

Can the PK drivers of anti-tumour response be xenograft specific ? – a mathematical analysis



Heinrich J. Huber¹ and Hitesh B. Mistry²

¹Boehringer Ingelheim RCV GmbH & Co KG, Drug Discovery Sciences, Dr. Boehringer-Gasse 5-11, 1121 Wien, Austria

²SEDA Pharmaceutical Development Services, Oakfield Road Cheadle Royal Business Park, Cheadle, SK8 3GX, United Kingdom

Introduction: In oncology, the use of in-vitro to in-vivo correlations (IVIVC) is prevalent, linking in-vitro parameters like IC50 to in-vivo drug exposure in plasma and tumor growth inhibition (TGI). These correlations are crucial for experimental design and for dosage decisions of tumour xenograft studies based on in vitro efficacy from cell line models. We provide a mathematical analysis that primarily focuses on exploring the connection between these empirical IVIVCs of exposure-response relationships and a PD model of semi-mechanistic tumor-growth.

IC50 coverage and TGI across compounds and cell lines (*)

Empirical sigmoid fit

$$TGI = \frac{TGI_{max} - TGI_{min}}{1 + (PD_{inflex} / \frac{c_{coverage,ub}}{IC50})^{hill_{exp}}}$$

or using the area under curve AUC_{ub} over time $c_{ub}(t)$ over a dosing interval τ

$$TGI = \frac{TGI_{max} - TGI_{min}}{1 + (\tau * PD_{inflex} / \frac{AUC_{ub}}{IC50})^{hill_{exp}}}$$
$$AUC_{ub} = dose_{stasis} \times AUC_{DN,ub}$$

With Stasis condition

$$dose_{stasis} = \frac{PD_{inflex}}{(\frac{TGI_{max} - TGI_{min}}{100} - 1)^{1/hill_{exp}}} \cdot \frac{IC50}{AUC_{DN,ub} / \tau}$$

coverage factor (e.g 1.4) IC50 coverage

Conclusion

Stasis and dose linearity assumptions allows estimation of stasis dose from in vitro IC50

(*) Ongoing tyrosine kinase inhibitor program

Used PKTGI Model assuming linear tumour growth (Mayneord-like model)

Model: Derivation of Linear Law
Assume viable rim has thickness d , assumed small to radius r , grows rate a , volume is approximately:
 $V_p = 4\pi r^2 d$
and it is growing at a rate
 $\frac{dV}{dt} = aV_p = a4\pi r^2 d$

growth equation for the radius is given by
 $\frac{dr}{dt} = \frac{dr}{dV} \frac{dV}{dt} = \left(\frac{1}{4\pi r^2}\right) a4\pi r^2 d = ad$
which is solved to give the linear equation
 $r = R_0 + adt$
 R_0 is initial radius, ad replaced by constant c .

Linear radius growth validated in several models

EC50 coverage

$$\frac{dR}{dt} = g - d \frac{conc_{plasma_free}(t)^{hill}}{conc_{plasma_free}(t)^{hill} + IC50^{hill}} R$$

Effective AUC/EC50 coverage

$g \dots$ tumour specific growth rate for radius
 $d \dots$ compound-independent drug sensitivity of xenograft model
 $IC50 \dots$ proliferation IC50 (can be taken from *in vitro* panels)

Calculating Stasis Dose from the model using linear, simplified 1cmp PK

$$R = R_0 + g\tau - d \int_0^\tau \frac{c_{plasma, free}(t)^{hill}}{IC50^{hill} + c_{plasma, free}(t)^{hill}} dt$$
$$\frac{1}{hill} \cdot \frac{\tau}{\ln(PTR)} \ln \left[\frac{\frac{c_{max}^{hill}}{c_{trough}^{hill}} + IC50^{hill}}{c_{trough}^{hill} + IC50^{hill}} \right] \quad PTR = \frac{C_{max}}{C_{trough}}$$
$$AUC_{ub} = dose_{stasis} \times AUC_{DN,ub}$$

$$dose_{stasis} = \frac{MEF(PTR, g/d, hill)}{\left(\frac{PTR - 1}{\ln(PTR)} - \frac{PTR^{hill \cdot q/d} - 1}{PTR^{hill} - PTR^{hill \cdot q/d}} \right)} \cdot \frac{IC50^{hill}}{AUC_{DN,ub} / \tau}$$

Xeno-model and compound dependent coverage factor IC50 coverage

Doses can be sampled with different (g/d, IC50, AUC) to simulate populations

Conclusion: Mayneord -like model under simplified PK consistent to IVIVC coverage with respect to tumour stasis dose

AUC vs PTR as driver of stasis dose (hill=1)

Include Hill (g/d=0.4)

Illustration of g/d and PTR effect on IVIVC

- We provided here a theoretical analysis of the Mayneord-like model, exploring drug-induced tumor responses, tumor stasis mechanisms, and the interplay between pharmacokinetics, pharmacodynamics, and xenograft-specific tumor growth and decay rates
- **Drivers of tumour stasis can be xenograft specific**
 - Tumor stasis is normal driven by dose-normalized AUC and IC50 coverage, with mild dependence on peak-to-trough ratios (PTR).
 - However, g/d ratios close to 1, cooperativity (hill>1) and large PTR can lead to PK-shape dependency (PTR, max, trough).
 - Clinical back-translation using patient-specific g/d ratios could enhance understanding of resistance.
 - Stasis doses can be evaluated on a population level using in vitro IC50, AUC variation and g/d distributions (at least preclinically)
 - **Resistance Mechanisms are covered by the tumour model:**
 - Tumor stasis is unattainable if tumor growth (g) exceeds decay (d), highlighting in-vivo resistance mechanisms
 - **Broader Applicability:**
 - The tumour model is a simple effect/inhibition model, broader applicability to other therapeutic area is possible.

Ref: Huber, H.J., Mistry, H.B. *J Pharmacokinet Pharmacodyn* 51,169–185 (2024)