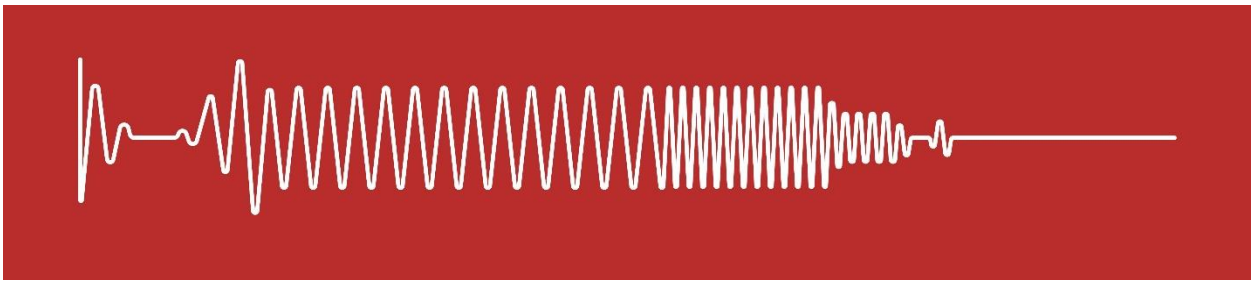
MarinBio Blog

Next Gen Cancer Subunit Vaccines: Broad, Rapidly Deployable Immunity



Introduction
Subunit vaccines are increasingly at the forefront of cancer immunotherapy. They are termed 'subunit' vaccines because they are constructed to combine only the core units needed for a robust targeted immune response. For example, a nanoparticle vaccine can be made of four subunits: 1) The matrix; 2) The cancer target peptide antigen; 3) A T-cell helper peptide and 4) an adjuvant. For cancer therapy, subunit vaccines contain engineered fragments of tumor proteins or peptides (antigens) that induce a specific anti-cancer immune response.

Recently, there have been several pivotal advances in subunit vaccine development for cancer therapy. One major advance has been improved identification of tumor specific neoantigens. (A tumor neoantigen is a novel peptide antigen that arises from tumor-specific genetic alterations, such as point mutations, insertions, deletions, or gene fusions. A personalized tumor neoantigen that is unique to an individual patient). Personalized neoantigen-based vaccines have shown durable immune responses in pancreatic, melanoma, bladder, and lung cancers. Computational methods (including artificial intelligence) have improved epitope prediction, enabling more precise vaccine design. In addition, improved antigen delivery systems (nanoparticles, lipoplex mRNAs) and advanced adjuvants have increased the magnitude and persistence of T-cell responses. In early clinical trials, subunit vaccines given in combination with checkpoint inhibitors (e.g. anti-PD-1/PD-L1 agents) have led to significantly reduced relapse rates compared with immunotherapy alone. These developments give hope that subunit vaccines may do more than merely delay disease progression, they have real potential to improve survival, reduce recurrence, and in some settings, push toward cures by educating the immune system to durably eliminate residual disease.

Advances In Cancer Subunit Vaccine Architecture

There have been several important advances in the architecture of cancer subunit vaccines, especially peptide- or protein-based vaccines, aimed at improving immunogenicity, breadth, and safety. One key trend is multivalency, where vaccine constructs co-deliver multiple epitopes/antigens rather than a single peptide: for example, supramolecular trivalent peptide hydrogels that co-assemble three epitope-conjugated peptides, enabling simultaneous presentation of diverse epitopes and eliciting a broader $CD8^+$ T cell response without additional adjuvant or delivery components.

Another advance is in self-assembling peptide conjugate nanoparticles that combine neoantigen peptides with adjuvant moieties (such as TLR agonists) in a single self-assembling particle. These architectures protect the peptide from degradation, promote uptake by antigen-presenting cells, and allow for slow or controlled release.

Architectural improvements in nanocarrier design are another theme: more precise control of core-shell structure, particle size, surface charge, and incorporation of immune-stimulating or targeting ligands are used to better target dendritic cells and modulate the tumor microenvironment. For instance, PLGA-based nanoparticles loaded with antigens/adjuvants, sometimes coated with tumor cell membranes or immune-activating molecules, have been used to enhance antigen cross-presentation and shift immune responses towards stronger $CD8^+$ T cell activity.

Finally, computational design of vaccine constructs has improved: in silico methods to optimize epitope selection (for MHC binding, immune dominance, etc.), better prediction of antigen structure, codon usage, and stability contribute to more refined subunit vaccine candidates that are safer (less off-target risk) and potentially more effective.

Together, these architectural advances, multivalent epitope presentation, self-assembling nanoscale delivery, enhanced adjuvant integration, better targeting and computational optimization, are pushing cancer subunit vaccines toward greater efficacy in preclinical models and into more ambitious clinical trials.

Neoantigen Discovery

Cancer neoantigen discovery has advanced rapidly as researchers integrate genomic, proteomic, and immunological data with computational methods to better identify vaccine candidates. The overarching challenge is to distinguish the few tumor-specific peptides that are both processed and presented by MHC molecules and capable of eliciting a strong T-cell response. To address this, four major conceptual approaches have emerged, each bringing a different layer of biological validation and prioritization to the process.

Approach	How the Approach Works	Computational Tools (examples)	Value of the Approach
Genomic sequencing–driven prediction	Uses tumor and normal sequencing to identify somatic mutations, generates mutant peptides, and evaluates their binding to patient-specific HLA alleles. Filtering is done based on binding affinity, expression, and peptide length.	pVACtools, MuPeXI, NeoPredPipe; MHC-binding predictors like NetMHCpan, MHCflurry	Provides a systematic and scalable way to generate a wide pool of candidate neoantigens, serving as the foundation for most vaccine discovery pipelines.
Immunopeptidomics validation	Directly measures peptides naturally presented by HLA molecules on tumor cells through immunoprecipitation and mass spectrometry. Confirms which predicted peptides are actually displayed.	MaxQuant, MSFragger, MSBooster	Offers direct biological evidence of presentation, reducing false positives and increasing confidence in candidate selection.
Modeling antigen processing & presentation	Simulates biological steps such as proteasomal cleavage, TAP transport, and peptide anchoring on HLA to predict which peptides are realistically processed and presented.	NetChop, NetCTLpan, updated anchor-residue models	Improves biological plausibility of candidate neoantigens by filtering out peptides unlikely to survive natural processing pathways.
Immunogenicity & T-cell recognition prediction	Uses machine learning and deep learning to predict whether a peptide–MHC complex will be recognized by T-cell receptors, incorporating sequence, structure, and repertoire data.	NetTCR, MixTCRpred, VitTCR, DeepImmuno, iTCep	Prioritizes peptides most likely to trigger effective immune responses, addressing the gap between presentation and actual immunogenicity.

Together, these four approaches form a multi-layered pipeline: sequencing-driven predictions define the candidate pool, immunopeptidomics confirms presentation, antigen processing models refine feasibility, and immunogenicity prediction highlights peptides most likely to work in patients. The integration of these concepts has reshaped neoantigen discovery, moving the field closer to reliable and personalized cancer vaccines.

Multi-Antigen Vaccine Design

Using multiple cancer neoantigens in a subunit vaccine offers several advantages for cancer therapy. By including a diverse set of neoantigens, the vaccine broadens the immune response, reducing the risk that tumor cells will escape detection through antigen loss or mutation. This diversity also increases the likelihood that at least some of the neoantigens will be effectively presented by the patient's HLA molecules, ensuring more consistent T-cell activation across

individuals. Additionally, targeting multiple tumor-specific antigens enhances both $CD8^+$ cytotoxic T-cell and $CD4^+$ helper T-cell responses, leading to stronger, more durable immunity. Overall, a multi-neoantigen approach improves therapeutic efficacy, minimizes tumor immune evasion, and increases the chance of long-term tumor control.

The Evolving Role of Adjuvants

Adjuvants are agents that, when administered with vaccine antigens, improve the body's immune response to those antigens, allowing for stronger and often longer-lasting protection. Many adjuvants act by stimulating early innate immune responses, guiding the adaptive immune system to produce higher levels of antibodies, or targeting cell-mediated immunity.
Adjuvants are viewed as core determinants of vaccine efficacy, shaping T-cell quality, breadth, and persistence.
Below are 5 structurally distinct adjuvants currently being used in subunit vaccine clinical trials for cancer, including their immunological mechanism, and associated vaccine names.

QS-21 (Saponin-Based)

- Mechanism: Activates the NALP3 inflammasome, promoting maturation of IL-1β/IL-18 and robust CD4+ and CD8+ T-cell and antibody responses; triggers membrane disruption aiding antigen delivery to APCs.
- Vaccine Example: Used in the GVAX cancer vaccine (pancreatic cancer); also present in ISCOMATRIX and AS01/AS15-containing clinical candidates, such as trials for melanoma and prostate cancer.

Poly(I:C) (TLR3 Agonist)

- Mechanism: Binds to TLR3 (endosomal) and MDA-5 (cytosolic), leading to type I interferon (IFN-α/β) production, TNF-α, dendritic cell maturation, and Th1-polarized cytotoxic T-cell and NK activation.
- Vaccine Example: Used as an adjuvant for cancer peptide vaccines such as those for melanoma targeting NY-ESO-1, and in combination with checkpoint inhibitors.

CpG ODN (TLR9 Agonist)

- Mechanism: Activates TLR9 in dendritic cells/B cells (endosomal), promoting type I interferon and other Th1 cytokines production and cross-presentation for CTL induction.
- Vaccine Example: Used in clinical trials for NY-ESO-1 subunit peptide vaccines in combination with Montanide, especially for skin and ovarian cancers.

STING Agonists (Cyclic Dinucleotide-Based)

- Mechanism: Stimulates intracellular STING (endoplasmic reticulum–resident), activating IRF3, production of type I interferons and inflammatory cytokines, leading to DC maturation and CTL priming.
- Vaccine Example: Ongoing clinical trials with STING agonists as adjuvant for neoantigen-based melanoma vaccines and others, often via intratumoral injection.

Amplivant (TLR1/2 Ligand).

- Mechanism: Stimulates dendritic cell activation via TLR1/2 on the cell surface, leading to NF-κB activation, strong Th1 response, and enhanced antigen uptake and cross-presentation.
- Vaccine Example: Modi-1 vaccine (Phase I/II trial for solid tumors), employing covalent linkage of citrullinated tumor peptides to Amplivant.

Clinical Observations from Subunit Cancer Vaccine Trials

Subunit cancer vaccines are emerging as a promising immunotherapeutic modality, designed to elicit targeted T-cell responses against tumor-associated antigens while maintaining a favorable safety profile. Recent clinical studies have provided key insights into their mechanisms of action and therapeutic potential.

Subunit vaccines can elicit durable antigen-specific T-cell responses, with persistence supported by effective priming and memory formation. Importantly, these T cells show the capacity to infiltrate tumors, overcoming immune exclusion through chemokine-driven trafficking and modulation of the tumor microenvironment, enabling effector function within otherwise “cold” tumors. Clinically, such immune activity has translated into delayed relapse in melanoma and disease stabilization in pancreatic cancer, highlighting their potential to control both immunogenic and poorly responsive tumors.

A consistent finding is the strong synergy with checkpoint inhibitors, where vaccines provide novel pools of tumor-specific T cells, and checkpoint blockade sustains their function in the face of inhibitory signaling. This combination underscores their promise as components of multifaceted regimens rather than standalone therapies.

Safety and tolerability remain favorable, with adverse events limited to mild injection reactions or transient systemic inflammation, reflecting the selective, antigen-directed immunity conferred by subunit formulations. Together, these observations establish subunit vaccines as safe, immunologically potent, and particularly effective in combination with checkpoint inhibition.

Conclusion

The recent evolution of subunit cancer vaccine research and development is offering a promising view towards achieving clinical efficacy. Advances in antigen discovery have made it possible to precisely identify immunogenic tumor-specific epitopes, including mutation-derived, splicing-derived, and spontaneously immunogenic antigens. Structural innovations, ranging from virus-like nanoparticles to cytokine-integrated carriers, demonstrate that architecture directly influences immunogenic potency. Adjuvants are now central drivers of immune quality and durability, while RNA-LNP and next-generation carriers provide the technological foundation for effective in vivo delivery.

Clinically, these innovations are moving beyond safety demonstrations to show measurable benefit. Patients are experiencing durable CD8+ and CD4+ T-cell responses, tumor infiltration, delayed relapse, and synergy with checkpoint blockade. For the first time, cancers long resistant to vaccination, including pancreatic carcinoma and hepatocellular carcinoma, are showing signs of a clinical response.

The future of subunit vaccines lies in integration: combining rational antigen selection, precision structural design, optimized adjuvant strategies, and advanced delivery systems within comprehensive treatment regimens. In parallel, addressing tumor microenvironment barriers and improving manufacturing scalability will be critical for widespread application. With continued progress, these vaccines hold the potential to improve cancer care by enabling highly personalized, durable, and safe immune-based interventions across a broad spectrum of malignancies.