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Therapeutic Targeting of Cystine Addiction of Renal Cell Carcinoma

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Institution Receiving Award: DUKE UNIVERSITY
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TECHNICAL ABSTRACT

Background: Despite recent advances using anti-angiogenic or immune checkpoint inhibition to treat advanced renal cell carcinoma (RCC), median overall survival for patients with advanced or metastatic RCC is still unsatisfactory. Therefore, there is an urgent and unmet need to develop new therapeutics to improve the outcome. One of the earliest and most common genetic events in conventional, or clear cell, (cc)RCC is loss or somatic mutation of the Von Hippel-Lindau (VHL) tumor suppressor gene. VHL inactivation leads to abnormal activation of HIFs and other alterations that underlie ccRCC oncogenesis. However, there is currently no strategy that directly targets inactivated VHL. Recently, we found that VHL loss renders ccRCC cells profoundly "addicted" to exogenous cystine (dimeric form of cysteine) as an unexpected "metabolic Achilles' heels." Cystine deprivation triggers rapid ferroptosis, which may be immunogenic and enhance the immune response. We have performed mechanistic studies and RNAi screens to identify genetic determinants of cystine-deprived death to better predict the responses to cystine-deprivation therapeutics.

Areas of Emphasis: Metabolisms, Novel Interventions, and Immunotherapies

Objective/Hypothesis: Our central hypothesis is that the cystine-addiction of VHL-null RCC opens a significant therapeutic window that can be therapeutically targeted with engineered cyst(e)inase, alone or combined with immune-therapies. Our objectives will be to identify genetic determinants and predictive markers of cystine addiction (Aim 1), and determine the ability of cyst(e)inase to treat patient-derived xenografts (PDXs) of human RCCs, either alone or combined with checkpoint blockade (Aim 2).

Specific Aims:

Aim 1: Identify the genetic determinants and underlying mechanisms of cystine addiction in RCC

Aim 2: Determine the therapeutic potential of cystine deprivation using patient-derived xenografts (PDXs)

Study Design: Through our preliminary mechanistic investigations and completed RNAi screens, we have identified several genes and pathways essential for cystine-deprived cell death. In Aim 1, we will first identify the metabolic and signaling events affected by VHL loss, which may contribute to the cystine-deprived cell death. These experiments will identify the relevant pathways in VHL-null and VHL-restored cells to elucidate the mechanisms and genetic determinants of cystine-deprived cell death. In addition, these experiments will allow better prediction of response to cystine deprivation and recombinant cyst(e)inase. In Aim 2, we will continue developing a panel of ccRCC patient-derived xenografts (PDXs) murine model that include tumors acquired from patients who have evidence of disease progression following treatment with VEGFR TKIs (sunitinib, pazopanib) as well as immune checkpoint inhibition (nivolumab). We will then determine the in vivo efficacy of cyst(e)inase to reduce tumor growth in ccRCC PDXs. In addition, we will develop immune-competent PDX models by reconstituting human CD34+ cells to determine the potential of cyst(e)inase to enhance the anti-RCC efficacy of immunotherapies via checkpoint blockade. In addition, we will identify the relevant tumors' endpoints of cyst(e)inase treatment and validate the predictive values of genetic determinants.

Innovation: The novel finding of profound cystine addiction of VHL-null ccRCC indicates (1) a wide therapeutic window that can allow therapeutic targeting; (2) A novel engineered cyst(e)inase under clinical development for in vivo cystine depletion; (3) Clinically relevant models of ccRCC PDXs with reconstituted human immune systems to test the potential of cyst(e)inase to enhance immunotherapies; (4) Cystine deprivation triggers ferroptosis with potential to enhance tumor immune response and bypass the anti-apoptotic mechanisms employed by many treatment-resistant RCC tumors.

Impact: Our project is relevant to the area of metabolism, targeted therapeutics, and immunotherapies. Based on our observed cysteine addiction associated with VHL loss in RCC and exquisite sensitivity to cyst(e)inase, we will identify genetic profiles that predict which tumors are cystine-addicted and their likely response to cyst(e)inase. We will determine the therapeutic potential of cyst(e)inase in the treatment of resistant and metastatic RCC, either alone or with immunotherapies. Since cyst(e)inase is being developed by Aeglea BioTherapeutics (AEB3103) for near-future IND and clinical trials, the successful completion of the proposed projects may provide crucial rationale and information as a basis for clinical trials in the near future to target this metabolic "Achilles' heel" of RCC as a novel and crucial means of overcoming resistance. The novel therapeutic strategy proposed here could potentially offer a completely new way to treat this disease in a way that dramatically improves the health of affected military service personnel or their family members.

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