Project Details	
Project Code	IIAR27Ca Parker
Title	Receptor to Remedy: Rewiring adenovirus-host protein dynamics to engineer next-generation nanomedicines.
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Wet lab
Summary	How do viruses hijack our cells, and how can we turn this process to our advantage? This project will explore the fascinating molecular interactions between viruses and human cells, uncovering how viruses recognise, enter and manipulate their hosts. Using adenoviruses as a model system, you will investigate the virus–host relationships that drive infection and disease. The insights gained will be used to re-engineer viruses into precision medicines that selectively target and destroy cancer cells while leaving healthy tissues unharmed. Combining virology, cancer biology and biotechnology, this project offers the opportunity to contribute to the development of next-generation cancer therapies.
Description	Background Viruses have evolved highly specialised mechanisms to bind host proteins, enter cells, and exploit cellular machinery for replication and spread. Understanding these virus–host interactions provides opportunities to develop both antiviral medicines and advanced viral therapeutics. By controlling the molecular mechanisms that govern viral infection, viruses can be engineered with greater selectivity, safety, and efficacy for applications including gene therapy, gene editing, and cancer immunotherapy. The Viral ImmunoTherapies and Advanced Therapeutics Laboratory (VITAL) has extensive expertise in precision-engineered adenoviral therapeutics. This work led to the development of Ad5NULL-A20 (ATTR-01; Trocept), the first precision-targeted oncolytic adenovirus from Cardiff University to enter clinical testing. ATTR-01 selectively infects tumour cells expressing the cancer-associated integrin αvβ6 and delivers a locally produced anti-PD-L1 immunotherapy. Although significant progress has been made in understanding adenovirus interactions with target cells, therapeutic viruses also engage numerous circulating host proteins following intravenous administration. Antibodies, complement components, platelet factor 4 (PF4), von Willebrand factor, immunoglobulins and other blood proteins may influence biodistribution, immune recognition, toxicity, and efficacy. However, the full spectrum of these interactions—the adenoviral interactome—remains largely unknown. A comprehensive understanding of the adenoviral interactome could reveal previously unrecognised determinants of viral behaviour and identify opportunities to engineer next-generation vectors that avoid detrimental host interactions and display improved clinical performance. Central Research Question How do circulating host proteins influence adenoviral biology and therapeutic activity, and can these interactions be exploited to engineer safer and more effective viral therapeutics? Project Overview This interdisciplinary PhD project will combine virology, proteomics, structural biology, and viral engineering to define the adenoviral

	interactome and translate these discoveries into improved therapeutic vectors. The student will take ownership of assay development, data interpretation, and prioritisation of newly identified host-protein interactions, providing substantial scope to shape the direction of the research. Objective 1: Define the Adenoviral Interactome The student will develop approaches to identify host proteins that bind adenoviruses. Multiple adenoviral serotypes and engineered variants will be incubated with human serum, and virus–protein complexes analysed by liquid chromatography–mass spectrometry (LC-MS). Working with partners in the European INVECTA consortium, this objective will generate the first comparative map of host proteins associated with clinically relevant adenoviral vectors. The student will prioritise newly identified binding partners and determine whether different adenoviral serotypes possess distinct interactomes. Objective 2: Define the Molecular Basis of Host-Protein Binding Interactions identified through proteomics will be validated using quantitative binding methods, including surface plasmon resonance. Recombinant viral proteins will be used to identify the viral components responsible for host-protein recognition. The structural basis of selected interactions will then be investigated using cryo-electron microscopy and X-ray crystallography through collaborations with leading structural biology groups. These studies will reveal how circulating proteins engage adenoviral capsids and identify targets for future vector engineering. Objective 3: Determine the Biological Consequences of Host-Protein Interactions The project will assess how identified host proteins influence adenoviral function. Reporter viruses will be tested in the presence and absence of candidate proteins to determine effects on viral transduction, persistence, and cellular uptake. Additional studies will analyse immune activation using peripheral blood mononuclear cells, measuring viral uptake, cytokine production, and activation markers. Potential interactions with red blood cells will also be explored. This objective provides flexibility for the student to investigate mechanistic hypotheses arising from earlier discoveries. Objective 4: Engineer Next-Generation Adenoviral Therapeutics Using insights from earlier objectives, the student will design and generate adenoviruses with reduced affinity for detrimental host factors. Engineered viruses will be produced using established recombineering methods and assessed for altered protein binding, reduced immune activation, and retained therapeutic activity. This translational phase will provide experience spanning the therapeutic development pipeline, from fundamental discovery to rational vector design and pre-clinical evaluation. Translational Impact A major challenge in the clinical translation of viral therapeutics is the limited understanding of interactions between therapeutic viruses and circulating host proteins after systemic administration. By delivering the first comprehensive characterisation of the adenoviral interactome, defining the structural basis of key interactions, and determining their

	biological consequences, this project will generate fundamental insights into virus–host biology while identifying new opportunities for therapeutic intervention. Importantly, the study extends beyond discovery science. The findings will directly inform the engineering of next-generation adenoviral vectors with enhanced safety, improved biodistribution, and increased therapeutic efficacy. These advances are highly relevant to clinical programmes such as ATTR-01 and to broader applications in cancer virotherapy, gene therapy, and gene editing. Ultimately, the project may establish new design principles for precision viral medicines, accelerating the development of safer and more effective advanced therapeutics for patient benefit.
Can be completed part time?	Yes
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