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 1st September 2009 to 31st October 2009

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Business Development

■ Collaborations, partnerships & alliances

Codevelopment agreement:

Gamida & Cellerix

Gamida Cell Ltd, from Jerusalem, Israel (www.gamida-cell.com), and Cellerix, S.A., from Madrid, Spain (www.cellerix.com), are collaborating on a feasibility study to evaluate the added value of combining the proprietary technologies of each. Gamida Cell is developing a series of technologies to expand *ex vivo* populations of stem/progenitor cells that display increased *in vivo* homing and engraftment activities. The company's lead product, StemEx®, comprised of expanded populations of stem cells derived from umbilical cord blood, is used as an experimental treatment for blood cancers such as leukemia and lymphoma. The company anticipates StemEx will reach the market in 2011. Cellerix is developing a new generation of cell-based medicines using expanded adult stem cells obtained from adipose tissue. The company is also very active in developing its allogeneic expanded adult stem cells platform as second-generation products through its Cx611 program for high-potential markets.

Collaboration agreement:

Roche & Yissum

Yissum Research Development Company of the Hebrew University of Jerusalem Ltd (www.yissum.co.il), the technology

transfer arm of the University, has signed a long-term multi-project research and license collaboration agreement with Swiss-based Roche (www.roche.com). According to the terms of the agreement, Roche has selected six promising research projects in the fields of stem cells, biomarkers, and novel molecules for the treatment of metabolic diseases, initiated by Hebrew University researchers. The expected duration of each collaborative research project is 1–3 years. Following successful completion of the different research plans, Roche shall have exclusive license to commercialize the results in consideration for the payment of transfer fees, milestone payments and royalties. The chosen projects are:

- A novel pathway and new strategies for the treatment of Type 2 diabetes and obesity;
- Novel technologies for minimizing the risk of tumor development and for decreasing the risk of immunogenic rejection when using stem cells to treat human diseases;
- Novel technologies for converting human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) into liver cells;
- Identifying novel biomarkers for progressive stages of vascular complications (e.g., ischemic heart diseases);

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- Novel ways to differentiate stem cells into β -cell lineages for organ transplants by using proprietary scaffolds;
- Using cannabinoids for the treatment of Type I and II diabetes.

Collaboration agreement:

VitroLife & Cellartis

Vitrolife from Sweden (www.vitrolife.com), a global biotechnology/medical device group that works with developing, manufacturing and selling advanced products and systems for the preparation, cultivation and storage of human cells, tissue and organs has entered into a new 3-year collaboration agreement with a hESC company, Cellartis AB, also from Sweden (www.cellartis.com) regarding the development of new products for the culture, handling and differentiation of stem cells. The agreement extends the previous collaboration between the companies.

Distribution agreement:

Cryo-Cell International & S-Evans Biosciences

Cryo-Cell International, Inc., FL, USA (www.cryo-cell.com) has signed an exclusive distribution agreement with its Chinese partner, S-Evans Biosciences, Inc. (www.sebio.net.cn), a privately-held company for the distribution of C'elle (www.celle.com), menstrual stem cell technology, in Thailand. The agreement will allow S-Evans to market and sell proprietary C'elle menstrual stem cell services exclusively throughout Thailand. C'elle specimens collected from clients in Thailand will be shipped to S-Evans' laboratory in Hangzhou, China for processing and storage. The distribution agreement is anticipated to provide Cryo-Cell with future royalties from the processing and annual storage of C'elle service sold in Thailand, in addition to royalties expected from the previous exclusive license agreement established with S-Evans for C'elle in mainland China.

Licensing agreement:

Cleveland BioLabs & Zhejiang Hisun Pharmaceutical

Cleveland BioLabs, Inc., from OH, USA

(www.cbiolabs.com), and Chinese pharmaceutical manufacturer Zhejiang Hisun Pharmaceutical Co. Ltd (www.hisunpharm.com/en/) announced the execution of a license agreement granting Hisun exclusive rights to develop and commercialize Protectan CBLB612 in China. Under the terms of the license agreement, Cleveland BioLabs will receive upfront product development payments of US\$1.65 million. Zhejiang Hisun will be responsible for all development and regulatory approval efforts for Protectan CBLB612 in China. In addition, Zhejiang Hisun will pay Cleveland BioLabs a 10% royalty on net sales over the 20-year term of the agreement. This royalty may decrease to 5% of net sales only in the event that patents for CBLB612 are not granted. Cleveland BioLabs will retain all rights to CBLB612 in the rest of the world. Protectan CBLB612 is a proprietary synthetic agent that acts as a potent stimulator of hematopoietic stem cell proliferation and mobilization to peripheral blood in both mice and nonhuman primates.

Manufacturing agreement:

BrainStorm & Harlan

BrainStorm Cell Therapeutics Inc., based in Israel and NY, USA (www.brainstorm-cell.com) has entered into an agreement with Israel's Good Laboratory Practice contractor Harlan Biotech Israel Ltd (www.harlanisrael.com), in order to complete preclinical safety experiments for the company's innovative therapy for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. Under the agreement, Harlan will perform preclinical safety experiments using the company's current Good Manufacturing Practice (GMP)-compliant stem cells. The experiment will be performed immediately following production of the company's current GMP-compliant stem cells, which is currently performed by Brainstorm's scientists at the facilities of Protein Production Services Ltd (www.pps.co.il).

■ Launching new products & services

Biocell Center

Biocell Center, an Italian/Swiss company (www.biocellcenter.com/en/), has opened its first US branch in Medford, MA, for amniotic stem cell preservation. The

company preserves stem cells from amniotic fluid and for families interested in paying for the liquid nitrogen preservation of the stem cells in Biocell Center's cryo-bank.

BioLife Solutions

BioLife Solutions, from WA, USA (www.biolifesolutions.com), launched BloodStor™ biopreservation media product platform. The product family includes BloodStor 55–55 for cryopreservation of umbilical cord blood stem cells, as well as other variants for peripheral blood-derived stem cells. BloodStor 55–55, packaged in standard, single-use sterile vials of various fill volumes, is formulated with 55% US Pharmacopoeia (USP) grade dimethyl sulfoxide and 5% USP grade dextran-40 in 'water for injection' quality water and supports a common cord blood processing protocol. BioLife's manufacturing facility and quality system are compliant with 21 CFR part 820 – Quality System Regulation for GMP of medical devices, 21 CFR parts 210 and 211 covering GMP for Aseptic Production, Volume 4, EU Guidelines, Annex 1 for the Manufacture of Sterile Medicinal Products, and ISO14644 for Clean Rooms and Associated Controlled Environments. The company expects to achieve the ISO13485 medical device quality management systems certification by the end of 2009. All BloodStor products are tested for sterility to USP 71, endotoxin to USP 85, pH, appearance and cell-based preservation efficacy.

BioTime Asia

BioTime Inc., from CA, USA (www.biotimeinc.com), is working with Nanshan Memorial Medical Institute Ltd, from Hong Kong, an Asian subsidiary, to develop and market potential stem cell products in China – targeting eye, skin, musculoskeletal and hematologic treatments – as well as research products in China and other Asian countries. Nanshan will be a minority shareholder in BioTime Asia Ltd and will provide initial laboratory facilities, research personnel, and arrange financing for clinical trials.

Cardiotox

Cellular Dynamics International, from WI, USA (www.cellulardynamics.com), and VivoMedica plc, from Kent, UK (www.vivomedica.com),

vivomedica.com), launched Cardiotox, a pharmaceutical industry consortium to validate a human cell model and analysis system for preclinical cardiotoxicity testing of pharmaceutical candidate compounds. Pharmaceutical companies are invited to participate in the consortium, which aims to provide the industry with a human cardiomyocyte-based solution to predict pro-arrhythmic effects of new chemical entities. Human cardiomyocytes express the relevant cardiac proteins and are thought to be more predictive of a drug compound's effect than animal cell-based technologies. The consortium will validate the testing system using Cellular Dynamics' iCell™ Cardiomyocytes and VivoMedica's DrugPrint® analysis system. Extracellular microelectrode array recordings from Cellular Dynamics' fully functional iPSC-derived human cardiomyocytes will be analyzed using VivoMedica's proprietary electrical waveform analysis technology. This approach will identify drug-induced changes that indicate the arrhythmogenic potential of new chemical entities under investigation. These technologies, combined into an integrated test, will provide the industry with a validated pro-arrhythmia reference database for comprehensive early assessment of the new chemical entities' arrhythmogenic potential, the end result being greater predictive power, reduced reliance on animal testing, reduced cost, and an overall increase in efficiency in the drug discovery and development process.

Cyntellect

Cyntellect, Inc., from CA, USA (www.cyntellect.com), announced the commercial availability of Stem Cell Manager™, powered by Laser-Enabled Analysis and Processing System (LEAP™). This new application manages a series of stem cell research processes, including automated physical passage of stem cells, automated embryoid body generation and purification of specialized cell types derived from stem cells. Stem Cell Manager is powered by Cyntellect's LEAP Cell Processing Workstation. Current approaches to physical stem cell passage require specialized knives, razors or pipettes to manually section stem cell colonies. Traditional enzymatic methods using collagenase or trypsin

result in significant cellular trauma. By contrast, the Stem Cell Manager application automates physical passage of stem cell colonies using noncontact, closed-system laser manipulation instead of invasive mechanical devices. Laser-mediated sectioning of ESCs and iPSCs maintains a stable stem cell phenotype, reduces labor cost, improves standardization and produces superior consistency of stem cell cultures, coupled with a lack of enzymatic dissociation of these sensitive cells. The application also reduces the skill and training threshold for generation of consistent high-quality ESC and iPSC cultures.

Fibrocell Science

Isolagen, Inc., has reorganized and emerged from bankruptcy as Fibrocell Science, Inc., based in PA, USA (www.fibrocellscience.com), a biotechnology company focused on developing regenerative fibroblast cells for esthetic, medical and scientific applications. The company has also named a new Board of Directors. The US FDA is currently reviewing the biologics license application for Fibrocell Science's lead therapy, azfibrocel-T (formerly Isolagen Therapy™), in development to treat nasolabial fold wrinkles.

OncoCyte

BioTime Inc., from CA, USA (www.biotimeinc.com) has organized a new subsidiary, OncoCyte Corporation, for the purpose of developing novel therapeutics for the treatment of cancer based on stem cell technology. BioTime will license certain technology to the new company restricted to the field of cell-based cancer therapies, including early patent filings on targeting stem cells to malignant tumors. A private investor has purchased 3,000,000 common shares of OncoCyte for \$2 million, representing an initial 15% stake in the new company, and the investor has the option of purchasing an additional 3,000,000 common shares for \$2 million on or before 15 April 2010, based on an agreed initial market cap of approximately \$15,000,000. OncoCyte's new therapeutic strategy and goal will be to utilize hESC technology to create genetically modified stem cells capable of homing to specific malignant tumors while carrying genes that can cause the destruction of the cancer

cells. This therapeutic use of hESC differs from most proposed industrial uses of stem cell technology in that OncoCyte's goal is not the stable engraftment of the cells to regenerate tissue function, but rather a use of the unique properties of stem cells as a tool to eliminate malignant cells.

Stem Cell Technologies

STEMCELL Technologies Inc., a Canada-based life sciences company (www.stemcell.com), launched MethoCult® Express, an innovative methylcellulose-based medium specifically formulated to allow enumeration of total colony-forming cells after only 7 days of culture. With this new medium, reliable information on hematopoietic progenitor cell numbers in cord blood can be obtained much earlier than with standard 14-day assays. The company also released TeSR™2, a defined, animal-protein free maintenance medium for hESCs and iPSCs. Furthermore, STEMCELL announced that they are now selling all their products directly to customers in Spain too.

■ Advancements

Aeolus

Aeolus Pharmaceuticals, Inc., from CA, USA (www.aeoluspharma.com), announced that recent experiments in preclinical models conducted by the NIH National Institute of Allergy and Infectious Diseases Radiation/Nuclear Medical Countermeasure Development program have shown that AEOL 10150 can effectively increase regeneration of gastrointestinal stem cells, reduce the severity and duration of diarrhea and improve survival when administered at 24 h after doses of total-body irradiation that produce the lethal gastrointestinal syndrome. There are no published studies of agents that accomplish this enhanced stem cell regenerative effect while maintaining gastrointestinal functions and improving survival when administered postirradiation. AEOL 10150 is a small molecule that catalytically consumes reactive O₂ and N₂ species (free radicals). The Mn²⁺-containing compound manganoporphyrin

is able to accept from and to give electrons to reactive O_2 and N_2 species. In preclinical studies AEOL 10150 has been able to downregulate oxidative stress and severe inflammation, which is responsible for much of the tissue destruction that occurs as a result of radiation exposure.

California Stem Cell

California Stem Cell, Inc., from CA, USA (www.californiastemcell.com), and Families of Spinal Muscular Atrophy (www.fsma.org), an international support group and resource center, have completed a formal pre-Investigational New Drug (pre-IND) meeting with the FDA for guidance on the clinical and regulatory pathway and requirements for submission of an IND to initiate human trials for a stem cell-derived motor neuron replacement therapy for spinal muscular atrophy type I. California Stem Cell has developed a stem cell-derived motor neuron replacement product, for the treatment of spinal muscular atrophy type I. Preclinical studies, completed in collaboration with professor Hans Keirstead of the University of California, Irvine, have shown clinical proof of concept through the demonstration of functional benefit in animal models treated with California Stem Cell's motor neuron replacement product, MotorGraft™. MotorGraft has the potential to provide benefit for spinal muscular atrophy by two mechanisms:

- Direct replacement of the motor neurons lost during the disease course, resulting in new muscle innervation;
- Providing a nursing support function to remaining motor neurons.

Fate Therapeutics

Fate Therapeutics, Inc., from CA, USA (www.fatetherapeutics.com), generated human iPSCs using a combination of small molecules that significantly improves the speed and efficiency of reprogramming. The discoveries, which were made under a research collaboration between Fate Therapeutics and The Scripps Research

Institute (www.scripps.edu), represent a more than 200-fold improvement in reprogramming efficiency and reduce the reprogramming period to 2 weeks as compared with methods using only four reprogramming factors (Oct 3/4, Sox2, Klf4 and c-Myc). This latest advance has broad implications for the creation of 'pharmaceutical-grade' iPSCs, reprogrammed cells that can be produced without genetic modification at commercial-scale quantity, quality and consistency, and continues to bolster the leadership position of Fate Therapeutics in industrialized iPSC technology. The company is developing minimally invasive techniques for reprogramming and differentiation and has exclusively in-licensed from Scripps and the Whitehead Institute for Biomedical Research an intellectual property portfolio related to iPSC technology, dating back to November 2003.

Medtronic

Medtronic, Inc., headquartered in MN, USA (www.medtronic.com), published results of a study comparing the safety and effectiveness of INFUSE® Bone Graft with autogenous bone graft when used in maxillary sinus floor augmentation [1]. These data were part of the premarket approval submission to the FDA that led to the March 2007 approval of INFUSE Bone Graft in certain oral maxillofacial and dental regenerative uses. INFUSE Bone Graft was shown to have very similar rates of effectiveness as autogenous bone graft, the standard of care, for sinus lifts, which is a common dental surgical procedure. The advantage of using INFUSE Bone Graft is that it avoids harvesting autogenous bone and the associated morbidity, cost and increased surgical time. The study provided actual human histological evidence that the bone generated by INFUSE Bone Graft is normal, mature, 100% viable bone with no residual graft material, as evidenced by core samples taken at the time of dental implant placement. INFUSE Bone Graft, an absorbable collagen sponge combined with recombinant human bone morphogenetic protein 2, was originally approved for an anterior lumbar interbody fusion with a Medtronic titanium interbody fusion device in July 2002 and is also indicated for the treatment of acute

open tibial fractures. INFUSE Bone Graft has received the prestigious Prix Galien USA 2008 Award for Best Biotechnology Product. Patients and physicians can learn more about INFUSE Bone Graft at www.infusebonegraft.com. More information about the company's clinical trials can be found at www.clinicaltrials.gov.

Mesoblast

Australia's regenerative medicine company, Mesoblast Ltd (www.mesoblast.com), announced successful preclinical trial results of its adult stem cells in the treatment of degenerative intervertebral disc disease, the leading cause of low back pain. A single low-dose injection of Mesoblast's allogeneic adult stem cells into severely damaged intervertebral discs resulted in dramatic reversal of the degenerative process, regrowth of disc cartilage, and sustained normalization of disc pathology, anatomy and function. The results of a placebo-controlled, randomized trial of Mesoblast's cells for the treatment of degenerative disc disease in 36 sheep has been presented and highlighted at the World Congress on Osteoarthritis, Osteoarthritis Research Society International, in Montreal, Canada, in September 2009. A total of 6 months after a single direct intradiscal injection of Mesoblast's cells, discs that were initially severely damaged and degenerated were found to have become indistinguishable from healthy nondegenerated discs in their histopathology, cartilage content, height and structure. By contrast, severely degenerated discs that served as controls and were either not injected or were injected with hyaluronic acid, continued to demonstrate significantly reduced disc height ($p < 0.01$), disordered disc structure ($p < 0.01$), disrupted histopathology ($p < 0.01$) and reduced cartilage content ($p < 0.05$), compared with healthy nondegenerated discs over 6 months of follow-up. Three blinded independent experts reviewed the results of disc x-rays, MRI and histopathology.

Nissan Chemical Industries & ReproCELL

Signaling by thrombopoietin via its myeloproliferative leukemia receptor (c-MPL) plays a crucial role in the

maintenance of hematopoietic stem cells. Small-molecule c-MPL agonists have recently been shown to be beneficial in the treatment of thrombocytopenia. However, their effects on hematopoietic stem cells have not yet been explored. Nissan Chemical Industries (www.nissanchem.co.jp/english/index.html) and ReproCELL (www.reprocell.net), in a collaboration with University of Tokyo, Japan, and Chiba University, Japan, evaluated the effects of NR-101, a novel small-molecule c-MPL agonist, on the *ex vivo* expansion of human cord blood stem cells [2]. During a 7-day culture of CD34⁺ or CD34⁺CD38⁻ hematopoietic stem and progenitor cells, NR-101 efficiently increased their numbers, with a greater than twofold increase compared with thrombopoietin, although its effect on megakaryocytopoiesis was comparable to that of thrombopoietin. Correspondingly, severe-combined immunodeficiency repopulating cells were increased 2.9-fold during a 7-day culture with NR-101 compared with freshly isolated CD34⁺ cells, and 2.3-fold compared with that with thrombopoietin. Of note, NR-101 persistently activated signal transducer and activator of transcription 5 but not 3. Furthermore, NR-101 induced a long-term accumulation of hypoxia-inducible factor-1 α protein and enhanced activation of its downstream target genes.

SANUWAVE

SANUWAVE, Inc., from GA, USA (www.sanuwave.com), an emerging medical technology company focused on the development and commercialization of noninvasive, biological response activating devices in the regenerative medicine area, presented at the 2009 International Bone-Tissue-Engineering Congress in Hannover, Germany, held on 9–11 October 2009 scientific findings that Pulsed Acoustic Cellular Expression (PACE™) stimulated a dramatic proliferation of osteoprogenitor stem cells and thickening (up to tenfold) of the cambium layer of the periosteum in the femur of the adult rats within 4 days. Neovascularization and new bone formation within the thickened periosteum were also evident after 4 days. Results support the proposition that PACE could be employed as a noninvasive technique to cause proliferation and thickening of the cambium layer of the femur's periosteum for the subsequent intraoperative harvesting of progenitor stem cells days later for bone or cartilage regeneration.

StemCells

StemCells, Inc., from CA, USA (www.stemcells.com), demonstrated for the first time that transplantation of its proprietary, purified human neural stem cells delays the loss of motor function in a mouse model of infantile neuronal ceroid

lipofuscinosis [3]. The disease, commonly referred to as Batten disease, is a fatal neurodegenerative disease caused by a deficiency in the lysosomal enzyme palmitoyl protein thioesterase-1 (PPT1). Ppt1^{-/-} mice display hallmarks of Batten disease and mimic the human pathology: accumulation of lipofuscin, degeneration of neurons in CNS and a shortened lifespan. Purified nongenetically modified human CNS stem cells, grown as neurospheres, and supplied by StemCells, were transplanted into the brains of immunodeficient Ppt1^{-/-} mice where they engrafted robustly, migrated extensively and continuously secrete the missing lysosomal enzyme characteristic of Batten disease, which is needed to process cellular waste and keep neurons functioning and healthy. Compared with the control group, the mice that received the transplanted neural stem cells showed statistically significant reduction in cellular waste build-up, protection of critical host neurons and delayed loss of motor function. The study was conducted in collaboration with the UK-based King's College London (www.kcl.ac.uk), and the US-based Stanford University School of Medicine (www.med.stanford.edu) and The Salk Institute for Biological Studies (www.salk.edu).

Clinical Trials

■ Biocomposites

Biocomposites, a privately held developer, manufacturer and distributor of synthetic tissue regeneration products headquartered in UK (www.biocomposites.com), announced that their product geneX® has been successfully used in a combination with mesenchymal stem cells to treat fracture nonunions in a pioneering study in Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK (www.rjah.nhs.uk). The stem cells

are collected in a sample of bone marrow, then purified, cultured and expanded at the Ocell GMP laboratory (www.oscell.enta.net/stem-cells.html). A total of 5–10 million stems cells are then combined with geneX and implanted around the fracture site. All patients are part of a clinical trial with long-term follow-up data held independently by the Oswestry Outcome Centre. geneX is a synthetic bone graft material with a unique biphasic composition manufactured through a

proprietary process that confers the product with a reproducible negative surface charge. This property stimulates bone cell activity, accelerating bone formation and fusion by harnessing key proteins and directing cell adhesion and proliferation for rapid osteogenesis. geneX is fully resorbable and is completely replaced by bone. geneX overcomes the surgeons reliance on donor tissue, presenting both a cost saving and a reduction in the risks associated with its use.

■ Bioheart

Bioheart, Inc., from FL, USA (www.bioheartinc.com), presented positive efficacy data of autologous skeletal myoblasts (or MyoCell®, Bioheart's flagship biologic product), from part 1 of its Phase II/III clinical trial at the Heart Failure Society of America Meeting in Boston, MA, USA. Over the 6-month observation period, the most pronounced changes were seen in the cell-treated groups. The 6-min walk distance, an established parameter of efficacy utilized in heart failure studies and one of the primary end points in the trial, increased on average by more than 91 m in cell-treated patients, whereas in the placebo-treated group a decrease of nearly 4 m was seen. This may suggest that patients with heart failure could return to a more active lifestyle after receiving Bioheart's treatment. Moreover, important safety objectives were met. The occurrence of early (within 4 weeks of orMyoCell implantation) ventricular tachyarrhythmias appeared in the orMyoCell-treated groups, similar to observations in other clinical trials involving heart failure patients. However, the arrhythmias were detected and treated with no adverse results, and disappeared in many cases early on and completely by 6 months post-treatment; the investigators believe that early detection and management strategies, as were implemented and refined during enrollment in MARVEL part 1, reduce the risk of recurrent arrhythmias and may enhance 6-month event-free survival. There were no deaths in this study.

■ BioMimetic

Shares of BioMimetic Therapeutics Inc., from TN, USA (www.biomimetics.com), dropped 16% after announcing that its experimental product to help bone growth showed lower rates of bone-fusion compared with the standard-of-care in a late-stage trial. In an intent-to-treat population, 24-week fusion rates were 57.9% for patients receiving the product Augment™ and 60.4% for patients on autograft. Achieving bone fusion was defined as 50% or greater bone bridging at 24 weeks in the study, the company said in a statement.

The company's Augment bone graft was being tested for use in hindfoot and ankle fusion surgery to treat chronic pain. The positive spin given by the company is that, with the use of Augment, patients can expect a comparable treatment outcome while being spared the pain and potential morbidity associated with traditional autograft bone harvesting and transplantation.

■ Opexa

Opexa Therapeutics, Inc., from TX, USA (www.opexatherapeutics.com), a company developing Tovaxin®, a personalized T-cell immunotherapy for multiple sclerosis, announced results from further analysis of the double-blind, placebo-controlled, 52-week Phase IIb TERMS clinical study of 150 patients with relapsing remitting multiple sclerosis. This analysis evaluated patients with an annualized relapse rate of one or greater at study entry. More than 83% of the Tovaxin-treated group (n = 85) remained relapse-free at 1 year and the annualized relapse rate after treatment decreased to 0.20, a 42% reduction compared with placebo. Tovaxin is derived from T cells isolated from peripheral blood, expanded *ex vivo* and reintroduced into the patients via subcutaneous injections. This process triggers a potent immune response against specific subsets of autoreactive T cells known to attack myelin, believed to be a primary cause of multiple sclerosis attacks and nervous system damage. Shares of Opexa Therapeutics went up from \$1.53 to \$5.66 per share after the announcement.

■ Osiris

Osiris Therapeutics, Inc., from MD, USA (www.osiris.com), announced preliminary results for two Phase III trials evaluating Prochymal™ for the treatment of acute graft-versus-host disease (GvHD). GvHD, the most common complication of bone marrow transplantation, is a life-threatening disease for which there is currently no approved treatment. In one trial, in which Prochymal was used along with steroids, 45% of patients responded to Prochymal and steroids compared with 46% who had a response to steroids and a placebo. In a second trial, in which Prochymal was tested in patients who were not benefiting from steroids, 35% of those getting the drug had a resolution of GvHD for

at least 28 days, compared with 30% getting the placebo. The difference was not statistically significant. Shares of Osiris fell 34%, to \$8.03.

■ Pluristem

Pluristem Therapeutics, Inc. from Haifa, Israel (www.pluristem.com), has begun enrolling patients in the USA for a Phase I clinical trial with its unmatched placenta-derived stem cell product, PLX-PAD, the company's leading product candidate for the treatment of critical limb ischemia, the end-stage of peripheral artery disease. Enrollment began at the Center for Therapeutic Angiogenesis in Birmingham, AL, USA. The initiation of this study follows the approval of the company's IND application to begin clinical trials with PLX-PAD by the FDA. The Phase I study is designed to evaluate the safety of PLX-PAD in patients with critical limb ischemia. A total of up to 12 adults with the disease will be included in this dose escalating trial.

■ Soligenix

Soligenix, Inc., from NJ, USA (www.soligenix.com), formerly known as DOR BioPharma, Inc., has initiated enrollment in its confirmatory Phase III randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating orBec® for the treatment of acute gastrointestinal GvHD. The initiation of enrollment in this trial also triggered the payment and receipt by Soligenix of a \$1 million milestone pursuant to the company's collaboration agreement with Sigma-Tau Pharmaceuticals, Inc. This Phase III clinical trial, also referred to as the SUPPORTS protocol (Sparing Unnecessary Prednisone Phase III orBec® Randomized Treatment Study), will enroll an estimated 166 patients to confirm the clinically meaningful end points observed in previous Phase II and Phase III clinical studies. The primary end point is the treatment failure rate at study day 80. This end point was successfully measured as a secondary end point (p-value 0.005) in the company's previous Phase III study as a key measure of durability following a 50-day course of treatment with orBec® (i.e., 30 days following cessation of treatment). The SUPPORTS trial will be conducted at major transplant centers throughout the USA and is expected to complete with clinical data available in the

first half of 2011. The SUPPORTS trial will be conducted pursuant to a Special Protocol Assessment agreement that the company had reached with the FDA. An agreement via the Special Protocol Assessment procedure is an agreement with the FDA that a Phase III clinical trial's design (e.g., end points, sample size, control group and statistical analyses) is acceptable to support a regulatory submission seeking new drug approval. The European Medicines Agency (www.emea.europa.eu) also agreed that should the new confirmatory Phase III study produce positive results, the data would be sufficient to support a marketing authorization approval in all 27 EU member states.

■ TaiGen

Taiwanese TaiGen Biotechnology Co., Ltd (www.taigenbiotech.com.tw) announced that in a Phase I study in healthy volunteers TG-0054, a chemokine (C-X-C motif) receptor 4 antagonist, was well tolerated and rapidly mobilized stem cells and endothelial progenitor cells from bone marrow into peripheral blood. The number of CD34⁺ stem cells in circulation after one dose of TG-0054 was equal or higher than reported cell numbers needed for stem cell transplantation in cancer patients. The observed adverse effects were all mild and transient. A Phase II study

in stem cell transplantation for multiple myeloma, non-Hodgkin lymphoma and Hodgkin disease patients is currently being initiated. The trial was a randomized, double-blind, placebo-controlled, single intravenous dose study including 64 healthy volunteers in USA, to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of TG-0054 in eight cohorts. The mobilized stem and progenitor cells peaked at 4–6 h following one single intravenous dose. Furthermore, TG-0054 has the potential to be used alone, not in combination with granulocyte-colony stimulation factor.

■ TCA Cellular Therapy

TCA Cellular Therapy, from LA, USA (www.tcacellularthrapy.com), presented advances in adult stem cell treatments for severe limb ischemia at the World Stem Cell Summit in Baltimore, MD, USA. A total of 33 patients have been treated during the Phase I and II safety/efficacy clinical trials using a combination of the patient's own endothelial progenitor cells and mesenchymal stem cells. A total of 40 patients will have completed the study by the end of 2009. According to the presentation, there were no adverse effects as a result of the infusions. All of the patients participating in the program have experienced improvement in their walking tests,

ankle brachial pressure index, O₂ pressure, angiography and quality of life. Several of the patients were spared from amputation. The TCA Cellular Therapy combination cell product that was injected in areas with damaged blood vessels developed mature stable vessel formation in ischemic limbs, improving circulation, nonhealing ulcers, gangrene and pain.

■ Vical

Vical, Inc., from CA, USA (www.vical.com), has reported that its TransVaxTM vaccine, designed to ward off a potentially fatal virus in stem cell transplant patients, performed well compared with a placebo in a midstage clinical trial. The TransVax cytomegalovirus vaccine demonstrated an overall increase in cellular immune response in the ongoing trial, Vical said in a statement. The virus, which can cause respiratory illness, is suppressed by the immune system in most people. However, it can cause transplant rejection, destruction of internal organs or death if it flares up when a transplant recipient's immune system is suppressed during recovery. Approximately 80 patients are involved in the midstage study, and Vical expects to have final data from it by the middle of next year.

Regulations, Approvals & Acquisitions

■ Green light

CryoLife

The FDA gave the go ahead for US-based CryoLife, Inc. (www.cryolife.com) to start human trials for its BioFoam[®] Surgical Matrix protein hydrogel technology. The product will be used to help seal liver parenchymal tissue when halting bleeding by ligature or other conventional methods is ineffective or impractical, CryoLife said. BioFoam is a protein hydrogel biomaterial

that has an expansion agent that generates a mixed-cell foam. The foam creates a mechanical barrier to decrease blood flow and pores for the blood to enter, leading to cellular aggregation and enhanced hemostasis. The study will evaluate safety outcomes of BioFoam compared with a standard topical bloodstopping agent. The feasibility investigation will be conducted at two investigational sites and will enroll 20 eligible subjects with ten subjects in

each treatment group. CryoLife is now asking for approval from the US Department of Defense, which will be the final step necessary to begin this trial.

Neuralstem

Neuralstem, Inc., from MD, USA (www.neuralstem.com), has received the green light to begin the first human stem cell trial to treat ALS. The Phase I trial will study the safety of Neuralstem's cells and the

surgical procedures and devices required for multiple injections of Neuralstem's cells directly into the gray matter of the spinal cord of human patients with varying degrees of the disease. A total of 12 patients will receive five to ten injections of Neuralstem's patented human neural stem cells in the lumbar area of the spinal cord. In addition to establishing the safety and feasibility of the treatment, Neuralstem hopes to be able to measure a slowing down of the ALS degenerative process. Final results from the trial are expected in approximately 2 years. The trial will be under the direction of principal investigator Eva L Feldman, Director of the University of Michigan Health System ALS Clinic and the Program for Neurology Research & Discovery. News of the FDA's approval of the trial, which had been delayed in February, sent Neuralstem shares up as much as 57% in trading on the day of announcement. At close, Neuralstem stock was up 21 cents to \$2.08.

Stemedica Cell Technologies

Stemedica Cell Technologies, from CA, USA (www.stemedica.com), has been granted a license by the State of California's Food & Drug Branch (www.dhs.ca.gov/fdb) to manufacture stem cells for human clinical trials. This Drug Manufacturing License recognizes Stemedica as being compliant with California law and the applicable provisions of the Code of Federal Regulations.

VitroLife

Vitrolife has received approval from TGA (Therapeutic Goods Administration) for its new needle for the collection of human oocytes, Swemed Sense™ (patent pending), which reduces the risk of tissue damage and pain. It was launched in Australia in October. The Swemed Sense™ oocyte aspiration needle is designed with a thinner front part and tip so as to minimize tissue damage, bleeding and pain. However, the rear part of the needle has a larger diameter. This makes the needle stable and therefore does not reduce the handling ability.

■ Pending

Geron

Geron Corporation, from CA, USA (www.geron.com), is planning to advance clinical development of its hESC-based product, GRNOPC1, for the treatment of spinal cord injury. The plan is expected to enable Geron to re-initiate the Phase I clinical trial of GRNOPC1 in patients with complete thoracic spinal cord injury and to support future expansion of the trial to patients with cervical injuries. Geron has been performing a series of preclinical studies to expand the clinical program for spinal cord injury beyond patients with complete thoracic injuries. The company's goal is to test the safety and utility of GRNOPC1 in patients with complete and incomplete injuries in both thoracic and cervical regions. As announced previously, in one preclinical study, a higher frequency of animals developed cysts in the injury site than had been seen in numerous foregoing preclinical studies with clinical grade GRNOPC1. These cysts are nonproliferative, confined to the injury site, smaller than the injury cavity and were not associated with adverse effects on the animals. As part of ongoing work to optimize GRNOPC1 manufacturing and product release, the company developed new candidate markers and assays. Data from studies using the new markers were submitted to the FDA. The IND for spinal cord injury was placed on clinical hold pending FDA review of the data. Geron will complete a confirmatory preclinical study using GRNOPC1 that has been characterized by the new markers and assays, as agreed upon in discussions with the FDA. As part of the ongoing plan to advance clinical development for cervical patients, Geron had already initiated this preclinical study in an animal model of cervical injury. In discussions with the company, the FDA has advised that it concurs with Geron that positive data from this study can be used to support both release of the clinical hold and expansion to cervical patients. Geron expects the data from this study to enable re-initiation of the clinical trial in the third quarter of 2010. The company is initially developing GRNOPC1 for spinal cord injury, but is also exploring

application for other neurological diseases, including multiple sclerosis, stroke and Alzheimer's disease.

■ Acquisitions

NeoStem

NeoStem, Inc. from NY, USA (www.neostem.com), has received note from the US Securities and Exchange Commission (SEC; www.sec.gov) declaring effective its Registration Statement on Form S-4 filed with the Commission. The Registration Statement, including the joint proxy statement, is being used in connection with NeoStem's acquisition of China Biopharmaceuticals Holdings, Inc. It is anticipated that this acquisition will expand the capabilities and worldwide reach of NeoStem. China Biopharmaceutical's primary asset is a 51% ownership interest in Suzhou Erye Pharmaceutical Co. Ltd, located in Suzhou, China (www.2-pharmacy.com), which in 2008 generated gross revenues of approximately \$50 million and net income of approximately \$8 million. NeoStem's 51% controlling interest in Erye will enable it to benefit from the over 100 drugs on seven GMP lines, including small molecule drugs being manufactured by Erye. Erye has been in business for more than 50 years and is respected for its quality, service and reliability. Erye has begun its 3-year expansion and relocation program, which is anticipated to enhance revenues, profits and manufacturing capabilities.

Riverside

The Riverside Company (www.riverside-company.com and www.riversideeurope.com), a global private equity firm focused on acquiring leading small and medium-sized enterprises with a value of up to US\$150 million, and partnering with strong management teams to enhance their success, has acquired Crioestaminal, a Portuguese company that isolates and cryopreserves stem cells from umbilical cord blood (www.crioestaminal.pt). Crioestaminal is the third largest player in Europe in terms of number of samples stored. The company is also present in Italy through an exclusive agreement with an Italian distributor, Hematos, since 2006 (www.cryo.hematos.com), and in

Spain, where it established a subsidiary with its own sales force, starting operations in April 2008. Crioestaminal also offers innovative prenatal tests such as a baby gender test ('Menino ou Menina') and a DNA test to precociously detect human papillomavirus. Riverside is acquiring the company with some of the founders and key members of the management team.

■ Capital market & finances

Aldagen

Aldagen, Inc., from NC, USA (www.aldagen.com), which pulled its registration to go public in October 2008, is taking a second shot at listing on Nasdaq (www.nasdaq.com). The company, which has raised approximately \$56 million from Aurora Funds (www.aurorafunds.com), Intersouth Partners (www.intersouth.com), Tall Oaks Capital (www.talloakscapital.com), Tullis Health Investors (www.thi-funds.com) and others, is developing regenerative cell therapies in late-stage clinical trials. Aldagen's therapies consist of specific populations of adult stem cells isolated through its technology. The system enables it to select adult stem cells that express high levels of the enzyme aldehyde dehydrogenase. This enzyme plays an important role in controlling the development state of stem and progenitor cells. To identify these cells, Aldagen uses a chemical compound that accumulates in cells with high aldehyde dehydrogenase levels. The compound causes these cells to emit a green fluorescence that can be detected by a cell-sorting device. The company has launched Phase III studies for ALD-101 to test its effectiveness in improving engraftment following cord-blood transplants used to treat inherited metabolic diseases in children. In addition, Aldagen intends to begin Phase III clinical trials of another product, ALD-301, in 2010 to test the product's efficacy in treating critical limb ischemia. It has also completed a Phase I trial of ALD-201 for the treatment of ischemic heart failure. Aldagen has two commercial products, Aldefluor® and Aldecourt®. Aldefluor is a reagent system for use in research activities to identify and isolate stem cells and progenitor cells based on aldehyde dehydrogenase activity. Aldecourt is a diagnostic

product for identification and counting of adult stem cells expressing high levels of aldehyde dehydrogenase. Neither product, however, is a significant source of revenue.

CellCyte Genetics

The SEC (www.sec.gov) filed suit against former Chief Executive Officer Gary Reys and former Chief Scientific Officer Ronald Berninger of CellCyte Genetics, WA, USA (www.cellcyte.com), for falsely telling investors that the company's cutting-edge stem cell technology had been proven successful and was headed for human trials. CellCyte falsely claimed that it had received FDA approval to begin human clinical trials with a special stem cell compound to repair the heart. The SEC alleges that CellCyte did not know how to properly formulate the stem cell compound, had never attempted experiments with the compound to repair organs and had not satisfied any of the FDA requirements to begin human clinical trials. Furthermore, CellCyte engaged in an illegal stock distribution by partnering with a Canadian stock promoter, who sent millions of spam emails, faxes and newsletters containing false information about CellCyte. During the promotional campaign from August to December 2007, CellCyte's stock price rose from \$4.00 to \$7.50, briefly giving the fledgling company a market capitalization of nearly \$450 million. The stock now trades at less than \$0.08 per share, leaving investors who were deceived by the fraudulent materials with massive losses.

Intercytex

Intercytex Group plc, from Cambridge, UK (www.intercytex.com), is temporary suspended from trading of its shares on Alternative Investment Market (AIM), a submarket of the London Stock Exchange (www.londonstockexchange.com/companies-and-advisors/aim/aim/aim.htm).

Novocell

Novocell, Inc., from CA, USA (www.novocell.com), will receive a Disease Team award totaling US\$20 million from the California Institute for Regenerative Medicine (www.cirm.ca.gov). The Disease Team includes a group of scientists at the

University of California, San Francisco (www.diabetes.ucsf.edu), led by Dr Jeff Bluestone, which is contracted to receive \$2.8 million. The funding will advance Novocell's development of a first-in-kind cellular therapy for the treatment of diabetes.

Sangamo

Sangamo BioSciences, Inc., from CA, USA (www.sangamo.com), will receive a \$14.5 million Disease Team Research Award from the California Institute for Regenerative Medicine (www.cirm.ca.gov) to develop an AIDS-related lymphoma therapy based on the application of its zinc finger nuclease gene-editing technology in stem cells. The 4-year grant supports an innovative research project conducted by a multidisciplinary team of investigators led by John Zaia from City of Hope clinical research hospital in CA, USA (www.cityofhope.org). The grant application entitled 'Zinc Finger Nuclease-Based Stem Cell Therapy for AIDS' won the highest score of all grants CIRM received in the first round of Disease Team Research Award funding.

Stemedica Cell Technologies

The Jordanian Stem Cell Company headquartered in Amman, and chaired by His Royal Highness, Prince Asem Bin Nayef, has signed a 5-year multimillion dollar agreement to purchase the technology from Switzerland-based Stemedica International, S.A. (www.stemedica.com/international), a wholly owned subsidiary of Stemedica Cell Technologies, Inc., from CA, USA (www.stemedica.com).

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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