Project Details	
Project Code	MRCIIAR26Ca Parker
Title	Developing precision guided, viral based therapies using machine learning approaches
Research Theme	PHS
Project Type	Wet lab
Summary	The Viral ImmunoTherapies and Advanced Therapeutics Laboratory engineers “smart viruses” for targeted treatment of cancer and genetic diseases. These viruses can distinguish between healthy and diseased cells, selectively infecting the latter and delivering therapeutic payloads—such as anticancer agents or gene-editing tools. This project will integrate machine learning to design more precise gene delivery vectors, optimizing their ability to target specific cells while minimizing off-target effects. These vectors will be validated in disease-relevant models to ensure safety and effectiveness. Our goal is to develop next-generation virus-based therapies that are highly specific, adaptable, and effective across a range of human diseases.
Description	Research in the Viral ImmunoTherapies and Advanced Therapeutics Laboratory (VITAL) focuses on engineering viral platforms—primarily adenoviruses—for therapeutic applications. Adenoviruses are DNA viruses that are genetically tractable and can be produced at high titres, making them well-suited for clinical translation. Our work has defined how adenoviruses infect healthy cells and initiate pathogenesis and has also revealed mechanisms behind adenovirus-induced hepatotoxicity and rare vaccine-induced thrombosis with thrombocytopenia (VITT). These findings emphasize the importance of understanding virus–host interactions to design safe and effective viral therapies. We have developed class-leading adenoviral platforms for precision targeting of tumour cells. Our first-generation vector, Ad5NULL, incorporates patented mutations in all three major capsid proteins to fully eliminate natural tropism. A second platform, Ad10, based on a species D adenovirus, exhibits naturally low infectivity. Both vectors have been engineered to selectively target cells expressing αvβ6 integrin using the high-affinity A20 peptide, derived from the foot-and-mouth disease virus VP1 protein. The lead construct, Ad5NULL-A20, has been licensed to Accession Therapeutics and has entered first in human clinical evaluation (known as Trocept). However, αvβ6 integrin is not expressed in all tumour types. Despite efforts to target other tumour-associated receptors—such as EGFR, FGFR2, folate receptor α, CD133, CD44, and nestin—most peptides derived from phage display fail to function when incorporated into the adenoviral capsid due to structural incompatibilities. This has led us to move beyond traditional peptide display methods. We now wish to apply structure-guided design strategies to engineer the fiber knob protein of the adenovirus. By incorporating receptor-binding regions from natural ligands, we have developed recombinant knob proteins that exhibit low-affinity binding to new targets. Using tools such as AlphaFold, we aim to refine these interactions and improve receptor specificity.

	Moving forward, and through this project, we propose to integrate machine learning for in silico directed evolution of viral capsid proteins. Predicted interactions will be experimentally validated through recombinant protein and viral vector assays. This approach will expand the targeting capacity of adenoviral vectors and accelerate the development of next-generation precision therapies for cancer and genetic diseases. This project will require a computational biochemist ideally with previous experience or interest in machine learning (ML), structural biology, and protein engineering. The focus, and key project aim is on modifying the adenoviral fiber knob protein to alter its tropism—specifically, to enable selective binding to alternative tumour or disease associated receptors. Objective 1: In Silico Engineering of the Fiber Knob Protein Using available crystal structures of the adenoviral fiber knob, the candidate will develop ML-based approaches to hypermutate and insert sequences into loop regions known to tolerate modification (e.g., HI, AB, DE, FG loops). The goal is to optimise receptor binding through: • FGFR2bIIIc–FGF10 interaction, leveraging its crystal structure. This is considered as a test study for a receptor: ligand interaction, however the recruited PhD student may wish to research alternatives which are promising and where structural information already exists. • Stepwise Engineering: o Introduce mutations/insertions in single loops (starting with HI). o Progress to multiple-loop modifications to increase contact points and binding affinity. • Expansion: o Apply the workflow to other tumour-or disease associated receptors: this may be alternative cancer antigens, fitting with the remit of the host lab, or may be cellular receptors (linking with Wadey, Bristol) or brain restricted receptors (linking with Pingen) This will be supported by automation pipelines combining: • AlphaFold for structure prediction, • 3D feature extraction, • Custom ML models to predict receptor binding and guide evolutionary design. Objective 2: Experimental Validation of Binding Selected in silico-designed knob variants will be: • Gene synthesised and expressed as His-tagged recombinant proteins. • Purified via Ni-affinity chromatography. • Screened for binding to receptors: o Biophysically, via surface plasmon resonance (in-house and through Accession Therapeutics), o Cell-based, using flow cytometry with receptor-expressing cell lines. Objective 3: Functional Testing in Viral Vectors Lead knob candidates will be inserted into the adenoviral genome using in-house recombineering technology (adz.cf.ac.uk). The resulting viruses will be: • Produced and purified, then

	• Tested for altered tropism in vitro via: o Receptor-specific cell lines, o Blocking experiments to confirm targeted delivery. Successful candidates can be advanced to in vivo validation in relevant murine models of disease. Within this project, there is considerable scope for the student to drive the project in a direction of main interest for themselves. Whilst the host lab focusses on oncology, we link with experts in cardiovascular disease (Wadey) and neurotropic viruses (Pingen), and the student will be expected to drive the selection of receptor target and disease model as they see fit.
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