Lecture 6

HLA Epitope Immunogenicity and Nonself-Self Paradigm

HLA **Epitope** Immunogenicity

1. Empirical approach: Determine the frequency of the antibody response to a mismatched epitope
2. Based on the Physiochemical properties of epitopes (Vas Kosmoliaptsis et al. Transplantation 88: 791, 2008, Human Immunology 72:1049, 2011)
3. Nonself-self paradigm of epitope immunogenicity (Int. J Immunogenetics, 39:1-9, 2012; Frontiers in Transplant and Alloimmunity, 2: 1-6, 2011; Human Immunology 73: 267-277, 2012)

Preliminary Results: Eplet Immunogenicity in 62 Cases

Eplet	Nr. Reactive (%)	Eplet	Nr. Reactive (%)	Eplet	Nr. Reactive (%)
116D	0/9 (0%)	253Q	4/10 (40%)	82LR	8/11 (73%)
171H	0/9 (0%)	275EL	4/10 (40%)	180E	8/11 (73%)
113HD	1/10 (10%)	113YR	6/13 (46%)	151AHV	16/22 (73%)
116Y	1/10 (10%)	113YH	8/17 (47%)	138MT	17/22 (77%)
207S	3/15 (20%)	41T	5/10 (50%)	145KHA	17/22 (77%)
113HN	3/13 (23%)	151AHE	5/10 (50%)	167ES	7/9 (78%)
113YN	2/8 (25%)	70AQA	5/9 (56%)	177DK	8/10 (80%)
184A	5/15 (33%)	167DG	8/14 (57%)	66RKV	16/19 (84%)
193AV	5/15 (33%)	76EN	6/10 (60%)	62GE	16/18 (89%)
70AQS	3/8 (38%)	76AN	5/8 (63%)	161D	9/10 (90%)
76VD	5/13 (38%)	127K	13/20 (65%)		

Duquesnoy, RJ and Claas FHJ: Progress Report of 14th International Histocompatibility Workshop Project on the Structural Basis of HLA Compatibility, *Tissue Antigens*, 69 (Suppl. 1): 1-5, 2007

Relative Immunogenicity of HLA-C Epitopes

Eplet	Equivalent	Numbers of Mismatches	Reactive Eplets	Reactive as Pairs	Total	Antibody Frequency	Eplet	Equivalent	Numbers of Mismatches	Reactive Eplets	Reactive as Pairs	Total	Antibody Frequency
79RK	TerEp#244	14	8	4	12	86%	35Q		10	2	0	2	20%
138K		10	8	0	8	80%	73AS		11	2	0	2	18%
76TVN		10	7	0	7	70%	69RA		7	0	1	1	14%
173K	TerEp#5081	11	7	0	7	64%	193PV		8	1	0	1	13%
177KT	TerEp#40	10	6	0	6	60%	77VSN		10	0	1	1	10%
14WR		6	3	0	3	50%	79VRN	TerEp#246	10	0	1	1	10%
73AN	TerEp#5037	9	4	0	4	44%	184H		11	1	0	1	9%
193PL	TerEp#37	12	5	0	5	42%	116F		12	1	0	1	8%
21H	TerEp#39	14	5	0	5	36%	267QE		12	1	0	1	8%
151ARE		6	1	1	2	33%	69RT		14	1	0	1	7%
69KRQ		7	1	1	2	29%	151ARA		14	1	0	1	7%
77TVS	TerEp#421	14	3	1	4	29%	9D		11	0	0	0	0%
156RA		11	0	3	3	27%	9Y		4	0	0	0	0%
147L		8	2	0	2	25%	12AVR		10	0	0	0	0%
156WA		8	0	2	2	25%	71AT		10	0	0	0	0%
163EW	TerEp#222	4	1	0	1	25%	90D		9	0	0	0	0%
163LW	TerEp#245	4	1	0	1	25%	103L		5	0	0	0	0%
166LE		4	1	0	1	25%	113YD		7	0	0	0	0%
219W	TerEp#5075	13	3	0	3	23%	113YN		12	0	0	0	0%
35Q		10	2	0	2	20%	Total		372	78	15	93	25%

Duquesnoy and Marrari, *Transplant Immunology* 24: 164-71, 2011

Frequencies of antibodies to donor DQB eplet mismatches

DQB Eplet	Expressed on	Nr of cases	Antibody Frequency
79ED2	DQ4	6	100%
52PQ3	DQ1	18	89%
45GE5	DQ2	24	88%
55PPP	DQ3	14	79%
70GT	DQB1*0602/3	19	68%
45EV	DQ7	16	63%
57PA	DQ2,8	24	50%
14GL5	DQ5	12	50%
77DR	DQ2,5	27	30%
45GV	DQ1,4,8,9	14	29%
74SV2	DQ4,5	11	29%
140A2	DQ2,6	15	27%
52PL3	DQ3,4	15	27%
84QL2	DQ2,3,4	13	23%
74EL2	DQ3,6	14	14%
14GM	DQ2,4,6,8	15	13%
26L	DQ2,8,9 DQB1*0602/3/4/9	18	11%
66DI	DQ2,4,6s	25	8%
70RT	DQB1*0602 *0603	15	0%
26YL3	DQB1*03 *0601/4/9	12	0%

Duquesnoy et al Transplant immunology, 18:352-360, 2008

Frequencies of antibodies to donor DQA eplet mismatches

DQA Eplet	Eplet on	Nr of cases	Antibody Frequency
160AE	DQA1*0501/5	15	80%
41GR3	DQA1*04 *05 *06	23	74%
75SL4	DQA1*05	21	67%
47EK2	DQA1*02	16	56%
50EF11	DQA1*01	21	45%
48LF	DQA1*02 *03	14	43%
56RR5	DQA1*03	10	40%
69L	DQA1*02 *03 *05	17	35%
60QF5	DQA1*02 *03 *04 *05 *06	22	32%
80IRS2	DQA1*02 *03 *04 *06	20	30%
75ILR	DQA1*02 *04 *06	17	29%
56RB	DQA1*02 *04 *05 *06	31	23%
47ERW	DQA1*0101/4/5	10	10%
34HE	DQA1*0101/4/5 *02 *03	15	7%
25YT	DQA1*01/2/4 *04 *05	24	4%
41ER	DQA1*0101/2/4/5 *02 *03	12	0%
160AD	DQA1*01 *02 *0301 *04 *06	16	0%

Duquesnoy et al Transplant Immunology, 18:352-360, 2008

Predominant Eplets Reacting with anti-HLA-DP Antibodies

Locus	Mismatched Eplet	Eplet Carrying Alleles	Antibody Frequency	Donor- Specific Antibody Frequency
DPB	84DEAV	DPB1 *01 *03 *05 *06 *09 *10 *11 *13 *14 *16 *17 *19 *20 *21 *30	18/23 (78%)	5/6 (83%)
DPB	55DE*	DPB1*0201 *03 *0402 *06 *09 *10 *14 *16 *17 *18 *20	15/19 (79%)	5/6 (83%)
DPB	84DEAV and/or 55DE		27/34 (79%)	11/11 (100%)
DPA	51RA,83A	DPA1 *02 *04	18/56 (32%)	nd
DPA	51QA,83T	DPA1 *01 *03	5/56/ (9%)	nd
DPA	Other Eplets		0/33 (0%)	nd

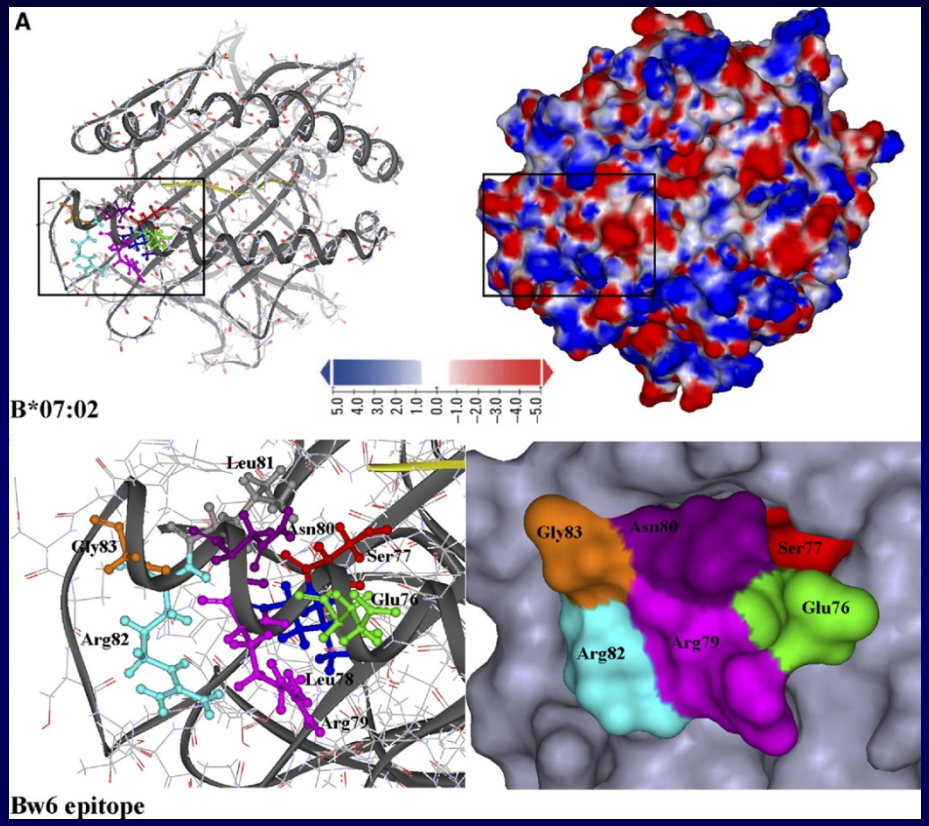
* 55DE is similar to the 57DE eplet on DR11
All 55DE-reactive sera reacted also with DR11

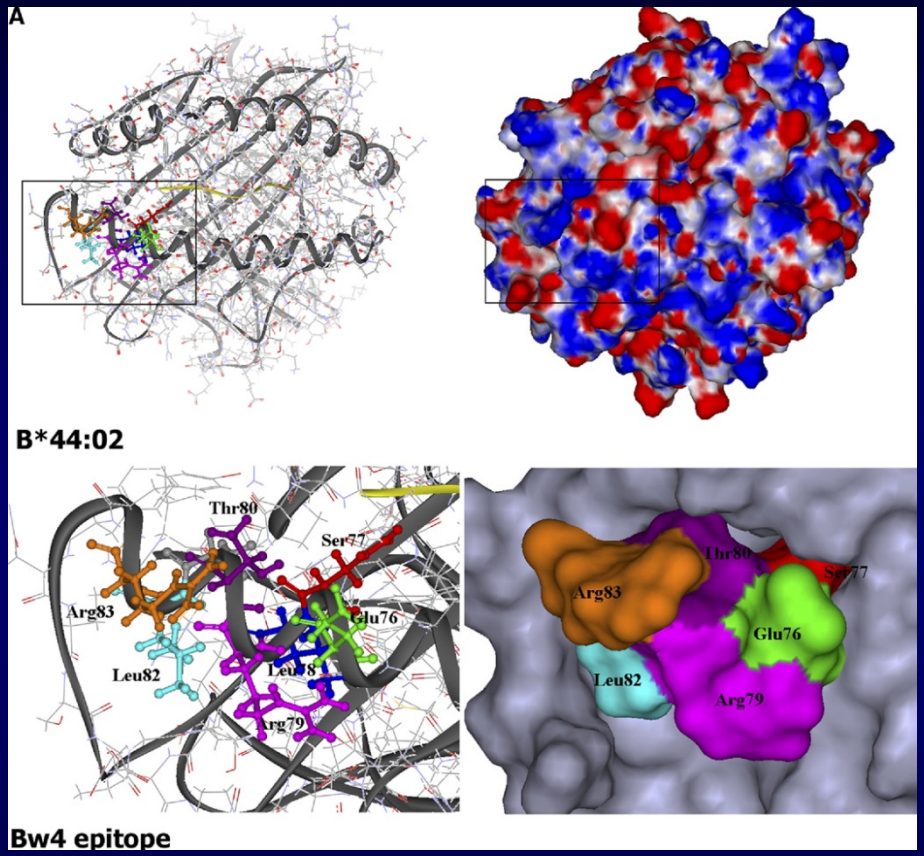
Duquesnoy et al Transplant Immunology, 18:352-360, 2008

HLA Epitope Immunogenicity

- A patient produces an antibody to a mismatched epitope on the immunizing antigen
- *What are the conditions for HLA epitope-specific antibody production?*
  - HLA phenotype of antibody producer?
  - Physiochemical properties of epitopes (Vas Kosmoliaptsis et al. Transplantation 88: 791, 2008, Hum Immunol. 72:1049, 2011)
  - Nonself-self paradigm of epitope immunogenicity (Int. J Immunogenetics, 39:1-9, 2012; Frontiers in Transplant and Alloimmunity, 2: 1-6, 2011; Human Immunol. 73: 267-277, 2012)

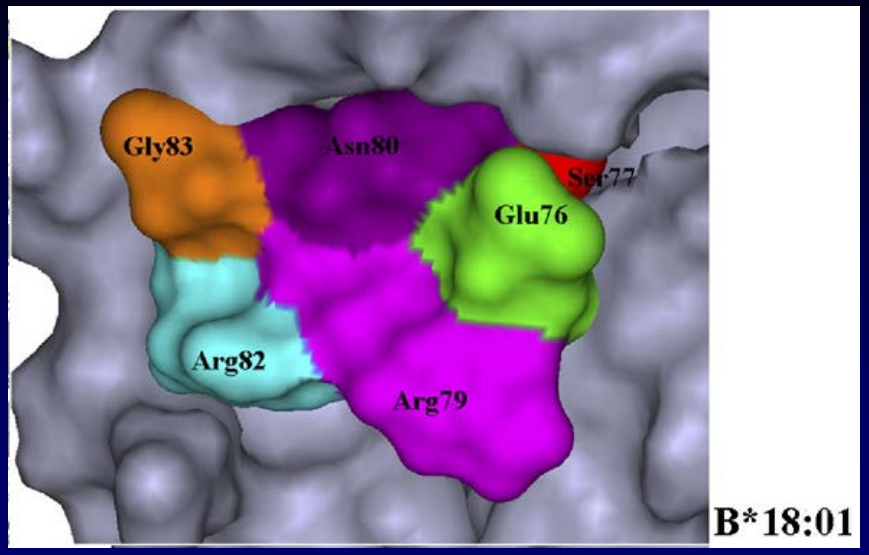
Physiochemical properties of epitopes (Vas Kosmoliaptsis et al. Transplantation 88: 791, 2008, Human Immunology. 72:1049, 2011)

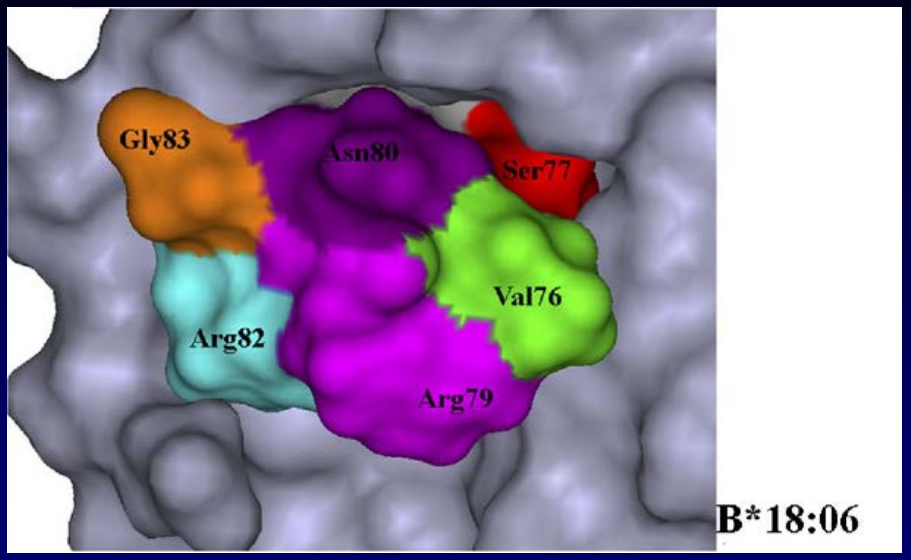




Homology modeling was used to determine the atomic coordinates of common HLA-A, -B, and –C molecules the MODELLER computer algorithm

HLA electrostatic surface topography was determined with the DelPhi program within Discovery Studio 2.1





Electrostatic potential of solvent-accessible residues in kT/e

B*18:01	Bw6 pos	76E	79R	80N	82R	83G
		-75.09	+65.86	+1.51	+42.65	-10.05
B*18:06	Bw6 neg	76V	79R	80N	82R	83G
		-11.71	+79.53	**+26.38**	+52.94	-2.53

Kosmoliaptsis et al. Human Immunology. 72:1049, 2011

The capacity of an HLA antigen to induce an alloantibody response depends not only on the number of mismatched amino acid polymorphisms but also on the physiochemical disparities (hydrophobicity and electrostatic charge) between mismatched amino acids

- Kosmoliaptsis V, Chaudhry AN. Predicting HLA class I alloantigen immunogenicity from the number and physiochemical properties of amino acid polymorphisms. *Transplantation* 2009;88:791-798.
- Kosmoliaptsis V, Sharples LD, Chaudhry AN, Halsall DJ, Bradley JA, Taylor CJ. Predicting HLA class II alloantigen immunogenicity from the number and physiochemical properties of amino acid polymorphisms. *Transplantation*. 2011;91:183-90

HLA Epitope Immunogenicity

- A patient produces an antibody to a mismatched epitope on the immunizing antigen
- *What are the conditions for HLA epitope-specific antibody production?*
  - **HLA phenotype of antibody producer?**
  - **Physiochemical properties of epitopes** (Vas Kosmoliaptsis et al. Transplantation 88: 791, 2008, Hum Immunol. 72:1049, 2011)
  - **Nonself-self paradigm of epitope immunogenicity** (Int. J Immunogenetics, 39:1-9, 2011; Frontiers in Transplant and Alloimmunity, 2: 1-6, 2011; Human Immunol. 73: 267-277, 2012)

HLA Mismatch Permissibility?

Observation: Antibody-verified epitopes defined by pairs have a nonself eplet together with a self configuration

Nonself-self paradigm analysis for eplet pairs*

Case	Monoclonal	Isotype	HLA type -Antibody producer	Immunizer	Eplet specificity	Distance	Reactive Antigens	Self eplet on
1	HDG4B1	IgG	A2, 24; B7, 60; Cw7, w10	A32	65RNA+s82LR	11 Å	A25/A32/B17/B63	A24
2	WK1D12	IgG	A1,-; B8,-; Cw7,-	B27	163EW+s73TE	16 Å	B7/B13/B27/B40/B47/ B48/B81	B8
3	HDG11G12	IgG	A2, 24; B7, 60; Cw7, w10	B35	163LW+s62RQI	8 Å	B15/B35/B49/B50/B51/ B52/B53/B56/B78	B7, B60
4	MUL4C8	IgG	A2, 25; B18, 51; Cw12, 15	A11	144KR+s151H	7 Å	A1/A3/A11/A24/A36	A2, A25
5	MUL9F4	IgM	A2, 25; B18, 51; Cw12, 15	B55	65QIA+s76ES	7 Å	B7/B*2708/B42/B54/ B55/B56/B67/B81/B82	A25, B18
6	OK4F10	IgM	A2, 28; B7, 27; Cw2, w7	A3	142MI+s79GT	13 Å	A1/A3/A11/A26/A29/A30/A31/ A33/A34/A36/A43/A66/A74/A80	A2, A28

Two mismatched eplets 65RNA and 65QIA are located in the α1 domain and four mismatched eplets 142MI, 144KR, 163EW and 163LW are on the α2-domain. Three immunizing epitopes reside on HLA-A and the other three are on HLA-B.

* Reported in Marrari M, Mostecki J, Mulder A, Claas F, Balazs and Duquesnoy RJ, Transplantation 90:1468-72, 2010

Observation: Antibody-verified epitopes defined by pairs have a nonself eplet together with a self configuration

Question: How does the alloantibody response to a mismatched eplet have an autoimmune component?

Publication: The antibody response to an HLA mismatch: a model for nonself-self discrimination in relation to HLA epitope immunogenicity, International Journal of Immunogenetics, 39:1-9, 2011

Nonself-Self Paradigm of HLA Epitope Immunogenicity

- Theorem: the immune repertoire has B-cells with low-avidity Ig receptors for self HLA-A, HLA-B and HLA-C epitopes
- These receptors can interact through their CDRs with different portions of the HLA molecular surface but the binding strength is so weak that B-cell activation and antibody production cannot occur
- In contrast, exposure to mismatched eplets induces often strong alloantibody responses

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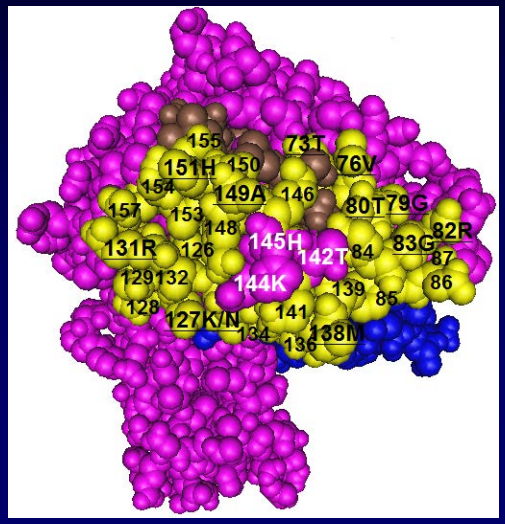
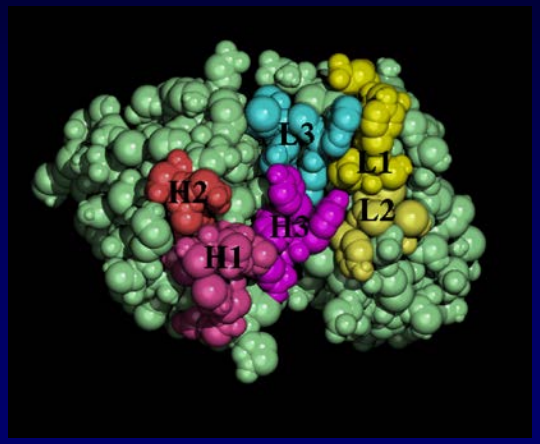
- In contrast, exposure to mismatched eplets induces often strong alloantibody responses
- ***Hypothesis: B-cell activation by a nonself eplet can only occur if the remainder of the corresponding structural HLA epitope consists primarily of self residues shared with the antibody producer***

Residues within 15 Ångstroms of 144TKH

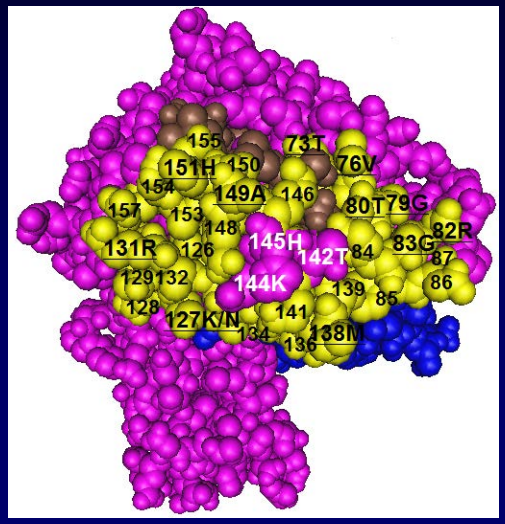


HLA-A*02:01

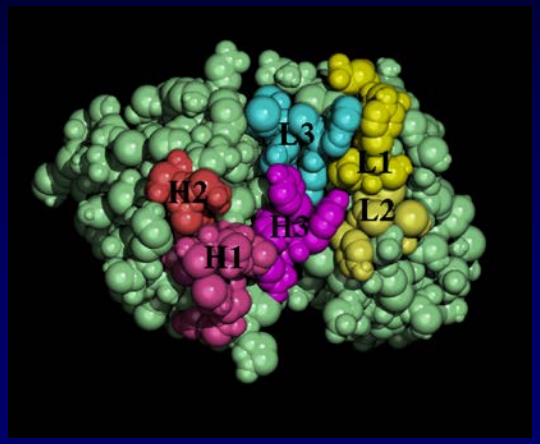


Six CDRs of antibody

Residues within 15 Ångstroms of 144TKH



HLA-A*02:01

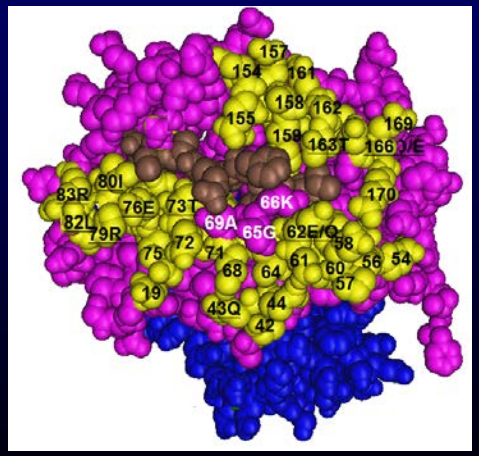


Six CDRs of antibody

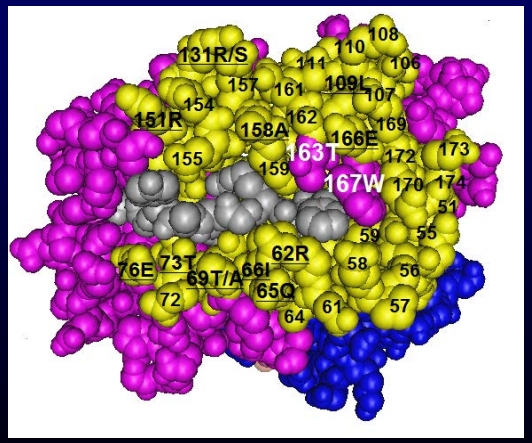
Case 4		Eplet		Number of	Polymorphic Surface Residues within 15 A										
144KR+s151H	142	144	145	Differences	73	76	79	80	82	83	127	131	138	149	151
A*11:01 *Immunizer*	I	K	R		T	V	G	T	R	G	N	R	M	A	H
Antibody producer															
A*02:01	**T**	**K**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-	-
A*25:01	I	Q	R	6	-	E	R	I	L	R	-	-	-	T	-
B*18:01	I	Q	R	6	-	E	R	N	-	-	-	S	T	-	R
B*51:01	I	Q	R	8	-	E	R	I	L	R	-	S	T	-	R
C*12:03	I	Q	R	5	A	-	R	N	-	-	-	-	T	-	R
C*15:02	I	Q	R	4	-	-	R	K	-	-	-	-	T	-	R

Case 1	Eplet			Number of	Polymorphic Surface Residues											
65RNA+s82LR	65	66	69	Differences	43	62	73	76	79	80	82	83	152	163	166	
A*32:01 *Immunizer*	R	N	A		Q	Q	T	E	R	I	L	R	V	T	E	
Antibody producer																
A*02:01	R	K	A	6	-	G	-	V	G	T	R	G	-	-	-	
A*24:02	**G**	**K**	**A**	**2**	-	**E**	-	-	-	-	-	-	-	-	**D**	
B*07:02	Q	I	A	7	P	R	-	-	-	N	R	G	E	E	-	
B*40:01	Q	I	T	6	P	R	-	-	-	N	R	G	-	E	-	
C*07:02	Q	K	R	7	P	R	A	V	-	N	R	G	-	-	-	
C*03:04	Q	K	R	8	P	R	T	V	-	N	R	G	E	L	-	
Case 2																
163EW+s73TE	163	167			62	65	66	69	71	73	76	109	131	151	158	166
B*27:05 *Immunizer*	E	W			R	Q	I	A	T	T	E	L	S	R	A	E
Antibody producer																
A*01:01	R	G		10	Q	R	N	-	S	-	A	F	R	H	V	D
B*08:01	**T**	**W**		**2**	-	-	-	**T**	-	-	-	-	**R**	-	-	-
C*07:01	T	W		6	-	-	N	R	A	A	V	-	R	-	-	-

Case 1

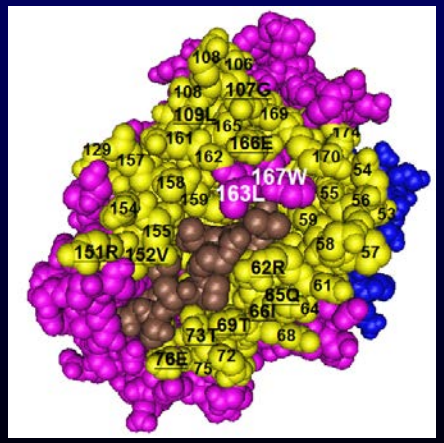


Case 2

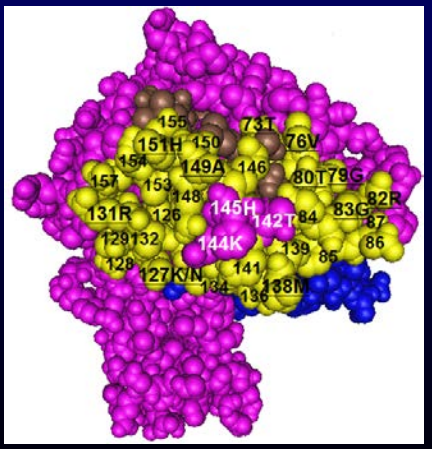


Case 3																
163LW+s65RQI	163	167			62	65	66	69	71	73	76	107	109	151	152	166
B*35:01 *Immunizer*	L	W			R	Q	I	T	T	T	E	G	L	R	V	E
Antibody producer																
A*02:01	T	W		9	G	R	K	A	S	-	V	W	F	H	-	-
A*24:02	T	G		8	E	G	K	A	S	-	-	-	F	H	-	D
B*07:02	E	W		3	-	-	-	A	A	-	-	-	-	-	E	-
B*40:01	**E**	**W**		**0**	-	-	-	-	-	-	-	-	-	-	-	-
C*07:02	T	W		6	-	-	K	R	A	A	V	-	-	-	A	-
Case 4																
144KR+s151H	142	144	145		73	76	79	80	82	83	127	131	138	149	151	
A*11:01 *Immunizer*	I	K	R		T	V	G	T	R	G	N	R	M	A	H	
Antibody producer																
A*02:01	**T**	**K**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-	-	
A*25:01	I	Q	R	6	-	E	R	I	L	R	-	-	-	T	-	
B*18:01	I	Q	R	6	-	E	R	N	-	-	-	S	T	-	R	
B*51:01	I	Q	R	8	-	E	R	I	L	R	-	S	T	-	R	
C*12:03	I	Q	R	5	A	-	R	N	-	-	-	-	T	-	R	
C*15:02	I	Q	R	4	-	-	R	K	-	-	-	-	T	-	R	

Case 3

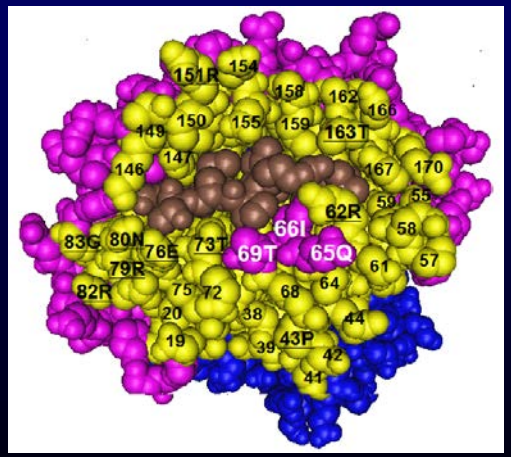


Case 4

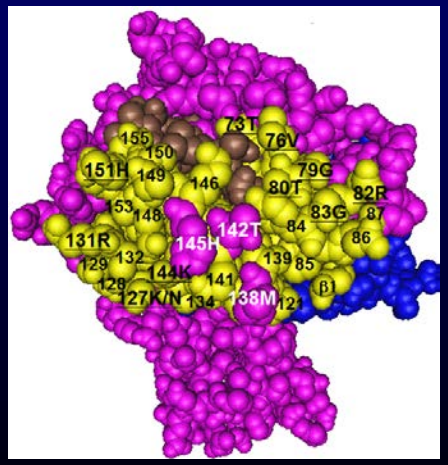


Case 5															
65QIA+s76ES	65	66	69		43	62	73	76	79	80	82	83	151	163
B*55:01 *Immunizer*	Q	I	A		P	R	T	E	R	N	R	G	R	T
Antibody producer														
A*02:01	R	K	A	6	Q	G	-	V	G	T	-	-	H	-
A*25:01	R	N	A	6	Q	-	-	-	-	I	L	R	H	R
B*18:01	**Q**	**I**	**T**	**0**	-	-	-	-	-	-	-	-	-	-
B*51:01	Q	I	T	4	-	-	-	-	-	I	L	R	-	L
C*12:03	Q	K	R	2	-	-	A	V	-	-	-	-	-	-
C*15:02	Q	N	R	2	-	-	-	V	-	K	-	-	-	-
Case 6														
142MI+s79GT	138	142	145		73	76	79	80	82	83	127	131	144	151
A*03:01 *Immunizer*	M	I	R		T	V	G	T	R	G	N	R	K	H
Antibody producer														
A*02:01	**M**	**T**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-
A*68:01	**M**	**T**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-
B*07:02	T	I	R	5	-	E	R	N	-	-	-	-	Q	R
B*27:05	T	I	R	7	-	E	R	-	L	R	-	S	Q	R
C*02:02	T	I	R	4	-	-	R	K	-	-	-	-	Q	R
C*07:02	T	I	R	5	A	-	R	N	-	-	-	-	Q	R

Case 5

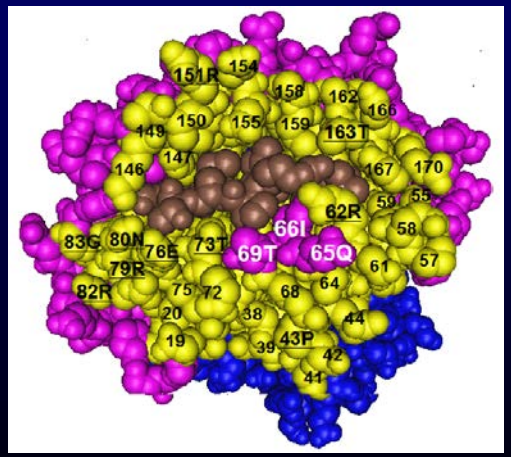


Case 6

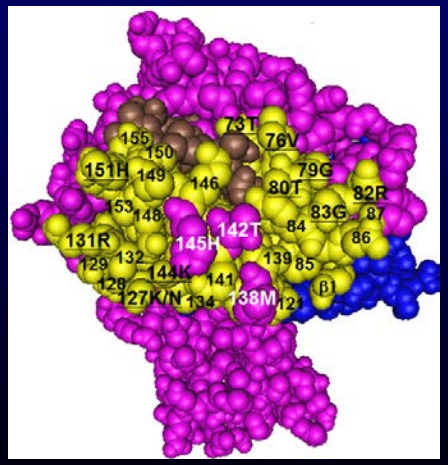


Case 5															
65QIA+s76ES	65	66	69		43	62	73	76	79	80	82	83	151	163
B*55:01 *Immunizer*	Q	I	A		P	R	T	E	R	N	R	G	R	T
Antibody producer														
A*02:01	R	K	A	6	Q	G	-	V	G	T	-	-	H	-
A*25:01	R	N	A	6	Q	-	-	-	-	I	L	R	H	R
B*18:01	**Q**	**I**	**T**	**0**	-	-	-	-	-	-	-	-	-	-
B*51:01	Q	I	T	4	-	-	-	-	-	I	L	R	-	L
C*12:03	Q	K	R	2	-	-	A	V	-	-	-	-	-	-
C*15:02	Q	N	R	2	-	-	-	V	-	K	-	-	-	-
Case 6														
142MI+s79GT	138	142	145		73	76	79	80	82	83	127	131	144	151
A*03:01 *Immunizer*	M	I	R		T	V	G	T	R	G	N	R	K	H
Antibody producer														
A*02:01	**M**	**T**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-
A*68:01	**M**	**T**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-
B*07:02	T	I	R	5	-	E	R	N	-	-	-	-	Q	R
B*27:05	T	I	R	7	-	E	R	-	L	R	-	S	Q	R
C*02:02	T	I	R	4	-	-	R	K	-	-	-	-	Q	R
C*07:02	T	I	R	5	A	-	R	N	-	-	-	-	Q	R

Case 5



Case 6



	Eplet						Polymorphic surface residues within 15 Å of eplet														Number of
Case 10	69AA	69	71				41	43	46	59	62	65	66	73	76	79	80	82	83	149	158	Differences
Imm	B*55:01	A	A				A	P	E	Y	R	Q	I	T	E	R	N	R	G	A	A	
Antibody Producer																						
	A*02:01	A	S				-	Q	-	-	G	R	K	-	V	G	T	-	-	-	-	7
	A*25:01	A	S				-	Q	-	-	-	R	N	-	-	-	I	L	R	T	-	7
	B*18:01	T	T				-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	B*51:01	T	T				-	-	-	-	-	-	-	-	-	-	I	L	R	-	-	3
	C*12:02	R	A				-	-	-	-	-	-	K	A	V	-	-	-	-	-	-	3
Case 11	69AA	69	71				41	43	46	59	62	65	66	73	76	79	80	82	83	149	158	
Imm	B*07:02	A	A				A	P	E	Y	R	Q	I	T	E	R	N	R	G	A	A	
Antibody Producer																						
	A*25:01	A	S				-	Q	-	-	-	R	N	-	-	-	I	L	R	T	-	7
	A*29:02	A	S				-	Q	-	-	L	R	N	-	A	G	T	-	-	-	-	7
	B*15:01	T	T				-	-	A	-	-	-	-	-	-	-	-	-	-	-	-	1
	B*44:02	T	T				T	-	-	-	-	-	-	-	-	-	T	L	R	-	-	4
	C*05:01	R	A				-	-	-	-	-	-	K	-	V	-	K	-	-	-	-	3
Case 12	80ERILR	76	79	80	82	83	43	65	66	69	71	73	90	138	144	145	149	150				
Imm	B*49:01	E	R	I	L	R	P	Q	I	T	T	T	A	T	Q	R	A	A				
Antibody producer																						
	A*01:01	A	G	T	R	G	Q	R	N	A	S	-	D	M	K	-	-	V				9
	A*26:01	A	G	T	R	G	Q	R	N	A	S	-	D	M	-	-	T	-				8
	B*08:01	E	R	N	R	G	-	-	-	-	-	-	-	-	-	-	-	-				0
	B*27:05	E	R	T	L	R	-	-	-	A	A	-	-	-	-	-	-	-				2
	C*01:02	V	R	N	R	G	-	-	K	R	A	-	-	-	-	-	-	-				3
	C*07:02	V	R	N	R	G	-	-	K	R	A	A	D	-	-	-	-	-				5

Duquesnoy RJ, Marrari M, Mulder A, Claas FJH, Mostecki J and Balazs I: Structural Aspects of HLA Class I Epitopes Detected by Human Monoclonal Antibodies, Human Immunology, In Press, 2011

HLA Epitope Immunogenicity (Summary)

- In each case, the HLA type of the antibody producer has one allele with an exceedingly high surface residue similarity within the structural HLA epitope of the immunizing allele with the mismatched eplet

Mouse Monoclonal Antibodies Specific for HLA Class I Epitopes

- Mostly produced by BALB/c mice that type for H-2 class I genes: Dd, Kd and Ld

- Although H-2 and HLA class I molecules have similar structures, they have considerably more interspecies-related amino acid sequence dissimilarities than MHC class I gene and allele differences within each species

Mouse and Human Class I MHC Protein Sequence Differences

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
H2-Dd	G	S	H	S	L	R	Y	F	V	T	A	V	S	R	P	G	F	G	E	P	R	Y	M	E	V	G	Y	V	D	N	T	E	F	V	R	F	D	S	D	A
H2-Kd	-	P	-	-	L	-	-	-	V	-	-	-	-	-	-	-	L	L	-	-	-	F	I	A	-	-	-	-	-	D	T	Q	-	-	-	-	-	-	-	-
H2-Ld	-	P	-	-	M	-	-	-	E	-	-	-	-	-	-	-	L	G	-	-	-	Y	I	S	-	-	-	-	-	N	K	E	-	-	-	-	-	-	-	-
A*02:01	-	S	-	-	M	-	-	-	F	-	S	-	-	-	-	-	R	G	-	-	-	F	I	A	-	-	-	-	-	D	T	Q	-	-	-	-	-	-	-	-
B*07:02	-	S	-	-	M	-	-	-	Y	-	S	-	-	-	-	-	R	G	-	-	-	F	I	S	-	-	-	-	-	D	T	Q	-	-	-	-	-	-	-	-
C*01:02	C	S	-	-	M	K	-	-	F	-	S	-	-	-	-	-	R	G	-	-	-	F	I	S	-	-	-	-	-	D	T	Q	-	-	-	-	-	-	-	-

	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
H2-Dd	E	N	P	R	Y	E	P	R	A	R	W	I	E	Q	E	G	P	E	Y	W	E	R	E	T	R	R	A	K	G	N	E	Q	S	F	R	V	D	L	R	T
H2-Kd	D	-	-	-	F	-	-	R	-	-	-	M	-	-	-	-	-	-	-	-	-	E	Q	-	Q	R	-	-	S	D	-	-	W	-	-	-	S	-	-	-
H2-Ld	E	-	-	-	Y	-	-	Q	-	-	-	M	-	-	-	-	-	-	-	-	-	R	I	-	Q	I	-	-	G	Q	-	-	W	-	-	-	N	-	-	-
A*02:01	A	S	Q	-	M	-	-	R	-	-	-	I	-	-	-	-	-	-	-	-	D	G	E	-	R	K	V	-	A	H	S	-	T	H	-	-	D	-	G	-
B*07:02	A	S	-	-	E	-	-	R	-	-	-	I	-	-	-	-	-	-	-	-	D	R	N	-	Q	I	Y	-	A	Q	A	-	T	D	-	E	S	-	-	N
C*01:02	A	S	-	-	G	-	-	R	-	P	-	V	-	-	-	-	-	-	-	-	D	R	E	-	Q	K	Y	-	R	Q	A	-	T	D	-	-	S	-	-	N

	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
H2-Dd	A	L	R	Y	Y	N	Q	S	A	G	G	S	H	T	L	Q	W	M	A	G	C	D	V	E	S	D	G	R	L	L	R	G	Y	W	Q	F	A	Y	D	G
H2-Kd	A	Q	R	-	-	-	-	-	K	-	-	S	-	-	F	-	R	-	F	-	-	-	-	-	-	-	W	-	-	-	-	-	-	Q	-	-	-	-	-	-
H2-Ld	L	L	G	-	-	-	-	-	A	-	-	T	-	-	L	-	W	-	Y	-	-	-	-	-	-	-	G	-	-	-	-	-	-	E	-	-	-	-	-	-
A*02:01	L	R	G	-	-	-	-	-	E	A	-	S	-	-	V	-	R	-	Y	-	-	-	-	-	-	-	W	-	F	-	-	-	-	H	-	Y	-	-	-	-
B*07:02	L	R	G	-	-	-	-	-	E	D	-	S	-	-	I	-	I	-	Y	-	-	-	-	-	P	-	G	-	F	-	-	-	-	R	-	D	-	-	-	-
C*01:02	L	R	G	-	-	-	-	-	E	A	-	S	-	-	L	-	W	-	C	-	-	-	L	G	P	-	G	-	-	-	-	-	-	D	-	Y	-	-	-	-

	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160
H2-Dd	C	D	Y	I	A	L	N	E	D	L	K	T	W	T	A	A	D	M	A	A	Q	I	T	R	R	K	W	E	Q	A	G	A	A	E	R	D	R	A	Y	L
H2-Kd	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	T	-	-	L	-	-	-	-	-	-	-	-	-	-	D	-	-	Y	Y	-	-	-	-
H2-Ld	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	-	-	Q	-	-	-	-	-	-	-	-	-	-	A	-	-	Y	Y	-	-	-	-
A*02:01	K	-	-	-	-	-	K	-	-	-	R	S	-	-	-	-	-	M	-	-	Q	-	-	K	H	-	-	-	A	-	H	V	-	-	Q	L	-	-	-	-
B*07:02	K	-	-	-	-	-	-	-	-	-	R	S	-	-	-	-	-	T	-	-	Q	-	-	Q	-	-	-	-	A	-	R	E	-	-	Q	R	-	-	-	-
C*01:02	K	-	-	-	-	-	-	-	-	-	R	S	-	-	-	-	-	T	-	-	Q	-	-	Q	-	-	-	-	A	-	R	E	-	-	Q	R	-	-	-	-

	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200
H2-Dd	E	G	E	C	V	E	W	L	R	R	Y	L	K	N	G	N	A	T	L	L	R	T	D	P	P	K	A	H	V	T	H	H	R	R	P	E	G	D	V	T
H2-Kd	-	-	-	-	-	-	-	-	R	-	-	-	E	L	-	N	E	-	-	-	-	-	-	S	-	-	-	-	-	-	Y	-	P	-	S	Q	V	D	-	-
H2-Ld	-	-	-	-	-	-	-	-	H	-	-	-	K	N	-	N	A	-	-	-	-	-	-	S	-	-	-	-	-	-	H	-	P	-	S	K	G	E	-	-
A*02:01	-	-	T	-	-	-	-	-	R	-	-	-	E	N	-	K	E	-	-	Q	-	-	-	A	-	-	T	-	M	-	H	-	A	V	S	D	H	E	A	-
B*07:02	-	-	-	-	-	-	-	-	R	-	-	-	E	N	-	K	D	K	-	E	-	A	-	P	-	-	T	-	-	-	H	-	P	I	S	D	H	E	A	-
C*01:02	-	-	T	-	-	-	-	-	R	-	-	-	E	N	-	K	E	-	-	Q	-	A	E	H	-	-	T	-	-	-	H	-	P	V	S	D	H	E	A	-

Mouse Monoclonal Antibodies Specific for HLA Class I Epitopes

- Mostly produced by BALB/c mice that type for H-2 class I genes: Dd, Kd and Ld

- Although H-2 and HLA class I molecules have similar structures, they have considerably more interspecies-related amino acid sequence dissimilarities than MHC class I gene and allele differences within each species

- ***Does the nonself-self paradigm work for HLA epitope specific mouse monoclonals which are xenogeneic?***

Mouse Monoclonal Antibody MB40.2

(Parham: Immunogenetics 1981;13:509-527)

		Eplet			Residues within 15 Angstroms of Sequence Position 180																		
Allele	React	**176**	**180**	**182**	**1**	**2**	**3**	**47**	**50**	**51**	**52**	**53**	**54**	**55**	**59**	**60**	**103**	**105**	**106**	**107**	**108**	**165**	**166**	**167**	**168**
B*40:01 IMM	Pos	K	E	A	G	S	H	P	R	W	I	E	Q	E	Y	W	V	P	D	G	R	V	E	W	L
B*0702	Pos	K	E	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*0703	Pos	K	E	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*41:01	Pos	K	E	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*42:01	Pos	K	E	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*40:02	Neg	K	Q	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Substitutions* with																								
Negative Effect	**K/Q**	**E/Q**	**A/P**							**W/R**														
No Effect				G/C	S/P			P/R			I/M	E/G	Q/R	E/K		W/M						V/M	E/Q	W/S

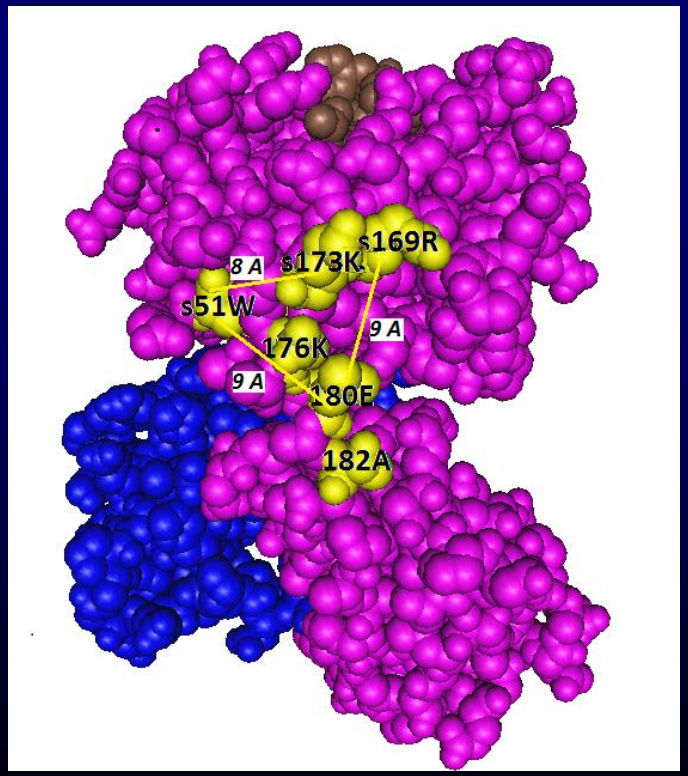
	Residues within 15 Angstroms of Sequence Position 180																				
Allele	**169**	**170**	**171**	**172**	**173**	**174**	**175**	**177**	**178**	**179**	**181**	**183**	**184**	**185**	**208**	**209**	**210**	**211**	**263**	**264**	**265**
B*40:01 IMM	R	R	Y	L	K	N	G	D	K	D	R	R	V	E	W	L	R	R	Y	L	K
B*0702	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*0703	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*41:01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*42:01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*40:02	-	-	-	-	-	-	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-

Substitutions with																					
Negative Effect	**R/L**				**K/E**																
No Effect		R/A	Y/H					D/E	K/T		R/G	D/E									

* Data from: Parham :Journal of Immunology 1984;132:2975-83; Ways et al.: Immunogenetics 1987;25:323-8; Parham et al.: Human Immunology 1986;15:44-67; McCutcheon and Lutz: Human Immunology 1992;35:125-31. McCutcheon et al.: Human Immunology 1993;36: 69-75; Barbosa at al.: Journal of Experimental Medicine 1987; 166:1329-50

MB40.2 Epitope Description

		Eplet			Critical Contact Sites		
Allele	**React**	**176**	**180**	**182**	**51**	**169**	**173**
B*40:01 IMM	Pos	K	E	A	W	R	K
B*0702	Pos	K	E	A	W	R	K
B*0703	Pos	K	E	A	W	R	K
B*41:01	Pos	K	E	A	W	R	K
B*42:01	Pos	K	E	A	W	R	K



Nonself-Self Paradigm of MB40.2 Eplet Immunogenicity

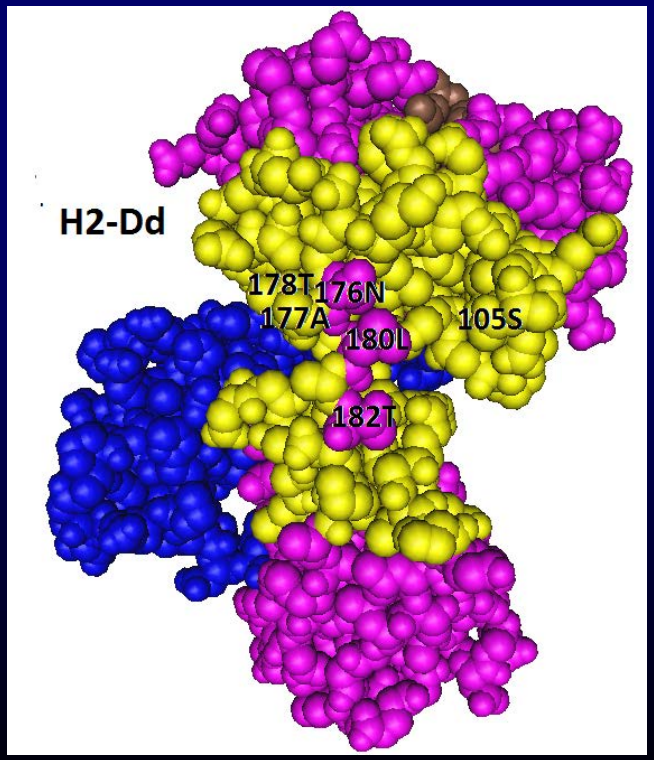
	Eplet			Residues within 15 Angstroms of Sequence Position 180																				
	176	180	182	1	2	3	47	50	51	52	53	54	55	59	60	103	105	106	107	108	165	166	167	168
B*40:01 IMM	K	E	A	G	S	H	P	R	W	I	E	Q	E	Y	W	V	P	D	G	R	V	E	W	L
H2-Dd	N	L	T	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-
H2-Kd	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	W	-	-	-	-	-
H2-Ld	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	-	-	-	-	-	-

Number of Residue Differences		Residues within 15 Angstroms of Sequence Position 180																				
		169	170	171	172	173	174	175	177	178	179	181	183	184	185	208	209	210	211	263	264	265
	B*40:01 IMM	R	R	Y	L	K	N	G	D	K	D	G	R	V	E	W	L	R	R	Y	L	K
3/42	H2-Dd	-	-	-	-	-	-	-	A	T	-	-	-	-	-	-	-	-	-	-	-	-
8/42	H2-Kd	-	-	-	-	-	L	-	E	-	-	R	-	S	-	-	-	-	-	-	-	-
6/42	H2-Ld	H	-	-	-	-	-	-	-	-	-	R	-	S	-	-	-	-	-	-	-	-

Nonself-Self Paradigm of MB40.2 Eplet Immunogenicity

	Eplet			Residues within 15 Angstroms of Sequence Position 180																			
	176	180	182	1	2	3	47	50	51	52	53	54	55	59	60	103	105	106	107	108	165	166	167	168
B*40:01 IMM	K	E	A	G	S	H	P	R	W	I	E	Q	E	Y	W	V	P	D	G	R	V	E	W	L
H2-Dd	N	L	T	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-
H2-Kd	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	W	-	-	-	-	-
H2-Ld	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	-	-	-	-	-	-

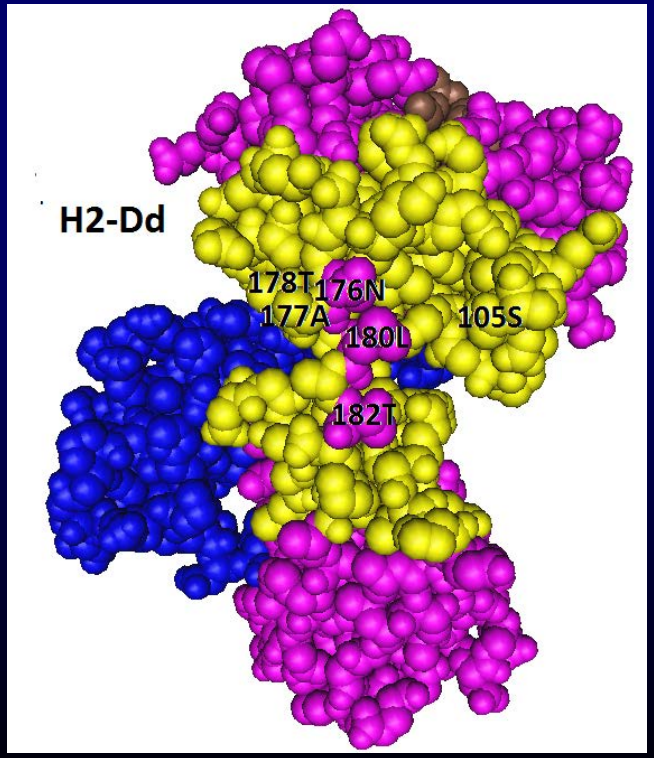
Number of Residue Differences		Residues within 15 Angstroms of Sequence Position 180																				
		169	170	171	172	173	174	175	177	178	179	181	183	184	185	208	209	210	211	263	264	265
	B*40:01 IMM	R	R	Y	L	K	N	G	D	K	D	G	R	V	E	W	L	R	R	Y	L	K
3/42	H2-Dd	-	-	-	-	-	-	-	A	T	-	-	-	-	-	-	-	-	-	-	-	-
8/42	H2-Kd	-	-	-	-	-	L	-	E	-	-	R	-	S	-	-	-	-	-	-	-	-
6/42	H2-Ld	H	-	-	-	-	-	-	-	-	-	R	-	S	-	-	-	-	-	-	-	-



Nonself-Self Paradigm of MB40.2 Eplet Immunogenicity

	Eplet			Residues within 15 Angstroms of Sequence Position 180																			
	176	180	182	1	2	3	47	50	51	52	53	54	55	59	60	103	105	106	107	108	165	166	167	168
B*40:01 IMM	K	E	A	G	S	H	P	R	W	I	E	Q	E	Y	W	V	P	D	G	R	V	E	W	L
H2-Dd	N	L	T	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-
H2-Kd	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	W	-	-	-	-	-
H2-Ld	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	-	-	-	-	-	-

Number of Residue Differences		Residues within 15 Angstroms of Sequence Position 180																					
		169	170	171	172	173	174	175	177	178	179	181	183	184	185	208	209	210	211	263	264	265
	B*40:01 IMM	R	R	Y	L	K	N	G	D	K	D	G	R	V	E	W	L	R	R	Y	L	K
3/42	H2-Dd	-	-	-	-	-	-	-	A	T	-	-	-	-	-	-	-	-	-	-	-	-
8/42	H2-Kd	-	-	-	-	-	L	-	E	-	-	R	-	S	-	-	-	-	-	-	-	-
6/42	H2-Ld	H	-	-	-	-	-	-	-	-	-	R	-	S	-	-	-	-	-	-	-	-

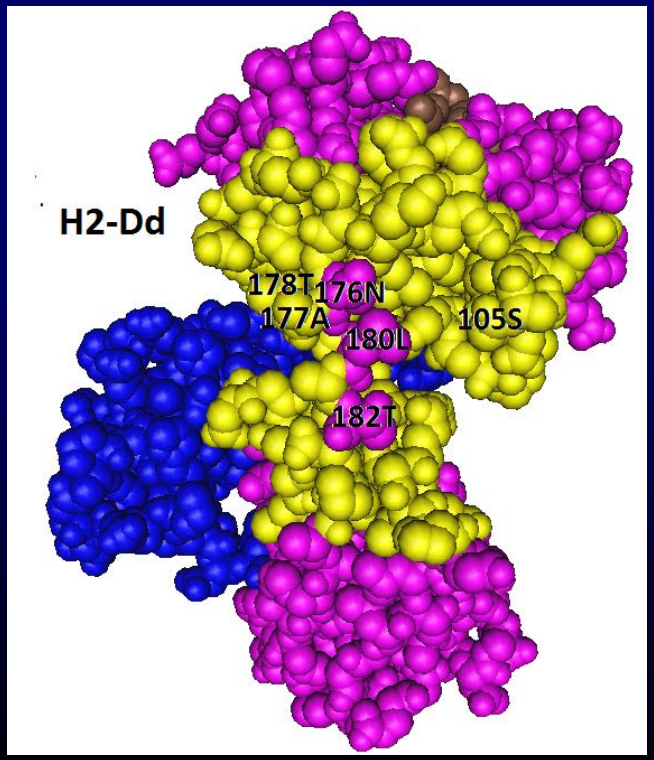


	Updated Eplet Description					Number of Remaining Residue Differences within 15 Angstroms
	176	177	178	180	182	
B*40:01 IMM	K	D	K	E	A	
H2-Dd	N	A	T	L	T	1/42
H2-Kd	N	E	K	L	T	8/42
H2-Ld	N	D	K	L	T	6/42
Substitutions with						
Negative Effect	K/Q			E/Q	A/P	
No Effect		D/E	K/T			

Nonself-Self Paradigm of MB40.2 Eplet Immunogenicity

	Eplet			Residues within 15 Angstroms of Sequence Position 180																			
	176	180	182	1	2	3	47	50	51	52	53	54	55	59	60	103	105	106	107	108	165	166	167	168
B*40:01 IMM	K	E	A	G	S	H	P	R	W	I	E	Q	E	Y	W	V	P	D	G	R	V	E	W	L
H2-Dd	N	L	T	-	-	-	-	-	-	-	-	-	-	-	-	-	S	-	-	-	-	-	-	-
H2-Kd	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	W	-	-	-	-	-
H2-Ld	N	L	T	-	P	-	-	-	-	M	-	-	-	-	-	-	S	-	-	-	-	-	-	-

Number of Residue Differences		Residues within 15 Angstroms of Sequence Position 180																					
		169	170	171	172	173	174	175	177	178	179	181	183	184	185	208	209	210	211	263	264	265
	B*40:01 IMM	R	R	Y	L	K	N	G	D	K	D	G	R	V	E	W	L	R	R	Y	L	K
3/42	H2-Dd	-	-	-	-	-	-	-	A	T	-	-	-	-	-	-	-	-	-	-	-	-
8/42	H2-Kd	-	-	-	-	-	L	-	E	-	-	R	-	S	-	-	-	-	-	-	-	-
6/42	H2-Ld	H	-	-	-	-	-	-	-	-	-	R	-	S	-	-	-	-	-	-	-	-



	Updated Eplet Description					Number of Remaining Residue Differences within 15 Angstroms
	176	177	178	180	182	
B*40:01 IMM	K	D	K	E	A	
H2-Dd	N	A	T	L	T	1/42
H2-Kd	N	E	K	L	T	8/42
H2-Ld	N	D	K	L	T	6/42
Substitutions with						
Negative Effect	K/Q			E/Q	A/P	
No Effect		D/E	K/T			

Conclusion MB40.2 antibodies originated from B-cells with BCR specific for a self-epitope on H2-Dd

HLA Epitope Immunogenicity (Summary)

- In each case, the HLA type of the antibody producer has one allele with an exceedingly high surface residue similarity within the structural HLA epitope of the immunizing allele with the mismatched eplet
- Similar observations with HLA (xeno)antibodies produced by Balb/C mice
- These findings support the concept that *antibody responses to mismatched eplets originate in B-cells with self-MHC epitope Immunoglobulin receptors*

Nonself-Self Paradigm of HLA Epitope Immunogenicity

- Duquesnoy RJ: The antibody response to an HLA mismatch: a model for nonself-self discrimination in relation to HLA epitope immunogenicity (Invited Article), Int. J Immunogenetics, 39:1-9, 2011

- **Marrari M, Conca R, Praticò-Barbato L, Amoroso A and Duquesnoy: RJ: Brief Report: Why did two patients who type for HLA-B13 have antibodies that react with all Bw4 antigens except HLA-B13? Transplant Immunology, 25: 217-220, 2011**

- Duquesnoy, RJ: Humoral Alloimmunity in Transplantation: Relevance of HLA Epitope Antigenicity and Immunogenicity, Frontiers in Transplantation and Alloimmunity, 2: 1-6, 2011

- Duquesnoy RJ, Marrari M, Mulder A, Claas FJH, Mostecki J and Balazs I: Structural Aspects of HLA Class I Epitopes Detected by Human Monoclonal Antibodies, Human Immunol. 73: 267-277, 2012

Why did two patients who type for HLA-B13 have antibodies that react with all Bw4 antigens except HLA-B13?

Marrari M, Conca R*, Praticò-Barbato L*, Amoroso A* and Duquesnoy: RJ
Transplant Immunology, 25: 217-220, 2011

- *Transplant Immunology Service, San Giovanni Hospital, Torino, Italy
- Patient 1 is a 52-year old female with focal glomerulosclerosis. She typed as HLA-A*30:01, A*66:01; B*13:02, B*14:02; and had three pregnancies from a husband who types as HLA-A*03:01, A*68:01; B*18:01,B*44:02. No blood transfusion history

- Patient 2 is a 66 year-old female with cystic nephropathy. She typed as HLA-A*02:01, A*11:01; B*07:02, B*1302; C*06:02, C*07:02 and had two pregnancies from a husband who typed as HLA-A*11:01, A*24:02: B*18:01, B*44:02. She received one red blood transfusion in 1993

Antibody reactivity with single alleles

Patient 1

Allele	MFI	Eplet
A*23:01	3400	82LR
A*24:02	2278	82LR
A*24:03	2453	82LR
A*25:01	1625	82LR
A*32:01	3365	82LR
B*13:02 SELF	**41**	**82LR**
B*15:13	1781	82LR
B*15:16	2130	82LR
B*27:05	3217	82LR
B*37:01	4593	82LR
B*38:01	2795	82LR
B*44:02 IMM	2636	82LR, 167ES
B*44:03	3034	82LR
B*47:01	1641	82LR
B*49:01	3688	82LR
B*51:01	2252	82LR
B*51:02	3127	82LR
B*52:01	2705	82LR
B*53:01	2938	82LR
B*57:01	2626	82LR
B*57:03	2655	82LR
B*58:01	2035	82LR
B*59:01	2787	82LR
B*45:01	2263	167ES
B*82:01	3820	167ES
Others	139±167	

Patient 2

Allele	MFI	Eplet
A*23:01	2917	82LR/127K
A*24:02	2627	82LR/127K
A*24:03	2681	82LR/127K
A*25:01	1361	82LR
A*32:01	3098	82LR
B*13:02 SELF	**30**	**82LR**
B*15:13	1734	82LR
B*15:16	2040	82LR
B*27:05	3079	82LR
B*37:01	2639	82LR
B*38:01	2586	82LR
B*44:02 IMM	2363	82LR
B*44:03	2426	82LR
B*47:01	1803	82LR
B*49:01	3399	82LR
B*51:01	1936	82LR
B*51:02	2765	82LR
B*52:01	2318	82LR
B*53:01	2648	82LR
B*57:01	2389	82LR
B*57:03	2235	82LR
B*58:01	1903	82LR
B*59:01	2474	82LR
A*02:01 IMM	939	127K
A*02:03	1095	127K
A*02:06	1062	127K
A*68:01	1623	127K
A*68:02	1505	127K
A*69:01	972	127K
A*01:01	3686	third party ?
Others	65 ± 84	

Antibody reactivity with single alleles

Patient 1		
Allele	**MFI**	**Eplet**
A*23:01	3400	82LR
A*24:02	2278	82LR
A*24:03	2453	82LR
A*25:01	1625	82LR
A*32:01	3365	82LR
B*13:02 SELF	**41**	**82LR**
B*15:13	1781	82LR
B*15:16	2130	82LR
B*27:05	3217	82LR
B*37:01	4593	82LR
B*38:01	2795	82LR
B*44:02 IMM	2636	82LR, 167ES
B*44:03	3034	82LR
B*47:01	1641	82LR
B*49:01	3688	82LR
B*51:01	2252	82LR
B*51:02	3127	82LR
B*52:01	2705	82LR
B*53:01	2938	82LR
B*57:01	2626	82LR
B*57:03	2655	82LR
B*58:01	2035	82LR
B*59:01	2787	82LR
B*45:01	2263	167ES
B*82:01	3820	167ES
Others	139+167	

Patient 2		
Allele	**MFI**	**Eplet**
A*23:01	2917	82LR/127K
A*24:02	2627	82LR/127K
A*24:03	2681	82LR/127K
A*25:01	1361	82LR
A*32:01	3098	82LR
B*13:02 SELF	**30**	**82LR**
B*15:13	1734	82LR
B*15:16	2040	82LR
B*27:05	3079	82LR
B*37:01	2639	82LR
B*38:01	2586	82LR
B*44:02 IMM	2363	82LR
B*44:03	2426	82LR
B*47:01	1803	82LR
B*49:01	3399	82LR
B*51:01	1936	82LR
B*51:02	2765	82LR
B*52:01	2318	82LR
B*53:01	2648	82LR
B*57:01	2389	82LR
B*57:03	2235	82LR
B*58:01	1903	82LR
B*59:01	2474	82LR
A*02:01 IMM	939	127K
A*02:03	1095	127K
A*02:06	1062	127K
A*68:01	1623	127K
A*68:02	1505	127K
A*69:01	972	127K
A*01:01	3686	third party ?
Others	65 + 84	

According to HLAMatchmaker: 82LR on the immunizing B*44:02 is an intralocus match which cannot induce antibodies because the patients have the 83LR-carrying 82LR

Antibody is specific for 145R+82LR pair

	Patient 1 MFI	Patient 2 MFI	Eplet Pair
Positive control	6314	8852	
Negative control	11	33	
Self Alleles	45±23	96±45	
Patient B*13:02	24	41	**145L**+ 82LR
B*44:02 IMM	2246	2636	145R+ 82LR
A*23:01	2635	3400	145R+ 82LR
A*24:02	2303	2278	145R+ 82LR
A*24:03	2266	2453	145R+ 82LR
A*25:01	1270	1625	145R+ 82LR
A*32:01	2764	3365	145R+ 82LR
B*15:13	1582	1781	145R+ 82LR
B*15:16	2078	2130	145R+ 82LR
B*27:05	2732	3217	145R+ 82LR
B*37:01	2259	4593	145R+ 82LR
B*38:01	2280	2795	145R+ 82LR
B*44:03	2326	3034	145R+ 82LR
B*47:01	1750	1641	145R+ 82LR
B*49:01	2634	3688	145R+ 82LR
B*51:01	1888	2252	145R+ 82LR
B*51:02	2467	3127	145R+ 82LR
B*52:01	1958	2705	145R+ 82LR
B*53:01	2521	2938	145R+ 82LR
B*57:01	1904	2626	145R+ 82LR
B*57:03	1964	2655	145R+ 82LR
B*58:01	1551	2035	145R+ 82LR
B*59:01	2255	2787	145R+ 82LR

Antibody is specific for 145R+82LR pair[a]

	Patient 1 MFI	Patient 2 MFI	Eplet Pair
Positive control	6314	8852	
Negative control	11	33	
Self Alleles	45±23	96±45	
Patient B*13:02	24	41	**145L**+ 82LR
B*44:02 IMM	2246	2636	145R+ 82LR
A*23:01	2635	3400	145R+ 82LR
A*24:02	2303	2278	145R+ 82LR
A*24:03	2266	2453	145R+ 82LR
A*25:01	1270	1625	145R+ 82LR
A*32:01	2764	3365	145R+ 82LR
B*15:13	1582	1781	145R+ 82LR
B*15:16	2078	2130	145R+ 82LR
B*27:05	2732	3217	145R+ 82LR
B*37:01	2259	4593	145R+ 82LR
B*38:01	2280	2795	145R+ 82LR
B*44:03	2326	3034	145R+ 82LR
B*47:01	1750	1641	145R+ 82LR
B*49:01	2634	3688	145R+ 82LR
B*51:01	1888	2252	145R+ 82LR
B*51:02	2467	3127	145R+ 82LR
B*52:01	1958	2705	145R+ 82LR
B*53:01	2521	2938	145R+ 82LR
B*57:01	1904	2626	145R+ 82LR
B*57:03	1964	2655	145R+ 82LR
B*58:01	1551	2035	145R+ 82LR
B*59:01	2255	2787	145R+ 82LR

But both 145R and 82LR are intralocus matches !!

Antibody is specific for 145R+82LR pair[a]

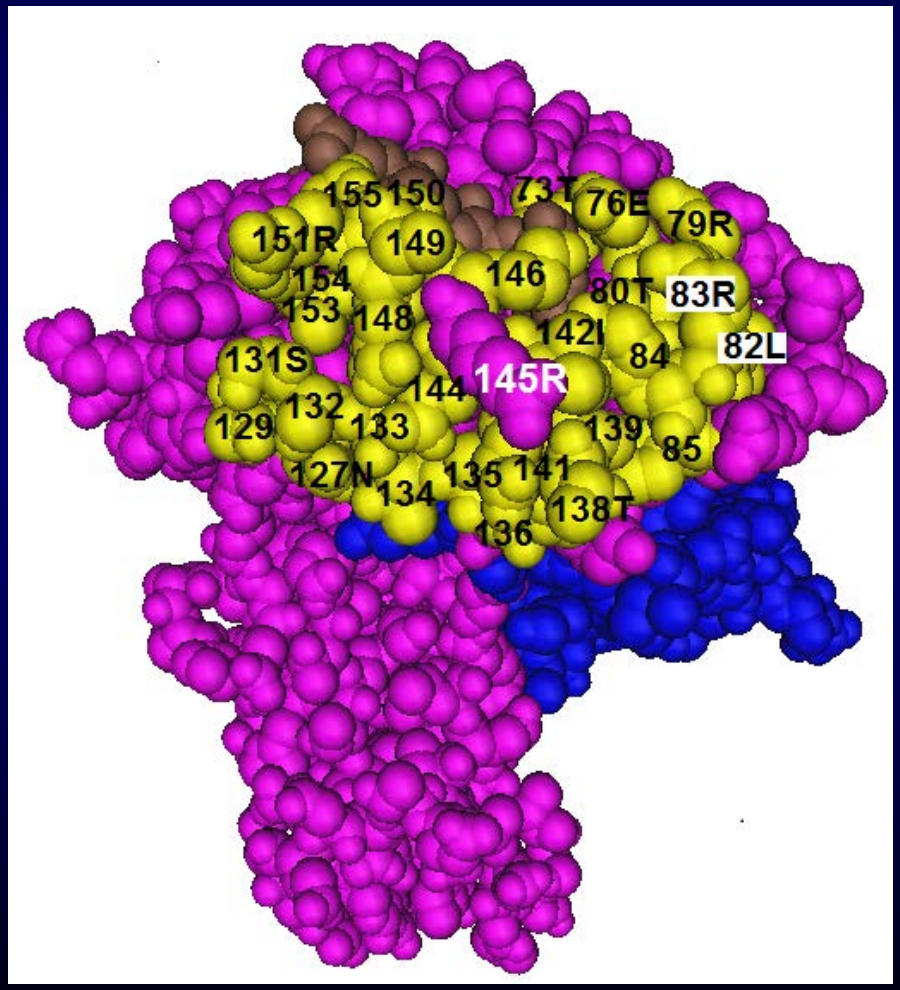
	Patient 1 MFI	Patient 2 MFI	Eplet Pair
Positive control	6314	8852	
Negative control	11	33	
Self Alleles	45±23	96±45	
Patient B*13:02	24	41	**145L**+ 82LR
B*44:02 IMM	2246	2636	145R+ 82LR
A*23:01	2635	3400	145R+ 82LR
A*24:02	2303	2278	145R+ 82LR
A*24:03	2266	2453	145R+ 82LR
A*25:01	1270	1625	145R+ 82LR
A*32:01	2764	3365	145R+ 82LR
B*15:13	1582	1781	145R+ 82LR
B*15:16	2078	2130	145R+ 82LR
B*27:05	2732	3217	145R+ 82LR
B*37:01	2259	4593	145R+ 82LR
B*38:01	2280	2795	145R+ 82LR
B*44:03	2326	3034	145R+ 82LR
B*47:01	1750	1641	145R+ 82LR
B*49:01	2634	3688	145R+ 82LR
B*51:01	1888	2252	145R+ 82LR
B*51:02	2467	3127	145R+ 82LR
B*52:01	1958	2705	145R+ 82LR
B*53:01	2521	2938	145R+ 82LR
B*57:01	1904	2626	145R+ 82LR
B*57:03	1964	2655	145R+ 82LR
B*58:01	1551	2035	145R+ 82LR
B*59:01	2255	2787	145R+ 82LR

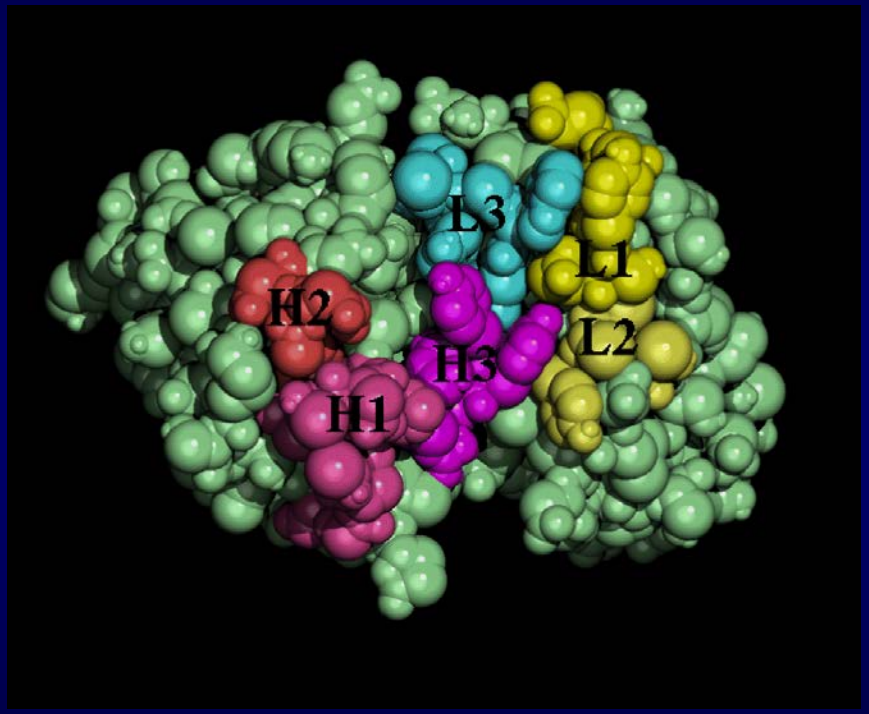
But both 145R and 82LR are intralocus matches !!

Apply the nonself-self paradigm of HLA epitope immunogenicity

Residues within 15 Ångstroms of 145R

B*44:02





Six CDRs of antibody

Application of Nonself-Self Paradigm of Epitope Immunogenicity

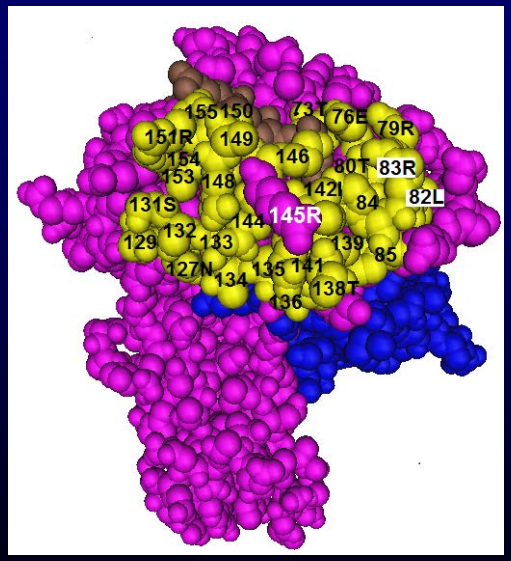
		Polymorphic residues within 15 Ångstroms of 145R													
Residue Positions	145	73	76	79	80	82	83	127	131	138	142	144	149	151	152
B*44:02 Immunizer	R	T	E	R	T	L	R	N	S	T	I	Q	A	R	V

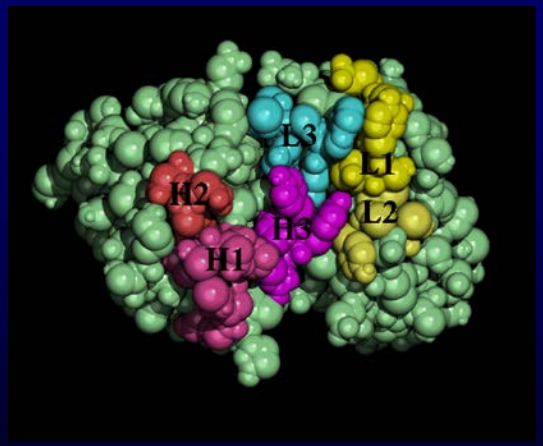
Application of Nonself-Self Paradigm of Epitope Immunogenicity

			Polymorphic residues within 15 Ångstroms of 145R													
Residue Positions	145		73	76	79	80	82	83	127	131	138	142	144	149	151	152
B*44:02 Immunizer	R		T	E	R	T	L	R	N	S	T	I	Q	A	R	V
Patient 1		Number of Differences														
A*30:01	-	7	-	V	G	-	R	G	-	R	M	-	-	-	-	W
A*66:01	-	9	-	V	D	-	R	G	-	R	M	-	-	T	H	E
B*13:02	L	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B*14:02	-	4	-	-	-	N	R	G	-	-	-	-	-	-	-	E
C*06:02	-	7	A	V	-	K	R	G	-	R	-	-	-	-	-	E
C*08:02	-	6	-	V	-	N	R	G	-	R	-	-	-	-	-	E
Patient 2																
A*02:01	H	10	-	V	G	-	R	G	K	R	M	T	K	-	H	-
A*11:01	-	9	-	V	G	-	R	G	-	R	M	-	K	-	H	A
B*07:02	-	5	-	-	-	N	R	G	-	R	-	-	-	-	-	E
B*13:02	L	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C*06:02	-	7	A	V	-	K	R	G	-	R	-	-	-	-	-	E
C*07:02	-	7	A	V	-	N	R	G	-	R	-	-	-	-	-	A

Conclusions

- These 145R+82LR specific antibodies originated from B-cells with Ig receptors for a self 145L-carrying structural epitope on B*13:02
- This finding illustrates the usefulness of the nonself-self paradigm of HLA epitope immunogenicity to increase our understanding of HLA sensitization





Transplant Immunology, Submitted, Feb 2015

HLA-A2 Reactive Antibodies in a Patient Who Types as HLA-A2: The Importance of High Resolution Typing and Epitope-Based Antibody Analysis

A.B. Hahn, V. Bravo-Egana, J.L. Jackstadt, D.J. Conti (Albany Medical College) and R.J. Duquesnoy

A 41 year-old African-American female patient with no pregnancies and 5 transfusions types as HLA-**A2**,A3; B7,B45; Cw7,Cw16; DR11,DR15. She had received a kidney transplant in 1998 from a zero-HLA-A,B,DR antigen mismatch deceased donor: HLA-**A2**,-; B7,B45; Cw6,Cw7; DR11,DR15 and in 2000 she received a zero-HLA-A,B,C,DR antigen mismatch pancreas transplant: HLA-A3,-; B7,-; Cw7,-; DR15,-.

Both transplants failed eventually and in November 2014 the patient was evaluated for a possible second kidney transplant.

Serum screening with single allele Luminex beads showed **positive reactions with all three HLA-A2 alleles**, HLA-A80 and the following HLA-C antigens: Cw2, Cw4, Cw5, Cw6, Cw12, Cw15, Cw17, Cw18. The calculated Panel-Reactive Antibody (cPRA) was 84%.

Hahn's case:

Patient High-resolution type:
A*02:02,A*03:01;B*07:02,B*45:01;C*07:02,C*16:01
Patient types as A*02:02 and the antibody-reactive SAB are A*02:01, A*02:03 and A*02:06

Amino acid sequence analysis:
Only one difference in an antibody-accessible position: A*02:02 has 43R; A*02:01, A*02:03 and A*02:06 have 43Q.
All other HLA-A alleles in the SAB panel have 43Q
Patient's A*03:01 has 43Q which indicates that 43Q is a self-residue

Conclusion: epitope is defined by 43Q paired with another configuration unique to A*02:01, A*02:03 and A*02:06

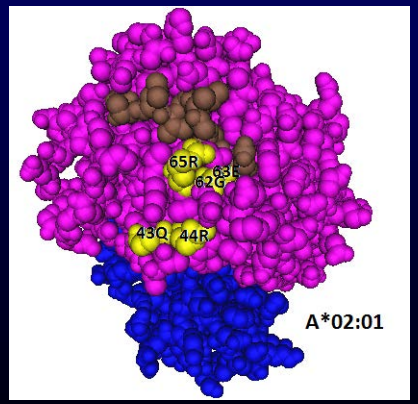
Hahn's case: Epitope specificity analysis of antibody reactivity with HLA-A and HLA-B alleles

Patient Phenotype		MFI	Epitope 43Q+62G+63E+65R Nonself for A*02:02	Self for A*02:02		
A*02:02	self	not done	43R	62G	63E	65R
A*03:01	self	187	43Q	62Q	63E	65R
B*07:02	self	211	43P	62R	63N	65Q
B*45:01	self	210	43P	62R	63E	65Q
C*07:02	self	308	43P	62R	63E	65Q
C*16:01	self	246	43P	62R	63E	65Q
A*02:01	Immunizer	6631	43Q	62G	63E	65R
A*02:03		5561	43Q	62G	63E	65R
A*02:06		4542	43Q	62G	63E	65R
A*80:01		2324	43Q	62E	63E	65R
A*01:01		426	43Q	62Q	63E	65R
A*11:01		442	43Q	62Q	63E	65R
A*11:02		532	43Q	62Q	63E	65R
A*23:01		284	43Q	62E	63E	65G
A*24:02		376	43Q	62E	63E	65G
A*24:03		759	43Q	62E	63E	65G
A*25:01		549	43Q	62R	63N	65R
A*26:01		470	43Q	62R	63N	65R
A*29:01		471	43Q	62L	63Q	65R
A*29:02		378	43Q	62L	63Q	65R
A*30:01		187	43Q	62Q	63E	65R
A*30:02		221	43Q	62Q	63E	65R
A*31:01		218	43Q	62Q	63E	65R
A*32:01		266	43Q	62Q	63E	65R
A*33:01		196	43Q	62R	63N	65R
A*33:03		183	43Q	62R	63N	65R
A*34:01		620	43Q	62R	63N	65R
A*34:02		533	43Q	62R	63N	65R
A*36:01		337	43Q	62Q	63E	65R
A*43:01		506	43Q	62L	63Q	65R
A*66:01		646	43Q	62R	63N	65R
A*66:02		329	43Q	62R	63N	65R
A*68:01		210	43Q	62R	63N	65R
A*68:02		323	43Q	62R	63N	65R
A*69:01		287	43Q	62R	63N	65R
A*74:01		241	43Q	62Q	63E	65R
Negative HLA-A alleles		384±159	43Q			
All HLA-B alleles (N=50)		253±87	43P			

Hahn's case:

Subsequent testing with an expanded Luminex panel:
Positive reactions for the 43Q+62GER-carrying A*02:07 (MFI=1093) and A*02:10 (MFI=3082) whereas A*02:05, which has 43R, was negative (MFI=395).
All other HLA alleles were nonreactive (MFI=101 ± 180, N=31) except the 80K-carrying C*18:01 (MFI= 11,596).

Conclusion:
This patient's antibodies reacted with an epitope determined by residues 43Q+62G+63E+65R. According to the eplet notations in HLAMatchmaker, this epitope is called 43Q+62GER.
These configurations are about 8 Ångstroms apart and would be contacted by different CDRs of antibody.



Hahn's case: Epitope specificity analysis of antibody reactivity with HLA-C alleles

			First Epitope:80K	Second Epitope:73A+147W	
Patient	Phenotype	MFI		Non-self for C*16:01	Self for C*16:01
A*02:02	self	nd	80T	73T	147W
A*03:01	self	187	80T	73T	147W
B*07:02	self	211	80N	73T	147W
B*45:01	self	210	80N	73T	147W
C*07:02	self	308	80N	73A	147L
C*16:01	self	246	80N	73T	147W
C*06:02	Immunizer	14000	80K	73A	147W
C*04:01		10831	80K	73A	147W
C*18:02		13688	80K	73A	147W
C*17:01		14413	80K	73A	147L
C*05:01		16325	80K	73T	147W
C*02:02		15727	80K	73T	147W
C*15:02		4364	80K	73T	147W
C*12:03		4185	80N	73A	147W
C*01:02		226	80N	73T	147W
C*03:02		235	80N	73T	147W
C*03:03		256	80N	73T	147W
C*03:04		256	80N	73T	147W
C*08:01		242	80N	73T	147W
C*14:02		261	80N	73T	147W
C*16:01		246	80N	73T	147W

Implications of the nonself-self paradigm of eplet immunogenicity

- It is well known that sensitized patients develop specific antibodies to a restricted number of mismatched epitopes
- It seems possible that certain mismatched eplet-carrying antigens have significant structural epitope differences with all patient alleles and this would not permit B-cell activation through its self-HLA immunoglobulin receptor

Implications of the nonself-self paradigm of eplet immunogenicity

- It is well known that sensitized patients develop specific antibodies to a restricted number of mismatched epitopes
- It seems possible that certain mismatched eplet-carrying antigens have significant structural epitope differences with all patient alleles and this would not permit B-cell activation through its self-HLA immunoglobulin receptor

Example: Would a patient who is homozygous for A25 develop a antibody to 144KR+s151H presented by an A11 mismatch?

Case 4	Eplet			Number of	Polymorphic Surface Residues within 15 A										
144KR+s151H	142	144	145	Differences	73	76	79	80	82	83	127	131	138	149	151
A*11:01 *Immunizer*	I	K	R		T	V	G	T	R	G	N	R	M	A	H
Antibody producer															
A*02:01	**T**	**K**	**H**	**1**	-	-	-	-	-	-	**K**	-	-	-	-
A*25:01	I	Q	R	6	-	E	R	I	L	R	-	-	-	T	-
B*18:01	I	Q	R	6	-	E	R	N	-	-	-	S	T	-	R
B*51:01	I	Q	R	8	-	E	R	I	L	R	-	S	T	-	R
C*12:03	I	Q	R	5	A	-	R	N	-	-	-	-	T	-	R
C*15:02	I	Q	R	4	-	-	R	K	-	-	-	-	T	-	R

Conclusions

- The nonself-self paradigm of HLA epitope immunogenicity represents a significant step in the development of the HLAMatchmaker algorithm since the introduction of the eplet concept in 2006
- This paradigm may increase our understanding of the immunogenicity and antigenicity of HLA epitopes
- Its application might be clinically relevant in determining HLA mismatch permissibility

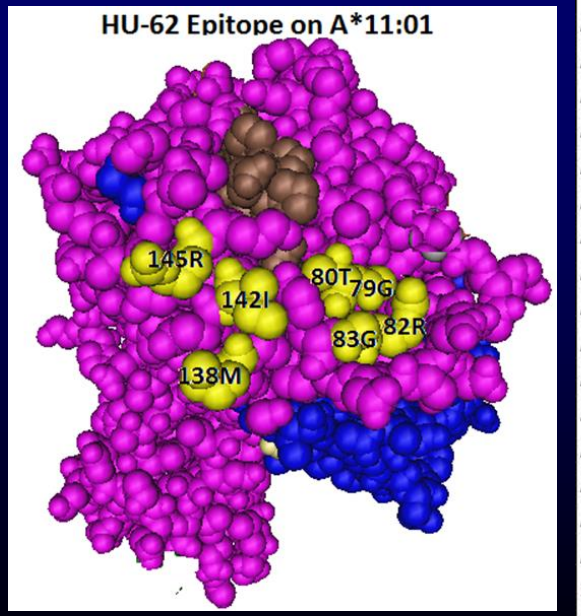
Application of the nonself-self algorithm of HLA epitope immunogenicity in the specificity analysis of monospecific antibodies induced during pregnancy

These epitopes could not be defined with HLAMatchmaker which considers matching at intralocus and interlocus levels

Rene J. Duquesnoy, Marilyn Marrari and Arend Mulder
Manuscript Submitted

Hypothesis: Antibody originate from B-cells with Ig receptors to self-142T145H on A*02:06

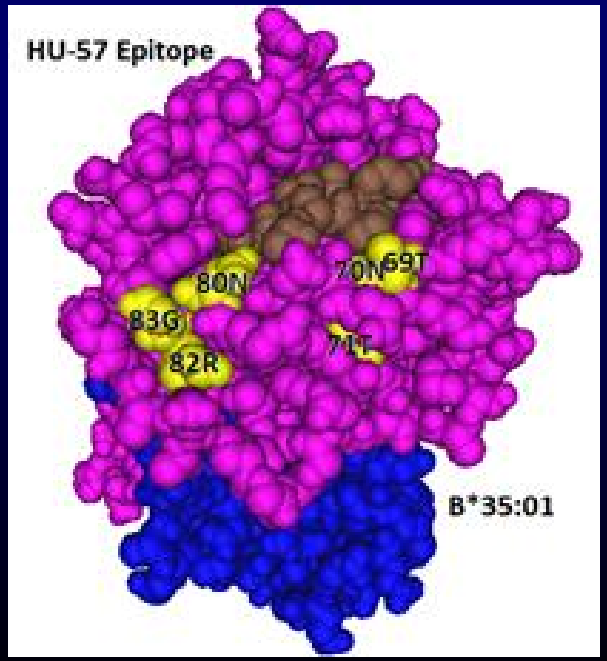
HU-62 is specific for an epitope defined by 142I145R+138M +79G80T82R83G



HU-62 MUL7-C7	MFI	nonself	nonself	self	self	self	self	self
A*11:01 IMM	13720	142I	145R	138M	79G	80T	82R	83G
A*02:06 Self	not tested	142T	145H	138M	79G	80T	82R	83G
A*25:01 Self	9	142I	145R	138M	79R	80I	82L	83R
B*18:01 Self	10	142I	145R	138T	79G	80T	82R	83G
B*51:01 Self	12	142I	145R	138T	79R	80I	82L	83R
C*12:03 Self	29	142I	145R	138T	79G	80T	82R	83G
C*15:02 Self	15	142I	145R	138T	79G	80K	82R	83G
A*11:02	14523	142I	145R	138M	79G	80T	82R	83G
A*30:01	14028	142I	145R	138M	79G	80T	82R	83G
A*31:01	13898	142I	145R	138M	79G	80T	82R	83G
A*03:01	13870	142I	145R	138M	79G	80T	82R	83G
A*29:01	13596	142I	145R	138M	79G	80T	82R	83G
A*29:02	13297	142I	145R	138M	79G	80T	82R	83G
A*33:03	13083	142I	145R	138M	79G	80T	82R	83G
A*01:01	13049	142I	145R	138M	79G	80T	82R	83G
A*34:02	12728	142I	145R	138M	79G	80T	82R	83G
A*33:01	12058	142I	145R	138M	79G	80T	82R	83G
A*36:01	11719	142I	145R	138M	79G	80T	82R	83G
A*80:01	11501	142I	145R	138M	79G	80T	82R	83G
A*74:01	9508	142I	145R	138M	79G	80T	82R	83G
A*66:01	9270	142I	145R	138M	79G	80T	82R	83G
A*26:01	9240	142I	145R	138M	79G	80T	82R	83G
A*34:01	6772	142I	145R	138M	79G	80T	82R	83G
A*43:01	6679	142I	145R	138M	79G	80T	82R	83G
A*66:02	6640	142I	145R	138M	79G	80T	82R	83G
A*30:02	2797	142I	145R	138M	79G	80T	82R	83G
A*23:01	146	142I	145R	138M	79R	80I	82L	83R
A*24:02	122	142I	145R	138M	79R	80I	82L	83R
A*24:03	67	142I	145R	138M	79R	80I	82L	83R
A*32:01	8	142I	145R	138M	79R	80I	82L	83R
A*02:01	22	142T	145H	138M	79G	80T	82R	83G
A*02:03	12	142T	145H	138M	79G	80T	82R	83G
A*02:06	28	142T	145H	138M	79G	80T	82R	83G
A*68:01	335	142T	145H	138M	79G	80T	82R	83G
A*68:02	96	142T	145H	138M	79G	80T	82R	83G
A*69:01	120	142T	145H	138M	79G	80T	82R	83G
50 HLA-B alleles	26±51	142I	145R	138T				
15 HLA-C alleles	20±5	142I	145R/L	138K/T				

Hypothesis:
Antibody originated from B-cells with Ig receptors to self-69T70Q71A on B*07:02

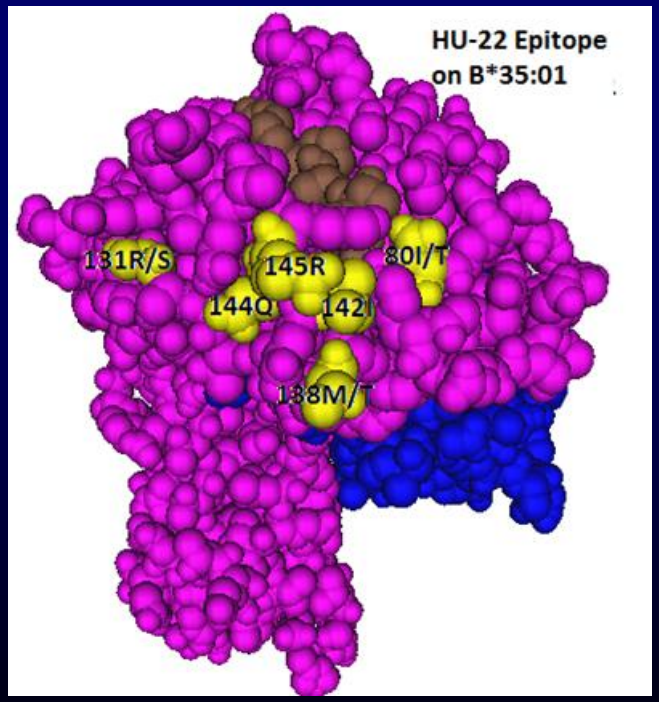
HU-57 is specific for an epitope defined by 69T70N71T+ 80N82R83G



HU-57 DMS4-G2		MFI	nonself	nonself	nonself	self	self	self
B*15:01	IMM	18413	69T	70N	71T	80N	82R	83G
A*03:01	self	294	69A	70Q	71S	80T	82R	83G
A*68:01	self	283	69A	70Q	71S	80T	82R	83G
B*07:02	self	225	69A	70Q	71A	80N	82R	83G
B*51:01	self	375	69T	70N	71T	80I	82L	83R
C*07:02	self	316	69R	70Q	71A	80N	82R	83G
C*15:02	self	338	69R	70Q	71A	80K	82R	83G
B*15:12		17902	69T	70N	71T	80N	82R	83G
B*40:01		17895	69T	70N	71T	80N	82R	83G
B*15:03		17751	69T	70N	71T	80N	82R	83G
B*18:01		17182	69T	70N	71T	80N	82R	83G
B*40:02		16895	69T	70N	71T	80N	82R	83G
B*41:01		16736	69T	70N	71T	80N	82R	83G
B*15:02		15739	69T	70N	71T	80N	82R	83G
B*45:01		14551	69T	70N	71T	80N	82R	83G
B*35:01		13459	69T	70N	71T	80N	82R	83G
B*39:01		14369	69T	70N	71T	80N	82R	83G
B*08:01		14177	69T	70N	71T	80N	82R	83G
B*78:01		13570	69T	70N	71T	80N	82R	83G
B*35:08		11639	69T	70N	71T	80N	82R	83G
B*50:01		9797	69T	70N	71T	80N	82R	83G
B*15:18		9766	69T	70N	71T	80N	82R	83G
B*07:03		9660	69T	70N	71T	80N	82R	83G
B*48:01		8970	69T	70N	71T	80N	82R	83G
B*14:05		5362	69T	70N	71T	80N	82R	83G
B*14:06		2531	69T	70N	71T	80N	82R	83G
B*15:13		325	69T	70N	71T	80I	82L	83R
B*38:01		534	69T	70N	71T	80I	82L	83R
B*49:01		457	69T	70N	71T	80I	82L	83R
B*52:01		344	69T	70N	71T	80I	82L	83R
B*53:01		330	69T	70N	71T	80I	82L	83R
B*13:02		409	69T	70N	71T	80T	82L	83R
B*37:01		705	69T	70N	71T	80T	82L	83R
B*44:02		466	69T	70N	71T	80T	82L	83R
B*44:03		856	69T	70N	71T	80T	82L	83R
B*47:01		344	69T	70N	71T	80T	82L	83R
9 HLA-B alleles		295±55	69A/R	70K/Q	71A	80N	82R	83G
5 HLA-B alleles		313±35	69A	70S	71A	80I	82L	83R
27 HLA-A alleles		306±31	69A	70H/Q	71S	80T	82L	83R
17 HLA-C alleles		359±27	69R	70Q	71A	80K/N	82R	83G

Hypothesis:
Antibody originate from B-cells with Ig receptors to self-142T144K145H on A*24:02

HU-22 is specific for an epitope defined by 142I144Q145R+80I or 80T



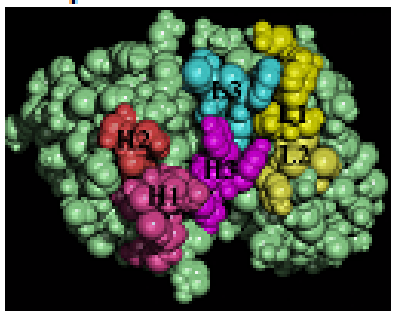
HU-22 HDG2-G7	MFI	self	nonself	self	self	self
A*32:01 IMM	21268	142I	144Q	145R	80I	138M
A*02:01 self	5	142T	144K	145H	80T	138M
A*24:02 self	13	142I	144K	145R	80I	138M
B*07:02 self	8	142I	144Q	145R	80N	138T
B*40:01 self	18	142I	144Q	145R	80N	138T
C*03:04 self	22	142I	144Q	145R	80N	138T
C*07:02 self	20	142I	144Q	145R	80N	138T
A*23:01	21369	142I	144Q	145R	80I	138M
A*25:01	20516	142I	144Q	145R	80I	138M
A*31:01	17890	142I	144Q	145R	80T	138M
A*30:01	15330	142I	144Q	145R	80T	138M
B*53:01	13137	142I	144Q	145R	80I	138T
A*33:03	12678	142I	144Q	145R	80T	138M
A*34:02	11459	142I	144Q	145R	80T	138M
A*29:01	11214	142I	144Q	145R	80T	138M
A*33:01	10704	142I	144Q	145R	80T	138M
B*51:02	10585	142I	144Q	145R	80I	138T
A*29:02	9484	142I	144Q	145R	80T	138M
B*38:01	9469	142I	144Q	145R	80I	138T
B*51:01	9396	142I	144Q	145R	80I	138T
A*66:01	9036	142I	144Q	145R	80T	138M
B*15:16	8839	142I	144Q	145R	80I	138T
B*59:01	8630	142I	144Q	145R	80I	138T
B*57:03	8570	142I	144Q	145R	80I	138T
A*66:02	7735	142I	144Q	145R	80T	138M
A*26:01	7371	142I	144Q	145R	80T	138M
A*74:01	7350	142I	144Q	145R	80T	138M
B*52:01	7238	142I	144Q	145R	80I	138T
B*15:13	6916	142I	144Q	145R	80I	138T
A*30:02	6831	142I	144Q	145R	80T	138M
A*34:01	6365	142I	144Q	145R	80T	138M
B*44:02	5945	142I	144Q	145R	80T	138T
B*49:01	5919	142I	144Q	145R	80I	138T
B*44:03	5800	142I	144Q	145R	80T	138T
B*27:05	5372	142I	144Q	145R	80T	138T
A*43:01	5352	142I	144Q	145R	80T	138M
B*57:01	5081	142I	144Q	145R	80I	138T
B*37:01	4382	142I	144Q	145R	80T	138T
B*58:01	4116	142I	144Q	145R	80I	138T
B*47:01	3788	142I	144Q	145R	80T	138T
29 HLA-B alleles	71 + 90	142I	144Q	145R	80N	138T
14 HLA-C alleles	26 + 8	142I	144Q	145R	80N/K	138T
B*13:01/02	13 + 12	142I	144Q	145L	80T	138T
7 HLA-A alleles	8 + 5	142I	144K	145R	80T	138M
5 HLA-A alleles	7 + 3	142T	144K	145H	80T	138M

Nonself-Self Paradigm of the Antibody Response to HLA

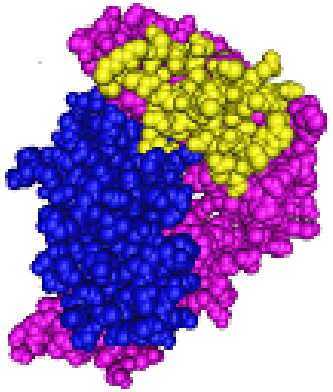
B cell development: Ig gene V(D)J rearrangements

Clonal Selection: B cells with high affinity Ig receptors are eliminated

High and low affinity Ig receptors for self HLA

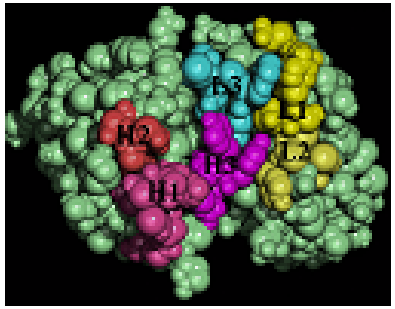


Self HLA Molecule

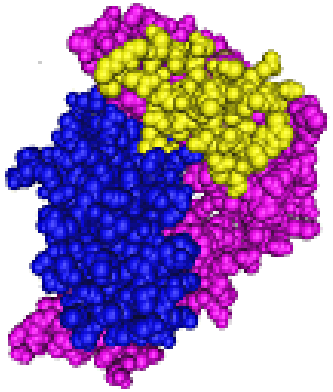


B cells with low affinity Ig receptors survive

Low affinity Ig receptor for self HLA

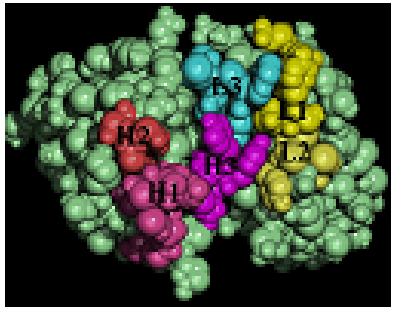


Self HLA Molecule

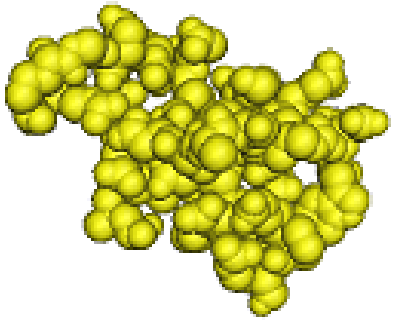


How many self epitopes do such B cells recognize?

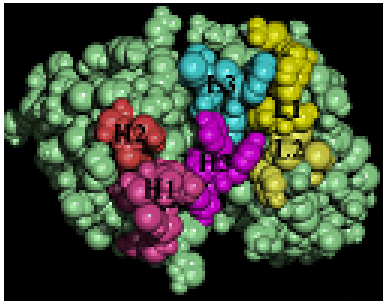
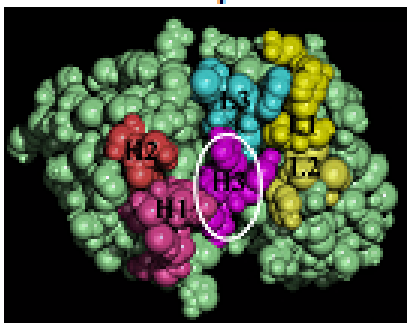
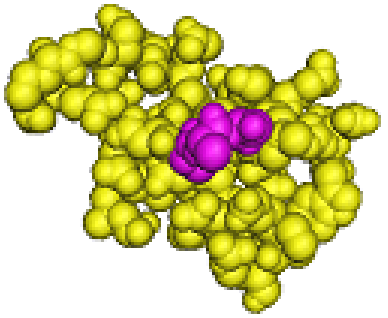
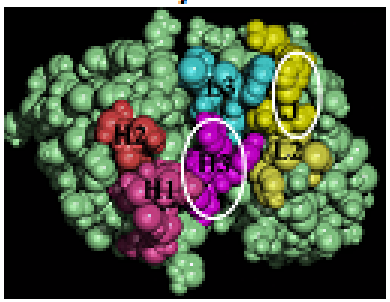
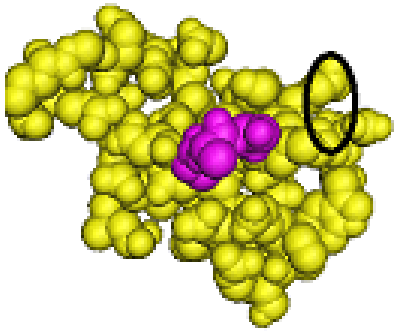
Low affinity Ig receptor for self HLA



Structural Self Epitope



Nonself-Self Paradigm of the Antibody Response to HLA

B cells with low affinity Ig receptors; they cannot be activated by self epitopes	Ig receptor for self HLA 	Structural Self Epitope 
B cells with low affinity Ig receptors can be activated by HLA epitopes with nonself eplets that are surrounded by self residues. CDR-H3 plays a central role in eplet recognition	Self HLA Ig receptor react with nonself eplet 	Structural epitope with mismatched eplet 
Activated B cells undergo affinity maturation which increases the binding of other CDRs to the structural epitope. For instance, they can produce antibodies to epitopes defined by eplet pairs	Epitope specific Ig receptor after affinity maturation 	Epitope defined by eplet pair 

Conclusions

- The nonself-self paradigm of HLA epitope immunogenicity represents the most significant step in the development of the HLAMatchmaker algorithm since the introduction of the eplet concept in 2006
- This paradigm may increase our understanding of the immunogenicity and antigenicity of HLA epitopes
- Its application might be clinically relevant in determining HLA mismatch permissibility

HLA Epitope-Based Mismatch Permissibility in Transplantation

- Epitope loads of HLA antigen mismatches
  - Clinically useful information in the post-transplant management of patients at risk for antibody-mediated rejection
  - May lead to permissible HLA mismatch strategies for non-sensitized patients to reduce humoral rejection and increase transplant success

- Avoid highly immunogenic epitopes
  - Identified from frequencies of specific antibody responses.
  - Determined from physiochemical characteristics
  - Application of the nonself-self paradigm of HLA epitope immunogenicity