Project Details	
Project Code	MRCIIAR24Ca Bliss
Title	Developing virus-based cancer vaccines with molecular enhancers
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Cancer immunotherapy has revolutionised the field of oncology. This project uses molecular enhancement of an established vaccine platform to develop cancer vaccines with increased potency. The project will harness the power of extracellular vesicles to augment vaccine-induced T cell immunity against cancer and oncogenic viruses, using interdisciplinary in vitro, ex vivo and in vivo (zebrafish, mice) methodologies and approaches.
Description	AIM: Develop adenoviral (Ad) vectors as cancer vaccines by encoding cancer-specific antigens and enhance induction of anti-cancer T cells using novel molecular adjuvanting techniques. BACKGROUND & SIGNIFICANCE: The COVID-19 pandemic highlighted the impact of vaccination, utilising platform delivery technologies such as Ad vectors as prophylactic vaccines. Vaccine efficacy relies on induction of immune responses, including T cells that target a disease-specific protein, termed antigen. This approach can be applied to the development of therapeutic cancer vaccines, to drive the body's own immune system to eliminate cancer through induction of strong T cell immunity against cancer antigens. Cancer antigens are often identified as "self" by the body's immune system, and therefore require particularly strong immune stimulation to break this immune tolerance. The Ad vector platform is proven to induce potent T cell responses against viral proteins and is therefore a promising candidate platform to develop as cancer vaccines. To enhance the Ad platform, this research harnesses the power of the body's natural cell-to-cell communication system of protein transport comprising of extracellular vesicles (EVs), to further increase vaccine immunogenicity. PROJECT OVERVIEW: Implement "Exosome Display" by tethering cancer antigens to small EVs (namely exosomes) using Ad vectors as the delivery platform, as a mechanism by which to enhance antigen dissemination and immune recognition of vaccine antigens, and evaluate the technology as a cancer immunotherapy. AIM 1: Explore Ad vector platform compatible methodologies to tether proteins to the surface of EVs and confirm tethering using in vitro assays. This objective will evaluate different exosome targeting motifs, their intracellular trafficking and EV specificity, using both model and cancer antigens. AIM 2: Deploy the "Exosome Display" technology in zebrafish to define antigen biodistribution following in vivo tethering to exosomes. This includes live imaging of endogenously produced antigen-tethered exosomes, identifying the spatio-temporal distribution and specific cell types involved in EV release/uptake, in addition to characterising early innate immune stimulation in transgenic zebrafish. AIM 3: Evaluate the technology as pre-clinical therapeutic cancer immunotherapy in mice. This will utilise well-characterised oncogenic viral antigens/cancer antigens combined with the optimised "Exosome Display" approach as a vaccination strategy, delivered by encoding the full technology in the Ad vector platform. Downstream immune responses and vaccine efficacy to be measured in mouse immuno-oncology models of disease. TRAINING: The student will receive expert training in tissue culture,

	exosome biology, molecular virology, immunological techniques, cellular genetic manipulation, rodent/fish husbandry and procedures. This will equip the researcher with the skills to develop hypotheses, design and execute experiments, and obtain outputs to explore the research question. Extensive opportunities to communicate research across multiple platforms will include lay audiences during public engagement activities, and academic and industrial research scientists at internal and external meetings. Supported by the supervisory team, the student will steer the project in a number of ways, including but not limited to: 1) Identification and down-selection of tethering motifs for characterisation (support by Bliss/Richardson) 2) Selection and generation of fluorescent, transgenic zebrafish to study biodistribution of EVs using established zebrafish models (support by Richardson) 3) Identification of appropriate antigens for Exosome Display, supported by established mouse models of infection/disease (support by Bliss/Parker) 4) Application of appropriate Ad vectors to encode the technology, using a large panel of Ad vectors already under development (support by Parker/Bliss).
Supervisory Team	
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