**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Epigenetic ageing in a model insect |
| **Project Summary** | |
| This project will help establish a malleable insect epigenetic clock by measuring the effect of a longevity drug on insect epigenetic ageing. This extends our discovery of DNA methylation’s role in several insect life history traits. The establishment of a malleable insect epigenetic clock will open up a new area in biogerontology.  Ageing is the combination of DNA, cellular and organ damage leading to a decline in function and increased chance of dying. Aging 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, sequenced genome. However, the current models are of little use in the study of epigenetics in ageing.  An epigenetic clock is an emergent property of the epigenome which is a better measure of true biological age than chronological age. They are used widely through-out biogerontology. The first invertebrate epigenetic clock has just been discovered in Daphnia, a crustacean. Epigenetic clocks are calculated by regressing chronological age against the methylation status of a large number of genes. Penalised regression leads to a number of these genes being selected. The weighted average of these genes’ methylation state is epigenetic age. Current invertebrate models of ageing (Drosophila and C. elegans) do not possess DNA methylation, reducing their generality.  *Nasonia vitripennis*, like other hymenoptera (ants, bees and wasps), has a functional methylation system making it an ideal system to investigate epigenetics of ageing. It possesses all the other advantages of an insect model (see above).  We need to show that the insect epigenetic clock is malleable to get the full advantage of a model system. α-Ketoglutarate is a metabolite in the Krebs cycle, but also assists in demethylation as a cofactor for TET enzymes. In mice, supplementation with α-Ketoglutarate extends both healthspan and lifespan. It seems to do this by altering DNA methylation. In humans, supplementation with α-Ketoglutarate reduced epigenetic ageing by 8 years. The PhD candidate will calculate the rate of epigenetic ageing using epigenetic clocks in α-ketoglutarate fed and control Nasonia in order to discover if the known lifespan increasing effects of alpha-ketoglutarate are associated with a reduction in epigenetic ageing in insects.  Techniques that will be undertaken during the project  This project will use life span experiments, whole genome bisulfite sequencing and advanced modelling to measure chronological and epigenetic ageing in drug altered isogenic lines of Nasonia.  BBSRC Strategic Research Priority: Integrated Understanding of Health - Ageing | |
| **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. | |