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Characterizing and Targeting the Microenvironmental Barriers to Immunotherapeutic Response in Renal Cell Carcinoma

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TECHNICAL ABSTRACT

Background: ICB therapies engage and activate the host immune system to help eradicate tumor cells. In RCC patients, the response rate to anti-PD-1 and combined anti-PD-1/CTLA4 is approximately 25%-40%, and, in some cases, responses can be dramatic and durable. However, only a minority of patients with RCC respond, and these patients can develop acquired resistance. The long-term objective of this proposal is to elucidate mechanisms of sensitivity and resistance to ICB alone and in combination with anti-VEGF agents in RCC and to develop rational combinatorial approaches that overcome resistance to ICB. The central hypothesis of this proposal is that the tumor microenvironment (specifically macrophage and various T effector cells) together with intrinsic tumor genomics underlie primary and acquired resistance to ICB and that these mechanisms can be targeted to enhance clinical benefit of ICB in RCC patients.

Building on strong preliminary data by our group and others, we propose a systematic approach employing large-scale analysis of tumor samples from ICB-treated patients, dissection of molecular determinants of resistance and response, and utilization of animal models to evaluate the efficacy of combinations to target mechanisms of resistance. We can then use this knowledge to design data-driven, biology-based therapeutic combinations.

Objective: The objective of this proposal is to understand what drives clinical benefit to ICB in RCC and to use this information to evaluate effective combination regimens. We plan to accomplish our objective by pursuing the following three aims.

Aim 1: Define the microenvironmental and molecular determinants of response to immune checkpoint blockade therapy in RCC. Based on our extensive preliminary data, our working hypothesis is that ICB response in RCC can be predicted by specific genomic and microenvironmental features, in particular, by high T effector cell and low macrophage infiltration. To test this idea, we will assess how specific TME features (T cell, myeloid, and TAM infiltrate; angiogenic programs) along with genomic features of the RCC (mutation/neoantigen burden, indel burden, etc.) predict for clinical benefit from treatment with ICB. Our innovation will be in (1) utilizing RCC-specific immune signatures and (2) assessing the biomarkers in combination to achieve accurate prediction of response across the range of ccRCC patient characteristics. This aim will leverage the pretreatment tumor and blood samples from patients on several ICB clinical trials along with a large cohort of patients treated with ICB at our institution.

Aim 2: Characterize and target macrophages and other microenvironmental features that promote primary resistance to ICB and combination therapies using mouse models. We propose to build on our preliminary data and the results of Aim 1 by performing in-depth characterization of the features that underlie primary sensitivity/resistance to anti-PD-1 with or without an anti-VEGF agent. For this, we will use genetically engineered and novel humanized mouse models. We hypothesize that specific microenvironmental targets account for the observation that co-treatment with PD-1 blockade and VEGF inhibition induces a more favorable anti-tumor immunity. We will test this by dissecting the effects of single-agent and combination treatment with comprehensive genomic and immunologic profiling. We further hypothesize, based on robust preliminary data, that resistance to single-agent and combined therapy can be overcome by targeting TAMs (or any other predictors of resistance from Aim 1). We will work to overcome resistance by targeting TAMs alone and in combination (i.e., CSF1R inhibitor + PD-1 blockade).

Aim 3: Elucidate the microenvironmental and genetic mechanisms of acquired resistance to ICB and combination immunotherapy. In this aim, we hypothesize that specific molecular determinants (e.g., immune editing) and microenvironmental determinants (e.g., TAM infiltration, T effector phenotype) underlie acquired resistance to ICB therapy. We will systematically identify these determinants. In collaboration with, we will examine gene expression of pre- and on-treatment biopsies from patients receiving nivolumab (BMS009 trial) as well as paired tumor samples collected pretreatment and at the time of recurrence in patients who develop acquired resistance to ICB. Using murine models, we will precisely characterize these processes.

Impact: If successful, our proposal will establish a more precise foundation for ICB treatment of RCC patients and open the door for novel therapeutic approaches to overcome immunotherapy resistance in RCC.

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