History of MHC – 1971 – 2011

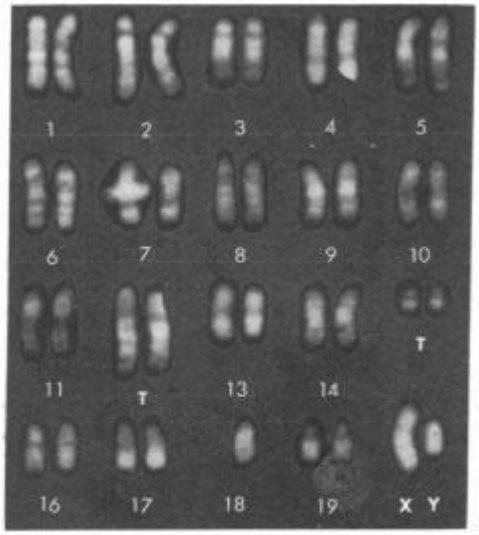
1971
1971
HL-D

TABLE 3. *One-way MLR of HL-A identical mother and son (a = Minnesota family H), two-way MLR of HL-A-identical father and son (b = Duke family Q-H), and grandfather and grandson (c = Duke family 0035)*

	Responding cells	Am	Bm	Xm
(a)	A (2-12/3-7) mother	205	3,421	4,321
	B (2-12/3-7) son	3,124	328	4,858
	X (1,8,2,12) unrelated	17,428	20,342	784
		Father	*Son*	*Unrelated*
(b)	Father (1-7/2-5)	1,205	20,809	54,545
	Son (1-7/2-5)	—	2,337	100,061
	Unrelated (11-W18/Ao54-)	—	—	4,569
		Grand-father	*Grandson*	*Unrelated*
(c)	Grandfather (Ao77-12/1-8)	420	7,438	34,825
	Grandson (Ao77-12/1-8)	—	264	14,501
	Unrelated (9-5/10-)	—	—	433

In 1971, Yunis and Amos (Proc Nat Acad Sci USA 68:3031, 1971) showed that the mixed leukocyte reaction (MLR) was controlled by an independent locus (HL-D), centromeric to the serologically detected HL-B.

1971
Chromosome 17



The H-2 complex was assigned to mouse chromosome 17 by Miller et al. (Proc Natl Acad Sci USA 68:1530, 1971)

1972
1972
HLA and Human Diseases

Table 1. HL-A Antigen Frequency in Unrelated 44 Caucasian Psoriatic Patients and 89 Controls.

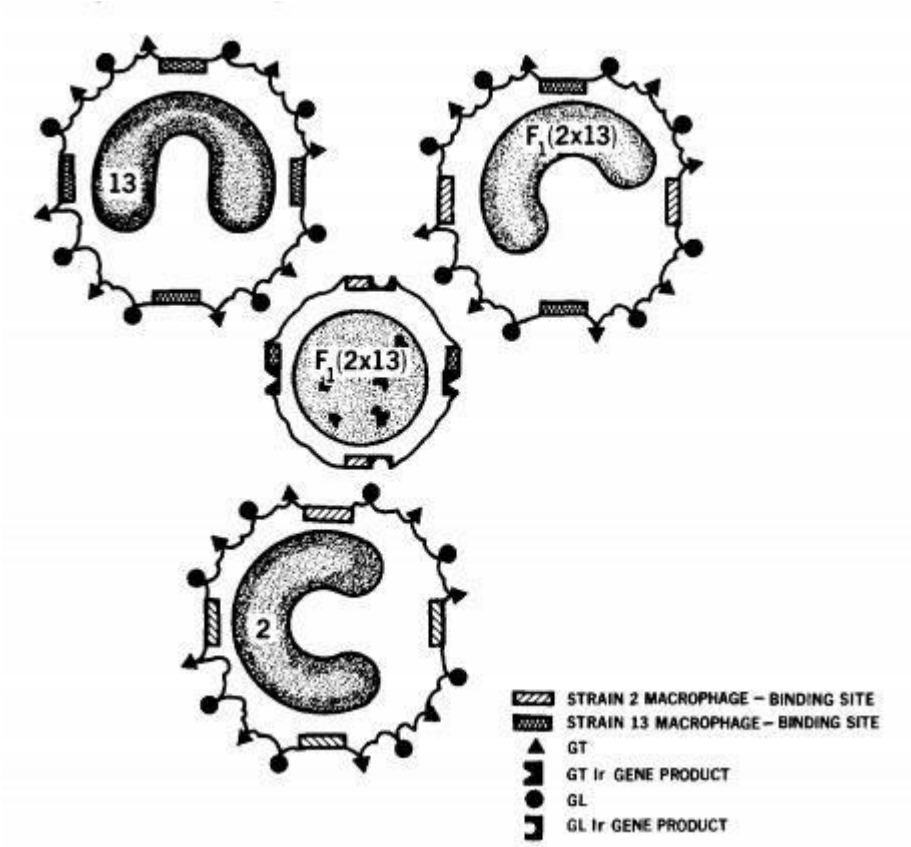
Antigen	Percentage Positive	
	Controls	Patients
HL-A1	28.1	29.5
HL-A2	48.3	56.8
HL-A3	25.8	31.8
HL-A9	19.1	15.9
HL-A10	13.5	13.6
HL-A11	15.7	9.1
W28 (Te40)*	7.9	6.8
W29 (Te63)	5.6	4.5
W30 (Te66)	6.7	9.1
W32 (Te59)	6.7	2.3
HL-A5	15.7	9.1
HL-A7	20.2	18.2
HL-A8	20.2	13.6
HL-A12	24.7	22.7
HL-A13	3.4	27.3†
W5 (Te50)	16.9	18.2
W10 (Te60)	13.5	18.2
W14 (Te54)	6.7	4.5
W15 (Te55)	13.5	11.4
W17 (Te57)	9.0	22.7†
W18 (Te58)	10.1	4.5
W22 (Te51)	4.5	0.0
W27 (Te52)	10.1	13.6

*Nomenclature before 5th International Conference on Histocompatibility, Evian, France, May 23-27, 1972.
†Significantly different from controls ($p < 0.0001$).
‡Significantly different from controls ($p = 0.056$).

Three groups published their data on the possible association of HLA with human diseases: Falchuck et al (J Clin Invest 51:1602, 1972) reported that the frequency HLA-B8 was

increased in patients with celiac disease while Russell et al. (N Engl J Med 287:738, 1972) and White et al (N Engl J Med 287:740. 1972) showed an association of HLA-B13 and B17 with psoriasis.

1973
1973
Linked Ir Genes



Allan Rosenthal and Ethan Shevach (J Exp Med 136: 1207, 1972; J Exp Med 138: 1194 and 1213, 1973) demonstrated that antigen recognition by guinea pig T cells was regulated by macrophages and restricted by the MHC class II linked Ir genes.

1973
Ankylosing Spondylitis

Table 1. Phenotype Frequencies of HL-A Specificities in Ankylosing Spondylitis (AS), Rheumatoid Arthritis (RA) and Gout (All Caucasian).

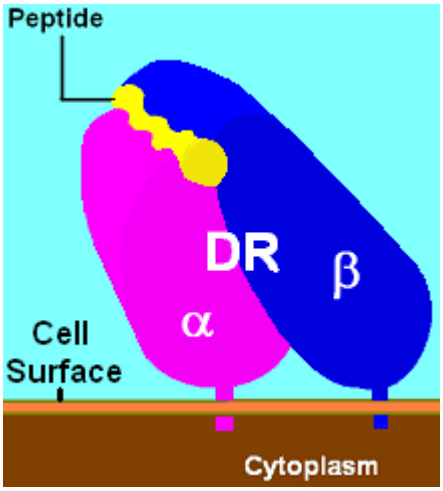
Antigen	% in 906 Controls	% in 40 Patients with AS	% in 119 Patients with RA	% in 66 Patients with Gout
HL-A1	27	10	28	36
HL-A2	48	60	49	44
HL-A3	24	18	26	30
HL-A9	22	30	20	18
HL-A10	11	8	17	12
HL-A11	12	10	10	6
W28	12	18	8	12
W29	7	10	8	8
W30	10	15	10	6
W32	8	13	5	6
HL-A5	11	5	3	14
HL-A7	25	3*	13	27
HL-A8	21	15	14	21
HL-A12	24	18	22	24
HL-A13	4	3	8	6
W5	22	18	25	17
W10	14	18	10	8
W14	7	5	8	8
W15	8	8	11	8
W17	8	5	13	17
W18	9	5	6	9
W21	5	3	0	2
W22	5	3	3	5
W27	8	88†	8	9

*Chi square = 9.32 ($p<0.05$ when multiplied by 24).

†Chi square = 236.41 ($p<0.0001$ when multiplied by 24, no. of specificities tested).

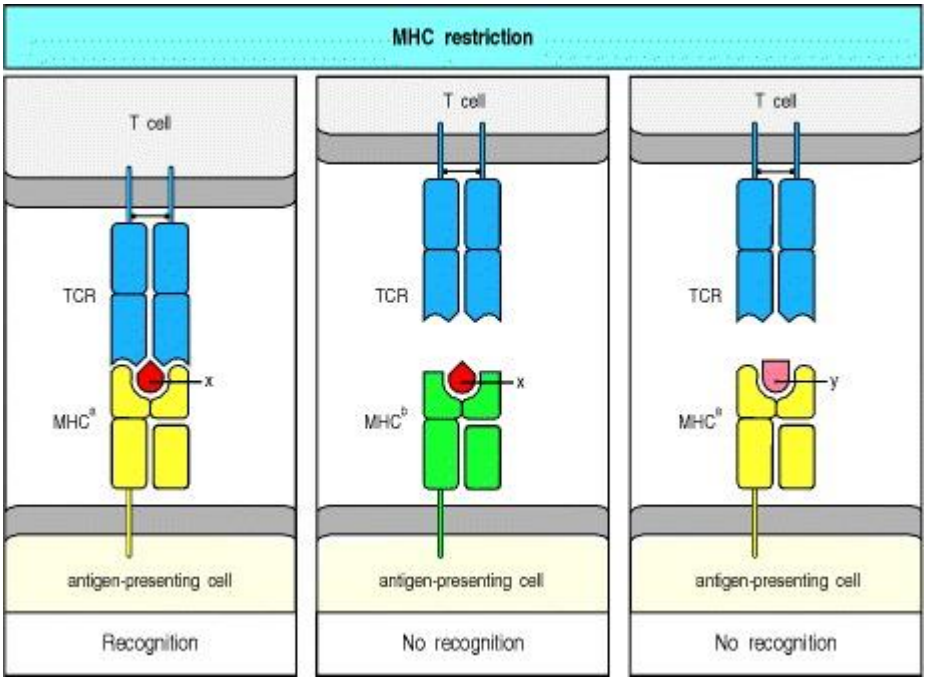
A strong association of HLA-B27 and Ankylosing Spondylitis was reported by Caffrey and James (Nature 242:121, 1973), Brewerton et al. (Lancet 1(7809):904, 1973) and Schlosstein et al (N Engl J Med 288:704, 1973)

1973
HLA-DR



The HLA-DR (HLA-D Related) antigens were serologically detected on B lymphocytes using immunofluorescence (van Leeuwen et al., Transplant Proc 5:1539: 1973)

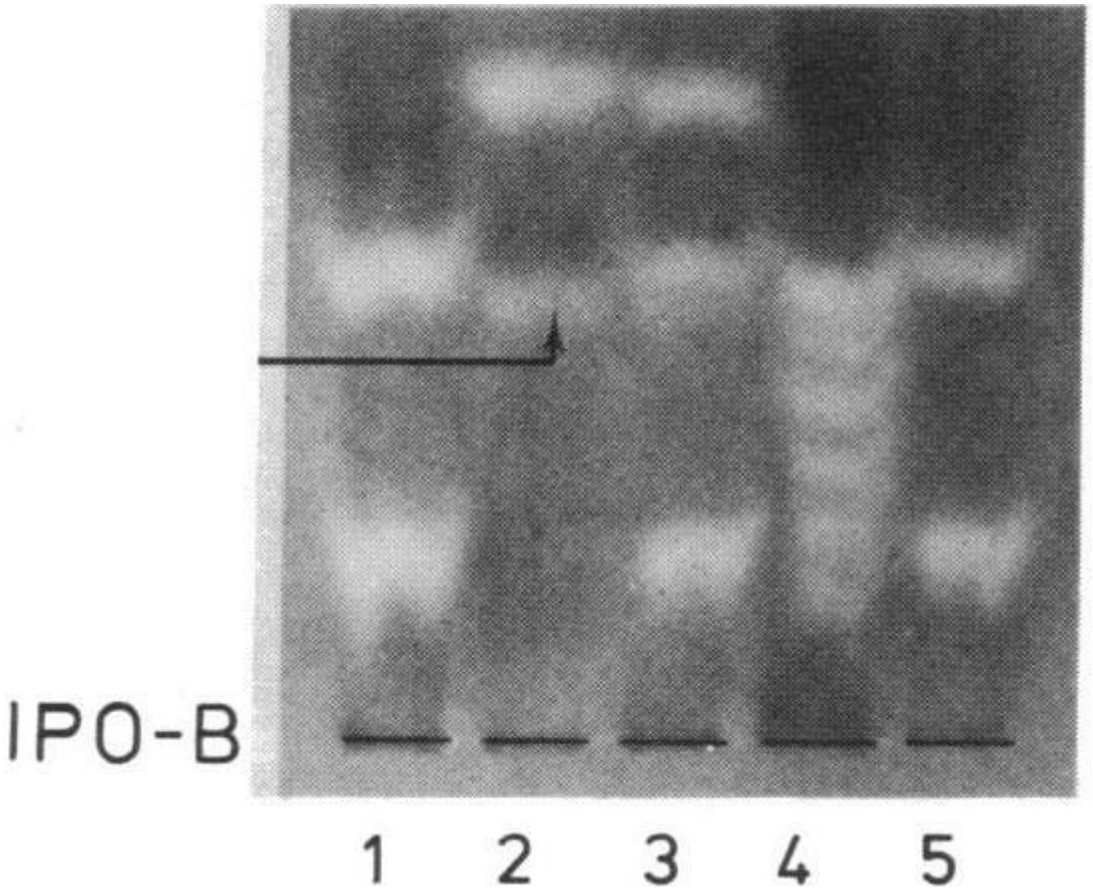
1974
1974
MHC Restriction



In 1974, Peter Doherty and Rolf Zinkernagel published a series of papers (Nature 248:701, 1974; Nature 251: 547, 1974) demonstrating that recognition of viral infected target cells by CD8+ T cells is restricted by MHC class I genes. They put forward the concept of ‘MHC restriction’.

1974

HLA Complex



In 1974, van Someren et al. (Proc Natl Acad Sci USA 71:962, 1974) and Lamm et al. (Hum Hered 24:273, 1974) assigned the HLA complex to human chromosome 6.

1974
Gene Linkage

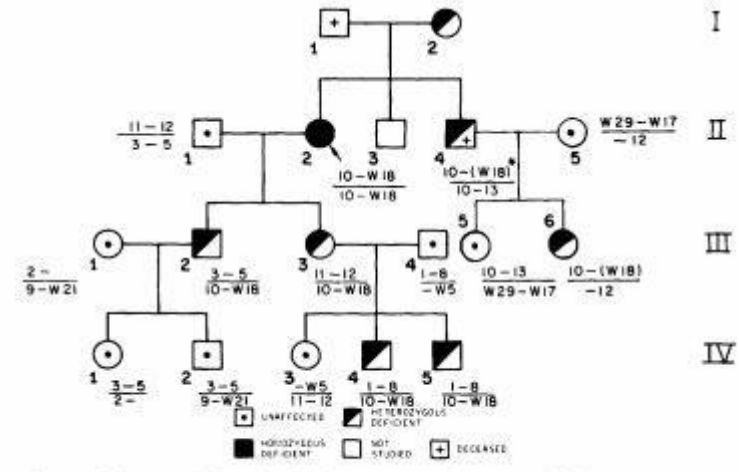
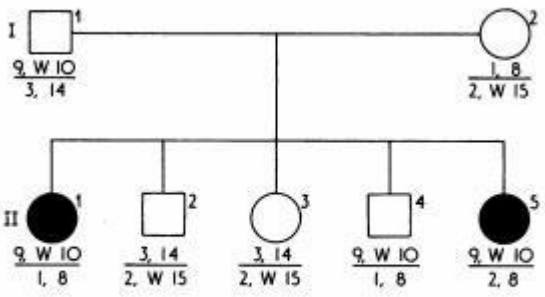


FIG. 1. Pedigree of the S family. The heterozygous and homozygous C2-deficient cases are indicated by the solid black symbols and the HL-A type is given in adjoining space.

Fu et al. (J Exp Med 140:1108, 1974) demonstrated a linkage between HLA and the gene responsible for complement component C2. Allen (Vox Sang 27:382, 1974) reported that the complement

Factor B (Bf) gene is in linkage with HLA genes.

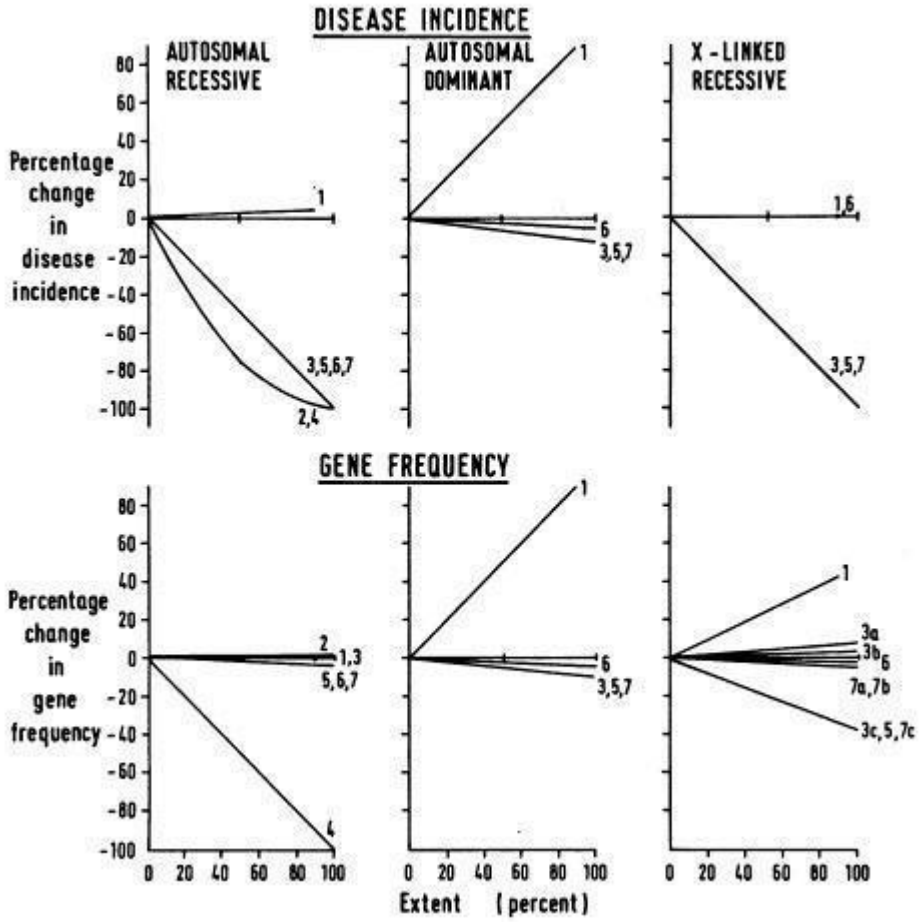
1975
1975
Diabetes



Family with two diabetic siblings showing cross-over between first and second HL-A loci.

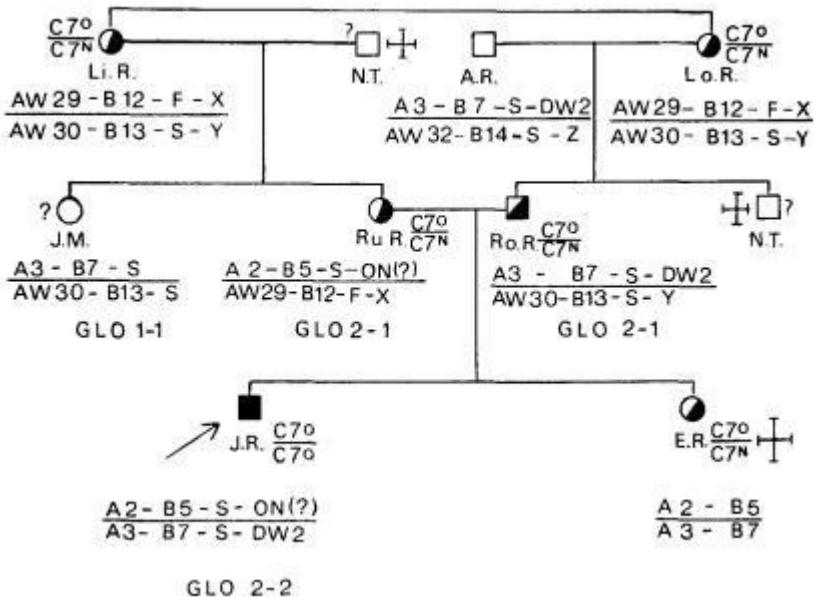
The association of Type I diabetes (IDDM) and HLA was first reported by Singal et al. (Diabetes 22:429, 1973) and confirmed by the classical studies of Nerup and colleagues (Lancet 2(7885): 864, 1974) and Cudworth and Woodrow (Br Med J 3:133, 1975).

1975
B2-microglobulin



Goodfellow et al. (Nature 254:267, 1975) and Smith et al. (Am J Hum Genet 39:21, 1975) assigned the human b2-microglobulin locus to chromosome 15.

1975
Linkage



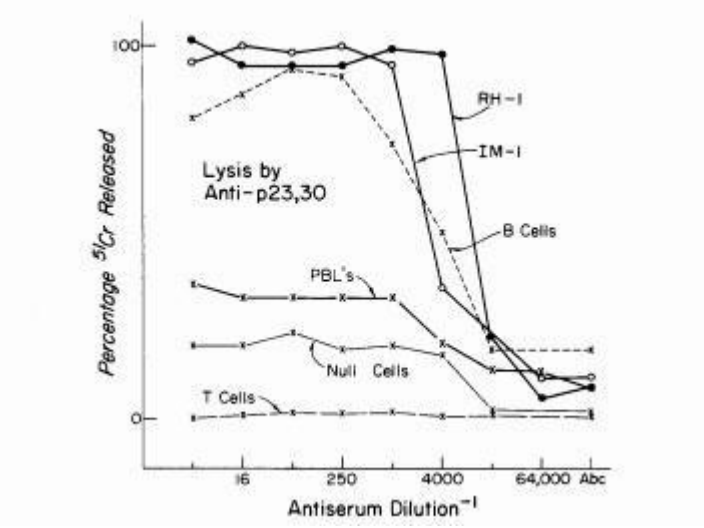
Rittner and colleagues (Histocompatibility Testing, p945,

1975) demonstrated a linkage between HLA genes and the complement component C4.

1977
1977
Antigen Recognition

In 1977, Els Goulmy et al. (Nature 266:544, 1977) demonstrated that antigen recognition by CD8 T cells was restricted by class I molecules, while Bergholtz and Thorsby (Scand J Immunol 6:779, 1977) showed that class II molecules restrict antigen recognition by CD4 T cells.

1978
1978
alpha and beta chains



The class II α and β chains were identified during the late 1970s by many groups, for both H-2 (Cullen et al. Transplantation 30:236, 1976; Freed et al. J Immunol 121:91,

1978; Cook et al. J Immunol 123:2799, 1979) and HLA-DR systems (Humpreys et al. J Exp Med 144:98, 1976; Kaufman and Strominger, Proc Natl Acad Sci USA 576:6304, 1979).

1978
HLA-DR matching

Table 3. Predictors of Graft Failure

Predictor	Hazard Ratio (95% CI)	*P* Value
0-HLA-DR mismatch	1 [Reference]	
1- or 2-HLA-DR mismatches	0.5 (0.1-2.2)	.40
Recipient race		>.05
Age at transplantation, y		
<13	1 [Reference]	
13-16	8.9 (2.4-32.5)	.001
>16	8.4 (1.9-37.1)	.005
History of rejection	7.7 (1.6-37.7)	.01
Posttransplantation lymphoproliferative disorder	46.6 (6.9-312.0)	<.001

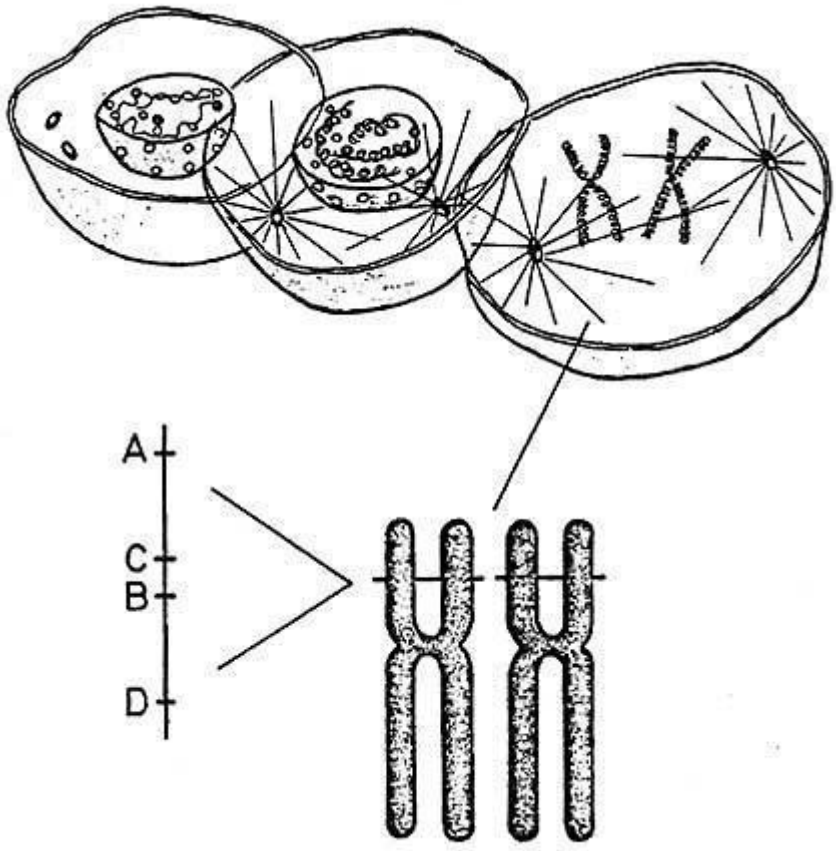
Abbreviation: CI, confidence interval.

Ting and Morris (Lancet 1(8064):575, 1978) and Albrechtsen et al. (Lancet 2(8100):1226, 1978) reported a strong effect of HLA-DR matching on kidney graft survival.

1979
1979
Invariant Chain

Jones et al., (Mol Immunol 16:51, 1979) reported the existence of an invariant chain (Ii) that binds the α and β class II chains in the endoplasmic reticulum (ER), before the trimer moves to the Golgi apparatus.

1980
1980
1980 Nobel Prize



In 1980, Jean Dausset, George Snell and Baruj Benacerraf were awarded the Nobel Prize in Medicine and Biology for their discoveries on the MHC. Peter Gorer could not make the list

because he had passed away in 1961.

Nobel Prize 1980 – Discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions.

1982
1982
Collaborative Transplant Study

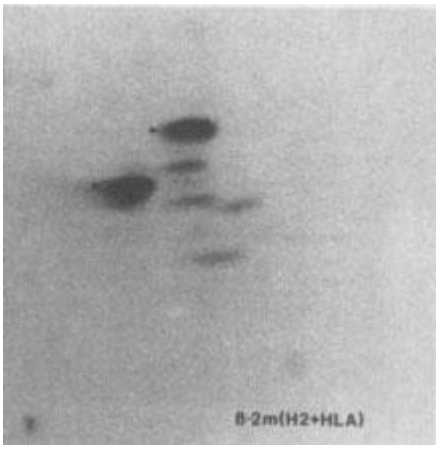
In 1982, Gerhard Opelz, at the University of Heidelberg (Germany), launched the Collaborative Transplant Study (CTS), an international collaborative program involving a large number of transplant groups and tissue typing laboratories. The data collected through CTS clearly demonstrated an important effect of HLA matching on kidney graft survival. The CTS has been a great source of very important information on factors influencing long-term graft survival following organ transplantation.

1983
1983
Flow Cytometry

Garovoy et al. (Transplant Proc: 15:1939, 1983) introduced

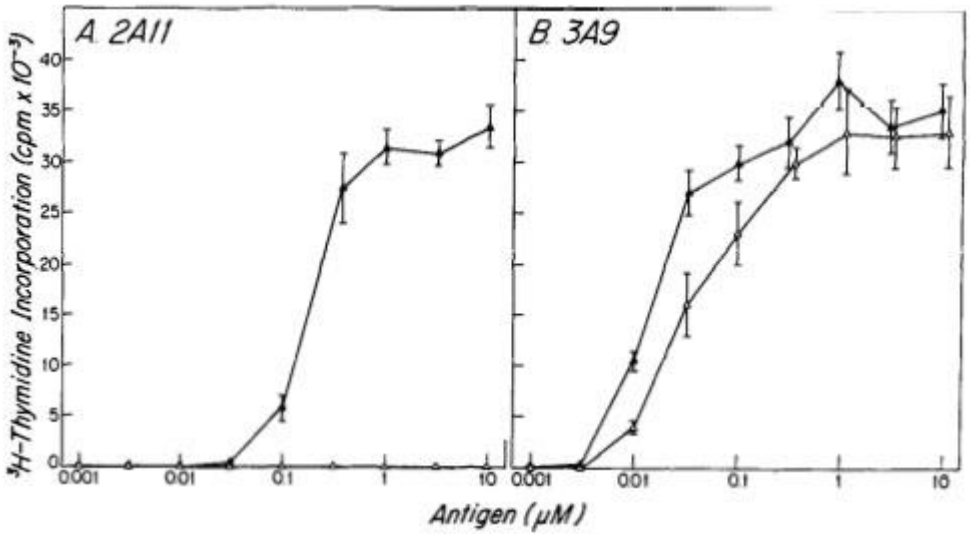
flow cytometry as the more sensitive technique for the pre-transplant crossmatch analysis.

1983
Single Recombinant HLA



Bernabeu et al. (J Immunol 131:2032, 1983) reported the production of single recombinant HLA molecules, opening the possibility to use these molecules for the detection of antigen-specific responses.

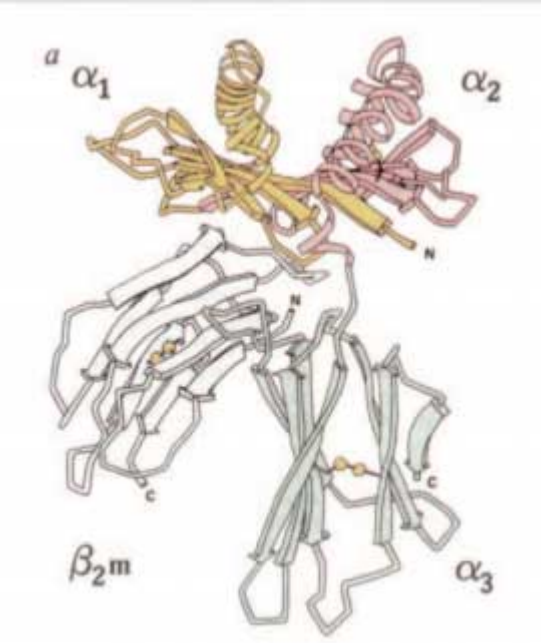
1985
1985
H-2k and I-Ak molecules



In 1985, Emil Unanue and his colleagues described the characteristics of the peptides binding H-2^k (Class I) (J Immunol 135:368, 1985) and I-A^k (Class II) (Nature 317:359, 1985) molecules.

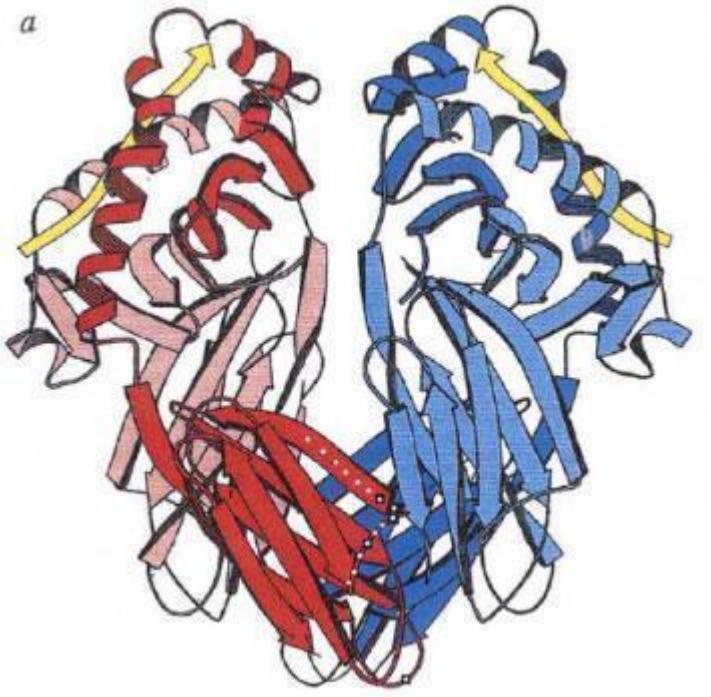
1987

1987
HLA bind antigenic peptides



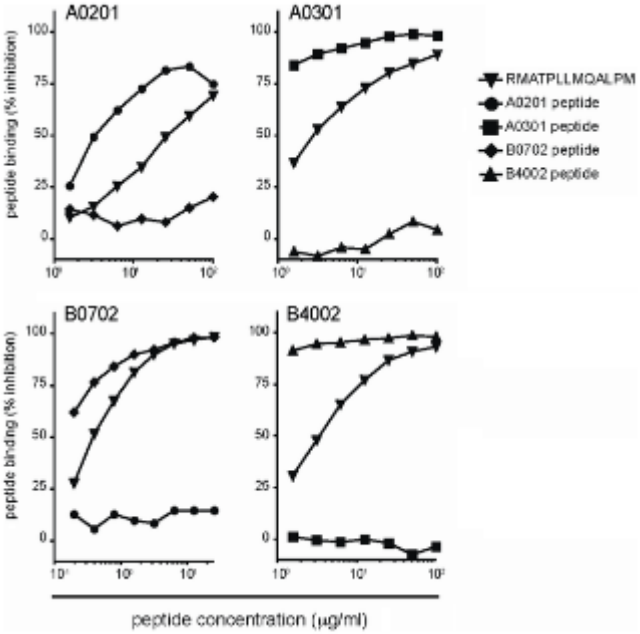
In 1987, Pamela Bjorkman, Jack Strominger and colleagues reported the three-dimensional structure of HLA-A2 by X-ray cristallography (Nature 329: 506, 1987; and 329:512, 1987). They demonstrated that polymorphic amino acid residues located in the floor or side chains of the peptide binding groove of HLA class I molecules bind antigenic peptides in specific residues, while other residues bind the T-cell receptor (TCR).

1988
1988
3D HLA Class II Molecules



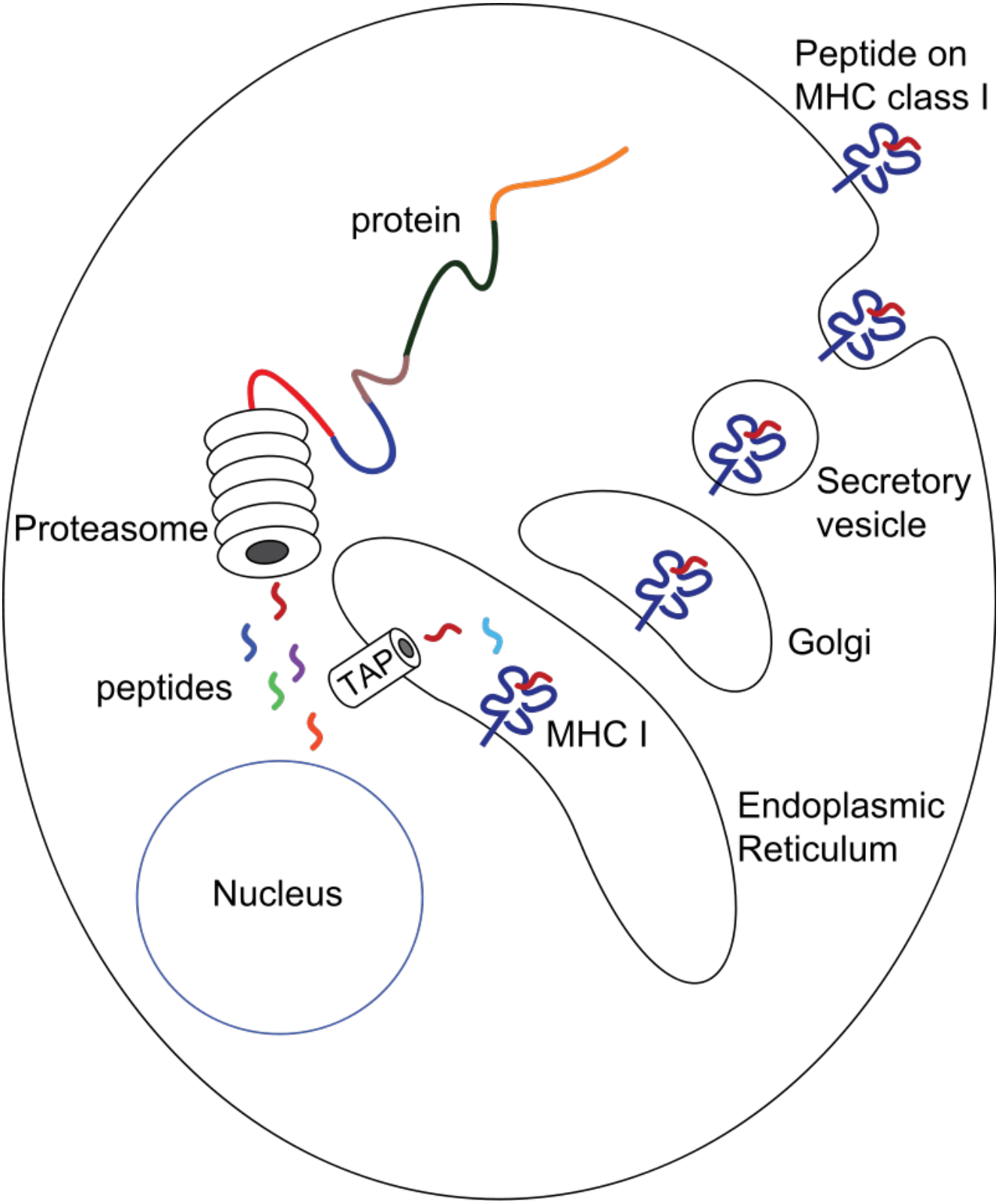
The three-dimensional structure of the HLA Class II molecules was proposed by Brown et al. in 1988 (Nature 332:845, 1988) and confirmed by the same group for HLA-DR1 (Nature 364:33, 1993).

1990
1990
CLIP



Roche and Creswell (Nature 345:615, 1990) demonstrated that a part of the invariant chain Ii, the class II-associated Ii peptide (CLIP), temporarily blocks the peptide-binding groove of nascent class II molecules.

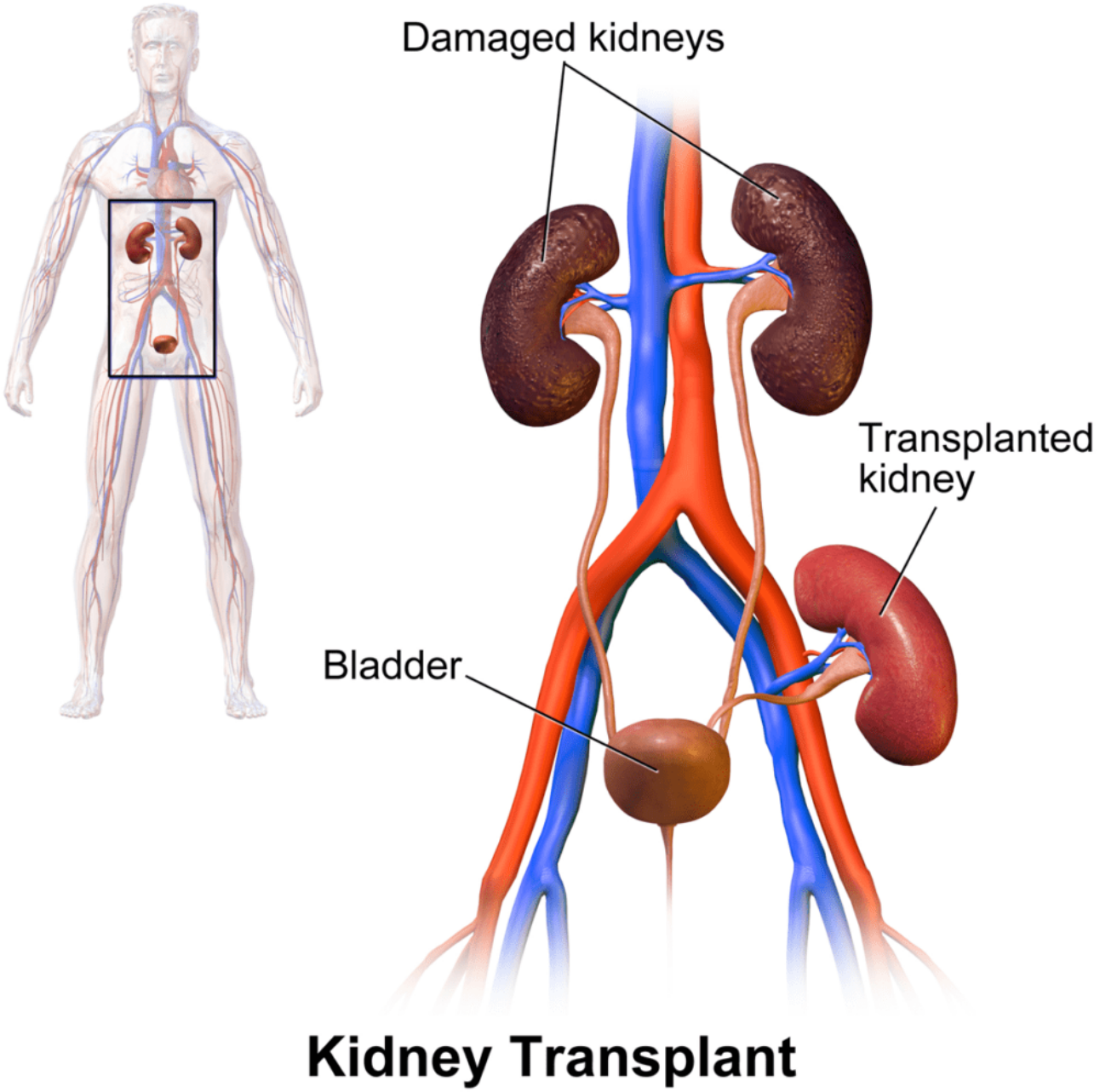
1990
TAP



In 1990, three groups simultaneously demonstrated that a gene located on the class II region regulates the class I antigen presentation (Deverson et al., Nature 348:738, 1990; Trowsdale et al., Nature 348:741, 1990; Spies et al., Nature 348:744, 1990). The gene codes for an ATP-binding cassette (ABC)

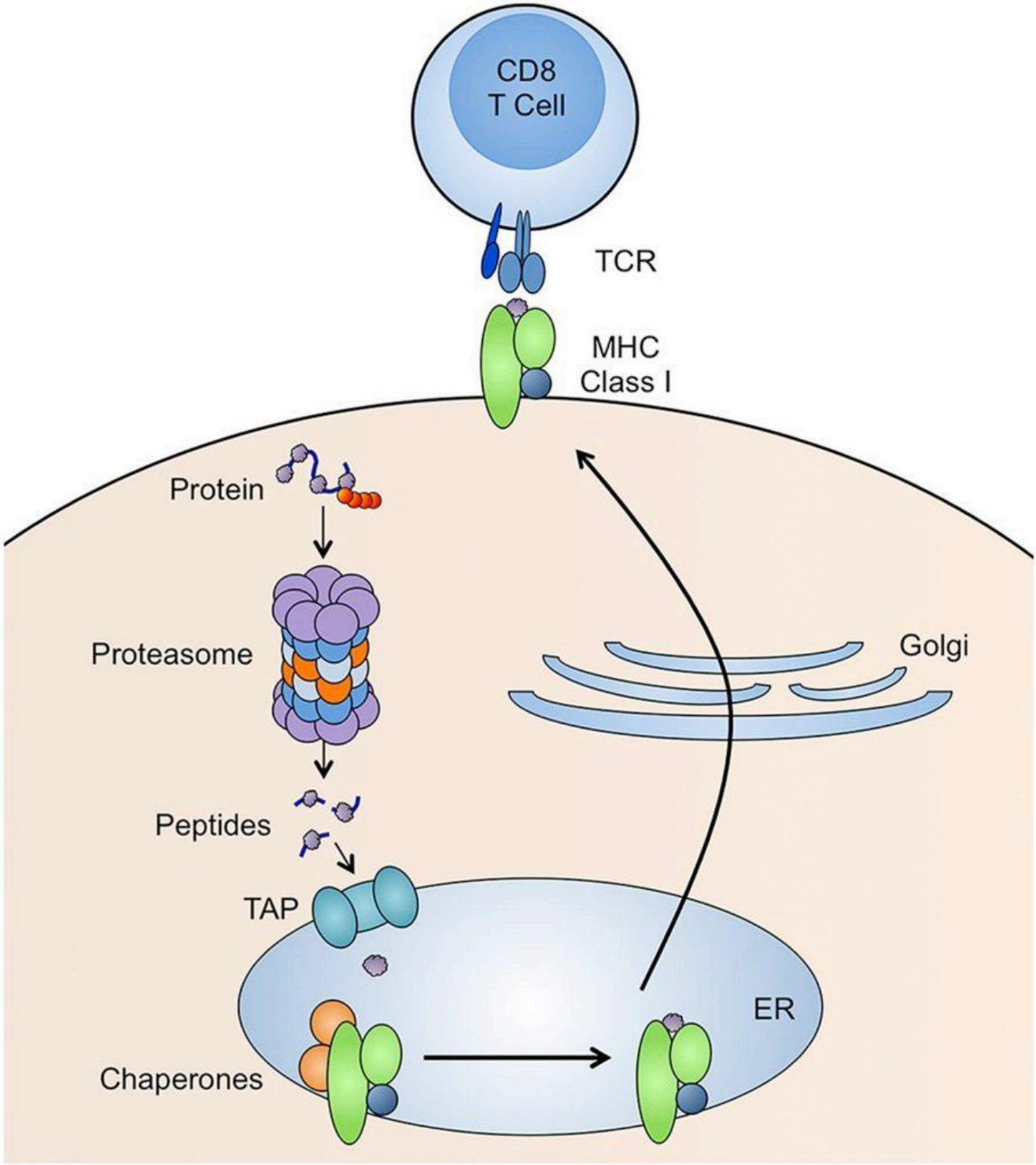
superfamily of transporter proteins that transport peptides from the cytoplasm into the ER, where peptides are loaded into nascent class I molecules. The protein was named TAP.

1990
Acute Rejection



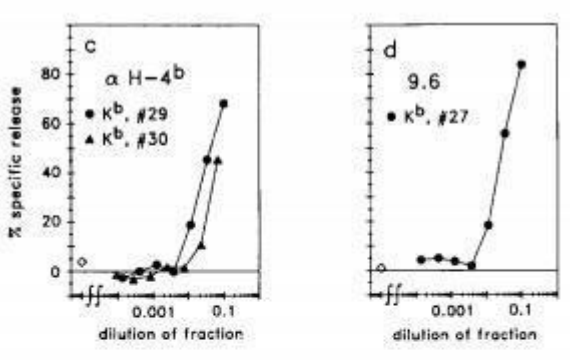
In 1990, Halloran and colleagues (Transplantation 49:85:1990) demonstrated that *de novo* produced, donor-specific HLA class I antibodies can induce acute rejection of kidney grafts.

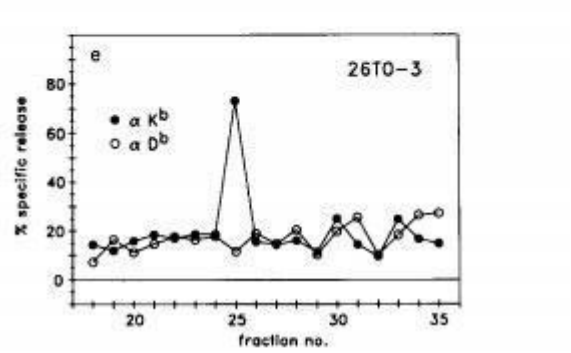
1991
1991
LMP



In 1991, a proteasome gene was found in the HLA class II region (Glynne et al, Nature 353:357, 1991). Soon after, Rock *et al* (Cell 78:761, 1994) demonstrated that the low molecular weight proteasome (LMP) was involved in the generation of peptides that are then transported into the ER by TAP.

1991
Direct Allorecognition





In 1991 Rotzschke et al (J Exp Med 174:1059, 1991) demonstrated that cytotoxic T lymphocytes could directly recognize allogeneic MHC-peptide complexes, without presentation by autologous antigen presenting cells. This phenomenon is known as direct allorecognition.

1992
1992
Polymerase Chain Reaction

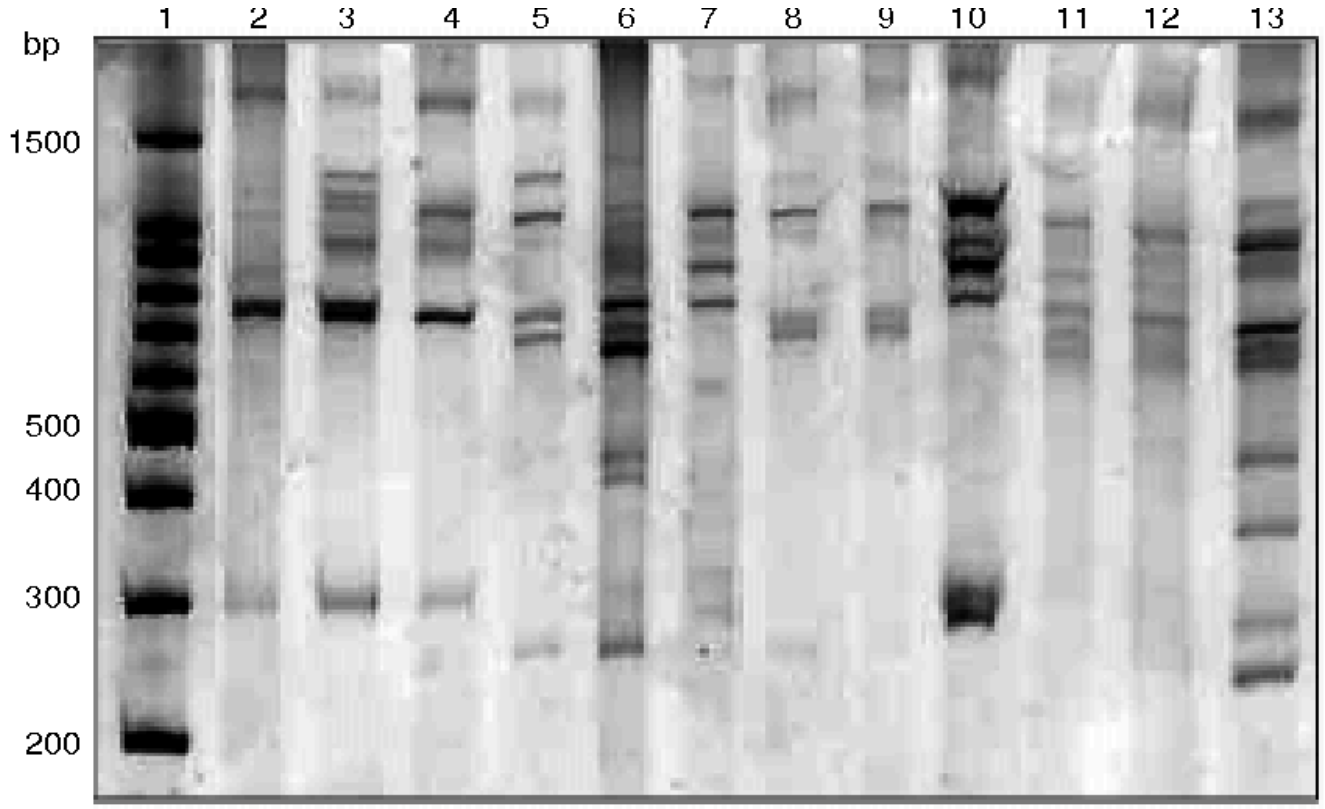
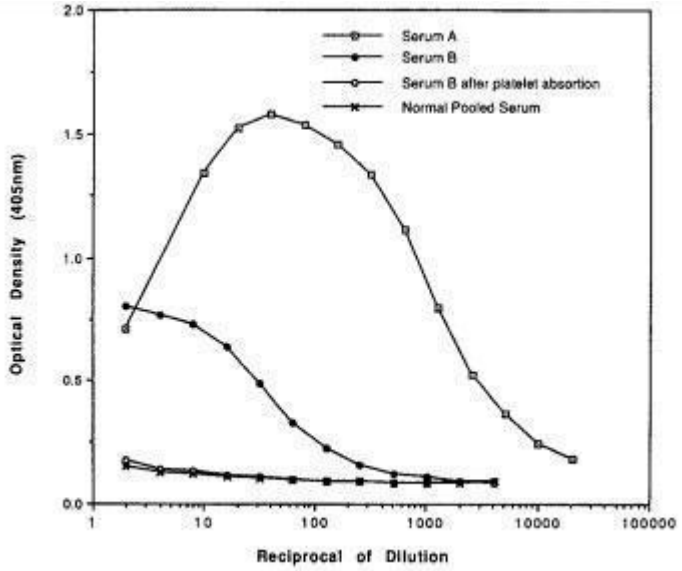


Figure 1. PCR-LIS-SSOP analysis of HLA-DQA1 group alleles. *Lane 1*: Molecular weight

Following the development of the Polymerase Chain Reaction (PCR) by Saiki (Science 230:1350, 1985), several DNA based procedures were developed for molecular HLA typing. This includes: Sequence Specific Oligo hybridization (SSOP) (Wordsworth, Immunol Lett 29:37, 1991) , PCR based Sequence Specific Primer technology or PCR-SSP (Olerup and Zetterquist, Tissue Antigens 39:225, 1992), PCR-Single Strand Conformation Polymorphisms or SSCP (Carrington et al., Hum Immunol 33:208, 1992), and Sequence Based Typing or SBT (Cereb et al., Tissue Antigens 45:1, 1995). These molecular methods have since replaced the serological methods for HLA typing in most clinical laboratories.

1993
1993
ELISA



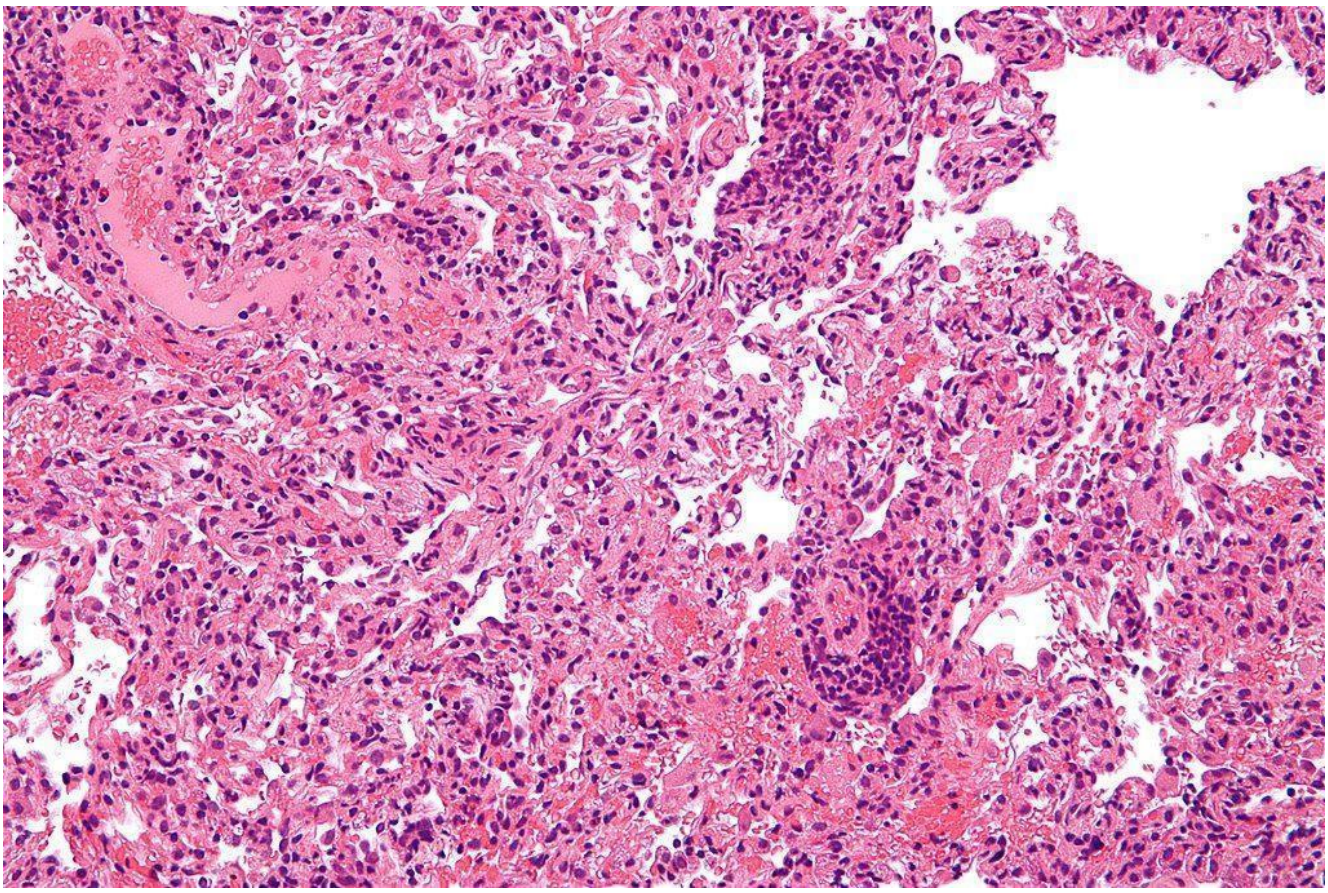
In 1993, Kao et al (Transplantation 55:192, 1993) introduced ELISA as an immunoassay for the detection of anti-HLA antibodies.

1993
Bare Lymphocyte Syndrome

In 1993, Steimie et al (Cell 75:135, 1993) demonstrated that

the ‘Bare Lymphocyte Syndrome’, characterized by the complete lack of HLA class II expression leading to severe combined immunodeficiency, is caused by deletion in a gene that regulates the expression of class II molecules, the Class II Transactivator (CIITA).

1995
1995
Chronic Rejection



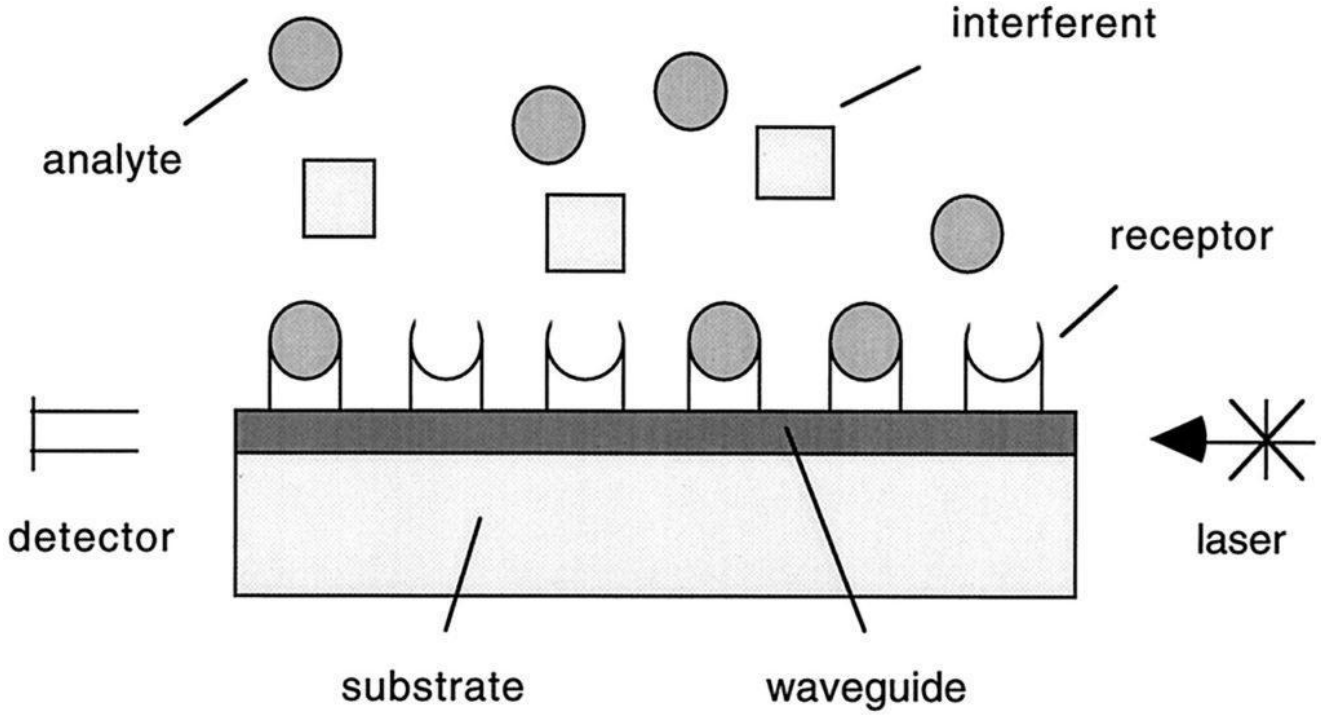
In 1995 Buchler et al (Transplant Proc 27:2478, 1995) reported that the development of post-transplant anti-HLA antibodies is associated with chronic rejection.

1996
1996
1996 Nobel Prize

In 1996, Peter Doherty and Rolf Zinkernagel shared the Nobel Prize for Medicine and Biology for their discovery on the role of MHC class I antigens in the recognition of viral-infected target cells by CD8+ T cells and “MHC restriction”.

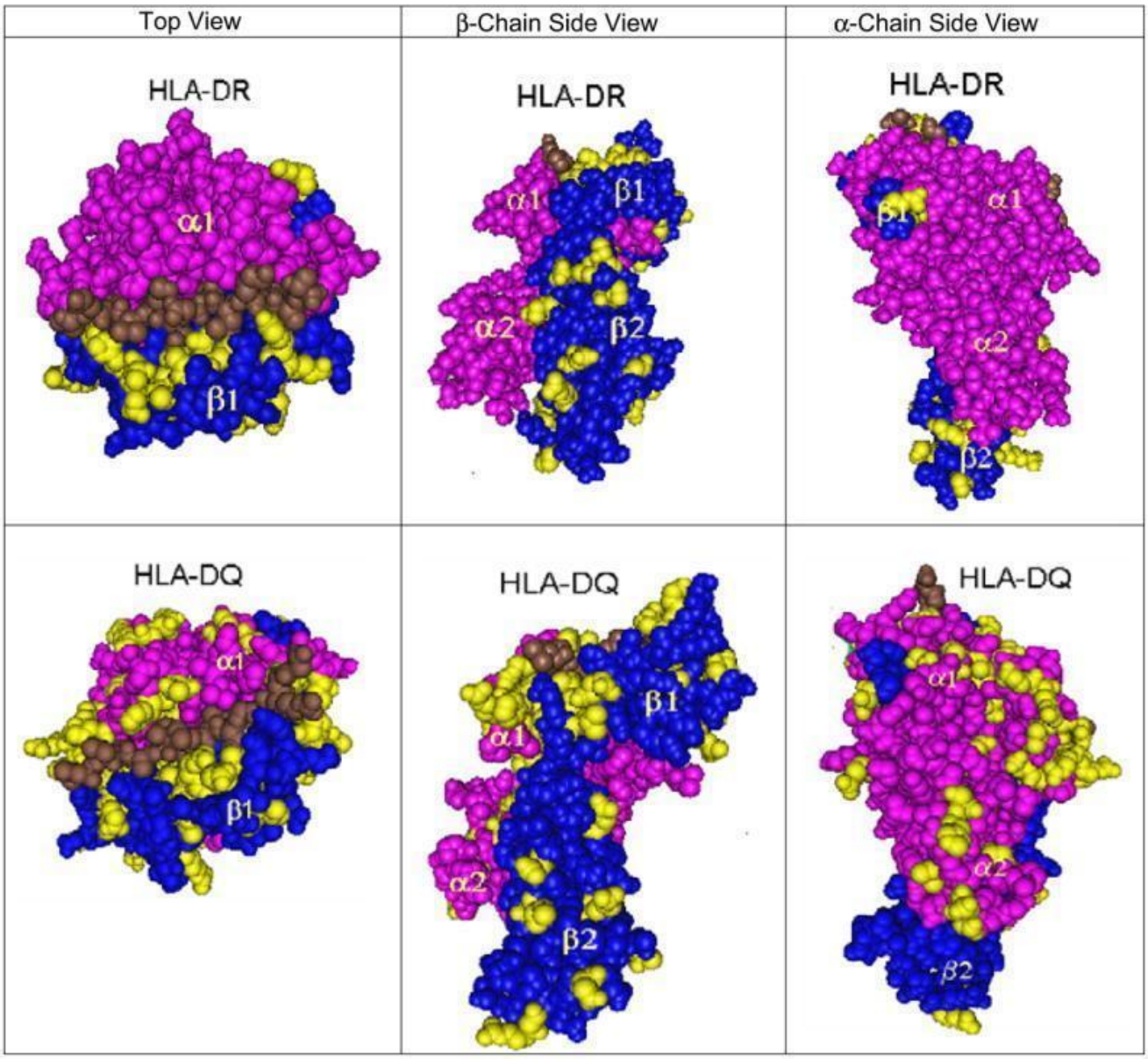
Nobel Prize 1996 – discoveries concerning the specificity of the cell mediated immune defence

1997
1997
Multiplex Analysis



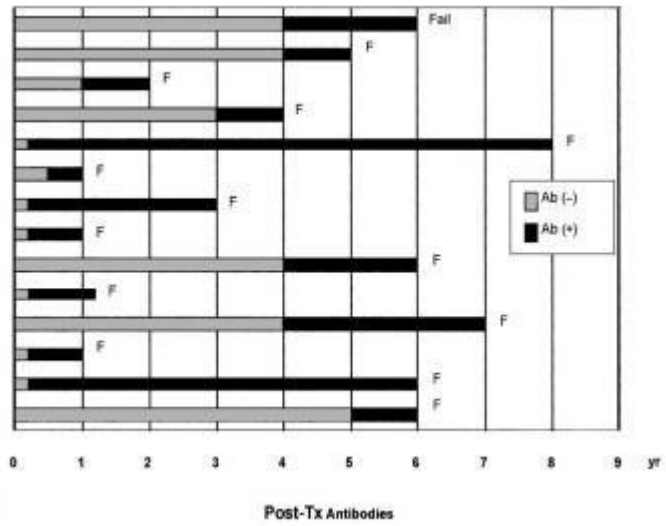
In 1997, Fulton et al (Clin Chem 43:1749, 1997) introduced the multiplex analysis technique for detection of HLA antibodies.

2002
2002
HLA Matchmaker algorithm



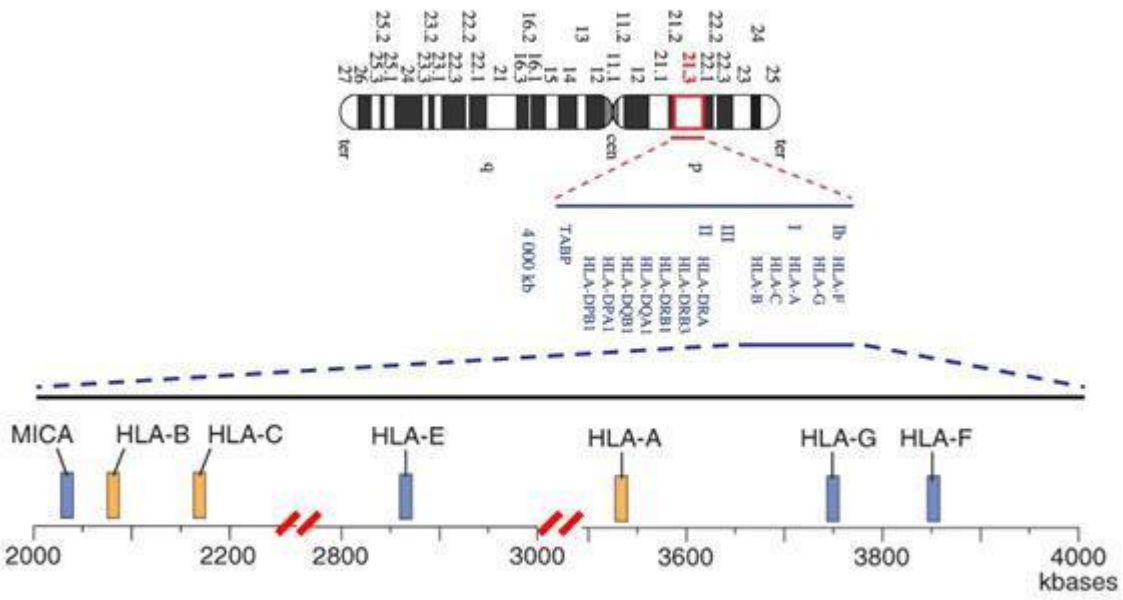
In 2002, Rene Duquesnoy (Human Immunol 63:339, 2002) introduced the HLA Matchmaker algorithm that allows to calculate the level of HLA sensitization.

2002
HLA Antibodies



In 2002, Terasaki´s group reported that all chronic rejection kidney failures were preceded by the development of HLA antibodies (Transpl 74:1192, 2002)

2008
2008
MICA



Since 2008, role of MICA (MHC class I associated) allelic polymorphism and the possible influence of non-HLA antibodies in organ transplantation is a subject of intense debate.

2011
2011
C1q Binding Assay

Table 2 Donor-Specific Antibody in Study Cohort

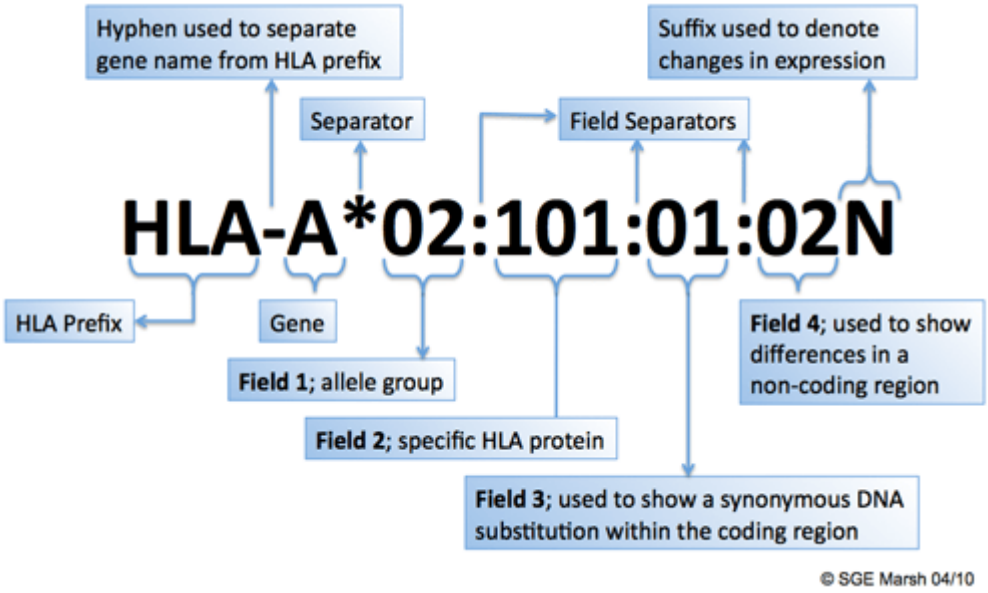
Pt	Sensitized CPRA >20%	VXM By IgG-SAB	VXM By C1q-SAB	DSA By IgG-SAB at Tx	DSA By IgG-SAB	DSA By C1q-SAB at Tx	DSA By C1q-SAB
2	Yes	Pos	NT	1	B51	NT	. . .
6	Yes	Pos	Pos	2	A2, DR51	1	A2
7	No	Neg	NT	0	. . .	NT	. . .
10	Yes	Pos	Neg	1	DR4	0	. . .
11	No	Neg	NT	0	. . .	NT	. . .
12	Yes	Pos	Pos	8	A23, A32, B35, B45, DR1, DR11, DQ5, DQ6	3	A23, A32, B45
13	Yes	Pos	Neg	2	DR13, DR14	0 (1)[a]	(DR13)[a]
14	No	Neg	NT	0		NT	
15	Yes	Pos	Neg	6	A29, A32, B44, B51, Cw15, DP2	0 (2)[a]	(B44, B51)[a]
16	Yes	Pos	Neg	3	A24, B61, DR12	0	. . .
17	No	Neg	Neg	0		NT	. . .
18	No	Neg	Neg	0		NT	. . .
19	Yes	Pos	Neg	1	B7	0	. . .
20	Yes	Neg	Neg	0		NT	. . .
22	Yes	Pos	Pos	7	A25, A68, B44, B52, DR13, DR14, DQ6	1	A68
23	Yes	Pos	Neg	2	DR4, DQ6	0	. . .
24	Yes	Neg	Neg	0	. . .	NT	. . .
25	Yes	Pos	Neg	6	Cw16, DR7, DR52, DR53, DP13, DP14	0	. . .

CPRA, calculated percent panel reactive antibody; DSA, donor-specific antibody; NT, not tested; SAB, single-antigen bead assay; Tx, transplant; VXM, virtual crossmatch.

[a]Historically present, desensitized, absent at transplant, rebound after transplant.

In 2011, Chin et al (J Heart Lung Transplant 30:158, 2011) introduced the C1q binding assay for detection of Complement-activating HLA antibodies.

2011
Nomenclature



In 2011 the WHO Nomenclature Committee for Factors of the HLA System updated the rules for the nomenclature of HLA loci and alleles (Marsh , Tissue Antigens 78:482, 2011; http://hla.alleles.org/nomenclature/naming). Presently, >18000 HLA alleles (HLA class I 13,324 and HLA class II 4857 have

become known primarily due to extensive improvements in molecular based technologies.

The next two decades will see developments in regenerative medicine/biology to re-create and/or repair damaged organs and a switch from standard to patient specific treatment.

Immunogenetics of the host, beyond MHC will make us understand why some organs survive despite having so many so many incompatibilities, while others are lost even though they are optimally matched. Prediction will become the key word for transplantation.

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