Reg. No. 200604393R

Research Theme: Cancer Immunotherapy
Research Project Title: Pre-clinical development of a cancer immunotherapy targeting tumor exosomal proteins
Principal Investigator/Supervisor: Newman Sze
Co-supervisor/ Collaborator(s) (if any): NA
Project Description

a) Background

The goal of this project is to develop novel methods of disrupting the exosome-mediated cell: cell communication pathways that promote tumor growth in cancer patients. Despite many decades of intensive research, cancer remains difficult to diagnose early and challenging to treat in the advanced stages, hence the disease is still a leading cause of premature death around the world. While data from clinical studies and animal models have definitely demonstrated that the immune system can mediate potent tumor killing without the need for toxic chemotherapy, host anti-cancer responses are typically restrained by tumor release of immunosuppressive factors, including both soluble mediators and protein-laden exosomes. In our laboratory, we have developed unbiased proteomic techniques that permit detailed analysis of the cancer cell 'secretome', which led to our discovery that tumor-derived exosomes contain bioactive proteins that induce angiogenesis, promote metastasis, and suppress host immunity. The current proposal aims to build on these novel findings by developing immunotherapies targeted against key tumor exosome proteins.

b) Proposed work

Using in-depth data mining techniques, we have already identified potent immunosuppressive molecules among the protein cargo of tumor-derived exosomes. We now aim to subject these candidate target proteins to a battery of functional assays and to determine their impact on host-tumor interactions in mouse models of pancreatic and ovarian cancers (two of the most aggressive human cancers with no effective treatments at present). Using this approach, our ultimate goal is to identify opportunities to modulate the biology of tumor-derived exosomes in order to enhance host immunity and promote cancer clearance in human patients with extremely poor prognoses.

We will use CRISPR/CAS genome editing to generate stable transgenic mouse pancreatic and ovarian cancer cell lines with individual target genes either knocked-out or overexpressed. The interaction of these transgenic cell lines with the host mouse immune system will be studied *in vivo* using a well-established pancreatic and ovarian cancer models. The tumor-derived molecules that display the most potent immunosuppressive properties and pro-tumoral effects will then be targeted with monoclonal antibodies suitable for pre-clinical development as novel cancer therapies.

Supervisor contact:
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