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

Yuri Kogan1, Karin Halevi-Tobias1, Moran Elishmereni1, Stanimir Vuk-Pavlović2, and Zvia Agur1

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. Cancer Res; 72(9): 2218–27. ©2012 AACR.

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 pretreatment 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 prostate-specific antigen 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).

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 U.S. Food and Drug Administration (FDA) recently approved the first cell-based vaccination therapy for castration-resistant prostate cancer, 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, whereas immunotherapy should affect cancer indirectly, by manipulating the immune system. Hence, successful immunotherapy must control the continuously coevolving 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...
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 naive sentinel dendritic cell (DC) precursors into mature antigen-presenting DCs at the rate \( k_a \). During maturation each DC takes up an amount of the vaccine, \( n_v \), reducing the amount of available vaccine at the linear rate \( k_m n_v \). Maturing DCs migrate into lymph nodes at the rate linearly proportional to their total number, \( D_m \), with the rate coefficient \( k_{DR} \). The migrating DCs join the pool of functional antigen-presenting DCs in the lymph nodes, \( D_F \), with probability \( \alpha_c \). Having “instructed” and activated immune effector cells, DCs become “exhausted” at the constant rate \( k_{CR} \) (Equation A).

\[
\dot{D}_C = \alpha_C k_m D_m - k_{CR} D_C. \tag{A}
\]

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 are described by

\[
\dot{D}_R = k_{CR} D_C - \mu_D D_R. \tag{B}
\]

Functional antigen-presenting DCs stimulate T-helper-1 (TH-1)-type immunity by recruiting and activating tumor-specific 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

\[
\dot{C} = a_c D_C - \mu_C C - k_R C R. \tag{C}
\]

Regulatory/inhibitory cells include regulatory T cells (TR), 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 \( \mu_R \):

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

Prostate cancer 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

\[
\dot{P} = rP - a_p CP - \frac{h_p}{h_p + P}. \tag{E}
\]

Model parameters were estimated from published experimental studies (see ref. 1 for details). Vaccination was modeled as instantaneous additions to \( V \) of the total 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 Materials, Section 1.

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 on the basis of 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, thus limiting model applicability. For clinical use, 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 benefit of the insight from models to the practicing physician.

For proof of concept and feasibility of the method, we analyzed the data from a clinical study of allogeneic whole-cell vaccination in castration-resistant patients with metastatic prostate cancer (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 4 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 the training sets (Fig. 1: Supplementary Materials, Section 2). The algorithm uses a customized Success-Of-Validation (SOV) criterion to determine when the personalized model can reliably predict individual 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 prostate cancer whole-cell vaccine administered to patients with prostate cancer on 14 occasions for more than 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, that is, in the linear rate of change in the logarithm of PSA levels (33). For the present study, we selected the 9 patients who completed the full course of treatment.
treatment and whose PSA velocity decreased in the first 2 months of treatment (1).

The mathematical model
To prove the concept, we used our recently developed prostate cancer 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-helper-1 (Th-1)–type immunity that includes tumor-specific CTLs that can kill the tumor. Subsequently, DCs yield regulatory DCs, which recruit T regulatory (Treg) cells that attenuate CTL function. The model is formally described by ordinary differential equations (see Quick Guide and Supplementary Materials, 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 4 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 2 parameters linearly correlating tumor load and PSA levels. The 4 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 SOV 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 the 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 Materials, 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 Materials, 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 before 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 \( P_0, P_{i-1}, \ldots, P_{i-1} \); 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 for the 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 [empirical dose (ED); 24 million cells] and administration frequency (every 28 days), denoted 1EDq28d (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 1 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 7-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 Materials, Section 2). At the preparatory stage the general mathematical model of the disease and immunotherapy is developed and its parameters are estimated on the basis of 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 with predictions generated at previous iterations using the SOV criterion. The criterion, defined uniformly for all treated patients, is a

**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 with predictions by 3 preceding models (thin gray lines). Symbol × marks the last available data point for the particular iteration, whereas open circles mark the 3 data points immediately preceding it; full circles represent all earlier data points. Treatment started on day zero.
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, that is, 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 prostate cancer vaccination study

We tested the feasibility of the method for in-treatment personalization of prostate cancer vaccination therapy. For convenience, we used the algorithm in conjunction with our recent mathematical model of prostate cancer 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 Materials, Section 5).

The selected SOV criterion compares the prediction of the personalized model at a given time to predictions of 3 preceding models. Figure 2 presents 2 examples of algorithm application using this criterion to patient 20 and patient 12 (patient numbers as in ref. 33). For patient 20, predictions of the most updated model and the 3 preceding models get closer at each subsequent iteration, until—at iteration 8—all 4 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 causes 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 3 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. Furthermore, we checked the accuracy of the validated personalized model by probing whether model predictions varied after adding the data subsequently collected until the end of treatment (iterations 9–11, 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), showing the increasing agreement between personalized models. Moreover, different patients required a different size of data set, from 4 to 11 months, to validate the personalized model (for details, see Supplementary Materials, Section 5).
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 increase in circulating PSA levels in all patients (Fig. 4). Because 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, using 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 and turn the disease into chronic state (Fig. 4). Overall, for 7 of 9 patients we identified individual treatments predicted to stabilize PSA levels if applied immediately after individual model validation. Collectively, required treatment modifications ranged from just doubling the administration frequency to the weekly injections of 10-fold increased ED (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 biologic and other obstacles impede the development of predictably effective immune treatment of malignancy (4, 11, 13–14). Development of treatments, particularly those using live or inactivated cells, is in addition 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. On the basis of this notion, development of cancer immunotherapy can be significantly enhanced by a paradigm shift in clinical studies, that is, 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, that is, with the time elapsed from the onset of treatment. Hence, there is an inherent trade-off 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) use 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 regimentes 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 patients with prostate cancer (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 the improvement of 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 physiologic 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 prostate cancer immunotherapy studies that use 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 subpopulations. 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 9 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 nonintuitive 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.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: Y. Kogan, K. Halevi–Tobias, M. Elishmereni, S. Vuk-Pavlovic, Z. Agur
Development of methodology: Y. Kogan, K. Halevi–Tobias
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Halevi–Tobias, S. Vuk-Pavlovic
Analysis and interpretation of data (e.g., statistical analysis, bios-statistics, computational analysis): Y. Kogan, K. Halevi–Tobias
Writing, review, and/or revision of the manuscript: Y. Kogan, K. Halevi–Tobias, M. Elishmereni, S. Vuk-Pavlovic, Z. Agur

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Halevi–Tobias, Z. Agur
Study supervision: Z. Agur

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