Professor Xunhai Xu

Title: Evaluating blood-based biomarkers in patients treated with an AKT inhibitor (MK-2206) in a pre-surgical model

Abstract

AKT is a serine-threonine kinase that is frequently activated in breast cancer. MK-2206 is the first allosteric inhibitor of AKT entering clinical development after demonstrating strong single agent in vitro AKT inhibition and anti-proliferative activity. We have recently developed an NCI-approved pre-surgical study to predict the biologic effects of MK-2206 in patients with operable invasive breast cancer. In the window between a diagnostic biopsy and definitive surgery, treatment is given for two weeks, thus providing a unique opportunity to quickly assess the in vivo biological effects of MK-2206. Specific blood-based surrogate markers to accurately predict the molecular effect of MK-2206 in humans have not been characterized. Given that they have been used previously as pharmacodynamic markers of cell signaling effects, peripheral blood mononuclear cells (PBMCs) provide an attractive substrate to evaluate the efficacy of MK-2206. Further, the evaluation of circulating tumor cells (CTCs) by immunofluorescence to assess cell signaling has emerged as a promising modality that may reflect the real-time biological response to drugs. With recent data reporting a 30-fold increased yield in detecting CTCs using currently available technology, it is feasible that this methodology will allow for accurate molecular analysis of CTCs, including the assessment of protein activation through measurement of critical phosphorylation signals. I hypothesize that the molecular impact of MK-2206 can be demonstrated by measuring phosphorylated AKT (p-AKT) levels in PBMCs and CTCs. I will test my hypothesis via the following aims: 1) Measure and correlate the changes in p-AKT in PBMCs and tumor before and after treatment with MK-2206. 2) Explore if CTCs can be enumerated sufficiently in this pre-surgical study and if there is concordant modulation of p-AKT by MK-2206 in CTCs and tumor tissues. Blood-based biomarkers have the potential to allow for minimally invasive monitoring of the biological effects of therapeutic interventions. If correlations of p-AKT levels in PBMCs/CTCs and tumor are verified, our study will provide a rationale to validate PBMCs as a pharmacodynamic marker and CTCs as a tumor tissue surrogate in future metastatic breast cancer studies, where frequent tumor biopsies are inherently difficult.