

MMVSola¹ is a web-based open access pharmacokinetic (PK)/ pharmacodynamic (PD) application for early prediction of (i) human PK and (ii) estimation of the dose required to deliver a defined reduction in parasitemia or to guarantee chemoprevention for a defined period. The tool assists teams in Lead Optimization to optimize compounds, without the need for specialist PK/PD simulation scientists, and reducing the necessity for numerous mice experiments. The application can be securely accessed at www.MMVSola.org

Input

From the File Input tab, the user inputs in-vitro or mouse experimentally derived parameters, by uploading a ScienceCloud data-base extract file or a previously generated MMVSola Excel report. The user can review and curate this data by excluding individual records from the input averaging.

MMVSola PredictorFile InputPredictionReport

Upload Science Cloud or MMVSola Report File

Browse...

MMVSola_MMV533.xlsx

Upload complete

You've uploaded a Science Cloud data file. The Science Cloud individual data are shown in the left table and the average parameter values are shown in the right table (below). The tab Prediction has been populated using the average parameter values, overwriting previous user inputs. You can curate the Science Cloud data by un-checking records in the raw Science Cloud data, or you can overwrite parameter values from the tab Prediction. You can upload additional MMVSola or Science Cloud files for a multi-compound comparison. Press the Reset compounds button to delete some or all compounds from the current session.

Active compound

TestCmp1

Reset compounds

Search:

Science Cloud Individual Data

INCLUDE	REASON TO EXCLUDE	COMPOUND ID	ASSAY PARAMETER NAME	ASSAY PARAMETER DESCRIPTION	ASSAY RESULT TYPE NAME	OP	value	TEST UNIT
☒		TestCmp1	Mouse	Plasma	% Bound	=	93.9	%
☒		TestCmp1	Mouse	Plasma	% Bound	=	93.16	%
☒		TestCmp1	Rat	Hepatocytes	% Bound	=	97.54	%
☐	outlier	TestCmp1	Rat	Hepatocytes	% Bound	=	49.94	%
☒		TestCmp1	Rat	Microsomes	% Bound	=	57.01	%
☒		TestCmp1	Rat	Plasma	% Bound	=	91.96	%
☒		TestCmp1	Rat	Plasma	% Bound	=	91.2	%
☒		TestCmp1	Human	Whole blood	Ratio	=	1.58	none
☒		TestCmp1	Human	Whole blood	Ratio	=	1.17	none
☒		TestCmp1	Mouse	Whole blood	Ratio	=	1.18	none

Science Cloud Average Parameters

PARAMETER	VALUE	UNIT
Albumax Binding	50.48	%
Dog Blood to Plasma Ratio		Ratio
Mouse Blood to Plasma Ratio	1.2	Ratio
Rat Blood to Plasma Ratio	1.7	Ratio
Blood to Plasma Ratio	1.6	Ratio
Dog CL		mL/min/kg
Mouse CL	5.7	mL/min/kg
Rat CL	3.88	mL/min/kg
Dog Hep. CLint	0.9	μL/min/10 ⁶ cells
Mouse Hep. CLint	2.3	μL/min/10 ⁶ cells

The input panel in the Prediction tab organizes all input parameters into foldable categories and indicates the source and acceptable range for each input parameter.

MMVSola PredictorFile InputPredictionReport

Compound

TestCmp_1

Simulation parameters

Chemical properties

PK in vivo

Fraction Absorbed (0 - 1)

H1R1M1D1

Plasma Binding [%]

94.0191.5893.5292.97

Blood to Plasma Ratio

1.581.711.161.58

Plasma CL [mL/min/kg]

3.885.7

Plasma Vss [L/kg]

2.431.75

Renal Plasma Clearance [mL/min/kg]

0000

PK in heps

PK in mics

PD in vitro

TCGLS 3D7 72h IC50 [nM]

30

Hill Slope

6.12

Log10 in-vitro PRR / 48h

3.25

Albumax Binding [%]

50.5

PRR Lag Time [hr]

0

Default values, calculated from other available inputs or informed from literature

Comopund-specific Average experimental values from ScienceCloud database extract

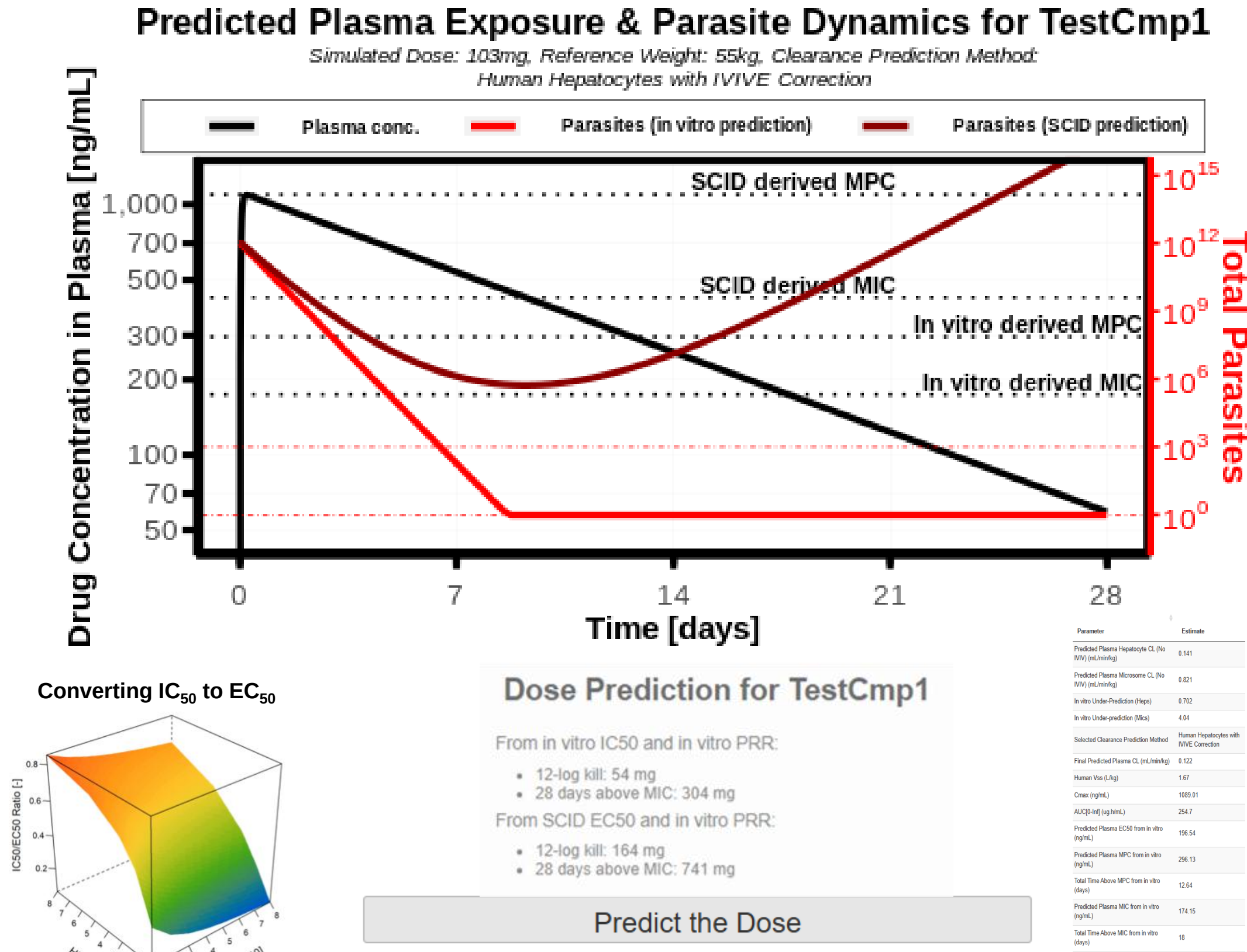
Values entered manually by the user overwriting other inputs

It is possible to upload multiple files. Each input file may contain data for multiple test compounds. At any time, the data for a single “active” compound is displayed in the web interface.

Prediction

The Prediction tab summarizes the PK/PD and dose prediction for the selected active compound and allows the user to interactively test changing the values of any input parameter.

- Human Pharmacokinetics:**
- PK is a function of Volume of distribution, Clearance (Vd, CL)²
 - MMVSola predicts the human plasma concentration-time profile based on:
 - a one-compartment in-vivo model
 - in-vitro to in-vivo extrapolation (IVIVE) from hepatocyte and/or microsome intrinsic clearance (CLint) data (the assay with best IVIVC_{m,r,d} is selected)
 - well-stirred liver model with full in-vitro and in-vivo binding correction
 - Volume of distribution (Vd_{ss,u}) and fraction absorbed estimated from animal data, i.e. $Hu Vd_{ss,u} = \mu Vd_{ss,u}(m,r,d)$
 - any known underprediction of clearance observed in the animal species
 - defined single or multiple doses



- Human Pharmacodynamics:**
- Parasite counts are computed dynamically using parasite growth and death kinetics and free drug concentrations, which are changing over time, using a direct E_{max} PD model.³ Parasite death depends on free drug concentrations via a sigmoid function with E_{max} (maximum kill rate), EC₅₀ (half-E_{max} drug concentration) and Hill slope.
- E_{max} is measured in vitro using a standardized parasite reduction ratio (PRR) assay
 - EC₅₀ and Hill slope can be determined in-vitro from a 72h TCGLS 3D7 assay (IC₅₀), or in-vivo from modelled mouse data
 - MPC (max parasitocidal concentration) is calculated from EC₅₀ and Hill.
 - Dose is calculated for defined PD endpoints (for a 55Kg adult):
 - 12-log₁₀ kill (treatment, i.e. TCP1-TPP1)⁴
 - t > MIC for 28d (prophylaxis, i.e. TCP1-TPP2)⁴
 - Predictions for single or multiple dose are possible.

Report

The Report tab allows to customize the generation of a report. This is a multi-sheet Excel document providing details on the predictions as well as coloured tables comparing the predictions for multiple candidate antimalarial drugs. An MMVSola Excel report can be uploaded as input file.

Implementation

MMVSola¹ was developed in a collaboration between MMV and IntiQuan AG, using the R-packages MMVshiny⁵, IQRtools⁶, and MMVmalaria⁵. MMVshiny orchestrates the high-level user interface, the specification of input parameters, and rule-based imputation of default values for missing inputs. IQRtools and MMVmalaria are the backbone of MMV’s PK/PD modeling and simulation framework. These packages are available under open-source licenses^{5,6}.

References:

(1) www.MMVSola.org was named to commemorate Suresh Solapure, a scientist at MMV who passed away in 2016. Suresh was an early champion of pharmacokinetic and pharmacodynamic data modelling to predict human dose. (2) Pharmacokinetics and Metabolism in Drug Design. Smith, D. A.; Allerton, C.; Kalgutkar, A. S.; Waterbeemd, Han van de.; Walker, D. K. Wiley, 2012, ISBN: 978-3-527-32954-0. (3) Pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of Actelion-451840 in an induced blood stage malaria study in healthy subjects. Krause, A. et. al. British Journal of Clinical Pharmacology 2016; 82: 412. (4) New developments in anti-malarial target candidate and product profiles. J.N. Burrows et al.. Malaria Journal. 2017; 16: 26. (5) <https://github.com/MMVverse> (6) <https://iqrtools.intiquan.com>