Cellular Reprogramming: Dissecting the Molecular Mechanism and Enhancing Efficiency

Grant Award Details

Cellular Reprogramming: Dissecting the Molecular Mechanism and Enhancing Efficiency

Grant Type: Basic Biology II

Grant Number: RB2-01628

Project Objective: To determine if iPSC derived astrocytes of brain or spinal cord origin can promote the maturation of iPSC derived brain or motor neurons in order to generate better in vitro models.

Investigator:

Name:	Irene Griswold-Prenner
Institution:	iPierian, Inc.
Type:	PI

Disease Focus: Neurological Disorders

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,458,000

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Cellular Reprogramming: Dissecting the Molecular Mechanism and Enhancing Efficiency

Public Abstract: Pluripotent stem cells have a remarkable potential to develop into virtually any cell type of the body, making them a powerful tool for the study or direct treatment of human disease. Recent demonstration that induced pluripotent stem (iPS) cells may be derived from differentiated adult cells offers unprecedented opportunities for basic biology research, regenerative medicine, disease modeling, drug discovery and toxicology. For example, using patient-derived iPS cells, one can model diseases in vitro and screen for drugs in ways never before possible, enabling the identification of promising new therapeutic candidates earlier in the drug discovery process. In addition, iPS cell derivatives represent an ideal source for autologous cell replacement therapies, as they would not be rejected upon transplantation back into the patient.

While it is clear that iPS cells hold great promise for finding therapies for diseases, there are significant hurdles that need to be overcome before full clinical potential is realized. The mechanism of iPS cell derivation is largely elusive, and the process used to generate them is very inefficient and needs to be improved in significant ways. Currently, iPS cells are generated by forced expression of four molecular factors using genome-integrating viruses. This may lead to mutations and altered differentiation potential of iPS cells, as well as tumorogenesis if transplanted back into the patient. The inefficient and stochastic nature of the reprogramming process indicates that additional, as yet unidentified mechanisms may exist and contribute to iPS cell generation. Finally, increasing the efficiency of current iPS cell derivation protocols will increase the ability to generate large panels of patient-specific iPS cell lines.

We propose to use a human cell-based assay to identify small molecules that can enhance the efficiency of iPS cell generation. Our strategy will allow us to identify small molecules that target events essential for derivation of iPS cells, as well as those that replace one or more of the four virally-delivered factors. We will use the identified small molecules to discover regulatory pathways and molecular targets involved in induction of pluripotency, gaining valuable insight into the mechanism of cellular reprogramming. Application of these small molecules themselves, as well as novel approaches derived from mechanism of action studies, will help overcome issues associated with viral integration and has the potential to transform personalized cell-replacement therapies as well as accelerate drug discovery based on iPS cell-derived disease models.

Statement of Benefit to California:

California's health care system faces significant challenges as millions of children and adults suffer from a host of incurable illnesses. It is expected that health care costs will continue to rise as California's citizenry ages and requires treatments for age-related, chronic metabolic, cardiovascular, and neurodegenerative disorders. Both the measureable economic impact on California's health care system and the incalculable emotional suffering of affected individuals, their families and communities, make it an imperative to develop novel therapeutic treatments to address these mounting medical and economic societal challenges.

Recognizing the potential utility of novel stem cell technologies to address California's unmet medical needs, California voters approved Proposition 71 which created the California Institute for Regenerative Medicine (CIRM), an agency that administers funds to support stem cell research that has the greatest potential for development of novel regenerative medical treatments and cures. The CIRM Basic Biology Awards II program is intended to fund studies that will lay the foundation for future stem cell-based translational and clinical advances. In keeping with this mission, our proposed research program aims to discover new methods for producing human induced pluripotent stem cells (iPS cells) on an industrial scale and in an efficient manner; and to develop a better understanding of the mechanisms underlying cellular reprogramming. As such, our research program will help accelerate the realization of the full potential of iPS cells in cell-based regenerative medicine therapies and drug discovery.

Our proposed research program will benefit the State of California and its citizens in several ways. Firstly, our research program will lay the foundation for future stem cell-based clinical and translational advances to treat and manage one of California's most pressing unmet medical needs. Secondly, execution of our research program will create new jobs in the academic, biotechnology and pharmaceutical sectors throughout California. Funding from CIRM will be expanded with additional funding from the applicant to augment achievement of the aims of this project. CIRM funding will leverage other sources of investment in this project to help ensure California's continued future as a world leader in biomedical innovation and translational medicine for the benefit of human health. Lastly, our proposed research program will stimulate California's economy by creating new enabling tools and technologies that can be broadly adopted across the life science industry, thus promoting development across the academic institutions and biopharmaceutical companies that create biomedical discoveries and advances. These activities will continue to strengthen California's leadership position at the forefront of the stem cell and regenerative medical revolution of the 21st century.

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