Applying mechanistic PKPD models to describe the growth and inhibition of xenograft tumors by targeted anti-cancer agents.

James WT Yates, Neil Evans, RD Owen Jones, Mike Walker, Patricia Schroeder, Joanne Wilson, Richard Dimelow, Frank Gibbons, Camila de Almeida

Oncology iMED, AstraZeneca
University of Warwick, UK.

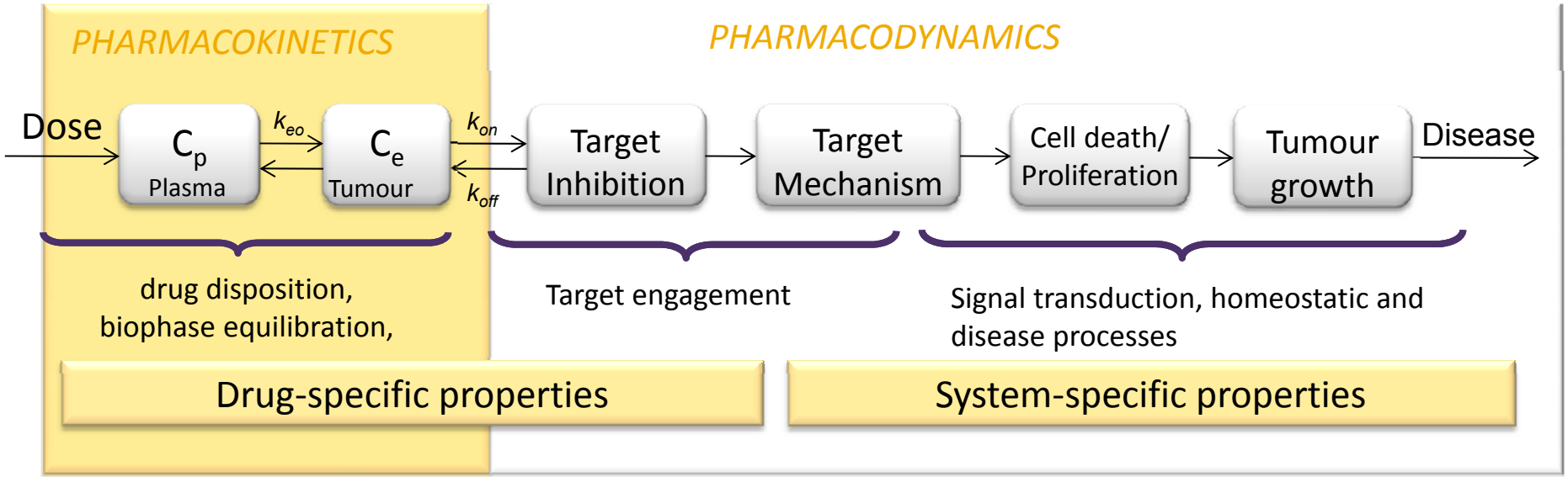
AstraZeneca

Modelling Pre-Clinical Oncology data

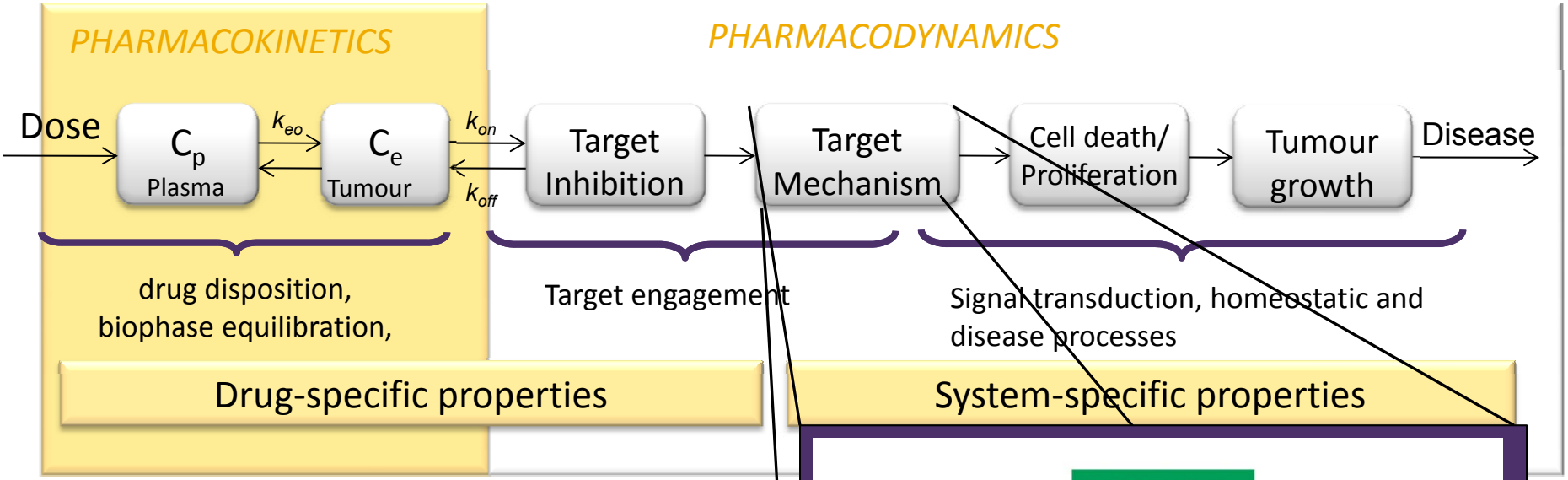
- What are the aims of pre-clinical PKPD?
  - Help validate the linkage between target and disease
  - Provide a quantitative framework
  - Identify drug exposures (and biomarker responses) that are efficacious to enable clinical predictions
  - Generate hypotheses for further experimentation
  - Optimal dosing schedules
  - Identify schedules that are efficacious in combination with standard of care

- Translate to the clinic
- Dose Escalation
- Balance with Safety
- Go/No Go

Cancer disease process:
Translation from animal to human



Cancer disease process: Translation from animal to human



Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
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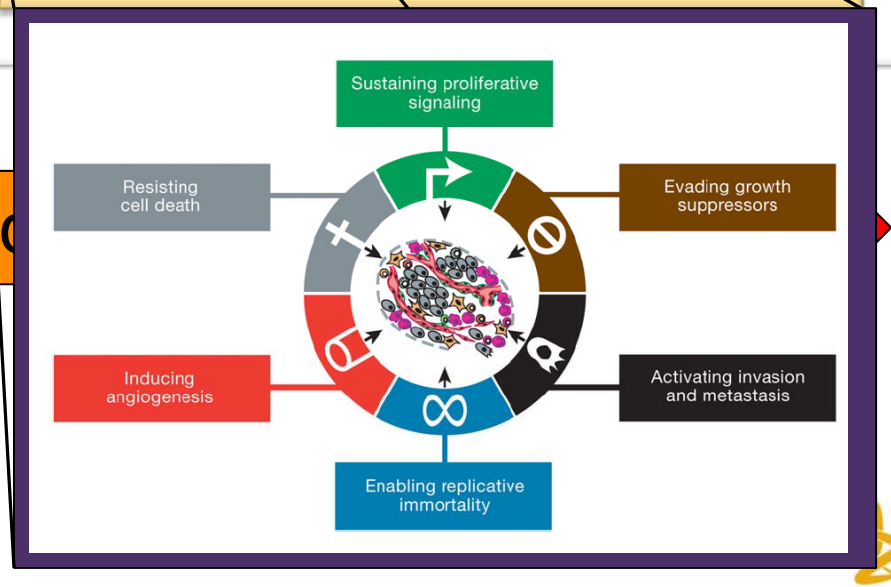


Overview of models in the literature

$$\frac{dY}{dt} = \lambda Y \qquad \text{Exponential}$$

$$\frac{dY}{dt} = Y\left(\alpha - \beta Ln\left(\frac{Y}{Y_0}\right)\right) \qquad \text{Gompertz}$$

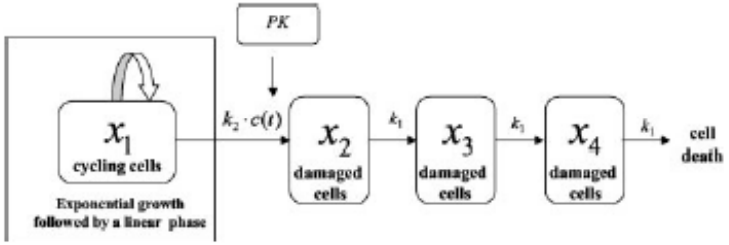
$$\frac{dY}{dt} = \alpha Y^{2/3} - \beta Y \qquad \text{Bertalanffy}$$

$$\frac{dY}{dt} = \alpha Y - \beta Y^2 \qquad \text{Logistic}$$

- Empirical models of control growth.
- No explanation of how the disease state results in this.
- No explanation of how the drug interacts with this process
- OK for prediction within drug, but not between drugs

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

Wang et al CPT 2009 for clinical NSCLC model. Links tumour growth to outcome in Drug Independent way



Model by Simeoni and co-workers. Allows for delay in drug effect. Drug effect linear

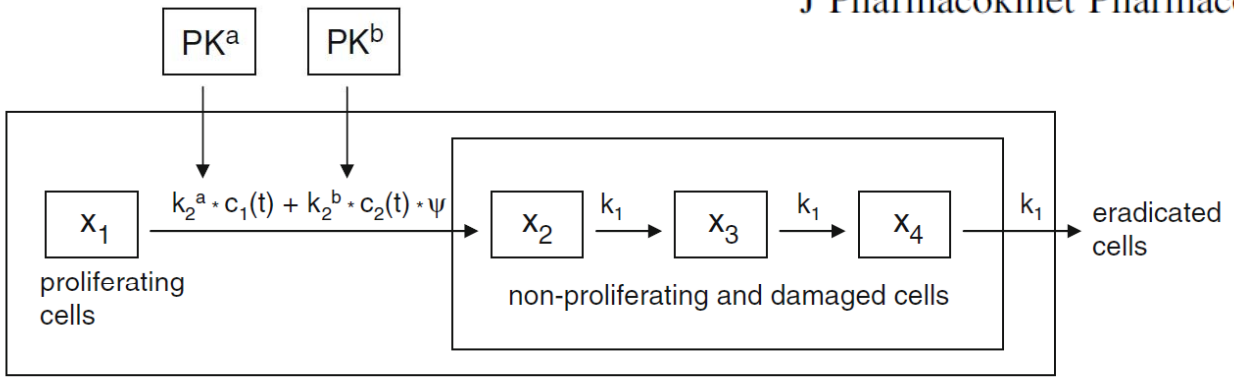
$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 \cdot c(t) \cdot x_1(t)$$

Overview of models in the literature:

Modeling of tumor growth and anticancer effects of combination therapy

Gilbert Koch · Antje Walz · Gezim Lahu · Johannes Schropp

J Pharmacokinet Pharmacodyn (2009) 36:179–197



Mechanism of interaction not explained – what if proliferating fraction is different? Interaction not related to concentration of both drugs – One drug is apparently more effective in the presence of the other

What are the issues?

Drug Dependent

- What effect does the drug have on the pathway?
- Can schedule dependent efficacy be explained?
- Can we extrapolate to untested doses and schedules?

System Dependent

•Pathway inhibition can have multiple consequences

•Connecting target mechanism to disease progression

•Multiple processes in tumours, these are likely to be different between xenografts, explants and clinical tumours

- •Vasculature
- •Cycling compartment
- •Drug distribution
- •Doubling rate

•Models of complexity allowed by the data

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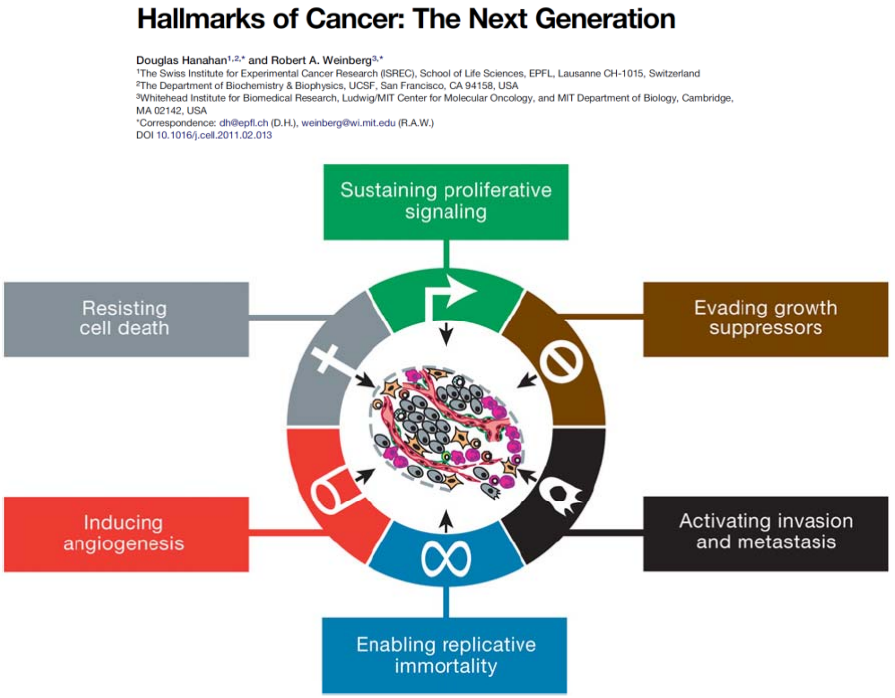
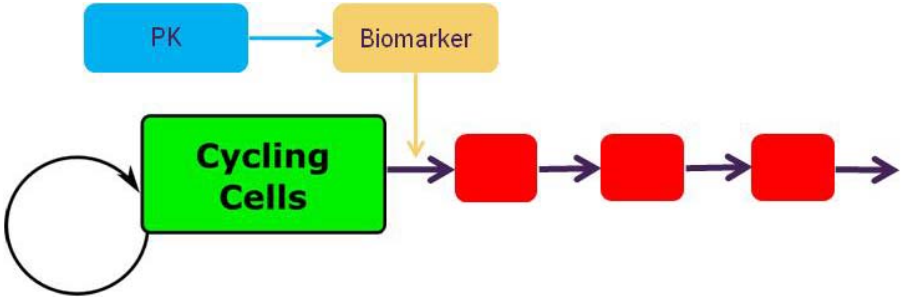
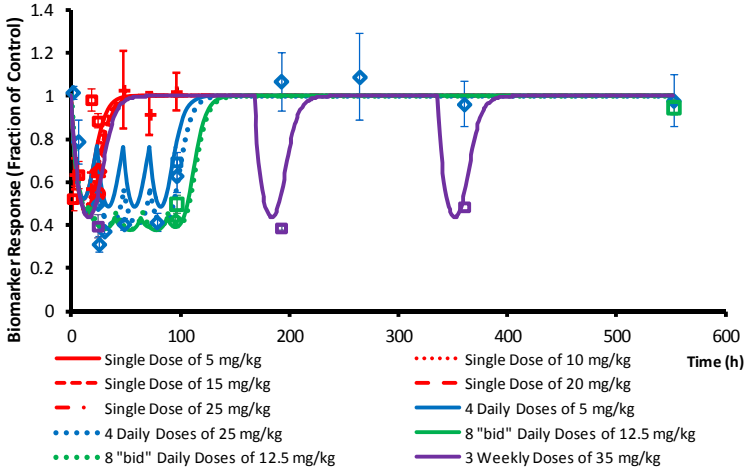


Example 1: connecting indirect response biomarker to xenograft growth

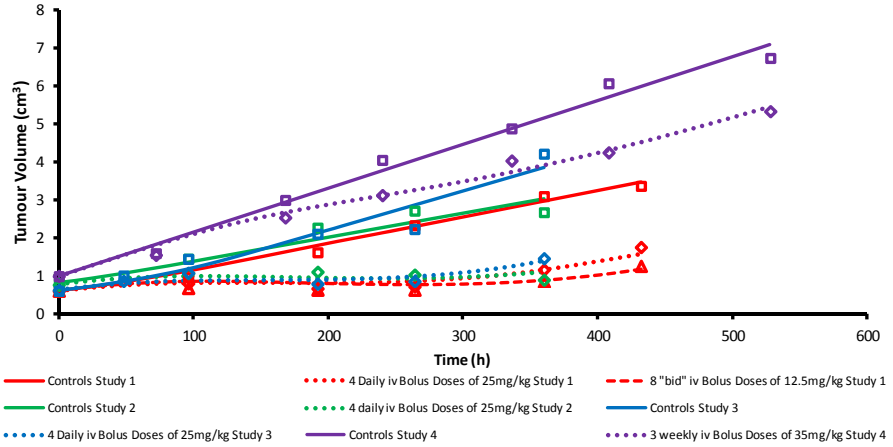
- Biomarker delay allowed explanation of delayed effects on xenograft growth
- Can test whether biomarker predicts efficacy for other drugs with same target – <u>confirms biomarker is appropriate</u>



PD



Efficacy



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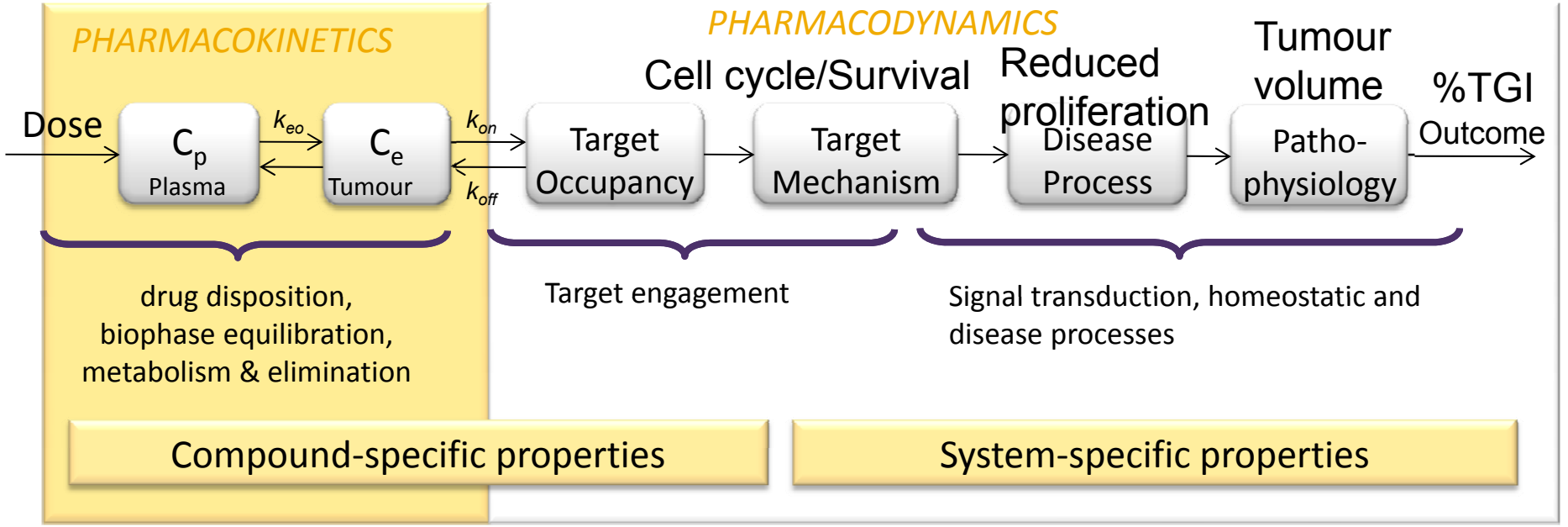
What do we need in a mechanistic tumour growth model

- Link between target, target effect and disease process that can rationalise different effect for different dosing regimen
  - Is the delay in drug effect observed due to delay in pathway or duration of cell death process?
  - Apoptosis is not the only mode of cell death
- Account for potential different effects the same agent has
- Mechanistically rationalise effects of combination therapy – additive, synergistic, antagonistic
- Mechanism (and system approach) allows differences between animal and human to be factored in
- Translation –linkage from target engagement to xenograft growth to translate PoM markers

Making models more mechanistic



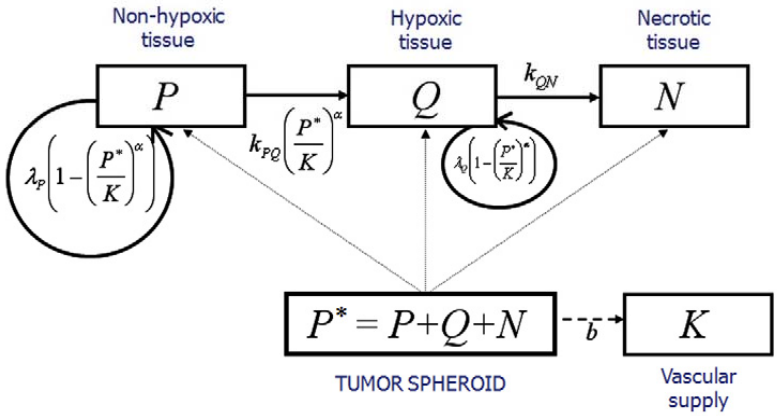
- Data can be generated at these various steps pre-clinically
- Some steps are measurable clinically
- Intermediate steps (eg Target Mechanism) are not
- Mechanistic link – assume pre-clinical mechanism is relevant to clinic (implicit assumption of xenograft studies)

Emerging models in the literature: More mechanism

A model of vascular tumour growth in mice combining longitudinal tumour size data with histological biomarkers

Benjamin Ribba [a,*], *Emmanuel Watkin* [b,c,d], *Michel Tod* [b,e,f], *Pascal Girard* [b,e,j], *Emmanuel Grenier* [a,g], *Benoît You* [b,e,h], *Enrico Giraudo* [i], *Gilles Freyer* [b,e,h]

EUROPEAN JOURNAL OF CANCER 47 (2011) 479–490



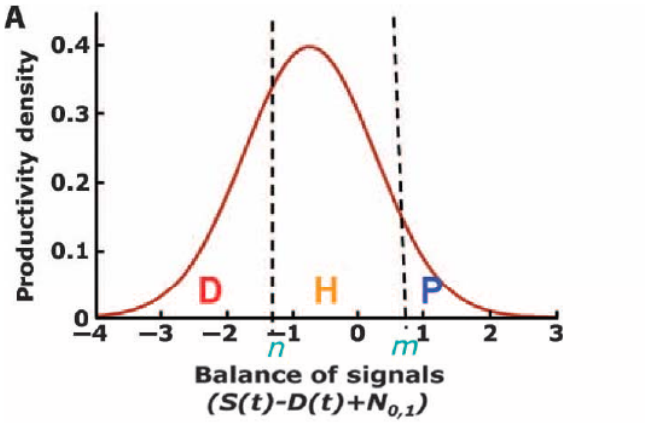
Model Considering different populations of cells and the effects of hypoxia and angiogenesis

Emerging models in the literature: More mechanism

Survival and Death Signals Can Predict Tumor Response to Therapy After Oncogene Inactivation

Phuoc T. Tran,[1*†] Pavan K. Bendapudi,[2*] H. Jill Lin,[3*] Peter Choi,[2] Shan Koh,[2] Joy Chen,[2] George Horng,[2] Nicholas P. Hughes,[3] Lawrence H. Schwartz,[4] Vincent A. Miller,[5] Toshiyuki Kawashima,[6] Toshio Kitamura,[6] David Paik,[3‡§] Dean W. Felsher[2‡§]

www.ScienceTranslationalMedicine.org 5 October 2011 Vol 3 Issue 103



C

Tumor vol. data: $\frac{dV}{dt} = \frac{1}{T_p} \cdot (1 - \Phi(m - S(t) + D(t))) \cdot \hat{V} - \frac{1}{T_a} \cdot (\Phi(n - S(t) + D(t))) \cdot \hat{V}$

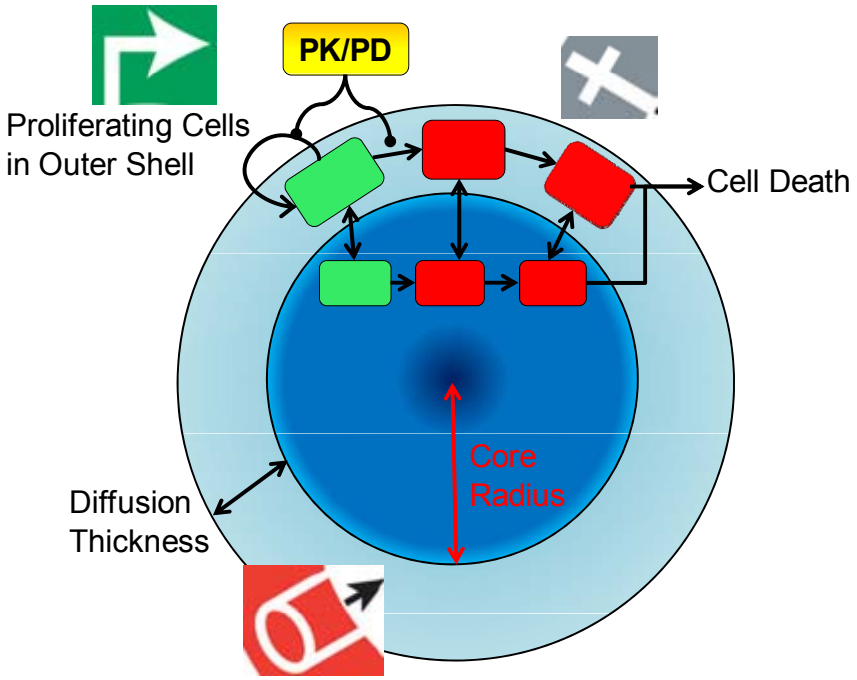
Ki-67 data: $PI = (\%\ \text{proliferation}) \cdot \frac{t_p}{T_p} = (1 - \Phi(m - S(t) + D(t))) \cdot \frac{t_p}{T_p}$

Cleaved casp-3 data: $AI = (\%\ \text{apoptosis}) \cdot \frac{t_a}{T_a} = (\Phi(n - S(t) + D(t))) \cdot \frac{t_a}{T_a}$

- Useful linkage between biomarker and drug effect
- Considers markers of proliferation and apoptosis
- Effect on tumour (cell population) is a balance of these effects. Normal distribution used to model proportion of cells in each state

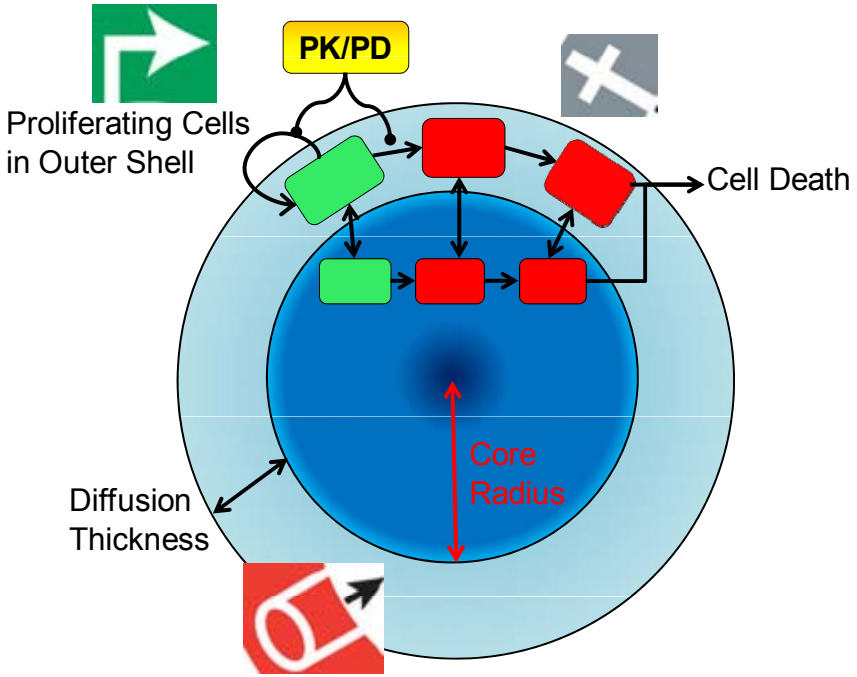
Can we make models more mechanistic?

- Simple framework of micro-environment offers the possibility to build in greater mechanistic detail.
- More physiological
- “Diffusion thickness” is vascular capacity to supply nutrients. Angiogenesis
- Movement of cells between shell and core as xenograft grows/shrinks. Allows for changing proportions of viable:dead cells after multiple treatment cycles
- Structurally Identifiable



Can we make models more mechanistic?

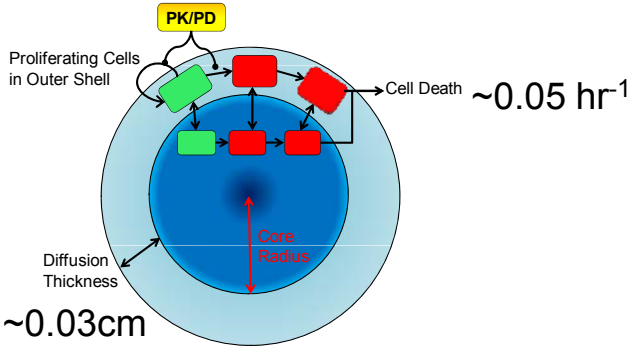
•Exponential to linear growth modelled as proliferating shell becoming a decreasing proportion of the total volume. Model by Jumbe et al (J. PK PD 2010) is case where diffusion thickness is zero.
•Can apply separate effects of anti-proliferation, pro-apoptosis and anti-angiogenesis driven by PK or biomarkers
•Drug effect applied to susceptible compartment (e.g. cycling cells) only



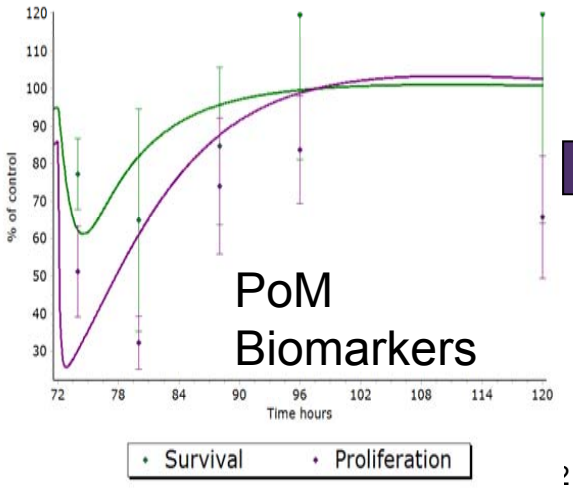
Example 2: Multiple effects of drug and combination

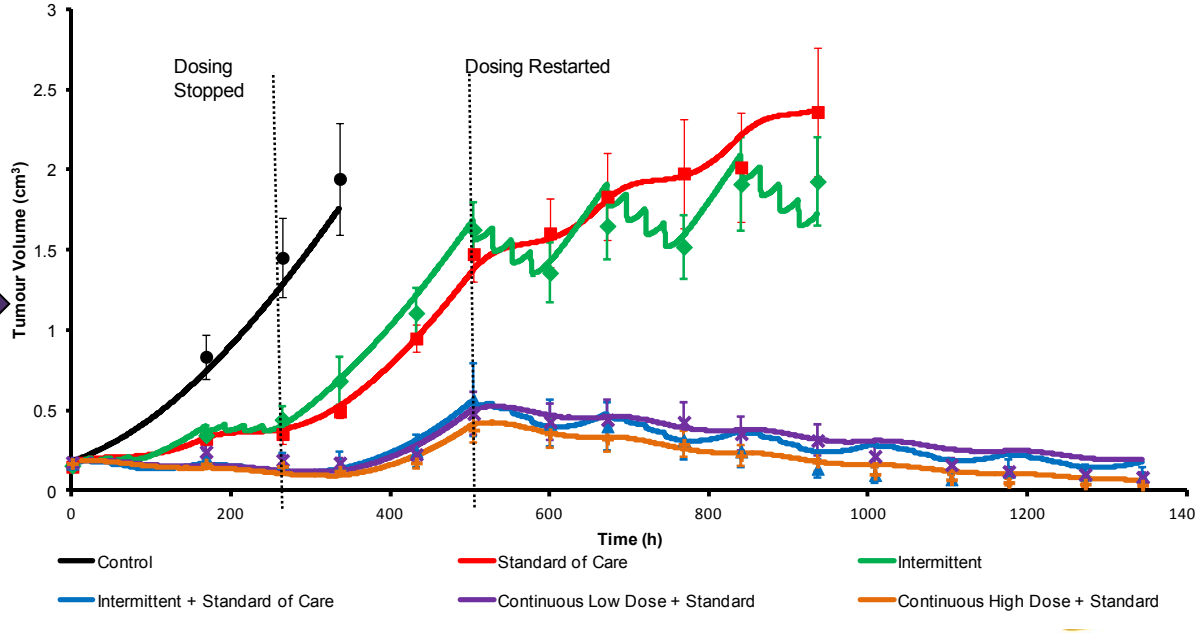
- Two biomarkers- one of proliferative, one survival
- SoC no PD so used PK to drive apoptotic effect
- Assumed SoC could only effect cycling compartment – potential for antagonism
- Assumed pro-apoptotic effect would increase effect of SoC – potential for synergism
- Model can capture differences in efficacy and drug effect on rechallenge

Anti-proliferative and pro-apoptotic



Efficacy





Conclusion

- More mechanism can be built in whilst ensuring identifiability
- More mechanism?
  - Cell Cycle
  - DNA synthesis
  - Metabolism
  - Resistance
- Are different phenotypic changes distinguishable from tumour growth data? Can we confirm mechanism is correct?
- What are the differences in explants vs. xenografts vs clinical tumours?
- What are the equivalent human tumour system parameters (for a given tumour type)
- Model is framework to be built upon– is identifiable despite complexity