Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Recent Development of Cancer Vaccines

Yanwen Dong *

University of Macau, Macau, China

* Corresponding Author Email: cc31653@um.edu.mo

Abstract. Immunotherapy, a truly innovative method in the field of cancer treatment, has attracted a great deal of attention because of its potential to bring about a revolution in the outcomes of cancer therapies. Even though there are many different ways being studied to make immunotherapy even more effective, fully realizing its potential, especially when it comes to cancer vaccines, is still a difficult goal to achieve. This review goes into detail about the different types of cancer vaccines, explaining the basic biological processes behind them and how they work with the immune system to fight cancer. We divide cancer vaccines into three main groups: virus-like particle (VLP) vaccines, peptide vaccines, and DNA/mRNA vaccines. Furthermore, this review also covers how these vaccines are being used in a wide range of infectious diseases and cancer types, emphasizing their versatility and the potential positive effects they can have on patients. Additionally, important topics related to the future of cancer vaccination are discussed, such as new ways to store vaccines to keep them effective, ways to reduce safety concerns, and the creation of personalized vaccines that are tailored to each patient's specific needs and cancer characteristics. By facing these challenges head-on and embracing the latest technologies, we hope to fully unlock the power of cancer vaccines, pushing the boundaries of cancer immunotherapy even further.

Keywords: cancer vaccine, virus-like particles, peptide vaccine, DNA and mRNA vaccine.

1. Introduction

Cancer vaccines demonstrate the potential to elicit durable immune responses against tumor-specific antigens. Remarkably, tumor-associated proteins (TAPs), exhibiting abnormal expression patterns within tumor tissues, occupy central stages in initiating, advancing, and disseminating tumor growth. Following the seminal identification of the pioneering tumor antigen, MAGE, in melanoma during 1991, there has been a proliferation in the discovery of a myriad of additional TAPs [1]. The rationale underlying therapeutic vaccines rests on the premise that cancer cells harbor unique chemicals, termed tumor-specific antigens, absent or minimally present in healthy cells. By administering therapeutic vaccinations, the immune system can be educated to recognize and mount a response against these antigens, ultimately leading to the elimination of cancer cells harboring them[2]. In recent years, cancer vaccines have been created to trigger an immune response and prevent cancer growth and recurrence. Due to an expanding comprehension of fundamental immunological principles, therapeutic vaccines aimed at eradicating infections have progressed into advanced clinical trials, yielding promising outcomes that underscore the potential for heightened vaccine efficacy through refined formulation strategies.

2. VLP vaccine

2.1. An outline

Virus-mimicking particles (VMPs), intricate multimeric protein assemblies that visually and structurally emulate authentic viruses or bacteriophages yet devoid of viral genetic content, render them non-pathogenic and incapable of propagation. Essentially, they constitute hollow constructs that mirror the overall morphology of viruses without conferring viral infectivity. Categorized as enveloped or non-enveloped contingent upon the presence of a lipid bilayer, VMPs' dimensional attributes influence their uptake by antigen-presenting cells (APCs), notably dendritic cells, pivotal

in immune response initiation. Particles within the 50 nm diameter can be straightforwardly delivered to lymph nodes for B cell engagement, whereas larger particles (spanning up to ten times larger) may be captured by APCs at the injection site and transported to lymph nodes[3].

2.2. A VLP-Based Vaccine for Metastatic Breast Cancer

Metastatic breast cancer (MBC), owing to its recurrence and refractoriness to conventional treatments, stands as the leading cause of mortality among females. Addressing MBC through innovative therapeutic avenues remains a pressing clinical challenge. In pursuit of this, various VLP-based vaccines, focusing on HER-2 as a key target, have been devised and evaluated for breast cancer management. A conceptual validation study was conducted employing a prototypical HER-2-VLP vaccine, which involved integrating the entire extracellular domain (ECD) of HER-2 onto AP205-derived virus-like particles (VLPs) through a refined Tag/Catcher ligation methodology. This approach aimed to demonstrate the feasibility of the concept. Alternatively stated, researchers re-engineered bacteriophage MS2 VLPs to present an extracellular segment of xCT, an attractive therapeutic marker implicated in tumor progression and metastatic establishment. These findings underscore the potential of xCT-directed immunotherapy in MBC treatment and advocate for the vaccine's exploration as second-line adjuvant therapy, either in tandem with chemotherapy or PD-1/PD-L1 immune checkpoint inhibitors. Notably, the vaccine's storage regimen necessitates neither stabilizing protein cocktails, cryoprotectants, and protease inhibitors, nor antimicrobial additives, thereby safeguarding vaccine purity and facilitating straightforward storage conditions, both pivotal for its human application. As a result, the vaccine may be a more effective combination therapy for achieving long-term responses in MBC patients, compared to other therapeutic options (**Figure 1.**).

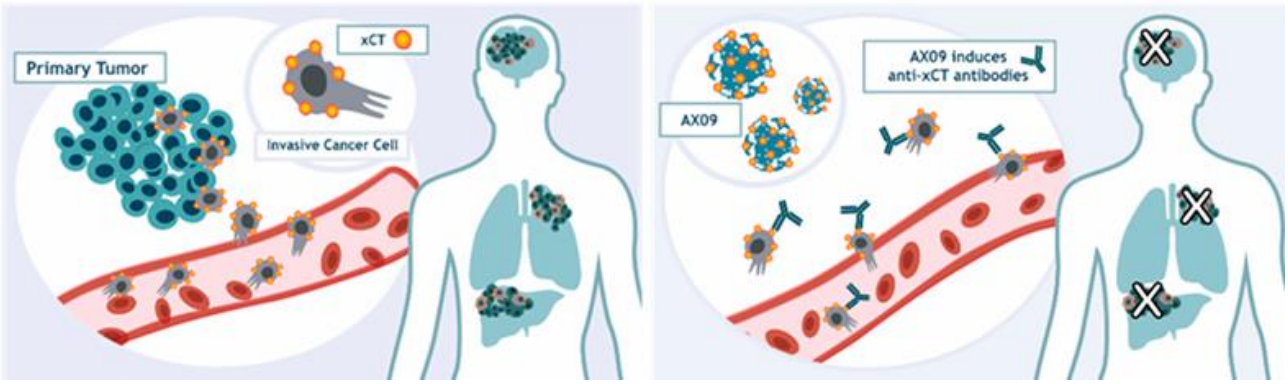

Figure 1. Exploring the Potential Mechanisms Underpinning the Impact of AX09-Induced Antibodies on Metastatic Progression [4]

2.3. Cross-Clade Neutralizing Antibodies Generated by EV-D68 Virus-Like Particle (VLP) Vaccines

Since the 1960s, Enterovirus D68 (EV-D68), a non-polio respiratory pathogen belonging to the enterovirus family, has emerged as a formidable health challenge, particularly for young children, frequently resulting in grave respiratory disorders. Among the infrequent yet concerning sequelae observed in pediatric patients infected with EV-D68 is acute flaccid myelitis (AFM), a condition where postmortem evaluations have unveiled the presence of EV-D68 genetic material and proteins embedded within the motor neurons. Although containment measures effectively contained the spread of EV-D68 in 2020, recent surges in detections during 2021 hint at the potential for future outbreaks. Current therapeutic approaches for severe respiratory disease remain supportive, while treatments for AFM progression are scarce and limited.

In preclinical studies utilizing animal models, monoclonal antibodies and human gamma globulin have exhibited protective effects against paralysis, highlighting the need for further exploration. Given the scarcity of clinical treatment options and the risk of severe, long-lasting consequences, the evolution of vaccines targeting EV-D68 is imperative to prevent both severe respiratory illnesses and

AFM. Notably, immunization with an EV-D68 virus-like particle (VLP) vaccine has elicited robust neutralizing antibodies in vitro, and passive antibody administration prior to intranasal challenge has successfully prevented viral replication and dissemination in vivo in mice.

Furthermore, an evaluation by researchers has encompassed the characterization of immunoglobulin G (IgG) subtype signatures prompted by B3 (VLPs) adjuvanted with varied enhancers, alongside an assessment of the cross-subclade and cross-clade neutralizing capabilities exhibited by antibodies stimulated in rats and non-human primates (NHPs) via these VLPs. This comprehensive assessment, encompassing multiple viral strains and adjuvants, provides valuable insights into the design and implementation of EV-D68 VLP vaccines, underscoring their potential to mitigate the burden of this pathogenic enterovirus (**Figure 2.**).

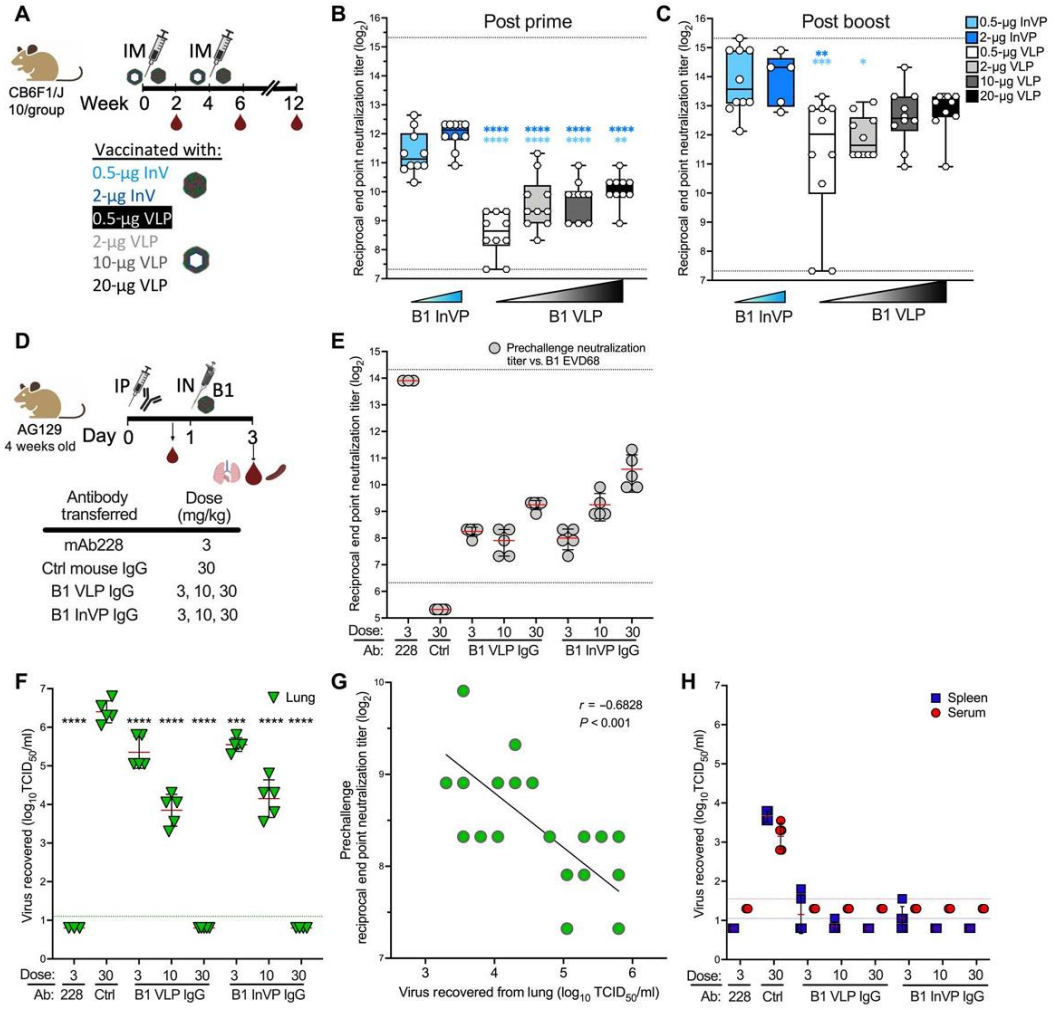

Figure 2. Potent Cross-Clade Neutralizing Antibody Induction by EV-D68 Virus-Like Particle Vaccines: Inhibition of Infection and Containment of Viral Transmission [5]

3. Peptide vaccine

3.1. An outline

Most infectious disease vaccines are inactivated or live attenuated pathogens, such as smallpox and seasonal influenza. These vaccines stimulate a robust immune response due to their relevant B- and T-cell epitopes. Subunit vaccines, primarily composed of peptides or proteins, face immunogenicity limitations and may require multiple immunizations[6]. Various approaches, such as multimeric epitope presentation or immunostimulatory adjuvants, have been used to enhance subunit vaccine responses.

3.2. Tailored Peptide Cancer Vaccine as a Strategy to Alleviate MHC-I Skewing in Calreticulin Mutant Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) originate from hematopoietic stem cells, excluding the Philadelphia chromosome, and encompass a category of myeloid blood malignancies. Recent research delved into MHC-I allele biases, specifically focusing on individuals diagnosed with CALRMUT MPN. The analysis encompassed haplotypes sourced from two American and eight Danish medical centers. The results suggest that uncommon MHC-I alleles demonstrate promising predicted affinity towards CALRMUT-derived peptides, contrasting with the suboptimal binding displayed by common alleles. Additionally, the research conducted a comparative analysis of MHC-I allele abundances at the protein level, contrasting them with those observed in the Caucasian population of the United States. This juxtaposition unveiled distinctive clustering trends, wherein the JAK2V617F MPN cohort mirrored the allele distribution of the U.S. Caucasian cohort, rather the CALRMUT MPN unit exhibited a divergent pattern. Notably, HLA-B51:01 emerged as the solitary allele overrepresented in both cohorts of CALRMUT MPN patients. Conversely, six MHC-I proteins were consistently underrepresented, with five of them displaying moderate predicted affinity towards approximately a quarter of all 9-mer and 10-mer peptides. Intriguingly, all overrepresented MHC-I alleles in CALRMUT MPN patients, excluding HLA-C*12:03 and HLA-B15:01, exhibited poor binding to CALRMUT-derived peptides. This trend underscores the need for further investigation, particularly considering the robust peptide binding capabilities of five out of six underrepresented MHC-I alleles.

The present investigation postulates that carcinogenic CALR mutation could potentially be more widespread than previously recognized, given that individuals harboring favorable MHC-I genetic configurations may effectively eliminate the disease at its nascent stage, thereby engendering a robust immunological memory. This suggests that a significant proportion of the healthy population is capable of mounting an immune response against CALRMUT fragments. However, CALRMUT MPN patients with negatively skewed, predicted immunogenic MHC-I alleles still succumb to the disease, possibly due to tumor evasion mechanisms such as inhibition of antigen processing or the establishment of an immunosuppressive tumor microenvironment. Consequently, these patients, characterized by negatively skewed MHC-I expression, may represent promising candidates for immune checkpoint blockade therapy and heteroclitic peptide cancer vaccines, as they may facilitate enhanced immune-mediated recognition of appropriately presented CALRMUT peptides within proper MHC-I contexts (**Figure 3.**).

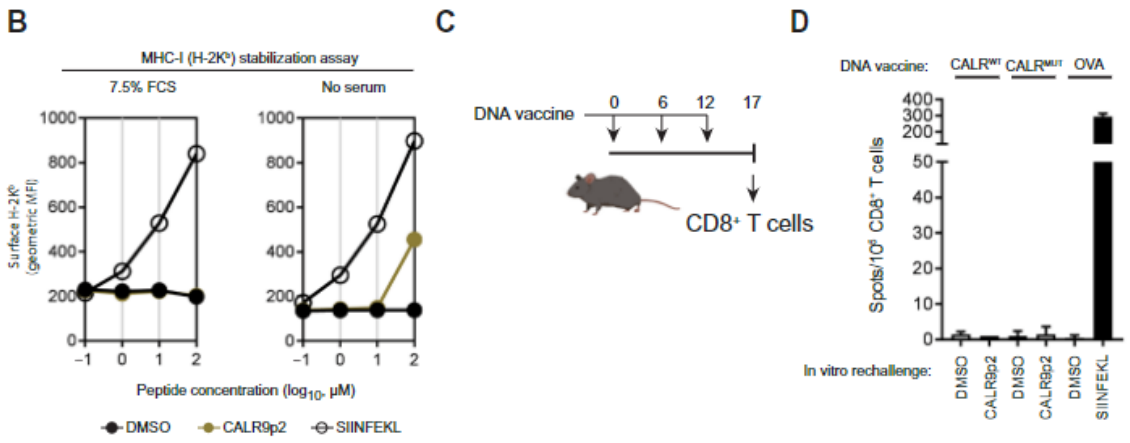

Figure 3. Overcoming MHC-I Skewing in Calreticulin Mutant Myeloproliferative Neoplasms with an Optimized Peptide Cancer Vaccine [7]

3.3. Impact of S 588410 Cancer Peptide Vaccine on Tumor-Infiltrating Lymphocytes and Microenvironment Alterations in Esophageal Cancer Patients

The crucial significance of preexisting tumor-infiltrating lymphocytes (TILs) in cancer immunotherapy is emphasized, as their absence has been shown to compromise the effectiveness of anti-PD-L1 therapeutic antibodies. Within the context of esophageal cancer, the coexistence of TILs and pertinent immune signatures, such as PD-L1, within the tumor microenvironment (TME) has been correlated with improved patient survival outcomes, thereby suggesting the promising potential of cancer peptide vaccines (CPVs) to bolster both cytotoxic T lymphocytes (CTLs) and TILs in esophageal malignancies.

The investigation highlights the immunostimulatory effects of the five-peptide CPV, S-588410, in esophageal cancer patients. Specifically, post-vaccination, we observed a notable elevation in functional T-lymphocytes and PD-L1 expression within the tumor mesenchymal stem (TMS) compartment. Notably, individuals with early-stage disease exhibited a more pronounced response to URLC10-mediated CTL induction compared to those with advanced disease. Immunohistochemical (IHC) analysis further corroborated these findings, revealing significant increases in CD8+ and CD4+ T-cell functionality along with a proliferation of PD-L1-expressing cells in vaccinated esophageal cancer patients.

Collectively, the findings suggest that the administration of S-588410 may facilitate a transformation within the TME, shifting it from an immunosuppressive 'desert' state to an inflamed phenotype. This transition holds therapeutic promise, particularly when S-588410 is combined with anti-PD-(L)1 therapies, offering a potential synergistic approach for esophageal cancer treatment (**Figure 4.**).

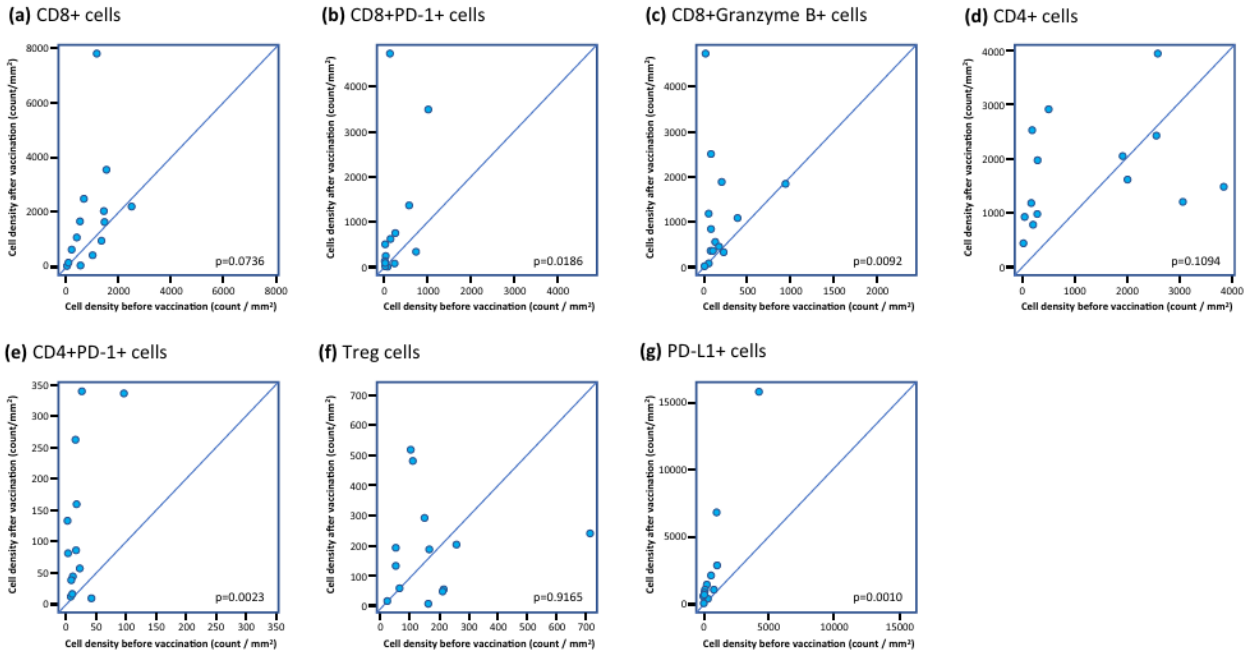

Figure 4. Delivery of Peptide-Based Cancer Vaccines Facilitated by the STINGΔTM-cGAMP Complex[8].

4. DNA and mRNA vaccine

4.1. An outline

The utilization of DNA vaccination arises as a promising approach for modulating the immune system, entailing the administration of plasmids that encode tumor-associated antigens (TAAs). This methodology enhances the immune response directed against TA-expressing tumor cells. Notably, these vaccines elicit not only an adaptive immune reaction but also initiate an innate immune response,

functioning as potent 'alarm signals' that stimulate diverse cytosolic DNA-recognition pathways in transfected cells. facilitated by CpG motifs and their double-stranded nature[9]. Cancer DNA vaccines are currently viewed as a highly promising technology for harnessing the immune system to combat cancer, with clinical trials demonstrating their exceptional safety profile and ability to elicit broad and specific immune responses. Nevertheless, the immunosuppressive nature of tumors often limits the therapeutic efficacy of these vaccines in clinical settings.

In parallel, the application of mRNA vaccines has garnered significant attention as a viable option in immunotherapy. Their remarkable advantages, including high efficacy, relatively mild side effects, and cost-effective production, have propelled their widespread adoption[10]. For instance, mRNA lipid nanoparticle (LNP) vaccines exhibit potential during influenza pandemics due to their rapid manufacturability and independence from egg-adapted vaccine strains[11]. While standardized in vitro manufacturing practices for mRNA production exist, challenges persist in synthesizing unconventional sequences and achieving cost-effective reagent production. Additionally, ensuring the long-term stability and consistent efficacy of mRNA vaccines during storage is a crucial aspect that merits emphasis.

4.2. Polyvalent Vaccine Elicits CD4bs Antibody Neutralizing Diverse Tier-2 HIV Strains

An investigation into a polyvalent DNA prime-protein spur strategy for HIV vaccination led researchers to isolate and thoroughly describe HmAb64, a novel monoclonal antibody precisely targeting CD4-binding sites (CD4bs). This antibody stems from the IGKV1-39 light chain germline gene and the IGHV1-18 heavy chain inconsistent germline gene characterized by a distinctive 15-amino-acid third heavy chain complementarity determining region (CDR H3). Upon assessment against a comprehensive panel of 208 cross-clade HIV-1 pseudoviruses, HmAb64 exhibited neutralization efficacy towards 20 (10%) of these strains, encompassing tier-2 variants from Clades G, C, B, and BC.

Further insights into the antibody's mechanism of action were gained through cryo-electron microscopy (cryo-EM) analysis of the HmAb64 antigen-binding fragment in complex with a CNE40 SOSIP trimer. This analysis illuminated the intricate recognition process, showcasing HmAb64's utilization of both light and heavy chain CDR3 loops to precisely interact with the CD4-binding ring, a crucial component of the CD4bs.

A comparative serum competition assay, pitting HmAb64 against the established CD4bs-targeting monoclonal antibody b12, indicated that rabbits vaccinated with the DNA prime-protein spur regimen developed CD4bs-specific antibodies in their sera, in contrast to those solely vaccinated with the recombinant protein-based HIV vaccine. This finding underscores the hypothesis that DNA vaccination may offer superior antigen presentation, preserving structural integrity better than recombinant proteins.

More precisely, the synthesis in vivo and folding process of Env protein, coupled with precise post-translational modifications, potentially replicates the native Env conformation more faithfully than those Env proteins that are synthesized and subsequently in vitro purified. Consequently, nucleic acid-based vaccines like DNA vaccines hold promise in preserving CD4bs-related epitopes.

In summary, immunization via this vaccination strategy has the potential to rapidly induce moderately potent neutralizing antibodies against CD4bs in humans. Nevertheless, it is imperative to undertake deeper exploration to definitively determine the existence of cross-subtype neutralizing antibodies directed against CD4-binding sites as well as additional epitopes among participants of the DP6-001 study or the recently completed HVTN124 trials, who have been administered the second-generation PDPHV52 vaccination(**Figure 5.**).

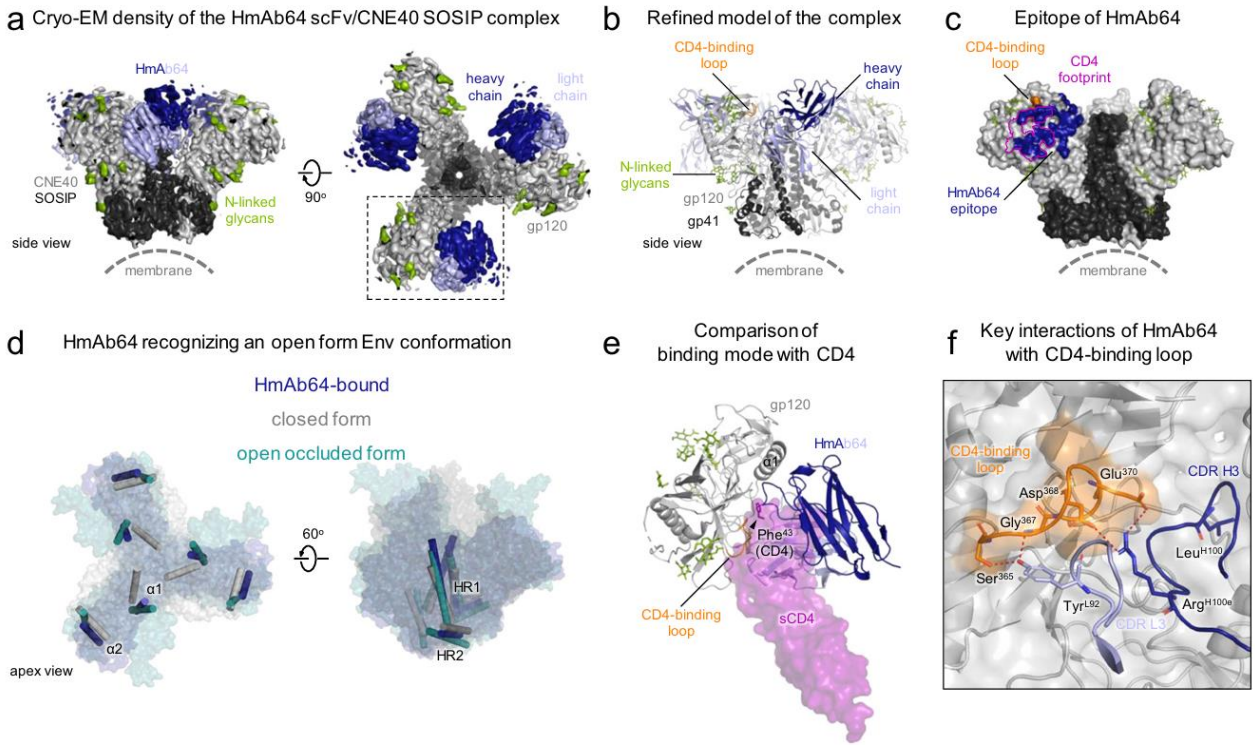

Figure 5. Multivalent DNA Prime-Protein Boost Immunization Strategy Elicits Broadly Neutralizing Human CD4-Binding Site Antibodies Effective Against Diverse Tier-2 HIV Strains Spanning Multiple Clades [12].

4.3. A mRNA vaccination against the Clade 2.3.4.4b, Subtype H5 Highly Pathogenic Avian Influenza Virus

The remarkable expansion of H5 clade 2.3.4.4b avian influenza viruses, spanning both wild and domestic avian species, represents a substantial hazard to human wellbeing. Commencing with their resurgence in 2020, these Gd/Gs lineage H5 strains have swiftly spread worldwide, encompassing extensive geographical regions including Europe, Asia, Africa, and the American continents. Notably, genetic alterations detected in some viral isolates from infected animals suggest an adaptation to mammalian hosts, emphasizing the possible danger of expanding host range.

In response to this looming danger, scientists have formulated an mRNA lipid nanoparticle (LNP) vaccine, incorporating the hemagglutinin (HA) glycoprotein sourced from a prototypical H5 strain belonging to the 2.3.4.4b clade. This innovative vaccine formulation triggers potent antibody and CD8+ T cell immune responses in murine models. with H5 antibody titers remaining high even one year post-immunization. In both mice and ferrets, the vaccine not only induced neutralizing antibodies but also broadly reactive HA stalk antibodies, indicative of a potent immune response.

In challenge experiments, while viral presence was detected in nasal washings, vaccinated ferrets demonstrated superior pathogen clearance compared to unvaccinated controls, who responded more sluggishly. Notably, vaccinated ferrets experienced less weight loss and exhibited fewer clinical symptoms post-H5N1 challenge. Ultimately, all vaccinated animals survived the challenge, whereas all unvaccinated animals succumbed.

Given the ongoing 2.3.4.4b H5 outbreaks in bovines, evaluating the efficacy of this mRNA-LNP vaccine in direct hosts like birds and intermediate hosts like swine and cattle has become imperative. These findings emphasize the versatility of the mRNA vaccine platform, enabling the rapid production and accurate targeting of immunogenic vaccine components against emerging influenza viruses that pose a pandemic threat(**Figure 6.**)

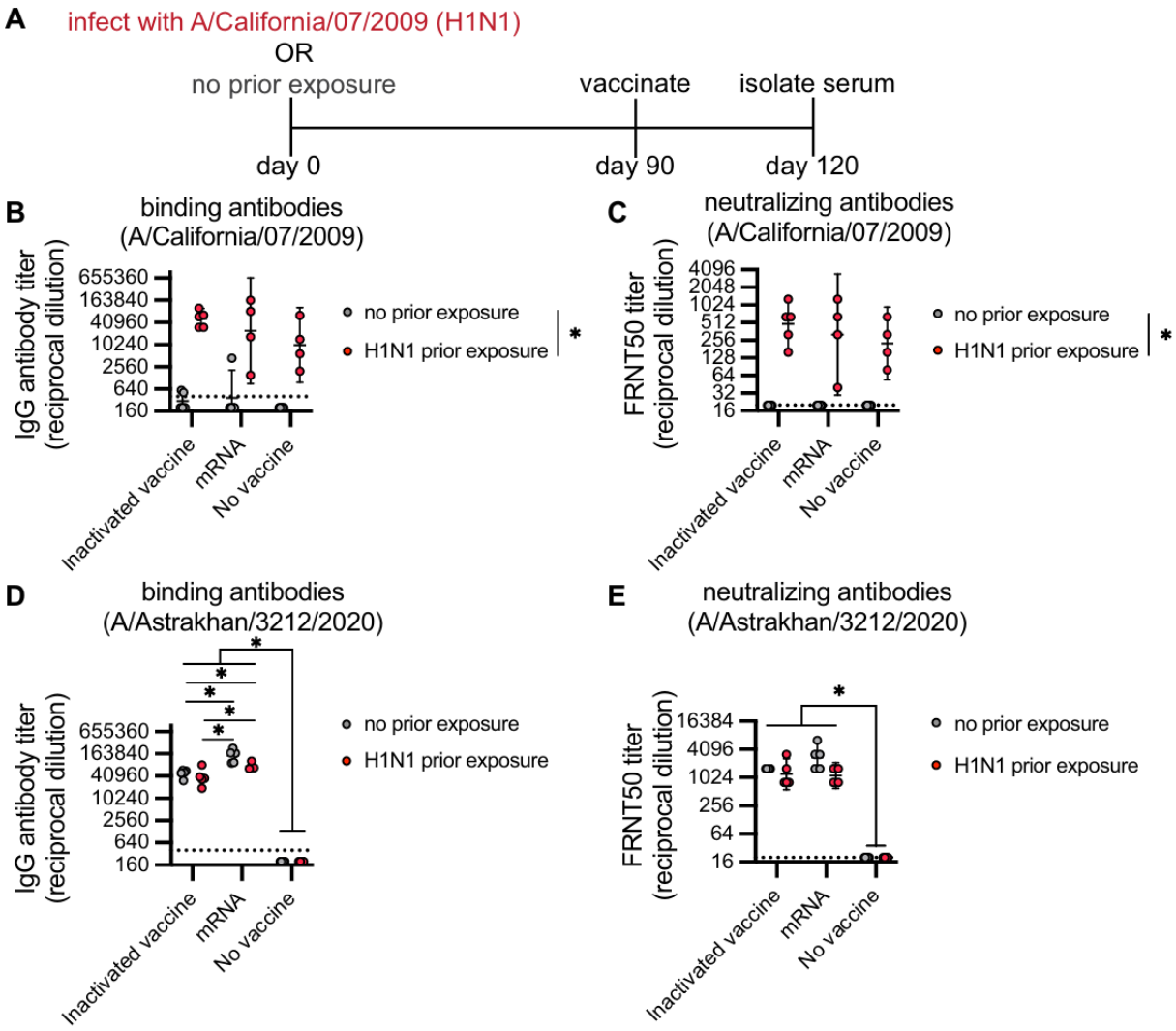

Figure 6. Creation of a mRNA Vaccine Specifically Targeting the Highly Pathogenic Avian Influenza Virus of Clade 2.3.4.4b, Subtype H5 [13].

5. Conclusion

Over the past few decades, cancer immunotherapy has experienced a remarkable revolution, characterized by the emergence and regulatory clearance of immune checkpoint inhibitors and adoptive cellular therapeutic strategies. Notably, therapeutic cancer vaccines have surfaced as promising avenues, demonstrating the potential to evoke distinct T-cell-mediated responses against tumor antigens, encompassing both tumor-associated and specific immunogenic epitopes. However, the current clinical endeavors to advance cancer vaccine development have confronted substantial obstacles, hindering the achievement of groundbreaking clinical successes. These challenges encompass the oppression of the tumor immune microenvironment, the identification of optimal vaccine antigens, difficulties in evaluating immune responses, and the need for expedited vaccine manufacturing processes.

Confronted with these complexities, the field stands poised to address these barriers and enhance patient outcomes by meticulously acknowledging clinical intricacies and relentlessly striving to transcend fundamental limitations. This trajectory echoes the historical trajectory of established efficacious cancer immunotherapies, which, despite periodic setbacks, have offered renewed optimism to patients with both solid and hematologic malignancies.

We hold the conviction that cancer vaccines are on the cusp of ultimate triumph, as they now demonstrate sufficient clinical advancements, backed by a clear rationale and compelling preclinical evidence, setting the stage for further development and success.

References

[1] A. Lopes, G.Vandermeulen, V. Préat, Cancer DNA vaccines: current preclinical and clinical developments and future perspectives, Journal of experimental & clinical cancer research: CR, 38(2019) 146.

[2] T. Fan, M. Zhang, J. Yang, Z. Zhu, W. Cao, C. Dong, Therapeutic cancer vaccines: advancements, challenges, and prospects. Signal transduction and targeted therapy, 8(2023) 450.

[3] F. Ruzzi, M. S. Semprini, L. Scalambra, A. Palladini, S. Angelicola, C. Cappello, O. M. Pittino, P. Nanni, P. L. Lollini, Virus-like Particle (VLP) Vaccines for Cancer Immunotherapy, International journal of molecular sciences, 24(2023) 12963.

[4] V. Rolih, J. Caldeira, E. Bolli, A. Salameh, L. Conti, G. Barutello, F. Riccardo, J. Magri, A. Lamolinara, K. Parra, P. Valenzuela, G. Francia, M. Iezzi, F. Pericle, F. Cavallo, Development of a VLP-Based Vaccine Displaying an xCT Extracellular Domain for the Treatment of Metastatic Breast Cancer, Cancers, 12(2020) 1492.

[5] P. W. Krug, L. Wang, W. Shi, W. P. Kong, D. L. Moss, E. S. Yang, B. E. Fisher, K. M. Morabito, J. R. Mascola, M. Kanekiyo, B. S. Graham, T. J. Ruckwardt, T. J, EV-D68 virus-like particle vaccines elicit cross-clade neutralizing antibodies that inhibit infection and block dissemination, Science Advances, 9(2023) eadg6076.

[6] R. J. Malonis, J. R. Lai, O. Vergnolle, Peptide-Based Vaccines: Current Progress and Future Challenges, Chemical Reviews, 120(2020) 3210–3229.

[7] M. Gigoux, M. O. Holmström, R. Zappasodi, J. J. Park, S. Pourpe, C. C. Bozkus, L. M. B., Mangarin, D. Redmond, S. Verma, S. Schad, M. M. George, D. Venkatesh, A. Ghosh, D. Hoyos, Z. Molvi, B. Kamaz, A. E. Marneth, W. Duke, M. J., Leventhal, M. Jan, T. Merghoub, Calreticulin mutant myeloproliferative neoplasms induce MHC-I skewing, which can be overcome by an optimized peptide cancer vaccine, Science Translational Medicine, 14(2022) eaba4380.

[8] Y. He, C. Hong, S. J., Fletcher, A. G. Berger, X. Sun, M. Yang, S. Huang, A. M. Belcher, D. J. Irvine, J. Li, P. T. Hammond, Peptide-Based Cancer Vaccine Delivery via the STINGΔTM-cGAMP Complex, Advanced Healthcare materials, 11(2022) e2200905.

[9] S. Pagliari, B. Dema, A. Sanchez-Martinez, G. Montalvo Zurbia-Flores, C. S. Rollier, DNA Vaccines: History, Molecular Mechanisms and Future Perspectives, Journal of Molecular Biology, 435(2023) 168297.

[10] S. Xu, K. Yang, R. Li, L. Zhang, mRNA Vaccine Era-Mechanisms, Drug Platform and Clinical Prospection, International Journal of Molecular sciences, 21(2020) 6582.

[11] S. H. Kiaie, N. Majidi Zolbanin, A. Ahmadi, R. Bagherifar, H. Valizadeh, F. Kashanchi, R. Jafari, Recent advances in mRNA-LNP therapeutics: immunological and pharmacological aspects, Journal of Nanobiotechnology, 20(2022) 276.

[12] S. Wang, KW. Chan, D. Wei, et al, Human CD4-binding site antibody elicited by polyvalent DNA prime-protein boost vaccine neutralizes cross-clade tier-2-HIV strains, Nature Communications, 15(2024) 4301.

[13] C. Furey, G. Scher, N. Ye, L. Kercher, J. DeBeauchamp, J. C. Crumpton, T. Jeevan, C. Patton, J. Franks, A. Rubrum, M. G. Alameh, S. H. Y. Fan, A. T. Phan, C. A. Hunter, R. J. Webby, D. Weissman, S. E. Hensley, Development of a nucleoside-modified mRNA vaccine against clade 2.3.4.4b H5 highly pathogenic avian influenza virus, Nature Communications, 15(2024) 4350.