

Philanthropy at Work



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I am grateful and honored to have the distinction of the Sandra J. Schulze Professorship.

My Inspiration

My inspiration is to revolutionize the development of novel therapeutics for cancer by creating potent and innovative strategies for cancer treatment.

Research Overview

Our group first introduced engineered measles virus strains in human clinical applications for the treatment of cancer. Early data showing promising biologic activity have led to randomized phase II trials. This project is focusing on identification of molecular characteristics of tumor cells that can affect the ability of the virus to replicate in tumors and therefore (a) impact virotherapy efficacy and (b) enhance the development of an immune response against the infected tumor. We are also developing small molecule-based approaches that can reverse tumor resistance to oncolytic virotherapy.

Long-Term Goals

The long-term goal of this project is to allow identification of patient populations that have a higher likelihood of benefiting from virotherapy approaches and match patients with the right virotherapy strategy, either single-agent treatment or rationally designed combinations. We believe that this approach can allow patients treated with virotherapy to live better and longer.

Recent Milestones

Clinical immunotherapy approaches are lacking efficacy in the treatment of glioblastoma (GBM). With support from the Sandra J. Schulze Professorship, we sought to reverse local and systemic GBM-induced immunosuppression using the *Helicobacter pylori* neutrophil-activating protein (NAP), a potent toll-like receptor 2 agonist as a novel immunostimulatory transgene expressed in an oncolytic measles virus (MV) platform, retargeted to allow viral entry through the urokinase-type plasminogen activator receptor. While single agent murine anti-PD1 treatment or repeat in situ immunization with MV-s-NAP-uPA provided modest survival benefit in MV resistant models, the combination treatment led to synergy with a cure rate of 80% in mice bearing intracranial GL261 and 72% in mice with CT-2A tumors. Combination NAP-immunovirotherapy induced massive influx of lymphoid cells in mouse brain, with CD8+ T cell predominance; therapeutic efficacy was CD8+ T cell dependent. Inhibition of the IFN response pathway using the JAK1/JAK2 inhibitor ruxolitinib significantly decreased PD-L1 expression on myeloid-derived suppressor cells in the brain and potentiated the therapeutic effect of MV-s-NAP-uPA and anti-PD1. Our findings support that measles virus strains armed with bacterial immunostimulatory antigens represent an effective strategy to overcome the

limited efficacy of immune checkpoint inhibitor-based therapies in GBM, creating a novel and promising translational strategy for this lethal brain tumor.

Next Steps

We plan to use this information to select patients who have a high likelihood of benefiting from virotherapy and immuno-virotherapy and similarly exclude patients who are unlikely to benefit from these approaches. In addition, we have initiated trials combining ruxolitinib with oncolytic viruses in order to further increase efficacy and test this promising concept in patients.

Impact of Philanthropy

Support from the Sandra J. Schulze Professorship is playing a critical role, allowing us to translate our trajectory of clinically applicable laboratory innovation in virotherapy, and give patients with cancer rapid access to novel and promising interventions against cancer. At Mayo Clinic, we have the knowledge and infrastructure to translate exciting preclinical findings to first-in-human trials faster than any other academic medical center. In addition, our in-house vector production facility and toxicology laboratory represent unique resources facilitating this process. In addition, our most recent data allow us to select patients who have a higher likelihood of benefit from virotherapy treatment, including restoring sensitivity of resistant tumors, an approach we plan to test in ongoing trials.

I'm deeply grateful for the support my research program receives through the Sandra J. Schulze Professorship.