THE HARTWELL FOUNDATION

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Host-Targeted Theranostic Dendrimer to Monitor and Treat Meningitis

Meningitis is a life-threatening infection that produces widespread inflammation to the tissues covering the brain and spinal cord (meninges). It affects over 2500 children in the USA each year, who are particularly vulnerable because their immune system is not yet fully developed. The cause may be bacterial, viral, the result of toxins, trauma to the brain (e.g., a car accident), or can be triggered by disorders that affect the brain (i.e., Rett syndrome or autism). Symptoms include fever, neck stiffness, change in personality, vomiting, seizures, weakness of limbs, paralysis, or coma. Nearly two-thirds of childhood meningitis survivors develop devastating, permanent brain injuries that retard normal development and result in long-lasting neurologic deficits including paralysis, seizures, and learning disabilities. The damaging inflammation in meningitis occurs in response to activated glial cells, the resident macrophages of the central nervous system that under normal conditions perform immune surveillance and host defense, which are crucial for normal brain development. Current therapy relies heavily on intensive care and antibiotics or antivirals to target the pathogen. Host-targeted steroids decrease inflammation by reducing the activity of the body's entire immune system, but their use is limited by undesirable side effects. Although vaccines have reduced the incidence of the infection, mortality in recent decades has remained virtually unchanged (7-16%). To address the need for a more effective therapy for meningitis, I propose a host-targeted steroid treatment designed to selectively target the activated glial cells responsible for neuroinflammation. Drug delivery will be enabled by ~4 nM nanoparticles created from synthetic dendrimers (tree-like molecules with repetitive branches from a common core) to which host-targeted steroids and PET imaging agents (radiotracers) will be attached. Such therapeutic and diagnostic (theranostic) dendrimers are known to localize in activated glial cells at a rate proportional to the extent of brain inflammation; the PET-labeled dendrimers serve as a biomarker of inflammation. Dendrimers loaded with different percentages of radiotracer will be injected into a rabbit meningitis model to determine the amount of radiolabeled dendrimer needed to detect a PET signal and optimize the signal-to-noise ratio. The optimized radiolabeled dendrimer will then be loaded with different doses of steroid and glial cell uptake in the rabbit model evaluated to determine the most effective dose-response. Treatment efficacy will be quantified using post-mortem analysis of glial cell activation, oxidative stress, and pro-inflammatory cytokine concentration, as well as compared with noninvasive PET imaging to quantify brain inflammation. If I am successful, an effective drug to monitor and suppress neuroinflammation in meningitis will decrease neurologic damage, reduce treatment duration, improve patient recovery, and decrease mortality in childhood meningitis patients without regard to cause.