Understanding the Biological Processes of Aging: Quantitative Studies of Protein Aggregation and Aging

The NIH Director's Pioneer Award Program is intended to support creative, innovative investigators who bring their ideas to bear on significant research challenges. The Ismagilov project is a multi-disciplinary research program that aims to develop, validate, and disseminate microfluidic technologies for quantitative studies of protein aggregation and aging.

Lead Agency: Office of Portfolio Analysis and Strategic Initiatives (OPASI) / Common Fund, NIH Office of the Director

Agency Mission:

- Strategic planning and implementation of trans-NIH initiatives that seek to transform the way health research is conducted
- Development and distribution of tools and methodologies to NIH Institutes and Centers for analysis and evaluation of NIH programs

Principle Investigator:

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Partner Agencies:

All NIH Institutes and Centers participate in the planning and implementation of NIH Common Fund/Roadmap Programs. The NIGMS plays a lead role in implementing the NIH Director's Pioneer Awards. The Ismagilov Pioneer Award is jointly funded by the Common Fund and the NIA.

General Description:

The NIH Director's Pioneer Award Program is intended to support creative, innovative investigators who bring their ideas to bear on significant research challenges. The program includes multiple awards focused on problems of aging; the Ismagilov project is an example. This is a multi-disciplinary research program that aims to develop, validate, and disseminate microfluidic technologies for quantitative studies of protein aggregation and aging. Protein aggregation is associated with aging and with a number of human diseases that affect both quality and duration of life. Many fundamental aspects of protein aggregation remain elusive, including connections between protein aggregation and toxicity, and the connection between protein aggregation and initiation and progression of diseases. Microfluidic platforms will be developed to understand these complex processes from both bottom-up and top-down

perspectives. Bottom-up, new droplet-based microfluidic systems will be developed to characterize quantitatively the connection between protein aggregation and toxicity *in vitro*.

This system will allow the reproducible real-time generation, manipulation, and characterization of aggregates for *in vitro* and *in vivo* toxicity screens. Multidimensional statistical analysis of toxicity patterns obtained in these devices may elucidate the connection between protein aggregation and toxicity, clarify the mechanism of action of existing drug candidates that target aggregation, and accelerate development of new drugs and drug cocktails. Top-down, microfluidic technologies will be developed to induce and monitor aggregation *in vivo* with high spatiotemporal resolution, and to observe the effects of aging, physiological state, neuronal activity, and presence of drug candidates on the initiation and progression of protein aggregation diseases. These two technologies will be used together to understand protein aggregation and aging, and may lead to new hypothesis and molecules for controlling these processes.

Excellence: What makes this project exceptional?

The NIH Director's Pioneer Award Program is a highly competitive program that seeks the most creative, innovative investigators through a combined process of written application and interviews. The combination of excellence, innovation, and creativity on the part of the investigator and significance on the part of the research project determine success in the competition. Dr. Ismagilov was chosen as a Pioneer Awardee because of his history of innovation and the fundamental challenges of studying mechanisms of protein aggregation associated with aging.

Significance: How is this research relevant to older persons, populations and/or an aging society?

The approaches Dr. Ismagilov has proposed offer the potential for fundamentally new ways of understanding how protein aggregation occurs during aging, how it exerts its pathological effects, and how it may be reversed. Microfluidic technologies will be developed to induce and monitor aggregation *in vivo* with high spatiotemporal resolution, and to observe the effects of aging, physiological state, neuronal activity, and presence of drug candidates on the initiation and progression of protein aggregation diseases.

Effectiveness: What is the impact and/or application of this research to older persons?

These technologies will be used to understand protein aggregation and aging, and may lead to new hypothesis and molecules for controlling these processes.

Innovativeness: Why is this research exciting or newsworthy?

Dr. Ismagilov combines elements of chemistry, physics, engineering, and biology to understand the protein aggregation and misfolding that occurs during aging and which underlies the pathology of diseases such as Alzheimer's Disease and Parkinson's Disease. The application of engineering and physical sciences to the understanding of the aging process and the ability to use the new technologies to be developed as an early indicator of therapeutic efficacy represents a pioneering approach with potential for very high payoff.