**Critical considerations for COVID-19 vaccines and possibilities for rational improvement**

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In a natural SARS-CoV-2 infection there is viral replication for around two weeks 1 in which, at least 25 immunogenic viral proteins are presented 2 to the host immune system, eliciting cellular and both mucosal serum antibody responses. But in the current gene expression-based adenoviral and mRNA vaccines, there is only spike presentation produced in several tissues unnecessarily and has been associated 3 with several serious adverse effects, such as myocarditis in adolescents and young adults.

To help the vaccine mRNA evade 4 the innate immune system, all uracil bases have, by design, been replaced by pseudouridines (y). This has a, perhaps unintended, role in preventing degradation by ribonucleases, and the poly-A 3' includes a GC rich domain inside a 100 bp-long poly-A tail 5 , hampering degradation by 3'-exonucleases, making this mRNA ‘quasi non-biodegradable’. Possibly, therefore, the vaccine mRNA ended up lasting for a minimum of 2 months 6 in germinal centers (GC) of the lymph nodes, in opposition of natural mRNAs that have a turn-over time that last 9-10 hours on average. It is worth mentioning that only a small percentage of cellular RNAs have a very small number of bases being y-modified after transcription, for increased stability to improve functional inter-molecular interactions 7. So, it becomes a possibly unreasonable option to design a AyGC molecule for which, unwanted implications were observed following a hurried population-level administration strategy. Why for the sake of safety, when expediency was at stake, time-tried, inactivated virus vaccine, with cross-linked but exposed structural proteins platforms, were not prioritized to start with, followed by attenuated platforms?

It is worthwhile discussing some of the problems with the current platforms that share the inherent complications and challenges of gene therapy. The spike is continuously produced and spread to tissues beyond the injection site. This was shown in a series of Biopsies of lethal cases of vaccine adverse effects 8. Its only product – complete spike glycoprotein – and its subproducts, were found to be secreted from cells transfected by the vaccine mRNA, via exosomes produced in the secretory pathway. The spike is presented in exosomes as in a virus-like particle (VLP), fusing with endothelial cells, via its binding with ACE2 and CD147 receptors 9. This is likely to agglutinate RBCs (which also have CD147, besides ACE2), possibly, in some cases nucleating clots associated with acute ischemic stroke due to mechanical thrombectomy and myocardial infarction 10.

The consequences of the bio magnification of spike-presenting VLP-like exosomes, the offspring of the mRNA vaccine, was studied in quite detail 11. It was shown by electron microscopy to present spike in a similar transmembrane fashion as the actual virion, while mass spectrometry indicated that both S1, including the receptor binding domain (RBD), and S2 domains are present as well as complete spike protein. Moreover, the secreted spike proteins inhibited the neutralization from antibodies, in a similar manner as defective, sub-particles do HIV and HBV do as a decoy to evade our immunity. This was also shown in assays using convalescent sera 11 .

These facts may indicate a conceptual blunder of an immunization strategy that, by design, inhibits the same very response it was supposed to induce. In all it is a devastating outcome, considering that, based on Jason McLellan’s ideas and previous work 12, the spike protein expressed on vaccines was locked 13, in a pre-fusion conformation via the insertion of two proline 14 amino acids and, should therefore have no fusogenic capabilities. Although the idea was clever, possibly deleterious activities of the S1 and S2 domains were not fully accounted for. Unfortunately, the S1 domain of spike was shown to persist in CD16+ Monocytes up to 15 months 15 post-infection in patients suffering of Post-Acute Sequelae of COVID-19 (PASC), in the absence of the detection of complete viral genomes. These facts hint to the notion that a full “stabilized” spike does not do the job and causes problems and, that the RBD alone may be a safer option for a better improved vaccine.

Immunohistochemistry/immunocytochemistry studies 16 with autopsy material show spike near the endothelia in several tissues. The indication that this is a consequence of the vaccine is the lack of reaction with anti-N (nucleoprotein) antibodies, which would incriminate the virus, exception made to inactivated vaccines that expose virion contents during its preparation, which was not the case with those patients.

Moreover, spike causes undesirable inflammatory responses 17, interferes with the cell DNA integrity 18 and causes mitochondrial dysfunction 19 associated with the COVID induced neuropathology. Moreover, the extensive list of observed events suggests comprehensive tissue injury (via ACE2), severe vasculitis and coagulopathies (via ACE2 and CD147). Nevertheless, the intranasal administration of spike S1 domain was shown to kill cancer cells in mice 20 , but one would like to see the same type of experiments done in healthy tissues as a control. Given the S1 impact in PASC, we need to consider if its suggested therapeutic use makes any sense. Indeed, it would also be necessary to question a vaccine said to be designed in a few hours in a single day 21 , making use of a synthetic mRNA designed to be almost "non-biodegradable" that has a half-life way greater than that of the detection time of viral genomic RNA, of about two weeks 22 and, that possibly bio magnifies spike for unreasonably longer periods of time and in quantities incompatible with that of a natural acute infection.

One could argue that the design of a spike-centered vaccine strategy in the human system, does not follow what would be expected from a natural acute infection and is seriously conceptually flawed. Notwithstanding, the criticisms raised herein have been put forward already by the tour de force of Seneff and Nigh 23 and by Altman 24, among others, in a more thorough and detailed way. Sadly, the worldwide impact of the accumulation of serious adverse reactions, low risk benefit ratio, deaths and excess deaths associated with the in vivo gene-expression vaccine platforms deployed, has helped deconstruct the reputation of important and effective vaccines such as smallpox, yellow fever, polio, measles, &c 25–29. This is made even worse, when most corporative media and even scientific journals, prefer to discredit any criticism, hijacking the issue away from the true, necessary scientific debate.

Why not use epitopes of the nucleoprotein (N), which induces comprehensive neutralizing cross-reaction between different clades of endemic betacoronaviruses and include epitopes of the membrane protein M and the envelope protein (E), which could prevent its apparent role in the cytokine storm following natural infection 30,31 ? Both structural proteins and several others would present additional promising, non-spike antigens for future prophylactic vaccines against COVID-19. Moreover, why not present only multimers of the spike's loop 2, containing the receptor binding domain (RBD)32,33 ? This was shown to have increased immunogenicity and to reduce adverse effects in preclinical phase studies in other SARS viruses 34 . Crucially, why not consider strategies including nasal mist administration that are known to cause much needed mucosal antibody response via IgA, to break the chain of transmission, the lack of which, besides adverse effects, has been an obvious, glaring and demoting non sequitur of the current gene-expression vaccines 35 ?

We believe that these aspects should be openly discussed by the scientific community and not suppressed in the way that it has been done by institutions, the press and by people without specific technical background. A better, safer vaccine for SARS-CoV-2 is possible, if the issue is dealt with in a more comprehensive manner considering cellular and antibody mediated immunity with the understanding that multiple epitopes must be engaged given the high mutagenic potential of SARS-CoV-2 and the failure of Spike protein-only based vaccines.

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