Immunology of transplant

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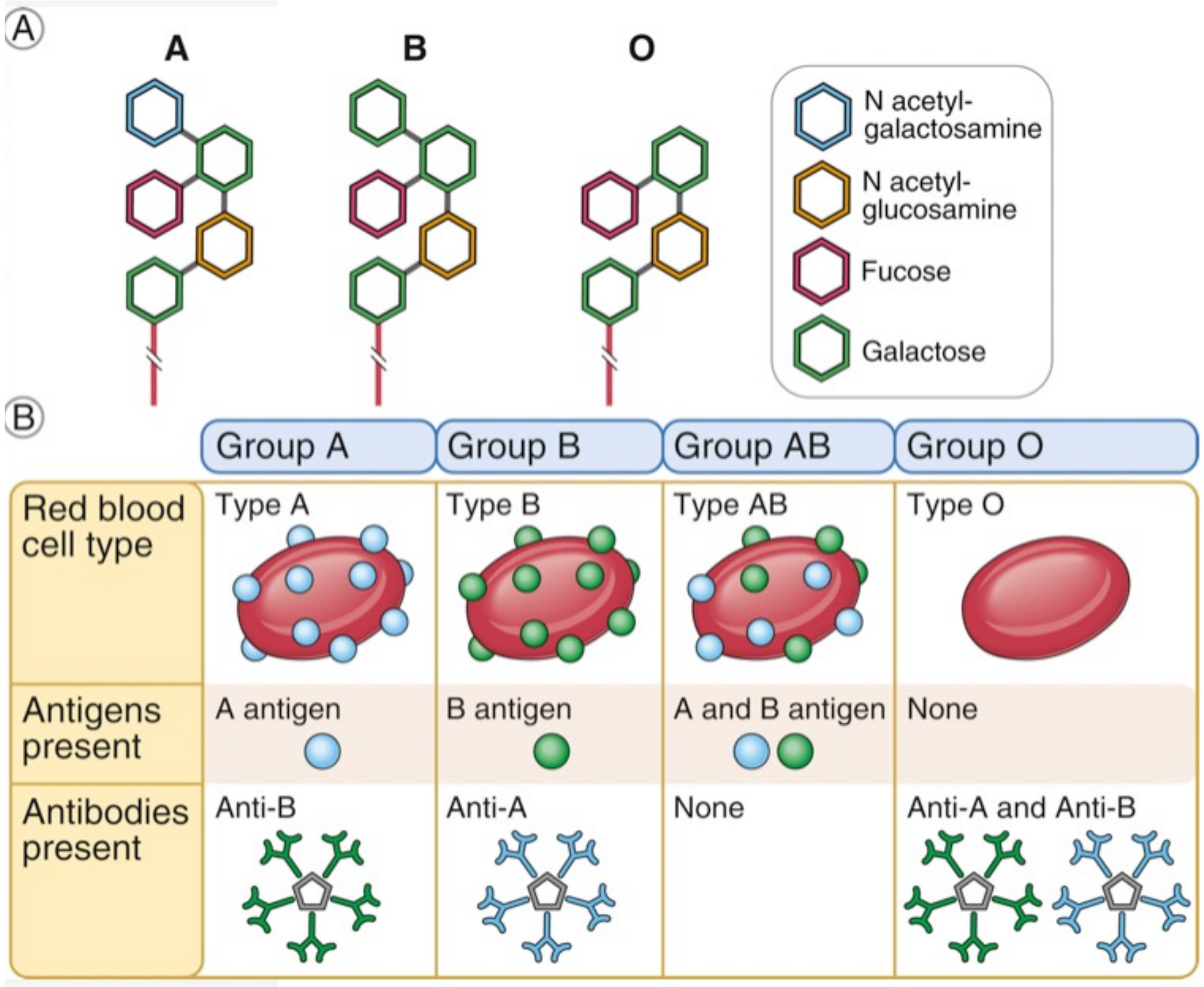
After today's lecture, you should know:

- What are the antigens in tissue transplants that are recognized as foreign by the immune system?
- How does the immune system recognize and react to transplants?
- How can immune responses to grafts be manipulated to inhibit graft rejection?

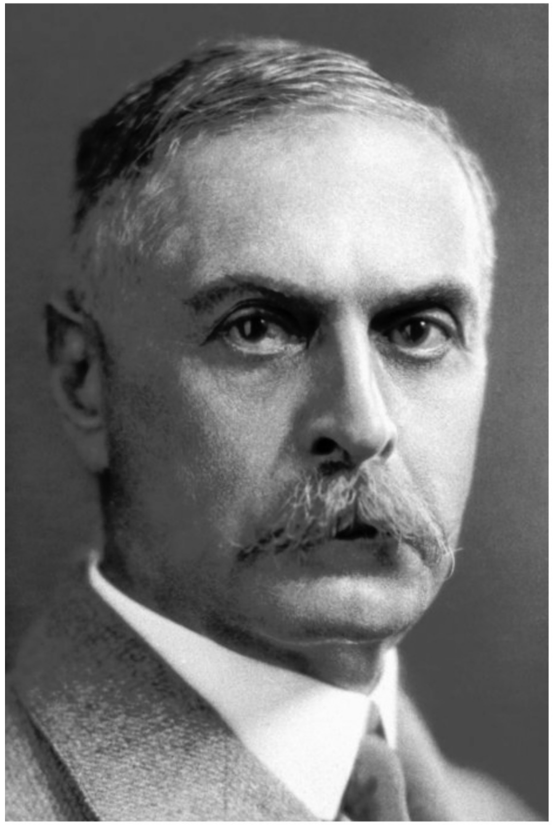
First successful solid organ transplant

1954, Hartwell Harrison and Joseph Murray (Boston, U.S.A.). The First Successful Kidney Transplantation, 1954. Joel Babb (1947–) Oil on canvas, 1996, Harvard Medical Library in the Francis A. Countway Library of Medicine.

Blood groups

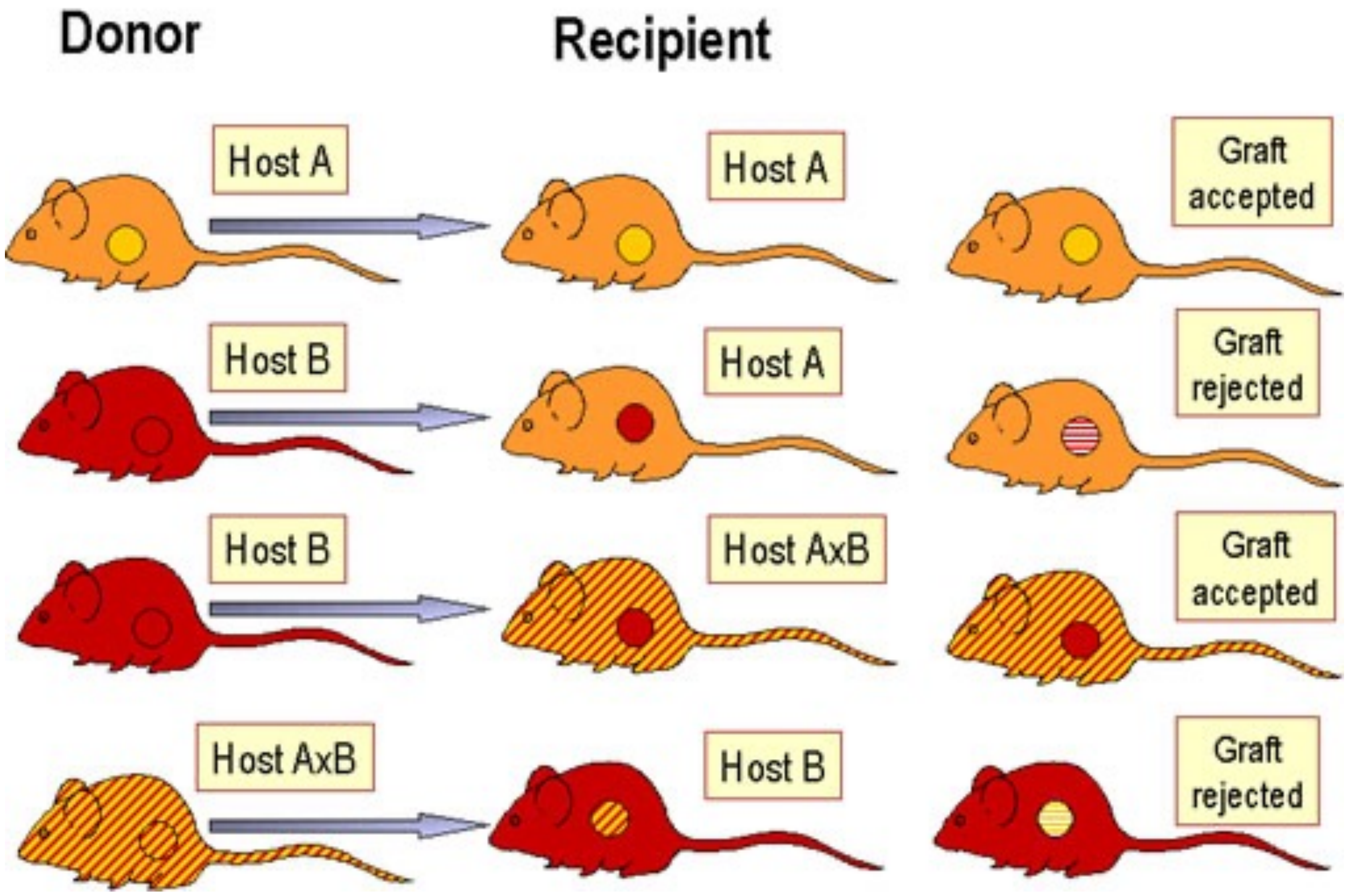


Nobel Prize in Physiology or Medicine 1930

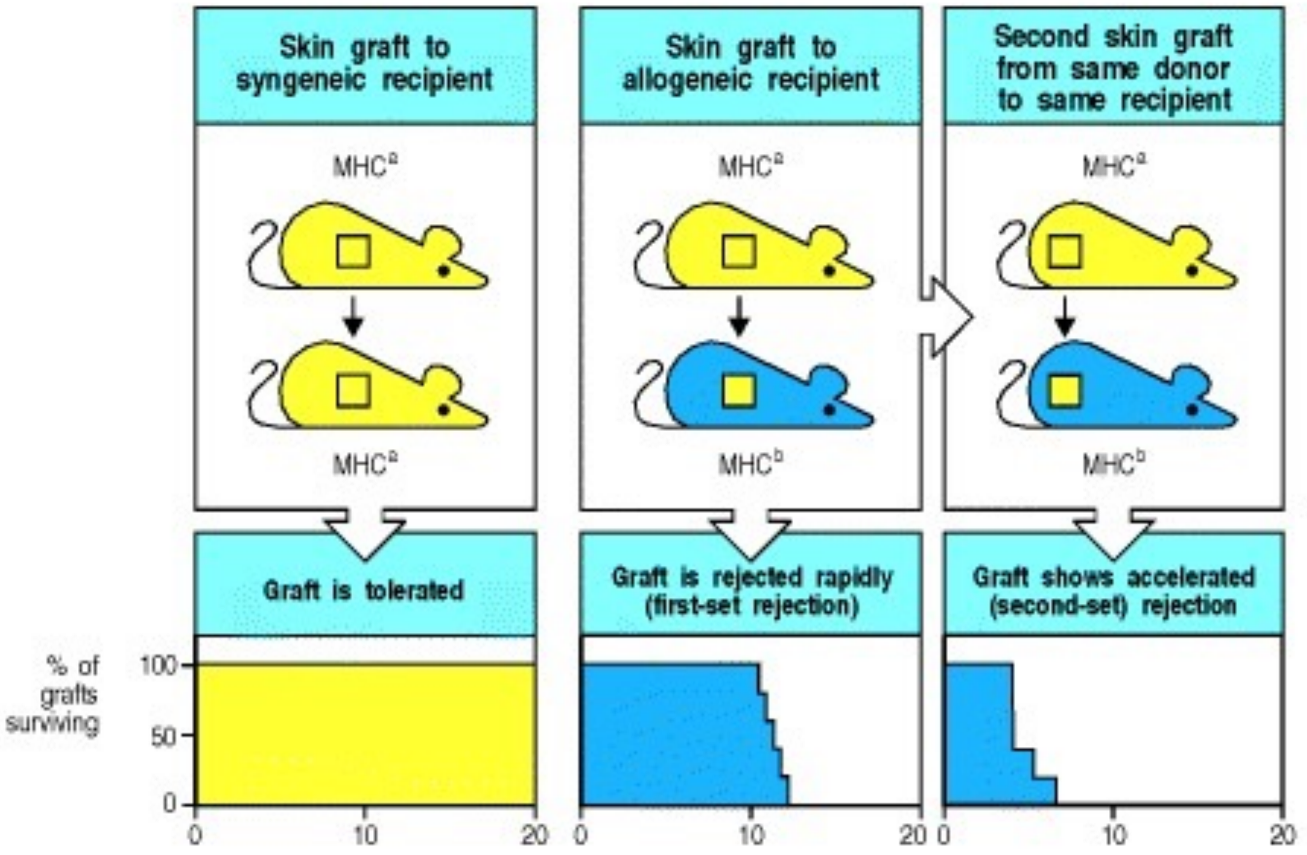


Karl Landsteiner

The laws of transplantation

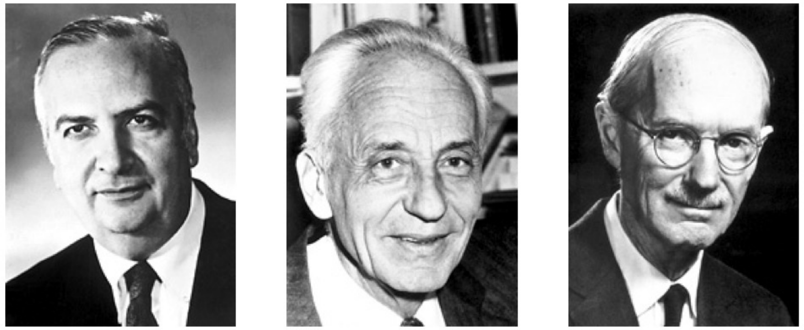


The laws of transplantation



Immunobiology: The Immune System in Health and Disease. 5th edition.
Janeway CA Jr, Travers P, Walport M, et al.
New York: Garland Science; 2001.

The Nobel Prize in Physiology or Medicine 1980



Baruj Benacerraf
Prize share: 1/3

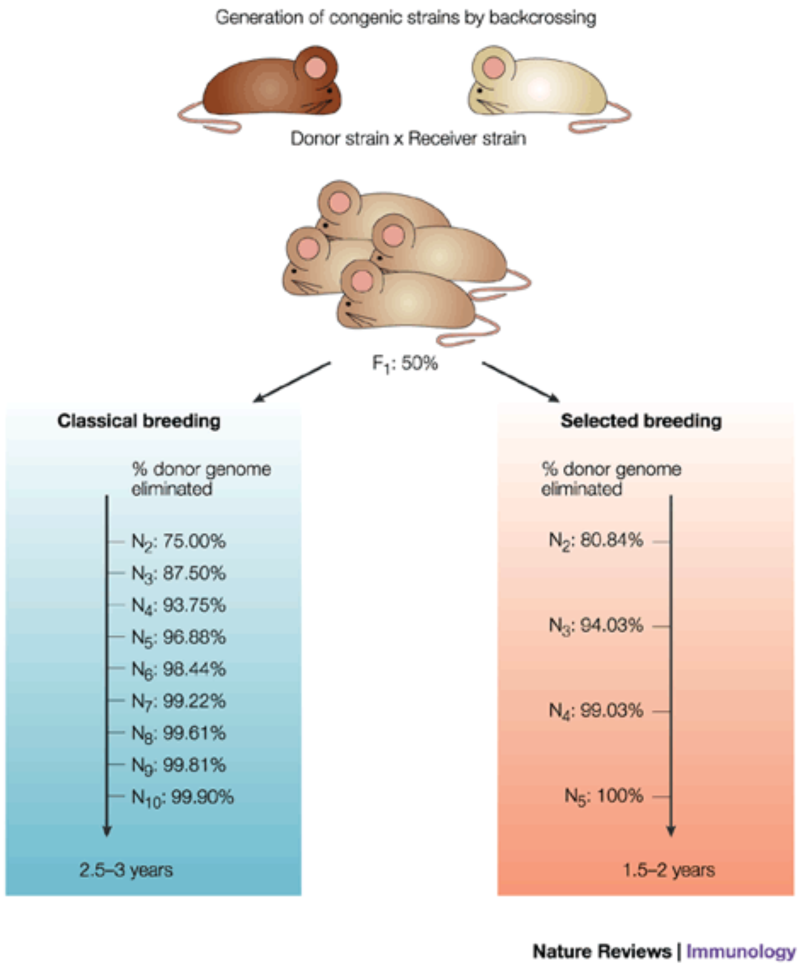
Jean Dausset
Prize share: 1/3

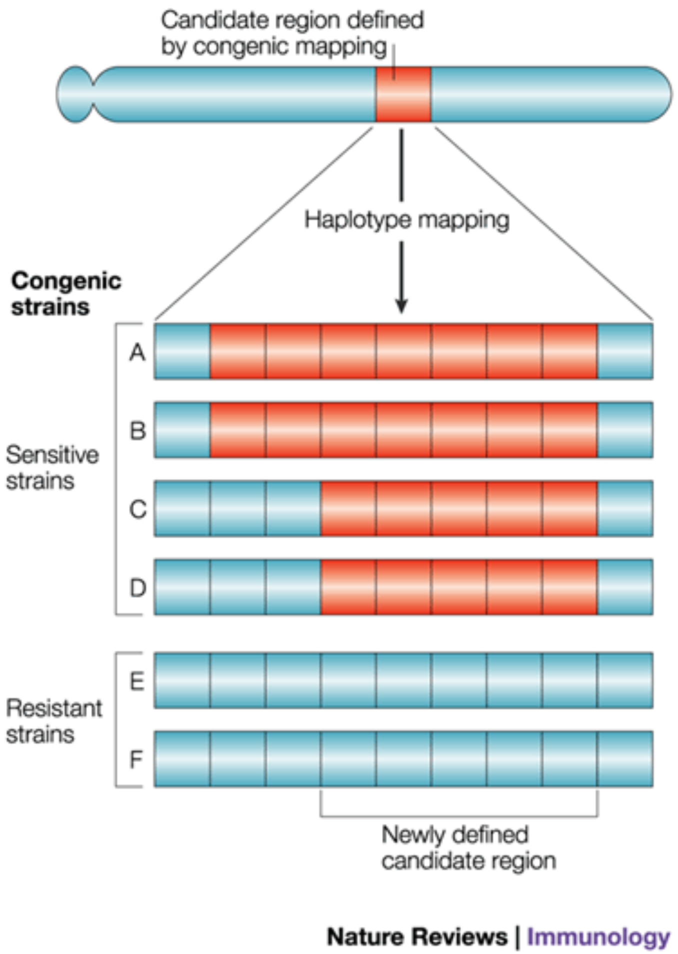
George D. Snell
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1980 was awarded jointly to Baruj Benacerraf, Jean Dausset and George D. Snell *"for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions"*.

- Syngeneic = between twins
- Autologous = self
- Allogeneic = foreign origin

Congenic mice

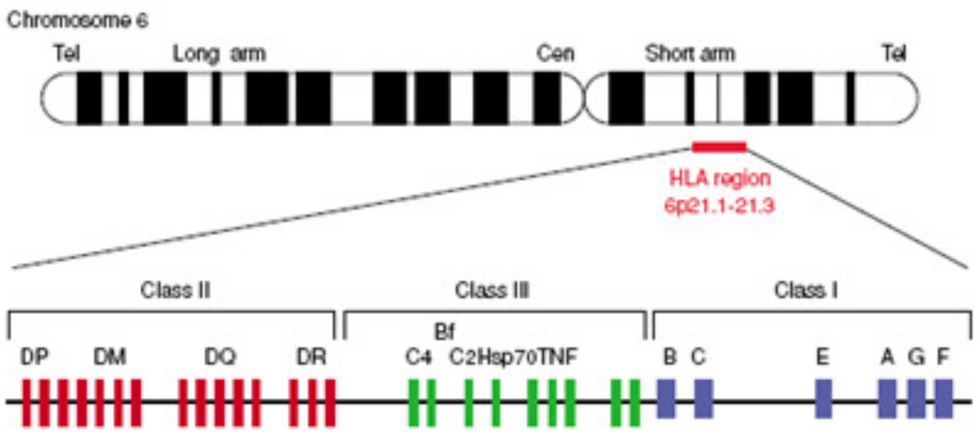




Rogner & Avner NRI 2003

What determines organ (in)compatibility?

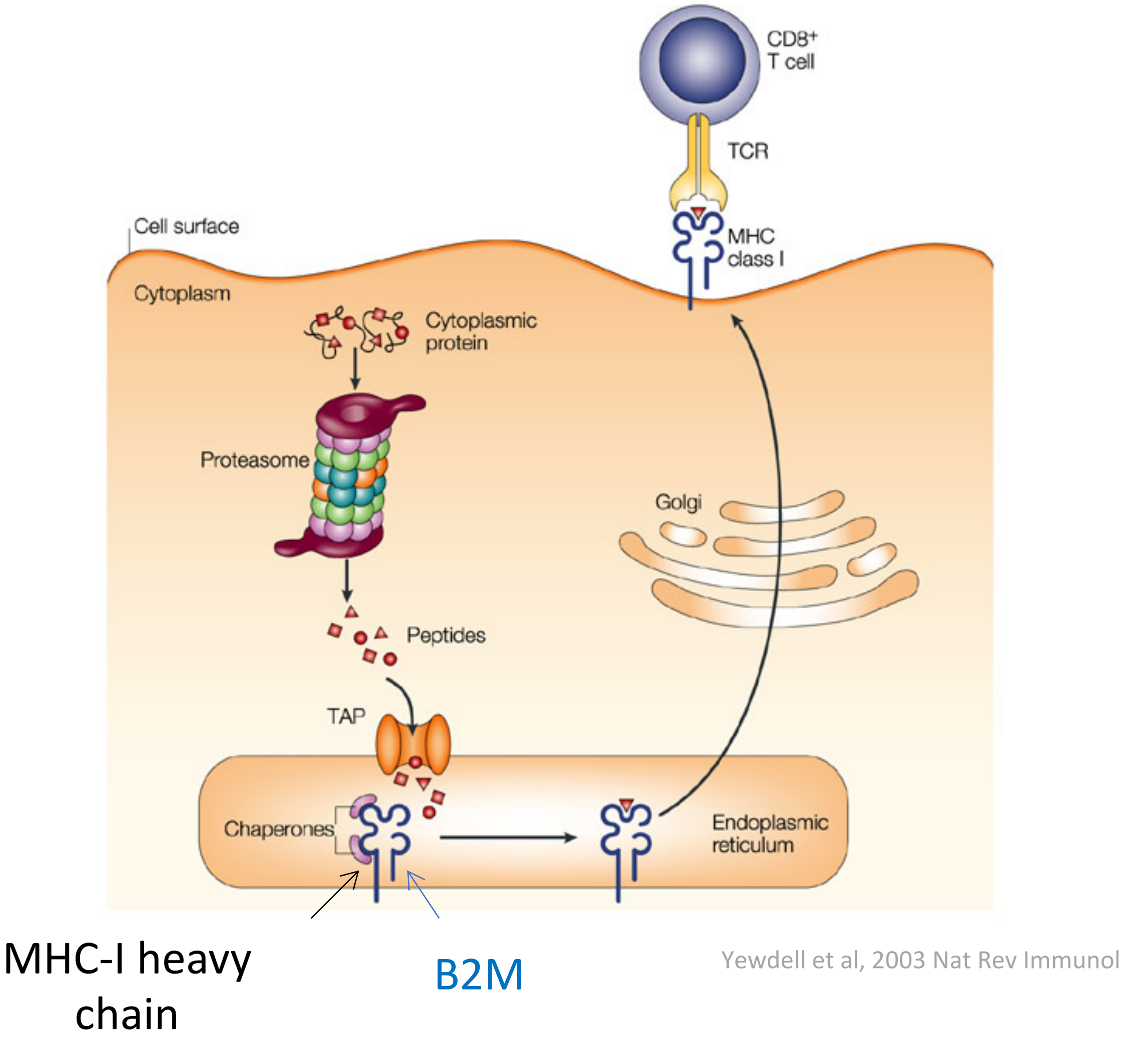
MHC - **Major histo(in)compatibility complex is locus on human Chr. 6p21, which encodes a highly polymorphic gene family of surface molecules that define donor compatibility during organ transplantation**



HLA – **Human Leukocyte Antigens**

MHC class I: HLA-A, -B, -C, -E, -G, -F
MHC class II: HLA-DR, -DP, -DQ

MHC molecules present self and non-self peptides to T cells



Yewdell et al, 2003 Nat Rev Immunol

Number of known HLA alleles in the population

https://www.ebi.ac.uk/ipd/imgt/hla/about/statistics/

Numbers of HLA Alleles	
HLA Class I Alleles	24009
HLA Class II Alleles	8888
HLA Alleles	32897
Other non-HLA Alleles	655
Number of Confidential Alleles	0

HLA Class I

Gene	*A*	*B*	*C*	*E*	*F*	*G*
Alleles	7354	8756	7307	298	48	94
Proteins	4302	5287	4042	118	7	30
Nulls	369	302	313	7	0	5

HLA Class I - Pseudogenes

Gene	*H*	*J*	*K*	*L*	*N*	*P*	*S*	*T*	*U*	*V*	*W*	*Y*
Alleles	67	27	6	5	5	5	7	8	5	3	11	3
Proteins	0	0	0	0	0	0	0	0	0	0	0	0
Nulls	0	0	0	0	0	0	0	0	0	0	0	0

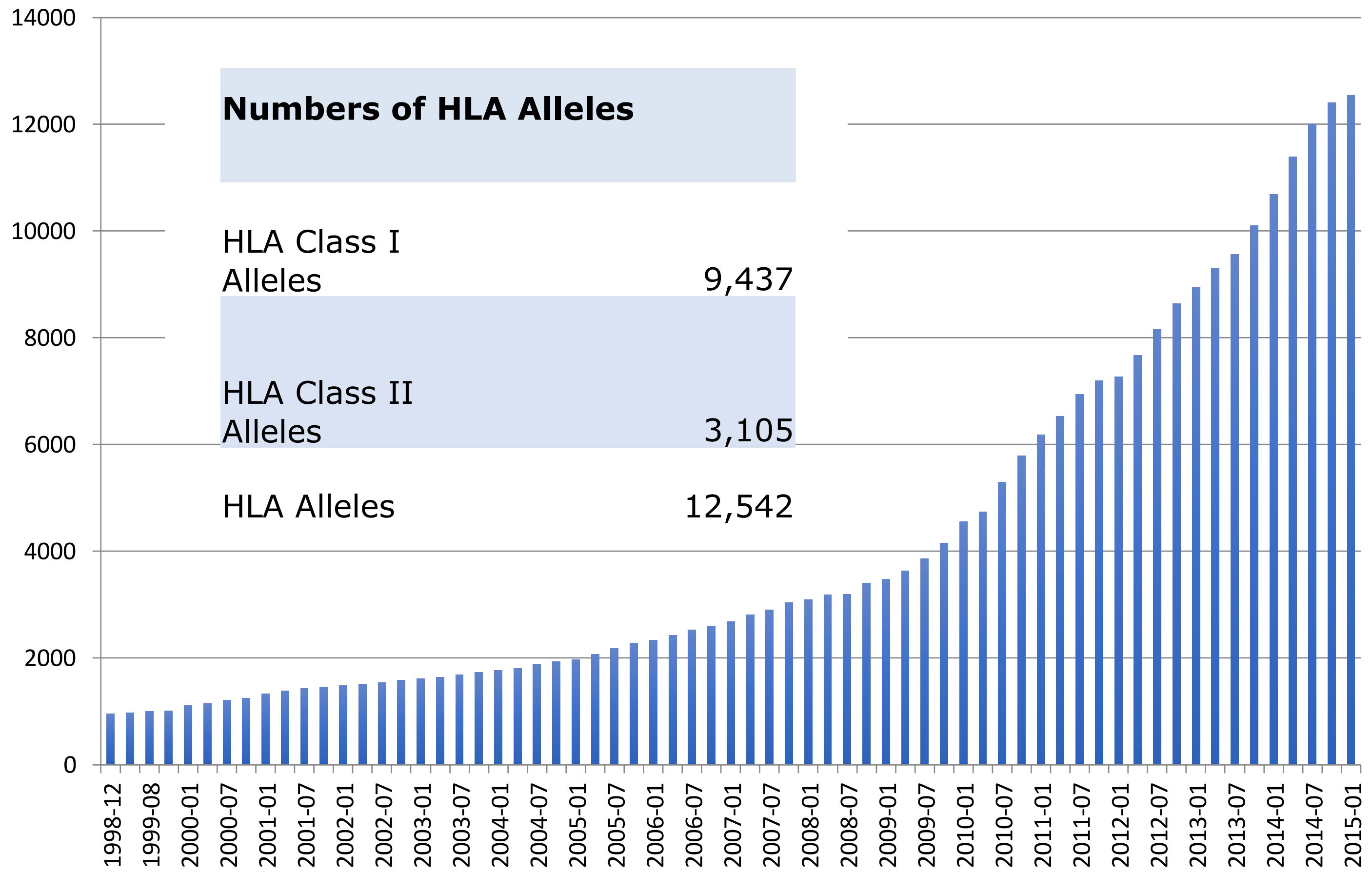
HLA Class II

Gene	*DRA*	*DRB*	*DQA1*	*DQA2*	*DQB1*	*DPA1*	*DPA2*	*DPB1*	*DPB2*	*DMA*	*DMB*	*DOA*	*DOB*
Alleles	32	3902	383	40	2193	373	5	1909	6	7	13	12	13
Proteins	5	2681	192	11	1386	158	0	1198	0	4	7	3	5
Nulls	0	165	9	0	96	10	0	101	0	0	0	1	0

HLA Class II - DRB Alleles

Gene	*DRB1*	*DRB2*	*DRB3*	*DRB4*	*DRB5*	*DRB6*	*DRB7*	*DRB8*	*DRB9*
Alleles	3094	1	417	211	167	3	2	1	6
Proteins	2107	0	310	136	128	0	0	0	0
Nulls	103	0	20	23	19	0	0	0	0

Number of known HLA alleles in the population

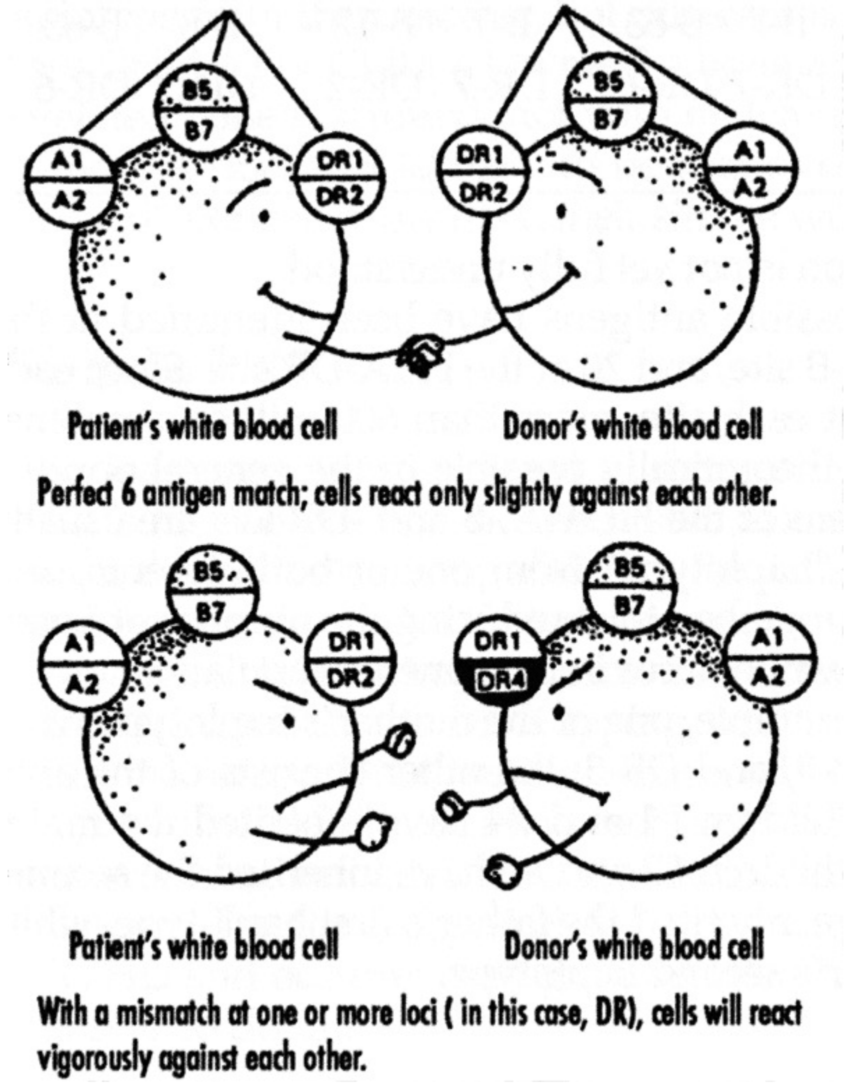


http://www.ebi.ac.uk/ipd/imgt/hla/stats.html

Full HLA haplotypes

Individual	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DRB3/4/5	HLA-DQA1	HLA-DQB1	HLA-DPA1	HLA-DPB1
1	24	7	7	4	4*01	1	3	1	04:01
	31	51	15	15	5*01	3	6	1	04:01
2	2	44	5	15	5*01	1	5	1	03:01
	31	51	14	16	5*01	1	6	1	04:01
3	29	13	2	7	3*02	2	2	1	06:01
	32	40	6	11	4*01	5	3	2	14:01
4	1	35	4	4	4*01	02:01	3	1	04:01
	2	39	7	7	4*01:03N	3	3	2	14:01
5	2	14	5	1	Null	1	5	1	02:01
	33	44	8	1	Null	1	5	1	02:01
6	2	44	4	7	3*01	02:01	2	1	04:02
	11	51	15	14	4*01	5	3	2	10:01
7	1	8	3	3	3*01	1	2	1	02:01
	3	40	7	13	3*03	05:01	6	1	06:01
8	1	35	4	7	3*03	1	2	1	02:01
	11	35	4	13	4*01	02:01	6	2	17:01
9	2	35	4	1	3*02	1	3	1	04:02
	11	44	16	11	3*02	5	5	1	04:02
10	1	8	6	7	4*01:03N	1	3	1	04:01
	3	57	7	15	5*01	02:01	6	1	04:01

HLA matching is essential for graft acceptance



Timeline of successful transplants

1905: First successful **cornea** transplant by Eduard Zirm [Czech Republic]

1954: First successful **kidney** transplant by J. Hartwell Harrison and Joseph Murray (Boston, U.S.A.)

1966: First successful **pancreas** transplant by Richard Lillehei and William Kelly (Minnesota, U.S.A.)

1967: First successful **liver** transplant by Thomas Starzl (Denver, U.S.A.)

1967: First successful **heart** transplant by Christian Barnard (Cape Town, South Africa)

1981: First successful heart/lung transplant by Bruce Reitz (Stanford, U.S.A.)

1983: First successful **lung** lobe transplant by Joel Cooper (Toronto, Canada)

1984: First successful double organ transplant by Thomas Starzl and Henry T. Bahnson (Pittsburgh, U.S.A.)

1986: First successful double-lung transplant (Ann Harrison) by Joel Cooper (Toronto, Canada)

1995: First successful laparoscopic live-donor nephrectomy by Lloyd Ratner and Louis Kavoussi (Baltimore, U.S.A.)

1997: First successful allogeneic vascularized transplantation of a fresh and perfused human knee joint by Gunther O. Hofmann

1998: First successful live-donor partial pancreas transplant by David Sutherland (Minnesota, U.S.A.)

1998: First successful **hand** transplant by Dr. Jean-Michel Dubernard (Lyon, France)

1999: First successful Tissue Engineered Bladder transplanted by Anthony Atala (Boston Children's Hospital, U.S.A.)

2005: First successful ovarian transplant by Dr P N Mhatre (wadia hospital mumbai,India)

2005: First successful partial face transplant (France)

2006: First jaw transplant to combine donor jaw with bone marrow from patient, by Eric M. Genden, Mt Sinai Hospital, New York

2008: First successful **double arm** transplant by Edgar Biemer, Christoph Höhnke and Manfred Stangl (Technical University of Munich)

2008: First **baby born from transplanted ovary** by James Randerson

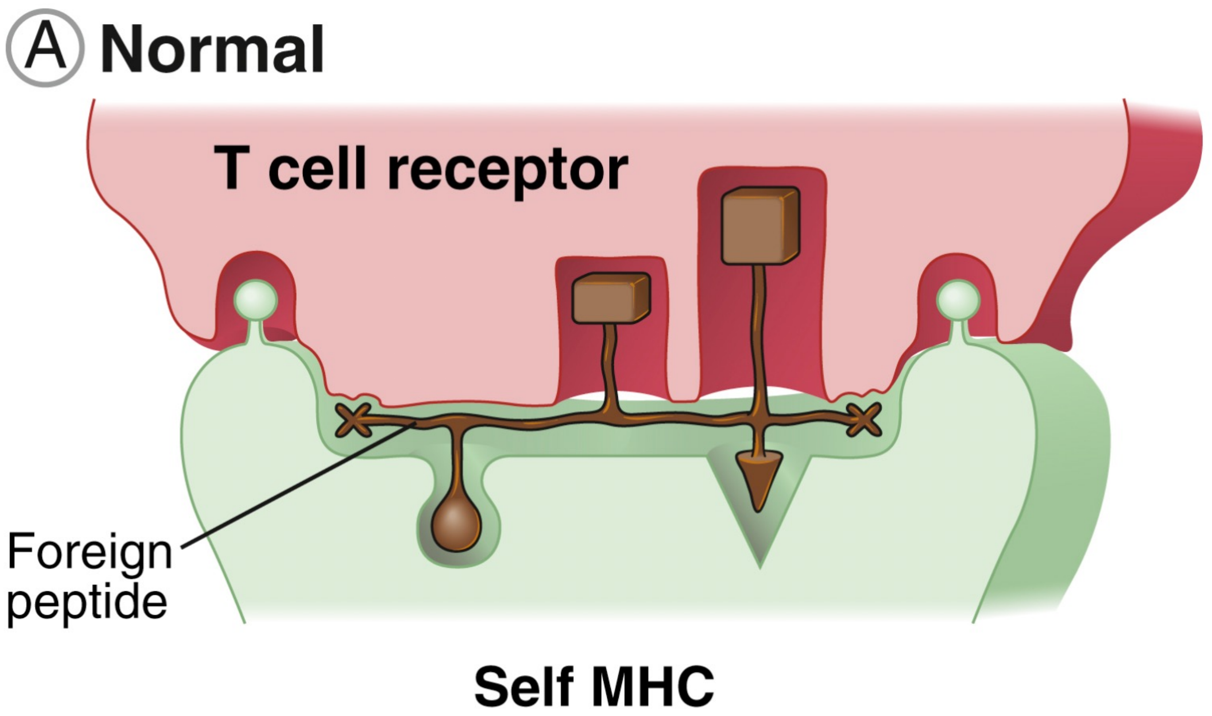
2008: First transplant of a vertebrate trachea using a patient's own stem cells, by Paolo Macchiarini (Barcelona, Spain)

2008: First successful transplant of near total area (80%) of face, (including palate, nose, cheeks, and eyelid) by Maria Siemionov (Cleveland)

2010: First **full facial transplant**, by Joan Pere Barret (Hospital Universitari Vall d'Hebron on July 26, 2010 in Barcelona, Spain.)

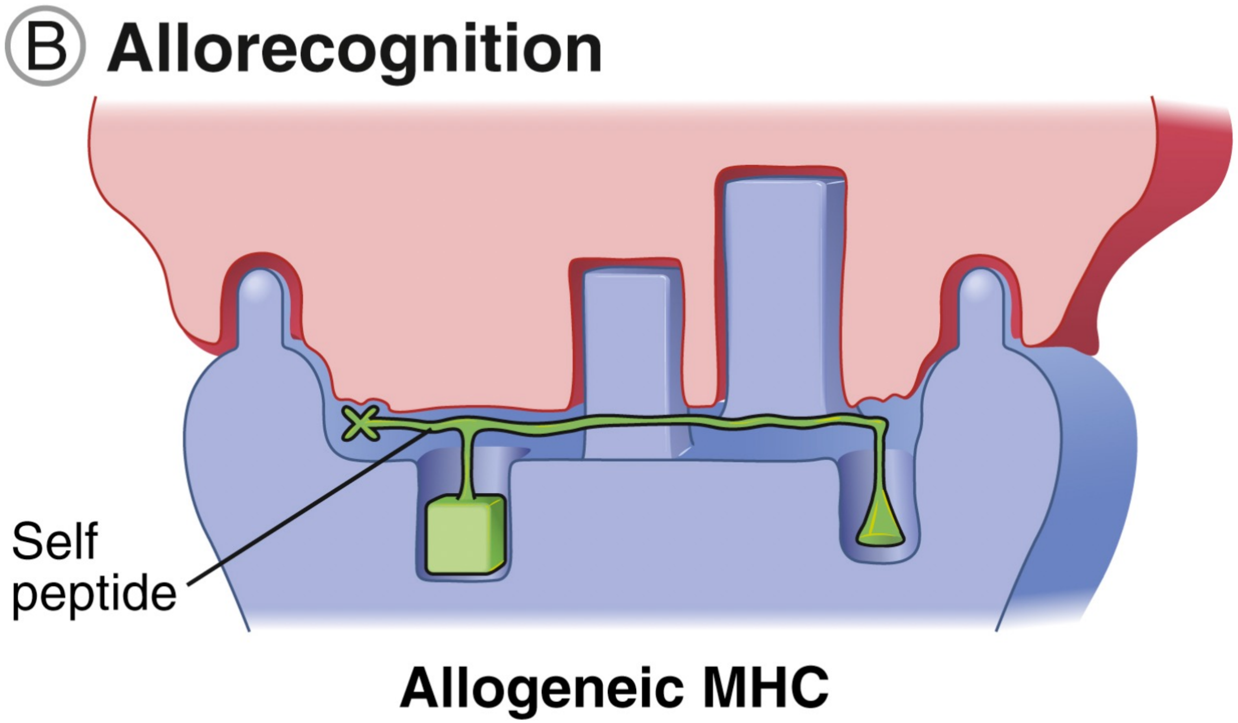
2011: First **double leg** transplant, by Dr Cavadas and team (Valencia's Hospital La Fe, Spain)

T cell recognition of self MHC and foreign peptide



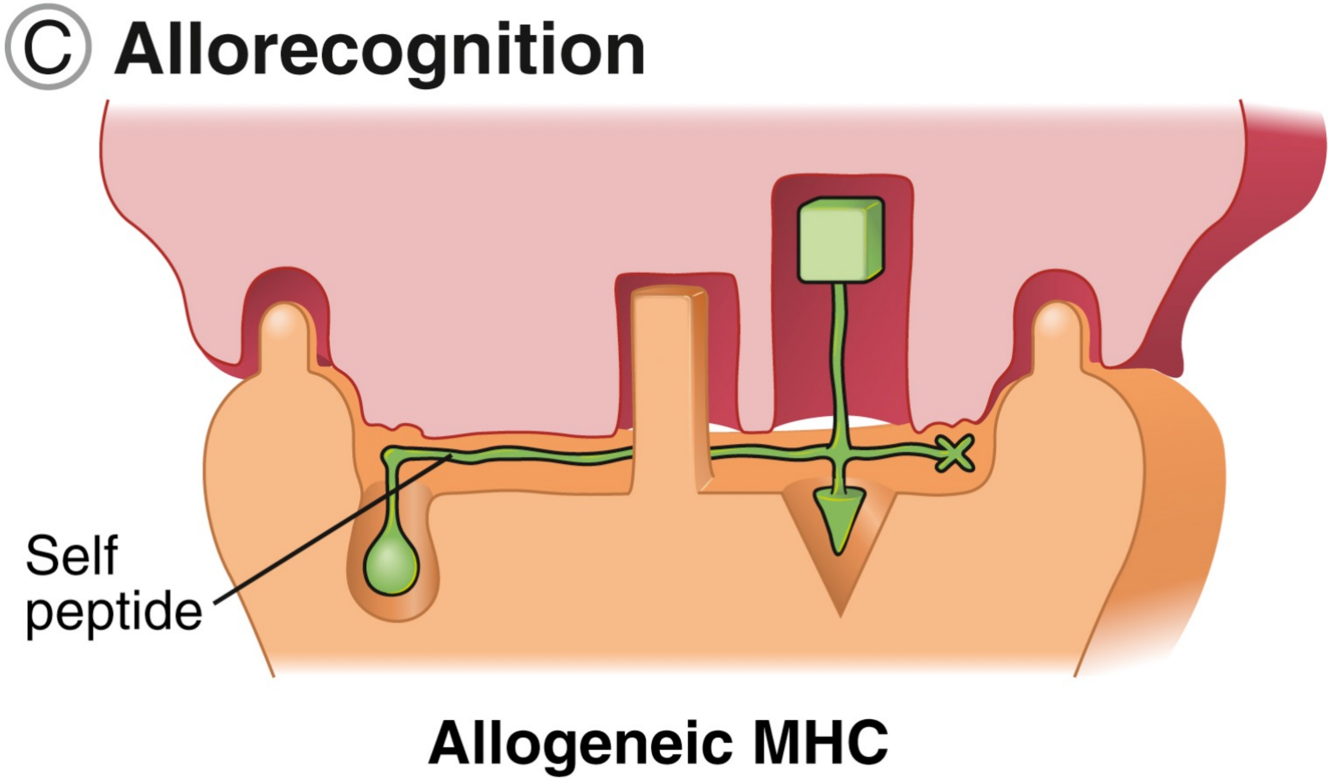
Self MHC molecule presents foreign peptide to T cell selected to recognize self MHC weakly, but may recognize self MHC-foreign peptide complexes well

T cell recognition of foreign MHC and self peptide I



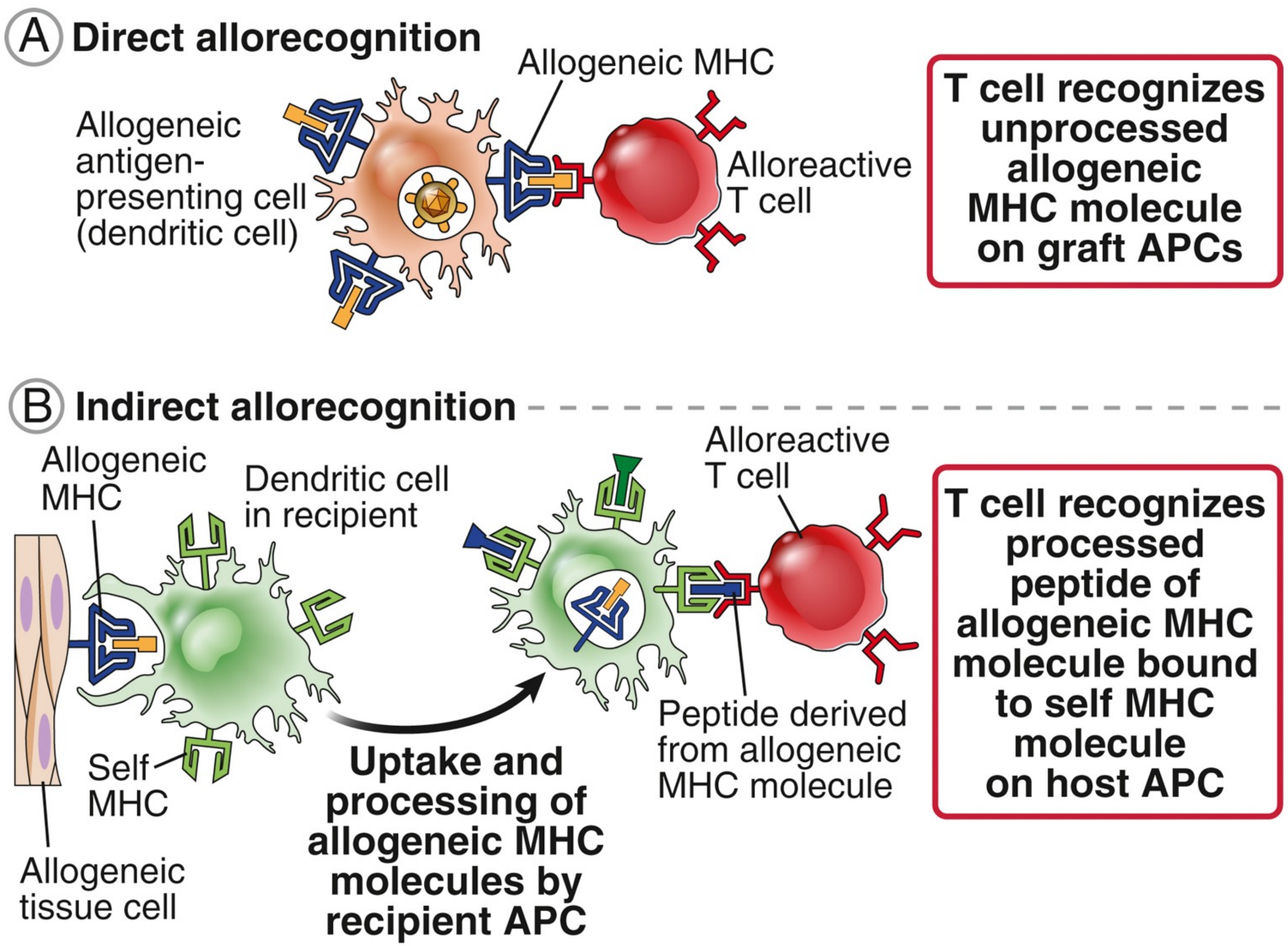
The self MHC-restricted T cell recognizes the allogeneic MHC molecule whose structure resembles a self MHC-foreign peptide complex

T cell recognition of foreign MHC and self peptide II

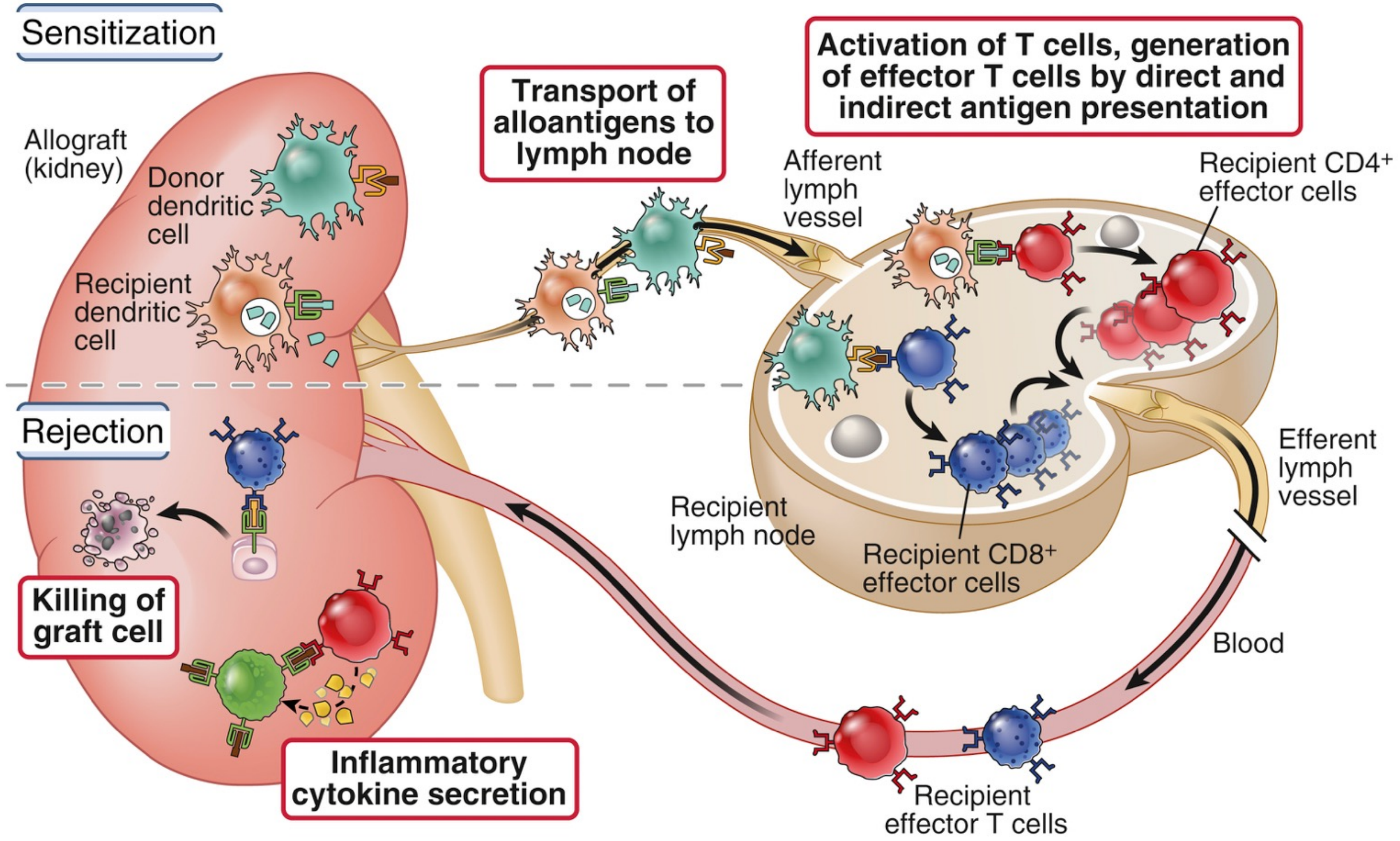


The self MHC-restricted T cell recognizes a structure formed by both the allogeneic MHC molecule and the bound peptide

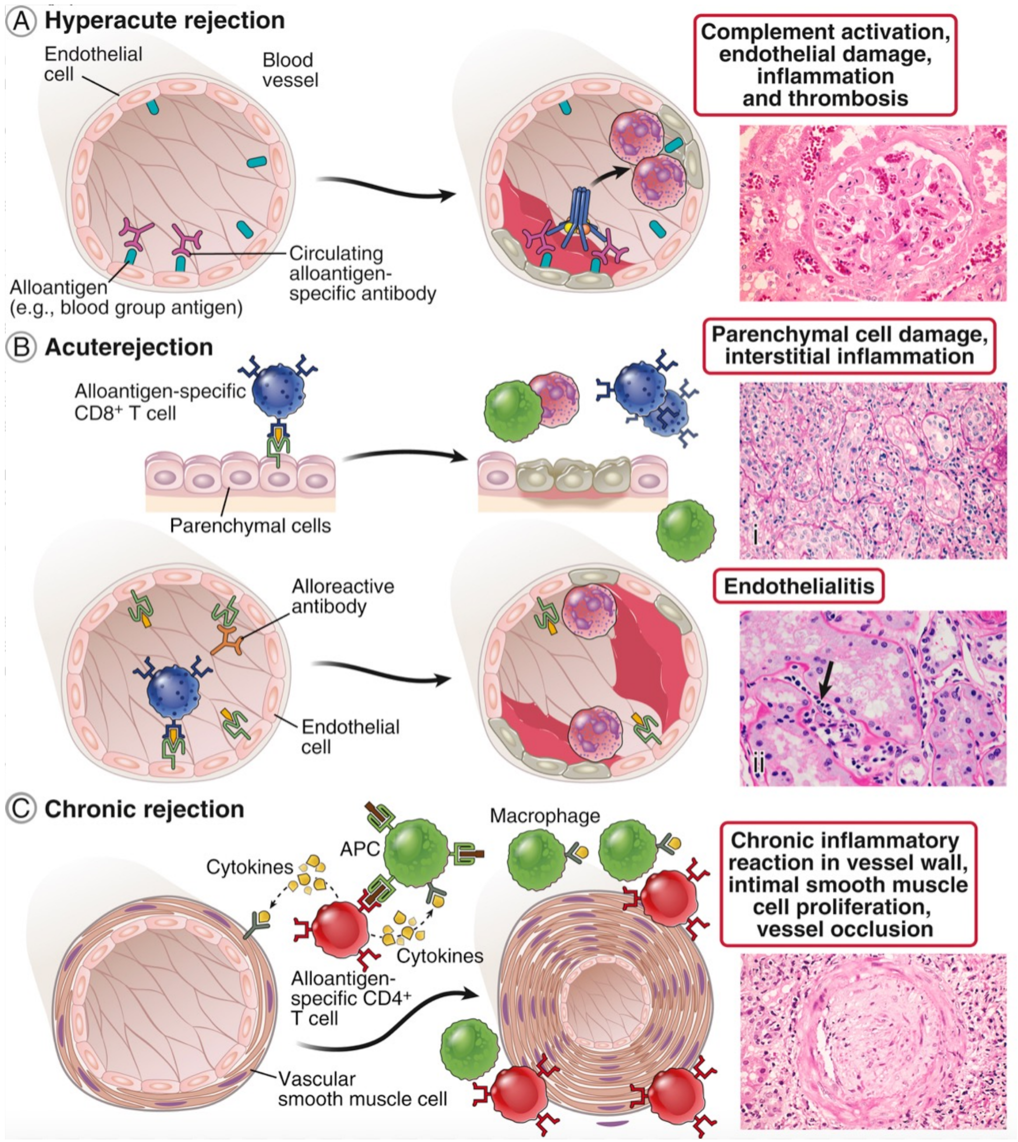
Direct and indirect presentation



Immune response against transplants



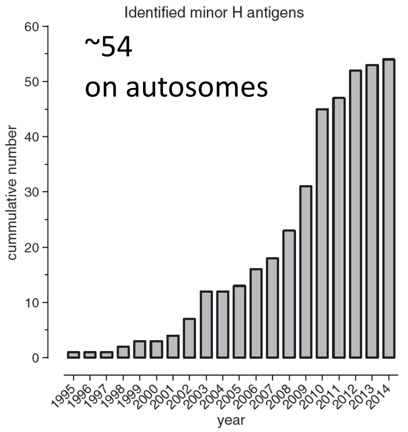
Forms of rejection



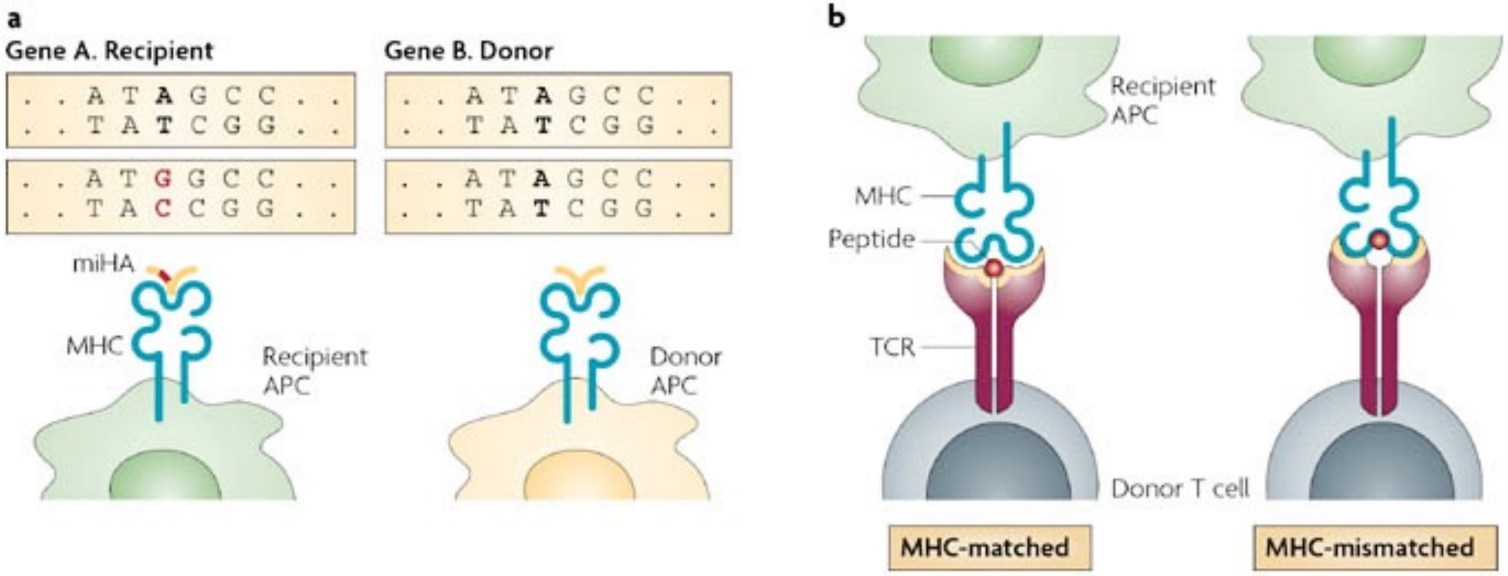
Minor histocompatibility antigens (mHAgs)

2 criteria:
- Polymorphic
- Immunogenic

	Human
MHC antigen	
Class I	A, B, C
Class II	DR, DQ, DP
MiHA	
Y chromosome related	SMCY, UTY, DBY, DFFRY, RPS4Y, TMSB4Y
Autosomal chromosome related	HA-1, HA-2, HA-3, HA-8, HB-1, ACC-1, ACC-2, UGT2B17, LRH-1, CTSH, ECGF1, PANE1, SP110, SLC1A5, SLC19A1, P2RX7



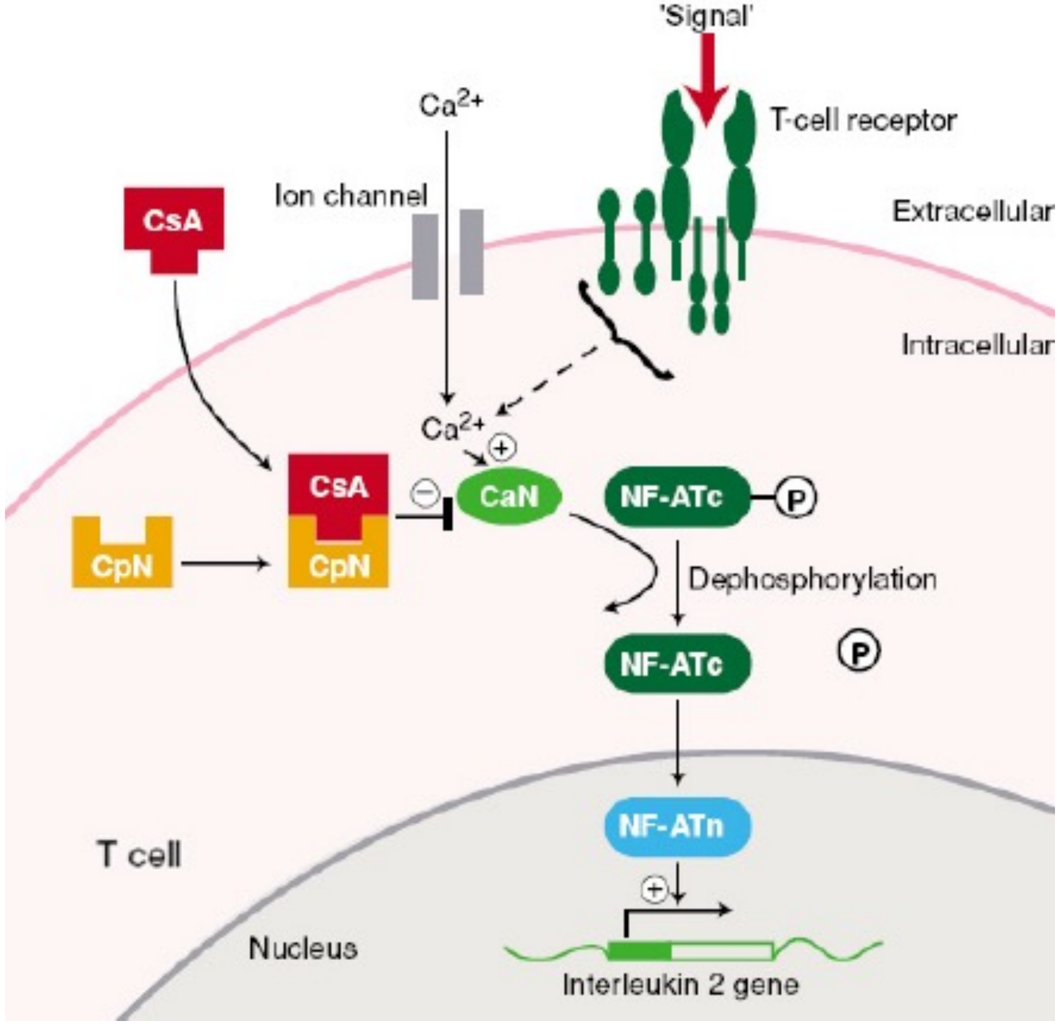
Spiering 2014 Tissue Antigens



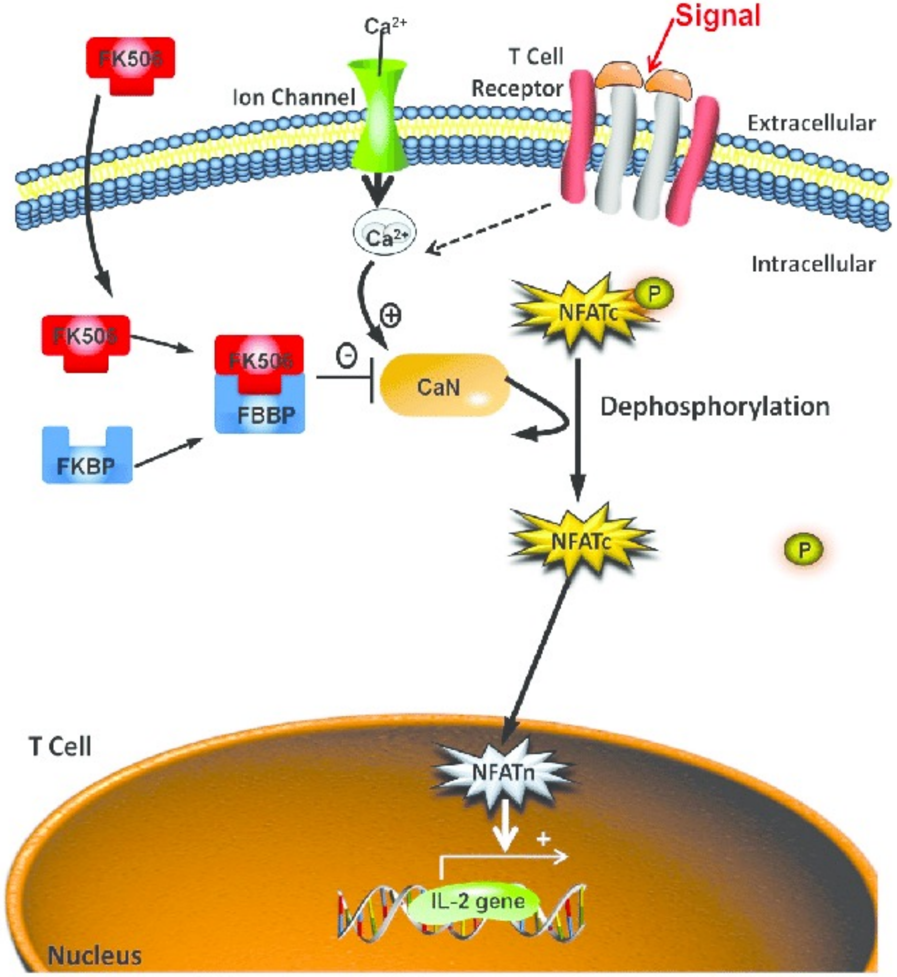
https://www.youtube.com/watch?v=Bj2hrMuHb-w

Cyclosporine

Tacrolimus



Colombo et al, Psoriasis 2012

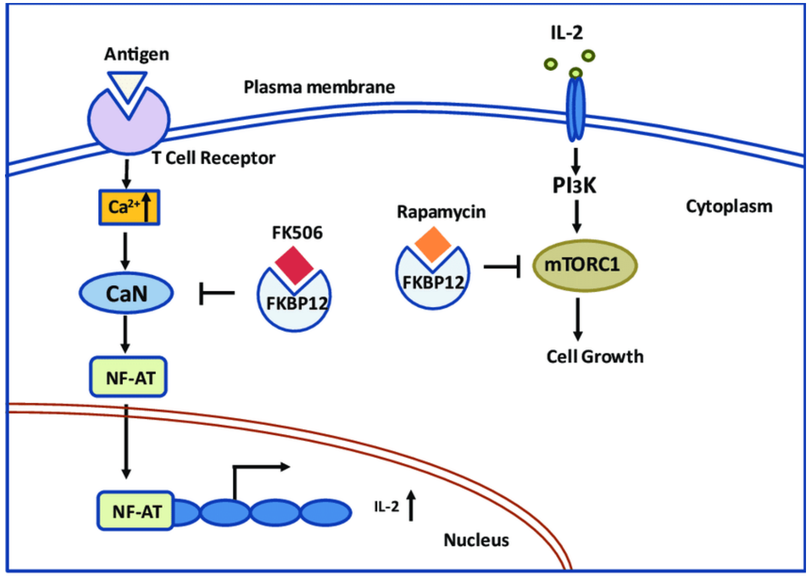


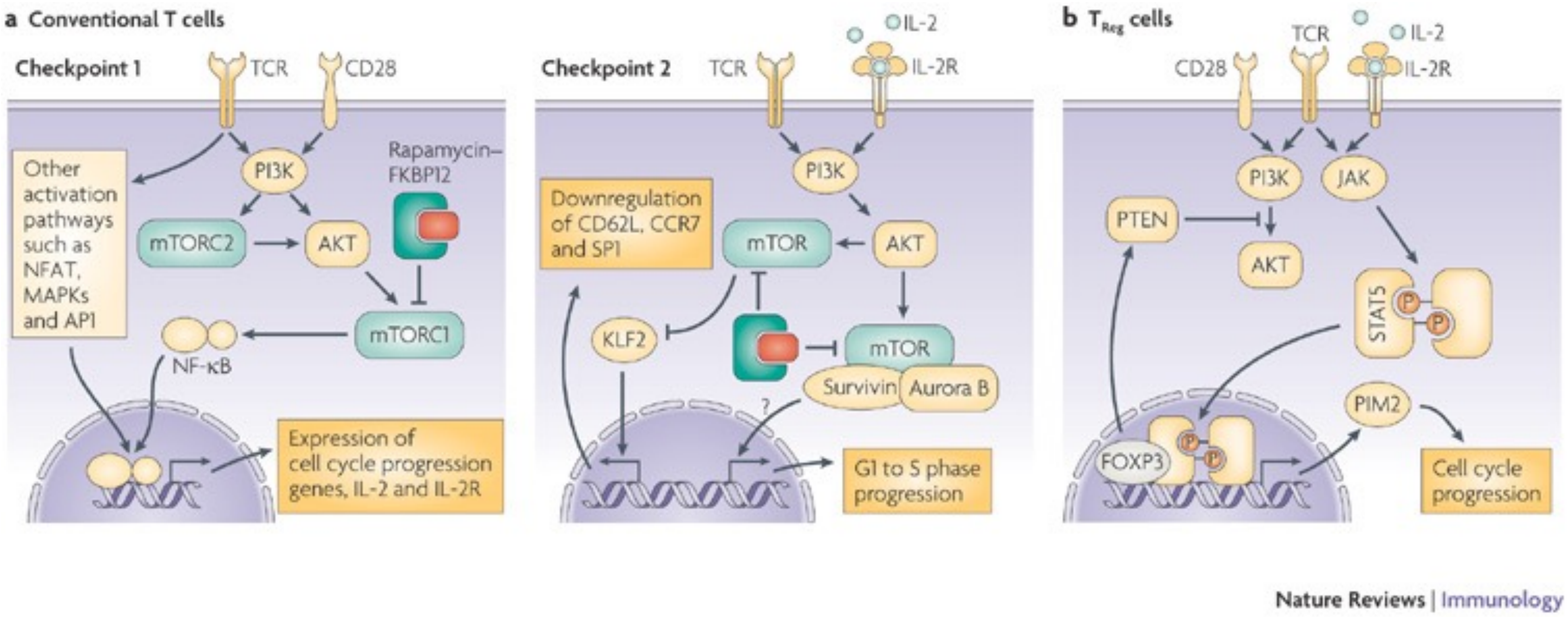
FK506 = Tacrolimus
CpN= cyclophilin
CaN = Calcineurin phosphatase

$NFAT_c$ = cytosolic NFAT
$NFAT_n$ = nuclear NFAT

Cassidy et al, J Clin Med 2016

Rapamycin





Tong & Jiang, Curr Mol Pharmacol 2015

Thomson et al, NRI 2009

Immunosuppressive drugs

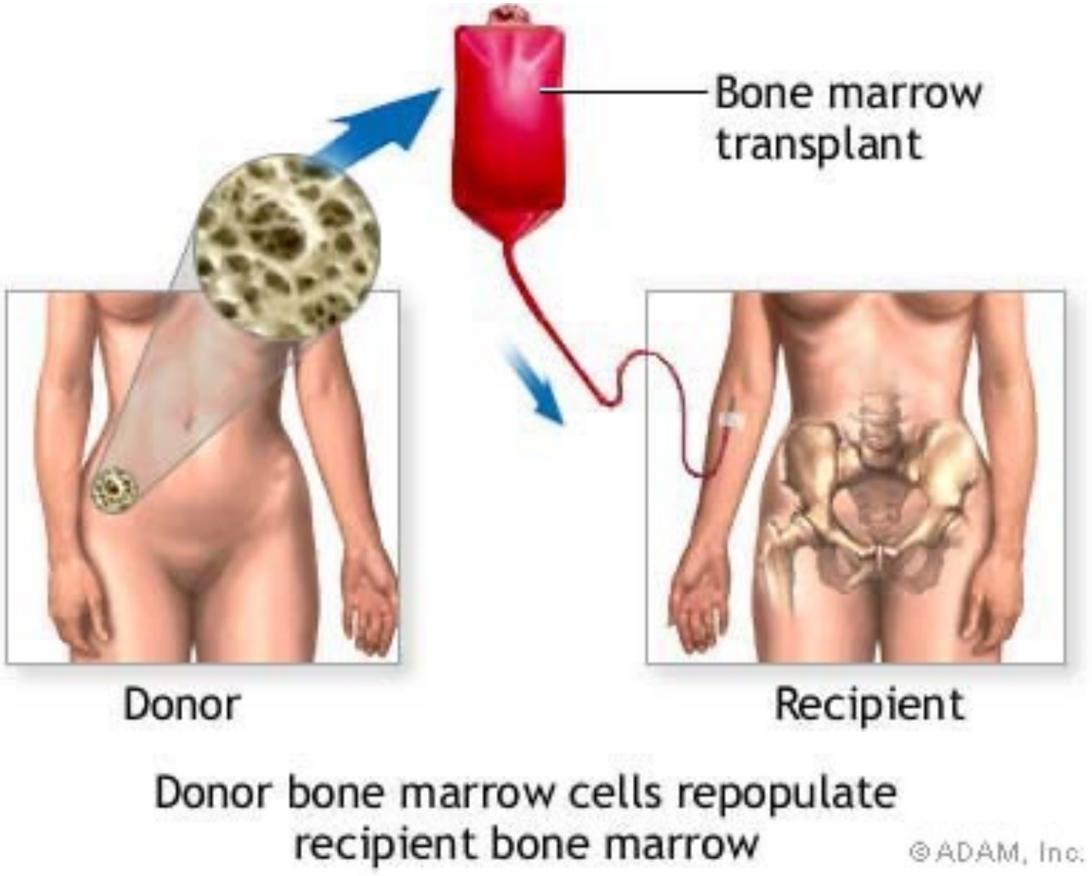
Drug	Mechanism of action
Cyclosporine and tacrolimus	Blocks T cell cytokine production by inhibiting the phosphatase calcineurin and thus blocking activation of the NFAT transcription factor
Mycophenolate mofetil	Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes
Rapamycin (sirolimus)	Blocks lymphocyte proliferation by inhibiting mTOR and IL-2 signaling
Corticosteroids	Reduce inflammation by effects on multiple cell types

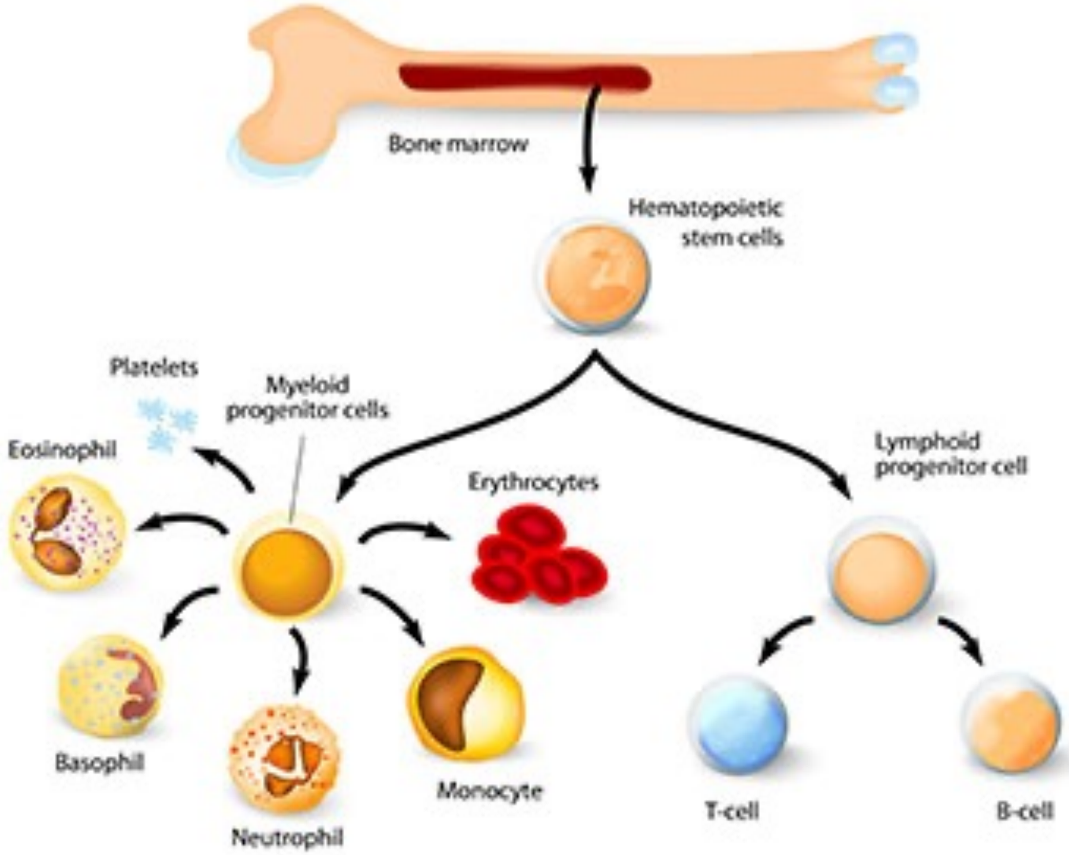
Drug	Mechanism of action
Antithymocyte globulin	Binds to and depletes T cells by promoting phagocytosis or complement-mediated lysis (used to treat acute rejection)
Anti-IL-2 receptor (CD25) antibody	Inhibits T cell proliferation by blocking IL-2 binding; may also opsonize and help eliminate activated IL-2R-expressing T cells
CTLA4-Ig (belatacept)	Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28
Anti-CD52 (alemtuzumab)	Depletes lymphocytes by complement-mediated lysis

Evidence indicating that the rejection of tissue transplants is an immune reaction

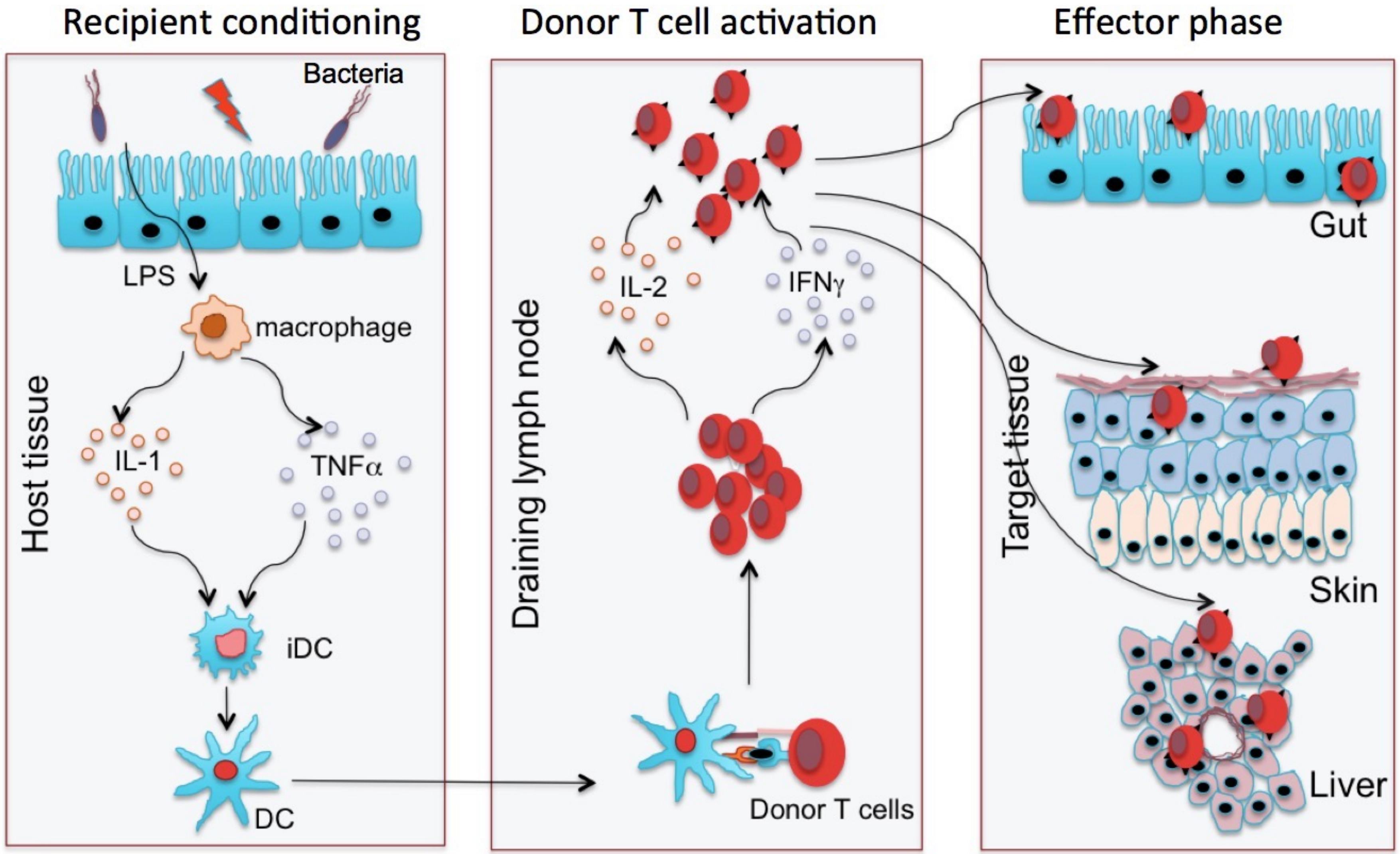
Evidence	Conclusion
Prior exposure to donor MHC molecules leads to accelerated graft rejection	Graft rejection shows memory and specificity, two cardinal features of adaptive immunity
The ability to reject a graft rapidly can be transferred to a naive individual by lymphocytes from a sensitized individual	Graft rejection is mediated by lymphocytes
Depletion or inactivation of T lymphocytes by drugs or antibodies results in reduced graft rejection	Graft rejection requires T lymphocytes

Bone marrow transplant

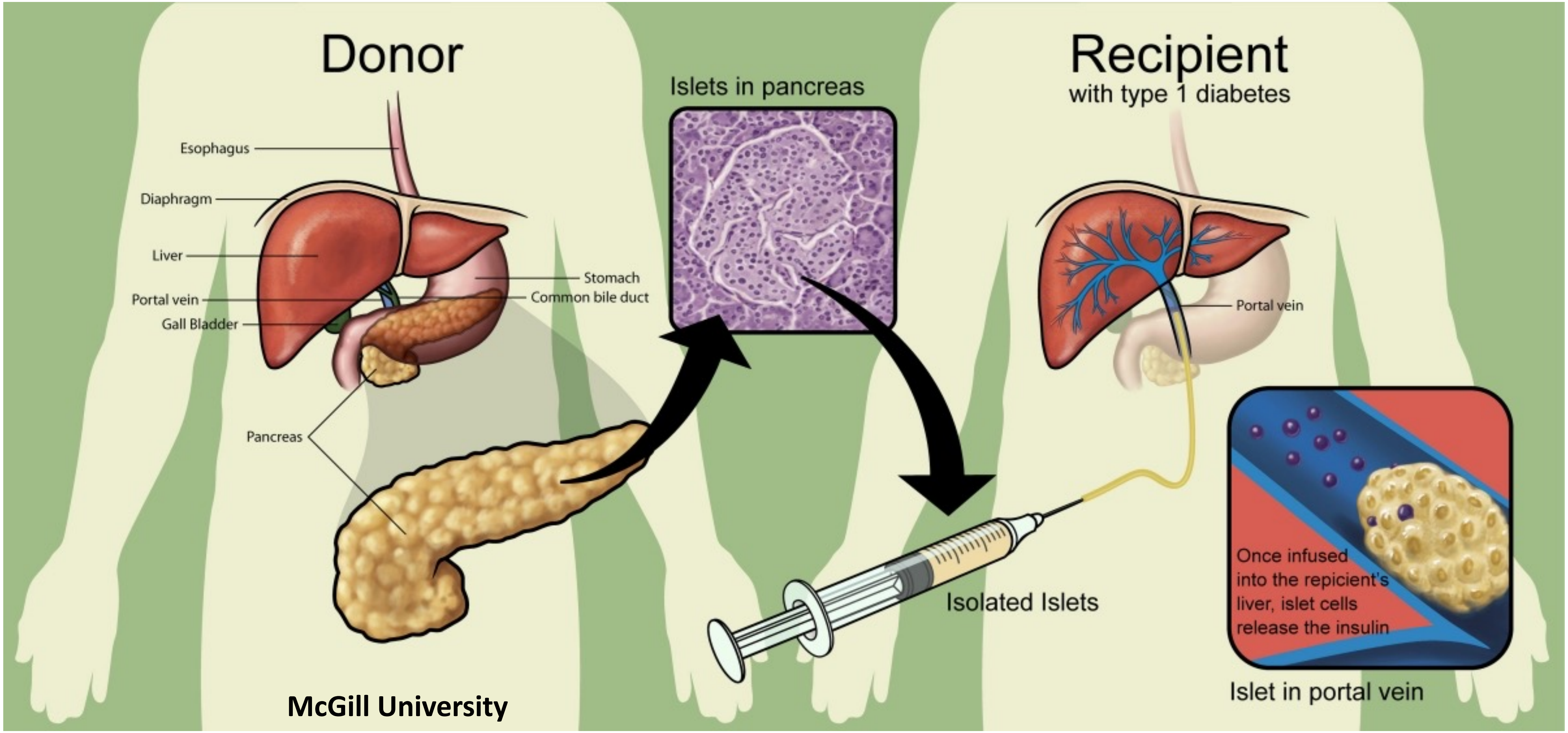




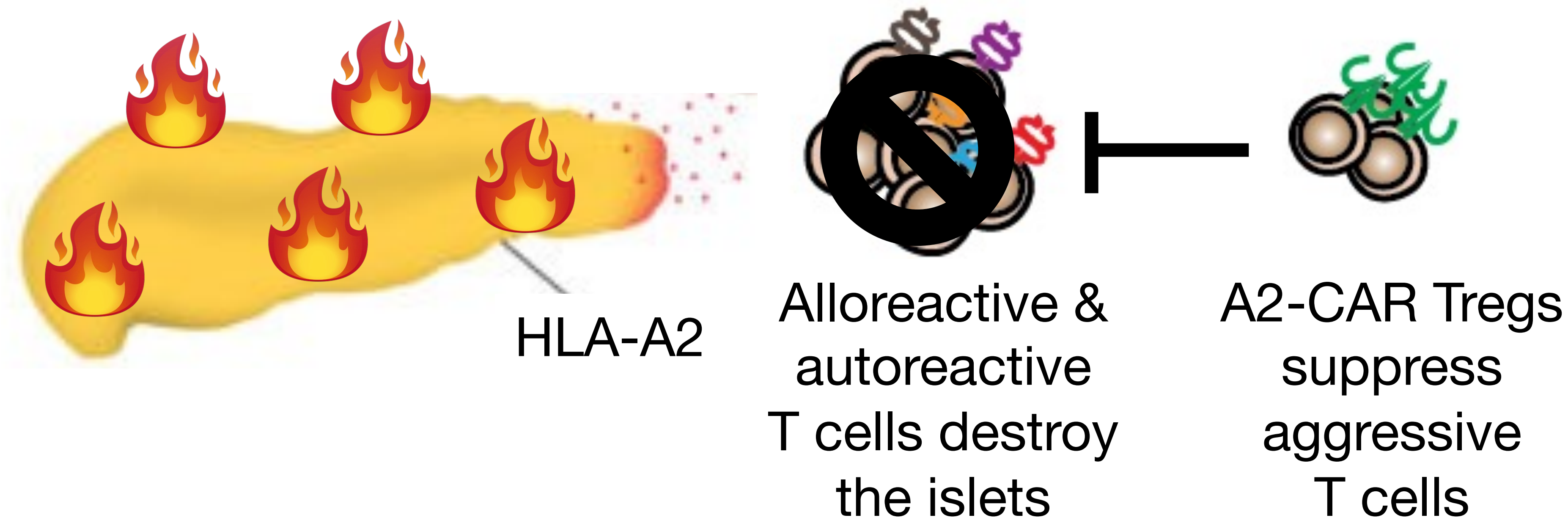
Graft-vs-host disease



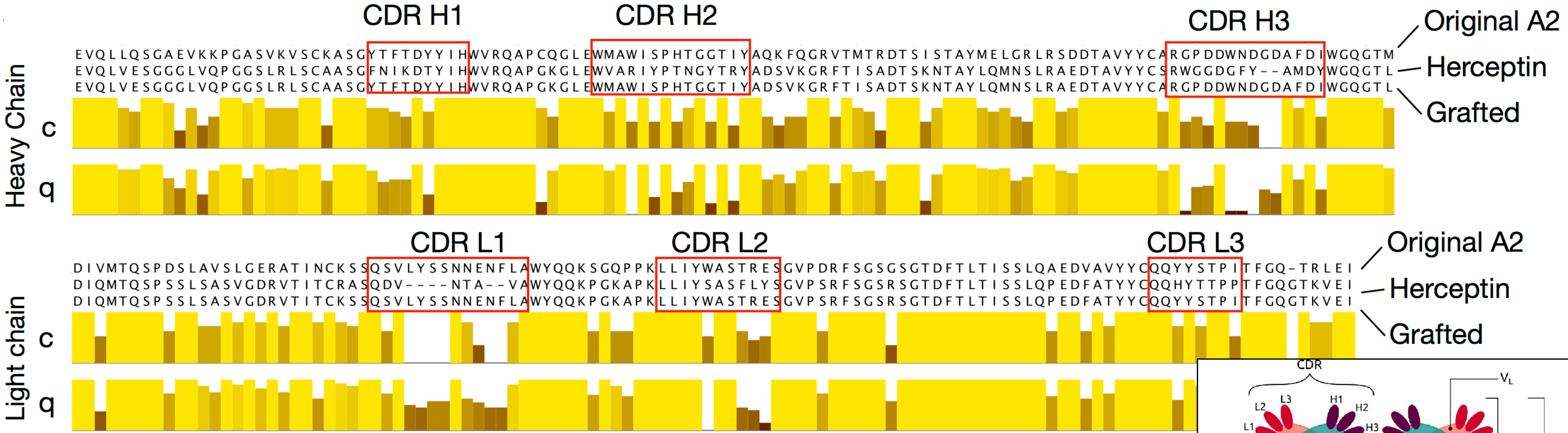
Islet transplant

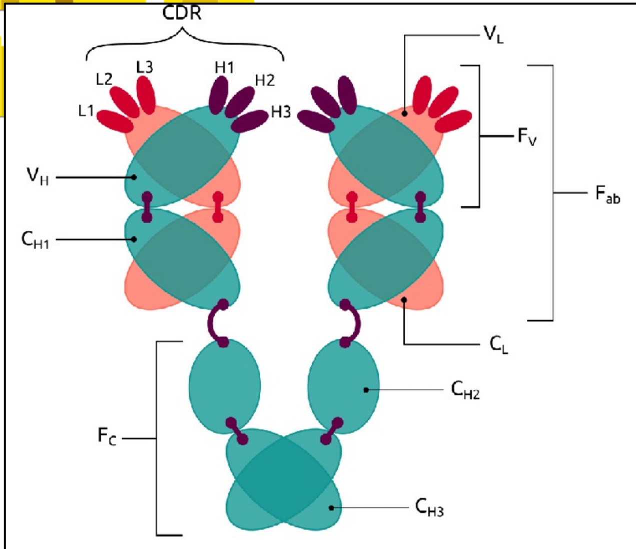


Anti-HLA-A2 CAR Tregs for HLA-A2$^+$ islets transplants to treat type 1 diabetes



Grafting A2-CAR scFv specificity



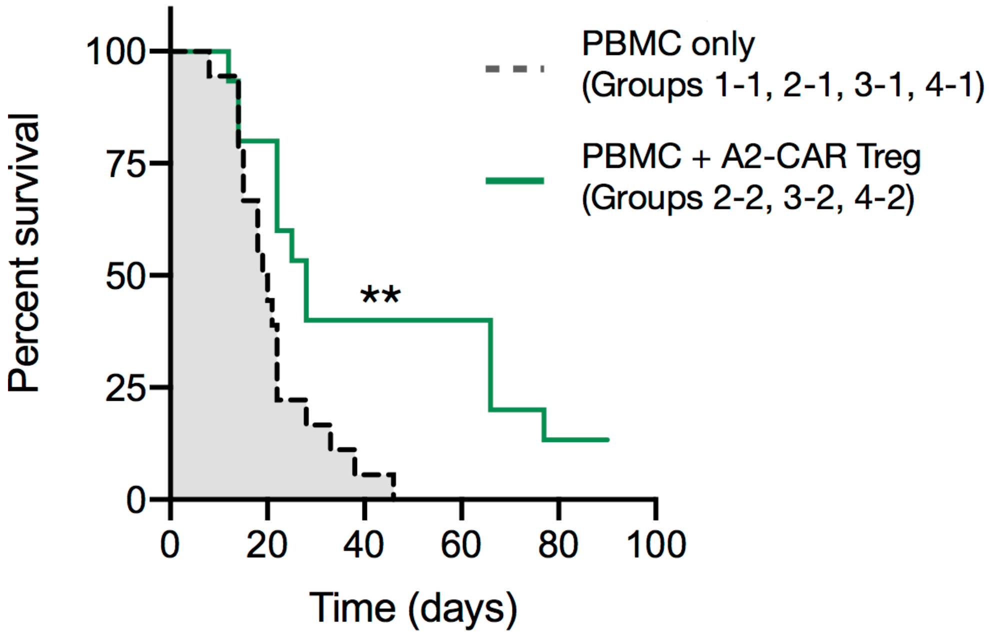


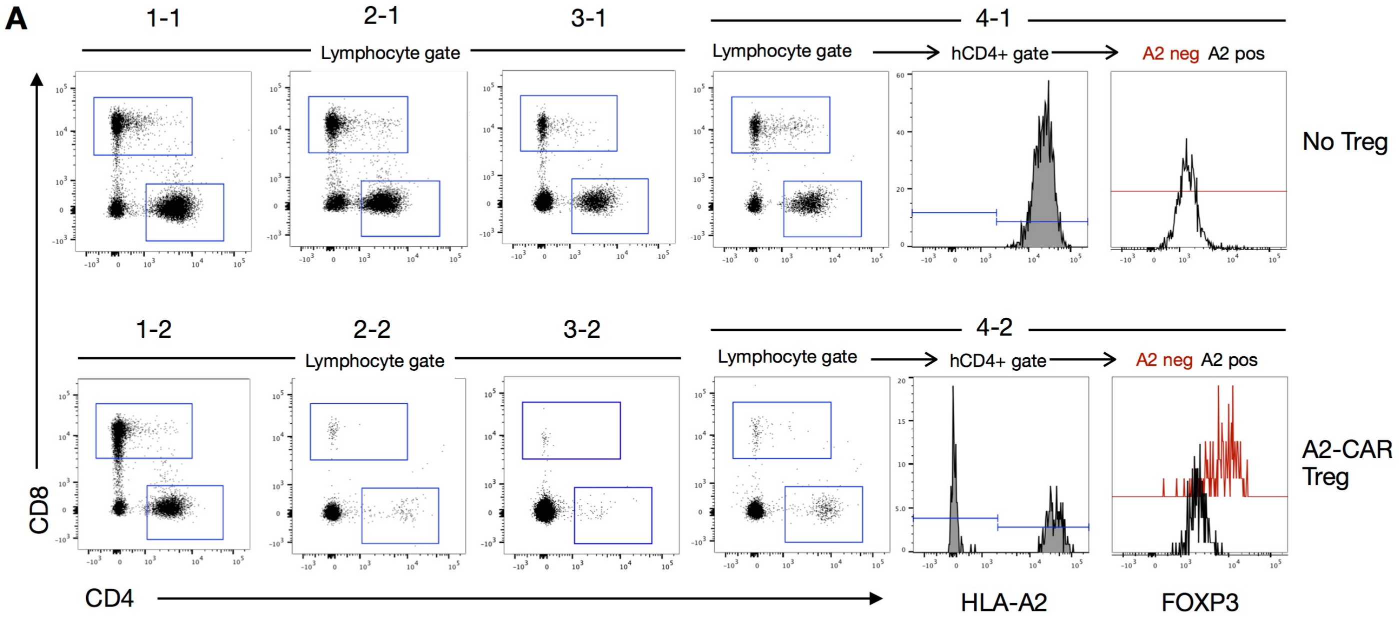
Muller, Ferreira et al, Front Immunol 2021

A2-CAR Tregs prevent graft-vs-host disease

A

	NSG		HLA-A2 Tg NSG	
	PBMC only	PBMC + A2-CAR Treg	PBMC only	PBMC + A2-CAR Treg
HLA-A2 neg	Group 1-1 (n=4)	Group 1-2 (n=6)	Group 2-1 (n=5)	Group 2-2 (n=5)
HLA-A2 pos	Group 3-1 (n=5)	Group 3-2 (n=5)	Group 4-1 (n=4)	Group 4-2 (n=5)

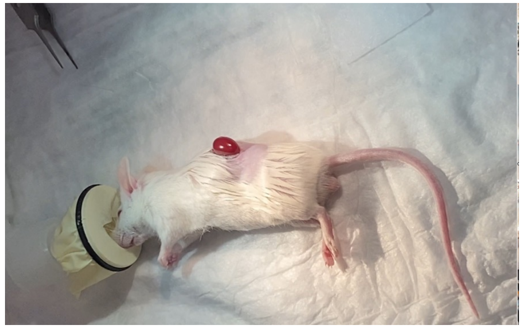




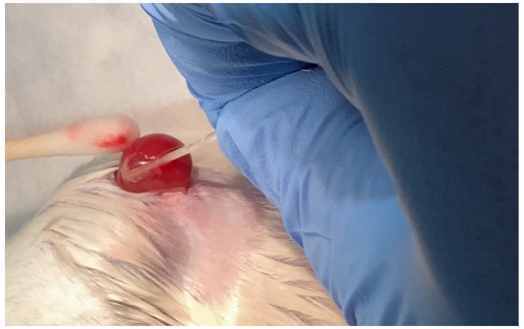
Muller, Ferreira et al, Front Immunol 2021

A2-CAR Tregs traffic to A2^{+} human islet grafts

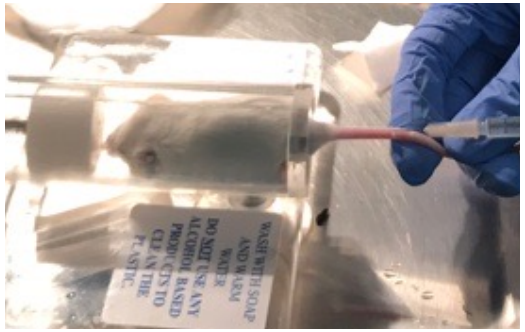
Kidney capsule exposure

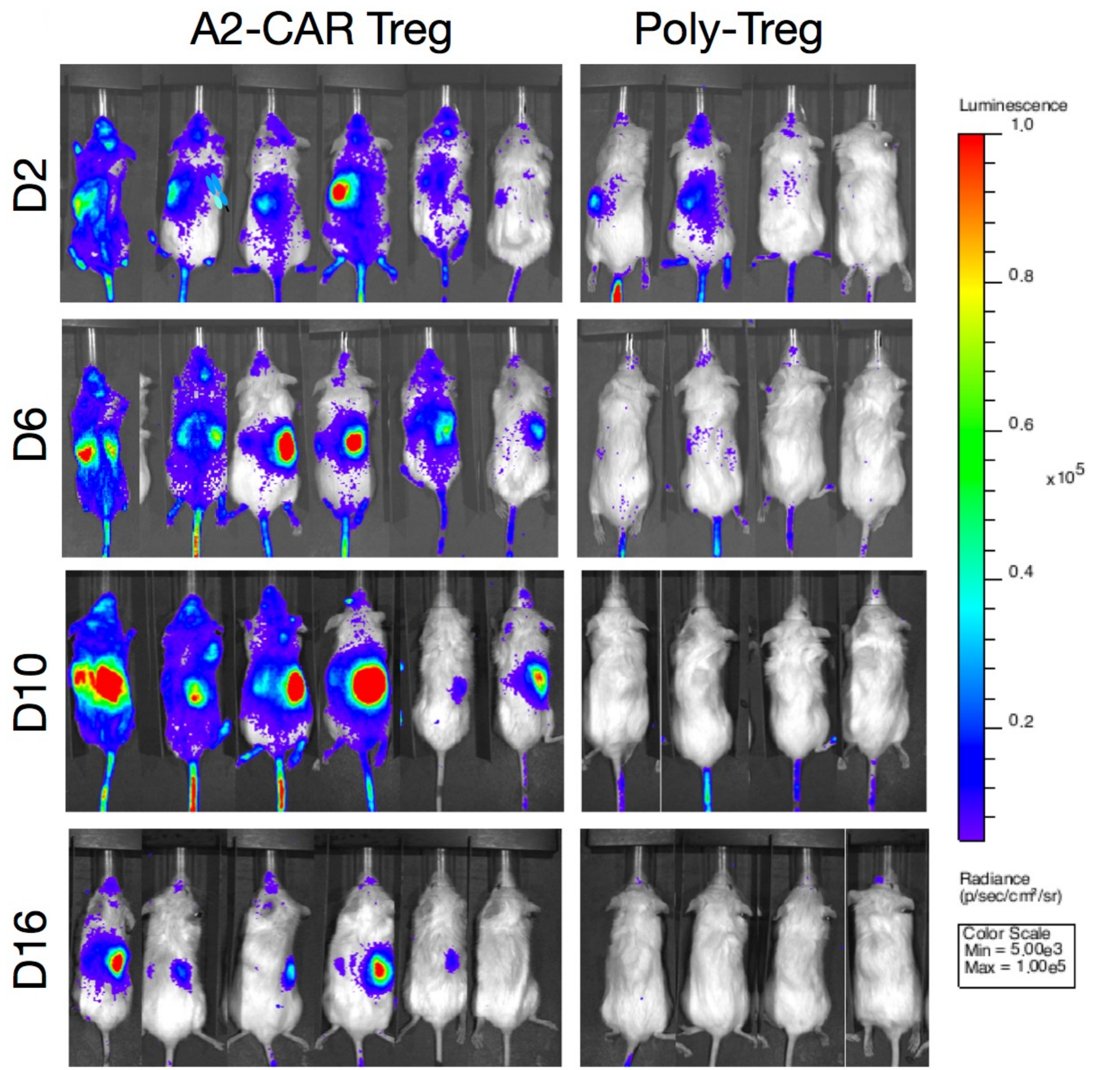


Human A2^{+} islet transplant

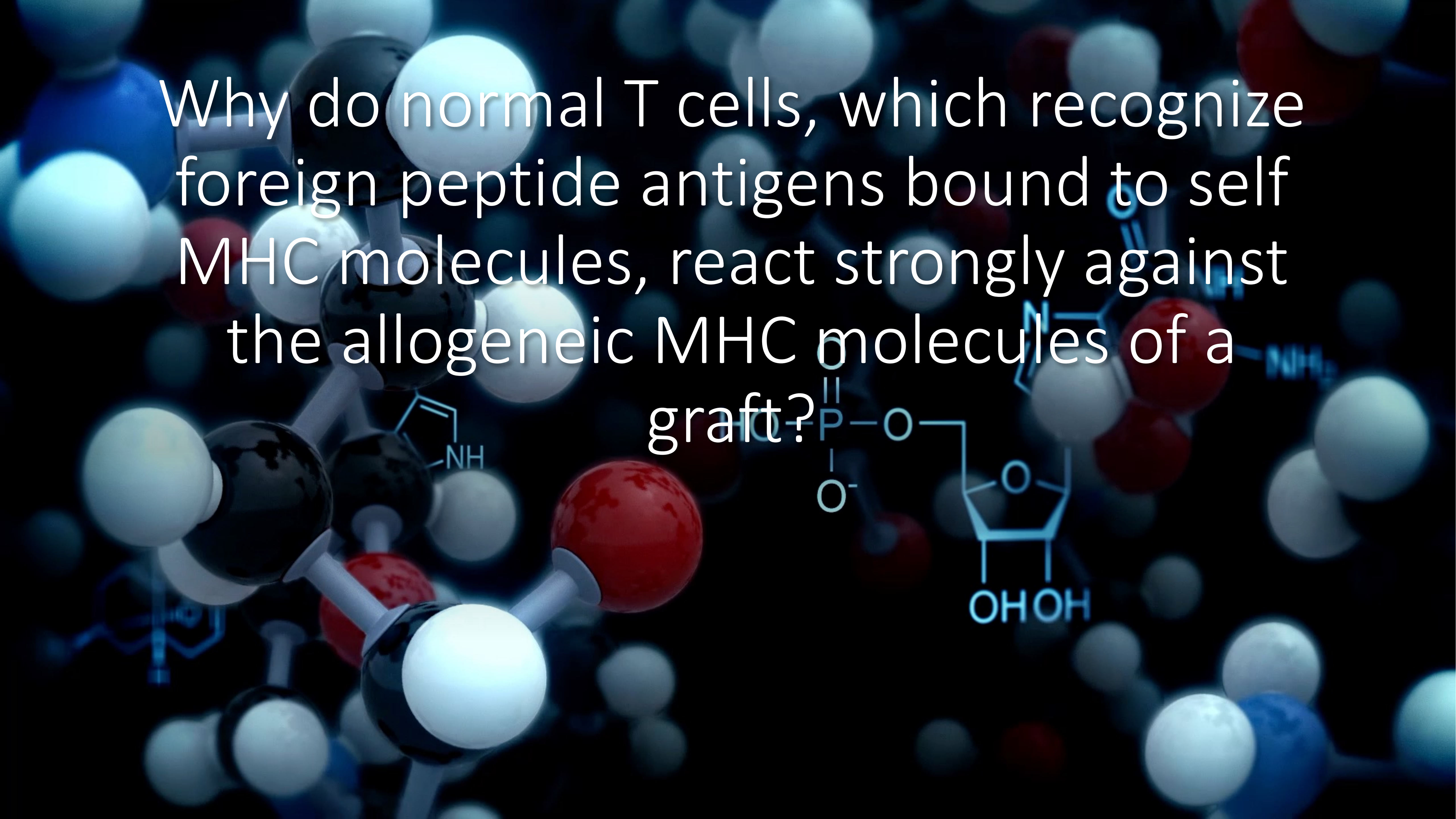


Luciferase^{+} A2-CAR Treg i.v. injection





Muller, Ferreira et al, Front Immunol 2021

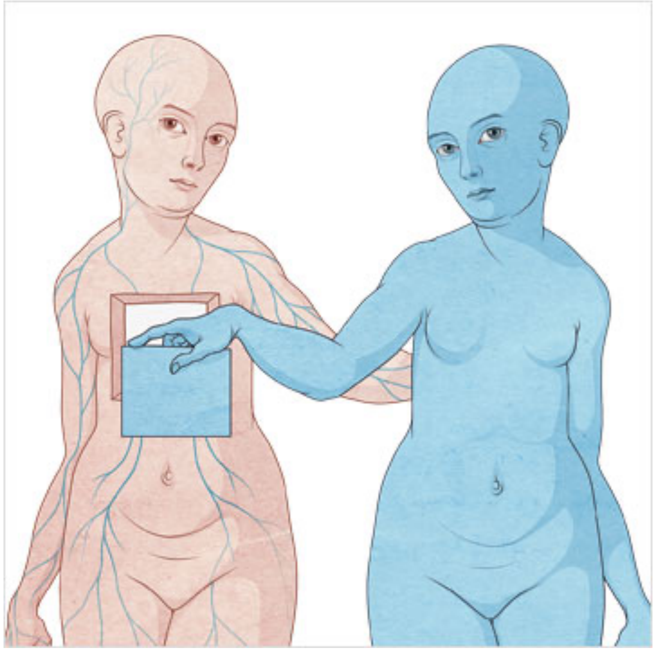


Why do normal T cells, which recognize foreign peptide antigens bound to self MHC molecules, react strongly against the allogeneic MHC molecules of a graft?

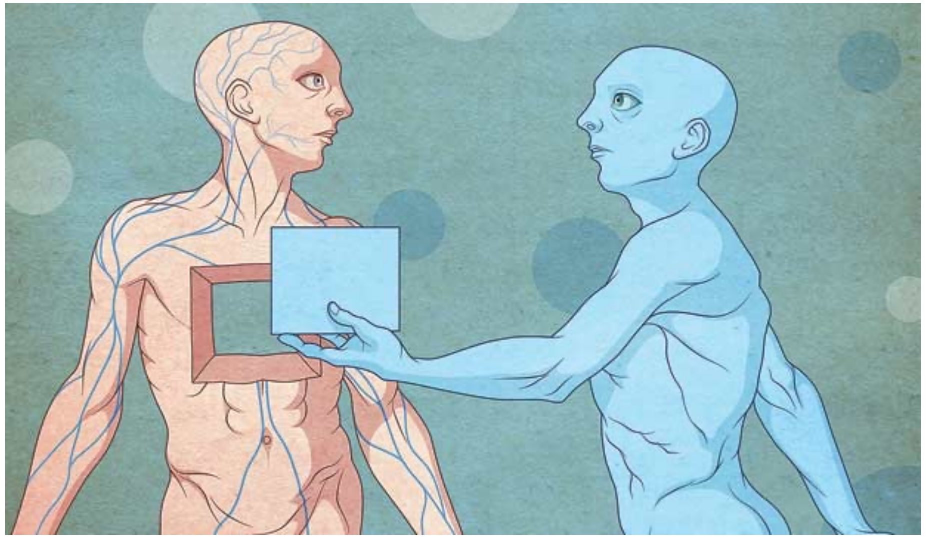
What are the main mechanisms of allograft rejection?

How is the likelihood of graft rejection reduced in clinical transplantation?

What are some of the problems associated with the transplantation of hematopoietic stem cells?



QUESTIONS ?



Illustrations by Richard Wilkinson