Scientific Abstract

SU2C Canada Metastatic Breast Cancer Dream Team:
"Targeting mRNA Translation to Effectively Treat Metastatic Breast Cancer"

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

The fact that current treatments for metastatic breast cancer (BC) are not curative provides strong motivation to bring novel leads from fundamental laboratory research to the clinic. We have pioneered research indicating a role for targeting dysregulated mRNA (messenger RNA) translation in breast cancer . Our recently published data demonstrate that aberrant mRNA translation, leading to altered gene expression, is universal in breast cancers, is involved in resistance to current therapies and is implicated in underpinning many hallmarks of malignancy. The strength of these results now makes a compelling case for studying their clinical relevance. To this end, we will focus on a novel drug candidate that attenuates abnormal mRNA translation in preclinical models: the MNK inhibitor eFT508.

This strategy is based on recent evidence that MNK kinase inhibition (which reduces eIF4E phosphorylation and therefore eIF4E activity) reduces translation of mRNAs encoding proteins (such as MYC), required for aggressive malignant behavior. Potentially paradigm-shifting studies have also recently revealed that expression of checkpoint proteins that limit the host immune response to breast cancers can be downregulated by targeting translation. Thus, the drug candidate we will study may act not only directly on malignant cells but also indirectly, by mitigating immune suppression.

We will carry out a phase Ib trial of eFT508 using the dose recently defined by a phase I trial (which was not carried out in breast cancer patients). Eligible breast cancer patients will have metastatic breast cancer (any subtype) not responsive to standard-of care therapies. In addition to conventional endpoints to document any clinical benefit and/or toxicities, we will carry out detailed pharmacodynamic studies. These will include assessment of baseline and on-treatment "translatomes" of biopsied neoplastic tissue.

To achieve our goals, we have assembled a unique multidisciplinary network of internationally recognized fundamental researchers and clinical trialists with access to state-of-the-art infrastructure to execute the clinical trial and explore pharmacodynamics endpoints.