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Review

Personalized Neoantigen-Based Cancer Vaccines Have Advanced Rapidly, Though Several Key Challenges Remain

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Abstract: Neoantigen-based personalized vaccines have emerged as an important innovation in the field of precision oncology through utilizing unique tumor somatic mutations to stimulate a targeted anti-tumor immune response. Unlike common tumor antigens, neoantigens can be recognized by the immune system as foreign because they exist only on tumor cells and thus do not contribute to any autoimmune reactions as a result of central immune tolerance. The emergence of techniques in next-generation sequencing, mutational profiling, and bioinformatics has made it possible to precisely identify neoantigens. In addition, breakthroughs in vaccine technology, such as synthetic long peptides, dendritic cell vaccination, and nucleic acid vaccination, have facilitated its clinical application. Studies have shown that neoantigen-based personalized vaccines are safe and can induce potent T-cell-mediated anti-tumor immune responses, especially when combined with immune checkpoint inhibitors. Randomized trials have indicated their potential in decreasing cancer recurrence. There still remain some limitations in developing personalized neoantigen vaccines due to the problem of tumor heterogeneity, immune evasion, neoantigen prediction, immunosuppression environment in the tumors, and high cost and long manufacturing time for personalized vaccines. This paper provides an overview of current methods and new approaches for neoantigen identification and vaccine development.

Keywords: Immunotherapies; Next-Generation Antigen; mRNA; T-Cell Responses; Dendritic Cell-Based Vaccines

1. Introduction

Cancer immunotherapy, which utilizes the immune system to recognize and destroy cancer cells, has brought about a revolution in the field of oncology in the last ten years, and using immune checkpoint inhibitors (ICIs) for various types of cancer is one of the most successful approaches [1]. Nevertheless, a significant proportion of the population does not show an initial response or shows acquired resistance to the therapy, making it imperative to adopt more personalized approaches [2]. Personalized cancer vaccines based on neoantigens have been developed to address this issue and induce a targeted immune response against existing tumors, which is very different from conventional vaccines used to prevent infectious diseases [3,4]. The unique sequence of peptides resulting from somatic mutations of the tumor cells of the patient constitutes the basis of this therapy. It is the perfect target to destroy tumor cells without the risk of autoimmunity and central tolerance, as this sequence is absent from the

normal human genome [5]. These vaccines are tailored to fit an individual patient's needs according to the mutations in their cancer, whereas in cancer patients with the same type of cancer, when viewed under a microscope, the mutations in their cancer can differ. It means that a treatment that works well for one cancer patient may not work equally well for another [6]. Customized therapy constitutes the highest degree of precision medicine, which entails the sequencing of the patient's tumor and normal tissue, computer prediction of the immunogenic neoantigen, and the design of a vaccine that targets the unique mutational signature of the tumor [7]. The biological basis and the technological, clinical, and major challenges associated with this exciting field will be extensively reviewed in this article. The shift from the universal treatment paradigm to the really tailored medical intervention marks one of the most important changes in contemporary oncology. The initial successes of immunotherapy agents such as ICIs prove the enormous potential of the immune system as an ally, as well as the limitations of the latter [8]. Sometimes, the treatment for cancer can result in the immune system attacking healthy cells, thereby causing side effects. However, one of the key things to note is that cancer is a genetic disease that results from random DNA mutations. The mutations result in cancer, and they are different for different patients and different cancers. In the past, this has been a problem for patients suffering from cancer. However, modern science has been able to utilize this information to treat patients. Modern science targets neoantigens, which are new proteins that result from mutations. The new proteins are not found in healthy cells, and this makes it easy for the body's immune system to recognize them and attack them. This method is advantageous because it helps to distinguish between cancer and healthy cells. In the past, this could not be possible because cancer cells were being targeted through tumor-associated antigens (TAAs), which are normal proteins that are overexpressed in cancer cells. However, these antigens are also found in healthy cells [9]. The purpose of this strategy is to provide an almost accurate cancer treatment, just like a laser that attacks cancer cells specifically without affecting the surrounding healthy tissues. Nevertheless, there are several factors to consider to accomplish this goal. Firstly, this strategy demands sophisticated knowledge in genomics, computational biology, and biopharmaceutical engineering. Secondly, the whole process starts with genomic analysis of the patient's tumor and continues with vaccine development under the conditions of GMP. Thirdly, time is another factor worth considering when applying this personalized vaccine. The whole process from tumor mutation identification to personalized vaccine production should be completed as fast as possible since cancer is characterized by its rapid progression. Additionally, there are also concerns relating to the cost-effectiveness of such a personalized treatment. Thus, the development of a personalized vaccine may turn out to be rather expensive and not affordable. This review highlights the scientific and technological innovations associated with personalized neoantigen vaccines along with the main obstacles in their way to becoming medicine, which is a regular practice in precision medicine [10]. The conventional cancer treatment vs. immunotherapy is mentioned in **Figure 1**.

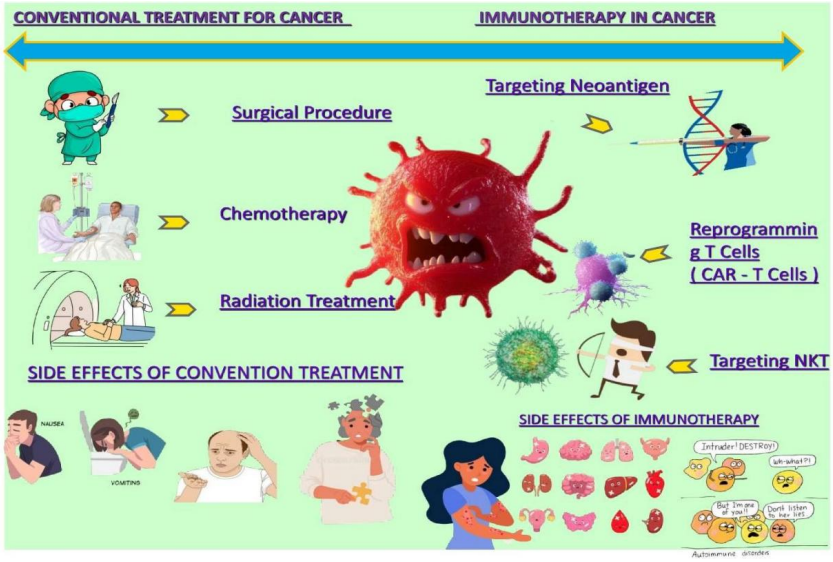

Figure 1. Conventional Cancer Treatment vs. Immunotherapy.

2. Host Immune Landscape and Its Impact on Vaccine Efficacy

The term "host immune landscape" is used to describe the immunological status of the individual, which includes immune cells, immune function, cytokine profile, genetic makeup such as HLA type, tumor microenvironment, and general immune health. In the context of pNV, the immune landscape is a key factor that influences therapeutic response.

Baseline Immune Status

The baseline immunocompetence of the individual is a key factor that influences vaccine response, and this is characterized by:

- T-cell repertoire diversity: This is a key factor that influences vaccine response, and a highly diverse and functional TCR repertoire is likely to recognize neoantigens encoded by the vaccine.
- Lymphocyte count and function: In immunocompromised individuals, chemotherapy, corticosteroids, and disease can impair vaccine response.
- Age-related immunosenescence: In elderly individuals, there is a general reduction in naive T cells and antigen presentation capacity. An "immune-inflamed" baseline status, as indicated by the presence of baseline $CD8^+$ T cells, is likely to respond better to vaccine therapy than an "immune-desert" status. The genetic disarray found in cancer cells is directly translated into neoantigens by the immune system. Many mutations have been discovered through tumor mutational landscapes, where exposure to carcinogens, defective DNA repair, or mistakes made by DNA polymerases are responsible for the process [11]. Not all these mutations give rise to neoantigens that possess immunogenic qualities; only certain mutations do [12].
- Neoantigen types according to their origin may include: SNV-derived neoantigens: They originate from point mutations causing a change in just one amino acid in the protein encoded by them. Such kinds of mutations are very common, though they exhibit weak affinity for MHC [13].
- Indels-derived neoantigens: These arise due to small frame-shift insertions or deletions that give rise to long stretches of new amino acid sequences, leading to immunogenic FSPs. These are more common in MSI tumors [14]. Chromosome translocations that result in chimeric proteins with completely new junctions produce fusion gene neoantigens. These may be strong clonal antigens [15]. Additional sources: Incorporate antigens from non-canonical sources such as viral oncogene antigens (e.g., HPV E6/E7), cryptic translation, and retroviral elements [16]. A number of features of a neoantigen's immunogenicity are rather complicated. First of all, it is the ability of the mutated peptide to bind with an individual's HLA molecules [17]. It is very important to use strong binders here. Secondly, the neoantigen should be efficiently processed and presented by APCs [18]. Thirdly, there should be at least some T-cell clones in one's repertoire with T-cell receptors that can perceive the peptide-HLA complex without getting destroyed by central tolerance [19]. One's sequence's foreignness, which usually depends on its peculiarity [20]. Compared to a human proteome and a wild-type peptide, it becomes the most important determinant of this process [20]. However, very few mutations succeed in completing their biological journey as neoantigens from a mutation through random changes in the genome into a target of destruction by the immune system [21]. In the first place, the transcription and translation processes faithfully decode the altered DNA and translate the information into a mutant protein [22]. Second, the proteasomes, whose function is to generate short peptides, act upon these proteins [23]. Third, an important gatekeeper on the road to the antigen-presenting process is the major histocompatibility complex (MHC), otherwise called the human leukocyte antigen in humans [24]. However, the immune system will never recognize a peptide that cannot firmly occupy the HLA groove because binding to HLA is non- negotiable. Since each person's particular HLA allotype has different peptide-binding preferences, this step introduces the first layer of patient-specificity [25]. One patient with HLA-A 02:01 may have a mutation that produces a potent neoantigen, while another patient with HLA-B 27:05 may not have it at all. After that, the peptide-HLA combination is carried to the cell surface, where it functions as a molecular display [26]. A cytotoxic $CD8^+$ T cell's TCR needs to bind to this complex with enough affinity to activate [27]. The immune system, however, is designed to prevent self-reactivity; clones that exhibit significant reactivity to self-peptides, including the wild-type form of the mutant peptide, are either eliminated or energized during T-cell formation in the thymus, a process known as central tolerance [28]. Consequently, the most effective neoantigens are those that result from mutations that produce peptides with a high affinity for HLA but are also sufficiently distinct from any self-

peptide to have avoided this purging. Immunogenicity is predicted by this "foreignness" or dissimilarity [29]. Because they can produce whole new amino acid sequences that the growing immune system has never seen before, neoantigens resulting from frameshift mutations or fusion genes frequently score highly here [30]. On the other hand, a frequent SNV may alter just one amino acid, producing a peptide that is still very similar to self [31]. This might either cause the T-cell repertoire to become ignorant or activate low-affinity T cells that are unable to perform strong effector activities [32]. New developments in biology add even more intricacy to this core belief. This mechanism is actively undermined by the tumour microenvironment [33]. The antigen presentation mechanism of tumour cells and dendritic cells can be compromised by elements such as low pH, food restriction, and immunosuppressive cytokines [34]. Moreover, not every neoantigen in the tumour mass is produced equally. Only a small percentage of cancer cells contain subclonal neoantigens, which provide a movable target and, if the dominant clone is eradicated, can result in immune escape [35]. In order to guarantee that a pre-existing, high-affinity T-cell clone exists and can be mobilized, the ideal neoantigen for vaccine targeting is clonal, has a high HLA binding affinity, comes from a highly expressed gene, and encodes a sequence that is maximally distinct from the human proteome [36]. Improving the computer prediction of which of thousands of mutations matter requires an understanding of this complex biological background [37].

3. Neoantigen Prediction

Tumor sampling and sequencing are the first steps in designing a personalized vaccine against cancer. Tumor DNA and RNA are collected from a tumor sample by a biopsy, while a blood sample is used to collect normal or germline variations [38].

Whole-exome sequencing is used to identify mutations in coding regions, while whole-genome sequencing is used to identify mutations in non-coding regions and structural variations [39]. RNA sequencing is done to verify whether these genes that have mutations are indeed expressed in tumor cells [40]. Different type of bioinformatics tools are then used to analyze this information. These include tumor-specific mutations, determining what type of HLA the patient has by analyzing the sequence data, and determining how well a mutated peptide will bind to MHC molecules [41]. A tool such as NetMHCpan is often used for this step. Finally, tumor antigens are ranked based on various criteria such as how well it binds, gene expression levels, and how commonly it is expressed in tumor cells [42]. However, current neoantigen prediction tools use more than just binding affinity between a peptide and MHC molecules [43]. They also use other factors such as how stable a peptide–MHC complex is, how likely it is to be seen by T-cells, as well as features that have been associated with successful neoantigens in clinical trials [44]. Moreover, current prediction tools are continually being improved upon through learning from experimental data, such as T-cell assays and studies conducted through mass spectrometry to identify peptides that are actually presented on cancer cells [45,46]. Another challenge is that there is a need to understand how to predict which neoantigens are likely to trigger an immune response in an individual patient [47]. This requires an understanding of how to predict which neoantigens are likely to trigger an immune response in an individual patient. After this, bioinformatics tools are used to compare the tumor DNA with normal DNA to identify real cancer-specific mutations while filtering out other variations such as those caused by inheritance [48]. This can be done using tools such as Mutect2 and GATK. The next step is to identify the HLA types of the patient, as this determines how well a peptide binds to an HLA molecule. For each mutation identified, tools such as NetMHCpan predict how well each of the peptides that can be produced from this mutation binds to the HLA molecule of the patient. This binding affinity is often given as an IC_{50} score [49]. However, it is also important to identify whether a particular peptide can be presented to a T-cell. Some peptides may never be produced due to structural features of a protein, so tools such as NetChop are also used to predict whether a particular peptide can be processed correctly [50]. Another important step is to use RNA sequencing to make sure that the gene that has been mutated is also being expressed in the first place [51]. Another key factor is clonality. Mutations that are present in all tumor cells, called clonal, are more valuable targets compared to those present only in a fraction of tumor cells, called subclonal, because there is less risk of immune escape [52]. In conclusion, neoantigen selection is a multi-faceted optimization problem involving different criteria, such as binding strength, expression level, processing efficiency, and clonality [53]. Modern workflows rely on machine learning algorithms that were trained on experimental data and can predict immunogenicity, connecting theoretical results with experimental facts and allowing precise cancer vaccine design [54]. Determination of Tumor-Specific Antigens mentioned in **Figure 2**.

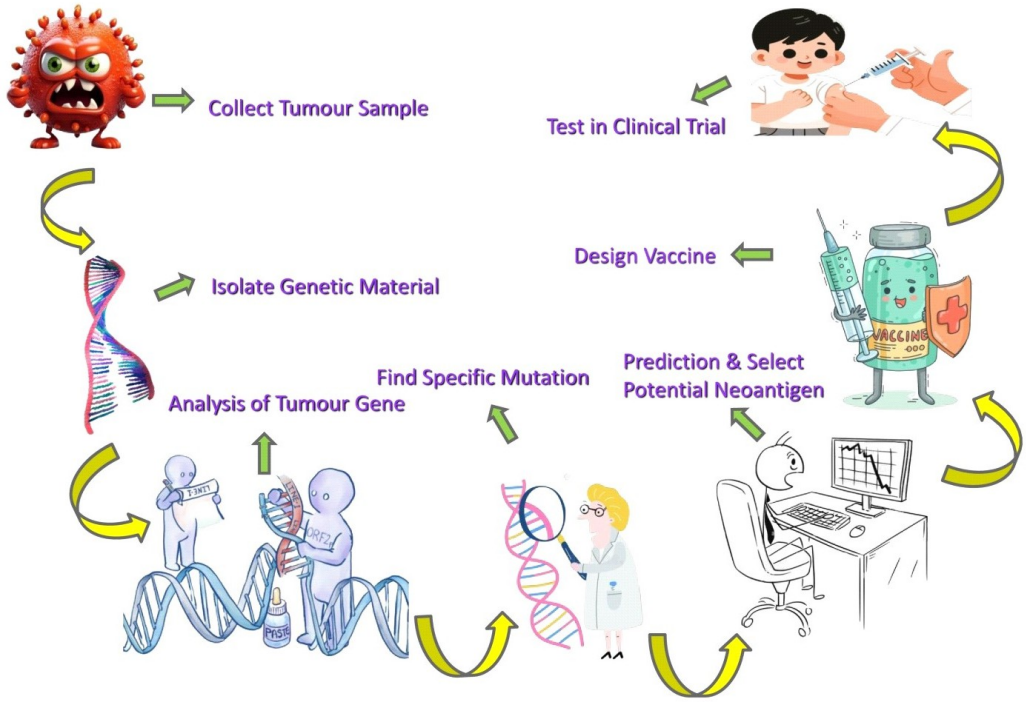

Figure 2. Determination of Tumor-Specific Antigens.

4. Vaccine Platforms: From Bench to Bedside

In case of immune activation antigen selection, synthetic long peptides (SLPs) are a very good option because they are safe and stable, but their population coverage may be limited by the need for adjuvants and particular HLA matching [55,56]. Second, vaccines involving nucleic acids: mRNA vaccines allow for endogenous antigen processing and robust $CD8^+$ T-cell responses by encoding neoantigen sequences that are translated in vivo. One of their main advantages is their quick, cell-free production [57]. DNA vaccines are similarly adaptable, but they have issues with human immunogenicity and delivery efficiency [58]. Vaccines for dendritic cells (DC): Neoantigens are loaded into autologous DCs ex vivo and then reinfused. Although it is costly and logistically challenging, this strategy specifically targets professional APCs [59]. The neoantigen genes are delivered by lipid nanoparticles (LNPs) and viruses like vaccinia and adenoviruses, but in that case, pre-existing immunity also affects. The main limitation is the presence, while the advantages include high transduction efficiency as well as intrinsic adjuvant properties [60]. The choice for clinical development is also affected by the special advantages and disadvantages of the different systems regarding immunogenicity, speed, cost, and potential for the induction of $CD4^+$ vs. $CD8^+$ T cells [61,62]. The most advanced vaccine for clinical use is the peptide-based vaccine, which consists of the synthesis of the predicted neo-antigen peptides, along with the administration of a strong adjuvant such as poly-ICLC [63,64]. The manufacturing of personalized vaccines is a patient-specific process mentioned in **Figure 3**. The ideal platform must strike a balance between immunogenic potency and practical considerations, such as cost-effectiveness for healthcare systems, speed of manufacturing for patients with aggressive disease, and the capacity to elicit a broad, polyfunctional, and long-lasting T-cell response that includes both $CD8^+$ "killers" for instant tumor destruction and $CD4^+$ "helpers" essential for memory [65].

The area is still developing, and combination platforms are being researched to increase immunological potency. However, the recent clinical success of mRNA-LNP platforms suggests that they now offer the best compromise [66,67]. For synthesizing vaccines, a multistep process biopsy to vial: biopsy → bioinformatics and sequencing (4–6 weeks) → vaccine construct design and quality control (2–3 weeks) → GMP production (4–8 weeks) → release testing → administration. A significant obstacle is the 10–20 week turnaround time, especially for patients with aggressive disease [68].

Because each product is unique, scalability is hindered [69]. Although the FDA and other regulatory bodies

are creating frameworks for "off-the-shelf" customized treatments, individual release testing is still necessary for every batch [70,71]. Adoption of the healthcare system and equitable access are severely hampered by cost considerations, which frequently exceed hundreds of thousands of dollars per patient [72].

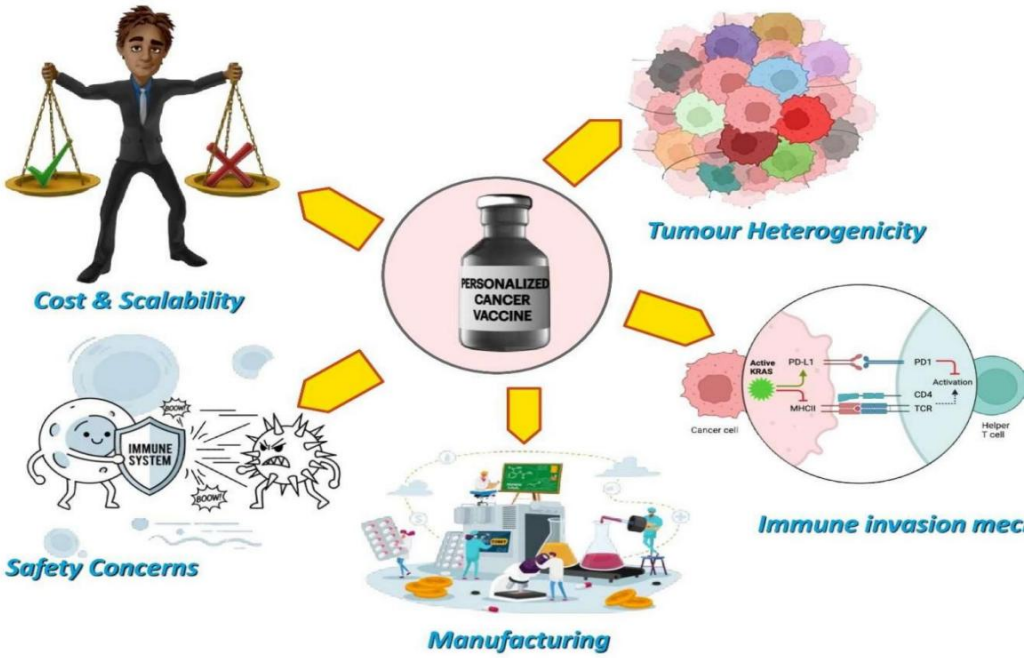

Figure 3. The manufacturing of personalized vaccines is a patient-specific process.

5. Immune Monitoring and Biomarkers

Furthermore, advanced immune monitoring is required to assess whether or not these neoantigen vaccines are actually working, as tumor size is not necessarily a measure of immune response. One of the main goals is to determine if specific T cells for these antigens are even present in the body and if they are active. Multiple different methods are used, including Enzyme-Linked Immuno Spot (Assay) ELISPOT and intracellular cytokine staining (ICS), which assess T cell capacity to produce cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) in response to a specific antigen [73–76]. T cell receptor sequencing is also performed for the tracking of vaccine-induced expansion and diversity of vaccine-reactive T cell clones in both blood and tumor tissues [77]. Furthermore, multiplexed assays for peptides with MHC tetramers can directly detect neoantigen-specific T cells without the need for any prior stimulation [78]. Many different factors affect vaccine response, including having certain immune-related genes already active, a high number of mutations in the tumor, and an increase in T cells that can recognize tumor-specific antigens in the blood. It is also important to study the tumor environment before and after treatment to understand how the vaccine is working. An immunosuppressive TME, with high levels of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), can inhibit vaccine-induced immune responses. Advanced immune monitoring uses several approaches to determine the efficacy of neoantigen vaccines on the level of the immune system [79]. One of the recent breakthroughs in the field is peptide-MHC (pMHC) tetramer technology, which enables scientists to detect antigen-specific T cells in the bloodstream, even in minute quantities. The technology uses fluorescent HLA molecules with bound peptide, which bind to T cells with the same specificity as the bound peptide, allowing the T cells to be quantitatively measured [80]. And also, the environment is an important factor for measuring vaccine activity in active immune cells, such as T cells, and signals such as interferon; the vaccine usually works better. On the other hand, if the tumor environment is less active, has high PD-L1 levels, and contains suppressive immune cells like Tregs, MDSCs, and M2 macrophages, the vaccine may not work as well [81]. Blood-based markers can also help show how well a vaccine is working. They help us study the type and behavior of T cells. If T cells have memory markers CCR7 and CD45RO, which means they can provide long-term protection, markers like CD38 and HLA-DR are shown in blood in the case of T cells that are active, and in the

case of tiredness or exhaustion, PD-1 is shown in blood [82]. From small-scale proof-of-concept studies to randomized clinical trials that have shown measurable survival benefits, the translation of tailored neoantigen vaccines from an interesting hypothesis to an evidence-based therapeutic tool has been achieved [83]. The establishment of the fundamental principles was significantly helped by the initial seminal studies, which used DC or peptide vaccines to treat melanoma and glioblastoma. They were, of course, conclusive evidence that a vaccine based on the patient's own tumor mutations could, indeed, be used to generate tumor-specific T cells that could migrate to the tumor sites. However, the rates of tumor regression were often low in the mono-therapy settings, which showed that activating the anti-tumor immune response was not the same as overcoming the tumor's immune suppressive microenvironment [84].

Rational combination approaches, especially with ICI, became possible as a result of this understanding. The latest study on KEYNOTE 942 is the turning point in this story. The study has found that the addition of the mRNA vaccine mRNA-4157 to the PD-1 inhibitor, pembrolizumab, resulted in a statistically significant improvement in recurrence-free survival (RFS) when given as an adjuvant treatment for resected melanoma. This suggests that there is a strong synergy between the two treatments, as the ICI removes the brakes that prevent the action of tumor-specific T cells, while the vaccine increases the diversity of the T cells [85]. Considering that the purpose of the adjuvant setting—post-surgery—is to eliminate any microscopic disease and prevent relapse, in which a robust and personalized immune response can actually cure disease, the data are particularly promising in this setting. Additionally, in combination with standard-of-care chemoradiation and other immunotherapies targeting various cancers, such as pancreatic and glioblastoma, promising data have been observed in preclinical and clinical trials [86]. In fact, early studies have shown that neoantigen vaccines can induce measurable T-cell responses in pancreatic cancer, a notoriously difficult-to-treat disease with immunotherapy. In combination with chemotherapy and checkpoint inhibition, it may actually help slow disease progression [87,88]. The neoantigen concept has also revolutionized adoptive cell therapy in addition to vaccinations. In fact, "neoantigen-targeted" TIL therapy, which has shown remarkable response rates in certain epithelial cancers, involves the expansion of T cells that specifically recognize neoantigens of individual patients [89]. With AEs limited to mild-to-moderate vaccine-associated reactions and no discernible impact on the toxicity profile of combination therapies such as ICIs, the safety profile remains an impressive feature among all the platforms. Overall, the clinical data gathered paints a promising picture of a therapy that is immunogenic, safe, and beginning to show promising results when used in the right combinations [90]. Expanding the successes to a broader range of cancers, identifying the optimal therapeutic combinations and sequences, and identifying the biomarkers that can help predict which patients will benefit the most from this complex and expensive intervention are the next hurdles. Clinical Trials of Customized Neoantigen Immunizations are mentioned in **Table 1**.

Table 1. Pivotal Clinical Trials of Customized Neoantigen Immunizations.

ID	Phase	Type of Cancer	Platform for Vaccine	Combination
NCT01970358 [30]	I	Melanoma	DC vaccine	None
NCT02035956 [47]	I	Glioblastoma	Peptide Vaccine	Poly-ICLC adjuvant
NCT03313778 [40]	I	Various	mRNA vaccine	None
KEYNOTE-942 [36]	IIb	Melanoma	mRNA vaccine	Pembrolizumab
NCT03953235 [41]	I	Pancreatic Cancer	Peptide Vaccine	Atezolizumab, Chemo

6. Challenges and Barriers to Success

Clonal evolution and tumor cell heterogeneity can lead to "immunoediting," where the clones targeted by the vaccine are cleared but the non-targeted cells continue to proliferate. The prediction of neoantigens is not always precise; there are some neoantigens that are not identified and others that are identified but not immunogenic [89,90].

Through checkpoint signals, metabolic restrictions, and inhibitory cells, the immunosuppressive tumor microenvironment (TME) can render vaccine-primed T cells inactive [91]. Additionally, many neoantigens have low intrinsic immunogenicity, particularly those derived from SNVs (Single Nucleotide Variants) [92]. Lastly, the clinical and commercial viability of custom therapies is threatened by their high cost and complexity of manufacturing [93]. The regulatory landscape is also changing rapidly for such personalized medicine interventions, including neoantigen-based vaccines, as they are quite different from traditional pharmaceutical agents. The US FDA and

EMA are both developing a regulatory framework to address these issues. The major issue is associated with the chemistry, manufacturing, and controls aspects of these vaccines, which need to be individually manufactured for each patient while meeting good manufacturing practices standards [94].

Another ethical issue is associated with the large amounts of genomic sequencing required for these types of therapy, which has raised concerns regarding data ownership, patient privacy, and potential misuse of sensitive patient data. The cost factor is also a major issue associated with these types of therapy, which is a significant issue when considering accessibility to these types of therapy for different populations based on various healthcare systems [95]. Therefore, regulatory policy, cost-effectiveness, and financial issues are likely to play a crucial role in making such advanced precision medicine interventions safe and accessible to a larger population [96].

7. Strategies to Overcome Limitations

It is crucial to use combination strategies; T-cell exhaustion in the TME can be reversed by combining vaccines with immune checkpoint inhibitors (ICIs), with clinical evidence supporting their synergistic efficacy [97]. To increase immunogenicity, new adjuvants and the STING method were used, which is a pathway that is a critical innate immune signalling mechanism that recognizes abnormal DNA in the cytoplasm and initiates antiviral and antitumor immune responses, and delivery methods that improve cross-presentation are being investigated [98]. Prediction is being improved by better computational models that incorporate deep learning on TCR specificity and mass spectrometry-based immunopeptidomes [99]. Targeting both neoantigens and related antigens through multi-epitope and customized combinatorial strategies may increase the scope of the immune attack and reduce escape [100]. The field is moving forward on several parallel fronts in order to overcome the current obstacles, turning obstacles into chances for creativity. Rational combination therapy is the most clinically proven approach. A potent "prime and release" mechanism is produced when neoantigen vaccinations are combined with immune checkpoint inhibitors (ICIs) such as anti- PD-1/PD-L1 or anti-CTLA-4 antibodies [101]. Tumor-specific T cells are primed and expanded by the vaccination, and their effector function within the TME is preserved by the ICI's removal of inhibitory signals. A model for this strategy is KEYNOTE-942's success. In addition to ICIs, combinations with other immunomodulators are being investigated, such as drugs that deplete Tregs or reprogram macrophages, agonists of co-stimulatory receptors (such as 4-1BB, OX40), or inhibitors of immunosuppressive enzymes [102]. The creation of next-generation adjuvants and delivery technologies is another frontier. For cancer vaccinations, conventional adjuvants such as aluminum salts are insufficient. More recent drugs, like Toll-like receptor (TLR) agonists (e.g., Poly-ICLC, CpG) or STING agonists, are intended to produce inflammation milieu at the injection site or even inside the tumor itself, changing the TME from immunosuppressive to immunostimulatory [103]. The delivery methods are also changing. The efficacy and strength of the immune response induced can be vastly enhanced through the use of nanoparticle vectors that target the dendritic cells within the lymph nodes, or that carry both the antigen and the adjuvant within the same nanoparticle. The inclusion of immunopeptidomes using mass spectrometry is an innovation when it comes to correcting the mistakes made in prediction algorithms. These can overcome the limitations of the algorithms used in that they sequence the peptides present on the surface of the tumor cells of the individual. These rules are becoming better understood through machine learning techniques applied to these databases in combination with TCR sequencing data from responding patients [104].

Moreover, the method of administration is changing. There will be an exponential increase in the efficacy and strength of the vaccination response if nanoparticles that deliver antigens to dendritic cells in the lymph nodes or the combined delivery of antigens using only one nanoparticle, are used. Line mass spectrometry technology is a revolutionary tool to deal with prediction mistakes. It bypasses the shortcomings of numerous prediction algorithms by creating a ground-truth database of the "presented" antigenome, as it sequences the peptides expressed on the surface of the patient's own tumor cells (or HLA-monoallelic cell lines are used). The subtleties of immunogenicity are being learned by machine learning models trained on these datasets in conjunction with TCR sequencing data from responsive patients. The addition of T cell receptor sequencing data from responding patients can also be important in the development and assessment of neoantigen-based therapies. This is because the T cell receptor repertoire is a measure of the diversity and clonality of T cell receptors in tumor tissues and blood cells. From such a repertoire, specific T cell clones can be identified as having expanded in a successful immune response and recognizing tumor-specific neoantigens, serving as proof that the vaccine or therapy is indeed working to induce antitumor immunity [105]. Tactics are expanding beyond focusing just on clonal neoantigens to counteract tumour

heterogeneity and escape. Personalized neoantigens are now combined with "shared" tumour- associated antigens (TAAs) or cancer-testis antigens (CTAs) in some strategies to expand the immune onslaught. Others suggest "off-the-shelf" vaccines that target common neoantigens present in tumours with viral aetiology or cancer subtypes caused by shared oncogenic mutations. Finally, efforts are being made to automate and decentralize production to address the manufacturing bottleneck. Research is being conducted on point-of-care manufacturing approaches, microfluidic devices for rapid mRNA synthesis, and the use of banked, pre- manufactured components that can be rapidly assembled based on a patient's neoantigen list.

8. Future Perspectives and Emerging Trends

Future directions in neoantigen discovery are expanding beyond more traditional mutation-derived antigens and into more diverse and biologically complex targets. Non-canonical neoantigens are increasingly important in this area. These include antigens from post-translational modifications, endogenous retroviral elements, and cryptic peptides [106]. Cryptic peptides are short peptides that arise from regions of the genome that are normally not translated into a protein. They may arise from alternative reading frames, non-coding DNA regions, untranslated regions of mRNA, or abnormal translation mechanisms in tumor cells. These are normally not expressed in healthy tissues and, therefore, are seen as foreign by the immune system and are attractive targets for immunotherapy and vaccine development. A further area that is being explored in this area is a combination of neoantigen vaccines and adoptive cell therapy, such as CAR-T and TCR-T cells [107]. Finally, artificial intelligence is increasingly playing a critical role in neoantigen discovery. It is capable of analyzing complex biological data and has shown promise in improving the predictability of neoantigens that have a high probability of being immunogenic. It does this by learning from experimental validation datasets such as T-cell assays and immunopeptidomics data. Artificial intelligence is also becoming an essential tool in the discovery of neoantigens [108]. AI is helping in the analysis of complex biological data and is also helping in the better prediction of immunogenic neoantigens. This is possible through the use of AI models that can learn from experimental validation datasets. Another important innovation in the field is the use of multi-omics data. This is helping in the comprehensive analysis of tumor-specific antigens. This is possible through the combined analysis of genomics, transcriptomics, proteomics, and immunopeptidomics data. This is helping in the precise identification of neoantigens that are MHC-associated and immunogenic [109]. These innovations are helping in the development of next-generation neoantigen discovery pipelines. This is possible through the use of AI and machine learning algorithms combined with multi-omics data. This is also helping in the analysis of immune repertoire sequencing data. This provides insights into T cell receptor specificities. All these innovations are helping in the accelerated development of personalized and precision medicine-based cancer vaccines [110].

9. Conclusion

The revolution in the application of precision immunotherapy is the development of personalized neoantigen vaccines. This application has moved from theory to reality due to major advances in genomics, bioinformatics, and vaccines. However, major hurdles remain in production, costs, immunosuppression, and prediction accuracy in the application of this therapy to cancer treatment. Neoantigen vaccines have enormous potential to become an integral part of the treatment of cancer in an individualized manner and offer hope to the future of cancer treatment through the ongoing advances in the fields of cancer treatment and the overcoming of ethical issues.

Author Contributions

Conception and design: S.K.C.; Data collection: A.S.; Analysis and interpretation of results: R.C. and S.S.; Draft manuscript: S.K.D. and M.; Review the paper: P.B. All authors reviewed the results and approved the final version of the manuscript.

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No new data were created in the study.

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AI Use Statement

During the preparation of this manuscript, the authors used Grammarly and ChatGPT for language editing, grammar improvement, summarization, and idea clarification, etc. After its use, the authors thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The authors take full responsibility for the integrity and final content of the published article.

Abbreviations

APC	Antigen-Presenting Cell
DC	Dendritic Cell
GMP	Good Manufacturing Practice
HLA	Human Leukocyte Antigen
ICI	Immune Checkpoint Inhibitor
Indel	Insertion- Deletion
LNP	Lipid Nanoparticle
MHC	Major Histocompatibility Complex
MSI	Microsatellite Instability
SNV	Single Nucleotide Variant
TCR	T-cell Receptor
TIL	Tumor-Infiltrating Lymphocyte
TMB	Tumor Mutational Burden
TME	Tumor Microenvironment
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing

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