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Review Article

Virus-like Particles (VLPs) based Vaccine Production: A Potentially Safe Candidate Vaccine against Worldwide COVID-19 Pandemic

Moumita Gangopadhyay[1]*, Subhendu Bandyopadhyay[2], Sanjukta Dey[1] and Arunima Saha[1]

[1]*School of Life Science and Biotechnology, Department of Biotechnology, Adamas University, Barasat, Kolkata, India*

[2]*School of Life Science and Biotechnology, Department of Biochemistry, Adamas University, Barasat, Kolkata, India*

***Corresponding Author:** Moumita Gangopadhyay, School of Life Science and Biotechnology, Department of Biotechnology, Adamas University, Barasat, Kolkata, India.

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Abstract

The sudden outbreak of highly contagious COVID 19 has challenged the existence of Homo sapiens. Although few repurposing old drugs are already used to prevent corona virus but presently, there is no specific promising treatment along with any vaccine for preventing COVID-19. The high infectivity of the causal pathogen SARS-CoV-2 virus combined with high mutation rates has been the greatest hurdle for the scientific societies to discover a potent vaccine or drug for cure which makes the situation even more alarming. Treatment unavailability of this fatal corona virus (COVID 19) has already caused more than 500,000 deaths and the curve is on the rise. Presently, there is no specific treatment for COVID-19 and the coming months will see the greatest public health challenge of this millennium. Development of safe and cheap treatment will prove to be a game changer in the race to move ahead of the curve. The conventional route of vaccine development though seems highly reproducible but not promising in terms of safety issues as the pathogen is highly infectious. In this aspect using Virus-like particles has been a promising vaccine development route for production of a low cost, safe, easy to manufacture and transportable vaccine to protect from novel corona virus (COVID-19). This review work would offer comprehensive fast hand information to medical practitioners and researchers dealing with COVID-19. A brief discussion has done about the ultra-structure of corona virus COVID-19, its systematic position and currently available treatments and their drawbacks. The prospects of vaccine development with their safety efficiency has elaborately discussed. A brief discussion has done on the safe route of vaccine development using Virus-like particles (VLPs) against worldwide COVID-19 pandemic.

Keywords: COVID-19; SARS-CoV-2; Corona Virus; Vaccine; Virus-like Particles

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Infectious Disease 2019; E-Protein: Envelop Protein; ACE-2: Angiotensin Converting Enzyme 2; CTL: Cytotoxic T-lymphocyte; LNP: Lipid Nanoparticle: VLPs: Virus-like Particles

Introduction

The World Health Organization (WHO) reported cases of pneumonia outbreak of unknown etiology in Wuhan city, Hubei province of People's Republic of China, on December 31, 2019 [1]. On January 7, 2020 the Chinese administration officially announced that the causal organism was a new fatal virus strain of Coronavirus family and WHO has named the disease as COVID-19 (Coronavirus Infectious Disease 2019) [2]. Later on, based on its similarity to Severe Acute Respiratory Syndrome-Corona Virus (SARS-CoV; 2002-2003), the CoV Study Group of the International Committee on Taxonomy of Viruses (ICTV) has named the virus as SARS-CoV-2 [3]. Since then, the exponential rise in the number of cases spread around all over the world has compelled World Health Organization (WHO) to announce this cosmopolitan medical emergency as worldwide pandemic from 11th March 2020 [4].

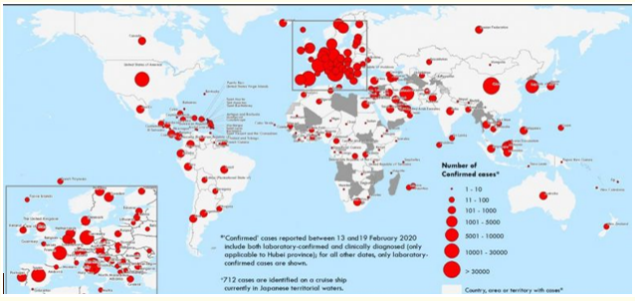

Figure 1: COVID-19 World Mapby WORLD HEALTH ORGANIZATION MARCH 24, 2020.

Source: [5].

This review work would offer comprehensive firsthand information about general idea of SARS-CoV-2, its taxonomic position and ultra-structure of COVID-19 which would be helpful both for medical practitioners and researchers dealing with COVID-19. In this review, an attempt has been made to provide an overview of the old drugs used purposefully for preventing COVID-19 and their side effects. Additionally, in the subsequent sections an attempt is made to give an overall outline of practical implementation for various types of vaccine development, their down side and finally a brief discussion for the safe route of vaccine development.

Systematic position and molecular structure of coronaviruses

Coronaviruses (Latin "Corona" means Crown like appearance) are a group of enveloped viruses with non-segmented positive sense RNA belonging to the family *Coronaviridae* and the order *Nidovirales* classified into three different genera: alpha, beta and gamma. Alpha and beta types have mammalian hosts which cause respiratory infections [6] while gamma type CoVs has avian hosts. The viral genome sequence of the enveloped positive sense RNA virus was released in public domain on January 10, 2020 (Wuhan-Hu-1, GenBank accession number MN9089477), followed by four other genomes deposited on January 12 (Global Initiative on Sharing All Influenza Data, GISAID) that showed the novel beta coronavirus possessed 89 and 82 per cent nucleotide identity to bat CoV, CoVZXC21, and SARS-CoV (2002 - 2003), respectively [7].

Based on the genetic sequence of SARS-CoV-2 and closely related SARS-CoV (2002-2003), the WHO shared protocols (E, N, RdRp and S genes) for screening and confirmation of probable cases [9]. On its surface the virion contains three main proteins- the Envelop protein (E-Protein), Hemagglutinin esterase and the Spike protein, these proteins are embedded into lipid bilayer. *Betacoronavirus* S

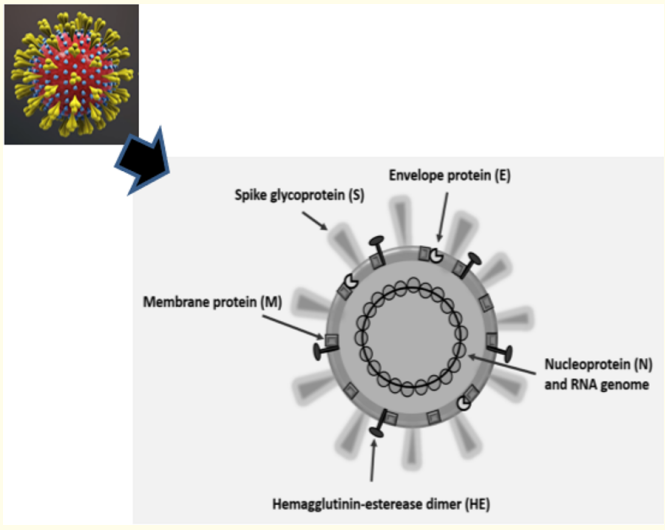

Figure 2: Pictorial diagram showing structure of the SARS-CoV-2 virus: Different parts of its structure is as follows, S (Spike glycoprotein)-It is the most important part of the virus which mediates the attachment with host cell receptors; it is considered as a critical target site for drug development; HE (hemagglutinin-esterase dimer)- another very important part of viral structure for mediating attachment to the host cell receptors and destruction of sialic acid residues; M (Membrane glycoprotein)-an important part of viral membrane; E (Envelop protein)- It forms the envelop by adhering to the M protein; N (Nucleocapsid protein)- it along with the RNA genome produces the nucleocapsid. (Source: Mendoza., *et al.* 2020 [8]).

proteins are processed into S1 and S2 subunits by host proteases [10] and like other class I viral fusion proteins, these two subunits trimerize and fold into a metastable pre-fusion conformation. The large spike protein is responsible for the spike like protrusions but it also recognizes the corresponding receptors on human cell called Angiotensin Converting Enzyme 2 (ACE-2) which act as receptor for both the SARS-CoV and the related human respiratory coronavirus NL63, that expressed in human airway epithelia as well as lung parenchyma [11].

Etiology of COVID19

As presently, there is no specific promising treatment for COVID-19, neither any antiviral drugs with proven efficacy has been found yet nor are there vaccines for preventing COVID-19. Treatment unavailability of this fatal corona virus (COVID 19) has already caused exponential rise in the number of cases and deaths already mark the greatest public health challenge of this millennium.

Therefore, practitioners have no way other than repurposing old drugs, which have already used to treat diseases such as diabetes and hypertension, to combat the viral spread. These drugs have been approved for Covid-19 treatment with a hope hopes that they'll be effective. After reviewing 2,700 published papers from all over the world detailing the treatment of COVID-19 David C. Fajgenbaum (Center for Cytokine Storm Treatment and Laboratory, CSTL at Pennsylvania, USA) and his team members gathered data on 9,152 patients and found doctors had already tried 115 different drugs [12]. Another group of scientists lead by Dr. Gina T Nguyen (Assistant Director of Communications and Events, Quantitative Biosciences Institute, University of California, San Francisco, UCSF, USA) has identified 69 drugs and experimental compounds which may be effective in treating COVID-19, among them 25 have already been approved by US Food and Drug Administration (FDA) [13].

SL No	Name of the drugs	Mode of action	Limitations
1	Sepsivac	An important immunomodulator against Leprosy	Not showing uniform results all the phases in infection
2	Hydrochloroquine	The anti-malaria drug also used to treat certain auto-immune and also as disease-modifying anti-rheumatic drug (DMARD) in arthritis like autoimmune diseases	Cardiac complications, arrhythmias and heart problems, for those suffering from co-morbidities, the drug has been known to induce side-effects such as headache, dizziness, stomach cramps, nausea, swelling, muscle weakness, vision disturbances
3	HIV drugs	Treatment of severe flu and infections	Failed Clinical trials in UK
4	Favilavir	Preventing the virus from replicating inside the organs and was also used in fighting the deadly Influenza virus	Not showing homogenous respond at different phases
5	Remesdivir	An antiviral drug which works by copying the coronavirus's genetic make-up, the RNA and slows down replication, previously used against Ebola	Appeared much more limited in patients who needed mechanical ventilation as part of their treatment
6	Plasma therapy	Involves the process of transfusing healthy antibodies from a recovered COVID patient to a sick person	Transfusion-related events, involving chills, fever, anaphylactic reactions, transfusion-related acute lung injury, circulatory overload and hemolysis

Table 1: List of few frequently used repurposing old drugs used recently for preventing COVID-19.

Vaccination is the ultimate goal in the fight against COVID 19

The pandemic has catalyzed the development of specific treatment protocol to fight against this pathogen. As SARS-CoV-2 comes with high transmissibility (asymptomatic and presymptomatic virus shedding, which results in a high number of patients with mild symptoms), vaccination is the most elective approach to control and ultimately eradicate infectious diseases. The straightforward path to generate vaccine candidates is the technology of inactivated vaccines, which can be formulated with SARS-CoV-2 virions previously inactivated by chemical or physical treatments. For SARS-CoV-1 and MERS-CoV, inactivated vaccine candidates have induced robust humoral responses leading to virus neutralization. Alternatively, the construction of a chimeric attenuated virus constitutes an interesting path. For instance, the influenza virus can be used as a scaffold to expose SARS-CoV-2 antigens and generate a bivalent vaccine targeting two relevant pathogens causing respiratory diseases [14]. Although inactivated vaccines will perhaps be the main avenue for generating the first experimental vaccines, alternative approaches should be explored in parallel, namely the development of subunit vaccines. Since the coronavirus spike (S) glycoproteins initiate entry into cells; they are considered the primary target for neutralizing antibodies. Cytotoxic T-lymphocyte (CTL) responses are also of key relevance to protect against viral infections [15,16]. Under these principles, vaccine development against COVID-19 has been initiated and efforts announced in this field include the development of RNA-based vaccines by Cure Vac [17], and an RNA vaccine candidate formulated with a novel lipid nanoparticle (LNP) carrying mRNA encoding for a full length, prefusion stabilized S protein [18]. Another candidate (developed by Shenzhen Geno-Immune Medical Institute [19] consists of a multi epitopic vaccine based on the generation of artificial antigen presenting cells through transduction as a way to express viral antigens and immune modulatory response.

The key issues forced to transform orthodox to modulated sustainable COVID 19 vaccine development

Since SARS-CoV-2 possesses high transmissibility (asymptomatic and pre-symptomatic virus shedding, which results in a high

Sl No.	Company names	Stages	Names
1	Altimmune	Preclinical	AdCOVID
2	BioNTech and Pfizer	Phase 1/2	BNT162 program
3	CytoDyn	Phase 2 and Phase 2b/3 clinical trials	Leronlimab
4	GlaxoSmithKline	Preclinical	AS03 adjuvant system for vaccines
5	Inovio Pharmaceuticals	Phase 1 clinical trial	INO-4800
6	Moderna	Phase 1	mRNA-1273
7	Novavax	Phase 1 clinical trial	NVX-CoV2373
8	Vaxart	Preclinical	No name yet
9	Sanofi	Preclinical	No name yet
10	Johnson & Johnson	Preclinical	No name yet

Table 2: List of probable Covid-19 vaccines: Pharmaceutical industries lakes leading role for development of coronavirus vaccine (https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/).

number of patients with mild symptoms). Henceforth, in parallel with conventional advances in vaccine design, the development of a novel, safe, easy to manufacture and transport along with cost-effective coronavirus vaccines is an urgent goal to fight against this pathogen. Unfortunately, the researchers have little knowledge of the molecular details of SARS-CoV-2 infection, especially key insights into effective molecular targets for developing broadly acting antiviral therapeutics against SARS-CoV-2. Vaccines based on whole viruses are associated with concerns about antibody-dependent enhancement of viral infection, reactogenicity and strain reversion to pathogenic forms, among other safety issues [13]. Therefore, the path for vaccine development will require a detailed characterization, not only in terms of efficacy but also safety [14].

Virus-like particles: A potent arsenal against fighting to COVID 19

As this causal organism is highly infectious safe and easy distribution and delivery are the required attributes to implement broad coverage of vaccination immediately. In this context Virus-like particles (VLPs),self-assembled constructs generated from viral antigens which mimic the native structure of viruses, but lack the viral genome, can be a potent premier vaccine platform due to less pathogenicity, enhanced immunogenicity, having both systemic and mucosal immune responses, stability and ease of manufacture and transport along with higher efficiency of displaying epitopes on their surface in a dense repetitive array of VLPs have numerous advantages over traditional immunogens which avoid the disadvantages of vaccines formulated with attenuated or inactivated viruses, namely the stability, reactogenicity and reversion to pathogenic forms [15,16]. This approach grabs the attention of the scientists due to attractive carriers for displaying foreign epitopes and easy licensing for human use but the major challenge, however, is to develop novel production platforms that can deliver VLPs based vaccines while significantly reducing production times and costs. A myriad of reports on the production of VLPs can be found in the literature that comprise the cases of the influenza virus, human papillomavirus, human immunodeficiency virus, foot and mouth disease virus, Norwalk virus, rift valley fever virus, and hepatitis B virus [17,18]. The immunogenicity of SARS-CoV-1 VLPs was tested and reported by several workers [19], as SARS-CoV-1 and SARS-CoV-2 have many resemblances, there is sky high expectation to use this VLP-based modular approach against newly emerging pandemic outbreaks.

Advantages of using VLPs for vaccine production

Followings are the primary reasons that VLPs are far more immunogenic other than subunit vaccines:

- Particulate nature of VLPs allow them to induce potent T-cell mediated immune responses through interaction with antigen presenting cells (APCs), especially dendritic cells (DCs).
- Like their cognate viruses, VLPs have a particle size ideal for DC and macrophage uptake and antigen processing to initiate antigen cross-presentation.
- Due to the high density of epitopes on their surface, uptake of a single VLP feeds thousands of epitopes into the processing and presentation machinery of APCs, further enhancing their potency in CTL (cytotoxic T lymphocytes) induction.
- In addition to T cell responses, VLPs can be presented efficiently to another crucial component of the immune system, the B cells, and induce strong B cell responses, due to their repetitive and high-density display of epitopes.

Sl No.	Virus names	Production system	Company name
1	HPV	Baculovirus	Cervarix (GSK)
2	HPV	Yeast	Gardasil (Merck)
3	HBV	Yeast	Engerix-B (GSK)
4	HBV	Yeast	Recombivax HB (Merck)
5	HBV	Mammalian	GenHevac B (Pasteur)
6	HBV	Yeast	Fendrix (GSK)
7	HEV	E. Coli	Hecolin (Xiamen Innovax Biotech)
8	Influenza A	Cell Free	Inflexal V (Crucell)
9	HAV	Cell Free	Epaxal (Crucell)

Table 3: List of licensed VLP- based vaccines commercially available (source: Velasco Cimica and Jose M. Galarza, Clin Immunol. 2017 October; 183: 99-108. doi: 10.1016/j.clim.2017.08.004).

Limitations of using VLPs for vaccine production

Though VLPs have shown promising results as vaccine candidates against many other difficult diseases, commercial production systems are currently limited to yeast, insect and mammalian cell cultures, which have several limitations and cannot be used for popularize commercial exploitations. The major factor is to develop novel production platforms that can overcome issues of the current production systems and can deliver VLP-based vaccines to clinics in a timely manner and at a lower cost. Due to these inherent limitations for providing the optimal environment in cell culture-based production system for maintaining appropriate protein posttranslational modification and authentic VLP assembly. Keeping in mind the safety and efficacy of VLP-based vaccines production system, the development of alternative VLP production platforms that provide appropriate protein glycosylation, efficient folding and assembly, versatile, robust, cost-effective, scalable, and safe are urgent need to save the suffering mankind from this fatal disease.

Conclusion

During our write up of this review there are 10.3 million confirmed Covid-19 cases along with 506 K deaths worldwide according to WHO. It seems as if the future of total human civilization is now resting in the hand of this tiny virus. It has also provided some very important lessons, that is to care about the mother nature, value the interrelationship with animal and environment. In our battle with the virus it is now a million dollar question that when we our going to get the much awaited vaccine against the deadly pathogen. Although several companies and institutes are trying hard for the development of an effective vaccine but currently there is little hope of getting that in near future. VLP based vaccines have been developed for several other viral diseases like HBV, HPV, Influenza A etc. and they are commercially available also but for Covid-19 the search is still on. Apart from vaccines several other aspects are also going to be important in near future i.e. herd immunity development within population, smart working protocols by practising effective cleanliness will be the key against our battle to this virus. Human endeavour has achieved great things in past, from technology to medicine we have progressed a lot; human civilization is facing a new challenge, may be hard but humanity will certainly overcome it.

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Conflict of Interest

None.

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