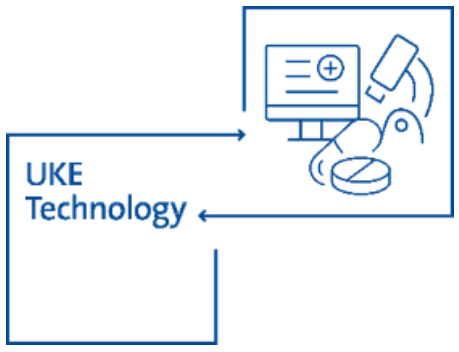

Viral vectors for gene transfer into vascular endothelial cells after systemic administration

Background & Innovation

Gene therapy holds great promise for treating a wide range of diseases across different organs. The method of gene transfer is of crucial importance for a therapeutic success. Adeno-associated virus (AAV)–based vectors are among the most successful gene delivery systems and are already used in approved gene therapies. While some organs like the liver are transduced rather easily after intravenous injection of different available AAV serotypes, other organs like the brain either require more invasive methods of vector application, or they depend on molecularly tailored AAV capsid variants optimized for the intended target tissue.

Vascular diseases represent a large group of serious conditions for which gene therapy would ideally be delivered intra-venously. However, currently available AAV vectors lack sufficient cell-specific vascular endothelial tropism and predom-inantly accumulate in liver hepatocytes. This off-target liver transduction can lead to severe and potentially fatal side effects and limits the applicability of systemic AAV gene therapy.

To date, numerous capsid-modified AAV vectors with endothelial tropism have been described in the prior art; however, none of these have been applied in gene therapy for vascular diseases in humans or appear to be as suitable for this purpose as the present invention.

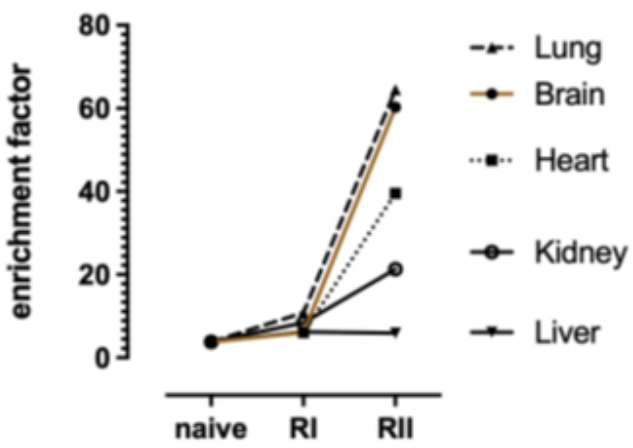

Fig. 1: Change in the frequency of the DWP motif in peptides during selection

Technical Description

We present here novel capsid-modified AAV vectors with enhanced targeting of vascular endothelium. These vectors demonstrate preferential accumulation in endothelial cells of the brain, heart, and lung tissue after intravenous administration in non-human primates, along with highly efficient transduction of human microvascular endothelial cells from these organs, while showing markedly reduced transduction of human hepatocytes.

Endothelial cell–specific peptide sequences were identified using randomized AAV2 capsid libraries. Following multiple in vivo selection rounds in the common marmoset, next-generation sequencing revealed a surprising enrich-ment of AAV2 capsid variants containing the amino acid motif DWP (aspartic acid–tryptophan–proline) in well-perfused organs such as brain, heart, and kidney (see figure 1). Subsequent in vitro studies in primary human microvascular endo-thelial cells from multiple organs confirmed that DWP-displaying AAV variants achieve superior endothelial transduction com-pared with natural AAV serotypes 1–9, while reducing off-target effects. These findings establish the DWP motif as a novel endothelial-targeting element and provide a robust platform for directing therapeutic agents, including recombinant viral vectors, to endothelial cells.

Competitive advantage

- Innovative vectors with high and precise transduction efficiency for human vascular endothelial cells and low affinity for hepatocytes.
- Targeted therapeutic treatment of a vascular or metabolic disorder or disease.
- Ex vivo studies demonstrate increased transduction efficiency in primary human cells from the above-mentioned organs, accompanied by reduced transduction of hepatocytes.

FOCUS SECTORS

- Therapeutics
- Gene therapy
- Vascular diseases
- Capsid-modified AAV vectors

PROJECT KEY WORDS

- Tropism
- Vascular endothelium
- Cell-specific peptide sequences

DEVELOPMENT STATUS

- Lead compound identified and validated
- In vitro efficasy demonstrated

PATENT PROCEDURE STATUS

- EP Patent application filed

POTENTIAL FOR COOPERATION

- R&D Cooperation
- Licensing

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