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Model-driven optimization of the scheduling of a novel anti-cancer prodrug administered subcutaneously

Anne Rodallec

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Anne Rodallec. Model-driven optimization of the scheduling of a novel anti-cancer prodrug administered subcutaneously. Pharmacometrics in France, Sep 2024, Paris, France. <hal-04726595>

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Submitted on 20 Nov 2025

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Inria

 **Inserm**

COMPO
COMPUTATIONAL ONCOLOGY

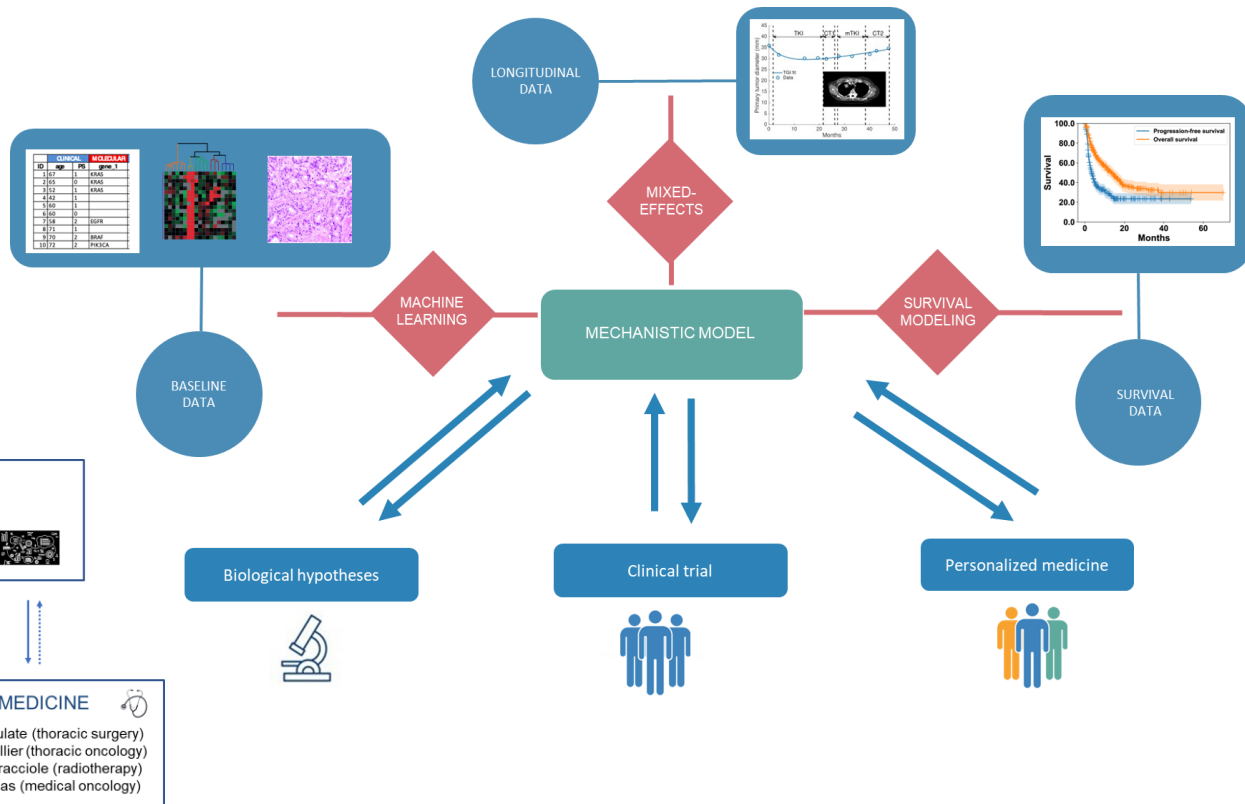
Model-driven optimization of the scheduling of a novel anti-cancer prodrug administered subcutaneously

Dr Anne Rodallec
COMPO - COMputational Pharmacology in Oncology

Our group



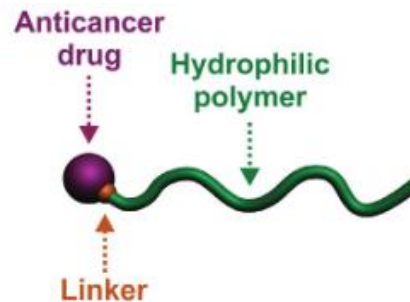
Dr S Benzekry & Pr J Ciccolini



- Taxanes: poor solubility and toxicities (Cremophor EL)
 - Development of new hydrophilic polymers (Applied to Paclitaxel)
- ➔ Subcutaneous administration
 - ➔ Cheaper
 - ➔ Less toxic, safe
 - ➔ More comfortable



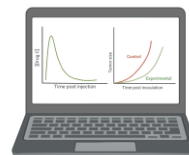
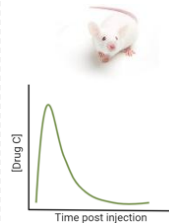
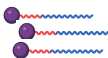
Dr Julien Nicolas





Dr Julien Nicolas

université
PARIS-SACLAY



Thermonano working plan

Polymer synthesis

Screening

PK studies

PD studies

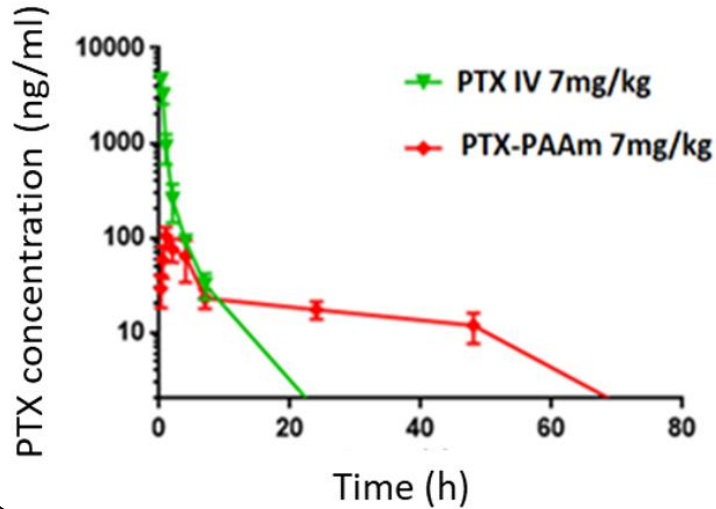
Data analysis

Optimization





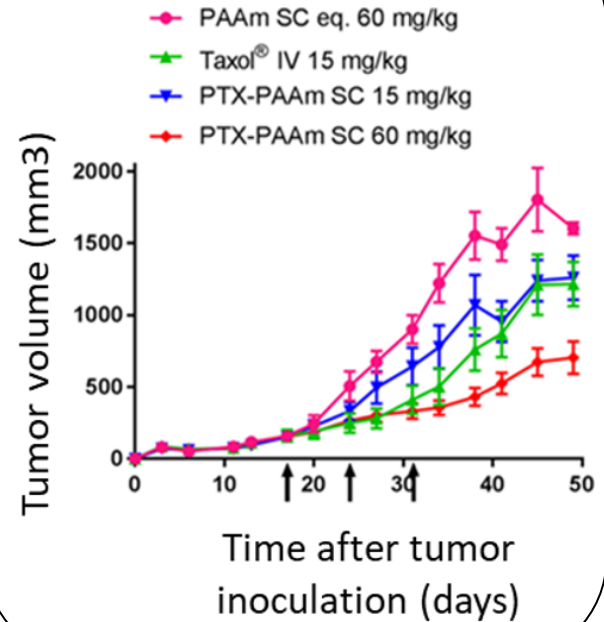
Data PK n=4



- ➔ Longer exposure
- ➔ Higher MTD
- ➔ Higher efficacy



Data PD n=9



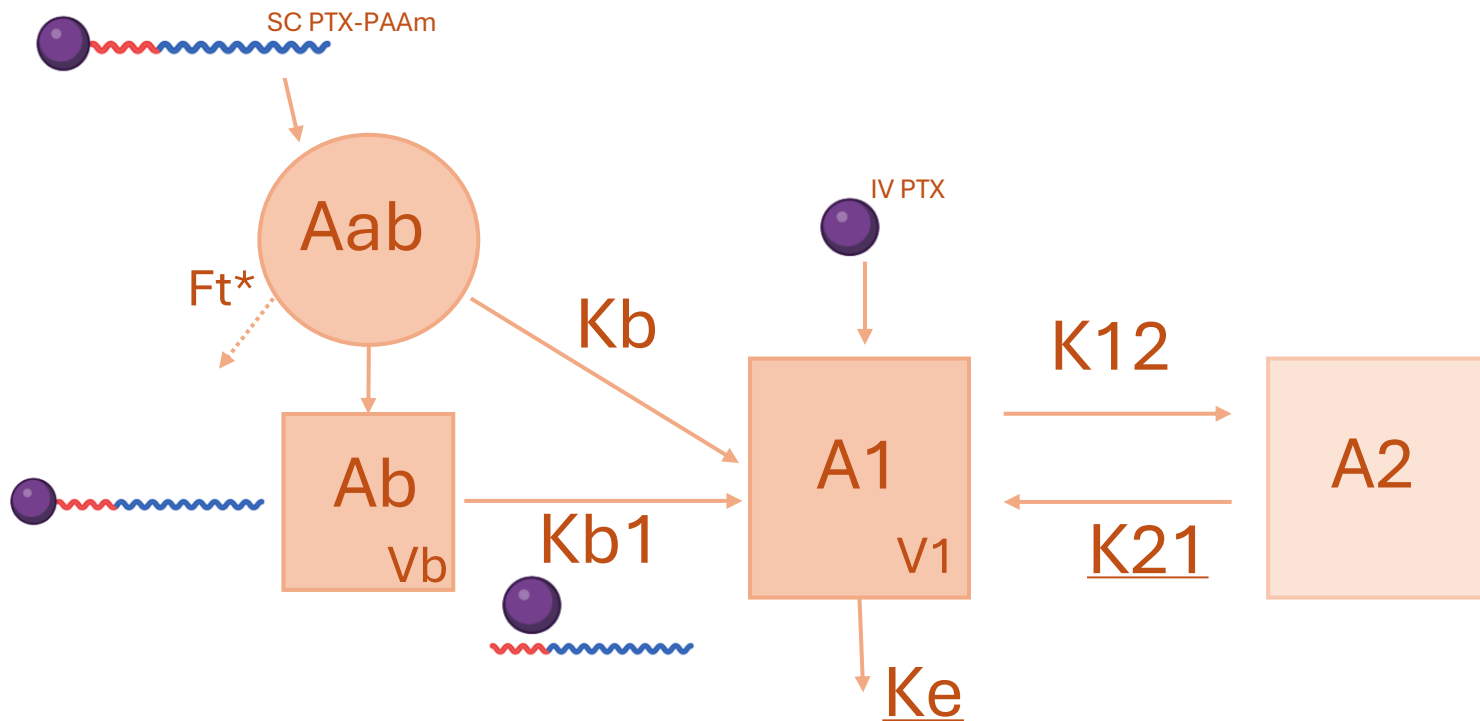
MTD: Maximal tolerated dose

PTX: Paclitaxel – PAAm: Polyacrylamide

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. *J. Am. Chem. Soc.* 2022, 144, 18844



- ① Experimental data from Julien Nicolas' team
- ② Pop PK Modeling
- ③ PK results
- ④ PD Modeling
- ⑤ Implementation of Pop_PK results in PD Model
- ⑥ Final results



* Defined by the model; parameters without RE

Unpublished data

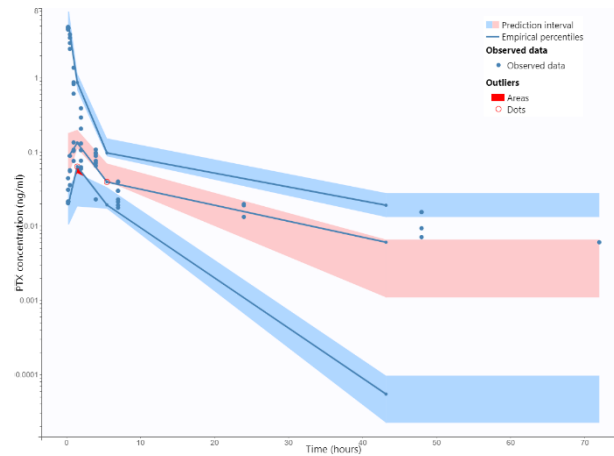
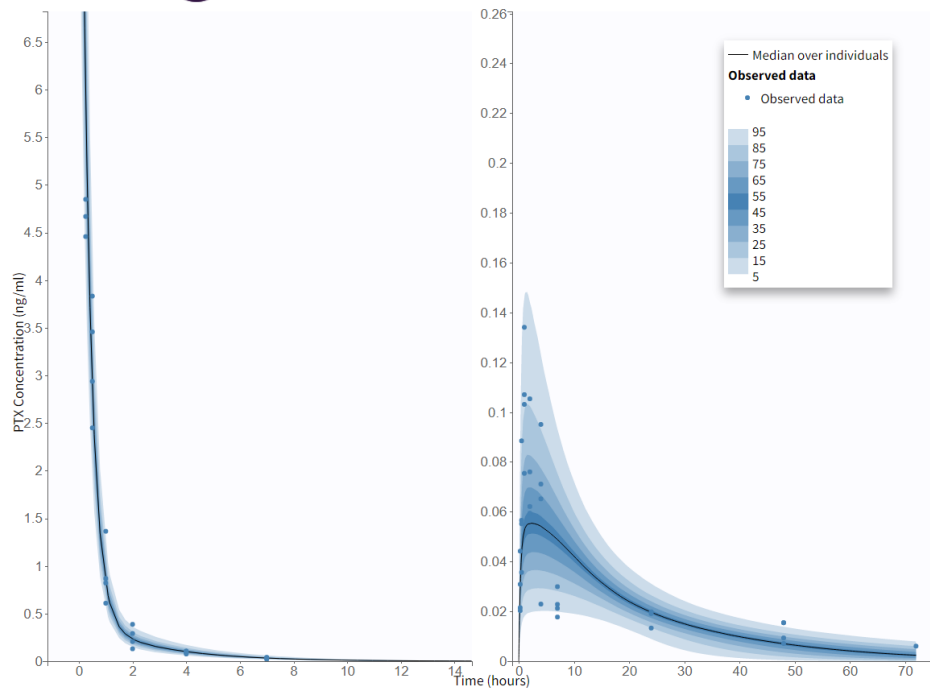
Non longitudinal data
Proportionnal error model set at 10 %

Model Pop PK

IV PTX



SC PTX-PAAm



| PARAMETER | ESTIMATE | RSE % |
|--|--------------|---------------|
| FIXED EFFECT | | |
| V1 (ml) | 10.73 | 5.82 |
| K₁₂ | 0.65 | 12.8 |
| K₂₁ | 0.51 | 0.0852 |
| K_e | 2.76 | 0.134 |
| K_b | 0.047 | 13.5 |
| STANDARD DEVIATION OF THE RANDOM EFFECT | | |
| ΩV1 | 0.26 | 19.4 |
| ΩK₁₂ | 0.21 | 37 |
| ΩK_b | 0.57 | 19.9 |

Unpublished data

Pop-PK (fixed)

Untreated tumor growth

Drug Effect

Drug Resistance

Exponential

$$\frac{dTV}{dt} = \lambda \cdot TV$$

Power Law

$$\frac{dTV}{dt} = \alpha \cdot TV^\gamma$$

Logistic

$$\frac{dTV}{dt} = \lambda \cdot TV \cdot \left(1 - \frac{TV}{TV_{max}}\right)$$

Gompertz

$$\frac{dTV}{dt} = \alpha \cdot \exp(-\beta \cdot t) \cdot TV$$

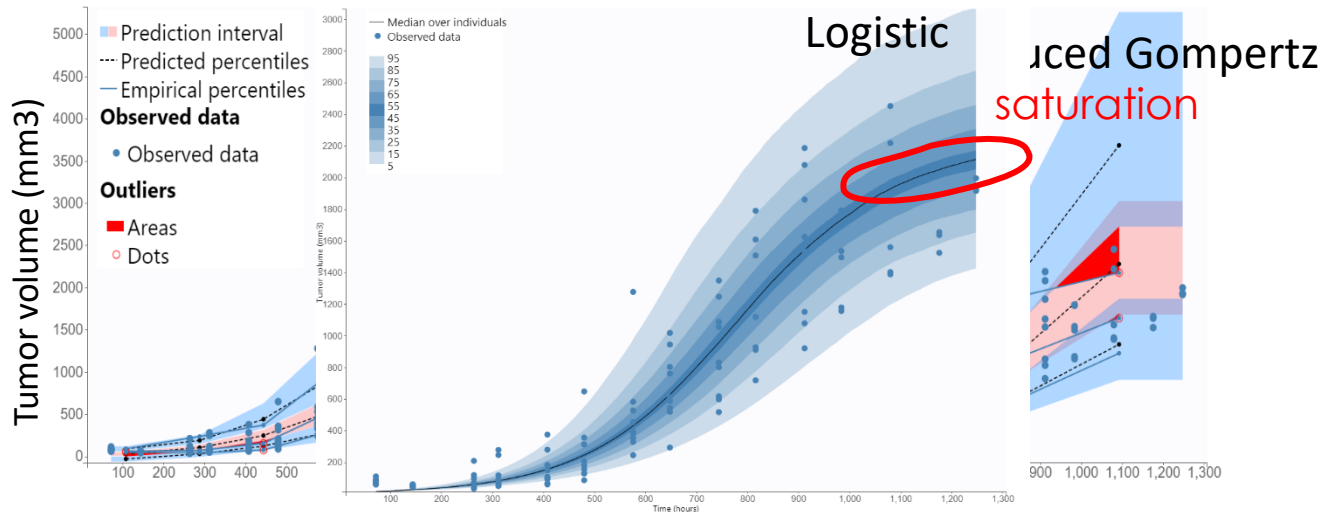
Reduced Gompertz

$$\frac{dTV}{dt} = (\beta \cdot \gamma) - \beta \cdot \log\left(\frac{TV}{TV_0}\right) \cdot TV$$

TV = tumor volume (mm³), TV₀ = initial tumor volume (i.e., 10, because 10 millions of cells were first inoculated), t = time (hours)

Model PD: Untreated Tumor Growth

| Model | -2LL | AIC | Nber of para (F + R) |
|------------------------|------|------|----------------------|
| Logistic | 1388 | 1394 | 4 (2+2) |
| Gompertz | 1394 | 1408 | 4 (2+2) |
| Reduced Gompertz | 1415 | 1425 | 3 (2+1) |
| Power Law | 1421 | 1433 | 3 (2+1) |
| Exponential | 1549 | 1557 | 3 (1+1) |



Vaghi C, Rodallec A, Fanciullino R, Ciccolini J, Mochel 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.

Pop-PK (fixed)

Reduced Gompertz

Drug Effect

Drug Resistance

Log Kill

$$\frac{dTV}{dt} = G - e \cdot C \cdot TV$$

Norton Simon

$$\frac{dTV}{dt} = G - e \cdot C \cdot G$$

Iliadis Barbolosi

$$\frac{dTV}{dt} = G - e \cdot (C - C_{min})^+ \cdot TV$$

Simeoni

$$\begin{aligned} \frac{dTV_1}{dt} &= G - k_{tran} \cdot C \cdot TV_1 \\ \frac{dTV_2}{dt} &= k_{tran} \cdot C \cdot TV_1 - k_{tran} \cdot TV_2 \\ \frac{dTV_3}{dt} &= k_{tran} \cdot (TV_2 - TV_3) \\ \frac{dTV_4}{dt} &= k_{tran} \cdot (TV_3 - TV_4) \end{aligned}$$

G = the tumor growth term, C = PTX free concentration ($\mu\text{g/ml}$)

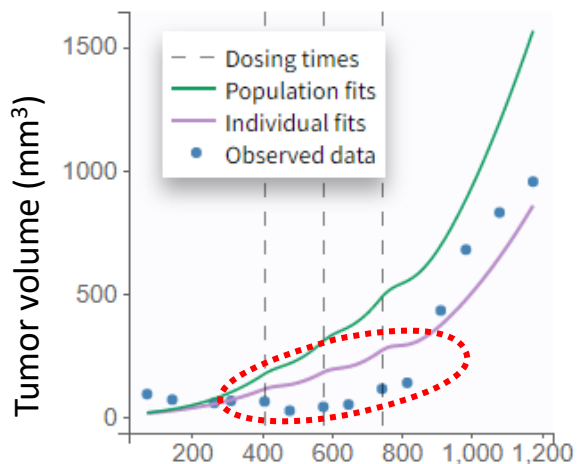
Model PD: drug effect

| Model | -2LL | AIC | Nber of para (F + R) |
|------------------------------|-----------------|-----------------|----------------------|
| Simeoni | 5624 | 5632 | 2 (1+1) |
| Iliadis Barbolosi | 5636 | 5646 | 4 (2+2) |
| Log Kill | 5637 | 5646 | 2 (1+1) |
| Norton Simon | 5684 | 5692 | 2 (1+1) |

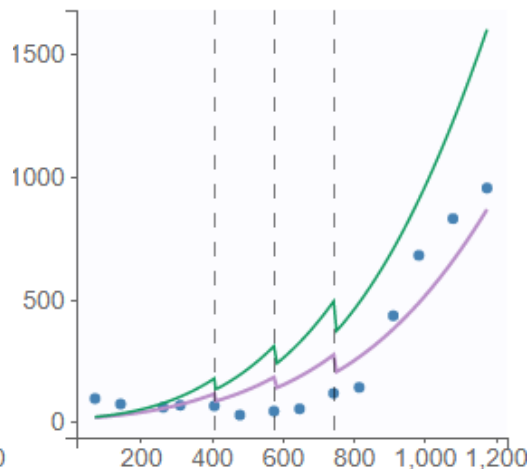
Simeoni

Iliadis Barbolosi

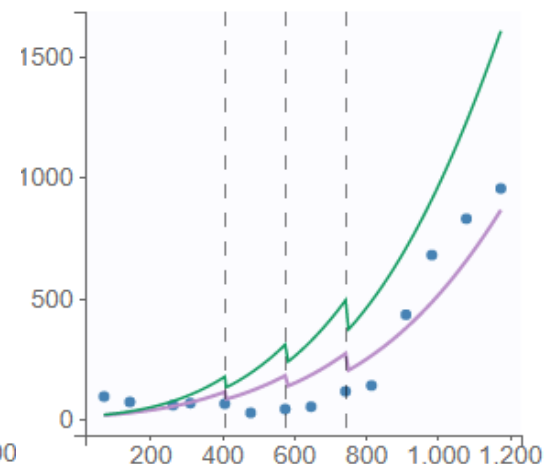
Log Kill



misspecification



Time (hours)



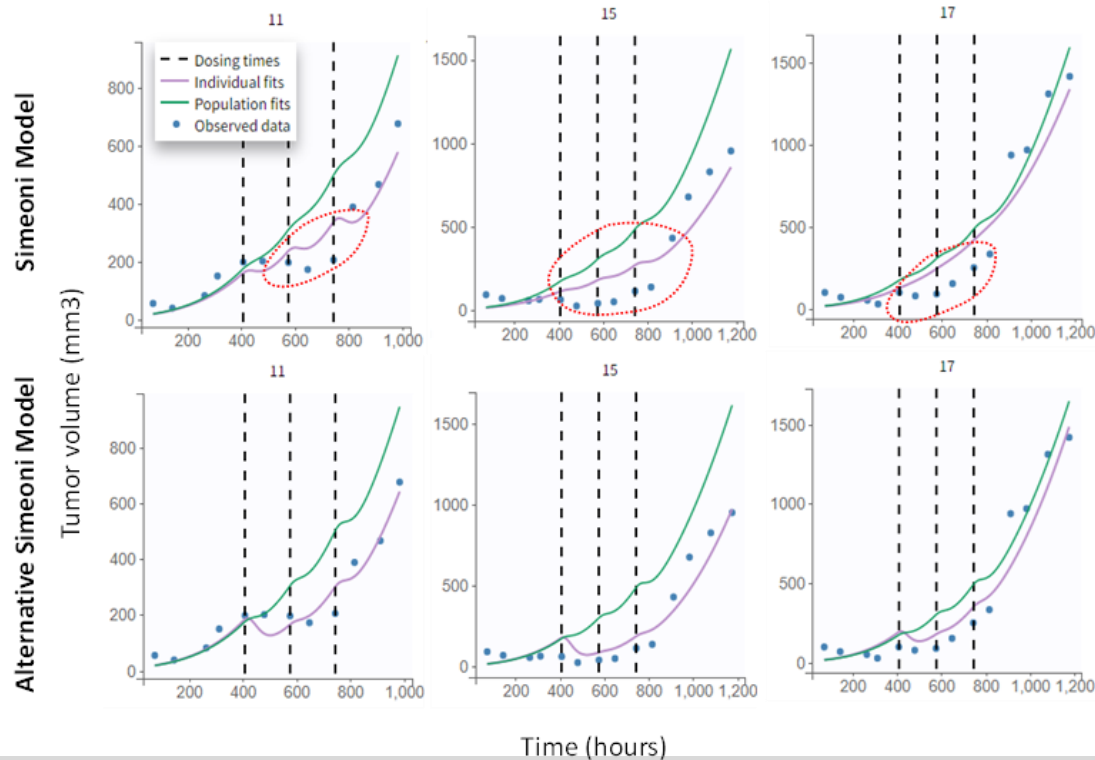
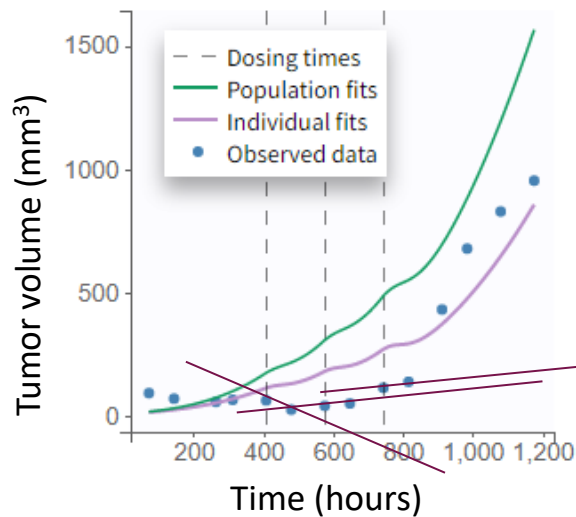
Unpublished data

Pop-PK (fixed)

Tumor growth

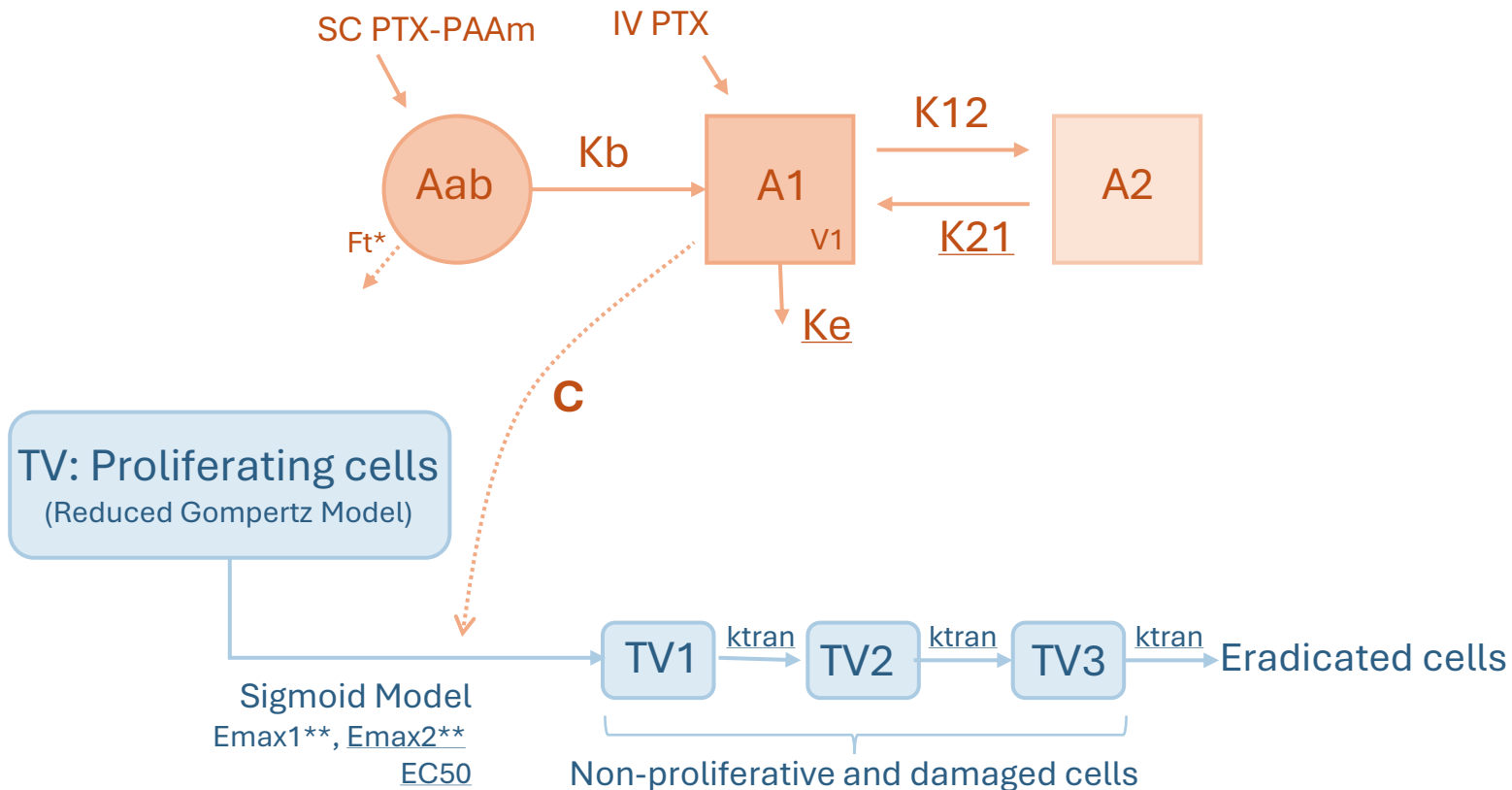
Drug effect

Drug Resistance



Unpublished data

Final PK/PD Model: Structure

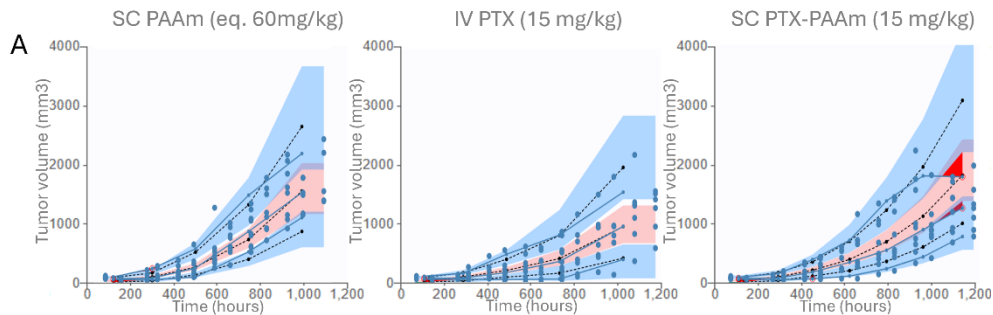


* Defined by the model; parameters without RE, ** Resistance acquired after second administration

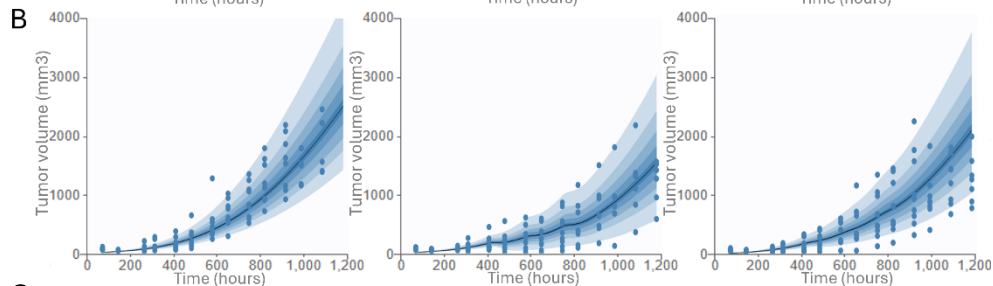
Unpublished data

Final PK/PD Model: Train sets

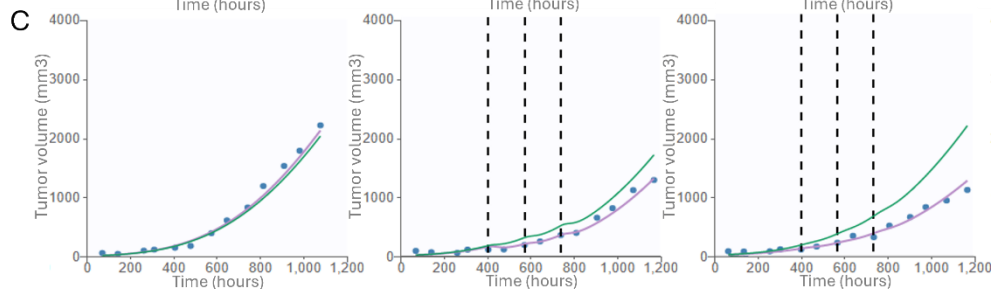
VPC



Prediction distribution



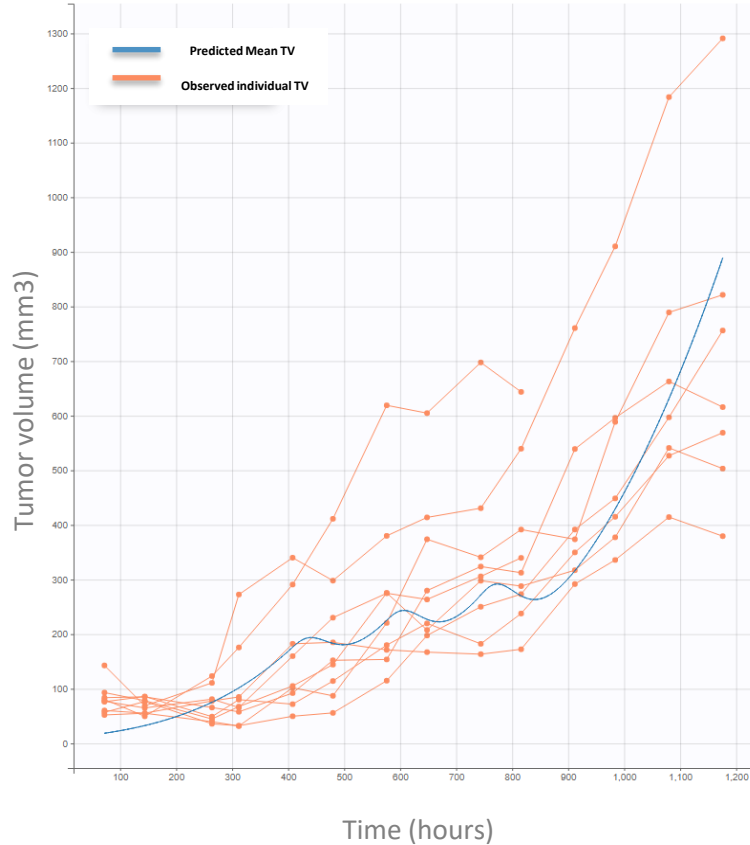
Individual fit



| PARAMETER | ESTIMATE | RSE % |
|-------------------------|----------|--------|
| FIXED EFFECT | | |
| V1 (ml) | 10.73 | 5.82 |
| K_{12} | 0.65 | 12.8 |
| K_{21} | 0.51 | 0.0852 |
| K_e | 2.76 | 0.134 |
| K_b | 0.047 | 13.5 |
| γ | 7.17 | 5.25 |
| β | 0.0013 | 10.3 |
| ktran | 0.05 | 0.402 |
| E _{max1} | 15.48 | 40.1 |
| E _{max2} | 13.8 | 3.51 |
| EC50 | 462.7 | 1.16 |
| SD OF THE RANDOM EFFECT | | |
| Ω_{V1} | 0.26 | 19.4 |
| $\Omega_{K_{12}}$ | 0.21 | 37 |
| Ω_{K_b} | 0.57 | 19.9 |
| Ω_{K_β} | 0.15 | 24.5 |
| $\Omega_{E_{max1}}$ | 1.23 | 25.4 |

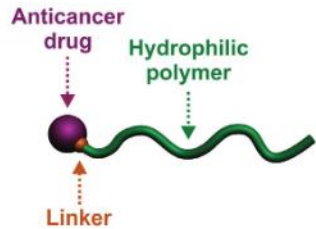
Unpublished data

Final PK/PD Model: validation



Prediction of SC PTX-PAAm 60 mg/kg group using our final PK/PD model on Simulx®

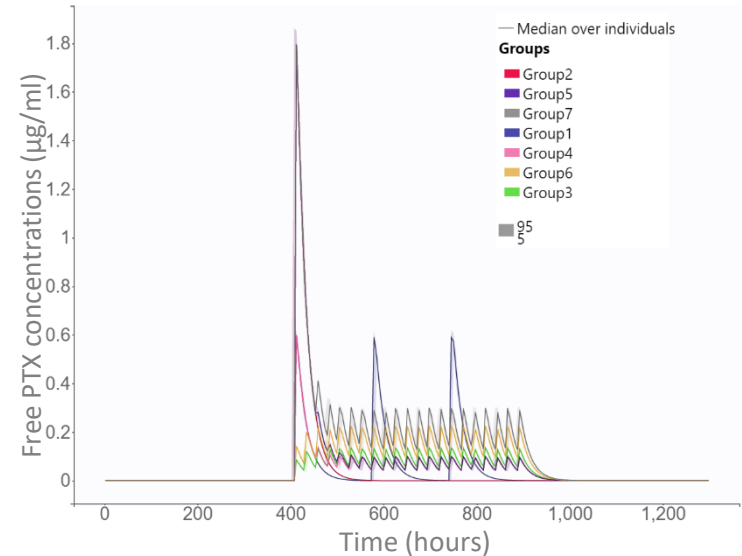
Unpublished data



MTD: 60mg/kg \longrightarrow > 180mg/kg

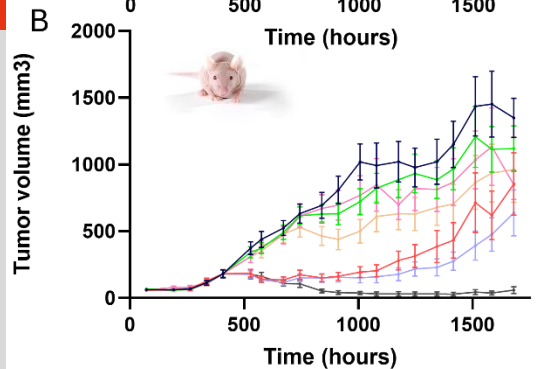
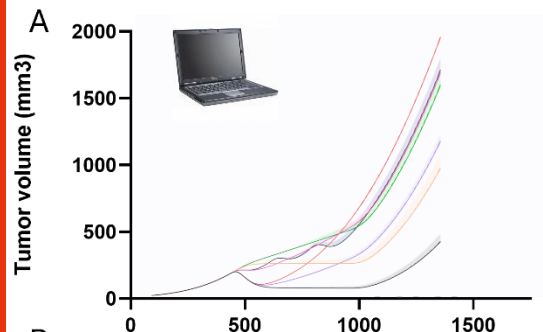
MRT: 0.9H \longrightarrow 22.2H

| Treatment groups | Total dose (µg) | Loading dose (µg - mg/kg) | Treatment dose (µg - mg/kg) | Consolidation treatment (µg - mg/kg) | Number of administrations |
|------------------|-----------------|---------------------------|-----------------------------|--------------------------------------|---------------------------|
| Group 1 | 3960 | - | 1320 - 60 | - | 3 |
| Group 2 | 3960 | - | 3960 - 180 | - | 1 |
| Group 3 | 3969 | - | 189 - 8.6 | - | 21 |
| Group 4 | 3961 | 1320 - 60 | - | 139 - 6.3 | 19 |
| Group 5 | 6601 | 3960 - 180 | - | 139 - 6.3 | 19 |
| Group 6 | 6594 | - | 314 - 14.3 | - | 21 |
| Group 7 | 11883 | 3960 - 180 | - | 417 - 19 | 19 |



MTD: Maximal tolerated dose; MRT: Mean residence time

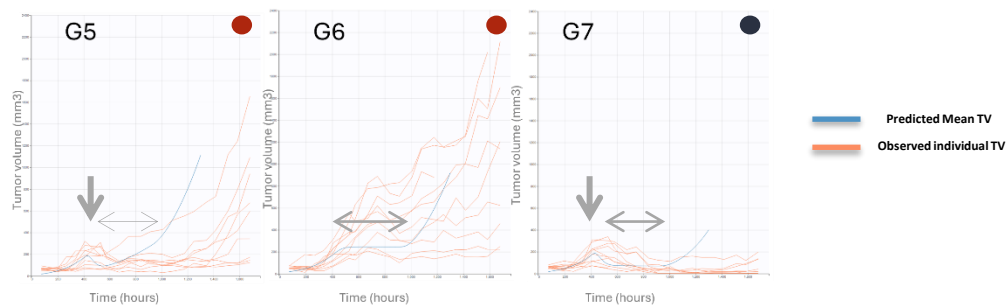
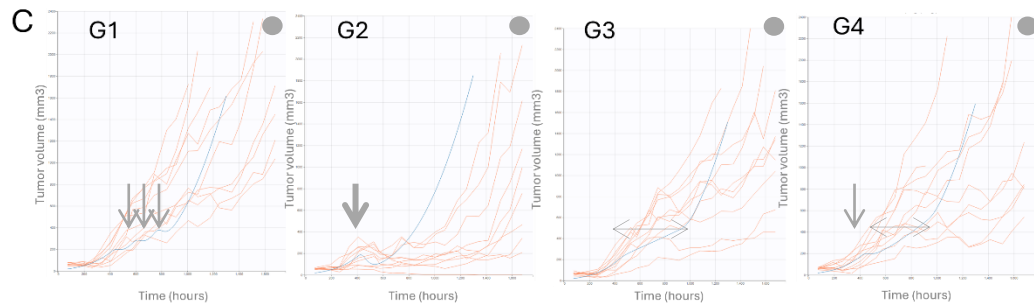
Unpublished data



n=9-10

- Group 1
- Group 2
- Group 3
- Group 4
- Group 5
- Group 6
- Group 7

- Group 1
- Group 2
- Group 3
- Group 4
- Group 5
- Group 6
- Group 7



↓ : Loading Dose ↔ : Daily administration Thickness is proportional to dose

Total Dose: ● 3960 μg ● 6600 μg ● 11880 μg

Unpublished data

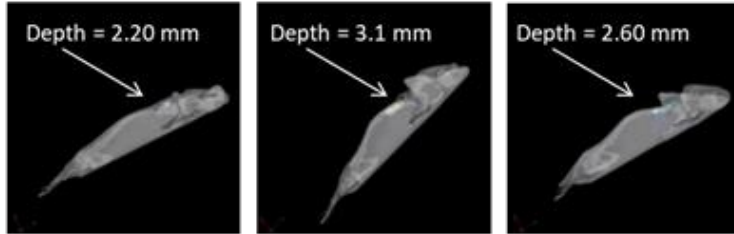
- Predictive PK/PD Model
 - interest of Loading dose (180 mg/kg)
 - + daily adm. (14.3-19 mg/kg)
- Limits:
 - Different doses for PK and PD data -> No data on PK linearity
 - Lack of safety studies (no toxicity observed)
- Perspectives:
 - Model optimization using the new data
 - Applications to new polymers and other linked chemotherapies (i.e., vinblastine)
 - Further mechanistic modeling of the resistance
 - Testing new device for daily administration



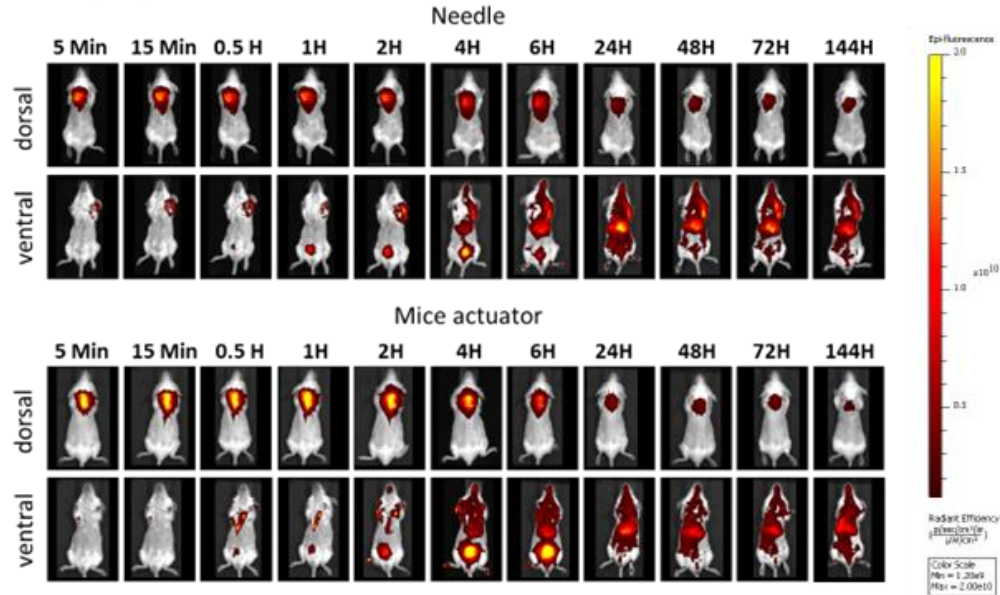
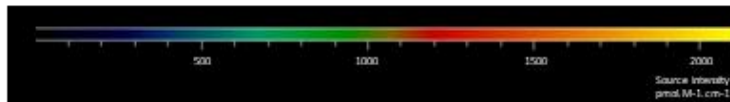
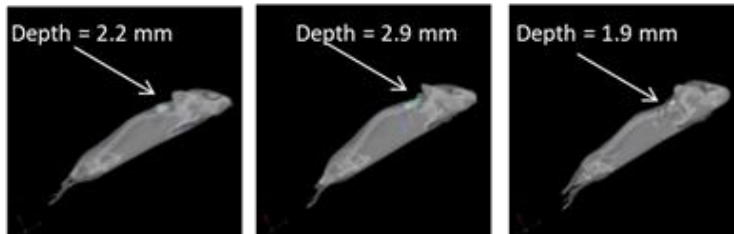
Dr Patricia Piris



Needle



Mice actuator



Unpublished data



Inria

Offre n°2024-08121

Post-Doctoral Research Visit F/M Optimization of therapeutic strategies for pediatric cancers using mathematical modeling of intra-tumor heterogeneity

Contract type : Fixed-term contract

Level of qualifications required : PhD or equivalent

Fonction : Post-Doctoral Research Visit

Level of experience : Recently graduated

Contact:
sebastien.benzekry@inria.fr

Thank you!

ZEUS project: ARTIFICIAL INTELLIGENCE TO OPTIMIZE CYTARABINE IN LEUKEMIA PATIENTS

☑ Position: Post-Doctoral Fellowship



☑ Duration: 24 months, full-time



☑ Starting: ASAP



☑ Location: COMPO Team, School of Pharmacy, Timone Health Campus, Marseille France



☑ Employer: Aix Marseille Uni

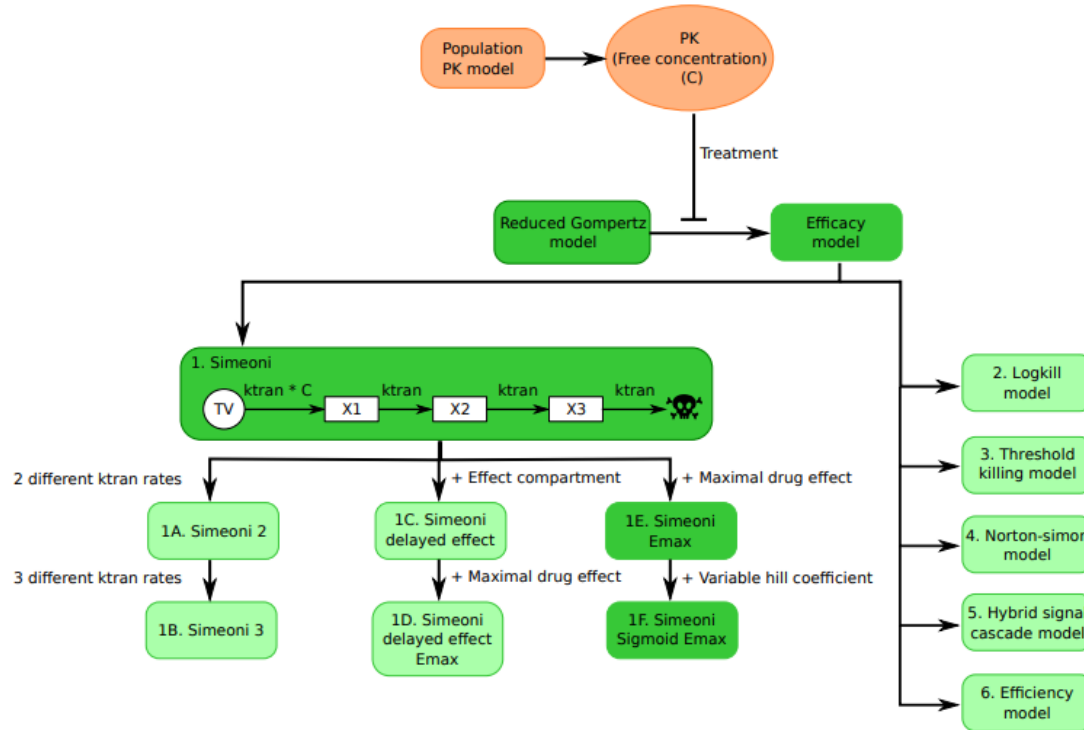


☑ Required skills: Pharmacometrics, Pop-PK, Machine Learning & Coding, Data Analysis, Oncology

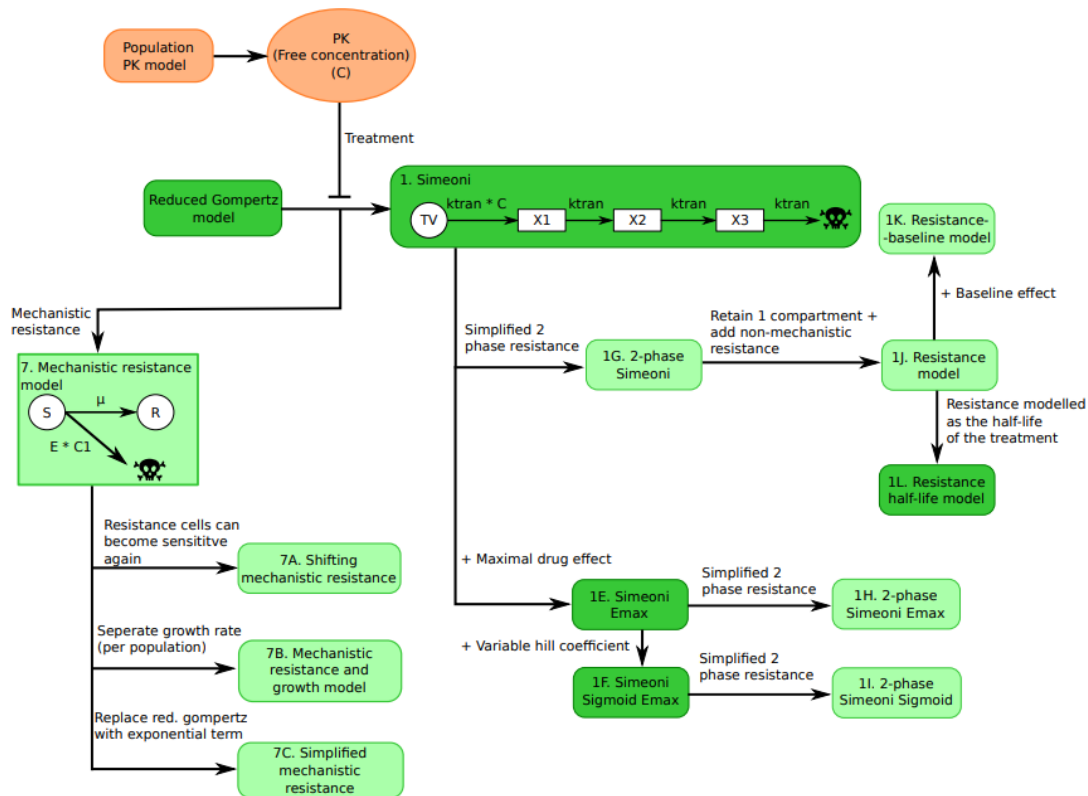


Contact:
raphaelle.fanciullino@univ-amu.fr

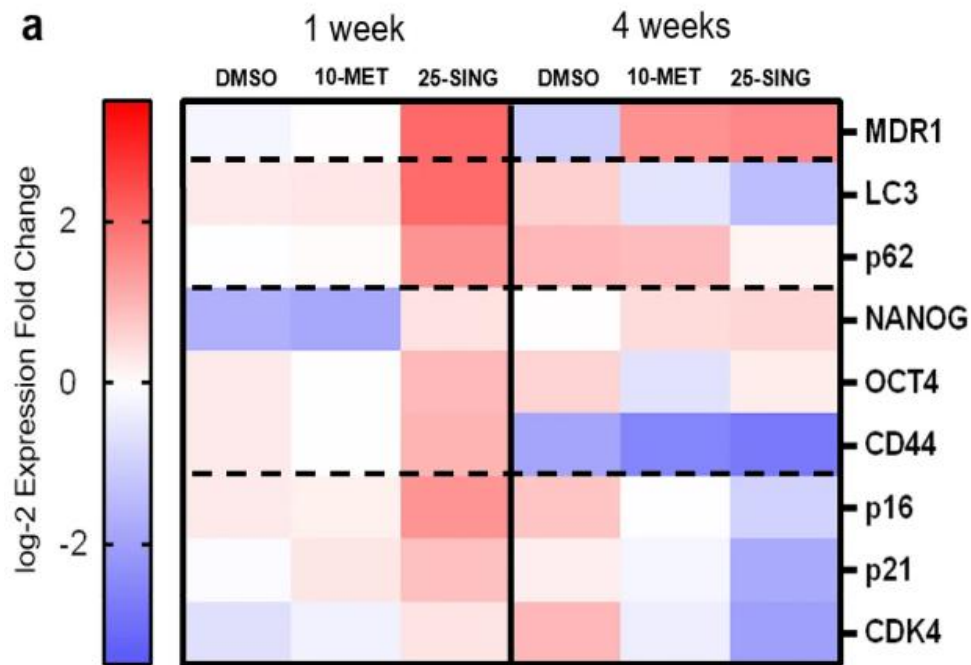
Overview of the tested efficacy models to fit the PD data (Randy. Lee)



Overview of the tested efficacy models that were extended with resistance (Randy. Lee)

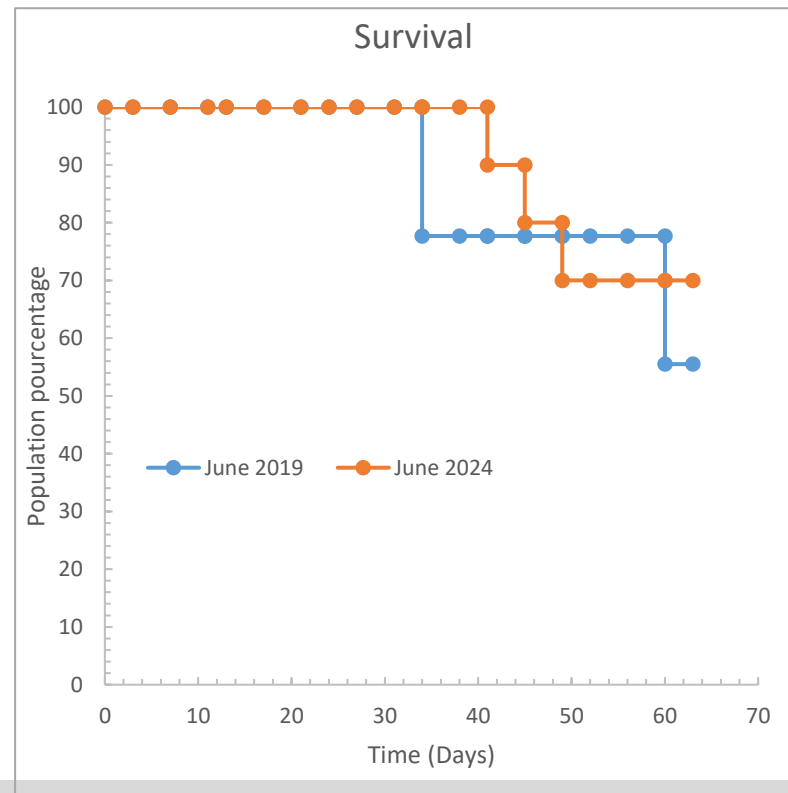
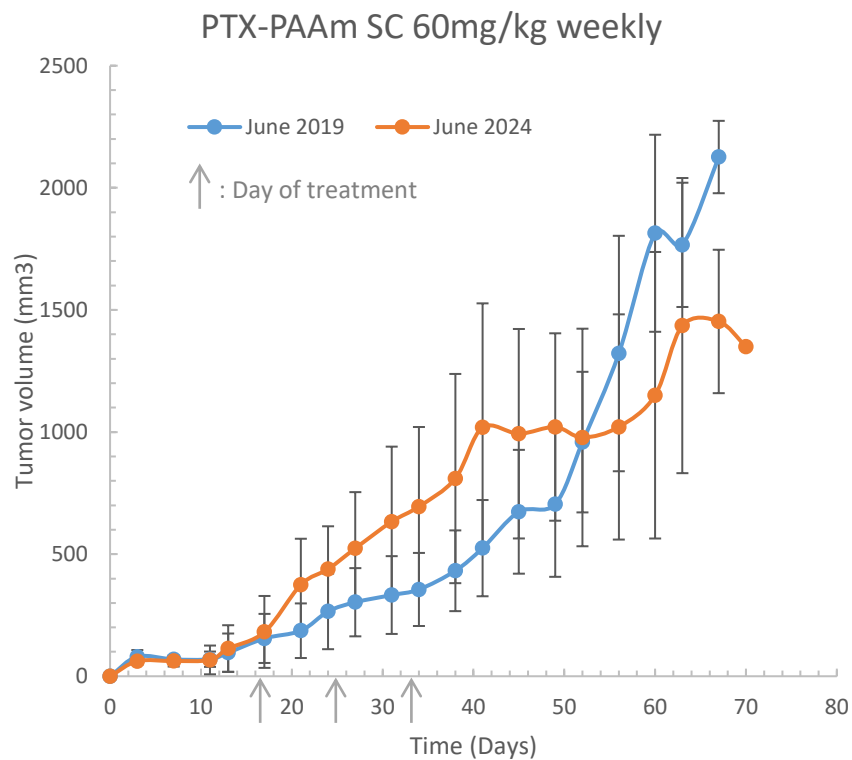


Biological reasoning behind the observed resistance model



“MDR1 transcript expression was elevated by the fourth week in the 10-MET group, but a single treatment of 10 nM was insufficient to promote MDR1 expression at week 1. In contrast, a single treatment of 25 nM PTX was sufficient to increase expression at week 1”

Comparaison experiment June 2019 and 2024



Subcutaneous injection and bioavailability

TABLE 1

Overview of marketed IgGs and IgG Fc-fusion proteins administered via the subcutaneous route

Data on time to maximum serum concentration and bioavailability collected from the European Medicines Agency (EMA) Summary of Product Characteristics (http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=), EMA assessment reports, or the Food and Drug Administration homepage (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda>).

| INN Name | Trade Name | Antibody Type | Target | T_{max} in Humans | Bioavailability in Humans and Animals |
|-------------|---------------------|-------------------|--|---------------------|---|
| | | | | days | % |
| Adalimumab | Humira | IgG1 | TNF | 5.5 | Humans: 64 Cynomolgus monkey: 96 |
| Canakinumab | Ilaris | IgG1 | IL-1 β | 7 | Humans: 70 Marmoset: 60 |
| Denosumab | Prolia | IgG2 | RANK-L | 10 | Humans: 78 Mice: 86 Cynomolgus monkey: 28–100* |
| Golimumab | Simponi | IgG1 | TNF | 2–6 | Humans: 53 Cynomolgus monkey: 77 |
| Omalizumab | Xolair | IgG1 | IgE | 7–8 | Humans: 62 Mice: 90 Cynomolgus monkey: 64–104 |
| Rituximab | Mabthera | IgG1 | CD20 | 3 | Humans: 71 Mice: 63 Minipig: 71 Humans: 80 Minipig: 84 Cynomolgus monkey: 72 |
| Tocilizumab | Actemra / RoActemra | IgG1 | IL-6R | — | Humans: 82 Mice: 83 Minipigs: 82 Cynomolgus monkey: ca. 100 |
| Ustekinumab | Stelara | IgG1 | IL-12/23p40 | 8.5 | Humans: 57 (24–95) Cynomolgus monkey: 97 |
| Abatacept | Orencia | Fc-fusion protein | CD80/86 | 3–5 | Humans: 79 Mice: 78–110 Rat: 41–63 |
| Etanercept | Enbrel | Fc-fusion protein | TNF | 3 | Humans: 76 Mice: 58 Cynomolgus monkey: 73 |
| Rilonacept | Arcalyst | Fc-fusion protein | IL-1 α , IL-1 β , IL-1 γ | — | Humans: 43 Mice: 78 Rats: 54 Cynomolgus monkey: 70 |
| Romiplostim | Nplate | Fc-fusion protein | Thrombopoietin receptor | 0.6 | Humans: — Rats: 21–28 Cynomolgus monkey: 19 Rhesus monkey: 45–74 |

If > 20 KDa:

first-pass catabolism at the subcutaneous administration site or in the draining lymphatics

Non compartmental PK

Table 2. Main Pharmacokinetic Parameters of Free Ptx Determined by LC–MS/MS after IV Injection of Taxol (Taxol^{IV}) at 7 mg kg⁻¹ and after SC Injection of P3d^{SC}, P3e^{SC}, and P3c^{SC} at 7 mg kg⁻¹ (Ptx equiv)

| parameter | Taxol ^{IV} | P3d ^{SC} | P3e ^{SC} | P3c ^{SC} |
|--|---------------------|-------------------|-------------------|-------------------|
| $t_{1/2}$ (h) | 1.7 | 1.5 | 13.9 | 1.6 |
| t_{\max} (h) | 0.25 | 1 | 1 | 2 |
| C_{\max} (ng mL ⁻¹) | 4657 | 310 | 105 | 41 |
| $AUC_{0 \rightarrow \infty}$ (ng mL ⁻¹ h) | 4631 | 986 | 1299 | 186 |
| MRT (h) | 0.9 | 2.5 | 22.2 | 3.3 |
| apparent bioavailability ^a (%) | 100 | 21 | 28 | 4 |