Scientific Abstract

SU2C-American Cancer Society Lung Cancer Dream Team:

"Targeting KRAS Mutant Lung Cancers"

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

KRAS mutant non-small cell lung cancer (NSCLC) is poorly sensitive to systemic therapies. Fortunately, new drugs targeting mutant KRAS and downstream pathways, as well as promising strategies to modulate the immune system, are emerging and present remarkable opportunities. There is now a critical need for laboratory and clinical investigations to determine how to optimize and integrate these approaches into effective and unified treatment regimens. To realize these goals, the Lung Cancer Dream Team consists of experts in KRAS signaling, cancer immunotherapy, and development of rational therapies for lung cancer. The overarching hypothesis is that the interactions between oncoprotein-activated pathways and the immune microenvironment regulate tumor growth, and this information can be applied to develop rational combination therapies. There are three Aims.

Aim 1 will define the most effective therapies to target KRAS and critical downstream pathways. The Team will develop a new class of direct inhibitors of mutant KRAS and advance novel compounds and combinations that more profoundly suppress critical downstream pathways such as MEK, ERK and LIF. Results from the laboratory are expected to flow quickly into the clinic with clinical trials that will directly test these concepts already designed.

Aim 2 will identify the determinants of response to immunotherapies, particularly in KRAS mutant NSCLC. In-depth studies of an extensive number of tumor specimens collected by Dream Team members from PD-1 blockade trials are planned. The Team will evaluate the impact of mutant KRAS, the overall mutational landscape, and immunophenotype of the tumor microenvironment on mediating response or resistance to PD-1 blockade. Studies of resistant cancers will inform novel immunotherapy combinations. In addition, clinical trials using a novel vaccine targeting both the tumor-associated antigen mesothelin and mutant KRAS epitopes will be performed, both as monotherapy and in combination with PD-1 blockade.

Aim 3 culminates in synthesizing these fields. The Team will investigate the immunologic effects of KRAS targeting agents to elucidate their impact on the immune system, tumor microenvironment, and expression of immunomodulatory proteins. Particular attention will be paid to dose and schedule, as the effects on the immune system are complex. To develop rational combination clinical trials, targeted therapies that maximally kill the cancer cells in manners that enhance or do not inhibit anti-tumor immune response will be combined with immunomodulatory agents to achieve profound and durable responses. The studies involve state-of-the-art animal models of KRAS mutant NSCLC, *in vitro* studies, and analysis of specimens from a total of 10 innovative clinical trials conducted by this highly collaborative Dream Team.