**Figure S1 Experimental timeline, related to Figure 1**

8 NHP were vaccinated with 100µg of mRNA-1273 at weeks 0 and 4. At week 41, NHP were split into 2 groups of 4 and boosted with 50µg of mRNA-1273 or mRNA-Omicron. Both groups, and 8 unvaccinated NHP which were given 50µg of mRNA control, were challenged with Omicron 1 month later.
Figure S2 B cell gating strategy, related to Figure 3

Representative flow cytometry plots showing gating strategy for B cells in Figures 3 and 4 and Figure S3. Cells were gated as singlets and live cells on forward and side scatter and a live/dead aqua blue stain. CD3-, CD4- cells were then gated on absence of CD14 and CD16 expression and positive expression of CD20 and CD19. Memory B cells were selected based on lack of IgD or IgM. Finally, pairs of variant S-2P probes were used to determine binding specificity. Probe-binding cells were further characterized as having a phenotype consistent with CD27-negative resting memory (CD27- RM), tissue-like memory (TLM), activated memory (AM) or resting memory (RM) cells according to expression of CD27 and CD21.
Figure S3

A  
WA1+, Omicron-  
% Memory B Cells  
Normalized to Wk 6

Week 41 43

0.01 0.1 1 3

WA1+, Omicron+

B  
Delta+, Omicron-  
% Memory B Cells  
Normalized to Wk 6

Week 41 43

0.01 0.1 1 3

Delta+, Omicron+

C  
WA1+, Delta-  
% Memory B Cells  
Normalized to Wk 6

Week 41 43

0.01 0.1 1 3

WA1+, Delta+

D  
WA1+, Beta-  
% Memory B Cells  
Normalized to Wk 6

Week 41 43

0.01 0.1 1 3

WA1+, Beta+

○ mRNA-1273 (x2)  ● mRNA-1273 boost  ● mRNA-Omicron boost
Figure S3 Expansion of memory B cells that recognize unique WA1 epitopes only occurs after homologous mRNA-1273 boosting, related to Figure 4

(A-D) Frequencies of memory B cells with indicated specificities as a percentage of total class-switched memory B cells (both S-2P-binding and non-S-2P-binding) were normalized to the corresponding frequencies from each individual NHP at week 6 post-immunization. Cross-reactivity shown for (A) WA1 and Omicron S-2P, (B) Delta and Omicron S-2P, (C) WA1 and Delta S-2P and (D) WA1 and Beta S-2P. Specificities not shown if memory B cell populations were indistinguishable from background staining. Circles indicate individual NHP. Boxes represent interquartile range with the median denoted by a horizontal line. A frequency of 1 indicates parity. 4-7 NHP per group.
Figure S4 Serum epitope reactivity following boost, related to Figure 4

(A-B) Relative serum reactivity was measured as fractional competition of total measured serum antibody S-2P binding competed by single monoclonal antibody (mAb) targeting epitopes on WA1 (A) or Omicron (B) S-2P at week 43 post-immunization. Antigenic sites are defined by mAbs B1-182 (RBD-A), A19-46.1 (RBD-D), A19-61.1 (RBD-F), S309 (RBD-G), A23-97.1 (RBD-H) and A23-80.1 (RBD-J). Circles indicate individual NHP. Boxes represent interquartile range with the median denoted by a horizontal line. Dotted lines are for visualization purposes and denote 0% competition. 4 NHP per boost group.
Figure S5 T cell gating strategy, related to Figure 4

Representative flow cytometry plots showing gating strategy for T cells in Figure S6. Cells were gated as singlets and live cells on forward and side scatter and a live/dead aqua blue stain. CD3+ events were gated as CD4+ or CD8+ T cells. Total memory CD8+ T cells were selected based on expression of CCR7 and CD45RA. Finally, SARS-CoV-2 S-specific memory CD8+ T cells were gated according to co-expression of CD69 and IL-2, TNF or IFNγ. The CD4+ events were defined as naïve, total memory or central memory according to expression of CCR7 and CD45RA. CD4+ cells with a T_{H1} phenotype were defined as memory cells that co-expressed CD69 and IL-2, TNF or IFNγ. CD4+ cells with a T_{H2} phenotype were defined as memory cells that co-expressed CD69 and IL-4 or IL-13. T_{FH} cells were defined as central memory CD4+ T cells that expressed CXCR5, ICOS and PD-1. T_{FH} cells were further characterized as IL-21+, CD69+ or CD40L+, CD69+. 
Figure S6 Both mRNA-1273 and mRNA-Omicron boost T cell responses to S peptides, related to Figure 4

(A-E) PBMC collected at weeks 0, 6, 41 and 43 post-immunization. Cells were stimulated with SARS-CoV-2 S1 and S2 peptide pools and then measured by intracellular staining. (A-B) Percentage of memory CD4$^+$ T cells with (A) T$_{H1}$ markers (IL-2, TNF or IFN$\gamma$) or (B) T$_{H2}$ markers (IL-4 or IL-13) following stimulation. (C) Percentage of CD8$^+$ T cells expressing IL-2, TNF or IFN$\gamma$. (D-E) Percentage of T$_{FH}$ cells that express (D) CD40L or (E) IL-21.

(F-H) BAL fluid was collected at weeks 8, 39 and 43 post-immunization. Lymphocytes in the BAL were stimulated with S1 and S2 peptide pools and responses measured by intracellular cytokine staining using T$_{H1}$ (F), T$_{H2}$ (G), and CD8 markers (H). Break in Y-axis indicates a change in scale without a break in the range depicted.

Circles in (A-H) indicate individual NHP. Boxes represent interquartile range with the median denoted by a horizontal line. Dotted lines set at 0%. Reported percentages may be negative due to background subtraction. 8 vaccinated NHP, split into 2 cohorts post-boost.
Figure S7 Omicron challenge stock sequence, related to Figure 5

(A-B) Omicron stock was sequenced and aligned with Wuhan-Hu-1.

(A) S gene only. Mutations listed above graphic. NTD = N-terminal domain. RBD = receptor binding domain. RBM = receptor binding motif. FP = fusion peptide. HR1 = heptad repeat 1. HR2 = heptad repeat 2. FCS = furin cleavage site. S2’ = S2’ site.

(B) Whole genome.
Table S1 Reciprocal ID50 geometric mean values and fold changes relative to D614G for live virus and pseudovirus neutralization values, related to Figure 1

NHP were immunized according to Figure S1. The values for reciprocal ID50 and fold change relative to D614G at weeks 6 and 41 are averages of 8 animals, while the values at week 43 are the averages of 4 animals. Conditional formatting applied to each individual assay.
<table>
<thead>
<tr>
<th>Variant</th>
<th>Mutations outside RBD</th>
<th>Mutations in RBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>WA1</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Table S2 List of mutations in variant-specific S-2P-ACE2 inhibition assays and B cell probes, related to Figure 2**

All variant positions in reference to Wuhan-Hu-1 sequence (Genbank: NC_045512). All S-2P constructs contained furin substitution (GSAS at positions 682-685) and 2P stabilization (K986P and V987P).