Stem cell and regenerative medicine industry highlights

September 1, 2010–August 31, 2011

BUSINESS DEVELOPMENT

» Hyperactivity: Biotime, Inc.

Michael West is known for his golden touch in stem cell research and regenerative medicine. He made a name as a visionary founder of Geron, CA, USA (www.geron.com) and Chief Scientific Officer of Advanced Cell Technology, MA, USA (www.advancedcell.com). In only 4 years, his California-based one-man band BioTime Inc. (www.biotimeinc.com) has turned into a corporation with multiple subsidiaries. The latest developments are discussed below:

In October 2010, BioTime's subsidiary, Cell Cure Neurosciences, entered into an exclusive license option agreement with Hadasit Bio-Holdings and Teva Pharmaceutical Industries to develop and commercialize Cell Cure's OpRegen™, a human embryonic stem (hESC)-derived retinal pigment epithelial (RPE) cell product for the treatment of age-related macular degeneration. The ongoing development is funded through US\$7.1 million equity investment of BioTime, Teva and Hadasit Bio-Holdings, made simultaneously with this agreement. Additional nondilutive funding has been provided by the Office of the Chief Scientist of the Ministry of Industry, Trade and Labor of the State of Israel.

The Biotime subsidiary Embryome Sciences was rebranded as ReCyte Therapeutics in January 2011. With the capital obtained from equity financing, ReCyte intends to begin to build a near-term revenue business by offering a service to reverse the developmental aging of human cells, and to generate blood and vascular progenitors for cell-banking purposes.

Also in January 2011, BioTime's subsidiary OncoCyte acquired all the assets of Cell Targeting, Inc., including an exclusive license to use phage display peptide technology. A group at the Sanford-Burnham Medical Research Institute invented it for use in cell therapy. The technology holds promise for use in directing hES and induced pluripotent stem (iPS) cells to sites in the body where they can have therapeutic effects. OncoCyte Corporation was formed in early 2009 with an aim to develop genetically modified stem cells capable of finding malignant tumors while carrying genes that can cause the destruction of the cancer cells.

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Following completion of animal preclinical studies on its two tissue-engineered therapeutic product candidates designated OTX-CP03 and OTX-CP07, formulated in Glycosan's HyStem®-C hydrogel, BioTime's subsidiary OrthoCyte, formed in 2010 with a goal to develop cell-based therapies for the treatment of orthopedic disorders, acquired Glycosan BioSystems in March 2011. Glycosan is known for its HyStem hydrogels: injectable, resorbable matrices that support the growth and directed differentiation of stem cells.

In April 2011, BioTime, in collaboration with Xenex, formed LifeMap Sciences to develop and commercialize, through paid subscriptions or on a fee-per-use basis, a database of the thousands of cell lineages branching from hES cells. The database will permit users to follow the development of hES cell lines to the purified progenitor cell lines created by BioTime using its proprietary ACTCellerate™ technology.

Since acquiring Singapore-based company ES Cell International, known for their current Good Manufacturing Practice-compliant hES cell lines, in April 2010 as part of a collaboration with the California Institute of Regenerative Medicine, BioTime has supplied research-grade versions of these lines to dozens of researchers throughout California. In June 2011, BioTime reported complete sequencing of the nuclear genome of five hES cell lines and received NIH approval for two lines – ESI-014 and ESI-017.

» Clinical-grade expansion of human mesenchymal stem cells

Microcarrier-based stirring culture systems and large-scale bioreactors have made efficient *ex vivo* expansion of mesenchymal stem cells (MSCs) feasible. However, lack of serum-free clinical-grade cell culture reagents has hindered progress toward clinical application. In March 2011, Life Technologies, CA, USA (www.lifetechnologies.com), received US FDA 510(k) clearance for StemPro® MSC SFM. This MSC culture medium, now cleared as a medical device, satisfies a crucial requirement for researchers involved in clinical trials in the USA.

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» Making iPS cells available worldwide

While Cellular Dynamics, WI, USA (www.cellulardynamics.com) announced commercial development of new multiple cell types derived from iPS cells, two prominent US organizations decided to make iPS cell lines available to medical researchers around the world, focusing primarily on lines made from samples of patients suffering from debilitating diseases.

The American Type Culture Collection (ATCC; www.atcc.org) was entrusted with the first cell line in 1962. Today, nearly 50 years later, ATCC produces and distributes over 3600 cell lines. To follow its strategic decision of forming an iPS cell line repository dedicated to providing characterized and readily accessible iPS cells to medical researchers around the world, ATCC obtained a patent license from iPS Academia Japan (<http://ips-cell.net/e/index.php>) and set up a collaborative agreement with Stemgent, MA, USA (www.stemgent.com), one of the most prominent providers of stem cell research tools, reprogramming reagents and related services.

The Coriell Institute for Medical Research, NJ, USA (www.coriell.org) was slightly faster. It has already made the following available to the scientific research community iPS cells derived from individuals with Huntington's disease, juvenile-onset diabetes, muscular dystrophy, spinal muscular atrophy and severe combined immunodeficiency.

“ One of the most anticipated clinical trials in the history of regenerative medicine...”

information on this clinical trial can be found at www.clinicaltrials.gov (ID: NCT01217008).

Whereas Geron's focus is acute spinal cord injury (the cells should be injected into the lesion sites between 7 and 14 days after injury), StemCells, CA, USA (www.stemcellsinc.com) received authorization from Swissmedic, the Swiss regulatory agency for therapeutic products, to initiate a Phase I/II clinical trial of its proprietary HuCNS-SC® human neural stem cells in chronic spinal cord injury. This trial is now open for enrollment, and will accrue patients who have a neurological injury level of T2–T11 with both complete and incomplete degrees of paralysis, who are 3–12 months post-injury. The trial is being conducted in Switzerland at the Balgrist University Hospital (www.balgrist.ch/en/Home.aspx), University of Zurich. Additional information about this clinical trial can also be found at www.clinicaltrials.gov (ID: NCT01321333) as well as at StemCells' company website.

CLINICAL STUDIES

» Spinal cord injury

One of the most anticipated clinical trials in the history of regenerative medicine, Geron's Phase I clinical trial of the hES cell-based therapy GRNOPC1 in patients with spinal cord injury enrolled the first patient on October 11, 2010. Data on the first two patients with neurologically complete American Spinal Injury Association (ASIA) Impairment Scale grade A thoracic spinal cord injuries were presented at two conferences in June 2011. According to Geron's press release, the patients received GRNOPC1 at a dose of 2 million cells delivered by injection into the lesion site using a specially designed syringe-positioning device, and no surgical complications during or after the

procedure nor adverse events have occurred to date related to the injection procedures or to GRNOPC1. Initial analyses have shown no evidence of immune responses to GRNOPC1 through day 90, which includes 30 days after complete withdrawal of immune suppression. There was also no evidence of cavitation in the spinal cord at the injury site on MRI through day 180. Geron has received clearance from the FDA to expand eligibility criteria from injuries between spinal segments T3 and T10 to include patients with injuries at T11. In addition, the FDA has approved a reduction of the current 30-day period between subjects to 10 days. Further

» Stroke

On November 16, 2010, ReNeuron, UK (www.reneuron.com) announced that the first patient had been treated with the company's ReN001 stem cells in the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients. ReNeuron is also the first company to have received regulatory approval for any stem cell-based

clinical trial in the UK. The last of three patients in the first cohort was treated in May 2011 and safely discharged from the hospital.

In December 2006, ReNeuron filed an Investigational New Drug application with the FDA to commence initial clinical studies in the USA with ReN001, its stem cell therapy for stroke. However, the agency subsequently put the proposed clinical trial on hold. After more than a year of unsuccessful negotiations, ReNeuron shifted efforts to satisfy UK regulatory bodies. The Medicines and Healthcare products Regulatory Agency cleared the Pilot Investigation of Stem Cells in Stroke (PISCES) study in January 2009, but additional pre-clinical data were requested by the Gene Therapy Advisory Committee (GTAC), which acts as the national research ethics committee for clinical trials with gene therapies and stem cell therapies in

“...the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients.”

the UK. ReNeuron was able to satisfy GTAC and move ahead. In June 2009, ReNeuron signed a contract with Angel Biotechnology Holdings for manufacturing clinical-grade ReN001 stem cell lots for the trial.

The PISCES trial is designed primarily to test the safety profile of ReN001 in ischemic stroke patients at a range of cell doses, but a number of efficacy measures will also be evaluated over the course of the trial. The 12 patients who will be taking part in the trial will be monitored for 2 years, with longer-term follow-up procedures in place thereafter. Additional information about this clinical trial can be found at www.clinicaltrials.gov (ID: NCT01151124).

» Macular degeneration

The US FDA gave Advanced Cell Technology the green light for two Phase I/II clinical trials using hES cell-derived RPE cells: Stargardt's macular dystrophy in November 2010 and dry age-related macular degeneration in January 2011. The first two patients, a 77-year-old woman with dry macular degeneration and a 27-year-old woman with Stargardt's macular dystrophy, were enrolled at the Jules Stein Eye Institute at the University of California, Los Angeles (www.jsei.org) in June and approximately 50,000

RPE cells were administered into one eye of each patient on 12th July 2011. Each study will enroll 12 patients, with cohorts of three patients in an ascending dosage format (50,000–200,000 RPE cells). The primary end point of both studies is to determine the safety and tolerability of hES cell-derived RPE cells at 12 months. Additional information about these clinical trials can also be found at www.clinicaltrials.gov (ID: NCT01345006 and NCT01344993). Recently, the European Medicines Agency's Com-

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mittee for Orphan Medicinal Products officially granted Advanced Cell Technology's hES cell-derived RPE cells designation as an orphan medicinal product for the treatment of Stargardt's macular dystrophy.

“ Private clinics and companies promising wonders with stem cell-based therapies are mushrooming all over the world. ”

REGULATION

» Regulation of stem cell tourism tightening – or is it?

Private clinics and companies promising wonders with stem cell-based therapies are mushrooming all over the world, primarily in developing countries where regulations are lacking or not enforced. The International Society for Stem Cell Research (www.isscr.org) released guidelines for the responsible development of safe and effective stem cell therapies for patients back in 2008. These guidelines provide an underlying concept and foundation on which regulations and laws on cell-based therapy should be built in countries that do not have clearly defined rules on standard levels of patient safety and healthcare. But are these guidelines being followed?

Reflecting mounting international pressure, the office of the Drugs Controller General of India has set up a new committee of experts to clarify the clinical trial programs related to stem cell research. The committee met in March 2011 and the first government-authorized clinical trials on patients with diabetes, liver cirrhosis, osteoarthritis

and chronic obstructive lung disease approved by the Drugs Controller General are on the way.

In Korea, the Ministry of Health and Welfare, in cooperation with the Korea Food and Drug Administration (KFDA; <http://eng.kfda.go.kr/index.php>) reviewed the practices of RNL Bio (<http://rnl.co.kr/eng/main.asp>), one of the most prominent stem cell companies in the country, and launched an investigation into allegations of illegal medical activity. The company was using adult, patient-specific stem cells, and over a period of 3 years approximately 8000 patients have been treated without approval from the authorities, with patients being charged US\$9000–27,000. In addition, the firm has allegedly sold stem cell treatments to five local clinics, as well as clinics in China and Japan.

However, the KFDA has approved for sale the world's first stem cell treatment for myocardial infarction. As from July 1st 2011, Hearticellgram-AMI

treatment, developed by the local company FCB-Pharmacell (www.fcbpharmacell.com/english), became the first stem cell medication in the world approved for clinical use by a governmental regulatory body. FCB-Pharmacell is using patients' own MSCs derived from the pelvic bone marrow cells.

In a similar manner to Korean RNL Bio, German stem cell clinic XCell-Center (www.xcell-center.com) caused controversy by offering unproven stem cell treatments. The clinic closed in May 2011, when the German authorities, the Paul Ehrlich Institute, denied further authorization for stem cell transplantation.

The stem cell tourism hot spot of the Dominican Republic is getting much needed and long-overdue attention from the local government. The Dominican Republic's Public Health Minister affirmed that the government plans to halt all treatments with stem cells unless they are authorized by the Bioethics Health Council (Conabios).

CAPITAL MARKET AND FINANCES

» Largest deal in the regenerative medicine sector

Successful biotechnology company Cephalon, PA, USA (www.cephalon.com), well-known for its portfolio of innovative treatments for CNS disorders, pain and cancer, made a strategic investment to expand into the field of regenerative medicine in December 2010. Cephalon paid Australian stem cell company Mesoblast (www.mesoblast.com) US\$130 million upfront and made a US\$220 million equity investment, which equates to 19.9% of Mesoblast's stake. The deal is to develop and commercialize adult mesenchymal precursor stem cell therapies based on Mesoblast's adult stem cell technology platform. Mesoblast could receive additional regulatory milestone payments from Cephalon of up to \$1.7 billion. Only 6 months later, Cephalon has announced its merger with Israeli giant Teva Pharmaceutical Industries in a US\$6.8 billion transaction. Teva's market value is approximately US\$57 billion.

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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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» Dermagraft® success story continues

UK-headquartered Smith & Nephew (www.global.smith-nephew.com) sold Dermagraft® to Advanced BioHealing, CT, USA (www.abh.com) in 2006 for an undisclosed sum after failing to win US regulatory approval for the product's use in the treatment of venous leg ulcers. Advanced BioHealing obtained FDA approval for the use of Dermagraft to heal diabetic foot ulcers, and that allowed the company to increase its sales from US\$9 million in 2007 to US\$147 million in 2010. In May 2011, Irish healthcare group Shire (www.shire.com) bought Advanced BioHealing for US\$750 million in cash.