HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2501844
https://doi.org/10.1080/21645515.2025.2501844

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BRIEF REPORT

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T-cell responses to highly conserved SARS-CoV-2 epitopes in Hispanic Americans receiving an mRNA COVID-19 vaccine

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ABSTRACT

This study reports the pre-clinical evaluation of peptides from EPV-CoV-19, a T cell epitope-based SARS-CoV-2 vaccine candidate, following spike-mRNA vaccination of a predominantly Hispanic American cohort. EPV-COV-19 peptides' potential to boost T cell responses to spike protein vaccines was evaluated, confirming previously observed memory recall responses in donors with prior immunity to COVID-19. The vaccinated subjects' averaged immune responses to the 15-peptide EPV-CoV-19 pool achieved 85% of the observed response to a spike protein peptide array containing a 7-fold greater epitope content, suggesting that the EPV-CoV-19 peptides have a higher relative concentration of T cell epitope content per-peptide. Ten of the 15 peptides contained spike epitopes conserved in the majority of variants of concern (VOC) evaluated over the 2020–2024 period. While commercial vaccines exhibited gradual loss of T cell epitope conservation with VOC over time, the EPV-CoV-19 epitope-peptides maintained conservation until the XBB variant emerged. The addition of one new peptide to the vaccine design reestablished broad T cell epitope coverage. These findings underscore the importance of identifying highly conserved T cell epitopes for vaccine designs that target rapidly-mutating strains of emergent pathogens, while also documenting broad memory T cell response to the vaccine in a predominantly Hispanic American cohort.

ARTICLE HISTORY
Received 16 December 2024
Revised 2 April 2025
Accepted 1 May 2025

KEYWORDS
T-cell epitope; peptide; vaccine; SARS-CoV-2; CoVID-19; EpiMatrix; conservatrix; EPV-CoV-19; Hispanic American; Latino

Introduction

Here we report the results of a pre-clinical study of the peptides comprising EPV-CoV-19, a T cell epitope-based SARS-CoV-2 booster vaccine. The EPV-CoV-19 peptides were tested for immune responses in peripheral blood samples obtained from a volunteer cohort primarily composed of Hispanic Americans who participated in COVID vaccine booster immunizations organized by Clinica Esperanza/Hope Clinic in Providence, Rhode Island. In previous studies, the immunogenicity of the proposed EPV-CoV-19 vaccine epitopes were validated using peripheral blood mononuclear cells (PBMCs) from predominantly white, non-Hispanic COVID-convalescent donors and un-exposed healthy blood donors, as well as in animal models.[1] The status of potential vaccine trial participants has shifted, as most individuals are exposed or vaccinated. Thus, the goal of this study was to characterize the immunogenicity of EPV-CoV-19 peptides selected for an epitope-based COVID booster vaccine in in vitro assays conducted with samples from previously vaccinated or exposed donors of Hispanic American origin. This selection of a study subject cohort was deliberate, as the current plan for a Phase I trial of the EPV-Cov-19 vaccine is to address the inequitable recruitment of Hispanic Americans to vaccine trials by conducting the trial in the same region of Providence, where many recent Hispanic American immigrants are living.

EpiVax has developed a T cell epitope-based vaccine, EPV-Cov-19, that was designed to reduce morbidity and mortality from COVID-19 by activating T cell responses. T cells are key to reducing the SARS-CoV-2 viral burden in the human body. These T cell responses may control the virus and reduce the severity of COVID-19 disease. T cell epitope vaccines have also been considered as a potential therapy for PASC.[2–4] Currently, a plan is being developed to deliver EPV-CoV-19 using patch delivery method, which has been tested and found to be safe and effective for inducing strong and specific T cell responses in pre-clinical studies. All 15 'cluster' peptides that were evaluated in this study would be included in the proposed patch-based, T cell epitope-driven vaccine to boost immunity to SARS-CoV-2 in previously exposed or immunized individuals, or for individuals who have PASC.

The inequity of COVID affecting Hispanic Americans and other minorities in the United States can be attributed to many factors, such as access to care, socioeconomic status, baseline health, environment, and occupation.[5–7] To support health equity, it is vital to raise awareness and conduct original research that includes studies of diverse populations. The

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21645515.2025.2501844.

underrepresentation of certain groups in clinical trials has long been recognized by the FDA.[8] In a 2021 study of 230 US-based clinical trials, researchers found that Hispanics and other racial and ethnic minority groups were underrepresented.[9] The characteristics and incidence of COVID of the predominantly Hispanic population recruited for this study have been described in previous reports.[10] Findings reported here expand support for the use of conserved T cell epitopes for boosting T cell responses in previously vaccinated or exposed subjects.

Methods

Study subjects and blood samples

Participants were recruited from Clínica Esperanza/Hope Clinic (CEHC), a 501(c) organization providing free healthcare to uninsured patients. Most of the patients participating in this study reported that they were of Hispanic ethnicity, consistent with the population of patients participating in care at CEHC (80–85% Hispanic). See previous publications about the clinic for additional information.[10]

A summary of the cohort information is shown in Table 1. The median age of the cohort was 48, and 85.2% (23/27) identified as Hispanic. Additional details, including the date of booster vaccination and participant HLA type, are found in Supplementary Table S1.

Enrolled participants ranged 19 to 79 years of age and were returning for the third or fourth booster immunization of the Pfizer/BioNTech SARs-COV-2 vaccine. Blood samples were collected before boost (Day 0) and seven to ten days post-booster (Day 7–10). Donor PBMCs were isolated using methods previously published (Figure 1a).[1]

Written informed consent was obtained from each subject by a bilingual staff member. The study protocol was approved by the AAHRPP-accredited Ethical & Independent (E&I) (now called Salus) external institutional review board (IRB 21,066–01).

Table 1. Study cohort characteristics ($n = 27$).

Age	
Average	47
Median	48
Range	19–79
Gender	
Male	51.85% (14/27)
Female	48.15% (13/27)
Ethnicity	
Non-Hispanic	14.8% (4/27)
Hispanic/Latino	85.2% (23/27)

Immunogenicity assessment

EPV-CoV-19 peptides were synthesized by 21st Century Biochemicals (Marlboro, MA) at greater than 90% purity determined by RP-HPLC (reversed-phase high-performance liquid chromatography). The EPV-CoV-19 vaccine is comprised of 15 peptides, down selected from an initial set of 32 peptides to improve the solubility once pooled,[1] with ten derived from spike and five derived from membrane protein. The methods for epitope identification and conservation analysis are published in Meyers et al.[1]

This study compares the resulting T cell responses to the Pfizer BioNTech vaccine spike protein versus the responses to the 15 peptides in EPV-CoV-19. Cells from each donor were plated in IFNγ/IL-4 dual color FluoroSpot plates and restimulated with pooled EPV-CoV-19 peptides (10 peptides containing 112 spike HLA-DR epitopes and 5 peptides containing 58 membrane epitopes) or a spike peptide array (USA-WA1/2020 strain) for 48 hours (Mabtech FluoroSpot Plus Catalog# FSP-0116-10). In contrast to the EPV-CoV-19 vaccine peptides, the spike peptide pool contains an array of 253 overlapping 15-mer peptides which collectively cover the entire spike protein sequence (Figure 1b). Spot forming cell (SFC) counts were normalized to 1×10^6 cells and adjusted following subtraction of background counts.

Interferon-γ/Interleukin-4 (IFNγ/IL-4) assays were performed with ex vivo PBMCs using Mabtech FluoroSpot Plus kits (Catalog# FSP-0116-10) and executed according to product specifications. The Spike array peptide pool (21st Century Biochemicals Marlboro, MA) was assessed at 2 µg/mL. EPV-CoV-19 peptides were assessed individually at 20 µg/mL or pooled at 10 µg/mL per peptide (15 peptides) in triplicate wells containing 250,000 PBMCs in RPMI medium supplemented with 10% human AB serum. Triplicate wells were

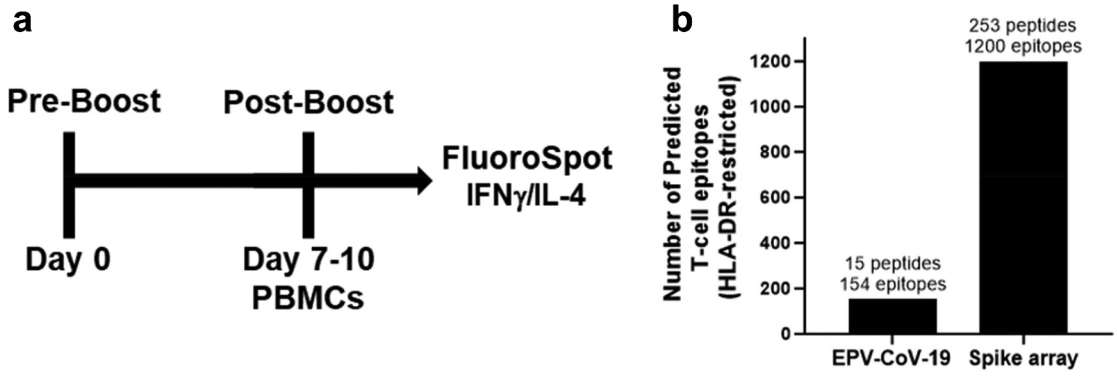

Figure 1. Schematic of the study. Peripheral blood mononuclear cells (PBMCs) were collected before receiving the Pfizer-BioNtech COVID-19 booster on day 0 (pre-boost) and 7–10 days post-vaccination (post-boost). IFNγ and IL-4 producing PBMCs were measured using FluoroSpot (a). Number of putative class II epitope hits for EPV-CoV-19 and spike array peptide pools (b).

plated with Concanavalin A (ConA; 5 µg/mL) as a positive control and six wells containing no antigen stimulus (0.2–0.4% dimethyl sulfoxide (DMSO)) were used for background determination. Cells were incubated for 40–48 h at 37°C under a 5% CO_2 atmosphere.

Results were calculated as the average number of spots in the triplicate wells, adjusted to spots per one million cells. FluoroSpot responses were considered positive (i) if the number of spot-forming cells was at least two times background, and (ii) if there were greater than 25 spot-forming cells per well above background (one response per 40,000 PBMCs). To compare IFNγ and IL-4 production between groups we used the Wilcoxon matched-pairs signed rank test. We determined the correlation between EPV-CoV-19 and spike array IFNγ stimulation index using the Spearman correlation. All statistical analyses were performed using GraphPad Prism software (version 10.0.3). A p value < .05 was considered statistically significant.

T cell epitope content comparison (EpiCC) analysis

We evaluated the conservation of the T cell epitopes in EPV-CoV-19 across VOC as compared to commercial vaccines produced during the pandemic, using the T cell epitope content comparison (EpiCC) algorithm.[11] This algorithm is in commercial use for examining vaccine efficacy against swine pathogens such as swine influenza A and porcine circovirus and has also been applied to influenza strains affecting humans.[12,13] Here, we used EpiCC to highlight the impact of T cell epitope conservation on predicted vaccine efficacy against circulating and emerging strains of SARS-CoV-2 VOCs.

Spike protein sequences were obtained from alpha and beta strain genomes downloaded from GISAID on March 13, 2021; gamma, delta, and lambda variant sequences were downloaded on August 19, 2021. BA2, BA4, BA.5, and XBB.1 spike sequences were downloaded from GenBank on March 1, 2023; JN.1 was downloaded on June 18, 2024; KP.3.1.1 and XEC on September 26, 2024. A frequency analysis was performed to generate a non-redundant set of the most frequently isolated spike sequences from each lineage and sublineage. The first collected isolate (the Wuhan strain) was selected as the representative strain.

Spike protein sequences of four approved vaccines and the set of most frequently isolated variants were screened for HLA-DRB1 T cell epitope content with EpiMatrix as previously described.[1] Using the Epitope Content Comparison (EpiCC) algorithm,[11] T cell epitopes cross-conserved between vaccines and variants were identified and quantified. Cross-conservation was defined using JanusMatrix.[14] Epitopes were considered cross-conserved if both epitopes were predicted to bind the same HLA-DR and both epitopes shared exactly matched TCR-facing residues. Dividing the number of cross-conserved T cell epitopes by the total number of predicted T cell epitopes in the spike sequence of the VOC gives percent cross-conservation. A similar EpiCC analysis was performed for 10 EPV-CoV-19 spike T cell epitope clusters and the corresponding peptide sequences in the set of most frequently isolated variants. For each variant, the number of putative T cell epitopes in the peptides that corresponded to the 10 EPV-CoV-19 spike T cell epitope clusters was used as the denominator to calculate percent cross-conservation.

To illustrate the impact of updating the EPV-CoV-19 T cell epitope clusters that had low cross-conservation with recent VOC, the EPV-CoV-19 T cell epitope cluster with the lowest cross-conservation with JN.1 was identified. This peptide was removed from the list, and the list was then updated by including either (1) the corresponding JN.1 peptide or (2) a previously validated highly cross-conserved and immunogenic T cell epitope cluster from Wuhan (peptide 11 as described in a previous publication.[1] Both peptides have been shown to be immunogenic in prior assays conducted and published by our group.

Results

Recognition of EPV-COV-19 epitopes after Pfizer-BioNTech mRNA booster vaccination

The EPV-CoV-19 vaccine is composed of a total of 15 peptides that contain (collectively) more than 250 individual T cell epitopes (83 class I and 170 class II), which may be administered in a patch format, or alternatively in sterile saline, admixed in Poly-ICLC immediately prior to intradermal delivery. Each individual peptide contains multiple CD4 (T helper) and CD8 (cytotoxic T lymphocyte) epitopes that are unique to SARS-CoV-2 and conserved across many of the 'variants of concern' (VOC) strains and have been carefully screened to remove any 'human-like' or tolerogenic epitopes. Included in the 15 peptides are 10 peptides that contain T cell epitopes derived from the spike protein of SARS-CoV-2 and 5 peptides containing membrane-derived epitopes. The peptides are designed to be broadly immunogenic for all human populations.

To investigate whether the predicted T cell epitopes contained in the EPV-CoV-19 vaccine are recognized in adults who were boosted with the Pfizer-BioNTech COVID-19 vaccine, we analyzed 54 PBMC samples, obtained pre- and post-vaccination from 27 individuals, using FluoroSpot assays. At the time of the study, the only vaccine offered at the study site was the Pfizer-BioNTech vaccine (related to vaccine availability from the local Department of Health). All study participants had a previous history of SARS-CoV-2 infection or COVID vaccination.

PBMCs from many of the SARS-CoV-2 exposed or vaccinated donors responded to stimulation with EPV-CoV-19 and the spike array peptide pools pre- and post-booster immunization (Figure 2a,b). Dotted horizontal lines in Figure 2b denote the established positivity criteria for the Fluorospot assay of IFNγ SFC ≥ 25. As expected, the IFNγ SFC response to the spike peptide array was greater than the response to the 15 EPV-CoV-19 peptides, owing to the array's greater epitope content. This is indicated by the higher stimulation index, calculated using the fold change in IFNγ SFC/million PBMCs over background after stimulation (Figure 2c). We then compared the ranked order of the fold change (post-boost divided by pre-boost) in IFNγ responses to the spike peptide array versus EPV-CoV-19 peptides and found a positive correlation (Figure 2d).

As compared to the pre-vaccination samples, there was an increase in the percentage of positive responses to the EPV-CoV-19 and spike pools post vaccination, by 77% and 92%, respectively (Figure 3a). Even though the spike "array" pool contained more peptides (253 vs. 15 peptides, a roughly 17 fold difference) than the EPV-CoV-19 pool, the difference between the increase in antigen recognition of the spike pool post vaccination, as compared to the EPV-CoV-19 pool, as measured by IFNγ Fluorospot, was merely 15%. Eight out of ten (80%) EPV-CoV-19 spike-derived peptides showed a higher level of recognition post-boost (Figure 3b). Separate from spike, there was no increase in recognition post vaccination for EPV-CoV-19 membrane (M protein) -derived peptides, consistent with the absence of M in current COVID-19 vaccine formulations.

Analysis of the IFNγ and IL-4 SFCs for each donor after re-stimulation with EPV-CoV-19 peptides indicates a Th1-type skewed response (Figure 4). In an in-vivo study examining

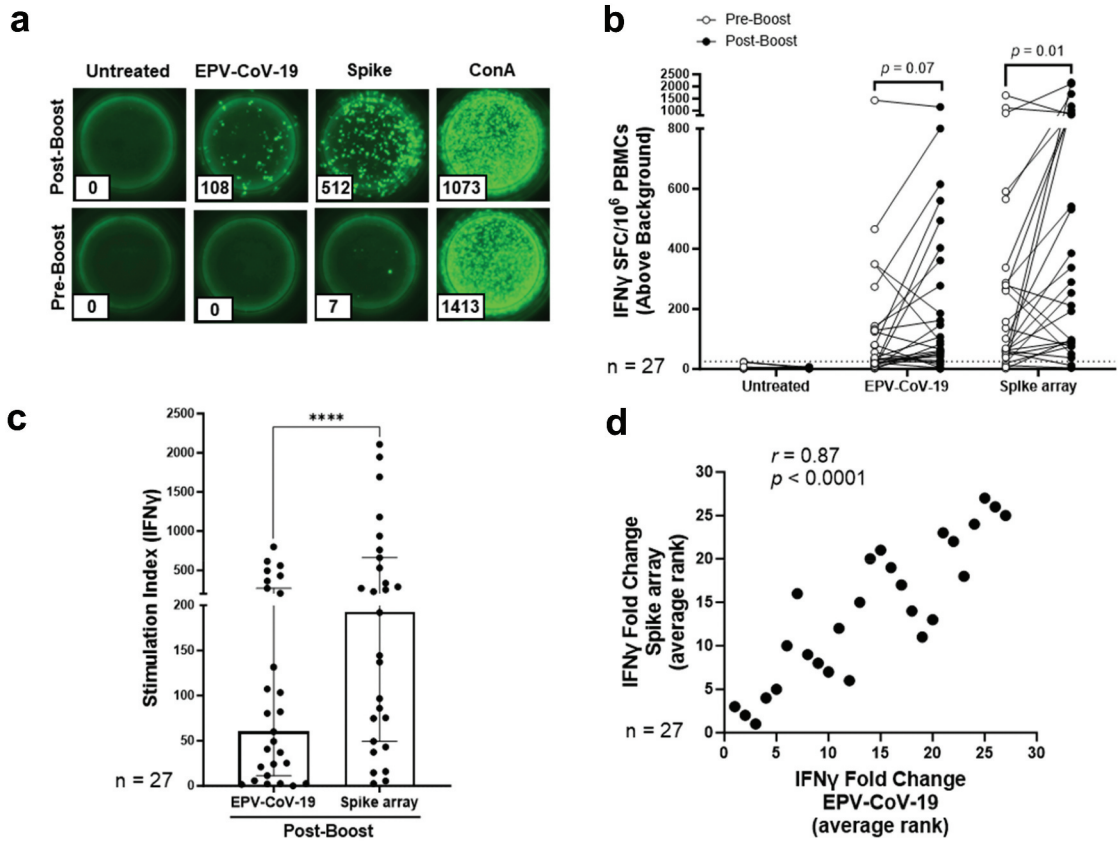

Figure 2. Predicted SARS-CoV-2 epitopes are antigenic in patients receiving the Pfizer-BioNtech COVID-19 booster vaccine. Representative FluoroSpot assay of one donor with IFNγ spot forming cells (SFC) to both EPV-CoV-19 and spike peptide pools; Concanavalin a (ConA) positive control (a). IFNγ SFC per million PBMCs pre-boost (open circles) and post-boost (closed circles) after exposure to EPV-CoV-19 and spike array peptide pools. The dotted horizontal line denotes the established positivity criteria of IFNγ SFC ≥ 25 (b). IFNγ stimulation index post-boost after exposure to EPV-CoV-19 and spike array (c). Correlation between the rank order of IFNγ recall responses post-vaccination induced by the Spike array peptides *(y-axis)* versus EPV-CoV-19 *(x-axis)* (d).

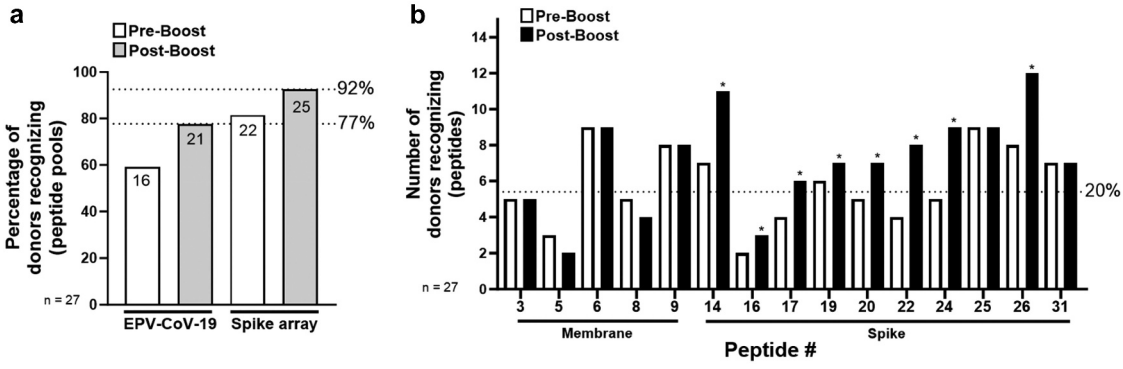

Figure 3. Recognition of EPV-CoV-19 peptides after Pfizer booster vaccination. (a) Bars indicate the percentage of donors with positive response to the EPV-CoV-19 pool and spike pool pre-vaccination *(white)* and 7–10 days post-vaccination *(grey)* (a). Bars indicate the percentage of donors with a positive response to the 15 individual EPV-CoV-19 peptides pre-vaccination *(white)* and 7–10 days post-vaccination *(black)* (b). Dotted horizontal lines denote positive responses above 20%. The peptides with a higher percentage of responders post-vaccination are shown (asterisks).

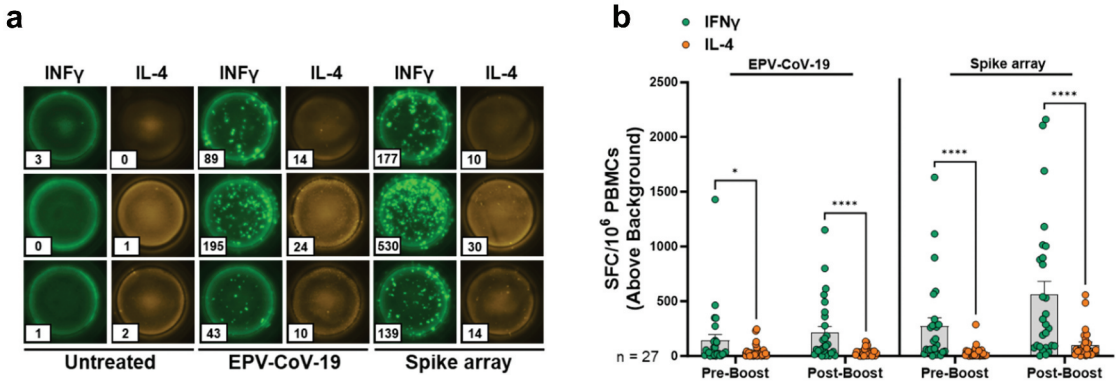

Figure 4. EPV-CoV-19 peptides stimulates type 1-skewed T-cell responses after Pfizer-BioNtech COVID-19 booster vaccination. Representative FluoroSpot assay with IFNγ and IL-4 responses to untreated (media alone), EPV-CoV-19, and Spike array peptides 7–10 days post-booster vaccination (a). EPV-CoV-19 versus spike array peptides, IFNγ *(green dots)* and IL-4 *(orange dots)* spot forming cells (SFC) per million PBMCs for each donor before (Pre-boost) and after vaccination (Post-boost) (b). Asterisks indicate significant differences using the Wilcoxon matched-pairs signed rank test (*$p \leq .05$; ****$p \leq .0001$).

HLA-DR3 transgenic mice vaccinated with the initial set of 32 EPV-CoV-19 peptides, the IFNγ/IL-4 ratio was also skewed toward a type 1 response. Altogether, this provides additional evidence that EPV-CoV-19 peptides avoid the imbalance of type 2 responses associated with higher disease severity and mortality.[15]

The responses shown in this study validate the previous finding that EPV-CoV-19 epitopes are broadly recognized in individuals with preexisting SARS-CoV-2 immunity. Using this cohort, we show increases in the recognition of EPV-CoV-19 epitopes post-booster vaccination, further supporting its use alone, or as a booster or combination vaccine (e.g., in combination with a VOC-specific RBD, antibody-directed vaccine).

EPV-CoV-19 T cell epitope conservation with VOC

EpiCC performs a comparison of the T cell epitopes in proposed vaccines such as EPV-CoV-19, or existing vaccines that were in use throughout the pandemic, to the T cell epitopes contained in circulating strains. Figure 5 shows T cell epitope conservation, assessed as percentage of cross-conserved T cell epitopes, of the 10 spike epitopes from EPV-CoV-19 with

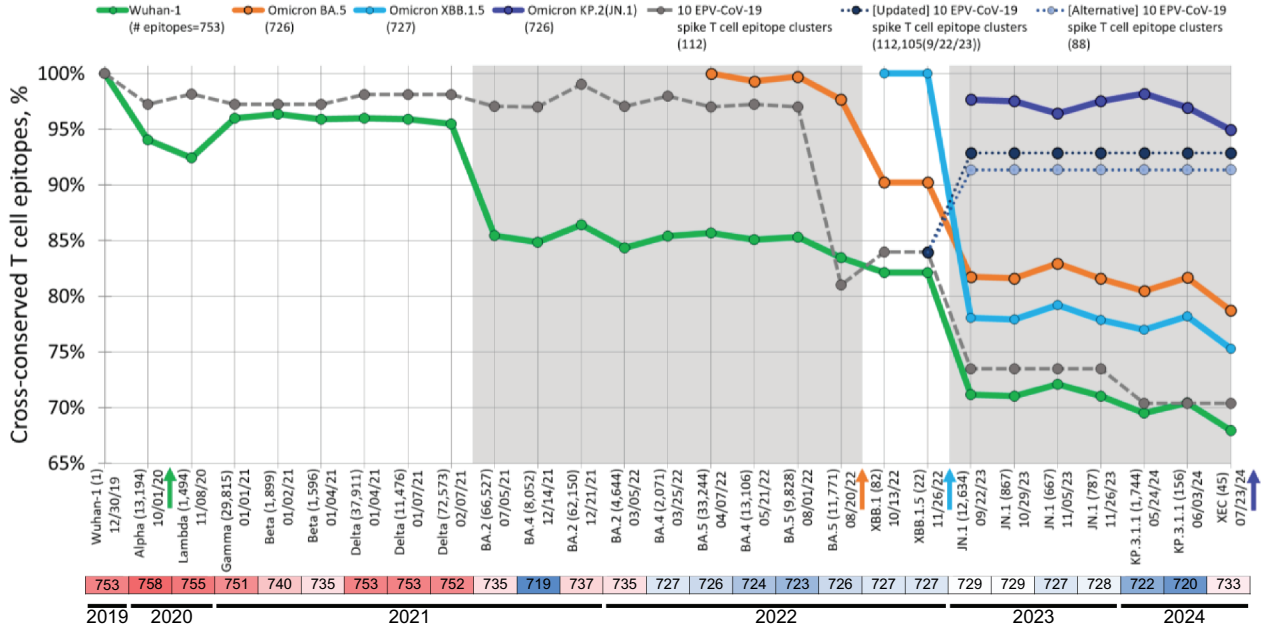

Figure 5. T cell epitope cross-conservation between vaccines and VOC. The percentages of predicted spike T cell epitopes in the most frequent VOC, cross-conserved with four approved vaccines are shown. Each vaccine is represented by a colored line. The number of predicted T cell epitopes in each vaccine is shown in the label. The strains in the x-axis represent the most frequent variants of each lineage or sublineage (frequency is in parentheses). Variants are ordered by collection date, which is included in the variants' labels. Cross-conservation results for each vaccine start from the first strain within the relevant sublineage of that vaccine. The numbers of predicted T cell epitopes in each spike sequence (# epitopes) colored from low (blue) to high (red) are also shown. The dashed line indicates the cross-conservation of 10 EPV-CoV-19 spike T cell epitope clusters with corresponding peptides in the VOC. The dark dotted line (Updated) shows cross-conservation after updating one EPV-CoV-19 T cell epitope cluster (peptide 20) to the corresponding JN.1 peptide when the first JN.1 representative strain was collected (09/22/23). The light dotted line (Alternative) shows cross-conservation replacing one EPV-CoV-19 T cell epitope cluster (P20) with a previously validated, highly cross-conserved and immunogenic T cell epitope cluster from Wuhan-1.[1] Grey-shaded regions in the timeline highlight time periods when major changes in the predominant circulating strain occurred. The colored arrows in the x-axis indicate FDA approval (or emergency use authorization) dates of each vaccine. Detailed data is provided in Supplemental Table S2.

VOCs. The cross-conservation of EPV-COV-19 is compared to cross-conservation for the consecutive commercial vaccines (Wuhan green, Omicron BA.5.5 orange, XBB.1.5 azure, and JN.1 purple) against consecutive VOC. (Details of this analysis are available in Supplemental Table S2).

Despite the reduced neutralizing antibody responses that were reported with VOCs, there was strong (95%) conservation of Wuhan strain spike T cell epitopes with commercial vaccines and with EPV-CoV-19, through the emergence of Delta, with a sudden drop off in conservation for commercial vaccines observed (Figure 5) when Omicron BA.2 emerged. In contrast, epitopes in EPV-CoV-19 remained highly conserved with circulating strains at least until XBB.1 emerged. This loss of conservation can be addressed with an easy 'fix' of the EPV-CoV-19 composition: replacing one peptide from EPV-COV-19 with an alternative recovers the T cell epitope conservation with Omicron sub-strain JN.1. Two such peptides are shown in Figure 5, one specific to JN.1, another from the original set of peptides selected from the ancestral Wuhan strain[1] as "updated" or "alternative" respectively in the figure. The impact of the substitution significantly increases epitope conservation as shown in the EpiCC analysis.

We have previously observed similar shifts in T cell epitope content for circulating human influenza strains as compared to flu vaccines[16] and PRRSV strains as compared to PRRSV vaccines (unpublished, Kimberly VanderWaal[17] that exhibited a temporal correlation with decreased vaccine efficacy. This data suggests that a decline in the conservation between the T cell epitopes in VOCs (Omicron BA.2, for example) and/or changes in the targeted B cell epitope may contribute to the emergence of a new strain in the human population and can also predict the need to change the dominant vaccine strain.

Based on the profile of conservation of T cell epitopes reported here, peptide booster vaccines may be optimal during periods when only neutralizing activity wanes but T cell levels hold steady. This is borne out as Figure 5 shows EPV-CoV-19 cross-conservation remains high during a period when the strain composition of spike vaccines was changed.

Discussion

The role of T-cell immunity in SARs-COV-2 protection

While antibody binding and titers are known markers of protection, the role of T cells in bolstering the protective response against COVID and preventing severe disease is often underestimated. Evidence from numerous studies conducted during the pandemic supports the concept that there is a strong correlation between T cell responses and protection from infection. For instance, a large prospective study found that higher counts of SARS-CoV-2-specific T cells were associated with lower disease risk. Individuals with low T cell responses to spike, membrane, and nucleocapsid proteins tend to develop COVID-19, whereas high responders remain protected, even when seronegative.[18] T cell response breadth also appears critical for effective protection. Patients with mild disease exhibit greater TCR clonality in both blood and bronchoalveolar lavage compared to those with severe disease.[19] In a prospective study of exposed healthcare workers, anti-COVID-19 IgG titers were associated with protection from subsequent PCR test positivity,[20] suggesting that either antibodies, T cell responses, or both were correlates of protection from infection. These publications underscore the importance of defining T cell epitopes in SARS-COV-2 VOC to better understand COVID-19 immunity and develop antibody- and T cell-directed vaccines.

The progress made by vaccinations has greatly reduced public health concerns surrounding COVID-19. However, for vulnerable and high risk populations, COVID-19 remains a significant threat, likely to last for many years. In addition, long COVID, characterized by a wide range of symptoms, can impact multiple systems such as respiratory, neurological, psychological, and cardiovascular.[21–24] Long COVID is a growing health crisis with over 65 million cases reported worldwide.[25] Given the continued threat of COVID-19 and the emergence of new variants, vaccine developers are seeking ways to improve protection.

T cell-epitope-driven vaccines

The contribution of T cell responses to vaccine-driven protection from COVID and other vaccine-preventable human pathogens is well-accepted and acknowledged in numerous publications published on this topic during and after the COVID pandemic.[26] Most vaccines used against COVID-19 induce CD4 T cell-dependent antibody responses against spike. Emerging VOCs containing mutations in spike could result in a loss of vaccine efficacy against infection, but T cells may sustain protection against severe disease and death.[27]

Rather than developing vaccines specifically tailored to drive antibody response to SARS-CoV-2, there may be an advantage to developing vaccines against VOC using conserved epitopes with the intent to boost T cell responses following exposure or prior vaccination.[28] Studies have linked T cell responses to reduced disease severity.[29–31] Overall, enhancing the T cell response could prevent immune escape and provide a better quality and longer lasting immunity.[27,32–35]This is also true for influenza as reflected in the recent emphasis on developing 'universal' vaccines based on conserved T cell epitopes.[36]

The EPV-CoV-19 vaccine is designed to elicit T cell responses. Its constituent epitopes were selected to maximize HLA-DRB1 binding potential, coverage of HLA-DR diversity, and conservation among circulating SARS-CoV-2 viruses. More than 250 T cell epitopes are contained in the 15 peptides that were selected for the EPV-CoV-19 vaccine and validated previously in a study that evaluated T cell responses to the peptides following natural infection. Similarly, these peptides stimulated immune responses in some individuals who had not been exposed to SARS-CoV-2, suggesting that the highly conserved epitopes stimulated preexisting immunity following other coronavirus exposures.[1,37,38]

In this pre-clinical study, we show that prior vaccination and/or infection can serve as a basis for generating effective memory T cell responses, as measured in vitro. Measurement of IFNγ and IL-4 SFC induced by EPV-CoV-19 peptides also indicate a type 1-skewed response, consistent with previous studies.[1]

The level of response to the two sets of peptides, EPV-CoV-19 containing only 15 peptides and the much larger spike array, was comparable. This suggests that much of the immunogenic content of the existing vaccines could be reduced to 15 key sequences (containing multiple epitopes, more than 250 in this case). Since our selection of the EPV-CoV-19 sequences avoided any potential tolerogenic epitopes, the similarity in the response could also be due to the absence of immunomodulatory sequences. Finally, the EPV-CoV-19 vaccine was designed to contain T cell epitopes from proteins other than spike, to which numerous subjects responded. Other groups have shown that sequences comprised of epitopes from non-spike proteins are more likely to be conserved than spike sequences as VOC continue to emerge.[39,40] In a phase I trial of CoVac-1, a SARS-CoV-2 peptide based vaccine, all participants exhibited higher vaccine-induced T cell responses 28 days after vaccination.[41] In a follow up phase I/II study, CoVac-1 produced a broad and potent T-cell responses in patients with B-cell/antibody deficiency.[42]

Health equity considerations

As was true for vaccines during the emergence of the HIV epidemic, consideration should be given to conducting preclinical studies of candidate vaccines in populations that may be most at risk for the disease addressed by the vaccine. In the United States, most racial and ethnic minority groups suffered a disproportionate burden of infection, hospitalization, and death during the coronavirus disease 2019 (COVID-19) pandemic.[43–49] For example, Hispanic Americans accounted for 24.3% of infections and 16.8% of deaths despite being 18.5% of the US population.[47]

Furthermore, Hispanic Americans experience a higher incidence of post-acute sequelae of SARS-CoV-2 infection (PASC, also referred to as long Covid) than majority populations, even as PASC cases may have been under reported.[50–52] Due to the higher prevalence of COVID infection in the US Hispanic population, and reduced access to vaccines,[53] it is reasonable to expect a higher incidence of long COVID among Hispanic Americans, when compared to majority groups, thus the need for trials of vaccines to treat PASC or to prevent against a novel SARS-CoV-2 strain can be anticipated for this target population.

To advance health equity, we also provide insight into the immunogenicity of these peptides among Hispanic Americans. This study would provide significant support for study of the EPV-COV-19 vaccine in a similar Hispanic American population, as it shows that broad host immune responses can be identified in response to the peptide vaccine candidate. We show broad reactivity to the T cell epitopes contained in the EPV-CoV-19 vaccine as well as to the spike array in this population.

EPV-CoV-19 and other epitope-based vaccines for COVID may also be a useful treatment for PASC as vaccination has been shown to have a positive effect on PASC symptoms.[2–4] Continued development of coronavirus therapeutics and vaccines are needed to address the detrimental and potentially lifelong health concerns posed by PASC.[54] This is particularly true for minority populations which have been disproportionately affected by the COVID pandemic and PASC due to higher rates of comorbidities, socioeconomic disparities limiting healthcare access, and increased exposure risks from frontline and essential work positions.

Altogether, this study supports the use of EPV-CoV-19 T cell epitopes as a strategy to boost T cell response in previously vaccinated individuals. The increased T cell responses following exposure to those epitopes in vitro nearly matched the responses generated by a pool of peptides that contained roughly 7-fold more epitopes. In addition, T cell epitope-based vaccines may be useful for providing or boosting protection when antibody-directed vaccines are not yet available or have waned in efficacy against infection, or for use in individuals for whom antibody responses are not expected (such as individuals who have B cell-related immunosuppression or are using immunomodulatory therapeutics). This is, however, a small study. While cognizant of health equity, it was not powered to compare responses to specific epitopes with respect to subject ethnicities. Relationships between antibody responses pre- and post-boost were also not considered, nor relationships between T cell and antibody responses both pre and post.

Further studies are warranted that will bring T-cell epitope-based vaccines to clinical use. EpiVax has developed extensive pre-clinical proof of efficacy of similar T cell-directed vaccines, including cancer vaccines designed using EpiVax's proprietary tools, an H. pylori vaccine,[55] a tularemia vaccine,[56] a universal flu vaccine[36] and a smallpox vaccine[57] among many others. In addition, a similar approach has produced peptides containing T cell epitopes for a pan-coronavirus vaccine that is in preclinical development.

A vaccine for the future?

T cell immunity supports protection against severe disease and death and could be sufficient to boost until a decline in T cell epitope conservation with new variants and a composition change is required. We illustrate how one might swap a single peptide in a T cell-epitope-based vaccine to improve coverage of new VOC, even mid-pandemic. We acknowledge that the effectiveness of the proposed changes to EPV-CoV-19 composition remains to be determined by experimental means.

In summary, T cell epitope-based vaccines may provide long-lasting protection across emerging variants, and T cell-epitope conservation may also explain why individuals were protected against severe disease, early in the pandemic, despite the circulating VOC.[28,58] While commercial vaccines exhibited a loss of T cell epitope conservation against emergent VOCs, the 10 spike derived EPV-CoV-19 T cell epitope-containing peptides maintained conservation until the XBB variant emerged, at which point the substitution of one peptide in the vaccine reestablished broad T cell epitope coverage. These findings underscore the importance of identifying highly conserved T cell epitopes for vaccines to protect against emerging strains of pathogens.

Acknowledgments

We are grateful to the study participants, and to Clinica Esperanza/Hope Clinic for their participation in this study. We also thank the EpiVax scientific, laboratory, and informatics teams for their support.

Disclosure statement

ADG and WDM are senior officers and majority shareholders of EpiVax, Inc, a privately owned immunoinformatics and vaccine design company. ADG, WDM, MM, CMB, and AHG are employees of EpiVax, Inc. KH is a former employee of EpiVax. Due to this relationship with EpiVax, these authors acknowledge that there is a potential conflict of interest inherent in the publication of this manuscript, and attest that the work contained in this research report is free of any bias that might be associated with the commercial goals of the company.

ADG is a reviewer and editor at Human Vaccines and Therapeutics. This had no impact on the peer review process and the final decision.

Funding

Funding for the activities related to the development of this manuscript was provided by internal research funds from EpiVax.

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Human studies approval

The study protocol was approved by the AAHRPP-accredited Ethical & Independent (E&I) (now called Salus) external institutional review board (IRB 21,066–01).

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