Minimally invasive delivery of AAV gene therapy in the Tay-Sachs Sheep

**Overall Goal:** To determine the efficacy of adeno associated viral (AAV) gene therapy after cerebrospinal fluid (CSF) delivery in Tay-Sachs disease (TSD) sheep.

In 2019, we dosed 4 additional TSD sheep with AAV gene therapy via the CSF space. Three sheep of these sheep were treated by a combination of bilateral intracerebroventricular, cisterna magna and lumbar intrathecal injection and the other was treated using a novel intrathecal AAV delivery technique delivered via catheter.

The Tay-Sachs sheep treated by CSF AAV delivery remain alive, therefore the results have not yet been analyzed. However, due to the extended survival, we are planning on moving this therapy forward in the treatment of late onset Tay-Sachs and Sandhoff disease (LOTS/LOS). TSD sheep treated by AAV gene therapy were treated by a combination of methods because the TSD sheep develop advanced disease globally throughout the brain. This is in contrast to LOTS/LOS patients, where the parts of the brain affected are most prominently the cerebellum and spinal cord. For this reason, we believe that the therapeutic strategy applied to the TSD sheep is likely more invasive than what would be required for LOTS/LOS patients. We believe that this catheter-based delivery is applicable for AAV gene therapy for LOTS/LOS. A manuscript summarizing the catheter delivery method is currently under peer review.