Characterization of the interaction between irinotecan, SN-38 and MBLI-98,a new BCRP inhibitor, with a multi-scale semi-mechanistic PKPD model

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- BCRP: Important role in drug absorption, distribution and elimination
  Anticancer drugs resistance (irinotecan, SN-38)
- MBLI-98: New BCRP inhibitor
  → **Efficacy *in-vitro* and *in-vivo*[1,2]**
- M&S useful in drug development[3]

- **Charaterizing the 2 levels of interaction between irinotecan, SN-38 and MBLI-98**
- **Finding key factors for treatment efficacy**
- **Applying M&S to early preclinical development**

PK Study and Proof-Of-Concept Animal Studies

PK study

- 1 single dose administered IP (irinotecan ± MBLI-98, MBLI-98 ± irinotecan)
- Plasma concentration measured during 24h
- 5 animals per time point

Proof-Of-Concept Animal Studies

- SCID mice xenografted with HEK293 tumour cells overexpressing BCRP
- 4 treatment groups: Control, irinotecan, MBLI-98, irinotecan+MBLI-98
- Irinotecan and MBLI-98 administered IP
- **POC1**: 2 weeks of treatment+2 weeks of wasch-out+2 weeks of treatment
  1st drug administration on day 2
- **POC2**: 4 weeks of treatment
  1st drug administration on day 7

	POC 1 (N=41)	POC2 (N=19)
Total amount (irinotecan) (mg)	6.6	6.4
Total amount (MBLI-98) (mg)	0.87	1.14
Treatment duration (d)	74	41
Treatment intensity (irinotecan) ($mg.d^{-1}$)	0.14	0.16
Treatment intensity (MBLI-98) ($mg.d^{-1}$)	0.018	0.028

Table 1: Dosing Regimens comparison

Multi-Scale Semi-Mechanistic PKPD Model

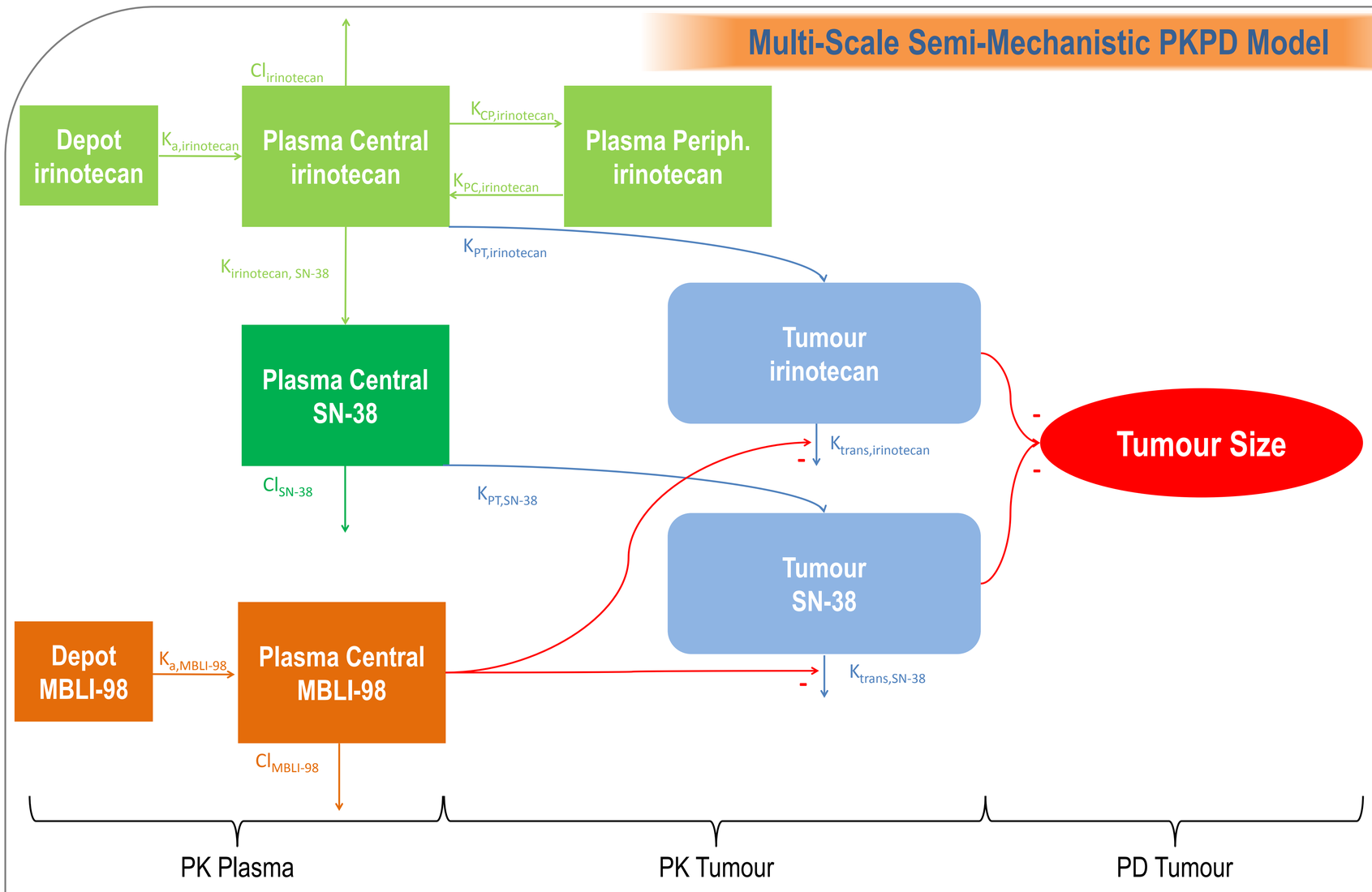

Figure 1: Multi-scale semi-mechanistic model

$K_{a,irinotecan}$	Absorption rate irinotecan
$K_{a,\ SN-38}$	Absorption rate SN-38
$K_{a,\ MBLI-98}$	Absorption rate MBLI-98
$Cl_{irinotecan}$	Clearance irinotecan
Cl_{SN-38}	Clearance SN-38
$Cl_{MBLI-98}$	Clearance MBLI-98
$K_{irinotecan,\ SN-38}$	Metabolization rate irinotecan, SN38
$K_{CP,irinotecan}$	Distribution rate central, peripheral
$K_{PC,irinotecan}$	Distribution rate peripheral, central
$K_{PT,irinotecan}$	Tumour accumulation rate due to passive diffusion
$K_{PT,SN-38}$	Tumour accumulation rate due to passive diffusion
$K_{trans,irinotecan}$	Active efflux rate irinotecan
$K_{trans,SN-38}$	Active efflux rate SN-38

- *PK data*
  irinotecan, SN-38 data fitted together
  M2 method for BQL data
  Assessment of PK interaction
- *1st interaction level* based on mechanistic model developed on *in-vitro* study[4]
  Drug influx: Passive diffusion
  Drug efflux: Active transport (Michaelis-Menten)
  Competitive interaction with MBLI-98
  (MBLI-98 inhibits active efflux)

$$K_{trans} = \frac{V_{max}}{K_m \times \left(1 + \frac{[MBLI98]_{pl}}{K_i}\right) + [irinotecan/SN38]_{pl}}$$

  Description of intracellular drug disposition
  Quantification of : irinotecan, SN-38 K_m value
  MBLI-98 K_i value
- *2nd interaction level*
  Irinotecan, SN-38 both active compounds
  Cooperative interaction on tumour growth[5]
  Quantification of irinotecan, SN-38 cytotoxic potencies

$$\text{Drug Effect} = \alpha \times \left(\frac{[irinotecan]_{tum}}{K_{i,irinotecan}} + \frac{[SN38]_{tum}}{K_{i,SN38}}\right)$$

- PK model fitted separately and then fixed in final model
- Natural tumour growth modelled with Simeoni *et al.* model[6]
- **K_m, K_i values corrected to take into account plasma protein binding**
- 4 submodels (intracellular, PK, tumour growth and drug effect) combined and fitted separately to POC1 and POC2

- Model parameters estimated in NonMem 7.1.2 software with FOCEI method
- Model validated with VPC (Figure 2)
- Based on plasma concentration, no plasma-PK interaction found between the 3 compounds
- Based on in-vitro data, BCRP affinity greater for SN38 than for irinotecan
- MBLI-98 BCRP-inhibitory constant (K_i) estimated at 2.5 µM

	POC 1	POC 2
$K_{PT,irinotecan}$ (d^{-1})	0.93 (-)	3.86 (30.4%)
$K_{PT,SN-38}$ (d^{-1})	1.15 (28.1%)	9.94 (33.6%)
$K_{trans,irinotecan}$ (d^{-1})	0.001 (-)	0.0126 (30.3%)
$K_{trans,SN-38}$ (d^{-1})	0.001 (-)	0.0116 (31.7%)
λ_0 (d^{-1})	0.0503 (22.9%)	0.0605 (24.6%)
λ_1 (d^{-1})	0.99 (0.5%)	0.99 (247.8%)
α/K_i ($\mu mol.d^{-1}$)	0.169 (18.1%)	0.0877 (3.3%)
Baseline	1* (21.9%)	1* (14.7%)
Residual error	0.199	0.168

Table 2:Parameters estimates
Typical value (%IIV)
* Fixed values

Parameter Estimates Comparison

- **Treatment intensity** **POC2 > POC1**
- **Treatment delay** **POC2 > POC1**
- **K_{PT}** POC2 > POC1 equilibration plasma / tumour faster in POC2
- **K_{trans}** POC2 > POC1 active efflux greater in POC2
- **α/K_i** POC2 < POC1 treatment less efficient in POC2

→ **Tumour vasculature / Proportion of quiescent cells: POC2 > POC1**

Treatment delay: Key factor for irinotecan + MBLI-98 efficacy

Model gets adequate predictive performances

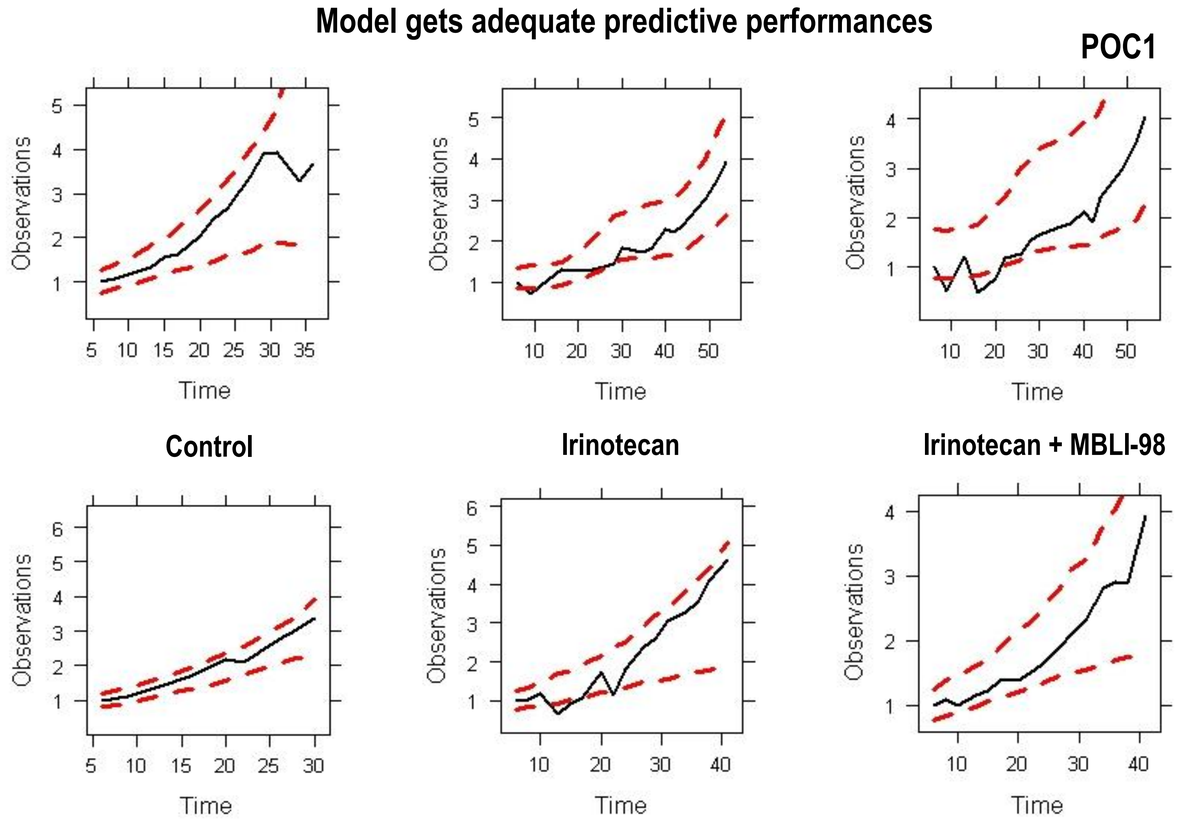

Figure 2: VPC
Red lines: 90% non-parametric confidence interval for the median
Black lines: Observed median

- **Development of a NLME model quantifying tumour growth and the 2 levels of interaction between irinotecan, SN-38 and MBLI-98**
- **Model developed on Proof-Of-Concept studies and *in-vitro* studies**
  → **M&S successfully applied to early preclinical drug development**
- **Treatment delay, tumour development stage: factors contributing to treatment efficacy**

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