International Journal of Scientific Research and Engineering Development-– Volume 6 Issue 4, July- Aug 2023
Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

BIOTECHNOLOGICAL ADVANCES in VACCINE DEVELOPMENT

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ABSTRACT
Every year, according to World Health Organization (WHO), 2–3 million lives are saved via modern immunization program, contributing to the marked reduction in mortality of youngsters less than 5 years of age globally from 93 number of deaths per 1,000 live births in 1990 to 39 deaths per 1000 stay births in 2018. Vaccines exploit the brilliant capability of the highly advanced human immune gadget to respond to, and remember encounters with pathogenic antigens.

A vaccine is a biological preparation that boosts your immune system against a certain disease. It contains certain agent that not only mimics a pathogenic microorganism rather the immune system is also stimulated, and foreign agents are recognized. Vaccines are given in liquid form via injection, oral administration, or intranasal administration. The vaccine that is injected contains a foreign microbe
that has an antigen, whenever the vaccine is effectively injected, the macrophages ingest the antigen, processes them and presents them to the T cells, the T cells thereafter produces four (4) clones.

This review puts together different biotechnological advances that has taken place in vaccine development.

Keywords: Antigen,Cell,Immune system,Microorganism,Vaccine

1.0 INTRODUCTION

Vaccines exploit the brilliant capability of the highly advanced human immune gadget to respond to, and remember, encounters with pathogen antigens. However, for a great deal, except for the involvement of immunologists, vaccinations have always been generated through empirical study. Today, there's a huge demand for better technology, appreciation of the immunological groundwork for vaccination to increase vaccines for hard-to-target pathogens (such as Mycobacterium tuberculosis, the bacterium that causes tuberculosis (TB)3 and antigenical

pathogens with a wide range of symptoms (e.g., HIV)4, to manipulate outbreaks that pose a global health risk (such as COVID-19 or Ebola)5,6 and to figure out how to reactivate immune responses in the aging immune system to protect an aging population from infectious diseases. (Pollard & Bijker 2021).

1.1 HISTORY AND OVERVIEW OF VACCINE DEVELOPMENT

Edward Jenner's experiments in 1798, when he used cowpox virus to immunize people against smallpox, can be traced back to the beginning of vaccination. [5].

The World Health Organizations extensive smallpox immunization campaign eventually contributed to the disease's worldwide elimination nearly 200 years later. That success story exemplifies vaccination's enormous potential, and it has led to the creation of vaccines against practically all disease pathogens that harm humans and animals.

Vaccine's ultimate purpose is to stimulate an immunological response that will recognize the infectious agent and fights the infection. Vaccination is often done with live agents that have been weakened or attenuated, inactivated organisms that can no longer cause disease, or sub-unit vaccines that include selected immunogenic sections of the disease agent. Traditional vaccine development strategies include using a comparable agent that has no effect on the disease, such as Jenner's cowpox virus, or passing a pathogenic disease agent via a laboratory host system to weaken or attenuate the agent.

Vaccines can also be created by using one or more chemicals to inactivate the disease virus. In addition, one or more pathogen elements can be isolated, purified, and used to trigger a protective immune response. When the immune system comes into contact with a foreign material called an antigen, it triggers an immune response.

A person's or animal's immune system can distinguish between a foreign substance, such as the proteins found in a virus or bacteria, and its own proteins. Whether the foreign proteins are from a disease agent or a vaccine against the disease agent, the immune response is the same. When the virus has infected the animal or bacterium again, the immune system detects it and in the best-case scenario, responds to protect the animal from the sickness. Vaccination has saved many lives, but it can have both positive and negative outcomes. Certain vaccines, particularly live vaccines, have the ability to revert harmful organisms, resulting in sickness and in some circumstances, death. The advancement of rDNA technologies has made it possible to pursue new opportunities for attenuating disease agents by altering their genetic makeup or genomes in order to create vaccines that are both safer and more effective. Every living entity has a genome, which comprises of a large number of genes that define the organism's characteristics. Nucleic acids (DNA and ribonucleic acid [RNA]) contain and convey genetic information via their bases (adenine, cytosine, guanine, and thymine; uracil replaces

thymine in RNA). To produce the gene's sequence, the nucleotides are arranged in a specific order. Using rDNA technologies, it is possible to modify or delete the genes that cause disease in an organism in the laboratory. "rDNA technology" refers to laboratory procedures for breaking and recombining DNA molecules from a wide range of creatures. Gene isolation, sequence modification, nucleic acid synthesis, and gene cloning are all examples of laboratory processes that have been added to the lexicon. Using rDNA technology, scientists can isolate a disease agent, break it down into its constituent parts, evaluate its genetic makeup, and change it so that it no longer causes disease but still triggers a potent immune response. Many laboratories have developed methods for gene extraction and purification of exceedingly minuscule quantities of even the slightest organisms.

After the nucleic acids have been isolated, the genes can be modified and reintroduced into the body to create a vaccine that is attenuated and/or capable of creating enhanced immune protection.

Using rDNA technology to produce vaccines necessitates a good understanding of the pathogen particularly the antigens that are crucial for generating protection. To guarantee vaccine stimulation of the optimal immunological response, it is also necessary to understand the pathogenicity of the agent of infection and the immune response of the host. Genetic information from both microbial genomics and proteome research is increasingly being used to acquire a better understanding of the relationships between the disease agent and the host.

Vaccines made with recombinant technology on the other hand, are meant to be safer, more effective, and/or less expensive than traditional vaccines. (Jackwood et al., 2008)

1.2. DEFINITION OF A VACCINE

A vaccine is an item that can be used to safely trigger an immune response that protects against infection and/or disease when exposed to pathogens in the future. To do this, the vaccine must include antigens generated from the pathogen as well as antigens synthesized to represent the infectious aspects of the pathogen. The quintessential element of most vaccines is one or higher protein antigens that result in immune responses that supply protection. However, polysaccharide antigens can also end result in defensive immune responses and are the groundwork of vaccines that have been developed to give up a quantity of bacterial infections, such as pneumonia and meningitis triggered via way of *Streptococcus pneumonia*). [6]

1.3.MECHANISM OF VACCINE ACTION

Humans have been infected with Coronavirus, one of the viruses that causes the common cold, for a long time. It is a contagious virus that can be spread through contact or inhalation. Virus droplets enter the body by coughing and sneezing. Touching an infected surface is one of the most common ways to become infected. The

coronavirus genome has 30,000 nucleotides in it. Spike (S) protein, Membrane (M) protein, Nucleocapsid (N) protein, and Envelop (E) protein are among the four structural proteins encoded by this gene, as well as a number of non-structural proteins (nsp). The capsid is the protein shell that surrounds the capsid. The nuclear capsid, also known as N-protein, is a nucleus-associated protein. The N-terminal of the RNA binding protein that binds to genomic and sub-genomic RNAs and process viral replication in MHV and IBV virions transcription. This is a significant open research project, issues with the growth of an effective medicine that targets inhibit the N-terminal of N-protein from making contact with a single strand of positive RNA that can inhibit viral replication as well as transcribing according to Sarma et al. 2020. The primary chemical classes are theophylline and pyrimidone. The coronavirus primary organizer is assumed to be the M-protein which is most abundant on the viral surface. The S-protein is incorporated into the virus's surface and facilitates viral entrance into the host cell by mediating attachment of the virus to the host cell surface receptors and membrane fusion between the membranes of the viral and host cells [15]

The E-protein is a tiny membrane protein of 76-109 amino acids that is the virus's small component particle. It's involved in virus assembly, permeability of host cell membranes, and virus-host cell interactions[10]

The genetic material is encased in a lipid wrap. The viral surface contain a hemagglutinin-esterase dimer (HE). The E-protein appears to be crucial for natural host-cell infection, even though it is not necessary for the virus replication [12]

Cryo-EM investigations have revealed the complete structure of the Spike (S) protein in both the closed and open (profusion) states. This glycoprotein consists of three identical chains, each containing 1273 amino acids, as well as two distinct protein domain regions: S1 and S2 sub-units which are involved in cell recognition and membrane fusion respectively.

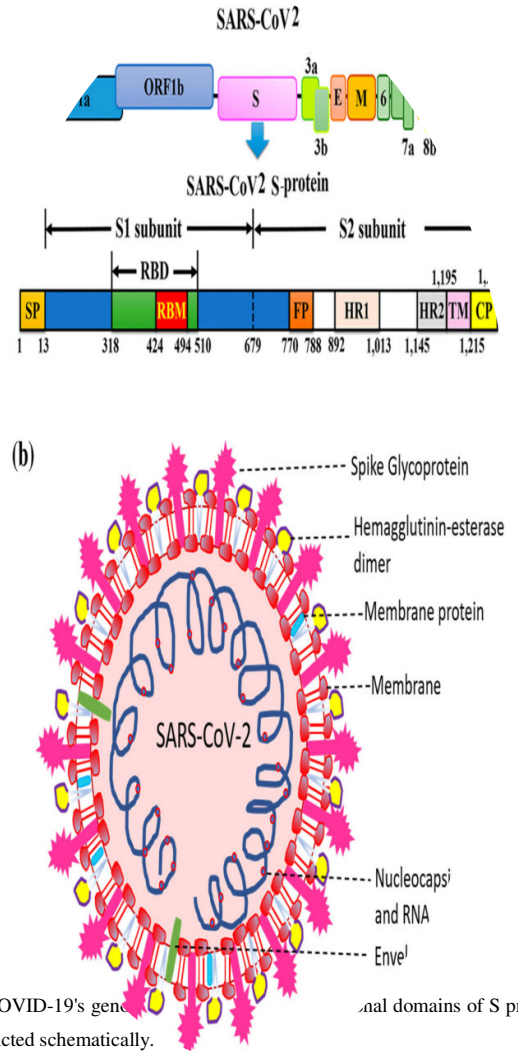

Figure i: COVID-19's gene nal domains of S protein is depicted schematically.

COVID-19's single-stranded RNA genomes encode the ORF1a and ORF1b genes, which

encode 16 non-structural proteins (nsp1—nsp16). Spike (S), envelope (E), membrane (M), and spike (S) are structural proteins.

The structural genes encode the nucleocapsid (N) (N). Auxiliary genes are found in various shades of green and have been used to color-code the information. The structure of the S protein lies beneath the genomic architecture. S1 and S2 are the two subunits that make up the S protein.

The S1/S2 cleavage sites are indicated by dotted lines. The domain of the cytoplasm (CP), the receptor-binding domain (RBD), the fusion peptide (FP), and the heptad repeat (HR) (RBD),

The S-signal protein's peptide (SP) and transmembrane domain (TM) are as shown in B. The viral surface proteins spike, envelope, and capsid are surrounded by a lipid bilayer membrane. The Nucleocapsid protein is linked to the single-stranded positive-sense viral RNA [10]

1.4.STAGES IN VACCINE DEVELOPMENT AND CLINICAL TRIALS.

Stages of vaccine development includes:

Exploratory or Preclinical phase- Research and Development, developing a vaccine candidate.

Phase I studies are used to ensure safety and preliminary results.

Phase II trials assess the treatment's effectiveness, Immunogenicity, dosing levels, and side effects. Hundreds of people are usually exposed to a potential vaccination. The randomized and placebo-controlled trials make up phases I and II. Several people usually Includes phase III trials at several locations, including a control group. Its goal is to determine the vaccine's efficacy in preventing the disease sickness, as well as keeping an eye on any negative consequences.[13]

1.5.VACCINE'S DEVELOPMENTAL STEPS

Vaccine have been shown in pre-clinical tests to minimize the risk of infection. Efficacy and safety of vaccines are determined through animal research, including challenge tests.

I. Phase 1 Clinical Trial: The vaccine is administered to small groups of healthy adult volunteers in order to ensure safety.
II. Phase II Clinical trial: Vaccine is given to a wider group of people who share comparable characteristics (such as age and physical health) as those who would be receiving the new vaccine.
III. Phase III Clinical Trial: Thousands of people are given the vaccine and it is tested for effectiveness and safety.
IV. Phase IV post-marketing surveillance after the vaccine has been approved and licensed, ongoing test will be conducted to keep track of negative events and investigate the vaccine's long-term effects in the population.

2.0 TRADITIONAL AND MODERN VACCINES.

2.0.1.TRADITIONAL VACCINES

The first vaccinations was developed using organisms with low pathogenicity. Plett and Jenner were among the early pioneers in this field,

using the cowpox or horse pox virus to create vaccinations against smallpox, these low-virulence vaccines have various advantages, including the fact that they only cause a moderate illness with symptoms that are comparable to those of the target pathogen, and the body then develops a powerful immune response with immunity lasting for years. Traditional vaccines likewise have one major disadvantage: they increase the risk of infection by allowing viruses with low virulence to become more virulent. In the second method of traditional immunization, inactivated vaccines are employed, which are safer than live vaccines. However, in order to acquire significant and long-lasting protection, such vaccinations requires numerous administrations. Although live attenuated or inactivated vaccines can be manufactured more easily and quickly than other vaccine's types, they have a poor safety record and a flaw in the manufacturing process might possibly lead to disease outbreaks, in fact, a similar incidence occurred in 1955, when a faulty polio vaccination was administered resulting in 10 fatalities, 200 cases of paralysis, and 40,000 cases of polio infection. As a result, developing alternative vaccinations with improved safety profiles is a top goal.

2.0.2.MODERN VACCINES/NEXT GENERATION VACCINES

Wolf et al. revealed in 1990 that mice injected with plasmids containing a cloned protein expressed the transgenic protein cloned in the plasmid's DNA. These findings sparked the creation of a new vaccination method and signaled the start of a new age of next-generation vaccines. The first strategy for developing these innovative vaccines was to use DNA which was followed by the invention of viral vectors for immunization such as adeno-associated virus (AAV), lentiviral, or adenoviral vectors and more recently RNA-based vaccines. The importance of this study is that it shows that only a small fraction of the viral protein structure is required to promote protection against a specific infection. As a result, instead of using the entire pathogen, these innovative vaccines tend to use only a single viral antigen, resulting in a better safety profile. However, because developing such vaccines needs a better understanding of viral architecture and the interactions between viral proteins and host cell receptors, more research is required. These next-generation vaccines typically necessitate a protracted phase of exploratory research before development can begin.

3.0. RECOMBINANT PROTEIN VACCINE

Using recombinant viral structural proteins, recombinant protein vaccines induce an immune response. The SARS-CoV-2 genome contains structural proteins such as the membrane, envelope, nucleocapsid, and spike. Spike protein is very significant because it interacts with angiotensin-converting enzyme 2 (ACE2) receptors on the surface of its host cells, making endocytosis simpler. Most immunization attempts for the SARS-CoV-2 virus have focused on this

protein. However, immunization with the entire spike protein has proven to cause liver damage in treated animals, thus using only a portion of the protein such as the receptor-binding domain (RBD), which interacts with the ACE2 receptor protein is the best option for creating a safer vaccine. According to preliminary research, vaccination with recombinant protein or just the RBD induces neutralizing antibodies to develop. According to these findings, the protein is digested by dendritic cells, then presented to naive B and T cells, resulting in their activation and subsequent immunity development. However, using this technique for vaccination has a significant disadvantage: because only a tiny portion of the protein is used for immunization, specific immune reactions elicited by the vaccine only provide partial protection. Furthermore, these immune responses aren't often very strong. As a result, recombinant protein vaccination involves the use of adjuvant, or substrates, to increase the immune response. Antigen presentation in antigen-presenting cells (APCs) is improved when such adjuvant are used, resulting in increased vaccine efficacy and long-term protection.

3.1.PLASMID DNA VACCINES

Wolff et al. proved In-Vivo production of a protein encoded by plasmid DNA, and it was later proven that immunization with plasmid DNA can generate a significant immunological response as previously indicated. The findings of these investigations taken together has provided proof of the Plasmid DNA with the ability to provide immunization through injection.

As a result, researchers began researching the use of DNA vaccines in the treatment of cancer infections, and other diseases. Allergies are an example of autoimmune illnesses. The early-stage clinical investigation subsequently, due to weak transfection efficacy and low transfection efficiency, in humans has tend to be unsuccessful immunogenicity. DNA vaccines since then have some advantages. First, there's the vaccination with plasmid DNA which is safer than some traditional vaccines because it does not require the use of a live virus. Second, unlike proteins, viruses or mRNAs, plasmid DNAs are more stable and may be freeze-dried and stored for lengthy periods of time. Third, these vaccinations are easier to make and less expensive to produce. Improved transfixion advanced method have been developed in recent years on plasmid transfer into cells, such as Electroporation, which uses electric pulses to perforate the cell membrane. The use of adjuvant to stimulate the immune response has progressed in the development of DNA vaccines, making them more suitable for mass delivery. In this regard, the business Inovio conducted one of the first MERS coronavirus vaccination studies in attempt to create a novel DNA vaccine for Covid-19. High levels of expression of the SARS-CoV-2 spike protein were seen after vaccination with the synthetic DNA-based vaccine (INO-4800). Likewise antigen-specific T cell reactions and antibody production are capable of binding to ACE receptors and neutralizing SARS-CoV-2

infection. Inovio had previously created DNA vaccines to combat the Ebola, SARS, MERS, and Zika viruses. Previously, DNA-based vaccines were utilized to establish immunity against Toxoplasma gondii in mice, as well as T-cell-dependent antibody response against glutamic acid decarboxylase.

3.2 VIRAL VECTOR VACCINES

Although the use of viral vectors for therapeutic purposes began in the late 1990s, the death of Jesse Gelsinger, who was given an adenoviral vector, and the development of leukemia in children with severe combined immunodeficiency (SCID) treated with retroviral vectors overshadowed the use of these vectors for disease treatment.

However, significant progress in the development of viral vector vaccines has yielded encouraging results in dendritic cells in recent years and an increasing number of studies have begun to focus on the use of various viral vectors, including RNA (retroviral and lentiviral), adenoviral, and Adeno associated virus (AAV) vectors. Immunization with viral vector vaccines requires cloning the immunogenicity-causing antigen in a *pseudo virus* that can't reproduce and spread transfer in dendritic cells, resulting in a more potent immune response than recombinant protein. [11]

4.0. EFFECTIVENESS OF VACCINES

Vaccines do not assure complete protection from a disease, but with the help of an adjuvants they are used in vaccines to boost the recipient's immune response to a given antigen while minimizing the amount of foreign material delivered. An adjuvant (Latin, adiuvare: to aid) is a pharmacological or immunological agent that modifies the effects of other agents, such as medicine or vaccines. [2,6]

5.0. CONCLUSION:COVID-19 has the potential to cause significant illness or death in some people. Getting vaccinated not only protects you from COVID-19, but it also protects individuals in your immediate vicinity by preventing the virus from spreading. Stopping a pandemic necessitates the use of all available prevention methods. Vaccines operate in conjunction with your immune system to prepare your body to fight the infection. Other precautions, such as wearing masks and avoiding social situations can help lower your risk of contracting the virus and spreading it to others. The best protection against COVID-19 is a combination of COVID-19 immunization and following the CDC's advice to protect yourself and others. DPH (Connecticut Department of Public Health).

ACKNOWLEDGEMENT: Special thanks goes to Dr. O.T.Kayode for her support and guidance

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