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Editorial

Computational Designs for Vaccines against SARS-CoV-2 Variants

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All vaccines, such as mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech), and Ad.26.COV2.S (Janssen) are based on the sequence of the original Wuhan-Hu-1 strain of the spike fusion glycoprotein (S) and are engineered to remain in the prefusion state, which is the primary target of neutralizing antibodies (nAbs) [1]. However, the efficacies of these first-generation vaccines are diminished against newly circulating variants of concern (VoCs) such as Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Omicron (BA.1, BA.2, BA.4/5, XBB, and BQ.1.1), which evade nAbs due to mutations in the S protein [2-9]. Although booster vaccines have been developed to match S protein sequences of circulating SARS-CoV-2 variants [10-13], there is no guarantee that these updated vaccines will protect against future strains of the virus [7,8,14-16]. A recent study demonstrated that three sets of antigens utilizing pre-Delta (T2_32) and post-Gamma sequence data (T2_35 and T2_36) were computational designed (Figure 1-3) [1]. T2_32 elicited superior neutralizing responses against variants of concerns (VOCs) compared to the Wuhan-1 spike antigen in DNA prime-boost immunization regime in guinea pigs [1]. Heterologous boosting with the attenuated poxvirus - Modified vaccinia Ankara expressing T2_32 induced broader neutralizing immune responses in all primed animals. T2_32, T2_35 and T2_36 elicited broader neutralizing capacity compared to the Omicron BA.1 spike antigen administered by mRNA immunization in mice [1]. This study demonstrated the utility of structure-informed computationally derived modifications of spike-based antigens for inducing broad immune responses covering more than 2 years of evolved SARS-CoV-2 variants [1].

In 2024, Bruun., *et al*. focused the antibody response towards the cryptic-face epitope recognized by the broadly neutralizing antibody S2X259 by utilization of the immunofocusing technique PMD (protect, modify, deprotect) to create RBD immunogens (PMD-RBD) specifically computational designed [19]. Immunization with PMD-RBD antigens induced robust binding titers and broad neutralizing activity against homologous and heterologous Sarbecovirus strains. A serum-depletion assay demonstrated direct evidence that PMD successfully skewed the polyclonal antibody response towards the cryptic face of the RBD. Their work demonstrated the ability of PMD to overcome immunodominance and refocused on humoral immunity, with implications for the development of broader and more resilient COVID-19 vaccines against current and emerging viruses with pandemic potential [19].

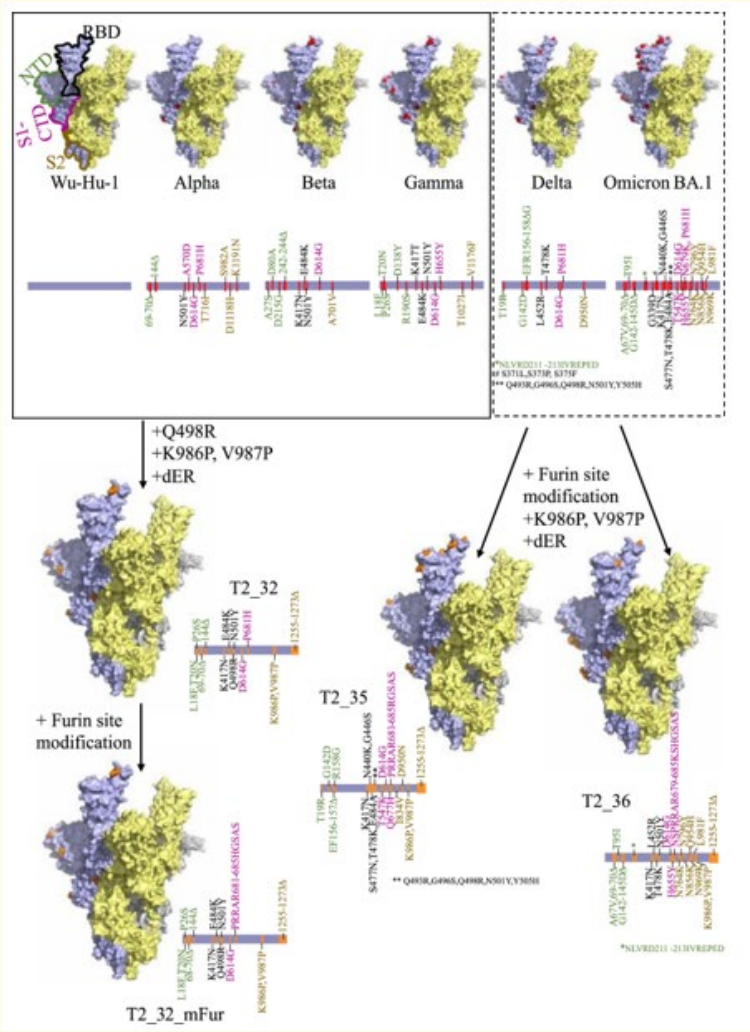

Figure 1: *In-silico design of Spike antigens [17,18]. Demonstrating surface representation of the extra-virion region of the Spike protein of SARS-CoV-2. The three subunits are colored in pale yellow, pale blue, and grey. The structural domains - N-terminal domain (NTD), receptor binding domain (RBD), C-terminal domain of the S1 region (S1-CTD) and the stalk region (S2) are highlighted by green, black, magenta, and yellow-brown outlines respectively. The mutations reported in different variants are colored as red sphere in the surface representation and indicated by red lines in the linear representation. The mutations introduced in the spike vaccine antigens are coloured as orange spheres in the surface representation and indicated by orange lines in the linear representation for T2_32, T2_35, T2_36 and T2_32_mFur. The surface representation was generated and rendered using PyMol [17] using PDB id. 7ZR9 [18].*

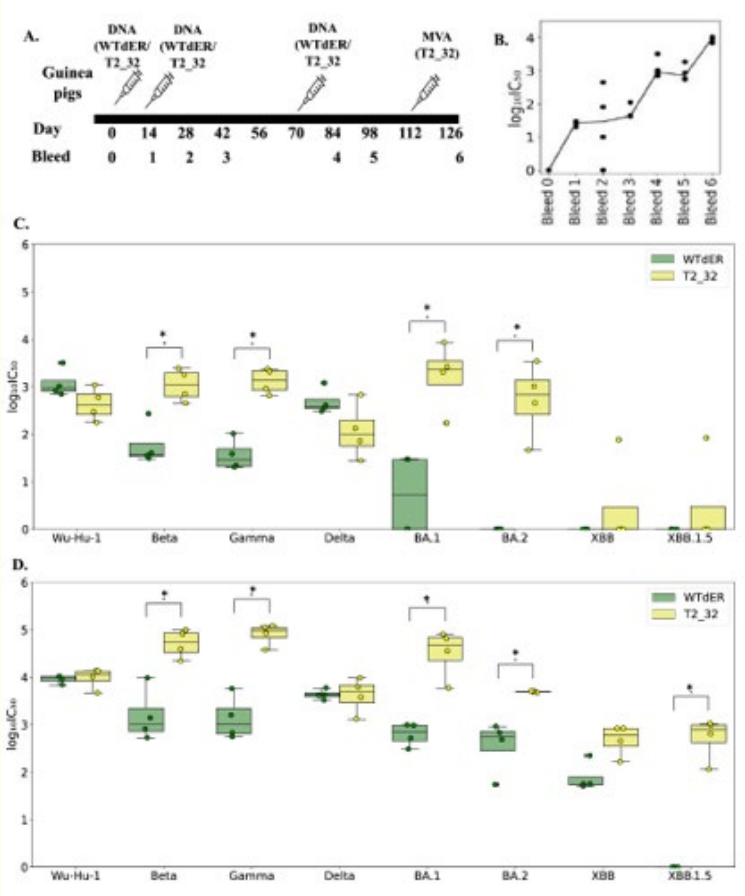

Figure 2: *Immunogenicity of T2_32 in Guinea pigs [1]. A Immunization and bleeding schedule in Guinea pigs. B Distribution of the neutralization titers against Wu-Hu-1 pseudotype on immunization with WTdER. The x-axis represents the bleed number, and the y-axis represents the* $\log_{10}(IC_{50})$ *values. C Distribution of the neutralization titers at bleed 4 against Wu-Hu-1 and the VOCs; Beta, Gamma, Delta, BA.1, BA.2, XBB, XBB.1.5. The x-axis represents the pseudoviruses tested for neutralization, and the y-axis represents the* $\log_{10}(IC50)$ *values. D Distribution of the neutralization titer of bleed 6 against Wu-Hu-1 and VOCs – Beta, Gamma, Delta, BA.1, BA.2, XBB, XBB.1.5. The x-axis represents the pseudoviruses tested for neutralization, and the y-axis represents the* $\log_{10}(IC_{50})$ *values. The boxplots are color coded according to vaccines. The boxes represent the quartiles (*25^{th}, 50^{th} *and* 75^{th} *percentiles) of the distribution, and the whiskers represent the minimum and maximum of the distribution (excluding outliers) and the fliers represented as filled circle represent the outliers. Mann–Whitney U test is used as statistical significance test in all the plots (p value: * ≤0.05, **<0.01, *** ≤ 0.001). The distributions that are not statistically significant are not labelled in the plot. n = 4 for C and D [1].*

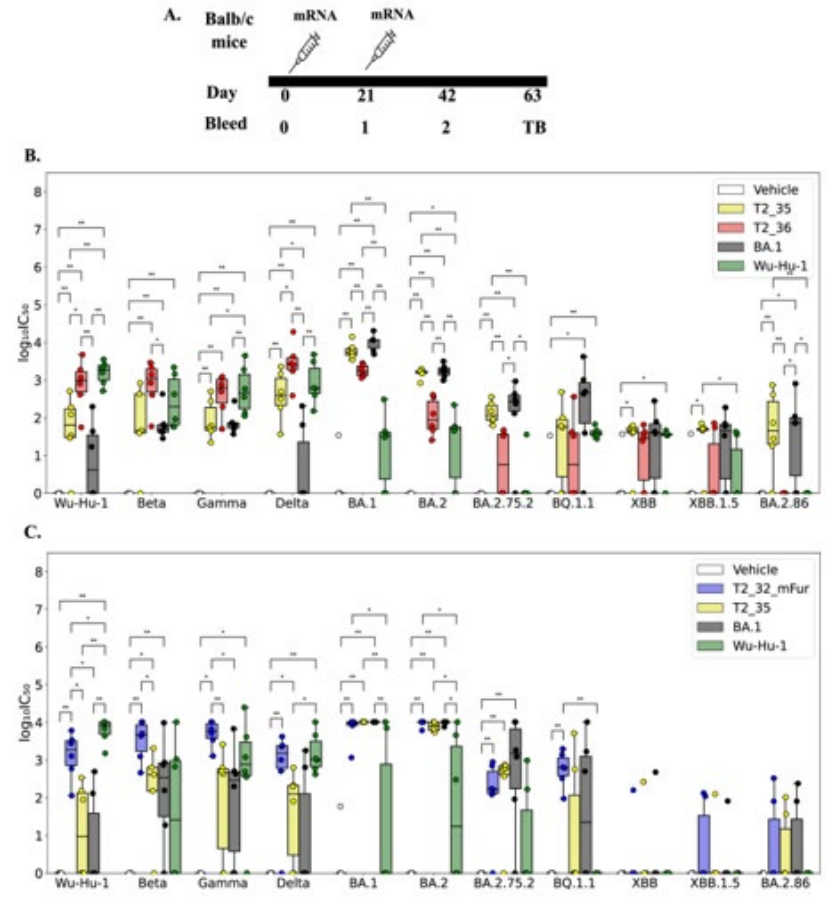

Figure 3: *Comparison of breadth of neutralization of T2_35, T2_36, and T2_32_mFur in mRNA immunized mice [1]. Demonstrating an immunization and bleed schedule in mice. B, C Distribution of the neutralization titers of terminal bleed against Wu-Hu-1 and VOCs. The x-axis represents the pseudoviruses tested for neutralization, and the y-axis represents the* $\log_{10}(IC_{50})$ *values. The boxplots are color coded according to vaccines. The boxes represent the quartiles (at* 25^{th}, 50^{th} *and* 75^{th} *percentiles) of the distribution, and the whiskers represent the minimum and maximum of the distribution (excluding outliers) with outliers are represented as filled circles. Mann-Whitney U test is used as statistical significance test in all the plots (p value: * ≤0.05, **<0.01, *** ≤ 0.001). The distributions that are not statistically significant are not labelled in the plot. n = 6 for B and C [1].*

In conclusion, urgent development of vaccine antigens by computational designs can elicit Abs that provides broader and/or longer-lasting protection are more efficient in neutralizing future variants.

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