Exploiting Homeostatic Repopulation to Increase DC Vaccine Efficacy in Multiple Myeloma

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Abstract- Standard of care for multiple myeloma involves autologous hematopoietic cell transplant (AHCT), which can extend life by a year; however the disease remains incurable. A dendritic cell vaccine developed at Moffitt will be used both immediately before and after AHCT, with the aim of achieving complete response. Data will be collected during the trial to test the biological activity of the vaccine. This data will parameterize a model that facilitates the exploration of outcomes when varying the timing of vaccination. This calibrated model will also inform the design of a follow-up trial, which will include vaccination in conjunction with other immunotherapies.

I BIOLOGICAL BACKGROUND

Ia Multiple Myeloma

Multiple myeloma is the second most common hematologic malignancy in adults, with approximately 26,850 patients diagnosed per year in the United States [10]. The disease is characterized by the proliferation of clonal plasma cells preferentially in the bone marrow, resulting in anemia, osteolytic bone disease and the detection of a monoclonal gammopathy in the majority of the patients [3]. The current standard therapy consists of induction therapy with immunomodulatory drugs or proteasome-inhibitor-based regimens, followed by autologous hematopoietic cell transplants (AHCT) in those patients with responsive disease [2, 7, 8, 9]. These treatment modalities induce high rates of complete remission and have significantly improved survival. However, molecular remissions are rare, and a significant proportion of patients are unable to achieve a complete response (CR) to induction therapy, both before and after transplant. Inevitably all patients relapse and die due to disease progression [6]. Therefore, the development of novel interventions for patients with resistant disease, and the targeting of minimal residual disease after autologous bone marrow transplantation, is greatly needed.

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II MATHEMATICAL MODEL

IIa Motivation

We have developed a mathematical model that utilizes the wealth of data that will be gathered during this clinical trial. The model

Figure 1: Interaction Network. See Equations section for full description
will be parameterized using this data, and will then be used to inform the design of a follow-up trial, which will include additional immunotherapies. The goal of this model is thus twofold: 1) Determine the optimum time at which to administer the DC vaccine, so as to maximize the expansion of cytotoxic T-cells specific for survivin positive tumor cells; 2) Explore the impact of administering additional immunotherapies, such as anti-PD-L1 or anti-CTLA4, which may augment the efficacy of the survivin vaccine.

The immune system is a complex mix of many cell types. To be included in the model, cell types had to meet certain criteria. First, the interactions of the cells selected must be well characterized. Second, the number of each cell type must be clinically measurable. Third, the interactions must either play a direct role in homeostatic repopulation and/or be targetable by available therapies. Finally, all cells and interactions must come together to form a model capable of realistically recapitulating the dynamics of homeostatic repopulation. The requirement that the size of each cell population be measurable will be particularly important when simulating tumor growth and treatment using individual patient data. Fortunately, we have access to a number of methods that allow us to do just that; flow cytometry will be used to measure the number of regulatory T-cells and the overall T-cell category; nanostring measurements will determine the number of survivin-positive effector T-cells, exhausted T-cells, and activated T-cells; and M protein and light chain ratios will measure the number of tumor cells. Having data at multiple time points also gives us the ability accurately estimate many of the parameters in our model.

### IIIb Equations

We have built a preliminary mathematical model consisting of a set of ordinary differential equations (ODEs) to describe the tumor burden and the immune response. The current model is developed for the period of time immediately following transplantation of stem and immune cells in the clinical protocol, such that the T-cells and tumor cells are both repopulating the depleted microenvironment. The system of 6 ODEs considers the following cell populations: tumor burden (P); activated T-cells (A); effector T-cells (E); tolerized T-cells (X); regulatory T-cells (R); and overall T-cells (T). The following system of ODEs was used as a preliminary model of the dendritic cell therapy.

1. \[ \dot{P} = gpP \left(1 - \frac{P}{CP} \right) - k_EPE \]
2. \[ \dot{A} = \frac{\alpha_MMF_{MFAR}}{\left(1 + k_E\right)} + \frac{g_APE_{AR}}{\delta_A} \]
3. \[ \dot{E} = \frac{\alpha_APE_{AR}}{\delta_A} + \frac{\left(1 + k_v\right)g_EPE_{RE}E_{RE}}{\delta_EE} \]
4. \[ \dot{X} = \frac{\alpha_APE_{AR}}{\delta_A} - \frac{s_XPE_{RE}E_{RE} - k_vX - \delta_XX}{rx} \]
5. \[ \dot{R} = \frac{\rho_{BC}D}{\delta_ER} + \frac{PE_{RE}E_{RE}}{\delta_RE} \]
6. \[ \dot{T} = g_TT - \left(1 - \frac{T}{CT} \right) - \delta_TT \]

### III Illustrative Results of Application of Methods

A sample result of our model’s ability to simulate the effect of timing of the vaccine can be found in Figure 2. These simulations highlight the importance timing has on the ability of the vaccine to stimulate a sufficient anti-tumor immune response. In panels A and C, the vaccine was given too early (day 10) and too late (90), respectively. In these cases, treatment fails because it misses the window of opportunity in which homeostatic repopulation can be exploited to increase expansion of survivin specific cytotoxic T-cells. Giving the vaccine too early will fail because there is an insufficient number of T-cells to stimulate, while administering it too late it will fail due to the return of peripheral tolerance. However, there is a sweet spot, where the T-cell population is neither too large nor too small, during which the vaccine will stimulate an immune
response strong enough to eliminate the tumor (panel D). In these simulations, this ideal time to administer the vaccine occurs 50 days post AHCT (panel B). The optimum is sensitive to the parameters and initial conditions, suggesting that the model can be used in a patient-specific way to predict individual optima for vaccination.

IV CLOSING REMARKS

The nature of multiple myeloma and the ability to collect key data at multiple time points provides the unique opportunity to develop a highly parameterized model of homeostatic T-cell repopulation, tumor growth, and the efficacy of immunotherapy. It is our hope that the model developed here will serve as a powerful tool for clinicians designing future clinical trials.

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