THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Inhibitors to Epigenetic Modifiers Improve the Efficacy of Immunotherapy Against High-Risk Neuroblastoma

Neuroblastoma (NBL) is the most common solid malignant tumor in children that occurs outside of the central nervous system. About 700-800 cases are diagnosed each year in the US, most often in infants and children less than 5 years of age. Sadly, many will have a diagnosis of "high-risk" cancer (HR-NBL) with less than a 50% survival rate. Nearly 60% of children respond well initially to an aggressive standard of care treatment plan (autologous stem cell transplant, surgery, chemotherapy, radiation, and immunotherapy) but will relapse, with most being refractory to further treatment. This occurs as a result of epigenetic modifiers: cellular molecules that alter the expression of genes and promote tumorigenesis. Characterized as "cold tumors", epigenetic modifiers in HR-NBL shut off the expression of important cell surface receptors called Major Histocompatibility Complex I (MHCI), which permits HR-NBL tumor cells to be recognized by T cells and also provide long term immune memory. MHCI expression is required for recognition by T cells, in order for cytotoxic killing of tumors and downstream T cell subset generation (effector and memory T cells). The immune response in HR-NBL supports macrophages and Natural Killer cells to reduce tumor volume, but with minimal involvement of T cells. The lack of T cell involvement likely contributes to the many patients with disease recurrence. In order to improve outcomes for HR-NBL patients, I propose to design new therapies to produce a more potent immune attack geared towards eliminating NBL and preventing it from ever recurring. My preliminary results show that this approach works in vitro. Translating these promising results into a murine syngeneic model of NBL *in vivo*, I will examine the effectiveness of inhibitors to epigenetic modifiers (EMi) to upregulate the expression of immunomodulatory genes like MHCI. Drugs that inhibit the effects of epigenetic modifiers restore the expression of MHCI on this cancer are expected to slow NBL growth and more importantly, enable immune cells to recognize and destroy the cancer. I will optimize the delivery route, dosing, and timing of EMi relative to the induction of MHCI expression on human NBL cells. I will also examine the antitumor recognition and function of a new class of engineered T cells, peptide-centric chimeric-antigen-receptor T cells (PC-CAR), which recognize MHCI on the tumor cell surface and are able to target proteins inside the cancer cells that are critical for tumor growth. Since the EMi and PC-CAR used in this study are clinically available drugs, identification of a successful regimen in NBL-bearing mice could move swiftly into human clinical testing. If I am successful, a new therapy to produce a more potent immune attack against NBL will prolong survival for all children diagnosed with this cancer and enhance their quality of life.