THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

Joshua C. "Josh" Mell, Ph.D.

Assistant Professor
Department of Microbiology & Immunology

Drexel University

Detecting and Disrupting Biofilms in Recurrent Ear Infections

Bacterial middle ear infection (otitis media, OM) is the most common childhood respiratory infection and the most common reason children receive antibiotics. Typically, bacteria from the mouth, eyes, and nasal passages get trapped behind the eardrum; producing inflammation, swelling of tissue and fluid build-up that may block the eustachian tube that connects to the throat to regulate pressure in the ear. The infections not only cause acute pain and distress for children, but if chronic, increase the risk of permanent hearing loss and delayed language development. If the infections become severe or chronic, a tube may be surgically inserted into the eardrum to alleviate symptoms. With more than one million children diagnosed annually with chronic or recurrent disease and greater than 60% who experience multiple episodes before age 3, it is essential to proactively diagnose and treat the infection with a robust course of therapy to avoid building antibiotic resistance. The bacterium nontypeable *Haemophilus influenzae* (NTHi), is the leading cause of OM and is very heterogeneous, with a genome that is continually mutating to evade host immunity and overcome antibiotic therapy. Unfortunately, other microbes like viruses or fungi can initiate opportunistic infections that may complicate the timing and choice of treatment. Worse, standard antibiotic therapy may fail to clear the infection, in part, due to formation of a bacterial biofilm, where instead of unattached single cells the bacteria adhere to tissue surfaces and each other to form a dense 3D matrix, making it difficult to eradicate them. Bacterial cells at the biofilm surface rapidly consume oxygen and nutrients, forcing those within biofilms to adopt a quiescent state. Since most antibiotics target bacterial processes active only during growth, cells within biofilms may survive through many classes of antibiotic therapy. This "multidrug tolerance is known to be mediated primarily through a widely conserved bacterial signaling pathway via RelA enzyme, which triggers inhibition of growth-promoting pathways and activation of starvation and other stress pathways. Utilizing a unique clinical repository of medical data and specimens from >1,200 children over the first 3 years of life in >5,000 clinical visits, Josh discovered a potential role for alkaline pH-induced biofilm formation in recurrent otitis media. In this regard, I now propose to evaluate if NTHi strains are prone to persist through recurrent OM episodes and predict likelihood of recurring acute infection; if gene expression signatures of NTHi strains likely to form biofilms share common signatures that may be useful as biomarkers; and whether designer drugs inhibiting RelA will improve the effectiveness of antibiotics against NTHi biofilm bacteria. If Josh is successful, biomarkers that identify middle ear infections with elevated risk of persisting or recurring will improve the diagnosis and prognosis of OM, while targeted therapy against biofilm formation will improve the frontline effectiveness of antibiotics, reducing the burden of persistent and recurrent OM infections in young children.