Autologous iPSC Therapy for Urinary Incontinence

Reporting Period: Year 1

The overall goal of this project is to develop a stem cell-based therapy for the treatment of urinary incontinence in women; therapies are also applicable for men. Urinary incontinence is very common and is linked to aging and to complications of pregnancy due to injury of the urethral sphincter. Our strategy consists of deriving induced pluripotent stem cell (iPSC) lines with a non-integrative technology that would not alter the gene content of cells, differentiating lines to smooth muscle cells, assessing characteristics of undifferentiated and differentiated cells, testing safety and efficacy and proceeding to initial discussions with the FDA. During this funding period, we have derived three affected and control lines, characterized the lines for standard properties of stem cell lines, optimized differentiation further and established initial benchmark assays for analysis of undifferentiated cells, as well as, established methods for animal studies. We have also focused on establishing protocols that eliminate animal cells and proteins from culture and media in order to provide the safest possible cells for eventual cell replacement therapies. We are on track with our milestones and are confident that the project will yield important results for the women, and men, of the state of California. In 2008, 20,330 women underwent surgery for urinary incontinence in California; this extrapolates to 172,500 UI procedures/year nationally (76,500 outpatient and 96,000 inpatient) and more than 100,000 procedures in California over the last 5 years. This number is forecast to increase by 55% by 2050. Yet, although short-term results of surgery are good, long-term results are not. Alternatives such as minimally invasive methods of injecting bulking agents, including collagen or autologous fat, provide only temporary and partial relief. Thus, our project is important as it aims to improve treatments in order to assist the significant number of patients without options for relief in the state of California.

Reporting Period: Year 2

The overall goal of this project is to develop a stem cell-based therapy for the treatment of urinary incontinence in women; therapies are also applicable for men. Urinary incontinence is very common and is linked to aging and to complications of pregnancy due to injury of the urethral sphincter. Our strategy consists of deriving induced pluripotent stem cell (iPSC) lines from patients with a non-integrative technology that would not alter the gene content of cells, differentiating these lines to smooth muscle cells, assessing characteristics of undifferentiated and differentiated cells, testing safety and efficacy in animal models, and proceeding to initial discussions with the FDA. We have derived three iPSC lines from patients, characterized the lines for standard properties of stem cell lines, optimized differentiation further and established initial benchmark assays for analysis of undifferentiated cells, as well as, established methods for animal studies. We have also established protocols that eliminate animal cells and proteins from culture and media in order to provide the safest possible cells for eventual cell replacement therapies. In the current funding period, we have concluded two animal efficacy studies using our stem cell-derived therapy. We demonstrated that the therapy consistently restores urethral function in the animal model. We are on track with our milestones and are confident that the project will yield important results for the women, and men, of the state of California. In 2008, 20,330 women underwent surgery for urinary incontinence in California; this extrapolates to 172,500 UI procedures/year nationally (76,500 outpatient and 96,000 inpatient) and more than 100,000 procedures in California over the last 5 years. This number is forecast to increase by 55% by 2050. Yet, although short-term results of surgery are good, long-term results are not. Alternatives such as minimally invasive methods of injecting bulking agents, including collagen or autologous fat, provide only temporary and partial relief. Thus, our project is important as it aims to improve treatments in order to assist the significant number of patients without options for relief in the state of California.

Reporting Period: Year 3

Urinary incontinence (UI) is common and serious, with two-thirds of the burden borne by women. Our proposed development candidate is intended to treat UI by restoring normal function to the internal urethral sphincter via regenerative therapy modalities. The initial focus is on the treatment of UI in women refractory to other surgical interventions. The urethra is comprised of an internal
urethral sphincter composed primarily of smooth muscle cells that control the flow of urine at the outlet of the bladder and an external urethral sphincter composed of voluntary skeletal muscle cells. The urethral wall also contains smooth muscle fibers and is supported by connective tissue. The total number of smooth muscle cells in the urethra decrease with aging, thus contributing to the high prevalence of incontinence amongst older individual. The discovery of genetic reprogramming methods to convert an adult cell into a cell with stem cell properties (induced pluripotent stem cells or iPSCs) has sparked strong interest in using these patient derived stem cells for regenerative therapies. The overall goal of this project is to develop an iPSC-based therapy for the treatment of stress urinary incontinence (SUI) in women. Our strategy consists of deriving iPSC lines with a non-integrative technology, differentiating lines to smooth muscle cells (SMC), assessing real-time characteristics of undifferentiated and differentiated cells, testing safety and efficacy in an animal model, and proceeding to initial discussions with the FDA. In previous reporting periods, we derived three patient lines, characterized the lines, optimized differentiation further and established initial benchmark in vitro assays for analysis of undifferentiated cells, as well as, established methods for animal studies. We have also focused on replacement of our protocol for differentiation with a protocol that removes rodent feeder cells and is carried out in chemically-defined media. In the current reporting period, we concentrated on optimizing our differentiation protocol for our patient-specific iPSC lines, increasing production of smooth muscle precursor cells, confirming SMC precursor in vivo integration and long term survival in animals, demonstrating efficacy of our pluripotent stem cell derived therapy, and examining mechanisms of action of our target therapy. We have completed four animal efficacy studies showing reproducible efficacy of our therapy derived from a human embryonic stem cell line and different iPSC lines (from different participants). Smooth muscle cell precursors derived from these lines are all able to restore urethral function and show long term survival and safety in animals. We also filed provisional patent application on our technology.

**Reporting Period:** Year 4 (NCE)

The overall goal of this project is to develop an induced pluripotent stem cell (iPSC)-based therapy for the treatment of stress urinary incontinence (SUI) in women. Our strategy consists of deriving iPSC lines with a non-integrative technology, differentiating lines to smooth muscle cells (SMC), assessing real-time characteristics of undifferentiated and differentiated cells, testing safety and efficacy in an animal model, and proceeding to initial discussions with the FDA about how to develop this product. During the previous reporting periods, we derived three patient iPSC lines, characterized the lines, optimized differentiation methods and established initial assays for analysis of undifferentiated cells, as well as established methods for animal studies. We have been successful in confirming SMC integration and survival in the animal model, as well as reproducible improvement in SUI in those animals. In addition we have established possible mechanisms of action of our target therapy and have filed a provisional patent application on our technology.

**Autologous iPSC Therapy for Urinary Incontinence**

**Grant Type:** Early Translational III

**Grant Number:** TR3-05569

**Project Objective:** The objective of this project is to identify a development candidate for the treatment of female urinary incontinence using iPSC-derived smooth muscle precursor cells (SMPC) and smooth muscle cells (SMC).

**Investigator:**

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<tr>
<th>Name:</th>
<th>Bertha Chen</th>
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<td>Institution:</td>
<td>Stanford University</td>
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**Disease Focus:** Incontinence
Human Stem Cell Use: iPS Cell

Award Value: $4,715,738

Status: Closed

Application Title: Autologous iPSC Therapy for Urinary Incontinence

Public Abstract: Urinary incontinence (UI) is common and serious, with two-thirds of the burden borne by women. UI impacts both quality and length of life; women with UI suffer debilitating falls, experience social isolation and are clinically-depressed more commonly than continent women. UI is the primary reason for elderly women to be institutionalized and carries an annual healthcare cost that exceeds $20 billion in the USA. Up to 7 million Californian women are affected with UI, a number forecast to increase by 55% in 2010 to 2050. Surgery is the main treatment today but results can be variable with a need for repeat surgeries in 30-50% of women. Here, we describe our intended target product for UI based on FDA-compatible stem cells and a minimally-invasive route of delivery that is very familiar to physicians and is currently used for injection of bulking materials to treat UI. Our stem cell approach has the potential to provide an unlimited source of cells for tissue engineering and regenerative medicine. Thus, as an added benefit associated with this research, we establish a foundation for broad applications in women's health including disorders that affect the same type of cells as in UI, smooth muscle, such as diseases of the blood vessels, respiratory tract (e.g., chronic obstructive pulmonary disease-COPD and asthma), digestive system (e.g. gastroesophageal reflux disorder-GERD and motility disorders) and others secondary to diabetes, neurodegeneration and common health problems.

Statement of Benefit to California:
Consider the tragic statistics that today the annual sale of diapers for urinary incontinence (UI) in women exceeds that of diapers for babies and that UI is the most common reason for families to institutionalize their elderly female relatives. The life expectancy of California women now exceeds 82 years. As we age, common age-associated tissue degeneration is a major physical, social, cultural and financial burden. Thus, UI is a major quality of life issue and public health concern both in terms of care and budgets. Overall, UI affects a staggering number of women resulting in annual health costs that exceed $20 billion nationally, a cost comparable to that of arthritis and greater than that of breast cancer and all gynecological cancers combined. Currently surgery is the most common treatment for UI, with good short-term but poor long-term data. Repeat surgeries are more morbid and have decreased efficacy; current alternatives provide even less relief. We suggest that we can "do better" by the women of California through step-wise research that leverages: 1) Small clinical trials that have already been conducted, 2) ability to produce large numbers of relevant cell types for UI treatment, and 3) unique expertise of our team. Our research overcomes major limitations to provide a ready stem cell-derived target product that we anticipate will provide a safe and effective treatment of UI resulting in improved quality of life of a significant fraction of our population.

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