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# MEMBRANE-ASSOCIATED ACCESSORY PROTEIN VARIANTS CONFER INCREASED AAV PRODUCTION

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## PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Published Application	20250304920	10/02/2025	2022-120

## BRIEF DESCRIPTION

The inventors have developed an engineering approach to identify novel and nonobvious membrane-associated accessory protein (MAAP) sequence variants that confer increased Adeno-associated virus (AAV) secretion during packaging. The technique is based upon the iterative process of sequence diversification and selection of functional gene variants known as directed evolution.

First, the inventors generated a library of more than 1E6 MAAP variants. The variants were subjected to five rounds of packaging into an AAV2 capsid for which MAAP expression was inactivated without altering the viral protein VP1 open reading frame (ORF) (AAV2-MAAP-null). Among each iterative packaging round, the inventors observed a progressive increase in both the overall titer and ratio of secreted vector genomes conferred by the bulk selected MAAP library population. Next-generation sequencing uncovered common mutational features that were enriched up to over 10,000-fold on the amino acid level. Individual MAAP variants were isolated and systematically tested for effect on recombinant AAV2-MAAP-null packaging in HEK293 cells.

The inventors predict that this work may be applicable to increasing per-cell AAV output in industrial settings, potentially reducing global costs and increasing functional vector recovery in downstream manufacturing processes.

## BACKGROUND

Parvoviruses are small, single-stranded DNA viruses that are ubiquitously found in many animal species. AAV is a prototypic dependoparvovirus whose replication cycle requires the function of helper genes from larger co-infected viruses such as Adenoviruses or Herpesviruses. The natural genome of AAV contains ~4.7 kb of ssDNA that encodes up to ten known proteins in a highly overlapped fashion. The rep gene encodes four protein products named based on their molecular weight: Rep72 and Rep68 facilitate genomic replication, whereas Rep52, and Rep40 play essential roles in loading nascent ssDNA genomes into assembled capsids. Downstream of rep lies the cap gene, which encodes three known protein products off of overlapping reading frames: VP1, VP2, and VP3 are structural proteins that assemble to form the capsid, the assembly activating protein (AAP) targets VP proteins to the nucleus and is involved in capsid assembly. The most recently discovered AAV-encoded gene is the membrane-associated accessory protein (MAAP). MAAP is encoded by an alternative ORF in the AAV cap gene that is found in all presently reported natural serotypes. Gene delivery by recombinant AAV (rAAV) have shown significant success in both research and clinical gene therapy applications. In the rAAV system, Rep and Cap are removed from between AAV's 5' and 3' inverted terminal repeats (ITRs) and provided in trans. Instead, a transgene of interest is inserted between the ITRs and subsequently packaged into the nascent AAV capsids. However, manufacturing quantities of good manufacturing practice (GMP)-grade rAAVs necessary to achieve current and projected dosing requirements—particularly in a clinical context—presents a significant hurdle to expanding rAAV-based gene therapies. Recently, evidence has emerged supporting a functional role of MAAP in AAV egress. This led to the hypothesis that MAAP could be engineered to facilitate increased levels of secreted AAV produced from HEK293 cells.

## CONTACT

Terri Sale  
terri.sale@berkeley.edu  
tel: 510-643-4219.



## INVENTORS

» Schaffer, David V.

## OTHER INFORMATION

### KEYWORDS

MAAP sequence variants, AAV-based gene therapy

## CATEGORIZED AS

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## RELATED CASES

2022-120-0

## SUGGESTED USES

Suggested uses include incorporation of the described membrane-associated accessory protein (MAAP) sequences into stable producer cells to improve internal manufacturing processes of adeno-associated virus (AAV)-based gene therapy vectors or parvovirus-based vaccines.

## ADVANTAGES

The technology has the potential to reduce global costs and increase functional vector recovery in downstream manufacturing processes.

## RELATED MATERIALS

### ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- ▶ [Human Central Nervous System \(CNS\) Targeting AAV Variants](#)
- ▶ [Improving Packaging and Diversity of AAV Libraries with Machine Learning](#)



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2150 Shattuck Avenue, Suite 510, Berkeley, CA 94704

Tel: 510.643.7201 | Fax: 510.642.4566

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