Department of Health & Human Services

DHHS

NEBRASKA

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, 2011

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 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 Council. The current membership of the Stem Cell Research Advisory Committee includes:

- Rodney Markin, M.D., Ph.D., University of Nebraska Medical Center
- Rowen Zetterman, M.D., Creighton University
- Bradley Keller, M.D., University of Louisville
- Dennis Roop, Ph.D., University of Colorado-Denver
- Gerald Spangrude, Ph.D., University of Utah
- Rebecca Morris, Ph.D., The Hormel Institute at the University of Minnesota

The Committee was responsible for developing the grant process and making grant awards to Nebraska institutions or researchers to conduct stem cell research that does not use human embryonic stem cells.

The Committee is also responsible for submitting a 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 that does not use human embryonic stem cells (e.g., the University of Nebraska-Lincoln, Creighton University, 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 $485,000. Applicants may apply for a one or two year grant award. No single institution or researcher is eligible to receive more than 70 percent of the funds available for distribution.

Each Sponsoring Institution or researcher is responsible to 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. The composition of the committee is at the discretion of the higher education institution. 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. Unfunded applicants may resubmit for funding on subsequent grant cycles.

Stem Cell Grants Awarded

Although the Stem Cell Research Act was created in 2008, grants were not awarded until 2009. The first Request for Applications was issued May 13, 2009, with the total amount of available funding at $970,000 (2008 and 2009 funding cycles). A total of 13 applications were submitted from the University of Nebraska Medical Center, Creighton University, the University of Nebraska-Lincoln, and the University of Nebraska-Omaha. The Stem Cell Research Advisory Committee reviewed all applications and approved six.

The total amount funded for these grants was $900,000 ($484,998 for year one and $415,002 for year two). Listed below are the 2009 grants:

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 February 12th. After reviewing 15 applications, four grants were approved for funding. The total amount funded was $483,580. Listed below are the 2010 grants:

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. Dr. Oyler is still waiting for IBC approval.
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.

Progress Report of Funded Grants

Although the first grants were not awarded until 2009, considerable progress has been made in several areas. Some of the major highlights include:

- Applications have been submitted to the National Institutes of Health (NIH) leveraging at least $1.25 million in funds.

- Eight articles have been published and nine articles have been prepared for publication.

- Eleven new research positions have been created (e.g., graduate assistants, post-doctoral research positions).

- Fifteen national and/or international presentations relating to Nebraska stem cell research have been presented.

- Six abstracts have been submitted to national and/or international conferences.

Summary of 2009 Funded Grants

Below is a summary of the stem cell grants that began July 1, 2009, with information provided by the Principal Investigator.

Dr. Iqbal Ahmad (UNMC): "Adult Stem Cells for Autologous Cell Therapy"

Stem cell approach holds promise to treat intractable neurodegenerative changes that lead to blindness in age-related macular degeneration (AMD) and retinitis pigmentosa (RP) by cell replacement. However, the approach remains clinically impractical because of two significant barriers: the lack of accessible, renewable and ethically acceptable sources of cells and the possibility of immune rejection. The goal is to characterize adult stem cells that regenerate cornea as a renewable source of retinal progenitors from which photoreceptors and their precursors can be derived for stem cell therapy.

Dr. Kirk Beisel (Creighton University): "Transcript Factors in Auditory Hair Cell Regeneration"

Hearing loss and balance disorder is a major health problem that affects over 37 million Americans, especially the elderly. Research has shown that human and rodent ear tissues can activate important elements of virtually identical biological machinery that underlies regeneration and our goal is to explore four transcription factors (Atoh1, Pou4f3, Gfi1 and Barhl1) that are required for maturation and maintenance of auditory hair cells (HCs). This proposal tests the hypothesis that maintenance of regenerated HCs requires a quantitative ratio of these transcription factors. The efficacy of regeneration and the resulting HC expression profiles will be examined. It is the goal of these studies to provide the necessary parameters for long term survival of the regenerated hair cells that will facilitate the use of an induced pluriopotent stem cell (iPSC)-based technology.

Dr. Andrea Cupp (University of Nebraska-Lincoln): "VEGF Isoform Regulation of Spermatogonial Stem Cells"

This project is determining how splice variants of the Vascular endothelial growth factor- A (VEGFA) gene (angiogenic and antiangiogenic) affect spermatogonial stem cell renewal and differentiation as a model for understanding more about the stem cell niche.

Dr. A. Angie Rizzino (UNMC): "Human iPS Cell Formation and Sox2-Associated Proteins"

The goal of these studies is to identify proteins that associate with the reprogramming transcription factor Sox2 and to determine whether these proteins are required for Sox2 to promote the reprogramming of somatic cells to an induced pluripotent stem (iPS) cell state. To achieve this goal, proteins that associate with Sox2 during the early stages of reprogramming were isolated and identified by a mass-spectrometry based method. The expression of select Sox2-associated proteins will be manipulated to determine whether they are required for somatic cell reprogramming.

Dr. Garrett Soukup (Creighton University): "MicroRNA Promotion of Hair Cell Differentiation"

Sensory hair cells are crucial to hearing and balance, but are not capable of regeneration in humans. Several factors are necessary for hair cell development and include certain microRNAs. The goal of this project is to establish whether such microRNAs in combination with other factors appear to promote conversion of precursor cells toward hair cells. Results indicate that a particular combination of the factors is more effective than others. The expectation is that this combination of factors might be applied to adult stem cell therapies for regenerating hair cells and maintaining hearing.

Dr. Jialin Zheng (UNMC): "Regenerative Therapy of Parkinson's Disease by iPS Cells"

This project proposes to develop induced pluripotent stem (iPS) cells from brain astrocytes and address the potential of using iPS cells as a therapeutic strategy to treat an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease (PD). In past two years, we have successfully generated astrocyte-derived iPS cells and further found that reprogrammed astrocytes retain a "memory" of the central nervous system, which confers additional potential upon neuronal differentiation. These findings provide strong support for astrocyte-derived iPSCs as a therapeutic strategy to treat an MPTP mouse model of PD.

Summary of 2010 Funded Grants

Below is a summary of the stem cell grants that began July 1, 2010, with information provided by the Principal Investigator.

Dr. Hesham Basma (UNMC): "Induced Pluripotent Stem Cells and COPD"

We have generated iPS-like cells from four COPD and four control lung fibroblasts. The colonies were passaged twice before measuring the undifferentiation markers Oct4 and Nonog in the cells before and after generation of iPS-like cells by real-time PCR. We performed microarrays for mRNA and microRNA for all the strains that generated iPS-

like cells and their corresponding iPS-like cells and we are in the process of analyzing these data.

Dr. Shi-Jian Ding (UNMC): "Proteomic Study of iPS and NPC Cell Induction

Yamanaka and other scientists have demonstrated the reprogramming of somatic cells to embryonic stem-like cell status. Although the occurrence of iPS cells is groundbreaking, the use of retroviral and lentiviral vectors for expressing the reprogramming transcription factors involves the risk of insertional mutagenesis, which would be a problem if the cells were used in regenerative medicine, so reprogramming with non-integrating virus or transient episomal gene expression, or more favorably by chemical means alone is a worthy goal. To achieve this goal, we propose to apply a quantitative proteomic approach to study the key intracellular signaling pathways and protein targets that control development of induced pluripotent stem (iPS) cells and their progression into neural precursor cells (NPCs) from mouse embryonic fibroblast cells (MEFs).

Dr. John Sharp (UNMC): "Mouse and Human iPS Cells: Tools to Probe Cellular Aging"

This project will determine if cells from old individuals (initially mice), versus young individuals, or cells of different tissues that age differentially, or cell populations that have a higher versus lower stem cell content are more or less difficult to reprogram. These studies commenced in July 2010 and are on-going.

Background: There is an increasing interest in the potential of converting adult tissue cells of an individual into stem cells with increased growth potential and ability to repair damaged tissues of that individual (technically, reprogramming of somatic cells to induced pluripotent stem (iPS) cells). This technology offers a non-controversial option to generate tissue-matched, i.e. one's own cells, for repair of damaged heart, or lung, or other tissues.

The majority of potential beneficiaries of such an approach to regenerative medicine are elderly. There is a major concern that the cells of elderly individuals may be more difficult to reprogram than cells of young individuals. This question has not been addressed previously, although a very recent paper from Japan (Cheng et.al, Journal of Molecular Biology, Jan 12, 2011) also raises this issue. It is possible that "young" cells are easier to reprogram or, alternatively, cells which already have some stem cell-like characteristics, may be easier to reprogram. Recently, we have shown that the numbers of such stem cell populations in man, decline with age (Brusnahan et.al, Mechanisms of Aging and Development 131:718, 2010).

Conclusions

Although the Nebraska Stem Cell Research Project has been in existence less than two years, substantial progress has been made 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, hearing loss, and Parkinson's disease. In addition, this program has created several new positions, multiple articles and publications have been submitted to research journals, 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).