A study of CDR3 loop dynamics reveals distinct mechanisms of peptide recognition by T-cell receptors exhibiting different levels of cross-reactivity

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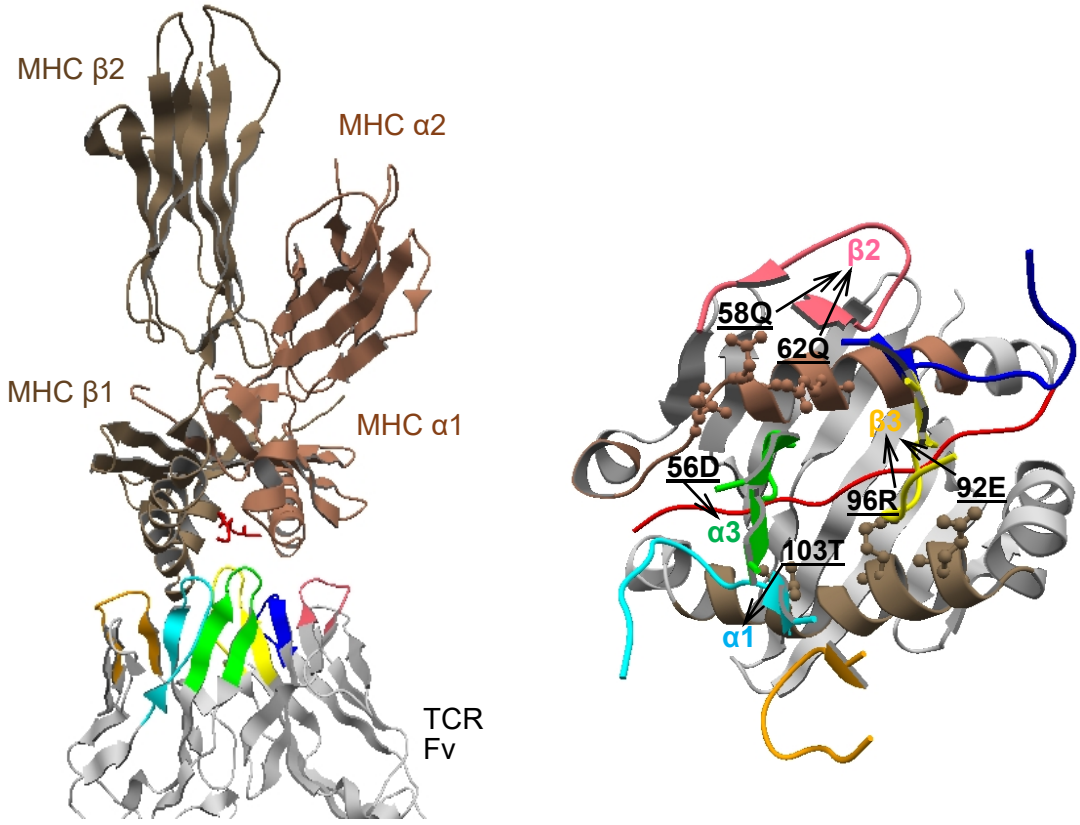
Supplementary materials

Figure S1



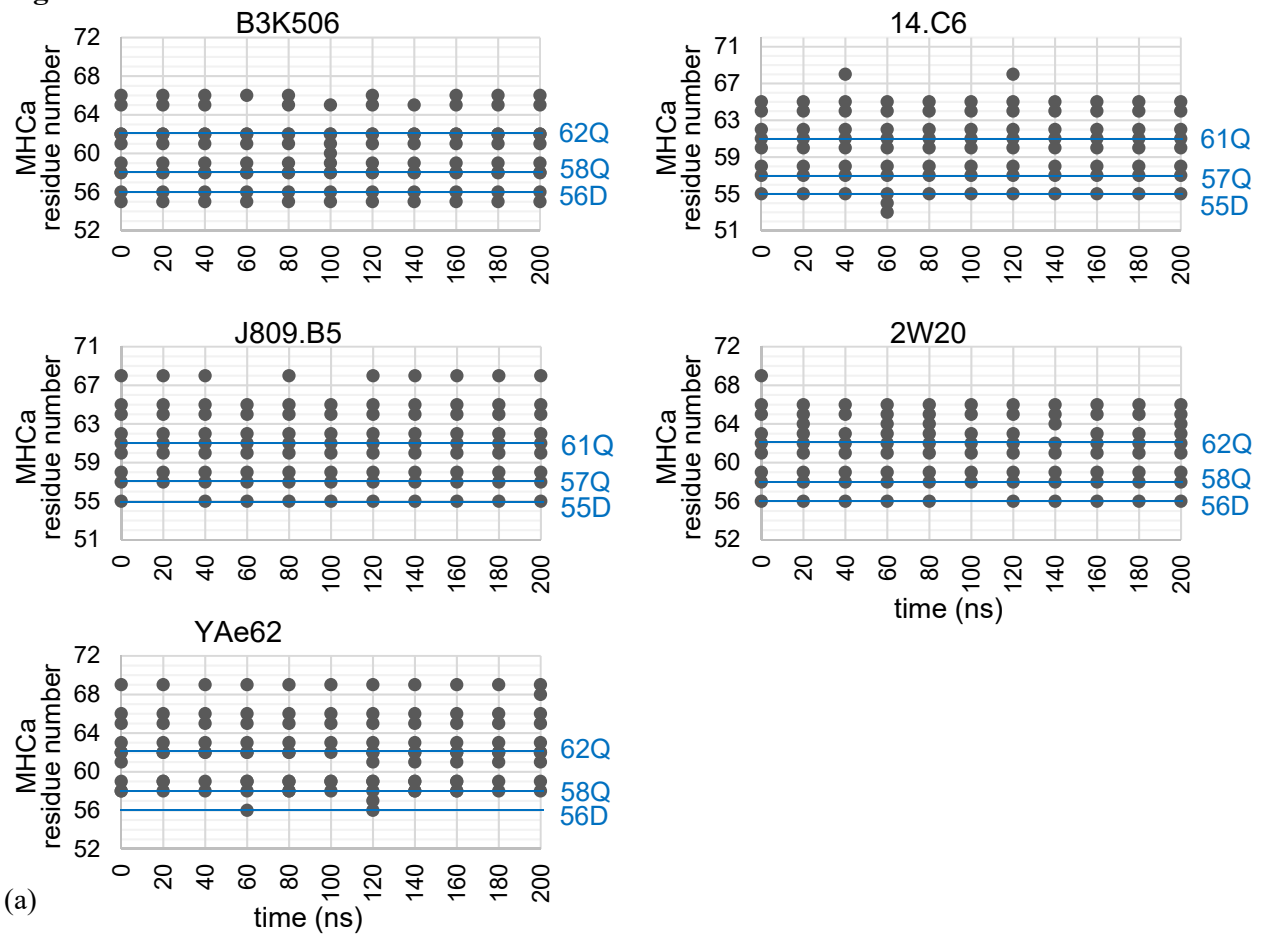
(a) (b)

Fig. S1. Structural features of a TCR-pMHC complex and the positions of conserved TCR-MHC interactions on MHC.

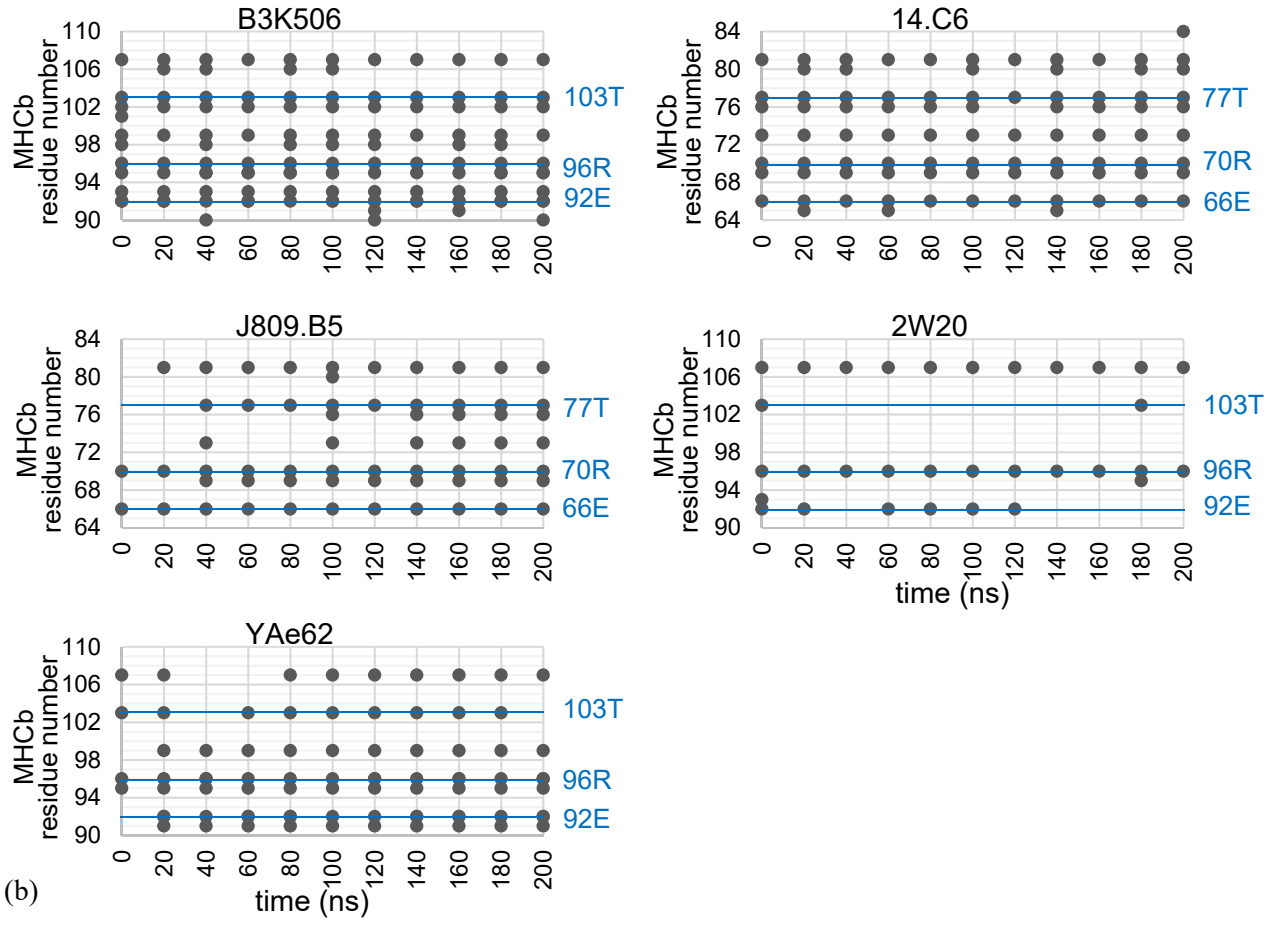
(a) Structure of the B3K506-1A^{b}-3K complex (PDB ID: 3c5z). MHC α and β molecules are shown in light brown and dark brown, respectively. The peptide is shown in red. CDR1α–3α and CDR1β–3β are shown in cyan, orange, green, blue, pink, and yellow, respectively.

(b) The positions of MHC residues involved in conserved TCR-MHC interactions, all of which are located on the recognition helices except for Asp56 in MHCα, in the B3K506-1A^{b}-3K complex. The relevant residues are shown using a ball-and-stick model with residue numbers. The arrows indicate the CDR loops in which the counterpart residues exist and which are observed in most of the complexes.

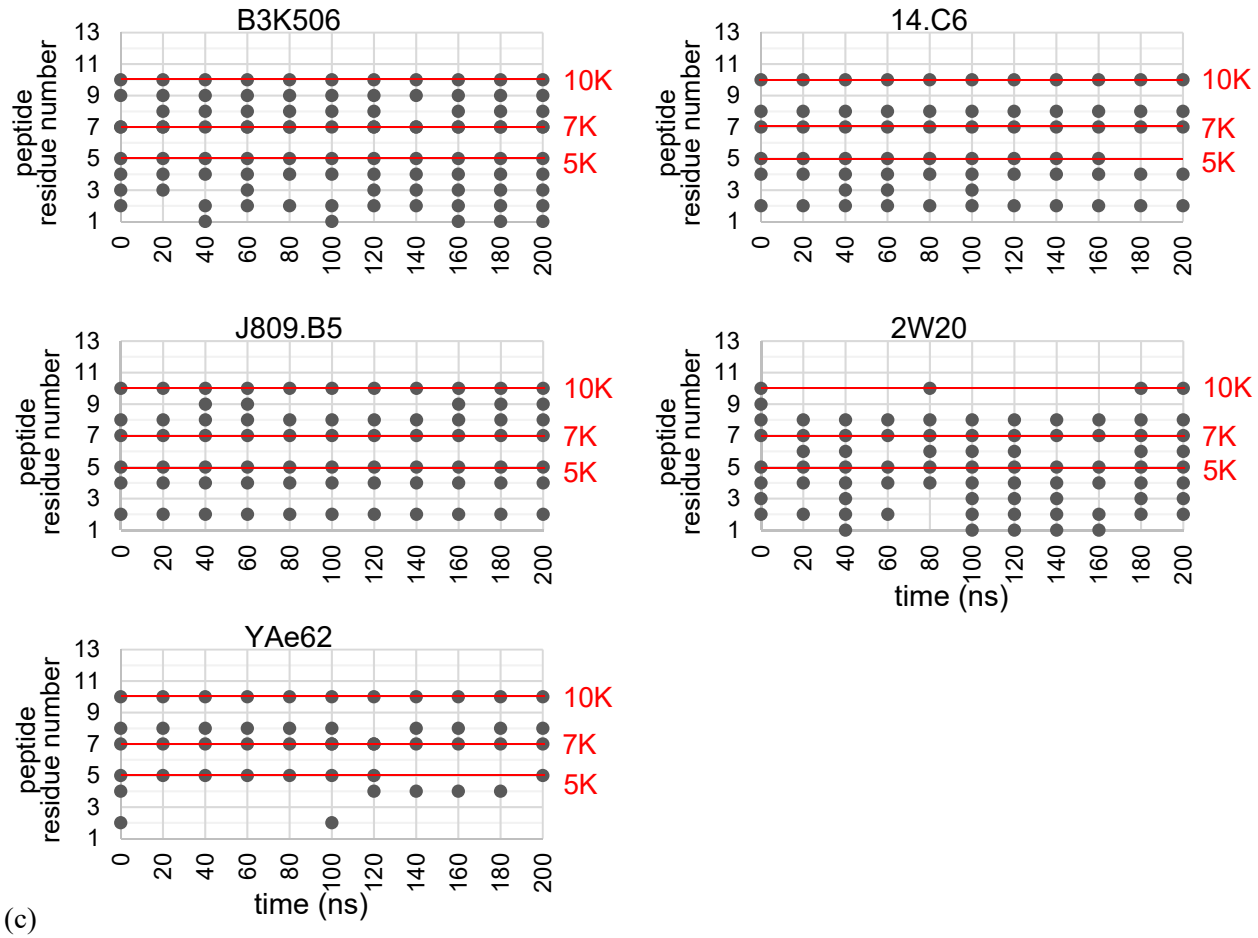
Figure S2


B3K506
14.C6
J809.B5
2W20
YAe62
MHCa residue number
time (ns)
62Q
58Q
56D
61Q
57Q
55D

(a)


B3K506
14.C6
J809.B5
2W20
YAe62
MHCb residue number
time (ns)
103T
96R
92E
77T
70R
66E

(b)



(c)

Fig. S2. Interactions between TCR and pMHC in crystal structures and MD snapshots.
Interactions of any TCR residues with the MHCα residues 51–71 (or 52–72), MHCβ residues 64–84 (or 90–110), and peptide residues 1–13 are shown in (a), (b), and (c), respectively, each of which contains the figures for B3K506, 14.C6, J809.B5, 2W20, and YAe62. The black dots indicate that at least one atom in the MHC or peptide residues specified is located within a distance of 4.5 Å from any of the atoms in the TCR, in the crystal structure (represented at time step 0) and the MD snapshots (at every 20 ns from 20 to 200 ns). The residues with blue lines in (a) and (b) are involved in the conserved TCR-MHC interactions, and those with red lines in (c) are the three important Lys residues in the peptide. Note that in the peptide in the 14.C6 and J809.B5 complexes, the residue numbers of the three Lys residues in the PDB data are −21, −19 and −16, instead of 5, 7, and 10, respectively.

Figure S3

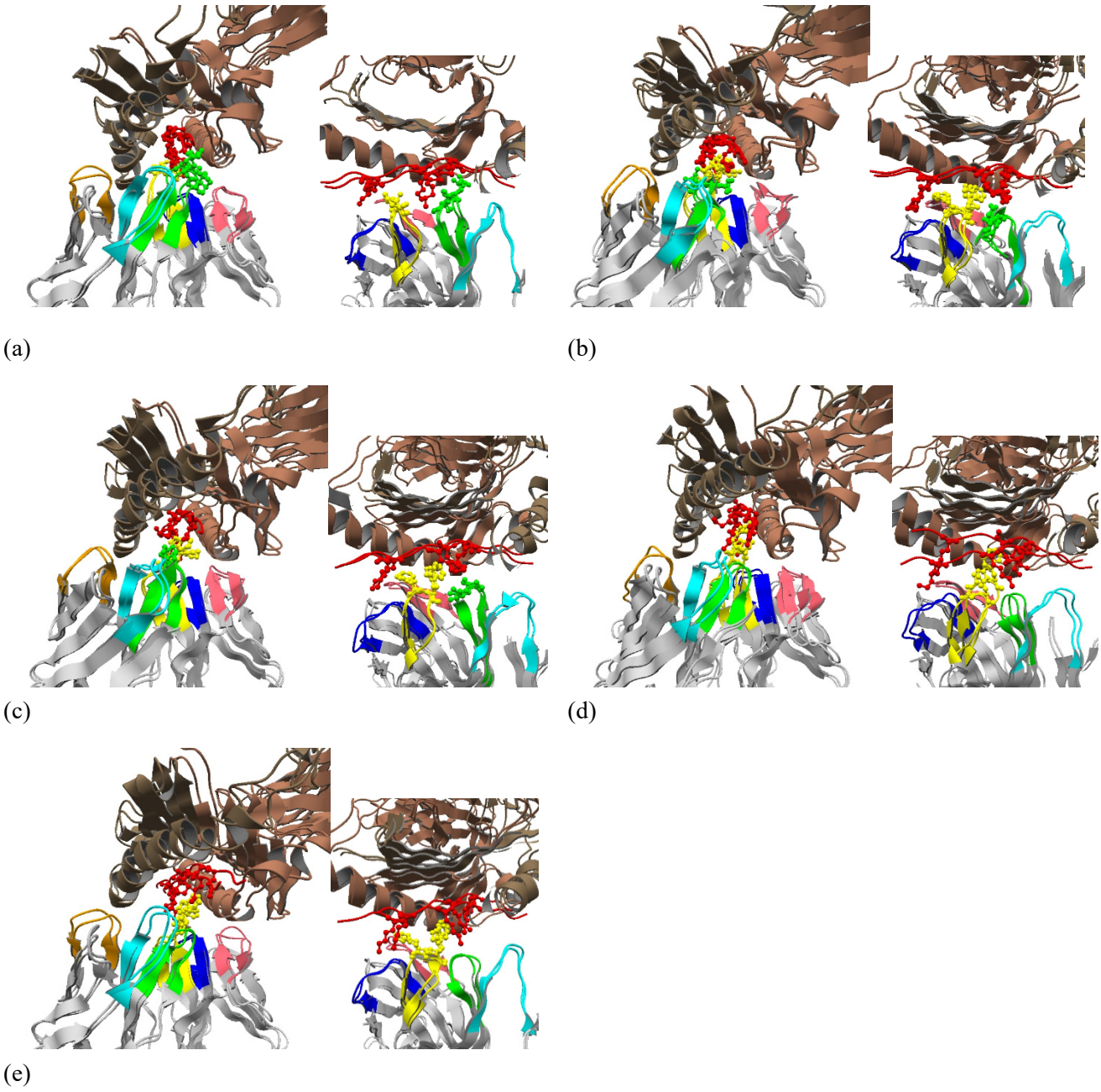
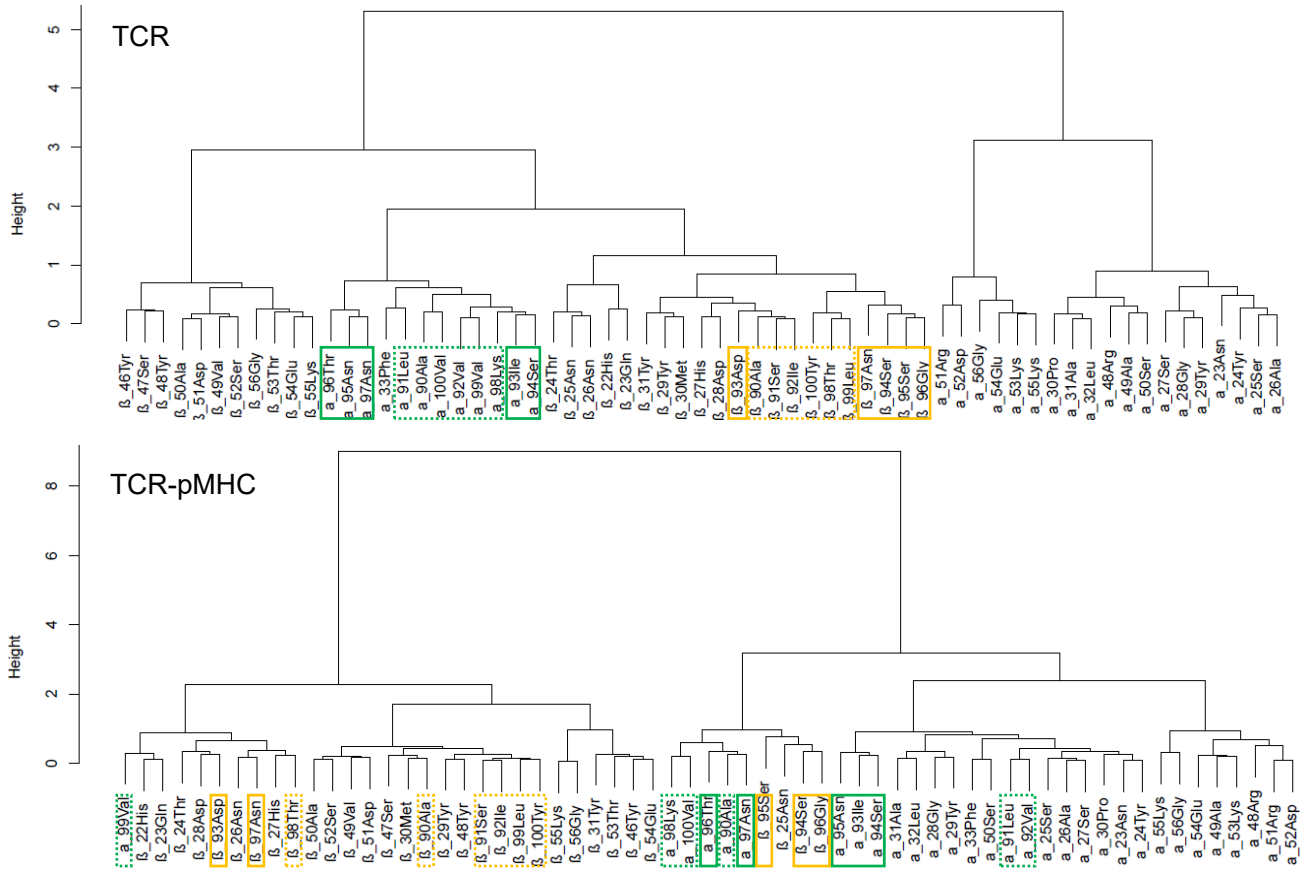
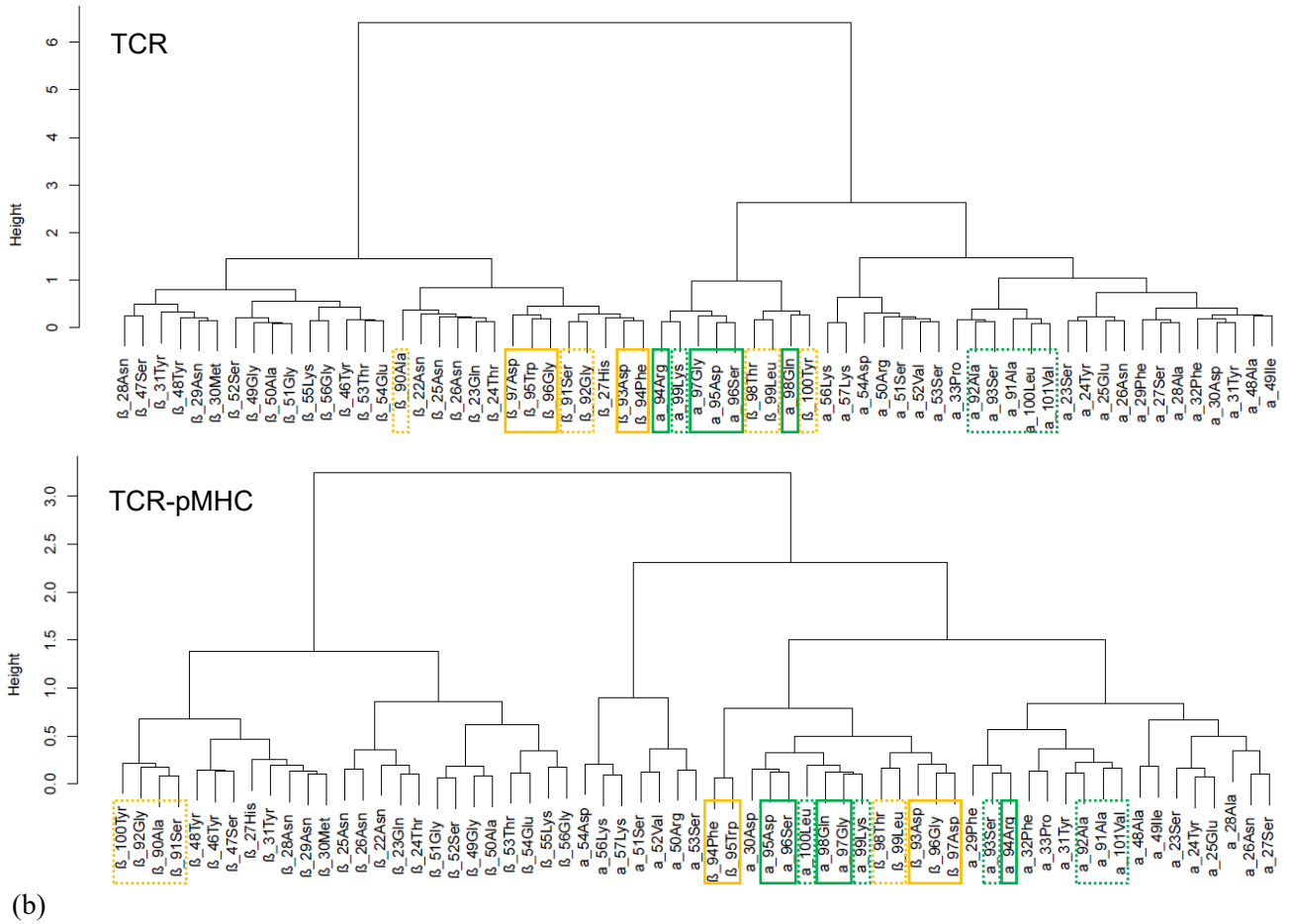


Fig. S3. Structural features of crystal structures and MD snapshot structures at 200 ns.
(a–e) Crystal structures and snapshots at 200 ns superimposed onto the crystal structure of B3K506 with respect to the TCR Fv regions except for CDR loops. (a), (b), (c), (d), and (e) show the figures from two angles of B3K506, 14.C6, J809.B5, 2W20, and YAe62, respectively, in complex with $1A^{b}$-3K. See caption of Fig. S1 for the interpretation of molecular colors. The 95^{th} and 96^{th} residues in CDR3α, the 94^{th} and 95^{th} residues in CDR3β, and the three Lys residues in the peptide are shown using a ball-and-stick model.

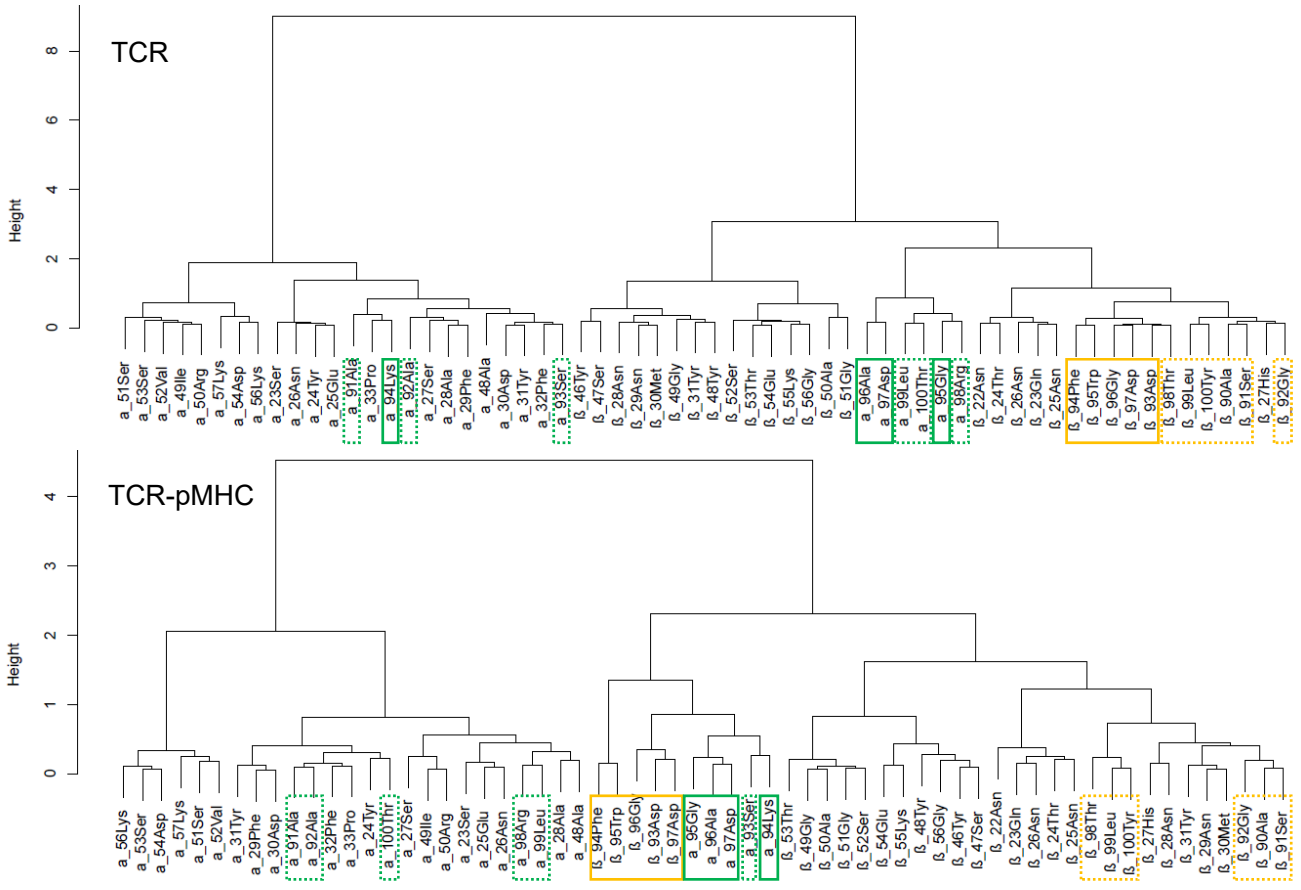
Figure S4



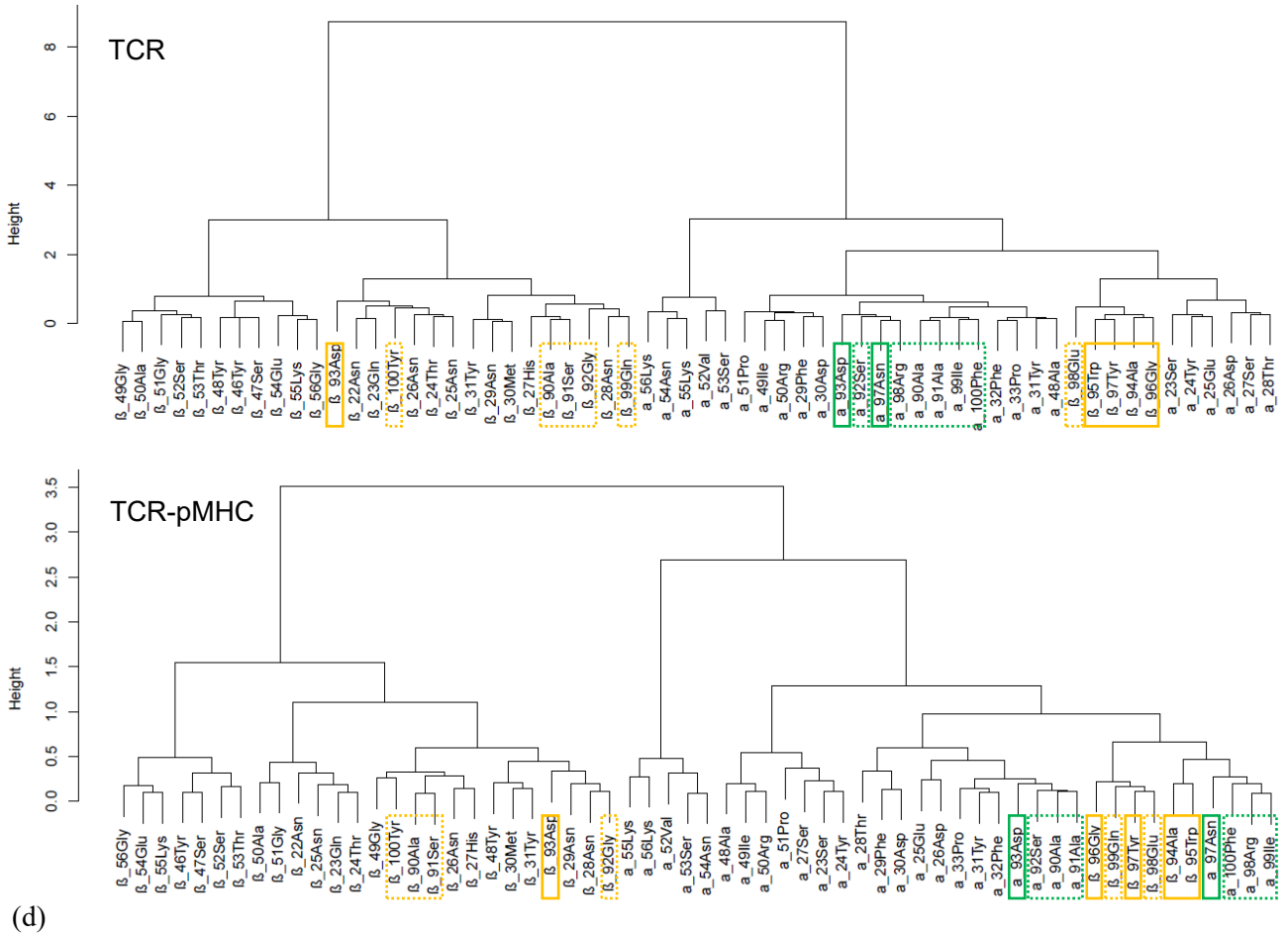
(a)



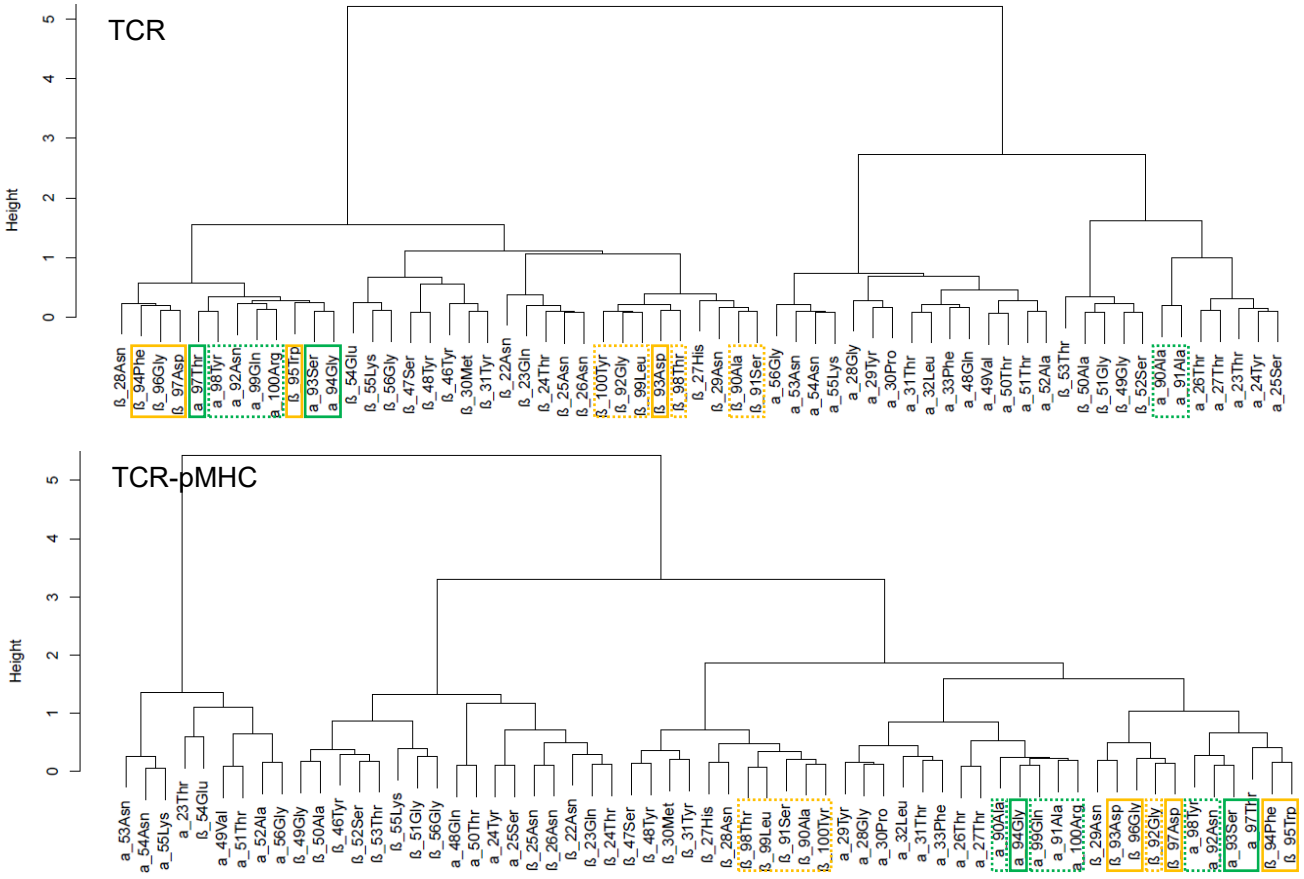
(b)



(c)



(d)



(e)

Fig. S4. Hierarchical clustering dendrograms of CDR residues of TCRs in the free and complex states.

The clustering of CDR residues based on the correlation of fluctuations during MD simulations from 20 to 200 ns of TCRs in the free (labeled as TCR) and complex (as TCR-pMHC) states are shown. The clustering dendrograms in the free and complex states for B3K506, 14.C6, J809.B5, 2W20, and YAe62 are shown in (a), (b), (c), (d), and (e), respectively. The residues surrounded by green and yellow lines belong to CDR3α and CDR3β, respectively. The solid and dotted lines indicate the turn and β-sheet regions of the CDR loops, respectively.

Figure S5

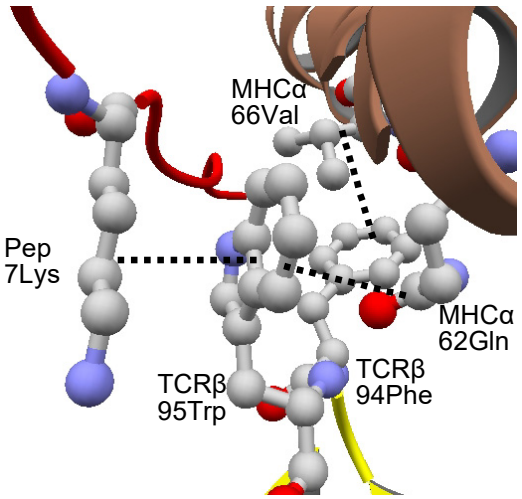
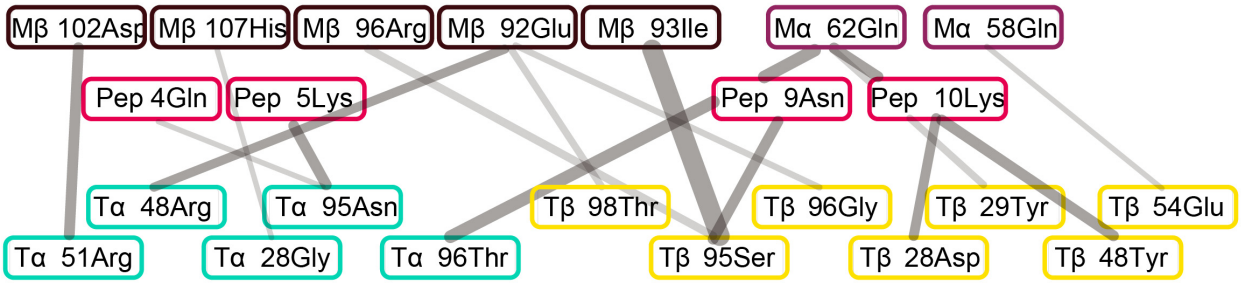


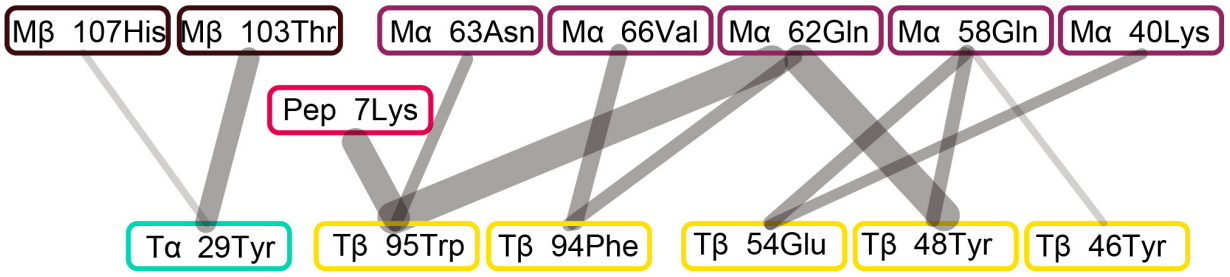
Fig. S5. CH-π interactions of 94Phe and 95Trp in CDR3β of YAe62.

CH-π interactions exist between 94Phe in CDR3β and 66Val in MHCα, 95Tpr in CDR3β and 7Lys in the peptide, and 95Tpr in CDR3β and 62Gln in MHCα, in the crystal structure and MD snapshot structures. The CH-π interactions are indicated by dotted lines.

Figure S6



(a)



(b)

Fig. S6. Scattered (B3k506 in a) and concentrated (YAe62 in b) interaction networks, both in complex with $1A^b$-3K. The residue-residue interactions formed by more than five atomic contacts are connected by the grey lines. The width of the line is proportional to the number of atomic contacts. The MHC α and β molecules (Mα and Mβ, respectively), peptide (Pep), and TCR α and β molecules (Tα and Tβ, respectively) are shown in light brown, dark brown, red, green, and yellow, respectively.

Table S1. Conserved TCR-MHC interactions

Residue in MHC [a]		# complex (%) [b]	TCR [c]		
MHCα	55 E, D	29 (94)	CDR3α (27)		
	57 Q	30 (97)	CDR2β (28)	CDR3α (19)	
	61 A, Q, R	30 (97)	CDR2β (27)	CDR3β (19)	CDR3α (18)
MHCβ	66 E, D	27 (96 [d])	CDR3β (26)		
	70 Q, R	28 (90)	CDR3β (24)		
	77 T, R, N	27 (87)	CDR1α (25)		

a) The most common residue numbers and amino acids in single letter code in the 31 complexes are shown. The corresponding residue numbers and amino acids in the MHCs in complex with B3K506, 2W20, and YAe62 are 56D, 58Q and 62Q in MHCα and 92E, 96R, and 103T in MHCβ, respectively.

b) The number of complexes, in which at least one atom in the TCR CDR is located within 4.5 Å from any atoms in the MHC residue is shown. The percentage of the 31 complexes represented by such complexes is given in parentheses.

c) The CDR loop that interacts with the MHC residue is specified. The number of complexes that contain such interactions is stated in parentheses.

d) Of the 31 complexes, only 28 complexes have this specified residue in the MHC. Therefore, the denominator of the percentage is 28 rather than 31.

Table S2. The number of TCR atoms in contact with the peptide and classification of the TCR atoms based on the CDRs they belong to for 31 complexes [a]

Complex	# atom	CDR1α	CDR2α	CDR3α	CDR1β	CDR2β	CDR3β	nonCDR	CDR3α+3β
1d9k	91	0.38	0.00	0.42	0.00	0.00	0.20	0.00	0.62
1fyt	72	0.10	0.00	0.28	0.19	0.00	0.43	0.00	0.71
1j8h	72	0.13	0.00	0.25	0.18	0.00	0.43	0.01	0.68
1u3h	66	0.12	0.00	0.71	0.00	0.00	0.17	0.00	0.88
1zgl	90	0.16	0.00	0.40	0.14	0.11	0.19	0.00	0.59
2iam	132	0.23	0.00	0.21	0.17	0.00	0.38	0.01	0.59
2ian	139	0.22	0.00	0.22	0.17	0.00	0.38	0.01	0.60
2wbj	126	0.00	0.00	0.41	0.00	0.02	0.46	0.10	0.87
3c5z	88	0.13	0.00	0.44	0.15	0.00	0.28	0.00	0.73
3c60	47	0.17	0.00	0.00	0.06	0.00	0.77	0.00	0.77
3c6l	101	0.35	0.00	0.11	0.07	0.00	0.48	0.00	0.58
3mbe	141	0.14	0.00	0.18	0.20	0.01	0.46	0.01	0.65
3o6f	108	0.06	0.00	0.16	0.15	0.00	0.61	0.02	0.77
3pl6	85	0.04	0.00	0.69	0.09	0.15	0.02	0.00	0.72
3qib	173	0.14	0.00	0.38	0.02	0.03	0.43	0.00	0.80
3qiu	156	0.12	0.00	0.33	0.01	0.06	0.48	0.00	0.81
3qiw	146	0.14	0.00	0.42	0.01	0.04	0.40	0.00	0.82
3rdt	77	0.01	0.00	0.32	0.13	0.00	0.53	0.00	0.86
3t0e	94	0.09	0.00	0.19	0.20	0.00	0.50	0.02	0.69
4grl	74	0.16	0.00	0.66	0.07	0.08	0.01	0.01	0.68
4h1l	120	0.11	0.00	0.20	0.04	0.00	0.64	0.01	0.84
4may	88	0.02	0.00	0.82	0.07	0.06	0.03	0.00	0.85
4p23	89	0.01	0.00	0.34	0.11	0.00	0.54	0.00	0.88
4p2o	99	0.20	0.00	0.42	0.01	0.06	0.30	0.00	0.73
4p2q	160	0.08	0.00	0.41	0.00	0.16	0.36	0.00	0.77
4p2r	131	0.12	0.00	0.37	0.00	0.16	0.34	0.00	0.72
4p46	87	0.01	0.00	0.39	0.09	0.00	0.51	0.00	0.90
4p4k	127	0.05	0.00	0.66	0.08	0.03	0.18	0.00	0.84
4p5t	96	0.24	0.00	0.29	0.01	0.00	0.49	0.00	0.78
4y19	21	0.00	0.00	0.00	0.00	0.86	0.00	0.14	0.00
4y1a	27	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00

a) In the first column, the 31 complexes are represented by their PDB IDs. In the second column, the number of TCR atoms that are in contact with the peptide are shown. Atomic contact is defined as at least one atom in the TCR being located within a distance of 4.5 Å from any of the atoms in the peptide. In the third to last columns, these TCR atoms are classified according to the CDRs to which they belong (the ratios to the number given in the second column are shown). NonCDR indicates the atoms that are not involved in the CDRs. CDR3α+3β is the sum of the ratios of CDR3α and CDR3β. The CDR regions are defined based on the IMGT 3D structure-DB [1] and Dunbrack definition [2].

Table S3. Interface areas in crystal structures and MD snapshots [a]

B3K506	T-pM	T-M	T-p	14.C6	T-pM	T-M	T-p
Crystal	1,163	932	455	**Crystal**	1,033	822	382
20 ns	1,191	963	434	**20 ns**	1,093	853	379
40 ns	1,202	993	439	**40 ns**	1,175	938	421
60 ns	1,229	971	462	**60 ns**	1,110	918	383
80 ns	1,219	997	423	**80 ns**	1,140	931	383
100 ns	1,291	1,039	476	**100 ns**	1,117	887	403
120 ns	1,231	1,030	435	**120 ns**	1,143	910	373
140 ns	1,243	986	475	**140 ns**	1,094	878	367
160 ns	1,171	940	468	**160 ns**	1,109	897	372
180 ns	1,275	1,055	478	**180 ns**	1,148	927	383
200 ns	1,245	1,005	470	**200 ns**	1,128	886	389
Average [b]	1,230	998	456	**Average [b]**	1,126	903	385

J809.B5	T-pM	T-M	T-p	2W20	T-pM	T-M	T-p
Crystal	836	635	343	**Crystal**	992	787	396
20 ns	915	695	357	**20 ns**	968	823	264
40 ns	1,050	887	314	**40 ns**	902	710	342
60 ns	1,030	866	324	**60 ns**	834	664	291
80 ns	1,020	793	360	**80 ns**	885	723	286
100 ns	1,091	877	341	**100 ns**	874	622	357
120 ns	1,015	833	313	**120 ns**	1010	750	383
140 ns	1,136	901	381	**140 ns**	938	691	356
160 ns	1,057	866	343	**160 ns**	899	677	328
180 ns	1,098	911	320	**180 ns**	999	796	326
200 ns	1,055	965	337	**200 ns**	919	699	352
Average [b]	1,047	850	339	**Average [b]**	923	716	329

YAe62	T-pM	T-M	T-p
Crystal	760	596	304
20 ns	789	691	185
40 ns	767	645	198
60 ns	834	714	215
80 ns	810	700	198
100 ns	811	687	227
120 ns	945	809	253
140 ns	955	816	255
160 ns	941	799	265
180 ns	874	769	221
200 ns	850	760	167
Average [b]	857	739	218

a) The interface areas (Å^2) between TCR and pMHC (T-pM), between TCR and MHC (T-M), and between TCR and peptide (T-p) in the crystal structure and the MD snapshot structures taken every 20 ns.

b) The average of the interface areas from the MD snapshots is shown.

Table S4. Number of atomic contacts in the crystal structure and MD snapshots [a]

(a) B3K506

	T-pM	T-M	Tα-Mα	Tα-Mβ	Tα-M	Tβ-Mα	Tβ-Mβ	Tβ-M	T-p	Tα-p	Tβ-p	94-pM	94-p	95-pM	95-p
Crys	288	200	35	57	92	42	66	108	88	50	38	8	7	51	17
20	370	299	56	101	157	79	63	142	71	39	32	9	7	28	13
40	367	289	50	92	142	61	86	147	78	43	35	13	10	37	19
60	313	237	43	67	110	43	84	127	76	42	34	10	8	32	15
80	378	299	45	89	134	75	90	165	79	43	36	10	8	42	17
100	408	314	63	117	180	61	73	134	94	62	32	9	9	28	15
120	384	296	55	126	181	47	68	115	88	53	35	6	5	36	18
140	350	247	61	91	152	44	51	95	103	66	37	9	9	28	11
160	372	264	66	79	145	56	63	119	108	68	40	13	10	35	19
180	425	320	56	101	157	66	97	163	105	73	32	11	9	32	8
200	373	271	51	83	134	58	79	137	102	73	29	13	10	30	10
Ave	374	284	55	95	149	59	75	134	90	56	34	10	9	33	15

(b) 14.C6

	T-pM	T-M	Tα-Mα	Tα-Mβ	Tα-M	Tβ-Mα	Tβ-Mβ	Tβ-M	T-p	Tα-p	Tβ-p	94-pM	94-p	95-pM	95-p
Crys	328	232	16	34	50	135	47	182	96	49	47	28	5	98	38
20	265	178	9	29	38	111	29	140	87	47	40	23	3	67	30
40	275	169	31	36	67	80	22	102	106	61	45	20	1	70	36
60	288	203	33	62	95	87	21	108	85	49	36	22	3	62	27
80	277	197	12	74	86	88	23	111	80	42	38	33	1	60	27
100	280	204	9	57	66	122	16	138	76	43	33	27	3	55	23
120	284	211	16	43	59	128	24	152	73	45	28	39	0	59	20
140	257	188	24	43	67	102	19	121	69	43	26	28	4	50	14
160	265	185	13	43	56	113	16	129	80	45	35	35	2	49	26
180	272	197	12	58	70	104	23	127	75	45	30	30	1	58	21
200	280	203	13	66	79	95	29	124	77	41	36	17	0	58	26
Ave	274	194	17	51	68	103	22	125	81	46	35	27	2	59	25

(c) J809.B5

	T-pM	T-M	Tα-Mα	Tα-Mβ	Tα-M	Tβ-Mα	Tβ-Mβ	Tβ-M	T-p	Tα-p	Tβ-p	94-pM	94-p	95-pM	95-p
Crys	279	202	11	0	11	156	35	191	77	26	51	34	5	90	36
20	278	197	8	4	12	144	41	185	81	32	49	31	1	77	36
40	282	237	15	36	51	137	49	186	45	24	21	35	5	71	16
60	290	226	31	30	61	115	50	165	64	29	35	15	5	85	30
80	318	236	30	34	64	124	48	172	82	41	41	39	5	58	28
100	287	230	26	48	74	109	47	156	57	31	26	26	1	49	17
120	302	221	21	20	41	125	55	180	81	31	50	33	2	76	37
140	285	201	24	32	56	99	46	145	84	41	43	20	1	70	35
160	300	227	36	40	76	106	45	151	73	36	37	38	2	59	26
180	242	182	22	37	59	78	45	123	60	26	34	23	1	57	24
200	273	213	32	25	57	107	49	156	60	20	40	28	2	68	30
Ave	286	217	25	31	55	114	48	162	69	31	38	29	3	67	28

(d) 2W20

	T-pM	T-M	Tα-Mα	Tα-Mβ	Tα-M	Tβ-Mα	Tβ-Mβ	Tβ-M	T-p	Tα-p	Tβ-p	94-pM	94-p	95-pM	95-p
Crys	301	200	20	19	39	113	48	161	101	46	55	8	0	86	46
20	245	197	48	32	80	110	7	117	48	19	29	5	0	79	29
40	241	161	79	12	91	63	7	70	80	54	26	5	0	75	26
60	213	161	39	37	76	81	4	85	52	20	32	8	0	68	32
80	231	176	59	36	95	77	4	81	55	24	31	10	0	62	30
100	244	156	35	33	68	88	0	88	88	61	27	5	0	73	27
120	296	193	51	48	99	94	0	94	103	64	39	5	0	72	39
140	281	183	47	31	78	105	0	105	98	69	29	9	0	59	29
160	242	160	63	25	88	71	1	72	82	51	31	4	0	58	31
180	246	161	46	28	74	83	4	87	85	47	38	6	0	78	37
200	244	155	61	22	83	72	0	72	89	41	48	6	0	72	47
Ave	248	170	53	30	83	84	3	87	78	45	33	6	0	70	33

(e) YAe62

	T-pM	T-M	Tα-Mα	Tα-Mβ	Tα-M	Tβ-Mα	Tβ-Mβ	Tβ-M	T-p	Tα-p	Tβ-p	94-pM	94-p	95-pM	95-p
Crys	274	227	8	33	41	185	1	186	47	8	39	42	2	84	34
20	203	174	3	58	61	112	1	113	29	0	29	36	6	49	17
40	180	145	1	46	47	89	9	98	35	0	35	22	0	66	28
60	221	188	3	58	61	126	1	127	33	0	33	48	5	53	19
80	220	178	5	62	67	110	1	111	42	0	42	25	5	63	28
100	250	193	2	51	53	140	0	140	57	8	49	44	5	77	35
120	275	215	4	36	40	165	10	175	60	19	41	31	3	68	30
140	306	260	7	80	87	172	1	173	46	9	37	39	5	65	23
160	273	231	14	69	83	144	4	148	42	10	32	35	2	59	21
180	254	211	2	45	47	164	0	164	43	7	36	44	6	62	23
200	194	169	1	33	34	123	12	135	25	0	25	38	2	46	14
Ave	238	196	4	54	58	135	4	138	41	5	36	36	4	61	24

a) The number of atomic contacts between components of TCR-pMHC are shown. The following abbreviations are used for the components: T: TCR, Tα: α subunit of TCR, Tβ: β subunit of TCR, M: MHC, Mα: α subunit of MHC, Mβ: β subunit of MHC, p: peptide, pM: peptide-MHC, 94: residue 94 of TCR β, and 95: residue 95 of TCR β. An atomic contact is defined as at least one atom in one component being located within a distance of 4.5 Å from any of the atoms in another component and vice versa. Data obtained from the crystal structure (Crys) and the MD snapshots taken every 20 ns from 20 ns to 200 ns are shown. The averages (Ave) of the data obtained from the 10 snapshots are also shown in the last row.

Table S5. The numbers of inter-CDR loop atomic contacts in the MD snapshots [a]

(a) B3K506

TCR in free state			TCR-pMHC complex		
CDR3β		CDR3α	CDR3β		CDR3α
90Ala	0		90Ala	0	
91Ser	0		91Ser	0	
92Ile	8		92Ile	54	97Asn (50)
93Asp	0		93Asp	0	
94Ser	0		94Ser	0	
95Ser	0		95Ser	0	
96Gly	0		96Gly	10	
97Asn	1		97Asn	96	97Asn (92)
98Thr	0		98Thr	1	
99Leu	20		99Leu	32	
100Tyr	0		100Tyr	0	
total	29		total	193	

(b) 14.C6

TCR in free state			TCR-pMHC complex		
CDR3β		CDR3α	CDR3β		CDR3α
90Ala	0		90Ala	0	
91Ser	3		91Ser	0	
92Gly	97	98Gln (97)	92Gly	76	98Gln (76)
93Asp	76	98Gln (76)	93Asp	115	98Gln (115)
94Phe	0		94Phe	4	
95Trp	215	96Ser (184) 97Gly (22)	95Trp	194	95Asp (101) 96Ser (62)
96Gly	92	98Gln (69)	96Gly	203	98Gln (121) 97Gly (53)
97Asp	37		97Asp	63	97Gly (38) 96Ser (23)
98Thr	30		98Thr	39	
99Leu	88	98Gln (59)	99Leu	111	98Gln (44) 100Leu (46)
100Tyr	0		100Tyr	0	
total	638		total	805	

(c) J809.B5

TCR in free state			TCR-pMHC complex		
CDR3β		CDR3α	CDR3β		CDR3α
90Ala	0		90Ala	0	
91Ser	0		91Ser	0	
92Gly	0		92Gly	0	
93Asp	0		93Asp	0	
94Phe	0		94Phe	0	
95Trp	429	97Asp (196) 96Ala (139) 98Arg (84)	95Trp	166	96Ala (120) 97Asp (28) 95Gly (18)
96Gly	1		96Gly	1	
97Asp	6		97Asp	1	
98Thr	1		98Thr	0	
99Leu	14		99Leu	20	
100Tyr	0		100Tyr	0	
total	451		total	188	

(d) 2W20

TCR in free state			TCR-pMHC complex		
CDR3β		CDR3α	CDR3β		CDR3α
90Ala	0		90Ala	0	
91Ser	0		91Ser	0	
92Gly	0		92Gly	0	
93Asp	0		93Asp	1	
94Ala	1		94Ala	0	
95Trp	250	97Asn (142) 93Asp (62) 92Ser (31)	95Trp	37	93Asp (36)
96Gly	128	92Ser (61) 99Ile (34) 97Asn (22)	96Gly	116	93Asp (58) 97Asn (28) 92Ser (30)
97Tyr	44		97Tyr	3	
98Glu	4		98Glu	0	
99Gln	38		99Gln	65	99Ile (63)
100Tyr	0		100Tyr	0	
total	465		total	222	

(e) YAe62

TCR in free state					TCR-pMHC complex				
CDR3β		CDR3α			CDR3β		CDR3α		
90Ala	0				90Ala	0			
91Ser	0				91Ser	0			
92Gly	0				92Gly	0			
93Asp	0				93Asp	0			
94Phe	0				94Phe	0			
95Trp	171	97Thr (77)	92Asn (40)	94Gly (46)	95Trp	257	97Thr (110)	92Asn (42)	94Gly (83)
96Gly	138	99Gln (55)	92Asn (50)	97Thr (25)	96Gly	103	97Thr (37)	92Asn (30)	99Gln (33)
97Asp	20				97Asp	8			
98Thr	17				98Thr	0			
99Leu	58				99Leu	32			
100Tyr	0				100Tyr	0			
total	404				total	400			

a) The sum of the atomic contacts observed in the 10 MD snapshots taken every 20 ns from 20 to 200 ns are shown for residues in CDR3β with CDR3α. The total number of the atomic contacts in CDR3β is shown in the last row. The partner residues in CDR3α are shown only if the number of the atomic contacts is larger than 50; the number of atomic contacts are shown in parenthesis

Table S6. Maintained, added, and lost hydrogen bonds between TCR and peptide/MHC during the MD simulations [a]

(a) B3K506

	TCR CDR	peptide/MHC
Added	α 27 Ser O	Peptide 2Glu N
Added	α 48 Arg NE	MHC β 95Glu OE1
Added	α 48 Arg NH2	MHC β 95Glu OE2
Lost	α 95 Asn ND2	Peptide 2Glu OE1
Lost	α 95 Asn ND2	Peptide 3Ala O
Added	α 95 Asn O	Peptide 5Lys NZ
Lost	α 95 Asn OD1	Peptide 5Lys N
Added	α 95 Asn OD1	Peptide 5Lys NZ
Maintained	α 96 Thr O	MHC α 62Gln NE2
Lost	α 97 Asn OD1	Peptide 7Lys NZ
Maintained	β 28 Asp OD2	Peptide 10Lys NZ
Lost	β 29 Tyr OH	MHC α 62Gln OE1
Added	β 46 Tyr OH	MHC α 58Gln OE1
Maintained	β 95 Ser O	MHC β 96Arg NH1
Maintained	β 95 Ser OG	Peptide 10Lys N
Added	β 97 Asn N	MHC β 92Glu OE2
Added	β 97 Asn ND2	MHC β 95Glu OE1
Added	β 98 Thr N	MHC β 92Glu OE2
Added	β 100 Tyr OH	MHC β 92Glu OE1

The numbers of hydrogen bonds maintained, added, and lost are 4, 10, and 5, respectively.

(b) 14.C6

	TCR CDR	peptide/MHC
Maintained	α 26 Asn ND2	Peptide -24Glu OE1/OE2
Maintained	α 28 Ala O	Peptide -22Gln NE2
Lost	α 30 Asp OD2	Peptide -19Lys NZ
Lost	α 50 Arg NH2	MHC β 69Glu OE1
Lost	α 94 Arg NH1	MHC α 55Asp OD2
Added	α 94 Arg NH2	Peptide -24Glu OE1/OE2
Added	α 94 Arg O	Peptide -22Gln NE2
Added	α 99 Lys NZ	MHC α 57Gln OE1
Added	β 46 Tyr OH	MHC α 57Gln OE1
Added	β 46 Tyr OH	MHC α 61Gln NE2
Lost	β 48 Tyr OH	MHC α 57Gln OE1
Lost	β 53 Thr O	MHC α 39Lys NZ
Added	β 54 Glu OE1/OE2	MHC α 39Lys NZ
Added	β 93 Asp OD1/OD2	Peptide -16Lys NZ
Maintained	β 95 Trp NE1	Peptide -18Ala O
Maintained	β 95 Trp O	MHC β 70Arg NH2
Lost	β 97 Asp N	MHC β 66Glu OE2

The numbers of hydrogen bonds maintained, added, and lost are 4, 7, and 6, respectively.

(c) J809.B5

	TCR CDR	peptide/MHC
Added	α 50 Arg NH2	MHC β 69Glu OE1
Added	α 94 Lys NZ	Peptide -24Glu OE1
Lost	α 95 Gly O	Peptide -21Lys NZ
Added	α 97 Asp OD1	Peptide -21Lys NZ
Added	α 98 Arg NH1	MHC α 55Asp OD1
Lost	β 28 Asn OD1	Peptide -16Lys NZ
Maintained	β 29 Asn ND2	MHC α 61Gln OE1
Maintained	β 48 Tyr OH	MHC α 57Gln OE1
Lost	β 53 Thr O	MHC α 39Lys NZ
Maintained	β 54 Glu OE1	MHC α 57Gln NE2
Lost	β 54 Glu OE1	MHC α 39Lys NZ
Added	β 93 Asp OD1	Peptide -16Lys NZ
Lost	β 95 Trp N	MHC α 61Gln OE1
Maintained	β 95 Trp NE1	Peptide -18Ala O
Maintained	β 97 Asp N	MHC β 66Glu OE1
Added	β 97 Asp OD2	MHC β 70Arg NH2

The numbers of hydrogen bonds maintained, added, and lost are 5, 6, and 5, respectively.

(d) 2W20

	TCR CDR	peptide/MHC
Lost	α 30 Asp OD2	Peptide 7Lys NZ
Added	α 93 Asp OD1/OD2	Peptide 4Gln NE2
Added	α 93 Asp OD1/OD2	Peptide 5Lys NZ
Added	α 97 Asn OD1	Peptide 5Lys NZ
Lost	β 29 Asn OD1	MHC α 62Gln NE2
Added	β 48 Tyr OH	MHC α 40Lys NZ
Maintained	β 54 Glu OE1/OE2	MHC α 40Lys NZ
Added	β 95 Trp N	MHC α 62Gln OE1
Lost	β 95 Trp NE1	Peptide 8Ala O
Lost	β 97 Try OH	MHC β 96Arg NH2

The numbers of hydrogen bonds maintained, added, and lost are 1, 5, and 4, respectively.

(e) YAe62

	TCR CDR	peptide/MHC
Lost	α 29 Tyr OH	MHC β 107His ND1
Added	α 50 Thr OG1	MHC β 92Glu OE1/OE2
Lost	α 51 Thr OG1	MHC β 95Glu OE1
Added	β 29 Asn ND2	MHC α 62Gln OE1
Added	β 29 Asn OD1	MHC α 62Gln NE2
Lost	β 48 Tyr OH	MHC α 58Gln NE2
Added	β 52 Ser OG	MHC α 40Lys NZ
Maintained	β 54 Glu OE2	MHC α 40Lys NZ
Added	β 93 Asp OD1/OD2	Peptide 10Lys NZ
Maintained	β 95 Trp N	MHC α 62Gln OE1

The numbers of hydrogen bonds maintained, added, and lost are 2, 5, and 3, respectively.

a) Maintained, added, and lost hydrogen bonds are defined as follows. Maintained: a hydrogen bond is formed in the crystal structure and maintained in at least 5 of the 10 MD snapshots taken every 20 ns during the MD simulation. Added: a hydrogen bond is not formed in the crystal structure but is formed in at least five MD snapshots. Lost: a hydrogen bond is formed in the crystal structure but lost in more than five MD snapshots.

Table S7. CH-π interactions and the dispersion and charge-transfer interaction energies in CDR3β [a]

(a) 14.C6

TCR	pMHC	Crystal structure		MD snapshot at 100 ns		MD snapshot at 200 ns	
		DI [b]	CT [b]	DI	CT	DI	CT
β 94 Phe	66 Val in MHCα	−5.40	−1.62	−5.53	−2.02	-	-
β 94 Phe	10 Lys in peptide	-	-	−2.65	−0.76	-	-
β 95 Trp	62 Gln in MHCα	−5.33	−2.26	-	-	-	-
β 95 Trp	63 Asn in MHCα	-	-	−2.37	−1.49	-	-
β 95 Trp	7 Lys in peptide	−8.11	−2.71	−6.36	0.00	−5.56	−1.31
β 95 Trp	94 Arg in MHCβ	−3.98	−2.48	-	-	−3.07	−1.38

a) The CH-π interactions were identified by Biostation-Viewer [3].

b) The dispersion (DI) and charge-transfer (CT) interaction energies (kcal/mol) calculated by FMO method.

(b) J809.B5

TCR	pMHC	Crystal structure		MD snapshot at 100 ns		MD snapshot at 200 ns	
		DI	CT	DI	CT	DI	CT
β 94 Phe	66 Val in MHCα	−5.81	−1.78	−3.97	−0.90	−3.32	−0.92
β 94 Phe	69 His in MHCα	-	-	-	-	−2.14	−0.99
β 95 Trp	62 Gln in MHCα	−9.56	−3.87	−11.93	−7.09	-	-
β 95 Trp	66 Val in MHCα	-	-	-	-	−2.39	−0.67
β 95 Trp	5 Lys in peptide	−3.08	−1.19	-	-	-	-
β 95 Trp	7 Lys in peptide	−7.15	−1.87	-	-	-	-
β 95 Trp	94 Arg in MHCβ	−3.31	−1.21	-	-	-	-

(c) 2W20

TCR	pMHC	Crystal structure		MD snapshot at 100 ns		MD snapshot at 200 ns	
		DI	CT	DI	CT	DI	CT
β 95 Trp	62 Gln in MHCα	−6.66	−4.16	−8.67	−6.03	-	-
β 95 Trp	7 Lys in peptide	−11.87	−3.61	-	-	−8.10	−2.29
β 95 Trp	8 Ala in peptide	-	-	−3.82	0.00	−4.24	−1.32

(d) YAe62

TCR	pMHC	Crystal structure		MD snapshot at 100 ns		MD snapshot at 200 ns	
		DI	CT	DI	CT	DI	CT
β 94 Phe	66 Val in MHCα	−6.50	−1.95	-	-	-	-
β 95 Trp	62 Gln in MHCα	−9.96	−20.42	−7.51	−2.19	−5.07	−2.73
β 95 Trp	7 Lys in peptide	−9.01	−3.15	−10.85	−3.46	−4.90	−1.19

References

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