Introduction For Transplant Immunology: an Update

EPLET MisMatching

A New Era of Allo-Tissue Typing

Dr Gamal Saadi

Prof of Int Med & Nephrology

Cairo University

SHORT-TERM SURVIVAL

- Delayed allograft function
- Human leukocyte antigen antibodies
- Type of kidney
- Center effect
- Donor age
- Donor illness
- Dialysis and preemptive transplantation

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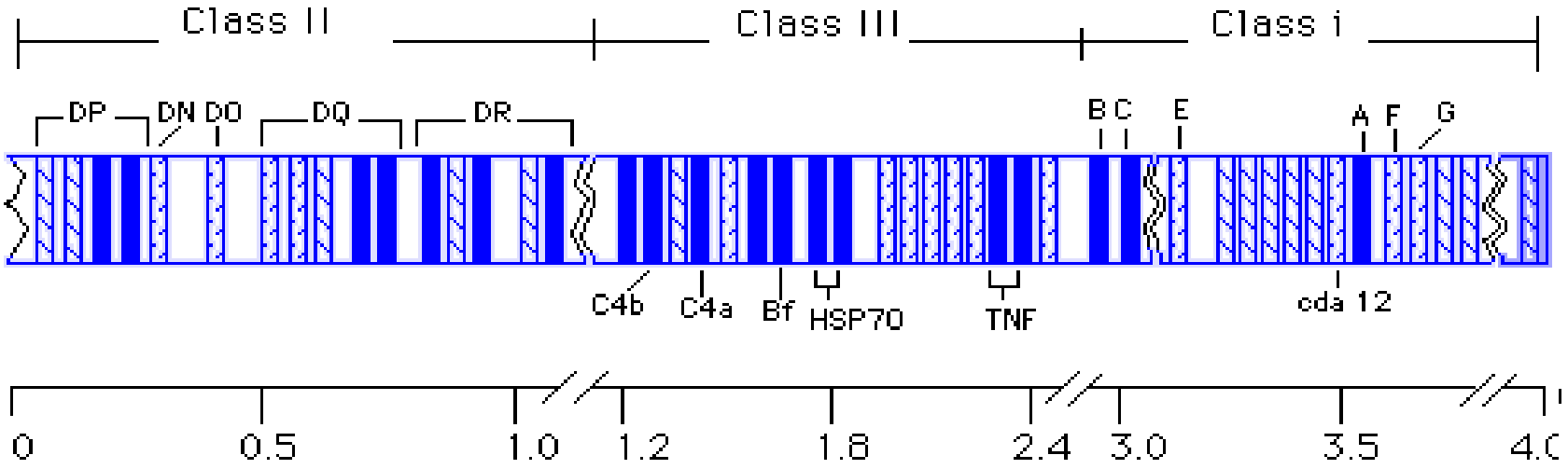
Human Major Histocompatibility HLA Complex



Expressed genes

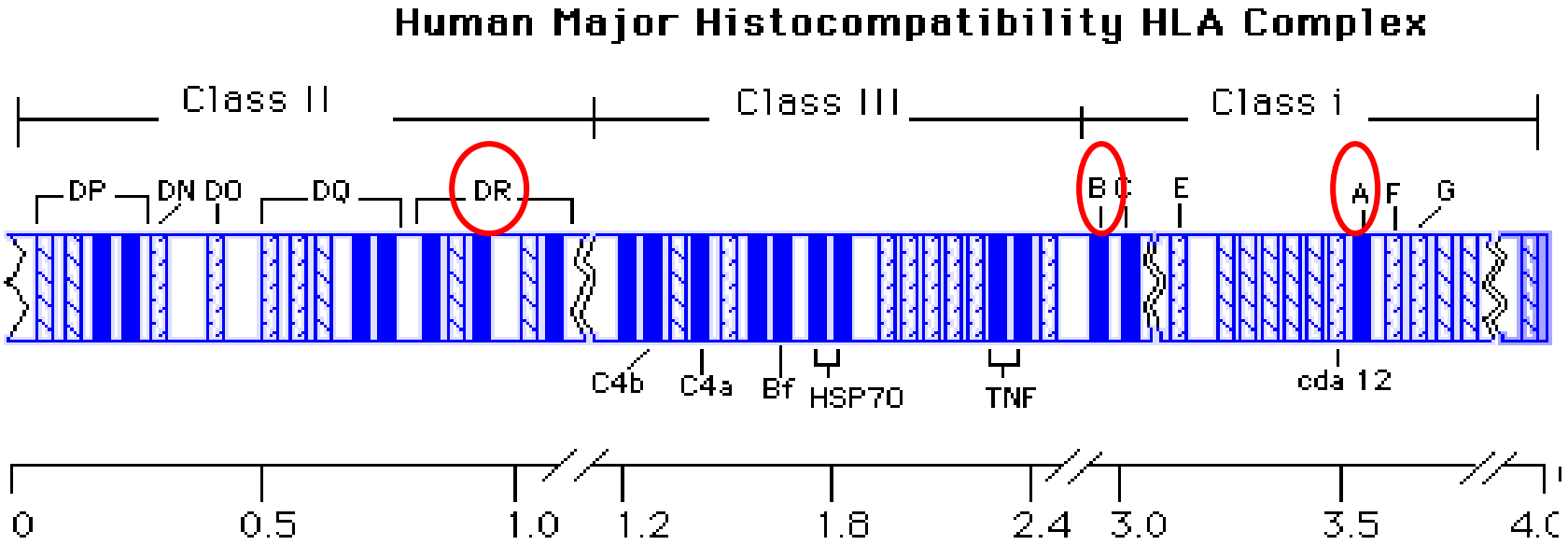
Unknown Status

Pseudogenes genes (which are homologous to expressed genes occurring elsewhere in the genome)

Class 1 antigens
Glycoproteins (40 ro 45kD) see figure 7.7

Class II antigens

Short limb of Chromosome 6



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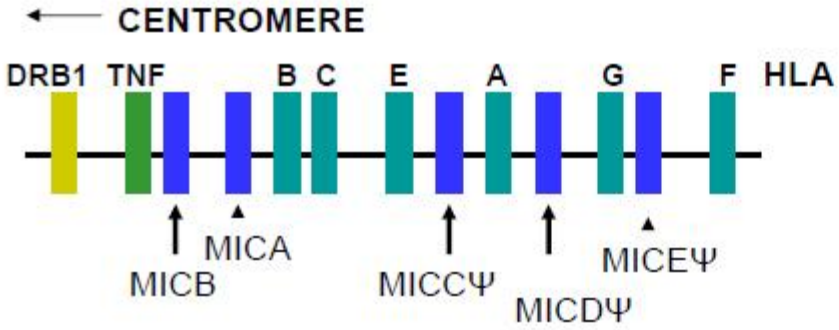
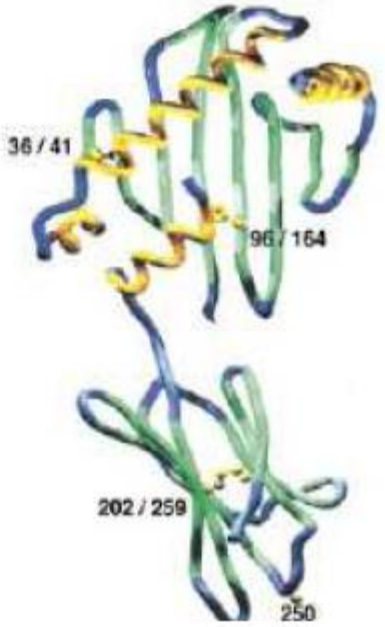
Short limb of

Chromosome 6

MIC Molecules





POLYMORPHISM

MICA 77 alleles
MICB 29 alleles (Release 3.6.0)
Nucleotide substitution in exons 2, 3 y 4 coding the extracellular domains α1, α2 y α3.
Exon 5 TM (GCT→A) variable tandem repeat polymorphism
Antibody detection by BAA based on Luminex platform

www.ebi-ac.uk/cgi-bin/imgt/hla/

Recent Res. Devel. Human Genet., 3(2005): 95-145 ISBN: 81-7736-244-5

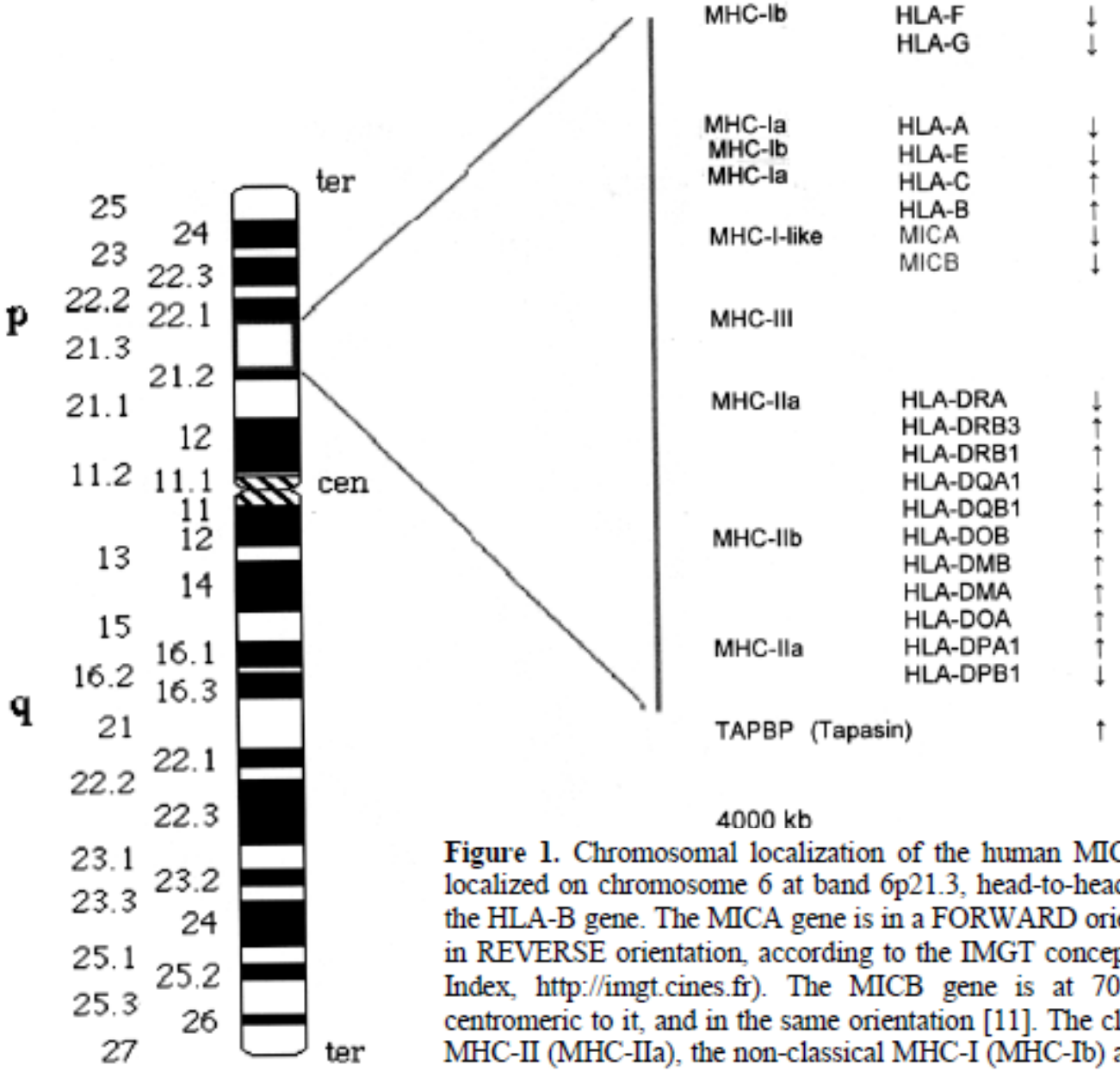
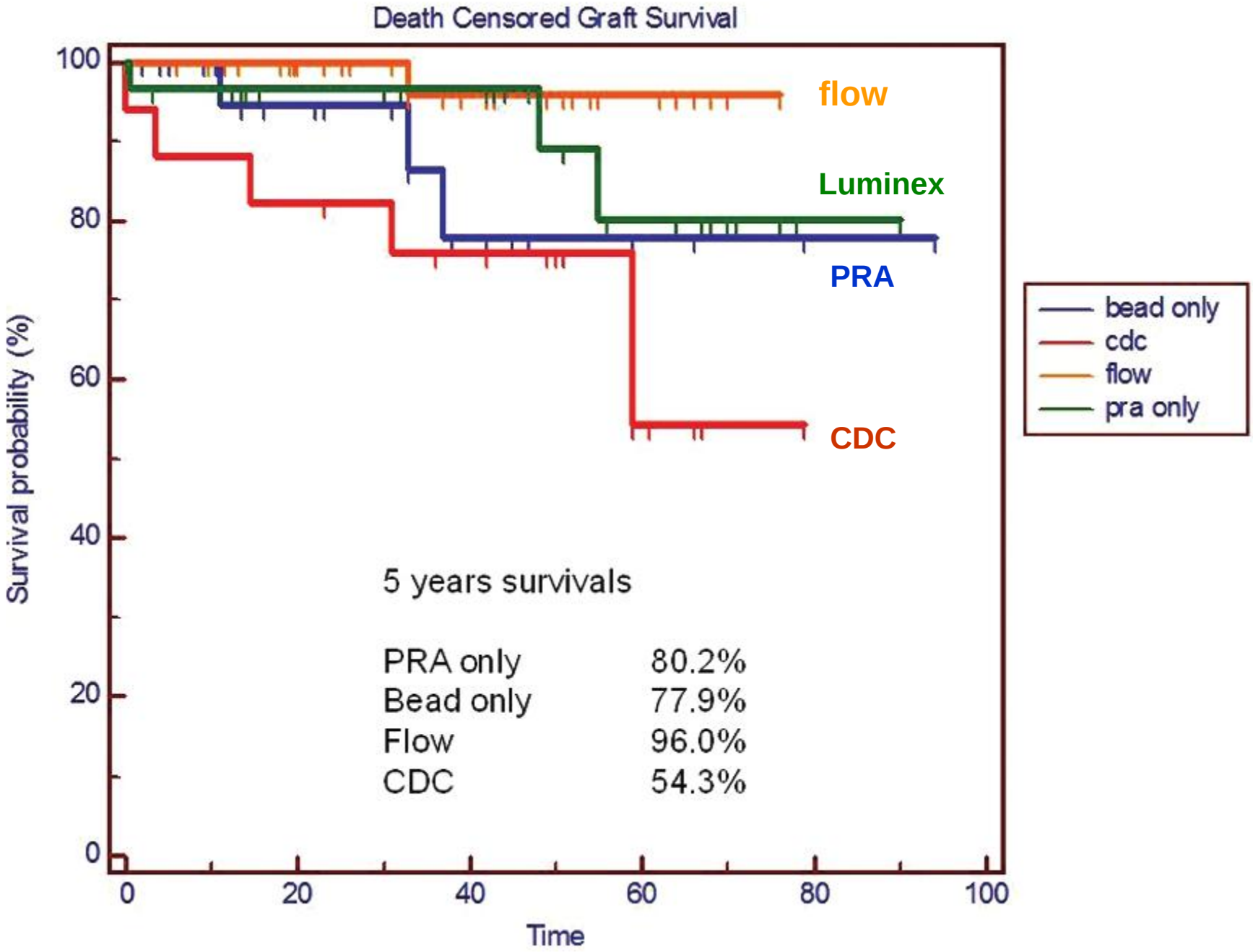
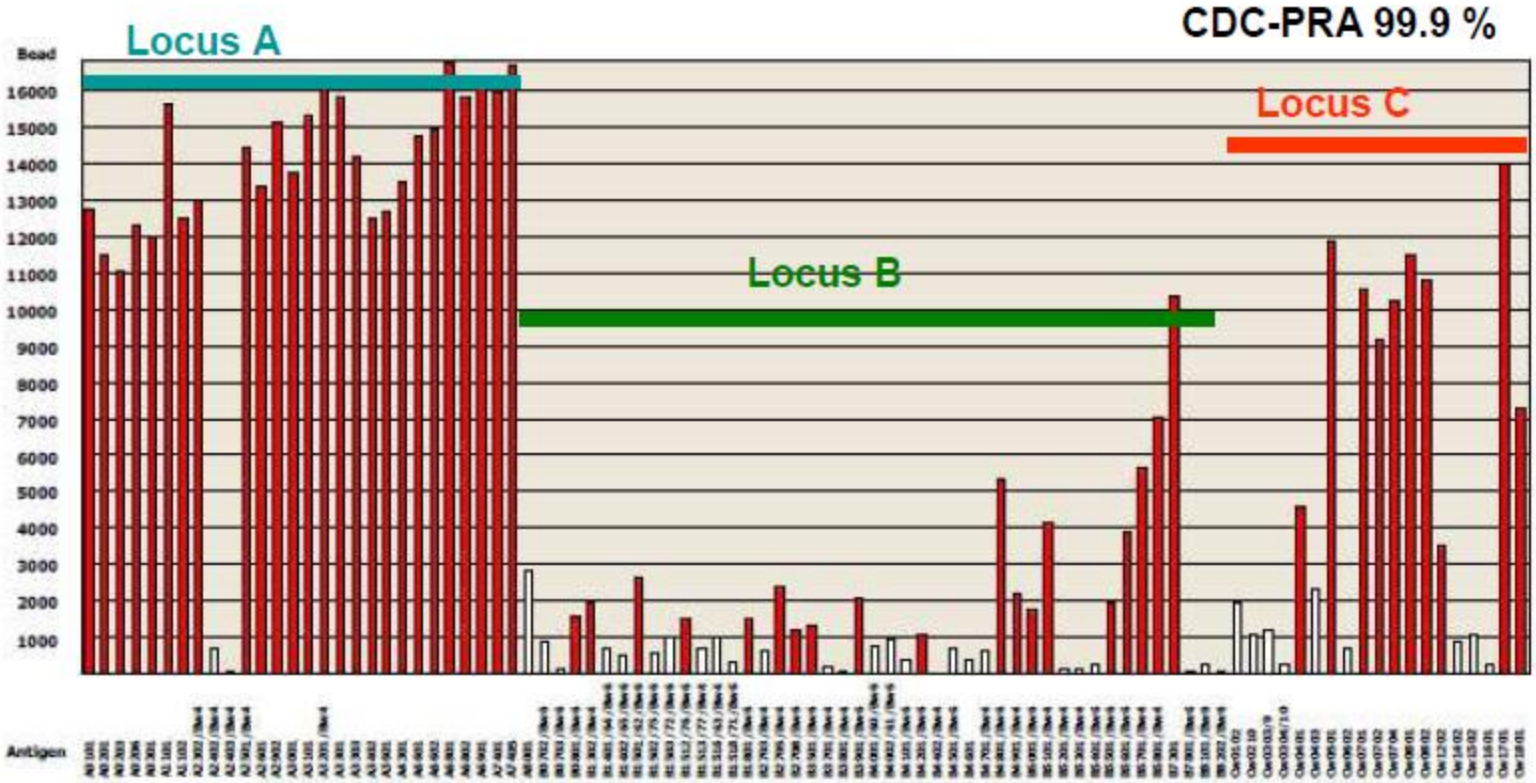


Figure 1. Chromosomal localization of the human MICA gene. The MICA gene is localized on chromosome 6 at band 6p21.3, head-to-head and 46.4 kb centrometric to the HLA-B gene. The MICA gene is in a FORWARD orientation, and the HLA-B gene in REVERSE orientation, according to the IMGT concept of ORIENTATION (IMGT Index, http://imgt.cines.fr). The MICB gene is at 70 kb from the MICA gene, centromeric to it, and in the same orientation [11]. The classical MHC-I (MHC-Ia) and MHC-II (MHC-IIa), the non-classical MHC-I (MHC-Ib) and MHC-II (MHC-IIb) genes are shown. Gene orientation is shown by arrows.

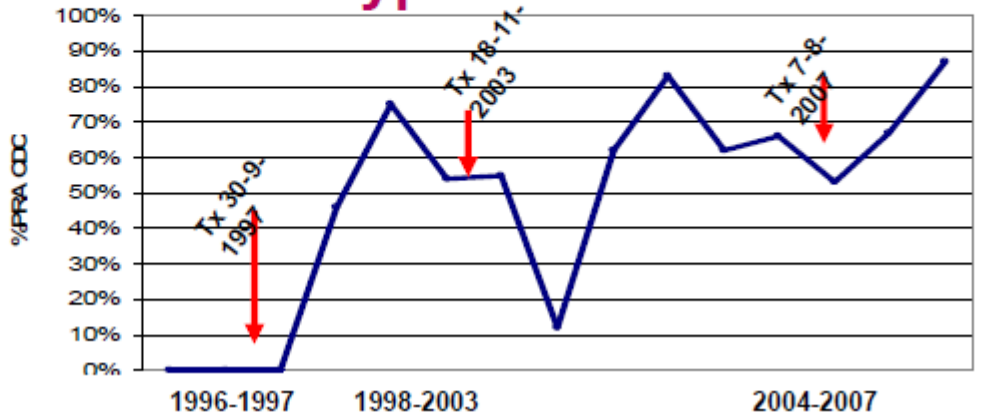

Death Censored Graft Survival
Survival probability (%)
100
80
60
40
20
0
0
20
40
60
80
100
Time
flow
Luminex
PRA
CDC
5 years survivals
PRA only 80.2%
Bead only 77.9%
Flow 96.0%
CDC 54.3%
bead only
cdc
flow
pra only

Antibodies anti HLA by SA-BAAssays
Definition of non acceptable mismatches
"Virtual Crossmatch"

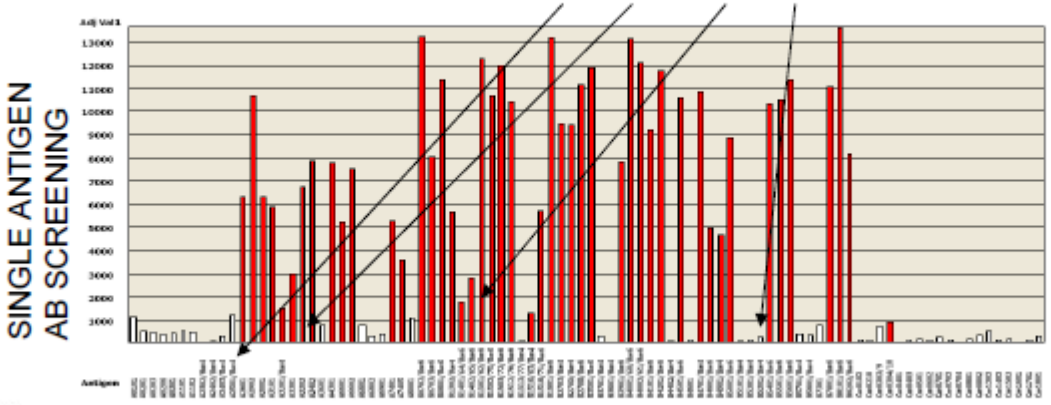


Use Of The Virtual Crossmatch Results To Select A Acceptable Donor For A Hyperimmunised Patient

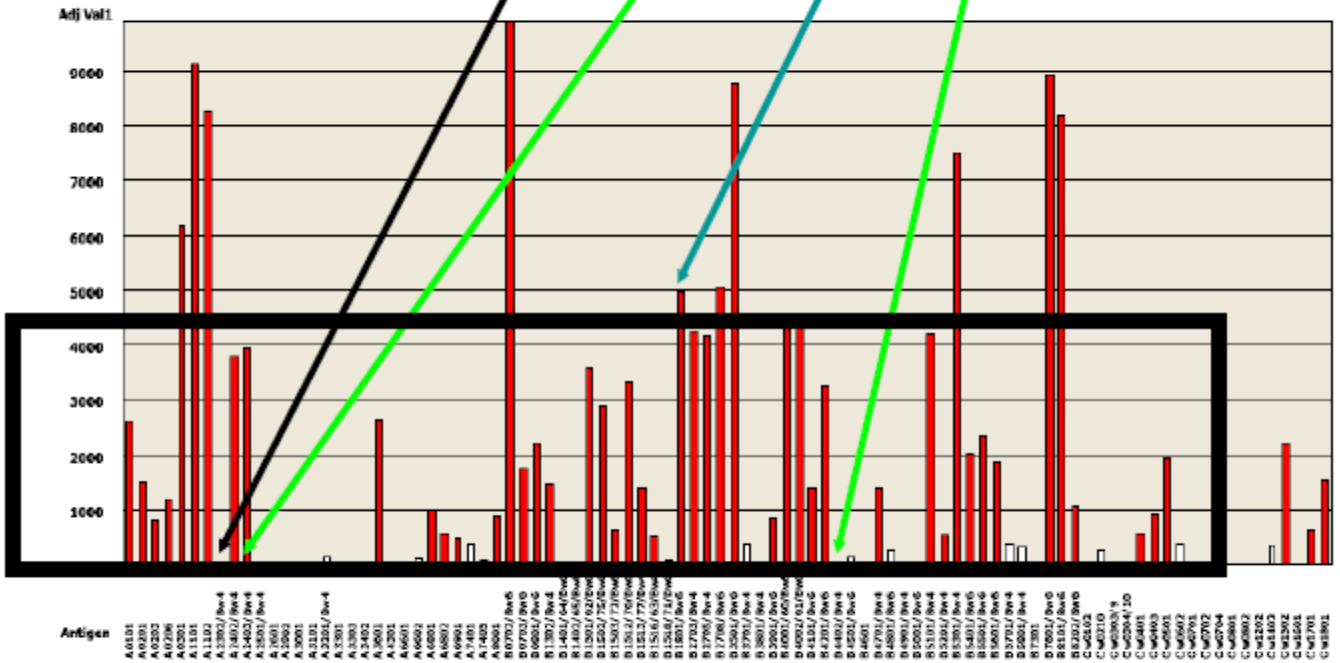
Patient 13024
Male 32y
HLA A*02,*11; B*44,*51;
DRB1*01,*07;
MICA*004



Donor **1st Tx 30/09/1997** **HLA A2, A29; B52, B13; DR1,DR13**
2º Tx 18/11/2003 **HLA A*02,*11; B*35,*53; DRB1*01,*11**
3rd Tx 8/08/2007 **HLA A*02,*24; B*14,*58; DRB1*07,*11**



Patient 6092: HLA A*26,A*31,B*1402,B*49,DRB1*01,*11
Donor 6092D3; A*23,A*25, B*18,B*44, DRB1*13,*15



22/02/2007 PRA-CDC 56 % Anti- A3, B40, B51

Crossmatch: XM-CDC Negative; XM-FCM Negative

FAMHS Program

(Finding Acceptable Mismatches for Highly Sensitized)

Aproved Oct-2006 Consultant Committee on Renal Trasplantation of Catalonia

AIM: To improve the probability to receive a graft, and the probability to increase graft survival in highly sensitized patients.

Patients with PRA>50 %

Single Antigen will be used to define:

- **Non Acceptable Missmatches. (NONAM)**
- **Acceptable Missmatches (AM)**

LONG-TERM SURVIVAL

- Alloantigen-dependent factors
  - Episodes of acute rejection
  - Human leukocyte antigen matching
  - Sensitization
- Alloantigen-independent factors
  - Tissue injury
  - Inadequate renal mass
  - Drug noncompliance
  - Posttransplant hypertension
  - Hyperlipidemia
  - Recurrent or de novo glomerular disease
  - Type of kidney donor
  - Gene polymorphisms
  - Ultrasonographic resistive index
  - Hyperhomocysteinemia
  - Proteinuria

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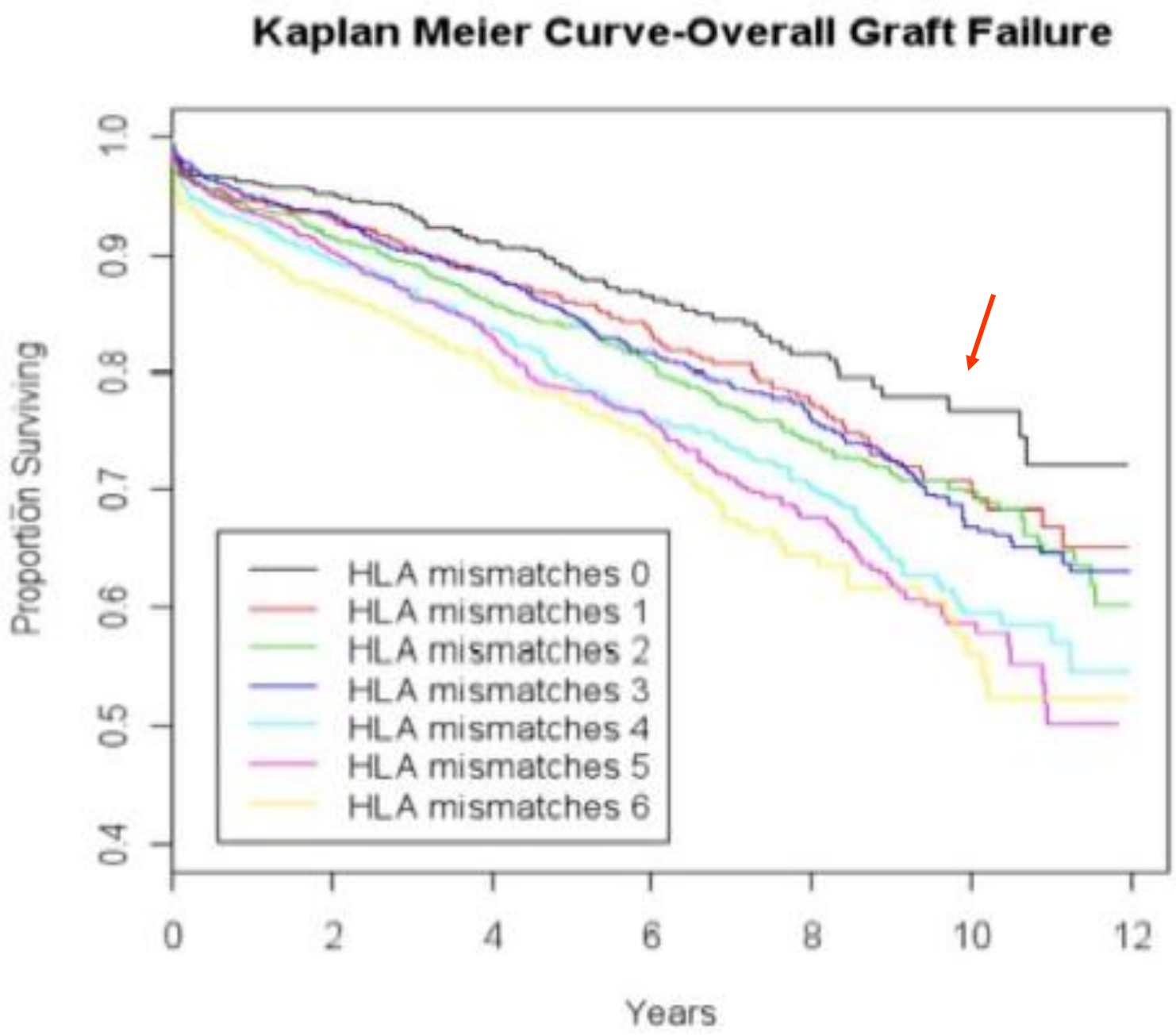

Kaplan Meier Curve-Overall Graft Failure
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
HLA mismatches 0
HLA mismatches 1
HLA mismatches 2
HLA mismatches 3
HLA mismatches 4
HLA mismatches 5
HLA mismatches 6
0
2
4
6
8
10
12
Years

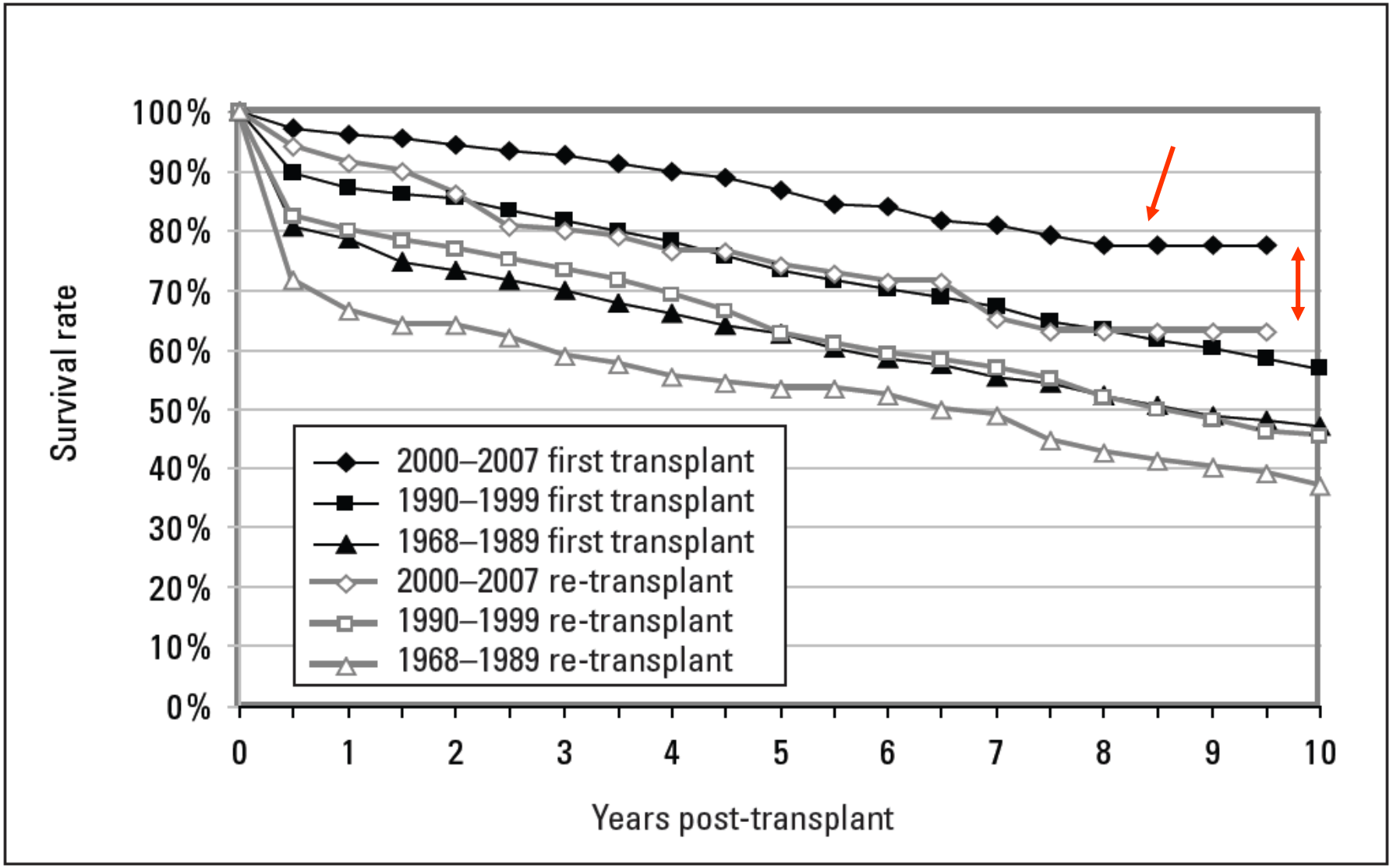


Figure 1. Graft survival for kidney transplants by graft number and year of transplant, 1968–2007.

Source: BC Transplant

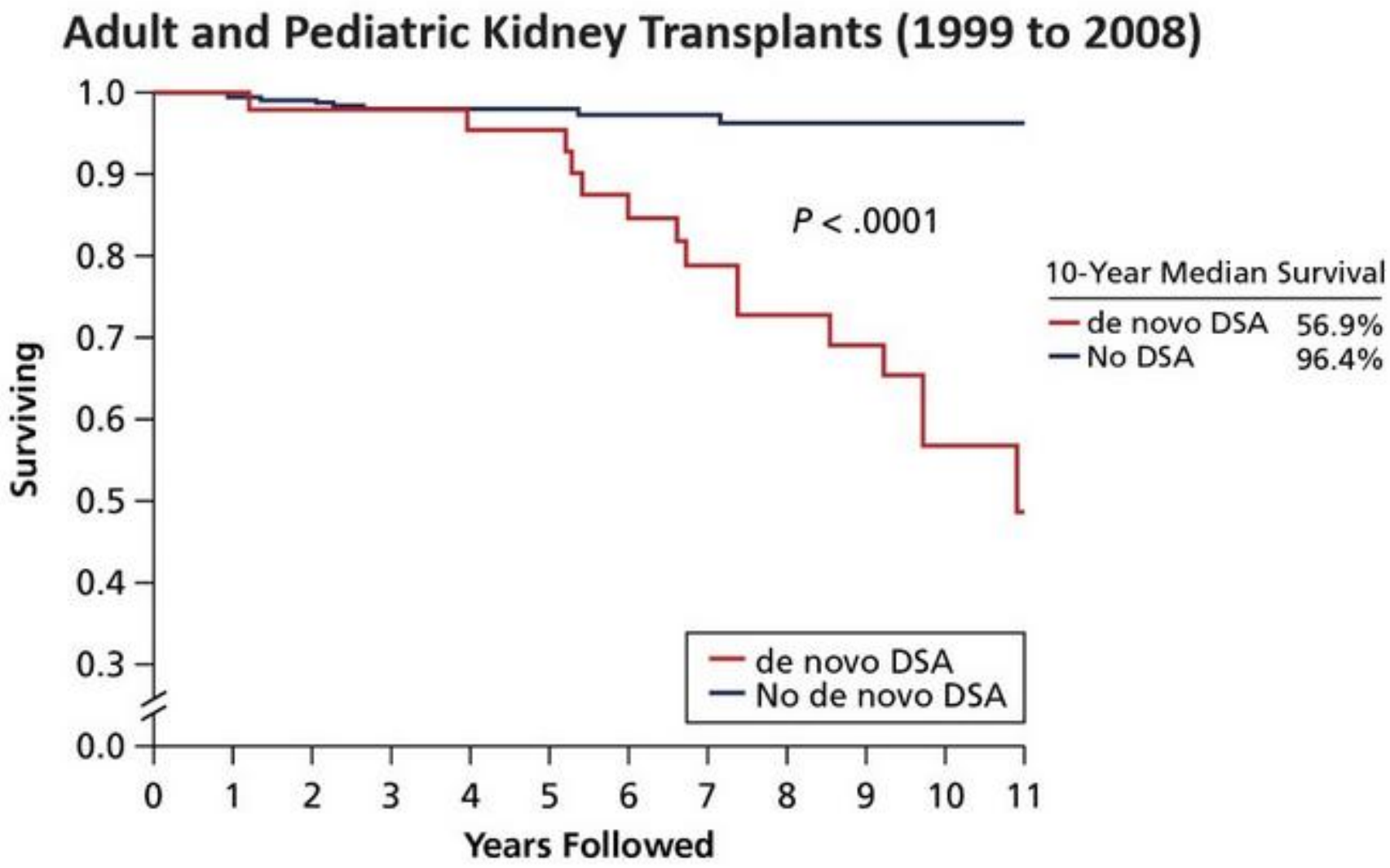
Allo-typing

- zero-antigen mismatches have the highest success rates
- Still with a zero mismatch results are not optimal

Allo-typing

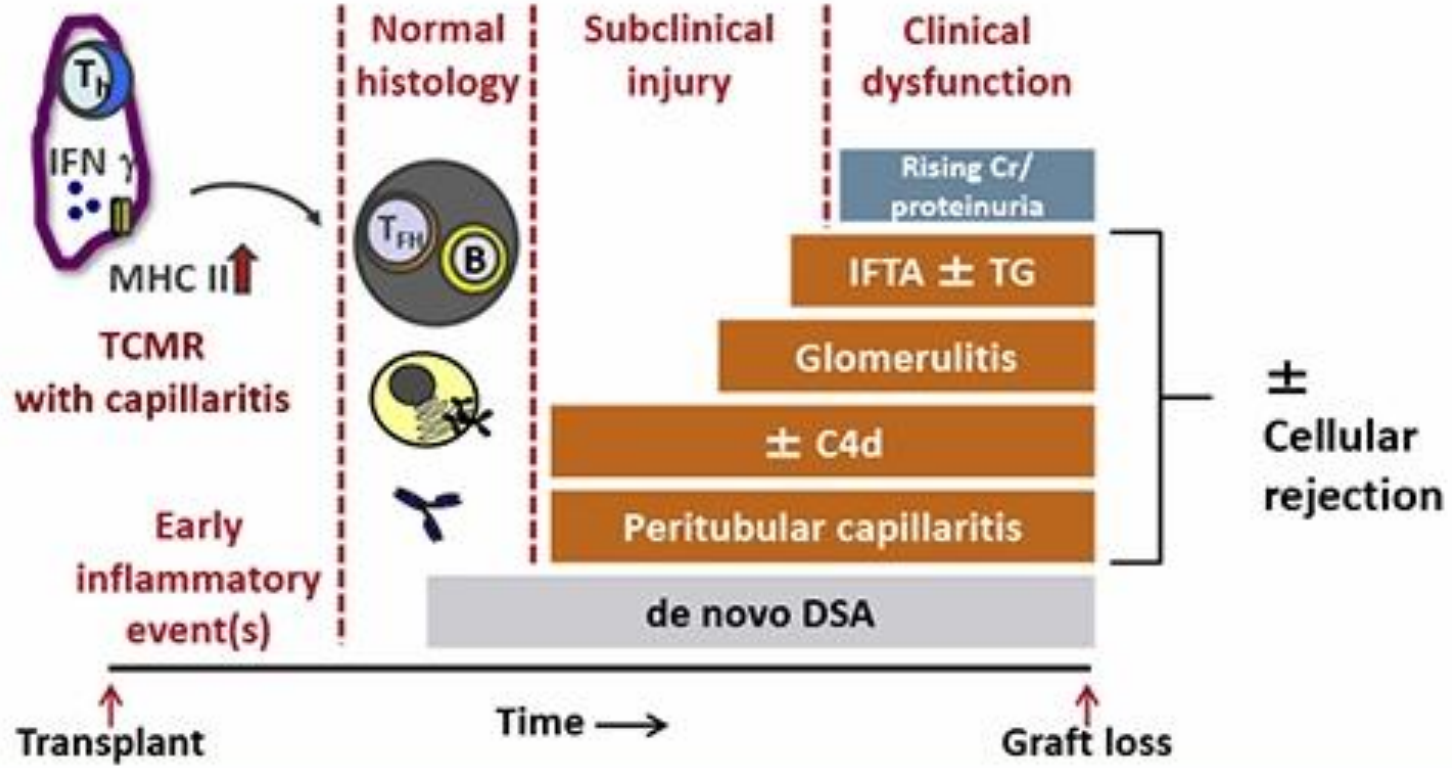
- many mismatched transplants do so well?

De Novo DSA and Graft Survival[1]



1. Wiebe C et al. *Am J Transplant*. 2012;12:1157-1167.

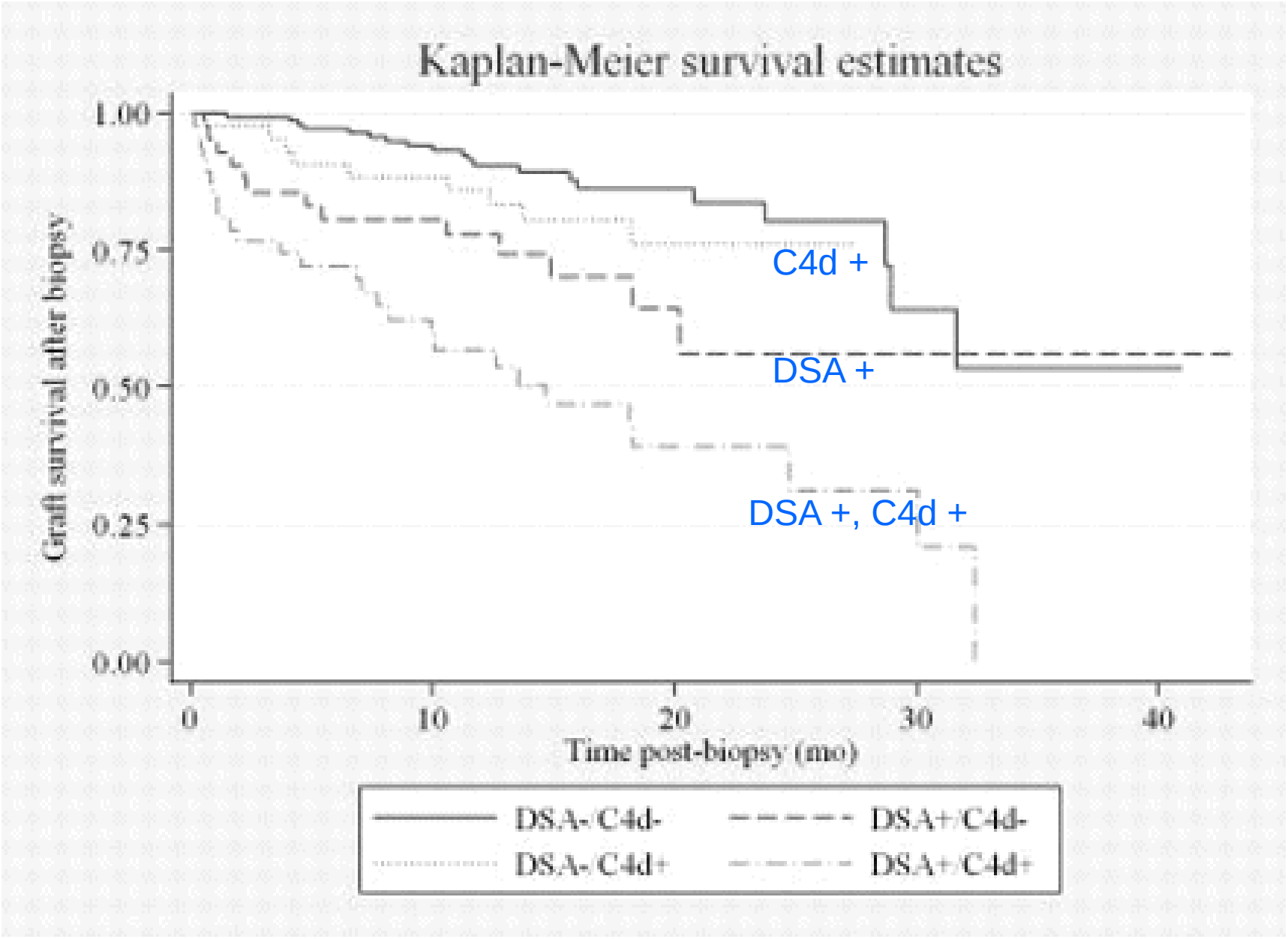
Proposed Natural History of dnDSA



Key strategies: class II match, avoid early TCMR, promote adherence

Cr: creatinine; IFN: interferon; IFTA: interstitial fibrosis and tubular atrophy.

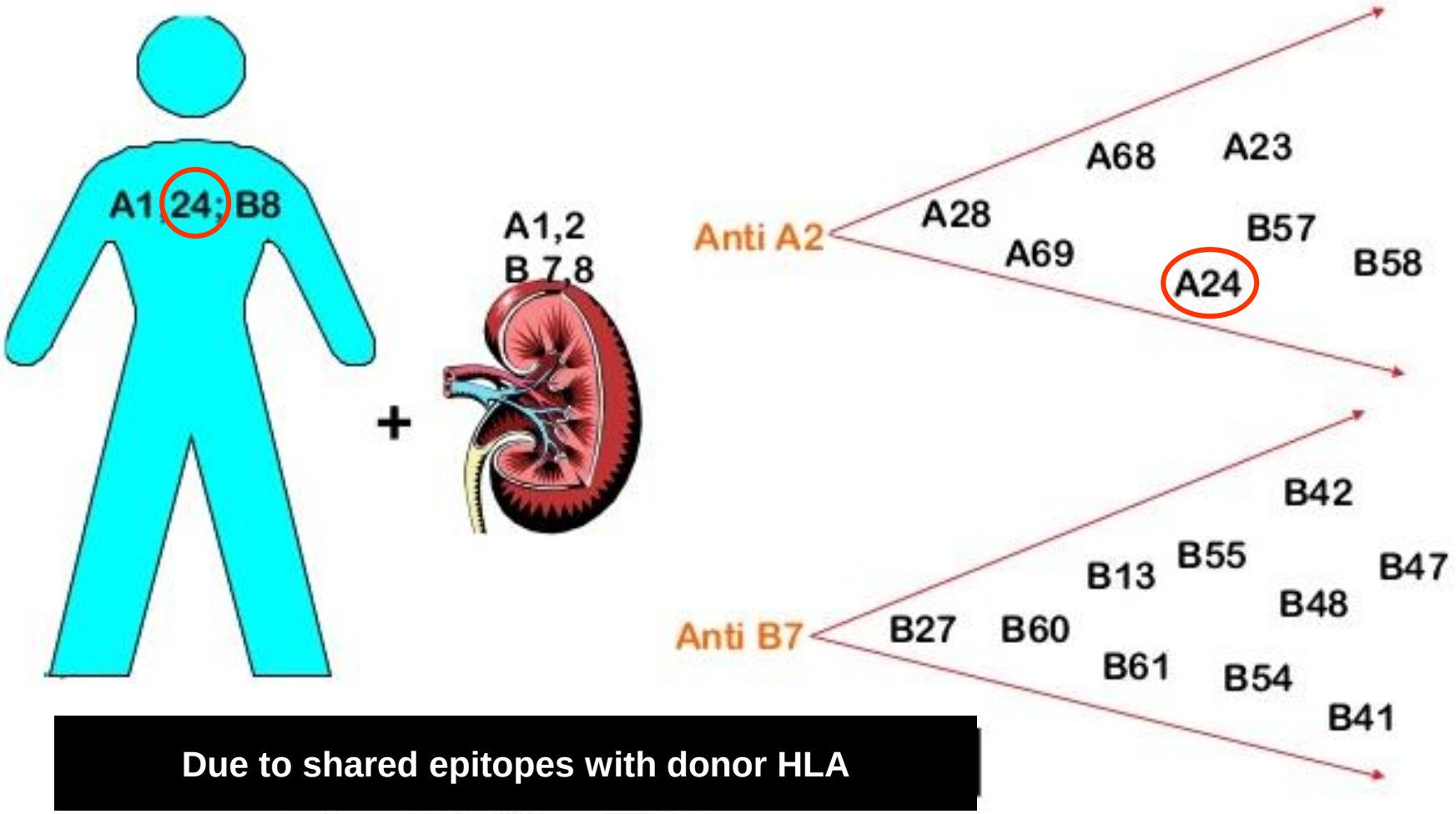
1. Wiebe C et al. *Am J Transplant.* 2012;12:1157-1167.



Wiebe C et al. Am J Transplant. 2012; 12: 1157-1167

Generation of DSA

DSA are rarely generated alone and generally antibodies to HLA molecules related to the donor HLA are also often found:



Due to shared epitopes with donor HLA

Wiebe C et al. Am J Transplant. 2012; 12: 1157-1167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Allo-typing

- Serologic
- Oligotyping
- DNA Sequence based typing

Smith LK, Methods Mol Biol. 2012;882:67-86

Allo-typing

- Terasaki's antihuman leukocyte antigen (HLA) antibodies from sera of sensitized patients
- HLA antigens have multiple epitopes that are determined by amino acid residues in polymorphic positions
- HLA epitopes recognized, especially by mouse monoclonal antibodies (mAbs)

R. J. Duquesnoy & M. Marrari, Tissue Antigens ISSN 0001-2815

HLA epitope repertoire

Empirical Terasaki's technique:

(TerEps)

- analyzing reactivity patterns using mouse mAb or an eluted alloantibody with recombinant HLA single antigen beads (amino acid sequences of HLA alleles used in the Luminex assays)
- Terasaki's epitopes 103 amino acid-defined epitopes on class I antigens encoded by HLA-A, -B and –C

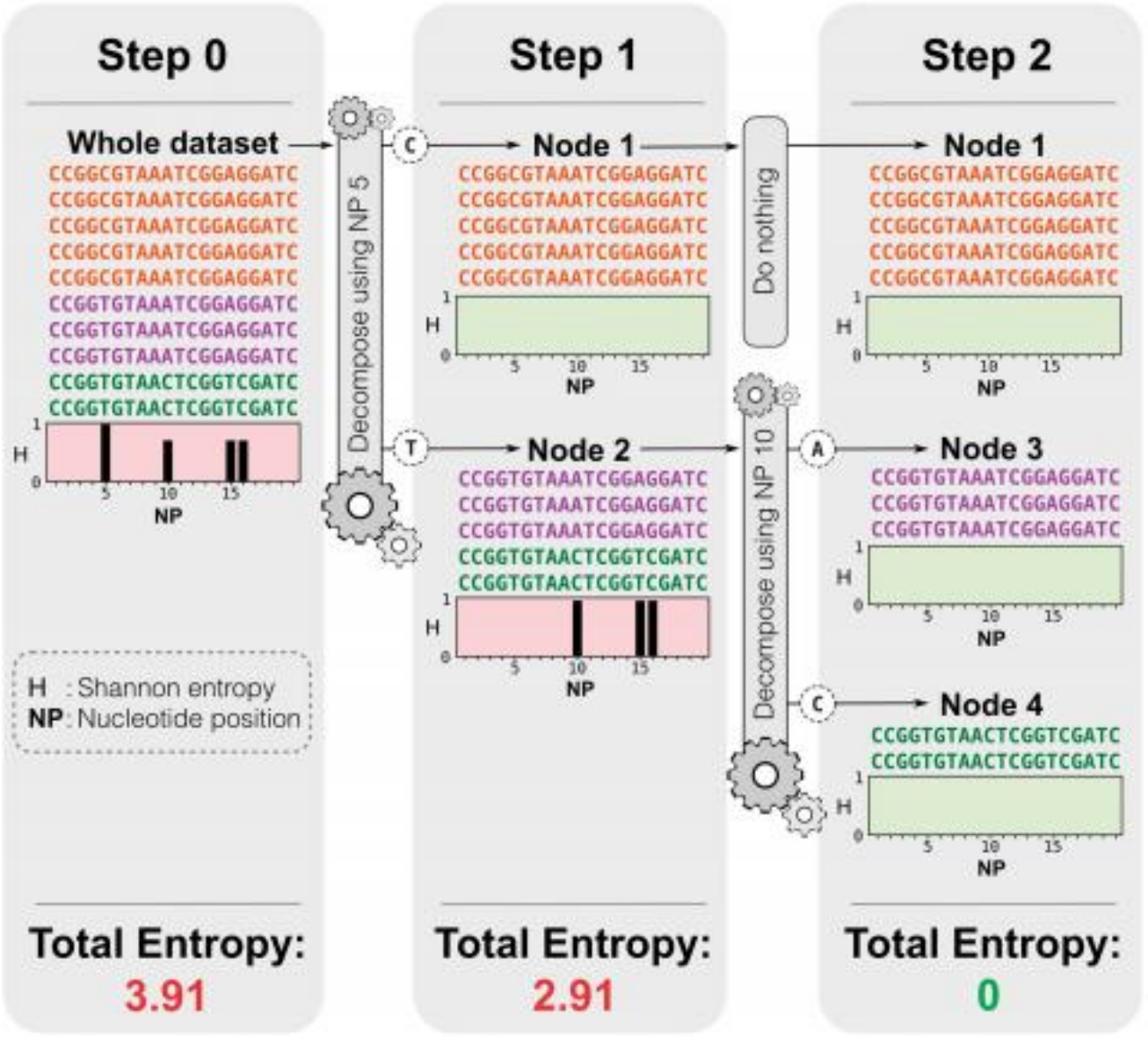
El-Awar NR, Akaza T, Terasaki PI et al. Transplantation 2007: 84: 532–40

R. J. Duquesnoy & M. Marrari, Tissue Antigens ISSN 0001-2815

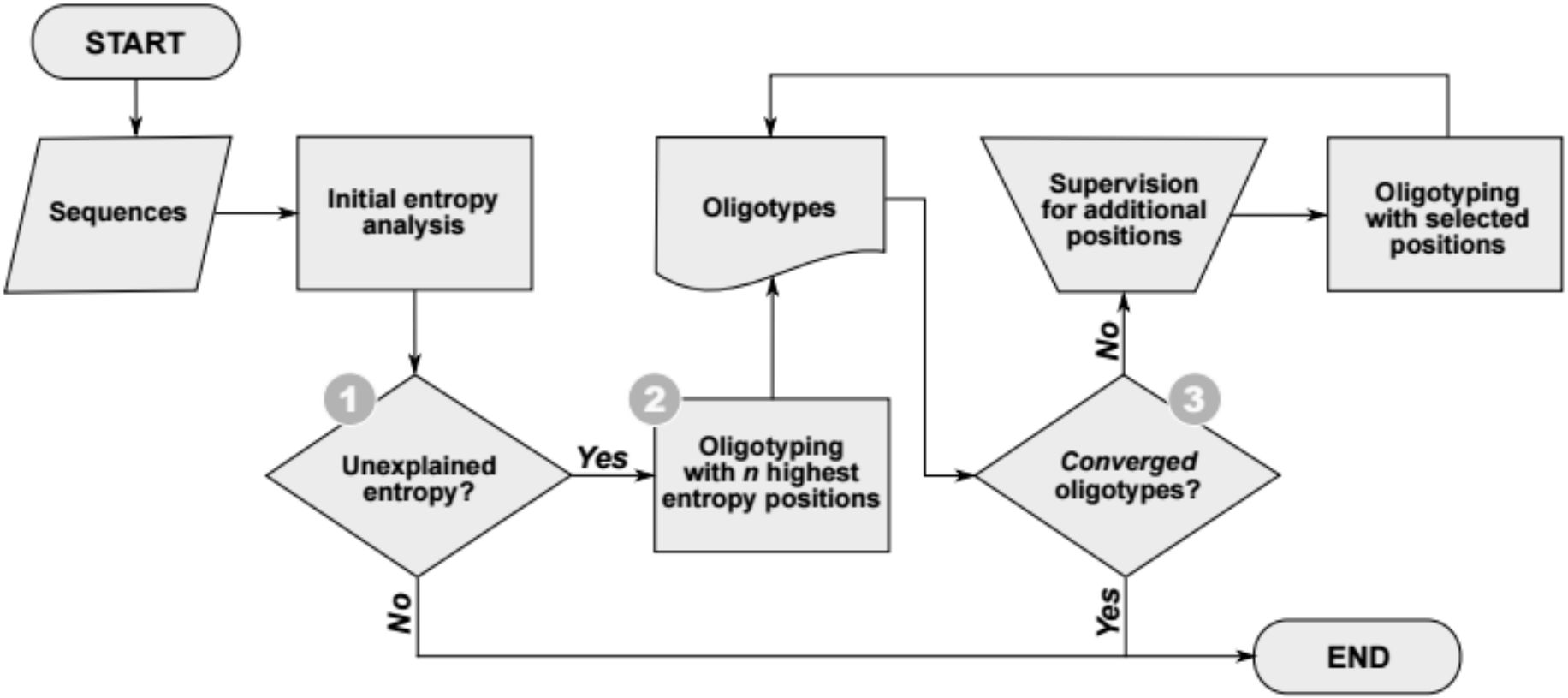
Oligonucleotide Probes Used for Identification of DR1, DR2, DR3, DR4, DR8, DR11, and DR13 Subtypes

Oligonucleotide	Sequence (5′ to 3′)	Amino Acids
E71	GGCCCGCTCGTCTTCCAGG	68–73
K71	CGGCCCGCTTGTCTTCCAG	68–73
R71	GGCCCGCCTGTCTTCCAGG	68–73
F67	CTTCCAGGAAGTCCTTCTG	64–69
I67	CTTCCAGGATGTCCTTCTG	64–69
G86	GAAGCTCTCACCAACCCCG	85–89
V86	GAAGCTCTCCACAACCCCG	85–89
N37	AGCGCACGTTCTCCTCCTG	34–39
S57	GTACTCGGCGCTAGGCCGC	55–60
QK71	CGGCCCGCTTCTGCTCCAG	68–73
QR71	CCGCGGCCCGCCTCTGCTC	69–74
E74	GTGTCCACCTCGGCCCGCC	71–77
S37	AGCGCACGGACTCCTCTTG	34–39
QR71/2	CGGCCCGCCTCTGCTCCAG	68–73
AV86	GCTCACCACAGCCCCGTAG	83–88
D37	GAAGCGCAAGTCCTCCTCT	35–40
R71/2	CCGCGGCGCGCCTGTCTTC	69–74
R11	CTCAGACTTACGCAGCTCC	9–14
E28	GGAAGTATCTCTCCAGGAAC	26–31
H30	GGAAGTGTCTCTCCAGGAAC	26–31

Tiercy JM, et al. Am. J. Hum. Genet. 51:592-608, 1992



Eren AM, et al, ISME Journal (2015) 9, 968–979



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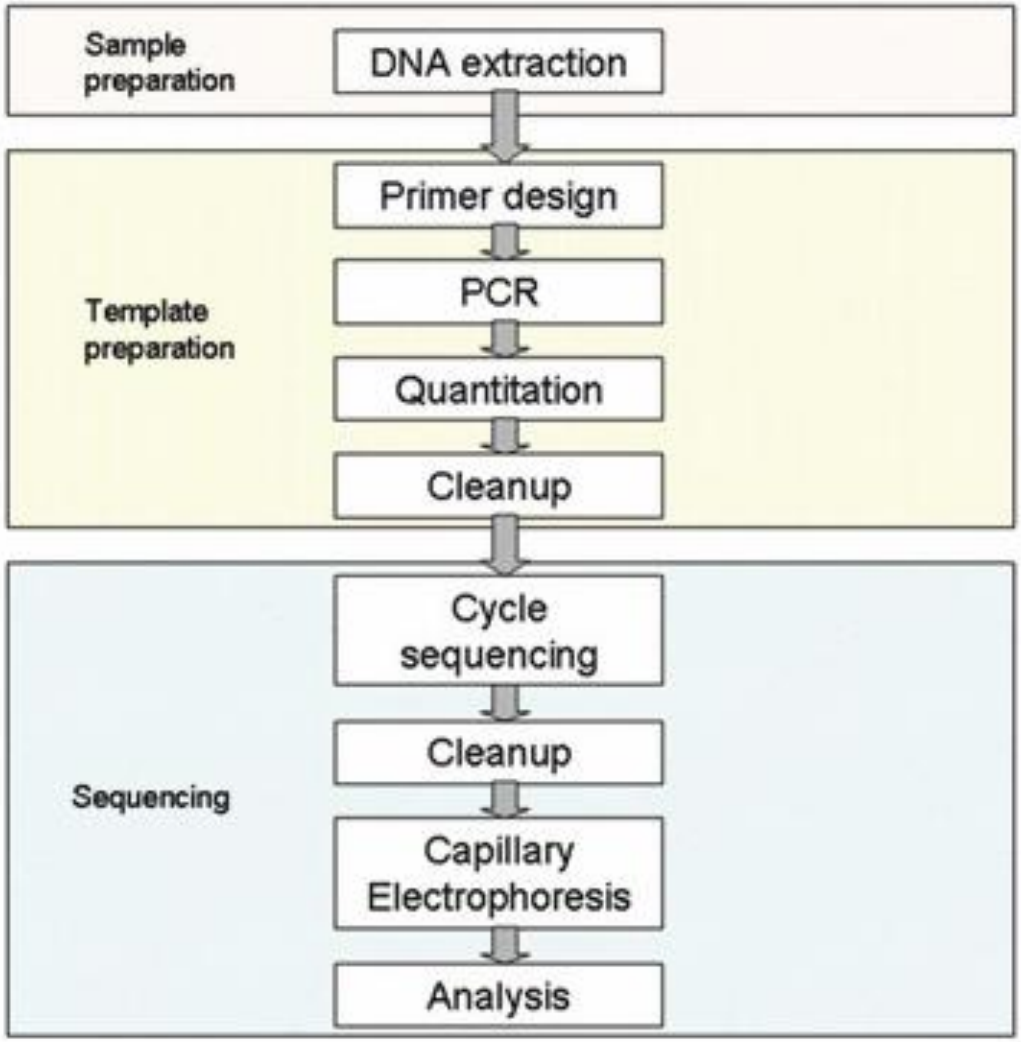
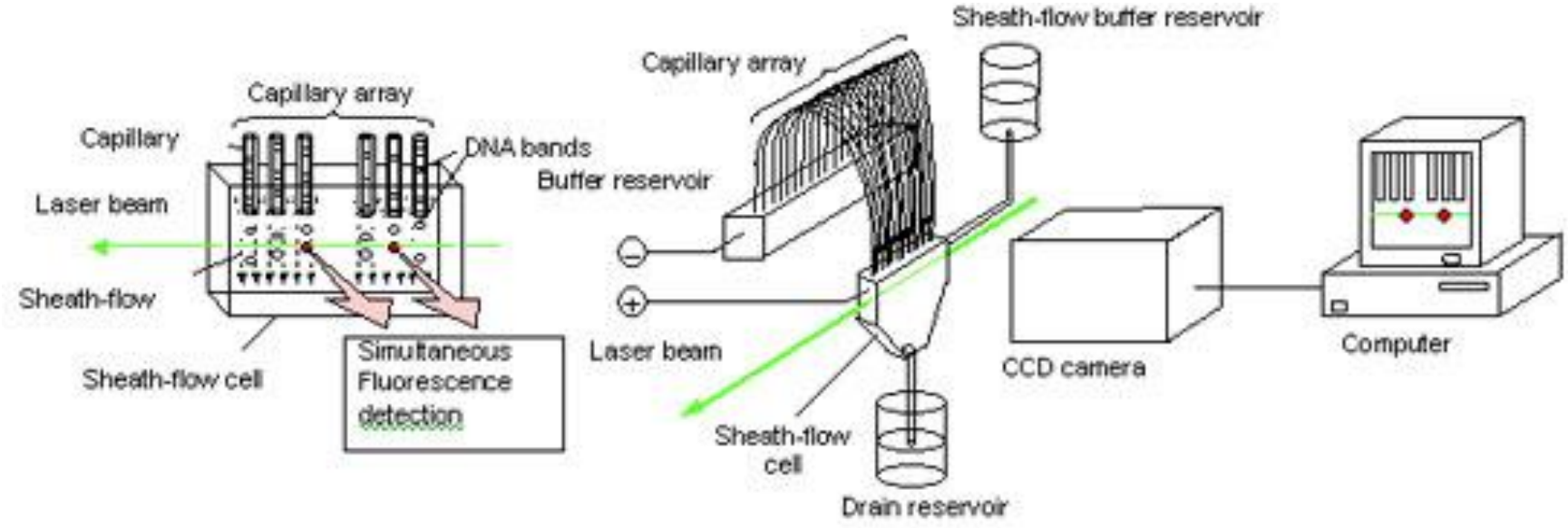
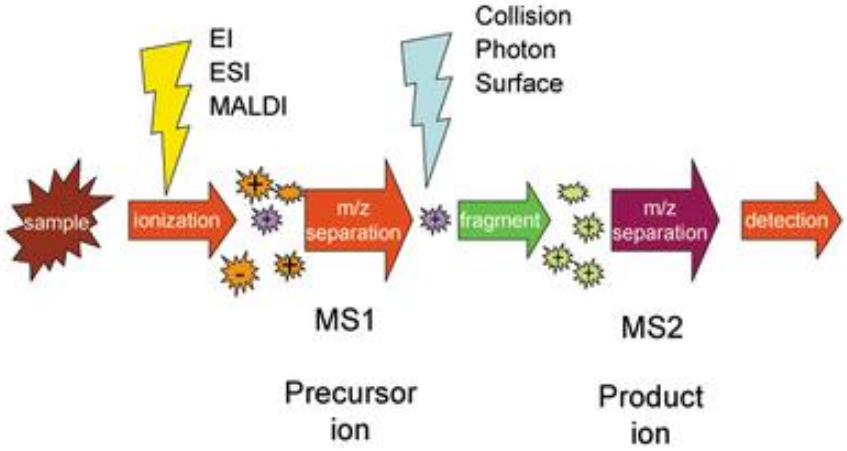
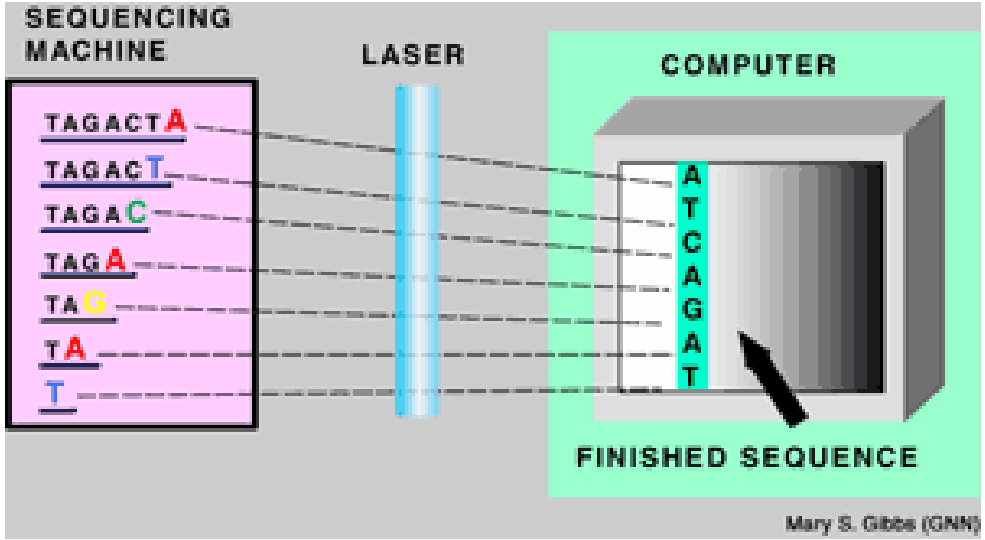


Smith LK, Methods Mol Biol. 2012;882:67-86


Capillary array
Capillary
DNA bands
Laser beam
Sheath-flow
Sheath-flow cell
Simultaneous
Fluorescence
detection
Sheath-flow buffer reservoir
Capillary array
Buffer reservoir
Laser beam
Sheath-flow
cell
Drain reservoir
CCD camera
Computer

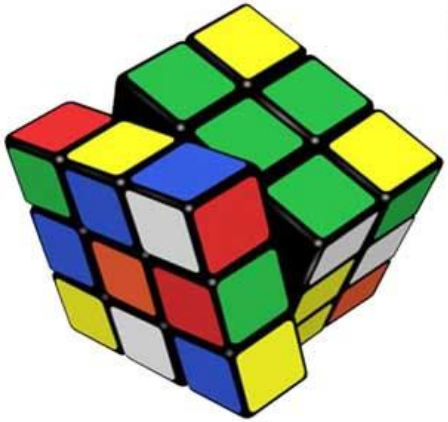

EI
ESI
MALDI
Collision
Photon
Surface
sample
ionization
m/z
separation
fragment
m/z
separation
detection
MS1
MS2
Precursor
ion
Product
ion


SEQUENCING
MACHINE
LASER
COMPUTER
TAGACTA
TAGACT
TAGAC
TAGA
TAG
TA
T
ATCAGAT
FINISHED SEQUENCE
Mary S. Gibbs (GNN)

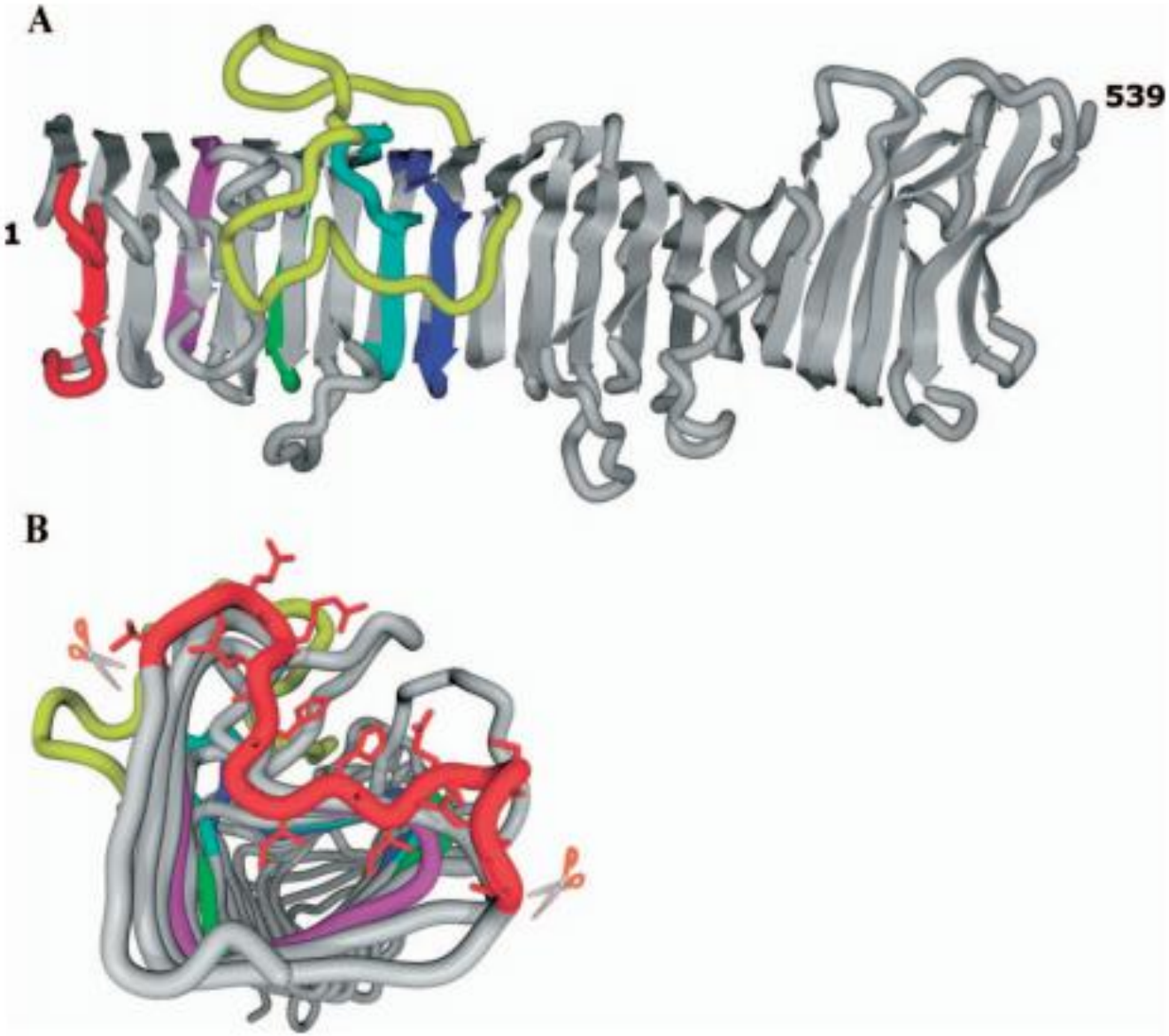
Allo-typing

- three-dimensional molecular structures
- detailed amino acid sequence differences between HLA antigens

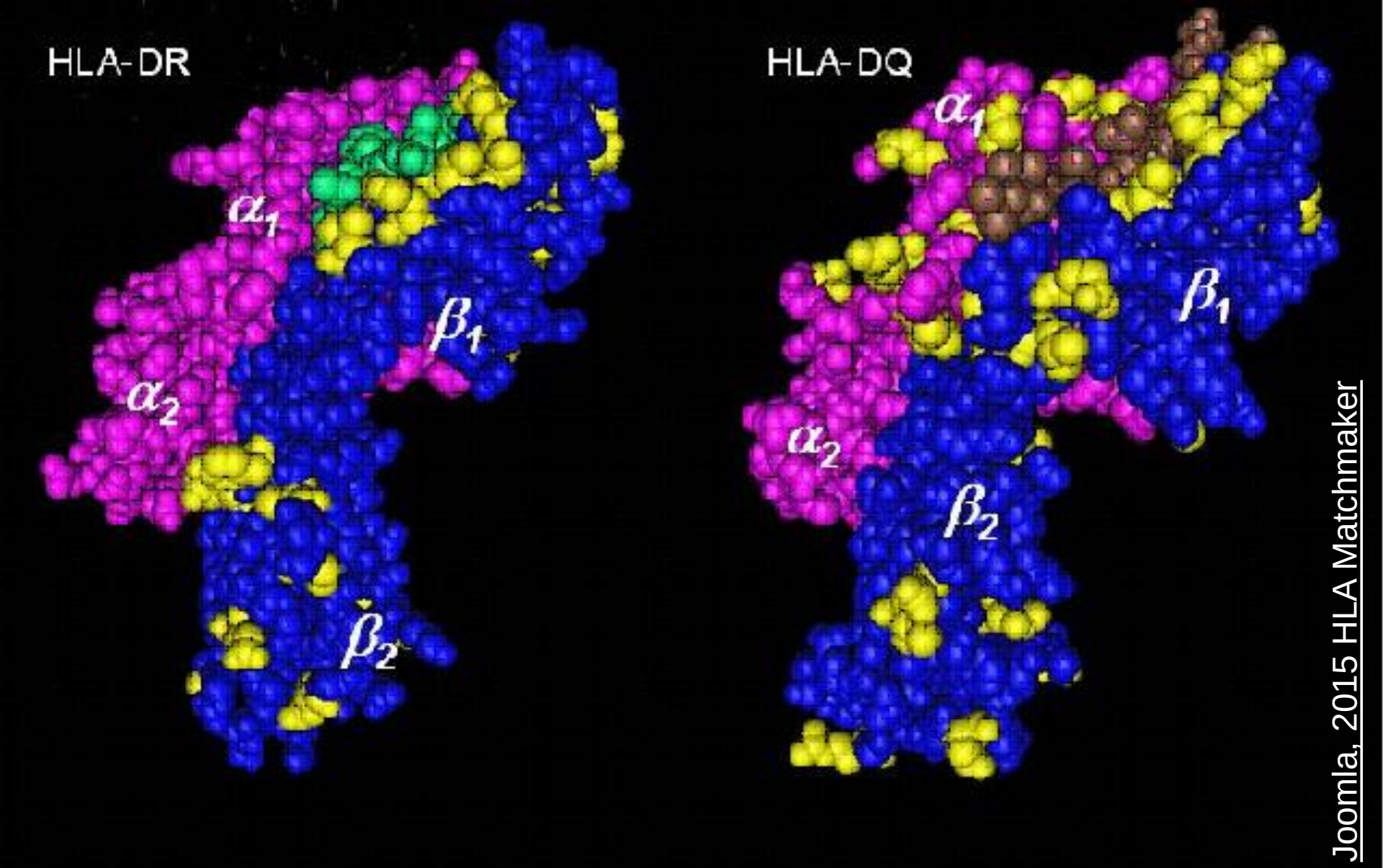
  made it possible to define the structural basis of HLA epitopes
- stereochemical modeling of crystallized complexes



Best Android Puzzle Game Apps



Stenger RM, et al, INFECTION AND IMMUNITY, Feb. 2009, p. 896–903

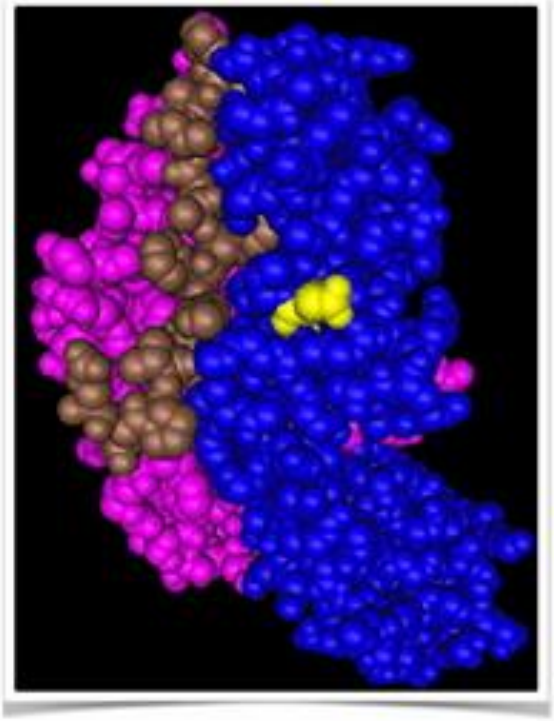


Joomla, 2015 HLA Matchmaker

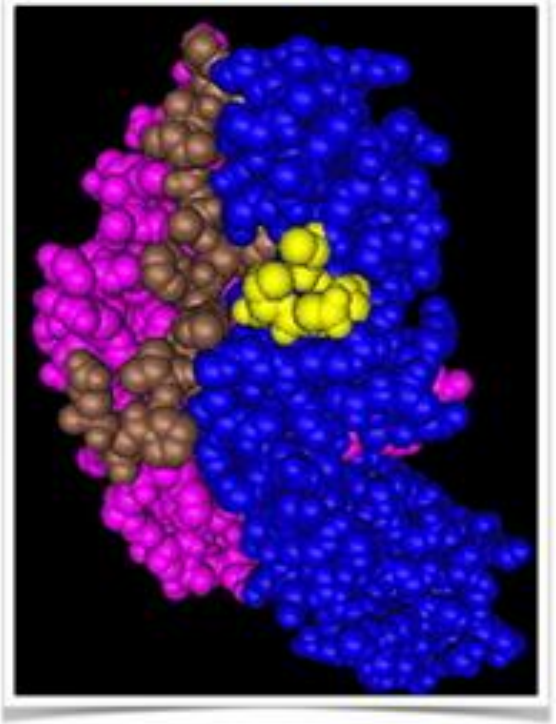
Figure 2 Topography of Polymorphic Residues on HLA-DR and HLA-DQ Molecules

Antibody-Reactive Epitope Determinations With HLAMatchmaker and Its Clinical Applications[1]

HLA-DR polymorphic amino acid



Eplet: Amino acids within a 3Å radius
(Epitope: Antibody binding site 15Å radius)



1. Duquesnoy RJ. *Tissue Antigens*. 2011;77:525-534.

HLA Matchmaker Algorithm

- Originally introduced for epitope matching
- Concept of triplet matching
- each HLA antigen is viewed as a string of short linear sequences (triplets)
- considered key elements of epitopes that can induce the formation of specific antibodies

HLA epitope repertoire

The HLAMatchmaker strategy
(HLA-MD-Eps) #

- stereochemical modeling of crystallized complexes of antibodies with different protein antigens (such as hen egg lysosome and horse cytochrome c)
- critical amino acid residues to antigen–antibody binding energy
  - structural epitopes hot spots
  - paratope consists of six complementary determining regions (CDRs)

Davies D, et al, Annu Rev Biochem 1990: 59: 439–73
Duquesnoy RJ. A Human Immunol 2006: 67: 847–62.
R. J. Duquesnoy & M. Marrari, Tissue Antigens ISSN 0001-2815

EPITOPE Function

An epitope has two characteristics

- immunogenicity, inducing Ab response
- antigenicity, determining Ab reactivity
- mismatch permissibility # reactivity

Table 3 Examples of eplets that correspond to antibody-verified epitopes reported by Terasaki and coworkers

Eplet	TerEp	Antibody-reactive antigens	Models
127K	#19	A2,23,24,68,69	Figure 1A
144KR	#208	A1,3,11,24,36,80	Figure 1A
65GKA	#3	A23,24	Figure 1A
62EE	#28	A23,24,80	Figure 1A
167DG	#14	A1,23,2402,80, B76	Figure 1A
82LR	#24	A23,24,25,32, B13,2705,37,38,44,47,49,51,52, 53,57,58,59,63,77	Figure 1A, B
79RI	#23	A23,24,25,32, B38,49,51, 52,53,57,58,59,63,77	Figure 1A, B
44RT	#35	B18,35,37,51,52,53,58,78	Figure 1B
71NT	#22	B8,13,18,35,37,38,39,3905,4005, 41,44,45,47,48,49,50,51,52,53, 59,60,61,62,64,65,71,72,75,76, 77,78	Figure 1B
163LW	#245	B35,4005,46,49,50,51,52,53,56, 57,58,62,63,71,72,75,77,78, Cw9,w10	Figure 1B, C
21H	#39	Cw2,w9,w10,w15	Figure 1C
80VRN	#246	B46,73, Cw1,w7,w8,w9,w10,w12, w14,w16	Figure 1C
77TVS	#421	B46, Cw1,w8,w9,w10,w14,w16	Figure 1C


dreamstime.com


Backset

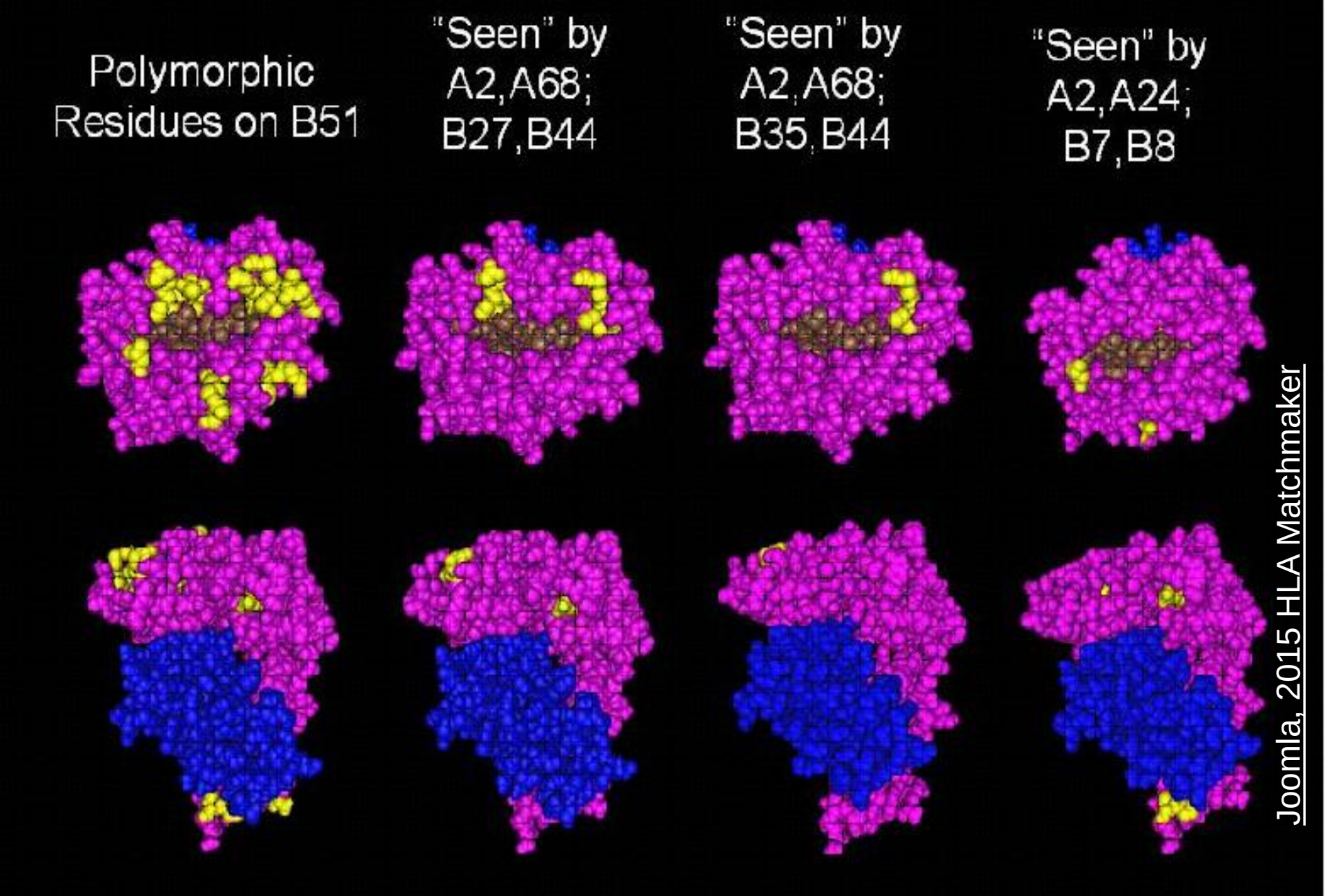


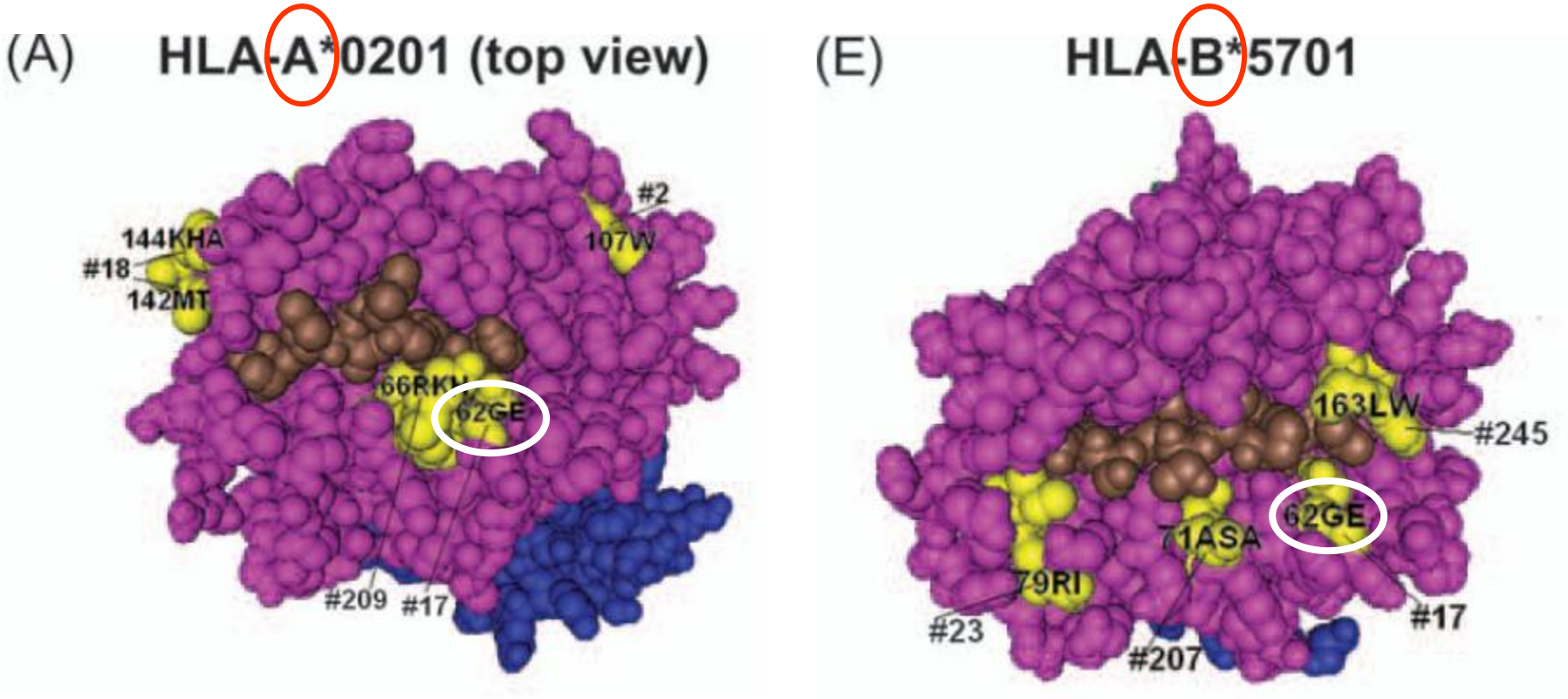
Figure 3 Structural Basis of a HLA-B51 Mismatch

Examples of polymorphic residue differences within 15 Å of mismatched eplets on antibody-defined epitopes on immunizing alleles and the alleles of the antibody producer.

Reference	Antibody case	Immunizing allele	Epitope	Numbers of residue differences for HLA alleles of antibody producer					
25	Monoclonal 1	A*32:01	65RNA+S82LR	A*02:01	A*24:02	B*07:02	B*40:01	C*07:02	C*03:04
				6	2	7	6	7	8
25	Monoclonal 2	B*27:05	163EW+S73TE	A*01:01		B*08:01		C*07:01	
				10		2		6	
25	Monoclonal 3	B*35:01	163LW+S65RQI	A*02:01	A*24:02	B*07:02	B*40:01	C*07:02	
				9	8	3	0	6	
25	Monoclonal 4	A*11:01	144KR+S151H	A*02:01	A*25:01	B*18:01	B*51:01	C*12:03	C*15:02
				1	6	6	8	5	4
25	Monoclonal 5	B*55:01	65QIA+S76ES	A*02:01	A*25:01	B*18:01	B*51:01	C*12:03	C*15:02
				6	6	0	4	2	2
25	Monoclonal 6	A*03:01	142MI+S79GT	A*02:01	A*68:01	B*07:02	B*27:05	C*02:02	C*07:02
				1	1	5	7	4	5
41	Patient 1	B*44:02	S145R+S82LR	A*30:01	A*66:01	B*13:02	B*14:02	C*06:02	C*08:02
				7	9	0	4	7	6
41	Patient 2	B*44:02	S145R+S82LR	A*02:01	A*11:01	B*07:02	B*13:02	C*06:02	C*07:02
				10	9	5	0	7	7
42	Monoclonal 7	B*44:03	41T	A*01:01	A*25:01	B*08:01	B*18:01	C*07:01	
				7	5	0	0	3	
42	Monoclonal 8	B*07:02	80NRG	A*02:01	A*24:02	B*27:05	B*37:01	C*02:02	C*06:02
				10	6	0	2	3	5
42	Monoclonal 9	B*15:03	163 LW	A*02:01	A*68:01	B*07:02	B*27:05	C*02:02	C*07:02
				6	4	2	0	1	1
42	Monoclonal 10	B*55:01	69AA+S76E	A*02:01	A*25:01	B*18:01	B*51:01	C*12:02	
				7	7	0	3	3	

- TerEp #17 is equivalent to the 62GE eplet represented on A2, B57 and B58

  similar molecular configuration on A*0201 (Figure 1A) and B*5701 (Figure 1E)



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Example showing how a high-resolution DR–DQ haplotype shows differences in class II eplet loads among serologically defined DR antigen mismatches (Adapted from Duquesnoy, 2008a).

RECIPIENT									
DR11	DRB1*11:01	DRB3*02:01	DQB1*03:01	DQA1*05:01					
DR16:	DRB1*16:01	DRB5*02:02	DQB1*05:02	DQA1*01:02	Eplet	DRB1	DRB3/4/5	DQB1	DQA1
Donor					Total	Eplets	Eplets	Eplets	Eplets
DR1	DRB1*01:01	None	DQB1*05:01	DQA1*01:01	12	8	0	2	2
DR4	DRB1*04:01	DRB4*01:01	DQB1*03:01	DQA1*03:02	16	3	8	0	5
DR7	DRB1*07:01	DRB4*01:01	DQB1*02:02	DQA1*02:01	28	7	8	7	6
DR8	DRB1*08:01	None	DQB1*04:02	DQA1*04:01	12	4	0	5	3
DR9	DRB1*09:01	DRB4*01:01	DQB1*03:03	DQA1*03:02	27	11	8	3	5
DR10	DRB1*10:01	None	DQB1*05:01	DQA1*01:01	12	8	0	2	2
DR11	DRB1*11:01	DRB3*02:02	DQB1*03:01	DQA1*05:01	0	0	0	0	0
DR12	DRB1*12:01	DRB3*02:02	DQB1*03:01	DQA1*05:01	6	6	0	0	0
DR13	DRB1*13:01	DRB3*01:01	DQB1*06:03	DQA1*01:03	20	3	7	8	2
DR14	DRB1*14:01	DRB3*02:02	DQB1*05:03	DQA1*01:04	13	8	0	2	3
DR15	DRB1*15:01	DRB5*01:01	DQB1*06:02	DQA1*01:02	9	0	2	7	0
DR16	DRB1*16:02	DRB3*02:02	DQB1*03:01	DQA1*05:01	2	2	0	0	0
DR17	DRB1*03:01	DRB3*01:01	DQB1*02:01	DQA1*05:01	19	5	7	7	0
DR18	DRB1*03:02	DRB3*01:01	DQB1*04:02	DQA1*04:01	18	3	7	5	3


NO SMOKING.

Table 1

Two examples showing how the HLA phenotype of the recipient affects the eplet load of a class I allele mismatch (Adapted from Duquesnoy, 2008b).

Case	Phenotype						B51 (B*51:01)		B61 (B*40:02)	
							#Ep	Mismatched eplets	#Ep	Mismatched eplets
1	A*01:01	A*02:01	B*14:02	B*07:02	C*07:01	C*07:02	7	11AMR, 44RTE, 76ERI, 82ALR, 113HN, 163L, 193PV	5	9H, 41T, 44RKE, 113HN, 151RV
2	A*01:01	A*02:01	B*07:02	B*08:01	C*07:01	C*07:02	6	44RTE, 76ERI, 82ALR, 131S, 163L, 193PV	3	9H, 41T, 44RKE
3	A*01:01	A*02:01	B*07:02	B*45:01	C*07:01	C*07:02	5	44RTE, 76ERI, 82ALR, 113HN, 193PV	1	113HN
4	A*01:01	A*25:01	B*07:02	B*08:01	C*07:01	C*07:02	4	44RTE, 131S, 163L, 193PV	3	9H, 41T, 44RKE
5	A*01:01	A*02:01	B*07:02	B*44:03	C*05:01	C*07:02	3	44RTE, 76ERI, 113HN	2	9H, 113HN
6	A*01:01	A*02:01	B*45:01	B*39:01	C*05:01	C*17:01	3	44RTE, 76ERI, 82ALR	0	None
7	A*01:01	A*25:01	B*55:01	B*37:01	C*06:02	C*07:02	2	116Y, 163L	4	41T, 44RKE, 116Y, 163E
8	A*01:01	A*25:01	B*35:01	B*41:01	C*06:02	C*04:01	0	None	1	163E

Front Immunol. 2011; 2: 59.

HLA matching protocols for kidney transplantation

- Matching for HLA-A, -B, and -DR antigens
- Mismatching for HLA-A, -B, and -DR antigens
  - Broad vs split antigens
  - Acceptable and unacceptable mismatches for highly sensitized candidates
  - Permissible mismatches with graft outcome similar to nonmismatched transplants
- DR matching
- CREG matching
  - Public and private class I epitopes
- Structurally based matching
  - Amino acid residue mismatching
  - HLAMatchmaker

Abbreviations: HLA = human leukocyte antigen; CREG = cross-reacting groups of antigens.

S. Takemoto et al. Human Immunology **65,** 1489–1505 (2004)

Table 1 Fifty TerEps that are equivalent to eplets

TerEp	Defined by	Antibody-reactive antigens	Residue description of TerEp[a]	Eplet(s)[b]	Models
#2	mAb	A2, 69	107W	107W	Figure 1A, B
#17	aAb	A2; B57, 58	62G	62GE	Figure 1A, B, E
#18	aAb	A2, 68, 69	142T/145H	142MT/145KHA	Figure 1A, B
#19	aAb	A2, 23, 24, 68, 69	127K	127K	Figure 1A, B, D
#201	mAb	A2	43Q+62G/62G+66K/62G+76V/62G+79G	66RKH	Figure 1A, B
#38	aAb	A2, 25, 26, 29, 31, 32, 33, 34, 43, 66, 68, 69, 74; B73; Cw7, w17	253Q	253Q	Figure 1A, B
#404	aAb	A11	149A+150A+163R/149A+158A+163R/149A+163R+166E/149A+163R+167W	151AHA	Figure 1C

aAb, alloantibody generally eluted from antigen used to absorb alloserum; mAb, monoclonal antibody; TerEps, Terasaki's epitopes.

[a] Amino acids in HLA protein sequence positions are listed with the standard single letter code. Amino acids not exposed on surface of molecule are in parenthesis. Residues shared with C locus antigens but not proven by single allele antibody testing are indicated as square brackets. TerEps described by combinations of residues are shown with + sign. Possible alternative residue combinations are separated by slash.

[b] Two and three unique eplets are separated by '/'.

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Table 2 Thirty-one TerEps that correspond to eplet pairs

TerEp	Defined by	Antibody-reactive antigens	Residue description of TerEp	Eplet pair(s)	Models
#212	aAb	A23, 24, 32; B38, 49, 51, 52, 53, 57, 58, 59, 63, 77	[80I+90A/80I+149A]	79RI+90A	Figure 2A
#419	mAb	B49, 51, 52, 63, 77	80I+90A+127N+(152E)/80I+109L+131S+(152E)/82L+90A+127N+(152E)/83R+90A+127N+(152E)	79RI+152RE	Figure 2B
#230	aAb	B38, 49, 51, 52, 53, 59, 77	65Q+80I/69T+80I	65QIT+79RI/71NT+79RI	Figure 2C
#219	aAb	B18, 35, 37, 51, 52, 53, 78	45T+62R/45T+65Q/45T+66I/45T+69T/45T+71T	44RT+71NT	Figure 2D
#403	aAb	B46, 62, 75, 76, 77	41A+46A+65Q	45RMA+79RN	Figure 2E
#221	aAb	B35, 4005, 46, 49, 50, 51, 52, 53, 56, 57, 58, 62, 63, 71, 72, 75, 77, 78	163L+167W	131S+163LW	Figure 2F
#415	mAb	B46, 57, 58, 63	[(63E)+(71A)+163L]	71AT+163LW (also on Cw9, 10)	Figure 2G
#204	mAb	A32, 74; B8, 18, 37, 38, 39, 41, 42, 54, 55, 59, 64, 65, 67	[109L+163T]	109L+163TW (also on Cw1, 4, 5, 6, 8, 12, 14, 15, 16, 18)	Figure 2H
#228	aAb	B18, 37, 38, 39, 54, 55, 56, 64, 65, 67	131S+163T	131S+163TW	
#215	aAb	A33, 34, 68, 69; B8, 18, 37, 38, 39, 41, 42, 54, 55, 59, 64, 65, 67	62R+163T	62RN+163TW	Figure 2I
#232	mAb	B54, 55, 59; Cw1, w4, w5, w6, w7, w8, w12, w14, w15, w16, w18	(103L)+163T	103L+163TW	Figure 2J
#225	aAb	B8, 59	(67F)+163T	66QIF+163TW	Figure 2K

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Table 5 Eplets not included in the Terasaki's epitope repertoire

Eplet	Associated antigen summary
1C.6K	Cw1
44RK	B60, 61, 4005, 41, 44, 45, 47, 49, 50
62QE	A1, 3, 11, 30, 31, 32, 36, 74
65RNA	A1, 3, 11, 25, 26, 28, 29, 30, 31, 32, 36, 43, 66, 74, 80; B63, 57, 58
66RNH	A1, 25, 26, 31, 32, 33, 36, 43, 74, 80
66RNQ	A3, 11, 29, 30, 66, 68, 69
70KAH	A2, 23, 24
71HS	A1, 2, 23, 24, 25, 26, 31, 32, 33, 36, 43, 74, 80
71QS	A3, 11, 29, 30, 34, 66, 68, 69
73AN	Cw4, w6, w17, w18
73ID	A31, 33
73TD	A2, 3, 11, 30, 34, 66, 68, 69, 74; B27, 37, 47
73TN	A1, 9, 26, 29, 36, 43, 80; B5, 13, 17, 27, 38, 44, 49, 53, 59, 63, 77; Cw2, w15
76EDT	B27, 37, 47
76ENT	B13, 44
76ESI	A25, 32
76VDT	A2, 3, 11, 30, 31, 33, 34, 66, 68, 69, 74
77TEN	A23, 24; B13, 63, 77, 27, 38, 44, 49, 51, 52, 53, 57, 58, 59
77TVN	Cw2, w5, w15, w16
78VGT	A2, 3, 11, 30, 34, 66, 68, 69, 74
105S	A2, 3, 23, 24, 29, 30, 31, 33, 68, 69, 80
109F	A1, 2, 3, 9, 11, 25, 26, 29, 30, 31, 33, 34, 36, 43, 66, 68, 69, 80
142MI	A1, 3, 11, 9, 25, 26, 29, 30, 31, 32, 33, 34, 36, 43, 66, 68, 74, 80

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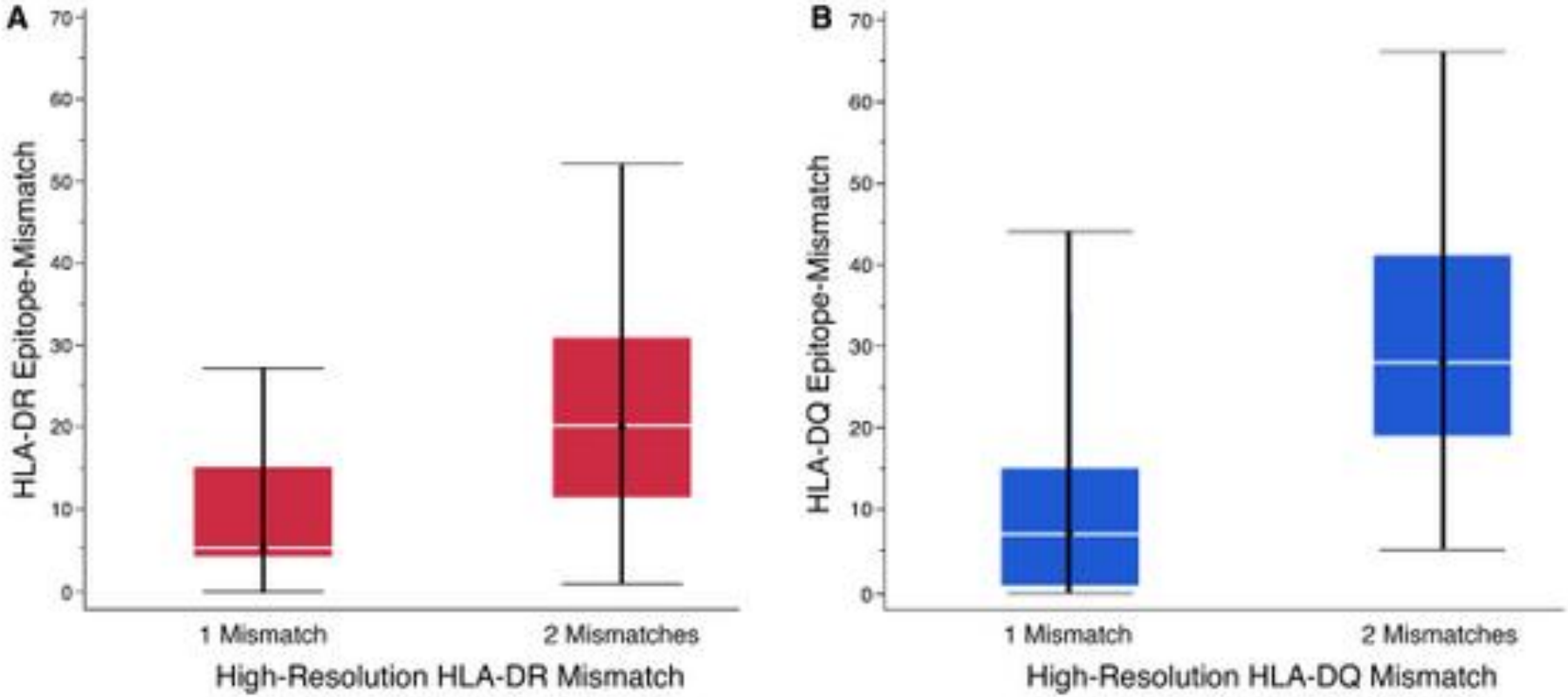
HLA epitope repertoire

- HLA Matchmaker determines structurally HLA compatibility at the epitope level and may better predict the immunological risk of kidney transplants compared with broad antigen matching

Do Nguyen H, et al, ATC 2015, Abstract number: 1066



Wiebe et al *American Journal of Transplantation* 2015; 15: 2197–2202

High Epitope MM Load in Patients With De Novo DSA[1]

	No dnDSA (n = 241)	DR dnDSA Alone (n = 9)	DQ dnDSA Alone (n = 24)	Both DR and DQ dnDSA (n = 12)
HLA-DR epitope MM	13.2 ± 13.5	21.4 ± 8.4[a]	12.8 ± 9.6	24.2 ± 9.9[b]
HLA-DQ epitope MM	17.3 ± 16.7	11.0 ± 10.5	27.5 ± 11.7[c]	28.2 ± 6.0[b]

[a] $P \leq .05$; [b] $P \leq .01$; [c] $P \leq .001$.

1. Wiebe C et al. *Am J Transplant.* 2013;13:3114-3122.

Transplant outcome

Epitope Matching Outperforms Traditional Antigen Matching as a Predictor of De Novo Donor Specific Antibody Development after Renal Transplantation

C. Wiebe, D. Pochinco, T. Blydt-Hansen, I. Gibson, D. Rush, P. Nickerson

Medicine, University of Manitoba, Winnipeg, Canada
Immunology, University of Manitoba, Winnipeg, Canada
Diagnostic Services of Manitoba, University of Manitoba, Winnipeg, Canada
Pediatric and Child Health, University of Manitoba, Winnipeg, MB, Canada
Pathology, University of Manitoba, Winnipeg, Canada

Meeting: 2013 American Transplant Congress

Abstract number: 408

Antigen / Epitope / Eplet Microchimerism

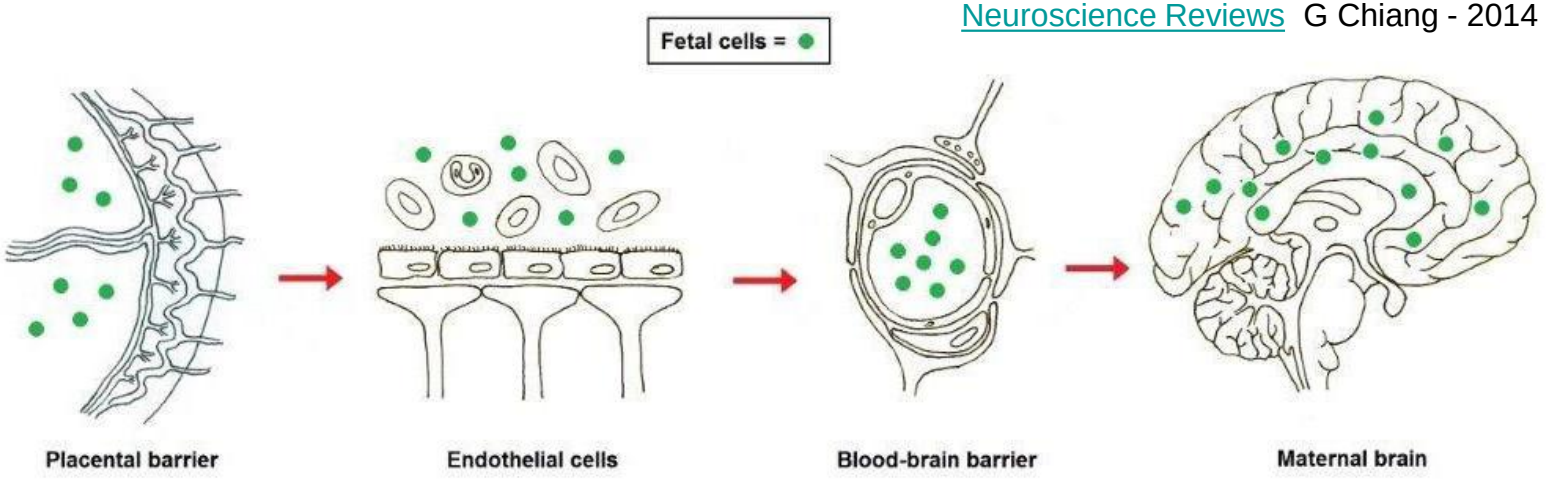
Women carry DNA of men they had sex with in their brains and organs?

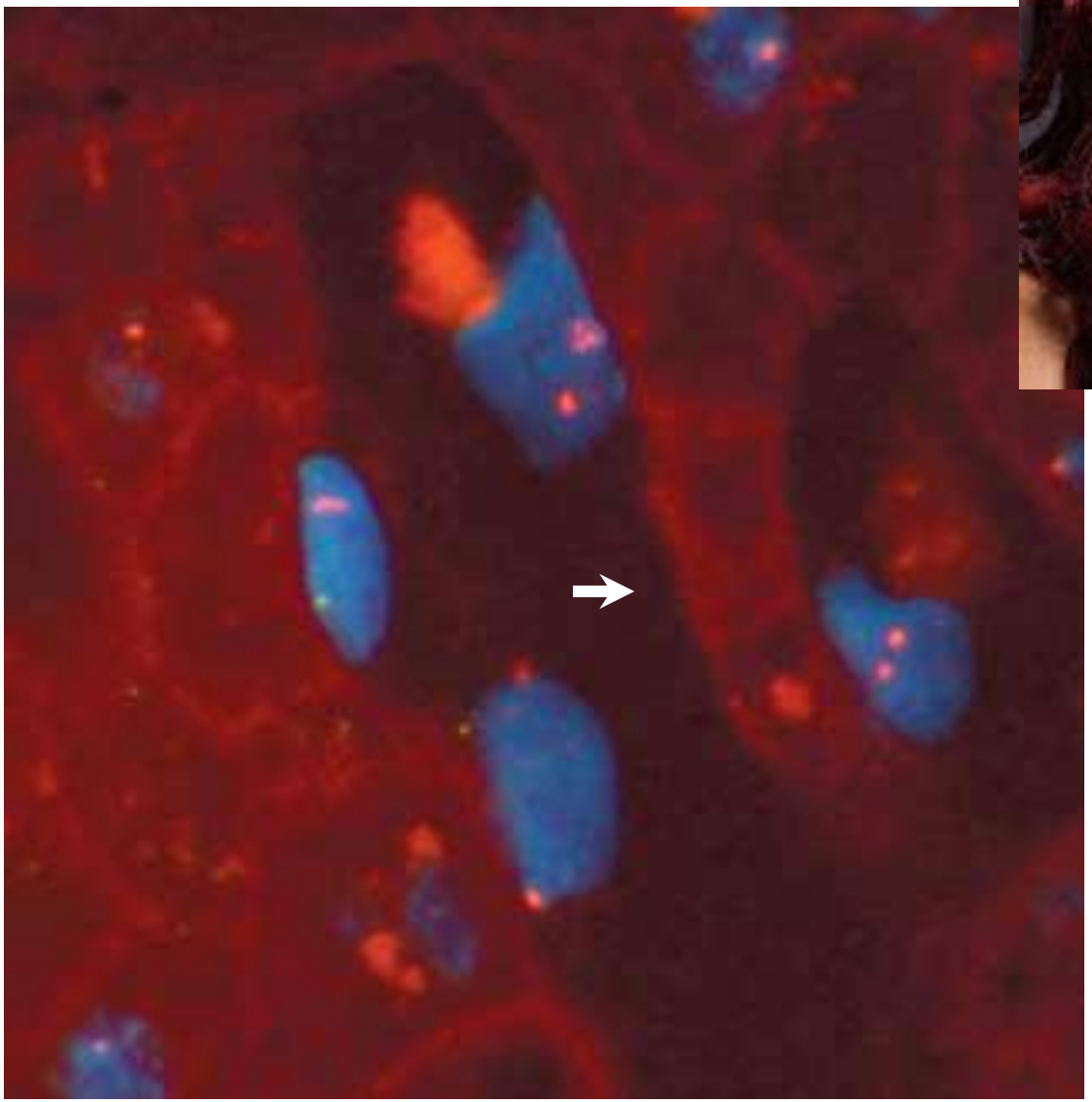
Started by Irene Sacrifices Universe , Aug 08 2013 09:04 AM

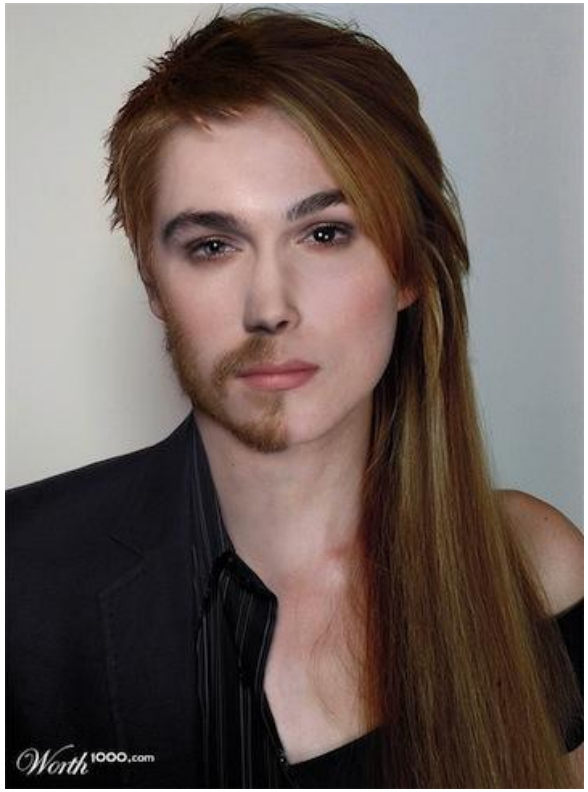
Male microchimerism was not infrequent in women without sons. Besides known pregnancies, other possible sources of male microchimerism include unrecognized spontaneous abortion, vanished male twin, an older brother transferred by the maternal circulation, or sexual intercourse. Male microchimerism was significantly more frequent and levels were higher in women with induced abortion than in women with other pregnancy histories. Further studies are needed to determine specific origins of male microchimerism in women.

In this study, we provide the first description of male Mc in female human brain and specific brain regions. Collectively with data showing the presence of male DNA in the cerebrospinal fluid, our results indicate that fetal DNA and likely cells can cross the human blood-brain barrier (BBB) and reside in the brain. Changes in BBB permeability occur during pregnancy and may therefore provide a unique opportunity for the establishment of Mc in the brain. Also unique to our study are the findings that male Mc in the human female brain is relatively frequent (positive in 63% of subjects) and distributed in multiple brain regions, and is potentially persistent across the human lifespan (the oldest female in whom male DNA was detected in the brain was 94 years).

Neuroscience Reviews G Chiang - 2014






Worth1000.com

Detection of michrochimerism after MSCs pretransplantation

PCR on arterial endothelium

Saadi et al, 2010, Dynamic Bioch

Lymphocyte DNA sequencing

Saadi et al, 2016, Unpublished

Dynamic Biochemistry, Process Biotechnology and Molecular Biology ©2010 Global Science Books

Mesenchymal Stem Cell Transfusion as a Novel Immunosuppressive Regimen with Possible Induction of Microchimerism

Gamal Saadi[1] • Mervat El-Ansary[2] • Samah Abd El-Hamid[2*] • Iman Abd El-Aziz[3]

[1] Department of Internal Medicine and Nephrology, Kasr EL-Aini, Cairo University, Manial EL-Rouda, Cairo, Egypt
[2] Department of Clinical Pathology, Kasr EL-Aini, Cairo University, Manial EL-Rouda, Cairo, Egypt
[3] Department of Clinical Pathology, Theodor Bilharz Research Institute, Kornish Elnile Street, Warrak Elhadar, Giza, Egypt

Corresponding author: * **samah_cpath@yahoo.com**

ABSTRACT

Human mesenchymal stem cells (MSCs) have immunosuppressive capacities. Although their efficacy is currently studied in graft versus host disease (GVHD), their effect on alloreactivity in solid organ transplant (SOT) patients is unknown. Our work aimed to use allogeneic donor-specific MSCs (DS-MSCs) transfusion prior to renal transplantation as an immunosuppressive induction regimen. Our study included 4 groups of patients, all of which were diagnosed with chronic renal failure and had undergone renal transplantation. The first group included 7 patients that were induced by DS-MSCs. The second included 6 patients induced by antithymocyte globulin (ATG). The third included 6 patients induced by anti-CD25 while the 4th group included 7 patients who received no induction. The immunosuppressive regimen was cyclosporine (CsA), Mycophenolate mofetil (MMF) and prednisolone (PRD) for all patients. Bone marrow (BM) (90 ml) were aspirated from the iliac bone of related donors, to separate MSCs, then about 10 million MSCs placed in 10 ml saline were infused intravenously in 2 divided doses 1 week apart. Our results showed that the lowest mean serum creatinine level measured after 1, 3, and 6 months were in those patients who received pre-transplantation DS-MSC infusion (group I). Also rejection was less frequent in patients of group I. Microchimerism was detected after MSCs transfusion in one case of group I. We conclude that MSCs can escape immune recognition, can inhibit immune responses and prevent the development of cytotoxic T-cells so their transfusion may be used to treat organ allograft rejection and reduce the need for an immunosuppressive regimen after renal transplantation.

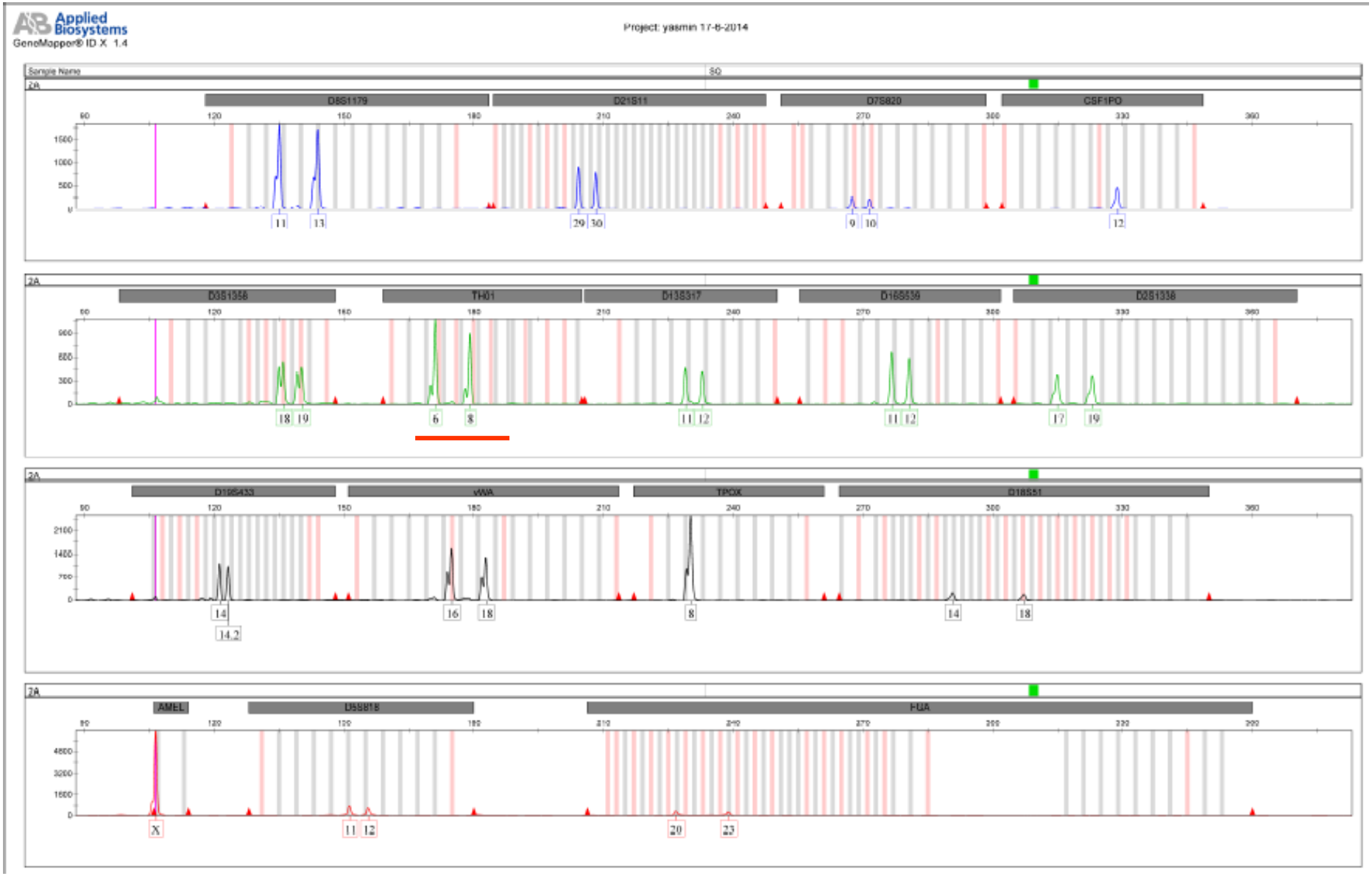
- **Chimerism was proven in patient after DS- MSCs transfusion by examination of HLA class II (HLA-DR) by molecular biology technique**

- **Before MSCs transfusion HLA typing of patient was DR7 , DR13(6)**

- **HLA typing of related donor was DR4, DR13(6)**

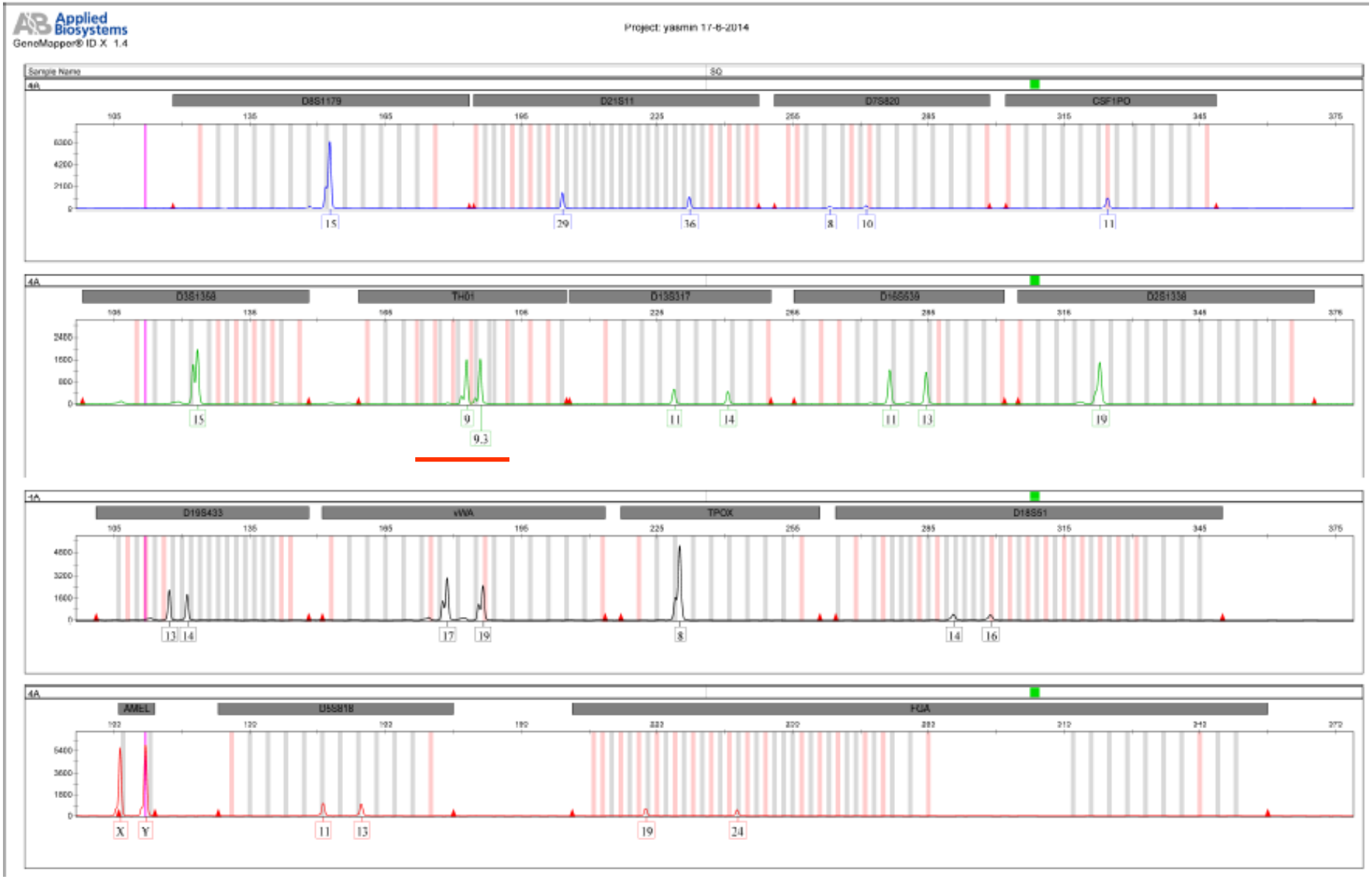
- **After MSCs transfusion HLA typing of patient was DR4, DR7, DR13(6)**

Saadi G et al, Dynamic Biochem 4(1): 55-60, 2010



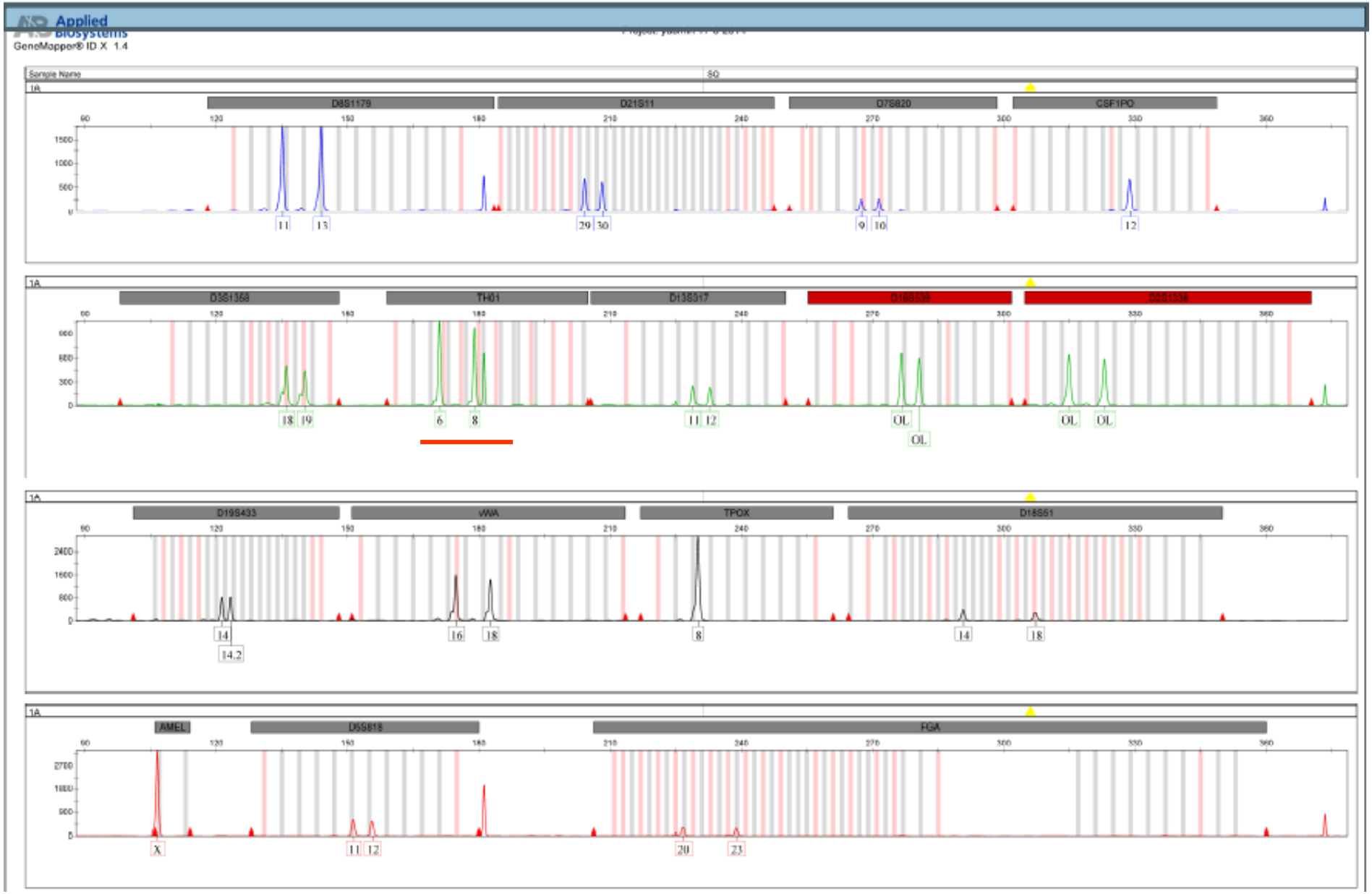
Recipient before MSCs

Saadi et al, 2016



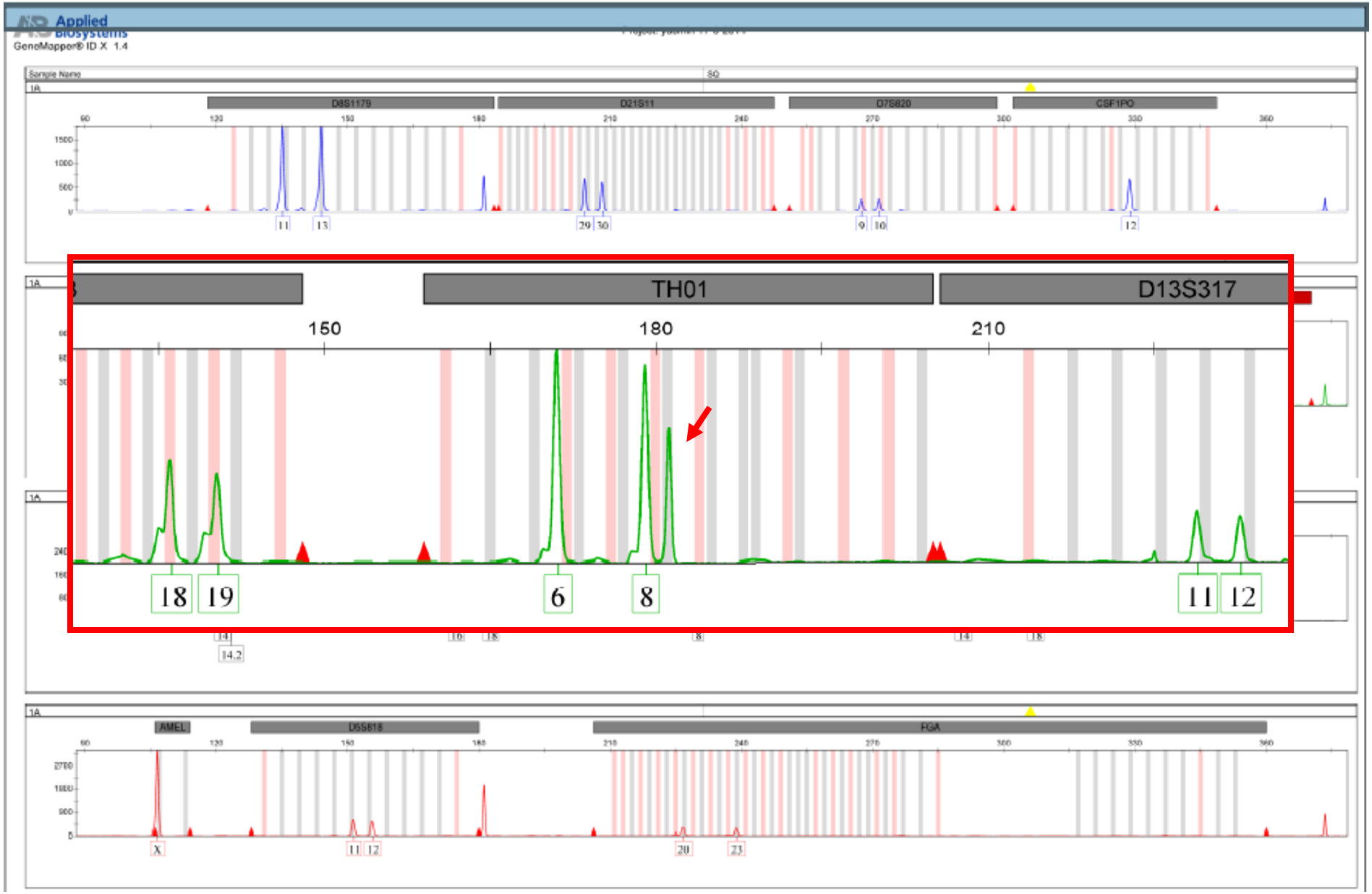
MSCs Donor

Saadi et al, 2016



Recipient after MSCs

Saadi et al, 2016

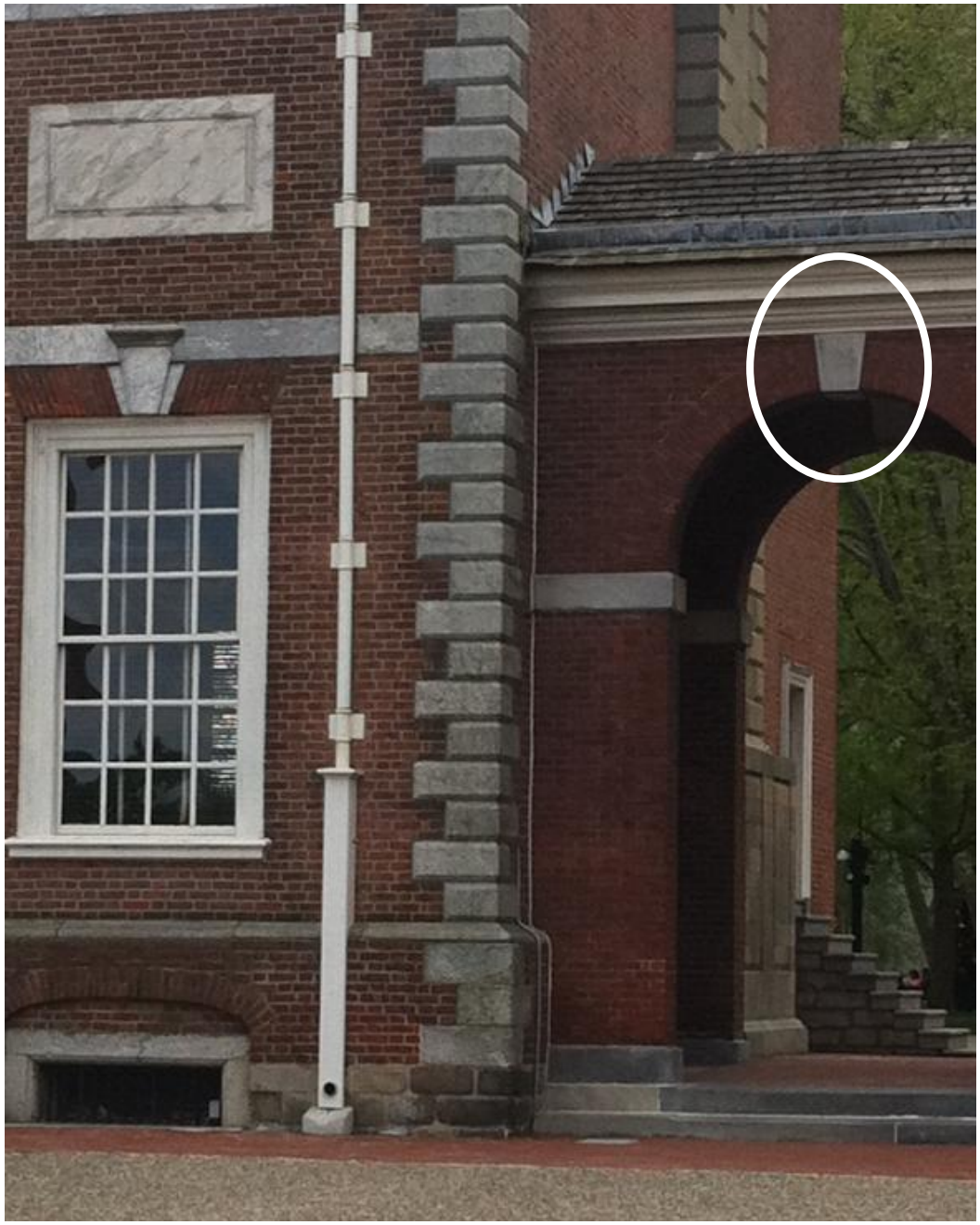


Recipient after MSCs

Saadi et al, 2016

Immunosuppression and Adherence is the corner stone of maintaining graft survival

Allospecific matching is the Key stone of ensuring graft survival



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Professor of Ped Nephrology
Cairo University

Prof May Hassaballa
Professor of Nephrology
Cairo University

Prof Mona Roshdi
Professor of Nephrology
Cairo University

Prof Ragaa Ramadan
Prof of Nephrology
Azhar University

Prof Mohamed Salah
Prof of Nephrology
Azhar University

Dr Amal Hussein
Ass Lecturer
Azhar University