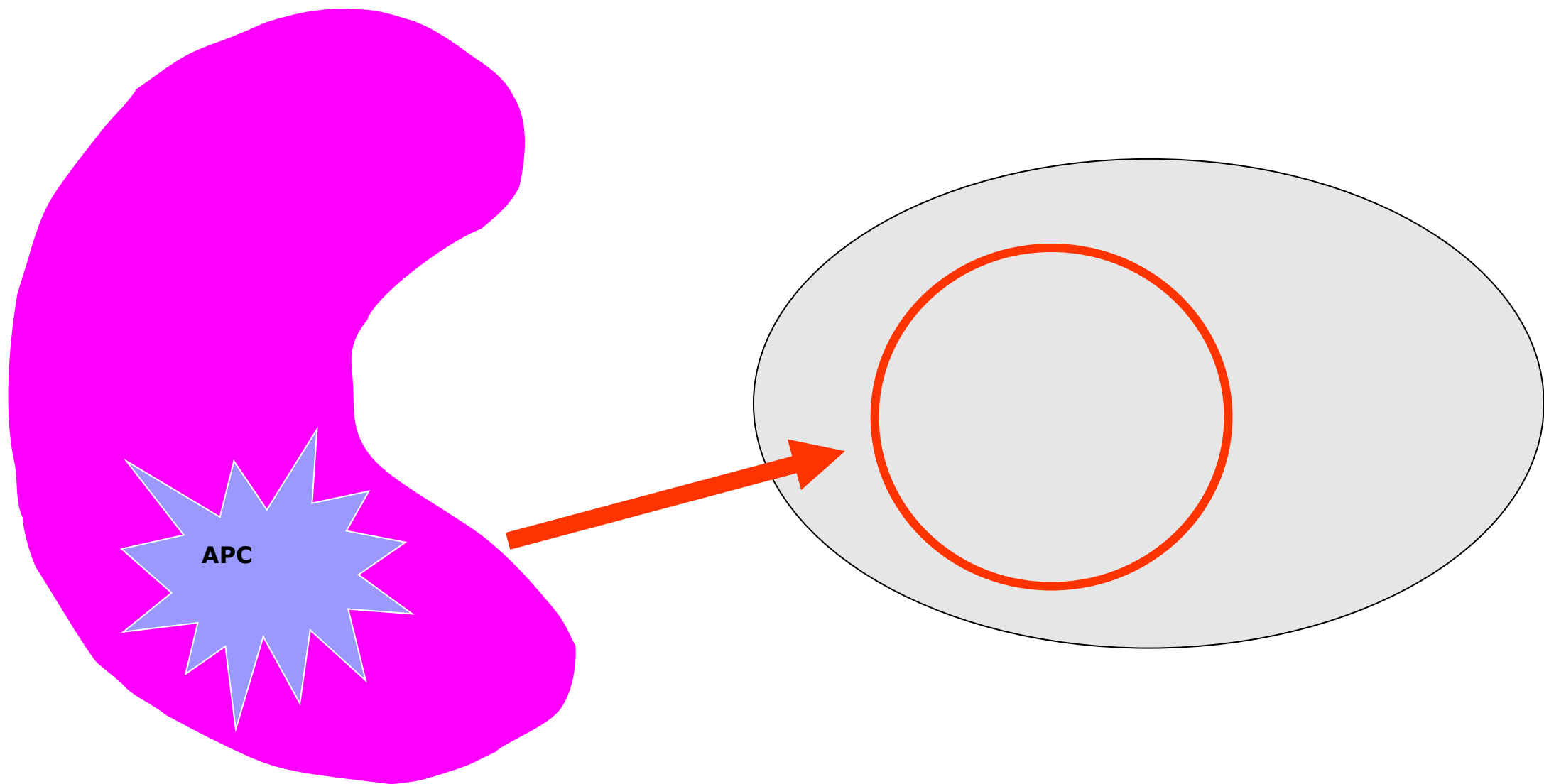


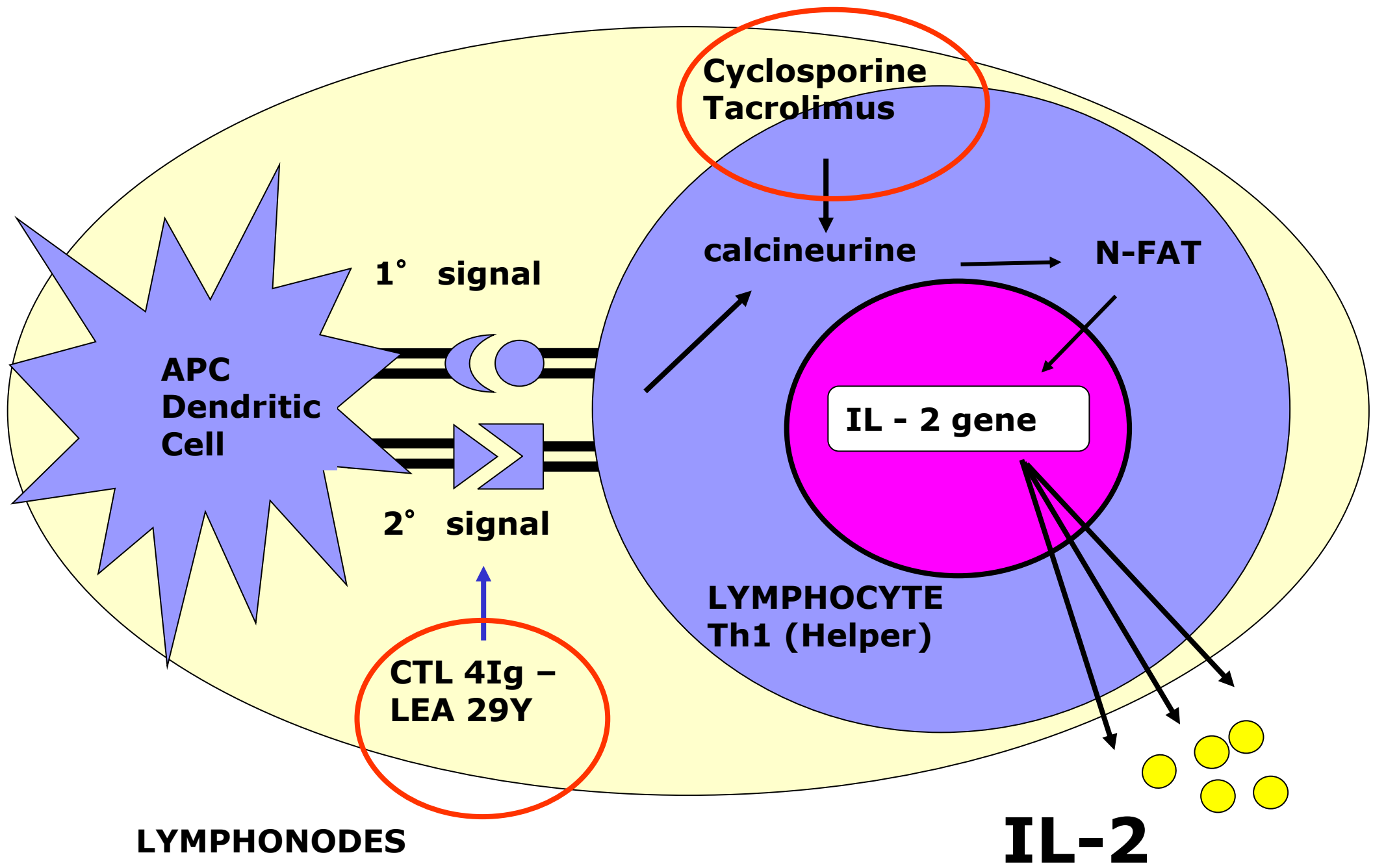
Immunology and renal transplantation

Luca Dello Strologo



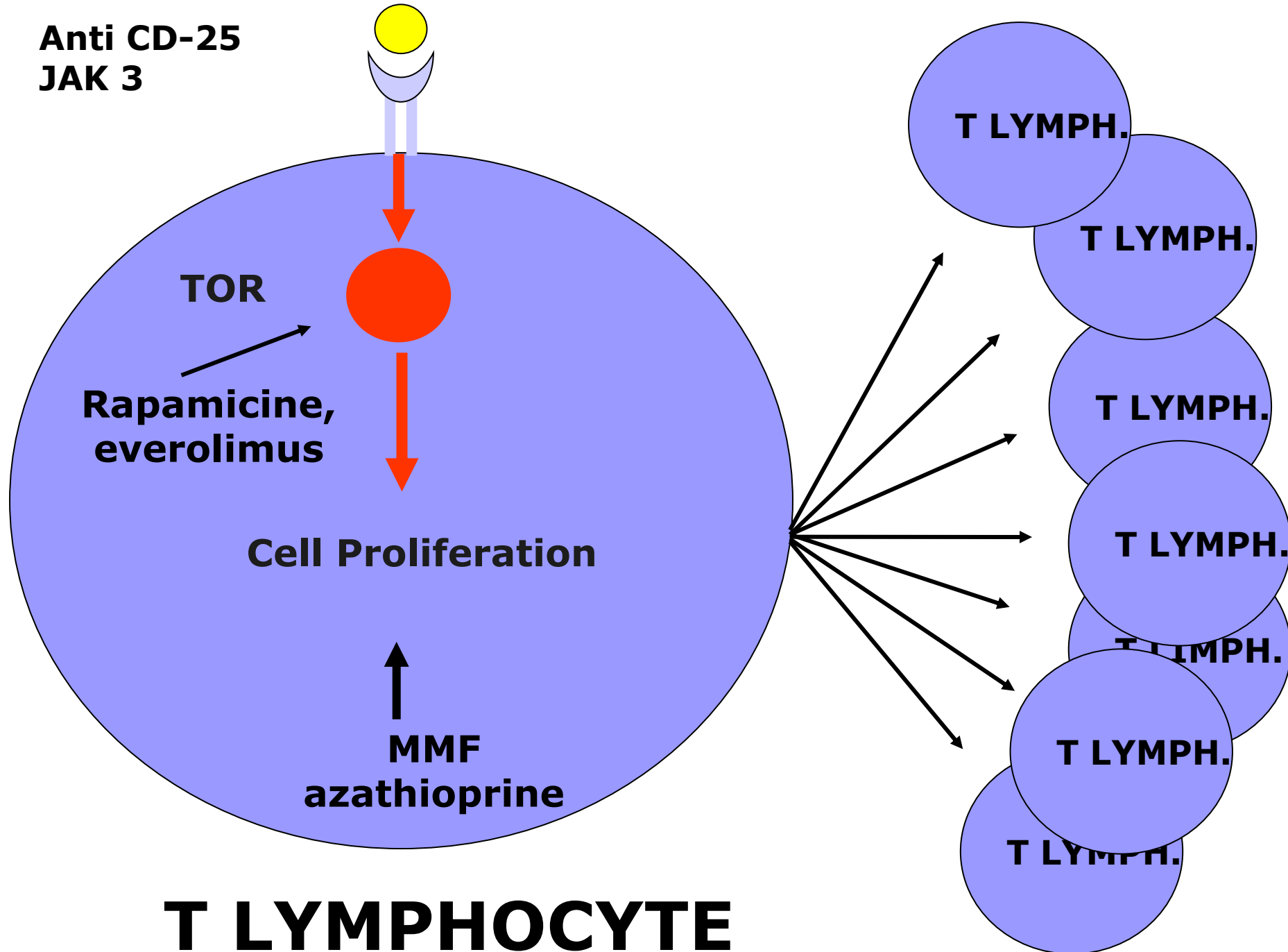
Bambino Gesù
OSPEDALE PEDIATRICO

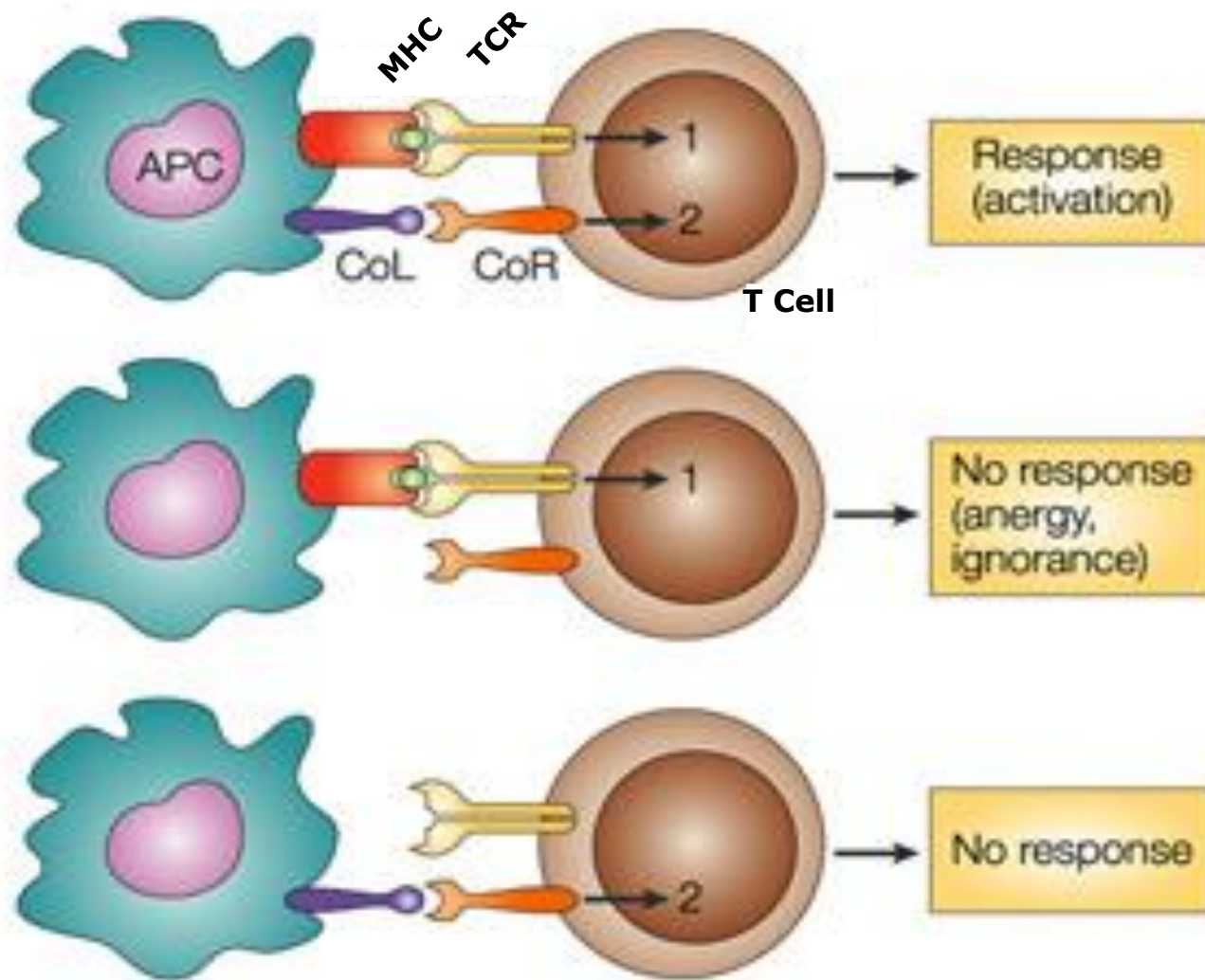




IL-2

**Anti CD-25
JAK 3**





Chen: Nat Rev Immunol. 2004

COSTIMULATION

- APC express CD-80 (B7-1) and CD-86 (B7-2)
- Most T cells express B7 (CD28 and CTLA-4) binding proteins
- Interaction B7-1/B7-2 with CD28 induces IL2 transcription IL2
- Interaction B7-1/B7-2 with CTLA-4 inhibits T cells proliferation (turn off mechanism?)

Antigen Presenting Cell

T Cell

CD28:B7 Superfamily

TNF:TNF-R Superfamily

Signal

-?

B7-1 or B7-2

-?

B7-1 or B7-2

B7-1 or B7-2

HVEM

PD-L1 or PD-L2

ICOS-L

B7-H3

MHC/Peptide

+

CD40

4-1BBL

CD70

OX-40L

CD28

CTLA-4

BTLA

PD-1

ICOS

Unknown Ligand

T Cell Receptor

CD40L

4-1BB

CD27

OX-40

Signal

+

-

-

-

+ /-?

+ /-?

+

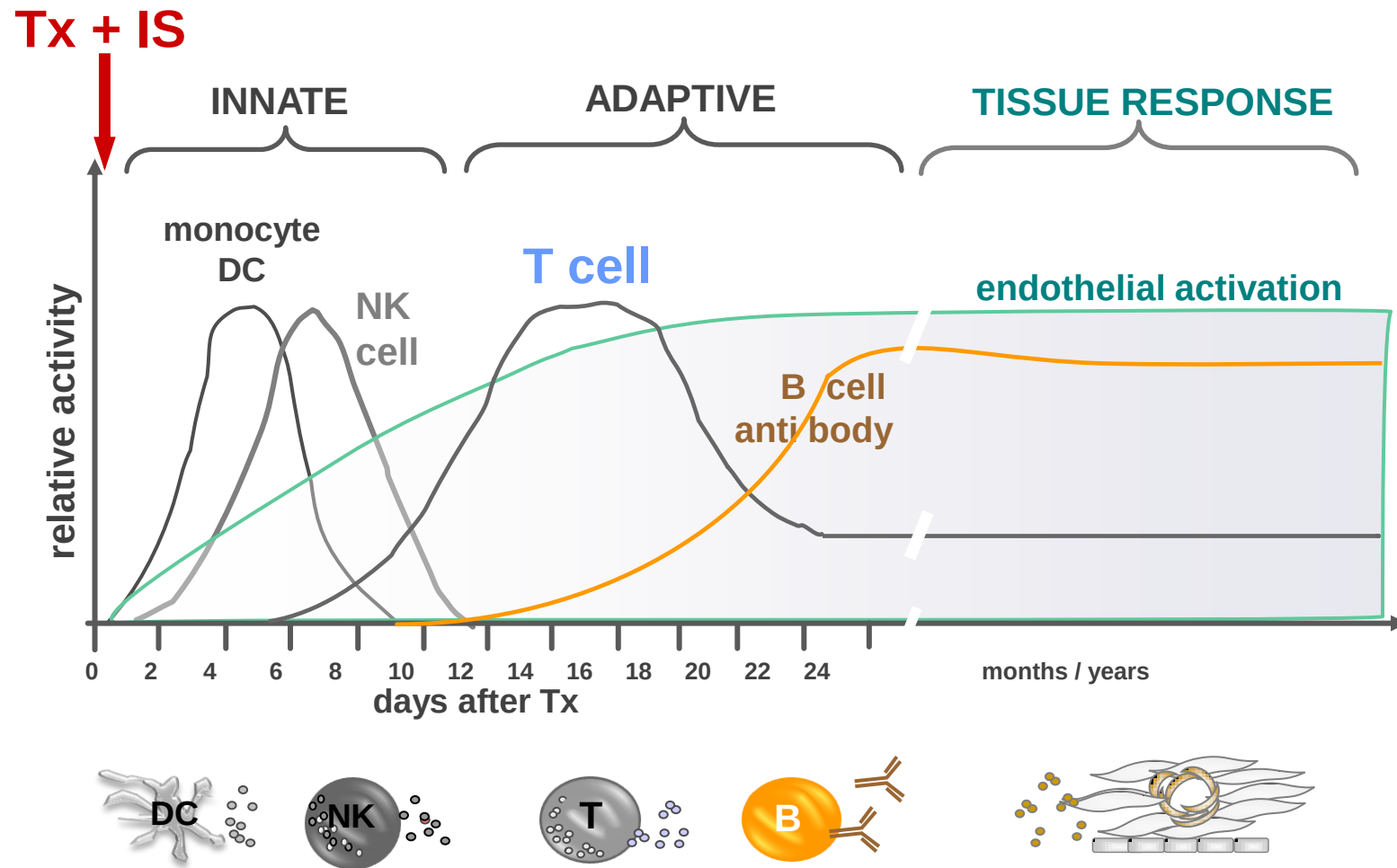
+?

+

+

+

Immune Responses – Sequence of Events in Time & Space



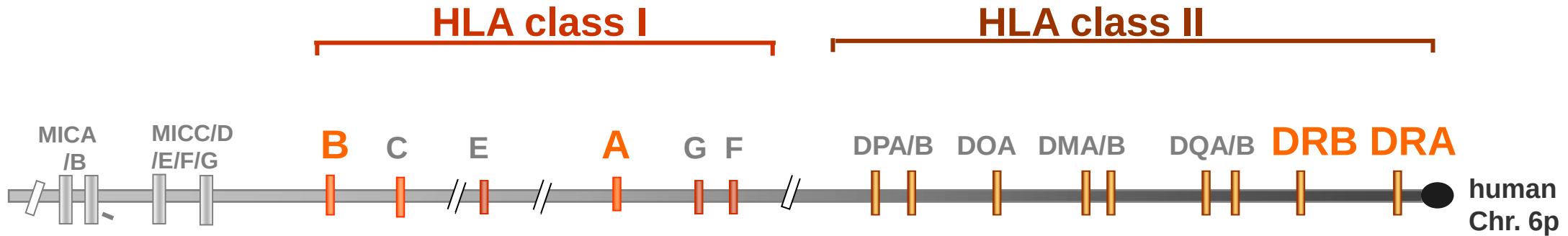
allorecognition

- T Cell ability to react to non-self antigens
- First event for acute/chronic rejection

Major histocompatibility complex

- HLA class I (A, B, C)
- HLA class II (DR, DP, DQ)

„Signal 1”: TCR recognition of HLA class I and class II molecules



HLA matching



HLA-A, B, C, DR, DQ (DP)



HLA-A, B, DR (C, DQ, DP)



NONE



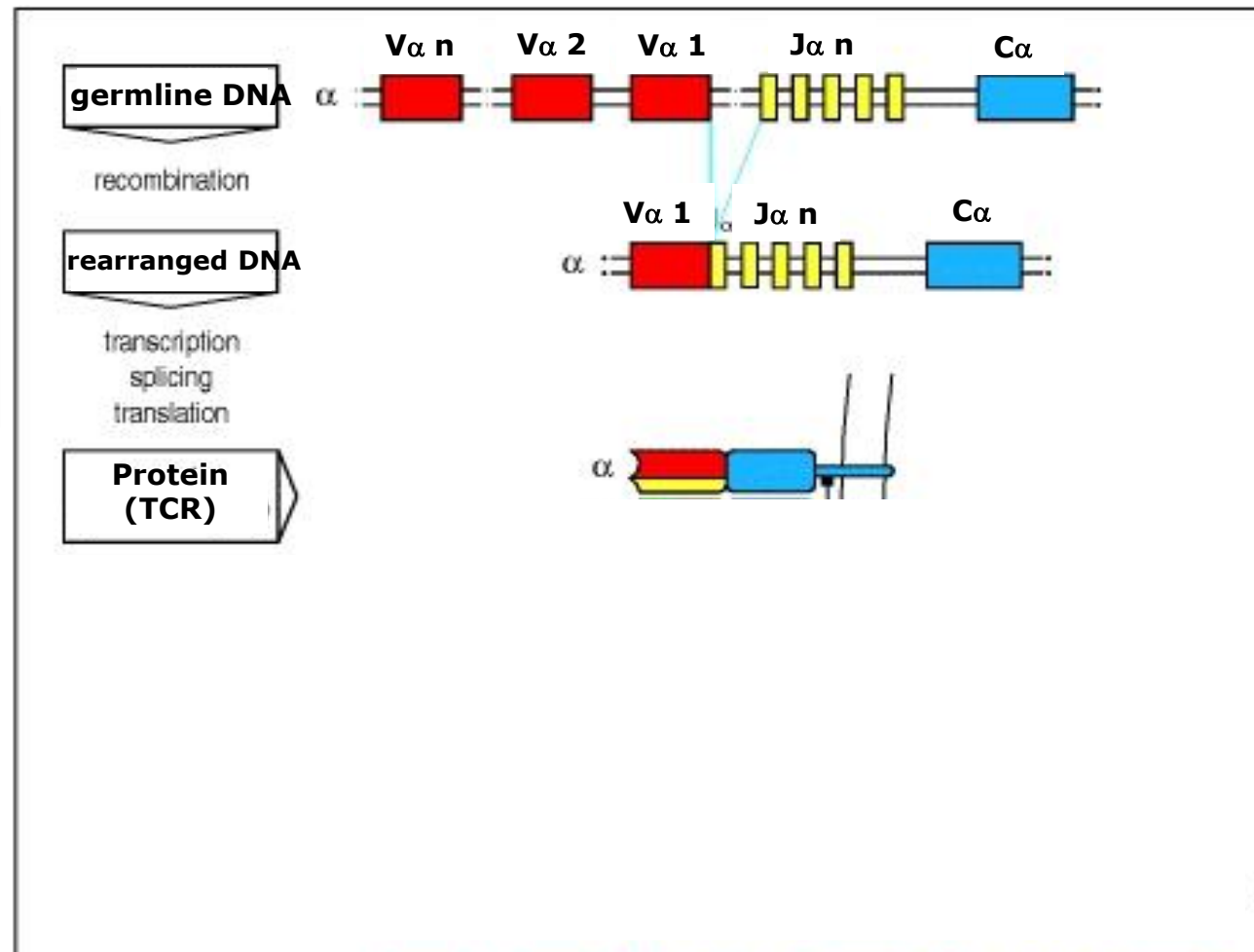
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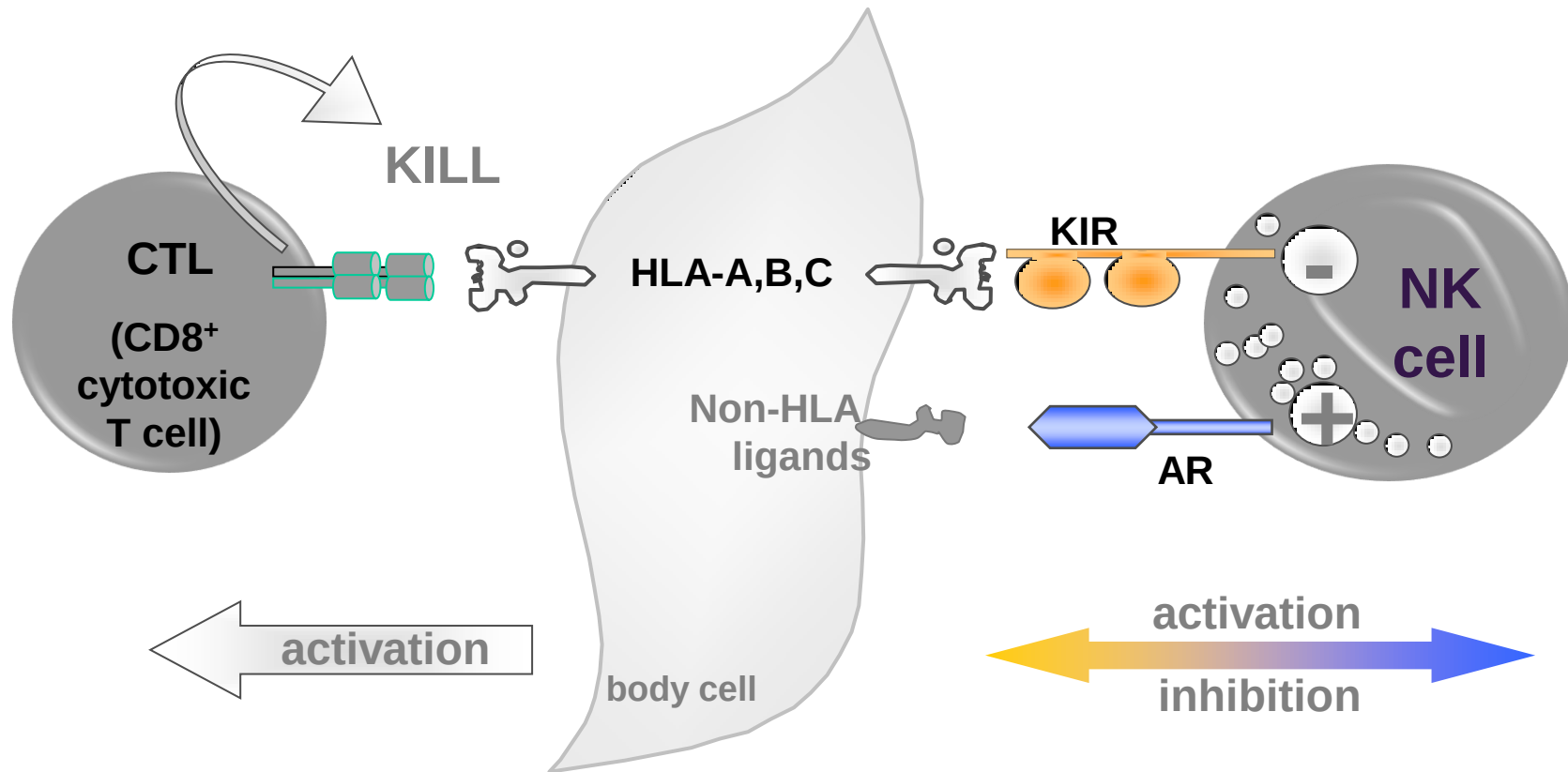
NONE

„Signal 1“: individual T Cell Receptor recognizes HLA molecules

„SPECIFIC“ → UNIQUE receptors



**Cytotoxic T cells recognize HLA Class I Molecules with their TCR
(NK cells by Killer-Immunoglobuline-receptors)**



HLA/peptide restriction:
classical HLA-A, -B, -C + peptides

IR-Ligands:
classical HLA-A, -B, -C molecules
non-classical HLA-E, -G molecules

COMING TO TRANSPLANTATION: ALLOCATION POLICY

MATCHING

- How many shared antigens?

- Donor

– HLA A 1 - 3 B 7 - 56 DR 7 - 13

- Recipient

– HLA A 1 - 3 B 7 - 35 DR 5 - 7

2 Matches in A, 1 in B and 1 in DR

MISMATCHING

- How many different antigens?

Homozygosis

- Donor
 - HLA A 1 - blank B 7 - 56 DR 7 - blank
- Recipient
 - HLA A 1 - 3 B 7 - 35 DR 5 - 7

1 Match in A – 1 in B and 1 in DR

0 Mismatch in A, 1 in B and 0 in DR

Note

- HLA antigens have the so called CREG (cross reactive antigen group) that must be considered

HLA A, B, and DR Matching Antigen Equivalences

PATIENT A LOCUS ANTIGEN	EQUIVALENT DONOR ANTIGEN(S)	PATIENT B LOCUS ANTIGEN	EQUIVALENT DONOR ANTIGEN(S)	PATIENT DR LOCUS ANTIGEN	EQUIVALENT DONOR ANTIGEN(S)
1	1	5	5,52,53,78	1	1,103
2	2,203,210	7	7,703	2	2,15,16
3	3	8	8	3	3,17,18
9	9	12	12	4	4
10	10,26,34,66,*6601,*6602	13	13	5	5,11,12
11	11	14	14,64,65	6	6,13,14,1403,1404
19	19,74	15	15,75,76,77,*1304	7	7
23	23	16	16,*3905	8	8
24	24,2403	17	17,58	9	9
25	25	18	18	10	10
26	26,*6601	21	21,4005,*1304	11	11,5
28	28,68,69	22	22,54,*8201	12	12,5
29	29	27	27	13	13,6
30	30	35	35	14	14,6,1403,1404
31	31	37	37	15	15,2
32	32	38	38	16	16,2,15
33	33	39	39,3901,3902,*3905	17	17,3,18
34	34,*6602	40	40,61,81	18	18,3,17
36	36	41	41	103	103,1
43	43	42	42	1403	1403,14,6
66	66,*6601,*6602,10	44	44	1404	1404,14,6
68	68,28	45	45	** 99	(No equivalent)
69	69,28	46	46		
74	74,19	47	47		
80	80	48	48		
203	203,2	49	49		
210	210,2	50	50,4005		
2403	2403,24	51	51,5102,5103		
*6601	*6601,66,10,26	52	52,5		
*6602	*6602,66,10,34	53	53,5,5102		
** 99	(No equivalent)	54	54,22		
		55	55		
		56	56		
		57	57		
		58	58		
		59	59		
		60	60		
		61	61,40		
		62	62		
		63	63		
		64	64,14		
		65	65,14		
		67	67		
		70	70,71,72		
		71	71,70		
		72	72,70		
		73	73		
		75	75,15		
		76	76,15		
		77	77,15		
		78	78,5		
		81	81,7,40,60,61,48		
		703	703,7		
		*0804	*0804,8		
		*1304	*1304,15,21,49,50		
		2708	2708,27,7		
		3901	3901,39		
		3902	3902,39		
		*3905	*3905,16,39		
		4005	4005,21,50		
		5102	5102,51,53		
		5103	5103,51		
		*8201	*8201,45,22,54,55,56		
		** 99	(No equivalent)		

Antigen Equivalences

- Examples of how “Antigen Equivalences” works:
- If patient has B60: Donors with B60 are considered not mismatched.
- If patient has B61: Donors with B61 or B40 are considered not mismatched.

Example of how “Unacceptable Antigen Equivalences” works:

- If a patient has B40 listed as an “unacceptable antigen”: Donors typed as B40, B60, or B61 are considered unacceptable.
- Therefore, if a patient has antibodies to all splits of a broad antigen, consider broad antigen as well as the splits as unacceptable antigens

HLA A, B, C, DR, and DQ Unacceptable Antigen Equivalences					
PATIENT'S UNACCEPT- ABLE A LOCUS ANTIGEN	DONOR EQUIVALENT ANTIGEN(S)	PATIENT'S UNACCEPT- ABLE B LOCUS ANTIGEN	DONOR EQUIVALENT ANTIGEN(S)	PATIENT'S UNACCEPT- ABLE C LOCUS ANTIGEN	DONOR EQUIVALENT ANTIGEN(S)
1	1	5	5,51,5102,5103,52,78	1	1
2	2,203,210	7	7,703,2708	2	2
3	3	8	8,*0804	3	3,9,10
9	9,23,24,2403	12	12,44,45	4	4
10	10,25,26,34,66,*6601,*6602	13	13	5	5
11	11	14	14,64,65	6	6
19	19,29,30,31,32,33,74	15	15,62,63,75,76,77	7	7
23	23	16	16,38,39	8	8
24	24,2403	17	17,57,58	9	9
25	25	18	18	10	10
26	26	21	21,49,50,4005	*12	*12
28	28,68,69	22	22,54,55,56	*13	*13
29	29	27	27,2708	*14	*14
30	30	35	35	*15	*15
31	31	37	37	*16	*16
32	32	38	38	*17	*17
33	33	39	39,3901,3902,*3905	*18	*18
34	34	40	40,60,61		
36	36	41	41		
43	43	42	42		
66	66,*6601,*6602	44	44		
68	68	45	45		
69	69	46	46		
74	74	47	47		
80	80	48	48		
203	203	49	49		
210	210	50	50,4005		
2403	2403	51	51,5102,5103		
*6601	*6601	52	52		
*6602	*6602	53	53,5102		
		54	54		
		55	55		
		56	56		
		57	57		
		58	58		
		59	59,*0804		
		60	60		
		61	61		
		62	62		
		63	63		
		64	64		
		65	65		
		67	67		
		70	70,71,72		
		71	71		
		72	72		
		73	73		
		75	75		
		76	76		
		77	77		
		78	78		
		81	81		
		703	703		
		*0804	*0804		
		*1304	*1304		
		2708	2708		
		3901	3901		
		3902	3902		
		*3905	*3905		
		4005	4005		
		5102	5102		
		5103	5103		
		*8201	*8201		
		Bw4	Bw4		
		Bw6	Bw6		
HLA A, B, C, DR, and DQ Unacceptable Antigen Equivalences (continued)					
PATIENT'S UNACCEPT- ABLE DR LOCUS ANTIGEN	DONOR EQUIVALENT ANTIGEN(S)	PATIENT'S UNACCEPT- ABLE DQ LOCUS ANTIGEN	DONOR EQUIVALENT ANTIGEN(S)		
1	1,103	1	1,5,6		

NOT ONLY HLA!

Antibody mediated rejection

- Preformed / *de novo* antibodies
Against class I or II anti HLA antigens
Ab vs Non-HLA antigens:
 - MICA: Major-histocompatibility-complex class I-related chain A antigens
 - AT₁R-AA : Agonistic antibodies against the Angiotensin II type 1 receptor
 - Others (Anti-endotheline type 1 receptor, antiperlecan antibodies,....)

What are MICA?

- MICA = Major-histocompatibility-complex class I–related chain A (MICA) antigens
- are surface glycoproteins with functions related to innate immunity .
- are expressed on endothelial cells, dendritic cells, fibroblasts, epithelial cells, but not on peripheral-blood lymphocytes.
- Therefore, antibodies directed against MICA are not detected with the methods generally used for cross-match.

N Engl J Med 2007;357:1293-300.

Agonistic antibodies against the Angiotensin II type 1 receptor (AT1R-AA)

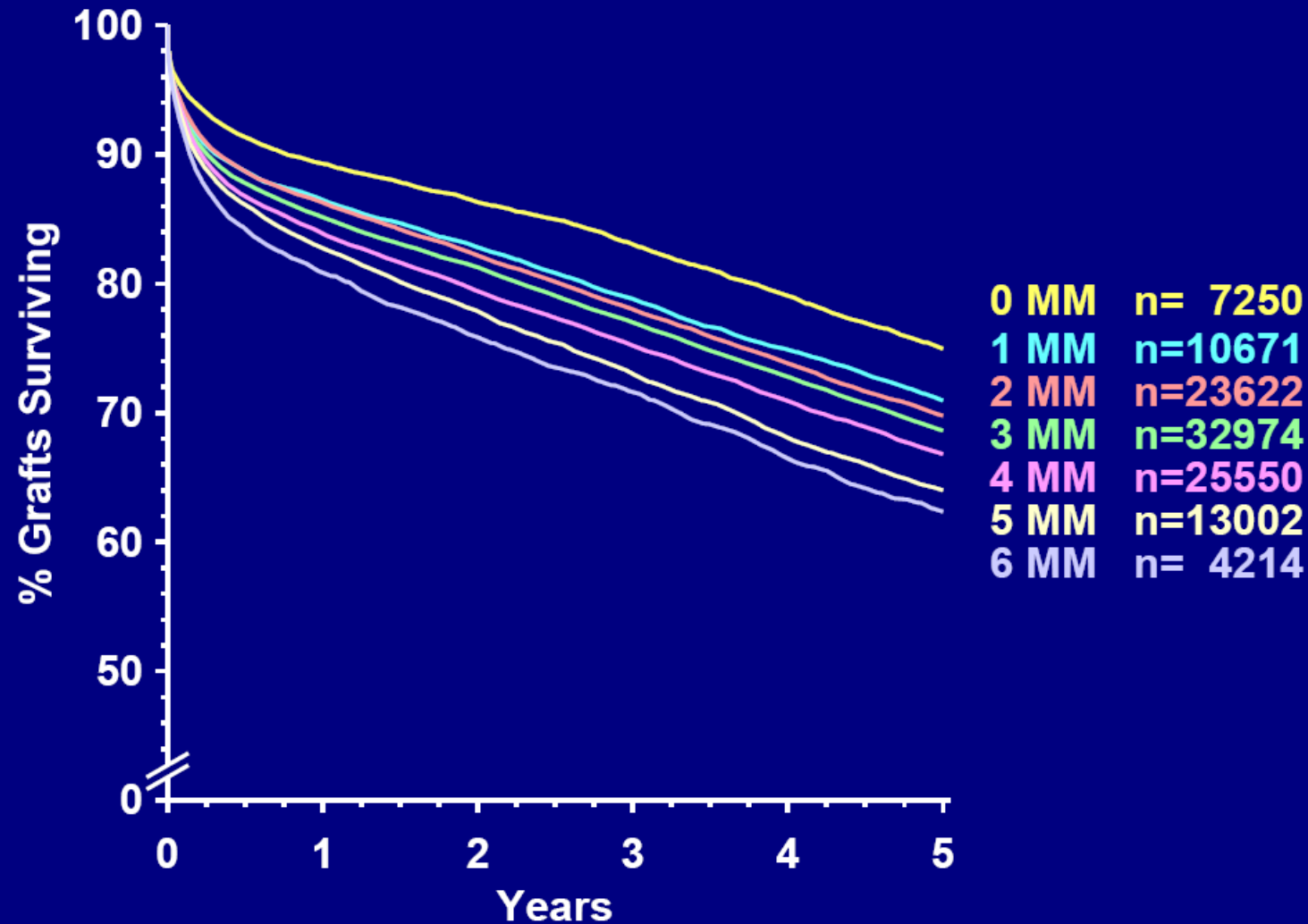
- Classically reported a rejection with severe hypertension
- Hystology: endarteritis, transmural arteritis and/or fibrinoid vascular necrosis (Banff IIb or Banff III rejection)
- Is it a “true-rejection” or an autoimmune phenomenon triggered in the permissive allogeneic and post-ischemic inflammatory enviroment?

Dragun N Engl J Med 2005; 352: 558–69

Do we still need to worry about matching or mismatching with modern immunosuppression?

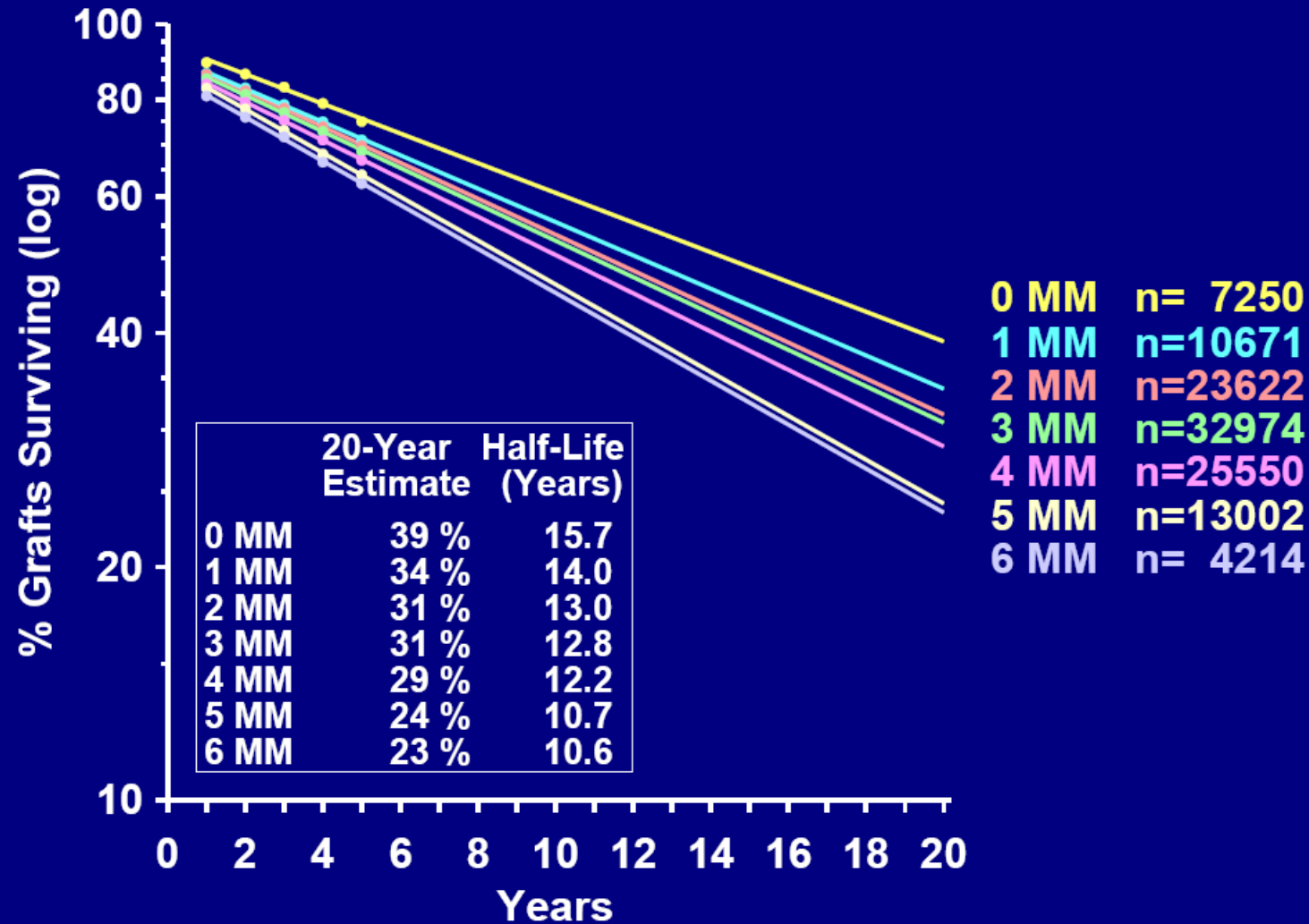
HLA-A+B+DR Mismatches

First Cadaver Kidney Transplants 1985-2003



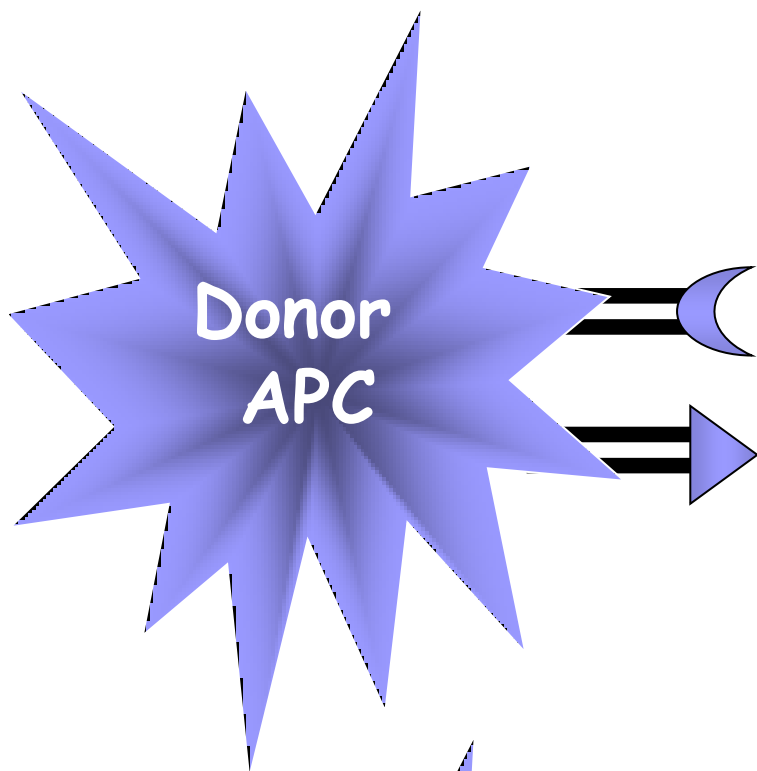
HLA-A+B+DR Mismatches

First Cadaver Kidney Transplants 1985-2003

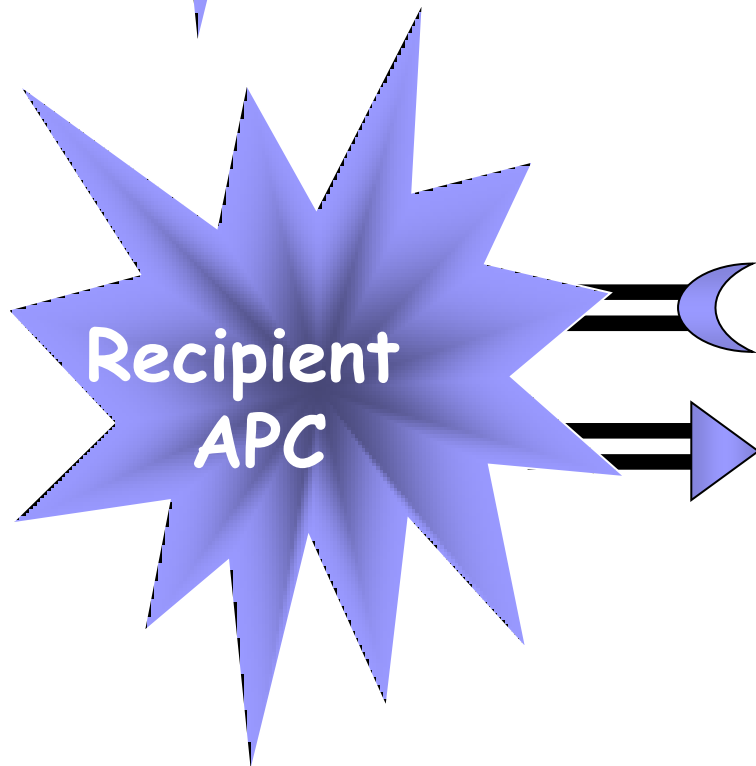
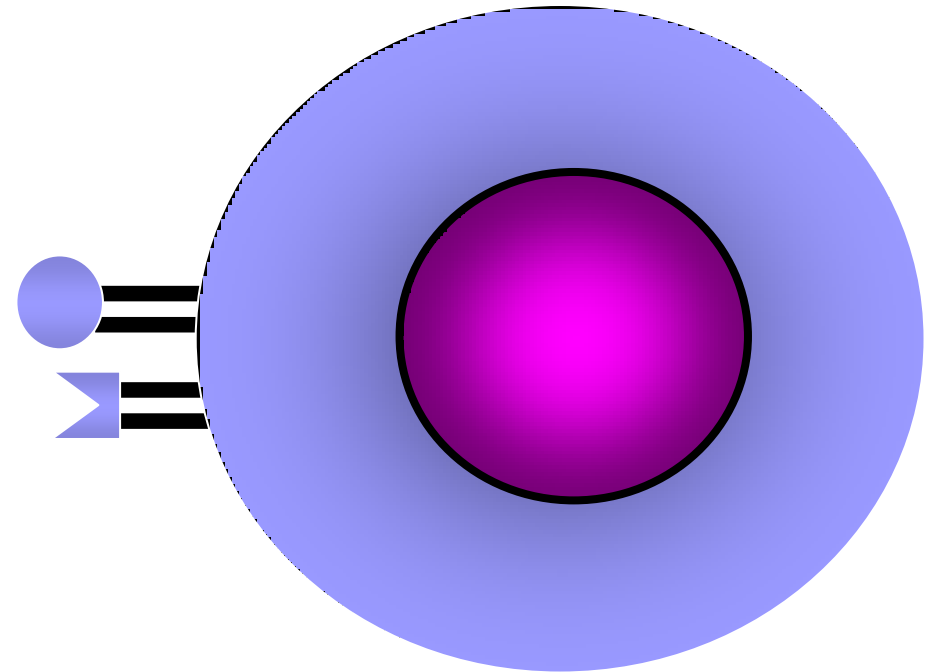


Why induction treatment is different from maintenance treatment?

ALLORECOGNITION MECHANISM



Direct pathway



T -LYMPHOCYTE

Indirect pathway
CD4 T-cell allorecognition

Direct and indirect allorecognition

- direct allorecognition: recipient CD4 T cells recognize intact MHC class II alloantigen. This is present on donor APCs migrating from the graft and on MHC class II-expressing donor parenchymal cells
- indirect allorecognition: donor alloantigen is internalized, processed, and presented as peptides in the context of recipient MHC class II by recipient APCs to recipient CD4 T cells.

To simplify: direct allorecognition

- Exposition to donor antigens from donor antigen presenting cells (APC) → many *non-self* antigens → **Acute rejection**
- Donor APC are dendritic cells which soon go in apoptosis
- It is therefore an early phase recognition

To simplify: Indirect allorecognition

- Exposition to donor antigens from recipient antigen presenting cells (APC) → less *non-self* antigens → **less acute response**
- It may occur anytime after transplantation