



H3D Foundation and Ersilia Present

Bringing data science and AI/ML tools to infectious disease research

Session 3: Skills session

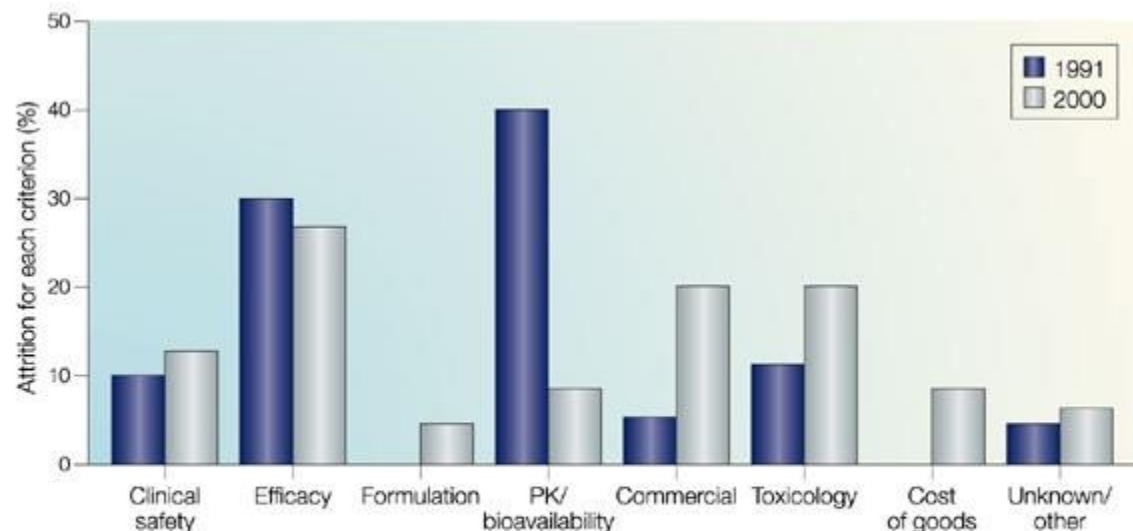
Event Sponsors



Evolution of DMPK



Ersilia



Nature Reviews | Drug Discovery

- Era of pharmacodynamic-based drug discovery led to multiple drug f

1950s – 1980s
Pharmacodynamic drug
discovery

1990s
High throughput DMPK driven
by revolution in analytical tools
and robotics

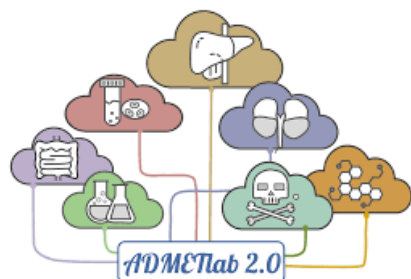
2000s
Assay refinement for IVIVC +
QSAR + mechanistic models

Modern era
High throughput DMPK +
Modelling and Simulation +
AI/ML-based predictions for
compound design etc

AI/ML and Mechanistic tools in DMPK



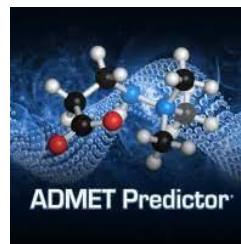
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Scientific



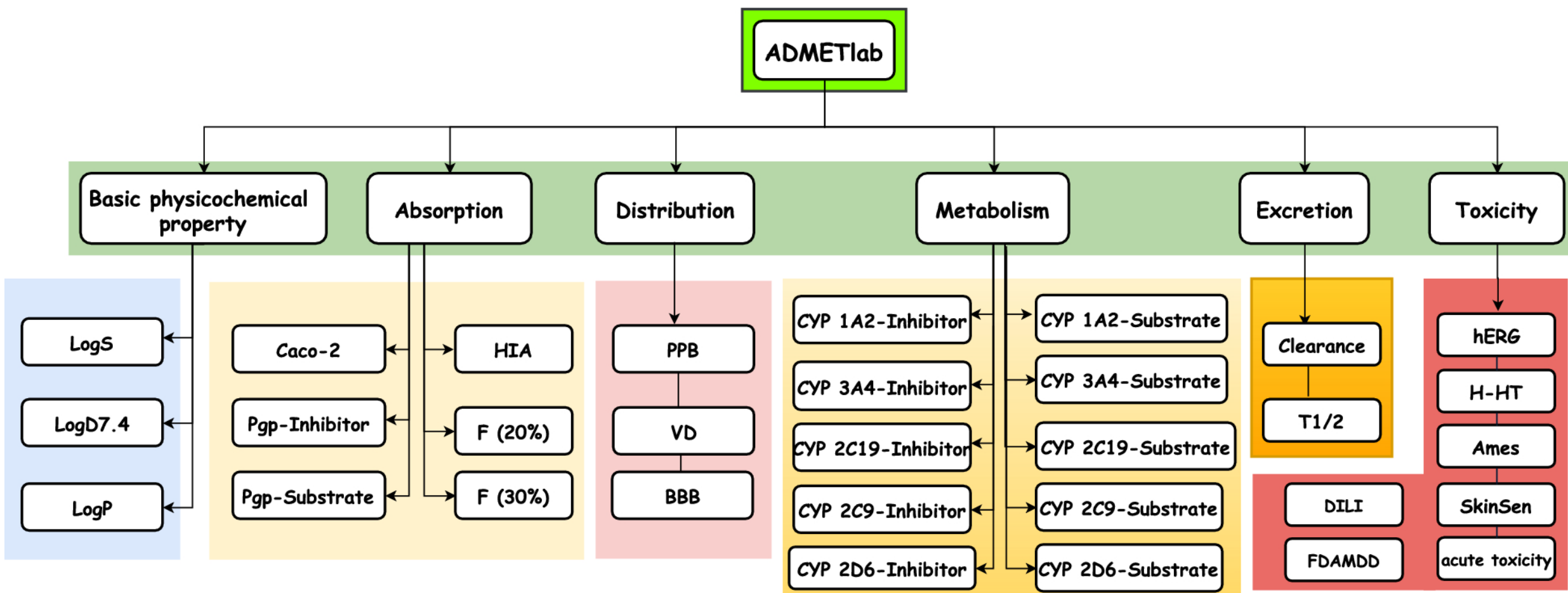
SwissADME



AI/ML tools



Mechanistic (PK/PD,
PBPK) tools



- Regression models – LogS, LogD, Caco-2, VD
- Classification models – HIA, BBB, Pgp-inhibitor/substrate, CYP-inhibitor/substrate

ADMETLab skills workshop



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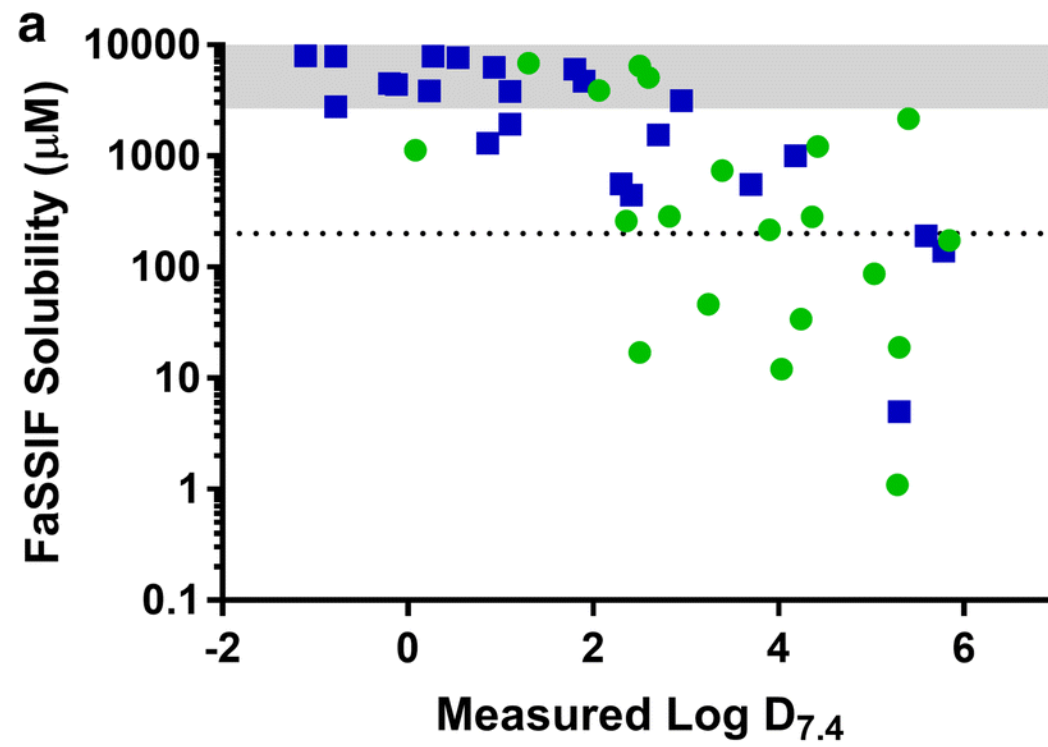
- We will now evaluate the ADMET properties of a series of clinically used drugs to demonstrate the process

Quinine
Chloroquine
Amodiaquine
Desethylamodiaquine
Artemether
Lumefantrine
Amlodipine
Nifedipine
Ritonavir

Solubility and Log D



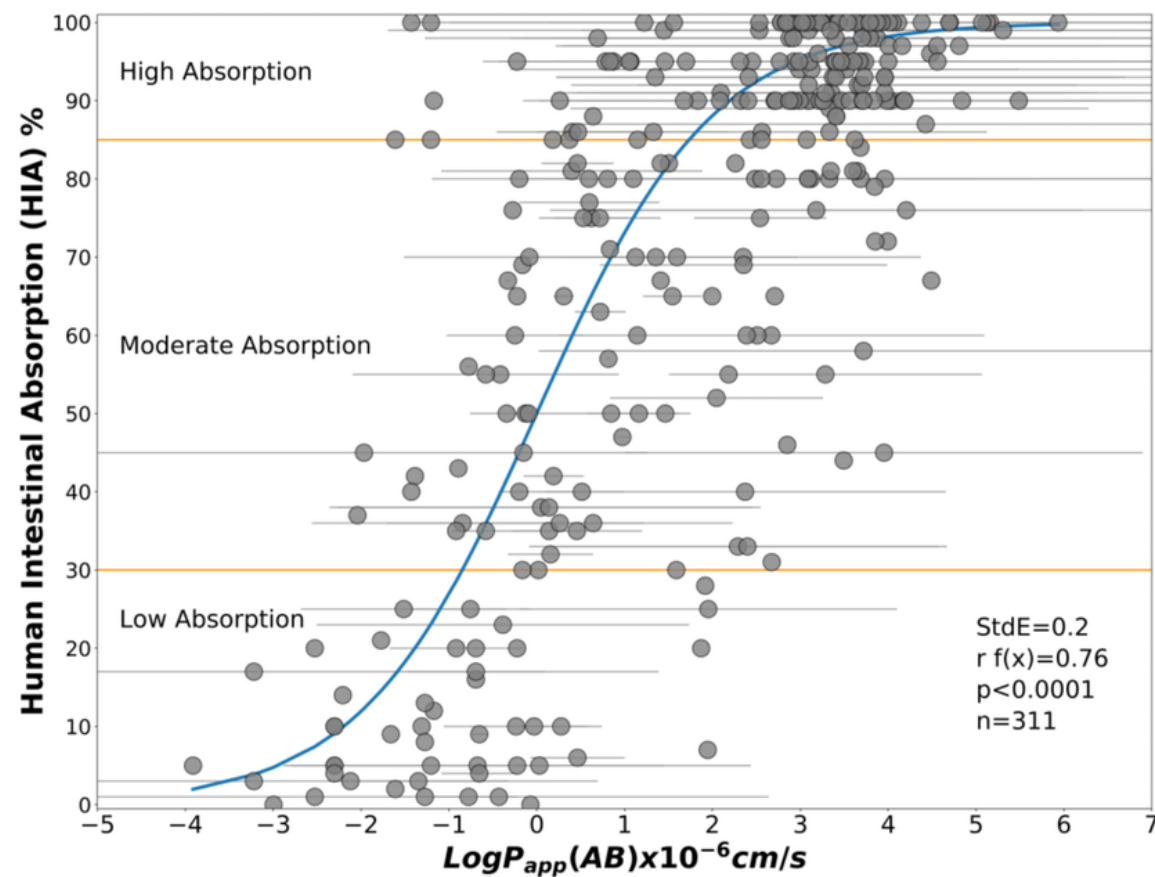
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Caco-2 vs HIA



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Clearance and unbound clearance

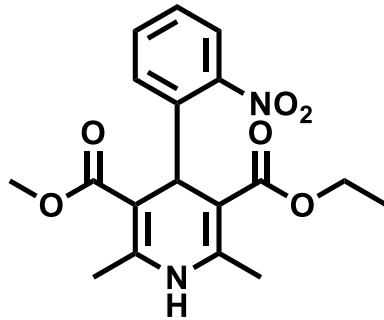
- Unbound clearance and its use for compound ranking

	CL	Fu	CLu
Quinine	3.3	18.49%	17.9
Chloroquine	5.8	25.79%	22.6
Amodiaquine	7.5	1.42%	529.5
Desethylamodiaquine	5.4	7.63%	70.7
Artemether	15.9	3.64%	436.3
Lumefantrine	5.6	0.67%	832.5
Amlodipine	6.9	42.93%	16.1
Nifedipine	10.1	19.50%	51.6
Ritonavir	6.4	0.74%	867.2

VD, half-life and dose



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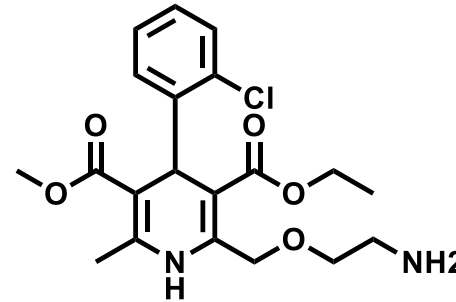
Nifedipine

Vd_u 19.5 L/kg

CL_u 175 ml/min/kg

$t_{1/2}$ 1.8h

Dose: 10 mg x 3 times a day



Amlodipine

Vd_u 228 L/kg

CL_u 85 ml/min/kg

$t_{1/2}$ 40h

Dose: 10 mg once a day

$$t_{1/2} = \frac{\ln 2 * Vd}{CL}$$



Dose prediction on MMVSola

- The impact of ADME/PK on the clinical efficacy of a compound can be described using mathematical equations allowing human dose prediction from *in vitro* data.
- Let's explore this using ADME/PK data of a hypothetical compound.
- Navigate to <https://www.mmvsola.org/>

MMVSola Predictor Basic Parameters Advanced Parameters

Upload Science Cloud or MMVSola Input file
Browse... No file selected

Reset inputs

CLINICAL PK DATA	PRECLINICAL PK DATA	DOSING & PD DATA
H Plasma Binding [%] <input type="text"/>	R R Plasma Binding [%] <input type="text"/>	Simulated Dose [mg] <input type="text" value="100"/>
H Blood to Plasma Ratio <input type="text" value="1"/>	NF54 72h IC50 [nM] <input type="text"/>	Hill Slope <input type="text"/>
LogD (or LogP for bases) <input type="text"/>	R Plasma CL [mL/min/kg] <input type="text"/>	Log10 In-vitro PRR / 48h <input type="text"/>
H Hep. CLint [$\mu\text{L}/\text{min}/10^6$ cells] <input type="text"/>	R Plasma Vss [L/kg] <input type="text"/>	Molecular Weight [Da] <input type="text"/>
	R Hep. CLint [$\mu\text{L}/\text{min}/10^6$ cells] <input type="text"/>	

To get an initial prediction you need to input:

- Plasma Protein Binding in Human
- Hepatocyte or Microsome Human CLint
- Vss in at least one preclinical species

Parameter	Estimate
Predicted plasma hepatocyte CL (No IVIV) (mL/min/kg)	Not Available
Predicted Plasma microsome CL (Mic Based) (mL/min/kg)	Not Available
in-vitro under-prediction (HEP)	Not Available
in-vitro under-prediction (MIC)	Not Available
Selected in-vitro assay	Human Hepatocytes
Final Predicted Plasma CL (mL/min/kg)	Not Available
Human Vss (L/kg)	Not Available
C _{max} (nM)	Not Available



Dose prediction on MMVSola

- Navigate to <https://www.mmvsola.org/>
- Load the data saved under your project folder

MMVSola Predictor Basic Parameters Advanced Parameters

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Selected in-vitro assay	Human Hepatocytes
Final Predicted Plasma CL(mL/min/kg)	Not Available
Human Vss (L/kg)	Not Available
C _{max} (ng/mL)	Not Available

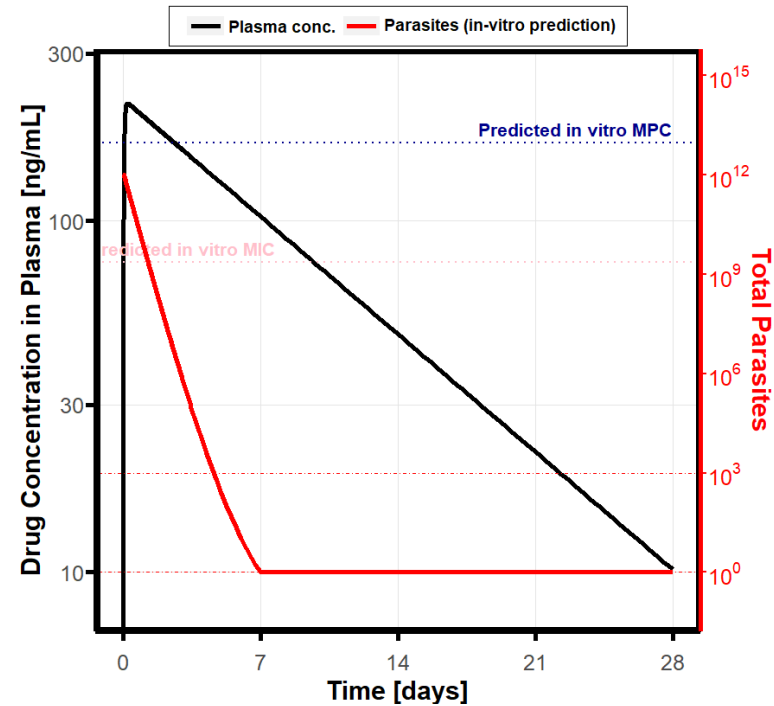
MMVSola dose prediction



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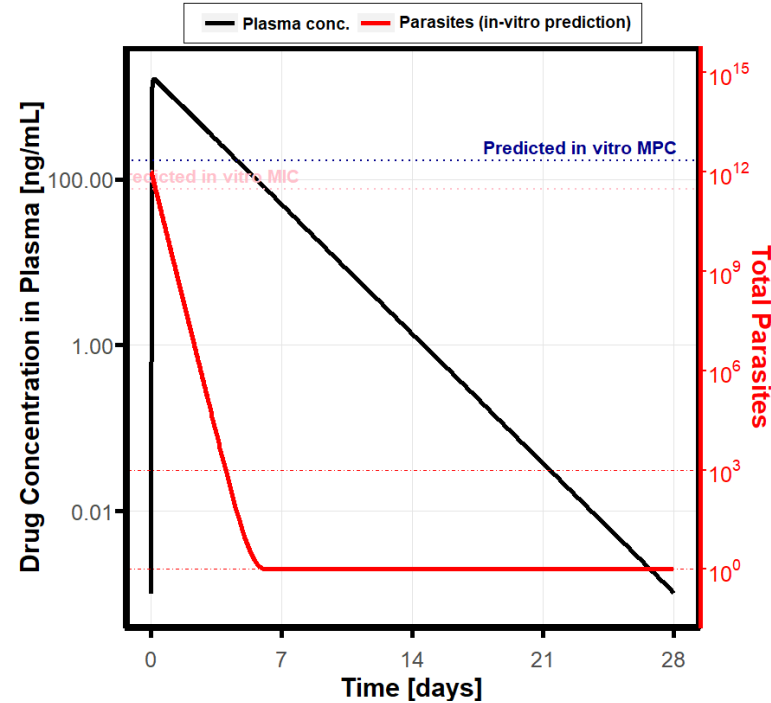


Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 62mg --- Clearance Method: Human Hepatocytes with IVIV correction



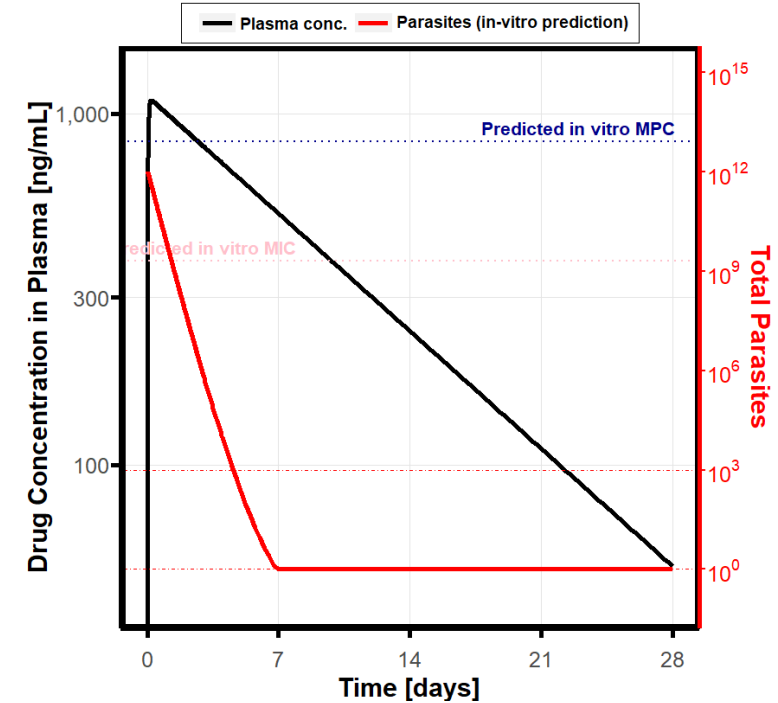
Heps CL_{int}: 1 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 62 mg

Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 525mg --- Clearance Method: Human Hepatocytes with IVIV correction



Heps CL_{int}: 5 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 525 mg

Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 313mg --- Clearance Method: Human Hepatocytes with IVIV correction



Heps CL_{int}: 1 µl/min/e6 cells
NF54: 100 nM
Predicted dose: 313 mg

ADME/PK and Dose



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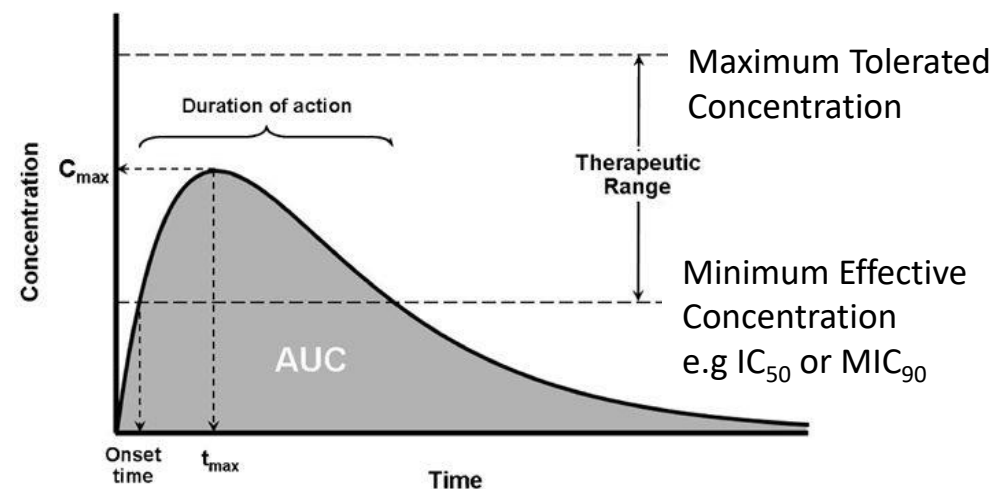
- The unbound Area Under the Curve (AUC_u) is one of the key measures of how much compound is in circulation

- For an oral drug;

$$AUC_u = F_{abs} \cdot F_{gut} \cdot \frac{\text{Dose}}{CL_{int,u}}$$

Therefore:

$$\text{Dose} = F_{abs} \cdot F_{gut} \cdot \frac{AUC_u}{CL_{int,u}}$$



- Increasing clearance increases the dose since more compound is required to achieve a similar AUC
- With an increase in IC₅₀ and increase in exposure levels is required resulting in an increased dose.