Industry Update

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Regenerative Medicine

Latest developments in the field of stem cell research and regenerative medicine compiled from publicly available information and press releases from non-academic institutions from May 1, 2014 until June 30, 2014

# Business Development

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## Collaborations, partnerships & alliances

### Collaboration agreement: Adaptimmune & GSK

Adaptimmune (UK; www.adaptimmune.com) has entered into a strategic collaboration and licensing agreement with GlaxoSmithKline (GSK; PA, USA; www.gsk.com) for the development and commercialization of its lead clinical cancer program. Using its unique T-cell receptor (TCR) engineering technology, Adaptimmune has created TCRs that are deployed to target the cancer testis antigen, NY-ESO-1, and other targets. The trials in the NY-ESO-1 program in multiple myeloma, melanoma, sarcoma and ovarian cancer in the USA are generating encouraging results, with European trials set to commence shortly, and it has a pipeline of follow-on programs. Under the terms of the agreement, Adaptimmune will codevelop its NY-ESO-1 clinical program and associated manufacturing optimization working together with GSK. GSK will have an option on the NY-ESO-1 program through clinical proof of concept, anticipated during 2016, and, on exercise, will assume full responsibility for the program. The companies will also codevelop other TCR target programs and collaborate on further optimization of engineered TCR products. According to the agreed development plan, the deal could yield payments in excess of US$350 million to Adaptimmune over the next 7 years, with significant additional development and commercialization payments becoming due in subsequent years if GSK exercises all its options and milestones continue to be met. In addition, Adaptimmune would also receive tiered royalties ranging from single to double digits on net sales.

### Collaboration agreement: BioRestorative & Pfizer

BioRestorative Therapies (FL, USA; www.biorestorative.com) has entered into a 2-year collaborative research agreement with Pfizer (NY, USA; www.pfizer.com). The companies will jointly conduct a study titled 'Development and Validation of a Human Brown Adipose Cell Model', which will seek to further characterize the identity and metabolic function of these cell lines. BioRestorative has accumulated a large collection of human brown adipose tissue samples, preadipocyte cell lines and immortalized cell lines for use in potentially developing a cell therapy product. The results of the research may be used by both companies.

### Collaboration agreement: Cellectis & Accelera

Cellectis (France; www.cellectis.com) signed an agreement with Accelera (Italy; www.accelera.info), the preclinical contract research organization within the Nerviano Medical Sciences Group (Italy; www.nervianoms.com/en), to complete the preclinical studies of Cellectis' advanced product candidate, UCART19 (for Universal Chimeric Antigen Receptor – T cells). Engineered allogeneic CD19 T cells currently stand out as a real therapeutic innovation for treating B-cell leukemias and lymphomas. Under the terms of this agreement, Accelera will perform *in vivo* preclinical studies to finalize the Investigational New Drug (IND)/Investigational Medicinal Product Dossier package for UCART19. The Phase I human clinical trial for UCART19 is planned for 2015.

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### License Agreement: OncoCyte & Cornell

OncoCyte Corporation (CA, USA; www.oncocyte.com), a majority-owned subsidiary of BioTime (CA, USA; www.biotimeinc.com), has entered into a license agreement with Cornell University (NY, USA; www.cornell.edu) through which Weill Cornell Medical College will provide blood samples derived from healthy people and lung cancer patients for comparative analysis using the Company's proprietary PanC-Dx™ diagnostic tests. OncoCyte will determine levels of tumor-associated gene expression in these samples, including assessing levels of its proprietary PanC-Dx cancer markers. These data will be used by OncoCyte to assess the performance of potential cancer markers for the purpose of developing a multi-marker test for the detection of lung cancer.

### License & commercialization agreement: Aratana & Vet-Stem

Aratana Therapeutics (KS, USA; www.aratana.com) entered into an exclusive license agreement with Vet-Stem (CA, USA; www.vet-stem.com) for its alogeneic stem cell technology. Under the agreement, Aratana obtains exclusive rights to commercialize Vet-Stem allogeneic stem cells in the US, which if approved, will be the first US FDA-regulated 'off-the-shelf' regenerative cell therapy for the treatment of osteoarthritis in dogs.

### Manufacturing agreement: Cellectis & CELLforCURE

Cellectis (France; www.cellectis.com) and CELLforCURE (France; www.cellforcure.com), a subsidiary of the French biopharmaceutical firm LFB Group (www.lfb.fr/en/our_group.html), had entered into an agreement for the manufacturing of clinical batches of Cellectis' allogenic UCART Cells.

### Manufacturing agreement: Roslin Cells & Pfizer

Roslin Cells (UK, www.roslincells.com) has signed a contract with Pfizer (NY, USA; www.pfizer.com) acting through Neusentis, a research unit of Pfizer based in Cambridge, UK (www.neusentis.com), to support the manufacture of retinal pigment epithelium cells to be used in a cell therapy clinical trial. This trial will evaluate the therapy for the treatment of patients suffering from age-related macular degeneration (AMD), as part of an ongoing collaboration with The London Project at the Institute of Ophthalmology, University College London (www.thelondonproject.org).

## Launching new projects, products & services

### Catapult

WuXi PharmaTech (China; www.wuxiapptec.com) has broken ground on a new facility in Philadelphia, PA, USA, for the manufacture of cell therapies. The facility is expected to become operational in the second quarter of 2015. The new facility will consist of 45,000 square feet of clinical and commercial manufacturing space and will supplement WuXi's existing 16,000-square-foot current Good Manufacturing Practice (cGMP) cell therapy manufacturing facility. WuXi AppTec has developed from four founders and a single laboratory in December 2000 to over 7000 employees and 3 million square feet of laboratory and manufacturing space.

### Taxus & Orbsen

Taxus Cardium Pharmaceuticals Group's (CA; www.cardiumthx.com) Excellagen® flowable dermal matrix in combination with Orbsen Therapeutics' (Ireland; http://orbsentherapeutics.com) mesenchymal stromal stem cell (MSC) therapy Cyndacel-M™ has been selected for clinical evaluation in the REDDSTAR (Repair of Diabetic Damage by Stromal Cell Administration) project. The project is a Phase Ib safety study for the potential treatment of chronic diabetic wounds coordinated by Ireland's Regenerative Medicine Institute (REMEDI; www.remedi.ie) and funded by the European Union under EU Framework 7 (FP7). Excellagen (www.excellagen.com) is a physiologically formulated homogenate of purified bovine dermal collagen (Type I) in its native 3D fibrillar configuration, supplied as a sterile professional-use syringe-based product.

## Achievements

### ImStem & Advanced Cell Technology

ImStem (CT, USA; www.imstem.com) and Advanced Cell Technology (MA, USA; www.advancedcell.com) have successfully treated an animal model of multiple sclerosis using human embryonic stem cells (hESC)-devived MSCs, called hES-MSCs [1].

# Clinical Trials

## Asterias

Asterias Biotherapeutics (CA, USA; www.asteriasbiotherapeutics.com) presented the results of its Phase I clinical trial assessing the safety of its product, AST-OPC1 (oligodendrocyte progenitor cells), in subjects with spinal cord injury at the American Society for Gene and Cell Therapy Annual Meeting in Washington, DC, USA. The study represented the first-in-

man trial of a cell therapy derived from hESC. The study was first initiated by Geron Corporation (CA, USA; www.geron.com) in 2010; in 2013 Asterias acquired all of Geron's stem cell assets. The results provide support for the safety of the product and provide a path for advanced clinical studies of AST-OPC1. The full contents of the presentation are available on Asterias' website and at http://clinicaltrials.gov (ID: NCT01217008).

### Bone Therapeutics

Bone Therapeutics (Belgium; www.bonetherapeutics.eu) announced that the first patient has been treated with its novel allogeneic osteoblastic cell therapy product ALLOB® in its Phase I/IIa study for the treatment of delayed union fractures. ALLOB is the first ever, allogeneic differentiated osteoblastic cell therapy product developed for the treatment of orthopedic conditions. ALLOB has shown safety and efficacy in preclinical studies and does not require any immunosuppressive side therapy. Further information about this clinical trial is available at http://clinicaltrials.gov (ID: NCT02020590).

### Calimmune

Calimmune (CA, USA; www.calimmuneinc.com) is ready to begin treating a second cohort in a clinical trial involving the use of Cal-1, an innovative gene-based stem cell therapy to help protect individuals infected with HIV from progressing to AIDS. Calimmune was given approval to move ahead following a review of safety data by their Data Safety Monitoring Board. The Board confirmed that none of the participants experienced any serious adverse events or dangerous side effects from the therapy. The Phase I/II clinical trial focuses on a protein called C-C chemokine receptor type 5 (CCR5 or CD195), which plays a critical role in enabling HIV to infect cells. Blocking CCR5 expression may provide the cells with a protective shield against HIV, which in turn would help retain immune system functionality. In the first phase of this study four HIV-positive participants were infused with their own blood stem cells as well as mature T cells that had been modified to carry a gene that blocks production of CCR5. The hope is that those stem cells will then create a new blood system that is resistant to HIV. To guard against the virus forming resistance, the team has used a second mechanism to prevent the virus from fusing with the patient's cells. Further information about this clinical trial is available at http://clinicaltrials.gov (ID: NCT01734850).

### ReNeuron

ReNeuron (UK; www.reneuron.com) provided a further update on the PISCES Phase I clinical trial of its ReN001 stem cell therapy for disabled stroke patients. There were no cell-related or immunological adverse events reported in any of the 11 patients treated in the study. Adverse events were related only to the implantation procedure or underlying comorbidities. Sustained reductions in neurological impairment and spasticity were observed in most patients compared with their stable pretreatment baseline performance. ReNeuron recently had received unconditional approval to conduct a UK multisite Phase II clinical trial to examine the efficacy of ReN001 in patients disabled by an ischemic stroke. This Phase II study is now open for patient enrolment at the Glasgow clinical site, with other UK centers expected to follow. The study will involve the treatment of up to 41 patients between 8 and 12 weeks after their stroke. Patients will be monitored on a number of validated stroke efficacy measures. Further information about the PISCES clinical trials is available at http://clinicaltrials.gov (ID: NCT01151124 and NCT02117635).

### RTI Surgical

RTI Surgical (FL, USA; www.rtix.com) announces that the first human implantation of the Company's map3® Cellular Allogeneic Bone Graft Strips Allograft (www.map3.com) took place during an anterior lumbar interbody fusion procedure last week. Map3 Strips Allograft is an implant that contains the three essential elements necessary for bone formation in a single allograft: a 3D osteoconductive scaffold, demineralized bone matrix that demonstrates verified osteoinductive potential and multipotent adult progenitor (MAPC®) class cells that provide osteogeneic and angiogeneic signals to support the bone healing process. This moldable implant is designed for ease of use, and its flexible yet cohesive properties make it ideal for filling bone voids in applications such as small joint repair, irregular defects or as an onlay in the posterolateral spine. Further information about the use of map3 in clinical trial in foot and ankle bone grafting is available at http://clinicaltrials.gov (ID: NCT02161016).

### StemCells

StemCells (CA, USA; www.stemcellsinc.com) has closed enrollment in its Phase I/II clinical trial for dry AMD in order to focus its efforts on a follow-on Phase II randomized, controlled proof-of-concept study, later this year. Interim results for the current AMD trial show a 70% reduction in the rate of geographic atrophy as compared with the control eye and a 65% reduction as compared with the expected natural history of the disease following a single dose of the Company's proprietary HuCNS-SC® human neural stem cells. In addition to these initial efficacy findings,

the Phase I/II trial has also demonstrated a favorable safety profile for HuCNS-SC as a treatment for dry AMD. Final results from this study are expected to be released mid-2015. More information about the program can be found on their website at: www.stemcellsinc.com/Therapeutic-Programs/AMD-and-Retinal-Disorders.htm Additional information about the clinical trial is available at: www.stemcellsinc.com/Therapeutic-Programs/Clinical-Trials.htm and at http://clinicaltrials.gov (ID: NCT01632527).

In unrelated news, StemCells presented an interim update on the Phase I/II trial in spinal cord injury at the Annual Meeting of the American Spinal Injury Association in San Antonio, TX, USA. Interim analysis of clinical data to date has shown that the significant post-transplant gains in sensory function first reported in two patients have now been observed in two additional patients. Information about this program can be found on the StemCells website at: www.stemcellsinc.com/Therapeutic-Programs/Spinal-Cord-Injury.htm. Additional information about the clinical trial is available at: www.stemcellsinc.com/Therapeutic-Programs/Clinical-Trials.htm and at http://clinicaltrials.gov (ID: NCT01321333).

# Regulations, Approvals & Acquisitions

## Green light

### BioLineRx

BioLineRx (Israel; www.biolinerx.com) has received approval from the Israeli Ministry of Health to commence a Phase I trial for BL-8040, a novel treatment for the mobilization of stem cells from the bone marrow to the peripheral blood circulation. The study is expected to commence during the third quarter of 2014 at Hadassah Medical Center in Jerusalem. BL-8040 is a clinical-stage drug candidate for the treatment of acute myeloid leukemia, as well as other hematological indications. It is a short peptide that functions as a high-affinity antagonist for CXCR4, a chemokine receptor that is directly involved in tumor progression, angiogenesis, metastasis and cell survival. CXCR4 is overexpressed in more than 70% of human cancers and its expression often correlates with disease severity. BL-8040 mobilizes cancer cells from the bone marrow and may therefore sensitize these cells to chemo- and bio-based anticancer therapy. Importantly, BL-8040 has also demonstrated a direct anticancer effect by inducing apoptosis. Preclinical studies show that BL-8040 is efficient, both alone and in combination with the anticancer drug Rituximab, in reducing bone marrow metastasis of lymphoma cells and stimulating lymphoma cell death.

### Stemedica

Stemedica Cell Technologies (CA, USA; www.stemedica.com) announced that its research partner The Stem Cell and Cancer Institute, a subsidiary of PT Kalbe Farma Tbk (Indonesia; www.kalbe.co.id), received an IND approval in April 2014 from the Badan Pengawas Obat dan Makanan (BPOM, or the Indonesian FDA; www.pom.go.id/new/index.php/home/en) for a Phase II study using Stemedica's MSCs to treat acute myocardial infarction in human subjects in Indonesia. The IND was filed by The Stem Cell and Cancer Institute with support from Stemedica Asia, a subsidiary of Stemedica, and was based on Stemedica's FDA-approved Phase II acute myocardial infarction trial protocol.

### TxCell

TxCell (France; www.txcell.com), a biotechnology company developing innovative, personalized cell-based immunotherapies using antigen-specific regulatory T cells (Tregs) for severe chronic inflammatory and autoimmune diseases, has been granted Certificate of Good Manufacturing Practice (GMP) compliance for its cell therapy manufacturing facility in Besançon, France. The certificate was granted by French National Agency for Drug Safety (ANSM), the French authority for the quality, safety and efficacy of medicines and health products. This certificate follows the Manufacturing Accreditation, also delivered by ANSM on December 3, 2013. The certificate of GMP compliance covers the manufacture, testing, blinding activities and release of investigational biological and cell therapy products. The certificate is valid for 3 years. It authorizes the manufacture of Phase IIb clinical batches of Ovasave®, personalized cell-based immunotherapy using ovalbumin-specific regulatory T cells (Ova-Tregs) for refractory Crohn's disease. This clinical study is planned to start in the second half of 2014, once necessary regulatory approvals are obtained.

## Red light

### European Commission

The European Commission (http://ec.europa.eu/index_en.htm) has turned down a request from more than 1.7 million citizens for new legislation to ban the funding of research using human embryonic stem cells, including those that do not involve destruction of new

embryos. The One of Us petition was among the first to be presented within the Commission's new European Citizens' Initiatives scheme, launched 2 years ago in a bid to widen participatory democracy. Any European Citizens' Initiative that can muster more than 1 million signatures across at least seven EU countries automatically triggers a parliamentary hearing and a formal response from the Commission. The parliamentary hearing for the One of Us initiative took place on April 10, 2014.

### WARF

The Consumer Watchdog (CA, USA; www.consumerwatchdog.org) had hoped to invalidate the patent held by the Wisconsin Alumni Research Foundation (WI, USA; www.warf.org), which it says puts a burden on California's taxpayer-funded research by requiring licensing agreements to use the cells, but on 4 June the US Court of Appeals for the Federal Circuit ruled that the Consumer Watchdog is not involved in work on hESC and, thus, cannot challenge the patent in court.

## Capital Market & Finances

### Americord & Medipost

Americord Registry (NY USA; http://cordadvantage.com) has provided funding to Medipost (Korea; www.medi-post.com) to support their clinical trial investigating the use of NEUROSTEM-AD® in the treatment of patients with Alzheimer's disease. NEUROSTEM-AD® is a treatment based on human umbilical cord blood-derived MSCs. Further information about the clinical trial is available at http://clinicaltrials.gov (ID: NCT02054208).

### Asterias

The California Institute for Regenerative Medicine (CIRM; www.cirm.ca.gov) recently awarded Asterias Biotherapeutics (CA, USA; www.asteriasbiotherapeutics.com) US$14.3 million to restart spinal cord injury trial; title of the funded application: a Phase I/IIa Dose Escalation Safety Study of AST-OPC1 in Patients with Cervical Sensorimotor Complete Spinal Cord Injury. In addition, Asterias has raised US$12.5 million through the sale of 5,000,000 BioTime (CA, USA; www.biotimeinc.com) common shares held by Asterias and the issuance of warrants to purchase 5,000,000 shares of Asterias Series B Common Stock. The majority of the funds raised through this privately negotiated transaction will be used to finance Asterias' product development programs, including AST-OPC1 for the treatment of spinal cord injury, and AST-VAC2, which is being developed as an immunotherapy for non-small-cell lung cancer.

### BioTime

BioTime (CA, USA; www.biotimeinc.com) has received approximately US$6.4 million in equity financing from current long-term investors in the Company and will be used for funding product development, including this year's anticipated pivotal Renevia™ clinical trial, as well as other general operating expenses. Renevia is a biocompatible, implantable hyaluronan and collagen-based matrix for cell delivery in human clinical applications.

### EpiBone

EpiBone (NY, USA; www.epibone.com) has received support from Breakout Labs (CA, USA; www.breakoutlabs.org) nonprofit fund that supports scientific innovation driving radical science to advance human health. The program provides up to US$350,000 for start-up companies to achieve specific milestones that are critical to their development. EpiBone uses computed tomography scans and fat-derived stem cells to engineer the patient's own living bone with the precise anatomical fit to the defect being treated.

### InVivo

InVivo Therapeutics has announced that the company is realigning resources behind its novel Neuro-Spinal Scaffold and the Neuro-Spinal Scaffold Plus Stem Cells program for spinal cord injury. Resources currently deployed towards InVivo's hydrogel drug delivery program will be eliminated. The refocusing of the company's R&D resources will result in reduction in force of 14 employees, or 28% of its workforce, which will bring approximately US$3 million in annualized savings and reduce cash expenditures by 23% compared with 2013 levels. With these savings, InVivo anticipates that existing funds will be sufficient to support its planned activities through March 2016.

### Sangamo

CIRM (www.cirm.ca.gov) has granted a US$5.6 million Strategic Partnership Award to Sangamo BioSciences (CA, USA; www.sangamo.com) to develop a potentially curative zinc finger protein therapeutic for HIV/AIDS in clinical trial at the City of Hope. The grant application title was: 'A Phase I, Open-Label Study to Assess the Safety, Feasibility and Engraftment of Zinc Finger Nucleases CCR5-Modified Autologous

CD34+ Hematopoietic Stem/Progenitor Cells (SB-728mR-HSPC) with Escalating Doses of Busulfan in HIV-1 (R5) Infected Subjects with Suboptimal CD4 Levels on combination antiretroviral therapy'.

### Financial & competing interest disclosures

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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## Reference

1 Wang X, Kimbrel EA, Ijichi K *et al.* Human ESC-derived MSCs outperform bone marrow MSCs in the treatment of an EAE model of multiple sclerosis. *Stem Cell Reports* 3(1), 1–16 (2014).