THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Mesenchymal Stem Cells Engineered to Express miRNA for Targeted Treatment of Neuroblastoma

Neuroblastoma is a malignant tumor of the central nervous system. It is the most common solid tumor affecting children under the age of five, accounting for 8% of childhood cancers. It develops from gene mutations that affect the development of immature nerve cells, where widespread tumors cause a host of painful and life-threatening symptoms. Children with high-risk disease undergo aggressive multimodal treatments that include chemotherapy, radiation, surgery, immunotherapy, and stem-cell transplant. Despite these rigorous treatments, children with high-risk disease have a survival rate of less than 45%. Children who do survive often develop long term debilitating side effects from their treatment that can be severely life-altering and even lethal. Novel methods to improve outcomes for children with high-risk neuroblastoma and decrease toxicity from therapy are desperately needed. Efforts to reduce devastating systemic treatment toxicity has focused on targeted therapy to deliver treatment directly to tumors, thereby improving effectiveness and reducing side effects. In this regard, mesenchymal stem cells (MSC) are multipotent differentiating cells found in abundance within bone marrow and known for their innate affinity for tumors. In cancers other than neuroblastoma, MSC have been successfully engineered to express small, single-stranded RNA (miR) that without directly coding for proteins, can control gene regulation and cell signaling to inhibit tumor growth and enhance chemosensitivity However, the combination of miR and MSC has not been previously tested in neuroblastoma. In preliminary research using a mouse model, I confirmed that MSC can target neuroblastoma tumors; and in separate experiments, have observed a reduction in tumor cell viability and promotion of differentiation effects of selected miR on neuroblastoma cells. Thus, I propose to engineer MSC to express specific miR (miR-124-3p and miR-34a-5p have significant potential as therapeutics for neuroblastoma due to their role in apoptosis and differentiation) and serve as a cellular drug-delivery vehicle for targeted treatment of neuroblastoma, with evaluation in vitro and in a mouse models. The ability of miR to act in combination with standard chemotherapy agents will also be examined, as synergistic effects of miR with chemotherapy would further strengthen the potential benefits of miR-MSC therapy as a strategy to reduce systemic toxicity. If I am successful, delivering treatment directly to the tumor to reduce systemic toxicity will be an important step forward in improving clinical outcome and prolonging survival in children affected by neuroblastoma.