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Review:

Employing Dynamical Computational Models for Personalizing Cancer Immunotherapy

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Abstract

Introduction: Recently, cancer immunotherapy has shown considerable success, but due to the complexity of the immune-cancer interactions, clinical outcomes vary largely between patients. A possible approach to overcome this difficulty may be to develop new methodologies for personal predictions of therapy outcomes, by the integration of patient data with dynamical mathematical models of the drug-affected pathophysiological processes.

Areas covered: This review unfolds the story of mathematical modeling in cancer immunotherapy, and examines the feasibility of using these models for immunotherapy personalization. The reviewed studies suggest that response to immunotherapy can be improved by patient-specific regimens, which can be worked out by personalized mathematical models. These studies further indicate that personalized models can be constructed and validated relatively early in treatment.

Expert opinion: The suggested methodology has the potential to raise the overall efficacy of the developed immunotherapy. If implemented already during clinical trials, it may increase the prospects of the technology being approved for clinical use. However, schedule personalization, per se, does not comply with the current, "one size fits all," paradigm of clinical trials. It is worthwhile considering adjustment of the current paradigm to involve personally tailored immunotherapy regimens.

1. Introduction – the arsenal of cancer immunotherapy

The immune system plays a pivotal role in the maintenance of the organism's integrity. In addition to the protection against pathogens, it is intensely involved in recognition and elimination of transformed cells and, therefore, in cancer prevention and in the inhibition of its progression. The latter process is referred to as immune surveillance. Diminished immune system function, due to organ transplantation or immunosuppressive agents, can predispose an individual to the development of spontaneous or virally induced cancers [1]. Cancer immune-editing emerges as a necessary condition for cancer progression. New cancer cell variants appear during this process, having various mutations that suppress immunity, either systemically, or by generating immunosuppressive microenvironments for the growing tumor. Reduced expression of tumor antigens, expression of surface proteins that induce immune cell inactivation, and induction of surrounding cells to release immune-suppressive substances, are some of the mechanisms that the progressing tumor exploits to ward off the immune system [2-4].

Different methods for increasing the potency of immune responses against cancer have been introduced over the last years, collectively termed *immunotherapy*. Anti-cancer immunotherapy employs biological substances to either enhance the activities of specific components of the immune system, or to counteract cancer-

induced immune suppression. Cancer immunotherapies comprise nonspecific immune system activators, monoclonal antibodies targeting tumor antigens, cytokines, adoptive cell transfer (ACT), therapeutic cancer vaccines and immunological checkpoint inhibitors [2, 5]. The first immunotherapy approved by the Food and Drug Administration (FDA) was a weakened bacterium, bacillus Calmette-Guérin (BCG). For many decades, BCG was used to treat early stage bladder cancer, reducing the risk of disease recurrence by stimulating the immune response against both the bacteria and the cancer. Approximately 70% of bladder cancer patients go into remission after BCG therapy [6, 7].

A more specific immunotherapy is achieved by tumor-specific monoclonal antibodies, which instigate cancer cell death by eliciting the immune response via various mechanisms of action. Some monoclonal antibodies operate by blocking essential signaling pathways; others trigger immune-mediated cytotoxic responses, etc. Several monoclonal antibody therapies comprise antibodies, or fragments of antibodies, chemically linked to a toxic substance. The antibody portion enables binding to the target molecule on the surface of cancer cells, and the toxic substance can be a poison, such as a bacterial toxin, a small-molecule drug, or a radioactive compound. Tumor-specific monoclonal antibodies are in common use in the treatment of leukemia, breast cancer, colorectal cancer, and head and neck cancer, having shown to improve overall survival and progression-free survival in randomized, Phase III clinical trials [8-11].

The first immunotherapies by cytokines, namely, interleukin 2 (IL-2) and interferon alpha-2b (hIFN-α-2b), were approved by the FDA for cancer treatment already in the 1990s. IL-2 stimulates T cell proliferation, continued cytokine production, and activation of multiple types of immune cells [12]. High dose IL-2 treatment is approved for metastatic melanoma and renal cell carcinoma, leading to objective response in 15-20% of patients [13]. Interferon-alfa 2b affecting the growth of various cancer cells via the JAK-STAT signaling pathway, has been approved as monotherapy or in combination with another anticancer drug, for the treatment of hairy cell leukemia, melanoma, follicular lymphoma, renal cell carcinoma, AIDS-related Kaposi's sarcoma, and chronic myelogenous leukemia [14].

More recently, identification of tumor-associated antigens (TAA) has prompted the development of different strategies for antitumor vaccination, aimed at inducing specific recognition of TAA. The underlying objective here is to elicit a persistent immune memory which may cause elimination of residual tumor cells and prevent relapses. Antitumor vaccine activity mostly depends on antigen-specific CD8+ T cells that become cytotoxic T lymphocytes (CTL) capable of eliminating cancer cells. Two main strategies have been employed to stimulate antitumor CTL: passive immunization and therapeutic vaccination. In passive immunization by adoptive T cell therapy, autologous or allogeneic T cells, tumor-infiltrating lymphocytes (TIL), or engineered T cells, are transfused into cancer-bearing patients. In therapeutic cancer vaccination, the administrated vaccines are aimed at intensifying the patient's own immune responses [15, 16]. An innovative treatment by gene-modified T cells,

expressing chimeric antigen receptors (CARs), has been developed (named CAR T-Cell Therapy). The chimeric receptors comprise extracellular tumor targeting antibody fragments, fused to the intracellular signaling domains of T cell receptors. This enables the T cells to recognize specific antigens on tumor cells. CAR T-cell Therapy has demonstrated success in eradicating hematological malignancies and various other clinical trials are still going on. Recently, encouraging preliminary signs of efficacy have been demonstrated in solid tumors [17].

In 2010, the FDA approved the first therapeutic cancer vaccine for use in men bearing metastatic prostate cancer (PCa), a dendritic cell-based vaccine, sipuleucel-T (Provenge®). Reduction of 22% in the risk of death was shown in the clinical trial, and the 36-month survival probability was 31.7% in the sipuleucel-T group, versus 23.0% in the placebo group [18]. Other therapeutic vaccines are currently in clinical trials for treating a range of cancers, including brain cancer, breast cancer, and lung cancer [19].

This wealth of new methods for increasing the potency of anticancer immune responses has revolutionized the field of cancer immunotherapy. Most notably, immunologic checkpoint inhibitors, having shown promise in a variety of malignancies, may cause a paradigm shift in the way oncology patients are being treated [20, 21]. Yet, significant challenges still exist, hindering this innovative approach from reaching its full potential [22].

2. Current challenges in immunotherapy application – the need to personalize therapy regimens

Unlike chemotherapy, which directly attacks the tumor, immunotherapies act via their effects on the immune system. Therefore, for immunotherapy to show success, it must keep in check the complex dynamic interactions between the patient's immune system and the disease. Since these multifaceted interactions are significantly more variable than tumor progression alone, it can be well understood why immunotherapy is much more difficult to route than chemotherapy.

Response of cancer patients to immunotherapy can be divided into three phases, which operate on different time scales: i) immune activation and T-cell proliferation, starting early after first administration and lasting for hours or days, up to the acquisition of functional properties [23], ii) clinically measurable changes in tumor size, mediated by activated immune cells and lasting over weeks or even months, and iii) delayed effects on patient survival, potentially occurring many months after first administration [24]. Unlike what is expected based on experience from chemotherapy, the effects of immunotherapies on the host antitumor response may require long periods of time to become observable. It remains unclear, though, how long a patient has to be under surveillance for inferring drug efficacy; do the delayed response patterns, reported in patients with melanoma, occur within the

same time frame and to the same extent in all patients with this indication, or in patients with other solid tumors?

The difficulty in determining the time to achieve an observable response to immunotherapy is intertwined with the problem that the standard of care (SOC) response criteria may be ill-suited to the characteristic patterns of immunotherapy dynamics. Conventional response criteria assume that early increase in tumor growth or development of new lesions indicate progressive disease, and, hence, drug failure. For immunotherapeutic agents, however, initial tumor growth, or appearance of new metastases, does not necessarily reflect immunotherapy failure. For example, in some cases, significant response has been observed only after an initial increase in total tumor burden. To attune to the specific clinical patterns associated with immunotherapy, new response criteria have been already defined [25], but these do not seem to be sufficient for reflecting all the decisive clinical phenomena in cancer patients receiving immunotherapies.

Yet, fundamental problems still prevail, even if improved response criteria are found. How to match the immunotherapeutic treatments to patients who are most likely to benefit from it is a crucial problem for oncologists applying immunotherapy. A small retrospective study evaluated the response to pembrolizumab in 96 previously treated patients bearing different metastatic cancers

who received the drug off-trial. When these patients were classified into three groups according to their performance status, no response to treatment was observed in more than 30 patients with the most compromised performance status (bed-ridden or moribund), persumably because the immune system of these patients was already too exhausted to be effectively stimulated by the drug. If one could predict the magnitude of the immunotherapy effect on the individual patient's lesions, one could avoid creating false hopes and save treatment costs. The accumulating knowledge on response biomarkers encourages the hope that in the near future these will be used in combination with immunotherapies, to forecast the patient's response (R. Leibowitz-Amit, personal communication).

Notwithstanding the general optimism, predicting patient response to cancer immunotherapy is a major issue. In spite of the tremendous efforts invested, diagnostic biomarkers for anti-cancer drugs have not provided a sufficient instrument for identifying patients who are most likely to benefit from treatment. More specifically, no single immunologic or tumor characteristic in a patient has been found to determine response to an immunotherapeutic agent. Given the high cost of current immuno-oncology monotherapy agents and the fact that many will be used in combination, together with the potentially higher hurdles in less immunogenic tumor types, the field is ripe for an 'out-of-the-box' innovation [26-28].

Recently, the potential role of computational biology in precision medicine has been highlighted, and it has been suggested that the effects of therapy may become more predictable by the integration of the effects of drug treatment in dynamical mathematical models of the pathophysiological process [29]. Indeed, mathematical models can be used to disentangle complex systems, such as mutually interacting immunity, tumor growth and immunotherapy. The models make relatively simple assumptions about the different processes in the system, which are then "verbalized" by the succinct language of mathematics. The formal mathematical description of the intricate biological processes allows simulation of the system's behavior under different conditions, thus predicting the patient's response to different administration schedules of the immunotherapy drug at hand. Below, we reviewed mathematical models for various cancer indications and diverse immunotherapy modalities, which are aimed at cracking the complexity involved in immunotherapy-host interactions. Next, we examined in more detail the development and analysis of a mathematical model for brain cancer, whose results pinpoint the need to personalize immunotherapy. Next, we went over the development and validation of a model for PCa progression, and its use for exemplifying the feasibility of tailoring personalized regimens early in treatment. Finally, we briefly discussed the potential of these computational developments to aid in solving some of the major dilemmas in this emerging clinical area.

3. Disentangling the complexity of cancer immunotherapy by mathematical models

Various approaches have been adopted in the biomathematical investigation of cancer immunotherapy, either analyzing a "universal" cancer immunotherapy system, or focusing on a specific immunotherapy type. This section briefly reviews some of the prominent mathematical models developed for the investigation of different specific cancer immunotherapy methodologies.

An interesting insight on cancer immunotherapy is given by De Angelis et al., [30], who investigated tumor–immune interactions, by methods borrowed from non-equilibrium statistical mechanics and generalized kinetic theory. The authors developed and numerically simulated a model for the competition between the tumor and the immune system with or without cytokine therapy, and numerically analyzed its global behavior, using bifurcation maps. Analysis shows that the system can have only two distinct fates, depending on its initial parameters: activation of the immune system and suppression of the tumor or, alternatively, inhibition of immune cells, leading to uncontrolled tumor growth. The general conclusion from this study is that immunotherapy by cytokines, counteracting cancer-induced immunosuppression, might cause a futile hyperactivation of the immune system. The authors stress that the only way to render immunotherapy efficacious is by controlling the cancer's immune inhibitory activity. This insight,

based on the analysis of a simple mathematical model was obtained long before the recent success of checkpoint blockade therapies; it highlights one of the important roles of biomathematics in cancer research, namely, to predict possible outcomes of different treatment scenarios, and suggest 'out-of-the-box' approaches.

The work by Kirschner and Panetta (KP) [31] generalizes the Lotka-Volterra model introduced by Kuznetsov to describe tumor-immune dynamics under immunotherapy by IL-2 or by ACT [32]. Non-intuitive results, obtained via theoretical analysis by stability and bifurcation theory, suggest different effects of tumor antigenicity in different settings. The work shows that although untreated tumors with low antigenicity can progress to large sizes, any little increase in antigenicity may lead to sizeable oscillations with period of about eleven years. During the first two months of each oscillation, the tumor mass grows to a maximum, but then shrinks significantly and remains small, i.e. dormant, in the rest of the period. Analysis of IL-2 and ACT application reveals interesting dynamic properties. When ACT is applied alone, treatment efficacy depends on its intensity and the antigenicity of the tumor. Thus, when both the antigenicity and the number of injected cells are small, the tumor progresses to become large and stable. In contrast, if antigenicity remains small, but the number of injected cells increases, a bistable state is observed- either tumor-free or a large tumor, depending on the initial conditions, namely, on three factors: the initial tumor size, the initial number of effector cells and IL-2 concentration in blood.

This implies that the success or failure of an immunotherapeutic treatment depend on the condition of the immune system and the tumor at treatment onset.

Analysis of the KP model suggests that IL-2 monotherapy will have no effect when applied at low doses. However, independently of the degree of tumor antigenicity, administration of large IL-2 doses yields an interesting theoretical result: the tumor is cleared and the number of effector cells grows with no limit (in the model) while the concentration of IL-2 reaches a steady-state value. This unbounded expansion of the immune system may reflect the adverse effects observed in patients receiving IL-2 treatments (e.g. the capillary leak syndrome associated with IL-2 dose escalation treatments). The theoretical results show that these adverse effects cannot be eliminated by combining IL-2 with ACT therapy; under large IL-2 doses the tumor can be cleared but adverse effects of an over-activated immune system compromise the benefits of tumor clearance [33]. Overall, this work indicates that mathematical models may enable an informed selection of the proper treatment, based on the state of the patient.

However, the KP model is too simple to enable clinical or even experimental validation, thus justifying the motivation to improve it to better account for the observed clinical dynamics. This was the motivation of Banerjee [34], who modified the KP model to reflect the clinically observed time-lag between IL-2

production by activated T cells and the stimulation of effector cells by IL-2 treatment [33, 35-37]. The analysis of [34] shows that IL-2 therapy alone can lead to tumor regression. Moreover, in contrast to KP [31], it is shown that the immune system can stabilize under IL-2 monotherapy, indicating that IL-2 therapy has the potential to completely eradicate the cancer with negligible side effects. But as the Banerjee itself was not validated experimentally or clinically, the contradicting conclusions stemming from the two model variations cannot be resolved at present.

Nani and Freedman developed a mathematical model for cancer treatment by ACT. The model, comprising four differential equations for immune cells, cytokines, cancer cells and normal cells, is analyzed thoroughly with regard to boundedness, dissipativity, invariance of non-negativity, stability, nature of equilibria, and bifurcations. Criteria for total cure, i.e. necessary and sufficient criteria for total elimination of all cancer cells, are derived. To this end, the conditions for global asymptotic stability of a rest point with zero cancer cells are derived by means of a Liapunov function. The authors show that bifurcations can lead to periodic orbits, and consequently to complications in cancer treatment [38].

Attempting to improve existing immunotherapeutic regimens of IL-21, Cappuccio et al. developed a mathematical model for IL-21 antitumor effects, to which they applied an optimization methodology [39, 40]. The results suggest that by

optimizing the inter-dosing intervals and the dosages, tumor burden and cumulative IL-21 toxicity can be minimized, so that maximal efficacy/toxicity ratio can be obtained; the optimal regimens included relatively early drug administration and sequentially decreased IL-21 intensities. In a following work, Elishemreni et. al. calibrated the mathematical model by data acquired from a preclinical study of IL-21 therapy in mice bearing various solid tumors. The accuracy of model predictions was validated retrospectively by comparison to data from independent murine experiments. Next, these predictions were validated *in-vivo*, in melanoma-bearing mice, possibly being the first instance of prospective validation of computational immunotherapy models [41].

In [40], the authors use optimal control theory to identify optimal dosages and inter-dosing intervals, ensuring maximal efficacy and minimal toxicity of IL-21. The work shows theoretically that the optimized schedules can lead to substantial cancer regression even with relatively low drug concentrations, and points towards the critical effect of the inter-dosing interval on immunotherapy efficacy. Working along similar methodological lines, Castiglione and Piccoli studied the efficacy of dendritic cell (DC) vaccination by a mathematical model of the tumor–immune interactions and applied optimal control theory to identify optimal treatment regimens [42]. Results show that the optimal regimen is a high dose vaccination at the beginning of treatment, followed by lower doses distributed over the rest of the treatment period. Of note, analysis by optimal control theory has an important

bearing on the clinical world: even though the mathematical model of the studied biomedical system must be much simplified to enable optimal control analysis, if carefully formalized, this analysis can add important insight on the universally optimal treatment strategy. Even if not applicable in the clinic at the present stage, the optimally identified policy can direct future pharmaco-medical developments.

De Pillis and Radunskaya developed and analyzed a mathematical model for tumor growth dynamics under immunotherapy, chemotherapy or combination of both [43]. The immunotherapy treatments considered are IL-2, TIL and cancer vaccines. Supported by mouse and human data, the theoretical results show that in some situations only combination of immunotherapy and chemotherapy can eradicate the disease. Model simulations imply that treatment efficacy strongly depends on patient-specific parameters, some of which can be measured experimentally. Although other model parameters are currently unmeasurable, these results lend support to the notion of customizing treatment regimens for individual patients by personalized mathematical models.

Isaeva and Osipov analyzed a mathematical model for the immune response in patients with avascular tumors under chemotherapy, immunotherapy by IL-2, IFN-α or vaccination, or by a combination of immunotherapy and chemotherapy [44]. Similarly to [43], their findings suggest that in the case of a weak immune response,

neither immunotherapy nor chemotherapy can diminish the tumor. The authors find that sequential application of chemotherapy and immunotherapy is more efficacious than concurrent administration of the two modalities.

Bunimovich-Mendrazitsky et. al. developed a mathematical model for tumor-immune interactions in the bladder under BCG vaccinations [45]. They identified multiple equilibrium points that are distinct in their stability properties, and characterized bi-stable regions in the parameter space. In these regions, BCG treatment can lead either to tumor-free equilibrium or to uncontrolled tumor growth, depending on initial conditions. Model analysis suggests that under low treatment intensity, the tumor can grow unrestrained; under intermediate treatment intensity the tumor is eradicated with transient adverse effects; when treatment intensity is large, the tumor can be eradicated exponentially fast.

The mathematical models reviewed in this section were developed for investigating the potential effects of different immunotherapy modalities. Most of these models have not been validated for their ability to depict the clinical setting, so that their conclusions should be taken with a grain of salt. Nevertheless, the body of work reviewed here is important in demonstrating the potential value of the mathematical models, which can illuminate the directions different immunotherapies can lead to, and the non-intuitive predictions which can arise from model analysis. Given the

clinical challenges in cancer immunotherapy, perhaps the most important role of mathematical models would be to serve as "virtual response biomarkers," predicting the clinical response of *individual* patients to varying immunotherapy protocols. The sections below show how mathematical models can be used for verifying the feasibility and benefit in immunotherapy personalization. As will be shown, immunotherapy personalization can be achieved by integrating clinical information into mathematical models of disease progression under different therapy regimens.

4. Immunotherapy of Malignant Glioma – personalization is essential

Malignant glioma (MG) is an aggressive brain cancer, with median survival of less than six months and about 6%, five-years survival, for the grade IV disease – Glioblastoma Multiforme (GBM) [46]. Significant efforts were invested in developing immunotherapy for gliomas, for supplementing the standard treatments (surgery, radiotherapy and chemotherapy) [47], and many of the tested modalities have reached clinical trials [48]. These approaches share the general idea that stimulation can help the immune system overcome the cancer-induced suppression, especially prominent in MG, and the limited access of immune cells to the brain, due to the blood brain barrier (BBB) [49, 50].

Cellular therapy of GBM by direct delivery of *ex vivo* activated CTL was developed to overcome the obstacles to effective immune reaction against brain cancer [51, 52]. Early results of alloreactive CTL (alloCTL) application were promising, yet they uncovered large variability in patient response. Inspired by systems thinking, a mathematical model of the MG treated by alloCTL immunotherapy was formulated and studied [53, 54]. The approach was to explain the population behavior, as well as account for individual variability, by theoretical analysis of the interactions between the major components of the system. For example, it may be discovered that a specific parameter, which varies in the population, accounts for most of the inter-patient difference in treatment response. Development of methods for estimating this parameter and consequently adapting the treatment can be the practical result of such discovery.

The MG model reflects the biological understanding of the major host-immunotherapy interactions. It describes the quantitative dynamics of six components (see Figure 1): tumor cells (T), CTL (C), two major cytokines: Interferon-gamma and Transforming Growth Factor-beta (IFN-γ and TGF-β; denoted by y and x, respectively), Major Histocompatibility Complex (MHC) class I receptors on a tumor cell (u) and MHC class II receptors on an antigen-presenting cell (v). The value of the variable T is related to the clinically observable tumor

volume by assuming a linear relation between cell number and observable volume, ca. 10^6 cells/cm^3

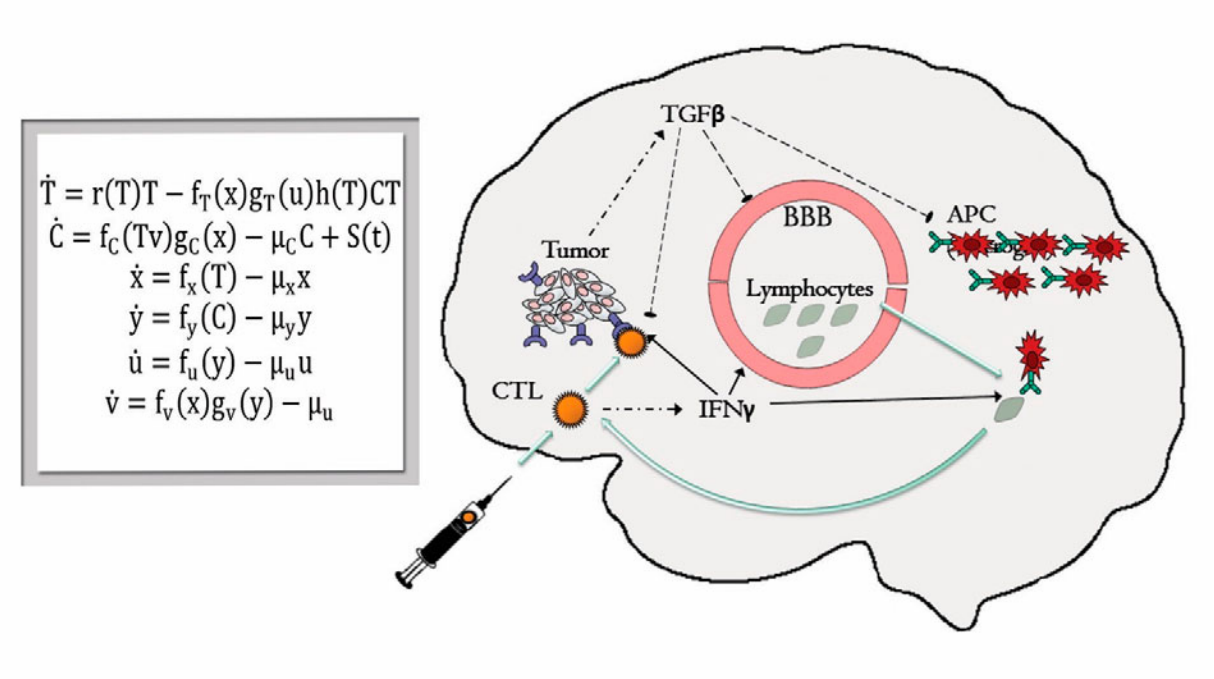

Figure 1. *A schematic description of the model of MG undergoing* alloCTL *immunotherapy (drawing) and the mathematical model reflecting these interactions (box). Endogenous CD4+ and CD8+ lymphocytes occasionally cross the BBB, attach to MHC class II on the surface of APC, eventually leading to CTL activation and recruitment; exogenous activated CTL are added by infusion; activated CTL attach to MHC class I molecules on the surface of tumor cells and destroy them (light green arrows). Tumor cells produce TGF-* β *and CTL produce IFN-*γ *(dashed dot black arrows);*

TGF-β reduces both BBB permeability, expression of MHC II molecules and activity of T lymphocytes (dashed black arrows). IFN-γ increases BBB permeability and activation of MHC I and II molecules (black arrows). In the first equation in the box, tumor cells (T) grow with rate $r(T)$, and their elimination by CTL (C) follows the law of mass action with saturation for large T ($h(T)$), suppressed by TGF-β ($f_T(x)$) and encouraged by MHC class I receptors ($g_T(u)$). In the second equation in the box, the CTL are recruited, depending on antigen presentation, being proportional to both tumor size and the abundance of MHC class II receptors ($f_C(Tv)$). Further, CTL are injected externally ($S(t)$), and eliminated at a rate μ_C. The recruitment is suppressed by TGF-β ($g_C(x)$). In the third and fourth equations, TGF-β and IFN-γ are secreted by tumor cells ($f_x(T)$) and CTL ($f_y(C)$) respectively; they are eliminated at the respective constant rates. The last two equations describe degradation and production of MHC class I and II receptors, both stimulated by IFN-γ, while MHC class II receptors are downregulated by TGF-β.

The model was used to analyze the reasons for treatment failure, and the likelihood of overcoming them. To this end, model parameters were fixed at the values estimated for the average patient, except for tumor growth rate which was set either

at a relatively large value to represent grade IV disease, or at a relatively small value to represent grade III disease. In the clinical trial, grade III patients responded well to alloCTL treatment, while grade IV patients progressed quickly and died [52]. Model analysis shows that this difference can be accounted for by the cancer growth rate: grade IV tumors whose growth is more aggressive overcome the treatment, due to faster expansion; the intrinsic growth rate of grade IV patients is estimated to be three-fold higher than that of grade III patients. Treatment can fail also in slowly growing cancers, as a result of higher initial tumor burden or smaller CTL efficacy. The MG model was simulated to indicate how to overcome such problems: in all these cases, response can be achieved by increasing the numbers of transferred CTL, in line with the personal patient's parameters [54].

Further mathematical investigation yields additional insights [53]. Theoretical analysis of scenarios with constant infusion shows dependence of outcomes on the infusion rate. Treatment is ineffective under low infusion rates for tumors of any size, while small tumors can be eliminated by ACT applied at intermediate infusion rates. With sufficiently large infusion rates, treatment eventually eliminates tumors of any size. The treatment intensity required to overcome the disease can be calculated from the initial tumor size and patient-specific parameters. The more realistic treatment scenario of intermittent daily CTL injections was studied numerically [53]. Also in this case, the outcomes depend on the dose: a low dose

allows the tumor to continue growing, while increased doses force a faster decline. This work demonstrates how, using a computational model, the dose-effect relation can be estimated, given individual patient parameters and the treatment schedule.

Preliminary clinical trials indicate that MG immunotherapy can be efficacious, but it has yet to become part of the SOC treatment. As in other indications, complex interactions between different arms of immune system and cancer generate a sizeable inter-patient variability in the response. The uniqueness in MG immunotherapy stems from the need to maintain a subtle balance between anti-cancer immune reaction and harmful brain inflammation, as the brain is isolated from the body's immunity [48]. Therefore, methods for using personal characteristics to predict patient's response are essential. The models reviewed here integrate the effects of biologically relevant parameters on the system behavior, predicting the effect of the treatment on a patient based on its personal parameters [53, 54]. Extending this work to integrate clinical patient data will allow developing personalized MG immunotherapy by computational models to evaluate an expected response based on personal clinical information.

5. Immunotherapy of PCa – the mathematical model as a personalization tool

The second most common cancer and the fifth leading cause of cancer death in males worldwide is PCa [55]. Following a hormone-sensitive stage of variable length (median is eight years), treated mainly by androgen deprivation therapy (ADT), patients progress to the most advanced disease stage, castrate resistant PCa (CRPC). The large variability in tumor progression among patients and lack of reliable predictive biomarkers impede prediction of the patient's response to therapy, thus complicating adequate planning of treatment for PCa patients [56-58]. The approval of sipuleucel-T for treatment of CRPC patients has been viewed as a milestone in the development of cellular immunotherapy. This success has strengthened the interest in vaccination therapy of cancer, a field that earlier had lost its appeal, partly, due to the absence of significant clinical progress [59]. But then, some of the recent experimental vaccines, which showed promising results in early studies, failed to meet the primary end point, in more advanced clinical studies. In a phase II clinical study an allogeneic PCa whole-cell vaccine stimulated expansion of tumor-specific immune cells in non-metastatic androgen-independent patients. The treatment was safe, but showed insufficient efficacy: the rate of increase of the prostate specific antigen (PSA; 'PSA velocity''), which serves as a surrogate marker for disease load in PCa, was reduced only in 11 out of the 26 studied patients [60]. The observed variability in PSA profiles, presumably, due to differences in individual immune characteristics and in tumor biology, points toward the possibility that trial results may be improved by personalized immunotherapy

regimens. This premise has been motivated by theoretical and experimental work, showing that the efficacy of chemotherapy may be improved by altering the inter-dosing intervals, rather than the dose itself, both in the patient population and in individual patients [e.g., [61-63]. The idea that adaptation of the immunotherapy regimen to the personal dynamics of the immune and disease processes would improve treatment efficacy differs from the more prevalent notion of personalized treatment, whose motivation is usually the expected toxicity of the drug, its price or the paucity of material for its preparation.

In view of the aforementioned need for personalized immunotherapy regimens, it is important to note that, *a priori,* it seems that the complexity of the cancer-immune system interactions would defy any attempt to determine the best individual regimen, based on the biomedical understanding alone. For this reason, the ability to personalize the adoptive immunotherapy treatment was studied by mathematical modeling, which had already shown success in methodically studying complex cancer-immune interactions (see Sections 3, 4 above). Accordingly, the first mathematical model for PCa therapy by an investigational vaccination was constructed and further used for studying the need for immunotherapy personalization, and the advantages of the computational approach. The model was initially validated by data from the above-mentioned phase II clinical study, hence establishing the feasibility of designing and validating robust mathematical models

and using them to suggest efficacious patient-specific immunotherapy regimens [64].

The constructed mathematical model describes the dynamic interactions of PCa cancer cells, immune cells and a cellular vaccine. The immune system components include antigen-presenting dermal DC, mature DC, "exhausted" DC and regulatory/inhibitory antigen-specific cells and CTL. A graphical portrayal of the model and its formulation can be found in Figure 2 [60].

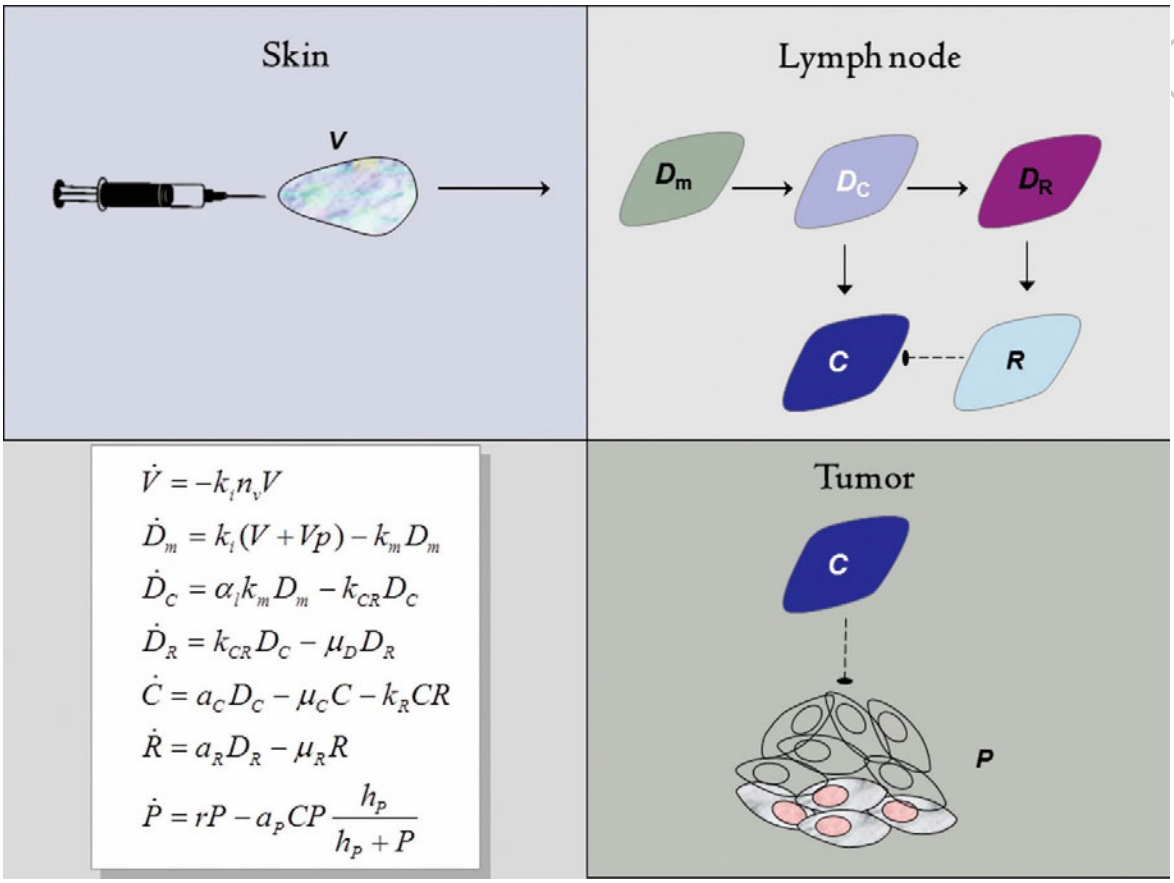

Figure 2. A graphical representation (drawing) of the mathematical model (box). *The model is based on several assumptions, as follows. A vaccine, V, is injected into the skin where it stimulates, maturation of naïve sentinel dendritic cells (DC) precursors into antigen-presenting DC. The vaccine is taken up by the naïve DC at rate* k_i *(first equation in box). During maturation, each DC takes up vaccine of amount* n_V*, so that the available vaccine is reduced at a linear rate,* $k_i n_V$*. Maturing DC migrate into lymph nodes at a constant rate* k_m *(second equation in box). The pool of functional antigen-presenting*

DC in the lymph nodes, D_C , grows with the addition of migrating DC, with probability α_1; functional DC become "exhausted" at the constant rate k_{CR} (third equation in box). Exhausted DC give rise to regulatory DC, D_R, which are eliminated at the constant rate μ_D (fourth equation in box). Functional antigen-presenting DC stimulate Th1-type immunity by recruiting and activating tumor–specific CTL, C, at the rate α_C. CTL die at the rate μ_C, or are inactivated by regulatory/inhibitory cells, R, at the rate k_R (fifth equation in box). Regulatory/inhibitory cells,R, are recruited by regulatory DC at the rate α_R and die at the rate μ_R (the sixth equation in box). With no immune suppression, the PCa cell population, P, is assumed to grow exponentially at a rate r. Tumor cells are removed by CTL at a rate proportional to CTL numbers; killing efficacy of CTL is taken as decreasing with increasing tumor burden, with coefficient α_P (seventh equation in box).

Next, the mathematical model was validated for its ability to predict the personal PSA profiles of the patients in the "real life" clinical study. To personalize the model, the PSA levels, measured in each patient before and during the initial five to nine treatment cycles, were used for adjusting the model parameters to reflect the characteristic biologic reaction rates of the individual patients ("training set").

Individual models successfully predicted the PSA course during the subsequent cycles and beyond treatment in 12 out of 15 responders (R^2=.972 in the "validation set"; Figure 3). Two important conclusions emerge from this simulation experiment: (i) by inputting pre-treatment and initial in-treatment PSA measurements, the mathematical model can be personalized and further used for accurately predicting future PSA dynamics of individual patients; (ii) an input of different numbers of PSA counts is required in order to obtain a sufficiently accurate personal model.

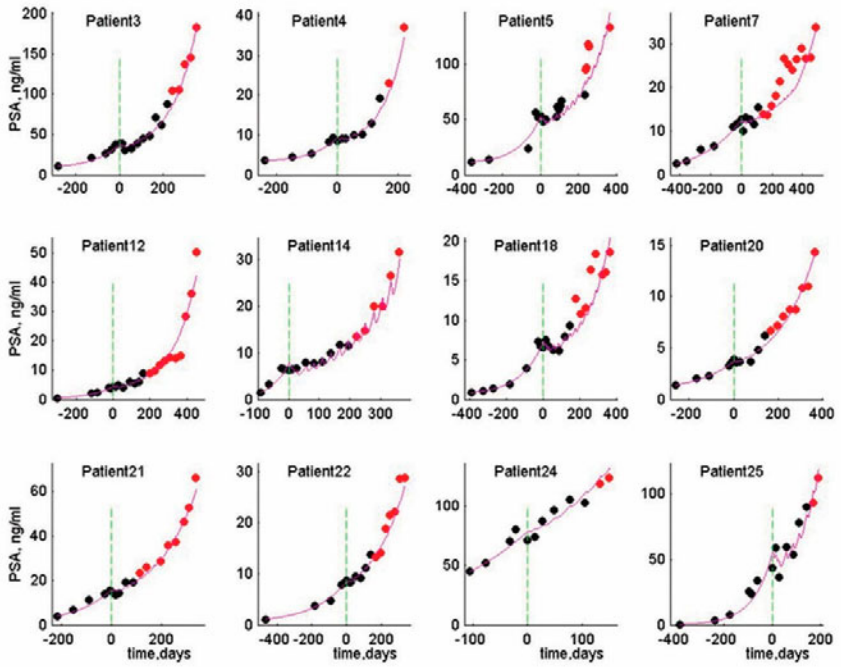

Figure 3. Validation of the personalized models*. Patient–specific models were obtained using the respective pretreatment and the patients' initial in–treatment PSA values ("training set"; black dots). The personal models were further employed for predicting subsequent individual PSA levels ("validation set"; red dots), showing high prediction accuracy* (purple line; R^2=0.972); *green vertical broken lines mark timing of vaccination onset. Note that a different size of the "training set" for each patient was required for reaching good predictive power.*

Having validated the accuracy of the model, it was then employed to examine whether personal changes in the immunotherapy regimens can increase their efficacy, e.g., stabilize the disease. Consequently, the personalized models were simulated with treatments which were different from the real-life protocol by various combinations of increased vaccine doses and reduced inter-dosing intervals.

The results of this "virtual trial" suggest that disease in different patients can potentially be stabilized by patient-specific regimens: a one week reduction in the inter-dosing interval is predicted to suffice for stabilizing disease in one patient, whereas other patients may require more frequent vaccinations with the standard dose (2.4×10^7 cells), or a double dose (Figure 4).

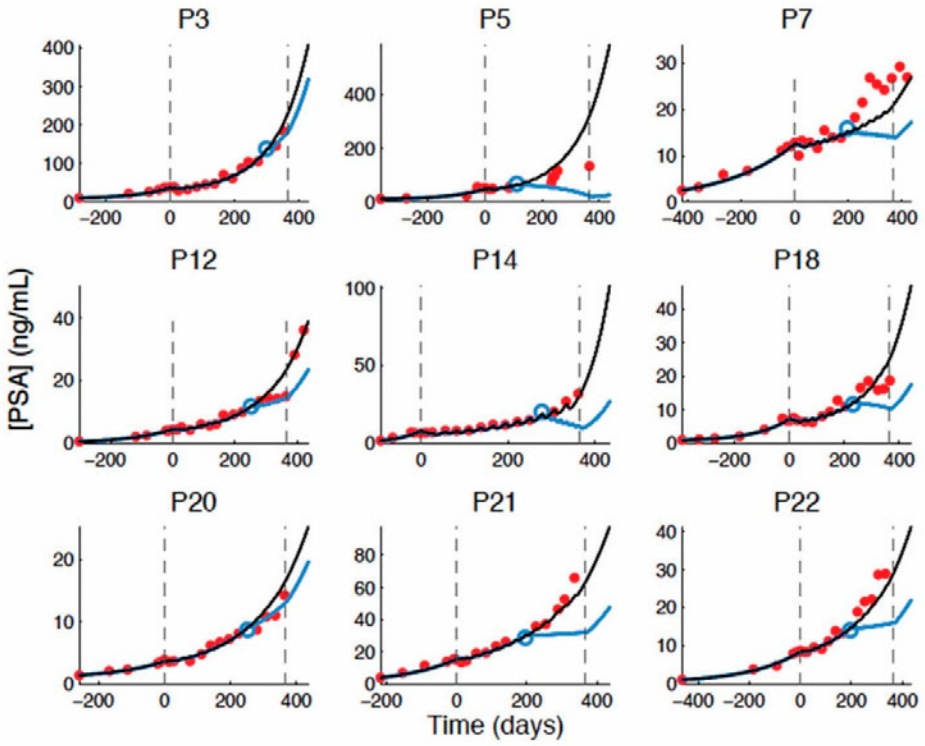

Figure 4. Model–suggested modification of the vaccination regimen, predicted to cause disease stabilization. *Personalized models were used to predict PSA dynamics under individually intensified vaccination regimens. Black lines represent the best-fit curves to the PSA dynamics clinically observed under the standard treatment regimen (red dots; 2.4×10^7 vaccine cells administered every 28 days; compare to Figure 3); blue lines are the predicted PSA levels under the individually modified vaccination regimens. The modified regimens simulated were standard treatment dose (STD)×10 once weekly (for*

Patients 3, 12, 20), STD×5 once weekly (Patient 22), STD×1 once weekly (Patients 5, 18, 21), or STD×1 bi-weekly (Patients 7,14). The times of treatment onset and treatment arrest are marked by vertical broken lines.

Simulation results indicate that personalized mathematical immunotherapy models can be created and employed for tailoring immunotherapy regimens to individual patients. In the above retrospective study, successive PSA counts were input until the precision of the personalized model was effectively validated; a different number of data points were required for validating the personal models of different patients. In reality, however, it may be desired to identify improved personal treatment schedules as early as possible during the actual treatment. This creates a new problem: how can we achieve this optimal balance between sufficiently reliable in–treatment validation of the personal model, and the earliest possible clinical implementation of the model-recommended regimen?

A solution to this optimization problem was suggested, which appears to be a new concept for personalizing cancer immunotherapy in real time [65]. The suggested solution is to optimize the balance between maximum model accuracy and minimum time for its realization by creating personal models that are sufficiently accurate for determining significantly better personal treatment regimens, yet are obtained in the minimum necessary time, that is, by the minimally necessary number of input data points. This concept, termed *in-treatment personalization*,

essentially prescribes how to employ the first cycles of treatment for i) continuously personalizing a mathematical immunotherapy model, ii) validating the personal model relatively early in-treatment, and iii) using the validated model to suggest improved personal treatments.

The suggested method was implemented as an algorithm encompassing four stages: preparation, personalization, prediction of an improved treatment and monitoring. The method trains and validates personalized mathematical models iteratively, using data of the patient collected before and early in treatment as "training sets". The algorithm employs a customized Success-of-Validation criterion to determine when the personalized model can reliably predict individual treatment outcomes under various treatment regimens (Figure 5; for further details, see Supplementary Material, Section 2 in [65]).

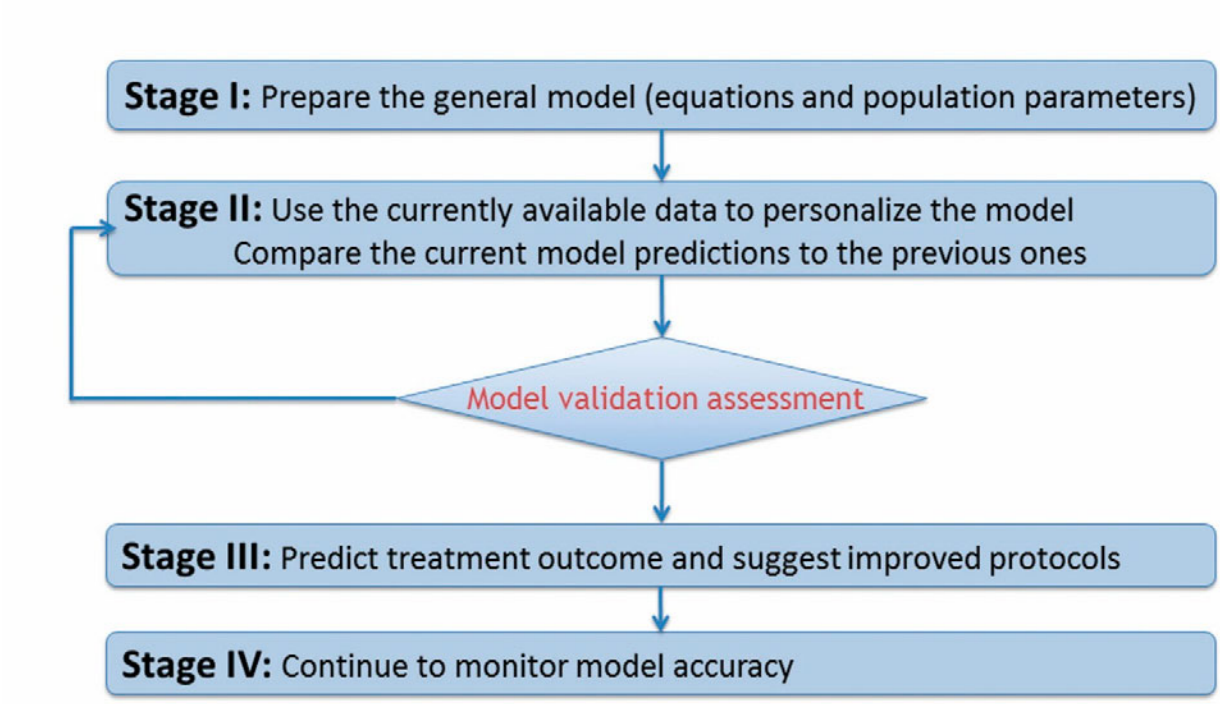

Figure 5. The algorithm for in-treatment personalization*. Model validation is iteratively assessed by a customized Success-of-Validation criterion, in order to determine the reliability of the predictions of individual treatment outcomes by the personalized model and to suggest improved personal regimens.*

To prove the concept of the suggested method, it was retrospectively applied to the clinical data set of the PCa patients under vaccination therapy (see above and in [60]). Results show that a reasonable model validation for individual patients enables a relatively early prediction of the observed individual PSA changes under the

currently applied regimen, and can indicate valuable treatment modifications; for most of the studied patients the model-suggested regimens would have stabilized PSA levels until the end of planned treatment. These results prove the feasibility of the method, namely, that it is possible to obtain a reliable personalized mathematical model of immunotherapy early in-treatment, and use it for improving personal immunotherapy regimen [65].

Note, however, that the PCa model describes PSA dynamics in treatment sensitive patients. From the results of the clinical trial it appears that 13 out of the 25 patients in the trial were completely unaffected by the treatment, so that a change in regimen was not expected to change their PSA profiles, or at least, such a possibility could not be explored by the dynamic mathematical models. These patients could not be included in the model validation exercise. Due to the small number of responsive patients in the original clinical trial, one may argue that the clinical results of this trial do not capture the full variation of response profiles in the patient population. Therefore, it is mandatory to revalidate both the PCa model and the regimen personalization methodology on larger groups of patients.

5. Conclusions

The research reviewed here represents an early exploratory stage in the development of a coherent methodology for using dynamical computational models in precision

medicine. We focused on immunotherapy and investigated the potential value and practicality of personalizing immunotherapy regimens by mathematical modelling, in conjunction with clinical data. Underlying this approach is the hypothesis that personalized models enable to forecast the patient's response to specific immunotherapy protocols, thus overcoming some major caveats to the full success of this treatment modality. The lesson learned from the mathematical explorations suggests that the efficacy of immunotherapy can be improved significantly by patient-specific regimens which can be worked out by personalized mathematical models, and that personalized models can be constructed early in treatment. Hopefully, increased use of predictive biomarkers in immunotherapy will enable efficient integration of personal covariates in the mathematical models, so that model personalization and schedule tailoring can be done pre-treatment.

The reviewed models are relatively simple. For example, when considering the efficacy of ACT by CTL it is borne in mind that dominant immunogenic mutations on the surface of cancer cells can vary among patients and can be replaced by others during the course of therapy. Consequently, the efficacy of ACT depends on the ability of the specific ACT treatment to focus on the most abundant mutations [28]. In the reviewed MG models, these considerations are partly reflected in the parameter of cytotoxic efficacy, which can vary among patients, accounting for the differences in response. However, in the future, when mathematical models are

developed for evaluating specific ACT modalities, it may become necessary to consider the selection rate of pertinent mutations. We expect that the recent advent of systems biology will enable this, especially, as increasingly relevant data become available from human specimens.

Information gathered from patient-specific *in vitro* or *in vivo* experimental models, for example by use of patient-derived xenografts, may be valuable for predicting individual response, hence, lead to better personalization. The predictive success of such a collaborative effort has been shown in the case of mesenchymal chondrosarcoma treated by chemotherapeutic and biological drugs [62]We are not aware of a similar endeavor in the field of immunotherapy, in spite of the numerous attempts to derive personal predictive markers from experimental analysis of patient samples. We believe that application of this information in conjunction with dynamic mathematical models will become inevitable in future research.

6. Expert Opinion

We anticipate that the use of personalized mathematical models for improving the efficacy of immunotherapy will be implemented already during clinical trials, thus raising the overall efficacy of the developed technology and increasing its prospects of being approved for clinical use.

However, the schedule personalization option *per se* does not comply with the "one size fits all" paradigm of drug development, which involves predetermined treatment schedules, applied uniformly to all patients in the trial arm. Therefore, we suggest altering the current paradigm of clinical trials for adapting it to this new concept of personalized immunotherapy ("P-trials"). Accordingly, in Phase II studies, the established paradigm by which each arm tests the patient response to one uniform dosing schedule, would be replaced by trials testing dosing schedules that are personalized during the course of treatment, within a restricted range previously determined by toxicity tests only. Acceptance of this new paradigm by regulatory authorities will hopefully lead to improved individual response and, hence, to more significant trial results of new immunotherapy modalities. The suggested method should be extended to the clinical practice and be validated and approved for different cancer indications [66, 67].

The vision of in-treatment regimen personalization and P-trials is delimited to cancer therapy by agents that are administered over relatively long periods of time, and are expected to elicit variable response in the population. In other immunotherapy modalities considerations may vary. For example, CAR T-cell therapy (see Section 1) may induce rapid and massive antitumor immune response, possibly associated with cytokine storms [68]. When such technology is approved, it may be important to predict patient response prior to treatment onset. This may

also be the case of drugs such as Imatinib, exhibiting 60% response in a Phase II study [69], but showing suboptimal efficacy in the clinic. In this case, the "one type fits all" paradigm may have been justified during drug development, but is less adequate for the clinic, where in-treatment regimen adjustment [70], or a prior evaluation of the individual patient response may be advantageous.

The results reported here suggest that it is feasible to create personalized mathematical models during treatment, rather than before its onset. In contrast, there exist various statistical algorithms for predicting individual response to anticancer drugs before treatment begins. Most notably, a number of nomograms (user-friendly graphic calculating scales designed to provide the likelihood of occurrence of a specific event) have been developed and used to predict the probability of particular treatment outcomes in an individual, including in prostate cancers, gastric cancers and colorectal cancers [71]. Yet, these nomograms are hardly employed in the clinic, probably due to the large variability in the quality of their predictions. More generally, the available statistical algorithms predicting response to cancer therapy, in general, show limited clinical utility. This is mainly because these methodologies are based on analysis of big data from past clinical trials and are incapable of predicting the outcome of any event, which is not recorded in a substantial patient data base. So, it is most likely that in the near future, statistical methods, *per se*, will not suffice for personal prediction of immunotherapy outcomes.

Another potential approach, which still requires validation, is the application of Machine Learning methods, integrating patient information e.g., clinical and biochemical metrics or genetic information, in order to adjust the personal mathematical models [72]. If successful, this integrated mathematical/statistical methodology can replace or improve the In-Treatment Personalization methodology reviewed here. These novel computational approaches give us hope that in the near future new predictive software tools will be introduced into the rather vacant toolbox of methods for immunotherapy personalization.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes

employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002 Nov;3(11):991-8.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013 Jul 25;39(1):1-10.
3. Kim R, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. Immunology 2007 May;121(1):1-14. *A good summary of the main immunotherapy modalities.
4. Zamarron BF, Chen W. Dual roles of immune cells and their factors in cancer development and progression. Int J Biol Sci 2011;7(5):651-8.
5. Institute NC. Immunotherapy: Using the Immune System to Treat Cancer. 9/14/2015 [cited; Available from: http://www.cancer.gov/research/areas/treatment/immunotherapy-using-immune-system
6. De Jager R, Guinan P, Lamm D, et al. Long-term complete remission in bladder carcinoma in situ with intravesical TICE bacillus Calmette Guerin. Overview analysis of six phase II clinical trials. Urology 1991 Dec;38(6):507-13.
7. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000 Apr;163(4):1124-9.
8. Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007 Jun 1;25(16):2191-7.
9. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007 Nov 15;357(20):2040-8.
10. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001 Mar 15;344(11):783-92.
11. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008 Sep 11;359(11):1116-27.
12. Bachmann MF, Oxenius A. Interleukin 2: from immunostimulation to immunoregulation and back again. EMBO Rep 2007 Dec;8(12):1142-8.
13. Hughes T, Klairmont M, Broucek J, et al. The prognostic significance of stable disease following high-dose interleukin-2 (IL-2) treatment in patients with metastatic melanoma and renal cell carcinoma. Cancer Immunol Immunother 2015 Apr;64(4):459-65.
14. Asmana Ningrum R. Human interferon alpha-2b: a therapeutic protein for cancer treatment. Scientifica (Cairo) 2014;2014:970315.
15. Lollini PL, Cavallo F, Nanni P, et al. Vaccines for tumour prevention. Nat Rev Cancer 2006 Mar;6(3):204-16.
16. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015 Apr 3;348(6230):62-8.* A summary of passive immunization options by adoptive cell therapy, including the use of genetically engineered lymphocytes.

17. Almasbak H, Aarvak T, Vemuri MC. CAR T Cell Therapy: A Game Changer in Cancer Treatment. Journal of Immunology Research 2016;2016:10.
18. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010 Jul 29;363(5):411-22.
19. Gajewski TF, Woo SR, Zha Y, et al. Cancer immunotherapy strategies based on overcoming barriers within the tumor microenvironment. Curr Opin Immunol 2013 Apr;25(2):268-76.
20. Jing W, Li M, Zhang Y, et al. PD-1/PD-L1 blockades in non-small-cell lung cancer therapy. Onco Targets Ther 2016;9:489-502.
21. Wieder T, Brenner E, Braumuller H, et al. Immunotherapy of melanoma: efficacy and mode of action. J Dtsch Dermatol Ges 2016 Jan;14(1):28-36.
22. Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015 Apr 3;348(6230):56-61.* A summary of immune checkpoint therapy and the need to identify predictive or prognostic biomarkers for this new treatment modality.
23. Valitutti S, Coombs D, Dupre L. The space and time frames of T cell activation at the immunological synapse. FEBS Lett 2010 Dec 15;584(24):4851-7.
24. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. Journal of the National Cancer Institute 2010.
25. Fox BA, Schendel DJ, Butterfield LH, et al. Defining the critical hurdles in cancer immunotherapy. J Transl Med 2011;9:214.
26. Miller ID. The emergence of immuno-oncology companion products. Personalized Medicine 2015 2015/09/01;12(5):435-38.
27. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. Journal of Clinical Oncology 2015;33(17):1974-82.
28. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015 Apr 3;348(6230):69-74.
29. Iyengar R, Altman RB, Troyanskya O, et al. MEDICINE. Personalization in practice. Science 2015 Oct 16;350(6258):282-3.
30. De Angelis E, Marasco A, Romano A. Bifurcation analysis for a mean field modelling of tumor and immune system competition. Mathematical and Computer Modelling 2003 6//;37(11):1131-42.
31. Kirschner D, Panetta JC. Modeling immunotherapy of the tumor-immune interaction. J Math Biol 1998 Sep;37(3):235-52. **One of the first modelling papers in the area of immunotherapy.
32. Kuznetsov VA, Makalkin IA, Taylor MA, et al. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull Math Biol 1994 Mar;56(2):295-321.
33. Keilholz U, Scheibenbogen C, Stoelben E, et al. Immunotherapy of metastatic melanoma with interferon-alpha and interleukin-2: pattern of progression in responders and patients with stable disease with or without resection of residual lesions. Eur J Cancer 1994;30A(7):955-8.
34. Banerjee S. Immunotherapy with interleukin-2: a study based on mathematical modeling. International Journal of Applied Mathematics and Computer Science 2008;18(3):389-98.
35. Curti BD, Ochoa AC, Urba WJ, et al. Influence of interleukin-2 regimens on circulating populations of lymphocytes after adoptive transfer of anti-CD3-stimulated T cells: results from a phase I trial in cancer patients. J Immunother Emphasis Tumor Immunol 1996 Jul;19(4):296-308.
36. Hara I, Hotta H, Sato N, et al. Rejection of mouse renal cell carcinoma elicited by local secretion of interleukin-2. Jpn J Cancer Res 1996 Jul;87(7):724-9.
37. Kaempfer R, Gerez L, Farbstein H, et al. Prediction of response to treatment in superficial bladder carcinoma through pattern of interleukin-2 gene expression. J Clin Oncol 1996 Jun;14(6):1778-86.
38. Nani F, Freedman HI. A mathematical model of cancer treatment by immunotherapy. Math Biosci 2000 Feb;163(2):159-99.

39. Cappuccio A, Elishmereni M, Agur Z. Cancer immunotherapy by interleukin-21: potential treatment strategies evaluated in a mathematical model. Cancer Res 2006 Jul 15;66(14):7293-300.
40. Cappuccio A, Elishmereni M, Agur Z. Optimization of interleukin-21 immunotherapeutic strategies. J Theor Biol 2007 Sep 21;248(2):259-66.
41. Elishmereni M, Kheifetz Y, Sondergaard H, et al. An integrated disease/pharmacokinetic/pharmacodynamic model suggests improved interleukin-21 regimens validated prospectively for mouse solid cancers. PLoS Comput Biol 2011 Sep;7(9):e1002206. *The first immunotherapy model prospectively validated in preclinical studies.
42. Castiglione F, Piccoli B. Cancer immunotherapy, mathematical modeling and optimal control. J Theor Biol 2007 Aug 21;247(4):723-32.
43. de Pillis LG, Gu W, Radunskaya AE. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. J Theor Biol 2006 Feb 21;238(4):841-62.** A thorough mathematical modelling work , examining the effects of several classes of immunotherapy including cytokines, TIL and cancer vaccines.
44. Isaeva O, Osipov V. Different strategies for cancer treatment: mathematical modelling. Computational and Mathematical Methods in Medicine 2009;10(4):253-72.
45. Bunimovich-Mendrazitsky S, Claude Gluckman J, Chaskalovic J. A mathematical model of combined bacillus Calmette-Guerin (BCG) and interleukin (IL)-2 immunotherapy of superficial bladder cancer. J Theor Biol 2011 May 21;277(1):27-40.
46. Calin G, Wijnen J, van der Klift H, et al. Marfan-like habitus and familial adenomatous polyposis in two unrelated males: a significant association? Eur J Hum Genet 1999 Jul;7(5):609-14.
47. Stupp R, Tonn JC, Brada M, et al. High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May;21 Suppl 5:v190-3.
48. Calinescu AA, Kamran N, Baker G, et al. Overview of current immunotherapeutic strategies for glioma. Immunotherapy 2015;7(10):1073-104.
49. Gomez GG, Kruse CA. Mechanisms of malignant glioma immune resistance and sources of immunosuppression. Gene Ther Mol Biol 2006;10(A):133-46.
50. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011 Mar 4;144(5):646-74.
51. Schuessler A, Smith C, Beagley L, et al. Autologous T-cell therapy for cytomegalovirus as a consolidative treatment for recurrent glioblastoma. Cancer Res 2014 Jul 1;74(13):3466-76.
52. Kruse CA, Cepeda L, Owens B, et al. Treatment of recurrent glioma with intracavitary alloreactive cytotoxic T lymphocytes and interleukin-2. Cancer Immunol Immunother 1997 Oct;45(2):77-87.
53. Kogan Y, Foryś U, Shukron O, et al. Cellular Immunotherapy for High Grade Gliomas: Mathematical Analysis Deriving Efficacious Infusion Rates Based on Patient Requirements. SIAM Journal on Applied Mathematics 2010;70(6):1953-76.* Demonstrating how the analysis of the mathematical models pinpoints the need for regimen personalization in immunotherapy.
54. Kronik N, Kogan Y, Vainstein V, et al. Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics. Cancer Immunology, Immunotherapy 2008;57(3):425-39.
55. IARC. Prostate Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012. GLOBOCAN 2012 [cited; Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
56. Alva A, Hussain M. Intermittent Androgen Deprivation Therapy in Advanced Prostate Cancer. Current Treatment Options in Oncology 2014;15(1):127-36.
57. Armstrong AJ, Eisenberger MA, Halabi S, et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. Eur Urol 2012 Mar;61(3):549-59.

58. Karantanos T, Corn PG, Thompson TC. Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches. Oncogene 2013 Dec 5;32(49):5501-11.
59. Pavlović SV. Towards systems based immunotherapy of cancer. Periodicum Biologorum 2012;114(2):187-99.
60. Michael A, Ball G, Quatan N, et al. Delayed disease progression after allogeneic cell vaccination in hormone-resistant prostate cancer and correlation with immunologic variables. Clin Cancer Res 2005 Jun 15;11(12):4469-78.
61. Agur Z, Arnon R, Schechter B. Effect of the dosing interval on myelotoxicity and survival in mice treated by cytarabine. Eur J Cancer 1992;28A(6-7):1085-90.
62. Gorelik B, Ziv I, Shohat R, et al. Efficacy of weekly docetaxel and bevacizumab in mesenchymal chondrosarcoma: a new theranostic method combining xenografted biopsies with a mathematical model. Cancer Res 2008 Nov 1;68(21):9033-40.
63. Ubezio P, Tagliabue G, Schechter B, et al. Increasing 1-beta-D-arabinofuranosylcytosine efficacy by scheduled dosing intervals based on direct measurements of bone marrow cell kinetics. Cancer Res 1994 Dec 15;54(24):6446-51.
64. Kronik N, Kogan Y, Elishmereni M, et al. Predicting outcomes of prostate cancer immunotherapy by personalized mathematical models. PLoS One 2010;5(12):e15482.
65. Kogan Y, Halevi-Tobias K, Elishmereni M, et al. Reconsidering the paradigm of cancer immunotherapy by computationally aided real-time personalization. Cancer Res 2012 May 1;72(9):2218-27.** A new methodology for optimizing the timing of application of personalized immunotherapy schedules in-treatment, by use of personally validated mathematical models.
66. Agur Z, Vuk-Pavlović S. Personalizing immunotherapy: Balancing predictability and precision. Oncoimmunology 2012;1(7):1169-71.
67. Agur Z, Vuk-Pavlović S. Mathematical modeling in immunotherapy of cancer: personalizing clinical trials. Molecular Therapy 2012;20(1):1.*Introduction of the concept of P-trials, namely testing personalized regimens in clinical trials.
68. Morgan RA, Yang JC, Kitano M, et al. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther 2010 Apr;18(4):843-51.
69. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002 Feb 28;346(9):645-52.
70. Jabbour E, Cortes JE, Kantarjian HM. Suboptimal response to or failure of imatinib treatment for chronic myeloid leukemia: what is the optimal strategy? Mayo Clin Proc 2009 Feb;84(2):161-9.
71. Kawai K, Sunami E, Yamaguchi H, et al. Nomograms for colorectal cancer: A systematic review. World J Gastroenterol 2015 Nov 7;21(41):11877-86.
72. Elishmereni M, Kheifetz Y, Shukrun I, et al. Predicting time to castration resistance in hormone sensitive prostate cancer by a personalization algorithm based on a mechanistic model integrating patient data. Prostate 2016 Jan;76(1):48-57.

Article highlights box

- How to match the immunotherapeutic treatments to patients, who are most likely to benefit from it, is a major issue for oncologists applying immunotherapy.
- Analysis of a mathematical model for brain cancer progression under immunotherapy by alloreactive cytotoxic T cells demonstrates the benefit of using mathematically-predicted personalized immunotherapy regimens.
- Application of a mathematical model for prostate cancer treatment by an allogeneic whole-cell vaccine shows that the efficacy of immunotherapy can be improved by patient-specific regimens obtained by personalized mathematical models, and that sufficiently precise personalized models can be constructed early in treatment.
- The authors anticipate that the use of personalized mathematical models for improving the efficacy of immunotherapy will be implemented already during clinical trials (P-trials), thus raising the overall efficacy of the developed technology, and increasing its prospects of being approved for clinical use.
- The most important role of mathematical models in the clinic may be to serve as "virtual response biomarkers," predicting the clinical response of *individual* patients to different immunotherapy protocols.