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Single AAV gene therapy with mini-Glycogen Debranching Enzyme for glycogen storage disease type III

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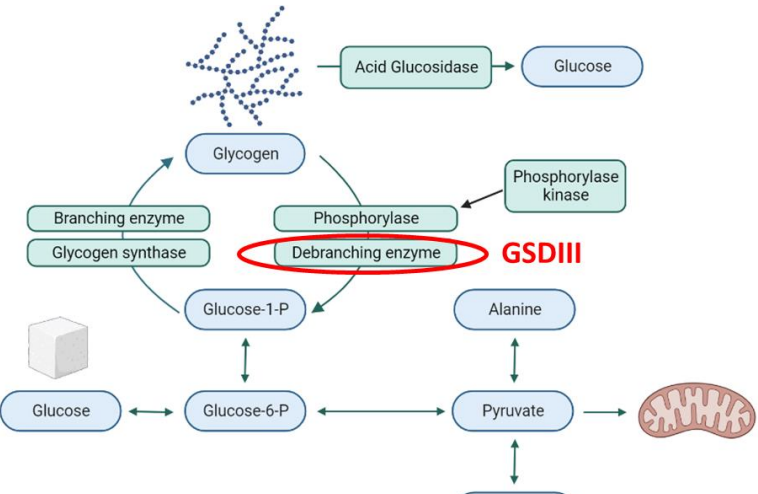
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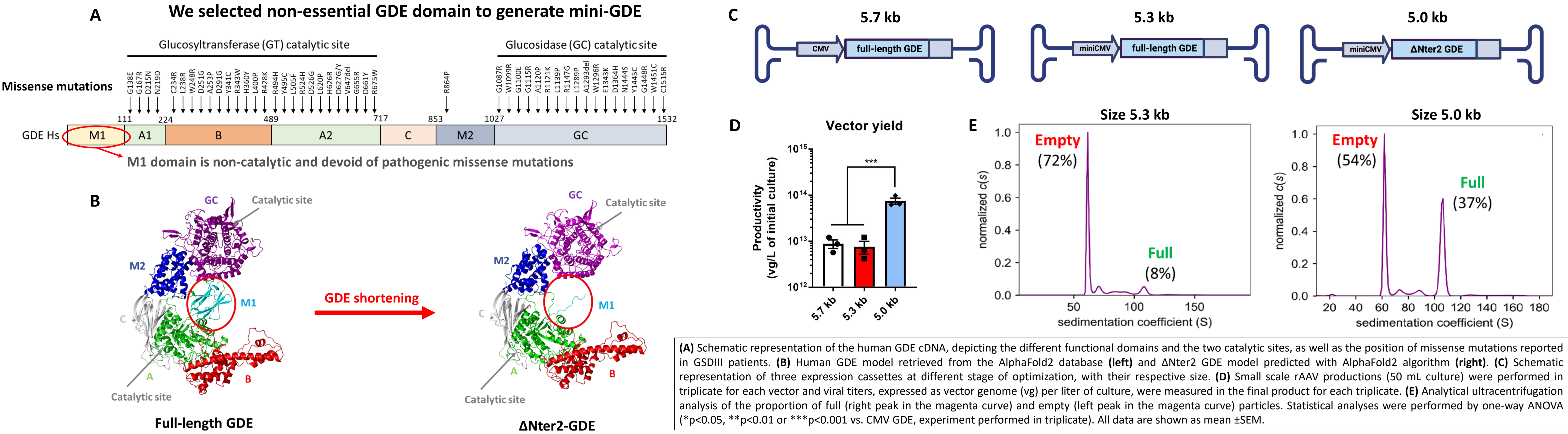
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Background

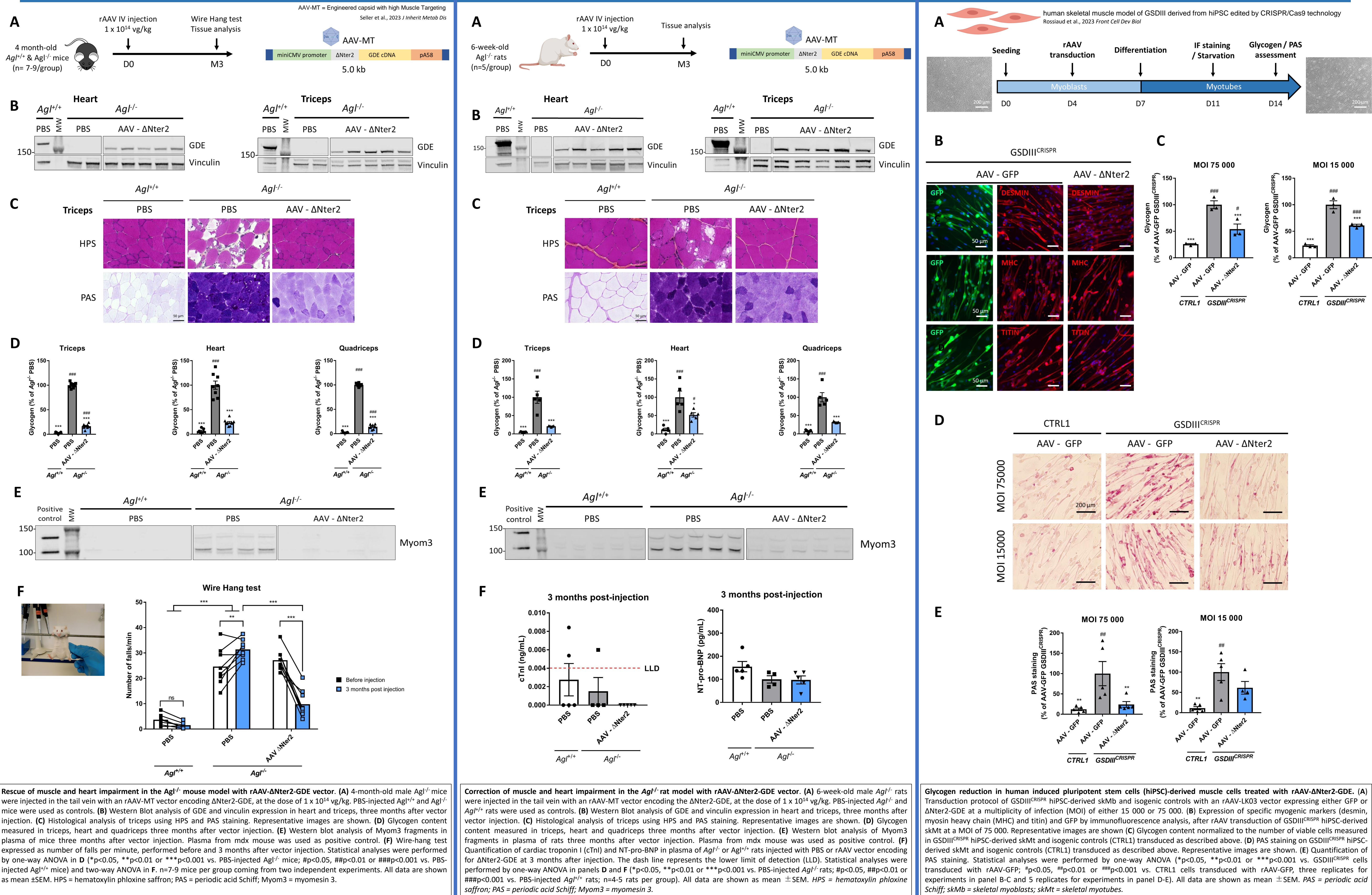
Glycogen storage disease type III (GSDIII) is a rare metabolic disorder that affects the liver, skeletal muscles, and heart. It is caused by mutations in the *AGL* gene, which encodes the glycogen debranching enzyme (GDE). However, the use of the full-length GDE cDNA in a single adeno-associated virus (AAV) vector strategy is a major challenge due to its large size (4.6 kb). Here, we developed a gene therapy strategy for GSDIII using a truncated version of the GDE enzyme delivered by a single rAAV vector to correct skeletal muscles and heart impairment in *Ag1*^{-/-} mice and rats and to decrease glycogen content in skeletal myotubes differentiated from *Ag1*^{-/-} human pluripotent stem cells (hiPSC).



Expression cassette optimization



Correction of multiple models of GSDIII using our optimized vector



Conclusions

The use of ΔNter2-GDE allowed us to generate a potent and high-quality product for GSDIII. rAAV-ΔNter2-GDE corrected muscle and heart phenotype in both mouse and rat models of GSDIII with extensive glycogen reduction, reflecting broader cell transduction. Treatment of *Ag1*^{-/-} mice with rAAV-ΔNter2-GDE vector promoted the recovery of muscle strength 3 months post-injection. This suggests that in GSDIII, the myopathy can be reversed, at least in rodent models. We also demonstrated, in a recently developed human skeletal muscle model of GSDIII derived from hiPSC, that ΔNter2-GDE clears the accumulated glycogen, suggesting that the truncation on the N-terminal region does not affect the enzyme function and regulation in a human cellular context. Our work provides proof-of-concept of the use of a single rAAV vector expressing a truncated form of GDE for the rescue of the muscle and heart impairment in two GSDIII rodent models as well as in a novel human muscle cellular model of GSDIII. This supports the clinical translation of this approach in GSDIII patients.

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