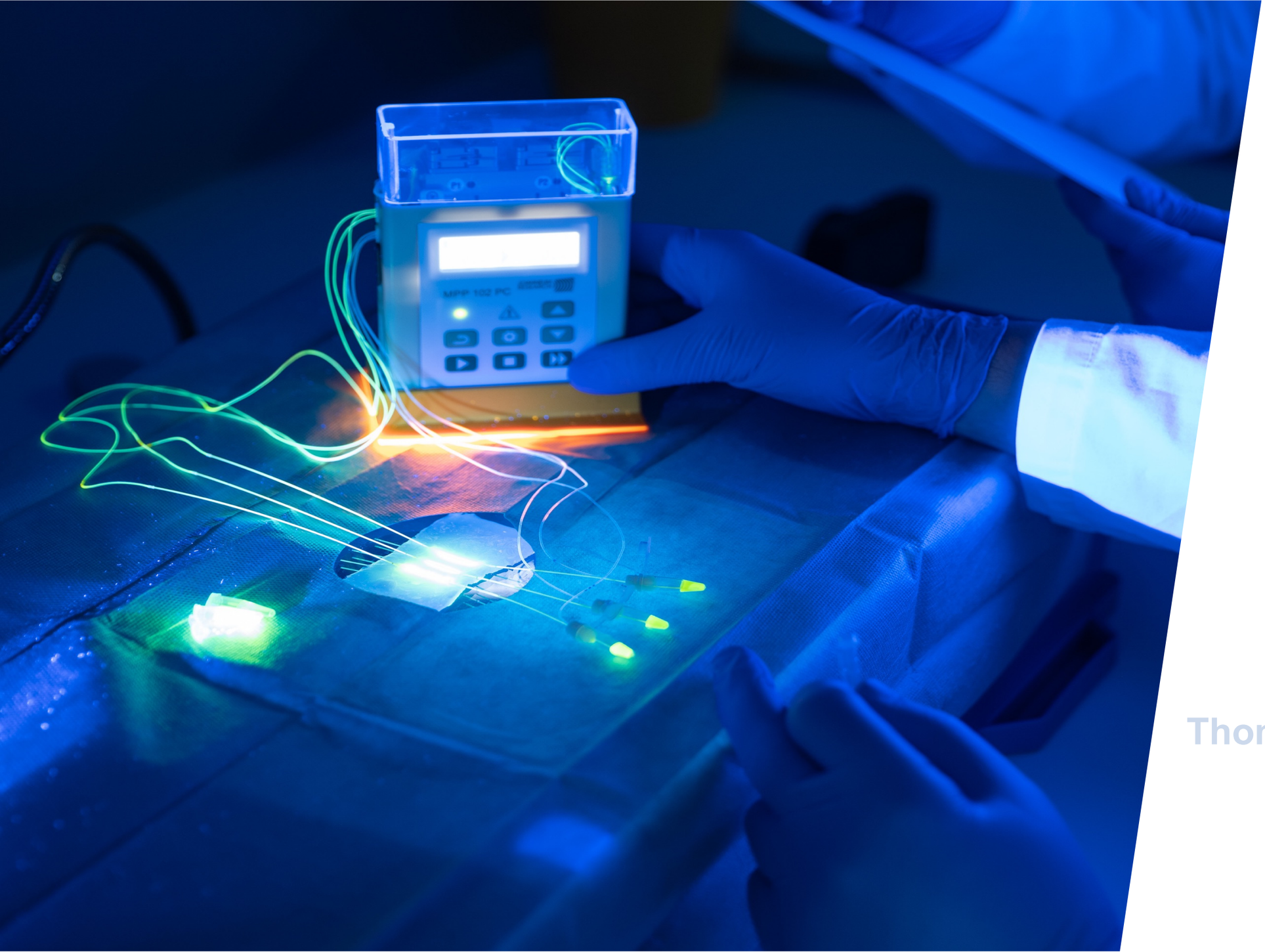

JOANNEUM RESEARCH HEALTH

Webinar

New Ways to Derisk and Accelerate Topical Drug Development

Thomas Birngruber, PhD

Graz, July 12th, 2023

NOFM

Who we are

Today‘s Speaker and Host

- **Thomas Birngruber, PhD**

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Webinar

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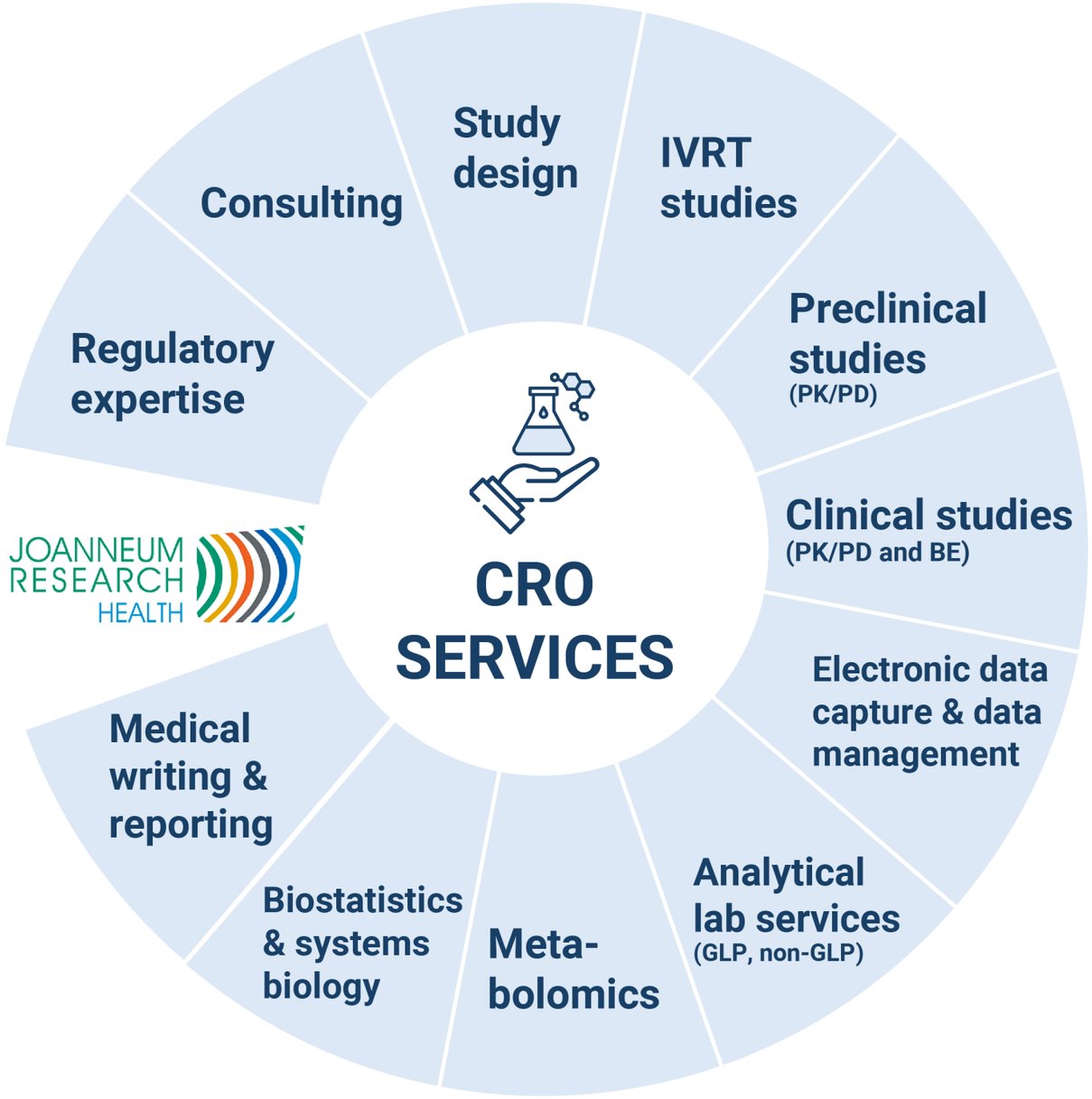


Who we are

We are a boutique CRO for research projects and drug development programs

About the Webinar

Key Learnings

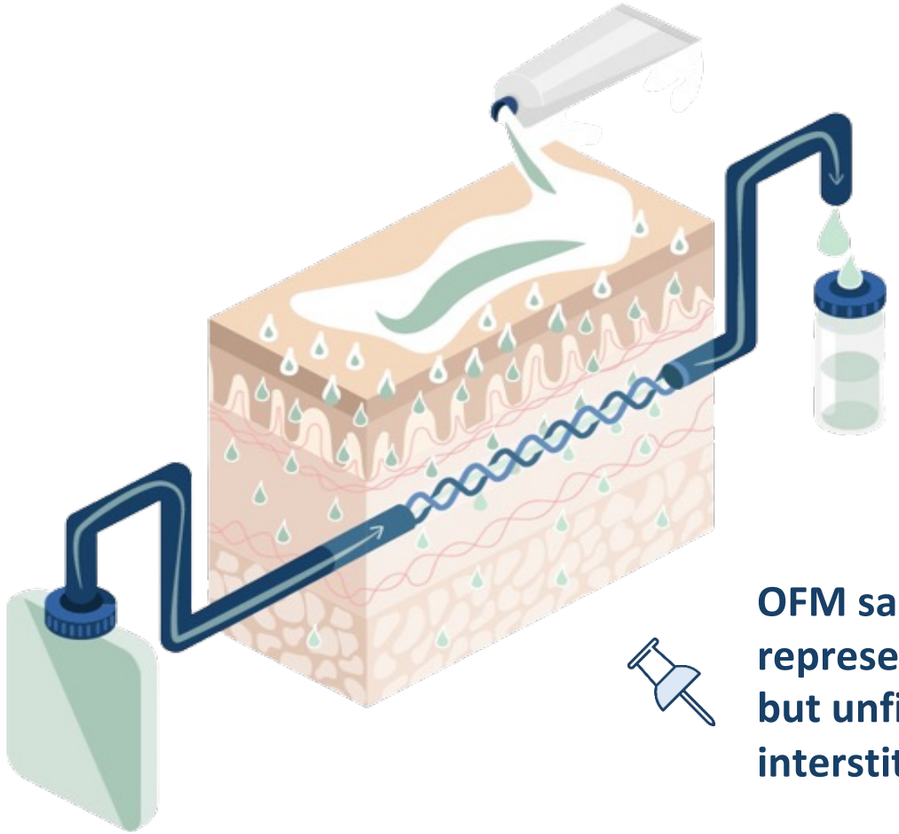
What is dOFM and what is it used for?

What can dOFM sampling contribute at the R&D sweet spot?

What is the difference between a biopsy and a dOFM sample?

How can clinical drug efficacy be predicted using dOFM?

dOFM Working Principle

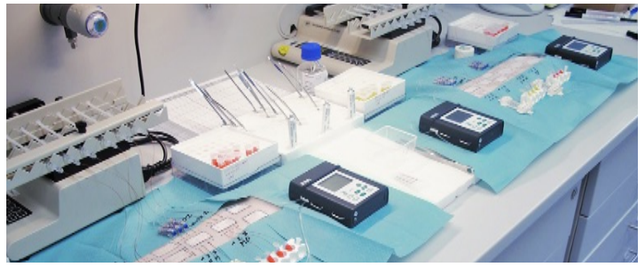


OFM samples represent diluted but unfiltered interstitial fluid.

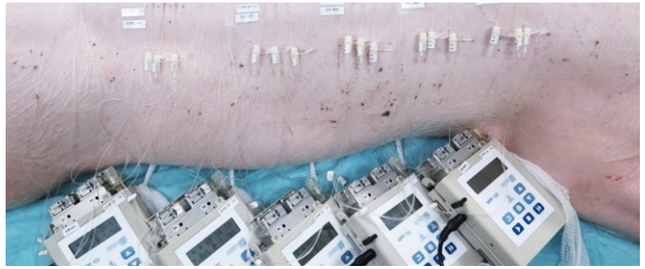
- Provides highly relevant information from the target tissue.
- Continuous time-resolved monitoring of PK and PD up to 72 hours.
- Sampling of lipophilic substances[1,2], high molecular weight substances[3,4], immune cells, etc.
- Substances can be applied directly into the dermis via dOFM.
- Excellent translatability: same dOFM setup in clinical, preclinical and ex-vivo studies.

[1] CP-17; logP 3.5 (Bodenlenz et al. 2016) [2] fentanyl; logP 4.5 (Holmgaard et al. 2011) [3] antibodies (Dragatin et al. 2016), [4] cytokines (Kolbinger et al. 2016)

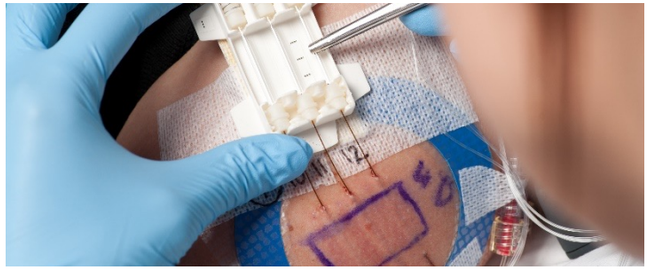
dOFM translational models



Ex-vivo models using animal and human explants

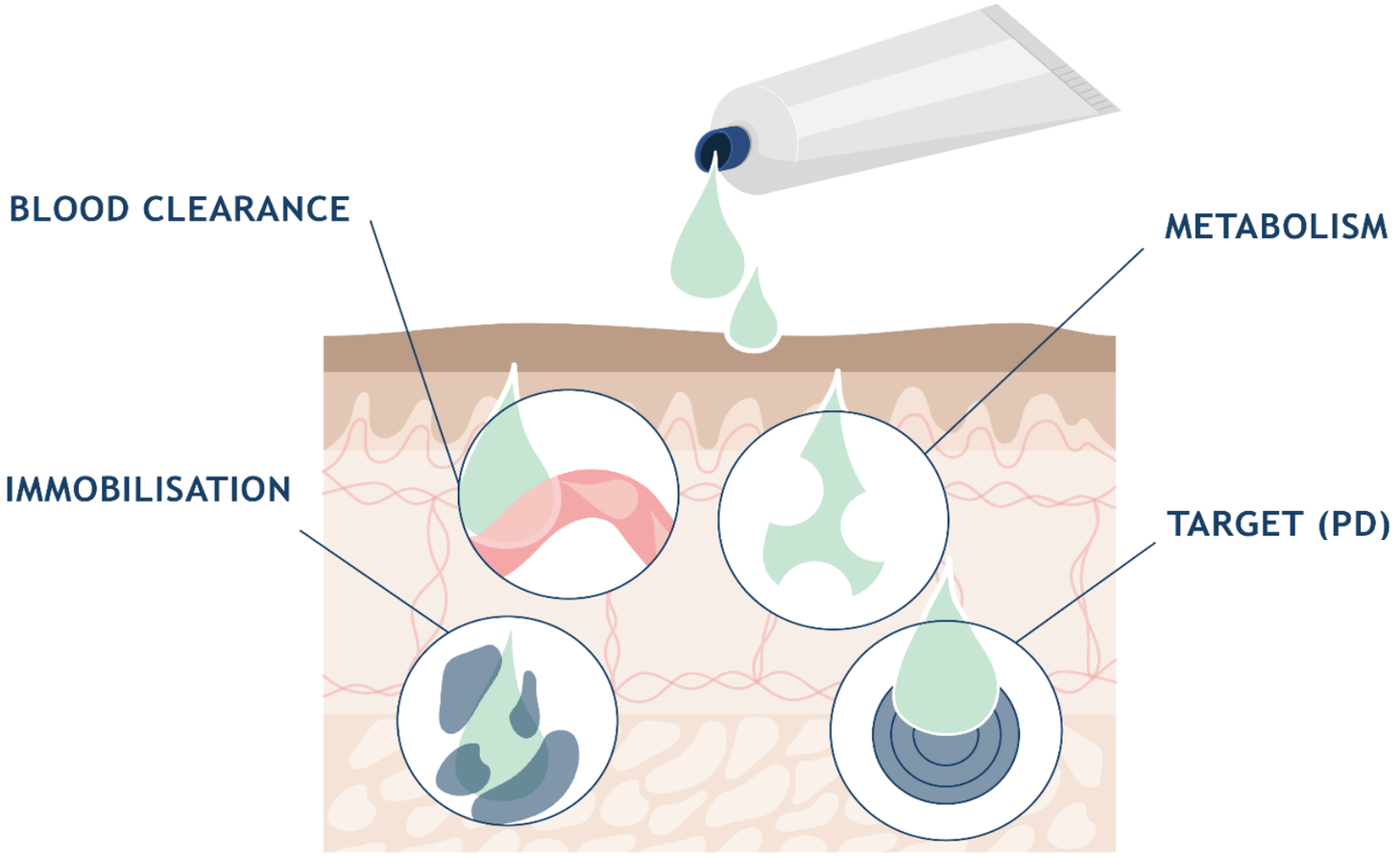


In-vivo animal models



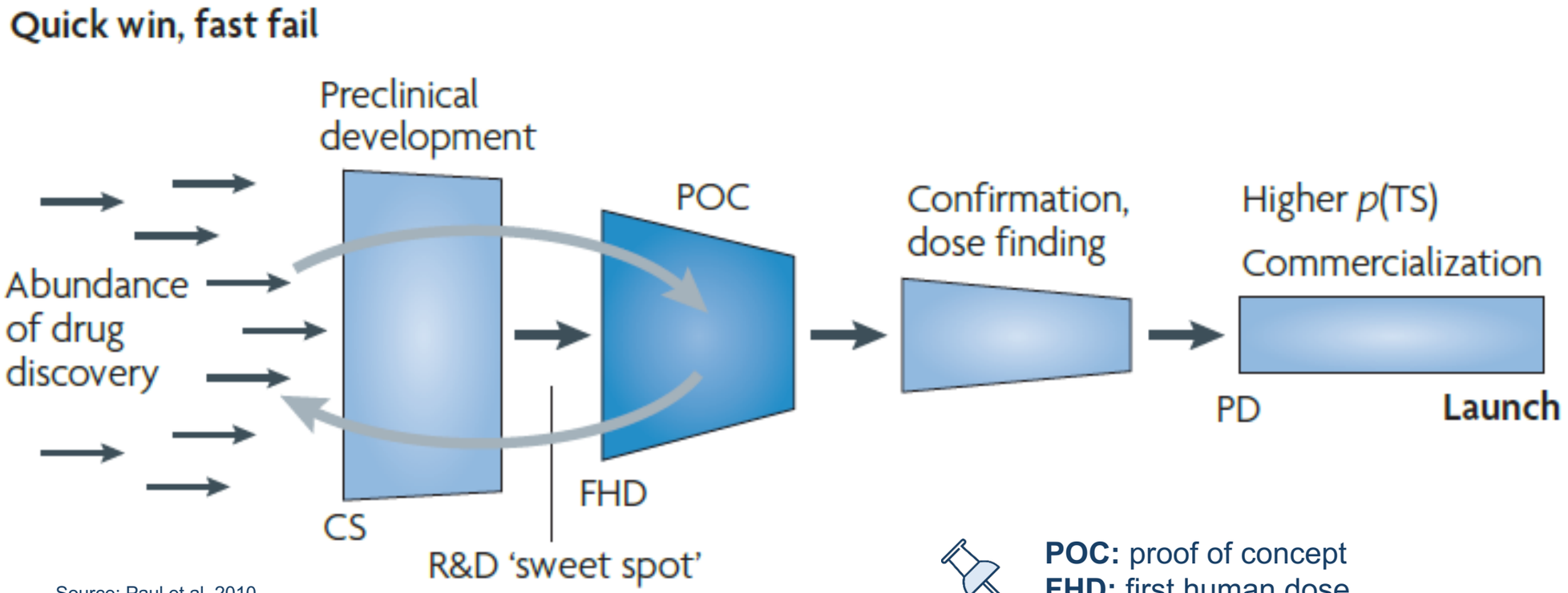
Clinical studies

What happens to the API after topical application?



Source: JOANNEUM RESEARCH

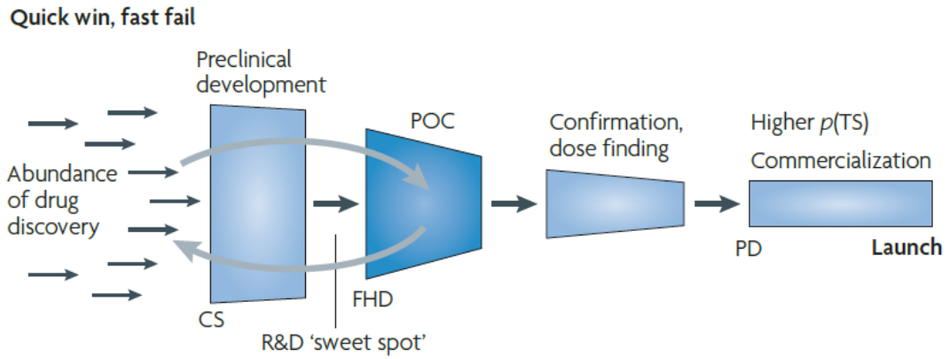
The „Quick Win, Fast Fail“ Paradigm



Source: Paul et al. 2010

POC: proof of concept
FHD: first human dose
PD: product decision
CS: candidate selection
PTS: probability of technical success

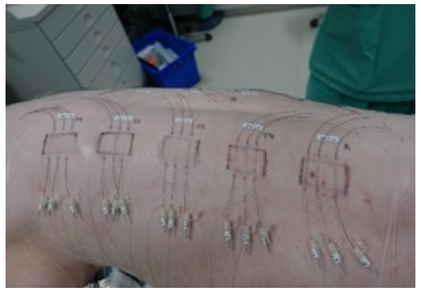
The „Quick Win, Fast Fail“ Paradigm



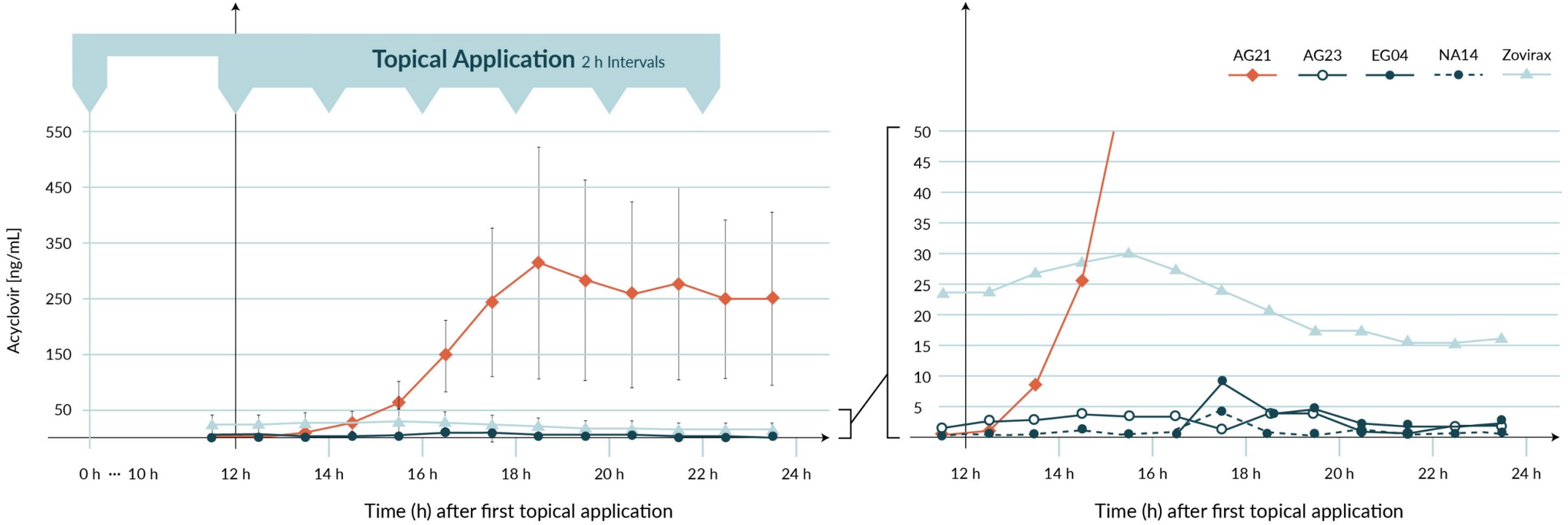
Source: Paul et al. 2010

- At the R&D sweet spot, the development costs increase with GMP, clinical study, etc.
- dOFM derisking has a focus on decision making at this R&D sweet spot.
  - Selection/Testing of Topical Formulations in the Skin
  - Prediction of Clinical Results at the R&D Sweet Spot
  - Early Dose-Response Studies via dOFM Microdosing

Selection and Testing of Topical Formulations in the Skin

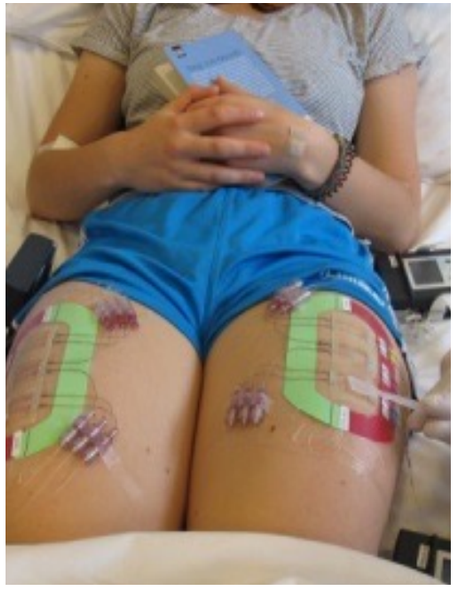


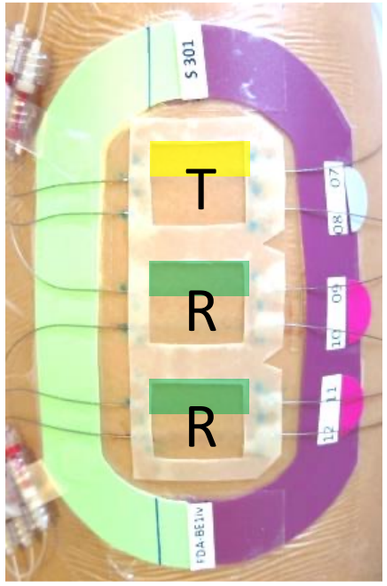
Direct Comparison of Formulations in One Subject



Formulation can be Selected with a Minimal Study Setup

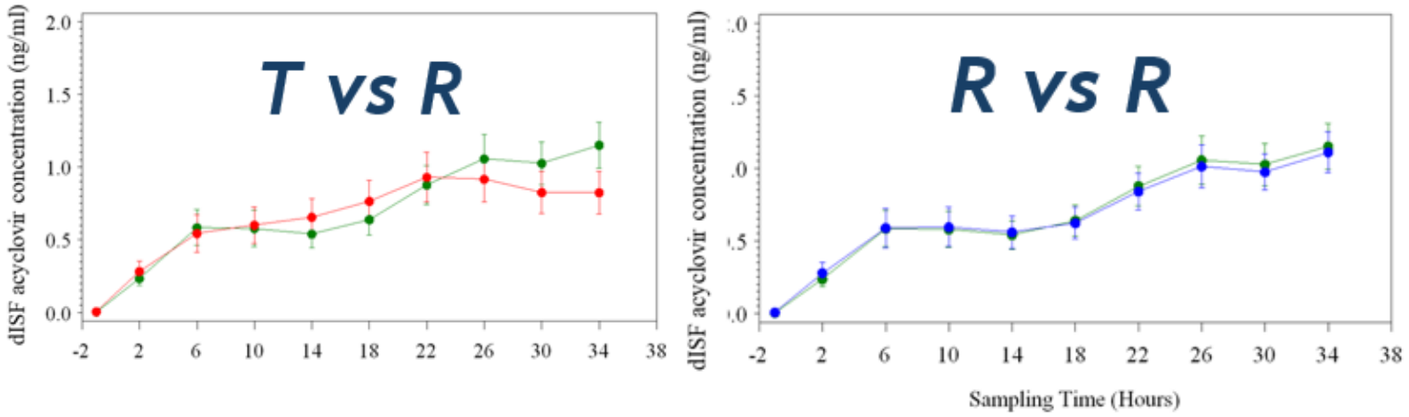
Comparing two marketed acyclovir formulations





(R) Zovirax vs. (T) Aciclovir 1A Pharma

- 20 healthy subjects (instead of ~1000 patients in standard endpoint setting)
- Application of multiple drugs on one subject …
  - allows direct comparison
  - reduces inter-subject variability (>80%)



"Variability of Skin Pharmacokinetic Data" Bodenlenz et al. Pharmaceutical Research. 2020

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Prediction of Clinical Results at R&D Sweet Spot

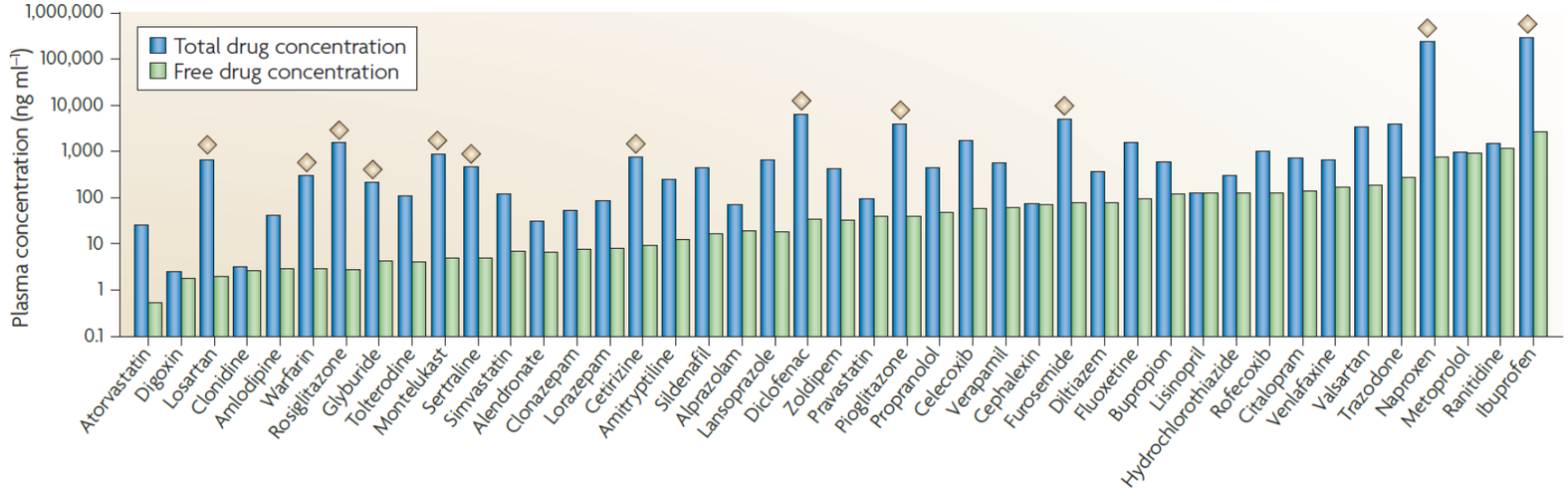
OFM

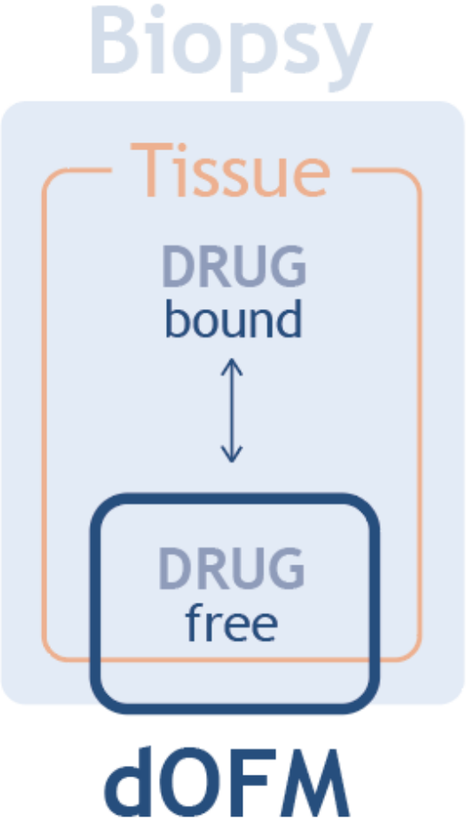
Prediction of Clinical Results

Comparison of dOFM and biopsy

Free drug fraction = active drug fraction

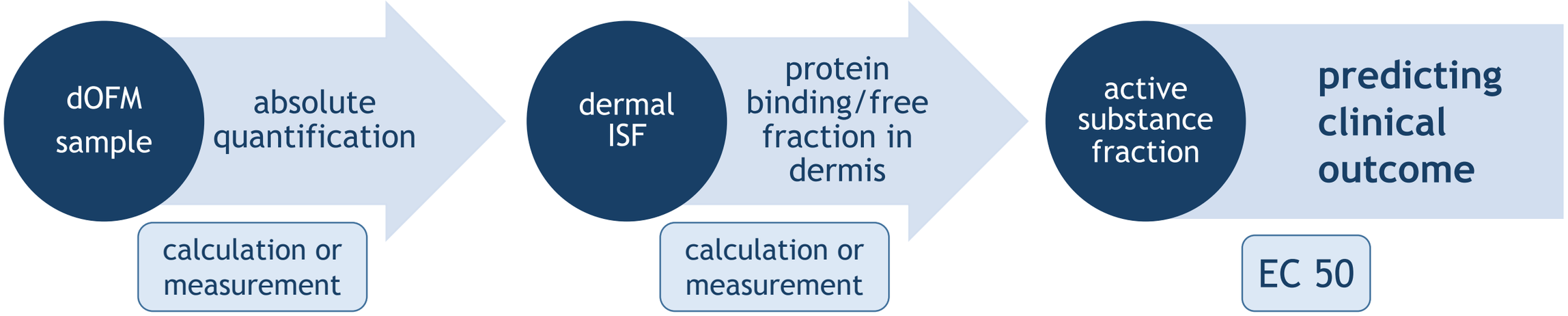
"The ADMEa Ecyclopedia – Free Drug Theory" Talevi et al. 2021





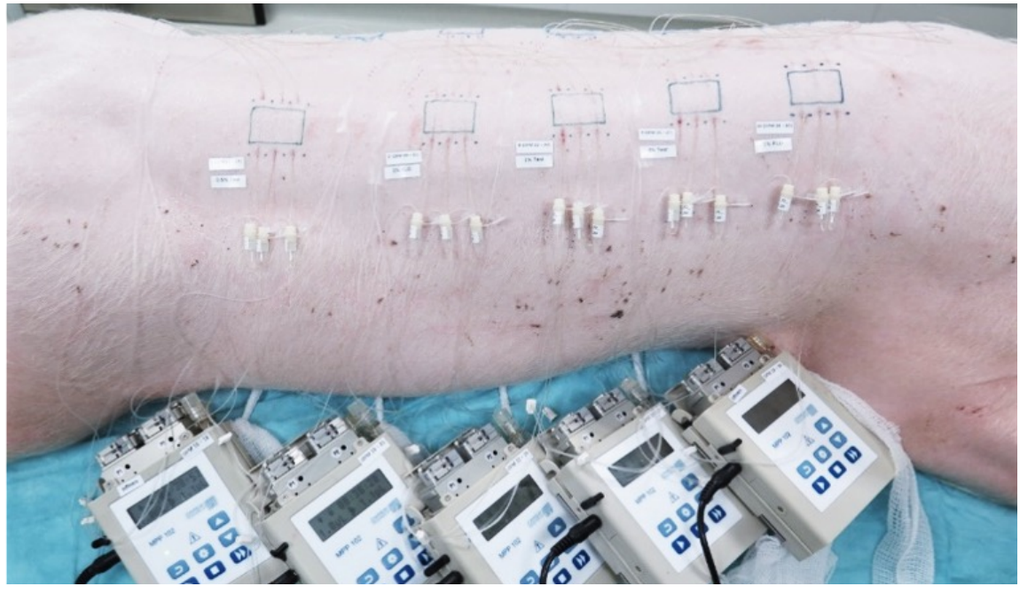
"Many of the most prescribed drugs have greater than 98% protein binding" (Smith – Nature Reviews Drug Discovery 2010)

Derisking Clinical Study Outcome

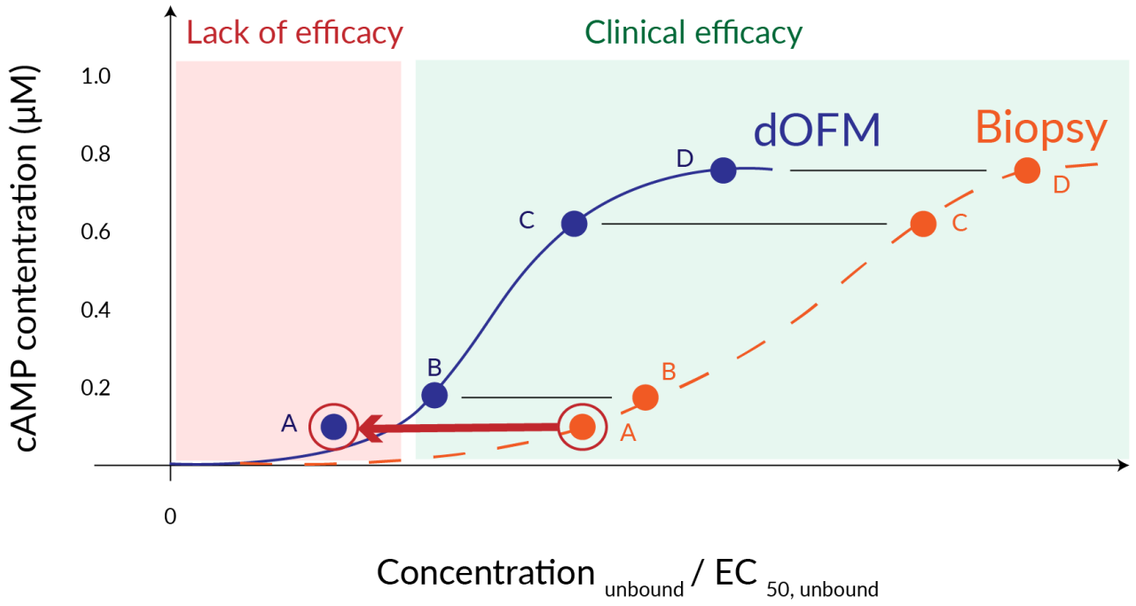


Derisking Clinical Study Setups

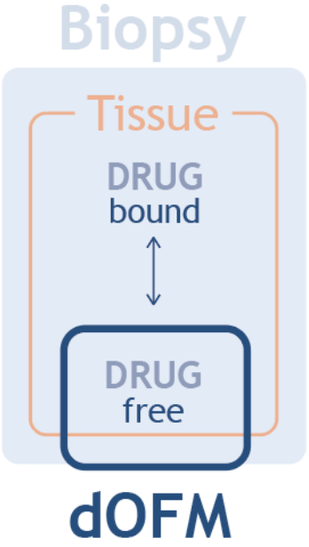
- ex-vivo human and in-vivo pig studies
  - determination of free fraction in the dermis
  - compare biopsies and dOFM sampling



dOFM – not Biopsy - Predicted Clinical Outcome



- dOFM identified ineffective concentration of study drug.
- dOFM concentration correlated with the drugs‘ clinical efficacies (rank order correlation).
- dOFM showed superior predictivity compared to biopsies.



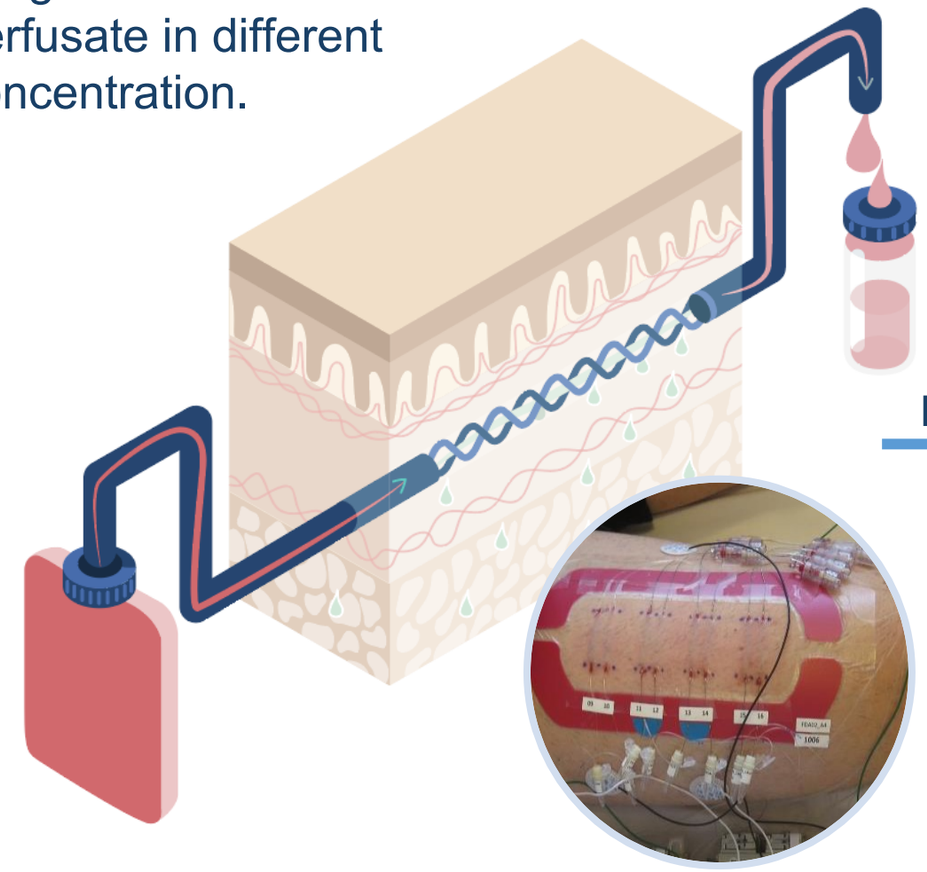
Results were confirmed in clinical study.

Eirefelt, S., et al. (2020). Evaluating Dermal Pharmacokinetics and Pharmacodymanic Effect of Soft Topical PDE4 Inhibitors: Open Flow Microperfusion and Skin Biopsies. Pharmaceutical Research, 37(12), 243. https://doi.org/10.1007/s11095-020-02962-1

Early Dose-Response Study via dOFM Microdosing

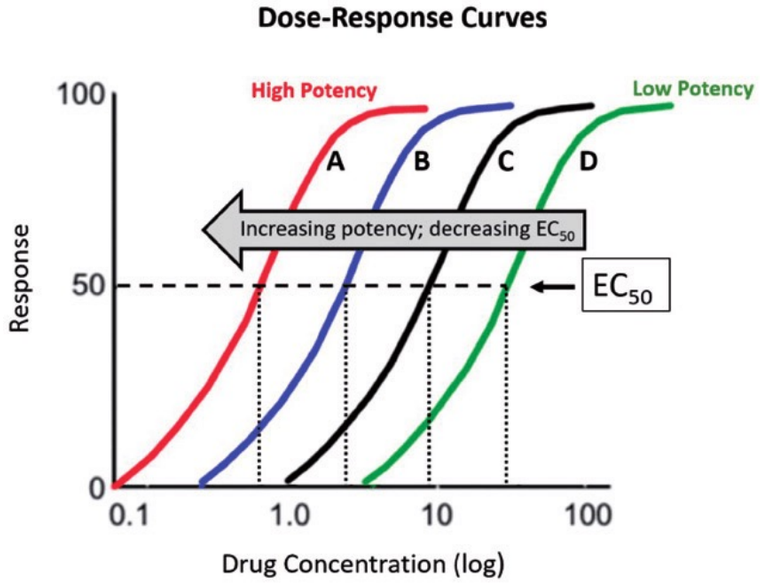
dOFM Microdosing Enables Minimal Systemic Exposure

Drug candidate is added to perfusate in different concentration.

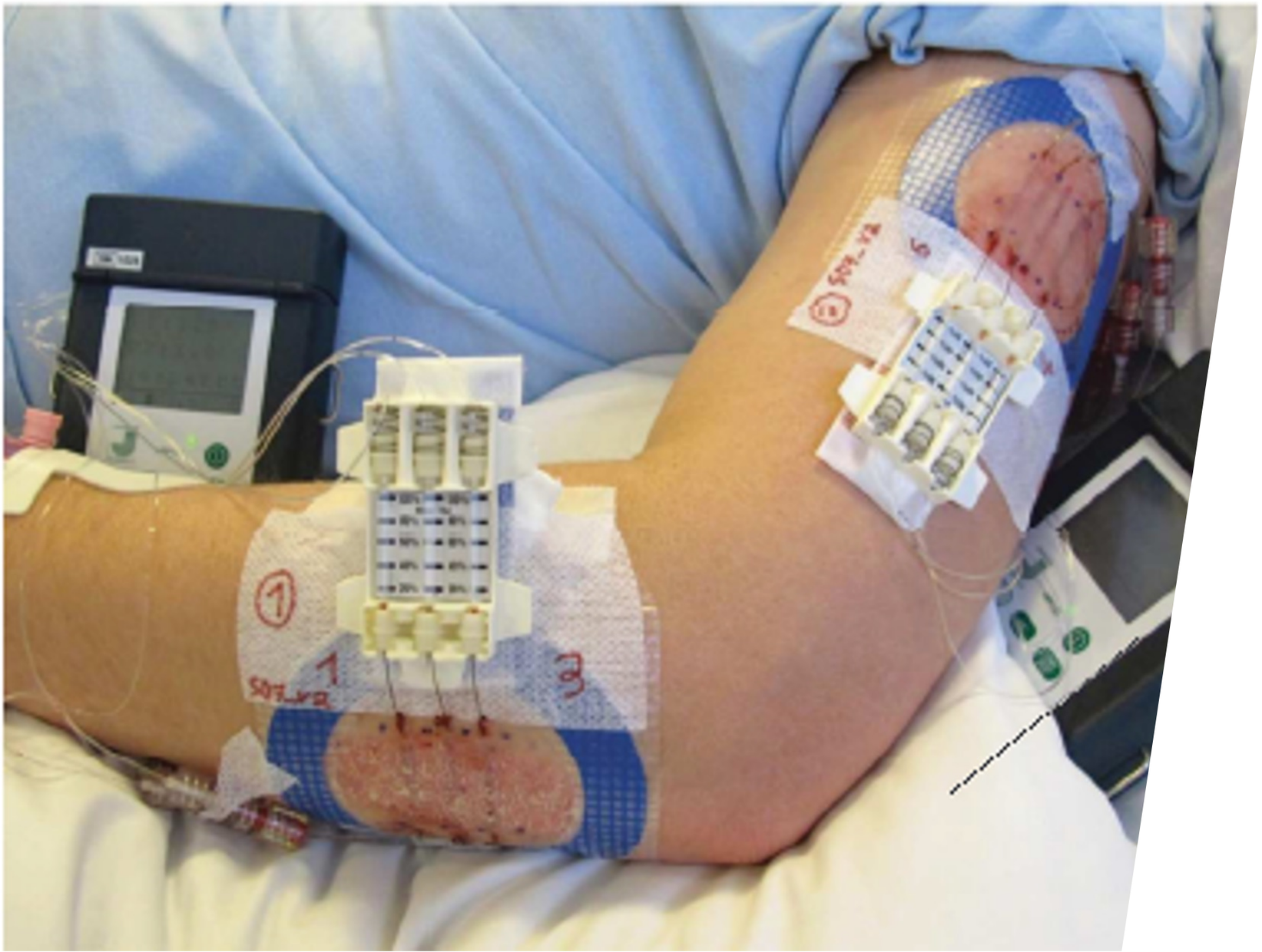


biomarker readout

Clinical studies for proof of mechanism + dose response



Source: 2019 Journal of Dermatological Treatment
DOI: 10.1080/09546634.2019.1643588



Show Case: Clinical Study for Systemic Drug: Novartis - Secukinumab

Clinical Case Study

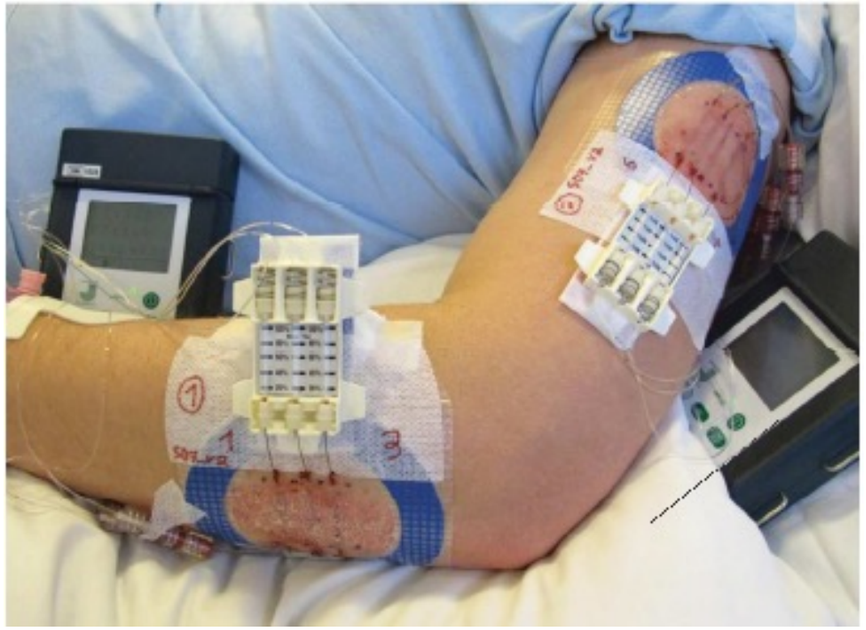
Proof of Concept for Systemic Antibody Drug

(1) Pharmacokinetics of API in human target tissue

(2) Target verification in small but efficient clinical setup

(3) Pharmacodynamics

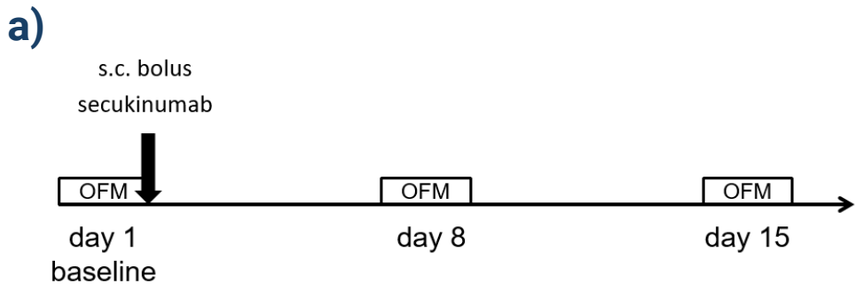
(4) Target-tissue specific biomarker

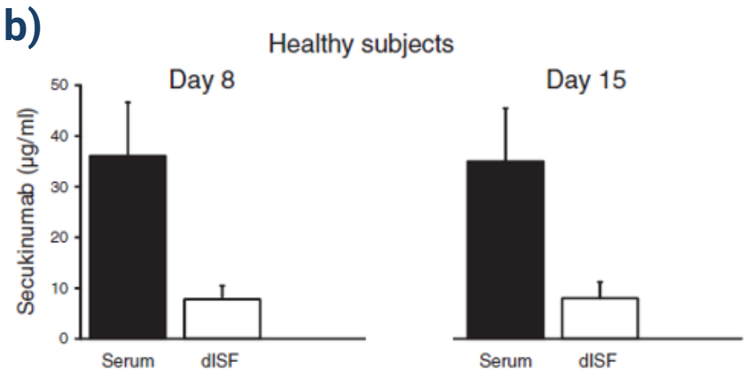


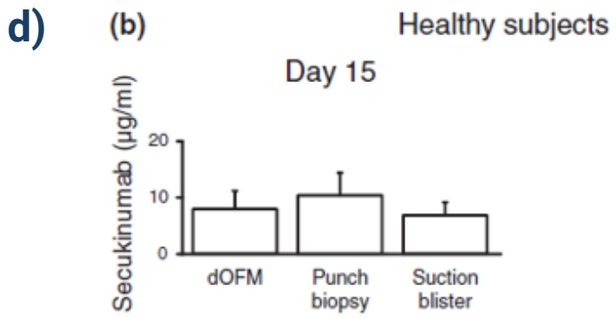
- Secukinumab: antibody drug for psoriasis (targets IL-17A)
- Clinical study in healthy volunteers and psoriasis patients
- Therapeutic target (IL-17A)
- PK in blood, healthy skin, lesional skin
- Monitoring of therapeutic effect with biomarkers
- Screening for biomarkers

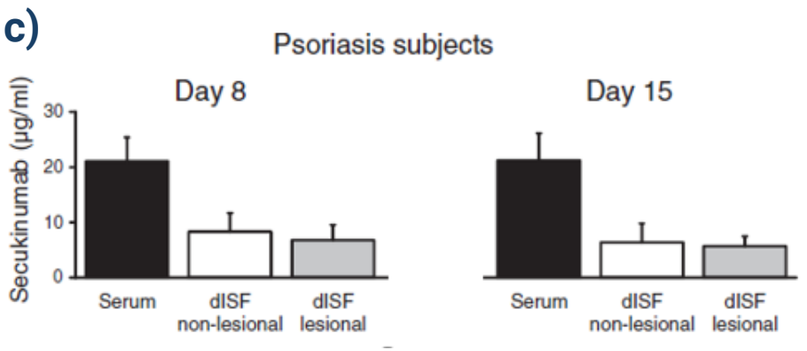
Source: JOANNEUM RESEARCH

(1) dOFM PK Data Show Sufficient Secukinumab Concentrations







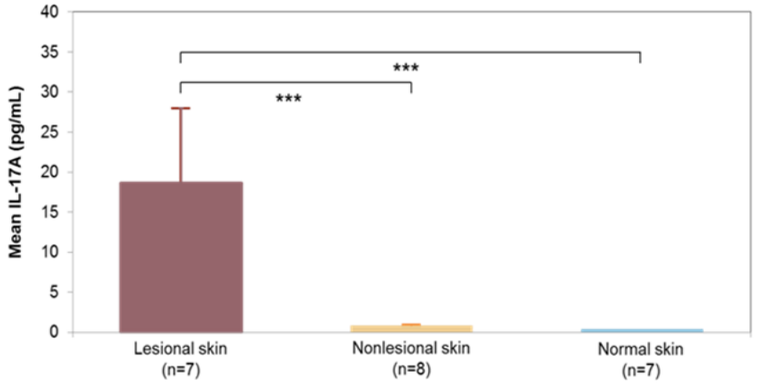


"Secukinumab distributes into dermal interstitial fluid of psoriasis patients as demonstrated by open flow microperfusion" Dragatin et al. Exp. Dermatology. 2016 doi: 10.1007/s40262-016-0442-z.– OPEN ACCESS

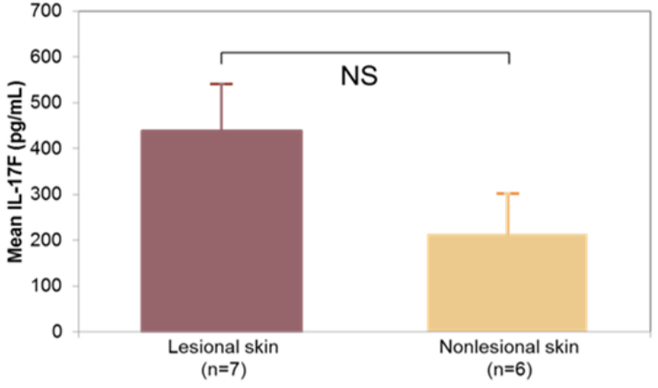
Clinical Case Study

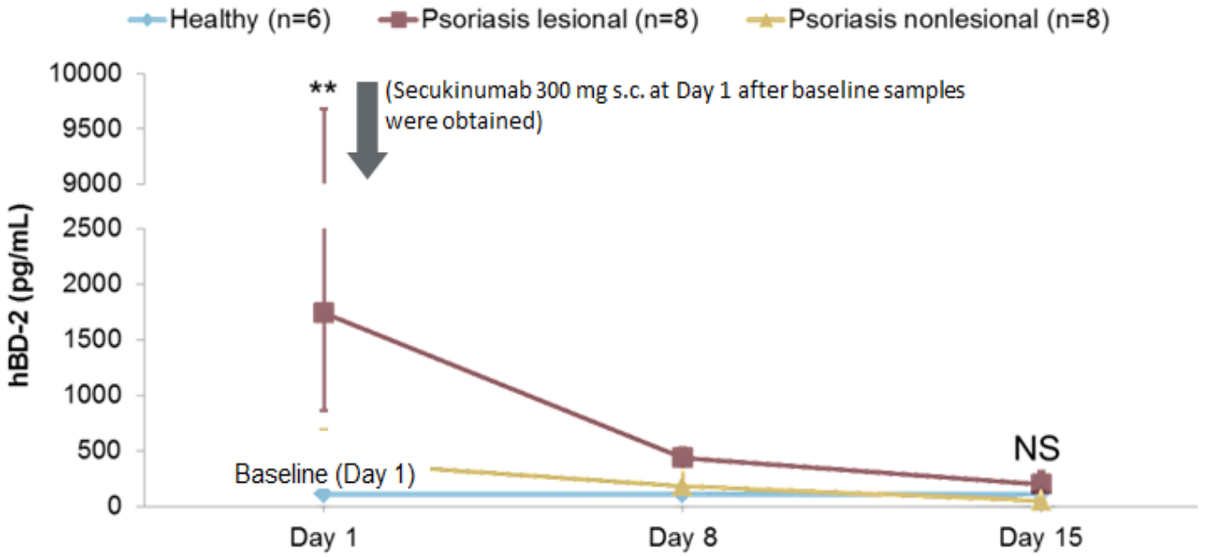
(2) dOFM Data Verified the Therapeutic Target
(3) Pharmacodynamics of Treatment

Therapeutic target (IL-17A)



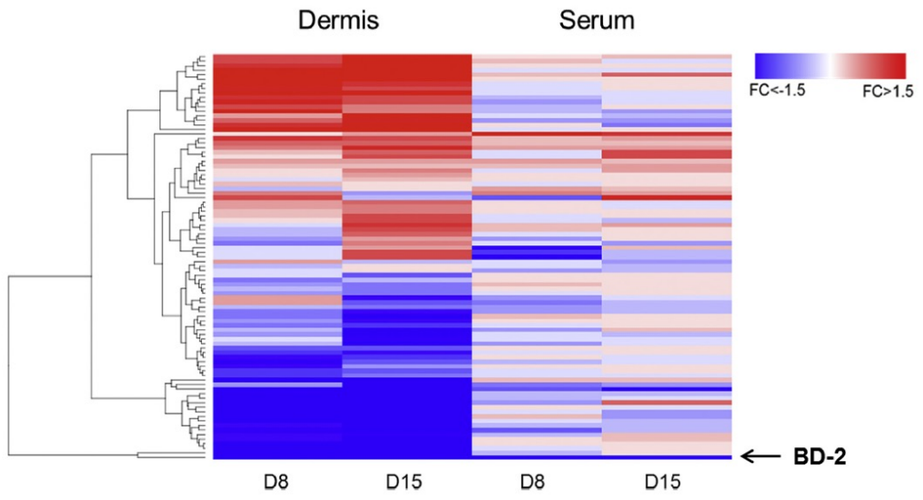
Therapeutic target (IL-17F)





Monitoring of therapeutic effect based on downstream biomarker of IL-17A (hBD-2)

Target-Tissue-Specific dOFM Provides Increased Sensitivity for Biomarkers



	Fold change relative to baseline			
	Dermis (dISF)		Serum	
Protein	Day 8	Day 15	Day 8	Day 15
Top 10 downregulated				
BD-2	−18.73	−32.20	−3.95	−3.66
MMP-1	−6.20	−15.19	−1.11	1.04
IL-1β	−2.71	−5.47	1.14	1.14
IL-1 receptor antagonist (IL-1ra)	−2.19	−4.37	−1.47	−2.32
MMP-8	−1.91	−3.42	−1.16	−1.07
Myeloperoxidase	−1.18	−3.20	−1.27	−1.18
CXCL1 (GRO-α, *CXCL1*)	−2.63	−3.13	−1.08	−1.17
Lipocalin-2 (NGAL, *LCN2*)	−2.14	−2.98	−1.11	−1.12
CCL20 (Macrophage inflammatory protein 3α, *CCL20*)	−2.62	−2.64	−1.24	1.45
CXCL5 (ENA-78, *CXCL5*)	−3.00	−2.50	1.05	−1.02
Other proteins of interest				
CXCL3 (GRO-γ, *CXCL3*)	−1.61	−2.20	−1.16	−1.08
CCL1 (I-309, *CCL1*)	−1.34	−1.88	1.09	1.03
TNF-α	1.00	1.18	1.04	1.03
Top 5 upregulated				
Endoglin	2.51	2.52	1.04	1.08
Leptin	2.59	2.62	1.09	1.39
Adiponectin (Acrp-30)	1.50	2.72	1.13	−1.04
Eotaxin-2 (*CCL24*)	1.56	2.77	1.06	1.14
IgE	1.92	3.19	−1.00	−1.06

Different signaling pathways in the dermis of patients with psoriasis.

“β-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis” Kolbinger et al. J Allergy Clin Immonol. 2016 doi: 10.1016/j.jaci.2016.06.038

Key Learnings

What is dOFM, and what is it used for?

dOFM (dermal open flow microperfusion) is a sampling technology that enables PK and PD studies on tissue level in clinical and preclinical settings.

What can dOFM sampling contribute at the R&D sweet spot?

A phase during drug development where decisions are very critical. All information that leads to de-risking of the processes following the R&D sweet spot makes the drug development process very efficient.

What is the difference between a biopsy and a dOFM sample?

A biopsy contains a big fraction of bound API that is inactive whereas dOFM contains the free and active drug fraction and is thus highly predictive for the drug effect.

How can clinical drug efficacy be predicted using dOFM?

Preclinical dOFM setups provide a PK-based ranking for candidate formulations. dOFM delivers the required API concentration to the target tissue in clinical microdosing studies.

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dOFM

Q & A session

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