Where AI and mechanistic PKPD modelling strengthen each other in drug development

Rob van Wijk | Leiden Drug Development Conference, Sept 19th, 2024

Universiteit Leiden
The Netherlands

LACDR

Systems Pharmacology and Pharmacy

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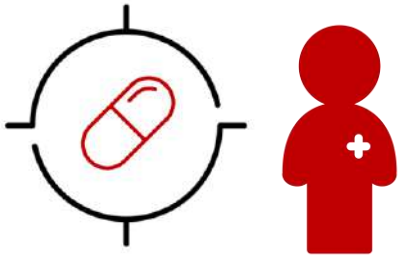
We aim to develop precision medicine approaches to characterize and predict variation in treatment response and enhance translational drug development strategies.

Systems & clinical pharmacology: Develop systems level understanding of drug action, disease heterogeneity, and inter-individual variation.

Molecular → Cellular → Organ → Organisms → Patient populations



Precision medicine approaches

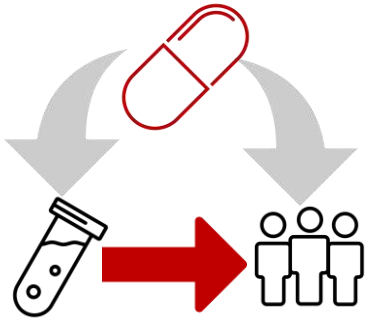
Measurement technologies & biomarkers

Experimental disease models

PK-PD modeling Mechanistic modeling

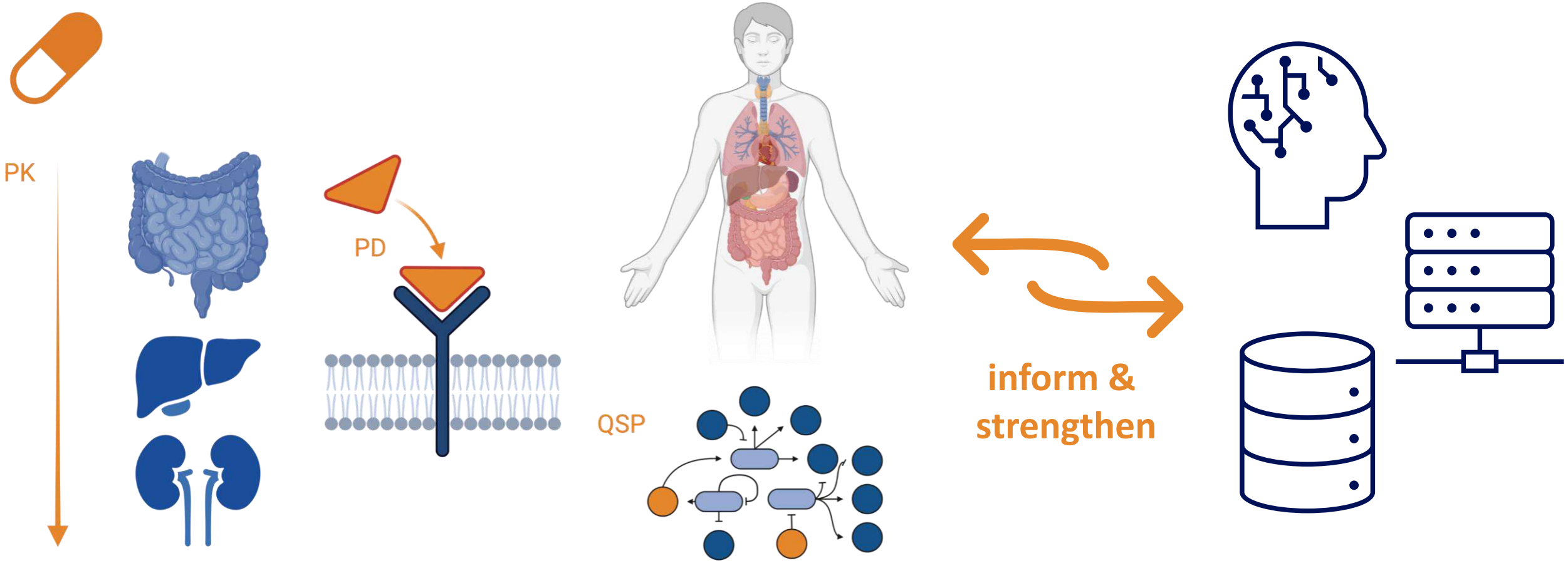
Clinical data & collaborations

Experimental and **computational approaches** to *translate* measurements and disease models to treatment response in patients.



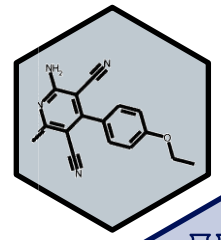
Translational drug development

Mechanistic pharmacological modelling and AI

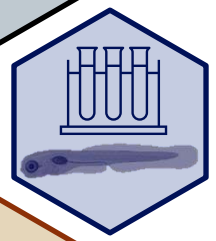


PK: pharmacokinetics, PD: pharmacodynamics
QSP: quantitative systems pharmacology

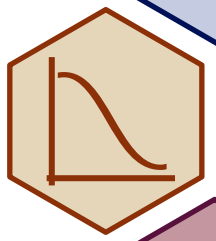
Model informed drug discovery and development (MID3)



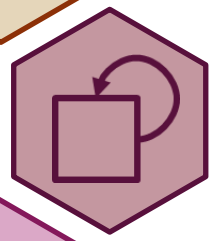
Generating novel compounds



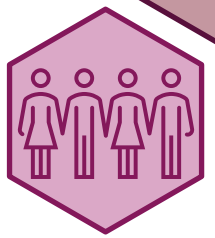
Bridging *in vitro* - *in vivo*



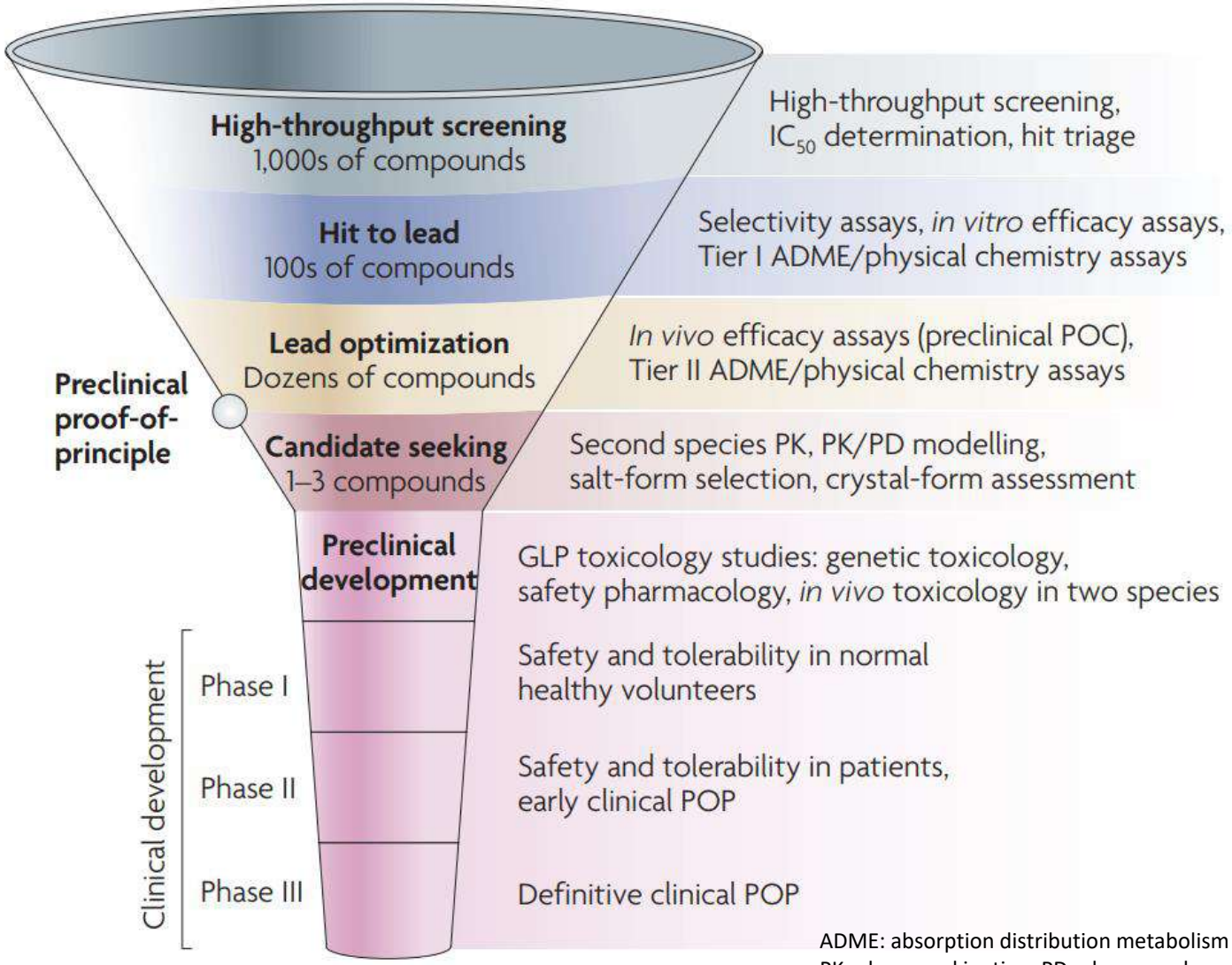
Predicting relapse infections



Informing tumor growth



Simulating virtual populations



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Kramer, J. et al, Nat Rev Drug Discov 6, 636–649 (2007)

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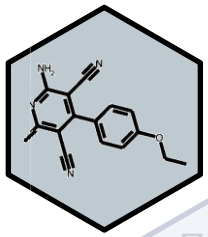

Generating novel compounds

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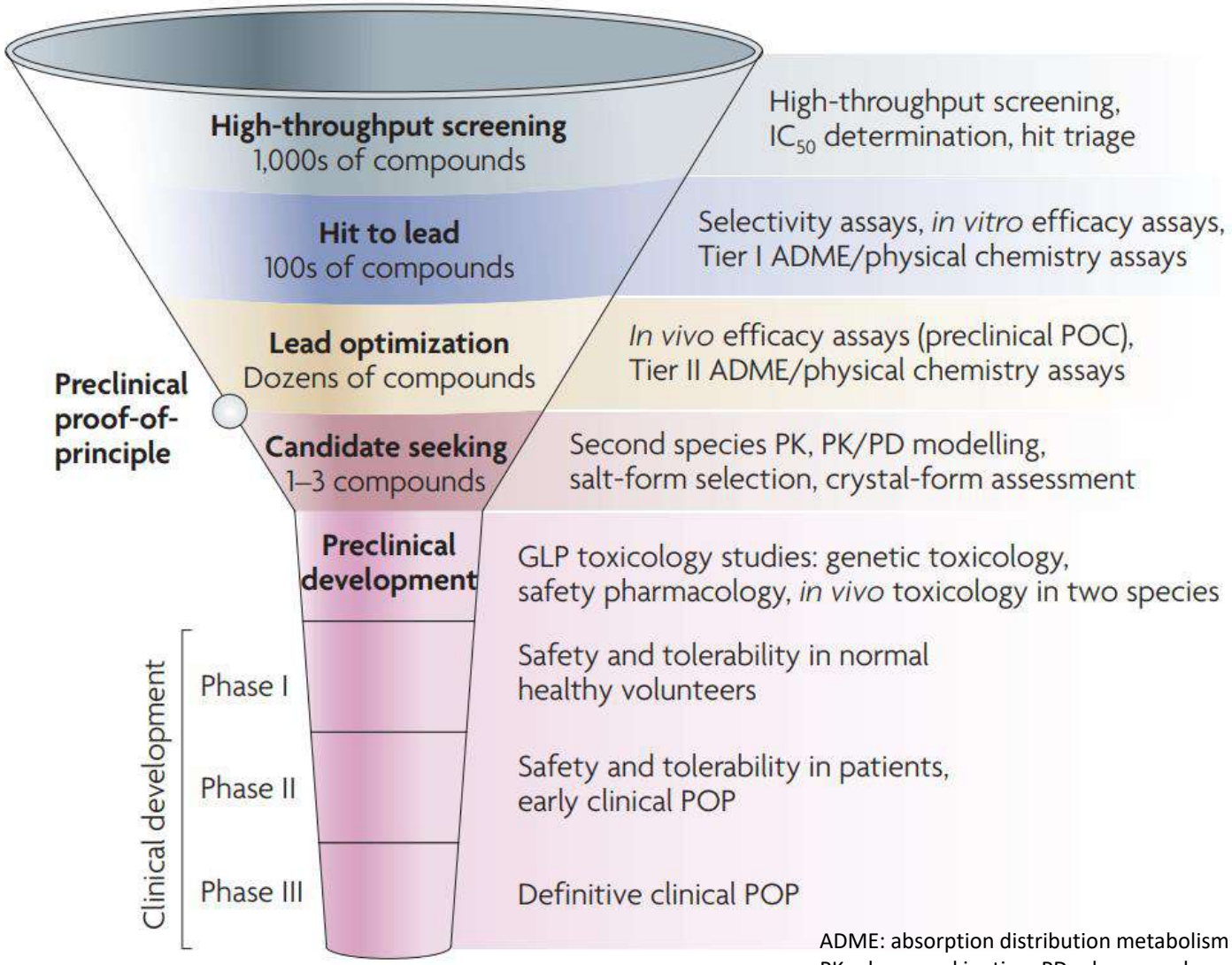

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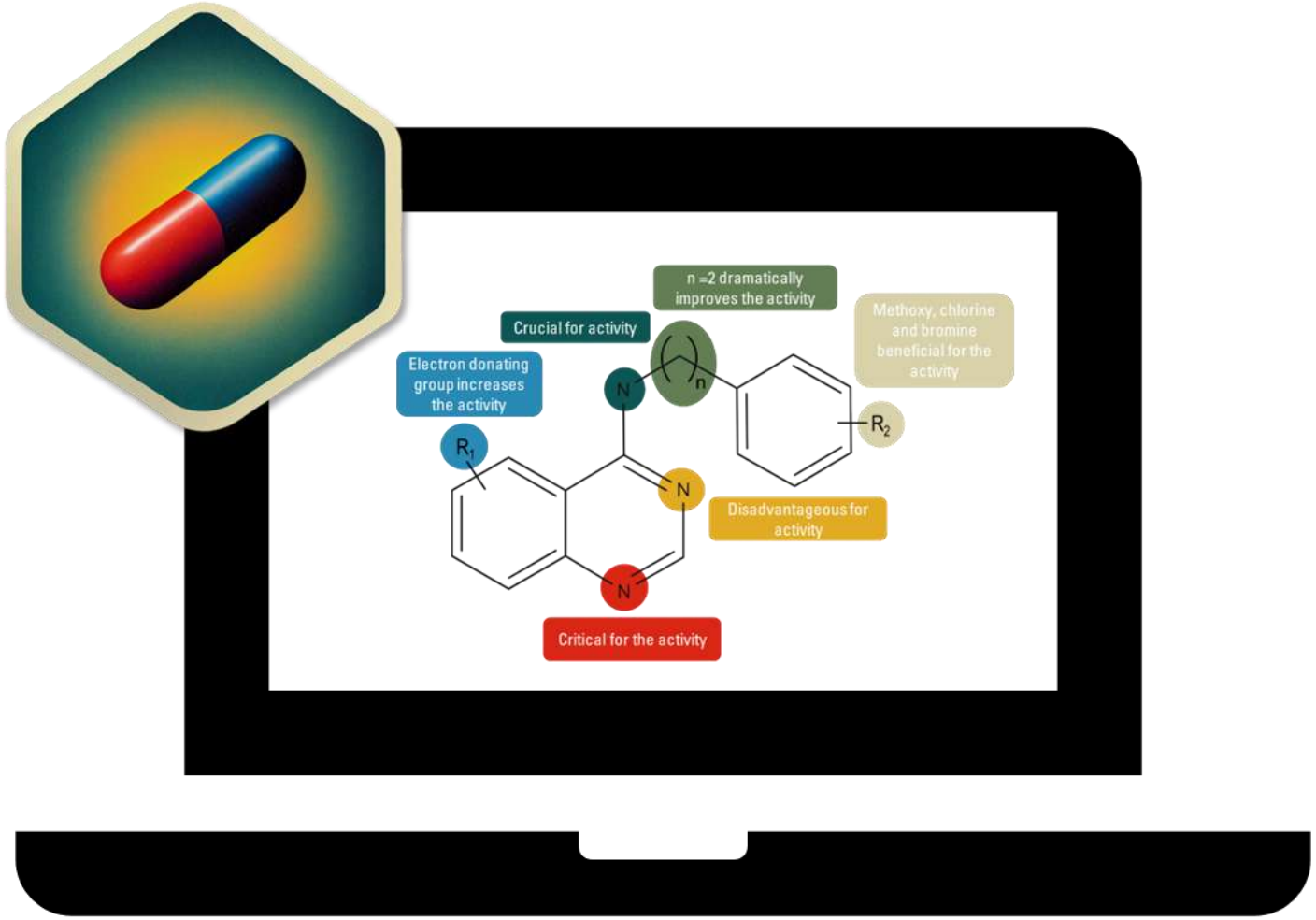
QSPRPRED: A FLEXIBLE OPEN-SOURCE QSPR MODELLING TOOL

Extensive data-preprocessing functionality.
Suitable for building single-task, multi-task and proteochemometric models.

GitHub

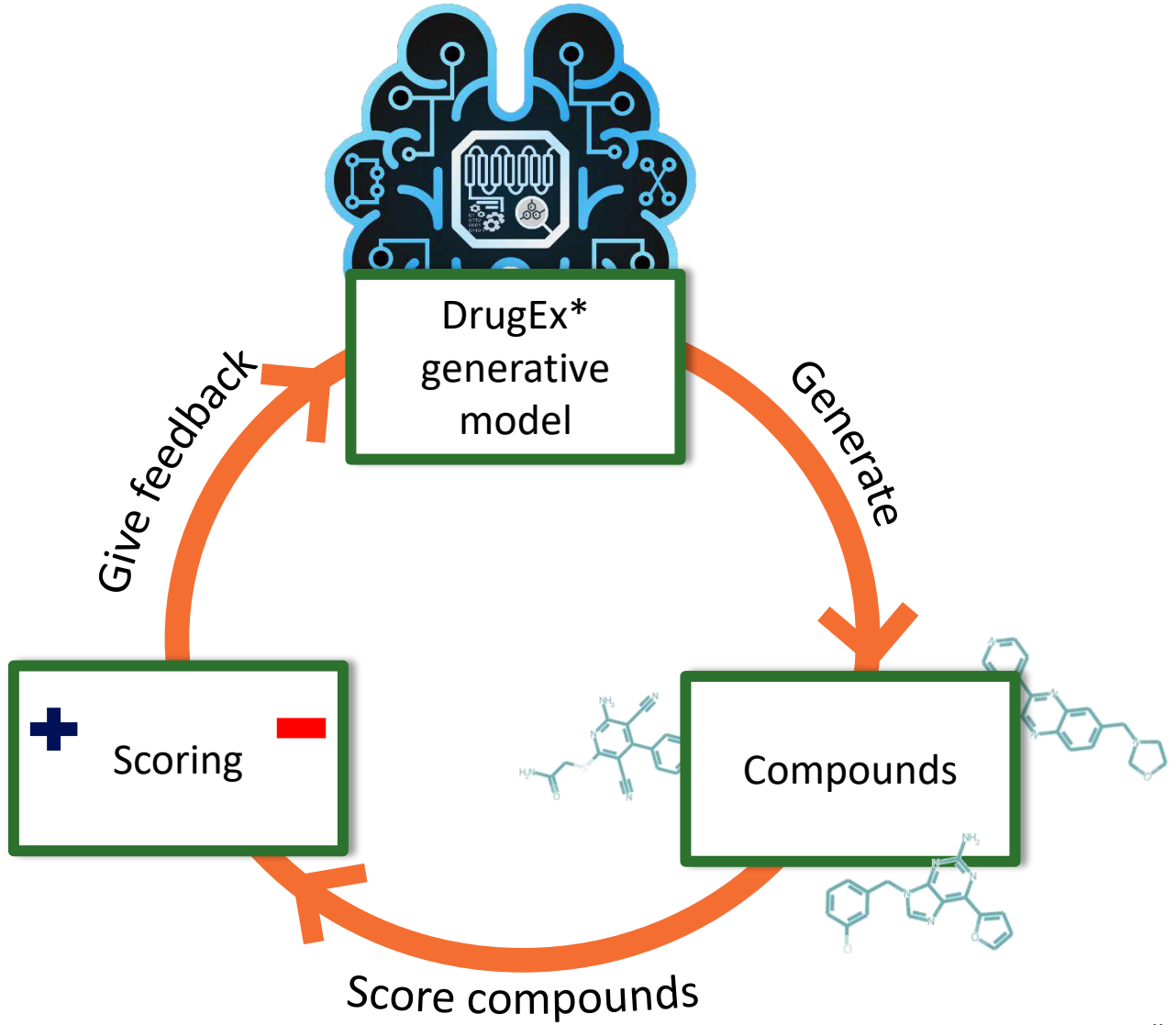
Preprint



Helle W. van den Maagdenberg, Martin Šícho, David Araripe, Sohvi Luukkonen, Linde Schoenmaker, Michiel Jespers, Olivier J. M. Béquignon, Marina Gorostiola González, Remco L. van den Broek, Andrius Bernativicius, J.G. Coen van Hasselt, Piet H. van der Graaf, and Gerard J. P. van Westen

*Example SAR study of Spautin-1 for novel NEK4 inhibitors from Elsocht et al. *Int J Mol Sci.* 2020

Learning and confirming cycle in generating novel compounds



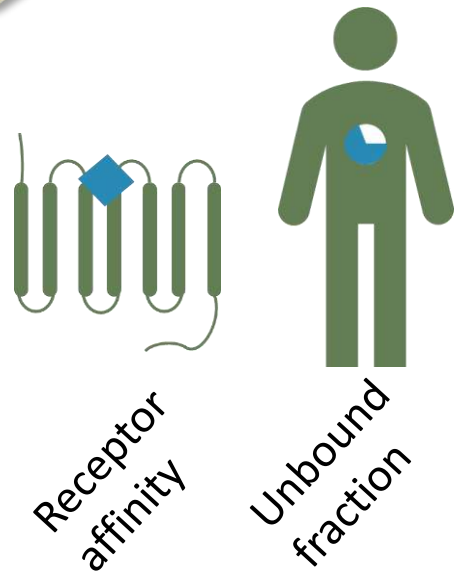
Helle W. van den Maagdenberg

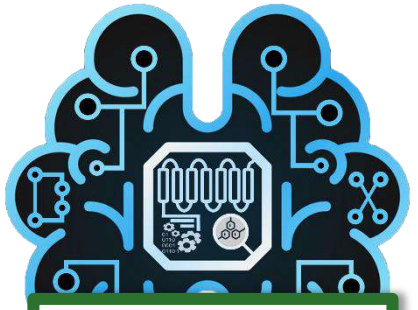
* Liu, X., et al. J Cheminf. (2019) * Šícho M. *et al.*, *J. Chem. Inf. Model.* 2023

Learning and confirming cycle in generating novel compounds

Scoring

QSPR models for adenosine $A_{2A}R$ binding affinity & human pharmacokinetics





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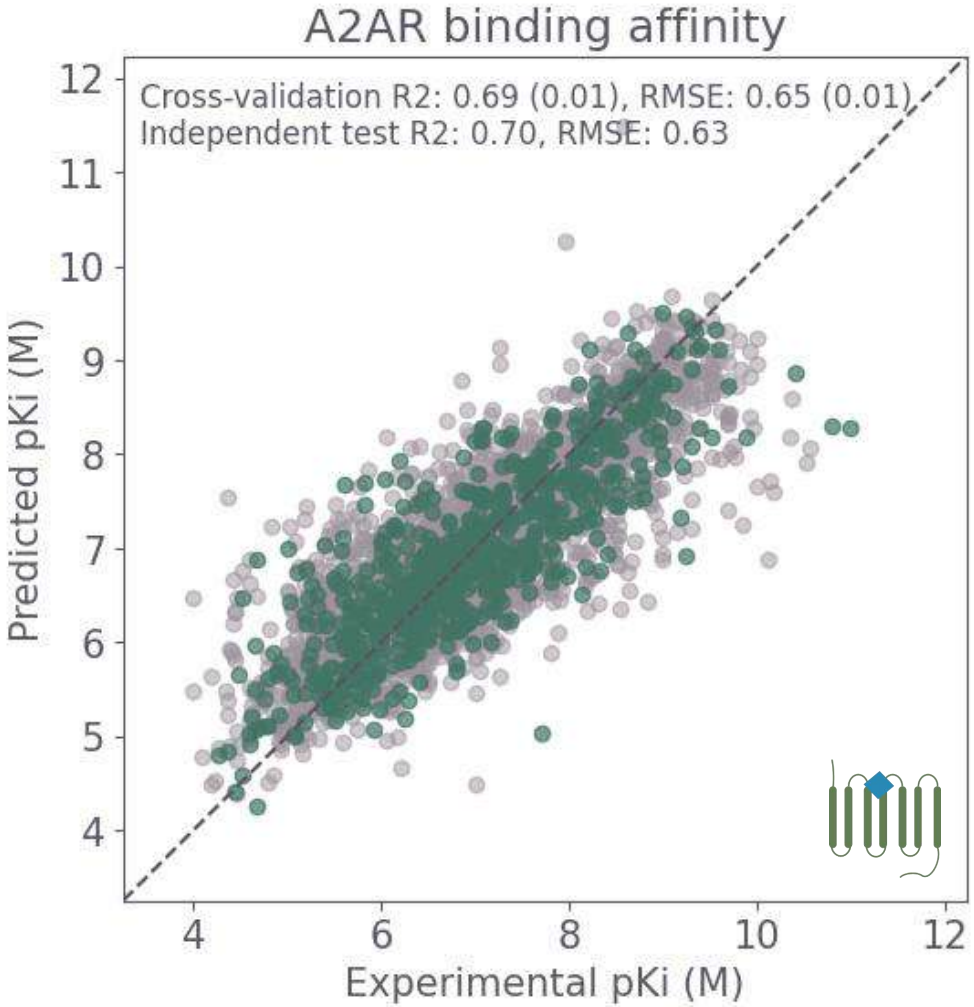
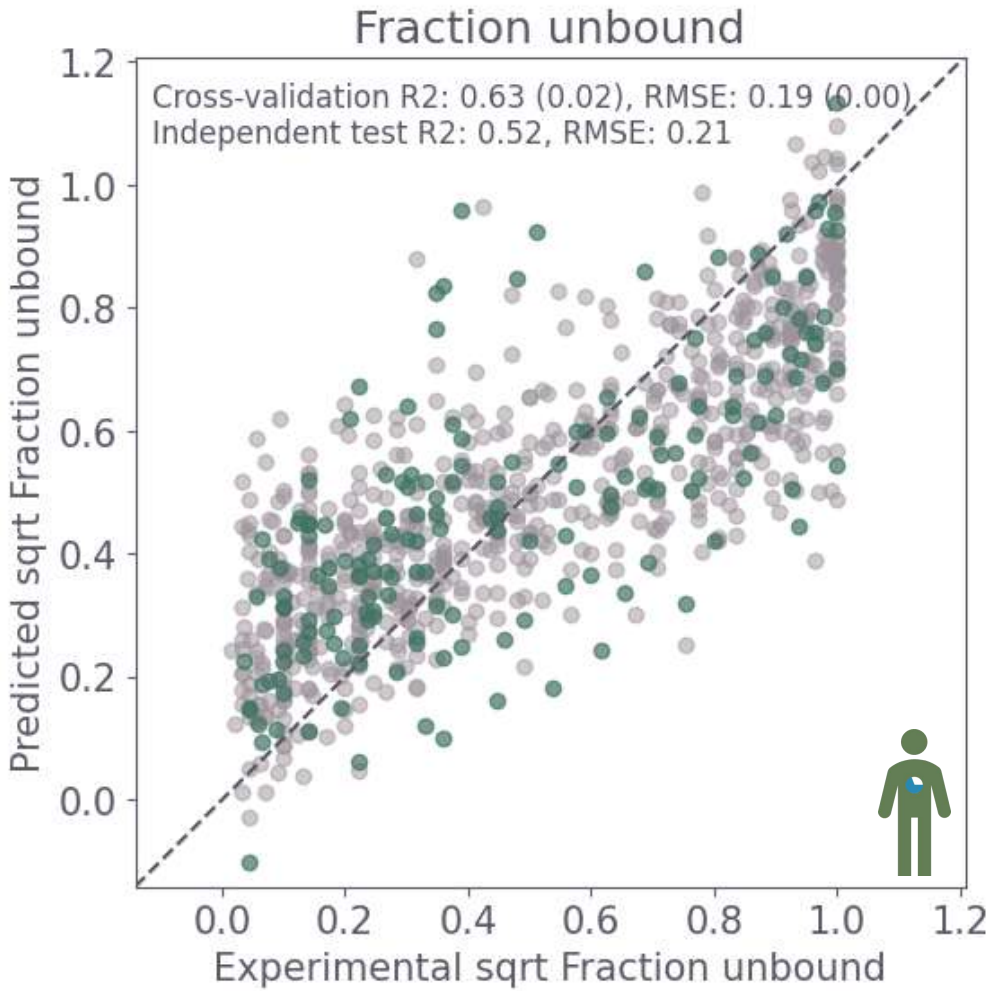
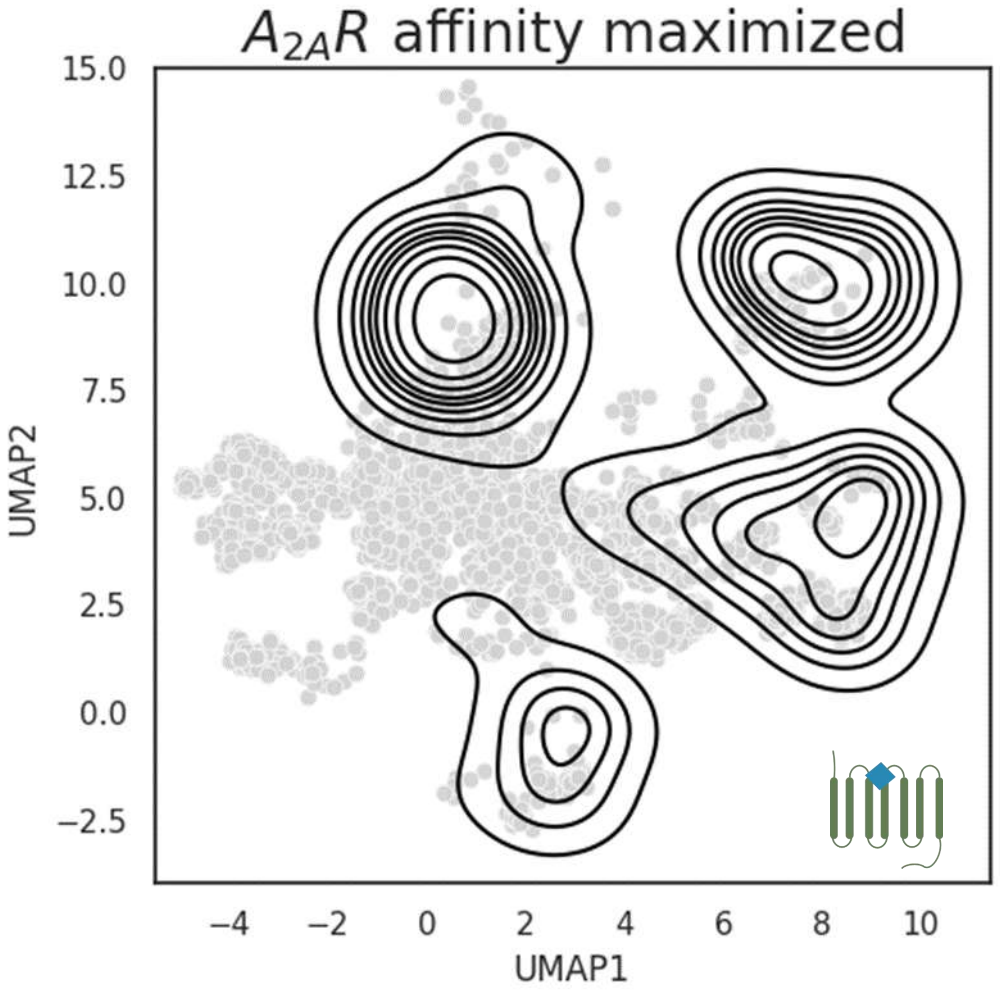
QSPR models trained with QSPRPRED

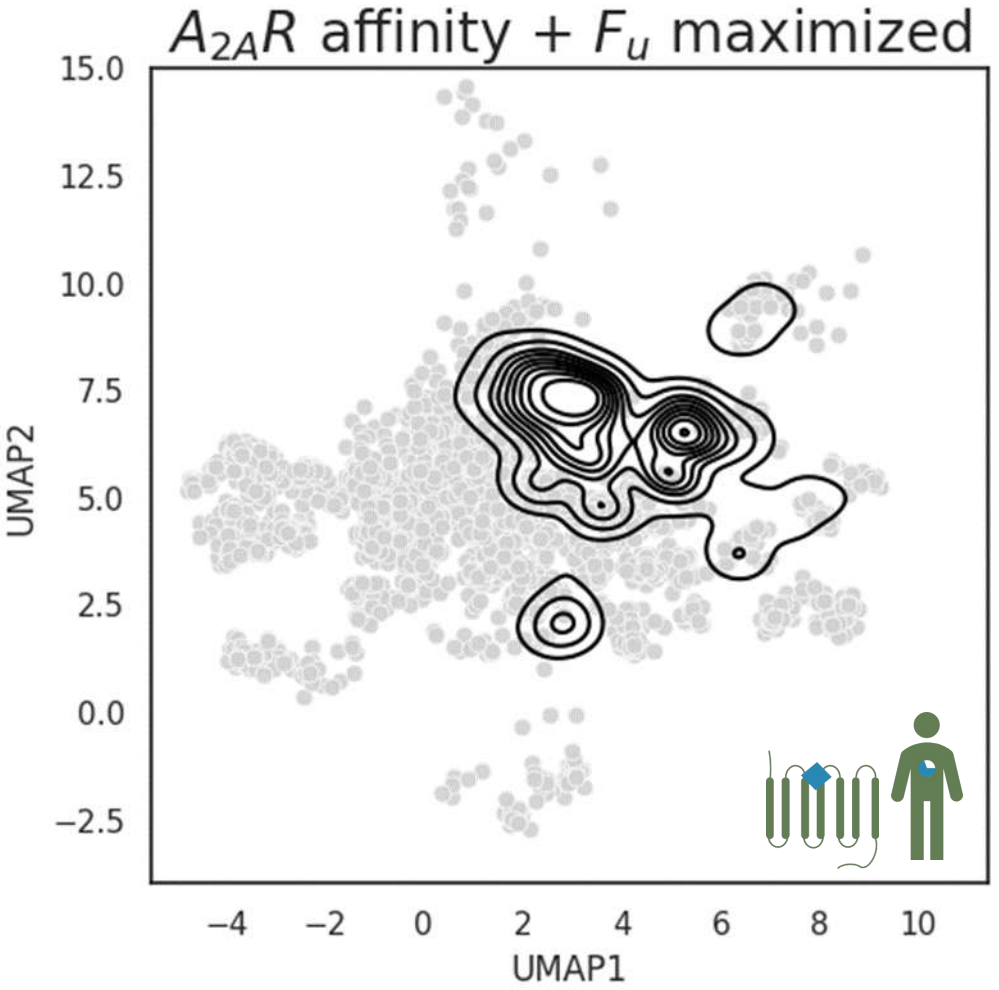




Helle W. van den Maagdenberg

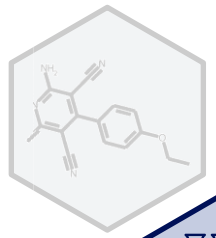
Model-informed novel molecules in chemical space





Helle W. van den Maagdenberg

Model informed drug discovery and development (MID3)



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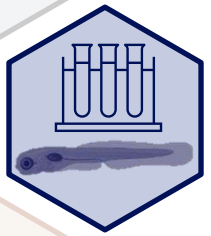

Bridging *in vitro* - *in vivo*

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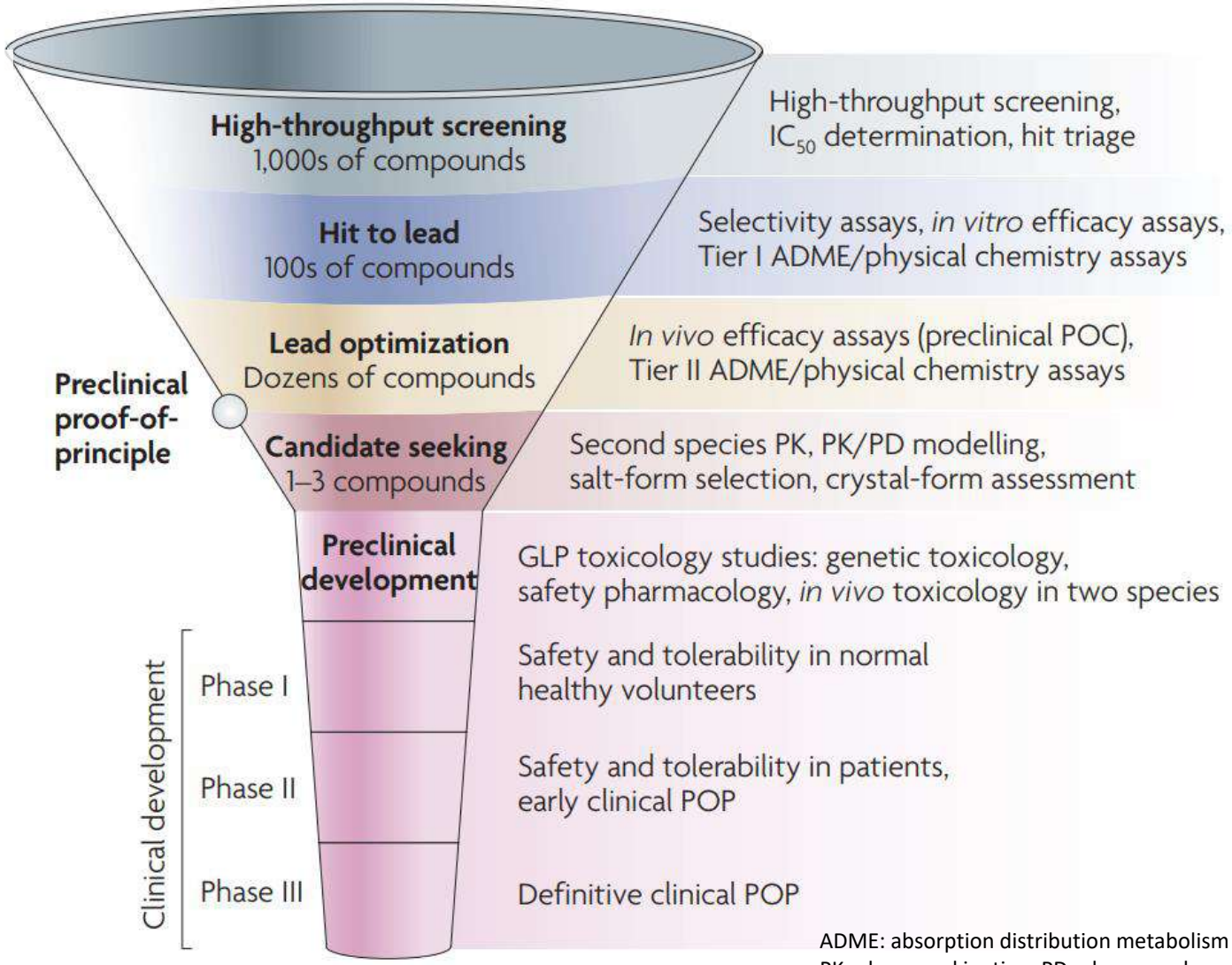

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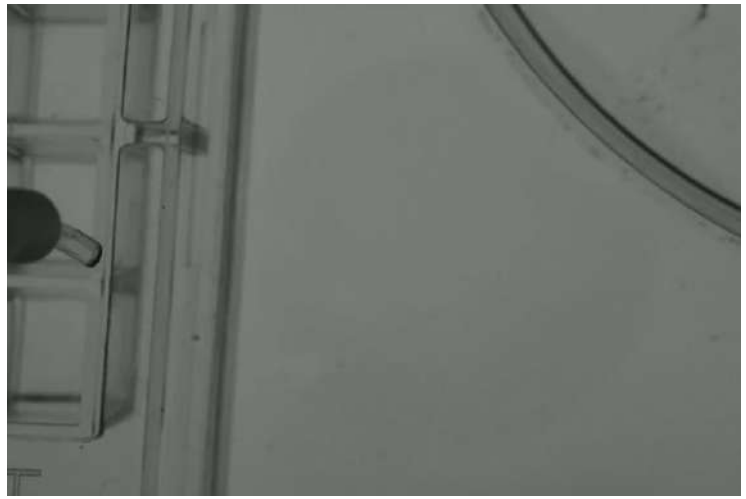
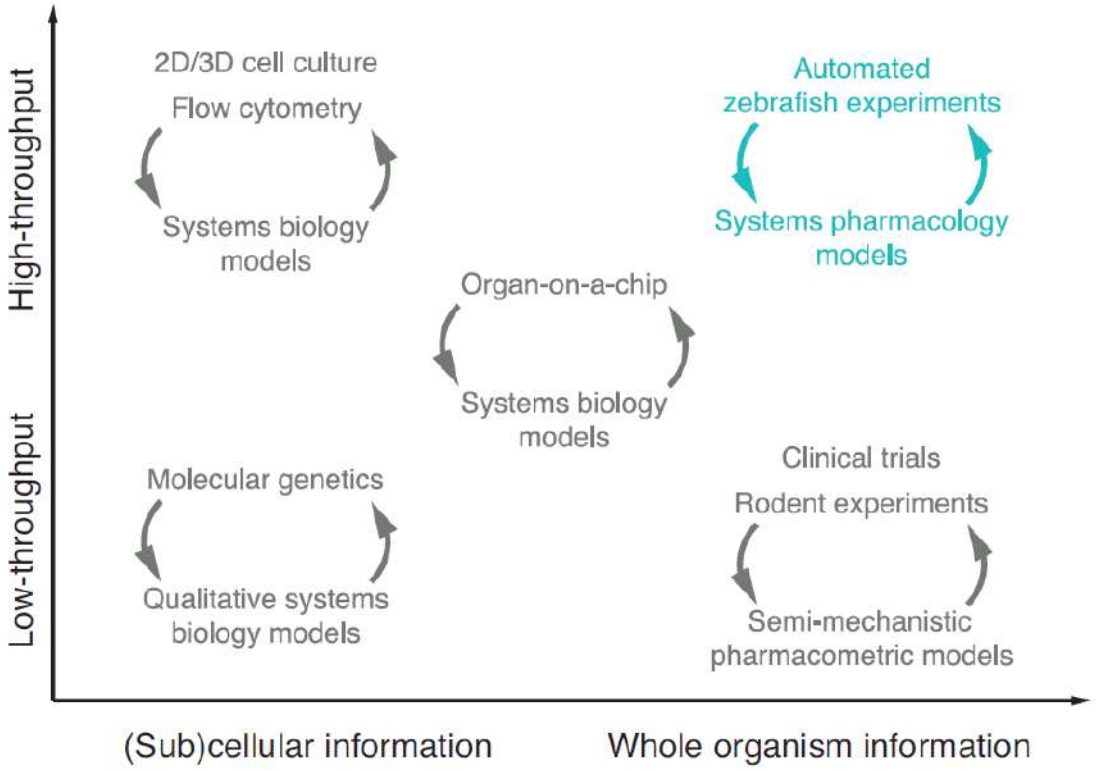
Kramer, J. et al, Nat Rev Drug Discov 6, 636–649 (2007)

Bridging the in vitro – in vivo gap in drug development

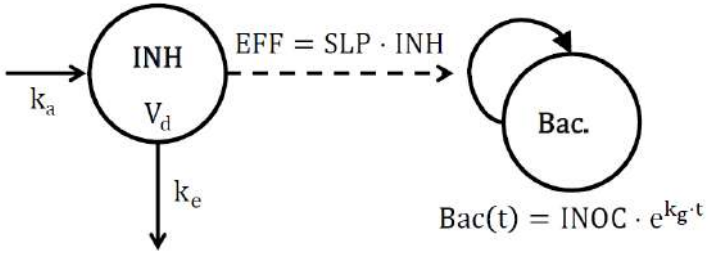
Transparency

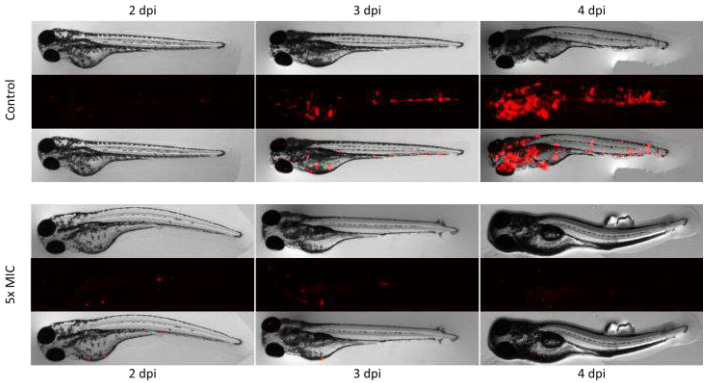


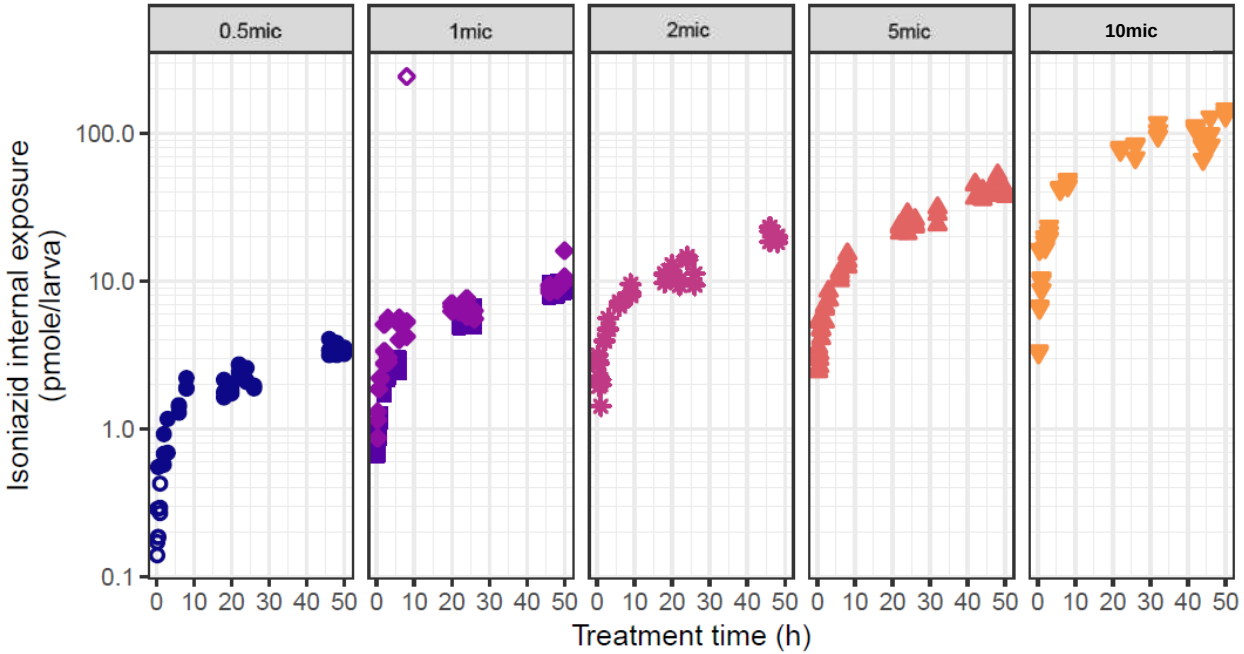
High-throughput (robotics)

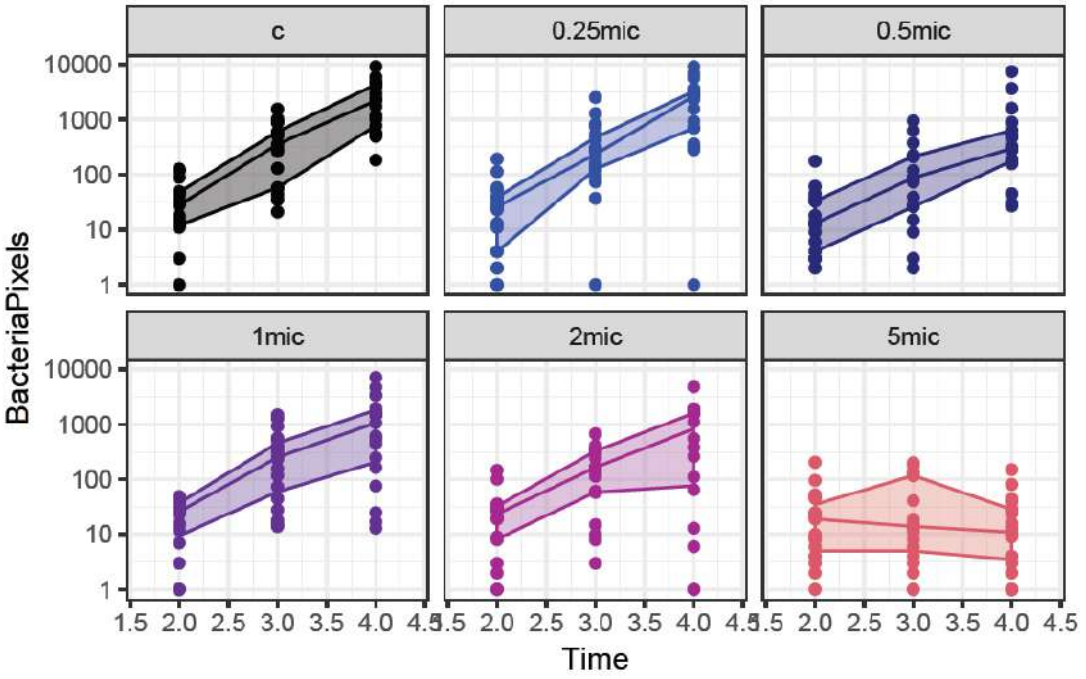


High-throughput quantification of PKPD in zebrafish



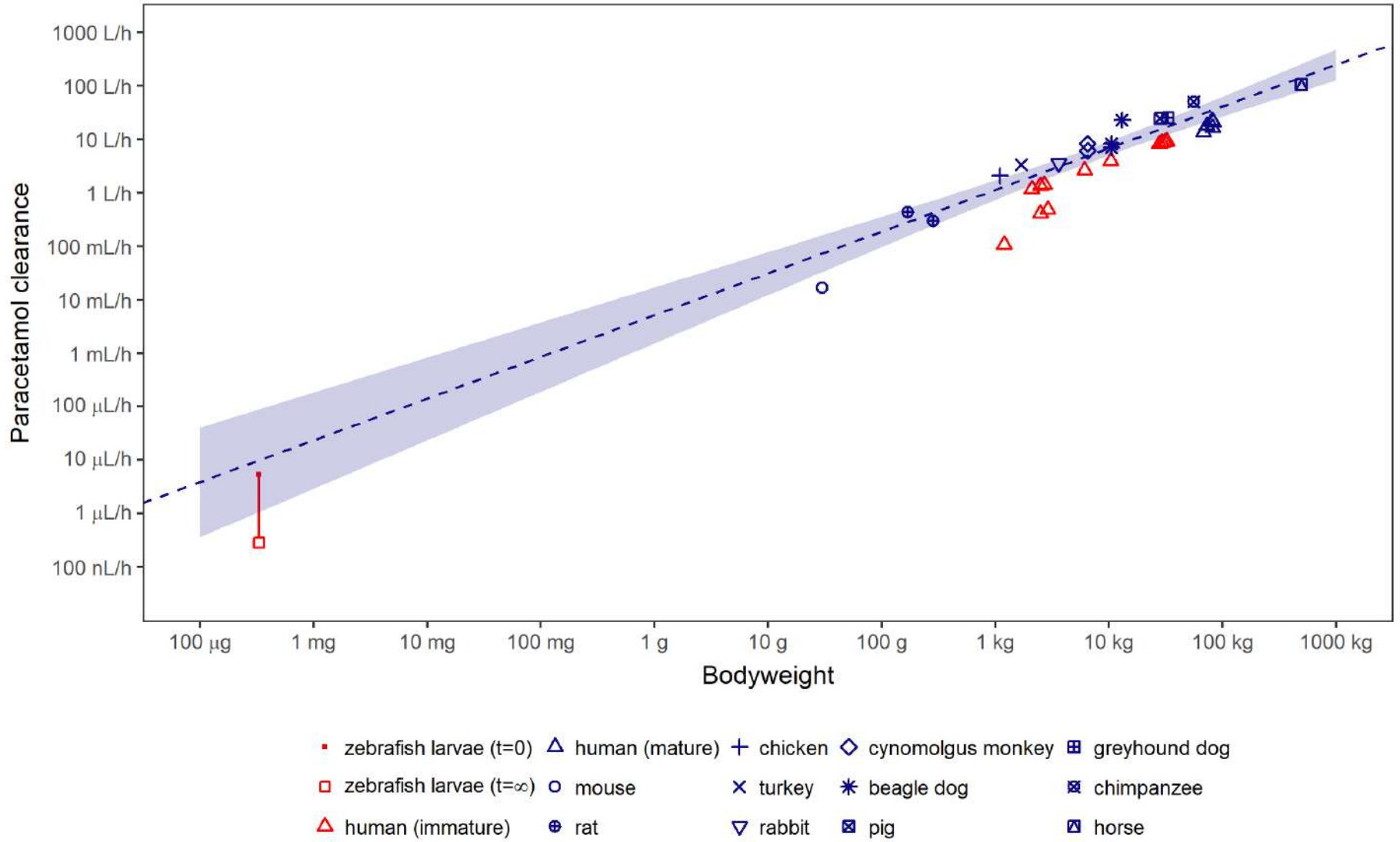






Van Wijk, *Translational pharmacokinetics-pharmacodynamics in zebrafish* (Dissertation, Leiden Library, 2020)

Drug exposure in zebrafish translates to higher vertebrates



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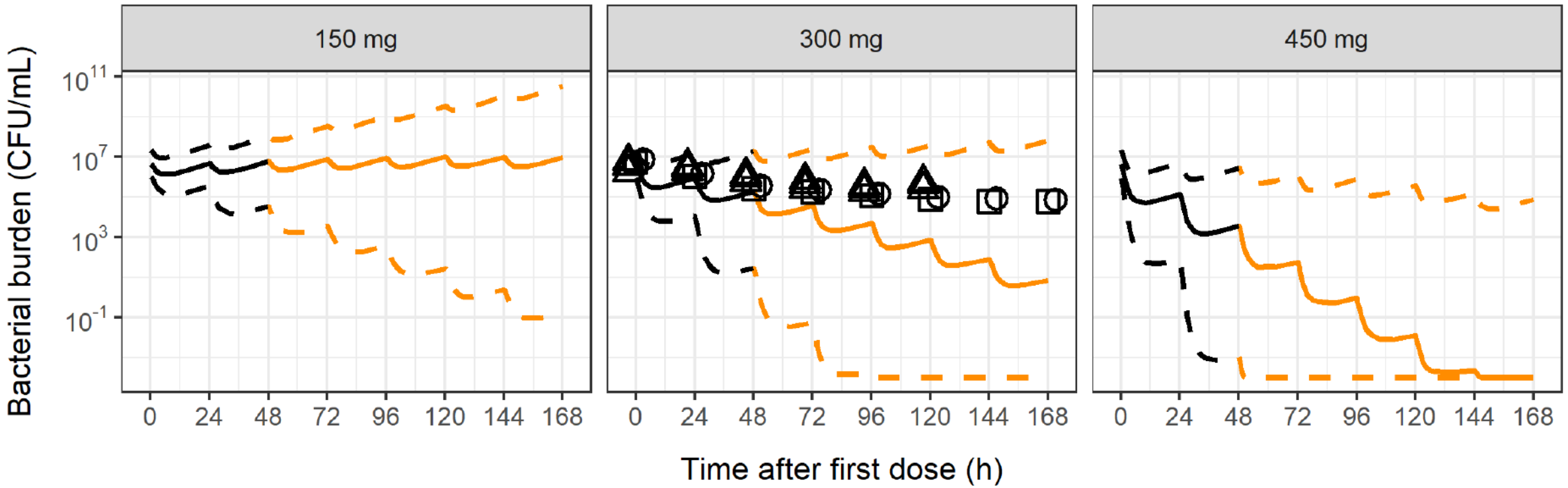

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Model informed drug discovery and development (MID3)

Generating novel compounds

Bridging *in vitro* - *in vivo*

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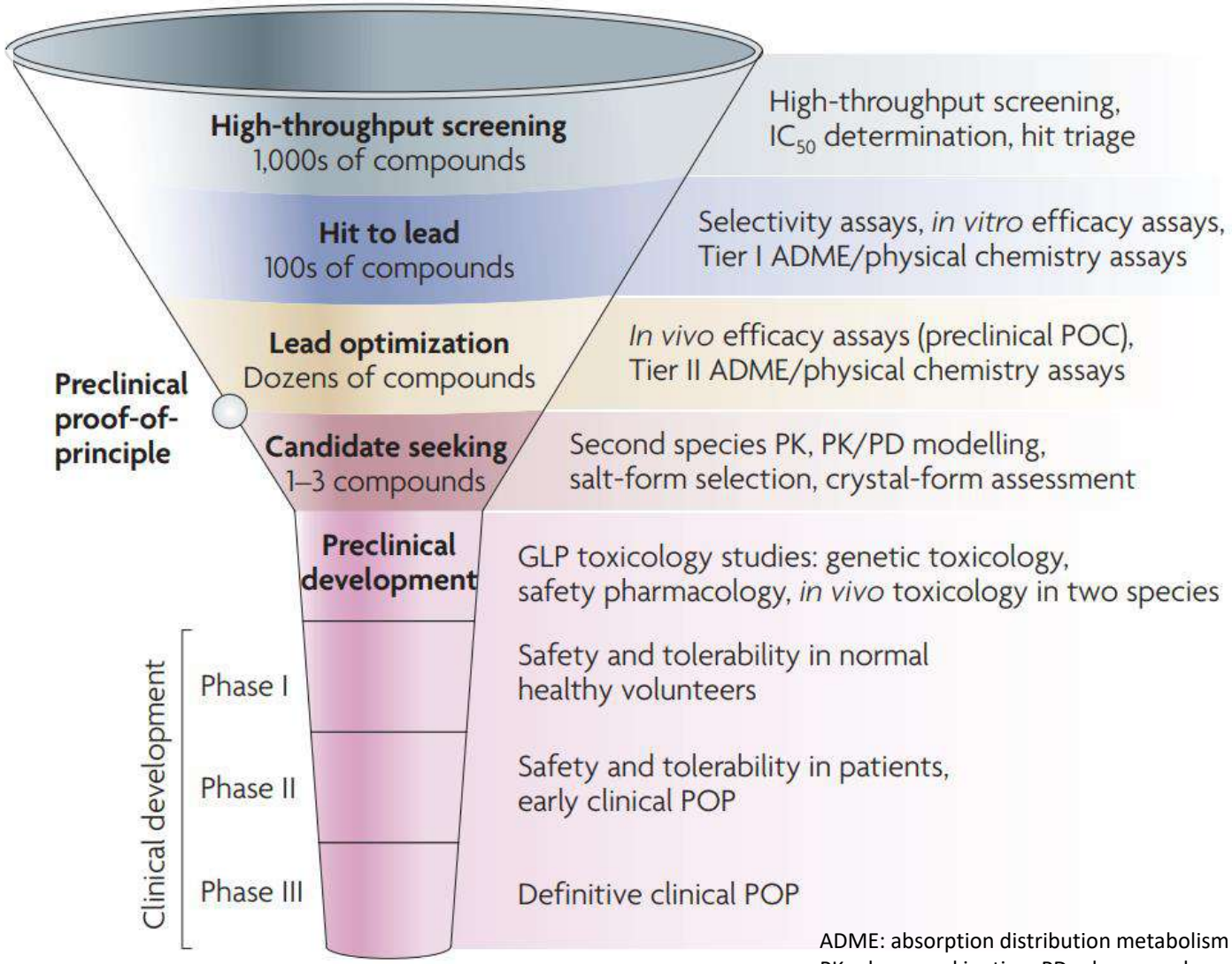

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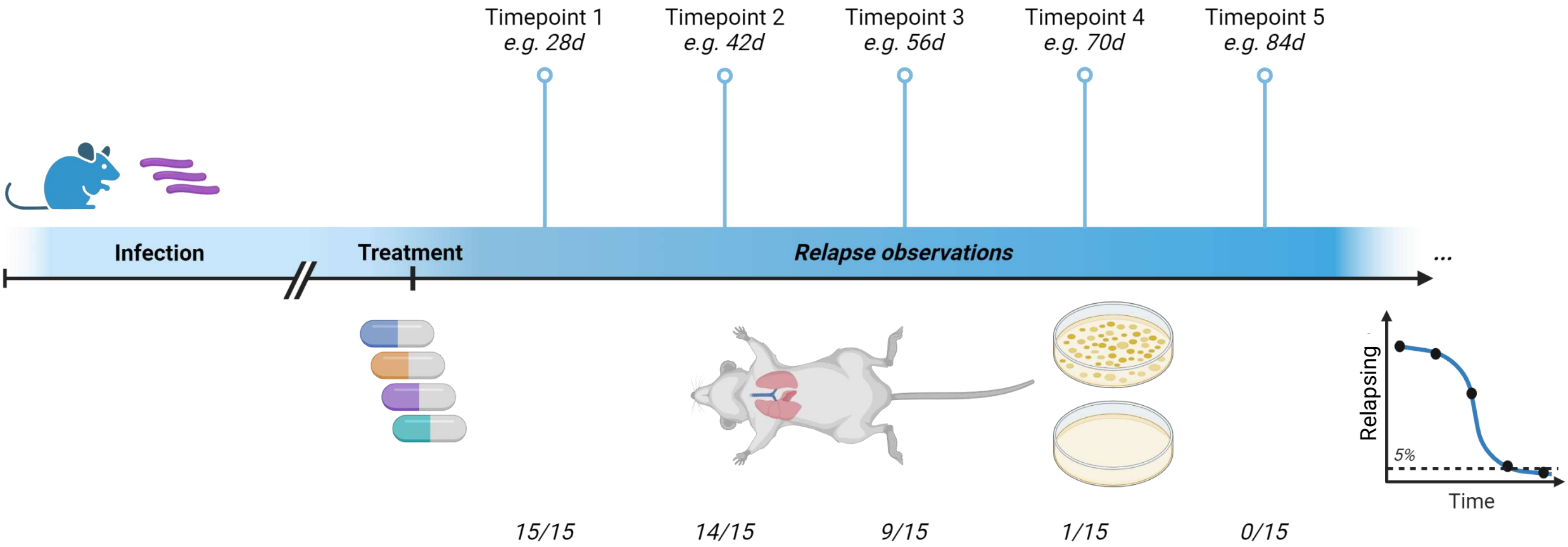
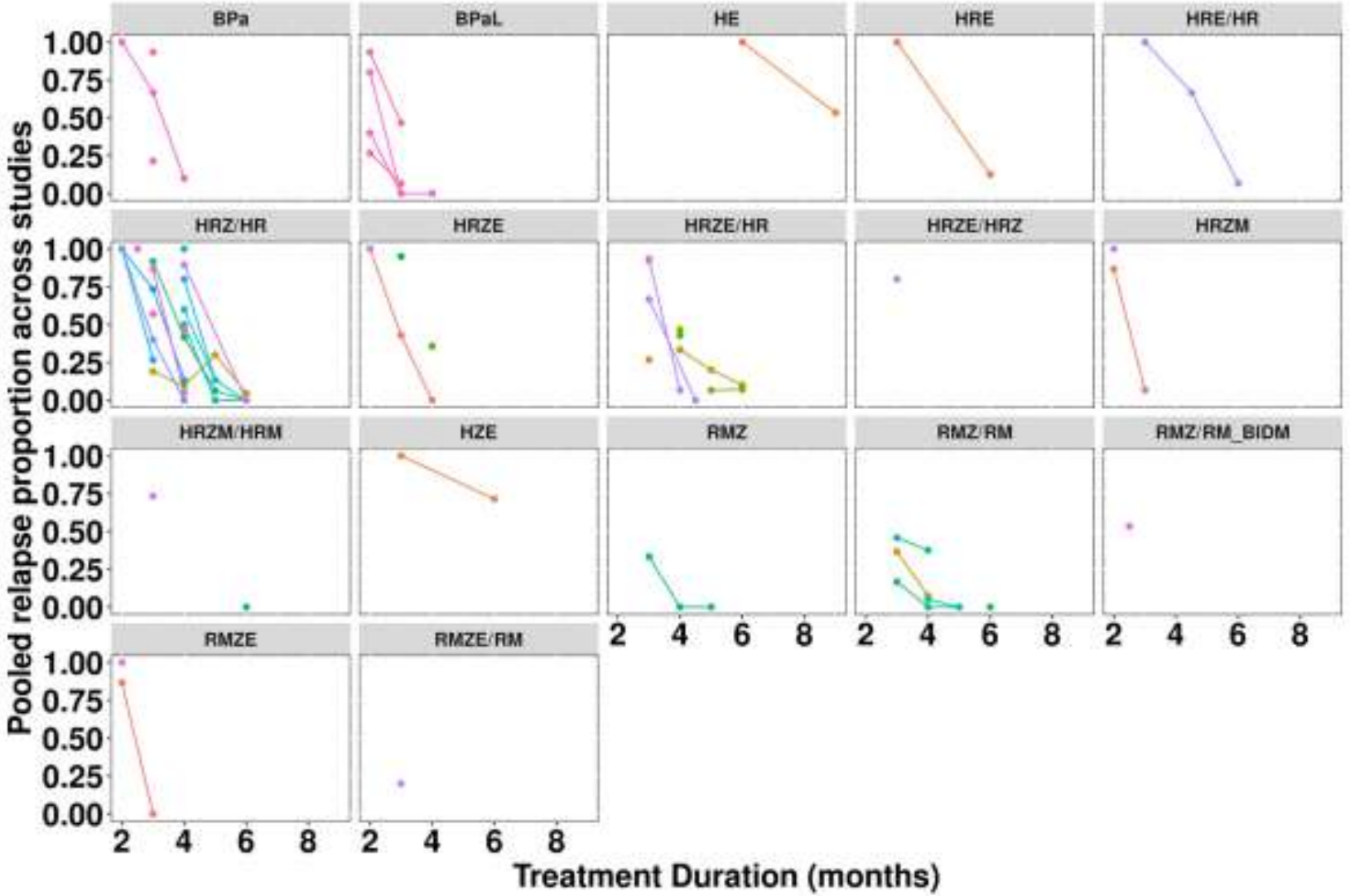
Kramer, J. et al, Nat Rev Drug Discov 6, 636–649 (2007)

Preclinical experiment of tuberculosis relapse



Relapse data published for different regimens of antibiotics



Berg A, et al, Antimicrob Agents Chemother. 2022 Mar 15;66(3):e0179321

Model-informed ranking of regimens based on relapse

Dataset with (overlapping) regimens

Machine learning (neural networks, random forest)

Training and performance

Predicting and ranking novel regimens

Predict regimen performance based on contribution of individual drug(s)

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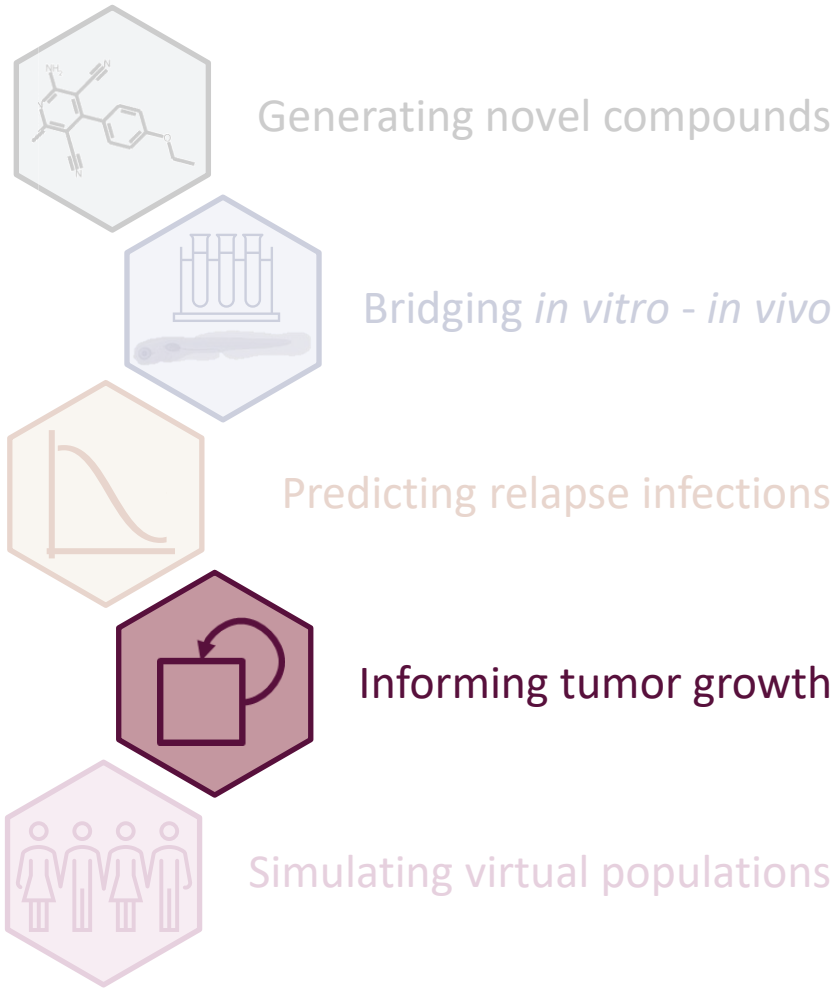

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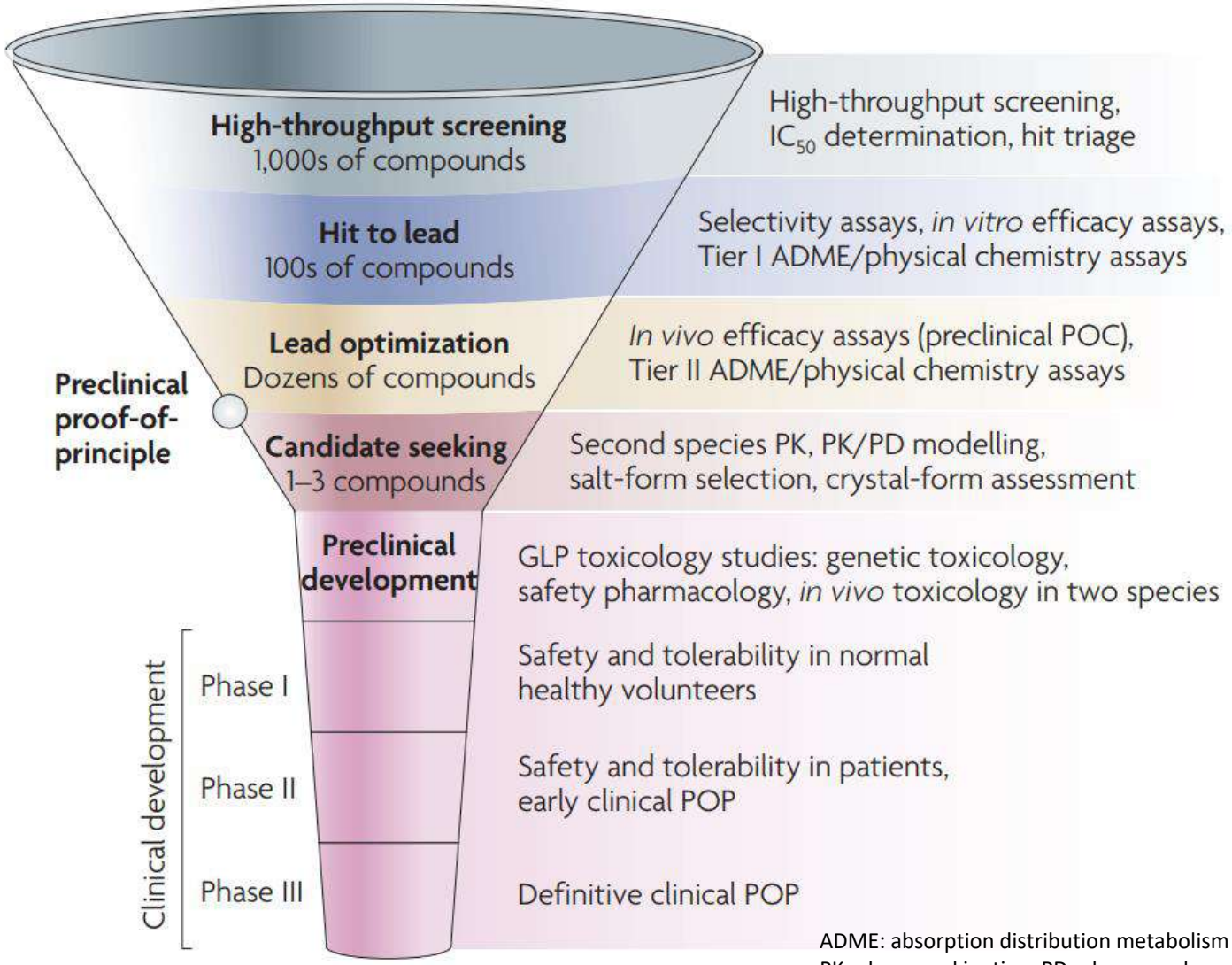

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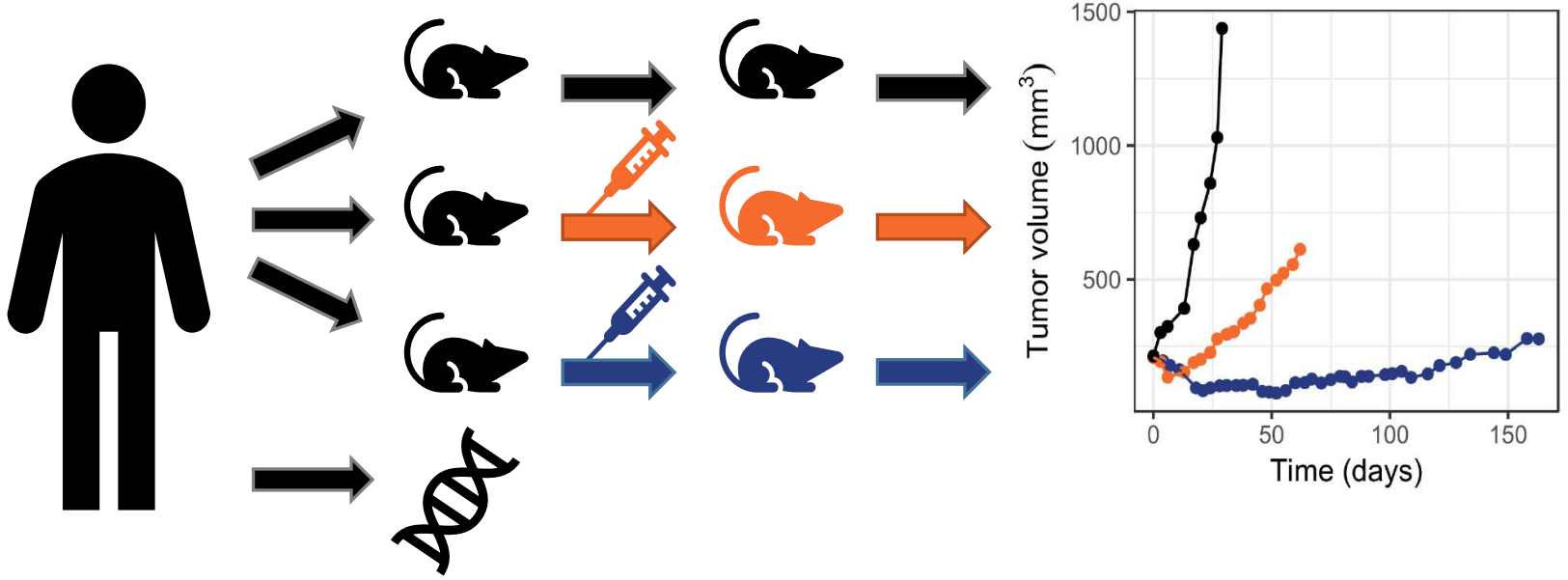
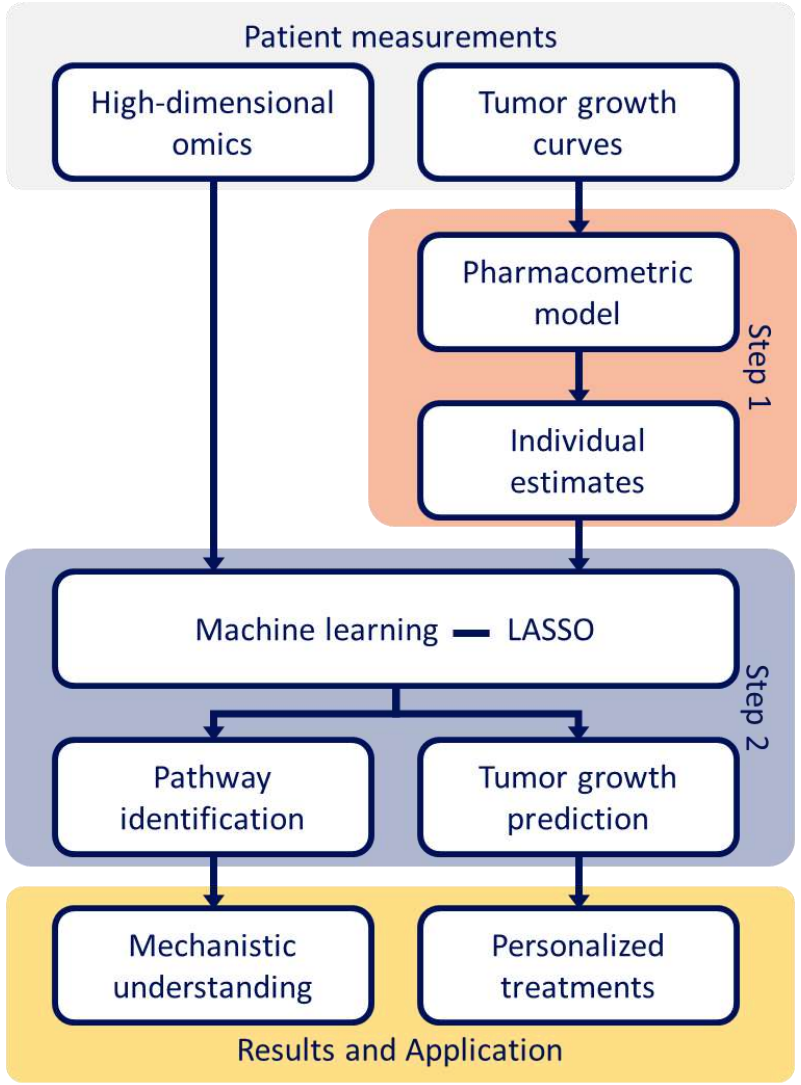
High-dimensional omics-derived predictors for tumor growth dynamics



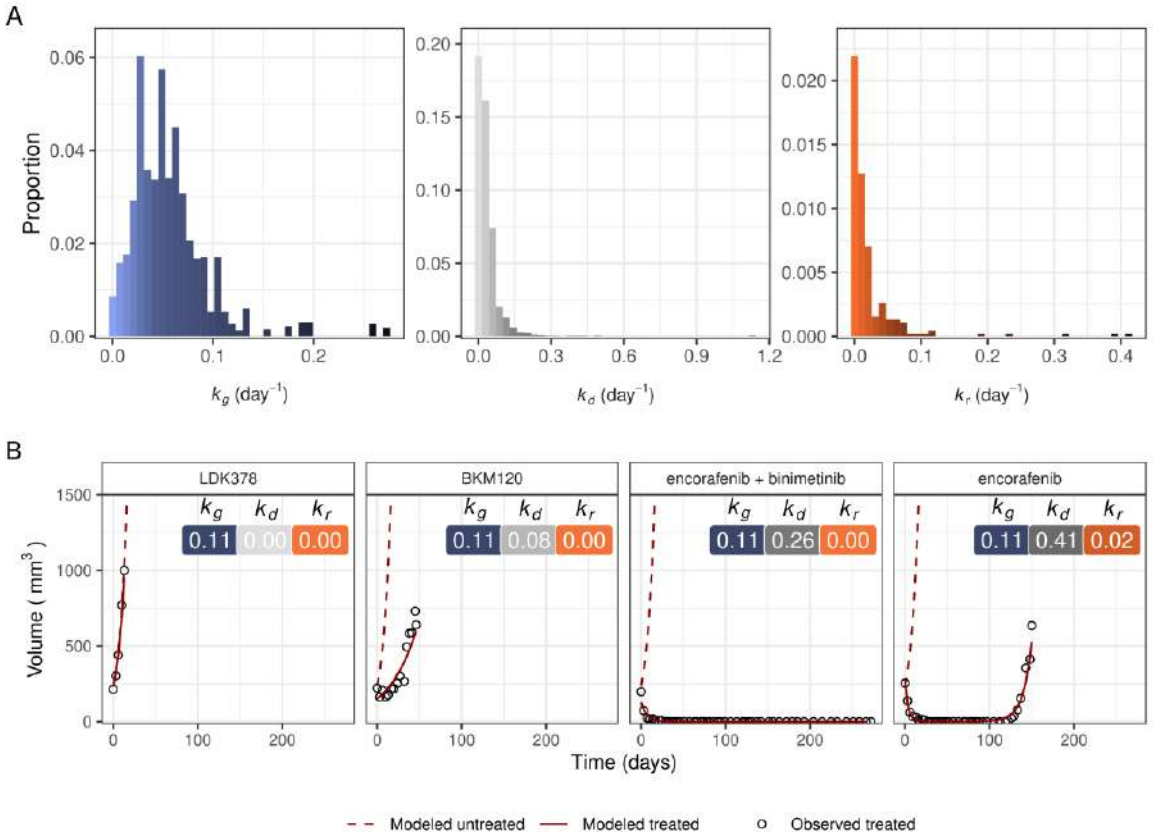


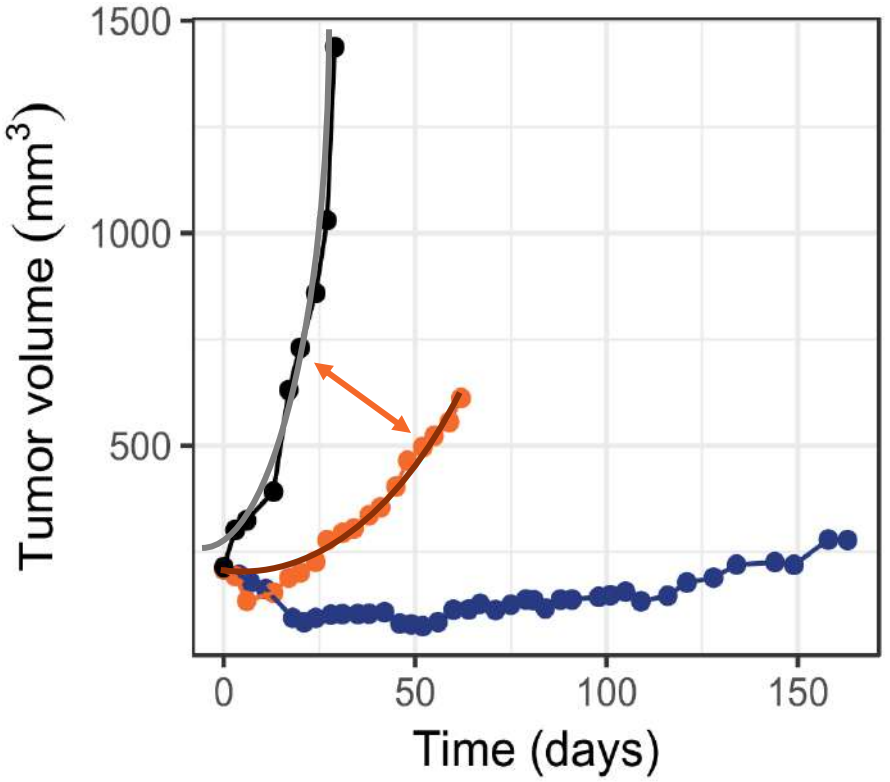
n = 173 patients; n = 2899 mice
53 treatments
>22,000 gene expression patterns
>19,000 copy number variations

L.B. Zwep et al, CPT: PSP 10(4); 350-361 (2021)

Mechanistic model of tumour growth inhibition

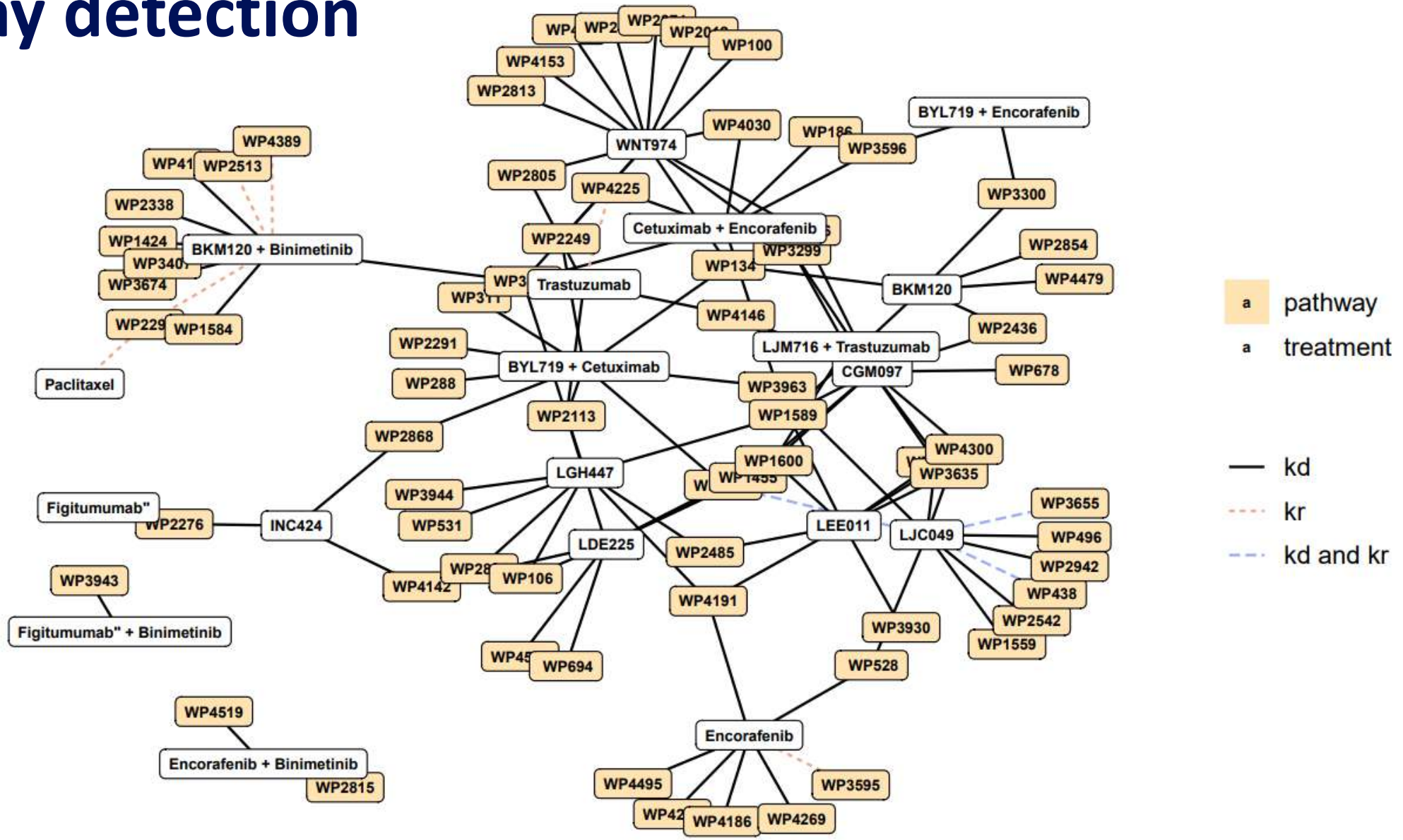
$$\frac{dV(t)}{dt} = K_G V(t) - K_{D,j} V(t) e^{-K_{R,j} t}$$





L.B. Zwep et al, CPT: PSP 10(4); 350-361 (2021); Claret et al, 2009

Pathway detection



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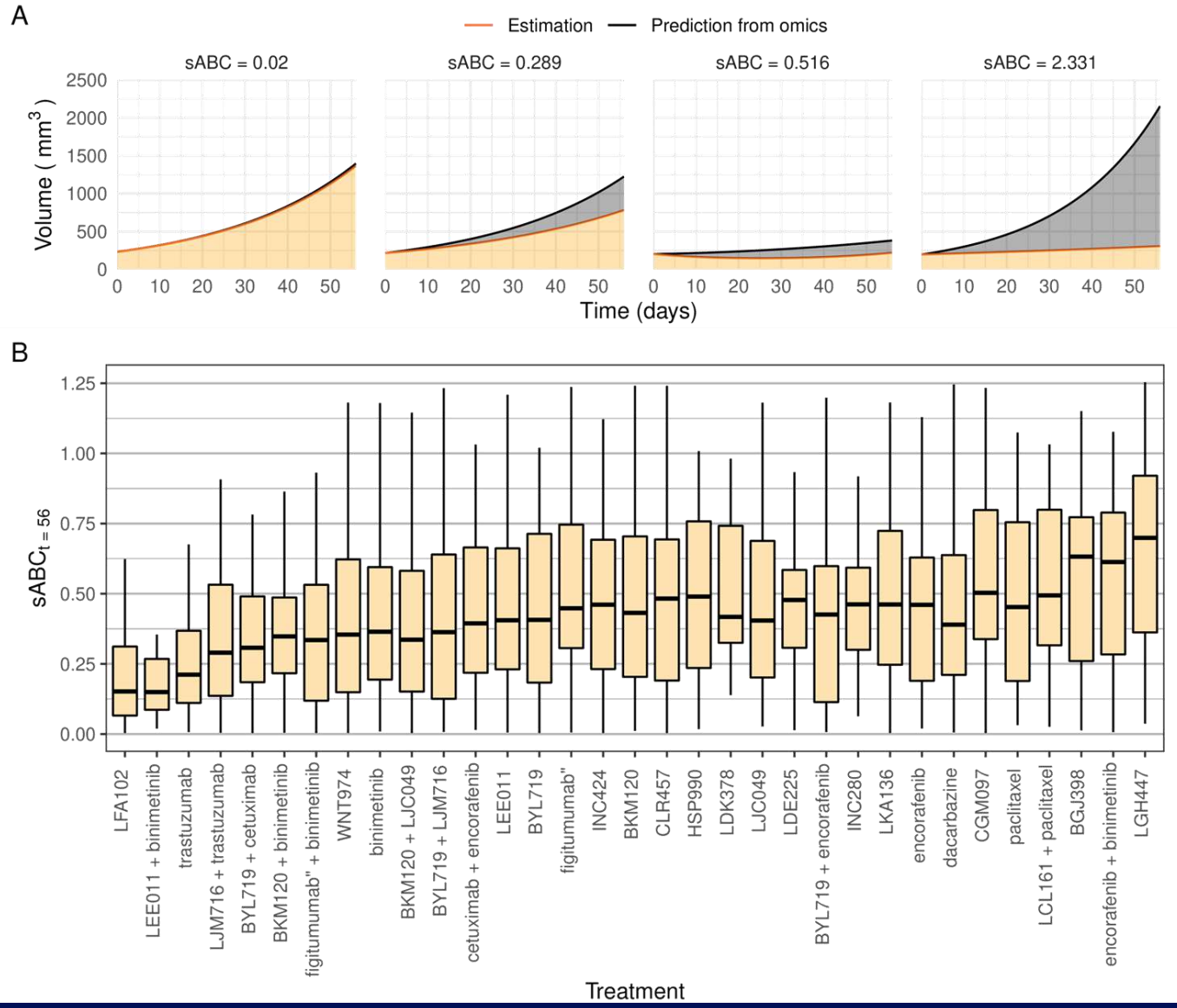
Individual tumour growth prediction to personalize treatment



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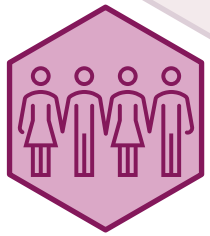
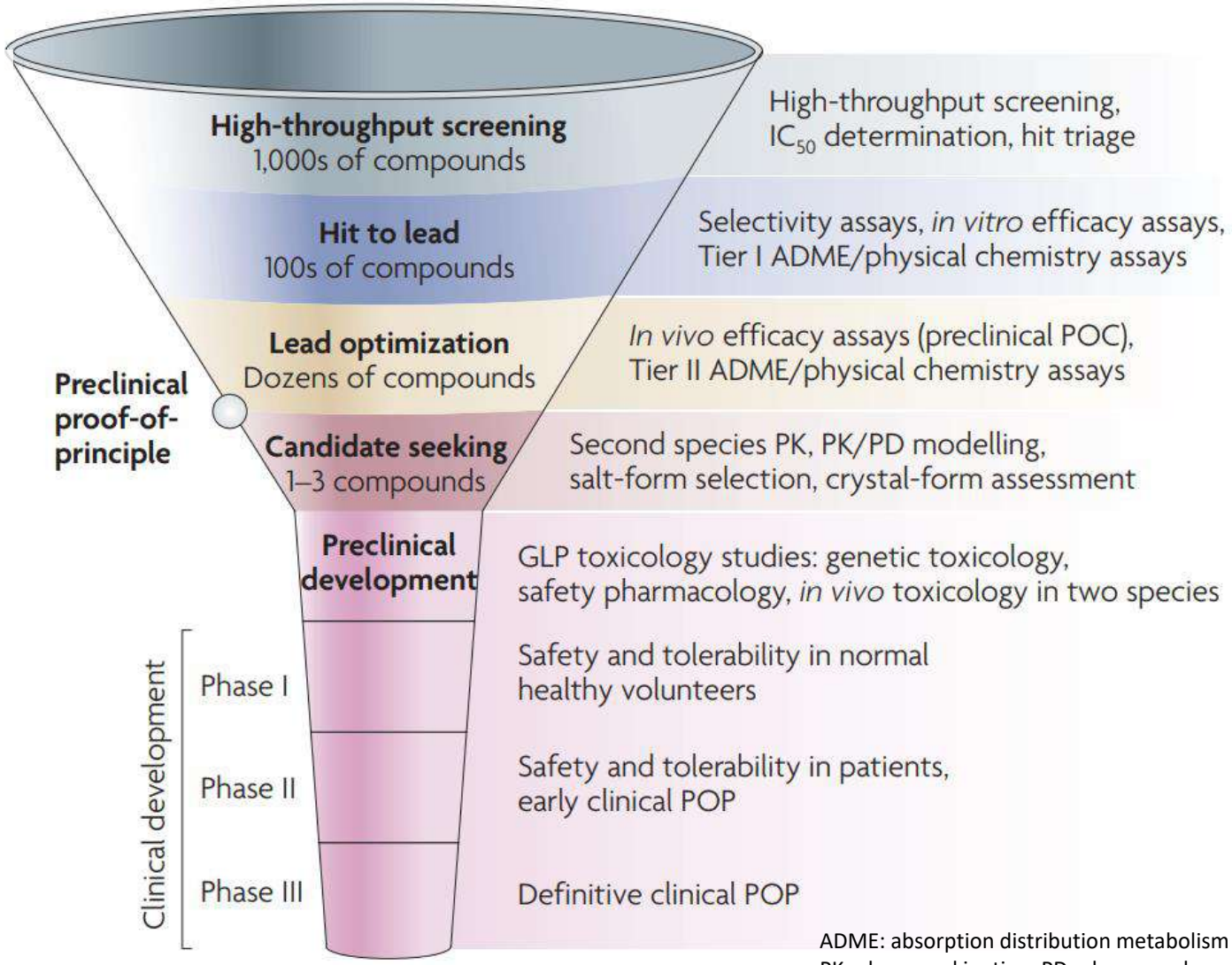


Simulating virtual populations



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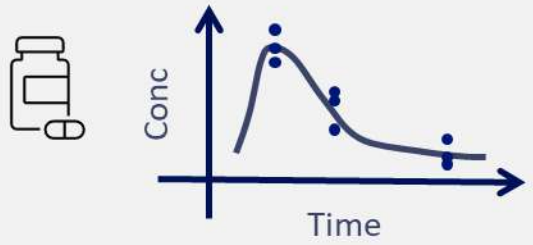
Simulating trial outcomes in virtual populations

Established model

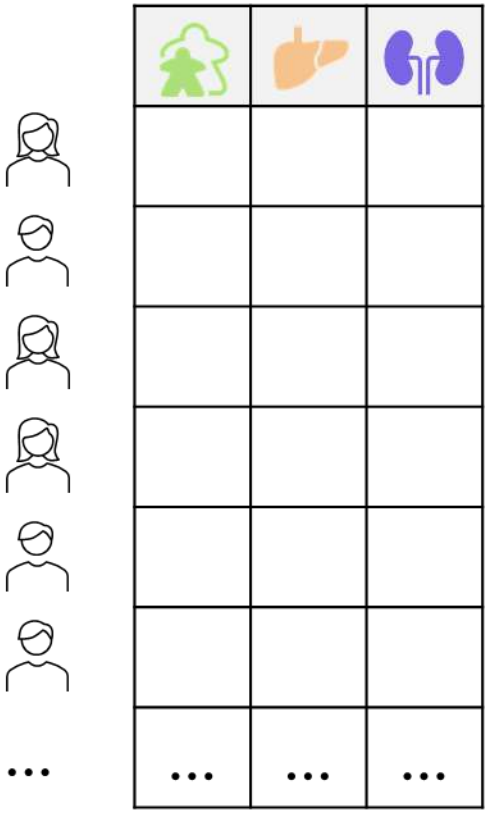
Pharmacometric model



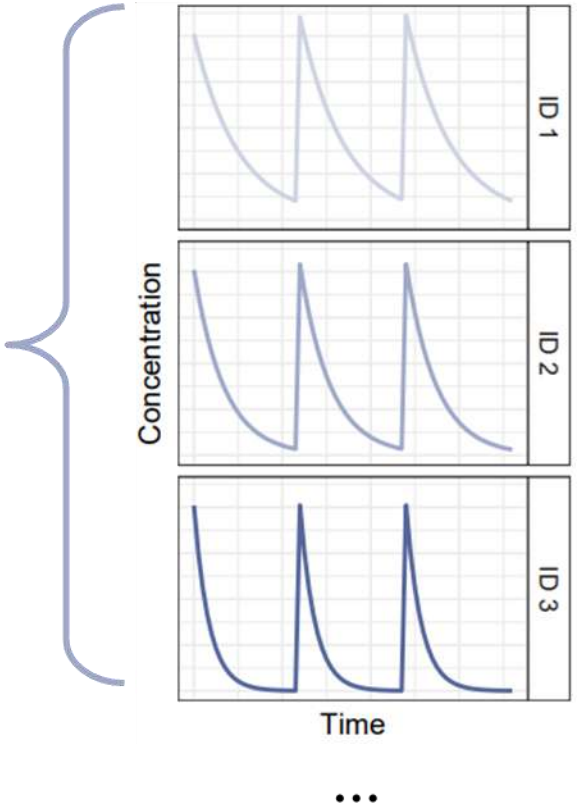
$$CL = f(liver_{function}, renal_{function})$$

$$V = f(body\_weight)$$

A set of patient characteristics



Simulation



Guo Y, et al, J Pharmacokinet Pharmacodyn. 2024 Jun 6; Zwep LB et al, Clin Pharmacol Ther. 2024;115(4):795-804

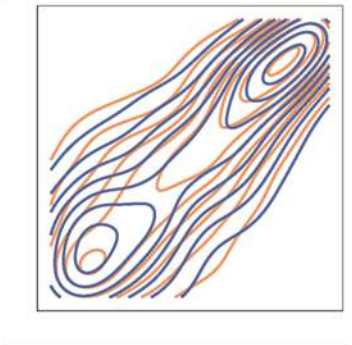
Using copulas (AI) to generate and share realistic virtual populations

A series of univariate distribution

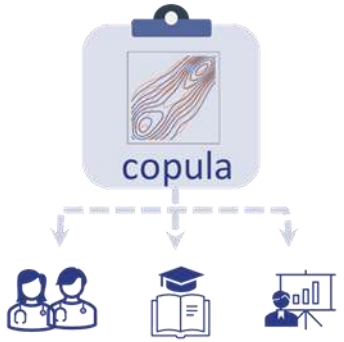
Multivariate guassian distribution

Bootstrap (resampling)

Copula, a joint distribution function



Generate realistic VP



Reduce data-sharing barrier

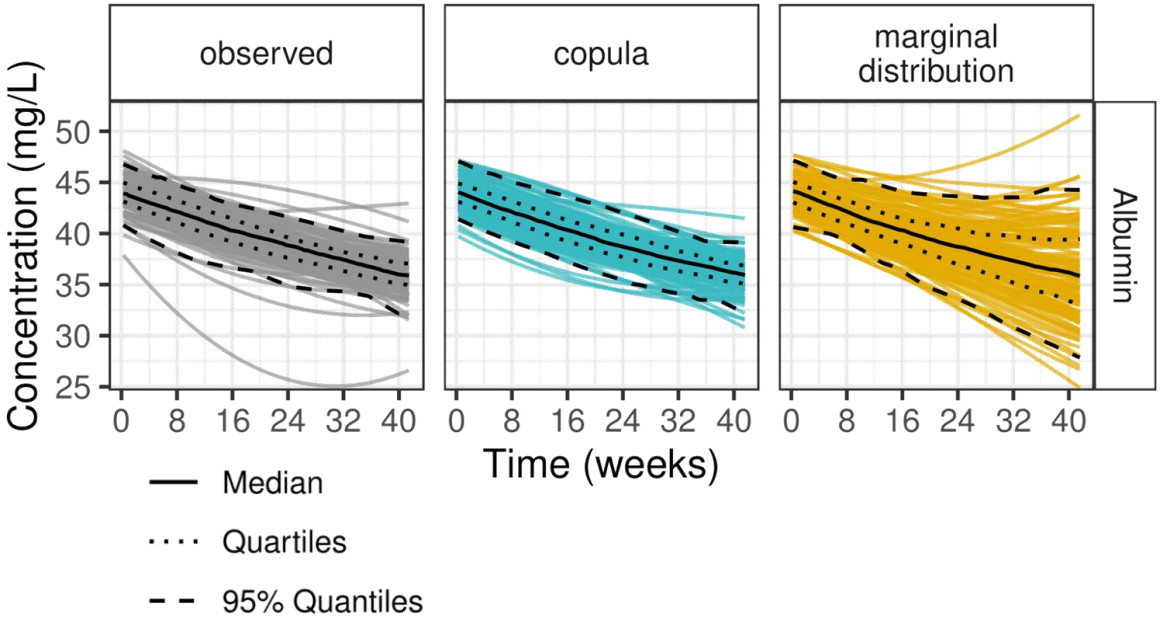
Observed population Virtual population

Guo Y, et al, J Pharmacokinet Pharmacodyn. 2024 Jun 6; Zwep LB et al, Clin Pharmacol Ther. 2024;115(4):795-804

Performance in time-dependent covariates and large data

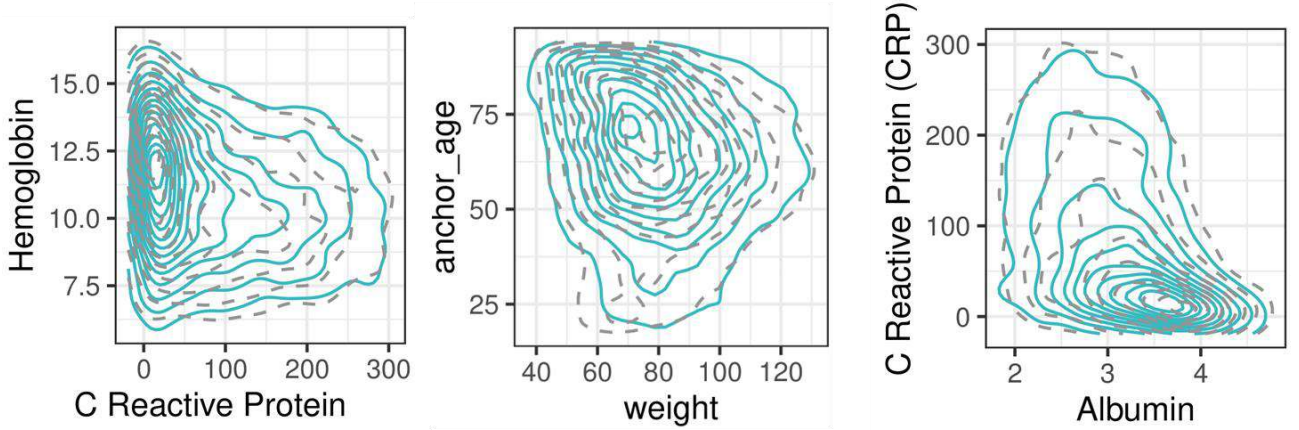
data Patel, *et al*. (2013)

pregnancy, 123 subjects
6 longitudinal covariates:
e.g. albumin, bilirubin
~14 measurements



data Johnson, *et al. (*2022)

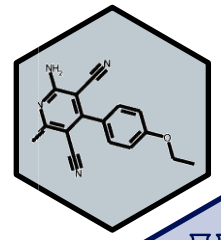
MIMIC: ICU patients
30 covariates
>53.000 patients



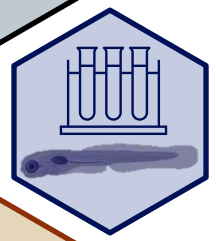
---- observed
— copula

Guo Y, et al, J Pharmacokinet Pharmacodyn. 2024 Jun 6; Zwep LB et al, Clin Pharmacol Ther. 2024;115(4):795-804

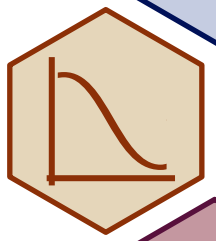
Model informed drug discovery and development (MID3)



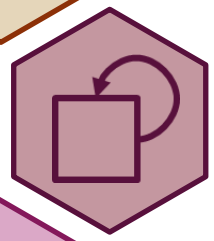
Generating novel compounds



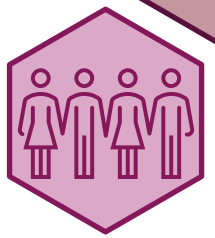
Bridging *in vitro* - *in vivo*



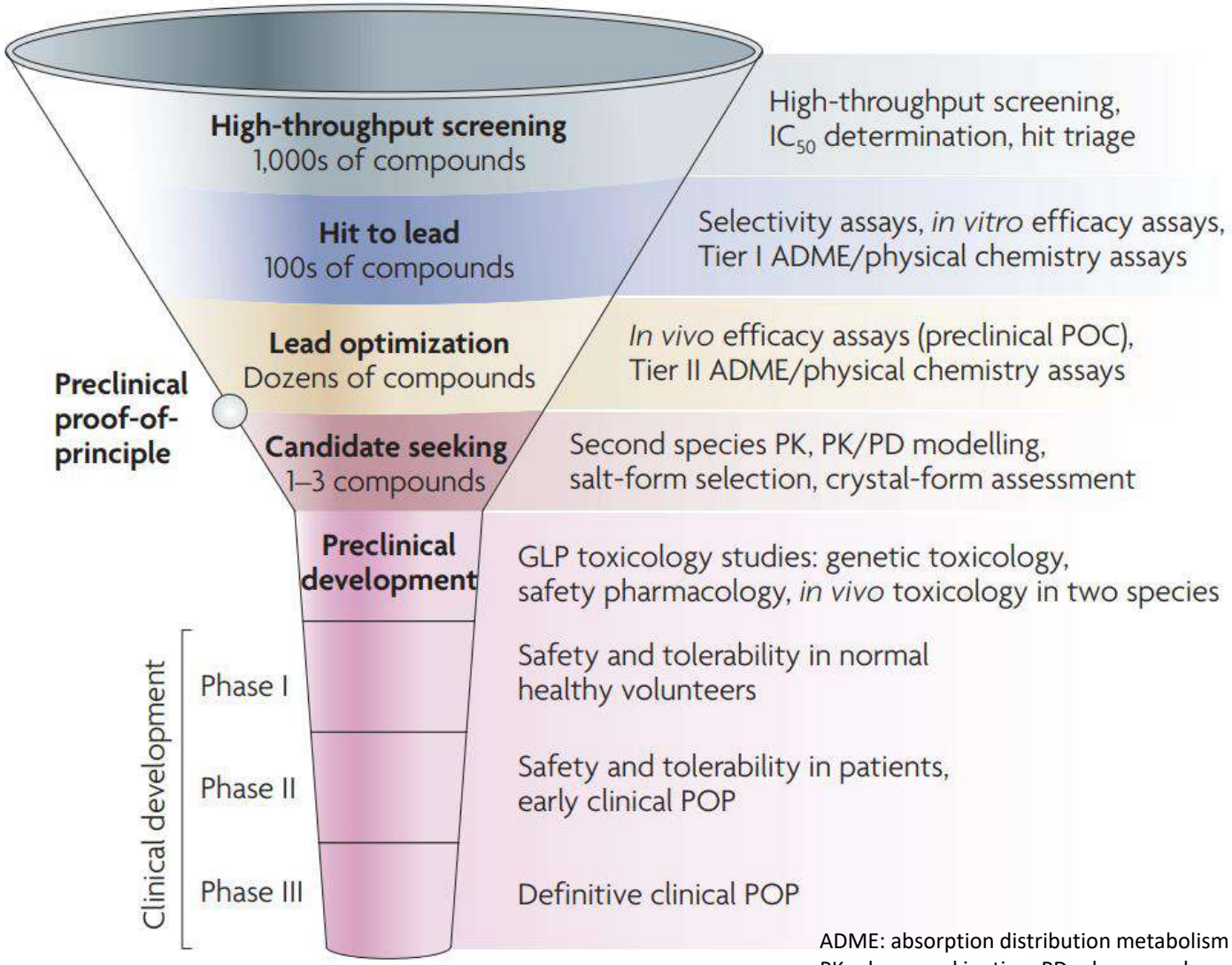
Predicting relapse infections



Informing tumor growth



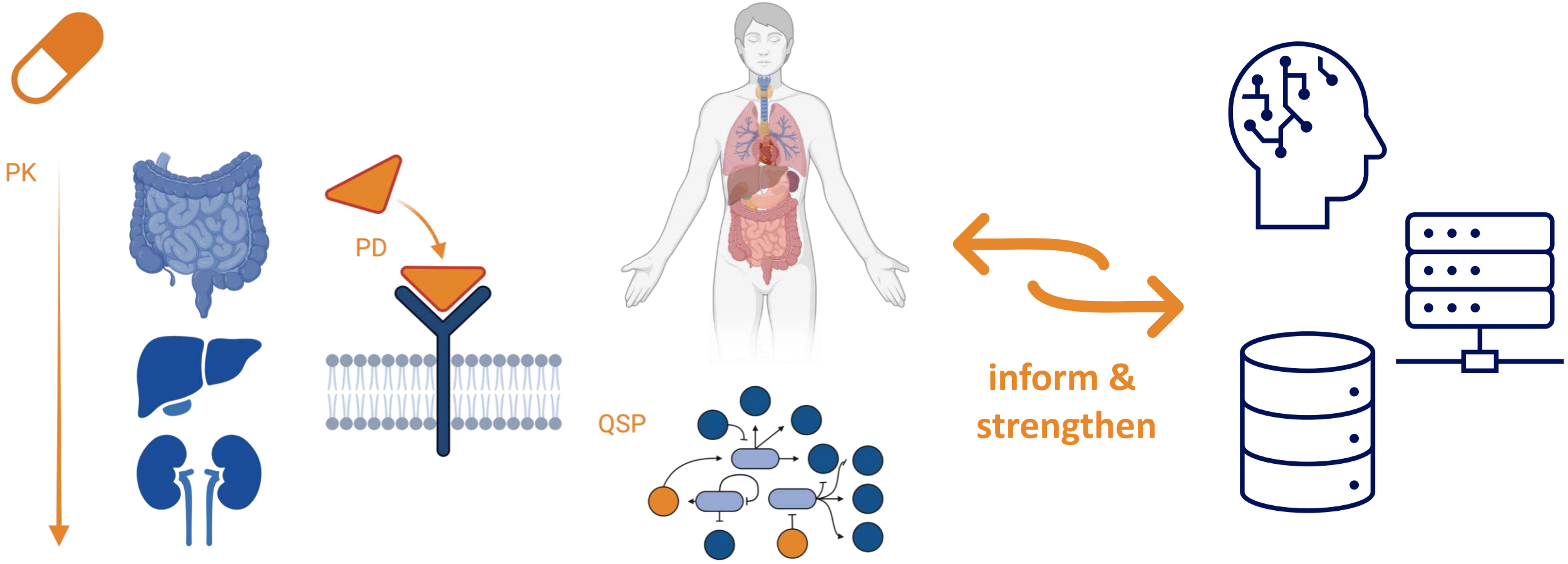
Simulating virtual populations



ADME: absorption distribution metabolism excretion
PK: pharmacokinetics, PD: pharmacodynamics
POC: proof of concept; POP: proof of principle

Kramer, J. et al, Nat Rev Drug Discov 6, 636–649 (2007)

Mechanistic pharmacological modelling and AI



PK: pharmacokinetics, PD: pharmacodynamics
QSP: quantitative systems pharmacology

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Translational Immuno-Pharmacology

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BioRender

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