Transplantation: Friendly organs in a hostile environment

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MIT Feb. 20, 2003

How is foreign tissue recognized?
How is the tissue rejected?
What limits transplantation?
What can be done about it?

Transplants

Acellular tissue	Heart valve
Cells	Blood Bone Marrow
Living tissue	Cornea Skin Islets
Organs	Kidney, Heart, Liver, Lung, Pancreas, Intestine

Transplants in USA

Organs (total 23,985) [1]

	Recipients	5 yr graft survival
Kidney	14,095	66-78%
Liver	5,157	64%
Heart	2,194	70%
Lung	1,053	43%

Tissues/Cells

Cornea[2]	~40,000	70%
Bone Marrow[3]	23,500	80%

80,617 patients waiting as of 2/15/03 unos.org
17 die each day waiting for transplant

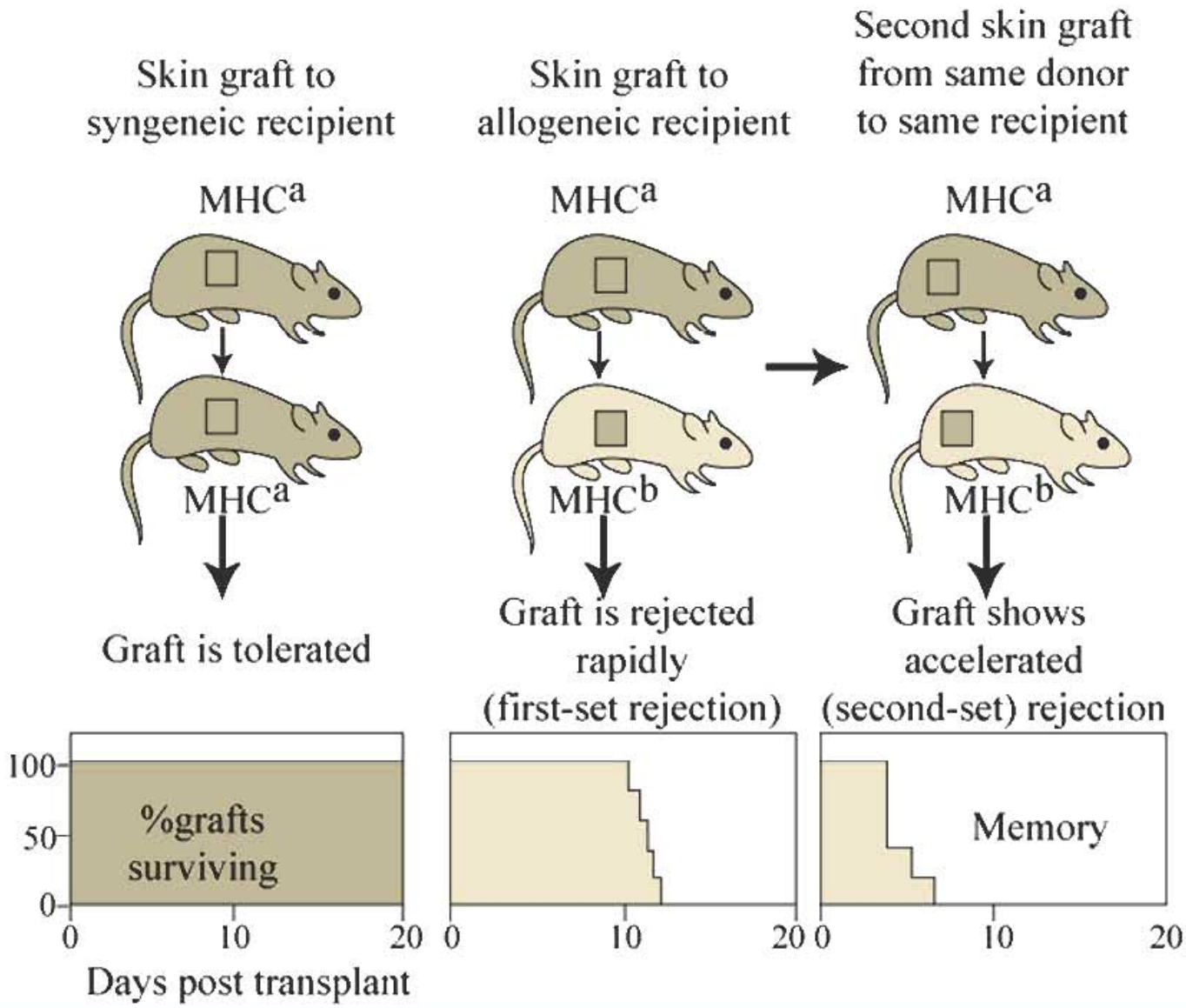
Why are grafts lost?

Acute rejection
Chronic rejection

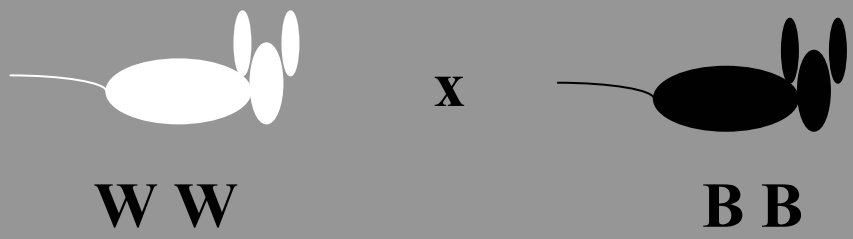
Infection
Drug toxicity

Recurrent disease
Complications of original disease

Graft	Source	Rejection
Auto-	Self	None
Iso-	Identical twin	None
Allo-	Same species non-identical	Yes +/-
Xeno-	Other species	Yes +++


Skin graft to syngeneic recipient
Skin graft to allogeneic recipient
Second skin graft from same donor to same recipient
MHC^a
MHC^a
MHC^a
MHC^a
MHC^b
MHC^b
Graft is tolerated
Graft is rejected rapidly (first-set rejection)
Graft shows accelerated (second-set) rejection
100
50
0
%grafts surviving
Memory
0
10
20
0
10
20
0
10
20
Days post transplant

Major Histocompatibility Complex determines graft outcome



W W x B B

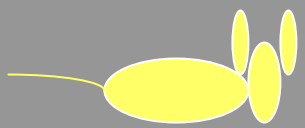
Parents Homozygous MHC

Graft accepted

Graft rejected

F1 Heterozygous MHC

3rd Party



W B

Grafts rejected

Y Y

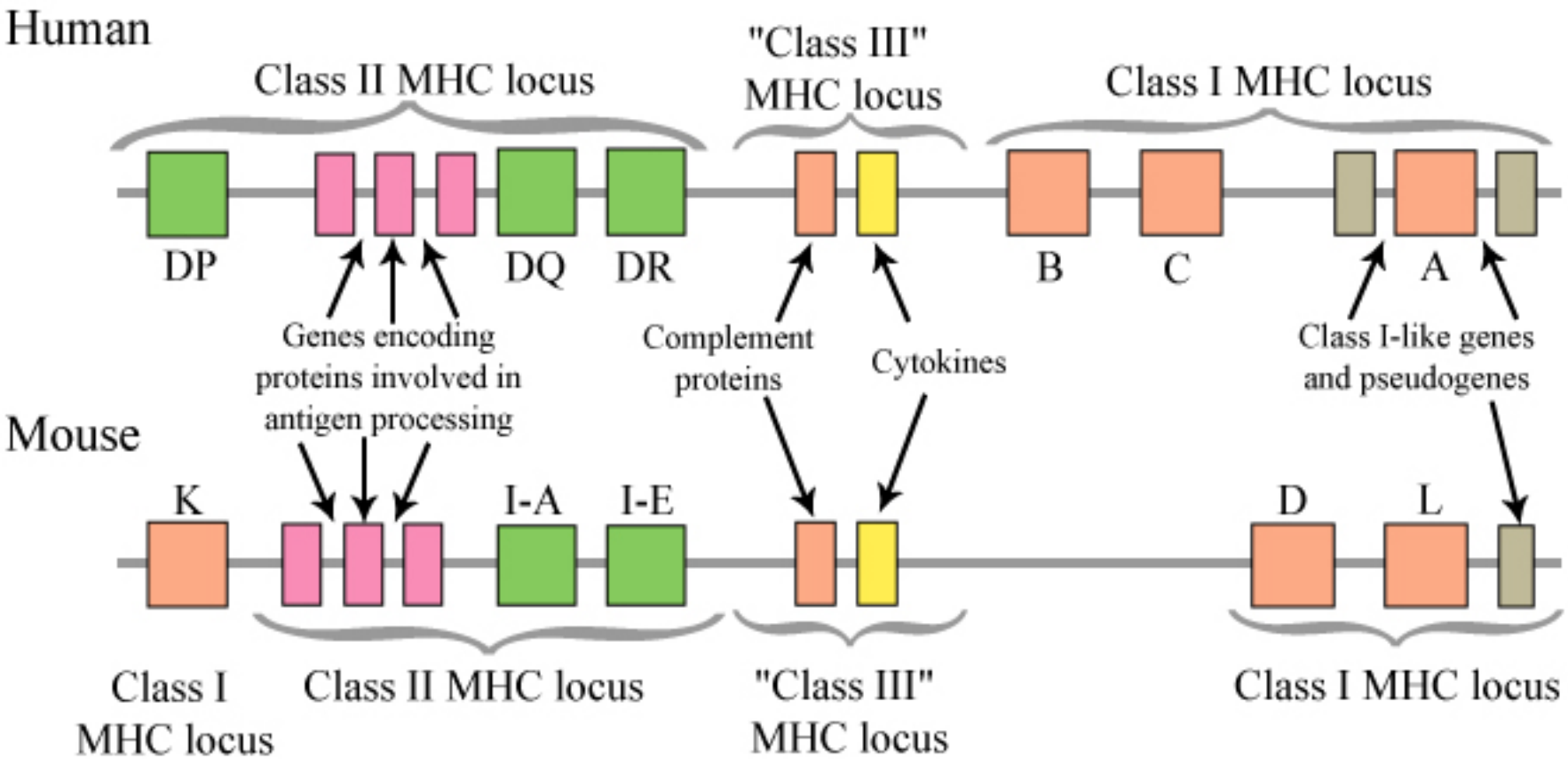
F1 accepts graft from either parent

Parent rejects graft from F1

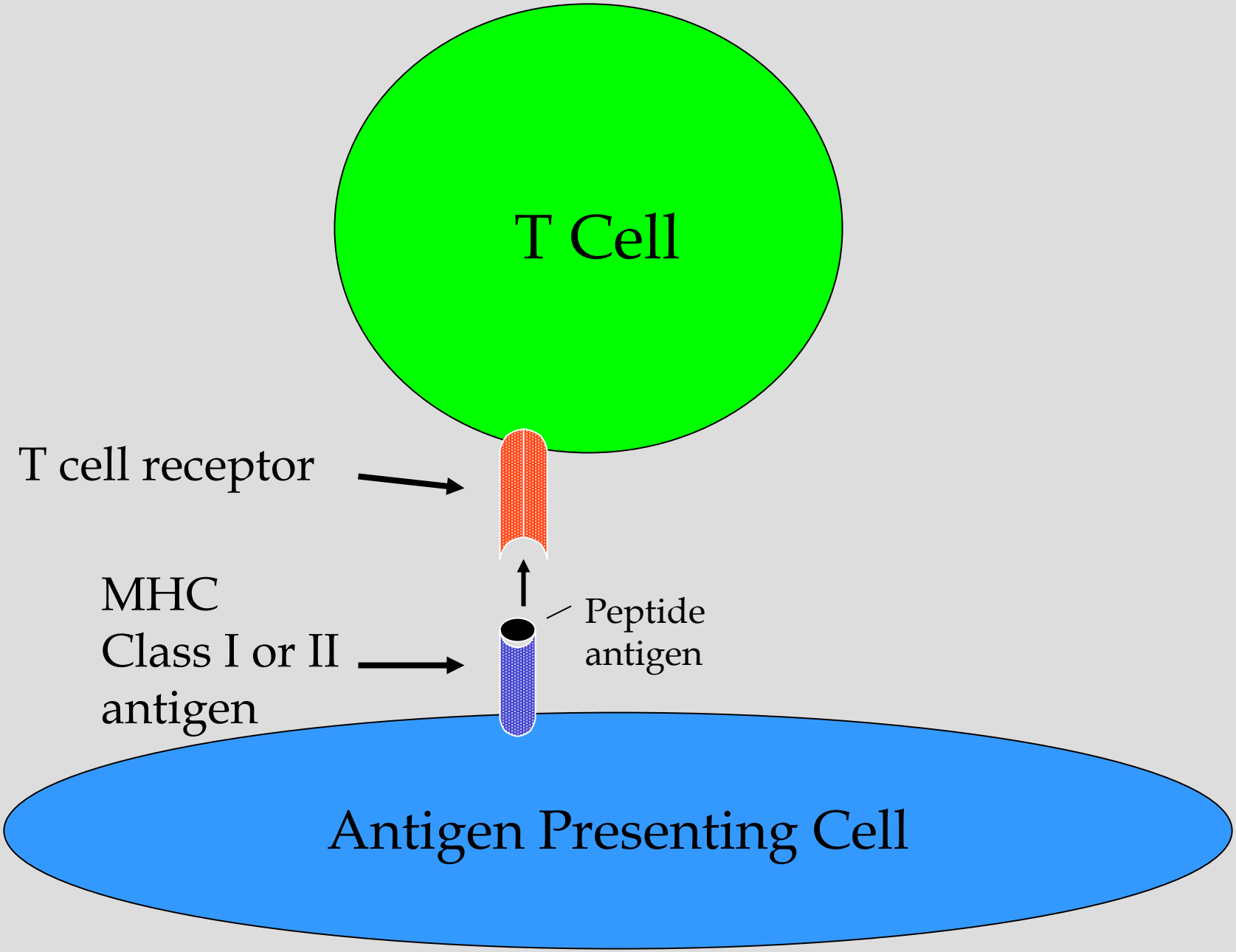
3rd party grafts rejected by all

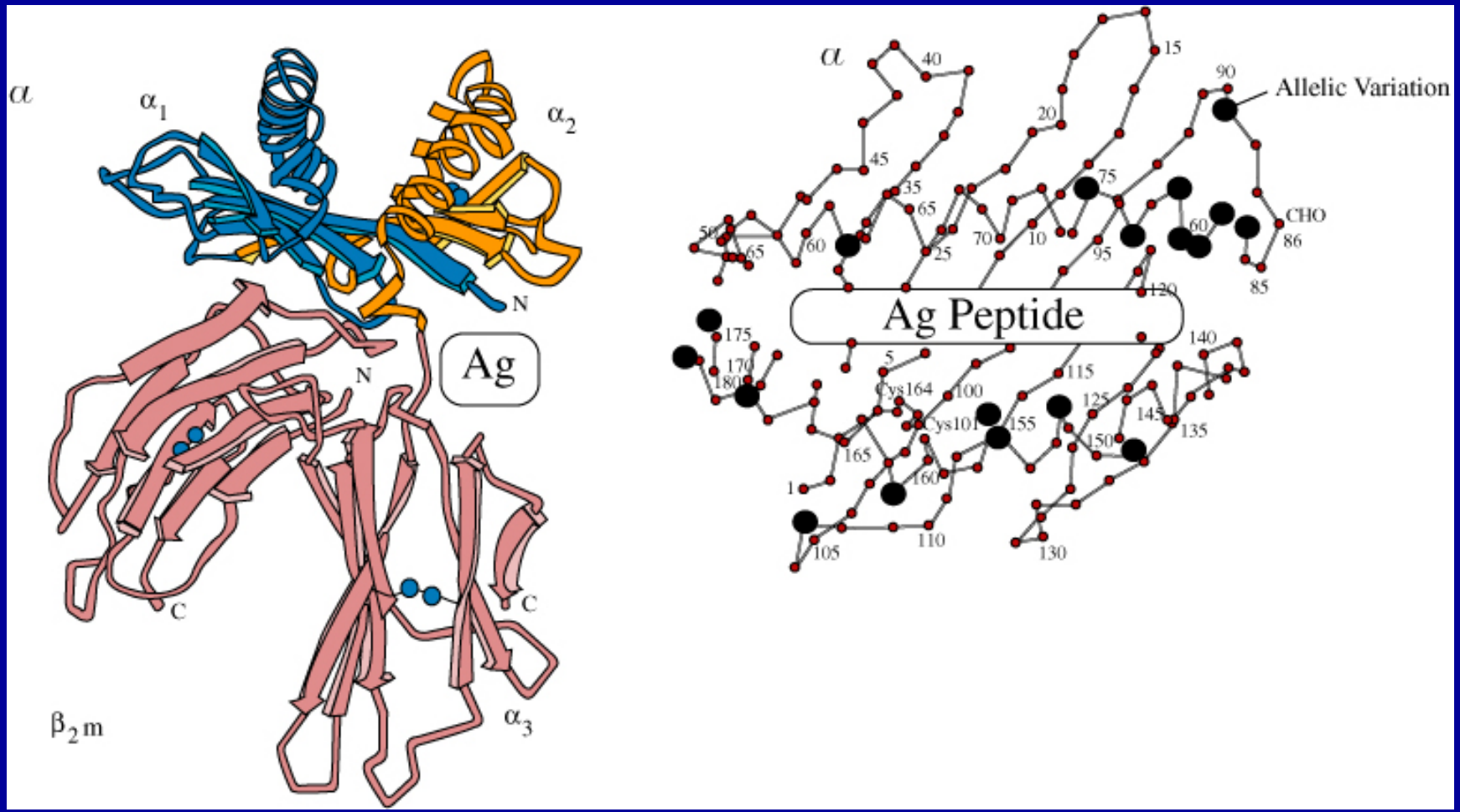
Major Histocompatibility Complex

Chromosome 6 human (HLA), 17 mouse (H-2)



HLA loci highly polymorphic


T Cell
T cell receptor
MHC
Class I or II
antigen
Peptide
antigen
Antigen Presenting Cell



Class II has 2 polymorphic chains
more open peptide grove

Thymic education for T cells

Eliminated:

T cells that fail to bind to self MHC

Nonreactivity

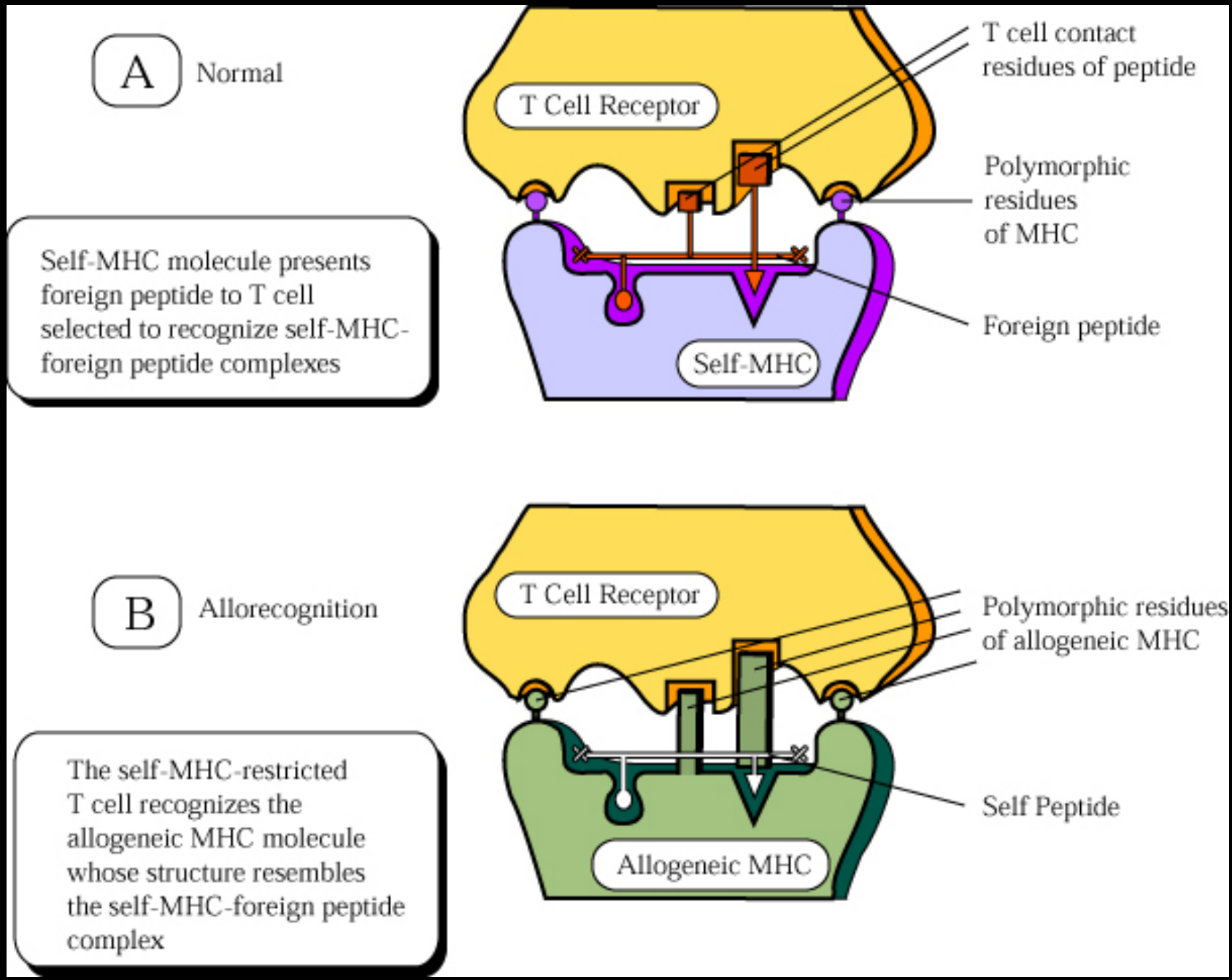
T cells that bind too avidly to self +self peptides

Self reactivity

Retained:

T cells that recognize self-MHC + foreign peptide

Foreign peptide reactivity


A
Normal
Self-MHC molecule presents foreign peptide to T cell selected to recognize self-MHC-foreign peptide complexes
T Cell Receptor
T cell contact residues of peptide
Polymorphic residues of MHC
Foreign peptide
Self-MHC
B
Allorecognition
The self-MHC-restricted T cell recognizes the allogeneic MHC molecule whose structure resembles the self-MHC-foreign peptide complex
T Cell Receptor
Polymorphic residues of allogeneic MHC
Self Peptide
Allogeneic MHC

How do the host T cells recognize foreign tissue?

Direct (on graft cells

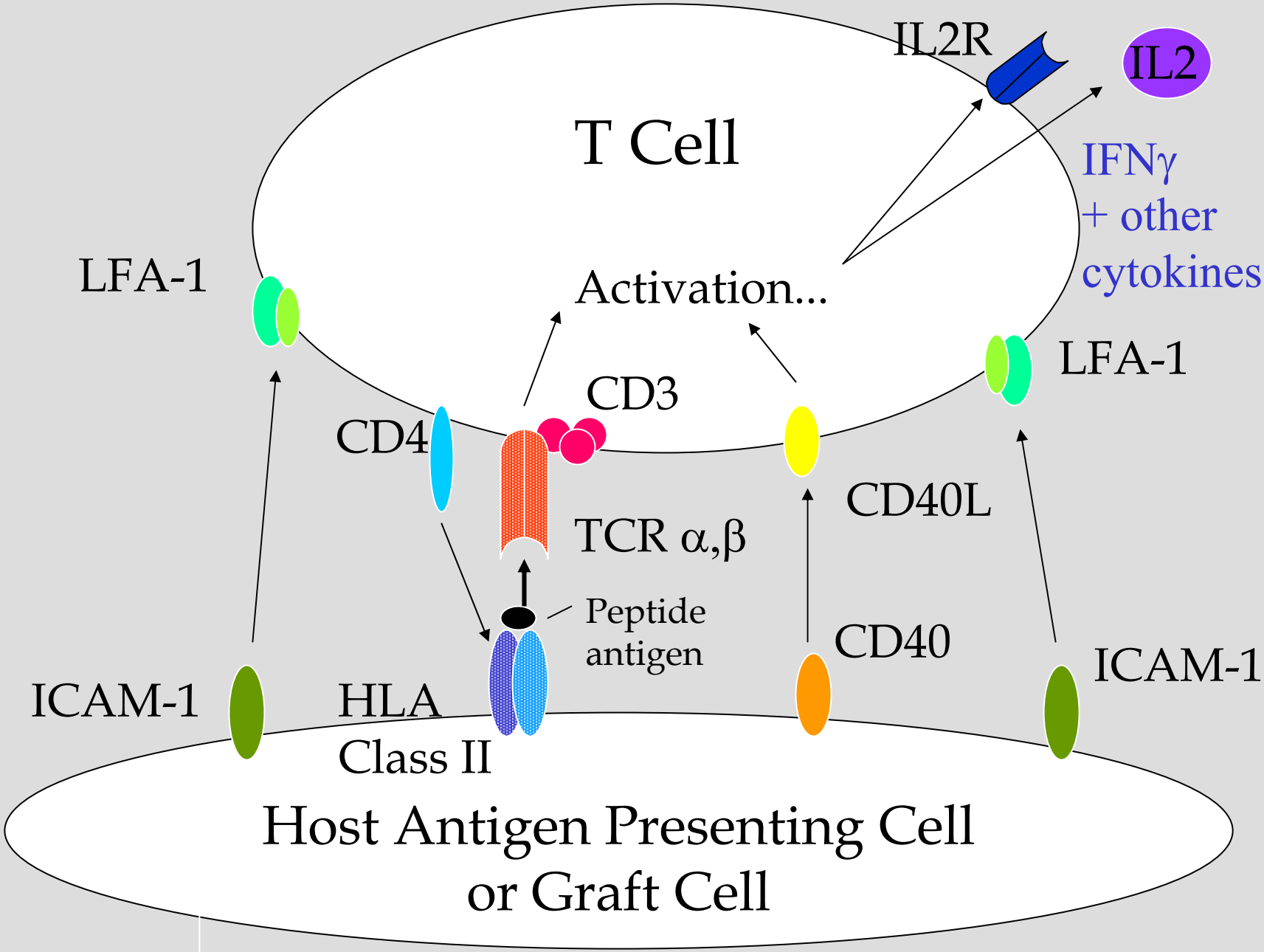
Foreign MHC ± peptide

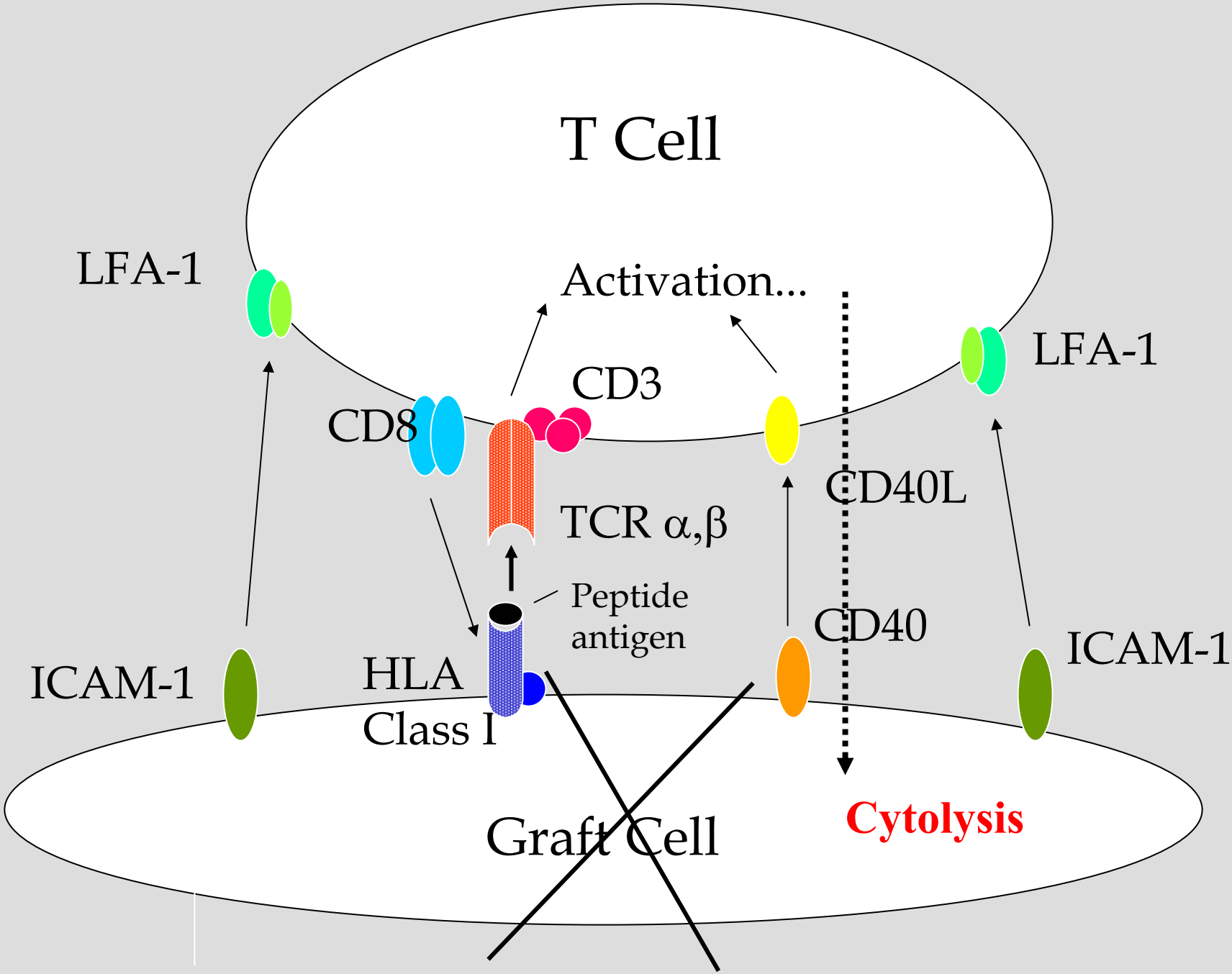
Mimics self MHC + foreign peptide

Indirect (on host antigen presenting cells)

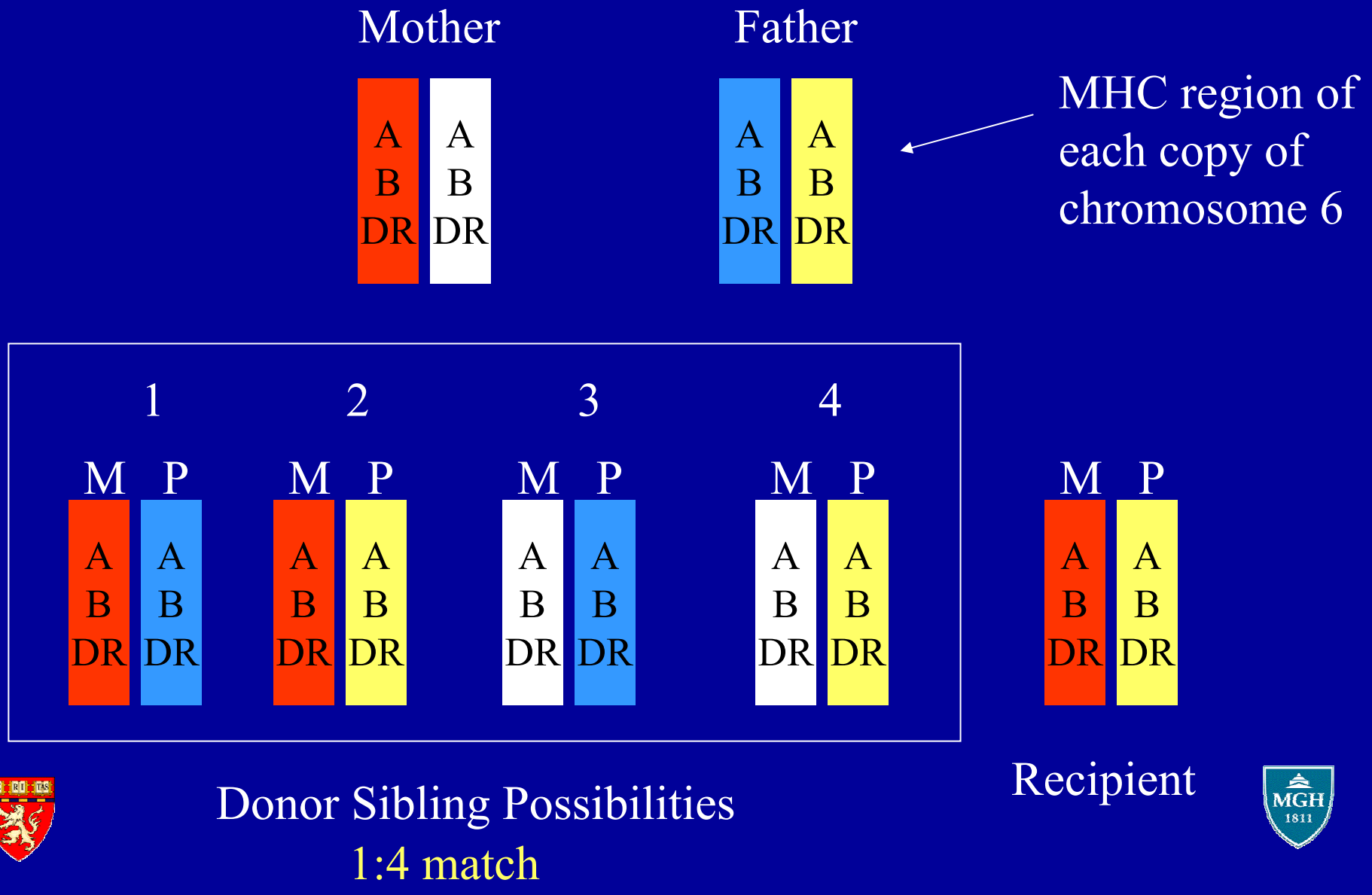
Self MHC + Foreign peptides (e.g. HLA)

The graft looks like a pathogen to the T cell.


IL2R
IL2
T Cell
IFNγ
+ other
cytokines
LFA-1
Activation...
LFA-1
CD3
CD4
CD40L
TCR α,β
Peptide
antigen
CD40
ICAM-1
ICAM-1
HLA
Class II
Host Antigen Presenting Cell
or Graft Cell

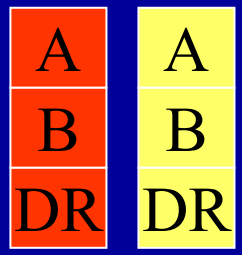

T Cell
LFA-1
Activation...
LFA-1
CD3
CD8
CD40L
TCR α,β
Peptide
antigen
CD40
ICAM-1
HLA
Class I
ICAM-1
Graft Cell
Cytolysis

Chances for a sibling being HLA-Identical 25%



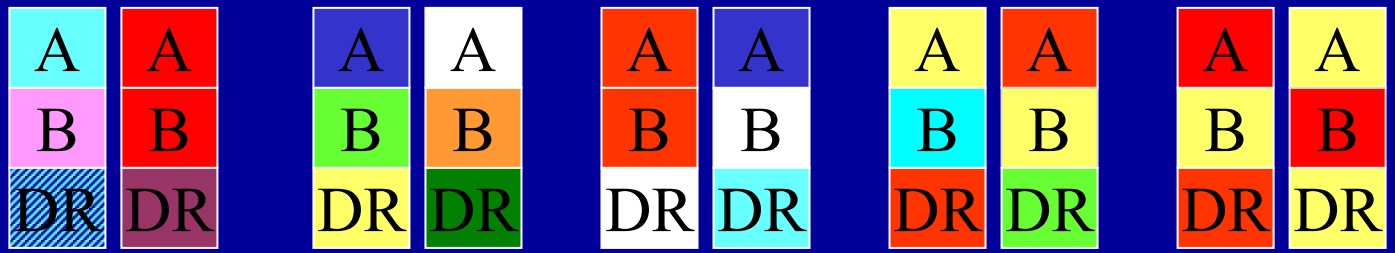
Chances of a Match from unrelated donor

Recipient



Depends on frequency of each allele in population and fineness of distinction

Donors

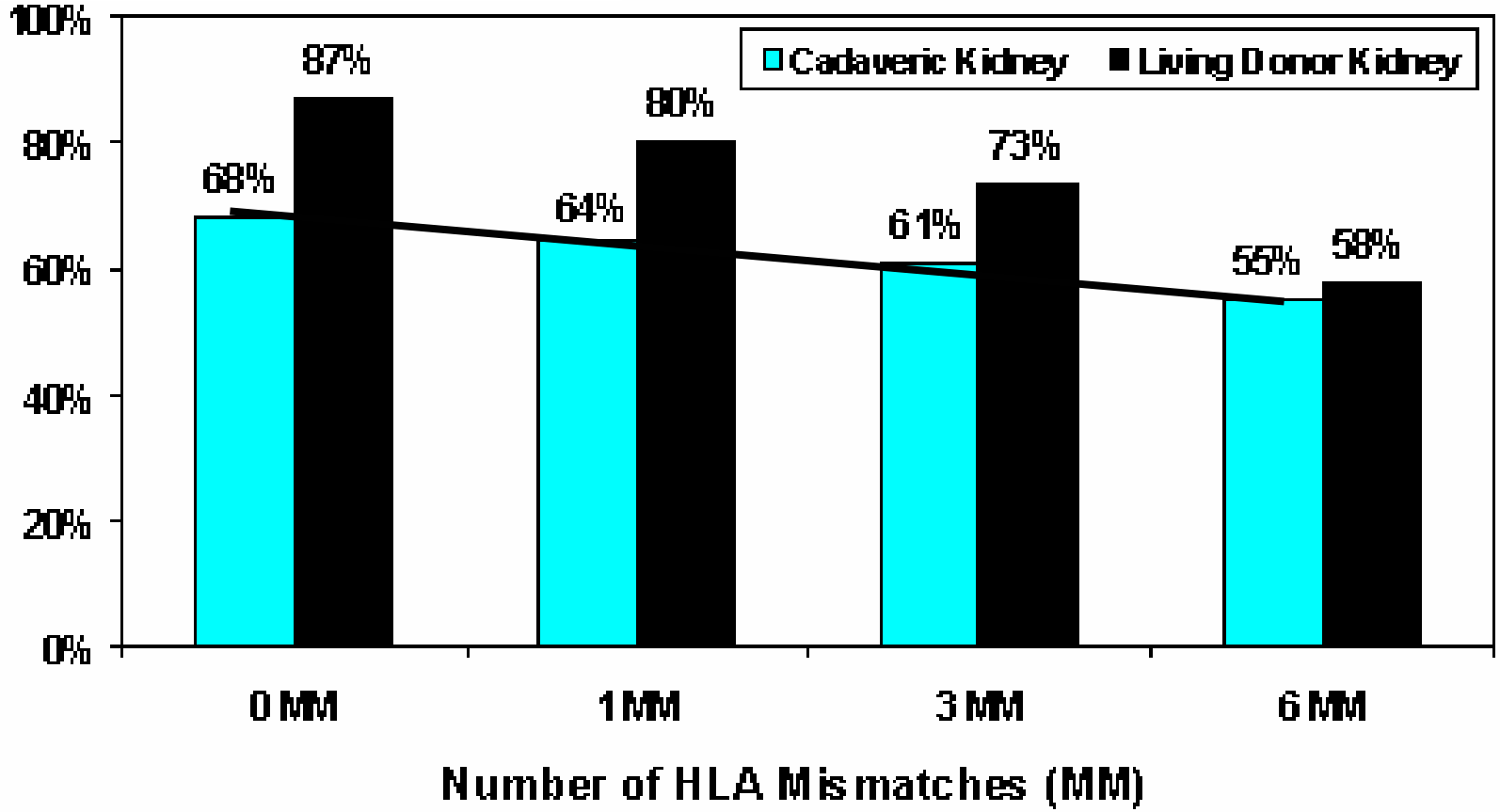


Match 0 1 2 4 6

for 6 antigen match of 10, 20, 20 alleles per locus
~1/16,000,000

HLA Mismatch Reduces Graft Survival

% Grafts Surviving 5 years



Kidneys transplanted in 1994-5

Acute Rejection

Cause: Reactivity to donor alloantigens

HLA Class I, II

Non-HLA antigens

Specific Agents:

T Cells

Antibody

Secondary Mediators:

Macrophages, granulocytes, NK cells
complement, clotting system, chemokines

How to diagnose rejection

Clinical: Loss of function of organ

Lab tests: serum creatinine (kidney), bilirubin (liver)

Imaging: blood flow, arterial diameter (heart)

Pathology: Biopsy

Light microscopy, immunofluorescence, markers of function

Molecular: PCR/proteomics markers of function

Acute Cellular Rejection (ACR)

PAS Tubulitis CD3

Tx 1460 1297

Tubulitis

Lymphocytes inside the renal tubules

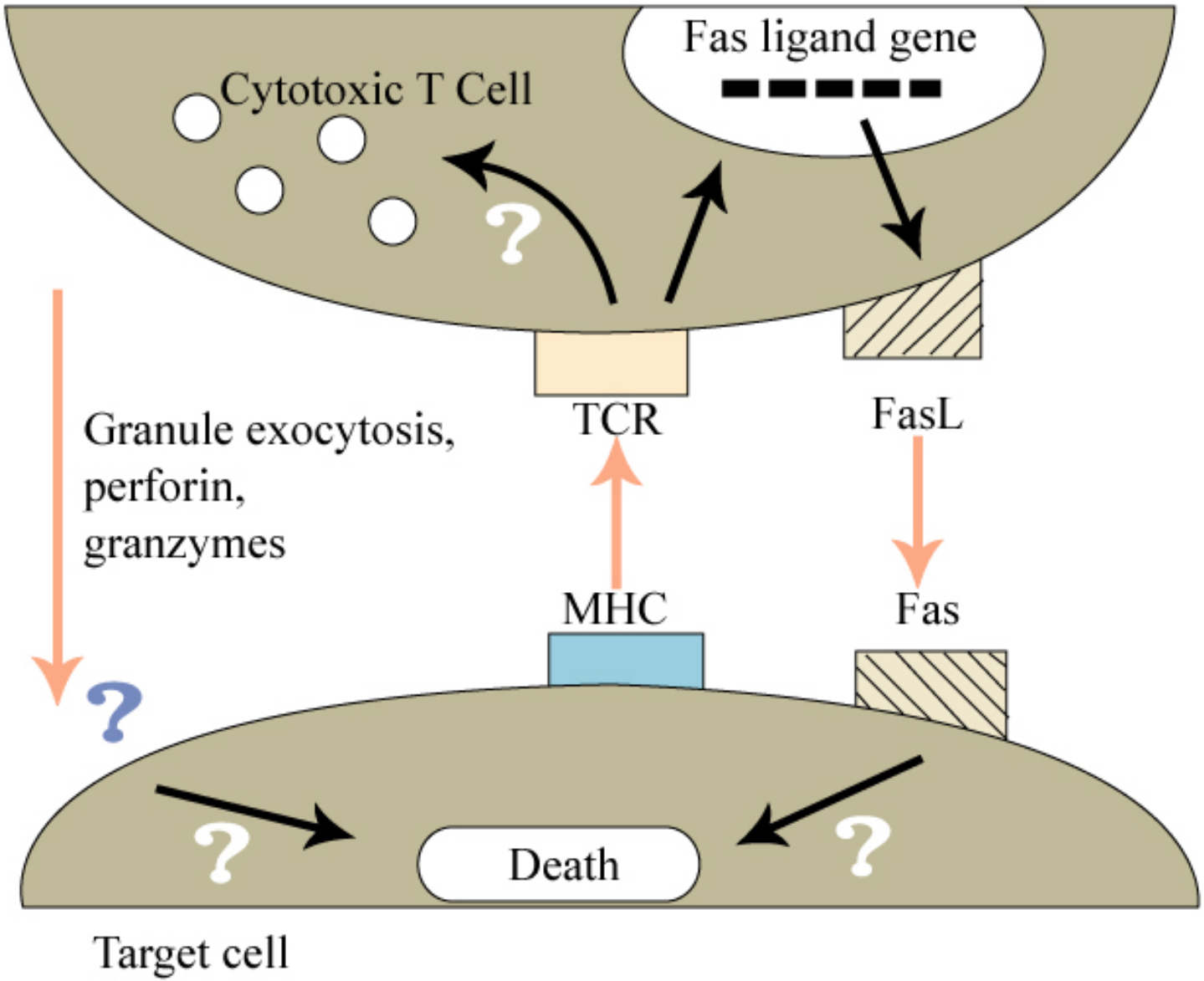
Chemokines (IL-8, RANTES, MCP-1, fractalkines)

Produced by tubular epithelium

in response to IL-1, TNFα

Cytotoxic T cells mostly CD8

Express receptors for E-cadherin


Fas ligand gene
Cytotoxic T Cell
?
TCR
FasL
Granule exocytosis,
perforin,
granzymes
MHC
Fas
?
?
Death
?
Target cell

Cytotoxic T cells in tubules with apoptosis

Please see Meehan SM et al. Cytotoxicity and apoptosis in human renal allografts: identification, distribution, and quantitation of cells with a cytotoxic granule protein GMP-17 (TIA-1) and cells with fragmented nuclear DNA. *Lab Invest.* 1997 May;76(5):639-49.

PCR Test for Rejection
Urine mRNA of cytotoxic granule proteins

	Acute Rejection	Stable
Perforin	1.4±0.3*	-0.6±0.2 p<.001
Granzyme	1.2±0.3	-0.9±0.2 p<.001
Cyclophilin	2.3±0.3	2.5±0.1

*fg mRNA/µg RNA ln transform

Li…Suthanthrian NEJM 344:947, 2002

Endarteritis (Type 2 ACR)