Gene therapy targets the brain vasculature

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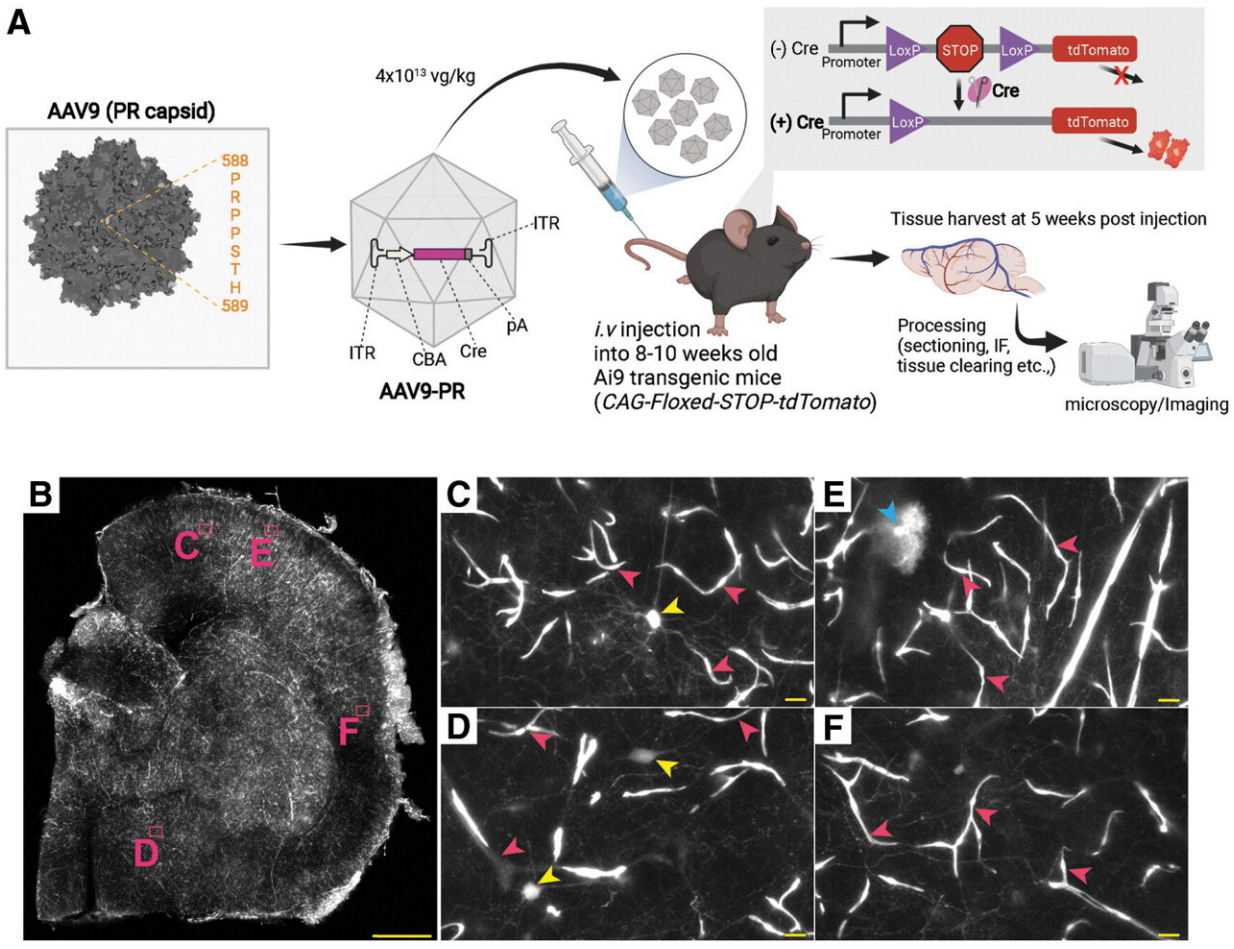

AAV-PR-CBA-Cre mediates vasculature-tropic transduction and gene modification in transgenic Ai9 mice (*CAG-floxed-STOP-tdTomato*). (A) AAV-PR peptide and insertion site. The peptide PRPPSTH is inserted after amino acid 588 of AAV9 VP1. A Cre-recombinase expression cassette is packaged inside AAV-PR and this is administered systemically to Ai9 mice, which contain a floxed-stop-tdTomato cassette in all cells. If AAV-PR mediates Cre expression, the loxP-stop is removed from the genome allowing tdTomato expression. (B)

Half brain hemisphere of Ai9 mouse injected i.v. with AAV-PR-CBA-Cre showing bright intrinsic fluorescence (*white* signal). *Letters* (C–F) indicate areas of zoomed images in (B). The cells that were transduced had morphology consistent with the vasculature (*pink arrowheads*), and neurons (*yellow* and *blue arrowheads*). Scale bar in (B) = 500 μm. (C–F) = 10 μm. AAV, adeno-associated virus; CBA, hybrid CMV early/chicken β-actin promoter; i.v., intravenous. Credit: *Human Gene Therapy* (2023). DOI: 10.1089/hum.2022.211

Researchers have developed an engineered adeno-associated virus (AAV) vector that yields high transduction of brain vascular pericytes and smooth muscle cells. The study describing the characterization of this novel AAV capsid is published in the journal *Human Gene Therapy*.

In the current study, Servio Ramirez, from Temple University School of Medicine, Patricia Musolino, from Massachusetts General Hospital, and Casey Maguire, from Harvard Medical School, and coauthors, characterize AAV-PR, the capsid that demonstrated high transduction of the brain vasculature.

AAV-PR offers the possibility of genetically modulating brain pericytes and smooth muscle cells in the context of neurodegeneration and other neurological diseases, according to the investigators. Many common neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis, involve the brain vasculature.

"Because so many neurologic conditions stem from vascular dysfunction, the ability to deliver genes to the cells comprising these vessels could be truly paradigm shifting," says Editor-in-Chief Terence R. Flotte, MD, Celia and Isaac Haidak Professor of Medical Education and Dean, Provost, and Executive Deputy Chancellor, University of Massachusetts Chan Medical School.

More information: Servio H. Ramirez et al, An Engineered Adeno-Associated Virus Capsid Mediates Efficient Transduction of Pericytes and Smooth Muscle Cells of the Brain Vasculature, *Human Gene Therapy* (2023). DOI: 10.1089/hum.2022.211