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Deciphering the Role of EGFR Splice Variants and Tumor-Immune Microenvironment in Renal Cell Carcinoma

Principal Investigator: MANLEY, BRANDON
Institution Receiving Award: H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, AT SOUTH FLORIDA, UNIVERSITY OF
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TECHNICAL ABSTRACT

Background: Currently, the most common classes of drugs used to treat those with advanced or metastatic renal cell carcinoma (RCC) are targeted therapies (TTs) and immunotherapies (ITs). However, there is a lack of reliable biomarkers to guide treatment sequencing and the large numbers of agents available have minimal comparative treatment data available.

Objective: The goal of our research project is to identify immune and molecular biomarkers that predict responses to the two most commonly used classes of systemic therapies in metastatic RCC: TT and IT. A cohort of 131 previously unreported RCC tumors that have undergone whole exome, RNA, and germline sequencing will be analyzed. This cohort includes samples from locally advanced and metastatic patients, along with both clear cell RCC and non-clear cell tumors, which are accompanied by prospectively collected clinical data that include systemic treatment data.

Aim 1. Identify and characterize the tumor immune microenvironment of 131 RCCs in regard to the presence and geographic location of candidate tissue biomarkers. A highly multiplexed immunofluorescence (IF) 7-channel platform will be used to characterize candidate markers: CD3, Tbet, FOXP3, CD8, CD206, CD163, CD68, and PD-L1.

Sub-Aim 1a. Evaluate clinical associations with tumor immune microenvironment biomarkers. Statistical analyses will be employed to delineate immune and genomic alteration markers for associations with patients' clinical and radiographic responses to a single systemic agent (TT or IT) for 9 months or greater.

Aim 2. Evaluate prevalence and determine clinical significance of recently identified novel epidermal growth factor receptor (EGFR) splice variant in 131 RCC tumors. We hypothesize that this variant will be associated with a lack of clinical response (treatment duration <9 months).

Study Design:

Aim 1. Patient tumor samples from the 131 RCC tumors have already undergone WES DNA and RNA sequencing according to standard extraction and sequencing protocols. Corresponding tissue blocks from these tumors and 10 non-cancer kidney controls will undergo standard preparation for IF and be stained with the described candidate antibody panel using the Opal multiplex system. Slides will be scanned on the Vectra platform. Directed regions of interest will be immunophenotyped via the software environment HALO.

Sub-Aim 1a. Corresponding radiological response (RESICT 1.1), duration, and type of systemic treatment, along with survival outcomes will be analyzed to generate response classifiers.

Aim 2. Alternate splice forms of EGFR will be quantitated, comparing the number expected versus novel exon-exon junctions across the RNAseq data from each sample and analyzed for associations with clinical outcomes.

Personnel: Dr. Brandon Manley (PI): Building upon his years of research in translational studies of kidney cancer, Dr. Manley's primary career goal is to become an independently funded surgeon-scientist specializing in RCC research and treatment. His institution supports this by ensuring that 50% of his time is protected for research. He has a busy RCC-focused clinical practice at Moffitt Cancer Center and holds faculty positions at the University of South Florida and Moffitt Research Institute. Dr. Manley has a rich team of multidisciplinary experts who mentor and collaborate with him, allowing him to expand his knowledge of translational research. Drs. Magliocco, Mulé, and Spiess possess unique expertise in the fields of immunology, digital pathology, and clinical RCC, have proven track records of mentoring junior faculty, and are dedicated to Dr. Manley's success.

Impact: With the identification of novel immune and molecular biomarkers, we can improve the effectiveness and sequencing of systemic treatment for those with aggressive RCC. By using biomarkers to identify the treatments most likely to benefit individual patients, RCC patient life expectancy will be improved.

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