Chimeric VP7-VP4 MVA-Vectored Equine Rotavirus Vaccines

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In this study novel chimeric vaccinia-vectored vaccines against equine rotavirus A G3 and G14, the leading cause of foal diarrhea, will be designed and evaluated in mice (proof-of-concept) and mares.

Equine rotavirus A (ERVA) is one of the most common causes of diarrhea in foals within their first 3 months of age. This virus infects and damages the intestinal lining, impeding appropriate absorption of food and water, leading to diarrhea and severe dehydration that requires rapid implementation of medical treatment in sick foals. These sick foals are also very contagious and shed up to 109 virus particles per gram of feces, contaminating the environment. In addition, rotavirus particles are highly resistant in the environment, therefore sustaining transmission to healthy but susceptible foals through the contaminated environment. ERVA is responsible for anywhere between 20% and 77% of diarrhea cases in very young foals, outbreaks occur every foaling season, and can cause important losses to breeding enterprises.

Surveillance efforts around the world have identified that there are two main genotypes of ERVA that cause diarrhea in foals, namely G3 and G14. Control and prevention strategies rely on: 1) enhancing maternal immunity to the foals via vaccination of pregnant mares and 2) biosecurity measures (including hygiene) to interrupt transmission.

There are only 3 vaccines available around the world (one of which is commercially available in the US), all of which are solely based on one of two prototype ERVA G3 strains isolated in the 1980's. All of these vaccines are inactivated, i.e., based on a killed virus preparation that is poorly immunogenic, which means that it does not elicit a strong immune response by the horse and multiple doses are required to reach adequate immunity. Mares are vaccinated during pregnancy with the hope to induce good maternal immunity. Even after multiple doses, the efficacy of this vaccine is limited as these are poorly immunogenic, induce G3-specific antibodies with limited cross-reactivity with other circulating strains of ERVA, depend on colostrum quality and intake, among other factors related to the mare, foal and environment that influence response to the vaccine.

An additional limitation on the development of rotavirus vaccines is related to the difficulties in isolating and propagating viral strains for use in vaccines. In light of this, there is a critical need to develop more effective, modern next generation vaccines that induce strong and effective maternal immunity and using novel platforms that do not depend on rotavirus propagation in the laboratory and that can be updated easily based on circulating strains. On our previously funded grant, we explored the use of a modified and attenuated vaccinia virus (Ankara) modified to express a highly immunogenic protein of the surface of ERVA specific to G3 and G14 strains known as VP7 in its native form. This attenuated vaccinia virus is non-pathogenic to horses, does not cause disease or is transmitted to other horses, and has proven efficacious in horses against the deadly African horse sickness virus.

We demonstrated that this attenuated vaccinia strain can successfully express ERVA G3 and G14 VP7 types but induces non-neutralizing antibodies (i.e., antibodies that bind to VP7 but do not block virus entry). This is likely associated with retention within the intracellular compartment known as endoplasmic reticulum, and limited exposure of neutralizing epitopes. Based on our preliminary findings, we hypothesize that adding a secretory and anchoring signal to VP7 as well as adding other immunogenic ERVA proteins (VP4 and VP6) will enhance immunogenicity and the generation of antibodies that will neutralize ERVA G3 and G14 strains.

This proposal focuses on developing two viral vectored vaccines that can address the existing issues identified with expression of only VP7 in its native form and improve the vaccine platform proposed by inducing antibodies that can effectively block rotavirus and confer protection.

We plan to evaluate these vaccines first in mice (including their protective efficacy in an ERVA G3 and G14 infection

model that we established in neonatal mice) and subsequently assess the immunogenicity of the most promising candidate in mares.

We expect that our novel vaccine design approach will build on our previous work and significantly improve the efficacy of current ERVA vaccines.

Importance to the Equine Industry: Diarrhea in foals due to equine rotavirus continues to be a significant health issue causing outbreaks of disease in farms during every foaling season. Twenty to 77% of diarrhea cases in foals within their first three months of age are associated with equine rotavirus, while other causes of diarrhea are of lower impact.

The impact of the disease is variable but most frequently associated with high numbers of sick foals (high morbidity), which require intensive medical management. These sick foals are highly contagious and, therefore, control of the disease also requires strict biosecurity protocols to try to minimize the contamination of the environment and continued spread. While vaccination of pregnant mares is a common method of control and prevention, the current available vaccine has limited and controversial efficacy and, therefore, the level of protection is far from optimal, undermining its wide use. No changes to this vaccine formulation have been made since its licensure in order to improve its efficacy and keep up with more current circulating strains of this virus in the horse farms.

Therefore, this proposal brings a novel vaccine platform that can significantly enhance current control and prevention efforts to minimize the impact of this disease in young foals.

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