Scientific Abstract

SU2C-LUNGevity Foundation-American Lung Association Lung Cancer Interception Dream Team:

"Intercept Lung Cancer Through Immune, Imaging, and Molecular Evaluation (InTIME)"

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

Lung cancer is the leading cause of cancer death in the United States and worldwide, in large part due to our inability to intercept the disease prior to it progressing to an advanced stage. There is a lack of effective lung cancer interception approaches due to our incomplete understanding of the earliest molecular events associated with lung carcinogenesis, as well as the challenge in developing personalized tools for early detection and prevention.

Our Lung Cancer Interception Dream Team aims to address these barriers and establish a critical foundation for lung cancer interception, with the potential for direct and immediate clinical impact. Our proposal is based on the hypothesis that premalignant lesions bear specific genomic and transcriptomic aberrations, and a subset of these lesions escape immune surveillance and progress to invasive cancer. Our team is applying novel molecular, imaging, and immunological approaches to biospecimens that are being collected prospectively and retrospectively from unique patient cohorts, to understand the biology of lung cancer precursor lesions and their response or resistance to therapies, and to develop biomarkers that predict these outcomes.

Our first aim is to build a genomic, transcriptomic and immune atlas of premalignant lung adenocarcinoma and squamous cell carcinoma lesions that will serve to 1) identify novel targets for disease interception including personalized immune-related approaches; 2) develop genomic biomarkers for early detection in noninvasive samples and 3) develop companion diagnostics to identify subjects at high risk for progression to invasive carcinoma who would benefit from interception trials as well as surrogate markers of efficacy in those trials. During the current funding period, although slowed by the pandemic, we have continued to collect and profile pre-invasive lung squamous preinvasive lesions, where we have begun to identify signatures of preinvasive lesions in the nasal airway. Additionally, we have analyzed the single-cell RNA sequencing data of immune infiltration in solid and subsolid lesions that show the increase of immune cells infiltrating subsolid lesions which may be indicative of an immunosuppressive microenvironment rather than effective immune surveillance. Additionally, multiplex immunofluorescence of 62 lesions suggest that there is a spatial relationship between the epithelial and immune cells in the developing tumor.

Our third aim leverages industry-sponsored interception trials to discover companion biomarkers that are predictive of response to immunotherapy, enabling precision lung cancer interception. The Swanton team has been collaborating closely with AstraZeneca to design a global phase III study using the Archer diagnostics MRD assay generated in part through this SU2C collaboration to stratify high risk patients to combination chemotherapy and immunotherapy or chemotherapy alone. This study opened internationally this year to recruitment and Professor Swanton is global PI on the study. The insights gained from successful completion of these aims and the data that will be made available to the research community will serve as a foundational resource for other investigators in the field and will result in a significant and sustained impact on the interception of early stage lung cancers.