

Development of a framework for mechanistic modelling and interspecies scaling for AAV gene therapy

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A modular framework to support the development of AAV gene therapies, reducing uncertainty and enhancing adaptability across various vectors, transgenes, tissues, and preclinical species

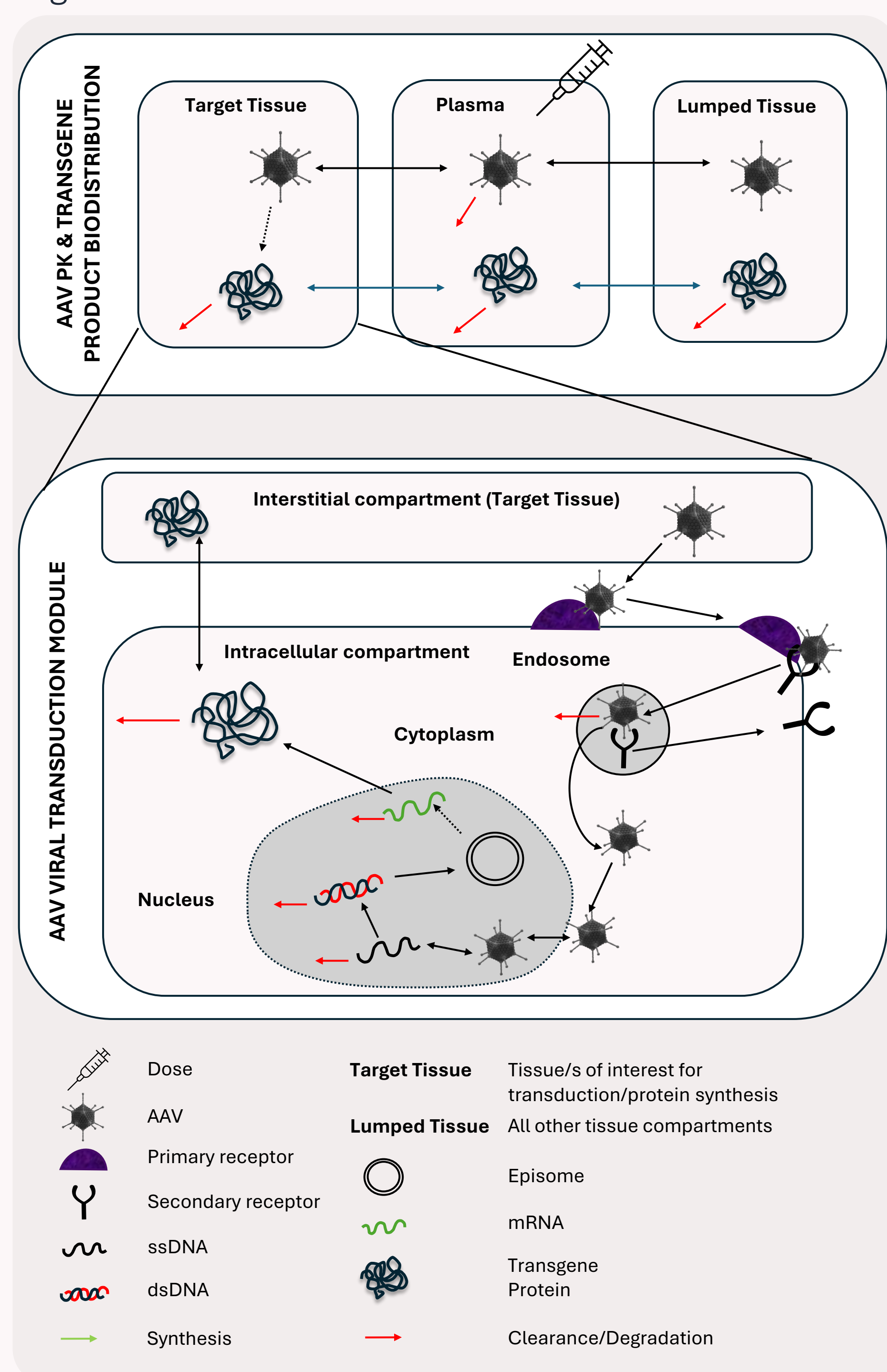
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Background and Objective

We developed a generic framework for mechanistic modelling of AAV gene therapeutics to capture their non-trivial PK/PD behaviour and to support translation across species, which is challenging with standard allometric approaches [1].

Methods

Fig. 1: Model framework



Our framework consists of three distinct modules 1) AAV PK/biodistribution, 2) AAV viral transduction model, and lastly, 3) transgene product (protein) biodistribution model. A fourth module linking expressed protein to disease pathway can be added where necessary. The model is based on ordinary differential equations. The first module describes PK-like distribution and clearance of the administered viral particles. The AAV viral transduction model involves virus internalization and downstream intracellular processes, which have been described previously [1-3]. The stable transduction is linked to transcription and protein synthesis from the transgene. Secretion of the synthesized protein and its downstream biodistribution is modelled in module 3. The model is largely parameterized using physiological parameters and mechanistic knowledge around viral transduction pathway. Vector and transgene-specific model parameters may be tuned using preclinical data, where available. Literature data on AAV PK and protein therapeutics and their biodistribution can be leveraged for parameterizing respective modules. Interspecies scaling approaches are applied to each module separately to arrive at the final scaled model. Next, we demonstrate the application of our framework using a case study based on anonymized data.

Results

We applied our framework to an anonymized case study based on data from multiple species including mouse, rat, non-human primates and human. In this example,

- Protein biodistribution (of transgene product) in preclinical species is parameterized using exposure data in plasma and various tissues after administration of recombinant protein therapeutic to mice (Fig. 4, Top). This module is scaled using standard mechanistic/physiology-based approaches and the predictions validated using available clinical data using the recombinant protein therapeutic (Fig. 4, Bottom).
- AAV PK is described using compartmental modelling and is scaled using standard allometric approaches and the predictions are validated using PK data from multiple species (Fig. 5).
- AAV viral transduction model, calibrated to mouse data and scaled for NHPs, captures viral transduction as well as transcription data of both species (Fig. 6 and Fig. 7).
- Transgene protein expression does not scale adequately using standard allometric approaches and a new power-law-based approach with an exponent of -2.6 was necessary to translate this module (Fig. 2 and 3). The combined scaled model including all the modules was used to predict human dose-response relationship from preclinical data.

Fig. 2: Transgene protein dose response

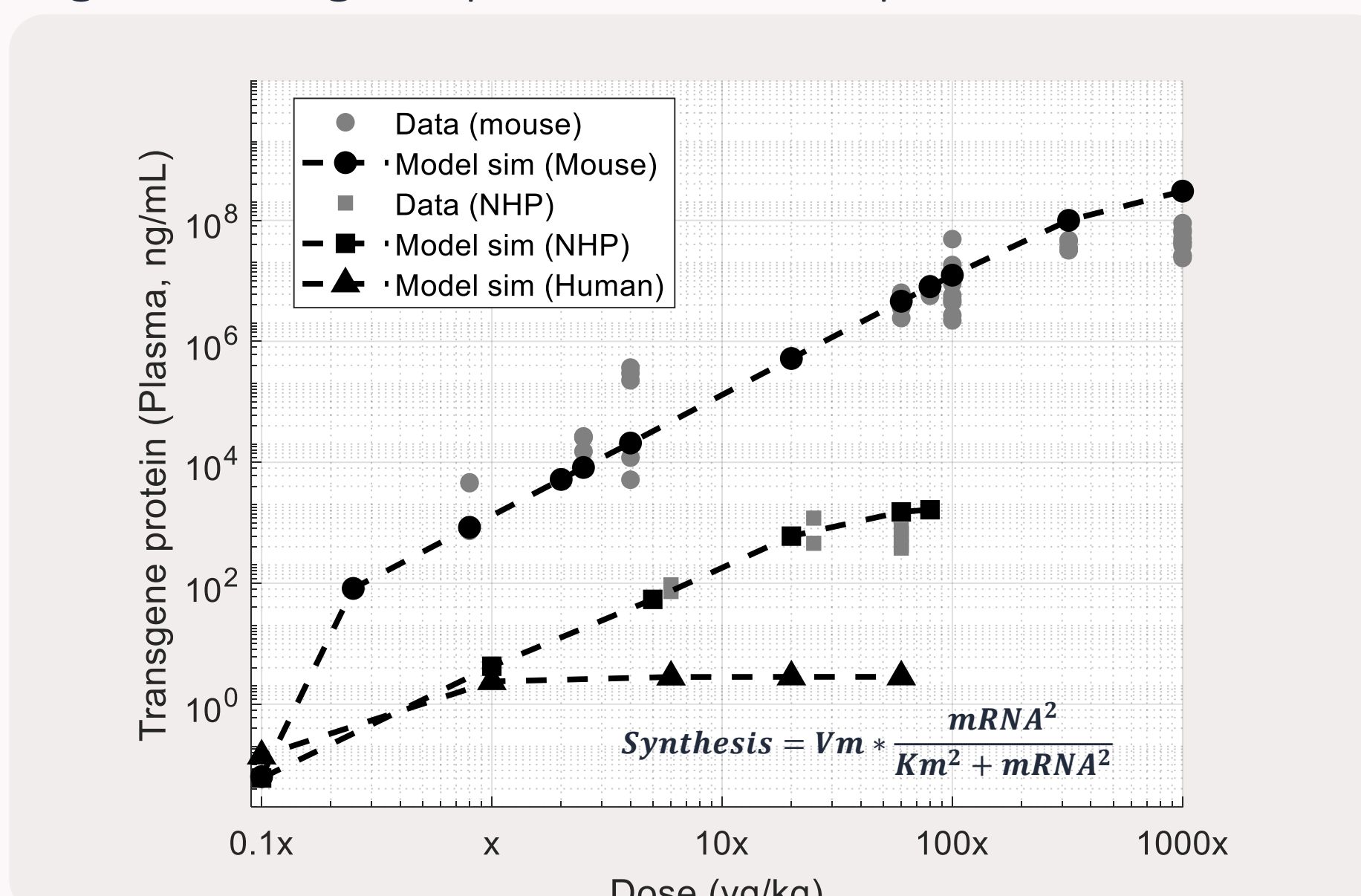
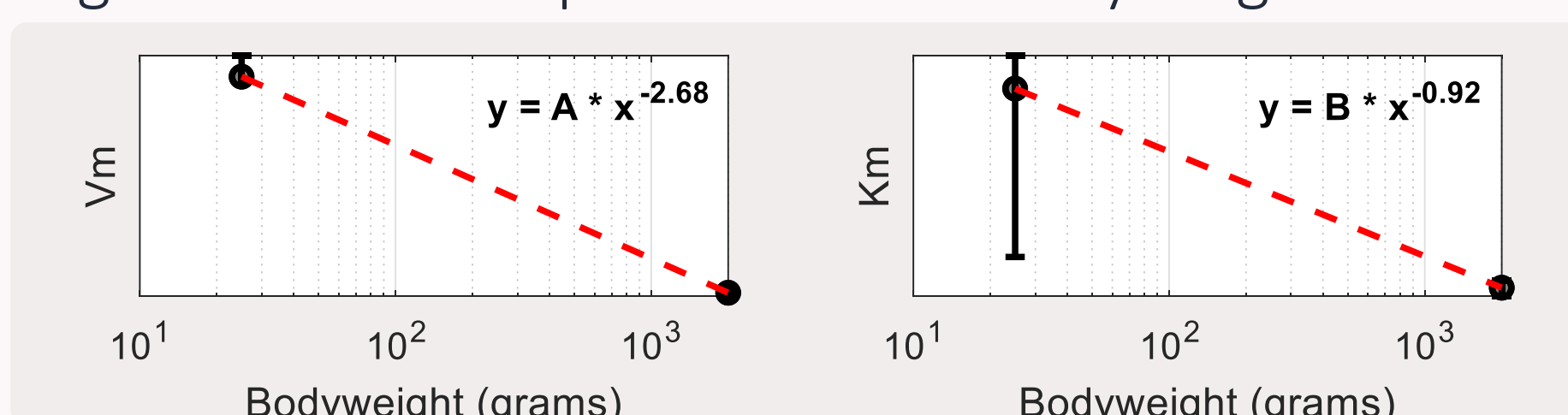


Fig. 3: Translation parameters vs Bodyweight



Discussion/Conclusion

We have developed a modular framework to support AAV gene therapy development. This framework describes complex PK/PD relationships, translates dose-response, and isolates processes where traditional scaling doesn't apply. It can be tailored to each AAV gene therapy program and allows us to draw on literature data/knowledge to reduce uncertainty in scaling of dose-response for better prediction of efficacious human doses. Its transgene/therapeutic area agnostic nature supports a diverse portfolio of AAV-based therapies.

Our framework has successfully supported FIH starting dose justifications for IND submissions. By improving dose-response predictions, it streamlines development and addresses unique AAV gene therapy challenges, fostering a robust pipeline of therapeutic options.

Additional Figures

Fig. 4: Transgene protein biodistribution

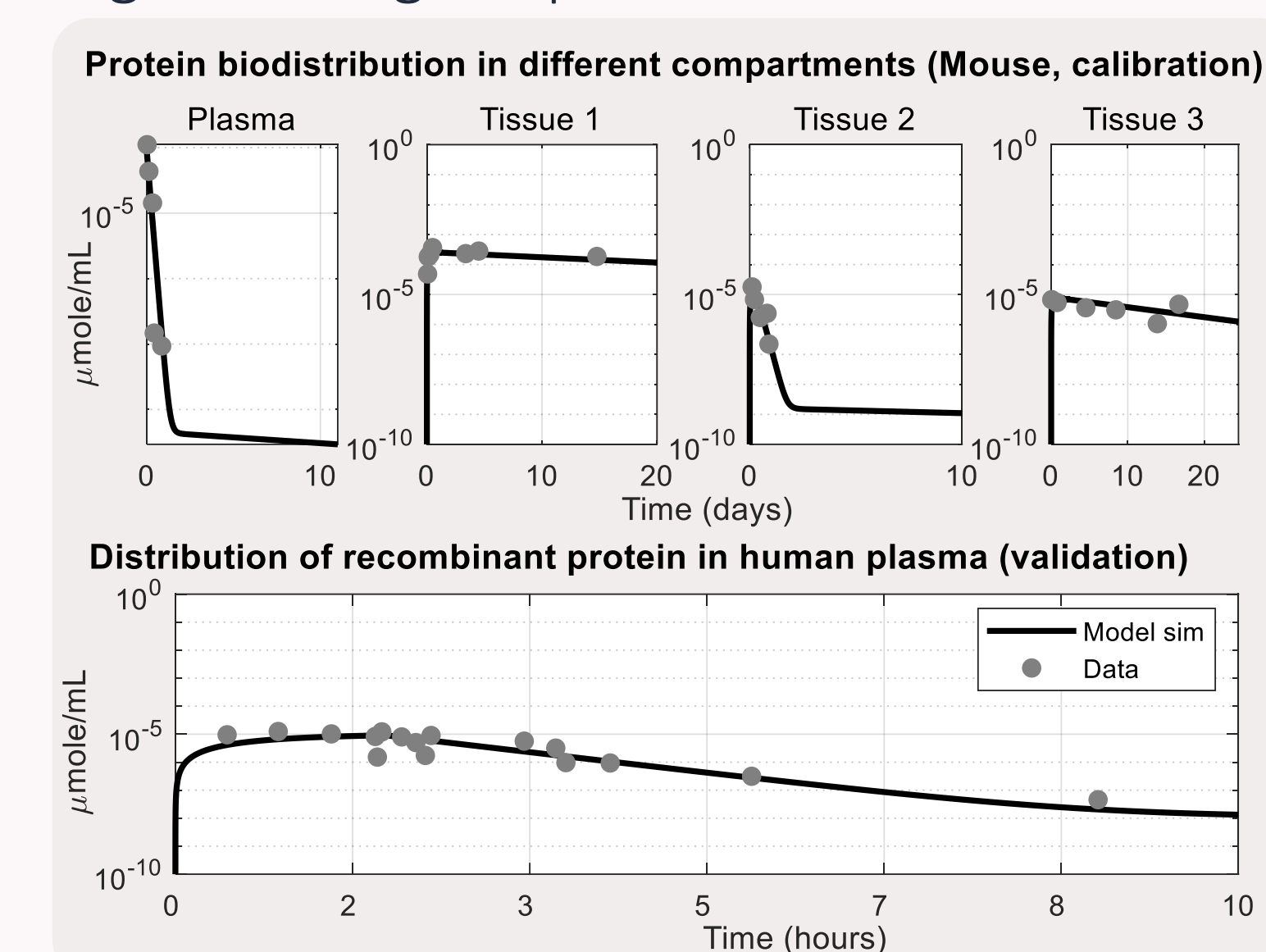


Fig. 5: PK model parameters. Black points represent fitted values, and red line refers to values allometrically scaled (using rat model as base)

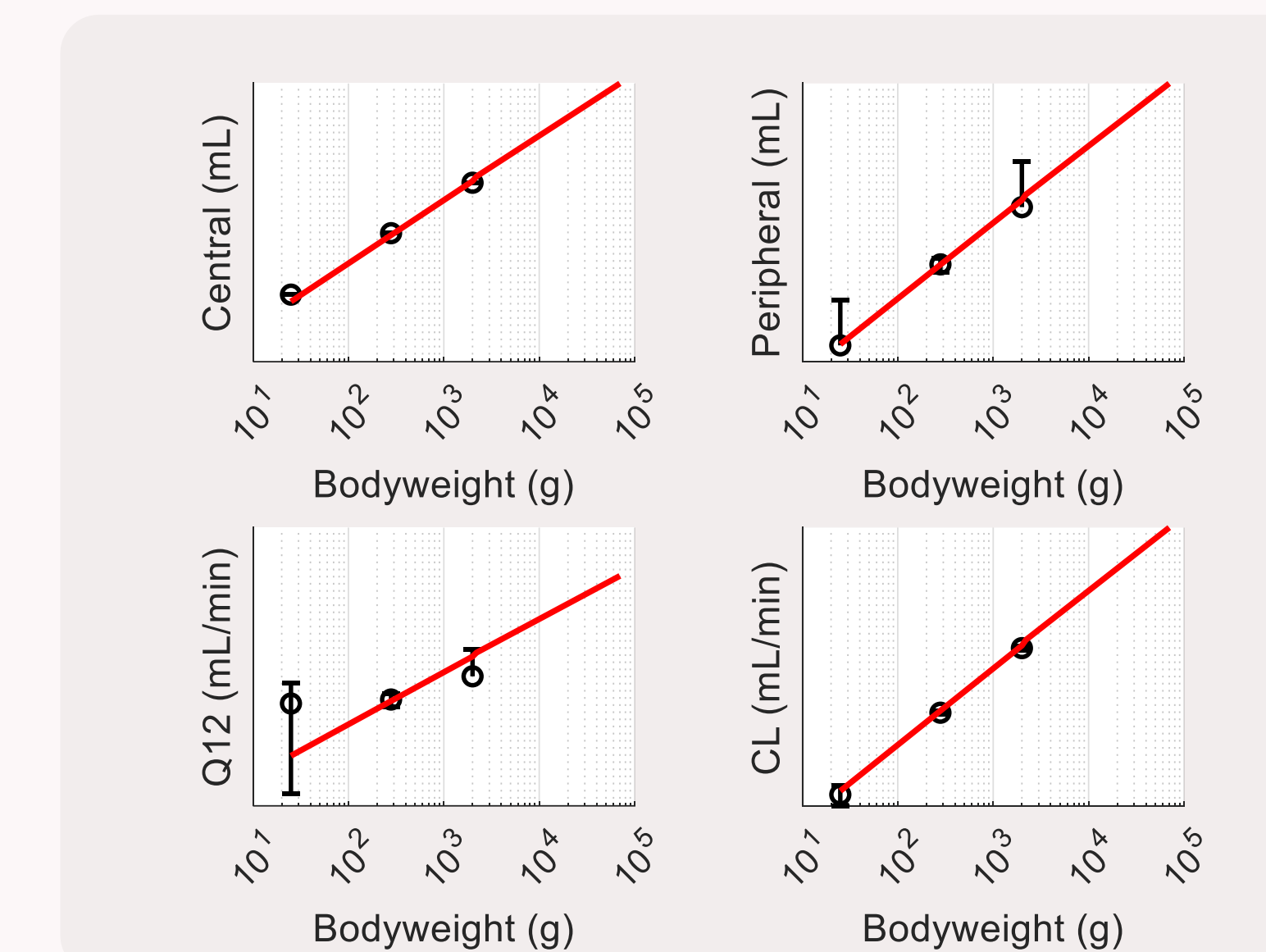


Fig. 6: VGCN in target tissue vs dose

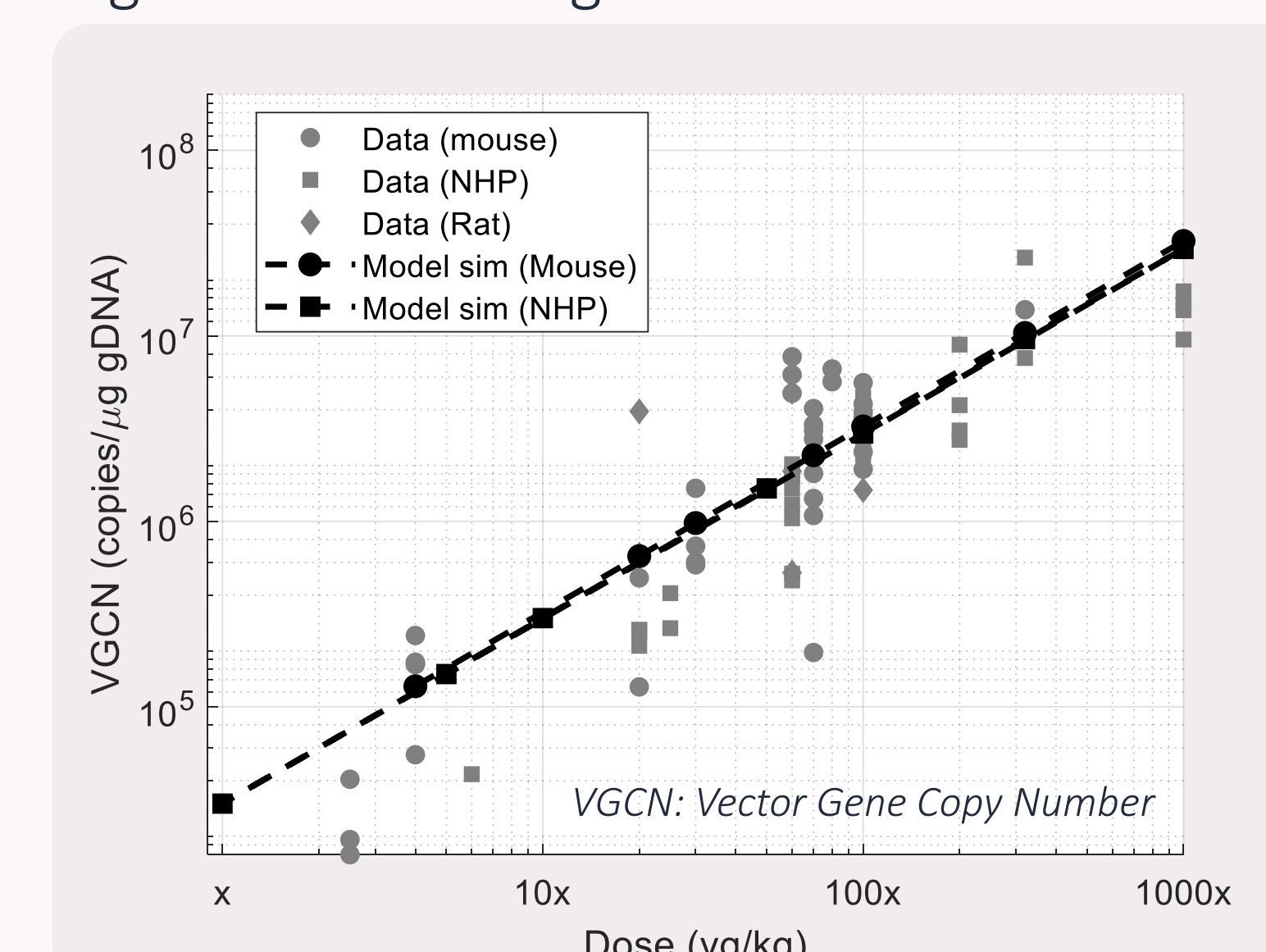
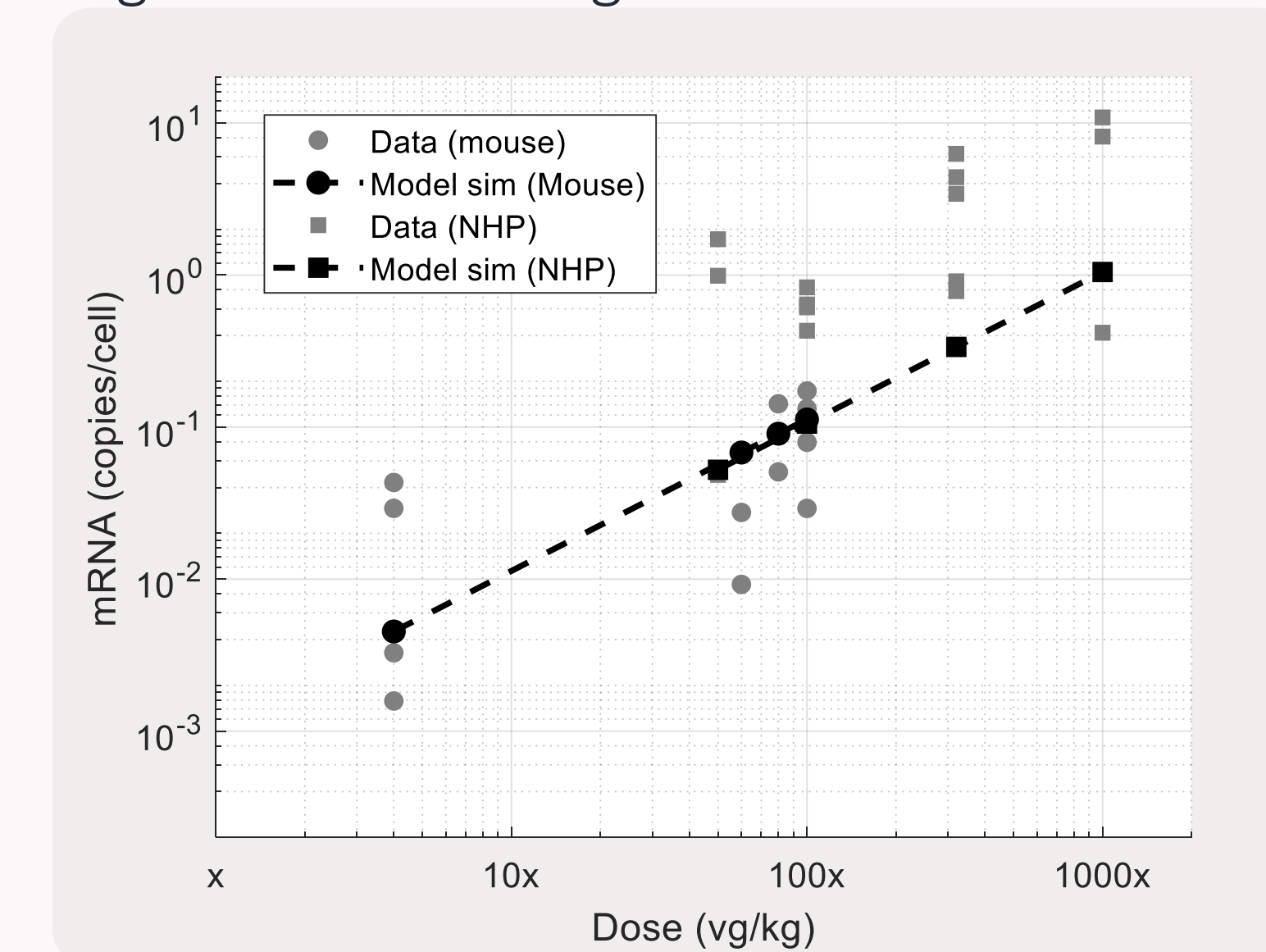


Fig. 7: mRNA in target tissue vs dose



References

- Rao et al., 2023. In: *Quantitative Systems Pharmacology*, pp. 61–86.
- Kamiya et al., 2003. *Drug Discovery Today*, 8(21), 990–996.
- Lagache et al., 2012. *Biophysical Journal*, 102(5), 980–989.
- Varga et al., 2001. *Molecular Therapy*, 4(5), 438–446.



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