

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, 2014

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. In addition, four scientists from outside Nebraska were approved by the 2009 Legislature as members of the Advisory Committee. These individuals were reappointed by the Legislature in 2012. Dr. Bradley Keller from the University of Louisville resigned from the Committee in January 2013 and his replacement (Dr. Joyce Bischoff) has received Legislative approval. 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 grant awards 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 those projects that have been awarded grants.

Eligibility

Grants are awarded 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 Grants Awarded

The first Request for Applications was issued on May 13, 2009. The Stem Cell Research Advisory Committee reviewed 13 applications and approved six. The total amount funded for these grants was \$900,000 (included two years of funding). These grants have ended.

1. Dr. Iqbal Ahmad (University of Nebraska Medical Center): “Adult Stem Cells for Autologous Cell Therapy”; awarded a total \$150,000 over two years.
2. Dr. Kirk Beisel (Creighton University School of Medicine): “Transcript Factors in Auditory Hair Cell Regeneration”; awarded a total \$150,000 over two years.
3. Dr. Andrea Cupp (University of Nebraska-Lincoln): “VEGF Isoform Regulation of Spermatogonial Stem Cells”; awarded a total \$150,000 over two years.
4. Dr. A. Angie Rizzino (University of Nebraska Medical Center): “Human iPS Cell Formation and Sox2-Associated Proteins”; awarded a total \$150,000 over two years.
5. Dr. Garrett Soukup (Creighton University School of Medicine): “MicroRNA Promotion of Hair Cell Differentiation”; awarded a total \$150,000 over two years.
6. Dr. Jialin Zheng (University of Nebraska Medical Center): “Regenerative Therapy of Parkinson’s Disease by iPS Cells”; awarded a total \$150,000 over two years.

The 2010 Request for Applications was issued on February 12th. After reviewing 15 applications, four grants were funded for a total amount of \$483,580. These grants have ended.

1. Dr. Hesham Basma (University of Nebraska Medical Center): “Induced Pluripotent Stem Cells and COPD”; awarded a total \$129,500 over two years.
2. Dr. Shi-Jian Ding (University of Nebraska Medical Center): “Proteomic Study of iPS and NPC Cell Induction”; awarded a total \$129,500 over two years.
3. Dr. George Oyler (University of Nebraska-Lincoln): “Tcd Based Protein Delivery of iPSC Reprogramming Factors”; awarded a total \$95,080 for one year.
4. Dr. John Sharp (University of Nebraska Medical Center): “Mouse and Human iPS Cells: Tools to Probe Cellular Aging”; awarded a total \$129,500 over two years.

The 2011 Request for Applications was issued on February 11th. After reviewing 11 applications, four grants were funded, totaling \$506,420. These grants have ended.

1. Dr. Jung Yul Lim (University of Nebraska-Lincoln): “Controlling Stem Cell Fate via Cell Patterning”; awarded a total of \$150,000 over two years.
2. Dr. Mayumi Naramura (University of Nebraska Medical Center): “Regulation of Hematopoietic Stem Cell Homeostasis by CBL”; awarded a total of \$150,000 over two years.
3. Dr. Anuradha Subramanian (University of Nebraska-Lincoln): “Mesenchymal Stem Cells, Scaffolds, and Ultrasound in Cartilage Tissue Engineering”; awarded a total of \$56,420 for one year. This grant ended June 30, 2012.
4. Dr. Zhao-Yi Wang (Creighton University School of Medicine): “ER-alpha36: Roles in Breast Cancer Stem Cells”; awarded a total of \$150,000 over two years.

The 2012 Request for Applications was issued on February 16th. After reviewing 11 applications, five grants were funded, totaling \$448,269. These grants have ended.

1. Dr. Andrea Cupp (University of Nebraska-Lincoln): “VEGFA Isoform Efforts on Spermatogonial Stem Cell Homeostasis”; awarded a total of \$80,000 for one year.
2. Dr. Shi-Jian Ding (University of Nebraska Medical Center): “Proteomic Study of iPSC and NPC Induction”; awarded a total of \$100,000 for one year.
3. Dr. Santhi Gorantla (University of Nebraska Medical Center): “Humanized Mouse Model to Test Immunogenicity of iPSCs”; awarded a total of \$68,269 for one year.
4. Dr. Woo-Yang Kim (University of Nebraska Medical Center): “Neural Stem Cells and Neurological Disorders”; awarded a total of \$100,000 for one year.
5. Dr. Anuradha Subramanian (University of Nebraska-Lincoln): “Clinically Relevant Cartilage in Ultrasonic Bioreactors”; awarded a total of \$100,000 for one year.

The 2013 Request for Applications was issued on March 5th. After reviewing 10 applications, four grants were funded, totaling \$439,824. These grants will end June 30, 2014.

1. Dr. Iqbal Ahmad (University of Nebraska Medical Center): “Therapeutic Regeneration in Diseased Retina”; awarded a total of \$110,000 for one year.
2. Dr. Hamid Band (University of Nebraska Medical Center): “Genetic Dissection of Intestinal Crypt Stem Cell Regulation ...”; awarded a total of \$110,000 for one year.
3. Dr. Janee Gelineau-van Waes (Creighton University): “CerS1-Gdf1: Bicistronic Balance of Neural Stem Cell Fate”; awarded a total of \$109,857 for one year.
4. Dr. Shadi Othman (University of Nebraska – Lincoln): “Multi-Model Imaging for Bone TE in a Defect Model”; awarded a total of \$109,967 for one year.

Progress Report of Funded Grants

Some of the major highlights of the Nebraska Stem Cell Research Project (2011 – 2013 grants):

- An application has been submitted to the National Institutes of Health (NIH) for \$1,700,000 for five years.
- NIH funded a project for \$501,290 and the Alzheimer’s Association funded a project for \$100,000.
- Eleven articles and one book chapter have been published. Eleven manuscripts/articles have also been submitted for publication.
- Ten research positions have been created (e.g., graduate assistants, post-doctoral, research technicians, part-time).

- Seventeen national and/or international presentations relating to funding from the Nebraska stem cell research project have been presented.

Summary of 2011 Funded Grants

Below is a summary of some of the funded 2011 stem cell grants. Information was provided by the Principal Investigator.

Dr. Jung Yul Lim (University of Nebraska-Lincoln): “Controlling Stem Cell Fate via Cell Patterning”: *To direct adult stem cell function and fate, controlling cell shape via micropatterning was exploited. We aimed to control cell-cell interaction, which plays a critical role in cell lineage commitment and differentiation, by patterning mesenchymal stem cells (MSCs) into inter-connected or isolated geometry as a novel way of directing stem cell fate. By evaluating micropatterned cell differentiation and revealing cell signaling mechanism, an integrated picture on how to control stem cells was provided.*

Dr. Mayumi Naramura (University of Nebraska Medical Center): “Regulation of Hematopoietic Stem Cell Homeostasis by CBL”: *Hematopoietic stem cell transplant (HSCT, also called “bone marrow transplant”) is now well established as a curative treatment for various malignant and non-malignant diseases. We identified the Cbl family E3 ubiquitin ligases as critical regulators of HSC homeostasis. Studies funded by this grant revealed that Cbl was required to maintain HSCs with the highest regenerative capacity.*

Summary of 2012 Funded Grants

Below is a summary of some of the funded 2012 stem cell grants. Information was provided by the Principal Investigator.

Dr. Andrea Cupp (University of Nebraska-Lincoln): “VEGFA Isoform Efforts on Spermatogonial Stem Cell Homeostasis”: *The central hypothesis to be tested is that an appropriate balance of pro and antiangiogenic VEGFA isoforms are necessary for the establishment and maintenance of the spermatogonial stem cell (SSC) niche within the testes. We have developed several different lines of conditional KO mice. VEGFA conditional KO mice using DMTRI-cre (Sertoli and germ cells) and Sry-cre (only Sertoli) and VEGF angiogenic isoforms KO mice using Nrp-1 floxed mice with Sry-cre (all angiogenic VEGFA isoforms in Sertoli) are less fertile since they take 12-20 days longer after the first litter to have another litter suggesting that there is less sper per ejaculate. Furthermore, there are alterations in testis morphology, in genes that affect the SSC niche resulting in reduced undifferentiated spermatogonia and reduce sperm in the epididymis in the DMTRI-cre X VEGFA mice. Thus, VEGFA isoforms appear to be critical to maintenance of the SSC niche and continued spermatogenesis.*

Dr. Woo-Yang Kim (University of Nebraska Medical Center): “Neural Stem Cells and Neurological Disorders”: *Abnormal control of neural stem cells can lead to structural and functional brain damages and is thereby implicated in neurological birth defects and neurodegenerative diseases. The goal of this proposed study is to establish a novel mechanism of neural stem cells that can be targeted by currently-available pharmacological drugs.*

Summary of 2013 Funded Grants

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

Dr. Iqbal Ahmad (University of Nebraska Medical Center): “Therapeutic Regeneration in Diseased Retina”: *The objective of the proposal is to identify molecular targets that will allow a facile activation of endogenous stem cells in the adult retina toward regenerating dying photoreceptors in blinding diseases such as the age-related macular degeneration. This is a stem cell approach to treat the disease from within to stem vision loss. The incident of such diseases is increasing in Nebraska’s aging population.*

Dr. Hamid Band (University of Nebraska Medical Center): “Genetic Dissection of Intestinal Crypt Stem Cell Regulation ...”: *The intestinal epithelium is essential for absorption of nutrients, warding off microbes and regulating metabolic/endocrine homeostasis. Intestinal failure is common after cancer treatment and other diseases. This project is examining the molecular controls that allow intestine-resident stem cells to expand and live longer in order to facilitate approaches for stem cell therapy to repair malfunctioning or surgically lost intestine.*

Dr. Jance Gelineau-van Waes (Creighton University): “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 TGF β 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-Model Imaging for Bone TE in a Defect Model”: *The proposed research will advance bone tissue engineering in two significant ways: the application of an MRI-compatible bone smart incubator that is ultimately expected to ensure high quality tissue engineered bone constructs prior to human transplantation and the application of multi-modal imaging that is expected to set a new standard of testing implants for engineered bone, thus improving the connectivity between pre-clinical animal models and human clinical trials.*

Conclusions

The Nebraska Stem Cell Research Project has shown substantial progress and a solid stem cell research foundation has been established. The stem cell research grants may lead to innovative medical treatment options for diseases such as blindness in age-related macular degeneration, repairing malfunctioning intestines after cancer treatment and other diseases, advancing bone tissue engineering, establishing novel mechanisms of neural stem cells that can be targeted by currently available pharmacological drugs, and hematopoietic stem cell transplant (HSCT – bone marrow transplant) as treatment for various malignant and non-malignant diseases. This program has also created new positions and articles have already been published in several research journals. In addition, numerous articles have been submitted for publication and presentations have occurred at national and international meetings. Finally, researchers are 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 Alzheimer's Association.