LUDWIG INSTITUTE FOR CANCER RESEARCH

Striking Immunodominance of anti-NY-ESO-1 CD8+ T cell responses

T-cell Laboratory, LICR

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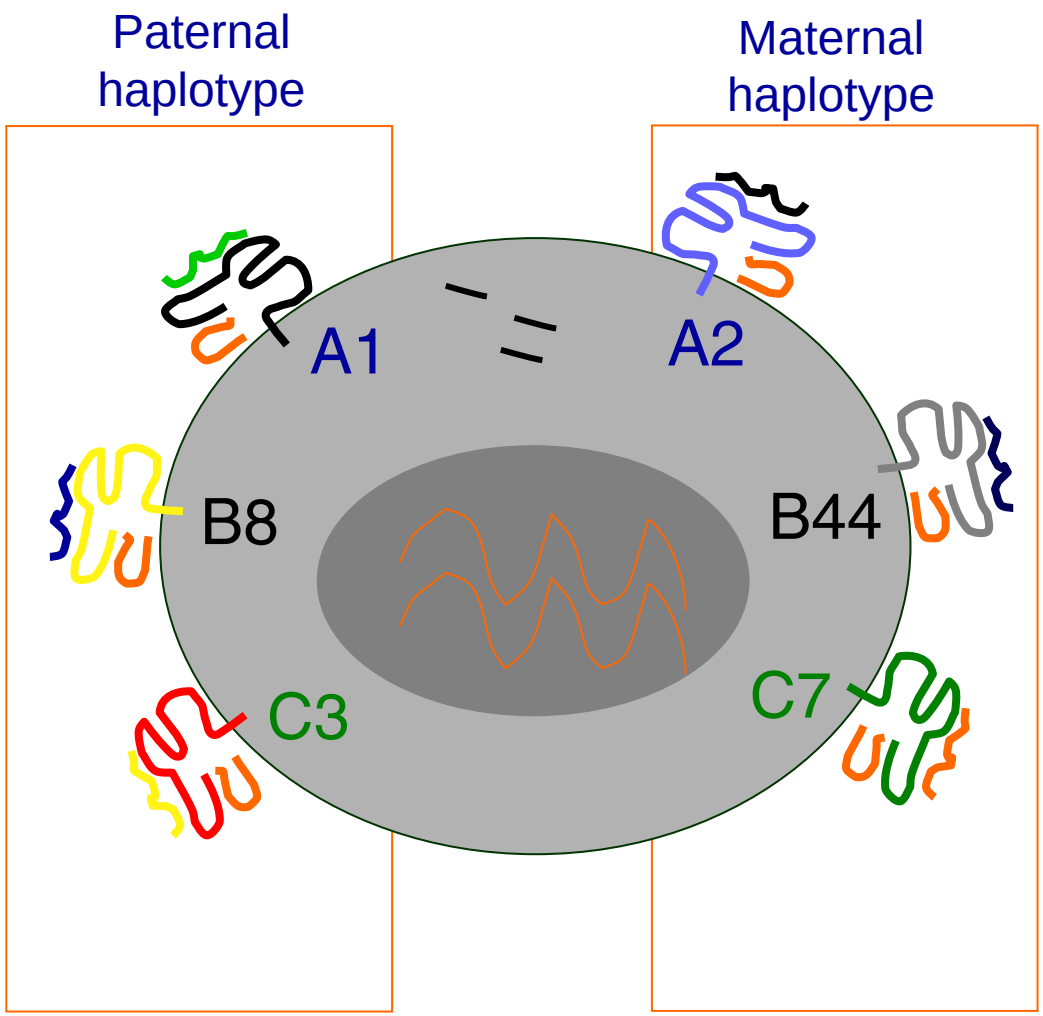
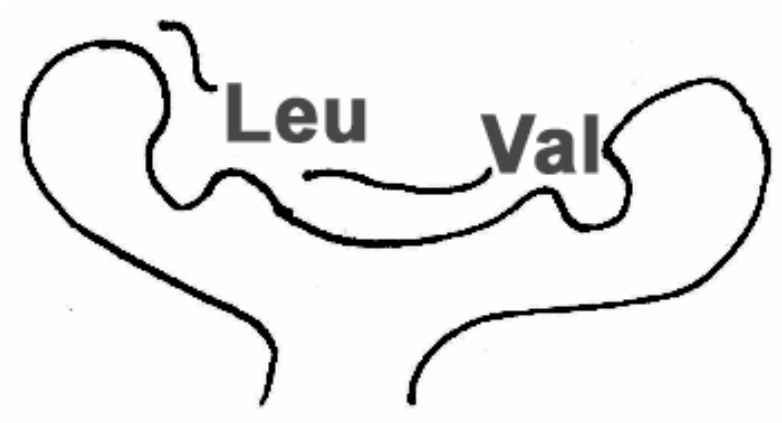
November, 2005

HLA class I molecules

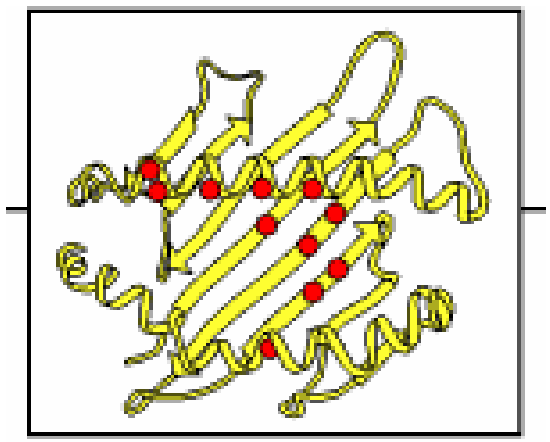


There are 1100 class I alleles and about 760 class II alleles

Peptides bind MHC by using "anchor" side chains



Class I
Allele
HLA-A2



Immunodominance

The preferential recognition of certain antigenic epitope(s) by T cells

Question we asked

- Most tumour Ag are self-Ag, are we dealing with already shaped T repertoire?
- Is immunodominance a general feature of anti-NY-ESO-1 T cell responses?

Monitor HLA-A2-restricted anti-NY-ESO-1 response

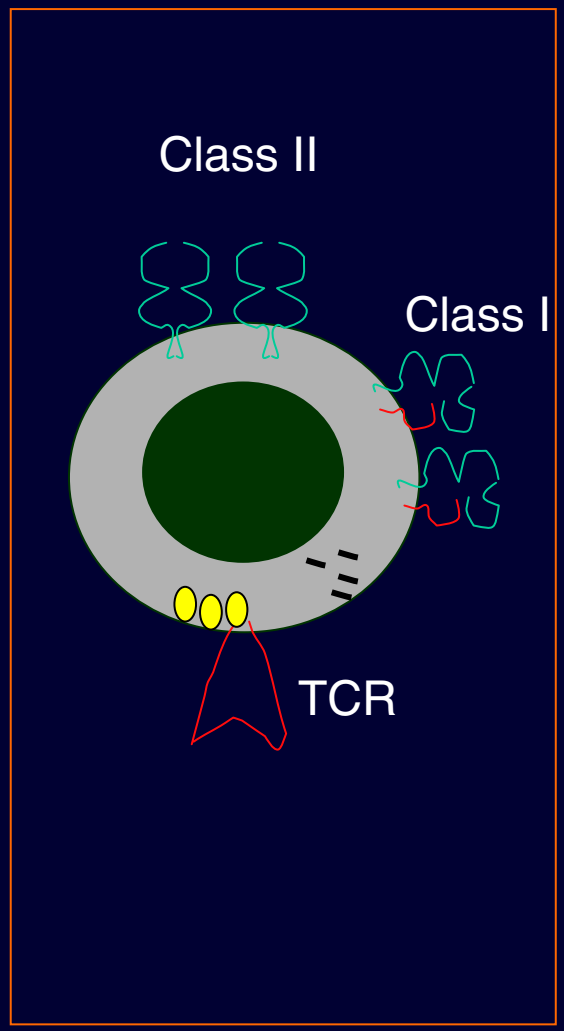
NY-ESO-1/157-165 SLLMWITQC

23 vaccinated patients monitored 3x small responses found

Identify the most immunodominant T cell epitopes systematically

- Algorithm prediction can be inaccurate
- Does not need detailed info on HLA or epitopes
- Can be done utilizing natural Ag presentation

bulk culture for CD4+ & CD8+ T cells



18 mer peptide
for 1hr at 37°C

$5x10^6$
PBMC

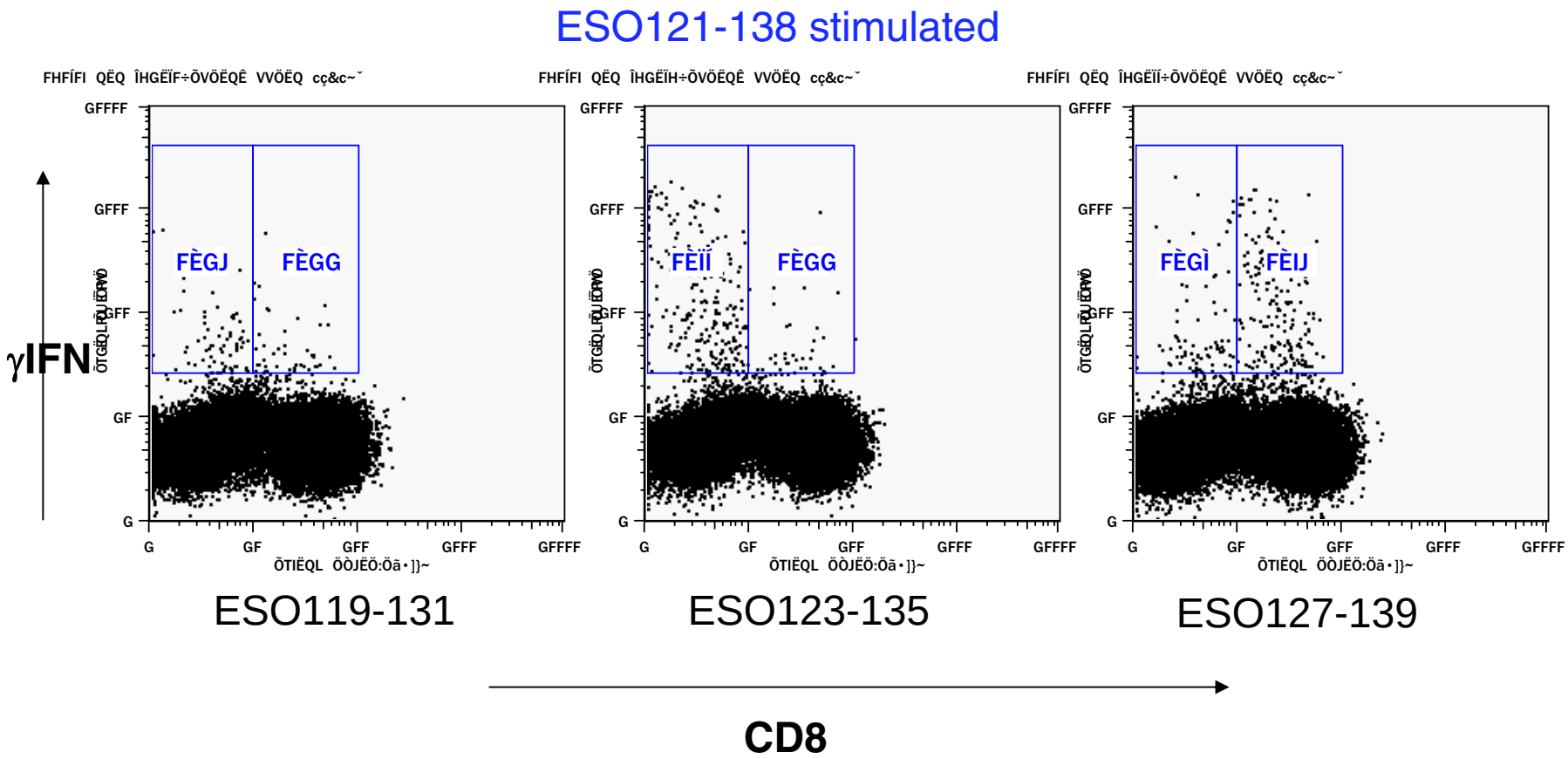
IL-2-containing
RPMI-1640 +FCS

11-15 days

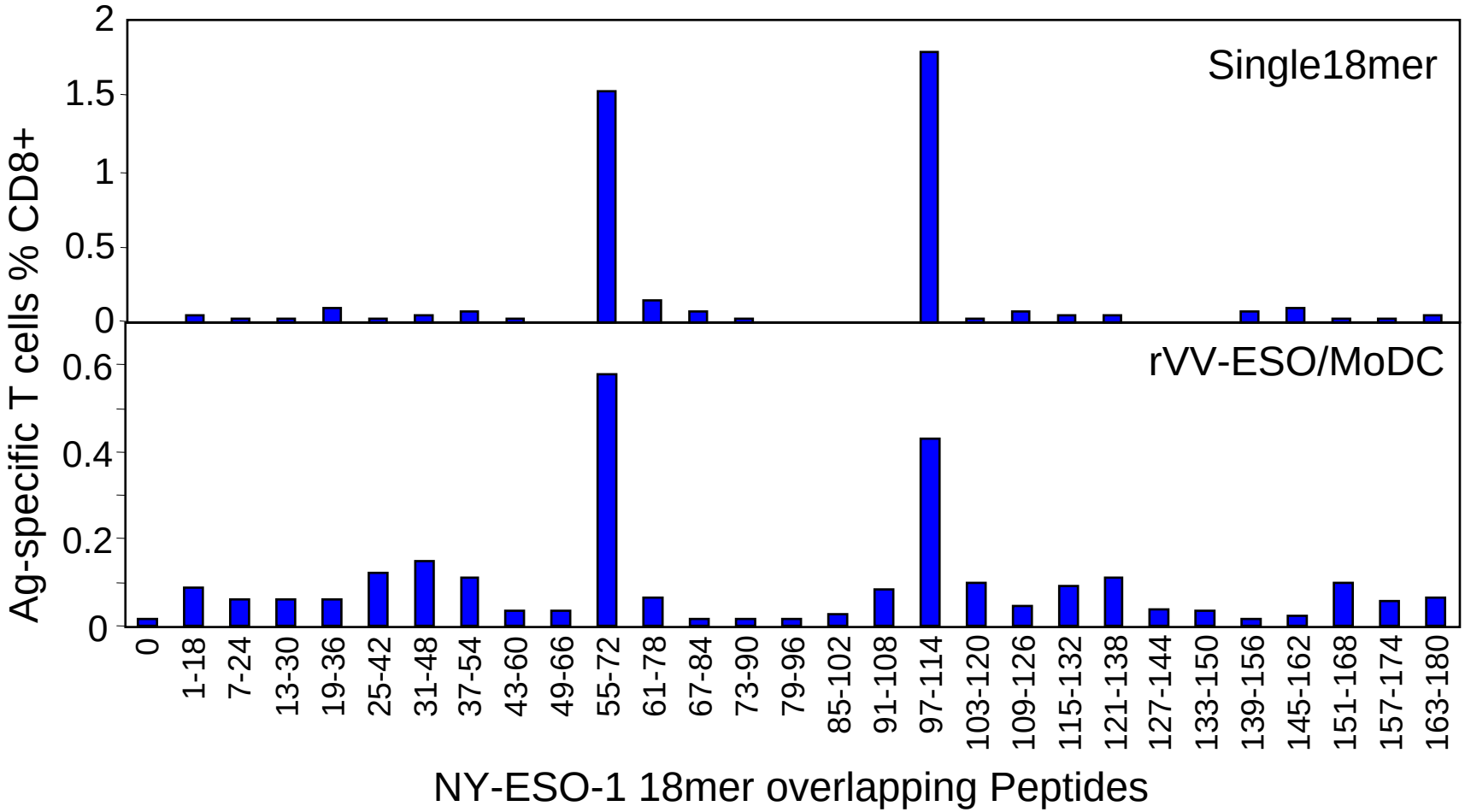
ICS with 18, 13, 10mers
minimum epitope

FACS analysis

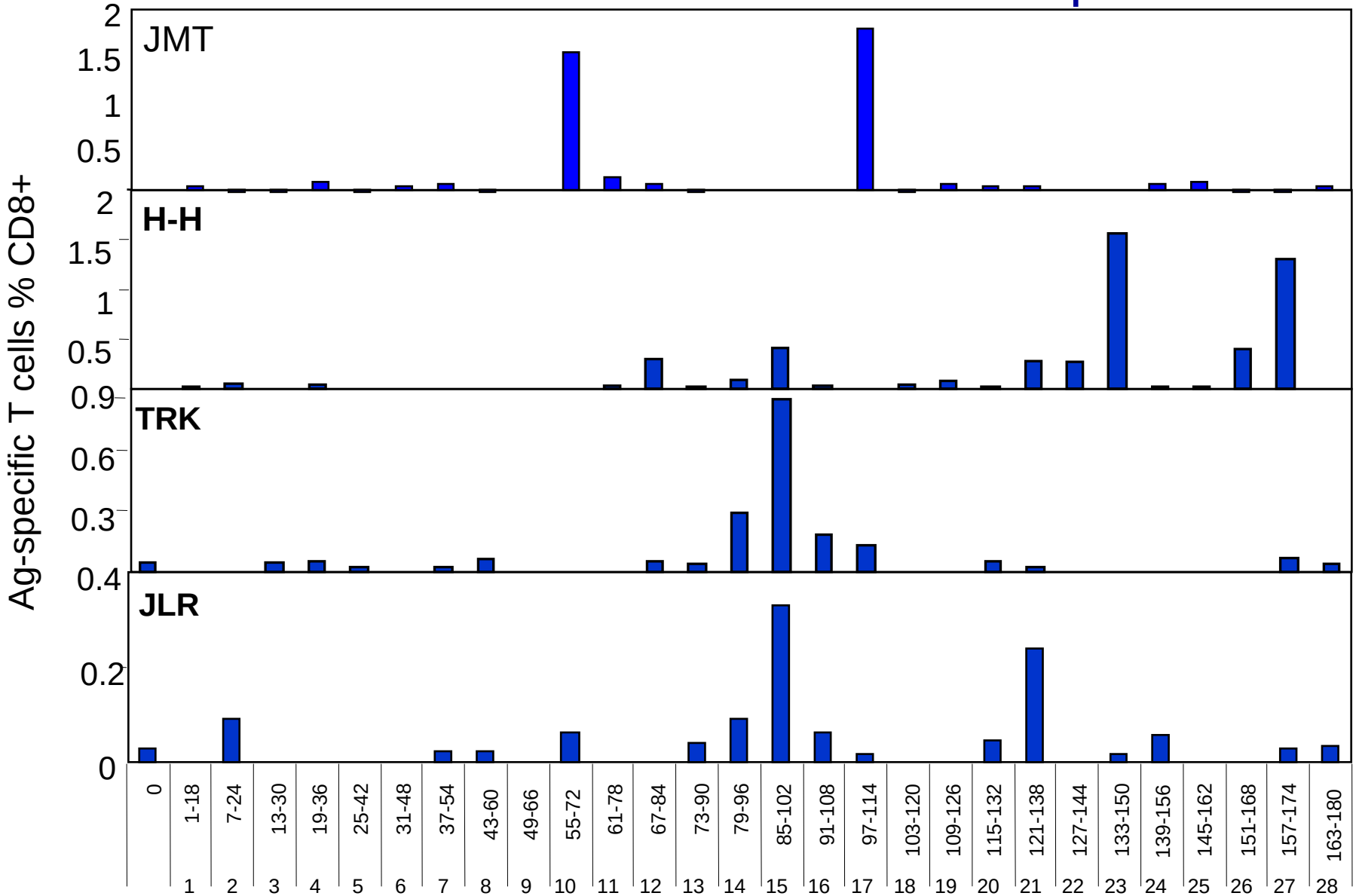
Detecting CD4+ and CD8+ T cells simultaneously



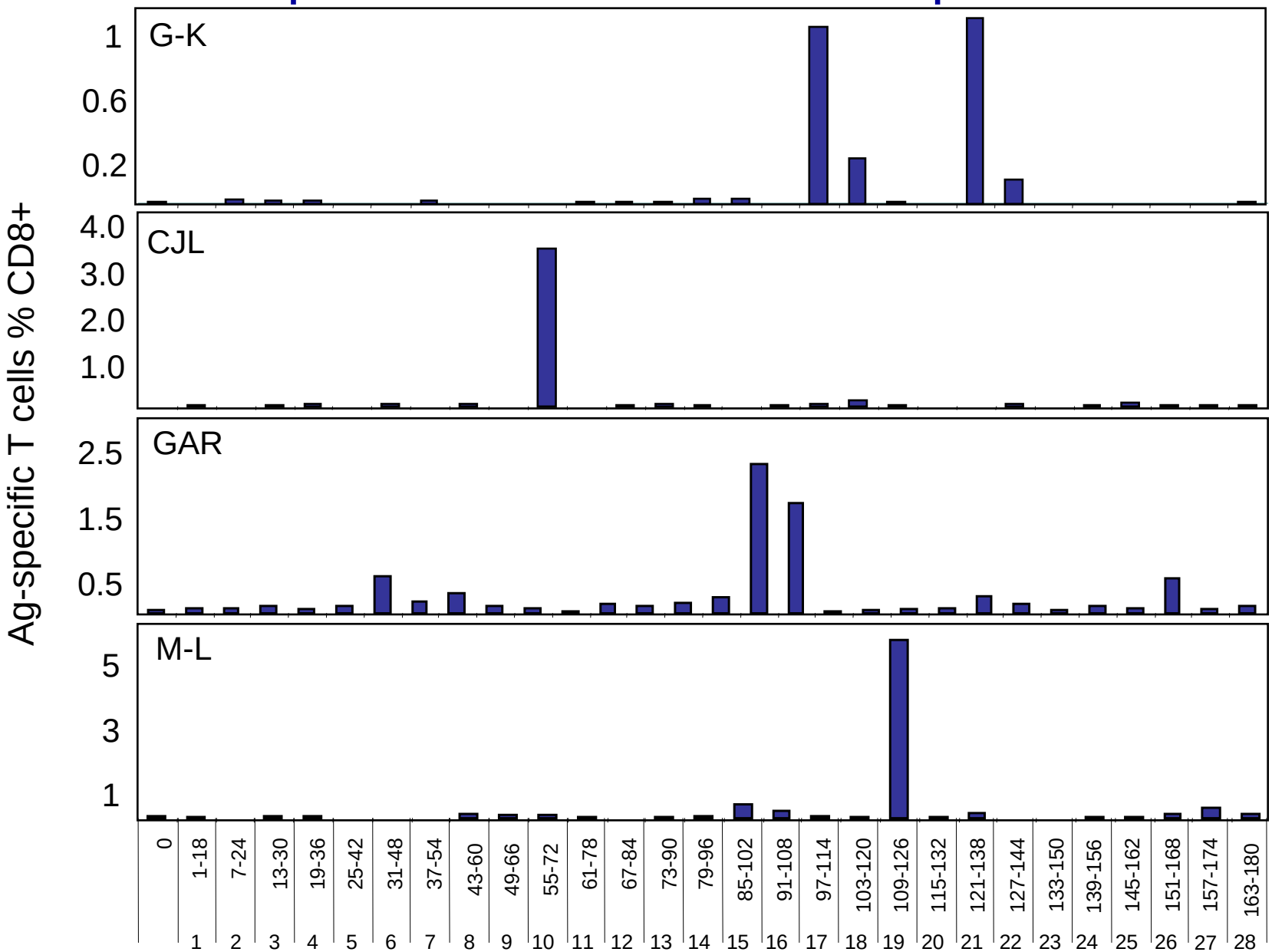
Immunodominant responses identified from a ISCOM/ESO vaccinated patient



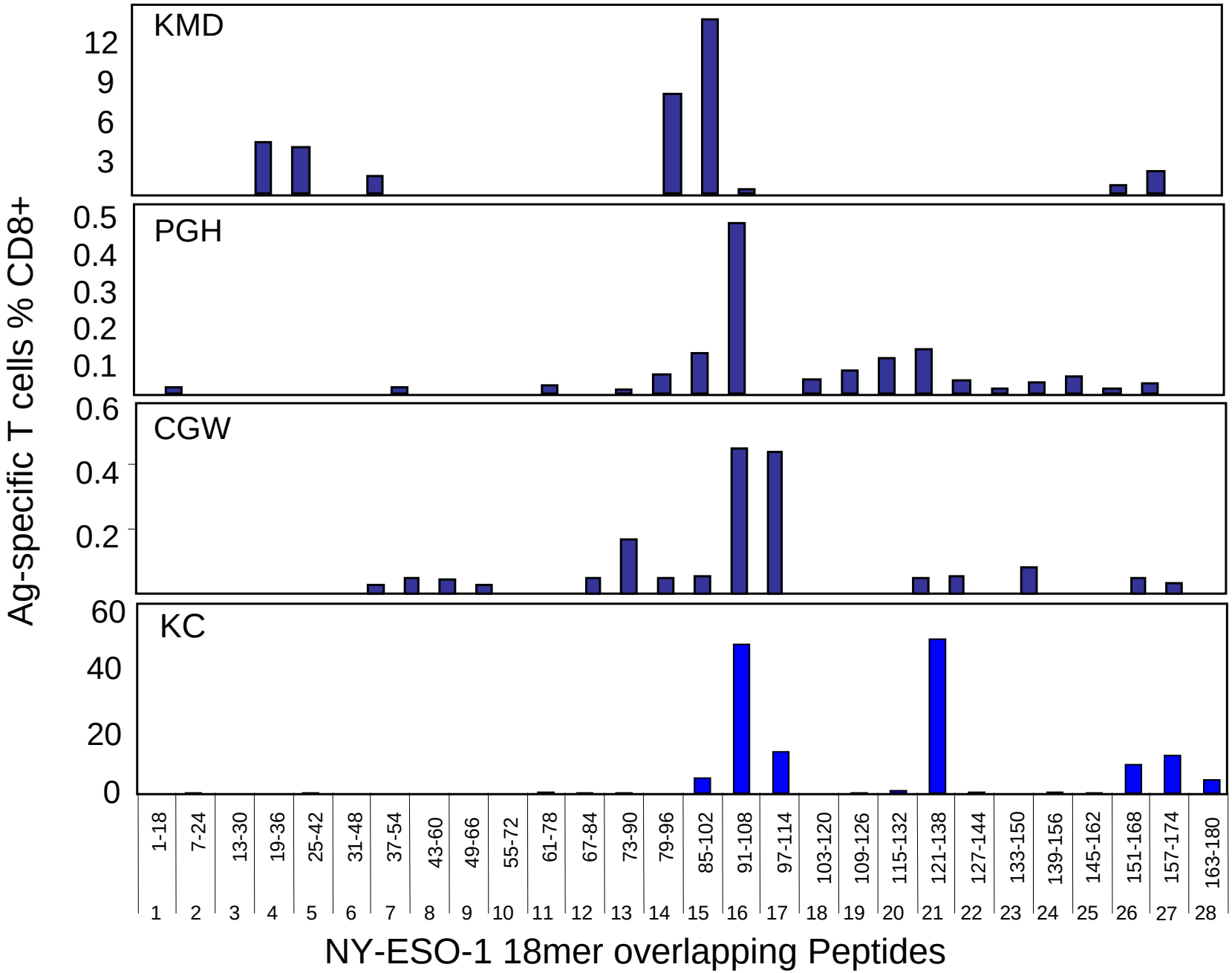
Immunodominant responses identified from a ESO/ISCOMATRIX™ vaccinated patient



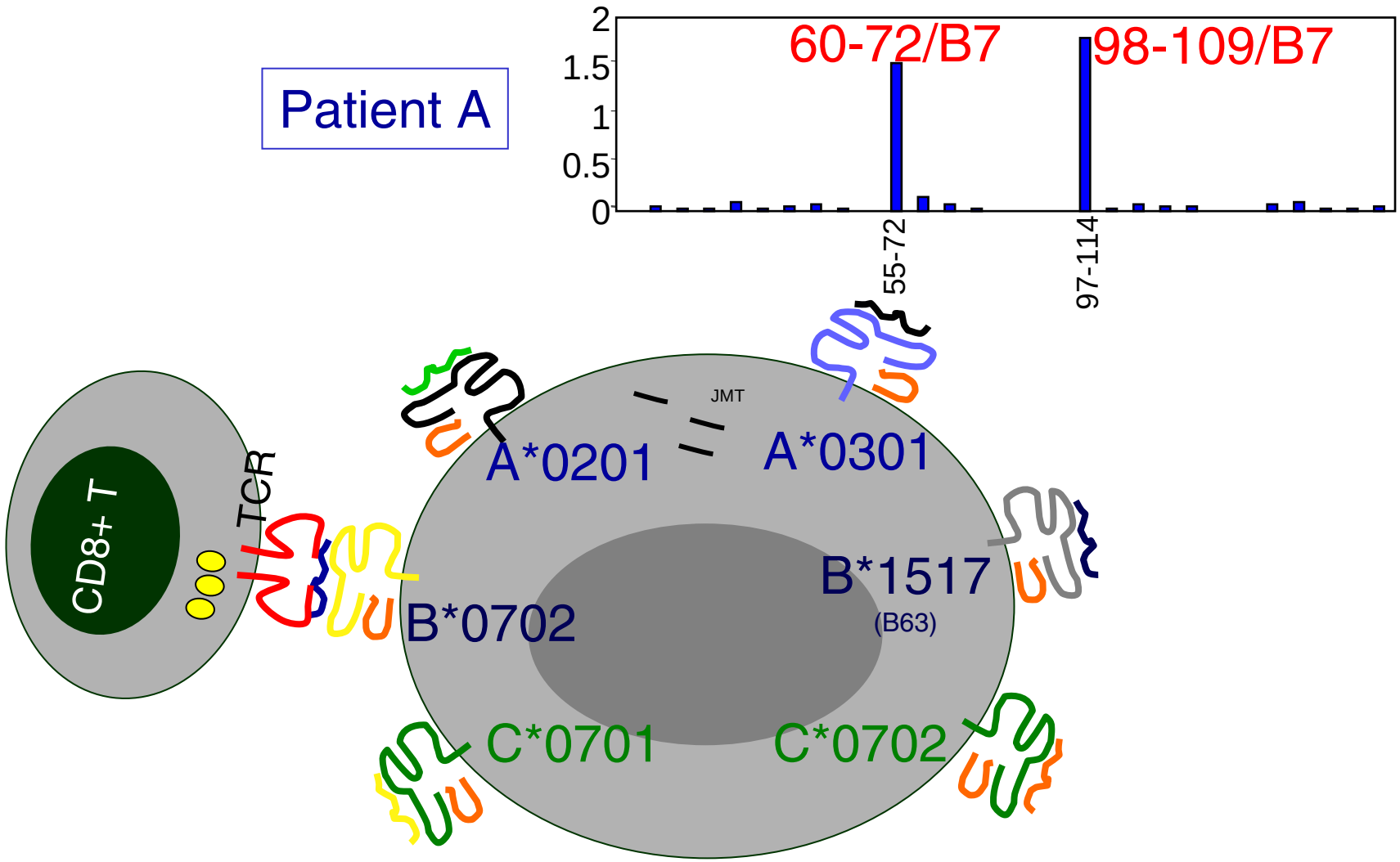
Spontaneous anti-ESO responses



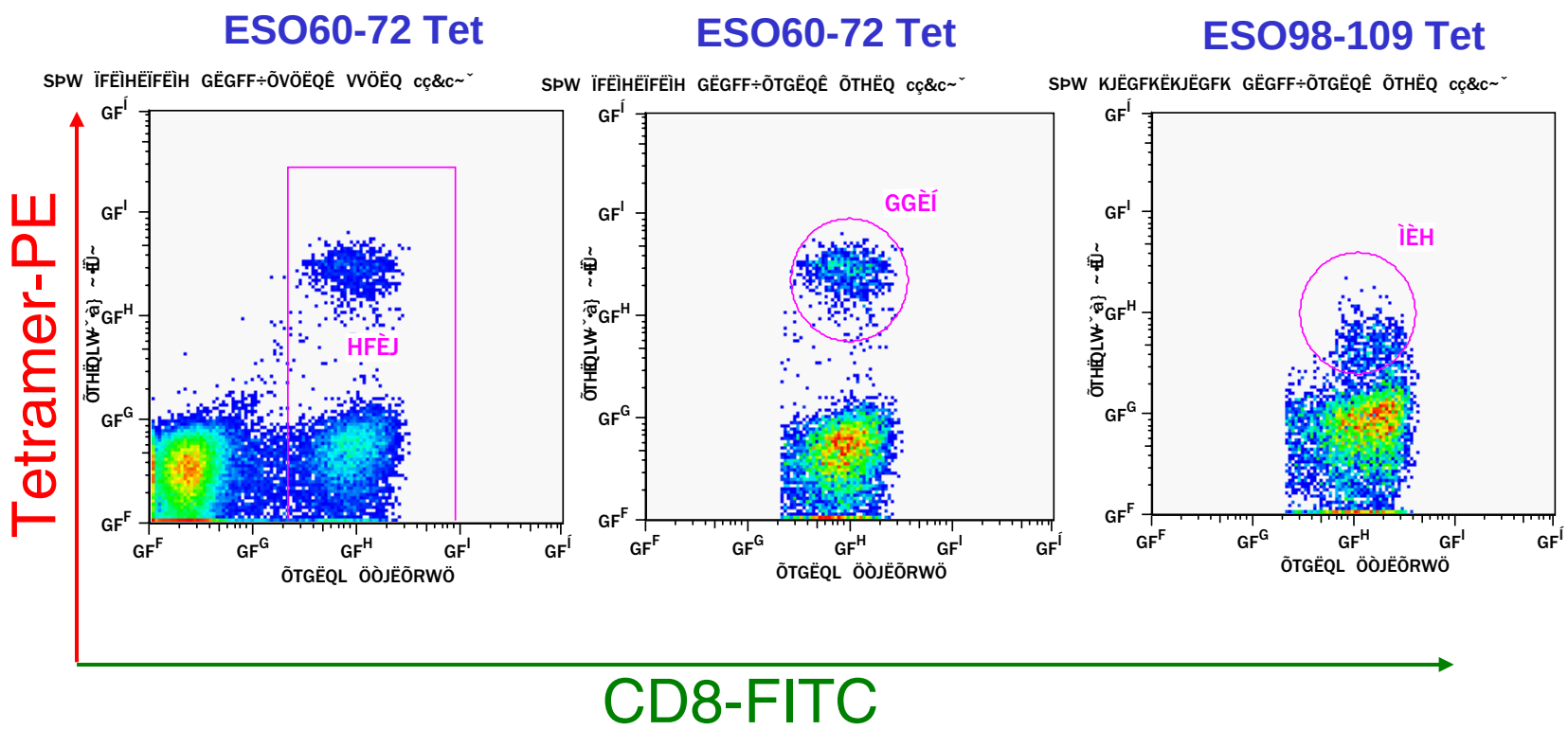
Spontaneous anti-ESO responses

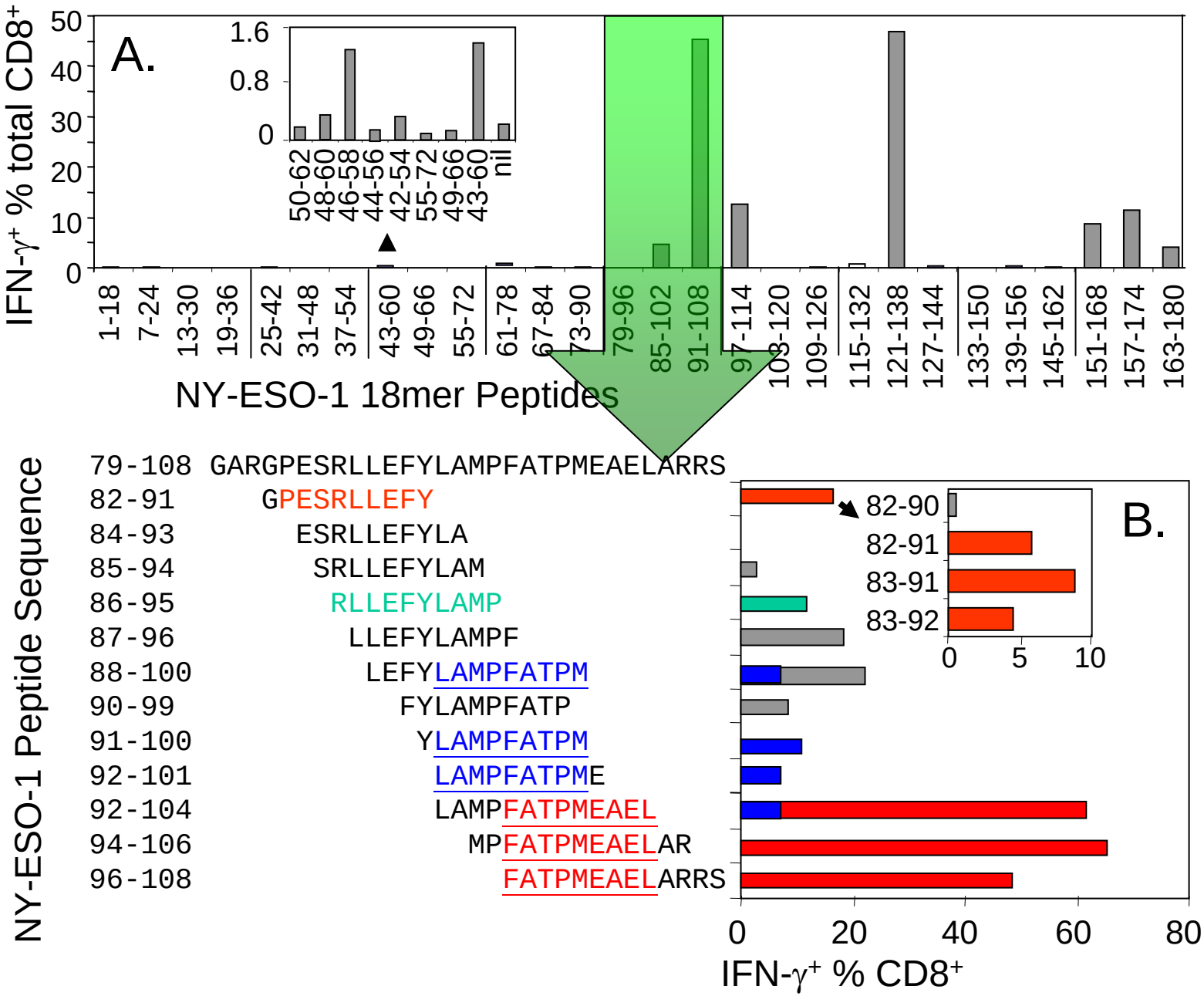


Emerging immunodominance pattern

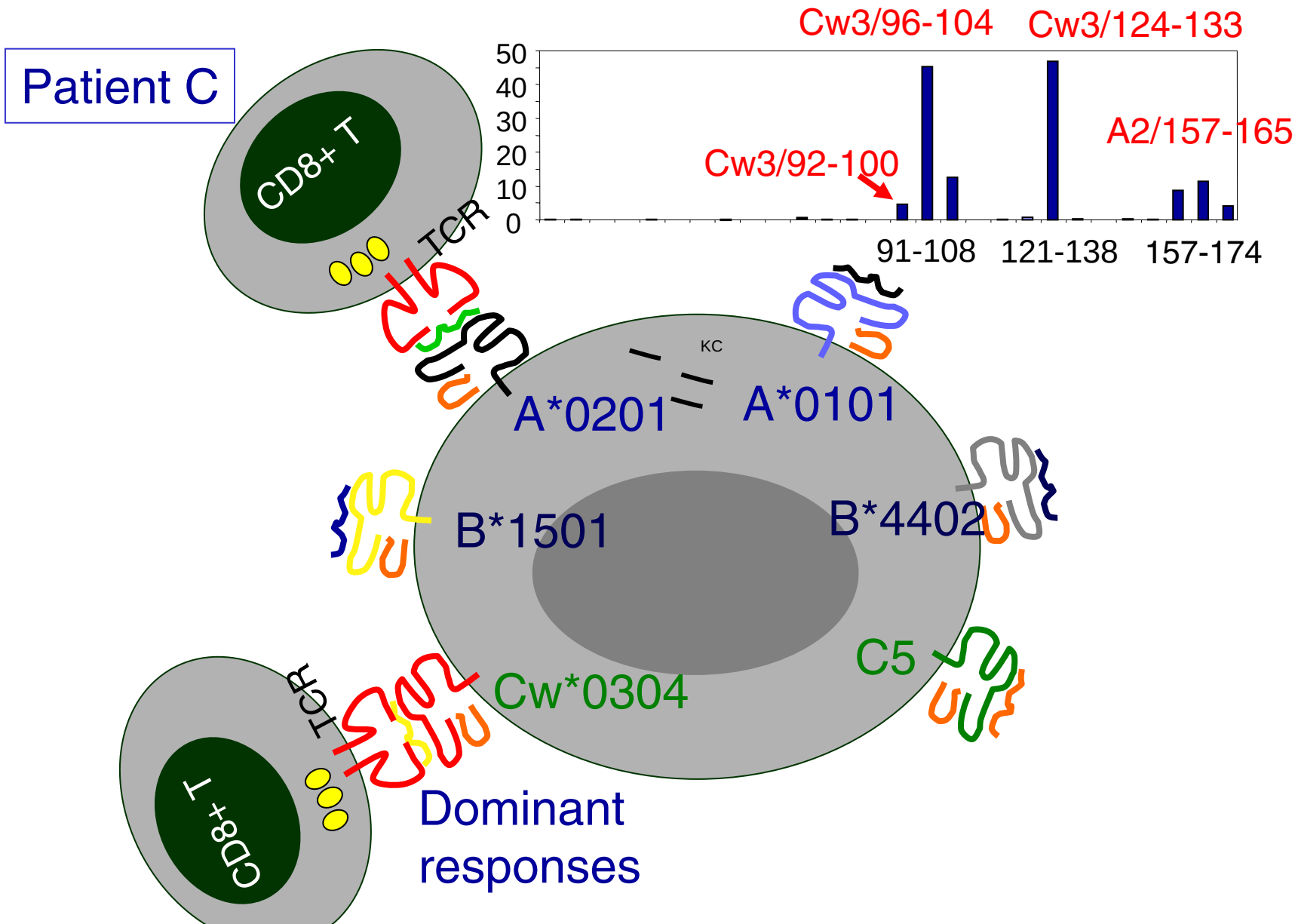


Tetramers incorporating long peptides confirm the original observations

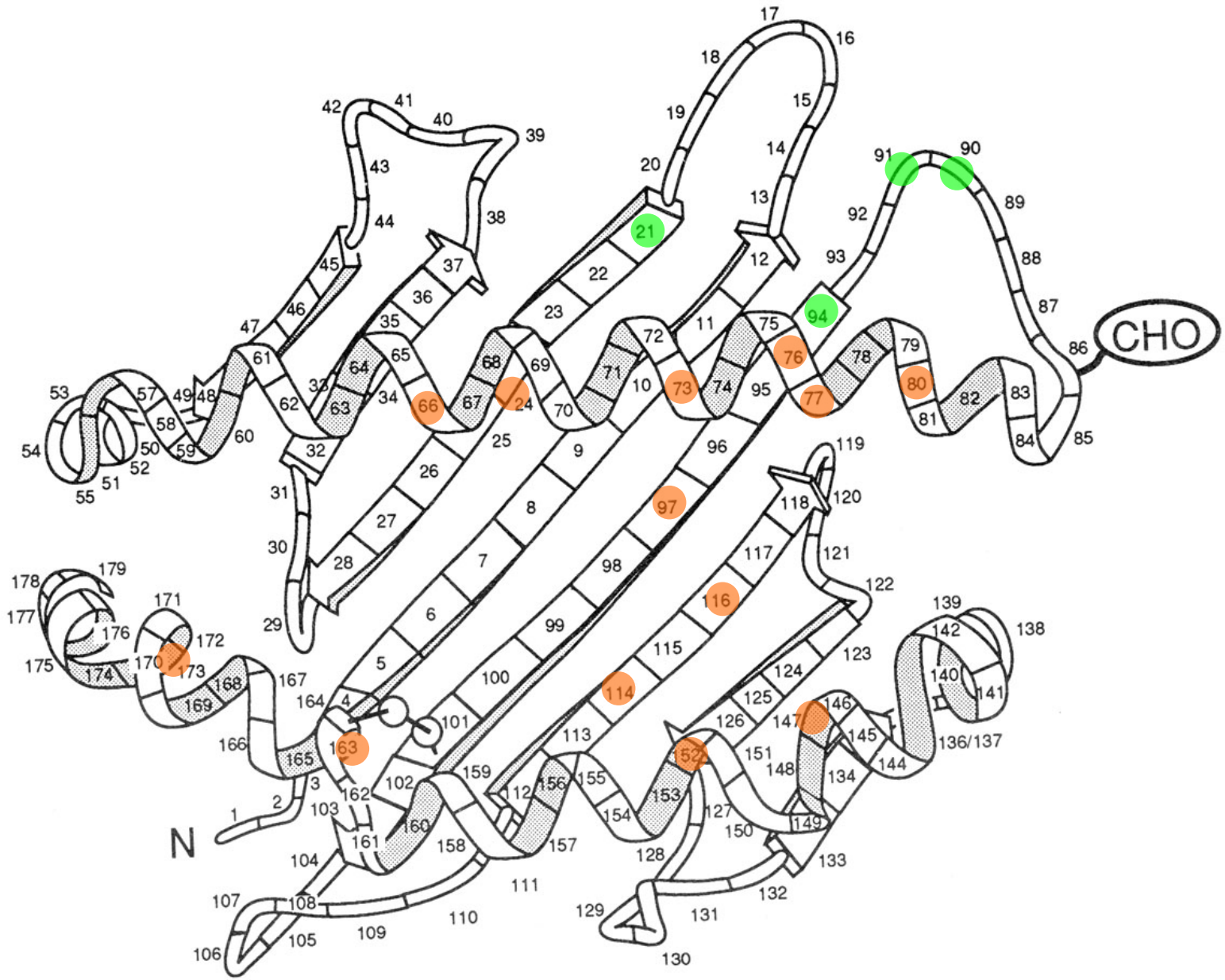



A.
IFN-γ+ % total CD8+
50
40
30
20
10
0
1.6
0.8
0
50-62
48-60
46-58
44-56
42-54
55-72
49-66
43-60
nil
1-18
7-24
13-30
19-36
25-42
31-48
37-54
43-60
49-66
55-72
61-78
67-84
73-90
79-96
85-102
91-108
97-114
103-120
109-126
115-132
121-138
127-144
133-150
139-156
145-162
151-168
157-174
163-180
NY-ESO-1 18mer Peptides
NY-ESO-1 Peptide Sequence
79-108 GARGPESRLLEFYLAMPFATPMEAELARRS
82-91 GPESRLLEFY
84-93 ESRLLEFYLA
85-94 SRLLEFYLAM
86-95 RLLEFYLAMP
87-96 LLEFYLAMPF
88-100 LEFYLAMPFATPM
90-99 FYLAMPFATP
91-100 YLAMPFATPM
92-101 LAMPFATPME
92-104 LAMPFATPMEAEL
94-106 MPFATPMEAELAR
96-108 FATPMEAELARRS
B.
82-90
82-91
83-91
83-92
0
5
10
0
20
40
60
80
IFN-γ+ % CD8+

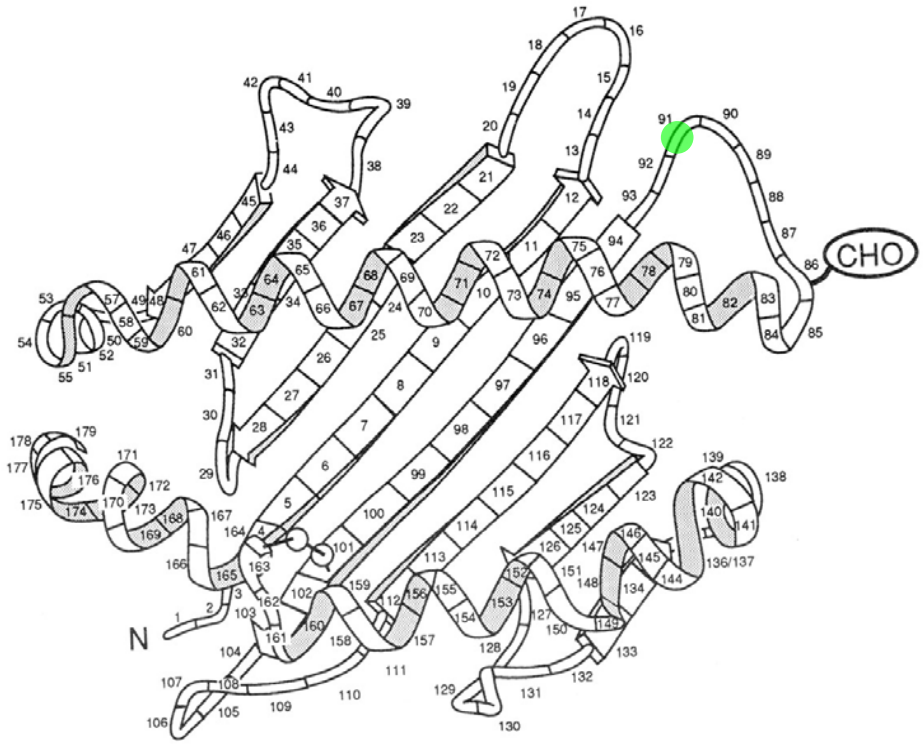
Emerging immunodominance pattern



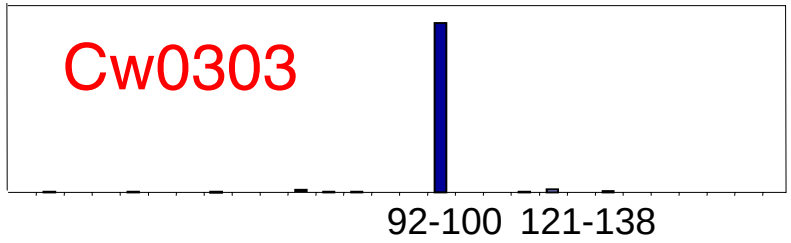
24 Cw3 sub-allele differences

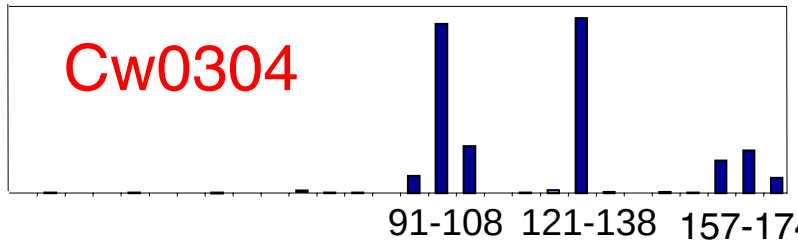


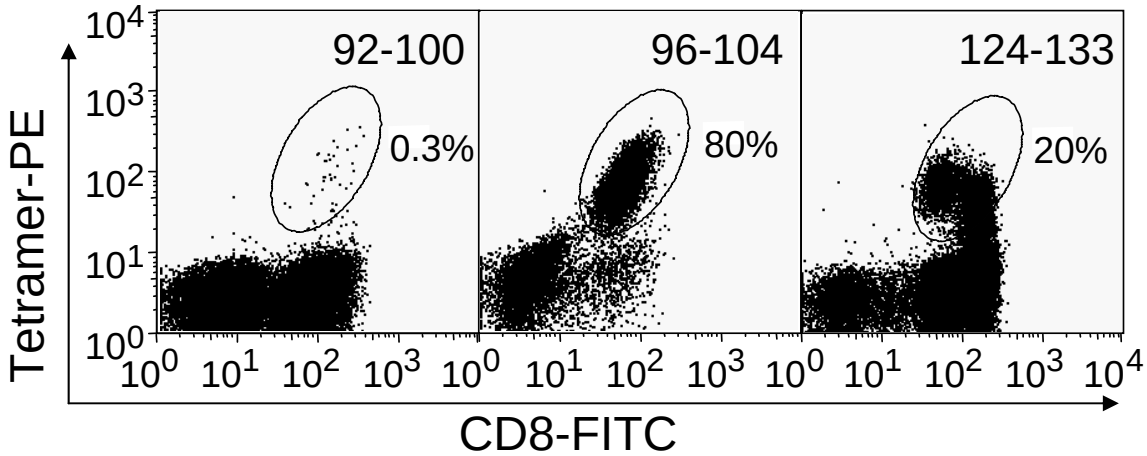
Cw0303(91R) vs Cw0304(91G)

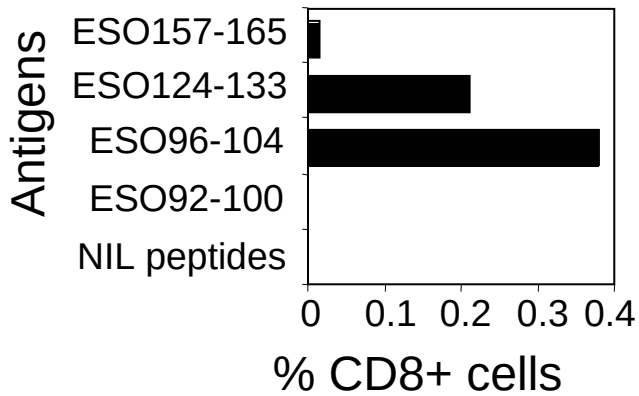


Published







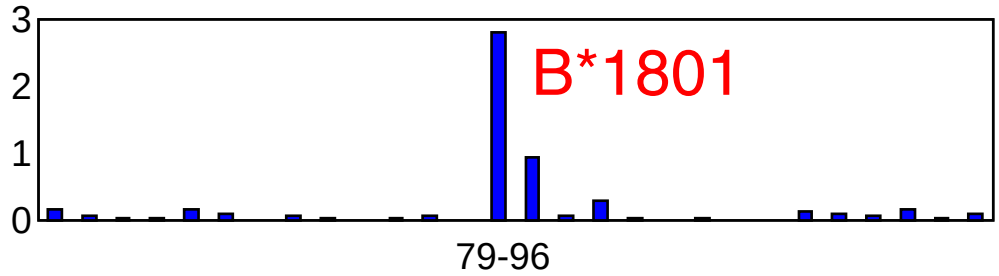


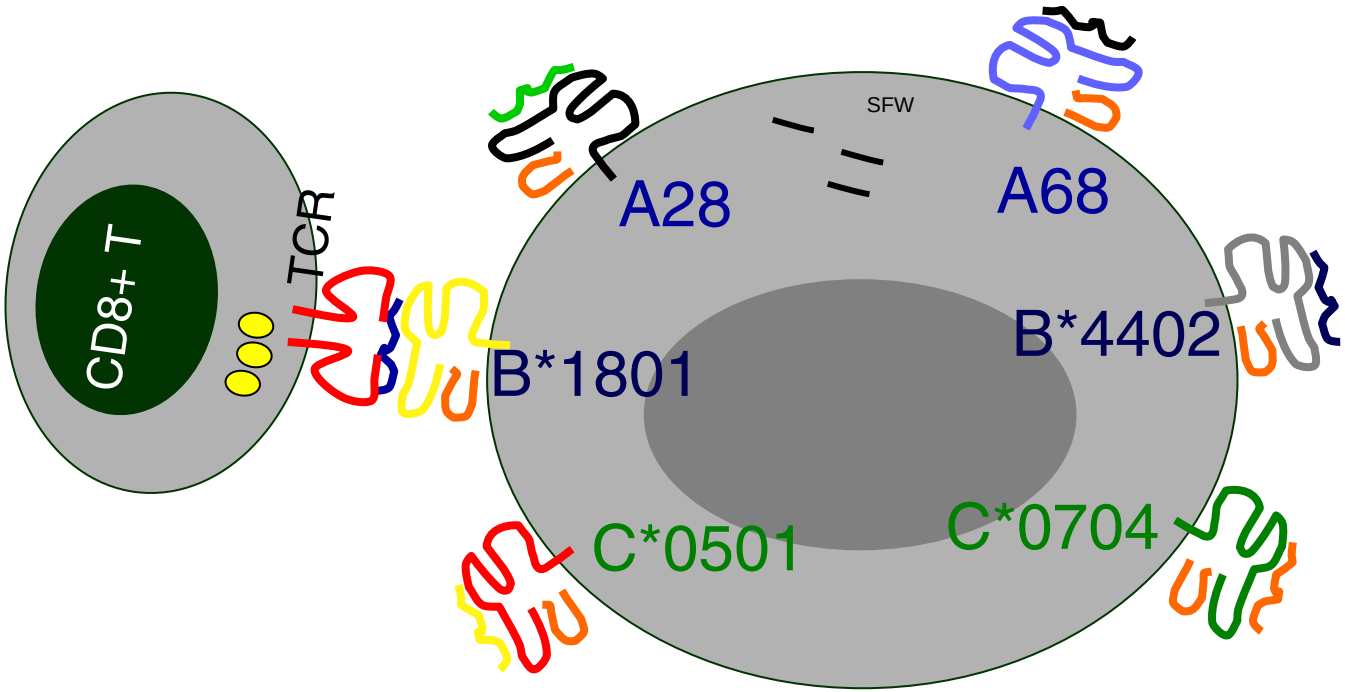
Screened Cw3+ melanoma patients

Tet/min epi +	92-100	96-104	124-133	Aby	
	ICS	ICS	ICS		
GB	+++	++	+	NT	Pattern 1
ML	++	++	+	+	
CGW	+++	++	+	-	
RGR	-	-	+	+	Pattern 2
PGH	+ pre	+ vac	-	?	Pattern 5
KC	+	+++	+++	+	Pattern 3
MDP	++	-	+++	-	Pattern 4
C3 min epi-/but Aby+					
AS	-	-	-	+	
RJB	-	-	-	+	
GAC	-	-	-	+	
XY	NT	-	-	+	
AC	-	-	-	+	

Emerging patterns could facilitate future vaccine design or T cell monitoring

Patient D





ESO88-96 is predicted for B4403 and Cw0701

Sum detected immunodominance patterns

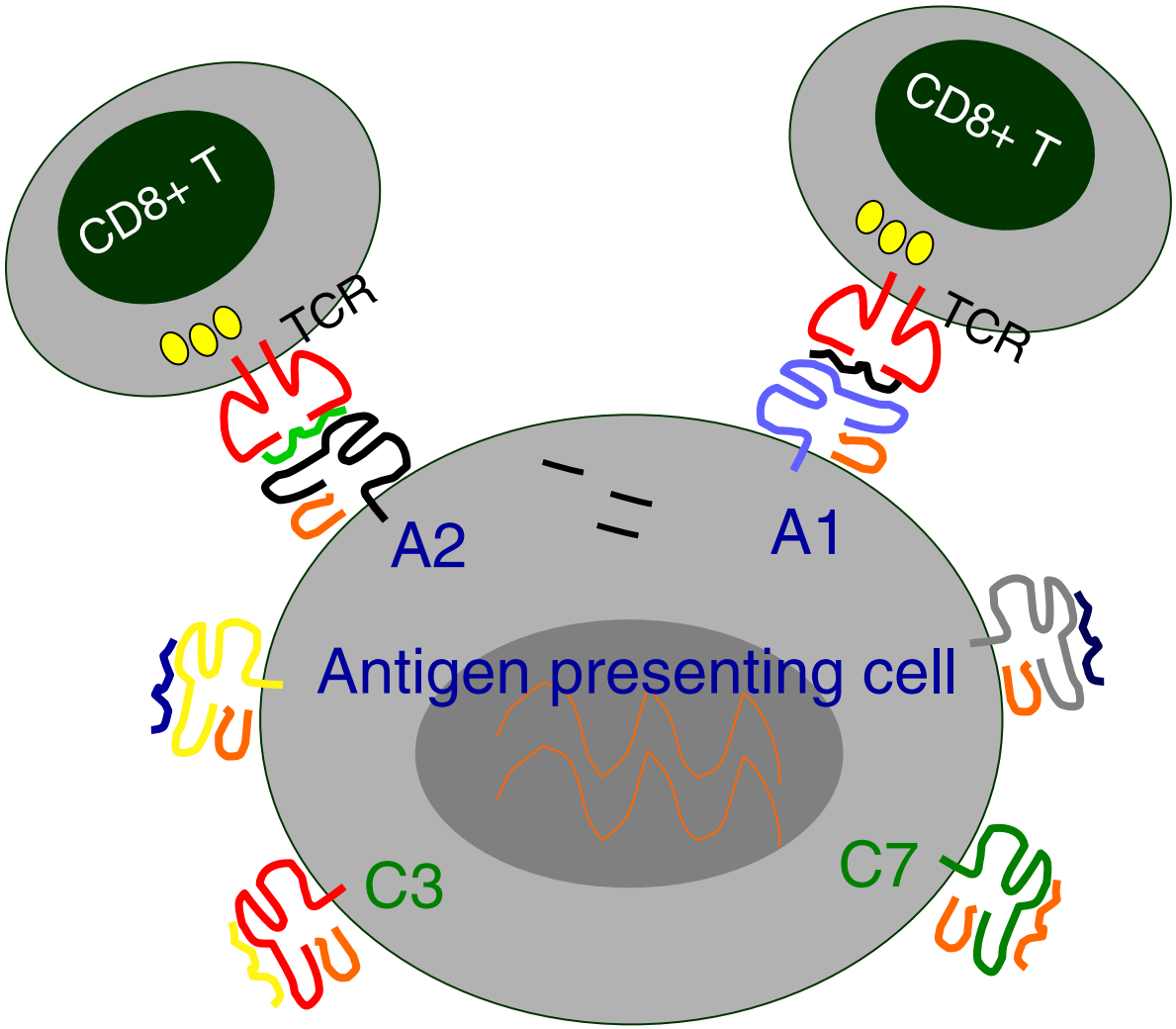
patient	HLA-A		HLA-B		HLA-C	
JMT	A2	A3	B7	B63	C7	C7
SFW	A1	A24	B18	B4402	C2	C7
K-C	A1	A2	B15	B4402	C3	C5
G-K (predicted)	A33	A66	B41	B4403?	C2	C6
KMD (predicted)	A2	A25	B18	B37	C6	C6
M-L (predicted)	A23	A32	B35	B49	C4	C7
H-H (predicted)	A1	A2	B8	B27	C1	C7
TRK (predicted)	A1	A11	B8	B60	C3	C7
MJV (predicted)	A1	A24	B8	B4405	C2	C7
KLE (predicted)	A2	A23	B7	B53	C4	C7
MEM	A1	A2	B8	B44	C5	C7
CJL (predicted)	A2	A23	B7	B44	ND	ND

immunodominant

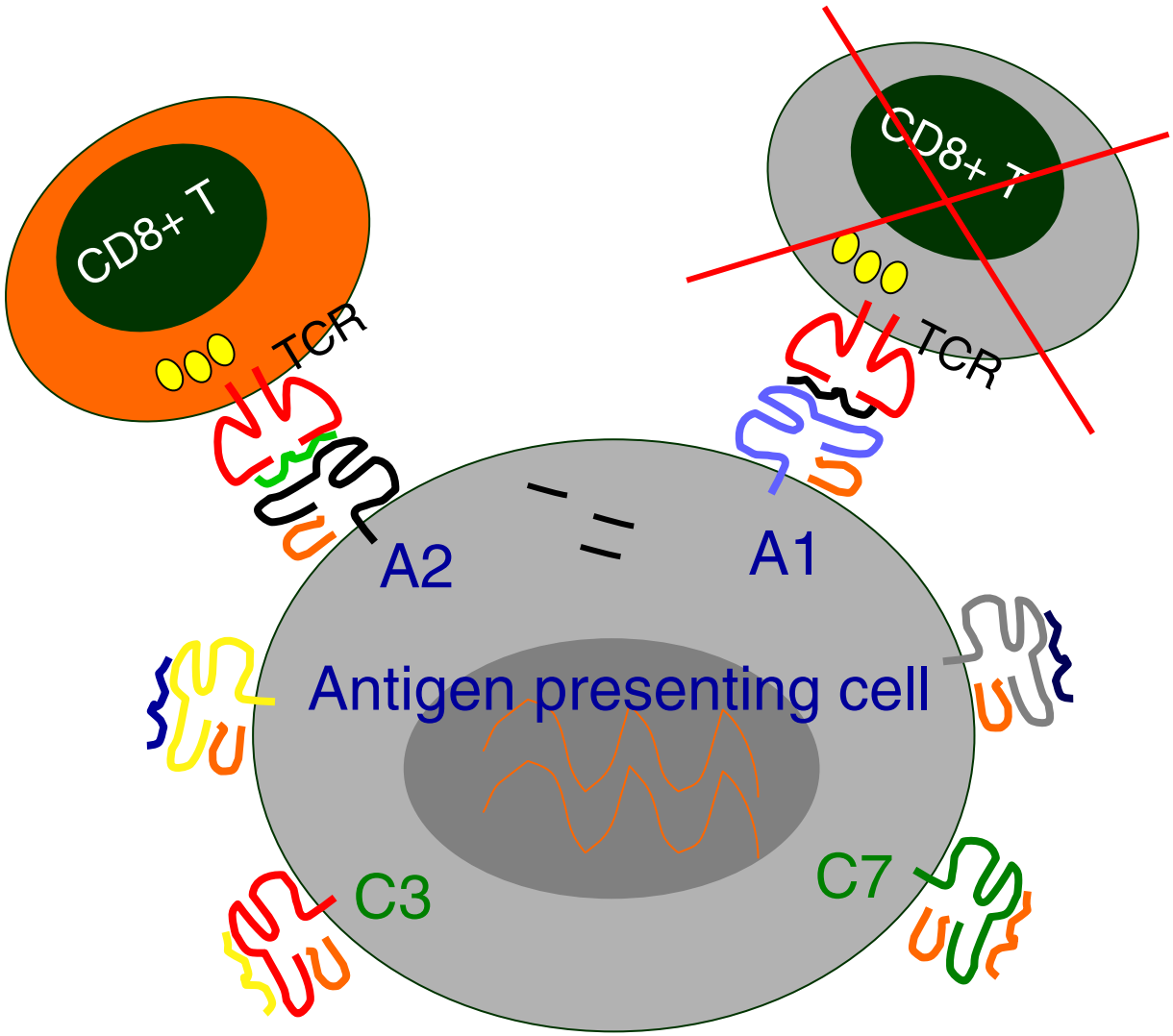
Subdominant

7/12 A2+

Immunodomination



Immunodomination?



Summary

- Systematic T cell monitoring identifies interesting T cell epitopes—13mer/B*0702
- Striking immunodominance hierarchy observed for both vaccinated and naturally occurred anti-ESO CD8+ T cell responses
- The acquired knowledge may help us in future vaccine design and T cell monitoring

Acknowledgements

LICR, Melbourne branch

Jonathan Cebon, Ian Davis

T cell Lab

Heather Jackson, Nektaria Dimopoulos, Qiyuan Chen, Nicole Mifsud, Bee Tan

DC Bubble

Juliet Quirk, Leone Morris, Tsin Yee Tai

CSL

Eugene.Maraskovsky, Lena Miloradovic

LICR, Lausanne branch

Immanuel Luescher, Philippe Guillaume

LICR, New York branch

Lloyd Old, Sacha Gnjatic, Gerd Ritter