iCase Project / AY 2023 -2024

Elucidating the mechanisms AAV employs to evade host cell immune responses

Supervisor: Dr Colin Crump (cmc56@cam.ac.uk)

Department/Institute: Pathology

Industrial Partner: AstraZeneca

Project outline:

Adeno-associated virus (AAV) is a non-enveloped Dependoparvovirus composed of a capsid that encompasses a single-stranded DNA (ssDNA) genome. Recombinant AAV vectors (rAAV) are the leading gene delivery platform for the treatment of a variety of human diseases with several regulatory approvals in Europe and the United States for gene therapy applications.

AAV enters cells via specific interactions with cellular receptors. Once inside the nucleus, it utilises endogenous DNA polymerases to convert its ssDNA genome into double-stranded DNA (dsDNA). In the case of rAAV, the majority of the synthesised dsDNA genomes concatemerise and form circular episomes. These episomal DNA species can persist in post-mitotic cells extrachromosomally leading to long-term gene expression and viral vector infection.

This project aims to develop a deeper understanding of mechanisms AAV exploits to circumvent host cell responses to establish long-term infection and identify potential host factors that work to combat this. The student can expect to gain a multi-faceted understanding of AAV virology and gene therapy taking advantage of a wide range of techniques including advanced microscopy imaging, proteomics, and high-throughput CRISPR and small molecule screens.

BBSRC DTP main strategic theme: Understanding the rules of life