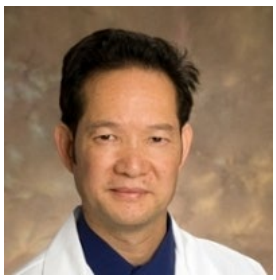
Project 3: Overcoming treatment resistance: Targeting Bax signaling



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I. EXECUTIVE SUMMARY

Our group has identified stem-like T cells that undergo proliferation after immune checkpoint inhibition. We will characterize these cells in lung tumors, draining lymph nodes and peripheral blood, and study their correlation with treatment outcome. In addition, we will study a novel combination regimen of mTOR inhibition and PD1 inhibition in lung cancer patients.

II. PROJECT AIMS

Aim 1: To determine whether and how KRAS and p53 mutations regulate Bax activity and treatment resistance in human lung cancer cells. Studies will determine whether pBax is a novel prognostic biomarker or therapeutic target in patients with NSCLC;

Aim 2: To develop novel small molecule Bax activator (CYD-2-11) by targeting the structural pocket around the Bax phosphorylation site for lung cancer therapy. Studies will test the antitumor efficacy of CYD-2-11 alone or in combination with ionizing radiation, chemotherapy, and/or mTOR inhibitor in patient-derived xenograft (PDX), radioresistant, and genetically engineered mutant KRAS-driven lung cancer animal models. By targeting Bax, we expect to develop a new class of anti-cancer agents and combination strategies for lung cancer treatment.

III. PROJECT DESCRIPTION

Bax functions as an essential gateway to apoptotic cell death. Targeting Bax provides a common pathway to treat NSCLC patients with KRAS or p53 mutations and to overcome resistance to radiotherapy and chemotherapy. We previously discovered that the serine (S)184 phosphorylation site of Bax is a critical switch to functionally control Bax's proapoptotic activity. AKT and PKCζ have been identified as physiological Bax kinases that can directly phosphorylate Bax at the S184 site, leading to inactivation of its proapoptotic function. It is known that KRAS and p53 mutations can activate the PI3K/AKT survival pathway leading to increased resistance to radiotherapy or chemotherapy in various cancers, including lung cancer. Increased levels of phospho-Bax (pBax) were observed in tumor tissues in patients with non-small cell lung cancer (NSCLC). We hypothesize that pBax may serve as a new predictive and

prognostic biomarker in NSCLC. Expression of KRAS G12D mutant or p53 R273H mutant or treatment with radiation, cisplatin or RAD001 resulted in activation of AKT and/or PKCζ leading to increased phosphorylation of Bax, which may contribute to radio-, chemo- or rapalog resistance. Development of small molecules that activate Bax may provide a novel approach for the treatment of mutant KRAS or mutant p53 lung cancer or for overcoming radio-, chemo- or rapalog resistance. We have identified a novel Bax activator, CYD-2-11, that selectively binds the S184 pocket of Bax protein but does not bind other Bcl2 family members. CYD-2-11 not only reverses radioresistance but also overcomes rapalog resistance in vitro. CYD-2-11 potently represses lung cancer xenografts by activating Bax and inducing apoptosis in tumor tissues.