Scientific Abstract

SU2C Canada–Canadian Cancer Society Breast Cancer Dream Team:
"Translational Development of Novel Drugs Targeting Tumor Vulnerabilities"

[This abstract was provided by the scientists when their application was accepted.]

Triple-negative/basal-like breast cancer (TNBC) and other aggressive forms of breast cancer lack targeted therapies. Initial responses to chemotherapy are followed by rapid progression and poor survival. More effective treatments are thus urgently needed. Few druggable mutations exist in TNBC, but these cancers often exhibit genomic instability, aneuploidy and defects in DNA damage repair. These properties may create vulnerabilities that can be therapeutically exploited. Our Dream Team will deliver innovative biomarker-driven therapies for TNBC via an integrated program of translational and clinical development of three novel drugs, which are based on our Leaders' scientific discoveries. These are CFI-400945 (PLK4 inhibitor), CX5461 (RNA Pol I inhibitor/GQ binder), and CFI-402257 (TTK inhibitor).

Project 1 of our proposal is comprised of the basic/translational development of each drug, while Project 2 encompasses Phase I/II clinical trials in advanced breast cancer patients.

For Aim 1 of Project 1, each drug will be subjected to in vitro drug screening, and functional genomic approaches will be applied to primary and chemo-resistant TNBC and established cell lines using CRISPR genome-editing technology. Mediators of resistance and synthetic lethality will be identified using computational approaches.

In Aim 2, a large, shared collection of molecularly characterized PDX representing the spectrum of treatment-naive, chemotherapy-resistant, and metastatic disease will be employed. Anti-tumour activity and biomarker/response relationships will be characterized by evaluation of clonal dynamics at the single cell level and in models of acquired drug resistance. Aim 3 will examine the impact of the tumor microenvironment on drug response variability. Single cell profiling will be used to evaluate tumor/stroma crosstalk in 3D organotypic cultures with matched cancer-associated fibroblasts.

For Project 2, each drug will enter biomarker-driven clinical trials carried out in collaboration with the NCIC Clinical Trials Group and a pan-Canadian network of sites. These trials will incorporate correlative programs and will be refined according to data emerging from our preclinical/translational program. The Dream Team Advocates will advise on trial-related design and consent issues, as well as support patient recruitment and knowledge translation.

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This Dream Team proposal has the potential for major near-term impact on breast cancer treatment. Clinical biomarker implementation and correlative studies will provide the proof-of-concepts necessary to support the efficacy trials that follow. Furthermore, state-of-the-art preclinical systems will identify and validate a pipeline of new targets for this devastating disease.