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Review Article

Personalized Neoantigen Vaccines in Melanoma: Current Workflow and Adjuvant Opportunities

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Summary
Personalized neoantigen vaccines represent a promising advance in cancer immunotherapy, with melanoma serving as a leading model due to its high mutational burden and immunogenicity. Unlike shared tumor-associated antigens, neoantigens arise from tumor-specific somatic mutations and are absent from normal tissues, enabling highly selective immune targeting. Advances in immunogenomic workflows now allow rapid identification of patient-specific neoantigens through integrated tumor–normal sequencing, transcriptome analysis, HLA typing, and computational epitope prediction, followed by individualized vaccine manufacturing. Multiple vaccine platforms, particularly mRNA-based approaches, have demonstrated robust induction of neoantigen-specific $CD4^+$ and $CD8^+$ T cell responses. Emerging evidence suggests that the adjuvant setting represents a critical window for clinical benefit, as vaccination after surgical tumor removal may enable elimination of microscopic residual disease and durable immune surveillance. Incorporation of presentation-informed strategies, including immunopeptidomics and refined computational models, may further improve target selection by prioritizing neoantigens that are truly presented on tumor cells. Together, these developments establish personalized neoantigen vaccination as a clinically feasible and biologically compelling strategy in melanoma, with potential applicability to other high-risk solid tumors.
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Introduction

Melanoma has long been at the forefront of cancer immunotherapy advances. Immune checkpoint inhibitors (e.g., anti-PD-1 or anti-CTLA-4 antibodies) can induce durable remissions in a subset of patients, but many still experience disease recurrence.[1,2] To further improve outcomes, attention has turned to therapeutic cancer vaccines targeting neoantigens, novel peptides arising from tumor-specific mutations. These neoantigens are absent from normal tissues and thus recognized as "foreign" by the immune system.[1] In contrast to shared tumor-associated antigens (TAAs) (like MAGE-A3 or gp100) that often failed to improve survival due to immune tolerance or low efficacy,[3,4] neoantigens offer truly tumor-specific targets. Early proof-of-concept studies in melanoma patients demonstrated that personalized neoantigen vaccines are feasible, safe, and highly immunogenic.[5] In a 2017 pilot trial, for example, six melanoma patients received a tailored vaccine of their own tumor's neoantigens after surgery, and four of six remained recurrence-free, highlighting the potential clinical benefit.[6] Melanoma's high mutational burden (hundreds of non-synonymous mutations per tumor) provides a large neoantigen pool, and indeed, tumor mutation burden correlates with neoantigen load and response to immunotherapies.[1] These findings set the stage for a new wave of personalized neoantigen vaccine trials in melanoma and other cancers.

Neoantigen Identification Workflow

Designing a personalized neoantigen vaccine starts with identifying suitable neoantigen targets for each patient. The state-of-the-art workflow is a multi-step "immunogenomics" pipeline[7]:

Tumor and Normal DNA Sequencing

A sample of the patient's tumor (and often normal blood for germline DNA) is subjected to next-generation sequencing, typically whole-exome or whole-genome sequencing. This reveals the catalogue of somatic mutations unique to the tumor while filtering out inherited variants. Then using bioinformatics tools compare tumor vs. normal sequences to call somatic mutations (e.g. single nucleotide variants and indels). Focus is placed on non-synonymous mutations that change amino acids in protein-coding genes, since these can create new peptide sequences.

Transcriptome (RNA seq) Integration

In parallel, RNA sequencing (transcriptome analysis) of the tumor is performed to determine which mutated genes are actually expressed. Integrating genomic and transcriptomic data is critical; candidate mutations are

filtered to prioritize those that are not only present in DNA but also transcribed into mRNA.[7,8] This ensures the downstream neoantigen peptides can be generated by the tumor.

HLA Typing and ability to activate T cell

The patient's HLA (human leukocyte antigen) alleles (especially class I and II) are identified, either by sequencing or computationally from the genomic data.[9] HLA molecules are the major histocompatibility complex (MHC) proteins that present peptides to T cells, so knowing a patient's HLA types is essential for predicting which mutant peptides can bind and be presented. Following this, the peptides undergo T cell recognition assays to evaluate their ability to activate T cells.

Neoantigen Prediction

Given the set of expressed mutations and the patient's HLA profile, algorithms predict which mutant peptide fragments are likely to bind strongly to the HLA molecules and be displayed on the cell surface. Peptides (often 8-11 amino acids for class I and longer for class II) spanning the mutated amino acid are evaluated for HLA binding affinity using in silico tools (e.g., NetMHCpan). Only a fraction of mutations yield peptides that can stably bind a patient's HLA. Predicted binders are further filtered by characteristics like high gene expression or suitable processing motifs. Modern computational pipelines (e.g., pVAC-Seq and others) automate this process, incorporating mutation calling, RNA expression filtering, HLA typing, and binding prediction to output a ranked list of candidate neoantigens.[9-14] Typically, dozens of candidate neoantigen peptides are identified per patient.

Candidate Prioritization

The candidate neoantigens may be prioritized based on factors such as HLA binding affinity, mutant allele frequency, expression level, and lack of similarity to any self-peptides (to avoid cross-reactivity). Some pipelines also consider predicted T-cell receptor recognition or immunogenicity scores for each epitope. The goal is to select a manageable number (often on the order of 10–30) of top neoantigen targets to include in a vaccine, balancing breadth and practicality.

Immunopeptidomics (Optional)

A cutting-edge (but not yet routine) addition to the workflow is immunopeptidomics, directly identifying which peptides are naturally presented on the patient's tumor HLA molecules. This involves isolating HLA proteins from tumor tissue, eluting the bound peptides, and identifying them by mass spectrometry.[15,16] By doing this, one can empirically confirm which mutant peptides from the tumor are actually presented on cell surfaces. If a candidate neoantigen from the computational list is detected among the tumor's eluted HLA ligands, confidence is very high that it's a bona fide target. Immunopeptidomics can also occasionally discover novel neoantigen peptides (for instance, from unannotated mutations or proteasomal splicing) that were missed by sequencing predictions. However, this approach requires sufficient fresh tumor material and specialized proteomics workflows, so it remains an optional step in most clinical pipelines.

Vaccine Construction

Finally, the selected neoantigen peptides must be incorporated into the vaccine platform of choice. For example, if using an mRNA vaccine, a synthetic RNA encoding all the selected mutant peptides (often concatenated as a polyepitope sequence) is designed.[17] For peptide vaccines, each peptide may be individually manufactured. This step involves good manufacturing practice (GMP) processes and typically takes a few weeks to produce the patient-specific vaccine product.

Throughout this workflow, turnaround time is a crucial consideration, especially in adjuvant settings where patients should start therapy soon after surgery. Recent advances in sequencing and computation have compressed neoantigen identification into a few weeks, and mRNA vaccine manufacturing can likewise be accomplished in roughly 4–6 weeks in current trials.[17] This rapid timeline has made truly personalized cancer vaccines clinically feasible.

Presentation-Anchored Selection: The Role of Immunopeptidomics

A major challenge in neoantigen vaccine design is distinguishing which predicted neoantigens are most relevant for immune targeting. Computational binding predictions, while improving, have significant false positives; many peptides predicted to bind HLA with high affinity are never actually presented by tumor cells in vivo. Some mutations may not generate stable peptides due to proteasomal processing quirks, or the peptide–MHC complex might not form in the cellular context. As a result, a vaccine that includes neoantigens based only on binding predictions could waste "slots" on peptides that the immune system never sees on the tumor.

This is where immunopeptidomics offers an important advantage: it grounds neoantigen selection in empirical evidence of presentation. By directly profiling the peptides bound to tumor HLA molecules, immunopeptidomics can verify the actual presence of specific neoantigen peptides on the cancer cell surface.[15,16] In other words, it asks: "Which mutant peptides has the tumor truly put on display for T cells?" Neoantigens confirmed by this method are highly attractive vaccine targets; they have cleared all hurdles of antigen processing and presentation in the patient's tumor. Including only such "presentation-

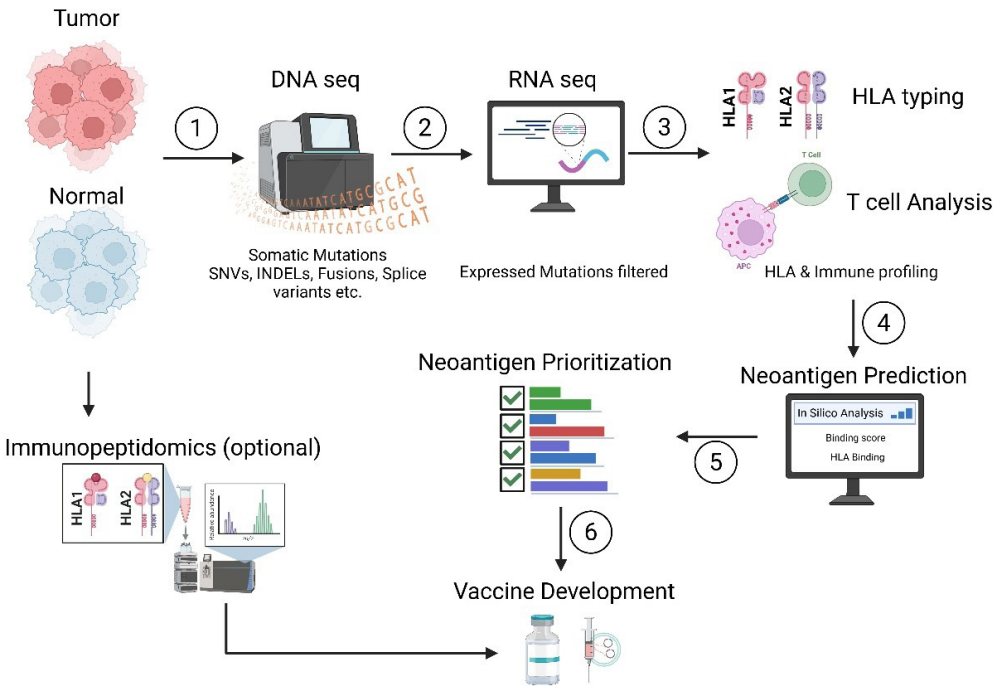

Figure 1. Personalized neoantigen vaccine identification workflow. Tumor and matched normal samples are analyzed through a stepwise immunogenomics pipeline. (1) Tumor and normal DNA sequencing identify somatic, non-synonymous alterations, including single-nucleotide variants, insertions/deletions, gene fusions, and splice variants. (2) Tumor RNA sequencing is integrated to filter for mutations that are transcriptionally expressed. (3) Patient-specific HLA class I and II typing and immune profiling are performed, together with T cell analysis, to define antigen presentation capacity and immune context. (4) Computational neoantigen prediction prioritizes mutant peptide–HLA binding using in silico algorithms and binding affinity scores. (5) Candidate neoantigens are ranked based on predicted HLA binding strength, tumor expression, variant allele frequency, and immunogenic potential. An optional immunopeptidomics step using mass spectrometry can further validate and enrich naturally presented HLA-bound peptides. (6) High-priority neoantigens are advanced to vaccine development, including GMP-compliant oligo-based, viral polyepitope, or peptide-based vaccine manufacturing.

anchored" neoantigens could enrich a vaccine for the most actionable targets. Indeed, direct detection of MHC-bound neoantigens addresses key limitations of purely bioinformatic prediction, especially for neoantigens that are rare or prone to immune evasion.

However, immunopeptidomics itself comes with challenges. First, its sensitivity is limited; low-abundance peptides might go undetected, meaning a neoantigen could be real but still missed by mass spectrometry. Second, the technique requires fresh/frozen tumor tissue and can be technically variable. The yield of eluted peptides may be low, and identifying mutant peptides amidst a complex mixture is analytically demanding. Third, the process adds time and complexity to an already tight vaccine production schedule. For these reasons, many trials have so far relied on computational predictions alone, which is faster but riskier in terms of target selection.

Looking forward, hybrid approaches are emerging. For example, researchers are training machine learning models on large immunopeptidomics datasets to improve prediction of which peptides get presented (e.g., the "EDGE" and "SHERPA" models incorporate mass-spec data to refine HLA-binding predictions).[16,18]

These efforts aim to capture the benefits of immunopeptidomics without requiring it for every patient. In the meantime, when feasible, integrating immunopeptidomics data can increase confidence in chosen neoantigens. Presentation-anchored selection is especially valuable in tumors with many candidate mutations; it helps prioritize the true targets among a sea of predictions. As neoantigen vaccines move toward clinical practice, improving accuracy in this selection step will be key to maximizing their efficacy.

Personalized Neoantigen Vaccine Platforms and Clinical Trials

Multiple vaccine platforms have been explored to deliver personalized neoantigens, including long peptides, dendritic cell (DC) vaccines, DNA plasmids or viral vectors, and most prominently mRNA vaccines.[8,19,20] The basic principle is to introduce the patient's own neoantigen sequences (usually as peptides or encoded in nucleic acids) alongside an immune-stimulating adjuvant to provoke a robust T cell response. Each approach has pros and cons:

Synthetic long peptides (SLPs)

Pioneering trials such as Ott et al[6] used up to 20 custom-made peptides (typically 15–30 amino acids long, spanning each mutation) emulsified with an adjuvant like poly-ICLC. Peptide vaccines can induce strong T helper ($CD4^+$) (60%) and T cytotoxic ($CD8^+$) (15%) cell responses.[21,22] They are chemically synthesized, which can be expensive and time-consuming for many peptides,

but they were the first to demonstrate the feasibility of neoantigen vaccines. In the Ott et al. study, all patients elicited T cell responses to multiple neoantigens, and some achieved durable tumor control.

mRNA vaccines

mRNA vaccines have rapidly become the frontrunners for personalized cancer vaccination. In this approach, a single synthetic mRNA molecule is engineered to encode multiple neoantigen peptides (often concatenated as a long protein sequence with linker segments). The mRNA is delivered in a lipid nanoparticle (LNP), similar to COVID-19 mRNA vaccines, for efficient uptake by host cells, which then produce the neoantigen peptides internally. Moderna's mRNA-4157 (also called V940) is a prime example; it encodes up to 34 neoantigen sequences tailored to a patient's tumor.[17] The mRNA platform offers several advantages: it's highly versatile (any sequence can be made on demand), it induces both $CD8^+$ and $CD4^+$ T cell responses (as host cells process and present the translated peptides on both MHC I and II), and production timelines have been optimized by leveraging advances from infectious disease vaccines. BioNTech has developed a similar individualized mRNA vaccine platform (e.g., autogene cevumeran), which has been tested in melanoma and other cancers. mRNA vaccines have shown strong immunogenicity, for instance, a recent Phase I study of an individualized mRNA neoantigen vaccine in pancreatic cancer elicited T cell responses against neoantigens in 50% of patients, correlating with delayed tumor relapse.[23] The flexibility and potency of mRNA make it a leading choice for ongoing trials.

DNA and Viral Vector vaccines

Some approaches cloned neoantigen-encoding DNA into plasmids or packaged viral vectors (such as adenovirus).[24] For example, Gritstone Oncology's program uses a two-vector system: a priming with an adenoviral vector encoding neoantigens, followed by a boost with an RNA vector (self-amplifying mRNA). This heterologous prime-boost is designed to maximize immune response.[25,26] DNA-based vaccines are generally slower to induce immune responses and may be less immunogenic on their own, but viral vectors can be very potent. These modalities are in earlier stages compared to mRNA and peptide vaccines, but trials (including in melanoma and lung cancer) are underway.

Dendritic cell (DC) vaccines

This method involves loading a patient's own dendritic cells ex vivo with neoantigen peptides or RNA, then infusing the primed DCs back into the patient. DC vaccines can effectively initiate immune responses and were an early form of personalized immunotherapy. However, they are logistically complex and expensive (requiring personalized cell therapy manufacturing).[27] As a result, DC vaccines are less common in recent neoantigen trials, but they have shown immunogenicity in small studies.

Across these platforms, clinical studies have consistently demonstrated that personalized neoantigen vaccines can induce robust T cell responses in cancer patients. In a phase Ib trial in advanced melanoma (and other cancers), combining a peptide neoantigen vaccine (NEO-PV-01) with PD-1 checkpoint blockade, vaccinated patients developed de novo T cell responses to multiple neoantigens that were not present before therapy.[28] The vaccine-induced T cells displayed cytotoxic markers, infiltrated tumors, and even led to "epitope spreading", the phenomenon were killing of tumor cells releases additional antigens, broadening the immune response. Notably, in that study, all 82 participants showed an immune response to the vaccine, underscoring the reliability of the approach in stimulating immunity. These immune correlative outcomes are encouraging, although in advanced disease, the clinical efficacy (tumor shrinkage or survival improvement) is still being evaluated in randomized trials.

Adjuvant Melanoma Vaccines: A Window of Opportunity

The most promising clinical results for personalized neoantigen vaccines have emerged in the adjuvant setting, treating patients who are clinically free of disease after surgery but at high risk of relapse. Melanoma is a prototypical scenario: a patient with a resected stage III or IV melanoma might have microscopic residual disease that will eventually recur in about half of cases despite current standard adjuvant therapy.[1] Preventing those recurrences could translate into cures. Adjuvant therapy with checkpoint inhibitors (pembrolizumab or nivolumab) already improves relapse-free survival in resected melanoma, but many patients still recur. Personalized vaccines offer a compelling addition here for several reasons:

Minimal residual disease

After surgical removal of all visible melanoma, the tumor burden is at its lowest. This is an ideal time to deploy a vaccine, which typically needs some time to stimulate a T cell response. With little tumor volume, any vaccine-induced T cells are more likely to eliminate the remaining cancer before it grows. In advanced metastatic disease, by contrast, vaccines might act too slowly to counter large, fast-growing tumors.

Synergy with checkpoints

The adjuvant use of PD-1 inhibitors sets up a fertile ground for combination with vaccines. Checkpoint blockers "release the brakes" on T cells but rely on the presence of tumor-specific T cells to be effective. Vaccines provide a fresh influx of T cells targeted to the patient's tumor

neoantigens. Indeed, the rationale for combining vaccines with PD-1 therapy is strong; checkpoint inhibitor success has been linked to spontaneous neoantigen-specific T cell responses, so boosting neoantigen presentation and recognition with a vaccine should augment outcomes.[1] The vaccine-checkpoint combo essentially aims to both increase the quantity of anti-tumor T cells (vaccine) and their functional quality in the tumor microenvironment (checkpoint inhibitor).

Immune environment

In the adjuvant period (after tumor removal), patients often have a more intact immune system and less immunosuppressive tumor microenvironment to contend with. There may be fewer myeloid suppressor cells and regulatory T cells active than when bulky disease is present, making the immune response more effective. Also, patients are generally healthier and better able to mount vaccine responses in the adjuvant setting than in end-stage disease.

Recent clinical trials support the promise of adjuvant neoantigen vaccination. The landmark KEYNOTE-942 study[1] evaluated Moderna's personalized mRNA vaccine mRNA-4157 (V940) in resected high-risk melanoma. In this phase 2b trial, 107 patients received the neoantigen vaccine (encoding neoantigens) plus pembrolizumab, while 50 patients received pembrolizumab alone. Patients began pembrolizumab treatment within 13 weeks of surgery; meanwhile, the vaccine, which was custom-made for each patient's unique tumor mutations, was typically administered starting at pembrolizumab cycle three, approximately 17 weeks after surgery. The results showed a clear improvement in outcomes; the combination of vaccine + PD-1 blockade significantly prolonged recurrence-free survival (RFS) compared to immunotherapy alone. At 18 months follow-up, 79% of patients in the vaccine group were recurrence-free, versus 62% in the control group. This translated to a hazard ratio of ~0.56 for recurrence or death, a ~44% relative risk reduction. While the p-value (0.053) was marginal due to the trial's size, the trend favored the vaccine and was clinically meaningful. Importantly, the addition of the vaccine did not significantly increase serious toxicity; side effects were mainly mild injection-site or flu-like symptoms, with no grade 4–5 vaccine-related events reported. The trial's interpretation concluded that an mRNA-based individualized neoantigen therapy can be beneficial in the adjuvant setting for melanoma. These findings mark the first randomized evidence that personalized cancer vaccines can improve clinical outcomes. On the strength of KEYNOTE-942, a larger phase 3 trial in melanoma has been initiated.

The adjuvant melanoma experience is likely just the beginning. If neoantigen vaccines can eliminate micrometastatic disease in melanoma, similar strategies could be applied to other cancers with high relapse risk after surgery. For instance, a recent *Nature* study[23] in pancreatic cancer (a traditionally immunotherapy-resistant disease), an individualized mRNA neoantigen vaccine, given with adjuvant atezolizumab and a four-drug chemotherapy regimen (mFOLFIRINOX, comprising folinic acid, fluorouracil, irinotecan, and oxaliplatin), induced substantial T cell responses and possibly delayed tumor recurrence. The adjuvant setting, where the immune system can be proactively educated to seek out residual cancer, appears to be a sweet spot for this modality. By contrast, therapeutic vaccines in patients with active bulky tumors have yet to show tumor shrinkage as monotherapy, but they could serve a role in combination regimens to broaden immunity.

Conclusion

Personalized neoantigen vaccines represent a paradigm shift toward highly individualized cancer treatment. By leveraging each tumor's unique mutational signature, we can create "made-to-order" vaccines that mobilize the immune system against targets found only on the cancer cells. The workflow, from tumor sequencing and bioinformatic neoantigen discovery to vaccine manufacture, is complex, but recent advances have made it clinically viable on a timescale of weeks. Melanoma has been the proving ground for this approach, given its immunogenic nature and high mutation load. Early trials demonstrated that these vaccines are safe and can elicit potent, multi-targeted T cell responses. Now, the first controlled studies are showing real clinical benefit, especially in the adjuvant setting, where elimination of microscopic residual disease may enable durable remission.

Challenges remain on the road to broader adoption. Ensuring that selected neoantigens truly correspond to peptides presented by the tumor (potentially via immunopeptidomics-informed methods) will be crucial to avoid "wasted" vaccine components. Streamlining and automating the manufacturing process will be important for scalability, as will reducing cost. Moreover, cancer heterogeneity means that some mutations present in one tumor deposit might not be present in another, so vaccines might need to target an array of neoantigens to cover all bases. Despite these hurdles, the momentum in the field is strong. Dozens of personalized vaccine trials are ongoing across cancer types, and collaborations between academia and industry are accelerating technology development. The allure of personalized neoantigen vaccines is their potential to achieve what earlier cancer vaccines could not: generate a precise immune attack on cancer cells without off-target effects. If upcoming phase 3 trials confirm the promise seen in melanoma, we could witness the introduction of a whole new class of therapy, patient-specific cancer vaccines in routine clinical practice. In the adjuvant melanoma setting, such vaccines may soon join checkpoint inhibitors as part of the standard of

care, aiming to boost the immune system's surveillance to obliterate residual cancer cells. The concept of "one vaccine for one patient" was almost science fiction a decade ago; today, it is a tangible reality at the cutting edge of oncology. Continued research will refine this approach, possibly integrating neoantigen vaccines with other immunotherapies (e.g., T cell adoptive transfer or novel adjuvants) to further amplify anti-tumor immunity. The journey from tumor genome to personalized vaccine showcases the remarkable convergence of genomics, bioinformatics, and immunology, and it heralds a new personalized era in the fight against cancer.

Authors' Contribution

Conceptualization: Behzad Mansoori, Mohsen Mohammadi.
Supervision: Mohsen Mohammadi.
Writing–original draft: Behzad Mansoori, Mohsen Mohammadi.
Writing–review & editing: Mohsen Mohammadi.

Competing Interests

The authors declare no conflict of interest.

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