THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Neutrophil-Mediated Drug Delivery to Minimize Antibiotic Exposure in Treatment of Ear Infection

Otitis Media (OM) is an acute infection of the middle ear that commonly begins after an upper respiratory infection. It has a prevalence of over 95% among U.S. children, with one in three children experiencing 6 or more episodes by age 7. The disease can lead to significant developmental defects of speech and language among young patients due to its associated conductive and sensorineural hearing loss. To manage OM, doctors typically prescribe oral antibiotics for 5-10 days. Unfortunately, the systemic therapy may produce undesirable side effects like diarrhea and vomiting, and lead to dangerous antibiotic resistance, making infections more difficult, if not impossible, to treat. Moreover, oral antibiotics have recently been correlated with health issues later in life, like asthma and obesity. As such, there is an unmet need for an efficient therapy to treat OM that does not rely on systemic delivery of antibiotics. While local delivery of antibiotics can provide much higher middle-ear drug concentrations than systemic administration, the difficulty is that the eardrum, while only 10 cell layers thick, presents an impermeable barrier that reduces the effectiveness of the therapy. In the most severe cases, mechanical disruption of the eardrum has been used to overcome the problem, but it is painful and requires recurring surgeries, which can lead to hearing loss. An improved approach delivers antibiotics to the middle ear using an antibiotic with a synergistic combination of chemical permeation enhancers in a hydrogel. The enhancers help the antibiotics to cross the eardrum and the hydrogel holds them in place for the duration of therapy. Unfortunately, antibiotic delivery efficiency is poor and in recurrent OM the buildup of biofilm shelters bacteria from the antibiotic, substantially reducing therapeutic effectiveness. Based on my discovery that neutrophils (the most abundant of all white blood cells) can readily traverse the infected eardrum, I propose to develop a revolutionary localized therapy for the middle ear that leverages the innate immune response triggered by middle ear infections. In preliminary experiments I have observed that an antibiotic can be delivered by lipid membranous vesicles that “hitchhike” on neutrophils attracted to the infection site. When the antibiotic-vesicles are applied to the outer ear canal in a chinchilla animal model of OM, the formulation appears not only to be biocompatible, but it also cures the infection rapidly and sterilizes the middle ear, with little to no off-target effects. To achieve efficient delivery of antibiotics across an intact eardrum I will optimize the design and delivery of the antibiotic-vesicles. If I am successful, this technology will reduce antibiotic usage for childhood middle ear infections by 100,000-fold! Effectively, at the time of diagnosis, the entire course of an antibiotic regimen could be applied to the child’s eardrum to cure the infection, while avoiding systemic antibiotic exposure and its side effects.