Early assessment of PK properties using ADMET predictor HTPK Simulation Technology: Deployment of a high-throughput mechanistic PBPK approach at Roche

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Roche pRED

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- Peter Curle

Small Molecule Research

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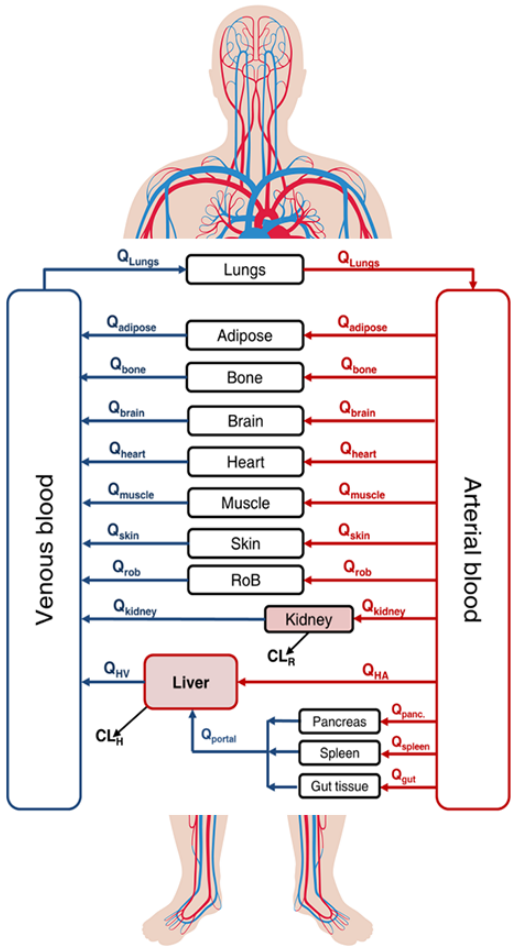
- Giuseppe Cecere

INTRODUCTION

Physiologically-based pharmacokinetic modeling (PBPK)

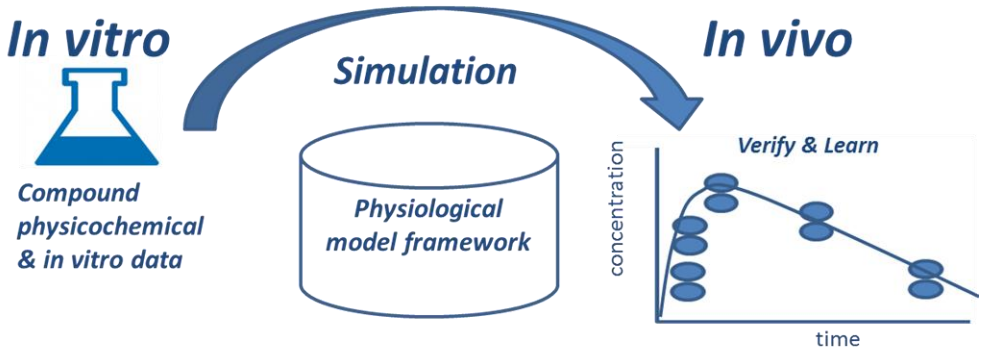


A mathematical modeling technique to predict pharmacokinetics

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



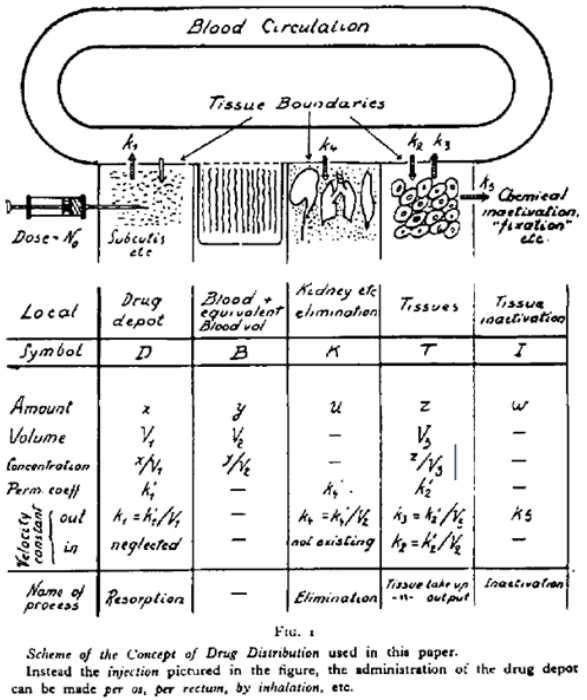


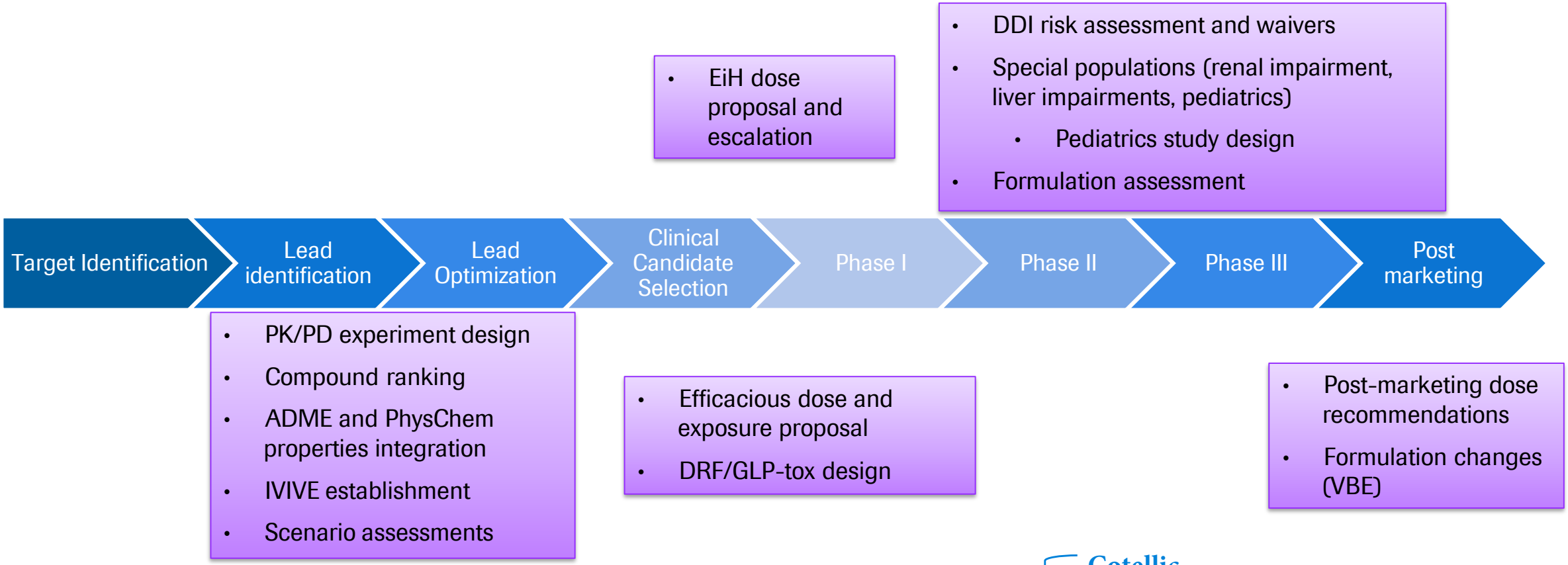
FIG. 1

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.

Teorell 1937

PBPK/PD in drug research and development

The applications span from early discovery to late development

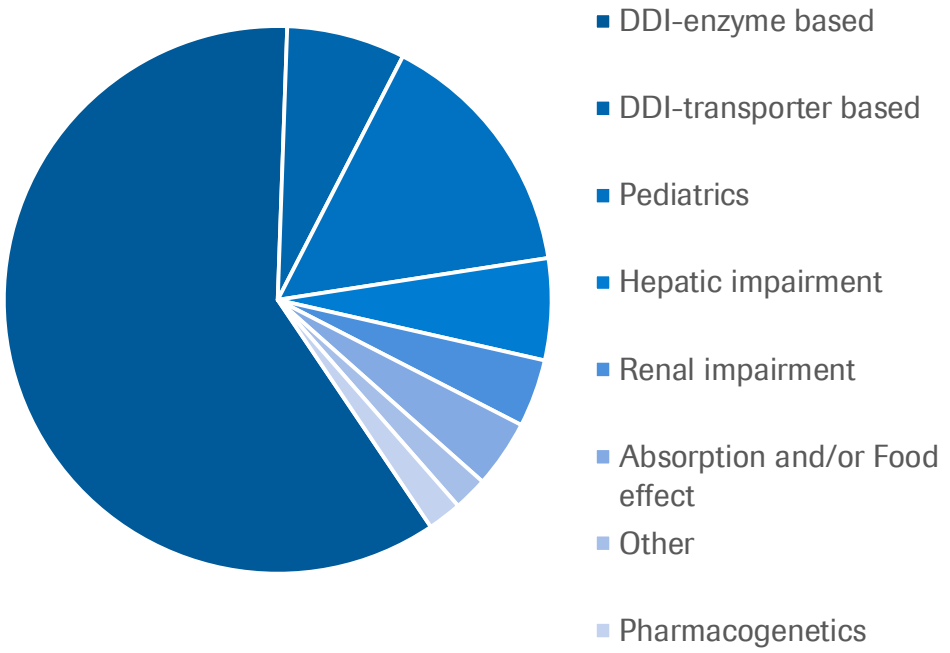


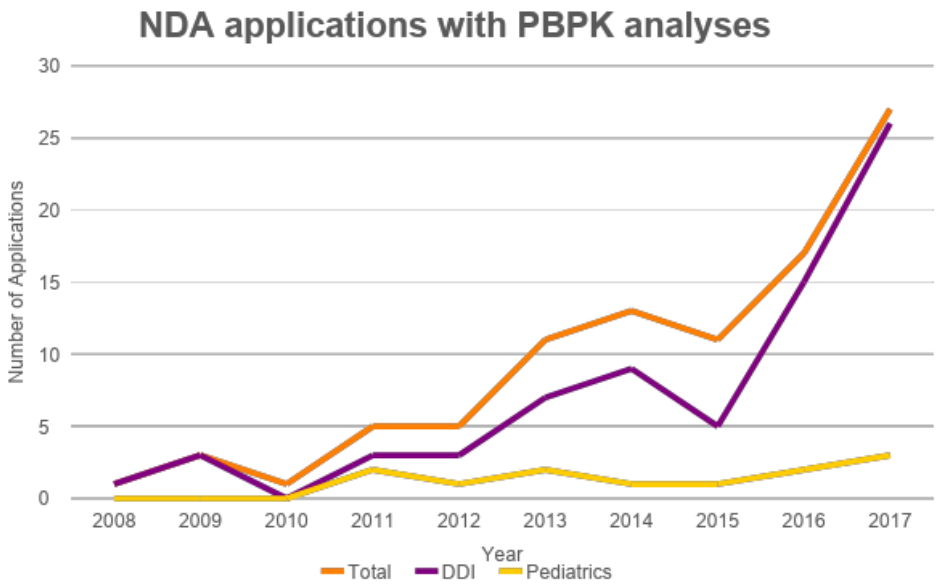
PBPK Informs Drug Labels e.g.

- Cotellic
- Alecensa
- Rozlytrek

PBPK model applications in drug development

Increased regulatory acceptance over the years



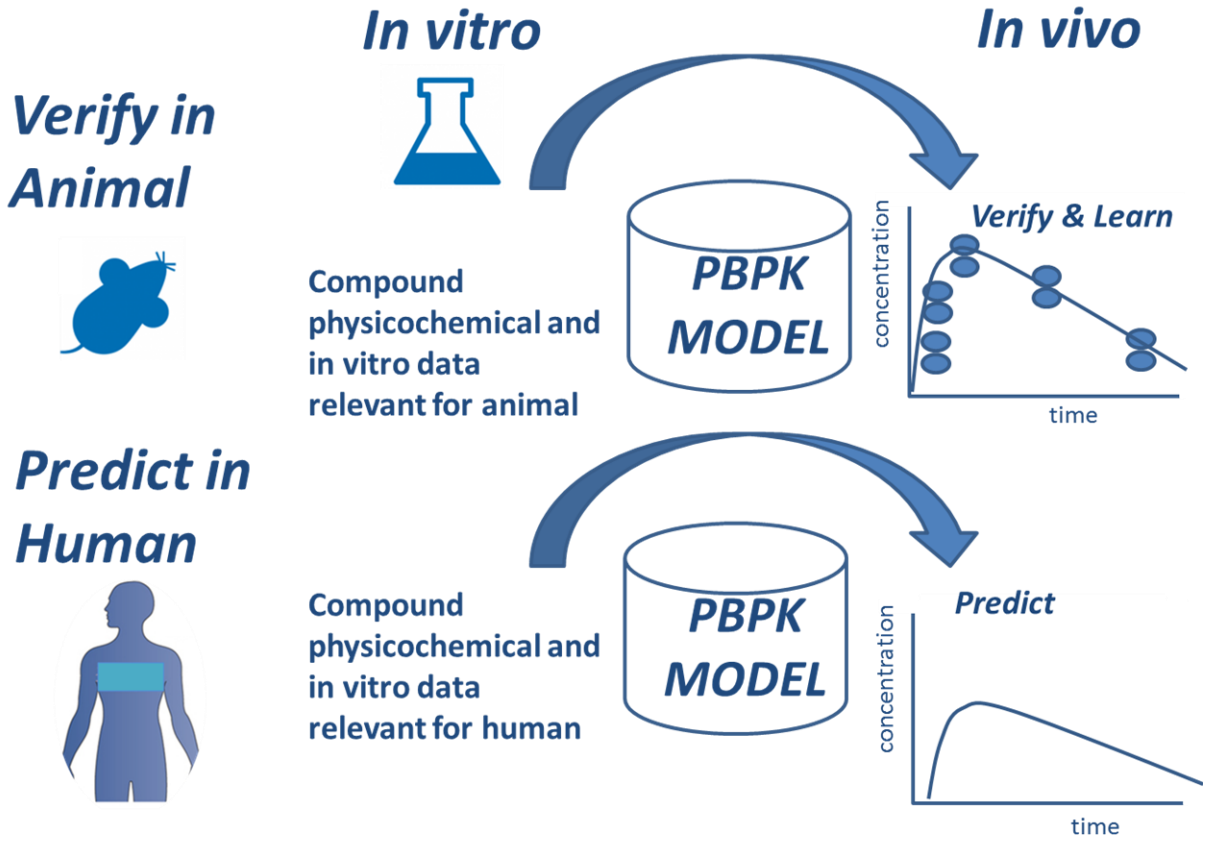


Grimstein et al 2019. J Pharm Sci 108:21-25

Roche's pRED PBPK strategy

A continuous learn and confirm approach

- ***Overarching goal is to predict therapeutic window in humans as a function of dose using a PBPK/PD approach***

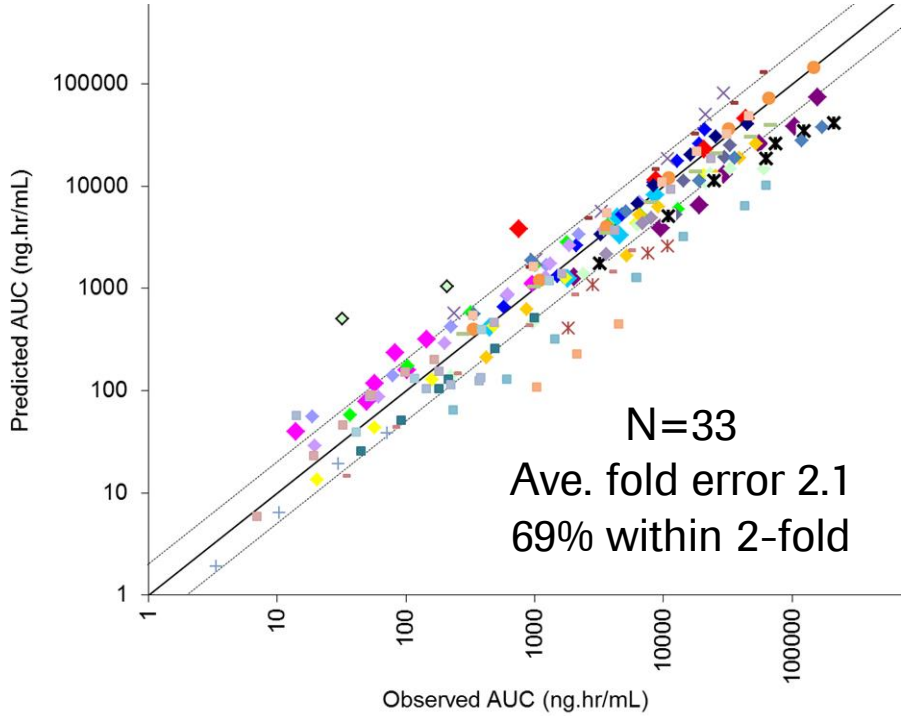


Jones, H., N. Parrott, et al. Clinical Pharmacokinetics, 2006. 45(5): p. 511-542.; Jones, H., I. B. Gardner, et al. Clinical Pharmacokinetics, 2011 50(5): 331-347

Roche has a long history of applying PBPK modeling

Successful prediction of EiH doses and exposures

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



Parrott N, Delporte M, Lave T, Peck R and Ricci B. CPT (2017) (Abstract PII-109)

PBPK application in the early small molecule portfolio

Early space is dominated by ranking equations, PBPK is seldom applied

Target Assessment → Lead Identification → Lead Optimization → Clinical Candidate Selection → Phase I to Phase III

Simple equations
LipE, eD2Man, Efficacy Index (EI), LipMET
Use: Ranking and design, early doses
Throughput: high (hundreds to thousands of compounds per project)
Implementation: Easy (spreadsheet based, easy to implement in current project tools)
Speed: Instant
Scope: Limited (single properties or two properties combined at the most, simplified and assumption heavy)

PBPK modeling
GastroPlus, SimCYP (commercial), in-house (R, Matlab)
Use: Human dose prediction, sensitivity analysis, biopharm, DDI, etc.
Throughput: low-to medium (handful of compounds per project, usually around CLS)
Implementation: Complex (manual data transfer and model set up. Learn and confirm cycle needed to gain confidence, data rich)
Speed: Moderate (minutes to hours)
Scope: All ADME and PK/PD properties as well as secondary parameters (half-life, Cmax, Bioavailability, Cmax)

The limits of PBPK in early drug discovery?

Several barriers identified

Current barriers to use in early discovery

- Multiple compounds & limited time
- Multiple software needed (e.g., GastroPlus, SimCYP, Phoenix, etc.)
- Lengthy set up & complex data transfers

This results in

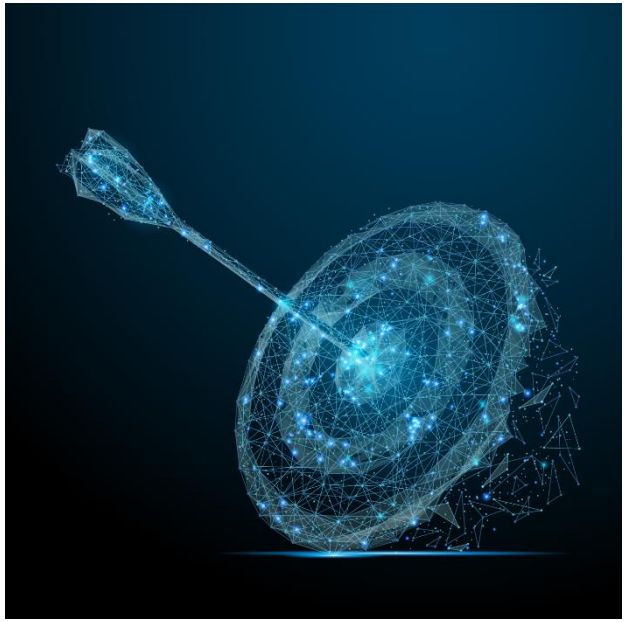
- Limited usage by “non-experts”
- Reliance on simplistic equation-based tools which are easier to implement


OVERVIEW

Project overview

Aims:

Faster, simpler, easier and accurate physiologically-based pharmacokinetic (PBPK) simulations in small molecule teams



Project overview

This will change the way we discover medicines by:

Bringing PBPK simulations and expertise to early discovery and design

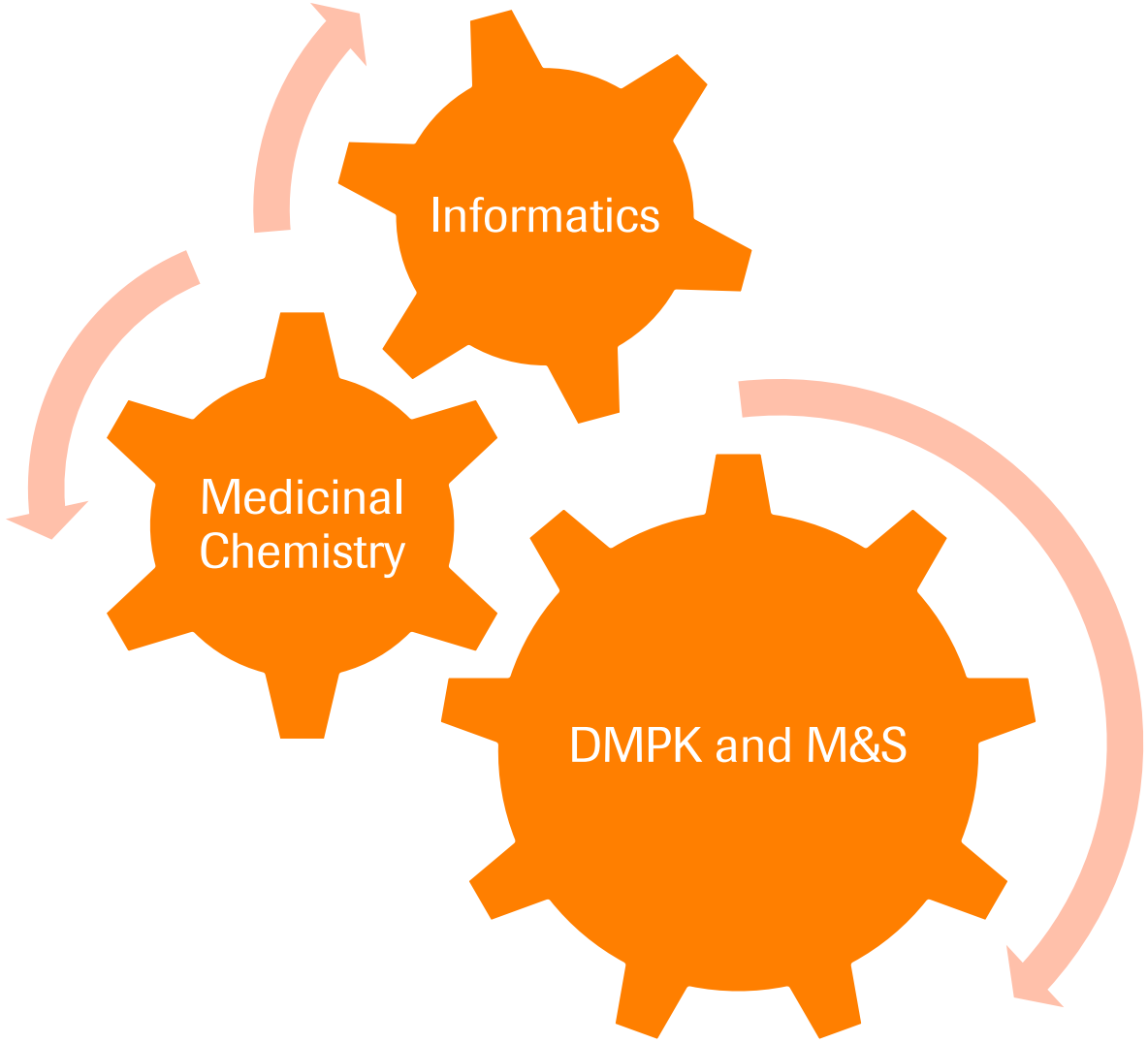
Eliminating manual data transfers and reporting

Providing model-based ADME and PK/PD insights that can lead to better compound design and selection

Reducing animal experimentation

Enabling predictions with **sparse or no data** (e.g. Machine Learning)

A cross functional collaboration



External Collaborators

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

CASE STUDY

Example of an a early PoC

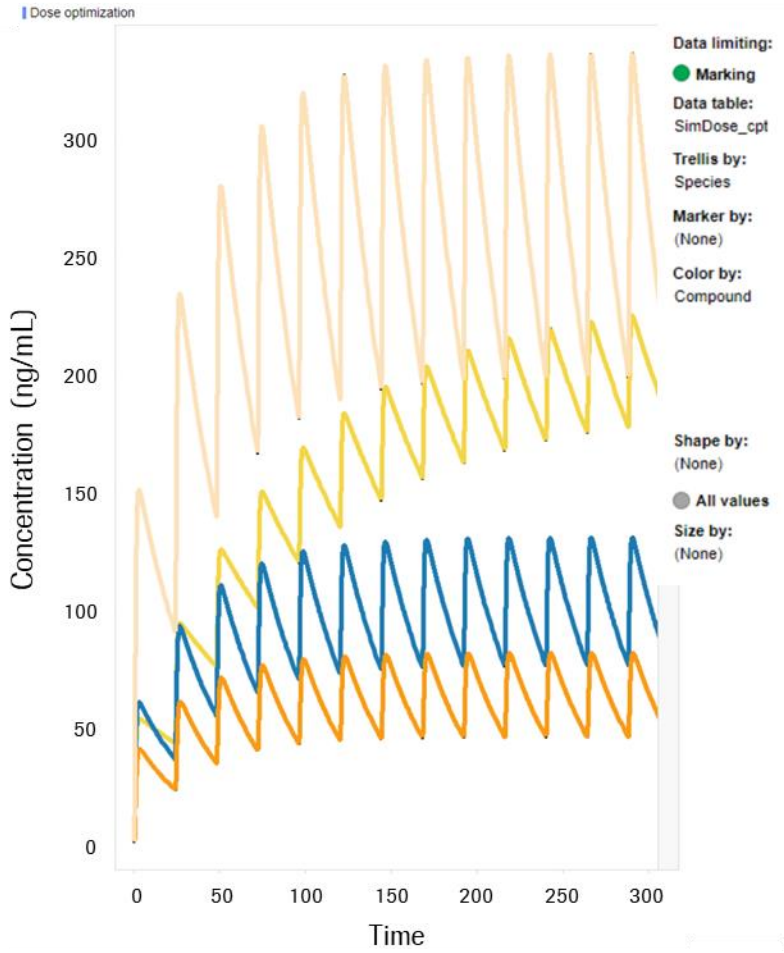
Small molecule program

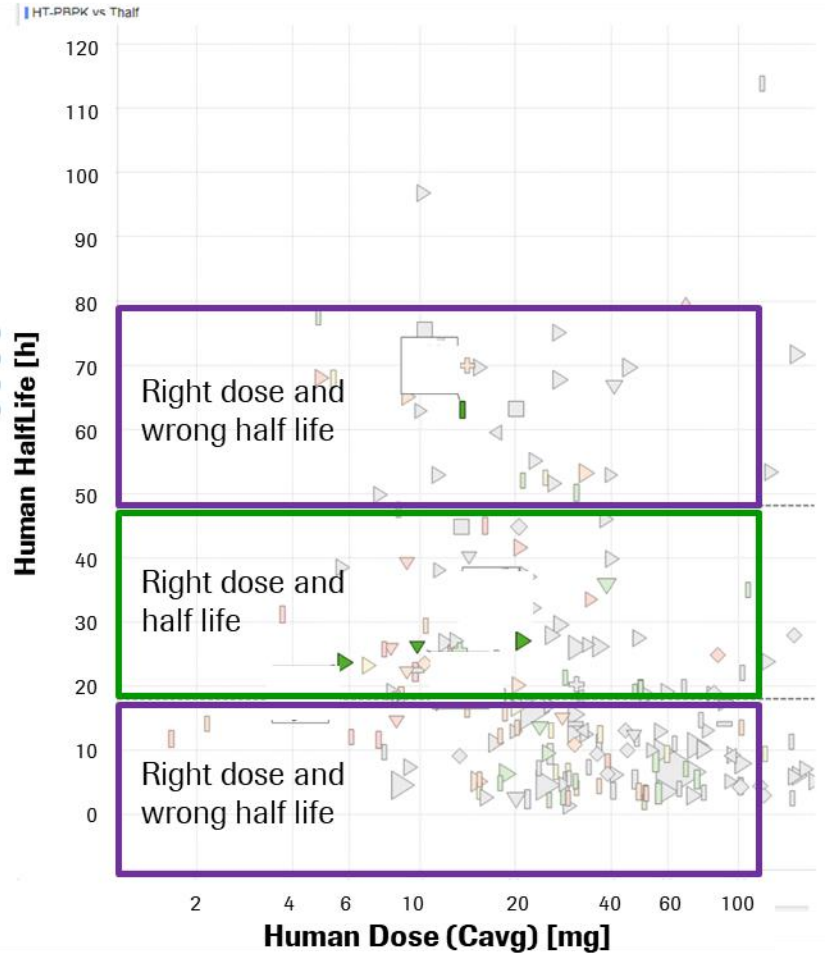
- Aim to find suitable molecules that can meet the following criteria
  - Projected early human dose target <200 mg
  - Predicted human **half-life of 12 – 48 h**
- **HT-PBPK** used by the team to generate design insights and find the right candidates

HT-PBPK insights

Dose and half life predictions in humans

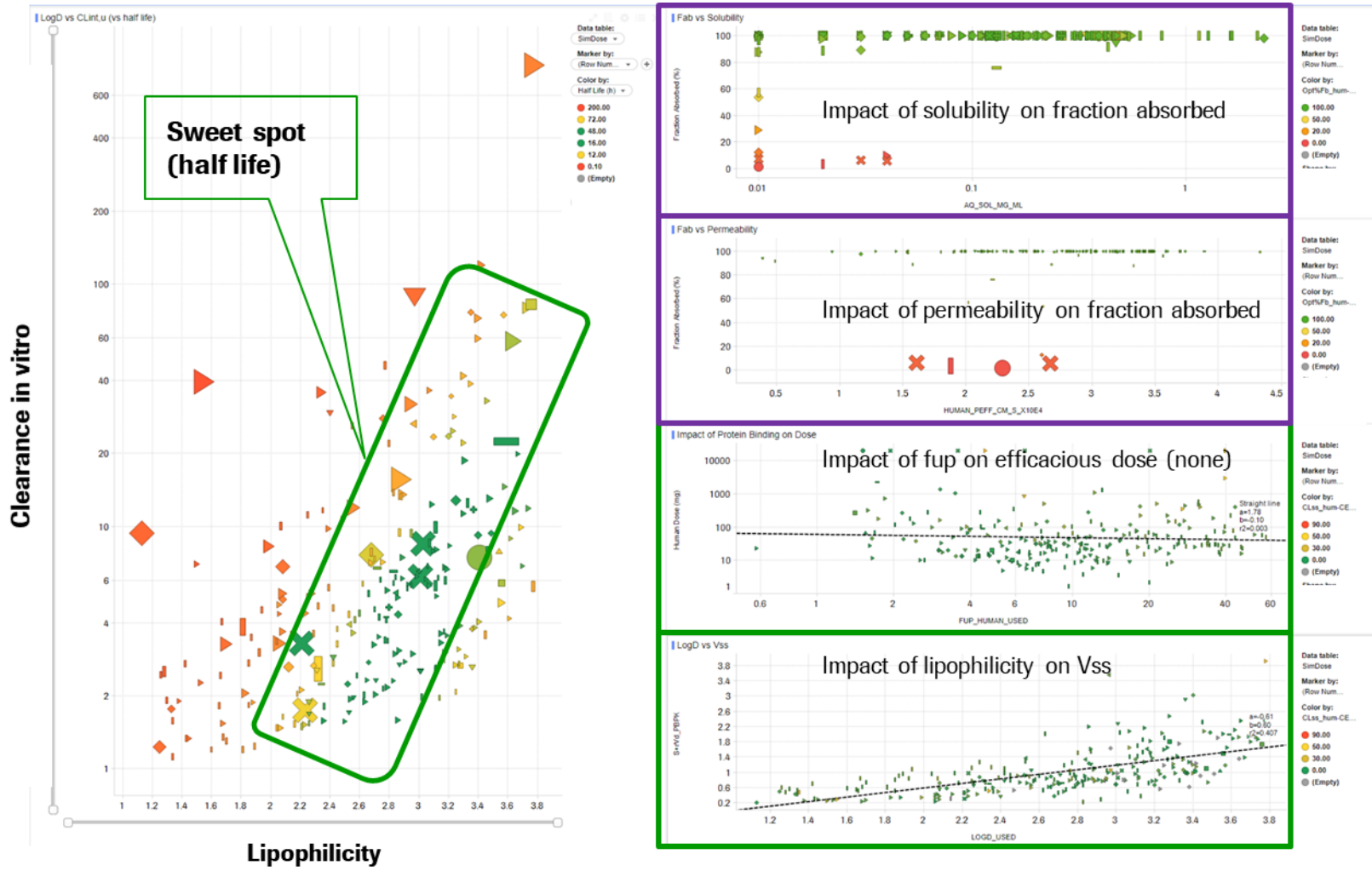
Total conc. needed to reach target





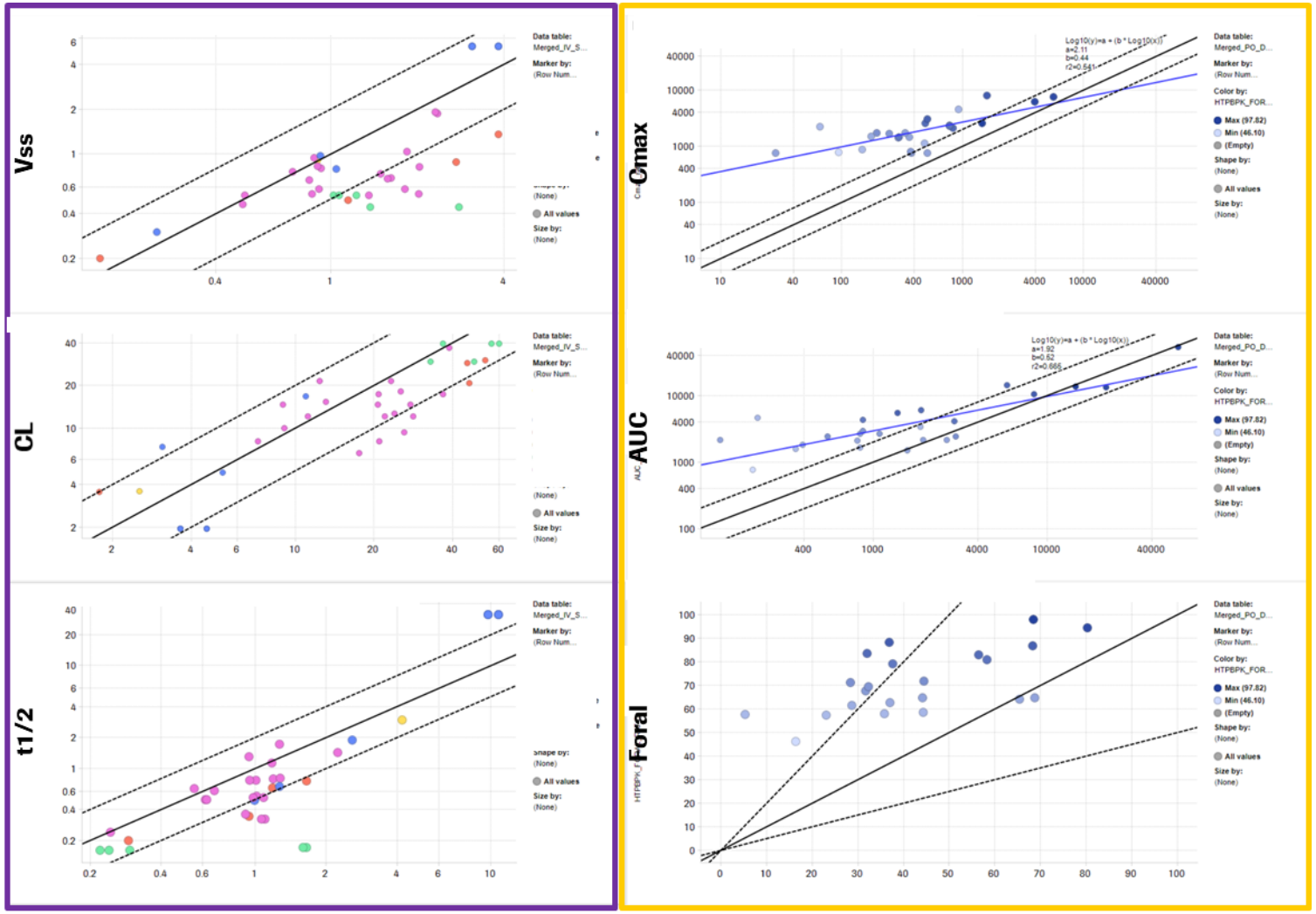
HT-PBPK insights

Dose and half life predictions in humans



Systematic model verification

Generating confidence in model-based approach



Most of the predictions within 2-3 fold for IV and PO parameters.

PO parameters highly correlated (good ranking)

PoC summary

Model-informed drug discovery

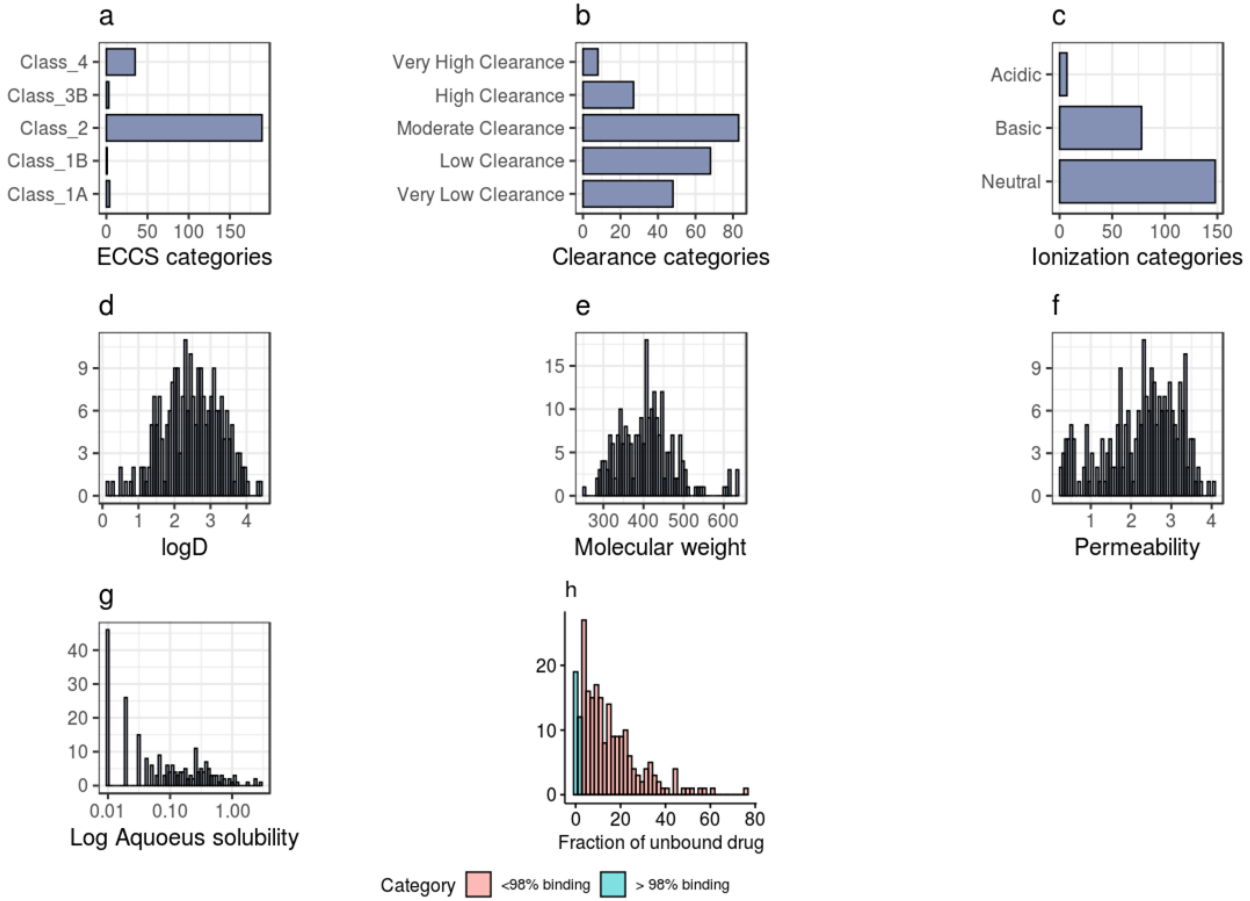
HT-PBPK insights  Better decision making and compound selection based on a truly multidimensional ADME optimization (e.g., t1/2 vs dose)

 Good and predictive assays available for the project (e.g., heps)

Not just a case study: Evaluation of early predictions

Can we predict PK using PBPK without the learning-confirming cycle (naive predictions)?

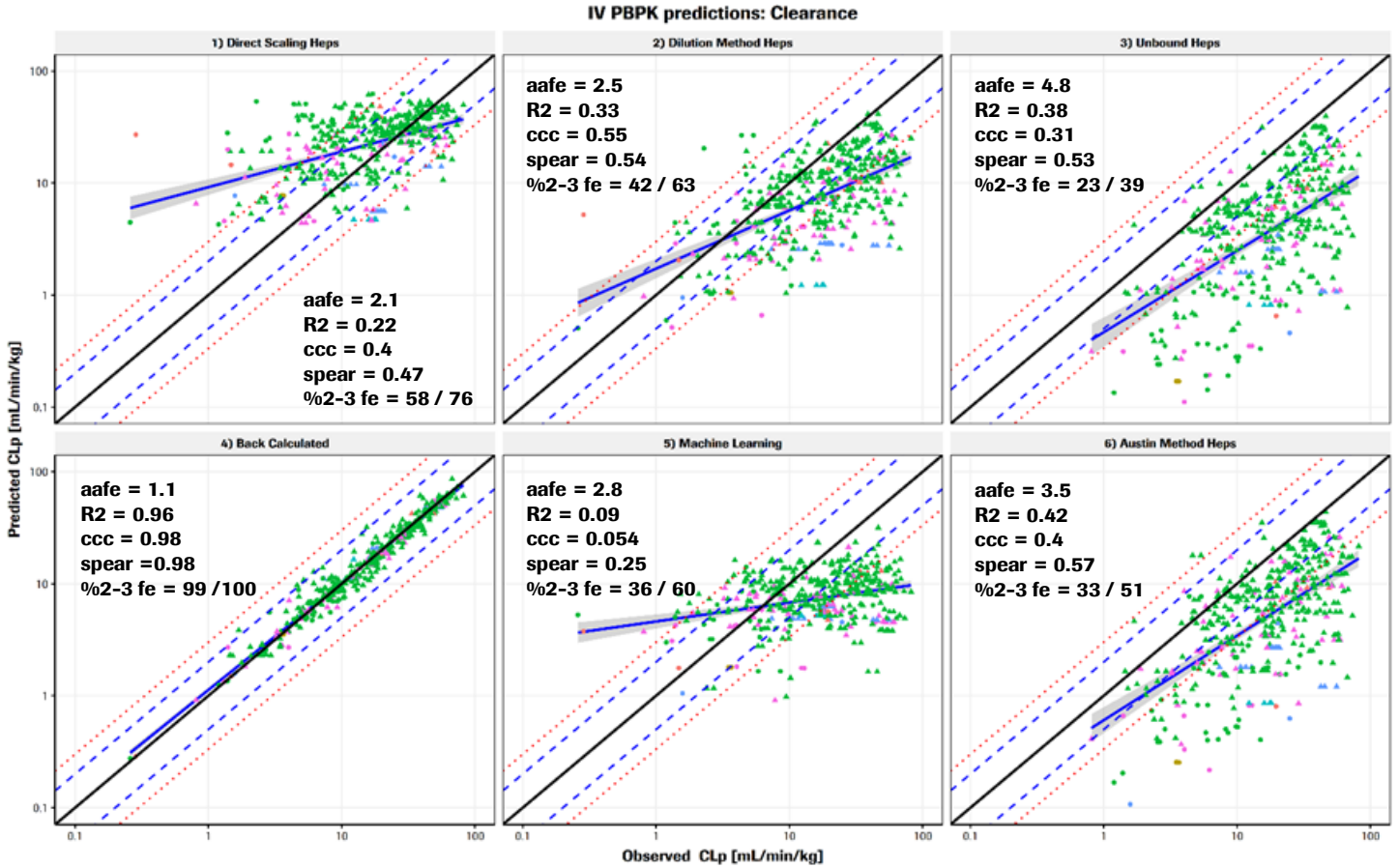
- Ca 250 structurally diverse Roche compounds
- **Simple research questions (rats)**
  - How does PBPK predict the IV PK in rats using in vitro and ML-predicted data (ADMET predictor)
  - How does PBPK predict the oral PK in rats using in vitro and ML-predicted data (ADMET predictor)
  - How does PBPK modeling predict oral absorption (when the CL is known)



Naga, D., Parrott N. and Olivares-Morales A (in preparation)

PBPK predictions for a large number of discovery compounds

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



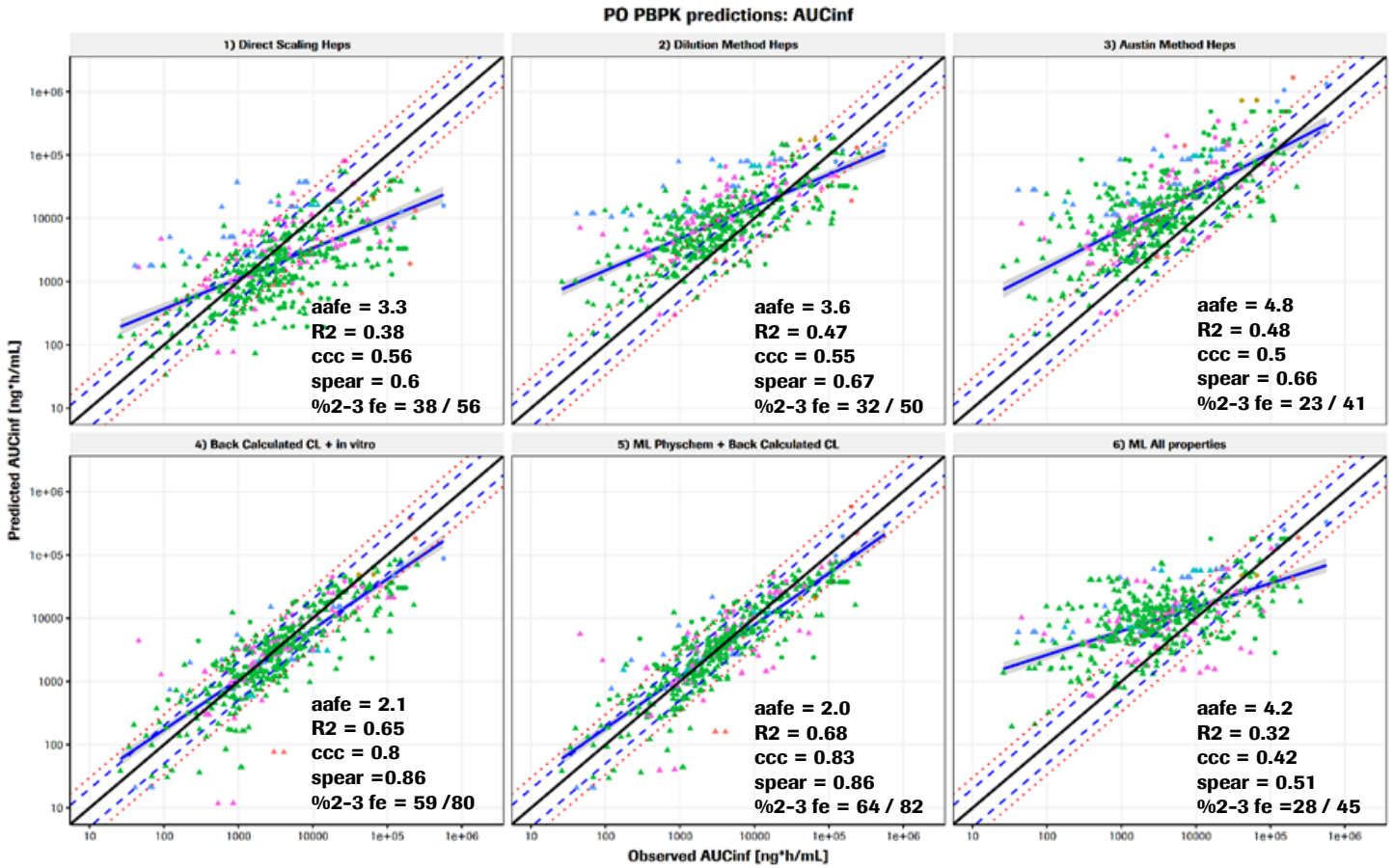
Naga, D., Parrott N. and Olivares-Morales A (in preparation)

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

*ADMET predictor

PBPK predictions for a large number of discovery compounds

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



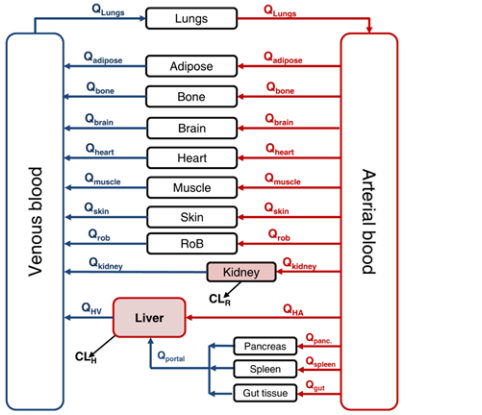
Naga, D., Parrott N. and Olivares-Morales A (in preparation)

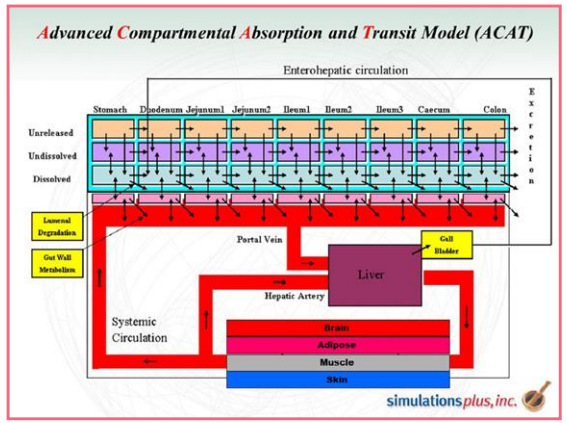
Substantial increase in prediction success of absorption model (up to 82% within 3 fold) when clearance is well predicted (back-calculated)

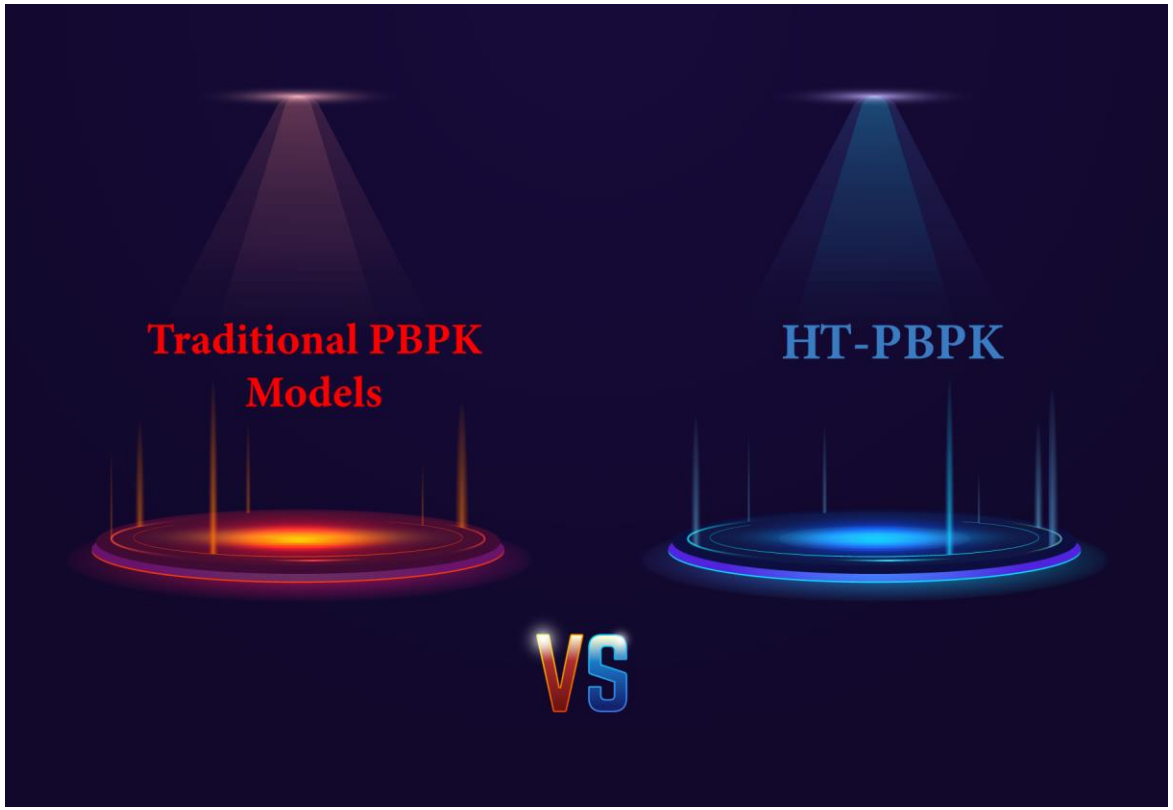
Machine learning: success of 45% within 3 fold

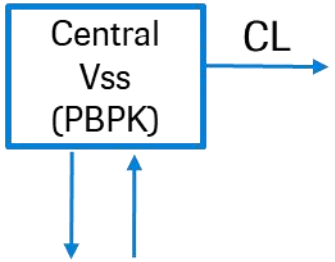
Science and Technology: HT-PBPK modeling vs PBPK

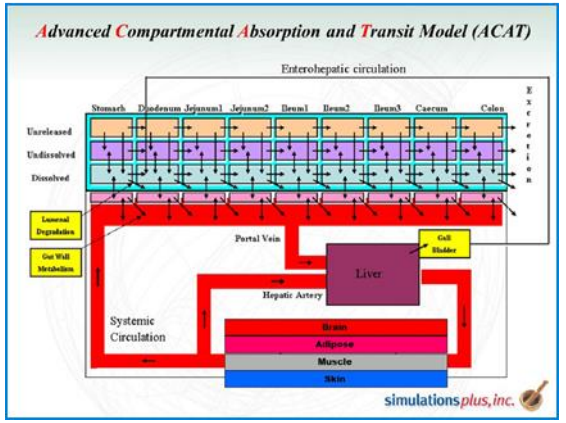
A game changing technology and the core of our project







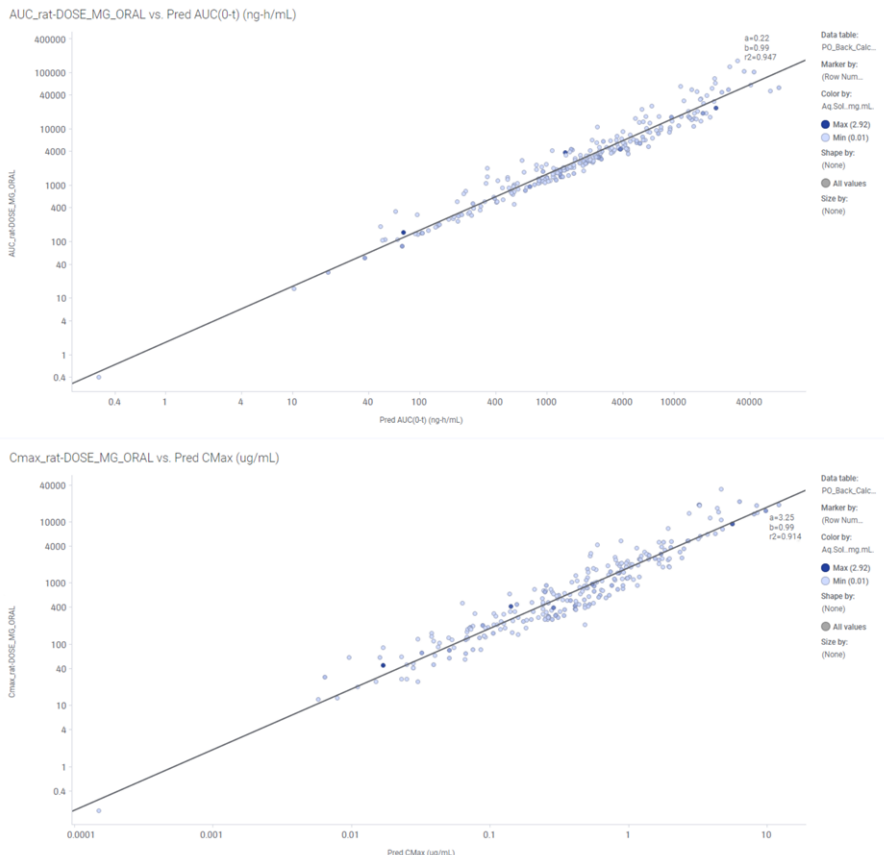




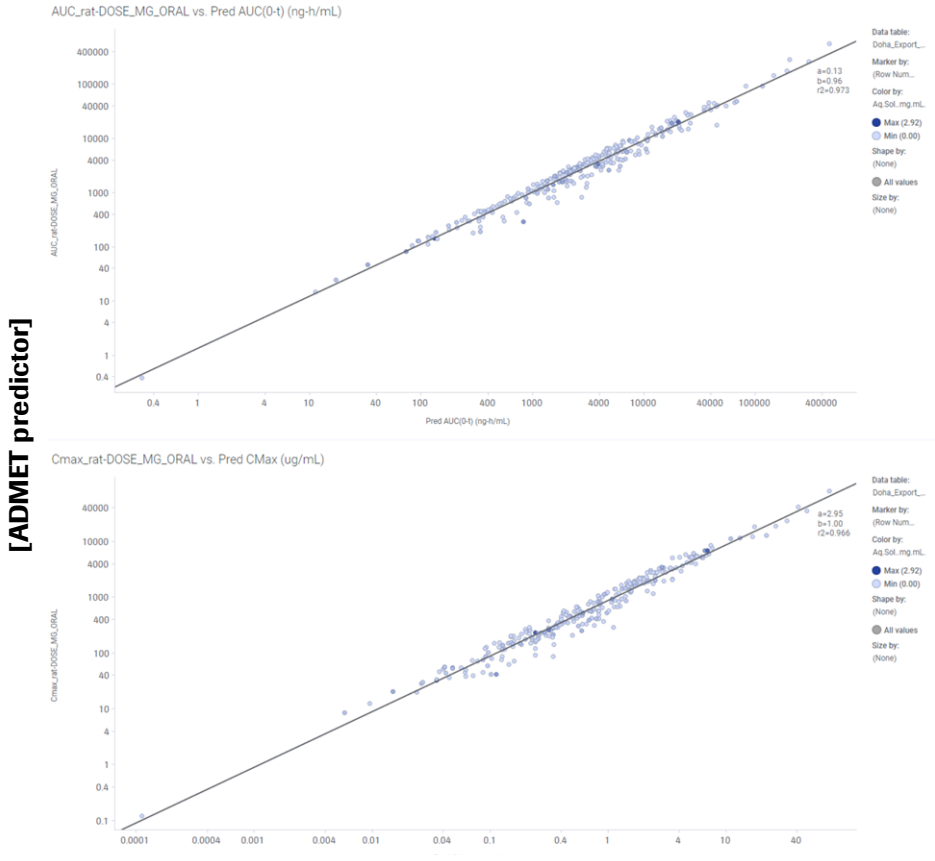
HT-PBPK (ADMET predictor) vs PBPK (GastroPlus)

Excellent reproducibility between the two approaches

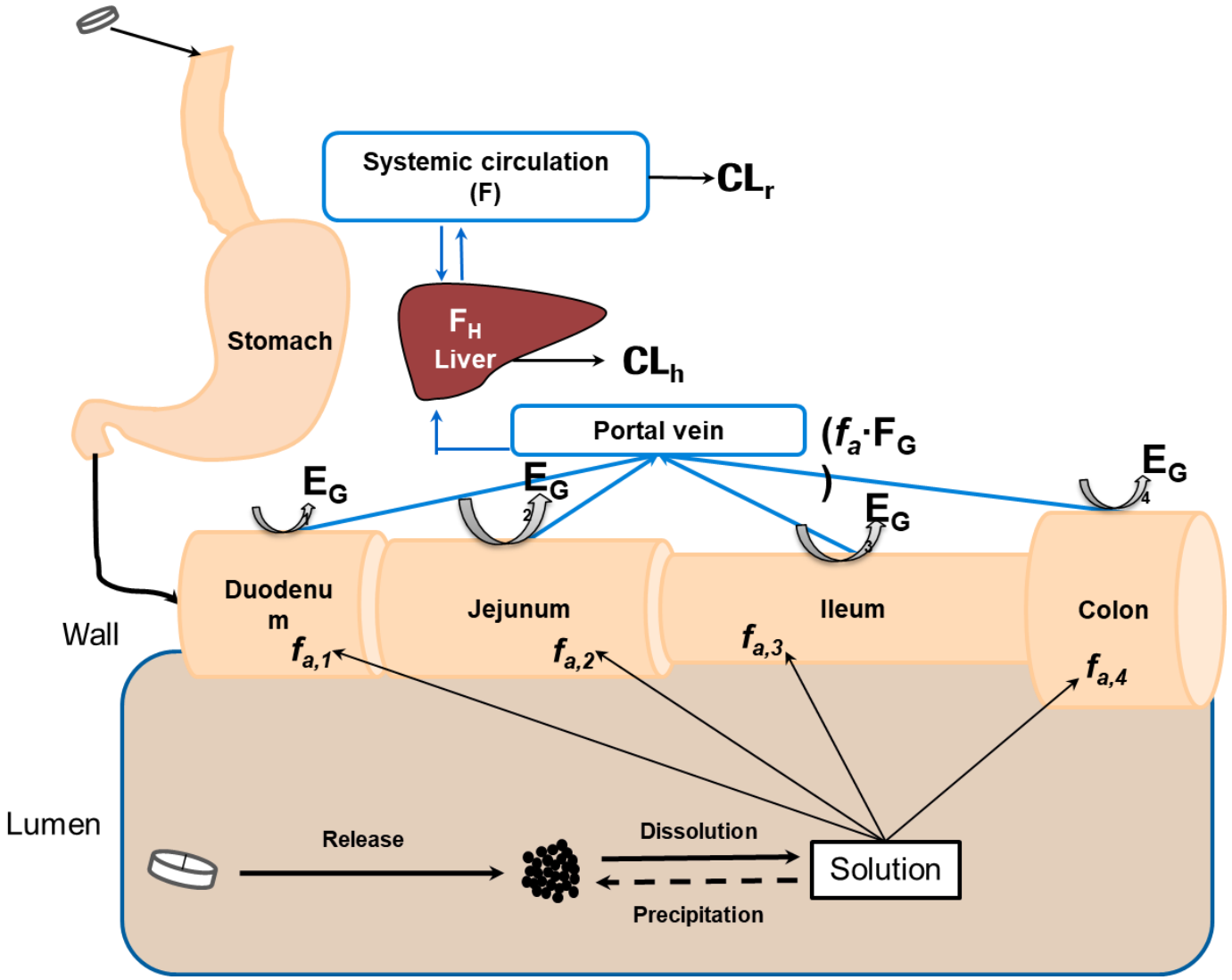
In vitro inputs



Machine Learning inputs



What can be predicted with HT-PBPK?



Species: rat and human
Dosage form: IR tablet or IV Bolus
Pharmacokinetics

- **PK profiles:** single dose and steady state
- **PK parameters:** AUC, Cmax, $t_{1/2}$, $CL_{hepatic}$ (IVIVE), CL_{total} from NCA (renal + metabolic), Bioavailability (Fb), fraction absorbed (Fa), Vss (Rodgers-Rowland-Lukakova)

PK/PD

- **Dose** needed to reach a given efficacious concentration (Ceff) as:
  - Caverage
  - Cmax
  - Cmin

A paradigm shift in the early PBPK strategy

Focus on speed, ranking and compound prioritization from design to optimization

Target Assessment → Lead identification → Lead Optimization → Clinical Candidate Selection → Phase I to Phase III

High-throughput PBPK predictions

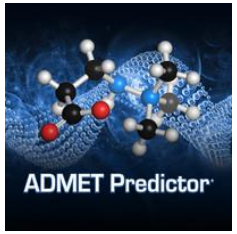
- Focus on compound optimization and ranking
- Rely on predictive models of properties (machine learning) for design compound
- Reduced learn and confirm cycle (at the project level)
- Constant PBPK prediction monitoring per project

Tailored PBPK modeling

- Single or limited compounds before EiH
- Traditional learn and confirm approach still apply (single species or two species validation)
- Further applications (DDIs, Biopharmaceutics, etc.)

Implementation of HT-PBPK in pRED

In house app and ADMET predictor service for de novo compounds



Existing compounds

Database

Retrieve and define compounds properties (in vitro and in silico)

Seamless

ADMET Predictor + In House App

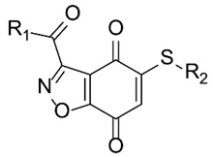
HT-PBPK simulations for all compounds in scope (parameters and PK profiles)

In House App

Read simulation outputs, enable visualization, data integration and advanced analytics

Project Team

De novo compound design



ADMET predictor service

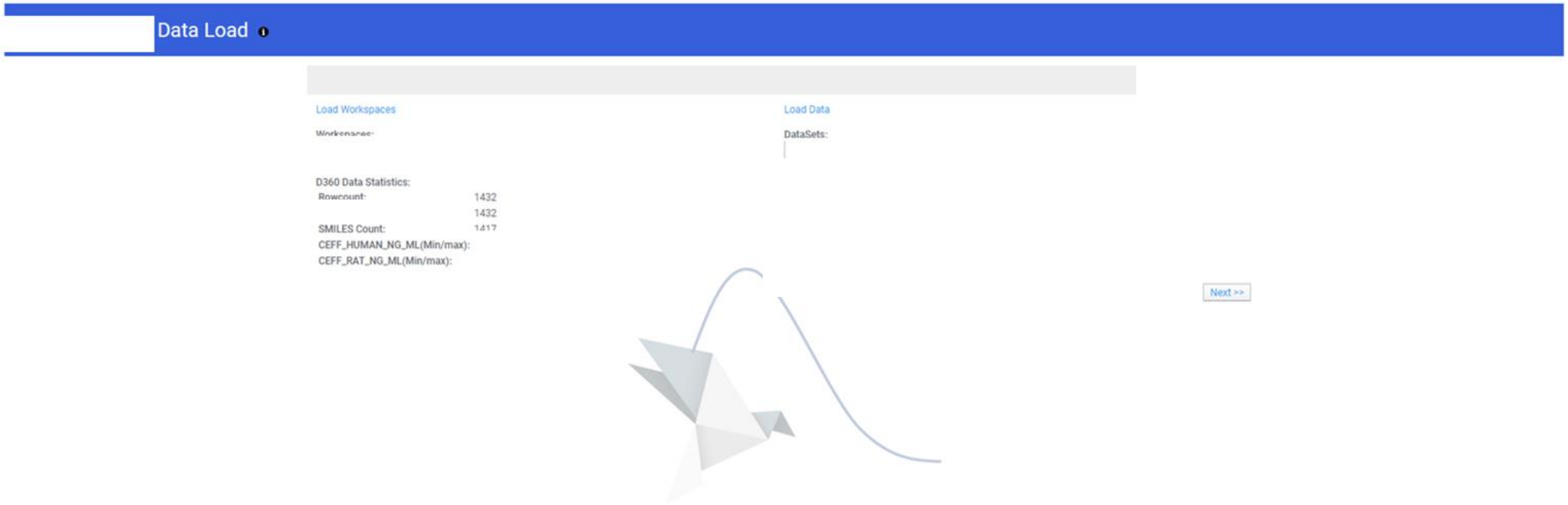
HT-PBPK simulations

(basic parameters)

PK database

Model validation

In house app for HT-PBPK simulations

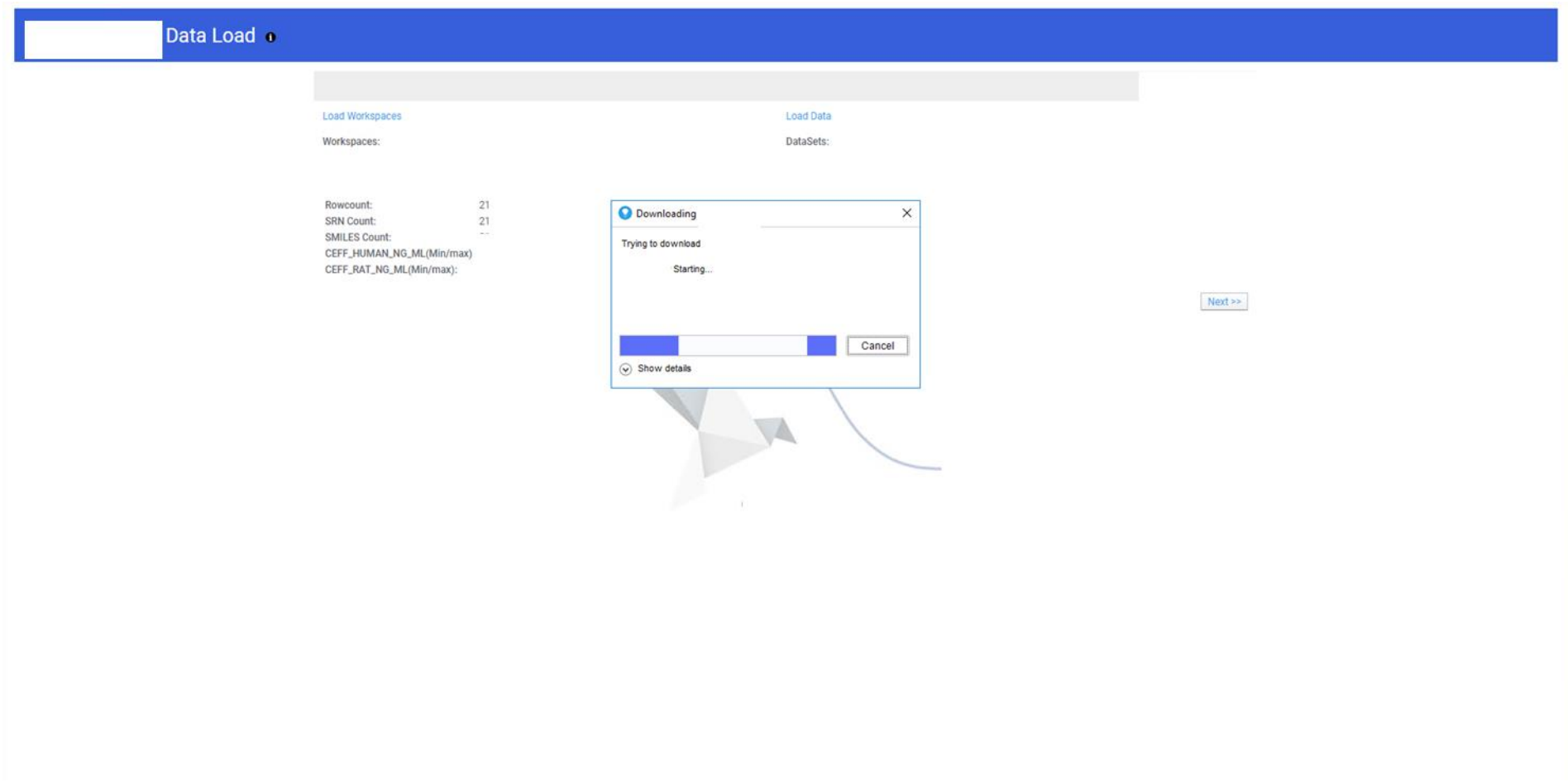


The App provides a simplified way:

- To interact with the ADMET predictor – guided analysis
- To retrieve and generate input data set
- To visualize the results

The landing page allows the user to log onto our central data repository select the data set or rerun a query.

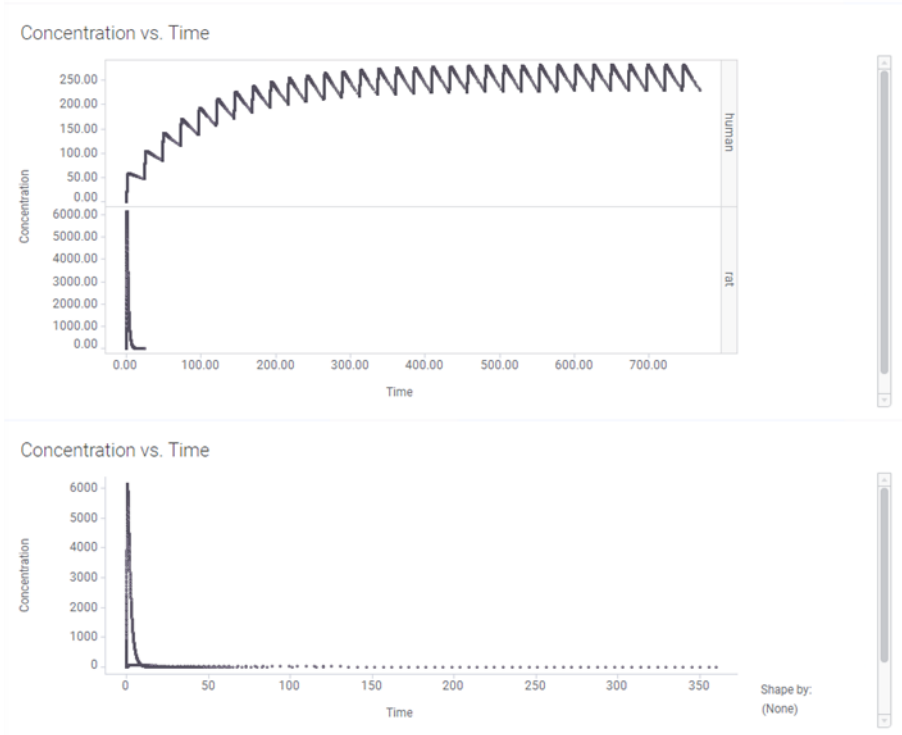
In house App

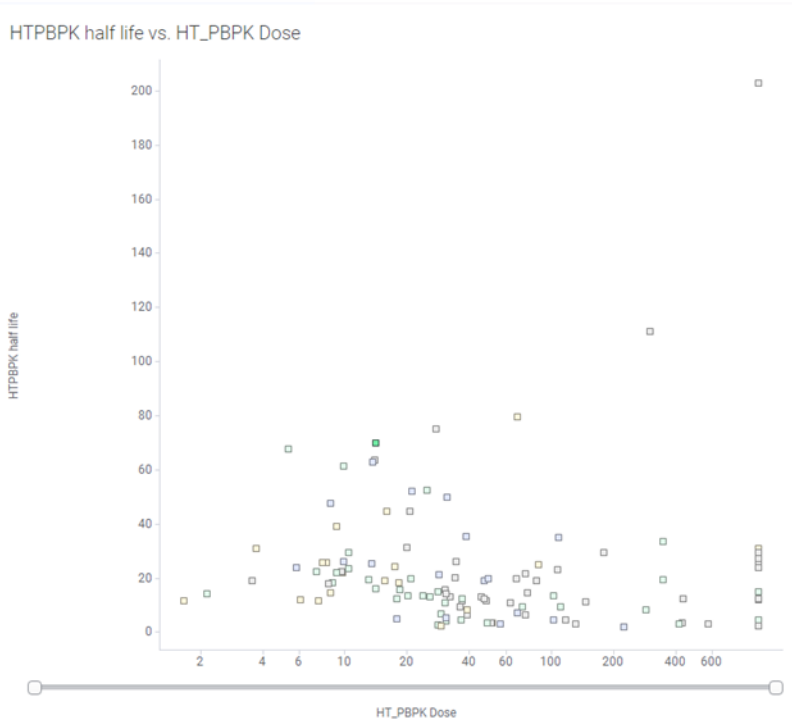

Data Load
Load Workspaces
Workspaces:
Load Data
DataSets:
Rowcount: 21
SRN Count: 21
SMILES Count:
CEFF_HUMAN_NG_ML(Min/max)
CEFF_RAT_NG_ML(Min/max):
Downloading
Trying to download
Starting...
Cancel
Show details
Next >>

Pre-defined results visualization

The interface to the ADMET predictor is designed according to Roche specification.

Once the data is loaded one is able to filter the data, set prediction parameters and select the desired prediction





The data retrieval and cleaning is fully automated, visualization are readily shared to project teams

Conclusions

- HT-PBPK simulations are now available for small molecule project teams using our in house data as input (in vitro, ML, etc.)
- The simulation process is seamless by creating an internal workflow and connecting ADMET predictor to our systems
- Simulations are easy to set up with minimal user intervention
- Pre-allocated visualization allow project teams to gain insights that are not generally available without PBPK modeling (bioavailability, half-life, Vss, etc.)
- Integration within our data systems allow for almost automatic model development and evaluation (e.g., PK predictions and learn-confirm cycles)

Acknowledgements

DMPK and M&S

- Neil Parrott
- Nenad Manevski
- Holger Fischer
- Matthias Wittwer
- Doha Naga
- Andrea Morger
- Kenichi Umehara

pRED Informatics

- Yaniv Cohen
- Peter Curle

Small Molecule Research

- Michael Reutlinger
- Giuseppe Cecere

Doing now what patients need next