NOVEL APPROACHES TO PREVENT AND TREAT PERTUSSIS

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Pertussis remains a significant health problem, killing up to 200,000 infants annually. We are pursuing two complementary approaches to this problem, (1) engineering the adenylate cyclase toxin as an additional antigen for inclusion in the current acellular vaccine and (2) developing a neonatal antibody therapeutic to protect infants during the most vulnerable period before they are fully vaccinated.

The current vaccine confers short-term immunity and prevents the symptoms of disease but does not reduce infection or transmission rates. The adenylate cyclase toxin (ACT) 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 multicomponent vaccine. We have engineered this protein for improved production and stability and have identified a panel of neutralizing and non-neutralizing antibodies to aid in further engineering efforts. We are currently using the original ACT and our engineered variant in mouse immunization experiments to dissect ACT’s role in protection. Notably, addition of our engineered protein to the current acellular vaccine results in 97% increased bacterial clearance during the early stages of disease, likely by protecting macrophages and neutrophils from toxin activites.

To provide a therapeutic option before a new vaccine is licensed, we have developed a humanized antibody, hu1B7, to both treat and prevent pertussis. This has been engineered for high affinity binding, reduced immunogenicity and extended serum half-life. We have shown hu1B7 is protective against disease in mouse and adolescent baboon models of disease. We have also characterized the antibodies’ mechanisms of action, using biochemical, structural and cellular assays. To determine if passive immunization could protect newborns from pertussis infection, hu1B7 was tested in newborn baboons. Two-day-old baboons received hu1B7 (40 mg/kg, IV) and five weeks later were infected with 10^8 cfu of B. pertussis. Animals were monitored for clinical signs of disease including leukocytosis, coughing, and bacterial colonization. Thus far, 7 hu1B7-treated and 6 control animals have completed the study. Antibody prophylaxis mitigated the clinical signs of pertussis, including leukocytosis (p = 0.004) and coughing, but as expected, did not prevent bacterial colonization (p = 0.15). As a step toward lowering the cost for developing world applications, we have generated and completed in vitro testing of an extended half-life version of hu1B7. Data from baboons treated with this variant will be reported.