

NEBRASKA



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DEPT. OF HEALTH AND HUMAN SERVICES

**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, 2022

Introduction

The Nebraska Stem Cell Research Act (LB 606) was passed in the 2008 Legislative Session (Neb.Rev.Stat. §71-8801 et seq). The Research Act requires the Stem Cell Research Advisory Committee annually submit a report to the Legislature providing details on the grants awarded to Nebraska institutions and researchers conducting nonembryonic stem cell research.

Stem Cell Research Advisory Committee

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 process is underway to fill a scientist vacancy on the Committee. The current membership includes:

- Bradley Britigan, M.D., Dean, University of Nebraska Medical Center, College of Medicine
- Robert Dunlay, M.D., Dean, Creighton University School of Medicine
- Alysson Muotri, Ph.D., University of California – San Diego
- David Owens, Ph.D., Columbia University
- Dennis Roop, Ph.D., University of Colorado – Denver
- Rui Yi, Ph.D., Northwestern University

The Committee is responsible for developing the grant process and making recommendations on grants for stem cell research 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.

Progress Report of Funded Grants

COVID-19 has impeded the progress of stem cell grants since 2019. However, major highlights of the Nebraska Stem Cell Research Project during 2018-2022, include:

- Nebraska researchers have received additional funds exceeding \$7 million from NIH, the University of Nebraska Collaboration Initiative, the American Society of Gene & Cell Therapy, the American Society of Hematology (ASH) Junior Faculty Scholar Award, and the Otis Glebe Medical Research Foundation directly related to funded projects.
- Nebraska researchers also have numerous NIH proposals pending, under submission or under review.
- 35 publications related to funded projects (i.e., abstracts, articles, manuscripts, papers) have been prepared, are under consideration for publication, or published.
- 17 research positions resulted from these grants (full and/or part-time).

- Over 35 national and international presentations relating to funding from the Nebraska Stem Cell Research Project.
- Nebraska researchers have applied for 2 patents (one provisional and one pending) based on research in this program.
- Nebraska researchers have developed 3 inventions as a result of the Stem Cell Research Act.

2021 Stem Cell Grants

After reviewing nine applications, five grants were funded totaling \$436,500. These grants will end June 30, 2022. The Principal Investigators provided the following summaries.

Andrew Hamann, PhD (University of Nebraska – Lincoln): MSCs for miRNA-Loaded and Cell-Targeting Exosomes: received \$25,000 for one year

Project Summary: This project aims to develop a system to genetically engineer adult stem cells to produce nanosized vesicles loaded with a class of biomolecules called microRNAs, which are promising new drug candidates. These vesicles, called exosomes, will specifically be loaded with microRNA-133a, which our collaborator has shown could be potentially used as a new therapeutic to treat a specific type of heart failure frequently caused by diabetes (i.e., diabetic cardiomyopathy). This process will optimize microRNA loading into exosomes and engineer the system to present molecules that can specifically target cells of the heart to deliver this potential new drug system. These microRNA-loaded and heart-targeted exosomes will then be investigated for their therapeutic properties using cell culture models of diabetic cardiomyopathy.

Robert Lewis, PhD (University of Nebraska Medical Center): Determinants of Stem Cell Formation in Colorectal Cancer: received \$110,000 for one year

Project Summary: The goal of this research is to identify mechanisms required for the generation of cancer stem cells, which are responsible for tumor initiation. Cancer stem cells are also major contributors to resistance to therapy, which limits treatment. Preliminary data indicate that disruption of a protein called KSR1 prevents resistance to two clinically approved cancer therapeutics in both human colorectal cancer cells and human lung cancer cells. Ongoing experiments will determine how KSR1 contributes to cancer drug resistance with a long-term goal of testing approaches to inhibit KSR1 to improve cancer treatment.

Brian North, PhD (Creighton University): Targeting SIRT2 in Glioblastoma Cancer Stem Cells: received \$95,750 for one year

Project Summary: Cancer stem cells (CSCs), a subset of cancer cells within a tumor that harbor characteristics similar to stem cells, play a role within tumor initiation, propagation, metastasis and therapeutic resistance. Researchers have increasingly appreciated this interplay over the past decade. In particular, CSCs play a major role in the development and maintenance of glioblastoma, a cancer which initiates in the brain and is one of the most aggressive and difficult types of cancer to treat. This project is assessing the role of

the NAD+/SIRT2/BubR1 pathway in regulating glioblastoma CSC stemness, or molecular process of self-renewal, both *in vitro* and *in vivo*. The short term goals of this project are to generate data for publication as well as preliminary data to serve as the basis for grant submissions to federal agencies with a long-term goal of developing novel therapeutic strategies based on targeting glioblastoma CSCs.

A. Angie Rizzino, PhD (University of Nebraska Medical Center): SOX2: MYC Axis and Drug-Tolerant Cancer Stem Cells: received \$95,750 for one year

Project Summary: Many drugs used in the treatment of cancer have unintended side effects, including activation of signaling pathways that reduce the efficacy of the drug. This project is testing the hypothesis that drug treatment can activate a vicious feed-forward loop where drug treatment elevates the stem cell transcription factor SOX2, which then downregulates the cMYC oncoprotein and causes the formation of quiescent, drug-tolerant cancer stem cells. This project tests that hypothesis by blocking the elevation of SOX2 induced by clinically-used drugs and determining whether this blocks the decrease in cMYC. We will also screen a large set of clinically-used drugs to identify ones that eradicate quiescent tumor cells when SOX2 is elevated.

Jian Zuo, PhD (Creighton University): Cochlear Stem Cells for Hearing Restoration: received \$110,000 for one year

Project Summary: Damage and loss of inner ear cochlear hair cells (HCs) leads to hearing loss. We have recently successfully induced the formation of new HCs (cHCs) in mouse models with therapeutic drugs. This project proposes to analyze transcriptional changes at the single-cell level via RNA sequencing to identify pathways and restore hearing pharmaceutically.

Conclusions

The Nebraska Stem Cell Research Project continues to show substantial progress, establishing a solid stem cell research foundation. Over the years, research included projects addressing glaucoma, facilitation of chronic wound healing, cranial bone regeneration, tendon regeneration to manage shoulder tendon injuries, strategies to regenerate damaged auditory epithelium promoting ultimate hearing restoration, glioblastoma, bone marrow transplantation, heart failure frequently caused by diabetes, improvement of cancer treatment, and pediatric brain tumors.

Researchers have also used their Nebraska stem cell funds as leverage in applying for new grant applications from the National Institutes of Health, the University of Nebraska Collaboration Initiative, the American Society of Gene & Cell Therapy, and the Otis Glebe Medical Research Foundation.