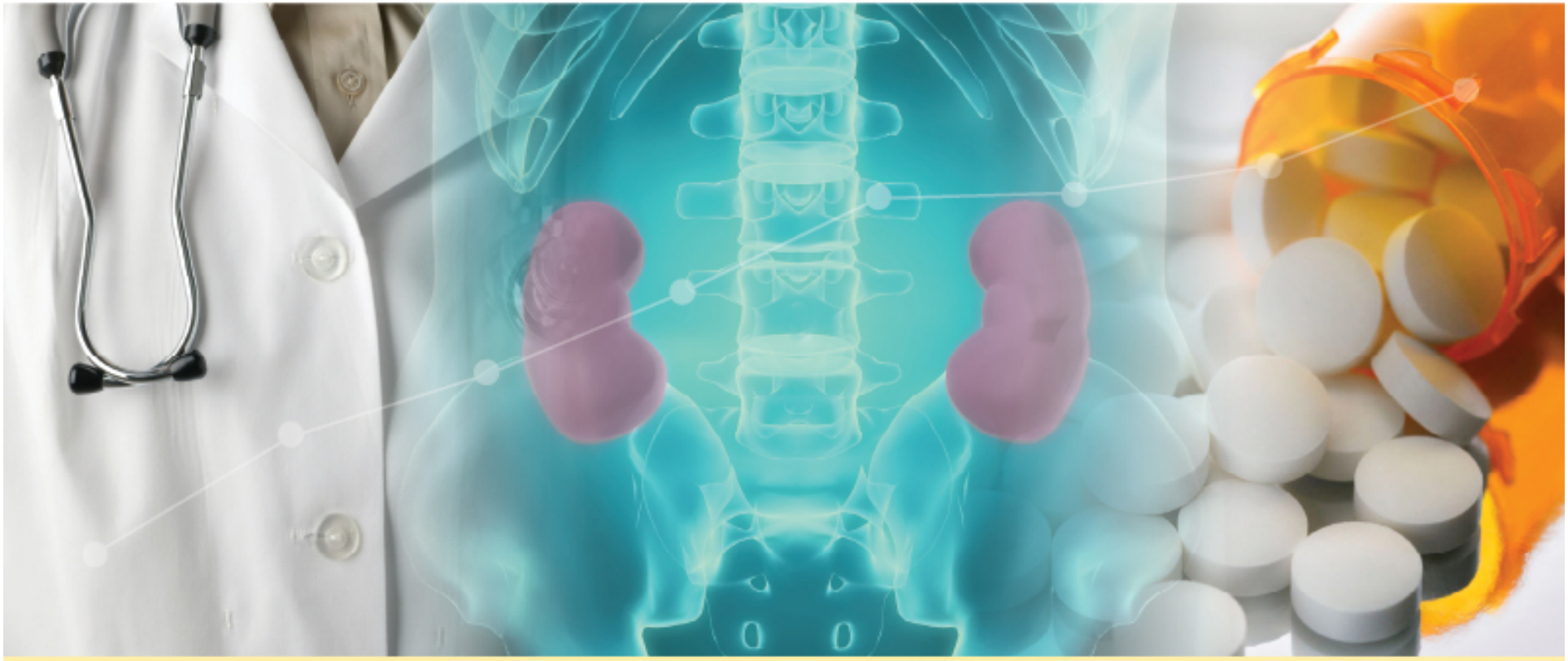
Optimizing Long-Term Outcomes with Kidney Anti-rejection Therapies



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Common Immunosuppressive Regimens: Risks, Benefits and Appropriate Use

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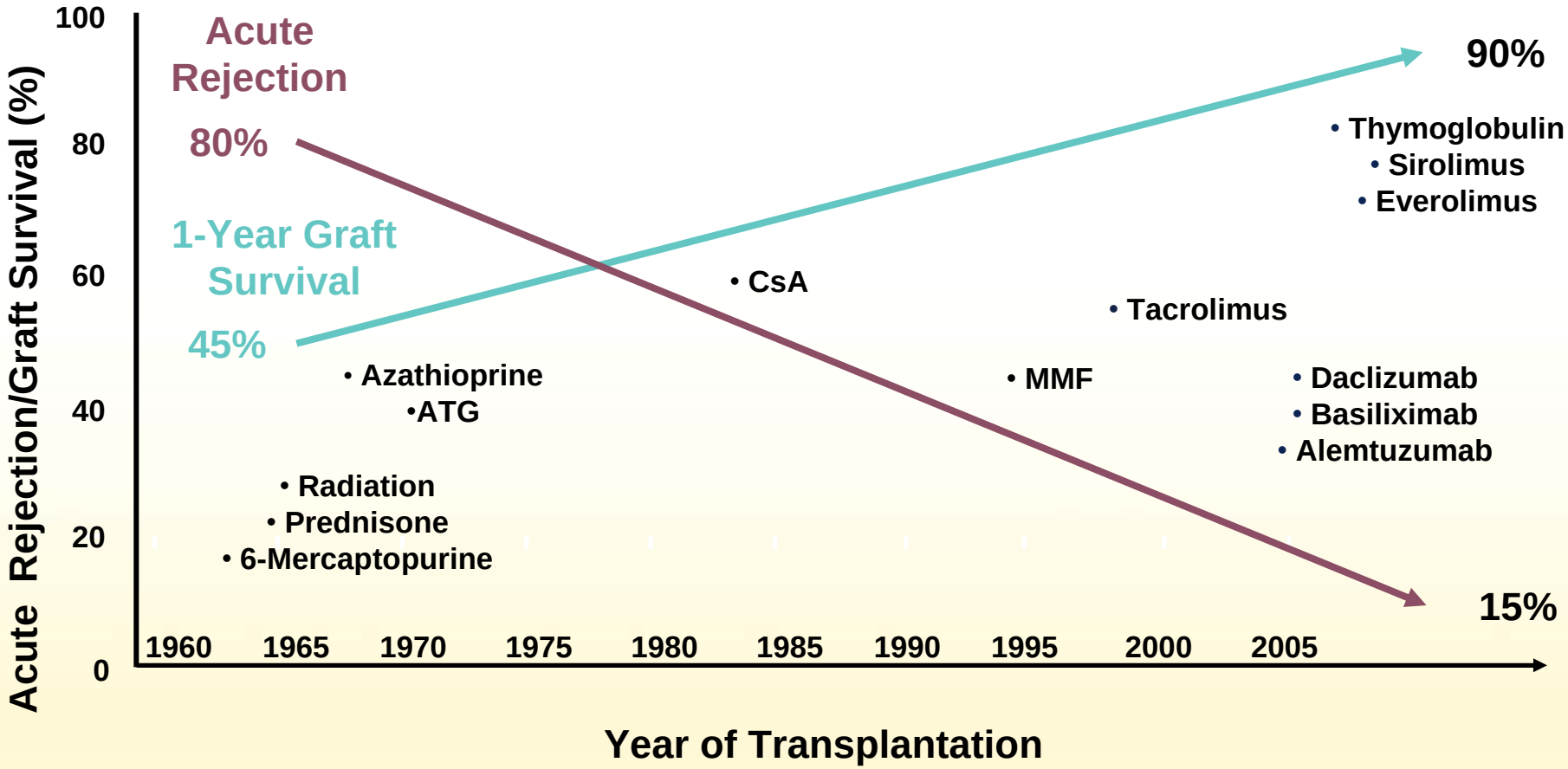
Immunosuppressive Treatment Strategies for the Transplant Recipient

- Identification of commonly used immunosuppressive drugs
  - Mechanism of action
  - Clinical efficacy
  - Adverse events
- Insights on selecting the most appropriate immunosuppressive regimen for a given patient

Improving Outcomes of Renal Allografts



ATG=antithymocyte globulin; CsA=cyclosporine; MMF=mycophenolate mofetil

Bedrock Principles of Transplant Immunosuppression

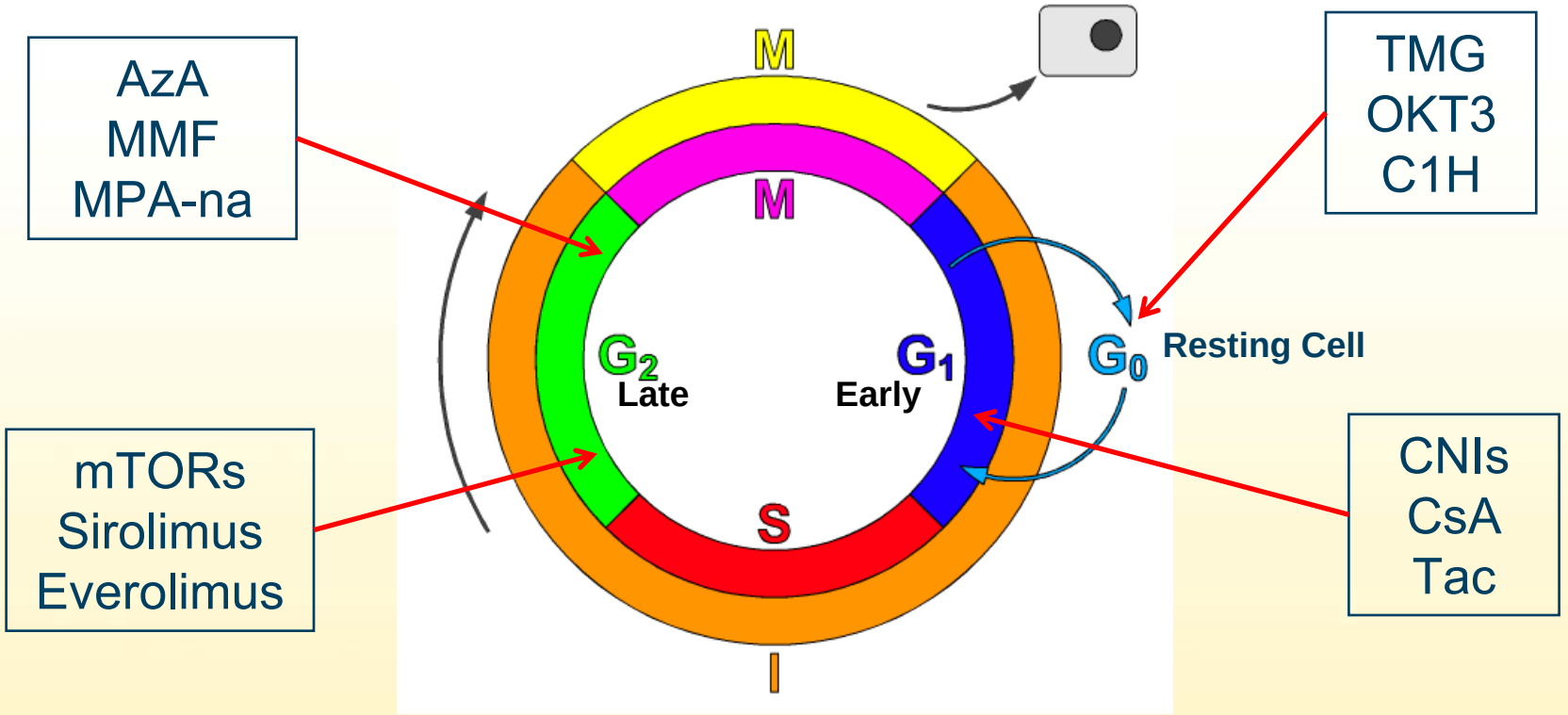
1. Alloimmunity follows the same rules as the immune response to other microbes and foreign invaders.

   These include:

   - The ability to identify self from non-self
   - Specificity
   - Memory
   - Rapid amplification

Bedrock Principles of Transplant Immunosuppression

2. The Cell Cycle of the lymphocyte responds to immunosuppressive drugs like a cancer cell to chemotherapy.



Bedrock Principles of Transplant Immunosuppression

3. Clinical Immunosuppression is a careful balance between too much and not enough.

Too Little

-Rejection
-Recurrent Disease

Too Much

-Infection
-Cancer

Renal Transplantation in Identical Twins in United States and United Kingdom

Nicos Kessaris,[1,3] Dayal Mukherjee,[2] Pankaj Chandak,[2] and Nizam Mamode[2]

Review of 120 twins in the USA and 12 in the UK between 1988-2004

	1 yr.	3 yr.	5 yr.
Graft Survival (%)	99.2	91.8	88.9
Patient Survival (%)	100	97.1	97.1

82 Recipients (68%) were discharged on immunosuppression

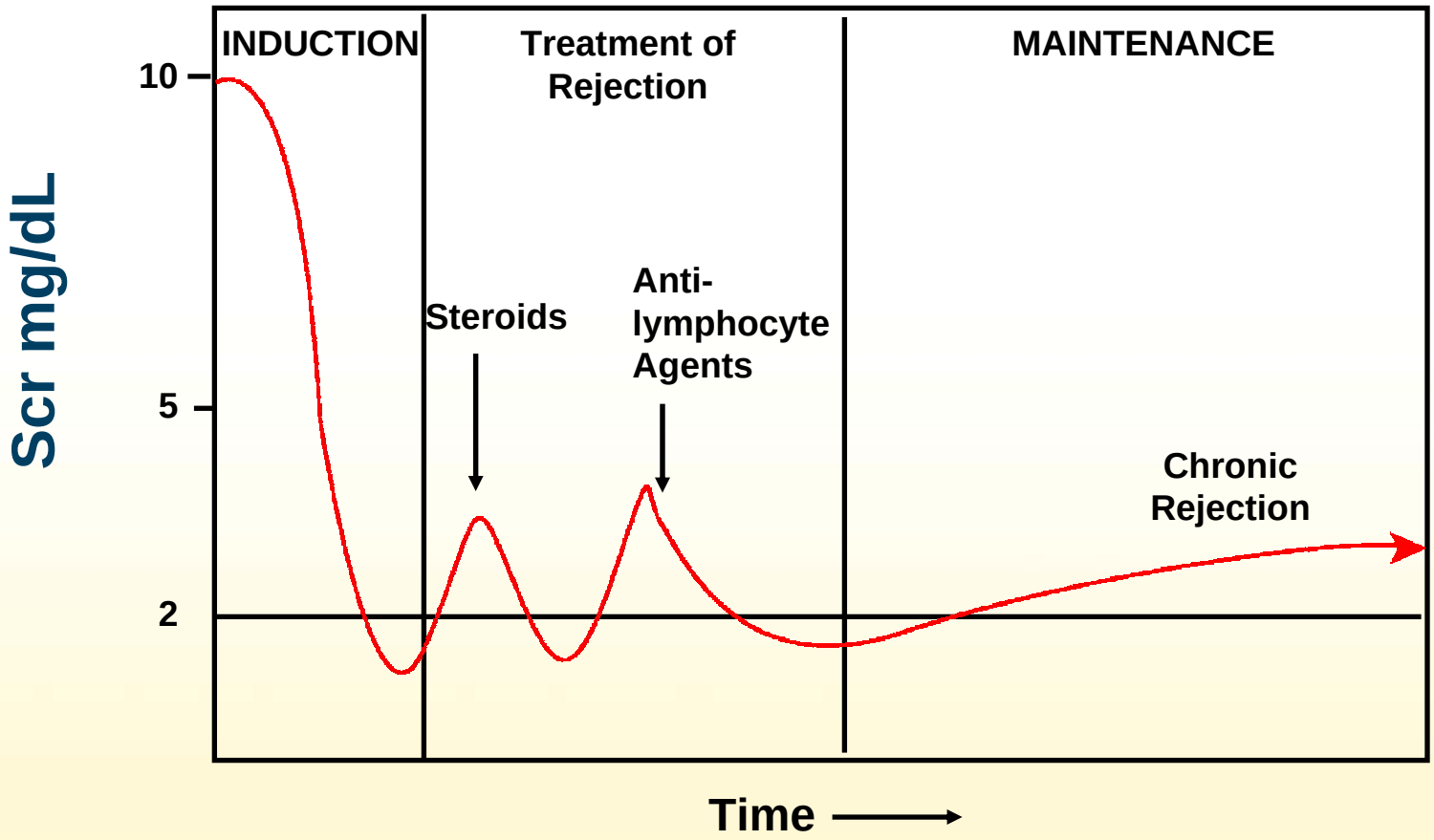
	US group		UK group	
Immunosuppression	Immediately after transplantation	At last follow-up	Immediately after transplantation	At last follow-up
Steroids	70	30	4	3
MMF	45	27	2	2
FK506	23	17	1	1
AZA	18	4	1	1
CYA	30	2	3	2
Sirolimus	5	7	0	0
MMF, mycophenolate; AZA, asathioprine; CYA, cyclosporine A				

Transplantation **2008;86:1572-77.**

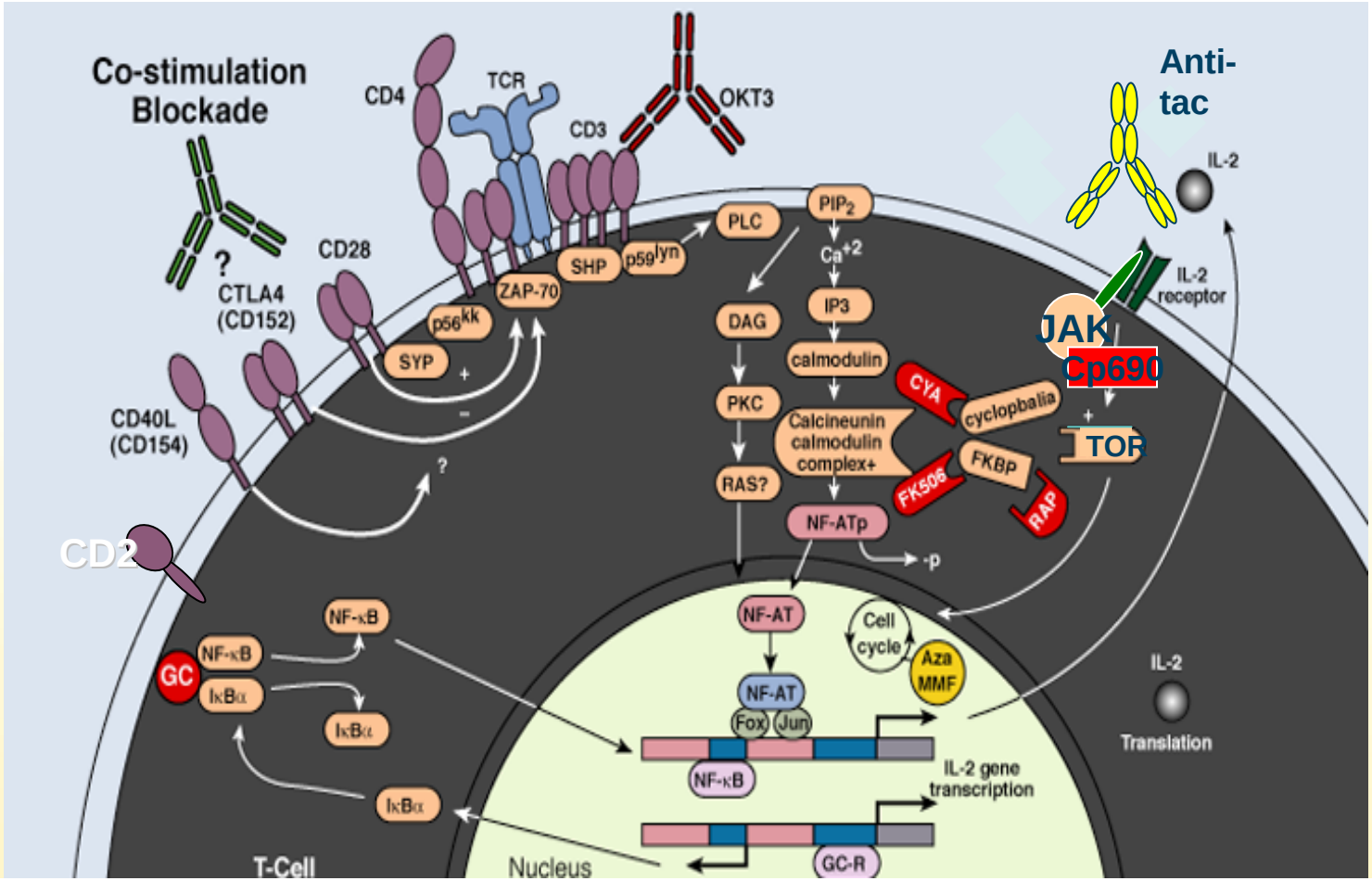
Clinical Implications for the Principles of Transplant Immunosuppression

1. It is important to prevent a primary immune response; No acute rejection is better than some rejection.
2. It is better to use lower doses of IS drugs that work at different points in the cell cycle than larger doses of a single agent. Impact on tolerability and toxicity.
3. The total amount of IS should be decreased over time as the host accommodates to the foreign HLA phenotypes.

The Fate of Renal Allografts: Immunosuppression



Biologic Targets for Immunosuppressive Agents



Immunosuppressive Strategies

1. Induction Therapy - high dose therapy
   - prevent a primary immune response
   - decrease passenger leukocytes
   - permit resolution of ischemic renal injury
2. Maintenance Therapy - lowest tolerated
   - minimize toxicity
   - rejection prophylaxis
3. Anti-Rejection Therapy - high dose therapy
   - limit number of interventions

Comparative Modes of Action: Induction Antibodies

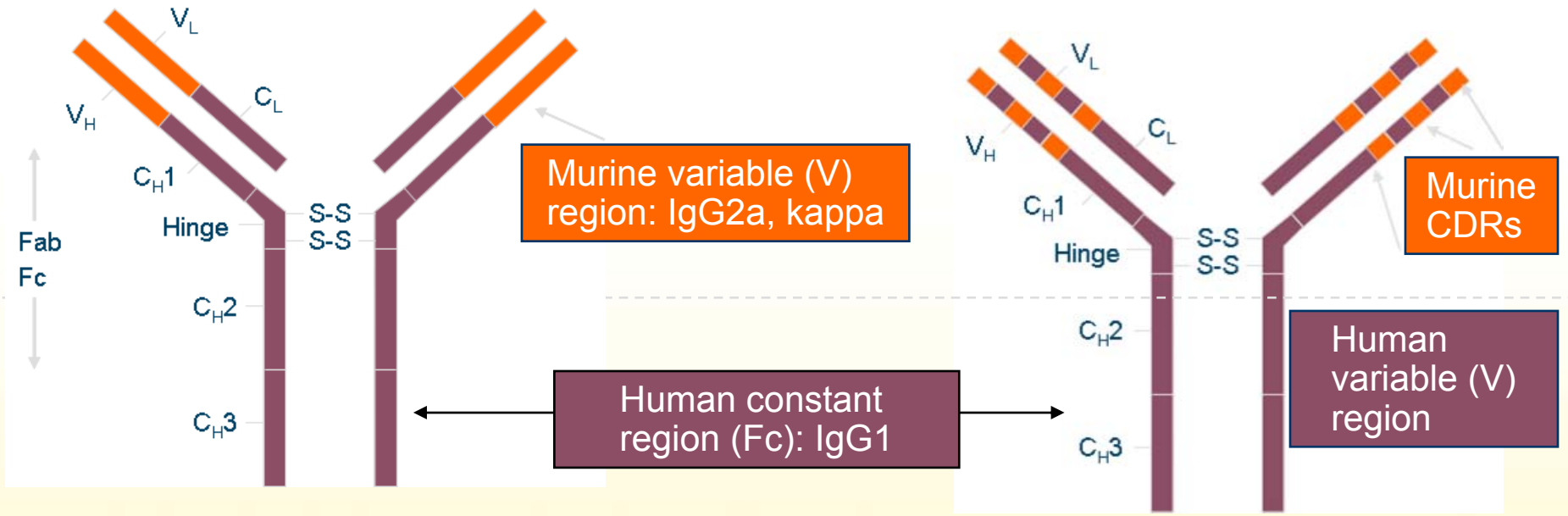
Agent	Type of Ab	Target	Principle Adverse Events	Effective Time
Basiliximab Daclizumab	Chimeric mAb Humanized mAb	αChain of the IL2R non T-cell depleting	Mild cytokine release; pneumonitis	2 months
OKT3	Murine mAb	CD3: resting & activated T-cells T-cell depleting	Cytokine release syndrome	1 month
Thymoglobulin	Rabbit polyclonal Ab	All resting & activated T-cells T-cell depleting*	Increased risk of infection and PTLD	6 months
Alemtuzumab	Humanized mAb	CD 52: resting & activated T-cells T-cell depleting	Increased risk of infection and PTLD	12 months

*Polyclonal Abs also target surface antigens on B-cells, NK cells, macrophages, neutrophils, and platelets.

Differences in Complementarity-Determining Regions Between IL-2Rα mAb Structures

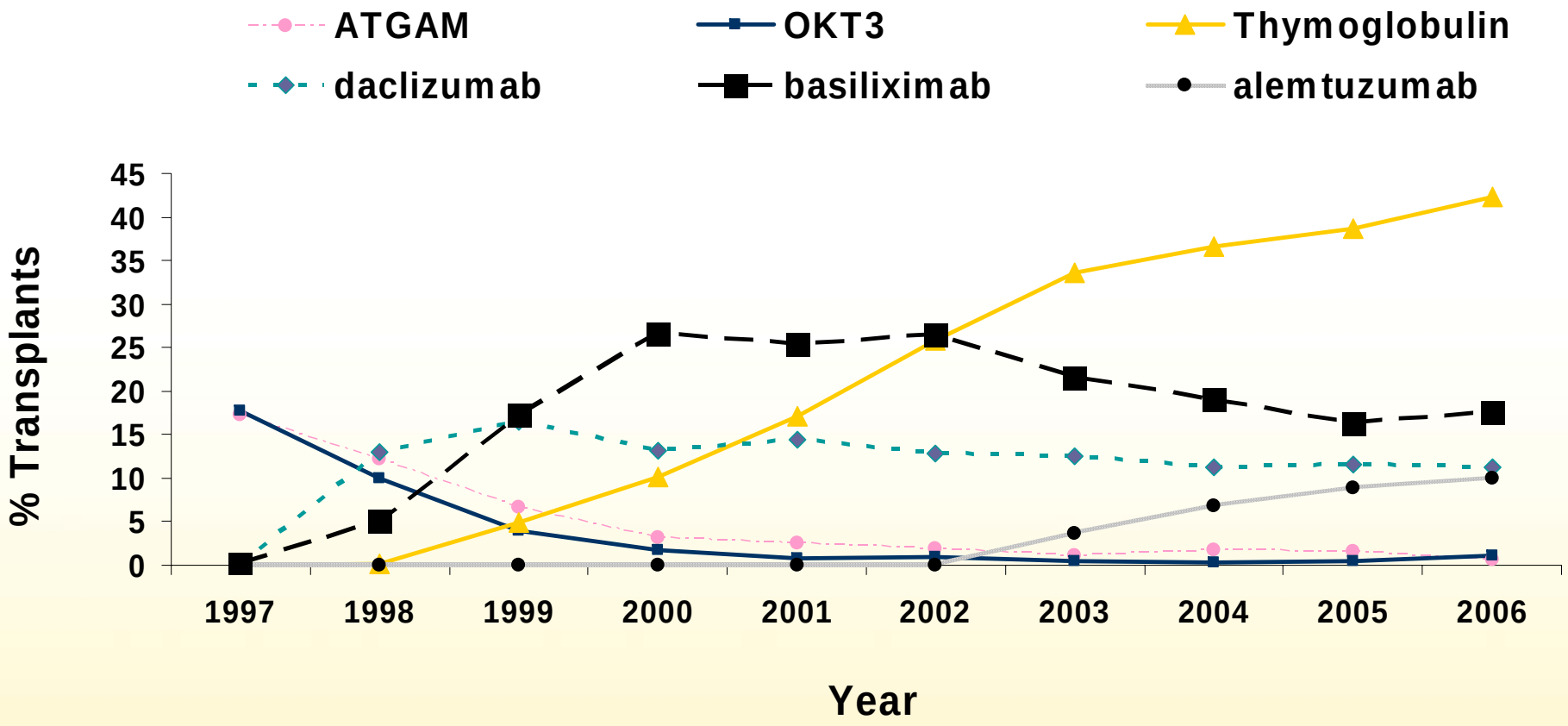
Chimeric—Basiliximab

Humanized—Daclizumab



CDRs=complementarity-determining regions

Trends in the Use of Induction Antibody Therapy in Kidney Transplantation



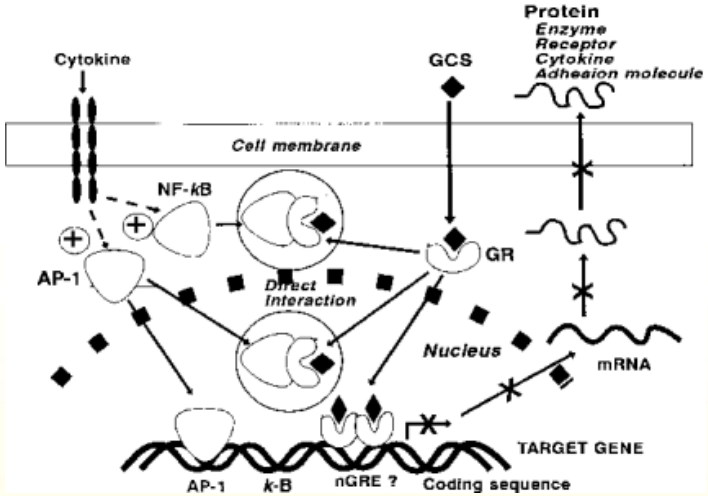
ATGAM= lymphocyte immune globulin, anti-thymocyte globulin (equine); OKT3= muromonab)

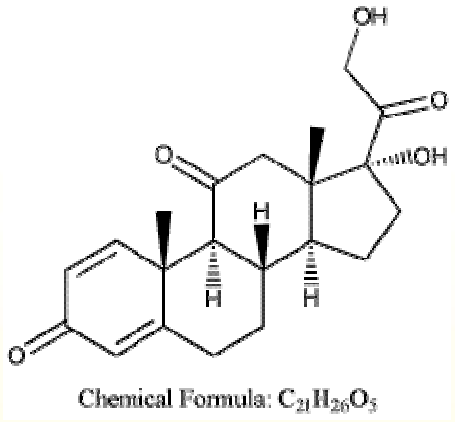
US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients (OPTN/SRTR). 2007 Annual Report. Available at: http://www.ustransplant.org/annual_reports/current/. Accessed August 12, 2009.

Maintenance Immunosuppression: Multi-drug Therapy with Small Molecules

1. Calcineurin or mTOR Inhibitor:
   - cyclosporine, tacrolimus, sirolimus
2. Anti-proliferative Agents:
   - azathioprine, mycophenolic acid
3. Corticosteroids:
   - low dose, avoidance, withdrawal

Corticosteroids: Have numerous effects on the immune system that include sequestration of lymphocytes in lymph nodes and the bone marrow resulting in lymphopenia. Glucocorticoids become bound to intracellular receptors that interfere with cytokine production. Their primary immunosuppressive effect is inhibition of monocyte production and release of interleukin (IL-1), with subsequent inhibition of T cell IL-2 and interferon-gamma; thus interfering with lymphocyte activation and production of effector cells.





TDM targets: None, 0.05-0.1 mg/kg

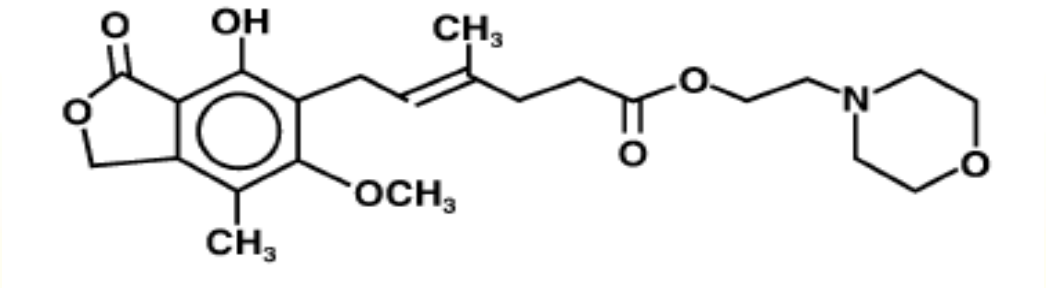
The principal adverse reactions include:

- Cushingoid features, hypertension, hyperlipidemia, diabetes
- GI ulcerations, osteoporosis, poor wound healing, cataracts
- Growth retardation, psychiatric disturbances, myopathy, acne

Why Steroids at All?

- Anti-inflammatory
- Induce lymphopenia via lympholysis
  - But do enhance lymphatic flow
- Lymphocyte sequestration in RE system
- Demarginate adherent WBC from endothelium
- Enter nucleus and bind to steroid response elements on DNA, resulting in inhibition of transcription of immune regulatory cytokines
  - Inhibit AP-1 and NF-κB
  - Suppression of IL-1 and IL-6 from Monos and Macs
  - Suppression of TNFα and INF-γ from T cells

Mycophenolate Mofetil: The 2-morpholinoethyl ester of mycophenolic acid (MPA); potent, selective, non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH). MMF inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Since T and B Lymphocytes are critically dependent for their proliferation on the de novo synthesis of purines, and other cell types can utilize salvage pathways, MMF has potent cytostatic effects on lymphocytes.

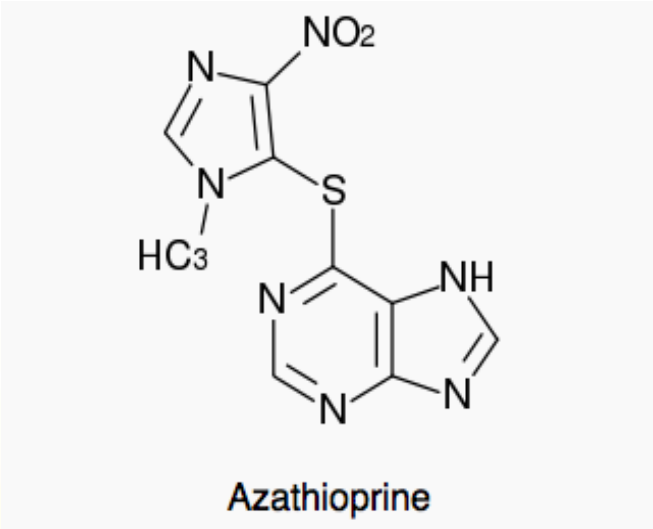


TDM targets:
C_o 2-4 mg/L

The principal adverse reactions include:

- GI: nausea, vomiting, diarrhea, colitis
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Infection: opportunistic, cases of PML
- Pregnancy: should be avoided

Azathioprine: Competitive inhibitor of purine biosynthesis preventing the proliferation of activated T and B cells, thereby blocking both cellular and humoral immune responses inhibits lymphocyte proliferation in late G2 phase of the cell cycle



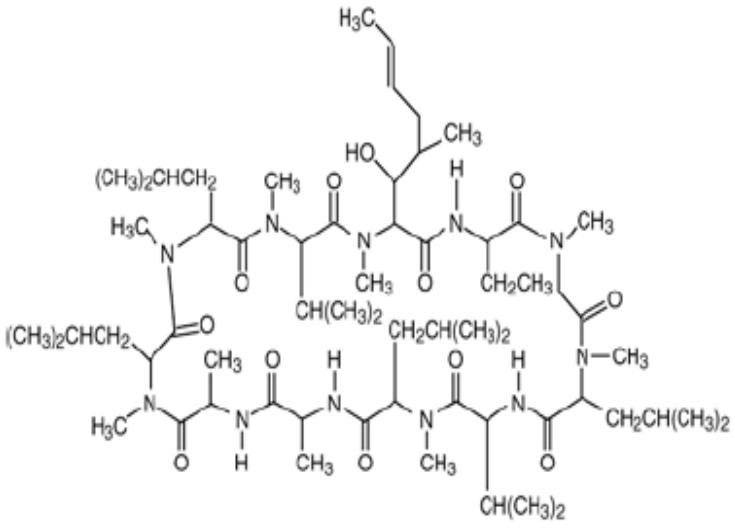
Azathioprine

TDM targets:
None, WBC

The principal adverse reactions include:

- GI: nausea, vomiting, diarrhea
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Infection: opportunistic
- Liver toxicity-transaminasemia, alopecia

Cyclosporine: A fungal endecapepetide binds to a specific intracellular immunophillin (cyclophillin) with subsequent engaging of the enzyme calcineurin phosphatase; thereby preventing the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation.



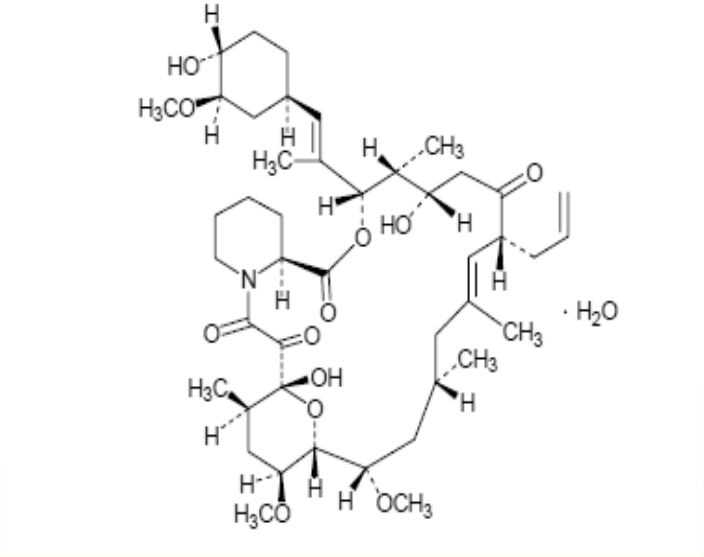
Formula: $C_{62}H_{111}N_{11}O_{12}$ **Mol**. Wt.:1202.6

TDM targets:
C_o 100-250 ng/mL
C_2 500-1000 ng/mL

The principal adverse reactions include:

- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Acute and Chronic Nephrotoxicity; hepatotoxicity
- Gingival hyperplasia, hirsutism
- Hypertension, hyperkalemia, hyperuricemia, dyslipidemia

Tacrolimus: A fungal peptide. Binds to a specific intracellular immunophillin (FKBP12) with subsequent engaging of the enzyme calcineurin phosphatase; thereby preventing the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation.

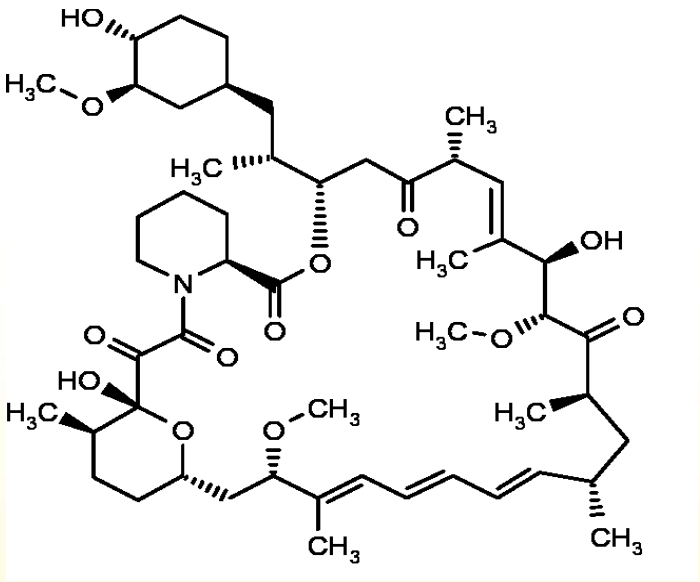


TDM targets:
C_o 6-12 ng/mL

The principal adverse reactions include:

- Acute and Chronic Nephrotoxicity; Neurotoxicity, tremors
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Hyperglycemia and diabetes
- Hyperkalemia, hypomagnesemia

Sirolimus: A fungal peptide. Similar molecular structure to the calcineurin inhibitors, and binds to the same immunophillin (FKBP-12) as tacrolimus. However, their mode of action appears to be distinct, as the sirolimus complex does not inhibit calcineurin. Instead, the sirolimus-FKBP complex appears to engage a distinct p70 kinase called mTOR (molecular target of rapamycin). The inhibition of mTOR blocks IL-2 signal transduction pathways that prevent cell-cycle progression from G1 to S phase in activated T cells.

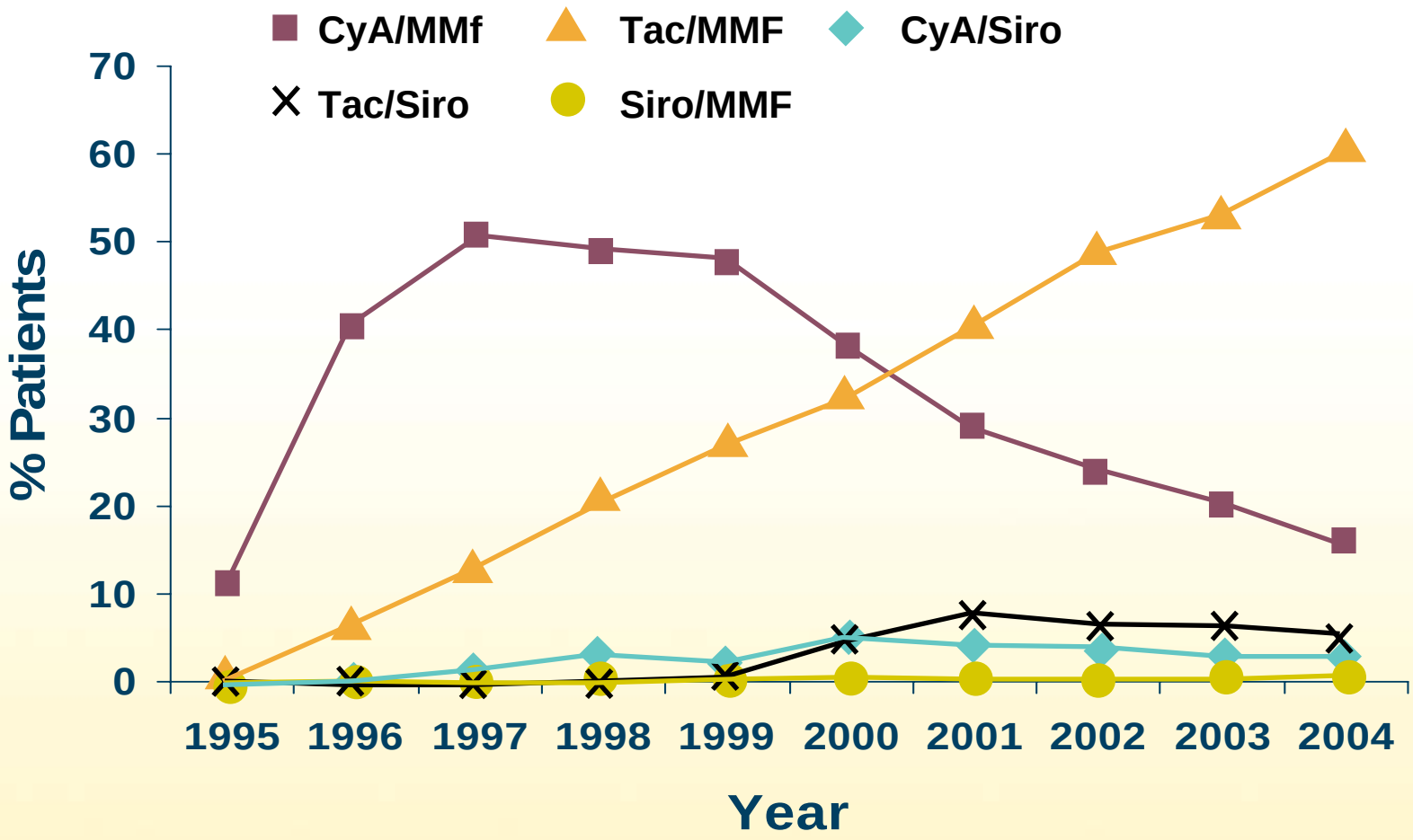


TDM targets:
C_o 8-12 ng/mL

The principal adverse reactions include:

- Dyslipidemia, delayed wound healing and lymphoceles
- Marrow suppression: leukopenia, anemia, thrombocytopenia
- Oral ulcer, skin rash-acne, non infectious pneumonitis

Trends in Discharge Immunosuppression Regimens for Kidney transplantation, 1995-2004



SRTR

Meier-Kriesche et al. *Am J Transplant.* 2006;6:1111-1131.

Tailoring Immunosuppression to Limit Potential Side Effects

Limiting Side Effects	Depleting Antibodies	Cyclosporine	Tacrolimus	Sirolimus Everolimus	Steroids	MMF
NODAT		↑↑	↑↑↑	↑	↑↑	
Dyslipidemia		↑↑	↑	↑↑↑	↑↑	
Hypertension		↑↑	↑		↑	
Nephrotoxicity		↑↑↑	↑↑↑			
Hirsutism		↑↑			↑	
Gingival Hyperplasia		↑↑↑				
Wound Healing		↑	↑	↑↑↑	↑	↑↑
Solid/Skin Cancers	↑↑↑	↑↑	↑↑	↓↓	↑	↑
Neurotoxicity			↑↑		↑	

Immunosuppressive Treatment Strategies for the Transplant Recipient

- Immunosuppressive Therapy is necessary to prevent the rejection of organ allografts
- Organ allografts are subject to the same rules that govern the immune response to microbes and other foreign invaders
- Induction therapy using antibodies are more frequently used today to prevent a primary immune response
- Multidrug maintenance regimens are most often used to maximize efficacy and minimize individual drug toxicity
- Tailoring immunosuppression is possible to further control side effects in higher risk recipients