

## **Dr. David Aggen**

Immunotherapy directed towards programmed-death protein-1 (PD-1) has improved overall survival (OS) in a variety of solid malignancies with a trend towards improved objective response rates (ORR) in high mutation burden diseases. Metastatic renal cell carcinoma (RCC) is an immunotherapy responsive cancer with a relatively high-mutation burden. In a phase III, randomized study evaluating nivolumab in metastatic RCC, the ORR was 20-30%. More recently, combination PD1/CTLA-4 blockade with nivolumab and ipilimumab showed an ORR approaching 42% in metastatic RCC (Checkmate 214). In nonresponders the immunosuppressive factors and tumor characteristics that prevent anti-tumor activity are unclear. One hypothesis is that myeloid-derived suppressor cells (MDSCs) contribute to immunosuppression and prevent immune mediated anti-tumor activity.

To date there are few combination therapies in solid malignancies targeting other immunosuppressive cell types including MDSCs in part due to the complex biology and heterogeneity of intratumoral myeloid cells. Interleukin-1 beta (IL-1 beta) is one cytokine known to direct MDSCs towards immunosuppressive phenotypes (M2 phenotype macrophages and granulocytic-MDSCs). Blockade of IL-1 beta in preclinical models decreases circulating and intratumoral MDSCs which may inhibit PD-1 based immunotherapy responses.

The overall goal of this proposal is to evaluate the efficacy of a PD-1 targeted therapy in combination with a novel therapy directed against IL-1 beta. We hypothesize that combination therapy with anti-IL-1 beta and anti-PD-1 will promote intratumoral inflammation, change the phenotype of MDSCs within the tumor microenvironment, and improve antitumor immune responses.

The key objectives of this proposal are to evaluate the efficacy of combination anti-PD-1/anti-IL1 beta in the well described Renca mouse model of RCC and quantify intratumoral regulatory T cells and myeloid cells in the presence and absence of IL-1 beta blockade. Initial studies will use a commercially available antibody specific to interleukin-1 beta. We anticipate that targeting MDSC by IL-1 beta depletion will result in increased potency and additional efficacy studies to evaluate the optimal timing of MDSC depletion. To understand the effects of IL-1 beta blockade on the myeloid stem cell compartment, gene expression profiling of sorted MDSC populations using Nanostring will assess changes in pro-inflammatory gene expression (IFN-gamma and IL-1 beta centric genes) in Renca murine tumors. To understand the primary cells driving intratumoral IL-1 beta expression, we will compare IL-1 beta expression between banked untreated and nivolumab treated human RCC specimens. The proposed studies will facilitate successful translation of this combination immunotherapy into a clinical trial setting in RCC.