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MEETING ABSTRACTS

PARAOXONASE 1 VARIANT I-F11 GENE THERAPY USING ADENO-ASSOCIATED VIRUS8 (AAV8) OFFERS LONG-TERM PROTECTION AGAINST G-TYPE CHEMICAL WARFARE NERVE AGENTS

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The paraoxonase 1 variant I-F11 affords asymptomatic protection against the lethal effects of G-type chemical warfare nerve agents (CWNA). Here, we tested whether adeno-associated virus8 (AAV8) is able to deliver I-F11 for extended periods of time and at levels affording asymptomatic protection against 2-5LD50 doses of G-type CWNA in mice. I-F11 gene expression levels in mouse blood were assessed under the influence of three different promoters and found to be significantly higher with TBG compared to CMV and CASI. A single tail vein or intramuscular injection of AAV8-TBG-I-F11 resulted in robust production of the enzyme, which reached concentrations of up to 1 to 2 mg/ml in mouse blood for up to 6 months. Mice containing 0.75 mg/ml or higher concentrations of I-F11 in their blood were afforded asymptomatic protection against multiple 5LD50 exposures of GD, GF, GA, and GB, a total of 9 exposures over a seven-week period. We also conducted studies showing that I-F11 is most efficacious in offering protection against GD followed by GF, GB and GA. Analysis of the mouse blood for serum chemistry and hematology parameters, and tissues by H&E staining, indicated no appreciable changes between control mice, mice overexpressing 1-F11 for 6 months, and mice surviving repeated G-agent exposures. These data suggest that AAV8-mediated catalytic bioscavenger gene therapy using 1-F11 is a safe, efficacious, and long-lasting pre-treatment strategy against G-agents.

Keywords: Gene Therapy; AAV8; Chemical Warfare Nerve Agents; Paraoxonase 1 variant I-F11; Safety and Efficacy

Disclaimers/Acknowledgments

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