



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.]

Development of therapeutic strategies to improve the survival of patients with KRAS-mutant lung cancer is a critical unmet need in oncology. The molecular heterogeneity of KRAS-mutant lung cancers, characterized by a variety of distinct *KRAS* point mutations, specific co-mutations, and poorly defined immune microenvironments, has presented a challenge to developing effective therapies. Two major treatment modalities, targeted therapies and immunotherapies, have profoundly altered the treatment paradigm for patients with lung cancer over the past decade.

The team's objective is to determine how targeted therapies and immunotherapies can be optimized and integrated in order to improve the outcomes of patients with KRAS-mutant lung cancer. They hypothesize 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.

Our research plan has three specific aims:

1) Targeting KRAS and downstream pathways. This aim will be accomplished by direct targeting of KRAS G12C using a new class of drugs specifically designed to inhibit mutant KRAS, inhibiting novel KRAS-dependent pathways (KRAS-calmodulin interaction and LIF expression), and maximizing ERK inhibition with inhibitors of the MEK/ERK pathway. These studies will be performed in the laboratory and in clinical trials.

2) Targeting the immune system for treatment of KRAS-mutant lung cancers. This aim will be accomplished by identifying determinants of response to PD-1 pathway blockade, identifying mechanisms of resistance to PD-1 inhibitors, and performing first-in-human trials of a *Listeria*-based vaccine targeting mutant KRAS and mesothelin epitopes. These studies will be performed on patient specimens and by clinical trials.

3) Integration of targeted therapies with immunotherapies for KRAS-mutant lung cancers. This aim will be accomplished by determining the impact of different schedules and doses of targeted therapies on the immune system and microenvironment, determining the immunologic consequences of directly targeting mutant KRAS and downstream pathways, and optimizing targeted therapy/immunotherapy combinations to achieve maximal apoptosis. These studies will be performed on patient specimens, in pre-clinical mouse models, and by clinical trials.

