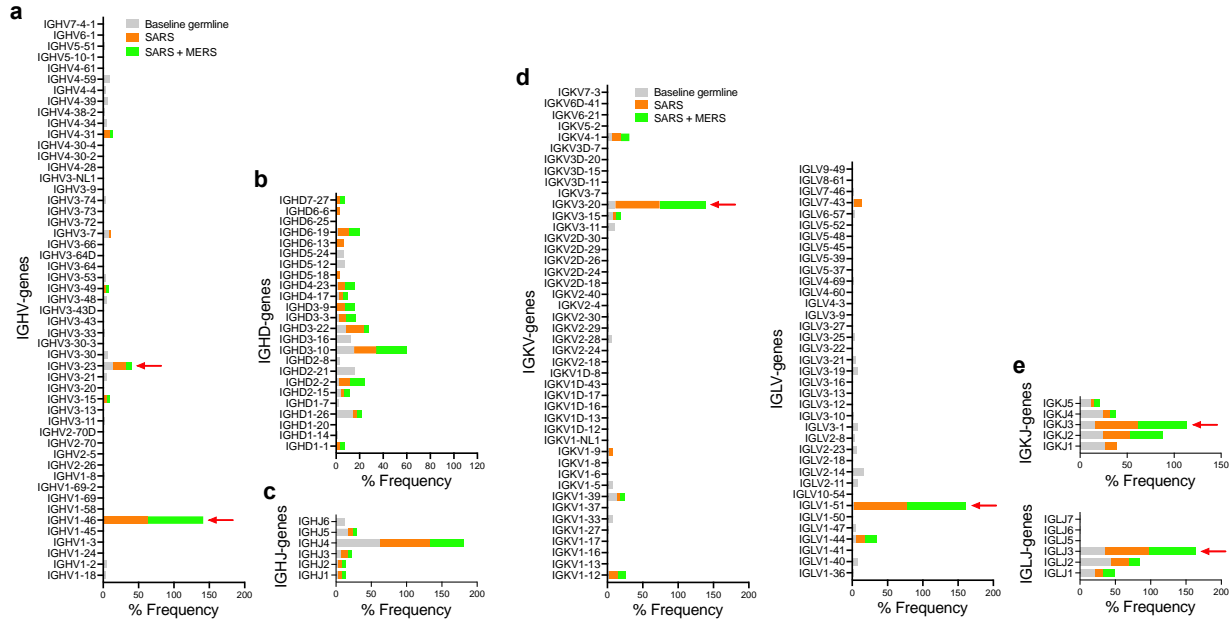


Donor	SARS-2/MERS spike double positive B cells	H/L paired antibodies recovered	(% Efficiency)	Antibodies positive for SARS-2/MERS stem helix peptides binding*	% stem-helix directed	
CC9	50	38	76	10	26	
CC24	20	15	75	2	13	
CC25	26	16	62	7	44	
CC26	3	0	0	0	0	
CC67	40	31	78	3	10	
CC68	16	11	69	2	18	
CC84	44	20	45	2	10	
CC92	99	83	84	2	2	
CC95	52	27	52	9	33	
CC99	8	6	75	3	50	
Total	10	358	247	69	40	16

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 972 **Supplementary Figure 1. Flow cytometry B cell profiling, sorting strategy and**
 973 **SARS-CoV-2 and MERS-CoV S-protein specific B cells in infected-vaccinated**
 974 **donors. a.** Gating strategy for analysis of IgG⁺ B cell populations that bind MERS-CoV
 975 S-protein only (CD3⁻CD4⁻CD8⁻CD14⁻CD19⁺CD20⁺IgM⁻IgG⁺CoV2⁻MERS-CoV⁺), SARS-
 976 CoV-2 S-protein only (CD3⁻CD4⁻CD8⁻CD14⁻CD19⁺CD20⁺IgM⁻IgG⁺CoV2⁺⁺MERS-CoV⁻),
 977 or both MERS-CoV and SARS-CoV-2 S-proteins (CD3⁻CD4⁻CD8⁻CD14⁻CD19⁺CD20⁺IgM⁻
 978 IgG⁺CoV2⁺⁺MERS-CoV⁺). **b.** The frequencies of SARS-CoV-2 S-protein-specific IgG⁺ B
 979 cells (left), SARS-CoV-2 and MERS-CoV double positive S-protein-specific IgG⁺ cross-
 980 reactive B cells (middle) or MERS-CoV S-protein-specific IgG⁺ B cells (right) in PBMCs of
 981 10 infected vaccinated-vaccinated donors. **c.** Summary of the number of SARS-CoV-2 and
 982 MERS-CoV double positive S-protein specific cross-reactive B cells recovered from each
 983 of the donor, number and efficiency of heavy and light chain paired recovered, number of
 984 stem-helix mAb in each donor and their frequency out of the S-protein specific cross-
 985 reactive IgG B cells.

Antibody ID	Hy-gene	D1-gene	H-gene	HC-REGION Identity %	CDRL3-MGMT length	HC-AAA FUNCTION	K/KL-GENE	L-gene	LC-REGION Identity %	CDRL3-MGMT length	LC-AAA FUNCTION	S-Proteins						Spikes						Polyreactivity									
												EC ₅₀ (Binding)						MFI (Binding)						Antibody ID	CHO-SMP	Insulin	ssDNA	HEp2 assay					
												SARS-CoV-2	MERS-CoV	HCoV-OC43	HCoV-NL63	HCoV-229E	MOCK-203T	SARS-CoV-2	SARS-CoV-1	MERS-CoV	HCoV-OC43	HCoV-NL63	HCoV-229E										
CC9-104	IGHV1-46*01	IGHD3-19*01	IGHJ4*02	95	8	CARGSGGKFFW	IKRV3-20*01	IGKJ3*01	96	11	CGQYSSPPPIFF	CC9-104	0.01	0.01	0.02	8.31	0.06	>10	>10	2358	1E+05	1E+05	1E+05	7527	24414	3151	3361	CC9-104	N	N	N	+	
CC9-106	IGHV1-46*01	IGHD3-19*01	IGHJ4*02	95	8	CARGSGGKFFW	IKRV3-20*01	IGKJ3*01	97	11	CGYSSPPPIFF	CC9-106	0.01	0.02	0.03	2.98	0.18	>10	>10	2159	2E+05	8706	1E+05	77010	25364	2475	2163	CC9-106	N	N	N	+	
CC9-111	IGHV1-46*01	IGHD3-3*01	IGHJ4*02	91	13	CASGFGKFLFDW	IKRV3-20*01	IGKJ4*01	95	11	CGYSSPPPIFF	CC9-111	0.01	0.04	0.08	>10	0.30	>10	>10	1407	1E+05	4913	1E+05	77178	29361	2266	2150	CC9-111	Y	N	N	+	
CC9-113	IGHV1-46*01	IGHD3-3*01	IGHJ4*02	94	11	CASGFGKFLFDW	IKRV3-20*01	IGKJ4*01	95	11	CGYSSPPPIFF	CC9-113	0.01	0.02	0.01	0.66	0.19	>10	>10	1978	1E+05	5702	1E+05	1E+05	4367	2516	2481	CC9-113	N	N	N	++	
CC9-131	IGHV1-46*01	IGHD3-3*01	IGHJ4*02	92	11	CASGFGKFLFDW	IKRV3-20*01	IGKJ3*01	95	11	CGYSSPPPIFF	CC9-131	0.02	0.03	0.02	0.28	0.87	>10	>10	1996	1E+05	4421	1E+05	8203	8180	2448	2401	2418	CC9-131	N	N	N	++
CC9-116	IGHV1-46*01	IGHD3-19*01	IGHJ4*02	93	8	CARGSGGKFFW	IKRV3-20*01	IGLJ7-4*01	95	10	CGYSSPPPIFF	CC9-116	0.02	0.10	0.28	>10	>10	>10	>10	2003	1E+05	3630	1E+05	6462	3108	2173	2021	CC9-116	N	N	N	+	
CC9-130	IGHV3-23*01	IGHD2-2*02	IGHJ4*02	95	13	CAFFLQKQLHFLFDW	IKRV3-20*01	IGKJ3*01	96	9	CGQYSSPPPIFF	CC9-130	0.02	0.02	0.17	>10	>10	>10	>10	2304	1E+05	8262	94209	14406	2264	20725	15004	CC9-130	Y	Y	Y	++	
CC9-107	IGHV3-49*05	IGHD3-2*01	IGHJ5*01	89	8	CATTHADYK	IKGV4-1*01	IGKJ5*01	92	9	CGYSSPPPIFF	CC9-107	0.01	0.03	0.02	>10	0.58	>10	>10	2488	1E+05	4348	6298	4787	1791	2481	2259	CC9-107	N	N	N	++	
CC9-114	IGHV3-49*05	IGHD3-2*01	IGHJ5*01	89	8	CATTHADYK	IKGV4-1*01	IGKJ5*01	91	9	CGYSSPPPIFF	CC9-114	0.02	0.05	0.02	>10	0.38	>10	>10	1991	1E+05	3073	6425	4252	3048	2121	2027	CC9-114	Y	Y	Y	++	
CC9-124	IGHV3-7*03	IGHD3-2*01	IGHJ4*02	95	7	CATKRGK	IKGV4-1*01	IGKJ3*01	97	9	CGYSSPPPIFF	CC9-124	0.02	0.05	1.43	>10	3.34	>10	>10	1947	1E+05	41976	18331	7938	6762	2295	2026	CC9-124	N	N	N	+	
CC9-105	IGHV1-46*01	IGHD3-3*01	IGHJ4*02	91	10	CAMTLKDFYD	IKRV3-20*01	IGKJ3*01	95	11	CGYSSPPPIFF	CC9-105	0.02	0.05	0.14	>10	0.68	>10	>10	16287	2E+05	4126	36379	4595	16081	11601	8381	CC9-105	Y	Y	Y	++	
CC9-107	IGHV1-46*01	IGHD3-3*01	IGHJ4*02	94	10	CAMTLKDFYD	IKRV3-20*01	IGKJ3*01	96	11	CGYSSPPPIFF	CC9-107	0.01	0.03	0.08	>10	0.36	>10	>10	2342	2E+05	52719	4919	2470	3236	3627	2787	CC9-107	N	N	N	+	
CC9-104	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	92	10	CAMLSKDFYD	IKRV3-20*01	IGKJ3*01	97	11	CGYSSPPPIFF	CC9-104	0.01	0.02	0.01	1.95	0.60	>10	>10	2377	2E+05	7530	2E+05	8603	3095	2677	2475	CC9-104	N	N	N	-	
CC9-108	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	95	10	CAMLSKDFYD	IKRV3-20*01	IGKJ3*01	97	11	CGYSSPPPIFF	CC9-108	0.01	0.01	0.03	>10	>10	>10	>10	2620	2E+05	6181	8038	4115	2818	2938	2294	CC9-108	N	N	N	+	
CC9-103	IGHV1-46*01	IGHD3-2*01	IGHJ4*02	97	13	CARGSGGKFFW	IKRV1-12*01	IGKJ3*01	96	11	CGYSSPPPIFF	CC9-103	0.01	0.02	0.01	0.88	0.11	>10	>10	1636	2E+05	1E+05	2E+05	9996	4763	2889	2623	CC9-103	N	N	N	++	
CC9-106	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	93	10	CARGSGGKFFW	IKRV3-20*01	IGLJ1-1*01	97	11	CGYSSPPPIFF	CC9-106	0.02	0.03	0.02	0.67	0.47	>10	>10	2056	2E+05	8360	2E+05	8819	3996	2385	2661	CC9-106	N	N	N	++	
CC9-112	IGHV3-23*01	IGHD3-19*01	IGHJ4*02	96	12	CAVYVTVYVFDW	IKRV3-20*01	IGKJ5*01	98	9	CGYSSPPPIFF	CC9-112	0.01	0.02	1.36	>10	>10	>10	>10	2189	2E+05	1E+05	3709	7237	2988	3584	2531	CC9-112	N	N	N	++	
CC9-101	IGHV3-23*04	IGHD4-1*01	IGHJ2*01	95	13	CAMTVYKDFYD	IKRV3-20*01	IGKJ2*01	96	9	CGYSSPPPIFF	CC9-101	0.04	0.04	0.05	>10	>10	>10	>10	2387	2E+05	8012	6598	9978	2511	2545	2382	CC9-101	N	N	N	++	
CC9-105	IGHV4-31*03	IGHD3-2*01	IGHJ3*01	93	15	CAMTSAGGSGSAMFW	IKGV1-51*01	IGLJ2*02	95	10	CGAMSSSLWF	CC9-105	0.02	0.05	0.03	>10	>10	>10	>10	15034	2E+05	59737	7865	7757	3707	3468	2951	CC9-105	N	N	N	++	
CC9-108	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	94	10	CYVAVSGDFD	IKRV3-20*01	IGKJ3*01	94	11	CGYSSPPPIFF	CC9-108	0.02	0.03	0.04	>10	>10	>10	>10	2292	2E+05	6480	95054	6317	4595	3183	2843	CC9-108	N	N	N	-	
CC9-105	IGHV3-23*01	IGHD3-13*01	IGHJ4*02	92	11	CAMTVYKDFYD	IKRV3-20*01	IGKJ1*01	97	9	CGYSSPPPIFF	CC9-105	0.01	0.02	0.43	>10	>10	>10	>10	16486	2E+05	6105	5485	2615	4737	4821	3821	CC9-105	N	Y	N	++	
CC9-130	IGHV3-23*04	IGHD3-19*01	IGHJ4*02	92	12	CAMTVYKDFYD	IKRV3-20*01	IGKJ4*01	94	9	CGYSSPPPIFF	CC9-130	0.01	0.02	2.97	>10	>10	>10	>10	2551	2E+05	1E+05	1E+05	665	2391	391	3561	CC9-130	N	N	N	-	
CC9-104	IGHV1-46*01	IGHD3-2*01	IGHJ4*02	94	11	CARGSGGKFFW	IKRV3-20*01	IGKJ3*01	98	11	CGYSSPPPIFF	CC9-104	0.01	0.01	0.01	4.08	0.58	>10	>10	1719	1E+05	4036	2E+05	6849	2881	2438	2047	CC9-104	N	N	N	-	
CC9-109	IGHV1-46*01	IGHD3-2*01	IGHJ4*02	95	11	CARGSGGKFFW	IKRV3-20*01	IGKJ3*01	98	11	CGYSSPPPIFF	CC9-109	0.01	0.04	0.01	>10	0.45	>10	>10	1763	1E+05	4668	1E+05	6761	3200	2161	2117	CC9-109	N	N	N	-	
CC9-102	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	95	12	CAMTVYKDFYD	IKRV1-4*01	IGLJ2*01	97	10	CGAMSSSLWF	CC9-102	0.01	0.02	0.10	0.18	0.33	>10	>10	2471	1E+05	7538	1E+05	7243	3036	2788	2428	CC9-102	N	N	N	++	
CC9-115	IGHV1-46*01	IGHD3-6*01	IGHJ4*02	95	13	CASFPGSSSLGW	IKGV1-12*01	IGKJ3*01	96	11	CGYSSPPPIFF	CC9-115	0.01	0.01	3.06	>10	>10	>10	>10	2159	1E+05	5075	2096	2697	3033	2512	2279	CC9-115	N	Y	N	++	
CC9-133	IGHV1-46*01	IGHD1-26*01	IGHJ2*01	96	11	CARGSGGKFFW	IKRV3-20*01	IGKJ2*01	93	11	CGYSSPPPIFF	CC9-133	0.04	0.03	0.04	>10	0.43	>10	>10	1185	1E+05	5025	2E+05	4835	2648	2316	2148	CC9-133	Y	Y	Y	++	
CC9-127	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	91	11	CAMTVYKDFYD	IKRV3-20*01	IGKJ2*01	92	11	CGYSSPPPIFF	CC9-127	0.01	0.02	0.10	0.18	0.33	>10	>10	2471	1E+05	7538	1E+05	7243	3036	2788	2428	CC9-127	N	N	N	++	
CC9-108	IGHV1-46*01	IGHD3-15*01	IGHJ4*02	93	10	CARGSGGKFFW	IKRV1-51*02	IGLJ2*02	95	11	CGAMTVYKDFYD	CC9-108	0.01	0.02	0.01	0.68	0.09	>10	>10	1631	1E+05	8062	2E+05	8045	4096	4152	3558	CC9-108	N	N	N	++	
CC9-109	IGHV1-46*01	IGHD3-15*01	IGHJ4*02	95	10	CARGSGGKFFW	IKRV1-51*02	IGLJ2*02	95	11	CGYSSPPPIFF	CC9-109	0.01	0.03	0.02	>10	1.37	>10	>10	1959	1E+05	5296	1E+05	20142	3434	2381	2101	CC9-109	N	N	N	++	
CC9-118	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	93	10	CAMTVYKDFYD	IKRV3-20*01	IGKJ3*01	95	11	CGYSSPPPIFF	CC9-118	0.01	0.01	0.01	>10	>10	>10	>10	1897	2E+05	6219	1E+05	2973	3668	2793	2890	CC9-118	N	N	N	-	
CC9-122	IGHV1-46*01	IGHD3-10*01	IGHJ4*02	91	12	CAMLSKDFYD	IKRV1-51*02	IGLJ2*02	93	11	CGAMSSSLWF	CC9-122	0.01	0.01	0.01	0.08	0.65	>10	>10	2778	2E+05	8401	2E+05	2E+05	3441	3415	2942	CC9-122	N	N	N	++	
CC9-110	IGHV1-46*01	IGHD2-2*01	IGHJ5*01	89	10	CARGSGGKFFW	IKRV1-51*02	IGLJ2*02	91	11	CGYSSPPPIFF	CC9-110	0.01	0.02	0.01	3.27	1.08	>10	>10	1830	1E+05	5218	1E+05	7102	2317	3473	2922	CC9-110	N	N	N	+	
CC9-116	IGHV3-15*01	IGHD1-1*01	IGHJ4*02	92	11	CAMTVYKDFYD	IKRV4-1*01	IGKJ2*02	96	8	CGYSSPPPIFF	CC9-116	0.01	0.02	0.01	>10	0.88	>10	>10	1959	2E+05												

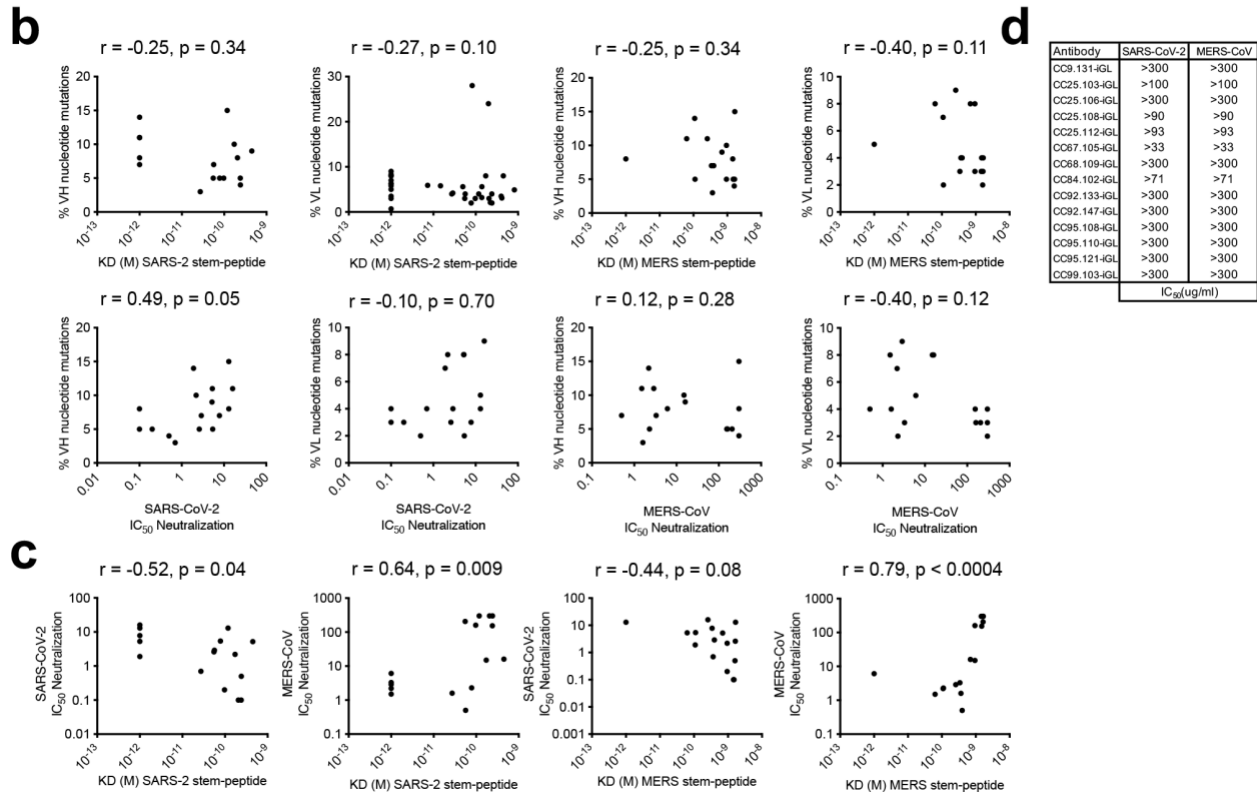


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Supplementary Figure 3. Immunoglobulin heavy and light chain gene usage and enrichment in isolated mAbs compared to a reference human germline database. Baseline germline frequencies of heavy chain genes (IGHV, IGHD and IGHJ genes) (**a**., **b**., **c**) and light chain genes (IGKV, IGLV, IGKJ and IGLJ genes) (**d**., **e**) are shown in grey, and S2 stem helix sarbecovirus bnAbs (SARS: orange) and sarbecovirus + MERS-CoV bnAb (SARS + MERS: green) are shown. Arrows indicate gene enrichments compared to human baseline germline frequencies.

a

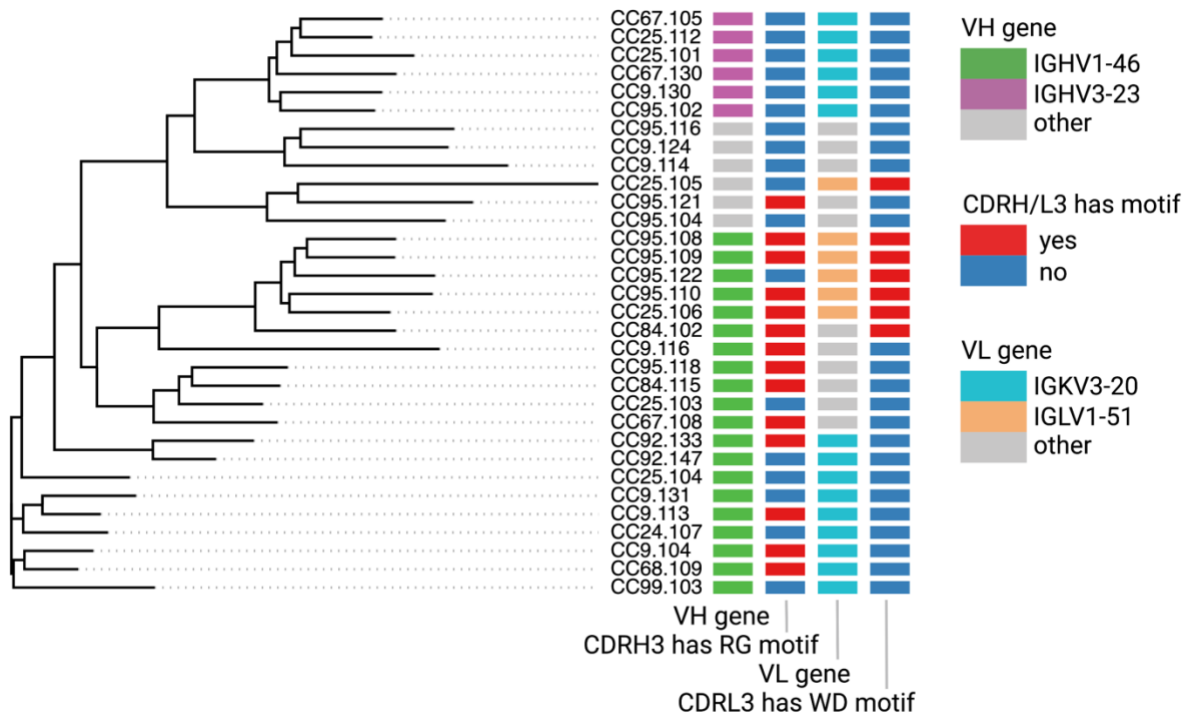
Antibody	Stem-helix peptide								S-protein							
	SARS-CoV-2				MERS-CoV				SARS-CoV-2				MERS-CoV			
	Response	KD (M)	kon(1/Ms)	koff(1/Ms)	Response	KD (M)	kon(1/Ms)	koff(1/Ms)	Response	KD ^{app} (M)	kon(1/Ms)	koff(1/Ms)	Response	KD ^{app} (M)	kon(1/Ms)	koff(1/Ms)
CC9.130	5.92	2.40E-10	6.16E+05	1.48E-04	6.43	1.50E-09	7.64E+05	1.15E-03	1.14	<1.0E-12	5.47E+05	<1.0E-7	1.22	1.89E-09	3.22E+05	6.11E-04
CC9.131	4.77	<1.0E-12	6.64E+05	<1.0E-7	4.53	<1.0E-12	7.64E+05	<1.0E-7	0.95	1.07E-10	4.01E+05	4.27E-05	0.69	6.98E-10	1.85E+05	1.29E-04
CC25.103	5.09	2.72E-11	6.46E+05	1.76E-05	5.51	3.64E-10	7.51E+05	2.73E-04	1.12	<1.0E-12	4.80E+05	<1.0E-7	1.15	1.32E-09	2.71E+05	3.57E-04
CC25.106	5.50	<1.0E-12	6.25E+05	<1.0E-7	5.98	3.42E-10	7.32E+05	2.50E-04	0.96	<1.0E-12	4.01E+05	<1.0E-7	0.97	4.51E-10	2.65E+05	1.19E-04
CC25.108	5.33	9.73E-11	6.25E+05	6.08E-05	5.72	9.47E-10	7.39E+05	6.99E-04	1.17	<1.0E-12	5.46E+05	<1.0E-7	1.21	2.04E-09	2.92E+05	5.95E-04
CC25.112	6.08	2.41E-10	6.80E+05	1.64E-04	5.70	1.61E-09	9.26E+05	1.49E-03	1.09	<1.0E-12	4.27E+05	<1.0E-7	0.91	4.40E-09	3.05E+05	1.34E-03
CC67.105	5.88	2.06E-10	7.05E+05	1.46E-04	6.53	1.45E-09	8.26E+05	1.20E-03	1.20	<1.0E-12	5.66E+05	<1.0E-7	1.11	1.96E-09	3.06E+05	6.00E-04
CC68.109	4.72	7.83E-11	5.60E+05	4.38E-05	4.78	1.11E-10	6.53E+05	7.23E-05	0.88	6.96E-11	3.64E+05	2.53E-05	0.74	<1.0E-12	1.98E+06	<1.0E-7
CC84.102	5.92	5.49E-11	7.23E+05	3.97E-05	5.09	1.64E-09	1.17E+06	1.92E-03	0.99	<1.0E-12	4.41E+05	<1.0E-7	0.99	2.17E-09	2.93E+05	6.36E-04
CC92.133	5.48	<1.0E-12	9.60E+05	<1.0E-7	5.36	1.09E-10	1.16E+06	1.27E-04	1.11	2.33E-11	4.62E+05	1.08E-05	1.04	6.54E-10	2.32E+05	1.52E-04
CC92.147	3.90	4.48E-10	2.60E+05	1.16E-04	4.08	6.95E-10	2.91E+05	2.02E-04	0.80	3.17E-10	3.49E+05	1.11E-04	0.63	4.84E-10	2.19E+05	1.06E-04
CC95.104	5.63	1.72E-10	5.73E+05	9.82E-05	5.93	9.43E-10	8.30E+05	7.82E-04	1.24	<1.0E-12	8.02E+05	<1.0E-7	1.23	8.65E-10	3.80E+05	3.28E-04
CC95.108	5.81	5.64E-11	5.39E+05	3.04E-05	6.45	3.98E-10	6.13E+05	2.44E-04	1.06	<1.0E-12	5.28E+05	<1.0E-7	1.09	3.41E-10	3.45E+05	1.18E-04
CC95.110	5.18	<1.0E-12	6.28E+05	<1.0E-7	5.35	2.56E-10	7.54E+05	1.93E-04	0.87	2.81E-10	3.33E+05	9.34E-05	0.80	5.18E-10	2.04E+05	1.05E-04
CC95.121	4.84	1.18E-10	6.04E+05	7.11E-05	4.91	1.67E-09	9.08E+05	1.51E-03	0.93	7.09E-11	3.74E+05	2.65E-05	0.80	3.13E-09	2.10E+05	6.56E-04
CC99.103	5.43	<1.0E-12	9.27E+05	<1.0E-7	5.39	6.30E-11	1.01E+06	6.35E-05	1.11	<1.0E-12	5.38E+05	<1.0E-7	1.10	3.09E-10	2.80E+05	8.66E-05
CC9.130-iGL	0.76	1.08E-08	2.88E+05	3.10E-03	0.15	ND	ND	ND	0.12	ND	ND	ND	0.13	ND	ND	ND
CC9.131-iGL	3.22	1.77E-09	2.68E+05	4.75E-04	2.12	5.61E-09	5.16E+05	2.16E-03	0.31	9.29E-10	1.69E+05	1.57E-04	0.02	ND	ND	ND
CC25.103-iGL	4.47	1.35E-09	3.56E+05	4.81E-04	1.01	3.45E-09	1.19E+06	2.95E-03	0.66	5.53E-10	2.30E+05	1.27E-04	0.01	ND	ND	ND
CC25.106-iGL	7.23	4.09E-10	1.08E+06	4.42E-04	4.84	1.12E-09	3.01E+06	2.85E-03	0.92	<1.0E-12	2.56E+05	<1.0E-7	0.43	7.14E-09	3.08E+05	2.20E-03
CC25.108-iGL	5.45	8.75E-10	5.12E+05	4.48E-04	2.65	1.72E-09	4.32E+05	6.08E-04	1.10	<1.0E-12	4.74E+05	<1.0E-7	0.39	2.23E-09	1.87E+05	4.18E-04
CC25.112-iGL	4.42	3.10E-09	5.00E+05	1.55E-03	1.34	2.81E-09	7.46E+05	1.64E-03	0.66	1.21E-09	2.06E+05	2.49E-04	0.04	ND	ND	ND
CC67.105-iGL	4.16	1.19E-09	2.49E+05	2.96E-04	2.24	4.99E-09	2.63E+05	1.21E-03	0.57	7.96E-10	2.92E+05	2.33E-04	0.29	3.87E-09	2.24E+05	8.69E-04
CC68.109-iGL	4.89	9.469E-10	5.24E+05	4.96E-04	3.89	2.027E-09	7.10E+05	1.44E-03	0.74	2.06E-10	2.37E+05	4.89E-05	0.31	1.26E-09	1.15E+06	1.45E-03
CC84.102-iGL	5.65	3.11E-09	3.57E+05	1.11E-03	2.25	2.20E-09	8.08E+05	1.36E-03	0.91	<1.0E-12	3.70E+05	<1.0E-7	0.53	3.27E-09	2.64E+05	8.65E-04
CC92.133-iGL	4.63	1.52E-09	4.32E+05	6.56E-04	2.08	2.11E-09	7.45E+05	1.57E-03	0.69	<1.0E-12	1.99E+05	<1.0E-7	0.02	ND	ND	ND
CC92.147-iGL	1.61	1.95E-09	5.03E+05	9.82E-04	0.16	ND	ND	ND	0.08	ND	ND	ND	0.01	ND	ND	ND
CC95.104-iGL	2.55	1.131E-10	8.63E+04	<1.0E-7	1.78	3.05E-09	1.75E+05	2.03E-04	0.62	1.44E-09	1.06E+06	1.52E-03	0.12	ND	ND	ND
CC95.108-iGL	6.20	3.41E-10	3.78E+05	1.29E-04	6.61	1.72E-09	4.63E+05	8.02E-04	0.89	3.23E-10	4.38E+05	1.41E-04	0.87	1.85E-09	3.06E+05	5.66E-04
CC95.110-iGL	6.36	1.94E-09	4.36E+05	8.46E-04	3.74	3.69E-09	1.04E+06	2.80E-03	0.69	6.83E-09	4.11E+05	2.80E-03	0.44	2.60E-09	2.01E+05	5.22E-04
CC95.121-iGL	2.50	4.07E-09	5.97E+05	2.43E-03	0.54	2.27E-09	6.91E+05	1.57E-03	0.26	1.27E-08	5.43E+05	6.90E-03	0.22	4.02E-09	1.87E+05	7.53E-04
CC99.103-iGL	4.62	1.83E-09	4.00E+05	7.30E-04	2.71	3.51E-09	7.27E+05	2.35E-03	0.68	1.00E-10	2.17E+05	2.18E-05	0.06	ND	ND	ND
DEN3	0.16	ND	ND	ND	0.16	ND	ND	ND	0.01	ND	ND	ND	0.05	ND	ND	ND



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Supplementary Figure 5. BLI Binding of S2 stem bnAbs and their iGLs with SARS-CoV-2 and MERS-CoV stem-helix peptides and S-proteins and association with SHMs and Neutralization. **a.** BioLayer Interferometry (BLI) binding kinetics of 16 S2 stem-helix bnAbs and their inferred germline (iGL) Ab versions with SARS-CoV-2 and MERS-CoV stem-helix peptides and S-proteins. Binding kinetics were obtained using the 1:1 binding kinetics fitting model on ForteBio Data Analysis software and maximum binding responses, dissociations constants (K_D) and on-rate (k_{on}) and off-rate constants (k_{off}) for each antibody peptide interaction are shown. K_D , k_{on} and k_{off} values were calculated only for antibody-antigen interactions where a maximum binding response of

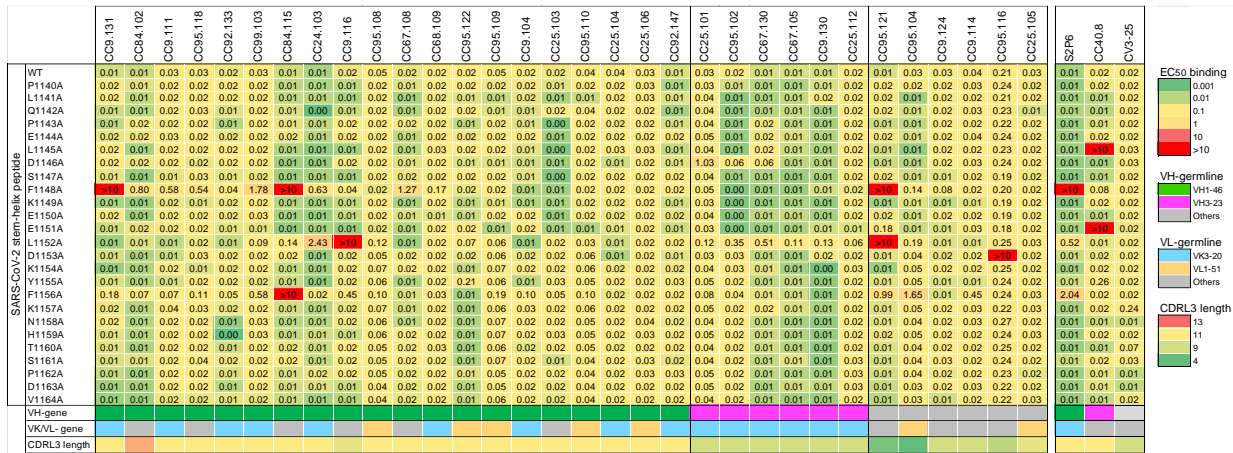
1039 0.2nm was obtained. MAbs were also tested with SARS-CoV-2 and MERS-CoV S-
1040 proteins and the responses, apparent binding constants (K_D^{App}) and k_{on} and k_{off} constants
1041 for each antibody-antigen interaction are indicated. The iGL Ab versions of stem-helix
1042 bnAbs showed reduced binding compared their mature versions. **b.** Correlations of stem-
1043 helix mAb binding (K_D (M) values) to SARS-CoV-2 and MERS-CoV peptides and virus
1044 neutralization with heavy (VH) chain and light (VL) chain SHM levels. **c.** Correlations of
1045 stem-helix mAb binding (K_D (M) values) to SARS-CoV-2 and MERS-CoV peptides with
1046 neutralization against their corresponding viruses. Correlations were determined by
1047 nonparametric Spearman correlation two-tailed test with 95% confidence interval. The
1048 Spearman correlation coefficient (r) and p-value are indicated. **d.** IC₅₀ neutralization of S2
1049 stem-helix bnAb iGLs with SARS-CoV-2 and MERS-CoV.



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Supplementary Figure 6. Immunogenetics analysis of heavy and light chain sequences of 32 unique S2 stem-helix mAbs. The phylogenetic tree represents concatenated heavy and light chain amino acid sequences of 32 S2 stem-helix mAbs. mAbs IDs are shown on the right. Four colored columns on the right show the following characteristics of mAbs (from left to right): (1) the germline V gene of each heavy chain (IGHV1-46: green, IGHV3-23: plum, others: gray), (2) the presence of RG motif in the amino acid sequence of each CDRH3 (motif is present: red, motif is missing: blue), (3) the germline V gene of each light chain (IGKV3-20: sky, IGLV1-51: cantaloupe, others: gray), (4) the presence of WD motif in the amino acid sequence of each CDRL3 (motif is present: red, motif is missing: blue).

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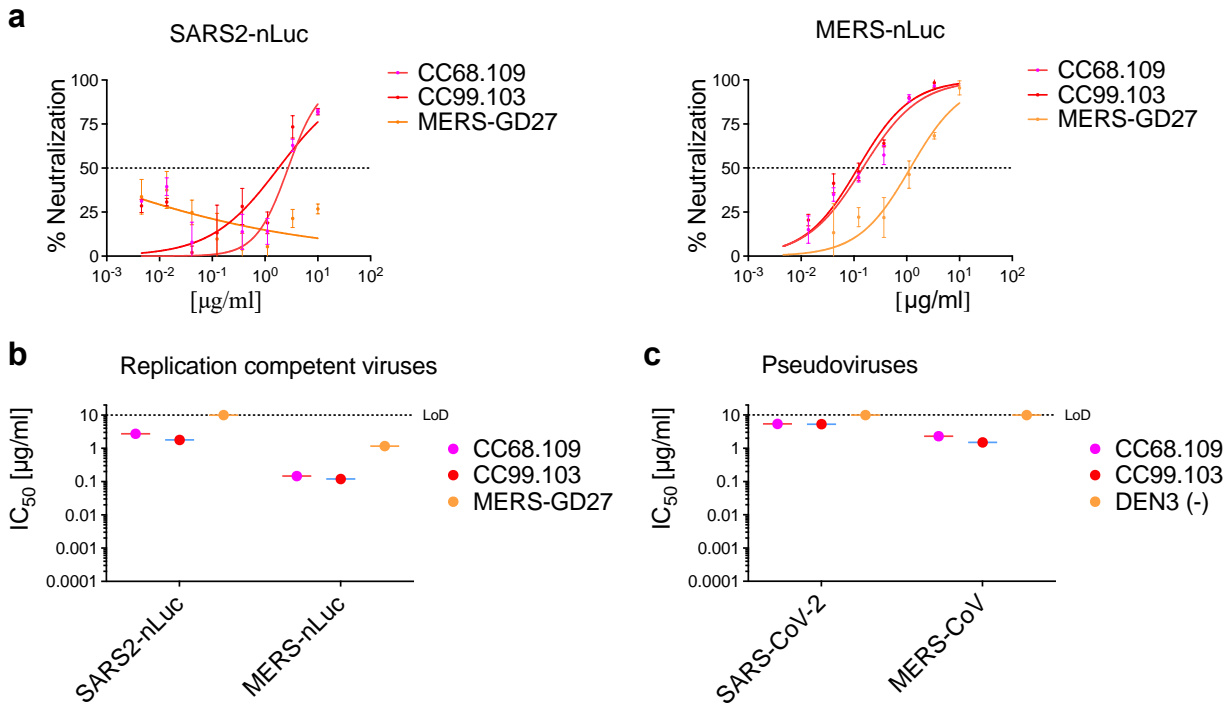
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Supplementary Figure 7. Epitope mapping of S2 stem-helix bnAbs with SARS-CoV-2 stem-helix peptide alanine scan mutants. Heatmap showing EC₅₀ ELISA binding titers of S2-stem helix bnAbs to 25mer SARS-CoV-2 stem-helix peptide and its alanine scan mutants. Three hydrophobic residues, F¹¹⁴⁸, L¹¹⁵² and F¹¹⁵⁶ were commonly targeted by stem-helix bnAbs. S2 stem-helix bnAbs are grouped based on their heavy chain gene usage (IGHV1-46, IGHV3-23 and others). The light chain germline genes (IGKV3-20, IGLV1-51 and other) and CDRL3 lengths are shown. S2P6, CC40.8 and CV3-25 S2 stem-helix mAbs were used as controls.



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Supplementary Figure 8. Neutralization of replication competent betacoronaviruses by select S2-stem helix bnAbs. **a.** Neutralization of replication competent viruses encoding SARS-CoV-2 (SARS2-nLuc), and MERS-CoV (MERS-nLuc) by 2 select S2 stem-helix bnAbs, CC68.109, and CC99.103. MERS-GD27 antibody (2) was a positive control for the MERS-CoV neutralization assay. **b-c.** Comparison of IC₅₀ neutralization titers of S2 stem-helix bnAbs with replication-competent (**b**) and pseudoviruses (**c**) of SARS-CoV-2 and MERS-CoV.

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