THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

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Reprogramming Tumor-Infiltrating Macrophages for the Treatment of Brain Cancer

Cancer causes more childhood mortality in the United States than any other disease. Brain cancer is the second most frequent and the most lethal type of pediatric cancer, taking the lives of more than 400 of the approximately 2,300 American children diagnosed in a given year. Because brain tumors are frequently surgically inaccessible, standard therapies rely on intensive radiation and chemotherapy. However, such interventions are toxic for developing brains, and hundreds of young brain cancer survivors suffer long-term side effects that often include severe, irreversible physical and intellectual disabilities. Worse, a single surviving cancer cell can lead to recurrent disease that is highly likely to resist further therapy. Even therapeutic regimens with daunting toxicity are ineffective for some types of brain tumors; for example, four out of five children will not survive a high-grade glioma. To circumvent such refractory tumors Anthony proposes a new paradigm, one that targets essential tumor-supporting immune cells known as macrophages rather than the tumor itself. Although macrophages normally function to defend against infections, it is clear that within the tumor microenvironment they support tumor growth and not tumor regression. Despite this fact, tumor-infiltrating macrophages have not been targeted successfully as an anti-cancer therapy. To address this unmet need, he proposes the precise modulation of macrophage activity in pediatric brain cancer by reprogramming their tumor-supportive properties toward more beneficial functions. He will do so using a unique humanized mouse model (MISTRG) that he developed to reveal how macrophages support tumors. Leveraging an available repository of pediatric brain cancers in the Fred Hutch Brain Tumor Resource Laboratory, Anthony will reconstruct examples of patient tumors and their corresponding immune systems in MISTRG mice. He proposes to reprogram macrophage function by down-regulating transcription factors that drive macrophage differentiation toward tumor-supporting state(s) and up-regulating factors responsible for neutral or anti-tumor states. If Anthony is successful in reprogramming tumor-infiltrating macrophages to trigger tumor regression, the clinical translation of such an approach would synergize with current cancer therapies to enable tumor eradication with less toxic doses of chemotherapy and radiotherapy. Reprogramming macrophages might also prevent tumor recurrence from those cancer cells that escape existing treatments. The availability of such a combination therapy would make a truly lifesaving difference for young brain cancer patients in the United States.