STEMCELLS INC
Form 10-K
March 15, 2016
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2015

or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

COMMISSION FILE NUMBER 0-19871

STEMCELLS, INC.

(Exact name of Registrant as specified in its charter)

A Delaware Corporation	**94-3078125**
(State or other jurisdiction of	**(I.R.S. Employer**
incorporation or organization)	**Identification No.)**
7707 GATEWAY BLVD	**94560**

NEWARK, CA **(zip code)**

(Address of principal offices)

Registrant s telephone number, including area code:

(510) 456-4000

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.01 par value	NASDAQ Capital Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer x
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

Aggregate market value of common stock held by non-affiliates at June 30, 2015: $57,426,079. Inclusion of shares held beneficially by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of management policies of the registrant, or that such person is controlled by or under common control with the Registrant.

Common stock outstanding at March 11, 2016: 112,507,589 shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive Proxy Statement relating to the registrant s 2016 Annual Meeting of Stockholders to be filed with the Commission pursuant to Regulation 14A are incorporated by reference in Part III of this report.

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FORWARD LOOKING STATEMENTS

THIS REPORT CONTAINS FORWARD-LOOKING STATEMENTS AS DEFINED UNDER THE FEDERAL SECURITIES LAWS. ACTUAL RESULTS COULD VARY MATERIALLY. FACTORS THAT COULD CAUSE ACTUAL RESULTS TO VARY MATERIALLY ARE DESCRIBED HEREIN AND IN OTHER DOCUMENTS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION. READERS SHOULD PAY PARTICULAR ATTENTION TO THE CONSIDERATIONS DESCRIBED IN THE SECTION OF THIS REPORT ENTITLED MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS AS WELL AS ITEM 1A UNDER THE HEADING RISK FACTORS. FORWARD-LOOKING STATEMENTS SPEAK ONLY AS OF THE DATE OF THIS REPORT. WE DO NOT UNDERTAKE ANY OBLIGATION TO PUBLICLY UPDATE ANY FORWARD-LOOKING STATEMENTS.

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NOTE REGARDING REFERENCES TO OUR COMMON STOCK

Throughout this Form 10-K, the words we, us, our, and StemCells refer to StemCells, Inc., including our directly a indirectly wholly-owned subsidiaries. Common stock refers to the common stock of StemCells, Inc., $0.01 par value.

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PART I

Item 1. *BUSINESS*

Overview

StemCells, Inc. is engaged in the research, development, and commercialization of stem cell therapeutics. We believe that understanding cells and cell biology, and in particular stem cells, will play an increasingly important role in the understanding of human diseases and in the discovery of new medical therapies. Consequently, we are focused on developing and commercializing stem and progenitor cells as the basis for novel therapeutics and therapies.

Our primary research and development efforts are focused on identifying and developing stem and progenitor cells as potential therapeutic agents. Our lead product development program is our CNS Program, in which we are developing applications for our HuCNS-SC® platform technology, highly purified human neural stem cells, as a potential therapeutic to treat diseases and disorders of the central nervous system (CNS). We estimate that degenerative conditions of the CNS currently affect more than 30 million people in the United States. [1]

We are currently in clinical development with our HuCNS-SC cells for a range of diseases and disorders of the CNS. The CNS consists of the brain, spinal cord and eye, and we are currently the only stem cell company in clinical development for indications in all three compartments comprising the CNS, specifically:

(i) with respect to the brain,

in October 2012, we published in *Science Translational Medicine,* a peer-reviewed journal, the data from our Phase I clinical trial in Pelizeaus-Merzbacher Disease (PMD), a fatal myelination disorder in the brain. The data showed preliminary evidence of progressive and durable donor cell-derived myelination in all four patients transplanted with HuCNS-SC cells. Three of the four patients showed modest gains in neurological function; the fourth patient remained stable; and

we have completed a Phase I clinical trial in infantile and late infantile neuronal ceroid lipofuscinosis (NCL, also known as Batten disease), which is a neurodegenerative disorder of the brain. The data from that trial showed that our HuCNS-SC cells were well tolerated, non-tumorigenic, there was evidence of engraftment and long-term survival of the transplanted HuCNS-SC cells for up to six years; five years after stopping immunosuppression these data suggest that patients receiving human neural stem cell transplants should not need to be maintained on life-long immunosuppression; and

(ii) with respect to the spinal cord,

in May 2014, we completed the enrollment and dosing of twelve subjects in a Phase I/II clinical trial of our HuCNS-SC cells for the treatment of thoracic spinal cord injury. Under this trial, a total of twelve patients, seven patients with complete injury (AIS A) and five patients with an incomplete injury (AIS

B), were enrolled and transplanted with our HuCNS-SC cells. We reported the results from twelve-month data that revealed sustained improvements in sensory function that emerged consistently around three months after transplantation and persisted until the end of the study. The patterns of sensory gains were confirmed to involve multiple sensory pathways and were observed more frequently in the patients with less severe injury; three of the seven AIS A patients and four of the five AIS B patients showed signs of positive sensory gains confirming the previously reported interim results. In addition, two patients progressed during the study from the most severe classification, AIS A, to the lesser degree of injury grade, AIS B; and

[1] This estimate is based on information from the Alzheimer s Association, the Alzheimer s Disease Education & Referral Center (National Institute on Aging), the National Parkinson Foundation, the National Institutes of Health s National Institute on Neurological Disorders and Stroke, the Foundation for Spinal Cord Injury Prevention, Care & Cure, the Travis Roy Foundation, the Centers for Disease Control and Prevention, the Wisconsin Chapter of the Huntington s Disease Society of America, and the Cincinnati Children s Hospital Medical Center.

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in October 2014, we initiated our Pathway Study, a Phase II proof of concept clinical trial using our HuCNS-SC cells for the treatment of cervical spinal cord injury (SCI). The Pathway Study is designed to evaluate both the safety and efficacy of transplanting stem cells into patients with traumatic injury to the cervical spinal cord. The trial will be conducted as a randomized, controlled, single-blind study and efficacy will be primarily measured by assessing motor function according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The primary efficacy outcome will focus on change in upper extremity strength as measured in the hands, arms and shoulders. The trial will enroll approximately fifty-two subjects and follow the patients for twelve months post-transplant. The trial has three cohorts; the first cohort is an open-label dose escalation arm involving six patients to determine the cell dose to be used for the second and third cohort of the study; the second cohort will enroll forty patients and forms the single-blinded controlled arm of the Phase II study with the primary efficacy outcome being tested as change in motor strength of the various muscle groups in the upper extremities innervated by the cervical spinal cord; the third cohort is an optional open label cohort targeted to enroll six patients to assess safety and preliminary efficacy in patients with less severe injuries (AIS C). We transplanted our first subject in this Phase II trial in December 2014 and completed transplanting the six patients comprising the first cohort of this trial in April 2015. The six-month interim results for the first cohort showed an overall pattern of motor improvement in four of the six patients as measured by gains in both strength and fine motor skills. In addition, four of the six patients showed improvement in the spinal level of injury as defined by the ISNCSCI assessment of at least one level. Consistent with the changes in sensation seen in our prior study in spinal cord injury, these changes in muscle strength and function seen in our Pathway Study were observed around three months post-transplant. We commenced enrollment of the second cohort in the Pathway Study in June 2015; and

(iii) with respect to the eye,

in June 2012, we initiated a Phase I/II clinical trial designed to evaluate the safety and preliminary efficacy of our HuCNS-SC cells as a treatment for dry age-related macular degeneration (AMD). The trial, an open-label, dose-escalation study, was planned to enroll a total of sixteen patients. In June 2014, based on positive interim results, we closed enrollment after dosing fifteen patients. Multiple safety and efficacy assessments were incorporated into the study, including various assessments of visual function and measurements of disease status by direct retinal examination. The tests in the study included best-corrected visual acuity (BCVA), contrast sensitivity (CS), microperimetry for analysis of visual function, optical coherence tomography (OCT), and fundus autofluorescence (FAF) to measure the extent of the underlying geographic atrophy. Initial assessment of data from the Phase I/II trial indicate that the BCVA and CS measurements for the majority of the patients in the study either improved or remained stable in the treated eye. OCT analysis showed increases in central subfield thickness and in macular volume in the treated eye relative to the untreated eye. For those patients enrolled in the study with lesions sizes consistent with the eligibility criteria for enrollment in our Phase II efficacy study, the study showed GA growth rates in the study eye that were lower than those seen in the control eye. Patients will be followed for an additional four years in a separate observational study; and

in July 2015, we transplanted our first subject in our Radiant Study. This Phase II randomized, controlled proof-of-concept study was designed to evaluate both the safety and efficacy of our

proprietary HuCNS-SC cells for the treatment of dry AMD. The study was designed to enroll sixty-three patients between 50-90 years of age with bi-lateral GA-AMD (geographic atrophy associated with age related macular degeneration in both eyes). Designed as a fellow eye controlled study, all subjects were to receive subretinal transplantation of HuCNS-SC cells via a single injection into the eye with the inferior best-corrected visual acuity; the untreated eye would serve as a control. The objective of the trial was to demonstrate a reduction in the rate of GA disease progression in the treated eye versus the control eye. However, in December 2015, we

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initiated a strategic realignment plan to fully focus our resources on our proprietary HuCNS-SC cells for the treatment of chronic spinal cord injury. A key element of the plan included the suspension of further enrollment into our Phase II Radiant Study in dry AMD, while we seek a partner to fund continued development of HuCNS-SC cells as a potential treatment of retinal disorders, and discontinuation of certain third party services related to our AMD program.

The Potential of Our Tissue-Derived Cell-Based Therapeutics

Stem cells are building block cells as they are capable of producing many cell types needed for proper organ function. Stem cells are rare and have two defining characteristics: (i) they produce all of the mature cell types of a particular organ, and (ii) they self renew that is, some of the cells developed from stem cells are themselves new stem cells. Progenitor cells are cells that have already developed from stem cells, but can still produce one or more mature cell types within an organ. Tissue stem cells are rare cells within an organ and require sophisticated instrumentation and scientific rigor to identify, purify and characterize these cells. To date the human neural stem cell is one of only two adult tissue-derived cells to have been isolated to the single cell level, characterized extensively and confirmed to have all the characteristics of a true stem cell, namely self-renewal (*i.e.*, the ability to make more neural stem cells) and differentiation (*i.e.*, the ability to make neurons, astrocytes and oligodendrocytes, the building blocks of the CNS). Because of their self-renewal property and ability to make the mature cells of the organ we believe that tissue stem cell-based therapies may have the potential to return an impaired organ to proper function for the life of the patient. Many degenerative diseases are caused by the loss of normal cellular function in a particular organ. When cells are damaged or destroyed, they no longer produce, metabolize or accurately regulate the many substances essential to life. There is no technology existing today that can deliver these essential substances precisely to the sites of action, under the appropriate physiological regulation, in the appropriate quantity, or for the duration required to cure the degenerative condition. Cells, however, can do all of this naturally. Transplantation of stem or progenitor cells may therefore prevent the loss of, or even generate new, functional cells and thereby potentially maintain or restore organ function and the patient s health.

We have been focused on identifying and purifying tissue-derived stem and progenitor cells for use in homologous therapy. Homologous therapy means the use of cells derived from a particular organ to treat a disease of that same organ (for example, use of brain-derived neural stem cells for treatment of CNS disorders). Tissue-derived stem cells are developmentally pre-programmed to become the mature functional cells of the organ from which they were derived. We believe that homologous use of these purified, unmodified brain tissue-derived cells is the most direct way to provide for engraftment and differentiation into functional cells of the CNS. The purification of the right cell , the true human neural stem cell, not only facilitates a reproducible manufacturing process and product but also should minimize the risk of transplantation or growth of unwanted cell types.

We use cells derived from donated tissues, which are supplied to us in compliance with all applicable state and federal regulations. We are not involved in any activity directed toward human cloning, nor do we have any plans to start such activities.

Business Strategy

Our aim is to create a sustainable business based on our belief that understanding cells and cell biology will play an increasingly important role in life science research and in the discovery, development and implementation of new medical therapies. Our strategy has been to identify multiple types of human stem and progenitor cells with therapeutic and commercial importance, to develop techniques and processes to purify these cells for direct transplant and to expand and bank these cells. We are currently focused on advancing these cells through clinical development and into commercialized cell-based therapeutic products, with particular focus on the use of human neural stem cells as a potential treatment for acute spinal cord injury.

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The fundamental competencies required to execute this strategy are knowledge and expertise in cell biology, particularly stem cell biology, and a commitment to rigorous and robust research and development. We believe that these competencies are critical to identifying, characterizing and understanding cells with therapeutic potential and importance.

Consequently, we have made significant investments in our research and development, clinical and regulatory, and cell processing and process development capabilities. Our management and staff have many years of experience in the stem cell field and in developing potential cell therapies. Two of the four human stem cells identified and characterized to date (the hematopoietic and neural stem cells) were discovered by scientists who are currently on our staff, and we believe we were the first company to receive authorization from the FDA to conduct a clinical trial of a purified neural stem cell product candidate, as well as the first to complete such a clinical trial. We are committed to proving that groundbreaking science, especially in the field of stem cell biology, has the potential to create truly breakthrough medicine.

Therapeutic Product Development Programs

Overview

The following table summarizes the current status of, and the anticipated initial indications for, our therapeutic product development program. A more detailed discussion of each of these follows the table.

CNS Program	**Cell-based therapeutics to restore or preserve function to central nervous system tissue by protecting, repairing or replacing dysfunctional or damaged cells.**
Diseases and Disorders of the Brain	Pelizeaus-Merzbacher Disease: Four-patient Phase I clinical trial completed February 2012.

Data from the Phase I trial was published in *Science Translational Medicine,* a peer-reviewed scientific journal, in October 2012 and showed preliminary evidence of new myelin in all four patients, and three of the four patients showed modest gains in neurological function; the fourth patient remained stable. The data also showed that the HuCNS-SC cells, the transplantation procedure, and the immunosuppression were all well tolerated.

In August 2013, we presented data which show that, two years after transplantation of our HuCNS-SC cells into patients with PMD, the evidence of myelination, by magnetic resonance imaging (MRI), is more pronounced compared to one year post-transplantation, the gains in neurological function reported after one year were maintained, and there were no safety concerns. The neurological and MRI changes suggest a departure from the natural

history of the disease and may represent signals of a clinical effect.

Demonstrated *in vivo* proof of principle by showing in the myelin deficient shiverer mouse that transplanted HuCNS-SC cells can:

generate and integrate myelin producing oligodendrocytes into the mouse brain; and

tightly wrap the mouse nerve axons to form myelin sheath.

Neuronal Ceroid Lipofuscinosis (also known as Batten disease):

Six-patient Phase I clinical trial completed in January 2009. Trial results showed that the HuCNS-SC cells, the transplantation procedure, and the immunosuppression were well tolerated and the

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cells were not tumorigenic, and that there was evidence of engraftment and survival of the transplanted cells.

Demonstrated *in vivo* proof of principle by showing in a mouse model for infantile NCL that transplanted HuCNS-SC cells can:

continuously produce the enzyme that is deficient in infantile NCL;

protect host neurons from death;

delay the loss of motor function in HuCNS-SC transplanted mice; and

survive up to six years; five years after stopping immunosuppression.

Alzheimer s Disease:

In July 2012, reported data that showed our HuCNS-SC cells can restore memory in two mouse models relevant to Alzheimer s disease.

Demonstrated that our HuCNS-SC cells are capable of engrafting and surviving in the hostile environment reflective of an Alzheimer s brain, which characteristically features abnormal accumulations of brain lesions called plaques and tangles.

Diseases and Disorders of the Spinal Cord

Spinal Cord Injury:

Completed enrollment in a Phase I/II clinical trial in multiple sites for chronic spinal cord injury. The trial enrolled 12 patients with thoracic (chest-level) spinal cord injury, and included both complete and incomplete injuries as classified by the American Spinal Injury Association Impairment Scale (AIS). We reported the results from twelve-month data that revealed sustained improvements in sensory function that emerged consistently around three months after transplantation and persisted until the end of the study. The patterns of sensory gains were confirmed to involve multiple sensory pathways and were observed more frequently in the patients with

less severe injury; three of the seven AIS A patients and four of the five AIS B patients showed signs of positive sensory gains confirming the previously reported interim results. In addition, two patients progressed during the study from the most severe classification, AIS A, to the lesser degree of injury grade, AIS B.

In October 2014, we initiated our Pathway Study, a Phase II proof of concept clinical trial using our HuCNS-SC cells for the treatment of cervical spinal cord injury (SCI). We transplanted our first subject in this Phase II trial in December 2014 and completed transplanting the six patients comprising the first cohort of this trial in April 2015. The six-month interim results for the first cohort showed an overall pattern of motor improvement in four of the six

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patients as measured by gains in both strength and fine motor skills. In addition, four of the six patients showed improvement in the spinal level of injury as defined by the ISNCSCI assessment of at least one level. Consistent with the prior study, changes in muscle strength and function were observed around three months post-transplant. We commenced enrollment of the second cohort in the Pathway Study in June 2015; and

Demonstrated *in vivo* proof of principle by showing in a mouse model for spinal cord injury that transplanted HuCNS-SC cells can:

restore motor function in injured animals;

directly contribute to functional recovery (and that when human cells are ablated restored function is lost); and

become specialized oligodendrocytes and neurons.

Diseases and Disorders of the Eye

Age-Related Macular Degeneration:

in June 2012, we initiated a Phase I/II clinical trial designed to evaluate the safety and preliminary efficacy of our HuCNS-SC cells as a treatment for geographic atrophy (GA), the most advanced form of dry AMD.

In July 2015, we transplanted our first subject in our Radiant Study. This Phase II randomized, controlled proof-of-concept study was designed to evaluate both the safety and efficacy of our proprietary HuCNS-SC cells for the treatment of GA. However, in December 2015, we initiated a strategic realignment plan to fully focus our resources on our proprietary HuCNS-SC cells for the treatment of chronic spinal cord injury. A key elements of the plan included the immediate suspension of enrollment into our Phase II Radiant Study in GA-AMD.

Demonstrated *in vivo* proof of principle by showing in the Royal College of Surgeons rat, a widely accepted model for retinal degeneration, that HuCNS-SC cells can:

protect photoreceptor cells from death; and

prevent or slow loss of vision.

Many neurodegenerative diseases involve the failure of central nervous system tissue (i.e., the brain, spinal cord and eye) due to the loss of functional cells. Our CNS Program is initially focusing on developing clinical applications in which transplanting HuCNS-SC cells would protect or restore organ function of the patient before such function is irreversibly damaged or lost due to disease progression. Our initial target indications are (i) Pelizeaus-Merzbacher Disease, and more generally, diseases in which deficient myelination plays a central role, such as cerebral palsy or multiple sclerosis; (ii) spinal cord injury;, and (iii) disorders in which retinal degeneration plays a central role, such as age-related macular degeneration or retinitis pigmentosa. These disorders affect a significant number of people in the United States and there currently are no effective long-term therapies for them.

Our preclinical research has shown *in vivo* that HuCNS-SC cells engraft, migrate, differentiate into neurons and glial cells, and survive for as long as one year with *no sign* of tumor formation or adverse effects. Moreover, the HuCNS-SC cells were still producing progeny cells at the end of the test period. These findings show that our neural stem cells, when transplanted, act like normal neural stem cells, suggesting the possibility of a continual replenishment of normal human neural cells in transplant recipients. In the longer term, then, we believe stem cells have the potential to restore or replace lost cells and cellular function.

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Diseases and Disorders of the Brain

Pelizaeus-Merzbacher Disease (PMD).

Pelizaeus-Merzbacher disease, a rare, degenerative, central nervous system disorder, is one of a group of genetic disorders known as leukodystrophies. Leukodystrophies involve abnormal growth of the myelin sheath, which is the fatty substance that surrounds nerve fibers in the brain and spinal cord. PMD is most commonly caused by a genetic mutation that affects an important protein found in myelin, proteolipid protein. PMD is most frequently diagnosed in early childhood and is associated with abnormal eye movements, abnormal muscle function, and in some cases, seizures. The course of the disease is marked by progressive neurological deterioration resulting in premature death.

In February 2012, we completed a Phase I clinical trial in PMD. A total of four patients were transplanted with HuCNS-SC cells and were evaluated periodically over a 12-month period. The study was designed to help detect evidence of new myelin, including by magnetic resonance imaging (MRI) of the brain, changes in neuropsychological tests of development and cognitive function, and clinical changes in neurological function. The trial was conducted at the University of California, San Francisco. In October 2012, we published the results of the trial in *Science Translational Medicine,* a peer-reviewed journal. The clinical data from this study showed evidence of new myelin in all four patients who were transplanted with HuCNS-SC cells. In addition, three of the four patients showed modest gains in neurological function; the fourth patient remained stable. The data also showed that the cells, the transplantation procedure and the immunosuppression regimen were all well tolerated.

In our preclinical research, we have shown that HuCNS-SC cells differentiate into oligodendrocytes, the myelin producing cells, and produce myelin. We have transplanted HuCNS-SC cells into the brain of the mutant shiverer mouse, which is deficient in myelin, and shown widespread engraftment of human cells that matured into oligodendrocytes, and that the human oligodendrocytes myelinated the mouse axons.

Other Myelin Disorders.

Loss of myelin characterizes conditions such as multiple sclerosis, cerebral palsy and certain genetic disorders (for example, Krabbe s disease and metachromatic leukodystrophy). Loss of myelin can also play a role in certain spinal cord indications. Based on our preclinical data, we believe our HuCNS-SC product candidate may have applicability to a range of myelin disorders.

Neuronal Ceroid Lipofuscinosis (NCL; also known as Batten disease).

Neuronal ceroid lipofuscinosis, which is often referred to as Batten disease, is a neurodegenerative disease that affects infants and young children. Infantile and late infantile NCL are brought on by inherited genetic mutations which result in either a defective or missing enzyme, leading to the accumulation of cellular waste product in various neuronal cell types. This accumulation eventually interferes with normal cellular and tissue function, and leads to seizures and progressive loss of motor skills, sight and mental capacity. Today, NCL is always fatal.

In January 2009, we completed a six-patient Phase I clinical trial of our HuCNS-SC cells in infantile and late infantile NCL. We believe that this clinical trial was the first FDA-authorized trial to evaluate purified human neural stem cells as a potential therapeutic agent. The trial data demonstrated that the HuCNS-SC cells, the transplantation procedure and the immunosuppression regimen were well tolerated by all six patients, and the patients medical, neurological and neuropsychological conditions, following transplantation, appeared consistent with the normal course of the disease. In addition to this favorable safety profile, there was evidence of engraftment and long-term survival of the HuCNS-SC cells. This Phase I trial was conducted at OHSU Doernbecher Children s Hospital in Oregon.

Our preclinical data demonstrate that HuCNS-SC cells, when transplanted in a mouse model of infantile NCL, engraft, migrate throughout the brain, produce the relevant missing enzyme, measurably reduce the toxic

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storage material in the brain, protect host neurons so that more of them survive, and delay the loss of motor function compared to a control group of non-transplanted mice. A summary of this data was published in September 2009 in the peer-reviewed journal *Cell Stem Cell.* We have also demonstrated *in vitro* that HuCNS-SC cells produce the enzyme that is deficient in late infantile NCL.

Alzheimer s Disease.

Alzheimer s disease is a progressive, fatal neurodegenerative disorder that results in loss of memory and cognitive function. Today, there is no cure or effective treatment option. According to the Alzheimer s Association, an estimated 5.2 million Americans have Alzheimer s disease, including nearly 5 million people aged 65 and older. The prevalence of Alzheimer s disease is expected to increase rapidly as a result of our aging population.

In July 2012, we reported data that showed that our HuCNS-SC cells restored memory and enhanced synaptic function in two animal models relevant to Alzheimer s disease. This research was a result of a collaboration we entered into with a world renowned leader in Alzheimer s disease research at the University of California, Irvine (UCI) to study the therapeutic potential of our HuCNS-SC cells in Alzheimer s disease. Our collaborator s published research had shown that mouse neural stem cells enhance memory in a mouse model of Alzheimer s disease, and the goal of the collaboration was to replicate these results using our human neural stem cells.

Previously, we conducted studies of our HuCNS-SC cells in another model of Alzheimer s disease as part of a collaboration with researchers at the McLaughlin Research Institute. This research, which was funded by a National Institutes of Health (NIH) grant, demonstrated that our HuCNS-SC cells are capable of engrafting and surviving in the hostile environment reflective of an Alzheimer s brain, which characteristically features abnormal accumulations of brain lesions called plaques and tangles.

In September 2012, the governing board of the California Institute of Regenerative Medicine (CIRM) approved our application for a Disease Team Therapy Development Research Award for the study of HuCNS-SC cells as a potential treatment for Alzheimer s disease. CIRM would have provided up to approximately $19.3 million as a forgivable loan, in accordance with mutually agreed upon terms and conditions and CIRM regulations. The goal of the research was to have been the filing of an Investigational New Drug application with the U.S. Food and Drug Administration within four years. We have demonstrated that transplantation of our HuCNS-SC cells into the hippocampus, the area of the brain responsible for learning and memory, increases connectivity between the points of contact (synapses) between neurons an important finding given that clinical disability in humans correlates with synapse loss. The observation that our cells increase synapse density in the hippocampus opens the possibility that HuCNS-SC cells may improve neuronal function in human neurodegenerative disorders in general. However, this finding did not translate into a statistically significant improvement in memory as measured by specific behavioral tasks in the animal models, which was a pre-determined criteria for ongoing funding of this pre-clinical program by CIRM. We will continue to assess the data from this study but have wound-down this pre-clinical study funded by CIRM.

Diseases and Disorders of the Spinal Cord

According to a study initiated by the Christopher and Dana Reeve Foundation, an estimated 1.3 million people in the United States are living with chronic spinal cord injury. There are no therapies today that can address the paralysis or loss of function caused by a spinal cord injury, but neural stem cells may have the potential to provide a novel therapeutic approach.

In May 2014, we completed the enrollment and dosing of twelve subjects in a Phase I/II clinical trial of our HuCNS-SC cells for the treatment of thoracic spinal cord injury. The trial was initiated at University Hospital Balgrist

in Zurich and was authorized by Swissmedic, the regulatory agency for therapeutic products in Switzerland. A total of twelve patients enrolled in the study, all of whom were three to twelve months post-

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injury. The study followed a progressive study design, beginning with patients with complete injuries and then enrolling patients with incomplete injuries, all as classified by the American Spinal Injury Association Impairment Scale (AIS). Of the twelve patients transplanted with our HuCNS-SC cells, seven patients were categorized as having complete injury (AIS A) and five patients were categorized as having an incomplete injury (AIS B). In contrast to AIS A patients who have no mobility or sensory perception below the point of injury, AIS B subjects are less severely injured and, while still paralyzed they retain sensory perception below the point of injury. In addition to assessing safety, the trial evaluated preliminary efficacy using defined clinical endpoints, such as changes in sensation, motor function, and bowel/bladder function. Under this trial, a total of twelve patients, seven patients with complete injury (AIS A) and five patients with an incomplete injury (AIS B), were enrolled and transplanted with our HuCNS-SC cells. .In February 2013, we reported that the first patient cohort, all of whom had complete injuries classified as AIS A, had completed the trial, and that data from this first cohort showed that two of the three patients showed multi-segment gains in sensory function compared to pre-transplant baseline. The gains in sensory function were first observed at the six month assessment and persisted to the 12 month assessment. The third patient remained stable. To accelerate patient enrollment, we expanded the trial from a single-site, single-country study to a multi-site, multi-country program that includes, Switzerland, Canada and the United States. In May 2014, our principal investigator presented an interim update on the Phase I/II trial in spinal cord injury at the Annual Meeting of the American Spinal Injury Association. Interim analysis of clinical data to date has shown that the significant post-transplant gains in sensory function first reported in two patients have now been observed in two additional patients. The presentation included the first data on AIS B subjects to be transplanted in the Phase I/II chronic spinal cord injury trial with our HuCNS-SC cells. Two of the three AIS B patients had significant gains in sensory perception and the third remained stable. We reported the results from twelve-month data that revealed sustained improvements in sensory function that emerged consistently around three months after transplantation and persisted until the end of the study. The patterns of sensory gains were confirmed to involve multiple sensory pathways and were observed more frequently in the patients with less severe injury; three of the seven AIS A patients and four of the five AIS B patients showed signs of positive sensory gains confirming the previously reported interim results. In addition, two patients progressed during the study from the most severe classification, AIS A, to the lesser degree of injury grade, AIS B. The results to-date also continue to confirm the favorable safety profile of the cells and the surgical implant procedure.

In October 2014, we initiated our Pathway Study, a Phase II proof of concept clinical trial using our HuCNS-SC cells for the treatment of cervical spinal cord injury (SCI). The Pathway Study is designed to evaluate both the safety and efficacy of transplanting stem cells into patients with traumatic injury to the cervical spinal cord. The trial will be conducted as a randomized, controlled, single-blind study and efficacy will be primarily measured by assessing motor function according to the International Standards for Neurological Classification of Spinal Cord Injury. Patients eligible for the study have complete loss of motor control below the level of injury, the most severe degree of SCI as defined by the American Spinal Injury Association Impairment Scale (AIS). Clinicians used both ISNCSCI (International Standards for Neurological Classification of Spinal Cord Injury) and GRASSP (Graded Assessment of Strength Sensibility and Prehension) measures to establish a pre-transplant baseline for each patient and to assess post-transplant progress. The primary efficacy outcome will focus on change in upper extremity strength as measured in the hands, arms and shoulders. The trial will enroll approximately fifty-two subjects and follow the patients for twelve months post-transplant. The trial has three cohorts; the first cohort is an open-label dose escalation arm involving six patients to determine the cell dose to be used for the second and third cohort of the study; the second cohort will enroll forty patients and forms the single-blinded controlled arm of the Phase II study with the primary efficacy outcome being tested is the change in motor strength of the various muscle groups in the upper extremities innervated by the cervical spinal cord; the third cohort is an optional open label cohort targeted to enroll six patients to assess safety and preliminary efficacy in patients with less severe injuries (AIS C). We transplanted our first subject in this Phase II trial in December 2014 and completed transplanting the six patients comprising the first cohort of this trial in April 2015. The six-month interim results for the first cohort showed motor improvements in both strength and

function. Additional highlights of the six-month interim results include (i) muscle strength was improved in five of the six patients; (ii) four of the five patients with gains in muscle strength also demonstrated improved

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performance on functional tasks assessing dexterity and fine motor skills; (iii) four of the six patients had improvement in the spinal level of injury as defined by the ISNCSCI assessment; (iv) three upgraded one level and one upgraded two levels; (v) based on a Patient Global Impression of Change (PGIC) assessment, four of the six patients reported that their condition had improved post-transplant; (vi) changes in muscle strength and function were observed around three months post-transplant, consistent with the onset of sensory improvements seen in the Company s Phase I/II thoracic study;(vii) no adverse events were attributed to the cells; and (viii) the timing of the transplants ranged from ten to twenty-three months post-injury. We commenced enrollment of the second cohort in the Pathway Study in June 2015.

The results of numerous preclinical studies demonstrate the therapeutic potential of our human neural stem cells for the treatment of spinal cord injury. Using a mouse model of spinal cord injury, our collaborators at the Reeve-Irvine Research Center at the University of California, Irvine have shown that our HuCNS-SC cells have the potential to protect and regenerate damaged nerves and nerve fibers, and that injured mice transplanted with our HuCNS-SC cells showed improved motor function compared to control animals. Inspection of the spinal cords from the treated mice showed significant levels of human neural cells derived from the transplanted stem cells. Some of these cells were oligodendrocytes, the specialized neural cell that forms the myelin sheath around axons, while others had become neurons and showed evidence of synapse formation, a requirement for proper neuronal function. The researchers then selectively ablated the human cells, and found that the functional improvement was lost, thus demonstrating that the human cells had played a direct role in the functional recovery of the transplanted mice. Moreover, our preclinical studies show that our human neural stem cells enable a significant and persistent recovery of motor function when transplanted in spinal cord-injured mice at both sub-acute and chronic injury time points.

Diseases and Disorders of the Eye

The retina is a thin layer of neural cells that lines the back of the eye and is responsible for converting external light into neural signals. A loss of function in retinal cells leads to impairment or loss of vision. The most common forms of retinal degeneration are age-related macular degeneration (AMD) and retinitis pigmentosa. AMD is the leading cause of vision loss and blindness in people over the age of 55 and afflicts some 30 million people worldwide.

In June 2012, we initiated a Phase I/II clinical trial designed to evaluate the safety and preliminary efficacy of sub-retinal transplantation of our HuCNS-SC cells as a treatment for geographic atrophy (GA), the most advanced form of dry AMD. The trial, an open-label, dose-escalation study, was planned to enroll a total of 16 patients. In June 2014, after enrolling fifteen patients and based on positive interim results, we closed enrollment for this study. Multiple safety and efficacy assessments were incorporated into the study, including various assessments of visual function and measurements of disease status by direct retinal examination. The tests in the study included best-corrected visual acuity (BCVA), contrast sensitivity (CS), microperimetry for analysis of visual function, optical coherence tomography (OCT), and fundus autofluorescence (FAF) to measure the extent of the underlying geographic atrophy. The BCVA and CS measurements for the majority of the patients in the study either improved or remained stable in the treated eye. OCT analysis showed increases in central subfield thickness and in macular volume in the treated eye relative to the untreated eye. The prospective analysis of both cohorts in the study showed GA growth rates in the study eye that were lower than those seen in the control eye, consistent with the previously reported interim findings for Cohort I alone which showed for all four subjects of cohort one, a 70% reduction in the rate of GA as compared to the control eye and a 65 percent reduction in the rate of GGA as compared to the expected natural history of the disease following a single dose of our HuCNS-SC cells. However, to further investigate the possible effect of the cells on GA and to inform future clinical development, we subsequently engaged a reading center to perform a separate post-hoc assessment. The separate assessments have revealed greater than anticipated variability in grading of the images. While the prospective analysis for both Cohorts continues to show a decrease in the rate of GA progression in the treated eye for the majority of the patients, the post-hoc analysis did not reveal a similar trend.

Further analysis of the collective data is ongoing to determine possible explanations for these findings. Patients will be followed for an additional four years in a separate observational study.

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Our preclinical data have shown that our HuCNS-SC cells, when transplanted in a well-established animal model of retinal degeneration, engraft long-term, can protect photoreceptors (the key cells involved in vision) from progressive degeneration, and can slow or prevent loss of visual function. In this model, called the Royal College of Surgeons (RCS) rat, a genetic mutation causes dysfunction of the retinal pigmented cells, which leads to progressive loss of the photoreceptors and ultimately, loss of visual function in the rat. Our preclinical data shows that our human neural stem cells protect both rod and cone photoreceptors in the eye from progressive degeneration and preserve visual function long term. The cone photoreceptors are light sensing cells that are highly concentrated within the macula of the human eye, and the ability to protect these cells suggests a promising approach to treating AMD. A summary of our preclinical data was featured as the cover article in February 2012 edition of the international peer-reviewed *European Journal of Neuroscience*.

Other CNS Collaborations

We have collaborated on a number of research programs to assess both the *in vitro* potential of the HuCNS-SC cells and the effects of transplanting HuCNS-SC cells into various preclinical animal models. One such collaboration was with researchers at the Stanford University School of Medicine that evaluated our human neural stem cells in animal models of stroke. The results of these studies demonstrated the targeted migration of the cells toward the stroke lesion and differentiation toward the neuronal lineage. Another study with researchers at Stanford s School of Medicine demonstrated that HuCNS-SC cells labeled with magnetic nanoparticles could non-invasively track the survival and migration of human cells within the brain. We continue to search for and evaluate promising collaborations to supplement our efforts to develop and commercialize our proprietary human neural platform technology.

Operations

Manufacturing

We have made considerable investments in our manufacturing operations. Our team includes world-recognized experts with proven track records in the development, manufacture and delivery of a range of different cell-based products. For clinical trials, our highly-qualified personnel manufacture cell products in clean room environments within our California licensed facility that are in compliance with current Good Manufacturing Practice (cGMP) and to quality standards that meet U.S. as well as international regulatory requirements. We are currently investing in process development activities to scale the production of our HuCNS-SC cells to meet the requirements of Phase III clinical trials and eventually commercial volumes should we be successful in getting a cell-based product to market. By combining expertise and experience, we believe our expandable and bankable cell products can ultimately be manufactured and distributed at commercial scale as stem cells in a bottle, much like an off-the-shelf pharmaceutical product.

Marketing

Because of the early stage of our stem and progenitor cell-based therapeutic product development programs, we have not yet addressed questions of channels of distribution or marketing of potential future products.

Employees

As of December 31, 2015, we had 74 full-time employees, 16 of whom have Ph.D., M.D. or D.V.M. degrees. 62 full-time employees work in research and development and laboratory support services. No employees are covered by collective bargaining agreements. We consider our employee relations in general to be good.

Discontinued operations

As part of our strategy to focus on our clinical operations, in the fourth quarter of 2014 we sold our SC Proven reagent and cell culture business and wound-down our business operations at our Subsidiary Stem Cell Sciences (U.K.) Ltd. s (SCS UK) in Cambridge, UK. The results of operations from these operations have been

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classified as discontinued operations for all periods presented (see Note 19 Discontinued Operations in the Notes to Consolidated Financial Statements of Part II, Item 8 of this Form 10-K for further information).

Patents, Proprietary Rights and Licenses

We believe that proprietary protection of our inventions will be important to our future business. We therefore continuously evaluate intellectual property that we believe might be useful in connection with our products, and have an active program of protecting our intellectual property, including patents, copyrights, trademarks, and trade secrets. We may also from time to time seek to acquire licenses to important externally developed technologies.

We have exclusive or non-exclusive rights to a portfolio of patents and patent applications related to various stem and progenitor cells and methods of deriving and using them. These patents and patent applications relate to compositions of matter, methods of obtaining such cells, and methods for preparing, transplanting and utilizing these cells. We also own or have exclusive rights to exploit a number of patents that claim tools and techniques important to cell-based research. A number of these patents were acquired from Stem Cell Sciences Plc (SCS) in April 2009. Additional patents were acquired from NsGene A/S, a Danish company, in February 2013. These patents claim GFAP+ Nestin+ precursor cells capable of differentiating into neurons. Among our significant U.S. patents covering stem and progenitor cells are: (i) U.S. Patent No. 5,968,829, entitled Human CNS Neural Stem Cells, which covers our composition of matter for human CNS stem cells; (ii) U.S. Patent No. 7,153,686, entitled Enriched Central Nervous System Stem Cell and Progenitor Cell Populations, and Methods for Identifying, Isolating and Enriching such Populations, which claims the composition of matter of various antibody-selected neural stem cell populations; (iii) U.S. Patent No. 6,777,233, entitled Cultures of Human CNS Neural Stem Cells, which discloses a neural stem cell culture with a doubling rate faster than days; and (iv) U.S. Patent No. 6,468,794, entitled Enriched central nervous system stem cell and progenitor cell populations, and methods for identifying, isolating and enriching for such populations, which covers the identification and purification of the human CNS stem cell.

Because most of our issued patents will expire by 2019, absent the grant of any patent term extension, whether under the Hatch Waxman Act (Pub. L. 98-417) or otherwise, we continue to invest resources into the evaluation and prosecution of other potentially patentable technologies, including a patent family licensed from the University of Edinburgh claiming a highly purified population of human neural stem cells. We intend to file a provisional patent application claiming a novel methodology for producing genetically modified human neural stem cells.

In addition, we also rely upon trade secret protection for our proprietary information and know-how, and we take active measures to control access to this information. We believe that our know-how will also provide a significant competitive advantage.

Our policy is to require our employees, consultants and significant scientific collaborators and sponsored researchers to execute confidentiality agreements upon the commencement of any employment or consulting relationship with us. These agreements generally provide that all confidential information disclosed by us or developed during the course of the individual s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees and consultants, the agreements generally provide that all inventions conceived by the individual in the course of rendering services to us will be our exclusive property.

Licenses Agreements

Since inception, we have entered into a number of license agreements with academic organizations and commercial entities, including NeuroSpheres, Ltd. (Neurospheres), ReNeuron Ltd. (ReNeuron), Stem Cell Therapeutics Corp. (SCT), genOway SA (genOway), and the University of Edinburgh, to either acquire or

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license out intellectual property rights. Under these license agreements, there are typically obligations of due diligence and the requirement to pay royalties on products that use patented technology licensed under these agreements. The license agreements with some of these institutions relate largely to stem or progenitor cells or to processes and methods for the isolation, identification, expansion, or culturing of stem or progenitor cells. Generally speaking, these license agreements will terminate upon expiration, revocation or invalidation of the licensed patents, unless governmental regulations require a shorter term. Typically, the licensee under each of these license agreements can terminate the agreement at any time upon notice. At this time, we do not believe the future success of our research and development efforts depend significantly on any particular license agreement or research collaboration. Nevertheless, we describe the more important license agreements below.

University of Edinburgh

In January 2006, we entered into an exclusive, world-wide license agreement with the University of Edinburgh covering approximately twelve separate patent families in the stem cell field. Since then, the parties added some additional patent families and dropped some patent families which were not considered core to our business activities. Today, the license agreement patent families, including several that cover culture media and research technologies, one that covers purified populations of neural stem cells, some that cover cell reprogramming technologies, and one that covers the manipulation and use of embryonic stem cells for the derivation of research animal models, such as knock-out rats, with one or more missing genes. Under the license agreement, we have the exclusive right to commercialize the technologies in all fields. We have been paying royalties to the University of Edinburgh on the commercial sale of certain SC Proven products, and will pay royalties on all net sales of products covered by any of the intellectual property licensed under this agreement. All of the product-based royalty rates in the license agreement between the Company and the University of Edinburgh are in the single digits and there are no provisions under the University of Edinburgh license agreement for the payment of potential milestones by the Company.

ReNeuron

In July 2005, we entered into an agreement with ReNeuron under which we granted ReNeuron a license that allows ReNeuron to exploit its c-mycER conditionally immortalized adult human neural stem cell technology for therapy and other purposes. We received shares of ReNeuron common stock, as well as a cross-license to the exclusive use of ReNeuron s technology for certain diseases and conditions, including lysosomal storage diseases, spinal cord injury, cerebral palsy, and multiple sclerosis. The agreement also provides for full settlement of any potential claims that either we or ReNeuron might have had against the other in connection with any putative infringement of certain of each party s patent rights prior to the effective date of the agreement. As part of the agreement, we received in aggregate, approximately 10,097,000 ordinary shares of ReNeuron common stock, net of approximately 122,000 shares that were transferred to NeuroSpheres. Between 2007 and 2011, we sold our entire holdings of shares of ReNeuron common stock for aggregate net proceeds of approximately $3,743,000. As of June 30, 2011, we no longer hold any shares of ReNeuron.

genOway

In October 2008, we entered into a license agreement with genOway, a leading transgenics company located in France, in which we granted a non-exclusive sublicense to genOway for the use of Internal Ribosome Entry Site (IRES) technology. The IRES technology enables the dual expression of a protein of interest and a selectable marker, thereby enabling researchers to genetically modify any mammalian cell and monitor the activity of a particular gene of interest in living cells or tissues without blocking the normal function of the gene. The IRES technology is particularly important for evaluating the success of gene knock-outs or knock-ins in stem cells and for the successful creation of transgenic rodent disease models. The IRES technology has been used to develop hundreds of genetically modified

models in the past decade, and the technology is now considered to be the reference technology for transgene expression in some key rodent animal models, such as humanized models, reporter model, and cell trafficking models. The IRES technology is covered by one of the patent families

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exclusively licensed to us by the University of Edinburgh, specifically U.S. Patents No. 7,005,299 and 6,150,169 and their foreign counterparts.

In March 2012, we agreed to amend the genOway license agreement to give genOway exclusive worldwide rights, including a right to grant sublicenses, under the IRES patent family in order to commercialize transgenic mice, and provide related services such as the genetic engineering of such mice. Under this exclusive license agreement, as amended, we received a six figure lump sum payment in lieu of annual maintenance fees, and will receive single digit royalties on licensed products and services.

Takara Bio Inc.

In November 2014, we granted fully-paid up, worldwide, field-based licenses to Takara Bio Inc., a Japanese company, under some of our patents in connection with our divestiture of the SC Proven business. From the sale of the SC Proven business, we received $400,000 for certain business intellectual property rights, trademark and records and $400,000 as consideration for the licenses granted. The licenses give Takara the exclusive right to use and sub-license certain technology in order to sell and distribute products to distributors and end-user customers for use in research, including research involving induced pluripotent (iPS), embryonic, and adult stem cells. The licensed patents claim purified populations of human neural stem cells and the use of certain inhibitors to maintain pluripotent cells, among other things.

Other Commercial Licenses

We have approximately thirteen other license agreements with commercial entities, which we entered into in the ordinary course of business to monetize certain of our patents. A number of these include sublicenses to certain patents exclusively licensed to us from either NeuroSpheres or the University of Edinburgh. Some of these are license agreements to commercialize cells. A number of these are license agreements to our research tools patents, such as the IRES and selectable marker technologies described above. We have an on-going licensing program at the Company with the goal of identifying likely infringers of our intellectual property rights in order to generate license revenues.

Scientific Advisory Board

Members of our Scientific Advisory Board provide us with strategic guidance primarily in regard to our therapeutic products research and development programs, as well as assistance in recruiting employees and collaborators. Each Scientific Advisory Board member has entered into a consulting agreement with us. These consulting agreements specify the compensation to be paid and require that all information about our products and technology be kept confidential. All of the Scientific Advisory Board members are employed by employers other than us and may have commitments to, or consulting or advising agreements with, other entities that limit their availability to us. The Scientific Advisory Board members have generally agreed, however, for so long as they serve as consultants to us, not to provide any services to any other entities that would conflict with the services the member provides to us. We are entitled to terminate the arrangements if we determine that there is such a conflict.

The following persons are members of our Scientific Advisory Board:

Irving L. Weissman, M.D., Chairman of our Scientific Advisory Board, is the Virginia and Daniel K. Ludwig Professor of Cancer Research, Professor of Pathology and Professor of Developmental Biology at Stanford University, Director of the Stanford University Institute for Stem Cell Biology and Regenerative

Medicine, and Director of the Stanford Ludwig Center for Cancer Stem Cell Research and Medicine, all in Stanford, California. Dr. Weissman s lab was responsible for the discovery and isolation of the first ever mammalian tissue stem cell, the hematopoietic (blood-forming) stem cell. Dr. Weissman was responsible for the formation of three stem cell companies, SyStemix, Inc., StemCells, Inc. and Cellerant, Inc.
Dr. Weissman co-discovered the mammalian and human hematopoietic stem cells and the human neural stem cell. He has extended these stem cell discoveries

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to cancer and leukemia, discovering the leukemic stem cells in human and mouse acute or blast crisis myeloid leukemias, and has enriched the cancer stem cells in several human brain cancers as well as human head and neck squamous cell carcinoma. Past achievements of Dr. Weissman s laboratory include identification of the states of development between stem cells and mature blood cells, the discovery and molecular isolation and characterization of lymphocyte and stem cell homing receptors, and identification of the states of thymic lymphocyte development. His laboratory at Stanford has developed accurate mouse models of human leukemias, and has shown the central role of inhibition of programmed cell death in that process. He has also established the evolutionary origins of pre-vertebrate stem cells, and identified and cloned the transplantation genes that prevent their passage from one organism to another. Dr. Weissman has been elected to the National Academy of Science, the Institute of Medicine of the National Academies, the American Academy of Arts and Sciences, the American Society of Microbiology, and several other societies. He has received the Kaiser Award for Excellence in Preclinical Teaching, the Pasarow Foundation Award for Cancer Research, the California Scientist of the Year (2002), the Kovalenko Medal of the National Academy of Sciences, the Elliott Joslin Medal for Diabetes Research, the de Villiers Award for Leukemia Research, the Irvington Award for Immunologist of the Year, the Bass Award of the Society of Neurosurgeons, the New York Academy of Medicine Award for Medical Research, the Alan Cranston Award for Aging Research, the Linus Pauling Award for Biomedical Research, the E. Donnall Thomas Award for Hematology Research, the van Bekkum Award for Stem Cell Research, the Outstanding Investigator Award from the National Institutes of Health, Robert Koch Award for research in the hemopoieteic system, and many other awards. In 2010, Dr. Weissman was appointed as an Honorary Director of the Center for Biotech and BioMedicine and the Shenzhen Key Lab of Gene and Antibody Therapy at the Graduate School of Shenzhen at Tsinghua University. He was also appointed as an Honorary Professor at Peking Union Medical College and an Honorary Investigator at the State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Disease Hospital at the Chinese Academy of Medical Sciences and Peking Union Medical College. In 2011, Dr. Weissman was elected to the National Academy of Sciences Council.

David J. Anderson, Ph.D., is Seymour Benzer Professor of Biology, California Institute of Technology, Pasadena, California and Investigator, Howard Hughes Medical Institute. His laboratory was the first to isolate a multipotent, self-renewing, stem cell for the peripheral nervous system, the first to identify instructive signals that promote the differentiation of these stem cells along various lineages, and the first to accomplish a direct purification of peripheral neural stem cells from uncultured tissue. Dr. Anderson s laboratory also was the first to isolate transcription factors that act as master regulators of neuronal fate. More recently, he has identified signals that tell a neural stem cell to differentiate to oligodendrocytes, the myelinating glia of the central nervous system, as well as factors for astrocyte differentiation. Dr. Anderson is a co-founder of the Company and was a founding member of the scientific advisory board of the International Society for Stem Cell Research. Dr. Anderson also serves on the scientific advisory board of Allen Institute for Brain Science. He has held a presidential Young Investigator Award from the National Science Foundation, a Sloan foundation Fellowship in Neuroscience, and has been Donald D. Matson lecturer at Harvard Medical School. He has received the Charles Judson Herrick Award from the American Association of Anatomy, the 1999 W. Alden Spencer Award in Neurobiology from Columbia University, and the Alexander von Humboldt Foundation Award. Dr. Anderson has been elected to the National Academy of Science and is a member of the American Academy of Arts and Sciences.

Fred H. Gage, Ph.D., is Professor, Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, California and Adjunct Professor, Department of Neurosciences, University of California,

San Diego, California. Dr. Gage s lab was the first to discover Neurogenesis in the adult human brain. His research focus is on the development of strategies to induce recovery of function following central nervous system damage. Dr. Gage is a co-founder of StemCells and of BrainCells, Inc., and a member of the scientific advisory board of each. Dr. Gage also serves on the Scientific Advisory Board of Ceregene, Inc, and he is a founding member of the scientific advisory board of the International

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Society for Stem Cell Research. Dr. Gage has been the recipient of numerous awards, including the 1993 Charles A. Dana Award for Pioneering Achievements in Health and Education, the Christopher Reeves Medal, the Decade of the Brain Medal, the Max-Planck research Prize, and the Pasarow Foundation Award. Professor Gage is a member of the Institute of Medicine, a member of the National Academy of Science, and a Fellow of the American Academy of Arts and Science.

Government Regulation

Our research and development activities and the future manufacturing and marketing of our potential therapeutic products are, and will continue to be, subject to regulation for safety and efficacy by numerous governmental authorities in the United States and other countries.

U.S. Regulations

In the United States, pharmaceuticals, biologicals and medical devices are subject to rigorous regulation by the U.S. Food and Drug Administration (FDA). The Federal Food, Drug and Cosmetic Act, the Public Health Service Act, applicable FDA regulations, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, export, record keeping, approval, marketing, advertising, and promotion of our potential products. Product development and approval within this regulatory framework takes a number of years and involves significant uncertainty combined with the expenditure of substantial resources. In addition, many jurisdictions, both federal and state, have restrictions on the use of fetal tissue.

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FDA Marketing Approval

The steps required before our potential therapeutic products may be marketed in the United States include:

Steps	Considerations
1. Preclinical laboratory and animal tests	Preclinical tests include laboratory evaluation of the cells and the formulation intended for use in humans for quality and consistency. *In vivo* studies are performed in normal animals and specific disease models to assess the potential safety and efficacy of the cell therapy product.
2. Submission of an Investigational New Drug (IND) application	The IND is a regulatory document submitted to the FDA with preclinical and manufacturing data, a proposed development plan and a proposed protocol for a study in humans. The IND becomes effective 30 days following receipt by the FDA, provided there are no questions, requests for delay or objections from the FDA. If the FDA has questions or concerns, it notifies the sponsor, and the IND will then be on clinical hold until the sponsor responds satisfactorily. In general an IND must become effective before U.S. human clinical trials may commence.
3. Human clinical trials	Clinical trials involve the evaluation of a potential product under the supervision of a qualified physician, in accordance with a protocol that details the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. Each protocol is submitted to the FDA as part of the IND. The protocol for each clinical study must be approved by an independent Institutional Review Board (IRB) of the institution at which the study is conducted and the informed consent of all participants must be obtained. The IRB reviews the existing information on the product, considers ethical factors, the safety of human subjects, the potential benefits of the therapy, and the possible liability of the institution. The IRB is responsible for ongoing safety assessment of the subjects during the clinical investigation. Clinical development is traditionally conducted in three sequential phases, Phase I, II and III.