Mechanistic modelling of bioavailability and local immunogenicity after subcutaneous administration within the Open Systems Pharmacology framework

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Objectives

- Implement mechanisms of size dependent extravasation, according to the 2-pore formalism, in the mechanistic model framework for subcutaneous (SC) administration
- Introduce local endosomal uptake, degradation, endothelial trafficking, and FcRn salvaging according to the generic implementation in PK-Sim.
- Develop a QSP model for local SC immune cell activity and response upon injection based on preclinical observations.
- Integrate established local SC immunogenicity and absorption model with systemic pharmacokinetics and immunogenicity within the OSP framework.
- Evaluate implementations in terms of bioavailability and immunogenicity.

Background

- The subcutaneous (SC) route of administration is frequently used to deliver therapeutic proteins (TPs). However, the systemic bioavailability of TPs when given SC is often incomplete, which can significantly reduce the systemic exposure and therapeutic efficacy [1].
- Local proteolysis in lysosomes at the site of injection can mediate pre-systemic degradation. Similarly, local resident and, upon stimuli of the injection, migrating immune cells could expediate both first-pass degradation and a signal to immunogenetic response with injection dependent consequences for the systemic immunogenicity [2].
- These two elements were incorporated into a previously described mechanistic absorption and systemic immunogenicity PBPK-QSP model implemented and harmonized to the Open Systems Pharmacology (OSP) framework, to allow for more informed predictions of the pharmacokinetics and immunogenicity of TP following SC administration [3].

Subcutaneous disposition

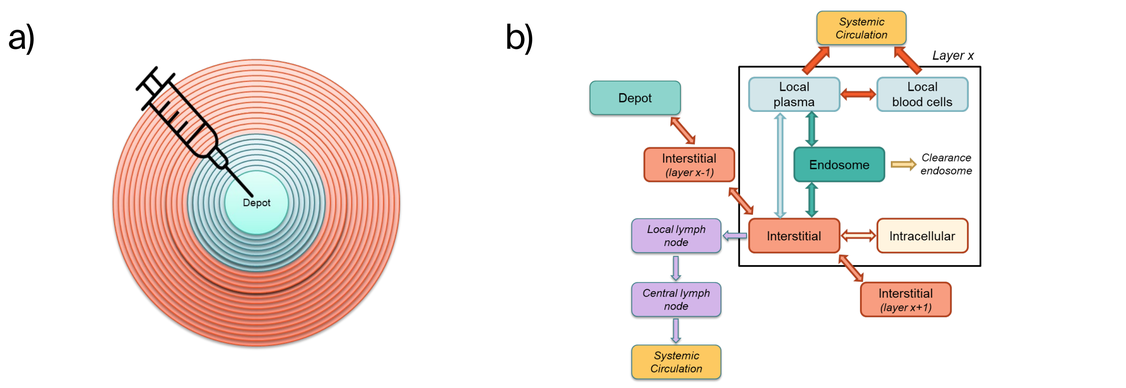

Figure 1. Subcutaneous absorption and disposition model. **a)** The physical injection site is represented by a volume including the injected formulation (Depot, blue) and the surrounding tissue (red) organized in layers with a discreet thickness. At injection, part of the volume will form a Depot while the rest, including solubilized drug, will disperse into the tissue immediate to the Depot. Spatio-temporal distribution of drug throughout the tissue is thereafter described by the passive diffusion in the interstitial space. **b)** Tissue organization, distribution and description of mass transfer as implemented in PK-Sim was adopted as physiological representation for each tissue layer. Translocation both via cell membrane permeability and endothelial fenestration may occur dependent on the molecule's properties. Moreover, generic representation of endosomal functionalities (uptake, re-circulation, clearance and FcRn salvaging) as well lymphatic drainage into local, and subsequent central lymph nodes, are represented within each layer's interstitial space. Systemic absorption rate and bioavailability are determined by the sum of said processes.

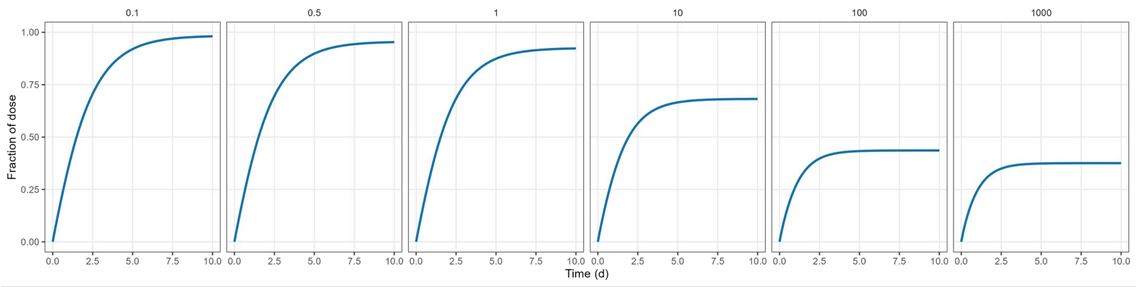

Figure 2. Subcutaneous absorption and bioavailability. Cumulative fraction of dose leaving the injection site for systemic absorption for a generic TP (150 kDa) with different Kd_{FcRn} affinity (µM)

Conclusions

- The open-source platform for modelling SC administration in the Open Systems Pharmacology framework was further developed with mechanistic descriptions.
- The results demonstrated how the model platform could aid drug development through multi-layered analysis including drug absorption, bioavailability, and exposure as well as immunogenic response.
- This provides a valuable tool for predictions of exposure and efficacy of TP after SC administration including the possibility to assess immunogenicity consequences of switching from intravenous to SC route of administration.

Subcutaneous immune cell dynamics

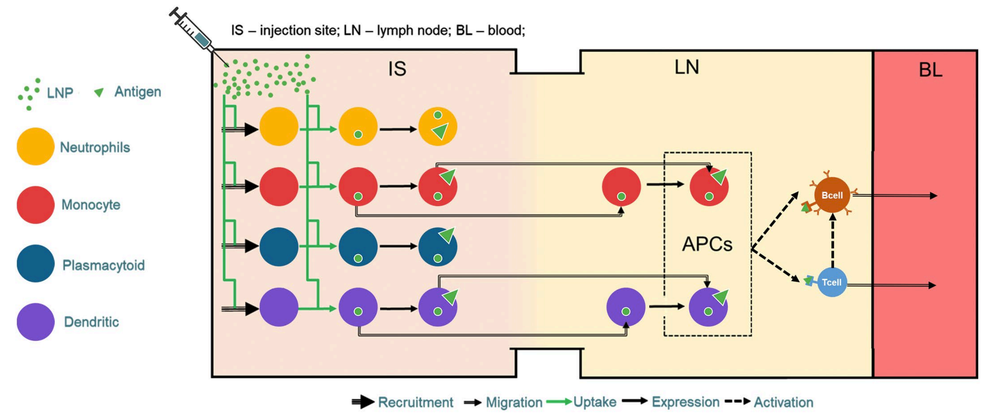

Figure 3. Subcutaneous immune cell model. Schematic representation of the compartments, cellular entities and processes included in the local subcutaneous immunogenicity model to dynamically trace the immunogenic response after injection both on site and in the draining lymph node. Resident and upon injection recruited immune cells are activated for uptake of the antigen. Monocytes and dendritic cell migrate and mature for subsequent B-Cell and T-Cell antigen presentation in the lymphatic nodes which triggers the systemic immunogenetic cascade.

Results

The model predicted size dependent retention and reduced systemic appearance rate with increased molecular size. First pass elimination via endosomal degradation increased because of increased retention while it was significantly reduced by FcRn salvaging. For a typical mAb (150 kDa) the predicted time to complete absorption was ~ 4-6 days, dependent of FcRn salvaging, and the bioavailability was >90% and <80% with (Kd_{FcRn}<=1 µM) and without (Kd_{FcRn}>1 µM) FcRn salvaging, respectively. The model for local immune cell dynamics increased the systemic immunogenicity response dependent on molecular size and epitope potency with effects on both local and systemic PK. This effect was mediated by local disposition and downstream effects on immune cell differentiation and memory cell pool.

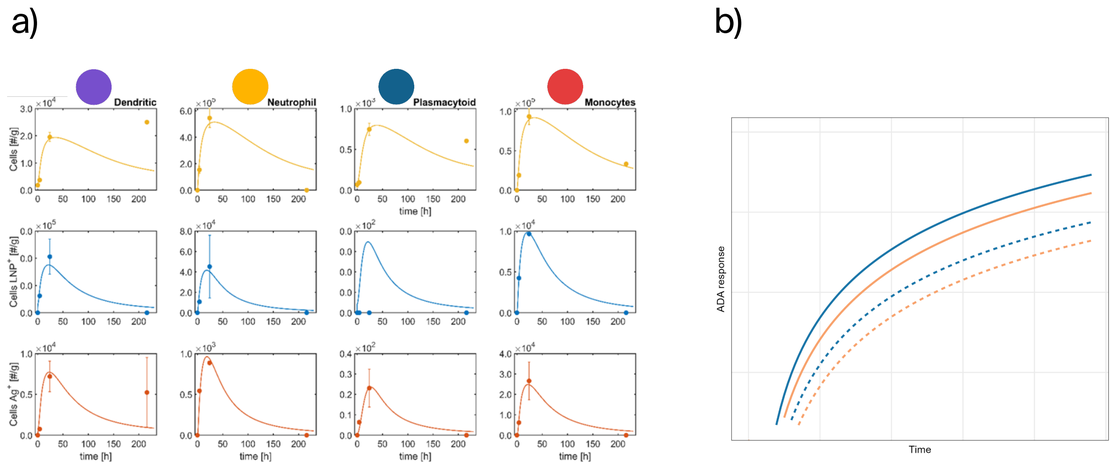

Figure 4. Subcutaneous immune cell dynamics and immune response. **a)** Observed (dots) and model fitted curves of the dynamic immune cell response to mRNA loaded lipid nanoparticles (LNP) after intradermal injection in non-human primates. **b)** Model simulated immunogenic response, visualized as formation of anti drug antibodies (ADA) over time, of two different sizes antigen, 50 kDa (blue) and 150 kDa (Orange), and epitope binding affinities, 1 nM (solid) and 100 nM (dashed).

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