Abstract: **P1516**

**Novel cardiotropic AAV variant C102 vectors show superior gene delivery & reduced immunogenicity in non-human primates, transduction of human cardiomyocytes, & correction of Fabry disease phenotype**

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**Topic(s):**
Renal Failure and Cardiovascular Disease

**Citation:**

**Background**
Cardiac-targeted gene therapy vectors are needed. Fabry disease is a rare, X-linked disorder caused by mutations in the GLA gene, which encodes a-galactosidase A (GLA). Storage and accumulation of glycolipid substrates of GLA leads to organ damage. Cardiovascular disease is the most common cause of mortality in Fabry disease (75% of deaths). Enzyme replacement therapy (ERT; first line treatment for most patients) demonstrates clearance of Gb3 from capillary endothelial cells. However, Gb3 accumulation in podocytes, cardiomyocytes, and vascular smooth muscle cells persists. Gene replacement strategies leveraging adeno-associated virus (AAV) vectors with high tropism for affected organs (namely the heart) may directly address the underlying pathophysiology of Fabry disease.

**Purpose**
To unlock the full potential of cardiac gene therapy, novel targeted vectors are needed with enhanced tropism for specific target tissues when delivered in vivo.

**Methods**
An industrialized "directed evolution" approach (Therapeutic Vector Evolution) was applied in the most relevant animal species (non-human primate; NHP) which led to the discovery of C102, a novel AAV variant capable of efficient gene delivery throughout the primate heart following a single intravenous (IV) administration. C102 biodistribution using a ubiquitous promoter was evaluated in mice and NHP at doses at least 10-fold lower than current AAV-based clinical trials for neuromuscular gene therapy. Animal studies conformed to the NIH Principles of Laboratory Animal Care. To evaluate the ability of the C102 capsid to transduce human target cells relevant to Fabry disease, human pluripotent stem cell-derived cardiomyocytes were transduced. To evaluate the ability of C102 to correct Fabry disease, cultured patient fibroblasts were transduced with the C102.GLA product.

**Results**
Following a single IV administration in mice, the onset of C102.luciferase expression was rapid (14 days) and durable. Dose-dependent luciferase activity was observed in Fabry disease target tissues, including heart and liver. Following a single IV administration in NHP, superior delivery to heart was demonstrated and immunogenicity was markedly reduced compared to first generation wild-type vectors (AAV8,9), and genomes were present throughout the heart and skeletal muscle groups. In human cardiomyocytes in vitro, C102.EGFP demonstrated significantly higher transduction compared to wild-type AAV1 and 9 vectors (immunofluorescence imaging and quantification by flow cytometry) at all doses. Following transduction with increasing doses of the C102.GLA product in Fabry patient fibroblasts, dose-dependent GLA expression and function was observed.

**Conclusion**
The data generated using the novel C102 capsid and the C102.GLA Fabry product validate the Therapeutic Vector Evolution approach for cardiac tissue targeting in vivo and provide a strong preclinical data package to enable clinical translation.
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