Reconsidering the Paradigm of Cancer Immunotherapy by Computationally Aided Real-Time Personalization

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Abstract

Although therapeutic vaccination often induces markers of tumor specific immunity, therapeutic responses remain rare. An improved understanding of patient-specific dynamic interactions of immunity and tumor progression, combined with personalized application of immune therapeutics would increase the efficacy of immunotherapy. Here, we developed a method to predict and enhance the individual response to immunotherapy by using personalized mathematical models, constructed in the early phase of treatment. Our approach includes an iterative real-time in-treatment evaluation of patient-specific parameters from the accruing clinical data, construction of personalized models and their validation, model-based simulation of subsequent response to ongoing therapy, and suggestion of potentially more effective patient-specific modified treatment. Using a mathematical model of prostate cancer immunotherapy, we applied our model to data obtained in a clinical investigation of an allogeneic whole-cell therapeutic prostate cancer vaccine. Personalized models for the patients who responded to treatment were derived and validated by data collected before treatment and during its early phase. Simulations, based on personalized models, suggested that an increase in vaccine dose and administration frequency would stabilize the disease in most patients. Together, our findings suggest that application of our method could facilitate development of a new paradigm for studies of in-treatment personalization of the immune agent administration regimens (P-trials), with treatment modifications restricted to an approved range, resulting in more efficacious immunotherapies.

Major Findings
We propose a new paradigm of cancer immunotherapy based on real–time treatment personalization. The method includes a novel computational algorithm involving mathematical modeling and pre–treatment and early in–treatment clinical data; it develops patient–specific models and verifies reliability of model–predicted treatment outcomes as early as possible. The method was tested using data from a study of prostate cancer vaccination therapy; it accurately predicted individual PSA dynamics and suggested personalized changes to treatment protocols for potentially more efficacious therapy, providing thus the foundation for clinical studies based on treatment personalization (P-trials).
Quick Guide to Equations and Assumptions

Mathematical model of vaccination therapy for prostate cancer

The model describes the dynamic interactions of tumor cells, immune cells and a cellular vaccine by a system of ordinary differential equations. The model is based on the following assumptions:

Vaccine, $V$, is injected into dermis where it stimulates maturation of naïve sentinel dendritic cells (DC) precursors into mature antigen–presenting DCs at the rate $k_i$. During maturation each DC takes up an amount of the vaccine, $n_V$, reducing the amount of available vaccine at the linear rate $k_i n_V$. Maturing DCs migrate into lymph nodes at the rate linearly proportional to their total number, $D_m$, with the rate coefficient $k_m$. The migrating DCs join the pool of functional antigen–presenting DCs in the lymph nodes, $D_C$, with probability $\alpha_l$. Having “instructed” and activated immune effector cells, DCs become “exhausted” at the constant rate $k_{CR}$ (Equation 1).

$$ \dot{D}_C = \alpha_l k_m D_m - k_{CR} D_C. \quad (1) $$

Exhausted DCs give rise to regulatory DCs, $D_R$, that die at the constant rate $\mu_D$. Accordingly, the dynamics of the regulatory DC population is described by

$$ D_R = k_{CR} D_C - \mu_D D_R. \quad (2) $$

Functional antigen–presenting DCs stimulate T_{H1}-type immunity by recruiting and activating tumor–specific cytotoxic T lymphocytes (CTLs), $C$, at the rate $a_C$. CTLs die at the rate $\mu_C$, or are inactivated by regulatory/inhibitory cells, $R$, at the rate $k_R$. The dynamics of $C$ are formulated by

$$ C = a_C D_C - \mu_C C - k_R CR. \quad (3) $$
Regulatory/inhibitory cells include T\(_{\text{reg}}\) cells, myeloid-derived suppressor cells and any other cells that attenuate immune functions. These cells are recruited by regulatory DCs at the rate \(a_R\) and die at the rate \(\mu_R\):

\[
R = a_R D_R - \mu_R R. \tag{4}
\]

Prostate cancer (PCa) cell population, \(P\), is assumed to propagate exponentially at the rate \(r\); it is destroyed by CTLs. The rate of tumor–cell removal is assumed to be proportional to CTL number with coefficient \(a_P\). Tumor killing efficacy decreases with increasing tumor burden, as reflected by the value of parameter \(h_P\). Thus, tumor dynamics are described by

\[
\dot{P} = rP - a_P C_P \frac{h_P}{h_P + P}. \tag{5}
\]

Model parameters were estimated from published experimental studies (see ref. 1 for details). Vaccination was modeled as instantaneous additions to \(V\) of the number of vaccine cells given at each injection time for a specific patient. Equations describing the dynamics of the vaccine, \(V\), and of the maturing DCs, \(D_m\), are presented in Supplementary Material, Section 1.
Introduction

Efficacy of cancer therapy is often unpredictable and significantly different among patients resulting from differences in age, gender, diet, organ function, and genetic variability (2-3). The overall response to treatment is determined by the complex interplay of these and other factors (cf. ref. 3). This is especially true for cancer immunotherapy where disappointingly few modalities are currently effective (4-10). Although the US Food and Drug Administration (FDA) recently approved the first cell–based vaccination therapy for castration–resistant prostate cancer (PCa), the overall response rates in cancer immunotherapy remain low (4, 11-12). Consequently, clinical development of immune cancer treatment must overcome major obstacles before becoming standard of care (13).

Cancer immunotherapy does not fit the standard paradigm of development typical of most modern therapeutics (13-15). Conventional cancer agents are designed to target the tumor directly, while immunotherapy should affect cancer indirectly, by manipulating the immune system. Hence, successful immunotherapy must control the continuously co-evolving tumor and tumor–specific immunity, both differing among patients. Inevitably, then, efficacious immunotherapy requires personalization; this calls for a paradigm change in clinical studies and, eventually, clinical practice.

Complex dynamic systems, such as interactions of cancer and therapeutics, have been analyzed by mathematical models with the aim of describing, quantifying and predicting the behavior of the disease. Mathematical models have facilitated rational design of cancer chemotherapy by suggesting optimal treatments that maximize drug efficacy and minimize toxicity (16-18). Model–based methods suggested for personalizing drug administration schedules (19) were prospectively validated in the clinic (20-21). Cancer immunotherapy has been mathematically
studied too (22-30) with some models retrospectively validated by preclinical and clinical population data (26, 31-32). In rare circumstances computational models of immunotherapy were personalized based on analysis of patient–specific information obtained early in treatment (1). Yet, these personalized models were validated only after completion of the full planned cycle of treatment limiting thus model applicability. For clinical utility, an individually adjusted model must be validated as early as possible following inception of treatment. The major barrier to the use of personalized models is too little data available for model validation early in treatment. To overcome this obstacle, we have developed a general method, formalized as an algorithm, for real–time in-treatment personalization of cellular cancer immunotherapy. The method provides the means to determine the crucial balance between sufficiently reliable in–treatment validation of personalized mathematical immunotherapy models and the utility of the insight from models to the practicing physician.

For proof of concept (POC) and feasibility of the method we analyzed the data from a clinical study of allogeneic whole–cell vaccination in castration–resistant metastatic prostate cancer (PCa) patients (33). We show that personalized mathematical models can predict patient response to immunotherapy rather early and suggest concomitantly the patient–specific modification of treatment expected to provide a more acceptable clinical outcome. Our method can derive and validate predictive personalized models early in treatment so that the need for therapy modification can be detected as soon as warranted and as often as needed.
Materials and Methods

A general method for in–treatment immunotherapy personalization

The method was implemented as an algorithm encompassing four stages: preparation, personalization, prediction of an improved treatment and monitoring. It iteratively “trains” and validates personalized mathematical models using patient data collected before treatment and those accruing early in treatment as training sets (Fig. 1; Supplementary Material, Section 2). The algorithm uses a customized success-of-validation (SOV) criterion to determine when the personalized model can reliably predict individual treatment outcomes under various treatment regimens. The validated model can be used to predict the outcome of the currently applied treatment for the patient and, if needed, suggest treatment modifications expected to result in more acceptable outcome.

Patient data

We studied the levels of circulating prostate–specific antigen (PSA) measured in a clinical study of an allogeneic PCa whole–cell vaccine administered to PCa patients on 14 occasions over a year (33). In this study, PSA levels were recorded before, during and after treatment. The endpoint for therapeutic response was the decrease in the PSA velocity, i.e., in the linear rate of change in the logarithm of PSA levels (33). For the present study, we selected the nine patients who completed the full course of treatment and whose PSA velocity decreased in the first two months of treatment (1).

The mathematical model

To prove the concept, we employed our recently developed PCa vaccination model describing the interactions of the tumor, antigen–presenting cells, immune effector cells, vaccine–induced immune stimulation and consequent immune suppression (1). Briefly, the model describes the
vaccine–stimulated maturation of naïve sentinel dendritic cell (DC) precursors in the dermis. These cells migrate to lymph nodes where, as functional antigen–presenting DCs, they induce T_{H1}–type immunity that includes tumor–specific cytotoxic T lymphocytes (CTLs) that can kill the tumor. Subsequently, DCs yield regulatory DCs, which recruit T regulatory (T_{reg}) cells that attenuate CTL function. The model is formally described by ordinary differential equations (see Quick Guide and Supplementary Material, Section 1), and used to simulate the dynamics of the system in response to different doses and administration schedules of the vaccine (cf. ref. 33).

All but four model parameters were common to all patients (“population model parameters”); their values were estimated from published in vitro and in vivo studies. Patient–specific parameters included the tumor growth rate, CTL killing efficacy, and two parameters linearly correlating tumor load and PSA levels. The four parameters were evaluated using individual “training sets” of PSA values singled out for calibration of patient–specific parameters as prescribed by the algorithm. This model was retrospectively personalized and validated using clinical data recorded for patients initially responsive to therapy (1).

**Selecting the best performing success–of–validation criterion**

The SOV criterion evaluates the difference between predictions of the model adjusted to the accumulated personal data at the current time and predictions by earlier models adjusted to previous, smaller data sets. We designed numerous SOV criteria differing in choice and number of previous personalized models to be compared and in the “stop” rule according to which comparison is halted and the model considered validated (see Supplementary Material, Sections 3 and 4). For each patient \( X \), the algorithm was applied with each tested criterion (v. infra) providing (i) the personalized model validated by the tested criterion, (ii) the corresponding validation time point \( t_X \), and (iii) the corresponding personal training set size \( C_X \). We selected the
best performing criterion by comparing its output to the results of previous retrospective analysis (1; see Supplementary Material, Section 5).

**Application of the algorithm with the tested criterion**

For each tested criterion, we applied the personalization stage of the algorithm to PSA values measured for each patient: the initial time point for algorithm application, $t_0$, was set to the time of the second vaccine injection; the first personal training data set $T_0$ included all individual PSA data collected prior to and including this point. The first personal parameter set, $P_0$, was evaluated by fitting the model to $T_0$. At each iteration $i \geq 1$, the preceding personal training set, $T_{i-1}$, was extended to the next individual PSA measurement to obtain the set $T_i$. The model was then fitted to $T_i$ to produce the new parameter set $P_i$ defining the current personalized model for this patient. For each $i \geq i_0$, the PSA course was predicted using personalized models defined by parameter sets $P_i, P_{i-1}, ..., P_{i-i_0}$; then we applied the tested SOV criterion. We repeated iterations until the criterion indicated that the personal model for the given patient was validated or the end of treatment was reached. If the algorithm validated the model at iteration $i$, for the tested criterion we recorded the patient-specific parameter set $P_i$, the validation time point $t_i$, and the size of the personal training set $T_i$. These results, over all patients, were used as the values for (i) the personalized model, (ii) $t_X$, and (iii) $C_X$ for the selection of the best-performing SOV criterion and modification of treatment.

**Model-guided modification of treatment regimens**

We used the validated personalized models to search for treatment regimens predicted to enhance clinical outcomes for each individual patient. Starting from the empirically determined initial vaccine dose (ED; 24 million cells) and administration frequency (every 28 days), denoted $1\text{EDq28d}$ (1, 33), we simulated the effects of more frequent administration and larger vaccine
doses. To emulate the application of the method to patient X, we used his model validated by the selected SOV criterion at time \( t_X \). Correspondingly, we simulated the application of the experimental regimen until validation time point \( t_X \) and of the modified treatment from \( t_X \) until completion of one year of treatment. First we simulated application of regimens with increased vaccination frequency (every 21, 14 and 7 days). Next, we tested the effects of vaccine dose escalation (1.5, 2, 2.5, 3, 4, 5, …, 10 times the ED, conceivably a plausible dose range) administered at seven-day intervals. The first regimen in this scheme that stabilized the PSA value within 10 percent above the value measured at the validation time point \( t_X \) (i.e., that turned the disease into chronic state) was recommended for treatment modification. If this effect was not achieved by any tested schedule, we recommended the potentially most effective protocol tested (i.e., high intensity treatment 10EDq7d).

Results

A general method for real–time in–treatment immunotherapy personalization

Figure 1 summarizes the suggested method (see also Supplementary Material, Section 2). At the preparatory stage the general mathematical model of the disease and immunotherapy is developed and its parameters are estimated based on available pertinent information. Selection of the general mathematical model, its population and patient–specific parameters, and adjustment of algorithm parameters (e.g., the size of initial personal training set), together with the exact formulation of the SOV criterion, depend on the nature of the disease, its underlying mechanisms, dynamics and treatment, as well as on the extent of available pertinent data.

For personalization, the values of parameters expected to be patient–specific are adjusted by fitting model predictions to the patient’s data. Following entry of new information, these
parameters are readjusted to all hitherto available data for that patient. The newly parameterized personalized model is used to predict the response to treatment when the agreement between predictions and current clinical data is verified. Subsequently, current predictions are compared to predictions generated at previous iterations using the SOV criterion. The criterion, defined uniformly for all treated patients, is a quantitative evaluation procedure testing whether predictions of consecutive personalized models are sufficiently close. When the criterion is satisfied for a given patient, we conclude that further clinical measurements are unlikely to add new information to the model, *i.e.*, the individual model has attained its maximal predictive power. Otherwise, the personalization stage for the patient is reiterated (Fig. 1).

Once validated, the personal model is used to predict the future response of that patient under the original regimen, or alternative immunotherapy regimens. If an alternative regimen is predicted to achieve better clinical results, the corresponding treatment modification is recommended for immediate application. Model accuracy is continuously monitored for possible cumulative or delayed effects, which may be apparent only later on. Personal model parameters are updated if necessary (Fig.1).

**Proof of concept for the personalization method in a clinical PCa vaccination study**

We tested the feasibility of the method for in–treatment personalization of PCa vaccination therapy. For convenience, we employed the algorithm in conjunction with our recent mathematical model of PCa vaccination (1) applied to data obtained in a clinical study (33). We tested many alternative SOV criteria differing in parameterization (*e.g.*, acceptance threshold). Among several thousand possible SOV criterion parameterizations, we chose the one with the best performance (see Supplementary Material, Section 5).
The selected SOV criterion compares the prediction of the personalized model at a given time to predictions of three preceding personalized models. Fig. 2 presents two examples of algorithm application using this criterion to Patient 20 and Patients 12 (patient numbers as in ref. 33). For Patient 20, predictions of the most updated model and the three preceding models get closer at each subsequent iteration, until—at iteration 8—all four models agree and the personalized model is declared validated.

The case of Patient 12 is more complicated. Comparison of predictions obtained at iteration 5 to those of iteration 4 and 3 shows the increasing agreement between consecutive predictions. However, the data point added at iteration 6 caused a notable change in parameters of the personalized model, so that now the prediction disagrees with the previous one. At this iteration it is difficult to estimate which model is more accurate. The criterion we chose addresses this question: we determine the current model valid only when the three preceding models agree with it. Indeed, by iterations 7 to 9 the models converge confirming that the personal model found at iteration 6 was accurate. Therefore, the personalized model was validated at iteration 9. Further, we checked the accuracy of the validated personalized model by probing if, after adding the data subsequently collected until the end of treatment, model predictions varied (iterations 9 to 11, Fig 2A and iterations 10–12, Fig. 2B). They did not.

For all patients in the study differences between consecutive model predictions tended to decrease (Fig. 3) demonstrating the increasing agreement between personalized models. Moreover, different patients required a different size of data set, from four to eleven months, to validate the personalized model (for details, see Supplementary Material, Section 5). We conclude that the selected criterion could yield accurate personalized models based on comparatively few data points.
Suggesting more effective personalized regimens

When model–predicted outcomes of therapy are not clinically satisfactory, the validated personalized model can be used to suggest more efficacious therapeutic regimens. To illustrate this point, we used personalized models to predict patients’ response to subsequent cycles of the tested standard regimen; the method accurately predicted the observed continuous rise in circulating PSA levels in all patients (Fig. 4). Since the observed therapeutic effect was generally transient and insufficient, we searched for individual regimen modifications that could improve responses before the patients completed the initially planned treatment cycle.

Hence, by personalized models we simulated the effects of increased vaccine doses and/or administration frequency (the change applied from the time of model validation) and compared them to the predicted effects of the hitherto applied regimen. We found that different patients required different therapy regimens to stabilize PSA levels turning the disease into chronic state (Fig. 4). Overall, for seven of nine patients we identified individual treatments predicted to stabilize PSA levels if applied immediately after individual model validation. Collectively, required treatment modifications ranged from doubling the administration frequency to the weekly injections of tenfold increased empirical dose (EDq14d, for Patients 7, 14; 10EDq7d, for Patient 20; Fig. 4). Conceivably, application of the proposed algorithm could considerably improve treatment outcome for a significant fraction of patients.

Discussion
Theoretical foundation and sporadic empirical evidence for efficacy of cancer immunotherapy abound, but numerous biological and other obstacles impede the development of predictably effective immune treatment of malignancy (4, 11, 13-14). Development of treatments, particularly those utilizing live or inactivated cells, is additionally hampered by inadequacy of standard preclinical in vitro and animal testing methods (as inadequate models of human immunity) and by regulatory requirements of a priori proofs of potency (cf. discussion in ref. 34). These factors require clinical testing as early as safe and possible, but it encounters the investigational paradigm traditionally based on minimizing patient variability and determining the average response in large patient populations (35).

“Training” immunity to reject malignant cells must take into account, at the minimum, the basic feed–forward and feedback interactions among the components of immunity, the disease, and immune therapy. As cancer is predominantly a disease of advanced age, it is countered by immunity shaped by individual genetic makeup, but also by personal history of morbidity and trauma as well as age–related attenuation. In other words, both qualitative (involvement of particular mechanisms) and quantitative (the extent of) interactions between the tumor and immunity will be particular to each patient. Based on this notion, development of cancer immunotherapy can be significantly enhanced by a paradigm shift in clinical studies, i.e., by clinical studies of cancer immunotherapy based on personalized treatment (P-trials; ref. 36). Current strategies to personalize immunotherapy attempt to use biomarkers for patient stratification, but the lack of practical methods to establish clinical significance of a given biomarker has severely hindered these attempts (37-38). Another approach to the enhancement of treatment efficacy, adopted here, includes accommodation of personalized treatment schedules into clinical trials.
The power of mathematical models to predict clinical effects of immunotherapy in individual patients has been documented before (26), as has been the validation of personalized models by clinical information (1, 28). Specifically, it was shown that response to a given treatment could be predicted with reasonable accuracy, based on partial data collected before and during early phases of treatment (1). Accuracy of a personalized model usually increases with the number of data points used for its personalization, i.e., with the time elapsed from the onset of treatment. Hence, there is an inherent tradeoff between the time-dependent accuracy of the personalized model and the commencement of clinical benefit from treatment modified by this model. The subject matter of the current work was to develop a method for achieving an optimal balance between (i) sufficiently reliable in–treatment validation and (ii) utility of the insight from the model to the treating physician. The new paradigm suggested here takes into account that this balance is personal and can be determined by our method.

To prove the concept, we have applied the method to a particular clinical data set (33) and shown that fair model validation for individual patients enables not only predicting the observed individual PSA changes rather early in treatment, but also suggesting valuable treatment modifications. For most studied patients, these altered regimens would have stabilized PSA levels until the end of planned treatment. This outcome is consistent with the clinical definition of stable disease, and therefore, the majority of responding PCa patients (33) could have benefited from our strategy, particularly as increased vaccine doses likely would have been well tolerated (39). These results prove the feasibility of the method, that is, that early acquisition of a reliable personalized mathematical model of immunotherapy is possible and can be valuable for improving design and implementation of treatment. The next stage of the work will constitute
prospective studies, aimed at statistically examining the contribution of the suggested method to improve efficacy of immunotherapy in a patient population.

Early validation of the personalized model permits its use for prediction of more effective personalized treatment and allows early screening for the subpopulation of responsive patients. Concomitantly, patients identified as unlikely to benefit from the treatment can be redirected to alternative therapeutic options, a valuable objective in itself. It has not eluded our notice that unforeseeable effects occurring later in treatment could render the previously validated personalized models incorrect. Therefore, the last stage of the proposed algorithm requires ongoing monitoring for ensuring model accuracy by the accruing patient data. This guarantees model’s validity throughout treatment.

In this study we used the example of changes in the measured PSA levels as correlates of tumor activity. However, as other pertinent measures of tumor characteristics become available, mechanistic models of interactions of disease and other physiological systems will be refined. In addition, establishment of mechanistically relevant measures of disease–specific immune function (14) will allow the development of more precise mathematical models to facilitate the resolution of a fundamental question of immunotherapy: What immune endpoints must immunotherapy attain to eradicate the particular tumor in the particular patient?

We determined a specific SOV criterion and found it appropriate for algorithm application in the particular clinical study. A similar criterion can be used in other PCa immunotherapy studies that employ similar treatments. In general, every new treatment modality will require an adjustment of the formulation of the SOV criterion. This can be achieved by retrospective analysis of data from previous studies of the same or related indications and treatments, similarly to what we
have shown here. Alternatively, small pilot studies could be used to calibrate the criterion formulation for larger planned studies of the same type.

The proposed paradigm shift for clinical studies poses the important question of the limits wherein patient–specific treatment modifications can be sought. In common clinical trials, usually a single drug regimen is uniformly applied to large patient sub-populations. We suggest that the individual treatments be selected *ad hoc*, within an approved range of schedules. Definition of the range is a cardinal issue when seeking regulatory approval for the clinical trial. In the present study of nine patients, we could define the range of recommended schedules within rather narrow limits of dose size and administration intervals. For larger populations, the range of could be wider, but still restricted by dose limiting toxicity. As cellular immunotherapy is generally safe (8, 12), our personalization paradigm appears feasible. Likewise, specific regulatory guidelines should be adopted for application of mathematically aided non-intuitive decision making in life–and–death situations (40).

Here we have focused on immunotherapy as its success may be hampered by the shortage of personalization methods more than some other therapies. Nevertheless, our approach is general and should be examined in other modalities of cancer treatment. Recently, similar approaches have been implicated in other fields of cancer therapy (41). If clinically supported, our approach could increase the response rates to cancer immunotherapy and pave the way for practical application of personalized immunotherapy. The approach is new in its intent to embed mathematical modeling into clinical practice for real–time tailoring of patient–specific treatment. Novel methods, such as the one proposed and tested here, can add a rational element to the process and provide new tools in disease management.
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References


Figure Legends

Figure 1. Schematic representation of the method for in–treatment therapy personalization. The Preparatory Stage designs the mathematical model and success–of–validation (SOV) criterion based on preliminary data and biological and clinical understanding of the system. At the Personalization Stage, collection of new individual data, model personalization and validation assessment are repeated until the SOV criterion is satisfied. The Prediction Stage utilizes the validated model to forecast therapeutic outcomes and suggest treatment modification, and alters the treatment regimen accordingly. The Monitoring Stage compares model predictions with clinical data resulting from modified treatment. If modified treatment fails, the procedure is repeated from the stage of model personalization.

Figure 2. Application of the iterative algorithm; a detailed example. At each iteration \(i\) the model was constructed using all data for Patient 20 (A) and Patient 12 (B) available at that time; for each patient, model prediction (thick line) was compared to predictions by three preceding models (thin grey lines). Symbol \(\times\) marks the last available data point for the particular iteration, while open circles mark the three data points immediately preceding it; full circles represent all earlier data points. Treatment started on day zero.

Figure 3. Time course of algorithm application for all patients. For each patient shown are the values of model comparison grade \(D(i)\) generated by the selected best-performing SOV criterion. This grade evaluates the agreement between the current model and three previous consecutive models over a prediction period of one year. When the value of the grade becomes less than the acceptance threshold of the SOV criterion, the model is declared validated (for details, see Supplementary Material). Full dots show model comparison grade values at successive algorithm iterations; open circles mark validation points when the grade is less than
the acceptance threshold ($D_0=0.05$, thin horizontal line). For convenience, y-axis is set to logarithmic scale.

**Figure 4. Model–suggested treatment enhancement.** Grey full circles, measured PSA levels; open circles, validation points; thin grey line, simulated PSA evolution during standard treatment (empirical dose, $ED=2.4\times10^7$ vaccine cells every 28 days); thick line, simulation of PSA evolution under protocols intensified just enough to stabilize PSA levels: $10EDq7$ (Patients 3, 12, 20), $1EDq7$ (Patients 5, 18, 21), $1EDq14$ (Patients 7 and 14) and $5EDq7$ (Patient 22); $q$, interval between vaccine administration (days). Dashed lines indicate the beginning and the end of the 12-month treatment. $C_i$, number of training data points at individualized model validation; duration of treatment in days at validation is indicated in parentheses. For details, see Methods.
Fig. 1

**Prepare**
- Collect and analyze personal pre-treatment data
- Construct a mathematical model for cancer immunotherapy
- Formulate the success-of-validation (SOV) criterion

**Personalize**
- Construct initial personal clinical data set ("training set")
- Construct a personalized model using the current training set
- Verify agreement between current model predictions and up-to-date pertinent clinical data
- Generate predictions of the current and previous models
  - Update individual training set by adding recent clinical data
  - SOV criterion satisfied?
    - No
    - Yes

**Predict Improved Regimen**
- Apply the model to suggest regimen modification
- Modify regimen

**Monitor Modified Regimen**
- Add new clinical data point
  - Model accurately predicts new data?
    - No
    - Yes
Fig. 2

A

\[ i = 4 \]

\[ i = 5 \]

\[ i = 6 \]

\[ i = 7 \]

\[ i = 8 \]

\[ \text{Validation} \]

\[ i = 9 \]

\[ i = 10 \]

\[ i = 11 \]

\[ i = 12 \]

\[ \text{Time (days)} \]

B

\[ i = 4 \]

\[ i = 5 \]

\[ i = 6 \]

\[ i = 7 \]

\[ i = 8 \]

\[ \text{Validation} \]

\[ i = 9 \]

\[ i = 10 \]

\[ i = 11 \]

\[ i = 12 \]

\[ \text{Time (days)} \]
Fig. 4

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