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

Business Development

Collaborations, partnerships & alliances

Co-development agreement: Fibrocell & Intrexon

Fibrocell Science (PA, USA; www.fibrocellscience.com) and Intrexon (MD, USA; www.dna.com), announced plans to file an investigational new drug application with the US FDA in the first half of 2015 for their drug candidate, GM-HDF-COL7 (genetically-modified human dermal fibroblast, collagen VII). The companies are developing this new cell-based therapeutic for the treatment of recessive dystrophic epidermolysis bullosa, the most severe form of the rare connective tissue disorder epidermolysis bullosa. Fibrocell and Intrexon commenced preclinical activities of GM-HDF-COL7 earlier this year and have since attained certain regulatory and development achievements including Orphan Drug designation in June and initiation of clinical material manufacturing in September.

Co-development agreement: Novartis & UPenn

Novartis (Switzerland; www.novartis.com) and the University of Pennsylvania (PA, USA; www.upenn.edu) reached an important milestone in its alliance as unveiling plans for the construction of a first-of-its-kind Center for Advanced Cellular Therapeutics (CACT) on the Penn Medicine campus in Philadelphia. The CACT will become the epicenter for research using chimeric antigen receptor (CAR) technology, which enables a patient's T cells to be reprogrammed outside of the body so when they are re-infused into the patient, the T cells have the ability to 'hunt' and destroy the cancer cells. Clinical trials

using this approach have made headlines around the world. Plans for the 30,000-sq. ft. facility cement the Penn–Novartis alliance, a marquee component of Penn's efforts in translational sciences that expedite the development of novel therapies for diseases of all kinds. The collaboration was announced in August 2012, when the two organizations entered an exclusive global research and licensing agreement to further study and commercialize novel CAR therapies. The CACT, which will be funded in part through a US\$20 million investment from Novartis, will be devoted to the discovery, development and manufacturing of these personalized cellular cancer therapies, through a joint research and development program led by scientists and clinicians from Penn and Novartis.

Co-development & licensing agreement: Sumitomo & SanBio

Sumitomo Dainippon Pharma (Japan; www.ds-pharma.com) and SanBio (CA, USA; www.san-bio.com), have entered into a joint development and license agreement for exclusive marketing rights in the US and Canada for SB623, a cell therapy for the treatment of patients with chronic stroke discovered and currently under development by SanBio. SB623 is an allogeneic cell product, derived from bone marrow mesenchymal stromal/stem cells (MSCs) isolated from healthy donors. Unlike autologous cell therapy, which requires individualized cell preparation for each patient, SB623 production can be scaled up from a single donor's cells, enabling delivery of uniform quality products to a large number of stroke patients. In preclinical and clinical studies to date,

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SB623 has shown beneficial results on stroke disability with no serious adverse events. SB623 is the first cell therapy product for stroke that has been approved by the FDA for human clinical trials. Phase I/IIa clinical tests have been completed in the USA. Further information about that clinical trial are available at <http://clinicaltrials.gov> (ID: NCT01287936). Currently, preparations are underway to begin a Phase IIb clinical trial in the USA. Under the terms of the Agreement, Sumitomo Dainippon Pharma and SanBio will jointly develop SB623 in the USA and Canada, and Sumitomo Dainippon Pharma will have the exclusive right to market SB623 in both countries. In consideration of the rights and licenses granted, Sumitomo Dainippon Pharma will make an initial payment of US\$6 million and milestone payments totaling an additional US\$74 million during the clinical development of SB623. After market launch, SanBio will supply the finished product to Sumitomo Dainippon Pharma and receive double-digit percentage royalties based on sales. Additionally, SanBio may receive sales milestone payments contingent upon the achievement of annual sales goals, up to a total of US\$125 million. The development expenses will be shared equally between the two companies.

Licensing agreement: Cynata & University of Wisconsin

Cynata Therapeutics (Australia; www.cynata.com) has entered into a license agreement with Cellular Dynamics International (WI, USA; www.cellulardynamics.com). The agreement provides Cynata with nonexclusive worldwide rights to a clinical grade human induced pluripotent stem cell (iPSC) line manufactured by Cellular Dynamics. Cynata intends to use this iPSC line as high quality starting material to manufacture its Cymerus™ MSC products for human therapeutic use.

Licensing agreement: ImmunoCellular & Caltech

ImmunoCellular Therapeutics (CA, USA; www.imuc.com) has established a licensing agreement with the California Institute of Technology (www.caltech.edu) for exclusive rights to novel technology for the development of certain antigen specific T-cell immunotherapies for the treatment of cancer. The technology utilizes the patient's own hematopoietic stem cells to create antigen-specific killer T-cells to treat cancer. ImmunoCellular plans to utilize this technology to expand and complement its dendritic cell-based cancer vaccine platform, with the goal of developing new immunotherapies that kill cancer cells in a highly directed and specific way, and that can function as single agents or in combination approaches. Caltech's technology addresses the challenge, and limitation, that CAR and

T-cell receptor technologies have faced of generating a limited, short-lived immune response. By putting T-cell receptors into stem cells rather than into T cells, the immune response can be transformed into a long-lived and potent response that could effectively treat previously resilient solid cancers. This observation has been verified in animal models by investigators at Caltech and the National Cancer Institute.

Partnership agreement: CellProThera & BioCardia

CellProThera (France; www.cellprothera.com/?lang=en) and BioCardia (CA, USA; www.biocardia.com) partnered on the EXCELLENT (Expanded Cell Endocardiac Transplantation) trial, a multicenter, controlled Phase I/IIb study to evaluate the safety and efficacy of *in vitro*-expanded peripheral blood CD34⁺ stem cells output by the CellProThera's StemXpand® Automated Process and delivered via the BioCardia Helix™ Transendocardial Delivery System.

Launching new projects, products & services

Bioheart

Bioheart (FL, USA; www.bioheartinc.com) opened of the laboratory and clinic in South Africa. The new facility, named South African Stem Cell Institute (SASCI), immediately began treating patients. Last week a total of 12 patients underwent autologous cell therapies for the treatment of spinal cord injury, diabetes, arthritis, autoimmune disease and more. All of the patients received an in-clinic treatment, as well as cell culture expansion and cryopreservation. The patient cells were multiplied and will be preserved in sub-zero temperatures for future treatments as required. Bioheart's new joint venture has established an important relationship within the South African government. The Ministry of Health will be adopting Bioheart protocols making them the standard of care for patients in South Africa. Bioheart will assume 49% ownership of the new entity.

Health 100

Medical entrepreneur Xia Jie, whose company Health 100 (www.health-100.cn) owns the largest chain of health clinics in China, plans to open facilities in Queenstown, New Zealand to cater for wealthy clients. Health 100 would invest with existing firms Queenstown Regenerative Medicine (www.queenstownrm.co.nz) and the Queenstown Skin Institute (www.skininstitute.co.nz).

Regeneus

Regeneus (Australia; <http://regeneus.com.au>) announced plans to open the HiQCell Regenerative Medicine Clinic at the Camden Medical Centre in

Singapore. The HiQCell treatment involves harvesting a small amount of a patient's own stem cells from their adipose (fat) tissue and after separating and concentrating the regenerative cells these are re-injected in osteoarthritic-affected joints such as knees, hips and ankles. The HiQCell treatment, which aims to reduce inflammation and repair damaged tissue is carried out under the supervision of the treating medical practitioner. HiQCell has been used to treat more than 500 patients and over 1000 arthritic joints. The cell therapy procedure is supported by safety data from a randomized controlled clinical trial and long-term

safety and efficacy data are tracked through Australia's first Joint Registry for stem cell therapy.

Royan Institute

Royan Institute's (Iran; www.royaninstitute.org) spin off stem-cell technology firm has received a positive response from the private and the government sector, to launch their activities in Oman. Royan Cord Blood Bank, founded in 2005 under the institute, storing more than 33,000 samples in branches in more than 22 cities nationwide, will be setting up cord blood bank in Oman.

Clinical Trials

Advanced Cell Technology

Advanced Cell Technology (MA, USA; www.advancedcell.com), has completed treatment of the final patient in its UK-based Phase I clinical trial for Stargardt's macular degeneration. The successful transplantation of the Company's proprietary retinal pigment epithelial cells in the last patient of 12 represents the completion of the enrollment stage of this trial. The trial is a prospective, open-label study designed to determine the safety and tolerability of the Company's retinal pigment epithelial cell therapy following subretinal transplantation into patients. Further information about this clinical trial are available at <http://clinicaltrials.gov> (ID: NCT01469832).

BioTime/Asterias

BioTime' (CA, USA; www.biotimeinc.com) subsidiary Asterias Biotherapeutics (CA, USA; <http://asterias-biotherapeutics.com>) has reached an agreement with Cancer Research UK (www.cancerresearchuk.org) and Cancer Research Technology (www.cancertechnology.co.uk), the charity's development and commercialization arm, to conduct a clinical trial of Asterias' novel immunotherapy treatment AST-VAC2 in subjects with nonsmall cell lung cancer. AST-VAC2 is an allogeneic cancer vaccine designed to stimulate patients' immune systems to attack telomerase, a protein that is expressed in over 95% of cancers but is rarely expressed in normal adult cells. AST-VAC2 is derived from human embryonic stem cells, meaning it can be produced on a large scale and stored ready for use, rather than having to produce a specific version of the drug for each patient. The trial of AST-VAC2 will evaluate the safety and toxicity of the vaccine, feasibility, stimulation of patient immune responses to telomerase and AST-VAC2, and clinical outcome after AST-VAC2 administration in patients with resected early-stage lung cancer and in

patients with advanced forms of the disease. Under the agreement, Asterias will complete development of the manufacturing process for AST-VAC2. Cancer Research UK will then produce the vaccine and conduct the Phase I/II clinical trial in the UK. On completion of the clinical trial, Asterias will have an exclusive first option to acquire a license to the data from the trial on pre-agreed terms including an upfront payment, milestones and royalties on sales of products. If Asterias declines this option, Cancer Research Technology will then have an option to obtain a license to Asterias' intellectual property to continue the development and commercialization of AST-VAC2 and related products in exchange for a revenue share to Asterias of development and partnering proceeds.

Cellular Biomedicine Group

Cellular Biomedicine Group (CBMG; CA, USA; www.cellbiomedgroup.com) launched a study on human adipose derived mesenchymal progenitor cell (haMPC) therapy for cartilage defects resulting from osteoarthritis or sports injury. Both arthroscopy and the use of magnetic resonance imaging will be deployed to further demonstrate the regenerative efficacy of ReJoin™ on cartilage defects. The clinical study is a single-blind, randomly assigned, controlled, clinical research study that will enroll 30 patients with the purpose of evaluating the safety and efficacy of haMPCs combined with lavage, debridement, and/or microfracture under arthroscopy treatment for cartilage defects. In addition, this study shall serve as a supporting study of ReJoin or the treatment of knee osteoarthritis so as to bring additional clinical data to the protocol of future knee osteoarthritis trials. The study will be conducted in Shanghai Ninth People's Hospital. The company performed a similar safety/efficacy clinical study on 18 patients in Shanghai Renji Hospital

a year ago ('Autologous Adipose Tissue Derived Mesenchymal Progenitor Cells Therapy for Patients With Knee Osteoarthritis') and it is running another one on 48 patients ('Clinical Trial of Autologous Adipose Tissue-Derived Mesenchymal Progenitor Cells [MPCs] Therapy for Knee Osteoarthritis') at the same hospital comparing effects of haMPC and sodium hyaluronate. Further information about these two clinical trials are available at <http://clinicaltrials.gov> (ID: NCT01809769 and NCT02162693).

Institute for Biomedical Research & Innovation

On September 12, a Japanese woman in her 70s was the first person to receive tissue derived from iPSC. In a 2-h procedure, a team of three eye specialists implanted a 1.3 × 3.0 mm sheet of retinal pigment epithelium cells into an eye of the patient, who suffers from age-related macular degeneration. The procedure took place at the Institute for Biomedical Research and Innovation (Japan; www.ibri-kobe.org/hospital/english). The patient had no effusive bleeding or other serious problems after the surgery.

Osiris

Osiris Therapeutics (MD, USA; www.osiris.com), announced interim data from an evaluation of Graftix® in the treatment of chronic venous leg ulcers. The analysis evaluated 18 wounds treated with Graftix and compression therapy compared with 13 case-matched control wounds with similar wound area and wound

age treated with standard compression therapy alone. Overall healing rates in the Graftix patients were 50% compared with 15.4% in the control group ($p < 0.05$). In addition, patients in the Graftix group had significantly reduced mean time to complete healing (11.9 vs 29.9 weeks; $p < 0.05$) and mean length of therapy (12.6 vs 106.3 weeks; $p = 0.015$) compared with the compression only group. The ongoing evaluation will include up to 50 total patients. Graftix is a cryopreserved placental membrane for acute and chronic wounds. It is a flexible, conforming membrane that is applied directly at the site of the wound. Graftix is produced using Osiris' BioSmart Intelligent Tissue Processing, which maintains the integrity of the extracellular matrix, growth factors and endogenous fibroblasts, epithelial cells and MSC of the native tissue.

Viacyte

University of California San Diego (CA, USA; www.ucsd.edu) will be initial site for the first-in-human Phase I/II clinical trial of a human embryonic stem cell-derived therapy for patients with Type 1 diabetes. The trial will assess the safety and efficacy of a new investigational drug called VC-01, which was recently approved for testing by the FDA. The 2-year trial will involve four to six testing sites, the first being at UC San Diego and will recruit approximately 40 study participants. Further information about this clinical trial are available at <http://clinicaltrials.gov> (ID: NCT02239354).

Regulations, Approvals & Acquisitions

Green light

Bone Therapeutics

Bone Therapeutics (Belgium; www.bonetherapeutics.com) has received clearance from the Competent Authorities and Central Ethics Committee in Belgium for a Phase II proof-of-concept study to assess safety and efficacy of its allogeneic osteoblastic cell therapy product ALLOB® in spinal fusion procedures for degenerative lumbar disc disease. ALLOB has been classified as a tissue engineered product under Advanced Therapy Medicinal Product regulation 1394/2007/EMA. In this pilot proof-of-concept study, 16 patients with symptomatic degenerative lumbar disc disease that require interbody fusion will be treated with a single dose of ALLOB mixed with bioceramic granules to promote bone formation and fusion at the degenerative disc level. Patients will be enrolled in four centers and safety and efficacy of the treatment will be monitored over 12 months by clinical (Oswestry Disability Index)

and radiological (fusion progression) evaluation, with an additional 24-month poststudy follow-up.

Cellular Dynamics International

US Patent and Trademark Office has awarded Cellular Dynamics International (WI, USA; www.cellulardynamics.com) the Patent No. 8,815,585 on the automated production of human pluripotent stem cells, including iPSCs. This patent has broad-reaching effects, covering research, cellular therapy development and stem cell banking. Large-scale applications, such as cellular therapeutic development as well as stem cell banking, require automation for parallel processing of samples from many donors. In addition, the patent broadly covers automated iPSC culturing without the use of feeder cells or the addition of serum to culture media, factors important to cellular therapy development in a current GMP environment. This patent joins an Intellectual Property portfolio of

over 800 patents awarded to, pending or in-licensed by Cellular Dynamics.

Medipost

Medipost America (MD, USA; www.medipostamerica.com) has received the FDA approval of Phase I/II clinical trial for PNEUMOSTEM®. The Phase I/II trial will assess the safety and efficacy of PNEUMOSTEM on prematurely born infants who will be at high-risk of developing bronchopulmonary dysplasia. PNEUMOSTEM is made from allogeneic human umbilical cord blood-derived MSCs, and is expected to have effect on regenerating the lung tissue and improving inflammatory responses in premature infants. Bronchopulmonary dysplasia is the leading cause of mortality and severe complications in premature infants and currently no therapy or approved drug exists. Hence, the PNEUMOSTEM trial is expected to draw global attention in the field of neonatal medicine. PNEUMOSTEM received Orphan Drug designation in Korea by the Ministry of Food and Drug Safety and the Phase II study in Korea is 80% complete.

Northwest

Northwest Biotherapeutics (MD, USA; www.nwbio.com), a biotechnology company developing DCVax® personalized immune therapies for solid tumor cancers, announced that its DCVax-L is the first product to receive formal designation as a 'Promising Innovative Medicine' (PIM) under the new 'Early Access to Medicines Scheme' (EAMS) launched in the UK in April 2014 [1]. A PIM is the first step in a two-step process for early access approval under the EAMS. The PIM

designation for DCVax-L covers all malignant gliomas, which would include both glioblastoma multiforme (the most severe grade), as well as less malignant grades, and would include both newly diagnosed and recurrent gliomas. The EAMS is an important new initiative in the UK, launched by the Medicines and Healthcare Products Regulatory Agency (MHRA, the FDA of the UK), to lead the way in accelerating patients' access to innovative new medicines for serious diseases. The first step under the EAMS is MHRA's scientific evaluation of whether a product candidate meets three criteria for a PIM designation: the product is for a serious disease or condition with high unmet medical need; the product is likely to offer a major advantage over treatments available today; and the potential adverse effects of the product are outweighed by the potential benefits. The second step under the EAMS is MHRA's determination of a Scientific Opinion about the product candidate's benefits and risks, based on available clinical data. A positive or negative Scientific Opinion will be judged by the same three criteria as for the PIM designation, as well as a fourth criterion: the Company's ability to manufacture the product to rigorous 'GMP' (clinical grade) standards. If the Scientific Opinion is positive, the product candidate may then be prescribed by physicians and provided to (and paid for by) patients before the product is formally licensed and while it is still in clinical development. MHRA aims to deliver the Scientific Opinion within 90 days after a party submits an application for step 2 of the EAMS process. NW Bio's DCVax-L has now become the first product to earn this PIM certification. There is no expiration on the PIM certification.

Capital Market & Finances

BioRestorative

BioRestorative Therapies (FL, USA; www.biorestorative.com) has been awarded up to US\$500,000 in performance-based Excelsior Tax Credits from Empire State Development, New York State's economic development agency, as part of a relocation incentive package from the State, as well an estimated US\$146,000 of sales tax exemptions and property tax abatement from the Suffolk County Industrial Development Agency. The incentive package awarded by Empire State Development is to assist the Company with its job-creation project related to the relocation of its corporate headquarters from FL to NY state. Under the package, the Company will be committed to employ 15 new full-time permanent employees at its Suffolk County headquarters by June 30, 2017,

and to maintain that level of employment through January 1, 2025.

Cellerant & BARDA

Cellerant Therapeutics (CA, USA; www.cellerant.com) has received US\$47.5 million from the government to develop its treatment for radiation poisoning. If approved, the feds could buy the drug for the Strategic National Stockpile, which is a part of Project Bioshield - a portion of the Bush-era War on Terror that medically readies the nation against 'chemical, biological, radiological or nuclear attacks.' This is part of a US\$163.8 million commitment from the Biomedical Advanced Research and Development Authority (BARDA; www.phe.gov/about/barda/Pages/default.aspx). The new dollars will go toward Phase II trial

in patients with acute myeloid leukemia, as well as the preclinical trials to treat radiation poisoning, or acute radiation syndrome.

Japan

Major nonlife insurance companies started selling new packages to insure cell-cultivating companies against errors in regenerative medicine. The new packages are expected to encourage patients and hospitals to make use of regenerative medicine, as they will help cell-culturing firms pay compensation if problems arise in cultivated cells during treatments and clinical tests. The sale of such packages was timed with the enforcement of the law to secure the safety of regenerative medicine, which enables hospitals to commission private companies specializing in cell cultivation to perform the work. Till then, hospitals were the only entities allowed to do so. The new packages are made available to such firms, which will pay premiums and receive insurance money when they commit errors in their procedures and be held responsible for compensating patients. For example, Sompo Japan Nipponkoa Insurance (www.sjnk.co.jp/english/) is selling regenerative medicine insurance packages that would

pay up to US\$5,900,000 (JPY¥500 million) in benefits. Tokio Marine & Nichido Fire Insurance (www.tokiomarine-nichido.co.jp/en/) and Mitsui Sumitomo Insurance (www.ms-ins.com/english/) also introduced similar packages. The packages were developed based on extensive discussions conducted by the insurance industry, the Economy, Trade and Industry Ministry and medical experts.

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Reference

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