HLA IN DER TRANSFUSIONSMEDIZIN

Wolfgang R. Mayr

Univ.-Klinik für Blutgruppenserologie und Transfusionsmedizin
Medizinische Universität Wien

wolfgang.mayr@meduniwien.ac.at

HLA 1968

---------- X ---------- X ----------

HLA-A1	(HL-A1)
HLA-A2	(HL-A2)
HLA-A3	(HL-A3)
HLA-A9	(LA4)
HLA-A11	(ILN*)
HLA-A28	(Ba*)

HLA-B5	(HL-A5)
HLA-B7	(HL-A7)
HLA-B8	(HL-A8)
HLA-B12	(T12)
HLA-B13	(HN)
HLA-B35	(R*)

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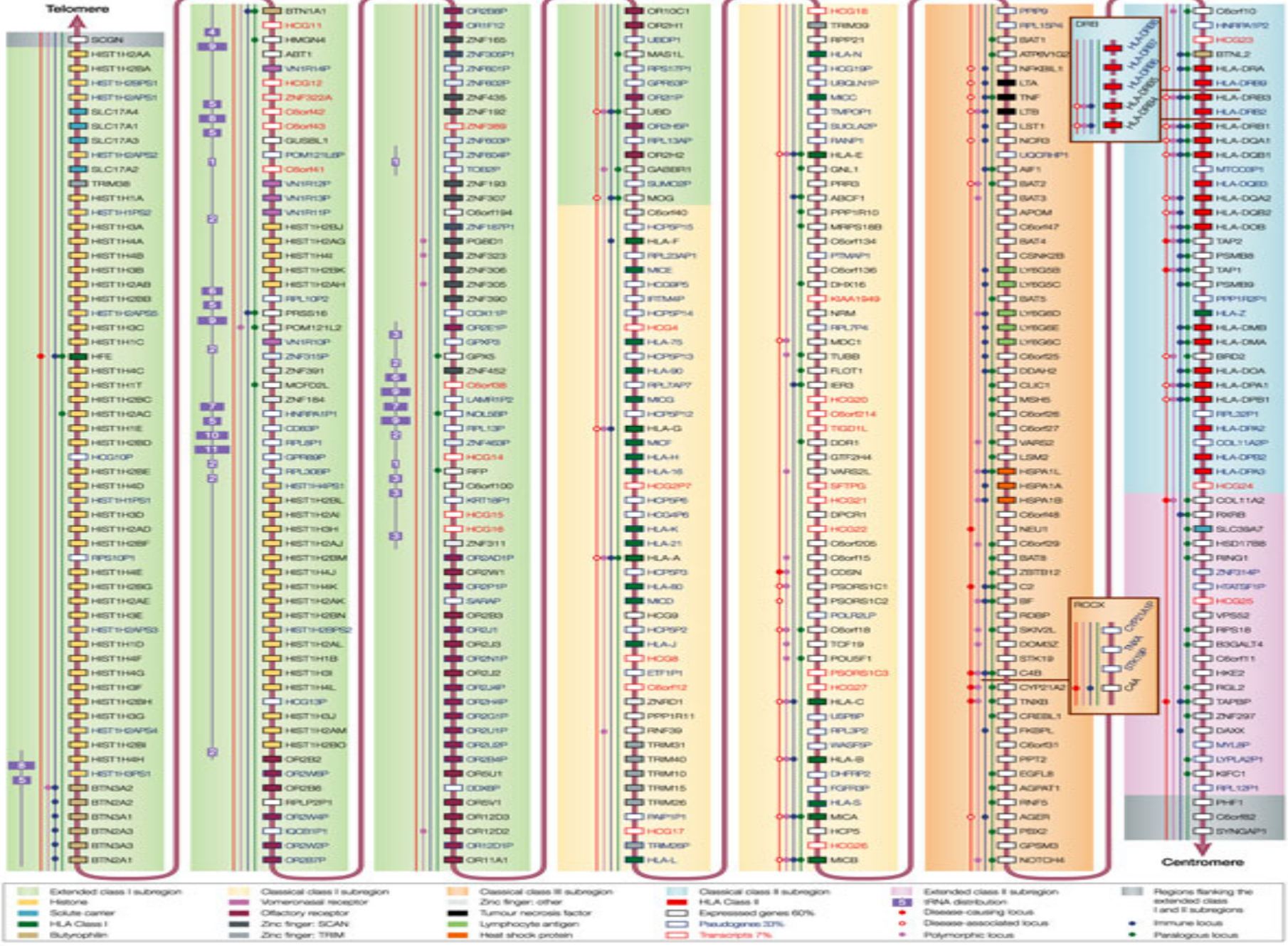

Telomere
Centromere
Extended class I subregion
Histone
Solute carrier
HLA Class I
Butyrophilin
Classical class I subregion
Vomeronasal receptor
Olfactory receptor
Zinc finger: SCAN
Zinc finger: TRIM
Classical class III subregion
Zinc finger: other
Tumour necrosis factor
Lymphocyte antigen
Heat shock protein
Classical class II subregion
HLA Class II
Expressed genes 60%
Pseudogenes 33%
Transcripts 7%
Extended class II subregion
tRNA distribution
Disease-causing locus
Disease-associated locus
Polymorphic locus
Regions flanking the extended class I and II subregions
Immune locus
Paralogous locus
Nature Reviews | Genetics

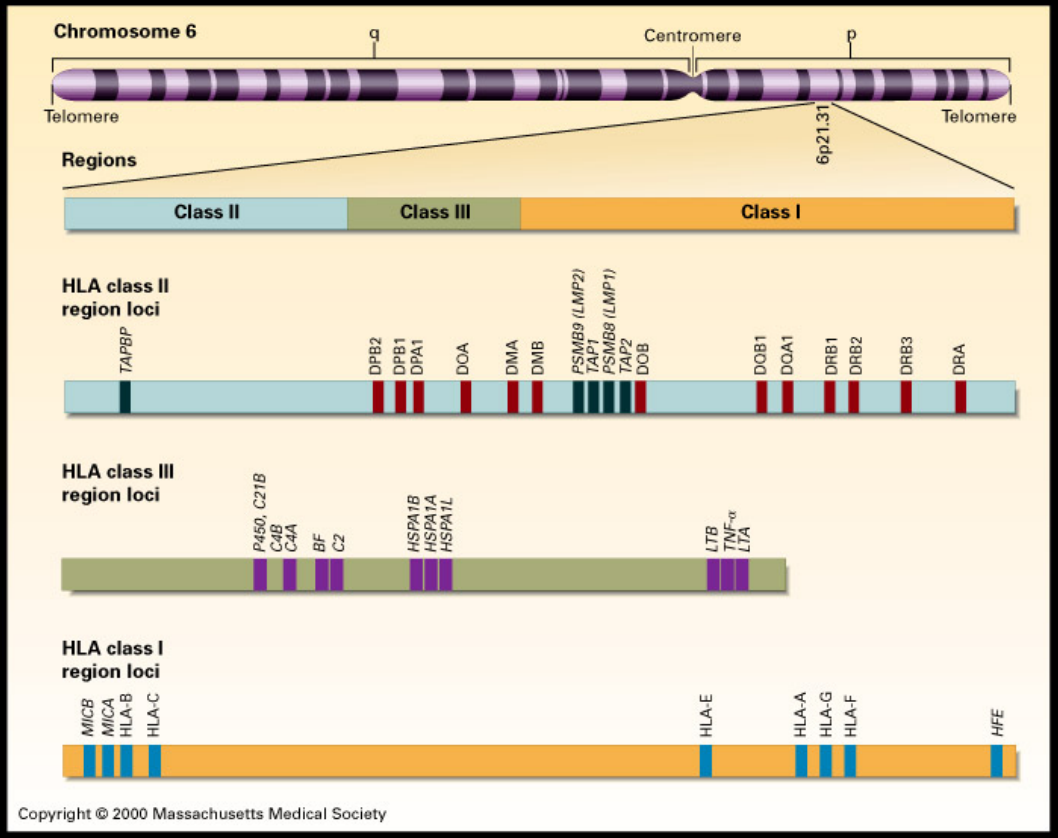
HLA GENE COMPLEX

> 400 loci

> 300 expressed loci

- 30% HLA class I
- 27% HLA class II
- 43% HLA „class III“

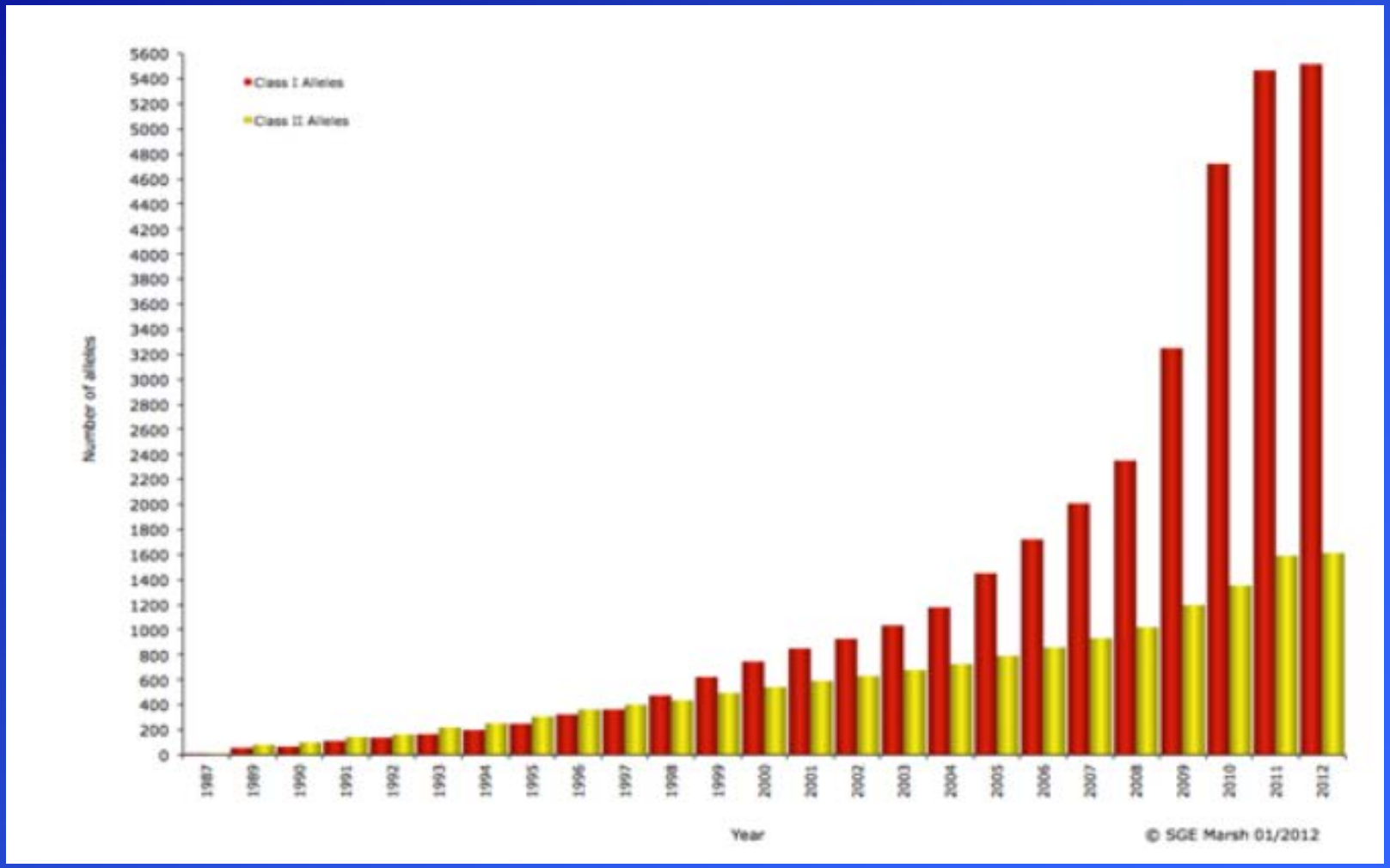
Location and Organization of the HLA Complex on Chromosome 6



Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.

The New England Journal of Medicine

HLA Alleles 1987 - 2012



Class I

Class II

HLA 2012

Numbers of HLA Alleles	
HLA Class I Alleles	5,518
HLA Class II Alleles	1,612
HLA Alleles	7,130
Other non-HLA Alleles	139
Number of Confidential Alleles	5

HLA Class I						
Gene	A	B	C	E	F	G
Alleles	1,757	2,338	1,304	10	22	47
Proteins	1,290	1,795	946	3	4	15
Nulls	87	73	35	0	0	2

HLA Class I - Pseudogenes									
Gene	H	J	K	L	P	T	U	V	W	X
Alleles	12	9	6	5	5	0	0	3	0	0
Proteins	0	0	0	0	0	0	0	0	0	0
Nulls	0	0	0	0	0	0	0	0	0	0

HLA Class II										
Gene	DRA	DRB	DQA1	DQB1	DPA1	DPB1	DMA	DMB	DOA	DOB
Alleles	7	1,166	47	162	33	152	7	13	12	13
Proteins	2	873	29	113	16	131	4	7	3	5
Nulls	0	20	1	1	0	3	0	0	1	0

HLA Class II - DRB Alleles									
Gene	DRB1	DRB2	DRB3	DRB4	DRB5	DRB6	DRB7	DRB8	DRB9
Alleles	1,067	1	57	15	19	3	2	1	1
Proteins	803	0	46	8	16	0	0	0	0
Nulls	15	0	0	3	2	0	0	0	0

Other non-HLA Genes				
Gene	MICA	MICB	TAP1	TAP2
Alleles	80	33	12	12
Proteins	63	22	6	5
Nulls	2	2	1	0

5518 class I alleles
1612 class II alleles

7130 HLA alleles

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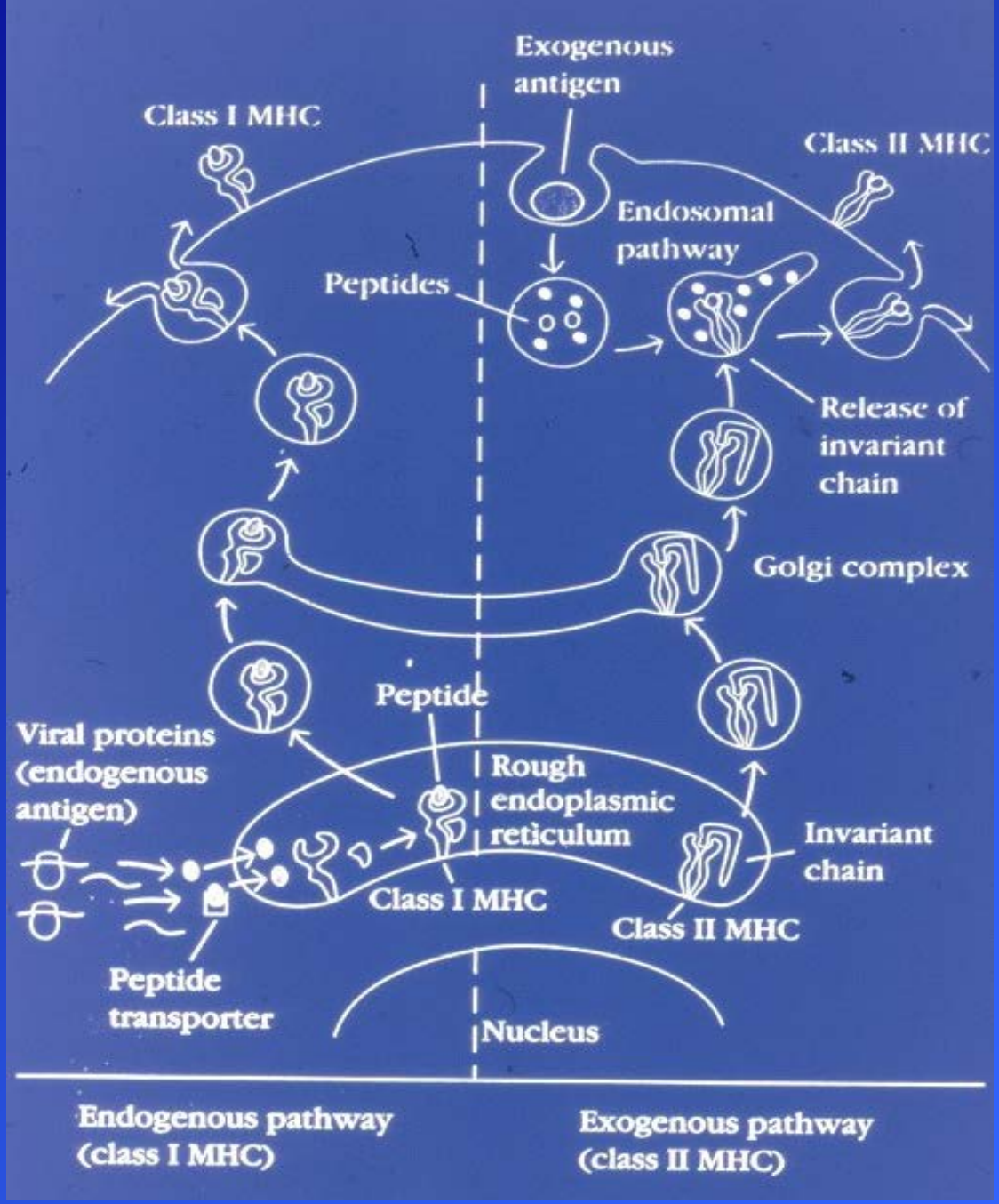

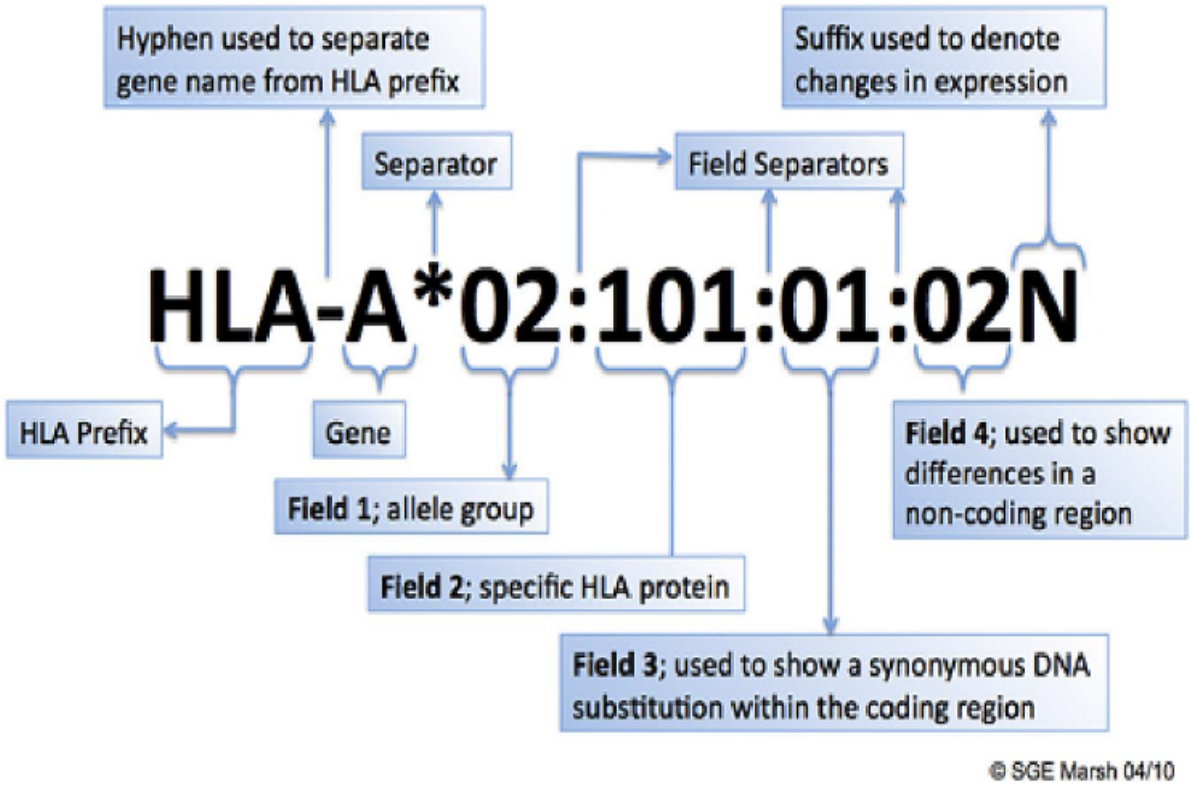

Figure 2. Convention for HLA allele naming. The figure illustrates the meaning of each component of an HLA allele name. Fields 3 and 4 may not be used in a name if no synonymous DNA substitutions or differences in a noncoding region are found for a particular allele. For example, based on the IMGT/HLA database Version 3.1.0, July 2010,[2] A*02:07 has not been found to have synonymous DNA substitutions or differences in the noncoding region; thus, fields 3 and 4 have not been assigned for this allele. Courtesy of Prof Steven Marsh, Anthony Nolan Research Institute, London, United Kingdom (www.hla.alleles.org).

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  - Assoziation mit Krankheiten
  - Arzneimittel – unerwünschte Reaktionen
  - TA-GvHD

- **Immunisierung**
  - FNHTR, HTR
  - Thrombocytentransfusion
  - TRALI
  - Granulocytentransfusion
  - (NAIT?, NAIN???)

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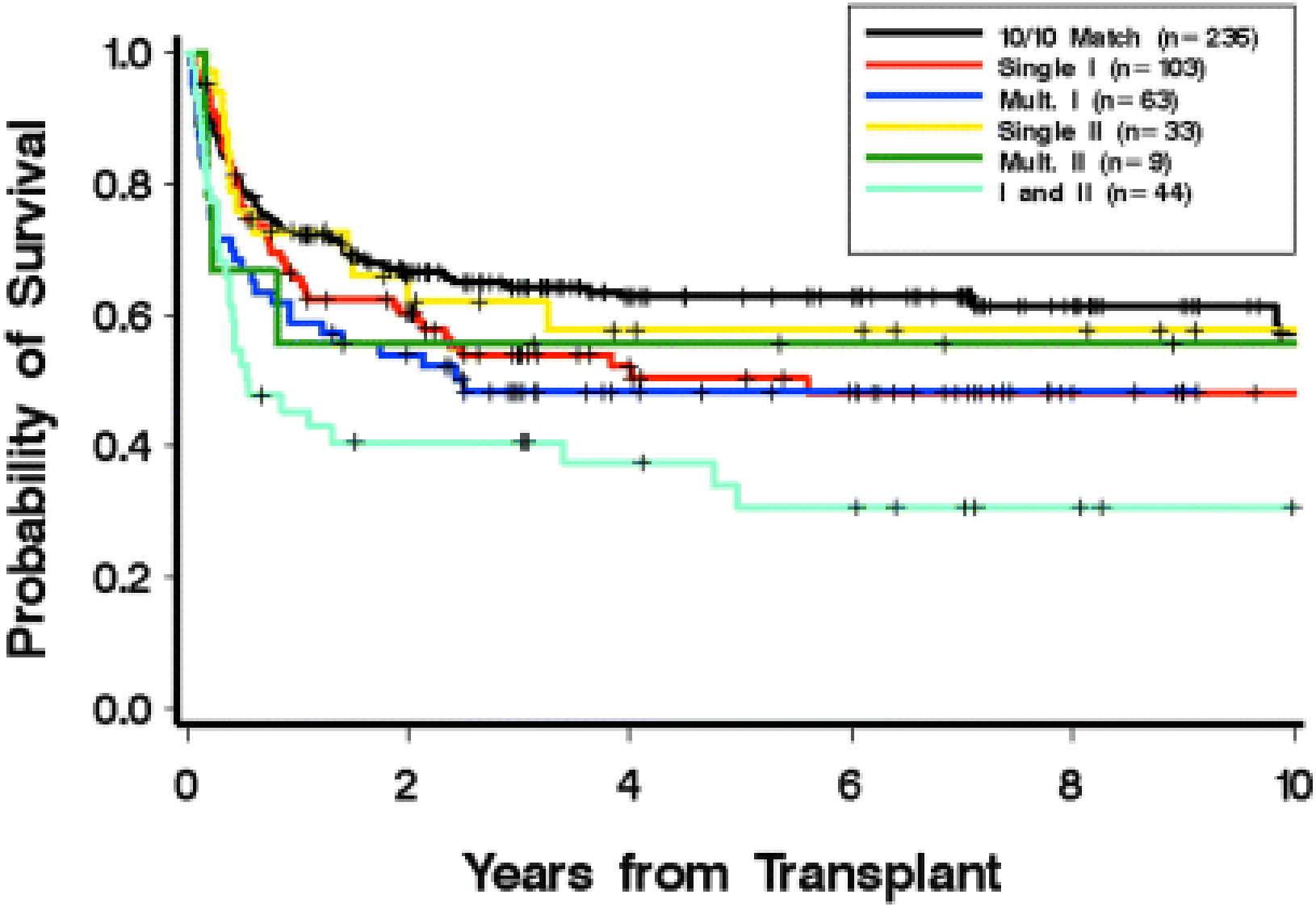

Seattle 2002

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Effect of Single Mismatches on Mortatility

(15th IHIWS)

DQB1	1.00
DRB1	1.08
C	1.18
A	1.20
B	1.29

Table 3. Logistic regression models for grades II-IV and grades III-IV acute GVHD and Cox regression models for relapse and overall mortality

	Unadjusted models				Adjusted models			
	Grades 2-4 aGVHD	Grades 3-4 aGVHD	Relapse	Overall mortality	Grades 2-4 aGVHD	Grades 3-4 aGVHD	Relapse	Overall mortality
Matched at HLA-DPB1	1	1	1	1	1	1	1	1
Mismatched at HLA-DPB1	1.33 (1.17-1.50; $P < .001$)	1.26 (1.10-1.45; $P < .001$)	0.82 (0.70-0.96; $P = .01$)	1.15 (1.05-1.27; $P = .003$)	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	1.30 (1.14-1.48; $P = .001$)	1.21 (1.04-1.40; $P = .01$)	0.82 (0.70-0.96; $P = .01$)	1.14 (1.03-1.25; $P = .01$)	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	1.37 (1.19-1.58; $P < .001$)	1.34 (1.15-1.57; $P < .001$)	0.82 (0.69-0.98; $P = .03$)	1.18 (1.07-1.31; $P = .002$)	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; $P = .11$)

Adjusted models include severity of disease; patient age at transplantation; number of mismatched alleles at HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1; patient/donor sex; patient/donor CMV status; source of stem cells; and use of T-cell depletion.

Ranges in parentheses are 95% CI.

Shaw BE et al, Blood 2007; 110: 4560 - 4566

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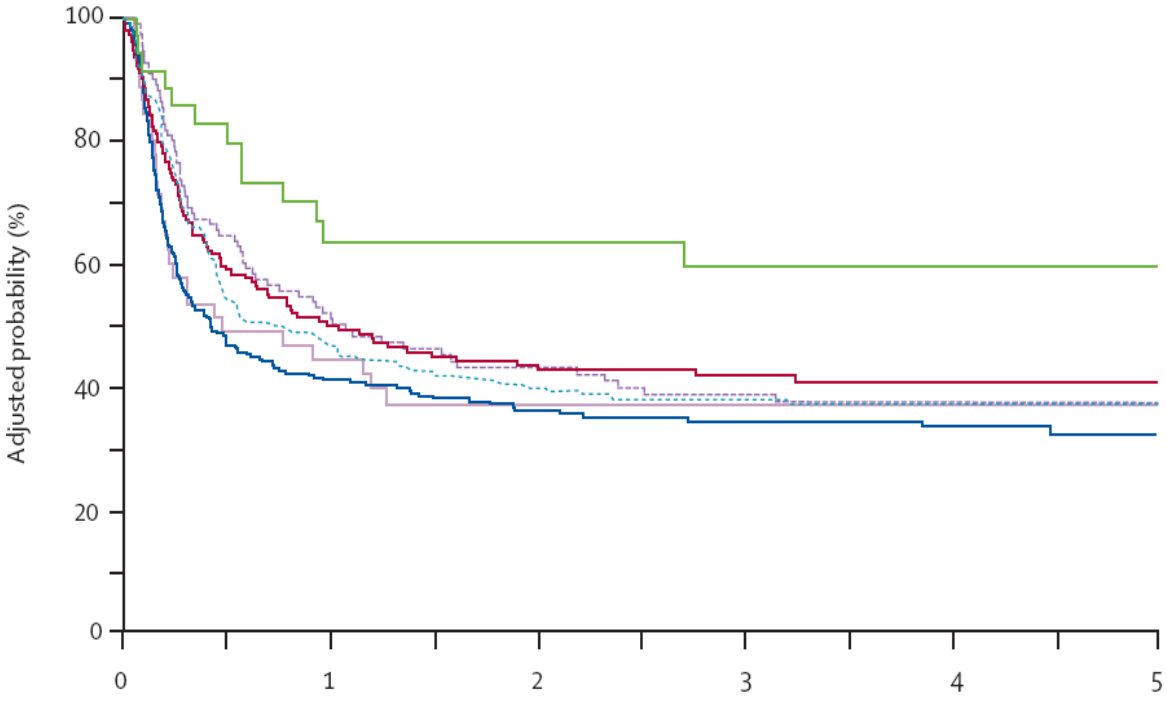
STEM CELL TRANSPLANTATION

- Family: HLA identical siblings
  Haploidental siblings

- HLA identical unrelated donors
  BMDW (Feb 7, 2012): **18,707,431 donors**



Numbers at risk						
HLA-matched cord blood	35	20	17	13	11	8
HLA-matched bone marrow	116	62	45	35	29	24
One-mismatched cord blood (high cell dose)	157	72	55	44	32	25
HLA-mismatched bone marrow	166	77	60	53	44	30
One-mismtached cord blood (low cell dose)	44	19	13	12	10	6
Two-mismatched cord blood	267	100	67	49	34	21

Figure: Probability of leukaemia-free survival after bone-marrow and cord-blood transplantation adjusted for disease status at transplantation

Eapen et al, Lancet 369, 1947, 2007

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STEM CELL TRANSPLANTATION

- Family: HLA identical siblings
  Haploidental siblings

- HLA identical unrelated donors
- Cord blood (1 oder 2 donors)

  BMDW (Feb 7, 2012): **19,217,639** (18,707,431 donors and 510,208 CBU's)

- KIR, minor histocompatibility antigens ???

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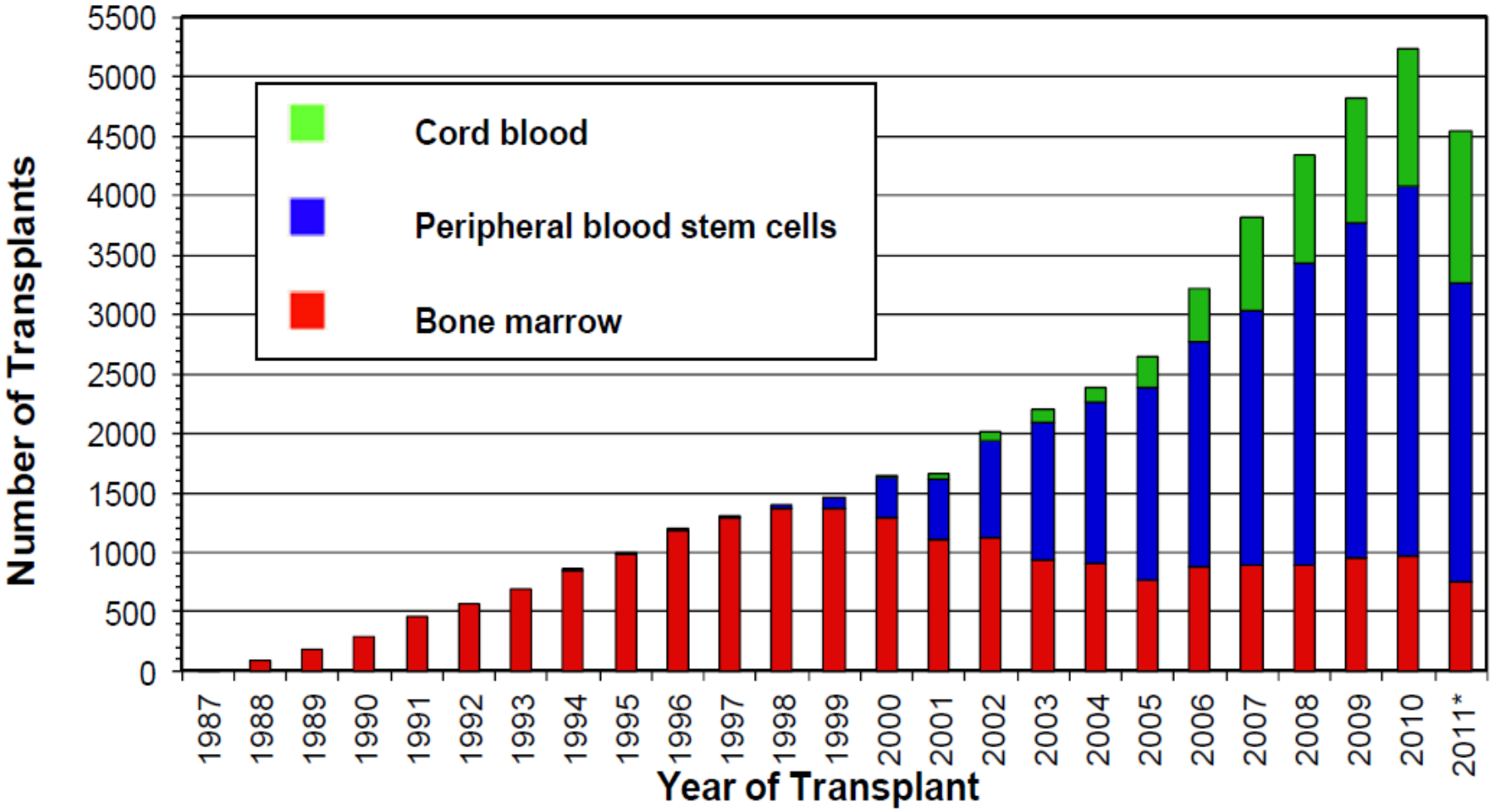

This graph used in Dr. Miller's presentation at the NIH symposium shows the NMDP transplants facilitated by fiscal year from 1987-2010, with 43,361 in total.

2011: > 5.500

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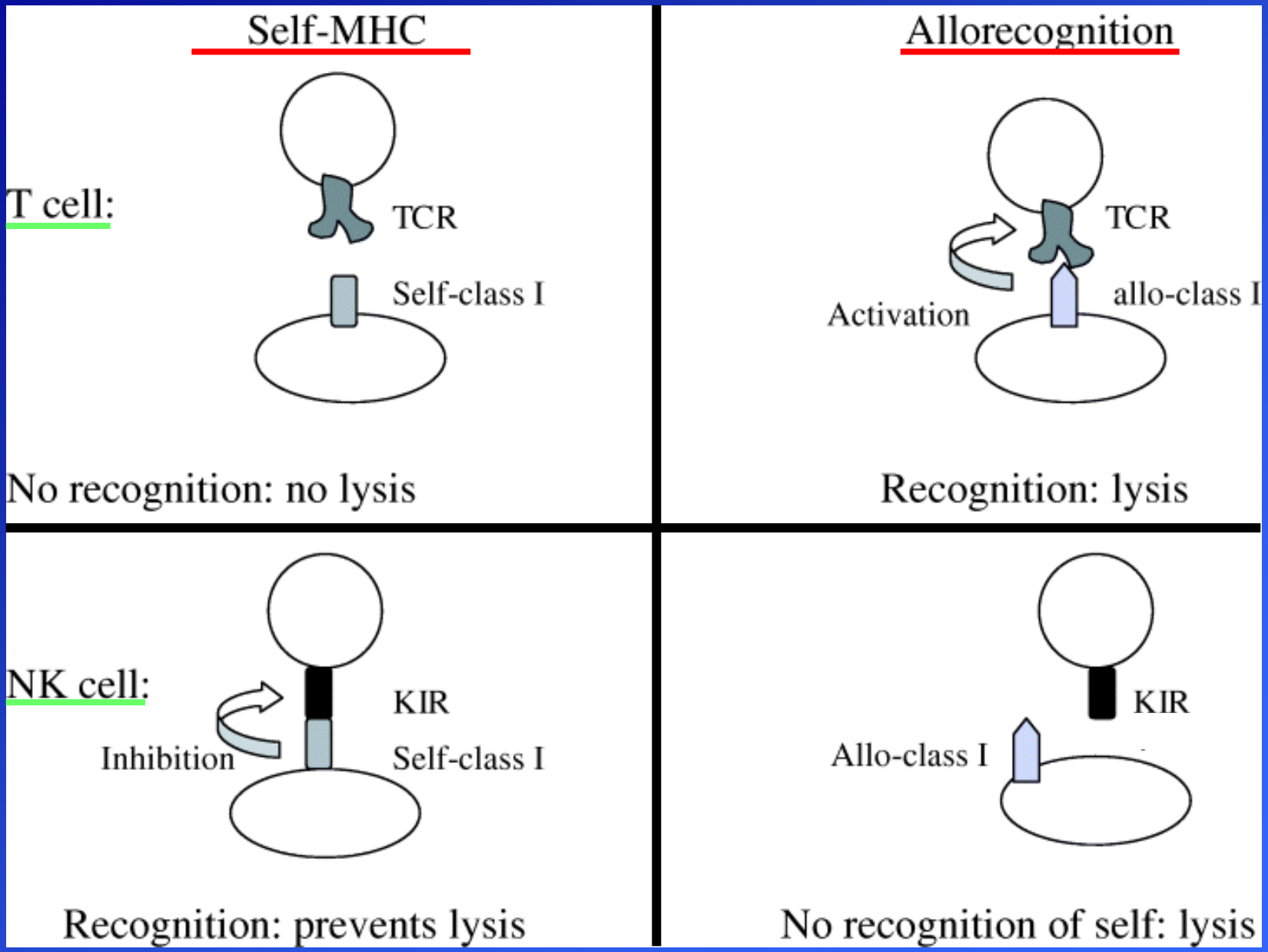

Allorecognition by T cells and NK cells

KIR (Killer-cell Immunoglobulin-like Receptor)

- **KIR3DL1-2, KIR3DS1, KIR2DL1-5, KIR2DS1-5**

- 2D = 2 Ig-like domains
  3D = 3 Ig-like domains

- L = Long cytoplasmatic tail – inhibitory
  S = short cytoplasmatic tail - activating

TABLE 1 Basic structural and functional features of KIR

KIR	Extracellular region (Ig-like domains)	Charged amino acid in tm region	Cytoplasmic tail (a.a.); ITIMs	Known ligands	mRNA
3DL1	D0-D1-D2	—	84; 2	HLA-B^{Bw4}	+
3DL2	D0-D1-D2	—	95; 2	HLA-A3, others?	+
3DS1	D0-D1-D2	Lys	22,27; 0	?	+
2DL1	D1-D2	—	84; 2	HLA-C^{Lys80}	+
2DL2,3	D1-D2	—	84,76; 2	HLA-C^{Asn80}	+
2DS1	D1-D2	Lys	39; 0	HLA-C^{Lys80}	+
2DS2	D1-D2	Lys	39; 0	HLA-C^{Asn80}	+
2DS3,5	D1-D2	Lys	39; 0	?	+
2DS4	D1-D2	Lys	39; 0	HLA-C?	+
2DL4	D0-D2	Arg	115; 1 or 11; 0	HLA-G	+
2DL5	D0-D2	—	115; 2	?	+(−)[a]
KIRC1	D0-D1-D2 (no stem)	—	67; 1	?	−(+)[b]

[a]Some *KIR2DL5* variants are not transcribed.

[b]Although generally nontranscribed, a cDNA sequence for *KIRC1* has been recently deposited in the GenBank (47a).

KIR ligand incompatibility in GVH direction

(absence in recipients of donor class I allele groups – e.g. for HLA-C)

Donor	Recipient	
C1, C1	C1, C1 C1, C2 C2, C2	 incompatible
C1, C2	C1, C1 C1, C2 C2, C2	incompatible incompatible
C2, C2	C1, C1 C1, C2 C2, C2	incompatible

C1 - HLA-C Ser77Asn80: Cw1, w3, w7, w8
C2 - HLA-C Asn77Lys80: Cw2, w4, w5, w6

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Table 1. Clinical data and transplantation outcomes in HLA haplotype-mismatched transplants with and without KIR ligand incompatibility in the GVH direction. KIR ligand incompatibility in the GVH direction was defined as absence in recipients of donor class I allele group(s) recognized by KIRs (*9–11*). Such groups are HLA-C alleles with Asn^{77}-Lys^{80}, Cw2, 4, 5, 6, and related alleles; HLA-C alleles with Ser^{77}-Asn^{80}, Cw1, 3, 7, 8, and related alleles; HLA-Bw4 alleles; and HLA-A3/A11. Twenty-six pairs (11 in ALL and 15 in AML) were mismatched for HLA-C groups, 8 (3 in ALL, and 5 in AML) were mismatched for HLA-Bw4 group; the HLA-A3/A11 mismatch was never found alone but only in conjunction with HLA-C group mismatches (2 pairs).

KIR ligand incompatibility in GVH direction	No	Yes
Number of transplants	58	34
Donors displaying antirecipient NK clones	1/58	34/34*
Disease		
ALL	21	14
AML	37	20
Transplantation outcomes		
Rejection	15.5%	0%*
Acute GVHD, ≥ grade II	13.7%	0%*
Probability of relapse at 5 years		
ALL	90%	85%
AML	75%	0%**

$P \leq 0.01$; **$P < 0.0008$ (*22*).

Ruggieri L et al,
Science 295, 2097-2100, 2002

KIR - Differences in studies

- Disease type (AML?)
- Conditioning regimen
- Type of hematopoietic stem cell graft
- Study population
- Genetic differences other than HLA-C possibly influencing NK-cell alloreactivity
- Allele polymorphism might influence surface expression, ...
- Specificity for ligand

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Cellular Therapy – Main Directions

- **Stem Cell Transplantation**
- **Dendritic Cells**: in vitro sensitization by tumour antigens and reinjection in order to stimulate T cell response
- **NK Cells**: killing of tumour cells that do not express the own HLA class I gene products
- **Cytotoxic T Lymphocytes**: stimulation by tumour antigens and reinjection into patient where they attack tumour cells
- **Regenerative Medicine**: e.g. in vitro preparation of autologous skin grafts, infusion of stem cells in hearts damaged by infarctions, ...
- **Gene Therapy**: introduction of gene in cells and reinfusion

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HLA Typing Demands for Peptide-Based Anti-Cancer Vaccine

Nagorsen D & Thiel E

Cancer Immunol Immunother, 2008, in press

„Taken together, proper tissue typing for cancer vaccine therapies represents the main pillar for successful immunotherapy. Clinical immunotherapists should be more aware of the importance of correct HLA determination to avoid vaccination of unsuitable patients.“

Correct HLA determination: high resolution genotyping (at the 4-digit level), in order to determine the binding of tumour-derived peptides

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  - FNHTR, HTR
  - Thrombocytentransfusion
  - TRALI
  - Granulocytentransfusion
  - (NAIT?, NAIN???)

HLA Class I

Disease	Specificity	RR
Idiopathic haemochromatosis	A3	8
Birdshot retinopathy	A29	>100
Morbus Behcet	B5	6
Morbus Bechterew – Ankylosing spondylitis	B27	90
Postinfectious arthritis	B27	40
Morbus Reiter	B27	37
Acute anterior uveitis	B27	10
Subacute thyreoiditis de Quervain	B35	14
Chron. active Hepatitis type B (HBs-Ag positive)	B35	5
Adrenogenital syndrome	B47	90
Psoriasis vulgaris	Cw6	13

HLA Class II

Disease	Specificity	RR
Narcolepsy	DR2, DQ6	>100
Goodpasture syndrome	DR2	16
Multiple sclerosis	DR2	10
Dermatitis herpetiformis	DR3	15
Idiopathic membranous glomerulonephretis	DR3	12
Sjögren syndrome	DR3	10
Idiop. M. Addison, SLE, CAH type A	DR3	6
M. Basedow, myasthenia gravis	DR3	4
Diabetes mellitus type I	DR4,DQ8/DR3,DQ2	6 / 3
Rheumatoid arthritis	DR4	4
Celiac disease	DQ2	>100

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HLA AND DISEASES

- 1. Restriction HLA class I
  HLA class II

- 2. Linkage disequilibrium with mutant genes

  Idiop. haemochromatosis

  Adrenogenital syndrome

PRESENTATION OF PEPTIDES

- DR3 – autoimmunity

- Birdshot retinopathy
  A29 binds a peptide of a soluble retinal antigen
  A29-transgene mice: similar symptoms

- Rheumatoid arthritis
  DR4 binds peptides of collagen II
  DR4-transgene mice: symptoms like RA

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Adverse Reactions to Drugs
HLA Association

Rheumatoid Arthritis: associated with HLA-DRB1*04

Adverse Reaction	Drug	HLA
Myasthenia gravis	D-Penicillamin	DRB1*01, DRB1*07
Nephropathy	Gold	DRB1*03

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HLA and Drug Induced Adverse Reactions

Disease	Drug	HLA	Adverse effect
Hypertonia	Hydralazine	DRB1*04	LE
AIDS	Abacavir ($)	B*57:01	Hypersensitivity
AIDS	Nevirapine	DRB1*01:01	Hypersensitivity
Epilepsy, ...	Carbamazepine ($)	B*15:02	Stevens-Johnson-Syndrome
Infections (Gram+)	Flucloxacilline	B*57:01	Hypersensitivity

($) included in the „Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels" published by the FDA

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HLA associations with hepatotoxicity

Aithal & Daly, Nature Genetics 2010; 42: 650-651

Table 1: HLA associations with hepatotoxicity.

Gene	Associated allele	Drug	Type of study	Replication	Ref.
Class I					
HLA-A	*3303	Ticlopidine	Candidate gene	No	15
HLA-B	*5701	Flucloxacillin	GWA	Yes	6
Class II					
HLA-DRB1	*1501	Amoxicillin-clavulanate	Candidate gene	Yes	7,8
	*1501[a]	Lumiracoxib	GWA	Yes	4
	*0701	Ximelagatran	GWA/candidate gene	No	5

[a]Association also seen with *DQB1*0602*, *DRB5*0101* and *DQA1*0102* alleles. GWAS, genome-wide association study. Other, more general HLA associations for drug-induced liver injury have also been described, but only associations relating to specific drugs are considered here.

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TA-GvHD

- **Pathogenesis**

  Caused by immunocompetent T lymphocytes transfused in a recipient who is unable to mount a host response to the cells due to HLA (one-way) compatibility (related donor, low HLA polymorphism, ...) and/or immunosuppression (e.g. by fludarabine, 2-CDA)

- **Prevention**

  Irradiation (recommended doses 25 to 50 Gy)

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FNHTR

- **Pathogenesis**

  Recipient possesses antibodies against HLA (class I) and/or HNA determinants of the donor

- **Prevention**

  Leukodepletion

Leukodepletion

Proven effects

- Quality of the RBC unit
- HLA alloimmunization
- FNHTR
- CMV transmission

Controversial effects

- Immunomodulation
- Prion transmission

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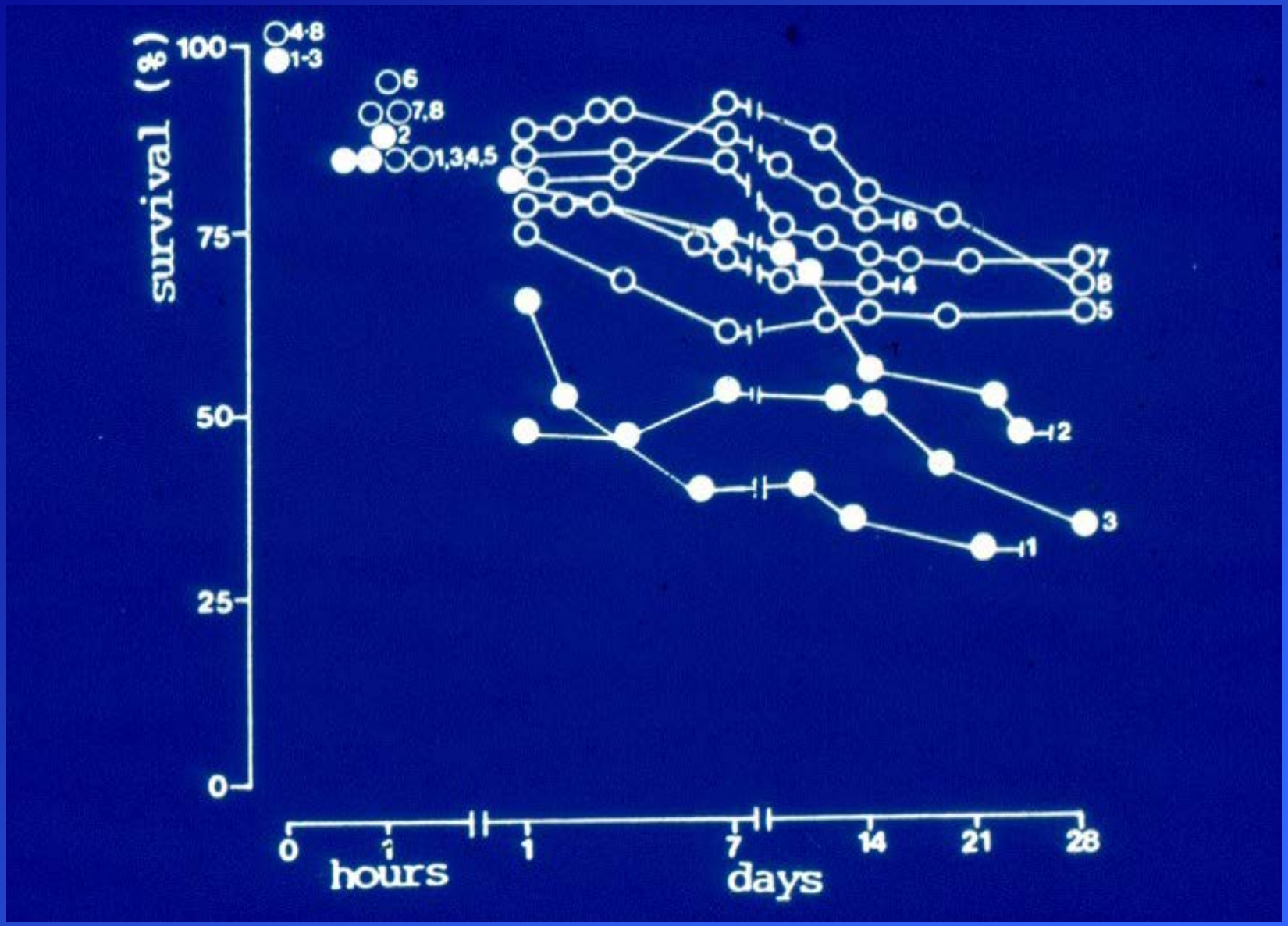
Bg (Bennett-Goodspeed)

- BG HLA class I on RBC

- Bg^a HLA-B7
- Bg^b HLA-B17
- Bg^c HLA-A28

- Variable expression (high on reticulocytes!)

- Immune antibodies
- Transfusion: low relevance



Panzer et al, Lancet 1987; 1: 474-478

Chido / Rodgers

- C4A: Rg, 2 determinants
- C4B: Ch, 6 determinants

- Epitopes on C4d
- High association with electrophoretic allotypes
- High correlation with aminoacid sequences

- Adsorbed onto the RBC membrane
- Destroyed by papain and ficin

- Immune antibodies
- Transfusion: low relevance

SURVIVAL OF Ch(a+) RBC IN A RECIPIENT WITH ANTI-Ch^{a}

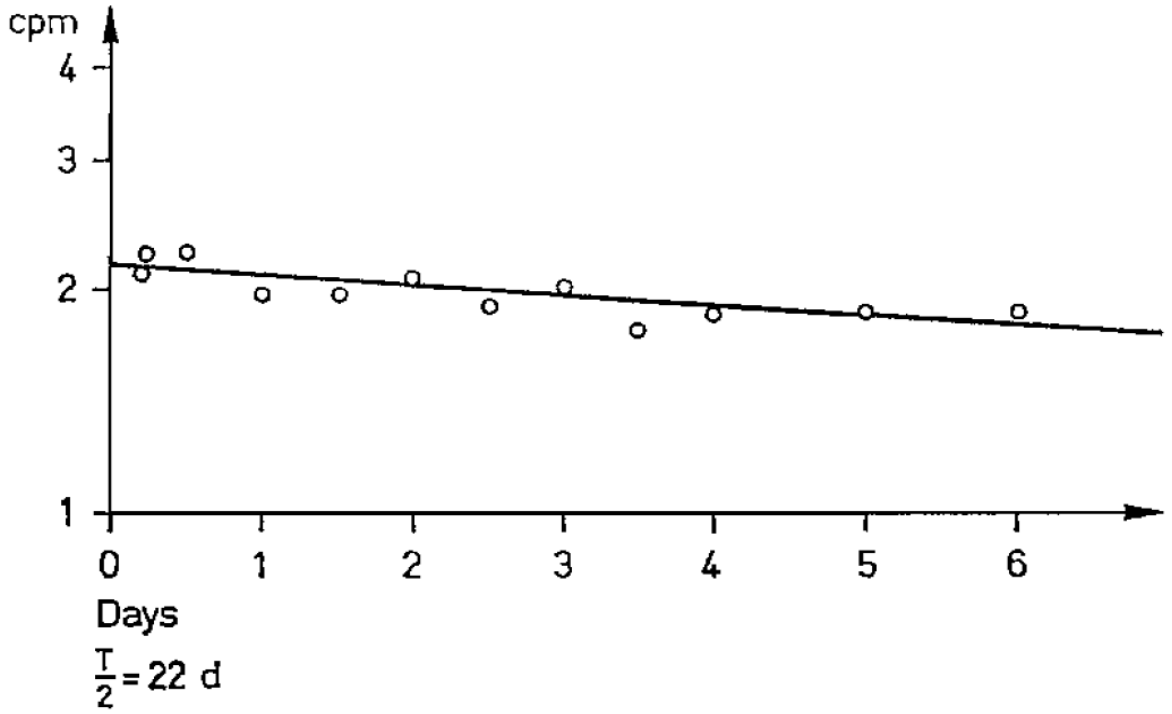


Fig. 1. Survival curve of Ch(a+) RBC in the circulation of patient O. O. The numbers on the ordinate represent cpm × 10^{-3}.

Nordhagen R, Aas M, Vox Sang 1979; 37: 179-181

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UBT

REFRACTORINESS

- **Alloimmune**
  - Prevention by AB0 compatibility, leukodepletion
- **Non-immune**
  - Spelomegaly
  - Bleeding
  - Fever, infection
  - Drugs (heparin, amphotericin, ...)
  - DIC
  - GvHD

ALLOANTIGENS ON PLATELETS

- 1. Alloantigens on platelets and other cells
  - HLA class I
  - AB0, Le, I, P
- 2. „Platelet specific alloantigens“

REFRACTORINESS
(alloimmune)

- HLA class I typing of patient
- Screening for HLA class I antibodies

- HPA typing of patient
- Screening for HPA antibodies

DONORS FOR REFRACTORY PATIENTS

- HLA class I identical or compatible donors
  - Class I homozygosity
  - Cross-reactivity
- Acceptable mismatches
  - HLA class I antibody screening
  - NIMA
- Disregard HLA-C and some HLA-B factors (e.g. HLA-B8)

DONORS FOR REFRACTORY PATIENTS

Cross-match with many platelet samples

HLA ASSOCIATED IMMUNE RESPONSE AGAINST HPA

	HLA	Imm. Patients	Controls
HPA-1a	DR3	71 – 95%	23%
	DR52	100%	68%
	DRB3*01:01	100%	50%
HPA-5b	DR6	63%	29%
	DR52	87%	60%

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HLA IN DER TRANSFUSIONSMEDIZIN

- **Funktion**
  - Transplantation: Organe, Stammzellen, zelluläre Therapie
  - Assoziation mit Krankheiten
  - Arzneimittel – unerwünschte Reaktionen
  - TA-GvHD

- **Immunisierung**
  - FNHTR, HTR
  - Thrombocytentransfusion
  - TRALI
  - Granulocytentransfusion
  - (NAIT?, NAIN???)

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FATALITIES BY TRALI

FFP	1	:	200.000
Platelets - apheresis	1	:	320.000
Platelets - pools	1	:	1.200.000
Erythrocyte concentrates	1	:	2.500.000

ARC, Eder et al, Transfusion 2007; 47:599

PLASMA IN HEMODERIVATIVES

- **ERYTHROCYTE CONCENTRATE** (leukodepleted, with additive solution) **15 ml**

- **THROMBOCYTE CONCENTRATE** (apheresis or pooled from buffy-coats)

  resuspended in plasma **250 ml**

  resuspended in T-Sol **75 ml**

- **FFP** **200 – 250 ml**

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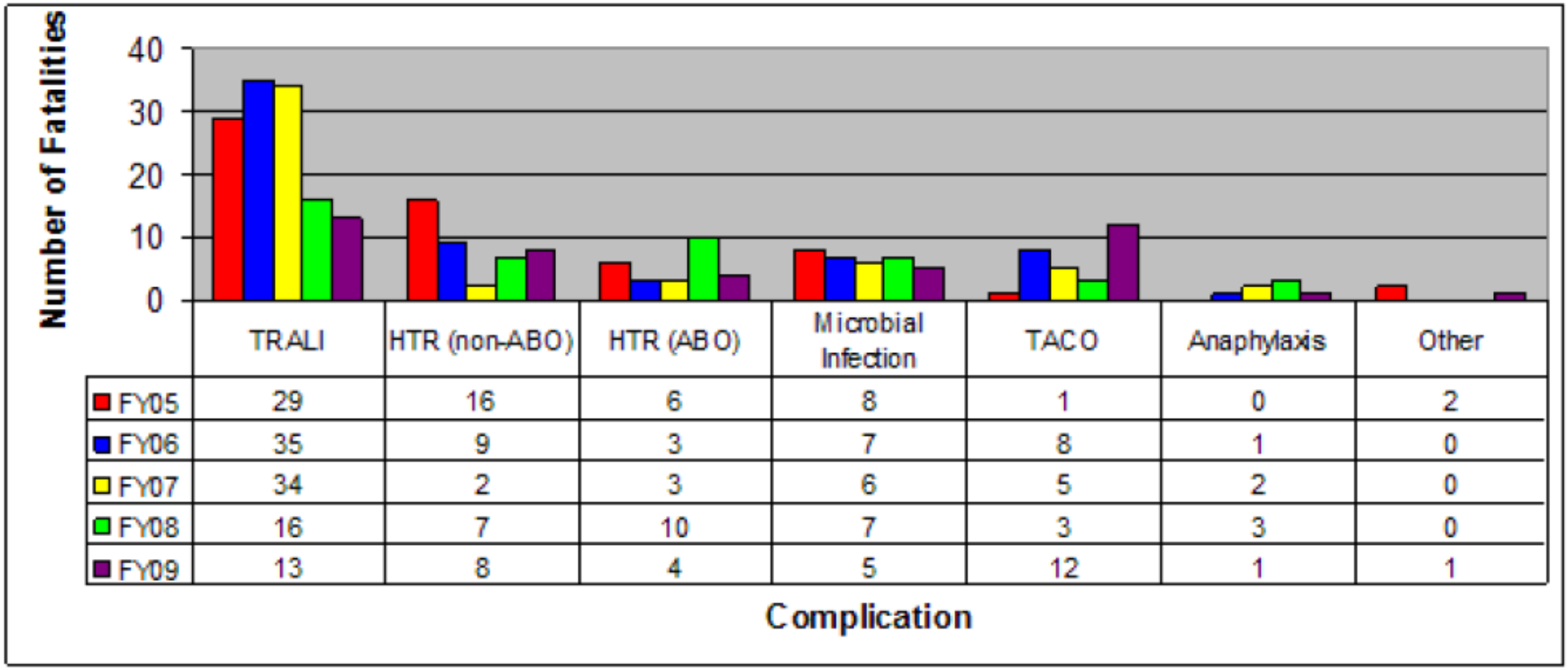
Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1

T R A L I

Immune TRALI

passive transfer of HLA and/or HNA antibodies in an antigen-positive recipient

Non-immune TRALI

???

Antibody specificities

(Reil et al, Vox Sanguinis 2008; 95: 313-317)

Antibody specificities	Number of cases
HLA class I	4 (2 anti-HLA-A2)
HLA class I + II	3
HLA class II	17
HNA-1a	1
HNA-2a	1
HNA-3a	10
Total	36

TRALI - VERMEIDUNG

- S/D behandelte Poolpräparate

- Einzelspenderpräparate von Männern ohne Transfusionsanamnese, Frauen ohne Transfusions- und Schwangerschaftsanamnese oder getesteten Frauen (keine Ak gegen HLA und HNA)

Table 1 Data on immune and non-immune mediated TRALI, blood components involved, donors involved, results of WBC-Ab testing and TRALI associated fatalities (2006 - 2010)

Period		2006 - 2007	2008 - 2009	2010	2006 – 2010
TRALI reported		187 (94, 93)	173 (83, 90)	59	419
Not confirmed		143	141	55	339
Non-immune mediated		9	8	3	20
Immune mediated		35	24	1	60
Donors involved in immune mediated TRALI*					
Female donors		39	25	0	64
Male donor		1	2	1	4
RBC donors		4	4	1	9
PC donors	Apheresis PC	1	3	0	4
	Pooled PC	1	1	0	2
FFP donors		34	19	0	53
Total number of donors		40	27	1	68
Number of donors with HLA- or HNA-Ab*					
HLA- Ab	HLA I – Ab positive	4	5	0	9
	HLA II – Ab positive	15	13	0	28
	HLA I - and HLA II-Ab positive	13	6	1	20
	Sum	32	24	1	57
HNA- Ab (2a / 3a)		8	3	0	11
Total		40	27	1	68
Immune mediated TRALI related fatalities					
Due to RBC donors		1	0	0	1
Due to PC donors		0	1	0	1
Due to FFP donors		7	5	0	12
Number of donors with HLA- or HNA-Ab involved in fatal TRALI					
HLA I- or HLA II- Ab		6	4	0	10
HNA-2a- Ab or HNA-3a- Ab		2	2	0	4
Total number		8	6	0	14

*8 recipients received WBC- Ab from 2 different donors

PEI
Funk et al,
Vox Sanguinis 2012;
102: 317-323

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