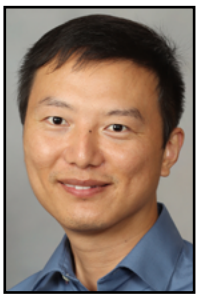
NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT



Xu Zhang, PhD

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2021 San Diego NSC Pilot Award
The dynamics and heterogeneity of cell fates during cellular senescence

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How did you become interested in aging?
At the beginning of my scientific career, I spent about ten years training in basic molecular biology, during which time I gained the knowledge and skills to pursue fundamental biological questions. I found aging an exciting field that has changed dramatically in recent decades. Due to advances in biology and medicine, the human lifespan has been greatly extended, however, this has led to increased rates of age-related chronic diseases, which dramatically influence the quality of life. I believe this is a crucial next challenge for both basic and clinical scientists to address.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?
Cellular aging, termed senescence, happens naturally when people age. The senescent cells can be triggered by various stressors like cell proliferation, oxidative stress, or DNA damage. Yet the mechanisms that govern cell fate in response to stress—ranging from repair to senescence to cell death—are not well understood. I want to study this process in detail, both the factors that determine each cell's response to stress and the resulting diverse cell populations.

What previous research or experience informed the development of this proposal?
I have a research background in cellular and molecular biology and experience in single-cell RNA-sequencing. I have spent a couple of years studying the role of senescent cells in skeletal muscle aging and characterized the secretome of senescent cells as biomarkers of age and medical risk. We and others found that senescent cells are highly heterogenous yet hard to investigate in-depth using traditional molecular biology methods. With the rapid development of next-generation sequencing and single-cell techniques, we have an excellent opportunity to dissect the cellular heterogeneity and development of senescent cells.

What's exciting about your project's potential impact?
We expect the proposed studies to reveal the mechanisms mediating senescent cell fate and illustrate the heterogeneity of senescent cells. This will be the first time we investigate the diversity of senescent cells in such depth, and this will enable us to identify potentially novel regulators that mediate the fate decision. We will also examine the susceptibility of senescent cell subtypes to senolytic drugs. Given the critical biological roles that senescent cells play during aging and the therapeutic potential of senolytic drugs, this study may provide the scientific basis for translational interventions for aging and aging-related diseases.

If your project is successful, what is the next step?
If we achieve all the goals in this pilot project, we will further pursue this topic in two directions. On the mechanistic side, we will further validate the molecular regulators identified in the project and investigate how they regulate cellular senescence utilizing in vitro cell models and high-throughput live-cell imaging

techniques. On the translational side, we will optimize senolytic treatment based on the heterogeneity of senescent cells identified in the study, for use in pre-clinical and clinical models.

How has support from and collaboration with the NSCs helped further this project and/or your research overall?
The Heterogeneity of Aging Core and the Integrative Models of Aging Core at the San Diego Nathan Shock Center have provided me with strong technical support on the project design and execution. In addition, I have benefited greatly from the San Diego Nathan Shock Center Annual Workshop and discussions with Dr. Jan Karlseder at the San Diego Nathan Shock Center. He has provided excellent suggestions on both this project and my career development. The support and collaboration from the Nathan Shock Center have greatly facilitated the project and my career.