iCase Project / AY 2023 -2024

Identifying the SARM1-dependent enzyme activity that drives axon death

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Department/Institute: Clinical Neurosciences

Industrial Partner: AstraZeneca

Research area: Mechanisms of axon degeneration

Project outline:

SARM1 is an NAD degrading enzyme that promotes axon or neuron death. In axons it is closely regulated by the upstream protein NMNAT2, which sequesters the molecule that activates SARM1, NMN. Recently we identified other enzyme activities that are intrinsic to SARM1, namely NADP degradation and cyclisation, and base exchange of the nicotinamide of either co-enzyme for another base, which can generate among other molecules that most potent known calcium mobilising agent, NaADP. It is important to determine which of these mechanisms actually drives axon and neuron death, because targeting the right enzyme activity is the best way to generate a specific inhibitor able to protect axons.

We have identified natural variants of SARM1 sequence where NADase diverges from axon death activity so we will determine which activity best correlates with axon and neuron death. We will also extensively mutagenise the catalytic region aiming to generate further SARM1 variants that differ in their specific enzyme activities and determine which ones support axon and neuron death.

BBSRC DTP main strategic theme: Bioscience for an integrated understanding of health

BBSRC DTP secondary strategic theme: Understanding the rules of life