

STEMCELLS INC  
Form 10-K  
March 13, 2014  
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**UNITED STATES**  
**SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**Form 10-K**

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

For the fiscal year ended December 31, 2013

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  
(State or other jurisdiction of

incorporation or organization)

94-3078125  
(I.R.S. Employer

Identification No.)

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7707 GATEWAY BLVD

NEWARK, CA  
(Address of principal offices)

94560  
(zip code)

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

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

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  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  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.

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   
 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

Aggregate market value of common stock held by non-affiliates at June 30, 2013: \$66,836,311. 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 3, 2014: 55,419,116 shares.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive Proxy Statement relating to the registrant's 2014 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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Throughout this Form 10-K, the words "we," "us," "our," and "StemCells" refer to StemCells, Inc., including our directly and 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 and related tools and technologies for academia and industry. 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 (i) stem and progenitor cells as the basis for novel therapeutics and therapies, and (ii) cells and related tools and technologies to enable stem cell-based research and drug discovery and development.

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 HuCNS-SC<sup>®</sup> cells, our proprietary human neural platform technology. We estimate that degenerative conditions of the central nervous system (CNS) currently affect more than 30 million people in the United States<sup>1</sup>.

We are currently in clinical development with our HuCNS-SC cells for a range of diseases and disorders of the central nervous system. 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 organs 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 Pelizaeus-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;

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, and there was evidence of engraftment and long-term survival of the transplanted HuCNS-SC cells; and

we are also conducting preclinical studies of our HuCNS-SC cells in Alzheimer's disease;

(ii) with respect to the spinal cord, we are conducting a Phase I/II clinical trial of our HuCNS-SC cells for the treatment of chronic spinal cord injury. To accelerate the trial, we have expanded this trial from a single-site, single-country study to a multi-site, multi-country program. This trial is being conducted in Switzerland, Canada and the United States. Data from the first three patients demonstrated a favorable safety profile and multi-segment gains in sensory function in two of the three patients 12 months after transplantation of HuCNS-SC cells compared to pre-transplant baselines; the third patient remained stable. As of February 2014, a total of eleven patients have been dosed with our HuCNS-SC cells in this trial and we expect to complete enrollment of the final patient in the first quarter of 2014;

(iii) with respect to the eye, in June 2012, we initiated a Phase I/II clinical trial for dry age-related macular degeneration (AMD), the most common form of AMD, with the first patient enrolled and dosed in

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<sup>1</sup> 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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October 2012. This trial is being conducted at three sites in the United States, and as of February 2014, we completed enrollment of the first of two planned patient cohorts with our HuCNS-SC cells. This cohort consisted of eight subjects, four of whom each received 200,000 cells and four of whom each received 1,000,000 cells. We expect to complete enrollment of the second cohort consisting of eight patients by the end of the second quarter of 2014.

In our tools and technologies programs, we are engaged in developing and commercializing applications of our technologies to enable stem cell-based research. We currently market a range of proprietary cell culture products, research grade human cells, and antibody reagents under the SC Proven® brand. Our cell culture products include iSTEM®, GS1-R®, GS2-M®, RHB-A®, RHB-Basal®, NDiff227, NDiffN2, and NDiff N27 supplements. Our cell lines available for research use include human neural stem cells and hFB101, ultra primary human fibroblasts for genetic reprogramming. Our antibody reagents include STEM24, STEM109, STEM121®, and STEM123®, which can be used for cell detection, isolation and characterization. Academic and industrial laboratories conducting stem cell research need specialized cell culture products and reagents for the derivation, growth, maintenance, and manipulation of stem cells, as well as their detection, isolation and characterization in both *in vitro* and *in vivo* models. As this type of research continues to grow, the market for such cell culture products and reagents should also continue to expand. We are seeking to leverage our proprietary technologies, including technologies relating to embryonic stem cells, induced pluripotent stem (iPS) cells, and tissue-derived (adult) stem cells, for use in stem cell-based research. Several of the cell technologies and intellectual property related to our enabling cell technologies programs were acquired in April 2009 through our acquisition of substantially all of the operating assets and liabilities of Stem Cell Sciences Plc (SCS).

### **The Potential of Our Tissue-Derived Cell-Based Therapeutics**

Stem cells are building block cells as they produce all the mature functional cell types found in normal organs. Stem cells have two defining characteristics: (i) they produce all of the mature cell types of the 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. Stem cells are rare; to date only four human stem cells have been identified and characterized *in vivo*: (i) the hemotopoietic stem cell, (ii) the mesenchymal stem cell, (iii) the neural stem cell, and (iv) the embryonic stem cell. Because of this self-renewal property, we believe that 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 are 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 purified, unmodified tissue-derived cells is the most direct way to provide for engraftment and differentiation into functional cells, and 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



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plans to start such activities. We are currently developing embryonic stem cells and iPS cells as potential research tools. We are not currently developing embryonic or induced pluripotent stem cells for therapeutic use.

### **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.

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.

Many of our core competencies in cell biology have applicability beyond the development of therapeutic products. Therefore, another element of our business strategy is to leverage these core competencies to develop non-therapeutic applications for our cell technologies, which we believe represent nearer-term commercial opportunities. As scientific and medical research increasingly focuses on stem cells and cell biology, our technologies are expected to have utility as tools to help enable this research. We currently market specialized cell culture products and antibody reagents through our SC Proven product line and are seeking to develop and commercialize applications of our technologies for use in stem cell-based research.

Further, a key element of our business strategy is to obtain patent protection for the compositions, processes and uses of multiple types of cells, as well as for those technologies that appear applicable and useful to enable cell-based research. We believe that patent protection will be available to the first to identify and isolate any of the finite number of different types of human stem and progenitor cells, and the first to define methods to culture such cells, making the commercial development of cell-based therapeutics and enabling applications financially feasible. In addition to discovering and developing technologies in-house, we have obtained from various academic and commercial institutions rights to certain inventions relating to stem and progenitor cells, cell culture media, and technologies to reprogram, isolate and manipulate cells. We expect to continue to expand our search for, and to seek to acquire rights from third parties relating to, new stem and progenitor cells and cell technologies. We have created an extensive patent estate, see Patents, Proprietary Rights and Licenses, below.

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**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**

*Diseases and Disorders of the Brain*

**Cell-based therapeutics to restore or preserve function to central nervous system tissue by protecting, repairing or replacing dysfunctional or damaged cells.**

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):*

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

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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; and

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

*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.

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 will provide 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 will be to file an Investigational New Drug application with the U.S. Food and Drug Administration within four years.

*Diseases and Disorders of the Spinal Cord*

*Spinal Cord Injury:*

Conducting a Phase I/II clinical trial in multiple sites for chronic spinal cord injury. The trial will enroll 12 patients with thoracic (chest-level) spinal cord injury, and will include both complete and incomplete injuries as classified by the American Spinal Injury Association (ASIA) Impairment Scale.

In February 2013, reported that the first patient cohort had completed the Phase I/II trial, and that two of the three patients in the first cohort showed multi-segment gains in sensory function; the

third patient remained stable. The data also showed that the cells, the transplantation procedure, and the immunosuppression were all well tolerated.

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We expect to complete enrollment of the final patient for this trial in the first quarter of 2014.

We plan to initiate by the middle of 2014, a controlled Phase II efficacy study to further investigate our HuCNS-SC cells as a treatment for cervical spinal cord injury.

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:*

16-patient Phase I/II clinical trial in dry AMD initiated in June 2012.

Trial is being conducted at three sites in the United States, and as of February 2014, we completed enrollment of the first of two planned patient cohorts. This cohort consisted of eight subjects. We expect to complete enrollment of the second cohort consisting of eight subjects by the end of the second quarter of 2014.

We plan to initiate by year-end 2014, a controlled Phase II efficacy study to further investigate our HuCNS-SC cells as a treatment for 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

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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; (iii) Alzheimer's disease, and (iv) 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.

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Our platform technology, HuCNS-SC cells, is a purified and expanded composition of normal human neural stem cells. Alternative therapies based on cells derived from cancer cells, embryonic stem cells, iPS cells, animal-derived cells, or unpurified mixes of cell types have a significantly higher safety hurdle to overcome and while they may provide an effective therapy, technologies to remove potentially harmful cells are still being developed and tested. Furthermore, our HuCNS-SC cells can be directly transplanted, unlike embryonic stem cells or iPS cells, which require one or more prerequisite differentiation steps prior to administration in order to preclude teratoma formation (tumors of multiple differentiated cell types). It is still unclear whether cellular transplants derived from embryonic stem cells or iPS cells can avoid forming teratomas or other abnormal cellular structures due to contaminating cell types in the transplant product.

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.

We hold a substantial portfolio of issued and allowed patents in the neural stem cell field, which cover the isolation, expansion and use of neural stem and progenitor cells, as well as the compositions of the cells themselves. See Patents, Proprietary Rights and Licenses, below.

### ***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.



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### *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 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. We committed to filing an IND by mid-2017, however, we are diligently exploring ways to accelerate this milestone and currently anticipate filing by mid-2016. In accordance with the award, in April 2013, we entered into an agreement with the California Institute for

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Regenerative Medicine (CIRM) under which CIRM will provide up to approximately \$19.3 million as a forgivable loan, in accordance with mutually agreed upon terms and conditions and CIRM regulations. We received, under the CIRM Loan Agreement, an initial disbursement of \$3.8 million in July 2013 and a subsequent disbursement of \$3.8 million in January 2014.

### ***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.

We are conducting a Phase I/II clinical trial to evaluate our HuCNS-SC cells as a treatment for chronic 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 are expected to enroll in the study, all of whom will be three to twelve months post-injury. The study will follow 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). In addition to assessing safety, the trial will evaluate preliminary efficacy using defined clinical endpoints, such as changes in sensation, motor function, and bowel/bladder function. 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 have expanded the trial from a single-site, single-country study to a multi-site, multi-country program. The trial is currently being conducted in Switzerland, Canada and the United States. As of February 2014, a total of eleven patients have been dosed with our HuCNS-SC cells in this trial and we expect to complete enrollment of the final patient in the first quarter of 2014.

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.

In July 2012, the governing board of CIRM approved our application for a Disease Team Therapy Development Research Award for the study of HuCNS-SC cells as a potential treatment for cervical spinal cord injury. Under this disease team program, CIRM would have provided up to \$20 million in the form of a forgivable loan. However, in March 2013, we elected not to borrow these funds from CIRM.

### ***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

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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 in dry age-related macular degeneration, the more common form of AMD, and in October 2012, the first patient was enrolled and dosed with HuCNS-SC cells. The trial, which was authorized by the FDA in January 2012, is expected to enroll a total of 16 patients and will evaluate the safety and preliminary efficacy of our HuCNS-SC cells as a treatment for dry AMD. Patients vision will be evaluated using conventional methods of ophthalmological assessment at predetermined intervals over a one-year period. This trial is being conducted at three sites in the United States, and as of February 2014, we completed enrollment of the first of two planned patient cohorts. We expect to complete enrollment of the second cohort consisting of eight patients by the end of the second quarter of 2014.

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 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.

## **Tools and Technologies Programs**

### ***Overview***

Cells, and stem cells in particular, are an important resource for researchers seeking to understand human diseases, advance medical research and develop more effective therapies. Stem cells provide potentially unlimited sources of different cell types owing to their ability to be expanded and subsequently differentiated into particular cell types. Embryonic stem cells, for example, have the ability to become any one of the more than 200 specialized cell types found in the human body (they are said to be *pluripotent*); induced pluripotent stem (iPS) cells also possess this ability. Because of this versatility, these cells are valuable tools for examining and researching the fundamental biology of cells and the pathways involved in early development and tissue formation. In recent years, the pharmaceutical industry has become increasingly interested in using stem cell-based assays in its drug discovery and development efforts. Academia and industry use specialty cell culture products and antibody reagents to enable stem cell-based research and drug discovery and development. We sell specialty cell culture products and antibody reagents under our SC Proven brand.

**Table of Contents*****Specialty Cell Culture Products and Antibody Reagents***

Stem cell research is a growing and highly specialized field. Because of their nature, stem and progenitor cells are rare and they require specific conditions to survive and thrive. For this reason, researchers require specialized cell culture products that enable the derivation, growth, maintenance, and manipulation of such cells. One of the greatest challenges facing researchers is the limited quality and quantity of available stem and progenitor cells. The challenge is in maintaining the pluripotency or multipotency of stem or progenitor cells in culture, *i.e.*, keeping these cells from differentiating into other cell types, which is their natural tendency. Our cell biology expertise has enabled us to develop and commercialize proprietary cell culture products to optimize the derivation, growth, maintenance, and differentiation of stem cells. In contrast to common industry practice, we have developed media formulations that are free of animal serum and feeder cells (helper cells added to promote cell growth), which are known sources of undesirable agents affecting stem cell performance and safety.

Our current range of cell culture products, which are sold under the SC Proven brand, includes iSTEM, GS1-R, GS2-M, RHB-A, RHB-Basal, NDiff N2, and NDiff 227. The following table describes each of these in more detail:

iSTEM	A serum-free, feeder-free medium that maintains mouse embryonic stem cells (ESCs) in their pluripotent ground state by using selective small molecule inhibitors to block the pathways which induce differentiation.
RHB-A	A defined, serum-free culture medium for the selective culture of human and mouse neural stem cells and their maintenance and expansion as adherent cell populations.
RHB-Basal	A defined, serum-free basal medium. When supplemented with specific growth factors, this media is specifically formulated for the propagation and differentiation of adherent neural stem cells. RHB-Basal can also be tailored to specific-cell type requirements by the addition of customer preferred supplements.
NDiff N2	A defined serum-free cell culture supplement for the derivation, maintenance, expansion and/or differentiation of human and mouse ESCs and tissue-derived neural stem cells supplement.
NDiff N2-AF	A serum-free and animal component-free version of NDiff N2.
NDiff 227	A defined, serum-free medium for the differentiation of mouse ESCs to neural cell types.
NDiff N27	Defined, serum-free cell culture supplement for the derivation, maintenance, expansion and/or differentiation of human and mouse ESCs induced pluripotent stem (iPS) cells and tissue-derived neural stem cells.
NDiff N27-AF	A serum-free and animal component-free version of NDiff N27.
GS1-R	The first defined, serum-free media formulation shown to enable the derivation and long-term maintenance of true, germline competent rat ESCs without the addition of cytokines or growth factors.
GS2-M	A defined, serum- and feeder-free medium for the derivation and long-term maintenance of true, germline competent iPS cells.

We also currently market a number of antibody reagents for use in cell detection, isolation and characterization. These reagents are also under the SC Proven brand. The following table describes each of these in more detail:

STEM24	A human antibody that recognizes human CD24, also known as Heat Stable Antigen (HSA), a glycoprotein expressed on the surface of many human cell types, including immature human hematopoietic cells, peripheral blood lymphocytes, erythrocytes, and many human carcinomas. CD24 is also a marker of human neural differentiation.
STEM101	A human-specific mouse antibody that recognizes the Ku80 protein found in human nuclei.

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STEM121 A human-specific mouse antibody that recognizes a cytoplasmic protein of human cells.

STEM123 A human-specific mouse antibody that recognizes human glial fibrillary acidic protein (GFAP).

We also market a number of human cell lines for use in research, including human neural stem cells derived from different areas of the CNS as well as hFB101, ultra primary human fibroblasts for use in genetic reprogramming and the creation of human IPS cells.

Other products marketed under SC Proven include total cell genomic DNA (gDNA), RNA and protein lysate reagents purified from homogenous stem cell populations for intra-comparative studies, such as Epigenetic fingerprinting, Southern, Western and Northern blots, PCR, RT-PCR, and microarrays. This range of purified stem cell line lysates includes:

Mouse ESCs propagated in proprietary SC Proven 2i inhibitor-based GS2-M media; and

Mouse ES cell-derived and fetal tissue-derived neural stem cells propagated in proprietary SC Proven RHB-A® media.

***Other Technologies***

In addition to our cell therapeutics and research reagent programs, we hold a number of non-core technologies which we feel present licensing opportunities, such as technologies for the generation of transgenic rats.

***Transgenic Rat Program.***

As part of our acquisition of assets from SCS in April 2009, we acquired exclusive rights to an intellectual property portfolio that broadly covers rat pluripotent stem cells, methods for using these cells to generate transgenic rats, and media for the culturing of these cells. This intellectual property was based upon research done at the University of Edinburgh, which showed for the first time the successful derivation and culture of true germline competent rat ES cells required for precise genetic engineering.

In August 2010, researchers demonstrated for the first time the creation of genetically modified rats using rat pluripotent cells that have been gene targeted via homologous recombination, a method which involves adding DNA sequences to the cells to delete ( knock-out ), add ( knock-in ) or otherwise modify genes of interest. This work resulted in the successful generation of knock-out rats missing the tumor suppressor gene p53 and served as a proof-of-principle for creating genetically engineered rats using rat ES cells. Prior to this breakthrough, these types of genetic manipulations were only possible in mice, and genetically engineered mice are widely used as disease models. While both mice and rats are used as animal models of human disease, aspects of the rat's physiology, behavior, and metabolism are closer to the human, making rats the preferred species for drug development and studying human disease. Moreover, the rat cells used to generate these genetically engineered rats were cultured using a proprietary 2i inhibitor-based media formulation marketed as part of our SC Proven line of specialty cell culture products under the product name GS1-R. GS1-R is the first and only commercially available medium shown to enable the derivation and long-term maintenance of the true rat pluripotent cells required for precise genetic manipulation.

We believe that over the past few years a number of researchers have used our rat pluripotent cell technology to derive different knock-out and knock-in rat models. And, over this time, the first of the patents in this portfolio issued (GB Patent No. 2451523), and the proprietary media patent application was allowed in Europe (EPO Patent No. 1999249). We are therefore exploring our rat pluripotent cell technology and our inhibitor-based media as licensing and commercial opportunities.

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### ***Contract Services and Supply Agreements***

Our team members have been at the forefront of the research, development, manufacture, and clinical translation of various different stem cells and cell-based therapies for over 20 years. We have demonstrated expertise in the development and implementation of state-of-the-art cell separation devices, bioreactors, closed systems, and robotic platforms for manufacture of cells at the required scales. Leveraging this expertise, we now offer contract services for process development, process scale-up/scale-out and production, including use of our automated TAP Biosystems CompacT® SelecT Robotic platform.

In an extension of the process development and production services we have been contracted to scale-up and supply quantities of cell lines, reagents, cell line derivatives, and assay protocols for use in client's drug development and other programs.

Our clients include the service division of a global biotechnology company developing new medicines, and a world-renowned scientific research institute.

### **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 in compliance with current Good Manufacturing Practice (cGMP) and to quality standards that meet US as well as international regulatory requirements. 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. We believe we also have sufficient ability to manufacture the cell culture media and reagent products that we are currently selling commercially, and that we have sufficient resources to add additional media and reagent manufacturing capacity should the business need arise.

#### ***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. We sell and ship our proprietary cell culture products directly from our facility in Cambridge, U.K. Customers can order these products through our dedicated website ([www.scproven.com](http://www.scproven.com)). In addition, we have a number of co-exclusive distribution agreements with Millipore Corporation for the marketing and sale of certain of our cell culture products, including HEScGRO and ESGRO Complete.

#### ***Employees***

As of December 31, 2013, we had 58 full-time employees, 13 of whom have Ph.D., M.D. or D.V.M. degrees. 47 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.

#### ***Patents, Proprietary Rights and Licenses***

We believe that proprietary protection of our inventions will be critical to our future business. We vigorously seek out intellectual property that we believe might be useful in connection with our products, and have an active program of protecting our intellectual property. We may also from time to time seek to acquire licenses to important externally developed technologies.

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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 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:

U.S. Patent No. 5,968,829, entitled Human CNS Neural Stem Cells, which covers our composition of matter for human CNS stem cells;

U.S. Patent No. 7,361,505, entitled Multipotent neural stem cell compositions, which covers mammalian neural stem cells derived from any tissue source, including embryonic, fetal, juvenile, or adult tissue;

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;

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;

U.S. Patent No. 6,497,872, entitled Neural transplantation using proliferated multipotent neural stem cells and their progeny, which covers transplanting any neural stem cells or their differentiated progeny, whether the cells have been cultured in suspension or as adherent cells, for the treatment of any disease;

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;

U.S. Patent No. 5,851,832, entitled *In Vitro* growth and proliferation of multipotent neural stem cells and their progeny, which covers methods and compositions of proliferating and expanding human CNS cell cultures; and

U.S. Patent No. 6,294,346, entitled Use of multipotent neural stem cells and their progeny for the screening of drugs and other biological agents, which describes the use of human neural stem cells as a tool for screening the effects of drugs and other biological agents on such cells, such as small molecule toxicology studies.

Among our significant U.S. patents covering cell-based research tools and technologies are:

U.S. Patent Nos. 7,005,299 and 6,150,169, both entitled Expression of heterologous genes according to a targeted expression profile, which cover the use of a gene sequence called IRES (internal ribosome entry site), a pivotal technology to target exogenous gene expression in stem cells, thereby facilitating their identification and use; and