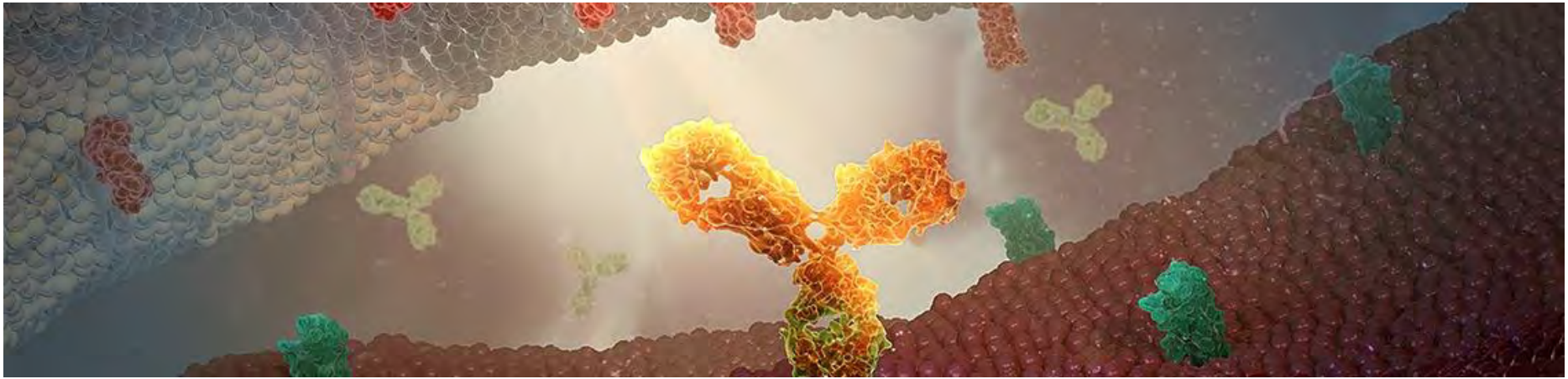
Why don’t xenografted tumour models translate to patients?

Dr James Yates, Oncology DMPK Modelling and Simulation

DMLG 2017 Managers Meeting

31st May 2017



Or:
Why xenografted tumour models might translate to patients if we thought about it and did some more work…

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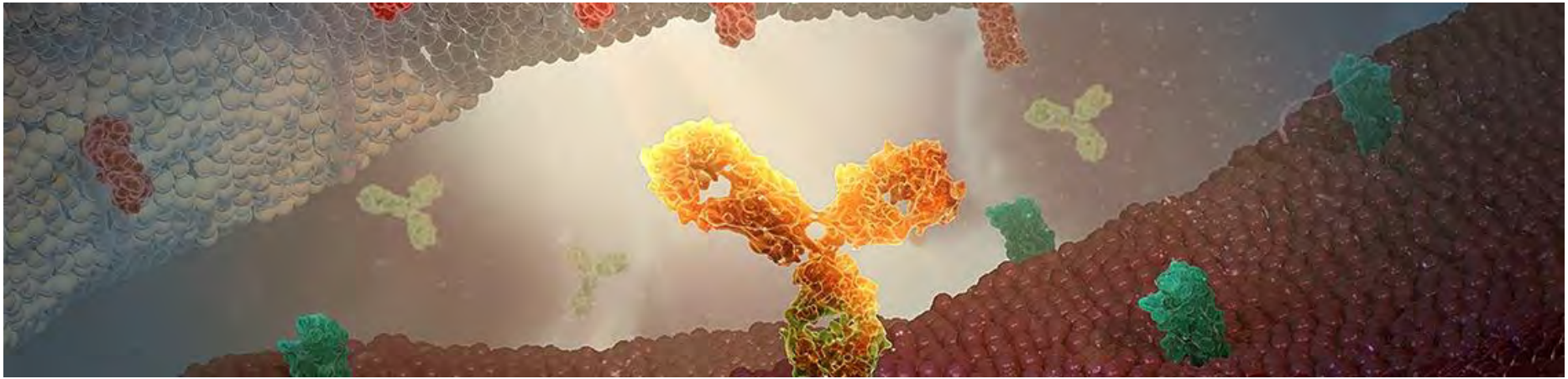


Why xenografted tumours might translate to patients if we thought about it and did some more work…

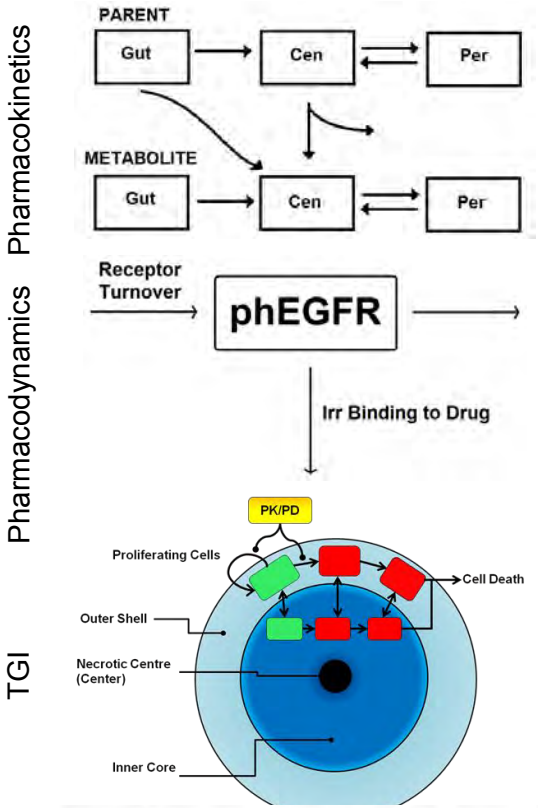
We use pre-clinical exposure – response relationships to predict active dose and schedule

There is very little evidence that animal models of cancer translate in a quantitative sense to the clinic

I believe that currently important differences between animal models and the human disease need to be taken into account

Motivating example 1: Tagrisso

Nonclinical PKPD-Efficacy relationship + Clinical PK to predict active clinical dose

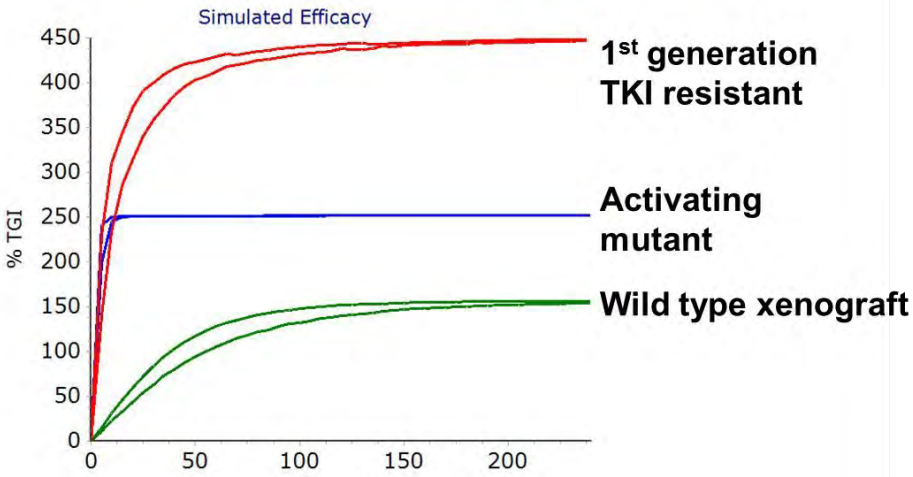


Mol Cancer Ther; 15(10) October 2016

+Human PK

95% Confidence intervals of efficacy

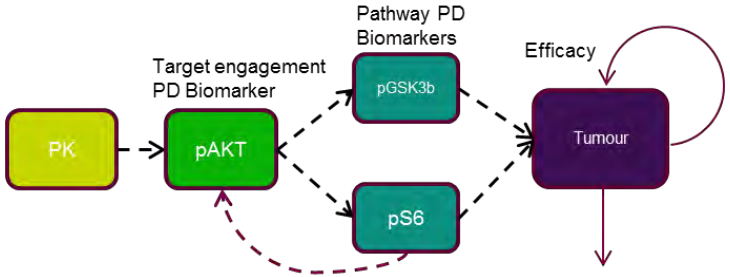
Even with variability effect saturates at low doses

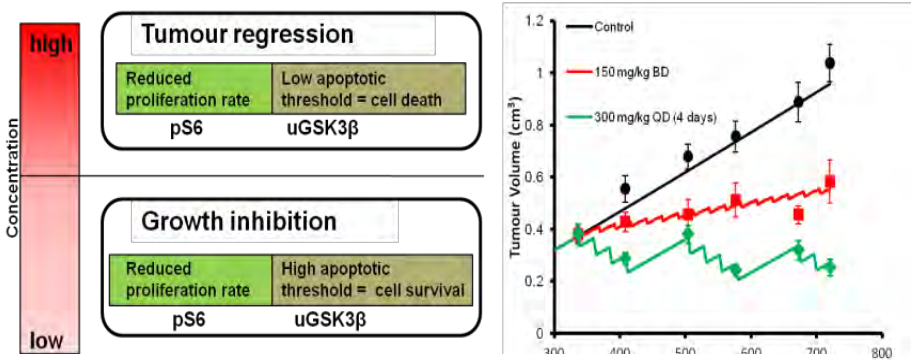


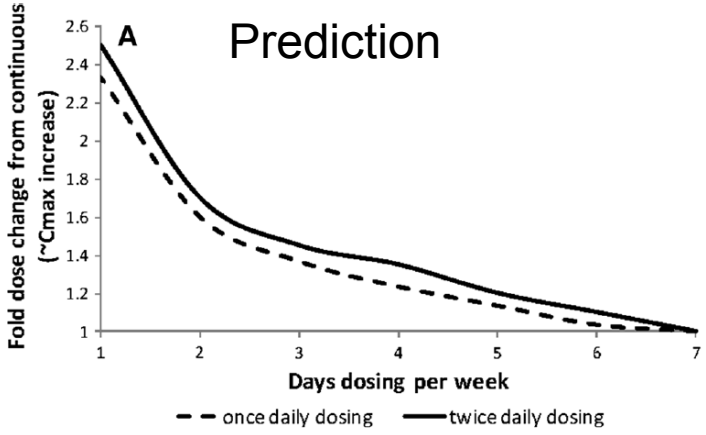
Clinical dose mg

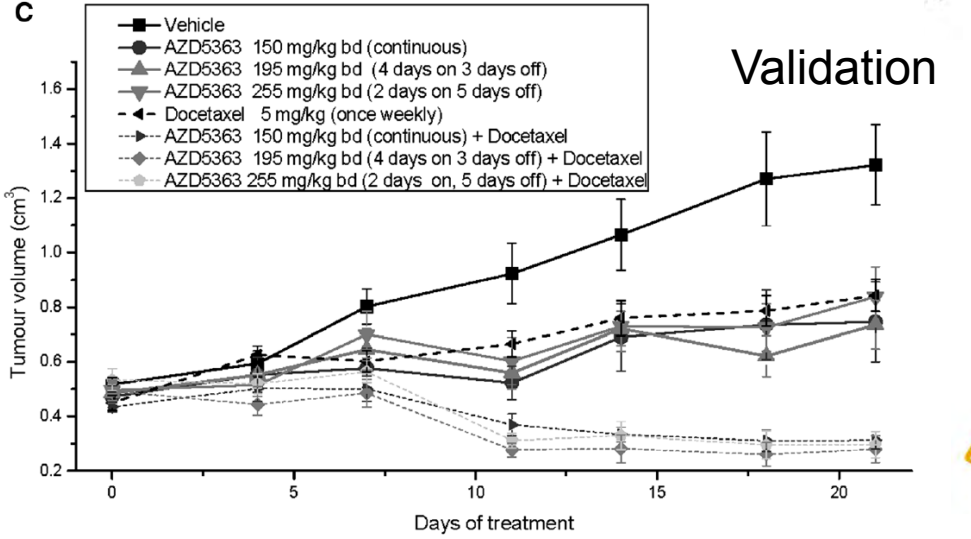
Response seen from 20mg up

Motivating example 2: Using pathway PKPD model to predict mouse efficacy and extrapolate to clinic



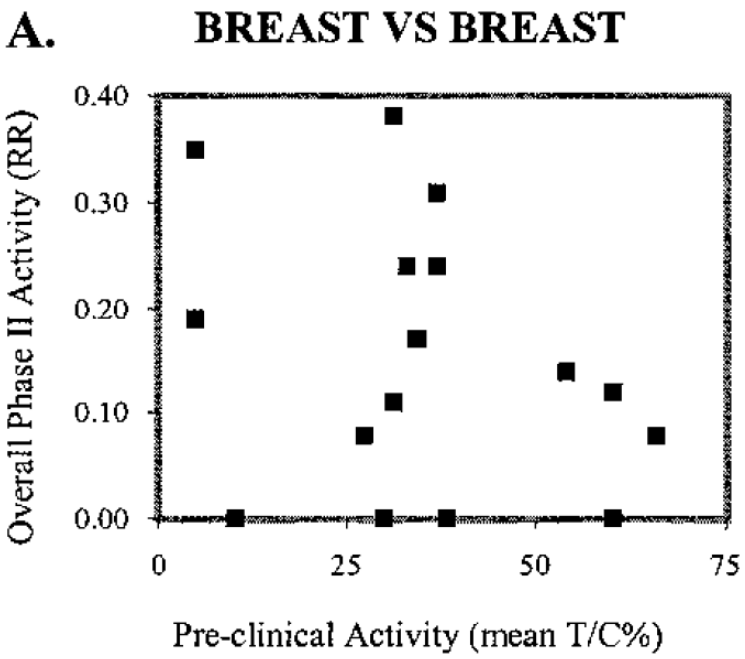






Cancer Chemotherapy and Pharmacology 76, 343-356 (20

The difficulty of translation



Theodora Voskoglou-Nomikos, Joseph L. Pater and Lesley Seymour

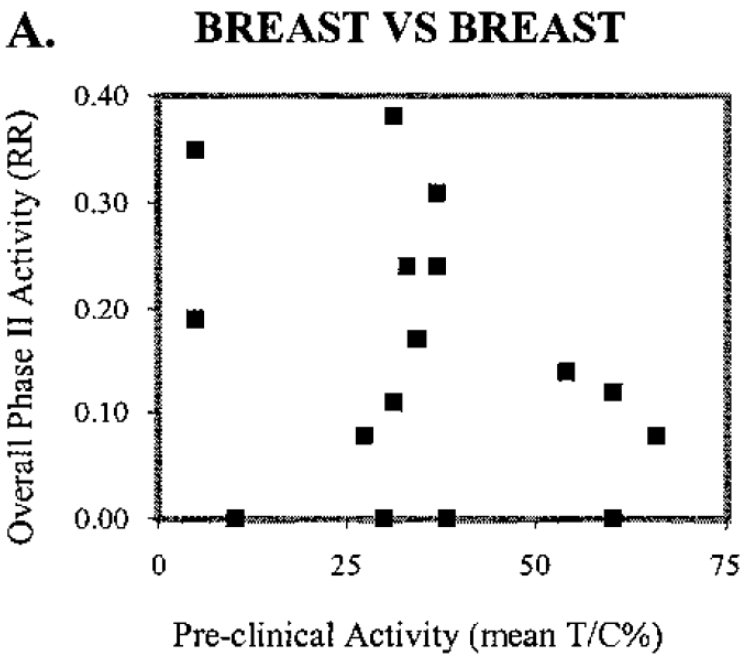
Clin Cancer Res 2003;9:4227-4239.

But….

1. **Pharmacokinetic differences**
2. **Genetics**
3. **Growth rate differences**
4. **Immune status**
5. **Heterogeneity**

Increasing R: can some variability on y axis be explained by these factors?

Evidence that animal models of cancer do not translate to the clinic



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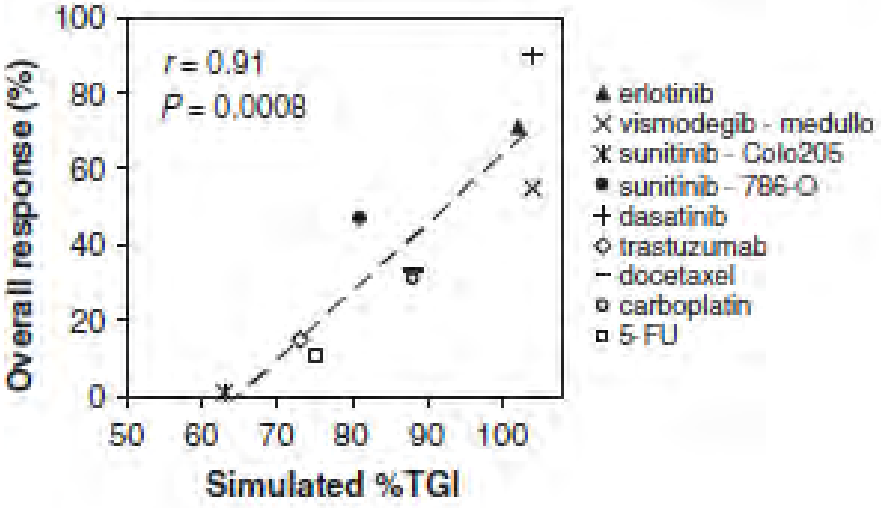
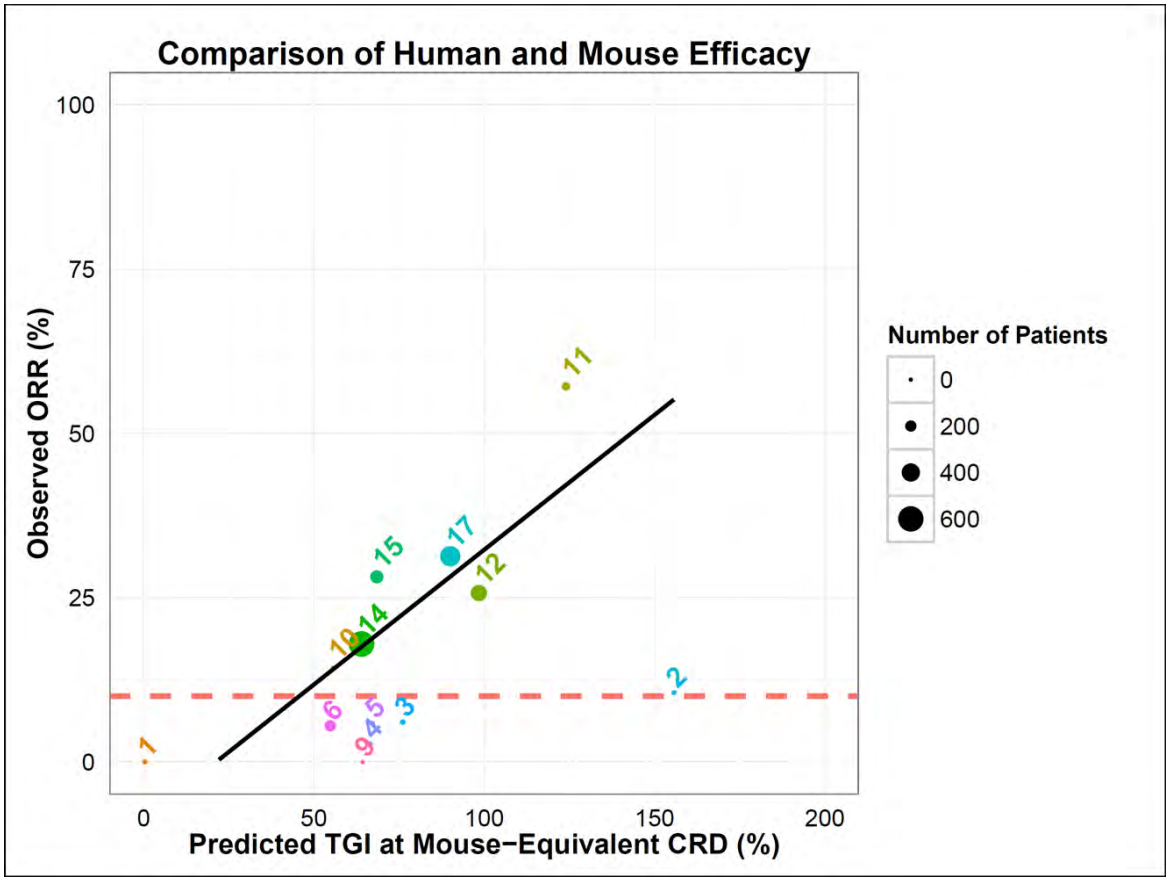


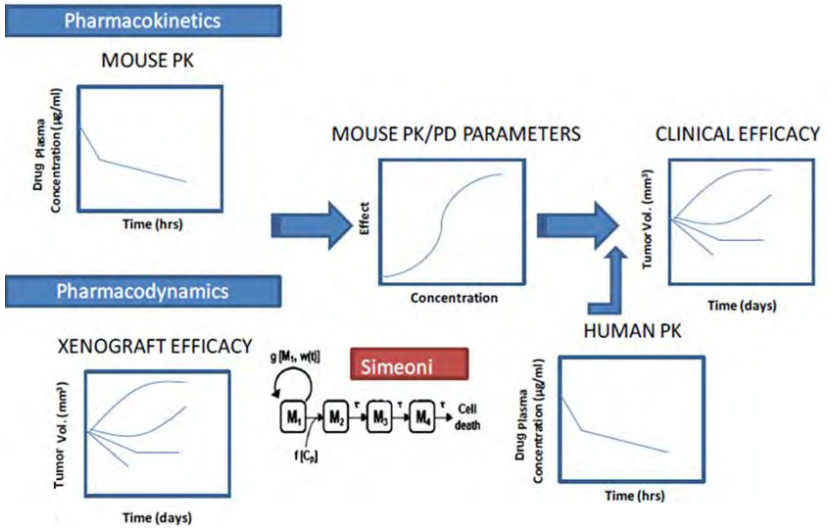
Wong H *et. al. Clin. Cancer Res.* 2012

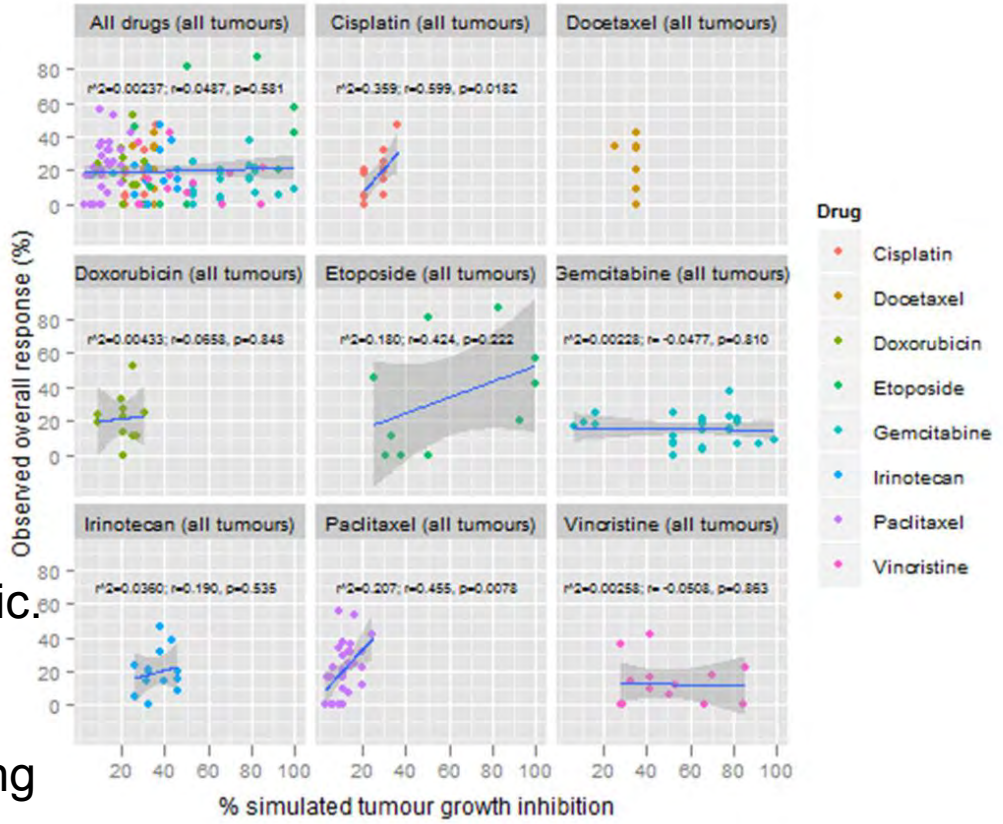
At AZ we've had similar findings



Linakis et al 2015
EORTC-NCI-AACR

PK corrections don't work for comparing schedules





- Translation appears to be drug specific.
- Useful for translating intermittent schedules?
- How can we bring in genetics, doubling time etc?

How can we increase the R-squared value of the correlation?

Challenge: Animal models grow quickly than the human disease

PDX

Xenograft

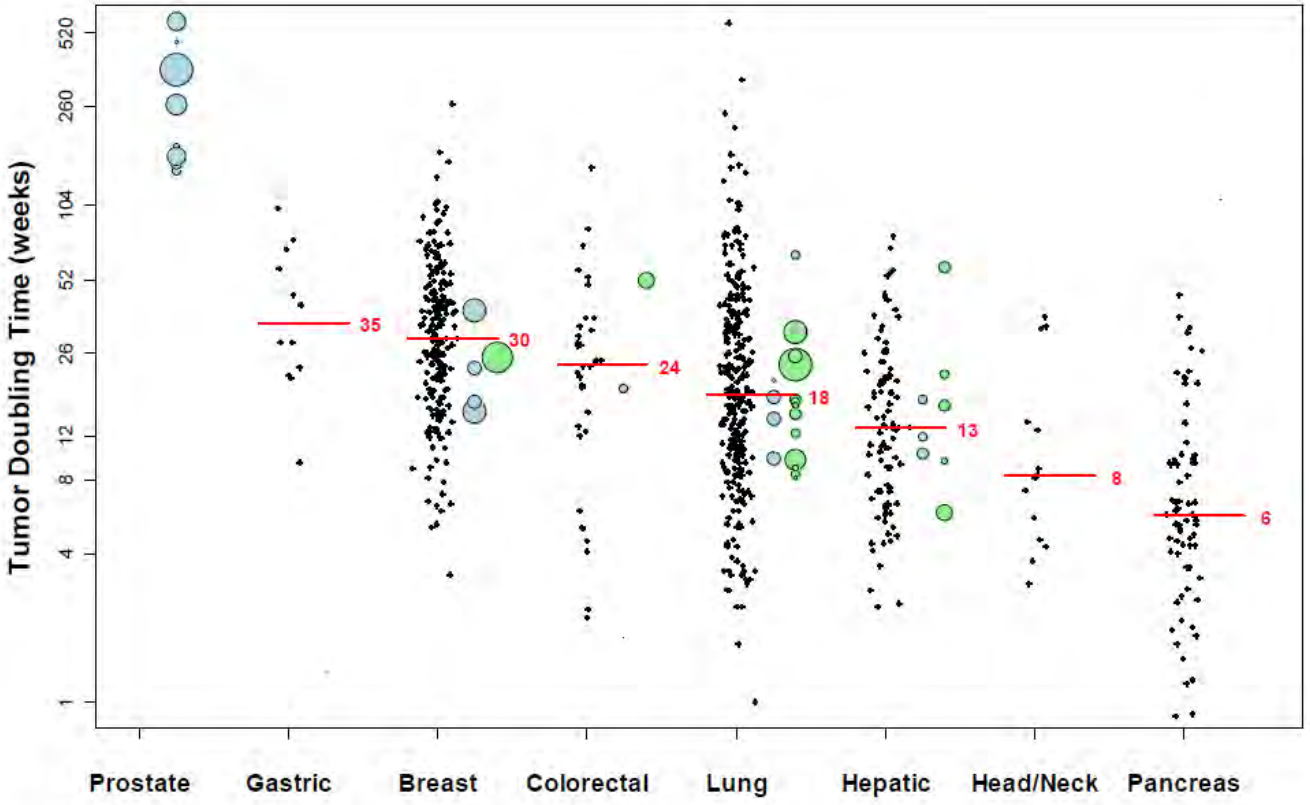
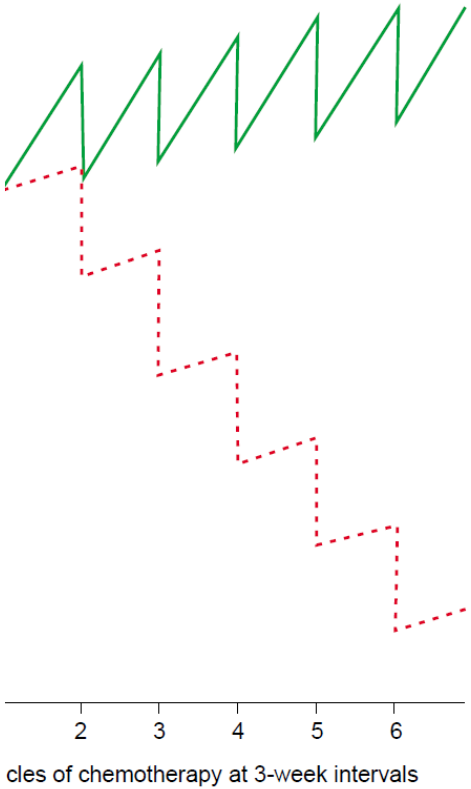


Fig.1. Tumour Doubling Time by Primary Cancer Site

Why is drug effect vs tumour recovery time important?



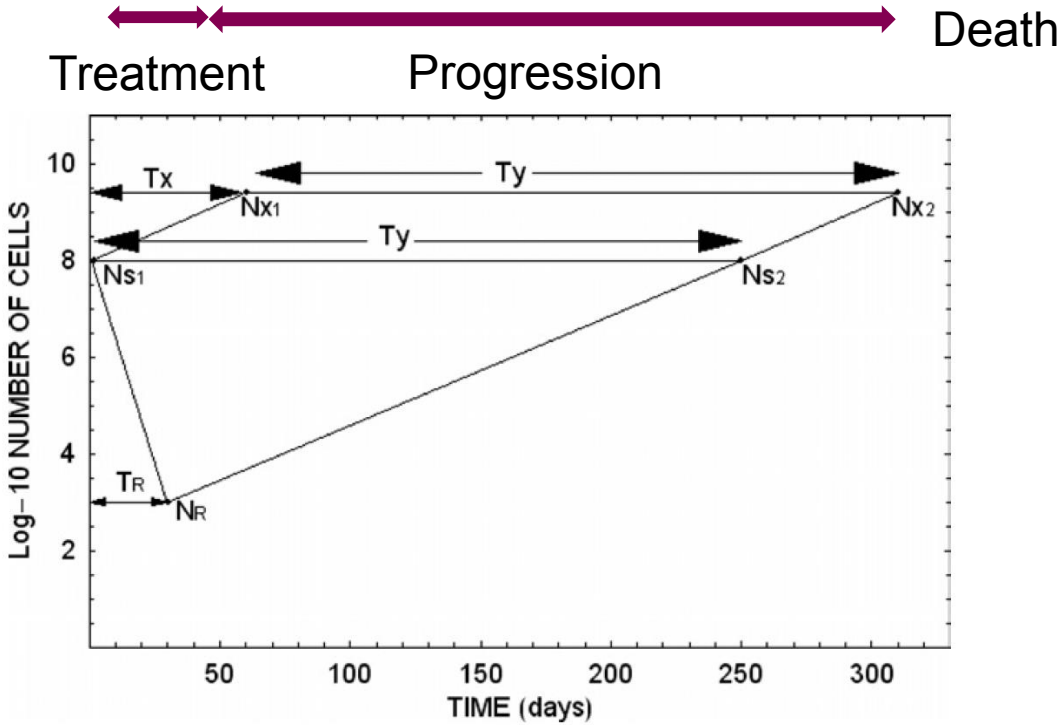
1. Tumours are equally sensitive in terms of kill per dose

2. Red line is for slow growing tumour which “responds” to treatment

3. Green line is for fast growing tumour that is “resistant” to treatment

IR Biologically equivalent dose and repopulation

Jones and Sanghera 2007



Can estimate loss of effectiveness due to tumour recovery

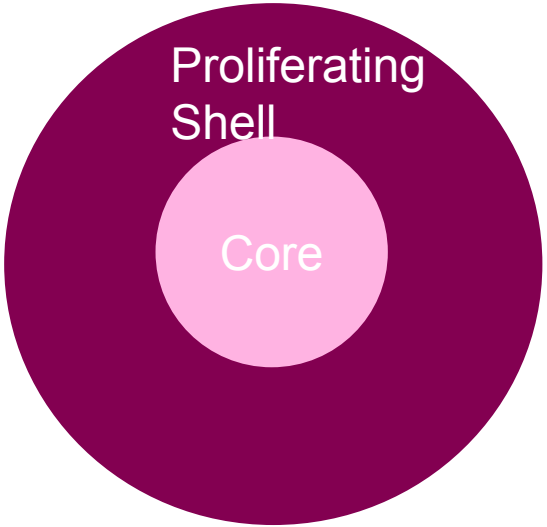
For Glioma K=0.23Gy per day lost, equivalent to 39 day doubling time

Opportunity: The theoretical treatment of IR is based upon 4 Rs. All of which have a corresponding "PKPD" terminology

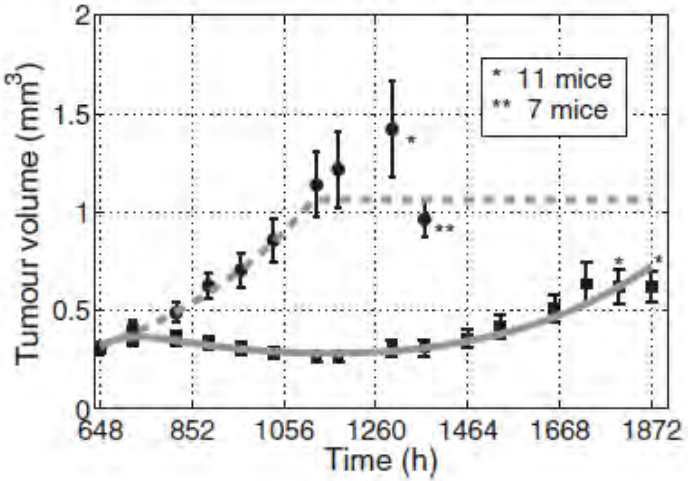
IR	PKPD
Repair	Pharmacodynamic persistence/overlap
Repopulation	Tumour volume made up during drug holiday
Redistribution	Cell cycle dependent effect. Treatment can deplete particular population of cells Can mediate combination antagonism (E.g AKTi+Taxane)
Reoxygenation	Slow onset of regrowth but can be accelerated due to larger proliferating fraction of smaller tumours
Resistance	Reversible (tolerance) vs Irreversible (clonal)

Note cell cycle time / proliferating fraction = doubling time

A simple mathematical model can be used to capture proliferating fraction and cell cycle time



Growth rate is function of proliferating fraction and intrinsic doubling time

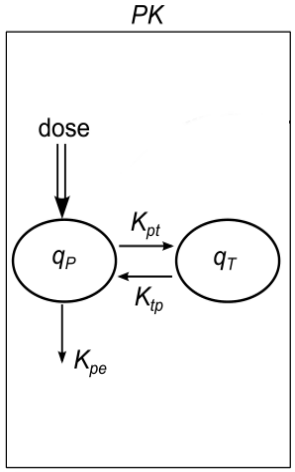


Get sensible parameter estimates in xenografts:

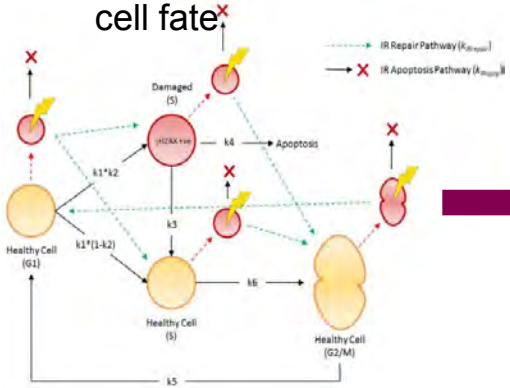
1. Depth of shell is 100-300um (effective oxygen penetration) .Increases to 10x this in PDX
2. Intrinsic proliferating fraction doubling time is typically 24-48hrs

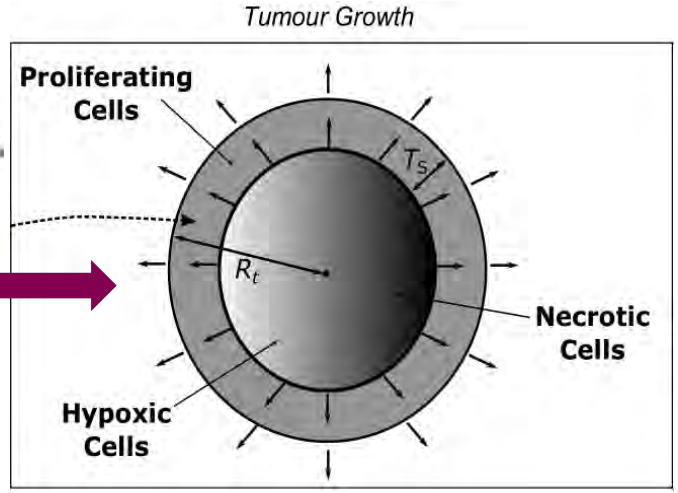
COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 114 (2014) e3–e13

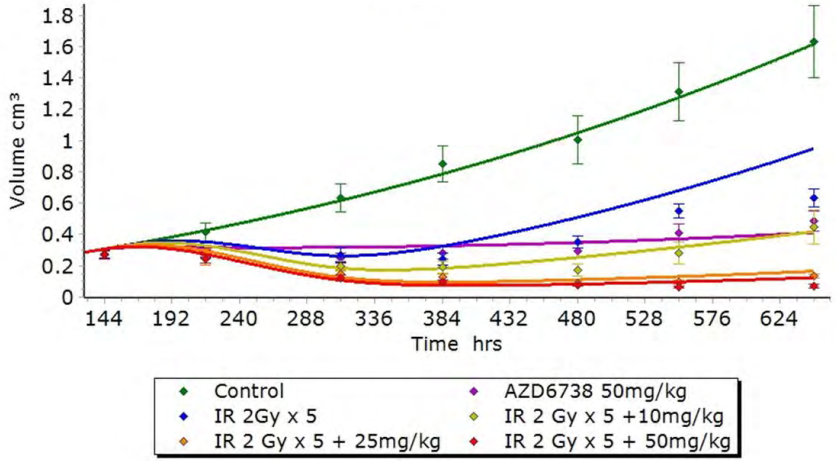
Timescales learned from in vitro data predict combination efficacy in vivo efficacy



In vitro: PD and cell fate:







Control

IR alone

ATRi alone

Combination

Confidence that mechanistic models developed using in vitro systems is predictive of in vivo

SCIENTIFIC REPORTS | 5:13545 | DOI: 10.1038/srep13545

Challenge: Clinical Heterogeneity

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 86 NUMBER 2 | AUGUST 2009

FDA NSCLC model with different outgrowth rates

$$TS_i(t) = BASE_i \cdot e^{-SR_i \cdot t} + PR_i \cdot t,$$

Treatment	M_BASE (cm)	M_SR (1/week)	M_PR (cm/week)
PCB	9.1 (0.33)	0.06 (0.004)	0.13 (0.02)
PC	8 (03)	0.038 (0.01)	0.14 (0.04)
DC	8.7 (0.31)	0.052 (0.01)	0.16 (0.02)
DCb	9.2 (0.38)	0.047 (0.005)	0.16 (0.02)
VC	8.5 (0.28)	0.063 (0.01)	0.17 (0.02)
DT	8.5 (0.82)	0.033 (0.01)	0.13 (0.02)
PT	7.4 (0.47)	0.023 (0.01)	0.25 (0.05)
PB[a]	8.6 (0.44)	0.0047 slow (0.001) 0.13 fast (0.004)	0.20 (0.02)
ET[a]	8.4 (0.32)	0.0045 slow (0.001) 0.11 fast (0.05)	0.058 (0.02)

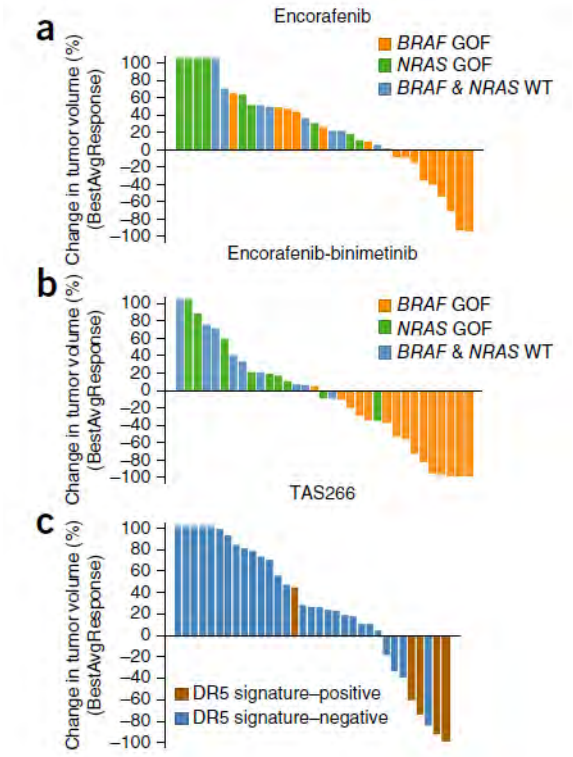
DC, docetaxel and cisplatin; DCb, docetaxel and carboplatin; DT, docetaxel; ET, erlotinib; PB, placebo; PC, paclitaxel and carboplatin; PCB, paclitaxel, carboplatin, and bevacizumab; PT, pemetrexed; VC, vinorelbine and cisplatin.

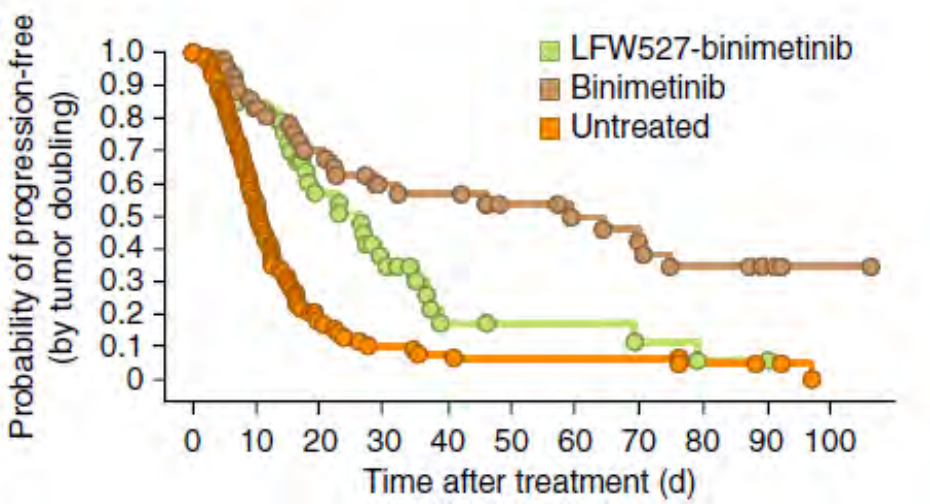
- Tumour reduction at 8 weeks shown to be predictive of OS
- Why do these treatments show different progression growth rates?
- Different resistant phenotype selected?
- But OS not impacted?

Opportunity to Embrace Heterogeneity: N=1 mouse trials

Genetic signals and patient like variability

doi:10.1038/nm.3954





Develop PKPD models using such data sets and get an estimate of PD variability (cf Tagrisso example)

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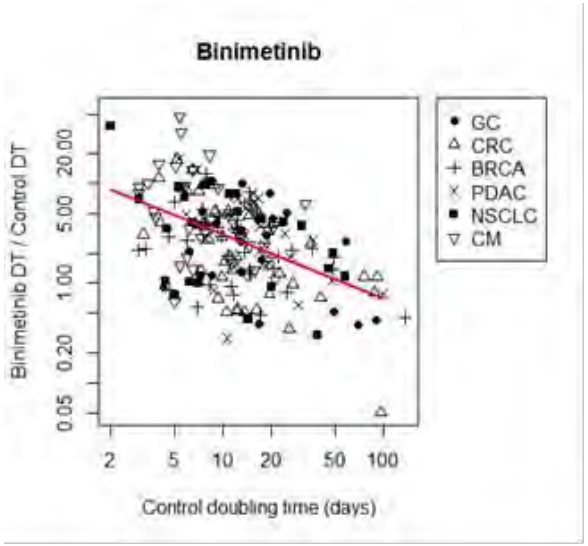
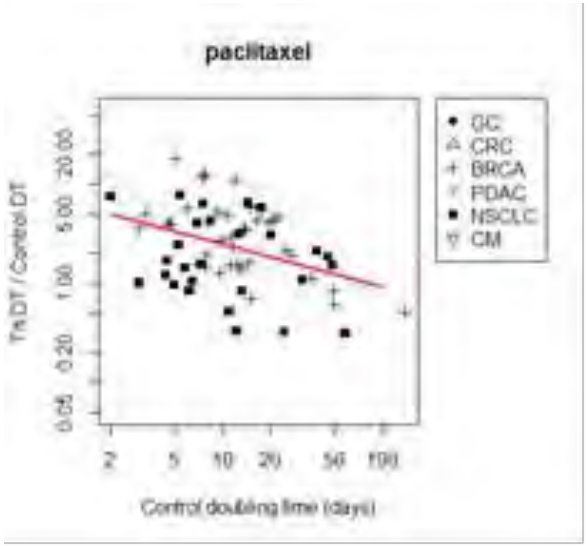
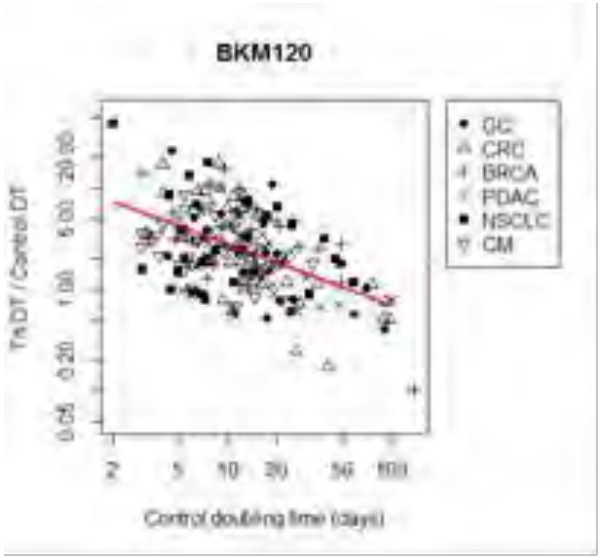
There is also evidence that doubling time of PDXs is an important predictor of drug sensitivity



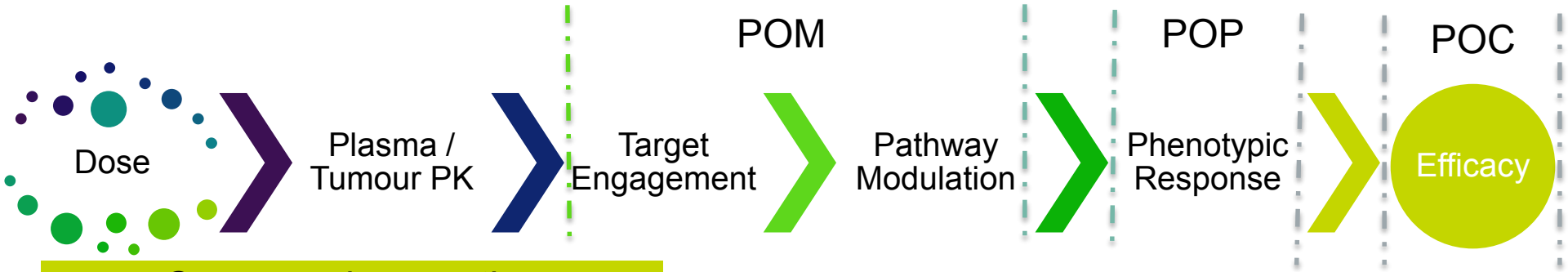




Can we use such datasets to build more translatable models of efficacy?

Data from Novartis (Gao et al 2015) on use of PDXs for patient selection
Y-axis is ratio of control to treated growth rate: big number=big effect

Summary: Translation via the biomarker cascade:



Compound properties

Pharmacology

Cancer Biology

PK differences

Heterogeneity of the disease

Growth rate of the disease

Resistance

Immune component

Conclusions

We need to take into account other things than PK

There exist data sets to investigate these differences

I haven’t even talked about the immune system

Modelling and simulation is key to take into account all of these differences

Confidentiality Notice