Managing the Response in Organ Transplantation

Jonathan S. Maltzman

FOCIS Clinical Immunology Course

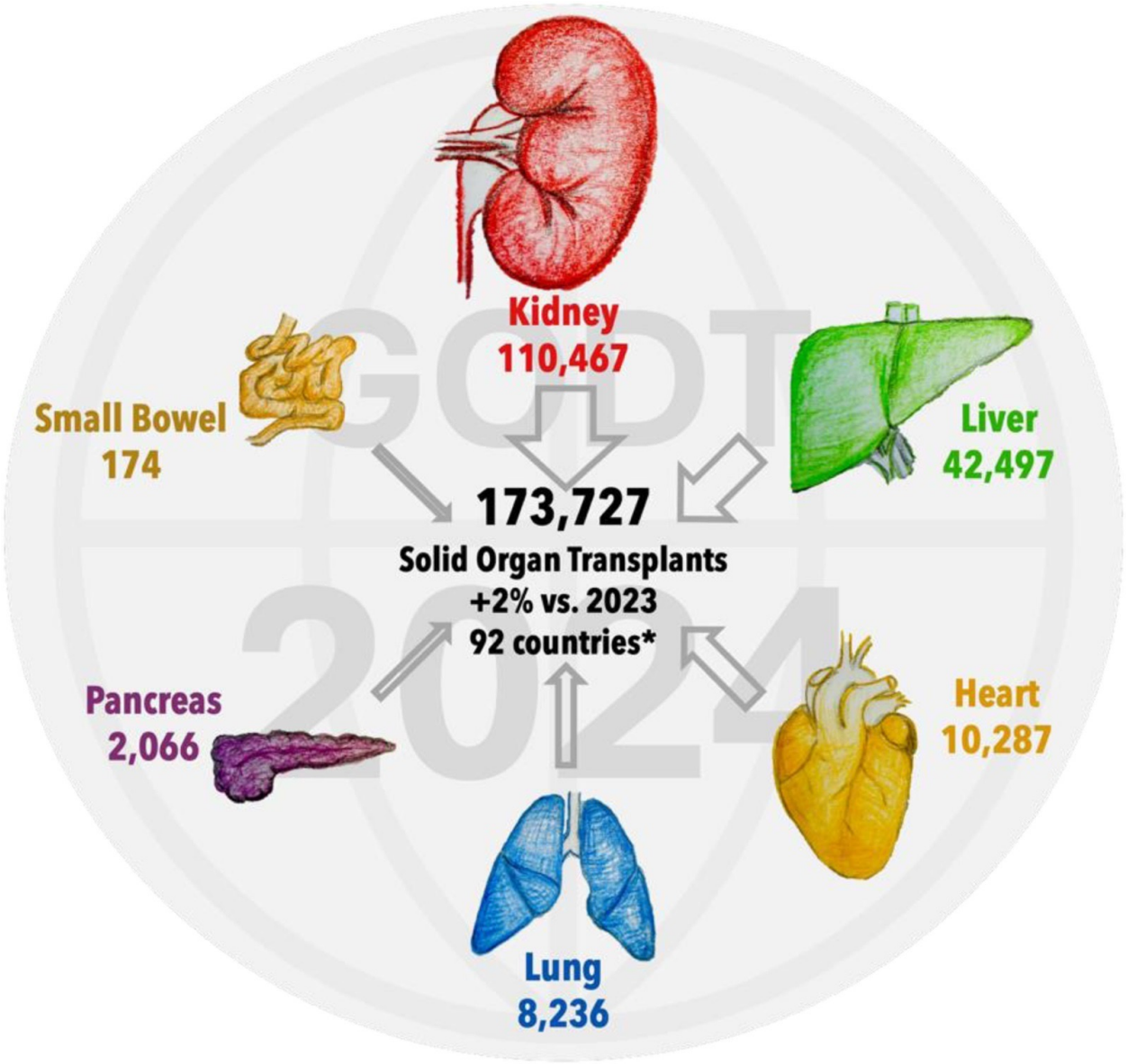
June 2026

San Francisco, A

Stanford MEDICINE

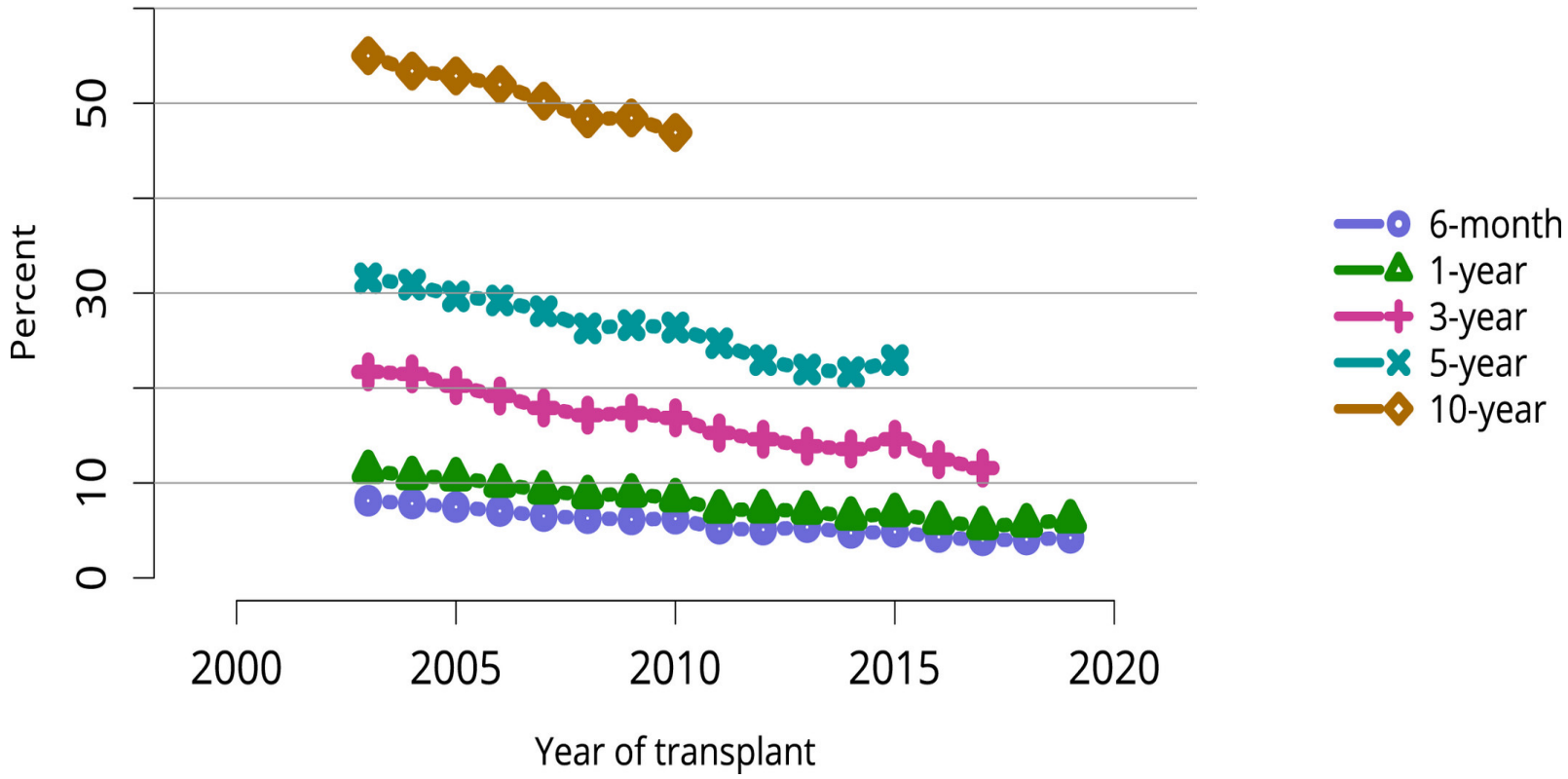
- Disclosures:
  - Qihan Biotech – SAB
  - Kamada -- SAB
  - My spouse is employed by and has an equity interest in Adicet Bio

  - I am employed by the US Department of Veterans Affairs. The views expressed in this presentation are my own and do not necessarily represent the views of the Department of Veterans Affairs or the US Government



Martin et al. Transplantation 110(3):e655-e669, March 2026

Outcomes: unadjusted graft failure from deceased donor kidneys in adults



While 1 year graft survival is superb, 10-year success lags considerably

SRTR annual data 2020
AJT 22 (s2):21-136 2022

A few quick definitions

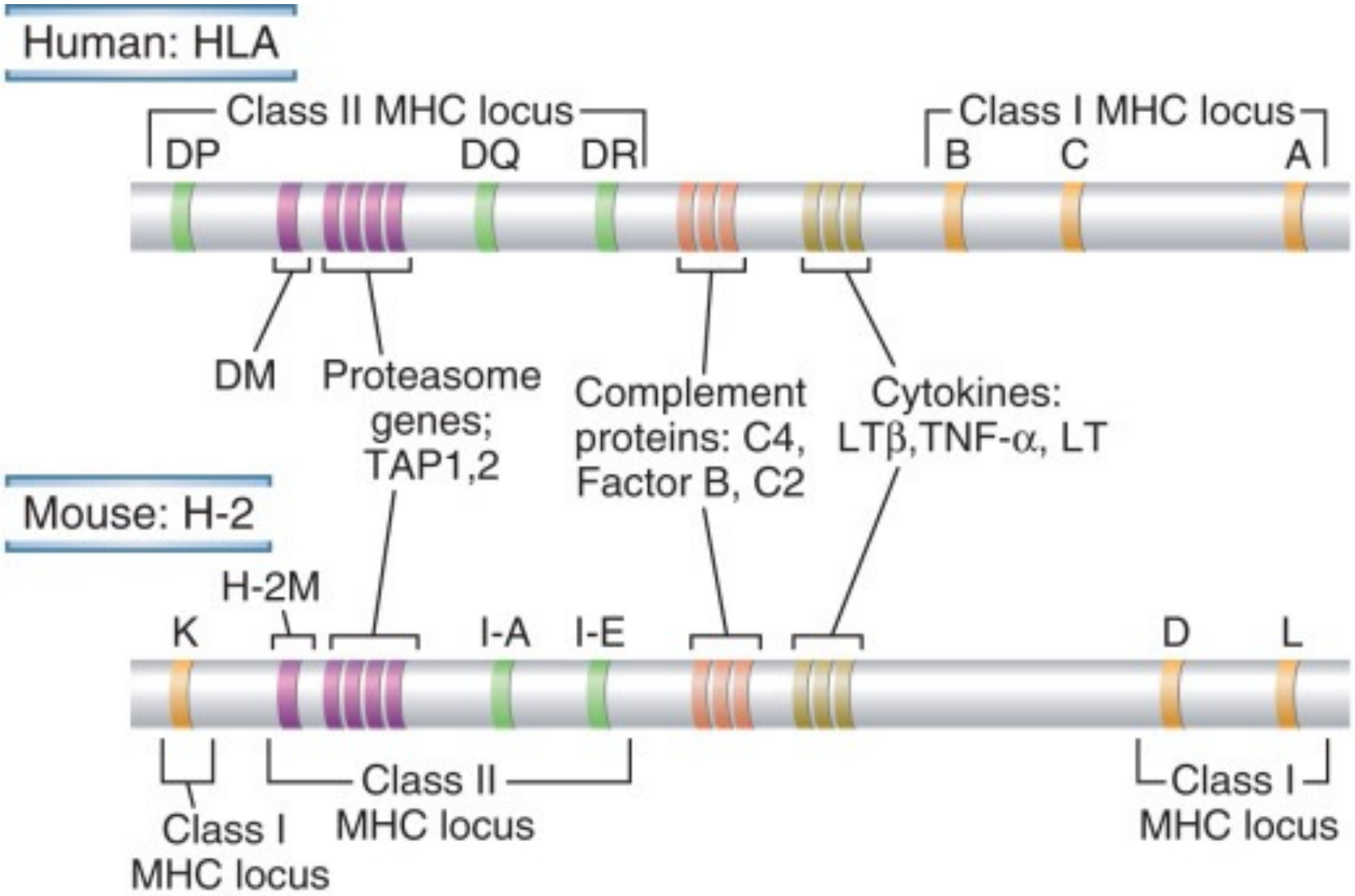
- Syngeneic: Refers transplants betweeen genetically identical animals (i.e. identical twins, inbred strains of animals). Accept transplants from one-another without immunosuppression.

- Allogeneic: Transplants between animals mismatched for MHC or other histocompatibility genes, within the same species.

- Xenogeneic: Transplants between species.

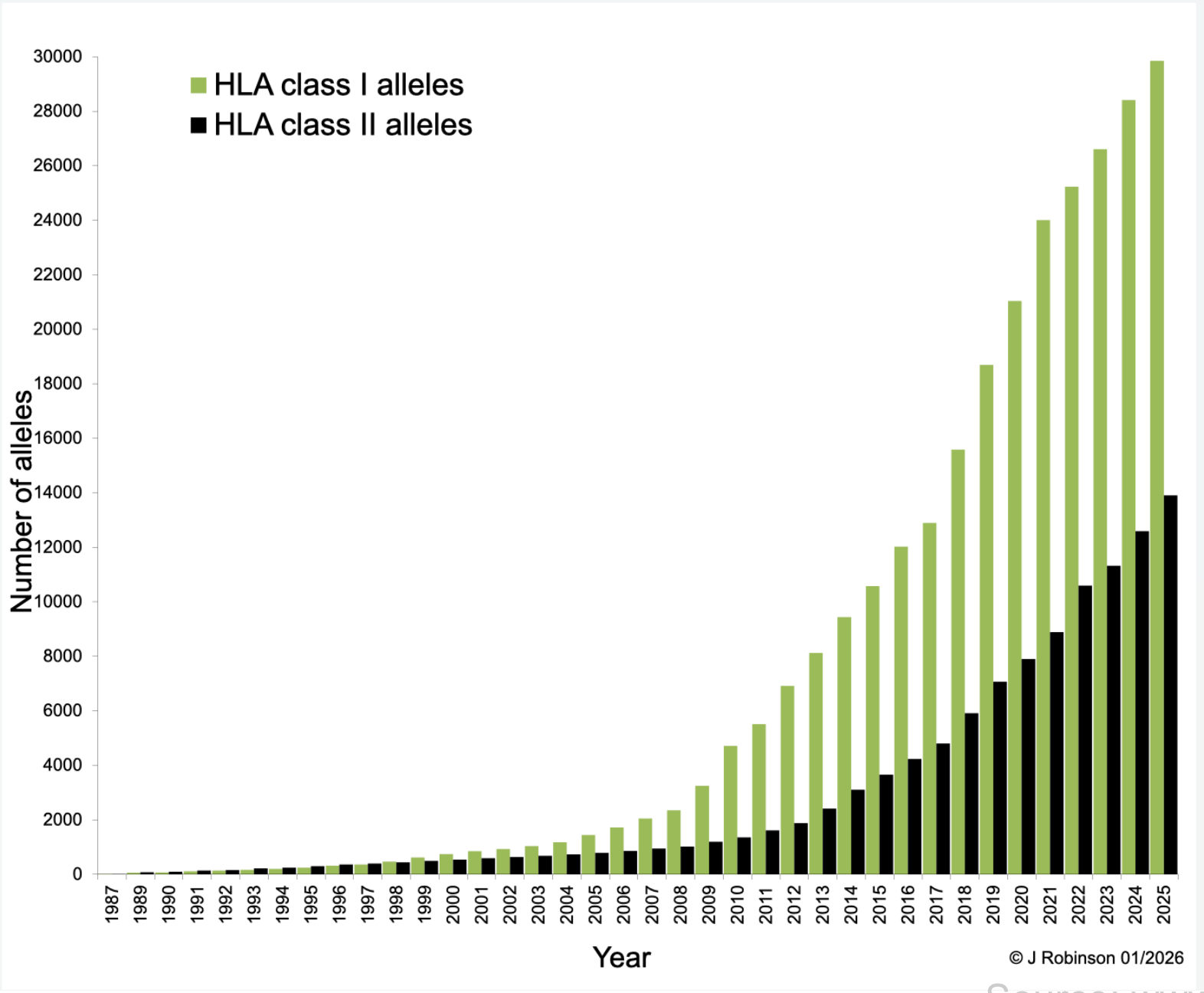
Which immune cells are important in transplant rejection?

HLA A, B, DR are most important for human matching



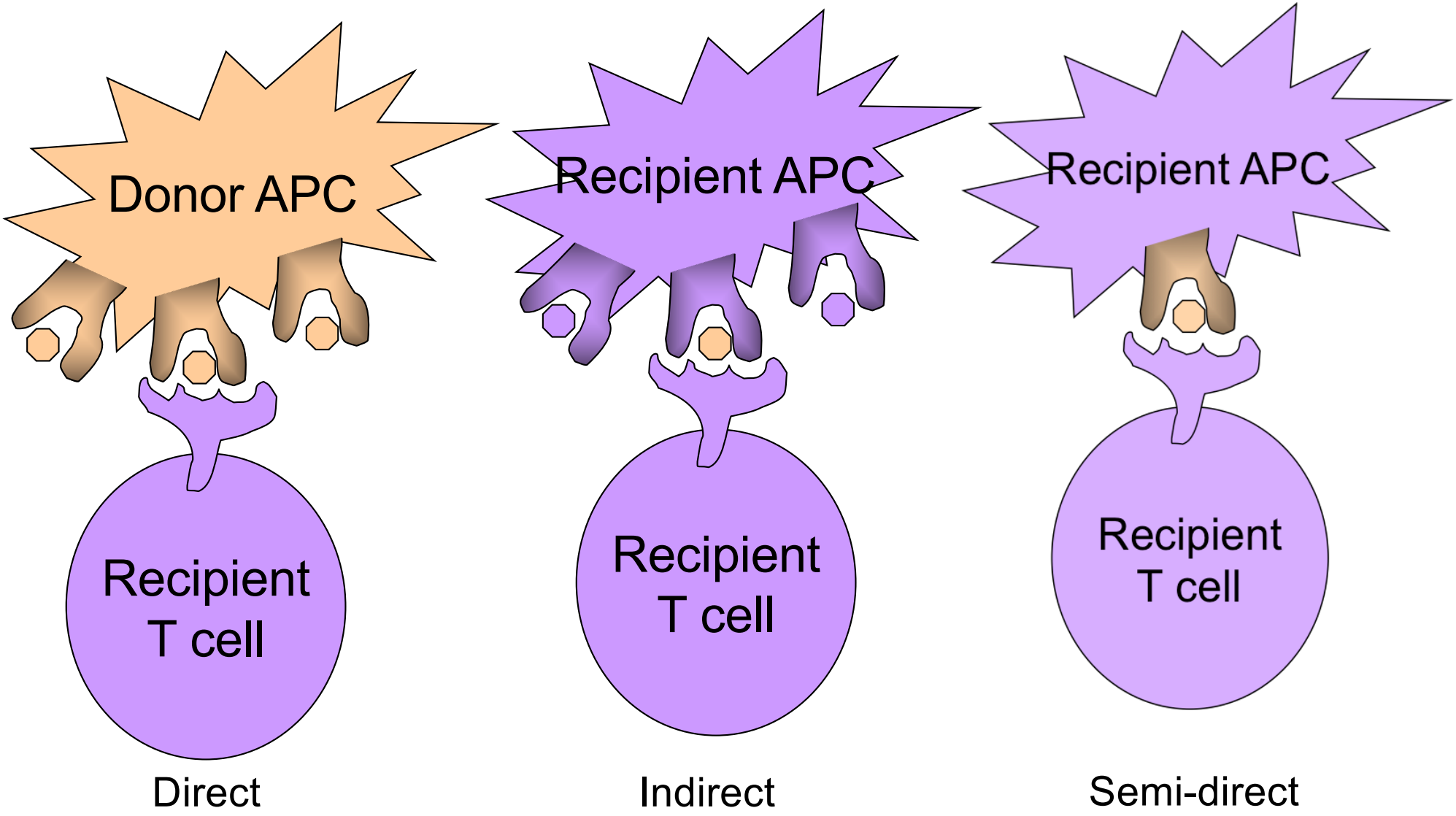
Abbas. Cellular and Molecular Immunology 2018

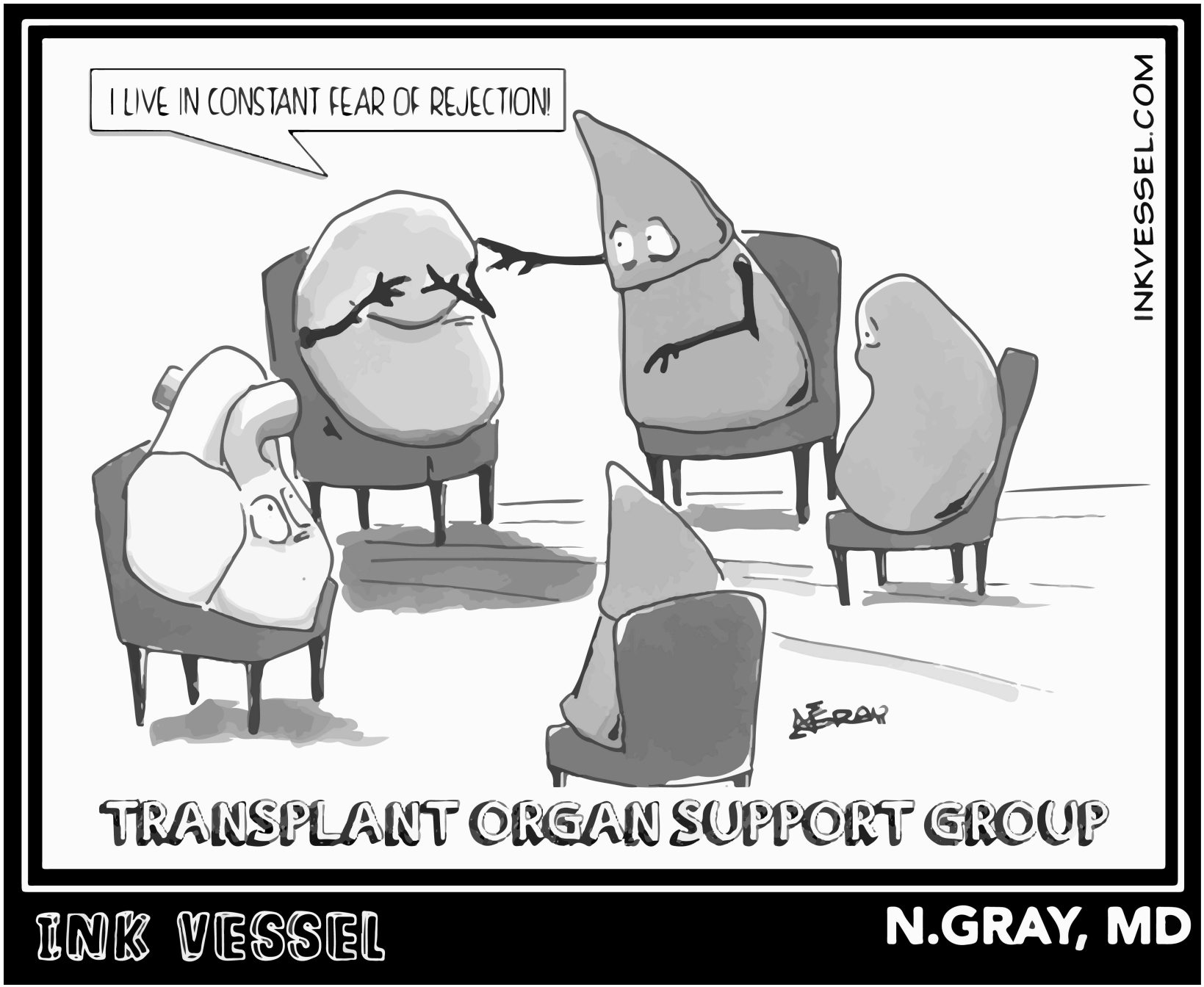
HLA is highly polymorphic



Source: www.hla.alleles.org

Multiple Mechanisms of Allorecognition




I LIVE IN CONSTANT FEAR OF REJECTION!
INKVESSEL.COM
TRANSPLANT ORGAN SUPPORT GROUP
INK VESSEL
N.GRAY, MD

Types of Immune Rejection

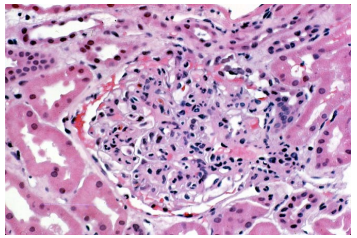
	Hyperacute	Acute Humoral	Acute Cellular	"Chronic"
Time Frame	Minutes	Days to weeks	Days to weeks	Years
Mediated by	Preformed Antibody	Antibody	T cells	Immune + Non-immune
Prevention/ treatment	Test PRA/cross-match	Immuno-suppression	Immuno-suppression	Immuno-suppression/ avoid damage

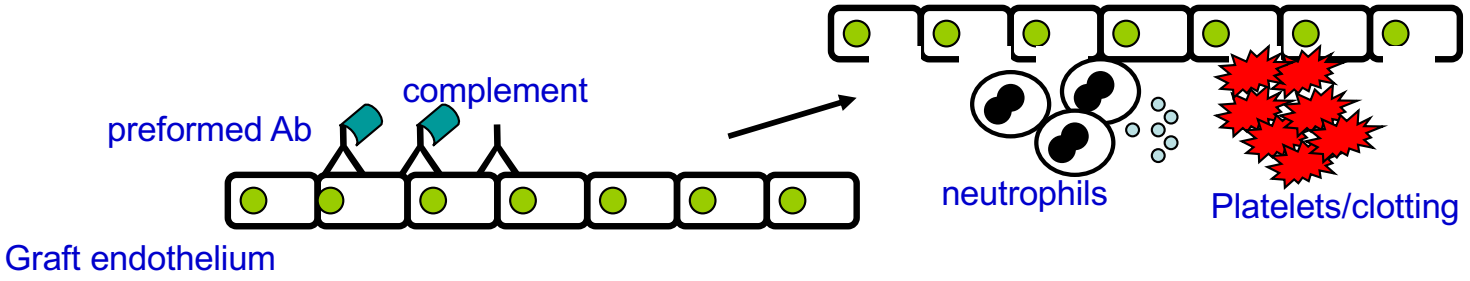
Hyperacute rejection

occurs minutes to hours after transplantation

- antibody-mediated and complement-dependent
- preformed antibodies specific for MHC antigens or carbohydrate determinants
- target is vascular endothelium
- can be avoided by prescreening

Image from tpis.upmc.com

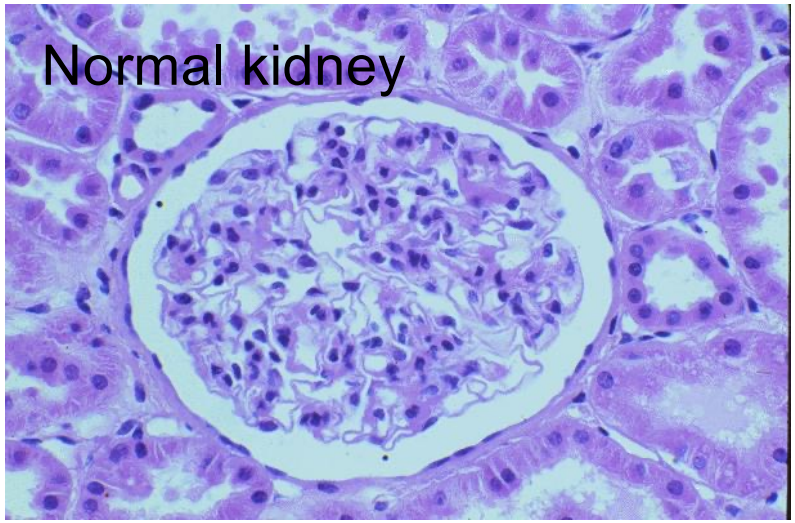


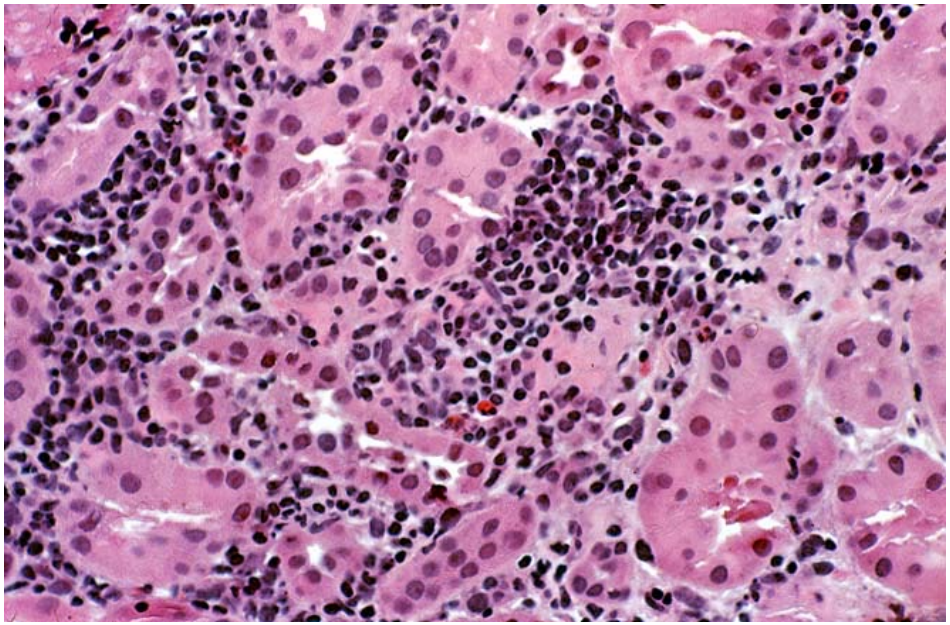


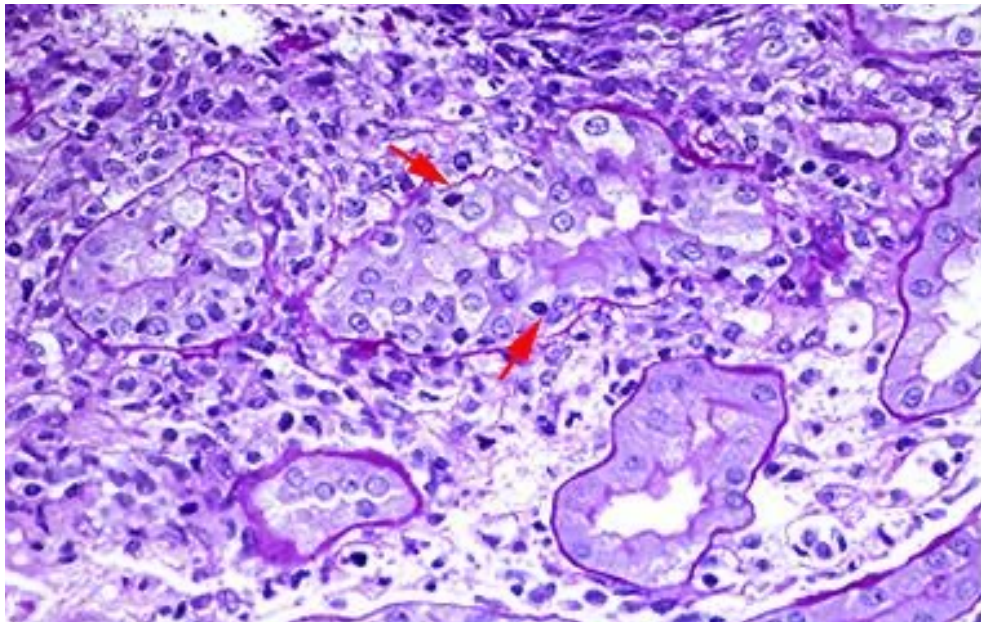
Acute T Cell Mediated Rejection

Direct alloreactivity

Mononuclear infiltrate
- tubulitis
- interstitial infiltrate



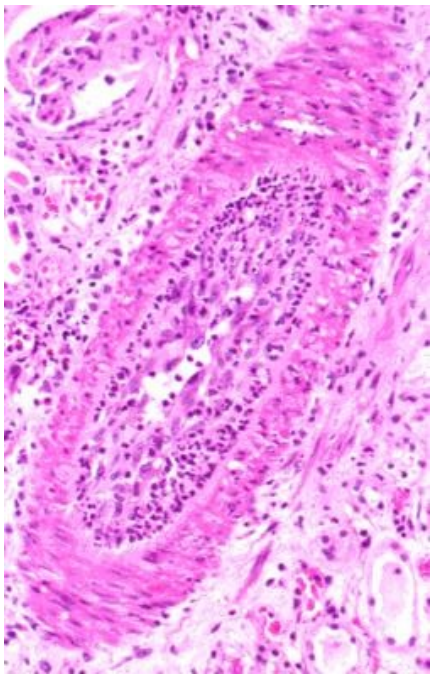


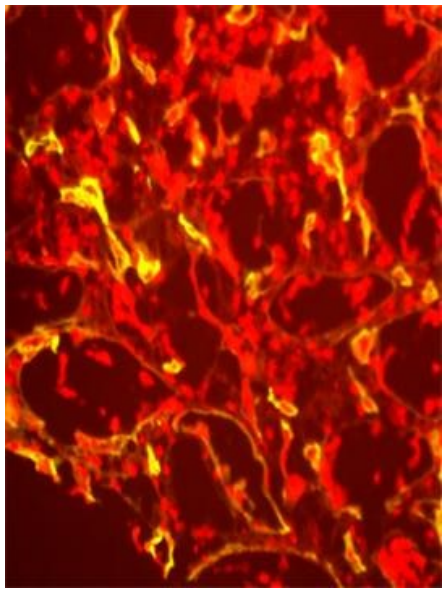


Acute Antibody-Mediated Rejection

<u>Pathophysiology</u>
Activation of both B and T cells
Circulating anti-donor antibodies
Complement activation

<u>Histopathology</u>
C4d+ immunofluorescence
Donor Specific Antibody (DSA)
Vasculitis/peritubular capillaritis
Interstital hemorrhage
Capillary-endothelial swelling
Lymphocytic infiltrate not required

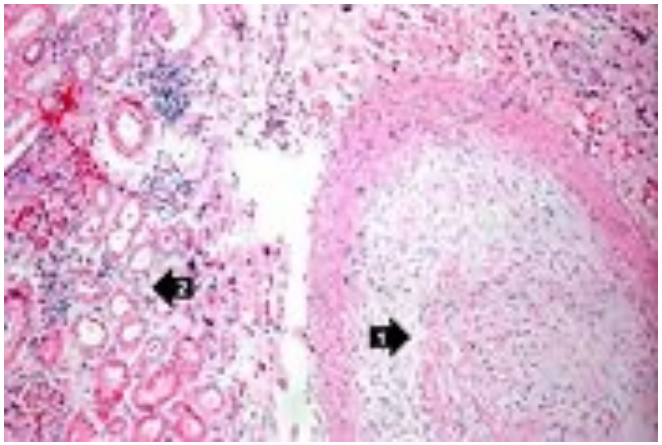


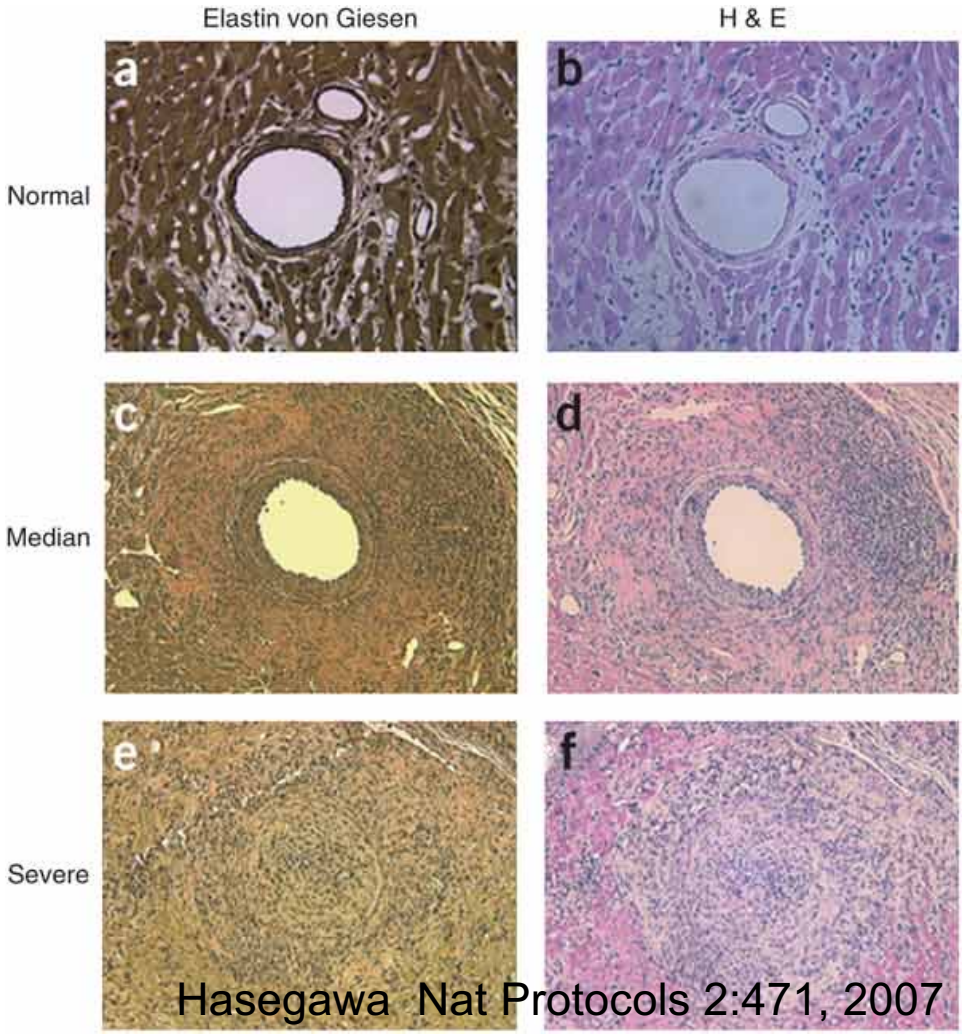


Chronic Rejection

<u>Non-immune and Immune mediated</u>
Ischemic injury
Calcineurin inhibitors
Previous acute rejection
Indirect Alloreactivity with antibody production

Fibrosis
Neointimal thickening



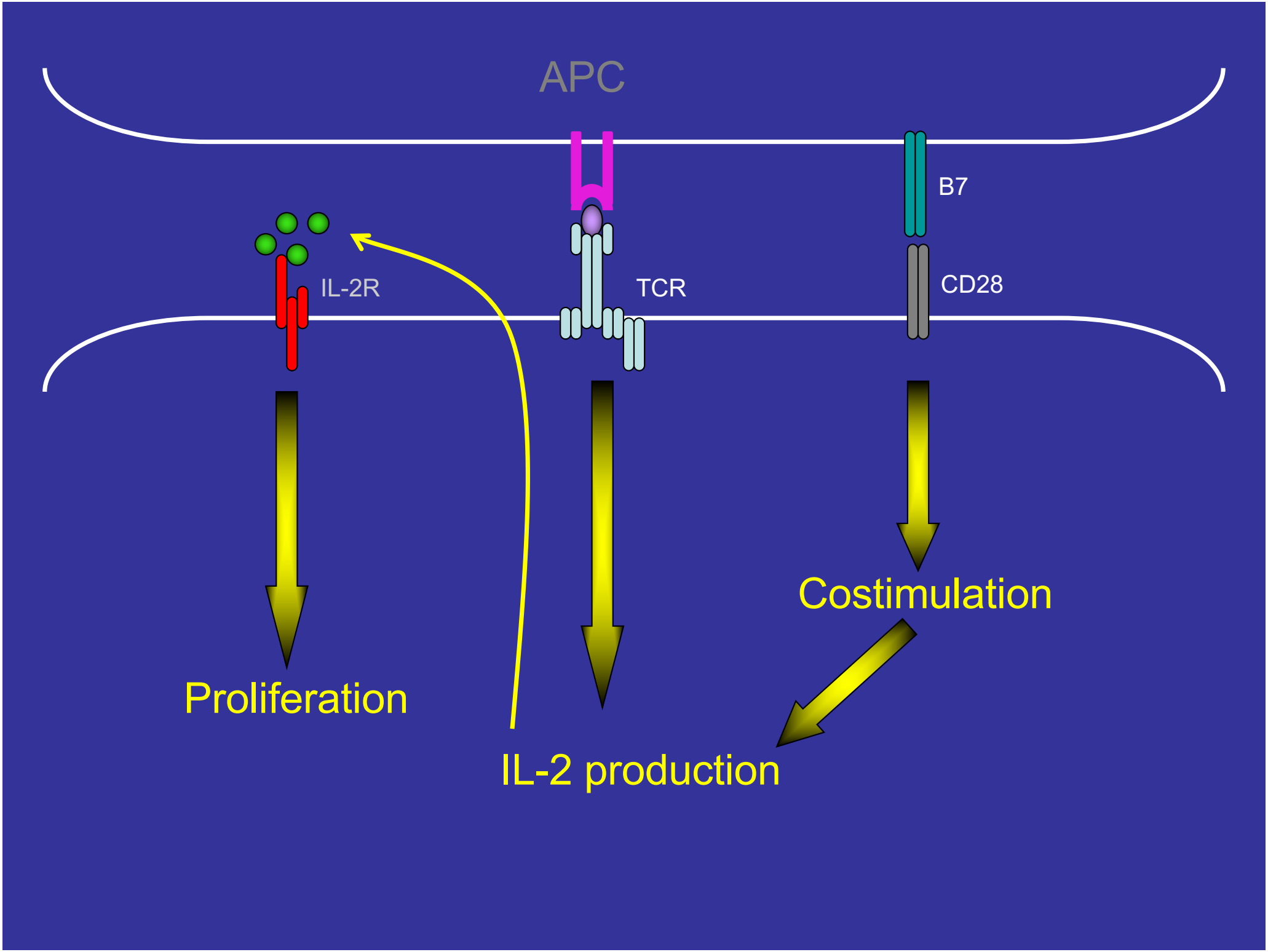


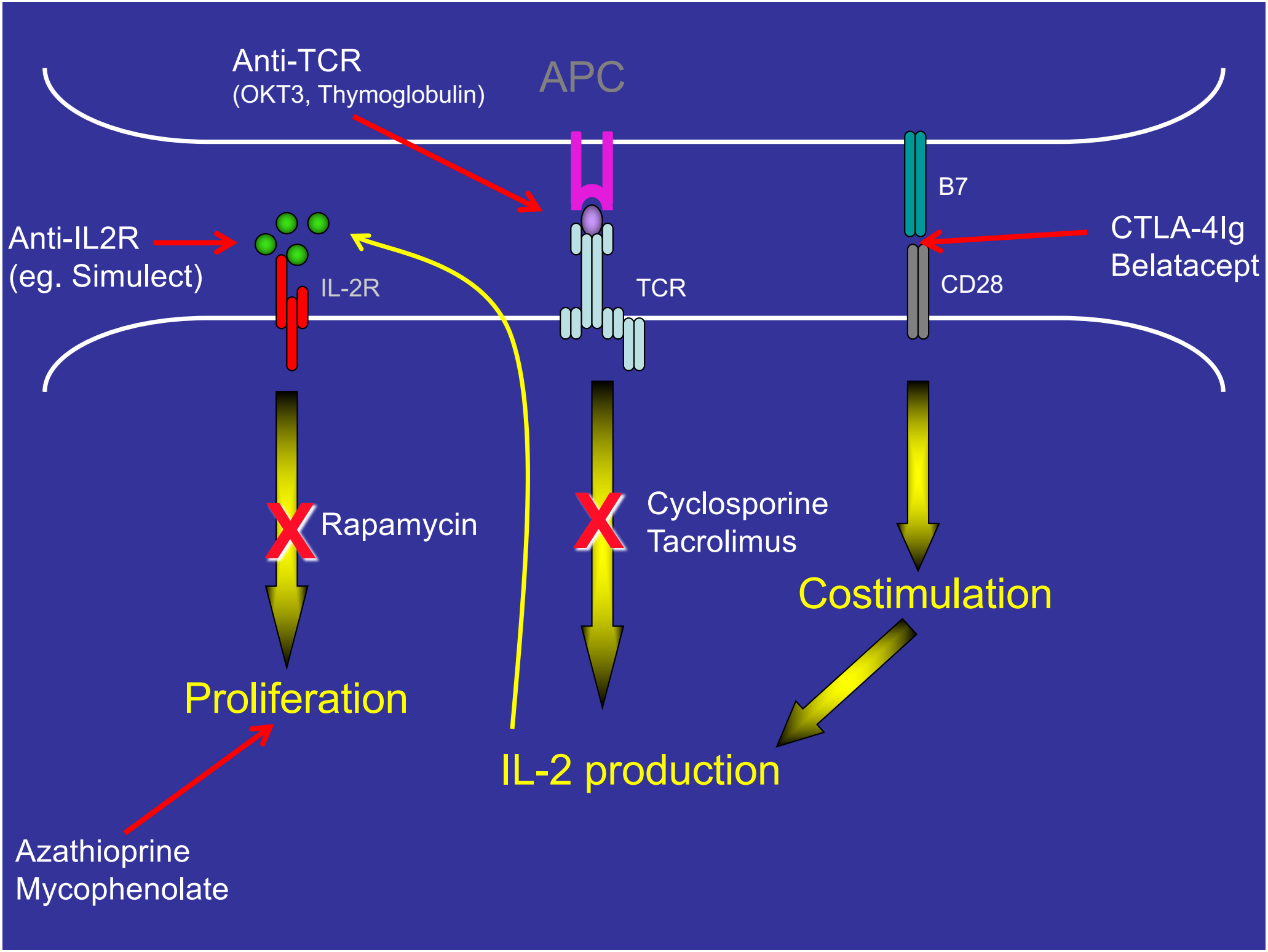
Hasegawa Nat Protocols 2:471, 2007

Immunosuppression

Axioms of Immunosuppression

- Three effects:
  - Immunosuppressive effect
  - Immunodeficient complications
  - Non-immune toxicity
- Non-immune toxicity is dose-limiting
- Immunosuppressive effect and immunodeficient complications are inherently linked. Increasing immunosuppression always increases immunodeficiency.


APC
B7
IL-2R
TCR
CD28
Costimulation
Proliferation
IL-2 production


Anti-TCR
(OKT3, Thymoglobulin)
APC
B7
Anti-IL2R
(eg. Simulect)
IL-2R
TCR
CD28
CTLA-4Ig
Belatacept
Rapamycin
Cyclosporine
Tacrolimus
Costimulation
Proliferation
IL-2 production
Azathioprine
Mycophenolate

Drugs that affect Signal 1

- Anti-T cell agents
  - Thymoglobulin: rabbit anti-thymocyte antiserum
  - ATGAM: horse anti-thymocyte antiserum
  - OKT3: monoclonal anti-CD3ε
    - Cytokine storm, anti-murine antibody reaction
  - Campath/anti-CD52

- Calcineurin Inhibitors
  - Cyclosporin A
  - Tacrolimus/FK506/Prograf

The New England
Journal of Medicine

Volume 313 AUGUST 8, 1985 Number 6

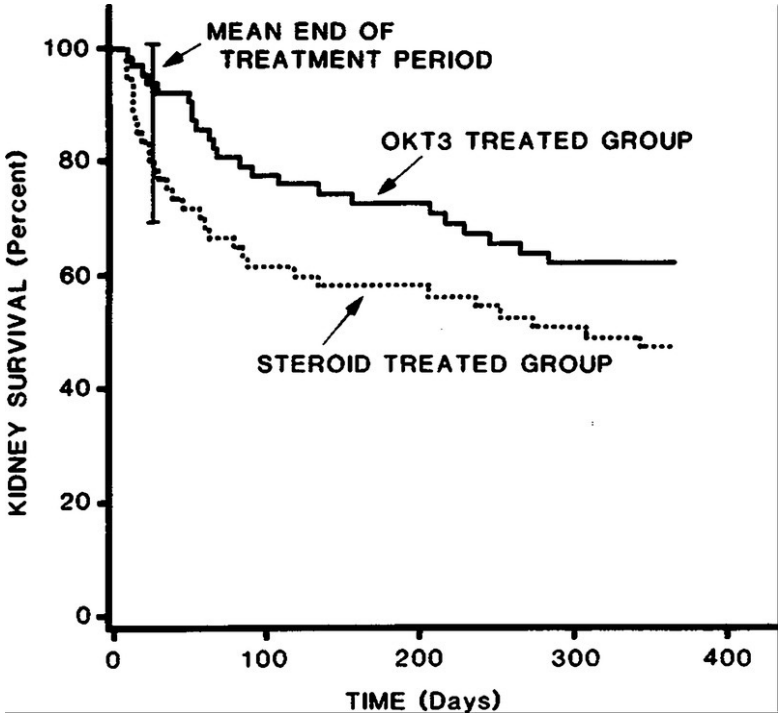
A RANDOMIZED CLINICAL TRIAL OF OKT3 MONOCLONAL ANTIBODY FOR ACUTE REJECTION OF CADAVERIC RENAL TRANSPLANTS

ORTHO MULTICENTER TRANSPLANT STUDY GROUP*

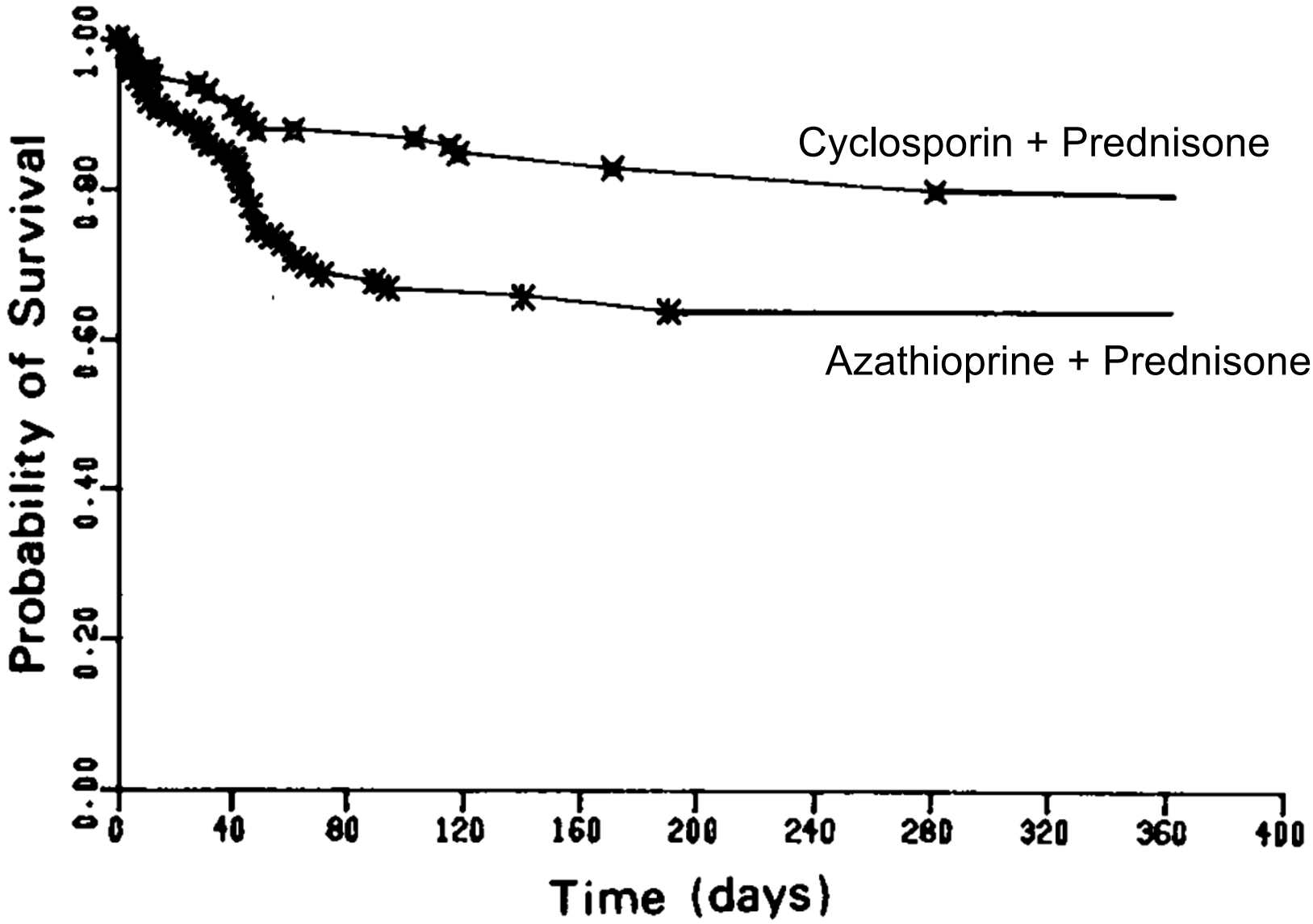
Indication: Acute rejection in kidney transplant

Adverse effects:

- First (and second) dose reactions
  - 45-60 minutes after infusion
  - fever, chills, dyspnea, chest pain, nausea, vomiting, pulmonary edema
- No increase in severe infection
- Anti-drug antibodies – 80% of subjects.
  - Human-anti-mouse antibodies

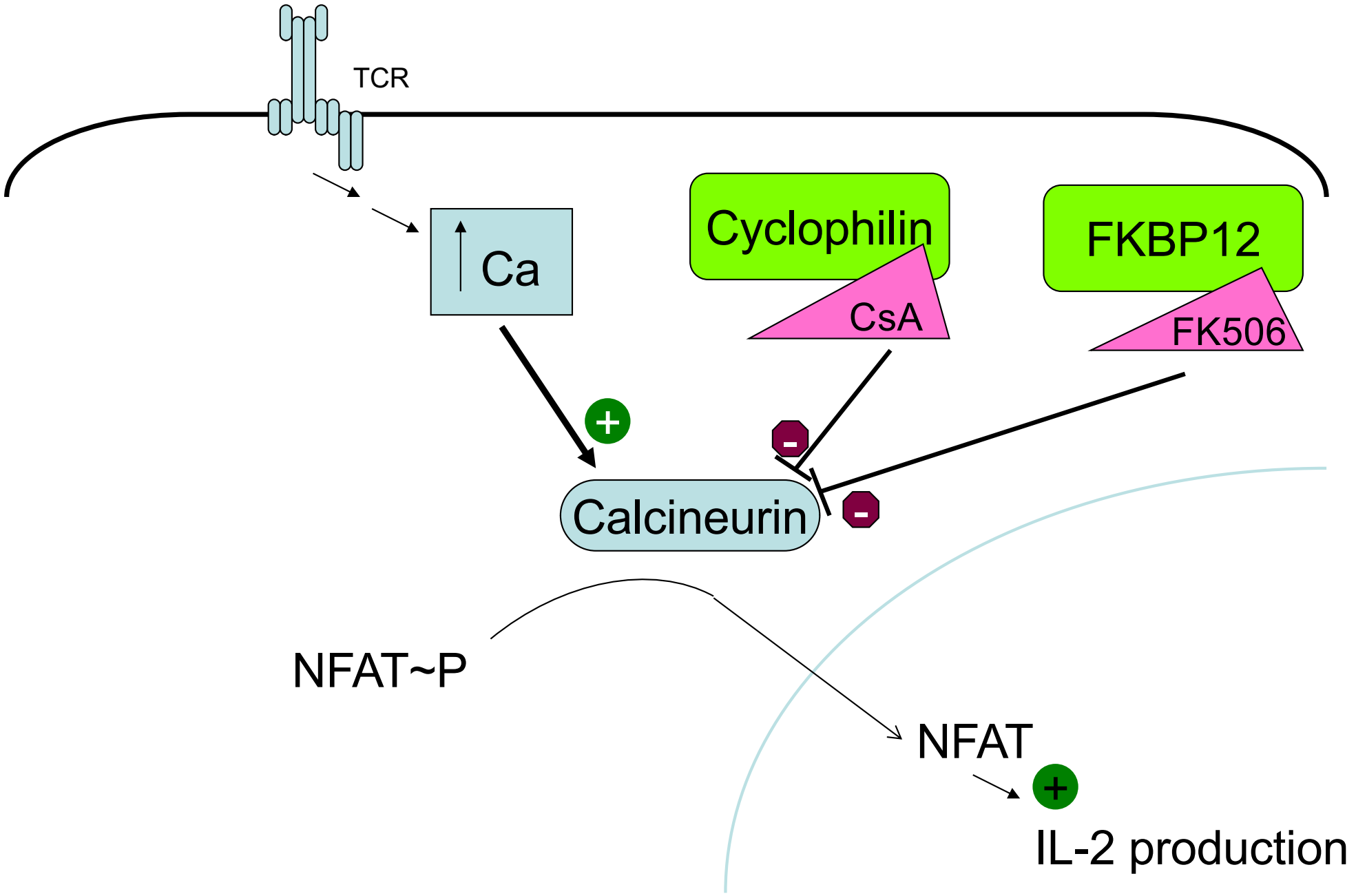


Cyclosporin vastly improved outcomes

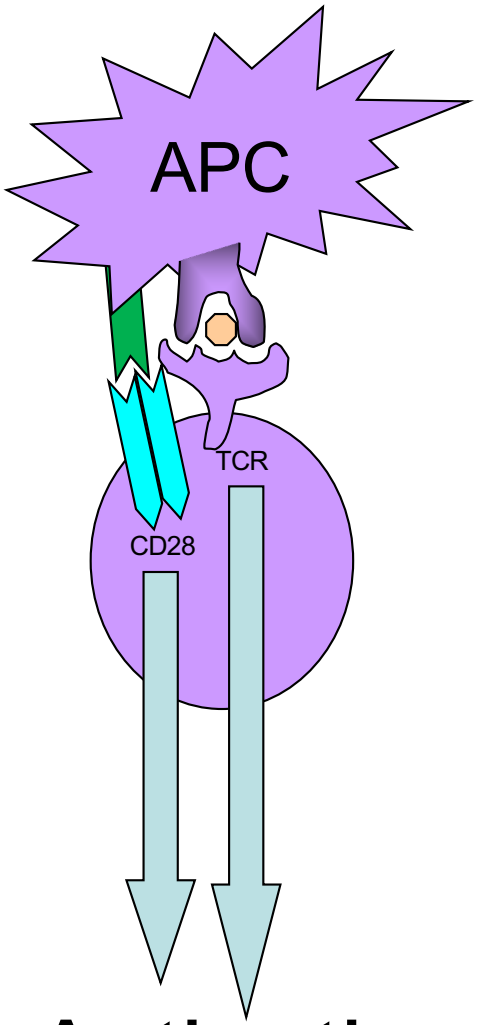


Adapted from NEJM 309:809 (1983)

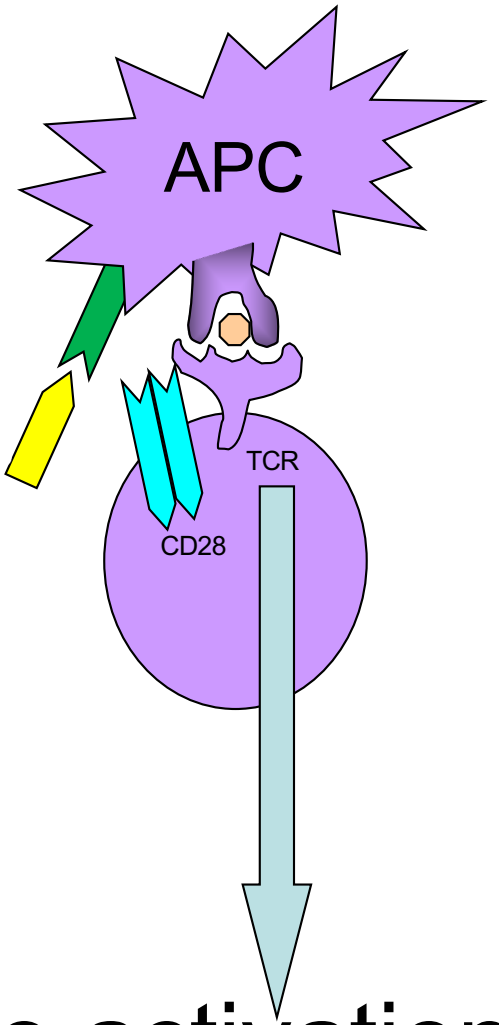
Calcineurin inhibitors -- mechanism of action



Antigen specific signals without costimulation lead to anergy



Activation

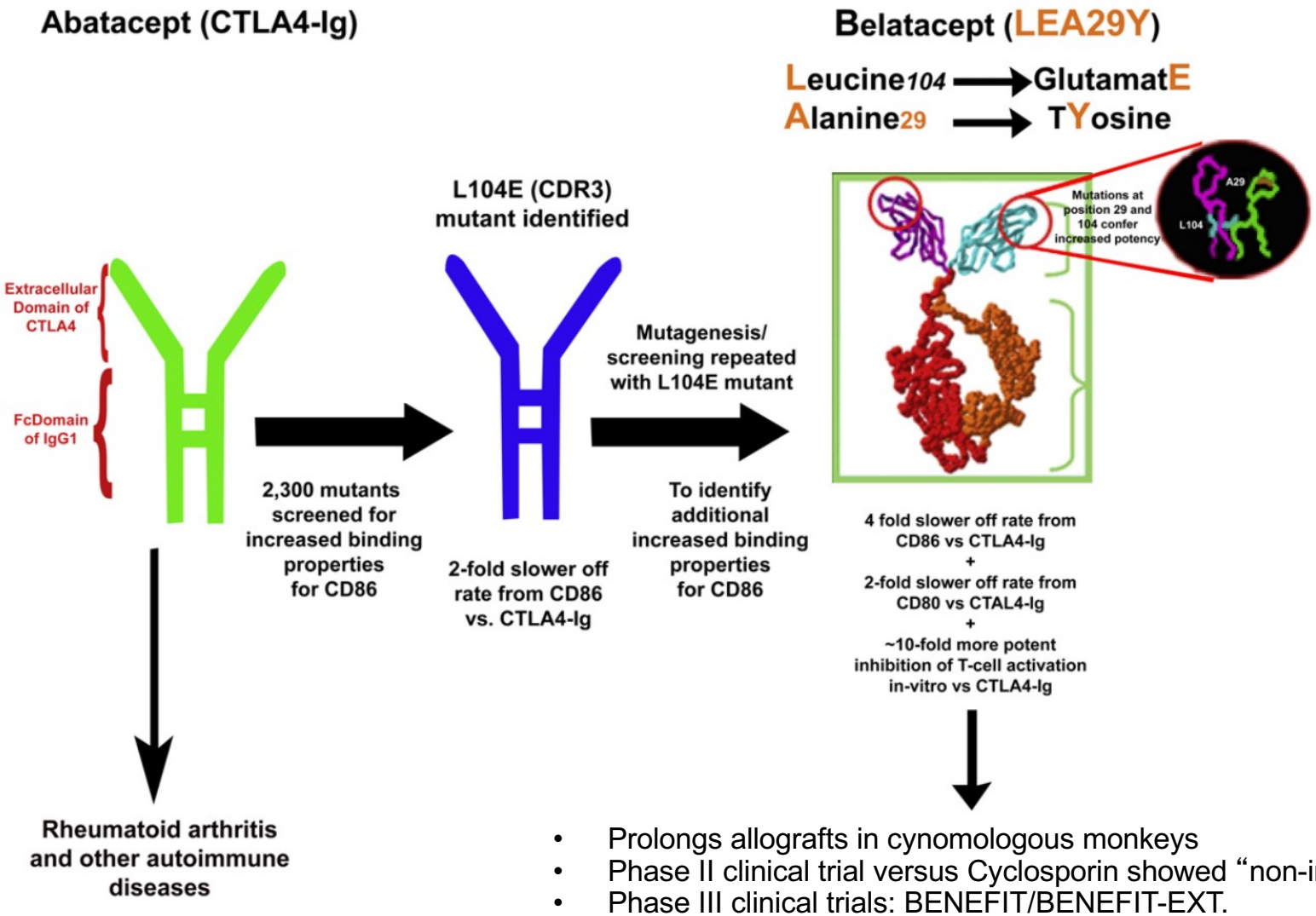


No activation
“Anergy”

Costimulatory Inhibition
CTLA4-Ig

- Binds to B7-1 and B7-2 inhibiting stimulation of CD28
- Induces T cell anergy in mice
- Abetacept -- failed in primate transplant setting but currently used in RA
- Belatacept developed by mutagenesis and is 10x increased binding affinity

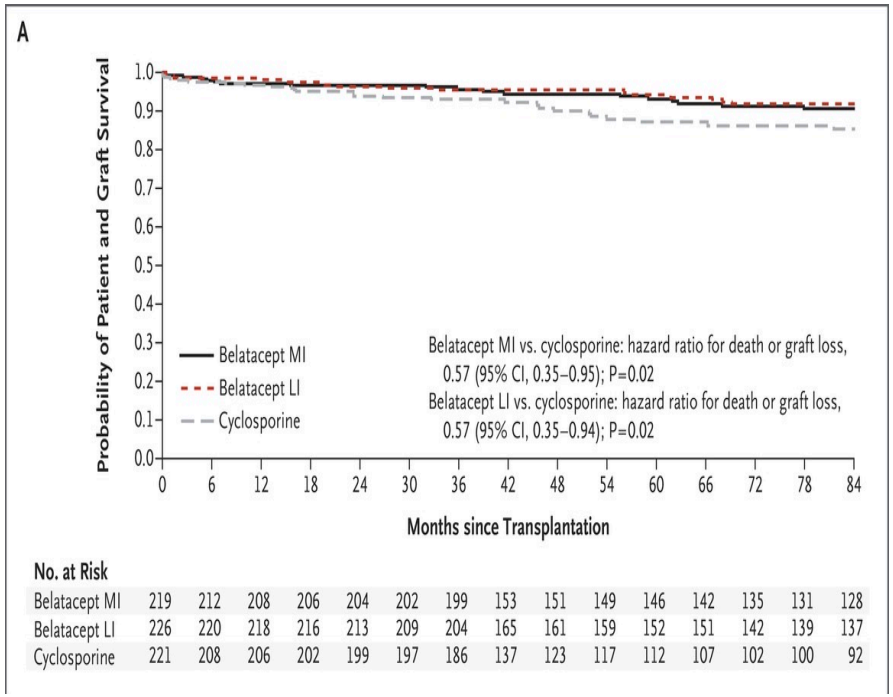
Development of LEA29Y

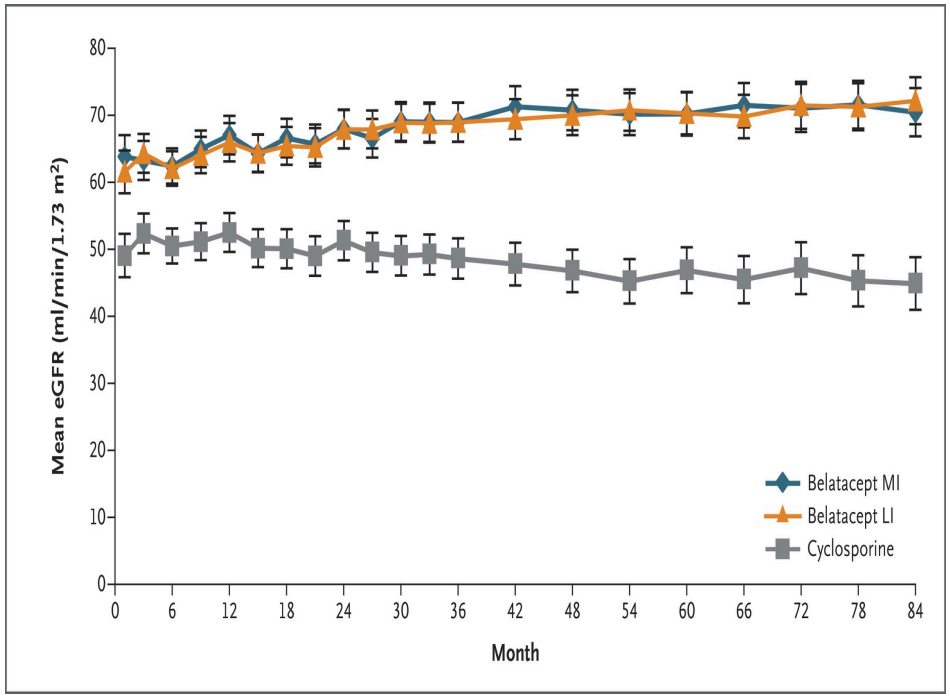


- Prolongs allografts in cynomologous monkeys
- Phase II clinical trial versus Cyclosporin showed “non-inferiority”
- Phase III clinical trials: BENEFIT/BENEFIT-EXT.
  - Better renal function
  - Slightly higher acute rejection and PTLD

Adapted from JACI 121:229 (2008)

BENEFIT – Phase III belatacept vs cyclosporin



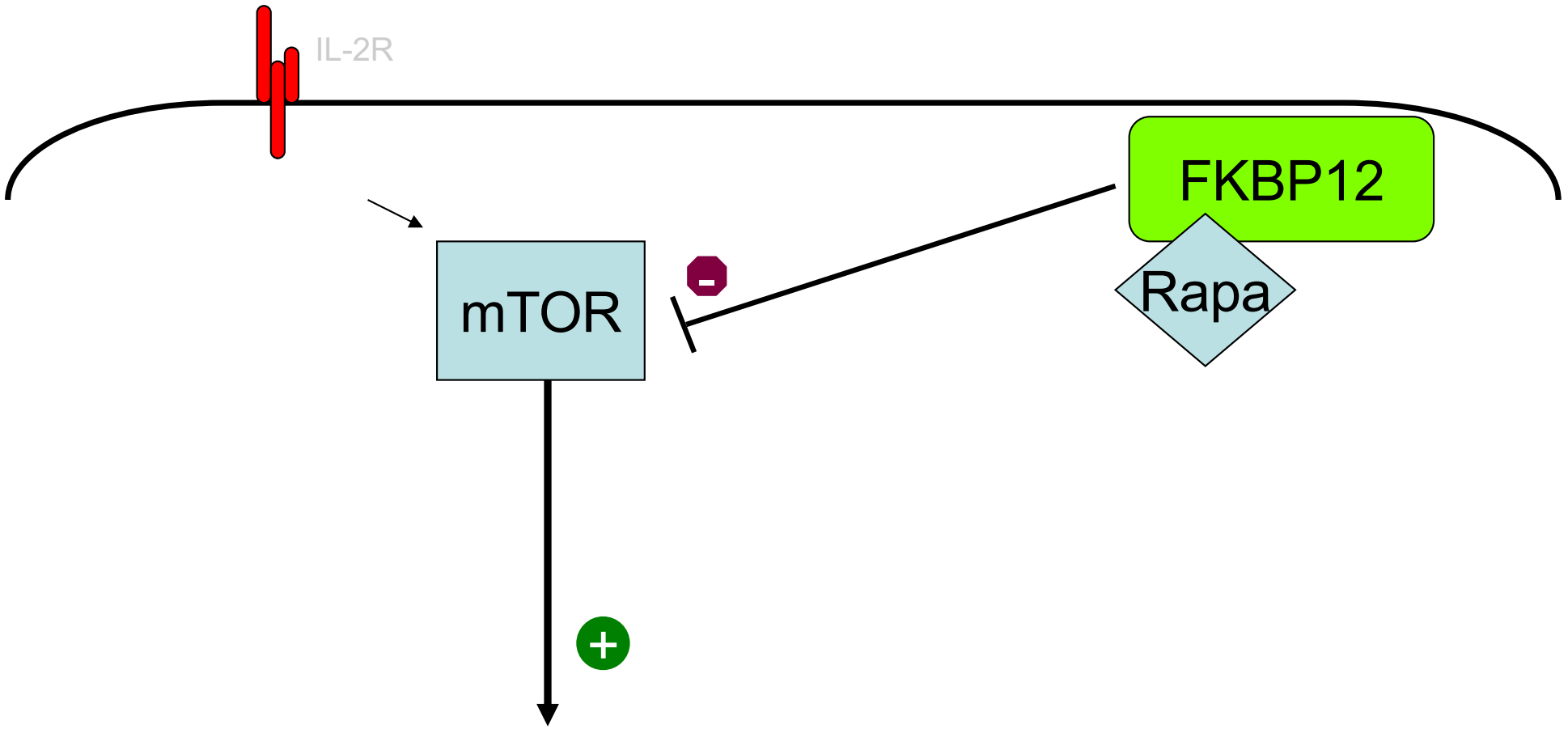


Vincenti F et al. N Engl J Med 2016;374:333-343

Cytokine Inhibition (signal 3)

- Anti-CD25: daclizumab or basiliximab
- Rapamycin/sirolimus and everolimus
  - Inhibits mTOR
  - Hyperlipidemia, poor wound healing
  - Anti-neoplastic properties/cardiac stenting

Rapamycin -- mechanism of action



- Protein synthesis
- Glycolysis
- Cell cycle progression
- Inhibition of Autophagy

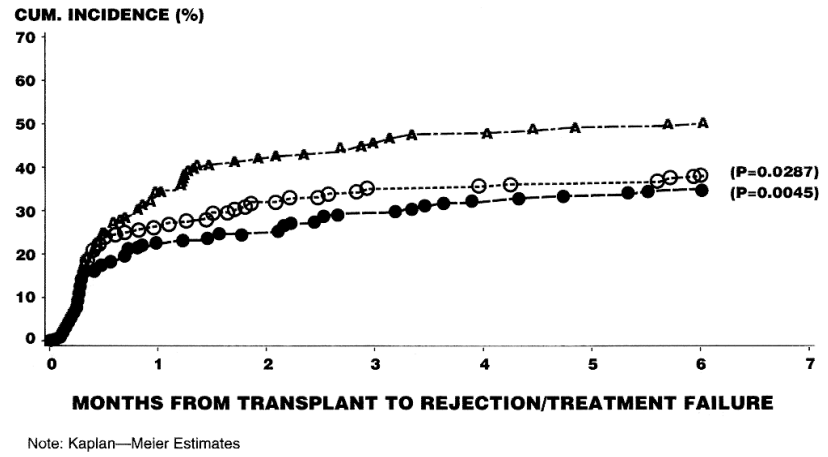
Anti-metabolites

- Azathioprine / BW57-322
  - discovered in 1957 by Gertrude Elion and George Hitchings who were later awarded 1988 Nobel Prize in Medicine 1988 for “rational drug design”

TABLE 1. *Experience with Kidney Transplantation in 13 Patients Treated Solely with Drugs.*

PATIENT	AGE	SEX	DATE OF OPERATION	DIAGNOSIS	KIDNEY SOURCE	INITIAL DRUGS	BLOOD GROUPS		RENAL FUNCTION	DURATION OF TRANSPLANT	COMMENT
							DONOR	RECIPIENT			
	yr.									days	
L.S.	21	M	Apr., 1960	Familial hereditary nephritis	Cadaveric kidney	6-mercaptopurine (3-4 mg./kg.)	O (Rh positive)	O (Rh positive)	Yes	26	
R.G.	52	M	Nov., 1960	Nephrosclerosis	Infant “hydrocephalic” kidney	6-mercaptopurine (4-5 mg./kg.)	A (Rh negative)	A (Rh negative)	Yes	14	
D.T.	22	M	Mar., 1961	Acute glomerulonephritis	Infant “hydrocephalic” kidney	Imuran (10-12 mg./kg.)	O (Rh positive)	O (Rh positive)	Yes	28	
W.F.	38	M	Dec., 1961	Chronic glomerulonephritis	Infant “hydrocephalic” kidney	Imuran (12 mg./kg.); actinomycin C (10 microgm./kg.).	A (Rh positive)	A (Rh negative)	Yes	3	
E.K.	20	M	Jan., 1962	Agenesis of kidney & chronic glomerulonephritis	Cadaveric kidney	Imuran (6 mg./kg.); actinomycin C (5 microgm./kg.).	B (Rh positive)	O (Rh positive)	No	—	
M.D.	23	M	Apr., 1962	Chronic glomerulonephritis	Cadaveric kidney	Imuran (2-4 mg./kg.)	O (Rh negative)	O (Rh positive)	Yes	365*	
E.K.	39	F	May, 1962	Familial hereditary nephritis	Cadaveric kidney	Imuran (4 mg./kg.)	A (Rh negative)	A (Rh negative)	No	—	Excessively prolonged period of ischemia of donor kidney
T.G.	24	M	Sept., 1962	Chronic glomerulonephritis	Infant “hydrocephalic” kidney	Imuran (3 mg./kg.); Azaserine (1.0 mg./kg.).	O (Rh positive)	O (Rh positive)	Yes	160	
J.W.	38	F	Oct., 1962	Absence of kidneys	Cadaveric kidney	Imuran (3 mg./kg.); Azaserine (1.0 mg./kg.).	O (Rh positive)	O (Rh positive)	No	—	Probable drug toxicity or excessively prolonged period of ischemia of donor kidney
C.R.	44	M	Nov., 1962	Chronic glomerulonephritis	Infant “hydrocephalic” kidney	Imuran (3 mg./kg.); Azaserine (1.0 mg./kg.).	A (Rh positive)	A (Rh positive)	No	—	Probable technical failure
F.C.	23	M	Dec., 1962	Nephrotoxic nephritis	Mother	Imuran (3 mg./kg.); Azaserine (1.0 mg./kg.).	A (Rh positive)	A (Rh positive)	Yes	110*	
H.R.	35	M	Jan., 1963	Chronic glomerulonephritis	Brother	Imuran (3 mg./kg.); Azaserine (0.5 mg./kg.).	O (Rh positive)	O (Rh positive)	Yes	60*	
G.B.	39	M	Feb., 1963	Polycystic disease	Adult, unrelated	Imuran (3-4 mg./kg.); Azaserine (0.5 mg./kg.).	O (Rh positive)	O (Rh positive)	Yes	40*	

Murray et al. NEJM 1963

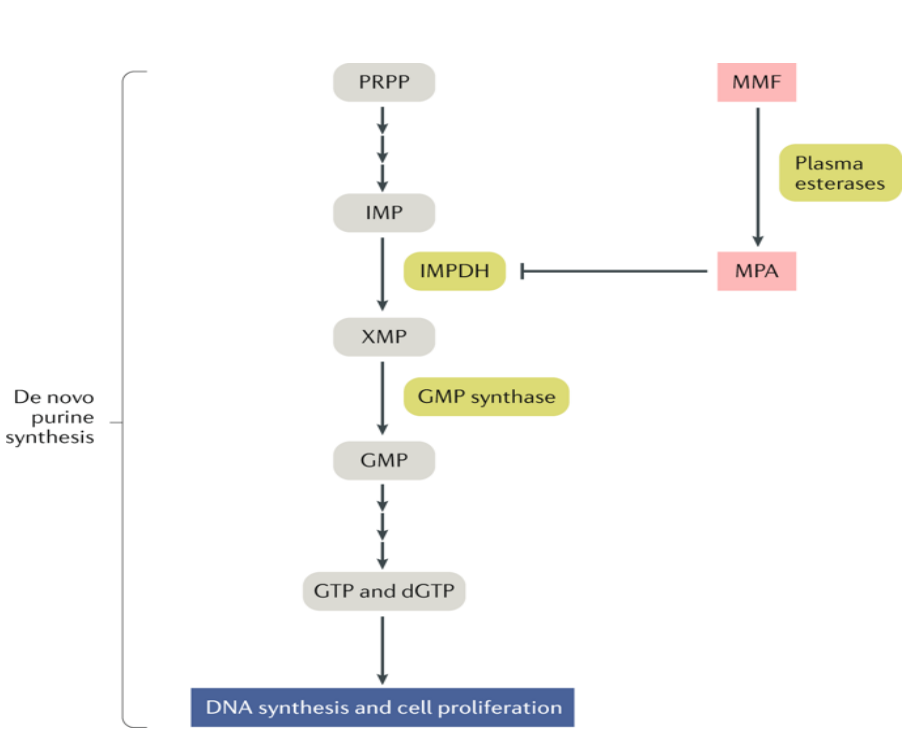


Note: Kaplan—Meier Estimates

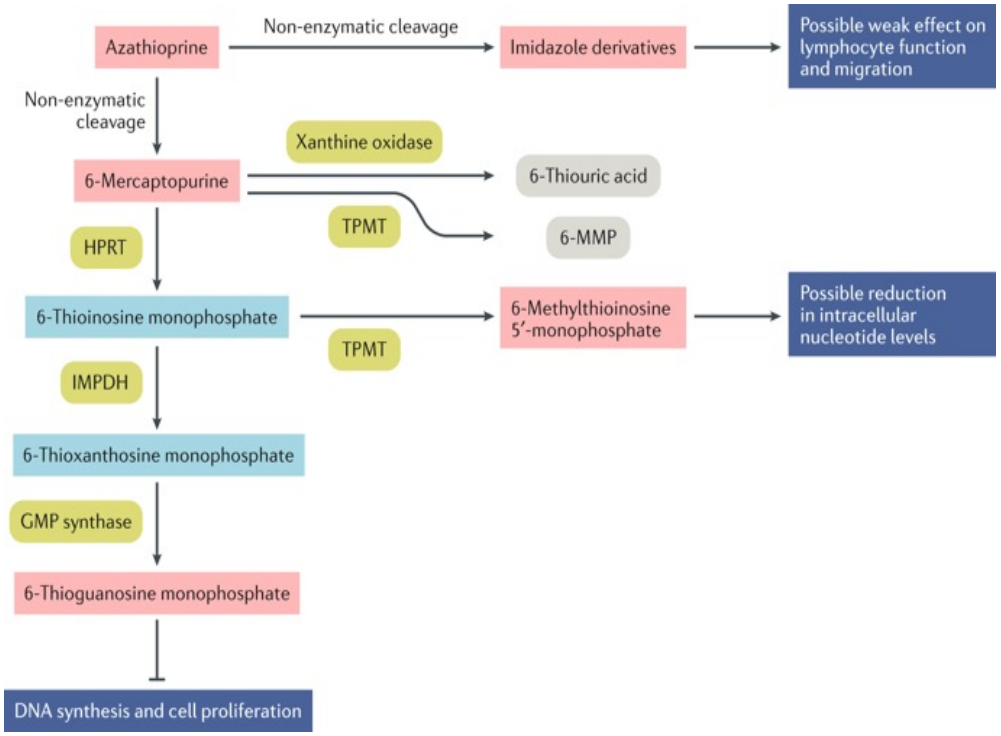
Transplantation 61:1026 (1996)

Anti-metabolites

Mycophenolate mofetil: inhibits IMP dehydrogenase in purine synthesis pathway



Azathioprine: inhibits enzyme required for synthesis of DNA



Broen et al Nat Rev Rheum 2020

Clinical Immunosuppression

- Induction vs maintenance
- Use many drugs at lower doses to enhance immunosuppression and decrease individual side effects
- Treatment of a rejection episode
- More immunosuppression ==> increased infection, increased risk of post-transplant lymphoproliferative disease (PTLD)

Induction Therapy – varies by organ

Figure KI 45: Induction agent use in adult kidney transplant recipients

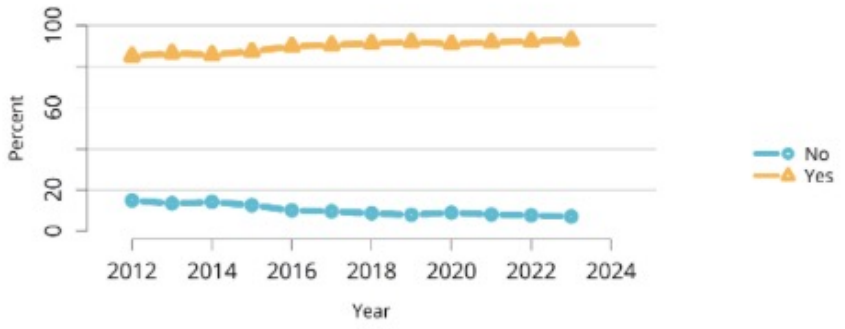
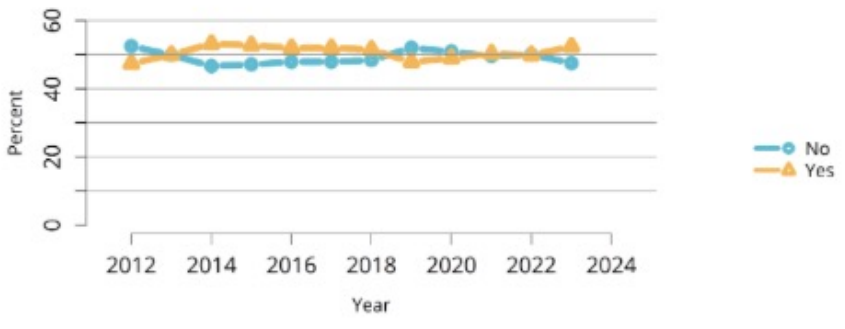
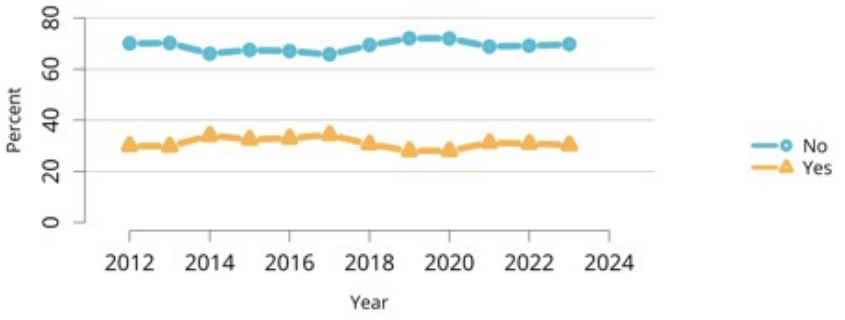


Figure HR 46: Induction agent use in adult heart transplant recipients



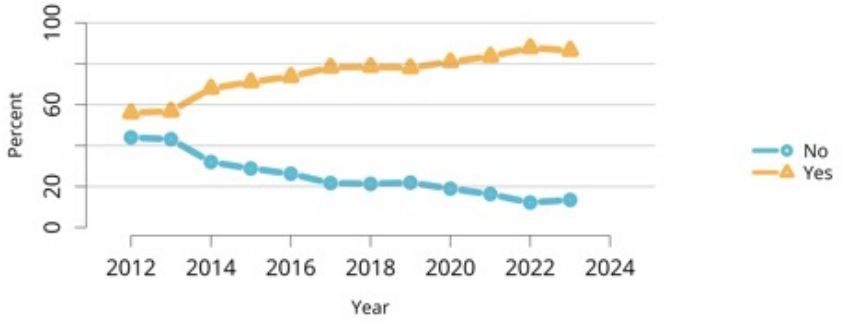
OPTN/SRTR 2023 Annual Data Report

Figure LI 46: Induction agent use in adult liver transplant recipients



OPTN/SRTR 2023 Annual Data Report

Figure LU 43: Induction agent use in adult lung transplant recipients

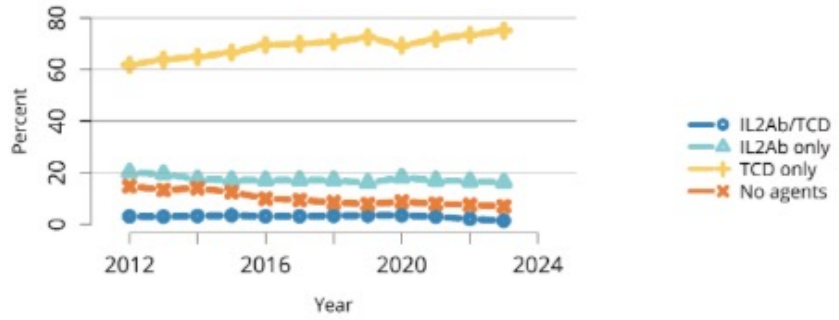


OPTN/SRTR 2023 Annual Data Report

SRTR 2024 report

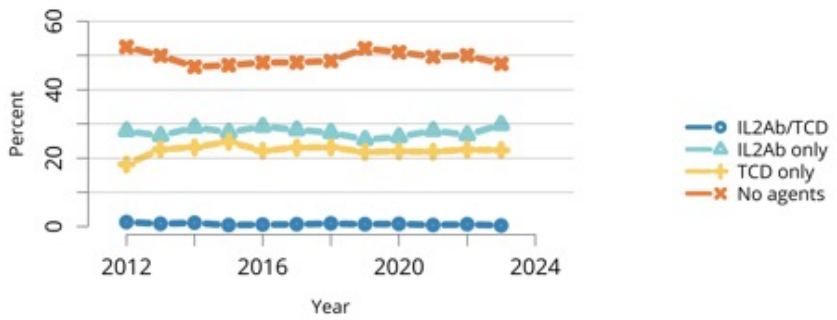
Type of Induction Used varies by organ

Figure KI 46: Type of induction agent use in adult kidney transplant recipients



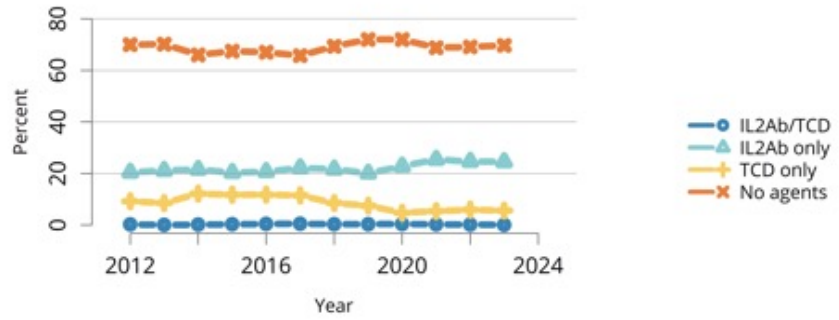
OPTN/SRTR 2023 Annual Data Report

Figure HR 47: Type of induction agent use in adult heart transplant recipients



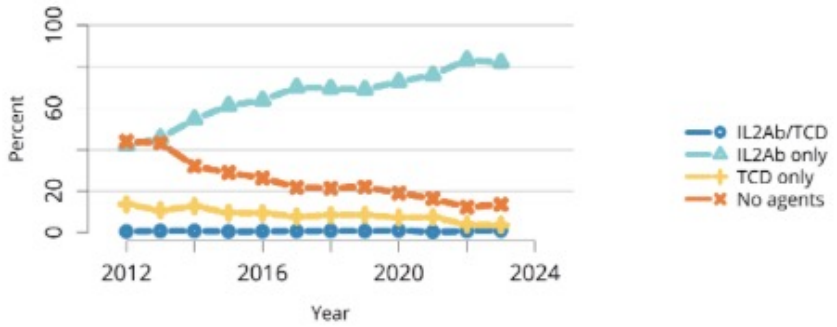
OPTN/SRTR 2023 Annual Data Report

Figure LI 47: Type of induction agent use in adult liver transplant recipients



OPTN/SRTR 2023 Annual Data Report

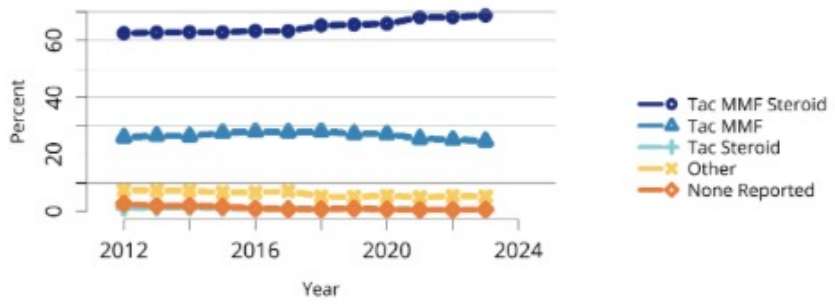
Figure LU 44: Type of induction agent use in adult lung transplant recipients



OPTN/SRTR 2023 Annual Data Report

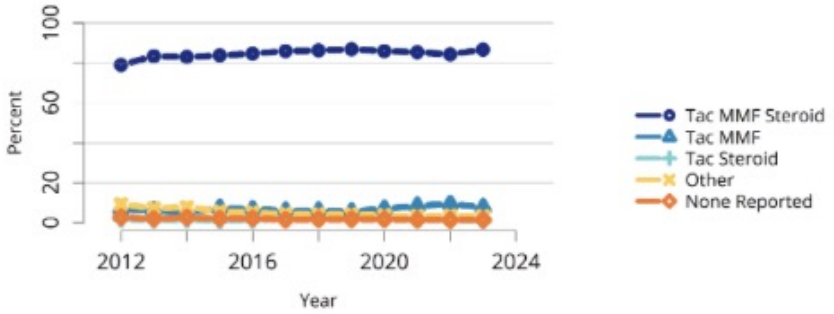
Most recipients are on 3-drug maintenance

Figure KI 47: Immunosuppression regimen use in adult kidney transplant recipients



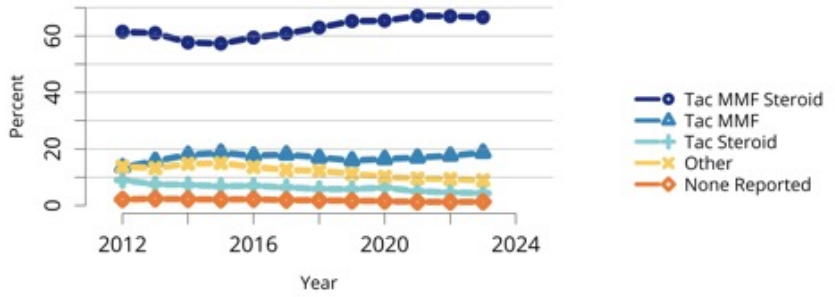
OPTN/SRTR 2023 Annual Data Report

Figure HR 48: Immunosuppression regimen use in adult heart transplant recipients



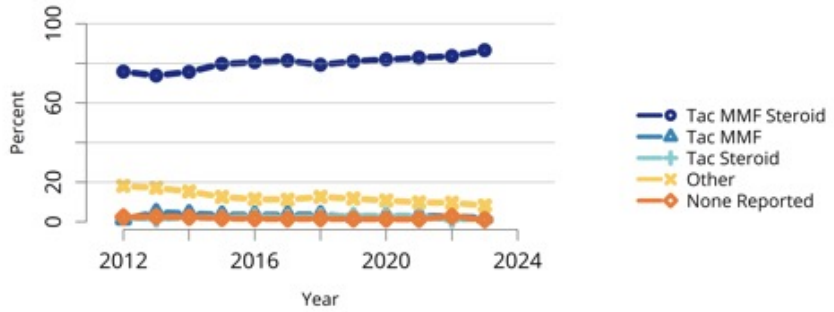
OPTN/SRTR 2023 Annual Data Report

Figure LI 48: Immunosuppression regimen use in adult liver transplant recipients



OPTN/SRTR 2023 Annual Data Report

Figure LU 45: Immunosuppression regimen use in adult lung transplant recipients



OPTN/SRTR 2023 Annual Data Report

Agents to target B cells and complement

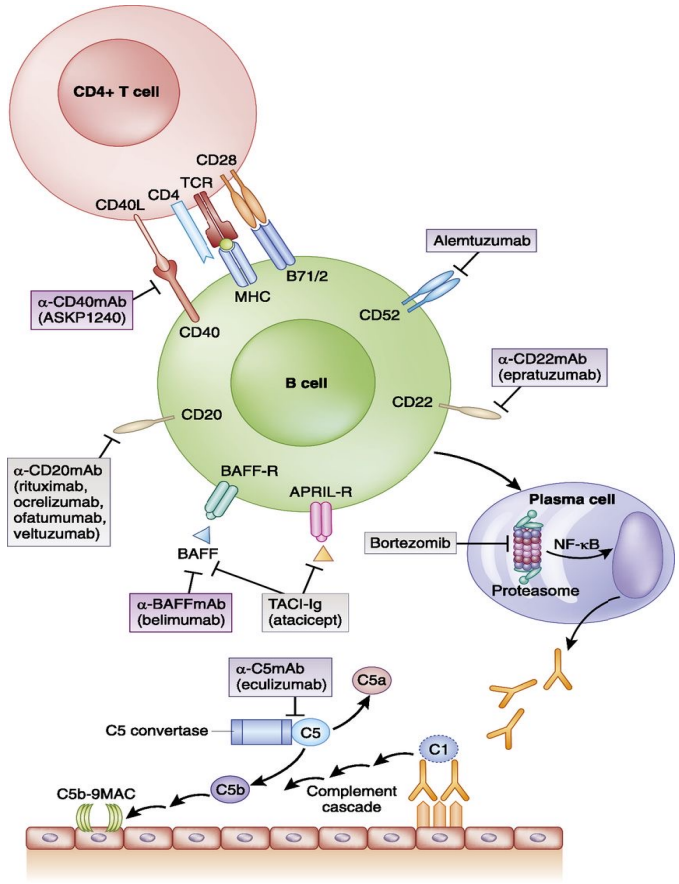
T/B cell interactions
- CD40/CD40L

B cell surface molecules/receptors
- CD20*
- CD52(*)
- CD22
- BAFF
- TACI-Ig
- CAR-T / bispecific antibodies

Plasma Cells
- Bortezomib*
- Carfilzomib*
- CD38

Immunoglobulin
- IVIG*

Complement Pathway
- anti-C5 mAb*
- Anti-C1

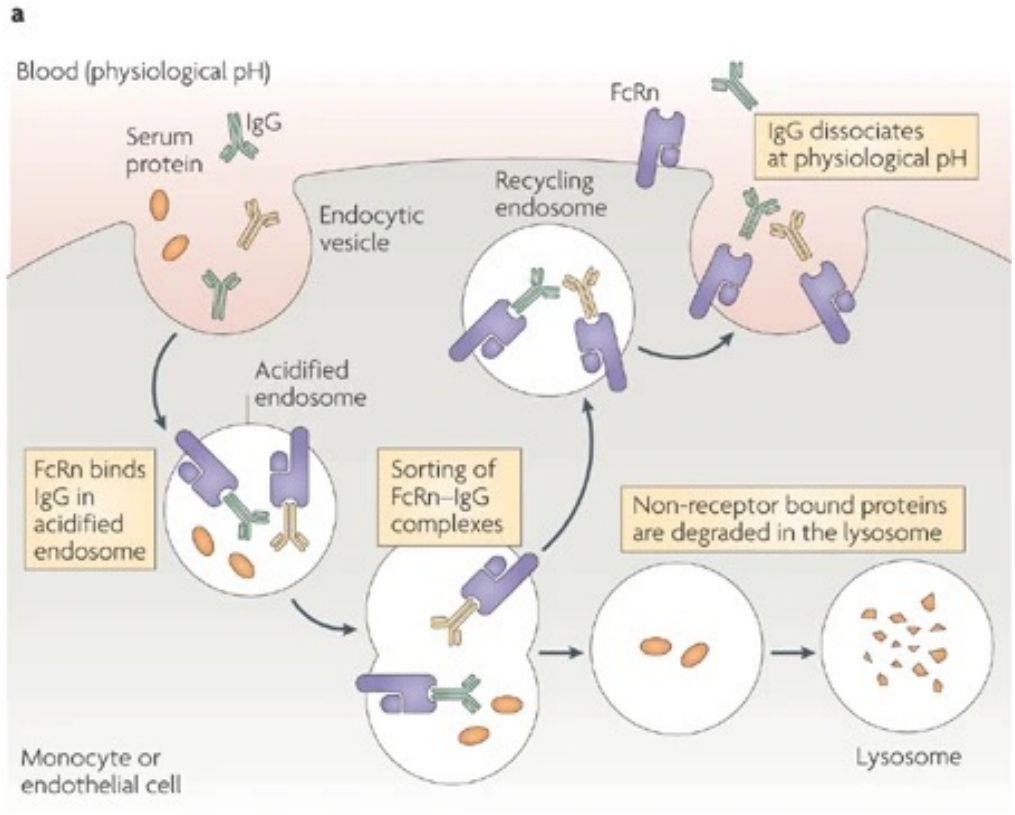


*used clinically

Wiseman CJASN 2016

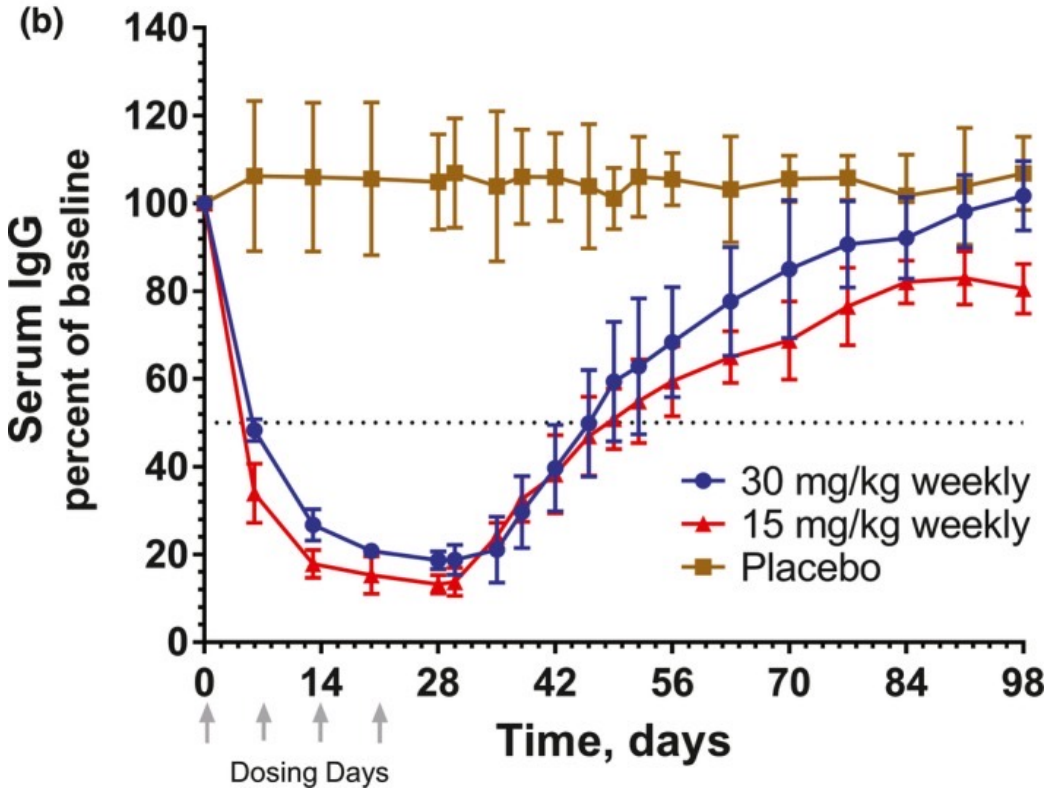
What if there are already donor specific antibodies?

1: Physical Removal – plasmapheresis
2: Inhibit effector function, i.e. complement fixation
3: Decrease antibody half-life



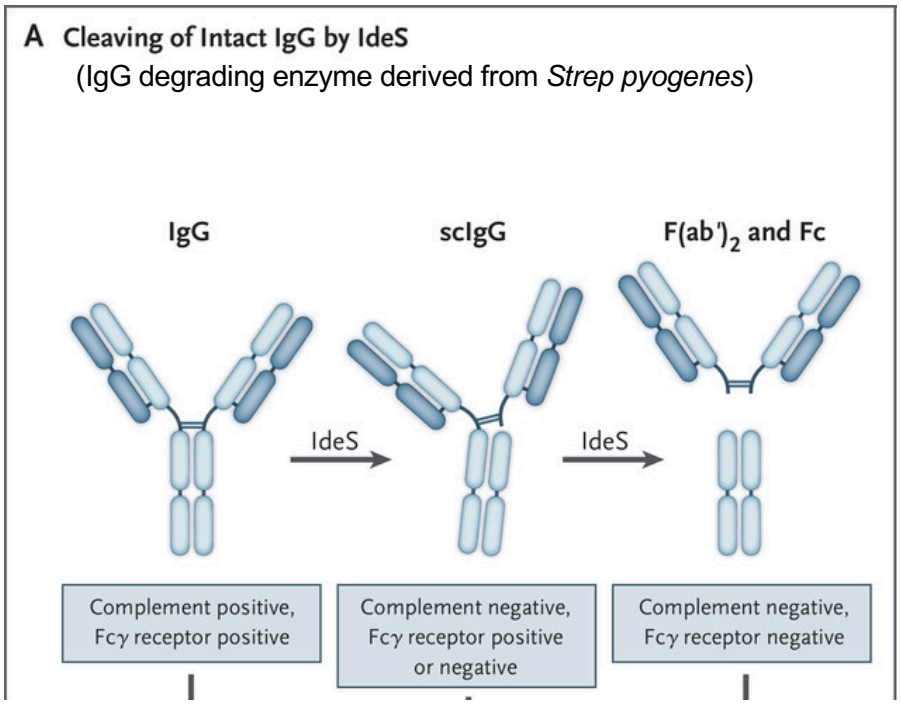
Roopenian and Akilesh. Nat Rev Immun (2007)

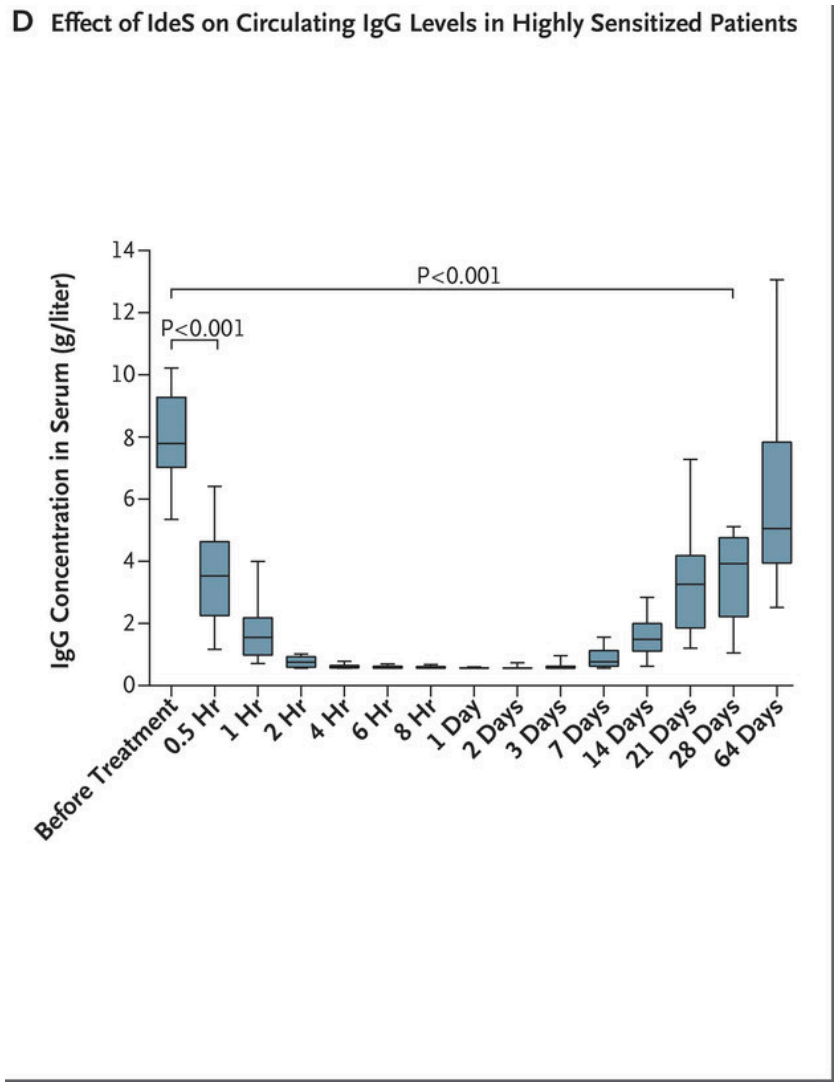
Block FcRn



Clin Pharm Ther (2018)

Modify pre-existing antibodies – IdeS/Imlifidase





Jordan SC et al. N Engl J Med 2017;377:442-453.

On the Horizon

- Signal 1
  - Fostamatinib – Syk inhibitor
  - AEB071 – pan-PKC inhibitor
- Signal 2
  - Anti-CD28
    - History of TGN1412
    - “domain antibody” or dAb, monovalent, pegylated
      - Lulizumab
      - Pegrizeprument (formerly VEL101/ FR104)
  - **Target CD40/CD40L pathway**
    - Anti-CD40L and thromboembolism
    - Anti-CD40
      - Bleselumb/ASKP1240
      - Iscalimab/CFZ533
    - Anti-CD40L
      - Dazodalibep/VIB-4920
      - Tegoprubart
- Desensitization / Antibody-mediated rejection
  - Costimulation blockade
  - Anti-CD38 to eliminate plasma cells
  - Imlifidase / Efgartigimod to decrease existing plasma antibodies
  - Complement inhibition (C3, C1s, etc)
  - Bispecifics / CAR-T

Questions