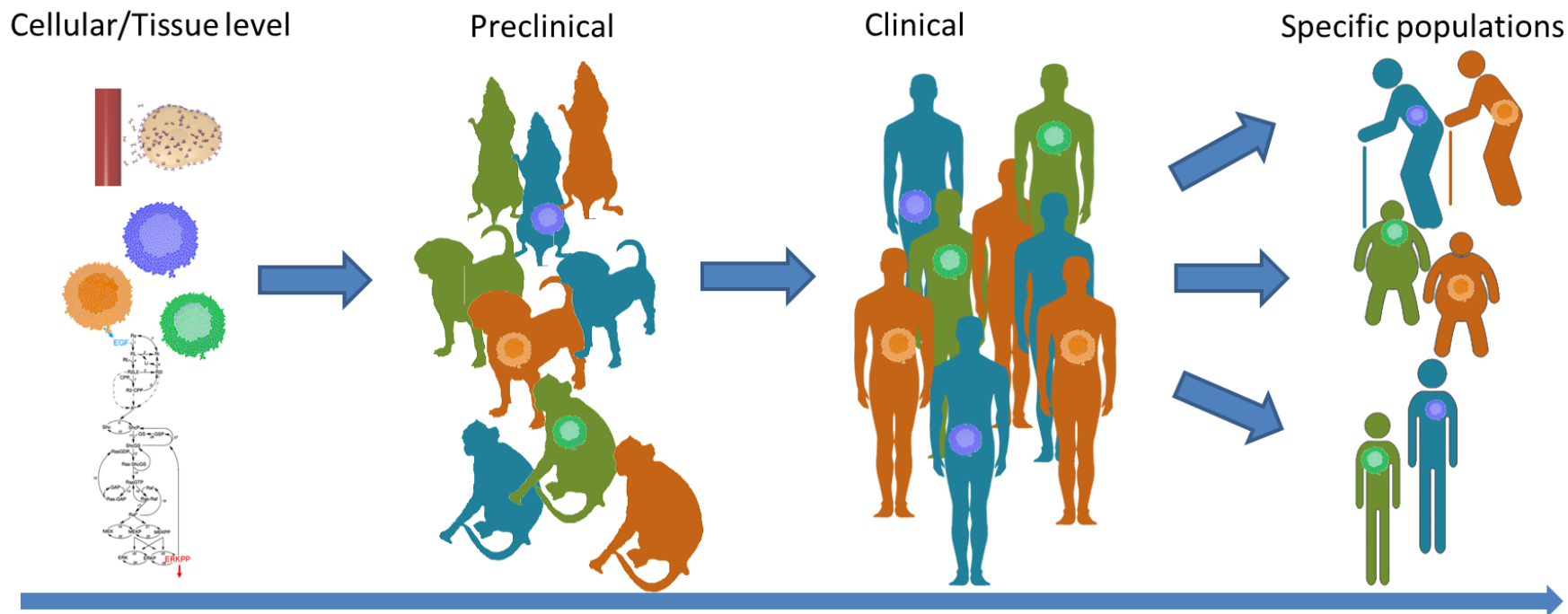PBPK/PD MODELING TO PROVIDE A TRANSLATIONAL RATIONALE BETWEEN DRUGS AND BETWEEN SPECIES - EXAMPLE OF TRAIL FUSION PROTEINS

Poster talk – ASCPT 2016, San Diego

Science For A Better Life

Michael Block

Application of modeling

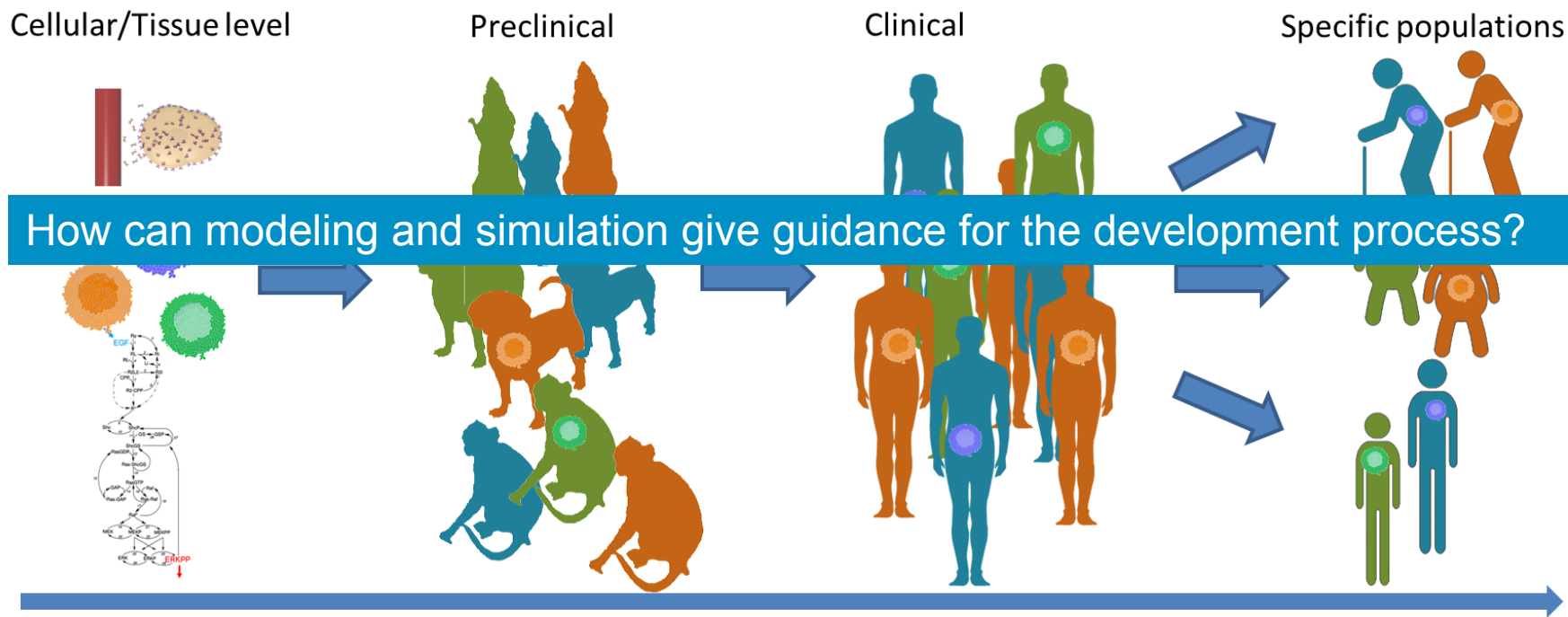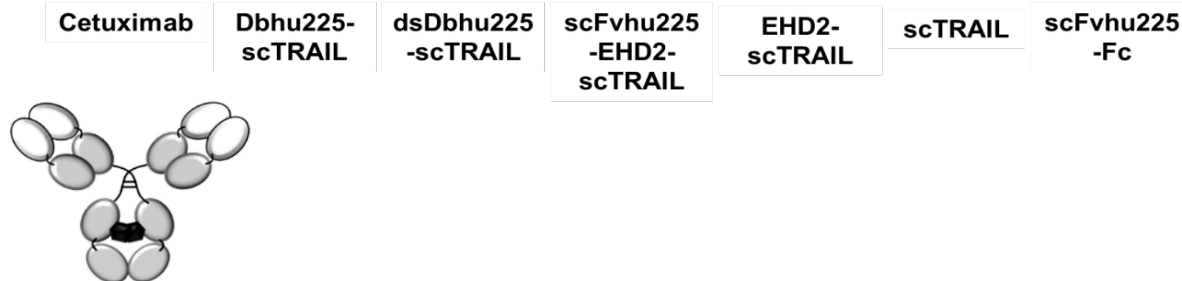Cellular/Tissue level   Preclinical   Clinical   Specific populations

Multi-scale approach for oncological PBPK/PD models in Pharma R&D

Learn and confirm   **Prediction and validation**

M. Block: Expert Opin Drug Metab Toxicol. 2015 May;11(5):743-56.

Application of modeling

Cellular/Tissue level   Preclinical   Clinical   Specific populations

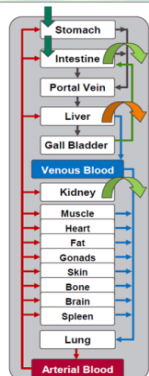How can modeling and simulation give guidance for the development process?

Multi-scale approach for oncological PBPK/PD models in Pharma R&D

Learn and confirm   **Prediction and validation**

M. Block: Expert Opin Drug Metab Toxicol. 2015 May;11(5):743-56.

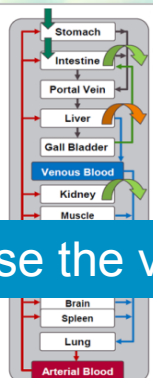# Translational rationale for TRAIL proteins

		Cetuximab	Dbhu225-scTRAIL	dsDbhu225-scTRAIL	scFvhu225-EHD2-scTRAIL	EHD2-scTRAIL	scTRAIL	scFvhu225-Fc
EGFR binding	mice							
	xenograft	x	x	x	x			x
	patients	x	x	x	x			x
DR5 binding	mice		x	x	x	x	x	
	xenograft		x	x	x	x	x	
	patients		x	x	x	x	x	
FcRn binding	mice	x						x
	xenograft	x						x
	patients	x						x

Learn EGFR binding for TRAIL molecules

Learn and confirm:
1. Binding of TRAIL fusion proteins to DR5 in mice
2. Binding of TRAIL fusion proteins to EGFR and DR5 in xenografts
3. Impact of TRAIL fusion proteins on tumor growth.

Learn FcRn binding for TRAIL molecules

Translational rationale for TRAIL proteins

Use the versatile toolbox to learn from the different fusion proteins

		Cetuximab	Dbhu225-scTRAIL	dsDbhu225-scTRAIL	scFvhu225-EHD2-scTRAIL	EHD2-scTRAIL	scTRAIL	scFvhu225-Fc
EGFR binding	mice							
	xenograft	x	x	x	x			x
	patients	x	x	x	x			x
DR5 binding	mice		x	x	x	x	x	
	xenograft		x	x	x	x	x	
	patients		x	x	x	x	x	
FcRn binding	mice	x						x
	xenograft	x						x
	patients	x						x

Learn EGFR binding for TRAIL molecules

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Learn FcRn binding for TRAIL molecules

Rationale for modeling and translation

Results – PBPK modeling

First step: Establish the PBPK model structure by use of a well known benchmark compound

- Exp. SD IV 0.04 mg
- Exp. SD IV 0.25 mg
- Exp. SD IV 1 mg
- Sim. SD IV 0.04 mg
- Sim. SD IV 0.25 mg
- Sim. SD IV 1 mg

- Exp. SD IP 0.04mg Plasma Concentration
- Exp. SD IP 0.04mg Tumor Concentration
- Sim. SD IP 0.04mg Plasma Concentration
- Sim. SD IP 0.04mg Tumor Concentration
- Sim. SD IP 0.04mg Receptor Occupancy

Results – PBPK modeling

First step: Establish the PBPK model structure by use of a well known benchmark compound

Legend (left chart):
- Exp. SD IV 0.04 mg
- Exp. SD IV 0.25 mg
- Exp. SD IV 1 mg
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- Sim. SD IV 1 mg

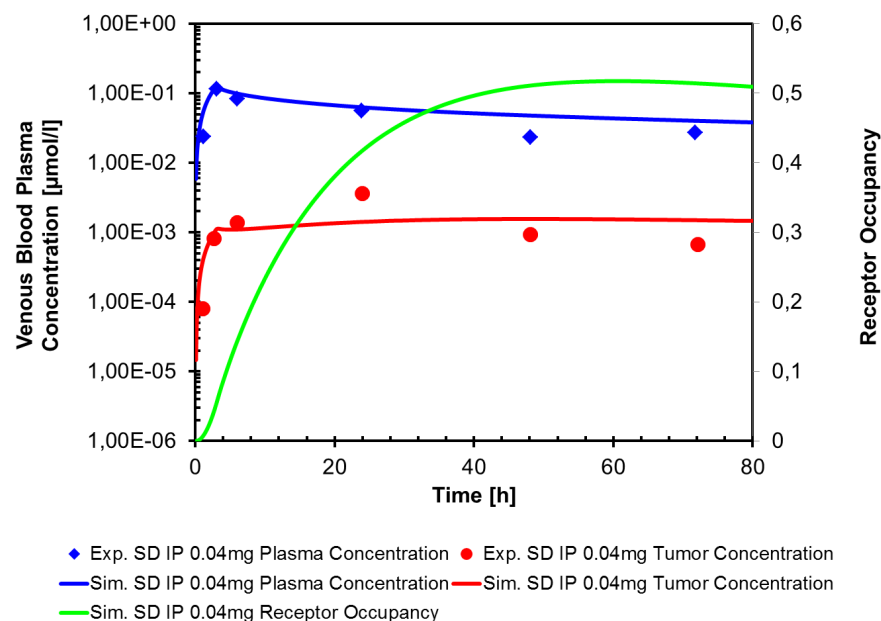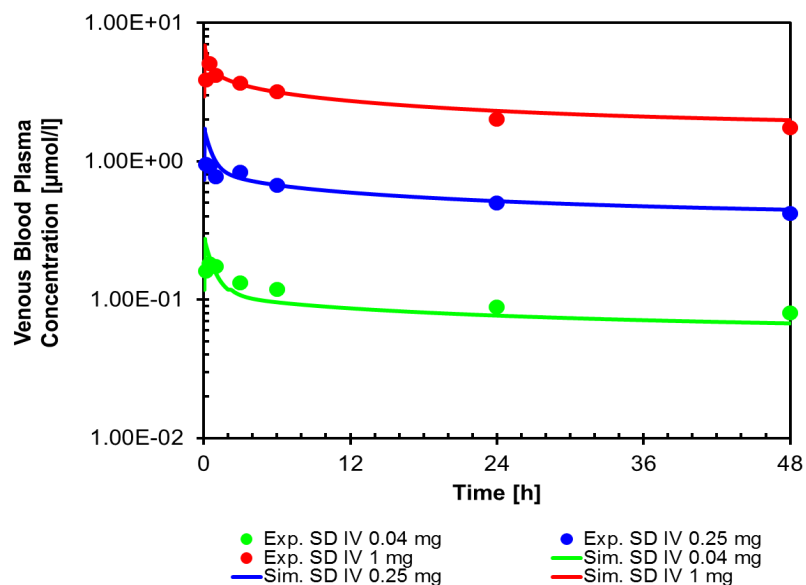Legend (right chart):
- Exp. SD IP 0.04mg Plasma Concentration
- Exp. SD IP 0.04mg Tumor Concentration
- Sim. SD IP 0.04mg Plasma Concentration
- Sim. SD IP 0.04mg Tumor Concentration
- Sim. SD IP 0.04mg Receptor Occupancy

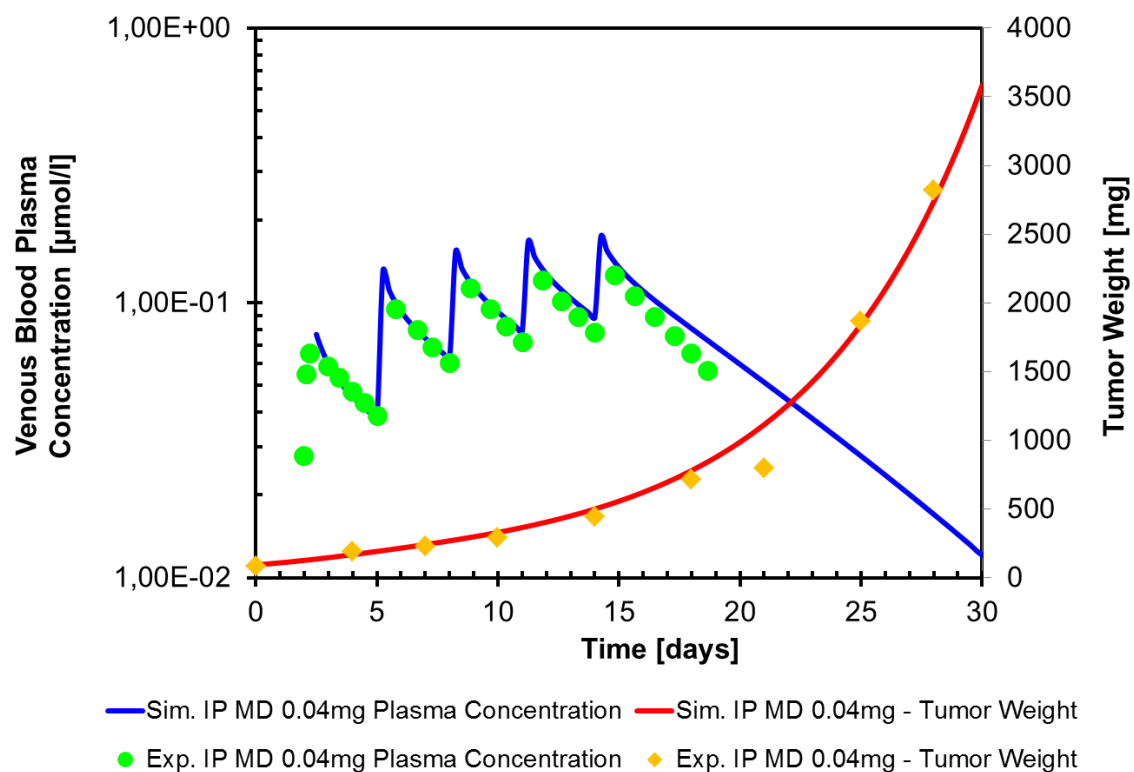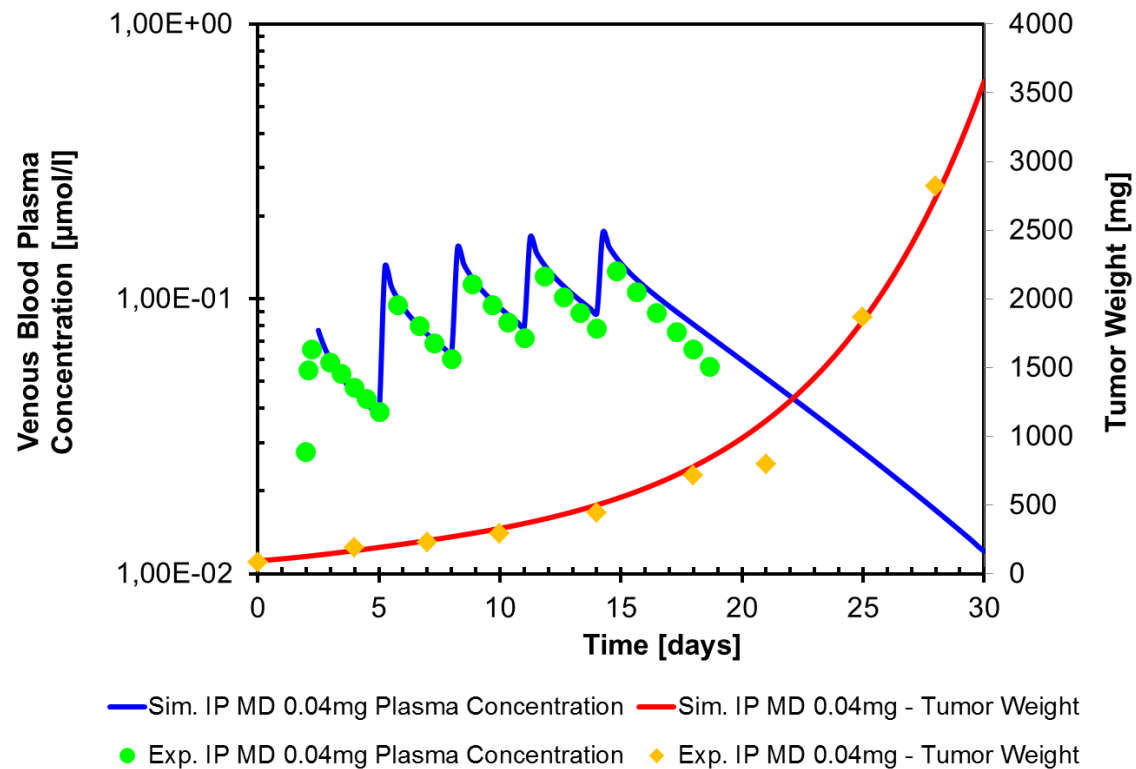**Plasma PK and receptor occupancy are in well agreement with existing data**

PK-Sim®   MoBi®
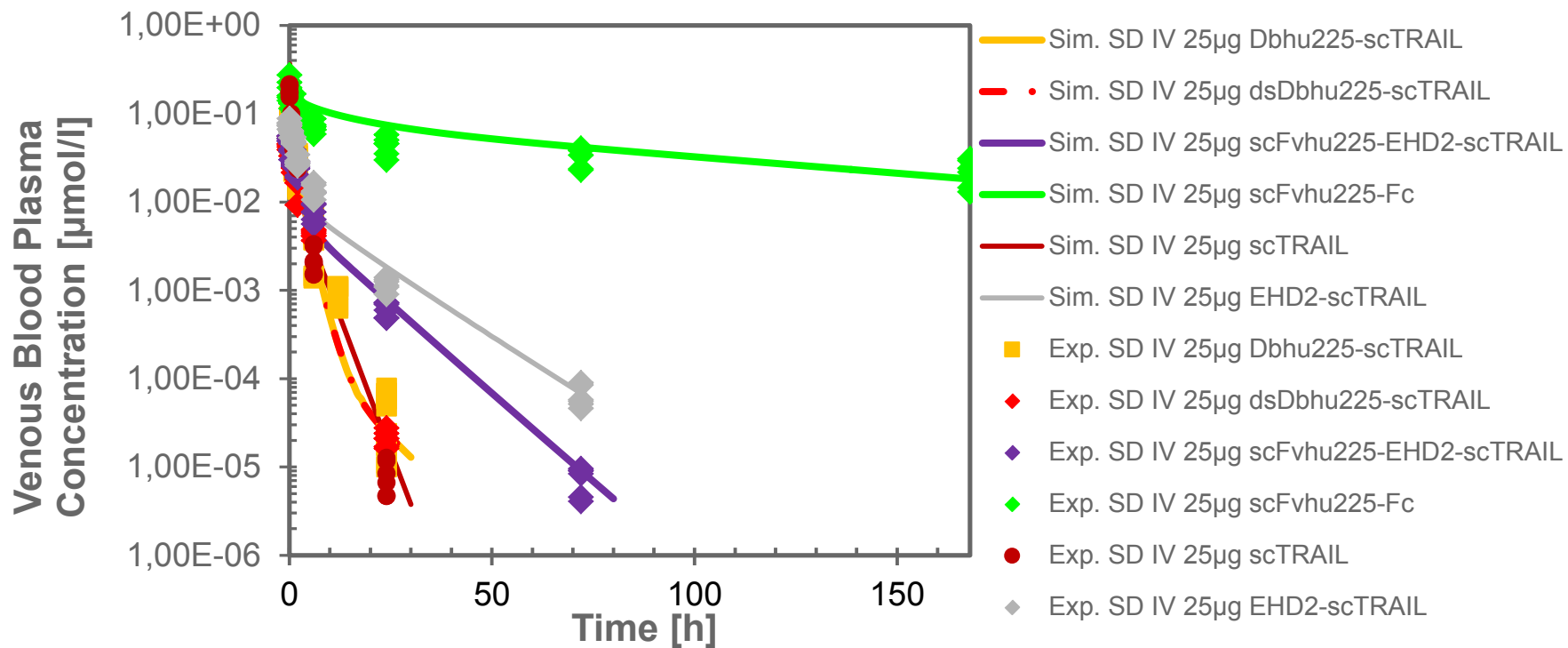
Results – PBPK/PD modeling

Plasma PK and tumor growth are in well agreement with existing data

PBPK modeling results for TRAIL

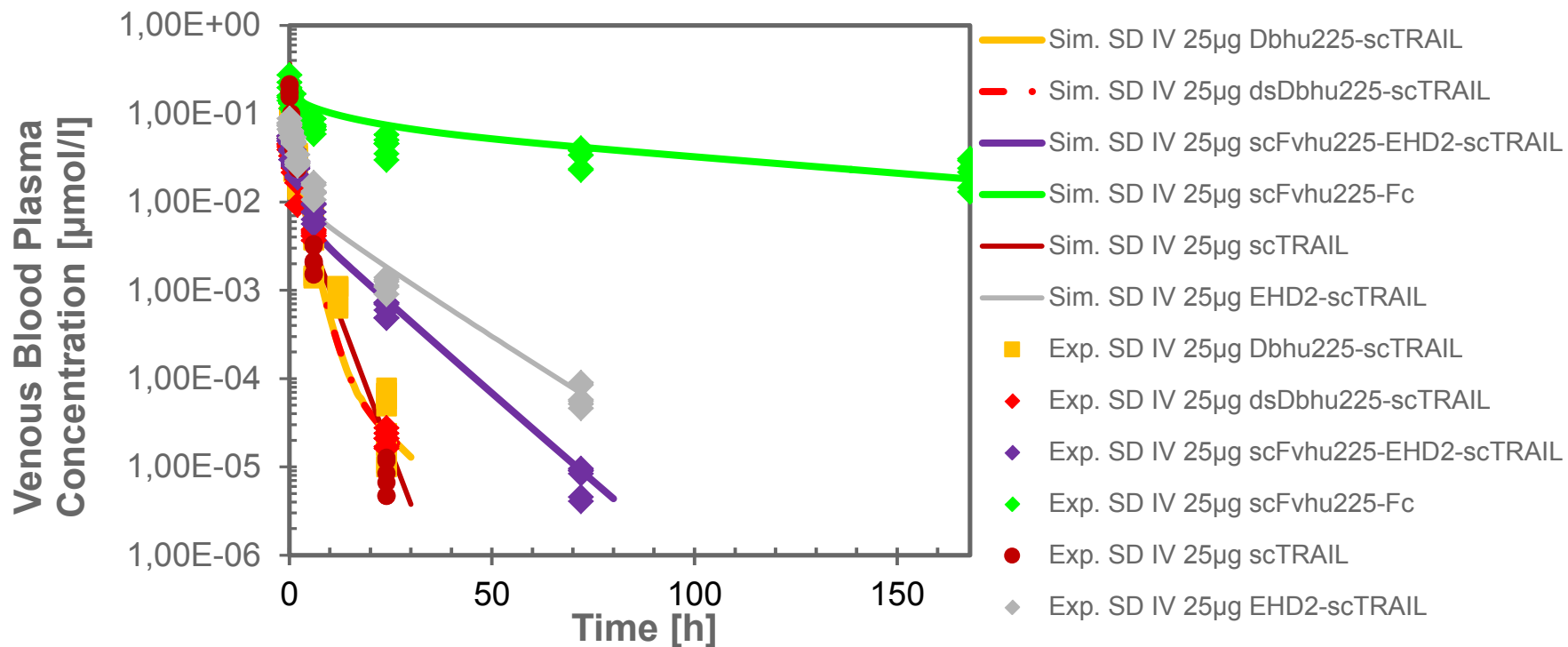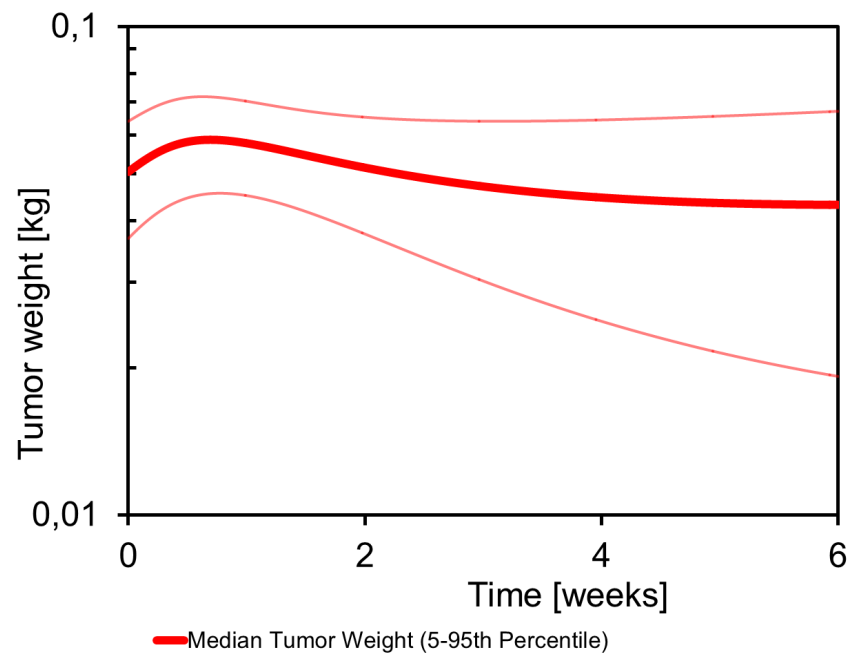# PBPK modeling results for TRAIL

Plasma PK of all TRAIL fusion proteins is consistently described by the PBPK model. Differences are due to different binding and physicochemical properties

Translation to human for Cetuximab
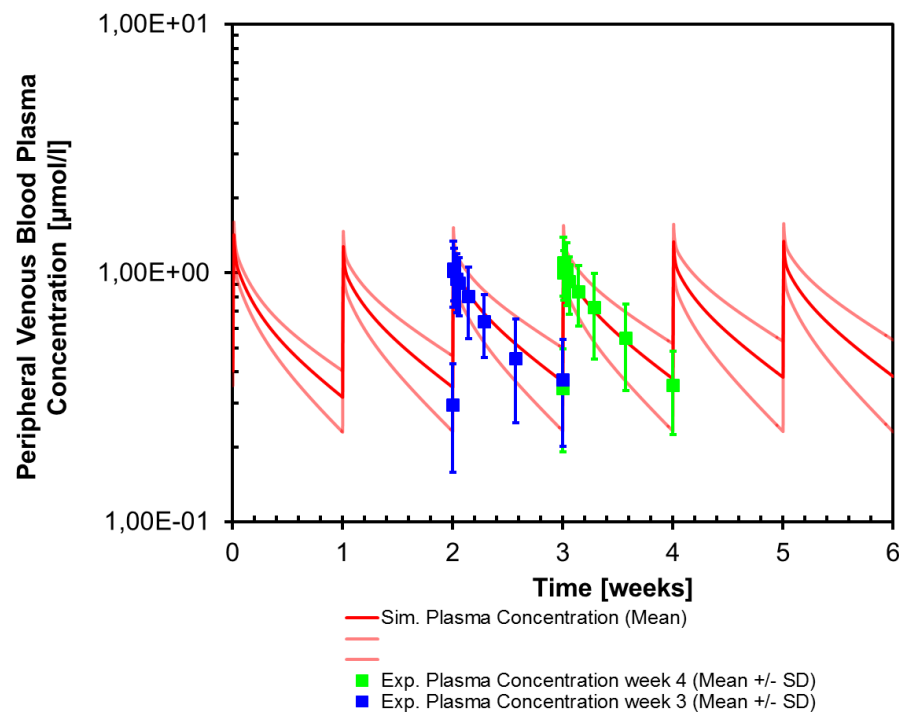
Translation to human for Cetuximab

Translation of nicely represented multiple dose data was performed for Cetuximab with reasonable growth rates from literature

Summary

- PBPK/PD translational rationale was shown

- Recent data for Cetuximab (preclinical/clinical) were consistently described

- Translation for preclincal data to TRAIL fusion proteins were performed

Summary

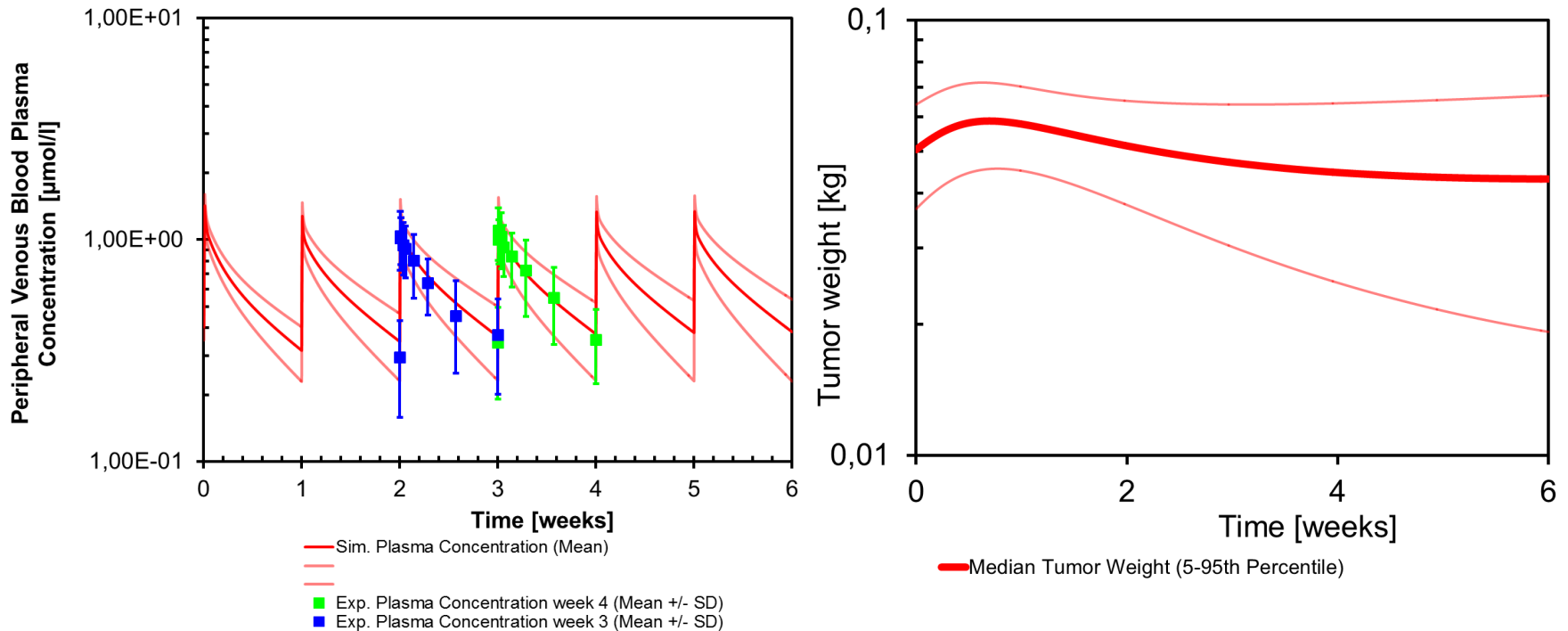- PBPK/PD translational rationale was shown

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- Quantitative data on tumor growth in the clinics for the reference compound

- Data on receptor dynamics including recycling, synthesis, and degradation

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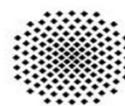**From a rationale to a workflow for translation**

Acknowledgements

Systems Pharmacology

Michael Block
Kristin Dickschen
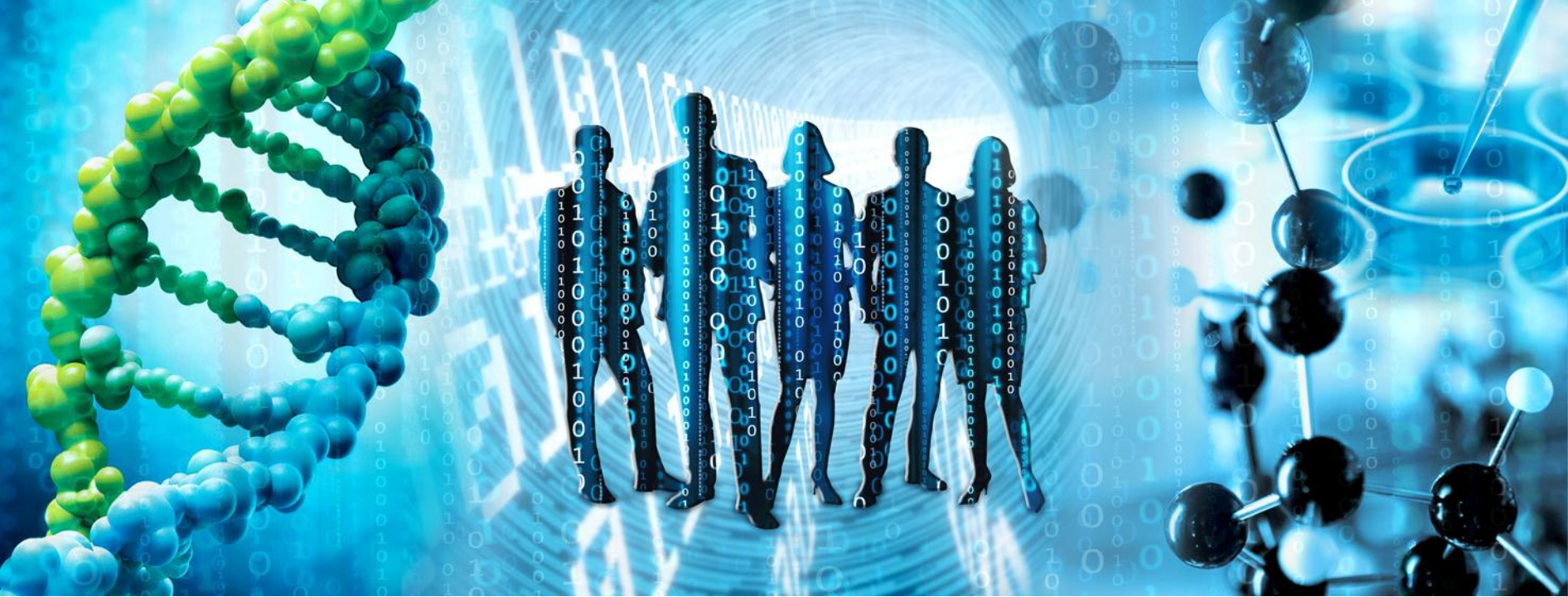Jürgen Jäger
Panteleimon Mavroudis

University of Stuttgart

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Nadine Pollak
Martin Siegemund
Oliver Seifert
Roland Kontermann
Klaus Pfizenmaier

Bayer
Science For A Better Life

Thank you!