**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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**Section 2 – *Project Information***

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| **Project Title** | Epigenetic ageing and calorie restriction in an insect model system.  |
| **Project Summary**  |
| This project will help establish an insect model for epigenetic ageing, by analysing the effects of calorie restriction on chronological and epigenetic aging in an important insect model, *Nasonia vitripennis*, extending our discovery of an epigenetic clock in *Nasonia*. An epigenetic clock is a biochemical test based on measuring the accumulation of chemical marks (DNA methylation) to DNA molecules. There is evidence epigenetic age mirrors true biological age and its associated morbidity and mortality better than chronological age. However, epigenetic clocks’ utility as measures of changes in biological age is limited as their mechanistic basis is not understood. Ageing is a complex process influenced by many environmental and genetic components. The effects of these components influence each other making them difficult to investigate, especially in complex mammalian models. Therefore, a large body of ageing research is based on simple model invertebrate organisms. Advantages include easy and cheap to keep in a laboratory, short life span, genetic and molecular tools available, and a sequenced genome. However, the current invertebrate models of ageing (Drosophila and *C. elegans*) do not possess detectable DNA methylation, reducing their utility in studying the epigenetics of ageing. *Nasonia vitripennis*, an emerging model system has a functional methylation system making it ideal to investigate the epigenetics of ageing. We therefore measured chronological ageing and changes in the epigenome using whole genome bisulfite sequencing (WGBS) in order to discover if *Nasonia vitripennis* possessed an epigenetic clock. The epigenetic age of each replicate is based on the average of each genes’ methylation state. This epigenetic age does indeed correlate with chronological age. This is similar to results in many vertebrates. However, this is the first time an epigenetic clock has been discovered in a tractable insect model. Caloric restriction, the reduction of caloric intake without causing malnutrition, is one of the most studied and effective interventions to increase lifespan in a wide range of organisms including yeast, nematodes, flies, and rodents. Calorie restriction increases lifespan in *Nasonia*, where a change from 30% sugar solution to 10% leads to a 20% increase in lifespan. We can therefore use calorie restriction in *Nasonia* to establish that a known ageing intervention affects epigenetic ageing in this insect. We hypothese that 1) Calorie restriction will decrease the rate epigenetic ageing in Nasonia and 2) that the lifespan and healthspan (measured behaviourally) increasing effects of calorie restriction will be blocked by our DNA methylation reducing treatment, thereby establishing that the epigenetic clock mediates the effects of calorie restriction on lifespan and healthspan. Techniques that will be undertaken during the projectThis project combines whole genome bisulfite sequencing of *Nasonia*, machine learning, RNAi knockdowns of methylation enzymes and high-throughput behavioural analysis, to analyse chronological and epigenetic ageing in calorie-restricted and control *Nasonia*.  |
| **References** |
| * Drew, L. Turning back time. Nature 601 S20 (2022) https://www.nature.com/articles/d41586-022-00077-8 A Nature outlook article that gets to the core of what this project will attempt. Is there a direct link between altering the epigenetic clock and changing lifespan?
* Horvath, S. DNA methylation age of human tissues and cell types. Genome Biol 14, 3156 (2013). https://doi.org/10.1186/gb-2013-14-10-r115. The original paper that discovered epigenetic clocks in humans.
* Brink, K., Thomas C. Jones, A., & Mallon, E.B. An epigenetic clock in an insect model system. bioRxiv 2023.02.14.528436; doi: <https://doi.org/10.1101/2023.02.14.528436>. Our preprint about the discovery of an insect epigenetic clock.
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