Supplementary Material:

Supplementary Tables 1 A-D: *Treatment regimens of IBD patients*

Patient ID, diagnosis, date of diagnosis, years since diagnosis, primary (1) medication with dose, dosing interval, form of application, and drug levels in µg/ml; furthermore, second (2) medication with dose and schedule are provided in Table A) for patients with anti-TNF-α treatment and B) patients receiving integrin-antagonists. Phase of treatment and clinical disease activity, as well as levels of CRP and fCP prior to 1st and 2nd dose are provided in Table C) for patients with anti-TNF-α treatment and D) patients receiving integrin-antagonists.

Abbreviations: ADA, adalimumab; admin, administration; AZA, azathioprine; CD, Crohn's disease; CRP, C-reactive protein; fCP, fecal Calprotectin; IBD, inflammatory bowel disease; IFX, infliximab; i.v., intra-venous; s.c., sub-cutaneous; UC, ulcerative colitis; VED, vedolizumab; y, year.

A)

Patient ID	Diagnosis	Date of Diagnosis	Years since diagnosis	Medication (1)	Dose (1)	Interval (1)	Application (1)	Drug levels (1) µg/ml	Medication (2)	Dose (2)	Schedule (2)	
1	CD	2017	4	ADA	40mg	every 10 days	s.c.	7.9				
2	CD	2001	20	ADA	40mg	every 7 days	s.c.					
3	CD	2002	19	ADA + AZA	40mg	every 10 days	s.c.	9..7	AZA	50mg	0-0-4	daily
4	CD	2014	7	ADA	40mg	every 2 weeks	s.c.					
5	UC	2014	7	ADA	40mg	every 2 weeks	s.c.	9.3				
6	UC	2013	8	ADA + AZA	40mg	every 7 days	s.c.	4.8	AZA	50mg	2-0-0	daily
7	CD	2020	1	ADA	40mg	every 7 days	s.c.	9.5				
8	CD	2009	12	ADA + AZA	40mg	every 2 weeks	s.c.		AZA	50mg	4-0-0/5-0-0	daily
9	UC	2018	3	ADA	40mg	every 7 days	s.c.					
10	CD	2016	5	ADA	40mg	every week	s.c.	< 0.3				
11	CD	2017	4	IFX	400mg	every 7 weeks	i.v.	>16				
12	CD	1997	24	IFX	500mg	every 5 weeks	i.v.	4.8				
13	UC	1988	33	IFX	400mg	every 7 weeks	i.v.	> 16				
14	UC	1999	22	IFX	500mg	every 7 weeks	i.v.					
15	UC	1992	29	IFX	700mg	every 8 weeks	i.v.	11.4				
16	UC	2007	14	IFX	800mg	every 7 weeks	i.v.	> 16				
17	CD	2000	21	IFX	500mg	every 6 weeks	i.v.	7.1				
18	CD	2008	13	ADA	40mg	every 2 weeks	s.c.	9.6				
19	CD	1987	34	IFX	400mg	every 5 weeks	i.v.	7.5				

B)

Patient ID	Diagnosis	Date of Diagnosis	years since diagnosis	Medication (1)	Dose (1)	Interval (1)	application (1)	Drug levels (1) µg/ml	Medication (2)	Dose (2)	schedule (2)	
1	CD	2017	4	VED	300mg	every 8 weeks	i.v.					
2	UC	2010	11	VED	300mg	every 6 weeks	i.v.					
3	CD	2013	8	VED	300mg	every 4 weeks	i.v.					
4	UC	1979	42	VED	300mg	every 8 weeks	i.v.	6.4				
5	UC	2007	14	VED	300mg	every 8 weeks	i.v.					
6	UC	1996	25	VED	300mg	every 7 weeks	i.v.					
7	UC	2016	5	VED	300mg	every 4 weeks	i.v.					
8	UC	2020	1	VED	300mg	every 8 weeks	i.v.	23.6				
9	UC	2017	4	VED	108mg	every 2 weeks	s.c.	34.9				
10	CD	1994	27	VED	300mg	every 6 weeks	i.v.	94.9				
11	UC	2020	1	VED	300mg	every 8 weeks	i.v.					
12	UC	2019	2	VED	300mg	every 4 weeks	s.c.	38.8				
13	CD	1982	39	VED	300mg	every 4 weeks	i.v.	23.5				
14	CD	2009	12	VED	108mg	every 2 weeks	s.c.	10.2				
15	UC	2017	4	VED	300mg	every 8 weeks	i.v.	5.2				
16	UC	2013	8	VED + steroid	300mg	every 4 weeks	i.v.	15.3	Prednisolon	10mg	1-0-0	daily
17	CD	2013	8	VED	300mg	every 6 weeks	i.v.	12.7				

C)

Patient ID	Phase of treatment with **anti TNF-α**	Clinical activity	CRP_1st vacc (mg/dl)	CRP_2nd vacc (mg/dl)	fCP_1st vacc (µg/g)	fCP_2nd vacc (µg/g)	COVID 19 exposure
1	stable dose ≥3 months	clinical remission/mild active	0.11	0.46	21	38	no
2	stable dose ≥3 months	clinical remission/mild active					no
3	stable dose ≥3 months	clinical remission/mild active	0.17	0.16	120	124	no
4	stable dose ≥3 months	clinical remission/mild active	0.07	0.05	58	29	no
5	stable dose ≥3 months	clinical remission/mild active	< 0.03	< 0.03		30	no
6	stable dose ≥3 months	clinical remission/mild active	0.37	0.34	895	230	no
7	stable dose ≥3 months	clinical remission/mild active	0.06	0.63	307	481	no
8	during induction	clinical remission/mild active	0.05	< 0.03		56	no
9	during induction	moderate active	0.04	0.11	291	355	no
10	within 3 mo after induction or dose escalation	moderate active	1.55	2.50	344	1256	no
11	stable dose ≥3 months	clinical remission/mild active	0.78	2.06	0	71	no
12	stable dose ≥3 months	clinical remission/mild active	0.27	0.13	190	110	no
13	stable dose ≥3 months	clinical remission/mild active	< 0.03	< 0.03	36	35	no
14	stable dose ≥3 months	clinical remission/mild active					no
15	during induction	clinical remission/mild active	0.14	0.10	404	475	no
16	stable dose ≥3 months	clinical remission/mild active	0.07		126		no
17	stable dose ≥3 months	clinical remission/mild active	0.41		1051		no
18	stable dose ≥3 months	clinical remission/mild active	2.32	< 0.03	80	56	no
19	stable dose ≥3 months	clinical remission/mild active	0.50		25		no

D)

Patient ID	Phase of treatment with **integrin-antagonists**	Clinical activity	CRP_1st vacc (mg/dl)	CRP_2nd vacc (mg/dl)	fCP_1st vacc (µg/g)	fCP_2nd vacc (µg/g)	COVID 19 exposure
1	stable dose ≥3 months	clinical remission/mild active		< 0.03		9	no
2	stable dose ≥3 months	clinical remission/mild active					no
3	stable dose ≥3 months	clinical remission/mild active		0.16		160	no
4	stable dose ≥3 months	clinical remission/mild active	0.19	0.31	166	144	no
5	stable dose ≥3 months	clinical remission/mild active	0.17	0.16		18	no
6	stable dose ≥3 months	clinical remission/mild active					no
7	stable dose ≥3 months	clinical remission/mild active					no
8	stable dose ≥3 months	clinical remission/mild active	0.07	< 0.03	0	0	no
9	stable dose ≥3 months	clinical remission/mild active	0.07	0.05	17	146	no
10	stable dose ≥3 months	clinical remission/mild active	0.32	0.15	60	311	no
11	within 3 mo after induction or dose escalation	clinical remission/mild active	0.47	0.44	3344	2350	no
12	stable dose ≥3 months	clinical remission/mild active	0.13	0.14	102	1688	no
13	stable dose ≥3 months	clinical remission/mild active	0.78	0.70		1699	no
14	stable dose ≥3 months	clinical remission/mild active	0.94	1.21		685	no
15	within 3 mo after induction or dose escalation	clinical remission/mild active	0.61		354	600	no
16	within 3 mo after induction or dose escalation	clinical remission/mild active	1.61	1.28	1129	3062	no
17	stable dose ≥3 months	clinical remission/mild active	0.19	0.18	0	0	no

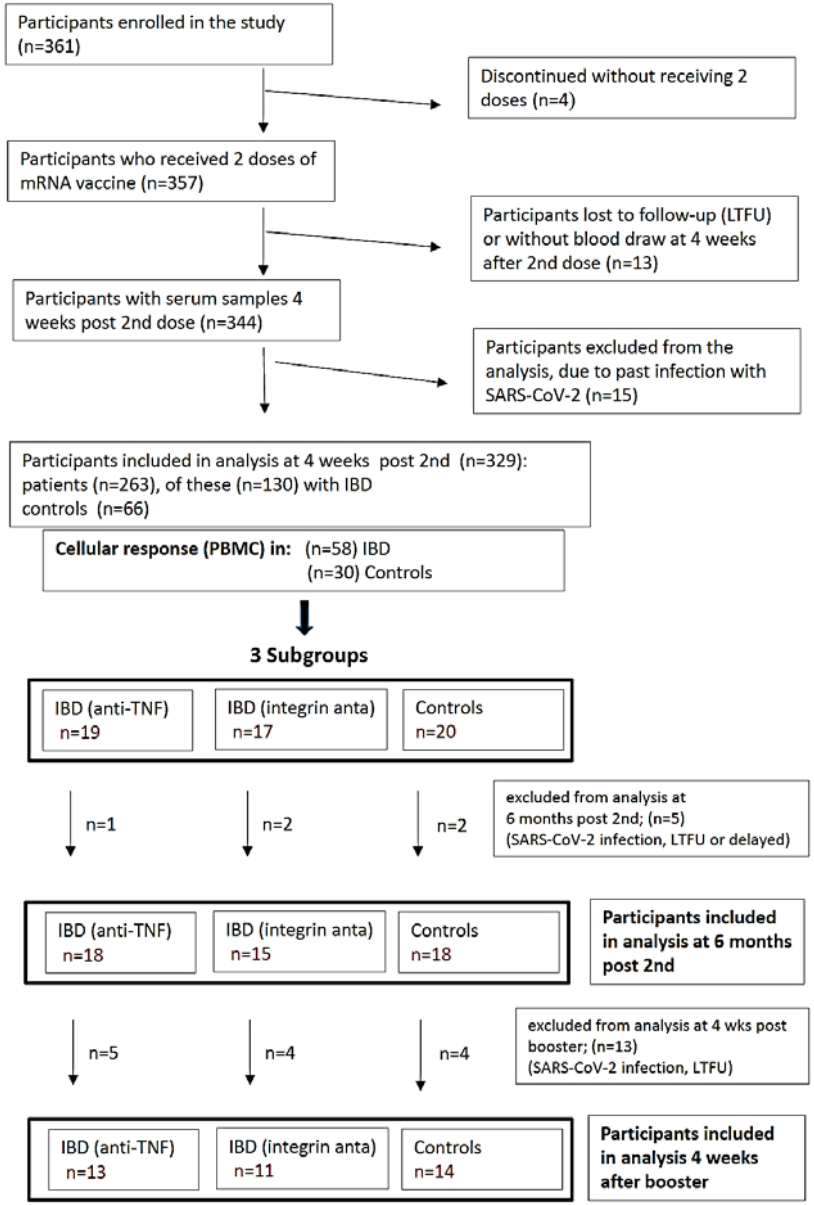
Supplementary Table 2*: Concentrations of cytokines IL-2, IFN-γ and TNF-α in PBMC culture supernatants and sera*

Cytokines were measured in supernatants of unstimulated and SARS-CoV-2 S1-protein stimulated PBMC obtained prior to vaccination and one week after 2nd dose and in sera obtained prior to vaccination and four week after 2nd dose; concentrations in pg/ml.

Abbreviations: ADA, adalimumab; IBD, inflammatory bowel disease; IFX, infliximab; pre vacc, prior to vaccination; S1, Spike subunit1- protein stimulated PBMC; unstim, not stimulated PBMC; VED, vedolizumab;

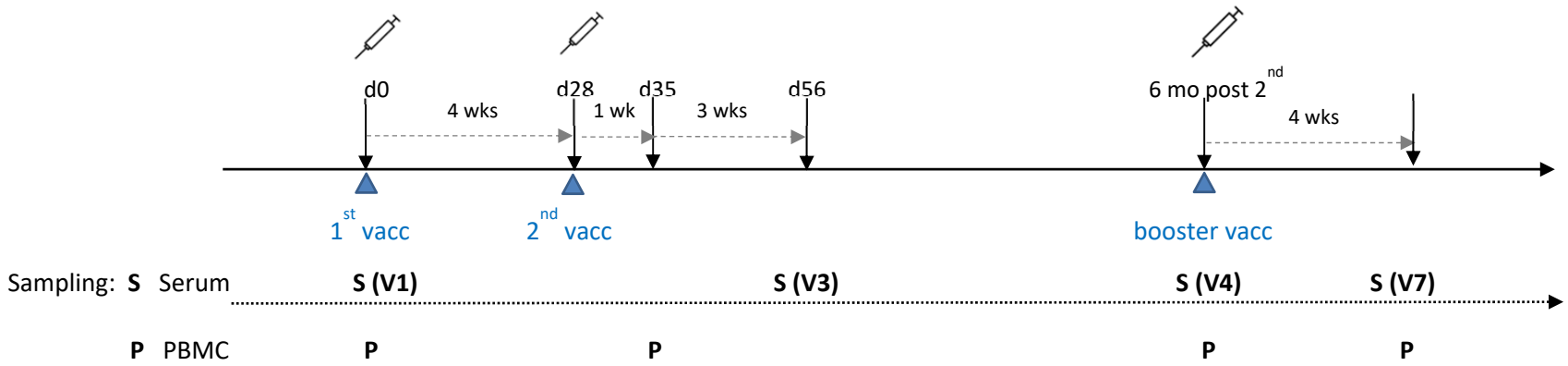
	Pat. ID	Therapy	Cytokines in Serum				IFN-gamma (pg/ml)				TNF-alpha (pg/ml)			
			IFN-gamma (pg/ml)		TNF-alpha (pg/ml)		pre vacc		post 2nd		pre vacc		post 2nd	
			pre vacc	post 2nd	pre vacc	post 2nd	unstim	S1	unstim	S1	unstim	S1	unstim	S1
IBD	303	VED	3.9	0.2	30.9	27.7	22·8	30·6	11·9	797·7	138·5	105·8	66·1	179·5
high responders	316	VED	0	0	2.3	10.4	4·5	8·2	5·5	1433·9	33·3	28·8	28·8	125·2
	400	VED	0	0	24.9	2.3	5·9	2·7	1·5	249·8	1·2	9·8	4·3	46·3
IBD	314	IFX	56.9	8.4	229.5	26.5	52·7	75·1	86·0	134·0	154·9	141·9	440·5	108·1
low responder	399	ADA	225.7	99.8	17.2	6.1	76·3	163·6	11·7	99·8	24·3	37·7	56·7	42·0
inflamm. baseline	403	IFX	0.2	0	0	0	270·0	365·8	106·8	457·0	781·2	793·1	38·0	45·8
	422	IFX	1.0	0	2.3	29.4	399·3	440·6	303·0	1248·0	234·9	2143	79·4	160·4
IBD	352	ADA	6.7	0	24.9	16.3	4·3	6·2	4·9	78·6	12·3	9·8	17·2	9·8
low responder	353	ADA	0.3	0.2	28.0	35.1	0·9	0·9	1·3	230·7	75·0	66·9	75·0	58·8
	359	IFX	2.9	0.2	13.3	16.8	10·4	8·8	5·1	130·0	84·9	84·9	58·8	48·4
	384	ADA	0	0	6.7	4.7	3·1	3·8	2·4	93·0	26·6	22·0	1·2	22·0
	402	ADA	0.2	0	51.3	35.2	1·7	1·4	2·2	907·3	141·9	90·7	104·3	96·6
Controls	c10	none	0	0	21.9	21.9	2·0	3·0	2·4	129·0	68·4	25·5	0·0	9·1
high responders	c22	none	0	0	17.1	23.5	1·3	1·1	1·6	826·3	73·0	56·7	9·8	37·7
	c24	none	1.4	0.3	21.9	25.0	3·8	3·6	2·4	1299·3	102·4	75·0	0·0	54·6
	c55	none	0	0	32.2	30.9	0·7	0·5	0·4	86·1	55·4	47·2	13·4	14·6
Control fast decline	c51	none	0.2	0.2	18.8	18.8	190·8	233·5	44·3	179·4	307·2	329·6	58·8	78·9
Control low resp	c54	none	0	0	65.2	93.8	168·8	115·3	27·4	82·2	457·4	375·9	78·9	94·6

Supplementary Figure 1: *Flow chart*



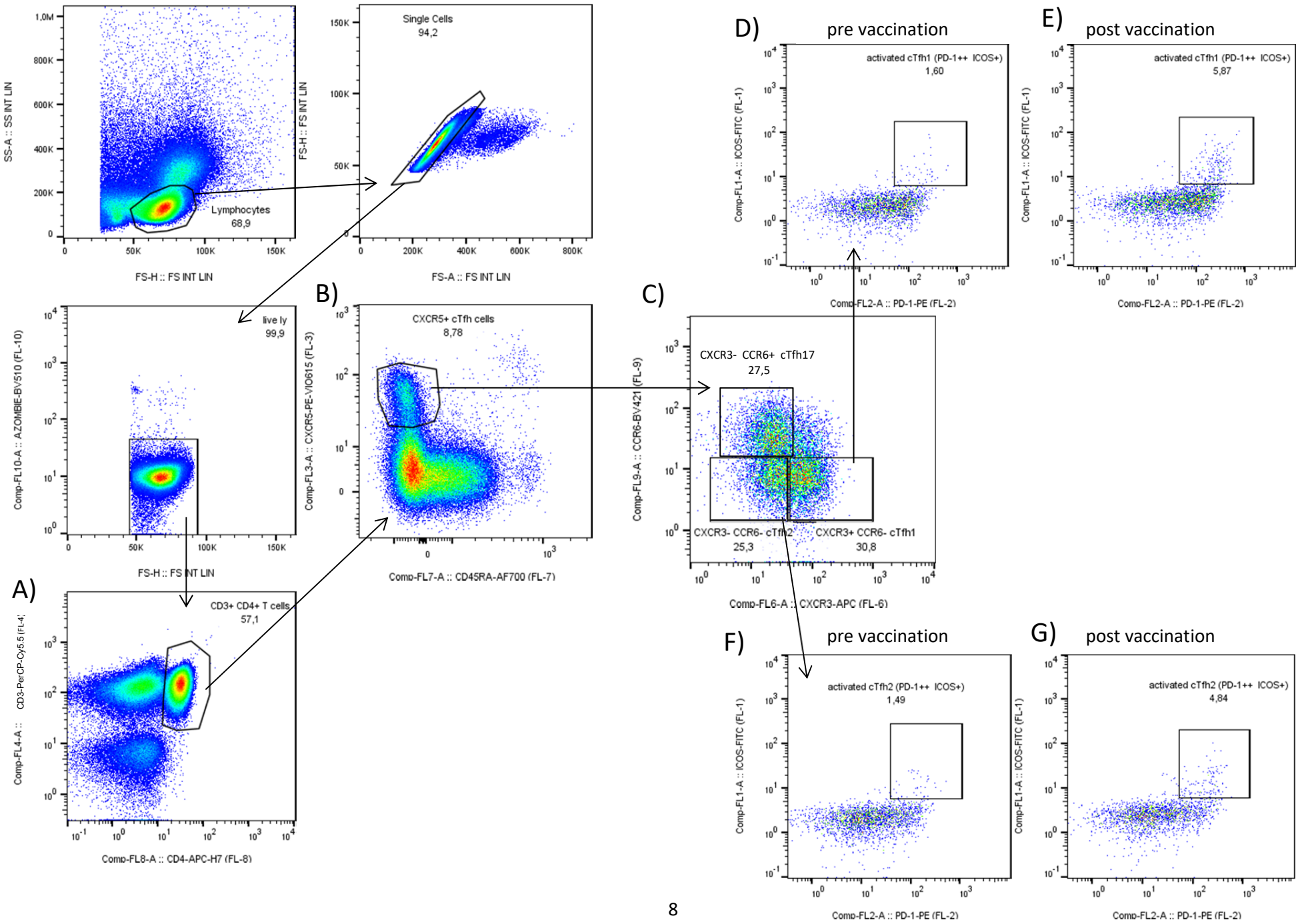
Supplementary Figure 2: *Timeline of Interventions*

Abbreviations: d, day; mo, months; wk, week; vacc, time point of SARS-CoV-2 mRNA vaccination (BNT162b2 or mRNA-1273): V, visit



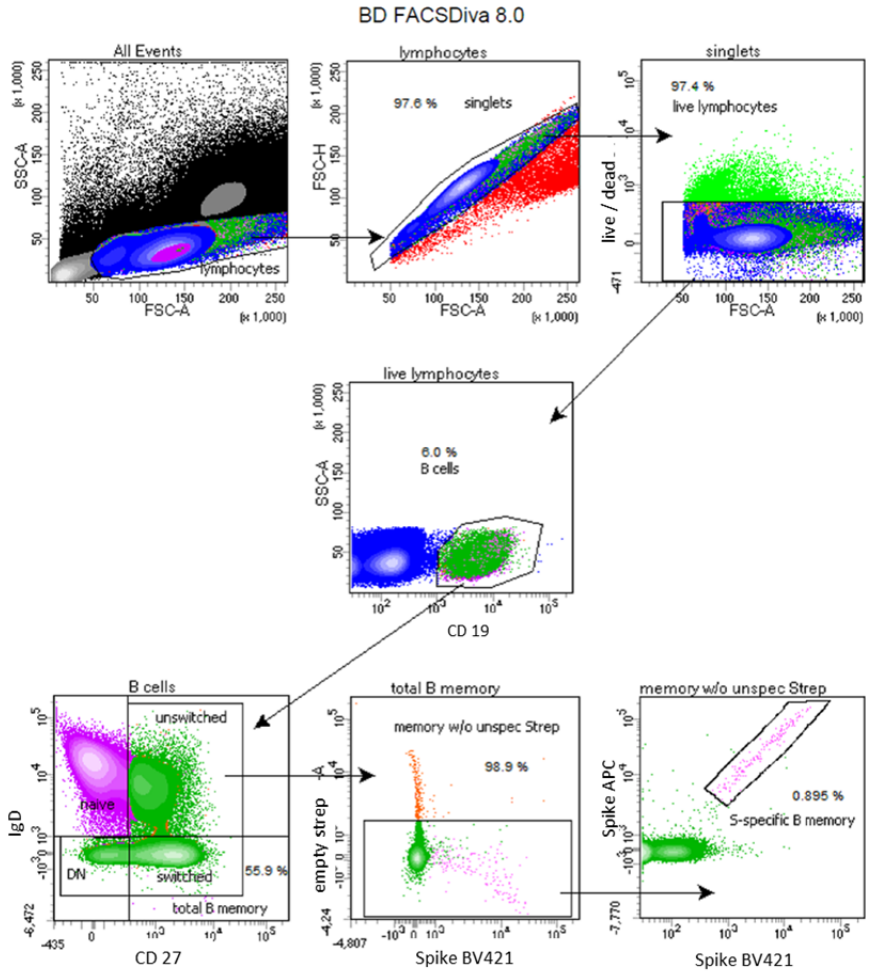
Supplementary Figure 3: *Gating strategy for quantification of activated circulating T follicular helper cells (cTfh) and cTfh1 and cTfh2 subsets*

PBMC were stained with fluorochrome-labeled mAbs and analyzed on a Beckman Coulter Navios Ex flow cytometer. FSC/SSC were applied to select lymphocytes, doublets were removed by means of FSC-A/FSC-H. Dead cells were excluded with the use of fixable viability dye Zombie Aqua™. Scatterplots with gating of A) total CD3+/CD4+ T cells, B) total cTfh cells (CD3+/CD4+/CD45RA-/CXCR5+) and C) cTfh1 (CXCR3+/CCR6−) and cTfh2 (CXCR3−/CCR6−) cell subsets; D, E) activated cTfh1 cells (PD-1++/ICOS+) pre- and post-vaccination, and F, G) activated cTfh2 cells (PD-1++/ICOS+) pre- and post-vaccination.


SS-A :: SS INT LIN
FS-H :: FS INT LIN
Lymphocytes
68,9
Single Cells
94,2
FS-A :: FS INT LIN
live ly
99,9
Comp-FL10-A :: AZOMBIE-BV510 (FL-10)
A)
CD3+ CD4+ T cells
57,1
Comp-FL4-A :: CD3-PerCP-Cy5.5 (FL-4)
Comp-FL8-A :: CD4-APC-H7 (FL-8)
B)
CXCR5+ cTfh cells
8,78
Comp-FL3-A :: CXCR5-PE-VIO615 (FL-3)
Comp-FL7-A :: CD45RA-AF700 (FL-7)
C)
CXCR3- CCR6+ cTfh17
27,5
CXCR3- CCR6- cTfh2
25,3
CXCR3+ CCR6- cTfh1
30,8
Comp-FL9-A :: CCR6-BV421 (FL-9)
Comp-FL6-A :: CXCR3-APC (FL-6)
D)
pre vaccination
activated cTfh1 (PD-1++ ICOS+)
1,60
Comp-FL1-A :: ICOS-FITC (FL-1)
Comp-FL2-A :: PD-1-PE (FL-2)
E)
post vaccination
activated cTfh1 (PD-1++ ICOS+)
5,87
F)
pre vaccination
activated cTfh2 (PD-1++ ICOS+)
1,49
G)
post vaccination
activated cTfh2 (PD-1++ ICOS+)
4,84

Supplementary Figure 4: *Gating strategy for quantification of SARS-CoV-2 S-specific B memory cells*

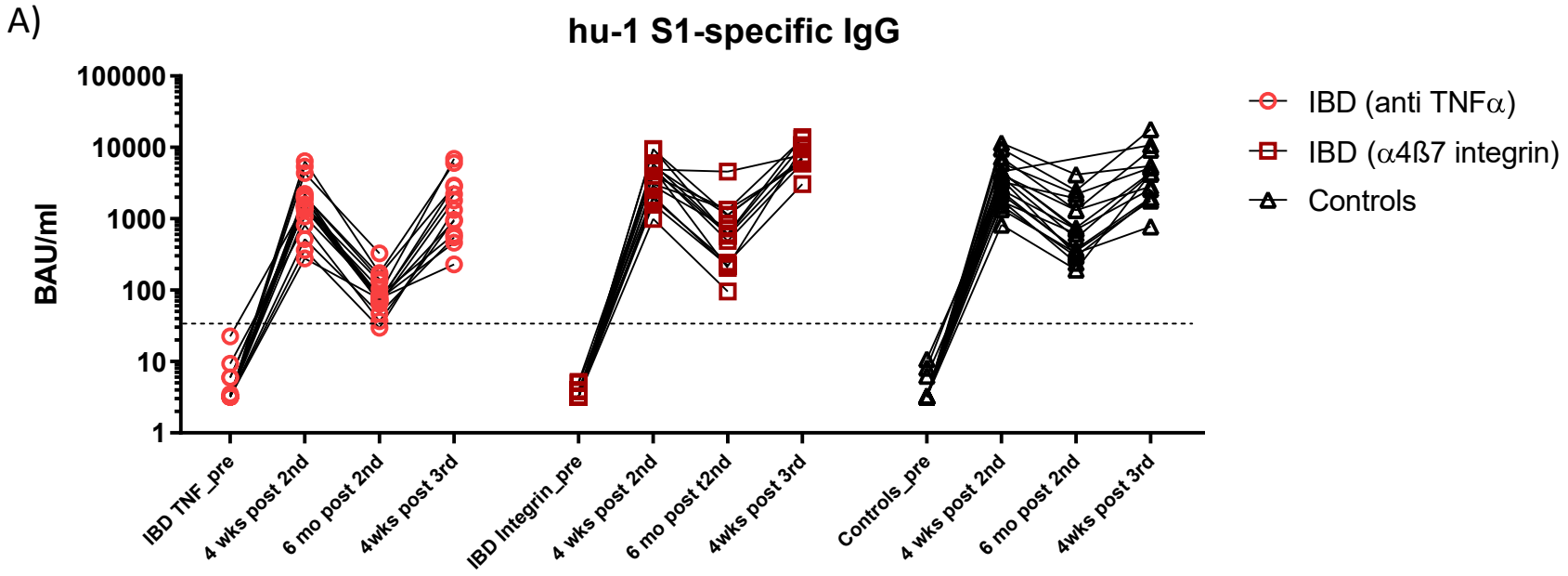
FSC/SSC were applied to select lymphocytes, doublets were removed by means of FSC-A/FSC-H. Dead cells were excluded with the use of fixable viability dye eFluor-506 (BV510). CD19+ B-cells were gated and S-specific memory B-cells were quantified as percentages of total memory B-cells, including the CD19+ un-switched (IgD+/CD27+), switched (IgD-/CD27+) and double-negative (IgD-/CD27-) memory subset after exclusion of cells positive for streptavidin-APC-Cy7 without biotinylated protein, which was used as decoy probe to gate out B cells with unspecific streptavidin binding.



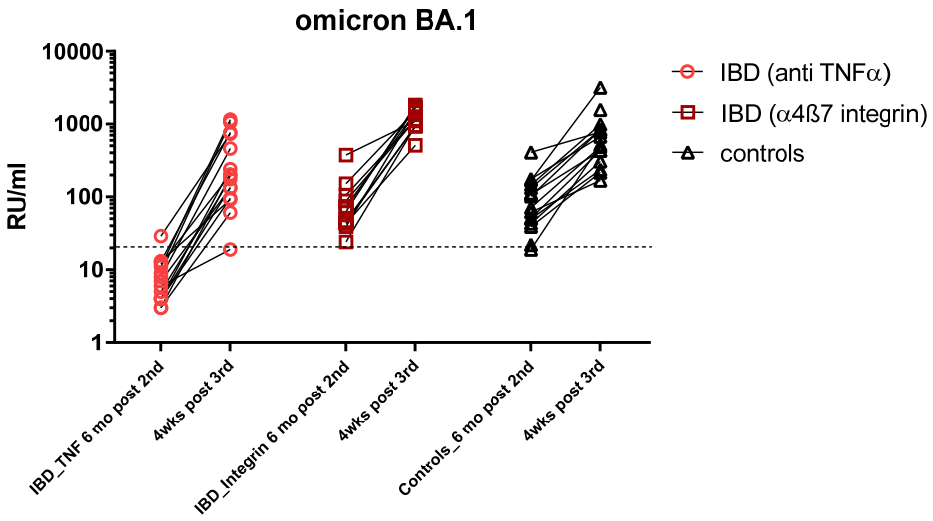
Supplementary Figure 5: *Individual kinetics of SARS-CoV-2-Spike (S1) specific IgG antibodies*

Kinetics of A) S1-specific IgG against ancestral virus hu-1 in BAU/mL in IBD patients treated with either anti-TNFα (n=19) or α4β7-integrin-antagonists (n=17) and controls (n=20) measured before the first and four weeks and six months after the second dose, as well as four weeks after booster dose of SARS-CoV-2 mRNA vaccine (BNT162b2 or mRNA-1273); dashed line - positive cut-off for S1-specific IgG at 35·2 BAU/mL; B) S1-specific IgG against Omicron BA.1 (in RU/mL), dashed line – positive cut-off for BA.1 S1-specific IgG at 11·0 RU/m; C) IgG specific for RBD of Omicron BA.4/5 (as OD) and D) inhibition capacity of BA.4/.5-specific Abs (as % inhibition) measured six months after the second dose and four weeks after booster dose; OD values >0.25 and inhibition levels of >20% were considered positive (black dashed line), inhibition levels >50% as relevant (red dashed line).

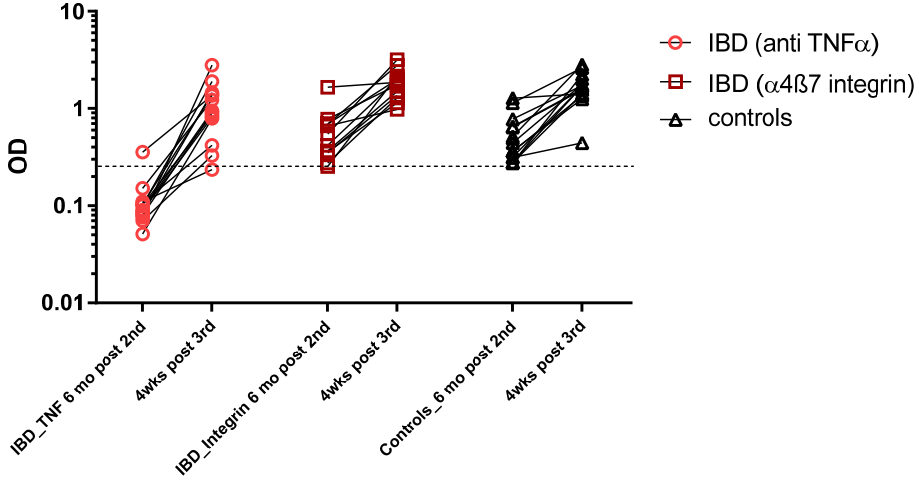
Abbreviations: BAU, binding antibody units; mo, months; RBD, receptor-binding domain; RU, relative units; S1, SARS-CoV-2 Spike protein 1



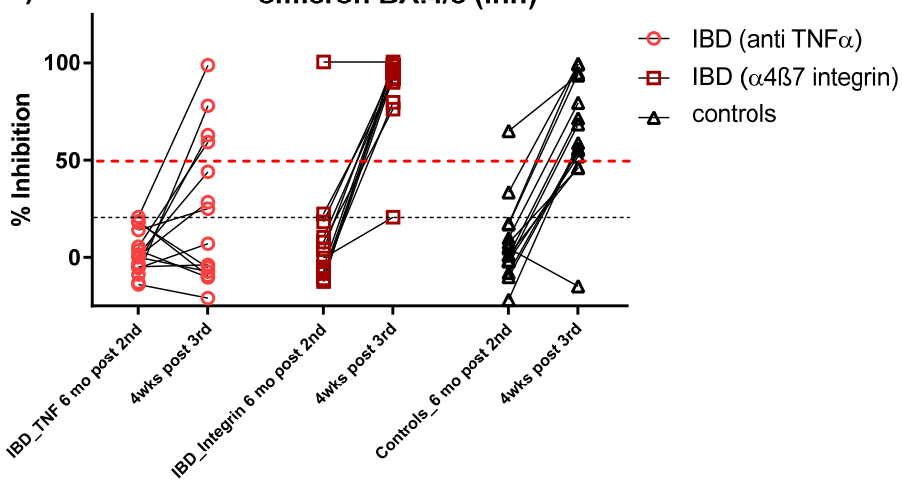
B)


omicron BA.1
RU/ml
10000
1000
100
10
1
IBD_TNF 6 mo post 2nd
4wks post 3rd
IBD_Integrin 6 mo post 2nd
4wks post 3rd
Controls_6 mo post 2nd
4wks post 3rd
IBD (anti TNFα)
IBD (α4ß7 integrin)
controls

C)


omicron BA.4/5
OD
10
1
0.1
0.01
IBD_TNF 6 mo post 2nd
4wks post 3rd
IBD_Integrin 6 mo post 2nd
4wks post 3rd
Controls_6 mo post 2nd
4wks post 3rd
IBD (anti TNFα)
IBD (α4ß7 integrin)
controls

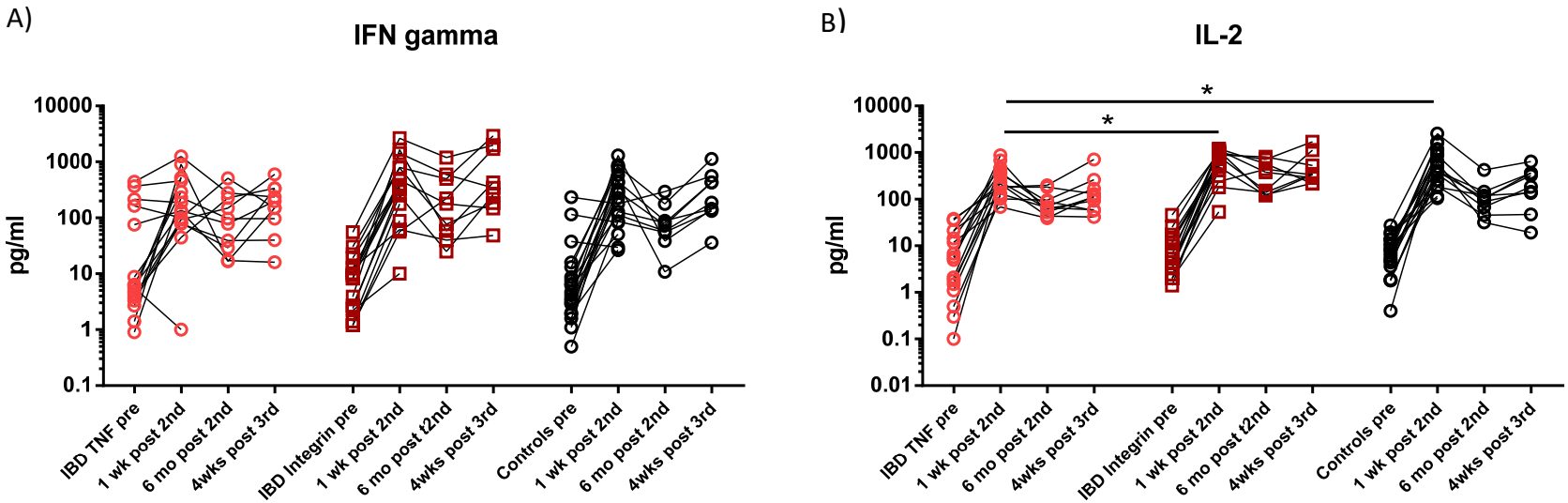
D)


omicron BA.4/5 (inh)
% Inhibition
100
50
0
IBD_TNF 6 mo post 2nd
4wks post 3rd
IBD_Integrin 6 mo post 2nd
4wks post 3rd
Controls_6 mo post 2nd
4wks post 3rd
IBD (anti TNFα)
IBD (α4ß7 integrin)
controls

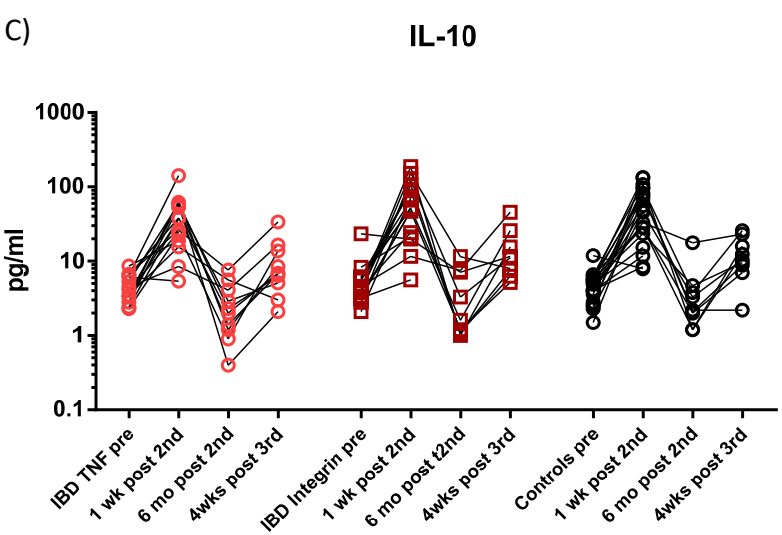
Supplementary Figure 6 A-E: *Concentrations of cytokines IFN-γ, IL-2, IL-10, GMCSF, and IL-5 in PBMC culture supernatants of PBMC obtained before and one week after 2nd, 6 months after 2nd, and 4 weeks after booster (3rd) vaccination*

Cytokines concentrations (pg/ml) were measured in supernatants harvested of PBMC stimulated with the peptide pool of the SARS-CoV-2 S1-subunit for 24 hours and measured with a Luminex system.

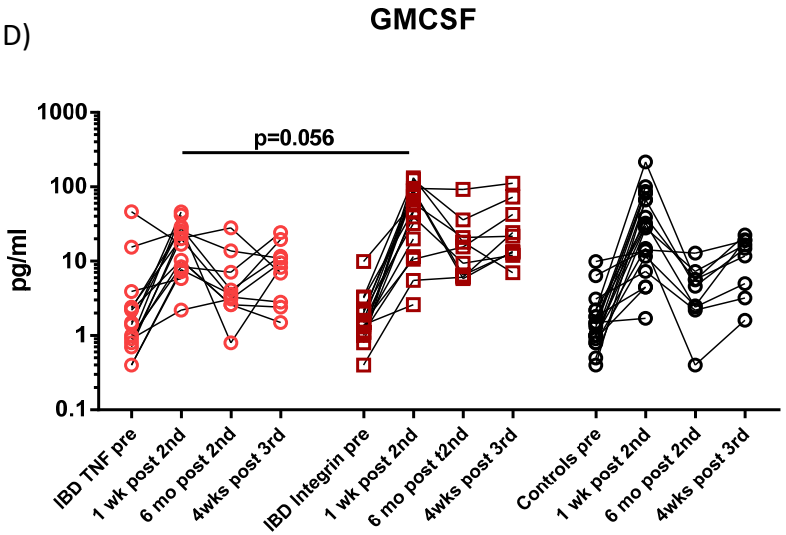
ANOVA with linear contrasts; **p ≤ 0·01; *p ≤ 0·05



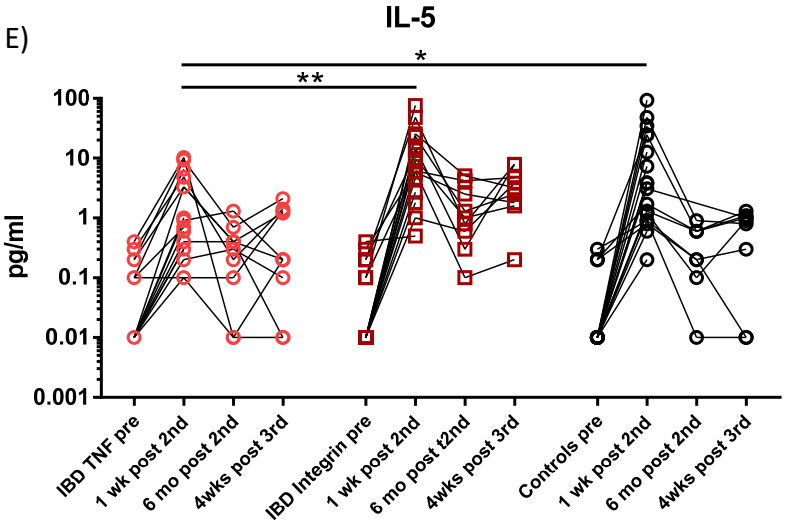
C)


IL-10
pg/ml
1000
100
10
1
0.1
IBD TNF pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd
IBD Integrin pre
1 wk post 2nd
6 mo post t2nd
4wks post 3rd
Controls pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd

D)

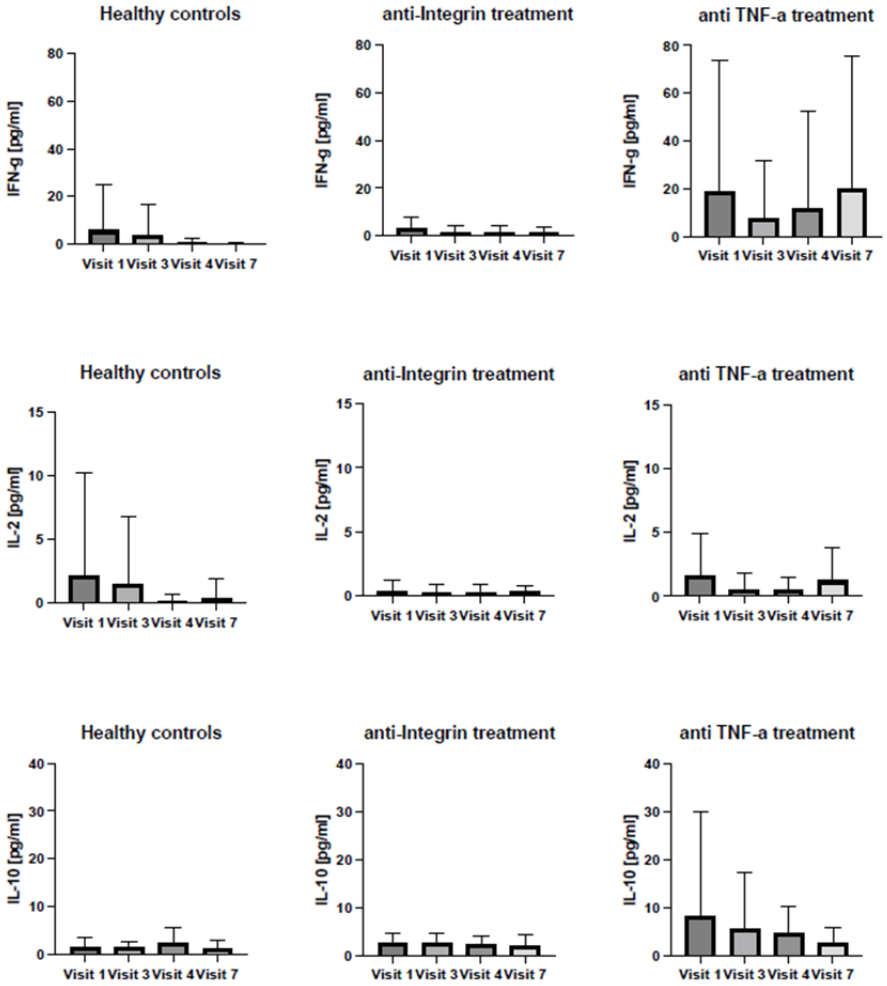

GMCSF
p=0.056
pg/ml
1000
100
10
1
0.1
IBD TNF pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd
IBD Integrin pre
1 wk post 2nd
6 mo post t2nd
4wks post 3rd
Controls pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd

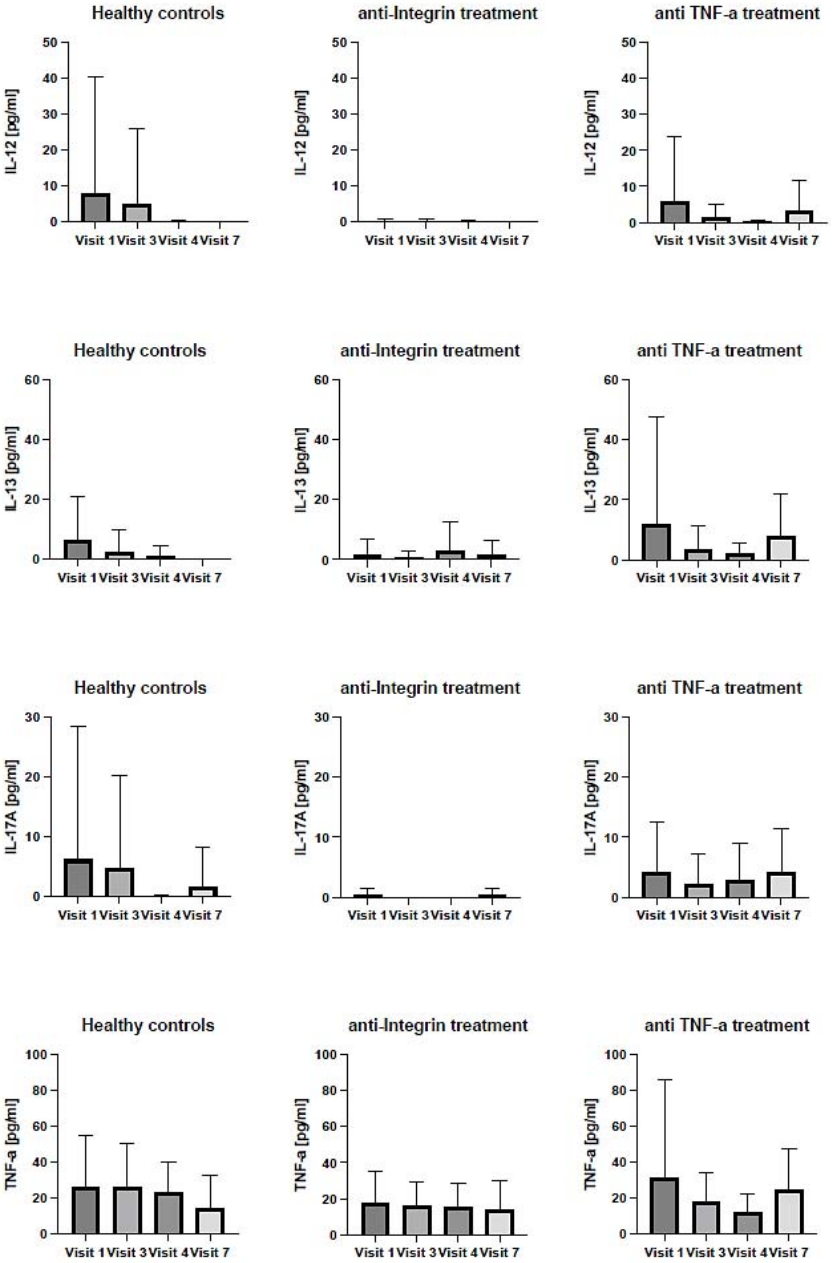
E)


IL-5
*
**
pg/ml
100
10
1
0.1
0.01
0.001
IBD TNF pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd
IBD Integrin pre
1 wk post 2nd
6 mo post t2nd
4wks post 3rd
Controls pre
1 wk post 2nd
6 mo post 2nd
4wks post 3rd

Supplementary Figure 7: *Cytokine concentrations in sera*

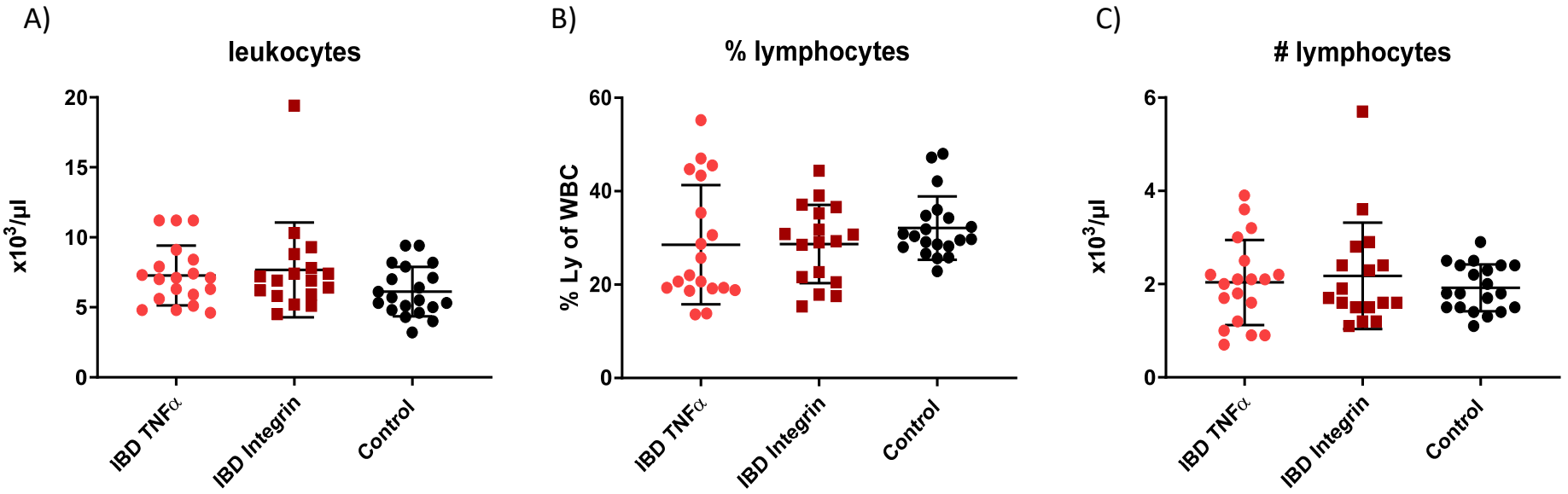
Shown are serum cytokine levels of 19 healthy controls (column 1), 17 IBD patients with integrin-antagonist treatment (column 2) and 17 IBD patients with anti-TNF-α treatment (column 3) taken before (visit 1) and four-weeks after 2nd (visit 3), 6 months after 2nd (visit 4), and 4 weeks after booster (3rd) vaccination (visit 7). Bars show mean values and error bars indicate the standard deviation. No significant differences were detected by Kruskal-Wallis test followed by Dunn's correction for multiple comparisons.




Healthy controls
anti-Integrin treatment
anti TNF-a treatment
IL-12 [pg/ml]
IL-13 [pg/ml]
IL-17A [pg/ml]
TNF-a [pg/ml]
Visit 1 Visit 3 Visit 4 Visit 7

Supplementary Figure 8.1 A-C: *Leukocyte and lymphocyte counts pre-vaccination*

Leukocytes and lymphocytes were measured in EDTA whole blood with SYSMEX XP-300 differential hematology analyzer in absolute numbers; A) leukocytes in peripheral blood (10^3/µl); B) lymphocytes as percentages of differential leukocyte count; C) absolute lymphocytes (10^3/µl) in the three investigated groups; median and interquartile range.
Abbreviations: anti-TNFα; anti-TNFα treated IBD patients; anti-Integrin, α4β7-integrin-antagonist treated IBD patients



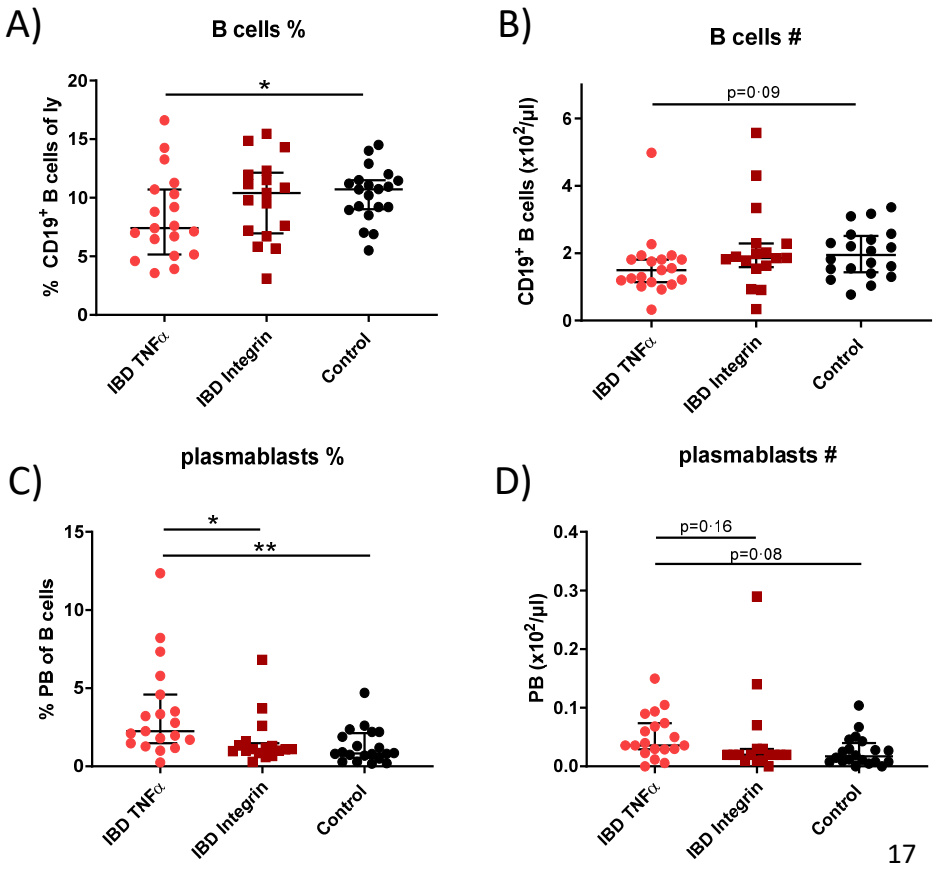
Supplementary Figure 8.2 A-J: *Quantification of B and T lymphocytes, plasmablasts, NK-T-cells and naïve CD4 T cells pre-vaccination*

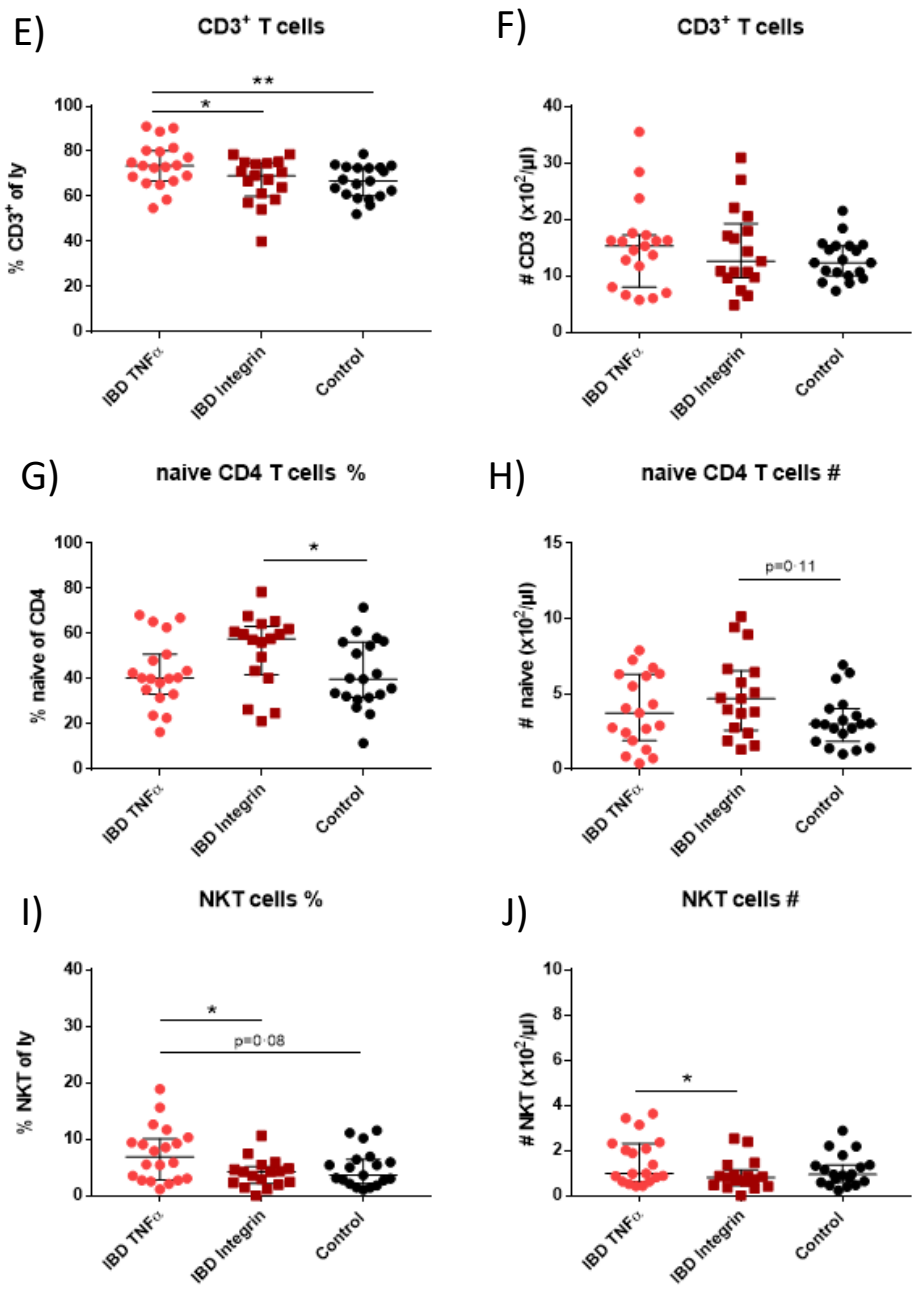
PBMC obtained prior to vaccination were stained with fluorochrome-labeled mAbs and analyzed on a BD FACS Canto II flow cytometer. Quantification of A) total CD19+ B-cells as % of lymphocytes and B) as absolute numbers (10^2/µl) calculated based on differential leukocyte counts in peripheral blood; C) Quantification

of plasmablasts (CD19+/CD27++/CD38 ^{high}) as percentages of total CD19+ B cells and D) as absolute numbers (10^2/µl); E) CD3+ T cells as % of lymphocytes and F) as absolute numbers (10^2/µl), G) naïve CD4 T cells (CD4+/CD45RA+/CCR7+) as % of total CD3+/CD4+ T cells and H) in absolute numbers (10^2/µl), I) CD3+/CD4-/CD8- NK-T cells calculated as % of lymphocytes and J) as absolute numbers (10^2/µl) in the three investigated groups, measured prior to vaccination; lines represent median and interquartile range.

Abbreviations: anti-TNFα; anti-TNFα treated IBD patients; anti-Integrin, α4β7-integrin-antagonist treated IBD patients

ANOVA with linear contrasts; ***p ≤ 0·001; **p ≤ 0·01; *p ≤ 0·05



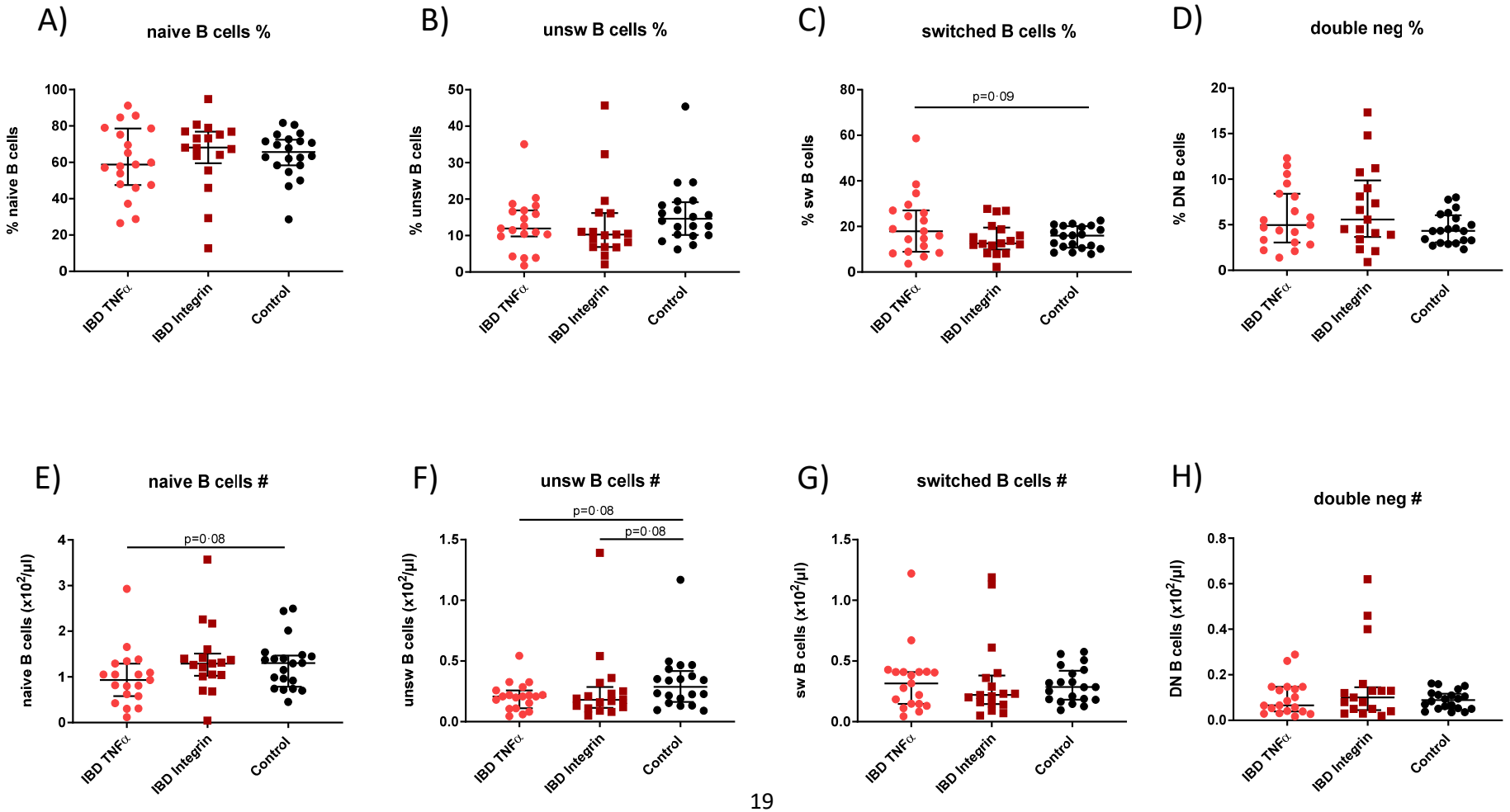

E)
CD3+ T cells
% CD3+ of ly
**
*
IBD TNFα
IBD Integrin
Control
F)
CD3+ T cells
CD3 (x10²/µl)
G)
naive CD4 T cells %
% naive of CD4
*
H)
naive CD4 T cells #
# naive (x10²/µl)
p=0·11
I)
NKT cells %
% NKT of ly
*
p=0·08
J)
NKT cells #
NKT (x10²/µl)
*

Supplementary Figure 9 A-D: *Distributions of naïve and memory B cell subsets pre-vaccination*

PBMC were stained with fluorochrome-labeled mAbs and analyzed on a BD FACS Canto II flow cytometer. Distributions of A-D) naïve, un-switched memory, switched memory and double-negative B cell subsets as % of total B cells and E-H) as absolute numbers (10^2/µl) calculated based on differential leukocyte counts in peripheral blood; measured prior to vaccination in the three investigated groups; median and interquartile range.

Abbreviations: anti-TNFα; anti-TNFα treated IBD patients; anti-Integrin, α4β7-integrin-antagonist treated IBD patients; DN, double-negative; unsw, un-switched

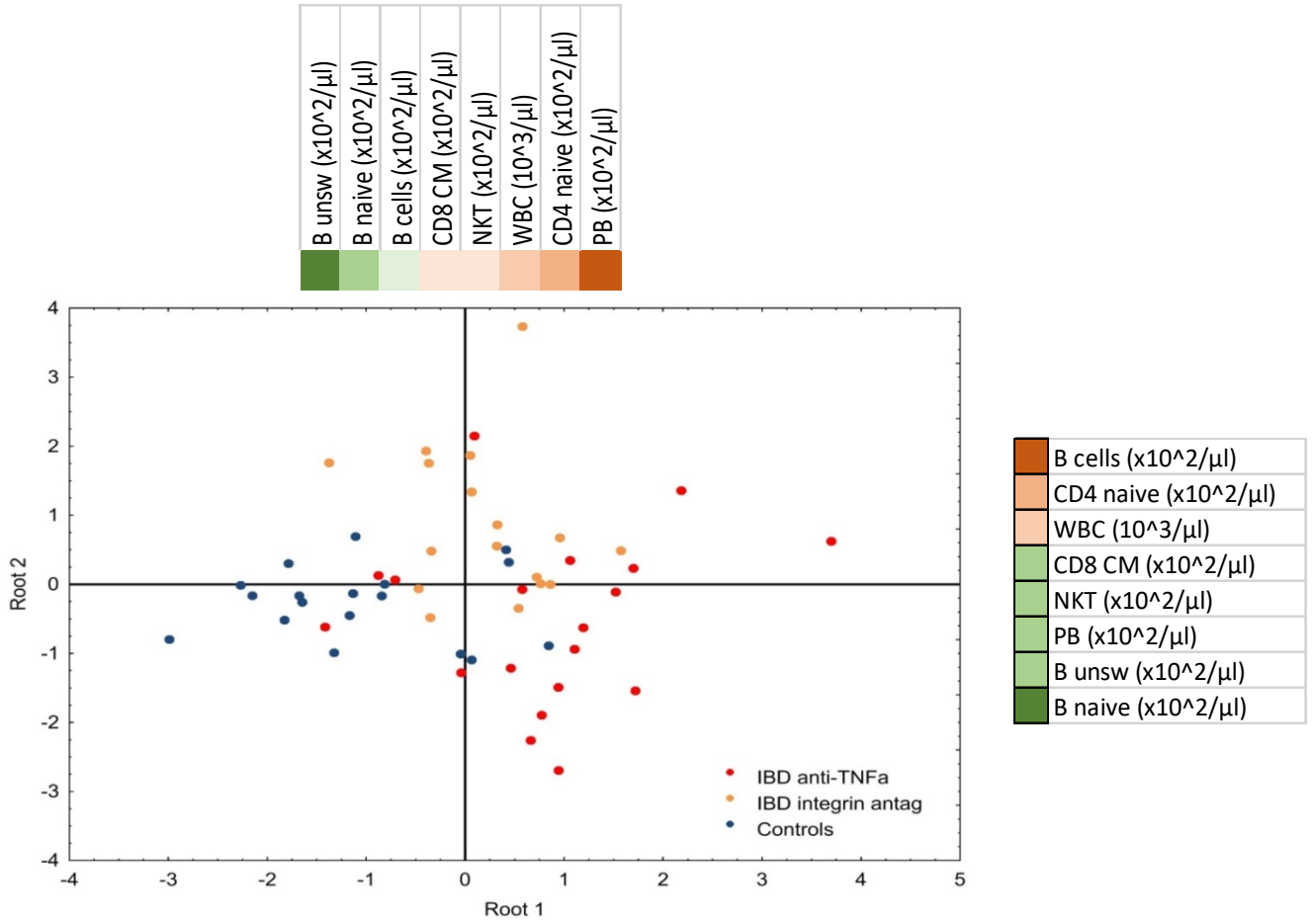
ANOVA with linear contrasts; *p<0·05



Supplementary Figure 10: *Multivariate discriminant analysis of B and T cell subsets*

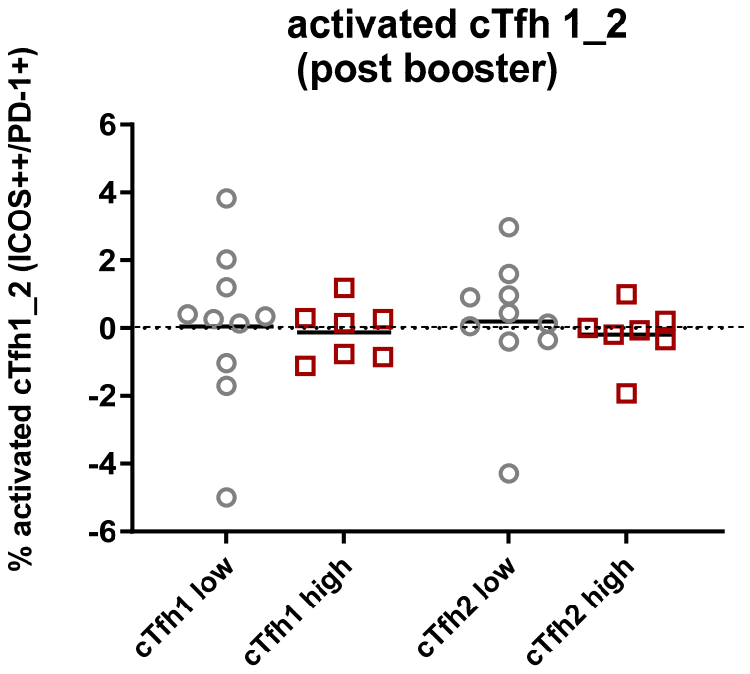
A multivariate discriminant analysis was performed to assess the contribution of the different subpopulations of B- and T-cells (in absolute numbers [10^2/µl]) for differentiating the two IBD groups and the control group. Results are graphically presented as dot-plots presenting each participant in the plane spanned by the two canonical roots. Contribution of the different components of the B- and T-cell subsets is shown color coded for positive (red) and negative (green) coefficients.

Abbreviations: CD8 CM, CD8 T cell central memory subset; IBD anti-TNFα; anti-TNFα treated IBD patients; IBD integrin antag, α4β7-integrin-antagonist treated IBD patients; PB, plasmablasts; unsw, un-switched memory; WBC, white blood cells;



Supplementary Figure 11: *Quantification of activated cTfh1 and cTfh2 cells pre- and post-booster*

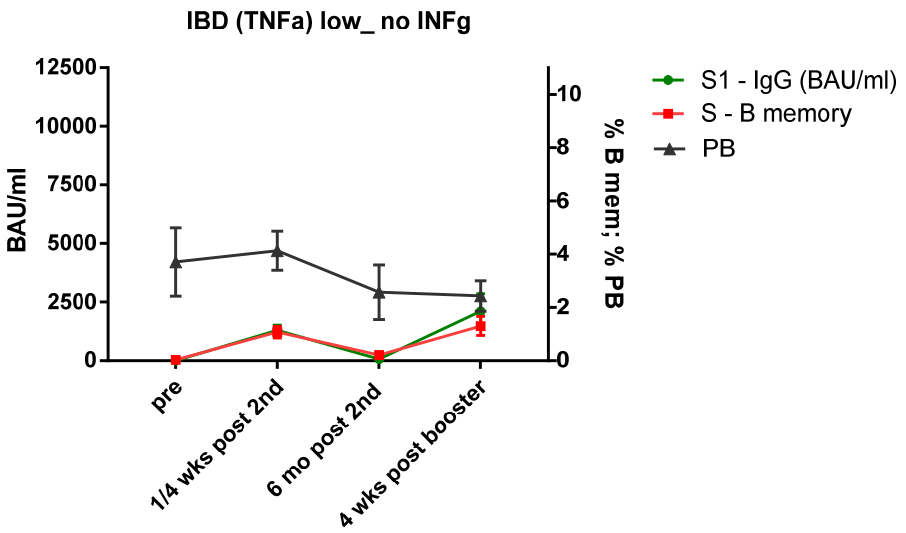
Quantification of activated cTfh1 and cTfh2 (as % of total cTfh1 and cTfh2 cells) in **7** high-responders (squares) (of these [n=2] IBD patients with integrin antagonists and [n=5] high-responder controls) and **10** low-responders (circles) (of these [n=7] IBD patients with anti-TNF α treatment and [n=3] low responder controls) pre and post booster, the shown percentage is [% activated post booster] minus [% activated pre booster], black line is arithmetic mean.



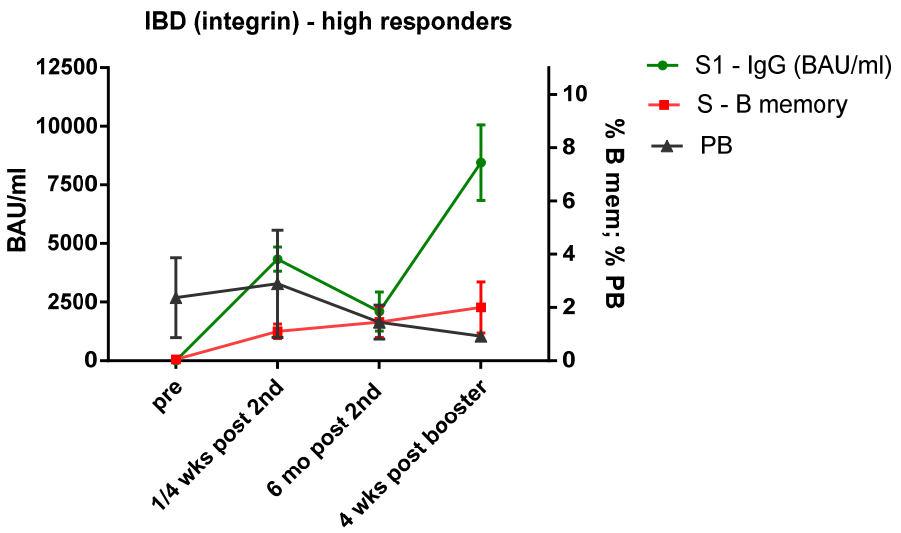
Supplementary Figure 12 A, B: *Kinetic of S1-specific IgG Abs, S-specific B memory cells and plasmablasts (PB)*

The kinetics of S1-specific IgG (in BAU/mL), Spike (S) protein-specific memory B-cells (as % of total B memory cells) and PB (as %of total CD19+ B cells) were determined at four time points: pre-vaccination, either one week (S-specific B memory, PB) or four weeks (S1-specific IgG) post 2nd dose, six months post 2nd dose and four weeks post booster vaccination; A) in anti-TNF-α treated IBD low-responders without elevated IFN-γ/TNF-α levels (n=9; S1-specific IgG <2000 BAU/mL after 2nd dose and <90 BAU/mL after six months) and B) in IBD high-responders receiving α4β7-integrin-antagonist therapy (n=4; S1-specific IgG >4000 BAU/mL four weeks after 2nd dose and >1100 BAU/mL after six months); mean with SEM.

A)



B)



Supplementary Figure 13 A-C: *Correlations of S1-specific IgG Abs and S-specific memory B cells*

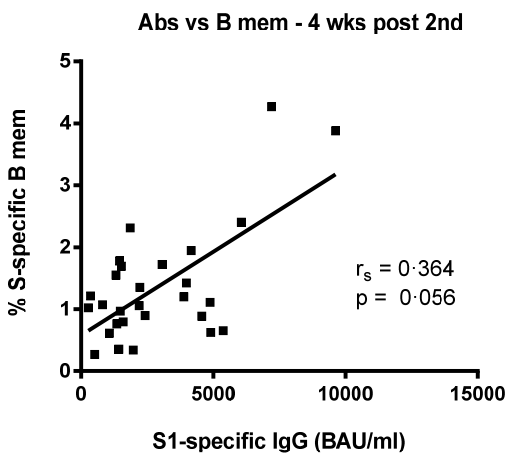
Spearman rank correlations (r_s) of Spike (S)-specific memory B-cells (as % of total B memory cells) and hu-1 S1-specific IgG concentrations (in BAU /mL) for all analyzed subjects at the time points A) 4 weeks after the 2nd dose; B) six months after the 2nd dose, and C) four weeks after booster dose.

Spearman rank correlation coefficient (r_s) and p values are indicated in graphs.

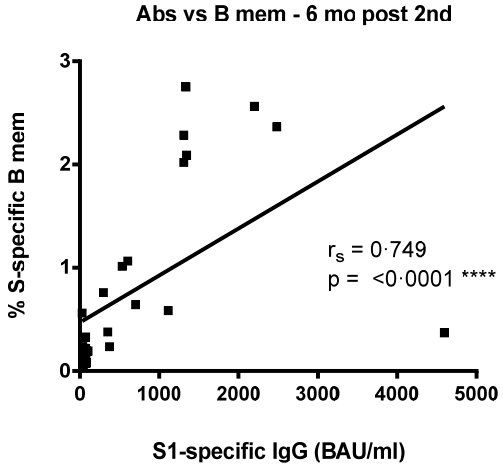
Abbreviations: Abs, antibodies; BAU, binding antibody units; B mem, S-specific B memory

****p ≤ 0·0001; ***p ≤ 0·001; **p ≤ 0·01; *p ≤ 0·05

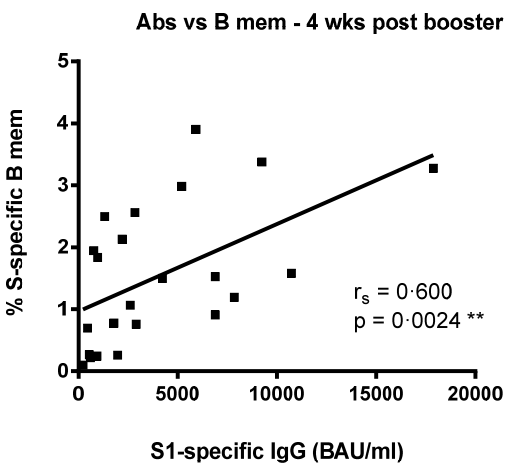
A)



B)



C)



Supplementary Data 1: *Inclusion and Exclusion criteria*

Inclusion criteria:

- >=18 years
- IBD diagnosis with or without immunosuppressive/immunomodulatory therapy
- No previous SARS-CoV-2 vaccination

Exclusion criteria

- Are not willing to get mRNA SARS-CoV-2 Vaccination
- If female, are pregnant or lactating

If belonging to the healthy control group, are immunosuppressed (suffer from or have a history of immune mediated diseases, long-term use of corticosteroids, haemodialysis, chronic renal insufficiency, liver cirrhosis Child-Pugh class C, haematooncologic malignant disease, solid organ transplant).

Supplementary Data 2: *Protocol for measurement of serum cytokine levels*

Serum cytokine levels were determined with a Milliplex® Human Cytokine/Chemokine/Growth Factor Panel A kit (Merck Millipore, Billerica, MA) according to the manufacturer's instructions. Briefly, human serum samples were gently thawed and centrifuged at 10.000g for 10 minutes. 25 µl of undiluted serum, standards or controls were incubated together with 25 µl of assay buffer and 25 µl of bead solution at 4°C overnight in duplicates (samples) or triplicates (standards). On the next day, samples were washed three times with 200 µl wash buffer on a BioTek plate washer (BioTek, Winooski, VT) and 25 µl of detection antibody mix was added for one hour at room temperature. Subsequentially, 25 µl of Streptavidin-PE was added for another 30 minutes at room temperature and finally plates were washed as described above and beads were resuspended in 25 µl of Luminex sheath fluid. Acquisition and analyzes were performed on a Luminex 100/200 (Luminex, Austin, TX). Quantification of samples was performed according to the standard curves obtained during the same measurements with the following detection limits: 1 pg/ml for IFN-γ, 0.6 pg/ml for IL-2, 0.7 pg/ml for IL-10, 5.1 pg/ml for IL-13, 3.0 pg/ml for IL-17A, 2.5 pg/ml for IL12p70 and 1.7 for TNF-α.

Supplementary Data 3:

- *A) Fluorochrome-conjugated monoclonal Abs for flow-cytometric analysis of B and T cell panel*

  The following monoclonal antibodies were used: anti–human CD3 PerCP-Cy5.5 (clone Ucht1), anti–human CD4 APC-H7 (clone L200), anti–human CD8 APC (clone RPA-T8), anti–human CD45RA BV421 (clone HI100), anti–human CD19 FITC (clone HIB19), anti–human CD27 PE (clone L128), anti–humanCD38 PerCP-Cy5.5 (clone HIT2), anti–human CD24 BV421(clone ML5), anti–human CD10 BV510 (clone HI10a), anti–human immunoglobulin D (IgD) PE-Cy7 (clone IA6-2), all from BD Biosciences; anti–human chemokine receptor 7 (CCR7) FITC (clone 150503) was obtained from R&D Systems, Inc. (Minneapolis, MN, USA). Dead cells were excluded by using fixable viability dye eFluor-780 (B panel) and eFluor-506 (T panel, both from eBioscience, now Thermo Fisher Scientific). Natural killer T cells were characterized as CD3+/CD4−/CD8− cells and were calculated as the difference of [CD3+/CD4+ plus CD3+/CD8+ T cells] to total CD3+ T cells as % of lymphocytes.

- *B) Fluorochrome-conjugated monoclonal Abs for flow-cytometric analysis of T follicular helper cells (Tfh)*

	Antibody	Conjugate	Clone	Species	Isotype	Catalogue No.	Company
1	ICOS/CD278	FITC	ISA-3	Mouse	IgG1, kappa	11-9948-42	Invitrogen
2	PD-1/CD279	PE	EH12.2H7	Mouse	IgG1, kappa	329906	Biolegend
3	CD3	PerCP- Cy 5.5	UCHT1	Mouse	IgG1, kappa	560835	BD Bio
4	CXCR5/CD185	PE-Vio615	REA103	Human	rIgG1	130-123-912	Miltenyi
5	CXCR3/CD183	APC	G025H7	Mouse	IgG1, kappa	353708	Biolegend
6	CD45RA	AF700	H100	Mouse	IgG2b, kappa	56-0458-42	Invitrogen
7	CD4	APC H7	L200	Mouse	IgG1, kappa	560837	BD Bio
8	CCR6/CD196	BV 421	11A9	Mouse	IgG1, kappa	565925	BD Bio
9	Zombie Aqua™	-	-	-	-	423102	Biolegend

Supplementary Data 4: *Protocol for quantification of SARS-CoV-2 Spike (S) protein-specific memory B cells*

For detection of **SARS-CoV-2 Spike (S) protein-specific memory B-cells**, biotinylated S protein (Wuhan, 1256 aa) antigen was tetramerized with streptavidin-APC or streptavidin-BV421 probes as described in Dan et al [13]. Streptavidin-APC-Cy7 without biotinylated protein was used as a decoy probe to gate out B cells that non-specifically bind streptavidin. Prior to staining, tetramerized S protein antigen probes and decoy probe were mixed in Brilliant Buffer (BD Bioscience, Cat# 566349) containing 5µM free D-biotin (to minimize potential cross-reactivity between probes) and for staining $3x10^6$ cryopreserved PBMC prepared in 96-well U-bottom plates were incubated with 50µL antigen probe cocktail, containing 100ng S protein tetramer and decoy probes, at 4°C for one hour. Thereafter, surface staining was performed with directly-labeled monoclonal antibodies towards human CD19 (FITC, clone HIB19), human CD27 (PE, clone L128), human CD38 (PerCP-Cy5.5, clone HIT2) and human immunoglobulin D (IgD) (PE-Cy7, clone IA6-2), all BD Bioscience, in Brilliant Buffer at 4°C for 30 min. Dead cells were excluded by using fixable viability dye eFluor-506 (eBioscience, now Thermo Fisher Scientific). Data were acquired on a FACS Canto II flow cytometer by gating on cells with forward/side light scatter properties of lymphocytes and analyzed with FACS Diva 8.0 software. S-specific memory B-cells were quantified as percentages of total memory B-cells, thus including the $CD19^+$ un-switched ($IgD^+/CD27^+$), switched ($IgD^-/CD27^+$) and double-negative ($IgD-/CD27^-$) memory subset (Suppl. Figure 4).