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REVIEW

How translational modeling in oncology needs to get the mechanism just right

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Abstract

Translational model-based approaches have played a role in increasing success in the development of novel anticancer treatments. However, despite this, significant translational uncertainty remains from animal models to patients. Optimization of dose and scheduling (regimen) of drugs to maximize the therapeutic utility (maximize efficacy while avoiding limiting toxicities) is still predominately driven by clinical investigations. Here, we argue that utilizing pragmatic mechanism-based translational modeling of nonclinical data can further inform this optimization. Consequently, a prototype model is demonstrated that addresses the required fundamental mechanisms.

INTRODUCTION

The failure rate in the research and development of new anticancer treatments has necessitated a more objective approach. The three pillars proposed by Pfizer[1] and the 5Rs that followed from AstraZeneca[2] 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 demonstrable[3] and the part that modeling and simulation has played in this is significant.[4,5] The application of these approaches in oncology is precedented[6] but less mature than in the broader pharmaceutical field[7] 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 baseline[12] 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 safely 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[19] 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 transitional 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 precedented and can be predicted reasonably accurately using both physiologically-based PK (PBPK) and allometry approaches.[20] In addition, accounting for differences in free drug exposure between animal models and patients improves translation of efficacious concentrations.[21]

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.[22]

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[23] 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/m^2 every three week (q3w) regimen. However, it has been shown that in combination with q3w carboplatin, a more dose dense and intense regimen of 80 mg/m^2 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/m^2 q3w, albeit in breast cancer rather than ovarian cancer,[25] showed no increase in PFS. These data suggest that 175 mg/m^2 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 metanalysis[30] 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 regimen[31–33] 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 OS[35] in metastatic breast cancer,[36] in early breast cancer and aggressive lymphomas,[37] and ovarian

cancer.[38] 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 ratio[41] 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 identifiability[42] 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_{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_{max}])
2. Redistribution in cell cycle - or between sensitive and tolerant phenotypes (E_{max} due to maximal achievable kill and time)
3. Re-oxygenation (as the tumor shrinks) will increase proliferating fraction (E_{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 φ.[45] The GF is defined as the ratio of proliferating to total tumor mass. Through radio labeling experiments it has been found that GF is ~50% in animal models[46] and in the clinic.[47] These estimates compare well to more recent imaging and biomarker based measurements in non-small cell lung cancer (NSCLC) and breast cancer,[48,49] as well as xenografted models. T_c has been estimated in the range of 12–48 h in animal models[50] and the clinic.[47] 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.[45] 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 $\varphi = 1 - T_{pot} / DT$.[45] Values of φ ~ 50% have been estimated in transplantable animal tumors,[50] whereas it was φ ~90%–95% in human tumors[51] where tumors grow comparably more slowly. Unfortunately, there are no studies demonstrating a relationship between φ 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[52] 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.[53] 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_S) 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.[39] 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[54] 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[55] 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[56] 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[46,56,57] 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[46,58] point to a reduction in the GF as well as φ 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.[59]

Tannock describes post-treatment acceleration as a form of treatment resistance[32] 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[61] 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[61] 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.[62] 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[63,64] and by anatomic site[65] 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.[66] 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.[67] 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.[68–73] The responses were lower at the clinically relevant doses than at mouse MTDs. What is surprising is by 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.[74–79] 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,[23] similar to the Gompertzian like growth, but the question remains whether these can make valid predictions.[80,81] Gompertzian growth models have been the most commonly applied, starting with Laird[59] and continuing with Norton and Simons,[82] 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[83]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[84] show that the two Gompertzian parameters are again highly correlated for a wide range of nonclinical tumors, something conjectured elsewhere,[85] and formalized by Vaghi et al.[86] 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[87,88] 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[89] 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[90] and later Jumbe et al.[91]

Generally, nonclinical tumor modeling suffers from issues of empiricism.[92,93] 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.[81] For example, in the widely used Simeoni et al. model,[93] drug effect is independent of the exponential or linear phase of tumor growth.

There are also a number of reviews of pharmacometric applications[6,7,9] 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.[6]

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.[94] 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.[95]

Parsimonious models considering cellular proliferation, proliferating, and nonproliferating compartments and cell death have been reported.[96] 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[97] 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.[98]

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 φ, while minimizing complexity. The Conger model,[89] 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:

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

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

Where r is the radius of the tumor assuming a spherical geometry, R_{diff} is the depth of the proliferating compartment (fraction GF) into the tumor, and β, μ_P, and μ_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,[57] however, it is more useful to write this using framework proposed by Kozusko and Bourdeau[98]:

$$\frac{d\mathrm{GF}}{dt} = m\left(\mathrm{GF} - \mathrm{GF}_\infty\right)\left(\left(1-\mathrm{GF}\right) - \left(1-\mathrm{GF}\right)^{\frac{2}{3}}\right); \mathrm{GF}\left(0\right) = \mathrm{GF}_0$$

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

where

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

and

$$\mathrm{GF}_\infty = \frac{\mu_Q}{m}$$

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 φ, are as follows:

$$\phi = \frac{\mu_P \mathrm{GF}_0 + \mu_Q \left(1 - \mathrm{GF}_0\right)}{\beta \mathrm{GF}_0}$$

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[99] of this type of model demonstrates parameter identifiability. For an initial proportion, α, 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:

$$\mu_P = \phi\beta\alpha$$

$$\mu_Q = \phi\beta\left(1 - \alpha\right) \cdot \frac{\mathrm{GF}_0}{1 - \mathrm{GF}_0}$$

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.

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

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

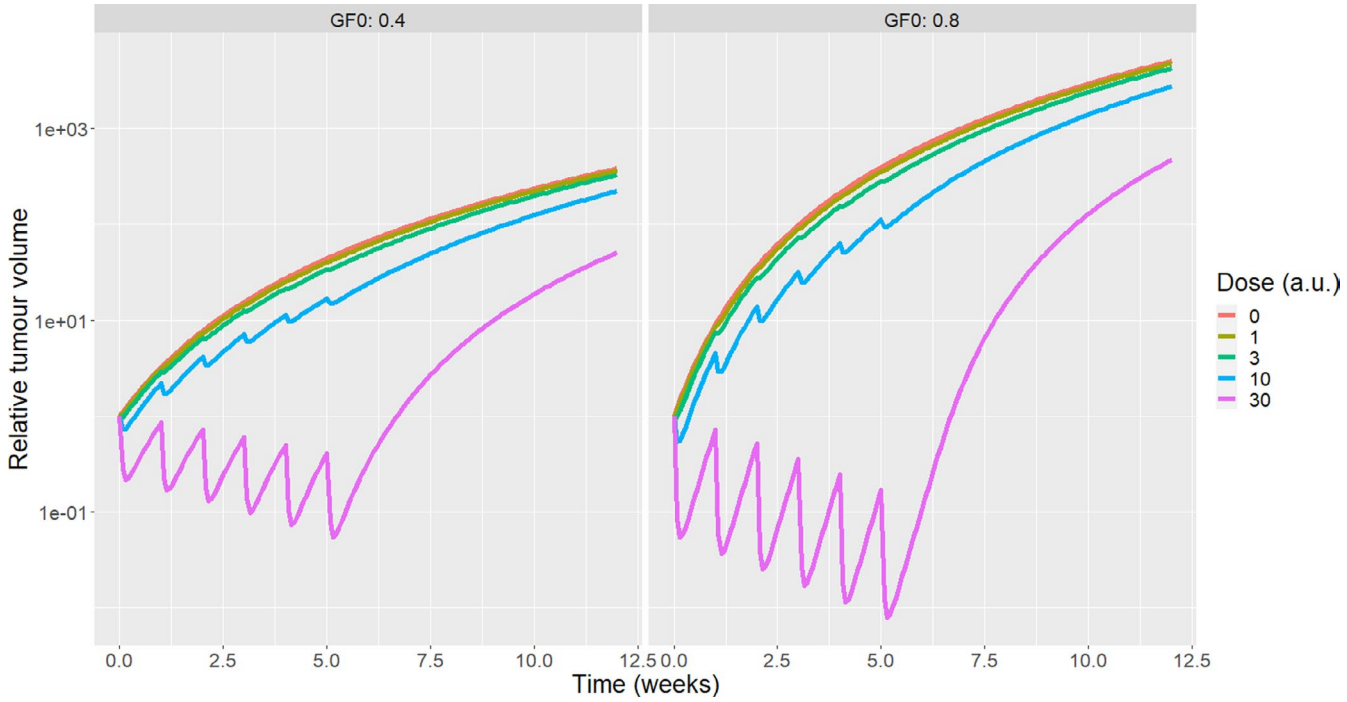

FIGURE 1 Increased growth fraction (GF) leads to more rapid control growth and greater cytotoxic drug effect per dose as measured by tumor size reduction. All parameters constant (β = 1/24, ϕ = 50%, α = 1, K_{kill} = 0.015) except for initial condition of GF0 with 40% on the left and 80% initial growing fraction on the right. CLF, cell loss factor

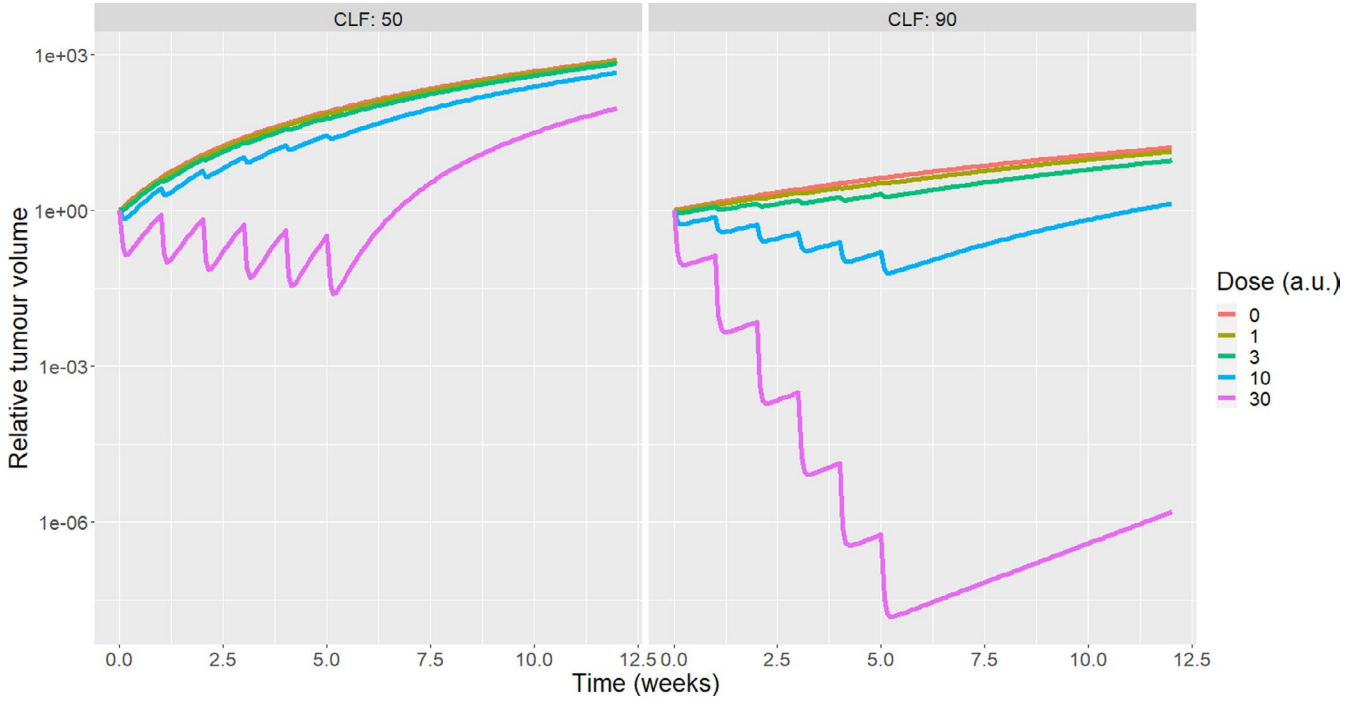

FIGURE 2 Increasing cell loss factor (50% vs. 90%) reduces control growth and increases the net drug effect. All other parameters are kept constant ($\beta = 1/24$, $GF_0 = 0.5$, $\alpha = 1$, $K_{kill} = 0.015$) except for cell loss factor. CLF, cell loss factor

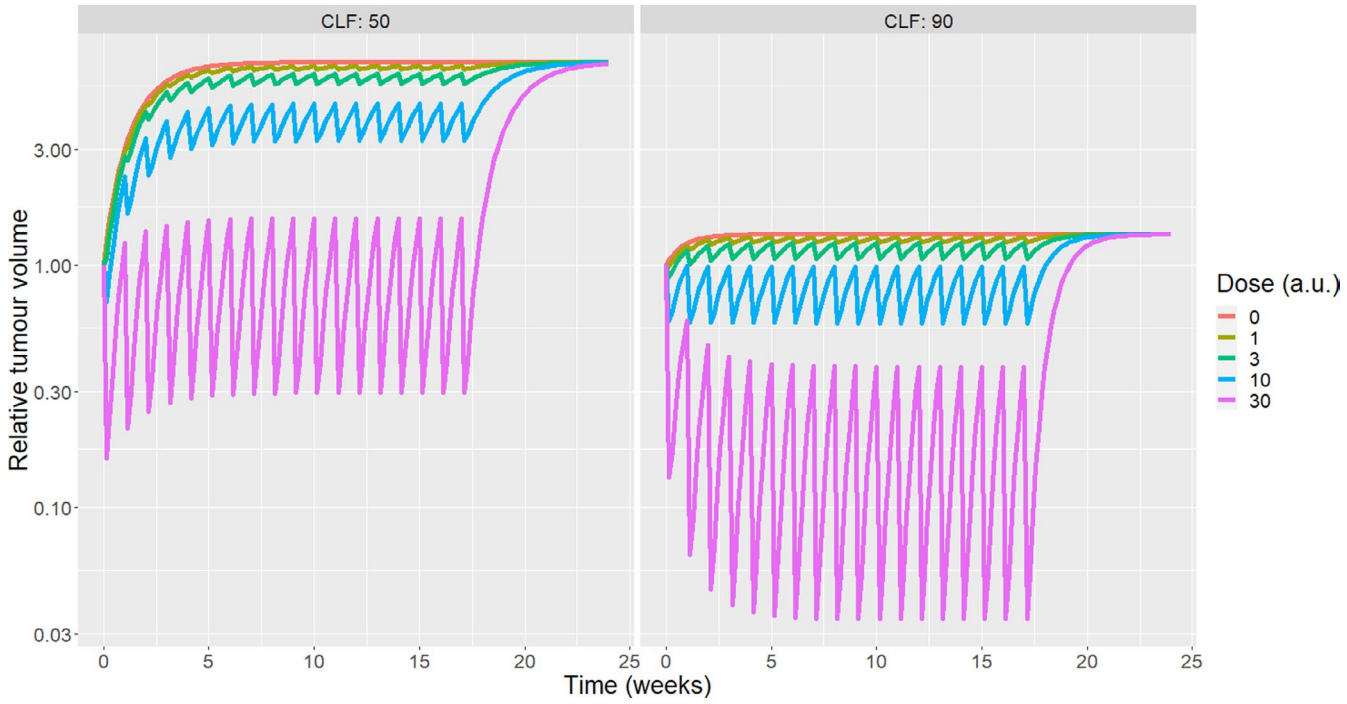

FIGURE 3 The effect of accelerated regrowth on long-term response to treatment. Here, the increased regrowth rate for small tumors balances the treatment effect and a plateauing similar to that for drug resistance is observed. All parameters are kept constant ($\beta = 1/24$, $GF_0 = 0.5$, $\alpha = 0.3$, $K_{kill} = 0.015$) except for cell loss factor (CLF)

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

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.[100] 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.[101] 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

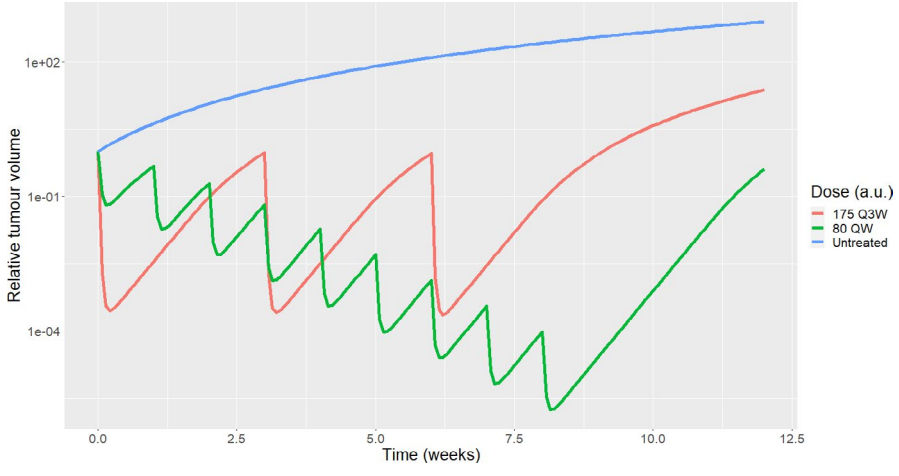

FIGURE 4 The effect of dose density: under this parameterization overall dose dense regimen at a lower dose level is more effective ($\beta = 1/24$, $\phi = 50\%$, $GF_0 = 0.5$, $\alpha = 1$, $K_{kill} = 0.007$)

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.[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.[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.

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