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While further characterization must be done, these new variants provide a potential new platform for achieving long-term dystrophin restoration and durability when AAV is used to deliver CRISPR components in DMD and other myogenic diseases that involve muscle degeneration and regeneration.

3028 A Multiplexed Epitope-Tagging Platform for Parallel In Vivo Assessment of AAV Capsid Variants

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Introduction AAV capsid engineering requires efficient and reliable in vivo evaluation of large numbers of candidate variants. Current approaches, which typically assess reporter gene expression in separate animals, are limited by throughput, cost, and inter-animal variability. To overcome these limitations, we developed CAMEL (Capsid Assessment via a Multiplexed Epitope-tagging Library), a platform enabling parallel, multi-level in vivo evaluation of multiple capsid variants within a single animal.

Methods Each capsid variant in CAMEL encodes a unique epitope-tagged reporter gene, enabling integrated multiplexed analysis at the levels of vector DNA distribution, transgene mRNA, and protein expression. The antibody-based detection system was systematically screened and optimized across 15 candidate epitope tags. Six tags were excluded due to poor detectability, high background, or cross-reactivity, while nine tags demonstrated stable expression and high specificity in mammalian cells and mouse tissues. Among multiple reporter proteins evaluated (firefly luciferase, modified Gaussia luciferase, GST, and EGFP), EGFP exhibited superior expression stability and overall performance and was therefore selected as the reporter. Multiplexed qPCR was optimized using variant-specific barcode primers in combination with tag-targeted TaqMan probes, replacing conventional shared-primer amplification strategies, which reduces amplification bias. Competitive effects in mixed-delivery conditions were assessed by comparing co-injected and individually injected groups.

Results Barcode primer-based qPCR yielded quantification results consistent with theoretical template ratios and reduced the competitive suppression of low-abundance variants observed with conventional multiplex qPCR using shared primers. mRNA expression levels in the liver, heart, and muscle showed no significant differences between co-injected and individually injected groups, indicating minimal competitive inhibition in the multiplexed system. Six muscle-targeting capsids, including four novel candidates, along with MyoAAV 1A and AAV9, were concurrently evaluated in mice. mRNA expression levels corresponded closely with protein expression levels. The platform faithfully recapitulated the known

muscle-targeting specificity and reduced liver tropism of MyoAAV 1A. Several novel variants demonstrated more than a 10-fold enhancement in skeletal muscle transgene expression, while the capsid BY103 exhibited 9- to 23-fold increase in cardiac transgene expression compared with AAV9.

Conclusion CAMEL enables scalable, accurate, and parallel in vivo screening of AAV capsids, providing a powerful platform for the rapid identification of tissue-targeting variants, including a novel capsid with substantially enhanced cardiac transgene expression.

3029 Novel AI-designed AAV capsids targeting Integrin alpha V beta 6 shows superior muscle transduction, especially in diaphragm and enables effective low-dose gene therapy in muscular dystrophy models

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Introduction

Adeno-associated virus (AAV)–mediated gene therapy has shown clinical promise for monogenic diseases, including Muscular Dystrophies (MD), yet its broader application remains limited by the need for very high systemic doses, dose-related toxicities, exclusion of patients with pre-existing neutralizing antibodies, and substantial manufacturing burden. Improving skeletal and cardiac muscle targeting while minimizing off-target transduction is therefore a central challenge in the field.

We previously demonstrated that cross-species AAV myotropism can be achieved by redirecting capsid tropism toward the conserved integrin αVβ6 receptor. Using a rational, structure-guided design strategy, we generated LICA1, a first-generation αVβ6-targeting capsid that enabled efficient, muscle-restricted transduction across species, including minipigs and non-human primates. Consequently, LICA1 has driven effective low-dose gene therapy in various DMD and LGMD models, both *in vitro* (2D human myotubes and 3D organoids derived from healthy donor or DMD patients) and *in vivo* (mouse and rat). In a severe LGMDR3 mouse model, systemic administration at 5E12 vg/kg resulted in ~100% myofiber transduction in skeletal muscles and >60% in the severely affected diaphragm and functional rescue. In DMD mouse model, low-dose delivery (5E12 vg/kg) of micro-dystrophin achieved comparable transduction efficiency and functional rescue, significantly outperforming AAV9. In a DMD rat model, LICA1-mediated delivery of dual-AAV mini-dystrophin (4E13vg/kg/AAV) enabled near-complete transduction of all examined skeletal and cardiac muscles, fully restoring muscle function to wild-type levels.