SUPPLEMENTARY TABLES

Supplementary Table S1

Patient	*Genetic characteristics*
MM195	n.d.
MM104	n.d.
MM078	Gain of 11q23
MM165	Gain of 8q24 (MYC), 9q34, 11q23, 19q13, 15q22, 1q21.
MM061	Deletion of 13q14. Gain of 9q34. IGH/CCND1 fusion (1-2 fusion signals).
MM112	n.d.
MM204	IGH/CCND1 fusion, subclone with IGH translocation with an unknown partner.
MM008	n.d.
MM003	Gain of 9q34, 11q23, 19q13, 15q22
MM157	IGH/CCND1 fusion. MYC rearrangement
MM050	Deletion of 13q14. Gain of MYC, 9q34, 11q23, 15q22, 19q13
MM139	Deletion of 1p32. Gain of 9q34, 11q23, 15q22, 19q13
MM160	Gain of 1q21, 9q34, 11q23, 15q22, 17p13, 19q13. Deletion of 13q14

Supplementary Table S1. Genetic characteristics of the study cohort.

Genetic characteristics were determined as part of routine clinical diagnostics by fluorescence in situ hybridization. n.d. indicates not determined.

Supplementary Table S2

Target	*Clone*	*Fluorescent dye*	*Vendor*	*RRID/Cat.No.*
CD8	RPA-T8	BV510	BioLegend	AB_2561942
CD57	HCD574	FITC	BioLegend	Cat.No. 322306
PD-1	EH12.2H7	PerCP-Cy5.5	BioLegend	AB_1595461
BTLA	J168-570	PE-CF594	BD Biosciences	AB_2738960
TCRαβ	IP26	APC	BioLegend	AB_10612569
CD45RA	HI100	AF700	BioLegend	AB_493763
CD38	HIT2	PE-Cy7	BioLegend	AB_2072782
CD39	A1	PE-Cy7	BioLegend	AB_2099950
CD25	CD25-4E3	PE-Cy7	eBioscience	AB_2573336
CTLA-4	BNI3	PE	BioLegend	AB_2566796
CCR7	G043H7	BV650	BioLegend	AB_2563867
CD28	CD28.2	BV421	BioLegend	AB_2561910
TIM-3	7D3	BV711	BD Biosciences	AB_2744370
CD4	SK3	APC-Fire750	BioLegend	AB_2572097
Live/dead		Zombie Yellow	BioLegend	Cat.No. 423103

Supplementary Table S2. Antibodies for FACS index sorting.

APC indicates allophycocyanin; BV, Brilliant Violet; FITC, fluorescein isothiocyanate; PerCP, peridinin chlorophyll; Cy, cyanine; PE, phycoerythrin; AF, Alexa Fluor; and n.a., not available.

Supplementary Table S3

Patient	TCR	TRAV	CDR3α amino acid sequence	TRAJ	TRBV	CDR3β amino acid sequence	TRBJ	Expressed in 58α⁻β⁻	Expressed in Human PBL
MM008	15C7	14/DV4*02	CAMREEMDSSYKLIF	12*01	9*01	CASSLRRGGPLQETQYF	2-5*01	Yes	No
MM008	15F10	21*01	CAVKGGSGTYKYIF	40*01	13*01	CASTLQGLPSYEQYF	2-7*01	Yes	No
MM008	14F10	9-2*01	CALSYGNNRLAF	7*01	6-5*01	CASRSRVSKTEAFF	1-1*01	Yes	No
MM008	15D7	8-6*01	CAALYNQGGKLIF	23*01	7-6*01	CASSSGGDYEQYF	2-7*01	Yes	No
MM008	11D7	12-2*01	CAVPTSYDKVIF	50*01	25-1*01	CASQTGGQSEQFF	2-1*01	Yes	No
MM008	14E10	20*01	CAVQPGGSYIPTF	6*01	3-1*01	CASSEGDYEQYF	2-7*01	Yes	No
MM008	15E10	17*01	CATVTRMDSSYKLIF	12*01	7-9*01	CASSLIGISSYNEQFF	2-1*01	Yes	No
MM008	15B1	20*01	CAVQAGRDSNYQLIW	33*01	19*01	CASKVGGHSSTEAFF	1-1*01	Yes	No
MM008	11F4	24*01	CAPSYSGAGSYQLTF	28*01	4-2*01	CASSPTESTGTYEQYF	2-7*01	Yes	No
MM008	11B3	14/DV4*02	CAMRGEMDSSYKLIF	12*01	9*01	CASSPRRGGPVSETQYF	2-5*01	Yes	No
MM008	13A6	25*01	CAGPPIAGANNLFF	36*01	5-1*01	CASSLVGRGQNEQFF	2-1*01	Yes	No
MM008	15G9	24*01	CALGYTGGFKTIF	9*01	3-1*01	CASSHTMMSPLPYSYEQYF	2-7*01	Yes	No
MM008	12H5	19*01	CALGPGSARQLTF	22*01	27*01	CASSVGPAWNTEAFF	1-1*01	Yes	No
MM050	11B7α1	12-2*01	CAVSYNFNKFYF	21*01	5-6*01	CASSLLEEQFF	2-1*01	Yes	Yes
MM050	11B7α2	12-1*01	CVVNKNYGGSQGNLIF	42*01	5-6*01	CASSLLEEQFF	2-1*01	Yes	Yes
MM050	1B3α1	38-2/DV8*01	SAGNMLTF	39*01	2*01	CASSWDGGSRDQPQHF	1-5*01	No	Yes
MM050	1B3α2	38-2/DV8*01	CASLFTGNQFYF	49*01	2*01	CASSWDGGSRDQPQHF	1-5*01	Yes	Yes
MM050	2D12	38-2/DV8*01	CAYRSSGDMRF	43*01	6-5*01	CASSPGTPRDTQYF	2-3*01	Yes	Yes
MM050	2E4	12-1*01	CVVTSGNTPLVF	29*01	10-1*01	CASSDLEEGPTDTQYF	2-3*01	Yes	Yes
MM050	2B3	20*01	CAVQAPIQGAQKLVF	54*01	4-1*01	CASSQVTRADIQYF	2-4*01	Yes	Yes
MM050	2H5	8-6*01	CAVSNMNTGFQKLVF	8*01	7-8*01	CASSLGGAGTGDTQYF	2-3*01	Yes	Yes
MM050	2B4	19*01	CALGTGGGNKLTF	10*01	4-2*01	CASSQEVAGVQETQYF	2-5*01	Yes	Yes
MM050	3D6	14/DV4*02	CAILTLTGTASKLTF	44*01	5-6*01	CASSTHRDIESYEQYF	2-7*01	Yes	Yes
MM050	2C8	38-2/DV8*01	CAYSGGGADGLTF	45*01	6-2*01	CASSYSDLRGTQYF	2-5*01	Yes	Yes
MM139	10F5	1-2*01	CAVIGEDDKIIF	30*01	7-8*01	CASSSRSTGELFF	2-2*01	Yes	Yes
MM139	10G9	1-1*01	CAVPGDSSYKLIF	12*01	10-3*01	CAISESGTVNTEAFF	1-1*01	Yes	Yes
MM139	10D7	38-2/DV8*01	CAYREGGAQKLVF	54*01	19*01	CASSIGRRGNQPQHF	1-5*01	Yes	Yes
MM139	10H7	19*01	CALRSSNTGKLIF	37*02	4-1*01	CASSQEMGSNQPQHF	1-5*01	Yes	Yes
MM139	10F7	12-1*01	CVVNIPANTGGFKTIF	9*01	10-2*01	CASSPGTGTYGYTF	1-2*01	Yes	Yes
MM139	10F3	35*01	CAGSGSLQGAQKLVF	54*01	19*01	CASRGTGTGSSYEQYF	2-7*01	Yes	Yes
MM139	6C1	5*01	CALRGFGNEKLTF	48*01	29-1*01	CSTRDDNYEQYF	2-7*01	Yes	Yes
MM139	10G1	17*01	CATGFSDGQKLLF	16*01	27*01	CASSPRAGGGSNYGYTF	1-2*01	No	Yes
MM139	10B5	24*01	CAFSTGTASKLTF	44*01	12-3*01	CASSLARPEAPLHF	1-6*02	Yes	Yes
MM139	10F4	1-2*01	CAVRDNDYKLSF	20*01	6-1*01	CASSQLGGEGTDTQYF	2-3*01	Yes	Yes
MM139	7D2	12-2*01	CAVGDSNYQLIW	33*01	6-5*01	CASSYSGQGGYEQYF	2-7*01	Yes	Yes
MM157	11A5	17*01	CATEGDFGNEKLTF	48*01	15*02	CATSSHGGETQYF	2-5*01	Yes	No

MM157	11D1α1	34*01	CGADNGSGYSTLTF	11*01	28*01	CASSLELAGEDYEQYF	2-7*01	Yes	No
MM157	11D1α2	21*01	CAVPSGGYNKLIF	4*01	28*01	CASSLELAGEDYEQYF	2-7*01	Yes	No
MM157	12G9	14/DV4*02	CAMREEEDNAGNMLTF	39*01	7-6*01	CASSLGWSTQYF	2-5*01	Yes	No
MM157	13D8	14/DV4*02	CAITQRYNAGNMLTF	39*01	12-3*01	CASSFSPGRTNTEAFF	1-1*01	Yes	No
MM157	12D1	12-2*01	CAVTGANNLFF	36*01	7-8*01	CASSLSLSYEQYF	2-7*01	Yes	No
MM157	12E1	27*01	CATAGTYKYIF	40*01	5-5*01	CASSPATEGIQYF	2-4*01	Yes	No
MM157	13B10	21*01	CAVTQFAYSGAGSYQLTF	28*01	28*01	CASSDPGQGNTGELFF	2-2*01	Yes	No
MM157	11D7	29/DV5*01	CAASLDYKLSF	20*01	27*01	CASSFGMGTDTQYF	2-3*01	Yes	No
MM157	13G1α1	27*01	CAGAKDAGNMLTF	39*01	7-9*01	CASSLIGVSSYNEQFF	2-1*01	Yes	No
MM157	13G1α2	17*01	CATVVRMDSSYKLIF	12*01	7-9*01	CASSLIGVSSYNEQFF	2-1*01	Yes	No
MM157	11E6	35*01	CAGQLLLYSGAGSYQLTF	28*01	27*01	CASRALAELYNEQFF	2-1*01	Yes	No
MM157	13E11	29/DV5*01	CAASADYKLSF	20*01	27*01	CASSFGQGADTQYF	2-3*01	Yes	No
MM157	11H9	14/DV4*02	CAMREGGVNRDDKIIF	30*01	2*01	CASRITETLSYEQYF	2-7*01	Yes	No
MM157	13D3	10*01	CVVTGRMDSSYKLIF	12*01	7-9*01	CASSLLGEGRQYEQYF	2-7*01	Yes	No
MM157	13C2	3*01	CAVRDRSSRDNYGQNFVF	26*01	4-1*01	CASSQELAWTYEQYF	2-7*01	Yes	No
MM157	11A11	29/DV5*01	CAASAGGNKLVF	47*01	2*01	CASSTRDEQYF	2-7*01	Yes	No
MM157	12H4	19*01	CALSEAESGGSYIPTF	6*01	7-6*01	CASSSFLVGLEADTQYF	2-3*01	Yes	No
MM157	12G1	5*01	CAETPLDKIIF	30*01	14*01	CASRAATYNEQFF	2-1*01	Yes	No
MM160	16C6	14/DV4*02	CAMREPPNRNNNARLMF	31*01	7-7*01	CASSLAGAGGNEQFF	2-1*01	Yes	No
MM160	16A9	19*01	CALSPRGGADGLTF	45*01	19*01	CASSIEGSSYNEQFF	2-1*01	Yes	No
MM160	16H9	8-2*01	CAVRPNFGNEKLTF	48*01	20-1*01	CSACVIRTSGQPSSTDTQYF	2-3*01	Yes	No
MM160	16A2	19*01	CALSEPGGGADGLTF	45*01	28*01	CASSLLAEYNEQFF	2-1*01	Yes	No
MM160	16F6	34*01	CGADMDSNSGYALNF	41*01	20-1*01	CSASEVEGAFEHSSYNEQFF	2-1*01	Yes	No
MM160	16F10	19*01	CALSEAWNAGNMLTF	39*01	13*01	CASSPDGPGLDYGYTF	1-2*01	Yes	No
MM160	18G9	19*01	CALSEEGSEKLVF	57*01	28*01	CASTEETPNEKLFF	1-4*01	Yes	No
MM160	17G7	16*01	CALSGRTGFQKLVF	8*01	7-9*01	CASSAPRTLAGTSYEQYF	2-7*01	Yes	No
MM160	17C11	19*01	CALSVGTSYGKLTF	52*01	19*01	CASSILPGGSYEQYF	2-7*01	Yes	No
MM160	16D10	19*01	CALSEASGYGGSQGNLIF	42*01	19*01	CASSTLPGQFYEQYF	2-7*01	Yes	No
MM160	18A12	19*01	CALSDNYGQNFVF	26*01	19*01	CASSTLPGQGARLGYTF	1-2*01	Yes	No
MM160	17C6	4*01	CLVGDLSSNTGKLIF	37*02	28*01	CASSWGYGYTF	1-2*01	Yes	No
MM160	17D1	26-2*01	CILRADSNYQLIW	33*01	2*01	CASSYGQFGESYEQYF	2-7*01	Yes	No
MM160	16E5	9-2*01	CALRPYNQGGKLIF	23*01	30*01	CAWSFTGEGYGYTF	1-2*01	Yes	No

Supplementary Table S3. Re-expressed TCRs of dominant T cell clones.

TRAV indicates TCRα V-gene and allele; TRAJ, TCRα J-gene and allele; TRBV, TCRβ V-gene and allele; TRBJ, TCRβ J-gene and allele; and PBL, peripheral blood lymphocytes.

Supplementary Table S4

Patient	*TCR-recombinant 58$\alpha^-\beta^-$ (cell number)*	*CD38-enriched BM, (cell number)*	*CD38-depleted BM, (cell number)*	*TCR-transduced human PBL (cell number)*
MM008	60 000	100 000	100 000	-
MM050	60 000	100 000	100 000	100 000
MM139	60 000	100 000	100 000	100 000
MM157	60 000	100 000	100 000	-
MM160	60 000	100 000	100 000	-

Supplementary Table S4. Cell numbers for incubation of TCR-recombinant cells with CD38-enriched and CD38-depleted bone marrow cells.

Co-incubations were done in 96-well plates in a final volume of 150 µL RPMI1640 including 10% fetal bovine serum and 100 U/mL penicillin and 100 µg/mL streptomycin for 16 hours at 37 °C and 5% CO_2. From patients MM139 and MM50, identical TCRs that were expressed in 58$\alpha^-\beta^-$ were also expressed in healthy donor human peripheral blood lymphocytes (PBL). Cell numbers of PBL indicate absolute numbers expressing the recombinant TCR determined by mouse TCRβ constant region staining and flow cytometry. BM indicates bone marrow.

Supplementary Table S5

Patient	*CD38-depleted BM*	*CD38-enriched BM*
MM008	0.4	38.5
MM050	0.9	73.8
MM139	15.1	83.2
MM157	6.9	88.6
MM160	23.4	87.8

Supplementary Table S5. Frequencies of $CD38^{++}CD138^{+}$ multiple myeloma cells after magnetic enrichment.

Percentages of $CD38^{++}CD138^{+}$ among all nucleated cells were determined by flow cytometry. BM indicates bone marrow.

Supplementary Table S6

Patient	*TCR*	*TRAV*	*CDR3α amino acid sequence*	*TRAJ*	*TRBV*	*CDR3β amino acid sequence*	*TRBJ*	*Target peptide*	*Label*	*Derived protein*
MM008	15E10	17*01	CATVTRMDSSYKLIF	12*01	7-9*01	CASSLIGISSYNEQFF	2-1*01	TPRVTGGGAM	TPR	CMV pp65 (417-426)
MM139	10F7	12-1*01	CVVNIPANTGGFKTIF	9*01	10-2*01	CASSPGTGTYGYTF	1-2*01	VTEHDTLLY	VTE	CMV pp50 (245-253)
MM157	13G1α2	17*01	CATVVRMDSSYKLIF	12*01	7-9*01	CASSLIGVSSYNEQFF	2-1*01	TPRVTGGGAM	TPR	CMV pp65 (417-426)

Supplementary Table S6. CMV peptide-specific TCRs.

TRAV indicates TCRα V-gene and allele; TRAJ, TCRα J-gene and allele; TRBV, TCRβ V-gene and allele; TRBJ, TCRβ J-gene and allele.

Supplementary Table S7

	Patient and mutation								
Gene	*MM061*	*MM165*	*MM112*	*MM003*	*MM008*	*MM157*	*MM050*	*MM139*	*MM160*
KRAS		G12R		G12C	G13D			G12D	
CGREF1					E249K	E249K		E249K	E249K
IGLL5					V43A			L39M	M42K
ANK2						Q641E	P1684Q		
LRP1B				I3739V			C4398S		
FAT4				L2703F	H4446P				
PCDHA6	S434L			S608L					
CEACAM19				R111H	D62N				
ATRX							E1017K		K1956T
TTN							L4994H		T8725N
NRAS						Q61K	Q61R		
RELN			M2699R					S2102P	
SIAH2				K139N				H25Y	
FAM46C							N352T	Y356H	
CD83	S2L			V31A					
MTMR4				S367G			F484L		

Supplementary Table S7. Mutation details of genes mutated in multiple patients.

Details on genes carrying somatic mutations in at least two patients determined by whole exome sequencing of CD38-enriched multiple myeloma cells.

Supplementary Table S8

Patient	*Mutation*	*Mutated peptide*	*Peptide label*	*Predicted HLA binding*	*Affinity (nM)*	*Rank (%)*
MM008	RNF168:M20I	CiEILVEPV	CIE	A*01:01	6519.1	1.9
MM008	PCDHGA3:Y402C	cRLVTATSL	CRL	C*07:02	3847.0	1.2
MM008	HMMR:N12S	FsDPSGCAPSPGAY	FSD	A*01:01	13.5	0.02
MM008	PCMTD1:K325T	tPEEPPQNL	TPE	B*07:02	971.2	1.7
MM008	KRAS:G13D	VVVGAGdVGK	VVV	A*03:01	936.8	1.9
MM008	KDM2B:R609H	ARRhRTRCR	ARR	C*07:01	354.0	0.175
MM008	BRCA1:T1661I	LiASTERVNK	LIA	A*03:01	116.2	0.5
MM008	URB1:R409Q	qAFQTREFI	QAF	C*07:01	1861.8	0.7
MM008	IGLL5:V43A	RPMaAPQSG	RPM	B*07:02	131.2	0.5
MM008	TBX22:I92F	KDfQMELQGSELWK	KDF	A*03:01	877.3	1.8
MM160	PPP1R15B:K80M	mVLIWSQLF	MVL	A*23:01	35.2	0.15
MM160	PPP1R15B:K80M	LPGLLQmVLI	LPG	B*51:01	192.1	0.03
MM160	PPP1R15B:K80M	LQmVLIWSQL	LQM	A*02:01	135.1	1.3
MM160	SACS:Y4119F	LISDTSfLI	LIS	A*02:01	28.1	0.4
MM160	COPZ2:R85W	KTSwTESEI	KTS	C*15:02	211.9	0.2
MM160	COPZ2:R85W	SwTESEIAFF	SWT1	A*23:01	111.3	0.4
MM160	COPZ2:R85W	SwTESEIAFFGGM	SWT2	B*44:03	502.1	0.7
MM160	CHST7:D155G	gMLRSLFRCDFSV	GML	A*02:01	54.8	0.7
MM160	SLC25A43:M111V	HISQWSSIv	HIS	C*15:02	343.5	0.3
MM160	SLC25A43:M111V	IvAGSLAGMV	IVA	A*02:01	473.1	3
MM160	FBXL12:H226Q	TLLAISRqL	TLL	A*02:01	349.9	2.5
MM160	HOOK2:R219Q	QENAGLqERM	QEN	B*44:03	1058.8	1.1

Supplementary Table S8. Mutation-derived peptides and potential HLA-binding.

From patients in whom re-expressed TCRs recognized CD38-enriched multiple myeloma cells, all mutation-derived peptides that were predicted to be presented on HLA were synthesized to test recognition by selected TCRs. Mutated amino acids are marked as lowercase letters. Potential HLA binding, affinity, and %Rank were determined using NetMHC 4.0 (http://www.cbs.dtu.dk/services/NetMHC/). Peptides with an affinity $\leq$ 1000 nM and/or %Rank $\leq$ 2 were considered binders and synthesized.

Supplementary Table S9

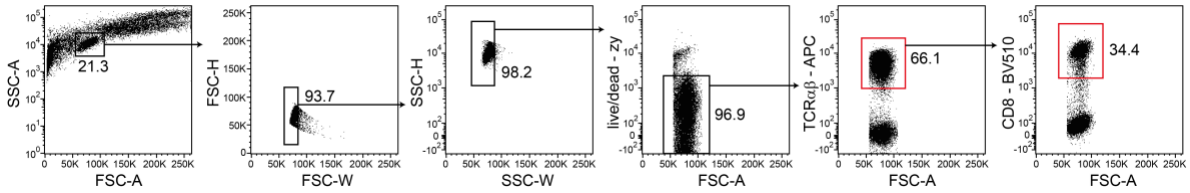
SPYPGLRLI	IPAIRDITL	SPQQKLVIV	LARPALLLL	RPFHGWTSL
IPYPRPIHL	SPYQNIKIL	VPRPPQTSL	APWLQIQLL	SPRVPNSSV
LPQPVPLSV	MPRPPETFL	RPPPIGAEV	RPRPTEATV	SPSDRPLSL
YPHSPGQVI	LPAPKWTEL	SPRPKMDAI	APVLPHTAV	VPFSVPKIPL
LPFKYPAVL	VPREPPVSL	RPVVQLTAI	APIERVKLL	VPASFRLQM
LPHLPSLEI	IPPPPPPAM	IPAKPPVSF	IEPFSSPPEL	RPQDKFLVL
LPYSVGRVL	TPHQTFVRL	RPFPKLRIL	QPNPLPLRL	RPRWVVPVL
IPRSITVLV	VPYLRDLGL	MPYSNGRPAL	SAIPHPLIM	SPKVFPLSL
FPRLPPASV	LPRQPPMSL	FPRLLDTKL	RPVMPSRQI	MPKKDARTL
LPFLRITSL	LPHNRLVSL	LPHAPGVQM	FPSLREAAL	NPRIPYTEL
IPALRDISI	YPAQITPKM	VPSKPPMSL	TPRPTAAEL	VPEEARPAL
IPFSNPRVL	FPREPRPKL	YPFKPPKVAF	APASVHSEI	APSPPPAPV
LPFGPFKEL	SPVKSTTSI	SPFHRNLFL	APAPTAVVL	QPASFAVSL
LPLPNFSSL	VPRVPTHTL	LPSKPSSTL	SPNSKVNTL	RPYPSPGAVL
SPYLRPLTL	LPRPPPPEM	NPISTVTEL	SPAPTHNSL	HASDRIIAL
IPYKPNYSL	IPKPLNPAL	FPRFGGSLAL	VAIKAGTTL	HPINPRVAL
LPHVPLGVI	RPRPPVLSV	HPRVPSLTTV	SPYPTKTQTM	RPHVAQPTL
QPRPPVTLI	TPAPVPTSL	RPDMIILQI	SPMSQRPVL	SAVGHVFSL
LPAPPHIDV	SPYPGLRL	APSPVIPRL	RPDLRMAAI	MPSQFRDIL
MPSPVSPKL	SPSPPSVAV	NPQERTLTL	VPRIQPQSL	IPMGPPRLPL
RPYHTIIEI	LPKQPPLML	LPSALRPLL	VPPPPHRPL	VARPLSTAL
SPAPPPPAV	SPHGHILVL	VPVPPNVAF	NPASKVIAL	TPSPARPAL
MPRGVVVTL	IPRLIVSQL	RPRAPIIAV	APFLRNVEL	LPAWPHRGL
SPRPPLISV	RPYKPVVLL	RPSPWVPAL	VPAEPKLAF	TPRGGVGSV
IPNERTMQL	MPALRSINL	IPAKLHNSL	IPYHSEVPVSL	SAMKAVTEL
FAYMPNNSL	LPPPPHVPL	SPKPMVSLL	APIGVHPSL	LAMRPLASL
TPMGPGRTV	TAAPVPTTL	IPRPVDGVEV	RPISDFLTL	MPPAFPRLEL
RPAPPPPTV	MPARWLTHL	SPQPRLIYL	SPSSILSTL	KPIQRTILM
SPQGRVMTI	RPKPIITSV	IPAEGRVAL	HPRSPNVLSV	APRDNVTLL
LPWPARPAL	RPSPPVQSV	APVYLAAVI	APVIRPII	SPLTKSISL
RPMPGTHTV	MPKPPNLIM	HPRDPNLLL	APTLGPAVI	HPRAPVLL
IPLPRLLAM	LPAPPTQNM	RPRPPITLL	MPALRPAL	APSPRPLSL
FPSMPSPRL	FPNIPGKSL	WPMEGSHWL	TPAVGRLEV	RPRPGNILL
QPITPGPSI	IPMTPTSSF	LPYLPSGESL	IARLPSSTL	APHLVGPHL
RPFPGLVI	FPHPVNQVTF	SPHPAATAL	LPRPPMLLAL	SPRPGPSSL
NPRSVTLLI	SPRDPVLTL	LPSLRILYM	YPKRPLLGL	FPRFGGSL
RPFERIMQL	IPLKPSNEL	KPRPIIPML	AAYLRALSL	APRPGLLSL
RPFERTITM	MARPQGSSV	KPRPVSQLV	LPKATILDL	APEEHPVLL
SPKPWIPVL	SPAPTITSL	RPILTIITL	NAINITSAL	GPLPRTVEL
VPRPIFSQL	TPSEPHPVL	RPAPHPLFL	RPIPQWIRM	SPQAPTHFL
LPRLTPPVL	LPKPPGRGV	RPVPPPPSL	APYSRPKQL	RPSGAVVTL
LPAPKGPAL	SPPWRLIAV	VPRPPATL	SPRYIFTML	YPRTGGTL
IPYTGPFNLL	RPAEVRLLI	FASFPHMVL	NPASPPLSL	RPAGPALLL
LPRPVPQNL	LPQGIVREL	TPKMPGQSV	SPISHFLDL	SPASRSISL
LPSPFLRAL	TPAPPTHAL	VPRLPGETL	TPFGGRLLVL	SPKLPVSSL
VPHGHITSL	HPRSPTPTL	SPMEVGKKL	SPNAEIHIL	GPPPPGPIL
SPKPVSSTV	SPWKPPTYL	APRLMITHI	RPYKPVVL	TPETVRMVL
SPLSSHPVV	APAPPSKVI	QPRYPVNSV	LPSRKLVAL	HPRVGDLIL
IPRHLQLAI	SPRPNHSYI	SPRWGGIMV	SPVVRVAV	KPSPLAPSL
TPWQPPTVL	VPRPVLRAL	RPPEVILEL	KPRPPLHLL	SPRFPAQYL
SPRAPVQVI	SPRPAPLLL	HAIPPTLAM	SPIEKSGVL	SPANPAHIL
APRAVFPSI	SPNQKLLAV	YAASSYLSL	APAPKAYVL	SPQSNSPVL
MPLPGTKAL	MPRKITEVL	SAHSHFISL	RPWLRPAAL	CPRPEGLNF
SPAPPPQQV	LPKQPPLAL	MPFPNIRSAEL	APSKPAASI	LPSPSPRISL
IPMPPPPLGL	VPVGPHLSL	YPRPGTPAA	APAPRPSLL	SPAFSTRVL

Supplementary Table S9. Potential target peptides for TCR 16A2 with predicted binding to HLA-B*07:02 and HLA-B*51:01.

Peptides selected as potential target peptides for TCR 16A2. The peptide that activated 58-16A2 is highlighted in red.

SUPPLEMENTARY FIGURES

Supplementary Figure S1

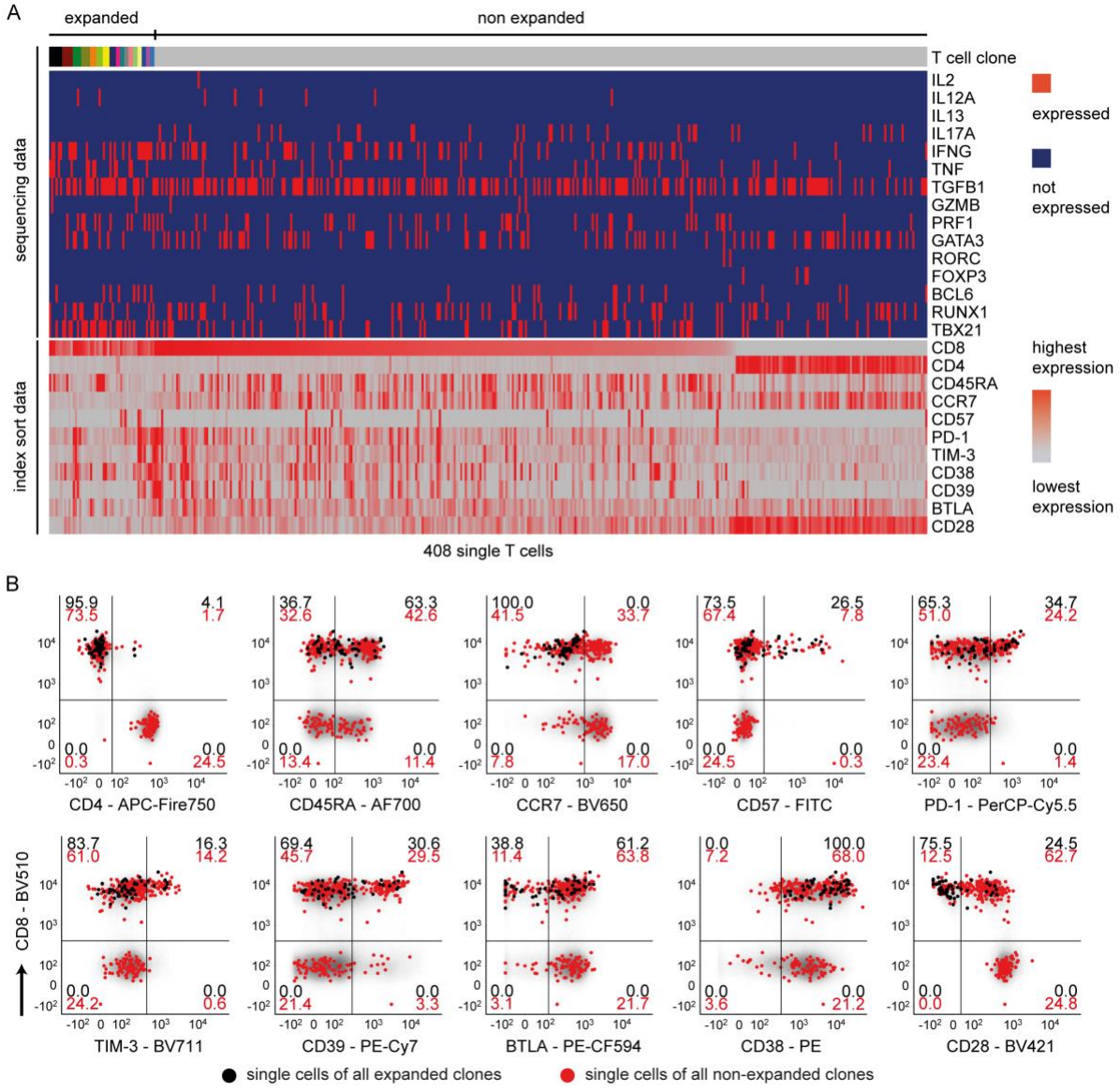


Supplementary Figure S1. Gates for single cell index sorting.

Sequential gating on lymphocytes, single cells, live cells, αβ T cells, $CD8^+$ cells. Gates from which cells were finally sorted are indicated in red. Primarily, the TCRαβ gate was used for sorting. If frequencies of $CD8^+$ T cells were low, we sorted additional single $TCR\alpha\beta^+CD8^+$ cells to ensure representation of approx. 50% $CD8^+$ T cells among all sorted cells. The figure shows sort gates of MM112 as representative example. zy indicates zombie yellow; APC, allophycocyanin; and BV, Brilliant Violet.

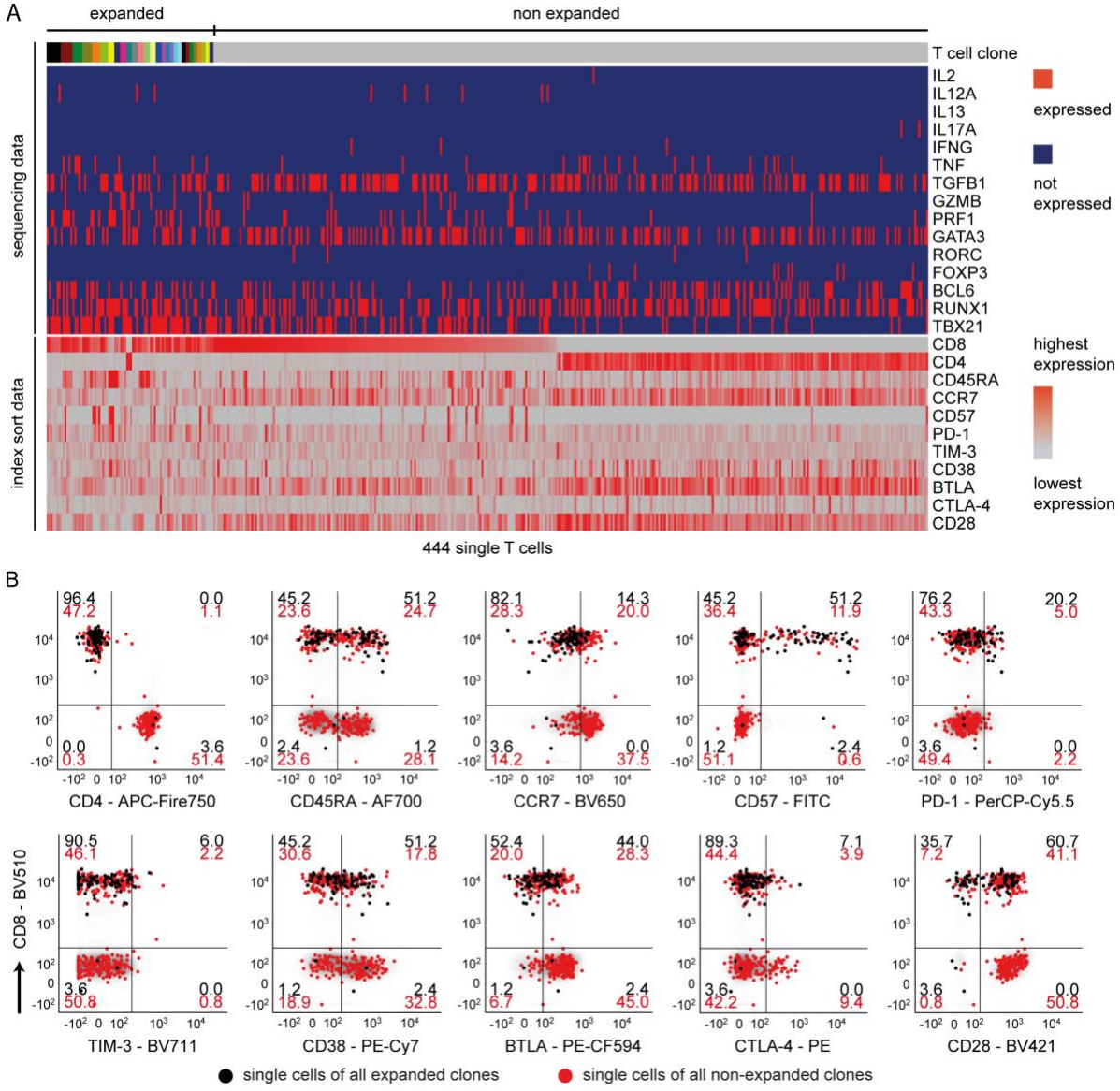
Supplementary Figure S2

MM195



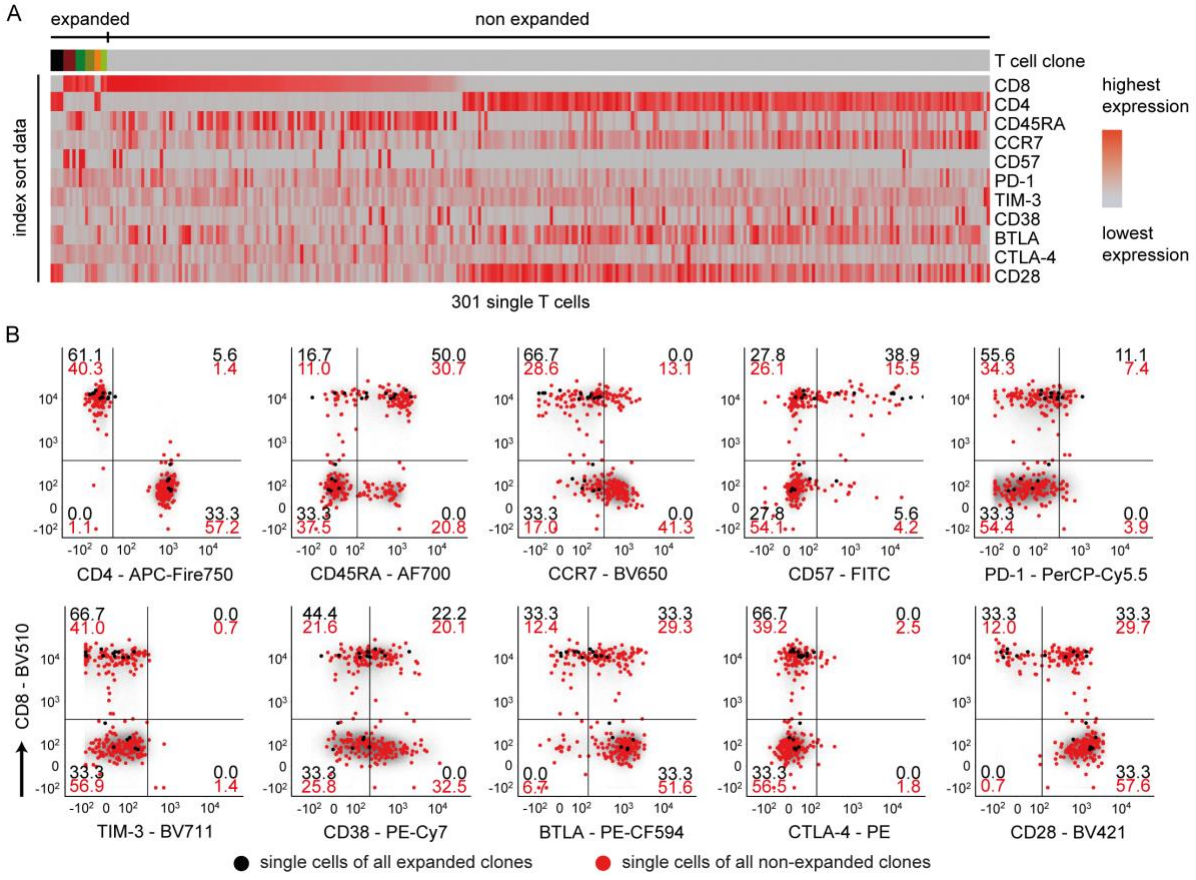
Supplementary Figure S2 continued

MM104



Supplementary Figure S2 continued

MM078



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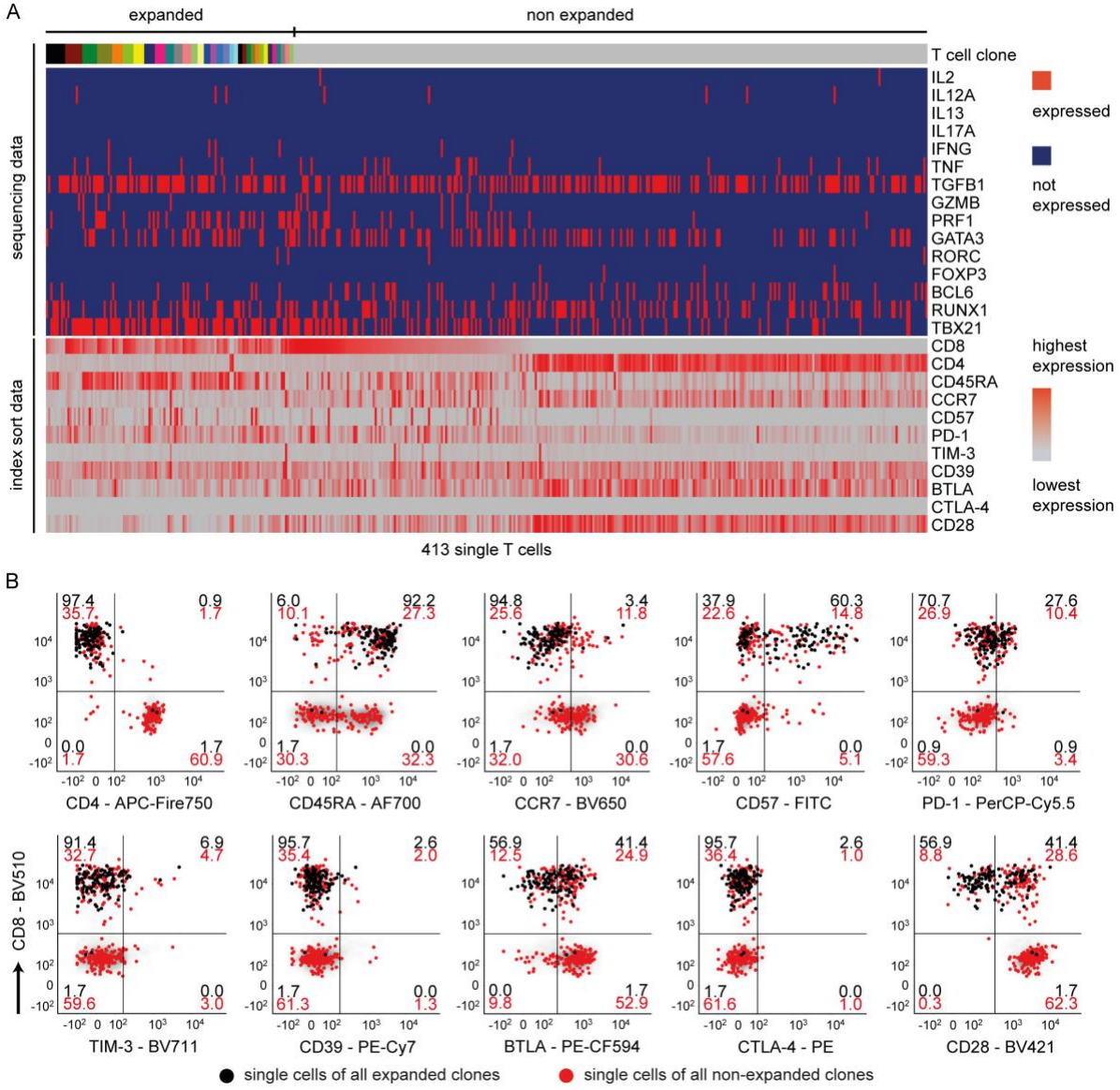
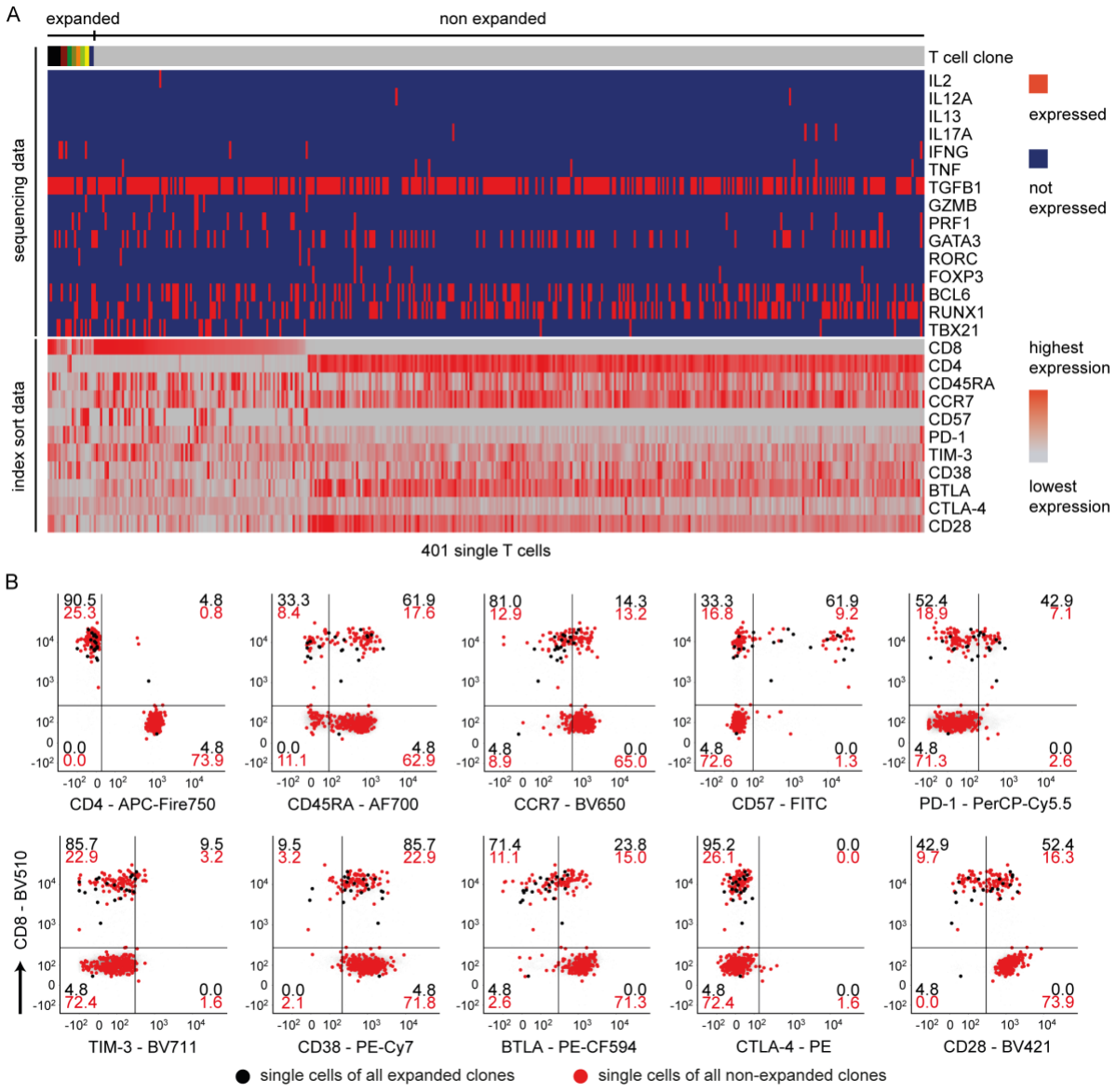
MM165



Supplementary Figure S2 continued

MM061



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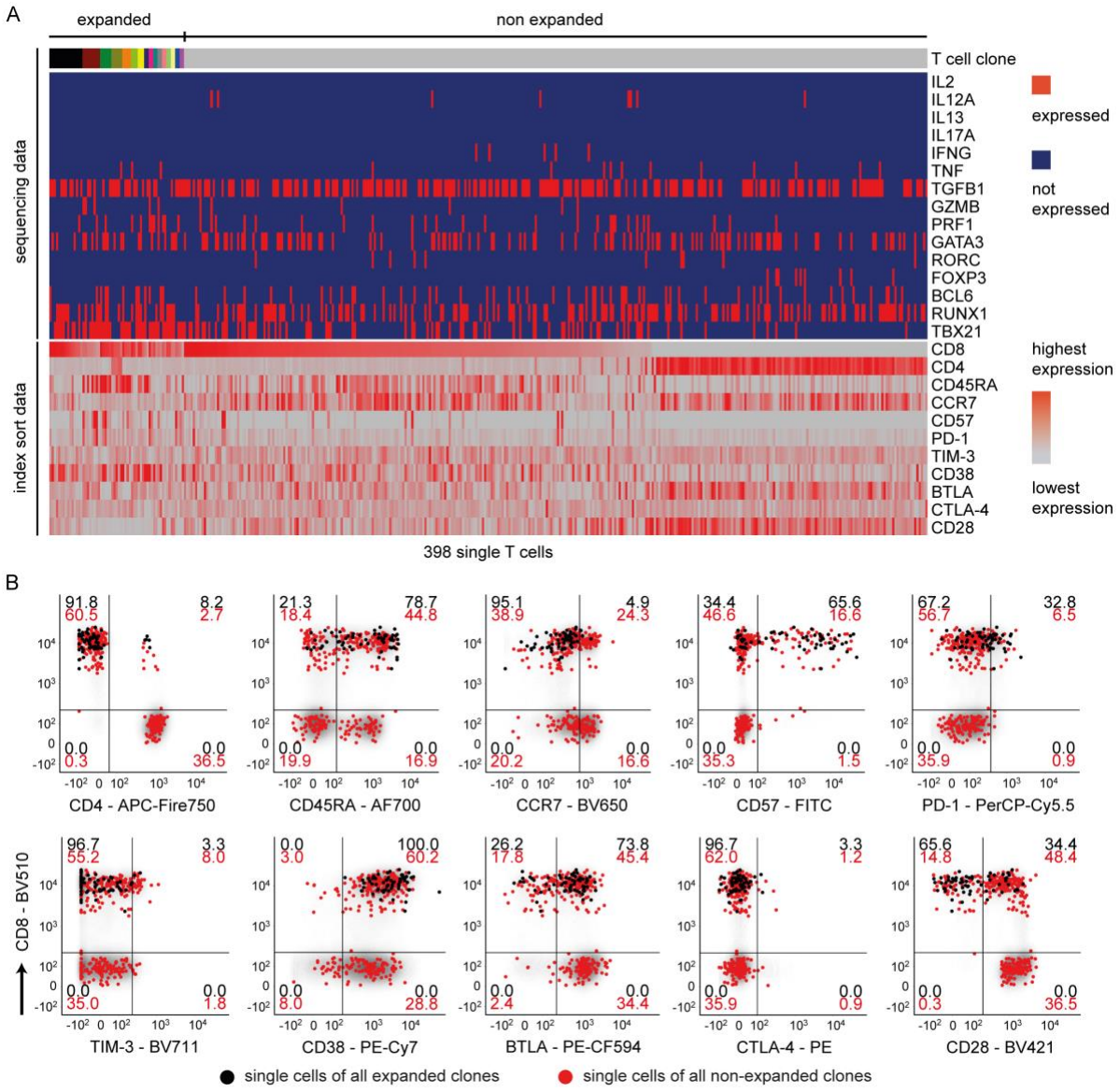
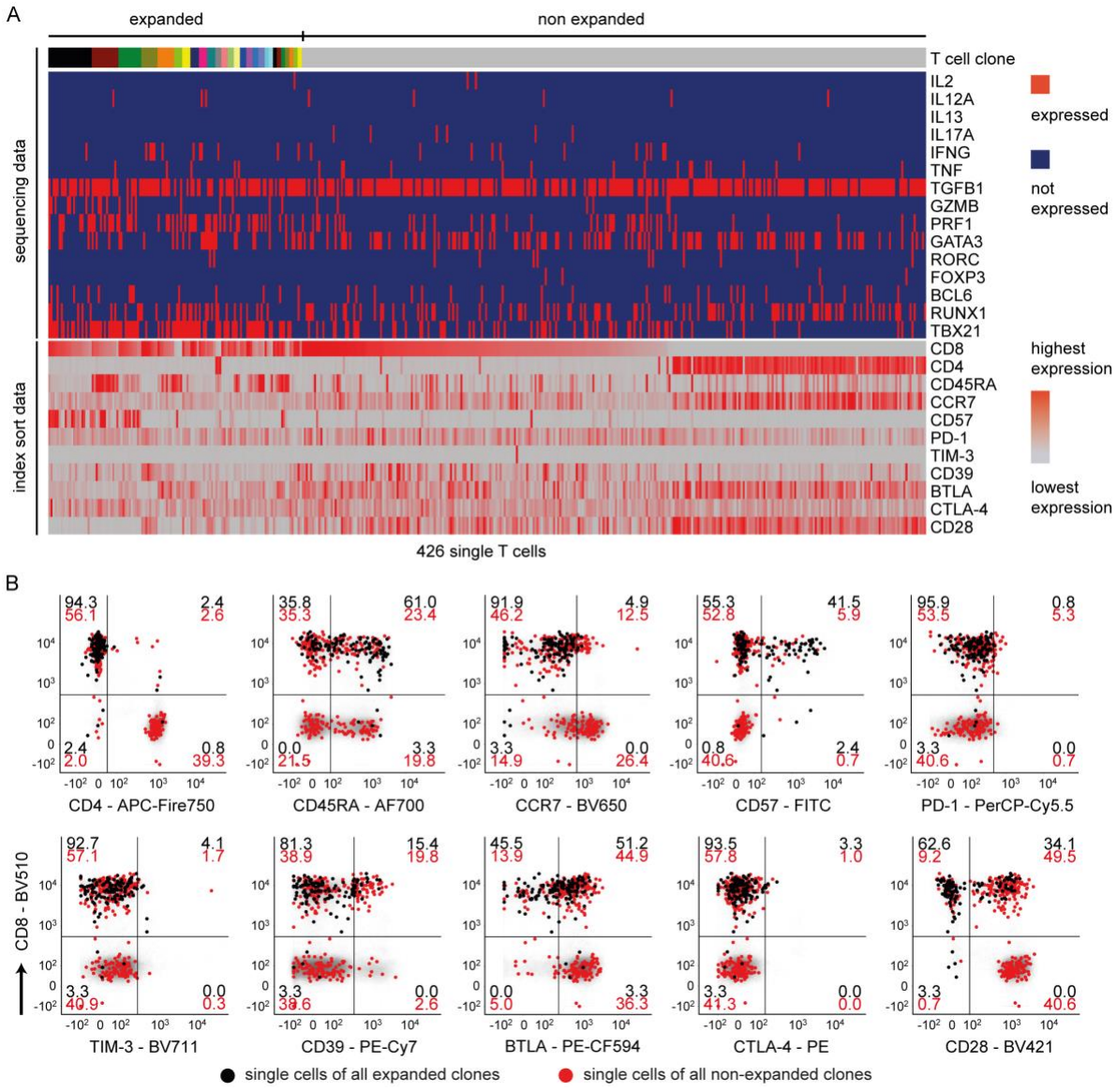
MM112



Supplementary Figure S2 continued

MM204



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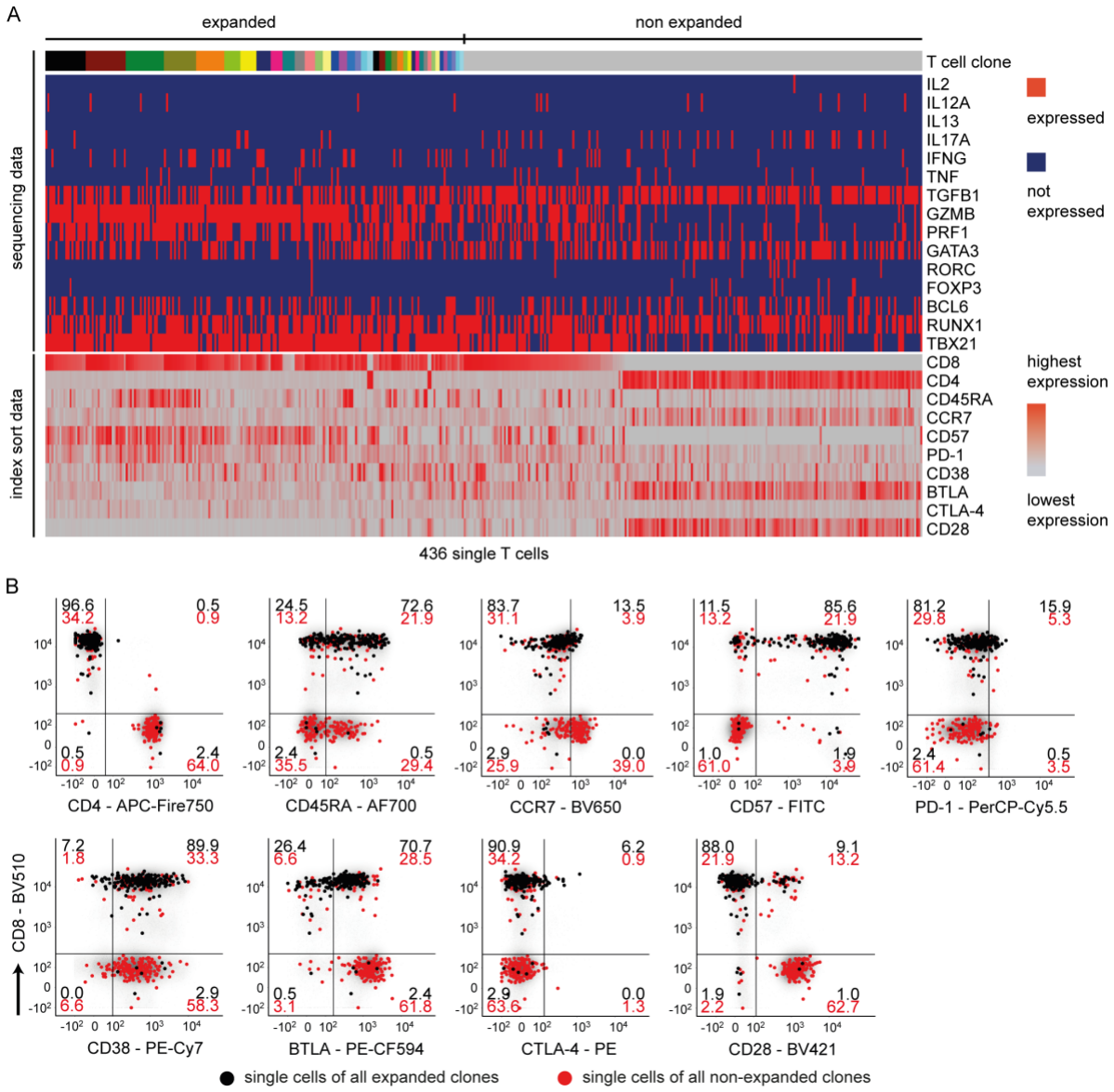
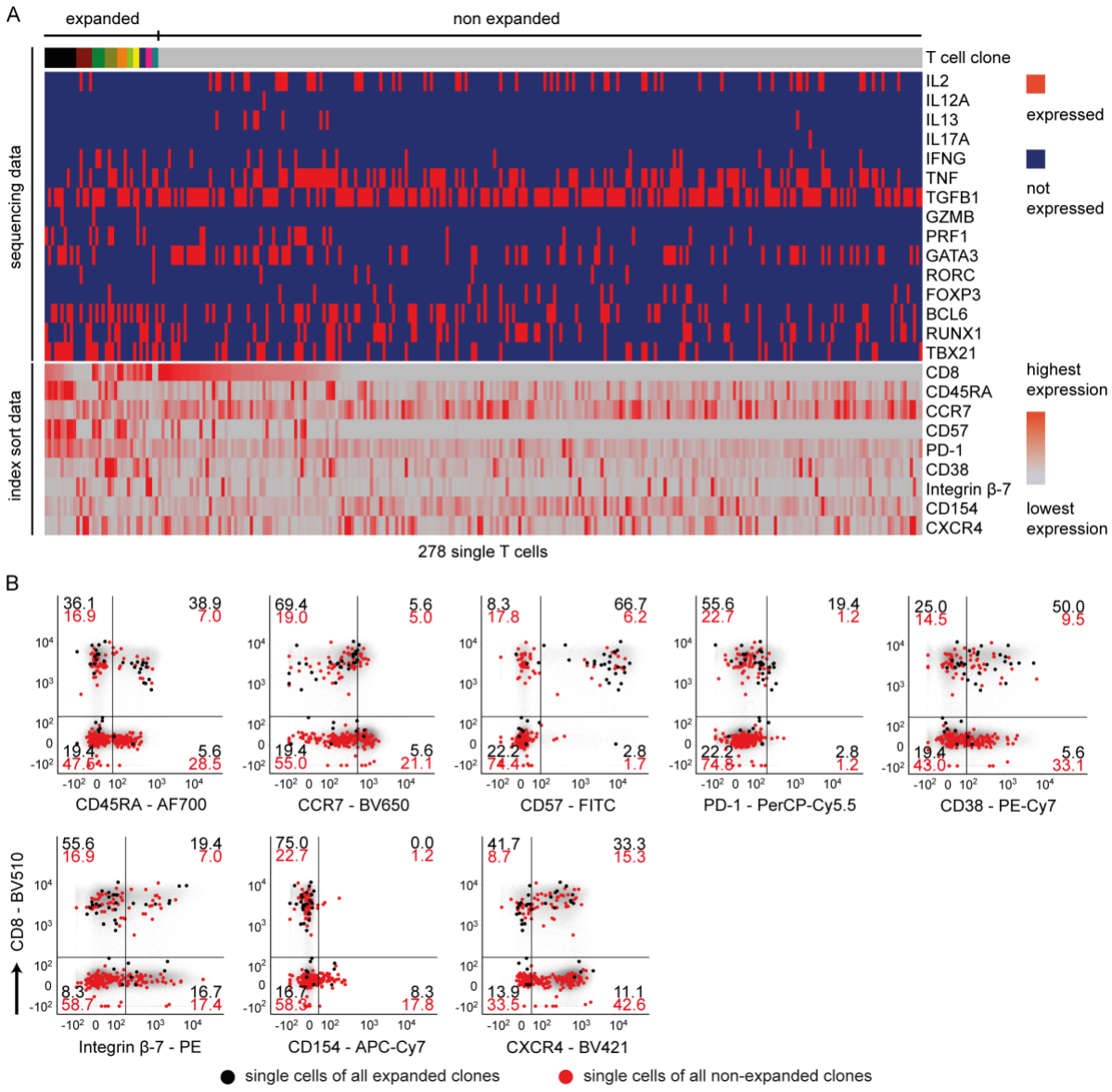
MM008



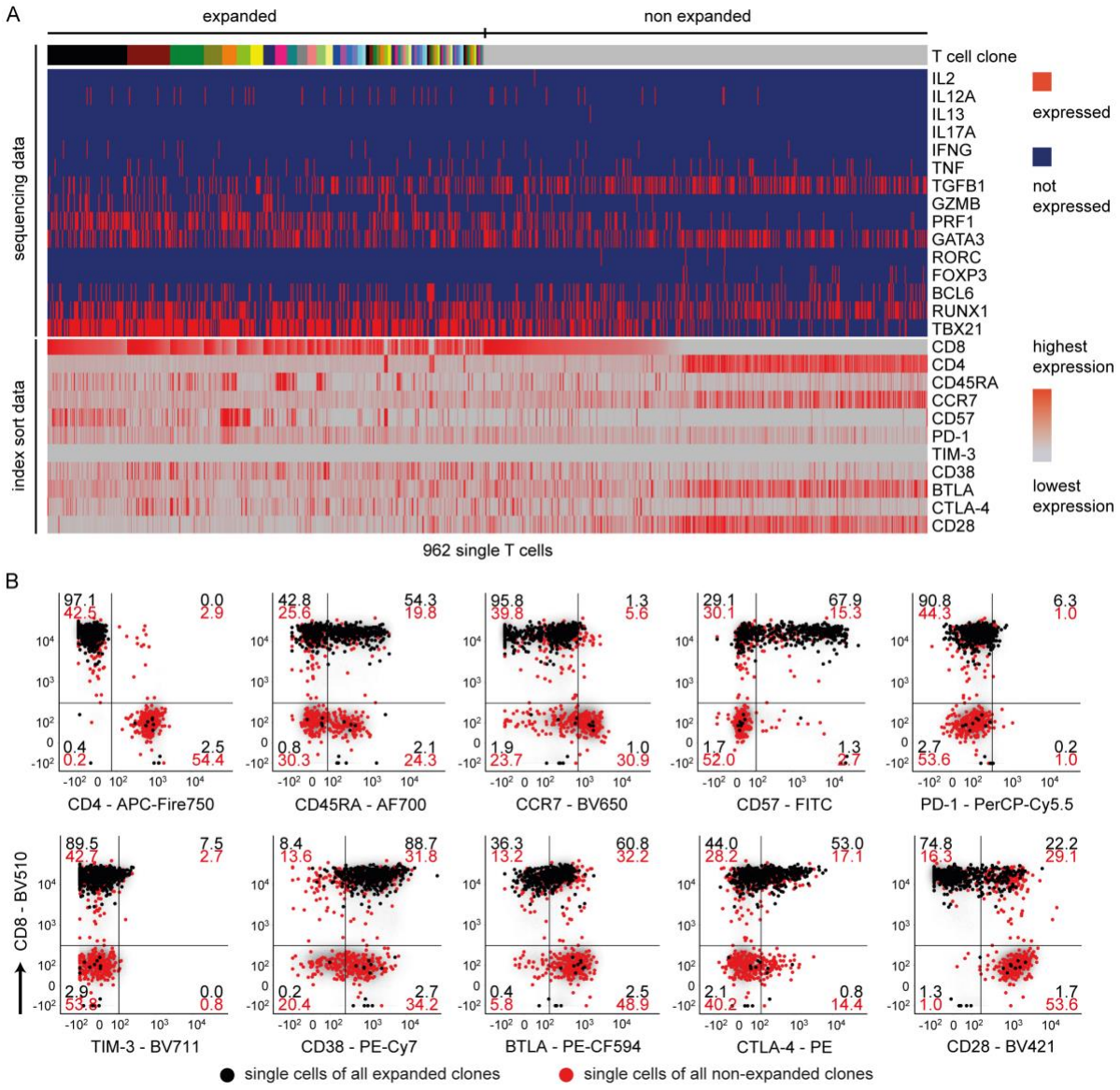
Supplementary Figure S2 continued

MM003



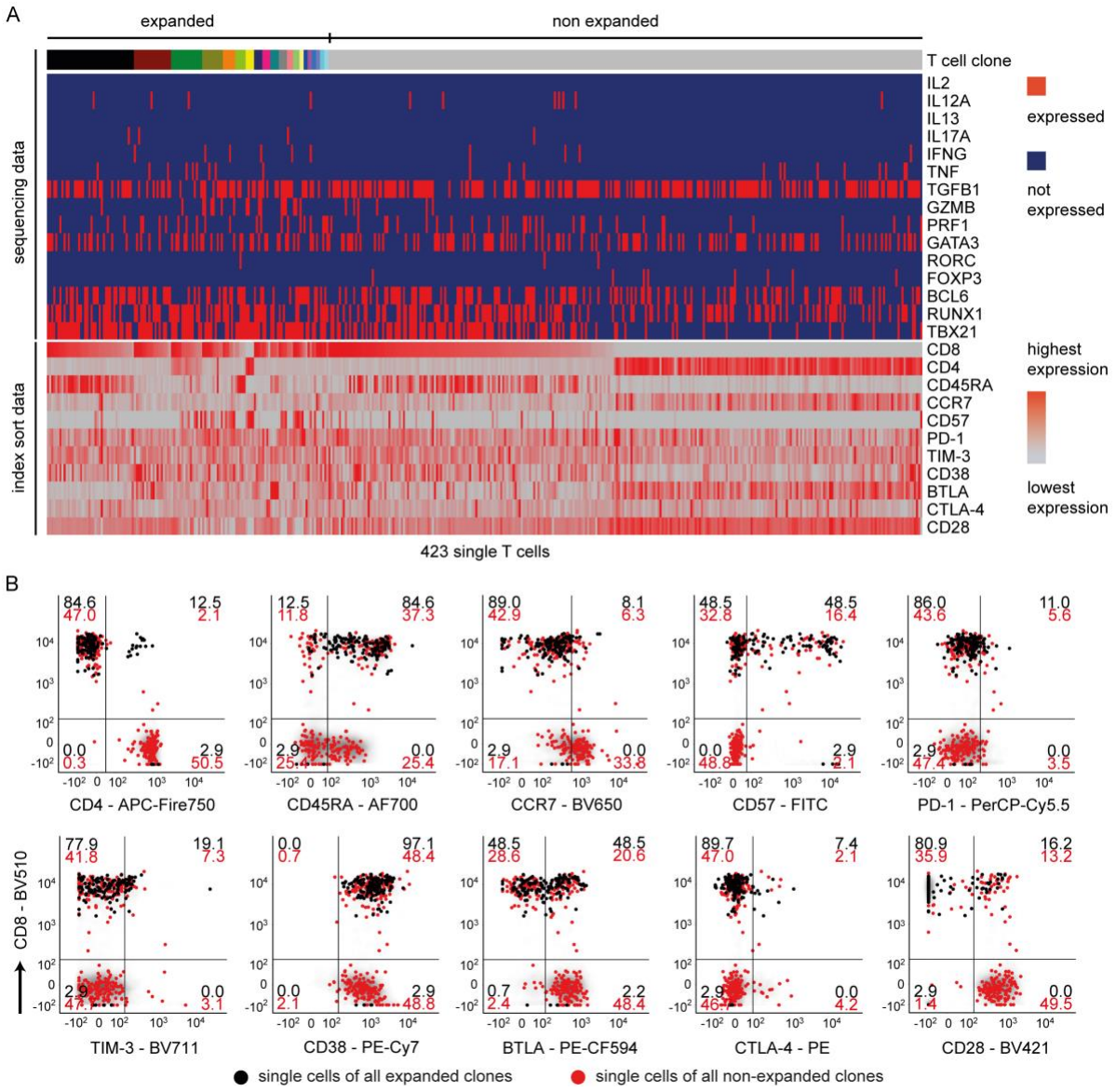
Supplementary Figure S2 continued

MM157



Supplementary Figure S2 continued

MM050



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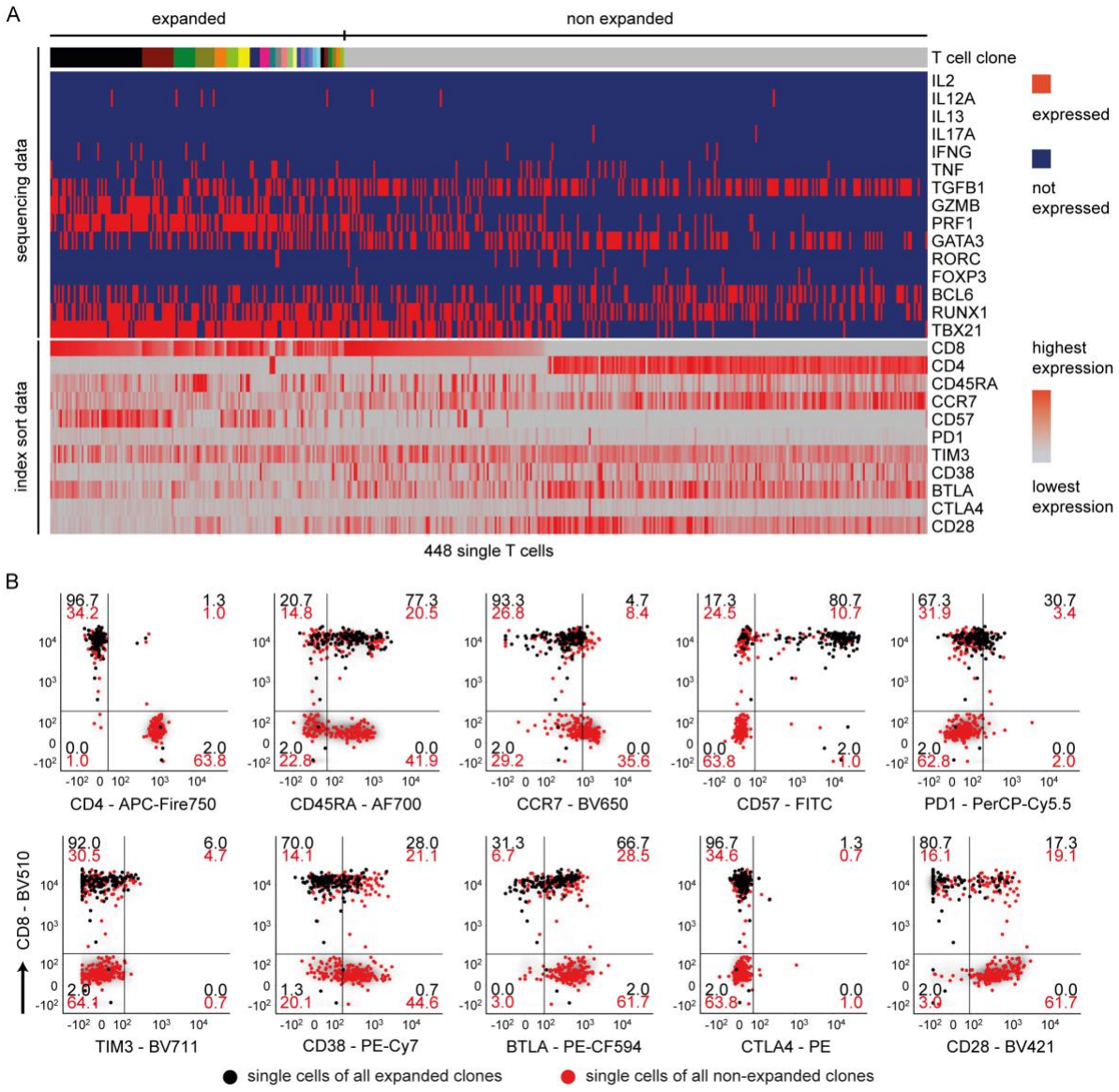
MM139



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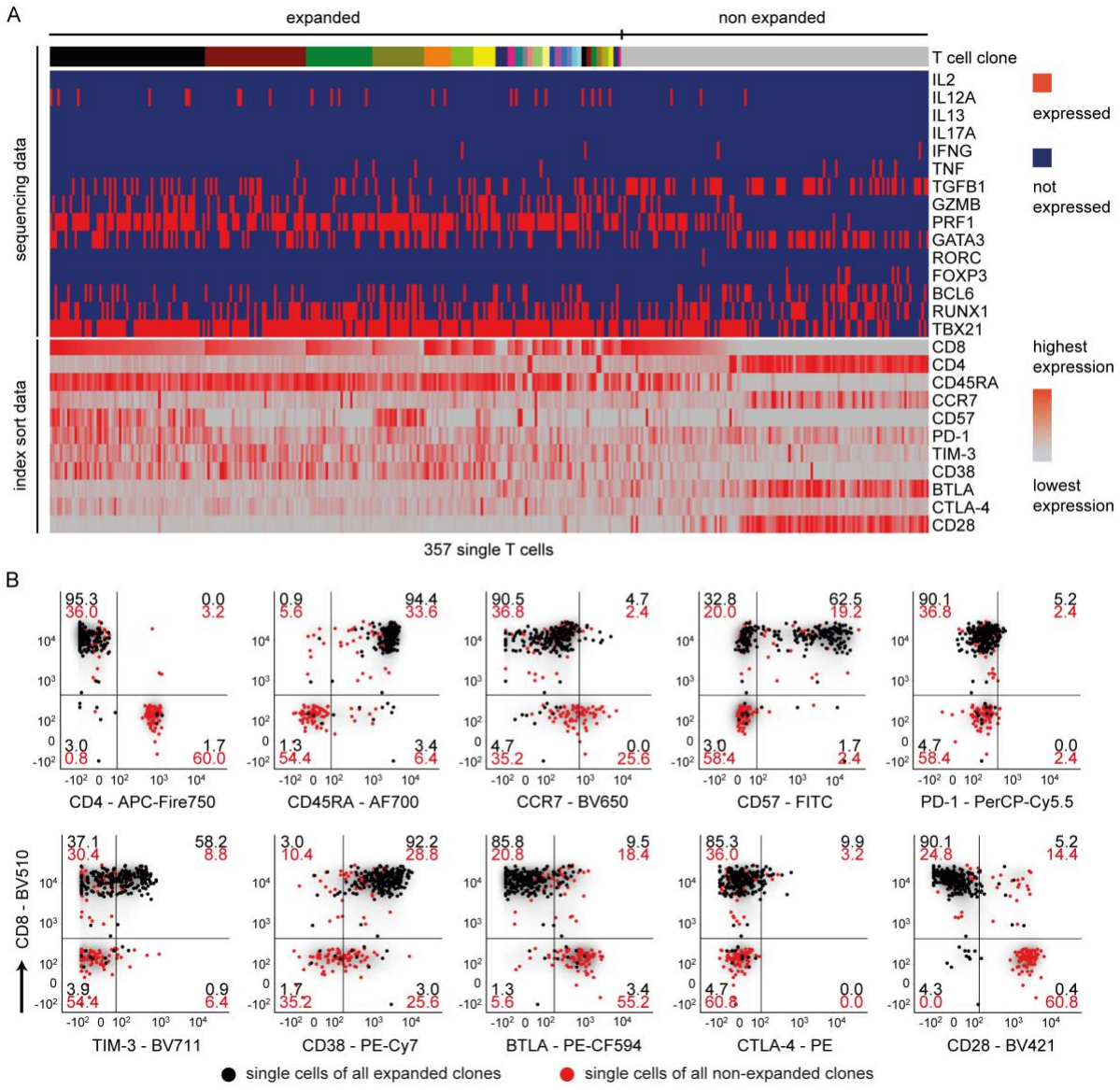
MM160



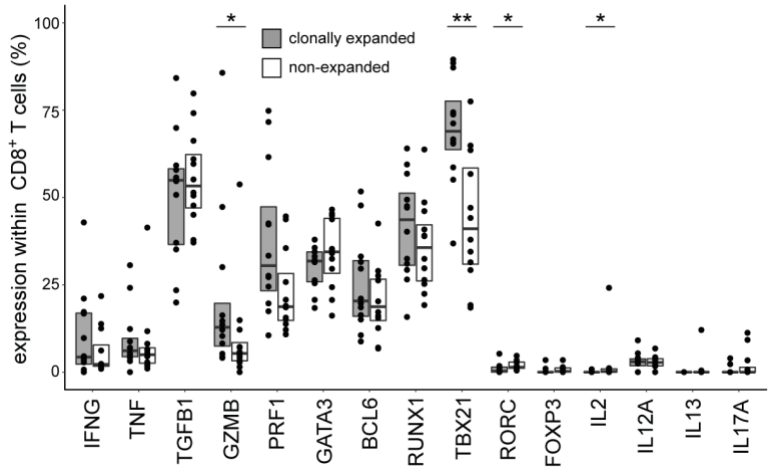
Supplementary Figure S2. Clonal expansion-associated phenotypes of bone marrow T cells.

(A) Sequencing of TCRαβ, transcription factor, and cytokine genes from amplified cDNA of single FACS-sorted T cells. Single cell data are arranged in columns with each column representing one single cell. The top bar indicates TCR sequences; adjacent columns with the same color in the top bar indicate single cells with identical CDR3 amino acid sequences of TCRαβ

genes. The lower part of the heatmap visualizes corresponding FACS index sort data. (B) FACS plots show immune phenotypes of expanded and non-expanded T cell clones determined by FACS index sorting. Each data point represents one single T cell belonging to an expanded (black) or non-expanded (red) clone. Numbers within gates indicate percentages.

From T cells of MM078, only TCRs were sequenced and immune phenotypes were determined by index sorting.

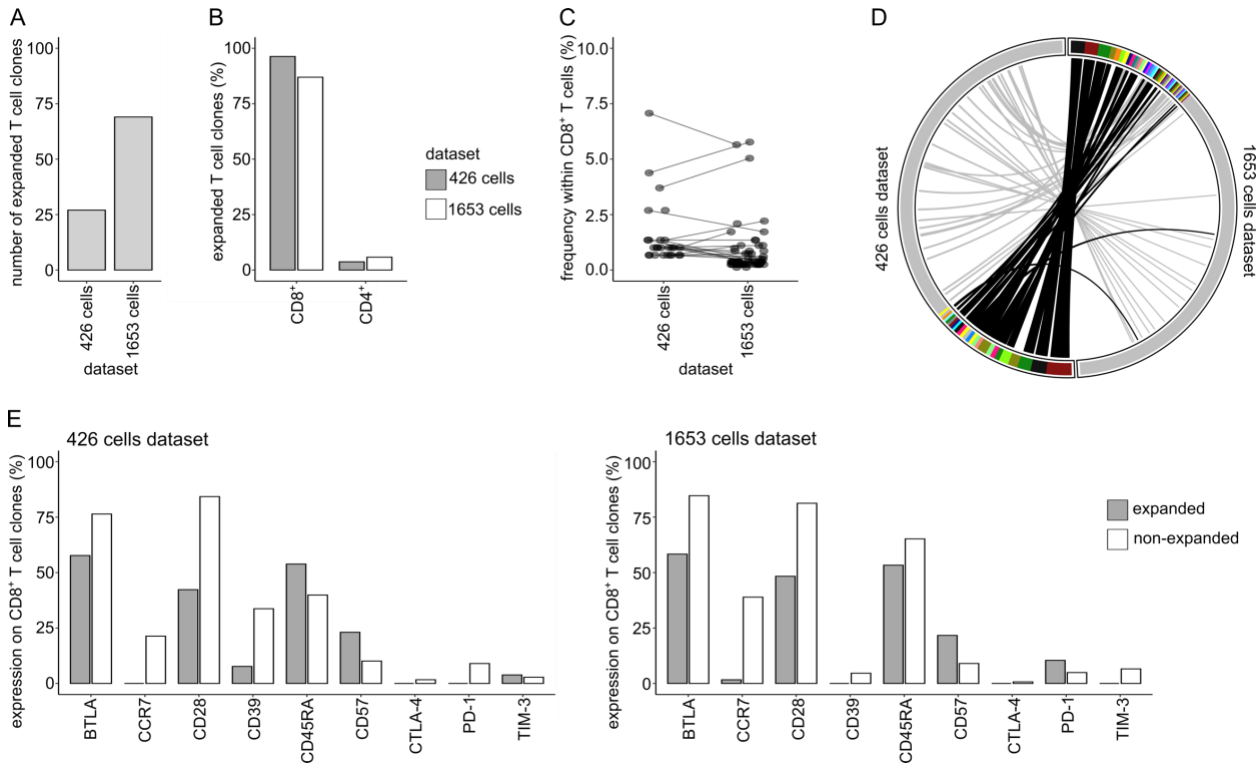
Supplementary Figure S3



Supplementary Figure S3. Cytokine and transcription factor expression in expanded and non-expanded bone marrow T cell clones.

Single cell gene expression of selected cytokines and transcription factors in expanded or non-expanded $CD8^+$ T cells. Data points represent individual patients. Boxes range from 25^{th} to 75^{th} percentiles, lines within boxes indicate medians. Data were acquired in n=12 experiments. Statistical significance was calculated using the two-sided Wilcoxon test, * $p<0.05$, ** $p<0.005$

Supplementary Figure S4

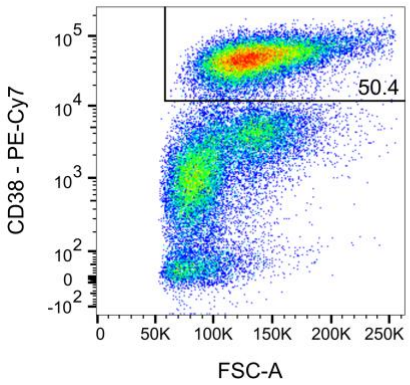


Supplementary Figure S4. Clonal expansion-associated immune phenotypes were not substantially affected by varying total numbers of sequenced cells.

FACS index sort and sequencing data from additional 1653 bone marrow T cells of patient MM204 as an example were generated from another cryopreserved bone marrow vial of the same bone marrow aspiration that was used to create the initial 426 T cell dataset (technical replicate). (A) shows total numbers of expanded T cell clones. (B) shows expression of CD8 and CD4 on expanded T cell clones. (C) compares frequencies of individual expanded T cell clones identified in the 426 cells dataset with frequencies of these clones within the new 1653 cells dataset. Each data point represents one expanded T cell clone. (D) illustrates frequencies and overlap of individual expanded and non-expanded T cell clones. (E) shows expression of phenotype parameters determined by FACS single cell index sorting compared between expanded and non-expanded clones. Data were acquired in n=2 experiments.

Supplementary Figure S5

A



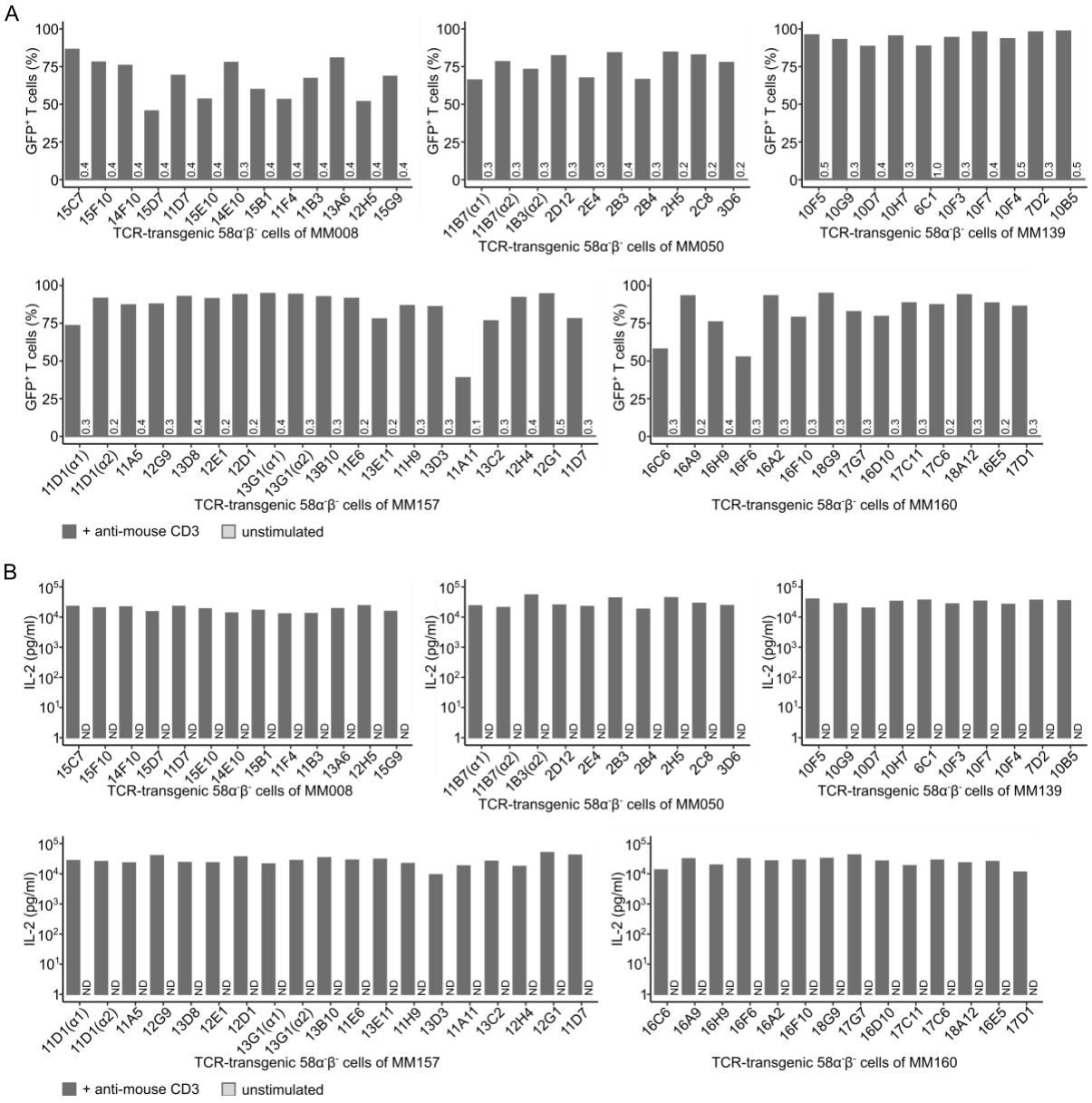
B

Patient	*BM CD38^{++} (%)*
MM008	22.8
MM050	50.4
MM139	25.0
MM157	26.3
MM160	20.8

Supplementary Figure S5. Frequencies of multiple myeloma plasma cells within bone marrow aspirate specimens.

Frequencies of multiple myeloma plasma cells, identified by high CD38 expression, were determined by flow cytometry within bone marrow specimens. (A) shows gating on multiple myeloma plasma cells of patient MM050 as an example. The plot is pre-gated on all events after exclusion of debris by scatter characteristics. (B) summarizes frequencies of multiple myeloma plasma cells, determined as shown in (A) for all patients from whom we determined clonal overlap with peripheral blood and re-expressed selected dominant TCRs for incubation with multiple myeloma cells.

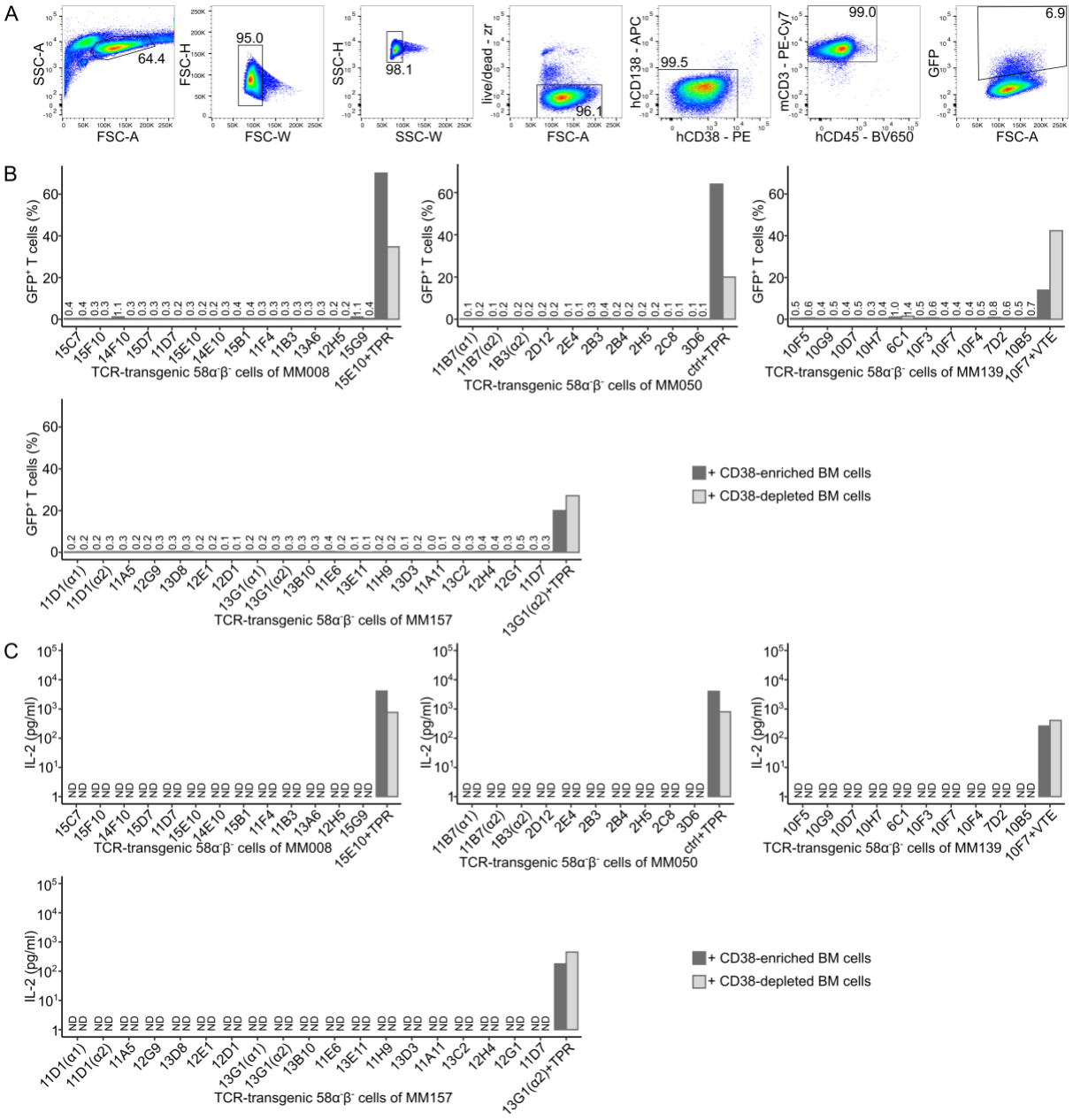
Supplementary Figure S6



Supplementary Figure S6. GFP and IL-2 production of TCR-recombinant 58α$^-$β$^-$ cell lines after CD3 stimulation.

TCR-recombinant 58α$^-$β$^-$ cell lines were stimulated with plate-bound anti-mouse CD3 or left unstimulated to confirm their capacity of (A) GFP and (B) IL-2 production upon stimulation. GFP was measured by flow cytometry, IL-2 was measured by ELISA. ND indicates not detectable.

Supplementary Figure S7

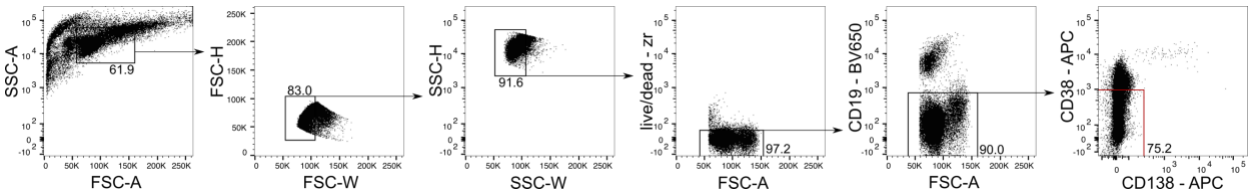


Supplementary Figure S7. Activation of TCR-recombinant 58α-β- cell lines by multiple myeloma bone marrow.

(A) Identification of TCR-recombinant 58α-β- cells. From left to right: Sequential gating on lymphocytes, single cells, exclusion of dead cells, exclusion of multiple myeloma cells, selection

of $CD3^+$ murine T cells, and gating on GFP^+ cells. The GFP gate was set based on unstimulated controls. zr indicates zombie red. (B and C) GFP and IL-2 production of TCR-recombinant $58\alpha^-\beta^-$ cell lines upon incubation with respective multiple myeloma and non-myeloma cells. In case one of the re-expressed TCRs had already been reported specific for a virus-derived peptide (e.g. 15E10 from MM008), we used peptide-loaded multiple myeloma and non-myeloma cells to confirm myeloma cells of the respective patient were capable of peptide presentation. TPR: derived from CMV pp65 (417-426), VTE: derived from CMV pp50 (245-253). In case of MM050, in which none of the expanded TCRs had already been reported virus-specific, we used the same TPR-specific, HLA-B*07:02-restricted TCR as control as in MM008 (“ctrl”). ND indicates not detectable.

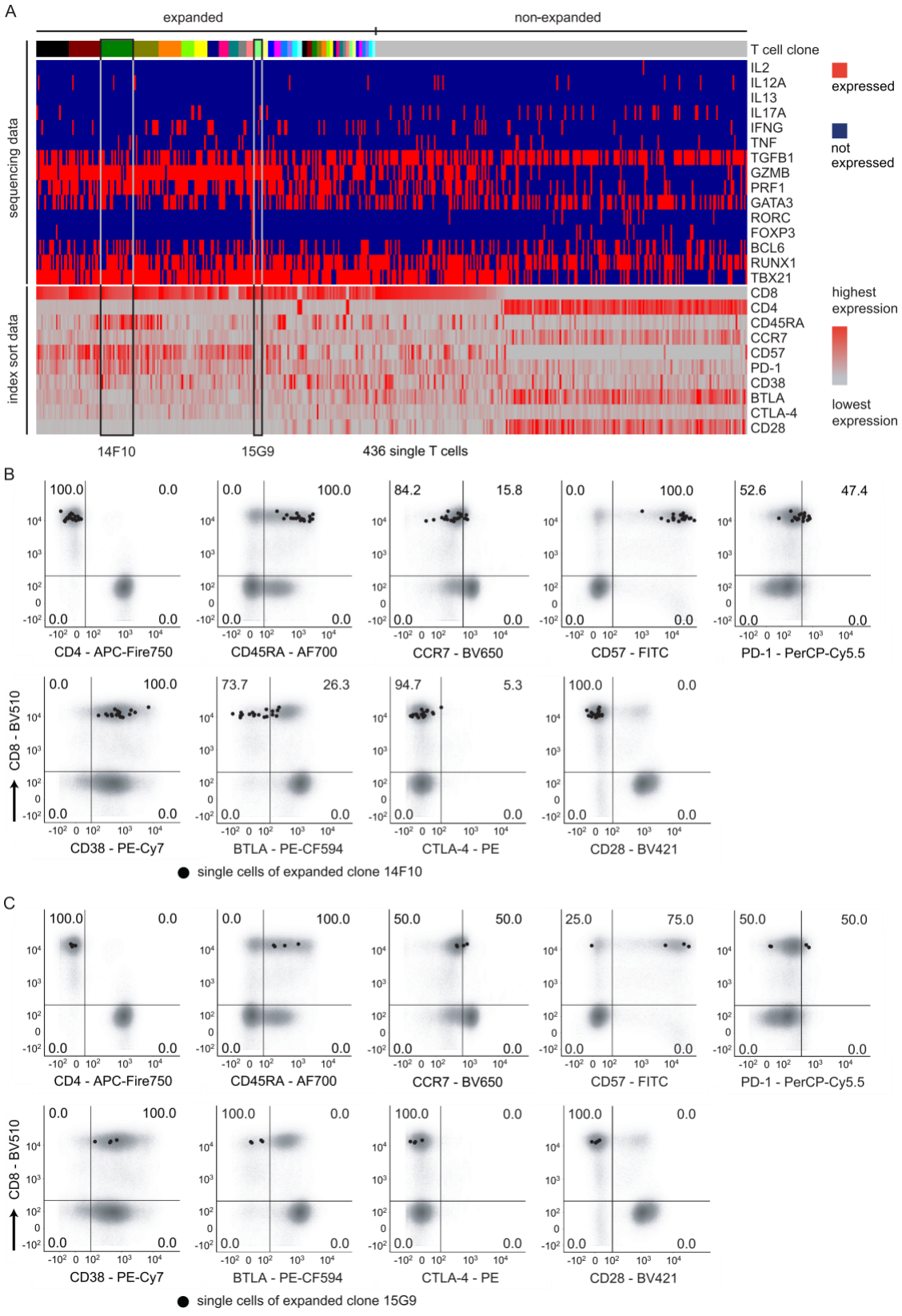
Supplementary Figure S8



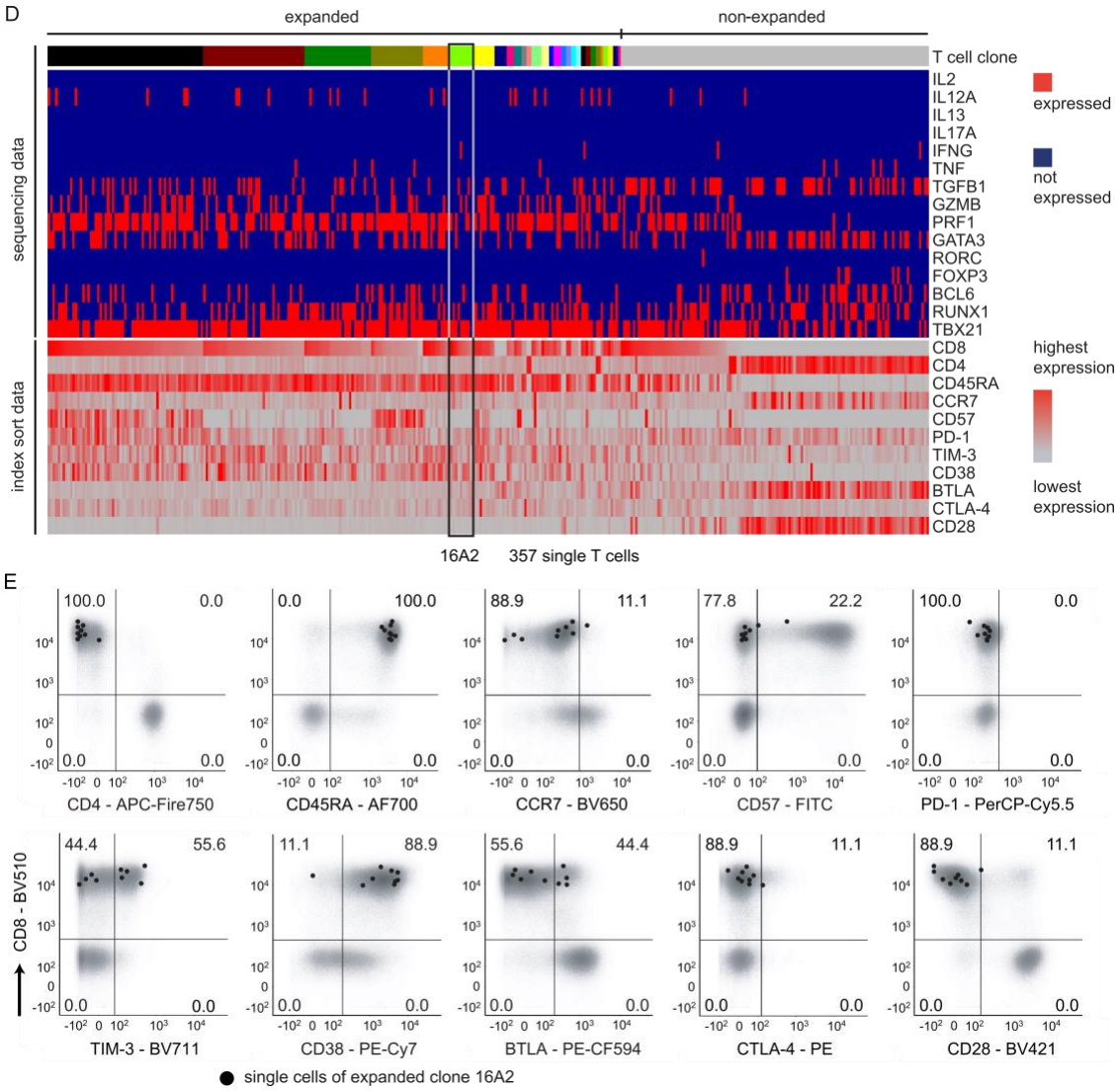
Supplementary Figure S8. FACS depletion of remaining multiple myeloma and B lineage cells from MACS CD38-depleted populations.

From left to right: Sequential gating on nucleated cells, single cells, exclusion of dead cells, exclusion of B cells, selection of $CD38^{-}CD138^{-}$ cells. The gate from which cells were finally sorted is highlighted in red. zr indicates zombie red.

Supplementary Figure S9



Supplementary Figure S9 continued

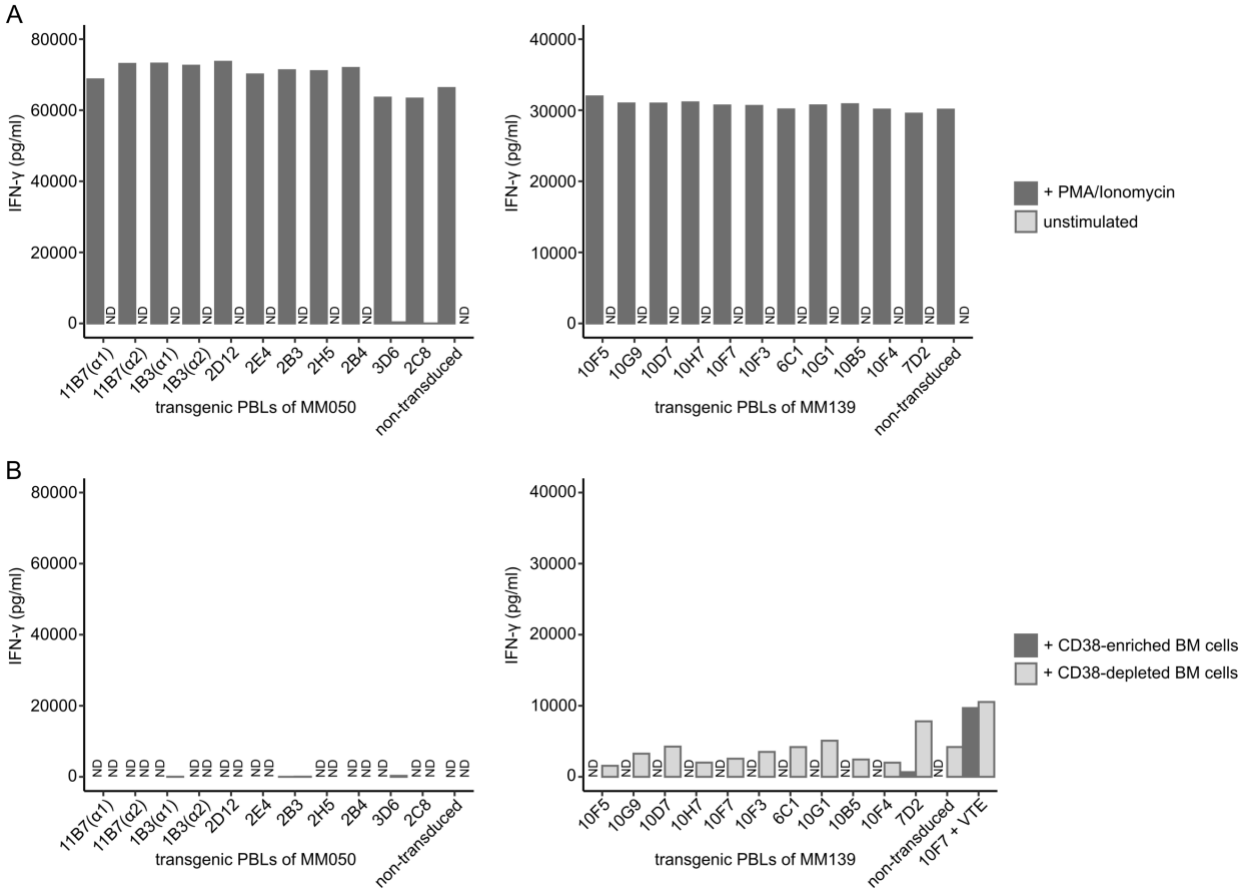


Supplementary Figure S9. Immune phenotypes of multiple myeloma-reactive expanded T cell clones.

(A and D) Sequencing of TCRαβ, transcription factor, and cytokine genes from amplified cDNA of single FACS-sorted T cells. Single cell data are arranged in columns with each column representing one single cell. The top bar indicates TCR sequences; adjacent columns with the same color in the top bar indicate single cells with identical CDR3 amino acid sequences of TCRαβ genes. The lower part of the heatmap visualizes corresponding FACS index sort data. Clones for

which detailed immune phenotypes are illustrated in FACS plots are highlighted. Data from MM008 are shown in (A), data from MM160 in (D). FACS plots show immune phenotypes of selected single T cell clones (data points in black) determined by FACS index sorting. Phenotypes of clone 14F10 are shown in (B), 15G9 in (C), and 16A2 in (E). Numbers within gates indicate percentages.

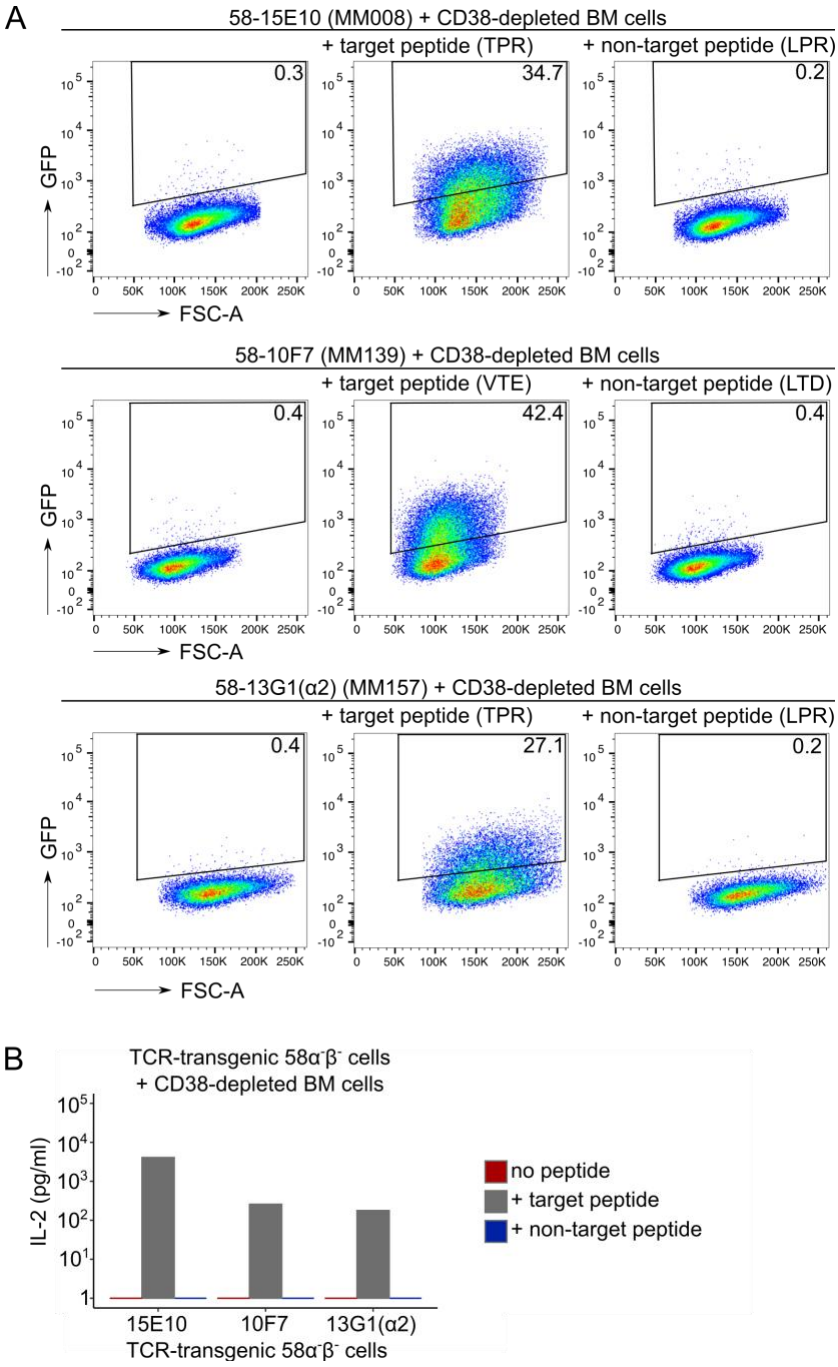
Supplementary Figure S10



Supplementary Figure S10. Activation of TCR-transduced human PBL by multiple myeloma and non-myeloma cells.

(A) PMA/ionomycin stimulation as positive control. (B) Incubation of all TCR-transduced human PBL with respective multiple myeloma and non-myeloma cells. Activation of TCR 7D2-expressing PBL by non-myeloma cells was not reproducible. The TCRβ chain of TCR 10F7 had previously been reported specific for the CMV-derived peptide VTEHDTLLY (VTE). We used this peptide to artificially load multiple myeloma and non-myeloma cells and confirm efficient peptide presentation. Plots show data from n=2 experiments. PBL indicates peripheral blood lymphocytes; BM, bone marrow; and ND, not detectable.

Supplementary Figure S11



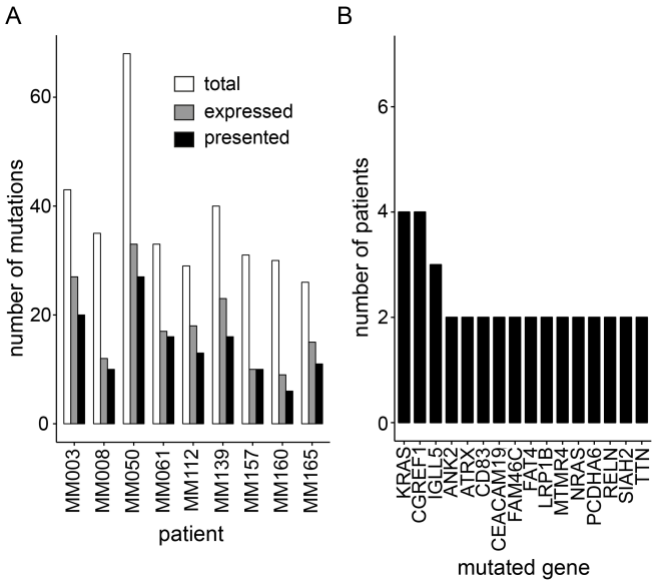
Supplementary Figure S11. Confirmation of virus peptide specificity of selected TCRs.

Selected potentially CMV peptide-specific TCR-transgenic 58α-β- cell lines were incubated with peptide-loaded CD38-depleted bone marrow (BM) cells from the respective patients. (A) FACS

plots in the left column show data from TCR-transgenic 58$\alpha^-\beta^-$ cells incubated with CD38-depleted bone marrow cells without additional peptide loading. (B) shows IL-2 detected in cell culture supernatants corresponding to co-incubations shown in (A).

Plots show data from n=3 experiments.

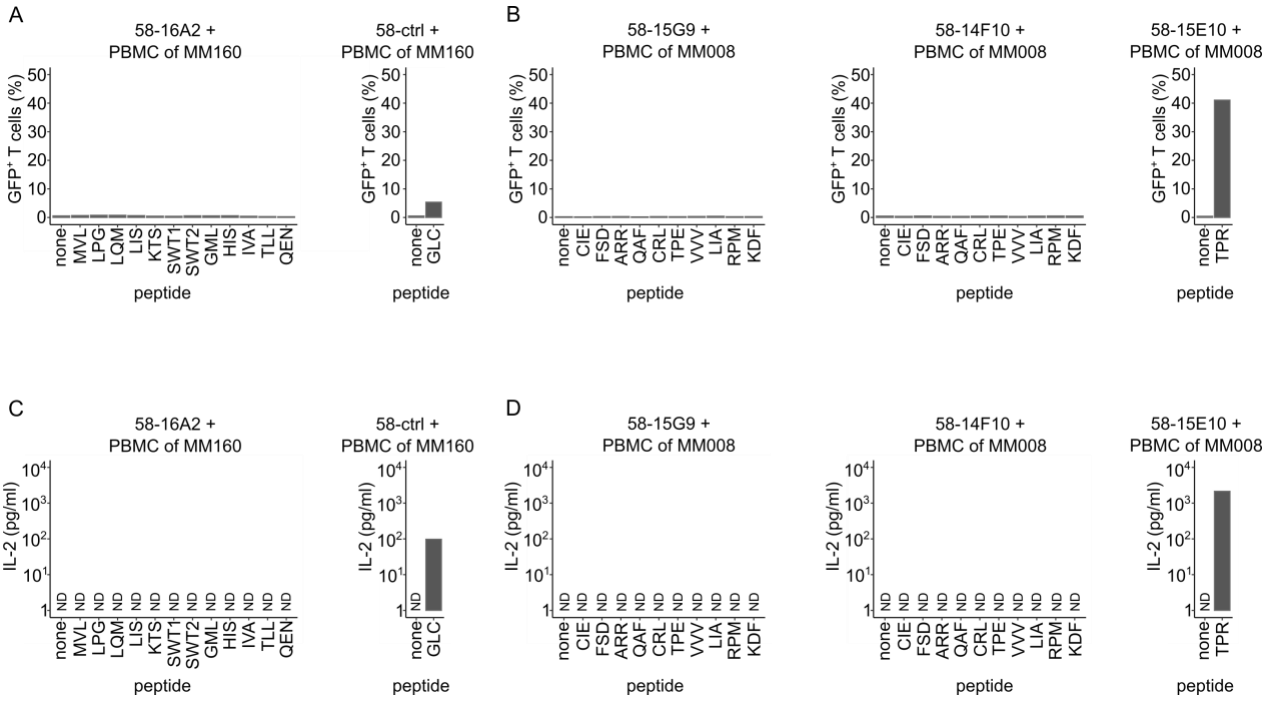
Supplementary Figure S12



Supplementary Figure S12. Neo-antigen load and recurrently mutated genes in nine selected multiple myeloma patients.

"Mutation" refers to non-synonymous mutations located within exon regions. (A) shows total numbers of somatic mutations within multiple myeloma cells. Somatic mutations were determined by comparative whole exome sequencing of DNA isolated from CD38-enriched multiple myeloma cells, and peripheral blood cells or FACS-sorted non-myeloma cells. Mutation expression was determined by RNA sequencing of enriched multiple myeloma cells. Potential presentation of expressed mutations was predicted bioinformatically. (B) shows genes in which we detected mutations in more than one patient. For mutation details, see Supplementary Tables S7 and S8.

Supplementary Figure S13

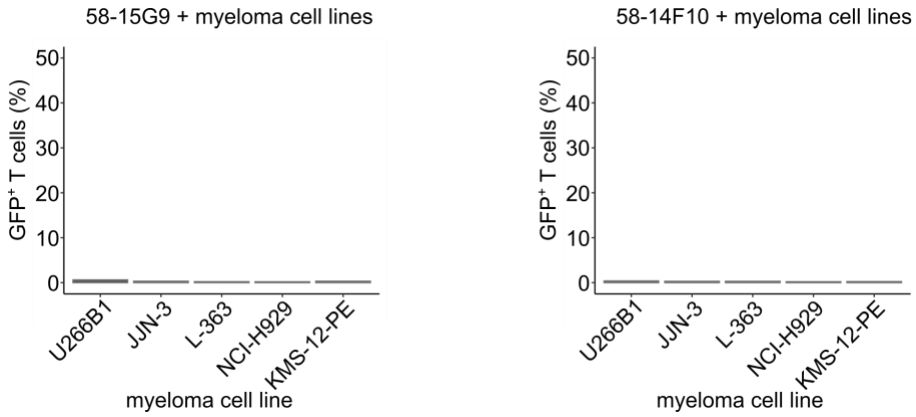


Supplementary Figure S13. Multiple myeloma-reactive expanded bone marrow T cell clones are not neo-antigen-specific.

Multiple myeloma-reactive TCR-transgenic cell lines were incubated with potential target peptide-loaded PBMC of the respective patients. (A, B) GFP expression in TCR-recombinant T cells, and (C, D) corresponding IL-2 production. For MM160, an HLA-A*02:01-restricted EBV epitope-specific TCR (target peptide: GLCTLVAML, named “GLC”) was used as positive control (A, C). For MM008, an HLA-B*07:02-restricted CMV epitope-specific TCR (target peptide: TPRVTGGGAM, named “TPR”) was used as positive control (B, D).

Data are representative for n=2 experiments.

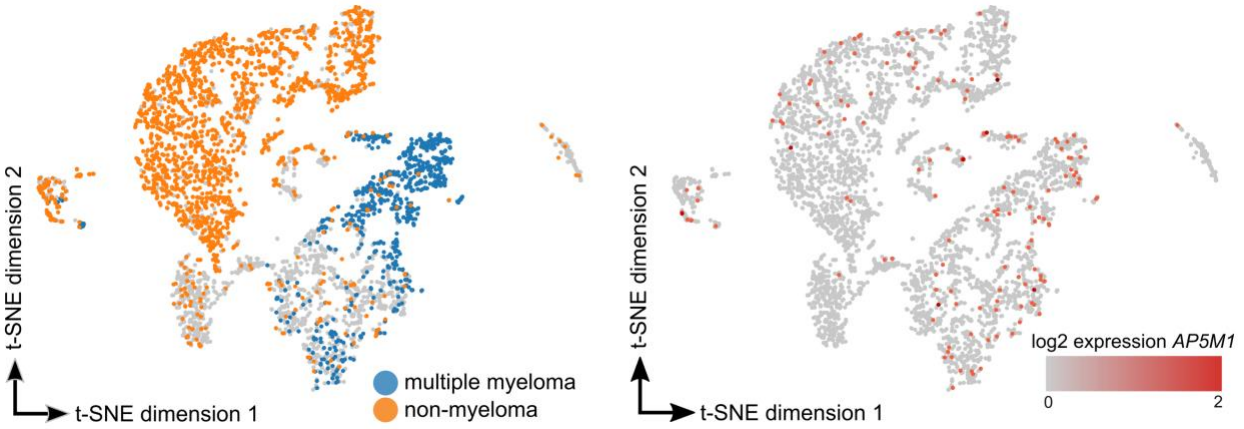
Supplementary Figure S14



Supplementary Figure S14. TCRs 15G9 and 14F10 do not recognize multiple myeloma cell lines.

60 000 58-15G9 or 60 000 58-14F10 were incubated with 100 000 cells of the respective cell lines. The plots show data from three technical replicates within n=1 experiment.

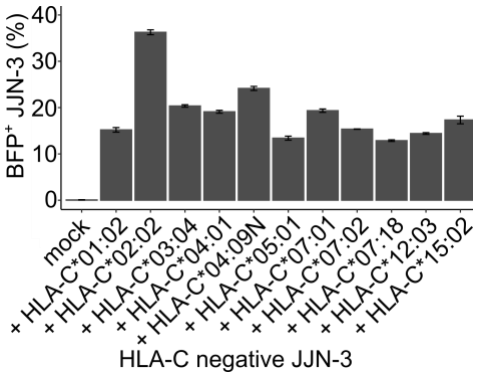
Supplementary Figure S15



Supplementary Figure S15. Single cell *AP5M1* expression in bone marrow cells of one additional multiple myeloma patient.

Each data point represents one out of 4379 single bone marrow cells. Left plot: Multiple myeloma cells were identified by expression of CD138, SLAMF7, and monoclonal immunoglobulin light chain in absence of CD45. Non-myeloma cells were selected by CD45 expression and absence of CD138. Right plot: *AP5M1* expression was generally low but not restricted to multiple myeloma cells.

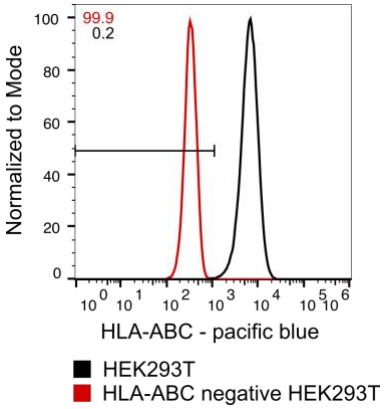
Supplementary Figure S16



Supplementary Figure S16. Recombinant HLA-C expression in HLA-C-negative JJN-3.

Selected HLA-C alleles were transiently expressed in HLA-C-negative JJN-3 by nucleofection. Plasmids for nucleofection also carried mTagBFP2 (blue fluorescent protein, BFP), which was measured to indicate HLA expression. The plot shows three technical replicates within n=1 experiment.

Supplementary Figure S17



Supplementary Figure S17. HLA-class I deletion in HEK293T

HLA-class I expression in HEK293T was deleted using CRISPR-Cas-9 technology. Numbers within the plot indicate percentages.