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Original Paper

Personalised Neoantigen Vaccine Combined with CAR-T Therapy for Solid Tumour Immunotherapy

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Abstract

Personalised neoantigen vaccines and CAR-T cell therapy are both for the same cancer but work differently. The former is recognised by T cells for altered peptides; CAR-T cells are directed by a particular externalisation marker. The above can be used to study the combined modes in heterogeneous solid tumours. Not all of these will work well together. Examine the individual results and distinguish them from the results of synergistic pairing. The study of BNT211/CARVac will be introduced separately; it is an RNA-based vaccine that activates CLDN6-engaged CAR-T cells and does not induce endogenous host responses in response to patient-specific changes. According to the three general types of differential equations, we will examine how different assumptions on immune interaction and dosing intervals affect the simulated level of the tumour. All are fake data. According to the above settings, adding vaccination to CAR-T therapy reduces the total tumour size at all times, but not by day 60. Turn off the interaction term here. Finally, we show neoantigen selection by a weighted formula and not a machine-learning model. The above will decide whether to continue to the next round of tests and does not indicate clinical effectiveness.

Keywords

personalized neoantigen vaccine, CAR-T-cell therapy, solid tumors, immunotherapy, conceptual mathematical modeling, antigen heterogeneity, neoantigen prioritization

1. Introduction

There are still three problems with solid-tumor immunotherapy: the antigenic targets of the cells are different; immune cell recruitment is inefficient; and the tumor microenvironment frequently suppresses the immune system after reaching the site [1, 2]. Personalised neoantigen vaccines will be developed to solve the problem mentioned above. Based on the mutations found in a person's tumour, peptides are

created that can be displayed by HLA molecules and recognised by endogenous T cells. Research on melanoma has found that vaccine-induced T-cell activity [3] is involved, and other studies have also found long-lasting memory cells and epitope expansion [4]. Studies of pancreatic cancer have also found neoantigen-specific immune responses [5]. Therefore, it can be seen that immune activation occurs in some places. However, they do not address what would happen if such a vaccine were given with CAR-T cells.

CAR-T therapy has started a new goal. Engineered receptors target antigens on tumor-cell membranes, bypassing the necessity of HLA-mediated peptide presentation. The above way has been used for several blood cancers [6]. The main reasons for the reduced efficacy of solid tumours are antigen loss, poor transport and regional immunosuppression [2]. There is a good case of a vaccine-enhanced CAR-T regimen: BNT211-01 has been combined with CLDN6-targeted CAR-T cells and CARVac, an RNA-based vaccine, to boost these CAR-T cells [7]. The immunogenic target and proposed mechanism are different from the individual mutant epitopes mentioned above.

Therefore, the main question will be narrower than the general assessment of combining particular therapies. Hopefully, personalised vaccination will change the microenvironment of CAR-T cells and strengthen the immune system. Based on the theory, there will be an increase in profit; why is this the case? We will conduct a literature review and a small-scale, deliberate experiment to investigate the problems mentioned above. The analysis is a test of hypotheses, and it does not match the clinical data.

2. Personalized Neoantigen Vaccines

2.1 Candidate Selection and Vaccine Preparation

A single tumour mutation is only the first step in identifying neoantigenic epitopes. A modified sequence is produced, and then this peptide is cleaved and presented by the corresponding HLA molecule for T-cell recognition. In fact, researchers have used tumour and matched-normal sequencing data to determine the expression levels of RNA, and based on a person's HLA type, have reduced the list of candidates. Then, the chosen antigens can be expressed as peptides, nucleic acids or dendritic cell preparations [1,8]. All are not the object. Therefore, a particular target immunotherapy needs to be computationally screened and then developed; it is not enough to choose only one good option.

Early clinical studies of melanoma have shown that the long-peptide and RNA immunisation methods mentioned above can induce some kind of T-cell response [3,9]. Another drawback of the ranking method is that the predicted HLA-binding score cannot be shown on the surface of the tumour, and therefore it will not be able to stimulate an appropriate T-cell response. Although some tools that use HLA-ligand and mass spectrometry data have improved some aspects of the prediction [10, 11], they are still a small number of candidates. The actual situation of antigen-presenting cells and T cells can also be examined to see if the above results are correct.

2.2 What Vaccine Studies Establish

The two are not the same; an immune response is not a therapeutic effect. Sustained neoantigen-attending

memory T cells and epitope spreading have been found after melanoma vaccination [4]. According to the full-coverage plan of the pancreatic cancer trial, the targeted mRNA vaccine was given, and some patients showed a response of vaccine-targeted T-cell activation [5]. Neither study considered the vaccine-CAR-T combination mentioned above. Vaccine-induced T-cell activation alone cannot achieve the migration of CAR-T cells to the tumour and thus cannot eradicate the disease. HLA deficiency, reduced priming, tumour heterogeneity, regional inhibition and the time it takes to produce a personalised product are all serious problems [8].

3. CAR-T-Cell Therapy and Barriers in Solid Tumors

3.1 CAR Design and Direct Tumor Killing

CAR cells have an extracellular antigen-binding site and a hinge or spacer, a transmembrane domain, and an intracellular signalling domain. Activation and costimulation work together in the second generation to increase the induced T-cell response [12]. The production process is to obtain T cells, modify them to express the receptor, expand these cells, and then administer them in line with the clinical schedule. Find the target and then activate the cytotoxic pathways, such as the perforin/granzyme and death receptor pathways. CD19-targeted agents have achieved sustained remission in many people with leukaemia [13]. Antigens and the microenvironment of solid tumours present a different type of problem.

3.2 What Limits CAR-T Activity in Solid Tumors

CAR-T cells need to reach the tumour, find a target, be active and live for a long time in order to achieve good results in a clinical setting. Solid malignancies can block all stages. Dysfunctional blood vessels and the extracellular matrix (ECM) are restrictive; chemokine dysfunction inhibits migration; alteration of antigen diversity and regulatory cells reduces effective killing [2, 14, 15]. The above are receptor modification, multi-antigen recognition, local administration and collaboration with other immunotherapies. They have good effects on tumours and may be harmful in other situations. Antigen depletion and short-lived CAR-T cells are known causes of treatment failure [14]. A vaccine will address some of these problems, but it cannot be expected that all of them will be solved.

4. Proposed Combination of Personalized Neoantigen Vaccines and CAR-T Cells

There are now two types of recognition. A mutation-specific vaccine increases the endogenous T-cell population by presenting several HLA-binding epitopes. CAR-T cells have a particular surface marker. A heterogeneous tumour will have a large number of cells that the immune system cannot identify. The extent of its effect is determined by antigen expression and presentation, T-cell response, etc. The following are considered separately because the results of one particular vaccine-enhanced CAR-T trial cannot be directly applied to another.

4.1 Mechanisms that could Connect the Two Treatments

4.1.1 Vaccination and the Tumor Microenvironment

Vaccination induces neoantigen-specific CD4+ and CD8+ T cells [1,4]. Next, we need to know how this

activation is expressed in the tumor microenvironment. It may change the inflammatory signal and chemokine secretion to affect the recruitment of CAR-T cells. T-cell activation is not the same as reducing the ECM or decreasing the proportion of Tregs and MDSCs. It does not indicate that PD-L1 expression has decreased. IFN-γ signalling may induce PD-L1 and promote innate immune evasion [16]. Therefore, the extent of the net effect will differ among various types of cancer. Direct observation would need to see the vaccine-responsive T cells, regional suppressive mechanisms and CAR-T cells before and after treatment.

4.1.2 CAR-T-mediated Tumor Killing and Possible Antigen Spreading

CAR-T cell therapy is another way to treat cancer. Detached cancer cells release antigens that dendritic cells can take up and then present to endogenous T cells. If there is cross-presentation and activation, then the following T-cell response will also recognise epitopes outside the CAR-targeted region. The first problem is whether the first release will lead to a functional new T-cell response; it is not guaranteed that this will happen. According to the first study, a vaccine that activates CAR-T cells can be used to recruit dendritic cells, promote anti-tumor immunity, and suppress tumors in all sorts of ways [17]. It will be able to spread antigens. It is not a direct proof of vaccination against particular mutant neoantigens.

4.1.3 Antigen Heterogeneity and Immune Escape

Assume that in a particular cancer, some cells do not recognise the CAR-targeting ligand. These people will remain after CAR-T-cell elimination [14]. A personalised vaccine with many different epitopes from various mutations may introduce new T-cell subsets into the immune system [3,8]. The effect of this is that the changes must be innate to the residual cells, HLA-presenting capacity should remain intact, and endogenous T-cell activity needs to be preserved. Vaccine-augmented CAR-T cells are also a kind of expanded immunological detection [17]. They do not say that the proposed particular vaccine reduces the frequency, onset or recurrence of solid tumours.

4.1.4 Immune Memory and Long-term Surveillance

The good effects of immune memory are not the same as the first attack on tumours. Individualised vaccination has demonstrated that antigen-specific memory T cells can be produced in melanoma [4]. It would be good to know if these cells are still functional after CAR-T treatment and whether they respond to recurrent cancer. CAR-T induced antigen shedding can increase this reaction, but an immunosuppressive microenvironment will reduce it. We will not assume that there is an autonomous positive feedback loop; instead, we will track changes in T-cell subsets, antigen levels and relapse over time.

4.2 BNT211/CARVac and Practical Barriers

BNT211-01 has been able to release more clinical trial data on this issue [7]. CAR-T cells and CARVac have targeted CLDN6, and gene therapy has been employed to introduce a CLDN6-coding gene and expand this particular subpopulation of CAR-T cells. Our proposed vaccine has the special effect of stimulating the body's own cells to react in light of mutations in people's genes. BNT211-01 has put forward that vaccine-assisted CAR-T therapy should be investigated in clinical trials. However, it has not been determined yet

whether the particular way of neoantigen activation will benefit patients with solid tumours.

There are many other realistic problems before any claim of effectiveness. Tumor sequencing, antigen identification, vaccine production and CAR-T cell manufacturing all take time and have special facilities. HLA type and the expression of tumour antigens may reduce the number of vaccine targets [8]. Another neglected problem is the order of administration; the reaction to immunisation and the proliferation of infused CAR-T cells may not be simultaneous. CAR-T therapy has had some immune-related adverse events, and the added safety benefits of combining it with personalised vaccines have not yet been established [2]. Therefore, this paper will determine the therapy schedule and immune response under toxic and antigen-evading conditions, and will not assume that the two active therapies are more effective together.

4.3 A Conceptual Mathematical Model of Vaccine–CAR-T Interactions

4.3.1 Model Structure and Assumptions

To present the basic assumptions of our model clearly, we have used three state variables: T(t) is the normalised tumor burden, C(t) is the CAR-T-cell population index, and E(t) is the endogenous effector T-cell index. These are mathematical indicators and not the actual results from cells. The endogenous effectors will increase after the modelled vaccine input, and the formula will also add an assumed effect of CAR-T-tumor interaction. Representative days are taken as the reference period. The above framework excludes spatial dispersion, antigen-presenting cells, different types of lymphocytes, ECM development and toxicity. This is done intentionally. It can help us distinguish the results of different hypotheses and does not mean that the mathematical framework is a real tumour.

The tumour burden will increase exponentially and then decrease according to the calculated eradication forces C(t) and E(t).

$$\frac{dT}{dt} = rT(1 - \frac{T}{K}) - k_C CT - k_E ET \quad (1)$$

r is the intrinsic rate of increase and K is the carrying capacity. The two elimination constants, k_C and k_E, are the effects of CAR-T cells and endogenous mediators. We are using CAR-T cells.

$$\frac{dC}{dt} = \alpha_C(1 + \gamma \mathrm{E}) \frac{T}{h_C + \mathrm{T}} \mathrm{C} - \delta_C \mathrm{C} + u_C(\mathrm{t}) \quad (2)$$

α_C is the antigen-dependent proliferation factor, h_C is its half-saturation constant, and δ_C is CAR-T decline. Administration is carried out by u_C(t). The term (1 + γE) is a heuristic hypothesis, and if γ is positive, then the endogenous effectors will increase the simulated CAR-T proliferation rate. We do not know how much it has increased. The Internal-Effector Relationship is:

$$\frac{dE}{dt} = \alpha_V \mathrm{V}(\mathrm{t}) + \beta \mathrm{CT} - \delta_E E \quad (3)$$

V(t) is the vaccine dose in this formula, α_V is the coupling factor for effector stimulation, and δ_E represents effector dampening. We will add another speculative internal reaction to CAR-T malignant cell interaction via βCT. The module above has many cell functions in one molecule and is not involved in antigen release, dendritic cell presentation or T-cell activation. Therefore, γ and β are hypotheses and not direct measures of synergism. Set one of the coefficients to zero and observe the change in the simulation; do not modify the tumor-regression and elimination systems.

4.3.2 Parameters, Inputs, and Numerical Method

Based on the pedagogical application of the model, we have set up a parameter system and recorded all the figures in Table 1 for computational studies. None of the variables have been optimised according to laboratory or clinical data. Also, we have verified the reference condition: C(0) is 0, so the neglected and immunization-specific scenarios do not arbitrarily start with administered CAR-T cells. All four groups have the same initial T, C and E values. Thus, the evaluation results will be verifiable and generalisable. The above calculations can be performed with the given code, but they should not be taken as biological facts.

Table 1. Explicit Synthetic Values, Initial Settings and Intervention Inputs are Used in the Updated Hypothetical Framework

Symbol / input	Meaning	Synthetic value	Units or scale
r	Intrinsic tumor growth	0.08	day^-1
K	Tumor carrying capacity	1.00	T units
k_C	CAR-T killing coefficient	0.12	(C unit · day)^-1
k_E	Endogenous killing coefficient	0.08	(E unit · day)^-1
alpha_C	CAR-T expansion coefficient	0.35	day^-1
h_C	Tumor stimulation half-saturation	0.20	T units
delta_C	CAR-T loss rate	0.08	day^-1
alpha_V	Vaccine-to-effector activation factor	0.12	E units / input unit
delta_E	Endogenous effector loss rate	0.10	day^-1
gamma	Hypothetical E-to-C enhancement	0.50	(E unit)^-1
beta	Hypothetical C/T-driven E activation	0.05	E units/(C unit · T unit · day)
T(0)	Initial tumor burden	0.50	T units
C(0)	Initial CAR-T population	0.00	C units
E(0)	Initial endogenous effectors	0.01	E units
Vaccine input	Total/duration/start day	0.50 / 2 days / day 10	arbitrary input units
CAR-T input	Total/duration/start day	0.10 / 1 day / day 20	C units

The Data Points are wrong. Tumour load is normalised to K=1; C and E are hypothetical index scales and may exceed 1. Vaccine and CAR-T amounts are the same in all treatment comparisons. None of the above values should be specific to a particular patient.

To make the time unambiguous, we used a rectangular input function. A dosing regimen with total volume D, initiation point s, and duration d has a rate $q(t; s,d,D)=D/d$ for $s \le t < s+d$ and zero otherwise. The immunization dose is $V(t)=q(t; s_V,d_V,D_V)$, and CAR-T administration is $u_C(t)=q(t; s_C,d_C,D_C)$. In the first protocol, the vaccine is given on days [10,12] and CAR-T cells on days [20,21]. Only one group is given that particular input. The control group is not treated. No other part of the initial state

changes among the groups.

Over the course of 60 days, solve_ivp from SciPy was employed with RK45 (tolerance = 1e-8 and 1e-10). Data were taken every 0.1 days. Since the doses were different at the boundaries, they were not considered a single smooth section but were divided into sections at the beginning and end of each injection. It was determined that the calculated state variables are well-defined and non-negative. The computational parameters and results are in the reproducibility package; they show the model construction process, not how accurate it is.

4.3.3 Four Treatment Arms and Interaction Controls

The control group without treatment (days 10-12), CAR-T therapy (days 20-21), and their respective combinations at the same dosing time all started from the initial state in Table 1. The baseline interaction parameters are γ=0.50 and β=0.05. We provided two evaluations: T(60) is the final simulated tumour load, and AUC_T is the total sum from day 0 to day 60. Therefore, the time when the path deviates from the ideal path is also known.

Table 2. Refined Comparative Analysis of the Four Rehabilitation Protocols Under Identical Initial Conditions (Gamma=0.50; Beta=0.05).

Regimen	Tumor T(60)	AUC_T, 0–60 days
No treatment	0.9915	51.342
Vaccine alone	0.9882	50.789
CAR-T alone	0.0016	25.662
Combined	0.0017	25.313

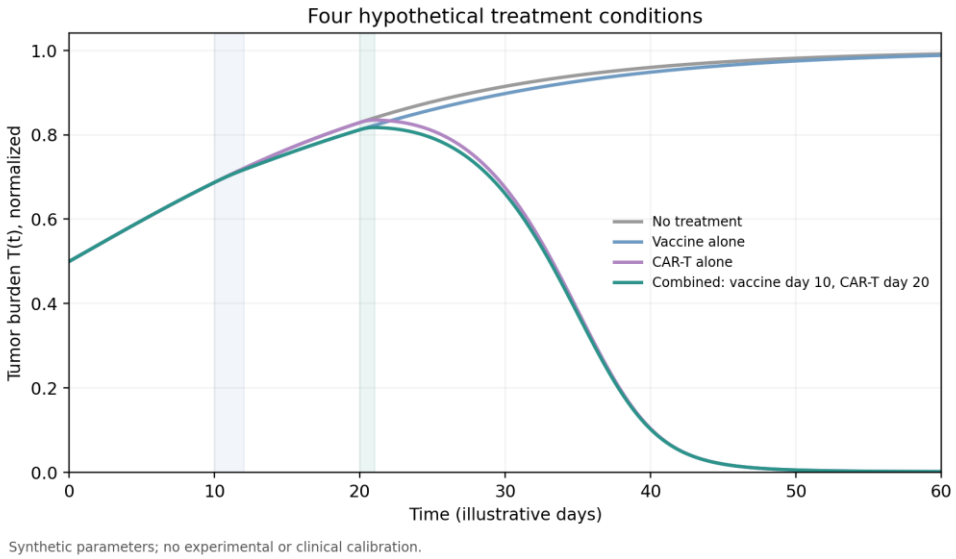


Figure 1. Predicted Tumor Load in the Four Treatment Groups According to Data in Table 1. The CAR-T-only and Integrated Curves are Close; all the Data is Theoretical

As shown in Figure 1, it is not true that adding a vaccine will necessarily improve the results. By day 60, T was 0.00161 for CAR-T alone and 0.00167 for the regimen. Therefore, this pair was no better than the first group at the end. Over the entire 60 days, the AUC of the tumour load was 25.313 instead of 25.662, and the difference was 0.349 (about 1.36%). The two evaluations are not the same; a lower total load does not necessarily mean a slightly higher end point. The simulated benefit will be small, and it is determined by the coefficients.

Then we checked the two extra positive interaction indicators. Do not assume that the combined curve alone is evidence of synergy; instead, we tested the effect of the same combined dosage in four scenarios: M0 (γ=0, β=0), M1 (γ=0.50, β=0), M2 (γ=0, β=0.05), and M3 (γ=0.50, β=0.05). Treatment variables and initial conditions are the same.

Table 3. Interaction-Switch Analysis for the Same Synthetic Combined-Treatment Schedule

Model	gamma	beta	T(60)	AUC_T
M0	0.00	0.000	0.0026	25.996
M1	0.50	0.000	0.0026	25.906
M2	0.00	0.050	0.0029	25.746
M3	0.50	0.050	0.0017	25.313

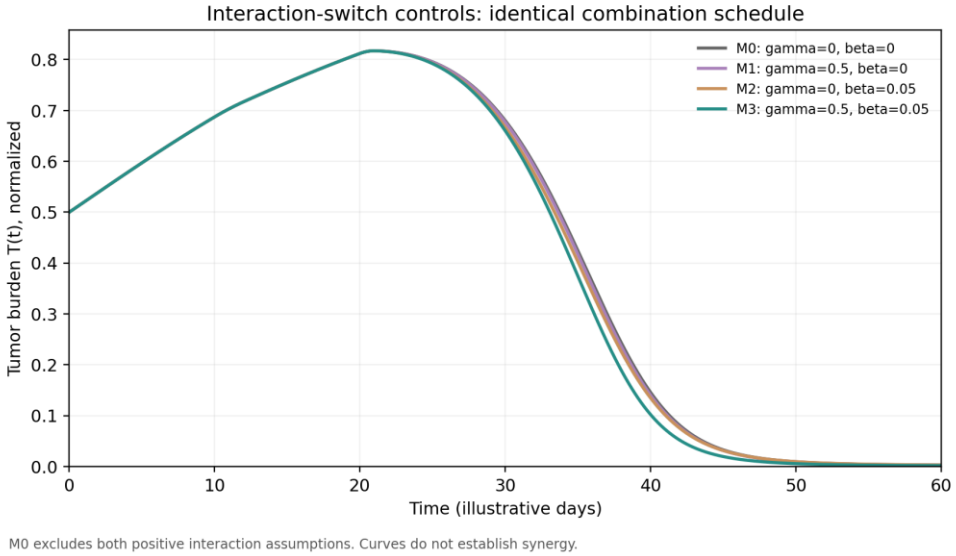


Figure 2. Integrated-Regimen Path Across Four Interaction Scenarios (M0-M3). Remove the Dependence of γ and β on Model Assumptions; do not Omit the Two Treatment Factors.

The calculated AUC_T without interaction terms (M0) is 0.26. Adding γ alone gave a result of 25.906, and adding β to this model resulted in 25.746. Add the interaction term (M3) and then increase the simulated AUC to 25.313. The amount of this improvement depends on the particular interaction

specification, and the scale for γ and β is quite different. It is hoped that the initial equations will be positive in terms of cross-talk. A small simulated AUC does not indicate biological synergy. Therefore, it will be necessary to specify an additive comparison, measured results and uncertainty evaluation.

4.3.4 Timing Effects and Model Limits

Then, we changed the doses but kept the total dose the same. Vaccine-first started the vaccine on day 10 and CAR-T on day 20 (AUC_T 25.313). Concurrent administration started both on day 15 (20.919). CAR-T-first established CAR-T on day 10 and vaccine on day 20 (16.950). The curves were different, but it was not clear whether they resulted from different treatments. Lower-AUC cases started earlier with CAR-T. Early start of active intervention will give us more time to reduce the 60-day AUC. Therefore, we present this as a scheduling demonstration and not as proof that CAR-T-first is the preferred order.

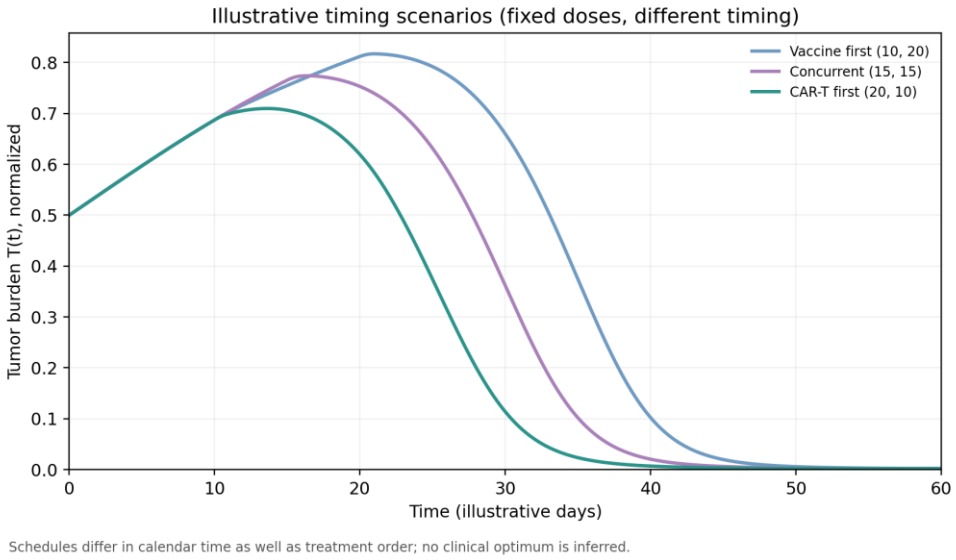


Figure 3. Three Model Dosing Patterns have the Same Total Load but Different Start Dates. The First CAR-T Product is not after Treatment.

To determine how far the interaction hypothesis affects the results, we carry out the integrated schedule for γ={0,0.25,0.50,1.00} and β={0,0.025,0.05,0.10}. The 16 combinations are recorded in the additional CSV. It is a parameter-effect evaluation and not a patient uncertainty study, so we do not assume a distribution for γ or β. The other reasons for the absence may be more serious than the two mentioned, such as CAR-T exhaustion, changes in antigen or HLA, stromal barriers, toxicity, etc. To understand the mechanism of the above syntheses, one must identify the reasons for their occurrence.

4.4 Experiments Needed to Test the Model

Therefore, there will be several good ways to do it. Determine whether neoantigen immunisation affects the migration and stability of CAR-T cells in the tumour microenvironment. Second, determine whether CAR-T-mediated killing induces new antigen-specific responses in the body or only causes the release

of antigens. Thirdly, ascertain whether there is an increase in recognition of the subgroup of antigen-negative malignancy. A pure chronological trial should keep the CAR-T induction time fixed and only change the time of vaccine administration to separate sequencing from the first CAR-T exposure. Based on the previous longitudinal data of immune cells and tumours, construct a model that includes both antigen-positive and antigen-negative sections. Only after achieving the above stages will there be clinical efficacy and risk assessment.

5. Computational Approaches to Neoantigen Prioritization and Treatment Design

5.1 A Five-candidate Ranking Example

Neoantigen identification entails multiple evaluations frequently debated collectively [10,11,18]. To keep the error low, we simply ranked the five speculative targets according to five standard indicators. The above indicators are MHC affinity (M_i), exposure (P_i), TCR recognition (R_i), immunogenicity (I_i) and off-target danger (O_i). The first four items had a good effect, and there was no off-target harm. We calculated it as follows:

$$S_i = w_1 M_i + w_2 P_i + w_3 R_i + w_4 I_i - w_5 O_i \quad (4)$$

The parameters were set manually: w_1=0.25, w_2=0.20, w_3=0.20, w_4=0.25 and w_5=0.10. Therefore, Table 4 shows the results of numerical calculations and not the development of vaccines. For example, candidate N1 is equal to 0.794 rounded to three decimal places. Changing the weight can change the order, and even the top-ranked peptide may not be recognised or detected in a tumour. Do not think that it is an advanced AI algorithm. All the attributes of the specifications and verifications need to be supported by practical examples, and biological confirmation of the selected short-list targets must be obtained.

Table 4. Proposed Candidate-feature Matrix and Refined Heuristic Scores (not Individual Case Data)

ID	MHC	Presentation	TCR	Immunog.	Off-target	Score	Rank
N1	0.91	0.86	0.88	0.92	0.12	0.794	1
N2	0.87	0.79	0.91	0.84	0.18	0.750	2
N3	0.76	0.82	0.73	0.81	0.09	0.694	3
N4	0.68	0.72	0.78	0.69	0.14	0.629	4
N5	0.63	0.67	0.61	0.72	0.20	0.574	5

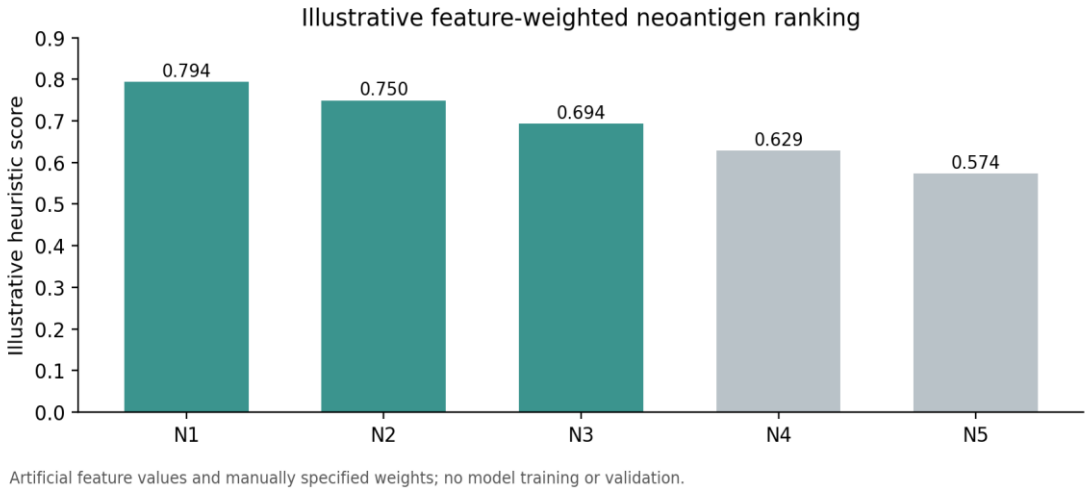


Figure 4. Ranking of the Five Proposed Neoantigen Targets Based on the Manually Set Coefficients in Equation (4). These Bars are not Forecasts or Medical Information

5.2 Prediction is not Intervention

Numerical Investigation and Biological Research should be separate. Sequencing, HLA profiling, immunopeptidomics and spatial or single-cell information can be used to find out which antigens are presented and where immune inhibition takes place [15,18]. A computational priority will not change the ECM or carry a CAR-T cell to a malignancy. The Scheduling Framework will find a low simulated tumour load for the chosen model, but this result will be influenced by the objective function and the accuracy of the model. Neither category of output is an experiment.

5.3 Computational Tasks and Validation

Table 5. The Above are the Problems for Future Computation and the Corresponding Verification

Task	Input	Proposed output	Minimum validation
Neoantigen prioritization	Tumor/normal sequencing; HLA; RNA	Ranked candidates	Presentation and T-cell assays
Immune-state characterization	Single-cell/spatial data	Spatial immune profile	Independent cohorts; tissue assays
CAR-T targeting design	Antigen and tissue expression	Candidate receptors/targets	On/off-tumor functional studies
Treatment-schedule exploration	Longitudinal response data	Hypotheses for sequence/interval	Matched experimental schedules

The ECM shows this division very clearly. A dense or restrictive stromal structure can reduce the entry of immune cells, and computational atlases have been used to map these barriers [2, 15, 19]. Modification

of the physical barrier will require some biological intervention and will be shown to increase CAR-T infiltration. This paper did not build a machine learning model, evaluate the prognosis of patients, or change the tumour microenvironment. Its contribution to this section is an open-ranking illustration, and it should be noted that verification of every suggested computational task is required.

6. Conclusion

Personalised neoantigen immunotherapy and CAR-T cells recognise tumours in different ways, so it is worth studying them together. Some of the previous vaccine trials have produced good immune stimulation and memory responses. CAR-T research has been carrying out some direct-targeting studies. It is still unknown whether the particular neoantigen-CAR-T combination increases the survival of solid tumors, so it cannot be considered a standard treatment. The structure of computation is not the same. Instead, it can be seen that there are predetermined interactions among the apparent synergies. Both the 60-day tumour burden area under the curve (AUC) and the tumour burden at day 60 were only slightly worse than that of CAR-T therapy alone in the baseline simulations. The treatments have shown some improvement, but the time for CAR-T therapy has been delayed. Therefore, it is not possible to determine the best treatment. Next, longitudinal data will be obtained to distinguish between endogenous responses, CAR-T cell dynamics and antigen escape, and then the therapeutic period will be studied under controlled conditions. The above are the testable hypotheses, not clinical suggestions.

Data and Code Availability

The evaluation did not use the participants' information. Model weights and chosen neoantigen indicators are artificial. The accompanying Python code and CSV files are the input and numerical results for Figures 1–4 and the calculations shown here; all the charts are simulated frameworks or rating systems, not observations of humans or lab animals.

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