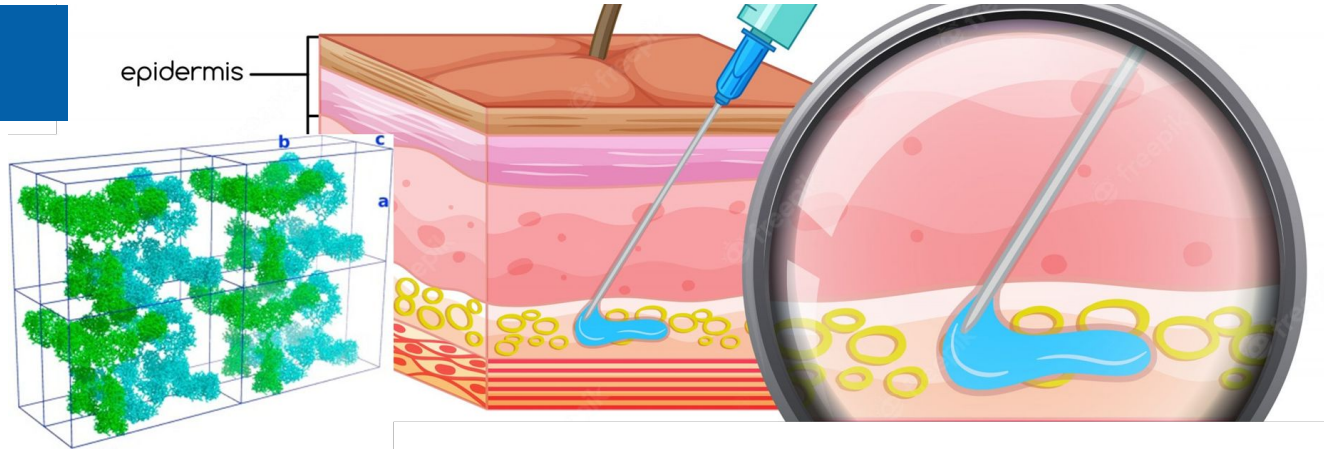
Technical Research & Development



Uncloaking In-vitro Subcutaneous Bioavailability Tools

Manuel Sanchez-Felix

CRS/IPEC 24th July 2023

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Introduction

Subcutaneous Drug Delivery & Development Consortium

Subcutaneous Bioavailability Challenge

In-vitro Tools

Summary

Subcutaneous Drug Delivery & Development Consortium

Vision

Our vision is to **transform patient care** and **improve patient outcomes** leading **fundamental advancements in subcutaneous drug development and delivery**

Mission

The mission of the Subcutaneous Drug Development & Delivery Consortium is to **collaboratively address the most pressing subcutaneous dosage and delivery issues and opportunities** in a **precompetitive manner**

https://subcutaneousconsortium.org/.

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Subcutaneous Drug Delivery & Development Consortium

Public

SC Consortium Officers:

SUBCUTANEOUS DRUG DELIVERY DEVELOPMENT CONSORTIUM

Donna French, PhD

President

Sachin Mittal, PhD

Vice President

Monica Adams, PhD

Marketing Officer

David Kang, PhD

Treasurer

Donna French

Rajesh Gandhi

Vibha Jawa

David Collins

Kathleen Lin

David Kang

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Sachin Mittal

Nicole Buist

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Beate Bittner

Johannes Schmidt

Ning Yu

Kevin Maloney

Ming Chen

Manami Tsutsumi

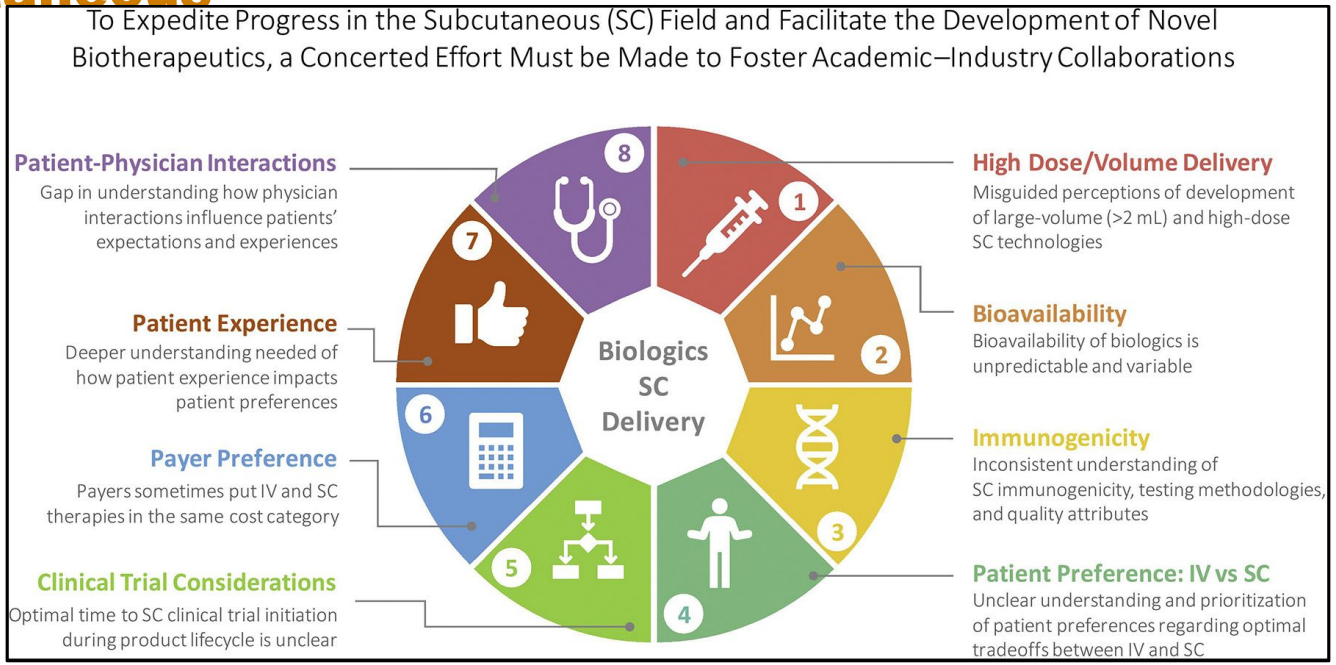
Advait Badkar

RK Maroju

Amgen	Novartis	Sanofi	Roche	Biogen	Boehringer Ingelheim	Pfizer

TIER 2 Members: KORU MEDICAL SYSTEMS, Nemera, kaléo, Comera LIFE SCIENCES

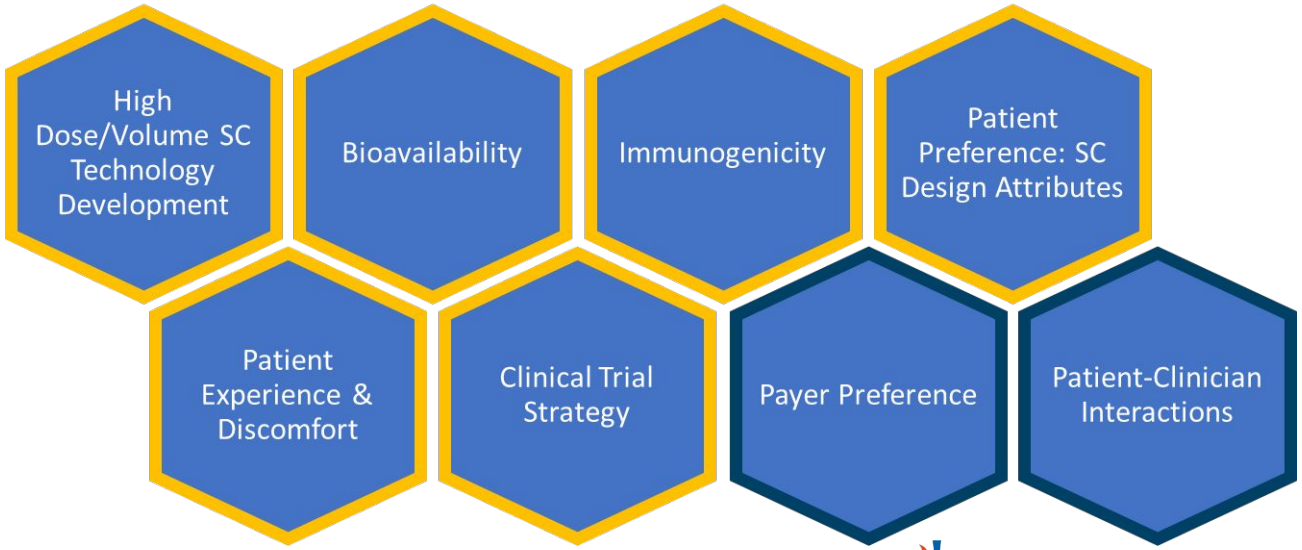
Accelerating the development of novel technologies and tools for subcutaneous delivery of biotherapeutics subcutaneous



David S. Collins, Manuel Sanchez-Felix, Advait V. Badkar, Randall Mrsny, Journal of Controlled Release, 221, (2020), p. 475-482

Subcutaneous Drug Delivery & Development Consortium

The **top 6 problem statements** have been prioritized for 2020, with **6 sub-teams created around these statements** (the 2 patient statements have been combined into 1 sub-team).



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Subcutaneous Bioavailability Challenges

ELSEVIER

Advanced Drug Delivery Reviews

Available online 27 May 2020

In Press, Corrected Proof

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]

Contents

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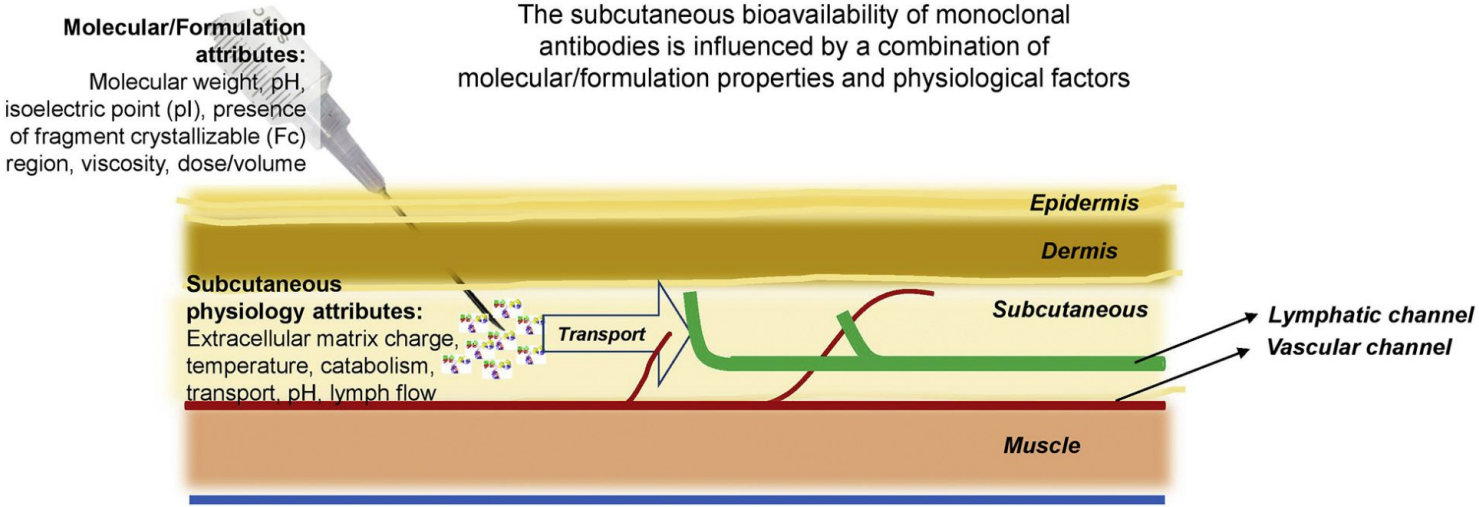
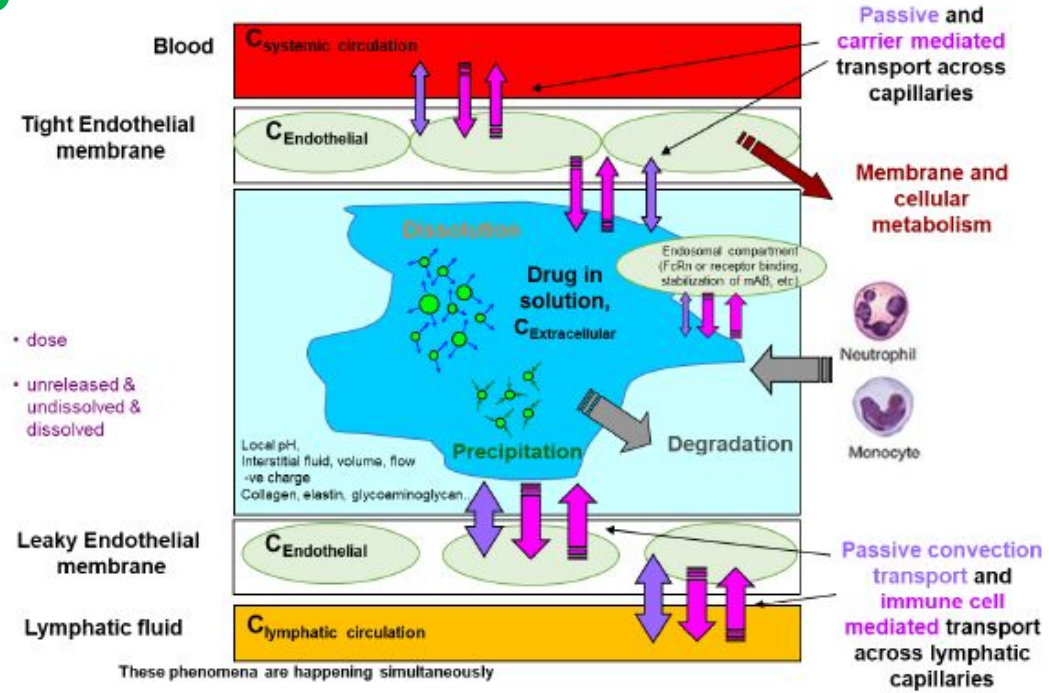
mAB Subcutaneous Bioavailability Challenge



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

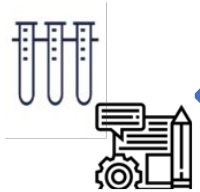
mAB Subcutaneous Bioavailability Challenge



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 Challenge

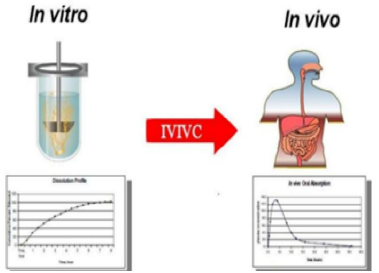
Vision

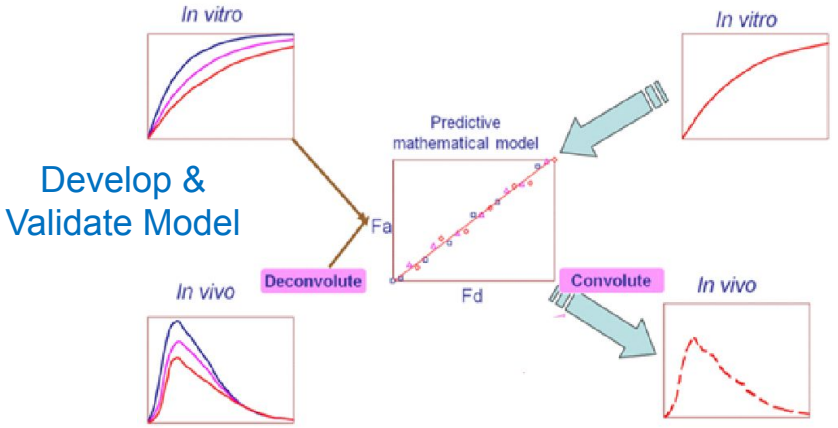


In-silico & In-vitro

Translation of Bioavailability

Bring Together Communities to Work on Needs



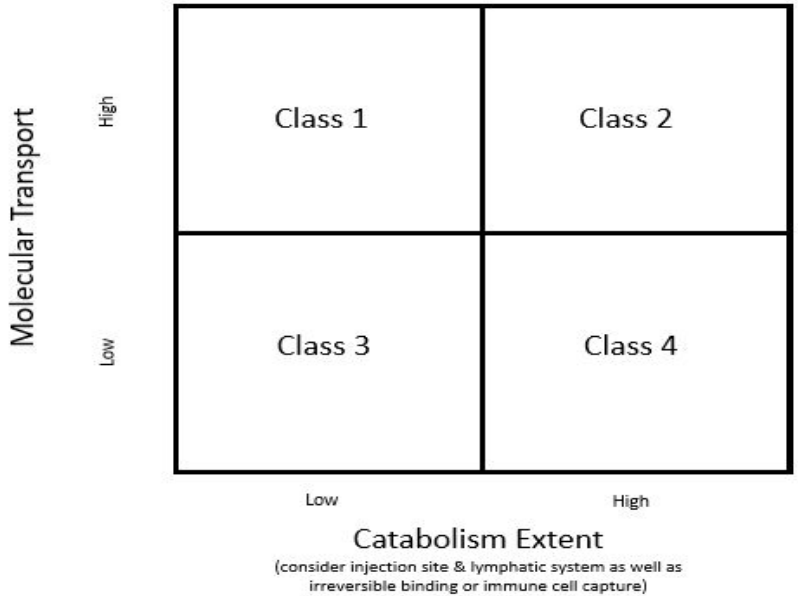


M. Sanchez-Felix, M. Burke, H.H. Chen, C. Patterson, S. Mittal, Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge, Adv Drug Deliv Rev, 167, (2020), p. 66-77

Subcutaneous Bioavailability Challenges

Open Challenge

Classification system concept for mAbs: molecular transport vs catabolism extent



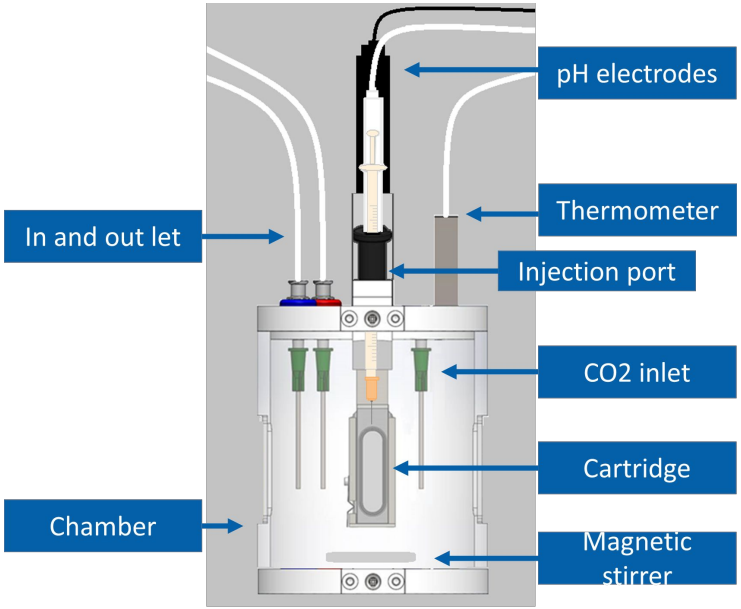
mAB Subcutaneous Bioavailability Challenge

- General confusion on what we want from In-vitro assay(s)

- Is it:
  - Amount retained at the site of injection
  - Diffusivity
  - Amount transported via lymphatic or blood capillaries
  - Immune response risk assessment
  - Absorption for in-silico modeling of PK
  - Catabolism
  - SC Bioavailability

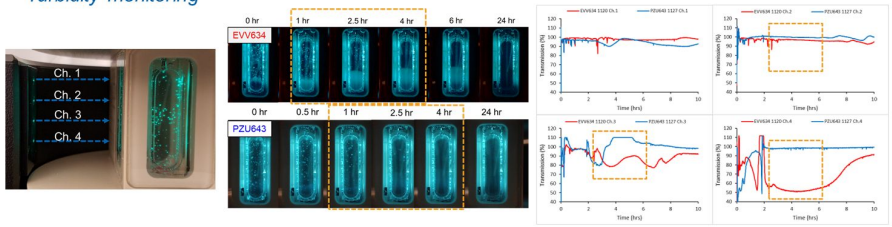
- Reality is that we will need different in-vitro assays; just as we have different assays for oral bioavailability for small molecules

In-vitro Tools: Scissor

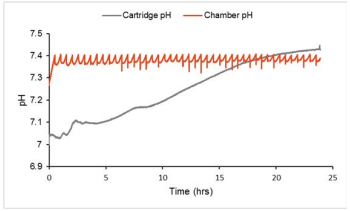


Monitoring data from Scissor

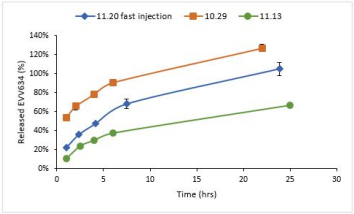
- *Turbidity monitoring*



- *pH monitoring*



- *Diffusion measurement*



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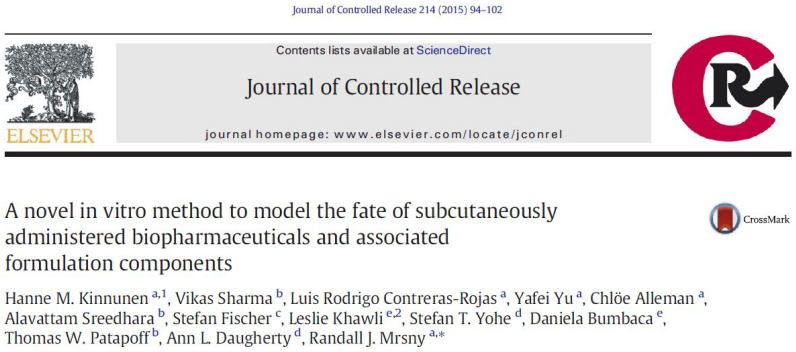
In-vitro: Scissor and other systems



Journal of Controlled Release 214 (2015) 94–102

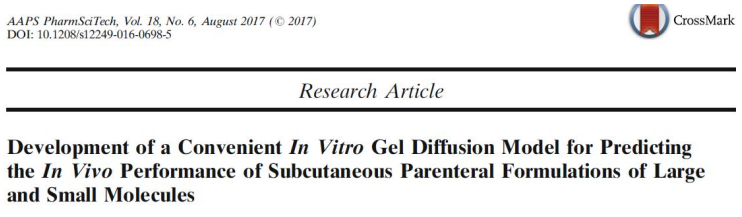
Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

A novel in vitro method to model the fate of subcutaneously administered biopharmaceuticals and associated formulation components

Hanne M. Kinnunen [a,1], Vikas Sharma [b], Luis Rodrigo Contreras-Rojas [a], Yafei Yu [a], Chlöe Alleman [a], Alavattam Sreedhara [b], Stefan Fischer [c], Leslie Khawli [e,2], Stefan T. Yohe [d], Daniela Bumbaca [e], Thomas W. Patapoff [b], Ann L. Daugherty [d], Randall J. Mrsny [a,*]



AAPS PharmSciTech, Vol. 18, No. 6, August 2017 (© 2017)
DOI: 10.1208/s12249-016-0698-5

Research Article

Development of a Convenient *In Vitro* Gel Diffusion Model for Predicting the *In Vivo* Performance of Subcutaneous Parenteral Formulations of Large and Small Molecules

Dennis H. Leung,[1,2,6] Yash Kapoor,[3] Candice Alleyne,[1] Erika Walsh,[1] Andrew Leithead,[1] Bahanu Habulihaz,[4] Gino M. Salituro,[4] Annette Bak,[1] and Timothy Rhodes[5]

International Journal of Pharmaceutics 605 (2021) 120824

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Simulating particle movement inside subcutaneous injection site simulator (SCISSOR) using Monte-Carlo method

Hao Lou [a,b,*], Cory Berkland [a], Michael J. Hageman [a,b,*]

[a] Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66047, USA
[b] Biopharmaceutical Innovation and Optimization Center, University of Kansas, Lawrence, KS 66047, USA

- Investigated insulin and 4 mAB on the scissor system
- R2= 0.927 correlation between observed % SC bioavailability and diffused fraction

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In-vitro: Scissor

Journal of Controlled Release 273 (2018) 13–20

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

In vitro model for predicting bioavailability of subcutaneously injected monoclonal antibodies

Hanne Kinnunen Bown[a], Catherine Bonn[a], Stefan Yohe[b], Daniela Bumbaca Yadav[c], Thomas W. Patapoff[d], Ann Daugherty[b], Randall J. Mrsny[e,*]

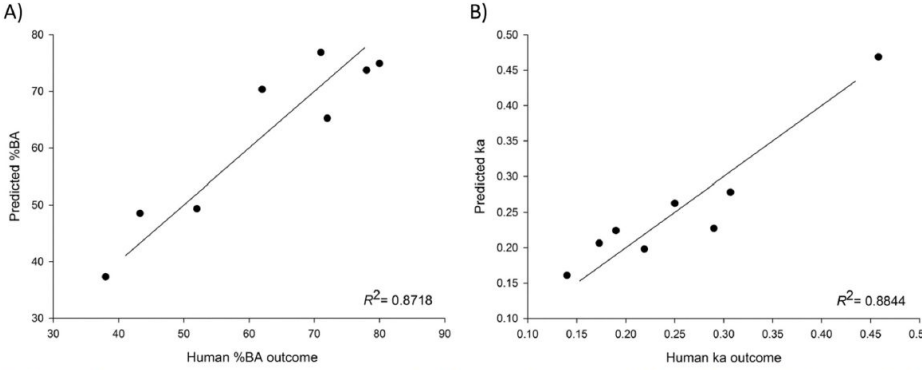

Fig. 6. Linear correlation assessment for human *in vivo* data and PLS-based modelling of Scissor system data outputs for A) %BA based on 4 components (R^2 = 0.87) and for B) ka bas on 4 components (R^2 = 0.88).

- Measured diffusion and profiles of the mAB's from the injection chamber into the larger volume chamber (6 hours)
- Curve fitting analysis of these profiles using the Hill equation identified parameters that were used, along with physiological properties for each mAB, in a partial least square analysis to define a relationship between molecule and formulation properties with clinical PK.
- Profile characteristics of diffusion provided a strong predictive correlation for these 8 mAB's
- Invitro tool provides a useful tool to predict the impact of the molecule and formulation properties that has the potential for predicting clinical outcomes.

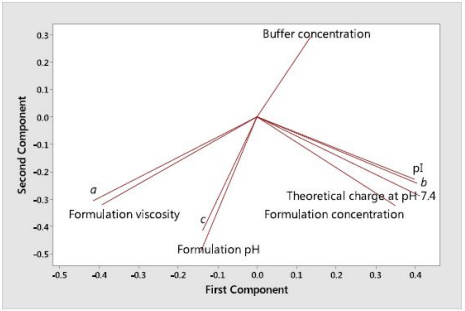

Fig. 3. Loading plot of the two first components describing the relationships between input parameters for the set of monoclonal antibodies tested in the Scissor system.

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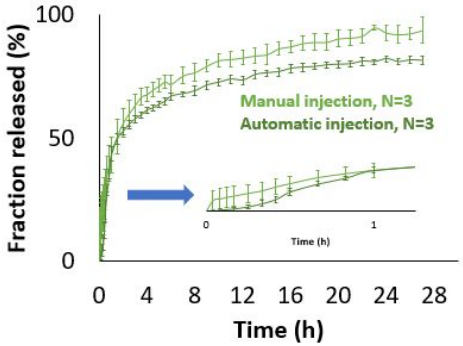
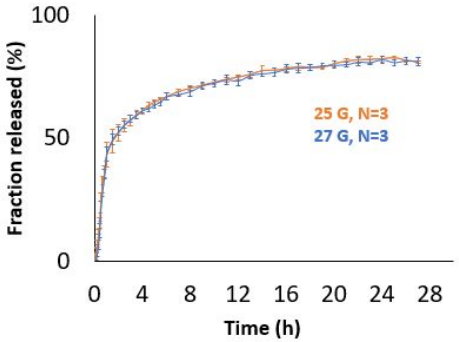
In-vitro Scissor

Investigating the subcutaneous injection site simulator for the administration of oligonucleotides



Injection method clearly had an impact on the individual release curves with greater reproducibility for automatic injected samples.

Automatic injection will be used for further Scissor optimisation



Needle type did not significantly impact the release curves for similar assay conditions (automatic injection).

27 G will be used for further optimisation due to improved patient compliance

Karin Somby

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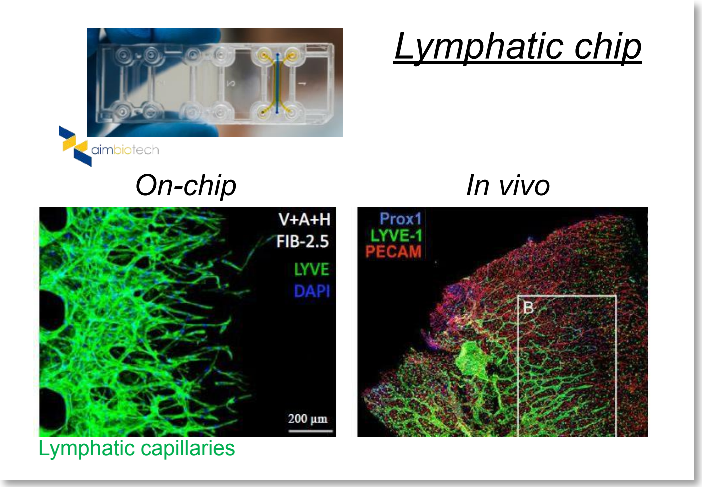
Skin-on-chip model

Collaboration partner: MIT (Professor Roger Kamm, Postdoc Giorgos Pavlou)

- The skin-on-chip models the **subcutaneous interstitium** and **lymphatic vasculature**
  - Used to quantify mAb **lymphatic drainage** as **key predictor of sc bioavailability** (based on
previous data from MIT in collaboration with
Amgen)



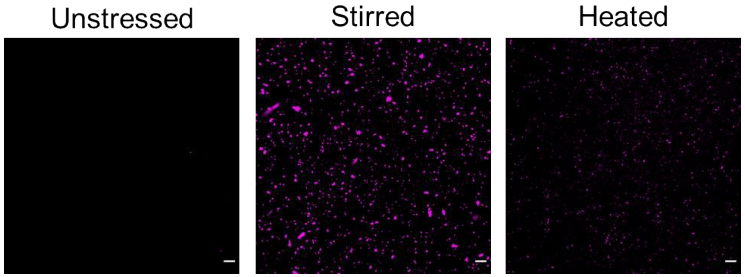
Serrano, J. C. et al., 2022

Project goal: implement the skin-on-chip model to assess lymphatic absorption of a panel of internal mAbs and perform IVIVC with clinical bioavailability data

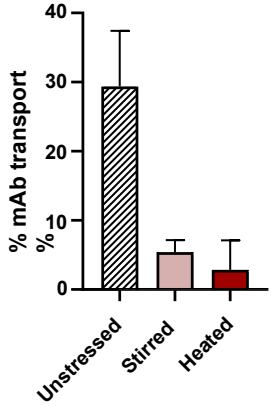
Skin-on-chip model

Pinpointing IgG aggregation

1. Induce and characterize IgG aggregates



2. Lymphatic absorption



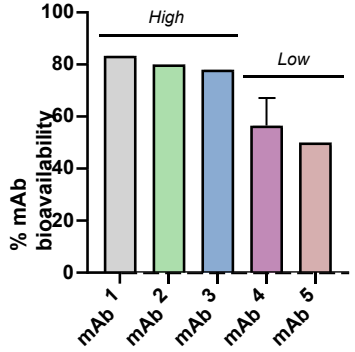
Model is able to detect the effect of IgG aggregation on lymphatic absorption: implications for mAb and formulation optimization

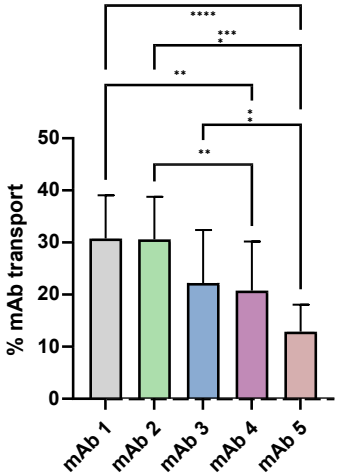
Jillian Handel, Gabriela Misiewicz & Adriana **Martinez Ledo**

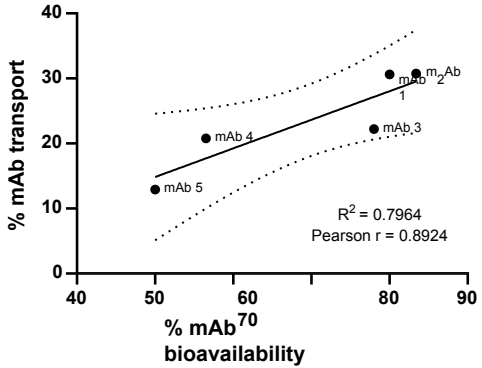
Skin-on-chip model

In Vitro–In Vivo Correlation: NVS mAbs

Clinical data *On-chip* *IVIVC*







Mean ± SD of four independent experiments; One-way ANOVA

The good IVIVC for the 5 mAbs tested supports the hypothesis that the main event(s) that impacts bioavailability is occurring in the subcutaneous region

William Tschantz

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Summary

- Subcutaneous bioavailability and PK will probably require more than one in-vitro model
- Community is not clear on what it wants from In-vitro assays
- Great advancements in in-vitro assays have been made over the last 5 years
- Consortiums are being formed to address known risks and gaps
- Multiple high-dose and high-volume formulation subcutaneous options are being advanced that will require in vitro models to de-risk development
- The Subcutaneous Drug Delivery & Development Consortium will be releasing its 2nd **"open"** SC bioavailability challenge

Acknowledgements

Scissor:

- Karin Somby
- Valerio Campagna
- Paulo Santos
- Driton Vllasiu (Kings College London)
- Ben Forbes (Kings College London)
- Randy Mrsny (Bath University)
- Imogen Anastasiou (Pion)
- Karl Box (Pion)
- Balint Sinko (Pion)

- **MIT Skin-on-Chip**
  - Adriana Martinez Ledo
  - *Gabriela Misiewicz*
  - Jillian Handel
  - Ryan Pelis
  - Thomas Dimke
  - Bruin Gerard
  - Marie Picci
  - Karolyn Bechtold-Peters
  - Roger Kann (MIT)
  - Giorgos Pavlou) (MIT)
  - Maria Proestaki (MIT)

- **TRD SC Group**
  - Marie Picci
  - Karolyn Bechtold-Peters
  - Jorge Nerkamp
  - Isabel Ottinger
  - Maxime Gaillot
  - Robert Hormes
  - Sabine Adler
  - Harry Tiemessen
  - Stephane Olland
  - Colleagues in PHAD/CPP

- **Subcutaneous Consortium**
  - Donna French (AZ)
  - David Collins (Lilly)
  - Renee Tannenbaum (Halozyme)
  - Sachin Mittal (Merck)
  - Advait Badkar (Pfizer)
  - Matt Burke (Radis Health)
  - Marie-Teresa Peracchia (Sanofi)
  - Neil Mathias (BMS)
  - Rajesh Gandhi (BMS)
  - Jennie Stevenson (Amgen)
  - Randy Mrsny (Bath University)

Thank you

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References

- David S. Collins, Manuel Sanchez-Felix, Advait V. Badkar, Randall Mrsny, Accelerating the development of novel technologies and tools for subcutaneous delivery of biotherapeutics, Journal of Controlled Release, 221, (2020), p. 475-482

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- Jean C. Serrano, Mark R. Gillrie, Ran Li, Sarah H. Ishamuddin, Roger D. Kamm, On-chip engineered human lymphatic microvasculature for physio-/pathological transport phenomena studies, bioRxiv, 2022

Experimental workflow

Lymphatic sprouting starts

Day 0 | Day 1 | Day 2 | Day 3 | Day 4

Seeding of LECs

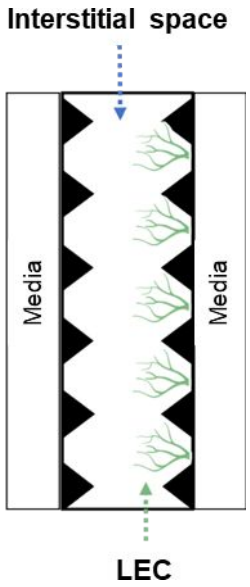
1. Induction of flow
2. Addition of growth factors

Medium change

Medium change

Analysis

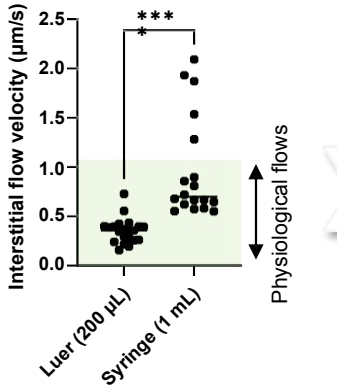
- **Model characterization**
  - Interstitial flow velocity
  - Lymphatic capillary morphology
- **Lymphatic absorption assay**



LEC: Lymphatic Endothelial Cell

Relevant lymphatic physiology on-chip

Tunable interstitial flow



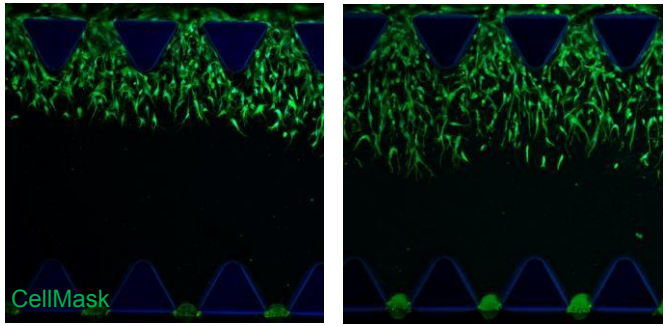
Luer (low flow)

Syringe (high flow)

Tunable capillary morphology

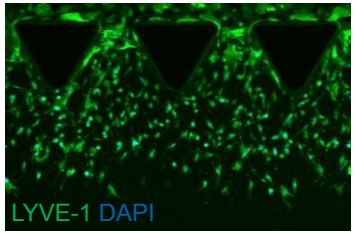
Low flow (luer)

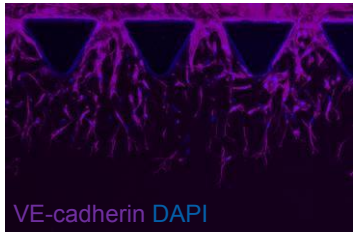
High flow (syringe)



	In Vivo	High flow
Vascular Density (%)	15-30	14.33
Length (µm)*	200-800	~651.10
Diameter (µm)	10-50	~10.09

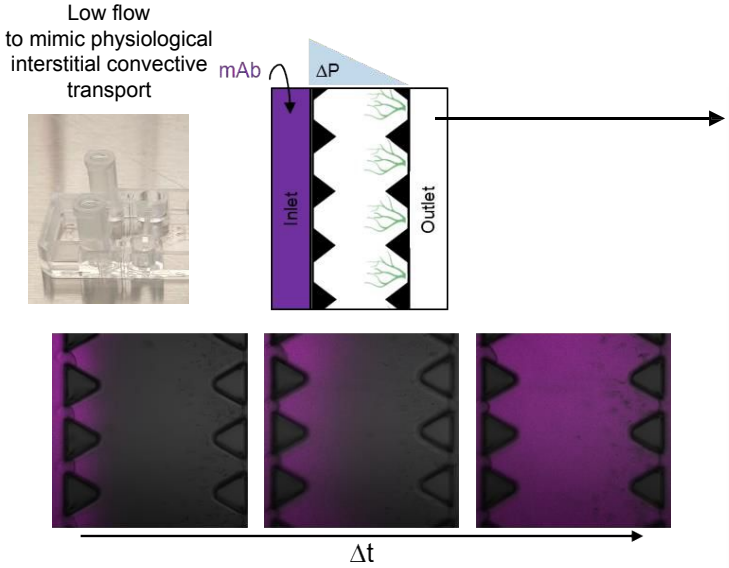
Phenotypic marker expression





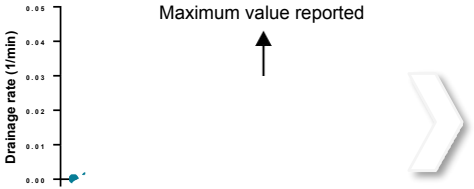
Gabriela Misiewicz

Lymphatic absorption assay



Imaging outlet:
Confocal microscope

Sampling outlet:
Plate reader



Model molecules

Optimization

NVS mAbs

IVIVC

Ned Kirkpatrick
Ishan Gupta