Non-Clinical and Translational Safety for Early Development of Oncology Compounds

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Quantitative Translational Approaches in Oncology

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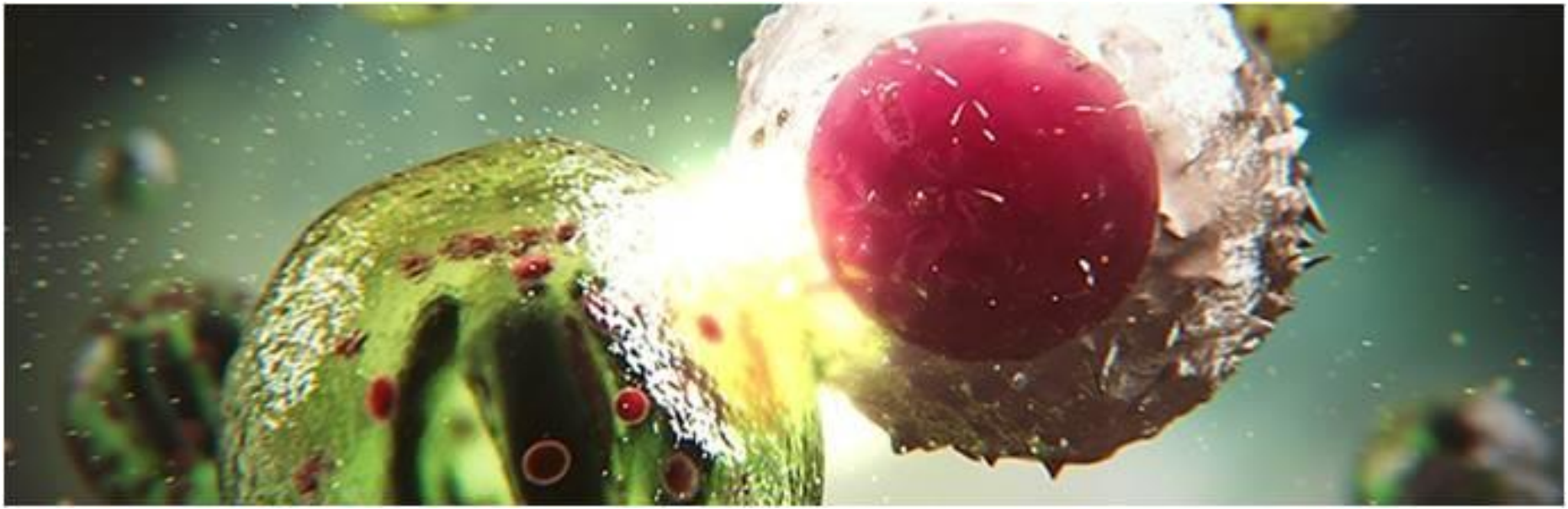
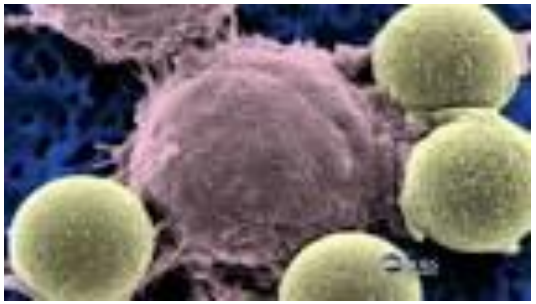


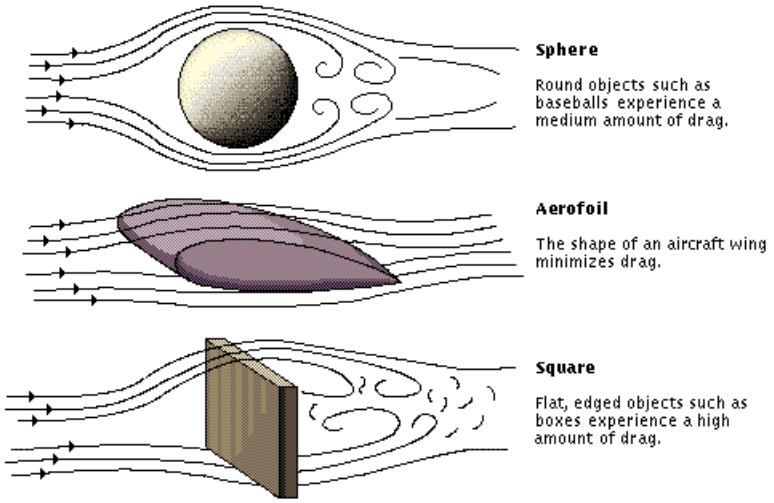
‘Oncology is different’



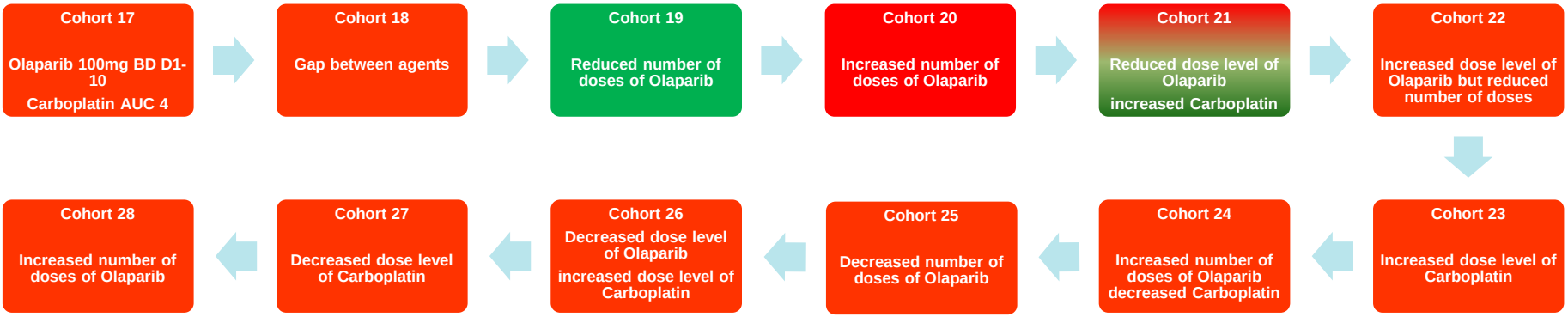
- Patients rather than healthy volunteers
- Heterogeneous population
- Poor prognosis, refractory disease, failed prior therapies
- Tolerance for side effects high
- Doses and duration of treatment are not limited by what was conducted pre-clinically
- Dosing to limit of tolerability (MTD)
- Dose limiting toxicities: nausea and vomiting, rash, fatigue, diarrhoea - understood and managed clinically

- Different perception of non-clinical safety in oncology given life-threatening nature of the disease

Development in Oncology: ‘efficacy’ and ‘tolerability’



Olaparib in combination with SoC



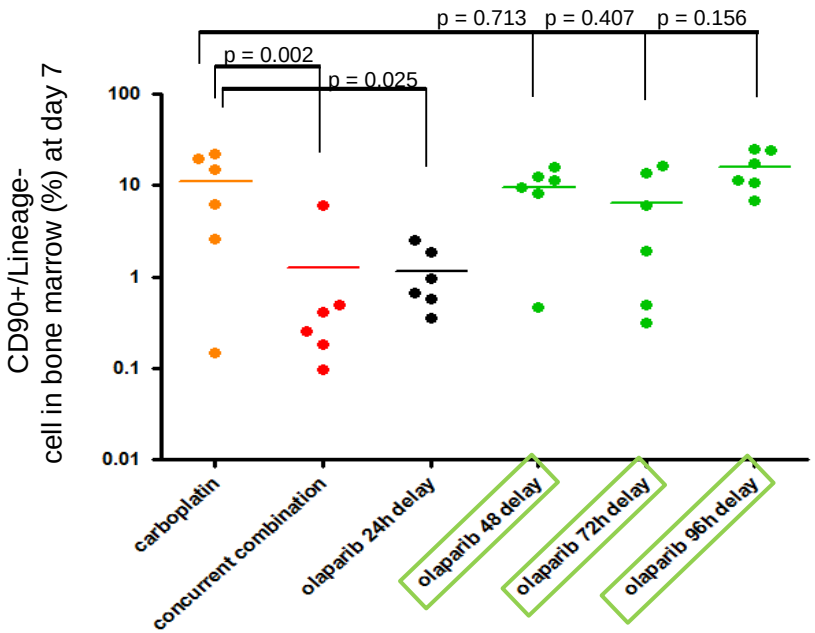
Preclinical data package: Standard monotherapy GLP (rodent and non-rodent)

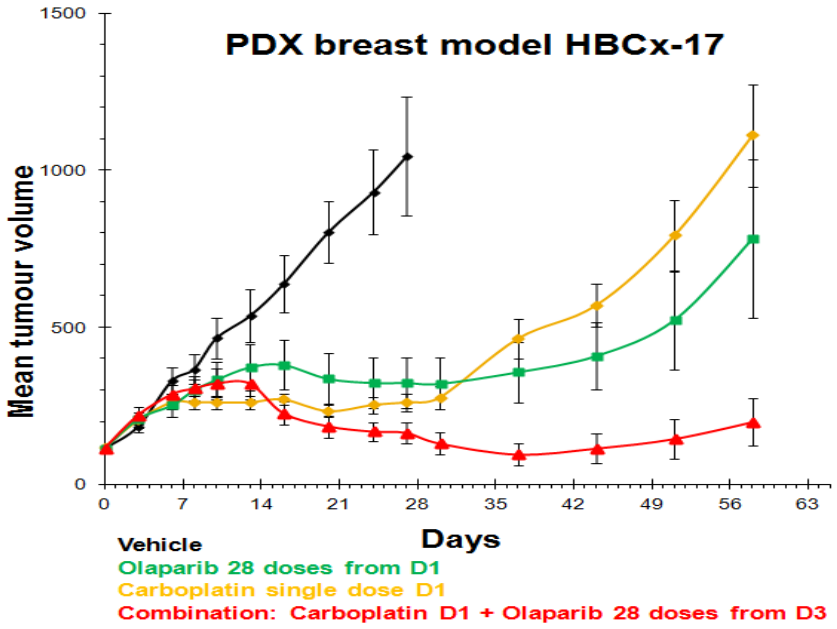
Initial Phase 1 trial: Study 96 – Olaparib given in combination on a backbone of Carboplatin +/- Paciltaxel. 28 cohorts; **198 patients**; 6 years; $14 million – tolerable schedule not determined

Opportunity: Exploit pre-clinical tools to better understand olaparib in combination-induced bone marrow toxicity to improve clinical outcome

Claire Sadler

Case Study 1: Olaparib in combination with SoC





- Used pre-clinical in vivo model (rat) to reproduce the clinical olaparib-carboplatin induced bone marrow toxicity
- Investigated mitigation strategies for bone marrow toxicity; assessed impact of schedules on efficacy
- Using PK/PD modelling to translate effects observed in rats to predictions for humans
- **This information gave confidence to the Olaparib team to re-instate the phase 1 adjuvant breast cancer clinical trial of Olaparib given in combination with Carboplatin.**

Claire Sadler

Preclinical Safety Input to Translational Decisions

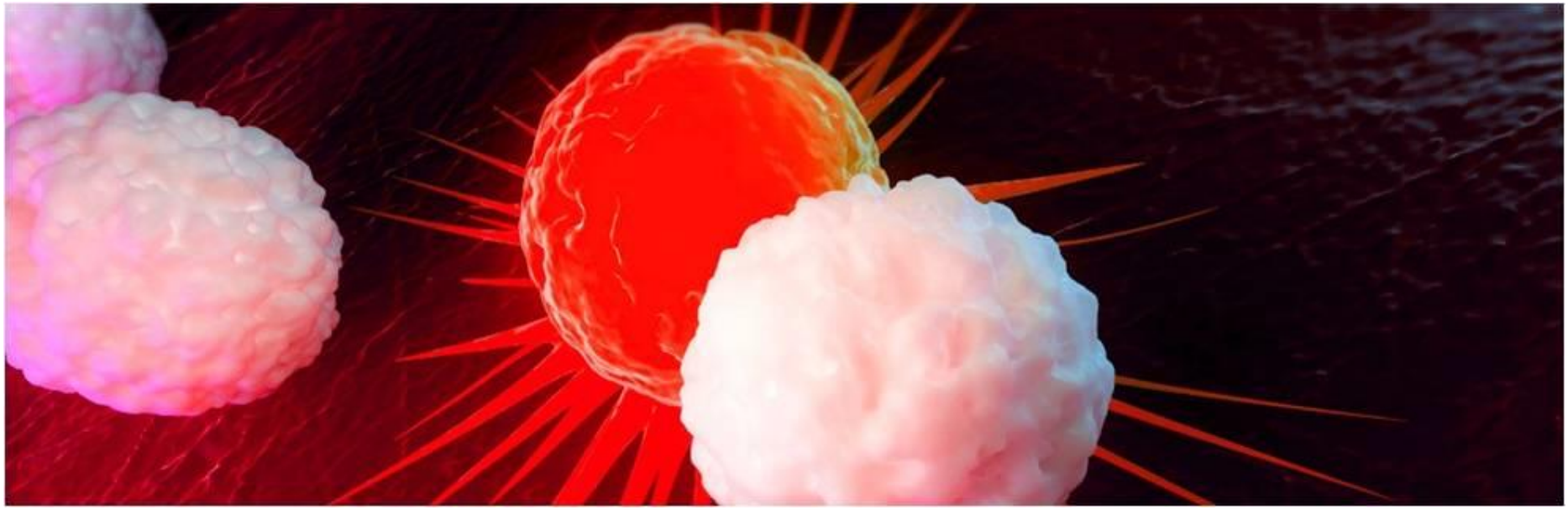
-Setting preclinical potency criteria (in vitro/in vivo)
-Compound selection (ranking safety)

-Hazard/risk assessment
-Select safe starting dose & Schedule

-Dose and Schedule Prioritization
-Combinations

Modelling can be applied to preclinical safety data across the pipeline
-Understanding of PK/PD relationships can be used to set potency criteria and select between compounds during discovery
-Identification of Therapeutic Index for in vivo findings to enable go/no-go to Candidate Selection / FTIM
-Safe Starting Dose Estimation (particularly important for combinations)

Bone marrow toxicity of a BRD4 inhibitor

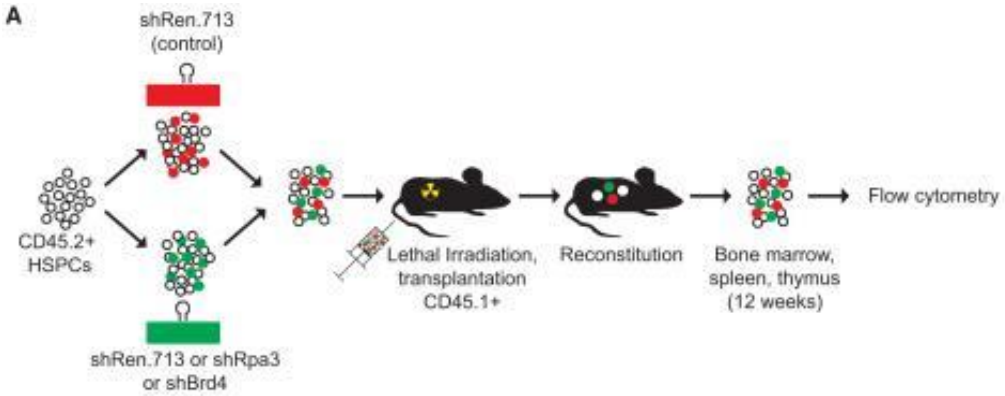


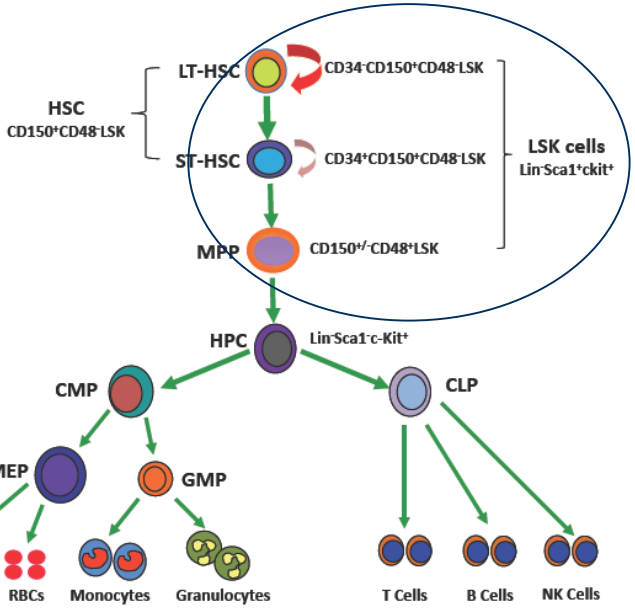
BRD4 knockdown affects bone marrow

Recent experimental data in rodent models demonstrates that Brd4 knockdown inhibits the bone marrow progenitor cells, i.e. LSK Cells (Lin-Sca1+cKit+)

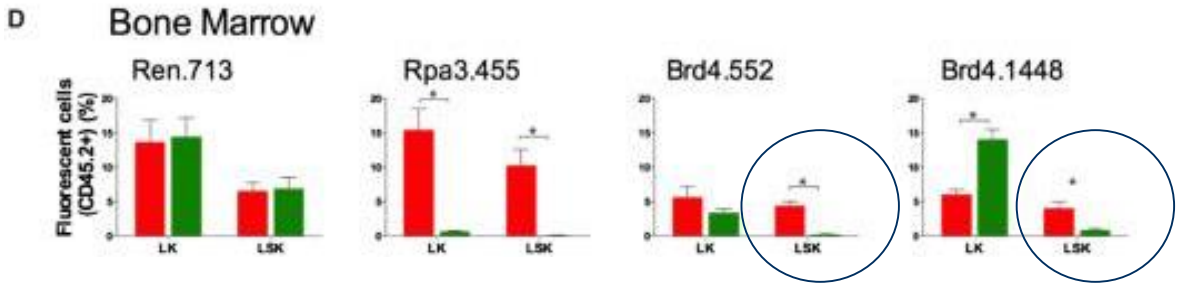
Inducible In Vivo Silencing of Brd4 Identifies Potential Toxicities of Sustained BET Protein Inhibition

Jessica E. Bolden,[1,8] Nilgun Tasdemir,[1,2,3,8] Lukas E. Dow,[1,8] Johan H. van Es,[4] John E. Wilkinson,[5] Zhen Zhao,[1] Hans Clevers,[4,6] and Scott W. Lowe[1,7,*]





doi: 10.3978/j.issn.2218-676X.2013.10.05



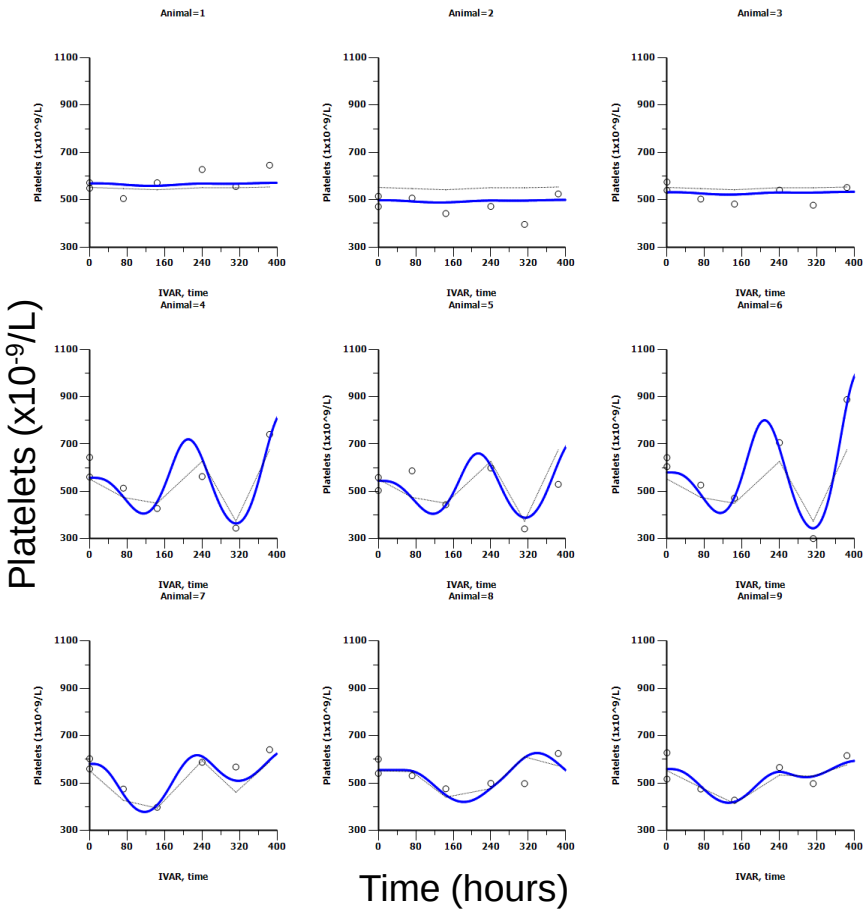
Modelling Platelet Dynamics in Rat

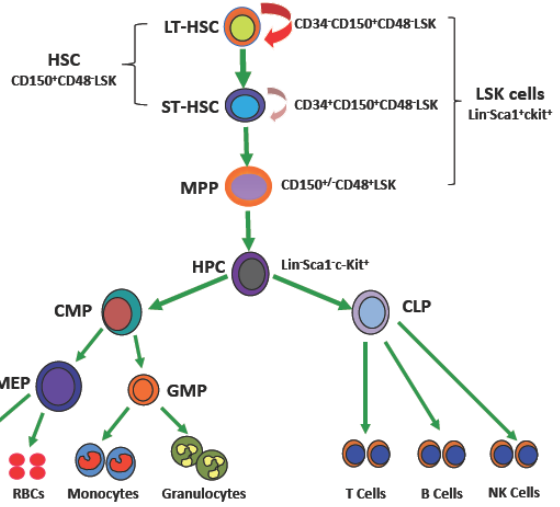
Individual and population fits to platelet data in the Rat.

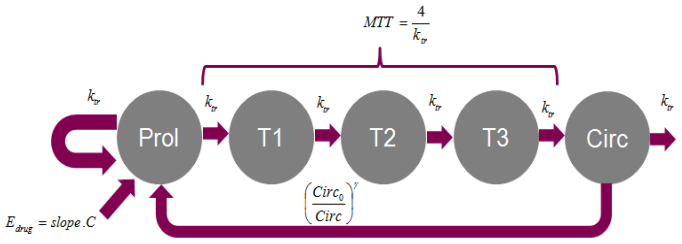
0.1 mg/kg QDx10

1 mg/kg BD (3 on, 4 off, 3 on)

1.5 mg/kg QDx10







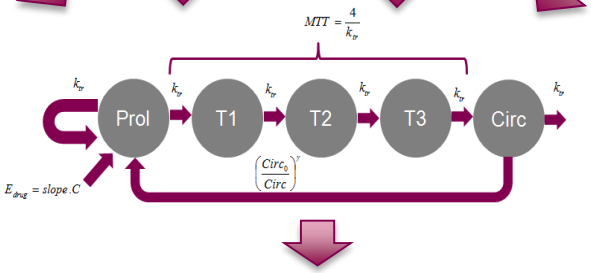
Human predictions at clinically relevant doses & schedules

Projected Human PK

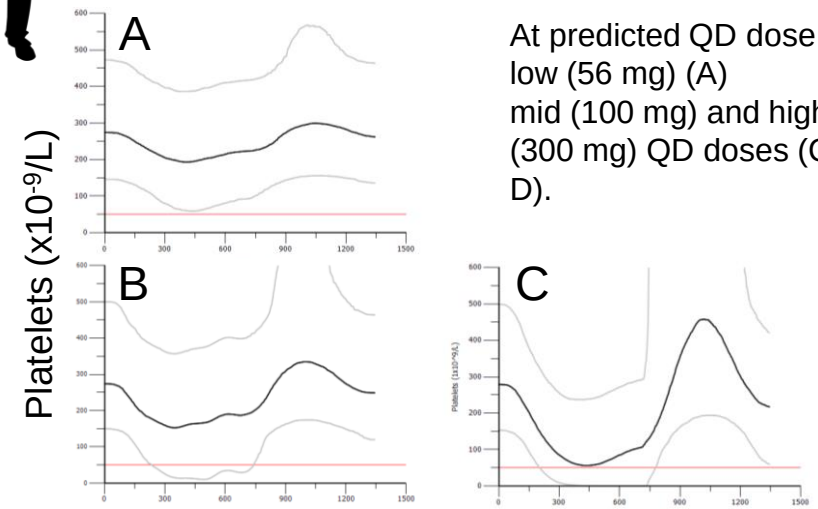
Human / Rat in vitro potency

Human System Parameters

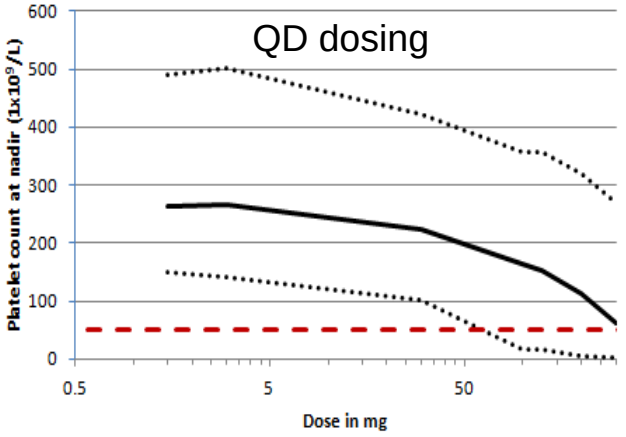
Rat Model

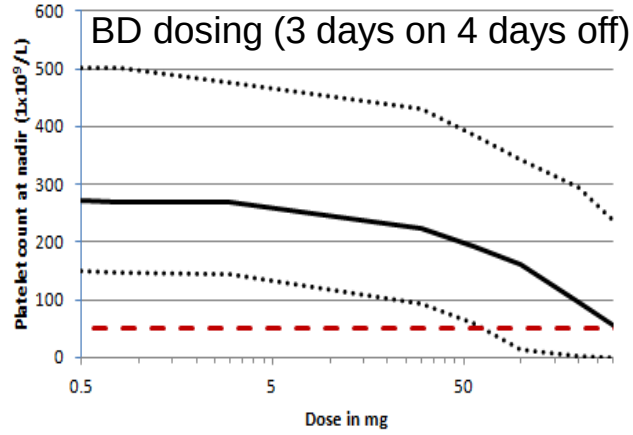


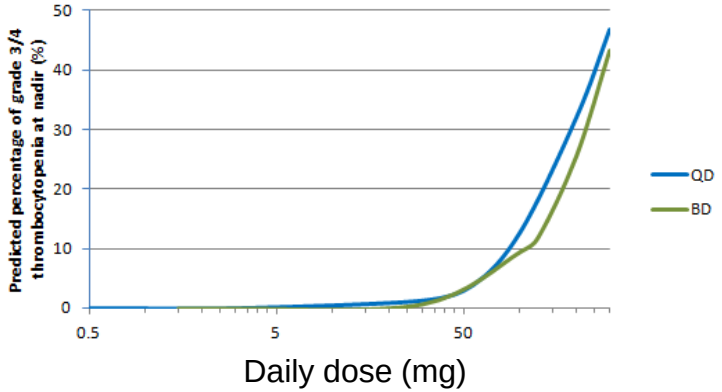
Simulation of human platelets over 28 day (672 hours) dosing period and washout period of inhibitor



At predicted QD dose of:
low (56 mg) (A)
mid (100 mg) and high (300 mg) QD doses (C & D).

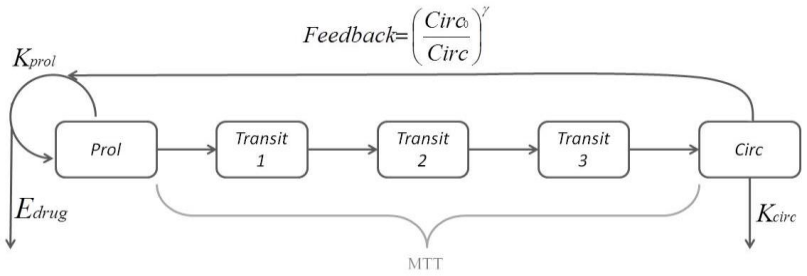




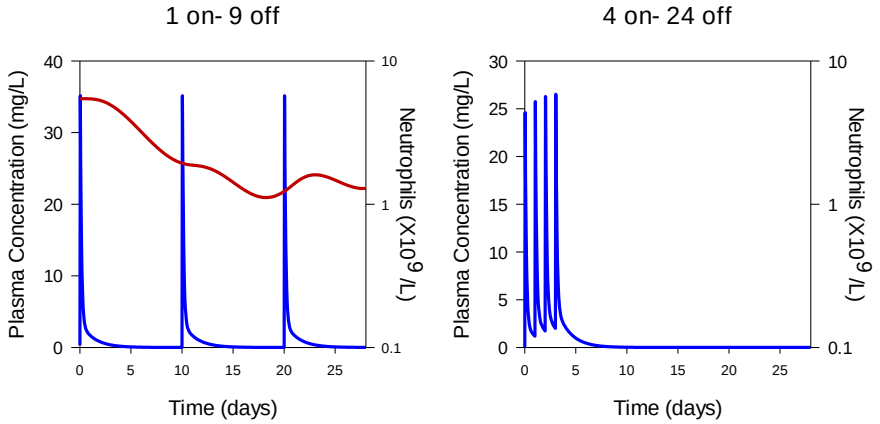


Comparison with dosing schedule optimization for Docetaxel

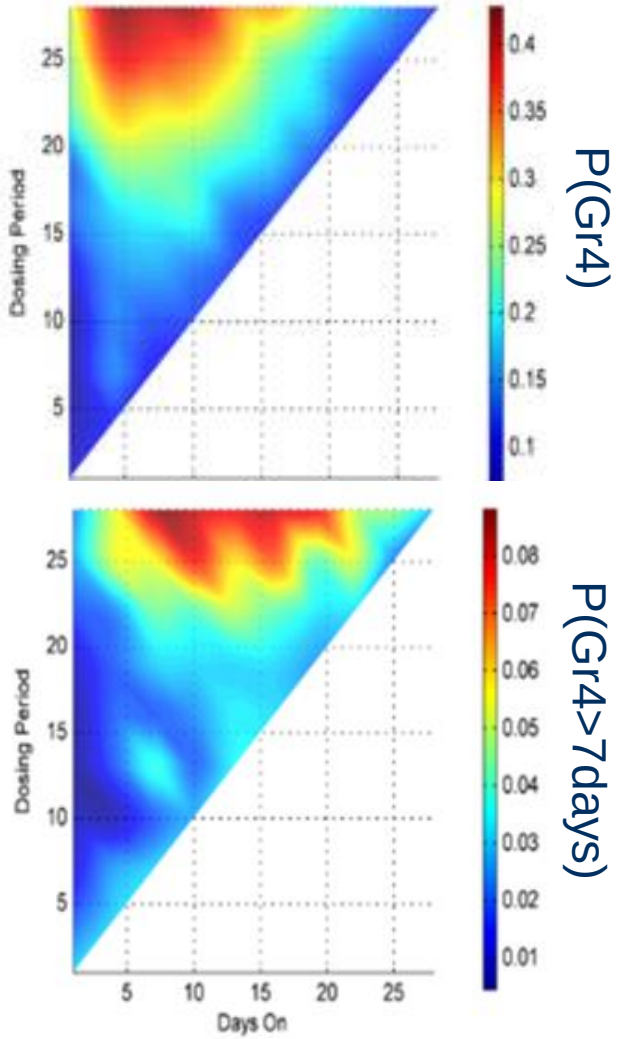
Fixed total cycle dose on different schedules (days-on/days-off)



Dose fractionation

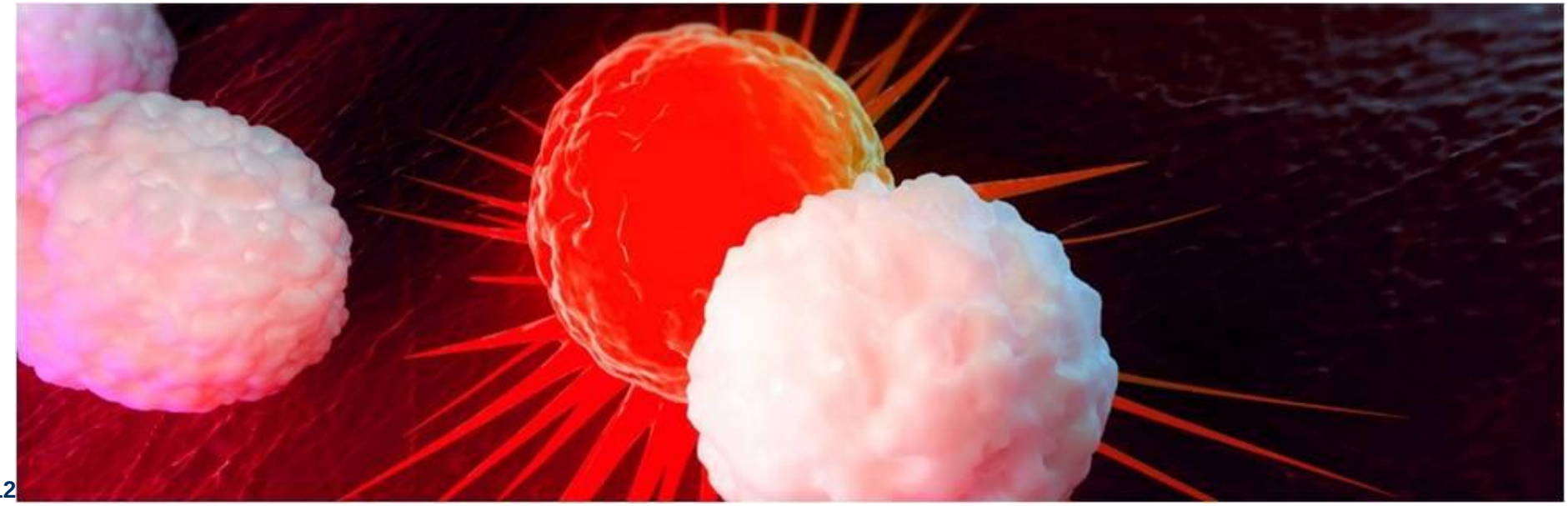


Neutropenia Predictions



Patel M, et al. (2014) Dose Schedule Optimization and the Pharmacokinetic Driver of Neutropenia. PLoS ONE
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0109892

Translating the bone marrow toxicity of combinations



Increase in combination therapies in Oncology

- When 2 agents demonstrate efficacy – possible next step is to combine them
  - May lead to increased efficacy
  - May combat resistance of targeted therapies
  - Go on top of SOC

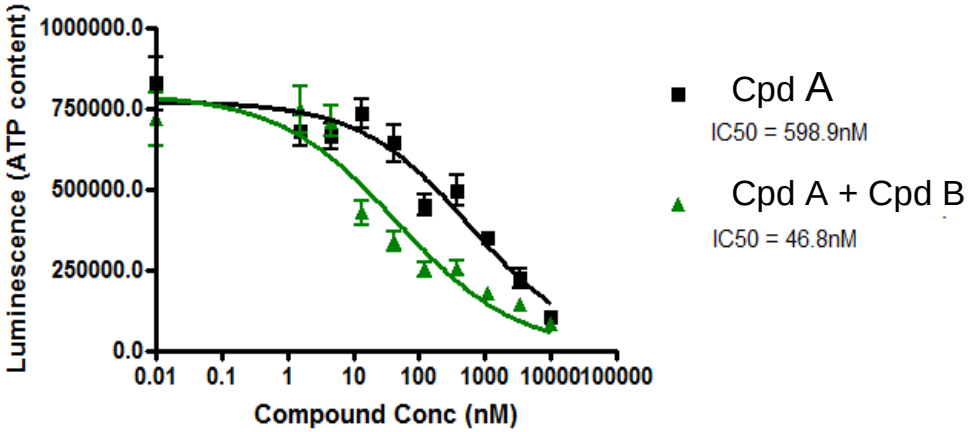
- Novel: SoC (one dose/ schedule often fixed)

- Novel: Novel (wide open!)

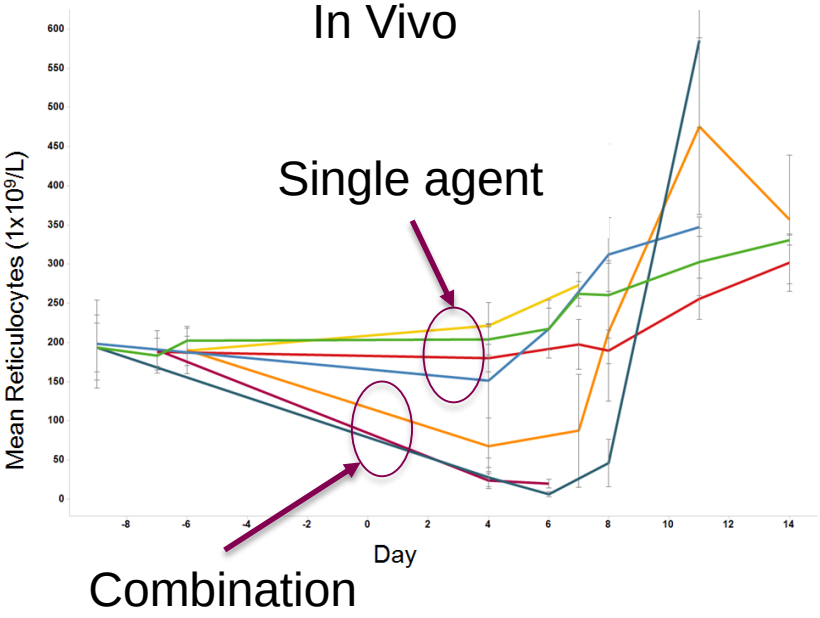
- Many permutations of combinations

Case Study 2 - Safe Starting Dose: Novel+Novel combination

In Vitro



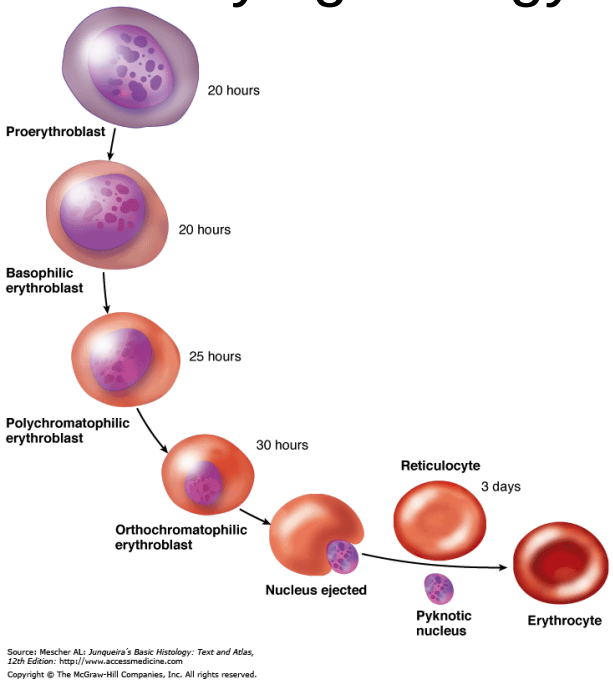
In Vivo



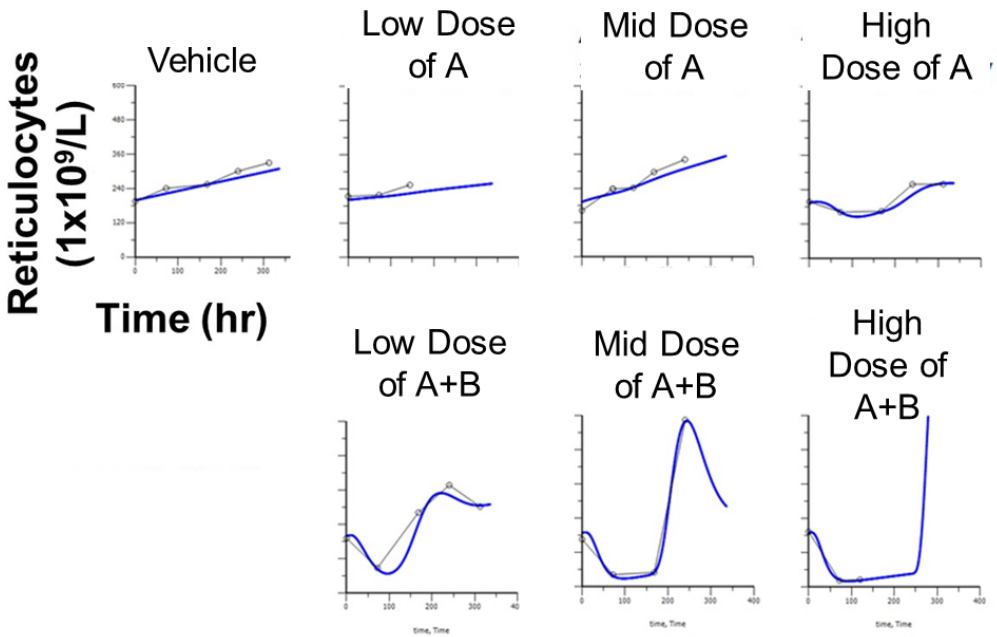
- In vitro: Hazard identification – synergistic bone marrow toxicity of combination
- In vivo: Risk assessment – bespoke in vivo combination study conducted to assess impact of agents dosed concurrently on bone marrow toxicity and peripheral blood.

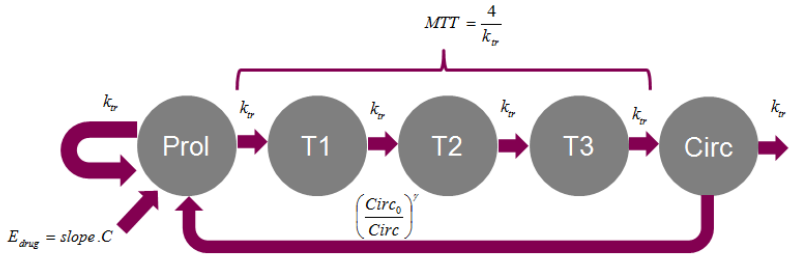
Modelling the hematopoietic effects

Underlying Biology



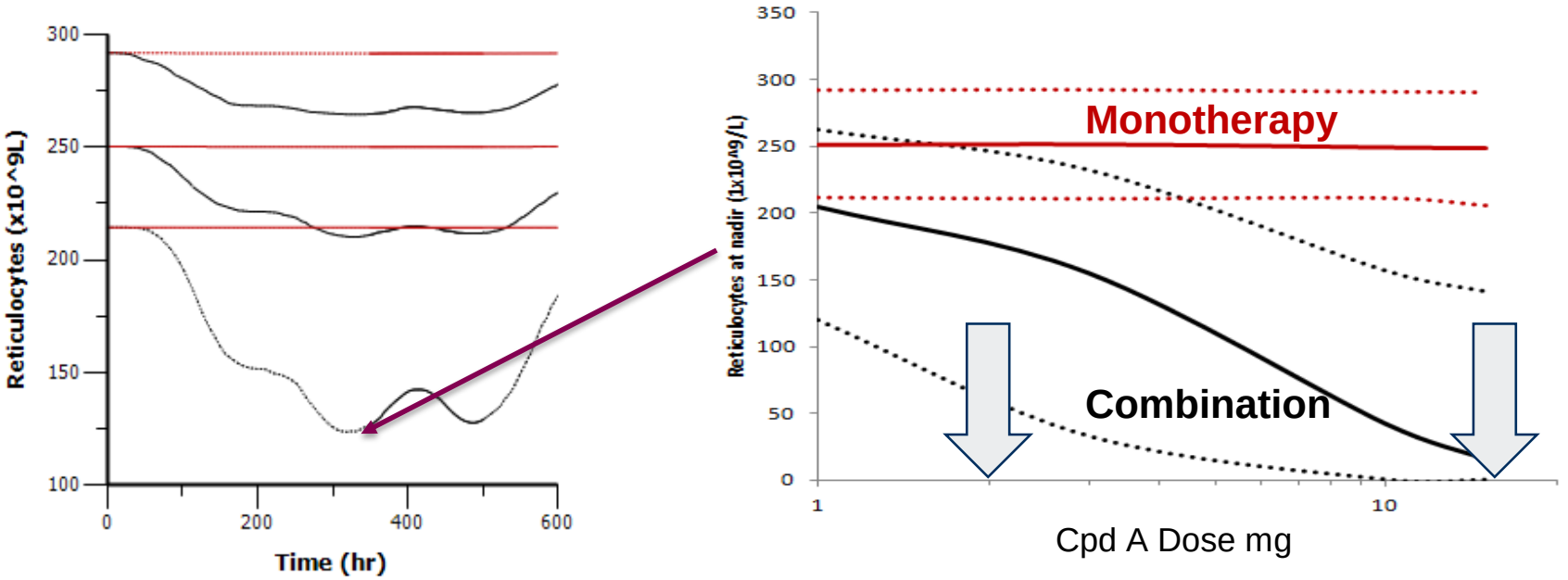
Data Analysis: Model Fits





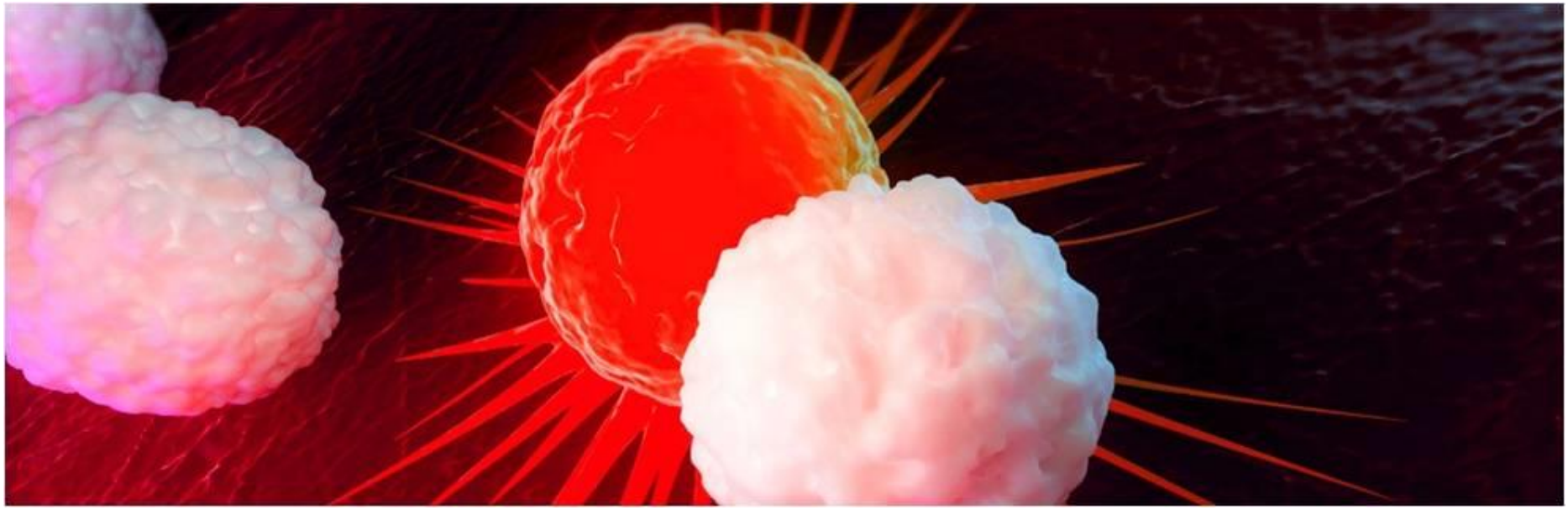
Mathematical representation

Example 2 - Safe Starting Dose: Novel+Novel combination



- **IMPACT:** Reduction in combination start dose
- Maximum effect on BM occurs after 2 cycles (not 1) therefore 2 cycles will be competed in the clinic before dose escalation
- Significant impact on bone marrow predicted in combination at 10mg of Cpd A – information used to assess degree of dose escalation

Predicting GI Toxicity from Rodent to Man



Prevalence of GI toxicity in oncology compounds

Oncology compounds often have on-target toxicity on rapidly dividing stem cells, even for targeted therapies (see table for AE's for new therapies)

This is manifested as frequent bone marrow/hematological and GI tox in the clinic

Neutropenia has been shown to be predictable in severity and time course from preclinic using Friberg model (JCO, 2012) for a wide variety of compounds/mechanisms

Here we employ a similar approach for toxicity induced through damage to GI crypt stem cells

Table 2 Incidence of drug-induced diarrhea in phase I–III studies of molecular-targeted cancer drugs.

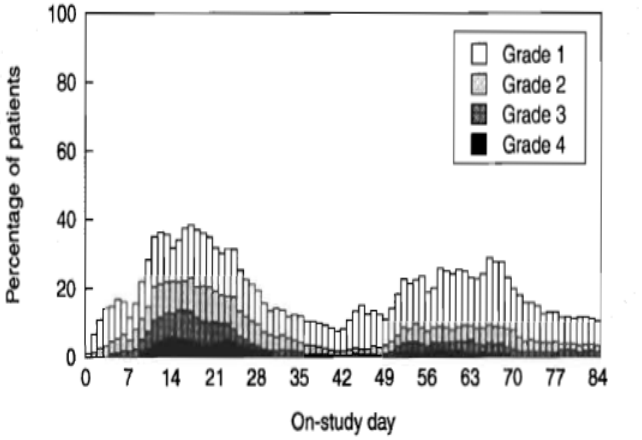
Drug	Incidence of diarrhea (%)	Reference
Erlotinib	55 (6% grade 3–5) 68 (12% grade 3–4)[a]	Shepherd *et al*. (2005)[2] Herbst *et al*. (2005)[65]
Gefitinib	40–60 (8% grade 2) 58 (3% grade 3–4)[a]	Fukuoka *et al*. (2003)[3] Herbst *et al*. (2004)[66]
Lapatinib	40 (10% grade 3) 60 (13% grade 3–4)	Burrhis *et al*. (2005)[24] Geyer *et al*. (2006)[67]
HKI-272	84	Wong *et al*. (2006)[19]
Sorafenib	33 (24% grade 2–3)	Escudier *et al*. (2005)[10]
Sunitinib	20 (grade 2–3)	Motzer *et al*. (2006)[11]
Imatinib	45	Demetri *et al*. (2002)[14]
Flavopiridol	50	Liu *et al*. (2004)[15]
Bortezomib	32 (8% grade 3–4) 29 (9% grade 3–4)	Fanucchi *et al*. (2003)[34]

[a]Drug used in combination with cytotoxic chemotherapy.

Loriot Y *et al.* (2008) *Nat Clin Pract Oncol*
doi:10.1038/ncponc1087

Known GI effects of irinotecan

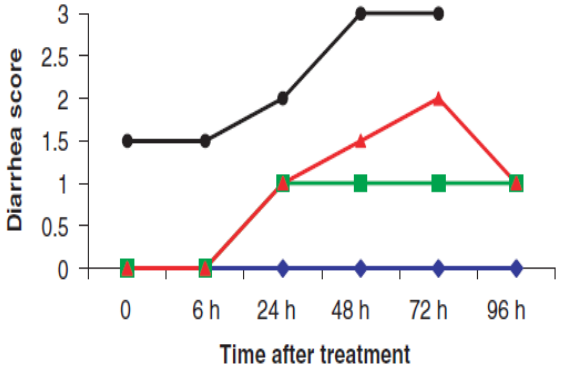
Patients

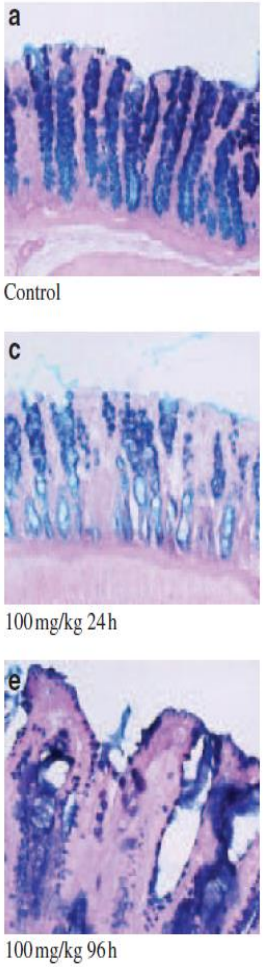


Diarrhea incidence for 125 mg/m^2/wk for 4 weeks on and 2 weeks off

Hecht, Gastrointestinal toxicity of Irinotecan, Oncology, 1998

Rats

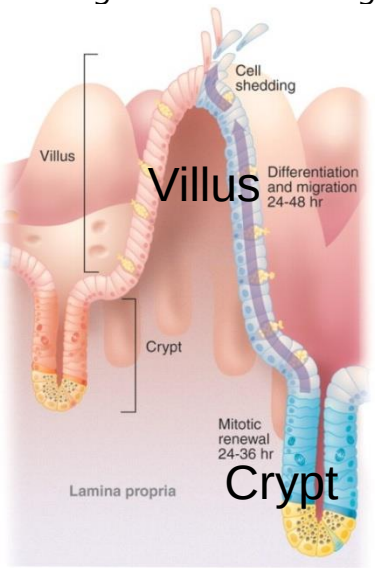


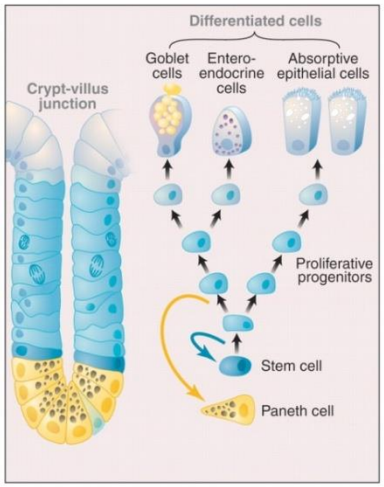


Gibson et al, J Gastroenterol Hepatol, 2003

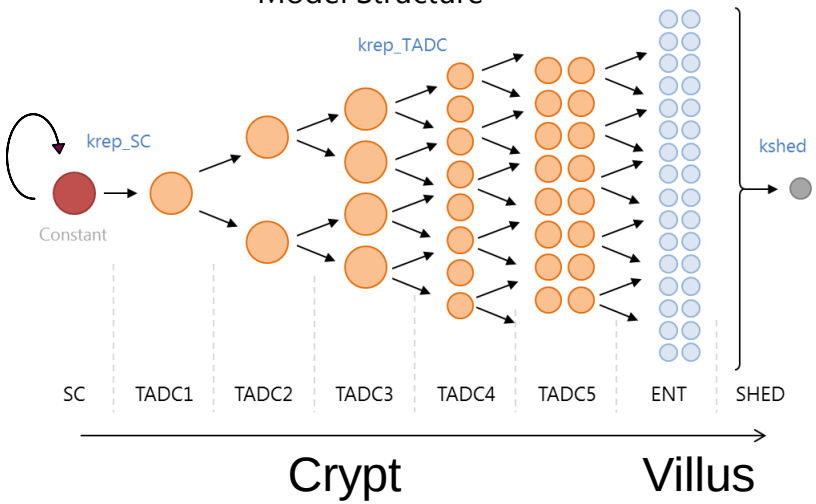
GI damage model built from literature

Biological Understanding



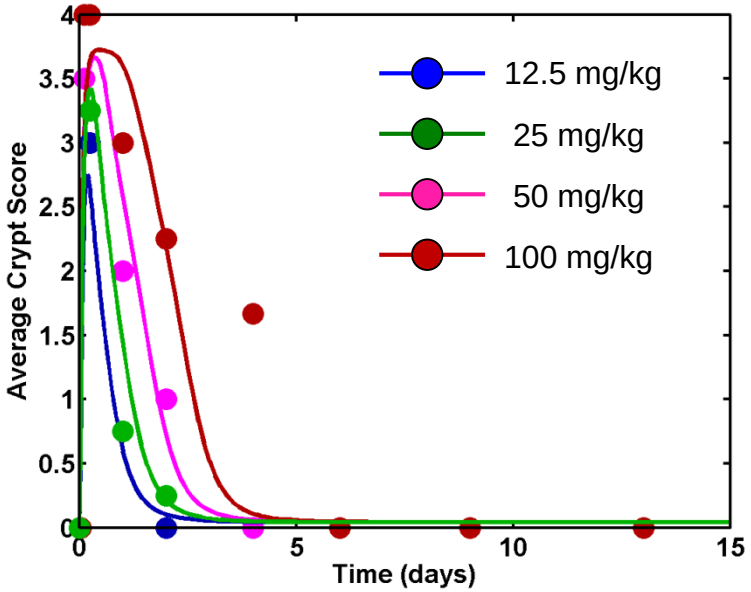


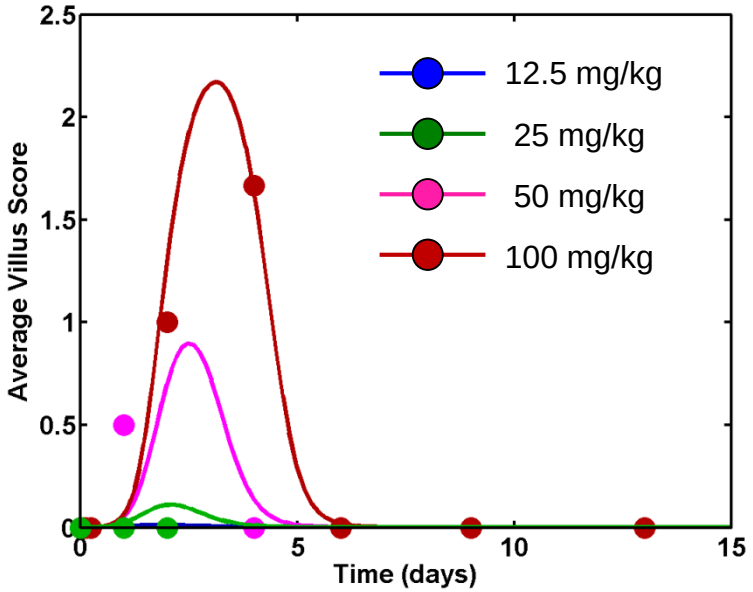
Model Structure



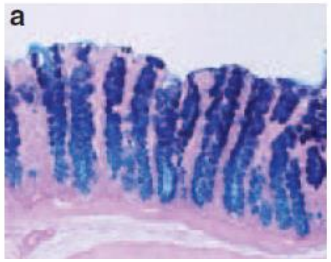
Parameter	Rodent Model	Human Model
Stem Cells/Crypt	10	10
Stem cell doubling time	16 hrs	72 hrs
TADC doubling time	12 hrs	32 hrs
Shedding rate	0.45 /day	0.2 /day
# of Transit compartments	4	5
# of Crypts feeding each villus	7	7

Data and predictions for the average score





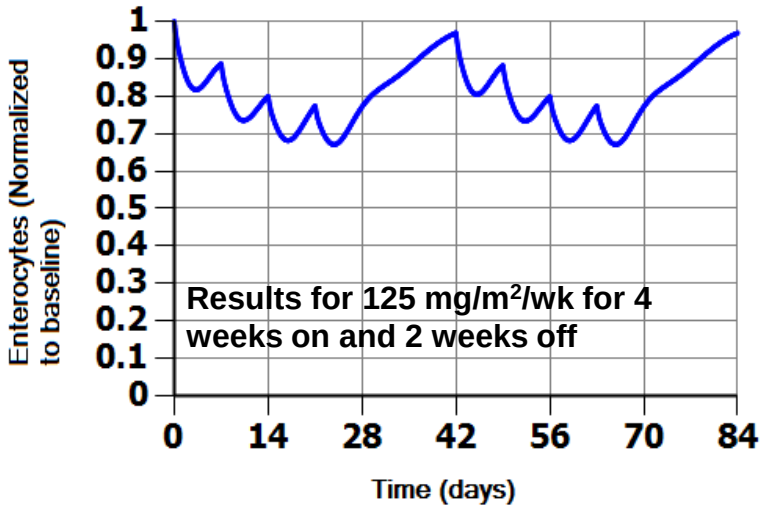
Observation

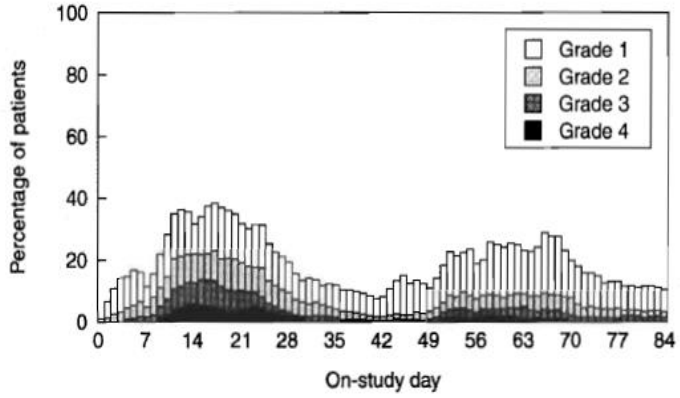


Pathology Score (N)

1 - Minimal
2 - Mild
3 - Moderate
4 - Marked
5 - Severe

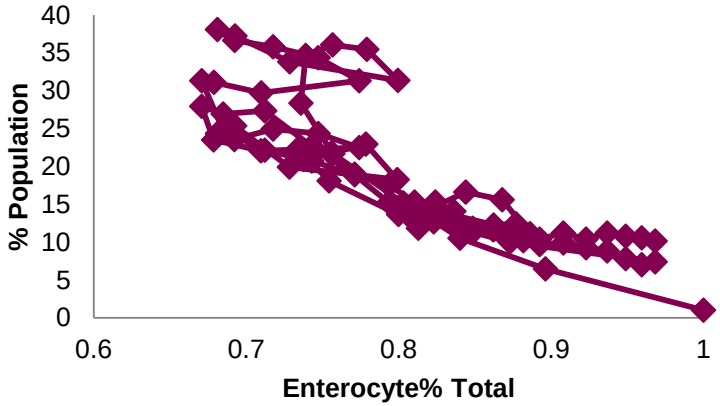
Prediction of clinical effects
Mechanistic model predicts well



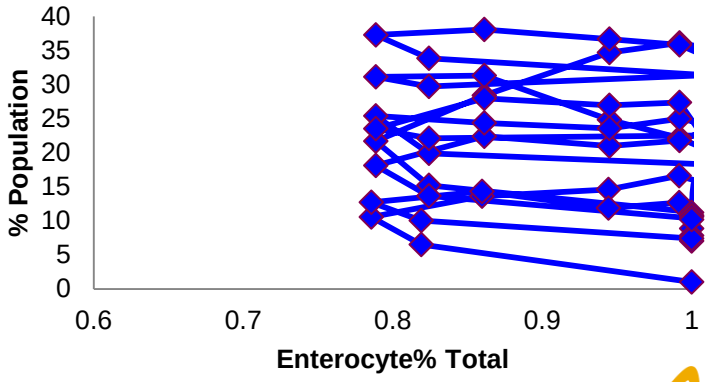


Hecht, Gastrointestinal toxicity of Irinotecan, Oncology, 1998

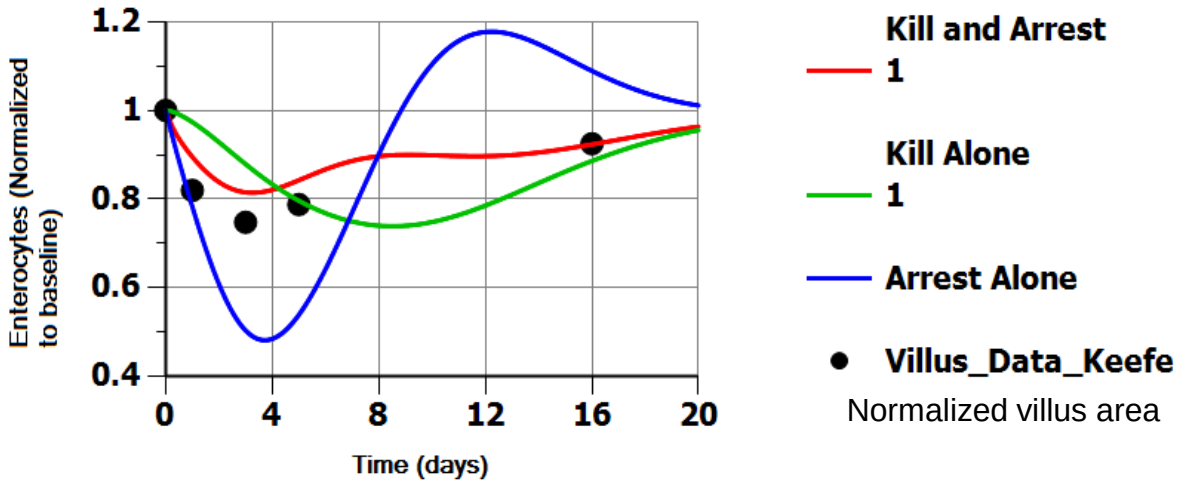
Systems Model



Rat PK/PD model



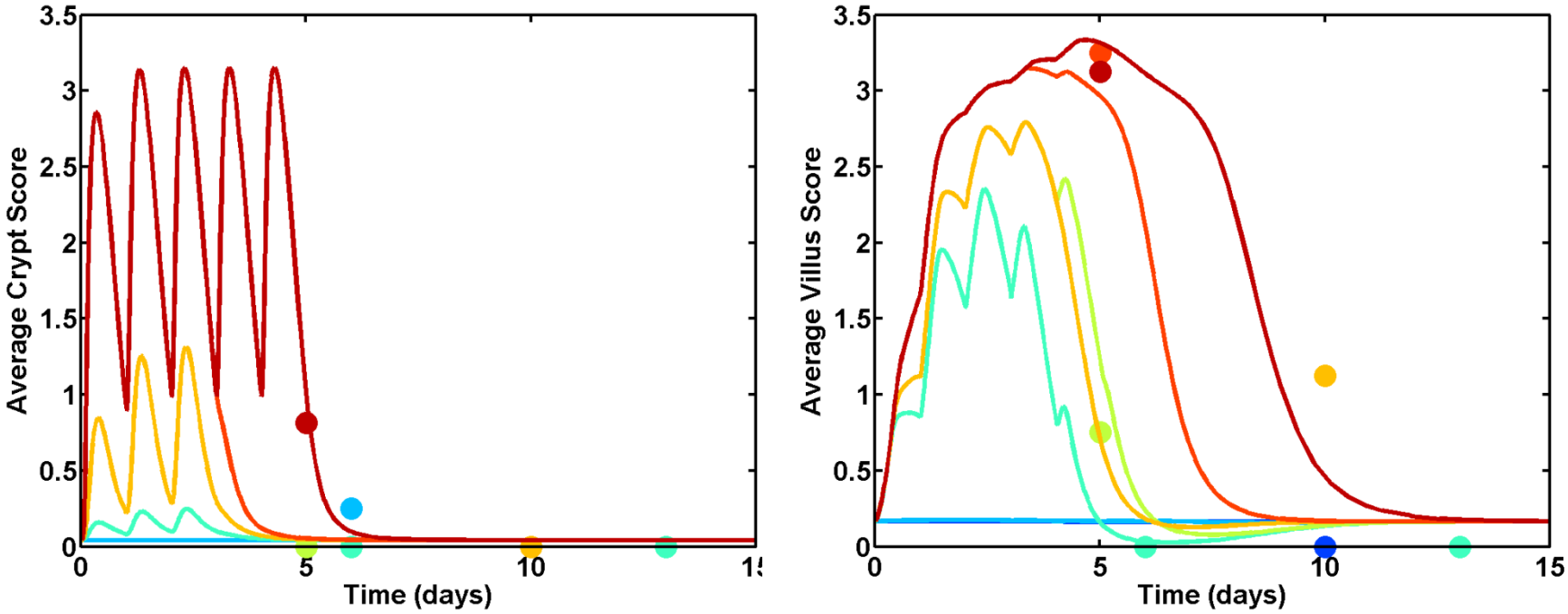
Clinical biopsy data can be predicted by model



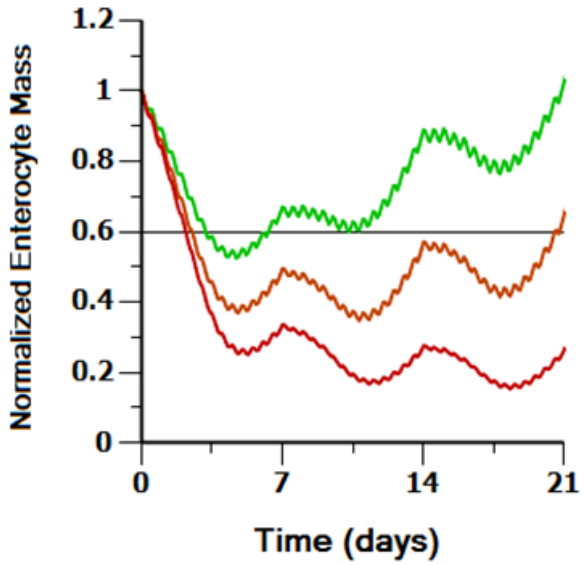
Data lends support to the model that has both cell cycle arrest as well as cell killing

Model predictions for extent of enterocyte loss in good agreement with villus shortening seen in biopsy data following chemotherapy

Fits to Novel:Novel combination data



Preliminary predictions for human enterocytes



1mg X
10mg X
30mg X

+100 mg BID Drug Y (Backbone)

1 mg, 10 mg or 30 mg Drug X (additional therapy) once a day for 3 days followed by 4 days off –

Repeat regimen every week for 3 weeks

Summary

- Regulatory requirement for non-clinical safety work for oncology is limited
  - Single agent: Hazard ID, Escalation, SSD, Safety Pharmacology
  - Combination: minimal

- Opportunity to assess apply preclinical models with mathematical translation to improve chances of success:
  - Starting dose & escalation scheme
  - Risk of increased toxicity in combination therapies
  - Dosing schedule
  - Selection of combination partners

  - Predictive models needed for many endpoints (e.g. skin or immune)
  - Biomarkers with translational power (e.g. citrulline for GI toxicity, KIM1 for kidney)

- Need to challenge existing ways of thinking!

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Rat PK and PD parameters estimated

	Estimate	%CV	%IIV
AZD5153 PK			
k_a (h^{-1})	1.7	(fixed)	-
V (L/kg)	0.39	16	-
Cl (L/hr/kg)	0.15	(fixed)	-
PD model			
$Circ_0$ ($x10^9$/L)	562.4	2.4	5.4
MTT (h)	57.7	3.6	$5x10^{-4}$
γ	0.5	10.3	0.1-
$slope_{AZD5153}$ (1/(µmol/L))	0.09	6.75	14