A novel in-vivo & in-silico approach for predicting bioavailability of subcutaneously administered antibody drugs

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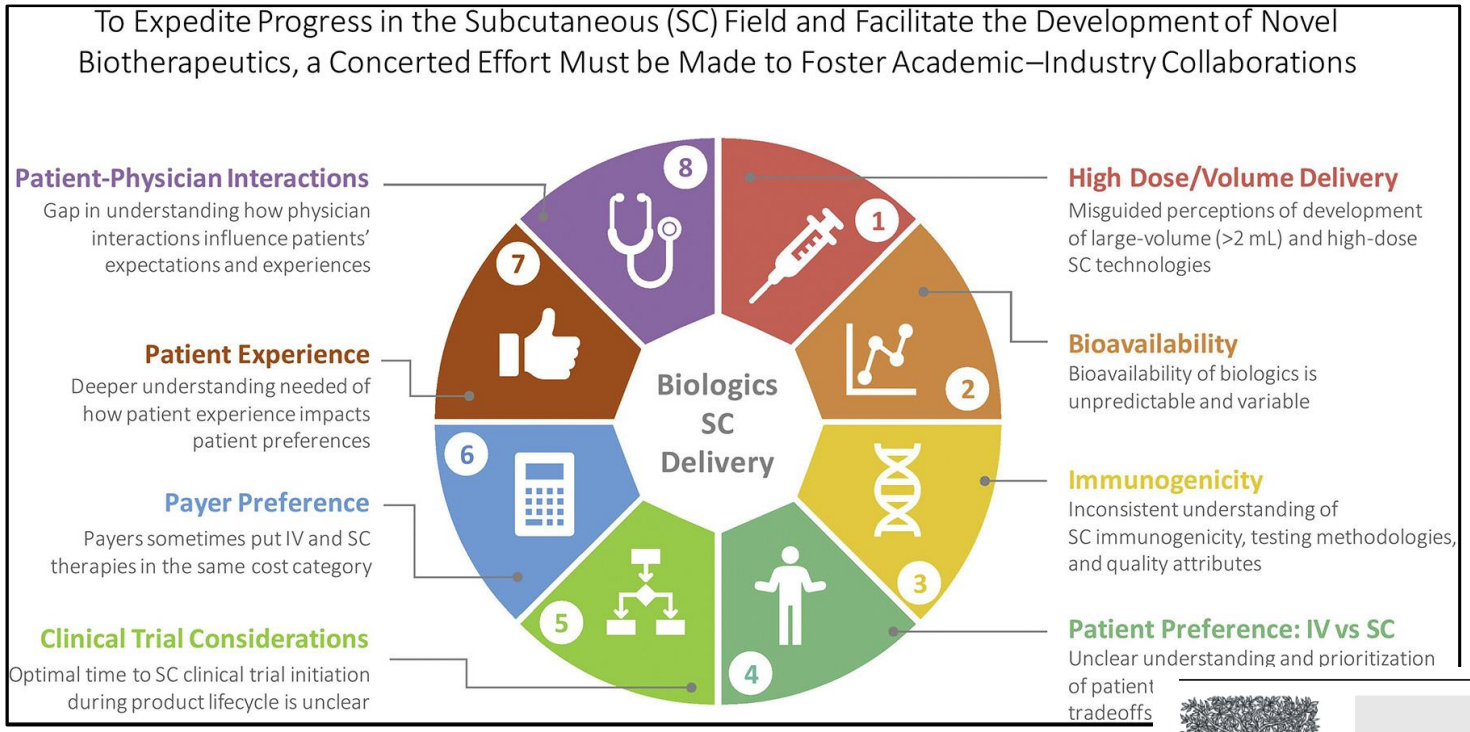
The Challenge:
Predicting bioavailability of mAB after sc administration



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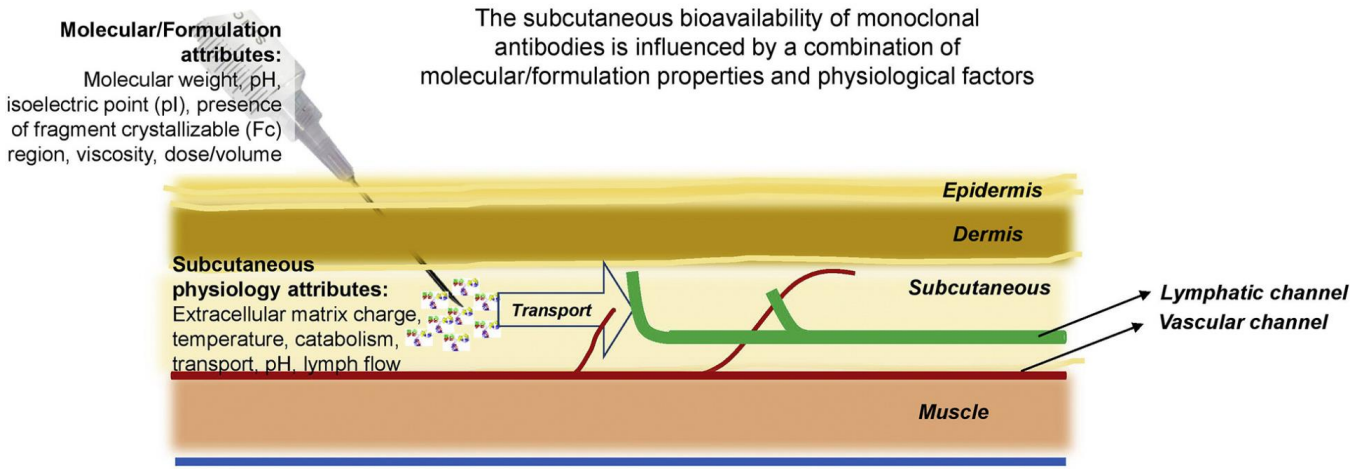
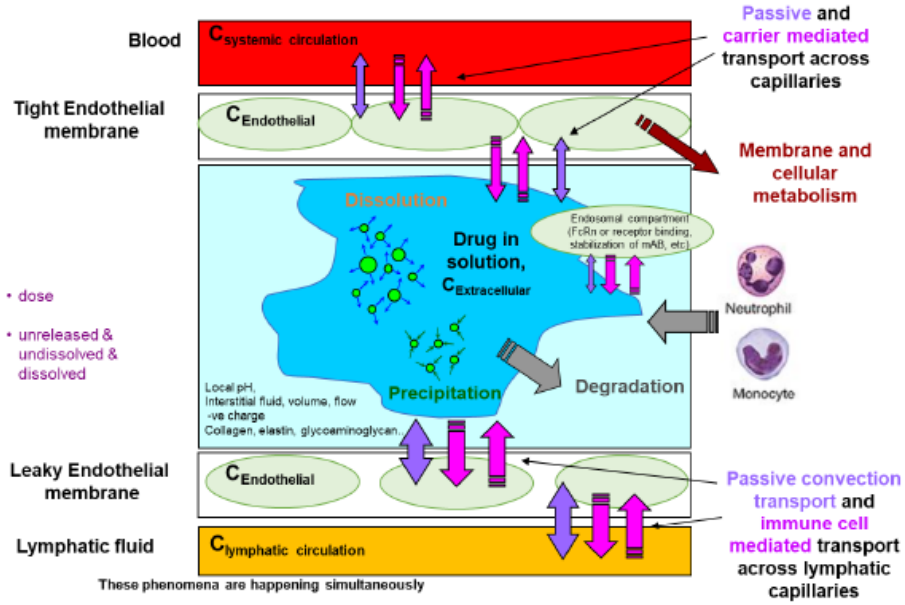
Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge

Manuel Sánchez-Félix [a,*], Matt Burke [b], Hunter H. Chen [c], Claire Patterson [d], Sachin Mittal [e]

mAB Subcutaneous Bioavailability

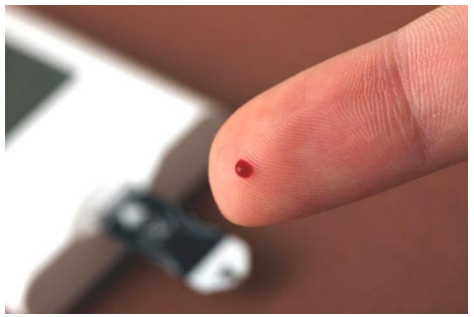




M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77

mAB Subcutaneous Bioavailability Testing

Standard BA Monitoring



Pre-Systemic Transport Processes following SC Administration

Injection mechanism

- Injection speed and volume
- Depot formation
- Viscosity

Tissue interaction

- ECM viscosity and tortuosity
- Receptor interaction (FcRn)
- Unspecific binding
- Immune reaction

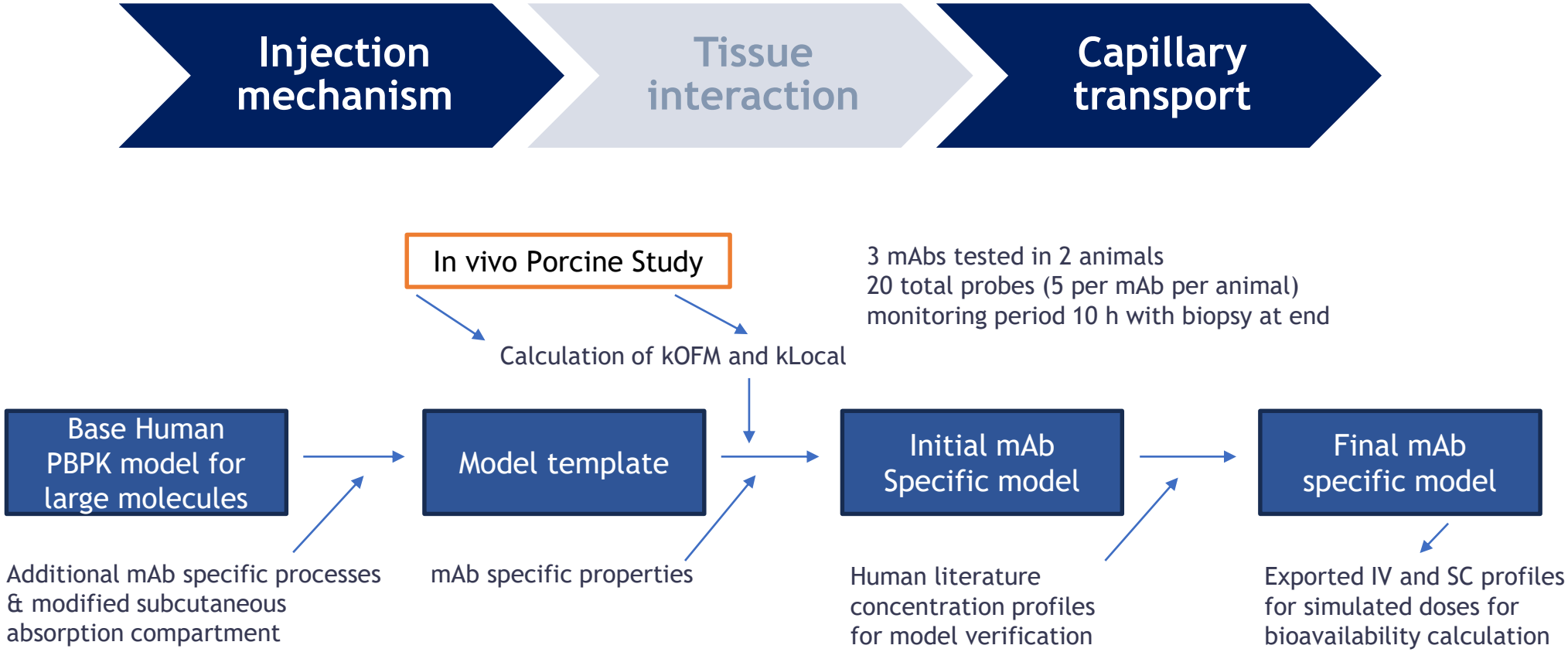
Protein changes

- Misfolding
- Aggregation

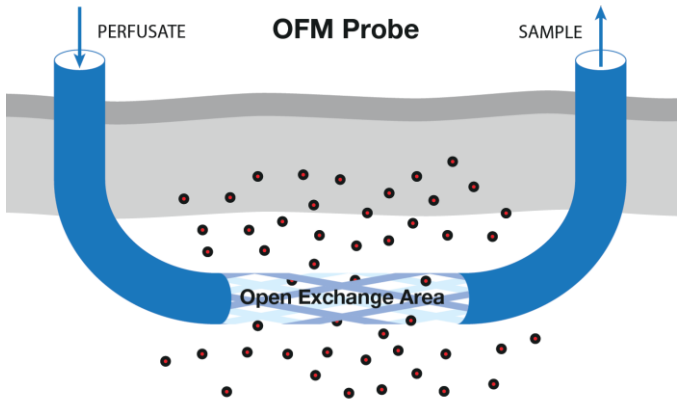
Capillary transport

- Lymph capillaries
- Blood capillaries

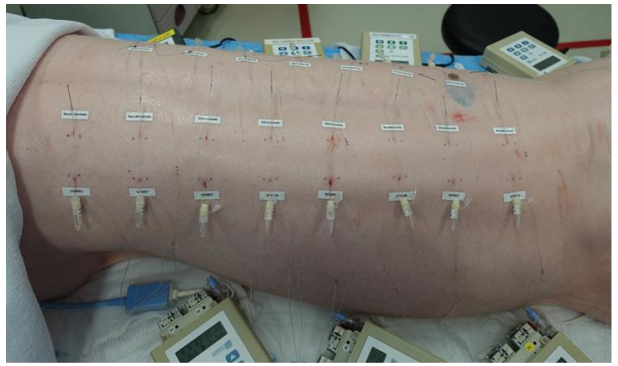
PBPK Modelling
(Open System Pharmacology PK-Sim and MoBi)



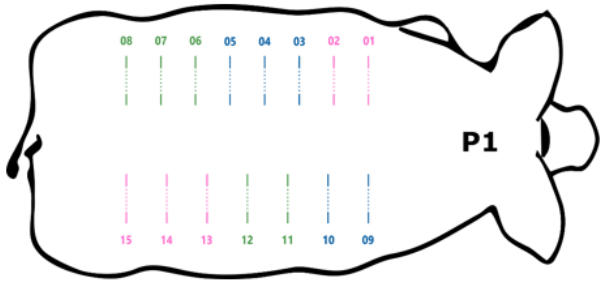
Investigation of mAB interaction with SC adipose tissue in pig model



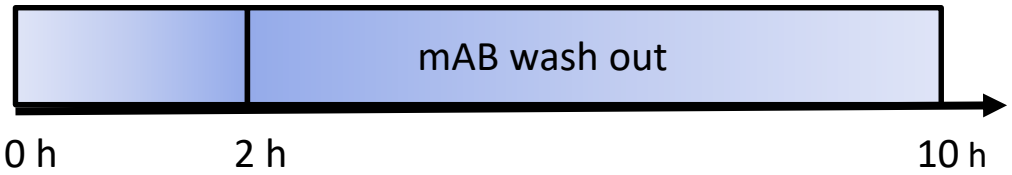
Open flow microperfusion (OFM)

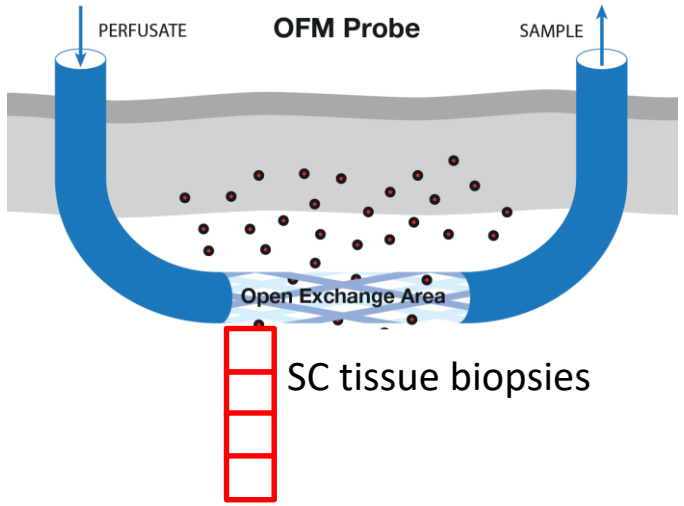


In-vivo porcine



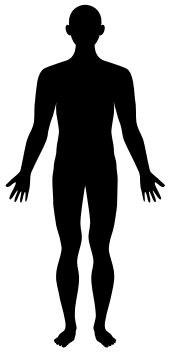
mAB application
60 µl – highly controlled

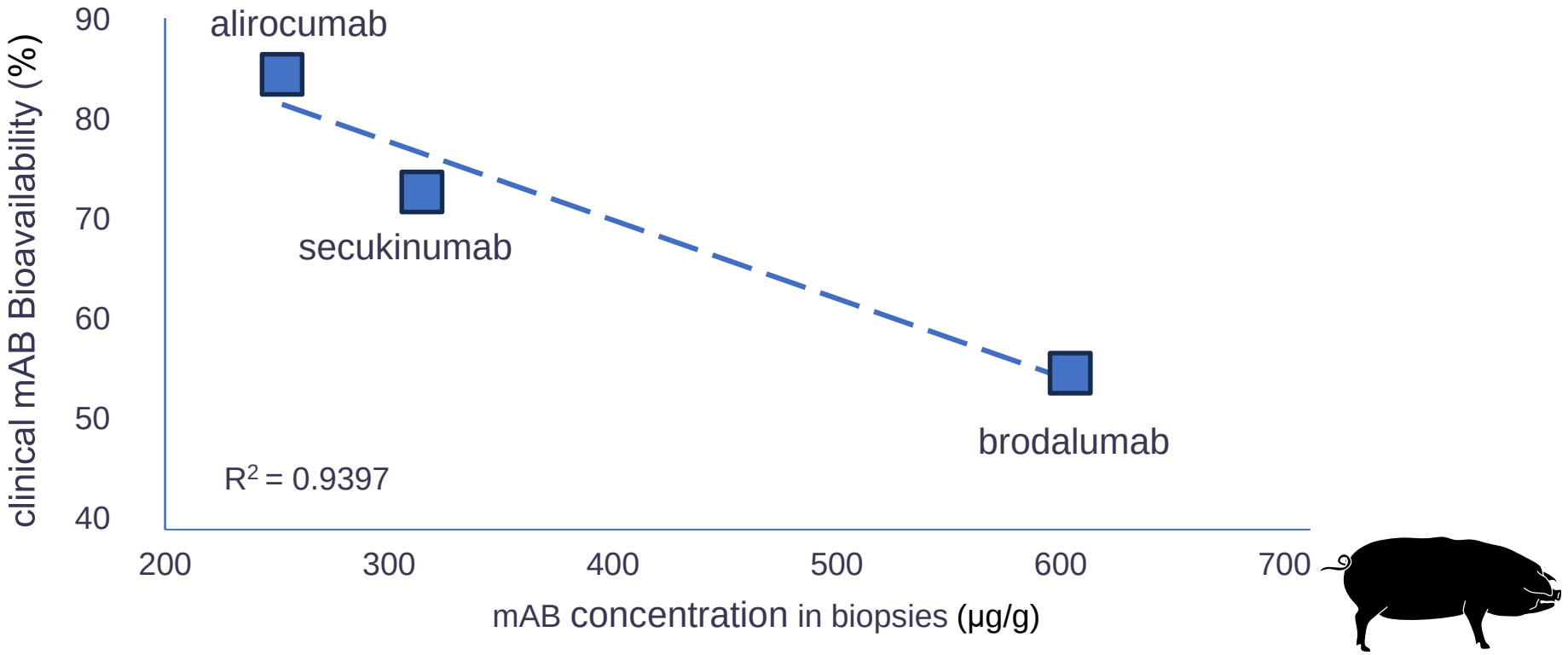




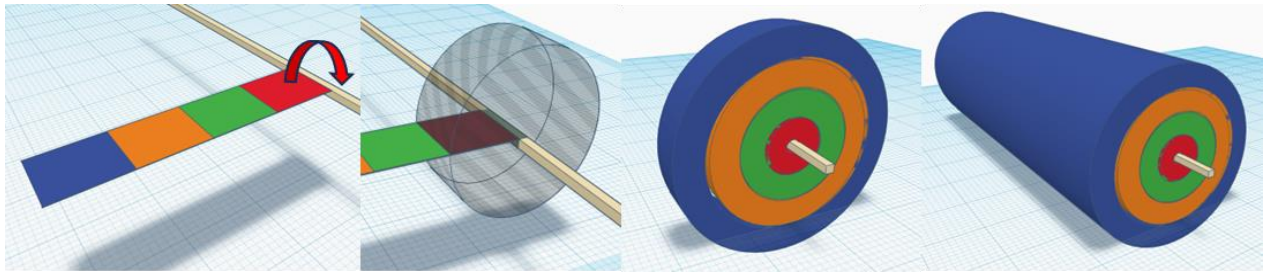
SC tissue biopsies

mAB concentration measured in sc biopsies correlate well with clinical bioavailability

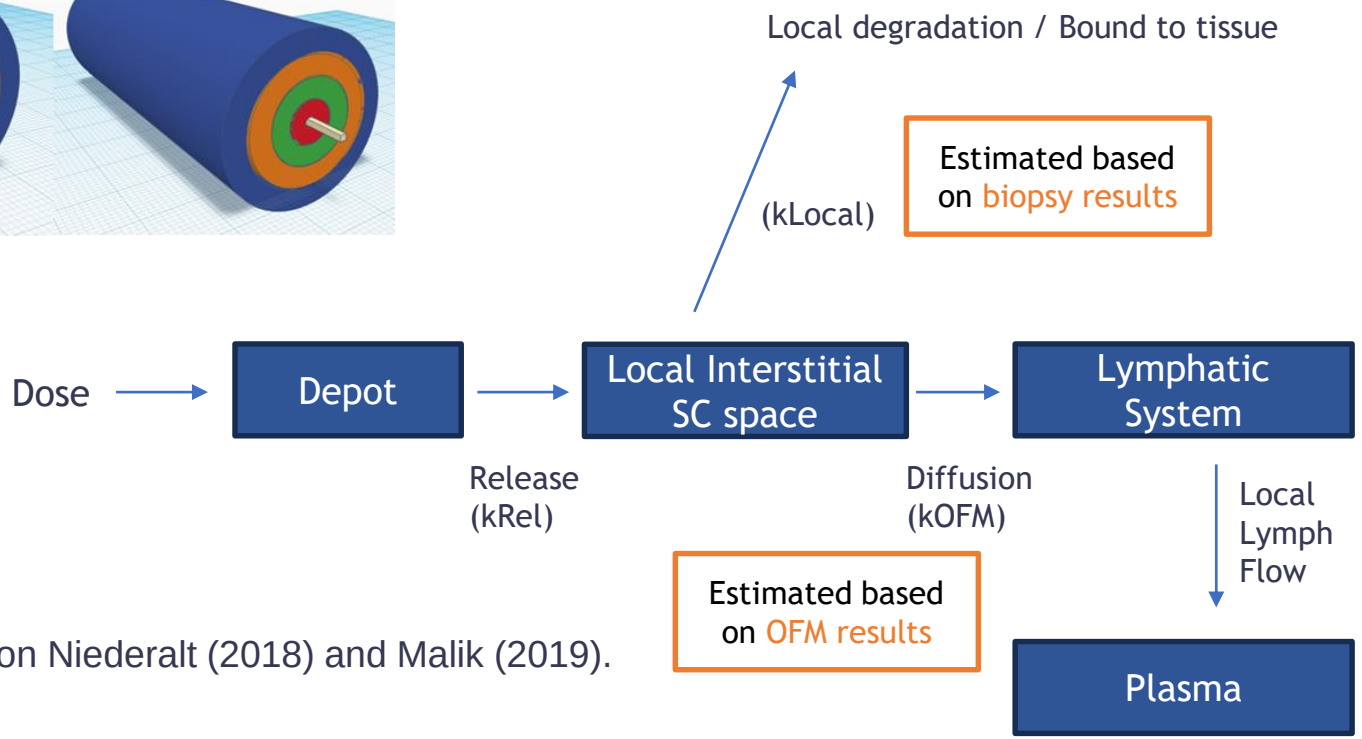




PBPK Modelling with a customized absorption compartment (kLocal + kOFM)

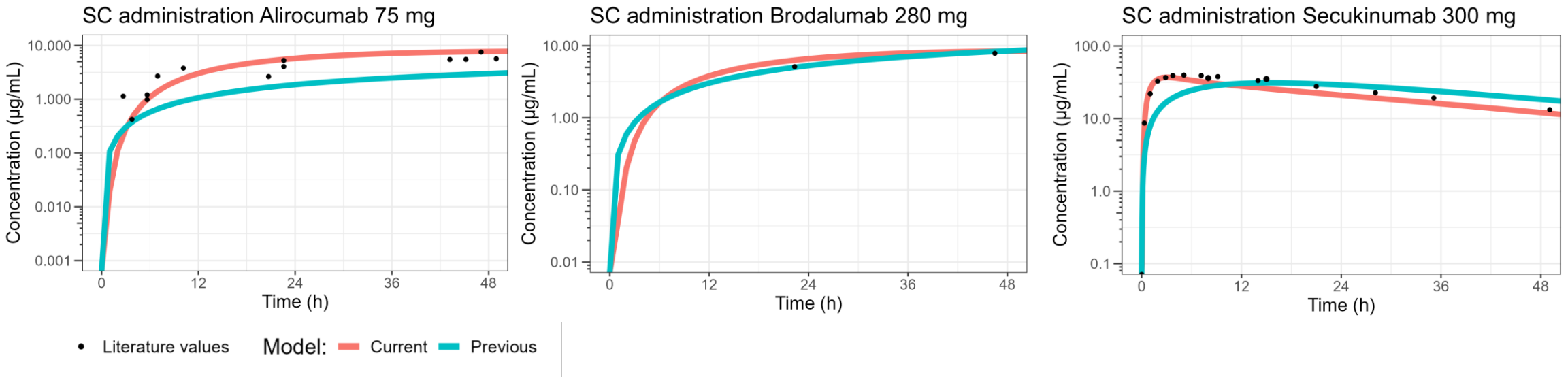


kLocal estimation is based on residual mAB within the local tissue (assuming a homogenous distribution around the OFM probe)



Based on Niederalt (2018) and Malik (2019).

Subcutaneous mAB adsorption (kLocal + kOFM) improves PBPK modelling



	Alirocumab	Brodalumab	Secukinumab
Average Model-predicted BA (%)	76.0	51.7	77.7
Literature BA (%)	85.0	55.0	77.0

The BA predictions were within a ± 9% absolute range from the BA reported in literature.

Summary

- Combining in-vivo preclinical data with in-silico modelling offers a new way to successfully predict mAB bioavailability.

- OFM technology allows a direct readout of mAB/SC adipose tissue interaction that is highly relevant for bioavailability.

- We are currently testing more mAB to validate the role of OFM adsorption data for bioavailability.

- By using the OFM approach, bioavailability of mAB can already be assessed and improved in a preclinical setting (more economical, no GMP, no clinical study).

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