Evaluating TAT-FXN Therapy Efficacy on Cardiac Manifestations of Friedreich's Ataxia: Insights from Murine Models and Echocardiography

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Background and Hypothesis: Friedreich's Ataxia (FRDA) is an autosomal recessive disease in which the loss of nuclear-encoded frataxin (FXN) causes loss of iron-sulfur cluster formation in mitochondria. This is associated with progressive loss of motor function and a hypertrophic cardiomyopathy leading to death in the second or third decade of life. In the FRDA murine model of heart failure, treatment with the fusion protein TAT-FXN significantly extends life span and improves gait. TAT-FXN has advanced to Phase II clinical trials, but effective dosing and mechanism of action biomarkers remain challenging. We hypothesized that treatment with TAT-FXN mitigates FRDA metabolic disruption and may result in improved cardiac function.

Project Methods: $Frda^{L2/L2}$::MCK-Cre (MCK-KO) mice and controls underwent echocardiography at 30, 45, and 65 days of life. The animals were anesthetized with isoflurane and maintained on a warming stage. Parasternal long-axis, short-axis, and apical four-chamber views were used to measure interventricular septum thickness, left ventricular posterior wall thickness, ejection fraction (EF), global longitudinal strain (GLS), and mitral E/A ratio. Statistical analysis included one-way ANOVA and Tukey's multiple comparisons test.

Results: Growth trajectories followed logistic curves across all groups. By day 65, MCK-KO mice showed significant impairment in EF, GLS, and cardiac index (CI) compared to controls. However, no significant differences in EF, GLS, or CI were observed between TAT-FXN-treated and vehicle-treated mice. Mitral E/A ratio and LV measurements were not significantly different between groups.

Conclusion and Potential Impact: TAT-FXN therapy did not significantly improve cardiac function compared to vehicle in this FRDA murine model. Thus, while TAT-FXN does not worsen cardiac impairment, it may not sufficiently mitigate existing cardiac dysfunction within the study's timeframe. These findings highlight the importance of further research to identify biomarkers of treatment response and elucidate the effects of TAT-FXN treatment on cardiac outcomes.