Solid Organ Transplantation

728-655

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Reading Assignment:

Pharmacotherapy. A Pathophysiologic Approach. 11th edition. Chapter 105 Solid-Organ Transplantation. pp 1473-1496.

Study Questions:

1. How are the immunosuppressants used in combination?
2. What are the complications that can occur following solid organ transplantation?
3. What side effects are specific to each pharmacologic class of immunosuppressants?
4. How are calcineurin inhibitors monitored for therapeutic effect and toxicities?

Objectives

- Understand the mechanism of action of commonly used immunosuppressive agents
- Discuss the rationale for using immunosuppressive agents in combination
- Assess the potential for drug interactions with commonly used immunosuppressive agents
- Develop a plan to manage adverse effects from immunosuppressive agents

Indications for Organ Transplant

Organ	Indication for Transplant
Kidney	Diabetes, hypertension, lupus, PCKD
Liver	Alcoholic cirrhosis, NASH, HBV, HCV, HCC, APAP toxicity
Pancreas	Diabetes, congenital abnormalities
Heart	Ischemic heart disease, congenital abnormalities, idiopathic cardiomyopathy, valvular diseases
Lung	CF, pulmonary HTN, pulmonary fibrosis, COPD, emphysema

Epidemiology

106,738
People need a lifesaving organ transplant (total waiting list candidates)

28,216
Transplants performed January – August 2021

13,737
Donors (total donors January - August 2021)

Organ donation and transplantation can save lives

Every ten minutes, someone is added to the national transplant waiting list.

On average, 95 transplants take place each day in the U.S.

One organ donor can save eight lives. Sign up to be a donor in your state.

https://optn.transplant.hrsa.gov

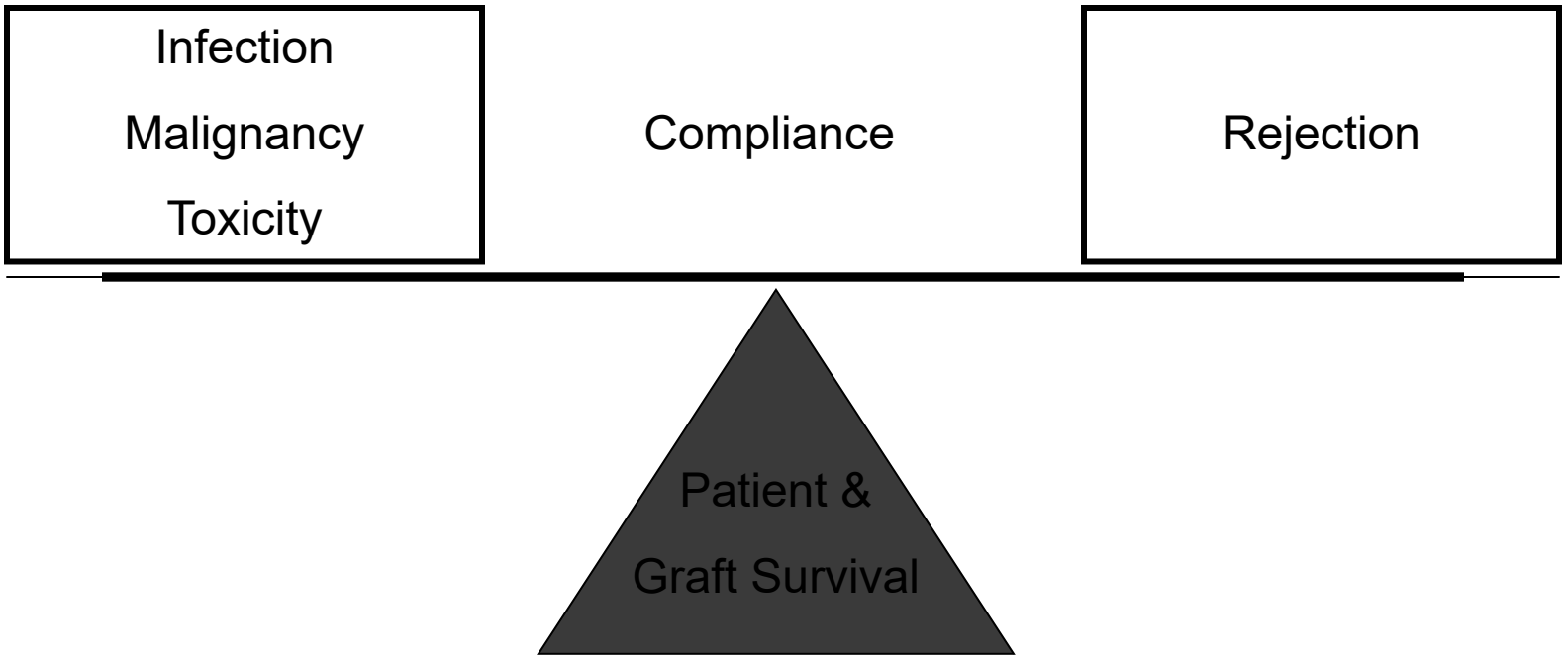
Epidemiology

Transplants By Organ Type January 1, 1988 - July 31, 2021 Based on OPTN data as of August 26, 2021

Organ	Transplants
Kidney	505,080
Liver	186,680
Pancreas	9,107
Kidney / Pancreas	25,887
Heart	81,494
Lung	44,924
Heart / Lung	1,381
Intestine	3,233
Abdominal Wall	20
Head & Neck: Craniofacial	18
Head & Neck: Scalp	1
Head & Neck: Larynx	2
GU: Penile	2
GU: Uterus	32
Upper Limb: Bilateral	18
Upper Limb: Unilateral	18
Trachea	1
Total	**857,898**

United Network for Organ Sharing. Based on data as of August 26, 2021.

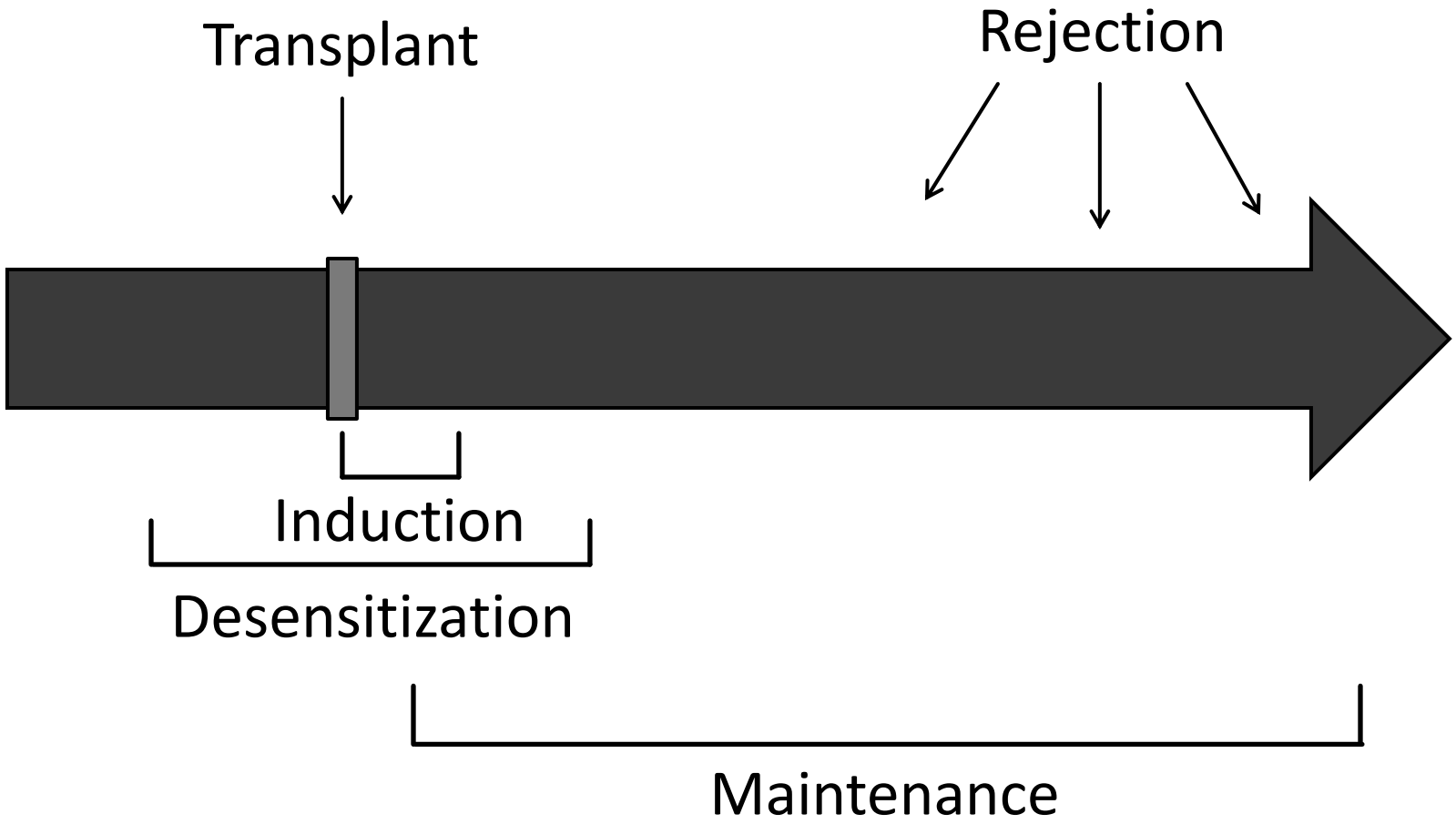
Goals of Immunosuppression



Goals of Immunosuppression

- Prevent rejection
- Avoid complications with high dose immunosuppressants
- Patient and graft survival
- Patient adherence

Phases of Immunosuppression



Determination of Regimens

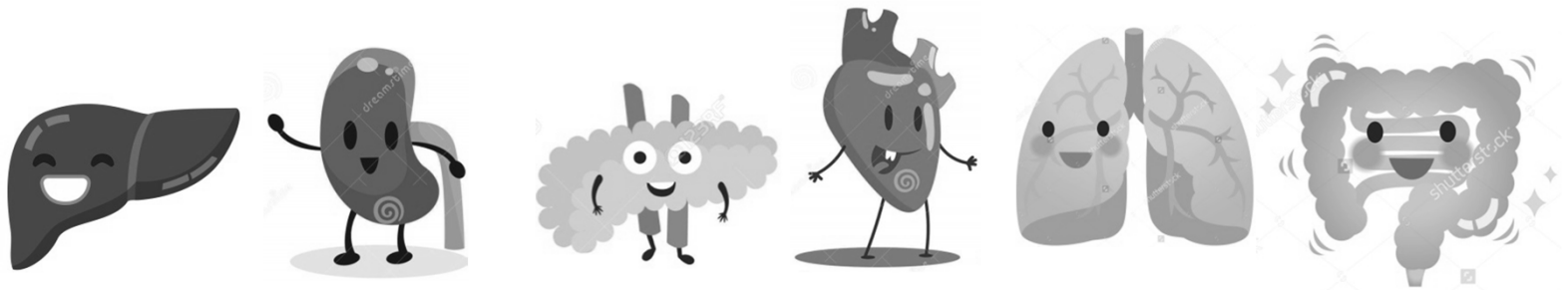
Evaluation of Immunologic Risk

- HLA mismatch
- Younger recipient and older donor
- African-American
- Panel Reactive Antibody (PRA) > 0
- Donor-specific Antibody (DSA)
- Blood group incompatibility
- Delayed onset of graft function (DGF)
- Cold ischemia time > 24 hours
- Multiple transplants

Evaluation of Infectious Risk

- Elderly
- TB exposure
- HBV exposure
- HCV exposure
- CMV status
- Endemic fungal exposure

Immunogenicity of Organs

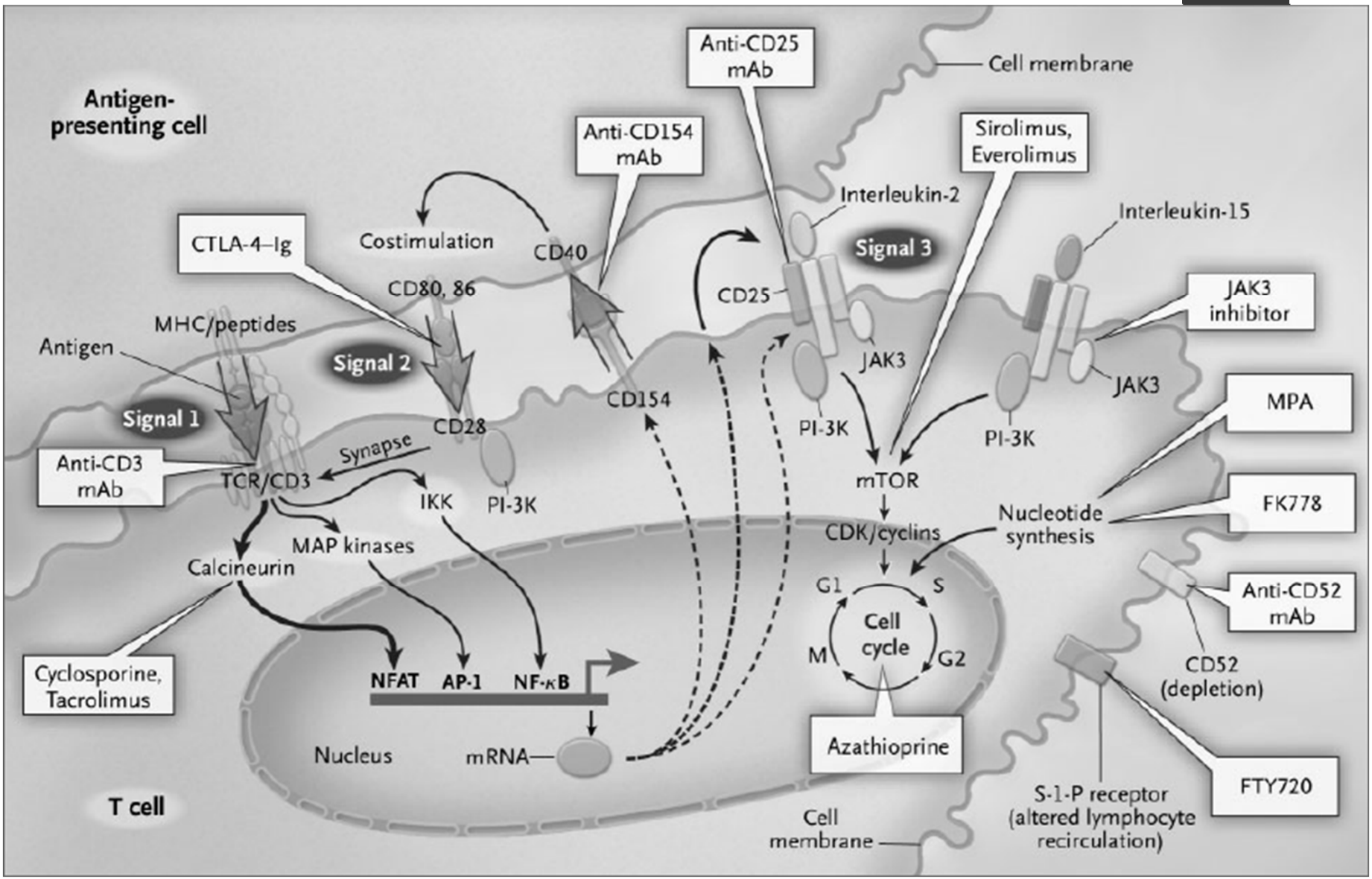


Less Immunogenic

Less immunosuppression
Able to wean

Highly Immunogenic

More immunosuppression
Unable to wean (as much)
More infectious complications



N Engl J Med. 2004 Dec 23;351(26):2715-29.

Induction Therapy

- **Goal:** *To prevent early acute allograft rejection post-transplant using intense, prophylactic immunosuppressive therapy*

- Agent determined by patient risk factors and maintenance immunosuppression

Induction Therapy

- **Corticosteroids**
  - Dexamethasone 100 mg IV
  - Methylprednisolone 125-500 mg IV
- **Polyclonal antibodies**
  - Thymoglobulin (4.5 – 6 mg/kg in divided doses)
- **Monoclonal antibodies**
  - Basiliximab 20 mg x 1-2 dose
  - Alemtuzumab 30 mg x 1 dose (x 2 doses in pediatric patients)

Maintenance Therapy

- Goals:
  - Prevent allograft rejection
  - Maintain an adequate balance of graft function, adverse effects, and prevention of infection
- Lifelong immunosuppression

Maintenance Therapy

- "Triple Therapy"

  CNI + Antimetabolite + Steroid

- Weaned over time based on graft outcome, infectious complications, or side effects

- Weaning strategies are variable

Maintenance Therapy

- Corticosteroids
- Calcineurin inhibitors
- Antimetabolites
- mTOR inhibitors
- Co-stimulation blocker

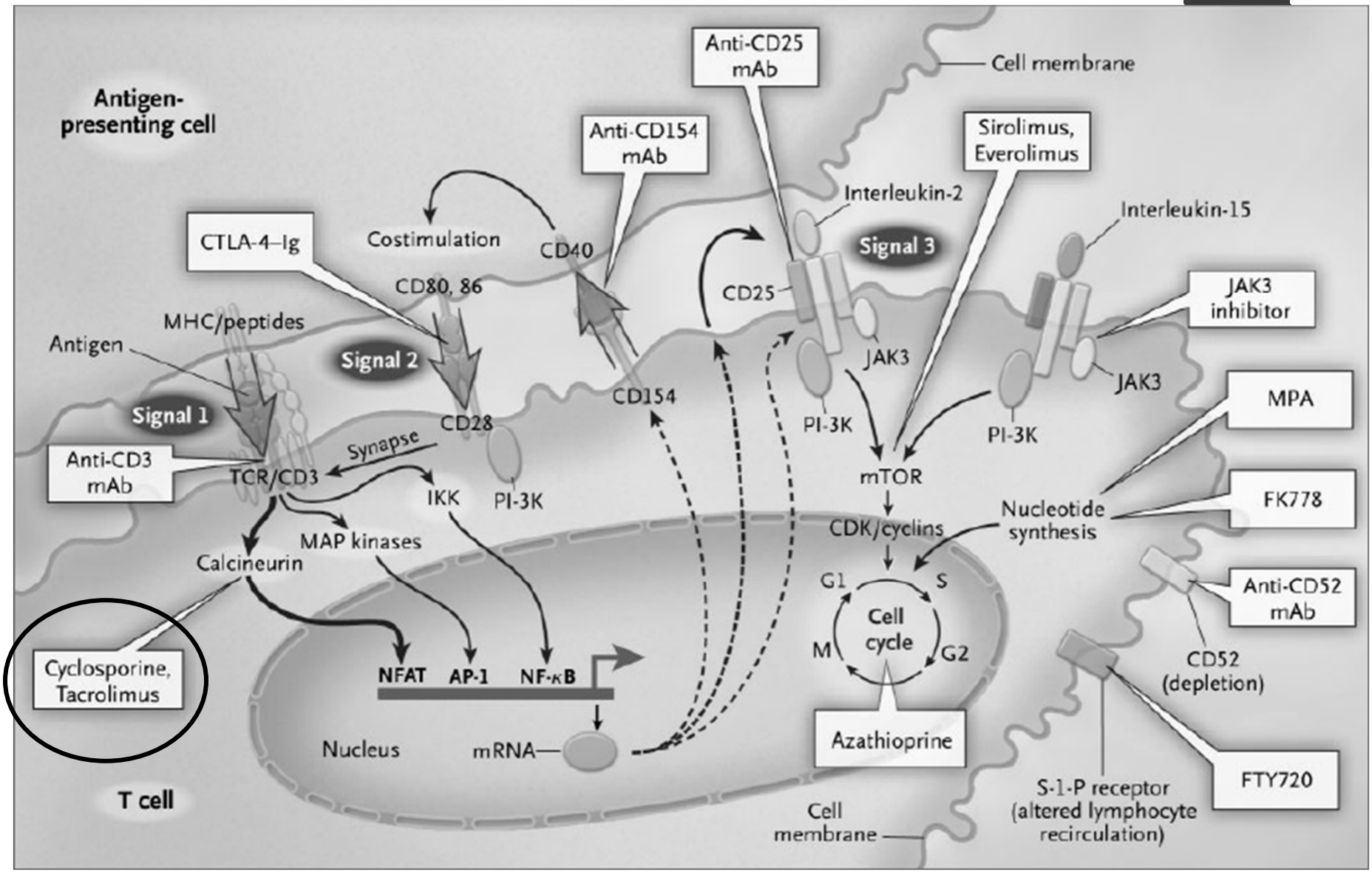
Corticosteroids

- Oldest immunosuppressive agent used in transplantation
- Mechanism of Action:
  - Inhibition of cytokine gene expression
  - Modification of lymphocyte distribution and function
  - Anti-inflammatory effects
- Dosing:
  - Prednisone 5-10 mg/day (maintenance dose)
    - Higher doses are used for induction & rejection therapy

N Engl J Med. 2004 Dec 23;351(26):2715-29.
Circulation. 2004 Dec 21;110(25):3858-65.

Corticosteroids: Adverse Effects

- Short Term
  - Mood changes
  - Hyperglycemia
  - Hypertension
  - Increased appetite
  - Insomnia
  - Acne
  - Leukocytosis
- Long Term
  - Osteoporosis
  - Chronic adrenal insufficiency
  - Ulcerative esophagitis
  - Hirsutism
  - Pancreatitis
  - Amenorrhea
  - Diabetes mellitus



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Calcineurin Inhibitors

- **Tacrolimus**

PROGRAF®
(tacrolimus)

ASTAGRAF XL®
(tacrolimus extended-release capsules)

Once-daily
Envarsus XR®
(tacrolimus extended-release tablets)

- **Cyclosporine**

Neoral®
(cyclosporine capsules, USP) MODIFIED

GENGRAF®
(cyclosporine capsules, USP [MODIFIED])

SANDIMMUNE® Soft Gelatin Capsules
(cyclosporine capsules, USP)

Tacrolimus

- **Products:**
  - Prograf® (capsules, IV)
  - Generic tacrolimus (capsules, IV)
  - Astagraf XL® (extended release capsules)
  - Envarsus XR® (extended release capsules)
    - Extended release products are NOT equivalent/interchangeable
  - Compounded oral suspension

*Also called FK506

- **MOA:**
  - Inhibits T-cell activity through inhibition of IL-2 production

Tacrolimus: PK & PD

- Absorption: incomplete and variable
  - Consistency
  - Best absorbed on an empty stomach
  - Bioavailability: 7 - 32%
- Distribution: highly lipophilic
  - 99% protein bound (albumin and a1-acid glycoprotein)
- Metabolism: extensive CYP3A4, p-glycoprotein
  - Half life: ~ 9 hours (immediate release)

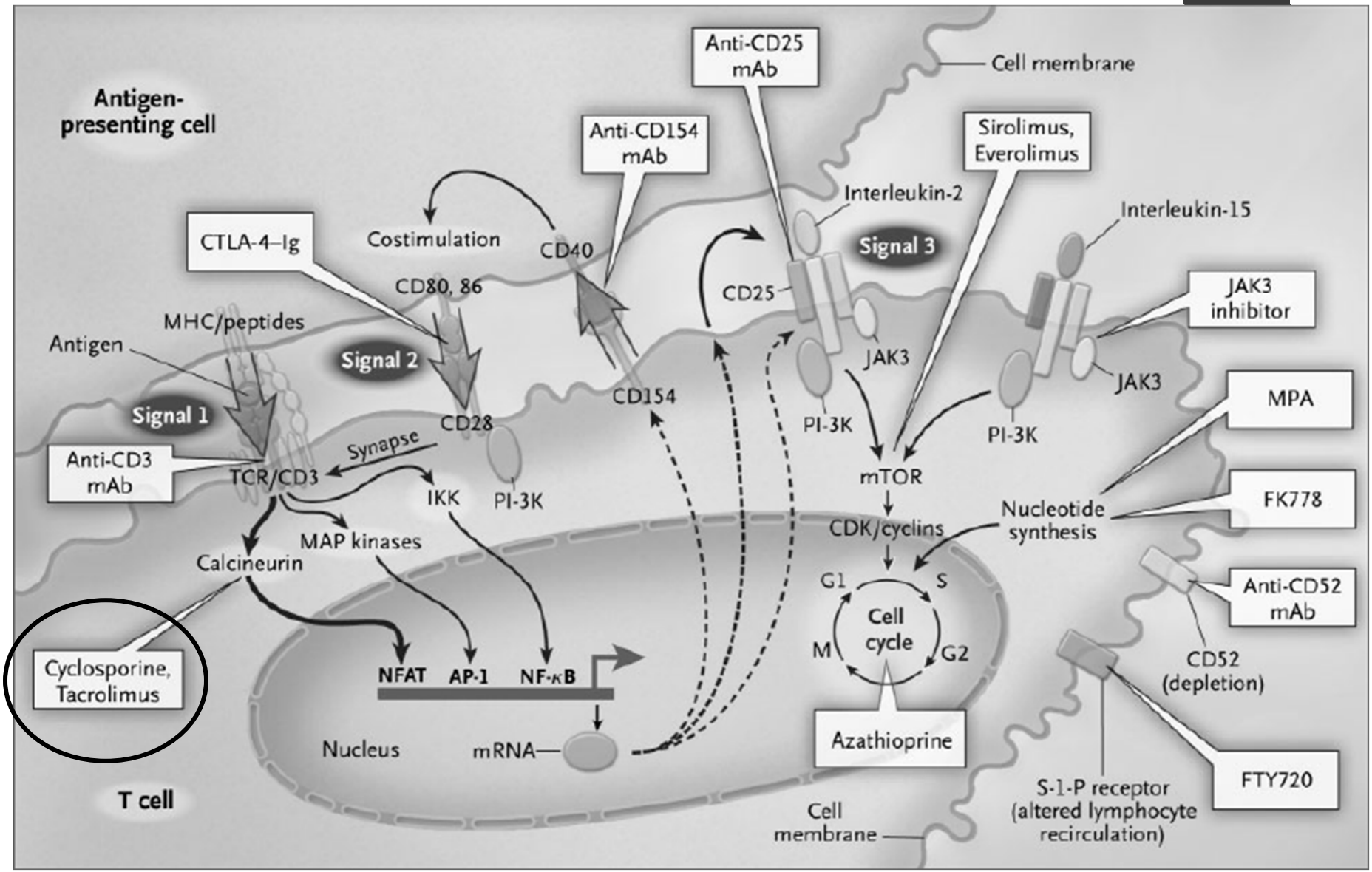
    ~ 34 hours (extended release)

Tacrolimus: Dosing

- Dosing:
  - **Immediate Release:** 0.05-0.1 mg/kg/day in divided doses
    - Generally ~1-4 mg BID
  - **Extended Release:** 0.1-0.2 mg/kg/day one time daily
- **Dose adjusted based on trough concentrations and renal function**
  - Goal concentration varies
  - Therapeutic range 5 – 15 ng/mL

Tacrolimus: Interactions

- **Primarily through hepatic metabolism CYP3A4: inhibition or induction**
  - Examples:
    - Ketoconazole, diltiazem, and grapefruit juice inhibit CYP3A4
    - Phenytoin and rifampin induce CYP3A4
- **P-glycoprotein substrate**
- **Antacids**
  - Physical interaction → reduced absorption
  - Separate by at least 2 hours



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Cyclosporine

- **Products:**
  - Modified microemulsion formulation
    - **Neoral® or Gengraf®**
  - Unmodified formulation
    - **Sandimmune®**
  - **Sandimmune® & Neoral®/Gengraf® are not equivalent/interchangeable**
- **MOA:**
  - Inhibits T-cell proliferation through inhibition of IL-2 production

Cyclosporine: PK & PD

- **Absorption:** erratic and incomplete
  - **Non-modified:** largely dependent on food, bile acids, and GI motility
  - **Modified:** up to 30% increase; less dependent on food, bile acids, and GI motility
- **Distribution:** highly lipophilic
  - 98% protein bound (lipoproteins)
- **Metabolism:** CYP3A4 (extensive), p-glycoprotein

Cyclosporine: Dosing

- **Dosing:**
  - 10-15 mg/kg/day in divided doses to attain target trough levels

- **Dose adjusted based on trough concentrations and renal function**
  - Goal concentration varies
  - Therapeutic range 50-200 ng/mL

Cyclosporine: Interactions

- **Primarily through hepatic metabolism CYP3A4: inhibition or induction**
  - Examples:
    - Ketoconazole, diltiazem, and grapefruit juice inhibit CYP3A4
    - Phenytoin and rifampin induce CYP3A4

- **P-glycoprotein substrate**

Calcineurin Inhibitors: Adverse Effects

	Tacrolimus	Cyclosporine
Nephrotoxicity	+++	++
Hyperglycemia & DM	+++	++
Neurotoxicity	+++	++
Electrolyte abnormalities	+++	++
Hypertension	+++	+++
Other	Alopecia	Hirsutism, hyperlipidemia, gingival hyperplasia, hyperuricemia

Question #1

A patient presents to your pharmacy with a new prescription for fluconazole 400 mg daily (a known 3A4 inhibitor) for 14 days. His current medication profile shows the following medications:

- Tacrolimus 3 mg BID
- Mycophenolate sodium 720 mg BID
- Prednisone 5 mg daily

- What question do you want to ask this patient?

A. Do you want brand or generic?

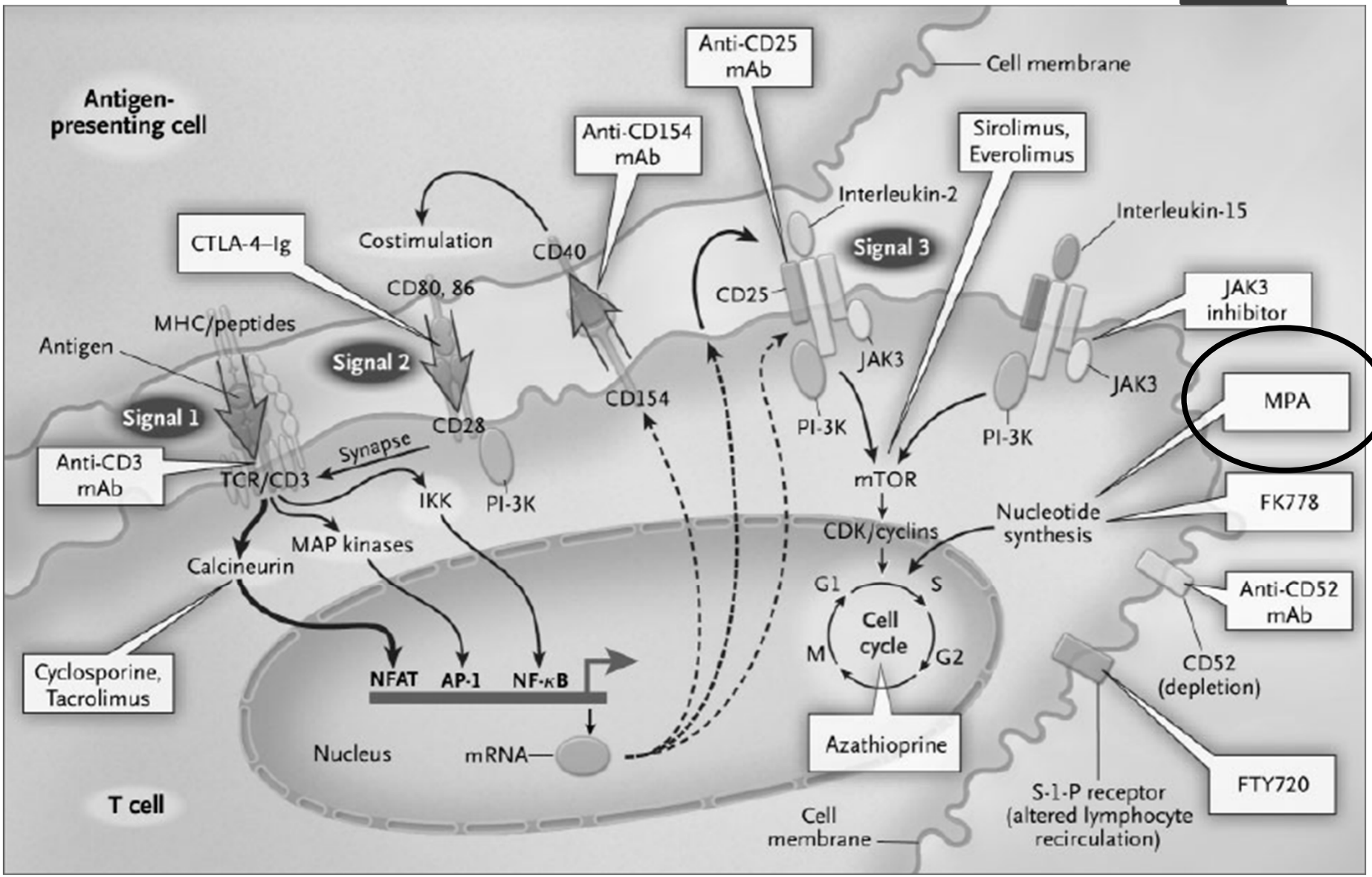
B. Did your tacrolimus dose recently get changed?

C. Why are you on three anti-rejection agents?

D. Do you really need to take this new medication?

Antiproliferatives

- Mycophenolate Mofetil (Cellcept®, MMF)
- Mycophenolate Sodium (Myfortic®, MPS)
- Azathioprine (Imuran®, AZA)



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Mycophenolate

- **Products:**
  - Mycophenolate Mofetil (Cellcept®, MMF)
  - Mycophenolate Sodium (Myfortic®, MPS)
- **Prodrugs for mycophenolic acid (MPA)**
- **MOA:**
  - Inhibition of inosine monophosphate dehydrogenase (IMPDH)→inhibits de novo guanosine nucleotide synthesis
  - Prevents T and B lymphocytes proliferation

Mycophenolate: Dosing

- **Dosing:**
  - 250-1000 mg PO twice daily (Cellcept®, MMF)
  - 180-720 mg PO twice daily (Myfortic®, MPS)
- **Dosing conversion**
  - 1,000 mg MMF = 720 mg MPS
- **Mycophenolate sodium (Myfortic®) is enteric coated for delayed release**
  - May reduce GI side effects

N Engl J Med. 2004 Dec 23;351(26):2715-29.
Circulation. 2004 Dec 21;110(25):3858-65.

Mycophenolate

- **Drug Interactions:**
  - Aluminum/magnesium containing antacids
    - Separate doses by at least 2 hours
  - Cholestyramine
  - Divalent/trivalent cations (iron)
  - Proton pump inhibitors
  - Oral contraceptives
- **Adverse Effects:**
  - Gastrointestinal intolerance:
    - Diarrhea
    - Nausea
    - Vomiting
  - Leukopenia, anemia, thrombocytopenia

Mycophenolate

- **Teratogenicity**
  - Shown to cause fetal harm
  - Negative pregnancy test prior to starting medication
  - Women of child-bearing age required to use at least two methods of contraception
  - Transition if pregnancy desired

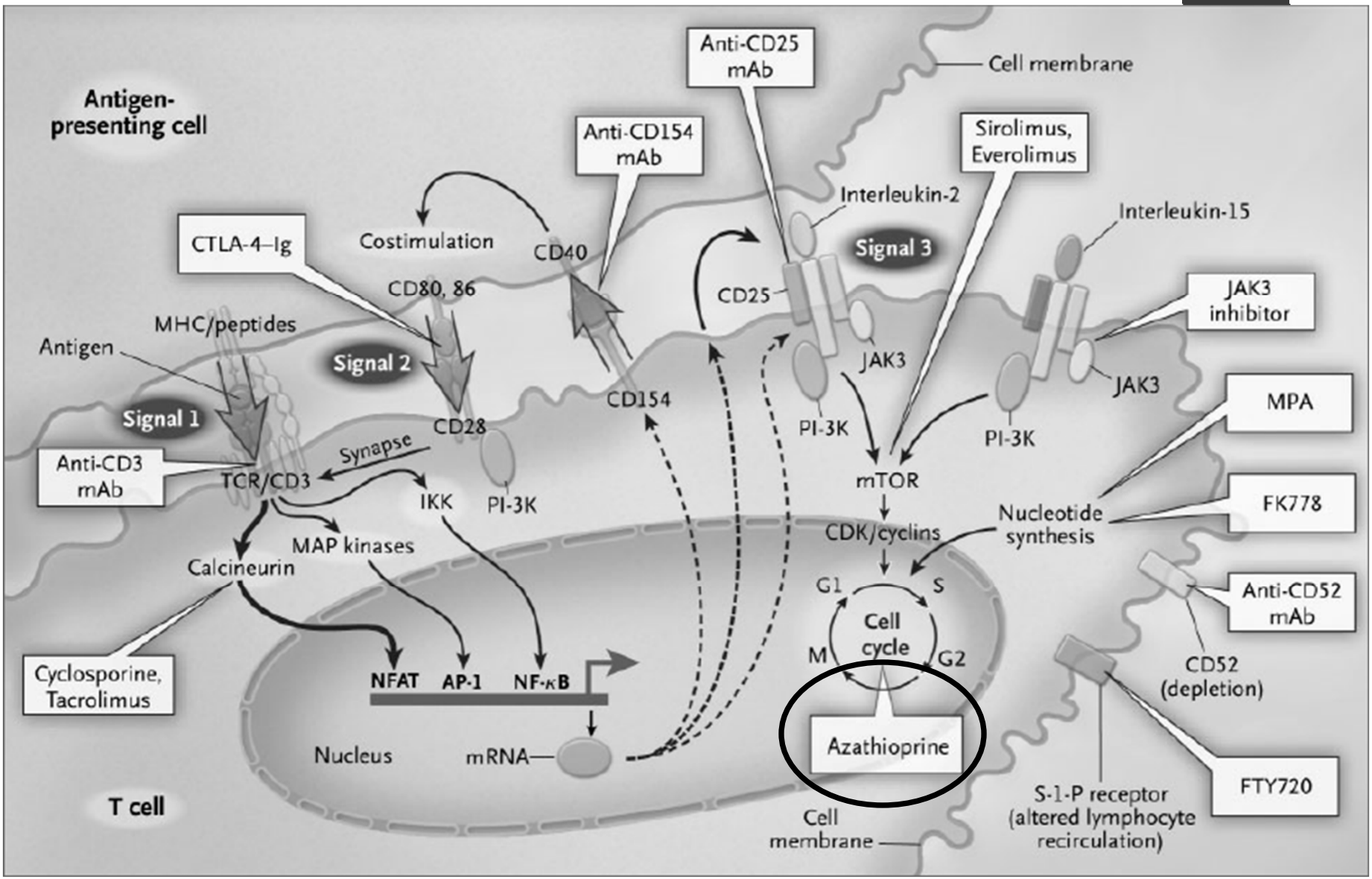
Question #2

A known transplant recipient on mycophenolate shows up to your pharmacy complaining of heartburn and is looking for milk of magnesia. What counseling point should you make to the patient?

A. Take as much as you need.

B. Phillips® brand is the best product.

C. Make sure to separate magnesium containing antacids from mycophenolate by at least 2 hours.



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Azathioprine

- **Prodrug of 6-mercaptopurine (6-MP)**
- **MOA:**
  - Antagonist of purine metabolism
  - Prevents T and B lymphocytes proliferation
- **Use (rare):**
  - Intolerance to mycophenolate
  - Women that want to become pregnant
- **Dosing:**
  - 3-5 mg/kg/day initially, then decrease to 1-3 mg/kg/day

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Circulation. 2004 Dec 21;110(25):3858-65.

Azathioprine

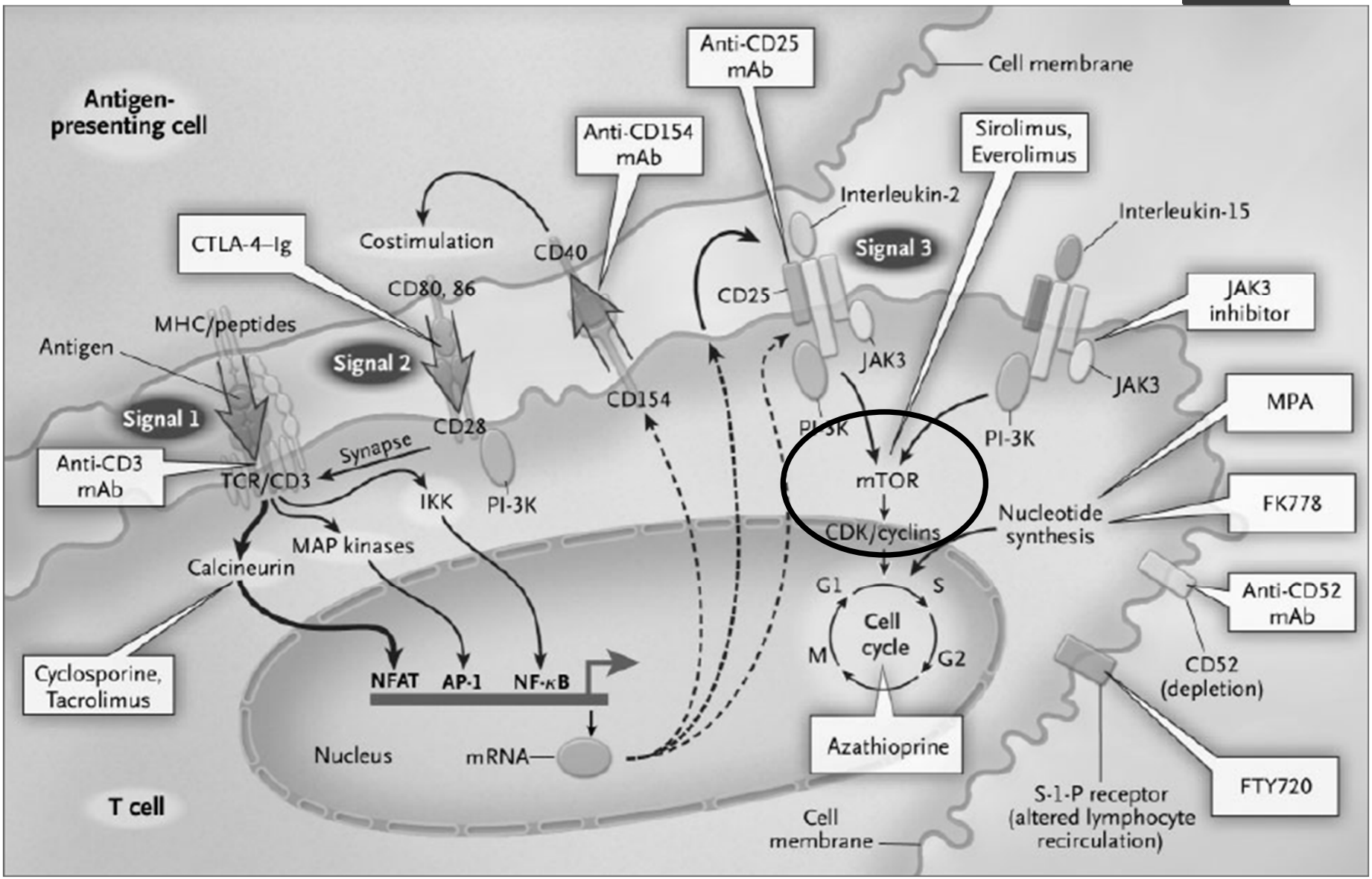
- **Drug interactions:**
  - Mercaptopurine – profound myelosuppression
  - Allopurinol – inhibits metabolism of azathioprine and 6-MP leading to profound myelosuppression

- **Adverse Effects:**
  - GI Intolerance
  - Leukopenia, anemia, thrombocytopenia
  - Increased alkaline phosphatase, total bilirubin & transaminases

mTOR Inhibitors

- Sirolimus (Rapamune®)

- Everolimus (Zortress®)



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Sirolimus

- **Mechanism of Action:**
  - Binding to FKBP-12→ inhibition of mTOR (mammalian target of rapamycin)
  - Suppresses cytokine mediated T-cell proliferation
- **Use:**
  - May be used to replace mycophenolate or a calcineurin inhibitor (tacrolimus or cyclosporine)
- **Dosing:**
  - 1-5 mg/day to attain target trough levels

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Circulation. 2004 Dec 21;110(25):3858-65.

Sirolimus

- **Interactions:**
  - Metabolized through CYP3A4
  - Similar interactions with cyclosporine and tacrolimus

- **Adverse Effects:**
  - Edema
  - Anemia
  - Impaired wound healing
  - Interstitial lung disease
  - Proteinuria
  - Hyperlipidemia

Everolimus

- **Mechanism of Action:**
  - Binding to FKBP-12→ inhibition of mTOR (mammalian target of rapamycin)
  - Suppresses cytokine mediated T-cell proliferation
- **Use:**
  - May be used to replace mycophenolate or a calcineurin inhibitor (tacrolimus or cyclosporine)
- **Dosing:**
  - 0.75-1 mg PO twice daily to attain target trough levels

N Engl J Med. 2004 Dec 23;351(26):2715-29
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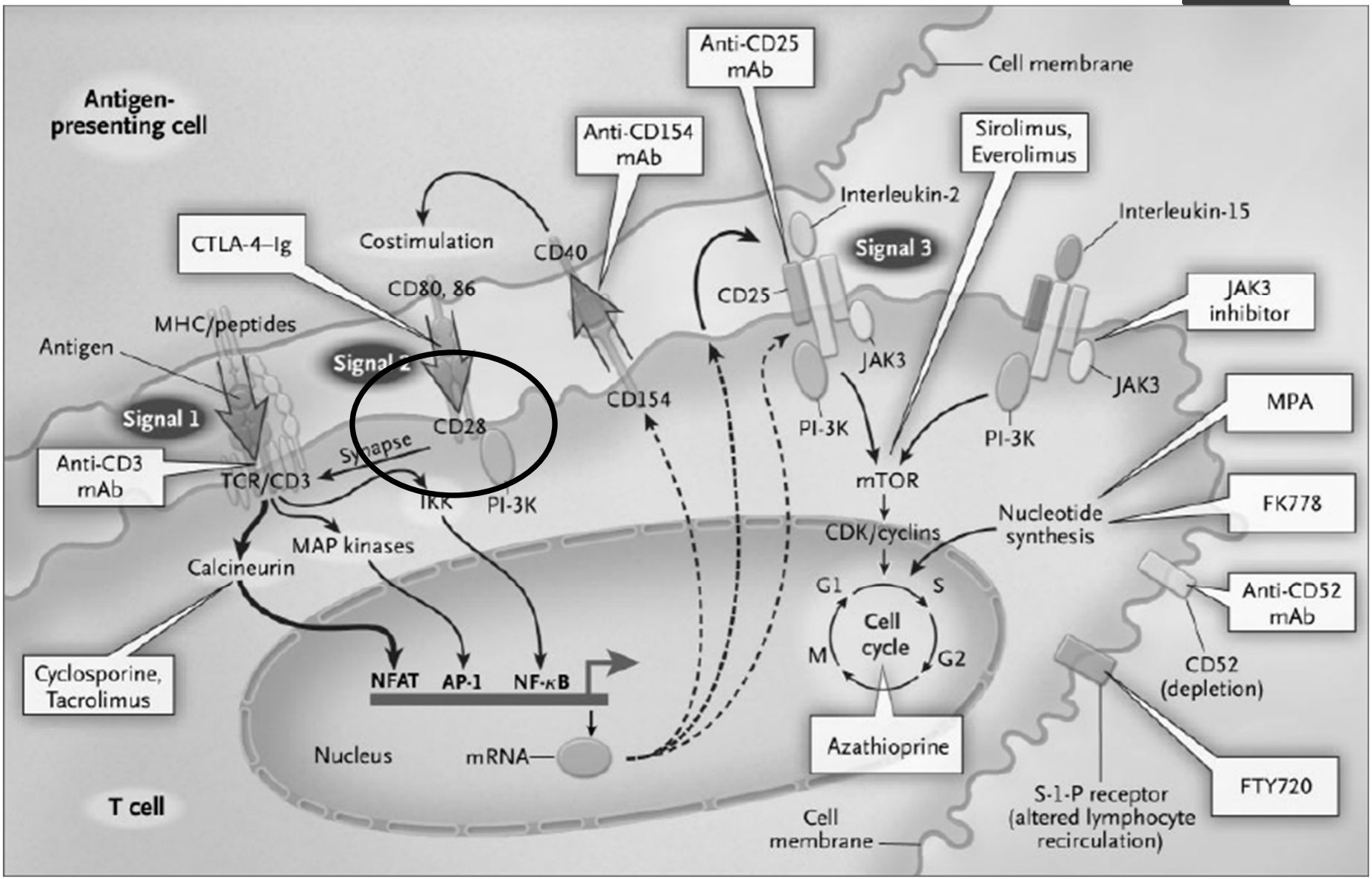
Everolimus

- **Interactions:**
  - Metabolized by CYP3A4
  - Similar drug interactions as cyclosporine and tacrolimus

- **Adverse Effects:**
  - Edema
  - Anemia
  - Impaired wound healing
  - Proteinuria
  - Hyperlipidemia



N Engl J Med. 2004 Dec 23;351(26):2715-29.

Belatacept

- **Indication:**
  - Maintenance immunosuppression therapy in renal transplant recipients

- **MOA:**
  - Binds to CD80 and CD86 receptors on APCs and blocking the CD28-mediated costimulation of T-cells

Pharmacotherapy. 2011 Apr;31(4):394-407.

Belatacept

- **Dosing:**
  - Initial phase:
    - **10 mg/kg IV post-operative day 0 and 4**
    - **10 mg/kg IV end of week 2, 4, 8, 12**
  - Maintenance phase:
    - **End of week 16**
    - **5 mg/kg every 4 weeks**

Pharmacotherapy. 2011 Apr;31(4):394-407.

Belatacept

- Adverse Effects:
  - **Black-Box Warning:** post-transplant lymphoproliferative disorder (PTLD)
  - Gastrointestinal disturbances
  - Hypertension
  - Peripheral edema
  - Anemia, leukopenia

Pharmacotherapy. 2011 Apr;31(4):394-407.

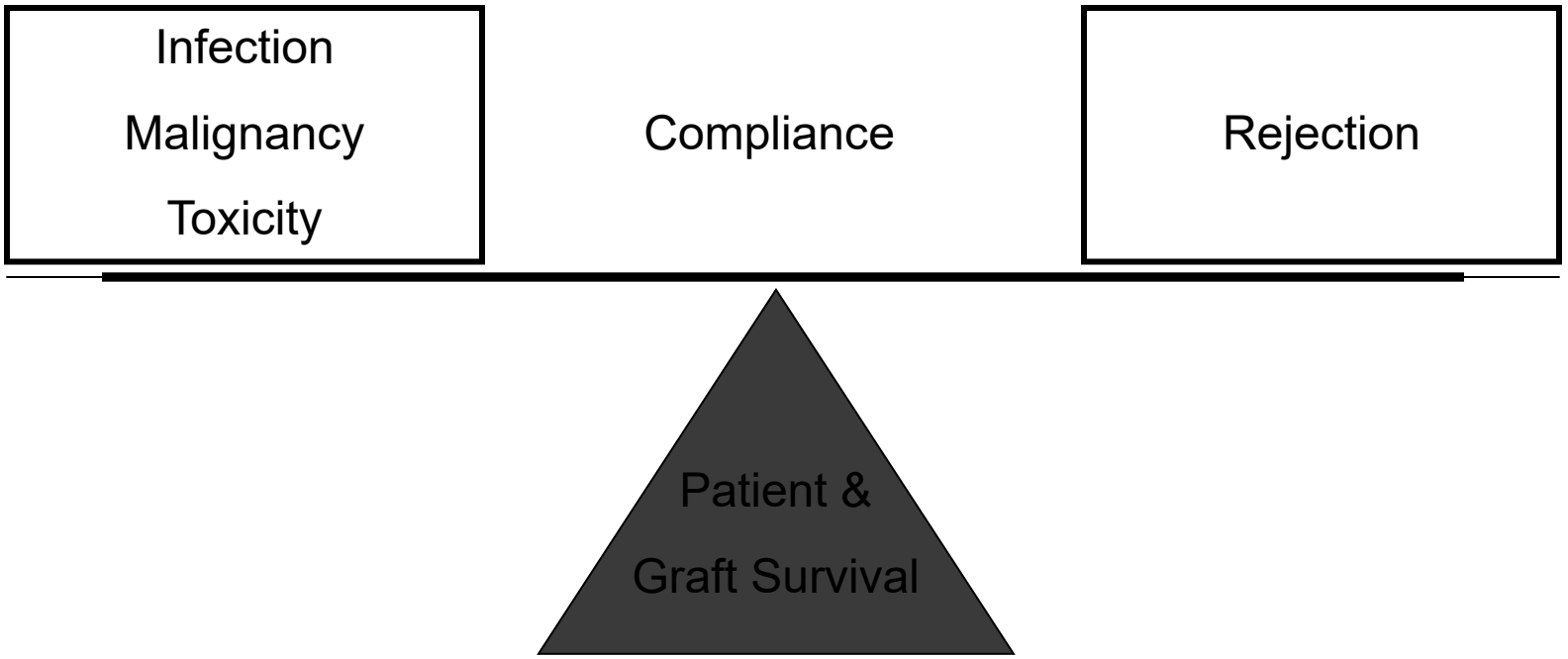
Immunosuppression Considerations

- Rejection
- Toxicity
- Adverse Effects
- Variability

Immunosuppression Considerations

- Drug-drug interactions
- Cost
- Malignancy
- Infection

Immunosuppression Considerations

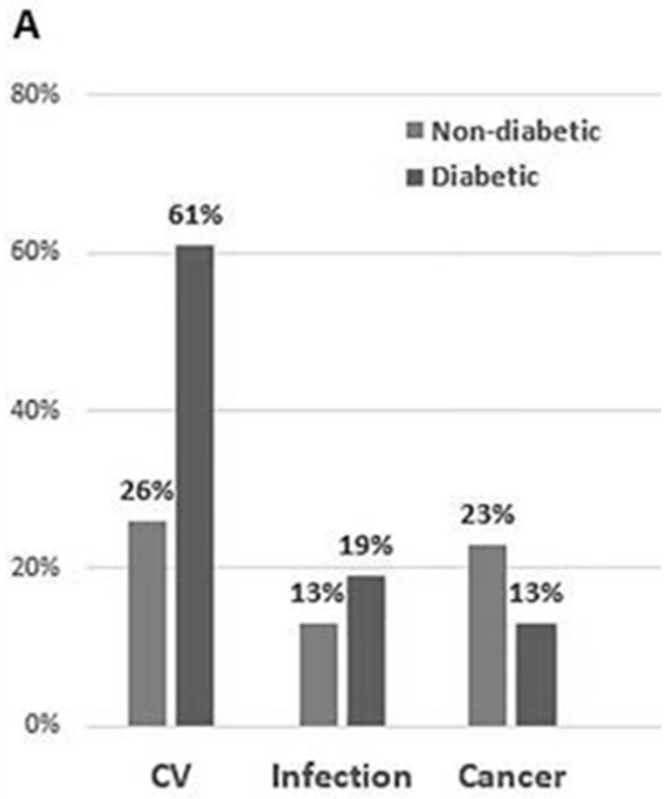


Immunosuppression Complications

- Cardiovascular
- Infectious
- Malignancy

Immunosuppression Complications

Causes of death post-transplantation



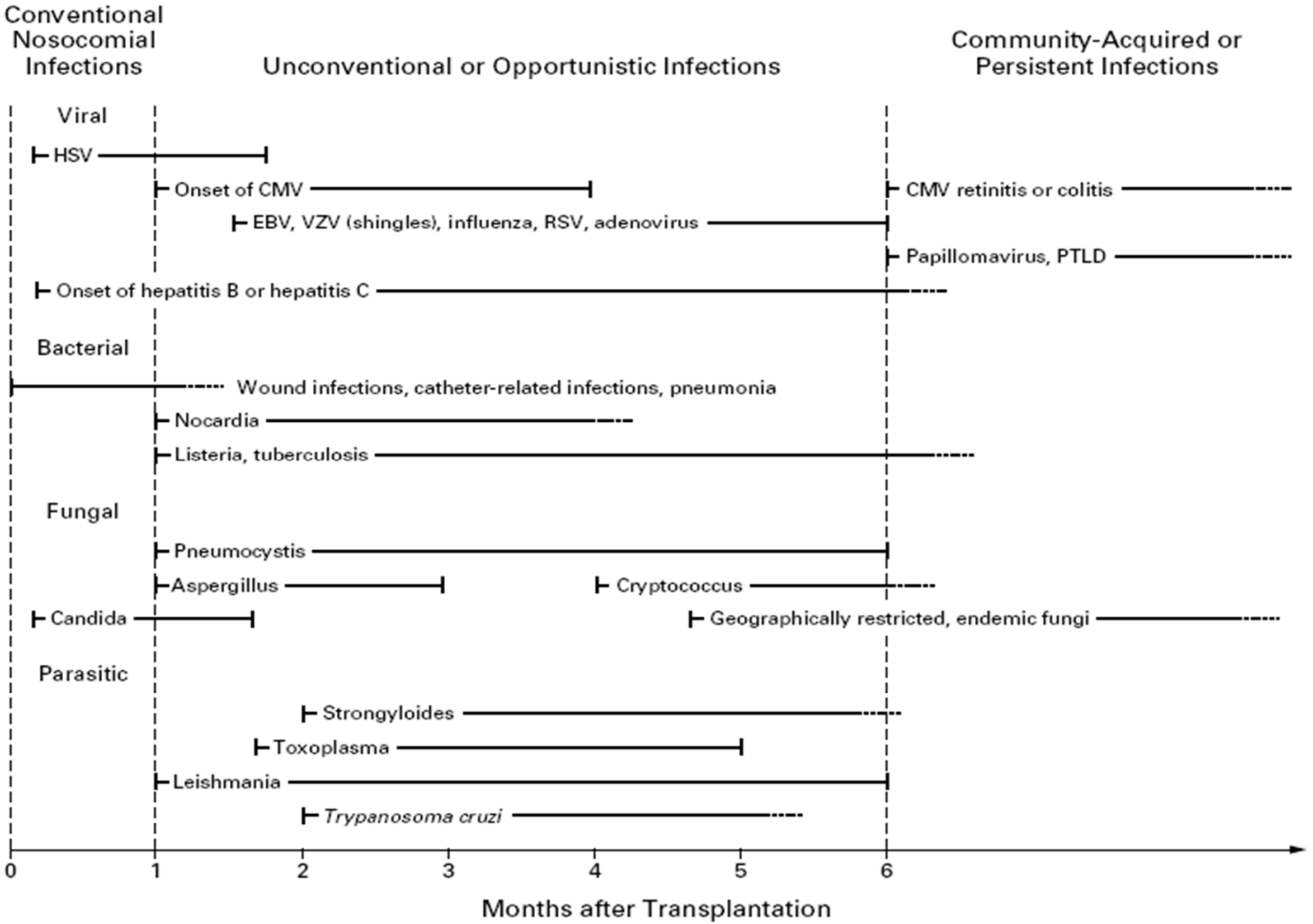
Riella LV. doi:10.1590/2175-8239-jbn-2018-0002-0003

Cardiovascular Complications

- Hypertension
- Hyperlipidemia
- Diabetes

Infectious Complications

- Highest risk immediately following transplant
- Opportunistic infections
- Atypical organisms
- Prophylaxis

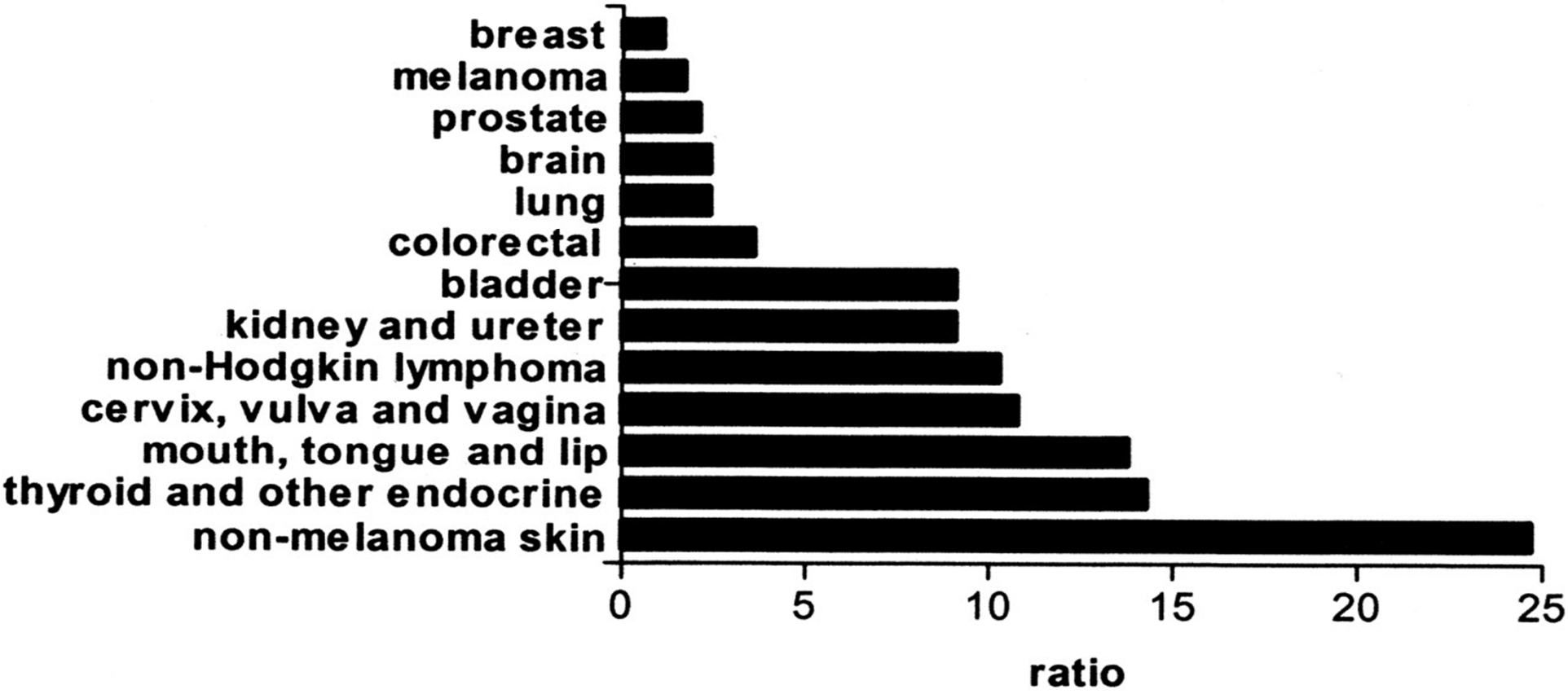


Fishman JA, et al. NEJM 98; 338 (24) 1741-51

Malignancy

- Related to degree of immunosuppression
- Increased risk with increased survival

Malignancy



Ratio of observed/expected malignancies

Morath C. *JASN*. 2004.

Question #3

A recent transplant recipient states that he needs a vacation override since he is going on vacation to the Caribbean. What counseling point should you give the patient?

A. Relax and enjoy your vacation.

B. Make sure to try some Pina Coladas.

C. Lay out in the sun to get a really nice tan.

D. Make sure to wear sunscreen while outside.

Conclusion

- Various phases of immunosuppression therapy
- Multiple classes of medications used in solid organ transplant
- Numerous considerations and complications of immunosuppression
- Clinical pharmacists have an extensive role in solid organ transplant