



Thematic Opinion

Landscapes of an ideal COVID-19 vaccine

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Abstract: This paper discusses the designing strategies for an ideal COVID-19 vaccine. It gives an illustrative methodology of a complete immunologic understanding of an ideal vaccine that can be used to formulate and prepare a COVID-19 vaccine antigen.

Keywords: *adjuvants; antibody production; antigen presentation; vaccine immunology*

सारांश : यो लेखको प्रमुख ध्येय कोभिड-१९ उपचारमा कामयावी हुन सक्ने खोप तयार गर्नको लागि आवश्यक पर्ने रणनीतिहरूको बारेमा चर्चा गर्नु हो । विशेष गरी यसमा शरीर प्रतिरक्षा विज्ञानको कोणवाट कुनै पूर्णरूपेण आदर्श खोपको बारेमा सचित्र व्याख्या गर्ने प्रयास गरिएको छ जसवाट कोभिड-१९ खोपको लागि आवश्यक एन्टिजेन तयार गर्ने काम गर्न मद्दत पुग्न सक्नेछ ।

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1. Introduction

On March 12, 2020, the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19), a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), pandemic. The disease has killed over three hundred ninety-five thousand lives threatening billions of people in 188 countries (<https://coronavirus.jhu.edu/map.html>, Retrieved June 6, 2020). Infected patients develop various symptoms and pathogenicity including, fever, cephalgia, myalgia, malaise, dry cough, runny nose, diarrhea, dyspnea, severe pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and or multiple organ failure. Also, following SARS-CoV-2 infection, excessive cytokine production (Jose and Manuel 2020), antibody secretion (Zhao et al., 2020; Zhang et al., 2020), and CoV antigen-specific robust CD4 and CD8 T responses (Braun et al., 2020; Grifoni et al., 2020)

have been reported. Due to the lack of particular, safe, and effective drugs, immunization is the only way to protect billions of lives from COVID-19. To date, several vaccine candidates have been going on experiments, and are still in pre-clinical and clinical settings. Few of them include DNA, non-replicating viral vectors, replicating viral vectors, RNA, inactivated virus with or without adjuvants, live attenuated virus, protein subunit with or without adjuvants, virus-like particle, and plant-derived virus-like particle (<https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines>, Retrieved on June 4, 2020).

2. Ideal COVID-19 Vaccine Landscapes

Our understanding of pathogen biology, molecular biology, biochemistry, and biotechnology has increased with advances in the diagnostic and analytics technologies. Thus, vaccine development

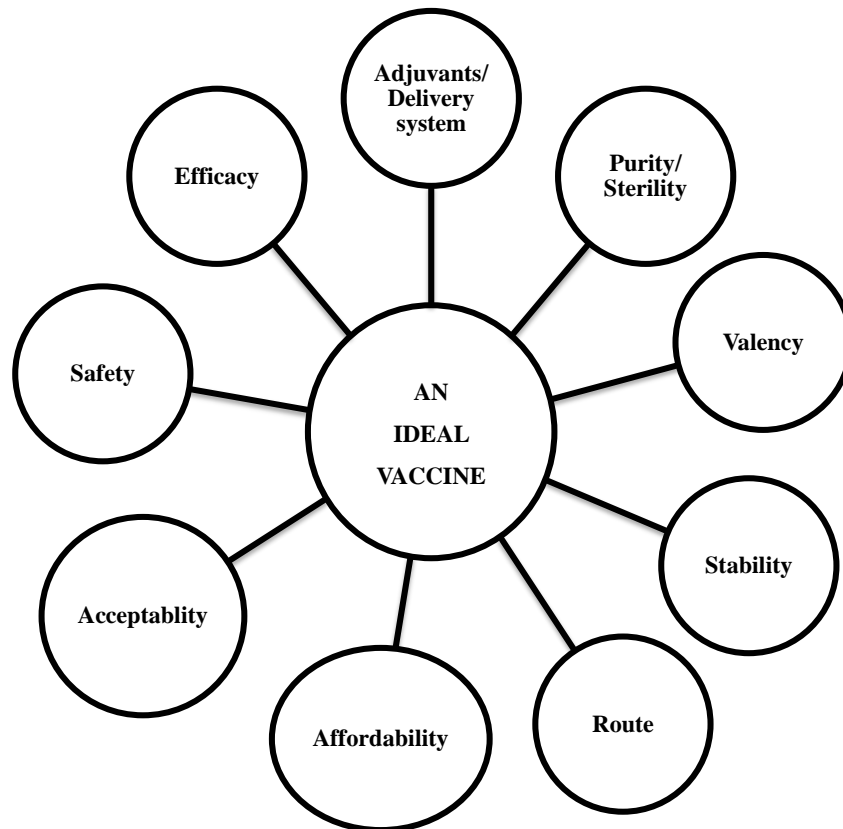


Figure 1. Landscapes to be considered while designing an ideal COVID-19 vaccine.

has progressed from trial and error-based empirical studies towards more rational and reductionist approaches (van Regenmortel 2004). However, these tools and techniques have resulted in the limited progress in developing effective vaccines against COVID-19, the 2020's major killer. A critical limitation of vaccine development is the incomplete understanding of the landscapes of an ideal vaccine. In this paper, I have addressed a few aspects necessary to be an ideal COVID-19 vaccine (**Figure 1**).

Landscape 1: Safety- An ideal vaccine should be safe for all people, including pregnant, ill, immunologically immature, inactive, and immunocompromised individuals. Although there is no 100% safe vaccine, a mortality rate higher than one in 1 million immunized individuals in many countries cannot be accepted (Ada 1991). Vaccine-immunized persons, in this context, however, should not be suffered from long-term side effects; for example, neurologic damage and deaths may occur following immunization with various vaccines (<https://www.cdc.gov/vaccines/vac-gen/side-effects.htm>, Retrieved on June 4, 2020).

Landscape 2: Efficacy- An ideal vaccine should be 100% effective. An effective vaccine would induce an antigen-specific, accurate, quick, strong, long-lasting, high quality, high magnitude, and protective

immune response following one or two doses of vaccines. Therefore, those types of vaccines would induce the generation of a large number of memory cells capable of quick and precise recognition of the specific epitope of an antigen and re-stimulation upon consequent antigen exposure within the body. They would secure the induction of long-lasting protective cellular and humoral immune responses (Supplementary material).

Landscape 3: Adjuvant/Delivery system- An ideal vaccine can contain adjuvants and delivery systems to enhance the efficacy, quality, magnitude, and duration of the vaccine antigen. Adjuvants can increase the immunogenicity of many weak and safe antigens like the soluble proteins, peptide, refined subunit, or recombinant protein vaccines. They can induce one or more of antibody, cellular, and cytotoxic T cell responses (Pulendran and Ahmed 2011; Ghimire 2015).

Vaccine candidates can also be encapsulated or fused within delivery systems. The systems may include many adjuvants like Alum, liposomes, immunostimulating complexes, lipid nanoparticles, microparticles, biodegradable microspheres, or capsules that work by targeting antigen to the particular cells (Ada 1991;1994; Ghimire et al. 2012; Ghimire 2014; Ghimire 2015; He et al. 2019).

While adjuvants and delivery systems might be useful to enhance the immune responses of a

vaccine, they have been blamed for leading many side effects, including allergy, autoimmune responses, and others. Thus, the safety standard of an adjuvant preparation or delivery system in the vaccine should be considered before clinical experiments.

Landscape 4: Purity/Sterility- An ideal vaccine must be pure and sterile. It may contain various ingredients like residual medium, stabilizers, preservatives, antibiotics, diluents, nutrients, and trace components in a dose that should not produce adverse effects like allergies, inflammations, or others (<http://www.vaccinesafety.edu/components-Allergens.htm>, Retrieved on 20 May, 2012). Besides, vaccines should not contain any germ outside of vaccine molecules.

Landscape 5: Valency- An ideal vaccine should be multivalent that can protect several pathogens, their strains, or their antigens. It can also save the administrative cost of the preparation of vaccines. Although changes in the genotypes of SARS-CoV-2 have not been associated with the changes in immune functions yet, if these happen in the future, using multiple epitopes in the vaccines would protect all genotypes or mutated strains.

Landscape 6: Thermal stability- An ideal vaccine should have high thermal stability. Due to the diverse geography of the earth, vaccines have to be transported from vaccine-producing areas to storerooms and then to the spot of immunization; thus, in this situation, the cold chain system protects the efficacy, potency, and stability (EPS) of vaccines. It is critical in a geographically isolated or remote area, where it is not easy to protect the EPS. Therefore, a potent and stable vaccine should avoid the needs of expensive and highly regulatory cold chain system.

Landscape 7: Route- An ideal COVID-19 vaccine should be administered, preferably through the oral/nasal routes. Infections by SARS-CoV-2 occurs via a mucosal pathway, the leading site being the respiratory and gastrointestinal tracts. Oral and subsequent anatomy within the digestive tract is characterized by a mucosal surface. Thus, cells sensitized by an antigen at one mucosal region can circulate to other mucosal areas because of the common mucosal system (McGhee et al. 1992). As a result, immunity can be systematically achieved. Mucosal sites provide intraepithelial T cell immunity and secretory IgA responses (McGhee et al. 1992; Mantis et al. 2011).

Landscape 8: Affordability- An ideal vaccine should be cheaper and affordable for the people and

for the country in which it is utilized. Vaccination is considered the most cost-effective public health intervention. The cost of vaccines matters for the people as well as the government of not only the low and middle-income countries but also the advanced countries. Even a provaccinist in a geographically remote area may not vaccinate himself/herself if he/she cannot afford the costs of transportation or vaccination (Hendrix et al. 2016). The price of a vaccine is different in different countries and depends on various factors like manufacturing, transportation, and administrative costs. For every euro spent on targeted influenza vaccination for the elderly in the UK, 1.35 euro savings were generated in terms of reduced medical spending in the healthcare system (Scuffham and West 2002). In these scenarios, however, several international organizations can commit to fair immunization coverage and global health security.

Landscape 9: Acceptability- An ideal vaccine should be acceptable to the public and the country's political and health delivery systems. For example, in the US, children cannot attend schools, including preschool programs, if they are not vaccinated, however, they are permitted to participate in the class depending on medical, religious, and philosophic contexts in some States (<https://edition.cnn.com/2017/06/06/health/vaccine-uptake-incentives/index.html>, Retrieved on June 4, 2020). In some areas, although the country's rules support the pro-vaccine decisions, many people become antivaccinists mainly because they are in the way of uncertainty, hesitation, and opposition (Hendrix et al. 2016). These antivaccinists may think that vaccines contaminate the body and may lead to dangerous consequences. Many people prefer oral/nasal vaccines because they fear that injections usually lead to pain, blood-borne transmission, anaphylactic responses, and further effects.

3. Conclusions

While vaccination is successful in the control and prevention of smallpox, swine cholera, parvovirus-induced enteritis, distemper, and pseudo-rabies viral infections and dramatically reducing vaccine-preventable diseases, global vaccinologists have been struggling in designing vaccines against COVID-19 pandemics for few months. Therefore, the discovery of an effective vaccine against this highly contagious disease has become the vital and critical target of the biomedical sciences. The rational design of the new vaccine depends on the vaccine parameters such as dose, route, and types of antigens that affect continuous activation of antigen-presenting cells and co-stimulation, leading to the sustained induction of T cell expansion,

differentiation and polarization, affinity maturation, isotype switching, and generation of immunological memory. Although vaccine design is a long, expensive, ethically critical, and complex process, as a whole, considering and reviewing different landscapes of an ideal vaccine would make it rational and scientific for a vaccinologist.

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Cellular and humoral immune response to an ideal vaccine

To initiate an adaptive immune response, the role of innate immune cells is crucial. These cells include macrophages, monocytes, dendritic cells, and natural killer T cells that contain various receptors like toll-like receptors (TLRs), phagocytic receptors, and others. There are usually three signals, namely vaccine antigen presentation (signal 1), co-stimulation (signal 2), and cytokine expression (signal 3) delivered by professional antigen-presenting cells (APCs) like (DCs) to activate antigen-specific naïve T cells. Therefore, DCs can process vaccine antigens and present them by binding them to major histocompatibility (MHC) class II and class I molecules on the cell surface. DCs also express costimulatory molecules like CD80, CD86, and others to cross-link CD28 molecules and other receptors on the T cell.

For induction of antigen-specific T cell clonal expansion, and prime immune responses, DC maturation is required (Reis e Sousa 2006). DCs undergo maturation processes when they get signals such as TLR ligands, necrosis, soluble inflammatory factors (cytokines), T cell ligands (such as CD40 ligands) and disruption of homotypic contacts between immature DCs (Sauter et al., 2000; Trombetta and Mellman 2005). The maturation is characterized by the appearance of dendritic processes, diminished antigen internalization efficiency and the increased expression of MHC class II molecules, costimulatory molecules (CD80 and CD86), and chemokine receptors (CCR7) (Sallusto et al., 1999; Dieu et al., 1998; Sozzani et al., 1998; Yanagihara et al., 1998). Then, the matured DCs begin their travel to the draining lymph node with the signal of the chemokine receptor (CCR7). In the entry site, there are many DCs that express Epstein-Barr virus-induced receptor-ligand chemokine (ELC) or chemokine ligand 9 (CCL19) and secondary lymphoid tissue chemokine (SLC) or CCL21 that enhance DC-T cell attraction (Ghimire 2015). In the paracortex, antigen-bearing DC-CD4⁺ T cell interaction results in the activation and expansion of CD4⁺ T cell, forming many effector CD4⁺ T cells. However, B cells can bind DCs Ag with their surface immunoglobulins and expand at the perimeter of the follicle. Then, B cells either initiate the germinal center response or differentiate into low-affinity antibody producing-short-lived extrafollicular plasma cells or memory B cells following interaction with T subsets like T helper (Th) 2 and T follicular helper (Tfh) cells (Chan et al., 2009; Takemori et al., 2014; Coffey et al., 2009). Although the antibody response is necessary for early control of infection, it may not be perfect to optimize the neutralization of SARS-CoV-2.

The story of T cells is different. The effector CD4⁺ T cells undergo polarization into various subsets like Th1, 2, Tfh cells, and others. Th1 cells are induced by IL-12, IL-18, IL-27, and IFN- γ . They predominantly produce pro-inflammatory cytokines like IFN- γ , TNF- α , and TNF- β (Wan and Flavell 2009). The role of Th1 cells in cell-mediated immunity is crucial because these cells clear virus-infected cells.

Th2 cells are induced by IL-4 (Wan and Flavell 2009). They predominantly produce IL-4, IL-5, IL-10, and IL-13 (Mosmann et al., 1986). Th2 may reach to the border of B cell follicle to activate B cells.

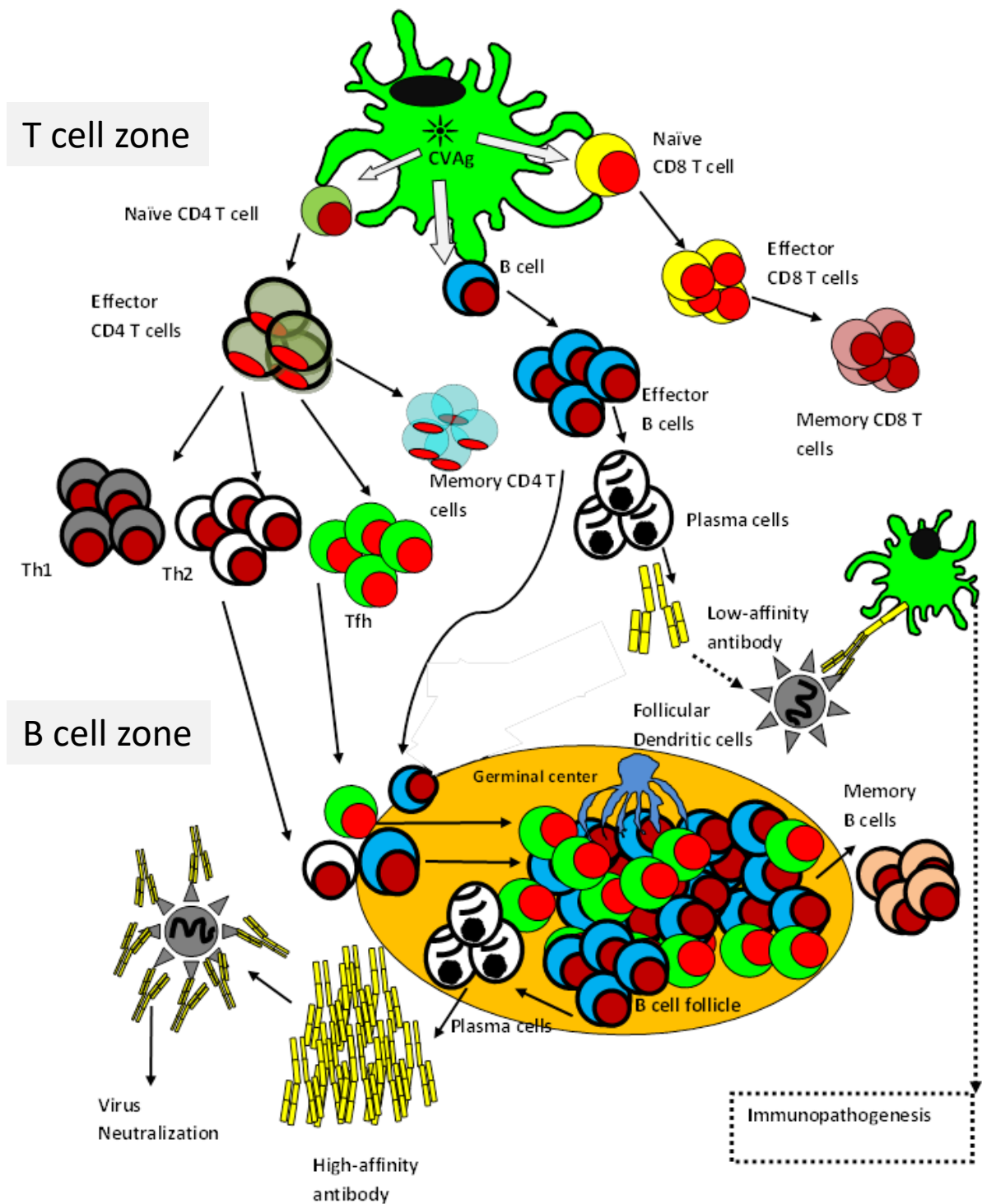
Tfh cells are induced by type I IFN signaling in DCs and non-hematopoietic cells (Cucak et al., 2009). Tfh cells express CXCR5 and various costimulatory molecules such as ICOS, CD40L, OX-40, and PD-1 that are signature molecules for follicular localization (Breitfeld et al., 2000; Schaerli et al., 2000; Hardtke et al., 2005; Deenick et al., 2010). Notably, Th2 and Tfh cells accompanied with follicular DCs (FDCs) may be associated with germinal center formation, B cell activation, long-lived memory B and plasma cell production and Ag-specific high-affinity antibody secretion (Miller III and Nossal 1964; Crotty 2011; Patakas et al., 2011; Rodda et al., 2015). Thus, an ideal vaccine antigen should target the generation of sustained Tfh response for optimum antibody response. In this context, native vaccine antigen within FDCs allows continuous formation and recruitment of memory B cells and antigen-specific antibody. However, an

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ideal vaccine antigen should not induce antibody-dependent enhancement (ADE). In the context of SARS-CoV-2 infections, ADE occurs when there are low quality, low quantity, and non-neutralizing antibodies because they bind to virus particles via the Fab domains (Wang et al., 2020). The Fc domains of antibodies bind with Fc receptors (FcR) expressed on monocytes or macrophages. As a result, viruses initiate entering into the endosomes. The interaction of FcRs with ITAMs induce signalling to enhance pro-inflammatory cytokines. In addition, various TLRs of endosomes like TLR-3, 7, 8 can interact with immune complexes and viral RNA to activate host cells leading to immunopathology (Wang et al., 2020).

In another context, following MHC class I presentation to naïve CD8 T cells, they undergo activation, expansion, and differentiation into effector CD8 T and finally into memory CD8 T cells. The effector CD8 T cells are cytotoxic in functions; thus, they kill virus-infected/damaged cells.

Hypothetical mechanisms of induction of immune responses in T cell B cell areas in the secondary lymphoid organs by dendritic cells carrying an ideal COVID-19 vaccine antigen (CVAg) have been illustrated in Supplementary **Figure S1**.



Supplementary Figure S1. Schematic mechanisms of induction of immune responses in T cell B cell areas in the secondary lymphoid organs by dendritic cells carrying an ideal COVID-19 vaccine antigen (CVAg) (Modified after Ghimire 2015).

An ideal vaccine antigen is processed via MHC class II or class I pathway to activate naïve CD4 T cell or naïve CD8 T cell. As a result, effector CD4 T cells and effector CD8 T cells are produced. Effector CD4 T cells are differentiated into Th1, Th2, or Tfh cells. Some effector CD4 T cells change into memory CD4 T cells, which can encounter vaccine antigen or exactly related natural pathogens in the future. The effector CD8 T cells either clear the infections or modify them into memory T cells for the second encounter of the vaccine antigen or exactly related natural pathogens in the future. B cells can bind to the antigen via its surface immunoglobulins. As a result, B cells undergo activation and produces effector B cells, which later differentiate into plasma cells. The plasma cells produce low-affinity antibodies. Some of the B cells, Th2, and Tfh cells migrate towards B cell follicle's edge border. Functional activities of Th2, Tfh, and follicular

dendritic cells result in the germinal center formation, B cell activation, long-lived memory B and plasma cell production, and Ag-specific high-affinity antibody secretion, for example, the secretion of neutralizing anti-spike viral antibodies. Dotted lines show immunopathogenesis via the interaction of Fc receptors of antigen-presenting cells with a low-affinity antibody, which should not be the mechanisms of an ideal vaccine.

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