Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 39 (2021) 4239–4241

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

The need for broadly protective COVID-19 vaccines: Beyond S-only approaches

Gregory A. Poland *, Inna G. Ovsyannikova, Richard B. Kennedy

Mayo Clinic Vaccine Research Group, Mayo Clinic, Rochester, MN, USA

1. Current problem

Early in the pandemic one of us (GAP) warned about reliance on S-only vaccines, given the high transmissibility of the SARS-CoV-2 RNA virus [1]. While the mRNA and Ad (adenovirus)-vectored COVID-19 vaccines have demonstrated high rates of efficacy and safety in the short- to mid-term, the development of multiple variants of interest and variants of concern (VOC) has become apparent. Some variants have demonstrated the ability to partially evade monoclonal antibodies, convalescent plasma, and immune responses to COVID-19 vaccines. Such variants have been characterized by a significant number of mutations in the S (spike) protein – particularly in and around the receptor binding domain. Thus, concern over future variants that might more fully evade vaccine-induced immunity is warranted. This leads to consideration of next generation, or so-called "2nd wave" SARS-CoV-2 vaccines and how they might be improved over first-generation vaccines. In particular, thoughtful awareness toward devising vaccines that may help avoid the analogy with influenza vaccines is imperative. For seasonal influenza vaccines, variants (drifted strains) arise requiring frequent change of new vaccine strains each year, necessitating the production of new vaccines whose strains vary each year. In large part this occurs because of mutations arising in the HA protein of the virus, again, analogous to mutations that occur in the S protein of the SARS-CoV-2 virus.

2. The immunologic rationale

SARS-CoV-2 undergoes mutation during replication within a susceptible host, albeit at a reduced rate compared to other RNA viruses such as influenza, due to limited proof-reading capabilities [2]. Mutations that confer a survival or fitness advantage are retained in the population and rapidly spread – a scenario that we have witnessed repeatedly during the COVID-19 pandemic. Variants are emerging that have increased infectivity/transmissibility, differences in viral load, and altered disease severity. Mutations in spike protein have received far more press than mutations in other proteins, however this may reflect a reporting bias given the importance of spike to both viral infection and antibody responses. Nevertheless, studies examining the rate and locations of viral mutations have confirmed that SARS-CoV-2 proteins do mutate at different rates [3], with the S and N proteins displaying the greatest degree of mutational variability. The immune response to SARS-CoV-2 (from both vaccine and disease) is likely to further increase mutational pressure on these proteins.

Protective immunity to specific pathogens is the result of a coordinated response by the adaptive immune system. The relative contributions of each component (B cells, antibody, $CD4^+$ T helper cells, $CD8^+$ cytotoxic T cells) vary by pathogen. The immune response to SARS-CoV-2 is similar to that of other respiratory viruses in that antibodies target accessible regions on structural proteins. This response can include epitopes in regions of the spike protein (e.g., RBD and NTD) that interfere with viral infection and confer neutralizing activity as well as the development of antibodies that are non-neutralizing and may or may not be involved in protection [4]. Neutralizing antibody is a correlate of protection for SARS-CoV-2 in animal models and was the primary goal of the first SARS-CoV-2 vaccines focused on spike protein [5]. In contrast to humoral immunity, the T cell response targets a broad set of structural (e.g., M, N, E), non-structural, and accessory proteins [6]. Cellular immunity has been correlated with less severe COVID-19 disease in humans. Similarly, depletion of CD8+T cells in naturally infected macaques diminished protection against rechallenge [6]. Furthermore, robust, durable, and high affinity antibody responses require T cell help.

Immunity after natural infection is associated with a significantly reduced risk of re-infection for months afterwards, but is also highly variable, with some patients displaying weak antibody and/or cellular immune responses. These individuals may be at increased risk of re-infection., and indeed, re-infections have been documented. Spike-only vaccines create immune responses that narrowly target the very regions most prone to mutation – an Achilles heel already observed among SARS-CoV-2 variants. As infection- and vaccine-induced herd immunity grows in the population, we will continue to see new variants arise that increasingly evade those responses [7].

* Corresponding author at: Vaccine Research Group, Mayo Clinic, Guggenheim Building 611C, 200 First Street SW, Rochester, MN 55905, USA.
E-mail address: poland.gregory@mayo.edu (G.A. Poland).

https://doi.org/10.1016/j.vaccine.2021.06.028

Fortunately, SARS-CoV-2 expresses multiple additional proteins that may serve as useful vaccine candidates [8]. SARS-CoV-2 contains three structural proteins (N: Nucleocapsid, M: Membrane, and E: Envelope), 16 non-structural proteins and 9 accessory proteins. The M and E proteins for coronaviruses have shown poor humoral immunogenicity, likely due to their small size and limited accessibility and have not proven successful as vaccine antigens in animal challenge models [9]. Despite not generating humoral immunity, these proteins do contain T cell epitopes, and inclusion in vaccines may provide a greater degree of cross-protection. The remaining structural protein, Nucleocapsid, is highly immunogenic, eliciting robust antibody responses and containing T cell epitopes [10]. N protein immunization has been found to be protective in animal models of other coronaviruses but adoptive transfer of sera from N-immunized animals did not protect against viral challenge in a mouse model [9]. Furthermore, N protein-containing vaccines for SARS-CoV were associated with enhanced respiratory disease. If the potential for immunopathology can be overcome, the inclusion of N protein may also lead to broader and more cross-protective immune responses.

Not all COVID-19 vaccines are limited to the spike protein. Multiple inactivated whole virus SARS-CoV-2 vaccine candidates are being developed in China (WIBP-CorV, BBIBP-CorV, CoronaVac), Russia (CoviVac), and India (Covaxin). Preclinical studies for several of these vaccines did not report immune-enhanced disease but did report poor or absent T cell responses [8]. This represents another challenge to overcome if we wish to fully realize the potential of inactivated vaccines.

3. The solution - next generation vaccines

Both current conventional (whole inactivated virus and protein-based) and new (viral vector, and nucleic acid-based) vaccine platforms are currently being used in COVID-19 vaccine development. In particular, genetic (mRNA- and DNA-based) vaccine platforms were developed and applied utilizing viral protein(s) coding sequence information. With ongoing COVID-19 cases worldwide, next-generation novel vaccine delivery platforms can potentially be utilized, such as liposomes, plant-like material, emulsions, polymeric and inorganic particles, outer membrane vesicles, immunostimulating complexes (ISCOMs) and others. Vaccine development against circulating and emerging variants also requires development of alternative delivery approaches, including mucosal/intranasal, oral, and/or transdermal skin patch microneedle vaccination to generate mucosal immunity [8]. As discussed above, other approaches are urgently needed that incorporate antigens beyond the S protein. One promising approach is the development of synthetic peptide-based candidate COVID-19 vaccines comprising both HLA class I and class II immunogenic peptides derived from SARS-CoV-2 structural and other proteins [11]. Other novel vaccine formulations could contain S- and other viral protein-derived B cell peptides/epitopes to induce protective high-titer neutralizing antibodies and HLA class I and II viral-derived peptides from other SARS-CoV-2 proteins to stimulate robust CD4+ and CD8+ T cell responses. A recent study by Tarke et al. [12], demonstrated an insignificant effect of SARS-CoV-2 variants of concern on global CD4+ and CD8+ T cell responses in convalescent COVID-19 individuals or vaccinees, suggesting that T cell responses could provide protection against multiple variants as they recognize a broad set of more highly conserved epitopes/peptides [12].

Optimally, the development of SARS-CoV-2 vaccines containing antigens/peptides with broad protective immunity - perhaps across all beta-coronaviruses or even a universal coronavirus vaccine – might be feasible given sufficient sequence similarity. Failing to explore novel SARS-CoV-2 vaccine formulations composed of non-S antigens/peptides will prove to dramatically slow the rate at which the SARS-CoV-2 pandemic can be combated by vaccines given the potential for further viral variants.

4. Conclusion

SARS-CoV-2 vaccine development is not "solved and over". With the pattern of S protein (particularly in the RBD region) mutations we have witnessed thus far, many which confer a selective advantage leading to higher viral loads, as well as reluctance on the part of many to be immunized with mRNA or Ad-vectored vaccines; second-generation COVID-19 vaccines are urgently needed. Unfortunately, the very heavy financial, political, and emotional investment in S-only vaccines, and their short- to mid-term efficacy, are likely to be inhibitors to further vaccine development in this space. And yet, vaccines with an improved ability to withstand immune evasion by variant strains, improved safety and reduced reactogenicity, acceptance by the public, and cost and cold chain considerations all argue for the development of next generation vaccines – ideally "universal coronavirus" vaccines, if possible.

We believe that further investment in a variety of research areas geared toward the development of more broadly active SARS-CoV-2 vaccines are critical to sustained control of SARS-CoV-2 and future SARS-like viruses. In particular, immediate areas of research need include:

(1) Short-term and long-term correlates of B and T cell immune protection
(2) A closer examination of the relative roles of mucosal and systemic immunity in protection against infection
(3) Identification of conserved and structurally important regions of viral proteins that can serve as broadly protective vaccine antigens
(4) Development of universal coronavirus vaccines
(5) Development of oral and nasal spray vaccines eliciting mucosal IgA immunity and providing efficacy
(6) Identifying the role of the S1 protein N-terminal domain (S1-NTD) to facilitate induction of a broad spectrum of neutralizing antibodies to diminish viral escape of host immunity
(7) A more complete understanding of the contribution of other structural, nonstructural, and accessory proteins to SARS-CoV-2 immunity
(8) An enhanced understanding of the role of binding but non-neutralizing antibodies vs. neutralizing antibodies produced by COVID-19 vaccines
(9) Development of single dose vaccine formulations that demonstrate superior efficacy and safety, and do not require a cold-chain

While the current COVID-19 vaccines are to be celebrated, we are already developing booster and variant virial vaccines given the emergence of VOC. To this end, we believe that next-generation COVID-19 vaccines must incorporate more than one vaccine antigen given the directly observed emergence of viral mutations capable of partial evasion of vaccine-induced immunity and the potential for limited protective durability. As we and others have observed, utilizing a single protein as a vaccine antigen to protect against highly transmissible RNA viruses, inevitably means the emergence of variants and the eventual need for yet newer vaccines. It has taken decades to finally commit to the idea that

universal influenza vaccines should replace seasonal influenza vaccines – a mistake we dare not make with coronavirus vaccines.

Declaration of Competing Interest

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Johnson & Johnson/Janssen Global Services LLC, Dynavax, Genentech, Eli Lilly and Company, Kentucky Bioprocessing, Bavarian Nordic, AstraZeneca, Exelixis, Regeneron, Vyriad, Moderna, and Genevant Sciences, Inc. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. Drs. Poland and Ovsyannikova hold patents related to vaccinia and measles peptide vaccines. Dr. Kennedy holds a patent related to vaccinia peptide vaccines. Drs. Poland, Ovsyannikova, and Kennedy have received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. Dr. Kennedy has received funding from Merck Research Laboratories to study waning immunity to mumps vaccine. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

References

[1] Poland GA. Tortoises, hares, and vaccines: A cautionary note for SARS-CoV-2 vaccine development. Vaccine 2020;38(27):4219–20.
[2] Sevajol M, Subissi L, Decroly E, Canard B, Imbert I. Insights into RNA synthesis, capping, and proofreading mechanisms of SARS-coronavirus. Virus Res 2014;194:90–9.
[3] Vilar S, Isom DG. One Year of SARS-CoV-2: How Much Has the Virus Changed?. Biology (Basel) 2021;10(2):91.
[4] Dugan HL, Stamper CT, Li L, Changrob S, Asby NW, Halfmann PJ, et al. Profiling B cell immunodominance after SARS-CoV-2 infection reveals antibody evolution to non-neutralizing viral targets. Immunity 2021;54(6):1290–303.
[5] McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature 2021;590(7847):630–4.
[6] Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021;184(4):861–80.
[7] Williams TC, Burgers WA. SARS-CoV-2 evolution and vaccines: cause for concern?. The Lancet. Respiratory Med 2021;9(4):333–5.
[8] Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nat Rev Immunol 2021;21(2):73–82.
[9] Sun J, Zhuang Z, Zheng J, Li K, Wong RL, Liu D, et al. Generation of a broadly useful model for COVID-19 pathogenesis, vaccination, and treatment. Cell 2020;182(3):734–743.e5.
[10] Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26(6):845–8.
[11] Crooke SN, Ovsyannikova IG, Kennedy RB, Poland GA. Immunoinformatic identification of B cell and T cell epitopes in the SARS-CoV-2 proteome. Sci Rep 2020;10(1):14179.
[12] Tarke A, Sidney J, Methot N, Zhang Y, Dan JM, Goodwin B, et al. Negligible impact of SARS-CoV-2 variants on CD4 (+) and CD8 (+) T cell reactivity in COVID-19 exposed donors and vaccinees. bioRxiv (2021).