

Department of Health & Human Services

DHHS

N E B R A S K A

**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, 2015

Introduction

The Nebraska Stem Cell Research Act (LB 606) was passed in the 2008 Legislative Session. The cite reference is 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:

- Joyce Bischoff, Ph.D., Boston Children’s Hospital/Harvard Medical School
- 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
- Dennis Roop, Ph.D., University of Colorado-Denver
- Gerald Spangrude, Ph.D., University of Utah

The Committee is responsible for developing the grant process and making recommendations on subawards to the Nebraska 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

Subawards are granted as defined below:

- Sponsoring Institution. Proposals for funding may be 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 (e.g., the University of Nebraska-Lincoln, Creighton University School of Medicine, the University of Nebraska Medical Center, and Boys Town National Research Hospital).
- 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. 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. 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 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 the Sponsoring Institutions are submitted via their Office of Sponsored Programs 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.

Stem Cell Subawards

During the first five years of funding (2009 – 2013), 60 applications were submitted and 23 subawards were approved. The total funding for these 23 subawards was \$2,778,093. All of these subawards have ended.

The 2014 Request for Applications was issued February 13th. After reviewing nine applications, four subawards were funded, totaling \$435,986. These subawards will end June 30, 2015.

1. Dr. Shashank Dravid (Creighton University School of Medicine): “mTOR Pathway and Glutamate Delta-1 in Neural Stem Cells”; awarded a total of \$110,000 for one year.
2. Dr. Andrew Dudley (University of Nebraska Medical Center) and Dr. Shadi Othman (University of Nebraska-Lincoln): “Calcium-Optimized Cartilage Formation from MSCs”; awarded a total of \$110,000 for one year.
3. Dr. Stephen Rennard (University of Nebraska Medical Center): “Reprogramming Airway Fibroblasts in Asthma”; awarded a total of \$105,986 for one year.
4. Dr. A. Angie Rizzino (University of Nebraska Medical Center): “Reprogramming Human Somatic Cells without Transgenes”; awarded a total of \$110,000 for one year.

Progress Report of Funded Subawards

Some of the major highlights of the Nebraska Stem Cell Research Project during 2013 – 2015:

- An R35-based application is pending with the National Institutes of Health (NIH) for approximately \$6.3 million over seven years.
- Two NIH proposals are pending, including one for \$3.1 million.
- An NIH-COBRE pilot project has been awarded.
- A DOD proposal is pending.
- Eleven manuscripts/articles are being prepared or have been submitted for publication.
- Five research positions were created.
- Twelve national and/or international presentations relating to funding from the Nebraska stem cell research project have been presented.

Summary of 2013 Funded Subawards

Below is a summary of the stem cell subawards that began July 1, 2013 and ended June 30, 2014. Information was provided by the Principal Investigator.

Dr. Iqbal Ahmad (University of Nebraska Medical Center): “Therapeutic Regeneration in Diseased Retina”: *The main objective of the proposal is to understand the mechanisms that regulate neurogenic potential of Muller stem cells in the adult eye. Once the*

molecular pathways are identified the endogenous stem cells can be pharmacologically targeted for therapeutic regeneration to treat blinding diseases such as age-related macular degeneration and glaucoma.

Dr. Hamid Band (University of Nebraska Medical Center): “Genetic Dissection of Intestinal Crypt Stem Cell Regulation ...”: *This project investigates a new mechanism, mediated by two members of the Cbl-family of ubiquitin ligase proteins, to regulate the renewal of stem cells that maintain the integrity of the intestinal epithelial layer. Using a unique mouse model, in which genes for Cbl proteins are ablated under controlled conditions, we have obtained evidence for a critical requirement of the Cbl protein family in the intestinal stem cell renewal. Studies underway explore the mechanisms and potential to extend these findings to intestinal epithelial stem cell biology and disease states.*

Dr. Janee Gelineau-van Waes (Creighton University School of Medicine): “CerS1-Gdf1: Bicistronic Balance of Neural Stem Cell Fate”: *This project evaluates the role of CerS1 (Ceramide Synthase 1) and Gdf1 (Growth and differentiation factor 1), a member of the TGFβ superfamily, in regulating the balance between self-renewal and differentiation of neural progenitor cells through modulation of nuclear vs. cytoplasmic levels of sphingolipid metabolites.*

Dr. Shadi Othman (University of Nebraska – Lincoln): “Multi-Modal Imaging for Bone TE in a Defect Model”: *The objective of this application is to develop mesenchymally derived TE bone constructs in vitro in a custom designed magnetic resonance imaging (MRI)-compatible smart incubator (termed the e-incubator) and to evaluate bone constructs implanted in a bone defect model using multi-modal imaging.*

Summary of 2014 Funded Subawards

Below is a summary of the stem cell subawards that began July 1, 2014 and will end June 30, 2015. Information was provided by the Principal Investigator.

Dr. Shashank Dravid (Creighton University School of Medicine): “mTOR Pathway and Glutamate Delta-1 in Neural Stem Cells”: *Fundamental roles of neural stem cells (NSCs) in dentate gyrus and mTOR signaling have been identified in regulating social behaviors relevant to mental disorders particularly autism spectrum disorders. Our data indicate that glutamate delta-1 receptor can regulate NSC proliferation and mTOR signaling and thereby may serve as a therapeutic target in conditions where NSC/mTOR dysfunction may underlie social deficits in mental disorders.*

Dr. Andrew Dudley (University of Nebraska Medical Center) and Dr. Shadi Othman (University of Nebraska – Lincoln): “Calcium-Optimized Cartilage Formation from MSCs”:

The objective of this project is to determine if changing the calcium concentration in the cell culture medium will improve tissue engineering of cartilage from human mesenchymal stem cells. In the initial experiments we showed that the calcium concentration in the cell culture media is crucial to promote the expression of chondrogenic (cartilage promoting) genes in human cartilage cells. We are currently working to adapt the mesenchymal stem cell cultures to the optimal calcium concentration before we test if these conditions improve cartilage formation from human mesenchymal stem cells.

Dr. Stephen Rennard (University of Nebraska Medical Center): “Reprogramming Airway Fibroblasts in Asthma”: *This project will determine if the altered function of fibroblasts cultured from the airways of asthmatics can be corrected by reprogramming of the cells into induced pluripotent stem cells (iPSCs) followed by reprogramming into fibroblasts. In addition, the source of the cells from which iPSCs are derived will be confirmed as fibroblasts using genetic markers for lineage tracing. These studies will set the stage for strategies designed to restore to normal the altered function of the structural cells of the asthmatic airways.*

Dr. A. Angie Rizzino (University of Nebraska Medical Center): “Reprogramming Human Somatic Cells without Transgenes”: *The goal of this project is to reduce the risk of generating induced pluripotent stem cells that acquire gene mutations during the reprogramming process, which can occur as a result of transgenes inserting into the genome. Accordingly, we seek to develop reprogramming protocols that replace the use of transgenes with small molecules during the conversion of somatic cells to induced pluripotent stem cells.*

Conclusions

The Nebraska Stem Cell Research Project has shown substantial progress and a solid stem cell research foundation has been established. These stem cell research subawards may lead to innovative medical treatment options such as therapeutic regeneration to treat age-related macular degeneration and glaucoma, renewal of stem cells that maintain the integrity of the intestinal epithelial layer, regulating social behaviors relevant to mental disorders (particularly autism spectrum disorders), changing the calcium concentration in the cell culture medium to improve tissue engineering of cartilage from human mesenchymal stem cells, designing strategies to restore to normal the altered function of the structural cells of the asthmatic airways, and regulating the balance between self-renewal and differentiation of neural progenitor cells through modulation of nuclear vs. cytoplasmic levels of spingolipid metabolites.

Since the inception of the program, new positions have been created, articles have been submitted and published in research journals, and presentations have occurred at

national and international meetings. Researchers are also using their Nebraska stem cell funds as leverage in applying for new grant applications from the National Institutes of Health (NIH) and other organizations such as the DOD.