INTRODUCTION

The failure rate in the research and development of new anticancer treatments has necessitated a more objective approach. The three pillars proposed by Pfizer1 and the 5Rs that followed from AstraZeneca2 demonstrate the importance of identifying the pharmacologically relevant drug exposure required in patients. The impact that such quantitative approaches are having on the drug development pipeline is demonstrable3 and the part that modeling and simulation has played in this is significant.4,5 The application of these approaches in oncology is preceded6 but less mature than in the broader pharmaceutical field7 with further work required to integrate nonclinical and clinical modeling.8 The majority of these reviews have concentrated on the determination of exposure-response relationships.9,10 These relationships are the foundations of any transitional strategy and are informative for an efficacious dose/exposure setting.

Successful translational strategies require the identification of tractable end point(s) that can be bridged across the nonclinical and clinical space. Overall survival (OS) is the gold standard end point for measuring efficacy in the clinic,11 and progression-free survival (PFS) is an important secondary end point. However, these end points are challenging from a nonclinical to clinical translational standpoint. Tumor size is a more accessible, immediate, and longitudinal measure for both clinical and nonclinical settings with greater potential for translation.

Tumor size and growth rates are important correlates of both OS and PFS. Indeed, many prognostic models feature tumor size at baseline12 as a major risk factor. In the past when few treatment options were available, data show that the growth rate correlates negatively with survival in breast cancer,13 ovarian cancer,14 and pulmonary metastases.15 Indeed, the observed pretreatment growth rate is predictive of re-occurrence.16

Within the oncology setting there are strong drivers to maximize exposure (increased efficacy, reduced likelihood of resistance, etc.) whereas often accepting a lower tolerability profile than in other settings. Optimizing the regimen to achieve maximal tumor reduction with acceptable safety is a key part of clinical development.17,18 Optimization can occur empirically in the clinic by comparing regimens in a...
randomized trial or using an early responding biomarker if available. However, this is not always possible or appropriate and so nonclinical data and modeling may be informative as long as the translational strategy includes both dose and regimen sensitivities.

The question is then what framework should be utilized to enable translational modeling of tumor growth? This model needs to capture both the key properties describing tumor growth in the nonclinical and clinical settings and drug effects in a way that facilitates assessment of both dose and regimen.

The first step in the dose-efficacy chain is the prediction of pharmacokinetics (PKs) from nonclinical data and this aspect is well preceded and can be predicted reasonably accurately using both physiologically-based PK (PBPK) and allometry approaches.19 In addition, accounting for differences in free drug exposure between animal models and patients improves translation of efficacious concentrations.20

Second, relevant biological differences in patient tumors that confer sensitivity/ resistance to a given treatment have to be accounted for, typically by matching these genetic/transcriptomic characteristics in animal models.21

Third, the experimental design and analysis should aim to identify the fundamental parameters of tumor growth, response, and resistance alongside the compound-related effects. Phenomenological models may be sufficient predictors for the same context but not for translation; balancing biological detail with rigorous inference is required.

Last, a similar level of rigor should be used to characterize toxicities in the nonclinical species to enable translation to the clinical setting. Care of course should be taken to understand the translational relevance of toxicity because some may be species specific and some, for example, nausea, may not be observable in animals.

**CLINICAL EVIDENCE THAT SCHEDULE MATTERS**

Paclitaxel was originally approved on a 175 mg/m² every three weeks (q3w) regimen. However, it has been shown that in combination with q3w carboplatin, a more dose dense and intense regimen of 80 mg/m² every week (q.w.) provides a PFS and OS advantage in ovarian cancer.24 What is most compelling about this observation is that it is not simply about dosing more paclitaxel in a cycle. A study looking at doses up to 250 mg/m² q3w, albeit in breast cancer rather than ovarian cancer,25 showed no increase in PFS. These data suggest that 175 mg/m² is near the plateau of the dose response curve and so lower more frequent dosing results in a greater net effect. A more recent meta-analysis of clinical data concludes that the weekly schedule does indeed have comparable or better efficacy with reduced toxicity.26

Radio-oncologists have investigated the optimal way to deliver radiation over many years from which a quantitative theoretical framework emerged. In ref. 27, Furneaux and colleagues demonstrated that the potential regrowth rate of brain cancers, as measured by ex vivo cell cycle time, was predictive of survival. Proving this point, a study in head and neck squamous cell carcinomas (HNSCC)28 showed similarly reduced survival in patients with increased regrowth rate. This study also demonstrated that modifying the radiation delivery to be more dose dense by hypofractionation increased the survival time in these patients.

Increasing dose density of chemotherapy improved outcomes in patients with breast cancer, as reported by Citron et al.29 The fact that sequential polychemotherapy was as effective as concurrent administration is suggestive of additive or independent drug action for the treatments. A second meta-analysis30 of the efficacy of a range of chemotherapies in breast cancer demonstrated that adjusting the regimen to deliver the same total dose in a shorter period, or even increasing the dose, resulted in better outcomes. Tannock published a number of reviews on the importance of treatment regimen31–33 and that response to treatment is a function of treatment effect and regrowth of the cancer between treatment. Skipper (e.g., ref. 34) explicitly modeled these as two exponential processes such that the dose effect lost due to regrowth is explicit:

\[
\log(\text{Tumour Reduction}) = K_s n - (\log 2/\text{DT})(n - 1) II'
\]

The first term, the dose-response \(K_s\) for \(n\) doses, is clearly important and there is a significant body of literature demonstrating how small reductions in dose can lead to suboptimal outcomes. The second term can be interpreted as the dose effect lost due to tumor regrowth of doubling time (DT) between treatment intervals of \(II\). It is important to understand the relationship between dose intensity (dose per time, e.g., \(K_s/II\)), dose density (administrations per time, \(II\)), and clinical outcome. These relationships will vary across treatment mechanisms and cancer types due to differences in the exposure-response relationship. Total dose, although well-correlated with outcome, will suffer from immortal time bias because it depends on the time a patient remains on treatment, whereas dose intensity, per cycle, is prespecified and will define the treatment effect that has to work against regrowth in each round of treatment. There are many reports citing a strong, positive relationship between dose intensity and OS35 in metastatic breast cancer,36 in early breast cancer and aggressive lymphomas,37 and ovarian...
cancer. Many of the reductions in dose intensity are of the order of 15%–30% of the recommended dose and yet a significant reduction in OS is observed in many cancers, suggesting a steep dose-response relationship that is also observed in animal models.39

**IMPORTANT PROPERTIES OF PREDICTIVE MODELS**

Translational models need to describe existing data but also predict to a new context. Therefore, the model must reflect how the system differs in that new context. That a complex model is required to do this is a hypothesis, not a fact.40 In reality, overly complex models can be poorly performing because of the low signal to noise ratio41 and challenges in estimation of parameter values. To enable informed translation, one needs to assert which parameters are altered and which remain constant between animals and humans. To achieve this, parameters need to be well-estimated and simulations of new contexts should be uniquely sensitive to parameter values. Thus, a mathematical model should have uniquely identifiable parameters both from a structural identifiability42 and a statistical inference perspective.

Structural uncertainty is important as well because this can lead to significant misprediction.43 A model that works at a more macroscopic scale has fewer equations and parameters associated with it and so will present with less structural and parameter uncertainty: fewer plausible permutations of the processes it describes are possible. The challenge to the translational scientist is to balance parameter identifiability while ensuring that the mathematical model has enough complexity to allow cross species predictions. Careful consideration of the implications of structural model assumptions should be made and the translational scientist should design experiments that test these assumptions. The greatest value is obtained from external validation efforts, such as utilizing parameter estimates from in vitro systems to predict in vivo effects or to predicting experimental results outside of experimental designs already studied. It is from these efforts that robust translational knowledge is gained, and structural model limitations revealed. In doing so, issues with a model can be recognized and the domain of applicability of the model can be understood.

A balance of model complexity and identifiability has been achieved in the study of PKs. Compartmental models are data descriptive models that are appropriate for the purposes of prediction and comparison within a fixed context. PBPK models have had an impact in drug development because they answer key questions of PK translation and they achieve this by reflecting the key parameters associated with observed PK variability. These key parameters have been well-characterized in the literature and our knowledge of mammalian physiology leaves little uncertainty about the structure a PBPK model should take. Complexity has still been controlled by describing organs as well-mixed subsystems. Qualification with nonclinical PK data is an important step in the model-building process, and may highlight additional processes, such as solubility limited oral absorption, saturable metabolic clearance, and target mediated drug-disposition and distribution. Without these, the predictive value of a PBPK model might be limited. However, there are nonclinical systems to investigate these processes (e.g., characterizing drug metabolism as an enzymatic mediated reaction with associated maximal rate of metabolism $V_{\text{max}}$ and kinetic metabolite $K_m$, measuring target binding affinity and expression etc.). Similarly, there are nonclinical systems and experimental approaches, some of which we outline below, that allow insight into an anticancer medication’s mechanism of action.

**THE KEY PARAMETERS AND PROCESSES FOR A TRANSLATABLE TUMOR MODEL**

We now ask what parameters and processes are required in an optimal model of tumor growth and treatment response? It will be shown that besides the PK/pharmacodynamic (PD) relationship, which is dependent on the particular treatment, the key parameters are the proliferating fraction, the cell cycle time, and the treatment independent cell death occurring in the tumor.

A great deal of effort has been made into quantifying the relationship between regimen and tumor response to radiotherapy. This has culminated in the framework of the 5Rs of radiotherapy.44 It can be extended to chemotherapy and potentially targeted treatments.33 Below, the 5Rs are listed alongside their systemic treatment equivalents:

1. Radio-sensitivity/ resistance (half-maximal effective concentration [EC$_{50}$] and maximum effect [E$_{\text{max}}$])
2. Redistribution in cell cycle - or between sensitive and tolerant phenotypes (E$_{\text{max}}$ due to maximal achievable kill and time)
3. Re-oxygenation (as the tumor shrinks) will increase proliferating fraction (E$_{\text{max}}$) and its effects on,
4. Repopulation, the regrowth of the tumor (tumor growth rate and time)
5. Repair - persistence of PDs (time).

Sensitivity to treatment will be both a function of the potency of the drug and, as discussed below, the duration
of exposure. Redistribution in the cell cycle, whereby the system re-equilibrates after treatment, is important when delivering successive doses very rapidly, as is the case in radiotherapy.

Repopulation and re-oxygenation are fundamental to the net efficacy of repeated cycles of treatment. The literature suggests that the key parameters are the growing fraction (GF), the cell cycle time $T_c$, and cell loss factor $\varphi$. The GF is defined as the ratio of proliferating to total tumor mass. Through radio labeling experiments it has been found that GF is $\sim 50\%$ in animal models and in the clinic. These estimates compare well to more recent imaging and biomarker based measurements in non-small cell lung cancer (NSCLC) and breast cancer, as well as xenografted models. $T_c$ has been estimated in the range of 12–48 h in animal models and the clinic. This is comparable to the DT of in vitro cell cultures.

If exponential growth is assumed, then the potential DT of a tumor is $T_{pot} = T_c / GF$. In most cases, the observed tumor DT is much greater than this. Hypothetically, this disconnect between potential and actual DT can be accounted for by intrinsic cell death. The ratio of death to proliferation is defined as the cell loss factor $\varphi = 1 - T_{pot} / DT$. Values of $\varphi \approx 50\%$ have been estimated in transplantable animal tumors, whereas it was $\varphi \approx 90\% – 95\%$ in human tumors where tumors grow comparably more slowly. Unfortunately, there are no studies demonstrating a relationship between $\varphi$ and biomarkers of cell death, such as cleaved Caspase-3. Cell death is perhaps greater in clinical tumors because (i) they are much larger and so more hypoxic than xenografts, (ii) tumor immunity is present in patients, and (iii) differing selection pressure has occurred in the patient than xenografts growing in an alien environment. This difference could be important because it has been observed that cell loss plays a role in the response to single high doses of radiation due to the relative ease of tipping the balance between proliferation and death. The fact that the above parameters are comparable suggests animal models are not that misleading but require a model-based interpretation.

Skipper et al. first noted that, under a broad range of experimental conditions, a given dose of chemotherapy kills a fixed proportion of proliferating cells. This principle of log cell kill ($K_0$) has guided the investigation of chemotherapy as well as radiotherapy (surviving fraction [SF]). It has been reported that proliferating cells have a tendency to be more sensitive to chemotherapies in vitro than cells at rest. Consistent with this, many chemotherapies act primarily on cells that are replicating their DNA, and so the fraction of cells in S-phase might be an important determinant. Skipper and co-workers further proposed that the effect of a dose of chemotherapy was determined by the proliferating fraction, the rate of proliferation (cell cycle time), the drug concentration, and duration of drug exposure. They demonstrated this principle both in vitro and in vivo. Importantly, parameters intrinsic to the disease were brought together with drug-specific PKs and PDs.

In a review of data in a number of experimental systems, Valeriote and van Putten showed that cell cycle specific agents had a plateau in survival curves. Conceptually, these observations are an explanation of the clinical observations of the superiority of increased dose density. Applying the drug effect to proliferating cells, and relating to cell cycle time, is an explanation of $E_{max}$ that limits the effect of high dose intermittent therapy. Van Peperzeel demonstrated similar phenomena with radiotherapy of pulmonary lesions. Consistently, slower growing tumors (with presumably lower GF) were more resistant to radiation, and this relationship was preserved across species.

The intrinsic growth rate reduces with tumor size and time and explains the successful application of the Gompertzian growth model. The converse of these observations is the impact of growth acceleration when tumors are shrunk significantly and grow at a rate closer to their $T_{pot}$. In-depth investigations in nonclinical models and point to a reduction in the GF as well as $\varphi$ increasing with tumor size. The balance of these two changes could account for the reduced growth rate and also the plateauing Gompertzian growth seen in larger nonclinical tumors when cell death balances proliferation.

Tannock describes post-treatment acceleration as a form of treatment resistance where there will be a point reached where regrowth between treatments balances the treatment effect, resulting in a plateau of tumor size. The impact of acceleration in the response of animal models to chemotherapy can be seen in such reports as ref. 60 where the growth delay is much smaller than the reduced surviving fraction would predict and suggests an increased growth rate of 2–10-fold for tumors whose volume has been significantly reduced by treatment.

The Norton-Simon principle attempts to encode these relationships mathematically by applying the log-cell kill concept in vivo by stating the kill is proportional to the growth rate as a surrogate of the proliferating fraction. This model states that the drug effect ($E_{max}$) will be limited in larger, slower growing tumors and that the dose should be adjusted as treatment proceeds to account for the changing treatment effect and repopulation rate. Predictions made by this framework have been validated by clinical trials. Further, it was noted above that a large tumor pretreatment confers a poor prognosis—this is a baseline risk but could also be due to the fact the tumor
may shrink less readily under treatment due to a reduced GF.

MODELING HETEROGENEITY OF DRUG SENSITIVITY AND REPOPULATION

The importance of biological variability within patients and by anatomic site point to the need to anticipate its impact on the optimal regimen. A National Cancer Institute (NCI) data review suggests the breadth of response in relevant animal models is predictive of clinical response. There also is a great deal of concern that nonclinical experiments are not reproducible in part because heterogeneity in drug response has been controlled out. Additionally, when considering translation of heterogeneity, data should be gathered from a range of disease-relevant animal models and cell lines, and not only from responding drug-sensitive systems. Controlling variability where possible and understanding heterogeneity in nonclinical studies in these ways will facilitate a more informed translation.

In a series of studies, Inaba et al. investigated the response rate to chemotherapies in a collection of mouse xenografted models at the maximum tolerated dose (MTD) and clinically relevant drug exposures. The responses were lower at the clinically relevant doses than at mouse MTDs. What is surprising is how much response reduced and, when considering a wide range of tumor types, how much more reflective of the heterogeneity of efficacy in the clinic they were.

Similar work was carried out with topoisomerase 1 inhibitors in multiple xenografted models for colorectal, rhabdomyosarcomas, and neuroblastomas by Houghton and colleagues. Again, variation in response seen across models was used to identify the minimum drug exposure to control most models. This drug exposure was shown to be comparable to that achieved in several clinical investigations where responses were observed. This approach explained the lack of activity for some camptothecin derivatives because the required drug exposure was intolerable in patients. It was also concluded that dose dense therapy was most optimal—echoing clinical findings.

Each animal model can be considered as a separate representation of clinical disease and the data used to estimate the potential interpatient variability. Certainly, the use of heterogeneity in experimental results and conclusions would lead us to believe the most negative data as least as much as the most positive, if not more. As demonstrated by the work of Houghton et al., overall response rate (ORR) and PFS are not about average patient drug cover—it is the proportion of patients covered. This could never be assessed in a single animal model.

Consider again the analogy of PBPK modeling: its success lies in its ability to predict between patient variability in drug exposure using knowledge of variability of underlying physiological parameters. Patient derived xenograft (PDX) “n = 1 mouse trials” could be used to inform on variability and heterogeneity. Although interest in the development of these types of studies has been primarily for signal searching and patient selection, parameterizing mathematical models using these data would be another application.

Therefore, a translational model should be able to capture both the heterogeneity of response across models and variability in response within models for maximal utility. Nonlinear mixed effects are a familiar tool for many researchers and thus a model structure is required that will work within this statistical framework.

MODELS CURRENTLY IN THE LITERATURE

There are a plethora of models in the literature, many with macroscopic behaviour, similar to the Gompertzian like growth, but the question remains whether these can make valid predictions. Gompertzian growth models have been the most commonly applied, starting with Laird and continuing with Norton and Simons, because of their ability to model growth retardation with an exponentially reducing rate of growth. One issue is that it predicts a plateau in tumor size that is rarely observed in individuals. Burton showed that a ratio of 7–8 between the two Gompertzian parameters (the initial exponential rate and the rate at which this decays) is predicted by considering diffusion limited growth and that this was the case for reported parameter sets at the time. Brunton and Wheldon show that the two Gompertzian parameters are again highly correlated for a wide range of nonclinical tumors, something conjectured elsewhere, and formalized by Vaghi et al. Remarkably, the ratio is consistently between 8 and 10 pointing to an underlying mechanism of diffusion limited growth.

Other models have approached a size dependent growth rate from a physical point of view. The seminal work by Greenspan considered tumor spheroids grown in vitro and solid tumors growing in vivo. It was assumed that oxygen and nutrients required for successful cellular proliferation were delivered external to a spherical mass. This results in the prediction of a proliferating region near the surface of the tumor. This was mathematically expressed as partial differential equations that can be challenging to deal with
numerically, including parameter estimation. Conger and Ziskin took a simplifying step and assumed that this proliferating region was of a constant depth. This allowed the diffusion limited model to be expressed as ordinary differential equations (ODEs) with the inclusion of a necrotic core compartment that develops in the extremely hypoxic region near the core. For very small, fully oxygenated tumors, the growth rate is exponential; as the tumor grows this constant depth proliferating shell becomes a decreasing fraction of the whole tumor mass, resulting in growth retardation. They note that for large tumors the tumor radius will increase linearly with time, a phenomenon first reported and modeled by Mayneord in the 1930s and later Jumbe et al.

Generally, nonclinical tumor modeling suffers from issues of empiricism. Few models consider effects proportional to proliferating fraction or other phenotype that might be sensitive to treatment mechanism. The limitations of such models have been discussed elsewhere. For example, in the widely used Simeoni et al. model, drug effect is independent of the exponential or linear phase of tumor growth.

There are also a number of reviews of pharmacometric applications, where the models have most of the required phenomenological components (growth law, drug effect, and sometimes resistance) but they are descriptive, often with emphasis on the correlation between initial tumor response and OS. Few explicitly stated the questions that needed to be addressed, especially with respect to translation. Many lack the explicit dependence of tumor response on regimen. In contrast to PK modeling, where most practitioners will use the same model structures, antitumor data have had a whole range of different models applied that are not directly comparable.

One issue with the application of a descriptive mathematical model to data is that it may give a biased estimate of drug effect, thus compromising translational potential. To consistently derive translationally unbiased exposure-response relationships, a modeling framework needs to incorporate important pathophysiological parameters. Few if any current models exhibit the key processes and can be readily parameterized with cell cycle time, GF, and cell loss. This limits computational exploration of regimen optimization: in fact, optimization is rarely discussed except in a few cases.

Parsimonious models considering cellular proliferation, proliferating, and nonproliferating compartments and cell death have been reported. These reports also considered the impact of the chemotherapy regimen. The transition rates in this model were constant and therefore the steady state GF is size independent. Kozusko and co-workers reasoned that the observed growth retardation is due to GF reducing with tumor size (in line with experimental data) and so modified the framework of Gyllenberg and Webb with tumor size-dependent transition rates between proliferating and nonproliferating states. By comparing this general framework to specific growth laws, they were able to express Logistic and Gompertzian growth with explicit proliferating fractions.

A PROTOTYPE SOLUTION

A prototype model is described that encodes the fundamental processes of size-dependent GF cell cycle time $T_c$, and cell loss factor $q$, while minimizing complexity. The Conger model, approaches modeling the GF from a physical point of view. It assumes that the proliferating fraction is a layer of constant depth near the surface of the tumor. Conceptually, ignoring a necrotic fraction, this model for the tumor volume ($V$) can be written as a single ODE:

$$
\frac{dV}{dt} = V \left( (\beta - \mu_P) \text{GF} - \mu_Q (1 - \text{GF}) \right); V(0) = V_0
$$

$$
\text{GF} = 1 - \left( 1 - \frac{R_{\text{diff}}}{r} \right)^3
$$

Where $r$ is the radius of the tumor assuming a spherical geometry, $R_{\text{diff}}$ is the depth of the proliferating compartment (fraction GF) into the tumor, and $\beta$, $\mu_P$, and $\mu_Q$ are the rates of proliferation, cell death in the proliferating (P) and quiescent (Q) compartments, respectively. This is a mathematical form proposed by Tannock, however, it is more useful to write this using framework proposed by Kozusko and Bourdeau:

$$
\frac{d\text{GF}}{dt} = m \left( \text{GF} - \text{GF}_{\infty} \right) \left( (1 - \text{GF}) - (1 - \text{GF})^2 \right); \text{GF}(0) = \text{GF}_0
$$

$$
\frac{dV}{dt} = mV \left( \text{GF} - \text{GF}_{\infty} \right); V(0) = V_0
$$

where

$$
m = \beta - \mu_P + \mu_Q
$$

is the growing fraction when tumor size plateaus.

The GF alters explicitly a function of the rate of tumor growth. Notice the first term of the last factor for GF is related to cell death in the quiescent compartment and the second is transfer of mass across the boundary between P
and Q. This factor is always negative and so the GF will reduce with increasing tumor size, and this decrease will be approximately exponential for small GF. Interestingly, the rate of change of GF is also independent of total tumor volume. These are very similar behaviors to the Gompertzian model. In fact, this model, when there is cell death in the quiescent compartment, will plateau with a non-zero GF. The tumor volume this occurs at will be dependent upon the initial GF.

In this model, there is cell death in both compartments. The relationship between these rates, the GF, and the cell loss factor $\varphi$, are as follows:

$$
\varphi = \frac{\mu_P GF_0 + \mu_Q (1 - GF_0)}{\beta GF_0}
$$

The data in the literature do not define to what extent the total cell loss factor should be apportioned to the proliferating (GF) and quiescent (1-GF) compartments. The increase in cell loss factor for larger tumors, and the tendency to plateau, suggests at least some cell death should be occurring in the quiescent compartment. The death in the proliferating compartment will only be distinguishable from proliferation if data are available for antiproliferative treatment. If only control data are available, then only $\beta - \mu_P$ can be identified. Besides this, a previous analysis of this type of model demonstrates parameter identifiability. For an initial proportion, $\alpha$, of cell loss factor in the proliferating compartment, with the remaining in the quiescent compartment, the rates of death in the proliferating and quiescent compartments required to account for the total cell loss factor are:

$$
\mu_P = \varphi \beta \alpha
$$
$$
\mu_Q = \varphi \beta (1 - \alpha) \cdot \frac{GF_0}{1 - GF_0}
$$

The parameter $m$ is now redefined to include an antiproliferative (saturable defined by maximum unbound systemic concentration $I_{max}$ and half-maximal inhibitory concentration $IC_{50}$) and cytotoxic (linear defined by $K_{kill}$) drug ($C_p$) effects to illustrate how drug effects might be implemented and so the behavior of this model under treatment can be demonstrated.

$$
m = \beta \left(1 - \frac{I_{max}C_p}{IC_{50} + C_p}\right) - \mu_P - K_{kill}C_p + \mu_Q
$$

The results of the control growth and response to a range of doses of a cytotoxic treatment are now demonstrated. In Figure 1, all parameters are kept constant except for the initial condition of the GF. Despite growing more rapidly and having a greater proportional repopulation between

---

**Figure 1** Increased growth fraction (GF) leads to more rapid control growth and greater cytotoxic drug effect per dose as measured by tumor size reduction. All parameters constant ($\beta = 1/24$, $\varphi = 50\%$, $\alpha = 1$, $K_{kill} = 0.015$) except for initial condition of GF0 with 40% on the left and 80% initial growing fraction on the right. CLF, cell loss factor.
cycles of treatment the tumor with the larger GF responds much more to each dose, resulting in tumor shrinkage at the top dose. Figure 2 shows the impact of cell loss for single and repeat dose. The impact is twofold—the greater background cell death results in a slightly stronger effect on tumor volume, even for the first dose. Second, the reduced rate of repopulation means there is an increased accrued effect. In addition, note in this case the increasing drug

**Figure 2** Increasing cell loss factor (50% vs. 90%) reduces control growth and increases the net drug effect. All other parameters are kept constant ($\beta = 1/24$, $GF_0 = 0.5$, $\alpha = 1$, $K_{kill} = 0.015$) except for cell loss factor. CLF, cell loss factor

**Figure 3** The effect of accelerated regrowth on long-term response to treatment. Here, the increased regrowth rate for small tumors balances the treatment effect and a plateauing similar to that for drug resistance is observed. All parameters are kept constant ($\beta = 1/24$, $GF_0 = 0.5$, $\alpha = 0.3$, $K_{kill} = 0.015$) except for cell loss factor (CLF).
effect as the tumor shrinks and the GF increases. Figure 3 shows the impact of accelerated regrowth. For both values of cell loss factor, the highest dose achieves a pseudo-steady state of volume reduction and regrowth. For the 90% cell loss factor scenario, significant shrinkage is achieved over the first few cycles, down to ~10% of the initial volume. Depending on the timing of measurement this would have been a partial responder who would then have been judged to be progressing. Finally, Figure 4 demonstrates the principle of fractionated dosing with increased dose density. In Figure 4, dose levels are taken from the paclitaxel treatment regimen discussed above; it can be seen that more frequent dosing at a lower strength maintains a greater response. Note also in all simulations that growth acceleration significantly reduces the resulting growth delay.

**DISCUSSION**

Mathematical modeling is a key component of drug research and development. Importantly, there is a need to have a translational model of tumor response kinetics. It has been argued that such a model should occupy a sweet-spot, containing necessary mechanisms to be translatable: purely descriptive models will have uncertainty of how they apply to a new context, more mechanistic models will suffer from structural and parameter uncertainty. A model does not need to be complex; it needs to be mechanistically informed. The processes and parameters that support a translatable approach have been reviewed, namely growing fraction, cell cycle time, and intrinsic cell loss.

A prototype translatable model that reproduces the observations in the literature has been presented. This model comprises two ODEs with five parameters: the initial conditions, rate of proliferation and cell death, in the proliferating and quiescent compartments. Such a level of model complexity is appropriate for the application of nonlinear mixed effects to quantify between tumor variability. One of the uncertainties associated with this model is how to apportion cell loss between the two compartments. This will impact the rate of growth retardation and the volume at which the tumor starts to plateau. A greater uncertainty is the geometry of the proliferating fraction. Here, it has been assumed to be determined by diffusion-limited oxygen delivery from the outside of the tumor, in line with the works of Conger and Ziskin as well as Greenspan. There is evidence that this geometry is appropriate. When investigating the differences in drug washout kinetics in healthy and cancerous tissue in animals, Baish et al. demonstrated a strong relationship with vascular architecture and that tumor drug kinetics behaved as a concave (blood vessels outside, distributing in) geometry.

Key to the success of any modeling approach is good experimental data for calibration purposes. Such data should be as informative as possible and investigate the effects of treatment over a wide dose range in animal cancer models. Of course, multiple scheduling options should be considered as well to validate the model’s ability to capture schedule dependence of antitumor activity.

There are several aspects of tumor growth modeling that have not been discussed here. For example, building PD biomarkers into the model to understand how target engagement is predictive of efficacy. In radiotherapy, DNA damage repair is an important determinant of the frequency of dosing. For systemic therapies, “repair” might be that of directly induced DNA damage, but more broadly the persistence of the PD effect in normal and malignant tissue. Similarly, a cell cycle model could be incorporated into a tumor growth model. This may give further insight into the mechanism of action of treatment, including combination treatment. In some cases, a delay between drug action and cell kill might have to be accounted for. The role of the immune system in animal models and patients has also not been considered. The aim here was to expose the wealth of knowledge for

![Figure 4](image_url) The effect of dose density: under this parameterization overall dose dense regimen at a lower dose level is more effective ($\beta = 1/24$, $\phi = 50\%$, $GF_0 = 0.5$, $\alpha = 1$, $K_{kill} = 0.007$)
tumor targeting approaches. There are modeling studies of tumor-immune interactions reported in the literature giving confidence that these aspects can be more systematically incorporated.\(^\text{102}\)

One clear gap is making predictions of potential patient heterogeneity and how this might impact optimal treatment regimens. One aspect that certainly requires greater attention is drug resistance.\(^\text{95,103}\) This requires us to model mathematically, and so experimentally, such sources of variability. To achieve this there is the opportunity to parameterize models either using different xenografted models, or to harness data from “\(n=1\)” PDX trials that attempt to model clinical heterogeneity.

Mathematical modeling has had a significant impact on the discovery and development of treatments for cancers. Here, an opportunity to increase the quantitative translation of information rich nonclinical studies to clinical treatment regimen has been discussed. Such information can inform the optimization of dose and schedule in the clinic. Models of tumor growth and response that capture the key differences between animal models and patients are vital to this endeavor.

**CONFLICT OF INTERESTS**

J.W.T.Y. is an employee of GSK. D.A.F. is an employee of GSK and a GSK shareholder.

**AUTHOR CONTRIBUTIONS**

J.W.T.Y. and D.A.F. reviewed the literature, wrote and reviewed the manuscript.

**REFERENCES**

1. Morgan P, Van Der Graaf PH, Arrowsmith J, et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. Drug Discovery Today. 2012;17:419-424.

2. Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework. Nat Rev Drug Discov. 2014;13:419-431.

3. Morgan P, Brown DG, Lennard S, et al. Impact of a five-dimensional framework on R & D productivity at AstraZeneca. Nature Publishing Group; 2016:1-38.

4. Milligan PA, Brown MJ, Marchant B, et al. Model-based drug development: a rational approach to efficiently accelerate drug development. Clin Pharmacol Ther. 2013;93:502-514.

5. Visser SAG, Aurell M, Jones RDO, et al. Model-based drug discovery: Implementation and impact. Drug Discovery Today. 2013;18:764-775.

6. Ribba B, Holford NH, Magni P, et al. A review of mixed-effects models of tumor growth and effects of anticancer drug treatment used in population analysis. CPT Pharmacometrics Syst Pharmacol. 2014;3:e113.

7. Bruno R, Bottino D, de Alwis DP, et al. Progress and opportunities to advance clinical cancer therapeutics using tumor dynamic models. Clin Cancer Res. 2019;26(8):1787-1796.

8. Yates JWT, Byrne H, Chapman SC, et al. Opportunities for quantitative translational modeling in oncology. Clin Pharmacol Ther. 2020;108:447-457.

9. Mould D, Walz A-C, Lave T, Gibbs B, Frame B. Developing exposure/response models for anticancer drug treatment: special considerations. CPT Pharmacometrics Syst Pharmacol. 2015;4(1):e00016.

10. Gibbs JP. Prediction of exposure-response relationships to support first-in-human study design. AAPS J. 2010;12:750-758.

11. FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA, Editor; 2018. https://www.fda.gov/media/71195/download

12. Zhang J, Gold KA, Lin HY, et al. Relationship between tumor size and survival in Non-Small-Cell Lung Cancer (NSCLC): an analysis of the Surveillance, Epidemiology, and End Results (SEER) registry. J Thorac Oncol. 2015;10:682-690.

13. Kusama S, Spratt JS, Donegan WL, et al. The gross rates of growth of human mammary carcinoma. Cancer. 1972;30:594-599.

14. Han LY, Karavasilis V, Hagen TV, et al. Doubling time of serum CA125 is an independent prognostic factor for survival in patients with ovarian cancer relapsing after first-line chemotherapy. Eur J Cancer. 2010;46(8):1359-1364.

15. Breur K. Growth rate and radiosensitivity of human tumours - II: growth rate of human tumours. Eur J Cancer. 1966;2:157-171.

16. Collins VP, Loeffler RK, Tivey H. Observations on growth rates of human tumors. Am J Roentgenol Rad Ther Nuclear Med. 1956;76(5):988-1000.

17. Double JA, Bibby MC. Therapeutic index: a vital component in selection of anticancer agents for clinical trial. J Natl Cancer Inst. 1989;81:988-994.

18. Minasian L, Rosen O, Auclair D, Rahman A, Pazdur R, Schilskey RL. Optimizing dosing of oncology drugs. Clin Pharmacol Ther. 2014;96:572-579.

19. Musuamba FT, Manolis E, Holford N, et al. Advanced methods for dose and regimen finding during drug development: summary of the EMA/EFPIA workshop on dose finding (London 4–5 December 2014). CPT Pharmacometrics Syst Pharmacol. 2017;6:418-429.

20. Davies M, Jones RDO, Grime K, et al. Improving the accuracy of predicted human pharmacokinetics: lessons learned from the AstraZeneca drug pipeline over two decades. Trends Pharmacol Sci. 2020;41(6):390-408.

21. Wong H, Choo EF, Aliche B, et al. Antitumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. Clin Cancer Res. 2012;18:3846-3855.

22. Gao H, Korn JM, Ferretti S, et al. High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. Nat Med. 2015;21:1318-1325.

23. Gerlee P. The model muddle: in search of tumor growth laws. Cancer Res. 2013;73:2407-2411.

24. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol. 2013;14:1020-1026.

25. Winer EP, Berry DA, Woolf S, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast
64. Mistry HB, Helmlinger G, Al-Huniti N, Vishwanathan K, Yates J. Resistance models to EGFR inhibition and chemotherapy in non-small cell lung cancer via analysis of tumor size dynamics. Cancer Chemother Pharmacol. 2019;84:51-60.

65. Mercier F, Kerioui M, Desmée S. Longitudinal analysis of organ-specific tumor lesion sizes in metastatic colorectal cancer patients receiving first line standard chemotherapy in combination with anti-angiogenic treatment. J Pharmacokinet Pharmacodyn. 2020;47(6):613-625.

66. Johnson JI, Decker S, Zaharevitz D, et al. Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. Br J Cancer. 2001;84:1424-1431.

67. Voelkl B, Vogt L, Sena ES, Würbel H. Reproducibility of preclinical animal research improves with heterogeneity of study samples. PLoS Biol. 2018;16:1-13.

68. Inaba M, Kobayashi T, Tashiro T, et al. Pharmacokinetic approach to rational therapeutic doses for human tumor-bearing nude mice. Jpn J Cancer Res. 1988;79:509-516.

69. Inaba M, Kobayashi T, Tashiro T, et al. Evaluation of antitumor activity in a human breast tumor/nude mouse model with a special emphasis on treatment dose. Cancer. 1989;64:1577-1582.

70. Inaba M, Tashiro T, Kobayashi T, et al. Responsiveness of human gastric tumors implanted in nude mice to clinically equivalent doses of various antitumor agents. Jpn J Cancer Res. 1988;79(4):517-522.

71. Inaba M, et al. Evaluation of response rates to various antitumor agents of human gastric tumors implanted in nude mouse. Jpn J Cancer Res. 1986;77:190-196.

72. Maruo K, Ueyama Y, Inaba M, et al. Responsiveness of subcutaneous human glioma xenografts to various antitumor agents. Anticancer Res. 1990;10:209-212.

73. Tashiro T, Inaba M, Kobayashi T, et al. Responsiveness of human lung cancer/nude mouse to antitumor agents in a model using clinically equivalent doses. Cancer Chemother Pharmacol. 1989;24:187-192.

74. Houghton PJ, Cheshire PJ, Hallman JD, et al. Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low dose levels in protracted schedules to mice bearing xenografts of human tumors. Cancer Chemother Pharmacol. 1995;36:393-403.

75. Houghton PJ, Cheshire PJ, Myers L, et al. Evaluation of 9-di-methylaminomethyl-10-hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. Cancer Chemother Pharmacol. 1992;31:229-239.

76. Houghton PJ, Stewart CF, Zamboni WC, et al. Schedule-dependent efficacy of camtothechins in models of human cancer. Ann N Y Acad Sci. 1996;803:188-201.

77. Houghton PJ, Cheshire PJ, Hallman JC, et al. Therapeutic Efficacy of the Topoisomerase I Inhibitor 7-Ethyl-10-[4-1-piperidino]-1-piperidino-carbonyloxy-camptothecin against Human Tumor Xenografts: Lack of Cross-Resistance in Vivo in Tumors with Acquired Resistance to the Topoisomerase I Inhibitor 9-dimethylaminomethyl-10-hydroxycamptothecin. Cancer Res. 1993;53:2823-2829.

78. Thompson J, Zamboni WC, Cheshire PJ, et al. Efficacy of systemic administration of irinotecan against neuroblastoma xenografts. Clin Cancer Res. 1997;3:423-431.

79. Zamboni WC, Stewart CF, Houghton PJ, et al. Relationship between topotecan systemic exposure and tumor response in human neuroblastoma xenografts. J Natl Cancer Inst. 1998;90:505-511.

80. Brady R, Enderling H. Mathematical models of cancer: when to predict novel therapies, and when not to. Bull Math Biol. 2019;81:3722-3731.

81. Yankelevitz TE, Quaranta V, Evans KJ, Rericha EC. Toward a science of tumor forecasting for clinical oncology. Cancer Res. 2015;75:918-923.

82. Sinal M, Norton L. A Gompertzian model of human breast cancer growth. Cancer Res. 1988;48:7067-7071.

83. Burton AC. Rate of growth of solid tumours as a problem of diffusion. Growth. 1966;30:157-176.

84. Brunton GF, Wheldon TE. Characteristic species dependent growth patterns of mammalian neoplasms. Cell Prolif. 1978;11:161-175.

85. Norton L, Simon R, Brereton HD, Bogden AE. Predicting the course of Gompertzian growth. Nature. 1976;264:542-545.

86. Vaghi C, Rodallec A, Fanciullino R, et al. Population modeling of tumor growth curves and the reduced Gompertz model improve prediction of the age of experimental tumors. PLoS Comput Biol. 2020;16:1-24.

87. Greenspan HP. On the growth and stability of cell cultures and solid tumors. J Theor Biol. 1976;56:229-242.

88. Greenspan HP. Models for the growth of a solid tumor by diffusion. Studies in Applied Mathematics. 1972;51:317-340.

89. Conger AD, Ziskin MC. Growth of mammalian multicellular tumor spheroids. Cancer Res. 1983;43:556-560.

90. Mayneord WV. On a law of growth of Jensen’s rat sarcoma. Am J Cancer. 1932;16:841-846.

91. Jumbe NL, Xin Y, Leipold DD, et al. Modeling the efficacy of trastuzumab-DM1, an antibody drug conjugate, in mice. J Pharmacokinet Pharmacodyn. 2010;37:221-242.

92. Ait-Oudhia S, Mager DE. Array of translational systems pharmacodynamic models of anti-cancer drugs. J Pharmacokin Pharmacodyn. 2016;43:549-565.

93. Simeoni M, Magni P, Cammia C, et al. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res. 2004;64:1094-1101.

94. Murphy H, Jafarri H, Dobrovolny HM. Differences in prediction of ODE models of tumor growth: a cautionary example. BMC Cancer. 2016;16:1-10.

95. Yin A, Moes DJAR, Hasselt JGC, et al. A review of mathematical models for tumor dynamics and treatment resistance evolution of solid tumors. CPT Pharmacometrics Syst Pharmacol. 2019;8(10):720-737.

96. Gyllenberg M, Webb GF. A nonlinear structured population model of tumor growth with quiescence. J Math Biol. 1990;28:671-694.

97. Kozusko F, Bajzer Z. Combining Gompertzian growth and cell population dynamics. Math Biosci. 2003;185:153-167.

98. Kozusko F, Bourdeau M. A unified model of sigmoid tumour growth based on cell proliferation and quiescence. Cell Prolif. 2007;40:824-834.

99. Evans ND, Dimelow R, Yates J. Modelling of tumour growth and cytotoxic effect of taxotere in xenografts. Comput Methods Programs Biomed. 2014;114(3):e3-e13.

100. Baish JW, Stylianopoulos T, Lanning RM, et al. Scaling rules for diffusive drug delivery in tumor and normal tissues. Proc Natl Acad Sci USA. 2011;108:1799-1803.

101. Checkley S, MacCallum L, Yates J, et al. Bridging the gap between in vitro and in vivo: Dose and schedule predictions for the ATR inhibitor AZD6738. Sci Rep. 2015;5:13545.
102. Milberg O, Gong C, Jafarnejad M, et al. A QSP model for predicting clinical responses to monotherapy, combination and sequential therapy following CTLA-4, PD-1, and PD-L1 checkpoint blockade. *Sci Rep*. 2019;9:1-17.

103. Terranova N, Girard P, Klinkhardt U, Munafo A. Resistance development: a major piece in the jigsaw puzzle of tumor size modeling. *CPT Pharmacometrics Syst Pharmacol*. 2015;4:320-323.

**How to cite this article:** Yates JWT, Fairman DA. How translational modeling in oncology needs to get the mechanism just right. *Clin Transl Sci*. 2022;15:588–600. [https://doi.org/10.1111/cts.13183](https://doi.org/10.1111/cts.13183)