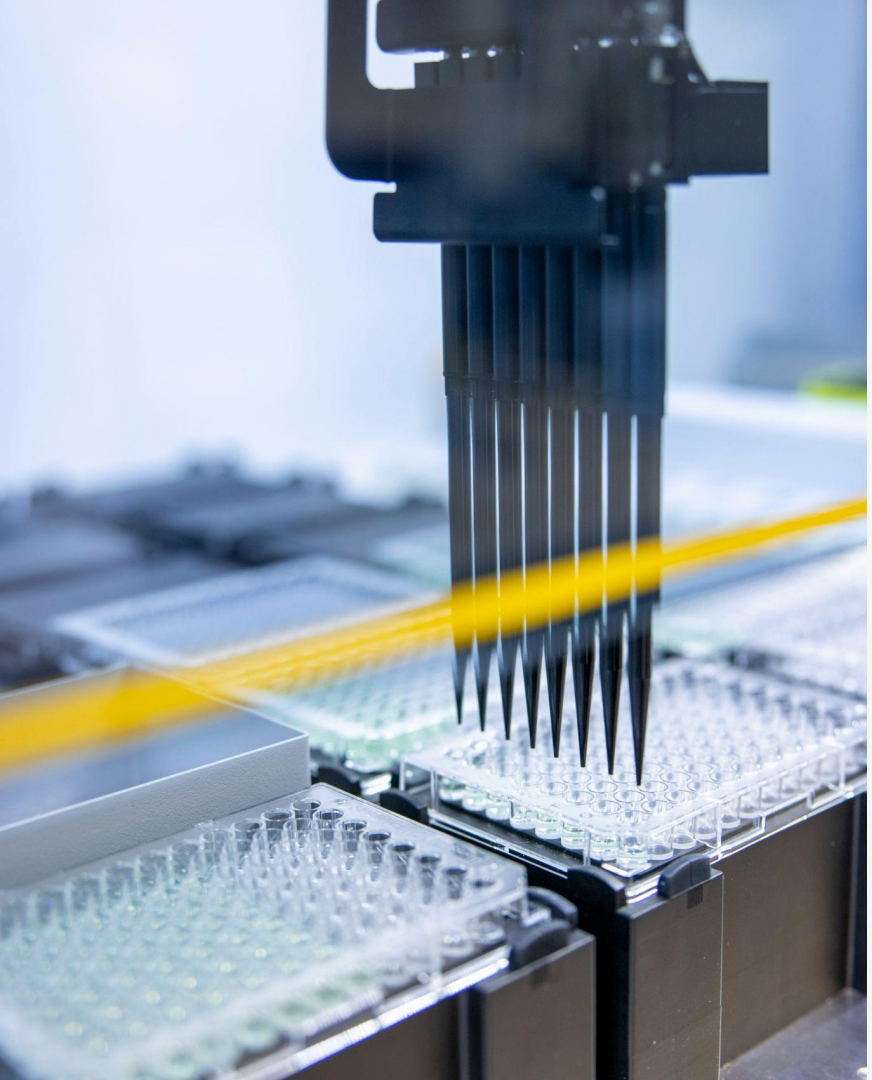


High-Throughput Physiologically -Based Pharmacokinetic Modeling and Simulation to Inform Early Drug Discovery

Dr. Andrés Olivares-Morales

Translational PK/PD and Clinical Pharmacology (TPCP)
Global Pharmaceutical Sciences
Roche Pharma Research and Early Development (pRED)
Roche Innovation Center Basel, Switzerland

MIDD+ Virtual Conference February 2023

Acknowledgements

Doha Naga

Scientific assessment of HT-PBPK predictions

PS/Tox Project Leads

Giuseppe Cecere

Subject Matter Expert, Medicinal Chemistry

TMo/MedChem

Neil Parrott

Senior Scientific Advisor, Subject Matter Expert PBPK

PS/M&S

Holger Fischer

Subject Matter Expert, DMPK

PS/TPCP

Andrea Morger

Business Owner

PS/PMDA

Yaniv Cohen

MVP development, pREDi liaison

pREDi

Peter Curle

Project Manager

pREDi

Michael Reutlinger

Subject Matter Expert, Machine Learning

TMo/CADD

Nenad Manevski

Subject Matter Expert, DMPK

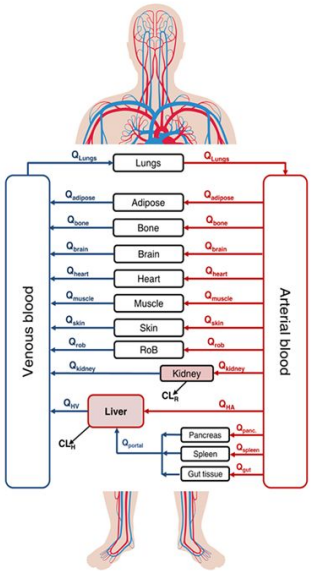
PS/DMPK-PD

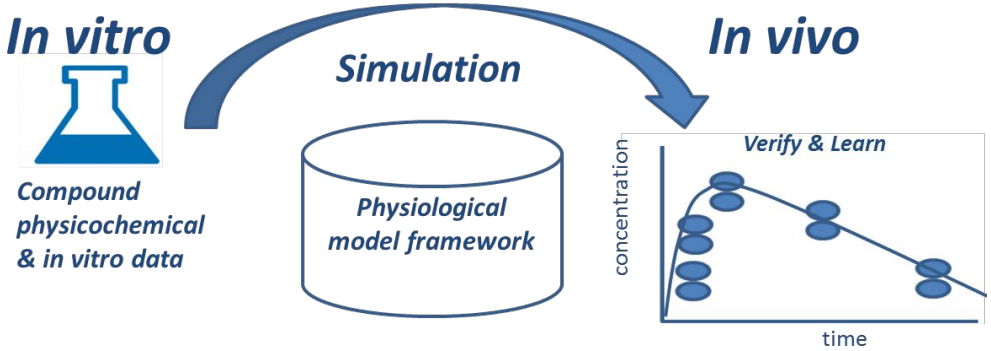
Matthias Wittwer

Subject Matter Expert, DMPK

PS/DMPK-PD

Physiologically-based pharmacokinetic modeling (PBPK)





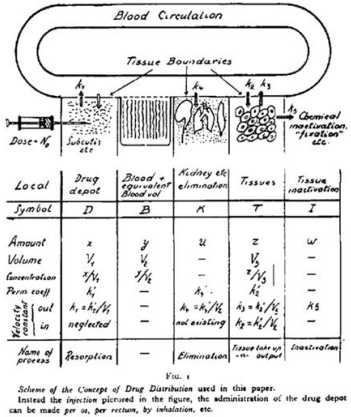
A mathematical modeling technique to predict pharmacokinetics

Combines physiological knowledge and compound properties

Input parameters can be in silico, in vitro or in vivo

Well established in the industry with user friendly commercial software available

TEORELL 1937

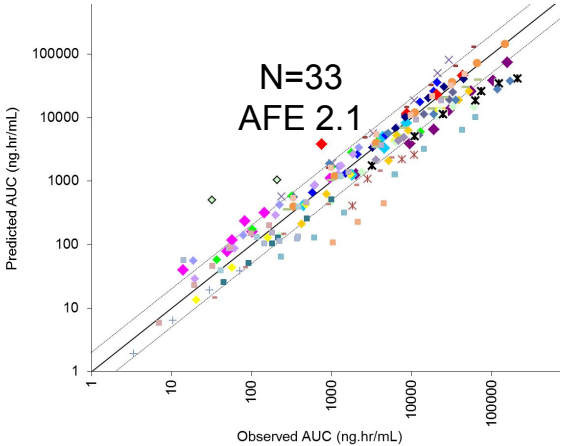


Scheme of the Concept of Drug Distribution used in this paper. Instead the injection pictured in the figure, the administration of the drug depot can be made per os, per rectum, by inhalation, etc.

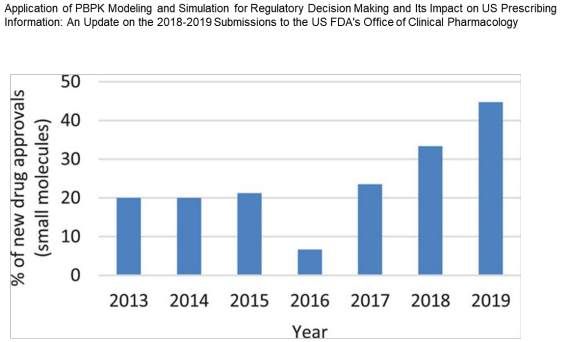
PBPK at Roche and Impact on out pipeline

- First applied in 2003
- Key validation efforts published 2006
- Systematic use since 2010
- Retrospective analysis in 2017 showed 69% success

Roche predictions for EiH



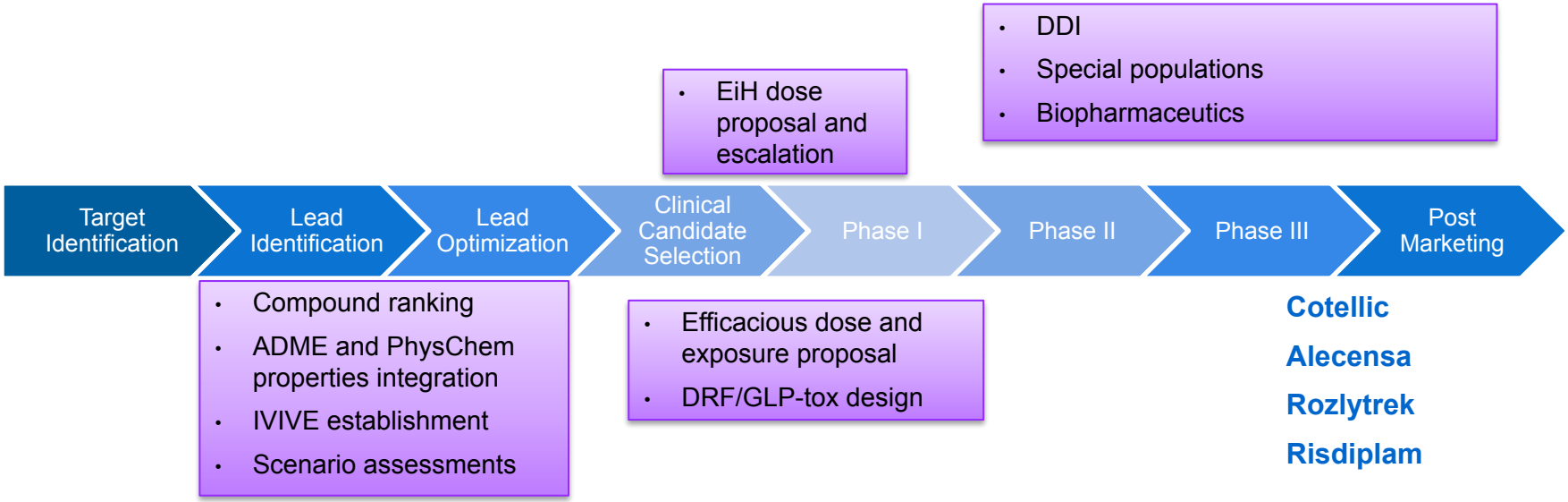
FDA submissions leveraging PBPK



Jones H, Parrott N, Jorga K and Lave T (2006): Clinical Pharmacokinetics 45(5): 511-542
Parrott N, Delporte M, Lave T, Peck R and Ricci B. CPT (2017) (Abstract PII-109);
Zhang X. et al (2020) Journal of Clinical Pharmacology 60: (S1) S16-S178

PBPK continuity throughout drug R&D

The applications span from early discovery to late development



Why PBPK is not systematically used in early drug discovery?

Several barriers were identified

Current barriers to use in early discovery

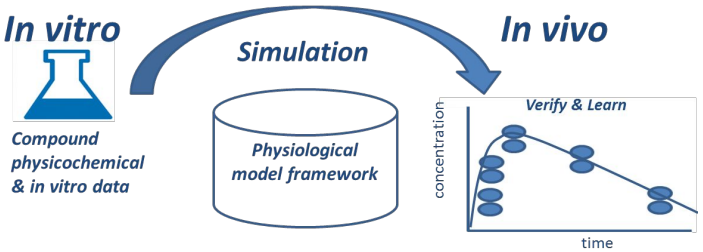
- Multiple compounds and limited time (**PBPK modeling needs time**)
- Multiple software needed (e.g., GastroPlus, BDS, ACTS/Phoenix)
- Lengthy set up & complex (manual) data transfers (from our data systems (e.g.D360) to the PBPK models such as GastroPlus/SimCYP)
- Limited pool of experts

This results in

- Limited usage by “non-experts”
- Reliance on simplistic equation-based tools which are easier to implement
- Rely heavily on animal experimentation for ranking and compound selection

But first…confidence!

Can we predict the PK of our discovery compounds?

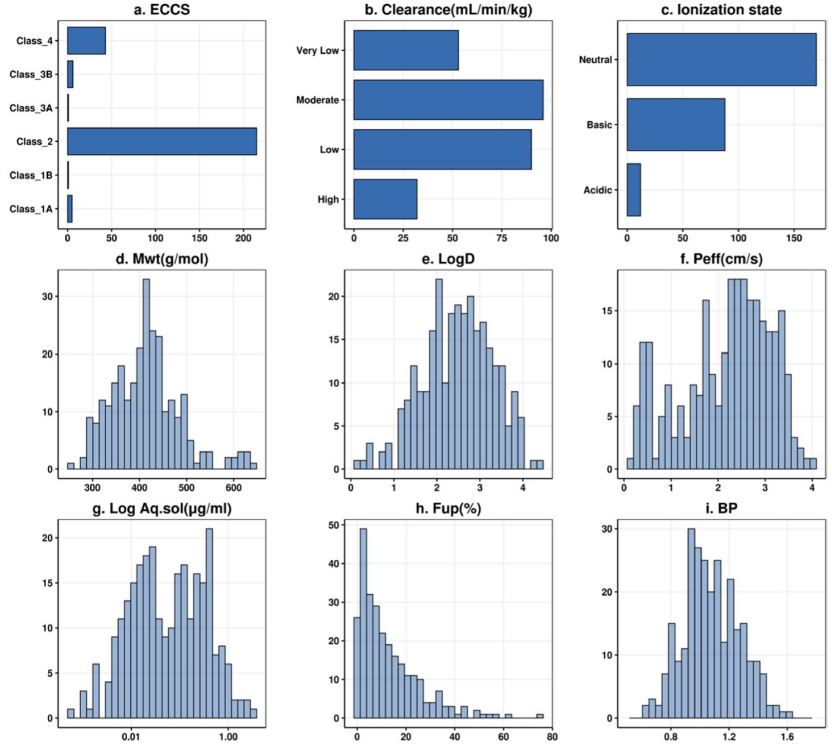


- Using only PBPK modeling combined with in vitro data only?
- What if we use Machine Learning inputs?
- Can we reproduce whole body PBPK simulations with a simplified PBPK model?

Jones H, Parrott N, Jorga K and Lave T (2006): Clinical Pharmacokinetics 45(5):

Our PBPK dataset

Large dataset of 240 (PO) and 271 (IV) structurally diverse compounds with PK in rats



Most of the in vitro data were available to inform oral PBPK simulations:

- LogD
- Aqueous solubility
- Biorelevant solubility (if available)
- Cellular permeability
- Fraction unbound in plasma (fup)
- Measured intrinsic clearance (suspension hepatocytes)

PK data

- Only single dose PK (ideally first in rat)
- 432 and 480 study arms (e.g., different dose levels, formulations, etc.)

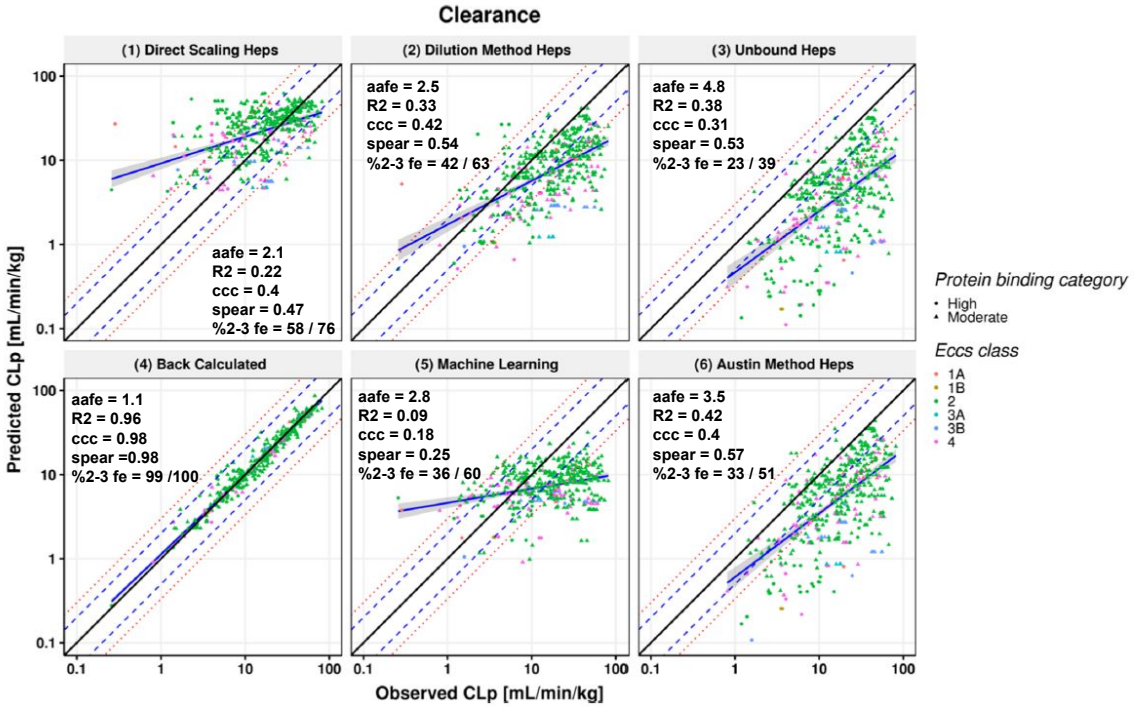
Predictions

- ADMET Predictor 10.1 and GastroPlus 9.8

Naga, D., Parrott N., Ecker G.F. and Olivares-Morales A (2022) Mol Pharmaceutics 19:2203-2216

PBPK predictions for a large number of discovery compounds (rats)

Clearance predictions within 3 fold for 63-76% of simulations



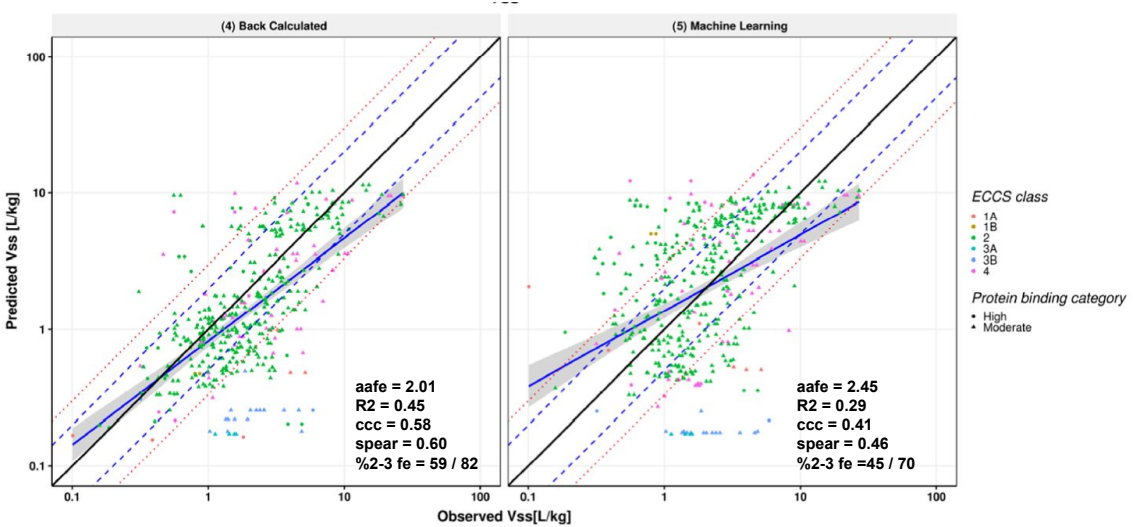
Machine learning inputs only predictions* were 36% to 60% within 2 to 3 fold, however correlation is poorer than when using the in vitro data

*ADMET predictor

Naga, D., Parrott N., Ecker G.F. and Olivares-Morales A (2022) Mol Pharmaceutics 19:2203-2216

PBPK predictions for a large number of discovery compounds (rats)

Volume of distribution predictions were within 2 -3 fold for 59% to 82% of the compounds

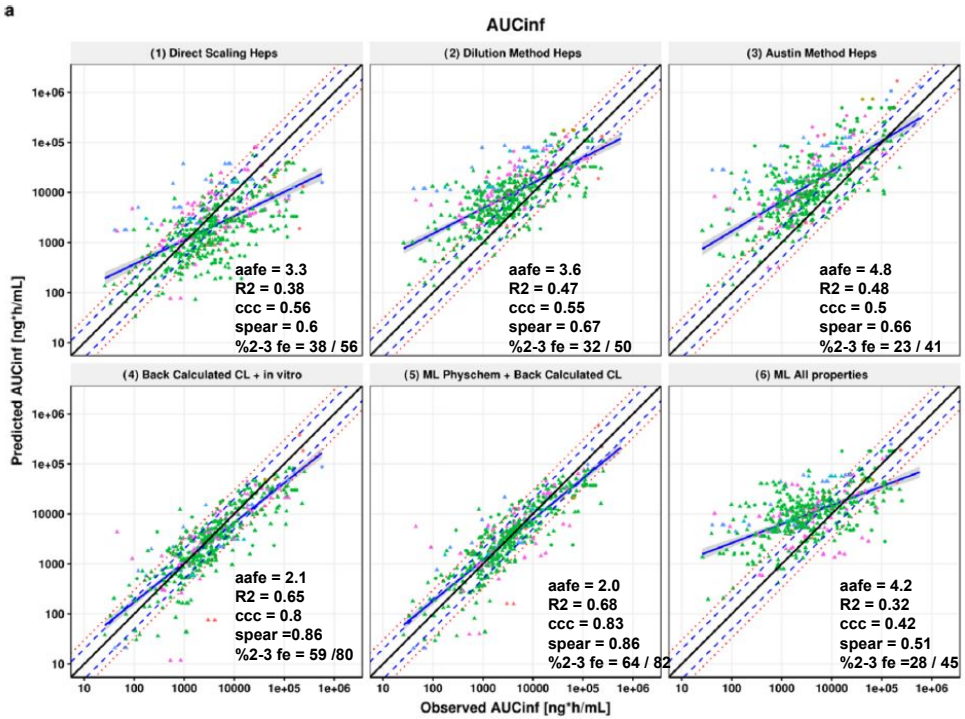


Vss is well predicted using the mechanistic Rodgers & Rowland method for the tested compounds

Naga, D., Parrott N., Ecker G.F. and Olivares-Morales A (2022) Mol Pharmaceutics 19:2203-2216

Absorption PBPK predictions

Oral AUCinf in rats predictions within 3 fold for 50-56% of observations



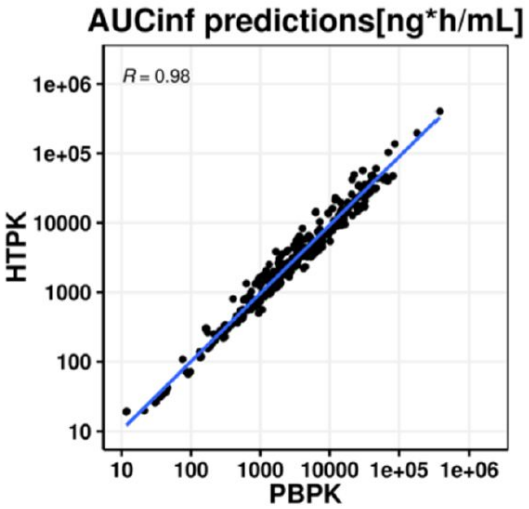
Substantial increase in prediction success of absorption model (up to 82% within 3 fold) when clearance is well predicted (back-calculated)

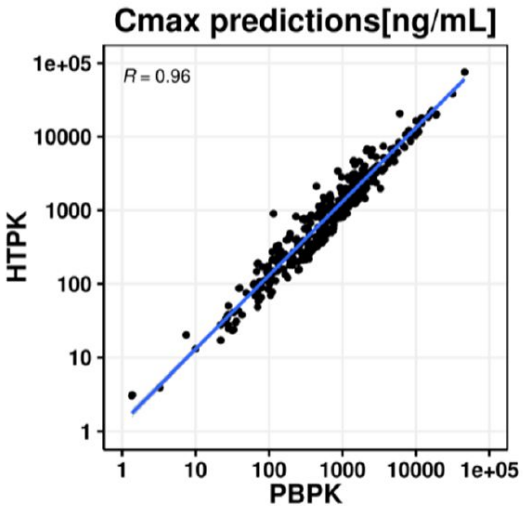
Machine learning: success of 45% within 3 fold

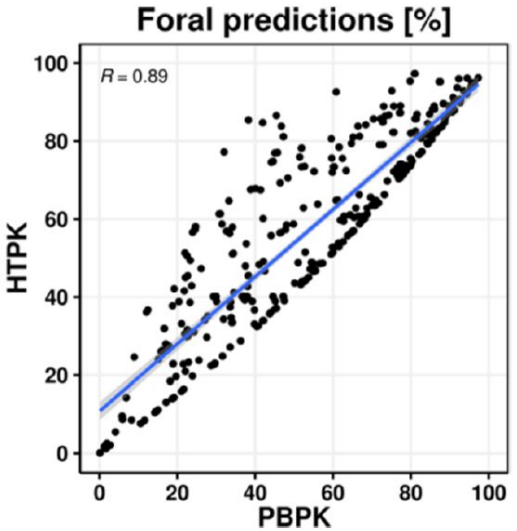
Naga, D., Parrott N., Ecker G.F. and Olivares-Morales A (2022) Mol Pharmaceutics 19:2203-2216

HT-PBPK (ADMET predictor) vs PBPK (GastroPlus)

Excellent reproducibility between the two approaches

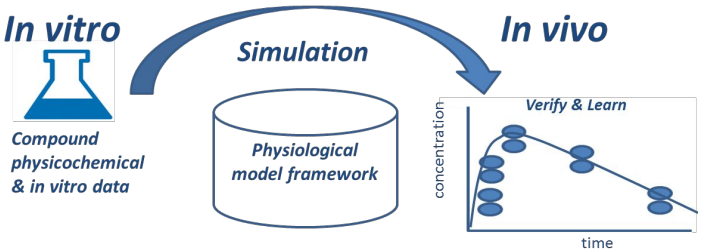






Naga, D., Parrott N., Ecker G.F. and Olivares-Morales A (2022) Mol Pharmaceutics 19:2203-2216

Can we predict the PK of our discovery compounds?

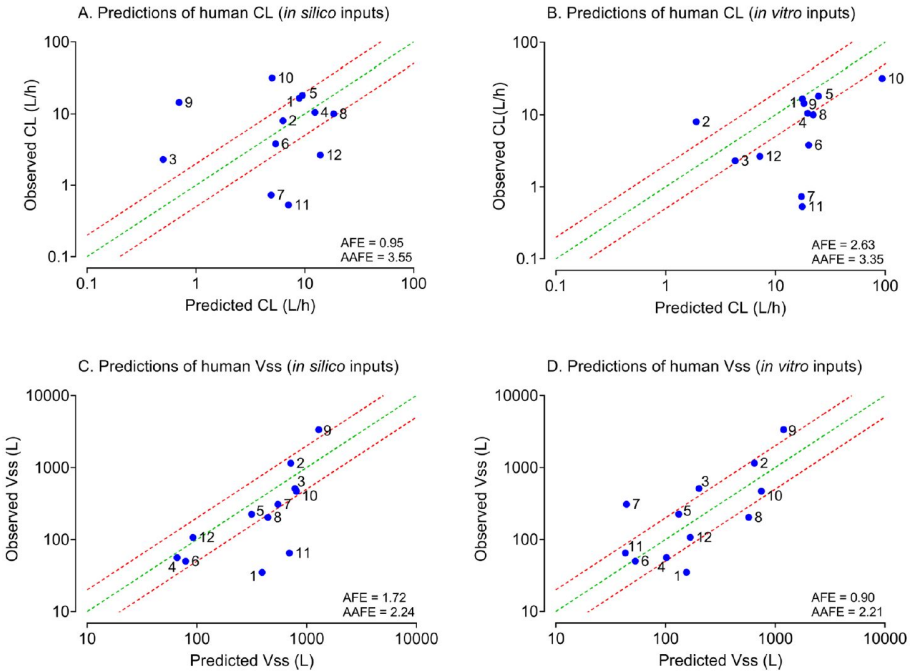


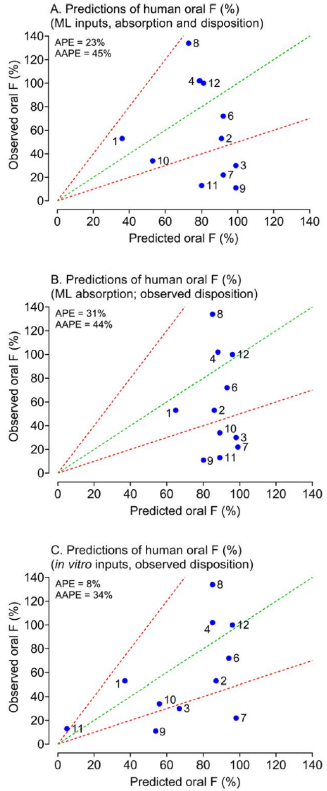
- Using only PBPK modeling combined with in vitro data only?
  Yes, to a certain extent. When CL is well predicted prediction success improves
- What if we use Machine Learning inputs?
  Yes, it gives a flavour however there's significant room for improvement
- Can we reproduce whole body PBPK simulations with a simplified PBPK model?
- Yes, overall and the predictions are faster

Jones H, Parrott N, Jorga K and Lave T (2006): Clinical Pharmacokinetics 45(5):

What about human predictions?

PBPK predictions for using ML inputs for 12 development compounds





Limited dataset but encouraging results, improvements needed in CL models and tight protein binding

Parrott N., Manevski N. and Olivares-Morales A (2022) Mol Pharmaceutics 19, 11, 3858–3868

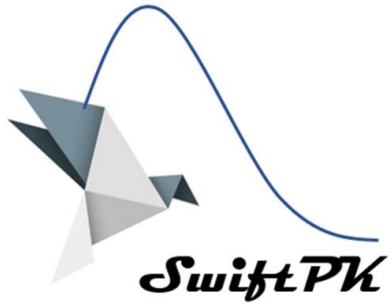
What is next?

SwiftPK

Faster, simpler, easier and accurate PBPK simulations for small molecule projects

Changing the way we discover medicines by

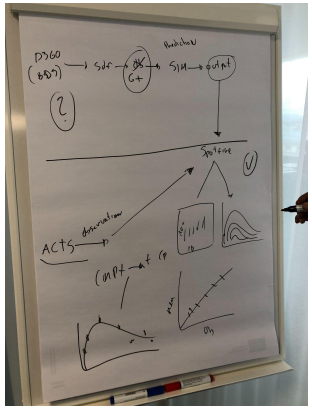
- Bringing PBPK simulations and expertise to early discovery and design
- Reducing animal experimentation
- Eliminating manual data transfers and reporting
- Providing model-based ADME and PK/PD insights that can lead to better compound design and selection
- Enabling predictions for compounds with sparse or no experimental data (e.g. using machine learning)



Project history

How it started and how is it going

2019

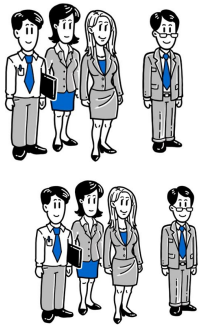


Basel, 15th of March 2019

Two scientists try to understand each other's languages and kick off an idea

Four scientists on a mission together with an external collaborator (Simulations Plus) worked to develop and evaluate the engine for the fast simulations (ADMET Predictor)

2020

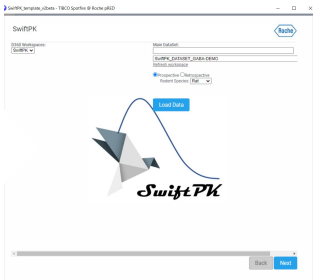


The project is sponsored by the **pRED's OneD** initiative with more resources and brain power to develop a professional app, improve engine and workflows (**pREDi, PS, TMo and pRED Ops working together**)

2021 (July)

MVP released to the whole pRED community, early project adoption by several teams

2022 (today)



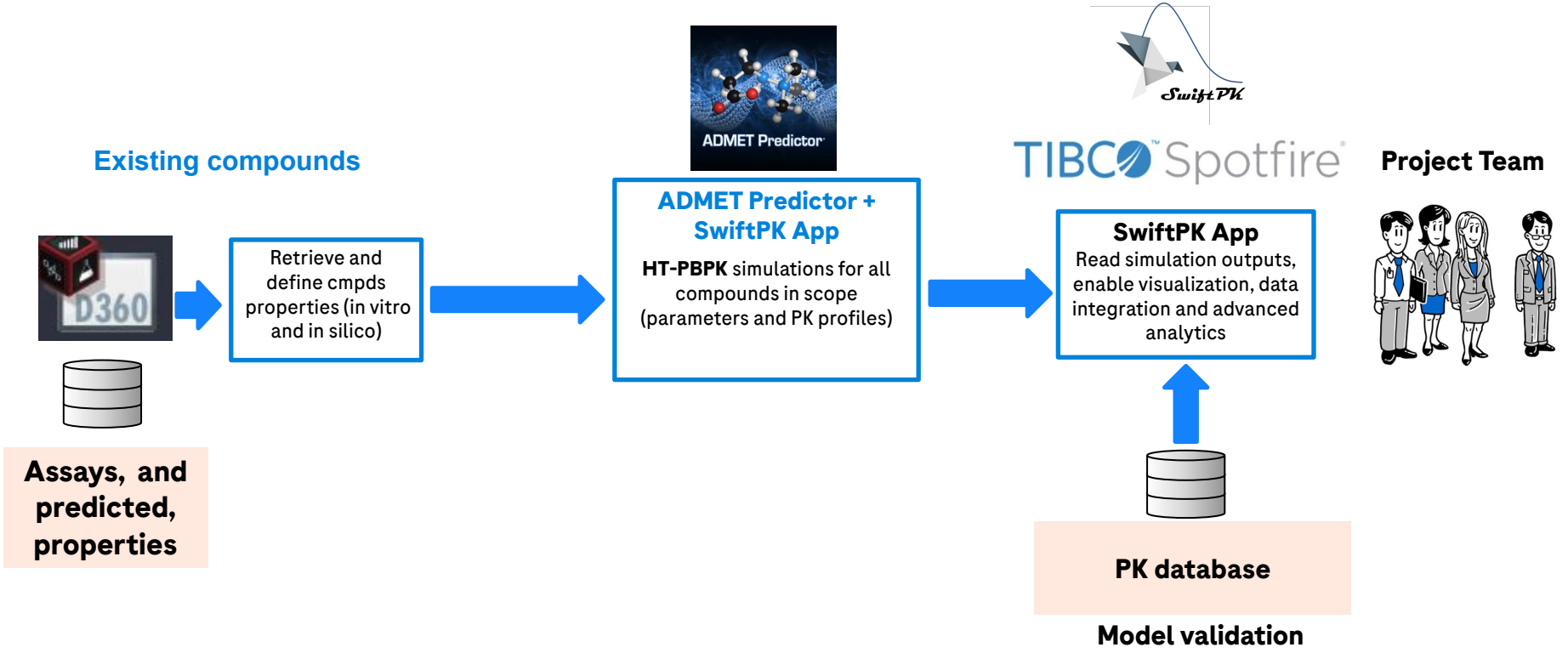
Adoption by more projects. Benefits already visible in at least 4 projects (cost savings, faster decision making)

Version 2 of the app Released

How does SwiftPK work?

How SwiftPK (HT-PBPK) is implemented in pRED

SwiftPK App workflow



SwiftPK retrieves all the necessary information for PBPK modeling

A combination of in vitro and in silico data is transferred to the software

			CEFF_HUMAN_NG_ML	CEFF_RAT_NG_ML	CEFF_MOUSE_NG_ML	EQDMDILUTION_MAN	EQDMAN_DILUTION_MG	EQDMAN_DIRECT_MG	DOSE_NUMBER_EQDM_DILUTION	DOSE_NUMBER_EQDMAN_DIRECT_MG	EQDMOUSE_MG_
11.8	70	1	1,860	4,340	4,340	23.9	94.5	638	0.737	0.737	
7.70	70	1	599	2,350	1,830	9.69	60.4	298	0.332	1.64	7.
6.34	70	1	47.5	188	188	4.84	12.3	30	0.104	0.104	
25.4	70	1	207	672	672	1.28	17.6	55	0.0781	0.244	2.
2.96	70	1	34.1	83.4	83.4						

This query retrieves all the necessary information in the right units ready to be used

For PK simulations

Our recommended approach for PBPK input parameters (when available) and the **logic mostly implemented in SwiftPK***

- **Clearance** = **Hepatocytes** > Microsomes > Machine Learning
- **Protein binding** = **Measured** > Machine Learning
- **Solubility** = **Thermodynamic, Biorelevant** > Kinetic > Machine Learning
- **Permeability** = **Cellular** > PAMPA > Machine Learning

For PK and dose simulations

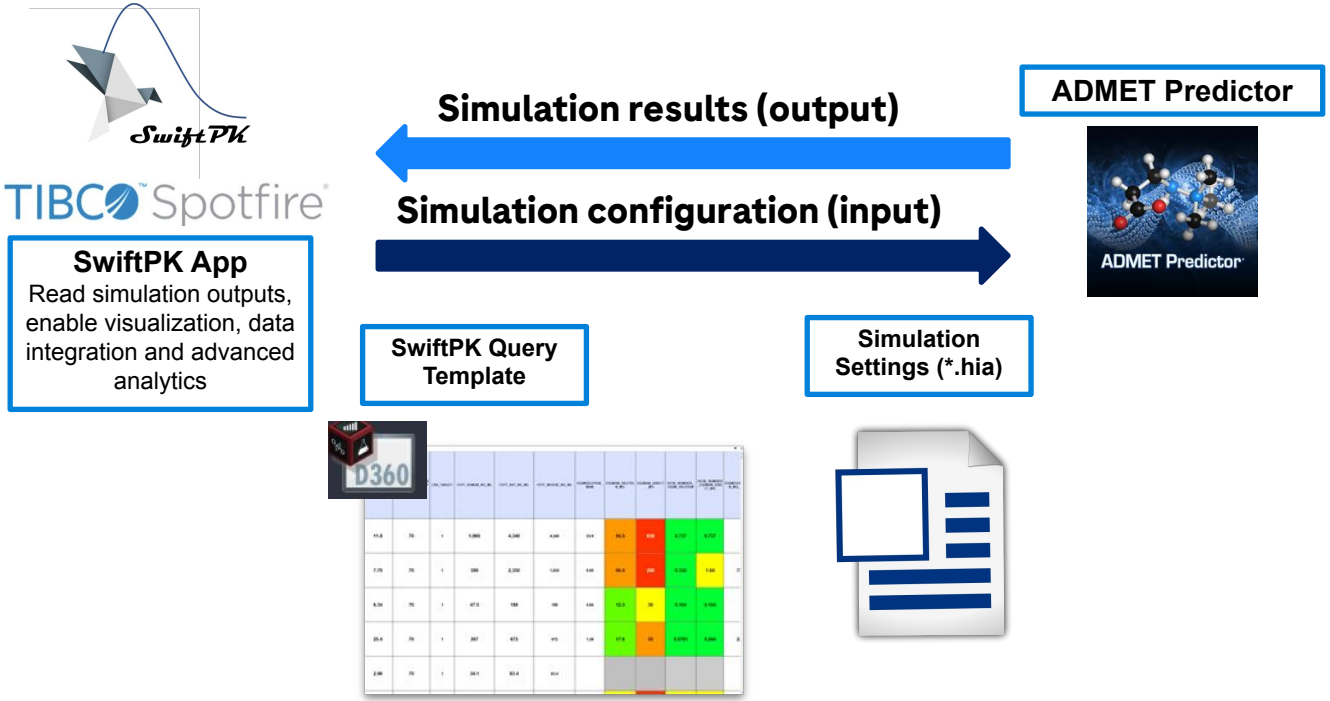
- **Efficacy assay** (a.k.a. "Main assay")
- Desired target binding/engagement level (ECx) (e.g., EC50, EC90, EC99, etc.)
- Dose selection criteria = AUC (Cavg), Cmax or Cmin
- The target efficacious concentration (*Ceff*) is **calculated automatically by SwiftPK**

$$C_{eff}[ng/mL] = \frac{ECx \times 1000}{fu_p \times Kp_{u,u}(or\ 1) \times MolecularWeight}$$

*Human, rat and/or mice

SwiftPK backend

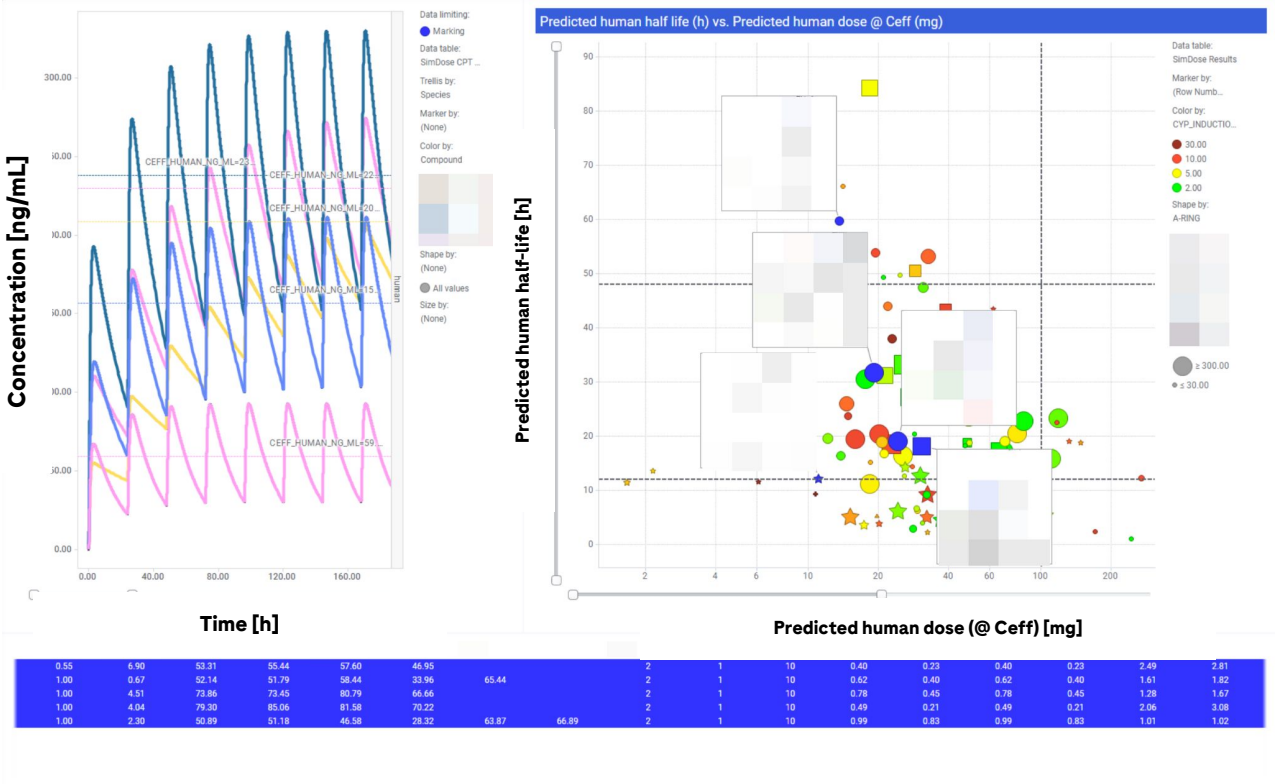
Seamless connection between data and simulation engine



Example

Project A

Three potential clinical lead candidates identified using SwiftPK

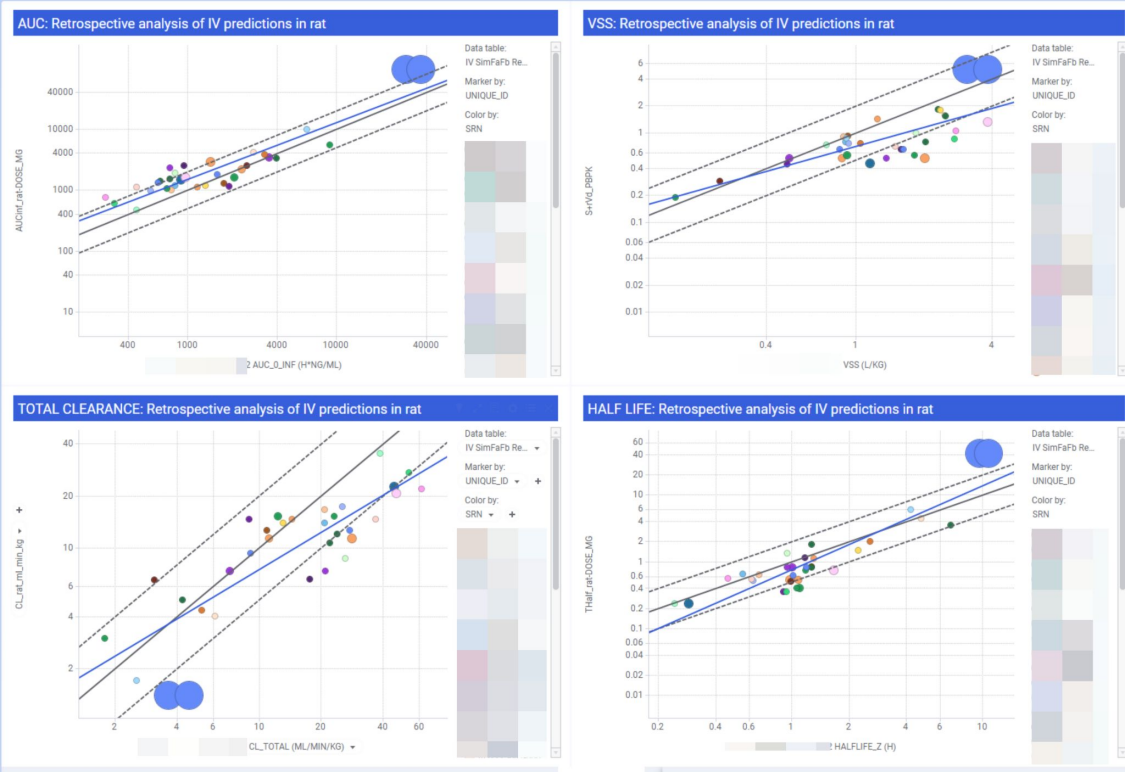


Program goals

- Human Half-life between 12-48h
- No-CYP induction
- Early dose in humans <100 mg

Validation increases confidence in model predictions

Project specific assessments



- Good IVIVE for project-specific compounds
- Increased confidence in model -based approach for ranking

Project A

Take home messages

- The strategy was focused on understanding the predictive power of the in vitro assays (heps, binding, PKPD)
- IVIVE was quickly demonstrated
- Simulations were used instead of actual in vivo experiments to inform our dose selection for PK/PD experiments
  - Saved significant time and reduced the need of dedicated PK studies
- The team trusted the approach (willingness to try a novel approach)
- In the end, **only 4 compounds were tested for PK from 2019 to 2021** (3 progressed to minitox)
  - Ca. 60 less rodents used in SDPK studies

Big thanks to the whole project team

Limitations of the HT-PBPK approach

Great for ranking and large data analysis, for mechanistic questions a mechanistic PBPK approach is recommended

- Predictions of high molecular weight (antibodies, oligos, etc.)
- Predictions for large-small molecules (i.e., BRO5)
- Transporter-mediated clearance
- Simulate complex formulations, dosing schedules
- Confidence generation is needed in a project-by project basis

Acknowledgements

DMPK/PD and M&S

- Andrés Olivares
- Neil Parrott
- Andrea Morger
- Matthias Wittwer
- Nenad Manevski
- Holger Fischer
- Doha Naga
- Axel Pähler
- Bianca van Groen

pRED D&A

- Yaniv Cohen
- Peter Curle
- Michal Jakubik (Dev)

Small Molecule Research

- Michael Reutlinger
- Giuseppe Cecere

Sponsors

- Sherri Dudal
- Fabian Birzele
- Alain Nanzer
- Hayley Binch

...and many more pRED colleagues from MedChem, DTAs, CADD, DMPK/PD and M&S

Doing now what patients need next