Computational model to predict response rate of clinical trials

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ABSTRACT

Background

Most therapeutic vaccine clinical trials (CTs) have failed to prove efficacy, even if immunogenicity was confirmed earlier. It was already shown that immune responses generated against multiple antigens are indicative of clinical responses. We aimed to find association between the heterogeneity of immune response and clinical efficacy and, based on this develop a tool that can predict the clinical outcome of cancer vaccines.

Methods

In an extensive literature search we collected the immune- and objective response rates (IRR, ORR) of 94 CTs in which 2,338 patients were treated with 64 different vaccines. Vaccine sequences were used to predict personal epitopes (PEPIs) that bind to at least 3 HLA alleles of the same subject, for all patients of a representative model population. Then we determined the percentage of subjects with at least 1 vaccine specific PEPIs (PEPI Score) and at least 2 vaccine specific PEPIs derived from different antigens (MultiAgPEPI-Score) and compared to the published IRR and ORR.

Results

PEPI Score was able to predict the immunogenicity of therapeutic vaccines; significant correlation was found with IRR (p=0.002). As expected, no correlation was found between ORR and IRR (p=0.294), neither between PEPI-Score and ORR (p=0.302), suggesting, that immune response against a single epitope is not enough for efficient tumor response. However, we found that MultiAg PEPI-Score significantly correlates with ORR (p<0.0001) consistent with earlier findings that the targeting of multiple antigens is required for tumor shrinkage.

Conclusions

Our results demonstrate that both IRR and ORR can be predicted by PEPIs. For clinical efficacy it is crucial to target and generate immune response against multiple antigens. Based on our analysis our computational model is useful and accurate for the prediction of the clinical outcome of cancer vaccines and can even be suitable for rescuing CTs with insufficient or missing responder selection.

METHODS

Literature search

Keywords: immunotherapy, immune response, clinical response, clinical trial, response rate, immunogenicity, peptide vaccine, DNA vaccine and any synonyms or relevant combinations of these

Inclusion criteria: trials with CD8+ T cell immune response (IR) and/or clinical response rate (ORR) data

Exclusion criteria: chemotherapy combinations with known negative effect on CD8+ T cell responses

185 papers possibly relevant based on abstract

↓ Full text review

93 excluded

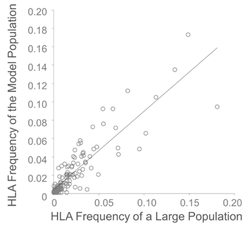
92 fit all criteria covering:

- 94 Clinical trials
- 2,338 subjects
- 64 immunotherapeutic vaccines
- 88 different antigens.

Eligible Vaccines	Eligible Immunoassays	Eligible Clinical Response Assessment
Peptide, Nucleic acid-based, Peptide-loaded dendritic cell vaccines with available amino acid sequence	IFN-g ELISPOT, MHC multimer, T cell proliferation, ICS, Cytotoxicity assay	RECIST, WHO, IWG, CALGB

Characteristics of the collected studies		Count (n)	Percentage
Subjects with	HIV infection	12	<1%
	neoplasia or dysplasia	208	9%
	cancer	2,118	91%
	solid tumors	1,938	83%
	liquid tumors	155	7%
Trials with HLA-pre-selected subjects		55	59%
Trials without HLA selection		39	41%

Model Population (MP) used in the *in silico* trials



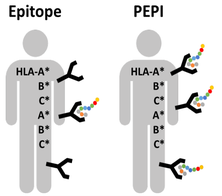
The HLA allele distribution of the MP significantly correlates with a large population (16x) of 7,189 subjects[4] (Pearson R=0.89, p<0.001).

n = 433 subjects

- ✓ **complete four-digit HLA class I genotype**
- ✓ **Demographic information**
- ✓ 270 subjects from the HapMap collection: 90 Yoruban, 90 European, 45 Chinese, and 45 Japanese subjects[1],
- ✓ 67 subjects from the ESTDAB database: from Canada, Australia, and New Zealand[2],
- ✓ 96 subjects from the HIV database[3].

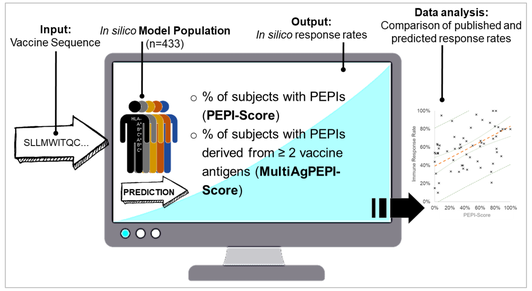
- ✓ **152 different HLA class I genotypes**
- ✓ **Representing cca. 85% of the Common and Well-documented (CWD) HLA-alleles**

Computation of immune responses and *in silico* model trials



Epitope: peptide that binds to at least one autologous HLA class I allele.

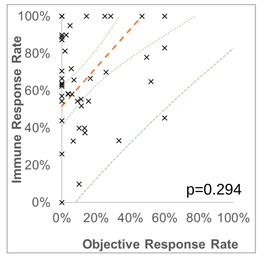
PEPI (Personal EPItope): peptide that binds to at least 3 autologous HLA class I alleles and are capable to induce cytotoxic T cell responses in a patient.[5,6]

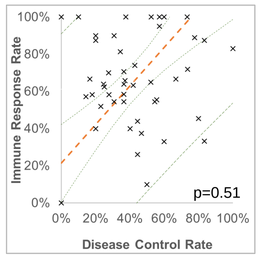


Statistical analysis: Correlations were identified using the Pearson correlation coefficient. Statistical significance was computed following the Student's t-distribution with degree of freedom n-2. Threshold of significance: p<0.05.

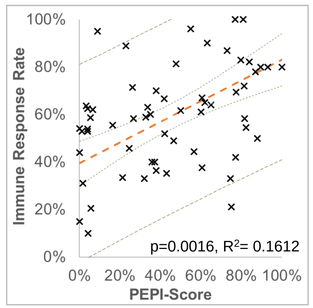
RESULTS

Immune response rate does not correlate with clinical response rates (ORR or DCR) n=49 CTs; 1,087 subjects, 32 vaccines





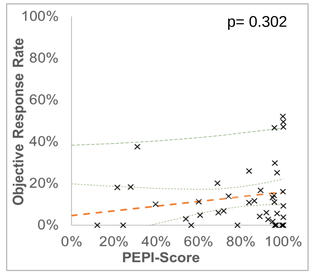
Correlation between predicted and measured immune response rates n=79 CTs; 1,842 subjects; 57 vaccines



PEPI-Score predicted immune response rates with median 23% difference

We found no significant difference in the IRR of trials with or without HLA pre-selection either (57% vs. 61%, p=0.711).

Predicted immune response rate does not correlate with clinical responses (ORR) n=54 CTs, 1,210 subjects, 64 vaccines

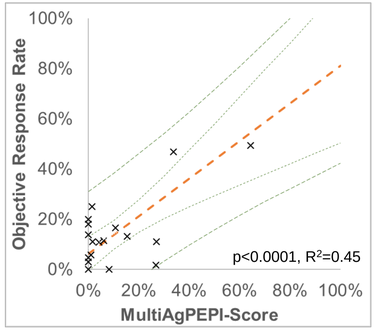


As expected, we did not find significant correlation between PEPI-Score and ORR

These results further confirm what was found earlier in many vaccine trials; the measured immunogenicity of a vaccine is not predictive for clinical benefit.[7,8]

Limitation: We found 10 CTs where IRR was high: between 33-90%, but no objective response was recorded for them

Multiantigenic PEPIs predict clinical outcome (ORR) n=20 CTs; 467 subjects; 19 vaccines



It has already been suggested that T-cell responses against multiple antigens were associated with longer progression-free and overall survival.[9] Therefore, we analyzed the subgroup of multi-antigen-targeting vaccines.

We found significant correlation between ORR and MultiAgPEPI-Score

Limitation of this analysis: lack of published ORR values between 25% and 50% and above 50%.

CONCLUSIONS

We provide evidence in a large systematic study for the 2 main limitations associated with cancer vaccines

- o Despite the induction of strong T- cell immunity, clinical outcomes have been disappointingly limited
- o Pre-selection of subjects based on only 1 HLA allele does not enrich immune responders nor clinical responders

However,

- o Predicting epitopes that bind multiple HLA alleles of an individual (PEPIs) is indicative for the estimation of the immune- and clinical responses
- o For clinical efficacy it is crucial to both target and generate immune response against multiple antigens

Consequently,

- o The *in silico* computational model is useful and accurate for the prediction of the clinical outcome of cancer vaccines, thus could be used as a preclinical tool to aid vaccine development
- o This *in silico* computational model was used for the design and pre-clinical development of PolyPEPI1018 vaccine against colorectal cancer[10] (NCT03391232)

Abbreviations:

CT: clinical trial, IRR: immune response rate, ORR: objective response rate, PEPI: personal epitope, IFN-g ELISPOT: interferon gamma enzyme-linked immunosorbent assay, ICS: intracellular cytokine staining, HLA: human leukocyte antigen, MHC: major histocompatibility complex, RECIST: Response Evaluation Criteria for Solid Tumors, IWG: International Working Group response criteria for leukemia, CALGB: Cancer and Leukemia Group B

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Conflict of interest:
All authors hold shares of Treos Bio LTD.

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