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INTRODUCTION: AAV GENE THERAPY

- Adeno-associated virus (AAV): A promising vector to deliver functional gene to patients with monogenic disorders
- Following infusion (IV) vectors reach target tissue, transduce cells, and cells express therapeutic protein

MOTIVATION: QSP APPROACH FOR GENE THERAPY

- As a new treatment modality, exposure-response for AAV gene therapy is not established yet
- Quantitative Systems Pharmacology modeling approach can integrate all available data (in vitro, pre-clinical in vivo) to guide human translation and dose prediction

OBJECTIVES: LIVER TARGETED GENE THERAPY MODEL

- Leverage QSP model for clinical application in Pfizer's Hemophilia B gene therapy trial to predict:
 - Cohort mean and individual patient Factor IX levels in blood
 - Dose-response prediction at higher doses
 - Dynamics following IV dosing

METHODS: QSP FRAMEWORK FOR HEMOPHILIA B GENE THERAPY

- AAV Distribution:** A minimal PBPK framework to capture biodistribution of vector capsids to liver following IV dosing
- AAV Intracellular Processing and Transduction:** Receptor binding, Endocytosis, Nuclear transport, Uncoating steps modeled
- Transgene Expression and Protein Distribution:** Transcription, Translation and Pharmacokinetics of distribution of secreted Factor IX

CONCLUSIONS:

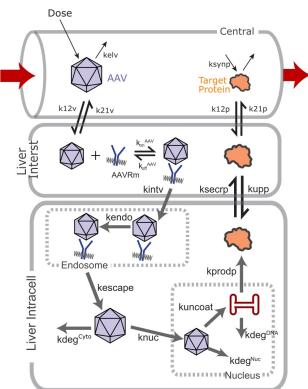
- Detailed QSP models capturing biological mechanisms between exposure and response can be calibrated integrating data from multiple studies
- Well-calibrated pre-clinical model and a clinical translation strategy can be used to inform dose selection and predict dynamics as well as dose-response relationships
- Models can offer testable predictions for mechanistic hypotheses

FUTURE APPLICATIONS:

- Adapt the Hemophilia B calibrated model for other liver targeted applications such as Hemophilia A
- Calibrate model to other AAV serotypes used in liver-targeted GTx
- Hypothesize mechanisms for observed non-linear (threshold-like) dose response in Hemophilia A gene therapy clinical trials^[2]

MODEL DEVELOPMENT

MODEL SCHEMATIC



MODEL CALIBRATION & VALIDATION

- Calibration of mouse model to published data (AAV8)^{[3][4]}
- Validation of mouse model. Model predicts linear transduction dose-response, in agreement with published data from multiple sources

APPLICATION: HEMOPHILIA B GENE THERAPY

- Vector: Fidanacogene elaparvovec (FidaVec)
- AAV capsid: Spark100 (Bioengineered)^[5]
 - Transgene: human Factor IX (hyperactive mutant)
 - Promoter: Liver specific
- Clinical trial data from Phase 1/2 study up to one year^[1]:
- Dose: 5×10^{11} vg/kg
 - 15 participants, mean Factor IX level 22% of normal

RESULTS

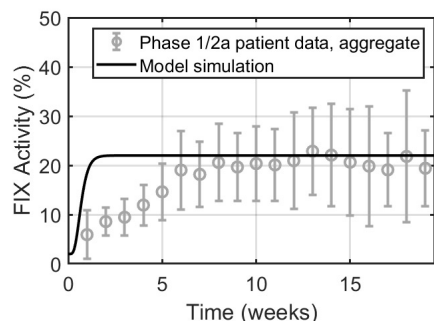


Figure 1: Model schematic for liver-targeted AAV gene therapy with intravenous infusion

HUMAN TRANSLATION OF MOUSE MODEL

Figure 2: Human model simulation (solid black line) at 5×10^{11} vg/kg dose of FidaVec compared to aggregate phase 1/2 patient data Human model predicts much faster time to steady state than observed in patients

In all figures: grey circles represent Mean +/- SD

HYPOTHESES FOR SLOW ACCUMULATION OF FACTOR IX IN HUMANS

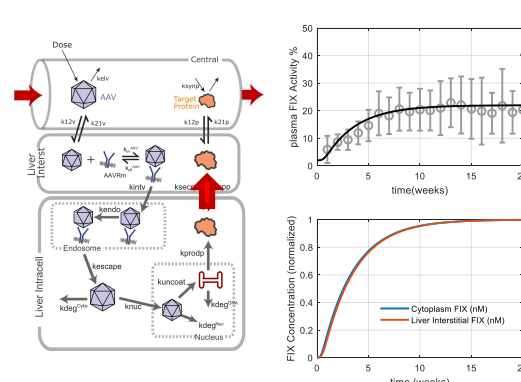
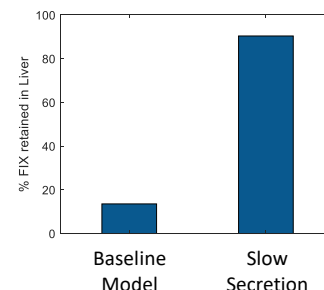
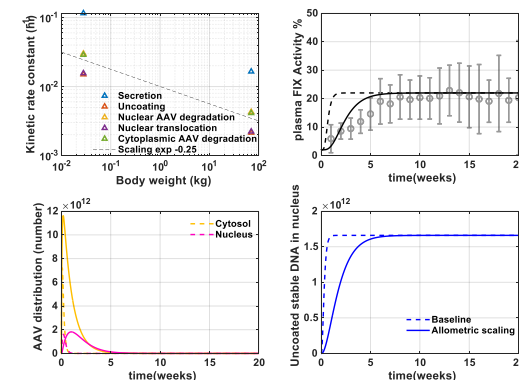


Figure 3: Model simulations with hypothesis of slow secretion of Factor IX protein from hepatocytes (red arrow). Panels on the right show fit to aggregate patient data, and slow accumulation of FIX in hepatocytes (bottom)

Figure 4: The hypothesis of slow secretion Factor IX would consequently result in high retention in the liver



RESULTS



- Figure 5: (a) Allometric scaling of AAV intracellular processing steps with species. (b) Model with species scaling (solid lines) can match observed clinical data (grey circles).
- Hypothesis can be tested by measuring dynamics of:
 - Intact viral capsid copies in cellular fractions (c)
 - Uncoated viral genome in nucleus (d)
- Scaling rates by bodyweight would result in longer times for clearance of viral capsids from cellular fractions in larger species

REFERENCES

[1] George L. et al, NEJM, 2017
 [2] Leavitt et al., American Society of Hematology Annual Meeting (December 2020) presentation
 [3] Tenney et al., J. Virol, 2014
 [4] Thomas et al, J Virol 2004
 [5] Anguela X et al, J Thromb Haemost, 2015; Suppl2:324-325
 [6] Hurlbut et al, Mol Ther, 2010
 [7] Inagaki et al, Mol Ther, 2006

DOSE-RESPONSE PREDICTION

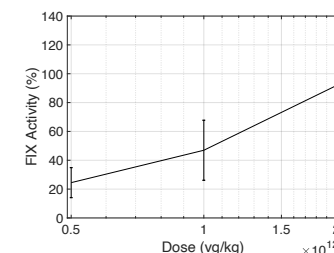


Figure 6: Dose response prediction. Model can be leveraged to predict mean Factor IX activity as well as standard deviation (individual Factor IX activity) at higher doses of FidaVec

- Linear dose-response prediction in line with previous non-clinical and clinical studies of HemB Gene Therapy^{[3][4][6][7]}