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Bacteriophage and nanotechnology in the management of COVID-19: A Review Article

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Abstract

An international panic has been sparked by the Covid-19 virus outbreak regarding our knowledge and preparedness against virus outbreaks and be calls whole scientific community to level up fight against this giant killer. Scientists are exhaustively testing already available drugs efficient associated diseases, the coronaviruses that cause severe acute respiratory syndrome (SARS-CoV) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) (MERS-CoV) and a concrete solution here too is outlying. In the present scenario nanotechnology envisages a more practical approach towards treatment of severe cases of covid-19. Bacteriophages have the innate capacity to regulate immunity and their nanoscale size makes them perfect candidates to peruse as nanomedicine against the severe cases of COVID-19.

Keywords: Antibody, Bacteriophage, Covid-19, Nanomedicine, SARS-CoV-2, Treatment

I. INTRODUCTION

Viruses are one of the most dynamic biological entities on this planet evolving through time gaining significant attributes to infect a whole range of organisms (Watkins 2018, Gorbalenya *et al.*, 2020). Viruses have adapted ways for penetrating host cells, surviving for extended periods of time within cells, evading targeted therapies, and altering or inhibiting the full range of host defenses (Lukashiev and Zamyatnin 2016). They have caused some of the deadliest diseases that have challenged the very existence of human race. During December 2019, several cases of pneumonia of unknown cause emerged in Wuhan, China (Huang et al., 2020, Chen *et al*., 2020, Wang *et al.*, 2020) and spread quickly to other provinces of China and then whole world. Subsequently, the patients' throat swabs tested positive for the presence of a new coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and reported to be the etiological culprit underlying the related pandemic disease, COVID-19. COVID-19 has been declared as a public health emergency of international concern (PHEIC) by WHO (Zarocostas 2020).

COVID-19 pandemic has caused a global outcry killing about 0.7 million and infecting 17 million people as of 30th july 2020. The pandemic constrained countries to enforce classical measures such as use of face masks, banning social gathering, mandatory social distancing, closing schools, shops, and restaurants; placing restrictions on transportation, lockdowns some of which were used during Spanish flu outbreak. Vaccination and therapies generated from targeting critical mechanisms, such the virus's entrance point or replication in the life cycle, are the backbone of conventional treatment approaches.

Old scientific information developed that could treat or dampen the spread of corona virus. Scientists have exhaustively tested effective drugs used in similar diseases such as SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome) and also exploited drug repurposing strategies but of no avail (Duarte *et al*., 2020, Colson *et al*., 2020, Gao *et al.*, 2020, Wang *et al*. ,2020). Nanotechnology has presented a distant ray of hope and a possible alternative approach to combat this disease. In addition to the currently used nano-vehicles used for drug delivery bacteriophages which act as natural nanoparticles are also seen as promising candidates having the potential to treat COVID-19. Further with the advent of increasing antibiotic resistance, bacteriophages provide an attractive approach due to their ability to modulate immune system while keeping intact the microbiota of gut (Roach *et al*., 2017). Here, this review has discussed the pivotal role that nanotechnology can play with special emphasis on bacteriophage mediated nano-approaches that can be employed in combating COVID-19.

A. The coronavirus structure and pathogenesis

To this day, four genera of coronaviruses (α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus) make up what is likely the biggest family of enveloped single-strand positive-sense RNA viruses (Chen *et al.*, 2020). To be

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specific, mammals are the primary hosts for the α- and β-coronaviruses, whereas birds are the hosts for the other two. Till date seven diseases causing corona viruses namely HCoV 229E, NL63, OC43, HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 have been isolated from humans (Wu *et al.,* 2020). In adults, HCoV 229E, NL63, OC43, and HKU1 are associated with mild upper respiratory tract infections; however, the most severe types, SARS-CoV, MERS-CoV, and SARS-CoV-2, cause lower respiratory tract infections that progress to acute respiratory distress syndrome (ARDS), likely to result in significant morbidity and mortality in humans (Paules *et al.,* 2020, Ji *et al.,* 2020). Although early research suggested that and SARS-CoV-2 was a recombinant virus, subsequent research has revealed that it is, in fact, a naturally occurring member of the β-coronavirus genus, which is part of the Coronaviridae (Paraskevis *et al*., 2020, Chen *et a*l., 2020). The SARS coronavirus type 2 genome has one open reading frame (ORF) encoding for a polyprotein and two un-translated sections (5′-cap structure and 3′-poly-A tail) (Chan *et al.,* 2020). The SARS-CoV-2 genome is encoded by 5′- ORF 1a and ORF1b (the viral replicase)-Spike (S)-Envelope (E)-Membrane (M)-Nucleocapsid (N) (structural proteins)]-3′; and ORF 3a, 7, and 8 (encoding for accessory proteins) inserted between genes of structural proteins (Wu et al., 2020). The ORF1a and ORF1b gene occupy roughly two-thirds of the coronavirus genome and codes for 16 non-structural proteins, while the residual one-third codes for accessory proteins and structural proteins (Lu et al., 2019). SARS-CoV-2 infects the human cells by the interaction between viral spike glycoprotein and its cellular receptor, angiotensin-converting enzyme 2 (ACE2) on human cells. Virus point of entry into the host cells is an important determinant of viral infectivity and one of the primary targets of anti-viral targeted therapies (Morse *et al.,* 2020). The SARS-CoV-2 spike protein is composed of two subunits, S1 and S2, with the S1 domain involved in receptor binding and the S2 domain involved in cell membrane fusion. The S1 protein was further dissected to show an N-terminal domain (NTD) and a receptor-binding domain (RBD) that consists of a core domain and an outside subdomain (ESD). A fusion peptide (FP) and two heptad repeats (HRs) are three of S2's functional domains (Gralinski and Menachery 2020, Wan *et al.,* 2020). The infectivity of the virus depends upon the compatibility of viral RBD with human cellular ACE2. Upon binding there is a subsequent conformational change in S2 aided by host cell surface protease TMPRSS2, cathepsins, HAT, furin, etc to facilitate membrane fusion (Li 2013, Heald-Sargent and Gallagher 2012). It was found that SARS-CoV-2 bound to ACE2 with 10- to 20-fold higher affinity as compared to SARS-CoV (Wrapp *et al.,* 2020) Moreover, SARS-CoV-2 was discovered to bind to ACE2 with 10- to 20-fold higher affinity than SARS-CoV. Viral RNA is transferred into the cytoplasm and translation begins once the viral and host membranes have fused. In order to direct viral replication, 16 non-structural proteins are released viral proteases that create polyproteins from ORF1a/b (Ge *et al.,* 2020). Synthesis of genomic length RNA and subgenomic RNA encoding structural genes S, E, M, N and other accessory ORFs ensues. The membranes serve as a construction site for newly formed virus particles that originate in the endoplasmic reticulum (ER)-Golgi complex and are secreted from the cell after they have undergone this process (Pericias *et al*., 2020).

B. Epidemology and clinical manifestations

Based on the current understanding bats have been speculated to be the most probable original reservoir of SARS-CoV-2. Bats were also natural reservoir of SARS-CoV and MERS-CoV. Bat coronavirus RaTG13, a small RNA-dependent RNA polymerase sequence, was shown to share 96.2-98.7% similarity with other species (Zhou *et al*., 2020). Furthermore, pangolins were suggested to be one of the intermediate hosts due to the isolation of various SARS-CoV-2 sublineages from pangolin internal organs by metagenomic sequence (Lam *et al.,* 2020). However, there may be multiple intermediate reservoirs, because SARS-CoV-2 was not originated directly from pangolin-CoV-like virus, as shown by the molecular and phylogenetic analyses in Liu's study (Liu *et a*l., 2020). In the study by Xiao *et al.,* it was reported the SARS-CoV-2 could be derived by reorganization of Bat-CoV-RaTG13-like virus and pangolin-CoV-like virus (Xiao *et al.,* 2020).

Airborne respiratory droplets (reaching up to 2 m distance), intimate contact with infected persons, or fomites (which can transmit the virus even after several days) are the primary modes of transmission of SARS-CoV-2 from person to person (Guo *et al.,* 2020). The basic reproduction number (R0) is a useful predictor of transmission that may be used to estimate the average number of secondary cases generated by an index case in a completely susceptible community during the early stages of an outbreak (Swerdlow and Finelli 2020, Riou and Althaus 2020, Althaus *et al.,* 2020). A R0 value of more than 1 suggests human-to-human transmission. Initial reports have predicted a R0 value in between 2.4-3.8 in case of COVID-19 (Liu *et al.,* 2020, van Doremalen *et al.,* 2020) which will surely change over period of time due to the advent of asymptomatic patients and super-spreader which can infect more than 100 patients. It's important to remember that even those who don't feel sick might spread disease (Rothe *et al.,* 2020, Wang and Jin 2020).

Viral infections are commonly established with severe pneumonia, ARDS or are often complicated by bacterial super-infections in many non-surviving patients (Chen *et al*., 2020). Patients infected with SARS-CoV-2 showed a spectrum of symptoms ranging from mild, non-specific flu-like symptoms to life-threatening pneumonia which progresses into rapid onset of severe illness involving the respiratory system with harm to organs, organ failure, and death. Complications include ARDS, RNAaemia, heart attacks, septic shock, and secondary infections. Fever (> 80%), cough (60-80%), weariness, dyspnea, myalgia, sputum production, headache, and so on were the most frequently reported symptoms etc (Wang *et al.,* 2020). The lack of synergy between innate and adaptive immunity is what actually contributed to the death of covid-19 patients. Initially during the attack by a new pathogen only innate immune response is active while adaptive response takes some to mount. The ability of the lungs to exchange gases is impaired when there is a high viral load because the innate immune system secretes inflammatory fluid and cells (Wojewodzic 2019). Human respiratory cells that have been infected by a virus and are dying serve as a substrate for bacterial development, prompting the innate immune system to produce additional inflammatory material into the area, depriving the alveoli of oxygen. At this time there is too much fluid in the lungs that there is hardly any gas exchange,

individual feels choked and require immediate ventilation or it may cause sepsis and ultimately death choking the lungs (Tay *et al*., 2020). This process helps to accelerate as the virus persists in its attack on lung cells, producing additional cell waste for the bacteria to consume. This can lead to sepsis and mortality as the innate immune system floods the lungs with inflammatory fluid, preventing gas exchange and necessitating immediate ventilation (Shi and Gewirtz 2018). One possible explanation for the severity of SARS-CoV-2 in the elderly and in individuals with weakened immune systems is a lag in the development of virus-specific antibodies.

It was observed that some severely ill patients ones, co-infected with bacteria and yeasts or molds. *K pneumoniae, A baumannii, A flavus, C albicans and C glabrata* were most prevalent bacterial secondary infections in those patients (Guo *et al.,* 2019). It is being acknowledged that the simultaneous presence of bacteria and viruses augments the course and severity of infections. These infections were associated with enhanced levels of inflammatory biomarkers such as procalcitonin and C-reactive protein in community acquired pneumonia (CAP) (Bello *et al.,* 2014). It has now been speculated that the majority of deaths during spanish flu pandemic were the consequence of complications due to bacterial infections with Streptococcus pneumoniae or S. aureus (Morens et al., 2008). At least half of the patients who died from SARS-CoV-2 had secondary illnesses, according to reports from Wuhan and most of world countries (Huang *et al*., 2020, Zhou *et al.,* 2020). As such bacteriophages come into play acting as a double-edged sword which can be nanoengineered to prevent viral binding to host targets and simultaneously reducing bacterial secondary secondary infections which are presumed to be the primary cause of mortality in older people, immunocompromised patients, diabetics, people with HIV infection and cardiovascular diseases.

C. Nanomedicine in COVID-19

Nanoparticles are one of transport mechanisms types for target specific and time dependent sustained release of therapeutic agents into the biological fluids, simultaneously preventing their degradation and increasing their bioavailability Features such as enhanced stability, sustained release, increased permeability across membranes, prolonged residency, increased bioavailability, target selectivity, and decreased cytotoxicity make them appealing vehicles for transporting medicinal substances (Sharma *et al.,* 2016).

D. Bacteriophages as nanomedicine in COVID-19

Bacteriophages are viruses that have the natural tendency to infect and kill bacteria. They are one of the most genetically diverse and abundant life forms on the earth. Among a wide array of phages few like T4 (Tao *et al.,* 2013), T7 (Gamkrelidze and Dabrowska 2014), Qβ (Kozlovska *et al*., 1996), phages λ (Nicastro *et al.,* 2014), MS2 (Fu and Li 2016), M13, f1, fd and related filamentous phage are of particular interest in nanomedicine because of their smaller size. Filamentous phages exist as rod shaped nanofibres of about 10 nm diameter with phage capsid surrounding the phage genome can mimic as natural nanocarrier for delivery of therapeutic agents into cells. These rod shaped naturally-occurring viruses serve as promising biological building blocks for the fabrication of diverse functional nanostructured materials and nanovechicles. These phage virions have the ability to self-assemble which employs structural information in the phase capsid to assemble into nanoscale structures without involvement of other proteins (Yang *et al*., 2013). Filamentous bacteriophages exhibit great genetic flexibility for introduction of large DNA chunks which express into appropriate phenotypic modifications. These manipulations pave way for their potential use as nanobuilding nanomaterials with potential use in disease prevention, diagnosis and therapy (Henry et al., 2015).

E. Bacteriophages modulate the immune system

Pattern recognition receptors (PRRs) frequently expressed on the host cells recognize pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) which are molecules commonly found on the surface of pathogenic viruses, bacteria or other microbes (Oakes et al., 2019). Toll-like receptors (TLRs), one very common PRR has a history of being able to spot various bacterium and virus products (Chang et al., 2017). Phage virions represent highly repetitive surface patterns which complement the subunits of major capsid proteins of pathogenic mammalian viruses (Rao and Black 2010, Moody 1996, Black and Rao 2012). Fusion of an antigen with the capsid protein of a phage results in the exposure of that antigen in a highly repeated fashion and function as such virus like particles (VLPs) (Fokine et al., 2007). These potentially harmless phage VLPs mimic as pathogenic viruses have excellent capability to stimulate the innate as well as adaptive immune system (Fig. 1).

Activation of TLRs also induces the production of inflammatory signals known as cytokines which recruit various immune cells to sites of infection or immune tissues like lymph nodes in order to mount an adaptive immune response. In order to stimulate an immune response, APCs like dendritic cells must first swallow a pathogen and its processed portion, termed antigen, before presenting it on the APC cell surface to T cells via major histocompatibility complex1/2 (MHC) (Tao et al., 2019). When a cytotoxic T lymphocyte (CTL) recognizes an antigen displayed in MHC-I, it is able to immediately destroy the cancer cell or infected host cell, preventing the infection from spreading further inside the host cell (e.g., viruses) (Fig. 1). T helper cells, which are effector T cells, are developed in response to antigen presentation via MHC-II and CD4+ T cells (TH). These TH cells aid B cells in making antigen-specific antibodies, which bind infections and label them for subsequent elimination by other immune cells with more cytotoxic effects (Hess and Jewell 2019). When creating a vaccine, it is preferable that the phage VLP contain a high concentration of the antigen in a small, localized area, as this is more conducive to B cell activation. Cross-linking of B cell receptors to antigens is aided by a high antigen density on the particle's surface, leading to increased production of peptide-specific IgG at high titers (Jegerlehner *et al.,* 2002, Cheng 2016).

Vaccine antigens must make their way from the injection site to the lymph nodes, where adaptive immune responses are started. Small antigenic particles (200 nm) are able to penetrate the lymphatic system via direct lymph channel wall crossing (Manolova *et al.,* 2008). Capsids of many phages,

including Qβ (28 nm), MS2 (26 nm), T7 (56 nm), λ (60 nm), and T4 (120 86 nm), have different sizes (Rumnieks and Tars 2017, Guo *et al*.,2014, Chen *et al*.,2017) successful delivery to lymph nodes where they can promote adaptive immune responses and entry into the lymphatic system. Co-delivery of antigen and adjuvant, in addition to particle size, is a major factor in the induction of a strong immune response. By fusing an antigen with a vaccine delivery system loaded with an adjuvant, both the antigen and the adjuvant can be delivered to antigen-presenting cells (APCs) and B cells at the same time (Gomes *et al.,* 2017). This results in the immune cells recognizing and processing the antigens while also receiving costimulatory signals from the adjuvant, greatly amplifying the immunological responses. The phage VLPs act as a potential natural adjuvant upon which a wide array of antigens can be displayed which induces a potent innate and adaptive immune response (Jonczyk-Matysiak *et al*., 2017).

F. Surface epitopes shown by phage

Phage displays a relatively new method that involves inserting foreign DNA into a specific location in the nucleotide sequence encoding one of the phage coat proteins. When a phage infects a bacterium, it injects foreign amino acids into the host cell and co-expresses the corresponding coat protein. The surface-expressed fusion protein of the phage virion binds to several different kinds of extracellular targets (Smith and Scott 1993). Using the phenotype-genotype relationship between the displayed peptide and the foreign DNA sequence encoding the peptide, scientists can now identify target-avid ligands displayed on the phage. When compared to hybridoma technology, which is traditionally used to create therapeutically relevant antibodies, phage display is viewed as a more effective alternative. When it comes to isolating monoclonal antibodies (mAbs) with specific binding properties, antibody phage display (APD) is an effective method. APD involves the design and construction of huge libraries of antibody fragments expressed on the outer layer of phage particles (Clementi *et al.,* 2012). From these disease-specific antibody libraries, monoclonal antibodies can be developed to target a particular pathogen, which has great potential for preventing pathogen attachment to the host cell, neutralizing pathogen-derived poisons, and inducing phagocytosis (Dibo *et al.,* 2019). ProteoGenix is taking advantage of this strategy in the context of SARS-Cov-2 by employing therapeutic antibody discovery via the phage display technique, which involves screening a naive antibody human library (LiAb-SFMAX TM, scFv, Fab, IgG, >51010) or human antibody obtained from plasma of COVID-19 survivors (Wojewodzic 2020). Thus discovery therapeutic monoclonal antibody against SARS-Cov-2 by phage display technique is quite imminent in the near future.

In one of the recent studies Lauster *et al.,*used phage nanoparticles for the treatment of influenza virus. The influenza virus infects via binding between homotrimeric haemagglutinin spike protein and terminal sialic acid residue on the surface glycans of host cells. Researchers employed bacteriopahage Qβ for the expression of chemically modified sialic acid residues on its coat protein. Upon infection into various human and avian strains it was observed that this chemically modified bacteriophage capsid which now mimic as haemagglutinin ligands bind influenza haemagglutinin spike protein and cover the entire viral surface rendering it unable to infect host cells in vitro, ex vivo, in vivo (Lauster *et al.,* 2020). Based on this study a similar approach by the researchers in case of Covid-19 is quite evident in near future. Zhang *et al*, the SARS-CoV S1 spike protein was shown to share some similarities with the influenza virus neuraminidase glycoprotein. The SARS-CoV S1 protein mediates entry of SARS-CoV into host cells, and the neuraminidase glycoprotein contained inside the viral envelope promotes the release of progeny virions from infected cells to other cells (Zhang and Yap 2004). However the biggest challenge is that even a difference of few key residues entirely changes the affinity of spike proteins with its receptor and to aggravate, some naturally selective mutations in S1 enhances its affinity with human ACE2. These fore mentioned phenomenon play a critical role in civet-to-human and human-to-human transmissions (Wu *et al.,* 2012, Wu *et al.,* 2011). Thus phages with appropriate chemical modifications on the capsid can be devised so that they bind to sars-cov-2 in a multivalent manner and entirely encapsulate it so that it no longer able to infect the lungs of already infected patients thereby simultaneously preventing its transmission to other individuals also.

G. Nanoapporaches in Covid-19 treatment

Using cellular nanosponges created from human lung epithelial type II cell (Epithelial-NS) and human macrophage (M-NS), Zhang *et al.,* conducted their research. To make these nanosponges, lung epithelial cells and macrophages were wrapped around polymeric nanoparticle (NP) cores (Zhang et al., 2020). The nanosponges acquire originating cell surface antigen profiles to bait SARS-CoV-2, inhibiting their binding with host cells blocking viral entry and viral infectivity. These nanosponges display same receptors such as (ACE2 and CD147) expressed on cells of the human alveolar epithelium type II to which the SARS-Cov-2 virus binds and is no longer able to infect host cells (Yan *et al*., 2020). Previous research has proven that MΦ-NS have a wide spectrum of neutralization against pathogens, bacterial toxins and inflammatory cytokines (Thamphiwatana *et al*., 2017). These MΦ-NS have shown a considerable potential to neutralize the viral activity of SARS-Cov-2, and lessen the impact of the virus on the body.

Bacterial based outer membrane vesicles (OMVs) represent naturally self-adjuvanting, highly safe, stable and unique pathogen mimetic vaccine delivery platforms. They have already shown excellent results in case of influenza virus, where 100% of mice displaying an antigen based on the influenza A virus matrix 2 protein survived a fatal challenge with two influenza A virus strains (H1N1 and H3N2). Based on similar lines researchers at the Quadram Institute have identified key antigen targets within the SARS-CoV-2, developed and assembled constructs for delivery through nanosized-OMVs via nasal or oral administration. It is being speculated OMV nanoparticle-based delivery system can have an edge over other currently exploited therapies due to their ability to specifically target at primary COVID-19 infection sites, the lung could (Watkins *et al.,* 2017).

NVX-CoV2373 a Recombinant Spike protein nanovaccine vaccine represents yet another nanobased approach for covid-19 treatment currently in phase1/2 clinical trials. Novavax has used its patented saponin-

based Matrix-M adjuvant therapy which acts by increasing antigen presentation in regional lymph nodes and promoting the arrival of antigen-presenting cells at the injection site, eliciting a potent immune response and by aiding the production of antibodies against the virus (Novavax 2020). In as similar study lipid nanoparticles have been use of these methods to provide mRNA vaccines to covid-19 patients. This nanobased MRNA vaccine candidate is still in phase I trial and results regarding no published data exist regarding the immunogenicity, efficacy, safety, or tolerance of RNA vaccines (BioNTech 2021). Ferritin is an iron storage found throughout all the species and presents unique attributes characteristics such as: high loading rate, high toxicity, and ease of genetic and chemical manipulation for the development of nanoparticles. Another nanobased strategy being developed by Army scientists at Walter Reed Army Institute of Research employs ferritin nanoparticles presenting Sars-cov-2 viral spike protein. These ferritin based nanoparticle will be conjugated with adjuvant, army liposome formulation which can further elicit immune response (Simmons 2020).

II. Figures and Tables

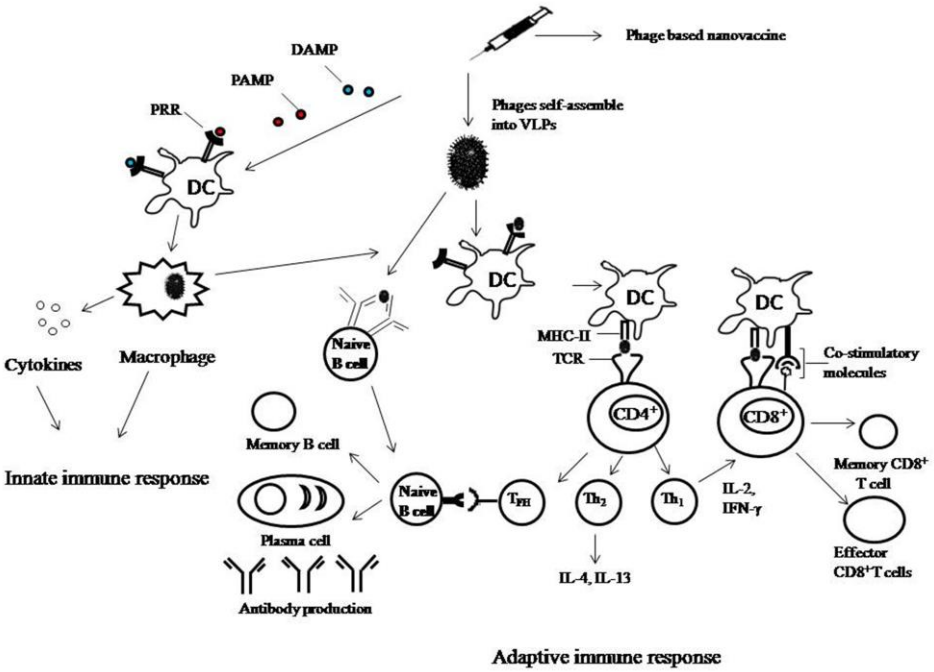
TABLE I. Developmental status of different COVID-19 vaccine candidates

Developer	Vaccine	Status	Name	Type	Clinical trials registry
Bharat Biotech International Limited	Whole Virion Inactivated SARS-CoV-2 Vaccine	Phase I/II	Covaxin	Inactivated SARS-CoV-2 Vaccine	NCT04471519
Beijing Institute of Biological Products, Sinopharm	Inactivated SARS-CoV-2 Vaccine	Phase I/II	-	Inactivated Vaccine	ChiCTR2000032459
Sinovac	Formalin inactivating whole virus particles combined with an alum adjuvant	Phase I/II	-	Inactivated vaccine	NCT04383574
Wuhan Institute of Biological Products, Sinopharm	Inactivated SARS-CoV-2 Vaccine	Phase I/II	-	Inactive vaccine	ChiCTR2000031809
Altimmune, Inc.	Adenovirus based NasoVAX expressing SARS2-CoV spike protein	Phase II	Nasovax	Inactive vaccine	NCT04442230
University of Oxford	Replication-deficient simian adenovirus vector ChAdOx1 Spike protein	Phase II/III	ChAdOx1 nCoV-19 (Abs 260)	Non-replicating viral-vector vaccine	NCT04400838
CanSino Biological Incorporation, Beijing Institute of Biotechnology, Canadian Center for Vaccinology	Adenovirus type 5 vectored recombinant SARS-CoV-2 intramuscular vaccination	Phase I/II	Ad5-nCoV	Non-replicating viral vector vaccine	NCT04398147
Shenzhen Geno-Immune Medical Institute	Synthetic antigen-presenting cells APCs expressing mini-genes for SARS-CoV-2	Phase I	Pathogen-specific aAPC	Non-replicating viral vector vaccine	NCT04299724
Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	Recombinant (CHO cell)	Phase II	Recombinant New Corona virus Vaccine	Recombinant Vaccine	NCT04466085
ModernaTX, Inc.	Stabilized form of the Spike (S) protein	Phase III	mRNA-1273	mRNA vaccine	NCT04470427
BioNTech, Pfizer, Fosun Pharma	Lipid nanoparticle mRNA vaccines	Phase II	BNT162b1/2/3	RNA vaccine	NCT04368728
Symvivo Corporation	bacTRL-Spike oral DNA vaccine encoding S of SARS-CoV-2	Phase I	bacTRL-Spike	DNA vaccine	NCT04334980
Inovio Pharmaceuticals	Electroporation-delivered DNA vaccination with enhanced efficacy	Phase I	INO-4800	DNA Vaccine	NCT04336410
Novavax	Adjuvant, Matrix-M, is used to administer pre-fusion S protein	Phase I	NVX-CoV2373	Subunit vaccine	NCT04368988

III. Conclusion

With a little hope from dry pipeline of repurposed drugs and vaccine development in various phases of trial, nanomedicine shows a distant ray of hope. Nanoscale dimensions of bacteriophages makes them excellent nanovehicle in diagnosis and drug delivery. The potential of bacteriophages VLPs to reduce secondary infection in patient's respiratory system and manufacture synthetic antibodies by phage display technique against SARS-CoV-2 makes them novel futuristic candidates to anticipate anti-viral strategy. A bacteriophage based nanomedicine would be much less likely to develop resistances and would have least cytotoxicty.

Fig. 1. Vaccination with phages can stimulate both the innate and adaptive immune systems. Dendritic cells (DCs) have pattern-recognition receptors (PRRs) that recognize PAMPs on or released by a phage vaccination, activating the innate and adaptive immune systems.



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