Project Details	
Project Code	MRCIIAR24Ca Parker
Title	Development of adenovirus type 11 (Ad11) as a platform for immuno-oncology applications.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Adenoviruses (Ad) are important for both vaccine and oncology applications, exemplified by their widespread use during the COVID pandemic. This project will characterise and develop a new platform, Ad11 for vaccine and targeted gene therapy/virotherapy applications. Building on preliminary studies, this studentship will include vector development, basic structural biology and transcriptomic studies to assess the therapeutic potential of Ad11.
Description	Background: The Viral ImmunoTherapies and Advanced therapeutics Laboratory (VITAL) develop adenoviruses (Ad) as therapeutic agents as advanced immunotherapies in the oncology arena and as platforms for vaccine applications. To make these agents safe and efficacious, we perform significant basic virological studies on these platforms to investigate their basic structure, mechanisms of cell entry and infection, and the vector: host interactions that dictate "off-target" toxicities. These findings underpin how we genetically refine these agents for clinical translation. Our lab therefore spans basic right through to translational virology, with our first refined oncolytic adenovirus due to undergo first in human clinical evaluation in 2024. Our previous work has focussed on the use of a high seroprevalence, highly active virus, Ad5, and low seroprevalence, low activity platforms based on species D Ads. In this project, the student will develop a new platform combining the benefits of low seroprevalence with high activity, developing the species B adenovirus, Ad11. This project therefore combines state of the art structural virology, capsid engineering and immunology to develop next generation intelligent adenovirus platforms for clinical applications. Key research question: To define the biology of Ad11 and refine genome and capsid to maximise the potential of Ad11 for translational applications. Objectives: The student will study the basic virology of Ad11, including structure (with input from Prof Chris Pudney, Bath, and Prof David Bhella, Scottish Macromolecular Imaging Centre), means of cell entry, and the transcriptomics of Ad11 infected cells (with Prof David Matthews, Bristol). They will build on our initial work, capturing an Ad11 genome encoding GFP in a manipulatable BAC based vector, and use this as the basis for genetic modification to develop platforms for oncology and vaccinology applications. Briefly, the main objectives will include: 1. Develop a compatible 293-Ad11E1 cell line using 293 flp in cells (available in house) for development of Ad11 based replication deficient vaccine platforms. 2. Using recombineering, delete early genes critical to Ad11 replication to produce Ad11 based viral vectors expressing reporter genes. 3. Using nanopore, compare the transcriptome of permissive cells to Ad11 infection (vector and wild type Ad11 infection) 4. Use viral vectors (Ad11.GFP) to assess to assess the immunological responses (antibody and T cell responses) to transgene in mouse model systems available in house (optimised and overseen by Dr Carly Bliss). 5. Generate and purify recombinant Ad11 fiber knob proteins, and mutants version predicted to be ablated for known

	receptor interactions (with Desmoglein-2 and CD46), and study their binding to model cell lines. 6. Incorporate peptides targeting receptors on interest on tumour cells (with a specific focus on the A20 peptide which binds αvβ6 integrin) and insert this into permissive regions of the Ad11 fiber knob protein and test the ability of the recombinant knob protein to bind the alternatively targeted receptor. 7. Engineer the promising knob protein constructs binding αvβ6 integrin into Ad11 and assess the ability to target αvβ6 integrin expressing tumour cell lines (comparing efficacy to Ad5 and Ad10 based constructs available in house). 8. Assess the ability of lead viral agents to circumvent anti-Ad immunity by screening activity in the presence of plasma obtained from Welsh Blood Service (available in house). Training: The student will benefit from training in all relevant techniques established in the host lab and extended team. The student will be encouraged to attend relevant training – both those offered by GW4 and those more niche to the research area. The student will attend conferences to present their findings to expert audiences and take part in the many public engagement opportunities offered by the host lab.
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