A computational approach to design a COVID-19 vaccine against a predicted SARS-CoV-2 variant: high immunogenicity, efficacy and safety of DELLERA vaccine

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2)) is an enveloped positive-sense single-stranded RNA (ssRNA) virus of the Betacoronavirus genus which has spread worldwide and causing 6,259,945 deaths since its first identification in 2019. (1,2) Even if the development of coronavirus disease 2019 (COVID-19) vaccines has proceeded at an extremely rapid pace due to an unprecedent acceleration of the traditional vaccine development, achieving global vaccine coverage remains a major hurdle due to the continue evolution and selection of vaccine escape variants under immune selective pressures. (3,4) Therefore the tireless development of new candidate vaccines remains critical. In the fight against the COVID-19, the use of computational biology tools was found to be crucial for different tasks. (5)

Objective

In this study, we use a computational approach for the design of a novel candidate vaccine for a predicted SARS-CoV-2 variant

Methods

A total of 393,594 Spike (S) protein genomes of SARS-CoV-2 were analyzed with the aim to find a reference sequence of the virus most widely spread in Europe at the time and predicted (MaxEnt niche-based model) to remain as the dominant clade for the next COVID-19 wave. Animals were immunized intramuscularly (IM) three times two weeks apart (0, 14 and 28 days) with two doses of 1µg (pink) and 10µg (fuchsia) Dellera. Age-matched animals administered with empty LNP (black) or buffer (gray) served as control. The results were used to evaluate: immunogenicity (BALB/c mice, (n=10 per group), efficacy (Syrian hamsters, n=6 per group) and toxicity (Sprague Dawley rats, n=5 per group).

Conclusions

In this study we have shown that Dellera vaccine:

- elicits potent binding and neutralizing antibodies in mice;
- confer protection against a high virulent challenge in hamsters;
- is safe, as proven by the lack of pathological clinical signs or toxicity in rats.

Thus, our study suggest that our approach represents a promising choice to design vaccines against new predicted variants of SARS-CoV-2.

References

1. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS Pathog. 2020;16(5):e1008536.
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141-54.
3.Funk CD, Laferrière C, Ardakani A. A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic. Front Pharmacol. 2020;11:937.
4.Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol. 2021;21(10):626-36.
5.Joshi G, Borah P, Thakur S, Sharma P, Mayank, Poduri R. Exploring the COVID-19 vaccine candidates against SARS-CoV-2 and its variants: where do we stand and where do we go? Hum Vaccin Immunother. 2021;17(12):4714-40.

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Results

1. Dellera vaccine design and characterization of expressed antigen

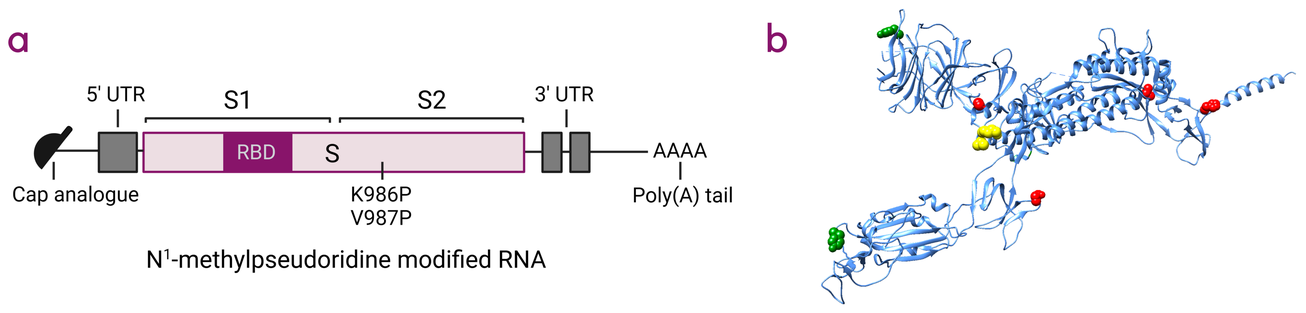

Fig 1. A) *Dellera RNA structure. UTR, untranslated region; S, SARS-CoV-2 S glycoprotein; S1, N-terminal furin cleavage fragment; S2, C-terminal furin cleavage fragment; RBD, receptor-binding domain. Positions of the P2 mutation (K986P and V897P) are indicated.* ***B)*** *S protein PDB structure of the predicted SARS-CoV-2 variant highlighting mutations shared with circulating variants and included in Dellera mRNA sequence. Green, common with omicron: H69-, V70-, Y144-, 501Y, D614G, P681H. Yellow, P2 mutation: K986P, V987P. Red: D119H, S982A, A570D, T716I shared with Alpha variant; P681H, shared by Alpha, Omicron-BA.1, BA.2, BA.4 & 5, Mu variants; N501Y, shared by Alpha, Beta, Gamma, Omicron BA.1, BA.2, BA.4 & 5, Mu variants; D614G, shared by all VoCs.*

2. Dellera immunogenicity in BALB/c mice

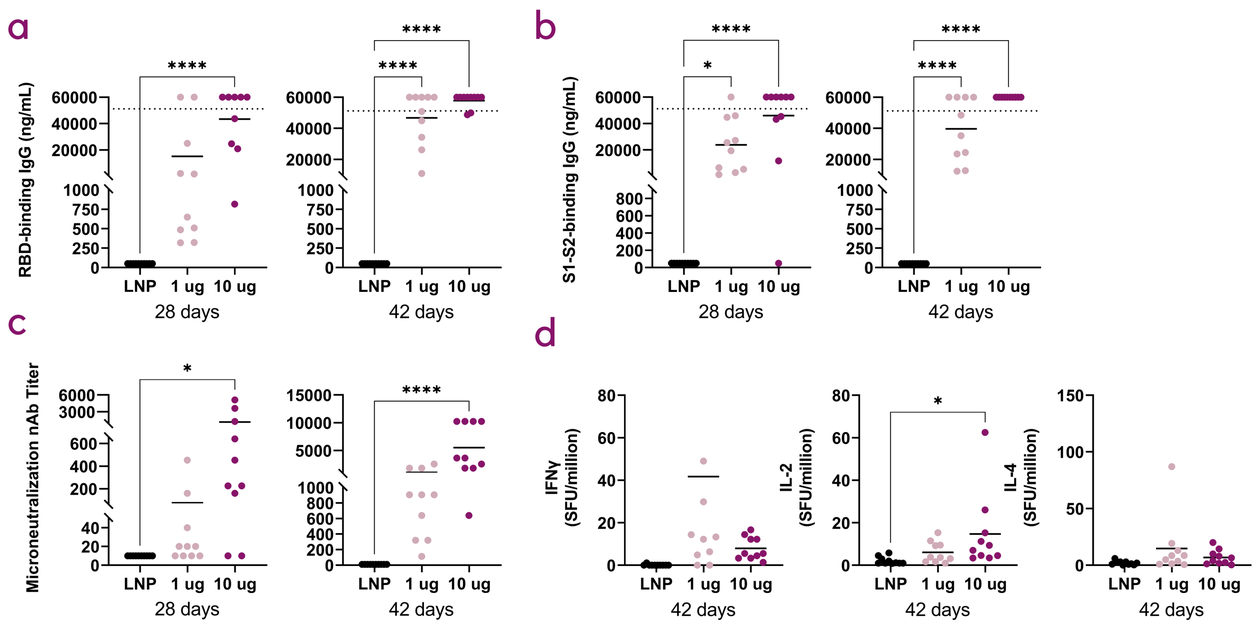

Fig 2. A) *RBD-binding IgG responses against the ancestral Wuhan variant in sera obtained 28 and 42 days after the first immunization, determined by ELISA.* ***B)*** *Full length s1-s2-binding IgG responses against the Alpha variant in sera obtained 28 and 42 days after the first immunization, determined by ELISA.* ***C)*** *Alpha aneutralizing sera titers, determined by MN-CPE based assay.* ***D)*** *Splenocytes of BALB/c mice immunized IM ex vivo re-stimulated with RBD peptide mix. Individual values and mean of each group, p-values were determined by One-Way ANOVA with post-hoc Dunnett's test. Dots above the depicted line are > 51200 (upper the limit of detection).*

3. Dellera efficacy in Syrian Golden hamsters

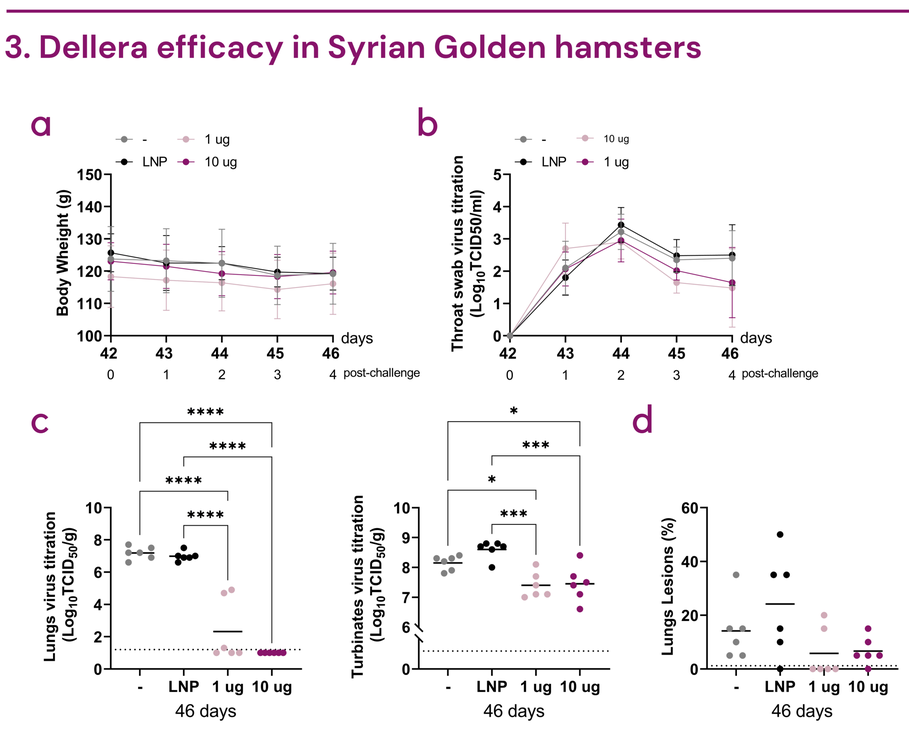

Fig 3. A) *Total body weight monitored once a day after the post-challenge period.*
B) *Viral titration of throat swab performed once a day during the study period.*
C) *Viral titres analysis on hamster lungs and nasal turbinates samples collected 5 days post-challenge. Individual values and mean±SD of each group, p-values were determined by Multiple Student's t-test.*
D) *% of lesions determined by histopathological analysis of lungs at the end of the study period. Individual values and mean of each group, p-values were determined by One-Way ANOVA with post-hoc Tukey's test.*

4. Dellera safety in Sprague Dawly rats

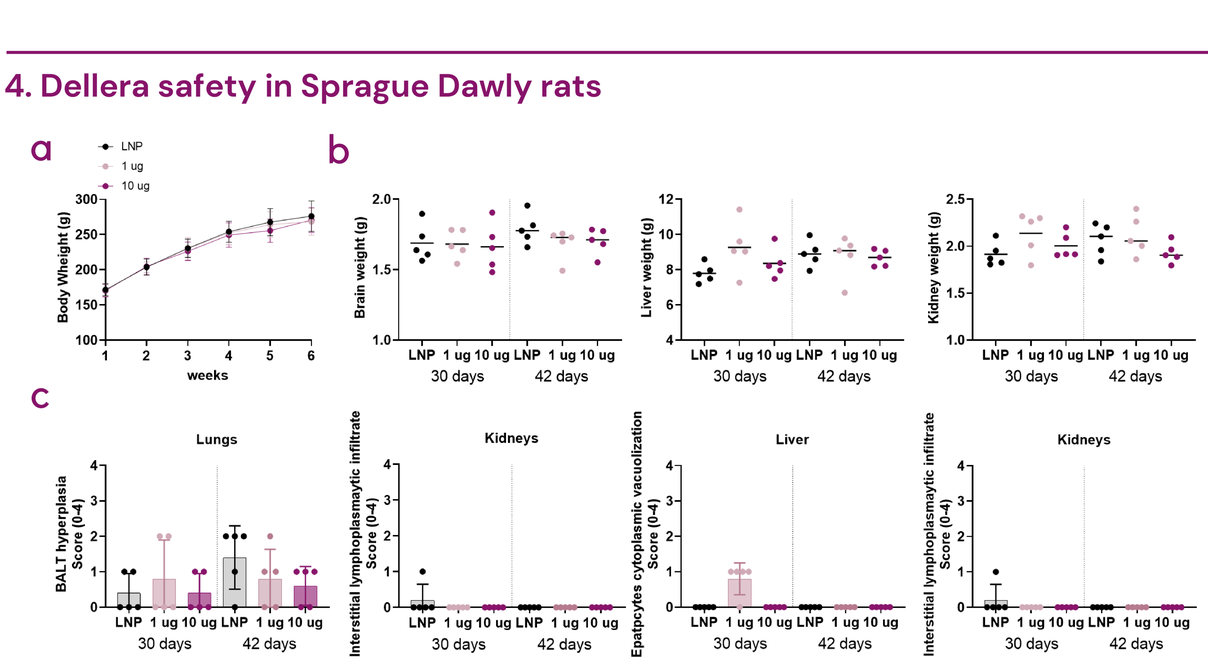

Fig 4. A) *Body weight of female rats (n= 5/group) following administration of 1 µg (orange) or 10 µg (green) of Dellera or empty LNP (black) as control. Individual values and mean±SD of each group, p-values were determined by Multiple Student's t-test.* ***B)*** *Organ weight of female rats (n = 5/group) 30 and 42 days after the first immunization. Individual values and mean of each group, p-values were determined by One-Way ANOVA with post-hoc Dunnett's test.*
C) *Histopathological scoring of microscopic alterations in lungs, liver and kidneys . 0=no lesions; 1=mild lesions; 2=moderate lesions; 3=severe lesions; 4= extremely severe lesions. No lesions were observed in brain, heart and spleen (data not shown).*

Authors declare no conflict of interests