 12-month data from its Phase I open-label, dose-escalation clinical trials conducted under protocols approved by the US FDA (www.fda.gov) in the USA and the Paul-Ehrlich-Institute (www.pei.de) in Germany. Placental expanded peripheral artery disease (PLX-PAD) cells met all the clinical studies' protocol end points (tumorigenesis, adverse events, immunological reactions, laboratory and ECG), demonstrating a safe immunologic profile

at all dosage levels and was found to be potentially effective in treating patients suffering from critical limb ischemia. No clinical evidence of adverse events or toxicities related to the intramuscular administration of PLX-PAD cells was observed in 26 of 27 patients. Only one patient in the US trial experienced a transient local cutaneous inflammation after PLX-PAD was administered. A transient change was noted in the leukocyte and lymphocyte counts in the patients, which returned to pre-injection baseline levels within 7 days and without evidence of absolute lymphopenia.

Additionally, five of the 27 patients received a double dose of PLX-PAD cells from the same placental batch 2 weeks apart without evidence of adverse events. Based on the above data, it was concluded that there were no significant safety issues, and PLX-PAD cells can be safely given intramuscularly to patients without matching, even if the patients are dosed twice from the same placental source. Additional information about this clinical trial can also be found at www.clinicaltrials.gov (ID: NCT00951210 for the USA-based trial and NCT00919958 for the Germany-based trial).

Regulations, Approvals & Acquisitions

■ Regulations

India

India has put in place the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). This 12-member committee "reviews all controversial and ethically sensitive stem cell research proposals" to "oversee, monitor and make policies on stem cell use in India." NAC-SCRT examines scientific, technical, ethical, legal and social issues involving hES cell research. All institutions and investigators carrying out research on human stem cells will have to be registered with NAC-SCRT through an Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). All research studies and clinical trials will have to have prior approval of IC-SCRT for permissive

research and of NAC-SCRT for restricted research. All new stem lines created and all established cell lines from any source, imported or created in India, will also have to be registered with IC-SCRT and NAC-SCRT. The permissible areas of research include *in vitro* studies on established cell lines from any type of stem cells – hES cells, human embryonic germ cells, human somatic stem cells or fetal adult stem cells – provided they are registered with IC-SCRT. hES cells can be isolated from 'spare' embryos from fertility clinics – those leftover from reproductive attempts via *in vitro* fertilization – and be used only for research and are in the 'restricted category' according to guidelines prepared by the Indian Council of Medical Research (<http://icmr.nic.in>) to provide

ethical direction to scientists working in the field [1].

■ Green light

New York Blood Center

The FDA approved HemaCord™ on 10 November 2011, the first licensed hematopoietic progenitor cell–cord cell therapy. HemaCord is indicated for use in hematopoietic stem cell transplantation procedures in patients with disorders affecting the hematopoietic system. In an effort to assist manufacturers in applying for licensure for certain cord blood units, FDA issued the 2009 guidance document entitled 'Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for

Specified Indications' [2]. FDA instituted a 2-year phase-in period for hematopoietic progenitor cell–cord cell manufacturers to submit either a license application or an investigational new drug application. That phase-in period ended 20 October 2011, and these manufacturers must now submit such applications. Approval of HemaCord was based on the reliance on safety and effectiveness data submitted to a public docket and data submitted in the license application demonstrating compliance with other regulatory requirements. This is the first approval of a license application for cord blood. HemaCord has a boxed warning regarding the risks of graft-versus-host disease, engraftment syndrome, graft failure and infusion reactions, each of which may be fatal. Patients who receive HemaCord should be monitored carefully. A risk–benefit assessment, unit selection and administration of HemaCord should be carried out under the direction of a physician experienced in hematopoietic stem cell transplantation. HemaCord is manufactured by the

New York Blood Center, Inc., NY, USA (<http://nybloodcenter.org>).

Stempeutics

Bangalore-based company Stempeutics (www.stempeutics.com) obtained approval from the Drug Controller General of India to start multicenter Phase I/II combined double-blind randomized allogeneic clinical trials on its drug candidate Stempeucel™ in patients with critical limb ischemia and acute myocardial infarction. This is the first allogeneic stem cell clinical trial to be approved in India. In addition, Stempeutics recently obtained approval for Phase II clinical trials for four indications: chronic obstructive pulmonary disease, liver cirrhosis, osteoarthritis and diabetes mellitus. In Malaysia, Stempeutics received governmental agency approval for cerebral stroke and osteoarthritis Phase I/II clinical trials. The company is in the process of devising cell-based medicine through a patented technique that uses mesenchymal stem cells taken from a healthy donor's bone marrow for the production of approximately 20,000 units of a potential medicine.

Stempeutics is not alone in the stem cell arena in India. The country's clinical trial registry indicates that there are over 40 stem cell-related clinical trials going on in over two dozens hospitals across the country. In addition to the efforts of individual hospital-based researchers, there is contract research on behalf of overseas firms and trials being carried out by a few other Indian companies.

■ Red light

UK National Stem Cell Network

UK National Stem Cell Network (www.uknscn.org) ceased operations on 31 December 2011 due to lack of continuous financial support from the UK Research Councils, which have funded the Network since 2006. Since its inception, the Network has played an important role in building a UK-wide research community in stem cell research. Its e-mail correspondence list stands at approximately 2600 individuals, covering diverse stakeholders: academics (of many disciplines), industrialists, charities, learned societies, professional associations, lawyers, venture capitalists, regulatory bodies, journalists, members of parliament and government and Research Council officials.

Capital Market & Finances

■ Athersys

Athersys, Inc., OH, USA (www.athersys.com) has entered into a Common Stock Purchase Agreement with Aspire Capital Fund, LLC, IL, USA (<http://aspirecapital.com>), whereby Aspire Capital has committed to purchase up to US\$20 million of Athersys' common stock in multiple transactions over the next 2 years at a modest discount to the then-prevailing market price. At closing, Aspire Capital purchased 666,667 shares of common stock for US\$1.50 per share, which adds to its current holdings in the Company, acquired through participation in the financing completed in February 2011.

On the same day, Athersys announced the termination of its collaboration

with Angiotech Pharmaceuticals, Inc., BC, Canada (www.angiotech.com) to codevelop cell therapy in the cardiovascular field. In connection with the mutual termination, Athersys has regained all rights in its MultiStem® cardiovascular program.

■ Azelon

Azelon Pharmaceuticals, formerly Zelos Therapeutics, PA, USA (www.azelon.com) secured US\$4.5 million from Prospect Venture Partners, CA, USA (www.prospectventures.com) in Series A financing to support a Phase II study of nasal spray teriparatide ZT-034 (PTH1-34) for the treatment of osteoporosis. The nasal spray ZT-034 is being developed as an alternative

to Eli Lilly, IN, USA (www.lilly.com) and Azelon's Forteo®, which is teriparatide for subcutaneous delivery (www.forteo.com; www.rxlist.com/forteo-drug.htm).

■ Azellon

Azellon Cell Therapeutics, Ltd, the University of Bristol, UK, spinout company (www.azellon-ltd.com), has completed a US\$1 million (£0.65 million) funding round and can now take its Cell Bandage™ technology, an alternative to meniscectomy, to human clinical trials. The Phase I/IIa trial approved by the Medicines and Healthcare Products Regulatory Agency (www.mhra.gov.uk) will treat ten meniscal tear patients with a cell bandage product, seeded with the patient's own stem cells. The trial will

be undertaken at Southmead Hospital in Bristol and is scheduled to begin in May 2012, with interim data available within 18 months.

■ California Institute for Regenerative Medicine

California Institute for Regenerative Medicine (www.cirm.ca.gov) is planning US\$30 million funding for creating a stem cells bank. It will consist of three parts. First will be awards to investigators to collect tissue samples from individuals with genetic diseases. The goal is to collect samples from 1200 people. Next, California Institute for Regenerative Medicine will give a single award to an organization that will take those samples and reprogram them into iPS cells. These cells can then be matured into the cell type that goes awry in the disease as a way of studying that disease. Finally, California Institute for Regenerative Medicine will fund a group to bank all of these newly created cells, along with other stem cell lines. With this resource, that same researcher hoping to study autism cell lines could go to one place, navigate one materials transfer agreement and receive cells that are consistently quality-controlled. The cells will be available to researchers in California and worldwide.

■ Geron

Geron Corp. (www.geron.com) announced discontinuation of its stem cell programs and is seeking partners for these novel assets. Discontinuation of the stem cell program also resulted in closing the highly publicized GRNOPC1 trial for spinal cord injury against further enrollment (www.clinicaltrials.gov; ID:

NCT01217008). The decision to narrow Geron's technology and therapeutic focus was made after a strategic review of the costs, value inflection timelines and clinical, manufacturing and regulatory complexities associated with the company's research and clinical-stage assets. With this decision, Geron is eliminating 66 full-time positions, representing 38% of its workforce. As a result, the company expects one-time monetary expenditures of approximately US\$5 million in the fourth quarter of 2011 and approximately US\$3 million in the first half of 2012. Geron expects to end 2011 with funds and investments in excess of US\$150 million.

■ Juvenile Diabetes Research Foundation & ViaCyte

NY, USA-based Juvenile Diabetes Research Foundation (www.jdrf.org) announced its support of a pioneering diabetes research program that is developing a first-of-its-kind cell therapy for Type 1 diabetes and other forms of insulin-dependent diabetes. The therapy is a combination product that packages immature cells made from hES cells that, over time, develop into mature pancreatic hormone-producing (proislet) cells, including insulin-producing cells. The research is an important step towards producing an unlimited source of insulin-producing cells that could serve as replacements for those destroyed in both Type 1 and insulin-dependent Type 2 diabetes. The diabetes program is being funded by Juvenile Diabetes Research Foundation, the largest charitable funder of Type 1 diabetes research in the world, the California Institute for Regenerative Medicine

(www.cirm.ca.gov) and ViaCyte, CA, USA (www.viacyte.com).

Ongoing research of this combination product in rodents has demonstrated that within 2–3 months of implantation, the immature human pancreatic hormone cells mature into functional pancreatic hormone-producing cells, including functional insulin-producing cells that can regulate blood glucose.

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The author has no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Websites

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