AAV9

Adeno associated virus serotype 9 (AAV9) vector has engendered considerable interest in its therapeutic development for treating neurological disorders, in part because it has been heralded as capable of traversing the blood brain barrier to target the central nervous system (CNS), where it has been shown to transduce astrocytes and neurons.

Systemic injection of AAV9 vectors provides widespread delivery to the brain and potentially the tumor/microenvironment.

Crommentuijn et al assessed AAV9 for potential glioblastoma therapy using two different promoters driving the expression of the secreted anti-cancer agent sTRAIL as a transgenic model; the ubiquitously active chicken Beta actin (CBA) promoter and the neuron-specific enolase (NSE) promoter to restrict expression in brain. Intravenous injection of AAV9 vectors encoding a bioluminescent reporter showed similar distribution patterns, although the NSE promoter yielded 100-fold lower expression in the abdomen (liver), with the brain-to-liver expression ratio remaining the same. The main cell types targeted by the CBA promoter were astrocytes, neurons and endothelial cells, while expression by NSE promoter mostly occurred in neurons. Intravenous administration of either AAV9-CBA-sTRAIL or AAV9-NSE-sTRAIL vectors to mice bearing intracranial patient-derived glioblastoma xenografts led to a slower tumor growth and significantly increased survival, with the CBA promoter having higher efficacy.

This is the first report showing the potential of systemic injection of AAV9 vector encoding a therapeutic gene for the treatment of brain tumors [1)].

Spinal pia membrane represents the primary barrier limiting effective AAV9 penetration into the spinal parenchyma after intrathecal AAV9 delivery. We develop a novel subpial AAV9 delivery technique and AAV9-dextran formulation. We use these in adult rats and pigs to show (i) potent spinal parenchymal transgene expression in white and gray matter including neurons, glial and endothelial cells after single bolus subpial AAV9 delivery; (ii) delivery to almost all apparent descending motor axons throughout the length of the spinal cord after cervical or thoracic subpial AAV9 injection; (iii) potent retrograde transgene expression in brain motor centers (motor cortex and brain stem); and (iv) the relative safety of this approach by defining normal neurological function for up to 6 months after AAV9 delivery. Thus, subpial delivery of AAV9 enables gene-based therapies with a wide range of potential experimental and clinical utilizations in adult animals and human patients [2)].

1)
Crommentuijn MH, Kantar R, Noske DP, Vandertop WP, Badr CE, Würdinger T, Maguire CA, Tannous BA. Systemically administered AAV9-sTRAIL combats invasive glioblastoma in a patient-derived orthotopic xenograft model. Mol Ther Oncolytics. 2016 Jun 22;3:16017. doi: 10.1038/mto.2016.17. eCollection 2016. PubMed PMID: 27382645.
2)
Miyanohara A, Kamizato K, Juhas S, Juhasova J, Navarro M, Marsala S, Lukacova N, Hruska-Plochan M, Curtis E, Gabel B, Ciacci J, Ahrens ET, Kaspar BK, Cleveland D, Marsala M. Potent spinal parenchymal AAV9-mediated gene delivery by subpial injection in adult rats and pigs. Mol Ther Methods Clin Dev. 2016 Jul 13;3:16046. doi: 10.1038/mtm.2016.46. eCollection 2016. PubMed PMID: 27462649.