Latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from nonacademic institutions from March 1, 2014 until April 30, 2014

Business Development

Collaborations, partnerships & alliances

Collaboration agreement: NeoStem & Harvard

NeoStem (NY, USA; www.neostem.com) has entered into sponsored research collaboration with Massachusetts Eye and Ear/Schepens Eye Research Institute, an affiliate of Harvard Medical School (MA, USA; www.schepens.harvard.edu). The objective of the research is to investigate the role of very small embryonic-like stem cells (VSELsTM), as well as CD34⁺ cells, in a study that will compare the efficacy of these two cell types for retinal repair.

Licensing agreement: TiGenix & Sobi

TiGenix (Belgium; www.tigenix.com) has licensed the marketing and distribution of ChondroCelect[®], the cell-based medicinal product for the repair of cartilage defects of the knee, to the international specialty healthcare company dedicated to rare diseases, Swedish Orphan Biovitrum AB (www.sobi.com). ChondroCelect was the first cell-based product to be approved in Europe. It is currently available for patients and reimbursed in Belgium, The Netherlands and Spain. Sales of ChondroCelect in 2013 were US\$5.76 (EU€4.3) million, a growth of 25% on a like-for-like basis over 2012. Sobi will continue to market and distribute the product where it is currently available and has also acquired the exclusive rights to expand the product's availability to patients in multiple additional territories, including the rest of the EU, Norway, Switzerland, Turkey and Russia, plus the countries of the Middle East and North Africa. TiGenix will receive a royalty of 22% of the net sales of ChondroCelect in the first year of the agreement, and 20% of

the net sales of ChondroCelect thereafter. There will be no upfront or milestone payments. The agreement took effect on June 1, 2014, and has a duration of 10 years.

Launching new projects, products & services

Catapult

The Cell Therapy Catapult (UK; <https://ct.catapult.org.uk>) is to manage the new UK Cell Therapy Manufacturing Centre. The center, which is expected to open in 2016/17, will provide vital large-scale manufacturing facilities, helping the country to retain manufacturing activity, attract inward investment and boost exports. The first such UK facility will have US\$93 (GB£55) million of funding from 2014/15. Analysis by the Cell Therapy Catapult and others has shown that the UK's small-scale academic facilities are an excellent source of materials for early-stage clinical trials. However, it is expected that this capacity will be full within 3–6 years as the industry's pipeline matures. The Cell Therapy Manufacturing Centre provides the UK with the manufacturing facilities needed for later studies and commercialization, promoting retention of domestic expertise and jobs. It is expected to create up to 100 jobs. Forecasts indicate that firms using the Cell Therapy Manufacturing Centre will generate US\$2 (GB£1.2) billion of revenue by 2020 (80% via export).

Cook Medical

Cook Medical (IN, USA; www.cookmedical.com) introduced StemulateTM Pooled Human Platelet Lysate cell culture media supplement. Stemulate provides researchers and cell therapy companies a cell expansion

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alternative to fetal bovine serum. Stemulate supports the expansion of multiple types of cells *in vitro*, including endothelial colony forming cells, fibroblasts and mesenchymal stem cells (MSCs) from a variety of tissue sources.

Dendreon

Dendreon (WA, USA; www.dendreon.com) plans to make PROVENGE® (autologous peripheral blood mononuclear cells activated with PAP-GM-CSF or sipuleucel-T) available in Europe, beginning with Germany and the UK. PAP-GM-CSF consists of prostatic acid phosphatase (PAP), an antigen expressed in more than 95% excellence using its contract manufacturing organization, PharmaCell. Centers of Excellence are institutions where a high volume of prostate cancer patients is treated by leading prostate cancer experts.

RTI Surgical

RTI Surgical (FL, USA; www.rtisurgical.com) launched two new biological solutions: NanOss® Bio-active 3D, a synthetic 3D bioscaffold that supports bone formation, and map3™ Cellular Allogeneic Bone Graft, an implant that contains the three essential elements needed to generate and maintain new bone (www.map3.com). Map3 chips allograft is comprised of cortical cancellous chips, demineralized bone matrix and viable adult stem cells based on the multipotent adult progenitor (MAPC®) cell technology.

Shiseido

Shiseido (Japan; www.shiseido.com) opened the Shiseido Cell-Processing and Expansion Center (SPEC). The center, located in the Kobe Biomedical Innovation Cluster in Kobe, Japan, will centralize research and development on hair regenerative medicine with an aim toward commercialization.

Achievements

Advanced Cell Technology

Advanced Cell Technology (MA, USA; www.advancedcell.com) and its collaborators have discovered a new method to generate a potent and replenishable

population of MSCs from pluripotent stem cells [1]. This new and proprietary population of pluripotent stem cell-derived MSCs display potent immunomodulatory and therapeutic properties and has a greater than 30,000-fold proliferative capacity, relative to ordinary bone-marrow-derived MSCs, the most commonly used source for MSCs in clinical trials.

Fate

Fate Therapeutics (CA, USA; <http://fatetherapeutics.com>) demonstrated high-throughput derivation of human-induced pluripotent stem cells (hiPSCs) that exhibit characteristics necessary for therapeutic application [2]. The publication describes the use of the Company's hiPSC platform, consisting of stage-specific cell culture systems, to enable rapid, parallel derivation of hiPSC clones and their subsequent expansion as transgene-free, single cells in culture. The company's proprietary combinations of small molecule modulators, which include ROCK, GSK3 and MEK pathway inhibitors, used in the culture systems were found to be critical in promoting characteristics of the ground state of pluripotency including pluripotent culture stability, homogeneity and survival. Earlier this year, the Fate scientists reported the efficient differentiation of hiPSCs to a homogeneous population of skeletal muscle cells using the company's proprietary hiPSC platform [3]. In support of the company's muscle regeneration therapeutic program, Fate scientists sourced fibroblasts from healthy volunteers, as well as from patients with Duchenne and Becker muscular dystrophies, reprogrammed the fibroblasts to hiPSCs, and then differentiated the hiPSCs to muscle myoblasts with extremely high efficiency. The hiPSC-derived skeletal muscle cells closely resembled primary muscle cells, and were functionally responsive to treatment with the hypertrophic proteins IGF-1 and WNT7A. Fate Therapeutics is currently developing proprietary WNT7A protein analogs for the treatment of muscle-related diseases and disorders. In addition, the company is currently researching therapeutic applications of hiPSC-derived myogenic progenitor cells and hematopoietic cells.

Clinical Trials

Athersys

Athersys (OH, USA; www.athersys.com) announced interim results from the Phase II clinical study of the administration of Athersys' MultiStem® cell therapy to treatment refractory ulcerative colitis patients being conducted by Pfizer (NY, USA; www.pfizer.com). The study results demonstrate favorable safety and

tolerability for MultiStem through 8 weeks following treatment. However, the cell therapy failed to show meaningful benefit, following a single administration, in patients suffering from chronic, moderate-to-severe ulcerative colitis who have failed other therapies. These results reflect patient data 8 weeks following cell therapy or placebo administration and include the

primary efficacy end points for the study. Additional 16-week results, including data about the impact from a second round of dosing for a subset of patients, longer term secondary clinical end points and biomarker evaluation, will be available after additional analysis has been completed. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT01240915).

Bioheart

Bioheart (FL, USA; www.bioheartinc.com) released 6-month data from its Phase I ANGEL trial. Fully funded by Bioheart, the trial is being conducted in Mexico at the Hospital Angeles in conjunction with the Regenerative Medicine Institute. At the 6-month time point, patients are demonstrating an average improvement in exercise capacity or a 6-min walk test of approximately 68 m as compared to an average improvement of 47 m at 3 months. In total, 80% of the patients showed an improvement in their exercise capacity 3–6 months post stem cell injection. Another end point in the study is ejection fraction by echocardiogram. At the 3-month time point, 100% of the patients demonstrated either improvement or stayed the same. The Phase I clinical trial for tumor stem cell-specific dendritic cell therapy for hepatocellular carcinoma is an open-label single-center trial conducted with Shanghai's PLA 85 Hospital, one of China's largest liver disease centers.

In unrelated press release, Bioheart announced that it will enroll up to 100 patients in a new study for chronic obstructive pulmonary disease to determine the safety and efficacy of adipose-derived stem cell (ADSC)-based product AdipoCell™. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT02041000).

Capricor

Capricor Therapeutics (CA, USA; www.capricor.com) presented positive data demonstrating that the Phase I portion of the company's ALLSTAR Phase I/II trial met its primary end point of safety. Based on these data, the NIH Data and Safety Monitoring Board has approved the advancement of CAP-1002 to the double-blinded, randomized, placebo-controlled Phase II cohort of the ALLSTAR clinical trial, which is currently underway and actively enrolling patients. CAP-1002, allogeneic-cardiosphere-derived stem cells, was introduced directly into a heart via infusion into a coronary artery using standard cardiac catheterization techniques in patients who have suffered a myocardial infarction. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT01458405).

CBMG

Cellular Biomedicine Group (CA, USA; www.cell-biomedgroup.com) announced positive results from its Phase I clinical trial, which evaluated the safety of tumor stem cell-specific dendritic cell therapy for hepatocellular carcinoma, the most common type of liver cancer. The last patient in the trial received treatment in December 2013, and a 2-month follow-up and clinical observation has been completed and data have been analyzed for all patients. Safety data to date from the trial have shown no adverse events related to the injection site; a few mild, transient adverse events related to the therapy, which were mitigated with drug treatment; one serious adverse event, which was deemed by the investigators to be pretreatment tumor recurrence; and no laboratory abnormalities.

Cytori

Cytori Therapeutics (CA, USA; www.cytori.com) announced the first investigator-initiated study evaluating Cytori Cell Therapy as a potential concomitant treatment for anterior cruciate ligament injury. Internationally, Cytori Cell Therapy has been evaluated in several investigator-initiated pilot studies during the past 2 years involving professional and amateur athletes with acute and chronic muscle injuries. The goal of these studies is to further the understanding of the potential utility of ADSCs in sports and orthopedic conditions.

In an unrelated press release, Cytori announced publication of safety and efficacy data from a 36-month European clinical trial in patients with chronic ischemic heart failure. Final data from the Company's PRECISE trial, a 27-patient, prospective, randomized, double-blind, placebo-controlled, feasibility trial (Phase I/IIa), demonstrated statistically significant differences in cardiac functional capacity between treated and placebo groups [4]. Metabolic equivalents and maximal oxygen consumption values were preserved over time in ADSC-treated patients but declined significantly in the control group. ADSC-treated patients showed significant improvements in total left ventricular mass by cardiac MRI and wall motion score index. Single-photon emission computed tomography results suggested a reduction in inducible ischemia in ADSC-treated patients up to 18 months. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT00426868).

Regenerative Sciences

Regenerative Sciences (CO, USA; www.regenexx.com) started a new clinical research study on the use of autologous stem cells for treating knee osteoarthritis. The primary objective of this study is to evaluate the

efficacy of Regenexx™ SD compared to exercise therapy at 3 months. Historical comparison will be made to total knee arthroplasty for treatment of knee osteo-

arthritis at 1 and 2 years. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT02034032).

Regulations, Approvals & Acquisitions

Green light

BrainStorm

BrainStorm Cell Therapeutics (Israel; www.brainstorm-cell.com) has received US FDA approval to start Phase II clinical trial of its adult stem cell treatment for patients with amyotrophic lateral sclerosis. The trial will be launched initially at Massachusetts General Hospital in Boston and the University of Massachusetts Memorial Hospital in Worcester. Dana-Farber Cancer Institute's Connell O'Reilly Cell Manipulation Core Facility will manufacture BrainStorm's NurOwn™ cells for these two clinical sites. The trial will also be conducted at the Mayo Clinic in Rochester.

CardioCell

CardioCell (CA, USA; www.stemcardiowell.com), a subsidiary of Stemedica Cell Technologies (CA, USA; www.stemedica.com) has just received the FDA's investigational new drug approval for a US-based, Phase IIa clinical study using its allogeneic stem-cell therapy to treat subjects with chronic heart failure of nonischemic etiology. Further information about the clinical trials is available at <http://clinicaltrials.gov> (ID: NCT02123706).

Neuralstem

The Institutional Review Board of the University of California, San Diego, School of Medicine has approved the Phase I safety trial to treat chronic spinal cord injury with Neuralstem's (MD, USA; www.neuralstem.com) spinal cord derived NSI-566 neural stem cells. The trial will enroll patients with thoracic spinal cord injuries (T2–T12) who have an American Spinal Injury Association Impairment Scale A level of impairment, between 1 and 2 years after injury. American Spinal Injury Association Impairment Scale A impairment, which is complete paralysis, refers to a patient with no motor or sensory function in the relevant segments at and below the injury. The trial, which already has FDA approval, has a 1-year completion goal. Further information about the clinical trials is available at <http://clinicaltrials.gov> (ID: NCT01772810).

Northwest Biotherapeutics

Northwest Biotherapeutics (MD, USA; www.nwbio.com) has received approval from the Paul Ehrlich Institute (Germany; www.pei.de/EN/home/node.html) of

a 'Hospital Exemption' early access program, under Section 4b of the German Drug Law, for its DCVax® personalized immune therapies for solid tumor cancers. Under this Hospital Exemption, the company may provide DCVax-L to patients for the treatment of any glioma brain cancers (both glioblastoma multiforme and lower grade gliomas), both newly diagnosed and recurrent, outside of the company's clinical trial and charge full price. The patients may be from Germany or elsewhere. This approval has a term of 5 years, and can be re-applied for and re-issued at the end of that period. Patients, physicians and others who would like to make inquiries about the program may do so using the following email addresses: patients@nwbio.com, physicians@nwbio.com, investors@nwbio.com and media@nwbio.com. DCVax-L is the first product of its kind to receive hospital exemption from the German regulator.

Pluristem

The FDA has reviewed Pluristem's (Israel; www.pluristem.com) comparability studies of its PLacental eXpanded (PLX) cell products and granted approval for the company to manufacture these products in its new commercial-scale cell manufacturing facility in which Pluristem has implemented its proprietary, fully automated 3D cell expansion manufacturing platform that uses its patented high-throughput culturing technologies, 3D bioreactors and downstream equipment. Pluristem's facility, located in MATAM industrial park, in Haifa, and equipped with 500 m² of clean rooms, has the ability to efficiently produce approximately 150,000 doses of PLX cells annually, with batch-to-batch consistency, which potentially translates into significant economic value. The new manufacturing facility has also received the EU's Qualified Person Declaration, which means that Pluristem's manufacturing and cell expansion operations were deemed compliant with EU GMP requirements.

ReNeuron

ReNeuron (UK; www.reneuron.com) has been given final UK regulatory and ethical clearance to start two new clinical trials assessing stem-cell therapies in stroke and critical limb ischemia. The UK group said the green light has been given to kick off a Phase II clinical

trial in stroke disability, recruiting up to 41 patients and treating 8–12 weeks poststroke, which is thought to be the optimum treatment window for efficacy. The trial will assess ReN001, an investigational therapy for disabled stroke patients, at National Health Service hospital trusts throughout the UK, monitoring a number of validated stroke efficacy measures up to 6 months post-treatment. The study is expected to read out by the end of 2015. A separate Phase I trial is designed to investigate ReN009 in critical limb ischemia, a common condition in patients with diabetes that can lead to amputation of the affected limb. In preclinical studies, ReN009 therapy has shown the potential to restore sufficient blood flow in the affected lower limb to avoid amputation, and the associated health consequences. This dose-escalation trial will be carried out through National Health Service Tayside at Ninewells Hospital and Medical School, Dundee, Scotland, with patients to be monitored for up to 12 months to assess the treatment's safety and tolerability. Assuming a good short-term safety profile for ReN009 at its highest dose, ReNeuron expects to file for approval to start a Phase II efficacy study during the first half of 2015. Further information about the clinical trials is available at <http://clinicaltrials.gov> (ID: NCT02117635 and NCT01916369).

Acquisitions

Aastrom & CTRM

Aastrom Biosciences (MI, USA; www.aastrom.com) has entered into a definitive agreement to acquire Sanofi's (France; <http://en.sanofi.com>) Cell Therapy and Regenerative Medicine (CTRM) business for a

purchase price of US\$6.5 million, with US\$4 million payable in cash at closing and US\$2.5 million payable in the form of a promissory note. Through the CTRM acquisition, Aastrom is acquiring global commercial rights to three marketed autologous cell therapy products. Carticel® (autologous cultured chondrocytes) is an autologous chondrocyte implant currently marketed in the USA for the treatment of articular cartilage defects. Epicel® (cultured epidermal autografts) is a permanent skin replacement for full thickness burns greater than or equal to 30% of total body surface area, and is marketed in countries around the world. MACI® (matrix-induced autologous chondrocyte implant) is a third-generation autologous chondrocyte implant product currently marketed in the EU. Revenues of those three products were estimated to be US\$44 million in 2013. Aastrom will also acquire global manufacturing and production centers located in the USA and Denmark.

NeoStem & California Stem Cell

NeoStem (NY, USA; www.neostem.com) has entered into a definitive agreement to acquire California Stem Cell (CA, USA; www.californiastemcell.com) in a stock-and-cash deal that could total more than US\$124 million. California Stem Cell has received FDA approval to commence a Phase III trial, granted Special Protocol Assessment and Fast Track designation, assessing the efficacy of its own autologous cancer immunotherapy Melapuldencel-T in patients with late-stage metastatic melanoma. Further information about the clinical trial is available at <http://clinicaltrials.gov> (ID: NCT01875653).

Capital Market & Finances

Akron

Akron Biotech (FL, USA; www.akronbiotech.com) was awarded a Phase I Small Business Innovative Research Award from the NIH to develop enzyme-based formulations for the isolation of stem cells from various tissues. The Phase I project proposes an alternative to develop and use optimal formulations of a family of novel engineered enzymes capable of catalyzing the degradation of virtually all extracellular matrix components, with the goal of liberating viable stem cells with good and stable proliferative capabilities.

EMD Millipore

EMD Millipore (MA, USA; www.emdmillipore.com), the Life Science division of Merck (Germany; www.merck.com), has received a US\$400,000 grant from the Massachusetts Life Sciences Center (MA, USA;

www.masslifesciences.com) to fund a partnership with Promethera Biosciences (Belgium; www.promethera.com). Through this collaboration, EMD Millipore's microfluidic technology will enable the researchers at Promethera to mimic the liver microenvironment long-term, allowing for increased consistency and scale-up potential for live cell models. Using liver stem cells provided by Promethera and EMD Millipore's CellASIC® microfluidic cell culture platform, both organizations strive toward improved preclinical liver toxicity testing methods. Current methods for liver toxicity testing are limited by technical challenges that the CellASIC platform can address.

Pluristem

Pluristem's (Israel; www.pluristem.com) wholly owned subsidiary Pluristem Therapeutics has received approval

for a 14.6 million New Israeli Shekel (US\$4.2 million) grant from the Office of the Chief Scientist (OCS; www.economy.gov.il/CmsTamat/Rsrc/MadaanEnglish/MadaanEnglish.html) within the Israeli Ministry of Economy for its operations in 2014. According to the OCS grant terms, Pluristem Ltd is required to pay royalties in the rate of 3–5% on sales of products and services derived from technology developed using this and other OCS grants until 100% of the dollar-linked grants' amount plus interest are repaid. In the absence of such sales, no payment is required.

SynGen

SynGen (CA, USA; www.syngeninc.com), a medical device company with a 510(k) approved bench-top system for isolating stem cells from umbilical cord blood, peripheral blood and bone marrow, has received a US\$2.5 million from GE Capital, Healthcare

Financial Services (MD, USA; www.gehealthcarefinance.com), to support its commercialization efforts. With in-depth industry knowledge and expertise, GE Capital, Healthcare Financial Services has provided more than US\$65 billion in financing over 10 years to companies in 45 healthcare sectors including senior housing, hospitals, medical offices, outpatient services, pharmaceuticals and medical devices.

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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