Adaptable PBPK-QSP gene therapy model applied to i.v. administration of AAV-2 across different species

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Objectives

Modeling biodistribution & transduction

- Translation of gene therapy dose from animals to humans is not easily predictable
- Recently, PBPK and QSP approaches have been used to better understand the mechanisms that impact gene therapy distribution to tissues of interest and efficiency of gene transduction[1-3]
- We present a PBPK-QSP model capable of representing the biodistribution of any Adeno-associated virus (AAV) or Lipid Nanoparticle (LNP) vector
- AAV-2 delivered by i.v. administration is used as case study, leveraging available mouse and non-human primate (NHP) data from preclinical models

Methods

Mouse to human calibration

- The virtual species were calibrated to model biodistribution in relevant tissues

	Parameters	Mouse	NHP	Human
Extracellular parameters	PBPK values	Taken from literature		
	Tissue permeability	Calibrated →	From mouse values; similar across species	
	Number of cells per tissue	Estimated from literature		
	Binding rates (per total # of receptors)	Calibrated →	Scaled from NHP	
Intracellular parameters	Transport rates	Taken or estimated from literature →	From mouse values; similar across species and tissues	
	Clearance rates			
	Other rates (uncoating, AAV-to-dsDNA conversion rate…)	Calibrated →		

Conclusions

Versatile gene therapy research tool

- The PhysioPD® Platform can:
  1. Simulate different biodistribution scenarios and perform transgene protein analysis
  2. Predict upon calibration based on human clinical data
  3. Be adapted and extended to include local delivery to inaccessible tissues, such as the ocular space, and other routes of administration, such as intravitreal delivery
- Parameters can be modified to:
  1. Reflect both local and systemic routes of administration
  2. Target any prioritized tissues of interest
  3. Use any AAV or LNP vector
  4. Deliver desired payload
  5. Assess the biodistribution of non-native AAVs, such as engineered capsids

PBPK-QSP Model

AAV Gene Therapy PhysioPD® Platform

- The four identical compartments (C1-4) include vasculature, tissue, and cellular representation comprising membrane, cytoplasm, and nucleus (Fig. 1). These compartments are connected through the plasma
  1. Extracellular processes occur in the vasculature and tissue (AAV biodistribution) (Fig.2)
  2. AAV binds tissue receptors at the membrane to enter the cell cytoplasm
  3. Intracellular processes take place in the cell cytoplasm and nucleus (AAV transport and uncoating; mRNA translation)
  4. Transgene protein is produced and transported to the plasma

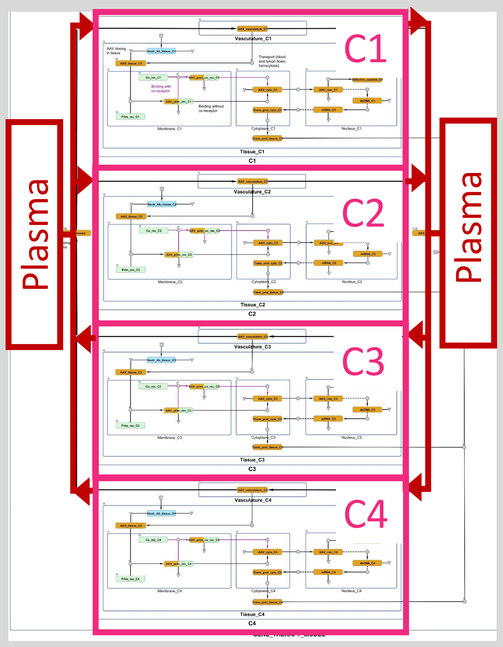

Figure 1. The AAV Gene Therapy PhysioMap® is a PBPK structure. Close-up of compartment C1 in figure below

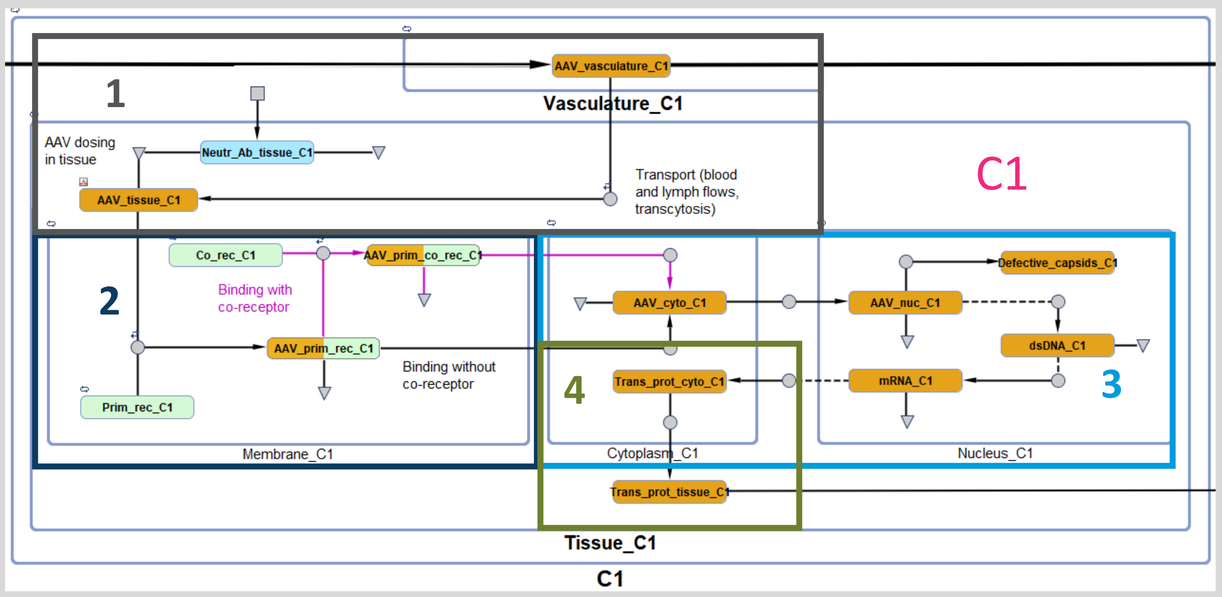

Figure 2. Graphical representation of a generic tissue compartment

Results

AAV levels in target tissues are consistent with data

- The main readout is calculated by adding vector genomes in all tissue compartments and dividing the total by the mass of DNA in the tissue
- Mouse calibration:
  - Korbelin et al.[4] reported AAV vector genome per mass of DNA at 2 min and 2 weeks post-administration (Fig. 3 green bars)
  - The Platform also captured 33% of viral particles remaining in blood at 2 min (not shown)
- NHP calibration:
  - Mori et al.[5] provided data for NHP calibration at 12 weeks after administration
  - The empty dots represent the AAV concentrations of four NHPs; the solid dot represents the mean concentration (Fig. 4)

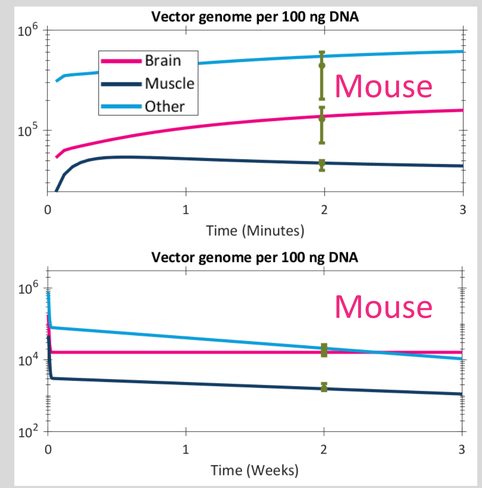

Figure 3. AAV levels in mouse tissue at 2 min (top) and 2 weeks (bottom)

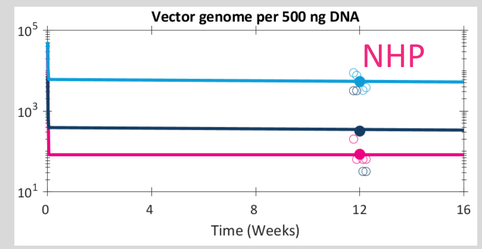

Figure 4. AAV levels in NHP tissue

- Human predictions:
  - AAV biodistribution for an i.v. dose scaled from NHP (Fig. 5)
  - Qualitative comparison of Factor IX activity in plasma[1] with protein levels predicted by our Platform (Fig. 6)

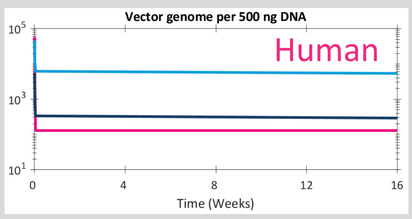

Figure 5. AAV levels in human tissue

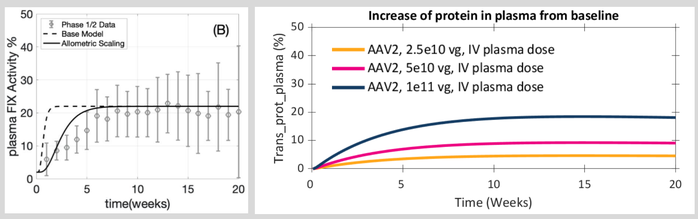

Figure 6. Published protein levels[1] (left) vs our simulation (right)

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