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PK/PD MODELLING TO ADVANCE THE PRECLINICAL DEVELOPMENT OF A NOVEL POLYMER PRODRUG IN ONCOLOGY

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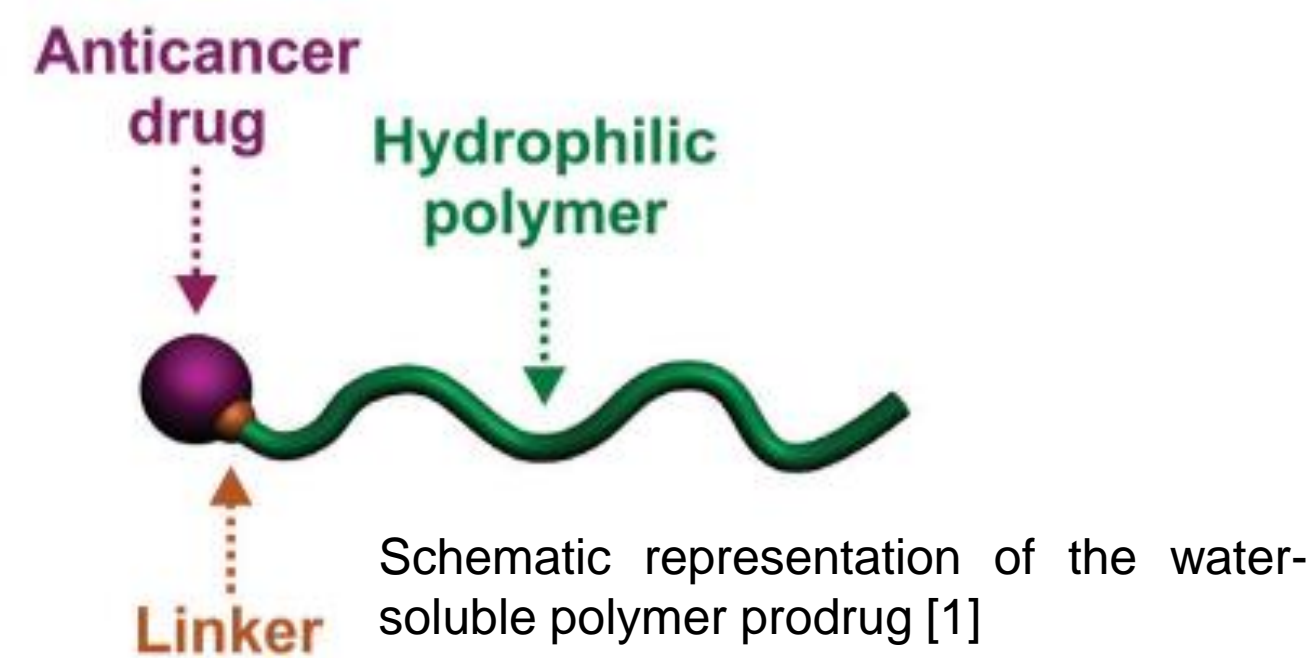
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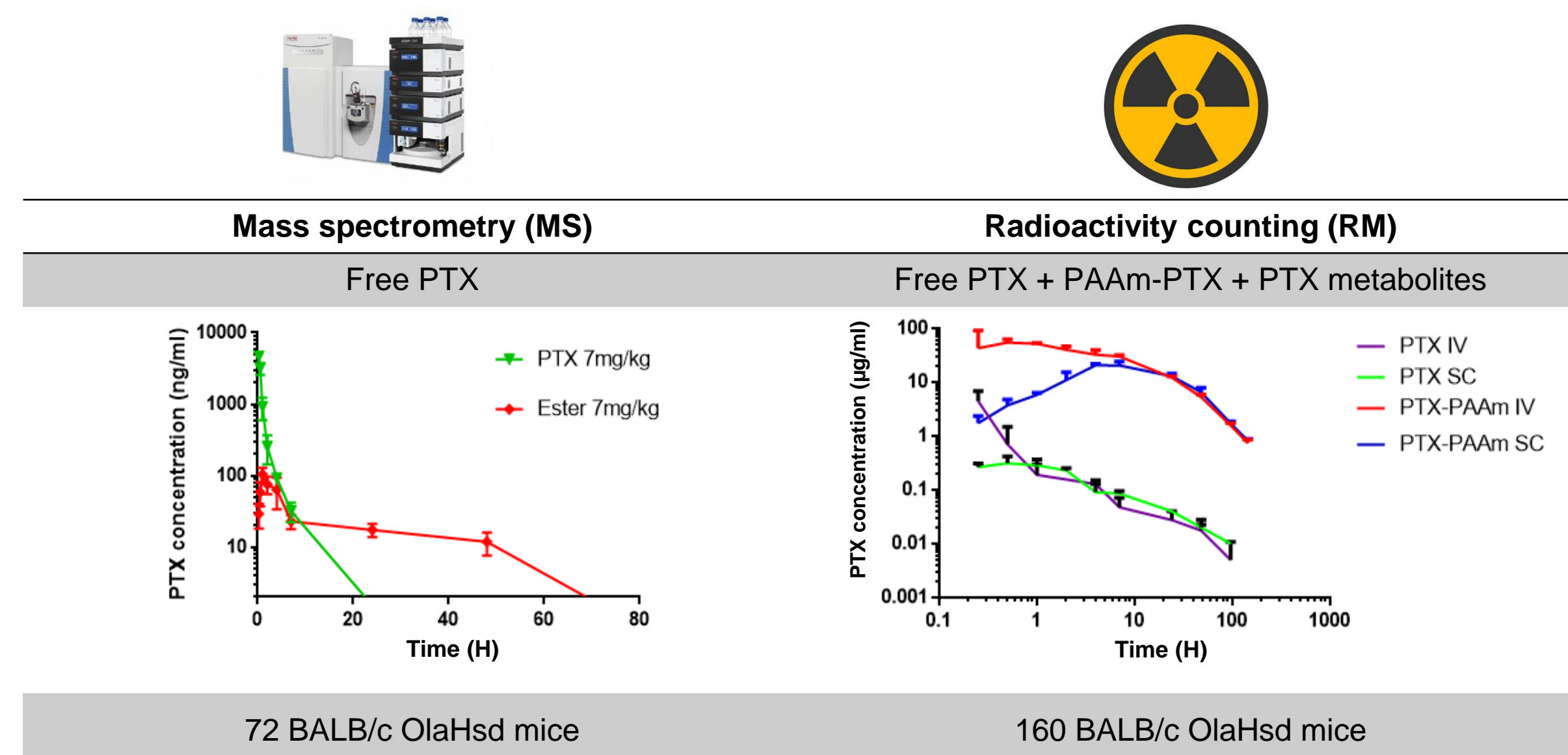
MOTIVATIONS & OBJECTIVES

- Taxanes such as **Paclitaxel** (PTX) are considered essential chemotherapeutics for the treatment of solid tumors. PTX formulations have been explored to **increase efficacy**, to **reduce toxicities** and have **improved pharmacokinetics** (PK).
- PTX linked to polyacrylamide (PTX-PAAm) is a new polymer prodrug which could result in an **effective** and **tolerable** anticancer treatment allowing for **subcutaneous** (SC) administration.



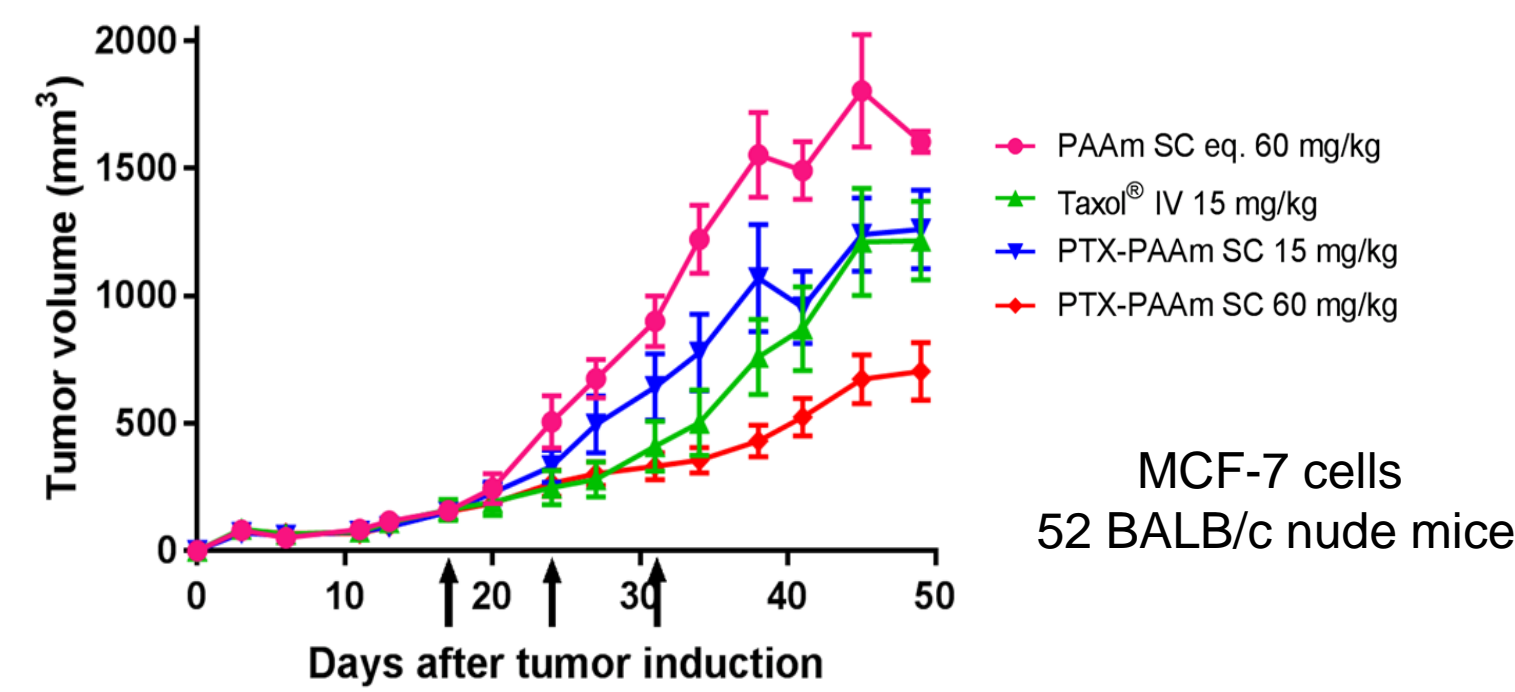
EXPERIMENTAL BACKGROUND

PHARMACOKINETICS



PHARMACODYNAMICS

- In vitro*: polymer characterization, cell viability (2D assay)
- In vivo*: tumor growth kinetics, biodistribution

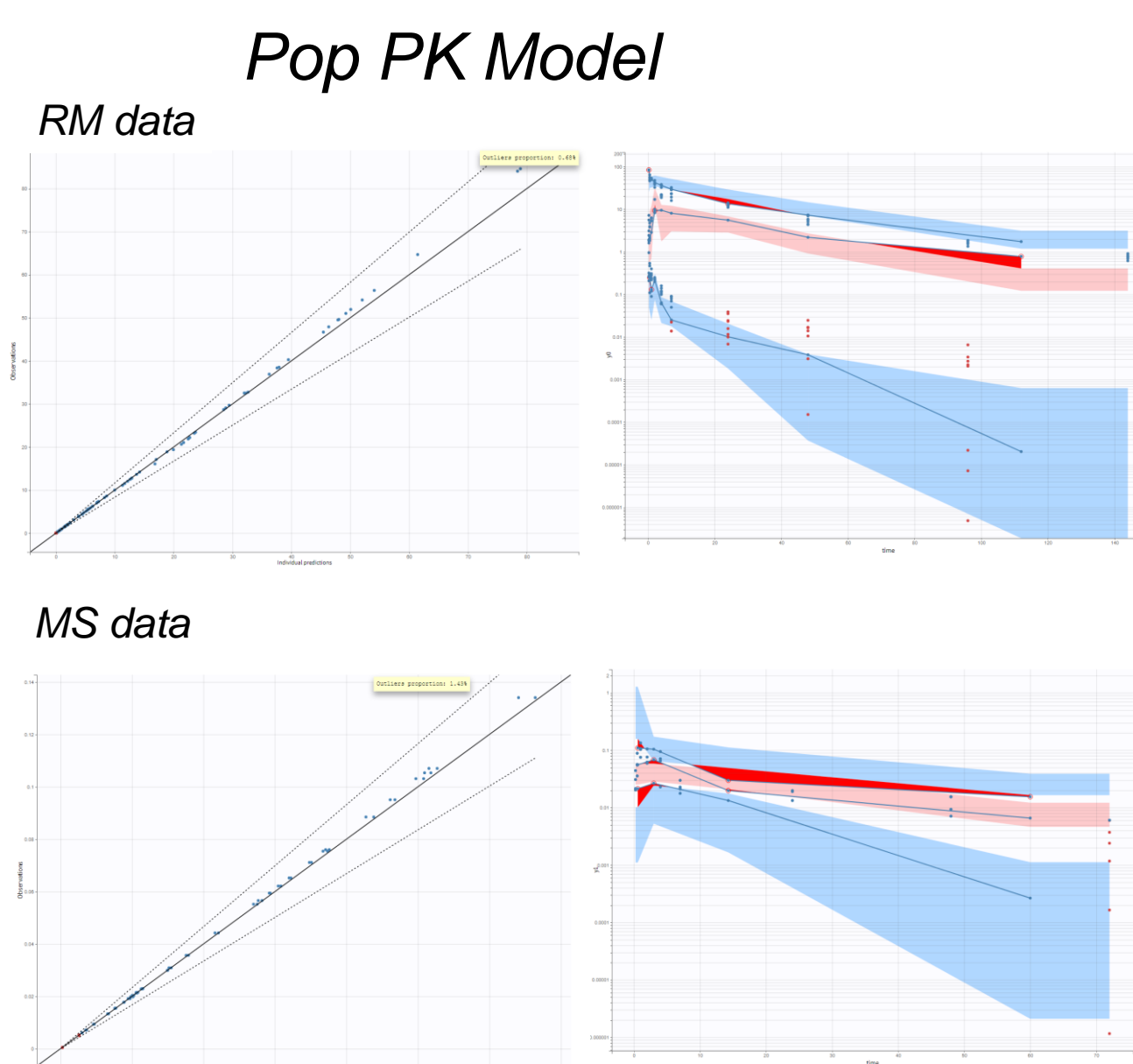


RESULTS

PHARMACOKINETICS

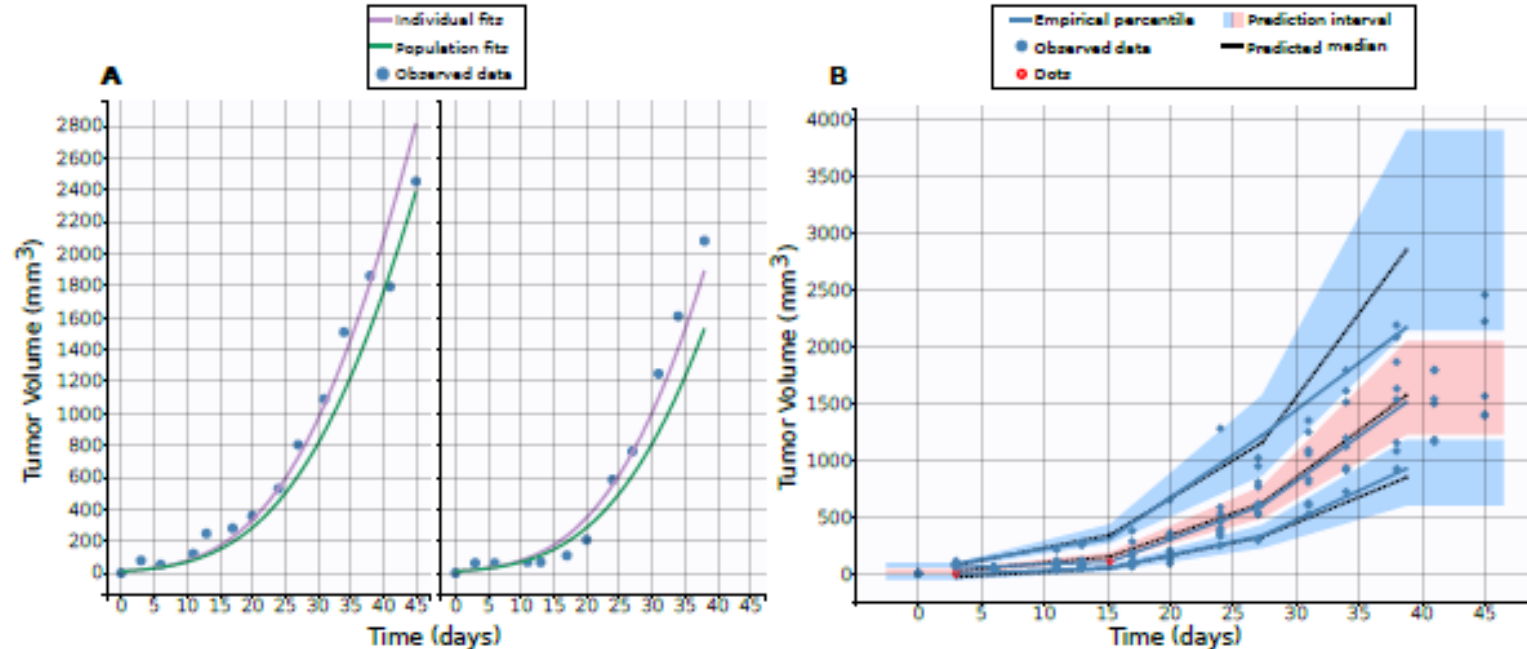
Non compartmental analysis

Parameter	PTX IV RM	PTX SC RM	PAAm IV RM	PAAm SC RM	PTX IV MS	PAAm SC MS
t1/2 (h)	2.39	5.33	22.36	28.88	1.69	14.75
T1ast (h)	7.00	7.00	144.00	144.00	7.00	72.00
Cmax (µg/ml)	4.45	0.31	84.32	20.62	4.66	0.10
Clast_obs (µg/ml)	0.03	0.09	0.74	0.82	0.03	0.00
CO (extrapolated)	28.16	-	130.85	-	6.85	-
AUC 0-t (µg/ml/h)	5.66	1.09	1070.47	881.00	4.55	1.27
AUC 0-inf_obs (µg/ml/h)	5.77	1.77	1094.01	915.08	4.63	1.30
MRT 0-inf_obs (h)	0.65	7.30	28.91	39.75	0.93	22.33
F (%)	-	31	-	84	-	-
Vz/F_obs (L)	-	0.63	-	0.0063	-	2.28
Vz_obs (L)	0.08	0.19	0.0041	0.0053	0.07	-
Cl/F_obs (L/h)	-	0.08	-	0.00015	-	0.11
Cl_obs (L/h)	0.02	0.024	0.00013	0.00013	0.03	-
Vss_obs (L)	0.02	0.18	0.0037	0.0060	0.03	-

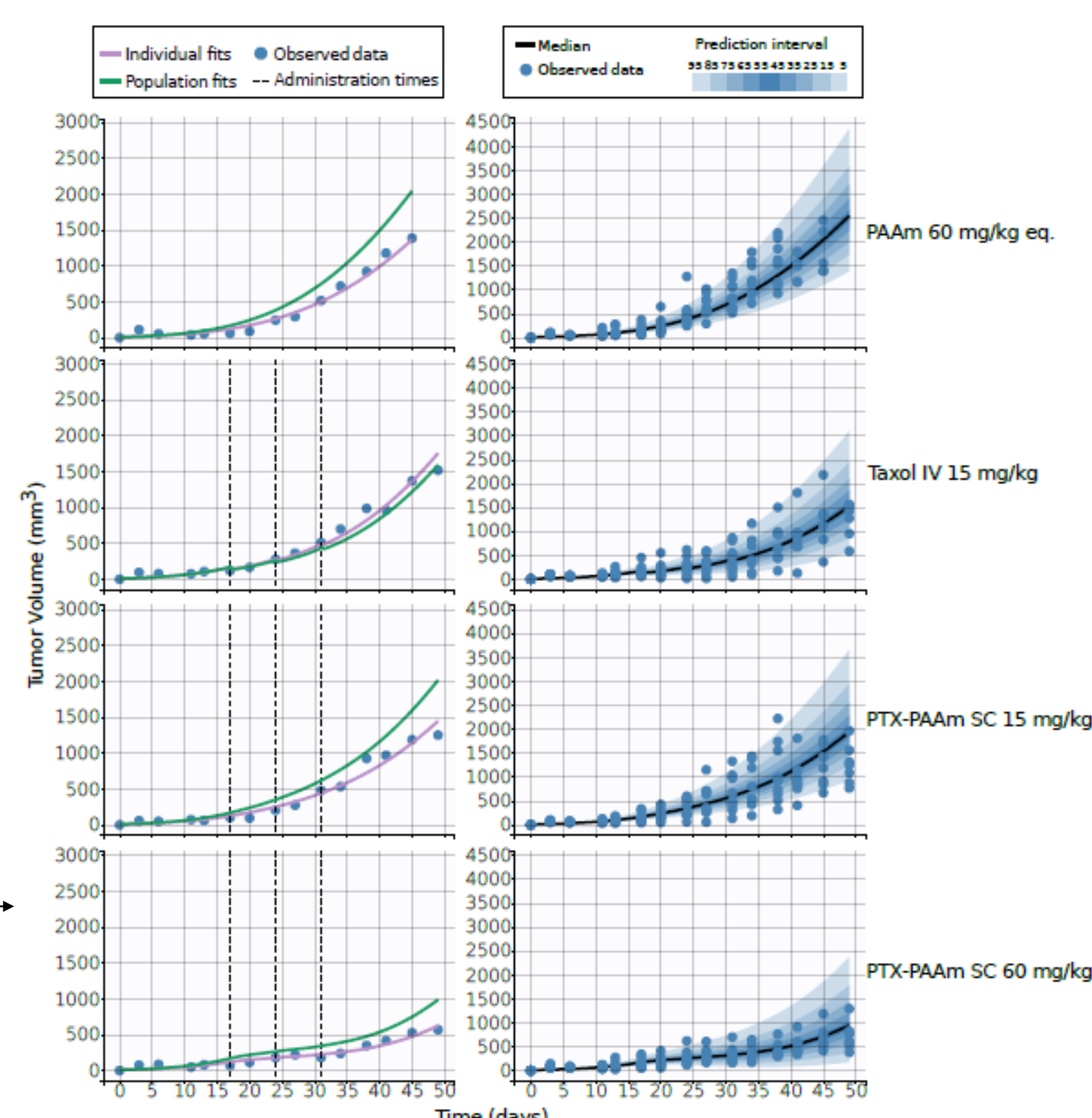


PHARMACODYNAMICS

Reduced Gompertz for tumor growth model



Simeoni with resistance for the efficacy model (Resistance modelled as the half-life of the treatment)

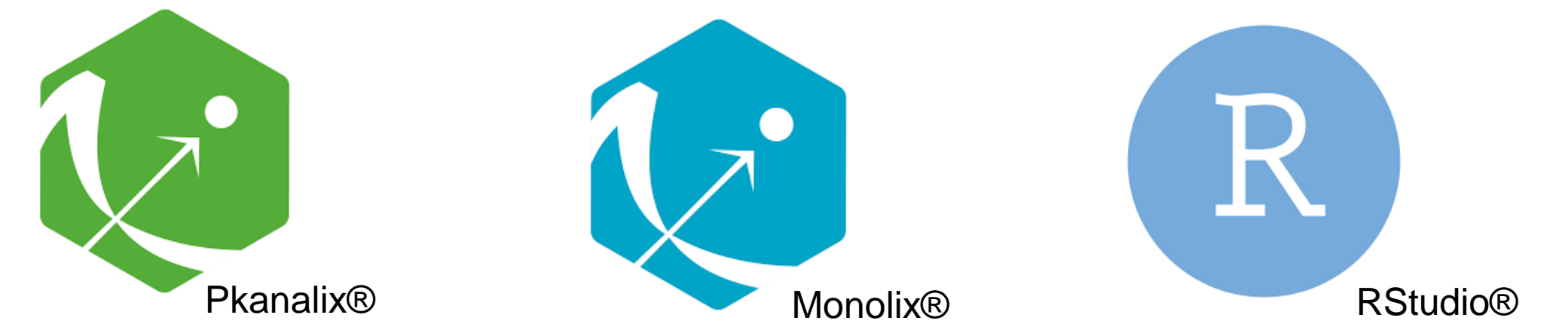


OUTLINE

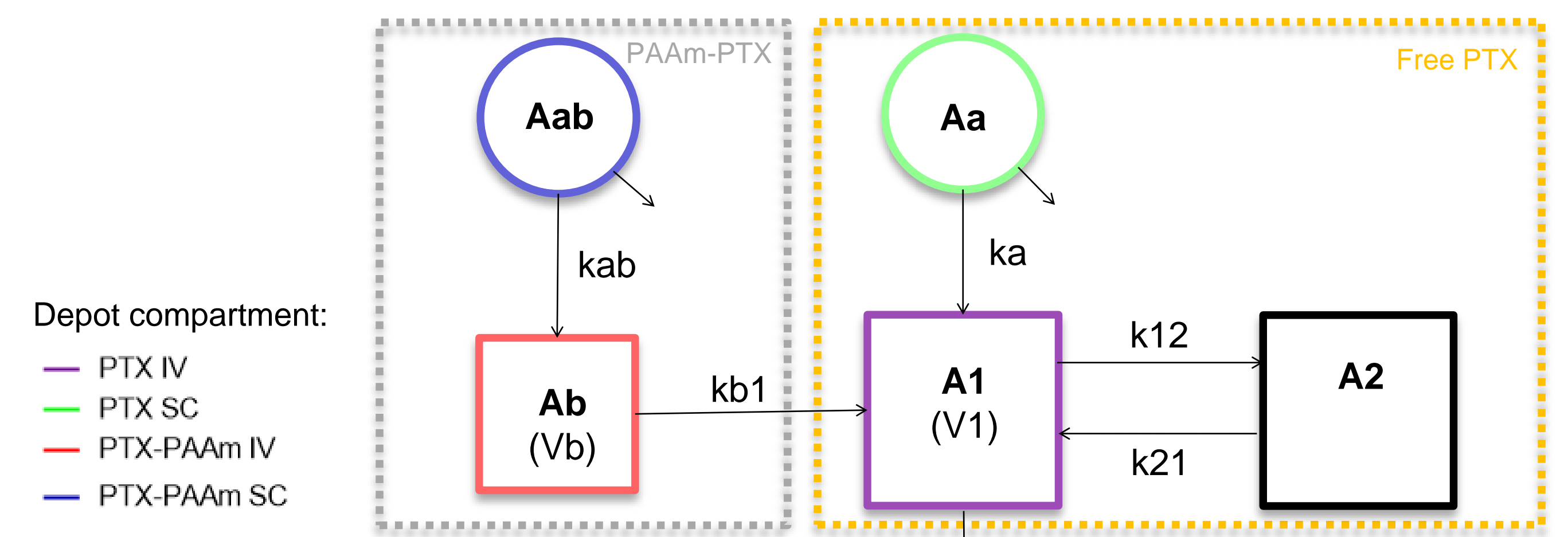
PK/PD modeling: **dose regimen optimization**

METHODS

SOFTWARES

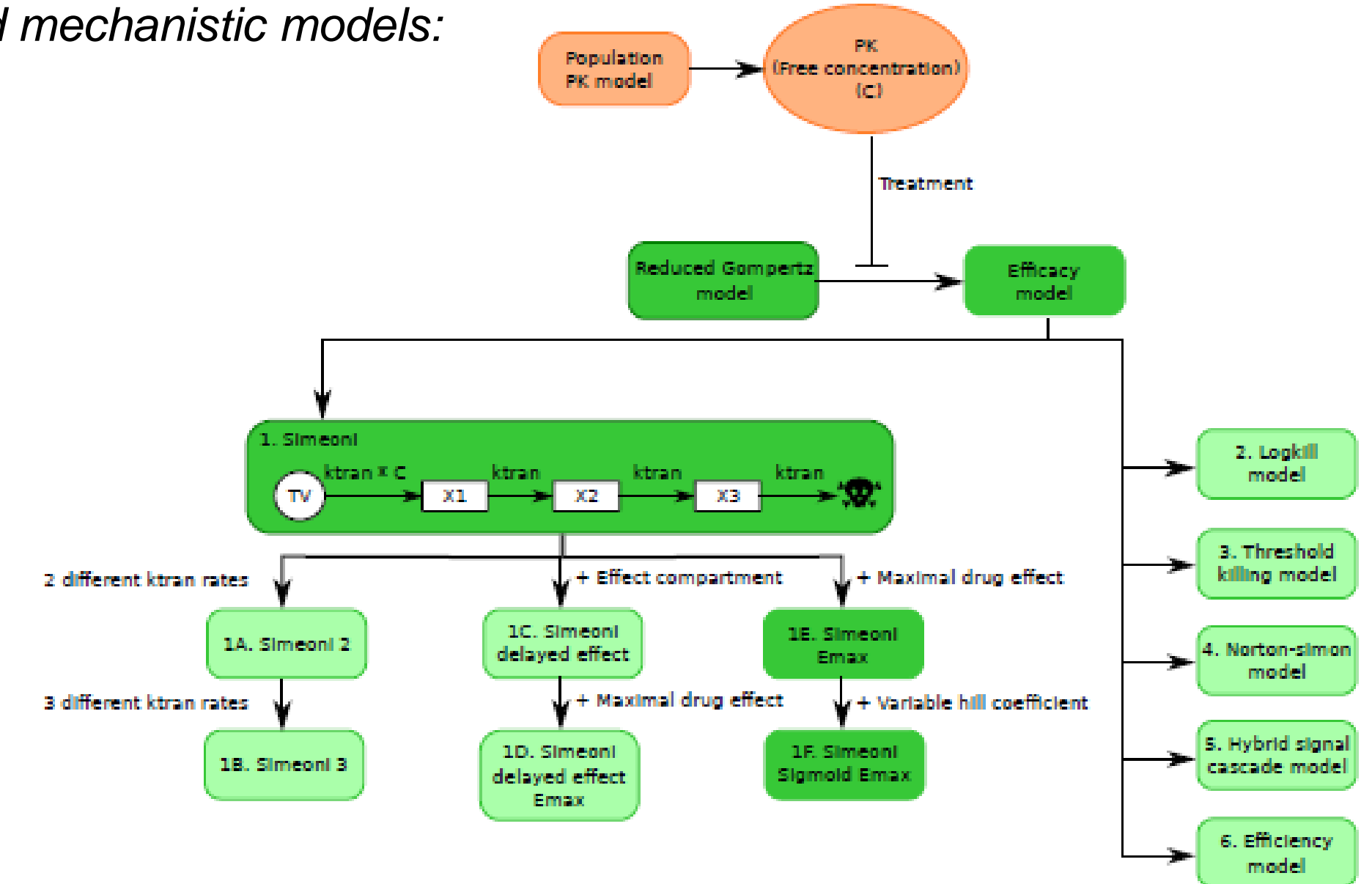


PHARMACOKINETICS

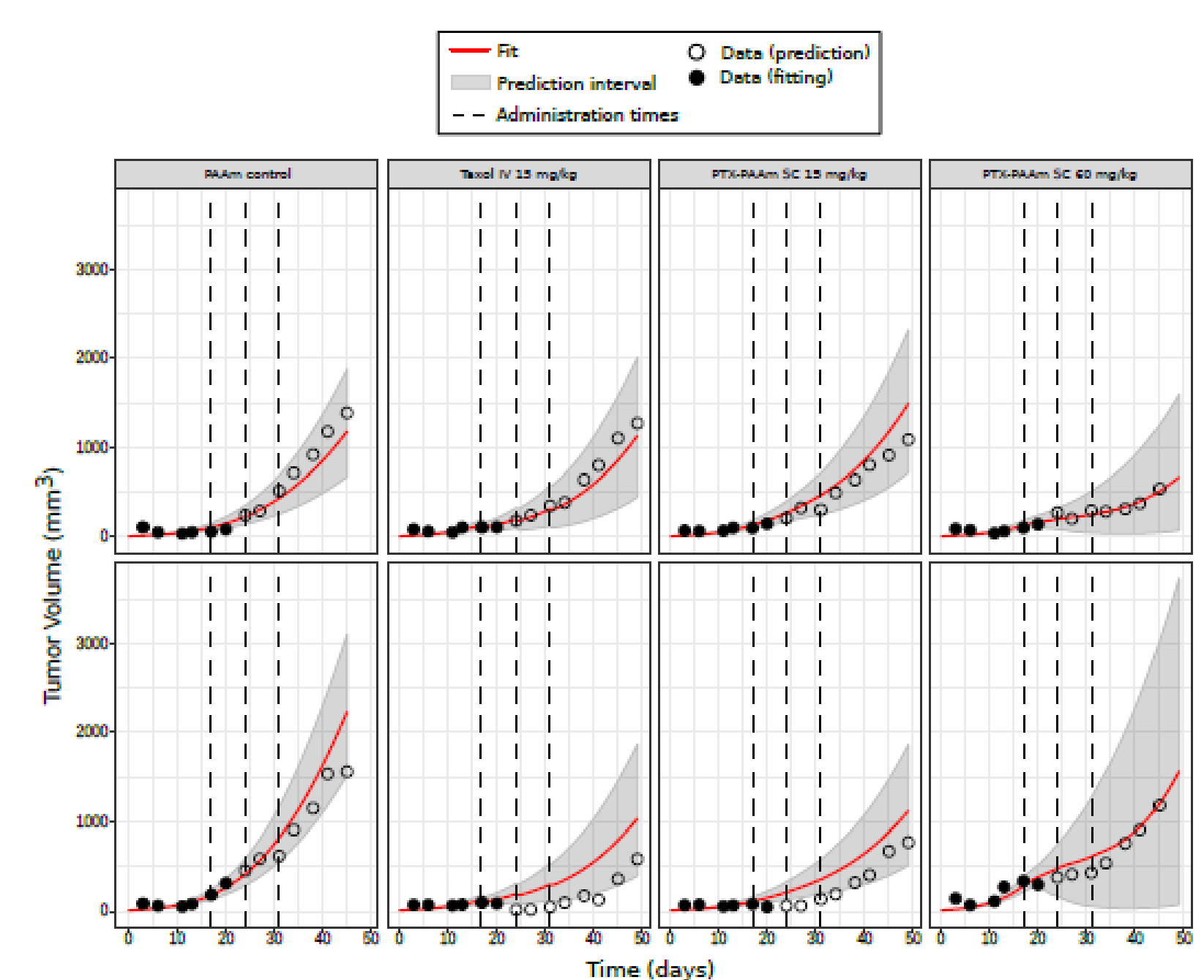


PHARMACODYNAMICS

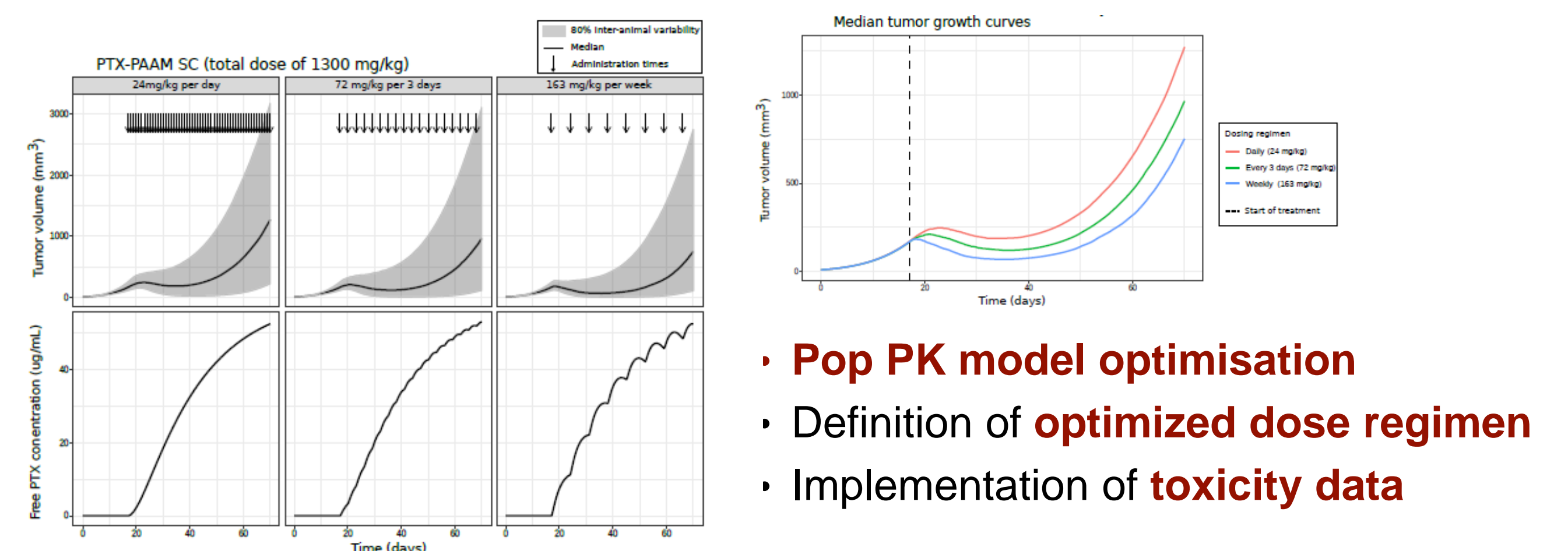
- Tumor growth Model on control group only: Exponential, Power Law, Logistic & Gompertz
- Efficacy and mechanistic models:



BAYESIAN ANALYSIS ON PK/PD MODEL PREDICTION



FUTURE PERSPECTIVES



ACKNOWLEDGMENTS

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[1] Bordat A, Boissenot T, Ibrahim N, Ferrere M, Levêque M, Denis S, et al. A Polymer Prodrug Strategy to Switch from Intravenous to Subcutaneous Cancer Therapy for Irritant/Vesicant Drugs. ChemRxiv. Cambridge: Cambridge Open Engage; 2021; This content is a preprint and has not been peer-reviewed.
 [2] Vaghi C, Rodallec A, Fanciullino R, Ciccolini J, Mocheil JP, Mastri M, Poignard C, Ebos JML, Benzekry S. Population modeling of tumor growth curves and the reduced Gompertz model improve prediction of the age of experimental tumors. PLoS Comput Biol. 2020 Feb 25;16(2):e1007178. doi: 10.1371/journal.pcbi.1007178. PMID: 32097421; PMCID: PMC7059968.