2024 IMPACT CIRCLE

Project Title: Unlocking the Molecular Mechanism of Longevity: Will the Long-Lived Honey Bee Queen Provide the Key?

Investigator(s) and collaborations: Nicolas Martin, PhD and Simon Melov, PhD

Unmet Need/Primary Question: Despite the growing research on aging and longevity, a significant gap in our understanding persists, particularly in the context of the molecular mechanisms driving the aging process in organisms with extraordinary variation in lifespan, such as social insects. Our objective is to investigate how queen bees live so much longer than worker bees**.** To achieve this, we are looking at the transcriptomes (gene expression) of flight muscles of sister workers and queens derived from the same mother (queen).

Background: In honey bees, females are genetically identical and can develop into queens or workers depending on the food they receive during larval development. While workers generally live for a few weeks, queens can live for years. This difference in longevity between the female caste outrivals by many-fold, any lifespan extension by any known intervention. The molecular mechanisms underlying the difference in longevity between female honey bees remain largely unknown.

Novel Hypothesis: Differences in gene expression patterns between queen and worker honey bees contribute significantly to their lifespan disparity. The gene expression and pathways identified in queens, who have a longer lifespan, will demonstrate a unique expression pattern that supports enhanced longevity and differs significantly from the profiles observed in genetically identical shorter-lived sister workers. We hope to identify a unique gene expression pattern to unravel novel molecular mechanisms that may underlie the dramatic difference in longevity between female honey bees.

Project Proposal: We will leverage a unique resource, the honey bee hives maintained at the Buck Institute, which consists of 20 hives of sister queen and worker bee cohorts derived from the same queen (i.e., all bees share the same mother). The Impact Circle previously funded this project, which helped to establish the honey bee as a new animal model for investigating aging at the Buck Institute. Since then, we have optimized and performed experiments using state-of-the-art single-cell transcriptomics and single-cell epigenetics on the flight muscles of honey bees. In December 2023, we extended our survey to several age-matched comparisons between workers and queens to provide further details on the transcriptome changes with aging in

honey bees. Altogether, we have profiled the transcriptomes of over 400,000 cells of sister queens and workers across multiple ages, from adult emergence to 12-month-old queens. The funds from the impact circle will help complete and extend this unique survey to provide a holistic view of the changes in gene expression between workers and queens across their entire lifespan. More precisely, the funds will purchase reagents for a new assay to examine gene expression in the tissue context (spatial transcriptomic profiling). This spatial transcriptomic information will help us understand changes in the flight muscle transcriptomes and characterize cell populations within the tissue context, which has yet to be explored in honey bees. The fund will also help cover the sequencing cost to complete the project and maintain our infrastructure.

Description of Potential Impact: Understanding aging is essential because ''aging'' is the dominant risk factor for most diseases, and understanding the mechanisms and processes of aging will likely help increase ''healthspan'' in humans. The female honey bee has evolved this up to a 20-fold difference in longevity over 34 million years. The difference in longevity observed between the female caste is equivalent to studying humans that can live for 800 years! Unraveling the molecular mechanisms underlying the difference in longevity between female honey bees will likely help our understanding of the basic mechanisms of aging and lead to the discovery of novel molecular mechanisms associated with this extraordinary difference in longevity. To our knowledge, the data emerging from this study will build the most extensive database of honey bee transcriptomes to date and provide a resource that would otherwise not exist. The results from those experiments will also help generate hypotheses on mechanisms that may underlie the striking difference in longevity between queen and worker honey bees and lead to further funding from the NIH.

Figure 1- A honey bee queen (white dot) surrounded by genetically identical sister worker bees. Picture Nicolas Martin.

Figure 2 - Genetically identical sister queens in development. Each cell had one female larva from which the queen phenotype was induced through experimental manipulation. Picture Paul Jones.