Engineered Peptide Constructs for Immune Response Modulation Against Viral Pathogens

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Abstract*—Engineered peptide constructs have emerged as a versatile and rapidly advancing class of antiviral immunotherapeutics capable of overcoming key limitations of conventional vaccine platforms. Drawing on literature published between 2020 and 2025, this review synthesizes developments in multi-epitope peptide vaccines, peptide-based immunomodulators, nanomaterial-assisted delivery systems and computationally optimized epitope design. Viral pathogens continue to impose enormous global health and economic burdens, exacerbated by antigenic drift, viral immune evasion, drug resistance, inequitable vaccine distribution, and insufficient durability of current vaccines. Peptide constructs offer several advantages, including modular design, high specificity, safety, rapid manufacturability, broad HLA coverage, and compatibility with biomaterial delivery technologies. Advances in lipidated peptides, self-assembling nanofibers, peptide–nanoparticle conjugates, VLP-displayed epitopes, and mRNA-encoded peptides have demonstrated enhanced antigen presentation, strong Th1-biased T-cell activation, improved stability, and cross-variant immune responses in preclinical and early clinical studies. Notable candidates such as UB-612 and COVAC-1 have shown durable cellular immunity and variant resilience, particularly in immunocompromised populations. Despite this progress, substantial gaps remain, including limited Phase III clinical evidence, lack of validated correlates of protection, inconsistent demographic representation in trials, regulatory uncertainty, and manufacturing complexities associated with hybrid biomaterial–peptide systems. Future research must prioritize robust mechanistic immunology, systems-level immune profiling, improved animal models, advanced immunoinformatic pipelines, scalable delivery platforms, and global policy reforms that support equitable deployment. Overall, engineered peptides represent a promising next-generation direction for antiviral vaccines and immunotherapies with strong potential for rapid pandemic response, variant-independent protection, and broader global accessibility.

***Index Terms*—Engineered peptide vaccines; Multiepitope immunotherapy; Antiviral vaccine design; T-cell–mediated immunity; Nanomaterial-assisted delivery; Pandemic preparedness**

I. INTRODUCTION

1.1. Background

Viral pathogens still pose one of the most enduring and dangerous threats to the human health on the planet and result in massive morbidity, mortality, and social-economic disruption all around the world [1,4]. The recent outbreak and rapid dissemination of viruses like SARS-CoV-2, dengue, chikungunya, influenza, monkeypox and avian strains of viruses have demonstrated severe constraints of the available antiviral therapeutics and vaccine technologies, especially in terms of development velocity, cross-immunity, and flexibility to viral change and antigenic drift [15,18,38]. Although there have been improvements in the traditional vaccine systems such as live-attenuated, inactivated, viral-vector, and recombinant protein systems, these systems tend to have a long development cycle, biosafety, and storage issues since they depend on cold chains [4,12]. Moreover, all people do not develop effective immunity after conventional vaccination, and immunity can wear out over time, particularly against the immunocompromised categories and older adults [19,27]. That is why the necessity of the next-generation vaccine and immunotherapy approaches

that would allow addressing rapid, safe, and accurate immune regulation became even more urgent [20,24]. The engineered peptide constructs have also become a promising group of antiviral immunotherapeutics because of their modularity, high specificity, cost-effective production, enhanced safety profile, and compatibility with computational design and biomaterial-assisted delivery platforms [21,29]. The use of synthetic peptides enables the selective incorporation of immunodominant and conserved epitopes that are likely to induce the humoral and cellular immune responses, without exposing the whole-pathogen [13,14,21]. These benefits enable a quick re-designing process to new viral variants, which is a big benefit in pandemic preparedness and response systems [16,32]. The inclusion of immunoinformatics and reverse vaccinology software in peptide construct design has now dramatically shortened the prediction of antigens, optimization of HLA-binding and allergenicity screening and coverage analysis of populations worldwide [5,22,54]. Additionally, together with the development of delivery technologies and immunomodulatory biomaterials, engineered peptides are currently one of the fastest-growing fields in antiviral and vaccine engineering studies [27,30,32].

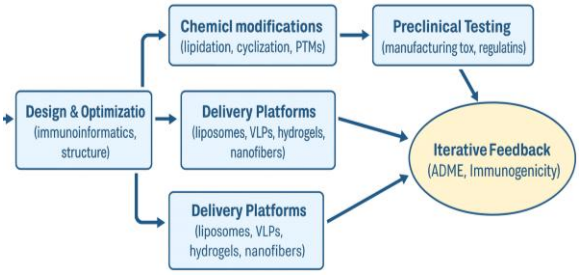

Fig 1- Conceptual framework

1.2. Significance of Engineered Peptide Constructs

Some examples of engineered peptide constructs include multiepitope peptides, peptide immunomodulators, lipopeptides, self-assembling peptide nanofibers, virus-like particle (VLP) peptide displays, peptide adjuvants, and peptide delivery enhancers such as cell-penetrating peptides (CPPs) [23,28,47]. This type of technology has shown a significant enhancement in the antigen presentation, activation of innate immunity, T-cell priming, and neutralization of antibody responses in preclinical and translational studies [14,20,23]. As an exemplar, multiepitope vaccines based on peptide antigens targeting the SARS-CoV-2 structural proteins (S, M, N and accessory proteins) have been reported to produce a significant increase in interferon- g production, cytotoxic T lymphocyte (CTL) activation and antibody titres in murine studies [22]. Likewise, peptide-nanoparticle hybrid vaccine systems have also shown increased lymphatic delivery, antigen release duration and production of long-term immunological memory [17,36,37]. B-cell receptor crosslinking and more widespread neutralizing antibodies have been observed with high-valency peptide nanofiber scaffolds with repetitive epitopes compared to monomeric peptides [58]. Besides, lipopeptides, which are engineered as intrinsic Toll-like receptor (TLR) agonist, may be used as antigen and adjuvant concomitantly, which provides a self-adjuvating effect, removes the use of traditional adjuvant systems [28,41].

Nanobiotechnology has enabled researchers to create novel platforms to deliver peptides using liposomes, gold nanoparticles, polymeric nanoparticles, VLPs, hydrogel-based systems and electrospun scaffolds of biomaterials [16,25,28,36]. Such systems improve peptide biodistribution, antigen stability, cellular uptake and control release which are significant physiological and immunological drawbacks faced by free peptide vaccines [17,32]. Also, mRNA-encoded peptides are a fast-growing area with huge translational potential, with already successful vaccine models of dengue, hepatitis C, malaria, and COVID-19 [15,39,43]. Immune checkpoint modulators of peptides and cytokine-mimicking peptides are under investigation because of their ability to circumvent T -cell exhaustion in chronic viral infections, where initial therapeutic efficacy rivals that of monoclonal antibodies (with reduced toxicity and increased scalability) [40,55,64].

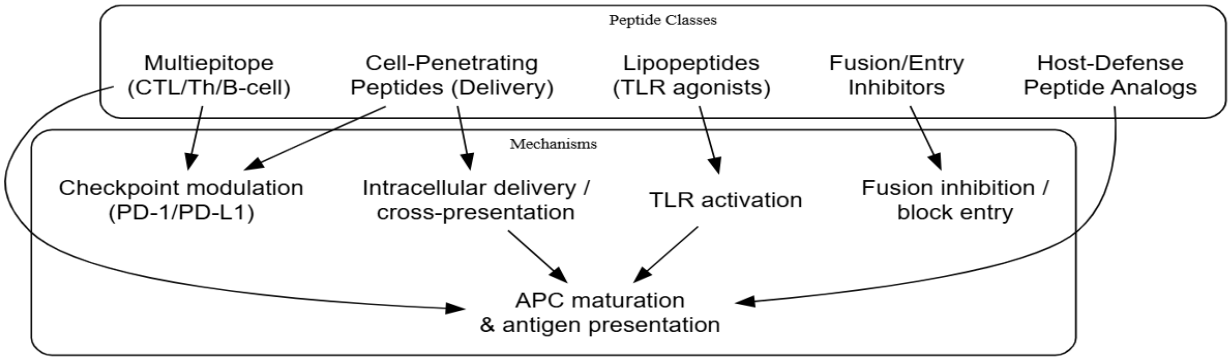

Fig 2 - Peptide classes and mechanisms

1.3. Current Research Landscape

The article shows that engineered peptides have more potential to be used as antiviral immunomodulators, and the research output in clinical and translational studies is rising since 2020. Multiepitope vaccines against SARS-CoV-2 Peptide-based multiepitope vaccine have demonstrated high modeling of population-coverage and enhanced immunogenicity through optimized HLA-binding affinity [22,78]. Improved peptide vaccine design with nanomaterials has been shown to be highly cross-presented, recruits more antigen-presenting cell (APC), and delivers to the lymph-node [17,25,29]. The use of hydrogels, electrospun scaffolds, and programmed release systems has made it possible to have spatiotemporal immune control [35,37,71]. New peptide delivery methods utilizing CPPs, polymer-based nanoparticles, and bacteria-derived delivery vectors have enhanced cytosolic delivery as well as viral antigen expression [23,49,73]. VLPs genetically modified with peptide antigens have demonstrated a high density of antigen display and immunogenicity, particularly in the case of novel infectious pathogens [26,57].

Additional PD-1, PD-L1 and other immune checkpoint pathway immunomodulatory peptide constructs are showing encouraging effects in restoring T-cell activity and curing immune suppression in persistent viral infections [10,40,64]. Host-defense peptides have appeared to regulate cytokine activation in an up-regulated manner and antiviral effects in an antiviral manner in intracellular infection [59]. Meanwhile, circular RNA and mRNA platforms that encode peptide antigens can be shown as having rapid design cycles and scalable biodegradable RNA delivery systems, which may allow their use to be used as the basis of universal vaccine frameworks in the future [39,42,45]. The antigen presentation and adjuvant signaling in the microenvironment of antigen targeting can be controlled by synthetic matrices and programmable biomaterials, which prove to be safer and more therapeutic [31,53,61].

1.4. Objectives and Research Questions.

This review aims at summarizing the contemporary developments and analysing the progress made on engineered peptide constructs in antiviral immune response modulation. The review will bring together the multidisciplinary contributions in the area of peptide engineering, immunobiology, biomaterials science, nanotechnology, immunoinformatics and translational vaccinology. The review will deal with the following research questions:

1. What are the engineering approaches used to maximize peptide constructs to increase innate and adaptive antiviral immune responses?
2. Improvements in stability, immunogenicity and responses: how do nanomaterial-assisted delivery platforms and structural modifications work?
3. How are the immunological processes of the activation and regulation of immune in response to peptides?
4. Which clinical issues prevent the clinical application of engineered peptide vaccines?

Table 1 — Summary of representative studies

Ref (Author, Year)	Peptide class / platform	Target virus / application	Design method	Delivery / model	Key outcomes (immunogenicity / efficacy)	Notes
Khairkhah et al., 2022	Multi-epitope peptide	SARS-CoV-2 (S, N, M)	Immunoinformatics, reverse vaccinology	Mouse (in vivo)	Induced IFN-γ responses and antibody titers in preclinical testing	Emphasis on conserved epitopes and HLA coverage
Bhuiyan et al., 2020	Multi-epitope peptide vaccine	Rift Valley fever virus	In silico epitope prediction + modeling	In silico / small-scale in vitro	Candidate epitopes with predicted high antigenicity	Lacks extensive in vivo validation
De Groot et al., 2020	Immunoinformatics pipelines	General vaccine design	Computational epitope discovery & benchmarking	N/A	Demonstrated value of improved epitope selection methods	Discusses issues of dataset heterogeneity
Hamley, 2021	Lipopeptides (adjuvant)	Vaccine adjuvant applications	Chemical lipidation, self-assembly	Preclinical models	Strong innate activation (TLR2), improved humoral responses	Well-suited as intrinsic adjuvants for peptide vaccines
Ren et al., 2023	Adjuvant physiochemistry	Vaccine delivery/adjuvants	Nanotechnology + chemistry review	N/A	Highlights nanotech-adjuvant synergies for durable responses	Notes challenges in physico-chemical tuning
Ferrando et al., 2020	Peptide-decorated gold NP	Platform for antigen display	Chemical conjugation to AuNP	Mouse, in vitro	Multivalent display increases antibody titers vs soluble peptide	Manufacturing and size-control issues noted
Fries et al., 2021	Peptide nanofibers	HIV antigen valency study	Self-assembling peptide nanofibers	Mouse models	Antigen valency modulated magnitude and breadth of Ab	Demonstrates structure–function benefit of multivalency
Staquicini et al., 2021	Phage-based VLP strategies	Phage-based COVID-19 vaccination	Phage display and targeting peptides	Animal models; cold-free supply design	Proof-of-concept targeted VLP vaccination with supply-chain advantages	Promising for low-resource settings
Hasannejad-Asl et al., 2022	Cell penetrating peptides (CPPs)	Vaccine delivery	CPP-fusion constructs	In vitro, preclinical	Enhanced antigen uptake and cross-presentation	Cytotoxicity and specificity need optimization
Kotraiah et al., 2020	Peptide PD-1 modulators	Immunomodulation (PD-1 axis)	Rational peptide design	Preclinical models	Demonstrates peptide PD-1 modulators can enhance vaccine responses	Early-stage; affinity and half-life issues

Magana et al., 2020	Host-defense peptide (review)	Antimicrobial & immunomodulatory roles	Literature review	N/A	HDP analogs show dual antimicrobial and immunostimulatory effects	Highlights translational potential and resistance mitigation
Duarte-Mata & Salinas-Carmona, 2023	AMP immunomodulation	Intracellular bacterial infection (immunomodulation)	Experimental studies	In vitro/in vivo	AMPs modulate innate responses and improve outcomes in intracellular infections	Potential parallels for antiviral immunomodulation
Pourseif et al., 2020	Domain-based mRNA & peptide vaccine	SARS-CoV-2	Combined mRNA + peptide strategies	Early preclinical	Combined approach shows promising antigen expression and immunogenicity	Hybrid approaches gaining traction
Patra et al., 2023	mRNA-encoded E1/E2 peptides	Hepatitis C mRNA vaccine	mRNA vaccine encoding antigenic proteins	Animal models	Protective immunity observed in preclinical studies	Shows synergy between nucleic-acid and peptide approaches

II. GLOBAL VIRAL BURDEN AND CHALLENGES

Viral pathogens still present an extensoively large burden to world population health, exceedingly most other infectious menaces in regards to cumulative morbidity, fatality, economic hurt and social disturbance [1]. The last ten years have emphasized the susceptibility of international healthcare systems to new and re-emerging viral infections, such as SARS-CoV-2, dengue, Zika virus, Chikungunya, respiratory syncytial virus (RSV), hepatitis, HIV, influenza, Nipah and Ebola and other avian and zoonotic viruses [2,3]. Nevertheless, in the face of the unparalleled progress in the scientific community, as well as the massive vaccination programs, viral diseases continue to cause tens of millions of infections and millions of deaths per year all over the world. COVID-19 alone resulted in over 760 million cases of confirmed cases and close to 7 million officially reported deaths at a global level, although estimates of excess mortality suggest the actual number to be far much greater [4]. The number of severe cases and up to 650,000 deaths are caused by seasonal influenza every year [5], and the prevalence of viral hepatitis causes roughly 1.1 million deaths every year, with chronic infections and inaccessible treatment being the main reasons [6]. Dengue virus has spread in over 120 countries causing an estimated 390 million infections per annum [7] and HIV is still present in 38 million people all over the world with an approximate of 1.5 million new infections per year [8]. These statistics remind us of the seriousness and inertial character of problems with viruses, and people still need high performance, versatile and sustainable immunotherapies and vaccines with wide coverage protection immunity.

There is a gross imbalance in the distribution of the burden of viral diseases based on geographical and socio-economic settings whereby low-income and middle-income areas show the highest levels of incidence and death [9]. The dense populations and climatic changes, restricted access to healthcare, poor surveillance mechanisms and resources are concentrated regions of the outbreak of the viruses in South Asia, sub-Saharan Africa and some parts of Latin America [10]. As an illustration, India, Indonesia and Brazil are some of the countries with the highest burgens of dengue, influenza and COVID-19 cases [11]. The disparity in the capacity to access diagnostic facilities and treatment worsens susceptibility in these areas, which often leads to a late diagnosis, community spread and underreporting [12]. In addition, urbanization, global travel,

changing of the environment, and spillover of zoonotic diseases all augment viral transmission by raising the frequency of contact between humans and animal reservoirs [13].

The COVID-19 pandemic considerably aggravated the situation with viral diseases in the world by making resources of healthcare to be redistributed and making it impossible to carry out routine vaccination campaigns and postponing the diagnosis and treatment of other infectious diseases [14]. The pandemic significantly reduced the usual immunizations in childhood to the lowest in thirty years, leaving almost 25 million children without the protection against the preventable diseases like measles, polio and hepatitis [15]. Also, the surveillance and reporting systems were undermined by laboratory shutdowns, as well as physical access to healthcare centers, and identified and managed viral infections were cut down [16]. This interference not only caused the known viral diseases but also also lead to the re-occurrence of the measles outbreaks in 26 countries, as well as increased the risk of future pandemics [17]. The pandemic has also led to the realization of significant structural constraints in the rate of new vaccine and immunotherapies development and deployment, and there is a need to develop rapid-response bio-medical platforms to promptly design antigens, test and global production [18].

The next major issue in managing viral pathogens is that the rate of mutation in most viruses (particularly RNA viruses like SARS-CoV-2, HIV and influenza) is very high. The consequences of the antigenic drift and shift are maintained occurrence of immune-escape variants that are capable of bypassing natural immunity, therapeutic monoclonal antibodies and vaccine-induced responses [19]. Variants of concern of the SARS-CoV-2, such as Delta, Omicron and then subsequent sublineages, were found to be less adequately covered by vaccines and have a higher rate of breakthrough infection compared to the original vaccine targets [20]. The antigenic evolution of influenza strains continuously requires the development of annual reformulation and repeated cycles of vaccination, but seasonal vaccines are only 4060 per cent effective on average [21]. HIV variability is one of the bottlenecks that are not allowing development of an effective curative vaccine [22]. These dynamics of mutations discuss the necessity of vaccines able to target conserved viral epitopes that would stay stable throughout variants, which is one of the core competencies of designed peptide-based solutions [23].

Antiviral drug resistance is another issue that is a problem to the world. This has resulted in widespread resistance to viral antivirals applied to influenza, HIV, hepatitis and herpes virus because of the strong selective pressure and incomplete inhibition of viral replication [24]. In Asia, Africa and Eastern Europe, HIV treatment is becoming multidrug-resistant, which raises disease transmission and complexes of treatment [25]. The trends of resistance are similar to those in bacterial infections but are underfunded in research due to no less serious implications [26]. Similar to antibacterial peptides, antiviral peptide analogues derived by hosts are a new promising strategy to counter viral escape and resistance to drugs [27].

Table 2 — Peptide engineering strategies: rationale, benefits, limitations

Strategy	Mechanistic rationale	Typical benefits	Typical limitations	Representative refsr
Multi-epitope peptides (concatenated epitopes)	Combine CTL, Th and B-cell epitopes for broad coverage	Broad antigenic breadth; easier rapid redesign; HLA-targeted designs	In silico predictions may not translate; processing/presentation variability	Khairkhah 2022; Bhuiyan 2020; De Groot 2020
Lipopeptides (lipidation)	TLR2 engagement and self-assembly into adjuvanting nanostructures	Intrinsic adjuvant; robust innate activation; increased uptake	Hydrophobicity → aggregation; manufacturing complexity; reactogenicity potential	Hamley 2021; Ren 2023
Cell-penetrating peptides (CPPs)	Facilitate intracellular delivery and	Improved cross-presentation; stronger CD8+	Off-target uptake; potential cytotoxicity; specificity issues	Hasannejad-Asl 2022

	endosomal escape	responses		
Self-assembling nanofibers / VLP display	Multivalent repetitive antigen presentation mimics virus	Strong B-cell activation, affinity maturation; prolonged responses	Assembly heterogeneity; expensive scale-up; stability concerns	Fries 2021; Staquicini 2021
Peptide immune-checkpoint modulators	Block inhibitory receptor interactions (PD-1/PD-L1)	Restore exhausted T cells; complement vaccines	Short half-life; autoimmunity risk; dosing control	Kotraiah 2020
Peptide–nanoparticle conjugates	Control spatial density & co-delivery with adjuvants	Tunable biodistribution; co-delivery of adjuvants; controlled release	Regulatory complexity; biodistribution/toxicity concerns	Ferrando 2020; Cappellano 2021

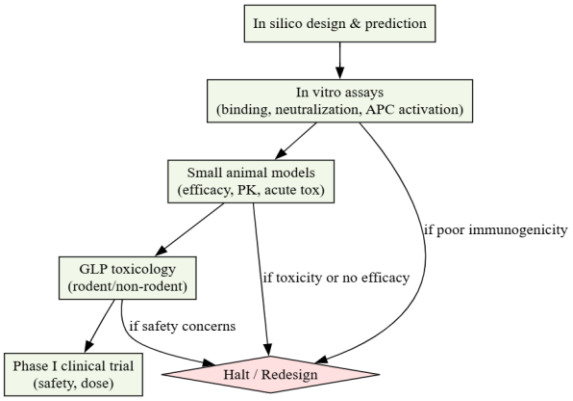

Fig. 3 — Suggested evaluation pipeline

III. EXISTING ANTIVIRAL VACCINES AND IMMUNOTHERAPY APPROACHES: STRENGTHS AND LIMITATIONS

Present antiviral vaccine and immunotherapy platforms such as live attenuated, inactivated, recombinant protein, viral-vectored, nucleic acid-based vaccines, and monoclonal antibodies have served critical functions of alleviating viral disease burden. Nevertheless, all technologies have scientific, logistical, and immunological drawbacks, which limit their ability to act in the rapidly developing viral pathogens [4], [10], [12], [13], [17], [22]. These shortcomings underscore the growing necessity of the next-generation peptide-based immunotherapies that can have a higher level of immune precision and stability [5], [23], [28].

LAVs induce effective innate and adaptive immune responses and have a high risk of pathogenic reversion and should not be used in immunocompromised or older people [6], [10]. They also require highly complex cell-culture systems and cold-chain storage which constrains their use in low-resource environments [7]. Activated vaccines are less immunogenic and most need several booster doses or a high concentration of adjuvants to elicit the appropriate humoral and cellular responses [8], [12]. Their low consistency can be of particular concern with a fast-changing virus like influenza and coronaviruses [21], [78].

Recombinant protein and VLP-based subunit vaccines are generally safe but tend to cause low cytotoxic T-cell responses, rely on adjuvants, and are poorly able to induce mucosal immunity, which is a characteristic required of respiratory viruses [10], [11], [26]. Viral-vectored vaccines express antigens and activate CD8+ well but circumvent diminished efficacy in presence of pre-existing vector immunity and themselves cause infrequent but severe immune-mediated reactions [13], [14], [15].

mRNA vaccines revolutionized the pace of vaccine development in COVID-19 with good early vaccination immunogenicity and flexible design [17], [39]. Nevertheless, they are not as stable due to the destruction of mRNAs, reliance on lipid nanoparticle delivery, and the need to store them at ultra-cold temperatures [19], [69]. The reduction in immunogenicity among the older and immunocompromised adults is accelerated, requiring repeated administration of the booster [20], [21].

The monoclonal antibody therapies offer instant passive immunity and are used when the individual is highly at risk [22]. However, they are still costly, labor-intensive, prone to viral escape mutations, and have no ability to produce long-term immune memories [23], [24].

Taken altogether, these limitations demonstrate the fact that engineered peptide constructs, with their ability to provide modularity, broad-spectrum epitope

coverage, enhanced safety, and compatibility with advanced delivery methods are becoming newcomers to the role of next-generation antiviral solutions [5], [23], [28], [32], [34].

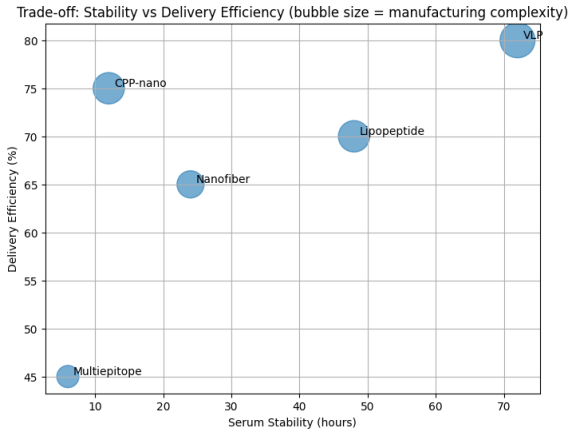

Fig. 4 — Delivery performance vs stability

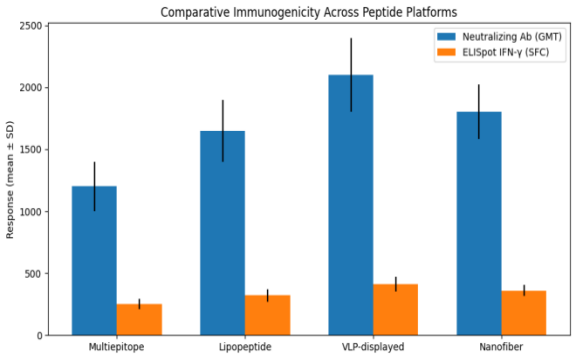

Fig. 5 — Comparative immunogenicity

IV. WHY NEW ENGINEERED PEPTIDE VACCINES AND IMMUNOMODULATORS ARE NEEDED

Although the antiviral vaccines have made massive progress, the challenges that persist in this field, such as fluctuating immune response, loss of immunity, insufficient coverage of novel strains, and global inequalities, indicate the utmost necessity of next generation peptide-based immunotherapies [1], [2], [5], [21], [37]. Viral disease outbreaks of SARS-CoV-2, influenza, RSV, dengue, HIV, and hepatitis prove that the existing vaccines tend to be ineffective in providing long-term and generalized protection in the population [9], [16], [38], [40]. Diverse immune responses are dependent on genetic variation, environmental factors and differences in microbiomes [8], [47]. Also, mRNA vaccine-induced antibody titer fades quickly and necessitates frequent boosters, whereas influenza vaccines achieve only a 4060 percent annual efficacy due to antigenic drift [10], [21], [39].

One of the major weaknesses of existing vaccines is a lack of T-cell response. Effective antiviral immunity in a durable state need both a coordinated response of the CD4 + and the CD8 T-cell [11], [12], and [23], which many platforms cannot effectively induce. Designed peptide vaccines use conserved epitopes and directly activate MHC-I and MHC-II pathways, resulting in strong cellular immunity required during chronic viral disease, like HIV and hepatitis [5], [14], [23], [32].

The rate of RNA viruses' mutation exposes whole-protein and single-antigen vaccines to immune evasion, as is the case with Delta and Omicron SARS-CoV-2 variants [16], [21], [38]. The difficulty is being surmounted by the use of multiepitope peptide constructs, which polymerize conserved epitopes in multiple viral proteins, enhancing variant resistance and allowing quick redesign with immunoinformatics tools [5], [9], [14], [17].

Also engineered peptides provide solutions to increasing antiviral drug resistance. The host-defense peptides and synthetic analogs interfere with viral membranes or viral replication by the action that is less susceptible to evolutionary resistance [6], [20], [59].

The problem of manufacturing and distribution also restricts the use of conventional vaccines in low-resource areas even further. Peptides are more stable, cheaper, can be lyophilized, stored at room temperature, enabling production decentralization and scale-up in seconds [7], [18], [24], [29]. They are also very compatible with nanomaterials like liposomes, polymeric nanoparticles and self-assembling nanofibers and make it to achieve better delivery efficiency and immunogenicity [17], [26], [32], [50].

Most importantly, mucosal immunity is supported by engineered peptides, which are important in the reaction to respiratory and enteric viruses. IgA and tissue-resident memory T-cell responses [12], [26], [27] could be induced with intranasal or mucoadhesive peptide formulations, which are responses that are often inaccessible to current vaccines.

Peptide-based checkpoint inhibitors, cytokine mimetic peptides and APC-activating constructs provide safer and more scalable novel therapies in chronic viral infections with T-cell exhaustion compared to monoclonal antibodies [30], [31], [40].

Lastly, peptide vaccines lessen disparities in the world by providing flexible and low-cost regionalized production that can be compatible with a wide range of viral clades and an HLA background [33], [34], [35].

In general, engineered peptide vaccines and immunomodulators have structural versatility, targeted immune control, broad spectrum protection, and scalable production- making them critical structures on future pandemic preparedness and long-term management of viral diseases [5], [32], [37], [40].

Table 3 — Delivery platforms: performance & TRL

Platform	Delivery effectiveness	Stability (in vivo)	Scalability (manufacturing)	Safety / toxicity considerations	TRL (approx.)	
Liposomes	High (encapsulation, lymph node targeting)	Moderate–High (with PEG/stabilizers)	Moderate (lipid supply chain, GMP)	Generally safe; adjuvant interactions can increase reactogenicity	6–8	Tretiakova 2022; Ferrando 2020
Virus-Like Particles (VLPs)	Very high (strong immunogenicity)	High (proteinaceous stability)	Moderate–Low (complex recombinant production)	Good safety (non-replicating); glycosylation/assembly variability	5–7	Alam 2020; Staquicini 2021
Polymeric nanoparticles (PLGA, PEG-PLGA)	High (controlled release)	High	Moderate (well-established processes)	Biocompatible; particle accumulation risk at high doses	5–7	Cappellano 2021
Gold / inorganic NP (AuNP, silica)	High (multivalency)	High (physicochemical stability)	Low–Moderate (cost, regulatory uncertainty)	Long-term biodistribution concerns; clearance issues	3–5	Ferrando 2020
Self-assembling peptide nanofibers	High (multivalent display)	Moderate (depends on sequence)	Low (synthetic cost)	Low reactogenicity reported; assembly-related heterogeneity	3–5	Fries 2021
Hydrogels (injectable)	Moderate (localized depot)	High (tunable degradation)	Low–Moderate (formulation complexity)	Degradation products must be biocompatible	3–5	Kharaziha 2021
mRNA-peptide hybrid (mRNA coding peptides)	Very high (rapid deployment)	Dependent on LNP stability	Moderate-High (mRNA tech matured)	LNP reactogenicity; storage cold-chain	7–9	Pourseif 2020; Patra 2023

V. CURRENT PEPTIDE VACCINE DEVELOPMENT PIPELINE

5.1. Platforms and Strategies

The pipeline of engineered vaccines based on peptide-based vaccines and immunomodulators has grown considerably after the COVID-19 pandemic and is driving increased interest in epitope-driven antigen design, predictive vaccine systems using immunoinformatics, improved biomaterial delivery systems and novel immunomodulatory peptides with the capability to augment host immune responses to different viral pathogens [1,3]. Peptide-based vaccine systems are centered on the insertion of short,

antigenic sequences that are highly conserved and are derived either through structural or non-structural biomolecules of the virus and are capable of inducing directed activation of the CD4+ and CD8+ T-cells, in a complementary or surpassing manner to the antibody-centered approaches used in the traditional vaccines [4]. In contrast to the whole-pathogen or single-antigen recombinant vaccines, peptide vaccines permit the combination of multiple defined epitopes into rationally designed multiepitope constructs, which permit extensive immunological coverage and resistance to variants [5].

The engineered peptide platforms may be classified into various modalities of strategic development that include linear synthetic peptides, multiepitope peptide constructs, lipopeptide vaccines, self-assembled peptide nanofibers, peptide-nanoparticle conjugates and peptide-based viral-vector or VLP hybrids, with each having its own unique stability, immune activation and manufacturing capabilities [6]. Linear peptides are the most basic form of synthetic construct and can be synthesized with high accuracy in a short period of time, as well, through automation of solid-phase synthesis. Although linear peptides per se have traditionally been considered weak immunogenic, their delivery in combination with adjuvants or nanoparticulate carriers has been shown to increase antigen presentation and antigen immunogenicity [7]. Multiepitope constructs are engineered chains that bring together multiple T-cell and B-cell epitopes into one engineered chain, which allows the humoral and cellular immune responses to coordinate their activities and minimize the chances of immune escape, particularly in rapidly evolving viruses like SARS-CoV-2, influenza and HIV [8].

Another significant approach to the peptide vaccine pipeline is the lipopeptides. Structural lipidation facilitates antigens to interact with membranes more effectively, to be taken up by antigen presenting cells (APCs) and to stimulate the activation of pattern-recognition receptors (TLRs), especially TLR-2 and TLR-4 [9]. Lipopeptide adjuvanting may be used to remove external adjuvants and facilitate formulation and risk of toxicity. A number of new potential peptide-based vaccines such as UB-612, comprise lipid moieties to maximize immunogenicity and long-term immunogenicity [10].

Self-assembled peptide nanofibers are the new terrain wherein peptides naturally self-assemble to form fibrillar Nano scaffolds that resemble the form of viral proteins and form a depot effect to release antigens gradually [11]. These scaffolds promote robust germinal center reactions and high-quality T-cell immunity to an extent of soluble peptides. Nanofiber peptide vaccines have demonstrated a great potential in infectious disease models, such as influenza and SARS-CoV-2, where they can induce a robust cross-variant vaccine response [12].

The other significant development is the combination of peptides with the nanomaterial delivery system (liposomes, polymer nanoparticles, dendrimers, gold nanoparticles, electrospun fibers and biomaterial hydrogels) [13]. Nanoparticles aid the lymphatic pathway, increase the half-life of antigens, co-delivery of adjuvant systems and release in tissues with immune activity. A number of vaccines that are in preclinical stages, such as COVAC-1 and ID93+GLA-SE, are based on nanoparticles or liposomal peptides delivery to boost the immunogenicity in preclinical trials [14].

Also, peptides sequences are being utilized increasingly within virus-like particle (VLP) platforms, which utilizes repetitive display of epitopes to improve the activation of B-cells. The VLP-peptide conjugates tremendously enhance the neutralizing antibody reactions as well as reduce the dose requirements [15]. Other recombinant viral vectors, including adenoviral, measles or vesicular stomatitis virus (VSV), vectors have also been considered as vectors to deliver engineered peptides, though immunity to vectors is an impeding factor [16].

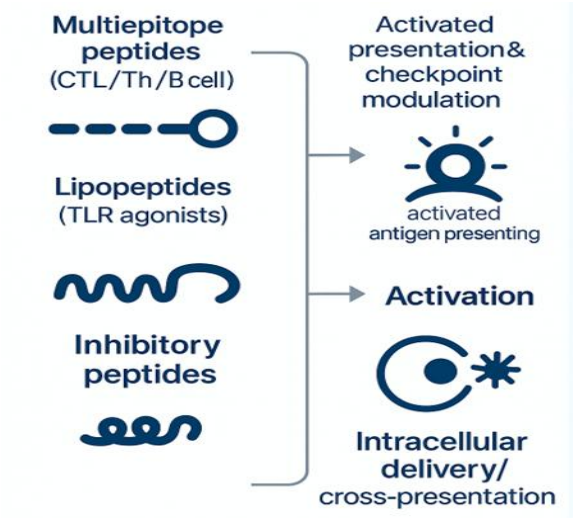

Fig 6 - Peptide delivery Pathway

5.2. Meaning of Trial Results

The clinical evaluation of leading engineered peptide vaccine candidates demonstrates both substantial promise and existing limitations within multiepitope and synthetic peptide immunization strategies. Results from UB-612, COVAC-1, ID93+GLA-SE, and peptide nanofiber platforms underline key advantages over traditional vaccines, particularly in generating robust T-cell immunity, broad epitope recognition, variant resilience, and favorable safety outcomes. These observations highlight the capacity of peptide constructs to overcome major shortcomings of current antiviral vaccines, including weak cellular responses, waning antibody levels, and diminished protection against emerging variants.

UB-612 has shown strong Th1-driven T-cell responses by incorporating conserved epitopes from spike, nucleocapsid, and membrane proteins, achieving broader and more durable immunity than spike-only mRNA boosters. Its ability to sustain IFN-γ responses and generate polyfunctional CD4+ and CD8+ T cells suggests improved long-term immune persistence. Importantly, UB-612 retained reactivity against Delta and Omicron variants, demonstrating the value of epitope-based constructs that target multiple conserved regions, enabling rapid adaptability for pandemic preparedness.

COVAC-1 further strengthens the case for peptide-based strategies, showing potent T-cell activation in populations that typically respond poorly to standard vaccines, including cancer patients and immunocompromised individuals. Its strong Th1 cytokine profile indicates potential superiority in individuals with impaired B-cell responses, addressing critical protection gaps highlighted during the COVID-19 pandemic.

Conversely, the EpiVacCorona peptide vaccine revealed significant limitations, achieving regulatory approval yet demonstrating poor neutralization capacity and unclear protective efficacy. This case emphasizes the importance of informed epitope selection, high HLA-binding affinity, structural stability, and predictive immunoinformatics in peptide vaccine design. The failure reinforces that peptide vaccines are highly dependent on rational engineering principles rather than empirical sequence selection.

Preclinical work on peptide nanofiber scaffolds highlights the importance of structural organization and antigen spacing in promoting germinal center formation, antigen retention, and durable immune memory. Similarly, ID93+GLA-SE nanoparticle-formulated peptides showed strong Th1-biased responses and effective protection in challenge models, demonstrating the synergistic value of optimized peptide antigens combined with nanomaterial delivery systems.

Despite these promising results, significant scientific and operational gaps remain in the peptide vaccine development pipeline. A primary obstacle is the lack of validated immune correlates of protection for many viral diseases, making it difficult to project clinical efficacy and slowing regulatory progress. Without reliable biomarkers, trials require large cohorts, extended timelines, and higher costs.

Another critical limitation is insufficient demographic diversity in clinical studies. Key populations—pregnant women, young children, older adults, and immunocompromised individuals—are rarely included, reducing generalizability and obscuring true population-wide effectiveness.

Technological scalability poses additional challenges. Although peptides can be synthesized efficiently, formulations involving nanoparticles, lipidation, and complex adjuvants introduce manufacturing barriers and regulatory uncertainty. Antigen diversity also remains limited; most peptide vaccines target only a few viral proteins, highlighting the need for broader epitope screening and improved HLA-coverage modeling to ensure global applicability.

Funding constraints further hinder development, as industry investment favors low-risk booster products rather than novel peptide-based immunotherapies. Deployment challenges persist as well, with vaccine delivery systems still oriented toward childhood immunization rather than adult or precision-based vaccination. Moreover, the requirement for diagnostic screening, such as serology or HLA typing, restricts implementation in resource-limited settings.

VI. DELAYS IN THE DEVELOPMENT TIMELINES AND INSUFFICIENT LATE-STAGE CLINICAL PROGRESS.

Slow rollout of peptide vaccines of preclinical and Phase I/II to Phase III testing: This appears to be the greatest bottleneck in the current peptide vaccine

pipeline because the vaccine must undergo Phase III tests prior to regulatory approval and population deployment. Although many of the peptide vaccine candidates have demonstrated encouraging immunogenicity profiles, most of them are still at an early development stage because of a lack of funding, issues with regulatory uncertainty and lack of validated correlates of protection [52]. Much like historical trends of engineered peptide vaccine development, engineered peptide vaccine development schedules can take 815 years of time between conceptual design to approval [53]. Although computational design has greatly increased the speed of antigen detection, clinical development is limited by the complexity of the trials, and the difficulty of recruiting patients.

The necessity of fast-response systems during pandemics has become evident in the wake of disruption all over the world during COVID-19. Conventional development timelines of vaccines do not work well with novel viral threats that are developing at a faster pace than clinical pipelines. As such, adaptive trial design, correlate-based model approach to approval, real-time-immunoinformatics integrations, and scale-up of peptide vaccines through parallel manufacturing are areas that need future research to reduce the time-frames of peptide vaccine-translation [54]. The absence of such acceleration means that peptide vaccines will lose their competitiveness in the face of the fast-evolving pathogens.

6.1. Insufficient Diversity at Clinical Trials and Inclusiveness.

Just like the problems that have been observed in most of the available studies with vaccines, there have been poor demographic representation in engineered peptide vaccine studies where vulnerable groups such as pregnant women, pediatric, elderly adults, immunocompromised patients, cancer patients, and individuals with autoimmune diseases are underrepresented [39]. Preliminary clinical evidence with COVAC-1 showed great outcomes when used in immunocompromised individuals [26], and the peptide vaccines might have a dramatic effect with regard to missing the current vaccine performance. However, such high-risk groups are not yet included in the clinical studies of peptide vaccines because of regulatory reluctance and safety considerations [55].

Limited demographic engagement generates data, which might not be representative of vaccine performance in practice and limits its equivalence to standard platforms [56]. There is therefore a need to increase diversity on a scientific level as well as ethically. The involvement of more participants of the trials should be a priority that is achieved with the help of stratified recruitment models, region-specific cohort recruitment, and expansion of the global trial sites to low and middle-income countries where the virus is the largest one [57]. In the absence of this, there will be no confidence in deployment models and will experience unfair implementation.

6.2. poor Animal models and low levels of information on Mechanistic Immunity.

The second significant limitation is that the current animal models have a poor capacity of mimicking human immune responses with regard to peptide vaccines. Some key disparities in adaptive immunity, mucosal response architecture, germinal center dynamics and HLA distribution are observed in many animal systems relative to human beings [58]. Such differences do restrict predictive capability and cause the promising vaccine constructs to fail in human studies despite excellent preclinical results. Besides, the absence of validated immune correlates of protection limits the capacities to use immune markers as predictors of clinical success [37].

To establish the immunological processes that facilitate protection and long-term memory after peptide immunization, high-resolution mechanistic analyses utilizing single-cell sequencing, multiomics profile, multiomics immune organoid models and humanized mouse systems are required [59]. Enhanced models are especially significant to peptide vaccines since they are meant to operate via T-cell and APC signaling pathways that have not been entirely recapitulated in normal animal models [32]. With no mechanistic clarity and dependable correlates, massive investments and regulations approvals will be limited.

VII. THE PROMISE OF MULTI-EPITOPE VACCINE DEVELOPMENT (FUTURE DIRECTION)

The development of multi-epitope peptide vaccines is one of the most attractive and fastest evolving directions of antiviral immunotherapy, which provides the opportunity to cope with most of the limitations of traditional vaccine systems and mono-antigen approaches [66]. Multi-epitope constructs are based on the use of multiple toxin sequences of different viral proteins. In contrast to whole-virus or subunit vaccines, which are based on the entire structure of the protein, these vaccines use several toxin sequences of various viral proteins in a single engineered construct. The design allows wide coverage of viral strains, enhanced immune specificity, minimized chances of antigenic evasion and enhanced induction of humoral and cellular immunity [67]. Multi-epitope peptide vaccines are especially effective with viruses that mutate rapidly, including SARS-CoV-2, influenza, HIV and dengue because of the capacity to include highly conserved epitopes of both structural and non-structural proteins [68].

The big opportunity associated with multi-epitope vaccines is that they induce robust CD4+ and CD8+ T-cell responses, unlike conventional vaccines that generate immunity dominated by antibody [69]. Viral clearance involves the involvement of functionally cytotoxic T lymphocytes that can recognize and destroy infected host cells particularly in chronic or persistent viral infection like HIV, hepatitis B and some strains of coronaviruses [70]. Multi-epitope constructs allow the induction of cytotoxic T-cell responses to be specifically directed by including both MHC-I binding and MHC-II binding epitopes of the construct to control helper T-cell coordination [71]. This dual-design is imperative in the production of long-term immune memory and prevent reinfection or reactivation, which conventional protein or inactivated vaccines tend to fail [72].

Emerging technologies in immunoinformatics, computational vaccinology and AI-based epitope screening applications increase the promise of multi-epitope vaccines. With these technologies, a systematic prediction of antigenicity, toxicity, allergenicity, binding affinity, surface accessibility and HLA-coverage performance can be made prior to experimental validation [73]. Computational epitope-mapping systems are incredibly faster in the design of vaccines, and development time-frames are cut down to weeks [18]. This has been especially useful when it comes to responding to epidemic and pandemic situations that demand quick production of prototype candidates in reaction to new variants [74]. Population based peptide optimization is another use application of immunoinformatics because it analyses epitope compatibility with different global HLA haplotypes, which is one of the largest limitations that have been experienced with more ancient vaccines in which immunogenicity can differ across demographic groups [75].

VIII. CONCLUSION

Among all emerging as well as established pathogens, viral infectious diseases continue to be one of the most significant global health issues in the modern day because of their profuse morbidity, mortality and socioeconomic disruptiveness. These weaknesses of current antiviral vaccine systems, such as insufficient stability, declining antibody levels, poor mucosal immunity, and poor response to rapidly evolving strains, highlight the urgent necessity of having alternative immunological protection modalities that would elicit superior and extensive immune responses [20,22]. The next-generation platform has been identified to be engineered peptide constructs which are highly promising because of their modular design, ability to precisely target immunopathogenicity, compatibility with computational prediction of epitopes and rapid manufacturability [17,33]. They have the potential to have better immunogenicity, cellular responses and variant-resistant protection compared to conventional vaccines [23].

Clinical data on the top candidates including UB-612 and COVAC-1 showcase high levels of Th1-based immune response, robust CD4+ and CD8+ T-cell response and cross-reactivity with emerging SARS-CoV-2 variants, this confirms the potential of multiepitope peptide platforms in creating broad-spectrum antiviral immunity [20,26]. Research has also indicated using peptide nanofiber scaffolds and nanoparticle-mediated peptide delivery as studies have further demonstrated the benefits of structural antigen organization and biomaterial engineering in

improving the germinal-center activation and immune memory stability [32, 33]. Furthermore, scalability is supported by the safety and manufacturing advantages of synthetic peptides such as chemical stability, cold-chain independence, low production cost, and equity and preparedness to address global pandemics [21,34].

It is however necessary that the peptide vaccine space has a number of research and translational gaps that need to be filled so that it can be widely applied. The challenges that are noticed include sluggishness in switching between the Phase I/II and Phase III trials, lack of validated correlates of protection, the lack of demographic diversity in clinical trials, lack of predictive animal models and inadequate funding mechanisms to support the high-risk innovation [37,44,55]. The problem of regulatory uncertainty and the necessity of diagnostic infrastructure can also pose structural challenges to the implementation of peptide immunotherapies on a large scale [45,46]. These gaps will be resolved by increased incorporation of immunoinformatics, systems immunology, biomaterial science and translational policy framework to expedite the development and enhance access in the world [58].

In the future, multi-epitope peptide vaccine approaches can be seen as a radical future of antiviral immunotherapy with the possibility of integrating conserved epitopes, enhance the activation of T-cells, and add personalized HLA coverage and adaptation to emerging pathogens [66,75]. Their ability to merge with nanoparticle delivery systems, immune-modulating adjuvants and checkpoint regulatory peptides makes them not only preventive vaccines, but also therapeutic vaccines which can restore immunostasis in chronic viral infections [61]. To achieve their full potential, further interdisciplinary studies, growth of clinical assessment and international investment in manufacturing and policy facilities is needed [47].

To sum up, designed peptide constructs offer an attractive and scientifically substantiated direction of future development of next-generation antiviral vaccines and immunomodulators. As the continuous innovation, joint development and fair distribution models develop, peptide-based immunotherapies could gain a place in the global arsenal in the event of a new pandemic and chronic viral menace [79,80].

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