The University of Sheffield

Faculty of Medicine, Dentistry & Health

(Department/School name)

**Project title: Meals for macrophages – investigating how macrophages engulf and process dying cells in vivo**

**Supervisor(s):** Iwan Evans (primary supervisor); Phil Elks and Simon Johnston (secondary supervisors)

**Project details:**

A critical role for phagocytic cells such as macrophages is the engulfment and subsequent degradation of dying cells and debris. Failure to clear targets such as apoptotic cells can lead to damaging autoimmune conditions and immune cell dysfunction (Morioka et al., 2019; Roddie et al., 2019). This project aims to understand how macrophages engulf and process dying cells in vivo and how apoptotic cell fragmentation assists in these fundamental cellular events.

We use the fruit fly (*Drosophila melanogaster*) to understand regulation of the innate immune system, taking advantage of this organism’s lack of genetic redundancy, excellent genetic tools and imaging capabilities and the presence of blood cells called hemocytes. Hemocytes are comprised of three types of cell, one of which is a macrophage lineage also known as plasmatocytes (Ratheesh et al., 2015). These macrophages are critical for normal development and immunity of this organism (Defaye et al., 2009), with apoptotic cell clearance a key role for these innate immune cells; apoptotic cell clearance also helps sculpt and programme the subsequent behaviour of these immune cells (Weavers et al., 2016; Coates et al., 2020).

The aims of this project are to understand how the shape changes that apoptotic cells undergo contribute and regulate their subsequent engulfment, degradation and re-programming of macrophages. We will use fly genetics to manipulate apoptotic cell death processes and cell shape changes specifically within dying cells. The University of Sheffield’s state-of-the-art live imaging facilities will be used to follow and understand these fundamental processes live, in vivo. We will translate novel findings to vertebrates and demonstrate relevance to higher organisms through the use of zebrafish and human cell culture.

This project involves fly and zebrafish genetics, cell culture, molecular biology, cell biology techniques, live cell imaging, confocal microscopy and image analysis. The project will be hosted in the world-leading Bateson Centre at the University of Sheffield, which aims to use non-mammalian model organisms to understand developmental biology and human disease processes.

**References:**

1. Morioka, S., Maueröder, C. & Ravichandran, K. S. Living on the Edge: Efferocytosis at the Interface of Homeostasis and Pathology. Immunity 50, 1149–1162 (2019).

2. Roddie, H. G., Armitage, E. L., Coates, J. A., Johnston, S. A. & Evans, I. R. Simu-dependent clearance of dying cells regulates macrophage function and inflammation resolution. PLoS Biol. (2019). doi:10.1371/journal.pbio.2006741

3. Ratheesh, A., Belyaeva, V. & Siekhaus, D. E. Drosophila immune cell migration and adhesion during embryonic development and larval immune responses. Current Opinion in Cell Biology 36, 71–79 (2015).

4. Defaye, A. et al. Genetic ablation of Drosophila phagocytes reveals their contribution to both development and resistance to bacterial infection. J. Innate Immun. 1, 322–334 (2009).

5. Weavers, H., Evans, I. R., Martin, P. & Wood, W. Corpse Engulfment Generates a Molecular Memory that Primes the Macrophage Inflammatory Response. Cell 165, (2016).

6. Coates, J. A., Brittle, A., Armitage, E. L., Zeidler, M. P. & Evans, I. R. Identification of functionally-distinct macrophage subpopulations regulated by efferocytosis in Drosophila. bioRxiv 2020.04.17.047472 (2020). doi:10.1101/2020.04.17.047472

**Funding:**

This project is suitable for a self-funded student or a student with a government scholarship including from overseas.

**Entry Requirements:**

Candidates must have a first or upper second class honors degree or significant research experience.

**Enquiries:**

Interested candidates should in the first instance contact Iwan Evans (i.r.evans@sheffield.ac.uk). Please visit <http://iwanrevans.weebly.com/> for more information about the Evans lab.

**How to apply:**

Please complete a University Postgraduate Research Application form available here: [www.shef.ac.uk/postgraduate/research/apply](http://www.shef.ac.uk/postgraduate/research/apply)

Please clearly state the prospective main supervisor in the respective box and select Department of Infection, Immunity and Cardiovascular Disease as the department.

**Closing date: *(please enter closing date for applications here)***

Proposed start date: applications are accepted all year round

Salary/stipend rate:

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