Solid Organ Transplant Immunosuppression

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Northwell Health®

Disclosure

- No conflicts of interest

Objectives

- Discuss the purpose and role of immunosuppressive therapy
- Describe the pharmacology, dosing, and adverse effects of medications used in transplant recipients
- Identify important drug interactions involving transplant medications

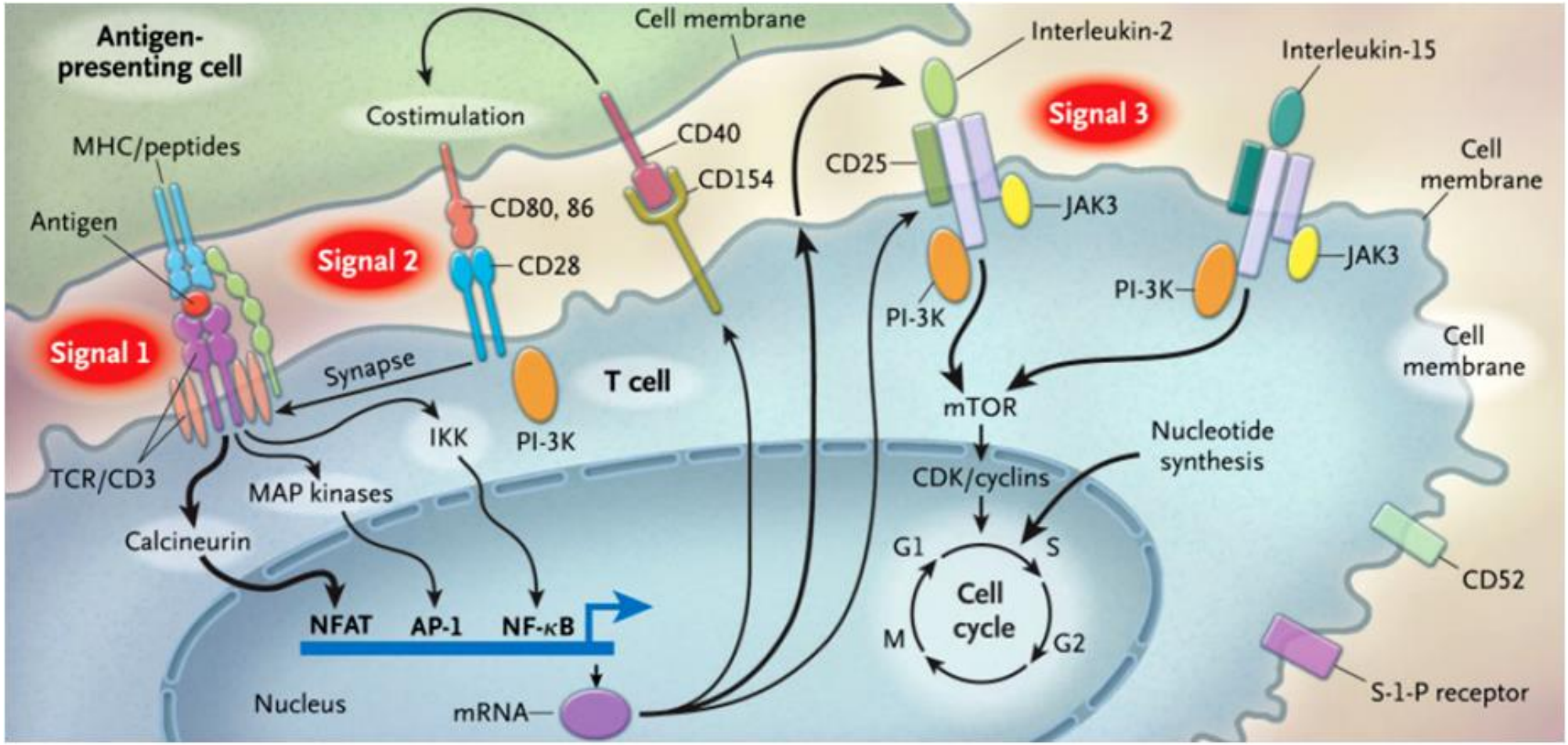
Transplant Immunosuppression

Rejection

Infection

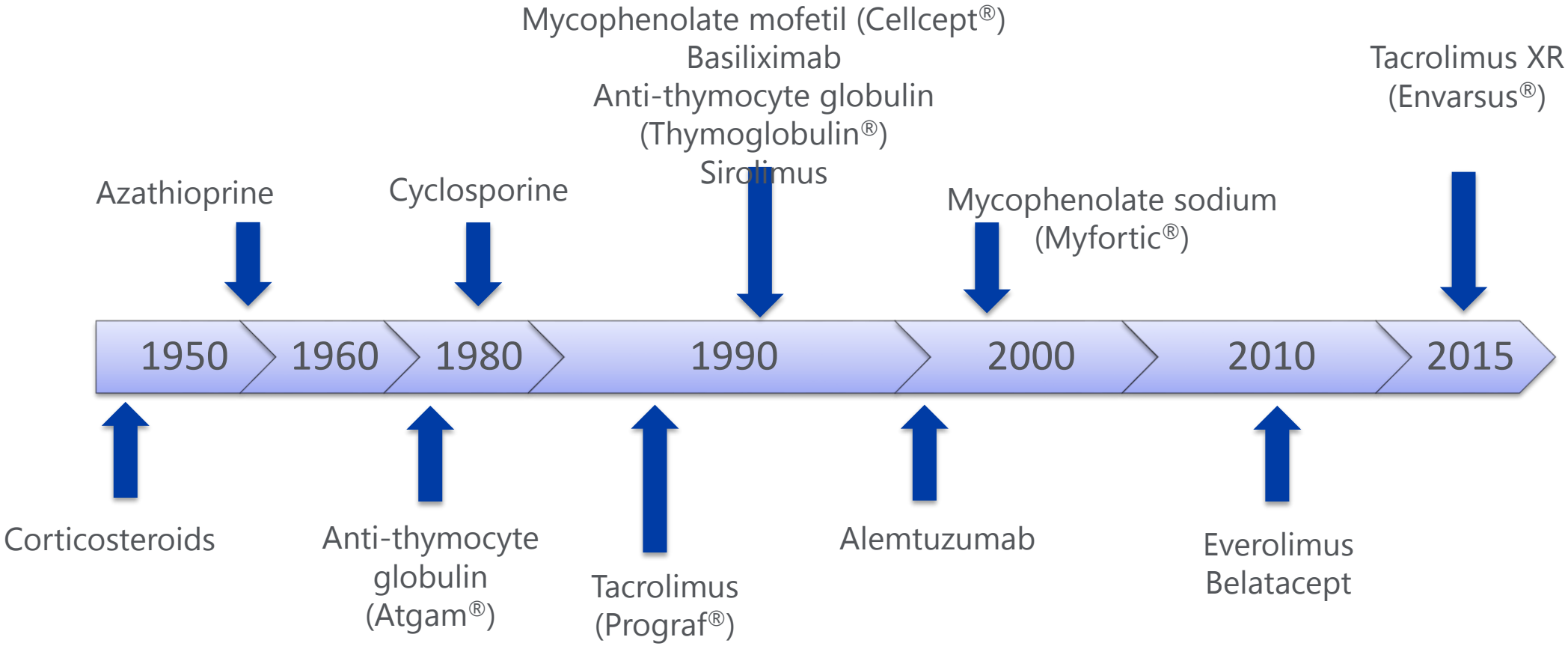
Toxicity

T-cell Activation



Halloran PF et al. *N Engl J Med* 2004;351:2715-29.

Immunosuppression Timeline



Induction vs. Maintenance Immunosuppression

Induction

- High dose, short term immunosuppression given pre- and peri-transplant
- Reduces acute rejection
- Delays the onset of maintenance immunosuppressants

Maintenance

- Low dose, long term immunosuppression given post-transplant
- Prevents acute and chronic rejection

Induction Therapy

High dose corticosteroids

Basiliximab

Anti-thymocyte globulin

Alemtuzumab

Corticosteroids

Mechanism of Action	Dose dependent inhibition of immune response Suppresses IL-1,2,3,6, gamma interferon, TNF-alpha, platelet activating factor, prostaglandins, leukotrienes and TNF
Target	Antigen Presenting Cells (APCs)
Dosing	500 – 1000 mg given intra-operatively and then tapered

Kahan BD. *Nat Rev Immunol*. 2003;3(10):831-8

Corticosteroids: Adverse Effects

Acute Changes

Hyperglycemia
Leukocytosis
Impaired wound healing
GI disturbance
CNS effects (euphoria, depression, insomnia)

Chronic Changes

Weight gain
Osteoporosis, avascular necrosis
Fluid retention / hypertension
Hyperlipidemia
Cataracts / glaucoma
Growth retardation
Acne
Hirsutism
Infection

Antibody Agents

Lymphocyte depleting	Polyclonal	Anti-thymocyte globulin (Thymoglobulin®, Atgam®)
	Monoclonal	Alemtuzumab (Campath®)
Non-lymphocyte depleting	Monoclonal	Basiliximab (Simulect®)

Anti-thymocyte Globulin

- Cytotoxic antibodies directed against human T-lymphocytes

Rabbit-derived (rATG):

Thymoglobulin®

Thymoglobulin® > Atgam®

- Greater potency
- Better tolerated

Horse-derived: Atgam®

Halloran PF. *N Engl J Med*. 2004;351(26):2715-29.; Kahan BD. *Nat Rev Immunol*. 2003;3(10):831-8.; Brennan DC, et al. *Transplantation* 1999; 67(7): 1011-18.

Anti-thymocyte Globulin

Mechanism of Action	Antibodies specific for lymphocyte surface markers CD2,3,4,8,16,25,45 Opsonize platelets, lymphoid, and PMN cells
Target	T and B cells, dendritic cells, plasma cells, NK cells, adhesion molecules
Adverse Effects	Thrombocytopenia, leukopenia, cytokine-release syndrome, infection, malignancy, flash pulmonary edema, allergic reactions, serum sickness
Cost	~ $800/ vial (25 mg)
Duration	Lymphocyte depletion: 24 hours Duration: 6 – 12 months

Laftavi MR. *Immunol Invest*. 2014;43(8):790-806.; Halloran PF. *N Engl J Med*. 2004;351(26):2715-29.; Kahan BD. *Nat Rev Immunol*. 2003;3(10):831-8

rATG Dosing and Administration

- Typical Dosing: 1.5 mg/kg/day for 4 doses
  - Round dose to nearest 25 mg
  - Typical maximum daily dose: 150 mg
- Pre-medications: acetaminophen, diphenhydramine, corticosteroid
- Infuse over at least 6 hours through a 0.22 micron filter

Laboratory Parameter	Dose Adjustment
WBC >3 or ANC ≥1.5 or Platelets >75,000	No change
WBC 2–3 or ANC 1–1.4 or Platelets 50,000–75,000	Decrease by 50%
WBC <2 or ANC <1 or Platelets <50,000	Hold

WBC: White blood cell;
ANC: absolute neutrophil count

Atgam [package insert]. New York, NY: Pfizer, 2014.; Thymoglobulin package insert]. Cambridge, MA: Genzyme Corporation, 2016.; Tsapepas DS. *Transplantation.* 2012;94(4):325-30.; Hardinger KL. *J Transplant.* 2010;2010:957549.

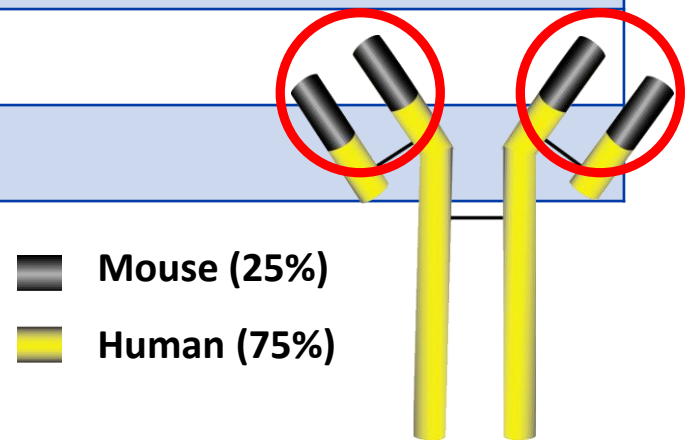
Alemtuzumab (Campath®)

Mechanism	Monoclonal antibody against CD52 that triggers antibody-dependent cytotoxicity and lysis
Target	B and T cells, macrophages, NK cells, some granulocytes
Dose	30 mg IV infusion (central or peripheral) over 2 hours x 1 dose Pre-medications: acetaminophen, diphenhydramine, steroids
Adverse Events	Cytokine release syndrome, rash, myelosuppression, infection, malignancy, infusion reaction
Duration	12 months

Laftavi MR. *Immunol Invest.* 2014;43(8):790-806.; Campath [package insert]. Cambridge, MA: Genzyme Corporation, 2014.

Basiliximab

Mechanism of Action	Chimeric monoclonal anti IL-2 receptor antibody (CD 25) Non-depleting
Target	Activated T-cells only
Dosing	20 mg IV infusion over 30 minutes on POD 0 and POD 4 Does not require pre-medications
Adverse Effects	Infection, malignancy, hypersensitivity
Cost	~ $3500/vial (20 mg)
Duration	2-4 weeks



Basiliximab
[chimeric monoclonal]

Simulect [package insert]. East Hanover, New Jersey: Novartis, 2005; Laftavi MR. *Immunol Invest*. 2014;43(8):790-806.

Assessment Question

Horton is a 45 year old male s/p deceased donor renal transplant receiving his fourth and final dose of anti-thymocyte globulin (ATG) 125 mg for induction therapy

Wt: 80 kg **WBC: 1.9** **Platelets: 102**

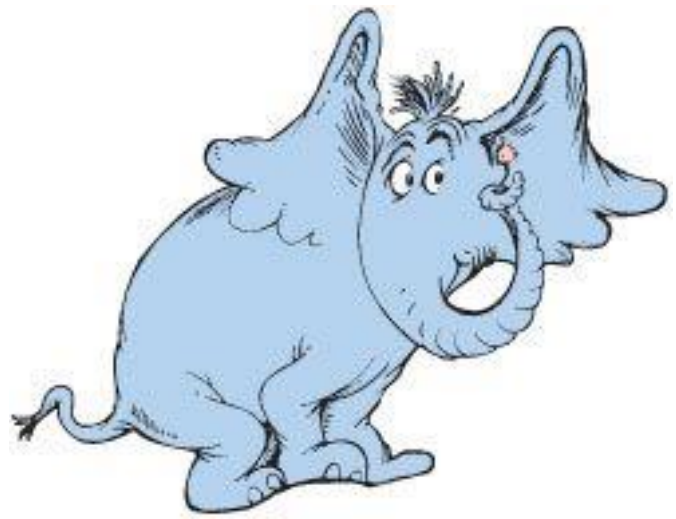
What dose of ATG should CW receive?

A. CW should not receive any ATG

B. CW should receive 75 mg of ATG

C. CW should receive 125 mg of ATG

D. The maximum daily dose of ATG is 100 mg, so CW should only receive 100 mg



Choosing an Induction Agent

Induction agent

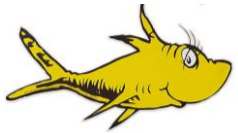
No induction < Basiliximab < Alemtuzumab < Anti-thymocyte globulin

Lower risk	**Higher risk**
Zero HLA mismatch	Increased # of HLA mismatches
Live donor	Younger recipient and older donor age
Caucasian ethnicity	African-American ethnicity
Low panel reactive antibody	High panel reactive antibody
Absence of donor specific antibody	Presence of donor specific antibody
Blood group compatibility	Blood group incompatability
Immediate graft function	Delayed onset of graft function
Short cold ischemia time	Long cold ischemia time
First transplant	Retransplant

Hardinger KL. *Transpl Int*. 2013;26(7):662-72.

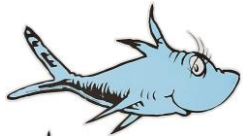
Maintenance Therapy

Maintenance therapy



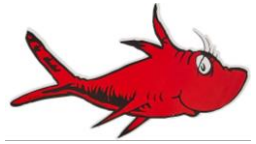
Calcineurin Inhibitors (CNI)

- Cyclosporine
- Tacrolimus



Anti-metabolites

- Azathioprine
- Mycophenolate

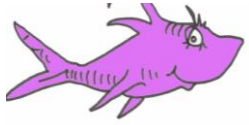


Mammalian target of rapamycin (mTOR) inhibitors

- Sirolimus
- Everolimus

CD80/86 Inhibitor

- Belatacept

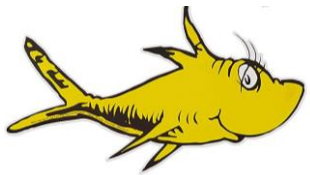


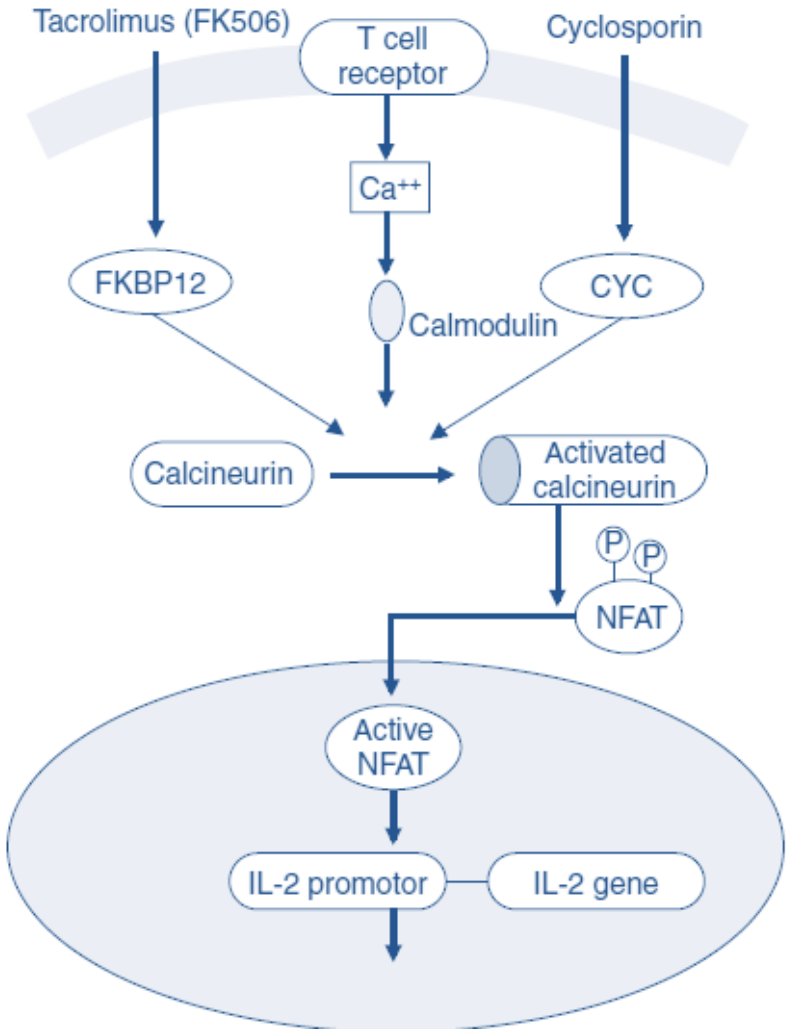
Corticosteroids

- Methylprednisolone
- Prednisone

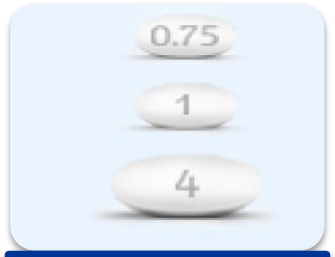
Calcineurin Inhibitors

- Tacrolimus (FK) and Cyclosporine (CsA)
- Backbone of maintenance immunosuppressive regimen
- Therapeutic trough monitoring
  - Organ transplanted
  - Time since transplant
  - Concomitant immunosuppression
  - Adverse effects

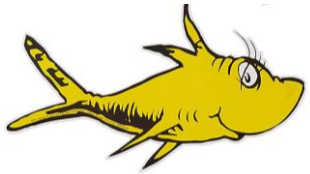




Tacrolimus and Cyclosporine

					
Prograf® Immediate release Twice daily dosing 0.5, 1, 5 mg capsules 1 mg/mL suspension	**Astagraf®** Extended release Once daily dosing 0.5, 1, 5 mg capsules	**Envarsus®** Extended release Once daily dosing 0.75, 1, 4 mg tablets	**Sandimmune®** Erratic absorption Twice daily dosing 25, 100 mg capsules 100 mg/mL solution	**Neoral®*** Microemulsion Better absorption Twice daily dosing 25, 100 mg capsules 100 mg/mL solution	**Gengraf®** Microemulsion Better absorption Twice daily dosing 25, 50, 100 mg capsules 100 mg/mL solution

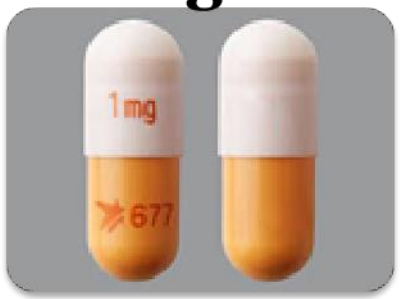
Sandimmune ≠ Neoral, Gengraf



Prograf® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.; Astagraf® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.; Envarsus® [package insert]. Cary, North Carolina: Veloxis Pharmaceuticals, Inc.; 2017.; Neoral® [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation.; 2015. Sandimmune® [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation.; 2015. Gengraf® [package insert]. North Chicago, IL: AbbVie Inc.; 2015.

Tacrolimus: Converting between Formulations

Astagraf®



10 mg once daily

1 mg : 1 mg

Prograf®

5 mg twice daily

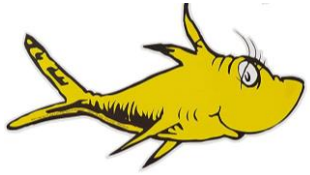
Envarsus®

8 mg once daily

80% of the total daily dose of Prograf®

Prograf®

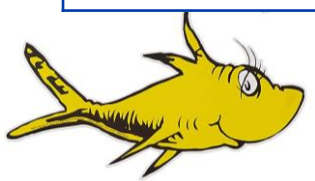
5 mg twice daily



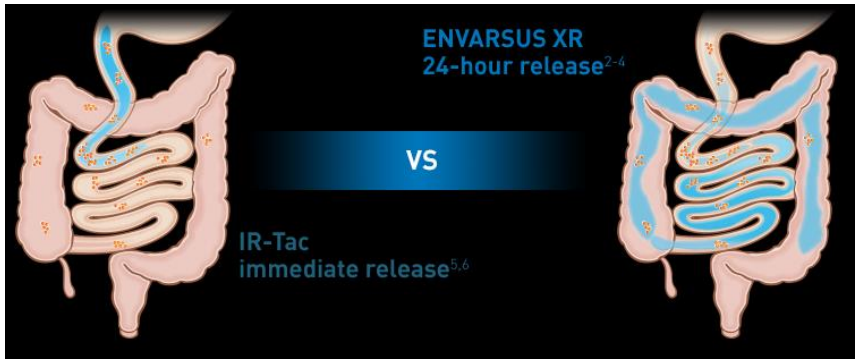
Prograf® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.
Astagraf® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.
Envarsus® [package insert]. Cary, North Carolina: Veloxis Pharmaceuticals, Inc.; 2017.
van Hooff J, Van der Walt I, Kallmeyer J, et al. *Ther Drug Monit*. 2012;34:46–52.
Alloway R, Steinberg S, Khalil K, et al. *Transplant Proc.* 2005;37:867–870.

CNI: Formulations and Dose Conversions

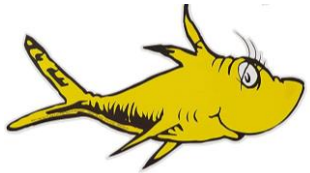
Formulation		Tacrolimus IR (Prograf®)	Cyclosporine
Suspension	Preparation	1 mg/mL	100 mg/mL
	Dose Conversion	1:1	1:1
Intravenous (IV)	Administration	Administer as a continuous infusion over 24 hours to minimize nephrotoxic effects	
	Dose Conversion	Calculate IV tacrolimus by taking one-fifth of the total daily oral dose	Calculate IV cyclosporine by taking one-third of the total daily oral dose
Sublingual (SL)	Administration	Only use tacrolimus capsules for SL administration. Oral suspension should not be used for SL administration	Not Applicable
	Dose Conversion	Oral → SL = 50% of tacrolimus dose SL → oral = tacrolimus dose is doubled	



CNI Pharmacokinetics



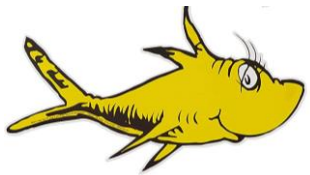
- **Absorption:** small intestine
- **Distribution:** highly protein bound (99%) and binds to RBCs
- **Metabolism:** CYP3A4 (liver and intestine) and P-glycoprotein (intestine)
- **Excretion:** bile



Prograf® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2015.; Envarsus® [package insert]. Cary, North Carolina: Veloxis Pharmaceuticals, Inc.; 2017.; Neoral® [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation.; 2015.

CNI Adverse Effects

Adverse Effects	CsA	FK
Hypertension	++	+
Hyperlipidemia	++	+
New-onset diabetes	+	++
Electrolyte abnormalities Hyperkalemia, hypomagnesemia, hypophosphatemia	+	+
Nephrotoxicity	++	++
Neurotoxicity	+	++
Alopecia		+
Gingival Hyperplasia	+	
Hirsutism	+	



Assessment Question

Which of the following formulations of tacrolimus are dosed once daily?

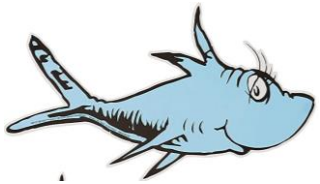
A. Prograf®
B. Astagraf®
C. Envarsus®
D. A and B
E. B and C
F. All of the above

Anti-metabolites

Mycophenolate mofetil (CellCept®)	Mycophenolic Sodium (Myfortic®)	Azathioprine (Imuran®)
• Twice daily dosing • 250 mg capsules, 500 mg tablets • Suspension: 200 mg/mL • IV to PO is 1:1 conversion	• Twice daily dosing • 180, 360 mg tablets • Enteric-coated sodium salt	• Once daily dosing • 50 mg tablet (Can be cut in half) • 1 – 3 mg/kg/day

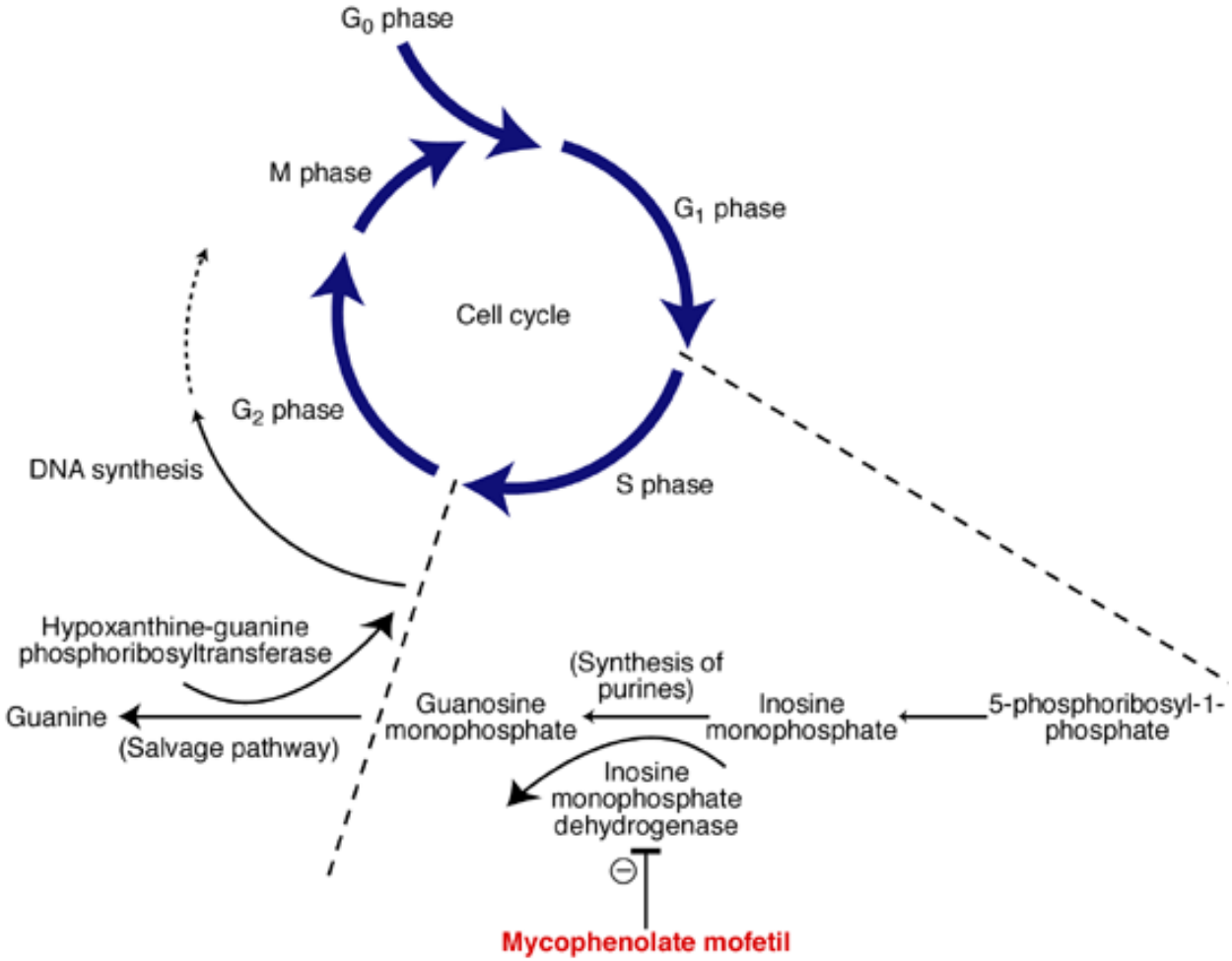
1000 mg twice daily = 720 mg twice daily

500 mg twice daily = 360 mg twice daily



Cellcept [package insert]. San Francisco, CA: Genentech Inc; 2015.; Myfortic [package insert]. East Hanover, NJ: Novartis; 2016.; Imuran [package insert]. San Diego, CA: Prometheus Laboratories Inc; 2014

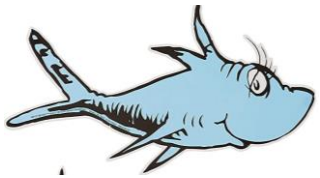
Mycophenolic Acid (MPA): Mechanism of Action



MPA inhibits inosine monophosphate dehydrogenase (IMPDH)

IMPDH is responsible for *de novo* purine synthesis and DNA synthesis in T and B cells

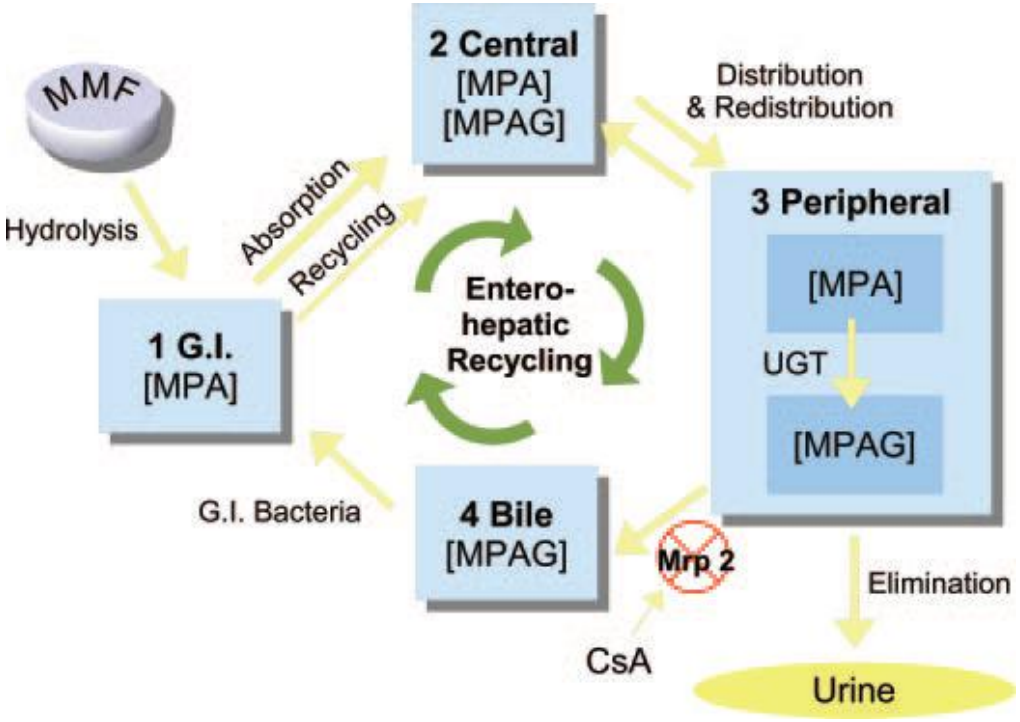
Lymphocytes cannot utilize salvage pathways to make DNA

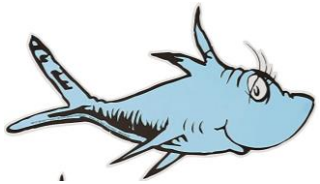


Staatz CE, Tett SE. Arch Toxicol. 2014;88(7):1351-89.

MPA: Pharmacokinetics

- Absorption → ~90%
  - Non-linear PK
- Distribution → 99% plasma protein bound
- Metabolism →conjugation in the liver
  - Major metabolite (MPAG)- enterohepatic recycling
  - Minor metabolite (AcMPAG)
- Excretion → metabolites excreted into urine

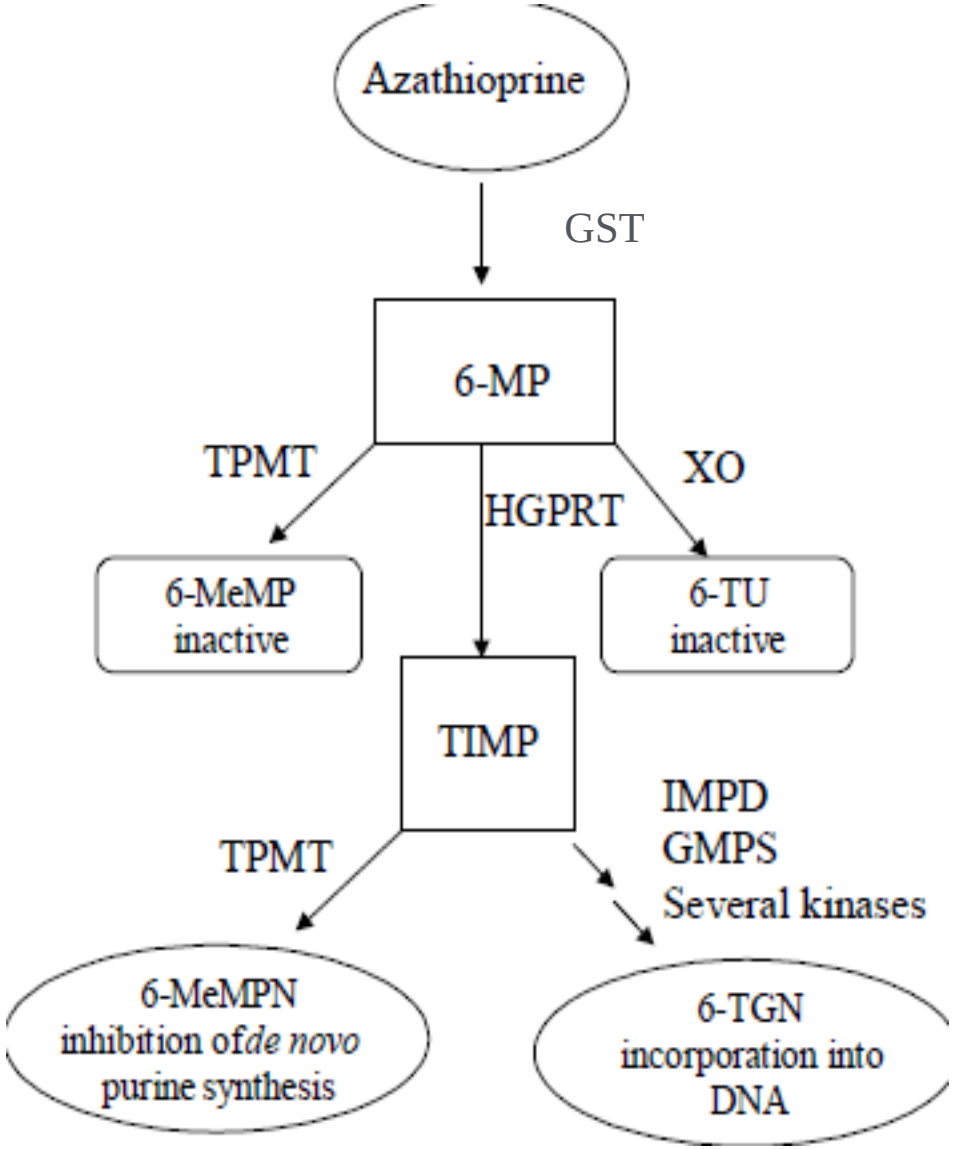


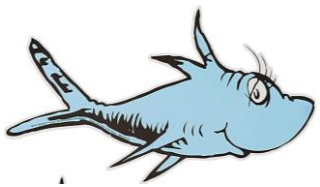


Cellcept [package insert]. San Francisco, CA: Genentech Inc; 2015.; Myfortic [package insert]. East Hanover, NJ: Novartis; 2016.

Azathioprine (Imuran®)

- Prodrug and derivative of 6-mercaptiopurine (6-MP)
- Mechanism of action
  - Purine mimetic antimetabolite
  - Resembles guanosine purine
  - Inhibit DNA synthesis to decrease circulating T and B cells

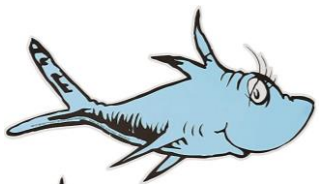




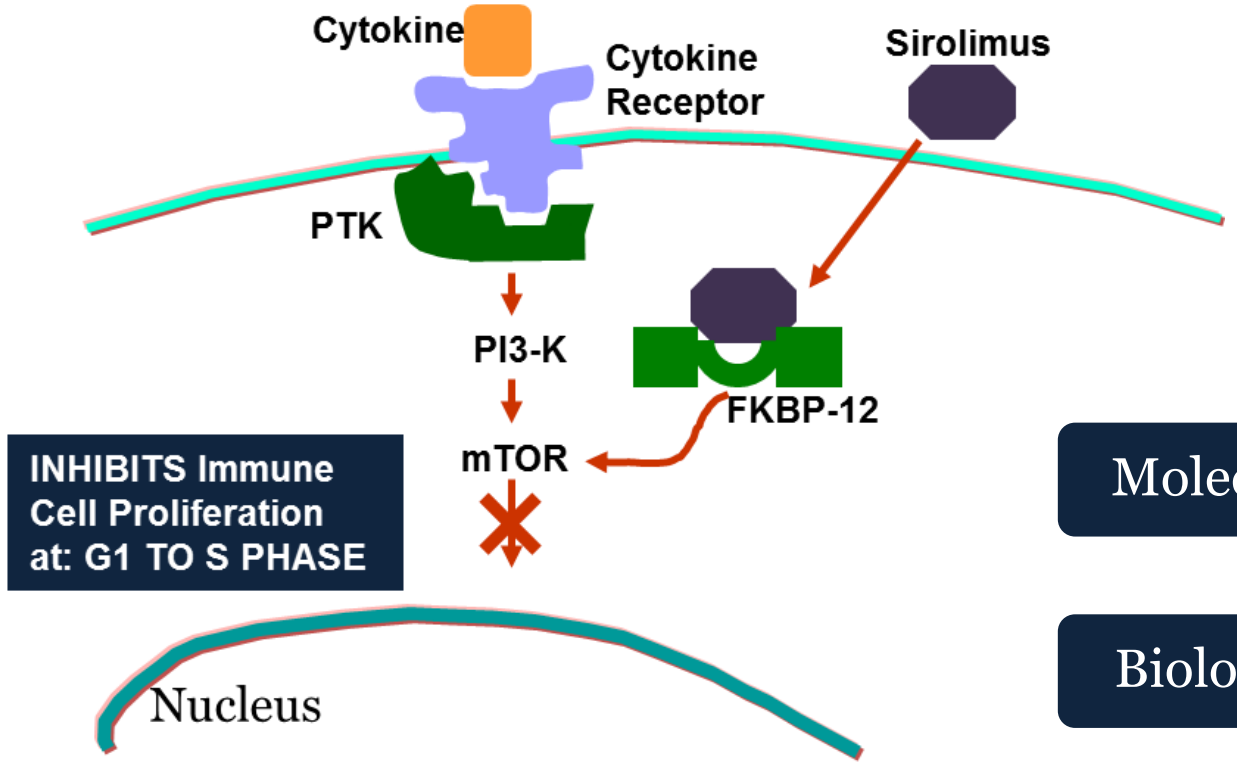
Maltzman JS, Koretzky GA. *J Clin Invest*. 2003;111(8):1122-4.

Anti-metabolites: Adverse Effects

Adverse Effects	MPA	AZA
Gastrointestinal (N/V/D)	++	
Leukopenia	++	+/-
Thrombocytopenia	+ +	+ /-
Teratogenic	+	
Hepatotoxicity		+



mTOR Inhibitors: Mechanism



Molecular

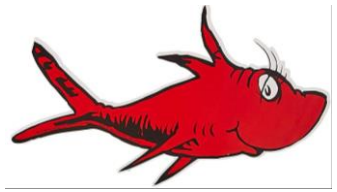
- Inhibit DNA synthesis at G1 to S phase progression

Biological

- Down regulation of: T cells, B cells, Endothelial cells, smooth muscle cells

Clinical

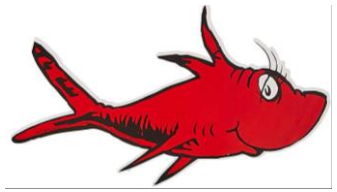
- Decrease acute rejection
- Decrease chronic allograft nephropathy
- Decrease would healing
- Anti-cancer effects



Mammalian target of rapamycin (mTOR) inhibitors

	Sirolimus	Everolimus
Dose	2-15 mg PO **once** daily	0.75 mg PO **twice** daily
Dosage forms	0.5, 1, and 2 mg tablets 1 mg/mL oral solution	0.25, 0.5, 0.75 mg tablets
Metabolism	CYP 3A3/4	CYP 3A3/4
Excretion	91% feces, 2.2% urine	80% feces, 5% urine
Half life	62 hours	30 hours
Trough 5-7 days	3-8 ng/mL*	

*Target concentrations will vary depending on organ transplanted, time since transplant, concomitant immunosuppressive and other medications, assay used, side effects experienced



Zortress (everolimus) [product information]. Novartis 2015.; Rapamycin (sirolimus) [product information]. Pfizer 2015.

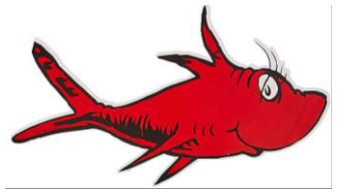
Niche in SOT

Differing adverse effects

Anti-viral properties

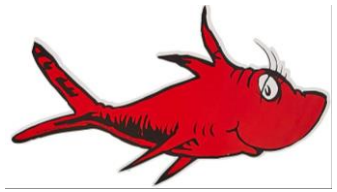
Anti-fibrotic properties

Anti-proliferative properties



mTOR Inhibitors Adverse Effects

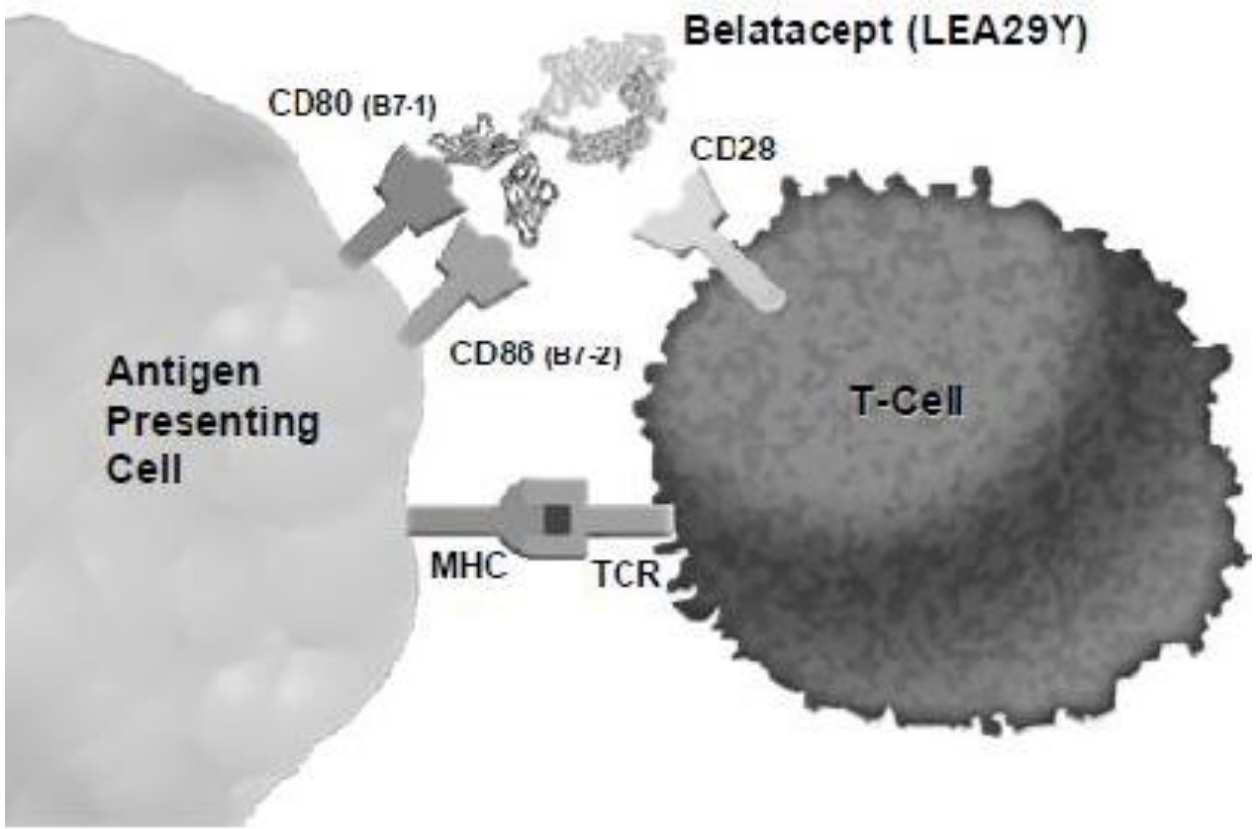
Adverse Effects	mTOR
Dyslipidemia	++
Mouth Ulcers	++
Pulmonary toxicity	+
Wound complications	+
Nephrotic syndrome (proteinuria) (proteinuria)	+



Rapamycin (sirolimus) [product information]. Pfizer 2015.; Zortress (everolimus) [product information]. Novartis 2015.

Belatacept

- Fusion protein
- Co-stimulation antagonist at CD80 and CD86 receptors on APCs
- Inhibition of T-cell activation and proliferation
- Inhibits production of cytokines interleukin-2, interferon-γ, interleukin-4, and TNF-α



Nulojix (belatacept) [product information]. Bristol-Myers Squibb 2016.

Belatacept

- Approved in kidney transplantation
- Use in EBV seropositive patients ONLY
- No dose adjustments for renal or hepatic dysfunction
- No therapeutic drug monitoring

Nulojix (belatacept) [product information]. Bristol-Myers Squibb 2016.

Dosing

Initial Phase (10 mg/kg)

- Day 1 (day of transplantation)
- Day 5
- End of Week 2, 4, 8, and 12

Maintenance Phase (5 mg/kg)

- End of Week 16
- Every 4 weeks

Administered over 30 minutes

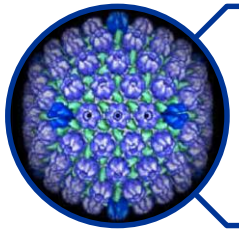
No pre-medications required

Dose based on actual body weight

Doses must be divisible by 12.5

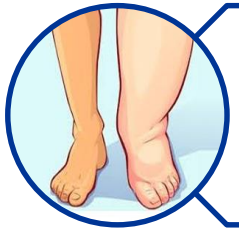
Nulojix (belatacept) [product information]. Bristol-Myers Squibb 2016.

Black Box Warnings and Adverse Effects



PTLD

Increased risk of graft loss and death in liver transplant



Peripheral edema

Nulojix (belatacept) [product information]. Bristol-Myers Squibb 2016.

Niche in SOT

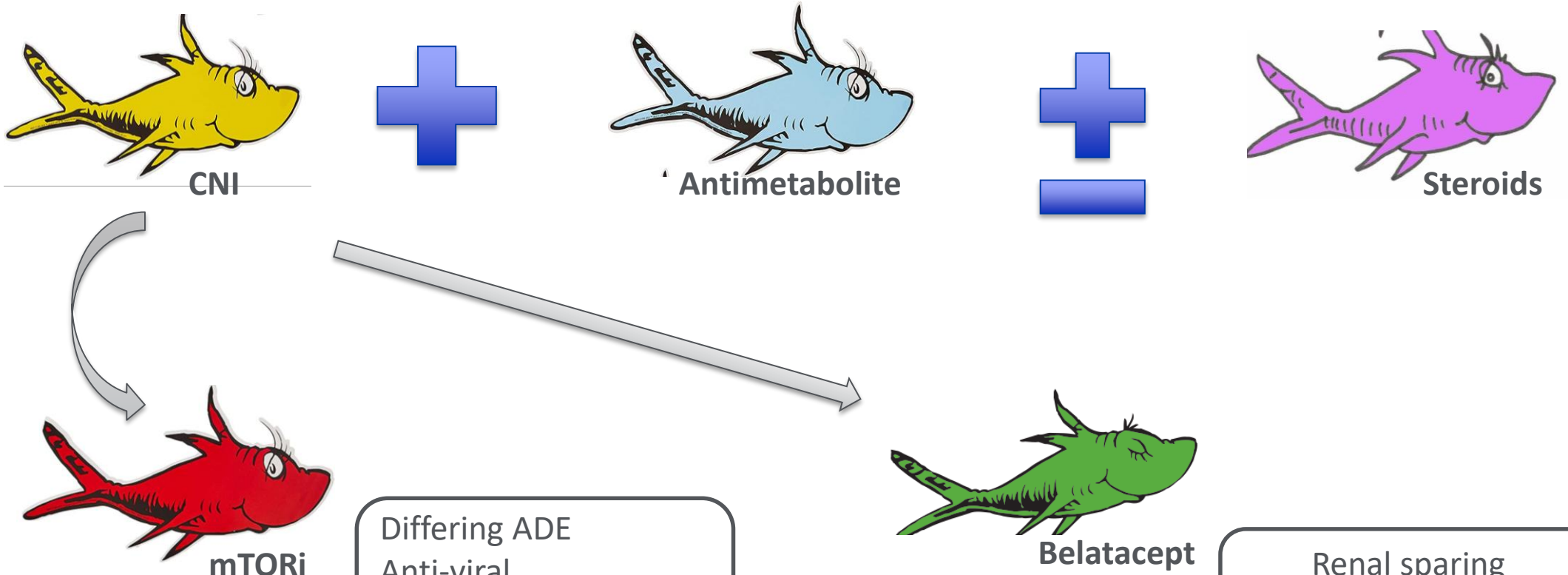
Renal sparing

Lack of metabolic ADE

Adherence

Nulojix (belatacept) [product information]. Bristol-Myers Squibb 2016.

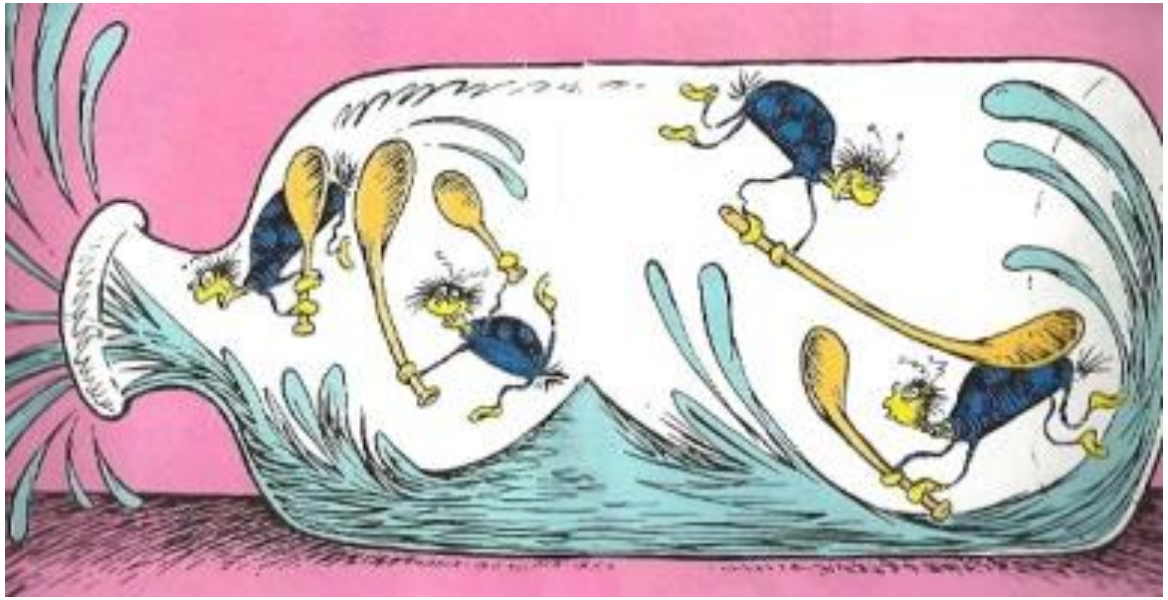
Maintenance therapy



Differing ADE
Anti-viral
Anti-fibrotic
Anti-proliferative

Renal sparing
Lack of metabolic ADE
Adherence

Drug-Drug interactions



CYP3A4/PGP Inducers

Drug	Mechanism of interaction	Effect on CNI levels	Effect on mTOR levels	Management
Anti-epileptics: Phenytoin Phenobarbital Carbamazepine	Induce CYP3A4 (INCREASE metabolism)	 ↓ ↓ ↓	 ↓ ↓ ↓	 Double CNI dose Monitor levels Monitor levels
Rifamycins Rifampin Rifabutin		↓↓ ↓	↓↓ ↓	Double CNI mTOR: alternative therapy Monitor levels
St. John's wort		↓	↓	Avoid therapy

Glotzbecker B, Duncan C, Alyea E, et al. *Biol Blood Marrow Transplant.* 2012;18(7):989-1006.
Manitpisitkul W, Mccann E, Lee S, Weir MR. *Curr Opin Nephrol Hypertens.* 2009;18(5):404-11.

CYP3A4/PGP Inhibitors

Drug	Mechanism of interaction	Effect on CNI levels	Effect on mTOR levels	Management
Azole antifungals Clotrimazole Fluconazole Isavuconazole Posaconazole Voriconazole	Inhibit CYP3A4 (DECREASE metabolism)	 ↑ ↑ ↑ ↑↑ ↑↑	 ↑ ↑ ↑ ↑↑ ↑↑	 ↓ ↓ ↓ ↓ ↓
CCB Diltiazem& Verapamil		↑	↑	↓ CNI 25- 50%
Macrolides Erythromycin Clarithromycin		 ↑ ↑	 ↑ ↑	 ↓CNI 50-75% ↓CNI 50-75%
Protease inhibitors Ritonavir Darunavir		↑↑↑	↑↑↑	Dose by level
Amiodarone		↑	↑	↓CNI 50%
Cobicistat		↑↑↑	↑↑↑	Dose by level

Glotzbecker B, Duncan C, Alyea E, Campbell B, Soiffer R. *Biol Blood Marrow Transplant.* 2012;18(7):989-1006.
Manitpisitkul W, Mccann E, Lee S, Weir MR. *Curr Opin Nephrol Hypertens.* 2009;18(5):404-11.

Azole Antifungal Agents

Drug	Degree of CYP3A4 Inhibition	PK $T_{1/2}$	Dose reductions	
			CNI	mTOR
Fluconazole	++	30 hours	↓25-50%	↓ 50-70%
Isavuconazole	++	130 hours	↓ ? Monitor levels	↓ 50-70% Monitor levels
Voriconazole	+++	Variable, dose-dependent	↓ 66-75%	↓ 90% Avoid
Posaconazole	+++	~30-35 hours	↓ 66-75%	↓90% Avoid

Trofe-clark J, Lemonovich TL. *Am J Transplant*. 2013;13 Suppl 4:318-26 .; Glotzbecker B, Duncan C, Alyea E, Campbell B, Soiffer R. *Biol Blood Marrow Transplant.* 2012;18(7):989-1006.; Dodds-ashley E. *Pharmacotherapy*. 2010;30(8):842-54

Assessment Question

The Grinch is a 42 year old male s/p heart transplant on maintenance immunosuppression with tacrolimus 6 mg twice daily, mycophenolate mofetil 1,000 mg twice daily, and prednisone 10 mg daily. The team would like to start therapy with voriconazole for *aspergillus*.

How would you dose adjust his medications?

A. No dose adjustments are necessary

B. Reduce mycophenolate mofetil to 500 mg twice daily

C. Increase tacrolimus to 8 mg twice daily

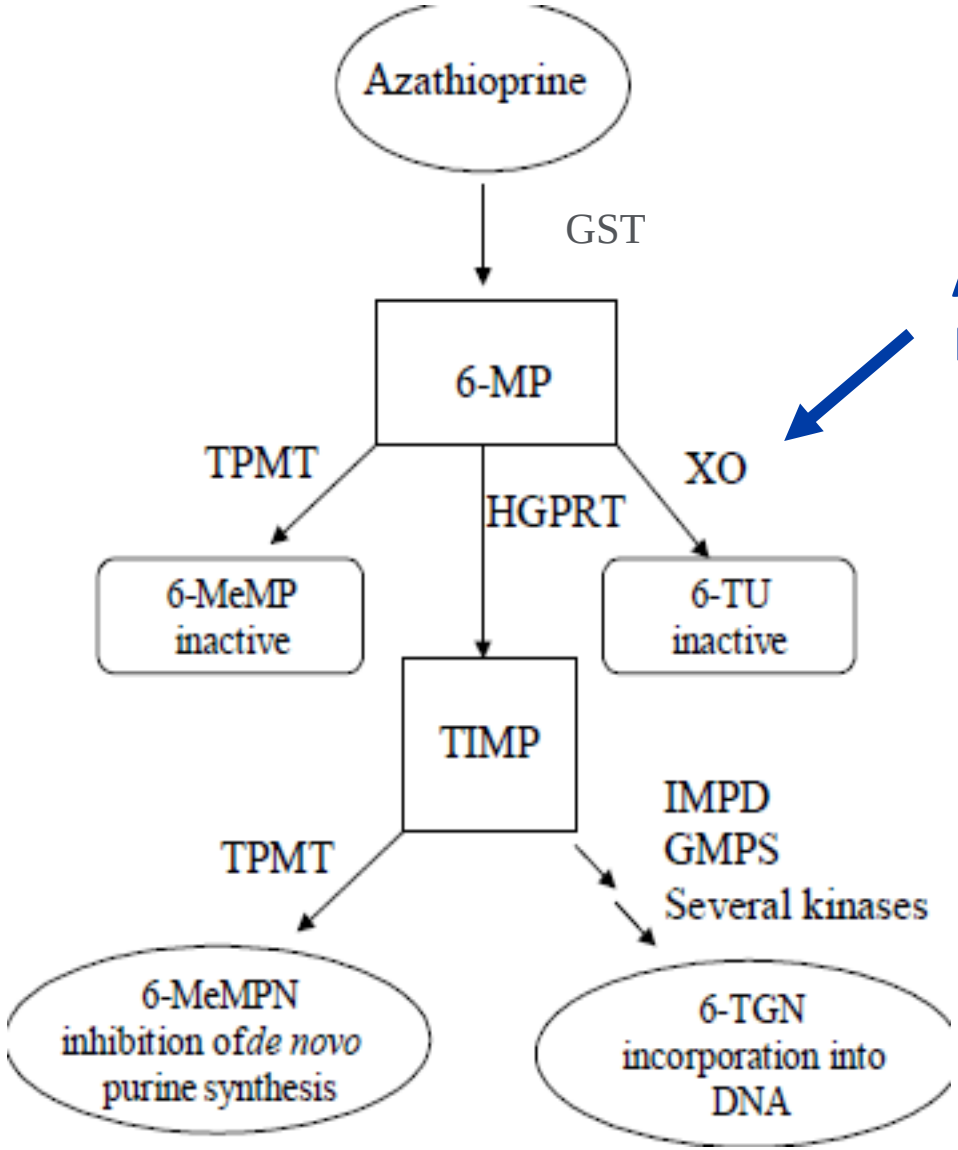
D. Decrease tacrolimus to 2 mg twice daily

E. Dose tacrolimus by levels

Azathioprine and Xanthine Oxidase (XO) Inhibitors

Severe myelosuppression

Reduce azathioprine dose by 50 - 75%
Avoid combination if possible



Maltzman JS, Koretzky GA. *J Clin Invest*. 2003;111(8):1122-4. Manitpisitkul W, Mccann E, Lee S, Weir MR. *Curr Opin Nephrol Hypertens.* 2009;18(5):404-11.

Pharmacodynamic Interactions

Nephrotoxicity

- NSAIDs (ibuprofen, naproxen, ketorolac)
- ACE-i/ARB (lisinopril, losartan)
- Aminoglycosides (gentamicin, tobramycin)

QT prolongation

- Antipyschotics (quetiapine, haloperidol, olanzapine)
- Antifungals (fluconazole, voriconazole, posaconazole)
- Fluoroquinolones (levofloxacin, ciprofloxacin)

Hyperkalemia

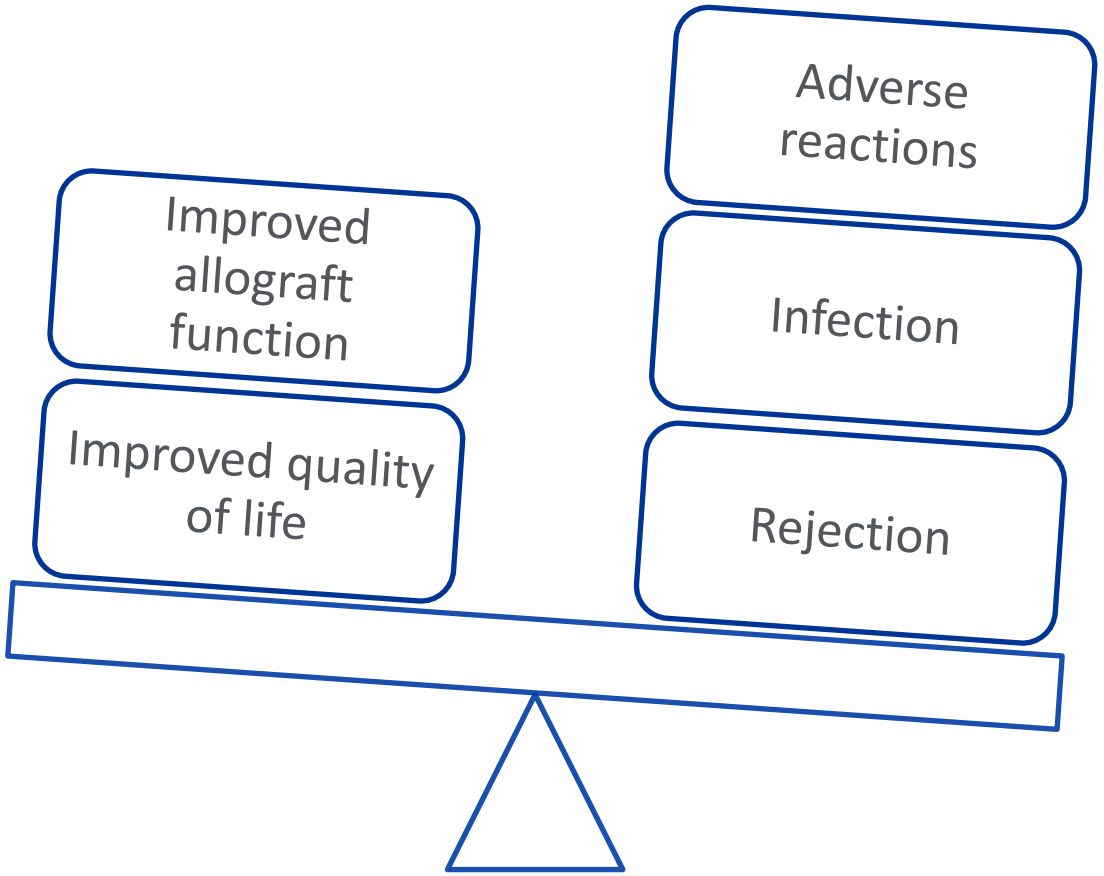
- ACE-i/ARB (lisinopril, losartan)
- Potassium-sparing diuretics (spironolactone, triamterene)

Leukopenias and thrombocytopenias

- Anti-thymocyte globulin
- Linezolid
- Valganciclovir/Ganciclovir

Manitpisitkul W, Mccann E, Lee S, Weir MR. *Curr Opin Nephrol Hypertens.* 2009;18(5):404-11.

Transplantation is a Balancing Act



Conclusion

- Immunosuppression is essential in organ transplant recipients
- Immunosuppression should be individualized to optimize medical management and minimize adverse reactions
- Adjusting dosing of medications for drug interactions is multifactorial

Solid Organ Transplant Immunosuppression

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