

Molecular Mimicry between hPF4 and SARS-CoV-2 Spike Protein: Response to Comment

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To help foster scientific debate, we would like to reply to Mungmunpantipantip and Wiwanitkit,¹ addressing their perplexities in relation to our previous report.² Hafeez et al, in their review of the literature on COVID-19 vaccine-associated thrombosis with thrombocytopenia syndrome (TTS), including 25 articles and 69 patients, reported that “patients having received messenger ribonucleic acid (mRNA) COVID-19 vaccines are also present.”³ They never stated that these vaccines “have also been implicated” as Mungmunpantipantip and Wiwanitkit concluded.¹ Moreover, Hafeez et al also reported that one of the limitations of their study was the small sample size. In fact, of the 69 patients with vaccine-induced TTS analyzed within the review, only 4 patients had received an mRNA vaccine (5.7%), while the others had received an adenovirus-based vaccine, and no other details regarding their comorbidities was present and no statistical analysis was performed proving the relationship between mRNA COVID-19 vaccines and TTS.

Mungmunpantipantip and Wiwanitkit¹ also stated in response to our prior report² that “there was no data provided on similarity score. Moreover, a comparative genomics analysis can give a similarity score but it cannot provide the statistical level of similarity or difference.” We raise several objections to this statement; the first one is that SWISS-Model has not shown any similarity between spike glycoprotein and platelet factor 4 (PF4) since they have very different structures, and since no similarity was found the similarity score could be estimated as approximately 0. The second objection is that the sentence is self-contradictory because it states that a similarity score cannot provide a

statistical level of similarity (i.e., a similarity score). The third objection is that we have performed a structural/amino-acidic analysis, not a genomic analysis. In addition, we would like to specify that we have provided all the information necessary to replicate what we have performed. Moreover, Baker et al⁴ demonstrated that all three adenoviruses deployed as vaccination vectors bind to PF4, enforcing the hypothesis that TTS is related to viral vector vaccines rather than to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA.

Finally, Mungmunpantipantip and Wiwanitkit¹ stated that “there are additional means of providing such proof. One good example is using a bioinformatics molecular docking technique to enable prediction of the interaction between two studied molecules.” This was not the original aim of our article² since we wanted to investigate the possibility of structural similarities and cross-recognition between SARS-CoV-2 spike glycoprotein and PF4 protein (i.e., molecular mimicry); however, following the suggestion of Mungmunpantipantip and Wiwanitkit,¹ we have also performed molecular docking analysis using RaptorX Web server and no possible statistically significant interaction has been found (the highest aminoacidic interaction probability reached between spike glycoprotein and PF4 reached 50% of probability).⁵ Moreover, the aminoacidic positions with the highest interaction probability are in an internal region of spike glycoprotein. In conclusion, we believe that the statements made by Mungmunpantipantip and Wiwanitkit¹ are contradictory, and do not provide any new evidence or information. On the contrary, McGonagle et al⁶ reported in their review that many scientific articles have demonstrated

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our initial hypothesis with different methods and provided much useful information to better understand this terrible virus.

Conflict of Interest

None declared.

References

- 1 Mungmunpantipantip R, Wiwanitkit V. Molecular mimicry between hPF4 and SARS-CoV-2 Spike Protein: comment. *Semin Thromb Hemost* 2023;49(01):105–105
- 2 Carnevale S, Giovanetti M, Benvenuto D, Ciccozzi M, Broccolo F. Is Molecular Mimicry between hPF4 and SARS-CoV-2 Spike Protein a Potential Basis for Autoimmune Responses in Vaccinated and Naturally Infected Patients? *Semin Thromb Hemost* 2023;49(01):103–104
- 3 Hafeez MU, Ikram M, Shafiq Z, et al. COVID-19 vaccine-associated thrombosis with thrombocytopenia syndrome (TTS): a systematic review and post hoc analysis. *Clin Appl Thromb Hemost* 2021; 27:10760296211048815
- 4 Baker AT, Boyd RJ, Sarkar D, et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. *Sci Adv* 2021;7(49):eabl8213
- 5 Zeng H, Wang S, Zhou T, et al. ComplexContact: a web server for inter-protein contact prediction using deep learning. *Nucleic Acids Res* 2018;46(Suppl 1):W432–W437
- 6 McGonagle D, De Marco G, Bridgewood C. Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. *J Autoimmun* 2021;121:102662