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Profilin 1 as a Novel Target in Patients with Renal Cancer

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TECHNICAL ABSTRACT

Background: Malignant tumors of the kidney account in 2018 for 63,000 new cases and 15,000 deaths in the U.S. The most common subtype, clear cell renal cell carcinoma (ccRCC), is found in >75% of cases. Approximately 20%-30% of patients have metastasis at the time of diagnosis. About one-third of patients following initial treatment will develop either local recurrence and/or distant metastasis. The 5-year survival of patients with advanced ccRCC is still only 10%. A distinguishing hallmark of ccRCC is the highly vascular tumor microenvironment (TME). Therefore, a more in-depth molecular understanding of the pathogenesis and progression of the exuberant vascularization of ccRCC, coupled with understanding of the immunologic sequelae, will lead to new integrated therapies. There is clear evidence of upregulation of actin-binding protein profilin1 (Pfn1) in RCC (a molecule of focus of this study), primarily in vascular cells, and higher Pfn1 expression associated with clinicopathological features of advanced tumors and poor patient outcome. The major goals of the proposed study are to study how Pfn1 contributes to RCC progression, demonstrate Pfn1's association to therapeutic response and survival of RCC patients, and investigate whether Pfn1 inhibition is an effective strategy to modulate TME and retard RCC progression.

Areas of Emphasis: Our studies will address several major emphasis areas of FY18 KCRP program including targeted therapies, microenvironment and immunology, and prognosis of RCC.

Hypothesis: We hypothesize that Pfn1 promotes ccRCC progression through stimulating tumor angiogenesis and limiting immune responses that can be targeted by small molecule approaches.

Specific Aims: To test our hypothesis, we propose two specific aims. In Aim 1, we will address whether (a) Pfn1 dysregulation in vascular cells is a key contributing factor for alteration in TME and ccRCC progression, and (b) Pfn1 expression has any correlation with responsiveness of RCC patients to immunotherapy. In Aim 2, we will determine whether small molecule antagonists of Pfn1 function suppress tumor angiogenesis and enhance T-cell infiltration in TME, stimulate T-cell function, and, in turn, inhibit ccRCC progression.

Study Design: We will undertake a comprehensive experimental approach utilizing novel knockout mouse model studies, single cell-transcriptome analyses, in-vitro tumor-endothelial cell (EC) co-culture studies, IHC/ELISA-based analyses of archived clinical samples (primary tumors and serum) from a recently concluded immunotherapy clinical trial for metastatic RCC patients, and immunological studies to complete the specific aims.

Innovation: This study is conceptually innovative as it would establish Pfn1 as a novel regulator of ccRCC progression and a biomarker for predicting therapeutic response of ccRCC patients. Technical innovation lies in the generation of a novel mouse model, utilization of a novel 3D microfluidic assay to study perivascular invasion of tumor cells, and identification of new small molecules capable of modulating TME and ccRCC progression.

Impact: A successful completion of Aim 1 will for the first time establish a direct causal relationship between Pfn1 and ccRCC progression, and further provide mechanistic insights into how Pfn1 expression regulates the TME mediating crosstalk between tumor cells, immune (CD8+ T-cells) and vascular EC. These studies may also reveal Pfn1 as a novel prognostic marker for predicting therapeutic response of RCC patients. A successful proof-of-concept demonstration of the efficacy of Pfn1-targeting chemical tools in retarding angiogenesis-dependent disease progression in Aim 2 will establish the conceptual basis for laying a path forward to advance a new direction of Pfn1-targeted therapy for patients with ccRCC.

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