Immunosuppression Meds in Solid Organ Transplant

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Relevant Financial Disclosure(s)

R. Erik Edens

- I have nothing to disclose

Objectives

- Recognize medications commonly used in solid organ transplant
- Recognize common side effects of immunosuppression medications used in solid organ transplant
- Recognize disease states that occur more frequently in transplant recipients
- Understand the mechanisms for how immunosuppression medications increase risk of other chronic disease

Discussion outline

- Commonly used medications
  - “Induction” medications
  - Maintenance meds
  - Acute rejection therapies
- For each med:
  - History & development
  - Mechanism of action
  - Common med side effects
- Diseases & conditions associated with immunosuppression

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Immunosuppression Med History

J George in Heart Transplantation, Ed. Kirklin et al, Churchill Livingstone, 2002

TABLE 13–1 Evolution of Immunosuppression in Organ Transplantation

YEAR	APPROACHES
1959	Total body irradiation
1960–1962	6-Mercaptopurine and azathioprine
1960–1965	Additional myelotoxic agents
1962–1963	Steroids used systematically
1966	Lymphocytotoxic sera/antibodies
1978	Cyclosporine
1989	Tacrolimus
1997	Mycophenolate mofetil
1998	Sirolimus

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“Induction Therapy”

At time of transplant surgery

Three types of “Induction Therapy”

1. Triple Immunosuppression: Steroids, Tacro/Cyclo, CellCept/Imuran
2. Cytolytic + Triple Immunosuppression
3. IL-2 rector Blocker + Triple Immunosuppression

Other strategy: Just start “Maintenance Therapy” at time of transplant

- Start with higher doses of Maint meds, then wean to lower after few months

“Induction Therapy”

- Also known as “Cytolytic therapy”
- Thymoglobulin most commonly used now: Rabbit anti-human thymocyte antibodies
  - Depletes all lymphocytes (B & T cells, all classes)
  - Name “Induction Therapy” because thought would deplete immune system like in Bone Marrow Transplant
    - Doesn’t actually “induce” like BM, does incr risk of PTLD & infection
    - Many clinical studies show no benefit
    - Does allow less rejection early out so can minimize other meds
  - Very useful for acute compromising rejection
  - ATGAM: Horse anti-human thymocyte antibodies
  - OKT3: mouse anti-human CD3 receptor on T-cells

“Induction Therapy” continued

- Anti-IL-2 receptor antibodies

1. Basiliximab (Simulect): mouse anti-human IL-2 receptor blocker

2. Daclizumab: Withdrawn from market in 2018
   - Reports of auto-immune encephalitis

Maintenance Immunosuppression:
Traditional Triple Agent Approach

- Steroids: Methylprednisilone, prednisone
  - Broad based, non-selective
  - Inhibit cytokines, WBC function, inflam mediators
- Calcineurin inhibitors:
  - Cyclosporine & Tacrolimus
  - Inhibit T-cell translation of cytokines (IL-2)
- Antimetabolites (inhibit WBC proliferation):
  - Imuran: inhibs purine synthesis (intercalates into DNA)
  - CellCept: blocks *de novo* purine synthesis
- Adjunct Meds: Sirolimus & Everolimus
  - Used for antibody mediated rejection as knocks out B-cells also
  - Used to minimize or avoid calcineurin inhibitors (protect kidneys)
  - Anti-proliferative meds for coronary vasculopathy in heart

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Specific Immunosuppressives: Most Commonly Used Agents

- Steroids
- Azathioprine
- Mycophenolate Mofetil
- Cyclosporine
- Tacrolimus
- Sirolimus
- Everolimus

Steroids: Background

- Methylprednisilone, Prednisilone, Prednisone

- Oldest immunosuppressive—
  - Used in skin grafts in animals 1951
  - Used clinically 1960
  - Widespread in transplant since 1962

Steroids: Mechanisms

1. Anti-inflammatory
   - Inhibit inflammatory mediators
     - Leukotrienes & prostaglandins
   - Induce release of lipocortin which inhibits phosphodiesterase A2

Steroids: Mechanisms

2. Immunosuppressive
    - Complex since a “hormonal med”
    - “Principal effect”: impairs T-cell transcription of various cytokines
        - IL-1, IL-2, IL-3, IL-6, TNF-alpha, IFN-gamma)
    - Suppress macrophage function
    - Reduction of adhesion molecules
    - Inhibition of leukocyte migration
    - Induction of lymphocyte apoptosis
    - Reduction of HLA expression

Steroids: Pharmacokinetics

- $T_{1/2}$ = 3 hrs
- Metabolized in liver
  - Liver disease can prolong $T_{1/2}$
  - Drugs that induce hepatic enzymes
    - May shorten $T_{1/2}$
    - Phenytoin, barbiturates, rifampin
- Titration of dose somewhat arbitrary
  - No levels to monitor, titrate to effect

Steroids: Toxicities

- Hypertension
- Lipid abnormalities
- Diabetes
- Osteoporosis
- Bone/joint pain
- Obesity
- Cushingoid changes
- Cataracts
- GI ulcerations
- Poor wound healing
- Sleep disturbances
- Personality changes
- Pancreatitis

Steroids: Uses

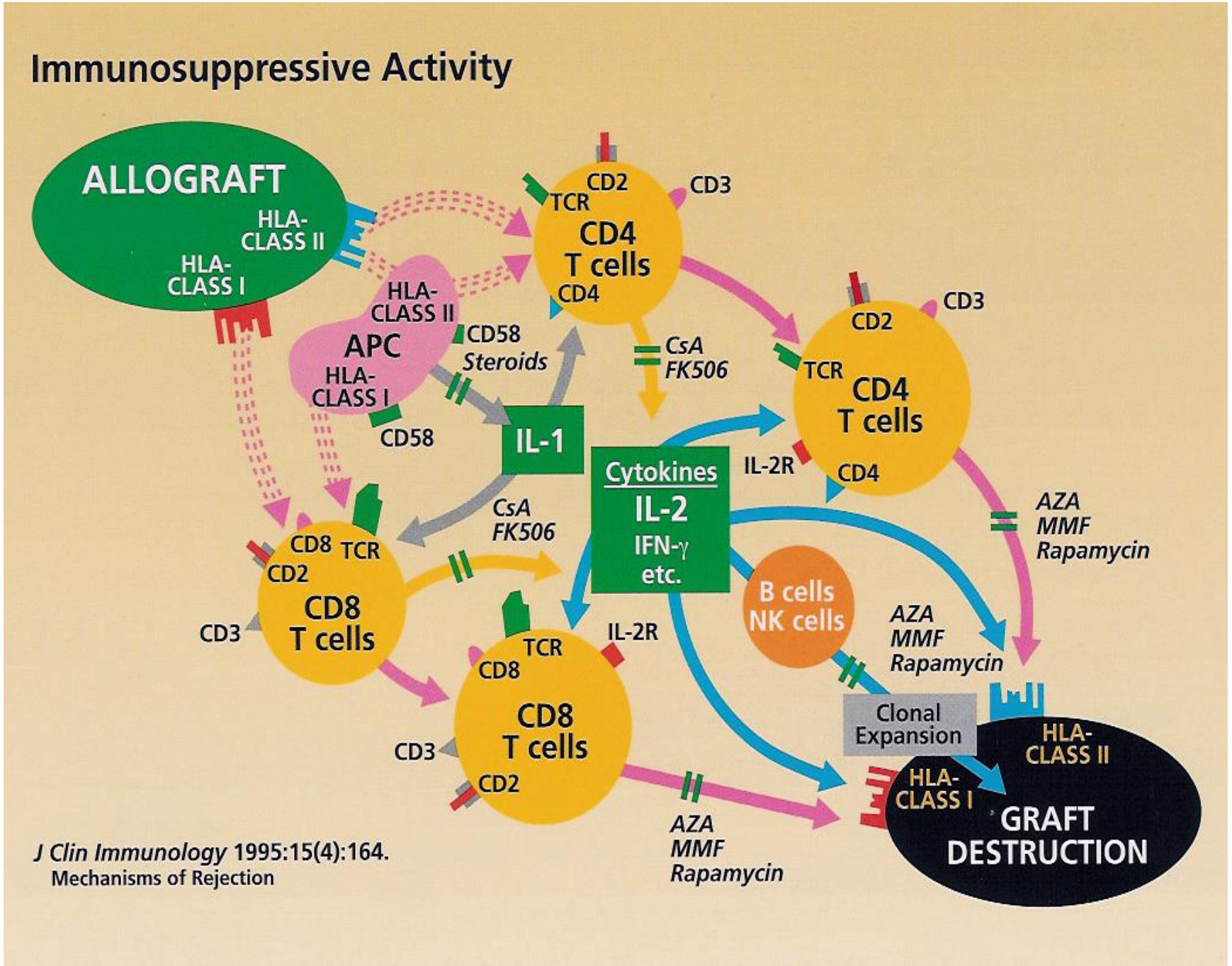
- Commonly used immediately after tpx
  - Often first dose in OR
  - High doses used post transplant
  - Weaned over months-years
- Some programs use chronically
- Commonly used to treat acute rejection
  - May have a noticeable effect within hours
  - IV solumedrol penetrates organ tissue quickly

Azathioprine (AZA) = Imuran

- First synthesized in 1961
  - Discovered immunosuppressive activity
- First used clinically in 1961
- Mainly as part of 2 or 3 drug regimen
  - Titrated to keep WBC low (3-7K)

Azathioprine: Mechanism

- A thiopurine that interferes with DNA and RNA synthesis
  - Inhibits both T and B-cell proliferation
  - Inhibits IL-2 production by a different mechanism than calcineurin inhibition
  - Can result in chromosome breakage
    - May predispose to malignancy
    - In adult heart, 4x increase in malignancy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TCR
CD3
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APC
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CD58
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B cells
NK cells
AZA
MMF
Rapamycin
Clonal Expansion
GRAFT DESTRUCTION
J Clin Immunology 1995:15(4):164.
Mechanisms of Rejection

Azathioprine: Toxicities

- Myelosuppression
  - Dose dependent
  - Delayed onset
  - WBC > platelets
  - Anemia common
- Hepatotoxicity
  - Mainly ↑ transaminases
- Pancreatitis
- Alopecia
- Malignancies*
- Diarrhea

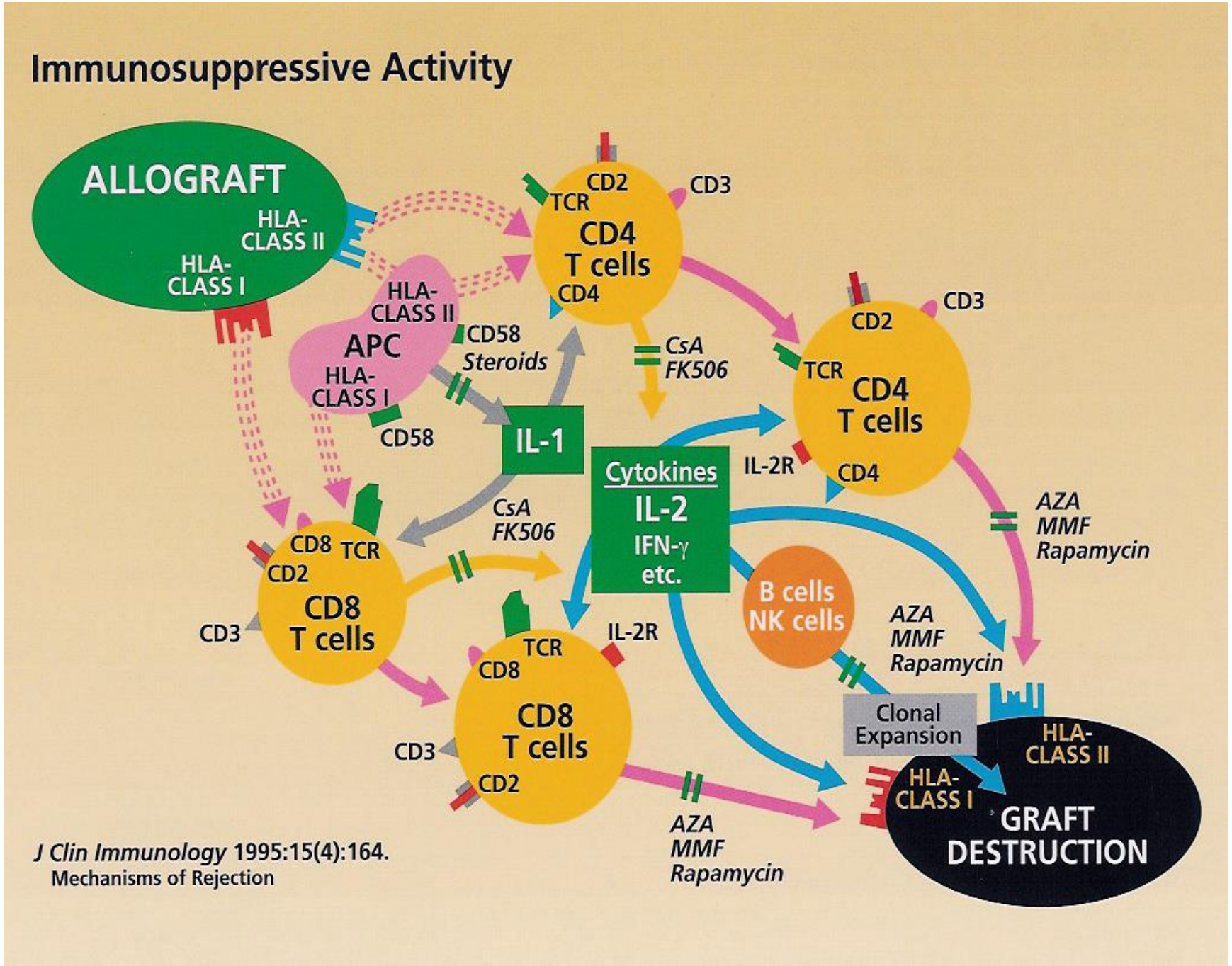
Mycophenolate Mofetil (MMF) = Cell Cept

- Isolated from bacteria in 1898
- Original use was in psoriasis
- Found to inhibit guanine synthesis
- Syntex Corp developed as a drug as a lymphocyte inhibitor (1990)
  - First clinical trial 1992

- Mainly as part of 2 or 3 drug regimen
  - Titrated to keep WBC low (3-7K)

Mycophenolate Mofetil: Mechanism

- Reversible, non-competitive inhibitor of inosine monophosphate dehydrogenase, which is critical to guanine synthesis
- Lymphocytes one of the few cells sensitive to this med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Mycophenolate Mofetil: Toxicities

- Mainly GI
  - Diarrhea
  - Nausea
  - Vomiting
  - Gastritis
- Urinary urgency
- Dysuria
- Cholestasis
- Leukopenia*

Immunosuppression Trends
Helderman et al Am J Transpl (2003) 3: 41-52

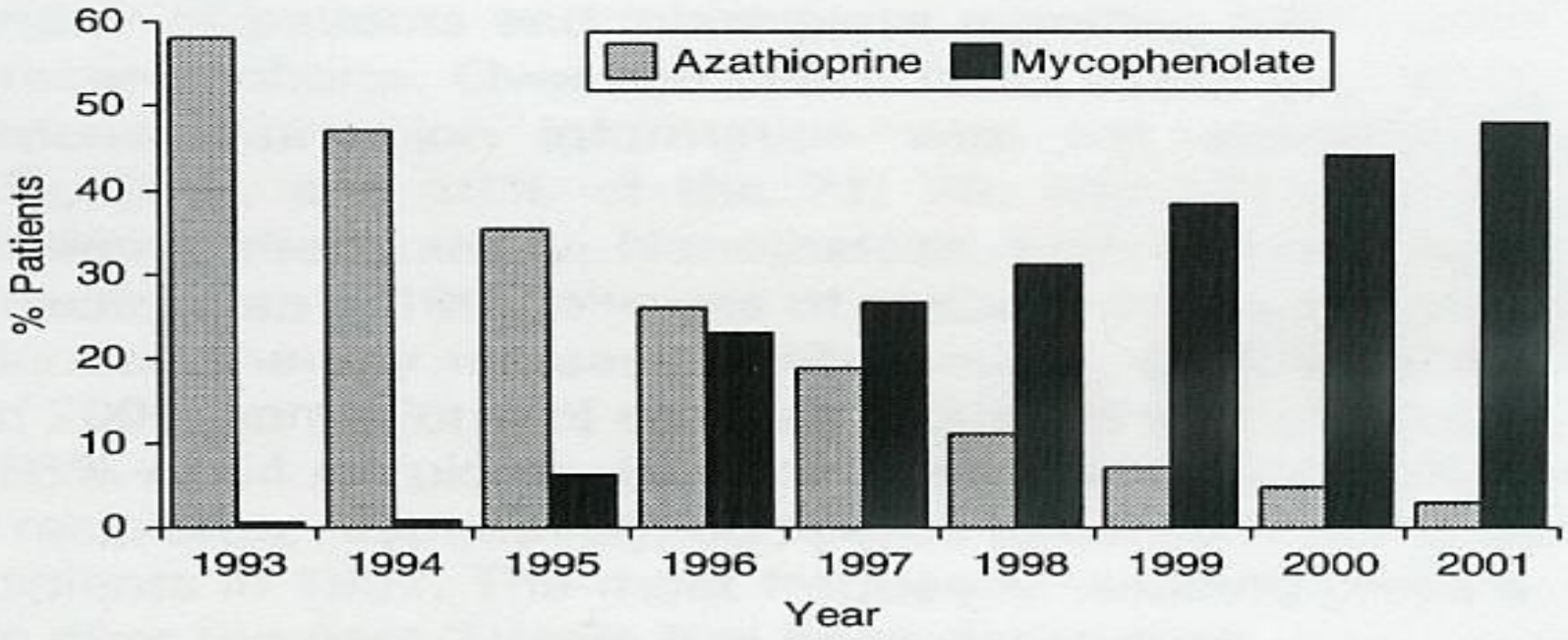


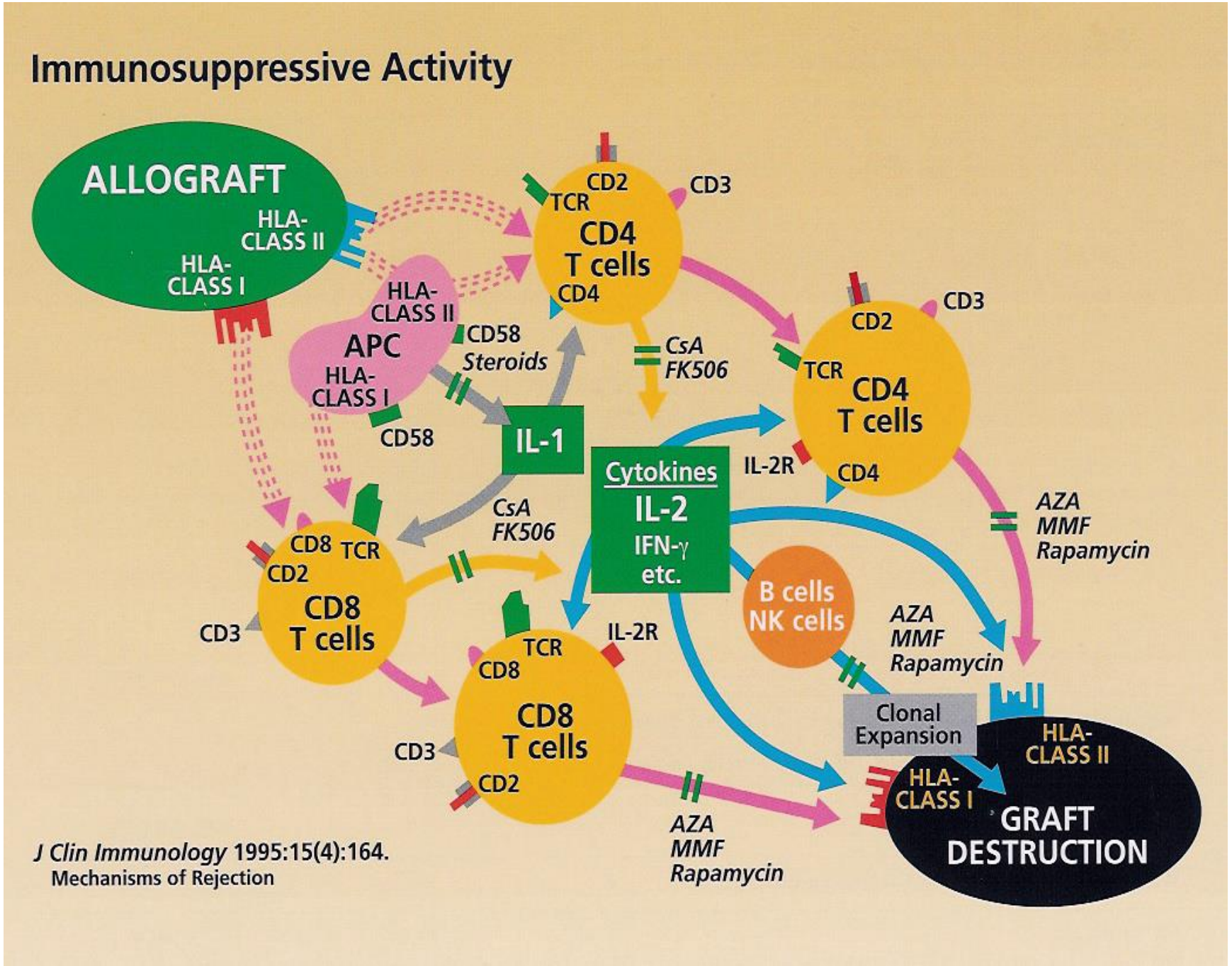
Figure 6: Liver transplant immunosuppression prior to discharge: azathioprine vs. mycophenolate mofetil, 1993–2001. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6.

Cyclosporine: Background

- 1950s Sandoz Labs decided to check fungal isolates for other activities besides antimicrobial
  - Found one fraction inhibited tumor cell line
- Investigated effects on immune system
  - 1972, Barel *et al* noted immunosuppressive activity
  - Late 1970s—used in animals
- First used clinically in 1979—saved the transplant world, allowed transplant
- Mainly used as a chronic maintenance med

Cyclosporine: Mechanisms

1. Blocks T-cell cycle at G_0-G_1 phase
2. Limits T-cell activation
    - Does not impair killing effect if activated
3. Inhibits IL-2 receptor formation
4. Impairs responsiveness to IL-1
    - IL-1 promotes IL-2 production
    - So Cyclo thereby inhibits IL-2 production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Mechanisms of Rejection

Cyclosporine: Mechanisms

- Mainly affects cytotoxic T-cells & T-helpers
- Little to no effect on suppressor T-cells
- No direct effect on B-cells
  - Does inhibit primary B-cell responses that are T-cell dependent (humoral responses)
- No effect on granulocytes or macrophages

Cyclosporine: Pharmacokinetics

- Highly lipophilic, absorbed in upper GI
  - Fatty meals delay aborption of standard prep but not microemulsion (Neoral)
  - Fatty meal may ↑ absorption in some px
- Peak level 3-4 hrs
- Bioavailability varies widely between px

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Cyclosporine: Toxicities--Renal

- Often with initial dose
- Renal artery constriction
- Oliguria possible
- ↑ BUN/Cr
- Stimulates renin synthesis and release
- Unclear if ↑ angiotensin II causes problems or is caused by arteriole constriction
- Subacute-- ↓ GFR
- Chronic-glomerular sclerosis & fibrosis
- Risks: underlying renal disease, chronic high CSA levels

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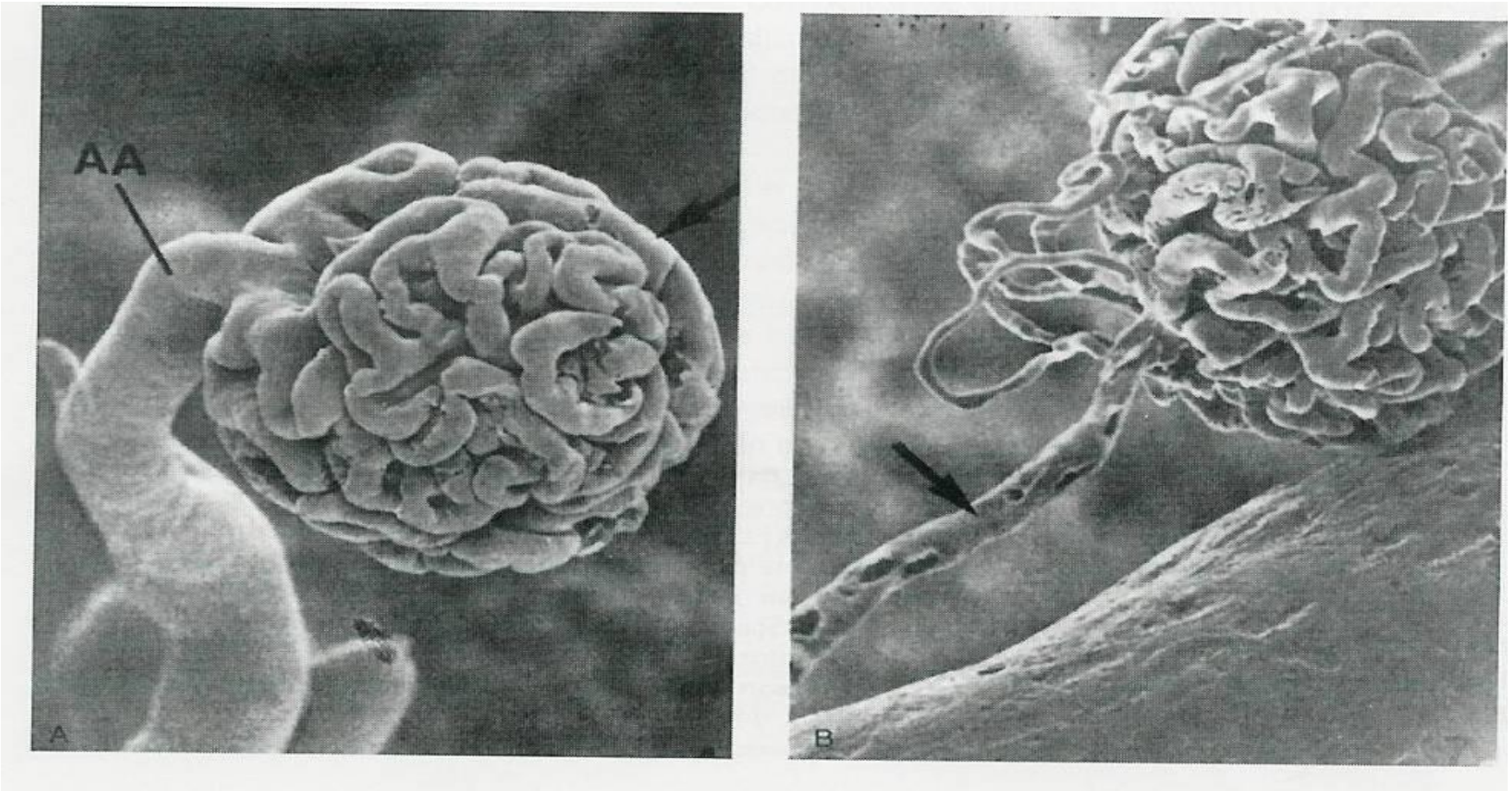
Cyclosporine Renal Effects

J George in Heart Transplantation, Ed. Kirklin et al, Churchill Livingstone, 2002

Control versus 50 mg/kg cyclo in rats



Cyclosporine: Toxicities

- Hypertension:
  - 60-80%
  - Arterial constriction?
  - Renin-angiotensin?
- Hepatotoxicity
  - Idiosyncratic
- ↑ Gall stones
- Hyperkalemia
- Acidosis
- Hypomagnesemia
- Hyperuricemia
- Neurologic
  - Tremor
  - Parathesias
  - HA
- Excess hair growth*
- Gingival hyperplasia*
- Hyperlipidemia

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Cyclosporine: Drug Interactions

↓ Levels (↑ c P-450)

- Rifampin
- Isoniazid
- Phenobarbital
- Phenytoin
- Carbamazepine

↑ Levels (use c P-450)

E-mycin

Keto/Itraconazole

Diltiazem

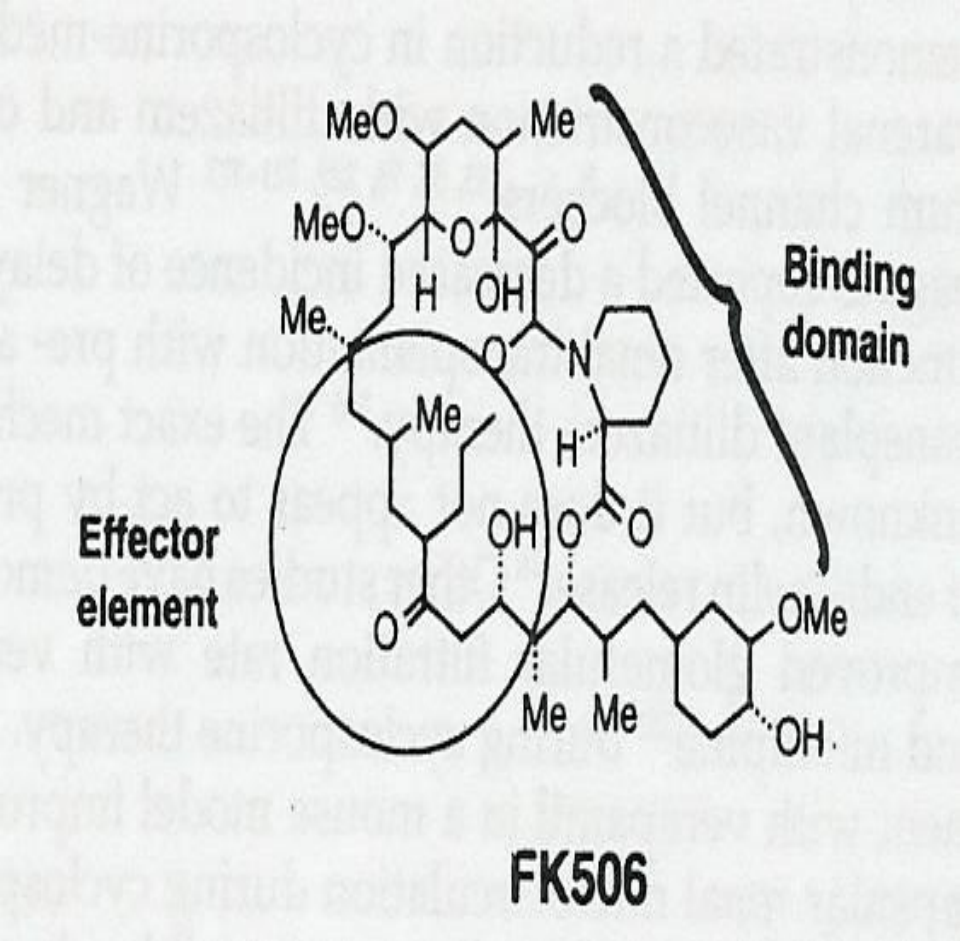
Verapamil

Cimetidine

Methylprednisilone

Metaclopramide

Tacrolimus: Background



- First isolated from bacteria 1984
- First clinical use 1989
  - Liver rejection rescue
- Mainly used as a chronic maintenance med

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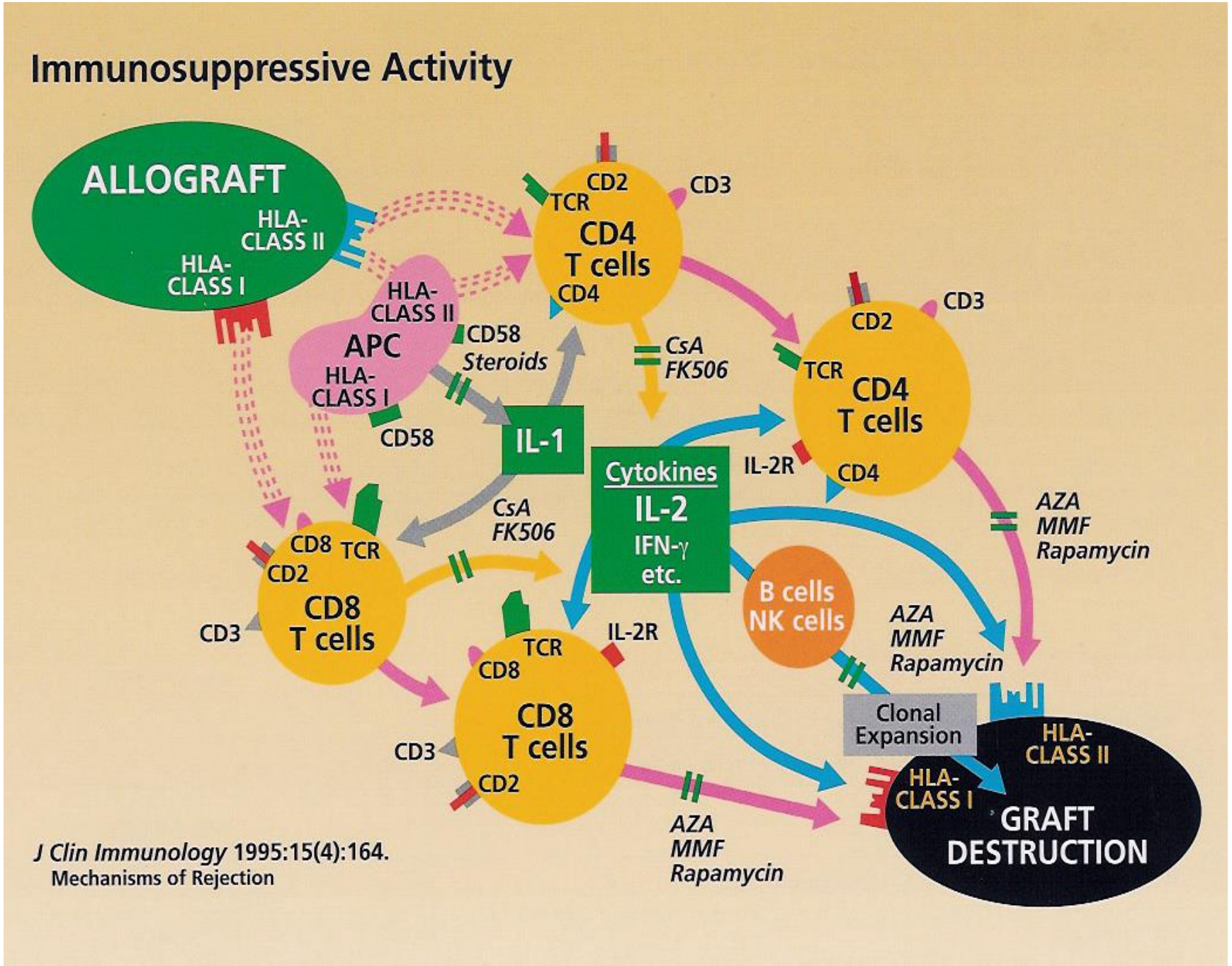
Tacrolimus: Mechanisms

- Prodrug—like cyclosporine
  - Binds to FK binding protein, then inhibits calcineurin
- 100x more potent than cyclo on wt basis
- Blocks cytokine expression—like cyclo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Mechanisms of Rejection

Tacrolimus: Pharmacokinetics

- Highly lipophilic
- BA variable with oral administration
  - *(Our program doses as npo 1 hr before and after)*
- Absorbed through small bowel
- Peak 2-3 hrs
- Metabolized:
  - Small bowel and liver
  - Cyto P-450
- Excreted in bile and by kidneys

Tacrolimus: Toxicities

- Renal: similar to cyclo, less severe
  - Dose related, unclear mechanism
  - Induces less renovascular resistance
  - Chronic lesions of similar type as with cyclo
  - Kidney effects more pronounced when dehydrated
- Neuro:
  - Mainly tremor, also HA, insomnia, seizure (especially when with steroids)

Tacrolimus: Toxicities

- Hypomagnesemia (common)
- Hyperkalemia (ocass)
- Hyperuricemia (ocass)
- Glucose intolerance
  - Rarely insulin dependent
  - Mainly with steroids
- Hypertension (less than cyclo)
- Hypercholesterolemia (ocass.)
- Drug interactions
  - Similar to cyclo*
  - Cyto P-450

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Immunosuppression Trends
Helderman et al Am J Transpl (2003) 3: 41-52

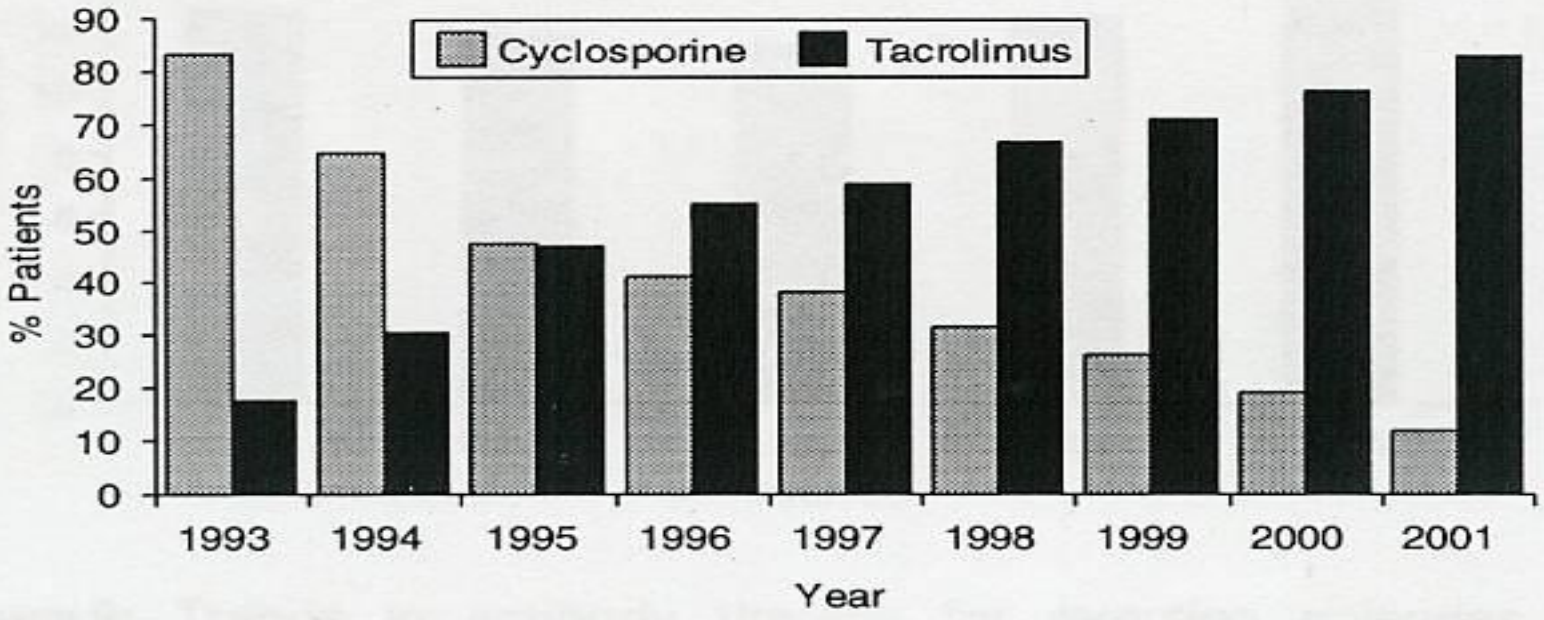

Figure 5: Liver transplant immunosuppression prior to discharge: cyclosporine vs. tacrolimus, 1993–2001. Source: *2002 OPTN/ SRTR Annual Report*, Table 9.6.

Immunosuppression Trends
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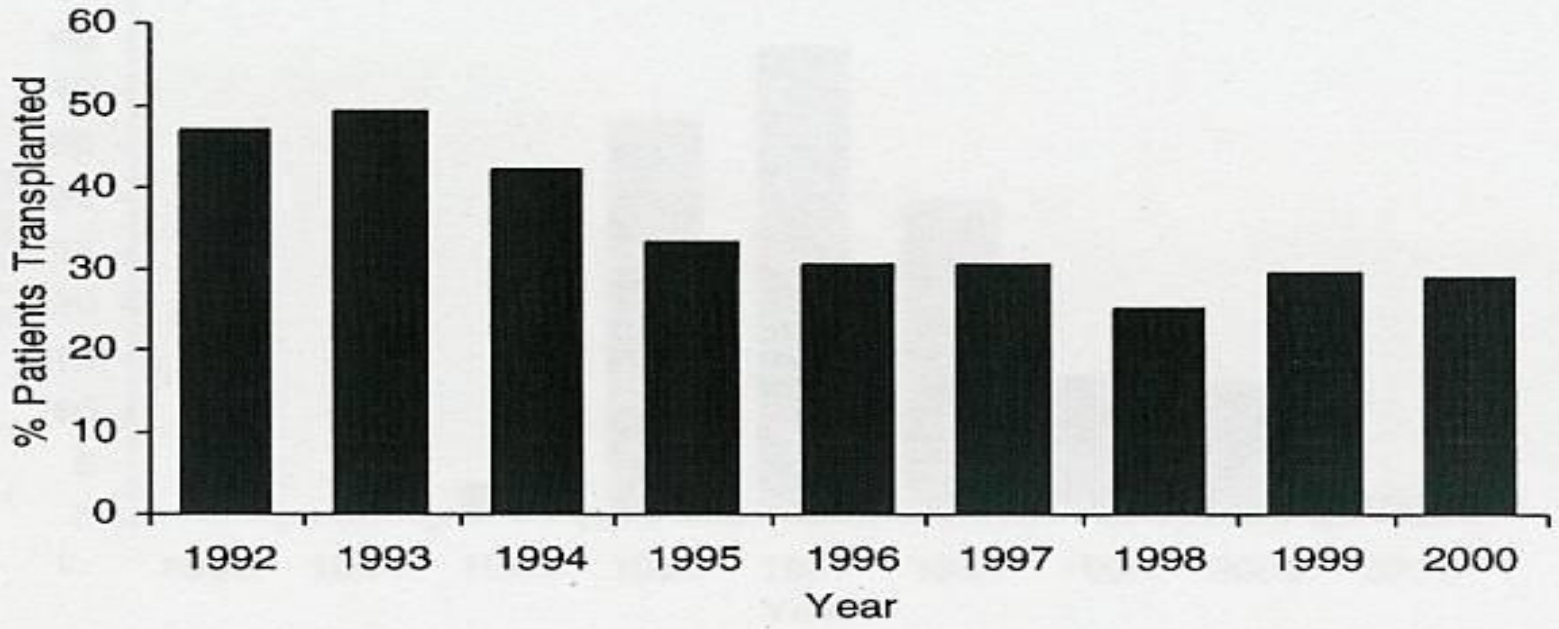

Figure 7: Incidence of rejection at 1 year in liver transplant recipients, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Table 9.6.

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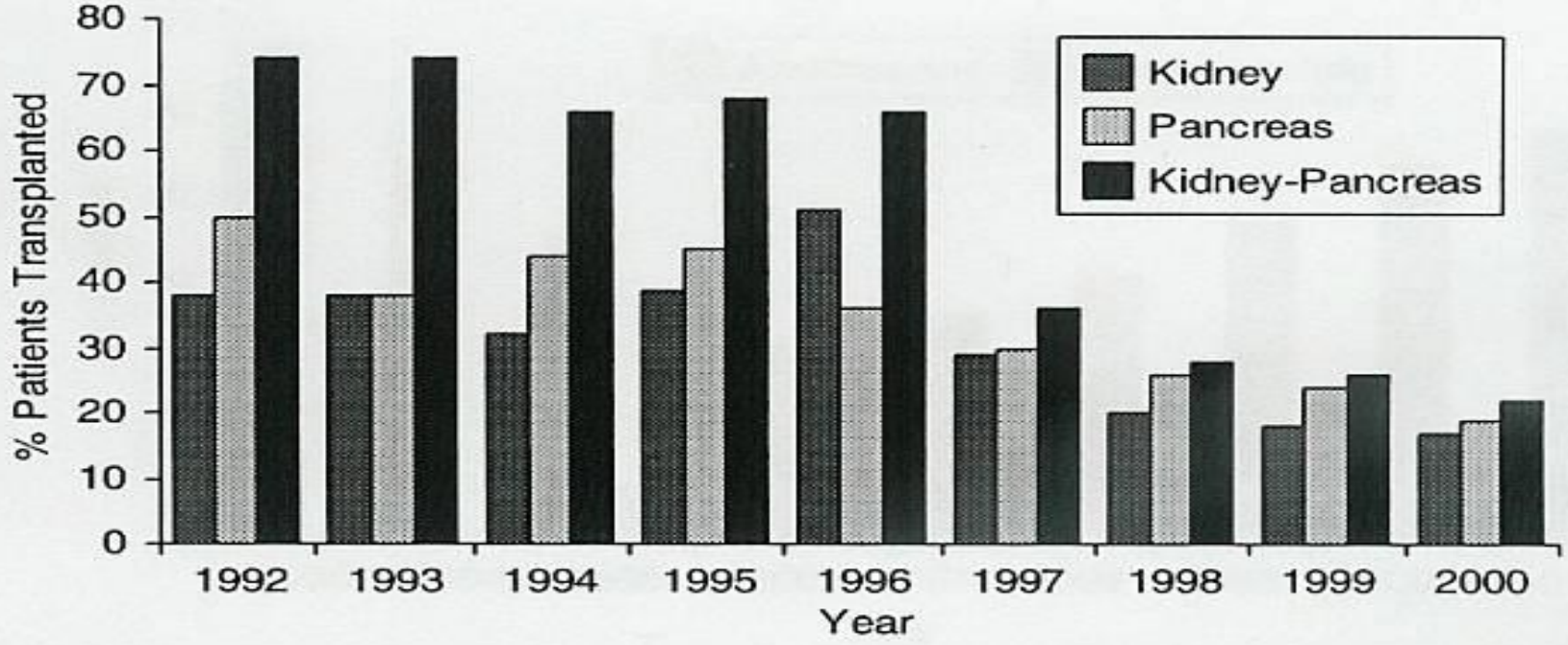

Figure 4: Incidence of rejection at 1 year in kidney, pancreas, and kidney–pancreas transplant recipients, 1992–2000. Source: *2002 OPTN/SRTR Annual Report*, Tables 5.6, 6.6, 7.6, 8.6.

Sirolimus (Rapamycin)

- Naturally occurring in *streptomyces*
- Isolated 1970s
- Approved 1999 for organ rejection prophylaxis in renal tpx

- A macrolide antibiotic, similar in structure to tacro

Everolimus: Mechanisms

- These are “Proliferation signal inhibitors”
- Inhibits cellular proliferation
  - Interferes with growth factor-driven transduction signaling
- Does NOT inhibit IL-2 production
  - Likely why these are not as good at anti-cellular rejection as Tacro

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Sirolimus: Pharmacokinetics

- Peak = 1-3 hrs
- $T_{1/2}$ = 60 hrs
- Once daily dosing, steady state 7-14 days
- 90% excretion via feces

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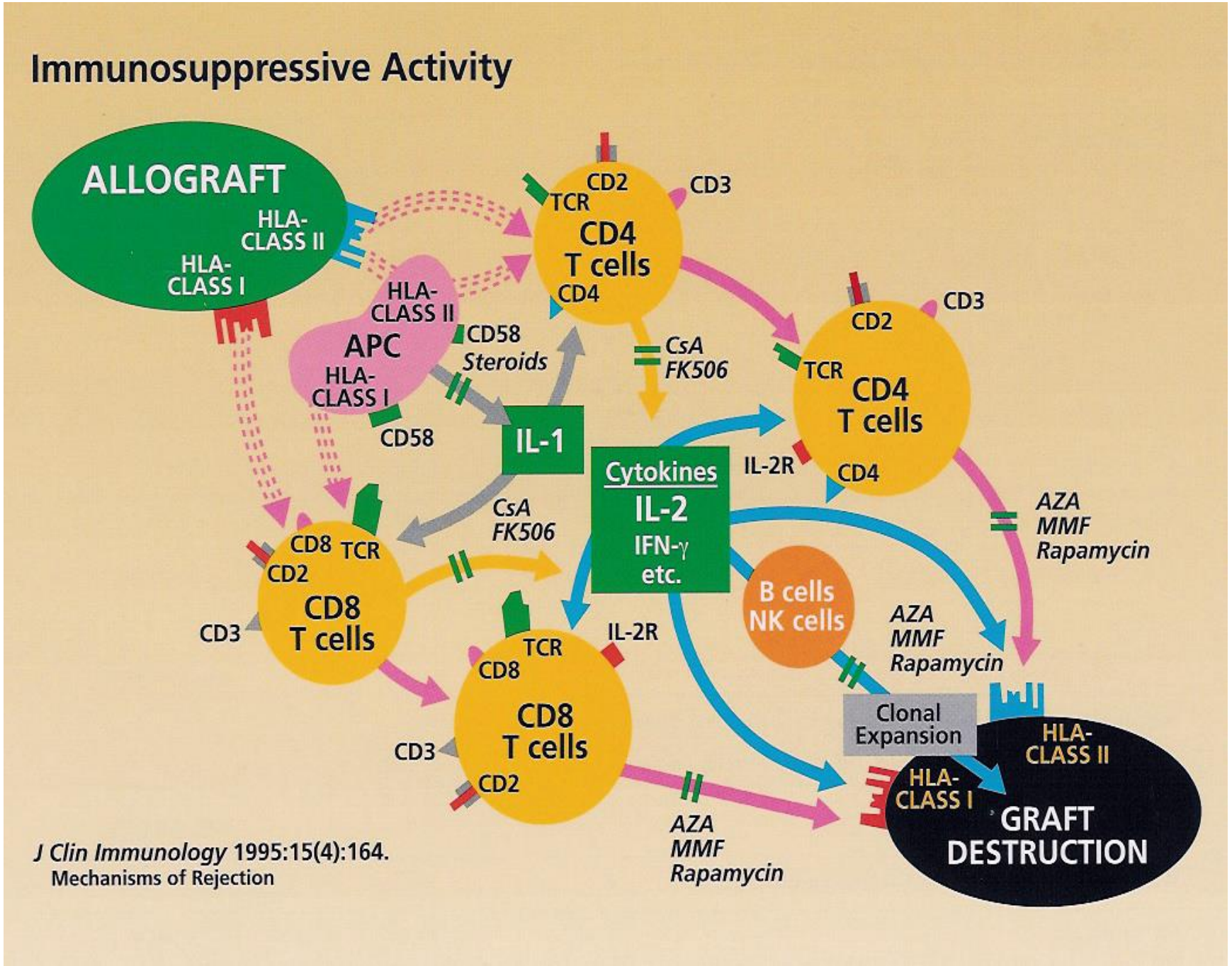
Sirolimus: Toxicities

- No significant renal toxicity
- Dyslipidemia: high cholesterol and TG common
- Mouth ulcers and rashes biggest limiting side effect
- Anemia common
- Thrombocytopenia > leukopenia
- Proteinuria
- Weight loss
- Testicular atrophy
- Growth retardation (in animals)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Mechanisms of Rejection

Everolimus:

- Similar mechanism to sirolimus
- Similar long half life and daily dosing
- Also follow drug levels
- Everolimus less side effects than sirolimus
  - Especially mouth ulcers and rashes

Cellular Rejection

1. IV steroids—Solumedrol typically
2. Cytolytic therapy
   - Knocks out all leukocytes
     - Thymoglobulin: Rabbit polyclonal, mult CDs
     - ATGAM: equine polyclonal to multiple CDs
   - Knocks out all T-cells
     - OKT3: murine monoclonal anti-CD3 antibody
3. Review compliance
4. Increase maint med doses/levels if have been compliant
5. Monitor more closely

Antibody Rejection

1. Plasmapharesis: controversial as not much removed
2. Rituximab—anti-CD20 antibody so knocks out circulating B-cells
   - IV infusion
   - Lytic syndrome early risk
   - Low IgG longer term risk
3. IVIg infusions
4. Add mTOR (sirolimus or everolimus)
5. Bortezomib- proteasome inhibitor
   - Potent, lots of side effects, high death rate from infection

Lab abnormalities you may see

- Low magnesium—tacro & cyclo
- Slightly high potassium—tacro & cyclo
- Low WBC—Cellcept & Imuran
- Low lymphocyte count—tacro & cyclo
- Anemia—Cyclo, Everolimus, Sirolimus
- High uric acid—tacro & cyclo
- Rising BUN/Cr—tacro & cyclo

Immunosuppression related conditions

1. Infection risk
   - Viruses: chronic EBV & CMV viremia possible
   - Fungus: foot, groin, hair
   - Bacteria: otitis and sinusitis
2. Post Transplant Lymphoproliferative Disorder (PTLD)
   - Often EBV associated
   - Presents like lymphoma: nodes, swollen turbinates in nose, big tonsils
   - Mild → decrease immunosuppression
   - Moderate → Rituximab or mild chemo
   - Severe → Can be life threatening and need full chemo
   - Chronic severe: rarely, chemo doesn't work very well

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Immunosuppression related conditions

1. Eczema very common, esp on tacro—Rx standard. Encourage emollients
2. Warts: hands, feet especially; treatment is standard
3. Auto-immune hematologic issues
   - Most common is attacking platelets
     - Many of these are self limited
   - Next most common is attacking RBC
   - Attacking WBC is rare and deadly
4. Auto-immune disorders
   - All auto-immune disorders at increased risk
   - Lupus most common one triggered
5. Increased risk of cancers: especially skin cancer
   - Peds– most common is lymphoma
   - Adults skin cancer is most common

General Clinic findings

- Diarrhea—CellCept> Imuran
- Headaches- Cyclo >> tacro
- Nasal congestion– if PTLD or just chronic sinus
- Frequent infections
  - Easier to get viruses, get sicker, stay sicker longer
  - Don’t usually need admission for common viruses
- Frequent sinusitis can happen > general public
- If chronic steroids—lots of infection risks and health problems
- Most program recommend no live virus vaccines: MMR, varicella

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Questions?

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