Supplemental Information

Severe impairment of T-cell responses to BNT162b2 immunization in multiple myeloma patients

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Content:

Supplemental material & methods

Study design and participants

To study the response to SARS-CoV-2 vaccination in patients, we performed a longitudinal observational study on 108 patients with MM that were treated at the Hematology Department of the University Hospital Frankfurt, Germany, between September 15th, 2020, and June 30th, 2021, and were eligible for SARS-CoV-2 vaccination. Regarding the timing of SARS-CoV-2 vaccination, we implemented the recommendations previously published by the International Myeloma Society (IMS) (https://myelomasociety.org/wp-content/uploads/2021/03/PM-COVID-vaccination-in-MM-guidelines-The-Final.pdf). To compare and rank the results to general population, we included 30 age-matching healthy individuals. At the timepoint of this interim analysis, we report on 77 MM patients and 24 healthy controls that have received two applications of the SARS-CoV-2 vaccine (BNT162b2, BioNTec-Pfizer) according to the recommendation of the federal health authorities. All patients and healthy controls declared written informed consent. This study was approved by the local ethics committee Frankfurt, Germany (Ethics vote number: UCT-5-2021).

Sample and clinical data acquisition

All patients and healthy controls received two doses of 30 µg BNT162b2 mRNA-based SARS-CoV-2 vaccine. During the conduction of this study, federal health authorities updated the recommendation on the timepoint of the second BNT162b2 dose from 3 to 6 weeks after the initial dose.[1] Therefore, 35 patients displayed a timespan of around 21 days between both doses and 42 patients received their second vaccination dose with a delay of up to 6 weeks after the initial dose. In the healthy control group, 12 controls received the second vaccination dose around 21 days after the initial vaccination and 12 controls had a timespan up to 42 days (**Fig. S3**).

Basic disease and clinical characteristics of the patients were retrieved from the electronical health care record system at our institution. Regular outpatient clinic visits as well as systematic adverse event documentation by a questionnaire were carried out to monitor possible reactogenicity and safety concerns. For grading, Common Terminology Criteria for Adverse Events (CTC AE) v5.0 were used. If any potential symptoms of an infection by SARS-CoV-2 were present, nasopharyngeal swab test were obtained to perform real-time RT PCR analysis. The primary endpoint of this study was achievement of a WT neutralising titer of ≥1:20 after 2 doses of the BNT162b2 vaccine in multiple myeloma patients. Secondary endpoints were seroconversion to the SARS-CoV-2 specific S protein after one and two vaccine doses, neutralization of the most prevalent alpha variant B.1.1.7 after two doses, T-cellular response and immune cell status at the beginning of and after the vaccination regimen.

Sample preparation

Patients' whole blood was collected in Lithium Heparin tubes (Sarstedt, Germany) and serum tubes (Sarstedt, Germany). Peripheral blood mononuclear cells (PBMCs) were isolated from the heparinized blood by Pancoll (PAN-Biotech, Aidenbach, Germany) density gradient centrifugation, washed in sterile PBS (Gibco, Thermo Fisher Scientific, Waltham, USA) counted and cryopreserved in RPMI1640 (Gibco, Thermo Fisher Scientific, Waltham, USA) + 10% DMSO (Sigma-Aldrich, St. Louis, USA) + 10%FBS (Gibco, Thermo Fisher Scientific, Waltham, USA) using controlled temperature decrease in a Mr. Frosty (Nalgene, Rochester, USA) to -80°C. Frozen PBMCs were stored in liquid nitrogen until further use.

For serum isolation, the serum tubes were centrifuged at 1000g for 10 min with break off at room temperature. Afterwards, the serum was transferred to microreaction tubes in aliquots á 1mL and stored at -80°C until further use.

Immune monitoring analysis

EDTA blood samples were evaluated concerning the distribution and activation status of immune subpopulations. Immune cell subtypes were quantified via Sysmex and flow cytometry from patients' whole blood. Absolute cell counts of leukocytes, lymphocytes, neutrophils, monocytes and thrombocytes were derived by Sysmex analysis. Patients' whole blood were analyzed with the BD Multitest™ 6-color TBNK and the BD Multitest™ CD8/CD38/CD3/HLA-DR staining kits (both BD Biosciences, Germany) according to the manufacturer´s protocols. The percentage of lymphocytes, CD4+ T-cells, CD8+ T-cells, CD19+ B-cells, CD56+ CD16+ NK-cells and activated T-cells (CD8+CD38+ and CD3+HLA-DR+ T-cells) were determined using the FACS Canto II flow cytometer and the FACS Canto software (BD Biosciences, Germany). Absolute cell counts of immune cell subtypes were calculated based on the lymphocyte count by the Sysmex analysis.

T-cell response measurement by IFN-γ ELISpot

For measurement of the SARS-CoV-2 specific T-cellular response, cryopreserved PBMCs were thawed one day prior to seeding and rested in RPMI 1640 + Glutamax + 10% FBS over night at a cell concentration of 5mio PBMCs/mL medium. The IFN-γ ELISpot (Mabtech, Nacka Strand, Sweden) was performed in filterplates (MSIPS4510, Merck Millipore, Burlington, USA) according to the manufacturer's recommendations. Briefly, $3x10^5$ PBMCs per well were stimulated with either CEF/CEFT peptides (0.25µg/mL per peptide, CEF Pool extended, CEFT MHC-II pool; JPT, Berlin, Germany), SARS-CoV-2 Spike-Protein receptor binding domain (RBD) peptides (0.25µg/mL per peptide; JPT, Berlin, Germany), or SARS-CoV-2 Spike-Protein unit 2 (S2) peptides (0.25µg/mL per peptide; JPT, Berlin, Germany) in 100µL X-Vivo-10 medium (Lonza, Basel, Switzerland) per well for 22 hours. For the negative control, DMSO (Sigma-Aldrich, St.

Louis, USA) was added in the same concentration as present in the wells supplemented with peptides. Each condition was measured in duplicates. Samples with a viability <85% at timepoint of seeding were not included in the final analysis as sample quality was considered as insufficient. For normalization, the negative control was used for individual samples. Cut-off of the ELISpot was analyzed by ROC analysis of 26 positive (TP3) and 18 negative (TP1) samples of healthy individuals, analyzed for RBD or S2 specific IFN- γ responses.

T-cell response measurement by Flow cytometry

For measurement of the SARS-CoV-2 specific T-cellular response, 500 µl heparinized blood was incubated overnight under standard conditions in the presence of no activator (negative control), cytostim (a TCT-MHC-cross-linking reagent, positive control) or S1 peptide library (all reagents Miltenyi, Bergisch Gladbach, Germany) and Brefeldin A according to the manufacturer's suggestions except that half the recommended amount of negative control, positive control and peptide library were used. 15-16 hours later, samples were subjected to hypotonic lysis of RBCs, leukocytes were fixed-permeabilized and stained for CD14/CD3/CD4/CD8/IFN-γ/TNF-α/IL-2 and subsequently analyzed by flow cytometry (LSR Fortessa, BD, with Diva software). Gates were set according to negative controls. Data based on origin populations with less than 10.000 counts or data sets with unconclusive results for negative or cytostim control were not included into the final data analysis.

SARS-CoV-2 IgG measurement

To exclude natural SARS-CoV-2 infection of included individuals, samples taken at TP1 were analyzed for anti-SARS-CoV-2 Nucleocapsid (N)-protein IgG (SARS-CoV-2-IgG, chemiluminescent microparticle immunoassay (CMIA), Abbott). Samples taken at TP2 and TP3 were analyzed for SARS-CoV-2 Spike IgG (Abbott SARS-CoV-2 IgG II Quant CMIA,) by the

automated Abbott Alinity i platform (Abbott GmbH, Wiesbaden, Germany) according to the manufacturer's recommendation for quantification of vaccine-induced SARS-CoV-2 specific antibodies.

Plaque reduction neutralization test (PRNT)

For a neutralizing capacity test of SARS-CoV-2 specific antibodies, Caco-2 cells (human colon carcinoma cells, ATCC DSMZ ACC-169 (American Type Culture Collection, Manassas, Virginia, USA)) were seeded on a 96-well plate 3-5 days prior infection. 2-fold dilutions series of the test sera (1:10; 1:20; 1:40; 1:80; 1:160; 1:320; 1:640 and 1:1280) were made in culture medium (Minimum essential medium, MEM; Sigma-Aldrich, St. Louis, USA) before mixed 1:1 with 100 $TCID_{50}$ (Tissue culture infectious dosis 50) of reference virus (SARS-CoV-2 B.1.1.7. isolate [B.1.1.7], SARS-CoV-2 FFM1 isolate [wild, type, WT]). The test was performed as described earlier.[2-4]

Statistical analysis

For statistical analysis, R version 4.1.0 was used (R Core Team, 2021) and GraphPad Prism version 9.0.2. (GraphPad Software, San Diego, California USA).[5] Continuous variables were compared with the Mann-Whitney-U test for two independent groups and Kruskal-Wallis test for three or more independent groups, categorical variables with the Fisher's exact test and the chi-square test. P-values were adjusted by the Benjamini-Hochberg method for multiple testing. For differences in flow cytometric immune cell status, 2-way ANOVA and Šídák's multiple comparisons test was performed. Logistic regression was calculated for multivariate analysis. For logarithmic graphical visualisation, continuous variables were transformed by addition of 1 to each value.

References to supplemental material & methods

1. Rößler M JJ, Risch L, Tesch F, Enders D, Wende D, Jucknewitz R, Weidinger O, Batram M, Ballesteros P, Baßler S, Hertle D, Repschläger U, Richter N, Schulte C, Schramm A, Sobik F, Treskova-Schwarzbach M, Scholz S, Schmitt J, Walker Hierarchisierung von Risikofaktoren für schwere COVID-19-Erkrankungs-verläufe im Kontext der COVID-19-Schutzimpfungen – Eine gepoolte GKV-Routinedatenanalyse basierend auf 30 Mio. Versicherten. *Epid Bull* 2021(19):3-12.
2. Kohmer N, Ruhl C, Ciesek S, Rabenau HF. Utility of Different Surrogate Enzyme-Linked Immunosorbent Assays (sELISAs) for Detection of SARS-CoV-2 Neutralizing Antibodies. *J Clin Med.* 2021;10(10).
3. Kohmer N, Westhaus S, Ruhl C, Ciesek S, Rabenau HF. Brief clinical evaluation of six high-throughput SARS-CoV-2 IgG antibody assays. *J Clin Virol.* 2020;129:104480.
4. Widera M, Wilhelm A, Hoehl S, et al. Limited neutralization of authentic SARS-CoV-2 variants carrying E484K in vitro. *J Infect Dis.* 2021.
5. *R: A Language and Environment for Statistical Computing* [computer program]. Version 4.1.02020.

Supplementary tables

Supplementary Table S1. Patients characteristics

	All	Non-Responder	Responder	p-value
Number	77	36	41	
Female sex, n (%)	35 (45.5)	15 (41.7)	20 (48.8)	0.692
Age, median [IQR]	67.00 [60.00, 72.00]	70.00 [63.75, 73.00]	64.00 [57.00, 71.00]	0.028
MM Type, n (%)				0.843
IgG	37 (48.1)	16 (44.4)	21 (51.2)	
IgA	19 (24.7)	9 (25.0)	10 (24.4)	
light chain	16 (20.8)	8 (22.2)	8 (19.5)	
Non-secretoric	1 (1.3)	1 (2.8)	0 (0.0)	
smoldering MM	4 (5.2)	2 (5.6)	2 (4.9)	
ISS, n (%)				0.887
1	31 (40.3)	15 (41.7)	16 (39.0)	
2	19 (24.7)	8 (22.2)	11 (26.8)	
3	17 (22.1)	9 (25.0)	8 (19.5)	
NA	10 (13.0)	4 (11.1)	6 (14.6)	
Revised ISS, n (%)				0.944
1	23 (29.9)	10 (27.8)	13 (31.7)	
2	28 (36.4)	13 (36.1)	15 (36.6)	
3	9 (11.7)	4 (11.1)	5 (12.2)	
NA	17 (22.1)	9 (25.0)	8 (19.5)	
High-risk, n (%)				0.169
no	45 (58.4)	17 (47.2)	28 (68.3)	
yes	18 (23.4)	11 (30.6)	7 (17.1)	
NA	14 (18.2)	8 (22.2)	6 (14.6)	
Remission status, n (%)				0.528
CR	30 (39.0)	10 (27.8)	20 (48.8)	
VGPR	17 (22.1)	10 (27.8)	7 (17.1)	
PR	9 (11.7)	4 (11.1)	5 (12.2)	
SD	5 (6.5)	3 (8.3)	2 (4.9)	
PD	14 (18.2)	8 (22.2)	6 (14.6)	

NA	2 (2.6)	1 (2.8)	1 (2.4)	
Previous SARS-CoV-2 infection, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1
SARS-CoV-2 infection after vacc., n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1
BNT162b2 vaccine, n (%)	77 (100.0)	36 (100.0)	41 (100.0)	1

CR, complete remission; HDCT, high dose chemotherapy; IQR, interquartile range; ISS, international severity score; MM, multiple myeloma; NA, not annotated; PD, progressive disease; PR, partial remission; SD, stable disease; VGPR, very good partial remission;

Supplemental Table S2:
Healthy control characteristics

	Healthy controls
Number	24
Female sex, n (%)	11 (45.8)
Age, median [IQR]	66.00 [50.25, 77.50]
Previous SARS-CoV-2 infection, n (%)	0 (0.0)
SARS-CoV-2 infection after vacc., n (%)	0 (0.0)
BNT162b2 vaccine, n (%)	24 (100.0)

IQR, interquartile range

Supplementary Table S3. Serologic response

	All	Healthy controls	MM patients	p-value
Number	101	24	77	
TP2 SARS-CoV-2 IgG AB (BAU/ml) for n=97, median [IQR]	2.07 [0.00, 52.67]	101.12 [21.93, 216.84]	0.00 [0.00, 19.90]	<0.001
TP3 SARS-CoV-2 IgG AB (BAU/ml), median [IQR]	421.90 [52.10, 1609.46]	1520.30 [677.58, 3124.50]	191.40 [29.80, 756.70]	<0.001
TP3 SARS-CoV-2 IgG AB < 143.5 BAU/ml, n (%)	34 (33.7)	0 (0.0)	34 (44.2)	<0.001
No SARS-CoV-2 IgG AB, n (%)	6 (5.9)	0 (0.0)	6 (7.8)	0.36
TP3 WT Neutralisation Titer, median [IQR]	20.00 [0.00, 80.00]	80.00 [35.00, 160.00]	20.00 [0.00, 80.00]	<0.001
WT Neutralisation Titer				
< 1:20, n (%)	36 (35.6)	0 (0.0)	36 (46.8)	<0.001
No WT Neutralisation Titer	31 (30.7)	0 (0.0)	31 (40.3)	0.001
TP3 B.1.1.7 Neutralisation Titer for n=69, median [IQR]	20.00 [0.00, 80.00]	40.00 [20.00, 80.00]	10.00 [0.00, 40.00]	0.02
B.1.1.7 Neutralisation Titer				
< 1:20 for n=69, n (%)	33 (47.8)	2 (14.3)	31 (56.4)	0.012
No B.1.1.7 Neutralisation Titer for n=69, n (%)	26 (37.7)	0 (0.0)	26 (47.3)	0.003

AB, antibody; BAU, binding antibody units; IQR, interquartile range; TP2, timepoint 2; TP3, timepoint 3; WT, wildtype

Supplementary Table S4. T-cell response

	All	Healthy controls	MM patients	p-value
Number	52	14	38	
RBD SFU per 3x10E5 cells, median [IQR]	34.75 [8.12, 96.00]	86.50 [37.00, 130.25]	27.75 [5.62, 62.50]	0.019
S2 SFU per 3x10E5 cells, median [IQR]	16.00 [0.00, 49.50]	25.25 [2.88, 62.75]	15.25 [0.00, 46.25]	0.544
CEF/CEFT SFU per 3x10E5 cells, median [IQR]	144.25 [62.50, 661.62]	144.25 [60.88, 465.50]	153.75 [66.62, 729.88]	0.470
T-cell responder, n (%)	23 (44.2)	10 (71.4)	13 (34.2)	0.037

CEF, cytomegalia-, Epstein Barr-, influenza-virus; CEFT, cytomegalia, Epstein Barr-, influenza-, tetatanus-virus; IQR, interquartile range; MM, multiple myeloma; RBD, receptor binding domain; S2, Spike protein subunit 2

Supplementary Table S5. Impact of therapy-associated factors on response levels

Serological response

	All	Non-Responder	Responder	
Number	77	36	41	
Current line of therapy, n (%)				0.620
no	5 (6.5)	2 (5.6)	3 (7.3)	
1	48 (62.3)	24 (66.7)	24 (58.5)	
2	10 (13.0)	3 (8.3)	7 (17.1)	
3	8 (10.4)	3 (8.3)	5 (12.2)	
4	3 (3.9)	2 (5.6)	1 (2.4)	
5	1 (1.3)	1 (2.8)	0 (0.0)	
7	1 (1.3)	1 (2.8)	0 (0.0)	
9	1 (1.3)	0 (0.0)	1 (2.4)	
HDCT, n (%)				0.080
no	28 (36.4)	18 (50.0)	10 (24.4)	
1	28 (36.4)	12 (33.3)	16 (39.0)	
2	20 (26.0)	6 (16.7)	14 (34.1)	
3	1 (1.3)	0 (0.0)	1 (2.4)	
Months since HDCT, median [IQR]	22.00 [8.00, 46.00]	20.50 [7.25, 45.50]	29.00 [9.00, 44.50]	0.701
Status of therapy, n (%)				0.011
no	28 (36.4)	8 (22.2)	20 (48.8)	
under therapy	26 (33.8)	18 (50.0)	8 (19.5)	
under maintenance	23 (29.9)	10 (27.8)	13 (31.7)	
Current imid-based, n (%)	42 (54.5)	25 (69.4)	17 (41.5)	0.026
Current PI-based, n (%)	11 (14.3)	8 (22.2)	3 (7.3)	0.124
Current anti-CD38-based, n (%)	14 (18.2)	9 (25.0)	5 (12.2)	0.247
Type of maintenance for n=23, n (%)				0.398
Lenalidomide + Isatuximab	4 (17.4)	3 (30.0)	1 (7.7)	
Lenalidomide	19 (82.6)	7 (70.0)	12 (92.3)	

T-cell response

Number	38	25	13	
Current line of therapy, n (%)				0.534
no	2 (5.3)	2 (8.0)	0 (0.0)	
1	28 (73.7)	17 (68.0)	11 (84.6)	
2	3 (7.9)	3 (12.0)	0 (0.0)	
3	3 (7.9)	2 (8.0)	1 (7.7)	
4	2 (5.3)	1 (4.0)	1 (7.7)	
HDCT, n (%)				0.643
No	14 (36.8)	10 (40.0)	4 (30.8)	
1	13 (34.2)	9 (36.0)	4 (30.8)	
2	11 (28.9)	6 (24.0)	5 (38.5)	
Months since HDCT, median [IQR]	18.50 [7.00, 40.25]	18.00 [8.00, 39.00]	19.00 [4.00, 43.00]	0.787
Status of therapy, n (%)				0.835
no	14 (36.8)	10 (40.0)	4 (30.8)	
under therapy	10 (26.3)	6 (24.0)	4 (30.8)	
under maintenance	14 (36.8)	9 (36.0)	5 (38.5)	
Current imid-based, n (%)	21 (55.3)	13 (52.0)	8 (61.5)	0.828
Current PI-based, n (%)	4 (10.5)	3 (12.0)	1 (7.7)	1.000
Current anti-CD38-based, n (%)	6 (15.8)	4 (16.0)	2 (15.4)	1.000
Type of maintenance for n=14, n (%)				0.321
Lenalidomide + Isatuximab	2 (14.3)	2 (33.3)	0 (0.0)	
Lenalidomide	12 (85.7)	4 (66.7)	8 (100.0)	

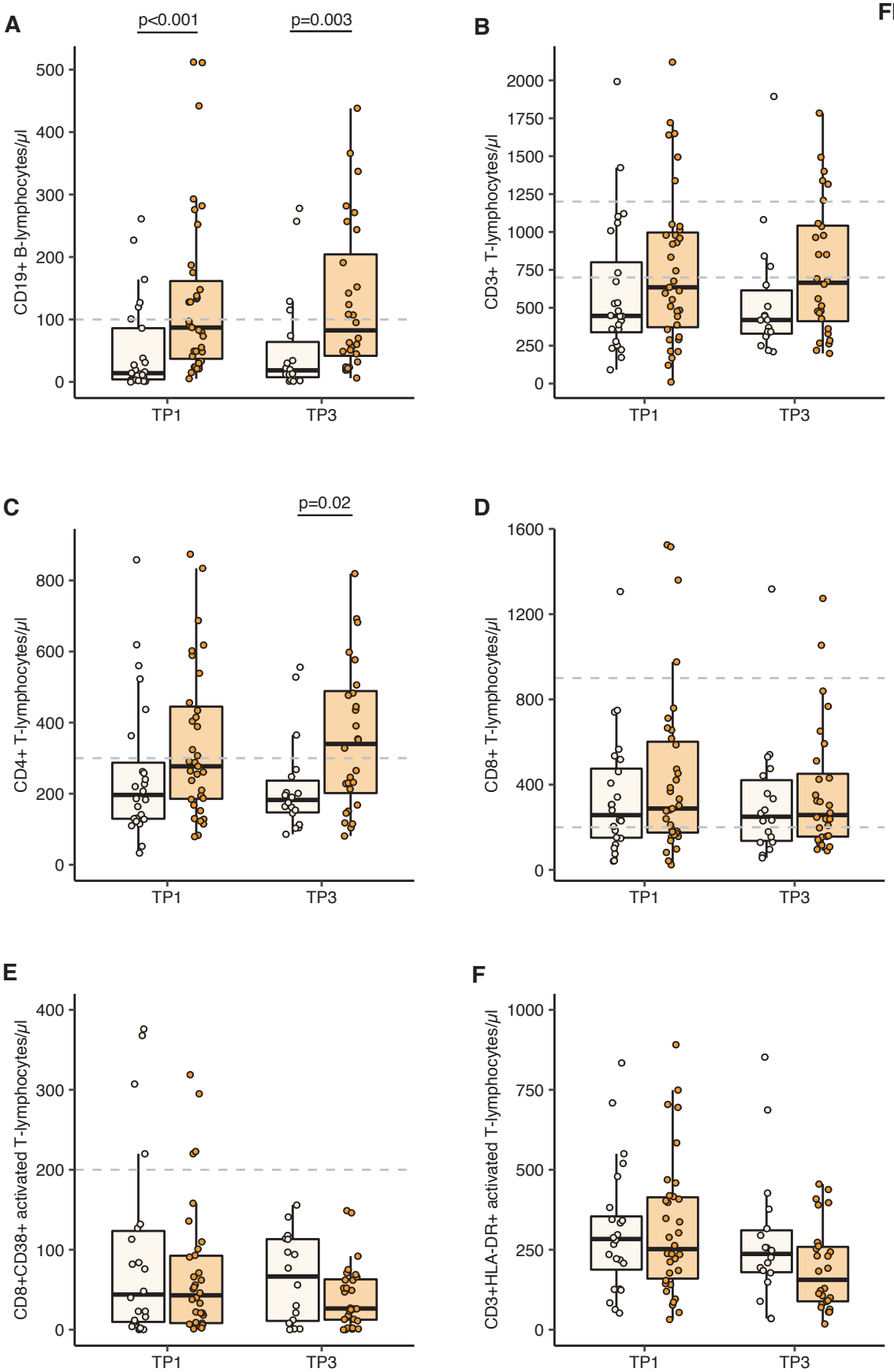
HDCT, high-dose chemotherapy; IQR, interquartile range; PI, proteasome inhibitor

Legends to supplemental figures

Supplementary Figure S1. Immune cell status before and after two doses of SARS-CoV-2 vaccination in MM patients. Comparison of CD19+ B-lymphocytes/µl (A), CD3+ T-lymphocytes (B), CD4+ T-lymphocytes/µl (C), CD8+ T-lymphocytes/µl (D), CD8+CD38+ activated T-lymphocytes/µl (E), CD3+HLA-DR+ activated T-lymphocytes/µl (F) stratified for non-responders (light orange) and serological responders (dark orange) at timepoint 1 (TP 1, before vaccination) and TP3 (~28 days after boost vaccination). Only differences with $p<0.05$ are indicated with the respective p-values. Dashed lines represent the normal range limits, where applicable.

Supplementary Figure S2. Bivariate representation and correlation analysis of serological and T-cellular responses. Bivariate representation of SARS-CoV-2 (Spike) IgG levels (A), WT and B.1.1.7 neutralization with either RBD (A-C) or S2 (D-F) specific SFU per 3 x 10^5 PBMCs in MM patients measured by IFN-γ ELISpot. Spearman correlation matrix for levels of serologic response and T-cell response (G). The color axis corresponds to the Spearman correlation coefficient for each correlation. P-values are reported as * <0.05, ** <0.01, *** <0.001. Increase in SARS-CoV-2 specific CD3+ T-cells expressing the respective cytokine marker after peptide stimulation dichotomized for healthy controls (grey) and MM patients (orange) (H). Percentage of CD4+ or CD8+ subset for respective cytokine positive CD3+ T-cells dichotomized for healthy controls (grey) and MM patients (orange) (I-N) Due to the limited number of cases, no statistical significance evaluation was applied. Gating strategy for T-cell subset and cytokine marker analysis after SARS-CoV-2 peptide stimulation (O,P).

Supplementary Figure S3. Adherence to sample acquisition. The graph indicates the days previous to initial SARS-CoV-2 vaccination (TP1), before the second (boost) vaccination (TP2) and after boost vaccination (TP3).


A
p<0.001
p=0.003
CD19+ B-lymphocytes/µl
0
100
200
300
400
500
TP1
TP3
B
CD3+ T-lymphocytes/µl
0
250
500
750
1000
1250
1500
1750
2000
TP1
TP3
C
p=0.02
CD4+ T-lymphocytes/µl
0
200
400
600
800
TP1
TP3
D
CD8+ T-lymphocytes/µl
0
400
800
1200
1600
TP1
TP3
E
CD8+CD38+ activated T-lymphocytes/µl
0
100
200
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F
CD3+HLA-DR+ activated T-lymphocytes/µl
0
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500
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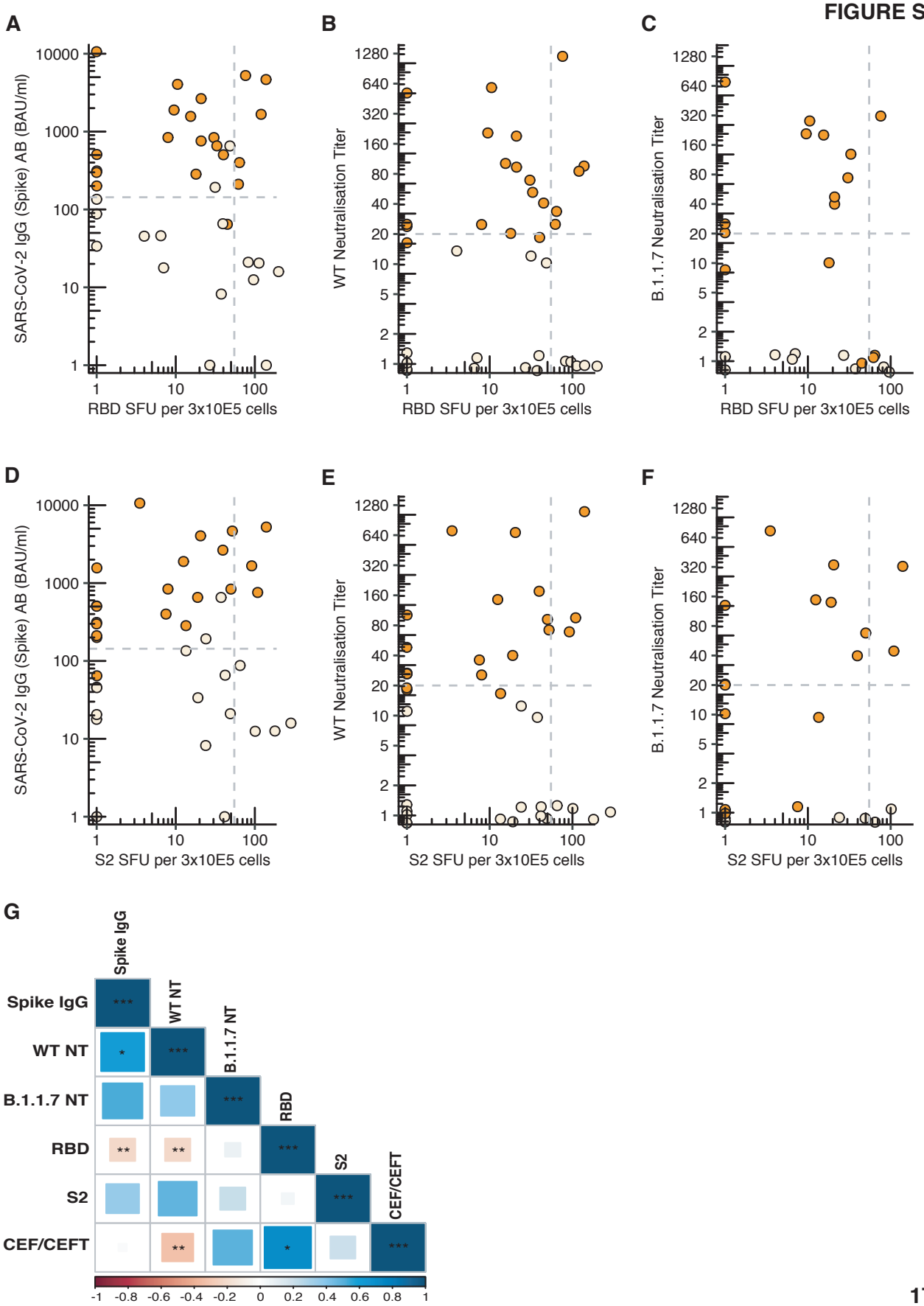
1000
TP1
TP3


A
SARS-CoV-2 IgG (Spike) AB (BAU/ml)
RBD SFU per 3x10E5 cells
B
WT Neutralisation Titer
RBD SFU per 3x10E5 cells
C
B.1.1.7 Neutralisation Titer
RBD SFU per 3x10E5 cells
D
SARS-CoV-2 IgG (Spike) AB (BAU/ml)
S2 SFU per 3x10E5 cells
E
WT Neutralisation Titer
S2 SFU per 3x10E5 cells
F
B.1.1.7 Neutralisation Titer
S2 SFU per 3x10E5 cells
G
Spike IgG
WT NT
B.1.1.7 NT
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CEF/CEFT
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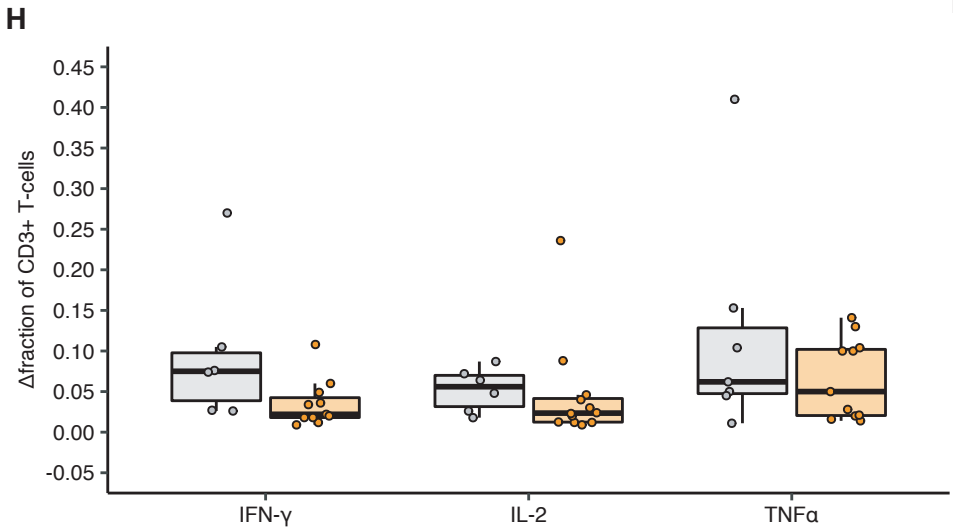
H
Δfraction of CD3+ T-cells
0.45
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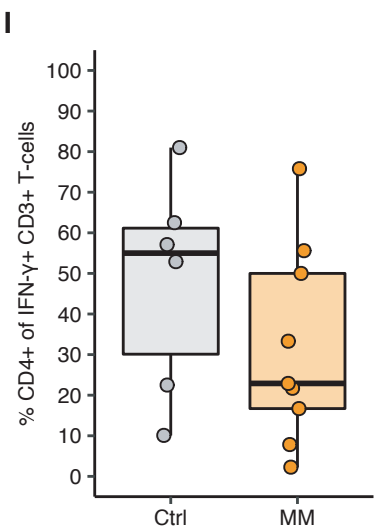
IFN-γ
IL-2
TNFα


I
% CD4+ of IFN-γ+ CD3+ T-cells
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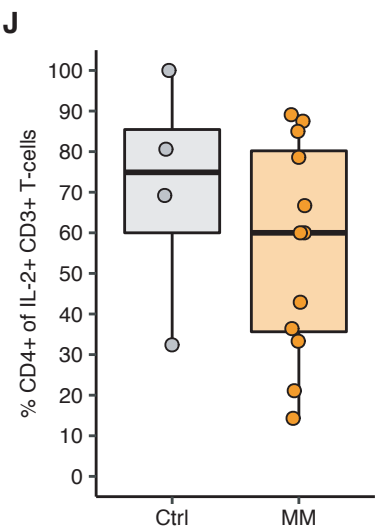
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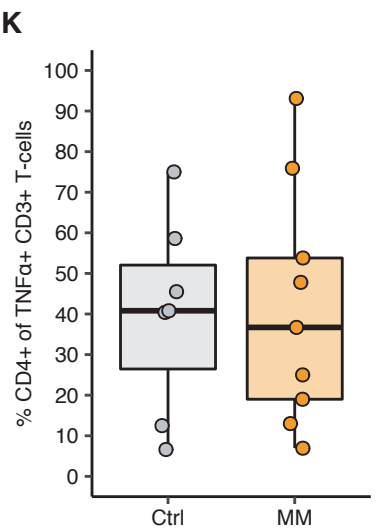
K
% CD4+ of TNFα+ CD3+ T-cells
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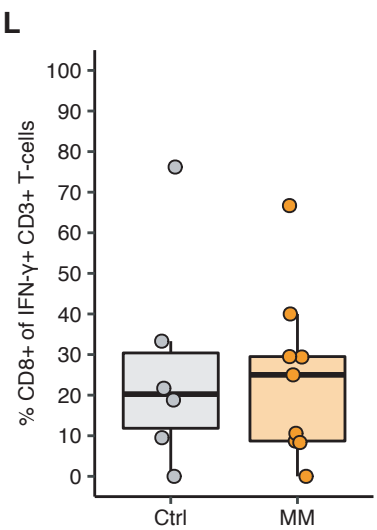
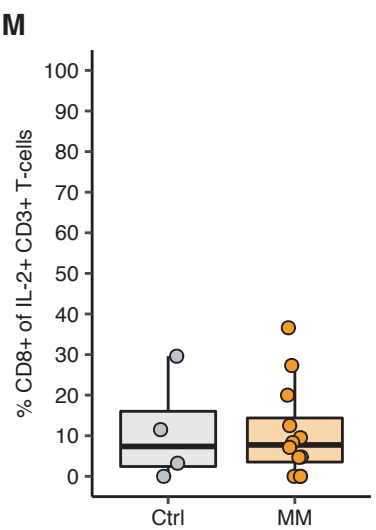
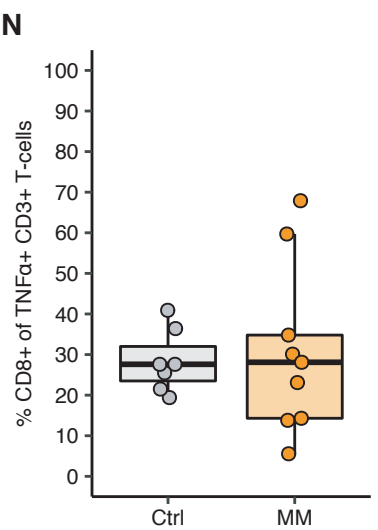
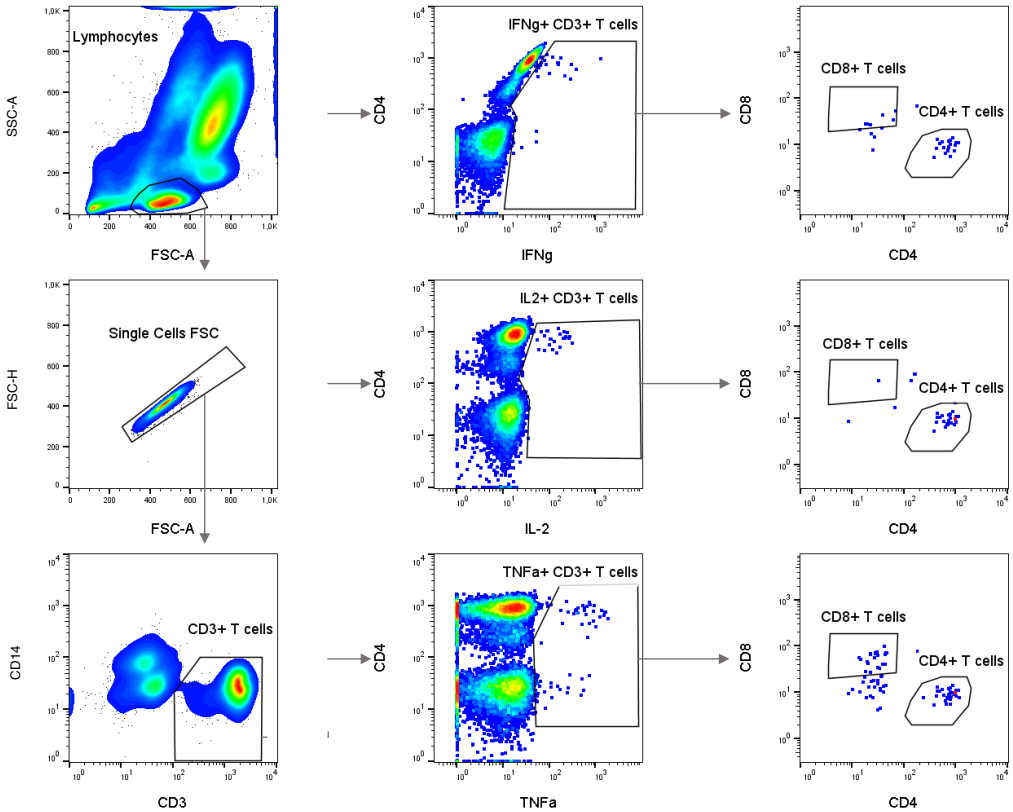
30
20
10
0
Ctrl
MM


L
% CD8+ of IFN-γ+ CD3+ T-cells
100
90
80
70
60
50
40
30
20
10
0
Ctrl
MM

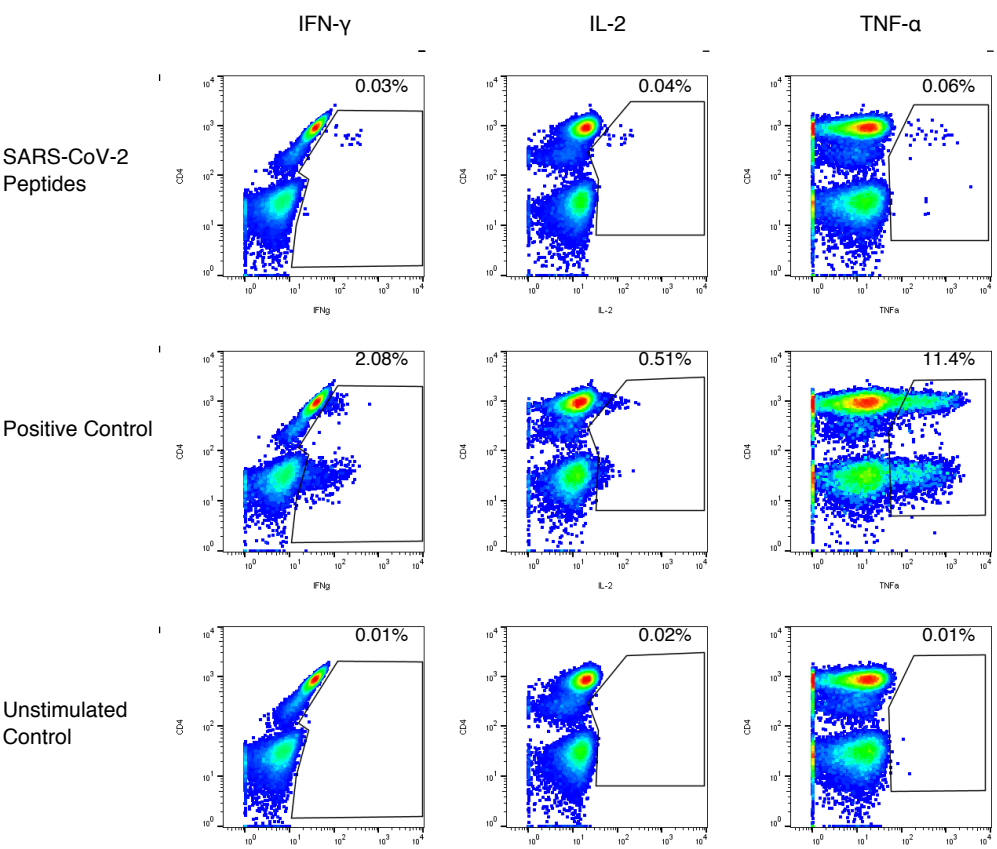

M
% CD8+ of IL-2+ CD3+ T-cells
100
90
80
70
60
50
40
30
20
10
0
Ctrl
MM

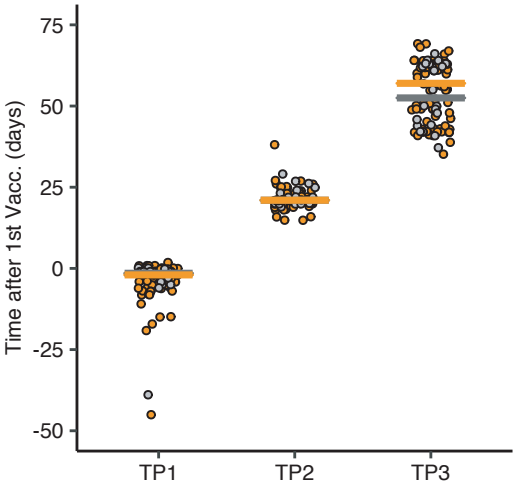

N
% CD8+ of TNFα+ CD3+ T-cells
100
90
80
70
60
50
40
30
20
10
0
Ctrl
MM

O


Lymphocytes
SSC-A
FSC-A
IFNg+ CD3+ T cells
CD4
IFNg
CD8+ T cells
CD4+ T cells
CD8
CD4
Single Cells FSC
FSC-H
FSC-A
IL2+ CD3+ T cells
CD4
IL-2
CD8+ T cells
CD4+ T cells
CD8
CD4
CD3+ T cells
CD14
CD3
TNFa+ CD3+ T cells
CD4
TNFa
CD8+ T cells
CD4+ T cells
CD8
CD4

P


IFN-γ
IL-2
TNF-α
SARS-CoV-2 Peptides
0.03%
0.04%
0.06%
Positive Control
2.08%
0.51%
11.4%
Unstimulated Control
0.01%
0.02%
0.01%
CD4
IFNg
IL-2
TNFa


Time after 1st Vacc. (days)
75
50
25
0
-25
-50
TP1
TP2
TP3