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CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

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PROGRAMME DE STAGES D'ÉTÉ
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Identifying drug-resistant mutations in Ph-like ALL harboring CSF1R, JAK2 and NTRK3 fusions

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Équipe de recherche

Dr Thai Hoa Tran
Maladies immunitaires et cancer

Coordonnées

thai-hoa.tran@recherche-ste-justine.qc.ca

Centre de recherche du CHU Sainte-Justine
3175 Chemin de la Côte-Ste-Catherine
Montréal, Qc, H3T 1C5

Responsable de la supervision du stagiaire

Thai Hoa Tran, Clinicien-chercheur

Description du projet

While cure rates for childhood acute lymphoblastic leukemia (ALL) approach 85% in the current era, relapse remains the most common cause of treatment failure and death, with adolescents and young adults having a worse outcome compared to their younger counterparts. Advances in cancer genomics have recently facilitated several important discoveries and deepened our understanding of the relationship between gene mutations, outcome, and potential therapeutic interventions. One recent discovery is the identification of a particular group of patients with B-lineage ALL who display a gene expression profile (GEP) similar to that of Philadelphia chromosome-positive ALL (Ph+ALL); but lacking the canonical BCR-ABL1 oncoprotein, otherwise known as Philadelphia chromosome-like ALL (Ph-like ALL). The latter comprises approximately 15% of pediatric ALL and more than 25% among young adults. Importantly, this group has a dismal prognosis compared to those without the Ph-like GEP despite modern chemotherapy regimens. It has also been shown that these patients harbor fusion genes involving tyrosine kinases that respond to different tyrosine kinase inhibitors (TKIs) such as dasatinib, ruxolitinib and larotrectinib. Clinical trials are currently testing the efficacy of incorporating the relevant TKIs into upfront therapy for Ph-like ALL. Although we are optimistic that many of these patients will be cured with the addition of TKI to chemotherapy, we hypothesize that a proportion of patients will develop resistance to TKIs and eventually relapse, similar to adults with Ph+ALL who have been treated with long-term imatinib/dasatinib. Therefore, the objective of this project is to predict

mutations that confer resistance to TKIs among Ph-like ALL patients using a validated in-vitro saturation mutagenesis screen. Anticipating these resistance mutations early in the course of therapy will serve as a novel biomarker to predict relapse and to identify novel therapeutic avenues for this population after relapse.

Mots clés

Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL); Tyrosine Kinase Inhibitors (TKIs); Drug-resistant mutations; Saturation mutagenesis screen; Translational research; Next-generation sequencing (NGS); Precision medicine; Targeted therapies.