Personalizing immunotherapy
Balancing predictability and precision

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Despite great expectations and research efforts, anticancer immunotherapy has not yet become a definitive cure. Perhaps, this is because past reductionist approaches were too simplistic for the patient-specific complex system of co-evolving tumor cells and host immunity. Recent efforts based on a systems-based approach promise improved clinical outcomes engendered by a dynamic modification of personalized therapeutic regimens.

The idea to manipulate immunity to cure cancer has been pursued in the laboratory and tested in the clinic for decades. Yet, success in bringing immunotherapy to the standard of cancer care remains elusive. Why is it so difficult to achieve effective cancer immunotherapy? Unlike cytotoxic therapy, immunotherapy targets malignancies indirectly, by manipulating the immune system. In this context, a plethora of interactions between the components of cellular and humoral immunity and the tumor allow the latter to evade immune surveillance.[1] These and other factors have raised the need to streamline investigations for the achievement of effective cancer immunotherapy. The resulting proposals have focused largely on standardizing[2] and streamlining the methodology of clinical studies.[3] However, the consistent variations in patients' responses to immunotherapy, a critical obstacle against clinical success, have not been sufficiently addressed.

Human immunity is shaped by individual genetic makeups, history of infection, age, nutritional status, etc. In other words, each patient's immunity is somewhat unique and likely to exert unique pressure on a genetically-defined tumor. In the absence of insights into the level and type of immune proficiency that must be attained for effective tumor eradication in each particular patient, it is unlikely that any "one-size-fits-all" approach will be predictably effective. Thus, no single reductionist or population-based approach for the development of cancer immunotherapeutics can be expected to be efficient. Rather, alternative systems-based approaches are needed. The results of these strategies must be personalized, i.e., they must take into account not only the general, but also individual factors pertinent to the unique co-evolution of a particular tumor and a particular immune system.

Mathematical modeling is a valuable tool in the study of systems of such complexity. In the process of modeling, the researcher disentangles complex dynamical processes into a "verbal model" (a set of rigorously formulated hypotheses) of relationships among major components of the system. The verbal model is translated into the precise, yet minimalist, language of mathematics (**Fig. 1**). This language facilitates the analysis of the model and yields solutions that embody the system's predicted behavior starting from particular initial conditions. Models can be verified by comparing their solutions with relevant clinical information. Rigorously verified models can be further applied to forecast responses in other situations, (e.g., untested treatment schedules), to suggest treatment modification postulated to lead to better clinical outcomes.

Mathematical modeling seems to be a promising approach for tailoring personalized immunotherapy. However, there is an inherent problem in the development of personalized models. Most mathematical models are constructed based on and verified by clinical response observed in population studies.[4,5] In contrast, a personalized mathematical model must suffice with data from a single patient—a "population of one." In addition, model construction and validation must be completed in time for the patient to benefit from the treatment recommended by the model. How can these requirements be met in the often short period in which the patient is receptive to immunotherapy?

Recently, our group studied the difficulties inherent in simultaneous formulation, validation and application of a personalized mathematical model and developed a method to resolve these issues. We validated the method retrospectively on the data gathered in a clinical study of vaccination therapy in androgen-independent prostate cancer patients.[6] We now hope to generalize the applicability of our method to other cancer treatment modalities.

A personalized mathematical model of immunotherapy can be applied to the clinic only if validated (hypothesis about the response to treatment affirmed) in the early stages of treatment, when clinical data may actually be too sparse for reliable validation. This calls for a strategy to resolve the apparent imbalance between fast model validation and the accrual of sufficient response data to ascertain model
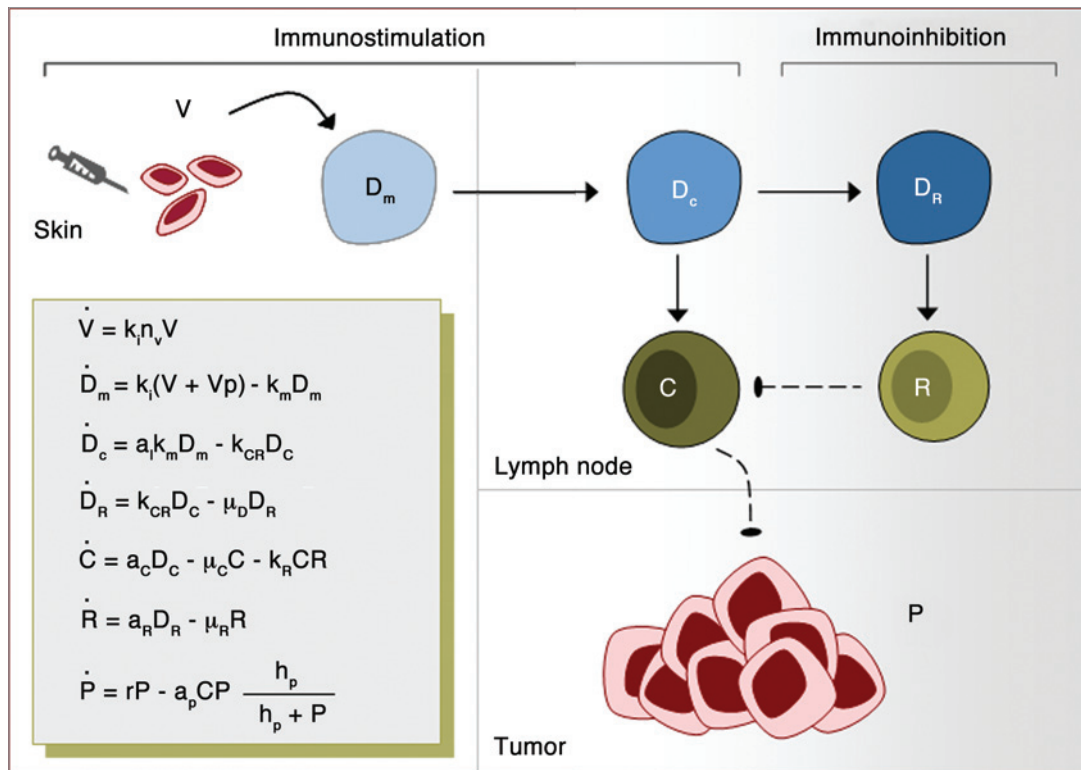
Figure 1. Model of interactions among the cellular vaccine (V), immune system and prostate cancer cells (P). D_m, antigen-presenting dermal dendritic cells; D_C, mature dendritic cells; D_R, "exhausted" dendritic cells; R, regulatory/inhibitory cells; C, antigen-specific effector cells (e.g., cytotoxic T cells). Originally published in reference 8.

accuracy. In our recent work, we showed that one can formulate and employ feasible criteria for the establishment of adequate validation of a personalized model shortly after treatment onset. When enough clinical data are obtained to satisfy validation criteria, the verified model can be used immediately to predict the subsequent clinical course of disease and, if needed, suggest treatment modifications. The mathematical model is re-tested and re-validated with each new data point obtained; this allows treatment to be modified dynamically, in real time, a radically new approach to cancer treatment that requires a new paradigm of clinical studies.[7]

To prove this concept, we formulated the procedure described above as an algorithm and tested it on retrospective clinical data[6] employing a mathematical model which describes major interactions between immune cells and prostate cancer cells (**Fig. 1**).[8] Utilizing only the data collected before treatment and early after treatment initiation, the algorithm successfully predicted the late clinical effects and suggested that potentially improved treatment schedules are available for most responding patients.[7]

These results demonstrate that rather simple mathematical models can quantitatively describe the interactions between

tumor cells and immunotherapy, that such models can be personalized and successfully validated, and that they can aid clinicians with real-time decisions about treatment, aimed at improving the clinical outcome. These results postulate the need for a novel paradigm of personalized clinical studies, where Phase I testing would define the range of permissible doses to be dynamically adjusted to the individual patient in subsequent phases of the study and clinical practice.[9] The suggested method is applicable to other cancer treatment modalities and introduces a new tool into the rather vacant toolbox of methods for immunotherapy personalization.

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