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Molecular Characterization and Therapeutic Targeting of TFE3 Fusion Kidney Cancers

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Institution Receiving Award: SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH
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TECHNICAL ABSTRACT

Background: TFE3 fusion kidney cancers, also called Xp11.2 translocation renal cell carcinomas (RCC), define a histologically variable group of approximately 1% to 2% of sporadic kidney cancers in adults. In contrast, TFE3 fusion kidney cancers are common in adolescents and children, representing 20% to 50% of all pediatric RCC cases. TFE3 fusion kidney cancers are characterized by various translocations and inversions involving chromosome Xp11.2 where TFE3 resides, which results in gene fusions including PRCC-TFE3, ASPSCR1-TFE3, SFPQ-TFE3, NONO-TFE3, and CLTC-TFE3. Clinical behavior of TFE3 fusion kidney cancers is aggressive with metastasis common at presentation. However, there is no standard pharmacological treatment for these patients due to the lack of knowledge on how these fusion genes cause kidney cancers. Here, we propose to investigate the molecular mechanisms by which TFE3 fusions contribute to kidney tumorigenesis with the hope of identifying new therapeutic targets for this dreadful disease. We have established patient-derived xenograft models and cell lines of TFE3 fusion kidney cancers and demonstrated an essential role of TFE3 fusions for cancer maintenance. Importantly, we have identified several potential therapeutic targets for TFE3 fusion kidney cancers, including the BCL-2 family, lysosomal biogenesis, mitochondrial biogenesis, and transcription elongation (CDK9). We plan to test the therapeutic effects of targeting these pathways in our preclinical models. To investigate whether TFE3 fusions are sufficient to promote kidney cancer initiation and to elucidate the underlying molecular mechanisms, we plan to model ASPSCR1-TFE3 fusion kidney cancer in mice using the reported Rosa26-LSL-AT3 transgenic mice. Our proposed studies will likely provide novel insights into the pathogenesis and treatment of TFE3 fusion kidney cancers.

Areas of Emphasis: Rare Kidney Cancers; Chromatin and Gene Regulation; Targeted Therapies; Immunotherapies; Metabolism

Hypothesis/Objective: Our preliminary results demonstrated an essential role of TFE3 fusion proteins for the maintenance of TFE3 fusion kidney cancers. Because TFE3 is a transcription factor, we hypothesize that TFE3 fusion proteins regulate specific transcriptional programs to promote kidney cancer maintenance and interrogation of these programs will help identify actionable therapeutic targets. Given that TFE3 fusion kidney cancers lack any of the common RCC-associated genetic alterations, we hypothesize that TFE3 fusions are sufficient to drive kidney tumorigenesis. Accordingly, we plan to model ASPSCR1-TFE3 fusion kidney cancer in mice using the Rosa26-LSL-AT3 transgenic mice. This mouse model will not only help elucidate the molecular mechanisms by which TFE3 fusions promote kidney cancer initiation but also offer a preclinical model for the assessment of immunotherapy in combination with targeted therapy for TFE3 fusion kidney cancers.

Specific Aims:

Aim 1. Investigate the molecular mechanisms by which TFE3 fusion proteins promote tumor maintenance.

Aim 2. Target the TFE3 fusion-regulated transcriptional programs for the treatment of TFE3 fusion kidney cancers.

Aim 3. Model TFE3 fusion kidney cancer in mice and determine whether immune checkpoint inhibitors alone or in combination with the BCL-2 family inhibitors can provide therapeutic benefits for TFE3 fusion kidney cancers.

Innovation: We have established invaluable preclinical models of TFE3 fusion kidney cancers for the mechanistic and therapeutic studies. An innovative approach involving RNA-seq, ChIP-seq, and ATAC-seq will be employed to establish the transcriptional networks of TFE3 fusions. Our goal is to identify actionable transcriptional programs/pathways that are required for TFE3 fusions to promote cancer maintenance. To this end, we have identified several actionable pathways and formulated novel mechanism-based therapeutic strategies for TFE3 fusion kidney cancers. Furthermore, a novel mouse model of TFE3 fusion kidney cancer will be generated to help elucidate the molecular mechanisms by which TFE3 fusion promotes kidney cancer initiation and facilitate the discovery and assessment of novel therapeutics including immunotherapy.

Impact: This proposal is mechanism-driven yet highly translational in nature, which will have broad impact across basic and translational kidney cancer research. Our elucidation of the molecular mechanisms by which TFE3 fusion proteins promote tumor initiation and maintenance will advance the knowledge regarding the biological function of TFE3 fusion proteins as well as the molecular pathogenesis of TFE3 fusion kidney cancer. Our preclinical studies testing various combination therapeutic strategies through molecular targeting of the TFE3 fusion-regulated transcriptional programs can be translated into clinical trials and benefit patients immediately. Our creation of a novel mouse TFE3 fusion kidney cancer model will offer a preclinical model for future therapeutic interventions including immunotherapy, thus accelerating clinical translation.

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