Scientific Abstract

SU2C PI3K Dream Team:
"Targeting the PI3K Pathway in Women's Cancers"

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

The successful implementation of personalized medicine through targeted therapies continues to be fraught with unexpected pitfalls, decreasing the speed at which patients benefit. The failure to understand the basic biology of therapeutic targets frequently results in the failure of targeted therapeutics to fulfill their promise. The key roadblock remains an inability to design and implement biomarker driven trials that match patients to targeted therapies most likely to inhibit their own tumor.

Genetic aberrations in the PI3K pathway are the most frequent events in women's cancers. We have assembled a Dream Team of basic, translational and clinical scientists who were the pioneers in the discovery of the PI3K pathway and in conducting the studies validating the role of this pathway in human cancers.

This Dream Team is involved in more than 30 clinical trials with PI3K inhibitors at their institutions and have access to the same clinical candidates for pre-clinical studies. The members of this Dream Team have already shared their unpublished data on the mutational status of components of the PI3K pathway from 1261 breast tumors, 332 ovarian tumors, and 246 endometrial tumors and are assembling an inter-institutional database that correlates the mutational status of this pathway with pathology, PET imaging responses and patient outcome in multiple ongoing clinical trials. This unprecedented level of collaboration was encouraged by formation of this Dream Team.

The key deliverable of this grant is a set of biomarkers that will predict the patients likely to benefit from PI3K pathway inhibitors in single agent and rational combination therapies that will determine the utility of PI3K pathway inhibitors in women's cancers. Our working hypothesis is that imaging modalities or other biomarkers will predict response to PI3K pathway inhibitors across breast, ovarian and endometrial cancers and that by comparing results in ongoing trials in these three areas at five major cancer centers, we will accelerate biomarker discovery. On the basis of our current understanding of this signaling network and our experience with the clinical compounds, we have designed proof of concept trials in breast and endometrial cancers that will go forward in the first year.

These trials will be paralleled by co-clinical trials in mice engineered to develop breast and endometrial cancers by introducing genetic aberrations that mimic the most frequent events in women's cancers.

The same imaging modalities and other biomarkers will be evaluated in the human and mouse trials. Importantly, drug responses will be compared in multiple mouse models with different genetic events

in order to correlate changes in FDG-PET responses, changes in pathway activation and changes in tumor volume with mutational status.

In concurrent research we will explore the effect of drug combinations on more than 100 breast, endometrial and ovarian cancer cell lines that we have characterized for mutational status of genes in the PI3K pathway as well as other genes frequently mutated in women's cancers. The most promising drug combinations will be evaluated in genetically engineered mouse models to evaluate efficacy and toxicity *in vivo*. On the basis of these results, we will leverage our ongoing support from the NCI and our collaborations with pharmaceutical companies to fund clinical trials in breast, endometrial and ovarian cancer using the most highly validated drug combinations linked to appropriate biomarkers.