Review 2: "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:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The article titled "A rational design of a multi-epitope vaccine against SARS-CoV-2 which accounts for the glycan shield of the spike glycoprotein" by Martin et al. is an effort to design a virtual vaccine. Generally, the authors have provided a comprehensive analysis and characterization of the vaccine candidate.

However, the authors are expected to give explanations for the following queries and to add appropriate references wherever needed.

1. The authors have used one spike protein, identified immunological epitopes, and further conjugated with an adjuvant to determine the vaccine shape. Can the authors provide the logic used to develop a multi-epitope vaccine from only one spike protein when the whole protein can be used for immunization purposes?
2. The role of glycosylation is a big deal when it comes to the design of vaccines due to the part played by glycans in abetting "immune evasion" and the subsequent masking of epitopes. The glycosylation analysis carried out by Wantanabe et. al (2020) indicates that the glycosylation is restricted to the N-terminal regions. During the receptor binding domain (RBD) interactions with hACE2, the glycan shield has pretty low coverage (with at most 2 residues implicated) and hence the role of glycosylation in the prediction of epitopes can be suitably avoided. In such cases, how can glycosylation be the deciding factor if, during RBD interactions, the glycan shield has pretty low coverage?
3. The molecular dynamics (MD) simulations are mapped across a microsecond timeline and the change in surface area based on the probe used is pretty intuitive. The method utilized in this paper seems cutting-edge, but the relevance is questionable. A similar probe-based measure has been used in other endeavors and

the specificity has been determined using a larger and a smaller probe. However, the glycan estimation and its role in the shielding effect can be circumvented by just refraining from selecting epitopes from the estimates of the residues shaded by glycans, since that has already been mapped out in papers. Can the authors address this comment?

4. The prediction of epitopes on IL-4 and IL-10 is interesting because it seems as though they indicate allergenicity and non-allergenicity respectively, such that the epitopes must have an opposite value between them. However, no such reference has been included in the data.

Decision

Accept with an explanation of above doubts and the addition of appropriate references.