Dated April 6, 2018
Research Progress Report Summary
AKC/CHF Grant 02210:
Gene Therapy for
Canine Degenerative Myelopathy

The American German Shepherd Dog

Charitable Foundation

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April 6, 2018 Report from the Principal Investigator Kathrin Meyer, PhD:
Degenerative myelopathy (DM) is a devastating neurodegenerative disease that affects multiple breeds of dog. It is characterized by progressive weakness and inability to control hindlimbs, ultimately leading to involvement of forelimbs and complete paralysis. With no current treatments available, euthanasia is the only option available for DM-affected dogs. Recent studies have identified mutations in the Superoxide dismutase 1 (SOD1) gene to be a high-risk factor associated with canine DM. In humans, mutations in the same SOD1 gene cause Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disorder very similar to canine DM. It is also shown that reduction of mutant SOD1 in ALS mouse models provides beneficial effects. Hence, therapeutic approaches to reduce the expression of mutant SOD1 in DM-affected dogs may improve survival and preserve neurologic function. The overall goal of this study is to improve survival and the quality of life of canine patients with Degenerative Myelopathy by a viral based gene therapy. Our main objective here is to determine the safety and efficacy of AAV9 mediated SOD1 reduction in DM patients. Moving towards our final goal, we had designed and tested 3 different shRNA construct that can reduce the levels of SOD1 in dog skin cells. The most efficient construct has been then molded into an AAV cassette that is optimal for the final preparation of AAV9 shRNA SOD1 virus. To determine if the AAV9 shRNA SOD1 virus is functional before its administration into patient dogs, we have also established a cell-based assay using dog skin cells. Finally, we have also established a screening method to select the suitable patient candidates for the administration of AAV9 shRNA SOD1 based on the levels of neutralizing antibodies in serum. Pre-existing neutralizing antibodies pose an obstacle against viral based therapies as they can clear the therapeutic viral particles thus neutralizing its biological effect. Hence, it is critical to screen and select the patient population with minimal levels of such antibodies to maximize the benefits of the gene therapy. Thus, with the final construct and the essential assays available, we are gearing up for the production of our final scAAV9-dSOD1 shRNA vector to be administered into DM dogs.

Original Project Description:

Original Project Description: Degenerative myelopathy (DM) is a devastating neurodegenerative disease that affects multiple breeds of dog. DM is an adult-onset disease that manifests at the later stages of life. It is characterized by progressive weakness and inability to control hindlimbs, ultimately leading to involvement of forelimbs and complete paralysis. With no current treatments available, euthanasia is the only option available for DM-affected dogs. Recent studies have identified mutation in the Superoxide dismutase 1 (SOD1) gene to be a high-risk factor associated with canine DM. In humans, mutations in the same SOD1 gene cause Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disorder very similar to canine DM. It is also shown that reduction of mutant SOD1 in ALS mouse models provides beneficial effects. Hence, therapeutic approaches to reduce the expression of mutant SOD1 in DM-affected dogs may improve survival and preserve neurologic function. In this study, a viral-based gene therapy approach to treat DM will be evaluated, utilizing Adeno-associated Virus 9 (AAV9) mediated delivery of shRNA to reduce the mutant SOD1 in DM affected dogs. AAV9 is a safe, well tolerated and widely used vector for gene therapy in animals as well as for humans. If successful, this one-time treatment with AAV9 SOD1 shRNA will result in improved quality of life, and significantly extend the survival of dogs affected with this previously hopeless disease.