Drug Metabolism and Pharmacokinetics in Mice Systemically Administrated with a Base Editing Drug for Duchenne Muscular Dystrophin (DMD)

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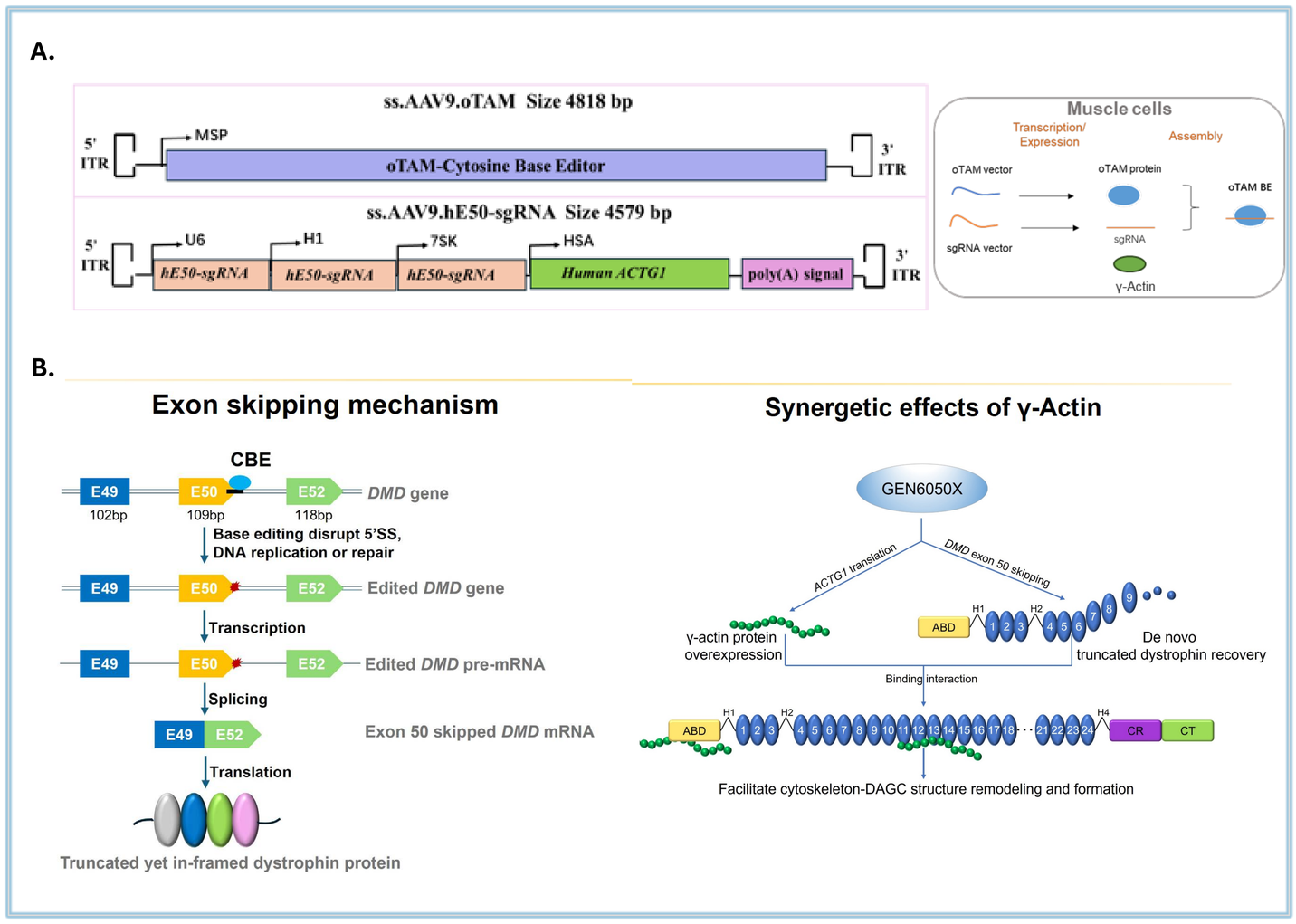
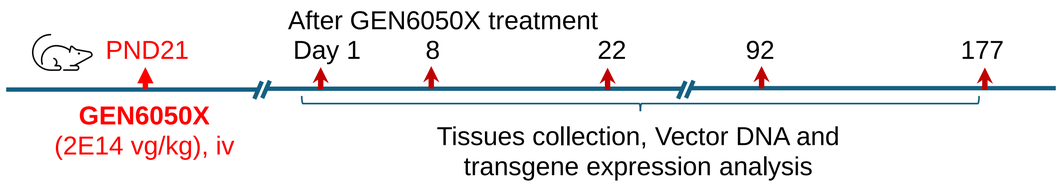
Introduction

- **DMD is a progressive muscle-wasting disease caused by mutations in the gene encoding the dystrophin protein. Until now, there is no effective drug for DMD.**
- **GEN6050X is an intravenously cytosine base editing drug for DMD exon 50 amenable patients. GEN6050X contains two AAV9 vectors, ss.AAV9.oTAM and ss.AAV9.hE50-sgRNA.**
- **In DMD patients amenable to exon 50 skipping, GEN6050X can restore the dystrophin protein through inducing exon 50 skipping. GEN6050X also carries a weak therapeutic gene ACTG1, which can provide a synergetic effect with *de novo* synthesized Dystrophin protein.**
- **The understanding of GEN6050X Drug metabolism and pharmacokinetics (DMPK) will facilitate the interpretation of toxicity and prediction of *in vivo* efficacy of base editors.**
- **In this study, we investigated the dynamics of vector DNA and transgene expression in wild-type B6 mice after a tail vein injection with 2E14 vg/kg GEN6050X for 6 months.**



Experimental Design



Results

Fig 1. The dynamic changes of GEN6050X vector DNA in the blood over time

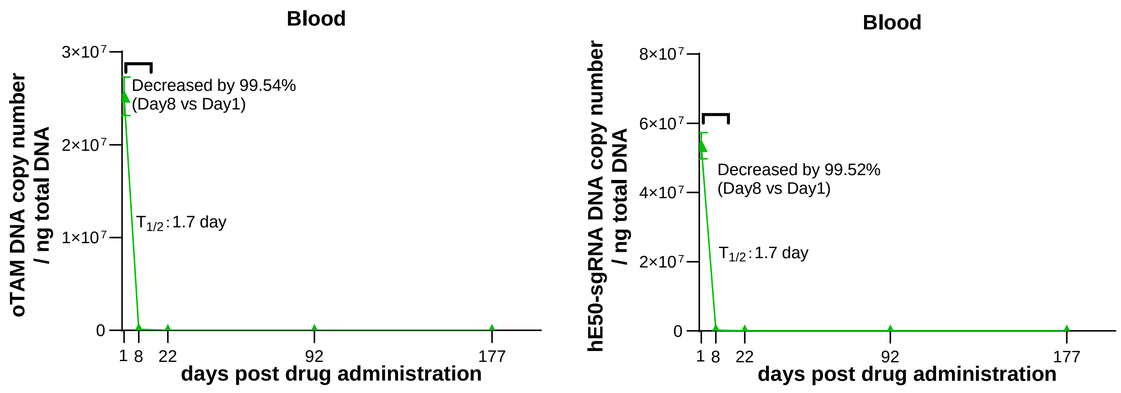


Fig 2. Biodistribution of GEN6050X vector DNA in different tissues over time

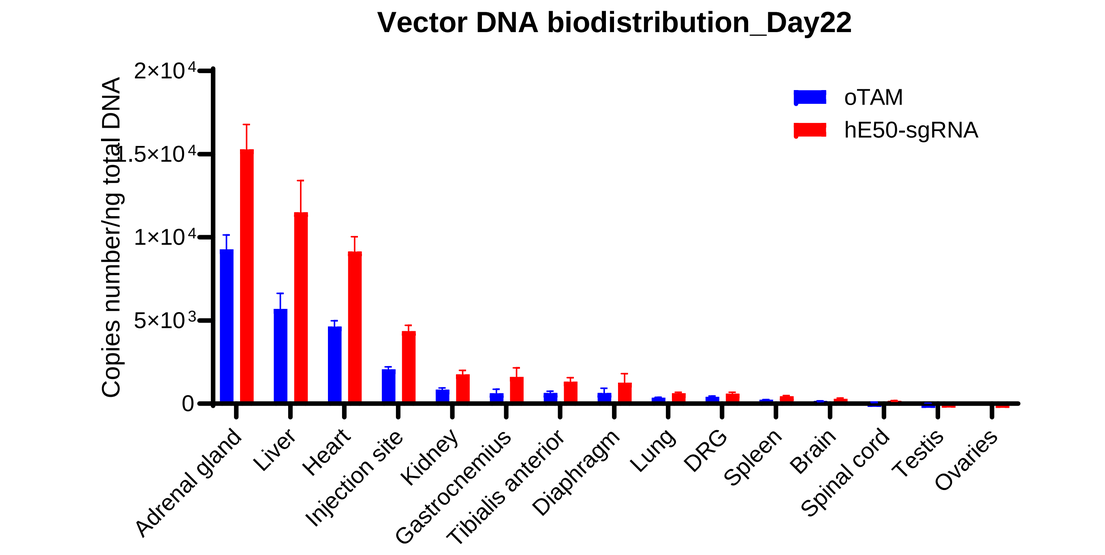


Fig 3. sgRNA transcripts expression in different tissues over time

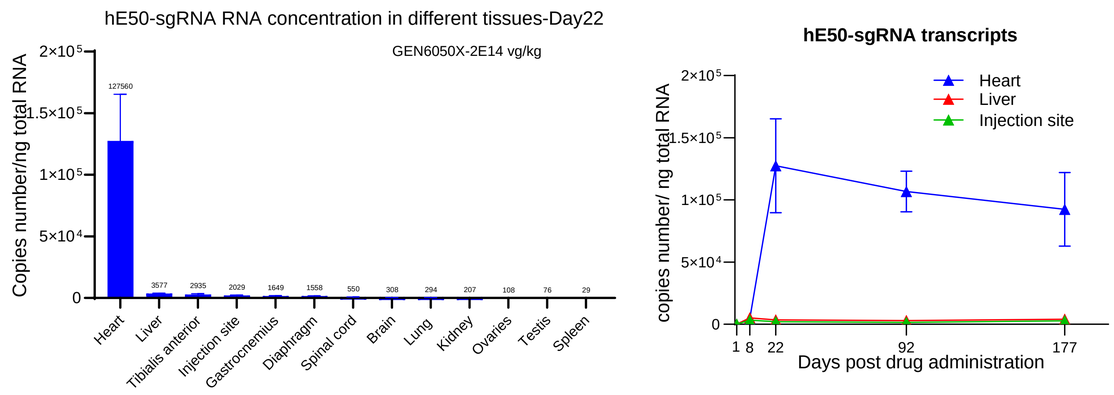
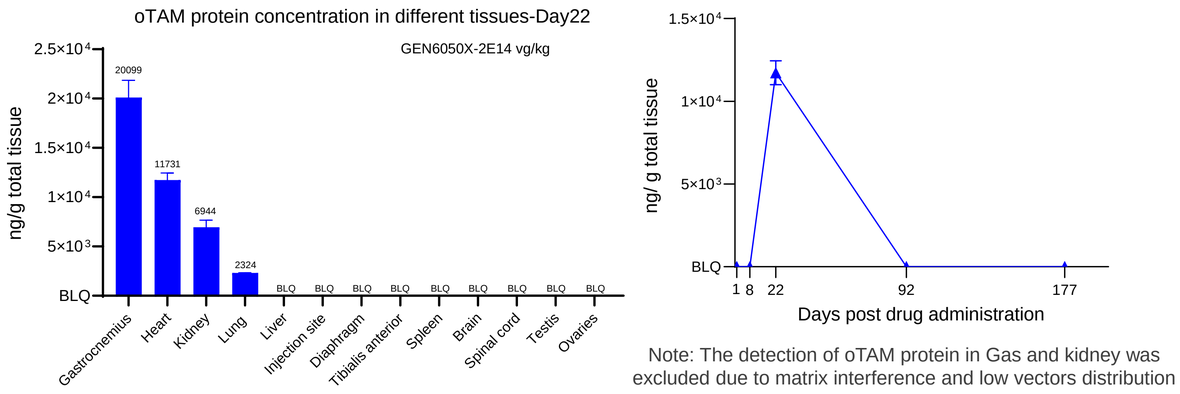


Fig 4. Transient expression of oTAM protein (only appeared at Day 22)



Note: The detection of oTAM protein in Gas and kidney was excluded due to matrix interference and low vectors distribution

Fig 5. ACTG1 protein level maintains homeostasis

Conclusion and Take-home message

1. Vectors DNA of invector mainly enriched in liver, adrenal gland since day 8 and then reduced over time in different metabolic patterns.
2. The sgRNA transcription was mainly distributed in heart, followed by liver, skeletal muscles and other tissues which extensively expressed since day 8.
3. The expression of oTAM protein was transient and only appeared at Day 22 at limited tissues, eliminating the concerns associated with constitutive expression of editing enzyme.
4. No substantial change of ACTG1 protein level was found in tested tissues.
5. **GEN6050X has initiated IIT in China in Augest, 2024.**
6. **FDA IND approved on March 6, 2025.**