



**Annual Report on the
Nebraska Stem Cell Research Act (LB 606)
(Neb.Rev.Stat. §71-8801 et seq)**

Presented to the State of Nebraska Legislature

**Nebraska Stem Cell Research Advisory Committee and the
Nebraska Department of Health and Human Services**

March 26, 2018

Introduction

The Nebraska Stem Cell Research Act (LB 606) was passed in the 2008 Legislative Session (Neb.Rev.Stat. §71-8801 et seq).

Stem Cell Research Advisory Committee

This Act created the Stem Cell Research Advisory Committee. Members include the dean of each medical school in Nebraska accredited by the Liaison Committee on Medical Education (Creighton University School of Medicine and the University of Nebraska Medical Center), or his/her designee. Four scientists from outside Nebraska also serve as members of the Advisory Committee. The current membership of the Stem Cell Research Advisory Committee includes:

- Bradley Britigan, M.D., Dean, University of Nebraska Medical Center, College of Medicine
- Robert Dunlay, M.D., Dean, Creighton University School of Medicine
- Rebecca Morris, Ph.D., The Hormel Institute at the University of Minnesota
- Alysson Muotri, Ph.D., University of California – San Diego
- Dennis Roop, Ph.D., University of Colorado – Denver
- Rui Yi, Ph.D., University of Colorado – Boulder

The Committee is responsible for developing the grant process and making recommendations on grants to the Division of Public Health Chief Medical Officer. Institutions or researchers may not receive stem cell funding if using human embryonic stem cells. The Committee is also responsible for submitting an annual report to the Legislature on the progress of awarded projects.

Eligibility

Awards are granted as defined below:

- Sponsoring Institution. Preference will be given to funding proposals submitted by an institution in Nebraska that has an ongoing, large-scale research program that is conducive to the completion of a complex project in stem cell research that does not use human embryonic stem cells.
- Principal Investigator. The leader of a project is the “principal investigator” (PI). Researchers with a doctoral degree in science (PhD or equivalent), or a professional degree in a medical field (MD, DMD, DVM, or similar), are eligible to submit a proposal to the Stem Cell Research Advisory Committee as a PI. The PI must be employed at an institution in Nebraska that meets the criteria for “Sponsoring Institution” (see above). Researchers that are classified as Post-doctorates or Fellows are not eligible.

Availability of Funds and Matching Requirements

The amount of money available each year is determined by the Legislature. As provided in Neb.Rev.Stat. §71-8805, no single institution or researcher is eligible to receive more than 70 percent of the funds available for distribution.

Each Sponsoring Institution or researcher must provide a dollar-for-dollar match. See Neb.Rev.Stat. §71-8805. The matching funds must be obtained from sources other than funds provided by the Stem Cell Research Act (e.g., principal investigator's salary provided by the sponsoring institution, other research grants from federal sources, stipends for students, and post-doctorates).

Submission Requirements

Each proposal must be vetted and approved by a local committee appointed by the Sponsoring Institution, or its equivalent, before it is accepted by the Stem Cell Research Advisory Committee for full review. Approval of the application by the Sponsoring Institution should be based upon the degree to which the proposal appears to meet the selection criteria.

Proposals that are vetted and approved by local committee or its equivalent, must be submitted to the Division of Public Health of the Nebraska Department of Health and Human Services. Each Sponsoring Institution may submit a maximum of five proposals in a given funding cycle and no Principal Investigator may hold more than a single award.

2017 Stem Cell Grants

After reviewing 11 applications, four grants were funded, totaling \$414,500. These grants will end June 30, 2018. The summaries were provided by the Principal Investigators.

Bin Duan, PhD (University of Nebraska Medical Center): MSC Derived Myelinating Schwann Cell for PN Regeneration; received \$101,500 for one year

Project Summary: For in vitro study we are differentiating adipose derived mesenchymal stem cells to schwann cell like cells (ADMSC-SC), and further inducing ADMSC-SC with neuronal differentiation medium to promote myelinating phenotype. Meanwhile, we are co-culturing human induced pluripotent cells derived neural progenitor cells (hiPSC-NPC) with ADMSC-SC by using microfluidic device provided by Dr. Hyung Joon Kim, co-investigator in this project, to verify the myelination. For in vivo study we have implanted the conduits with nanofiber yarns into the rat model with sciatic nerve defect.

Anna Dunaevsky, PhD (University of Nebraska Medical Center): Modeling Fragile X Syndrome with Stem Cells; received \$101,500 for one year

Project Summary: In this project we are modeling the Fragile X syndrome, a neuro-developmental disorder, using induced pluripotent stem cells from FXS and control patients. Specifically stem cells are differentiated into a type of glial cells astrocyte and the development and functional properties of these cells are compared between FXS and control cells. In addition, a chimeric human/mouse model is being developed by engrafting the differentiated induced human astrocytes into the mouse brain to understand how these cells develop in the intact brain and what effect they have on behavior.

Yuguo Lei, PhD (University of Nebraska – Lincoln): A Method for Culturing Induced Pluripotent Stem Cells; received \$110,000 for one year

Project Summary: This proposal will study a new technology termed AlgTubes to culture high quantity and high quality iPSCs and their derivatives. Specific Aim 1 is to systematically study how the parameters of AlgTubes influence iPSC viability, growth, yield, and pluripotency. Specific Aim 2 is to systematically compare culturing iPSCs in AlgTubes and the current 2D and 3D suspension culturing.

Jingwei Xie, PhD (University of Nebraska Medical Center): 3D Scaffolds Homing Stem Cells for Cartilage Repair; received \$101,500 for one year

Project Summary: 3D nanofiber scaffolds have been fabricated. We have incorporated kartogenin and SDF-1 to the nanofibers scaffolds. The release profiles of kartogenin and SDF-1 *in vitro* have been tested. We have implanted nanofiber scaffolds to the cartilage defect in a porcine cartilage defect model to test the idea we proposed. We will harvest the tissues after four and eight weeks, do the MRI imaging, and examine the histology.

2016 Stem Cell Grants

After reviewing 11 applications, four grants were funded, totaling \$435,000. These grants ended June 30, 2017. The summaries were provided by the Principal Investigators.

Shannon Buckley, PhD (University of Nebraska Medical Center): Role of E3 Ubiquitin Ligase, FBX08, in Maintaining & Inducing Pluripotency; received \$109,468 for one year

Project Summary: Pluripotent stem cells (embryonic stem cells; ESC and induced pluripotent stem cells; iPSC) have the unique characteristics that they can differentiate to all three germ layers and are capable of indefinite self-renewal. Our previous studies suggested that key elements of the pluripotency network (including the “master” regulators Nanog and Oct4) are controlled by ubiquitination and that a significant number of UPS members (mainly ubiquitin E3 ligases) regulate pluripotency and influence lineage differentiation. Within the E3 ligase family, FBX08 is an intriguing ligase to propose for further study for a number of

reasons: 1) very little is known about FBXO8; 2) loss of FBXO8 enhances efficiency of cellular reprogramming; and 3) it has recently been shown that E3 ligases, including F-box proteins represent a class of proteins that are “druggable” targets due to structure and number of downstream substrates. The goal of our studies is to understand the role of E3 ligase FBXO8 and its substrates in cellular reprogramming to achieve optimal cell reprogramming and accelerate clinical applications of induced pluripotent stem cells.

Xian-Ming Chen, MD (Creighton University): Intestinal Stem Cell Responses to C. Parvum Infection; received \$110,000 for one year

Project Summary: With a long-term goal to better understand the molecular mechanisms of gastrointestinal diseases for more efficient therapeutic interventions, this application aims to investigate the responses of distinct intestinal stem cells (ISCs) to pathogen infection at the intestinal mucosal surface, using models of intestinal infection by *Cryptosporidium parvum* (*C. parvum*), a protozoan parasite that usually only infects epithelial cells (enterocytes) at the villus tip.

Andrea Cupp, PhD (University of Nebraska – Lincoln): Purification & Proliferation of Mouse Spermatogonial Stem Cells (SSC); received \$110,000 for one year

Project Summary: The central hypothesis to be tested was that specific combination of proteins will define a more enriched population of SSC's. This enriched population of SSC's can then be increased through in vitro proliferation with growth factor combinations added to a 3-D alginate culture system. Aim #1: Evaluate combinations of protein antibodies – ID4, PAX7, TSPAN8 and NRP1 – for a purified population of SSC's through cell sorting and flow cytometry followed by transplantation to determine colonization efficiency. Aim #2: Determine combinations of growth factors (GDNF, FGF) that could be utilized in a 3-D alginate culture system followed by transplantation to identify greater proliferation of SSC's.

Haitao Wen, PhD (University of Nebraska Medical Center): O-GlcNAc Signaling in Intestinal Stem Cell Mediated Epithelial Regeneration; received \$105,532 for one year

Project Summary: The intestinal epithelium is the most rapidly self-renewing tissue in the mammalian body and its process is controlled by the intestinal stem cells (ISCs). This project is to investigate the role of the O-GlcNAc signaling in ISC-mediated epithelial regeneration following sepsis-induced intestinal tissue damage.

Conclusions

The Nebraska Stem Cell Research Project has shown substantial progress and a solid stem cell research foundation has been established. Over the past few years, research has included intestinal stem cell regeneration, Parkinson's Disease, chronic obstructive pulmonary disease (COPD), therapeutic intervention for various gastrointestinal diseases, studying the pathogenesis of neurodevelopmental diseases, retina repair, clinical

alternatives to creating replacements for restoring normal bone tissues, peripheral nerve regeneration, cartilage regeneration, developing new technology for culturing human induced pluripotent stem cells at high quantity and quality, male fertility, leukemia, and sepsis-induced intestinal tissue damage.

Researchers have also used their Nebraska stem cell funds as leverage in applying for new grant applications from the National Institutes of Health (NIH).

Progress Report of Funded Grants

Some of the major highlights of the Nebraska Stem Cell Research Project during 2016-2018:

- Nebraska researchers have received additional funds exceeding \$2 million from NIH that were directly related to their project.
- 19 publications (i.e., abstracts, articles, manuscripts, papers) have been prepared, published, or are under consideration for publication.
- 7 research positions resulted from these grants (full and/or part-time)
- 7 national presentations relating to funding from the Nebraska Stem Cell Research Project were presented.
- Pending patent with the Patent Cooperation Treaty for technology ability to produce a cell product for personalized treatment within a single 50 milliliter conical tube.