STEM CELL business news

Published Biweekly

- Company analysis
- Research news
- Finance & funding
- Patents
- Mergers & acquisitions
- Strategic alliances
- Policy & regulation

Volume 8, No. 7 *Our eighth year* April 13, 2009

News In This Issue…

(Active links … click on headlines after p. 1)

Public Company Analysis

Top of the News…

Preclinical Research

Human Stem Cells Integrate Into Nervous System Of ALS Model Rats

Transplanted human neural stem cells (hNSCs) developed by Neuralstem, Inc. (NYSE Alternext US: CUR) made synaptic contacts with the motor neurons of rats with amyotrophic lateral sclerosis (ALS)-like symptoms, according to a new study conducted at Johns Hopkins University.

According to the company, "this constitutes evidence that the transplanted cells integrated into the nervous system of the host."

The rats had a genetic mutation called SOD-1 G93A which gives them a disease similar to ALS in humans.

"This is the first demonstration of transplanted human neurons synapsing, or making mature structural connections, with the rat motor neurons, something which has not been demonstrated before," said chief scientific officer and a study co-author Dr. Karl Johe. "Our earlier work with this ALS model showed that the stem cells delayed onset of the disease and played a neuroprotective role. Now we have clear evidence that they can become an integral part of the rat nervous system that controls the muscles. I would expect these cells to be readily accepted by and integrated into a human nervous system, such as in an ALS or a spinal cord injury patient."

"This is an important milestone for Neuralstem," said CEO Richard Garr. "The underlying basis for 'replacement' therapy is that the cells can integrate into the host to provide function in addition to providing neuroprotection. We are pleased to be the first to demonstrate that our technology passes that test. Our application to begin the first human clinical trial to treat ALS with neural stem cells is currently under review by the FDA. We are delighted that our continuing animal work adds support for the potency of our cells to ad-

(Continued on page 2)

(Continued from page 1)

dress progressive neurological degenerations."

In the study conducted at Johns Hopkins Medical Institutions, laboratory-grown human neural stem cells (hNSCs) isolated from a fetal spinal cord region were grafted into the spinal cord of rats with a genetic mutation (SOD-1 G93A) that gives them a disease like a particularly aggressive form of ALS.

These rats received live-cell grafts or dead-cell grafts as controls.

In addition, four healthy rats (Spague-Dawley) received live-cell grafts to rule out whether or not any cell activity could be attributed solely to ALS in the SOD-1 rats.

The rats had been injected with a tracing material to track and characterize the synaptic connections.

Forty days after transplantation, the tissues were examined. In the rats receiving live-cell grafts, a large number of host motor neurons had been contacted by human neurons differentiated from the grafted neural stem cells. This occurred in both the ALS model and healthy rats, indicating that the activity was not a result of the disease.

"This study shows, at the ultra-structural level, that these cells make mature connections with host motor neurons in the spinal cord," said Dr. Vassilis E. Koliatsos, whose lab at Johns Hopkins conducted the study. "This demonstrates that these cells not only live, but integrate into the structure of the host's motor system. It also confirms our previous suspicion that many neural stem cells become inhibitory local neurons in the spinal cord."

The study was published online in the *Journal of Comparative Neurology*.

Neuralstem's technology enables production of neural stem cells of the human brain and spinal cord in commercial quantities, and the ability to control the differentiation of these cells into mature, physiologically relevant human neurons and glia.

The company is targeting ischemic spastic paraplegia, traumatic spinal cord injury, Huntington's disease and amyotrophic lateral sclerosis (ALS).

The company filed an IND (Investigational New Drug) application with the FDA for ALS clinical trials in December, 2008, and has entered into a collaborative agreement with Albert-Ludwigs-University, in Freiburg, Germany, to develop clinical trials for Huntington's disease.

Contact: http://www.Neuralstem.com

-=0=-

(Continued on page 3)

Stem Cell Business News does not forecast the market, nor does it recommend buys, sells, or holds. We analyze, interview, and report, so that competitors, suppliers, investors, etc., can make intelligent, and hopefully profitable, strategic decisions.

— The Editors

stem cell **business** news

Research: Ann Goldman
Marketing: Thomas Klein
Subscriber Services Manager: Sarah Dufour
Special Projects: Emma Barone
Production Assistant: Ken Davidson

Published 24 times a year
DataTrends Publications, Inc., 614 Jacob Ct. SW
Leesburg VA 20175-5004 USA
Phone: 703-779-0574
Fax: 703-779-2267
For-profit individual subscription: US$295.00
Nonprofit individual subscription: US$219.00
Site license (unlimited redistribution): US$1,495.00
info@stemcellresearchnews.com
http://www.stemcellresearchnews.com

Mergers & Acquisitions

StemCells Closes Acquisition Of Stem Cell Sciences Plc

Palo Alto, Calif.-based StemCells, Inc. (STEM) said on April 1 that it has closed the acquisition of substantially all of the operating assets and liabilities of Stem Cell Sciences Plc (UK).

The sale was accomplished through a combination of stock and cash.

StemCells acquired proprietary cell technologies relating to embryonic stem cells, induced pluripotent stem (iPS) cells, and tissue-derived (adult) stem cells; expertise and infrastructure for providing cell-based assays for drug discovery; the SC Proven media formulation and reagent business; an intellectual property portfolio with claims relevant to cell processing, reprogramming and manipulation, as well as to gene targeting and insertion; and existing business and license relationships with several major life science companies, such as Merck and Millipore.

Stem Cell Sciences shareholders received 2,650,000 shares of StemCells common stock and approximately $700,000 in cash in the transaction.

"We believe the acquisition of the SCS assets will enable us to leverage our investments in cell technologies to develop non-therapeutic applications, such as cell-based assays, media and reagent tools, in order to pursue nearer-term commercial opportunities," CEO Martin McGlynn said in a statement.

As part of the acquisition, the company added 20 employees in Cambridge, UK, and Melbourne, Australia, to its 55 employees.

The company said that Stem Cell Sciences lost about $225,000 a month in 2008.

StemCells, Inc. is developing cell-based therapeutics to treat diseases of the central nervous system and liver.

Contact: http://www.stemcellsinc.com

-=0=-

Clinical Research

First Patient Treated In Osiris Phase II Heart Attack Trial

Columbia, Md.-based Osiris Therapeutics, Inc. (OSIR) said on April 2 that the first patient had been treated in a Phase II clinical trial evaluating Prochymal for the treatment of heart attacks.

The first patient, a 58-year-old man, was treated at the Heart Hospital of Austin, Texas.

Prochymal is a formulation of adult stem cells designed to provide therapeutic benefit by controlling inflammation, promoting tissue regeneration, and preventing scar formation.

The double-blind, placebo-controlled study is designed to enroll approximately 220 patients following their first heart attack.

Only a few days earlier, on March 27, the company said that it had elected to end enrollment at 210 patients in a Phase III trial evaluating Prochymal for Crohn's disease, primarily because of what it called a "systemic design flaw" in the study.

The company had planned to enroll 270 patients.

The announcement bashed the company's shares in early trading on March 27, pushing the price down by 23 percent.

The company said it believed the design flaw in the trial resulted in significantly higher than expected placebo response rates.

But several analysts were skeptical of the company's explanation, stating instead that Prochymal simply does not do what the company claims it does.

Leerink Swann analyst William Tanner, perhaps the most supportive of Osiris's efforts with Prochymal, said he had expected the trial to end without difficulties. But he then told Reuters he expects the Crohn's disease trial to get pushed by a couple of years because of the new problem.

(Continued on page 4)

Tanner, however, said he does not expect the enrollment halt and design flaws to impact other indications in which the drug is being tested.

Lazard Capital Markets analyst Joel Sendek, on the other hand, was very skeptical of the drug in any indication.

"I don't think the drug works very well, and I have not seen any evidence that the drug works in Crohn's disease," Sendek told Reuters.

Sendek has a "sell" rating on the company.

"The company has moved too fast in the late-stage studies. They had very few early- and mid-stage data."

Analyst Adam Feuerstein was equally negative about the clinical trial.

"The Prochymal study failed a futility test," he told us. "That's a fact. The drug doesn't work. Osiris can try to explain it away by blaming placebo patients but it doesn't change the outcome."

Nevertheless, physicians participating in the study of Prochymal for heart attacks expressed excitement.

"The excellent safety profile and encouraging data from the Phase I trial makes Prochymal a promising therapy for the treatment of acute myocardial infarction," said Roger Gammon, M.D., medical director of research at Austin Heart. "This trial will provide valuable data on the ability of these cells to prevent pathological remodeling, which is expected to have positive long-term implications for improved clinical outcomes in patients following a heart attack."

The Phase II double-blind, placebo-controlled trial will evaluate the safety and efficacy of Prochymal in conjunction with standard of care to improve heart function in patients who experienced a first heart attack.

The trial will be conducted at institutions and academic research centers in the United States and Canada. This trial focuses on patients who have suffered a severe myocardial infarction.

Osiris is focused on developing products to treat serious medical conditions in the inflammatory, orthopedic and cardiovascular areas.

Contact: http://www.Osiris.com

Positive Interim Results From Indian CLI Trial

Privately held Harvest Technologies Corp. (Plymouth, Mass.) said on April 1 that interim results from the first thirty patients in a clinical trial of a stem cell-based treatment of patients in India with non-reconstructable critical limb ischemia (CLI) showed some positive results.

CLI due to advanced thromboangitis obliterans is commonly referred to as Buerger's disease.

The study is being conducted at Sri Ramachandra University in Chennai India and is designed to evaluate the therapeutic effect of a composition of nucleated bone marrow cells prepared using the Harvest SmartPReP System.

The study is being led by principal investigator Prof. K. S. Vijayraghavan, head of vascular surgery.

Harvest's SmartPReP System is a point-of-care device for concentrating a patient's own (autologous) bone marrow stem cells in approximately 15 minutes.

The interim evaluation of the patients conducted at 12 weeks showed convincing evidence that the treatment had significant clinical effect, the company said.

The most important finding was that 87.5 percent of patients were able to save their legs.

Other major endpoints also showed significance improvement. Quality of Life assessment (Rand-36 questionnaire) and individual perception of pain showed statistically significant improvement ($p=0.0009$ and 0.0001 respectively). There was 100 percent reduction in the use of pain medications. Limb perfusion, as measured by TcPO2 and ABI also showed statistically significant improvement ($p=0.0001$ and 0.0003 respectively).

Thirty-three percent of the patients had serious ulcers and 90 percent of these showed 90 percent or better wound closure in 26 weeks. There were no adverse events associated with the

(Continued on page 5)

treatment.

Harvest said it is hopeful that the data along with data generated in Europe will aid in obtaining the necessary clearances for the marketing the Harvest BMAC System for the treatment of CLI in India before the end of this calendar year.

In the United States, Harvest Tech is sponsoring a multi-centered randomized controlled double-blind study evaluating the therapeutic effect of BMAC for treating patients with non-reconstructable CLI.

Contact: http://www.harvesttech.com

-=0=-

Stem Cell Therapy Improves Severe Limb Ischemia

Preliminary positive results of a Phase I clinical trial using an adult stem cell treatment for severe limb ischemia results were presented March 29 at a meeting of the American College of Cardiology by Gabriel Lasala, M.D., medical director of Covington, La.-based Tchefuncte Cardiovascular Associates (TCA).

Lower limb ischemia is a condition where plaque build-up causes decreased circulation in the lower leg.

Symptoms of the condition include intense pain and swelling.

Lasala, together with the company's scientific director Jose Minguell, Ph.D., treated ten patients during the Phase I safety/efficacy clinical trial using a combination of the patient's own endothelial progenitor cells (EPCs) and mesenchymyal stem cells (MSCs).

The cells, obtained through bone marrow aspiration, were mixed and infused into damaged veins.

According to Lasala, there were no adverse effects as a result of the infusions. More importantly, their patients experienced a progressive improvement in all clinical parameters which are still persisting a year after treatment.

"All patients experienced improvement in their walking tests, ankle brachial pressure index, oxygen pressure, angiography and quality of life," Lasala said. "These findings, coupled with increase of blood flow in collateral vessels suggest that the therapy is both safe and effective."

The researchers believe that the use of adult stem cell therapy in ischemia patients allows for the development of new mature and stable capillaries.

"The similarity in the recovery of our patients is promising," said Lasala. "We find that the stem cells, once re-injected, go about forming new blood vessels, thus increasing circulation dramatically."

TCA is the only private company in the United States that is participating in FDA protocols related to stem cell research.

An affiliated company, LifeSource Cryobank, LLC, is a laboratory that collects and preserves stem cells derived from both umbilical cord blood and adult bone marrow.

Contact: http://www.tcaway.com

-=0=-

Strategic Alliances

Company Partners With Scientist To Explore Treatment For Pulmonary Fibrosis

Scottsdale, Ariz.-based ImmuneRegen BioSciences said on April 2 it will be collaborating with a University of Rochester (N.Y.) scientist on research to evaluate the ability of Homspera, an adult stem cell-active compound, to ease the effects of otherwise lethal radiation exposure in animals.

The company is partnering with Jacob Finkelstein, Ph.D., a professor in the departments of pediatrics, radiation oncology and environmental medicine at the University of Rochester

(Continued on page 6)

Medical School.

Finkelstein has explored radiation's effect on the human pulmonary system.

The University's Center for Biophysical Assessment and Risk Management Following Irradiation (CBARMFI) is one of eight Centers for Medical Countermeasures Against Radiation (CMCR) funded by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health.

The initial ImmuneRegen-CBARMFI relationship will include support of research efforts and co-development funding of "a mutually beneficial research strategy."

Finkelstein's laboratory studies the mechanisms of pulmonary injury to physiological, toxicological and radiological stimuli and specifically the role of the alveolar epithelium, the cells that line the airways in the lungs.

These studies include examination of inflammatory processes and the roles of cytokines in the regulation of cells in the lungs and the immune system.

Additionally, investigators at CBARMFI have identified a number of compounds that can mitigate the deleterious effects of radiation and other environmental toxins on pulmonary function.

Of particular interest to both ImmuneRegen and Finkelstein's laboratory are the mechanisms by which exposure to sufficient doses of radiation triggers pulmonary fibrosis, a debilitating and potential lethal long-term effect.

Finkelstein's laboratory has shown the involvement of pulmonary epithelial cells and fibroblasts in post-radiation fibrosis, specifically in the growth and regulation of connective tissues in the lung.

These are the same cell types that ImmuneRegen's Homspera has been shown to affect, as enhanced cell and connective tissue proliferation and appropriate developmental growth signals accelerate wound healing.

Homspera, an analog of the endogenous neurokinin Substance P, has been shown to have hematopoietic stem cell stimulatory activity as well as immunomodulatory and anti-inflammatory activity in a number of model systems.

ImmuneRegen, a subsidiary of IR BioSciences Holdings, Inc. (IRBS), is focused on the research, development and licensing of Homspera.

Contact: http://www.immuneregen.com

-=0=-

Spotlight On ... Neuralstem, Inc.

Company Needs Cash To Keep Its Research Moving Forward

Expected Removal Of FDA Clinical Hold on ALS Trial Could Help Secure Needed Funding

Small stem cell research firm ($27 million market cap) Neuralstem, Inc. (AMEX: CUR), of Rockville, Md., has had some good news and some not-so-good news recently.

The not-so-good news: On February 20 the U.S. Food and Drug Administration placed the company's spinal cord stem cell trial to treat amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) on clinical hold.

According to the company, the FDA provided specific comments, questions and recommendations for modifications to the protocol described in its Investigational New Drug (IND) application.

CEO Richard Garr said the agency asked for additional information regarding its product manufacturing process, pre-clinical studies, and clinical delivery injection device and technique.

"The agency has also requested various modifications to the protocol and eligibility criteria for patients in the trial, as well as slight changes to the timing of the surgeries," Garr said. "We are evaluating these changes and will respond accordingly. The agency had extensive 'non hold' comments, requests for information, and recommendations. These primarily concerned issues that will need to be addressed for final

(Continued on page 7)

product manufacturing and testing. We are appreciative of their work in this area."

The clinical hold could last only a short time. But it may take a lot longer, depending on the extent of the FDA's concerns.

The company insists, however, that the clinical hold will not last that long.

"We do feel we have enough in the way of preclinical data to meet the FDA's criteria," a spokesman said. "The FDA is *not* going to reject our ALS trial application. It is only a question of when, not if, [the clinical hold is lifted]. We expect to hear from the FDA by Monday (April 13, 2009). "

The good news was announced early in March: In a preclinical animal study conducted at Johns Hopkins University, transplanted human neural stem cells (hNSCs) developed by the company made synaptic contacts with the motor neurons of rats with amyotrophic lateral sclerosis (ALS)-like symptoms.

According to the company, "this constitutes evidence that the transplanted cells integrated into the nervous system of the host."

The rats had a genetic mutation called SOD-1 G93A which gives them a disease similar to ALS in humans.

"This is the first demonstration of transplanted human neurons synapsing, or making mature structural connections, with the rat motor neurons, something which has not been demonstrated before," said chief scientific officer and a study co-author Dr. Karl Johe. "Our earlier work with this ALS model showed that the stem cells delayed onset of the disease and played a neuroprotective role. Now we have clear evidence that they can become an integral part of the rat nervous system that controls the muscles. I would expect these cells to be readily accepted by and integrated into a human nervous system, such as in an ALS or a spinal cord injury patient."

"This is an important milestone for Neuralstem," CEO Garr said. "The underlying basis for 'replacement' therapy is that the cells can integrate into the host to provide function in addition to providing neuroprotection. We are pleased to be the first to demonstrate that our technology passes that test."

This is especially good news for Neuralstem, in light of the company's application to the FDA to begin a clinical trial to treat ALS with neural stem cells. As noted above, the application is under review, and this preclinical animal study may add support for the claim that the company's cells are potent enough to address progressive neurological degenerations.

Perhaps the key question about Neuralstem – aside from those related to the efficacy and safety of its neural stem cells for human therapies, which will be decided by clinical trials – is how the company will continue to pay for its various research programs.

The company told us it has ruled out a merger with or acquisition by another company.

And good news from the FDA would certainly boost its prospects for securing additional funding from other sources, which it definitely needs.

With a cash burn rate of $500,000-$575,000 a month, and very little cash reserves (about $5 million at the end of 2008), the company has to come up with significant funding to pay for ongoing operations and preclinical and clinical research.

Once it enters the clinical research phase, cash requirements will be even larger and more urgent.

Can the company attract investors with deep pockets? The company's common stock, which closed at $1.23 on April 10, 2009, is considered highly speculative, so the open market is not a practical source of significant cash. That leaves private placements and other financing vehicles.

The following is a look at Neuralstem as it struggles to get its products through the FDA approval process and into the marketplace.

Overview

Neuralstem has been around for more than a decade, though it hasn't been focused on stem cell research the entire time. Founded in 1996, the

(Continued on page 8)

company's early commercial efforts focused on genomics, drug discovery, and cell therapy. Contracts with Gene Logic, Inc., and with the U.S. Department of Defense brought in about $10 million from 2001 to 2002. But those ventures were not renewed and involvement in genomics and drug discovery ended.

In 2004, the company refocused its research on the development and commercialization of treatments based on transplanting human neural stem cells.

The company's goal now is to develop effective ways to replace damaged, malfunctioning, or dead neural cells with cells derived from neural stem cells.

Major disease targets for its cell replacement technology include: Alzheimer's disease, Parkinson's disease, multiple sclerosis, ALS, depression, and spinal cord injuries.

The company has developed reproducible processes to identify, isolate, expand, purify, and control cell differentiation in mature functioning human neurons and glia (i.e., non-excitable central nervous system cells that serve essential functions in support of neurons); and bank human neural stem cells derived from brain tissue.

Neuralstem believes that because the cells are purified neural stem cells, they may be better suited for transplantation and may provide a safer and more effective alternative to therapies that are based on cells derived from cancer cells, from animal cells, or from an unpurified mix of many different cell types.

The company's portfolio of patents and patent applications form the proprietary base of its research and development efforts in the area of neural stem cell research and related technologies.

However, the company is involved in two ongoing lawsuits with competitor StemCells, Inc., over certain stem cell patents.

Nevertheless, the company is confident that its intellectual property portfolio, technology base, stem cell know-how, and collaborative projects with various research institutions, give it a competitive advantage.

It is also confident that it will successfully commercialize products for use in treatment of an array of neurodegenerative conditions and in regenerative repair of acute disease. A couple of barriers stand in the way, however: cash and the FDA.

Technology & Intellectual Property

Neuralstem's technology offers the ability to isolate human neural stem cells from most areas of the human brain and spinal cord and to grow them into all types of human neurons.

Neuralstem either owns or has exclusive licenses to four patents and 13 patent applications pending worldwide in the field of regenerative medicine and cell therapy.

The company's core patents include:

– Isolation, Propagation, and Directed Differentiation of Stem Cell from Embryonic and Adult Central Nervous System of Mammal; and

– In Vitro Generation of Differentiated Neurons from Cultures of Mammalian Multi-potential CNS Stem Cell

These patents contain claims that cover the details of its isolation/differentiation process and the culture of cells created.

Neuralstem says its stem cell technology is different from that of other companies because its patented processes do not require "pushing" the cells toward a certain fate by adding specific growth factors. The company says its cells actually "become" the type of cell they are fated to be. This process and the resulting cells create a technology platform that allows for the efficient isolation and ability to produce, in commercially reasonable quantities, neural stem cells, according to the company.

Furthermore, the technology allows for cells to grow in cultured dishes (i.e., "in vitro") without mutations or other adverse events that would compromise their usefulness. According to

(Continued on page 9)

the company, this provides two distinct advantages:

– The growth or expansion of the cells in vitro occurs while the cells are still in their "stem cell" or blank state that allows for the creation of commercially reasonable quantities of neural stem cells. Once a sufficient number of blank cells have been grown, the technology allows programming or differentiating the cells into either neurons or glia;

– The technology offers the ability to sample the cells while still in vitro to confirm that the cells are differentiating in the desired cell type.

Neuralstem believes its technology also has ancillary uses with respect to drug development. The ability to grow and differentiate neural cells in vitro allows analysis of the potential biological effects of molecules on these cells. This has resulted in the identification of a group of small molecule compounds with the potential to enhance the survival of the endogenous cells residing in the hippocampus region on the brain.

Research & Development

Neuralstem's basic research has focused on isolating and developing a series of neural stem cell banks that can serve as a basis for therapeutic products.

The goal of this early research has been to develop methods to identify, isolate and culture large varieties of stem cells of the human nervous system, and to develop therapies using these stem cells.

The research is conducted both internally and through the use of third party laboratory consulting companies supervised by Neuralstem.

The company also conducts research and development through research collaborations, as noted above.

With its identification/isolation/culture technology in place, the company has expanded its basic research into the animal testing phase, and recently beyond animal to human testing.

There really hasn't been a whole lot of preclinical animal testing to report.

As to human testing, as noted above, it has filed an application with the FDA to launch a clinical trial for ALS. But the trial has been put on hold.

In 2007, the company announced that a University of Pennsylvania researcher would lead a clinical study using Neuralstem cells in the treatment of ischemic spastic paraplegia.

There was no further word on that, however, although in its SEC filing the company refers to "an agreement with the [University of Pennsylvania] to assist us in developing 'A Feasibility and Safety Study of Human Spinal Stem Cell Transplantation for the Treatment of Ischemic Spastic Paraplegia Due to Spinal Cord Ischemia.'"

[Editor's Note: We received no response from Dr. Albert Cheung of the department of anesthesiology at the hospital of the University of Pennsylvania to e-mailed questions regarding the status of the clinical study.]

Highlights of its research announcements over the past couple of years include the following:

– February 2007: Human neural stem cell grafts showed neuronal differentiation in the normal and injured spinal cord of adult rats. Neural stem cell grafts derived from spinal cord of a single eight week fetus were grafted into the lower spinal cord of normal or injured immune deficient adult rats. As part of the differentiation, the researchers found that some of these cells grew axons (the long arms of nerve cells) and some were able to form cell to cell contacts (synapses) with motor neurons of the host rats. The results, by researchers led by Vassilis Koliatsos of Johns Hopkins University, challenged previous assumptions that the spinal cord is unable to support the differentiation of neurons from stem cell grafts.

– May 2007: Rats paralyzed due to loss of blood flow to the spine returned to near normal ambulatory function six weeks after receiving grafts of human spinal stem cells (hSSCs). The study was

(Continued on page 10)

led by Martin Marsala, M.D., UC San Diego professor of anesthesiology. Neuralstem manufactured the hSSCs used in the study.

– August 2007: Neuralstem announced it would work with the ALS Clinic at the University of Michigan to develop further proof-of-principle data to move the company's spinal cord stem cells into patients with amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.

– December 2007: Neuralstem said that the University of Pennsylvania had agreed to use the company's neural stem cell-based technology in a clinical trial treating patients suffering from ischemic spastic paraplegia, a form of spinal cord paralysis.

– November 2008: Neuralstem said it would collaborate with Prof. Guido Nikkah, Ph.D, of Albert-Ludwigs-University (Freiburg, Germany) to advance development of Neuralstem's human neural stem cell therapies. The collaboration would focus on Huntington's disease.

– December 2008: The company announced it would collaborate with the China Medical University & Hospital of Taiwan to advance development of Neuralstem's human spinal cord neural stem cell therapies. The collaboration would focus on ALS with Dr. Shinn-Zong Lin, M.D., Ph.D., as principal investigator.

– December 2008: Neuralstem filed an Investigational New Drug (IND) application with the FDA to begin a clinical trial to treat ALS.

– February 2009: the FDA placed the trial on clinical hold. provided us with specific comments, questions and recommendations for modification to the protocol submitted in our IND. The trial is currently on clinical hold. The company is analyzing the notice and the FDA's comments and recommendations. It is certain the FDA will remove the clinical hold, sooner than later.

– March 2009: Transplanted human neural stem cells (hNSCs) developed by Neuralstem made synaptic contacts with the motor neurons of rats with amyotrophic lateral sclerosis (ALS)-like symptoms in a study conducted at Johns Hopkins University. According to the company, "this constitutes evidence that the transplanted cells integrated into the nervous system of the host." The rats had a genetic mutation called SOD-1 G93A which gives them a disease similar to ALS in humans.

Although Neuralstem's history of basic (animal-based) research results using its neural stem cells seems rather meager, the company insists it has enough data to move forward with human trials. Only the FDA knows for sure at this point.

Markets & Competition

Neuralstem believes that, if successfully developed, neural stem cell-based therapies have the potential to treat a broad range of diseases and injuries of the central nervous system (CNS).

The company believes its technologies can be applied to the treatment of a wide variety of CNS diseases and disorders. But its initial focus is on developing neural cell therapies to treat Parkinson's disease, ALS, and spinal cord injuries.

(Continued on page 11)

Indication	Potential market
Parkinson's disease	1,000,000
Spinal cord injury (SCI)	250,000
Amyotrophic lateral sclerosis (ALS)	30,000

Source: Neuralstem, Parkinson's Disease Foundation, the Parkinson's Action Network, the Foundation for Spinal Cord Injury Prevention, Care and Cure, and the Amyotrophic Lateral Sclerosis Association.

Competition

The biotechnology industry is characterized by rapidly evolving technology and intense competition. Neuralstem's competitors include major multinational pharmaceutical companies, specialty biotechnology companies and chemical and medical products companies operating in the fields of regenerative medicine, cell therapy, tissue engineering and tissue regeneration.

Many of these companies are well-established and possess strong technical, research and development, and financial, sales, and marketing resources.

In addition, certain smaller biotech companies have formed strategic collaborations, partnerships and other types of joint ventures with larger, well established industry competitors that afford these companies potential research and development and commercialization advantages.

Academic institutions, governmental agencies and other public and private research organizations are also conducting and financing research activities which may produce products directly competitive to those we are developing.

Although not necessarily direct competitors, some of the specialty biotechnology companies include Geron Corporation, Genzyme Corporation, StemCells, Inc., and Aastrom Biosciences, Inc.

Some of these companies are well-established and have substantial technical and financial resources. However, as cell-based products are only just emerging as medical therapies, many of Neuralstem's direct competitors are smaller biotechnology and specialty medical products companies that may become significant competitors through rapid evolution of new technologies.

Neuralstem is also embroiled in an ongoing legal battle with StemCells, Inc., over several patents. The battle began in 2006 with a suit filed by StemCells against Neuralstem. In 2008, the company sued StemCells, Inc., alleging that the two patents were invalid. Later in the year, StemCells filed a countersuit asserting of infringement of the two patents. The suit, countersuit, and other legal motions are still pending.

Business Strategy

Neuralstem's basic mission is to develop and commercialize stem cell therapeutics to treat, and possibly cure, a range of human diseases. The company's strategy has been to identify, isolate and patent important human neural stem and progenitor cells derived from human tissue with therapeutic and commercial importance, to develop techniques which enable the expansion and banking of those cells, and then to take them into clinical development as transplantable therapeutics.

A central element of the company's business strategy is to obtain patent protection for the compositions, processes and uses of these multiple types of cells that would make the commercial development of neural stem cell therapeutics financially feasible.

The company has obtained rights to certain inventions relating to stem cells and progenitor through its own research and from academic collaborators. It expects to continue to search for and acquire rights from third parties where relevant, and to further develop its intellectual property positions with respect to both in-house research and through research conducted at commercial and scholarly institutions.

Manufacturing

(Continued on page 12)

The company manufactures its cells both in-house and on an outsource basis.

The in-house cell manufacturing effort is not required to meet stringent FDA standards. The company uses these in-house cells in its research and collaborative programs.

For cells used in preclinical (animal) testing, and thus subject to more stringent FDA standards, Neuralstem outsources manufacturing and storage to Charles River Laboratories, Inc., of Wilmington, Mass. The Charles River facility has the capacity to be used for cell processing under the FDA determined Good Manufacturing Practices (GMP) in quantities sufficient for pre-trial and future clinical trial needs. Cells are ordered and manufactured on an as-needed basis.

Clinical Trial Approval Process: U.S. and Europe

Neuralstem is at the stage of pre-clinical development. The company has begun the complex process of gaining FDA approval for its therapeutics. On December 18, 2008, it filed its first investigational new drug application (IND) with the FDA to begin a clinical trial to treat amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease).

On February 20, 2009, the FDA notified the company that its trial was placed on clinical hold. As of this writing, the company was analyzing the notice and the FDA's comments and recommendations. The company is certain the FDA will lift the clinical hold soon.

It should also be noted that Neuralstem's product candidates will need to be approved by regulatory authorities comparable to the FDA in Europe and other countries in order to begin marketing there.

The regulatory authorities in each country may impose their own requirements and may refuse to grant approval, or may require additional data before granting approval, even though the relevant product has been approved by the FDA or another authority.

The regulatory authorities in the European Union, or EU, and other developed countries have lengthy approval processes for pharmaceutical products. The process for gaining approval in particular countries varies, but is generally similar to the FDA approval process.

In Europe, the European Committee for Proprietary Medicinal Products provides a mechanism for EU-member states to exchange information on all aspects of product licensing. The EU has established a European agency for the evaluation of medical products, with both a centralized community procedure and a decentralized procedure, the latter being based on the principle of licensing within one member country followed by mutual recognition by the other member countries.

Financial Information

Since it began operations in 1996 and through December 31, 2008, Neuralstem has raised $62 million while accumulated losses totaling $57 million.

At December 31, 2008, the company reported a working capital surplus of $3.8 million; cash and cash equivalents totaled about $4.9 million.

The company had about $7.4 million in cash at the end of 2007. The $2.5 million decrease in cash in 2008 was due to costs associated with preparing for the FDA clinical study applications, according to the company.

Because Neuralstem has no products on the market, and therefore no revenues from product sales, it relies on external financing (i.e., sale of common stock and the exercise of warrants) to fund its operations. This situation could continue for the foreseeable future.

With a cash burn rate somewhere between $500,000 and $575,000 a month, the company will need a substantial infusion of capital to maintain operations. If its clinical trial for ALS is finally approved by the FDA, the company will need much higher levels of funding to proceed. The company says the additional costs related to the trial will be phased in slowly over 12 months.

The costs to complete clinical trials vary

(Continued on page 13)

substantially depending upon the projects selected for development, the number of clinical trials required and the number of patients needed for each study.

The company expects that a clinical trial for an individual indication such as ALS will require at least 10 to 12 patients at an estimated cost of $100,000 per patient.

If the trial is delayed for any reason (e.g., difficulties in enrolling patients, delays in manufacturing, incomplete or inconsistent data from the pre-clinical or clinical trials, difficulties evaluating the trial results, etc.) the costs could soar.

Neuralstem says additional costs related to the ALS trial, if approved by the FDA, could total about $350,000 this year.

If the FDA approves the trial, Neuralstem will need enough cash to finance operations, and proceed with pre-clinical and clinical work through the end of 2009.

The top three employees – CEO Richard Garr, CSO Karl Johe, and CFO John Conron – are paid a combined total of more than $1 million a year in salaries alone. (Bonuses totaling another $750,000 were approved in 2009 for 2008 performance for Garr, Johe, and Conron. They chose to defer all or most of the payments until completion of a "financing.")

Of the outstanding shares of common stock (33.8 million shares), these three employees own nearly 20 percent.

Conclusion

Neuralstem is under a lot of pressure to succeed clinically with its neural stem cell products. Its stated goal is to generate revenues from commercialized products. But standing between it and that goal is the FDA (and similar international regulatory bodies.) The clinical hold placed by the FDA on the company's ALS trial only adds to that pressure, though the company says the hold will be lifted soon. The company had been saying it hoped to launch the ALS trial in the spring of this year. In his blog discussing the clinical hold, however, CEO Richard Garr said on February 20 that "perhaps this summer is more realistic than spring" as a launch time for the trial.

The company is thinly capitalized, with only enough cash at current burn rates to make it through the rest of 2009. It may not have enough time either to build its preclinical results portfolio or to endure further delays in its clinical study program. It needs breathing room.

The company insists it has enough of a track record of research success at the preclinical level to satisfy the FDA. Would potential investors be willing to back the company, even if the FDA approves the ALS study?

Would Neuralstem be open to acquisition by a larger, more established biotech or pharma?

Absolutely not, the company told us.

"We are not currently engaged in nor contemplating any acquisition or merger with any other company, nor do we expect to be involved in such talks," a spokesman said.

With that option off the table, that leaves some other form of external financing, which the company has been successful at over the years. Whether the promise of a substantial infusion of cash from a venture capital firm or other private investor would require tough compromises by management in the area of corporate control is another interesting question.

We'll be watching Neuralstem over the next few months to see if any of these questions get answered.

Contact: http://www.neuralstem.com

-=0=-

(Continued on page 14)

Spotlight On …
BrainStorm Cell Therapeutics, Inc.

BrainStorm: Eager To Prove Its Technology

But , Like Other Small Companies, Cash Is The Stumbling Block

Another player in the neurodegenerative disease space is BrainStorm Cell Therapeutics (OTC BB: BCLI), a very small cap stem cell research firm with offices in New York City and Petach Tikvah, Israel.

Though tiny – its market capitalization is about $4.7 million – the company has big plans, including the launch of a clinical trial in Israel late in 2009 or early 2010.

It is developing adult stem cell therapeutic products based on the use of a patient's own (autologous) bone marrow cells.

Its NurOwn patent pending technology is based on discoveries made by neurologist Prof. Eldad Melamed, head of neurology at Rabin Medical Center, and expert cell biologist Dr. Daniel Offen, head of the neuroscience laboratory at the Felsenstein Medical Research Center of Tel-Aviv University.

Their technology, tested successfully in animal models, allows differentiation of bone marrow-derived stem cells into functional neurons and astrocytes.

The company has licensed the commercialization rights to the technology through an agreement with Ramot at Tel Aviv University Ltd., the technology transfer company of Tel-Aviv University.

The company's initial focus is on Parkinson's disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and spinal cord injury.

The company hopes to apply the technology to the development of treatments for multiple sclerosis (MS), Huntington's disease, and stroke.

Despite a decade of research at Tel-Aviv University with a focus on Parkinson's disease, the company has decided that it will focus its limited cash and other resources on developing a marketable stem cell-based treatment for ALS, beginning with a clinical trial in Israel testing treatment safety.

As with many under-funded public companies, however, BrainStorm's ambitious plans are hindered by a lack of cash, a problem exacerbated in recent months by the global financial crisis.

The key question for BrainStorm is: Can it find the cash to pay for further pre-clinical studies and what is likely to be an expensive human trial with a year?

Overview

The Neuroscience Laboratory at Tel Aviv University focused on Parkinson's disease and multiple sclerosis research beginning in the late 1990s, during which time its scientific staff published more than 70 research papers. Beginning in 2001, research was concentrated on stem cells and in particular the behavior of neuronal-like cells capable of controllable synthesis of neurotransmitters. Research activity was aimed at defining and developing a proprietary therapy for transplantation of autologous (self) neuron-like cells capable of production of dopamine to treat Parkinson's disease.

Formerly known as Golden Hand Resources and Wizbang Technologies (which marketed digital data recorder products), BrainStorm was incorporated under the laws of Washington state in September 2000. In July 2004, the company entered into the licensing agreement with Ramot at Tel Aviv University Ltd., the technology transfer company of Tel-Aviv University, to acquire certain stem cell technologies and decided to discontinue all activities related to the sales of digital data recorder products.

In October 2004, the company opened its wholly-owned subsidiary, Brainstorm Cell Therapeutics Ltd. in Israel. In December 2006, the stockholders of the company approved a proposal to change the state of incorporation of the com-

(Continued on page 15)

pany from Washington to Delaware. The re-incorporation was completed that month through the merger of the company into a newly formed, wholly-owned Delaware subsidiary of Brainstorm, also named Brainstorm Cell Therapeutics Inc.

In December 2007, the company we entered into a cooperative research agreement with the W.M. Keck Center for Collaborative Neuroscience at Rutgers University (N.J.). A BrainStorm subsidiary company and Rutgers University were to work jointly in researching the use of differentiated stem cells for the treatment of spinal cord injury. The study was an effort to repair spinal cord injuries in animals through the transplantation of Brainstorm's neurotrophic factor (NTF) adult stem cells. The project began in January 2008.

The company announced interim results in July 2008 showing a positive trend of the NTF cells in the male animals.

During the experiment, two groups of rats, one of which received a treatment without NTF cells, were scored using the BBB test to evaluate their motor function. The results indicated improved recovery in the group that received the NTF cells by comparison to the control group.

The Keck Center researchers and Brainstorm scientists concluded that the results may lead to a possible treatment and therefore the study would continue. The next step was to transplant immunologically compatible syngeneic rat NTF cells to avoid rejection problems.

According to the Rutgers scientists, transplantation of human cells into rats was complicated by rejection problems. Although the human NTFs survived only several weeks after transplant into the rats, they saw improvement in the BBB scores in the test group. The scientists said that the next experiment would involve injection of rat NTF cells into spinal injured rats to limit rejection problems and clearer analysis of the effect of the BrainStorm technology.

No further results have been announced either by BrainStorm or Rutgers regarding the Rutgers SCI experiments as of this writing.

Later in July 2008, the company announced that its therapeutic approach for treating neurodegenerative diseases such as Parkinson's disease was highlighted in a scientific paper published in the journal *Stem Cells.* The paper, written by Tel Aviv University scientists, reported work analyzing rat NTF (neurotrophic factor) cells' ability to migrate in the brain from the place of transplantation to damaged regions.

NTF cells, generated from adult bone marrow derived stem cells and intended for autologous transplantation in Parkinson's patients, secrete neurotrophic factors essential for the survival and outgrowth of neurons. The study showed that in a rat model of Huntington's disease, a hereditary neurodegenerative disease, NTF cells that were transplanted at a distance site, migrated toward the lesion at19 days post grafting. According to the company, the finding indicates the survival, integration and migration abilities of NTF cells in the brain.

The company believes that the transplanted cells may know where they are needed in the human brain and migrate to the damaged part. There, it is hoped, the cells will demonstrate their therapeutic capacity, and provide trophic support for ill-functioning tissues.

Despite these positive results in Parkinson's and Huntington's, in September 2008 Brainstorm's intentions regarding ALS research became clearer when it added ALS medical expert, Dr. Robert H. Brown, Jr., M.D., Ph.D., of Harvard Medical School and Massachusetts General Hospital (MGH), to its scientific advisory board (SAB) to assist in preparations for ALS clinical trials .

Technology & Intellectual Property

BrainStorm's scientific team is among the first to demonstrate creation of neurotrophic-factor secreting cells (glial cells) from in vitro differentiated bone marrow cells that produce neurotrophic factors (NTF), including GDNF, BDNF, NGF and IGF-1.

The company's proprietary technology, NurOwn, processes human mesenchymal stem cells in bone marrow. These cells are capable of self-renewal and differentiation into many other

(Continued on page 16)

tissues.

The team successfully demonstrated release of dopamine from in vitro differentiated bone marrow cells. (Dopamine is an important neurotransmitter (messenger) in the brain. Parkinson's disease is related to low levels of dopamine in certain parts of the brain.)

In addition, the team implanted the differentiated cells into brains of animal models showing Parkinson's-like behavior and markedly improved their symptoms.

The company's goal in this area is to provide neural stem cell transplants that "replace" damaged dopaminergic nerve cells and diseased tissue by augmentation with healthy dopamine producing cells; and maintain, preserve and restore the damaged and remaining dopaminergic cells in the patient's brain, protecting them from further degeneration.

The company believes the ability to differentiate GDNF-producing cells makes NurOwn technology highly attractive for treating ALS as well.

ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord.

Approximately 5,600 people in the United States are diagnosed with ALS each year, the company says. It is estimated that as many as 30,000 Americans may have the disease at any given time, with 100,000 throughout the Western world. The total cost of treating ALS patients is approximately $1.25 billion.

BrainStorm's NurOwn technology has not yet been patented, though applications are pending in the United States and Israel. These include:

– NurOwn technology for differentiation of dopamine-producing neuron-like cells, covered by application number PCT/IL03/00972 filed in November 2003.

– NurOwn technology for differentiating astrocyte-like cells, covered by PCT patent application number PCT/IL2006/000699 filed on June 18, 2006.

– NurOwn technology for generating oligodendrocyte-like cells treatment of medical conditions of the central nervous system (CNS), covered by PCT patent application number PCT/IL2006/001410 filed on December 7, 2006.

Upcoming Clinical Trial

As early as September 2008, Brainstorm began to lay the groundwork for launching a clinical trial of its experimental treatment for ALS. As noted above, the company added Harvard ALS medical expert Dr. Robert H. Brown, Jr., M.D., Ph.D., to its scientific advisory board (SAB) to assist in preparations for ALS clinical trials.

In February 2009, the company hired an Israeli consulting firm, Bio-Medical Research Design (BRD, http://www.brd.co.il) to work with BrainStorm's regulatory team in preparations for clinical trials of ALS patients in Israel.

BRD is assisting the company with various final preclinical studies and the stem cells production process that will help fulfill the relevant regulatory requirements.

BrainStorm will now proceed with the plan outlined by BRD and expects to be ready to approach and start the clinical trials once granted the approval by the Israeli Health Ministry by the fourth quarter of 2009 or the first quarter of 2010.

Prior to commencing these trials, BrainStorm will need to obtain the necessary financing.

The first clinical trials will focus on showing safety. Being that BrainStorm's cell treatment is based on adult stem cells and an autologous transplantation, our scientists believe that the treatment is safe and do not expect any adverse effects. Once successful, we will be able to proceed to Phase II for efficacy.

Company Mission

As a development stage company, BrainStorm's overriding goal is to move past basic or preclinical research into human testing. Its key objectives in moving from the lab to the clinic are:

– Develop the cell differentiation process according to FDA and the European agency for evalua-

(Continued on page 17)

tion of medical products (EMEA) guidelines;

– Demonstrate safety and efficacy first in animals and then in human patients; and

– Set up centralized facilities to provide NurOwn therapeutic products and services for transplantation in patients.

As a result of limited cash resources and the faster path through necessary clinical trials, the company last year decided to focus all of its efforts on ALS, and no longer allocate resources towards Parkinson's disease research.

As a result of this new focus and the company's limited cash resources, the company significantly downsized its staff.

Financial Information

Without approved products to market, BrainStorm has never had any revenues. The company said it does not expect to earn revenues from operations until 2013. The company's research and development expenses have increased mainly because of an increase in salary expenses. This is due to a greater number of employees and subcontractors, partly as a result of the research agreement with Rutgers University and partly as a result of an expansion of research activities, including operating a new animal house.

The company lost $2.8 million during the nine months ending September 30, 2008.

It reported $21,000 in cash and another $40,000 in restricted cash.

From its inception, BrainStorm has financed operations primarily through private sales of common stock and the issuance of convertible promissory notes. At September 30, 2008, the company had $148,000 in total current assets and $2,703,000 in total current liabilities(trade payables, loans, etc.).

Net cash used in operating activities was $1,589,000 for the nine months ended September 30, 2008 ($177,000 per month). Cash was used primarily for payment of salaries and fees to our employees, consultants, subcontractors and services providers and purchase of laboratory materials.

The company received $1.68 million in financing during the nine months ended September 30, 2008, mainly from ACCBT (ACC Bio-Tech) under a subscription agreement.

ACCBT is a corporation organized in the British Virgin Islands whose principal business is to hold securities in biotechnology companies. Chaim Lebovits, a private investor with Israeli and U.S. citizenship and a background in mining and natural resource management, is president of ACCBT and president of BrainStorm.

Under the July 2007 subscription agreement with ACCBT, BrainStorm can sell up to 27,500,000 shares of common stock for an aggregate subscription price of up to $5 million. It can also sell, for no additional consideration, warrants to purchase up to 30,250,000 shares of common stock. As of the end of 2008, BrainStorm had received about $3.7 million from ACCBT. That would leave about $1.3 million available from the current subscription agreement.

The company was also awarded a grant from Israel's Chief Scientist Office (CSO) in 2008. The company received approximately $870,000 over the remainder of the fiscal year to fund the continuing development of treatments for ALS and Parkinson's disease.

The company's stock performance has been a negligible factor in its financial situation. In 2009, the stock price has hovered around 7-9¢.

Conclusion

BrainStorm's technology shows promise at the preclinical level. But whether the promise can be turned into safe and effective performance in the clinic is yet to be determined. It's still a long road through the animal experimentation phase, then to clinical trials, and into the commercialization phase.

It's no secret that BrainStorm needs a significant infusion of capital to meet its day-to-day operational expenses, fund continued preclinical and clinical research, and build the production,

(Continued on page 18)

sales, and marketing infrastructure it needs to sell products.

As always with development stage companies, there are many risk factors: ability to obtain funding from third parties, including future collaborative partners; scope, rate of progress and cost of our clinical trials and other research and development programs; time and costs required to gain regulatory approvals; terms and timing of any collaborative, licensing and other arrangements that might be established; costs of filing, prosecuting, defending and enforcing patents, patent applications, patent claims, trademarks and other intellectual property rights; the effect of competition, market, and technological developments; and future preclinical and clinical trial results.

The company has the financial support of the Israeli government, the backing of a generous (so far) investor, a competent scientific advisory board, dedicated and experienced management, and a promising technology (that must undergo substantial testing). That's a good start. Whether it can raise the cash it needs to make it all happen is the big question. The next few months should begin to provide an answer.

Contact: http://www.brainstorm-cell.com

-=0=-