

Targeted Project / AY 2026 -2027

Investigating mechanisms to modulate protein aggregation for healthy ageing

Project Reference: TRG-BAB-DD26

Supervisor: Dr Della David (della.david@babraham.ac.uk)

Department/Institute: Babraham Institute

Website: <https://www.babraham.ac.uk/our-research/signalling/della-david>

Co-supervisor: Dr Janet Kumita (Pharmacology)

Main BBSRC strategic theme: Bioscience for an integrated understanding of health

Secondary BBSRC strategic theme: Understanding the rules of life

Project outline:

Background

Perturbations in the molecular network managing protein health (proteostasis) in the organism is one of the hallmarks of ageing. Failure to maintain proteostasis ultimately leads to the accumulation of unstable proteins in solid aggregates in aged tissues. Our group has shown that age-dependent aggregates are toxic and accelerate the functional decline of tissues (Huang et al. 2019). While the aggregation of disease related proteins has been extensively studied, the regulation of protein aggregation in different tissues during normal ageing remains a relatively unexplored area of research. Recently, our lab has identified novel regulatory mechanisms that maintain protein health with age, both inside (Jung et al. 2023) and outside the cell (Gallotta et al. 2020).

Objective

This targeted project aims to perform a comprehensive characterisation of pro- and anti-aggregation factors that modulate protein aggregation in different tissues, by using a multidisciplinary approach combining in vivo studies in *C. elegans*, proteomic analysis of the aggregate interactome and in vitro reconstitution of the aggregation process.

Methodology

Proximity labelling of key endogenous aggregating proteins in *C. elegans* will identify interacting proteins. By RNA interference, we will determine if knocking down interactors accelerate aggregation potentially indicating an anti-aggregation role or inhibit aggregation, indicating a pro-aggregation role. Partnering with Janet Kumita in the Pharmacology department, we aim to reconstitute the aggregation process of *C. elegans* proteins in vitro. This will involve recombinant protein expression and purification and subsequently aggregation kinetics assays. To understand the mechanisms of the novel modulators, they will also be tested for their effects on amyloid formation by disease-related proteins such as beta-amyloid and alpha-synuclein (Bell et al. 2023; Manucat-Tan et al. 2023). By combining both approaches, we will determine which regulatory factors directly act to inhibit or promote aggregation and gain further insight into the mechanism of action. By labelling the interactome of aggregates in specific tissues, we will discover tissue-specific regulatory factors.

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Impact

Identifying the factors that influence protein aggregation will offer critical insights for developing strategies to protect mammalian tissues from age-related aggregate accumulation. By examining different tissues, we aim to uncover why some tissues are more susceptible to protein aggregation than others.

Techniques

Proximity labelling, CRISPR, RNA interference, *C. elegans* methodologies, recombinant protein production and purification, aggregation kinetics, proteomics, microscopy.