A fully integrated PK/IVTI/IVE model in mouse to help design the FHD trial for a cell cycle inhibitor X

Damien Cronier, PhD[1]; Lawrence Gelbert, PhD[2]; Graham Wishart, PhD[3]; Alfonso De Dios, PhD[2]

1, Global PK/PD/TS department, Eli Lilly and Company, Windlesham, Surrey, UK; 2, Division of Cancer Research, Eli Lilly and Company, Indianapolis, USA; 2, ADME department, Eli Lilly and Company, Windlesham, Surrey, UK; 5,

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OBJECTIVES

The primary objective of this modelling study was to describe the effect of compound X on the cell cycle of cancer cells by means of a multi-biomarker approach allowing full monitoring of the cell cycle kinetics.

The secondary objective of this study was to estimate a pharmacologically effective dose range for compound X in human, in preparation of the FHD study.

METHODS

The mouse PK model was developed using both oral and IV data from 9 studies over a total dose range of to 1 to 100 mpk. This PK model is a two-compartment model with a Michaelis-Menten elimination process (Fig. 1).

The mouse PK/IVTI model was developed using mouse Colo-205 xenograft data. *In vivo* target inhibition (IVTI) data was collected using 3 different biomarkers accounting for 3 different phases of the cell cycle (Fig. 1). These were used in a IVTI model made up of 4 transit compartment (1,2) accounting for the 4 different phases of the cell cycle. Cells were assumed to transit from one phase to the other by means of a first order process described by the first order rate constant k_{tr}. A zero order input of cells into the first compartment was assumed, as is described by the rate constant k_0. Finally, a first order elimination rate constant k_{EL} was added to this first compartment in order to account for the limited accumulation of cells. The cell cycle inhibitory activity of compound X was described by means of an indirect response (3) inhibiting cell cycle transition (Fig. 1).

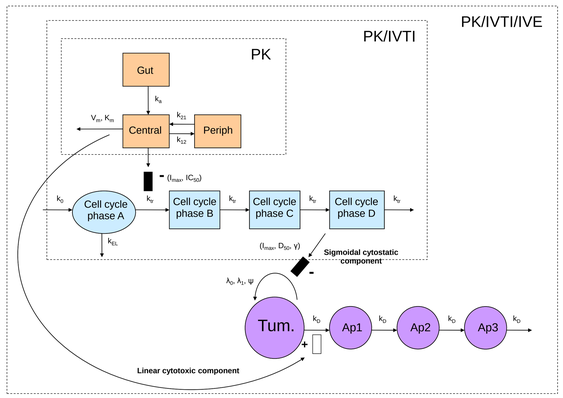


Fig. 1: schematic of the fully integrated PK/IVTI/IVE model

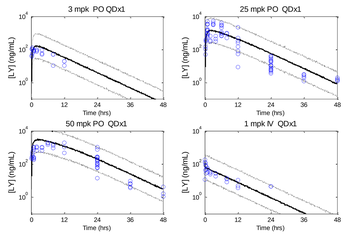
The level of *in vivo* efficacy (IVE) in Colo-205 was described by means of a fully integrated PK/IVTI/IVE model connecting the PK/IVTI model described above to a model describing the kinetics of tumour growth. The latter consists of a modified Gompertz model (Fig 1) using the following parameters: TS0, tumour size at the start of the experiment; Kgw1, exponential growth rate constant controlling cell proliferation; Kgw2, linear rate constant controlling cell proliferation; KD, rate constant controlling cell death (4). The effect of IVTI on the rate of tumour growth was accounted for by means of a sigmoidal cytostatic component driven by the value of biomarker D as well as a linear cytotoxic component directly related to the plasma concentration of X.

The projected human PK parameters were obtained by means of allometric scaling based on IV PK data from mouse, rat and dog. The method assumed the same structural model for all species, i.e. a two-compartment model has been selected.

RESULTS

PK model

The PK of X in the mouse were best-described by a two-compartment model with a non linear disposition following a Michaelis-Menten kinetics. The parameters were well estimated with reasonable precision, except for the bioavailability term, which was fixed to 1. As only one PK sample was drawn from each animal used in those studies, no inter-individual variability term was included in the model.



	Parameter	Estimate	SEE (%)
Absorption	ka (hr^{-1})	1.25	31.1
	lag (hr)	0.18	14.4
	F (%)	100	FIXED
Disposition	Vm (ug/hr/kg)	6710	6.6
	Km (ug/L)	2480	14.4
	V1 (L/kg)	7.16	36.2
	Q (L/hr/kg)	84.5	23.7
	V2 (L/kg)	7.91	34.1
Residual error (proportional)	σ2	1.07 (CV=103.4%)	10.1

Fig 2 and table 1: PK profile of compound X in the mouse and parameter estimates of the PK model

PK/IVTI model

The IVTI profile obtained from Colo-205-bearing nude mice was well fitted by the model with reasonable precision. As in the PK model, as only one data point was obtained from each animal, no inter-individual variability term was included in the model.

Table 2: PK/IVTI model parameter estimates for compound X in Colo-205 in mouse

	Parameter	Estimate	SEE (%)
Model parameters	K_0 (hr^{-1})	0.19	6.1
	k_{EL} (hr^{-1})	0.028	44.7
	Imax	0.94	2.1
	IC_{50} (ng/mL)	7.17	18.7
	γ	1	FIXED
Residual error (proportional)	σ^2_B	0.316 (CV=56.2%)	13.1
	σ^2_C	0.316 (CV=56.2%)	13.5
	σ^2_D	0.283 (CV=53.2%)	11.0

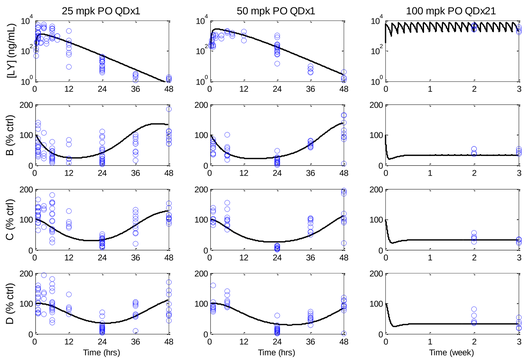


Fig. 3: time course of the 3 cell cycle biomarkers collected after oral administration of compound X at 25 and 50 mpk QDx21 and 100 mpk QDx21.

The model could successfully connect in a mechanistic manner the 3 biomarkers collected along the cell cycle in Colo-205 cancer cells. More specifically, it could account for the time shift observed for the peak of inhibition in the 3 compartment, thereby suggesting a block of the cell cycle associated with the emptying of several phases of the cell cycle following X administration.

Furthermore, the model could also account for the decrease in the level of IVTI observed after repeated dosing.

Finally, the model could reproduce the rebound effect observed post-dose, suggesting that the latter could be due to an *in vivo* synchronization of cancer cells, followed by a simultaneous release of the synchronised cells.

PK/IVTI/IVE model

The fully integrated PK/IVTI/IVE model could account for the dose-dependency of *in vivo* efficacy across a dose range of 25 to 100 mpk and over a dosing period of 21 days. Parameters were well estimated with reasonable precision.

In vivo efficacy was connected to the cell cycle biomarkers in a mechanistic manner. A cytostatic component was connected to biomarker D and a cytotoxic component was connected to X plasma concentration. Using this structural model, both the dose-dependency of *in vivo* efficacy and the sustained tumour growth arrest observed at higher doses could be accounted for.

Table 3: PK/IVTI/IVE model parameter estimates for compound X

	Parameter	Estimate	SEE (%)
Model parameters	λ_0 (day^{-1})	0.065	4.5
	λ_1 ($mg.day^{-1}$)	39.0	10.1
	Ψ	20	FIXED
	W_0 (mg)	50.4	3.3
	I_{max}	1	FIXED
	D_{50} (%)	35.1	1.3
	γ_2	27.9	23.5
	k_D (day^{-1})	1.69e-5	32.5
Inter-animal variability	$\omega^2_{\lambda 0}$	0.019 (CV=13.7%)	18.2
	$\omega^2_{\lambda 1}$	0.12 (CV=34.2%)	37.9
	ω^2_{KD}	1.55 (CV=124%)	47.4
Residual error (proportional)	σ^2	0.017 (CV=13.1%)	7.9

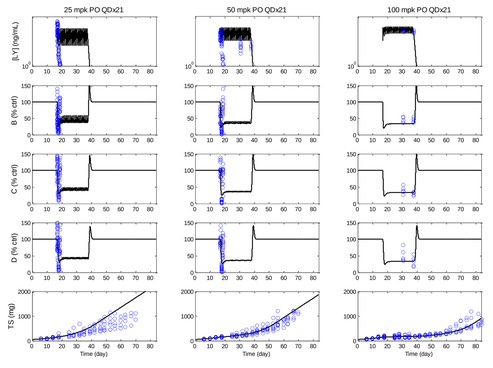


Fig. 4: time course of X PK, the 3 cell cycle biomarkers and tumour growth kinetics after repeated oral administration of compound X at 25, 50 and 100 mpk QDx21.

The model made it possible to correlate *in vivo* efficacy to a minimum level of 30 to 50% IVTI maintained throughout the whole treatment period. This IVTI threshold was subsequently applied in order to derive an efficacious dose range in human.

HUMAN DOSE PREDICITON

The IVTI model developed in mouse was connected to the projected human PK model obtained by allometric scaling. Using this projected PK/PD model, a dose range wass derived, that would maintain the level of IVTI between 30 and 50% throughout the whole treatment duration.

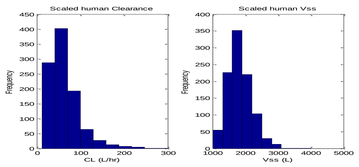


Fig. 5:projected human PK parameters of compound X

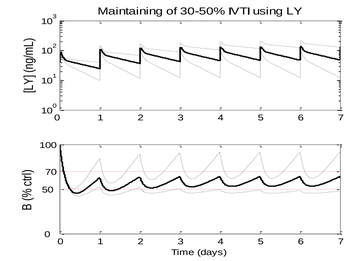


Fig. 5: projected human efficacious PK/PD profile, based on the maintaining of IVTI between 30 and 50%.

CONCLUSIONS

The PK/PD relationship of compound X in Colo-205 xenograft tumours was modelled by means of a fully integrated PK/IVTI/IVE model.

This model made it possible to understand the determinants of *in vivo* efficacy and correlate the latter to the maintaining of a minimum 30-50% IVTI throughout the whole treatment period.

Finally, the model was successfully applied to project an efficacious dose range in human to support the design of the FHD trial.

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