Supporting the development and optimization of mRNA-encoded therapeutics through a multiscale Physiologically Based Pharmacokinetic (PBPK) platform

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Background

In recent years, antibody-based therapeutics have shown promise, particularly in cancer treatment.
mRNA therapies harness the cellular machinery to instruct the production, within the patient's own cells, of therapeutic proteins tailored to their specific needs.
This innovative approach involves encapsulating the mRNA within lipid nanoparticles (LNPs), which provide a protective environment that reduces the likelihood of protein degradation, enhancing the effectiveness and longevity of the treatment.
Along with these new technologies comes the need for robust tools to explore the intricate dynamics of drug trafficking at the whole-body level and its efficacy.

Our model

We expanded upon a two-pore Physiologically-Based Pharmacokinetic (PBPK) model to simulate recombinant and mRNA-encoded protein trafficking. An entirely **new model layer** describing **LNP trafficking and uptake**, and **mRNA translation and clearance** was added to the PBPK model developed by Sepp *et al.* [1] (Fig. 1,2).

The model was also extended to support various administration routes, including intravenous, intradermal, and intramuscular injections.
Key drug-dependent parameters, including clearance uptake, FcRn affinity, and mRNA translation, were identified. This facilitates the adaptation of the model for fitting and validation across a broad spectrum of mRNA-based therapeutics.

The model was implemented using MATLAB2023b SimBiology.

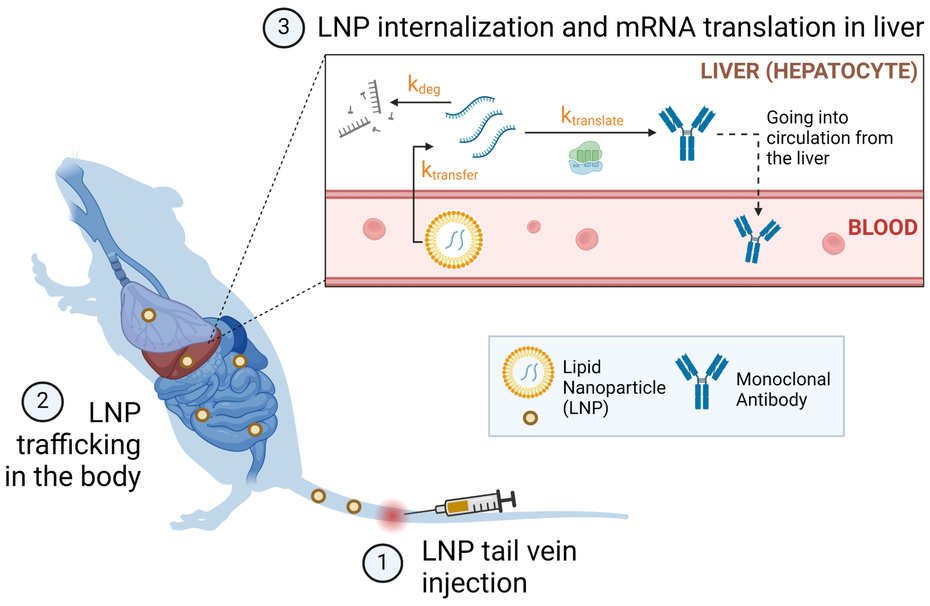

Fig. 1: New layer of the PBPK describing LNP injection, trafficking, and internalization and mRNA clearance, and translation. Created with BioRender.com

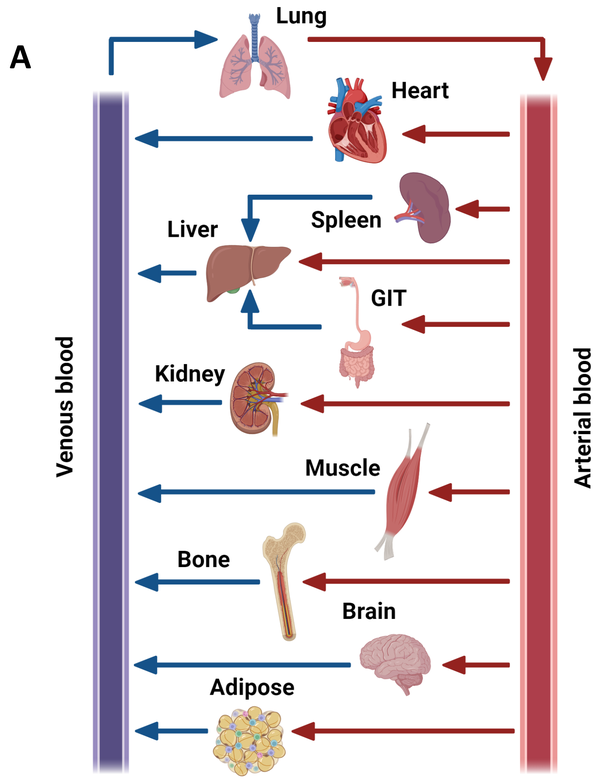

Fig. 2: (A) Structure of the whole-body PBPK model. (B) Structure of a generic tissue for monoclonal antibodies according to the two-pore hypothesis and the catabolism FcRn-mediated recycling in the endosomal space. Created with BioRender.com.

Results: model training and validation

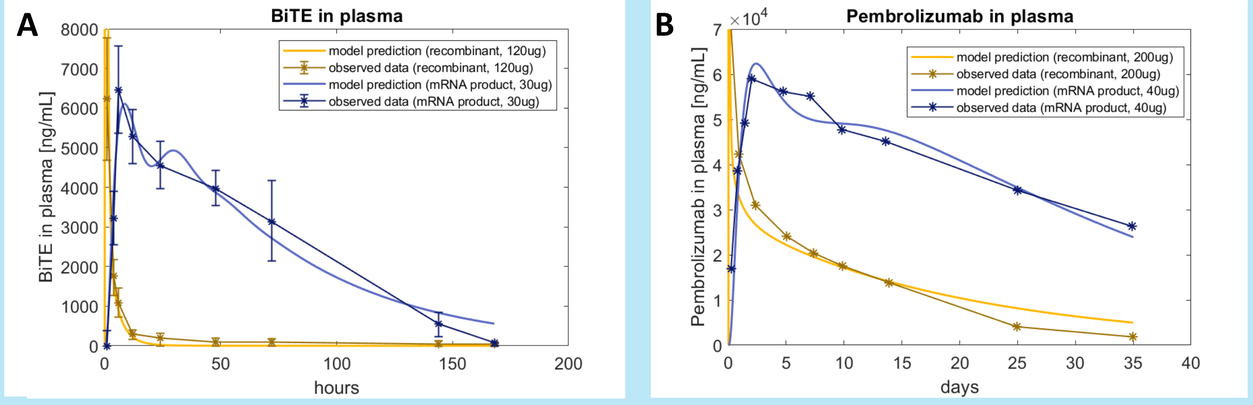

Fig. 3: Model fitting and observed data for plasma concentration of BiTE (A) and Pembrolizumab (B).

In both fittings, the parameters' calibration has been computed for the recombinant (yellow) and the mRNA-encoded (blue) protein.

Our model demonstrated good accuracy in fitting publicly available time-series PK data for mRNA-encoded proteins of various sizes. Specifically, we used the following studies to calibrate and validate our model:

- Huang *et al.* [3]: This study focused on the B7H3xCD3 Bispecific T-cell Engager (BiTE).
- Wu *et al.* [4]: This study centered on Pembrolizumab, a commercial anti-PD-1 mAb.

Both papers focus on cancer treatment and provide PK time-series for the recombinant and the mRNA-encoded protein, both used to calibrate and test the model (Fig. 3).
Despite differences in protein size and the presence or absence of the Fc receptor, our platform was successfully calibrated and validated in both cases (Fig. 4). This highlights its adaptability and versatility in supporting dose-finding applications for a range of mRNA-based therapeutics.

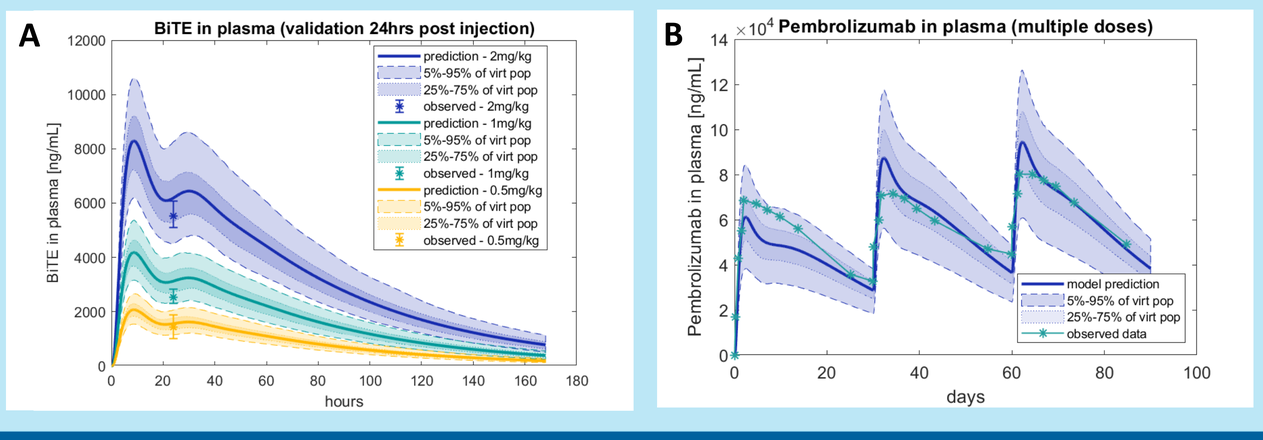

Fig. 4: Model validation performed on different dosages for BiTE (A) and on a multiple-dose regimen for Pembrolizumab (B) using virtual populations based on model predictions for plasma concentration. Simulated dynamics are overlapped with observed data.

Identifiability analysis

Among the rates of the mRNA model layer (Fig. 1), the parameter describing the mRNA degradation was derived from the literature, while the other parameters have been fitted.

An identifiability analysis utilizing GENSSI [2] was conducted on the estimated model parameters, resulting in their **global structural identifiability**, hence the possibility of uniquely determine their values from a single PK timeseries of the therapeutic in plasma.

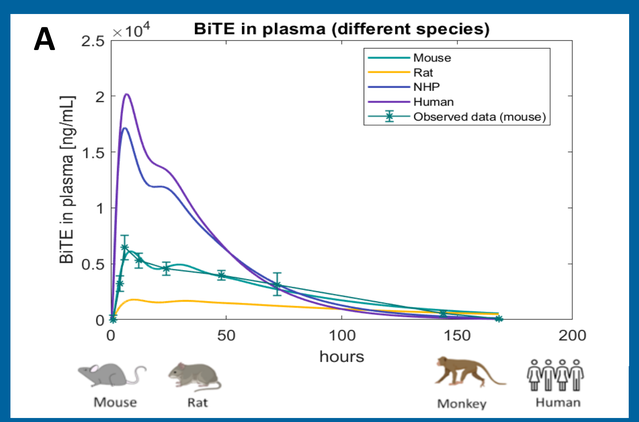

Fig. 5: (A) Model predictions in different species: mouse, rat, non-human primate, and human.

(B) Virtual populations based on model predictions in different organs: liver and plasma.

Conclusions and future perspectives

Our improved PBPK model builds upon the foundational properties of the original PBPK model by [1], with an added layer that offers a comprehensive framework for predicting mRNA-encoded drug concentration profiles in specific organs, e.g. in liver (Fig. 7), and especially at the site of action.

While validation was limited to preclinical animal models due to data availability constraints, preliminary tests suggest that our model could assist, *in silico*, with dose and schedule translation across different animal species and to humans (Fig. 8).

References

[1] Sepp, Armin, *et al.* "Computer-assembled cross-species/cross-modalities two-pore physiologically based pharmacokinetic model for biologics in mice and rats." Journal of pharmacokinetics and pharmacodynamics 46 (2019): 339-359.
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[3] Huang, Cheng, *et al.* "Lipid Nanoparticle Delivery System for mRNA Encoding B7H3-redirected Bispecific Antibody Displays Potent Antitumor Effects on Malignant Tumors." Advanced Science 10.3 (2023): 2205532.
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