Translational Studies to Improve the Therapy of Rhabdoid Tumors, June 2018

Alex Kentsis, MD, PhD

Rhabdoid tumors are cancers that affect infants and young children. Current treatment of rhabdoid tumors with chemotherapy is toxic, and for tumors that cannot be removed surgically, is largely ineffective. Our research into genetic and epigenetic mechanisms that drive rhabdoid tumor cell survival has revealed a new set of therapeutic targets. Ongoing work will enable us to determine the precise molecular mechanisms responsible for signaling and anti-tumor immune responses that sustain rhabdoid tumor cell growth. We will then use this knowledge to rationally devise new therapies to effect cure.

Project 1: Engineered immune therapy of rhabdoid tumors. Recent uses of checkpoint inhibitors in SWI/SNF-deficient tumors have shown extraordinary responses in individual patients, suggesting that immunotherapy of rhabdoid is possible. However, the antigens responsible for these effects are unknown, and their immune mechanisms are undefined. In this project, we will leverage the cellular and molecular analysis of patient rhabdoid tumors to i) identify neomorphic antigens expressed by rhabdoid tumor cells, ii) define cellular immune mechanisms of their recognition, and iii) investigate immunomodulatory therapies to treat rhabdoid tumors in genetically-engineered mouse models.

Project 2: Blockade of oncogenic mutators in rhabdoid tumors. Recently, our studies have led to the discovery of the DNA transposase PGBD5 in rhabdoid tumors. Remarkably, PGBD5 induces DNA rearrangements in rhabdoid tumor cells, leading to the acquisition of genetic mutations that cause rhabdoid tumors, and contributing to therapy resistance. This process depends on ongoing DNA damage repair signaling, but its specific molecular dependences are poorly understood. In this project, we will investigate the mechanisms of aberrant DNA

damage repair signaling in rhabdoid tumor cells, therapy identifying selective DNA damage repair signaling inhibitors with anti-tumor activitity in preclinical patient-derived xenograft mouse rhabdoid tumor models.

Project 3: Precision therapy of rhabdoid tumors. Our preclinical studies aim to define new and improved therapies for patients with rhabdoid tumors to improve patient outcomes and cures. We have identified both new immune therapies (combination of EZH2 and PD1 inhibitors) and new targeted therapies (combination of ATR and PARP inhibitors) are currently in clinical trials in patients and are promising candidates for investigation for the treatment of rhabdoid tumors. Our goal is to develop these concepts into two new clinical trials for patients with rhabdoid tumors.

We expect that the successful completion of these projects will lead to immediate translation of these approaches to improved treatment of patients with rhabdoid tumors, and should accelerate progress towards our long-term goal of rational curative therapy of rhabdoid tumors.