Advancing AAV Capsid Engineering for Targeted Gene Therapy Using PackGene's π-Icosa Platform

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Introduction

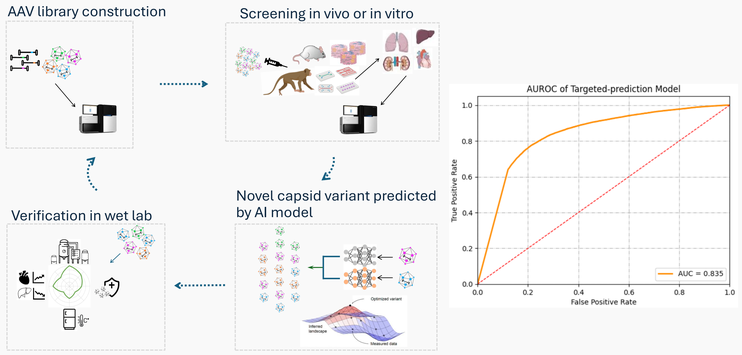
Adeno-associated virus (AAV) vectors are widely utilized in gene therapy for their ability to deliver genetic material to specific tissues with minimal immunogenicity. However, clinical application remains limited by suboptimal tissue targeting, inefficient transduction, and low manufacturability. Traditional methods of capsid development often fall short in addressing these multifaceted challenges. To bridge this gap, PackGene has developed the π-Icosa Capsid Engineering Platform—a next-generation solution that integrates rational design, directed evolution, and artificial intelligence to create capsids with enhanced specificity, efficacy, and production efficiency. This platform is designed to accelerate the discovery of novel AAV variants tailored for therapeutic delivery across CNS, muscle, eye, and immune tissues.

π-Icosa Capsid Engineering Platform

The π-Icosa platform is a multi-phase system for AAV capsid library construction, in vivo screening, and optimization. It enables the identification of top-performing capsid variants with improved tissue tropism and minimized off-target expression.

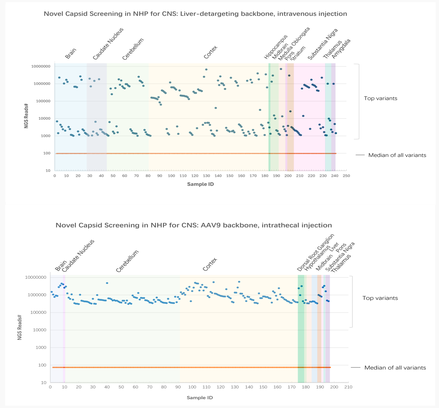
Key features include:

- AI-Based Capsid Design:
  - Incorporates a proprietary transformer-based prediction model pre-trained using protein language models.
  - Achieved AUC of 0.83 on directed evolution datasets for tissue-specific targeting.
- Workflow Overview:
  - AAV library construction
  - In vivo/in vitro screening
  - AI-predicted capsid variant selection
  - Experimental validation



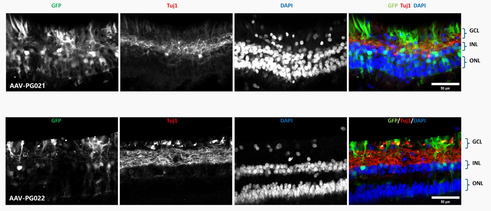
Result 1: CNS-Targeting AAVs in NHP

Ongoing screening of novel capsids derived from AAV9 and liver-detargeted backbones shows promising CNS transduction after intravenous administration.



Result 2: Retinal-Targeting Capsids in NHP

Variants PG021 and PG022 demonstrated effective transduction of retinal ganglion cells (RGCs), Müller glia, and INL cells.



PG021、PG022 - Retina targeting capsid screened from NHP

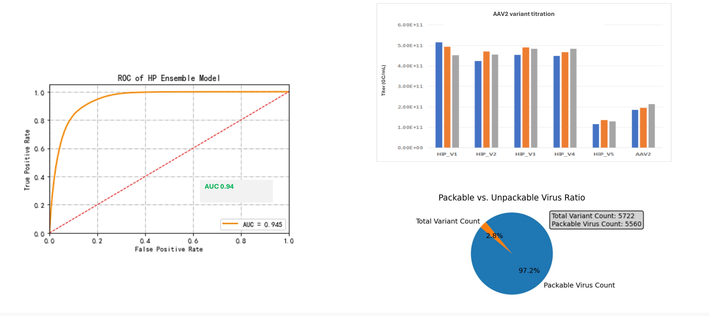
Result 3: Broad Tissue-Specific Capsid Library

Pre-screened libraries yielded optimized capsids targeting CNS, muscle, and ocular tissues.

Species	Organ	Injection	Novel capsid
Mouse	CNS	Intravenous injection	PG008
	Muscle	Intravenous injection	PG007
NHP	Muscle	Intravenous injection	PG007(screened from mouse but works well in NHP) PG0016,PG017, PG018, PG019, PG020
	CNS	Intrathecal injection	5 high potential variant in validation
		Intravenous injection	
	Eye/Cochlea	Local injection therapy	PG021, PG022, PG023
	Joint	Local injection therapy	2nd round NGS data analysis
	Liver, Kidney, Lung	Intravenous injection	2nd round screening
Human	T-cell	Infection	PG009, PG010, PG012, PG013, PG014

Result 4: Manufacturability Prediction Model

AI-guided selection produced high-yield AAV2 variants with packaging efficiencies up to 97% and 2–3x higher titers than wildtype.



High-yield AAV2 variant with tissue specificity generated by AI model

Reference

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