SEBASTIANSTRONG
FOUNDATION

2019 SEBASTIANSTRONG DISCOVERY SCIENCE AWARD

Re-purposing HIV Nucleoside Reverse Transcriptase Inhibitors for High-Risk Neuroblastoma Therapy

PI: Daniel Weiser, MD; Co-I: Brad Rybinski, BS; Albert Einstein College of Medicine

Neuroblastoma is a pediatric cancer of the developing nervous system that arises from early nerve cells called neuroblasts. Neuroblastoma accounts for one of six childhood cancer deaths, and half of children with aggressive, high-risk neuroblastoma succumb to disease within five years, suggesting that some children have a form of “ultra-high risk” (UHR) neuroblastoma that still lacks effective therapies. Therefore, new strategies to identify and treat children with UHR neuroblastoma are urgently needed. Recent research has demonstrated an association between UHR neuroblastoma and high levels of telomerase. Telomerase is an enzyme that allows cancer cells to keep proliferating without dying, suggesting that inhibiting telomerase would be an effective therapy for UHR neuroblastoma. No effective telomerase inhibitor has yet been developed. However, the crucial component of the telomerase enzyme that allows it to function is a reverse transcriptase, and reverse transcriptase inhibitors (RTIs) have been used as HIV medications for decades. Therefore, we hypothesize that the RTI tenofovir will inhibit telomerase in neuroblastoma cells and enhance the efficacy of conventional chemotherapy. Our project is designed to “re-purpose” tenofovir as novel telomerase inhibitor for patients with neuroblastoma. We have preliminary data that demonstrates activity of tenofovir against neuroblastoma cells directly and, to a greater extent, when combined with chemotherapy. We will expand this testing in the laboratory, as well as in mouse models of neuroblastoma. We anticipate that neuroblastoma with high levels of telomerase and associated poor prognosis will respond most remarkably to tenofovir, resulting in improved survival. Re-purposing of an FDA approved drug like tenofovir as a telomerase inhibitor for properly selected patients with neuroblastoma will allow swift translation of novel combination therapy concepts into the clinic. Therefore, successful completion of our research plan has the potential to lead to a rapid breakthrough for patients with UHR neuroblastoma by shifting it from a fatal diagnosis to one that is both identifiable and treatable.