Calling All Super Heroes

The Science Behind HLA Matching & A Bit More

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Baylor University Medical Center

Clinical Professor, Pathology & Lab Medicine
Texas A&M HSC College of Medicine

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November 10, 2018

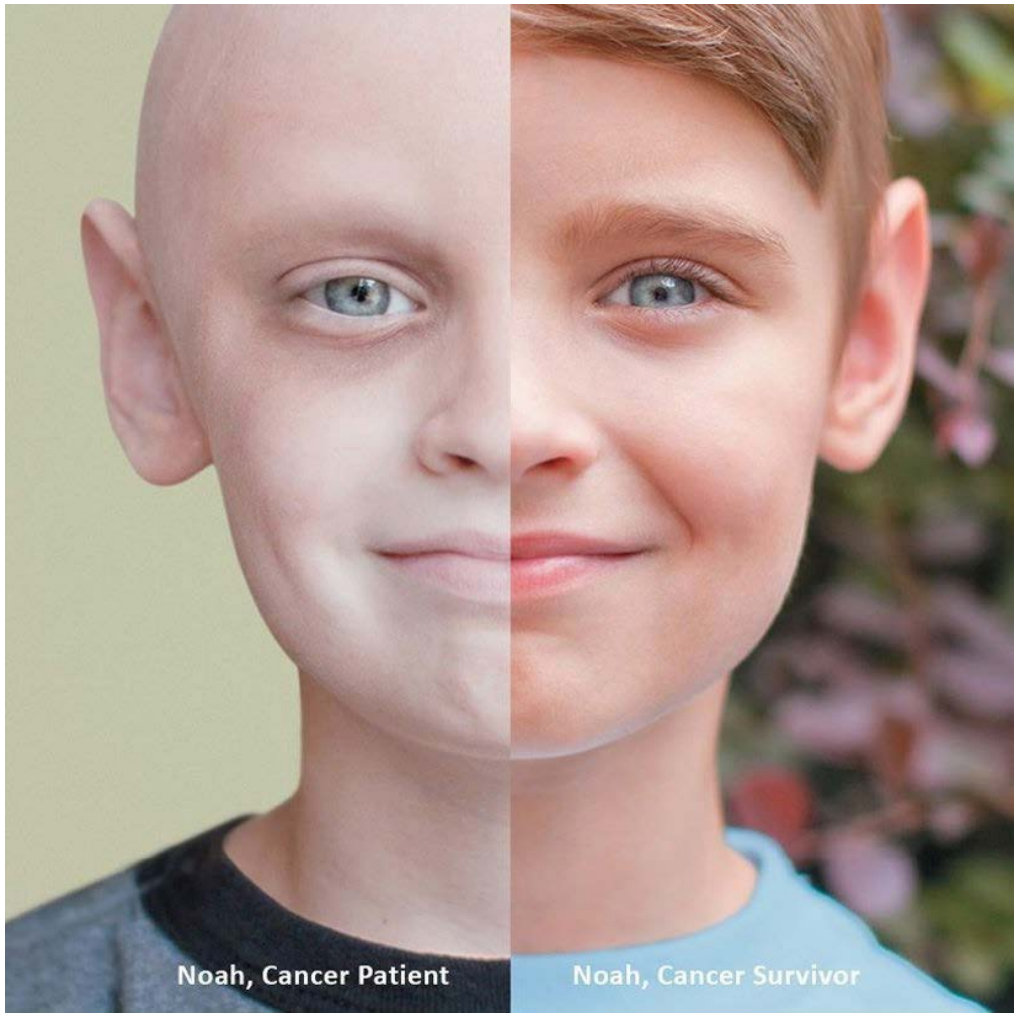
Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Medhat Askar, MD, PhD, FRCPath	Baylor University Medical Center Texas A&M HSC College of Med	None

OUTLINE

How does all of this work?



http://www.huffingtonpost.com

1 TYPE PATIENT

Consider:
High Resolution HLA Typing,
Antibody Testing, DPB1 Typing

Search Prognosis Tool

Related Donor Services

- ✓ High resolution HLA typing
- ✓ Antibody testing
- ✓ DPB1 typing
- ✓ Search prognosis tool
- ✓ Related Donor Services

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Let's go!

OUTLINE

Immunologic Concepts in Clinical Transplantation

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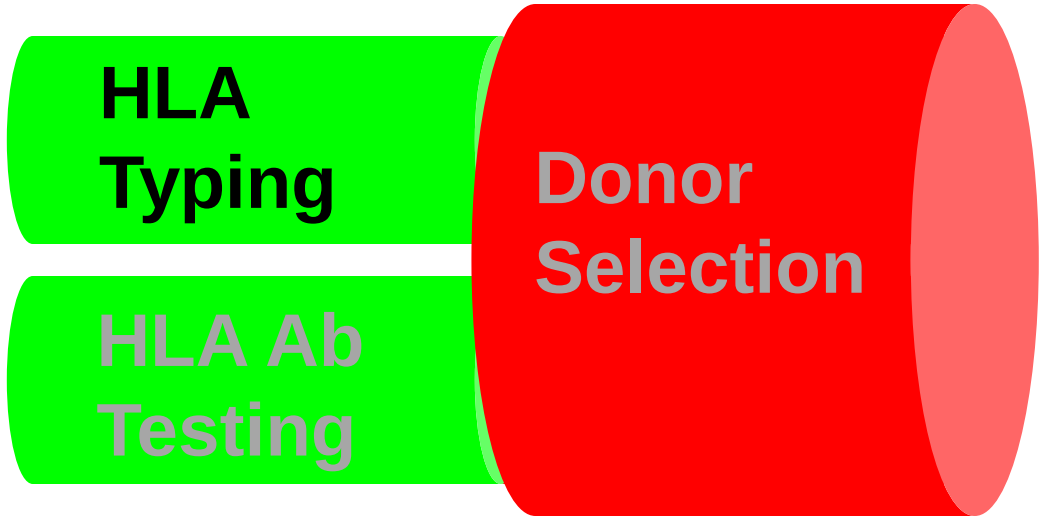
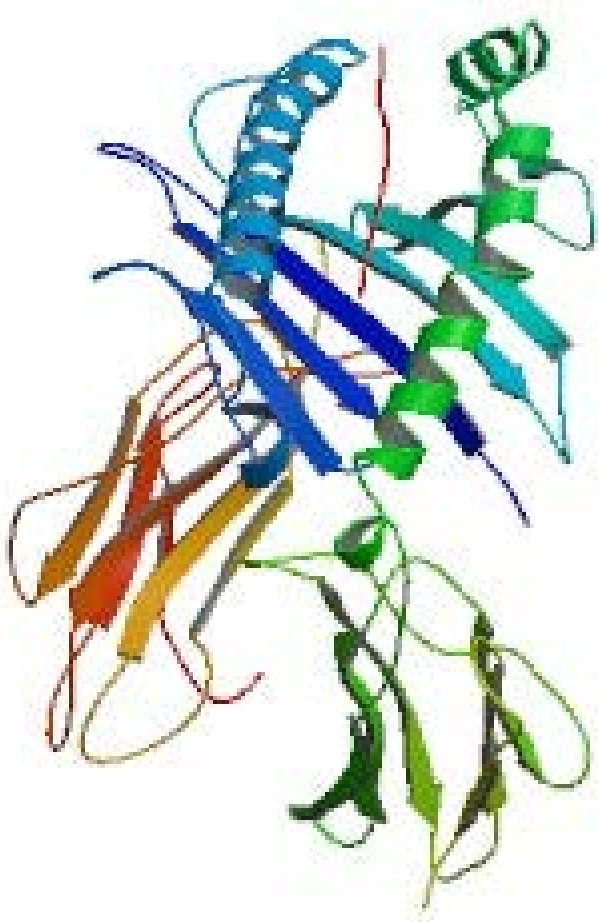

HLA Typing
HLA Ab Testing
Donor Selection

HLA?!



First HLA Antigen, 1953

Jean Dausset (1916-2009)

1980 Nobel Prize Laureate

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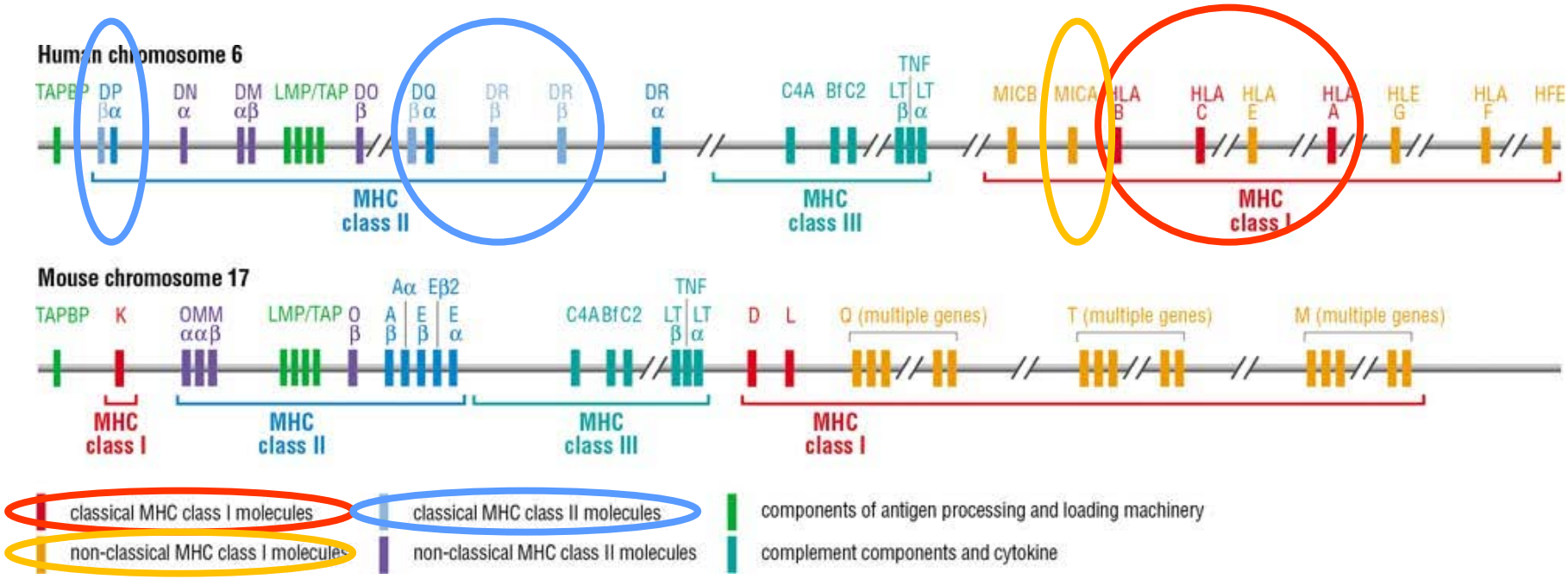
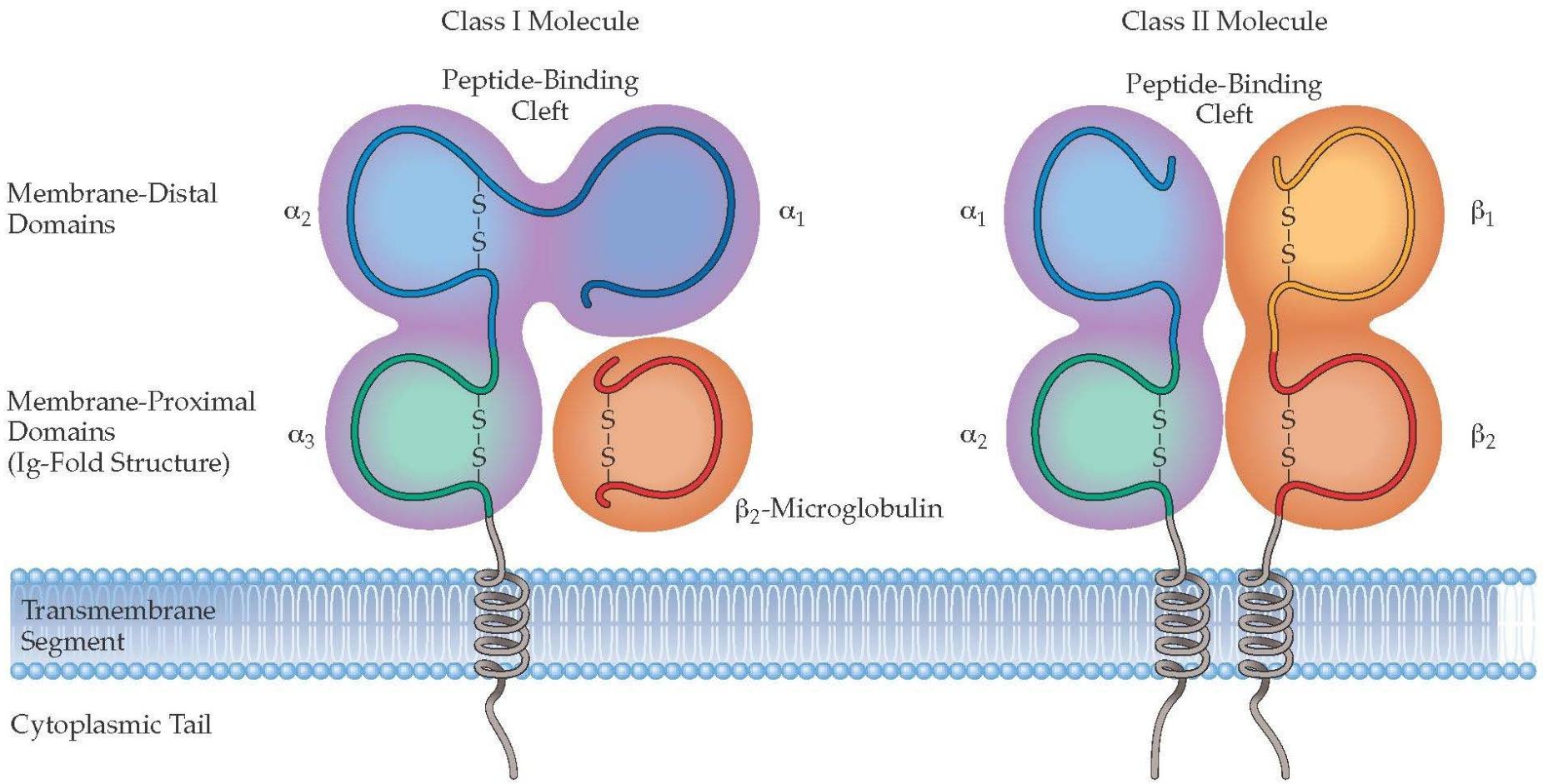
HLA??!!!


Human chromosome 6
TAPBP
DP βα
DN α
DM αβ
LMP/TAP
DO β
DQ βα
DR β
DR β
DR α
C4A
BfC2
TNF
LT β
LT α
MICB
MICA
HLA B
HLA C
HLA E
HLA A
HLE G
HLA F
HFE
MHC class II
MHC class III
MHC class I
Mouse chromosome 17
TAPBP
K
OMM ααβ
LMP/TAP
O β
Aα
A β
E β
E α
Eβ2
C4A
BfC2
TNF
LT β
LT α
D
L
Q (multiple genes)
T (multiple genes)
M (multiple genes)
MHC class I
MHC class II
MHC class III
MHC class I
classical MHC class I molecules
non-classical MHC class I molecules
classical MHC class II molecules
non-classical MHC class II molecules
components of antigen processing and loading machinery
complement components and cytokine



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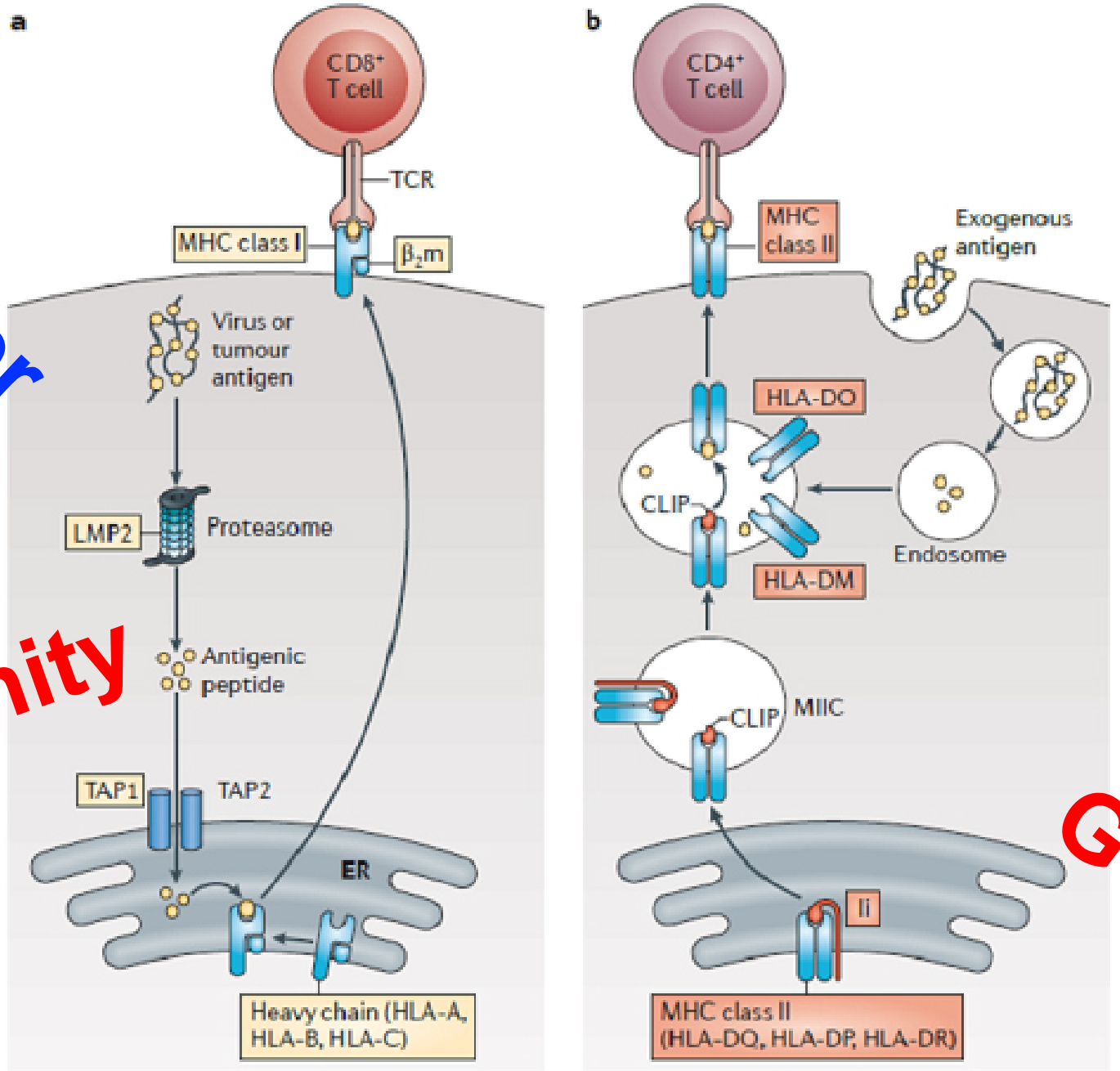
http://what-when-how.com/wp-content/uploads/2012/04/tmp4C9.jpg

Anti-Cancer Immunity

Autoimmunity



Antimicrobial Immunity

Rejection GVHD

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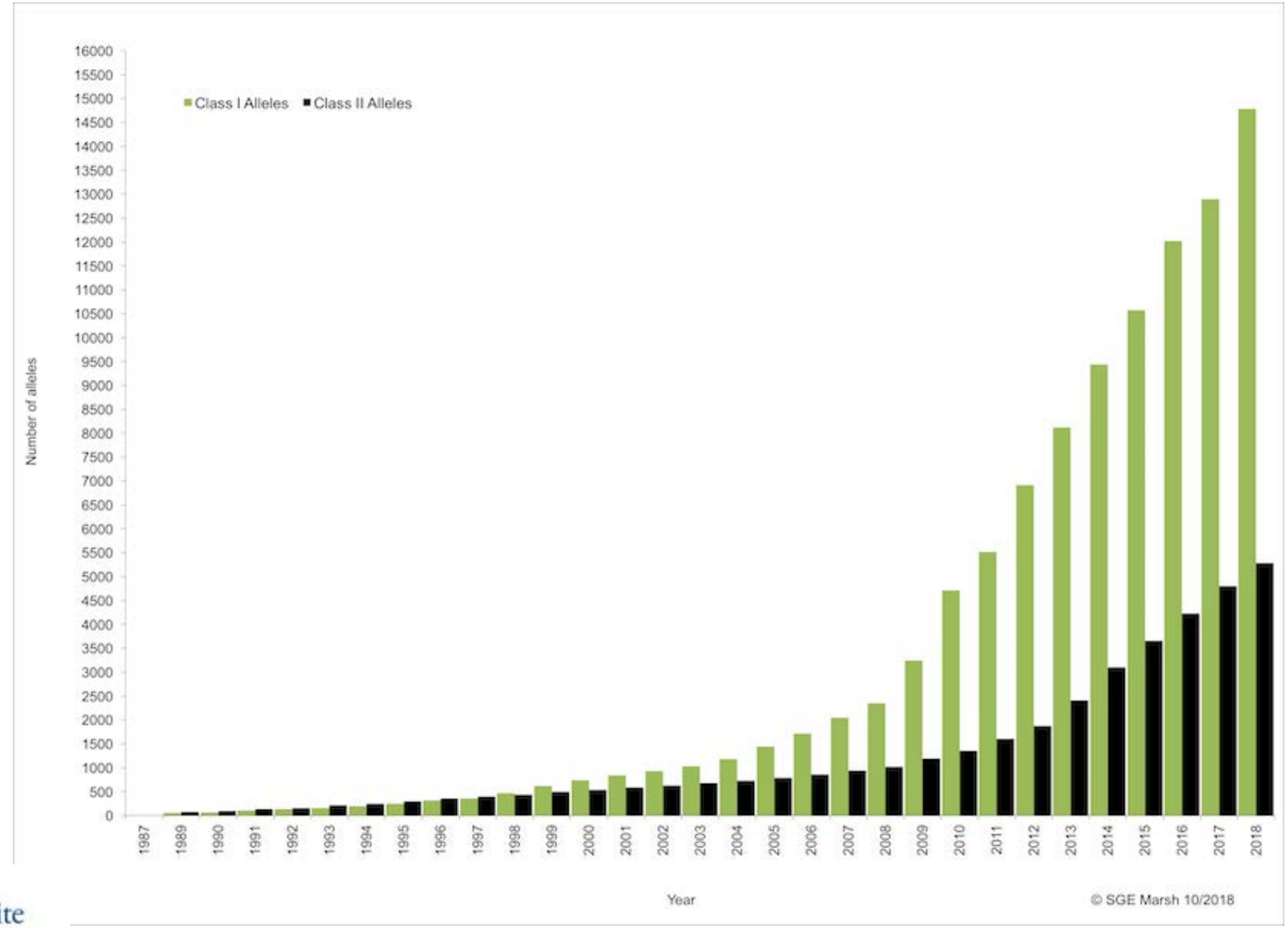
https://www.astro.org



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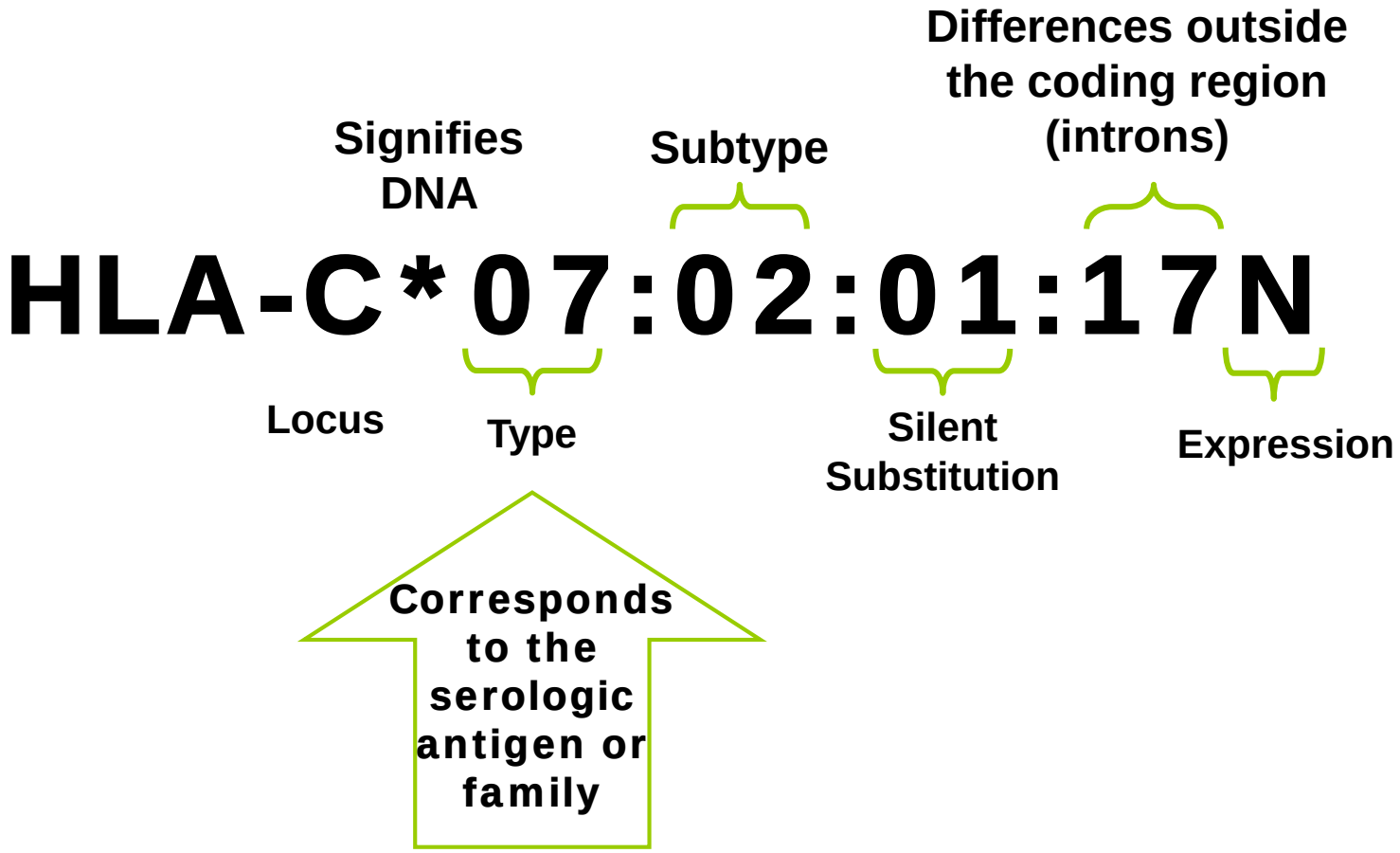
Database Release 3.34.0 (10/2018)

What is Nomenclature?



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B*15:01 = B62

B*15:02 = B71

C*03:03 = Cw9

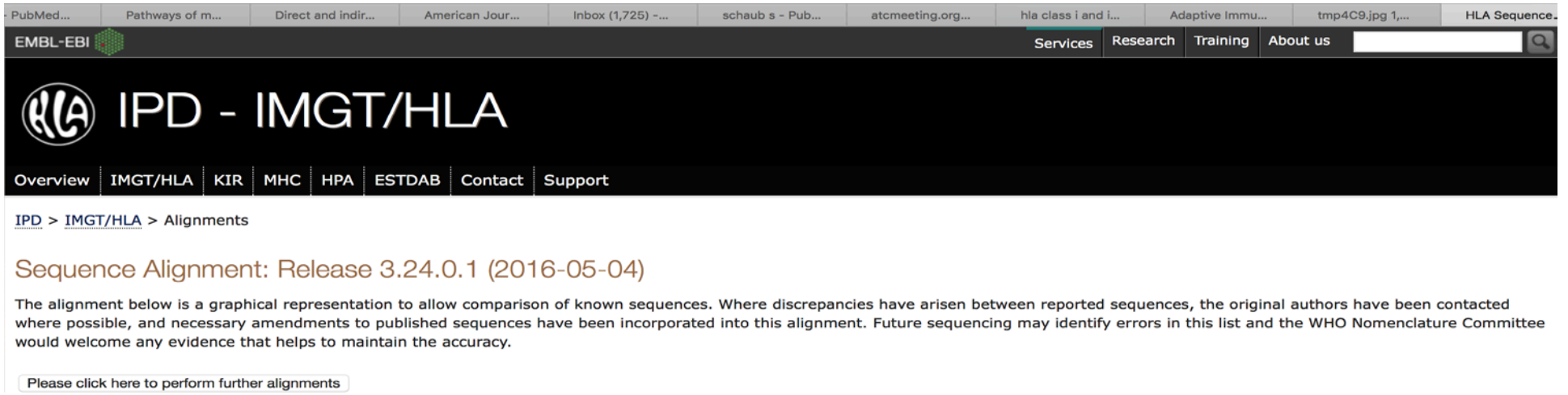
C*03:04 = Cw10

DRB1*03:01 = DR17

DRB1*03:02 = DR18

DQB1*03:01 = DQ7

DQB2*03:02 = DQ8



Numbers of Serologically Defined Antigens						
HLA-Locus	**A**	**B**	**Cw**	**DR**	**DQ**	**DP**
Serologically Defined Antigens	**28**	**62**	**10**	**24**	**9**	**6**

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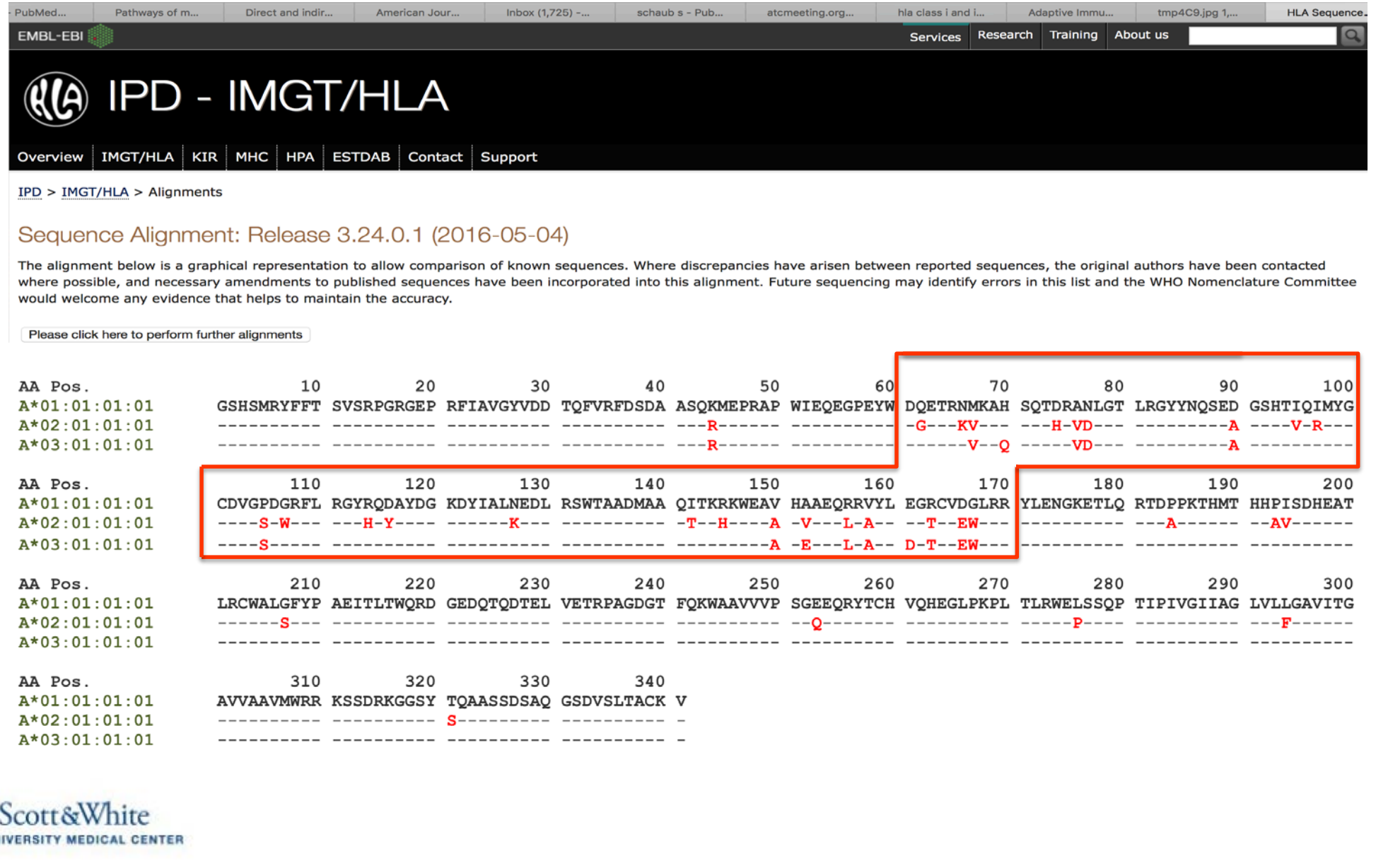

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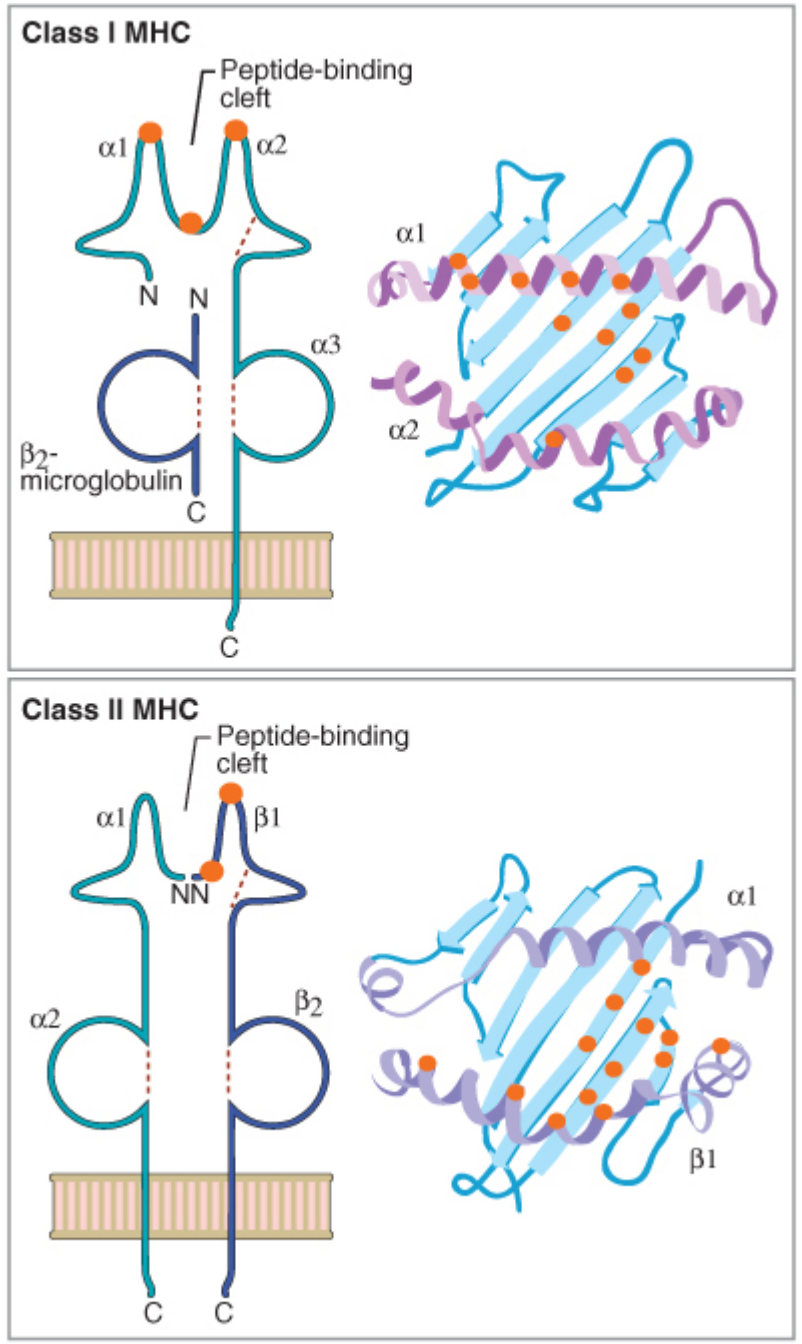
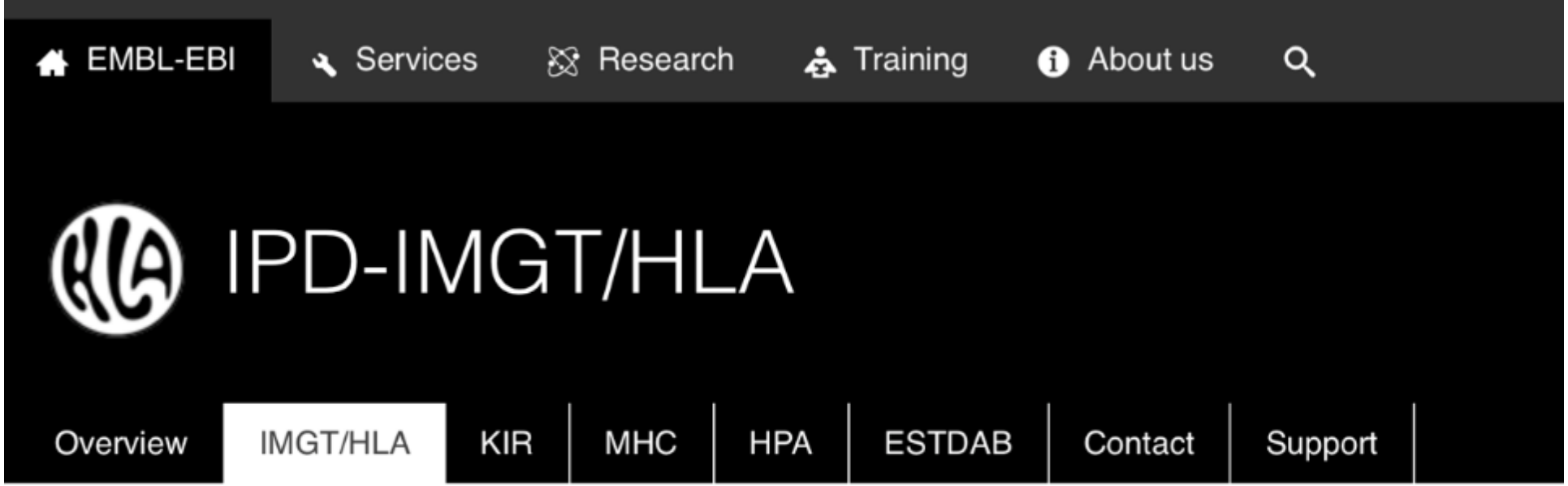
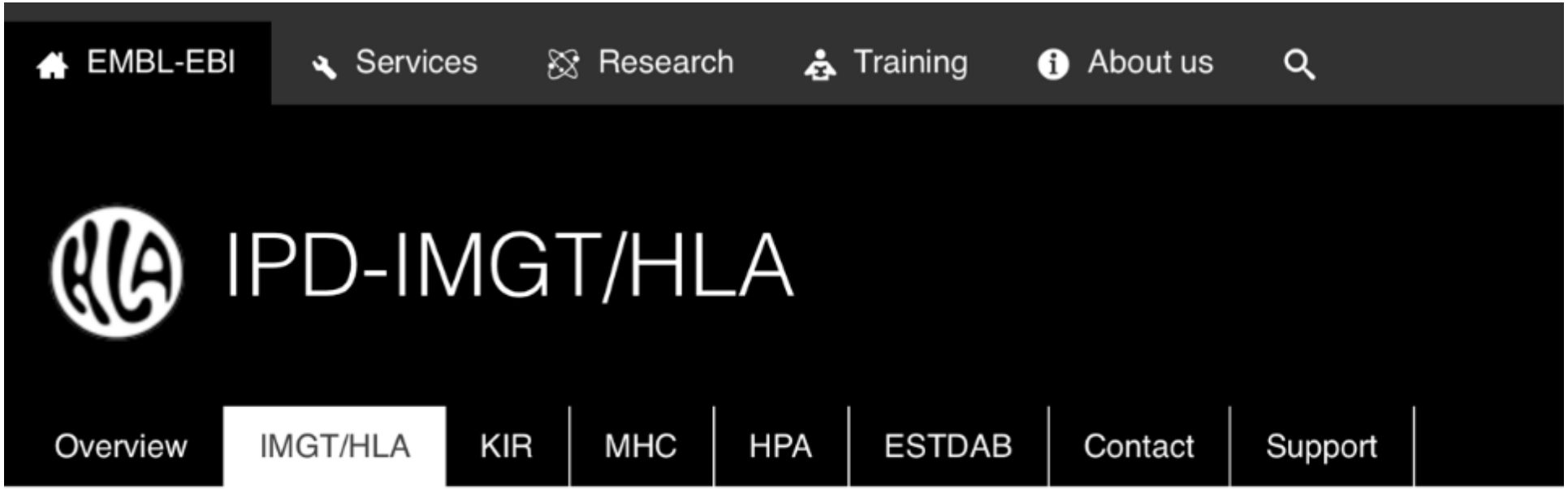




Statistics

HLA Class I				
Gene	***A***	***B***	***C***	***Total***
Alleles	4,638	5,590	4,374	14,592
Proteins	3,172	3,923	2,920	10,015
Nulls	224	169	171	564

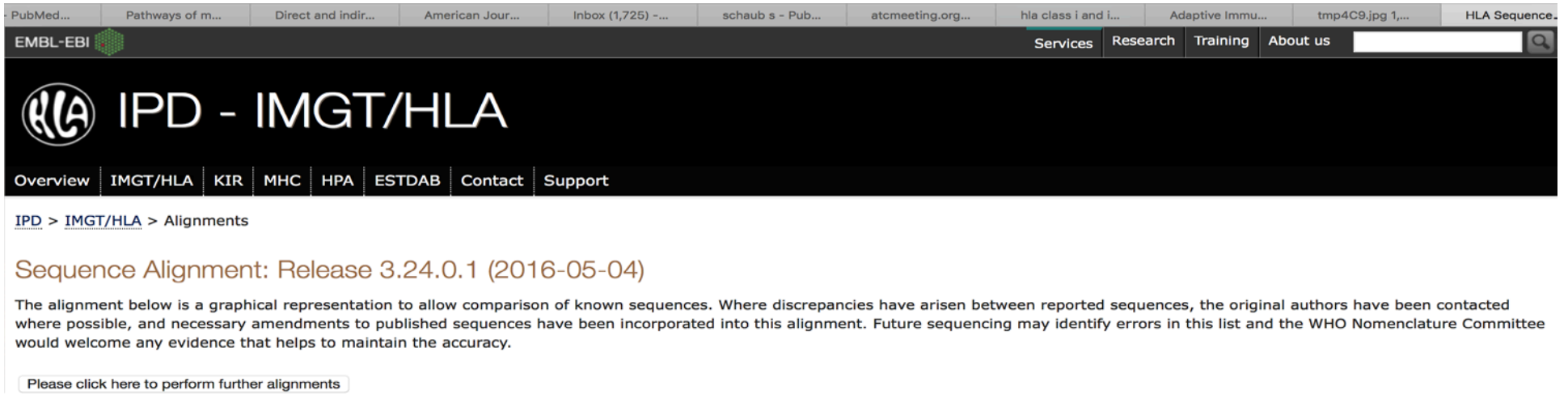
Database Release 3.34.0 (10/2018)



Statistics

HLA Class II							
Gene	***DRA***	***DRB***	***DQA1***	***DQB1***	***DPA1***	***DPB1***	***Total***
Alleles	7	2,693	100	1,316	73	1,097	5,286
Proteins	2	1,908	36	878	32	728	3,584
Nulls	0	84	4	35	0	34	157

Database Release 3.34.0 (10/2018)

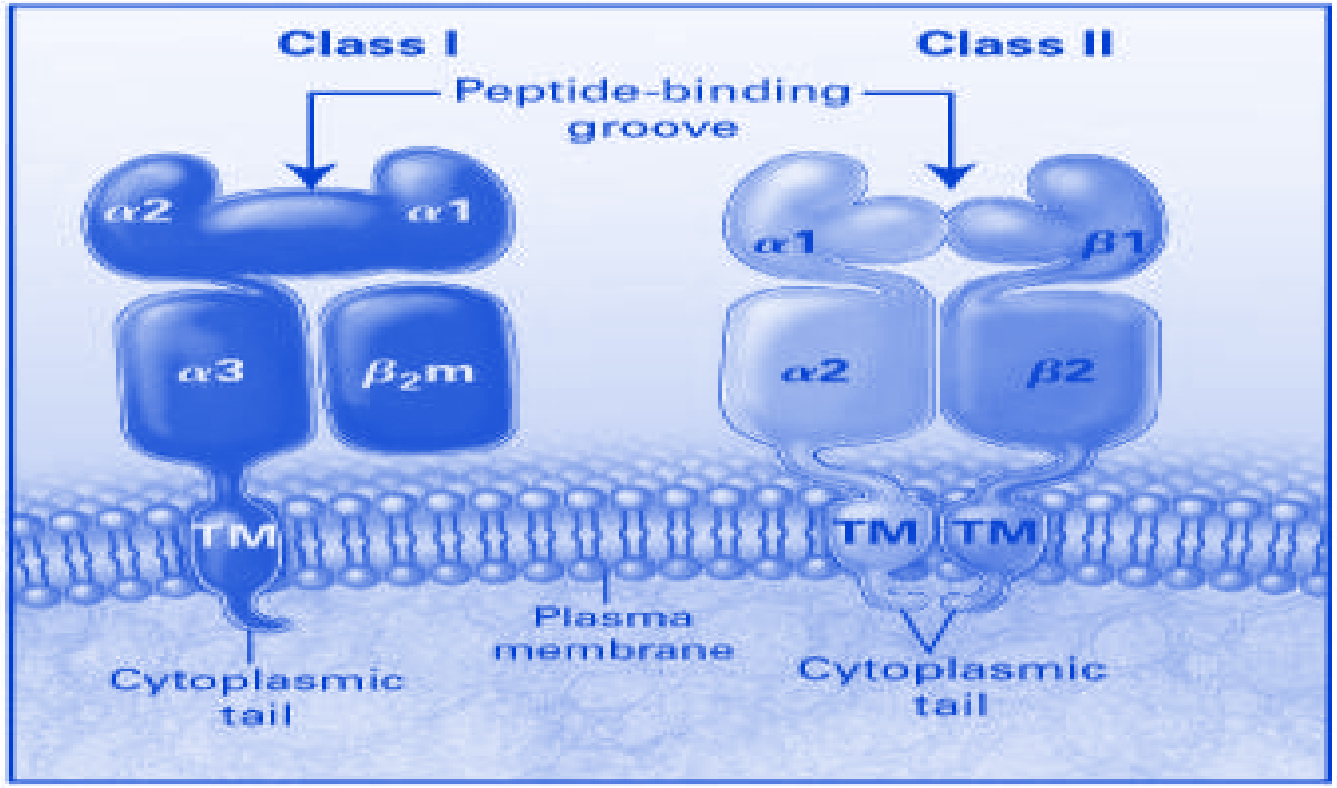


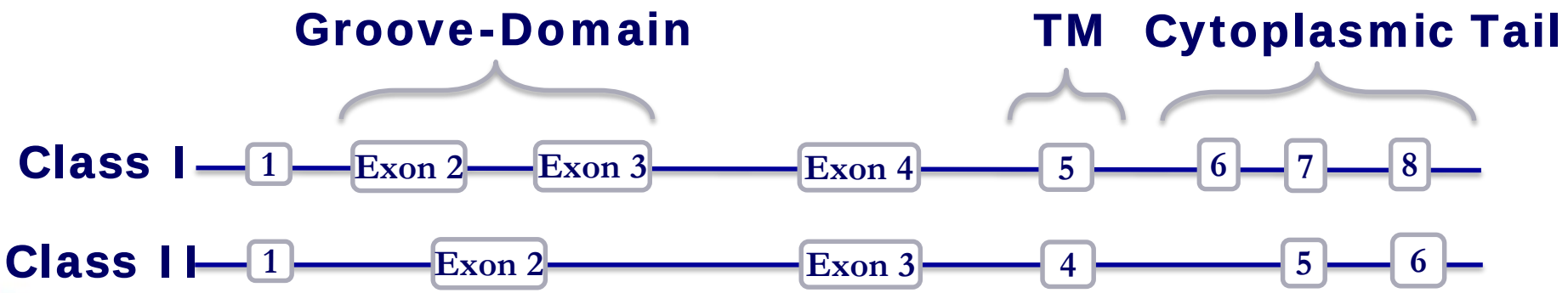

```
AA Pos.                10        20        30        40        50        60        70        80        90       100
A*01:01:01:01     GSHSMRYFFT SVSRPGRGEP RFIAVGYVDD TQFVRFDSDA ASQKMEPRAP WIEQEGPEYW DQETRNMKAH SQTDRANLGT LRGYYNQSED GSHTIQIMYG
A*02:01:01:01     ---------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:02:01:01     ---------- ---------- ---------- ---------- --RR------ ---------- -G---KV--- ---H-VD--- ---------A ----L-R---
A*02:03:01        ---------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:04           ---------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-M---
A*02:05:01        --------Y- ---------- ---------- ---------- --RR------ ---------- -G---KV--- ---H-VD--- ---------A ----L-R---
A*02:06:01:01     --------Y- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---

A*02:608N         ---------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:609          *--------- ---------- ---------- ---------- ---R------ ---------- -G-------- ---H-VD--- ---------A ----V-R---
A*02:610          *--------- ---------- ---------- ---------- ---S------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:611          *--------- --T------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:612          *--------- ------S--- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:613          *--------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
A*02:614          *--------- ---------- ---------- ---------- ---R------ ---------- -G---KV--- ---H-VD--- ---------A ----V-R---
```

AA6613

A*24:02:01:01	**A*31:01:02**		
A*24:02:01:02L	**A*31:01:02**	Intron 2	
A*24:02:01:03	**A*31:01:02**	Intron 3	
A*24:02:40	**A*31:01:02**	Exon 5	
A*24:03:01	A*31:05	Exon 3	Ruled out by RSSOP.
A*24:34	A*31:66	Exon 2	
A*24:57	A*31:29	Exon 3	Not on Common list.
A*24:71	A*31:41	Exon 3	Ruled out by RSSOP.
A*24:145	A*31:02	Exon 2	

Master Layer
822 bases between Intron 1 34 and Intron 4 30
Mean BCS: 85


Class I
Class II
Peptide-binding groove
α2
α1
α1
β1
α3
β2m
α2
β2
TM
TM
TM
Plasma membrane
Cytoplasmic tail
Cytoplasmic tail


Groove-Domain
TM
Cytoplasmic Tail
Class I
1
Exon 2
Exon 3
Exon 4
5
6
7
8
Class II
1
Exon 2
Exon 3
4
5
6

On June 26, 2000 President Clinton, with J. Craig Venter, left, and Francis Collins, announces completion of "the first survey of the entire human genome."

$ 3 Billion (2000)

10 years (1993-2003)

Schuster, Nature Methods 2008

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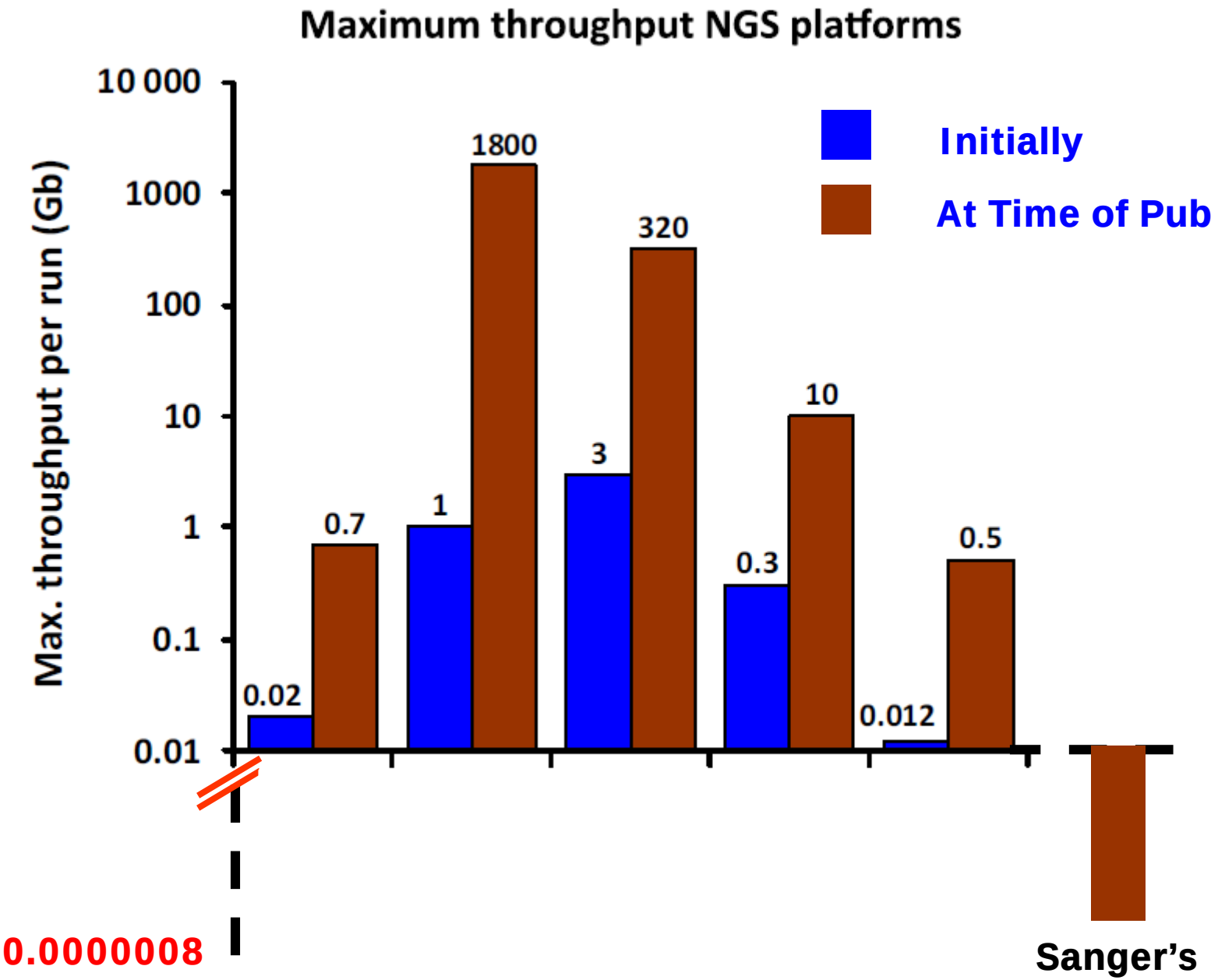
NATURE METHODS | VOL.5 NO.1 | JANUARY 2008 | 1

EDITORIAL

Method of the Year

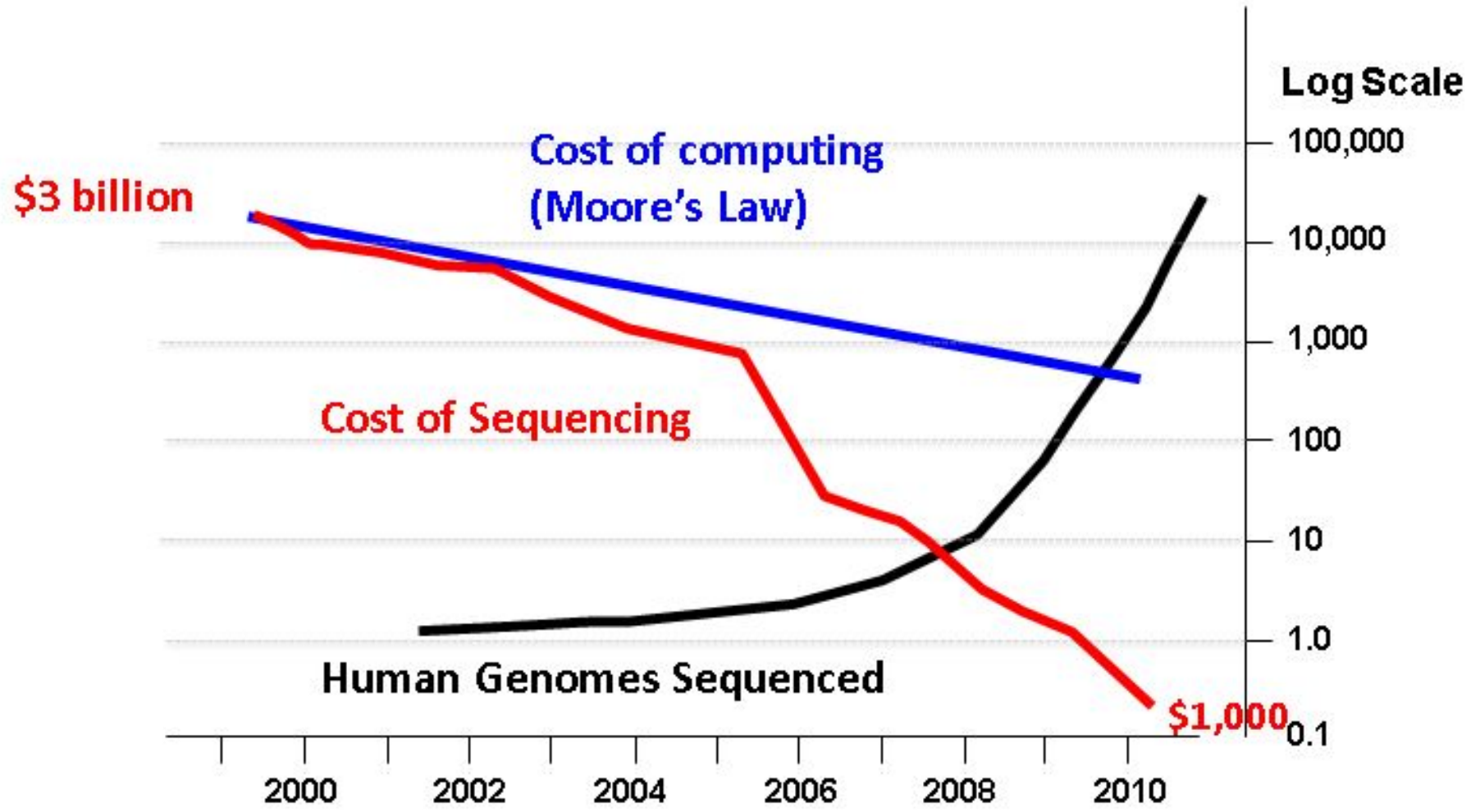
There are events of the year, persons of the year, images of the year.... We could not resist: why not a Method of the Year?



van Dijk et al, 2014

Adapted from The Economist

The Sequencing Explosion



AA6613

A*24:02:01:01			
A*24:02:01:02L		Intron 2	
A*24:02:01:03		Intron 3	
A*24:02:40		Exon 5	
A*24:03:01		Exon 3	Ruled out by RSSOP.
A*24:34		Exon 2	
A*24:57		Exon 3	Not on Common list.
A*24:71		Exon 3	Ruled out by RSSOP.
A*24:145		Exon 2	

Master Layer
822 bases between Intron 1 34 and Intron 4 30
Mean BCS: 85

NGS-ENGINE	**Best Match**	**A*24:02:01:01, A*31:01:02**
Standard Method	**Mappability**	44188/48644 (90%)
Total Mappability	**Reads**	223 [35-251]
190645/200000 (95%)	**Coverage**	(3385, 7611)
	# Matching Genotypes	1

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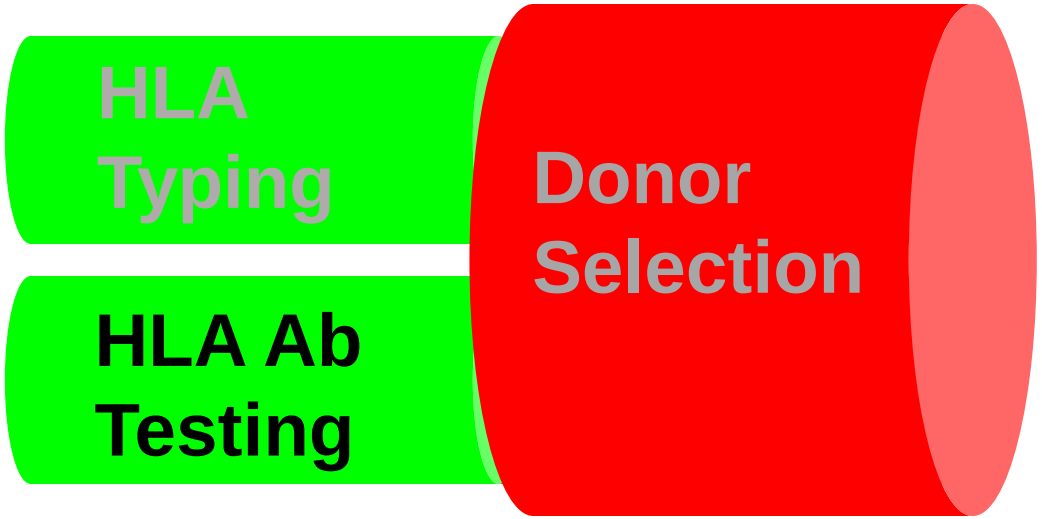
HLA Typing
HLA Ab Testing
Donor Selection

Allosensitization

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Let's go!

HLA Allosensitization

Allosensitization is defined as the development of HLA antibodies following exposure to a sensitizing event such as:

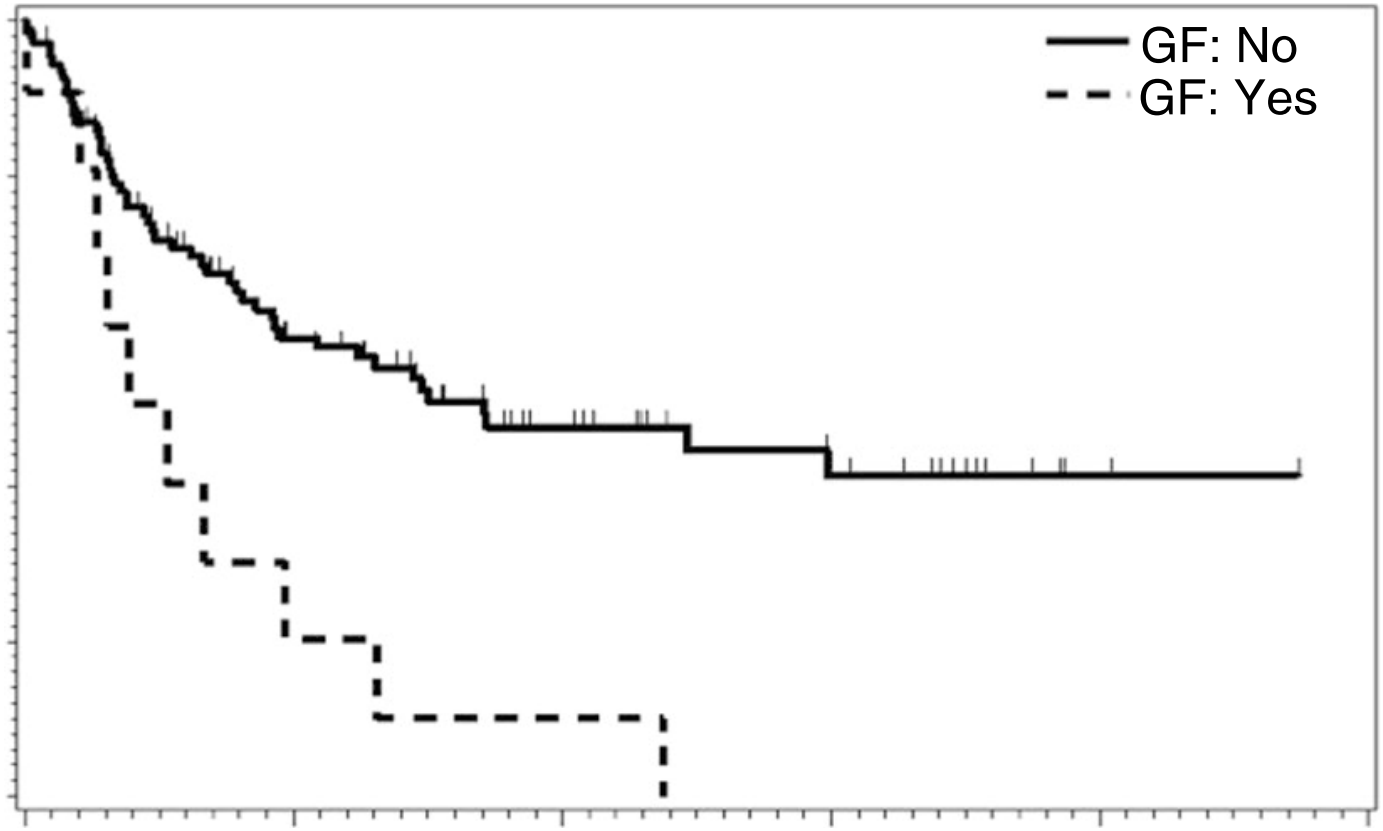
Pregnancy,

Blood/product transfusion, and

Organ transplantation.

TABLE 1 | Studies of DSA impact in different settings in AHSCT.

Reference	Patients (*n*)	Stem cell source	Conditioning	Anti-HLA%	DSA%	Graft failure with/without DSA
Spellman et al. (34)	115	Mismatched unrelated	RIC	ND	9	24 versus 1%
Ciurea et al. (36)	592	10/10 and 9/10 unrelated	MACorRIC	19.6	1.4	37.5 versus 2.7%
Yoshihara et al. (39)	79	Haplo-identical	RIC	20.2	14	27 versus 3%
Ciurea et al. (36)	24	Haplo-identical	RIC	ND	21	60 versus 5%
Chang et al. (40)	345	Haplo-identical	MAC	25.2	11.3	61% ($MFI_{>}$10,000) versus 3.2%
Ciurea et al. (36)	122	Haplo-identical	Non-specified	ND	18	32 versus 4%
Takanashi et al. (41)	386	Single CBU	MAC	23.1	5	83 versus 32%
Cutler et al. (42)	73	Double CBU	MACorRIC	ND	24	57 versus 5.5%
Ruggeri et al. (43)	294	Single and double CBU	RIC	23	5	81 versus 44%
Yamamoto et al. (44)	175	Single CBU	MACorRIC	39.4	ND	50% if anti-HLA-C, DP, DQ, DRB1/2/3 versus 16%



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Ciurea et al, 2015

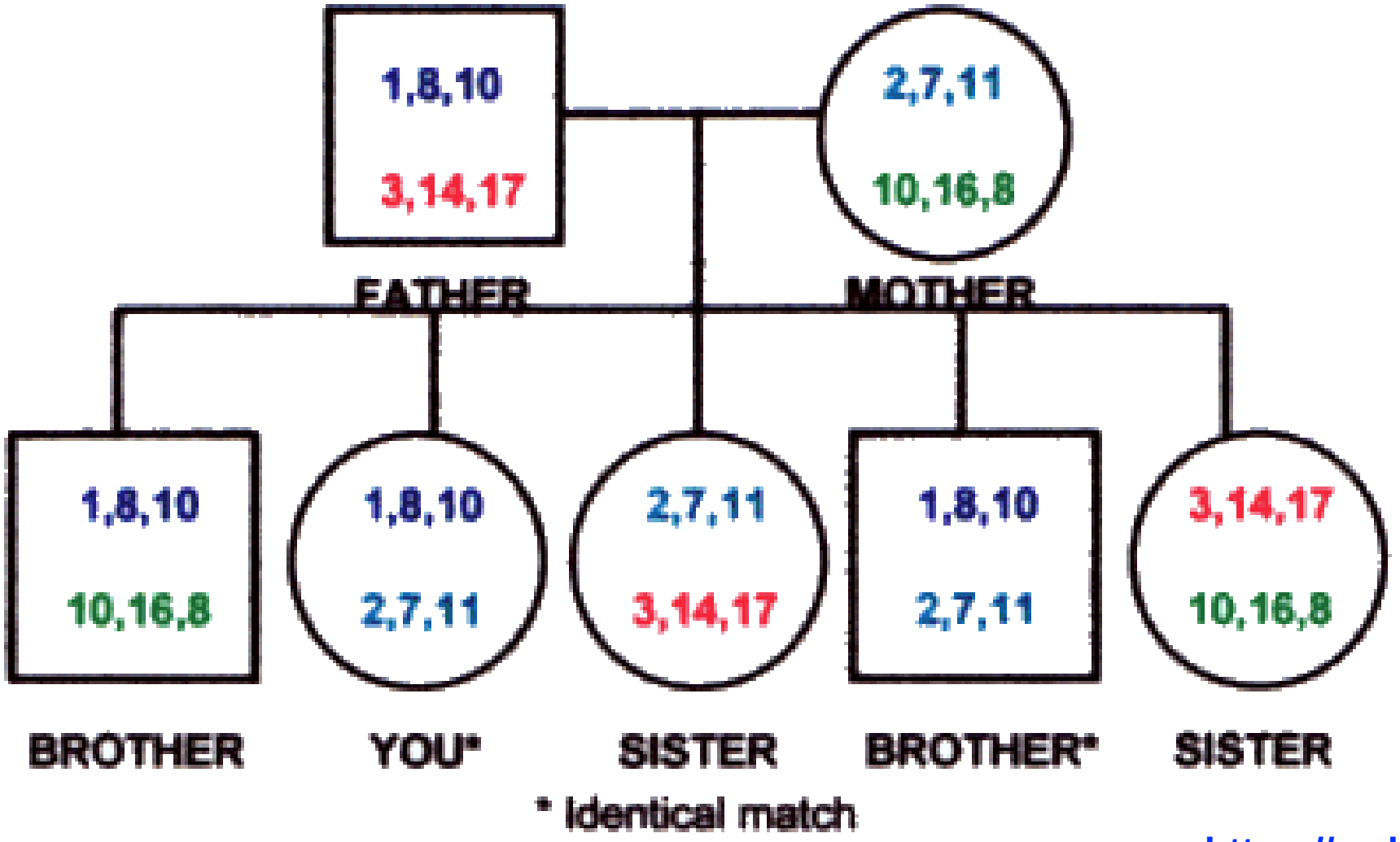
The NEW ENGLAND JOURNAL of MEDICINE

Volume 320 JANUARY 26, 1989 Number 4

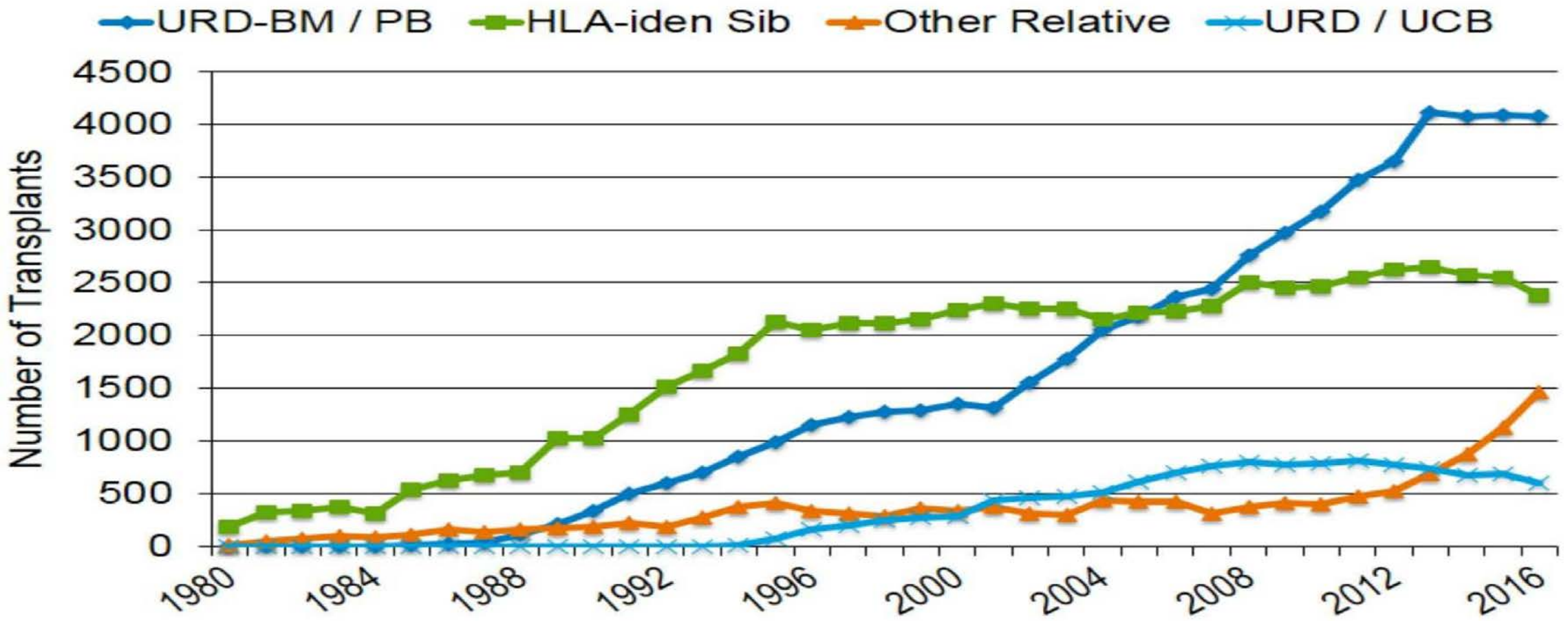
EFFECT OF HLA COMPATIBILITY ON ENGRAFTMENT OF BONE MARROW TRANSPLANTS IN PATIENTS WITH LEUKEMIA OR LYMPHOMA

CLAUDIO ANASETTI, M.D., DEBORAH AMOS, PATRICK G. BEATTY, M.D., PH.D., FREDERICK R. APPELBAUM, M.D., WILLIAM BENSINGER, M.D., C. DEAN BUCKNER, M.D., REGINALD CLIFT, KRISTINE DONEY, M.D., PAUL J. MARTIN, M.D., ERIC MICKELSON, BRENDA NISPEROS, JOHN O'QUIGLEY, PH.D., ROBERT RAMBERG, JEAN E. SANDERS, M.D., PATRICIA STEWART, M.D., RAINER STORB, M.D., KEITH M. SULLIVAN, M.D., ROBERT P. WITHERSPOON, M.D., E. DONNALL THOMAS, M.D., AND JOHN A. HANSEN, M.D.

HLA Mismatches & Donor Source



Allogeneic HCT Recipients in the US, by Donor Type



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-017-0062-8

REVIEW ARTICLE

Corrected: Correction

The European Society for Blood and Marrow Transplantation (EBMT) Consensus Guidelines for the Detection and Treatment of Donor-specific Anti-HLA Antibodies (DSA) in Haploidentical Hematopoietic Cell Transplantation

Stefan O. Ciurea[1] · Kai Cao[1] · Marcelo Fernandez-Vina[2] · Piyanuch Kongtim[3] · Monzr Al Malki[4] · Ephraim Fuchs[5] · Leo Luznik[5] · Xiao-Jun Huang[6] · Fabio Ciceri[7] · Franco Locatelli[8] · Franco Aversa[9] · Luca Castagna[10] · Andrea Bacigalupo[11] · Massimo Martelli[12] · Didier Blaise[13] · Rupert Handgretinger[14] · Denis-Claude Roy[15] · Paul O'Donnell[16] · Asad Bashey[17] · Hillard M. Lazarus[18] · Karen Ballen[19] · Bipin N. Savani[20] · Mohamad Mohty[21] · Arnon Nagler[22,23]

How To Measure Allosensitization

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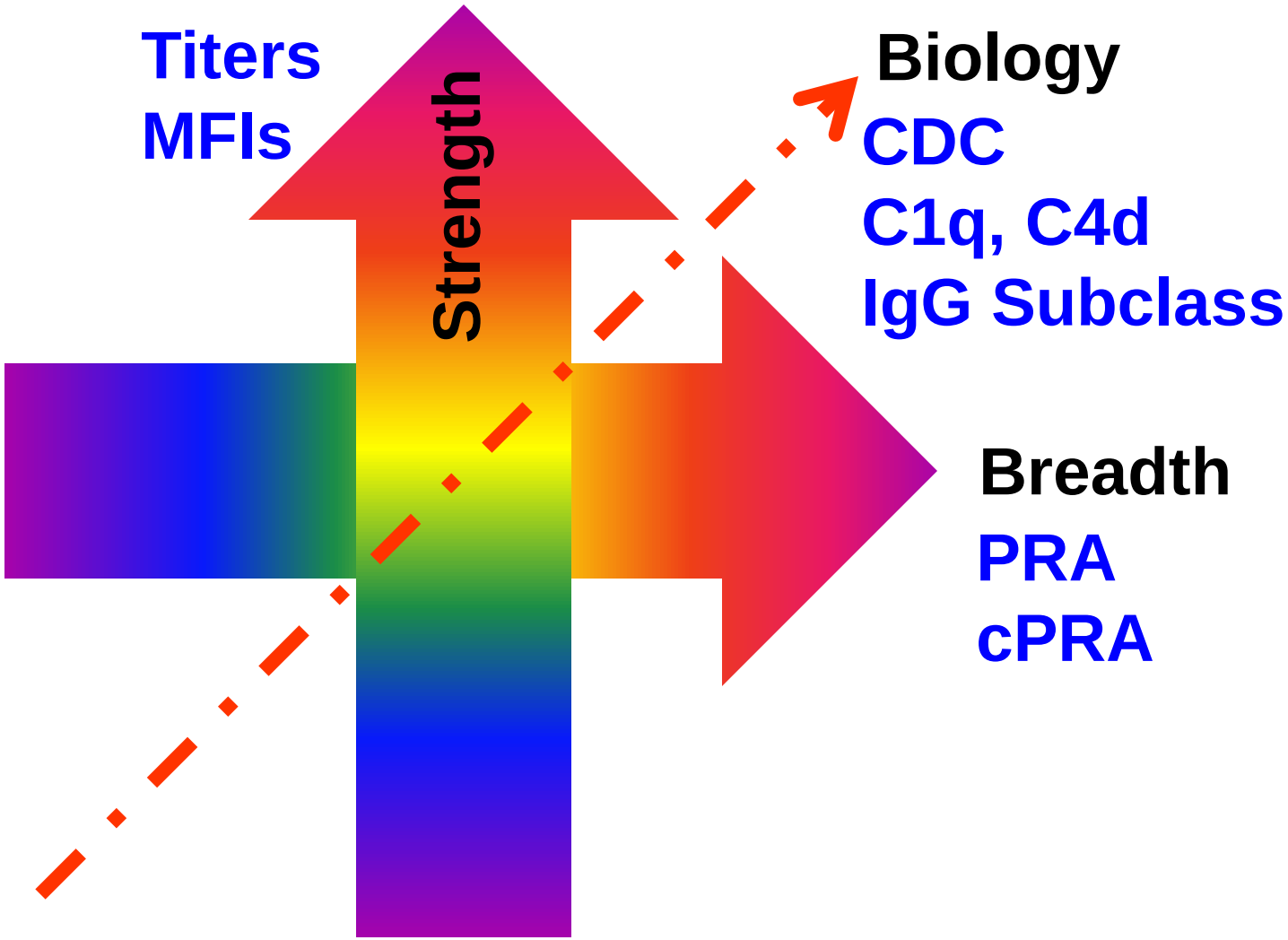
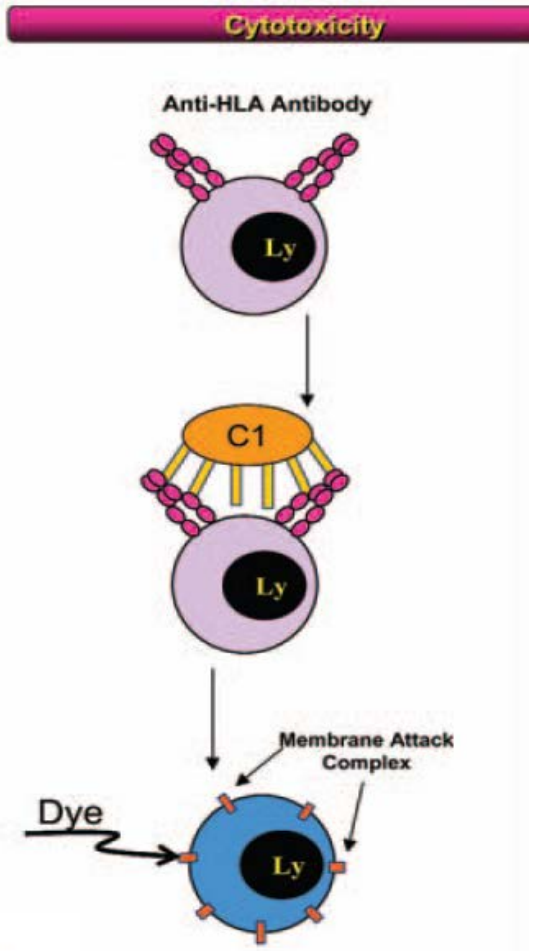
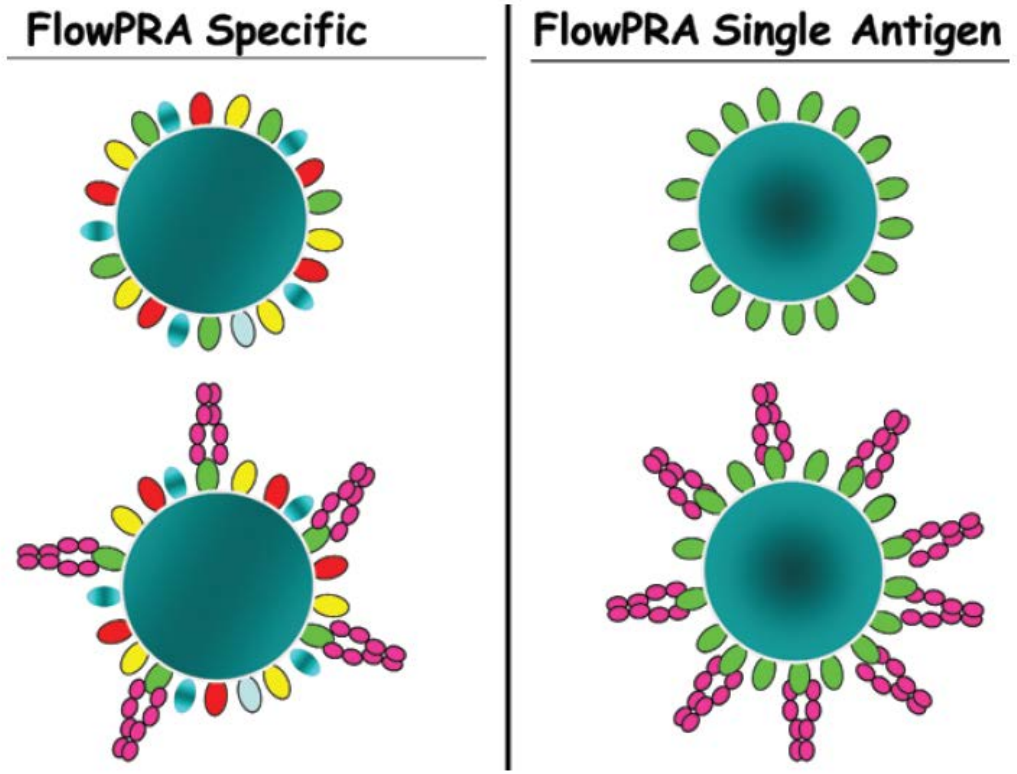
Parameters / Characteristics



Taxonomy Ab Detection Assays





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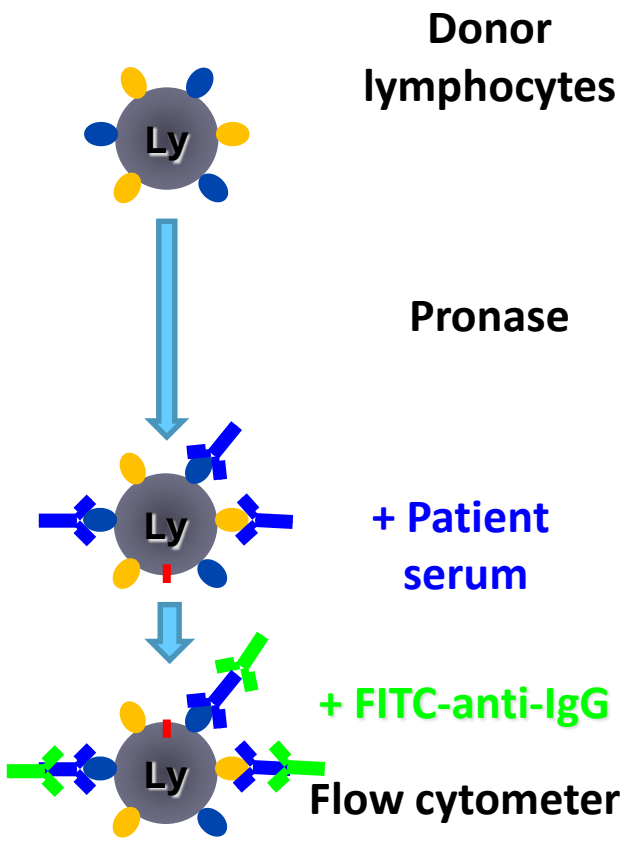
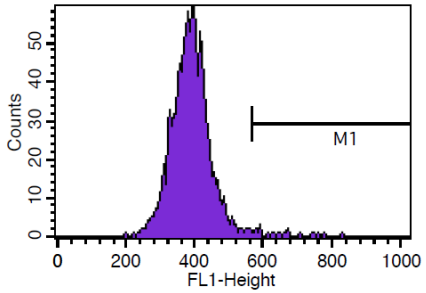
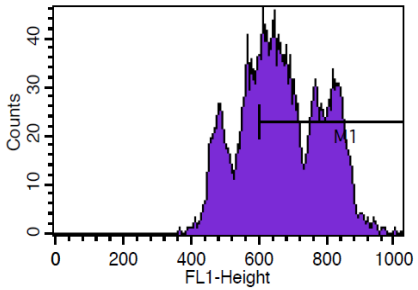
Bray et al 2004







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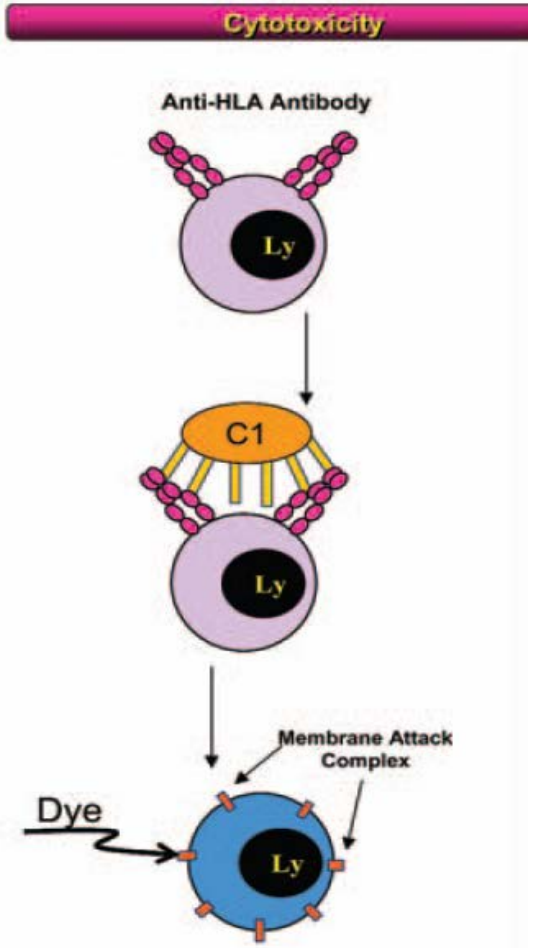
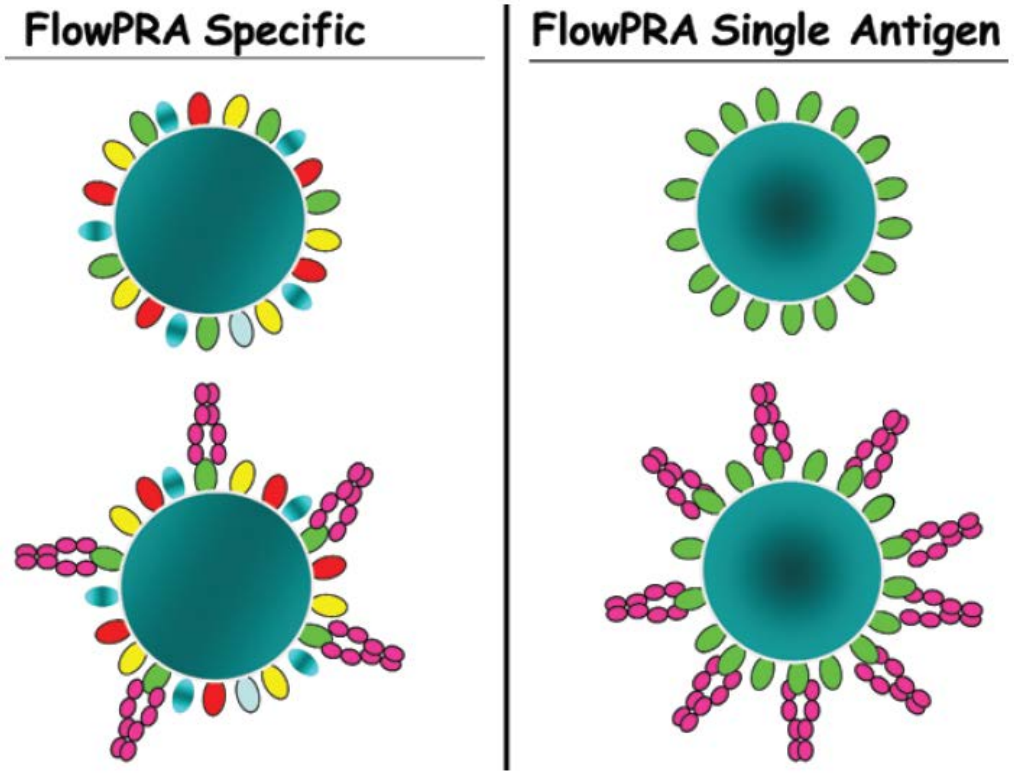
Taxonomy





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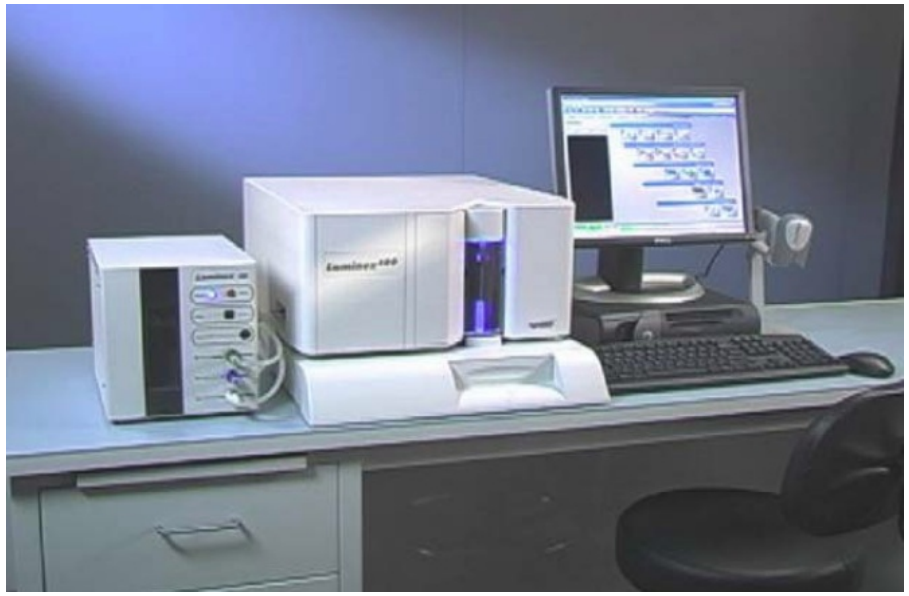
Bray et al 2004

Clinical Chemistry 43:9
1749–1756 (1997)

Oak Ridge
Conference

Advanced multiplexed analysis with the FlowMetrix™ system

R. Jerrold Fulton,* Ralph L. McDade, Perry L. Smith, Laura J. Kienker,[1] and John R. Kettman Jr.[1]



BaylorScott&White
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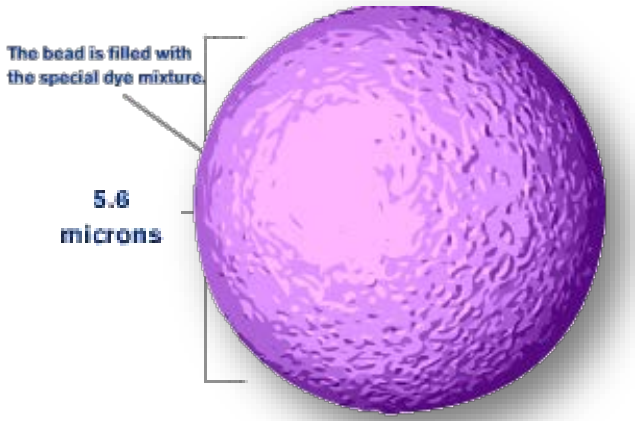
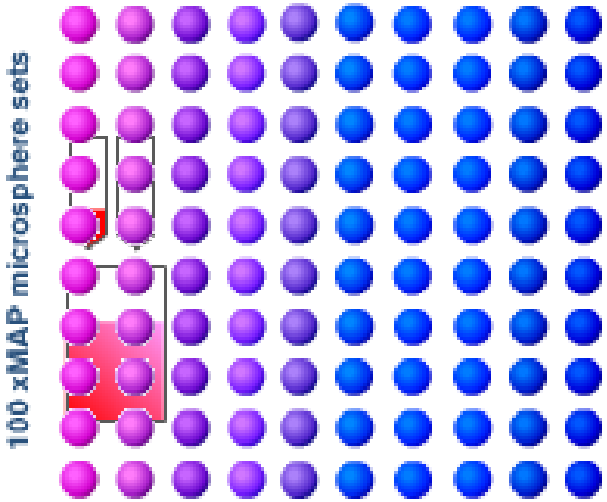
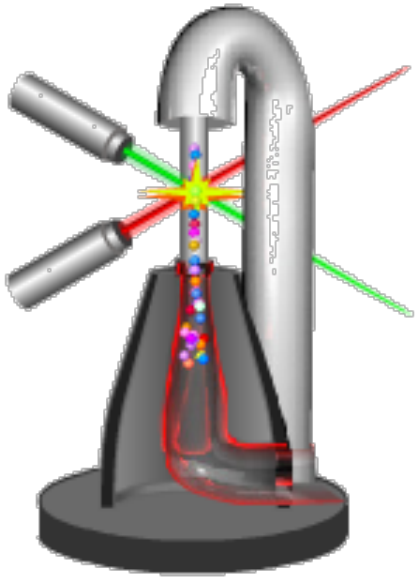
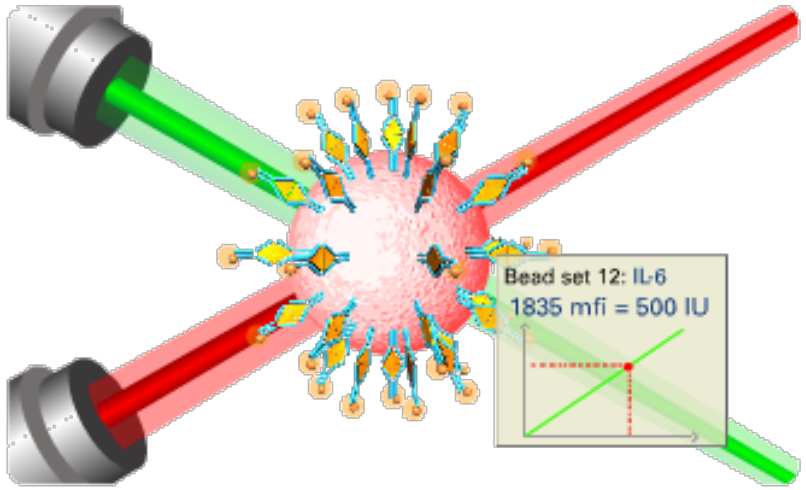
DALLAS


The bead is filled with
the special dye mixture.
5.6
microns


100 xMAP microsphere sets

LUMINEX





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DALLAS

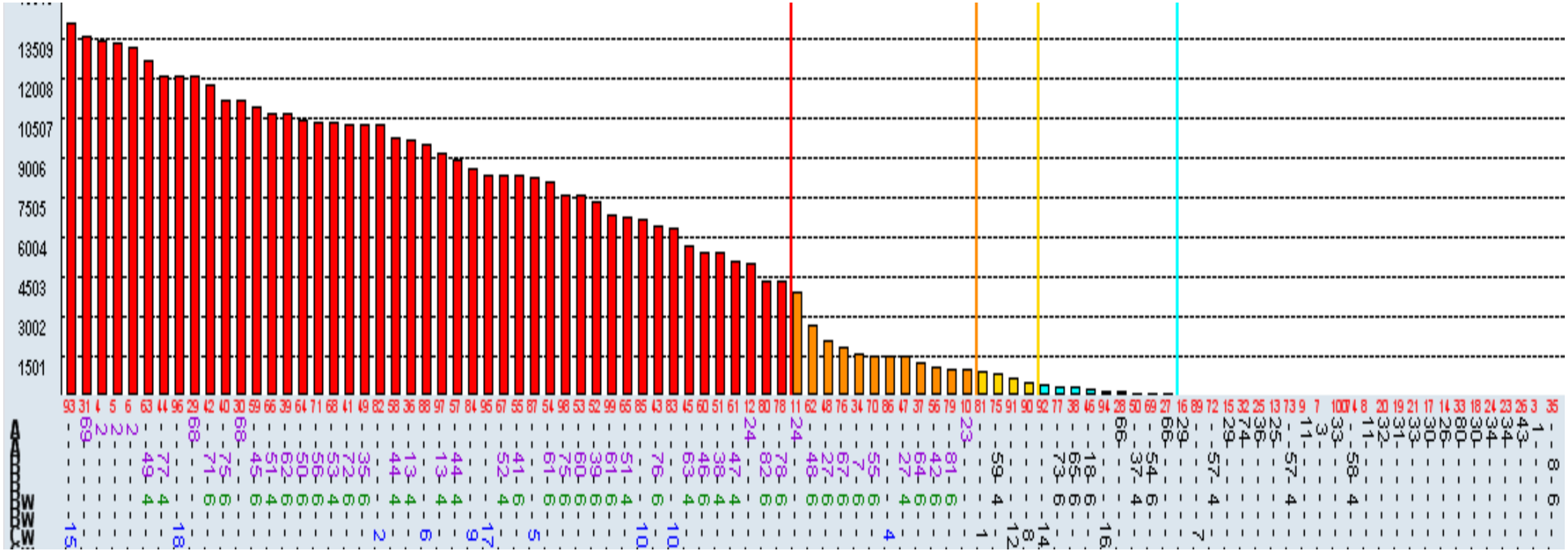
Antibody Assignment:	-	-	-

Test Configuration

	Threshold	%SA8	%SA6	%SA4	%SA2	PC	NC	PC/NC	Min #Bead:	10
Class I	X6	13	16	19	29	7928	30	260.266		
Class II	-	-	-	-	-					
MIC	-	-	-	-	-					

Test Details

Bead	Rxn	Raw	SFI Raw	Normal	SFI Normal	Cut	Specificity	Allele Specificity
048	8	10220		10164.0		172	B27,Bw6	B*27:08
016	8	10197		10147.0		148	B27,Bw4	B*27:05
056	8	9554		9496.0		132	B42,Bw6	B*42:01
079	8	8717		8648.0		167	B81,Bw6	B*81:01
062	8	7399		7336.0		125	B48,Bw6	B*48:01
036	8	7091		7022.0		127	B13,Bw4	B*13:02
070	8	6867		6823.0		154	B55,Bw6	B*55:01
053	8	5996		5941.0		135	B60,Bw6	B*40:01
076	8	5793		5717.0		118	B67,Bw6	B*67:01
034	8	5672		5588.0		165	B7,Bw6	B*07:02
054	8	5034		4972.0		133	B61,Bw6	B*40:02
097	8	4508		4436.0		161	B13,Bw4	B*13:01
099	8	4503		4421.0		139	B61,Bw6	B*40:06
077	6	3027		2945.0		163	B73,Bw6	B*73:01
061	6	2376		2319.0		153	B47,Bw4	B*47:01
071	6	2233		2177.0		123	B56,Bw6	B*56:01
055	4	855		794.0		174	B41,Bw6	B*41:01
080	4	743		646.0		176	B82,Bw6	B*82:01
028	2	513		437.0		143	A66	A*66:02
051	2	486		435.0		171	B38,Bw4	B*38:01
069	2	491		420.0		145	B54,Bw6	B*54:01


13509
12008
10507
9006
7505
6004
4503
3002
1501

DSA vs. XM

- **Positive DSA**: Recipient has HLA antibodies that correspond to the donor mismatched HLA antigens detected by solid phase assay
- **Positive Crossmatch**: Recipient has antibodies that react to antigens on donor lymphocytes (*HLA or Non-HLA including autoantibodies*)

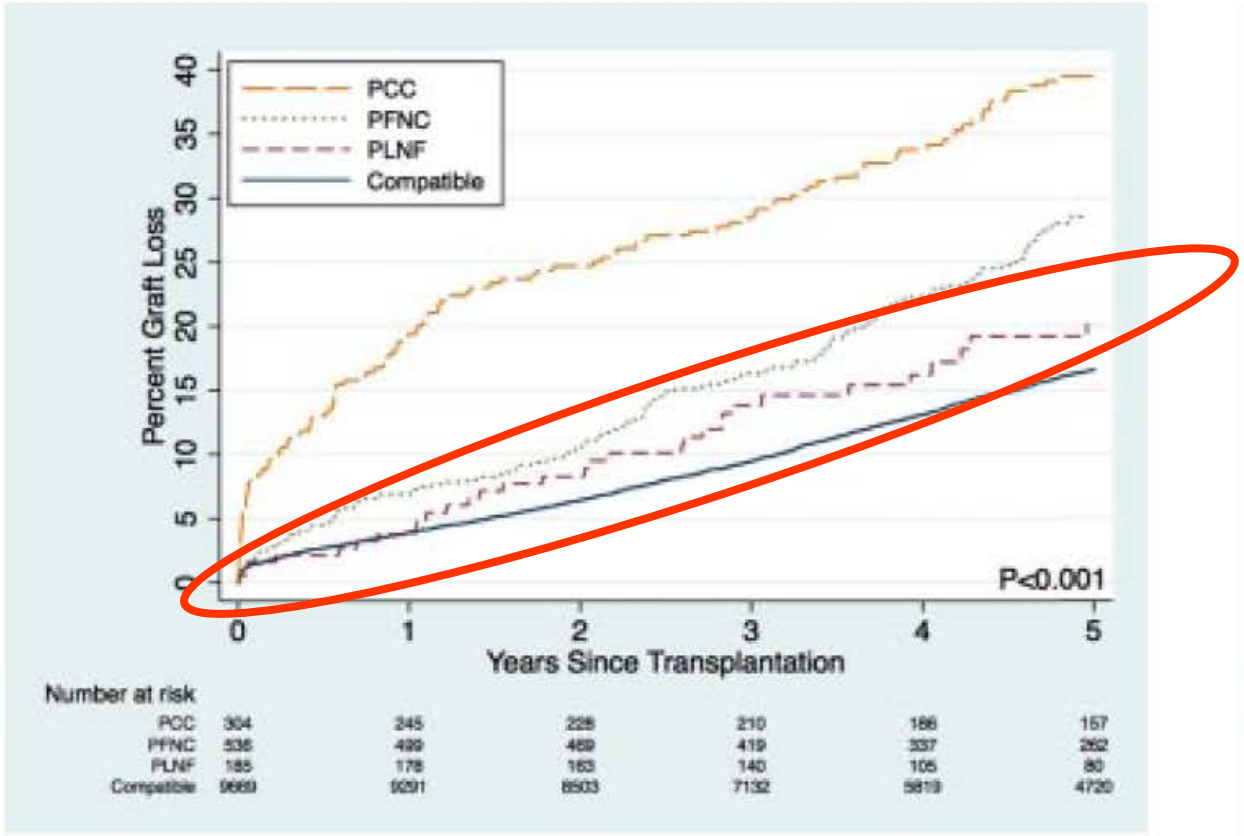


Figure 1: All-cause graft loss, by antibody strength. PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

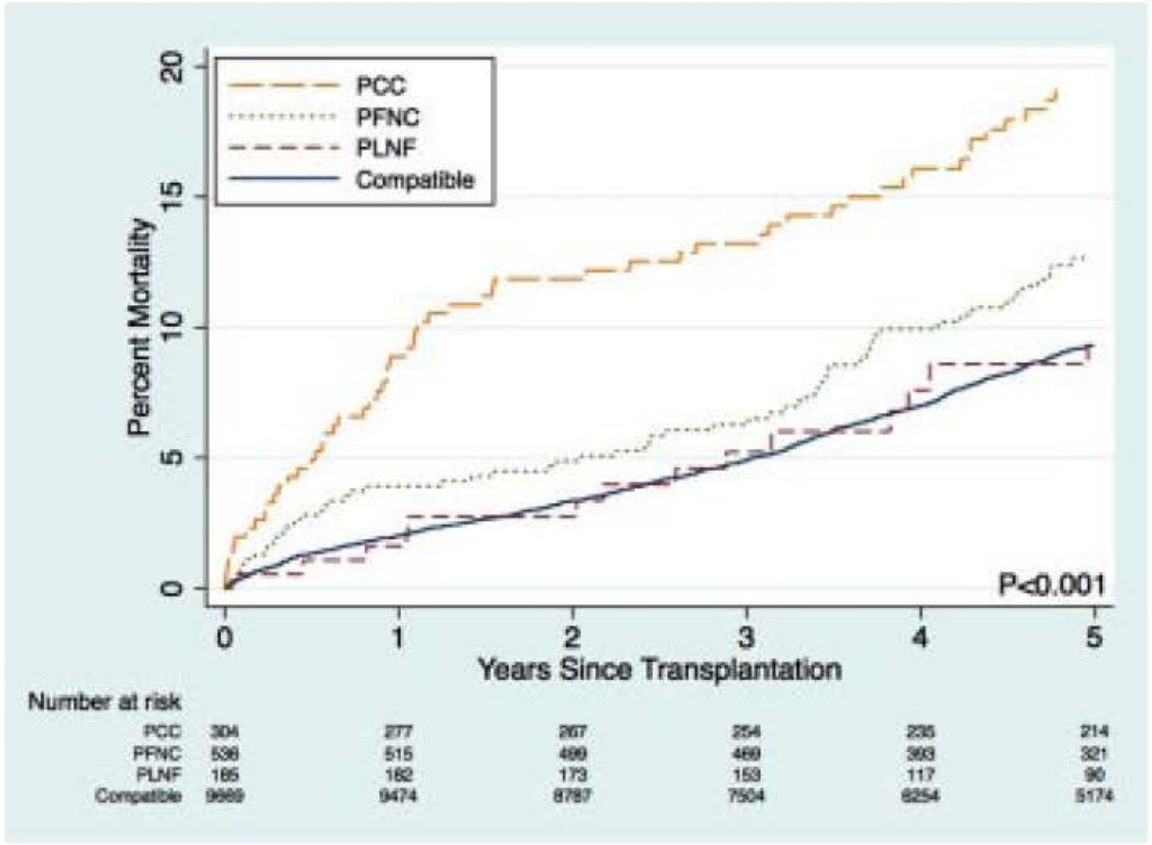


Figure 2: Posttransplant mortality, by antibody strength. PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch.

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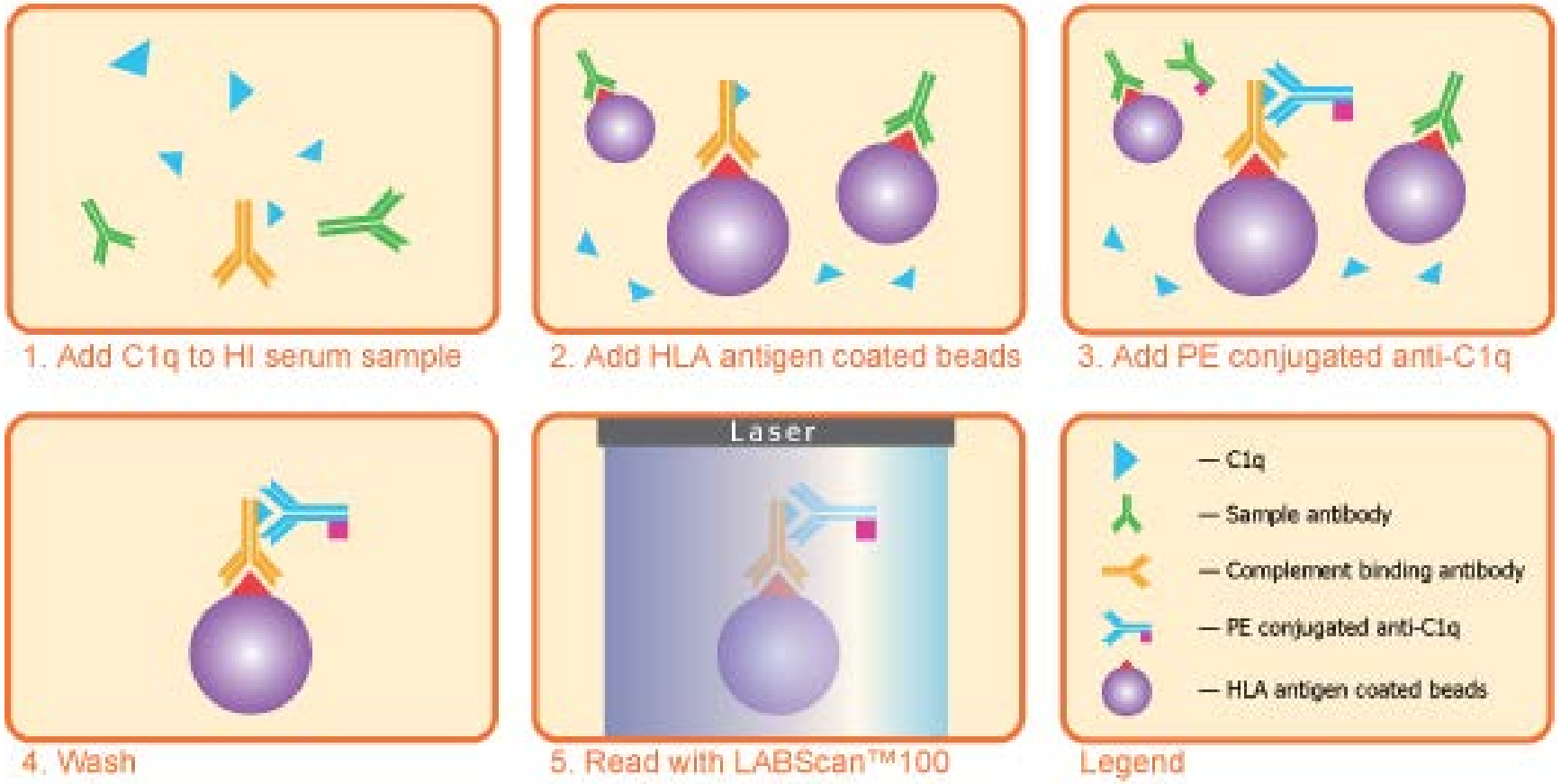
Orandi et al, 2014

Detection by PE Conjugated Anti-C1q



http://www.onelambda.com

Blood and
Marrow Transplantation

journal homepage: www.bbmt.org

Biology: Biomarkers

Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation

Stefan O. Ciurea [1,*], Peter F. Thall [2], Denái R. Milton [2], Titus H. Barnes [3], Piyanuch Kongtim [1], Yudith Carmazzi [3], Asdrúbal A. López [3], Dianne Y. Yap [3], Uday Popat [1], Gabriela Rondon [1], Benjamin Lichtiger [3], Fleur Aung [3], Vahid Afshar-Kharghan [4], Qing Ma [1], Marcelo Fernández-Viña [5], Richard E. Champlin [1], Kai Cao [3]

www.nature.com/bmt

REVIEW

Donor HLA-specific Abs: to BMT or not to BMT?

MS Leffell[1], RJ Jones[2] and DE Gladstone[2]

Table 2. General guidelines for desensitization for BMT

DSA/XM strength[a]	*Number of PP/IVIG treatments*		
	Preconditioning	*Day −1*[b]	*Day +1, +2*
Low-level DSA+, FCXM−	0	1	If needed, based on day −1 DSA level[c]
CDC XM−, FCXM+	3–4	1	Day +1; day +2 if needed, based on day −1 DSA level[d]
CDC XM titer 1–4	5–6	1	Day +1 and day +2; recommend monitoring DSA level on days +3 and +5[e]
CDC XM HLA class I titer ⩾8	Consider other options		
CDC XM HLA class II DSA ⩾1			

Leffell et al, 2015

HLA Ab Identification

Prediction of Crossmatch results (Virtual XM; vXM)

- Presence of DSA predicts Pos XM
- Absence of DSA Predicts Neg XM

BMT / TRANSPLANT IMMUNOLOGY LAB VIRTUAL CROSSMATCH FORM

To be completed by Transplant Coordinator

Date Completed: _____ Date Serum Drawn_____

Patient Name: _____ DOB: _____

Donor Selected: ○ Related ○ Unrelated ○ Haplo-matched

Donor Name or NMDP ID#:_____

DOB (if Applicable): _____

Planned date of transplantation: _____ / Conditioning Regimen Start Date:_____

Transplant Coordinator: _____ Physician: _____

Please review all antibody testing done up to this date. Please make sure the most recent antibody testing has been reported and the virtual crossmatch has been performed on the most recent sample.

To be completed by Transplant Immunology

Donor Selected: HLA-Identical Sibling: ○ YES ○ NO

HLA mismatched alleles/antigens: _____

Recipient and selected Donor are matched for all tested loci (A, B, C, DRB1, DRB345, DQB1, DPB1) and VXM and additional HLA antibody testing is not warranted: ○ YES ○ NO

Date Request Received: _____

* Serum Date: _____ Date Serum Received: _____

DSA Present: ○ YES ○ NO

DSA (MFI: 1,000-3,999): _____

DSA (MFI: 4,000-10,000): _____

DSA (MFI: >10,000): _____

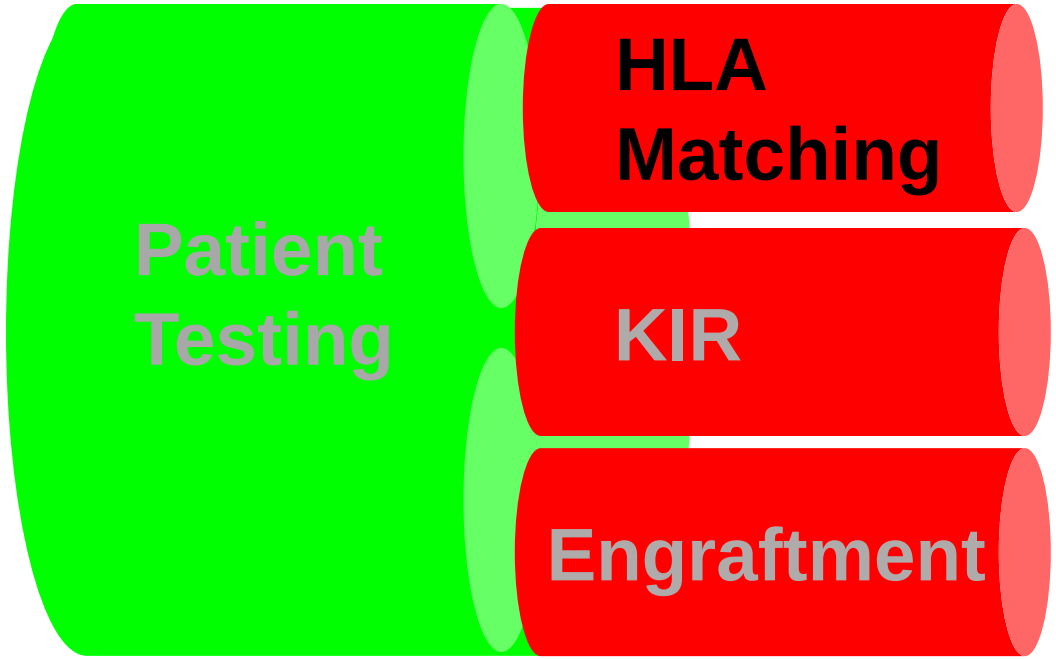
VXM: T cell crossmatch: _____ B cell crossmatch: _____

Reviewed By: _____ Date: _____

HLA Antibody Report will include VXM results

Comments: _____

* Note: VXM may change if blood products received after this date


Patient Testing
HLA Matching
KIR
Engraftment

MCat	Pr(n) of 10 (%)	Pr(n) of 8 (%)	A	B	C	DRB1	DQB1	A	B	C	DRB1	DQB1	DRB3	DRB4	DRB5	DQA1	DPB1	DPB1 TCE
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01	02:01	01:01			05:01	02:01 04:01	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:FX 01:FX				01:AETTA 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:01			05:01	01:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:01			05:01	01:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01					04:01 04:01	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01					02:01 04:01	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01	02:01					01:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01	02:01					01:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01	02:01	01:01			05:01	01:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01	02:01	01:01			05:01	04:01 02:01	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:FX 01:FX				01:AETTA 16:01	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:EWUD 01:EWUD				01:AETTA 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:FX 01:FX				01:AETTA 01:AETTA	Permissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	01:01 02:01	08:01 57:01	07:01 06:02	03:01 03:01	02:01 02:01	01:EWUD 01:EWUD				04:01 04:01	Permissive

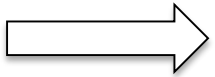
MCat	Pr(n) of 10 (%)	Pr(n) of 8 (%)	A	B	C	DRB1	DQB1	A	B	C	DRB1	DQB1	DRB3	DRB4	DRB5	DQA1	DPB1	DPB1 TCE
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	02:01 23:17	44:02 57:01	05:01 06:02	04:01 13:03	03:01	01:01	01:03		05:05 03:03	02:01 04:01	Nonpermissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	P P 99	P A 99	A P 99	A A 99	P P 99	02:ANGA 23:CJT	44:AMUT 57:01	05:01 06:DDAR	04:01 13:03	03:AFXPP	01:FX	01:AKJT		05:05 03:03	02:AEMGJ 04:AETTB	Nonpermissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	02:01 23:17	44:02 57:01	05:01 06:02	04:01 13:03	03:01	01:01	01:03		05:05 03:03	03:01 04:01	Match
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A P 99	A A 99	A A 99	A A 99	A A 99	02:01 23:01	44:02 57:01	05:01 06:02	04:01 13:03	03:01 03:01	01:01	01:03		03:03 05:05	02:01 04:01	Nonpermissive
10/10	10/10=99 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	A A 99	A A 99	A A 99	A A 99	A A 99	02:01 23:17	44:02 57:01	05:01 06:02	04:01 13:03	03:01	01:01	01:03		05:05 03:03	03:01 04:01	Match
10/10	10/10=11 9/10=18 8/10=46	8/8=13 7/8=45 6/8=61	P P 99	P P 54	 50	P P 21	 23	s2 s23	s44 s57		04:XX 13:XX							
10/10	10/10=11 9/10=18 8/10=46	8/8=13 7/8=45 6/8=61	P P 99	P P 54	 50	P P 21	 23	s2 s23	s44 s57		s4 s13							
9/10	10/10=0 9/10=99 8/10=99	8/8=99 7/8=99 6/8=99	P P 99	P P 99	P P 99	A P 99	P L 0	02:BGNHR 23:BFBYJ	44:BFBZD 57:AYVSY	05:BFBWF 06:BFBZY	04:BGNGB 13:BGNGK	03:BGNJH 03:AWFCX					04:BFBWY	Nonpermissive
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P P 99	P P 99	A A 99	P P 99	02:EMCH 31:DUKU	44:DZWM 57:EJRM	05:EJWP 06:EJWR	04:01 13:03	03:ENWH 03:ENWH						
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P P 99	P P 99	A A 99	P P 99	02:ZAKP 01:ZAKM	44:JGMU 57:RGPU	05:YGKG 06:ZAMM	04:01 13:03	03:ZAMW 03:ZAMW					04:FNVS 04:HJMR	Nonpermissive
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P P 99	P P 99	A A 99	A A 99	02:AFVFJ 02:AFVFJ	44:AAAVY 57:RGPU	05:AESTD 06:AETSY	04:01 13:03	03:01 03:01					04:FNVS 11:01	Nonpermissive
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P P 99	P P 99	A A 99	A A 99	02:NHBH 68:RFCF	44:NHWA 57:NHWG	05:WVUW 06:XKMV	04:01 13:03	03:01						
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P A 99	P P 99	A A 99	A A 99	02:ANGA 24:HJMV	44:AMUT 57:01	05:JSRJ 06:ZKTX	04:01 13:03	03:01	01:MS	01:XX				
9/10	10/10=0 9/10=99 8/10=99	8/8=0 7/8=99 6/8=99	P M 0	P P 99	P P 99	A A 99	A A 99	02:BGNHR 68:BFBYS	44:BFBZD 57:AYVSY	05:BFBZX 06:BFBZY	04:01 13:03	03:01 03:01					01:01 04:01	Nonpermissive
9/10	10/10=0	8/8=0	A	A	A	A	A	02:01	44:02	05:01	04:01	03:01	01:EWUD	01:EHN	NNNN		04:01	Nonpermissive

Genotype Frequency as a Search Prognosis Tool

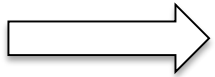
Patient HLA Type

HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1
11:01	18:01	07:01	01:01	05:01
68:02	35:01	04:01	14:01	05:03

+ Patient Ethnicity



Genotype Frequency Tool



- **Good**
  - ≥ 3 10/10 donors
- **Fair**
  - 1-2 10/10s or
  - No 10/10s and ≥ 3 9/10 donors
- **Poor**
  - No 10/10s and < 3 9/10 donors

NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Wadsworth, K. et. al. Bone Marrow Transplant 2016 Nov;51(11):1476-81

Grab your cape.

MCat	Pr(n) of 10 (%)	Pr(n) of 8 (%)	A	B	C	DRB1	DQB1	A	B	C	DRB1	DQB1	DRB3	DRB4	DRB5	DQA1	DPB1	DPB1 TCE
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P P 99	L M 0	P M 0	L A 0	L L 0	11:BFBYG 68:AYVSJ	18:03 27:BFBUF	07:BFBZZ 01:BGNJB	04:01 13:01	03:01 06:03					04:01 04:01	Permissive
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P P 99	M L 0	M P 0	L L 0	A M 0	11:BFBYG 68:BFBYS	35:BGNFD 42:02	04:BFBZV 17:BGNFK	04:03 13:03	03:02 03:BGCWT					01:YGTJ 04:BFCSW	Permissive
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	L M 0	P M 0	A L 0	A M 0	11:BFBYG 68:ASXJM	18:03 14:ANVB	07:BFBZZ 08:BCZHV	04:04 13:03	03:02 03:01					04:FNVS 02:AFCTE	Permissive
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	P M 0	L L 0	P M 0	11:SNFC 68:02	18:JDZZ 14:02	07:UBKJ 08:UBKN	04:03 13:03	03:RCH 03:SNFR	01:XX	01:XX			02:01 03:FYKD	Nonpermissive
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P P 99	P M 0	L M 0	L L 0	A L 0	11:XEWG 68:TXXF	18:TXYF 44:JGMU	07:ET 12:CNB	04:01 13:02	03:02 06:02					04:01 05:RGPW	Permissive
4/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	P M 0	L L 0	A M 0	11:BDFZ 68:02	18:RRG 14:02	07:CXSZ 08:BE	04:03 13:03	03:02 03:DAAR	01:MS	01:XX				
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	P M 0	L L 0	L M 0	11:KHME 68:02	18:JDZZ 14:02	07:NFCR 08:MJAB	04:08 13:03	03:JEAW 03:JEAW	01:MS	01:XX				
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P P 99	L M 0	P M 0	L L 0	L L 0	11:BFBYG 68:AYVSJ	18:03 14:02	07:BFBZZ 08:BCZHV	04:08 13:02	03:01 06:09					04:02 05:RGPW	Permissive
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	P M 0	L L 0	L M 0	11:BFBYG 68:24	18:BGNJA 55:HMCD	07:BFBZZ 03:BFBZR	04:BGNGB 13:15	03:01 03:01					04:FNVS 04:HJMR	Permissive
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	P M 0	L L 0	L M 0	11:BFBYG 68:ASXJM	18:BGNJA 14:ANVB	07:BFBZZ 08:BCZHV	04:BGNGD 13:03	03:01 03:01					03:FYKD 02:AHZAM	Nonpermissive
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	A L 0	P M 0	M M 0	L L 0	P M 0	11:01 68:02	18:RRG 14:02	08:02 12:AFCTH	04:01 13:03	03:YGKM 03:AFXPP	01:FX	01:AKJT			02:AEMGJ	Permissive
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P M 0	P L 0	L P 0	L L 0	L M 0	11:MXZM 32:MUHF	18:JDZZ 42:02	07:ET 17:MN	04:05 13:03	03:JEAW 04:02						
3/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	M M 0	L L 0	A M 0	11:BFBYG 68:ASXJM	18:BGNJA 35:BFBZB	04:BFBZV 05:BFBZX	04:01 13:05	03:02 03:01					04:BFCAJ 04:BFCAK	Permissive
2/10	10/10=0 9/10=0 8/10=0	8/8=0 7/8=0 6/8=0	P L 0	P M 0	M M 0	L L 0	L M 0	11:SNFC 68:02	18:JDZZ 14:02	08:UXFG 12:RTBU	04:HTWY 13:03	03:SNFR 03:SNFR	01:XX	01:XX			02:01 06:01	Nonpermissive

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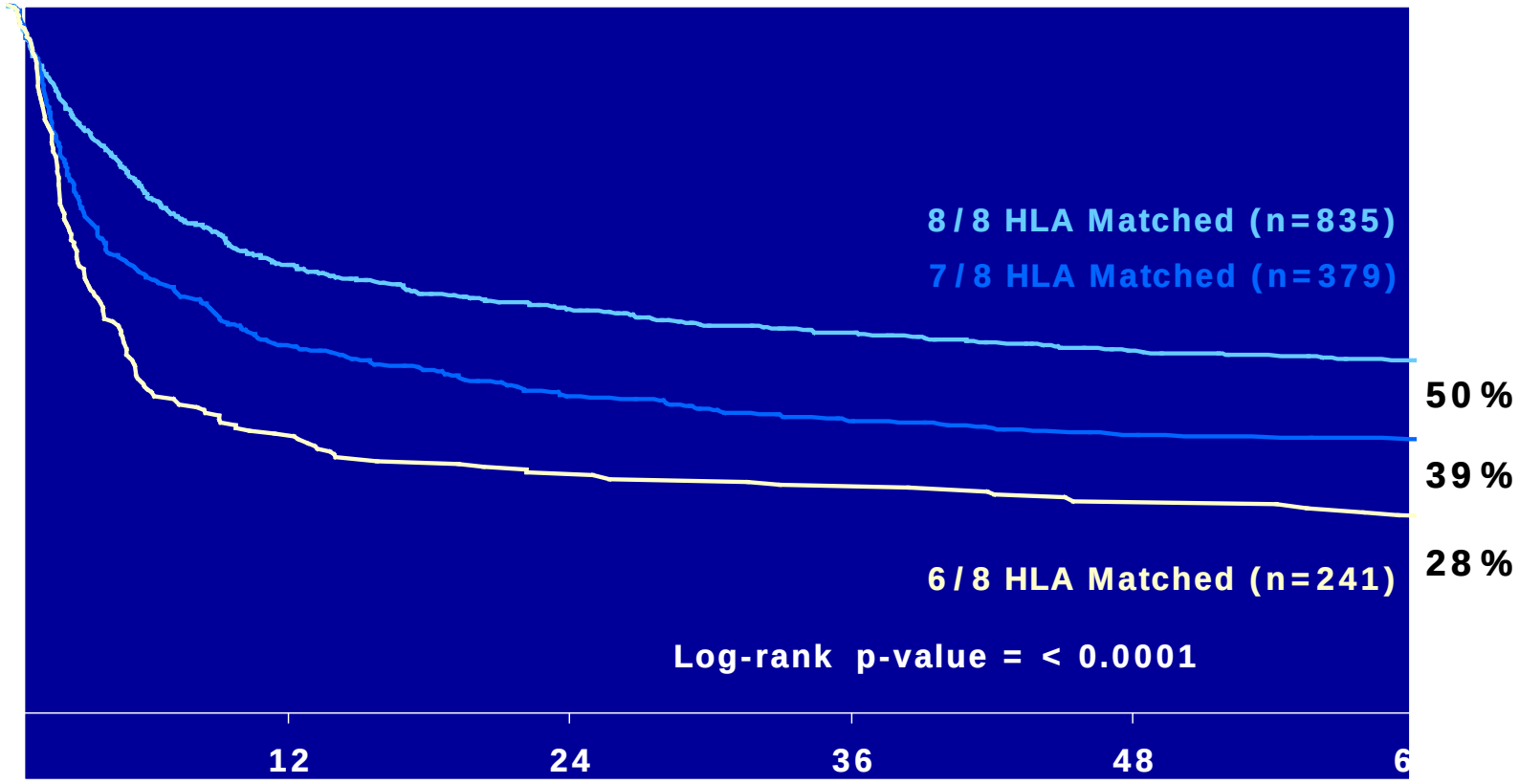
2007 110: 4576-4583
doi:10.1182/blood-2007-06-097386 originally published online September 4, 2007

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

Stephanie J. Lee, John Klein, Michael Haagenson, Lee Ann Baxter-Lowe, Dennis L. Confer, Mary Eapen, Marcelo Fernandez-Vina, Neal Flomenberg, Mary Horowitz, Carolyn K. Hurley, Harriet Noreen, Machteld Oudshoorn, Effie Petersdorf, Michelle Setterholm, Stephen Spellman, Daniel Weisdorf, Thomas M. Williams and Claudio Anasetti

BLOOD, 15 DECEMBER 2007 • VOLUME 110, NUMBER 13

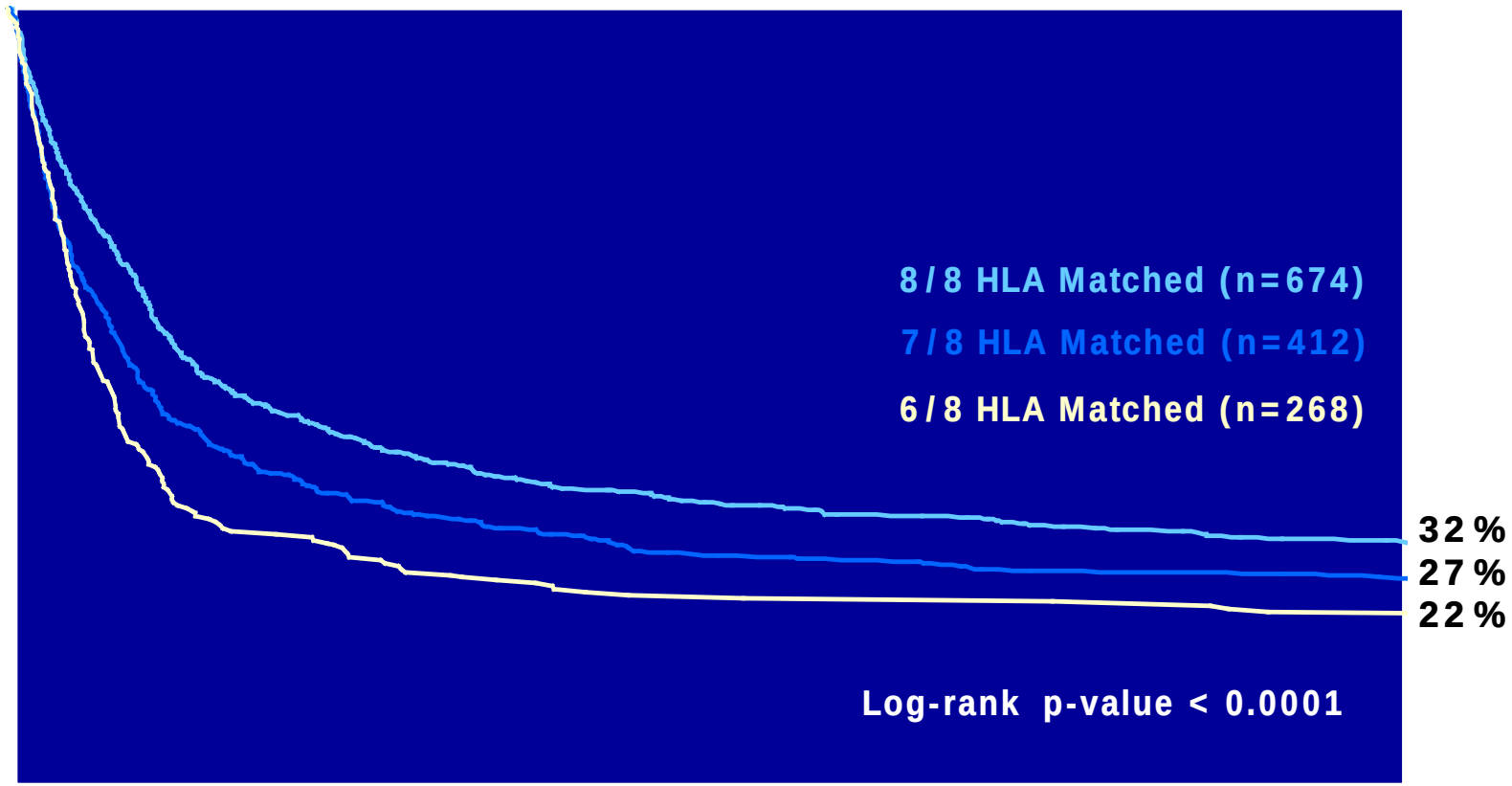
Probability of Overall Survival by HLA Matching for Early Disease Stage



Curtsey of Stephanie Lee

BAYLOR University Medical Center at Dallas

Probability of Overall Survival by HLA Matching for Intermediate Disease Stage



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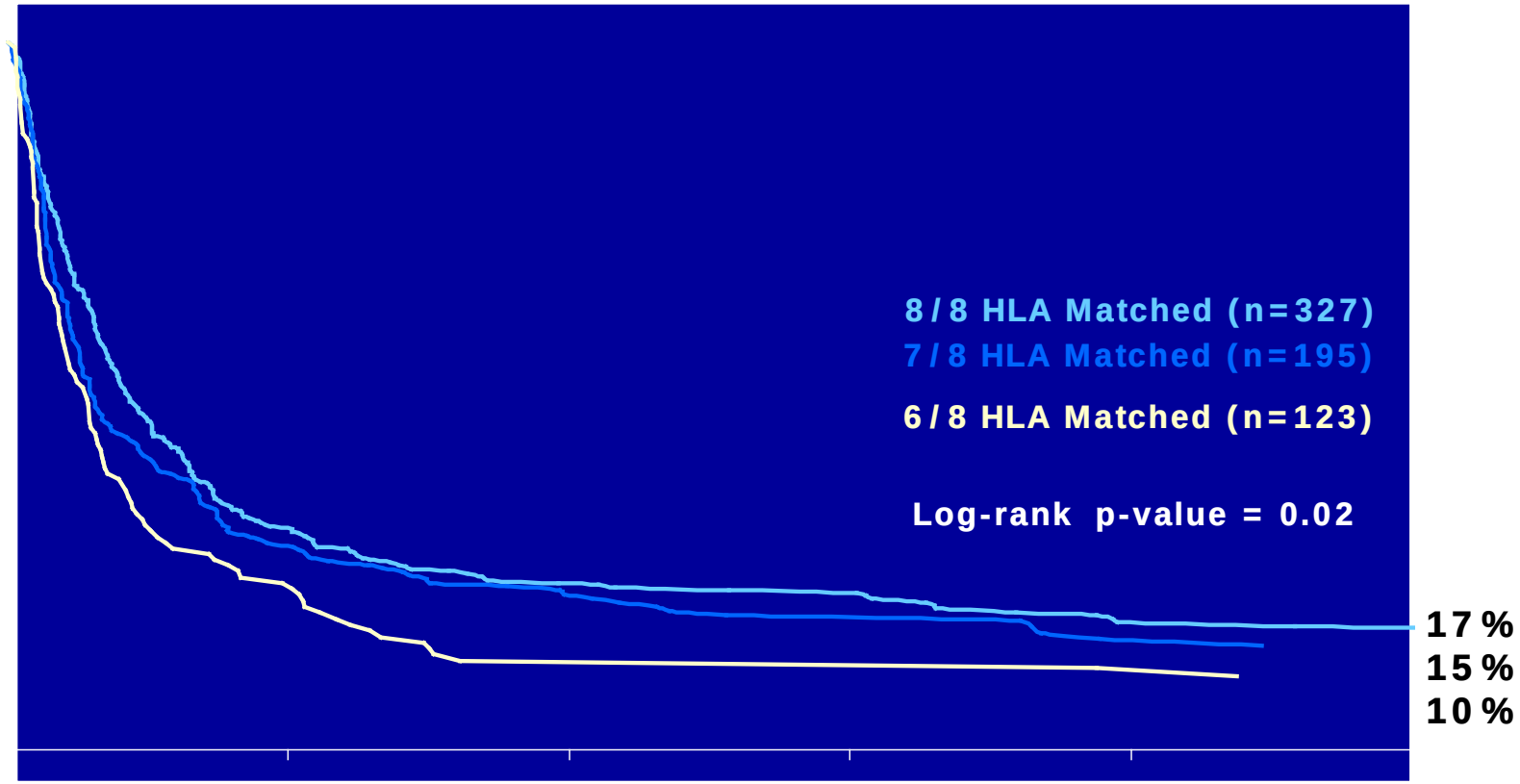
Probability of Overall Survival by HLA Matching for Advanced Disease Stage



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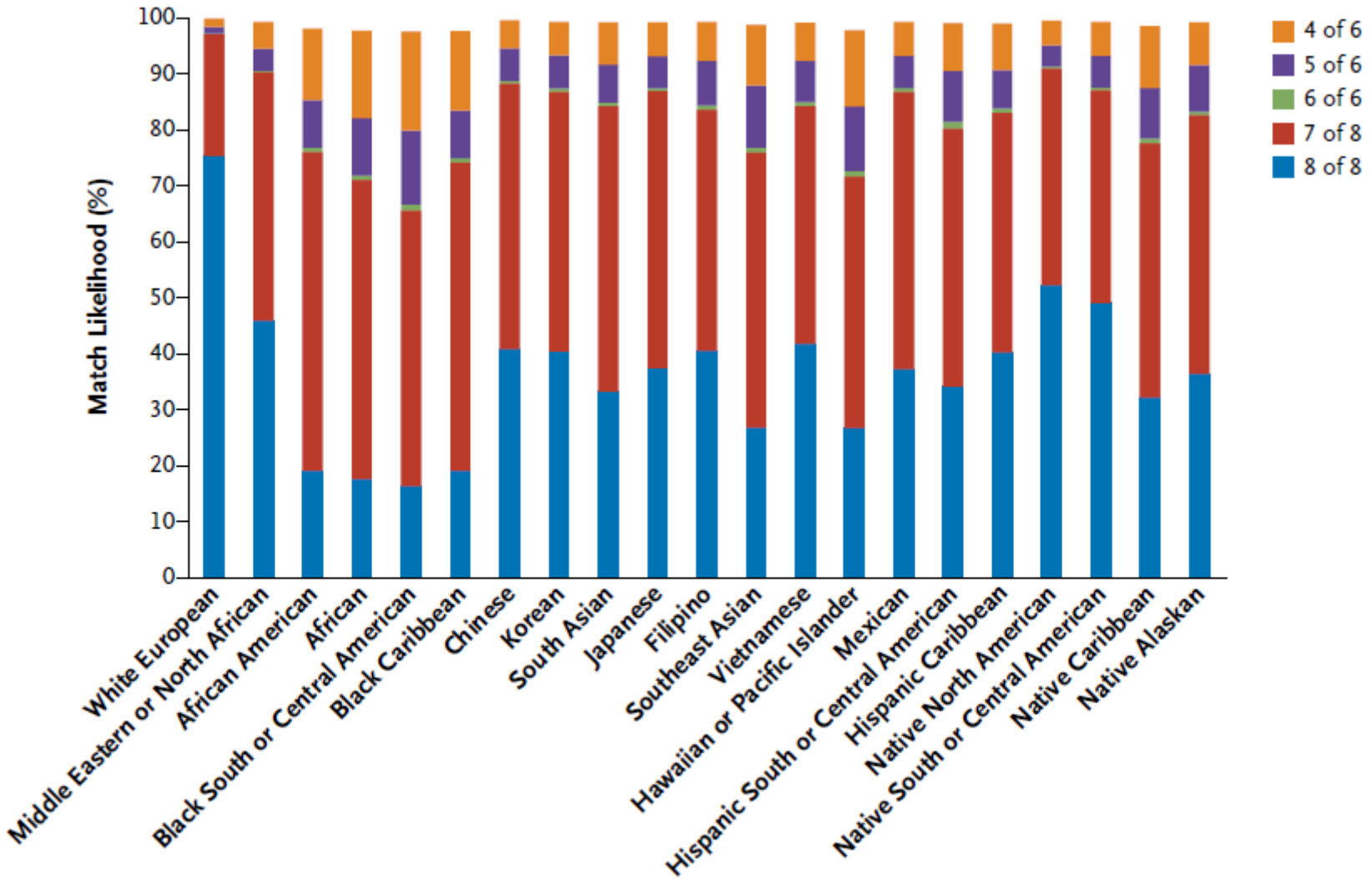
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.

Lee et al, 2007


Match Likelihood (%)
100
90
80
70
60
50
40
30
20
10
0
4 of 6
5 of 6
6 of 6
7 of 8
8 of 8
White European
Middle Eastern or North African
African American
African
Black South or Central American
Black Caribbean
Chinese
Korean
South Asian
Japanese
Filipino
Southeast Asian
Vietnamese
Hawaiian or Pacific Islander
Mexican
Hispanic South or Central American
Hispanic Caribbean
Native North American
Native South or Central American
Native Caribbean
Native Alaskan

blood

2007 110: 4576-4583
doi:10.1182/blood-2007-06-097386 originally published online September 4, 2007

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

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BLOOD, 15 DECEMBER 2007 • VOLUME 110, NUMBER 13

Table 2. Single locus mismatches at HLA-A, -B, -C, and -DRB1

	Treatment-related mortality			Acute graft-versus-host disease		
Factor	RR	95% CI	*P*	RR	95% CI	*P*
Any single locus (n = 985) vs matched (n = 1840)	1.40	1.25-1.56	<.001	1.48	1.29-1.68	<.001
Any single allele (n = 412) vs matched	1.40	1.20-1.63	<.001	1.34	1.12-1.61	.002
Any single antigen (n = 573) vs matched	1.40	1.22-1.60	<.001	1.59	1.35-1.86	<.001
Any single allele vs any single antigen	1.00	0.83-1.19	.98	0.85	0.68-1.04	.12

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Lee et al, 2007

Table 2. Single locus mismatches at HLA-A, -B, -C, and -DRB1

	Survival			Disease-free survival		
Factor	RR	95% CI	*P*	RR	95% CI	*P*
Any single locus (n = 985) vs matched (n = 1840)	1.25	1.13-1.38	<.001	1.23	1.12-1.36	<.001
Any single allele (n = 412) vs matched	1.30	1.14-1.46	<.001	1.28	1.13-1.46	.002
Any single antigen (n = 573) vs matched	1.22	1.08-1.37	.001	1.20	1.07-1.35	.002
Any single allele vs any single antigen	1.07	0.92-1.24	.40	1.07	0.92-1.24	.39

Lee et al, 2007

ARTICLE IN PRESS

Biol Blood Marrow Transplant ■■ (2018) ■■–■■

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Refractory Graft-Versus-Host Disease–Free, Relapse-Free Survival as an Accurate and Easy-to-Calculate Endpoint to Assess the Long-Term Transplant Success

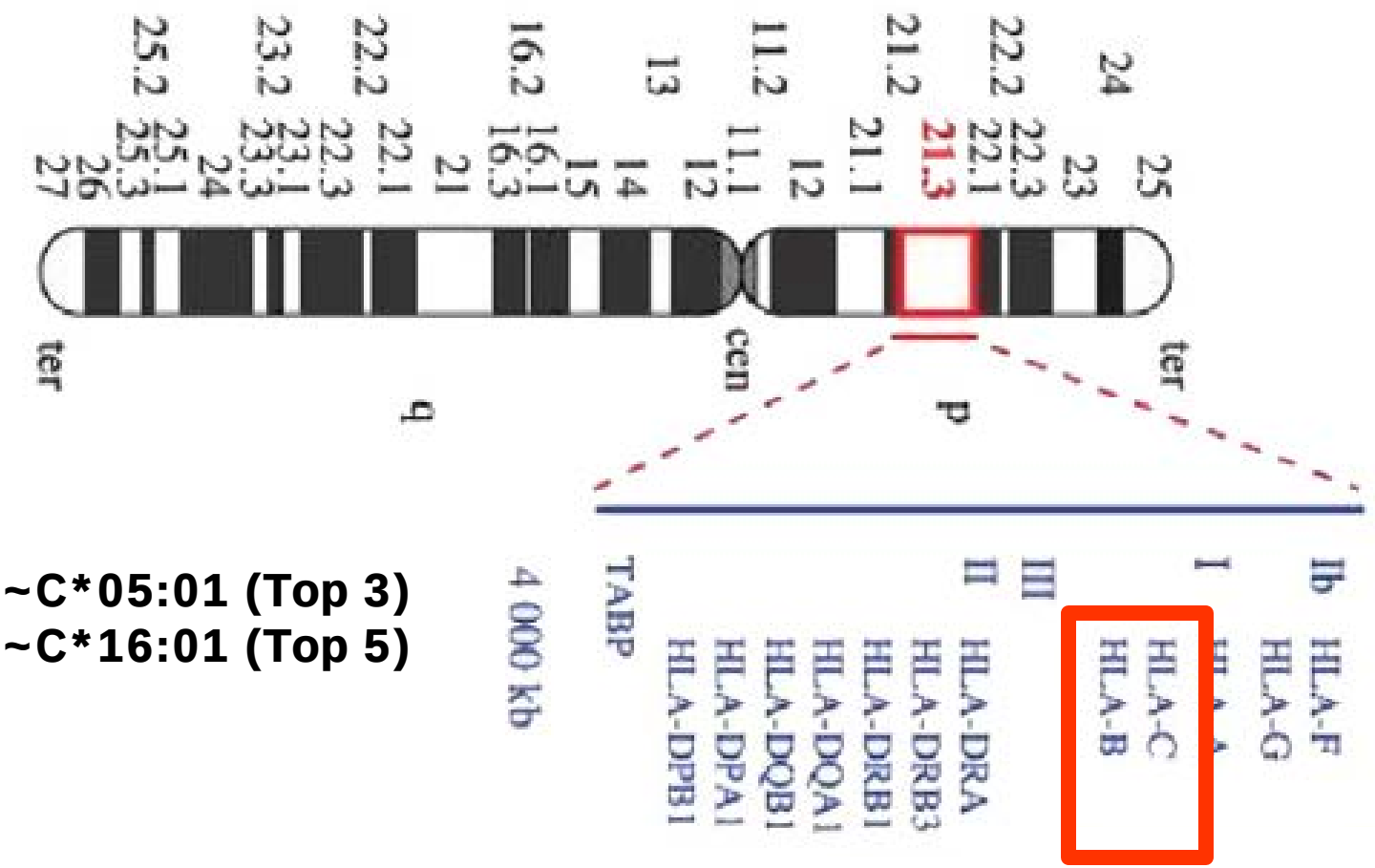
GRFS

Koji Kawamura [1], Hideki Nakasone [1], Saiko Kurosawa [2], Kazuki Yoshimura [1], Yukiko Misaki [1], Ayumi Gomyo [1], Jin Hayakawa [1], Masaharu Tamaki [1], Yu Akahoshi [1], Machiko Kusuda [1], Kazuaki Kameda [1], Hidenori Wada [1], Yuko Ishihara [1], Miki Sato [1], Kiriko Terasako-Saito [1], Misato Kikuchi [1], Shun-ichi Kimura [1], Aki Tanihara [1], Shinichi Kako [1], Heiwa Kanamori [3], Takehiko Mori [4], Satoshi Takahashi [5], Shuichi Taniguchi [6], Yoshiko Atsuta [7,8], Yoshinobu Kanda [1,9,*]

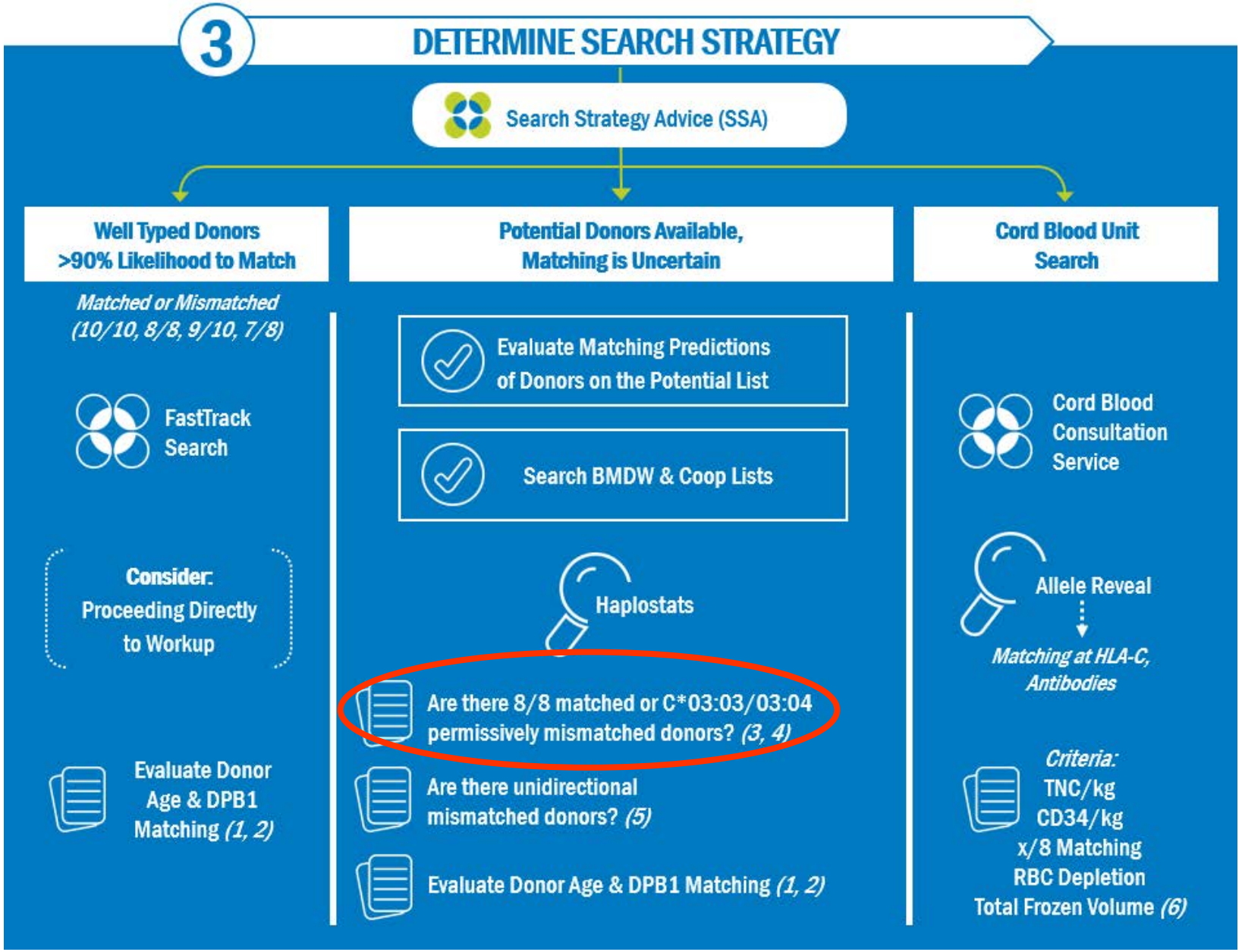
		OS			GVHD		
	n*	RR	95% CI	*P*	RR	95% CI	*P*
Matched	1840	1.00	—	—	1.00	—	—
HLA-A							
Allele	113	1.50	1.20-1.88	<.001	1.62	1.19-2.20	.002
Antigen	161	1.24	1.02-1.52	.03	1.54	1.18-2.03	.002
Allele vs antigen	—	0.83	0.62-1.10	.19	0.95	0.64-1.41	.81
HLA-B							
Allele	99	1.25	0.97-1.60	.09	1.63	1.19-2.23	.002
Antigen	17	0.78	0.42-1.45	.43	1.60	0.79-3.21	.19
Allele vs antigen	—	0.62	0.32-1.21	.17	0.98	0.46-2.08	.96
HLA-C							
Allele	96	1.03	0.79-1.34	.84	0.98	0.68-1.40	.90
Antigen	382	1.22	1.06-1.39	.004	1.60	1.33-1.93	<.001
Allele vs antigen	—	1.18	0.89-1.57	.24	1.63	1.11-2.42	.01
HLA-DRB1							
Allele	104	1.42	1.13-1.80	.003	1.20	0.83-1.73	.32
Antigen	13	1.81	0.96-3.41	.07	1.77	0.83-3.78	.14
Allele vs antigen	—	1.27	0.64-2.48	.49	1.46	0.64-3.37	.36

* is the number for survival model. Other models may have ha

Lee et al, 2007



B*44:02~C*05:01 (Top 3)
B*44:03~C*16:01 (Top 5)


3
DETERMINE SEARCH STRATEGY
Search Strategy Advice (SSA)
Well Typed Donors
>90% Likelihood to Match
Potential Donors Available,
Matching is Uncertain
Cord Blood Unit
Search
Matched or Mismatched
(10/10, 8/8, 9/10, 7/8)
FastTrack
Search
Consider:
Proceeding Directly
to Workup
Evaluate Donor
Age & DPB1
Matching (1, 2)
Evaluate Matching Predictions
of Donors on the Potential List
Search BMDW & Coop Lists
Haplostats
Are there 8/8 matched or C*03:03/03:04
permissively mismatched donors? (3, 4)
Are there unidirectional
mismatched donors? (5)
Evaluate Donor Age & DPB1 Matching (1, 2)
Cord Blood
Consultation
Service
Allele Reveal
Matching at HLA-C,
Antibodies
Criteria:
TNC/kg
CD34/kg
x/8 Matching
RBC Depletion
Total Frozen Volume (6)

		OS			GVHD		
	n*	RR	95% CI	*P*	RR	95% CI	*P*
Matched	1840	1.00	—	—	1.00	—	—
HLA-A							
Allele	113	1.50	1.20-1.88	<.001	1.62	1.19-2.20	.002
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HLA-C							
Allele	96	1.03	0.79-1.34	.84	0.98	0.68-1.40	.90
Antigen	382	1.22	1.06-1.39	.004	1.60	1.33-1.93	<.001
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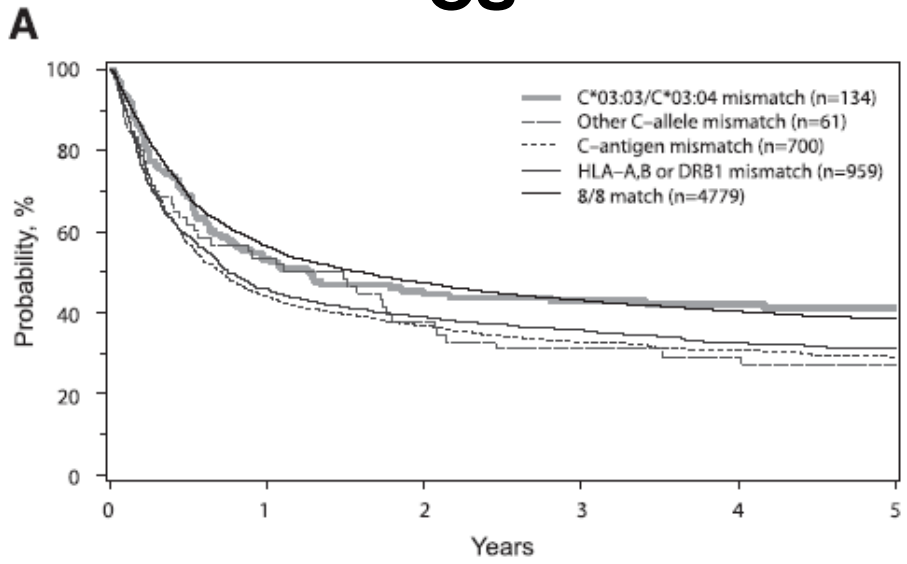
* is the number for survival model. Other models may have ha

blood
2014 123: 1270-1278
doi:10.1182/blood-2013-10-532671 originally published online January 9, 2014

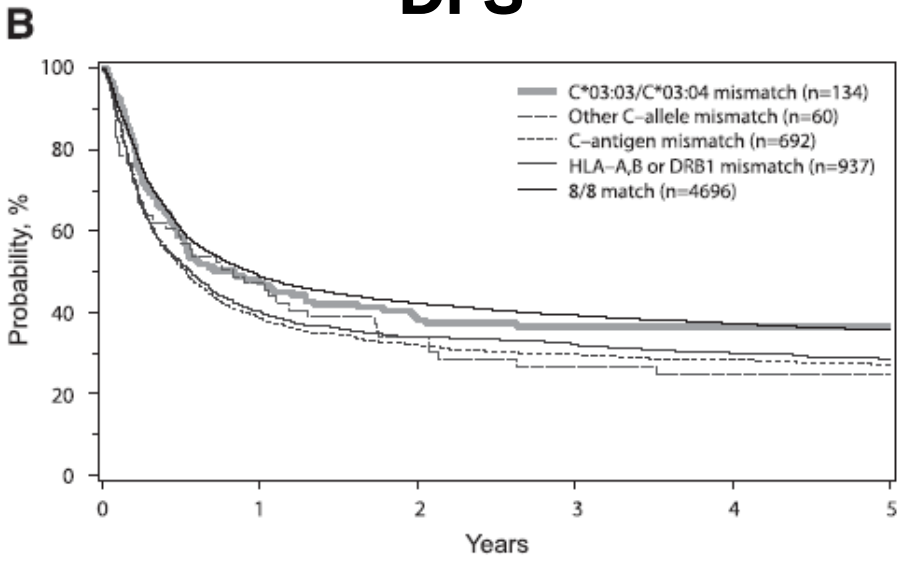
Identification of a permissible HLA mismatch in hematopoietic stem cell transplantation

Marcelo A. Fernandez-Viña, Tao Wang, Stephanie J. Lee, Michael Haagenson, Mahmoud Aljurf, Medhat Askar, Minoo Battiwalla, Lee-Ann Baxter-Lowe, James Gajewski, Ann A. Jakubowski, Susana Marino, Machteld Oudshoorn, Steven G. E. Marsh, Effie W. Petersdorf, Kirk Schultz, E. Victoria Turner, Edmund K. Waller, Ann Woolfrey, John Umejiego, Stephen R. Spellman and Michelle Setterholm

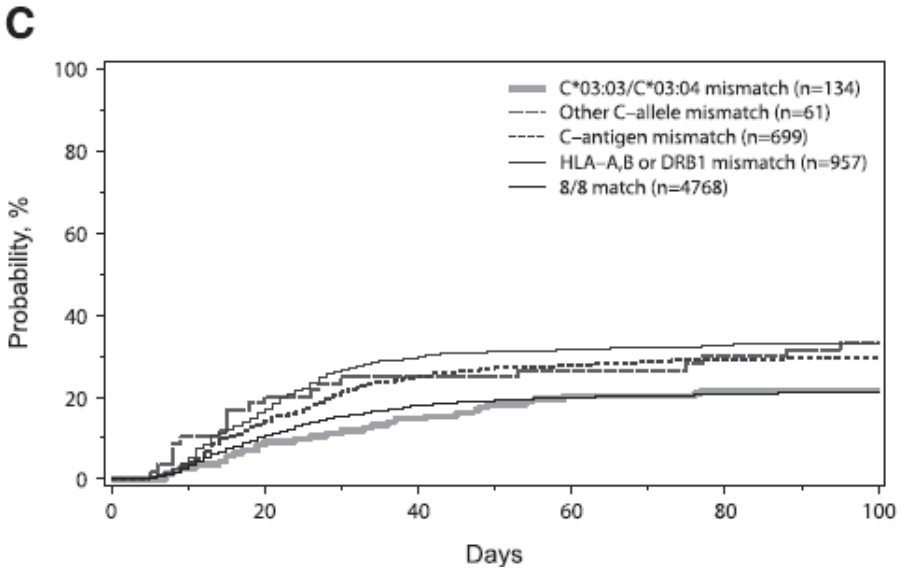
OS



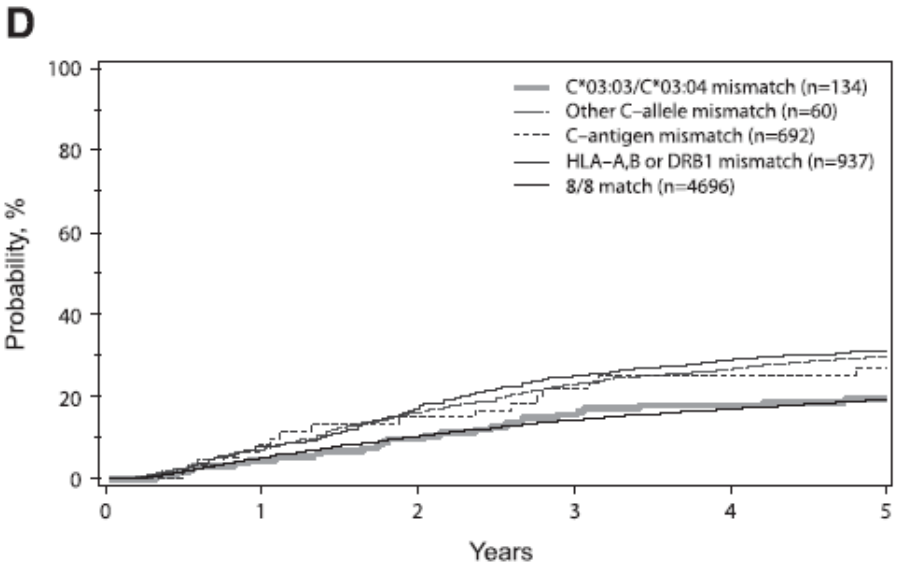
DFS



Grade 3-4 aGVHD



TRM



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American Society for Blood and Marrow Transplantation

www.bbmt.org

HLA Mismatch Is Associated with Worse Outcomes after Unrelated Donor Reduced-Intensity Conditioning Hematopoietic Cell Transplantation: An Analysis from the Center for International Blood and Marrow Transplant Research

Michael R. Verneris [1,*], Stephanie J. Lee [2], Kwang Woo Ahn [3], Hai-Lin Wang [4], Minoo Battiwalla [5], Yoshihiro Inamoto [2], Marcelo A. Fernandez-Vina [6], James Gajewski [7], Joseph Pidala [8], Reinhold Munker [9], Mahmoud Aljurf [10], Wael Saber [4], Stephen Spellman [11], John Koreth [12]

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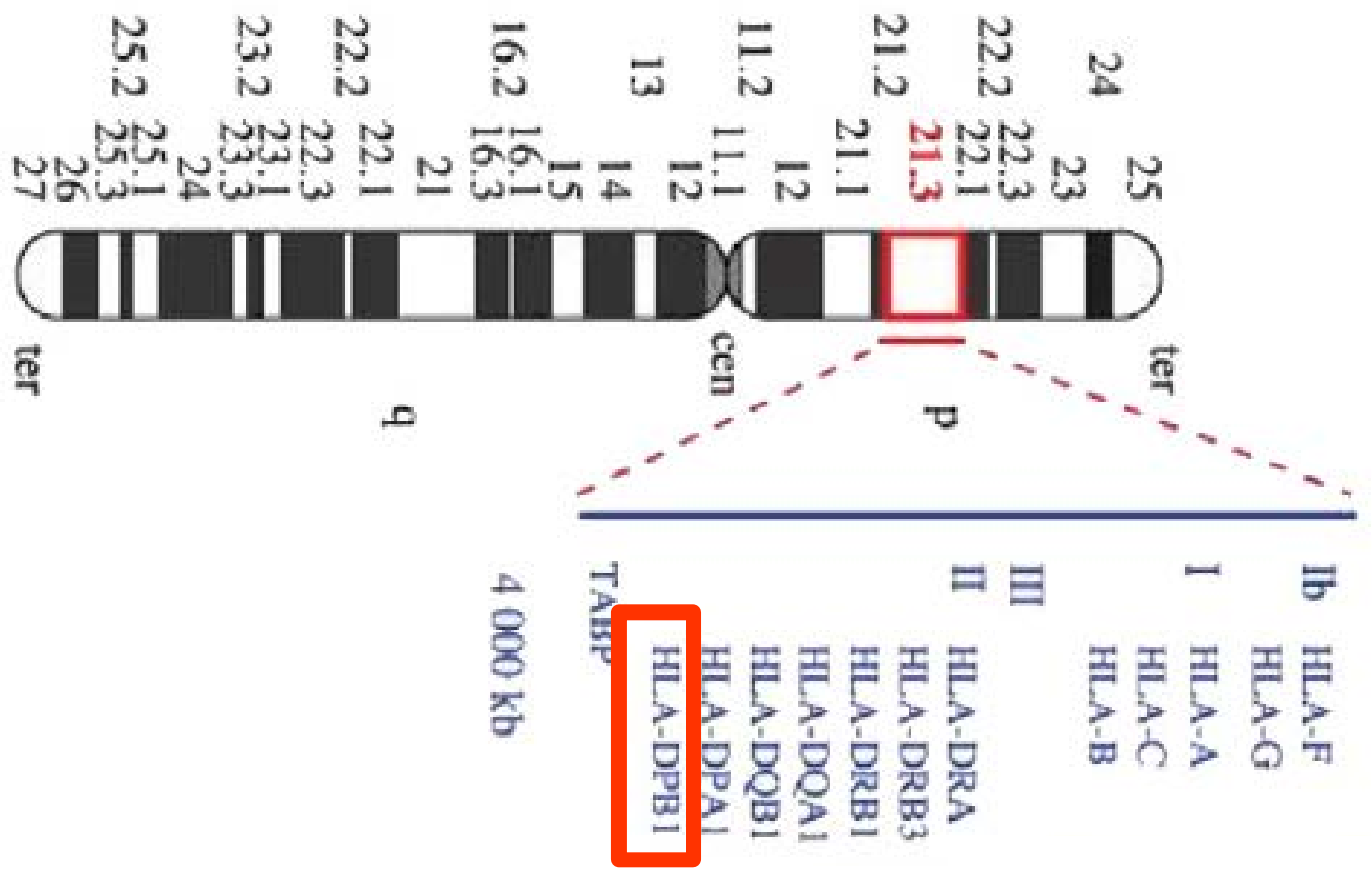
blood

Prepublished online August 26, 2014;
doi:10.1182/blood-2014-05-576041

Non-permissive -DPB1 mismatch among otherwise HLA-matched donor-recipient pairs results in increased overall mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation for hematologic malignancies

Joseph Pidala, Stephanie J. Lee, Kwang Woo Ahn, Stephen Spellman, Hai-Lin Wang, Mahmoud Aljurf, Medhat Askar, Jason Dehn, Marcelo Fernandez Viña, Alois Gratwohl, Vikas Gupta, Rabi Hanna, Mary M. Horowitz, Carolyn K. Hurley, Yoshihiro Inamoto, Adetola A. Kassim, Taiga Nishihori, Carlheinz Mueller, Machteld Oudshoorn, Effie W. Petersdorf, Vinod Prasad, James Robinson, Wael Saber, Kirk R. Schultz, Bronwen Shaw, Jan Storek, William A. Wood, Ann E. Woolfrey and Claudio Anasetti



The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation

Bronwen E. Shaw,[1,2] Theodore A. Gooley,[3] Mari Malkki,[3] J. Alejandro Madrigal,[1,4] Ann B. Begovich,[5] Mary M. Horowitz,[6] Alois Gratwohl,[7] Olle Ringdén,[8] Steven G. E. Marsh,[1,4] and Effie W. Petersdorf[3,9]

[1]Anthony Nolan Research Institute, London, United Kingdom; [2]Section of Haemato-Oncology, Royal Marsden Hospital/Institute of Cancer Research, Surrey, United Kingdom; [3]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; [4]Royal Free and University College London Medical School, London, United Kingdom; [5] Roche Molecular Systems, Alameda, CA; [6]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee; [7]Hematology Department, University Hospital Basel, Basel, Switzerland; [8]Division of Clinical Immunology, Karolinska University Hospital Huddinge, Stockholm, Sweden; and [9]Department of Medicine, University of Washington School of Medicine, Seattle

	Adjusted models			
	Grades 2-4 aGVHD	Grades 3-4 aGVHD	Relapse	Overall mortality
Matched at HLA-DPB1	1	1	1	1
Mismatched at HLA-DPB1	1.33 (1.18-1.51; $P < .001$)	1.22 (1.06-1.40; $P = .005$)	0.78 (0.67-0.92; $P = .002$)	1.09 (0.99-1.19; $P = .07$)
1 allele mismatched	1.31 (1.14-1.49; $P < .001$)	1.18 (1.02-1.37; $P = .03$)	0.79 (0.67-0.93; $P = .005$)	1.08 (0.98-1.19; $P = .13$)
2 alleles mismatched	1.36 (1.18-1.58; $P < .001$)	1.27 (1.09-1.49; $P = .003$)	0.76 (0.64-0.91; $P = .003$)	1.09 (0.98-1.21; $P = .11$)

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Shaw et al 2007

Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

Katharina Fleischhauer, Bronwen E Shaw*, Theodore Gooley, Mari Malkki, Peter Bardy, Jean-Denis Bignon, Valérie Dubois, Mary M Horowitz, J Alejandro Madrigal, Yasuo Morishima, Machteld Oudshoorn, Olle Ringden, Stephen Spellman, Andrea Velardi, Elisabetta Zino, Effie W Petersdorf, on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation*

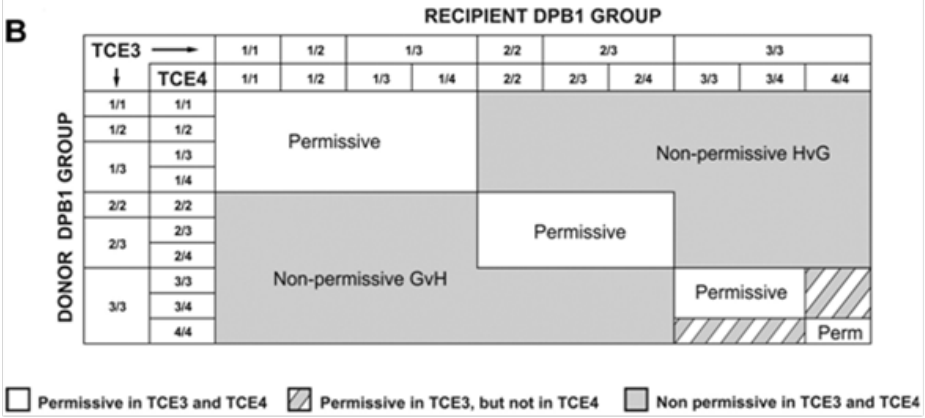
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 1 An algorithm for nonpermissive HLA-DPB1 disparities according to TCE3 or TCE4

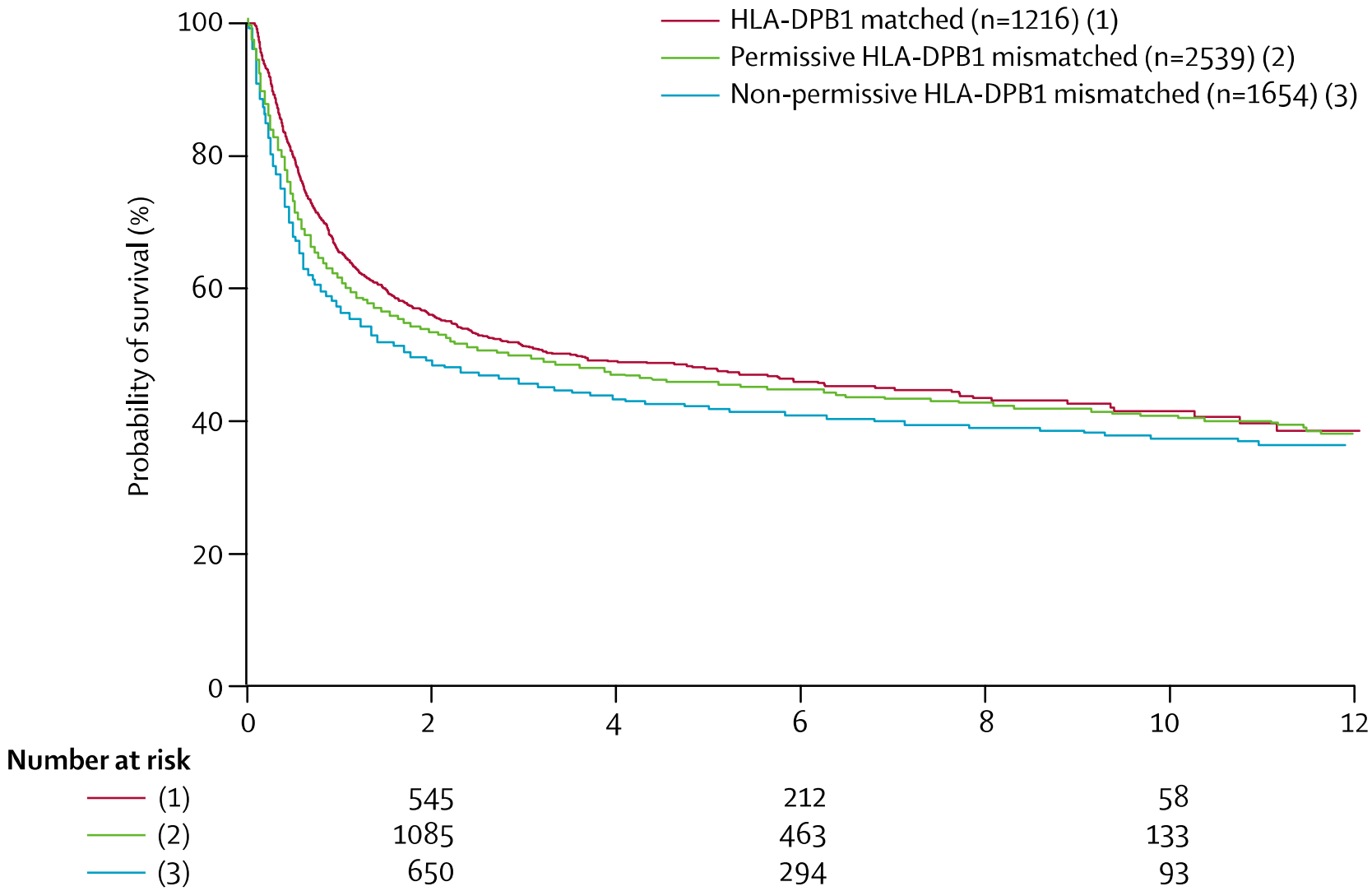
A

DPB1* alleles	TCE3 group	TCE4 group	Immunogenicity
0901 1001 1701	1	1	
0301 1401 4501	2	2	
0201 0202 0203	3	3	
Others		4	

B



Crocchiolo, R. et al. Blood 2009;114:1437-1444



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Biol Blood Marrow Transplant 17:1404-1415, 2011

Predictions in the Face of Clinical Reality: *HistoCheck* versus High-Risk HLA Allele Mismatch Combinations Responsible for Severe Acute Graft-versus-Host Disease

Medhat Askar,[1] Ronald Sobecks,[2] Yasuo Morishima,[3] Takakazu Kawase,[3] Amy Nowacki,[4] Hideki Makishima,[5] Jaroslaw Maciejewski[5]

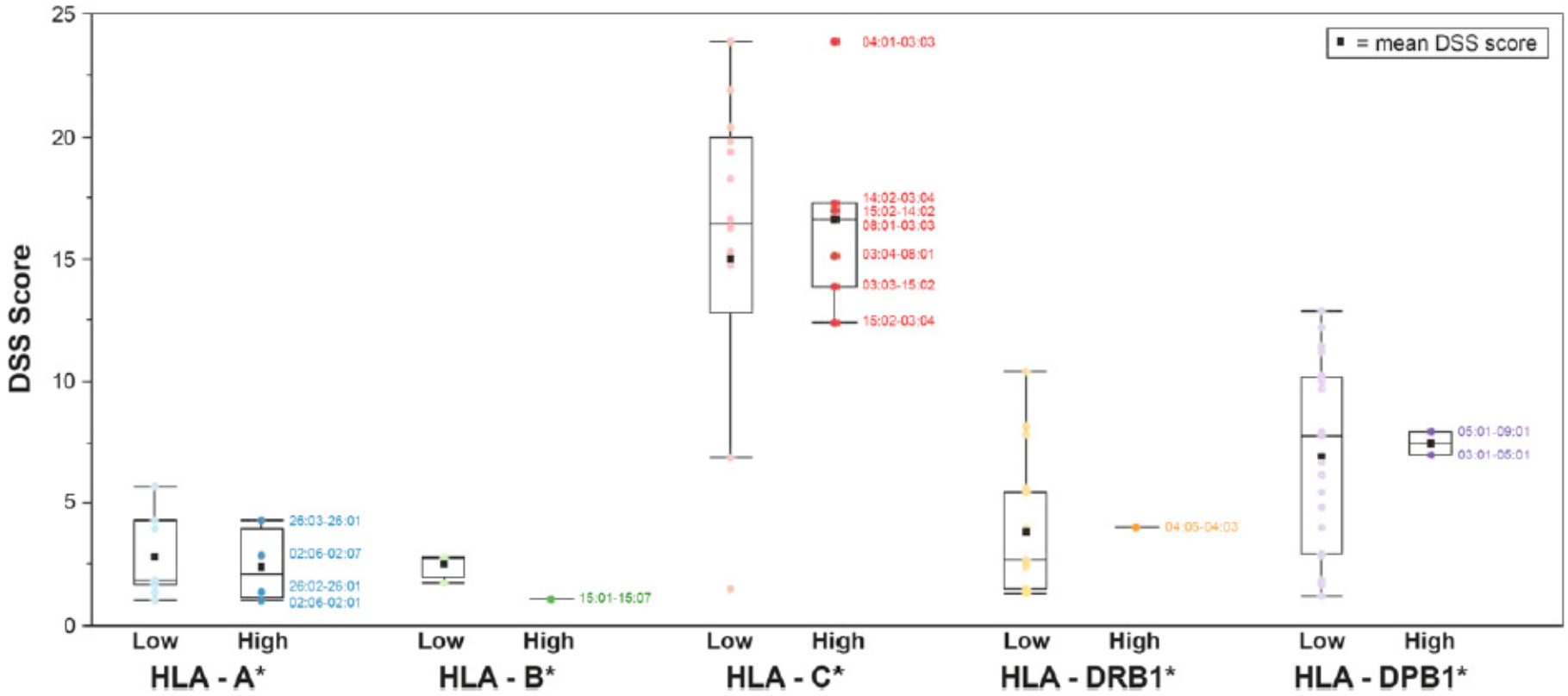

Figure 1. Comparison of SSM in high- versus low-risk mismatch allele combinations. SSM means are not significantly different, and SSM distributions are overlapping among high- and low-risk allele combinations within loci HLA-A, -B, -C, -DRB1, and -DPB1.

Scoring HLA Class I Mismatches by HistoCheck Does Not Predict Clinical Outcome in Unrelated Hematopoietic Stem Cell Transplantation

Stephen Spellman,[1] John Klein,[2] Michael Haagenson,[1] Medhat Askar,[3] Lee Ann Baxter-Lowe,[4] Jun He,[5] Susan Hsu,[6] Rainer Blasczyk,[7] Carolyn Hurley[8]

Biol Blood Marrow Transplant 18:739-746, 2012

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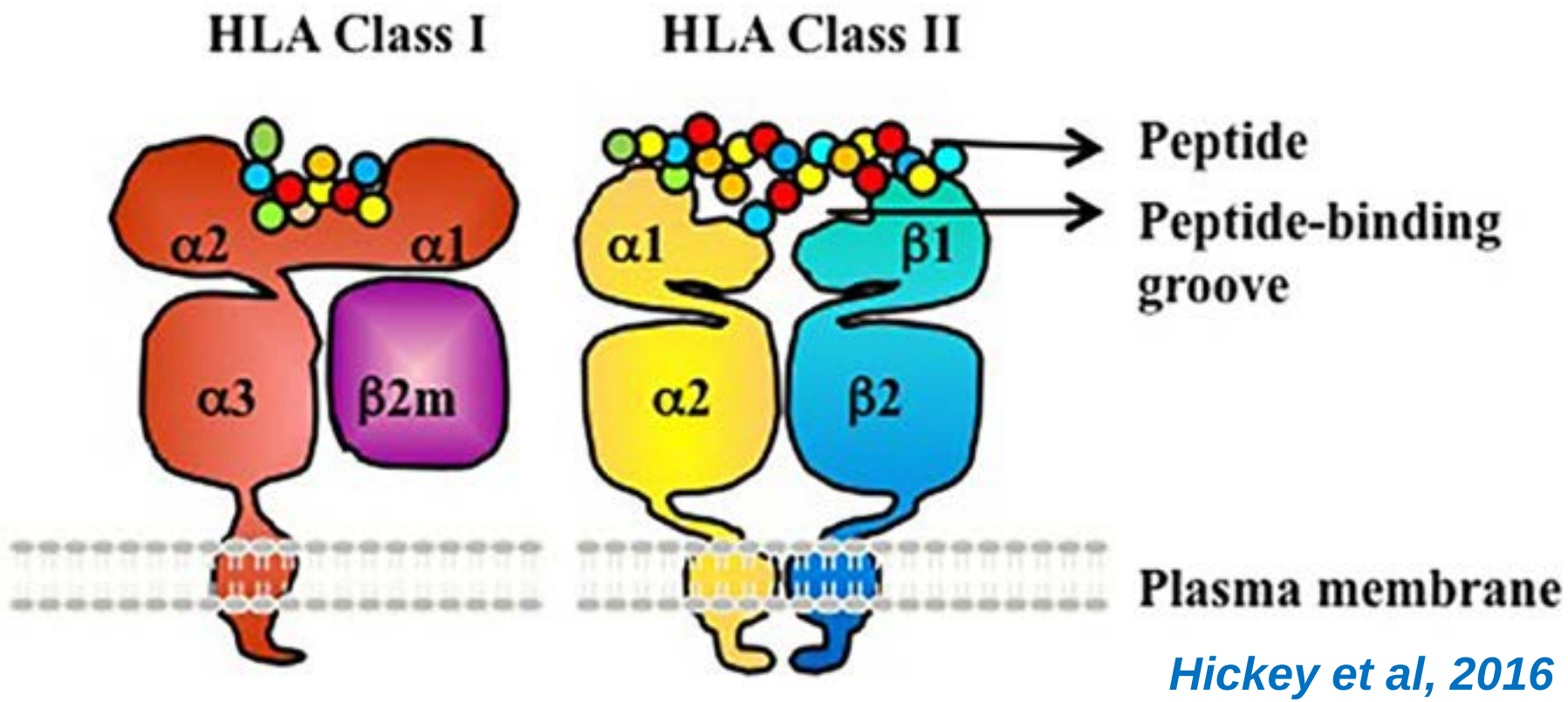
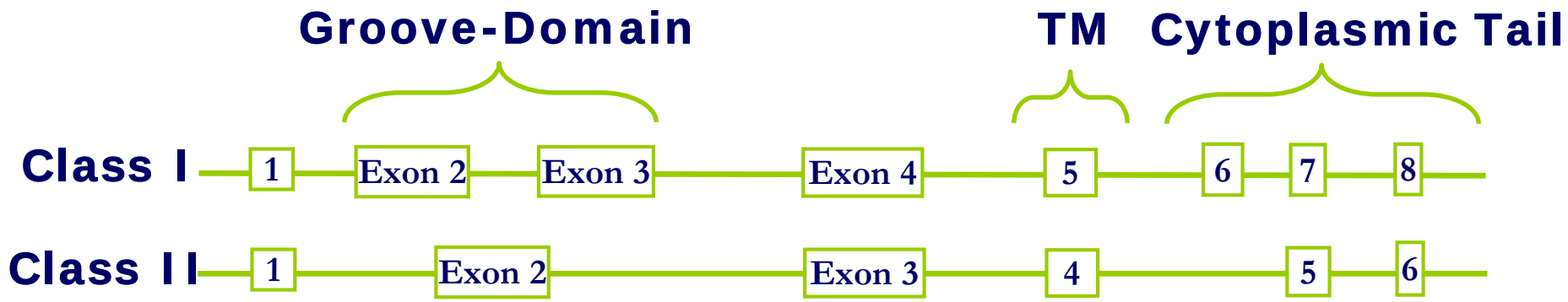
H_2O
$E=mc^2$
A+B=C



Hickey et al, 2016



Non-Coding Sequences

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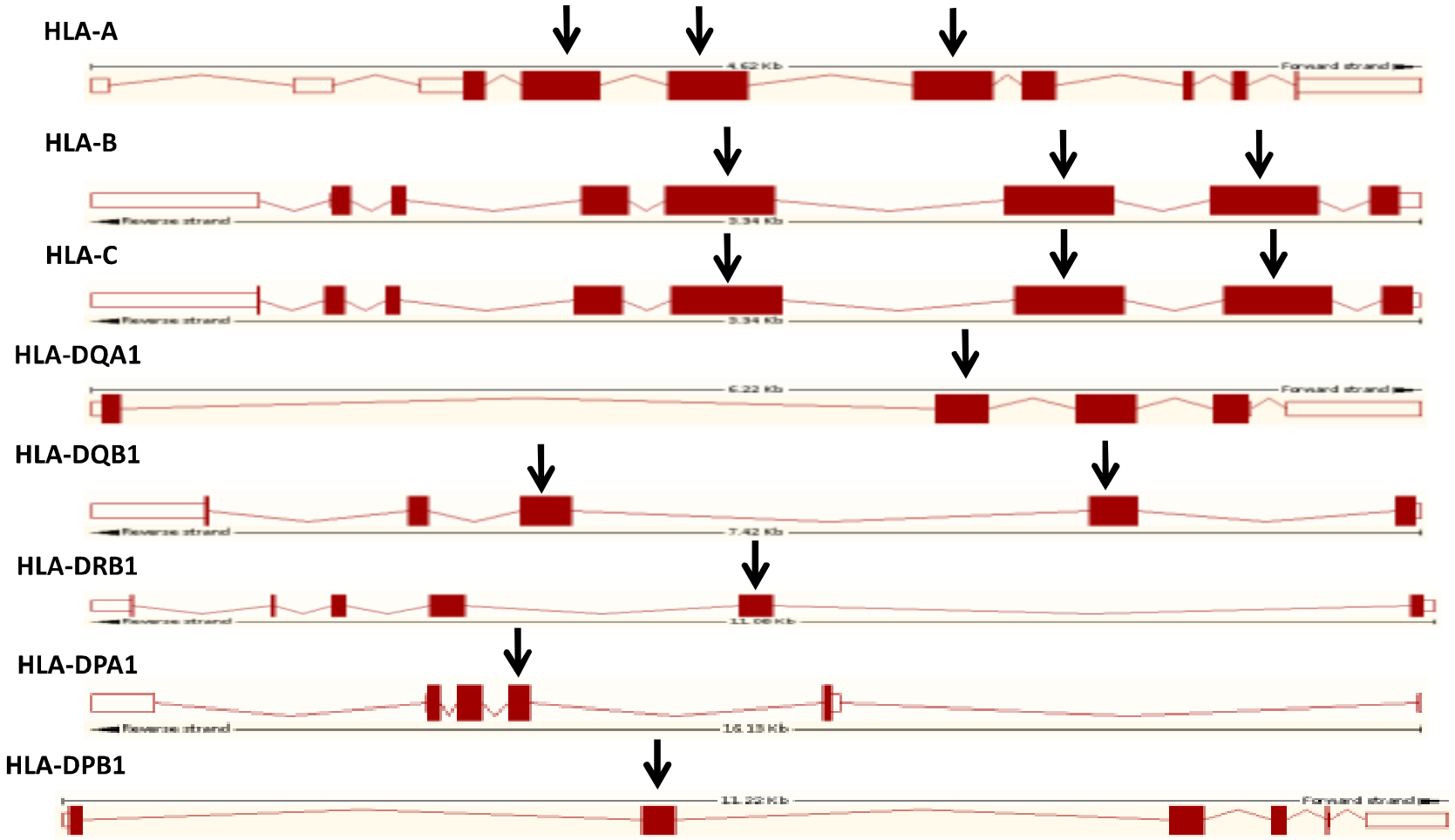
GENOMIC ORGANIZATION OF THE HLA GENES



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Courtesy of Marcelo Fernandez-Vina

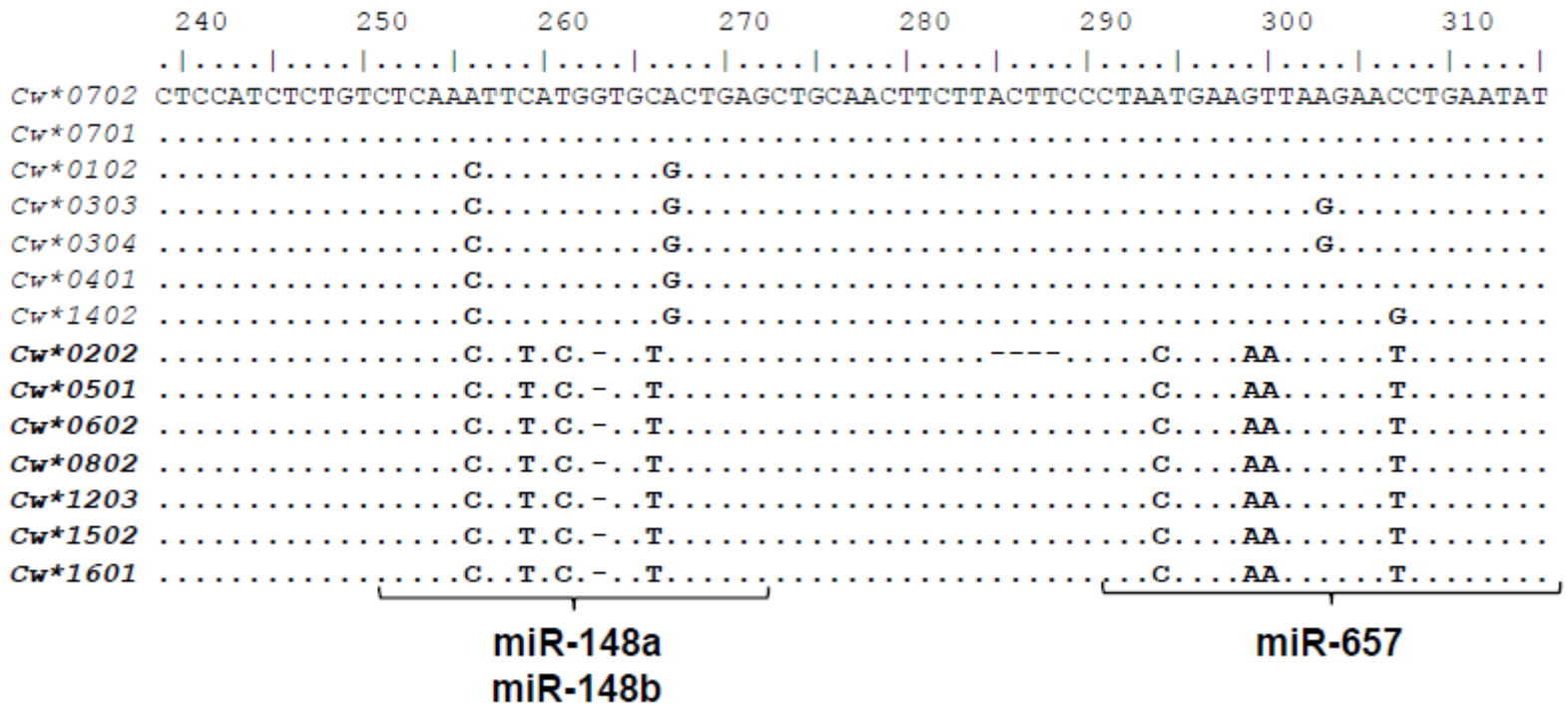
nature

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

Differential microRNA regulation of *HLA-C* expression and its association with HIV control

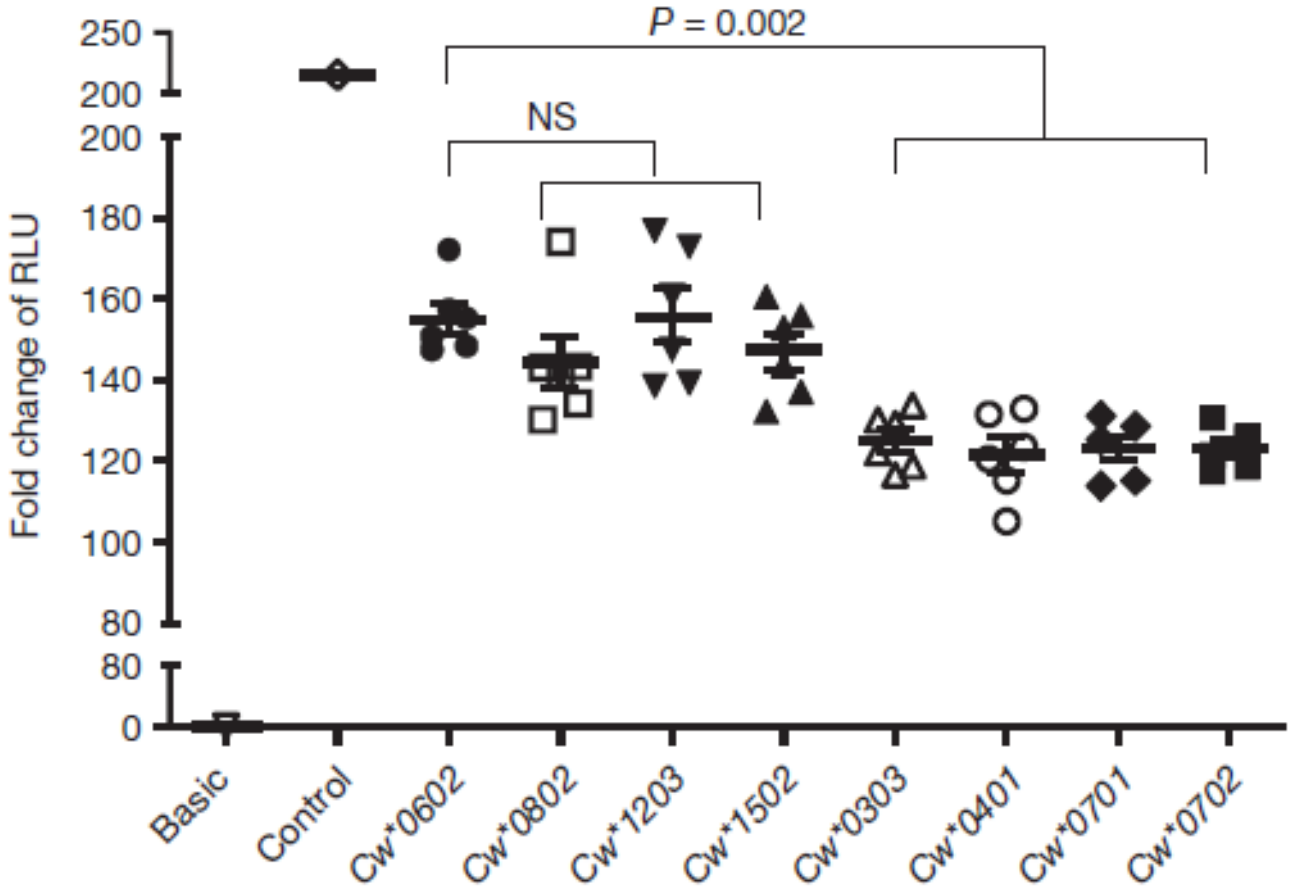
Smita Kulkarni[1,2]*, Ram Savan[3]*, Ying Qi[1,2], Xiaojiang Gao[1,2], Yuko Yuki[1,2], Sara E. Bass[1], Maureen P. Martin[1,2], Peter Hunt[4], Steven G. Deeks[4], Amalio Telenti[5], Florencia Pereyra[2], David Goldstein[6], Steven Wolinsky[7], Bruce Walker[2], Howard A. Young[3] & Mary Carrington[1,2]

28 APRIL 2011 | VOL 472 | NATURE | 495



Polymorphismsim the putative miRNA binding sites in the 3'UTR of *HLA-C*

Kulkarni et al 2011



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Kulkarni et al 2011

Science
AAAS

Influence of HLA-C Expression Level on HIV Control
Richard Apps *et al.*
Science **340**, 87 (2013);
DOI: 10.1126/science.1232685

Influence of HLA-C Expression Level on HIV Control

Richard Apps,[1,2] Ying Qi,[1,2] Jonathan M. Carlson,[3] Haoyan Chen,[4,5] Xiaojiang Gao,[1,2] Rasmi Thomas,[1*] Yuko Yuki,[1,2] Greg Q. Del Prete,[6] Philip Goulder,[2,7,8] Zabrina L. Brumme,[9,10] Chanson J. Brumme,[9] Mina John,[11] Simon Mallal,[11] George Nelson,[12] Ronald Bosch,[13] David Heckerman,[3] Judy L. Stein,[14†] Kelly A. Soderberg,[14] M. Anthony Moody,[14] Thomas N. Denny,[14] Xue Zeng,[4,15] Jingyuan Fang,[5] Ashley Moffett,[16] Jeffrey D. Lifson,[6] James J. Goedert,[17] Susan Buchbinder,[18] Gregory D. Kirk,[19] Jacques Fellay,[20] Paul McLaren,[20] Steven G. Deeks,[21] Florencia Pereyra,[2] Bruce Walker,[2] Nelson L. Michael,[22] Amy Weintrob,[23] Steven Wolinsky,[24] Wilson Liao,[4] Mary Carrington[1,2‡]

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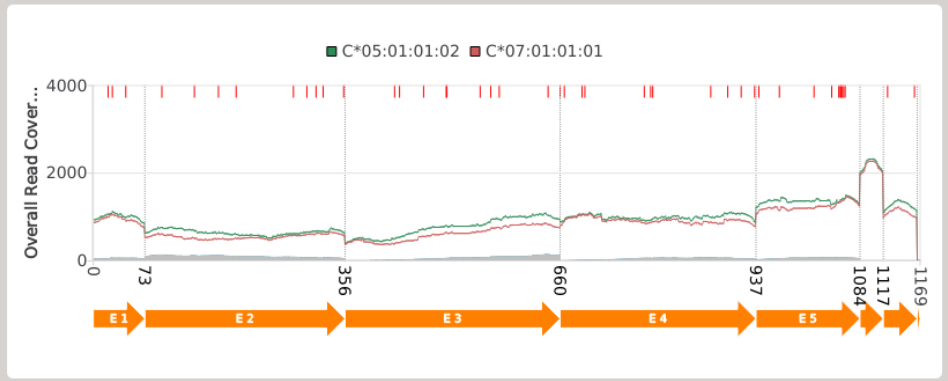
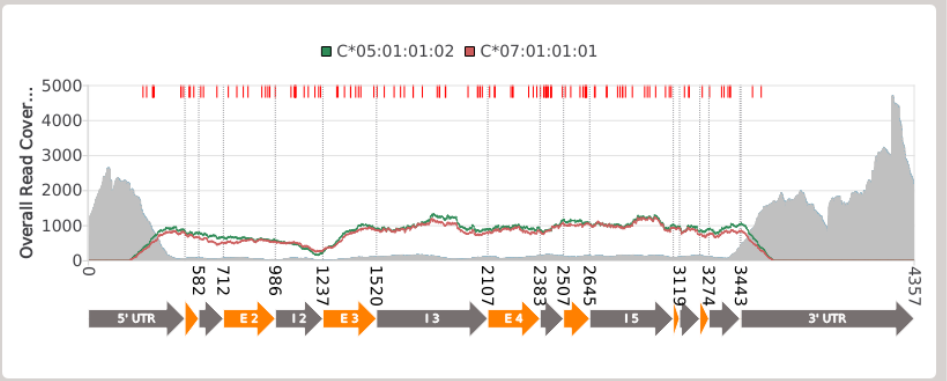
Candidate | Candidate Pair

Allele	Call	Cmt	MME	MMI	cRead	Cov	Cen	eRead	Cov	Cen	gRead	Cov	Cen	xRead	Cov	Cen
C*05:01:01:02	✓		0	0	14693	381	126	4162	381	126	18769	164	48	17209	164	61
C*07:01:01:01	✓		0	0	13239	369	127	3440	369	127	17415	266	80	16027	266	100
C*05:01:01:02e1			0	0	14693	381	126	4162	381	126	18783	164	48	17222	164	61
C*05:01:01:01e1			0	1	14693	381	126	4162	381	126	17446	29	4	15886	29	4
C*05:01:01:01			0	1	14693	381	126	4162	381	126	17433	29	4	15874	29	4
C*07:01:01:01e1			0	1	13239	369	127	3440	369	127	17435	266	80	16045	266	100
C*07:01:01:01e2			0	0	13239	369	127	3440	369	127	17438	266	80	16048	266	100
C*07:01:01:02			0	2	13239	369	127	3440	369	127	16047	-3	0	14670	-3	0
C*07:01:01:03			0	1	13239	369	127	3440	369	127	16591	2	0	15254	2	0
C*07:01:01:04			0	1	13239	369	127	3440	369	127	16307	35	4	14919	35	4

Coverage | Central | cDNA Browser | Genomic Browser | Reference Alignment | Consensus Alignment | Clear

Overall Read Coverage





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BLOOD, 18 DECEMBER 2014 • VOLUME 124, NUMBER 26

Regular Article

TRANSPLANTATION

HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation

Effie W. Petersdorf,[1,2] Theodore A. Gooley,[1] Mari Malkki,[1] Andrea P. Bacigalupo,[3] Anne Cesbron,[4] Ernette Du Toit,[5] Gerhard Ehninger,[6] Torstein Egeland,[7] Gottfried F. Fischer,[8] Thibaut Gervais,[9] Michael D. Haagenson,[10] Mary M. Horowitz,[11] Katharine Hsu,[12] Pavel Jindra,[13] Alejandro Madrigal,[14] Machteld Oudshoorn,[15] Olle Ringdén,[16] Marlis L. Schroeder,[17] Stephen R. Spellman,[10] Jean-Marie Tiercy,[18] Andrea Velardi,[19] Campbell S. Witt,[20] Colm O'Huigin,[21] Richard Apps,[21,22] and Mary Carrington,[21,22] for the International Histocompatibility Working Group in Hematopoietic Cell Transplantation

Key Points

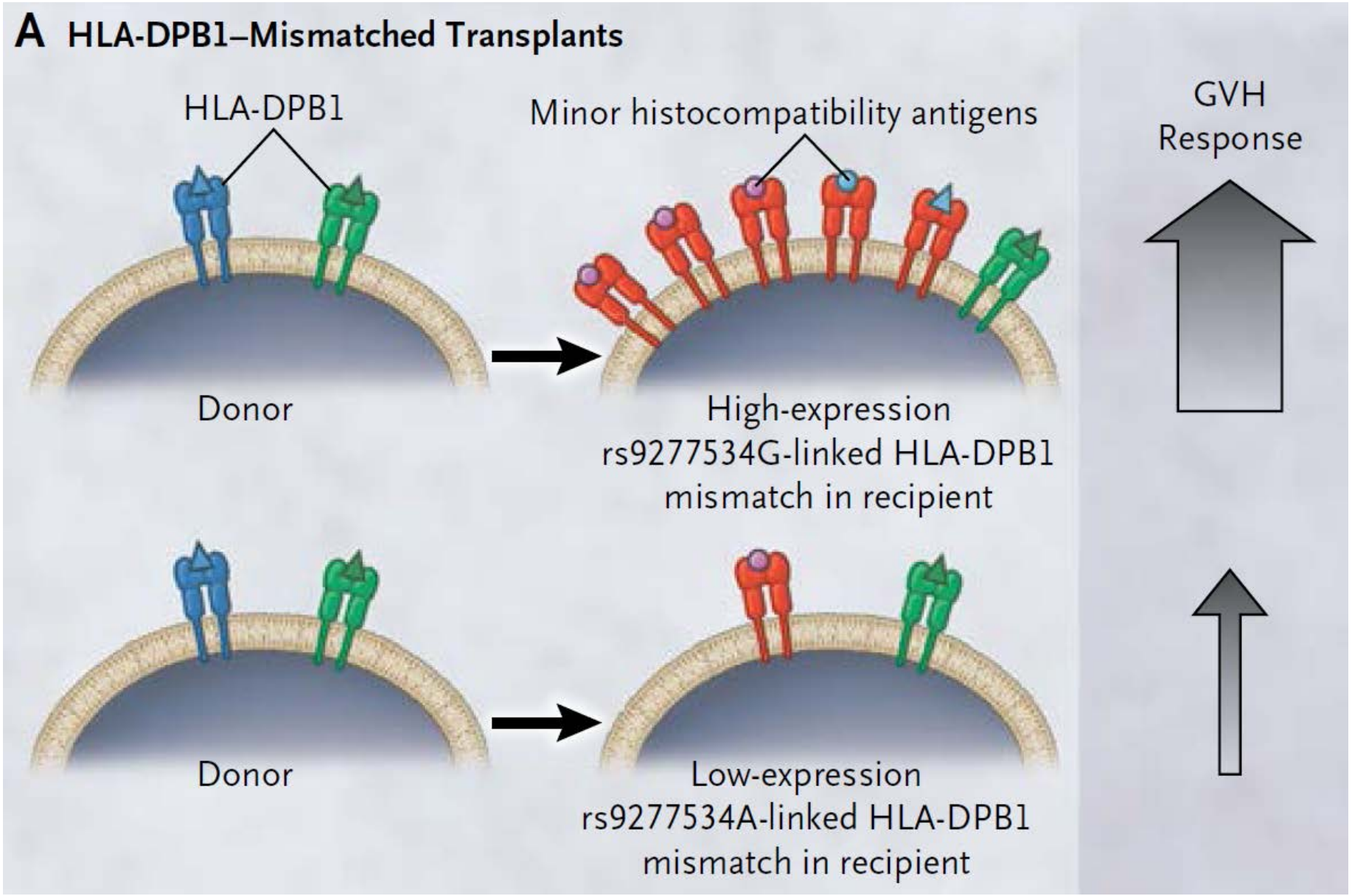
- The expression level of patient HLA-C allotypes affects GVHD and mortality after HCT from HLA-C-mismatched unrelated donors.
- Transplant outcome can be improved by avoiding high-risk HLA-C-mismatched donors when no matched stem cell source is available.

The NEW ENGLAND JOURNAL of MEDICINE

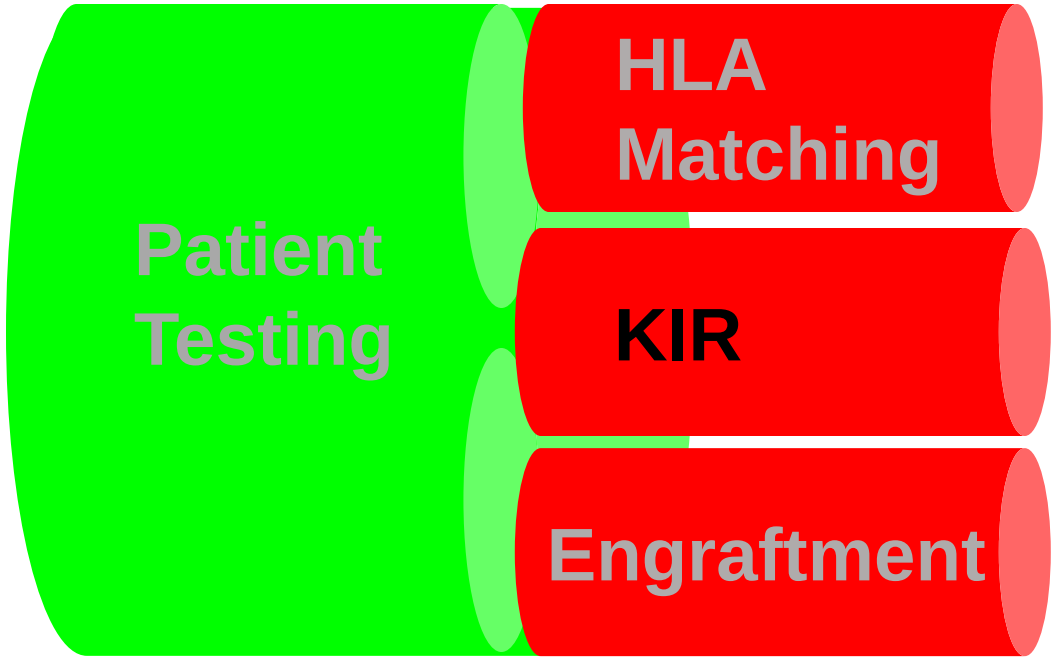
ESTABLISHED IN 1812 AUGUST 13, 2015 VOL. 373 NO. 7

High HLA-DP Expression and Graft-versus-Host Disease

Effie W. Petersdorf, M.D., Mari Malkki, Ph.D., Colm O'hUigin, Ph.D., Mary Carrington, Ph.D., Ted Gooley, Ph.D., Michael D. Haagenson, M.S., Mary M. Horowitz, M.D., Stephen R. Spellman, M.B.S., Tao Wang, Ph.D., and Philip Stevenson, M.S.



Petersdorf et al, 2015


Patient Testing
HLA Matching
KIR
Engraftment


KIR
What elephant?
Tomassi

Biol Blood Marrow Transplant 23 (2017) 535–537

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

The Bottom Line

The Killer Immunoglobulin-Like Receptor Dilemma: How Do We Harness the Power of Killer Immunoglobulin-like Receptors?

Medhat Askar *

Department of Pathology and Laboratory Medicine, Baylor University Medical Center, Dallas, Texas

Science

AAAS

Applications of KIR Genotyping

Effectiveness of Donor Natural Killer Cell Alloreactivity in Mismatched Hematopoietic Transplants

Loredana Ruggeri,[1] Marusca Capanni,[1] Elena Urbani,[1]
Katia Perruccio,[1] Warren D. Shlomchik,[2] Antonella Tosti,[1]
Sabrina Posati,[1] Daniela Rogaia,[1] Francesco Frassoni,[3]
Franco Aversa,[1] Massimo F. Martelli,[1] Andrea Velardi[1]*

www.sciencemag.org SCIENCE VOL 295 15 MARCH 2002

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-C–Dependent Prevention of Leukemia Relapse by Donor Activating *KIR2DS1*

Jeffrey M. Venstrom, M.D., Gianfranco Pittari, M.D., Ted A. Gooley, Ph.D., Joseph H. Chewning, M.D., Stephen Spellman, M.S., Michael Haagenson, M.S., Meighan M. Gallagher, B.A., Mari Malkki, Ph.D., Effie Petersdorf, M.D., Bo Dupont, M.D., D.Sc., and Katharine C. Hsu, M.D., Ph.D.

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THE JOURNAL OF IMMUNOLOGY

KIR and *HLA* Genotypes Predictive of Low-Affinity Interactions Are Associated with Lower Relapse in Autologous Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

John Marra,* Justin Greene,* Jimmy Hwang,† Juan Du,* Lloyd Damon,* Tom Martin,* and Jeffrey M. Venstrom*

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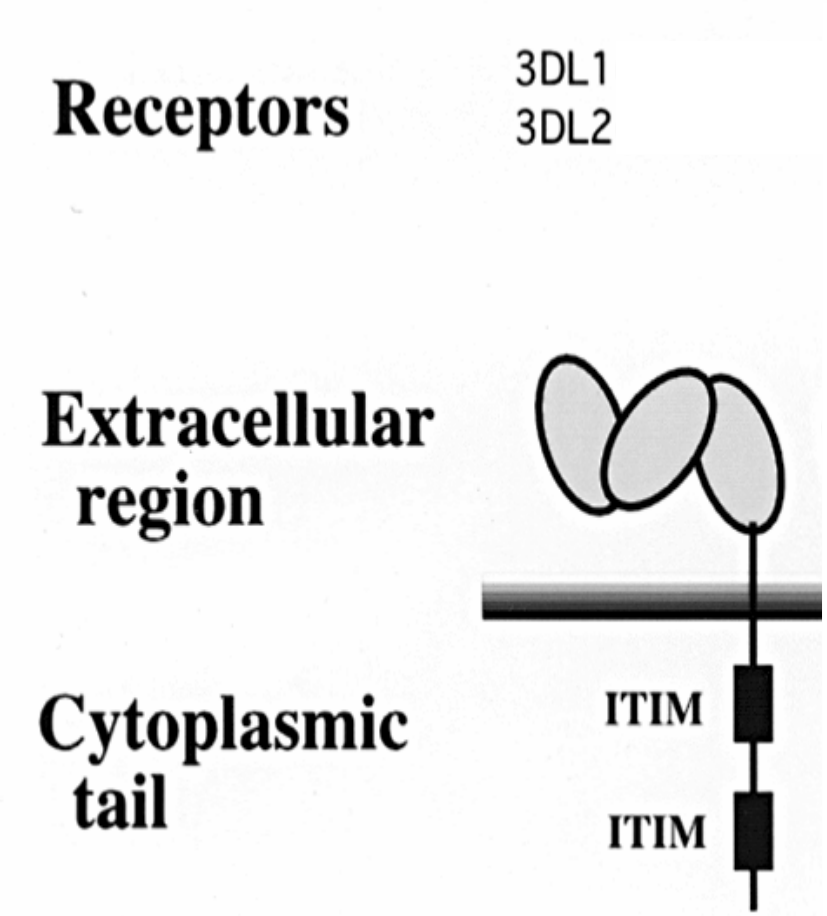
The Journal of Immunology, 2015, 194: 4222–4230

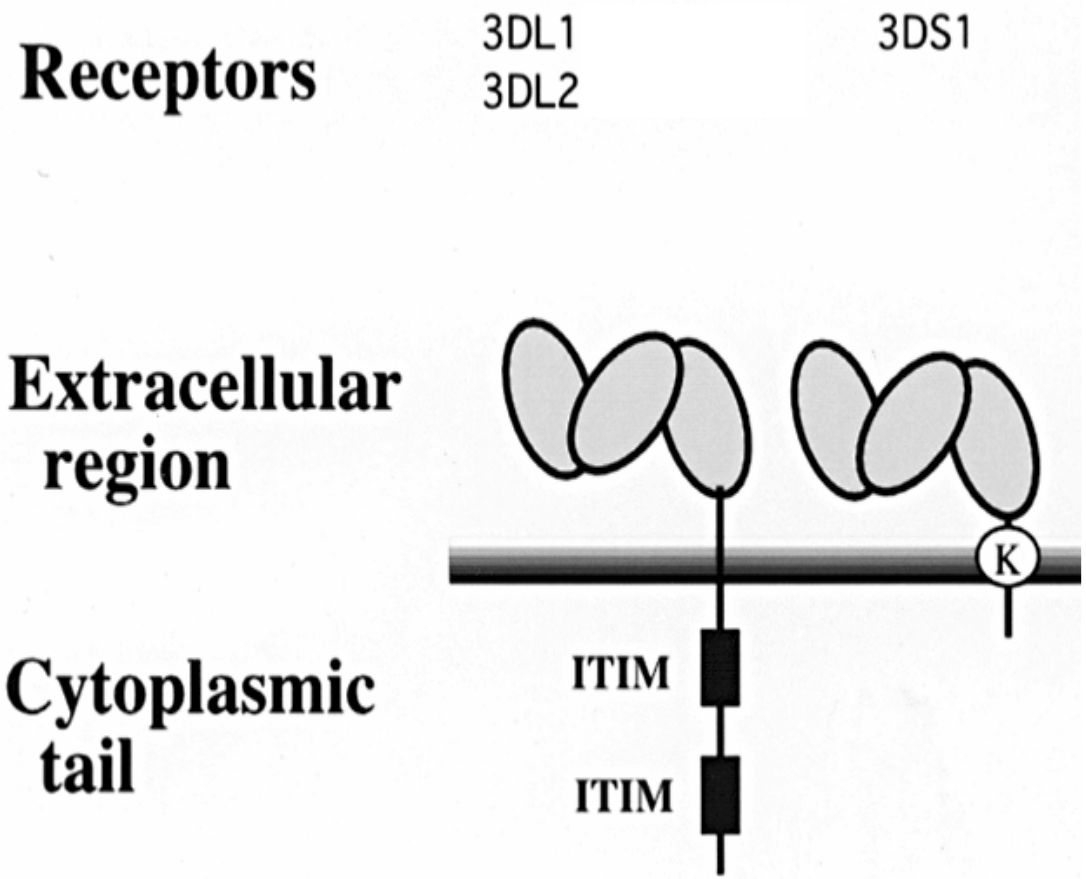
KIR Nomenclature

KIR Nomenclature



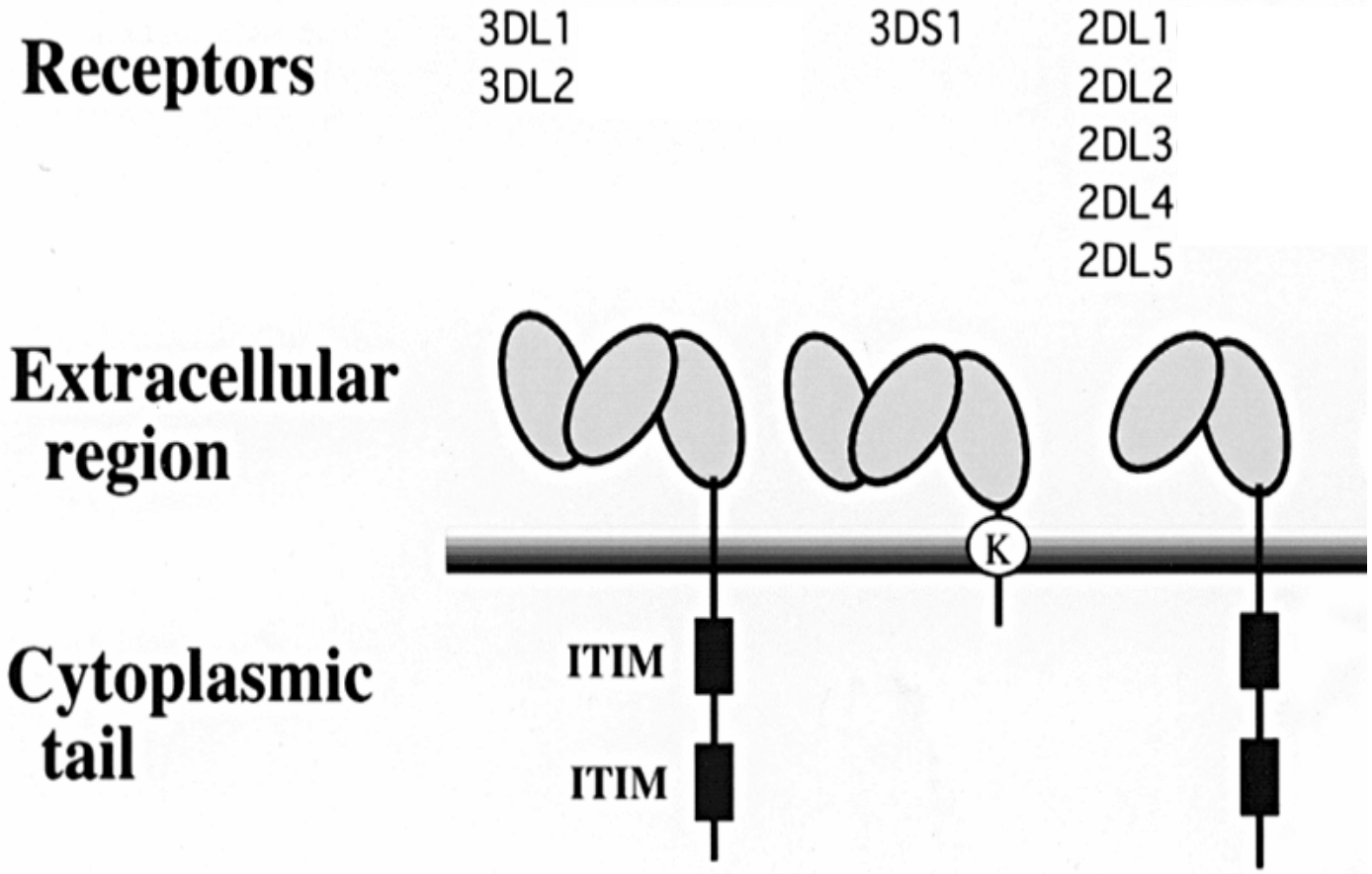
Rajalingam, 2002

KIR Nomenclature



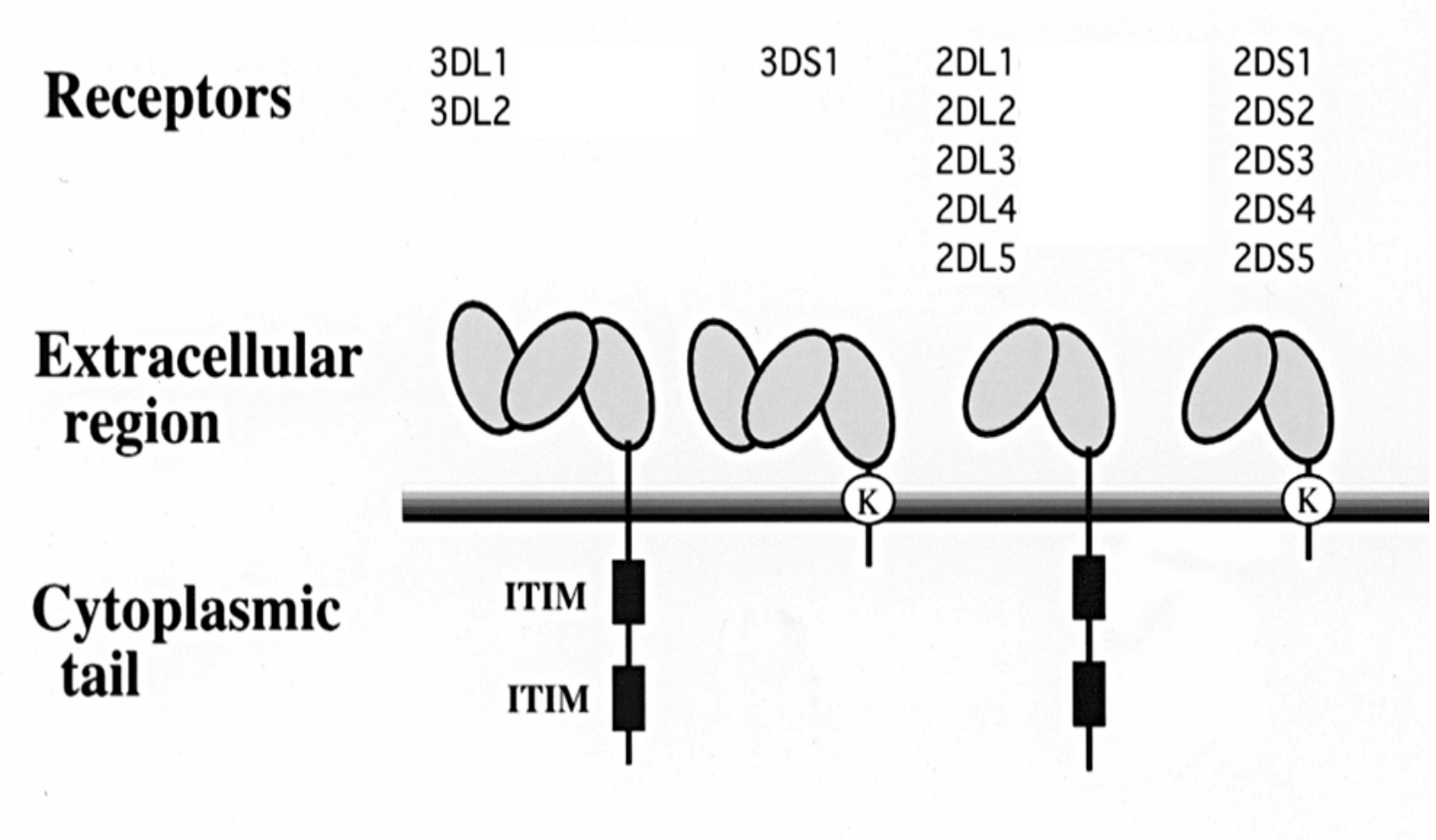
Rajalingam, 2002

KIR Nomenclature



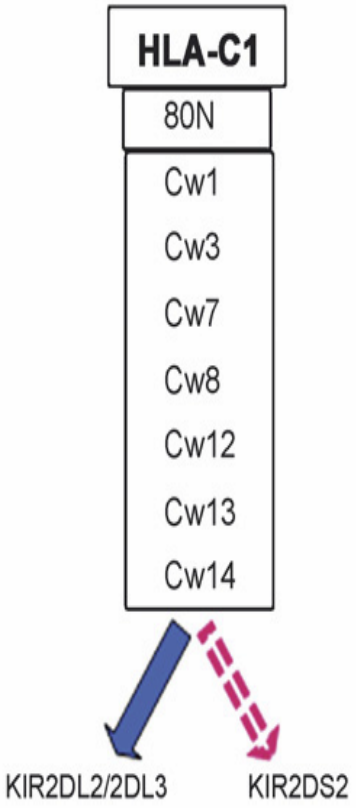
Rajalingam, 2002

KIR Nomenclature



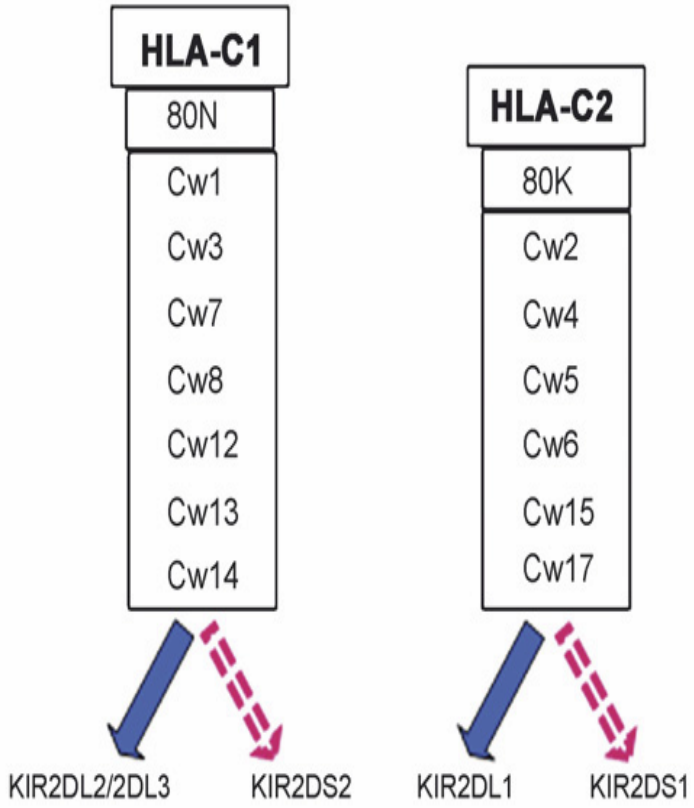
Rajalingam, 2002

KIR Ligands



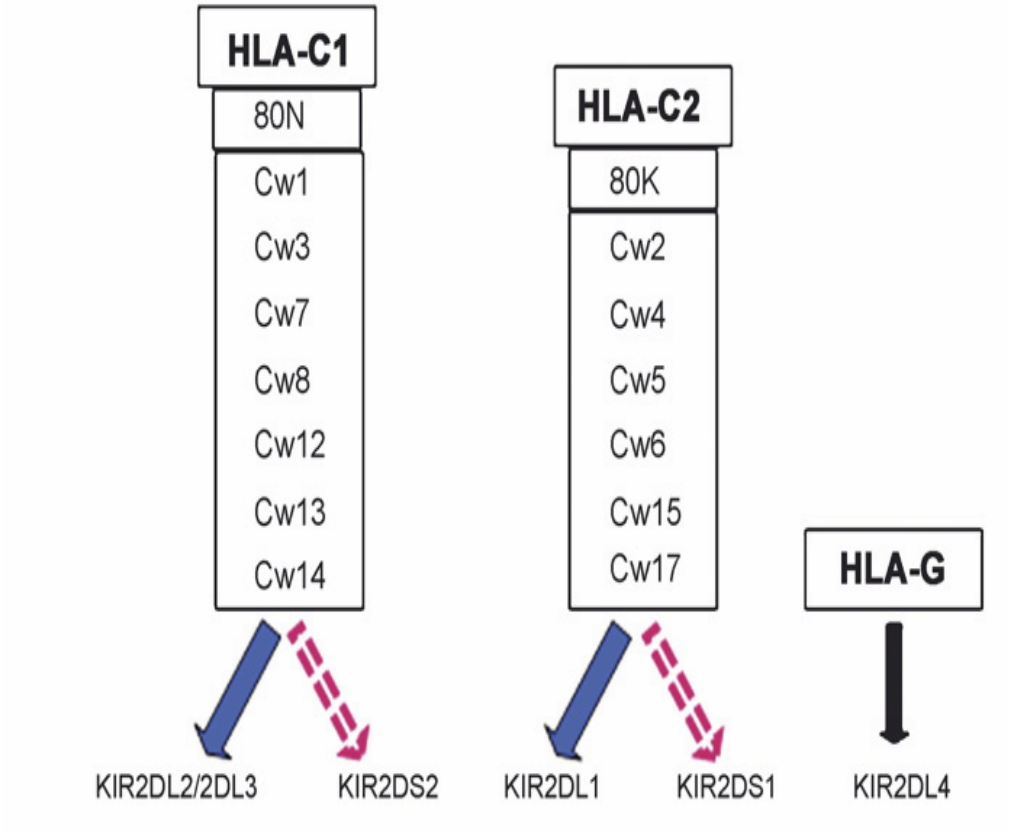
Kulkarni et al, 2008

KIR Ligands



Kulkarni et al, 2008

KIR Ligands



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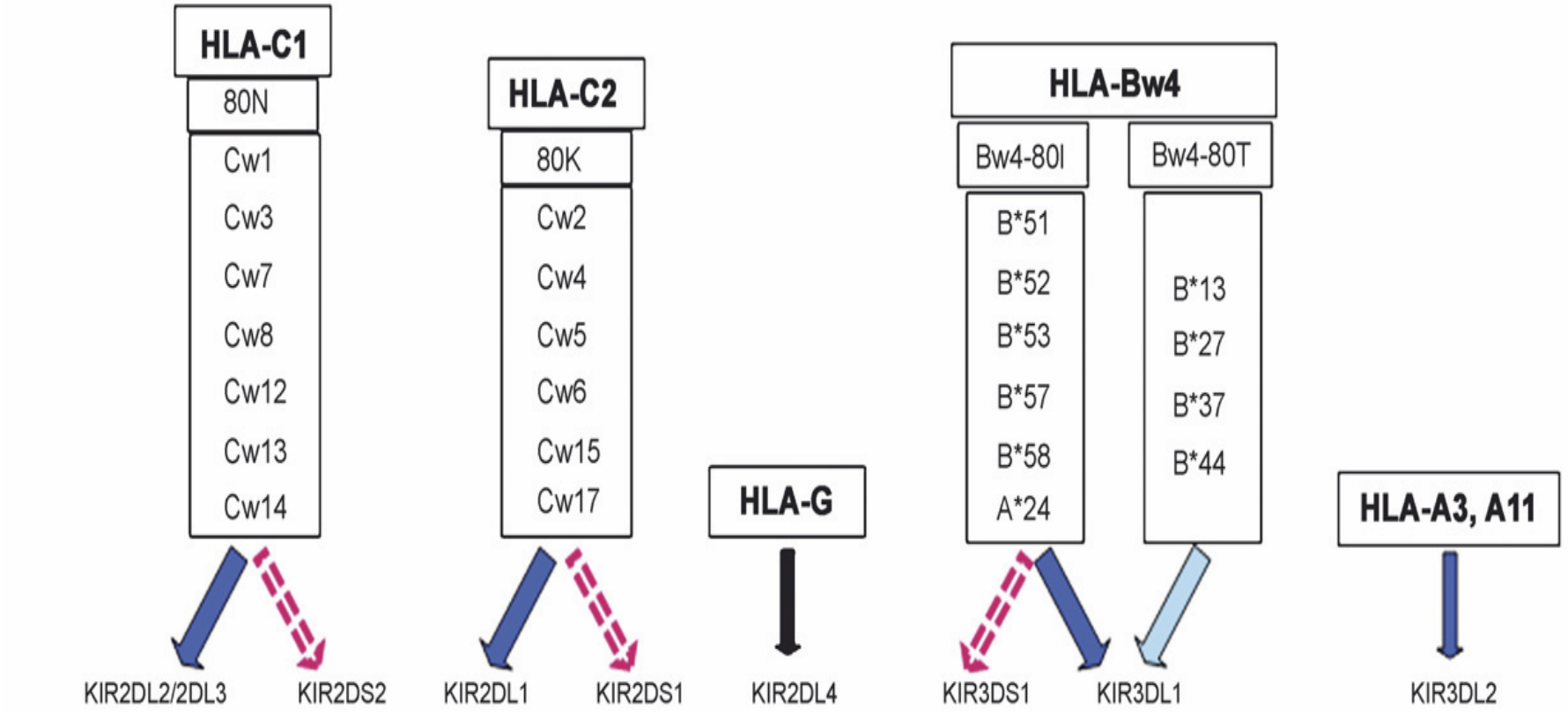
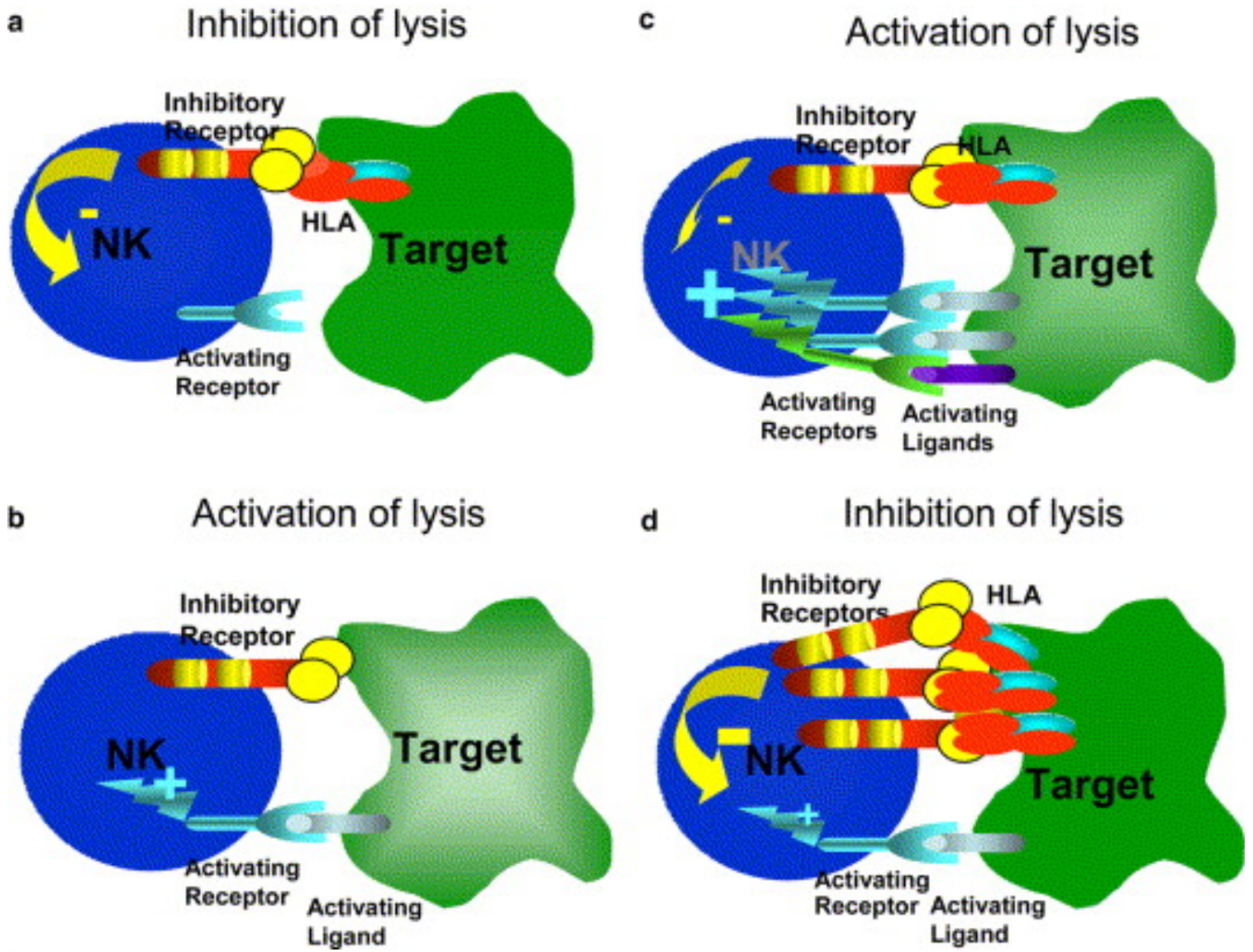
Kulkarni et al, 2008

KIR Ligands



Kulkarni et al, 2008



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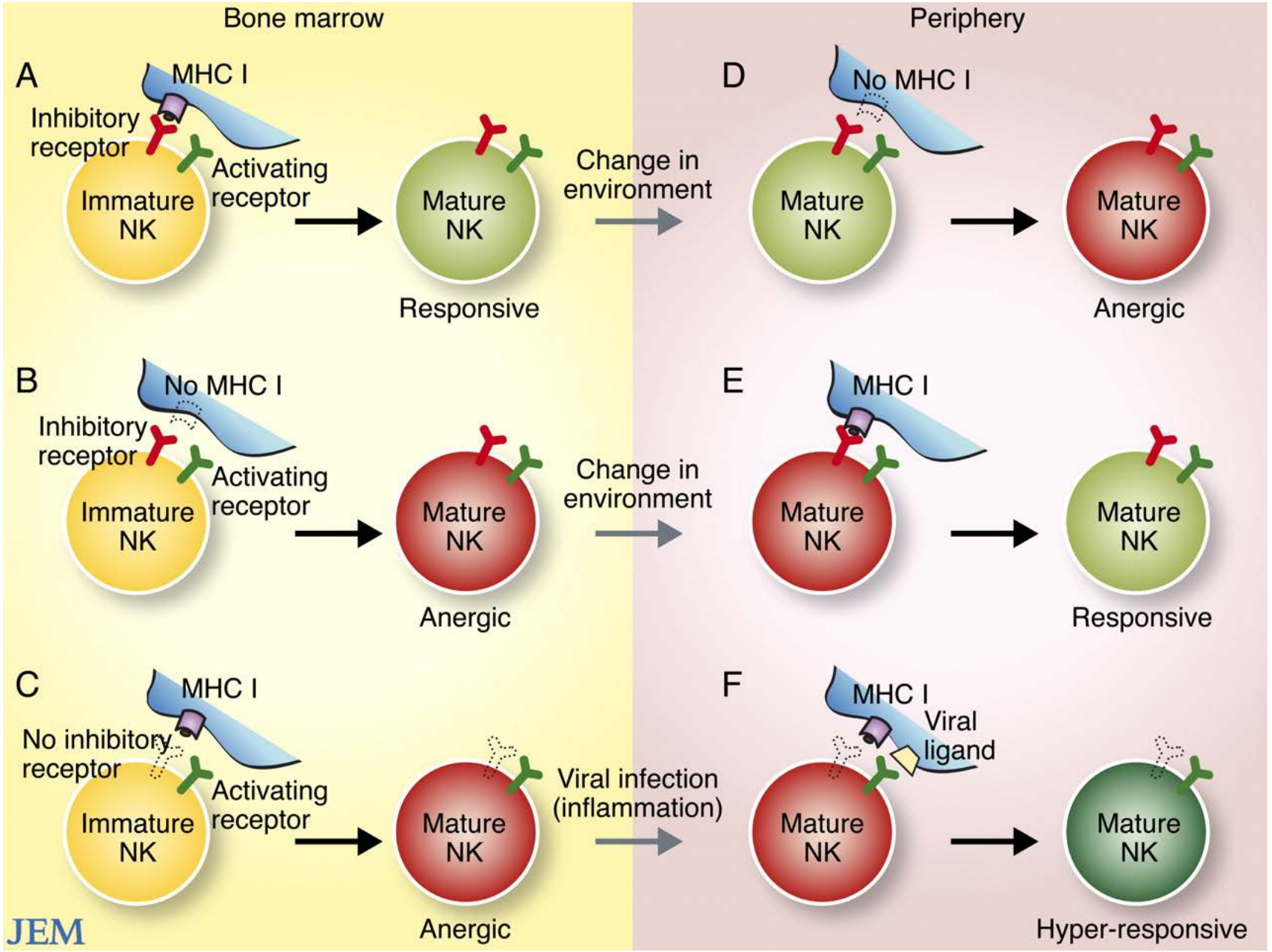
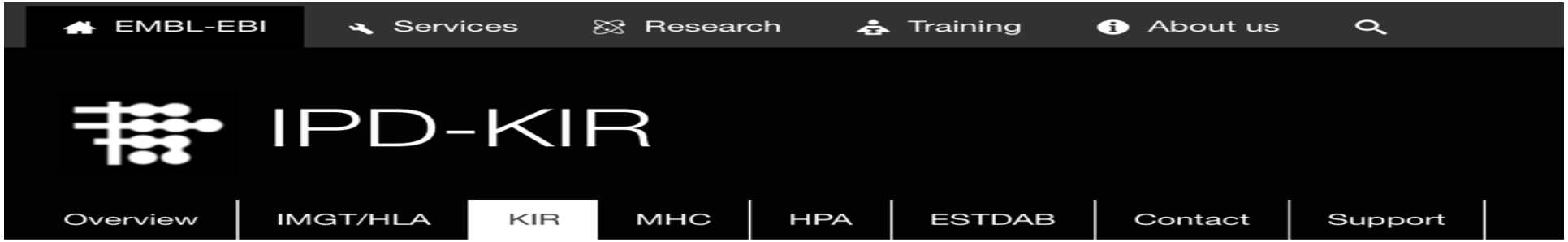
Farag et al, 2002


Bone marrow
Periphery
A
MHC I
Inhibitory receptor
Activating receptor
Immature NK
Mature NK
Responsive
Change in environment
D
No MHC I
Mature NK
Mature NK
Anergic
B
No MHC I
Inhibitory receptor
Activating receptor
Immature NK
Mature NK
Anergic
Change in environment
E
MHC I
Mature NK
Mature NK
Responsive
C
MHC I
No inhibitory receptor
Activating receptor
Immature NK
Mature NK
Anergic
Viral infection (inflammation)
F
MHC I
Viral ligand
Mature NK
Mature NK
Hyper-responsive
JEM



KIR Alleles

Gene	2DL1	2DL2	2DL3	2DL4	2DL5	2DS1	2DS2	2DS3
Alleles	59	31	59	65	51	16	23	16
Proteins	34	13	34	37	22	8	9	7
Nulls	2	0	1	0	0	0	0	1

Gene	2DS4	2DS5	3DL1	3DS1	3DL2	3DL3	2DP1	3DP1
Alleles	35	23	137	39	158	126	40	29
Proteins	16	17	84	22	109	69	0	0
Nulls	0	0	3	1	1	0	0	0

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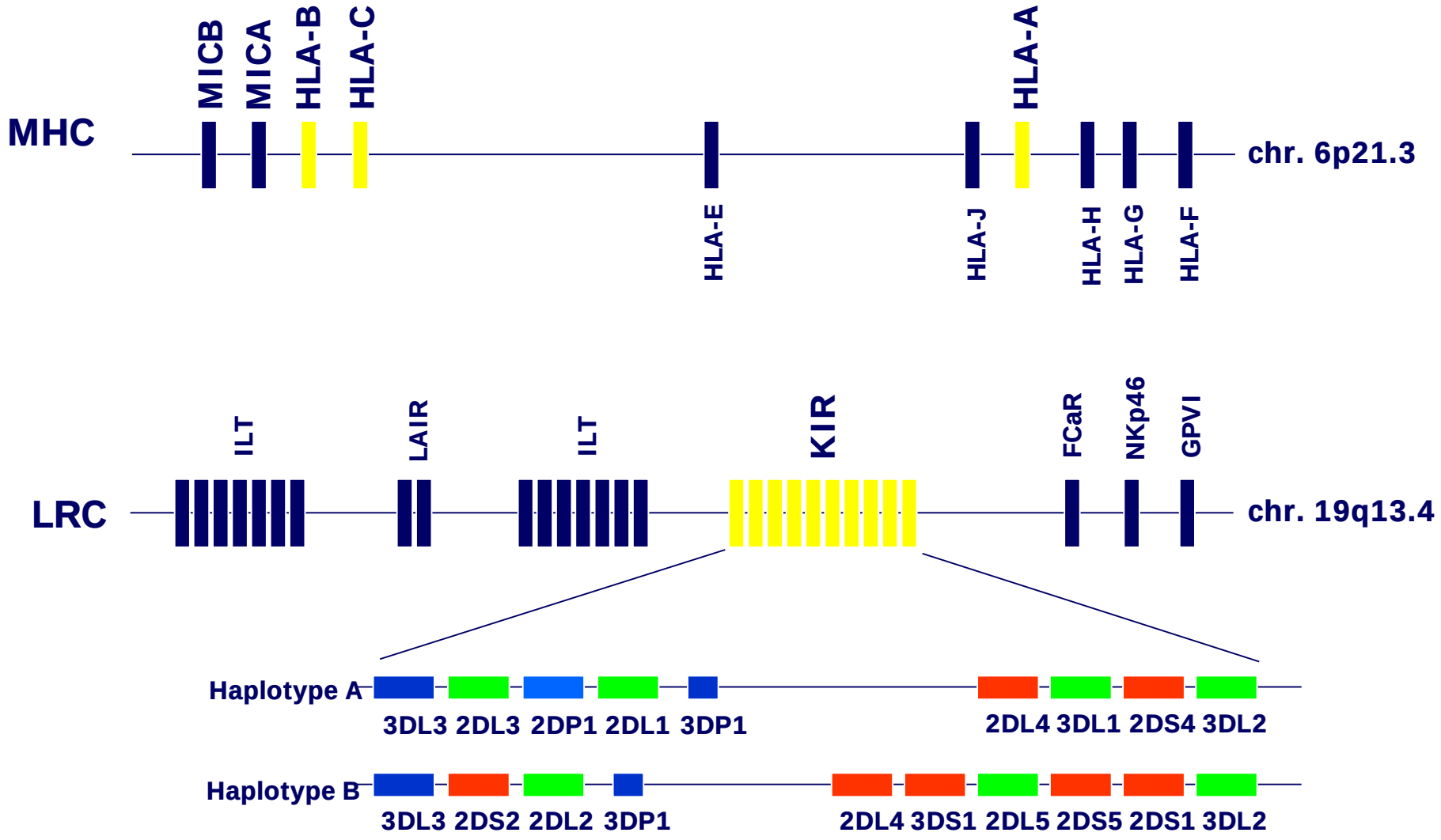
Statistics for Release 2.7.0 (July 2017)

HLA class I and KIR: functionally related gene clusters exhibiting extreme polymorphism



Plenary paper

Donor selection for natural killer cell receptor genes leads to superior survival after unrelated transplantation for acute myelogenous leukemia

Sarah Cooley,[1] Daniel J. Weisdorf,[1] Lisbeth A. Guethlein,[2] John P. Klein,[3] Tao Wang,[3] Chap T. Le,[4] Steven G. E. Marsh,[5] Daniel Geraghty,[6] Stephen Spellman,[7] Michael D. Haagenson,[8] Martha Ladner,[9] Elizabeth Trachtenberg,[9] Peter Parham,[2] and Jeffrey S. Miller[1]

BLOOD, 7 OCTOBER 2010 • VOLUME 116, NUMBER 14

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A

		Centromeric part									RS	Telomeric part								
Haplotype	Cen motif	3DL3	2DS2	2DL2	2DL3	2DL5B	2DS3/5	2DP1	2DL1	3DP1		2DL4	3DL1	3DS1	2DL5A	2DS3/5	2DS1	2DS4	3DL2	Tel motif
A	Cen-A1																			Tel-A1
B	Cen-A1																			Tel-B1
	Cen-B1																			Tel-A1
	Cen-B2																			Tel-A1
	Cen-B1																			Tel-B1
	Cen-B2																			Tel-B1

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Cooley et al, 2010

B

Centromeric (*2DS2, 2DL2, 2DL3*)		N (%)	
		AML	ALL
Cen-A/A	*2DL3* only	532 (49)	155 (48)
Cen-A/B	*2DL3* with *2DS2* and/or *2DL2*	439 (40)	140 (43)
Cen-B/B	*2DS2* and/or *2DL2*; no *2DL3*	115 (11)	28 (9)
Telomeric (*3DL1, 3DS1, 2DS1, 2DS4*)			
Tel-A/A	*3DL1* and *2DS4* only	659 (61)	185 (57)
Tel-A/B	*3DL1* and *2DS4* with *3DS1* and/or *2DS1*	382 (35)	119 (37)
Tel-B/B	lacking *3DL1* and/or *2DS4*	45 (4)	19 (6)

C

Donor *KIR* Genotype	*B* content score	*Cen*	*Tel*	N (%)	
				AML	ALL
A/A	0	*A/A*	*A/A*	374 (34)	99 (31)
B/x	1	*A/A*	*A/B*	374 (34)	121 (37)
		A/B	*A/A*		
	2	*A/A*	*B/B*	254 (23)	78 (24)
		A/B	*A/B*		
		B/B	*A/A*		
	3	*A/B*	*B/B*	84 (8)	25 (8)
		B/B	*A/B*		
	4	*B/B*	*B/B*		

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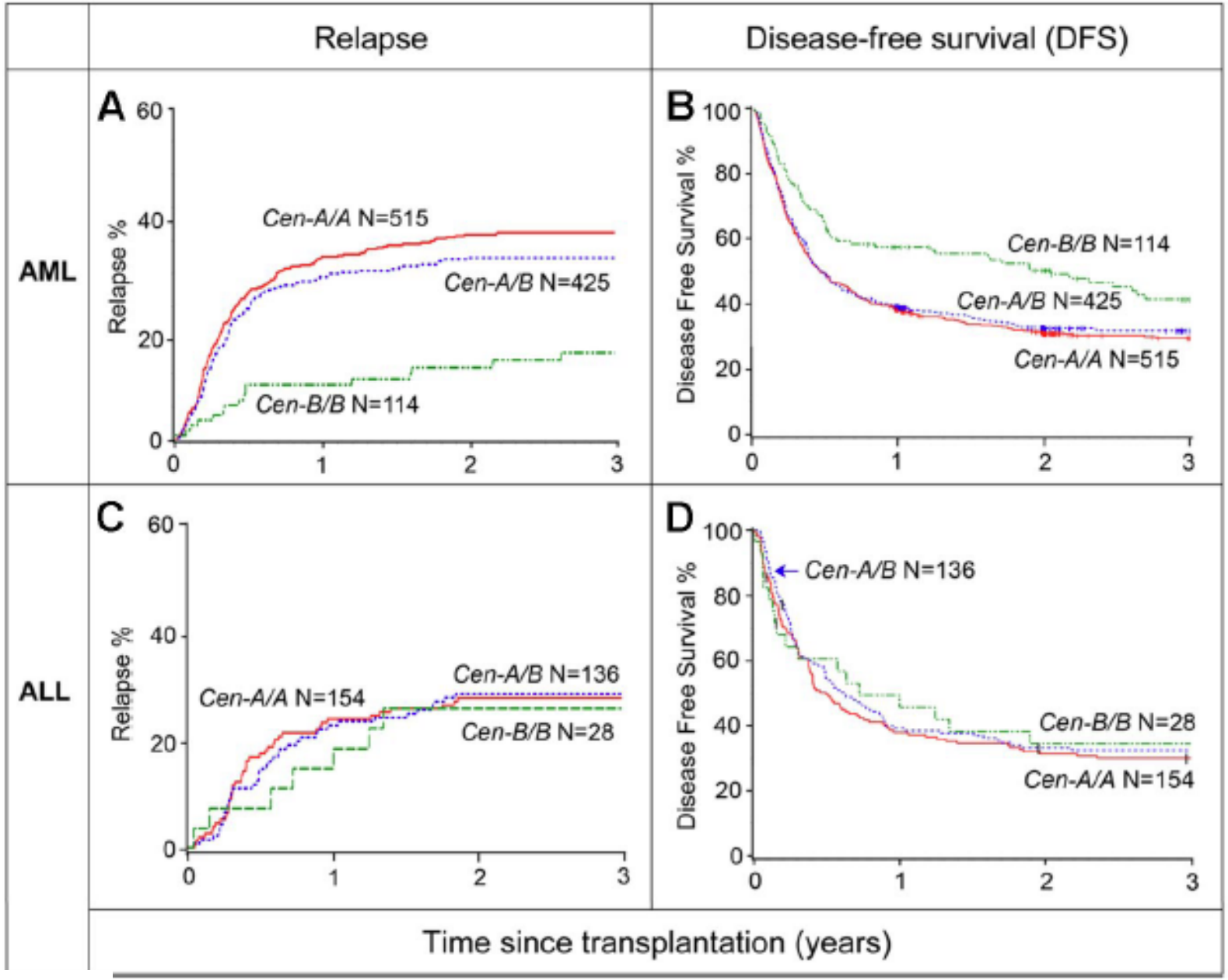
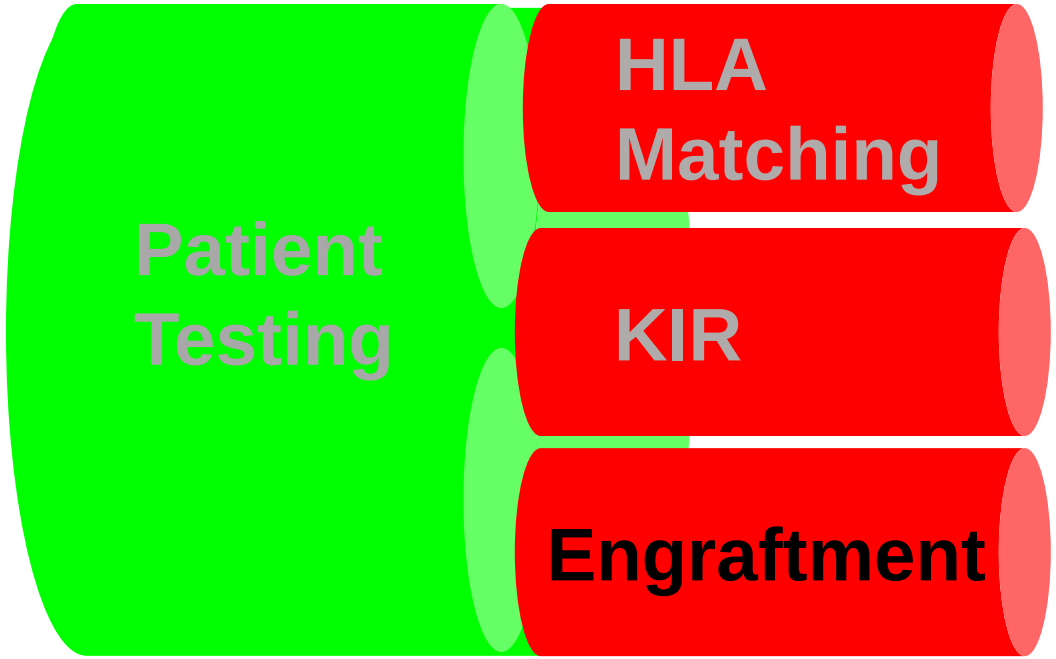
Cooley et al, 2010



Cooley et al, 2010


Patient Testing
HLA Matching
KIR
Engraftment

Engraftment Monitoring

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Biol Blood Marrow Transplant 23 (2017) 1658–1668

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Utility of Quantitative PCR for Chimerism and Engraftment Monitoring after Allogeneic Stem Cell Transplantation for Hematologic Malignancies

Müberra Ahci [1], Karin Stempelmann [1], Ulrike Buttkereit [2], Pietro Crivello [1], Mirko Trilling [3], Andreas Heinold [4], Nina Kristin Steckel [2], Michael Koldehoff [2], Peter A. Horn [4], Dietrich W. Beelen [2], Katharina Fleischhauer [1,5,*]

TRANSPLANTATION

Engraftment Kinetics After Nonmyeloablative Allogeneic Peripheral Blood Stem Cell Transplantation: Full Donor T-Cell Chimerism Precedes Alloimmune Responses

By R. Childs, E. Clave, N. Contentin, D. Jayasekera, N. Hensel, S. Leitman, E.J. Read, C. Carter, E. Bahceci, N.S. Young, and A.J. Barrett

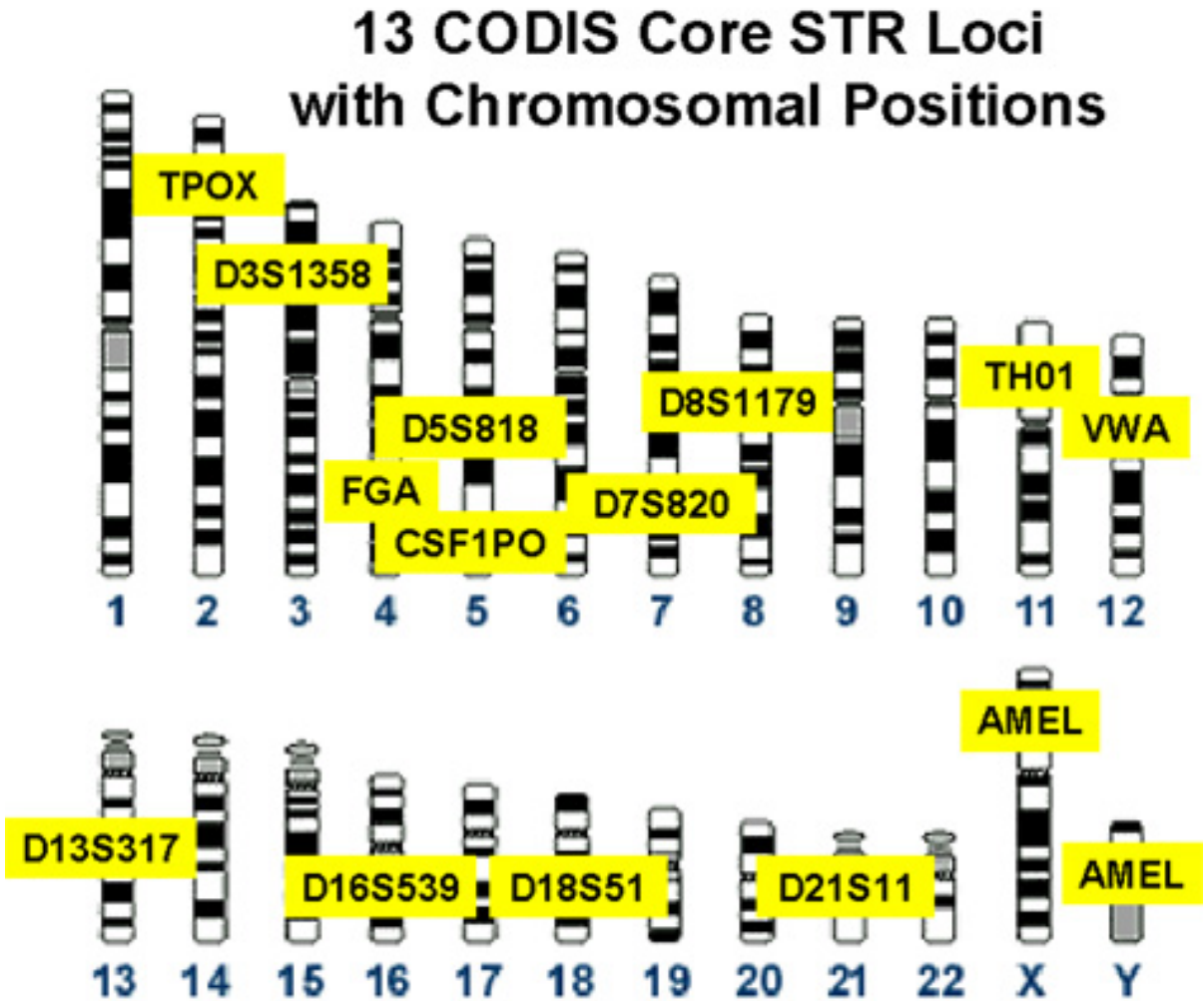
Blood, Vol 94, No 9 (November 1), 1999: pp 3234-3241

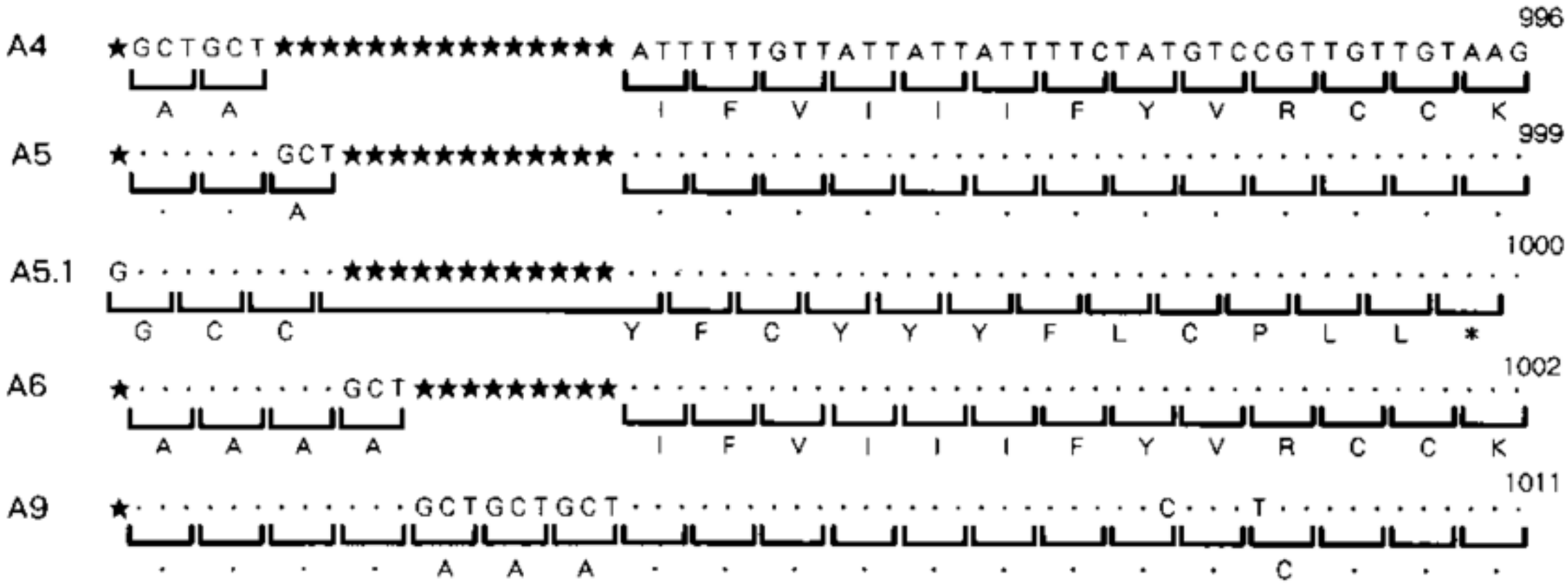
Table 1 Chimerism, definition and implications

Chimerism	Dynamic process	Definition	Implication
Complete chimerism (CC)		Only donor DNA in a given post-transplant sample.	Further follow-up to survey engraftment or to detect recurrence of autologous cells during later periods.
Mixed chimerism (MC)		Both donor and recipient DNA detectable in a post-transplant sample.	Close follow-up to recognize dynamic changes.
	Decreasing	Recipient DNA immediately post transplant, which spontaneously decreases over time.	Weekly follow-up until CC is established.
	Stable	Both donor and recipient DNA. Relation does not significantly change over time, for example, in patients with SCID or often in patients with nonmalignant disease after reduced conditioning regimens.	Close monitoring during engraftment, thereafter longer intervals, for example, bimonthly to realize late graft rejection.
	Increasing	Recipient DNA is increasing compared to the foregoing sample by at least 5%.	Pre-emptive immunotherapy in patients with hematological malignant diseases is recommended. In patients with nonmalignant diseases only when autologous cells exceed 30%.
Split chimerism		Recipient DNA is not detectable in all cell lines, for example, only in T cells, whereas the other cell lines are complete donors as in SCID patients or often in patients after reduced intensity conditioning transplants.	Analysis of T-cell and NK-cell chimerism can help to guide additional therapy to avoid graft rejection.
		Only recipient DNA in the post-transplant sample.	Reconditioning and second transplant probably necessary.

Bader et al., 2005

Short Tandem Repeats (STR)





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Engraftment Analysis (STR)

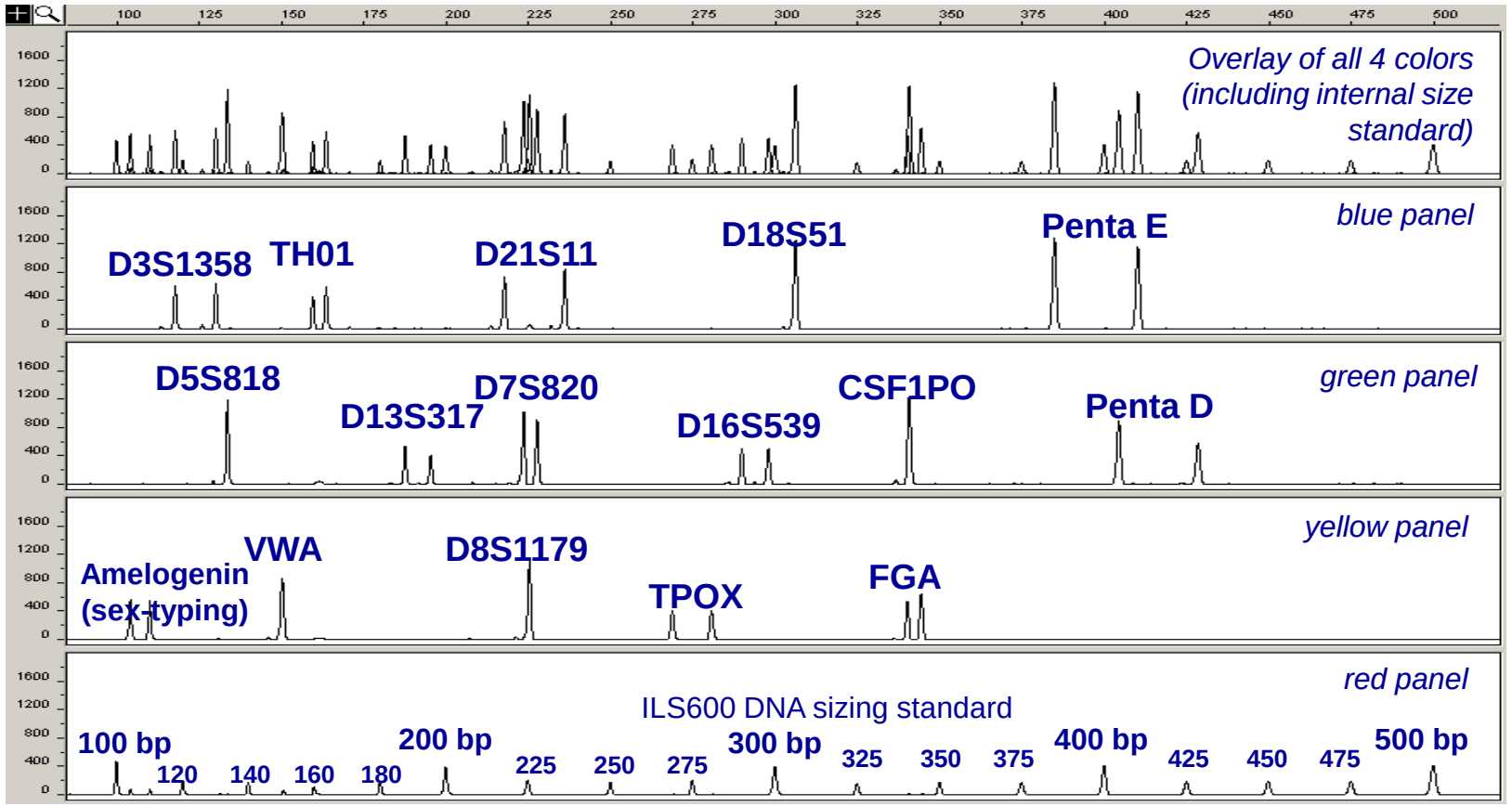
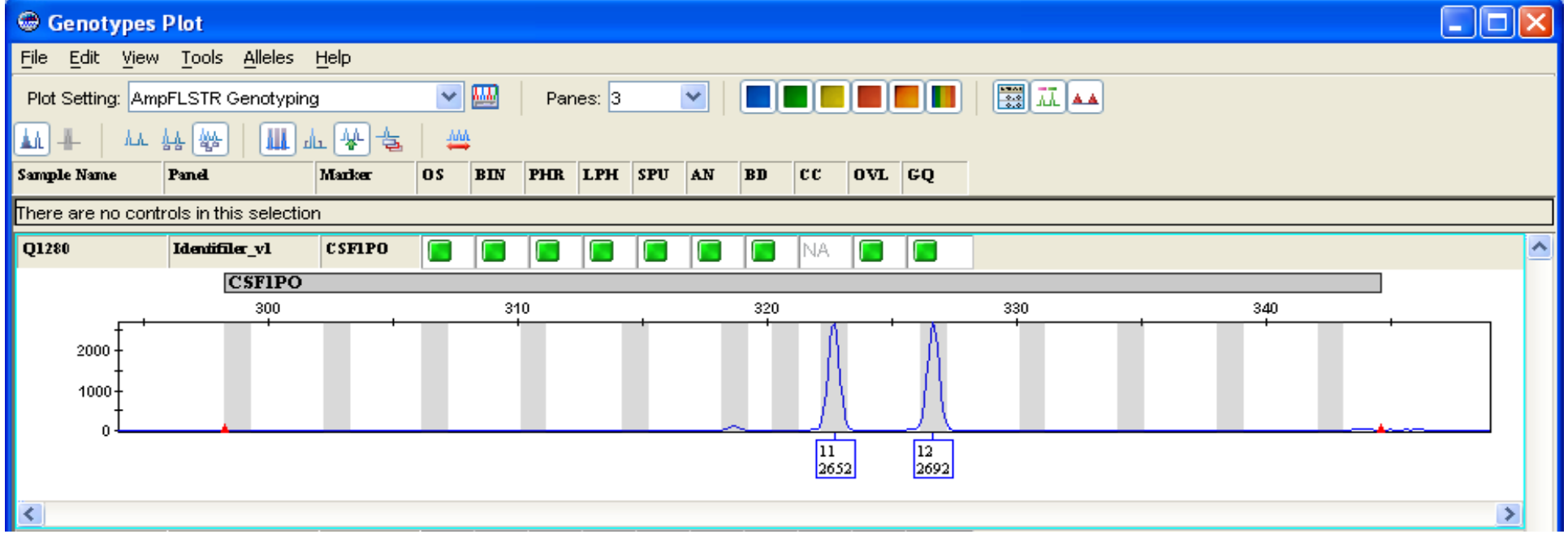


Figure 5.5, J.M. Butler (2005) *Forensic DNA Typing*, 2nd Edition © 2005 Elsevier Academic Press


Genotypes Plot
File Edit View Tools Alleles Help
Plot Setting: AmpFLSTR Genotyping
Panes: 3
Sample Name Panel Marker OS BIN PHR LPH SPU AN BD CC OVL GQ
There are no controls in this selection
Q1280 Identifiler_v1 CSF1PO
NA
CSF1PO
300 310 320 330 340
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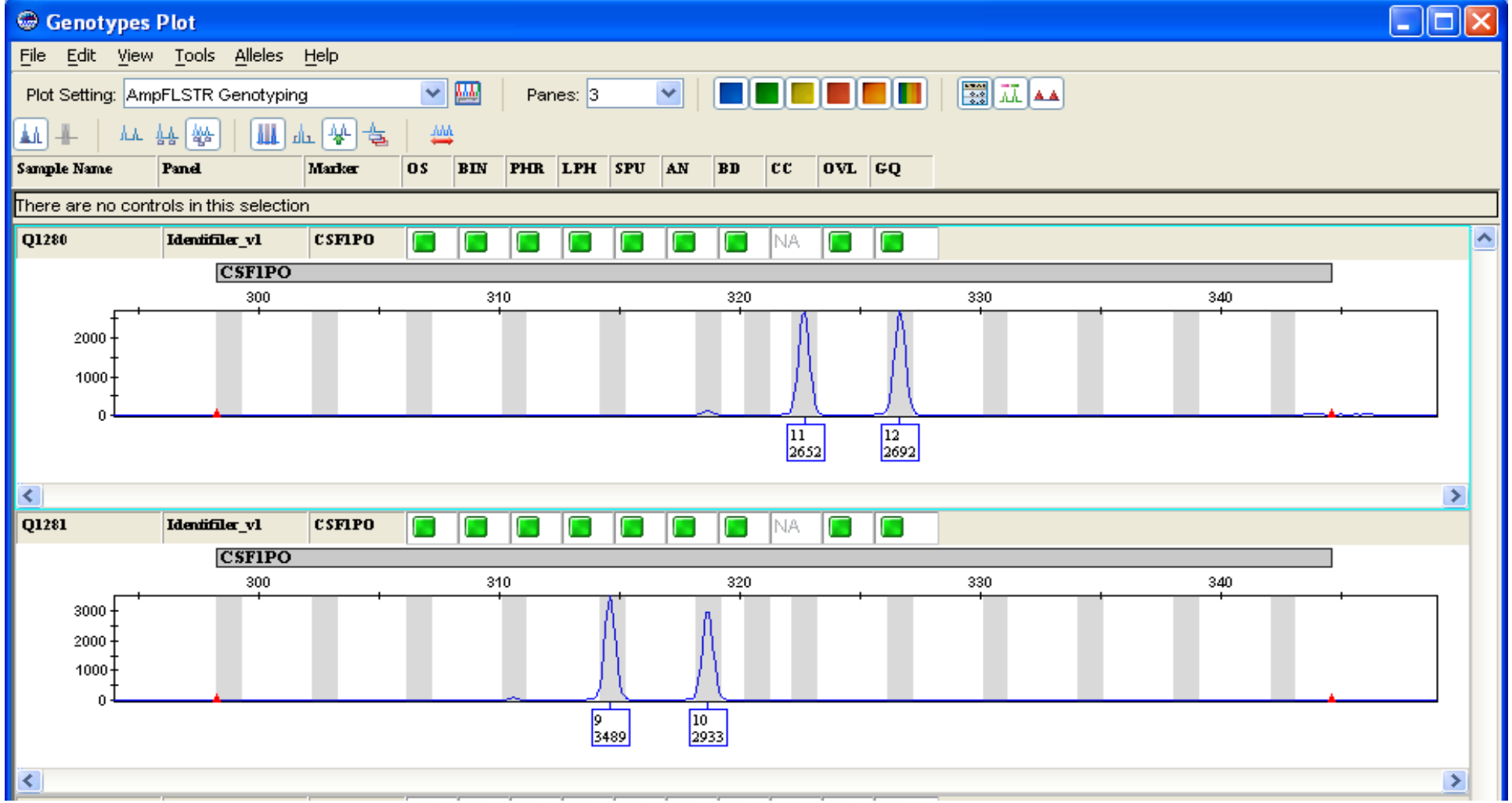
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File Edit View Tools Alleles Help
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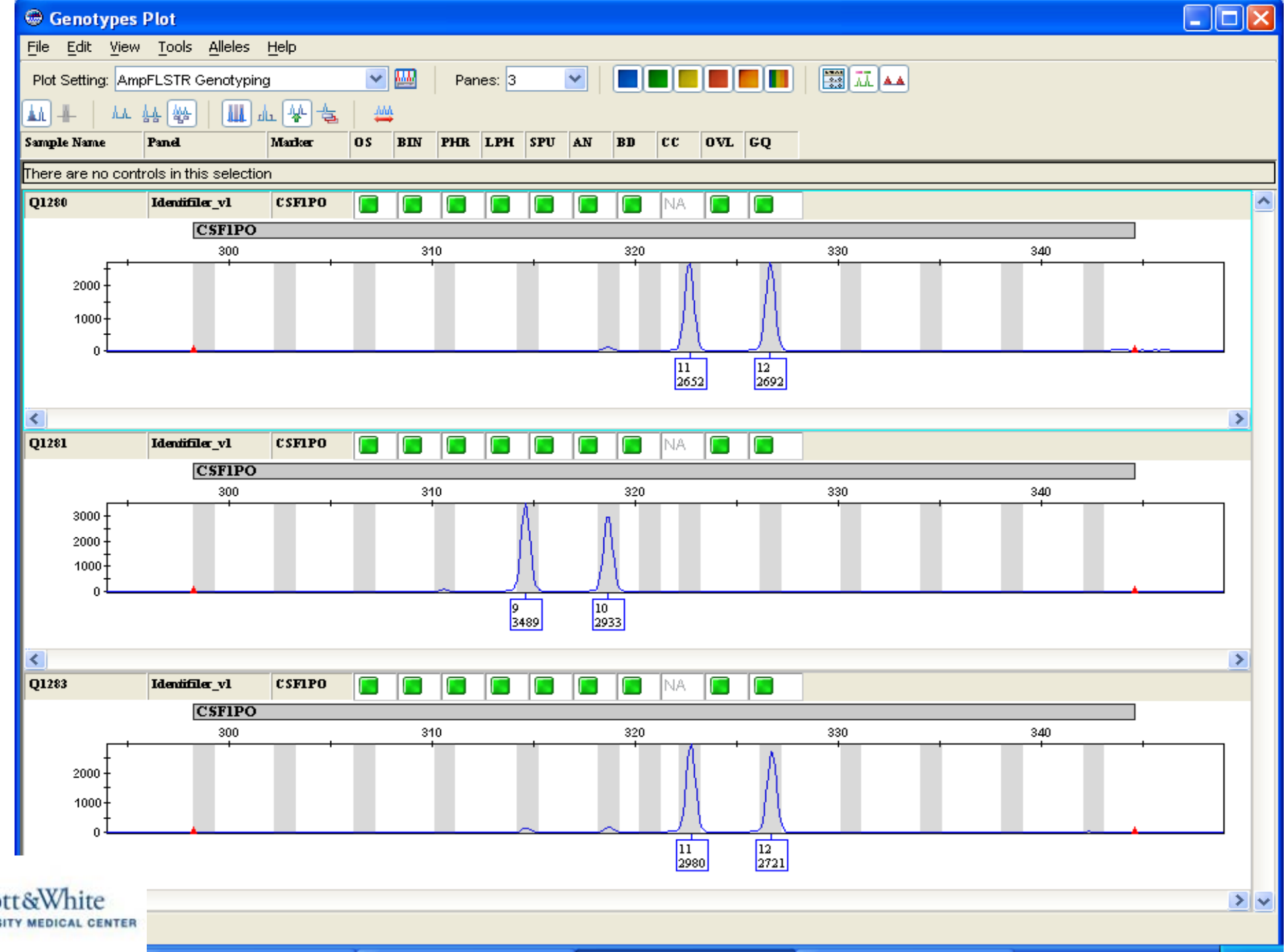

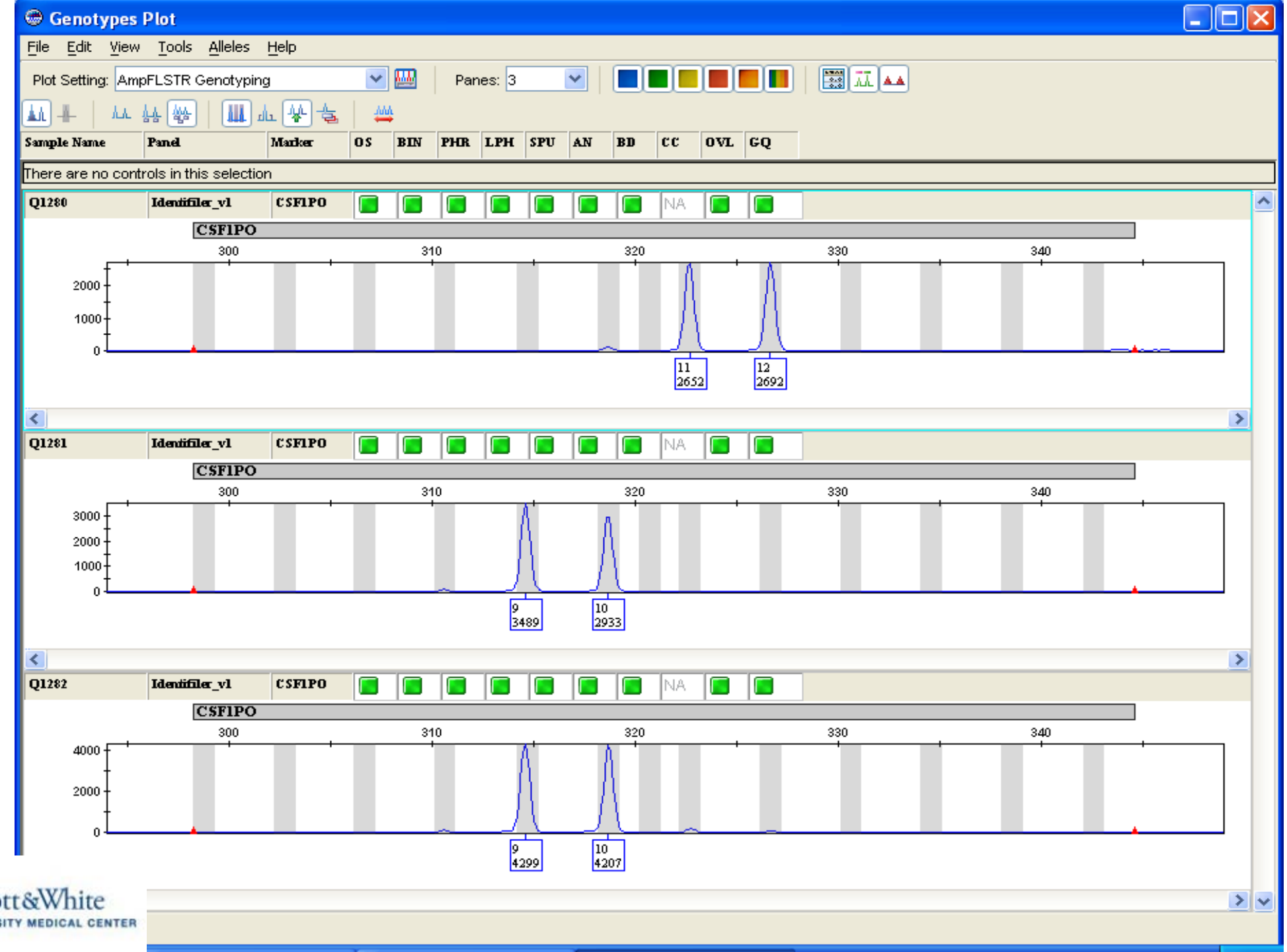

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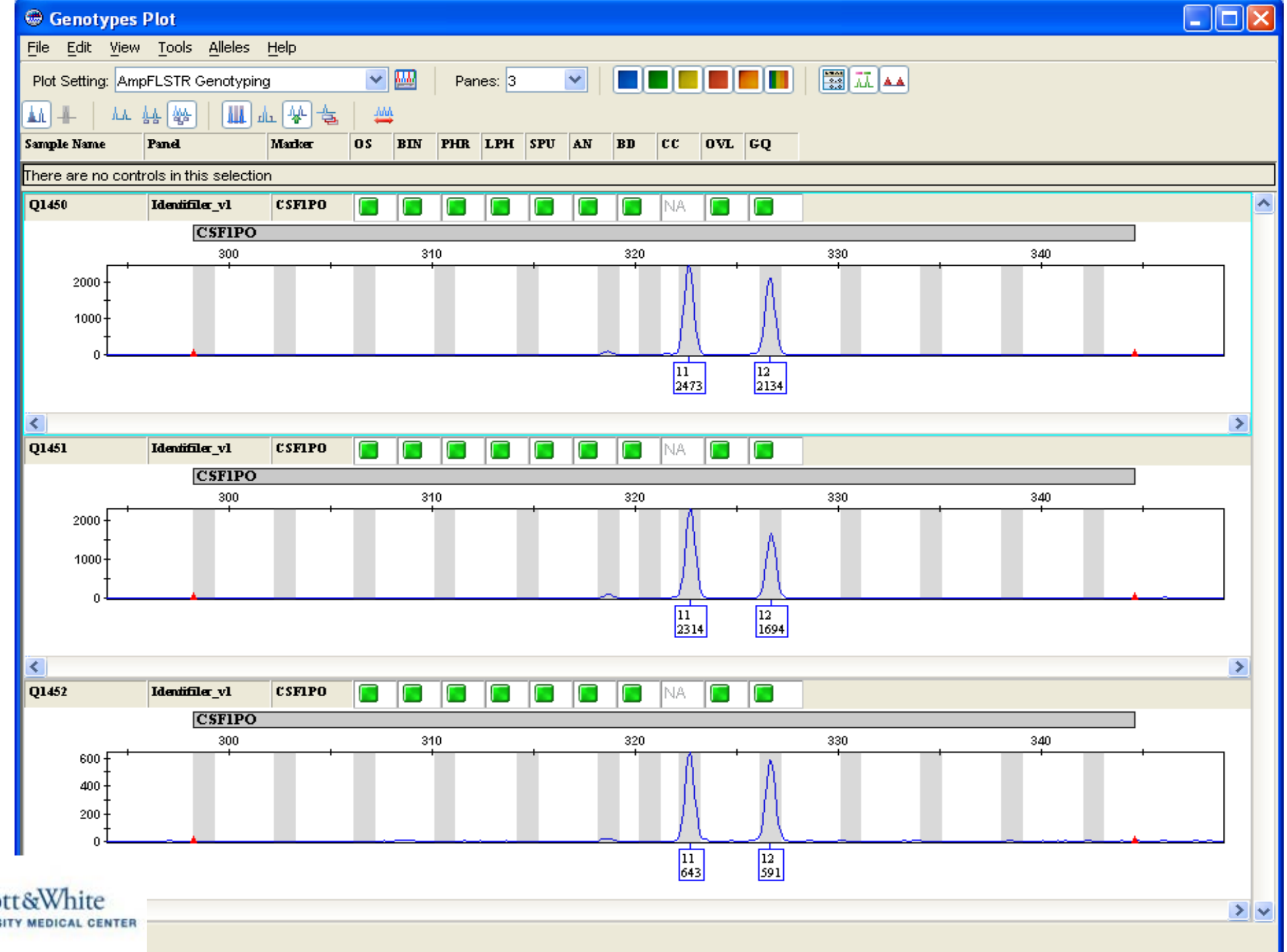

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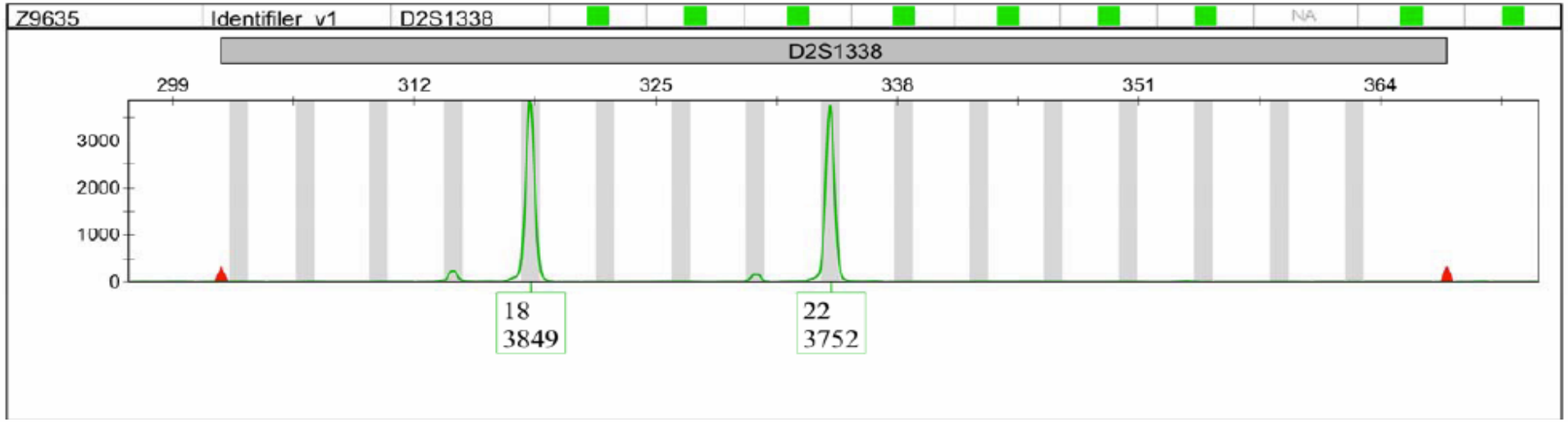

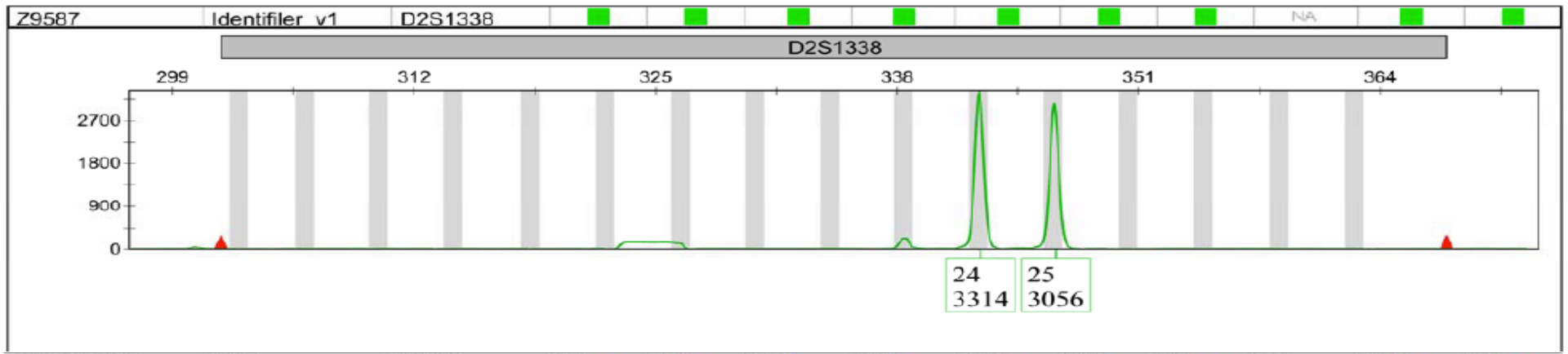

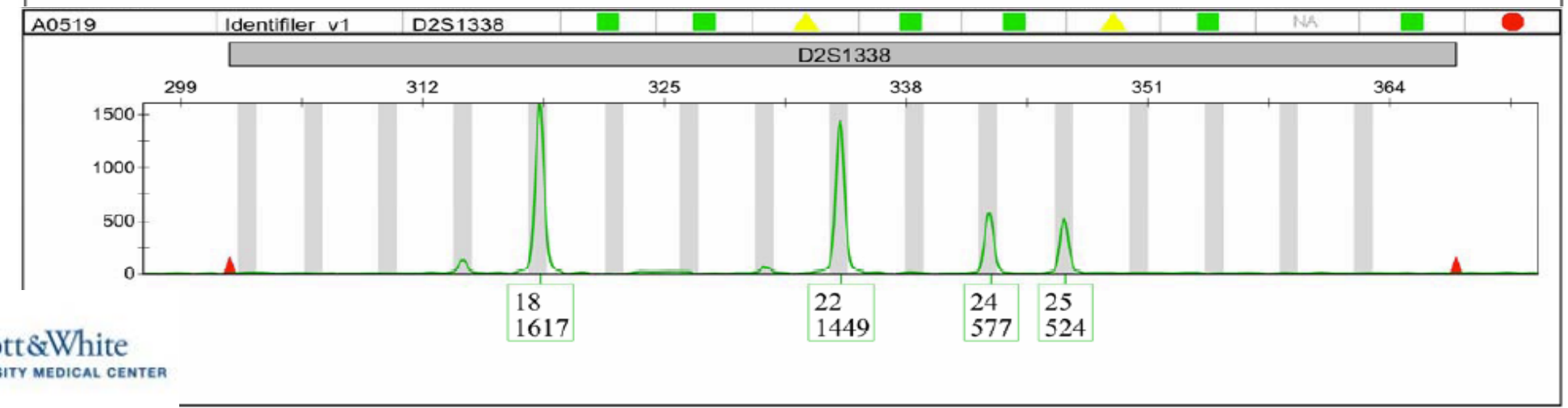

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Method Comparison

Table 2 Survey of methods for chimerism analysis

Technique	Merits	Problems	Sensitivity (%)	Applicability	References
RFLP	High informativity	Time consuming, labor intensive	5–10	High	24–27
Cytogenetics		Time consuming	5	Low	20, 21
Red cell phenotyping	Simple, accurate	Long latency, lineage specific	1–5	High	22–23
X/Y FISH	Low false positivity, large number of cells, high sensitivity	Restricted to sex-mismatched transplants	0.1–0.001	Low	28–33
Fluorescence-based STR–PCR	Robust, fast, high quantitative accuracy	Moderate sensitivity	1–5	Very high	44–47
STR in subpopulation	Very high sensitivity	Labor intensive, expensive	0.1–0.001	Very high	17, 59
Real-time PCR	High sensitivity, rapid	False-positive results in SNP-based assays, high specificity in Y-chromosome-specific PCRs	0.001–0.0001	Medium–high	49–50, 54–56

FISH= fluorescent in situ hybridization; RFLP= restriction fragment length polymorphism; STR= short tandem repeat markers.

Bader et al., 2005

OR27: Novel Next Generation Sequencing Based Chimerism Assay for Engraftment Monitoring in Hematopoietic Cell Transplantation

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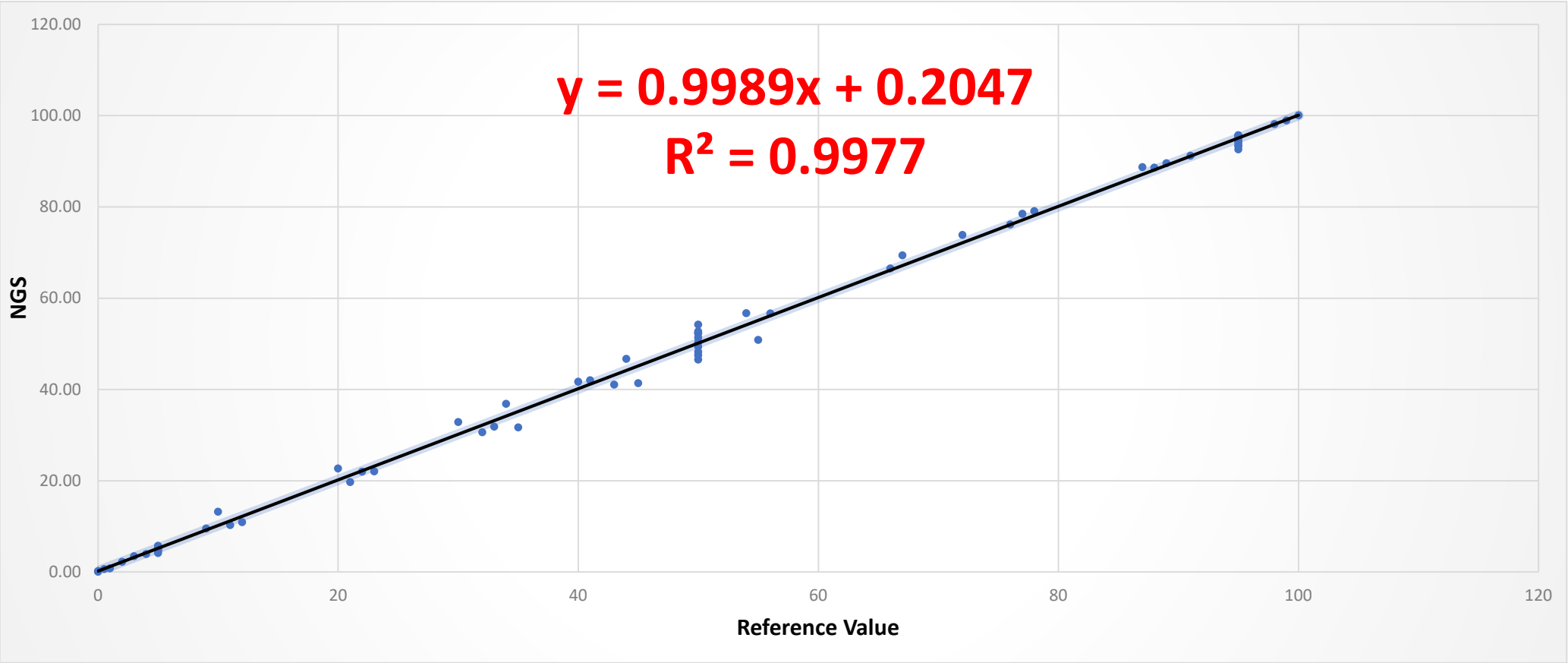
Artificial Mixes

- Samples of known chimeric status, ranging from 0%- 100% recipient DNA



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Artificial Mixes

Value	Patient %	95% CI (Lower)	95% CI (Upper)	# Markers	Limit of Detection
0	0.00	-0.07	0.06	15	0.14
0.5	0.56	0.41	0.71	10	0.12
1	1.13	0.97	1.30	13	0.15
2	2.16	1.95	2.37	16	0.07
3	3.10	2.78	3.41	21	0.12
4	4.02	3.63	4.40	20	0.15
5	5.65	4.58	6.71	14	0.11
11	11.35	10.26	12.44	16	0.13
21	22.63	21.08	24.18	23	0.20
50	51.54	49.95	53.14	31	0.17
95	95.31	94.89	95.73	10	0.16
100	100.06	100.01	100.10	28	1.16

Precision

Tech 1	Tech 2	Tech 3
0.56	0.53	0.57
1.13	1.52	1.24
2.16	1.94	2.43
3.1	3.08	3.73
4.02	3.58	4.19
5.65	5.41	5.01

The 18th International HLA & Immunogenetics Workshop

18th International HLA & Immunogenetics Workshop
May 2021 - Amsterdam - The Netherlands

Project: Haplotypes in Families

Haplotypes in Families by NGS

Project leaders: Medhat Askar & Kazutoyo Osoegawa

Anthropological study of families by NGS of full-length HLA genes to determine haplotype segregation in multiple populations. Samples from family quartets consisting of two parents and at least two non-HLA identical children or family trios consisting of one parent and at least two non-HLA identical children are required. The families should be previously HLA typed at any level (serology, DNA). Investigators may submit samples only or samples and NGS data.

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HLA Allele Cataloguing Project

Home / Component: Immunogenetics / HLA Allele Cataloguing Project

The HLA Allele Cataloguing Project

Project leaders: Faviel Gonzalez, Derek Middleton, Kazutoyo Osoegawa & Medhat Askar

In this project participants are invited to submit data of samples of HLA alleles that are novel, classified as rare or with no enough information in the Allele Frequency Net Database (AFND, http://www.allelefrequencies.net). The project has 2 components:

1. Submission of data to AFND confirming alleles that fulfill the criteria set above. These data will also be shared with the CWD alleles working group to be considered in generating future CWD alleles are equivalent/alternate lists.

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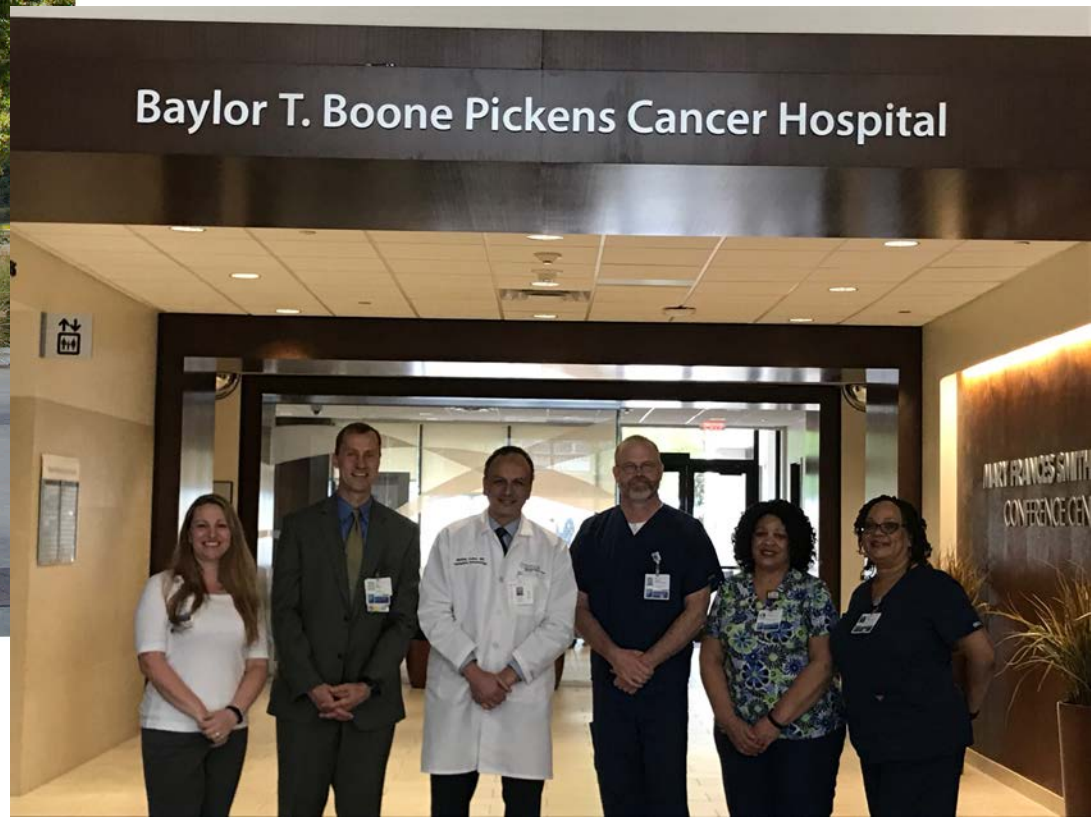
Summary

- Matching at HLA-A, -B, -C, and DRB1 remains to have the highest impact on clinical outcomes
- There is accumulating evidence of clinical relevance of DP, DQ and non-coding sequences
- Advances in sequencing technology will continue to reduce cost, increase HLA typing resolution, precision of engraftment monitoring
- Presence of donor HLA specific antibodies are associated with failure of engraftment and can be managed proactively

Thank you!



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