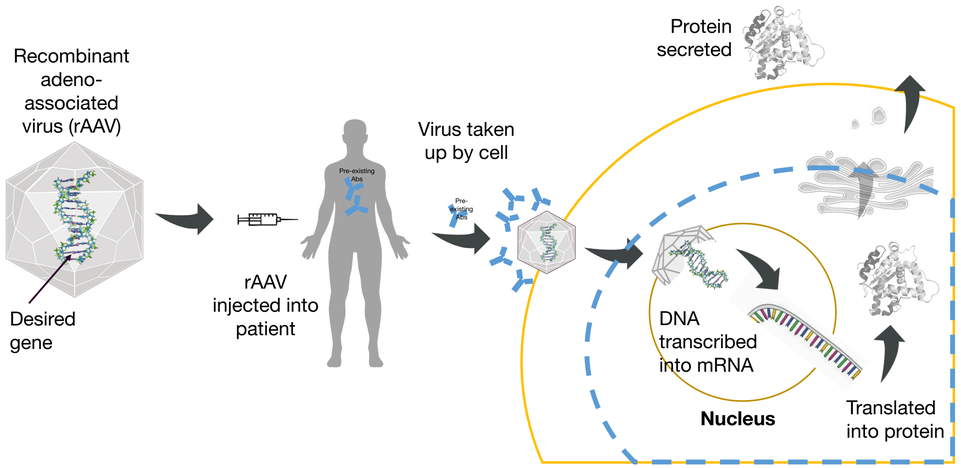
celerion
Translating Science to Medicine

Patient-Screening in AAV Gene Therapy: Only High Anti-AAV Titers Impact Transduction and Efficacy



Aligning Bioanalytical and Diagnostic Strategies for Effective Patient Pre-Screening

Marketed AAV therapies and their anti-AAV screening approach (adapted from 1)

Name	Hemgenix	Roctavian	Beqvez	Zolgensma	Elevidys	Luxturna	Upstaza
Serotype	AAV5	AAV5	AAVRh74var	AAV9	AAVrh74	AAV2	AAV2
transgene	hFIX-Padua	BDD hFVIII	FIX-Padua	SMN1	mini dystrophin	RPE65	ADCC
ROA	intravenous infusion	intravenous infusion	Intravenous infusion	intravenous infusion	intravenous infusion	subretinal injection	infused into putamen
Disease	Hem B	severe Hem A	Hem B	SMA	Duchenne muscular dystrophy	IRD with RPE65 mutation	AADC deficiency
Patient age	adults	≥18 years	≥18 years	<2 years	4–5 years	pediatrics, adults	≥18 months
SOC	ERT	ERT	ERT	N/A	steroids	N/A	N/A
Approved in	USA, EU (conditional)	USA, EU	USA	USA, EU, Japan	USA	USA, EU	EU
Patient selection in pivotal trials	no patient selection	no AAV5 TAbs	no AAVRh74var Tabs	TAb titer ≤50	AAVrh74 Ab titers <400	no patient selection	AAV2 NAb titers ≤20
Patient selection after GT launch (product label)	no patient selection requested	select AAV5 Tab-negative patients using CDx	no AAVRh74var TAbs	AAV9 TAb testing recommended;	select patients with AAVrh74 TAb titers <400	no patient selection requested	no patient selection requested
Companion diagnostic	no CDx	AAV5 DetectCDx Kit (USA); no CDx (EU)	nAbCyte approved CDx	no CDx (USA, EU); MEBCDX AAV9 test (Japan)	no FDA-authorized test for AAVrh74 TAb	no CDx[c]	no CDx

Risk-benefit assessment based on preexisting anti-AAV antibodies [1]

	High	Medium	Low
Business risk	high seroprevalence with high titers likely reduces the number of eligible patients in case of, e.g., systemic administration	high seroprevalence with low titers or low seroprevalence might potentially affect the number of eligible patients in case of, e.g., systemic administration	seroprevalence has a lower impact on the number of eligible patients in case of, e.g., local administrations, in particular to “immune privileged” tissues

		AAV screening required	AAV screening considered	AAV screening not necessary
Patient risk	Standard of Care (SOC) and Disease Severity	Disease manageable with approved SOC. Example: haemophilia	no optimal SOC available. Example: Alzheimer’s disease	no SOC available. Examples: Duchenne muscular dystrophy
	Route of administration	Systemic administration. examples: hemophilia A/B	Local administration into target tissues. examples: intracoronary or intramuscular administration	Local administration to “immune privileged” tissues. example: subretinal or into putamen administration

Clinical trial design strategy

- Avoid development of IVD assays for early clinical development to speed-up clinical enrolment
  - ✓ Use bioanalytical assays for non-patient management endpoints
  - ✓ Use ready-validated assays in clinical laboratories for patient management decisions
- Allow for additional timelines and budget for Lab Developed Tests (LDT) for IVD

General Considerations

- Investigational Device Exemption (IDE) and IVDR for Lab Developed Tests (LDT) are a considerable effort
- Clinical Laboratory accreditation is unusual for Bioanalytical laboratories
- Accreditation agencies don’t have a process for Bioanalytical laboratories

Download Poster

Johannes Stanta, PhD
Celerion
Johannes.stanta@Celerion.com

Reference:
Braun M, Lange C, Schatz P, Long B, Stanta J, Gorovits B, Tarcsa E, Jawa V, Yang TY, Lembke W, Miller N, McBlane F, Christodoulou L, Yuill D, Milton M. **Preexisting antibody assays for gene therapy: Considerations on patient selection cutoffs and companion diagnostic requirements.** Mol Ther Methods Clin Dev. 2024 Feb 20;32(1):101217.