MESSAGE FROM THE GRAYSON-JOCKEY CLUB RESEARCH FOUNDATION

CHALLENGES AND NEW PERSPECTIVES OF FOAL VACCINATION

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Vaccination is one of the most effective ways to prevent infectious diseases, but there are many challenges to design efficacious vaccines to protect foals.

First, their immune cells are immature. Innate immune cells in adult horses, such as neutrophils and macrophages, rapidly respond to microbe invasion by engulfing and destroying them (or infected cells). Adaptive immune cells, such as B and T lymphocytes, produce antibodies and stimulate other cells to kill pathogens, respectively, but respond slower than the innate cells (approximately 10-14 days from the first encounter with a microbe). Studies from the Equine Infectious Disease Laboratory and others suggest that both innate and adaptive immune cells of newborn foals are immature, and function less effectively than adult horse cells.

The second challenge for designing foal vaccines is the presence of maternal antibodies. Foals ingest these when drinking enough of good-quality colostrum, and those antibodies can potentially neutralize the vaccine. The third challenge is that, even if the adaptive immune cells of foals were mature and functioning at birth, it would still take 10-14 days to generate protection from B and T lymphocytes, leaving them susceptible to diseases in this period.

For these reasons vaccination of pregnant mares is the best method to protect foals from infectious diseases; yet, many diseases for which maternal vaccines are not available are still a threat to the health of foals.

One example is pneumonia caused by *Rhodococcus equi*, an insidious disease that affects foals and immunodeficient adult horses. Because *R. equi* is ubiquitously present in the equine feces and soil of breeding farms, virtually all foals are exposed to it soon after birth. Some foals will later develop clinical pneumonia, others develop lesions in lungs without clinical signs (the so-called subclinical pneumonia), and some remain entirely healthy. This disease has an important economic impact to the equine industry, not only because many foals die due to clinical pneumonia but also because foals with subclinical disease are less likely to race. Despite decades of research trying to understand why some foals are susceptible and others resistant, this question still puzzles scientists.

Many different approaches were used in an attempt to develop an effective vaccine to protect foals against this tragic disease. All foal vaccines have universally failed for the reasons discussed above (immaturity of their immune cells and the need for protection soon after birth).

The EIDL has demonstrated that maternal vaccination with PNAG (a molecule in the surface of *R. equi* and many other pathogens) protected foals against pneumonia in an experimental setting. Optimization (dose and frequency of administration, different formulations, etc.) of products, however, usually takes years before a vaccine is commercially available. Additionally, maternal vaccination has other limitations, such as variable immune responses generated in the dam, need of production of good quality colostrum, and ingestion of sufficient quantity of colostrum, etc. Thus, even if a maternal vaccine is commercially available, there is still a need for strategies that can be used directly in the foal to help them fight diseases. Transfusion of hyperimmune plasma has been successfully used to prevent *R. equi* pneumonia, but there are some limitations, such as being expensive and labor-intensive, and carrying risks to the foal.

The EIDL has focused for many years in researching strategies to stimulate the innate immune responses of foals. We have demonstrated that parts of the genetic material of bacteria (called CpG-ODNs) can stimulate foals' cells to produce molecules (called cytokines) that facilitate communication between immune cells. One example of a cytokine important for the response to *R. equi* that can be stimulated by CpG-ODN is called interferon-gamma, which newborn foals are known to be deficient.

Additionally, with the support of a continuum grant awarded by the Grayson-Jockey Club Research Foundation, we have shown the nebulization of CpG-ODN and Pam2 (a synthetic product that mimics a molecule in the surface of pathogen) can boost foals' innate immune responses directly in the lungs. This strategy is called host-directed therapy, and we have shown that it could potentially shorten duration of clinical signs (such as fever and cough) and presence of lung lesions in pneumonic foals.

We have recently started studying trained immunity in horses, a relatively new concept in which innate immune cells are stimulated to provide long-term protection against microbes by generating "memory" (i.e., they "remember" the microbe after the first encounter and respond better and faster afterward). This happens by "turning on and off" genes (called epigenetic modifications) that are associated with eliminating invading pathogens. This is an exciting new area because, until recently,

it was believed that only T and B lymphocytes had immune memory. Training innate immune cells of foals would be extremely important for their health because it would help eliminate the susceptible period before their adaptive immune responses are mature.

With this strategy we hope to design new products that can improve vaccines against *R. equi* and other pathogens and save lives of foals. BH

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