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Cover Page Footnote

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Mathematical Modeling of Tumor Immune Interactions: A Closer Look at the Role of a PD-L1 Inhibitor in Cancer Immunotherapy

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Abstract

Monoclonal antibodies have shown promising results as a form of cancer immunotherapy used either alone or in combination with another treatment. We model a monoclonal antibody in combination with a dendritic cell (DC) vaccine in order to study treatment optimization. Certain proteins on tumor cells allow the tumor cells to bind to specific receptors on immune cells, rendering the immune cells ineffective. Experiments using mouse models show that a combination of antibodies to these proteins with tumor suppressing drugs improves the effectiveness of cancer vaccines. We create independent models of each of the two treatments in combination with DC therapy, fit them to experimental data, and create a final, data-informed model of the combined treatment. This new model can be used to develop novel therapies involving monoclonal antibodies.

Keywords: tumor-immune model, cancer vaccines, immunotherapy, PD-L1 inhibitor

1 Introduction

Immunology is a scientific discipline that explores the development and function of the immune system. The immune system comprises many cells, including T cells and B cells, as well as lymphoid organs. When infections arise, the cells and lymphoid organs in the immune system work together to fight off pathogens and keep the immune system healthy and functioning [11]. T cells are a type of white blood cell crucial to the adaptive immune system because of their ability to protect the body against harmful pathogens. Programmed death-1 (PD-1) receptors on active T cells are being widely studied for their role in regulating T cell activity. PD-1 receptors bind to programmed death-ligand 1 (PD-L1), often on other immune cells, creating a natural pathway that suppresses T cell activity and helps prevent autoimmunity. Research shows that some tumor cells express PD-L1. This allows them to take advantage of PD-1/PD-L1 immune regulation and evade the T cell response [14]. Figure 1 below illustrates a side-by-side depiction of the binding interaction between the PD-1 receptor and PD-L1 ligand, as well as an anti-PD-L1 treatment blocking the pathway. The PD-1/PD-L1 pathway suppresses T cell receptor (TCR) signaling necessary for tumor identification by T cells. This ability of tumor cells to evade the immune response has been partially responsible for the limited success of

Figure 1: Tumor cells take advantage of the PD-1/PD-L1 pathway to evade the immune response by inhibiting TCR signaling (left). Anti-PD-L1 binds to PD-L1 and blocks the pathway, allowing the T cell to discern the tumor cell (right).

cancer vaccines to date. Ongoing research shows the potential efficacy of PD-1/PD-L1 pathway inhibitors in cancer therapy. Anti-PD-L1 monoclonal antibodies have benefited patients in clinical trials, though they have yet to be implemented in practice [12].

Experiments conducted by [24] show that the combination of anti-PD-L1 and ibrutinib creates an effective response against J558 cancer cells in mouse models. Ibrutinib is an orally administered anti-cancer drug that inhibits Bruton's tyrosine kinase (BTK) activity; the expression of BTK in tumor cells is associated with increased proliferation and survival [24].

In this paper, we develop a mathematical model that explores the effects of PD-1/PD-L1 therapy in combina-

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tion with immunotherapy. In particular, we are interested in the effects of anti-PD-L1 therapy in conjunction with dendritic cell (DC) vaccines. Finally, we look at the effect of adding an anti-cancer drug to these other therapies. Combination therapies are a common line of attack in treating cancer, and mathematical models can help unravel the complex interactions between the various treatments.

Dendritic cells are antigen-presenting cells that activate T cells to create an immune response. Upon encountering antigens, or foreign substances, dendritic cells mature and travel to the lymphoid organs where they present these antigens to T cells. The T cells then begin to proliferate and become active T cells or memory T cells. Active T cells presented with a tumor antigen travel to the tumor site to identify and destroy tumor cells, while memory T cells reside in the blood and lymphoid organs to prepare for future attacks [13].

Many mathematical models have been created in the past to study the interactions between tumor cells and the immune response in the context of dendritic cell vaccines. One existing model focuses on three main populations: regulatory T cells, helper T cells, and dendritic cells, and their response to tumor growth [22]. The equations focus on immunosuppression mechanisms to simulate dendritic cell vaccines. Another model uses a system of partial differential equations to simulate anti-PD-L1 along with DC vaccines [18]. While these models present interesting findings, we utilize a differential equations model [16] as our basis because it uniquely accounts for important mechanisms that take place in the spleen. This model, in turn, is based on a previous model of the immune activation and tumor-immune interactions that incorporates time delays [6]. We have confirmed the model presented in [16] using experimental data provided by [24]. This preliminary model studies dendritic cell vaccines using three compartments of differential equations. These equations describe the interactions between tumor cells, T cells, and dendritic cells throughout the spleen, blood, and tumor compartments.

In this paper, we present a modification of the model given in [16] to incorporate the effect of anti-PD-L1 on the tumor-immune kinetics. We also add the effect of *ibrutinib*, a drug that slows tumor growth. Exploring combination therapies is difficult in a clinical setting, so mathematical models can suggest how combinations of different treatments might affect outcomes [5]. The extended model developed in this paper would aid in the design of novel therapies, and, through *in silico* experiments, can be used to optimize treatment combinations and dosing methods.

Figure 2: DCs (D), active T cells (E^a), and memory T cells (E^m) travel between the spleen, blood, and tumor compartments. Natural cell deaths of these populations, including proliferating cells (P) and tumor cells (T), are indicated by “cell death.” The spleen compartment additionally contains conglomerate cells, DCs bind to naive T cells for activation. The model accounts for potential DC-therapy injections into the bloodstream and/or tumor site.

2 Background: Previous Model

The initial model from [16] consists of eleven differential equations in three compartments: spleen, blood, and tumor. The equations model the dynamics between dendritic cells, tumor cells, and activated/memory T cells. Figure 2 below illustrates an overview of the three compartments and their cell populations.

2.1 Spleen Compartment

In the spleen compartment, we observe interactions between three cell populations: dendritic cells, activated T cells, and memory T cells, each denoted by D_{spleen} , E^a_{spleen} , and E^m_{spleen} , respectively. Both the activated T cells and memory T cells enter the spleen from the blood at a rate of μ_{BSE} , while dendritic cells travel from the blood to the spleen at a rate of μ_{BS} . In addition to the entrance rates of the cells, we have the natural death rates of each cell population, marked by the parameters a_D , $a_{E^a_{spleen}}$, and $a_{E^m_{spleen}}$, for dendritic cells, activated T cells, and memory T cells, respectively.

After presentation of tumor-specific antigen to tumor cells by dendritic cells, the two cells attach to form a conglomerate represented by the population W in the model. Conglomerate cells enter the W population at a rate of γ and leave at a rate of λ , after the dendritic cell detaches from the conglomerate and deactivates. Newly activated T cells then enter the proliferating cell (P) population at a rate of $\omega\lambda$ to proliferate, where ω represents the average amount of nascent T cells that bind with dendritic cells. If you recall from earlier, after dendritic cells bind

to nascent T cells, T cells become activated and begin to proliferate. After this expansion phase, active T cells exit the spleen, while remaining cells become memory T cells available for later use against returning pathogens.

Memory T cells enter the P compartment for proliferation at a rate of λ^m . Activated T cells are released from the spleen into the blood at a rate that depends on how much antigen is present. This is captured in the terms in parentheses in equations (2) and (3). T cells remain in the proliferation, or expansion phase for an average time of $\frac{1}{\beta^E}$, and die at a rate of β^D . These rates are combined in the model in the parameter $\beta = \beta^E - \beta^D$ (5).

$$\frac{d}{dt}D_{spleen} = \mu_{BS}D_{blood} - (a_D + \gamma)D_{spleen} + \lambda W \quad (1)$$

$$\begin{aligned} \frac{d}{dt}E_{spleen}^a &= \mu_{BSE}E_{blood}^a - r_{am}E_{spleen}^a - a_{EaS}E_{spleen}^a \\ &\quad - \left(\mu_{SB}^* + \frac{\mu_{normal} - \mu_{SB}^*}{1 + \frac{D_{spleen}}{\theta_{shut}}} \right) E_{spleen}^a \\ &\quad + \beta^E P \quad (2) \end{aligned}$$

$$\begin{aligned} \frac{d}{dt}E_{spleen}^m &= \mu_{BSE}E_{blood}^m + r_{am}E_{spleen}^a - a_{Em}E_{spleen}^m \\ &\quad - \left(\mu_{SB}^* + \frac{\mu_{normal} - \mu_{SB}^*}{1 + \frac{D_{spleen}}{\theta_{shut}}} \right) E_{spleen}^m \\ &\quad - \lambda^m E_{spleen}^m D_{spleen} \quad (3) \end{aligned}$$

$$\frac{d}{dt}W = \gamma D_{spleen} - \lambda W \quad (4)$$

$$\frac{d}{dt}P = \omega \lambda W + \lambda^m E_{spleen}^m D_{spleen} - \beta P \quad (5)$$

2.2 Blood Compartment

The blood compartment serves as a vessel for cells to travel back and forth between the spleen and the tumor compartments. The cell populations present in the blood are dendritic cells, activated T cells, and memory T cells, corresponding to D_{blood} , E_{blood}^a , and E_{blood}^m , respectively. Cells are neither created nor destroyed in the blood compartment, since the blood compartment is merely a site for cell transportation. The rate at which the cells travel through the compartments are given by μ_B , μ_{TB} , μ_{SB}^* , μ_{BB} , and μ_{normal} . The term $v_{blood}(t)$ illustrates the pro-

tol for dendritic cell injection into the bloodstream.

$$\frac{d}{dt}D_{blood} = -\mu_B D_{blood} + \mu_{TB} D_{tumor} + v_{blood}(t) \quad (6)$$

$$\begin{aligned} \frac{d}{dt}E_{blood}^a &= \left(\mu_{SB}^* + \frac{\mu_{normal} - \mu_{SB}^*}{1 + \frac{D_{spleen}}{\theta_{shut}}} \right) E_{spleen}^a \\ &\quad - \mu_{BB} E_{blood}^a \quad (7) \end{aligned}$$

$$\begin{aligned} \frac{d}{dt}E_{blood}^m &= \left(\mu_{SB}^* + \frac{\mu_{normal} - \mu_{SB}^*}{1 + \frac{D_{spleen}}{\theta_{shut}}} \right) E_{spleen}^m \\ &\quad - \mu_{BB} E_{blood}^m \quad (8) \end{aligned}$$

2.3 Tumor Compartment

The tumor compartment illustrates the interaction between activated T cells and tumor cells. The populations in the tumor compartment are given by E_{tumor}^a , T , D_{tumor} , for activated T cells, tumor cells, and dendritic cells, respectively. As described in Section 2.1, T cells are activated in the spleen and travel to the tumor compartment to mount their attack on the tumor cells. The term d is a kill rate for the tumor cells by the activated T cells, characterizing the effectiveness of the activated T cells in eliminating the tumor cells. The ratio-dependent kill rate in equation (12) is derived in [7].

$$\begin{aligned} \frac{d}{dt}E_{tumor}^a &= \mu_{BB} \frac{T}{\alpha + T} E_{blood}^a - a_{EaT} E_{tumor}^a \\ &\quad - c E_{tumor}^a T \quad (9) \end{aligned}$$

$$\frac{d}{dt}T = rT \left(1 - \frac{T}{k} \right) - \mathcal{D}T \quad (10)$$

$$\begin{aligned} \frac{d}{dt}D_{tumor} &= \frac{mT}{q + T} - (\mu_{TB} + a_D) D_{tumor} \\ &\quad + v_{tumor}(t) \quad (11) \end{aligned}$$

where

$$\mathcal{D} = d \frac{\left(\frac{E_{tumor}^a}{T} \right)^l}{s + \left(\frac{E_{tumor}^a}{T} \right)^l} \quad (12)$$

This portion of the model is extended in sections 4.2 and 5.2 by the addition of new treatments. For all simulations, we use a non-dimensionalized form of this model provided in Appendix B of [16]. All parameters are described in Appendix A of this paper.

3 Experimental Data

Data from mouse models show that a combination of anti-PD-L1 and ibrutinib creates an effective response against J558 cancer cells in mice (Figure S6 in [24]). 6–8 week

old female BALB/c mice were inoculated with tumor cells subcutaneously, and tumor growth was monitored every 2 to 3 days. There were four treatment groups with thirteen mice per group: non-treated, ibrutinib, anti-PD-L1, and a combination of ibrutinib and anti-PD-L1. The initial size of the tumor injected was 5×10^6 cells for each mouse.

3.1 Initial Parameter Fitting

In order to capture individual variations in the tumors of the mice, we fit two parameters to each growth curve in the untreated group of mice in [24]: d (maximum kill rate) and r (tumor growth rate). Note that we call d the *maximum kill rate* because the per-cell kill rate represented by the function $\mathcal{D}$ given in Equation (12) approaches d as the ratio of active T cells to tumor cells, E_{tumor}^a/T , goes to infinity. These are the patient-specific parameters with the greatest influence on tumor size [16]. We note that the range of parameter values obtained is quite large, particularly for the parameter d , the maximum kill rate of tumor cells by immune cells. This parameter is also quite a bit smaller than the parameter value estimated in [16], presented in Appendix A. This makes sense, since the type of mice used, the BALB/c strain, are bred to be immuno-deficient. For the same reason, we are not surprised that the parameter r is generally larger than the estimate from [16]. The other model parameters are carried over from the original model presented in [16]. We used the MATLAB `fminsearch` function to minimize the squared distance of the model simulations to the data points for each curve in the data. Results of the data fitting are shown in Figure 3.

Tumor population curves in this control group resemble an exponential curve, or the beginning of a logistic curve. We assume that the growth law is logistic, rather than exponential, since this is a more realistic model. A tumor cannot grow without bound; its size is limited by available resources such as space and nutrients. For a more thorough discussion of growth models, see [25]. Fitted parameter values d and r for each curve are listed in Table 1. All other parameter values were maintained from the original model, and are provided in Appendix A.

3.2 Success with anti-PD-L1

Having confirmed that the initial model follows experimental data, we are interested in modeling ibrutinib and anti-PD-L1 treatments. In their study, [24] administered 24 mg/kg body weight of ibrutinib on days 12–20 after tumor inoculation for the ibrutinib group, and injected 0.2 mg of an anti-PD-L1 antibody every other day for the anti-PD-L1 group. Then, the two treatments were given simultaneously to the combination group. The ibrutinib treatment alone did not make statistically significant

	d	r
Curve 1	0.2045	0.3909
Curve 2	2.65E-04	0.2828
Curve 3	0.0298	0.2828
Curve 4	6.61E-05	0.2621
Curve 5	6.61E-05	0.2587
Curve 6	0.1285	0.287
Curve 7	0.1352	0.287
Curve 8	0.029	0.249
Curve 9	0.0716	0.2546
Curve 10	0.1017	0.2546
Curve 11	6.61E-05	0.2156
Curve 12	6.61E-05	0.2062
Curve 13	0.0603	0.209

Table 1: Each curve fits data for each mouse from the non-treated group in [24]. Fitted d and r values in the table represent individual differences in immune ability and tumor growth.

changes; however, anti-PD-L1 and the combined treatment both significantly improved survival, with greater success from the combined treatment [24].

4 Model with Ibrutinib

When modeling the effects of a drug on the system, it is important to consider how quickly the drug arrives at the site of action, and how quickly it is eliminated. These dynamics are called the “pharmacokinetics” of the drug. We use an exponential decay model for the amount of ibrutinib in the tumor compartment to capture the clearance of the drug near the tumor site. Ibrutinib was given by oral gavage every day from days 12–20 at a dosage of 24 mg/kg body weight. We approximate the arrival of the drug at the tumor site as happening immediately after the dosage is given. The details of the assumptions for the pharmacokinetic modeling are given below.

4.1 Assumptions

1. Ibrutinib activates at the site of the tumor. Model changes are made only in the tumor compartment for simplicity.
2. Ibrutinib decays exponentially. The half-life of ibrutinib is 4–6 hours [8]. Assuming an average half-life of 5 hours, the decay constant is calculated to be 3.3271.

Figure 3: Model predictions using equations (10) and (12) are compared to data from the untreated group of [24] experiments. In the color-printed version, the colors of the curves and their corresponding data points alternate for easier visibility.

Figure 4: Model predictions are compared to data from the ibrutinib treatment group [24]. Parameters d , r , and c_{ib} are fit using MATLAB's *fminsearch* to minimize the sum of squared residuals. In the color-printed version, the colors of the curves alternate for easier visibility.

3. Ibrutinib inhibits Bruton's tyrosine kinase (BTK) activity, which is important for tumor growth [20]. Hence, the tumor growth term is effected by the presence of ibrutinib. BTK is a protein in the body responsible for the production and maturation of B cells, which are vital in the fight against infection [9]. Similarly, BTK expression in tumor cells precipitates an increase in production of tumor cells.
4. 6–8 week old female BALB/c mice have an average weight of 16 grams [2]. An ibrutinib dosage of approximately $24 \times 0.016 = 0.384$ mg was used in the experiments [24].
5. We approximate the amount of ibrutinib added to the tumor site by simply using the amount administered at each time step.

4.2 Model Development

Let $X(t)$ be the amount of ibrutinib at the site of the tumor at time t . Following our assumption of the drug's exponential decay,

$$\frac{d}{dt}X = -\delta X \quad (13)$$

where $\delta = 3.3271$ is the decay constant of ibrutinib. We adjust our tumor growth equation (10) to describe ibrutinib's stunting of the tumor growth rate. Data from [23] suggest a reverse sigmoid curve for the performance of ibrutinib depending on the drug's dosage. The percentage of tumor cells decreases as more ibrutinib is introduced. A preliminary fit using a decreasing function of ibrutinib concentration to model its impact on tumor growth rate reveals that a *reciprocal function*, described in detail below, adequately captures the dynamics observed in experimental data, which is confirmed later in Figure 4.

In particular, we use a function of the form $\frac{1}{1+c_{ib}X}$ to model the effect of ibrutinib dosage, X , on tumor growth rate, where c_{ib} scales X to a non-dimensionalized value. We obtain the following tumor growth equation that accounts for the ibrutinib treatment:

$$\frac{d}{dt}T = \frac{r}{1+c_{ib}X}T \left(1 - \frac{T}{k}\right) - \mathcal{D}T \quad (14)$$

The tumor compartment of the initial model is modified to include the new ibrutinib equation (13) and the drug's effects on tumor growth (14).

We simulate the ibrutinib treatment by solving the final system of differential equations in steps and increasing the initial condition of X , the amount of ibrutinib at the tumor site, by 0.384 mg at the beginning of days 12–20 after tumor inoculation.

	d	r
Curve 1	0.058	0.3006
Curve 2	0.1299	0.32
Curve 3	0.1953	0.3395
Curve 4	0.2091	0.3395
Curve 5	0.209	0.335
Curve 6	6.61E-05	0.2485
Curve 7	0.1693	0.2933
Curve 8	0.0585	0.2518
Curve 9	0.1697	0.282
Curve 10	0.1062	0.2447
Curve 11	6.61E-05	0.2085
Curve 12	0.0501	0.2127
Curve 13	0.1002	0.2091

Table 2: Each curve fits data for each mouse from the ibrutinib treatment group in [24]. Fitted d and r values in the table represent individual differences in immune ability and tumor growth.

4.3 Parameter Fitting

We use the Nelder-Mead least squares algorithm by implementing MATLAB's *fminsearch* again to fit the newly adjusted model to data from Sagiv-Barfi's ibrutinib treatment group [24]. We fit parameters d , r , and c_{ib} to each curve, then compute the average ibrutinib scaling value (c_{ib}) to be 6.61×10^{-5} . We fix $c_{ib} = 6.61 \times 10^{-5}$ and fit parameters d and r again. Values for each mouse are reported in Table 2. Figure 4 depicts the model predictions of tumor size over time against experimental data.

5 Model with anti-PD-L1

To model the amount of anti-PD-L1 at the tumor site, we again use an exponential decay model to capture the pharmacokinetics. The anti-PD-L1 antibody was IP injected (into the body cavity) every other day.

5.1 Assumptions

1. Anti-PD-L1 decays exponentially at the tumor site, with a half-life of 15 days [3] and decay constant of 0.0462 day^{-1} .
2. Anti-PD-L1 injected at the tumor site binds to PD-L1 on tumor cells, acting as a blocker that prevents PD-L1 from binding to PD-1 receptors on effector immune cells. This fortifies the maximum kill rate, d .

3. Anti-PD-L1 injection began on day 5 on average, with the antibody having an almost instantaneous effect at the tumor site.

Let $Z(t)$ be the amount of anti-PD-L1 at the site of the tumor at time t . The blocker's exponential decay can be written as

$$\frac{d}{dt}Z = -\gamma Z \quad (15)$$

where $\gamma = 0.0462$ is the decay constant of anti-PD-L1. The performance of the PD-1/PD-L1 pathway blocker follows a sigmoid curve. Performance is defined by the ability of anti-PD-L1 to block immune checkpoint inhibitory signals. [21] quantifies TCR-mediated luminescence, indicating the amount of TCR activation depending on the concentration of anti-PD-L1. Figure 5, recreated from [21], illustrates anti-PD-L1 performance as anti-PD-L1 concentration increases. The figure utilizes a log-scale for anti-PD-L1 concentrations to aid in the visualization of sigmoidal behavior. Though data limitations make it difficult to observe graphically, this sigmoidal behavior is consistent when using non-scaled anti-PD-L1 concentration values. From Figure 5, we can see how sensitive the kill rate, as measured by activated T-cell receptors, is to the concentration of the PD-L1 antibody. This motivates the functional form that we choose for the dose-response function, $\mathcal{F}$, given in Equation (16).

Based on the assumption that the relationship between anti-PD-L1 and T cell ability follows sigmoidal behavior, we use $\mathcal{F}$ below to represent the blocker's effect on the kill term, dependent on Z , with c_{pd} and k_{pd} as our scaling parameters. We will obtain fitted parameter values using data from [24] again. A general sigmoid, or "switch", function can be written:

$$\mathcal{F} = \frac{c_{pd} - 1}{\pi} \left(\tan^{-1}((Z - 1) \cdot k_{pd}) + \frac{\pi}{2} \right) + 1 \quad (16)$$

Since anti-PD-L1 affects the kill rate of the tumor by active T cells, we multiply the previous ratio-dependent kill rate, (12), by (16) to give a new tumor growth equation:

$$\frac{d}{dt}T = rT \left(1 - \frac{T}{k} \right) - \mathcal{F}DT \quad (17)$$

Adding equations (15) and (17) to the original model (9), (11) and (12) gives a model of tumor-immune interactions in the presence of anti-PD-L1.

We simulate the anti-PD-L1 treatment by added a set value to Z , the amount of anti-PD-L1 at the tumor site, at the beginning of every other day, starting with day 5 after tumor inoculation. This value corresponds to the dose of 0.2 mg given every two days. This instantaneous increase in the amount of anti-PD-L1 at the tumor compartment is a simplification that we chose because the time it takes the antibody to reach the tumor site is negligible for a treatment length of 25 days.

	d	r
Curve 1	0.0846	0.3492
Curve 2	0.0925	0.3492
Curve 3	0.0973	0.3495
Curve 4	0.0018	0.2569
Curve 5	0.0813	0.3091
Curve 6	0.0078	0.248
Curve 7	0.0961	0.3092
Curve 8	0.1011	0.3082
Curve 9	0.0947	0.2977
Curve 10	0.0909	0.2977
Curve 11	0.0942	0.2977
Curve 12	0.1279	0.2956
Curve 13	0.1208	0.2844

Table 3: Each curve fits data for each mouse from the anti-PD-L1 treatment group in [24]. Fitted d and r values in the table represent individual differences in immune ability and tumor growth.

5.2 Parameter Fitting

We fit the newly adjusted model to data from the next treatment group, anti-PD-L1 injected every other day starting from day 5. We use the same parameter fitting strategies to fit d, r, c_{pd} , and k_{pd} for each mouse, then fix parameters c_{pd} and k_{pd} to their average values: $c_{pd} = 50$ and $k_{pd} = 97$. In our model fitting protocols, we first calculated d and r values for each individual curve from the Sagiv et al. experiments. Each new calculation for d and r generated a scaling value for c_{pd} and k_{pd} . Hence, we calculated the average c_{pd} and k_{pd} values to minimize variation and obtain a fixed scaling value(s) for all 13 curves. Then, we adjust parameters d and r again to obtain the best fit to each curve. These fits are shown in Figure 6, and parameter values for d and r provided in Table 3.

6 Combined Treatment

Experiments conducted by Sagiv et al. reveal that a combination of ibrutinib and anti-PD-L1 treatments improves survival in mouse models. Equations modeling both the effects of ibrutinib and anti-PD-L1 are added to simulate the combined treatment for varying d and r values. This new model combines both treatments with the previous model that incorporates DC vaccine injections. We gather all the equations here for clarity.

Figure 5: As anti-PD-L1 blocks the PD-1/PD-L1 pathway used by tumor cells to inhibit TCR signaling, an increase in anti-PD-L1 concentration leads to more TCR activation, quantified using TCR-mediated luminescence. Recreated from Figure 5 in [21].

Figure 6: Parameters d , r , c_{pd} , and k_{pd} are fit to the tumor growth data for each mouse using MATLAB's *fminsearch* to minimize the sum of squared residuals. In the color-printed version, the colors of the curves alternate for easier visibility.

6.1 Final Tumor Compartment Equations

$$\frac{d}{dt}X = -\delta X \quad (18)$$

$$\frac{d}{dt}Z = -\gamma Z \quad (19)$$

$$\frac{d}{dt}E_{tumor}^a = \mu_{BB} \frac{T}{\alpha + T} E_{blood}^a - a_{EaT} E_{tumor}^a - c E_{tumor}^a T \quad (20)$$

$$\frac{d}{dt}T = \frac{r}{1 + c_{ib}X} T \left(1 - \frac{T}{k}\right) - \mathcal{F}DT \quad (21)$$

$$\frac{d}{dt}D_{tumor} = \frac{mT}{q + T} - (\mu_{TB} + a_D)D_{tumor} + v_{tumor}(t) \quad (22)$$

where

$$\mathcal{F} = \frac{c_{pd} - 1}{\pi} \left(\tan^{-1}((Z - 1) \cdot k_{pd}) + \frac{\pi}{2} \right) + 1$$

$$D = d \frac{\left(\frac{E_{tumor}^a}{T}\right)^l}{s + \left(\frac{E_{tumor}^a}{T}\right)^l}$$

Having fit new parameters to the model, we are now in a position to explore combination therapies.

6.2 Simulations

Using MATLAB's *rand* function, we pick random d and r values uniformly distributed on $[0.029, 0.2091]$ and $[0.2062, 0.3909]$, respectively, since these are all viable parameter values from previous fits. The methodology for choosing these parameter values can be improved with enough data on the distributions of d and r for the patient population. Though normal distributions are commonly used for unknown distributions, we choose to randomize uniformly distributed values since each pair of r and d is sufficiently feasible, and the fitted d and r values do not follow normal distributions. The ranges above were obtained by finding the minimum and maximum values of d and r from previous fits, omitting outlying d (and their corresponding r) values (See Figure 7). These initial simulations consist of 13 runs to compare side-by-side with experimental outcomes.

As in the experiments conducted in [24], a combination of both ibrutinib and anti-PDL1 was more effective than each treatment alone. The importance of these simulations is that they demonstrate how separate experimental data can be used to predict the outcomes of a combined effect.

Additionally, new treatment strategies can be developed by simulating changes to treatment design. First,

we experiment with different anti-PD-L1 dosages. We run 1000 simulations for each anti-PD-L1 dose from 0.2 to 0.28 mg in increments of 0.001 (See Figure 8). For each dosage, we note the proportion of simulations for which the tumor cell population is completely eradicated, and plot this proportion against the anti-PD-L1 dose. We note that the proportion remains relatively constant at approximately 0.5 for doses between 0.2 mg and 0.25 mg, after which the proportion rises quickly to approximately 0.73, and remains relatively constant as the dose increases to 0.28 mg. This behavior is consistent with the “switch-like” effect of the drug on the T cell receptor activation, and is robust despite the variability in the tumor growth and kill rate parameters.

Using the information from Figure 8, we look more closely at tumor growth for the combined treatment group with an anti-PD-L1 dosage of 0.25 mg. The results for this set of simulations are shown in Figure 9.

Another possible adjustment to the combined therapy is to maintain the anti-PD-L1 dose at 0.2 mg, but implement a different treatment schedule. Instead of injecting anti-PD-L1 every other day, we experiment with a daily schedule. Figure 10 shows that a daily schedule yields better results than the original schedule, with tumor cells surviving and growing logistically in only 2 out of 13 individuals. The number of trials can easily be increased to 100 or more trials for a more powerful set of simulations. We choose to run 13 simulations to compare qualitatively with existing data for a preliminary analysis.

An additional set of 100 simulations with an adjusted daily schedule from days 5–10 yielded 85 cases of successful tumor eradication, suggesting the benefits of tweaking scheduling strategies. Using this information, we further look at the combined effect of daily scheduling and a higher dosage of anti-PD-L1 on tumor eradication. Figure 11 provides a glimpse into these effects.

7 Conclusion

The mathematical model described in this paper can serve as a powerful tool for cancer treatment design. Optimal combinations, doses, and scheduling of treatments can be efficiently predicted to speed up the development of individualized therapies. In this paper, we have used the model to study the effect of varying the dosage and treatment scheduling of one of the anti-PD-L1 drug. This serves an example of future studies in which treatment regimens of both drugs, as well as the vaccine itself, are varied. Studying patient-specific parameters such as d and r may improve our understanding of the treatment adjustments necessary for successful and nontoxic outcomes.

An optimal cancer treatment strategy would require

Figure 7: These simulations recreate behavior from the combined treatment experiments in [24]. Since r and d values are randomly chosen to simulate immune and tumor diversity, we cannot compare each curve to data individually, due to the lack of information about each mouse in the data. We are rather interested in qualitative behavior to confirm the model. Additionally, the difference in proportions between this group of simulations (tumor survived in 7 out of 13 mice) and the experimental non-treated group (tumor survived in 13 out of 13 mice) is significant at $p < 0.01$. When compared to the group treated with anti-PD-L1 (tumor survived in 11 out of 13 mice), the difference is also significant at $p < 0.01$.

Tumor eradication as a function of anti-PD-L1 dose

Figure 8: 1000 simulations were run for each anti-PD-L1 dosage, from 0.2 mg to 0.28 mg, with increments of 0.001 mg. For a fixed anti-PD-L1 dose, 1000 values of the parameters r (tumor growth rate) and d (maximum tumor kill rate by effector cells) were chosen uniformly from the intervals $r \sim \mathcal{U}([0.2062, 0.3909])$ and $d \sim \mathcal{U}([0.029, 0.2091])$. These ranges were determined from the maximum and minimum parameter values estimated from the experimental data shown in [24]. The graph shows the proportion of successful treatments, where the tumor was eradicated, out of 1000 simulations at the corresponding anti-PD-L1 dosage. We note that this proportion shows a distinct increase from approximately 0.5 to approximately 0.73 at doses just above 0.25 mg. All other parameters are as given in Appendix A.

Figure 9: Changing the anti-PD-L1 dosage from 0.2 mg to 0.25 mg resulted in 71 cases of successful tumor eradication out of 100 simulations. Successful treatments are indicated by solid blue lines, while unsuccessful treatments are indicated by dashed black lines.

Figure 10: Adjusting the anti-PD-L1 dosing schedule from every 2 days from days 5–20 to every day from days 5–10 yields better outcomes ($p < 0.05$) than from the simulated combined therapy in Figure 7.

Figure 11: 100 simulations were run using the new daily schedule from days 5–10, in addition to an increased anti-PD-L1 dosage of 0.25 mg. A combination of schedule and dosage adjustment led to 98 cases of successful tumor eradication out of 100 simulations.

low toxicity, minimized costs, and a high probability of cure. Finding the right balance between the pros and cons of a particular treatment is important for healthy long term effects, and can benefit from patient-specific approaches. In this mathematical model, some parameters that need to be measured for each individual are tumor growth rate (r) and “immune ability” determined by maximal tumor kill rate by T cells (d). As demonstrated above, these parameters help determine the tumor size outcome, with zero tumor cells as the ultimate goal.

The model could also benefit from examining other immune checkpoint inhibitors such as CTLA-4, another protein that helps regulate immune responses [1]. Additionally, the initial model and simulations could be combined with new human data to study the potential outcomes of cancer vaccines combined with monoclonal antibodies like anti-PD-L1.

Though the model was calibrated to mouse data, it can similarly be adjusted to fit human data and predict treatment outcomes. With enough data on individual or combined treatments, the model can be used to re-imagine personalized therapies.

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Appendix A

Table 4: Tumor Compartment Parameters

Parameter	Description	Value	Units	Source
a_D	Death rate of DCs	0.2310	1/day	[16]
$a_{E_a T}$	Death rate of activated T cells in tumor	0.462	1/day	[16]
α	Component of μ_{BTE}	1	cells	[16]
c	Rate for the deactivation of T cells by tumor cells	9.42×10^{-12}	1/(cell day)	[16]
d	Maximal fractional tumor kill by activated T cells	1.0497	1/day	[16]
k	Carrying capacity of the tumor	1×10^9	cells	[16]
l	Scaling exponent for immune strength	2/3	unit-less	[16]
m	Maximum recruitment rate of DCs to tumor cite	2.4388×10^4	cells/day	[16]
μ_{BB}	Scaled and shifted elimination rate of activated T cells from blood	5.7	1/day	[16]
μ_{TB}	Transfer rate of DC from tumor to blood	0.0011	1/day	[16]
q	T-value necessary for half-maximal DC recruitment	100	cells	[16]
r	Tumor growth rate	0.1655	1/day	[16]
s	Value of $(E_{tumor}^a/T)^l$ necessary for half-maximal activated T cell toxicity	1.4	unit-less	[16]

Table 5: New Tumor Compartment Parameters

Parameter	Description	Value	Units	Source
c_{ib}	Scales X, the amount of Ibrutinib, to a non-dimensionalized value	6.61e-5	mg^{-1}	Fit to [24]
c_{pd}	Scales Z, the amount of Anti-PD-L1 to a non-dimensionalized value	50	mg^{-1}	Fit to [24]
k_{pd}	Scalar for switch function, F , to model effects of Anti-PDL1	97	mg^{-1}	Fit to [24]

Table 6: Blood Compartment Parameters

Parameter	Description	Value	Units	Source
μ_B	Flow rate of DC from blood	27.072	1/day	[16]
μ_{BB}	Scaled Elimination rate of CTL from blood	5.7	1/day	[16]
μ_{normal}	Transfer rate of Normal DC from spleen to blood	0.512	1/day	[16]
μ_{SB}^*	DC Transfer rate from spleen to blood	0.012	1/day	[16]
μ_{TB}	Transfer rate of DC from tumor to blood	0.0011	1/day	[16]
θ_{shut}	Scaled threshold in DC density	1.3	Cells	[16]

Table 7: Spleen Compartment Parameters

Parameter	Description	Value	Units	Source
a_D	Death Rate of DCs	0.2310	1/day	[16]
a_{EaS}	Death Rate of activated T cells in spleen	0.1199	1/day	[16]
a_{Em}	Death rate of memory T cells in spleen	0.01	1/day	[16]
β	1/time spent in P compartment = average number of T cells leaving P in unit time	1	1/day	[16]
β_E	number of offspring from activated T cells transitioning to E^a	12	1/day	[16]
γ	Probability that 1 DC binds in unit time	0.12	1/day	[16]
λ	Average exit rate of activated T cells from W to P per unit time	4/3	1/day	[16]
λ_M	Proliferation of memory T cells in unit time	0.01	1/day	[16]
μ_{BS}	Rate of Transfer for DCs from blood to spleen	2.832	1/day	[16]
μ_{BSE}	Rate of Transfer (Scaled) for activated T cells from blood to spleen	7.33×10^{-4}	1/day	[16]
μ_{normal}	Transfer rate for normal DC from spleen to blood	0.512	1/day	[16]
μ_{SB}^*	DC transfer rates from spleen to blood	0.012	1/day	[16]
ω	Average number of nascent T cells that a DC binds to	5	cells	[16]
r_{am}	Rate of reversion of activated T cells to memory T cells	0.01	1/day	[16]
θ_{shut}	Scaled threshold in DC density in spleen for half-maximal transfer rate from spleen to blood	1.3	cells	[16]