Poster Session I (cont.)

P10

SPINAL CORD EXPRESSION OF VIRALLY DELIVERED MULLERIAN INHIBITING SUBSTANCE EXTENDS LIFE AND PROMOTES SURVIVAL OF MOTOR NEURONS IN TRANSGENIC SOD1 MUTANT MICE

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Purpose:
Motor neuron diseases are a group of neurological disorders caused by slowly progressive death of motor neurons, which control essential voluntary muscle activity. Mullerian Inhibiting Substance (MIS) is a member of the TGF-β superfamily, which includes other motor-neuron survival factors. Since MIS and its receptors are expressed in motor neurons, we hypothesized that heightened spinal cord expression of MIS would prolong survival in SOD1 mutated mice. .

Methods:
Adeno-Associated virus serotype 9 was used to deliver Mullerian Inhibiting Substance (AAV9-MIS) as a single intravenous injection at P28 (n=4 with 4 controls), P7 (n=7), or P1 (n=9) into C57/BL6 mice carrying the G93A superoxide dismutase (SOD1) mutation that occurs in 20-25% of patients with familial ALS. Genome copy number was analyzed from liver and brain specimens at disease end point to quantify the presence of vector. Phosphate buffered saline (PBS) was compared to Mullerian Inhibiting Substance for effect on the size and number of motor neurons by both immunohistochemistry and immunofluorescence of spinal cord sections using the motor neuron marker choline acetyltransferase.

Results:
SOD1 mutated mice injected with the AAV9-MIS vector demonstrated a 15 day survival benefit when compared to mice injected with PBS (P28, *p=0.026; P7, *p=0.038; P1, *p=0.013). In addition, endstage AAV9-MIS injected mice showed more robust ChAT staining in the ventral horns of the spinal cord by immunofluorescence (**FIGURE 1A-RED)** when compared to control (**FIGURE 1B-RED)**. Furthermore, AAV9-MIS injected mice demonstrated more axonal staining in the ventral horn of the spinal cord by immunohistochemistry (**FIGURE 1C-PURPLE)** when compared to control (**FIGURE 1D-PURPLE)**.

Conclusion:
The *in vivo* responses produced by virally delivered MIS indicates its use as an effective method for prolonging survival of patients with neurological diseases such as ALS and that neurotropic viral gene therapy may be an efficient mode of delivery of MIS.