Development of a Vaccine to Prevent Valley Fever in Dogs

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An avirulent mutant strain of the valley fever fungus has been created by cutting out a gene that is necessary for the fungal spores to cause disease in animals. Studies at the University of Arizona show that the mutant strain, called delta-cps1, does not make mice sick at all. In fact, even with doses up to 100 times a typical lethal dose of a normal strain of valley fever fungus the mice remain healthy and without any microscopic or cultural evidence of the infection. If we give megadoses of delta-cps1 to mice, they nearly eradicate it by day 10 post-infection. Furthermore, vaccinating mice with live spores of the mutant strain renders them resistant to infection with a normally fatal dose of the virulent valley fever spores. Delta-cps1 has strong potential as a vaccine to prevent valley fever in dogs.

**Background:** Valley Fever is a fungal disease in dogs (and other animals) in the southwestern United States. Dogs contract the disease living or traveling through areas where the fungus grows in the dirt. Dogs breathe in the spores and infection can develop in lungs, bones, skin, brain or other sites. The disease costs Arizona dog owners at least $60 million a year for diagnosis, treatment, and follow up care for valley fever. Some dogs die in spite of treatment or because their owners cannot afford treatment. A vaccine to prevent valley fever in dogs will improve animal health and reduce the financial burden of caring for dogs in Arizona and other southwestern states.

**Delta-cps1:** This mutant strain grows effectively on laboratory culture media similar to a normal strain of valley fever, but when mice inhale spores of delta-cps1, no illness results, while other mice infected with normal spores die within two weeks. Two different, very susceptible strains of mice were tested to verify the results. In addition, delta-cps1 spores were given to a third, immunodeficient strain of mice which lack the white blood cells that will fight a valley fever infection. These mice also remained healthy and required doses 1000-fold higher than a fatal dose to even find it in the lung tissue. When we were finally able to find the delta-cps1 in mouse lungs after infection with 1000-fold lethal doses, we observed that the fungal forms were breaking down instead of expanding and growing as happens with lethal strains of valley fever. The missing gene in the mutant strain affects its ability to reproduce and cause disease in animals.

**Vaccine Potential:** Delta-cps1 was used to vaccinate the same two susceptible, immunologically normal strains of mice and more than 90% of both strains survived following a lethal infection with normal valley fever spores. In addition, the mice that lived had very few fungal organisms left in their lungs. This vaccine appears to make the mice highly resistant to death and also to “train” their immune systems to control or kill virulent valley fever.

**Canine Vaccine Development:** In order to develop a canine vaccine that is licensed for use in dogs, delta-cps1 requires more studies and developmental work. We need to upscale growth of the fungus in a safe and clean environment and formulate it with stabilizing agents to manufacture the vaccine; the spores need to be studied for stability in a liquid or dehydrated state, so that when a vaccine is given to a dog it contains the number of live spores needed to generate protection but avoid dead spores as much as possible (dead spores cause vaccine reactions); the vaccine needs to undergo regulatory approval by the USDA, which means safety and efficacy testing in dogs once a formulation is derived. Additional studies for optimizing dosing and safety in mice must be followed by pilot studies in dogs to ascertain safety and determine if the dogs have responded to the vaccine using in vitro testing. Following these studies, the vaccine can then be manufactured for large scale safety testing, which will be performed in client-owned dogs in Tucson and Phoenix. Dogs will then be vaccinated or injected with a placebo in a large community-based trial and monitored for occurrence of valley fever in the two groups. A lower rate of valley fever in the delta-cps1 vaccinated dogs will be convincing evidence that the vaccine protects dogs against naturally occurring valley fever.

Funding is needed for all phases of the dog vaccine development.

**Financial Breakdown**

**Basic Science Studies**

There remain basic science experiments that must be performed, including two studies to help determine dosages of vaccine needed for dogs, cross-protection with the California species of valley fever fungus, and assessing stability of potential vaccine formulations. We also need to perform USDA-mandated potency studies of
the vaccine. Fungal studies include upscaled growth experiments to maximize spore production, stability testing, and freeze-drying studies to determine the final formulation of the vaccine for licensing and testing in dogs. Cost: $100,000-125,000.

Vaccine Manufacturing/Licensing
A dedicated facility needs to be set up to manufacture the vaccine and package it. This facility and the packaged vaccine both need to meet USDA regulatory specifications and undergo licensing in order to make a vaccine to complete the clinical studies and that can be marketed to prevent valley fever in dogs. This requires identifying approximately 1000 sq. ft. of space and dedicated equipment required to operate the facility using clean/sterile methods to grow the vaccine and package it. Cost: estimated $500,000 - $1,000,000 for set up and 2 years operation

Community-based Dog Studies
Licensing requires two separate studies to evaluate 1) safety of the vaccine and 2) effectiveness in preventing valley fever in dogs exposed to natural infection. Both studies will engage dogs in the community, which stand to benefit from vaccination. The first is a large safety study in which dogs are vaccinated with the potential vaccine and observed for adverse effects – a study dictated in scope by the USDA. The second study will assess the efficacy of the vaccine to prevent or reduce the severity of valley fever in client-owned dogs with naturally acquired infection. This will require enrolling approximately 500 dogs and vaccinating half with the vaccine and the other half with a placebo, then monitoring health over a one year period to determine if there is a difference in the rate of valley fever illness between the two groups of dogs. Cost: Est. $200,000-$250,000