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Julia Lang-Meli

University of Freiburg

Hendrik Luxenburger

University of Freiburg

Katharina Wild

University of Freiburg

Vivien Karl

University of Freiburg

Valerie Oberhardt

University of Freiburg

Elahe Salimi Alizei

University of Freiburg

Anne Graeser

University of Freiburg

Matthias Reinscheid

University of Freiburg

Natascha Roehlen

University of Freiburg

Sebastian Giese

University of Freiburg

Kevin Ciminski

University of Freiburg <https://orcid.org/0000-0001-5397-7497>

Veronika Götz

University of Freiburg

Dietrich August

University of Freiburg

Siegbert Rieg

University of Freiburg

Cornelius Waller

University of Freiburg

Tobias Wengenmayer

University of Freiburg

Dawid Staudacher

University of Freiburg

Bertram Bengsch

University of Freiburg

Georg Kochs

Freiburg University Medical Center <https://orcid.org/0000-0003-0187-559X>

Martin Schwemmle

University Medical Center Freiburg <https://orcid.org/0000-0002-2972-6855>

Florian Emmerich

University of Freiburg

Tobias Boettler

Department of Medicine II, Medical Center - University of Freiburg, Germany <https://orcid.org/0000-0002-1195-055X>

Robert Thimme

University Hospital Freiburg

Maike Hofmann (✉ maike.hofmann@uniklinik-freiburg.de)

University of Freiburg

Christoph Neumann-Haefelin

Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases),
Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany
<https://orcid.org/0000-0001-7351-1387>

Brief Communication

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SARS-CoV-2 specific T cells induced by both SARS-CoV-2 infection and mRNA vaccination broadly cross-recognize omicron

Julia Lang-Meli^{1,2*}, Hendrik Luxenburger^{1,2*}, Katharina Wild^{1,3*}, Vivien Karl^{1,4*}, Valerie Oberhardt^{1,4*}, Elahe Salimi Alizei^{1,3}, Anne Graeser¹, Matthias Reinscheid^{1,4}, Natascha Roehlen¹, Sebastian Giese⁵, Kevin Ciminski⁵, Veronika Götz¹, Dietrich August¹, Siegbert Rieg¹, Cornelius F. Waller⁶, Tobias Wengenmayer^{7,8}, Dawid Staudacher^{7,8}, Bertram Bengsch^{1,9}, Georg Kochs⁵, Martin Schwemmler⁵, Florian Emmerich¹⁰, Tobias Boettler^{1,11#}, Robert Thimme^{1#§}, Maike Hofmann^{1#§}, Christoph Neumann-Haefelin^{1#§}

¹Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases), Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

²IMM-PACT, Faculty of Medicine, University of Freiburg, Freiburg, Germany

³Faculty of Chemistry and Pharmacy, University of Freiburg, Freiburg, Germany

⁴Faculty of Biology, University of Freiburg, Freiburg, Germany

⁵Institute of Virology, Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

⁶Department of Haematology, Oncology & Stem Cell Transplantation, Freiburg University Medical Center, Faculty of Medicine, University of Freiburg

⁷Department of Medicine III (Interdisciplinary Medical Intensive Care), Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

⁸Department of Cardiology and Angiology I, Heart Center, Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany

⁹Signalling Research Centres BIOS and CIBSS, University of Freiburg, Freiburg, Germany

¹⁰Institute for Transfusion Medicine and Gene Therapy, Freiburg University Medical Center, Faculty of Medicine, University of Freiburg, Germany

¹¹ Berta-Ottenstein Programme, Faculty of Medicine, University of Freiburg

*equally contributing first authors; #equally contributing last authors; §corresponding authors

Materials and Correspondence:

Christoph Neumann-Haefelin: christoph.neumann-haefelin@uniklinik-freiburg.de

Maike Hofmann: maike.hofmann@uniklinik-freiburg.de

Robert Thimme: robert.thimme@uniklinik-freiburg.de

Hugstetter Straße 55, 79106 Freiburg, Germany

Abstract

The SARS-CoV-2 variant of concern (VOC) omicron (B.1.1.529) is associated with high infectivity and efficient evasion from humoral immunity induced by previous infection or vaccination. In omicron-infected individuals who have been vaccinated or infected before, severe disease seems to be relatively infrequent pointing towards protection by previously primed SARS-CoV-2-specific T cells that cross-recognize omicron. By performing a comprehensive in-depth comparison of the SARS-CoV-2-specific T cell epitope repertoire after natural infection versus after mRNA vaccination, we here demonstrate that spike-derived epitopes are not dominantly targeted in convalescents compared to non-spike epitopes. In vaccinees, however, we detected a broader spike-specific T cell response compared to convalescents reflected by a more diverse repertoire of dominantly targeted spike-specific T cell epitopes. Booster mRNA vaccination induced a broader spike-specific T cell response in convalescents but not in vaccinees with complete initial vaccination. In convalescents and vaccinees, the targeted T cell epitopes are broadly conserved between ancestral and omicron SARS-CoV-2 variants. Hence, our data emphasize the relevance of mRNA vaccine-induced spike-specific CD8⁺ T cell responses in combating emerging SARS-CoV-2 VOC including omicron and support the benefit of also boosting convalescent individuals with mRNA vaccines.

Keywords

T cells, SARS-CoV-2, mRNA vaccination, COVID-19, Omicron, B.1.1.529

Main

Continuously emerging variants of concern (VOC) sustain the pandemic state of SARS-CoV-2. Indeed, the current SARS-CoV-2 VOC omicron (B.1.1.529) is a global health care threat due to its substantially increased infectivity and efficient ability to evade neutralisation by spike-specific antibodies induced by previous infection or vaccination¹⁻⁶. Indeed, an approx. 5 to 25-fold higher concentration of neutralising antibodies is required to abolish infectivity of omicron compared to the delta VOC. Both, increased infectivity and evasion from the humoral response is at least partially based on mutations in the receptor binding domain (RBD) resulting in enhanced affinity to ACE2 receptor and disruption of antibody binding sites¹. Multiple additional mutations in the spike protein of omicron confer the risk of a broad evasion from the immune response that was readily established through vaccination and previous infection. This assumption is in line with the reportedly higher risk of break through infection with omicron in convalescents and vaccinees with complete initial immunization. Severe disease after omicron infection, is, however, not common and may be prevented by broadly cross-reactive cellular immunity⁷. Indeed, an important role of vaccine- and infection-induced T cells in preventing

severe COVID-19 has been reported prior to the emergence of omicron⁸⁻¹¹. Currently, very little information is available about the evasion of omicron from cellular immunity although first data indicate that this occurs to a lesser extent compared to evasion from humoral immunity. The SARS-CoV-2-specific T cell epitope repertoire has been studied in some detail¹¹⁻¹⁶ (reviewed in ¹⁷), however, comparative in-depths studies of the epitope repertoire targeted by infection- versus vaccine-induced T cell responses are so far lacking, hindering the precise prediction of the immune escape potential of emerging VOC including omicron from the T cell response in convalescents compared to vaccinees.

To address this important issue, we studied SARS-CoV-2-specific T cell responses in convalescents recovered from natural SARS-CoV-2 infection (n=19) as well as individuals after two (n=16) and three (n=7) doses of SARS-CoV-2 vaccination (Pfizer/BioNTech mRNA vaccine) (**Supplementary Table 1**). We first mapped the overall SARS-CoV-2-specific CD8+ T cell response and tested a set of 43 previously described immunodominant SARS-CoV-2-specific CD8+ T cell epitopes restricted by common HLA class I alleles¹¹⁻¹⁶ in epitope-specific T cell cultures followed by cytokine staining (intracellular interferon-gamma production). Convalescents displayed CD8+ T cell responses against the majority of epitopes that were distributed over all viral proteins, with spike-specific epitopes definitively not being dominant (**Figure 1A**, left column). In vaccinees, in contrast and as expected, CD8+ T cell responses were predominantly directed against spike epitopes (**Figure 1A**, right column). Few CD8+ T cell responses targeted non-spike epitopes, with the HLA-B*07/N₁₀₅₋₁₁₃ epitope being the main target. For this epitope, cross-recognition by T cells against common cold corona viruses has been previously suggested¹⁸⁻²⁰. Importantly, individual spike-specific CD8+ T cell epitopes were more often targeted in vaccinees compared to convalescents, and the spike-specific CD8+ T cell repertoire also appeared to be broader in vaccinees compared to convalescents. When we compared the corresponding viral sequences between ancestral and omicron SARS-CoV-2 variants, only a single tested optimal CD8+ T cell epitope was affected by viral variation (**Figure 1A**, shown in red).

To further analyze the striking differences in spike-specific CD8+ T cell responses in convalescents versus vaccinees and the nearly complete absence of viral variations in the targeted epitopes in more detail, we analysed these responses using overlapping peptides spanning the whole spike protein (180 18-mer peptides, sliding by 7 amino acids and thus overlapping by 11 amino acids). For all positive responses, we evaluated the overlapping peptide for described optimal epitopes restricted by the HLA class I alleles expressed by the respective individual. If no matching optimal epitopes has been previously described, we performed an *in silico* analysis to predict the most likely HLA class I restriction and optimal epitope. Using this comprehensive approach, we identified an overall substantially broader repertoire of spike-specific CD8+ T cell responses in vaccinees (**Fig. 1B**, lower panel, and

Supplementary Figure 1A) compared to convalescents (**Fig. 1B**, upper panel and **Supplementary Figure 1B**). Indeed, in convalescents, no HLA class I allele restricted more than two spike-specific CD8⁺ T cell epitopes, while several HLA class I alleles restricted five or more spike-specific CD8⁺ T cell epitopes in vaccinees. In addition, we detected more spike-specific CD8⁺ T cell responses per individual in vaccinees compared to convalescents (**Fig. 1C**). Hence, the increased breadth of the spike-specific CD8⁺ T cell response in vaccinees was evident on an individual and on a population level.

To test whether an increased breadth of the spike-specific response in vaccinees is also evident for CD4⁺ T cells, we analysed the CD4⁺ T cell response applying the overlapping peptides spanning the whole spike protein as described above. In contrast to the CD8⁺ T cell response, the spike-specific CD4⁺ T cell response showed a more limited repertoire of targeted epitopes after vaccination compared to natural infection (**Fig. 1D** and **Supplementary Figure 1**). In particular, fewer spike-specific CD4⁺ T cell epitopes were restricted by single HLA class II alleles (**Fig. 1D**) and fewer CD4⁺ T cell responses were detectable per individual (**Fig. 1E**) in vaccinees compared to convalescents. The spike-specific CD4⁺ T cell repertoire was therefore limited with respect to the individual and the population-based CD4⁺ T cell response in vaccinees. Still, the fewer targeted spike-specific CD4⁺ T cell epitopes in vaccinees exhibited high conservation between ancestral and omicron SARS-CoV-2 as it is also the case for the majority of targeted epitopes in convalescents (**Fig. 1D**, variant epitopes shown in red). Comparing CD8⁺ and CD4⁺ T cell response (**Fig. 1F**), mRNA vaccination appears to particularly broaden and thus increase a cross-reactive spike-specific CD8⁺ T cell response.

Next, to assess the effect of boosting vaccination- or infection-induced T cell responses by mRNA vaccination on the spike-specific CD8⁺ T cell repertoire, we performed the very same approach as described above using overlapping spike peptides to map spike-specific CD8⁺ and CD4⁺ T cell responses in longitudinally followed vaccinees getting their 3rd vaccine dose (Pfizer/BioNTech mRNA vaccine; n=7; **Supplementary Table 1**) and convalescent individuals that received an mRNA booster vaccination (n=3; **Supplementary Table 1**). After the third mRNA vaccination, we observed a similarly broad and cross-reactive spike-specific CD8⁺ T cell repertoire and similarly limited but still cross-reactive spike-specific CD4⁺ T cell repertoire compared to the completed initial immunization with two vaccine doses (**Fig. 2A** and **Supplementary Fig. 2A**). Strikingly, however, we detected CD8⁺ T cell responses targeting more overlapping peptides after the mRNA boost vaccination in convalescents, representing a broader spike-specific CD8⁺ T cell repertoire (**Fig. 2B** and **Supplementary Fig. 2B**). In contrast, the CD4⁺ T cell repertoire was similar before and after boost vaccination of convalescents (**Fig. 2B** and **Supplementary Fig. 2B**). Again, the identified CD8⁺ and CD4⁺ T cell responses targeted epitopes that are conserved in omicron. Thus, mRNA booster

vaccination increased SARS-CoV-2-specific CD8⁺ T cell responses targeting conserved regions within the spike protein of omicron in convalescent individuals.

To address the question whether the observed broader spike-specific CD8⁺ T cell repertoire after mRNA vaccination may also be beneficial for potentially emerging future SARS-CoV-2 VOC beyond omicron, we analyzed the T cell response targeting highly conserved selective sweep regions in SARS-CoV-2²¹ in convalescents versus vaccinees. Selective sweep regions mediate per definition an evolutionary advantage and therefore it is very likely that newly emerging SARS-CoV-2 VOC also harbor high conservation within these regions. Four different selective sweep regions have so far been described in the spike protein of SARS-CoV-2²¹ that also exhibit, as expected, a high degree of amino acid homology among the already evolved SARS-CoV-2 VOC (**Fig. 3A/B**). Importantly, compared to convalescents more vaccinated individuals showed spike-specific CD8⁺ T cell responses targeting epitopes within the highly conserved selective sweep regions indicating a spike-specific CD8⁺ T cell response with focussed targeting of highly conserved regions after vaccination (**Fig. 3C**). A similarly focussed spike-specific CD4⁺ T cell response was not evident after vaccination (**Fig. 3D**). Hence, a broadly cross-recognizing spike-specific CD8⁺ T cell response is induced after mRNA vaccination that may be also reactive towards emerging SARS-CoV-2 VOC in future beyond omicron.

In conclusion, our data indicate that (1) convalescents target a variety of SARS-CoV-2-specific CD8⁺ T cell epitopes over the complete SARS-CoV-2 proteome with spike-specific CD8⁺ T cell responses being not dominant; (2) in contrast to the CD4⁺ T cell response, CD8⁺ T cell responses in vaccinees are focussed on a broader repertoire of highly conserved spike-specific CD8⁺ T cell epitopes leading to an increased cross-recognizing potential; (3) boosting convalescents with mRNA vaccination results in a broader spike-specific CD8⁺ T cell response; and (4) CD8⁺ and CD4⁺ T cell responses in both, convalescents as well as vaccinees, target epitopes that are highly conserved between ancestral, omicron and potentially future emerging SARS-CoV-2 variants. Hence, our data emphasize the relevance of mRNA vaccine-induced spike-specific CD8⁺ T cell responses in combating emerging SARS-CoV-2 VOC including omicron and support the benefit of also boosting convalescent individuals with mRNA vaccines.

Data availability

All requests for raw and analyzed data and materials are promptly reviewed by the University of Freiburg Center for Technology Transfer to verify if the request is subject to any intellectual property or confidentiality obligations. Patient-related data not included in the paper were

generated as part of clinical examination and may be subject to patient confidentiality. Any data and materials that can be shared will be released via a Material Transfer Agreement.

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Author contributions

J.L.-M., H.L., K.W., V.K. and V.O. planned, performed and analyzed experiments with the help of E.S.A., A.G. and M.R.. J.L.-M., H.L., K.W., V.K. and V.O. contributed equally to this work. H.L., N.R., V.G., D.A., S.R., T.W., D.S. and C.F.W. were responsible for donor recruitment. F.E. performed four-digit HLA-typing by next generation sequencing. S.G., K.C., M.S. and G.K. provided virological expertise. B.B. and T.B. contributed to data interpretation. T.B. supervised the CD4+ T cell analysis and interpreted data. R.T., M.H. and C.N.-H. designed the study and contributed to experimental design and planning. J.L.-M., H.L., V.O., R.T., M.H. and C.N.H. interpreted data and wrote the manuscript. T.B., C.N.H., M.H. and R.T. are shared last authors.

Declaration of interest

The authors have nothing to declare.

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Online methods

Ethics

Patients were recruited at the Freiburg University Medical Center, Germany between August 2019 and January 2022. Written informed consent was obtained from all participants. The study was conducted according to federal guidelines and local ethics committee regulations (Albert-Ludwigs-University Freiburg, Germany; vote: #21-1135 and #21-1372) and the Declaration of Helsinki (1975).

Study Cohort & Clinical definitions

19 convalescent individuals following a mild course of SARS-CoV-2 infection were analyzed. All patients were confirmed to have a test positive for SARS-CoV-2 using PCR with reverse transcription from an upper respiratory tract (nose and throat) swab tested at an accredited laboratory. The degree of severity was identified according to recommendations from the World Health Organization. Moreover, 16 individuals were screened 2-4 weeks after first mRNA boost vaccination (Pfizer/BioNTech BNT162) and 7 of the same individuals 2-4 weeks after second boost vaccination (Pfizer/BioNTech BNT162). Three individuals were analyzed who had a mild course of SARS-CoV-2 infection and were vaccinated once with mRNA vaccine (Pfizer/BioNTech BNT162).

PBMC isolation

Peripheral blood mononuclear cells (PBMCs) were isolated from anticoagulated blood samples with density gradient centrifugation (Pancoll separation medium, PAN Biotech GmbH; Aidenbach, Germany). Subsequently stored at -80°C resuspended in RPMI 1640 medium supplemented with 10% fetal calf serum, 1% penicillin/streptomycin, and 1.5% HEPES buffer 1 mol/L (complete medium; all additives from Thermo Scientific (Waltham, MA)) until further usage.

Peptides

A total of 182 overlapping peptides that spanned the SARS-CoV-2 spike sequence (Gene Bank Accession code MN908947.3) were synthesized as 18-mers overlapping by 11 amino acids with a free amine NH₂ terminus and a free acid COOH terminus with standard Fmoc chemistry and a purity of >70% (Genaxxon Bioscience). Similarly, 60 predescribed SARS-CoV-2 specific optimal CD8⁺ T cell epitopes were synthesized.

In vitro expansion and intracellular IFN γ staining with overlapping peptides or optimal predescribed CD8⁺ T cell epitopes

In vitro expansion with OLPs or optimal epitopes was performed as follows: 20% of the PBMCs were stimulated with a pool of all 181 SARS-CoV-2 spike OLPs or optimal epitopes (10 μ g ml⁻¹) for 1 h at 37 °C, washed and co-cultured with the remaining PBMCs in RPMI medium supplemented 20 U ml⁻¹ with recombinant IL-2. On day 10, intracellular IFN γ staining was performed with pooled OLPs (45 pools with 4 OLP each). Therefore, cells were re-stimulated with OLP pools (50 μ M), DMSO as negative control or PMA and ionomycin as positive control in the presence of brefeldin A and IL-2. After 5 h of incubation at 37 °C, cells were stained for surface markers (CD8+, CD4+; Viaprobe) and intracellular markers (IFN γ). Subsequently, on day 12-14 the single overlapping peptides of positive pools and HLA-matched optimal CD8⁺ T cell epitopes were tested by intracellular cytokine staining. Viral amino acid sequences of positive individual OLPs were analysed for pre-described minimal epitopes¹⁻⁶ or the best HLA-matched predicted candidate using the Immune Epitope Database website (using two prediction algorithms ANN 4.0 and NetMHCpan EL 4.123 for 8-mer, 9-mer and 10-mer peptides with half-maximal inhibitory concentration (IC₅₀) of <500 nM).

Multiparametric flow cytometry

The following antibodies were used for flow cytometry: Anti-CD8-APC (SK-1, 1:200), anti-CD4-eFluor450 (RPA-T4, 1:250), anti-IFN- γ -FITC (25723.11, 1:8), fixable Viability Dye (eFluor506 1:200, 1:400). After fixation of cells in 2 % paraformaldehyde/PBS (Sigma; Germany), acquisition was performed on BD FACSCanto (BD; Germany). Data were analyzed with FlowJo, LLC (10.0.7r2, BD; USA).

ELISA

Spike-binding antibodies were assessed by Anti-SARS-CoV-2-QuantiVac-ELISA (IgG) (Euroimmun; Germany) detecting S1 IgG (<25.6 BAU/ml: negative; 25.6-35.1 BAU/ml: marginally positive; $\geq$ 35.2 BAU/ml: positive) according to manufacturer's instructions.

Sequence alignment

Sequence homology analyses were performed in Geneious® 11.0.5 (<https://www.geneious.com/>) using Clustal Omega 1.2.2 alignment with default settings⁷⁻⁹. Reference genome of human SARS-CoV-2 (MN908947.3) was downloaded from NCBI database. SARS-CoV-2 epitopes were then mapped to the corresponding protein alignment. Selective sweep regions were indicated as described by Kang et al.¹⁰. SARS-CoV-2 variants of concern were identified via CoVariants (<https://covariants.org/>).

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Figure 1: CD8+ and CD4+ T cell responses targeting conserved and mutated epitopes in omicron.
Percentages of CD8+ T cell responses to previously described optimal CD8+ T cell epitopes in ancestral SARS-CoV-2 protein (A). Number, location and percentages of spike-specific CD8+ (B) and CD4+ (D) T cell responses to overlapping peptides (OLP) that are detectable in SARS-CoV-2 convalescents and vaccinees who received two doses of Pfizer/BioNTech mRNA vaccine are depicted. Number of CD8+ (C,F) and CD4+ (E,F) T cell responses targeting spike-specific epitopes per individual in convalescents (n=19) and vaccinees (n=16). mean and range are depicted, statistical analysis was performed with paired t test.

Figure 2: Boosted vaccine- and infection-induced spike-specific CD8+ and CD4+ T cell responses.

Number, location and percentages of spike-specific CD8+ and CD4+ T cell responses to overlapping peptides (OLP) that are detectable in SARS-CoV-2 vaccinees after the 2nd versus after the 3rd dose (A) of Pfizer/BioNTech mRNA vaccine (measured 2-4 weeks after vaccination) and in SARS-CoV-2 convalescents who subsequently received a single dose (B) of Pfizer/BioNTech mRNA boost vaccination (measured 2 weeks after vaccination) are depicted. Targeted epitopes with sequence variations in omicron are marked in red. statistical analysis was performed with paired t test.

Figure 3: Spike-specific CD8+ and CD4+ T cell responses targeting selective sweep regions. Schematic representation of four selective sweep regions (SS1-4) in the spike protein of SARS-CoV-2 (A). Amino acid sequences of the selective sweep regions 1-4 in the spike protein of ancestral SARS-CoV-2 and VOC alpha, beta, gamma, delta and omicron (B). Vaccinees and convalescents with CD8+ (C) and CD4+ (D) T cell responses within and outside selective sweep regions 1-4.

Extended Data 1: Stable T cell repertoire after natural infection or mRNA vaccination.
Heatmap showing percentage and location of CD4+ and CD8+ T cell responses targeting spike OLPs in three individuals at two different timepoints after mRNA vaccination: early = 2-4 weeks, late = 4, 7 and 8 months, respectively (A). Number of spike-specific CD4+ and CD8+ T cell responses to OLPs in correlation to days post symptoms onset in the first year after natural SARS-CoV-2 infection. Spearman correlation is depicted (B).

A

B

Extended Data 2: Boosted vaccine- and infection-induced spike-specific CD8⁺ and CD4⁺ T cell responses in exemplary individuals.

Number and location of spike-specific CD8⁺ and CD4⁺ T cell responses to overlapping peptides (OLP) that are detectable in exemplary SARS-CoV-2 vaccinees after the 2nd versus after the 3rd dose (A) of Pfizer/BioNTech mRNA vaccine (bnt162b2) and in exemplary SARS-CoV-2 convalescents who subsequently received a single dose (B) of Pfizer/BioNTech mRNA boost vaccination are depicted.

Extended Data 3: Gating strategy

Lymphocytes were gated on FSC-A and SSC-A, Doublet exclusion on FSC-H and FSC-W, Exclusion of dead cells, Gating on CD8+ or CD4+ cells.

Supplementary Table 1: Characteristics of vaccinated and resoved subjects

Donor ID	Sex	Age	HLA class I	HLA class II	Cohort	Vaccine 1. dose	Vaccine 2. dose	Vaccine 3. dose	Natural infection	Serum S1 IgG1 levels (BAU/ml) after natural infection	Serum S1 IgG1 levels (BAU/ml) after 2. dose	Serum S1 IgG1 levels (BAU/ml) after 3. dose
										Anti-SARS-CoV-2 spike IgG: <35.2 binding antibody units (BAU) per ml: negative ≥35.2 BAU per ml: positive; upper limit of quantification: 3,000 BAU per ml)		
1	f	30	A*26:01, B*07:02, B*38:01	DQB1*03:02, DQB1*06:02, DRB1*04:01, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	>3000	-
2	m	47	A*02:01, A*24:02, B*27:05, B*51:01	DQB1*03:01, DRB1*11:01, DRB1*11:04	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	>3000	-
3	m	33	A*02:01, A*03:01, B*07:02	DQB1*06:02, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	>3000	-
4	m	41	A*01:01, A*02:01, B*08:01, B*40:01	DQB1*03:01, DQB1*06:02, DRB1*14:02, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	1522.56	>3000
5	f	37	A*02:01, A*68:01, B*15:01, B*40:01	DQB1*06:02, DQB1*06:03, DRB1*13:01, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
6	m	31	A*02:01, A*03:01, B*15:01, B*57:03	DQB1*03:02, DQB1*06:02, DRB1*04:01, DRB1*14:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
7	m	32	A*03:01, A*03:01, B*07:02, B*44:02	DQB1*03:01, DQB1*06:03, DRB1*11:198, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
8	m	43	A*03:01, A*32:01, B*07:02, B*40:02	DQB1*03:01, DQB1*05:03, DRB1*11:01, DRB1*14:54	vaccinated	BNT162b2	BNT162b2	-	-	-	1280.16	-
9	m	60	A*02:01, A*02:01, B*08:01, B*15:01	DQB1*02:01, DQB1*03:01, DRB1*03:01, DRB1*11:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
10	f	52	A*02:01, A*68:01, B*15:01, B*44:02	DQB1*03:01, DQB1*05:03, DRB1*11:03, DRB1*14:54	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	>3000	>3000
11	f	35	A*01:01, A*03:01, B*07:02, B*57:01	DQB1*03:03, DQB1*06:02, DRB1*07:01, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
12	f	44	A*01:01, A*11:01, B*15:17, B*35:01	DQB1*05:01, DQB1*06:04, DRB1*01:03, DRB1*13:02	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
13	f	30	A*01:01, A*02:01, B*07:02, B*37:01	DQB1*03:01, DQB1*06:02, DRB1*05:01, DRB1*11:03	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	1535.27	>3000
14	m	30	A*01:01, A*02:01, B*13:02, B*35:02	DQB1*02:02, DQB1*03:01, DRB1*07:01, DRB1*11:02	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
15	m	35	A*01:01, A*26:01, B*07:02, B*27:05	DQB1*05:01, DQB1*06:02, DRB1*01:01, DRB1*15:01	vaccinated	BNT162b2	BNT162b2	BNT162b2	-	-	>3000	>3000
16	m	41	A*01:01, A*03:01, B*08:01, B*35:01	DQB1*02:01, DQB1*05:01, DRB1*01:01, DRB1*03:01	vaccinated	BNT162b2	BNT162b2	-	-	-	>3000	-
17	m	57	A*02:01, A*68:01, B*07:02, B*44:02	DQB1*03:01, DQB1*06:02, DRB1*11:01, DRB1*15:01	resolved vaccinated	BNT162b2	-	-	mild	>3000	>3000 (after 1 dose)	-
18	m	55	A*02:01, A*23:01, B*07:02, B*35:01	DQB1*02:01, DQB1*03:01, DRB1*03:01, DRB1*11:01	resolved vaccinated	BNT162b2	-	-	mild	217.34	>3000 (after 1 dose)	-
19	w	56	A*02:01, A*31:01, B*07:01, B*15:01	DQB1*02:02, DQB1*06:02, DRB1*07:01, DRB1*15:01	resolved vaccinated	BNT162b2	-	-	mild	-	-	-
20	f	28	A*11:01, A*24:02, B*51:01	DQB1*03:03, DQB1*04:01, DRB1*04:01, DRB1*09:01	resolved	-	-	-	mild	21.42	-	-
21	f	31	A*02:01, B*18:01, B*38:01	DQB1*02:02, DQB1*06:03, DRB1*07:01, DRB1*13:01	resolved	-	-	-	mild	46.69	-	-
22	f	26	A*66:01, A*68:01, B*35:01, B*44:02	DQB1*03:01, DQB1*03:02, DRB1*04:04, DRB1*11:04	resolved	-	-	-	mild	46.69	-	-
23	m	37	A*02:01, B*18:01, B*39:24	DQB1*03:01, DRB1*11:01, DRB1*13:03	resolved	-	-	-	mild	104.29	-	-
24	f	56	A*02:01, A*03:01, B*40:12, B*51:01	DQB1*03:01, DQB1*06:02, DRB1*11:01, DRB1*15:03	resolved	-	-	-	mild	136.91	-	-
25	m	42	A*01:01, B*50:01	DQB1*02:02, DRB1*07:01	resolved	-	-	-	mild	40.32	-	-
26	f	40	A*03:01, A*11:01, B*15:01, B*35:01	DQB1*03:01, DQB1*06:03, DRB1*04:07, DRB1*13:01	resolved	-	-	-	mild	77.91	-	-
27	m	52	A*01:01, A*02:01, B*37:01, B*44:02	DQB1*03:01, DQB1*03:02, DRB1*04:04, DRB1*11:01	resolved	-	-	-	mild	151.47	-	-
28	m	34	A*01:01, A*03:01, B*08:01	DQB1*02:01, DRB1*03:01	resolved	-	-	-	mild	96.16	-	-
29	m	36	A*01:01, A*03:01, B*37:01, B*40:01	DQB1*06:02, DQB1*06:04, DRB1*13:02, DRB1*15:01	resolved	-	-	-	mild	7.41	-	-
30	f	50	A*01:01, A*02:01, B*15:01, B*39:01	DQB1*03:02, DQB1*05:03, DRB1*04:04, DRB1*14:54	resolved	-	-	-	mild	368.19	-	-
31	f	27	A*02:01, A*25:01, B*07:02, B*15:24	DQB1*05:03, DQB1*06:03, DRB1*13:01, DRB1*14:54	resolved	-	-	-	mild	101.34	-	-
32	m	36	A*01:01, A*29:02, B*07:02, B*40:01	DQB1*03:01, DRB1*01:03, DRB1*11:01	resolved	-	-	-	mild	13.64	-	-
33	m	26	A*02:01, A*31:01, B*07:02, B*15:01	DQB1*04:02, DQB1*06:02, DRB1*12:01, DRB1*15:01	resolved	-	-	-	mild	197.77	-	-
34	m	34	A*03:01, A*24:02, B*44:03, B*45:01	DQB1*03:01, DQB1*06:02, DRB1*04:01, DRB1*15:01	resolved	-	-	-	mild	33.97	-	-
35	m	31	A30:04, A*68:01, B*40:01, B*57:03	DQB1*06:02, DQB1*06:04, DRB1*13:02, DRB1*14:54	resolved	-	-	-	mild	141.05	-	-