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Overview on under development of vaccine candidates against SARS-CoV-2

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Severe acute respiratory syndrome SARS -CoV-2 is a newly emerging infectious disease caused by a novel coronavirus, SARS-CoV. The World Health Organization announced the outbreak of coronavirus disease (COVID-19) pandemic on 11 March 2020. SARS-CoV-2 and the Middle Eastern respiratory syndrome-related coronavirus (MERS-CoV) constitute the most life-threatening species among all human coronaviruses. Until now, not any vaccines have been developed against coronaviruses. Therefore, it is essential to develop vaccines to prevent outbreaks of COVID-19. Live attenuated, inactivated, subunit, recombinant protein, epitope, DNA, RNA based vaccines, adenovirus-based vectors, virus-like particle vaccine forms the bases of vaccine candidates against COVID-19. Each current vaccine strategy has distinct advantages and disadvantages. Therefore, it is paramount that multiple strategies be advanced quickly and then evaluated for safety and efficacy. According to the World Health Organization report, 42 COVID-19 vaccine projects are in clinical evaluation. Vaccine candidates developed against COVID-19 are different from the vaccine candidates previously developed against SARS-CoV, MERS-CoV, and have a wider platform and are new hopes to develop a vaccine against COVID-19.

Keywords: *SARS-CoV-2, COVID-19, vaccines*

INTRODUCTION

Severe acute respiratory syndrome SARS - CoV-2 is a newly emerging infectious disease caused by a novel coronavirus, SARS-CoV. The World Health Organization announced the outbreak of coronavirus disease (COVID-19) as a pandemic on 11 March 2020. WHO reported that ~80% of COVID-19 patients have mild-to-moderate symptoms, while ~20% develop serious manifestations such as severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and even death. The virus SARS-CoV-2 belongs to the genus Betacoronavirus (β-CoV) of the family Coronavirdae SARS-CoV-2 have a single-stranded positive sense RNA genome, Encoding 4 structural proteins; spike (S), envelope (E), membrane (M), and nucleocapsid (N) which S is a major protective antigen that elicits highly potent neutralizing antibodies (NAbs), 16 non-structural proteins (nsp1-nsp16) and several accessory proteins (Rabaan et al., 2020). The SARS-CoV spike (S) protein is composed of two subunits; The S1 subunit contains a receptor-binding domain that engages with the host cell receptor angiotensin-converting enzyme 2 (ACE2). The S2 subunit mediates fusion between the viral and host cell membranes. The S protein plays key parts in the induction of neutralizing-antibody and T-cell responses, as well as protective immunity, during infection with SARS-CoV. The vaccine is a non-pathogenic immunobiological substance that has specific protection against any disease. The immunobiological substance causing

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recognition and elimination of the foreign agent by stimulates the body's immune system cells. The immunobiological substance should consist of particles of microbial agents or synthetic forms of these particles. The ideal vaccine Should be Immune effective and cause long time immunity, Can be stored for a long time, Immunity should be sufficient with a single dose, Should not have any side and toxic effects, Should be cost effective and easy to find, Must be reliable Should not cause infection. The mRNA-based vaccine targeted to the S protein of SARS-CoV-2 works by active immunization (Rabaan et al., 2020; Chen et al., 2020). This technique will not use part of the virus but only recombine mRNA of the S protein in vitro according to the gene sequence, which is coated with lipid nanoparticles for effective delivery. Once injected into the muscle, the myocytes take up the lipid nanoparticle (LNPs) and then release the mRNAs into the cytoplasm for translation into the S proteins. These endogenously synthesized S proteins will be secreted to activate both humoral and cellular immune responses. S protein – spike protein; IM – intramuscular, LNP – lipid nanoparticle; DC – dendritic cell; MHC – major, histocompatibility complex; Ag – antigen. In one study researchers used S377–588-Fc protein as a pattern antigen and evaluated the effects of different adjuvants on the stimulation of host immune responses to MERS coronavirus recombinant binding domain (RBD) based subunit vaccine. They used dissimilarly formulated vaccines to immunize mice and then gave a demonstration of the comparison of MERS coronavirus typical humoral immune responses and neutralizing antibodies, as well as T cell-mediated immune responses (Zhang et al., 2016). No any specific drugs or vaccines have developed for the treatment and prevention of COVID-19 till now. This article aims to share information about the recent potential vaccine candidates against SARS-CoV-2.

Vaccine development against SARS-CoV-2

Various types of vaccines such as DNA-, RNA-based formulations, recombinant-subunits containing viral epitopes, adenovirus-based vectors, and purified inactivated virus are under development against SARS-CoV-2. Traditionally vaccine development methods such as Purified inactivated viruses have been found to be effective safe against viruses like influenza and poliovirus.

Inactivated vaccines

Inactivated virus vaccines are obtained by killing viruses by various methods. The methods used in the virus inactivation are essentially preserved antigenic properties by disrupting the reproductive abilities of the virus. It mostly stimulates the humoral immune response. Inactivated vaccines must be noninfective, biosafe. Methods used in inactivation vaccines include Heat, UV, Formaldehyde (exm HAV), Beta prophylactone (influenza, jerusalem), Phenol (Chua et al., 2018). In one study scientists developed a pilot-scale production of a purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc), which induced SARS-CoV-2-specific neutralizing antibodies in mice, rats, and non-human primates. These antibodies neutralized 10 representative SARS-CoV-2 strains, suggesting a possible broader neutralizing ability against SARS-CoV-2 strains. These data support the clinical development of SARS-CoV-2 vaccines for humans (Gao et al., 2020). Thus, the obtained results with the inactivated vaccine candidate against SARS-CoV and SARS-CoV-2 reveal that this approach is promising in developing the vaccine against both types of coronavirus.

Live attenuated vaccines

Live vaccines are vaccines which virulence is reduced or eliminated but are prepared without degrading their antigenic nature. Live vaccines create both humoral and cellular immunity and form a large number of memory cells. Immunization of live vaccines usually lasts a lifetime. Live-attenuated vaccines reveal high immune responses that can present to long term immunity after first or second time vaccination. These vaccines have been used against measles, yellow fever, chickenpox, infections, and several other diseases. This type of vaccine usually is comparatively easy to generate for viruses, but it is not easy to create for bacteria and parasites (Minor, 2015). An ideal vaccine candidate has to contain genetic selectors that could be separately attenuating and also could be stimulated by recombination processes. In one study researchers inoculated the mice with UV-inactivated SARS-CoV in the presence or absence of adjuvant. After vaccination, a high rate of humoral immune response that revealing to the production of long-term antibody expression and the memory B cells was recognized. Antibodies which was generated

in mice against SARS-CoV observed both S (spike) and N (nucleocapsid) proteins of the pathogen and could prevent the infection (Takasuka et al., 2004). Thus, the results obtained with the inactivated vaccine prepared against SARS-CoV reveal that this approach is important in developing the vaccine against SARS-CoV-2.

Subunit vaccines

A number of technologies that target S protein have been previously used for the development of vaccines and antiviral therapeutics. The generation of subunit vaccines appropriates to ensure wide prevention should target the variety of the major immunogenic agents of the Spike (S) protein (Malik et al., 2020). Subunit vaccines for both SARS coronaviruses rely on eliciting an immune response against the S-spike protein to prevent its docking with the host ACE2 receptor. scientists have developed and tested a subunit vaccine comprised of only the receptor-binding domain (RBD) of the SARS-CoV S-protein when formulated on alum, the SARS-CoV RBD vaccine elicits high levels of protective immunity on the homologous virus challenge. An advantage of the RBD-based vaccine is its ability to minimize host immunopotentiation (Wang et al., 2020). Initial findings that the SARS-CoV and SARS-CoV-2 RBDs exhibit more than 80% amino acid similarity and bind to the same ACE2 receptor offer an opportunity to develop either protein as a subunit vaccine. Thus, subunit vaccines do not include the whole pathogen, but only the specific compounds or antigens which induce the immune system.

Recombinant protein vaccines

A recombinant vaccine is a vaccine produced by using recombinant DNA technology. In this technology, certain protein antigens can be produced in bacteria, yeast, mammalian cells, or plants. Recombinant protein vaccines or recombinant subunit vaccines compared to other vaccine platforms have the best biosafety property, such as inactivated virus, live-attenuated virus, and viral vector-based subunit vaccines. Recombinant protein-based vaccines do not rise a risk for incomplete, inactivation, recovery of virulence of the attenuated virus, or undesirable responses of host cells to virus vectors. In one study researchers synthesized a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the S glycoprotein of a severe acute respiratory syndrome (SARS-CoV-2) strain. After an experiment on 18-60 years' adults, they demonstrated that the Ad5 vectored COVID-19 vaccine is tolerable and immunogenic at 28 days' post-vaccination. Humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination. The results suggest that the Ad5 vectored COVID-19 vaccine warrants further investigation (Zhu et al., 2020).

Preparation of plant based recombinant protein vaccines

Recombinant proteins based on plants are safe, effective, and inexpensive. In one study researchers showed that SARS-coronavirus (CoV) spike protein (S protein) and its truncated fragments have expressed (the N-terminal) in tomato and low-nicotine tobacco plants. Incorporation of the S1 fragment into plant genomes as well as its transcription was confirmed by PCR and RT-PCR analyses. High levels of expression of recombinant S1 protein were observed in several transgenic lines by Western blot analysis using specific antibodies. Plant-derived antigen was evaluated to induce systemic and mucosal immune responses in mice. Mice showed significantly increased levels of SARS-CoV-specific IgA after oral ingestion of tomato fruits expressing S1 protein. Sera of mice parenterally primed with tobacco-derived S1 protein revealed the presence of SARS-CoV-specific IgG as detected by Western blot and ELISA analysis

Epitope vaccines

Epitopes are the part of antigens that identify by the immune system, specifically by, B and T cells antibodies. in recent years new approaches in vaccine technology based on epitopes show great immunity both in humans and pathogens. Epitope-based vaccines can be consist of the short peptide with poor immunogenicity or longer peptides composed of multiple epitopes, based on dendrimer structures such as multiple-antigenic peptides (Palatnik-de-Sousa et al., 2018). In one study researchers demonstrated the potency of epitopes from the S protein of MERS-CoV and detected that

the antigenic epitopes may present as effective vaccines for the prevention of MERS-COV pathogen (Tahir Ul Qamar et al., 2019).

In another study researcher to obtain immunogenic epitopes, characterized spike glycoprotein. They choose 13 Major Histocompatibility Complex-(MHC) I and 3 MHC-II epitopes, having antigenic properties. To increase fast immunogenic property of these epitopes they performed immunoinformatics analysis. Moreover, they demonstrated that the molecular docking of vaccine components with the TLR-5 proves the significance and effectiveness of these epitopes as an ideal vaccine candidate against SARS-COV-2. Development of epitope-based peptide vaccine against novel coronavirus 2019 (SARS-COV-2) (Bhattacharya et al., 2020). in one study scientists designed a multi-peptide subunit-based epitope vaccine against COVID-19. The recombinant vaccine contains cytotoxic T-lymphocyte, an adjuvant, T-lymphocyte, and B-cell epitopes joined by linkers. The computational data demonstrate that the vaccine is non-toxic, non-allergenic, thermostable, with the capability to elicit a humoral and cell-mediated immune response. The stabilization of the vaccine construct is validated with molecular dynamics simulation studies. This unique vaccine consists of 33 highly antigenic epitopes derived from three proteins and plays an important role in viral entry and pathogenicity and host-receptor recognition. They recommend that this vaccine be synthesized and tested quickly (Kalita et al., 2020).

Virus-like particle vaccines

Compared to other traditional live virus vaccines, virus-like particles are more biosafe and effective. VLP based vaccines are not infective. As VLPs don't require inactivation or attenuation it makes this technology so important. If special natural proteins, that have the ability to suppress immune response, eliminated from the VLP structure can remarkably improve the potential of these particles. Virus-like particles, obtained by different expression methods, have been broadly used as vaccines and delivery systems for drugs and genes (Charlton Hume et al., 2019). VLPs have extremely repetitive surface they are capable to boost the high level of B-cell responses in case using adjuvant.

Bacterium like particle vaccines

The action of Bacterium-like particles based on the membrane surface receptor TLR2 (innate receptor) activation which is specific for different viral, fungal, and bacterial compounds. The BLPs are new types of immunostimulators (Van Braeckel-Budimir et al., 2013). To increase protective immunity BLPs can be used in combination with antigens. The successful attaches of antigen to particle could boost the immune response. BLPs have been successfully used for Streptococcus pneumonia, influenza, and Yersinia pestis (Nganou-Makamdop et al., 2012; Saluja et al., 2010). researchers designed a bacterium-like particle (BLP) vaccine against MERS-CoV, presenting the recombinant binding domain (RBD) antigen protein. The results of this research indicated that BLP based vaccine can stimulate a high characteristic mucosal immune response. They suggested that MERS-CoV bacterium-like particle with GEL01 adjuvant is a potential platform for vaccine development (Li et al., 2019).

Polymeric nanoparticle based vaccines

Nanoparticle-based vaccines have gained more importance in recent years because of their more effectiveness, offering numerous advantages over inactivated or subunit vaccines, the ways of immunization, and features such as boosting the immune response as a targeted carrier system. Nano particle-based vaccines could be produced by encapsulating vaccine compounds within nanoscale particles or by binding viral antigens to the surface of the particle. These nanoparticles can prevent the degradation effect of proteolytic enzymes on antigens along with their availability and preserve the prolonged and systematic release of antigens. These features of nanoparticle vaccines give the opportunity to stimulate high immune responses in contrast to soluble antigen vaccines (Dhakal & Renukaradhya, 2019). This technology also is considered a new approach to generating vaccines against MERS-CoV, RSV, and Epstein Barr virus.

Inorganic nanoparticle based vaccines

Physicochemical features of inorganic nanoparticles make it a suitable option for use in immunotherapy applications because these specifications prohibit the generation of antibodies against

the platform. In addition, some studies demonstrate that different immune cells, such as macrophages, dendritic cells, and lymphocytes, that are induced via Gold nanoparticles and AuNPs, cause the generation of pro-inflammatory and Th1 cytokines. One study, explored the effectiveness of AuNPs and TLR agonists. Of these two kinds of vaccine adjuvants, AuNPs are used as antigen delivery systems and adjuvants for subunit vaccines. The antibodies that were stimulated by recombinant S (spike) protein prevented SARS-CoV infection, but an eosinophilic immunopathology was recognized in the lungs of immunized mice after SARS infection. According to this study, an adjuvant is necessary for the prevention of eosinophilic immunopathology in the lungs after SARS-CoV infection, even with the spike (S) protein vaccine. Researchers in one study designed a recombinant spike (S) protein of SARS coronavirus by using the expression system of baculovirus. Furthermore, they investigated the effectiveness of the vaccine and its ability to stimulate lung eosinophilic immunopathology in the murine SARS model (Sekimukai et al., 2019).

DNA vaccines

DNA vaccine technology is a new effective way to induce humoral and cellular immune responses to protein antigens. Bacterial plasmids are the DNA vaccines component. antigen expression unit and production unit include bacterial sequences are expression plasmids which use in DNA-based vaccination technology. DNA vaccines have been used against several diseases (such as influenza, HIV, Ebola, West Nile and other viruses) in various animal models (Gurunathan et al., 2000). In contrast to success in animal models, the use of these vaccines on humans have been carried out just in recent years. More investigations are needed to demonstrate its potential to prevent human diseases. According to the disadvantages of the animal model for SARS-CoV pathogen, to determine the immunogenicity of plasmids in humans is important. The description of efficacious virus genes can lead to the option of inserts for vaccination technologies that based on genes According to one study, DNA vaccination has been used to stimulate cellular and humoral immunity against S glycoprotein of SARS-CoV. The humoral immunity that involves the expression of NA (neutralizing antibodies) can prevent the replication of viruses in the experimental animal model and recommend that this kind of vaccination reveals prophylactic immune response (Yang et al., 2004). In one study, researchers explored the biosafety, immunogenicity, and endurance of MERS coronavirus DNA-based vaccine (GLS-5300) They demonstrated that this DNA vaccine candidate did not reveal undesirable side effects and stimulated identical cellular and humoral responses. Immune responses were recognized in most of the persons (Σ85%) that participate in trials after vaccination twice and lasted through 1 year. They noted that this phase-1 clinical research does not evaluate the effectiveness of DNA vaccine and it needs further investigations in an endemic region of MERS-CoV (Modjarrad et al., 2019).

Messenger RNA vaccines

RNA or mRNA is a new vaccine technology that provides immunity through RNA containing the vector. mRNA vaccines have shown strong immunity against infectious disease, influenza virus, Zika virus, and others. The absence of genome integration, the production of multimeric antigens, rapid development capacity, the stimulation of immune response against different diseases, make mRNA vaccines more effective than traditional vaccine candidates. mRNA vaccine development technology involves the capability to combine several mRNAs into a single vaccine and to induce more potent protective immunity. Messenger RNA vaccine development technology involves the capability to combine several mRNAs into a single vaccine and to induce more potent protective immunity. However, some limitations also were evaluated, such as instability of messenger RNA, problems with carriage of mRNA into cells and etc. For this, the design of biosafe and effective products for *in vivo* carriage of mRNA and improved procedures to produce high-grade mRNA are required. Previously, scientists generated mRNA vaccine candidate that prevents Zika virus in mice and monkeys after injection of a single dose. Researchers were used mRNA vaccines produced for protection from influenza viruses (A H1N1, H3N2 and H5N1) vaccine prompts B and T cell-dependent protection. It purposes several antigens, containing strongly protected virus nucleoprotein, displaying

its profit as a cross-protective vaccine candida. Recombinant vector vaccines caused both cellular and humoral immunity, adenovirus vectored vaccines are one of the widely used recombinant vector vaccines against several diseases including HIV, influenza, malaria etc. According to previous animal researches, different vaccine candidates showed effectiveness, biosafety, and immunogenicity against MERS-CoV. Among these options, the recombinant viral vector-based candidates are evaluated as the most suitable platform (Wang et al., 2020; Pardi et al., 2017).

Recombinant vector vaccines

A vector vaccine is obtained by genetic engineering. Vector vaccines prepare from live microorganisms which are non-pathogenic or have low pathogenicity for the desired species and induce an immune response against micro-organisms by encoding antigens via genes. viral vectors are a tool used to deliver genetic material into cells. This process can be done in a living organism (*in vivo*) or in cell culture (*in vitro*).

In one study researchers synthesized AOaV-1 based topical respiratory vaccine candidate against CoVID-19. They engineered a virulent strain of AOaV-1 to express full-length spike (S) glycoprotein which is highly neutralizing and is a major protective antigen of the SARS-CoV-2. As a result, they mentioned that the recombinant vaccine vector stably expressed S protein after multiple propagations in chicken embryonated eggs, and this expression did not remarkably affect the in vitro growth characteristics of the recombinant. And they inform that the synthesized vaccine carries the potential for clinical studies against COVID19 (Rohaim & Munir, 2020).

CONCLUSION

According to the World Health Organization (WHO) report, 42 COVID-19 vaccine projects are in clinical evaluation. Vaccine candidates developed against COVID-19 are different from the vaccine candidates previously developed against SARS-CoV, MERS-CoV, and have a wider platform and are new hopes to developing of a vaccine against COVID-19. Until now, no vaccines have been applied against coronaviruses. Therefore, it is essential to develop vaccines to prevent outbreaks of COVID-19. Live attenuated, inactivated, subunit, recombinant protein, epitope, DNA, RNA based vaccines, adenovirus-based vectors, virus-like particle vaccine forms the bases of vaccine candıdates against COVID-19.

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SARS-CoV-2-ə qarşı hazırlanmaqda olan peyvənd namizədlərinə ümumi baxış

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Ağır kəskin tənəffüs sindromu koronavirus 2 (SARS-CoV-2) yeni bir koronavirüs olan SARS-CoV'un sebep olduğu yeni bir yoluxucu xəstəlikdir. Ümumdünya Səhiyyə Təşkilatı 11 mart 2020-ci il tarixində koronavirus xəstəliyinin (COVID-19) yayılaraq pandemiyaya səbəb olduğunu elan etdi. SARS-CoV-2 və Yaxın Şərq tənəffüs sindromuna (MERS-CoV) səbəb olan koronavirus insanlar üçün ən təhlükəli koronavirus növlərdir. İndiyə qədər koronaviruslara qarşı hər hansı bir peyvənd hazırlamaq mümkün olmamışdır. Bu ədəbiyyat icmalında COVID-19-a qarşı dünyanın müxtəlif laboratoriyalarında hazırlanan peyvəndlər haqqında məlumat verilməklə birlikdə onların müsbət və mənfi tərəfləri müzakirə edilmişdir. Hazırda COVID-19-a qarşı canlı, zəifləmiş, təsirsiz hala gətirilmiş, subunit, rekombinant zülal, epitop, DNT və RNT əsaslı vaksinlər, adenovirus əsaslı vektorlar, virusa bənzər hissəciklərin əsasında namizəd peyvəndlər üzərində tədqiqatlar aparılmaqdadır. Ümumdünya Səhiyyə Təşkilatının hesabatına görə 42 COVID-19_a qarşı peyvənd layihəsi klinik qiymətləndirmədədir. Hazırlanacaq peyvəndlərin qiymətləndirilməsində onların biotəhlükəsizliyinə və effektivliyinə diqqət emək çox vacibdir. COVID-19-a qarşı hazırlanan peyvənd namizədləri, əvvəllər SARS-CoV, MERS-CoV-a qarşı hazırlanan peyvənd namizədlərindən fərqli olub, daha geniş bir platformaya sahibdir. Buna görə də aparılan bu tədqiqatlar COVID-19-a qarşı peyvənd işlənilib hazırlanmasında yeni ümidlər verir.

Açar sözlər: *SARS-CoV-2, COVID-19, vaksinlər*

Обзор разрабатываемых вакцин-кандидатов против SARS-CoV-2

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Тяжелый острый респираторный синдром - коронавирус 2 (SARS-CoV-2) - это недавно возникшее инфекционное заболевание, вызывающее коронавирусную болезнь (COVID-19). Всемирная организация здравоохранения объявила о пандемии коронавирусного заболевания (COVID-19) 11 марта 2020 года. SARS-CoV-2 и коронавирус, связанный с ближневосточным респираторным синдромом (MERS-CoV), считаются наиболее опасными коронавирусами для жизни человека. До сих пор не было разработано вакцин против коронавирусов. Следовательно, для предотвращения вспышек COVID-19, очень важно разработать основы вакцин-кандидатов против COVID-19: аттенуированные, инактивированные, субъединичные вакцины, вакцины из рекомбинантного белка, эпитопа, вакцины на основе ДНК и РНК молекул, вакцины на основе векторов-аденовирусов, вакцины на основе вирусоподобных частиц. Каждая текущая стратегия вакцинации имеет определенные преимущества и недостатки. Поэтому крайне важно быстро разработать несколько стратегий и затем оценить их безопасность и эффективность. Согласно отчету Всемирной Организации Здравоохранения 42 проекта вакцин против COVID-19 проходят клиническую оценку. Вакцины-кандидаты, разработанные против COVID-19, отличаются от вакцин-кандидатов, ранее разработанных против SARS-CoV, MERS-CoV, имеют более широкую платформу и являются новой надеждой на разработку вакцины против COVID-19.

Ключевые слова*: *SARS-CoV-2, COVID-19, вакцины