HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 5, e2043105 (2 pages)
https://doi.org/10.1080/21645515.2022.2043105

Taylor & Francis
Taylor & Francis Group

COMMENTARY

Using a "systems therapeutic for physiological renormalization" approach to vaccine development. Covid-19 as an example

Greg Maguire

Laboratories, The California Physiological Society 2425 Channing Way, Berkeley, CA 94704 2425 Channing Way, Berkeley, CA 94704 Berkeley, USA

ABSTRACT

Current vaccines for Covid-19 have failed to prevent the disease from spreading and have allowed more transmissible and virulent variants to form through mutations and recombinations as they replicate during the massive spread of the virions. Here I suggest using a "systems therapeutic" vaccine and dosing strategy to induce "physiological renormalization" to induce mimicry in the innate and adaptive immune systems in the respiratory tracts and sera, similar to that when the body encounters the natural infectious agent.

ARTICLE HISTORY
Received 24 January 2022
Accepted 12 February 2022

As the US "chases variants" of the SARS-CoV-2 virus, a new vaccine strategy to update the constrained immunity induced by mRNA and DNA vaccines is underway and likely to be in clinical trials soon.[1] Given that the recent vaccines in the US are made to target a limited number of antigenic proteins only within the spike of the virions, a site in the virus that changes protein structure rapidly due to mutations and recombinations, the spike has quickly evolved to evade immunity. Protein crystallography studies suggest that non-spike protein interactions in the SARS-CoV-2 virion can mediate unique immune evasion and suppression activities.[2] Evidence that proteins in the virus other than those in the spike are important for immunity in Covid-19 include recent evidence that the common cold virus and its non-spike proteins provide cross reactive immunity against Covid-19 in T cells.[2] Further, the IM-only administration of these vaccines induces sera antibody levels to a high level against the spike proteins and provide neutralization of the original virus when measured in the blood, but the production of neutralizing IgA antibodies in the respiratory tracts is not robust.[3] However, as Bates et al. have found, vaccinated people with breakthrough infections now have a robust mucosal IgA response, likely because the antigens were presented to respiratory mucosa, unlike that in IM vaccines. Sera antibody levels and neutralization are biomarkers used as surrogate endpoints for infection and immune responses but are not predictive of disease state and immune response given that most of immunity, at least initially, is in the mucosa and not the sera and that there is much more to immune function than neutralizing a virion through antibodies.[4] While the strategy to develop a vaccine that targets more protein structures in the virion other than those currently targeted by the mRNA and DNA vaccines is a step in the right direction,[1] will it be sufficient to impede the development of future variants? With little induction of immunity in the respiratory tracts through IM administration, the site of initial infection and high levels of replication will allow the variants to cause breakthrough infections and foster further variant production. "Chasing of the variants" will likely continue with the new vaccine strategy. Even if the infections are mild to moderate, these infections need to be prevented because they can have long-term consequences, including long-term Covid sequalae with myriad disease states,[5] and even neurodegeneration.[6]

Here I suggest a different strategy, using an approach called "Systems Therapeutics",[7] to induce "Physiological Renormalization".[8] In the case of immunizing for Covid-19, what is meant by using systems therapeutics for physiological renormalization is to use an immunizing agent(s) at multiple sites of the body. This means delivering the vaccine nasally and intramuscular (IM) as a "systems therapeutic". And, to induce "physiological renormalization," as displayed by the human immune system when infected with SARS-CoV-2, an immune response by nasal vaccination will mimic the initial natural SARS-CoV-2 infection in the respiratory tract mucosa, where IgA dimers, the primary form of antibody in the nasopharynx, have been observed to be times more potent than IgA monomers against the same target,[10] while IM administration will induce high levels of sera antibodies found in natural infections. Other means in addition to vaccine have been described for renormalizing immune function in the mucosa to better prevent infection, acting by reversing immune cell senescence, thereby enabling innate immunity critical to the initial response to viral infection[9] and also by reducing inflammation and autoantibody production in post-infection[10] and post-vaccination[11] autoimmune sequalae. The choice of antigen is critical too for inducing broad immunity. Thus, whether the Chinese and French vaccines that use inactivated virions with their greater number of natural antigens proves better than the mRNA and DNA vaccines in such strategy awaits epidemiological, real-world data of disease, not the non-predictive sera antibody tests that are often used instead.[12] A "systems therapeutic for physiological renormalization strategy" may yield a more efficacious vaccine that induces broader immunity in the innate and adaptive immune systems, and one that is safer where antibodies are produced at

CONTACT Greg Maguire gregmaguire5@gmail.com The California Physiological Society, Berkeley, CA, USA

significant levels in the sera and mucosa, but not at levels that are extraordinarily higher in the sera but extraordinarily lower in the mucosa as compared to those in infection.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Greg Maguire http://orcid.org/0000-0001-5484-6157

References

1. Joyce MG, King HA, Elakhal-Naouar I, Ahmed A, Peachman KK, Macedo Cincotta C, Subra C, Chen RE, Thomas PV, Chen WH, et al. A SARS-CoV-2 ferritin nanoparticle vaccine elicits protective immune responses in nonhuman primates. Sci Transl Med. 2021. doi:10.1126/scitranslmed.abi5735.
2. Kundu R, Narean JS, Wang L, Fenn J, Pillay T, Fernandez ND, Conibear E, Koycheva A, Davies M, Tolosa-Wright M, et al. Cross-Reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts. Nat Commun. 2022;13(1):80. doi:10.1038/s41467-021-27674-x.
3. Bates TA, McBride SK, Winders B, Schoen D, Trautmann L, Curlin ME, Tafesse FG. Antibody response and variant cross-neutralization after SARS-CoV-2 breakthrough infection. JAMA. doi:10.1001/jama.2021.22898.
4. Russell MW, Moldoveanu Z, Ogra PL, Mestecky J. Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. Front Immunol. 2020;11. doi:10.3389/fimmu.2020.611337.
5. Bell ML, Catalfamo CJ, Farland LV, Ernst KC, Jacobs ET, Klimentidis YC, Jehn M, Pogreba-Brown K. Post-Acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. PLoS ONE. 2021;16(8):e0254347. doi:10.1371/journal.pone.0254347.
6. Liu S, Hossinger A, Heumüller SE, Hornberger A, Buravlova O, Konstantoulea K, Müller SA, Paulsen L, Rousseau F, Schymkowitz J, et al. Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions. Nat Commun. 2021;12(1):5739. doi:10.1038/s41467-021-25855-2.
7. Maguire G. Systems biology approach to developing "systems therapeutics". ACS Med Chem Lett. 2014;5(5):453–55. doi:10.1021/ml5000614. PMID: 24900858; PMCID: PMC4027758.
8. Maguire G. Physiological renormalization using systems therapeutics. Future Sci OA. 2019 ;6(1):FSO428. doi:10.2144/fsoa-2019-0106. PMID: 31915529; PMCID: PMC6920733.
9. Maguire G. Stem cells part of the innate and adaptive immune systems as a therapeutic for Covid-19. Commun Integr Biol. 2021;14(1):186–98. doi:10.1080/19420889.2021.1965356.
10. Chang SE, Feng A, Meng W, Apostolidis SA, Mack E, Artandi M, Barman L, Bennett K, Chakraborty S, Chang I, et al. New-Onset IgG autoantibodies in hospitalized patients with COVID-19. Nat Commun. 2021;12(1):5417. doi:10.1038/s41467-021-25509-3.
11. de Bruijn S, Maes M-B, De Waele L, Vanhoorelbeke K, Gadisseur A. First report of a de novo iTTP episode associated with an mRNA-based anti-COVID-19 vaccination. J Thromb Haemost. 2021 ;19(8):2014–18. doi:10.1111/jth.15418. Epub 2021 Jul 5. PMID: 34105244; PMCID: PMC8236927.
12. Mallapaty S. China's COVID vaccines have been crucial — now immunity is waning. Nature. 2021;598(7881):398–99. doi:10.1038/d41586-021-02796-w.