Prevention of Premature Lethality and Reversal of Cardiac Hypertrophy with an Optimized MYBPC3 Gene Therapy

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Cardiomyopathy is the number-one cause of sudden cardiac arrest in children under 18. Hypertrophic cardiomyopathy (HCM) affects 0.5 million Americans, potentially resulting in heart failure or sudden death. Loss-of-function mutations in *Myosin Binding Protein C3*, *MYBPC3*, are the most common genetic cause of HCM. The majority of *MYBPC3* mutations causative for HCM result in truncations, via nonsense, frameshift or splice-site mutations. The sarcomeric pathophysiology of the majority of HCM patients with *MYBPC3* mutations appears to be due to haploinsufficiency, as the total amount of MYBPC3 protein incorporated into sarcomeres falls significantly below normal.

The clearest path to the treatment of haploinsufficiency is the restoration of the insufficient gene product; in this case wild-type MYBPC3. Thus, we have successfully engineered an AAV vector (TN-201) with superior properties for selective restoration of MYBPC3 to cardiomyocytes upon systemic delivery. Critically, we have demonstrated for the first time with AAV the ability of both a mouse surrogate and TN-201, which encodes the human gene, to reverse cardiac dysfunction and hypertrophy and improve survival in a symptomatic murine model of disease. Dose-ranging efficacy studies exhibited restoration of wild-type MYBPC3 protein levels and saturation of cardiac improvement at the clinically relevant dose of 3E13 vg/kg. Further, pilot safety studies in adult and infant mice injected with >10X an efficacious dose exhibited no clinical observations and no alterations in cardiac function. Finally, we have established stable cardiac benefit for greater than one year post-injection, as well as reversal of cardiac dysfunction even in late-stage homozygote disease.