



NATHAN SHOCK CENTERS  
OF EXCELLENCE IN THE  
BASIC BIOLOGY OF AGING

## PILOT AWARDEE SPOTLIGHT



### Lei Zhang, PhD

Research Assistant/Professor

Institute on the Biology of Aging and Metabolism

University of Minnesota

**2022 San Antonio NSC Pilot Awardee**

*Unraveling the Mechanisms of a Novel Lipid Senolytic Using Lipidomics*

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#### **How did you become interested in aging?**

I had been working on drug discovery against type 2 diabetes or cancer for many years and my original career goal was to be a scientist developing new drugs for one specific disease such as cancer. However, a deeper understanding of the biology behind these diseases gradually convinced me that aging is the biggest driver and a promising target for many age-related diseases, as supported by the Geroscience hypothesis. So, I shifted my career path to pursue aging research, particularly on developing therapeutic interventions that could be translated to treat aging and a spectrum of age-related diseases simultaneously.

#### **Briefly describe your project in non-scientific terms. What questions are you trying to answer?**

As we grow older, our bodies accumulate “zombie-like” senescent cells that no longer function as they should and produce harmful substances. These cells contribute to various health issues. By using drugs called senolytics, we can target and eliminate these problematic cells, potentially enhancing health and reducing age-related conditions. Through our established senolytic screening platform, we have identified a natural polyunsaturated fatty acid as a novel lipid senolytic. Interestingly, the lipid induces senolysis through a process called ferroptosis in contrast to other known senolytics that work by inducing apoptosis. Given the key role of fatty acids in ferroptosis and the link between lipid metabolism with senescence, we hypothesize that our novel lipid senolytic may exert its senolytic activity through modulation of lipid metabolism pathways. In this pilot grant, I proposed to leverage the expertise of lipidomics in the San Antonio Nathan Shock Center to evaluate the mechanism of our novel lipid senolytic, especially within the lipidomic metabolism.

#### **What previous research or experience informed the development of this proposal?**

We have found that this novel lipid senolytic can efficiently kill senescent cells in multiple human and mouse cell types. When tested in mouse models of aging, this lipid senolytic not only improved overall healthspan but also reduced senescent cell burden in multiple tissues. Intriguingly, our preliminary mechanistic studies suggest that this compound may exert its senolytic activity through induction of a process called ferroptosis. Ferroptosis is a unique form of cell death mediated by the accumulation of iron-dependent lipid peroxidation products. Our data showed that the senescent cell death triggered by our compound can be suppressed by ferroptosis inhibitors and iron chelators, but not by inhibitors of apoptosis or necrosis. These results support a distinct death-inducing activity of our novel lipid senolytic.



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#### **What's exciting about your project's potential impact?**

This novel mechanism of inducing senescent cell death through ferroptosis is truly exciting. Our lipidomic analysis in this project will help identify key regulators in this unique cell death pathway, potentially unveiling novel targets for drug development. Considering that most known senolytic drugs trigger apoptotic cell death, identifying senolytics based on this new mechanism will provide a complementary approach to target a broader range of senescent cells and address potential drug resistance.

#### **If your project is successful, what is the next step?**

The insights from this lipidomic analysis, combined with our ongoing RNAseq studies, will hopefully validate the ferroptosis-based mechanism of our novel lipid senolytic drug and identify key regulators or new senolytic targets. These findings will facilitate our future efforts in optimizing the drug properties of this new class of lipid molecules and discovering new senolytic drugs for therapeutic applications. If successful, this could pave the way for novel therapies that can enhance healthspan and treat a variety of age-related diseases.

#### **How has support from and collaboration with the Nathan Shock Centers helped further this project and/or your research overall?**

The collaboration with the San Antonio Nathan Shock Center has been instrumental in our research. Their expertise in lipidomics will provide invaluable insights into how our novel lipid senolytic works. This collaboration not only enhances the quality of our research but also accelerates our progress in understanding the therapeutic potential of our drug as a novel treatment for age-related diseases.