Optimization of the Irinotecan – Efflux Transporters Inhibitor Combination for Treating Irinotecan Resistant Tumours

Alexandre SOSTELLY, Léa PAYEN, Benjamin RIBBA, Attilio DI PIETRO, Pierre FALSON, Ahcène BOUMENDJEL, Gilles FREYER, Pascal GIRARD, Michel TOD

Outline

- Clinical issue
- Aims
- Animals
- Model Building
- Model Based Development
- Perspectives

Clinical Issue

Multi-Drug Resistance

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- Issue
- Aims
- Animals
- Model Building
- MBD
- Discussion

Clinical Issue

Multi-Drug Resistance

- Efflux transporters:
  - Important role in drug absorption, distribution and drug resistance
  - Inhibition of efflux transporters could be useful for patients who expressed drug resistance phenotype

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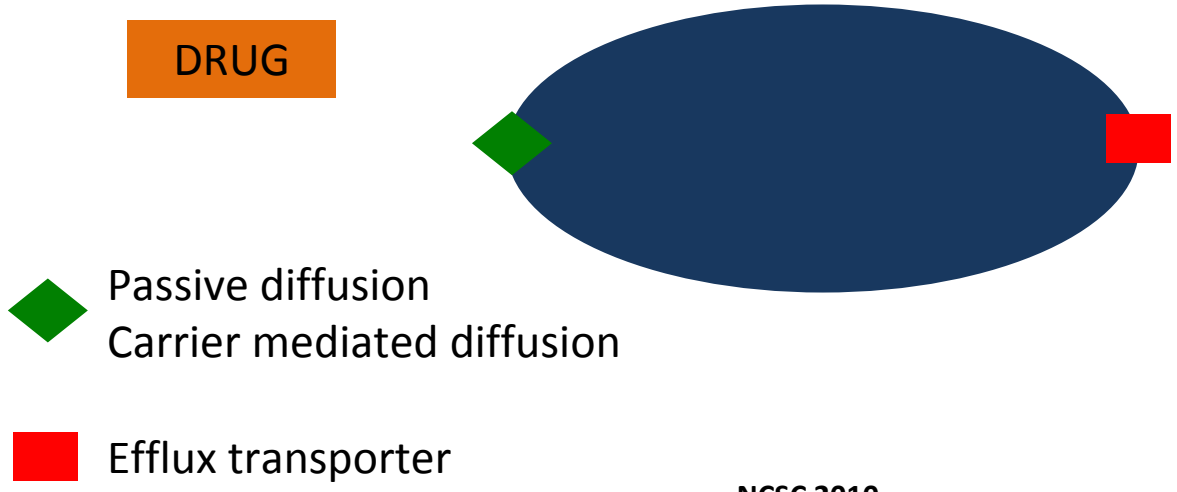

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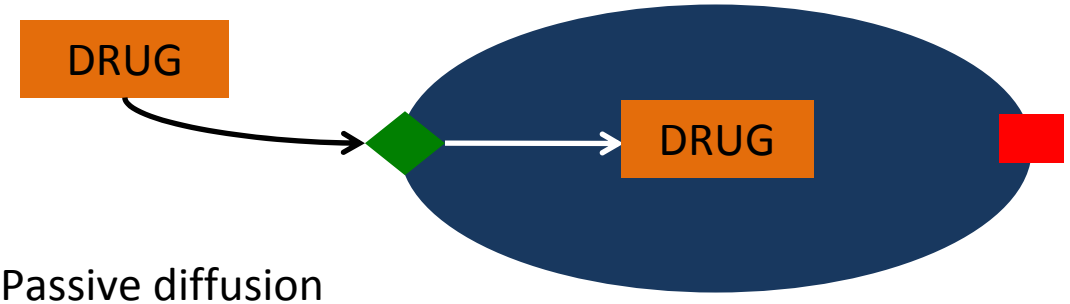

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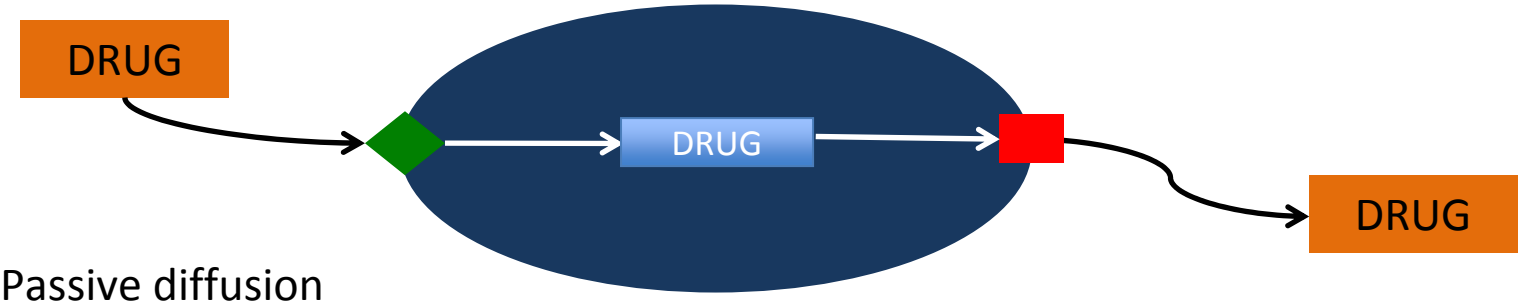

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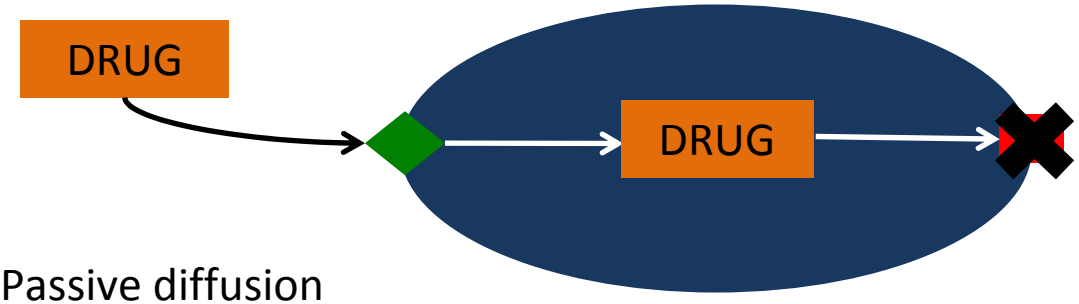

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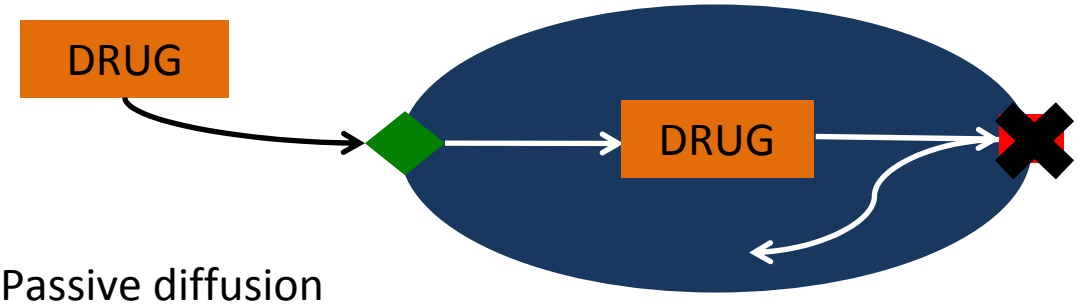

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Clinical Issue
ABCG2-BCRP

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  - Efflux transporter discovered recently
  - Important transporter that effluxes a wide range of substrates (Mitoxantrone, Irinotecan, SN-38)

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Development of new BCRP inhibitor
Non toxic and more specific

- One acridone (A. BOUMENDJEL): as potent *in vitro* as Gefitinib[1]
  - Able to inhibit BCRP mediated efflux (Mitoxantrone, Irinotecan)
  - With the advantage of not inhibiting other efflux transporters
  - Proof of concept in mice

1. Boumendjel A *et al.* BioOrg Med Chem 2007

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MBLI-87

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Aims

Optimizing a dose finding study

Optimizing the therapeutic regimen and effects of Irinotecan+MBLI-87 combination in mice

- **Model Building**
  Based on animal data, develop a non linear mixed effects model for Irinotecan+MBLI-87 effects on tumour growth in ABCG2 resistant xenografts
- **Simulation Study**
  Based on previous model, develop a simulation analysis in order to select the best therapeutic regimen

Animals

Proof of Concept Study Design

- Therapeutic regimen:
  - 1 cycle over 4 weeks: 2 weeks on + 2 weeks off
  - Mice received 2 chemotherapy cycles over 8 weeks

Arms	N	Dose
Control + Vehicle	18	-
Irinotecan	9	30 $mg.kg^{-1}$
Gefitinib	6	75 $mg.kg^{-1}$
MBLI-87	6	2.4 $mg.kg^{-1}$
Irinotecan+Gefitinib	3	30 $mg.kg^{-1}$ / 75 $mg.kg^{-1}$
Irinotecan+MBLI-87	3	30 $mg.kg^{-1}$ / 2.4 $mg.kg^{-1}$
TOTAL	45	

Animals

Data

- 2 tumours implanted per mouse (right, left flank)
- 2 measures performed per tumour every 2nd day
- Dependent variable:
  Geometric mean of the 4 measures (L, w on each flank)

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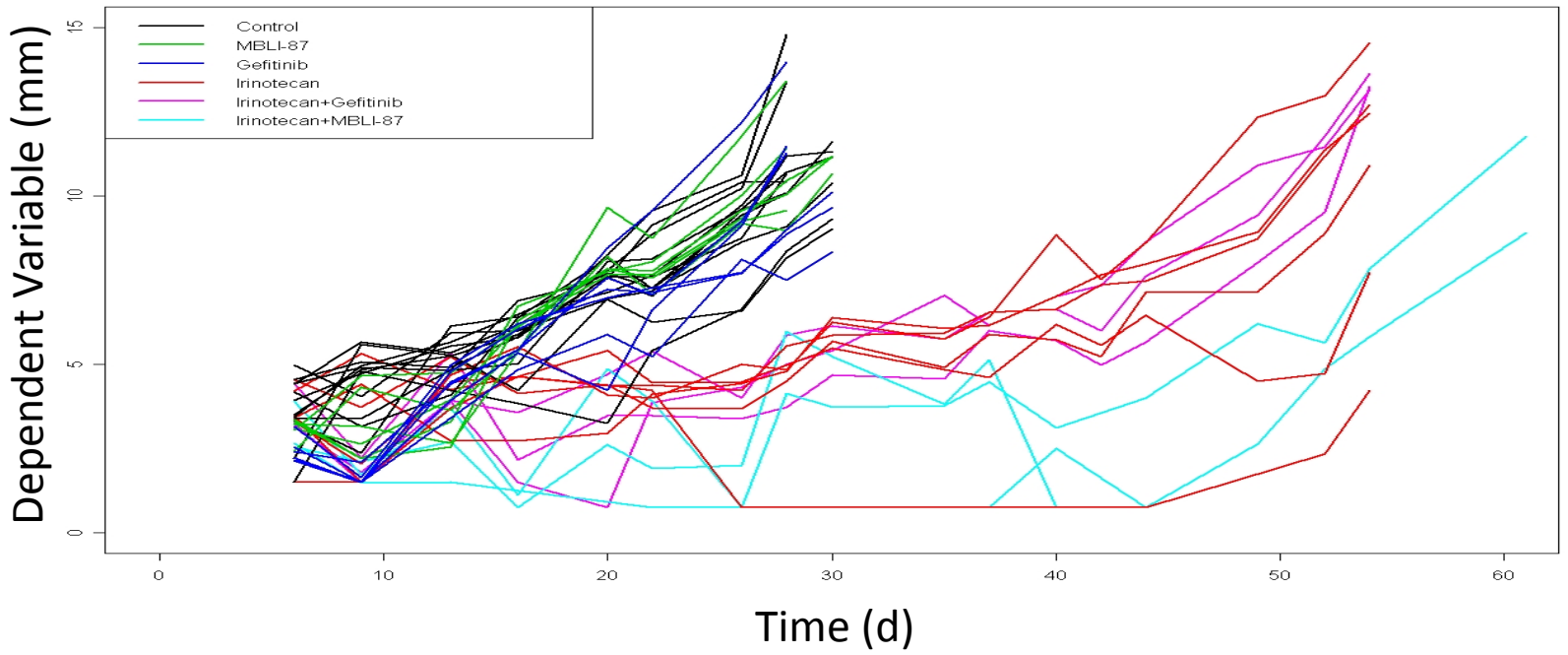

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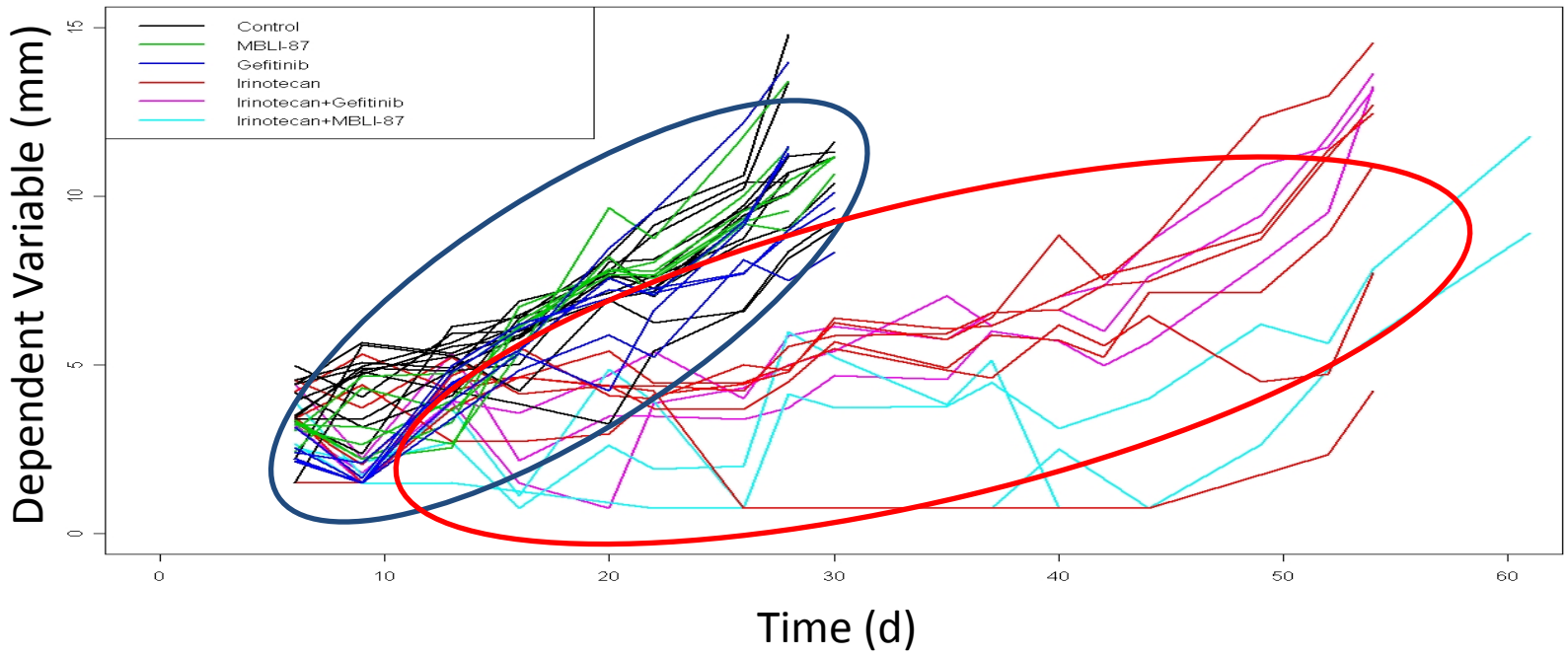

Model Building

Non linear mixed effects tumour growth inhibition models

- Tumour Growth Inhibition Models (*TGI*): Useful to evaluate oncology drugs in early development
  - Describing disease progression
  - Linking administration regimen to tumour growth dynamics
  - Allowing next steps development prediction

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- Non Linear Mixed Effects modelling (*NLME*):
  - Using information from the entire population to estimate model parameters
  - Mixed effects: fixed, random effects estimated in the model[2]

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$$P_i = \theta \times e^{\eta_i}$$

P_i: P individual value for the i^{th} individual
θ: fixed effect
η_i: random effect, $N(0,\omega^2)$

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$$y_{ij} = f(\theta_i, X_{ij}) \times e^{\varepsilon_{ij}}$$

y_{ij}: j^{th} observation for the i^{th} individual
f: prediction function for parameter P_i under X_{ij} condition
ε_{ij}: residual variability, $N(0,\sigma^2)$

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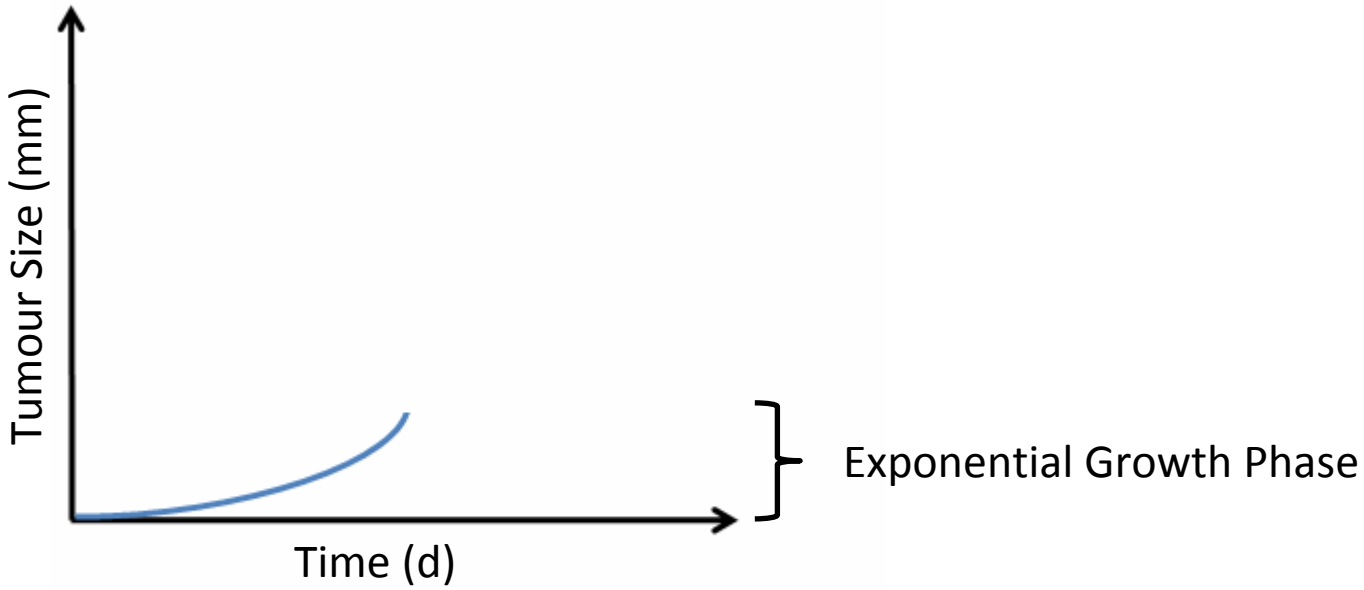
Model Building

"Unperturbed" Tumour Growth

- 2 different growth phases (Simeoni *et al.*)[3]:



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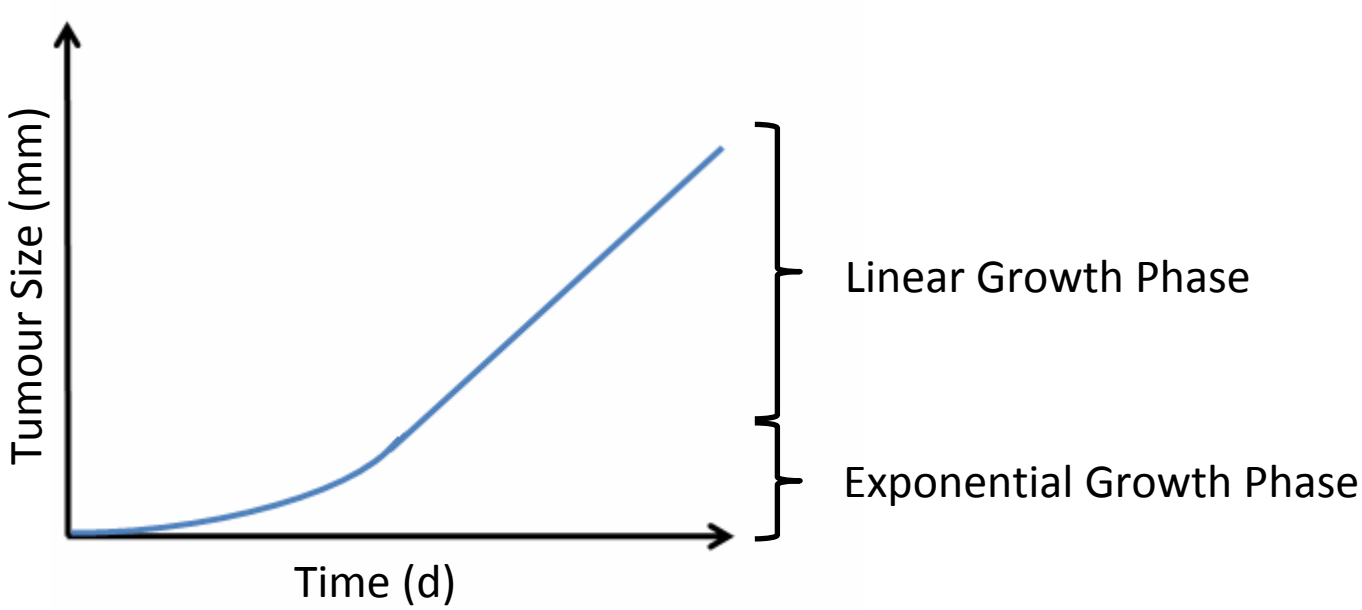

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λ_0: Exponential growth rate (d^{-1})

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Ψ: Switching parameter

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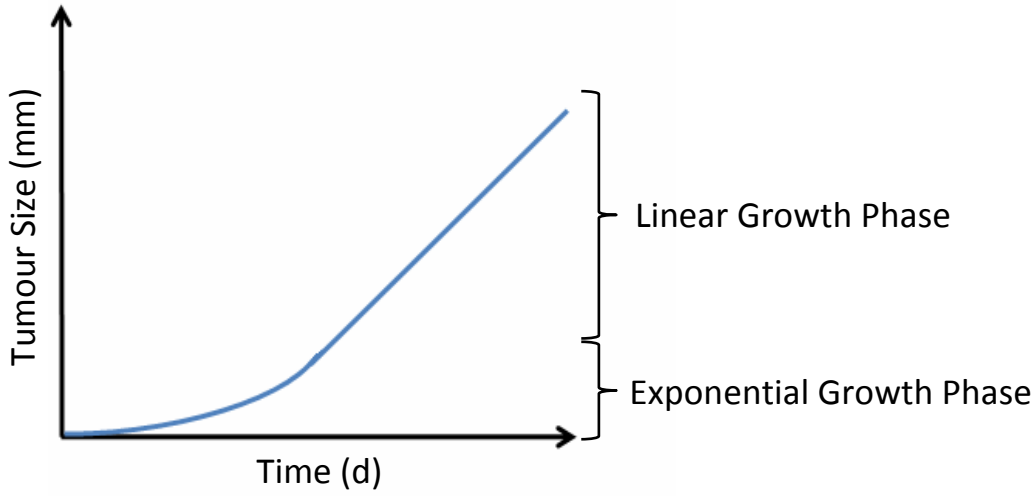

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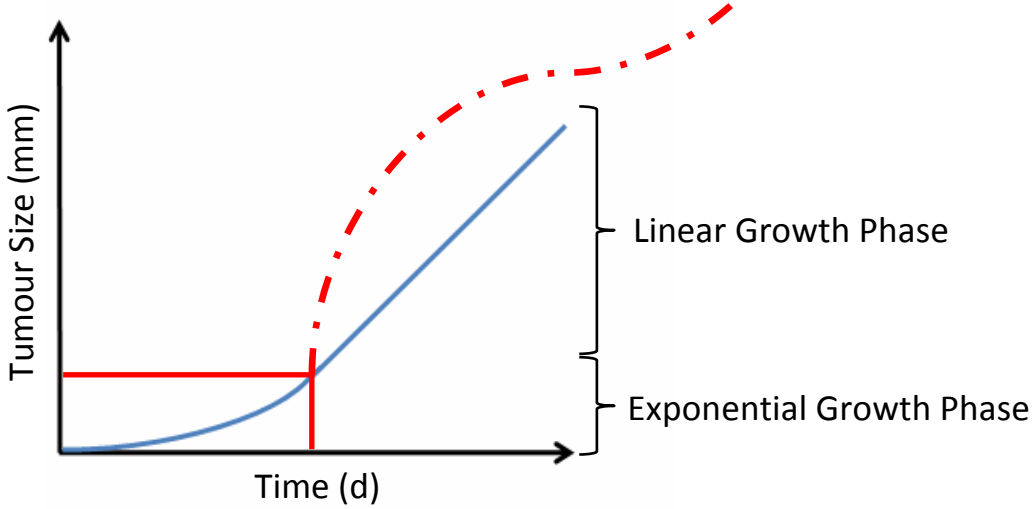

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NCSC 2010
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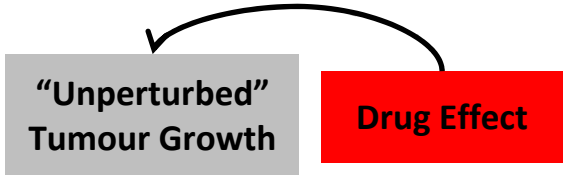
Model Building

"Perturbed" Tumour Growth

- Natural growth perturbed by drug effect
- Assumed that cell die directly after drug administration



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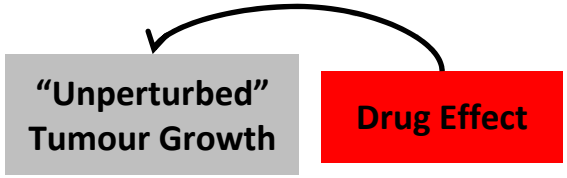
P_X: Potency of drug X ($mg^{-1}.d^{-1}$)
$A_{X,i}$: Amount of drug X (mg)



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Drug Accumulation Model

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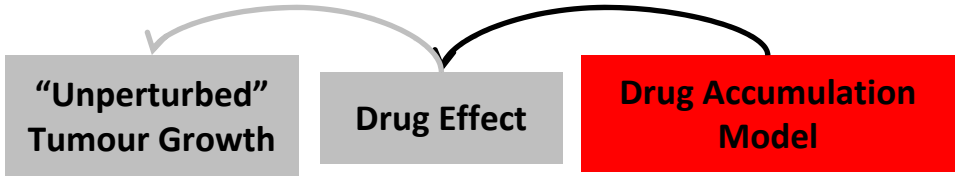

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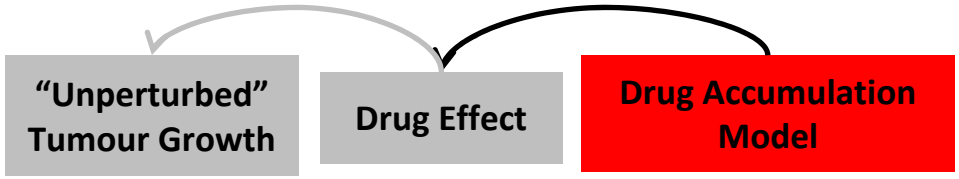

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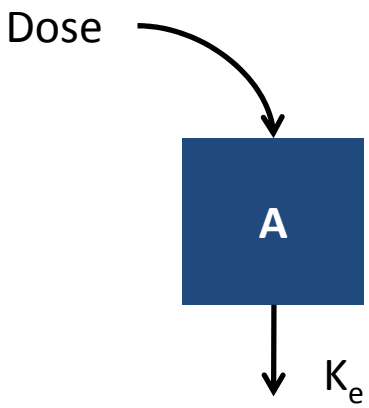

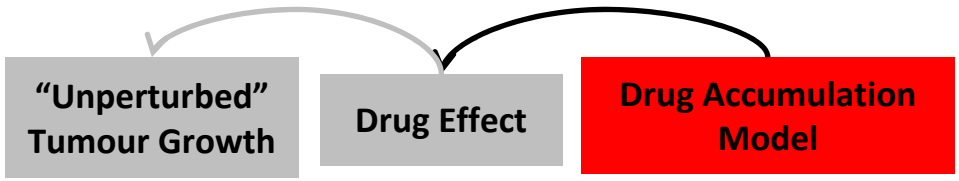

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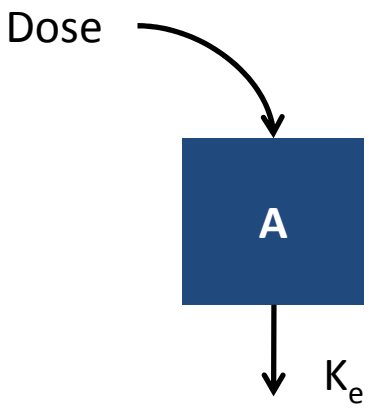
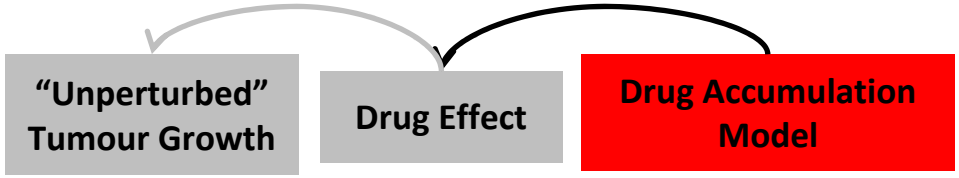


Amount of drug at time t: Latent variable

Estimation supported by tumour growth dynamics



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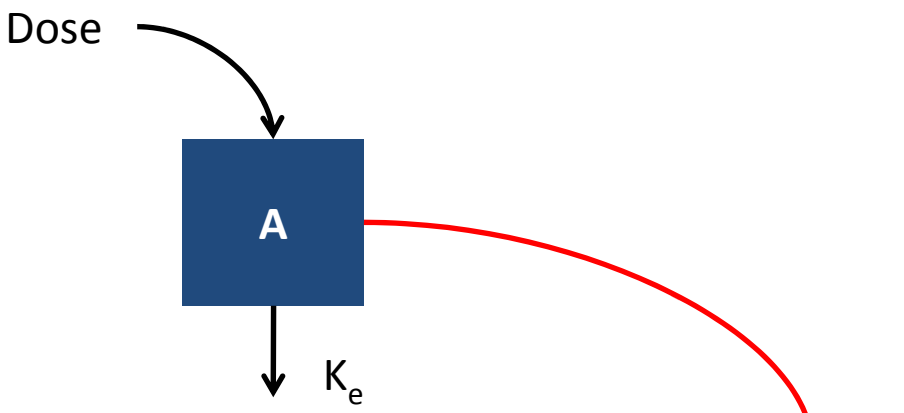

$$DR_{X,i}(t) = K_{e,X} \times A_{X,i}(t)$$

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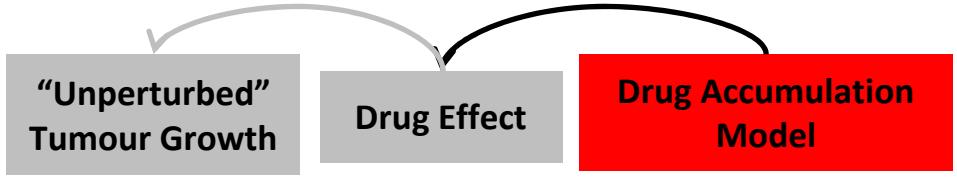

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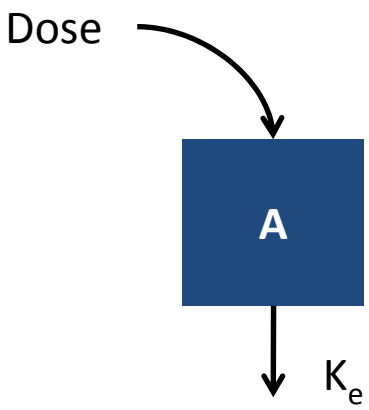

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"Unperturbed" Tumour Growth | **Drug Effect** | **Drug Accumulation Model**

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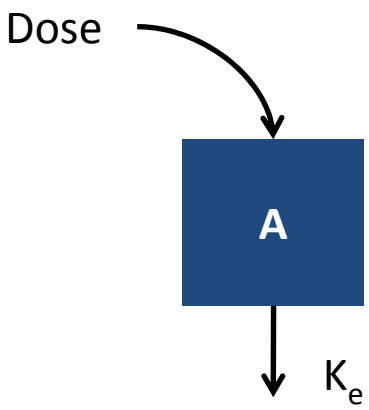

Drug effects directly dependent on drug amount in animals

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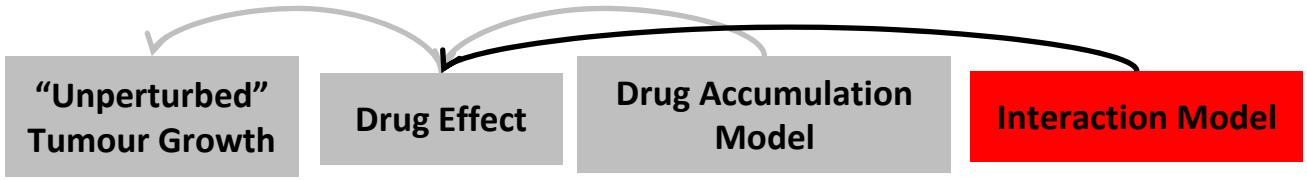
Interaction Model

- Assume that :
  - BCRP inhibitors have no cytotoxic effect when administered alone
  - BCRP inhibitors only modified Irinotecan potency



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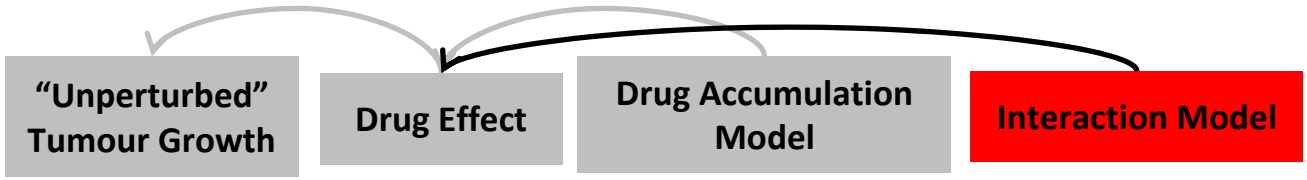
Irinotecan potency modified in presence of BCRP inhibitors ?



Model Building
Interaction Model

$P_{Irinotecan}$ decomposed into 2 terms:

$$P_{Irin|Inhib} = P_{Irin} + \beta_{Irin|Inhib} \times DR_{Inhib}(t)$$

$P_{Irinotecan}$: Irinotecan potency ($mg^{-1}.d^{-1}$)

$\beta_{Irinotecan|Inhibitors}$: Interaction parameter (mg^{-1})

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"Unperturbed" Tumour Growth | **Drug Effect** | **Drug Accumulation Model** | **Interaction Model**

Model Building
Summary

In case on single drug administration:

$$\frac{dA_{X,i}}{dt} = -K_{e,X} \times A_{X,i}(t)$$

$$DR_{X,i} = K_{e,X} \times A_{X,i}(t)$$

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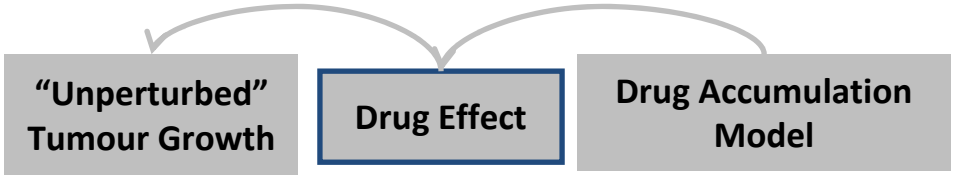
K-PD component



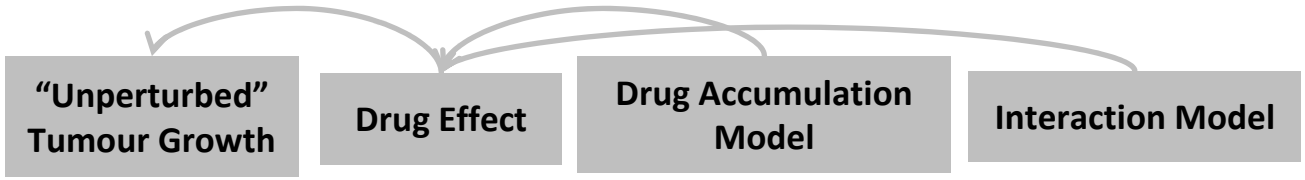
Model Building
Summary

In case of co-administration:

$$\frac{dA_{X,i}}{dt} = -K_{e,X} \times A_{X,i}(t)$$

$$DR_{X,i} = K_{e,X} \times A_{X,i}(t)$$

$$\frac{d\phi_{tumour,i}}{dt} = \frac{\lambda_{0,i} \times \phi_{tumour,i}(t)}{\left(1 + \left(\frac{\lambda_{0,i}}{\lambda_{1,i}} \times \phi_{tumour,i}(t)\right)^{\psi}\right)^{\frac{1}{\psi}}} - \left(P_{Irin} + \beta_{Irin|Inhib} \times DR_{Inhib,i}\right) \times DR_{Irin,i} \times \phi_{tumour,i}(t)$$



Model Building
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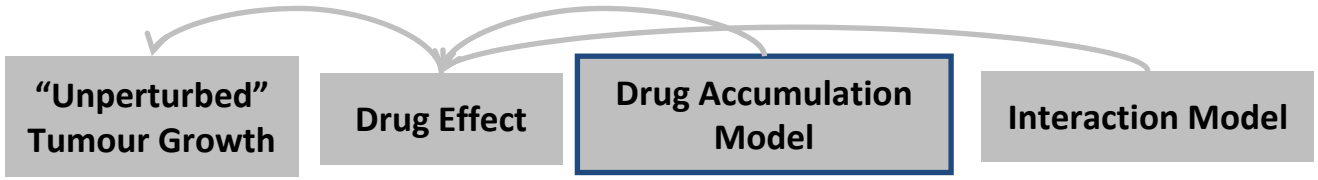
K-PD components



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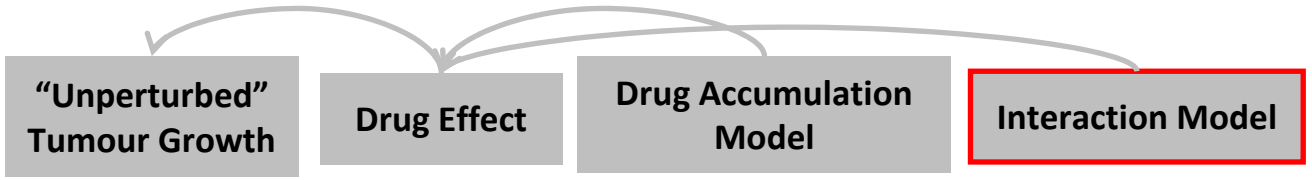
K-PD components

Interaction component

K-PD Tumour Growth Inhibition Model including Interaction Component



Model Building

Parameter Estimates

- Outline
- Issue
- Aims
- Animals
- Model Building
- MBD
- Discussion

Model Building

Parameter Estimates

Parameters	Value
λ_0 (d^{-1})	0.06
λ_1 ($mm.d^{-1}$)	0.2
$P_{Irinotecan}$ ($mg^{-1}.d^{-1}$)	0.3
$P_{Inhibitors}$ ($mg^{-1}.d^{-1}$)	10^{-2}

Values conform to values reported by Simeoni *et al.*

Inhibitors alone have no effect on tumour growth ($p>0.05$)

Interaction Parameter	Value
$\beta_{Irinotecan\|Gefitinib}$ (mg^{-1})	10^{-2}
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Model Building

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Interaction stronger with MBLI-87

Model Building

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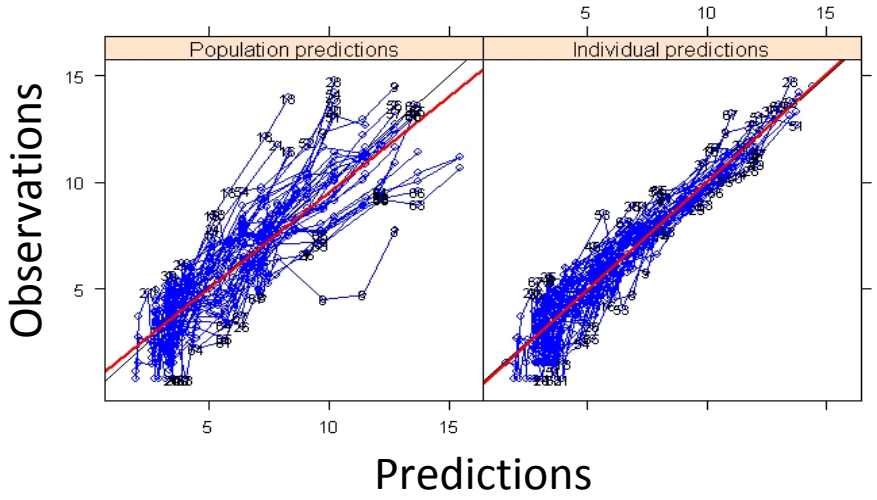
Interaction stronger with MBLI-87

MBLI-87 able to revert Irinotecan resistance at a 20-fold lower dose compared to Gefitinib

Model Building
Model Evaluation

- Goodness of fit plots:



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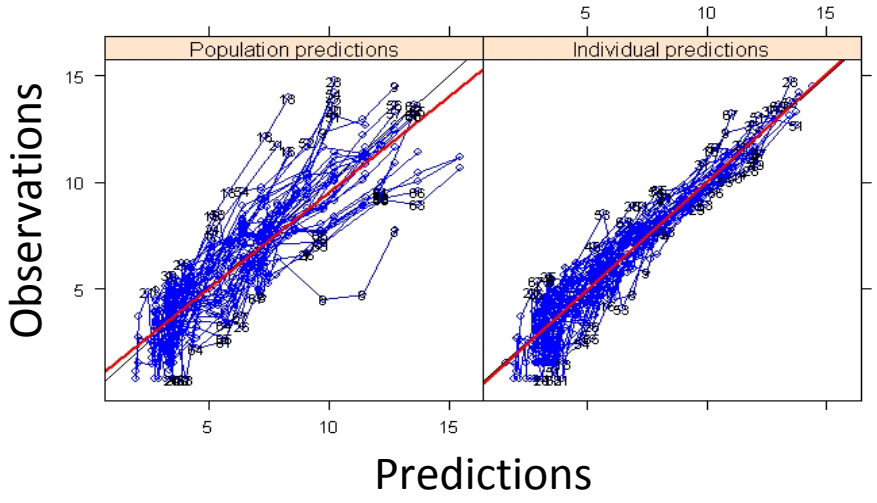
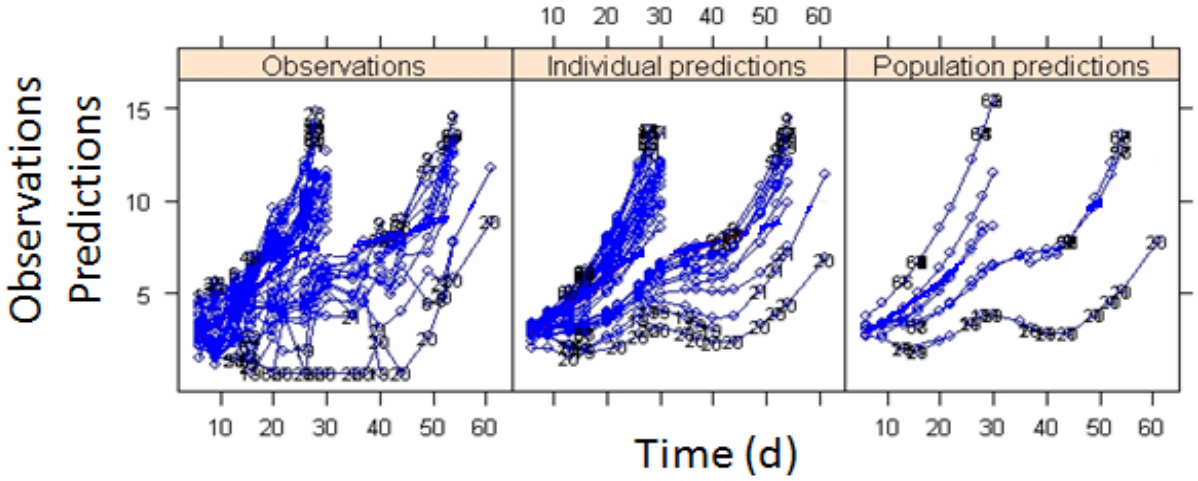
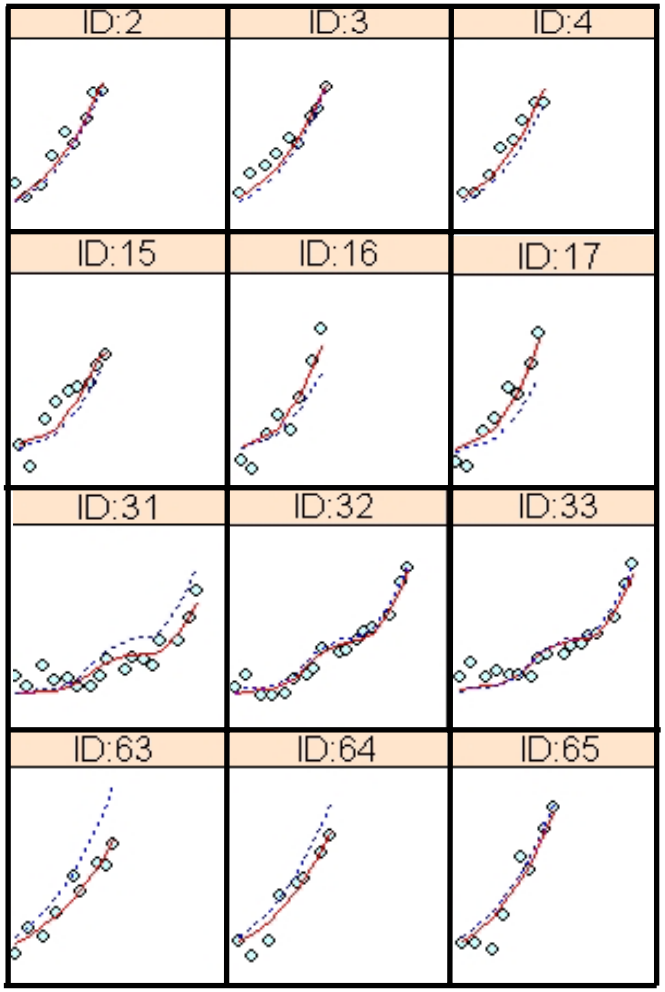




Model Building

Model Evaluation

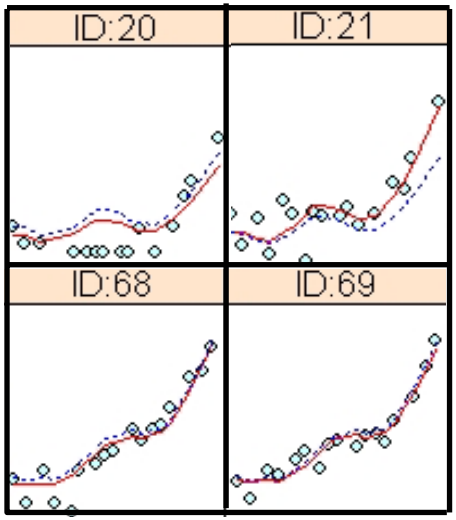


Control

Gefitinib

Irinotecan

MBLI-87

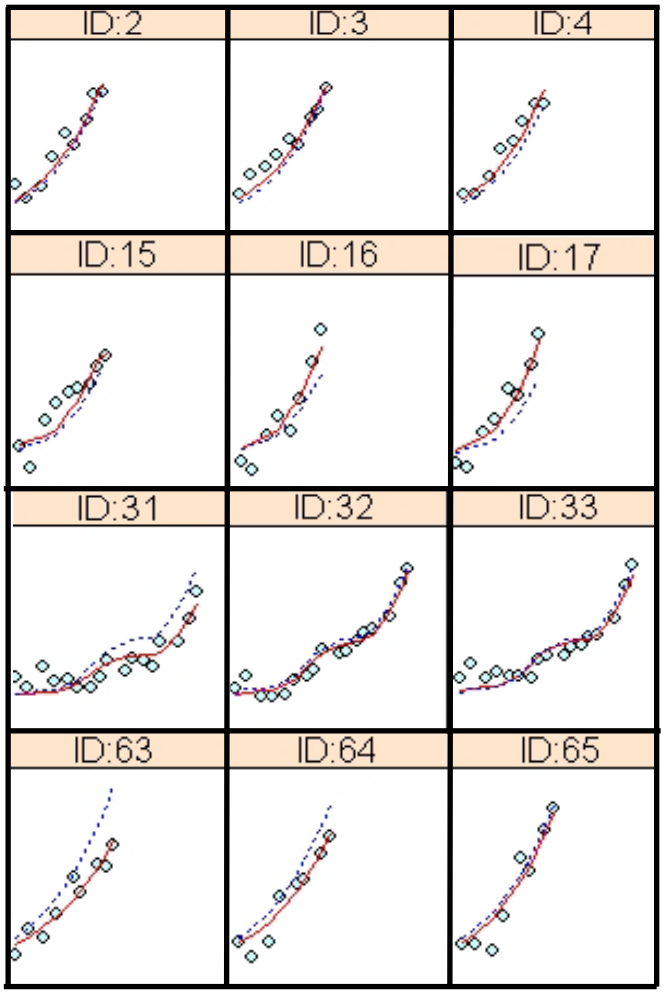


Gefitinib + Irinotecan

MBLI-87+ Irinotecan

Model Building

Model Evaluation

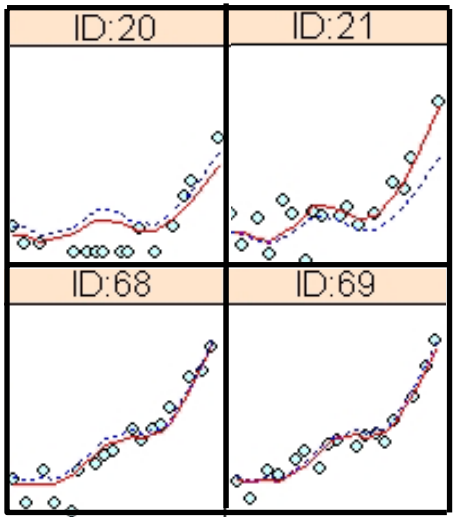


Control

Gefitinib

Irinotecan

MBLI-87



Gefitinib + Irinotecan

MBLI-87+ Irinotecan

Model fits quite well data in all groups

Model Building

Model Evaluation-Predictive Properties

- Visual Predictive Check:
  - Simulations of tumour growth profiles based on parameter estimates and model structure
  - Comparison of observed median and simulated median given the model

Model Building

Predictive Properties

- Outline
- Issue
- Aims
- Animals
- Model Building
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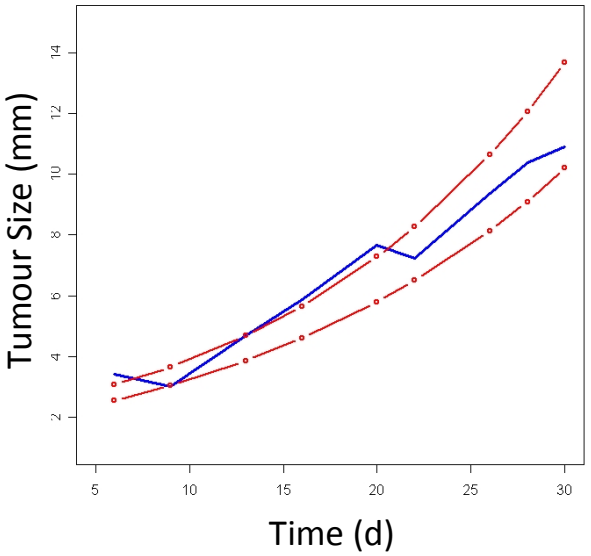
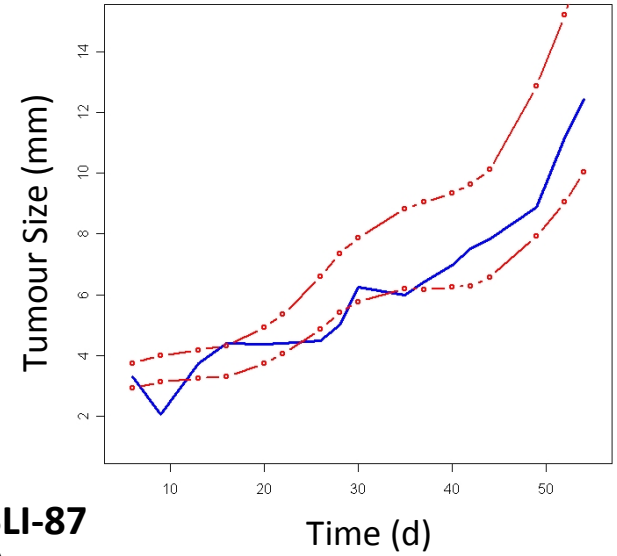
- Discussion
- Perspectives

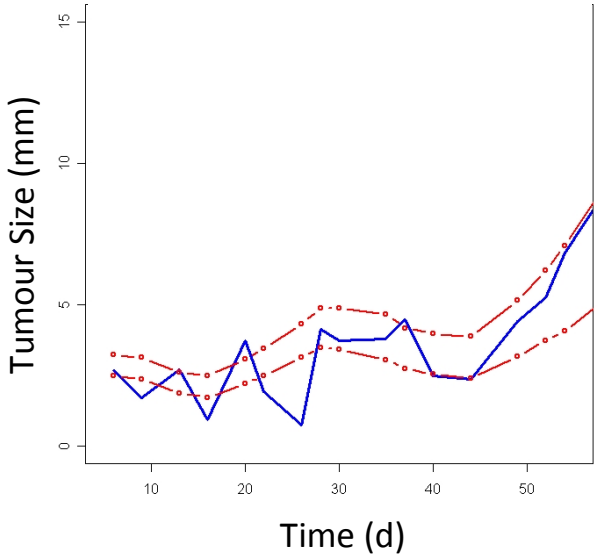
VCP: Control
(Based on 18 animals)



VCP: Irinotecan
(Based on 9 animals)



VCP: Irinotecan+MBLI-87
(Based on 3 animals)



- Observed Median
- 90% non parametric confidence interval

NCSC 2010
Alexandre SOSTELLY

Model Based Development
Objectives and Methods

- **Objectives**:
  - Optimizing Irinotecan/MBLI-87 combination schedule
  - Explore the impact of:
    - ✓ Doses
    - ✓ Administration schedules
    - ✓ Treatment duration

Model Based Development
Objectives and Methods

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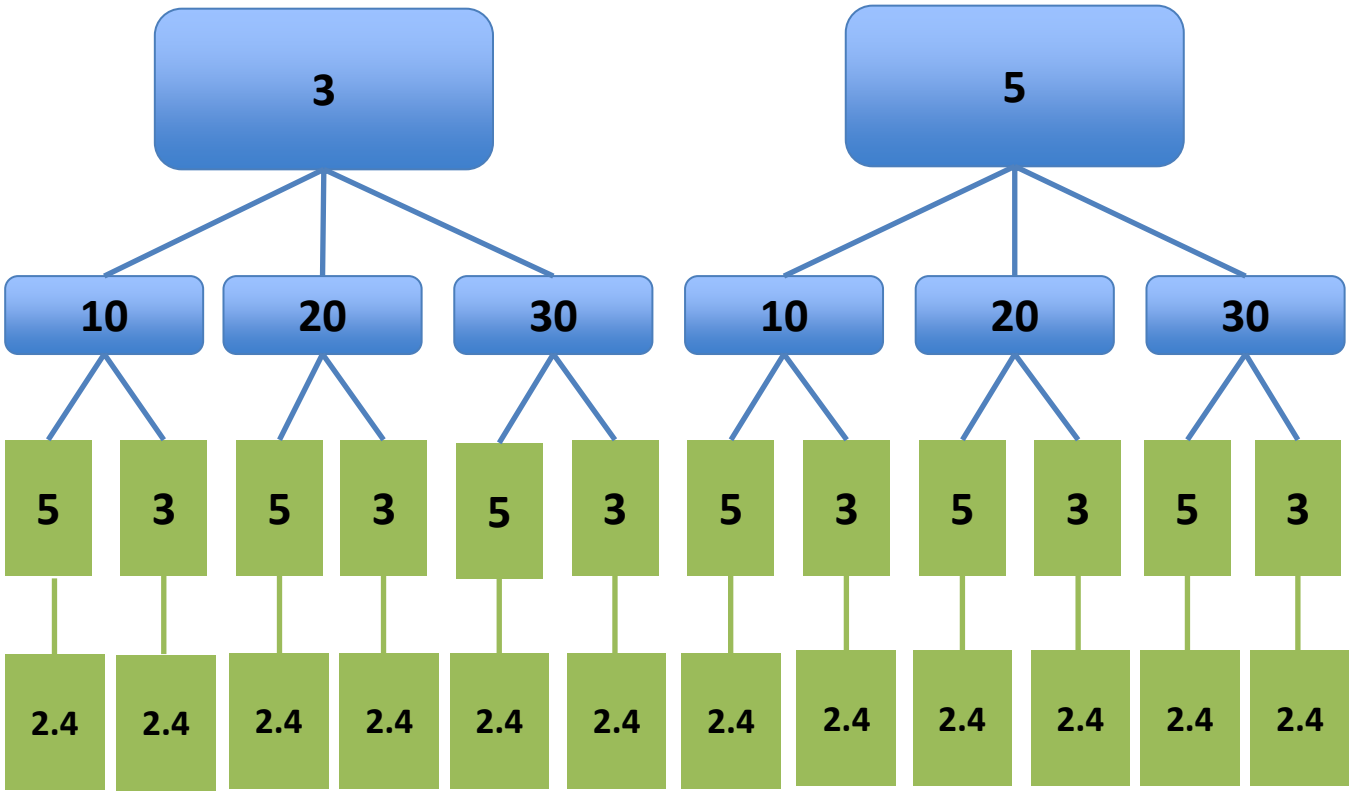
- **Methods:**
  - Simulation of 1000 virtual animals on the model structure and parameter estimates basis (Monte Carlo simulations)
  - Taking into account experimental constraints (drug formulation, animals care, ethics, …)

Model Based Development

Irinotecan Schedule



Model Based Development

Example

- Influence of Irinotecan schedule on tumour growth

Model Based Development

Example

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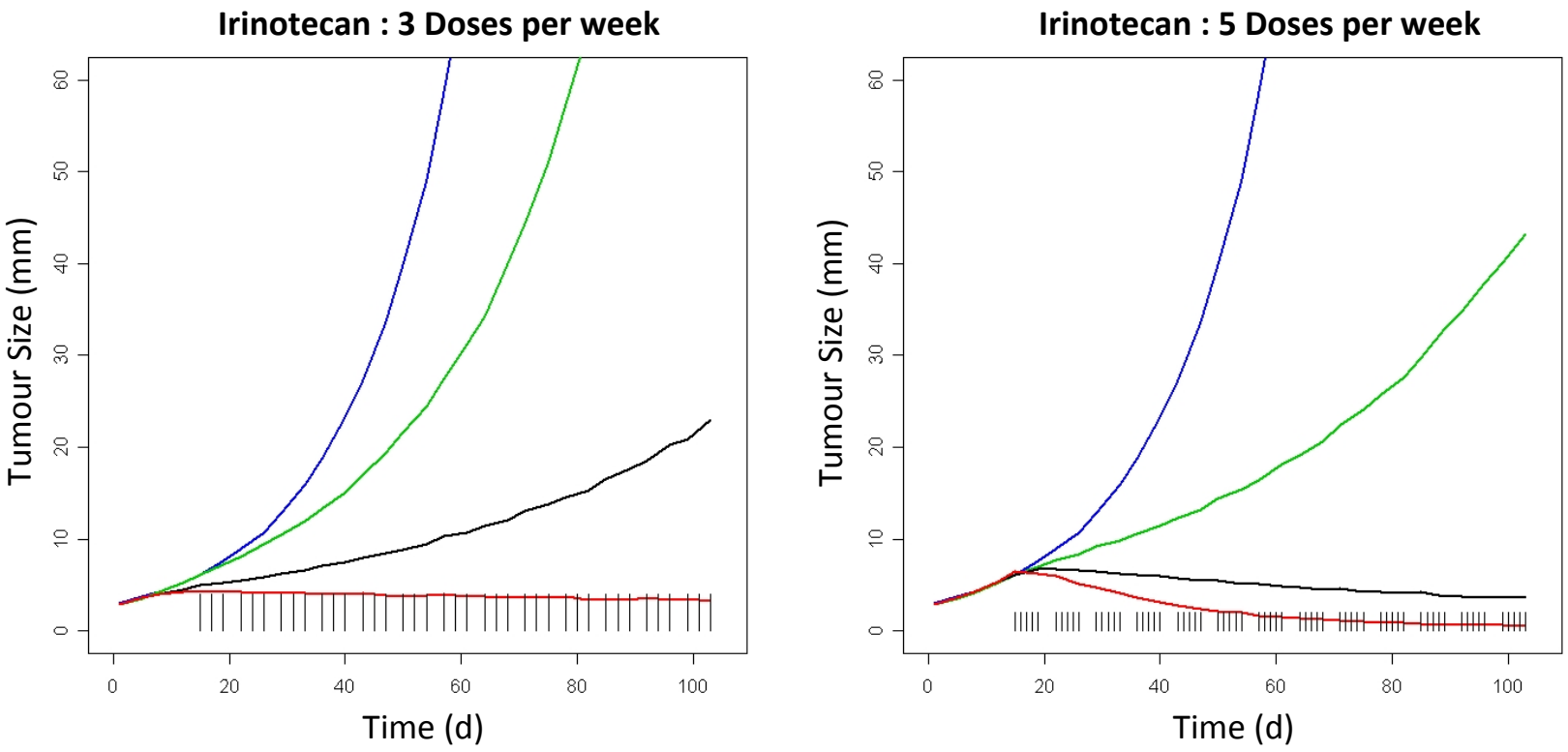
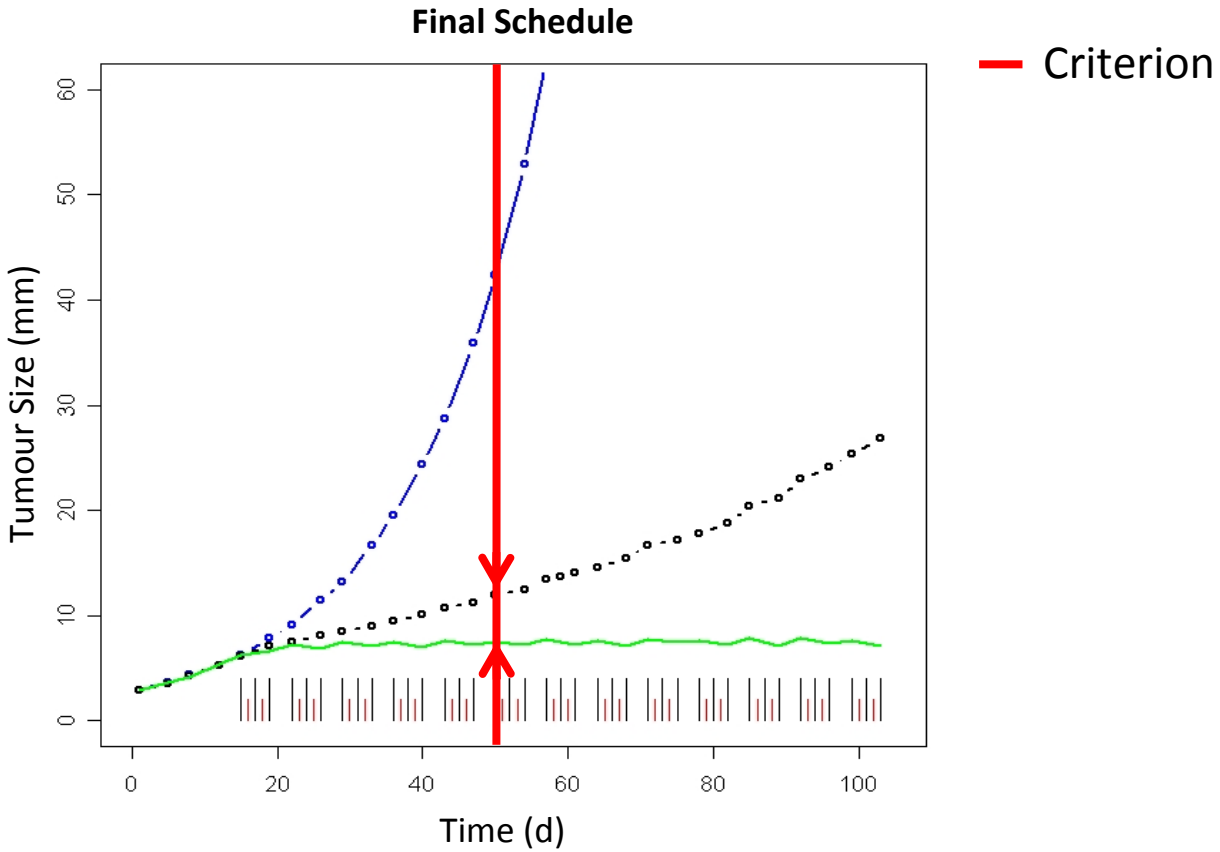


Model Based Development

Final Schedule



Control (median value)

Irinotecan 20 $mg.kg^{-1}$ + MBLI-87 2.4 $mg.kg^{-1}$ (median value)

Irinotecan 20 $mg.kg^{-1}$ (median value)

Irinotecan: 20 $mg.kg^{-1}$, 3 times per week

MBLI-87: 2.4 $mg.kg^{-1}$, 5 times per week

- Outline
- Question
- Aims
- Animals
- Model Building
- MBD
- Discussion

Synthesis and Discussion

- Development of a non linear mixed effects tumour growth inhibition model:
  - Based on Simeoni *et al.* model with some modifications
  - No PK data: K-PD approach (PK: latent variable)
  - Drugs co-administered: Drug-drug interaction parameter

- Parameter Estimates:
  - **Synergistic effect between MBLI-87 and Irinotecan**
- Adequate predictive properties

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- Parameter Estimates:
  - **Synergistic effect between MBLI-87 and Irinotecan**
- Adequate predictive properties

- Definition of new therapeutic regimens with biologists
- Simulation study:
  - Choosing the best therapeutic regimen

Synthesis and Discussion

- Small number of individuals and poor design of this 1st study:
  - Fisher Information Matrix unobtainable: no standard error
  - Only simulation based diagnostics

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  - Fisher Information Matrix unobtainable: no standard error
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BUT, this model is useful to take decision for the next development step

- A new dose finding study, based on simulation results, is ongoing:
  - PK analysis
  - Number of subjects increased

Confirmation of these 1st results ?

Thanks to

- Michel TOD, my supervisor
- Brigitte TRANCHAND, for valuable discussions

- Colleagues from Lyon and Uppsala

- Organization Committee

You, for your attention