Perspectivas en Ciencias Médicas y Biológicas

NARRATIVE REVIEW

Genetics, Genomics & Molecular Oncology

mRNA-Based Therapy in Melanoma, Personalized Neoantigen Vaccines and the Future of Precision Immunotherapy

Terapia basada en ARNm en melanoma: vacunas personalizadas de neoantígenos y futuro de la inmunoterapia de precisión

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Running title: mRNA therapy in melanoma

RESUMEN

El melanoma es una neoplasia altamente inmunogénica y un modelo relevante para la inmunoterapia de precisión. La tecnología de ARN mensajero (ARNm) permite traducir con rapidez la información genómica específica del tumor en tratamientos individualizados, principalmente mediante vacunas que codifican neoantígenos propios de cada paciente. Esta revisión narrativa resume el fundamento biológico, el desarrollo clínico, los sistemas de administración, la integración multiómica y las perspectivas de la terapia basada en ARNm en melanoma. El ensayo aleatorizado de fase IIb KEYNOTE-942 y su seguimiento a 5 años respaldan un beneficio sostenido relacionado con la recurrencia para intismeran autogene (V940/mRNA-4157) combinado con pembrolizumab después de la resección completa de melanoma de alto riesgo. En agosto de 2026, Merck y Moderna anunciaron resultados preliminares positivos del ensayo de fase III INTerpath-001, que alcanzó los desenlaces de supervivencia libre de recurrencia y de metástasis a distancia; las estimaciones detalladas del efecto aún esperan publicación científica completa. El futuro dependerá de mejorar la priorización de neoantígenos, la administración mediante nanopartículas lipídicas, la integración multiómica, las combinaciones terapéuticas y el seguimiento molecular longitudinal.

Palabras clave: Melanoma; ARNm; Vacunas; Neoantígenos; Inmunoterapia; Medicina de precisión.

ABSTRACT

Melanoma is a highly immunogenic malignancy and a leading model for precision immunotherapy. Messenger RNA (mRNA) technology enables rapid translation of tumor-specific genomic information into individualized treatment, most notably through vaccines encoding patient-specific neoantigens. This narrative review summarizes the biological rationale, clinical development, delivery systems, multi-omic integration, and future directions of mRNA-based therapy in melanoma. The randomized phase IIb KEYNOTE-942 study and its 5-year follow-up support durable recurrence-related benefit from intismeran autogene (V940/mRNA-4157) plus pembrolizumab after complete resection of high-risk melanoma. In August 2026, Merck and Moderna announced positive topline phase III INTerpath-001 results, reporting that the combination met the recurrence-free survival and distant metastasis-free survival endpoints; detailed peer-reviewed phase III effect estimates remain pending. Future development will depend on improved neoantigen prioritization, lipid nanoparticle delivery, integration of genomics and other omics, combination strategies, and longitudinal molecular monitoring. mRNA therefore represents not only a vaccine format but a programmable therapeutic platform that may support increasingly adaptive precision immunotherapy in melanoma.

Keywords: Melanoma; mRNA; Vaccines; Neoantigens; Immunotherapy; Precision medicine.

INTRODUCTION

Melanoma represents a major model for precision oncology because of its substantial genomic complexity, high tumor mutational burden, and strong interaction with the immune system. Immune checkpoint inhibitors and BRAF/MEK-targeted therapy have transformed the management of advanced melanoma, yet primary resistance, acquired resistance, and disease recurrence remain important clinical challenges. [1,2]

These limitations have stimulated therapeutic strategies capable of generating highly specific and durable antitumor immunity. Messenger RNA (mRNA) has emerged as a rapidly developing platform because it does not require genomic integration and is translated transiently in the cytoplasm, allowing flexible therapeutic design. [3]

In melanoma, the most clinically advanced concept is personalized neoantigen mRNA vaccination. Instead of targeting a shared tumor-associated antigen, individualized vaccines encode a selected set of neoantigens generated by somatic mutations in an individual patient's tumor. [4,5]

Contemporary cancer vaccine development increasingly emphasizes tumor-specific neoantigens, while next-generation sequencing and computational prediction have enabled increasingly individualized vaccine design. [5,6]

LITERATURE SEARCH AND SELECTION APPROACH

This narrative review was developed from a focused and iterative literature search intended to capture established evidence and recent scientific, technological, and clinical developments in mRNA-based cancer immunotherapy, with particular emphasis on melanoma. PubMed/MEDLINE and Google Scholar were searched, and reference lists of key publications and relevant clinical studies were screened manually. Search terms included combinations of mRNA, messenger RNA, melanoma, cancer immunotherapy, personalized cancer vaccine, individualized neoantigen vaccine, mRNA-4157, V940, intismeran autogene, pembrolizumab, KEYNOTE-942, and INTerpath-001.

Literature selection was guided by scientific relevance, methodological quality, clinical significance, and contribution to the evolving understanding of mRNA-based precision oncology. Priority was given to peer-reviewed original research, clinical trials, translational studies, and authoritative reviews addressing biological rationale, therapeutic mechanisms, clinical efficacy, safety, delivery, and emerging applications.

Because the field is evolving rapidly, the literature was updated during manuscript revision to incorporate recent developments in individualized neoantigen vaccines, computational prioritization, multi-omic tumor profiling, artificial intelligence, and clinical translation. The long-term KEYNOTE-942 results and the publicly announced phase III INTerpath-001 topline findings were considered separately according to their evidence status.

As a narrative rather than systematic review, study selection was expert-driven and was not based on a predefined systematic-review protocol. This design permits integration of established evidence with emerging developments but does not support claims of exhaustive literature coverage.

BIOLOGICAL RATIONALE FOR MRNA THERAPY IN MELANOMA

Melanoma frequently carries a high number of somatic mutations. A subset of these alterations can generate peptide sequences absent from normal tissues that, after processing and presentation by major histocompatibility complex molecules, may be recognized as neoantigens by T cells. [7,9-11]

Melanoma is also responsive to immune checkpoint blockade, demonstrating that tumor-reactive T cells can exist within the tumor microenvironment but may be functionally constrained by inhibitory pathways such as PD-1/PD-L1 and CTLA-4. Increasing the frequency and diversity of tumor-specific T cells can therefore complement checkpoint inhibition. [2,8]

mRNA vaccines provide transient intracellular expression of multiple encoded neoantigens. After uptake by antigen-presenting cells, the translated proteins are processed into antigenic peptides that can be presented through MHC class I and class II pathways, supporting activation of CD8+ cytotoxic and CD4+ helper T cells. [4,9,10]

Encoding multiple neoantigens in a single therapeutic construct may broaden immune recognition and reduce dependence on any single antigen. In this sense, individualized mRNA vaccination can be viewed as genomically informed immunotherapy in which tumor sequencing is translated directly into a patient-specific therapeutic product. [5,10,11]

PERSONALIZED MRNA NEOANTIGEN VACCINES

Development of a personalized mRNA vaccine generally begins with tumor tissue and matched normal material. Tumor DNA and, when available, RNA are analyzed to identify somatic alterations and characterize their expression. Candidate neoantigens are prioritized using factors such as mutation type, transcript abundance, HLA genotype, predicted peptide processing, MHC binding, and evidence of likely presentation. [10,28]

The candidate list is then filtered to select neoantigens with the greatest probability of being naturally processed and immunogenic. The selected sequences are incorporated into an mRNA construct, formulated in a delivery system, and administered with the aim of generating tumor-specific T-cell responses. [10,23,28]

Tumor biopsy → sequencing → mutation identification → neoantigen prediction → HLA assessment → prioritization → mRNA synthesis → formulation → vaccination → T-cell activation

One of the most advanced examples is intismeran autogene (V940; formerly mRNA-4157), an individualized mRNA-based neoantigen therapy designed from the mutational profile of each patient's tumor and capable of encoding up to 34 patient-specific neoantigens. [12,13]

This approach is particularly relevant to melanoma because its mutational burden can provide a large pool of candidate neoantigens. Mutation number alone, however, is insufficient: a useful target must be expressed, processed, presented, and immunologically recognizable. [11,15,28]

CLINICAL DEVELOPMENT: FROM PHASE II TO PHASE III

The KEYNOTE-942 clinical trial (NCT03897881) evaluated the combination of pembrolizumab and individualized neoantigen mRNA therapy (V940) in patients with resected high-risk melanoma.

primary analysis provided randomized evidence that an individualized neoantigen mRNA therapy could augment PD-1 blockade in the adjuvant setting. [12]

Five-year follow-up published in 2026 included 157 randomized patients and showed sustained improvement in recurrence-free survival (HR 0.510; 95% CI 0.294-0.887) and distant metastasis-free survival (HR 0.411; 95% CI 0.200-0.843) with intismeran plus pembrolizumab compared with pembrolizumab alone. Overall survival remained exploratory (HR 0.471; 95% CI 0.165-1.345), and no new safety signals were identified. [13]

For phase III INTerpath-001, Merck and Moderna announced positive topline results on August 19, 2026. In 1,137 patients with completely resected stage IIB-IV cutaneous melanoma, the

combination met the primary endpoint of recurrence-free survival and the key secondary endpoint of distant metastasis-free survival at a prespecified interim analysis. Detailed phase III effect estimates and a full peer-reviewed dataset were not yet available at the time of this revision, so the findings should be described as company-announced topline results rather than as a published comparative dataset. [14]

Table 1. Key clinical evidence for individualized mRNA neoantigen therapy in melanoma

Clinical trial	Phase / population	Treatment	n	Main findings	Evidence status
KEYNOTE-942 (NCT03897881)	Phase IIb; resected stage IIIB-IV cutaneous melanoma	Intismeran autogene + pembrolizumab vs pembrolizumab	157	5-year RFS HR 0.510 (95% CI 0.294-0.887); DMFS HR 0.411 (95% CI 0.200-0.843); exploratory OS HR 0.471 (95% CI 0.165-1.345); no new safety signals.	Peer-reviewed 5-year results published in 2026.
INTerpath-001 (NCT05933577)	Phase III; resected stage IIB-IV cutaneous melanoma	Intismeran autogene + pembrolizumab vs pembrolizumab	1,137	At prespecified interim analysis, RFS and DMFS endpoints were reported as statistically significant and clinically meaningful; detailed effect estimates not yet disclosed.	Positive topline announcement Aug 19, 2026; full peer-reviewed phase III data pending.

RFS: recurrence-free survival; DMFS: distant metastasis-free survival; OS: overall survival. Phase III information reflects publicly announced topline results, not a complete peer-reviewed dataset.

Taken together, the phase IIb publication and the phase III topline announcement strengthen the clinical rationale for personalized mRNA vaccination in adjuvant melanoma while preserving an important distinction between mature peer-reviewed estimates and newly announced phase III findings. [12-14]

BEYOND VACCINES: MRNA AS A THERAPEUTIC PLATFORM

Although personalized neoantigen vaccination is the leading clinical application, mRNA can also encode immune-stimulatory proteins such as cytokines or costimulatory molecules. Transient expression may permit therapeutic signaling without permanent genetic modification. [16,40]

Another direction is mRNA-mediated modulation of the tumor microenvironment. Melanoma progression is influenced by regulatory T cells, tumor-associated macrophages, dysfunctional myeloid populations, and other immunosuppressive mechanisms; mRNA formulations may eventually be used to deliver combinations designed to make the microenvironment more permissive to antitumor immunity. [17,41]

mRNA can also be used for transient ex vivo reprogramming of immune cells, allowing controlled expression of therapeutic receptors or signaling molecules without permanent genomic alteration. [18]

These applications support viewing mRNA as a programmable therapeutic platform rather than only as an RNA vaccine technology.

LIPID NANOPARTICLES AND NEXT-GENERATION DELIVERY SYSTEMS

The clinical success of mRNA therapeutics depends strongly on delivery. Naked mRNA is vulnerable to degradation and has limited membrane permeability, making lipid nanoparticles (LNPs) a major delivery platform. [19]

Modern LNP formulations can protect mRNA, facilitate cellular uptake, and promote endosomal escape, allowing cytoplasmic release and translation. In melanoma, formulation can influence biodistribution, antigen-presenting-cell targeting, and the magnitude of the immune response. [19,20]

Current melanoma vaccine research includes both LNP and dendritic-cell-based delivery strategies. Future systems may include tumor- or dendritic-cell-targeted nanoparticles, biodegradable or stimuli-responsive carriers, intradermal microneedles, controlled-release hydrogels, exosome-inspired delivery, and tissue-specific formulations. [21,23]

Local or lymph-node-directed delivery is especially attractive because effective vaccine responses depend on efficient antigen presentation and lymphocyte priming. [22]

INTEGRATION WITH GENOMIC AND MULTI-OMIC PRECISION MEDICINE

The next evolution of mRNA therapy is likely to integrate multiple molecular layers rather than rely exclusively on DNA mutation calls. Current neoantigen pipelines already combine somatic variants with HLA information and selected expression data, but melanoma biology is substantially more complex. [23,27,28]

- **Genomic sequencing:** identification of somatic mutations, structural variants, and clonality.
- **RNA sequencing:** confirmation that candidate alterations are transcriptionally expressed.
- **HLA typing and immunopeptidomics:** assessment of whether candidate peptides can be naturally presented.
- **Single-cell and spatial profiling:** characterization of intratumoral heterogeneity, immune states, and spatial organization.
- **Epigenomic and proteomic profiling:** additional evidence for regulatory context and protein expression.

Integrating these layers could support multi-omic neoantigen prioritization, in which targets are selected not simply because a mutation exists, but because evidence supports the full chain from genomic alteration to expression, presentation, and immune recognition. Immunopeptidomics can provide direct evidence of naturally presented peptides, while melanoma-specific multi-omic studies increasingly link tumor-intrinsic and immune features. [24,26,27,38]

For melanoma, this framework also creates a natural intersection between genomics, transcriptomics, epigenetics, microRNA biology, and immunotherapy. [27,33]

MRNA THERAPY AND MOLECULAR HETEROGENEITY

A major challenge for personalized mRNA vaccination is the molecular and cellular heterogeneity of primary and metastatic melanoma. Distinct subclones may carry partially overlapping but non-identical somatic alterations, and a neoantigen restricted to a minor subclone may elicit immunity without providing sufficient recognition of the dominant malignant population. Immune selection can further favor expansion of cells that lose or reduce expression or presentation of targeted antigens. [25-27,41]

Next-generation neoantigen selection should therefore consider predicted immunogenicity together with clonality, expression, HLA presentation, and biological relevance.

Prioritizing clonal or truncal alterations may reduce opportunities for immune escape, while sampling multiple lesions and using circulating tumor DNA could improve representation of tumor evolution. [26-28,39]

These concepts support an adaptive model of mRNA vaccination in which longitudinal molecular monitoring identifies emerging clones, antigen loss, or changes in the tumor microenvironment and informs subsequent redesign of the antigen repertoire. This remains investigational but is biologically consistent with the dynamic nature of melanoma. [27,39,41]

COMBINATION THERAPY: THE FUTURE OF MRNA TREATMENT

Clinical evidence currently supports mRNA-based therapy primarily as part of combination immunotherapy rather than as a standalone modality. Personalized mRNA vaccination can expand tumor-reactive T cells, while checkpoint blockade can enhance their activity by reducing inhibitory signaling. The most clinically advanced example is intismeran autogene plus pembrolizumab. [12-14,29,30]

Targeted therapy is also relevant in BRAF-mutant melanoma because BRAF/MEK inhibition can alter tumor signaling, antigen expression, and the immune microenvironment, although optimal sequencing and duration remain uncertain. [31]

Response to individualized mRNA therapy is unlikely to depend on a single biomarker. BRAF/NRAS status, tumor mutational burden, HLA genotype, neoantigen quality, antigen expression, immune infiltration, and tumor evolution may all contribute. Multidimensional molecular stratification may therefore be required to guide patient selection, combination partners, treatment sequence, and the vaccine repertoire. [11,26,27,32,33]

FUTURE PERSPECTIVES

Future advances are likely to arise from the integration of artificial intelligence, multi-omic profiling, and programmable RNA technologies. AI-based approaches may improve neoantigen prioritization by combining genomic, transcriptomic, HLA, immunopeptidomic, and proteomic features to increase the probability of selecting antigens that are expressed, presented, and immunogenic. [27,36]

Faster and more standardized manufacturing will also be essential to reduce the interval between tumor profiling and administration of individualized therapy. The programmability of mRNA creates opportunities for multiplexed delivery of neoantigens with immunomodulatory components and for iterative redesign without changing the underlying platform. [29,34,35,37,40]

Longitudinal monitoring using liquid biopsy and circulating tumor DNA could help detect residual disease, clonal evolution, antigen loss, and emerging resistance, providing a biological basis for adaptive redesign of personalized mRNA constructs. [39,41]

Although this adaptive framework remains constrained by prediction accuracy, manufacturing time, regulation, cost, and clinical logistics, it could move melanoma treatment from a static personalized intervention toward a therapeutic strategy that evolves with the molecular characteristics of the tumor. [15,41]

CONCLUSIONS

mRNA technology has progressed from an experimental molecular concept to a clinically advanced platform for precision cancer immunotherapy. Melanoma is a particularly compelling model because of its mutational burden, immunogenicity, and extensive molecular characterization. The 5-year KEYNOTE-942 results provide peer-reviewed evidence of sustained recurrence-related benefit for intismeran autogene plus pembrolizumab, while the positive INTerpath-001 phase III announcement represents an important but still topline clinical milestone for which detailed peer-reviewed effect estimates remain pending. [12-14,34,37]

Future development will require stronger neoantigen prioritization, integration of genomic and multi-omic evidence, improved delivery, and explicit management of tumor evolution and immune escape. Artificial intelligence and longitudinal molecular monitoring may help connect molecular diagnosis with iterative therapeutic design. [27,36,38,39,41]

The broader significance of mRNA lies in its programmability: therapeutic information can be redesigned while the underlying delivery and manufacturing architecture is retained. Whether increasing molecular personalization can consistently translate into durable clinical benefit, and whether therapeutic redesign can remain biologically matched to an evolving tumor, are central questions for the next generation of melanoma precision immunotherapy. [35,40,41]

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