Bordetella pertussis, the causative agent of whooping cough, was nearly eradicated upon the introduction of a vaccine in the 1920s. This whole cell vaccine was highly immunogenic and thus was replaced by an acellular vaccine in the mid-1990s. In recent decades, infection rates have risen dramatically in industrialized countries reaching a 60-year US high in 2012. Worldwide, B. pertussis remains a major cause of infant death, claiming approximately 195,000 lives annually. This appears partially due to shortcomings of the current vaccine, which confers short-term immunity and seems to prevent the symptoms of disease but not its spread.

The acellular vaccine varies between manufacturers, but consistently contains two important virulence factors, pertussis toxin (PTX) and filamentous hemagglutinin (FHA) and can additionally contain up to three adhesion factors. While this vaccine can mount neutralizing responses, the immunity it induces wanes over time. Current estimates have established the vaccine provides a decade of immunity and therapeutic strategies advise to boost often. This is especially detrimental to new parents who have become susceptible to the disease and have young infants who are too young to receive the vaccine.

A possible route to enhance the vaccine is inclusion of additional antigens. The adenylate cyclase toxin (ACT), an essential colonization factor, is the leading candidate for inclusion in future vaccines. Yet, there is surprisingly little data detailing the mechanisms by which ACT confers protection or its appropriateness for manufacturing and formulation as a part of a multi-component vaccine. We have performed protein engineering on ACT to identify domains that are well-expressed, protective, and elicit neutralizing antibodies. We are currently using the original ACT and our engineered, more stable, and immunodominant variant in mouse immunization experiments to dissect ACT’s role in infection.

Currently, our collaborators are working of including our recombinant RTX in the acellular vaccine in challenge models. Their work is showing promise in its inclusion. In parallel, we seek to provide an immunotherapy to vulnerable infants who are too young to receive the vaccine. Providing neutralizing anti-ACT antibodies to infant mice prior to bacterial challenge initially proved ineffective when injected intraperitoneally. We hypothesize this as a mass transfer limitation in getting to the site of action, the respiratory tract. Therefore, we have developed a proof-of-principle system in evaluating several lung delivery models. When delivered to the lungs, protection provides several insights. First, successful protection implies an effective prophylaxis to high-risk infants. This could be especially powerful as we currently have an anti-PTX antibody in non-human primate trials that successfully alleviates symptoms of elevated white blood cell count, but it does not mitigate colonization. A cocktail with anti-PTX and anti-ACT antibodies could therefore provide a one-two punch at the site of colonization and a systemic therapeutic. Secondly, protection with anti-ACT antibodies suggests inclusion of this antigen into the vaccine will adequately provide a robust immune response.

All in all, we have established the importance of an adenylate cyclase toxin, an essential colonization factor, in invoking immunity for Bordetella pertussis vaccine and passive immunization.