Sequential Immunization of Updated COVID-19 DNA and RNA Vaccines in Nonhuman Primates

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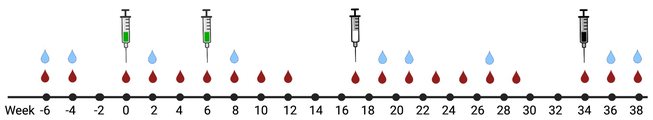
Background

- SARS-CoV-2 vaccines that expand immunity against emerging variants of concern (VOCs) are needed
- Current mRNA vaccines express Spike from the original strain, but waning antibodies and VOCs are diminishing efficacy
- We investigated the effects of sequentially boosting WA-1/A.1-primed NHP with updated DNA or RNA vaccines, comprising a novel immunogen, delivered by Gene Gun (GG) or intramuscularly (IM)

Erasmus et al., Sci Transl Med, 2020; Feikin et al., Lancet, 2022; Link-Gelles et al., MMWR, 2022; Hachmann et al, NEJM, 2022; Barouch, NEJM, 2022

Methods

SARS-CoV-2 RNA vs. DNA Vaccination Study Timeline



SARS-CoV-2 Vaccinations and NHP Sampling

- 20ug full length SARS-CoV-2 WA-1 prefusion Spike vaccination
- 40ug SHARP bivalent (Beta B.1.351, Delta B.1.617) vaccination
- 60ug SHARP trivalent (WA-1, Beta B.1.351, Delta B.1.617) vaccination
- blood
- nasal weck-cel, tracheal weck-cel, saliva, bronchoalveolar lavage (BAL)



Vaccine treatment groups

- n=5 repRNA via gene gun
- n=5 DNA via gene gun
- n=4 repRNA via LION™/IM

- Fourteen cynomolgus macaques were immunized by Gene Gun or intramuscularly with a cationic nanocarrier (LION™) formulation at weeks 0 and 6 with an IL-12 adjuvanted DNA vaccine (DNA, Gene Gun N=5) or with a self-amplifying replicon RNA (repRNA) vaccine (repRNA, Gene Gun N=5, repRNA/LION™, IM N=4) encoding SARS-CoV-2 WA-1/A.1 prefusion Spike
- Macaques were boosted at weeks 17 and 34 with bivalent DNA or repRNA vaccines expressing SHARP, a novel chimeric immunogen comprising B.1.351 and B.1.617 Spike receptor binding domains (RBD) fused to influenza HA2 stem domain (designed by AIR/JP). At week 34 the trivalent SHARP immunization also included WA-1/A.1 SHARP
- Binding antibody responses specific for full length Spikes and RBDs of WA-1/A.1 and VOCs in plasma and BAL supernatant were measured by ELISA; neutralization was measured by pseudovirus neutralization assays
- T cell responses specific for 11 peptide pools comprising full length WA-1/A.1 prefusion Spike were measured by IFNγ/IL-4 double-color ELISpot

Acknowledgements

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Results

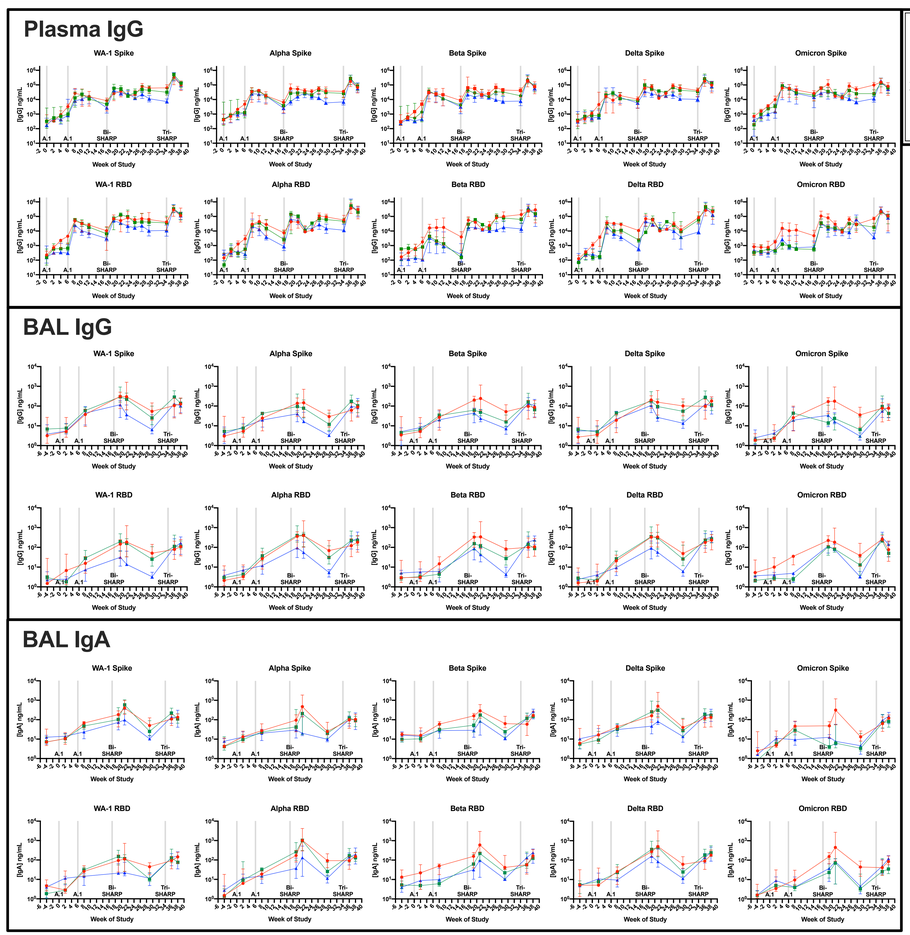


Figure 1. Plasma and BAL Supernatant Binding Antibodies Against SARS-CoV-2 Spike Concentrations . Antibodies to full length Spike and RBD immunogens for WA-1/A.1 and VOCs Alpha, Beta, Delta and Omicron (BA.2) were quantified by ELISA and shown for Plasma IgG, BAL supernatant IgG and IgA. Week 38 antibody concentrations were compared by 2-way Anova with Geisser-Greenhouse correction and Tukey's multiple comparisons test.

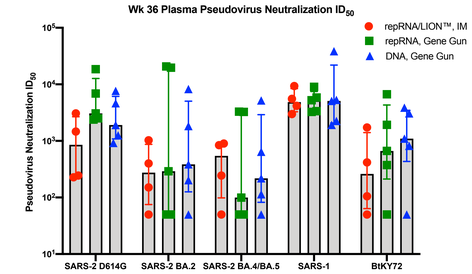
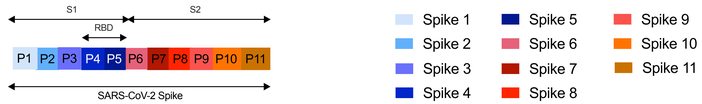


Figure 2. Plasma Neutralizing Antibody Titers Against Multiple SARS strains. Week 36 plasma pseudovirus neutralization ID_{50} values were compared by 2-way Anova with Geisser-Greenhouse correction and Tukey's multiple comparisons test.



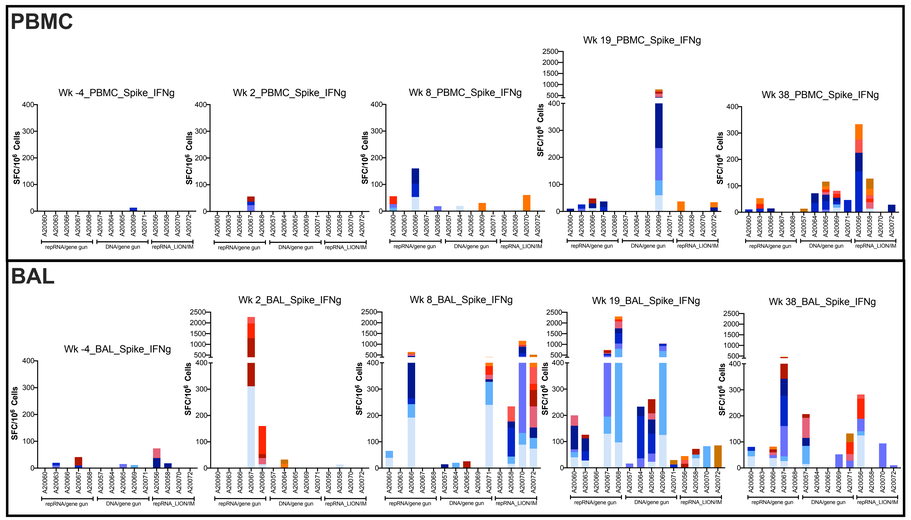


Figure 3. T cell IFNγ PBMC and BAL Responses to WA-1 Spike peptide pools. Baseline (week -4) and post-vaccines 1-4 (weeks 2, 8, 19 & 38, respectively) PBMC and BAL IFNγ T cell responses were assayed using 11 individual SARS-CoV-2 Spike peptide pools spanning the full length prefusion WA-1/A.1 Spike. Group responses were compared by 2-way Anova with Geisser-Greenhouse correction and Tukey's multiple comparisons test at week 38.

Conclusions / Main Findings

- Two doses of the WA-1/A.1 Spike vaccines induced broad antibody responses against all VOCs
- The repRNA/LION™ IM vaccine induced the highest binding antibody titers after WA-1 prime, prior to SHARP vaccination
- Updated VOC SHARP immunogens boosted antibody responses against all VOCs and **by weeks 36-38, all 3 groups had similar binding (Fig 1) and neutralizing (Fig 2) antibody titers against all VOCs tested**
- Updated VOC SHARP immunogens boosted T cell responses against multiple Spike peptide pools with no significant group differences by week 38 (**Fig 3**) and **interestingly, BAL T cell responses were significantly higher than PBMC at multiple post-vaccine timepoints (Fig 4)**
- These results demonstrate that **updated RBD-based vaccines can boost for broadly specific antibodies against VOCs including Omicron** (which was not included in the boosting vaccine) and show that **Gene Gun delivered DNA and RNA vaccines induce comparable responses to IM-delivered RNA vaccines**

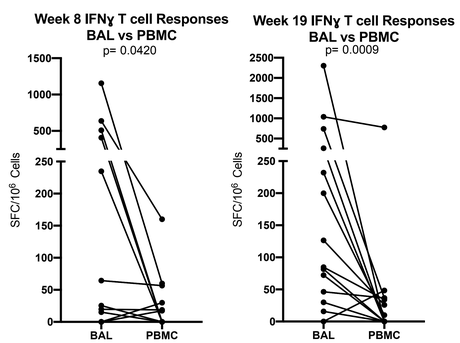


Figure 4. T cell IFNγ PBMC vs. BAL Spike Responses. Total magnitude of PBMC and BAL IFNγ T cell responses for weeks 8 (2 weeks post-2nd vaccine, WA-1 full length spike) and week 19 (2 weeks post-3rd vaccine, Bivalent SHARP) were assayed as above then added to determine total response magnitude. BAL cell vs PBMC responses were compared by Wilcoxon matched-pairs signed rank test.