

# Progress in the Application of Peptide Vaccines in the COVID-19

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**Abstract.** A brand-new coronavirus dubbed COVID-19 epidemic broke out in the winter of 2019 and quickly swept the globe. Additionally, the pandemic's high mortality rate and high infection have prompted sustained scientific efforts to treat the illness. Backing the history of the virus, vaccine development is the most effective method to mitigate this urgent public issue. Pharmaceutical firms from nations including China, the United States, and Russia subsequently started doing research on vaccine development. While Pfizer and Monard in the US utilize mRNA genetic vaccines, China uses inactivated vaccines and viral vector vaccines. As a result of the difficult inactivated vaccine manufacture procedure and the issue of toxicity rebound, there is also a chance that genetic vaccines will mate with host genes. It is thought that the creation of peptide vaccines will deal with these two problems. Peptide vaccines are therefore seen to be the safest, and they may be employed not only for preventative immunization but also for the treatment of solid malignancies. Clinical studies for peptide vaccines are underway. But because peptide vaccinations are quickly broken down by cells, their drug carriers play a crucial role as well. This article will outline the selection of the protein sequence for the COVID-19 peptide vaccine as well as the development of its tests.

**Keywords:** COVID-19; peptide vaccine; S protein; CoVac-1 vaccine.

## 1. Introduction

In the winter of 2019, a novel coronavirus found in Wuhan, China. And in short time, this virus spreads fast to the globe and shows high mortality [1]. According to WHO statistics, by 2022, there will have been more than 300 million confirmed infections worldwide, and there will have been more than 5 million fatalities, patients present severe acute respiratory syndrome, short-distance droplets, coming into touch with patient respiratory secretions, and close contact are all ways that this coronavirus might spread [1-3]. Fever, headache, muscular soreness, coughing, and diarrhea are the primary clinical signs, while severe patients may also have symptoms including difficulty breathing[2-4]. The patient's lungs are where the pathological alterations are most obvious, with both lungs significantly swollen [3-4]. Alveolar lesions, pulmonary edema, and the development of a transparent membrane can all be observed up close. Three weeks later, alveolar fiber blockage caused by pulmonary interstitial fibrosis may be seen. Microvascular thrombosis and pulmonary bleeding are two signs that can be noticed up close. Additionally, it may result in pleural and myocardial lesions [1-4].

The coronavirus most likely originated in certain animals, although it may currently spread between humans and animals. COVID-19 is a B-coronavirus, which is RNA heredity and S, M, N, some proteins structure [3-5]. Spike proteins, the majority of which are virus-adsorbed proteins, are the primary surface antigens of coronavirus among them, membrane fusion upon the binding of the spike (S) protein to its receptor, angiotensin-converting enzyme 2 (ACE2) [5]. Some of them also facilitate the entrance of viruses into cells. They interact with cell receptors to start a viral infection. The best strategy to avoid illness is through vaccination, according to the history of mankind and the battle against viruses. Vertebrates have a special immune system that can recognize and successfully eliminate invasive infections. Humans can obtain specific antibodies and develop memory characteristics through vaccination to prevent it [6-8].

At present, humans have successfully developed a variety of vaccines, such as smallpox vaccine, rabies vaccine, tetanus vaccine, hepatitis B vaccine, HPV and other vaccines [9-11]. The most

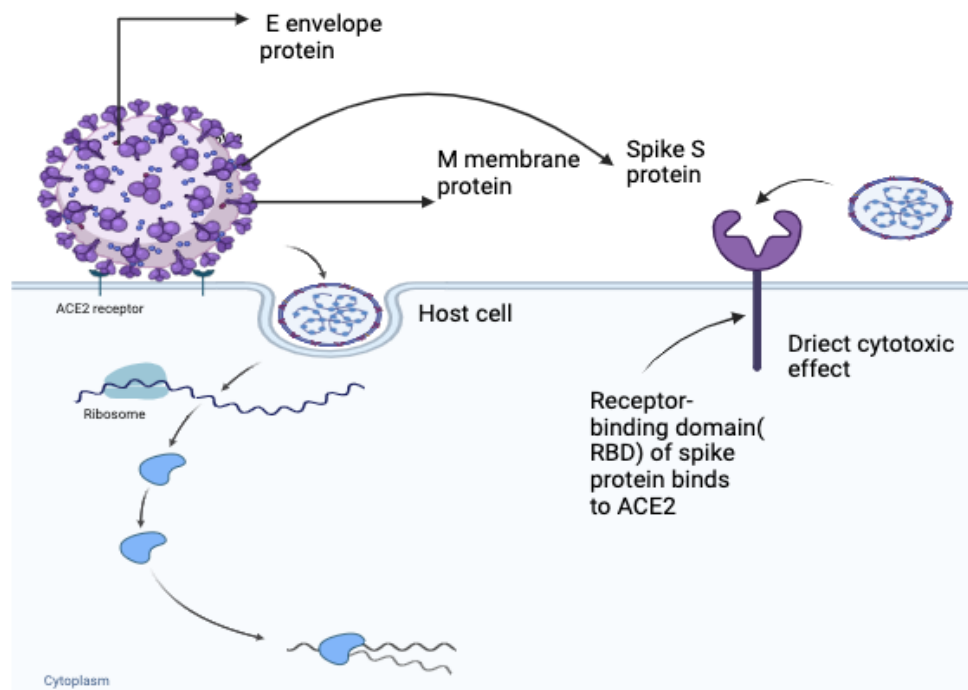


developed of them is the inactivated vaccine. Both the genetic and adenovirus vaccines for Ebola have shown great success. The creation of these types of vaccines, however, is not as quick because to the short research and development time and strict safety criteria, and there is also a concern with toxicity rebound in inactivated vaccines [10-13]. It may now think about creating peptide vaccines to deal with this problem. Peptide vaccines are created chemically because the viral proteins on the virus' surface serve as their target proteins. In contrast to inactivated and genetic vaccinations, peptide vaccines don't have toxicity recovery or virus gene fusion issues [12]. Additionally, peptide vaccinations can be utilized to treat cancer in addition to preventing viral infections. These peptides target cancer proteins that act as antigens on the surface of cancer cells and imitate antigenic epitopes that result in efficient or direct immune responses [11-14]. Peptide vaccines recognize tumor-related antigens and then exploit the MHC mechanism to stimulate potent anti-tumor T cell responses. The vaccinations can be kept stable under simple circumstances since they are water soluble [13-15].

## 2. Peptide vaccine manufacturing

### 2.1. Epitope -sequence selection

A full viral particle is mostly made up of proteins and nucleic acids, which together make up the virus's genome and act as a carrier of genetic data. This genetic data is used by the virus for its replication, inheritance, and mutation processes. There may be an envelope around certain viruses' nucleocapsids [7-9]. A virus having an envelope is called COVID-19. The biggest structural protein in coronaviruses, spike (S) is on the virus envelope, shown as fig1, glycoprotein, mediates receptor recognition, cell attachment, and fusion during viral infection [5,13].



**Figure 1. COVID-19 Structure and Infection Mechanism**

It is also important for virus penetration into host cells. A huge, noticeable structure called a "spike" can be observed on the surface of the virus because spike proteins have the capacity to create protein trimers. [5, 7] Once the viral membrane and host cell membrane have fused as a result of spike glycoprotein's interactions with cell surface receptors, the virus will eventually enter the host cell. High immunogenicity is seen in spike glycoproteins. [8-10] Searching the COVID-19 information on the NCBI website, which has 599 distinct genes, as of September 2023 since COVID-19 is a type of genetic material, RNA, and its structure is subject to variation. As a result, using Omicron to evaluate the sequences of the original sequence as well as two sample delta variants. It was discovered that the

virus's S protein is still very conserved in the altered sequence. S protein is the greatest option for making peptide vaccines because of its excellent stability [8-11]. The two subunits s1 and s2 make up the majority of the s protein. Unstable subunit conformations are produced when the RBD is exposed to S1 protein subunits [5,11]. As a result, S1 undergoes conformational rearrangement between the two states, referred to as the upper and lower conformations, throughout the binding process. COVID-19 S protein sequenc:

The S protein sequence information is shown in figure 2.



**Figure 2.** The COVID-19 S Protein Sequence Base Information

(The sequence information is obtained by the NCBI website)

## 2.2. Peptide synthesize

The majority of currently used vaccinations are made from infections that have been weakened, inactivated, or have the necessary elements (such as toxins) removed.[13] However, the immune system often reacts to very modest quantities of amino acids or peptides as antigens. Identifying the protein sequence, and manufacturing peptide vaccine through chemical reaction [12,13]. The fragment concentration method and the solid-phase synthesis method (also known as the Merrifield method) are the two basic synthesis techniques. A traditional synthesis process is fragment concentration. Prior to binding to produce larger peptides until the required sequence is reached, numerous short peptides are first synthesized, purified, and deprotected [11-13]. One way to attach the terminus of a peptide chain to a solid phase carrier is through solid-phase synthesis [10]. Peptide segment synthesis by progressively incorporating amino acids into the N-terminus. A few fresh innovations have also been made, such as enhanced protective genes, fresh solid-phase carriers, deprotection, and functional group protection techniques [14]. However, since antigen peptides are quickly broken down and eliminated by the body, bare peptides often only elicit a very weak immune response. Antigen peptide delivery method based on nanocarriers is thought to increase antigen peptide delivery efficiency with the rapid growth of nanotechnology [11-14]. The peptide vaccination is combined with nanomaterials as a drug carrier to enhance delivery, release, and certain activities involving the antigen, to the point where nanomaterials can lessen adverse medication reactions [11-13].

### 3. Clinical trails

#### 3.1. Inactivated vaccines

One of two whole inactivated viral COVID-19 vaccines created by Sinopharm's Beijing Institute of Biological Products is the Sinopharm BIBP COVID-19 vaccine, also known as BBIBP-CorV. Phase III studies in Bahrain and the United Arab Emirates yielded peer-reviewed data suggesting the vaccine is 78.1% effective. Due to the inactivated vaccine's effectiveness being less than 80%, some individuals who may still be COVID-19 infected might not be protected. However, another inactivated vaccine, developed by Beijing Institute of Biological Products Co. By the end of the worldwide phase III clinical study on December 31, 2020, one subject's severe nausea, vomiting, and other side effects had been linked to taking the medication, and the patient had been treated in a hospital [16-20].

#### 3.2. mRNA vaccines

Due to the fact that messenger ribonucleic acid is an unstable, negatively charged molecule, it is frequently enclosed in delivery carriers before being delivered to target cells. Messenger ribonucleic acid vaccines have several benefits over conventional vaccinations, including simple design, quick manufacture, low production costs, capacity to promote cellular and humoral immunity, and no contact with genomic DNA.[15] However, Pfizer's mRNA vaccine must be kept at minus 80 degrees Celsius, which presents certain challenges for the shipping and storage of vaccines. Both Pfizer and Moderna's mRNA vaccines caused mild adverse responses, with a larger percentage of adverse reactions happening after receiving Moderna's vaccinations [16,18,19]. Participants who got a second dose of the vaccine reportedly had false switching, and Bell's palsy has also been documented, according to a CDC report [21]

#### 3.3. CoVac-1 vaccine

Many other vaccines are being produced worldwide using COVID-19, inactive or attenuated viruses, virus-like particles, recombinant proteins, and antigen-coding mRNA [21,22]. CoVac-1 is a multi-peptide-based vaccine created to generate widespread and long-lasting SARS-CoV-2 T cell immunity after a single immunization that is unaffected by worrying viral variations that are emerging. Showing some clinical I phase data. Due to clinical purpose to confirm the drug toxicity and safety. In the clinical I phase, Sixty-one percent of subjects had baseline low-frequency T cell responses to single-vaccine peptides that could be at least two-fold enhanced by CoVac-1, which was shown on day 28 in all but one person. Events were mild to moderate (grade 1–2) in 81% of participants. And On day 28, seen 100% of part I and part II subjects had IFN-induced responses. However, the mRNA vaccines produced by Pfizer/BioTech and Moderna reveal 92% and 95% adverse effects, including painful injections, weariness, muscular soreness, fever, and some minor reactions after a second injection. As a result, peptide vaccines are believed to have more adverse reactions than the two types of mRNA vaccines in early clinical trials, in addition to showing benefits for immune cell response.[15] mRNA vaccine and CoVac peptide vaccine clinical adverse effects are shown in Table 1

**Table 1.** Compared the Pfizer, Moderna and CoVac-1 Adverse Event Rate

	Pfizer	Moderna	CoVac-1
Fever	14.2%	15.5%	-
Chill	31.9%	45.4%	2%
Muscle pain	38.3%	61.5%	21.0%
Headache	55.1%	64.7%	6%
Fatigue	62.9%	70.0%	11.0%
Pain at the injection	84.1%	92%	36%
Swelling	10.5%	14.7%	7%

#### 4. Summary

First off, making peptide vaccines is easier and more effective than making the other two vaccinations [23]. Additionally, peptide vaccines have proven to be safe in human, animal, and cell studies. Its immunological impact is also substantially greater than that of mRNA vaccines and inactivated vaccines [23,24]. Additionally, the vaccine's post-injection effect on antibody generation is excellent. While peptide vaccines may be maintained at room temperature, inactivated vaccines and mRNA vaccines must be transported and stored at temperatures between -20 °C and 80 °C [24]. As a result, peptide vaccinations are simpler to maintain and more easily transported. Furthermore, peptide vaccinations have remarkable long-term effectiveness. As a result, peptide vaccines can be thought of as a promising option for stopping COVID-19 [15]. Based on the antibody levels produced by the COVID-19 vaccination and clinical data in the treatment of lung cancer, the peptide vaccine has had some success despite the lack of peptide vaccines that the FDA has licensed for sale [18]. For instance, in Africa, South America, and Southeast Asia, dengue disease is similarly spread via mosquito bites and is an example of a typical RNA virus. Considering the benefits of creating a COVID-19 peptide vaccine described in this article. People may design and create vaccines for the dengue fever virus based on the same principles the peptide vaccine for COVID-19 can be licensed and commercialized through clinical trials [25,26].

#### References

- [1] Mohammad KO, Lin A, Rodriguez JBC. Cardiac Manifestations of Post-Acute COVID-19 Infection. *Curr Cardiol Rep.* 2022 Dec; 24 (12): 1775 - 1783.
- [2] Goyal PK, Mohammed TO, Mahmoud A, et al. Nguyen CV. COVID-19 infection leading to acute pustular dermatoses. *Arch Dermatol Res.* 2023 May; 315 (4): 685 - 697.
- [3] Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol.* 2020 May 1; 70 (9): 311 - 322. English, Spanish.
- [4] Fernandes Q, Inchakalody VP, Merhi M, et al. Emerging COVID-19 variants and their impact on SARS-CoV-2 diagnosis, therapeutics and vaccines. *Ann Med.* 2022 Dec; 54 (1): 524 - 540.
- [5] Gupta, A., Madhavan, M.V., Sehgal, K. et al. Extrapulmonary manifestations of COVID-19. *Nat Med* 26, 1017 – 1032 (2020).
- [6] Kaul R, Devi S. Coronavirus - A Crippling Affliction to Humans. *Recent Pat Biotechnol.* 2022 Aug 3; 16 (3): 226 - 242.
- [7] Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiol Mol Biol Rev.* 2005 Dec; 69 (4): 635 - 64.
- [8] Matta J, Wiernik E, Robineau O, Carrat F, et al., Relations et Inégalités Sociales en Population Générale Pendant la Crise COVID-19–Sérologie (SAPRIS-SERO) Study Group. Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results with Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. *JAMA Intern Med.* 2022 Jan 1; 182 (1): 19 - 25.
- [9] Nelde A, Rammensee HG, Walz JS. The Peptide Vaccine of the Future. *Mol Cell Proteomics.* 2021; 20: 100022.
- [10] O'Neill CL, Shrimali PC, Clapacs ZE, et al. Peptide-based supramolecular vaccine systems. *Acta Biomater.* 2021 Oct 1; 133: 153 - 167.
- [11] Zagorski K, Pandey K, Rajaiah R, et al. Peptide Nanoarray Scaffold Vaccine for SARS-COV-2 and Its Variants of Concerns. *Res Sq [Preprint].* 2022 Jan 24: rs. 3. Rs - 1206402.
- [12] TopuzoĖullari M, Acar T, Pelít Arayici P, et al. An insight into the epitope-based peptide vaccine design strategy and studies against COVID-19. *Turk J Biol.* 2020 Jun 21; 44 (3): 215 - 227.
- [13] He Y, Hong C, Fletcher SJ, Berger AG, et al. Peptide-Based Cancer Vaccine Delivery via the STINGΔTM-cGAMP Complex. *Adv Healthc Mater.* 2022 Aug;11 (15): e2200905.
- [14] Negahdaripour M, Golkar N, Hajighahramani N, et al. Harnessing self-assembled peptide nanoparticles in epitope vaccine design. *Biotechnol Adv.* 2017 Sep; 35 (5): 575 - 596.
- [15] Heitmann JS, Bilich T, Tandler C, et al. A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity. *Nature.* 2022 Jan; 601 (7894): 617 - 622.
- [16] Muchowska KB, Moran J. Peptide synthesis at the origin of life. *Science.* 2020 Nov 13; 370 (6518): 767 - 768.
- [17] Information on: <https://www.phgfoundation.org/briefing/rna-vaccines>.

- [18] Buonaguro L, Tagliamonte M. Peptide-based vaccine for cancer therapies. *Front Immunol*. 2023 Aug 16; 14: 1210044.
- [19] Li M, Wang H, Tian L, Pang Z, et al. COVID-19 vaccine development: milestones, lessons and prospects. *Signal Transduct Target Ther*. 2022 May 3; 7 (1): 146.
- [20] Hadj Hassine I. Covid-19 vaccines and variants of concern: A review. *Rev Med Virol*. 2022 Jul; 32 (4): e2313.
- [21] Al Kaabi N, Zhang Y, Xia S et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA*. 2021 Jul 6; 326 (1): 35 - 45.
- [22] Pardi N, Tuyishime S, Muramatsu H, et al. Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes. *J Control Release*. 2015 Nov 10; 217: 345 - 51.
- [23] Fiolet T, Kherabi Y, MacDonald CJ, et al. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clin Microbiol Infect*. 2022 Feb; 28 (2): 202 - 221.
- [24] S.A. MEO1, I.A. BUKHARI2, et al, COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines *European Review for Medical and Pharmacological Sciences* 2021; 25: 1663 - 1669.
- [25] Khetarpal N, Khanna I. Dengue Fever: Causes, Complications, and Vaccine Strategies. *J Immunol Res*. 2016; 2016: 6803098.
- [26] Wilder-Smith A. Dengue vaccine development: status and future. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheit Schutz*. 2020 Jan; 63 (1): 40 - 44.