Research proposal for Clinical Pharmacology Fellowship

Dr. Wan-Chun Chang & Dr. Bruce Carleton

Safety and Efficacy of the Treatment with an Immune Checkpoint Inhibitor-Immune-related Cutaneous Adverse Events (ircAEs)

Project Summary

Immunotherapy is a novel type of biological treatment that boosts the natural defenses of your immune system to find and attack cancer cells. Immune checkpoint proteins, in particular, including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1), play a key role in antitumor immunity, as well as maintaining immune homeostasis and preventing autoimmunity. Immune checkpoint inhibitors (ICIs), including PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors, have achieved significant therapeutic effects in a variety of tumors to significantly improve response rates, progression-free survival and overall survival. Although these drugs are altering the current state of treatment of tumors, activation of the immune system by ICIs may also cause several adverse reactions.

Immune-mediated adverse events (irAEs) are a spectrum of adverse events caused by general immunologic enhancement that can occur at any time during ICIs treatment or months after discontinuation. Whereas irAEs may affect all organ systems, immune-related cutaneous adverse events (ircAEs) are among the most common and earliest to develop, with an incidence of all-grade ircAEs in **up to 72%** with anti–CTLA-4/anti–PD-1 combination therapy. ircAEs range from grade 1 pruritus or maculopapular rash to grade 4 Stevens-Johnson syndrome (SJS), and severe (grade ≥ 3) ircAEs occur in approximately **10%** of treated patients. Some retrospective clinical studies have demonstrated that mild ircAEs, such as rash, are associated with a prolonged progression-free survival, and overall survival; however, symptoms can be severe or fatal if not recognized and treated quickly. Because the mechanisms underlying irAEs are thought to be driven by autoimmunity, some researchers proposed that genetic variation may impact risk for irAEs. However, the genetic association of ICIs-related ircAEs remains uncertain. **In this study, we aim to identify the clinical and genetic factors associated with severity of ICIs-induced ircAEs. The results can inform strategies for the prediction of severe ICIs-induced ircAEs and improve the safety and effectiveness of ICIs use.**

The role of Clinical Pharmacology Fellow

- Patient recruitment
- Develop an algorithm for assessment of ircAEs
- Collaborate with a multi-disciplinary network
- Co-lead the pharmacogenomics analysis
- Co-lead author on publication

What the Clinical Pharmacology Fellow would learn

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is a pan-Canadian active ADR surveillance network that aims to reduce adverse reactions and improve drug safety and effectiveness. The Network includes 14 pediatric and 18 adult academic health centers across Canada that has enrolled 10,453 cases of ADRs and 95,192 matched controls as of June 2020. With over 25 years of experience in drug safety and effectiveness, investigators and staff within the Network will assist the Fellow with patient recruitment and pharmacogenomic analyses. It can be expected that Clinical Pharmacology Fellow would develop extensive knowledge and practical skills underlying drug response heterogeneity, pharmacogenomics and bioinformatics that can be used within any medical subdiscipline in the future.