THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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Targeted Gene Therapy for Treatment of Hemorrhagic Hydrocephalus

Hydrocephalus refers to the build-up of cerebral spinal (CSF)_within the brain, leading to excessively high brain pressure, brain injury, and even death in children. This is a relatively common condition among pediatric patients, occurring in 1 of 1,000 live births, similar to the incidence of Down syndrome or cystic fibrosis. Post-Hemorrhagic Hydrocephalus (PHH), also called "hydrocephalus of prematurity" is caused by disruption of CSF flow following hemorrhagic stroke of deep brain structures and intraventricular hemorrhage, producing bleeding into the center of the brain. It is the most common cause of pediatric hydrocephalus in North America. Extremely premature babies are at greatest risk for PHH, where latent brain injuries may contribute to the build-up of fluid within the brain and the risk of cerebral palsy. Despite the high prevalence of PHH, the pathophysiology is still poorly understood. The disease course is extremely variable, with many patients requiring multiple brain surgeries over the course of their lifetime, with worsened cognition prior to each surgery. Without effective non-surgical options, the burden of this chronic neurologic disorder is high from the standpoint of the affected children's reduced quality of life, with a pressing need for new and durable treatments. The principal brain structure that regulates CSF is the choroid plexus (ChP), representing a promising target for the treatment of PHH. Located in the middle of the brain, within each brain ventricle (cavities in the brain that produce and circulate CSF), the ChP forms the dominant physiological interface between the bloodstream. With a large surface area, it provides unique opportunities for central nervous system surveillance and regulation of CSF volume and composition. Multiple lines of evidence support ChP involvement in the pathogenesis of PHH, where potassium levels in the brain fluid is insufficient and must be normalized to mimic the physiology of hydrocephalus survivors. This can be achieved by improving the bidirectional membrane transporter NKCC1, responsible for balancing sodium, potassium and chloride ions. In this context, I hypothesize that it should be possible to manipulate regulation of CSF by targeting the ChP using gene therapy with adeno-associated virus as a vector. My preliminary research demonstrates that a variation of this therapy works in a mouse model. Using piglets as a large animal model for pediatric hydrocephalus, I will test preclinical efficacy as compared to rodents *in vivo*, as well as by using patient-derived specimens in tissue culture *ex vivo*, which are foundational steps toward justification of a human clinical trial. If I am successful, I will have developed a non-surgical cure for the most common type of hydrocephalus in America and developed a platform of gene therapy in the brain that can be replicated for treating other neurologic conditions, thus improving the quality of life of children with hydrocephalus and other brain fluid disorders.