| Project Details | |
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| Project Code | MRC21IIRCa Parker |
| Title | Structural and biological insights into advanced virotherapies for immuno-oncolytic applications |
| Research Theme | Infection, Immunity & Repair |
| Summary | The host lab studies the adenovirus (Ad), and the basic interactions that underpin infection of host cells. This project focuses on novel Ads and their development as virotherapies for delivery immunotherapies in vivo. Cross cutting methodologies spanning molecular, proteomic, structural and immunological studies will be employed define how viruses infect cells, interact with host proteins and can be refined to optimise delivery of immunotherapies in vivo. |
| Description | Immunotherapy – the stimulation of the host immune system to fight cancer is having significant benefits across a range of cancer types. Amongst the most exciting developments are advances in a range of immunostimulatory agents including immune checkpoint inhibitors (ICIs) which reactivate dormant T-cells to fight tumour cells, by interfering with negative regulators of T-cell activation and Bispecific T-cell Engagers (BiTEs) which can directly synapse tumour cells to T-cells, directing T-cell activation and tumour cell killing. Systemic administration of ICIs and BiTEs is associated with significant toxicities. We have therefore focussed on a powerful means of delivering immunotherapies locally to the tumour, by encoding them within the DNA of tumour targeted viruses ("virotherapies"). This is extremely powerful since virotherapies hold unique ability to replicate and amplify millions of times over within the tumour microenvironment, though conditional, tumour selective replication, and can be engineered to overexpress additional therapeutic modalities, such as immunotherapies. No other therapeutic matches this selectivity or power, combining self-amplifying immune-stimulatory lytic effects with the benefit of in situ production of therapeutic protein. To drive local, tumour specific expression of immunotherapies from viruses, we have taken a two-pronged attack. Our first approach represents a "bottom up" approach, manipulating a "tried and tested" oncolytic adenovirus (Ad), Ad5, which is known to be clinically safe, but lacks tumour selectivity. By completely understanding the basic biology of how Ad5 infects cells, we successfully refined it to a tumour selective virotherapy (https://tinyurl.com/trainvir), generating versions encoding immunotherapies for evaluation. Our second approach, which this proposal will focus upon, represents a "top down" approach, evaluating new, unstudied species of Ad, with unique or exciting tropisms, and study their native infectious pathways, receptors and interactions with host proteins that can limit uptake to tumours and promote dose limiting toxicities. This area of research provides vital information about basic virology and mechanisms of cellular infection of wild type viruses, and we have recently made significant inroads in understanding at the molecular level, using x-ray crystallographic studies of viral proteins (Rizkallah) coupled with whole virus Cryo electron microscopy, through local collaboration (Mark Young, School of Biosciences), GW4 facilities, and external collaboration (Prof David Bhella, Scottish Centre for Macromolecular Imaging (SCMI), University of Glasgow) to elucidate how specific species of Ad utilise previously undocumented receptors |

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| | interactions to mediate cellular infection. The proposed studentship spans both immunity (both in the context of immunotherapies and innate anti-viral immunity) and infection (defining basic mechanisms underpinning Ad infection), is highly interdisciplinary in nature, spanning GW4 partners with extended access to national facilities (e.g. the Diamond Synchrotron facility via Rizkallah, SCIM via collaborative links to Parker). With key collaborators we will evaluate the "viral interactome" and how this influences innate immune responses Ad vectors and novel serotypes using state-of-the-art proteomic and transcriptomic based approaches (Matthews), and model virus: host receptor interactions (Rizkallah). Finally, the recruited student will study how efficiently tumour cells infected with virotherapies encoding immunotherapies activate T-cells, in vitro and in vivo (Gallimore, Bliss), to develop optimised agents for effective delivery of immunotherapies in vivo. Key to this project will be studying how viruses distribute following intravenous administration, and the innate immunological responses they elicit, which we will quantify using multiplex cytokine arrays on serum (available in house). |
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