497 S06-098: Novel AAV capsids with new transduction and nonimmune properties

Asset Overview

Product Type	Gene therapy
Indication	Genetic disorder
Current Stage	Discovery
Target(MoA)	hepatocellular carcinoma, mutations in somatic cells
Brief Description	Researchers from Dr. Mark Kay's laboratory at Stanford University have merged desirable qualities of multiple natural AAV isolates by an adapted DNA family shuffling technology to create a complex library of hybrid capsids from eight different wild-type viruses. One of the capsids was vectorized and used to express the human transgene factor IX in mice. This AAV vector was found to be as robust or better than the best AAV vector identified in nature to date. Moreover, this capsid does not react with the human immune response. Finally, this capsid is useful for transducing cells in culture, which has been problematic for many of the AAV vectors studied to date.
Organization	Stanford university

Differentiation

☐ **Gene Therapy Market by Vector Type**

- Gene therapy can fix the underlying defect and provide a path to produce the functional protein
- The global gene therapy market was valued at $584 million in 2016, and is estimated to reach $4,402 million by 2023, registering a CAGR of 33.3% from 2017 to 2023

☐ **Adeno-Associated Virus Gene Therapy**

- Adeno-associated virus (AAV) is a versatile viral vector technology that can be engineered for very specific functionality in gene therapy applications
- AAV has been shown to be safe and effective in preclinical and clinical settings
- AAV can be used in a wide range of clinical applications in multiple diseases due its unique biological and biophysical properties

☐ **Hybrid AAV serotype, AAV-DJ**

- AAV-DJ is distinguished from its closest natural relative (AAV-2) by 60 capsid amino acids
- AAV-DJ mediates efficient gene targeting in keratinocytes at clinically relevant frequencies with a low rate of random integration
- AAV-DJ based somatic cell targeting is a promising strategy for ex vivo therapy for this severe and often lethal epithelial disorders

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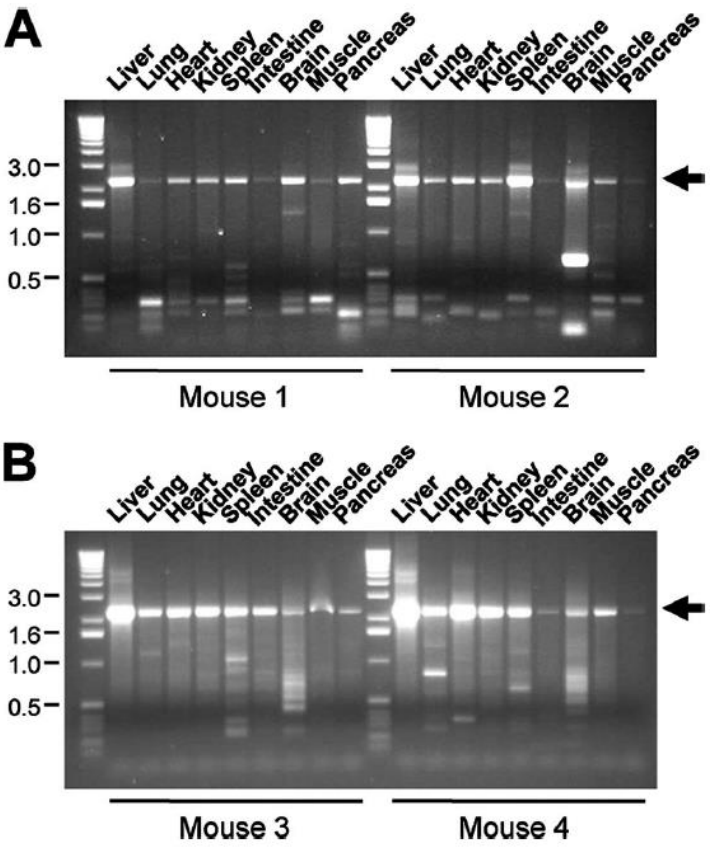
Key Data

AAV capsid library biopanning in all major organs



Biodistribution of AAV capsid libraries following peripheral delivery (via tail vein injection). Wild-type FVB mice were infused with 5 x 1011 particles of the shuffled (A) or AAV-DJ-based peptide display (B) library, and 1 week later, all major organs were harvested for the preparation of total genomic DNA. AAV DNA genomes were detected via PCR using primers flanking the entire cap gene (2.2 kb; arrows). Numbers (in kilobases) on the left refer to a DNA size marker. Shown are results from two representative mice per injection protocol. Note that AAV DNA signals could be detected in all analyzed tissues, including brain tissue, highlighting the potential for the biopanning and evolution of AAV capsids in all major organs in vivo. (Shuffled; AAV-2, AAV-4, AAV-5, AAV-8, AAV-9, avian and bovine AAV)

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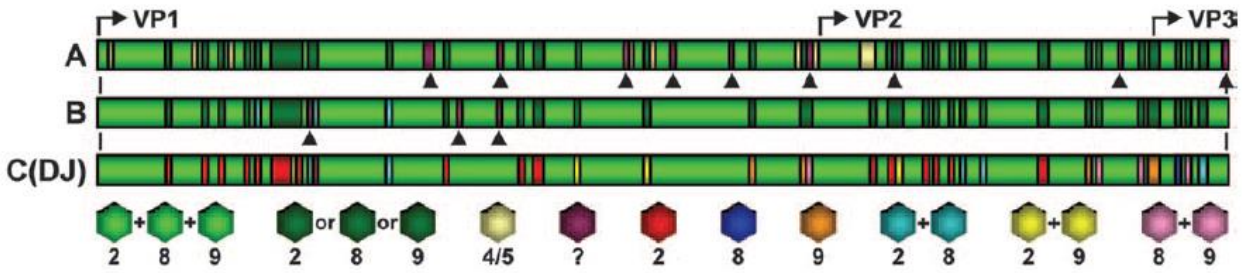
Molecular evolution of AAV vectors via DNA family shuffling



First 217 amino acids of the VP1 capsid protein for each pool. Colors represent the relationships to the parental strains (serotypes 2, 4, 5, 8, and 9). Arrowheads represent point mutations. Start codons for all three capsid proteins are shown. Pool C contained a single clone, designated AAV-DJ.

In vitro infectivities of AAV-DJ and wild-type vectors

Cell line	Tissue or cell type	Infectivity of vector:									
		AAV-1	AAV-2	AAV-3	AAV-4	AAV-5	AAV-6	AAV-8	AAV-9	AAV-DJ	AAV-DJ/8
Huh-7	hu liver	4e3	5e2	2e4	2e6	4e5	5e3	7e4	**7e6**	1e2	3e5
293	hu kidney	2e3	5e2	2e4	7e5	4e5	1e4	7e4	**7e5**	1e2	2e5
HeLa	hu cervix	7e4	2e3	1e5	**2e6**	3e4	2e5	1e6	**2e6**	3e2	1e6
HepG2	hu liver	2e6	5e4	3e5	2e7	3e6	1e6	2e7	**ND**	4e3	1e7
Hep1A	mu liver	1e4	2e3	1e6	2e5	2e6	2e5	1e6	**2e7**	5e2	2e6
911	hu retina	6e3	1e3	9e3	5e5	7e5	6e3	1e6	**ND**	2e2	4e5
CHO	ha ovary	1e4	1e4	7e4	7e5	3e3	2e4	1e5	**1e6**	4e1	2e5
COS	si kidney	3e3	1e3	3e3	3e4	2e4	7e3	5e4	**2e5**	2e2	3e5
MeWo	hu skin	2e3	2e2	1e3	7e4	3e3	2e3	2e4	**1e5**	7e0	2e4
NIH3T3	mu fibroblasts	2e5	2e4	7e5	7e5	7e6	2e5	7e6	**ND**	4e3	2e7
A549	hu lung	7e4	1e4	5e4	**ND**	2e6	1e5	2e6	7e6	1e3	2e7
HT1180	hu fibroblasts	5e4	1e4	1e5	7e6	3e6	3e4	2e6	**1e7**	3e3	5e6
Monocytes	hu primary monocytes	9e5	1e7	**ND**	**ND**	8e6	7e5	**ND**	**ND**	1e7	**ND**
Immature DC	hu monocyte-derived DC	8e5	2e7	**ND**	**ND**	9e6	7e5	**ND**	**ND**	1e7	**ND**
Mature DC	hu monocyte-derived DC	9e5	2e7	**ND**	**ND**	6e6	6e5	**ND**	**ND**	2e7	**ND**

Each cell line was infected with 10-fold serial dilutions of each serotype, AAV-DJ, or the mutant AAV-DJ/8 expressing a gfp reporter gene. Vector preparations were normalized to contain 2 x 109 total (vector DNA-containing) particles per ml prior to infection. Three days later, green fluorescent protein-expressing cells were counted and infectious titers were determined by taking into account the dilution factor. Numbers shown are average ratios (rounded) of total to infectious AAV particles from at least three independent titrations. Lower numbers indicate higher levels of infectivity. For each cell line, values corresponding to the most efficient AAV are underlined, while boldface indicates the lowest level of efficiency. AAV-DJ vectors showed the highest levels of infectivity on all tested cell lines. hu, human; mu, murine; ha, hamster; si, simian; DC, dendritic cells; ND, not detectable (>2 x 107).

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Intellectual Property

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