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Neoantigen Vaccines Pass the Immunogenicity Test

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Abstract

Neoantigens arising from tumor-specific genomic alterations constitute authentic “non-self” antigens and represent a new class of targets for cancer immunotherapy. Recent reports on various vaccine platforms targeting neoantigens suggest a basis for precision therapies customized to each patient’s tumor mutational profile.

A Historical Framework

Cancer vaccines have had a disappointing history. Earlier cancer vaccines targeted shared (non-mutated) “self” antigens and showed limited clinical efficacy. However, the immunogenicity of amino acid-substituted peptides encoded by tumor-specific mutations, so-called neoantigens, was demonstrated in human studies in the 1990’s [1]. Unfortunately, rudimentary technologies related to DNA sequencing and data analysis hampered testing these genomic alterations as antigens for cancer vaccines and the field stalled. The decoding of the Human Reference Genome and later, The Cancer Genome Atlas, created a critical resource that afforded the expertise and infrastructure for cancer immunologists to address the relevance of cancer neoantigens [2]. A series of recent vaccine studies targeting tumor missense mutations now point investigators in a new direction that will hopefully, someday, enable facile development of neoantigen-directed vaccines.

Proof-of-Concept Achieved

Two recent reports in Nature provide further evidence on the immunogenicity of tumor-encoding missense mutations and offer clues that may direct future clinical development of cancer vaccines [3,4]. In the first report, Sahin et al. employed a novel RNA-based vaccine approach to immunize 13 patients with advanced cutaneous melanoma, including 5 patients

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with measurable disease [3]. 10 candidate neoepitopes were selected based on the predicted binding affinity of mutation-encoding peptides to each patient's major histocompatibility (MHC) class I and class II molecules, and subsequently formulated into synthetic RNAs encoding 5 linker-connected 27-mer peptides [3]. Multiple vaccine doses (8–20 doses) were administered to each patient by percutaneous injection of inguinal lymph nodes. Elispot analysis was primarily employed to monitor T cell immune responses; although, in some patients, cells were also stained for intracellular cytokine production and peptide-MHC multimer binding to complement the functional readout. In sum, responses were detected against 60% of the candidate neoepitopes. Consistent with prior preclinical murine data using this vaccine platform, the majority of elicited T cell responses were $CD4^+$, directed against MHC class II-restricted antigens. Additionally, approximately 25% of the tested neoepitopes elicited MHC class I restricted $CD8^+$ T cells. [3]. In the second report, Ott et al. employed synthetic long 15 to 30-mers peptides with poly-ICLC (Hiltonol) to immunize 6 patients with advanced cutaneous melanoma, including 2 patients with measurable lung metastases [4]. Up to 20 neoepitopes were selected based on the predicted binding affinity of a given peptide to each patient's MHC class I molecules; 7 vaccine doses were provided by subcutaneous injection. T cell immune responses were assessed in a similar manner to that employed by Sahin et al [3]. In this setting, vaccine-elicited $CD4^+$ (class II-restricted) T cell responses were directed against 60% of neoantigens, while $CD8^+$ (class I-restricted) responses were detected against 16% of candidate neoantigens [4]

These two studies, together with another published report on 3 melanoma patients to whom a dendritic cell-based neoantigen peptide vaccine was administered [5], provide persuasive proof-of-concept that various personalized cancer vaccine formulations can, indeed, elicit neoantigen-specific T cells in patients with advanced/metastatic disease [Table 1].

Clues, Surprises, Challenges

In all 3 reports discussed here, vaccination promoted pre-existing, as well as de novo neoantigen-specific T cell immunity [3,4,5]. The recruitment of new neoantigen specificities by vaccination is likely to have clinical benefit by targeting various malignant clones in each patient. Cumulative evidence suggests that most/all neoantigen-specific T cell populations show strong preference for the mutated peptide and little cross-reactivity to the wild type (normal) peptide [3,4,5]. Vaccines targeting neoantigens, independent of the platform studied, appear safe and well tolerated with no unexpected adverse events. The various bioinformatics pipelines employed appear to reliably identify candidate neoantigens, as all patients mounted T cell responses against 3 or more of the candidate neoepitopes delivered. As our collective experience widens, one hopes that bioinformatics pipelines will improve neoepitope selection to allow a more precise formulation, and increase the rate of immunogenicity for the selected antigens. Importantly, patients that developed recurrent/progressive disease after vaccination were subsequently treated with anti-programmed death-1 (PD-1) immunotherapy (immune checkpoint blockade); both studies reported clinically significant disease regression in patients following anti-PD-1 treatment [3,4]. Indeed, combinatorial therapy of neoepitope vaccine with concurrent (or sequential) anti-PD-1 has obvious appeal, and is likely to be the first combination approach to be formally examined in a clinical trial.

A notable surprise was the predominant $CD4^+$ T cell response in the 2 recent reports. However, the RNA-based poly-neoepitope platform developed by Sahin and co-workers was previously shown to elicit primarily $CD4^+$ T cell responses in mice [6], so this should not have been a big revelation. Moreover, $CD8^+$ T cells were detected that corresponded to a small minority of neoepitopes confirming proof-of-concept, but suggesting additional optimization might be required to recruit the entire TCR repertoire directed against MHC class I-restricted neoantigens. The data using synthetic long peptides with a Toll-like receptor 3 (TLR3) agonist revealed a similar bias in favor of $CD4^+$ over $CD8^+$ T cell responses. The bigger question for scientists is to better understand the contribution of neoepitope specific $CD4^+$ T cells beyond the provision of "help" in the form of cytokines (ie. Interleukin 2 (IL-2) and CD40L) [7]. How important are $CD4^+$ T cells that express granzymes and perforin in effector responses, and how can we best optimize their function? Furthermore, what impact will $CD4^+$ T cell responses have on malignancies that are not MHC class II positive, and will the generation of regulatory $CD4^+$ T cells be a cause for concern, or not?

Significant challenges remain, including our limited understanding of neoantigen processing and presentation and the impact of tumor heterogeneity. In the study by Wu's laboratory, only 2 (of the 6) patients generated T cell responses with reactivity against autologous melanoma cells. In the report by Sahin's group, a patient presented with diminished recognition of autologous tumor due to loss of MHC class I, suggesting vaccine-induced antigen escape [3]. This patient went on to receive anti-PD-1 therapy but experienced disease progression and died. Consequently, these observations should remind us that many obstacles remain in our pursuit of personalized therapeutic treatments against melanoma.

Looking towards the Future

In our opinion, in order to deliver precision therapies to the most relevant patient population, the next hurdle in neoantigen vaccine design will be the feasibility of integrating next generation sequencing technologies, bioinformatics and proteomics pipelines with vaccine manufacture. Validated by the recent reports from Sahin et al. and Ott et al., our experience has taught us that manufacturing personalized neoantigen cancer vaccines is labor-intensive, costly, and time consuming. Presently, it takes 3 months to generate these vaccines, regardless of the manufacturing platform and eventually, this process will need to be streamlined in order to be applicable. Moreover many additional considerations remain, including assessing the role of non-mutated shared tumor antigens in protective immunity; and the potential of developing combination therapies with neoepitiopes for cancer treatment. Once feasibility is established, larger trials to determine the efficacy and safety of vaccination against cancer neoantigens might move forward. Ideally, this will be accomplished once the role of $CD4^+$ T cells in tumor eradication is better understood, and the multiple questions related to the role of the tumor microenvironment in malignant transformation and therapeutic resistance are addressed [8].

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Table 1

Summary of Neoantigen Vaccines

	Carreno *et al.*[5]	**Ott *et al.*[4]**	**Sahin *et al.*[3]**
# Patients	3	6	13
Vaccine	Mature Dendritic Cells[a]	Synthetic Peptide+ poly IC:LC	RNA
Administration Route	Intravenous	Subcutaneous	Intra-nodal
Epitope Length	9 aa[c]	15–30 aa	27 aa
# Epitopes / Patient	7	13–20	10
# Doses	3	7	8–20
Immunogenicity (total # peptides tested)	21 peptides	91 peptides	125 epitopes
$CD8^+$ T cell response rate[d]	43%	16%	25%
$CD4^+$ T cell response rate[d]	NT[b]	60%	66%

[a] Ex-vivo manufactured and pulsed with synthetic peptides;

[b] NT, Not tested;

[c] aa, Amino acids,

[d] Immune response rate to MHC class I or class II epitopes (per vaccine trial)