Review 1: "A Rational Design of a Multi-Epitope Vaccine Against SARS-CoV-2 Which Accounts for the Glycan Shield of the Spike Glycoprotein"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Review:

The preprint title "A Rational Design of a Multi-Epitope Vaccine Against SARS-CoV-2 Which Accounts for the Glycan Shield of the Spike Glycoprotein[10.26434/chemrxiv.12770225]" presents convincing evidence towards predicting a suitable epitope vaccine candidate for COVID-19.

S protein has been widely studied as a suitable target for vaccine candidates. However, the inclusion of a combination of 9 other mutants and addressing the major challenge of the glycosylation of S protein are the major unique selling points (USPs) of this approach. Moreover, the antibody accessible surface area (AbASA) analysis serves as a proof of concept.

The study also demonstrates a high-level combination of immunoassays and bioinformatics with appropriate validations. All the simulations have been run for 500ns and all systems were found to be stable. The highlight of the paper was the construction of the multi-epitope vaccine candidates and their linkage with suitable adaptors.

Taking out all the points of consideration, it can be concluded that the identified targets are of much interest and must be followed up by in vitro as well as in vivo validation as soon as possible. Since this pandemic started, mankind has seen some terrible things and the situation is only getting worse. Therefore, such studies shed rays of hope towards the identification of an effective vaccine candidate.

The following suggestions are to be addressed:

1. Recent references from 2020 should be included.

2. The introduction should be revised to include recent developments in the field. At present, it is very brief. A few suggestions to read over include:
Verma, S., et al (2020). Computational approaches in epitope design using DNA binding proteins as vaccine candidate in Mycobacterium tuberculosis. *Infection, Genetics and Evolution*, 104357.
Jaiswal S, et al (2020) Systems Biology Approaches for Therapeutics Development Against COVID-19. *Front. Cell. Infect. Microbiol.* 10:560240. doi: 10.3389/fcimb.2020.560240.
3. The comparison of similar studies to the present study should be provided in a tabular form.
4. The authors can also suggest suitable tools for enhancing the understanding of rational design.
5. The article should be proofread for grammar and English.
6. The concept and standard procedure for the construction of multi-epitope vaccine candidates must be highlighted.
7. The conclusion needs to be enhanced to include important highlights from the paper.
8. The whole procedure should have a figurative description for easy understanding.
9. The abstract needs to be revised and the novel aspects of the data presented should be added.
10. The title is like a sentence; it should be revised to convey the exact outcomes coming out of this study.