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 2012 until 31 December 2012.

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Business Development

■ Collaborations, partnerships & alliances

Partnership agreement: EMD Millipore & Sistemic

EMD Millipore (www.emdmillipore.com), the Life Science division of Merck, Germany (www.merckgroup.com), announced a new initiative with Sistemic, UK (www.sistemic.co.uk), a provider of miRNA-based problem-solving services and kit-based products. The two companies are jointly developing a proprietary monitoring methodology utilizing Sistemic's miRNA marker detection capability to enable consistent growth of stem cells in EMD Millipore's Mobius® CellReady platform. These markers could also be incorporated into a commercially available kit for quality control of stem cells in culture.

Partnership agreement: GE Healthcare & CDI

GE Healthcare Life Sciences, UK (www.gelifesciences.com), has licensed Cellular Dynamics International, WI, USA (www.cellulardynamics.com), to develop, manufacture and sell cellular assays and models derived from human induced pluripotent stem (iPS) cells for use in drug discovery and toxicity screening. The agreement follows the recent announcement that GE Healthcare has expanded its license with Geron, CA, USA (www.geron.com), to obtain exclusive global rights to Geron's intellectual property and know-how for the development and sale of cellular assays derived from iPS cells. Financial terms were not disclosed.

Partnership agreement: HumanZyme & PacificGMP

HumanZyme, IL, USA (www.humanzyme.com), and PacificGMP, CA, USA (www.pacificgmp.com), entered into a partnership to manufacture clinical-grade human growth factors and cytokines. The goal is to provide a source of these proteins to regenerative medicine developers to differentiate stem cells into cell types that will be used to treat various diseases or injuries. HumanZyme brings its HumanKine® growth factor and cytokine product line to the partnership with PacificGMP, which has experience in manufacturing GMP-certified recombinant human proteins intended for human clinical use.

Partnership agreement: Organovo & Autodesk

Organovo, CA, USA (www.organovo.com), have partnered with Autodesk Research, ON, Canada (www.autodeskresearch.com), to develop 3D bioprinting software. The software, which will be used to control Organovo's NovoGen MMX Bioprinter™, has the potential to open up bioprinting to a broader group of users.

■ Launching new projects, products & services

BioTime

BioTime, CA, USA (www.biotimeinc.com) and its subsidiary LifeMap Sciences (www.lifemapsc.com), have announced the launch of LifeMap BioReagents™ (http://bioreagents.lifemapsc.com), a new portal offering researchers access to BioTime's research product lines including

Regenerative Medicine

PureStem™ human progenitor cell lines, PureStem packages, clinical- and research-grade human embryonic stem (hES) cell lines, HyStem® hydrogels, culture media and cell differentiation kits. The company also launched LifeMap Discovery™ (http://discovery.lifemapsc.com), a roadmap of embryonic development and stem cell biology. The platform integrates embryonic development and stem cell biology with molecular, cellular, anatomical and disease-related information, and provides data-mining capabilities and bioinformatics applications.

GE Healthcare

GE Healthcare Life Sciences (www.gelifesciences.com) opened a new US$4.87 million (£3 million) cell science laboratory in Cardiff, UK. The investment creates a world-class facility for research and technology innovation in cell science, to help advance the rapidly emerging fields of cell therapy and cell bioprocessing, and to support the development of new, more effective and safer cell-based medicines. The new laboratories will employ 43 scientists and technical support staff.

Healthpoint

Healthpoint Biotherapeutics, TX, USA (www.healthpointbio.com), introduced a 5 × 7 cm size of OASIS® Ultra Tri-Layer Matrix, a naturally derived extracellular matrix material formed from three layers of porcine small intestinal submucosa designed to provide increased structure for difficult-to-heal and chronic wounds.

Irvine Scientific

Irvine Scientific, CA, USA (www.irvinesci.com), launched the cell therapy PRIME-XV™ product portfolio as part of the company's commitment to accelerate basic research and clinical applications in cell therapy and regenerative medicine. PRIME-XV products include: a recombinant human matrix protein MatrIS F, intended for the culture of human stem/progenitor cells under serum-free conditions; mesenchymal stem cell (MSC) serum-free medium, specifically designed for the culture of primary human MSCs derived from bone marrow and adipose tissues; and a defined protein-free hypothermic biopreservation solution, intended for storage and stable shipping of cells and tissue samples under hypothermic conditions (2–8°C).

ReproCELL

ReproCell (www.reprocell.com/en), a Japanese stem cell technology company, is opening its first branch and US office in Boston (MA, USA). The new office currently employs three people, with plans to hire an additional nine employees by 2016.

Roche

Roche, Switzerland (www.roche.com), and the Innovative Medicines Initiative (www.imi.europa.eu), a joint undertaking between the EU and the European Federation of Pharmaceutical Industries and Associations (www.efpia.eu), launched StemBANCC, a new academic–industry partnership that unites ten pharmaceutical companies and 23 academic institutions. Initiated and coordinated by Roche and managed by Oxford University (UK), StemBANCC aims to use human iPS cells as research tools for drug discovery with the goal of using this new technology to develop human disease models and enhance drug development. The project is backed by US$34.3 million (€26 million) from the Innovative Medicines Initiative and US$27.7 million (€21 million) of 'in-kind' contributions from the European pharmaceutical industry. Over 5 years, it will derive three iPS cell lines from skin and blood samples taken from 500 patients that it hopes to enroll in the project. The StemBANCC project will focus on peripheral nervous system disorders (especially pain), CNS disorders (dementias), neurodysfunctional diseases (migraine, autism, schizophrenia and bipolar disorder) and diabetes. It will make these cells available to other researchers, and use them within the project to develop new tools for drug development.

StemCells

StemCells, CA, USA (www.stemcellsinc.com), has partnered with R Biomedical, UK (www.rbiomedical.com), to develop and commercialize a range of cell lines and reagents to facilitate human iPS cell-based research for regenerative medicine applications. The first product under the partnership, an 'ultraprimary' human fibroblast cell line from which researchers can generate iPS cell lines, was launched on 30 October 2012, under StemCells' Proven® brand (www.scproven.com).

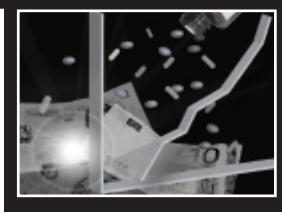
WiCell & Agilent

Agilent Technologies, CA, USA (www.agilent.com), and WiCell, WI, USA (www.wicell.org), announced that WiCell is now offering comparative genomic hybridization (CGH) plus single nucleotide polymorphism (SNP) microarray analysis using the Agilent SurePrint G3Human Genome CGH + SNP microarray. Unlike previous assays that required performing CGH and SNP separately, the CGH + SNP microarray detects copy number changes by both SNP and CGH, and simultaneously delivers copy-neutral change information such as loss or absence of heterozygosity. The assay maintains the high resolution quality achieved with CGH-only microarrays, using probes that have been carefully optimized and validated for maximal sensitivity and specificity. Additional information about WiCell's CGH + SNP microarray service can be found at www.wicell.org/cytogenetics.

Achievements

Advanced Cell Technology

In the Christmas and New Year special issue, science and technology weekly magazine *New Scientist* (www.newscientist.com) named the iPS cell-derived human platelet program from Advanced Cell Technology, MA, USA (www.advancedcell.com), one of the 'Ten Ideas That Will Shape The Year'. Since platelets do not have nuclei they cannot form tumors, which could make them ideal for the first iPS cell clinical trial. The long-term goal of the pioneering trial of iPS cell-derived cells is to provide blood platelets to people undergoing cancer therapy, who need platelet transfusions to repair damaged tissues and prevent uncontrolled bleeding. Initially, however, platelets grown from iPS cells will be given to healthy volunteers to ensure that the cells are well tolerated before moving on to people with cancer and other blood-related conditions.



AxoGen

AxoGen, FL, USA (www.axogeninc.com), the regenerative medicine company dedicated to advancing the science and commercialization of peripheral nerve repair solutions, announced publication of new clinical results for the use of Avance® Nerve Graft for repair of peripheral nerve injuries in the upper extremity [1]. The article included outcomes data for 51 peripheral nerve repairs across 12 leading US surgical institutions (including level 1 trauma, academic, military and community centers, as well as ambulatory surgery centers). Outcomes were reported for surgical repairs performed on ulnar, median and digital nerves with nerve tissue gaps ranging from 5 to 50 mm in length. Repairs of 5–14 mm in length demonstrated 100% meaningful recovery, 15–29 mm 74% meaningful recovery and 30–50 mm 90% meaningful recovery. The publication is based on the upper extremity nerve injury subgroup of the RANGER® study, which the company believes is the largest multicenter, multisurgeon study focused on the treatment of peripheral nerve discontinuities. Initiated in 2007, RANGER tracks outcomes in contemporary clinical practice from the use of Avance Nerve Graft, the only nerve allograft processed using the Avance Processing Technique. Previously, results from the RANGER study demonstrated that across all nerve injury locations and gap lengths, 87% of those repaired using Avance Nerve Graft reported meaningful recovery [2]. Additional information about the RANGER clinical trial can be found at www.clinicaltrials.gov (ID: NCT01526681).

Cytori

Cytori Therapeutics, CA, USA (www.cytori.com), announced publication of a peer-reviewed case series using Cytori's Celution® system [3]. Three patients suffering from long-standing complex cryptogland ular fistula *in ano* were treated using fat grafts enriched with their own adipose-derived stem and regenerative cells, processed using Cytori's Celution system. The stem cell-enriched graft was injected directly into the tissue surrounding the fistula to close the fistula track. The interior opening of the fistula was closed with a mucosal advancement flap. All three patients remain fully healed at 2–3-year follow-up, with one patient undergoing colostomy reversal to restore bowel continuity.

VistaGen

VistaGen Therapeutics, CA, USA (www.vistagen.com), a biotechnology company applying stem cell technology for drug rescue, predictive toxicology and drug metabolism screening, announced a significant advance in its development of LiverSafe 3D™, a human liver cell-based bioassay system designed to predict liver toxicity and drug metabolism issues in connection with the company's drug rescue activities.

VistaGen's LiverSafe 3D, together with optimized culture protocols and without the need for any purification, is now capable of producing differentiated populations of cells containing greater than 70% albumin-positive human hepatocytes, and greater than 40% of these hepatocytes express the mature CYP3A4 drug-metabolizing enzyme. CYP3A4 is a crucial enzyme in adult liver functions and widely viewed as an important functional marker for adult stem cell-derived hepatocytes. This enzyme is responsible for metabolizing over 50% of the drugs approved by the US FDA. After purification, nearly 90% of LiverSafe 3D hepatocytes expressed the CYP3A4 enzyme.

Clinical Trials

Advanced Cell Technology

Advanced Cell Technology, MA, USA (www.advancedcell.com), completed the second patient cohort in the company's US and European clinical trials for Stargardt's macular dystrophy and age-related macular degeneration using hES cell-derived retinal pigment epithelial cells. The patients were injected with 100,000 cells, as compared with 50,000 cells in the first cohort. The outpatient transplantation surgeries were performed successfully and the patients are recovering uneventfully. Further information about the company's clinical trials for macular dystrophy is available at www.clinicaltrials.gov (ID: NCT01469832, NCT01345006 and NCT01344993). The company is eagerly anticipating proceeding to the third, 150,000-cell patient cohort.

Avita

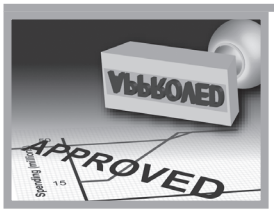
Avita Medical, UK (www.avitamedical.com), has initiated a multicenter randomized control study on the use of ReCell® Spray-On Skin® in the treatment of venous leg ulcers. Up to five European centers from countries including the UK, Germany, France and Denmark will participate in the study. The study will enroll 65 participants. The control group will receive standard care (debridement, cleansing) and Profore® multilayer compression therapy (replacing the wound contact layer with Telfa™ Clear). The ReCell group will receive ReCell in addition to care received by the control group as described. Additional information about the clinical trial can be found at www.clinicaltrials.gov (ID: NCT01743053).

Fate Therapeutics

Fate Therapeutics, CA, USA (www.fatetherapeutics.com), initiated a randomized, controlled, Phase II multicenter study of its investigational hematopoietic stem cell therapy, ProHema™, in adult patients undergoing double umbilical cord blood transplantation for hematologic malignancy. ProHema is produced through a proprietary, 2-h, *ex vivo* modulation process, which has been shown to significantly activate key biological pathways involved in hematopoietic stem cell homing, proliferation and survival in preclinical models. The Phase II study is expected to enroll at least 45 adult patients. Patients will be randomized, with a ratio of 2:1, to receive either ProHema plus an unmanipulated cord blood unit or two unmanipulated cord blood units. The study will evaluate time to neutrophil and platelet recovery, incidence of serious infections and graft-versus-host disease, 100-day mortality and relative dominance of ProHema over the unmanipulated cord in contributing to reconstitution. Additional information about the clinical trial can be found at www.clinicalTrials.gov (ID: NCT01627314).

Gamida

Gamida Cell, Israel (www.gamida-cell.com), enrolled the first patient in its pilot study of NiCord® as an investigational treatment for sickle cell disease, at Duke University, NC, USA. NiCord is an expanded cell graft derived from an entire unit of umbilical cord blood and enriched with stem cells. NiCord was developed based on Gamida Cell's proprietary technology. Ten patients, aged 2–21 years, will be enrolled in the NiCord study, a single-center, single-arm trial evaluating the safety and efficacy of transplanting NiCord together with a second unmanipulated cord blood unit in patients with sickle cell disease following myeloablative therapy. The study will also assess transplant-related mortality, event-free survival and overall survival at 100, 180 and 365 days, respectively. Additional information about the clinical trial can be found at www.clinicalTrials.gov (ID: NCT01590628).



Regulations, Approvals & Acquisitions

Green light

Cardio3 BioSciences

The Belgian biotechnology company, Cardio3 BioSciences (C3BS; Belgium) (www.c3bs.com), has received authorization from the Belgian Federal Agency for Medicines and Health Products (www.fagg-afmps.be/en) to begin its Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) European Phase III trial for C3BS-CQR-1 in Belgium. This represents a world premiere for a regenerative medicine product targeting heart failure to be tested in the context of a Phase III trial. This Phase III trial builds on the successful outcome of the Phase II trial conducted between 2009 and 2010 in multiple clinical sites in Belgium, Serbia and Switzerland. C3BS-CQR-1 consists of a patient's own cells that are harvested from the patient's bone marrow and engineered to become new heart muscle cells that behave identically to those lost to heart disease. Cardio3 BioSciences has also developed C-Cathez®, an injection catheter for delivery of biotherapeutic agents into the myocardium.

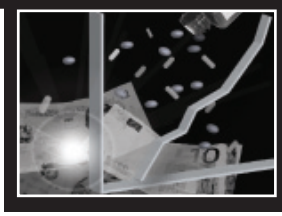
Living Cell Technologies

Living Cell Technologies (LCT), based in New Zealand and Australia (www.lctglobal.com), has received ethical approval for its planned New Zealand Phase I trial of its NTCELL® treatment candidate in Parkinson's disease. The open-label safety and efficacy study will involve four patients who have been diagnosed with Parkinson's for at least 4 years. The NTCELL treatment involves transplanting choral plexus cells from Auckland Island pigs into a patient's brain, with the aim of helping the brain repair damaged nerve tissue and protecting it from further damage. Cells are encapsulated with proprietary Immupel™ microcapsule technology to prevent the immune system from rejecting them as foreign.

NTCELL will be codeveloped with Otsuka Pharmaceutical Factory, Japan (www.otsukakj.jp/en), for the treatment of Parkinson's disease and other neurological disorders. LCT will receive an upfront payment of US$3.11 million (AU$3 million) within 30 days of signing. In addition, Otsuka will fund all development costs, estimated at US$2.08 million (AU$2 million), to complete the previously announced Phase I trial of NTCELL in Parkinson's disease. LCT will receive a further milestone payment of US$2.08 million (AU$2 million) when the first patient in the Phase I Parkinson's trial has been safely implanted with NTCELL. This is expected to occur in the second quarter of 2013. In return, LCT has granted Otsuka an exclusive option to jointly develop and commercialize NTCELL in Parkinson's and other neurological diseases, including hearing loss, through Diatranz Otsuka, the 50:50 joint venture formed between LCT and Otsuka.

Mesoblast

Mesoblast, Australia (www.mesoblast.com), has reached agreement with the FDA on the manufacturing process to supply its proprietary mesenchymal precursor cells for Phase III clinical trials. In addition, it has established with the FDA a clear pathway for commercial manufacturing supply of its cell therapy products.



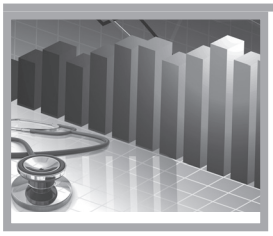
Opexa

Opexa Therapeutics, TX, USA (www.opexatherapeutics.com), announced that Health Canada (www.hc-sc.gc.ca) has approved the Company's Clinical Trial Application for Tcelna™, a novel T-cell therapy for multiple sclerosis. The application was filed with the Biologics and Genetic Therapies Directorate. With this approval by the Canadian Health Authority, Opexa expects to expand its ongoing clinical trial in secondary progressive multiple sclerosis patients to include several sites in Canada. The Abili-T trial, which is a Phase IIb study of Tcelna in subjects with secondary progressive multiple sclerosis, is currently enrolling patients in the USA. To date, over half of the clinical sites have been initiated and approximately 10% of subjects have been enrolled. The trial is expected to enroll 180 patients in approximately 30 sites in the USA and Canada and conclude in 2015. Additional information about the clinical trial can be found at www.clinicaltrials.gov (ID: NCT01684761).

Acquisitions

Smith & Nephew & Healthpoint

Smith & Nephew, UK (www.smith-nephew.com), has signed an agreement to acquire substantially all of the assets of Healthpoint Biotherapeutics, TX, USA (www.healthpointbio.com), for US$782 million in cash. Healthpoint Biotherapeutics, founded in 1992, has been focused on biopharmaceutical leadership in acute, chronic and burn-related wound care over the last several years. The company has driven impressive growth in its commercial platform, led by sales of Collagenase Santyl® ointment, and is developing a novel cell therapy, HP802-247, a spray formulation of allogeneic neonatal keratinocytes and fibroblasts, which completed a successful Phase IIb in 2011 [4] and for which a North American Phase III trial was initiated in September 2012.



Capital Market & Finances

BioTime

BioTime, CA, USA (www.biotimeinc.com), and its recently formed subsidiary BioTime Acquisition Corporation (BAC) have jointly entered into a nonbinding letter of intent (LOI) for a US$10 million investment from a private investor to provide financing for the recently announced proposed acquisition of Geron's stem cell assets by BAC. Under the terms outlined in the LOI, the investor will invest US$5 million in BioTime by purchasing 1.35 million BioTime common shares at a purchase price of approximately US$3.70 per share, and warrants to purchase 650,000 additional BioTime common shares with an exercise price of US$5 per share and a 3-year term. In addition, the investor will contribute US$5 million in cash to BAC in exchange for shares of BAC common stock that, upon issuance, will represent approximately 7% of the BAC common stock then issued and outstanding, plus warrants to purchase approximately 350,000 additional shares of BAC common stock at an exercise price of US$5 per share, with a 3-year term.

In related news, BioTime and BAC have jointly entered into a nonbinding LOI with Geron Corporation, CA, USA (www.geron.com). The LOI contains broad terms of a potential transaction through which Geron would contribute to BAC its intellectual property and other assets related to Geron's discontinued hES cell programs. BioTime would contribute US$5 million in cash, US$30 million of BioTime common shares, warrants to purchase 8 million common shares of BioTime at a prespecified price, rights to use certain hES cell lines and minority stakes in two of BioTime's subsidiaries to BAC. In addition, a private investor would invest US$5 million in cash in BAC. Following consummation of the potential transaction, Geron stockholders would receive shares representing 21.4% of the common stock of BAC, as well as warrants to purchase 8 million shares of BioTime common stock at a prespecified price. BioTime would own approximately 71.6%, and a private investor would own approximately 7.0% of the outstanding BAC common stock for their US$5 million investment. BioTime would also receive warrants that would enable it to increase its ownership in BAC by approximately 2%, which would reduce the Geron stockholders' ownership in BAC to 19.2%. BAC would also be committed to pay royalties to Geron on the sale of products that are commercialized in reliance upon Geron patents acquired by BAC. The LOI is not a binding agreement to complete the transaction. Consummation of the transaction is necessarily subject to entering into a definitive agreement between the parties containing terms and conditions yet to be negotiated.

BrainStorm

BrainStorm Cell Therapeutics, Israel (www.brainstorm-cell.com), was awarded a US$800,000 (3 million NIS) grant from Israel's Office of the Chief Scientist for the year 2013. The grant is intended to support BrainStorm's research and development program for its proprietary NurOwn™ technology for the propagation and differentiation of autologous MSCs into neurotrophic factor-secreting cells. Following the award, BrainStrom has signed an agreement with Octane Biotech,

ON, Canada (www.octaneco.com), to jointly develop a proprietary bioreactor for production of the NurOwn stem cell therapy candidate.

Cytori

Cytori, CA, USA (www.cytori.com), announced the sale of 7,020,000 shares of its common stock in an underwritten public offering at a price of US$2.85 per share to the public. The net offering proceeds to Cytori from the sale of the shares are expected to be approximately US$18.5 million, after deducting underwriting discounts and commissions and other estimated offering expenses, but excluding any exercise of the underwriters' overallotment option. Cytori anticipates using the net proceeds from this offering for general corporate purposes, including the continued development, manufacture, marketing and sale of its Celution System family of products, including related research and clinical trials, and other related research and development, sales and marketing, and general administrative expenses, working capital, capital expenditures and future acquisitions.

Kiadis

Kiadis Pharma, The Netherlands (http://kiadis.com), has raised US$13.22 million (€10 million) in an equity financing round. The financing will enable Kiadis Pharma to perform a confirmatory multicenter Phase II proof-of-concept study with its lead product ATIR™, and to prepare a pivotal Phase II/III study. ATIR is administered as an adjunctive treatment on top of a haploidentical stem cell transplantation, with the goal of enhancing early immune reconstitution without causing graft-versus-host disease.

Financial & competing interests disclosure

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.

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