Bivalent mRNA COVID Vaccines Elicit Predominantly Cross-reactive CD4+ T cell Clonotypes

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Background

- Omicron BA.5 variant emerged in February 2022, quickly becoming globally predominant.
- Bivalent vaccines containing mRNA for both ancestral and BA.5 spike protein were developed to enhance immunity.
- The T cell response to BA.5 was similar in monovalent and bivalent vaccines.

Objectives

- Investigate T cell responses to bivalent vaccines in healthy donors (HDs) and people living with HIV (PLWH).
- Explain why bivalent vaccines did not induce stronger BA.5-specific T cell responses than monovalent vaccines.
- Explore the impact of BA.5 mutations on T cell epitopes.

The T cell responses to the ancestral/BA.5 spike were similar in HDs and PLWH

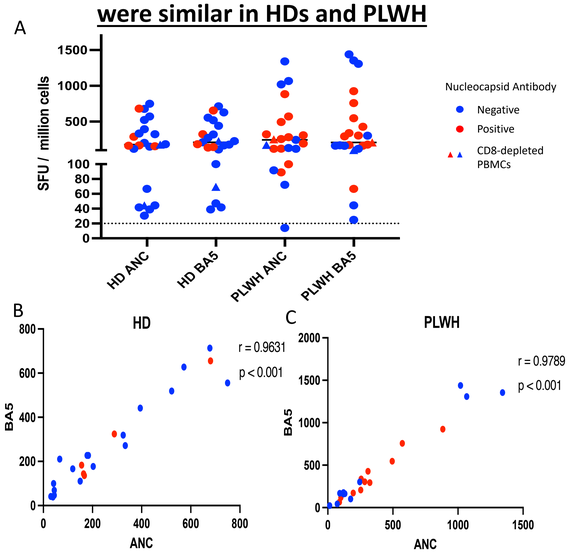


Figure 1: T cell IFN-γ responses to Ancestral and BA.5 spike proteins in participants who received the bivalent vaccine. IFN-γ ELISpot assay results are shown for PBMCs and CD8+ T cell-depleted PBMCs in response to Coronavirus peptides (A). Each data point represents the mean of 3 replicates (n = 21 for HDs and n = 22 for PLWH). Participants positive for nucleocapsid protein antibodies are in red, negatives in blue. CD8+ T cell-depleted PBMCs samples are marked with triangles. The dotted line indicates the threshold for positive responses (SFU ≥ 20). *** p < 0.001. Correlation between BA.5 and ancestral spike protein responses for HDs (B) and PLWH (C) shown (Pearson's correlation test, r = 0.9631 and 0.9789, respectively).

Summary

- Healthy donors and PLWH who received the ancestral/BA.5 spike bivalent vaccine had similar T cell responses to the 2 spike proteins.
- The majority of spike-specific T cells target epitopes that are not affected by BA.5 mutations.
- T cells with receptors that cross-recognize ancestral and BA.5 spike peptides dominate the spike-specific T cell response.

Results

T cells with receptors that cross-recognize ancestral and BA.5 spike peptides dominate the spike-specific T cell response

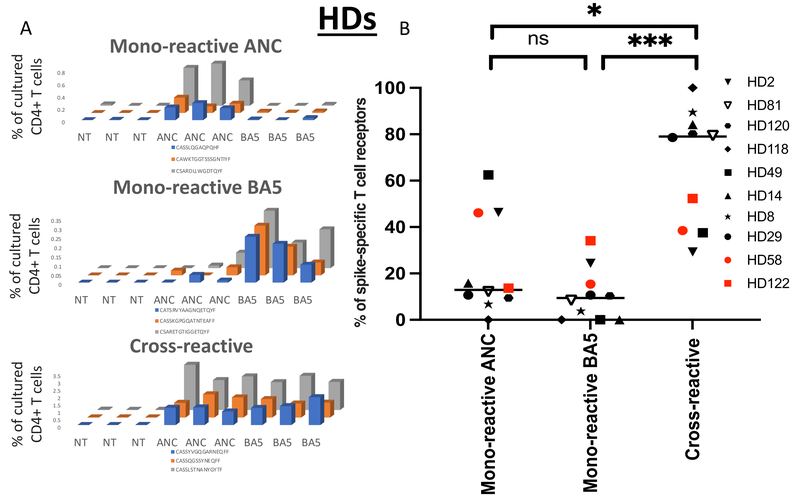


Figure 3 and 4. Detection of T cell clonotypes that cross-recognized both ancestral and Omicron BA.5 spike proteins and those that were mono-reactive for either ancestral or BA.5 spike proteins in HDs and PLWH. After culture, TCR Vβ CDR3 sequencing was performed to identify antigen-specific memory T cells that expanded in response to spike peptide pools (FEST assay). Cross-reactivity was defined by the functional expansion of the same CD4+ TCR clonotypes in response to pooled ancestral (ANC) and Omicron BA.5 (BA.5) peptides. Mono-reactivity was defined as expansion to just one of the 2 spike peptide pools. Each peptide culture was performed in triplicate. A representative mono-reactive and a representative cross-reactive TCR beta clonotypes is shown for 1 HD and 1 PLWH (A). Data are shown as the (%) frequency after culture (y axis) of antigen-specific CD4+ T cell clonotypes (z axis) for the peptide pools tested (x axis). (B). The percentage of spike-specific TCRs that were cross-reactive versus mono-reactive for all 10 HDs and 10 PLWH are shown. Study participants who tested positive for antibodies to the nucleocapsid protein are represented in red whereas those that tested negative for these antibodies are represented in black. ns (not significant), * p < 0.05 ,*** p < 0.001, **** p <0.0001.

The majority of spike-specific T cells target epitopes that are not affected by BA.5 mutations.

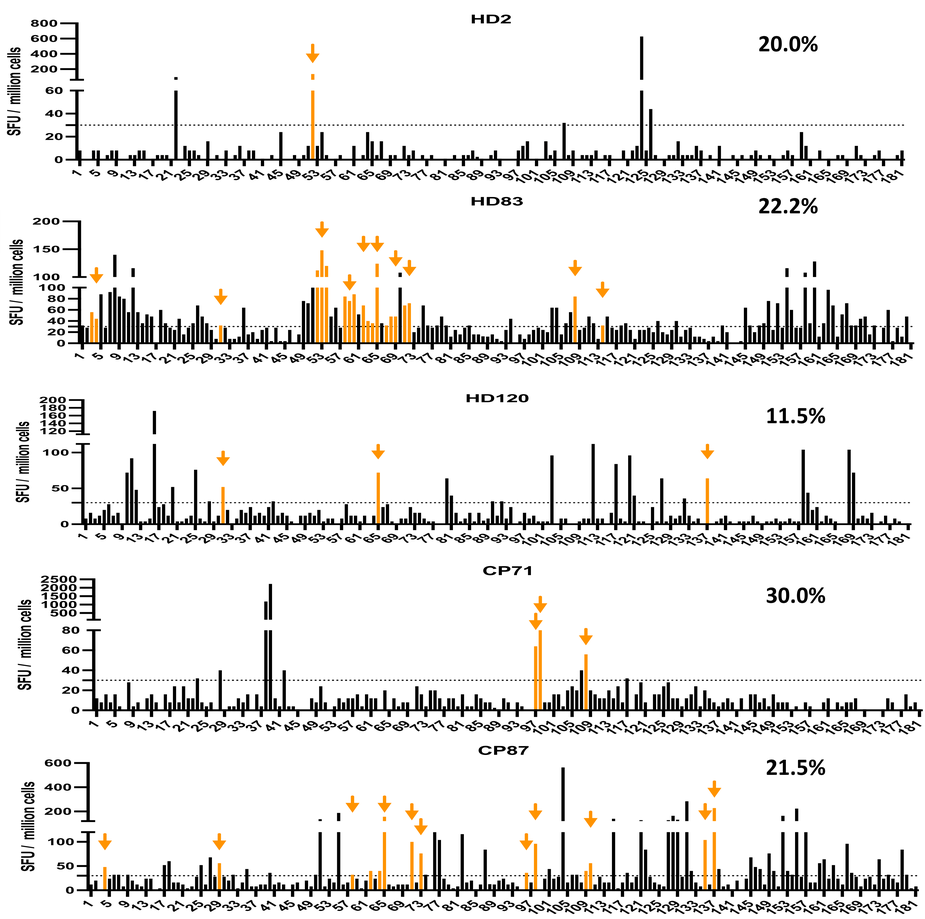


Figure 5: T cell responses to individual overlapping ancestral spike peptides. The IFN-γ ELISpot assay was performed on samples obtained from participants who have received the bivalent vaccine. The SFU of PBMCs in response to each of the 181 overlapping peptides is shown. Each data point represents the mean of 2 replicate values (n = 3 for HDs and n= 2 for PLWH). The dotted horizontal line represents the threshold for positive responses (SFU greater than or equal to 30). The orange vertical bars represent targeted peptides that would contain a BA.5 mutation. The percentages on the right represent the percent of targeted peptides that would contain a BA.5 mutation.

Acknowledgments

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