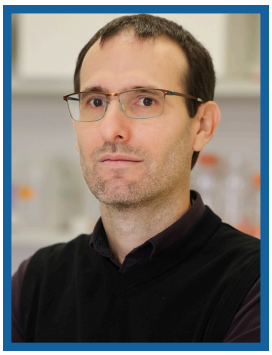
NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

# PILOT AWARDEE SPOTLIGHT



## Carlos Diaz Garcia, PhD

Assistant Professor
University of Oklahoma Health Sciences Center

**2023 Oklahoma NSC Pilot Awardee**

***Metabolic reprogramming and oxidative stress in the brain of mice with mitochondrial Ca2+ uniporter hemizygosity***

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**How did you become interested in aging?**
I became interested in aging during my postdoctoral training while developing a proposal for what later became my independent research program. Understanding the association between age-related metabolic dyshomeostasis and disrupted Ca2+ signaling in the brain, or insulin resistance, were particularly interesting topics for me considering my previous research experiences. I studied the relationship between energy metabolism and Ca2+ signals in active neurons from juvenile and young mice, and quickly became enthusiastic about applying my tools and approaches to the field of Geroscience. Inspired by the efficacy of broad dietary interventions in prolonging lifespan and healthspan, I decided to aim my efforts at identifying mechanisms that improve neuronal bioenergetics as a potential strategy to prevent age-related cognitive decline.

**Briefly describe your project in non-scientific terms. What questions are you trying to answer?**
Aged cells are at risk of mishandling calcium ions in different cellular compartments, including the mitochondrion. In this organelle, calcium can boost not only the production of energy, but also of reactive oxygen species and the antioxidant defenses that counteract them. This proposal seeks to assess the oxidative imbalance resulting from impaired mitochondrial Ca2+ uptake, and to define the adjustments that may occur in the metabolic infrastructure of the brain in response to this challenge.

**What previous research or experience informed the development of this proposal?**
My previous studies showed that a strong downregulation of the mitochondrial Ca2+ uniporter (MCU) impairs the elevation of mitochondrial Ca2+ and NAD(P)H levels in active hippocampal neurons from young mice, as well as the cognitive flexibility of middle-aged mice. Interestingly, recent studies indicate that MCU expression may decrease in several tissues during aging, and that partial MCU deficits like those observed in a mouse model of MCU haploinsufficiency can be manifested as altered synaptic plasticity. However, how brain metabolism responds and adapts to these deficits, and whether these processes are influenced by sex in adult mice, remain an enigma.

**What's exciting about your project's potential impact?**
This proposal seeks to elucidate the metabolic vulnerabilities arising from impaired mitochondrial Ca2+ uptake in the brain, and whether they are sexually dimorphic. We are particularly interested in the potential redox imbalance due to decreased mitochondrial NAD(P)H levels, which are crucial to sustaining the cellular antioxidant systems. Our proteomic studies are designed to identify potential metabolic remodeling in MCU-deficient neural tissue, with emphasis in fuel preference and oxidative stress.

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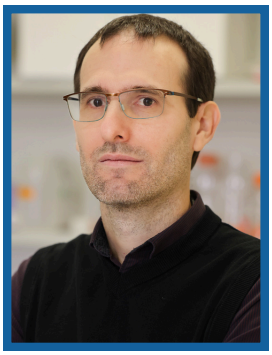

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**If your project is successful, what is the next step?**

Lessons from these studies will guide future investigations on how mitochondrial Ca2+ deregulation affects the bioenergetics and oxidative stress of aging neurons. Furthermore, we aim to test whether disrupted Ca2+ signaling in mitochondria can orchestrate a cell-type specific transcriptomic remodeling in the aging brain.

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

Our group has closely worked with the leadership and staff from the Multiplex Protein Analysis Core and the GeroScience Redox Biology Core of the Oklahoma Nathan Shock Center (OK-NSC), from optimizing the sample preparation and running the pilot tests, to the actual processing and analysis of the experimental samples. The progress already made on this project is largely because of the timeliness in their feedback and the rigorous approach of all parties involved. We are grateful for the support that the OK-NSC has provided to our research program, and we very much look forward to continuing with these fruitful collaborations.