國軍左營總醫院

Kidney Transplantation

GU鄭人豪

《列子·湯問篇》記載說：“扁鵲遂飲二人毒酒，迷死三日，剖胸探心，易而置之；投以神藥，既悟如初，二人辭歸。

1900 年卡爾·蘭德施泰納（Karl Landsteiner）發現人類的血型.

亞歷克西·卡雷爾（Alexis Carrel）:血管縫合的開發，以及器官、血管的移植--1912 年諾貝爾醫學獎.

近代器官移植最早起源於俄國，1936 年，俄國醫師渥若諾（Voronoy）執行了歷史上首例人和人之間的腎臟捐贈手術(48小時後死亡).

但第一例成功的屍體腎臟移植是美國波士頓大學醫師休謨（David Milford Hume） 於1947年完成， 並發表論文，寫下里程碑。

1954美國波士頓的穆雷（Murray）醫師的團隊完成第一例成功的腎臟移植（活體移植），捐贈者和受贈者是同卵雙胞胎。

1968年，台大醫院外科教授李俊仁則是完成了亞洲首例成功的腎臟移植手術

Outline

- Basics of transplantation
- Benefits of transplantation
- Immunosuppressive medications
- Common post-transplant problems

人體器官移植條例

第 1 條

為恢復人體器官之功能或挽救生命，使醫師得摘取屍體或他人之器官施行移植手術，特制定本條例。本條例未規定者，適用其他法律之規定。

第 1-1 條

本條例所稱衛生主管機關：在中央為行政院衛生署；在直轄市為直轄市政府；在縣（市）為縣（市）政府。

第 4 條

醫師自屍體摘取器官施行移植手術，必須在器官捐贈者經其診治醫師判定病人死亡後為之。

前項死亡以腦死判定者，應依中央衛生主管機關規定之程序為之。

第 5 條

前條死亡判定之醫師，不得參與摘取、移植手術。

第 6 條

醫師自屍體摘取器官，應符合下列規定之一：

一、經死者生前以書面或遺囑同意。

二、經死者最近親屬以書面同意。

前項第一款書面同意應包括意願人同意註記於全民健康保險憑證（以下稱健保卡），其格式由中央主管機關定之；經意願人書面表示同意者，中央主管機關應將其加註於健保卡，該意願註記之效力與該書面同意正本相同。但意願人得隨時自行以書面撤回其意願之意思表示，並應通報中央主管機關廢止該註記。

經註記於健保卡之器官捐贈意願，與意願人臨床醫療過程中明示之意思表示不一致時，以意願人明示之意思表示為準。

第一項第一款書面同意，應由醫療機構或衛生機關以掃描電子檔存記於中央主管機關之資料庫。

中央主管機關應責成中央健康保險署，並應會商戶政單位或監理單位對申請或換發身分證、駕照或健保卡等證件之成年人，詢問其器官捐贈意願，其意願註記及撤回依第二項至第四項規定辦理。

第 7 條

非病死或可疑為非病死之屍體，非經依法相驗，認為無繼續勘驗之必要者，不得摘取其器官。但非病死之原因，診治醫師認定顯與摘取之器官無涉，且俟依法相驗，將延誤摘取時機者，經檢察官及最近親屬書面同意，得摘取之。

第 8 條

醫院自活體摘取器官施行移植手術，除第二項另有規定外，應符合下列各款規定：

一、捐贈者應為二十歲以上，且有意思能力。

二、經捐贈者於自由意志下出具書面同意，及其最近親屬之書面證明。

三、捐贈者經專業之心理、社會、醫學評估，確認其條件適合，並提經醫院醫學倫理委員會審查通過。

四、受移植者為捐贈者五親等以內之血親或配偶。

十八歲以上之人，得捐贈部分肝臟予其五親等以內之親屬。

第一項第三款所定醫院醫學倫理委員會，應置委員五人以上，包含法律專家學者及其他社會公正人士，醫院以外人士應達五分之二以上；任一性別委員不得低於三分之一。委員會之組織、議事、審查程序與範圍、利益迴避原則、監督、管理及其他應遵行事項之辦法，由中央主管機關定之。

第一項第四款所定配偶，應與捐贈者生有子女或結婚二年以上。但待移植者於結婚滿一年後始經醫師診斷須接受移植治療者，不在此限。

腎臟之待移植者未能於第一項第四款規定範圍內，覓得合適之捐贈者時，得於二組以上待移植者之配偶及該款所定血親之親等範圍內，進行組間之器官互相配對、交換及捐贈，並施行移植手術，不受該款規定之限制。

前項器官互相配對、交換與捐贈之運作程序及其他應遵行事項之辦法，由第十條之一第二項之專責機構擬訂，報中央主管機關核定發布。

第 8-1 條

前三條規定所稱最近親屬，其範圍如下：

一、配偶。

二、直系血親卑親屬。

三、父母。

四、兄弟姊妹。

五、祖父母。

六、曾祖父母或三親等旁系血親。

七、一親等直系姻親。

第 12 條

任何人提供或取得移植之器官，應以無償方式為之。

Basics of Transplantation

- Kidney transplantation is the most effective therapy for end-stage renal disease.
- The transplanted organ can come from either a live donor or deceased donor.
- Most deceased donor organs come from brain dead donors.
- Non-standard criteria donors:
- Expanded criteria donors (ECD).
- Donation after cardiac death (DCD).

Box 47-1

Recommendations for Pretransplant Nephrectomy

Symptomatic renal stones not cleared by minimally invasive techniques or lithotripsy

High-grade solid renal tumors with or without acquired renal cystic disease

Polycystic kidneys that are symptomatic, extend below the iliac crest, have been infected, or have solid tumors

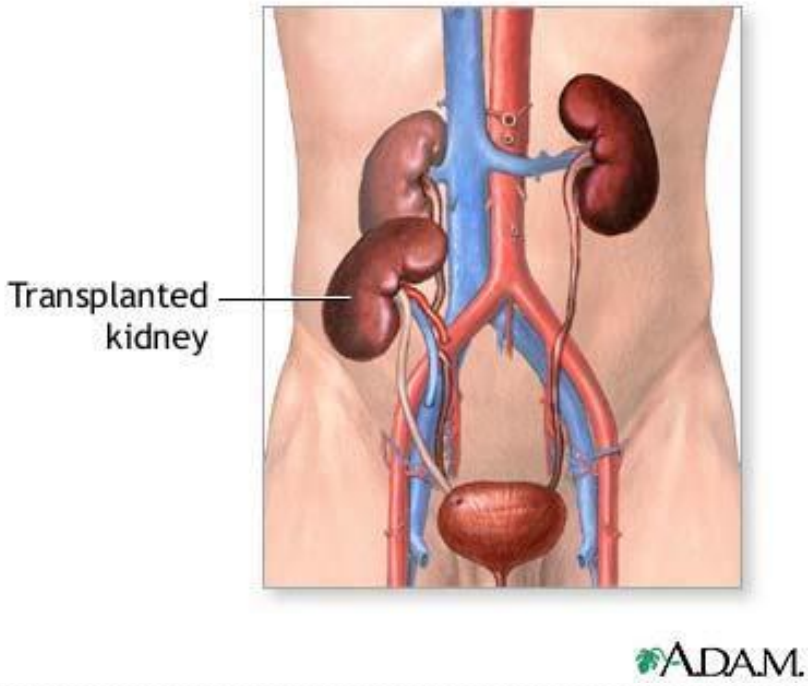
Persistent anti–glomerular basement membrane antibody levels

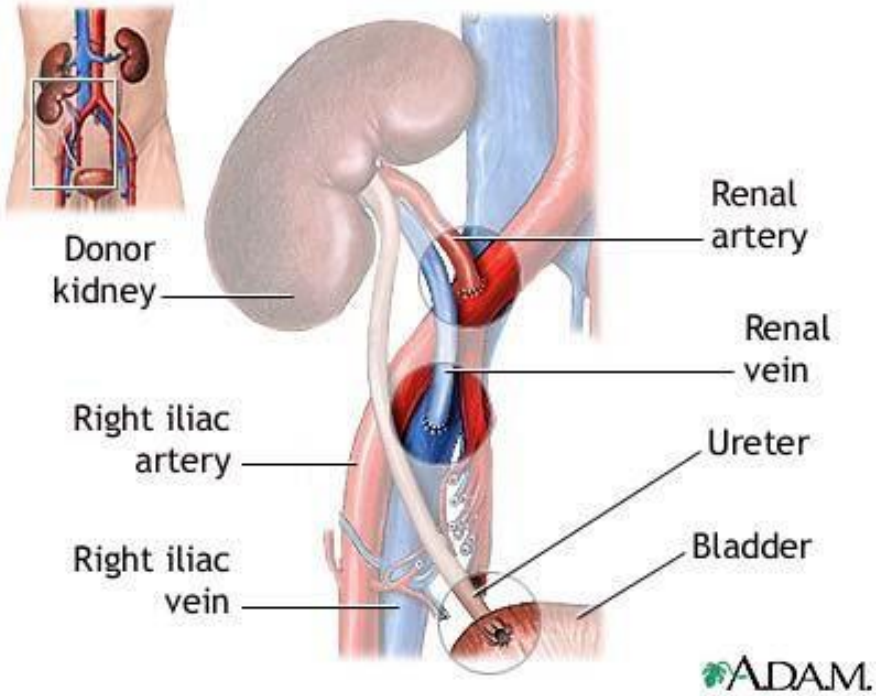
Significant proteinuria not controlled with medical nephrectomy or angioablation

Recurrent pyelonephritis

Grade 4 or 5 vesicoureteral reflux with urinary tract infections

Anatomy of KTx





- living donor nephrectomy原則
  - 取較差的一侧(差10%以上), 血管較單純的, 女性reproductive age盡量留左側(右腎孕期可能發生生理性 hydronephrosis)
  - 多條血管盡量conjoin ex vivo，以減少吻合時間
  - upper pole artery若<2mm可綁掉, 但lower pole artery要盡量保留(for ureter blood supply)
- 器官 harvest 順序:心 → 肺→胰-→肝→腎 (取胸腔時腹腔器官要灌UW or HTK cooling).
- 種腎盡量種右側 → 右側external iliac artery較長較水平較淺.

Recipient Selection

- Very few contraindications.
- General medical condition.
- Cardiovascular screening.
- Age-appropriate routine cancer screening (pap smear, mammography, colonoscopy, PSA).
- Infection (HIV, Hepatitis, TB).
- Presence of preformed antibody (PRA).
- Pregnancy, prior transplant, blood transfusion
- Psychosocial evaluation, including compliance.

受贈者禁忌症

1. 年齡65歲以上（年齡超過需經專案審查）
2. 有無法控制的感染者
3. 愛滋病帶原者
4. 活動性肺結核未完全治療者
5. 有惡性腫瘤者

    1) in situ carcinoma, low-grader bladder cancer, basal cell carcinoma，以上不影響肝臟移植。

    2) malignant melanoma, breast cancer, GI carcinoma, lung cancer，完整治療後，無癌症復發，未達五年者（disease-free interval < 5 years）。

    3) 其他癌症，完全治療後，無癌症復發未達二年者（disease-free interval < 2 years）。

6. 心智不正常者或無法長期配合藥物治療者
7. 嚴重心肺功能障礙
8. 嚴重腦血管或週邊血管病變，使日常生活無法自理，且無法接受 重建手術者
9. 免疫系統不全或自體免疫疾病，雖經治療仍預後不良者
10. 藥癮患者
11. 酒癮戒除未足半年

B型肝炎 → Donor為HBsAg(+)或HBsAg(-)且Anti-HBs(-) 且Anti-HBc(+) → 僅能分配予HBsAg(+) or Anti-HBs(+) or Anti-HBc(+)之Receipient。

C型肝炎 → Donor Anti-HCV(+) → 僅能分配予Anti-HCV(+)且尚未治癒的Receipient。

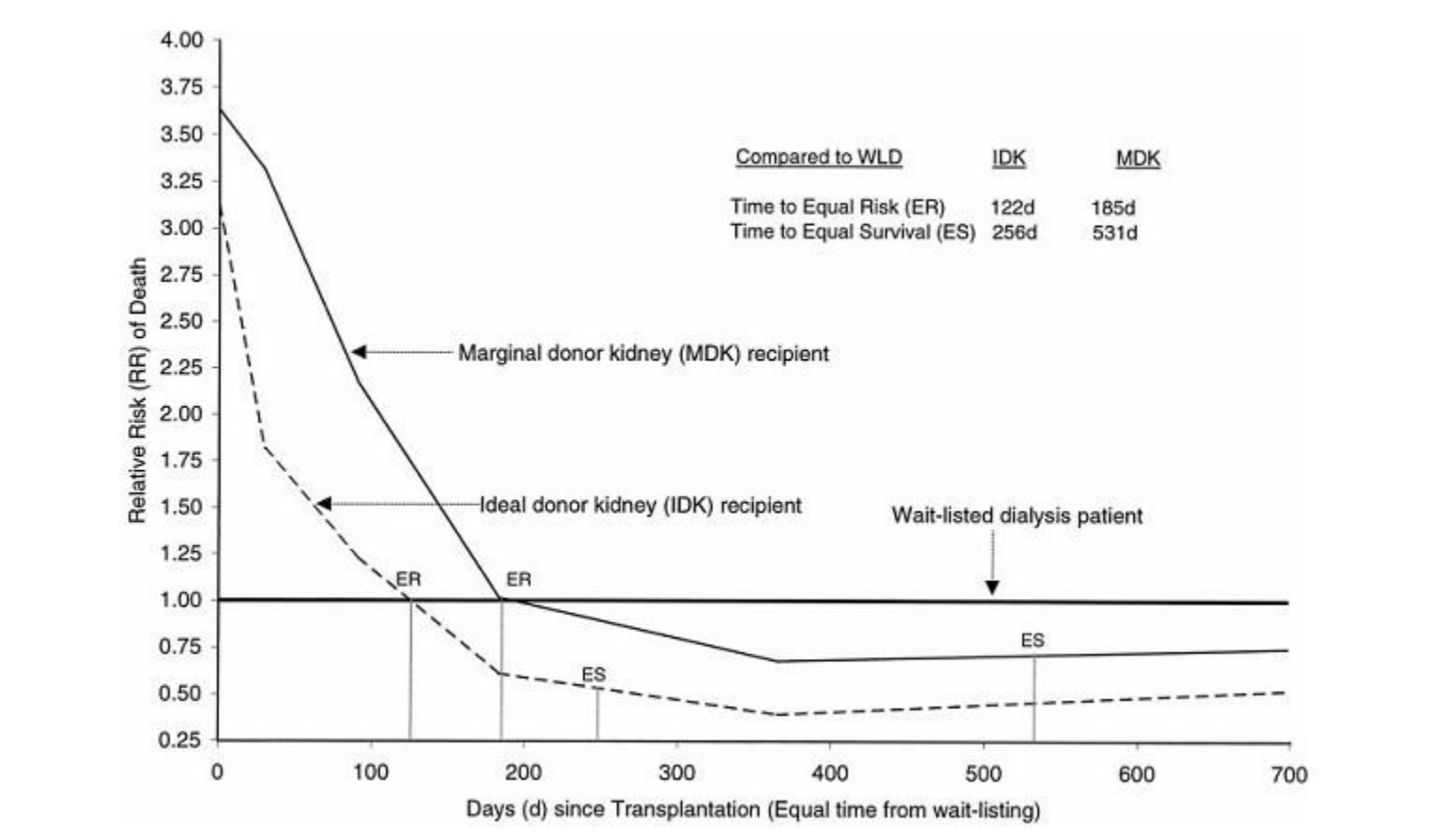
HIV(+)原則上為禁忌，惟符合以下四項標準時，可以移植： (1) CD4 數值大於 200 cells/μL 至少六個月 (2) 遵循醫囑並穩定接受雞尾酒療法（HAART），且最近六個月內側量病毒量<50 copies/ml (3)排除有未受控制、潛在致命之伺機感染或腫瘤 (4)) 日後仍有抗逆轉錄病毒之治療選擇者（應事先與感染科醫師討論及確認）

- 待移植者之優先順序：
  - 無錯配「zero ABDR mismatch」且其配偶/三親等以內曾為死後器官捐贈者
  - → 一般無錯配「zero ABDR mismatch」
  - →非無錯配且其配偶/三親等以內曾為死後器官捐贈者
  - →一般非無錯配。
- 辦理器官捐贈者之醫療照護、腦死判定、必要性檢查與檢驗、協助司法相驗、器官分配聯繫運送、遺體禮儀及資料登錄通報等事項之醫院。
- 地理位置：D及R所在區域相同為優先。
- 評分基準:「評分高」優先於「評分低」之R。
- 血型相同者加三分。
- 評分相同時，優先順序為「HLA組織抗原符合配對」、「病人年齡」、「等候時間長短」，最後由移植醫師以「臨床診斷預後最佳考量」為前提，確認待移植者序位。
- 曾為活體肝臟或腎臟器官捐贈者。

Benefits of Transplantation

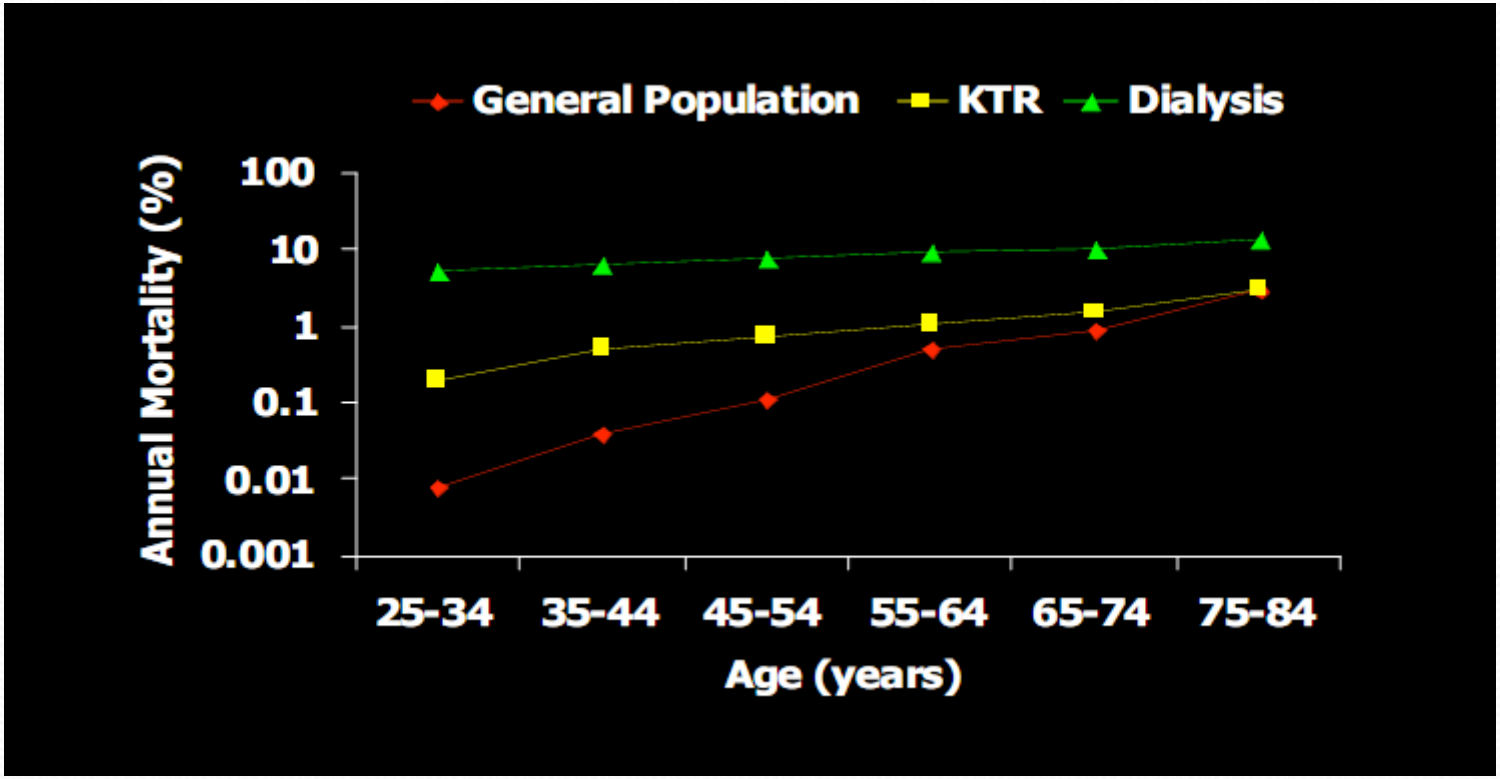
- Life expectancy
- Cardiovascular benefits
- Quality of life
- Socioeconomic benefits

Life Expectancy



Ojo, *J Am Soc Neph*, 2001;12:589

Cardiovascular Benefits



Foley, *Am J Kidney Dis*, 1998;32(S1):8
Slide courtesy of Dr. Robert Gaston

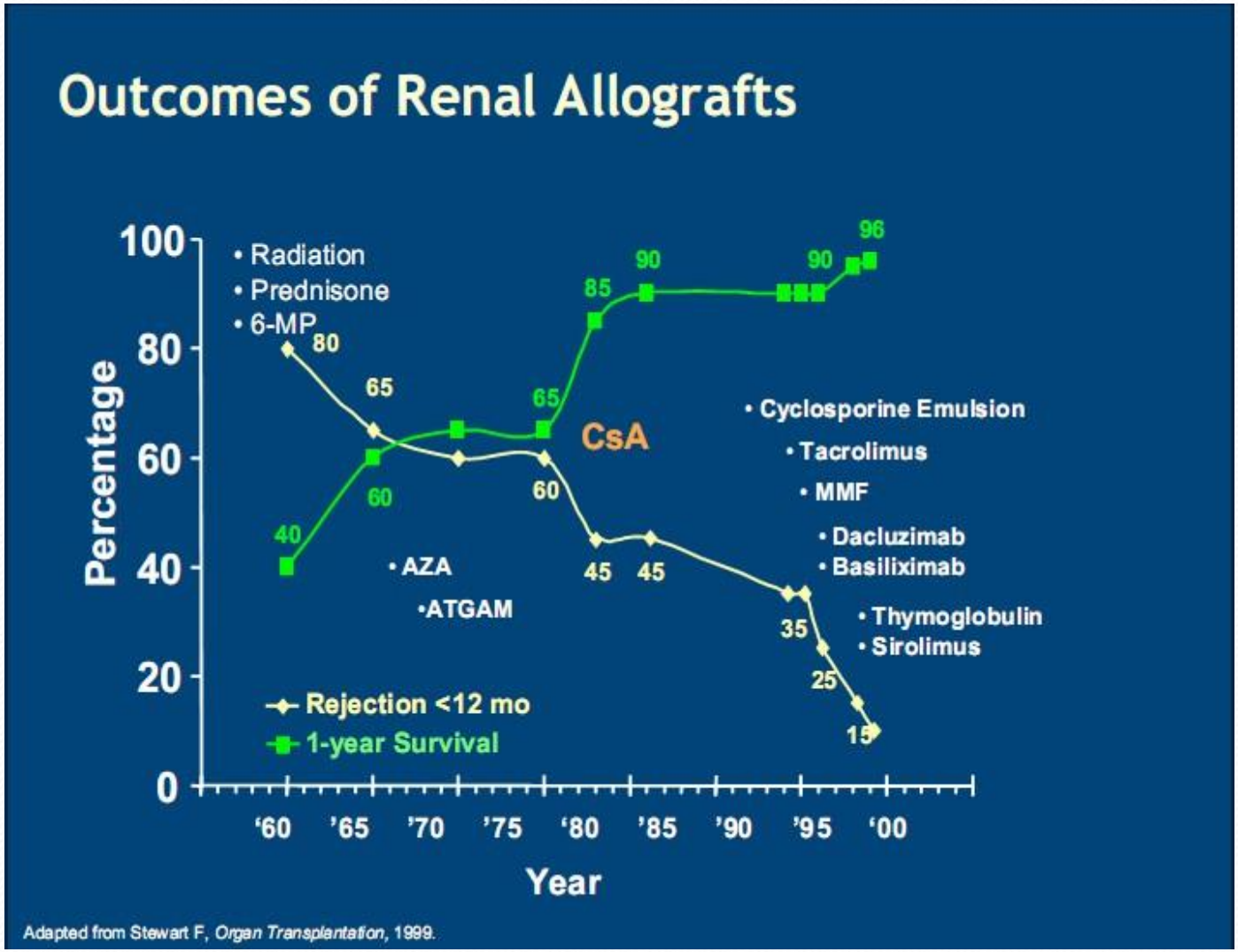
Quality of Life

- Numerous studies have detailed improved quality of life.
- Life satisfaction, physical and emotional well-being and ability to return to work higher in transplant recipients.
- Uremic complications more fully reversed.
- Fertility returns.

Socioeconomic Benefits

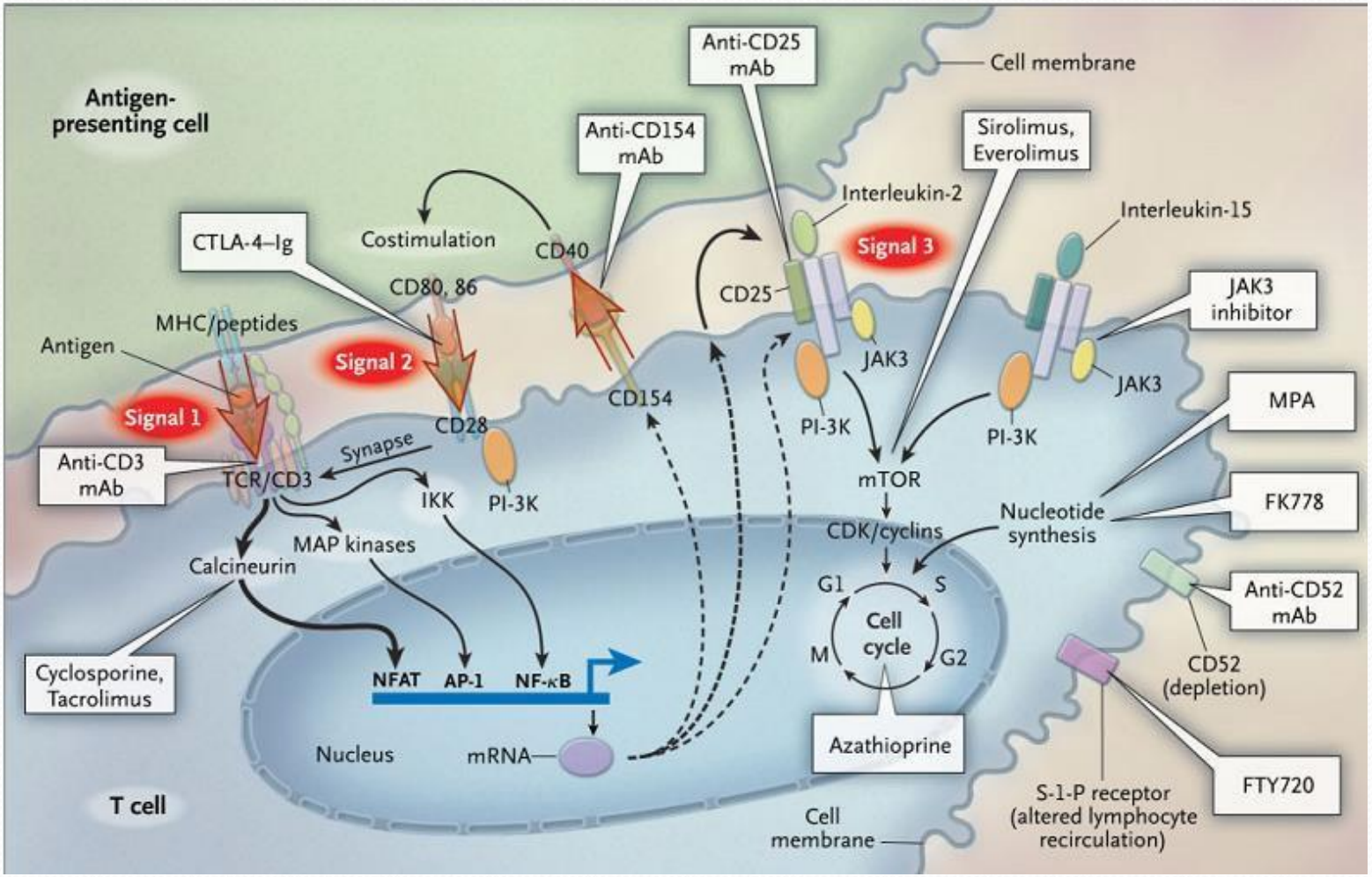
- Increased rates of return to work.
- Cost to society:
- Annual cost of hemodialysis: $60,000-$80,000
- First year after transplantation: >$100,000
- Thereafter: $10,000 per year.
- Mean cumulative costs of dialysis and transplantation are equal for first 3-4 years, then lower for transplantation.

Immunosuppressive Medications



Slide courtesy of Dr. Meier-Kriesche

Three-Signal Model



Halloran, *N Eng J Med*, 2004;351:3715

Immunosuppressive Medications

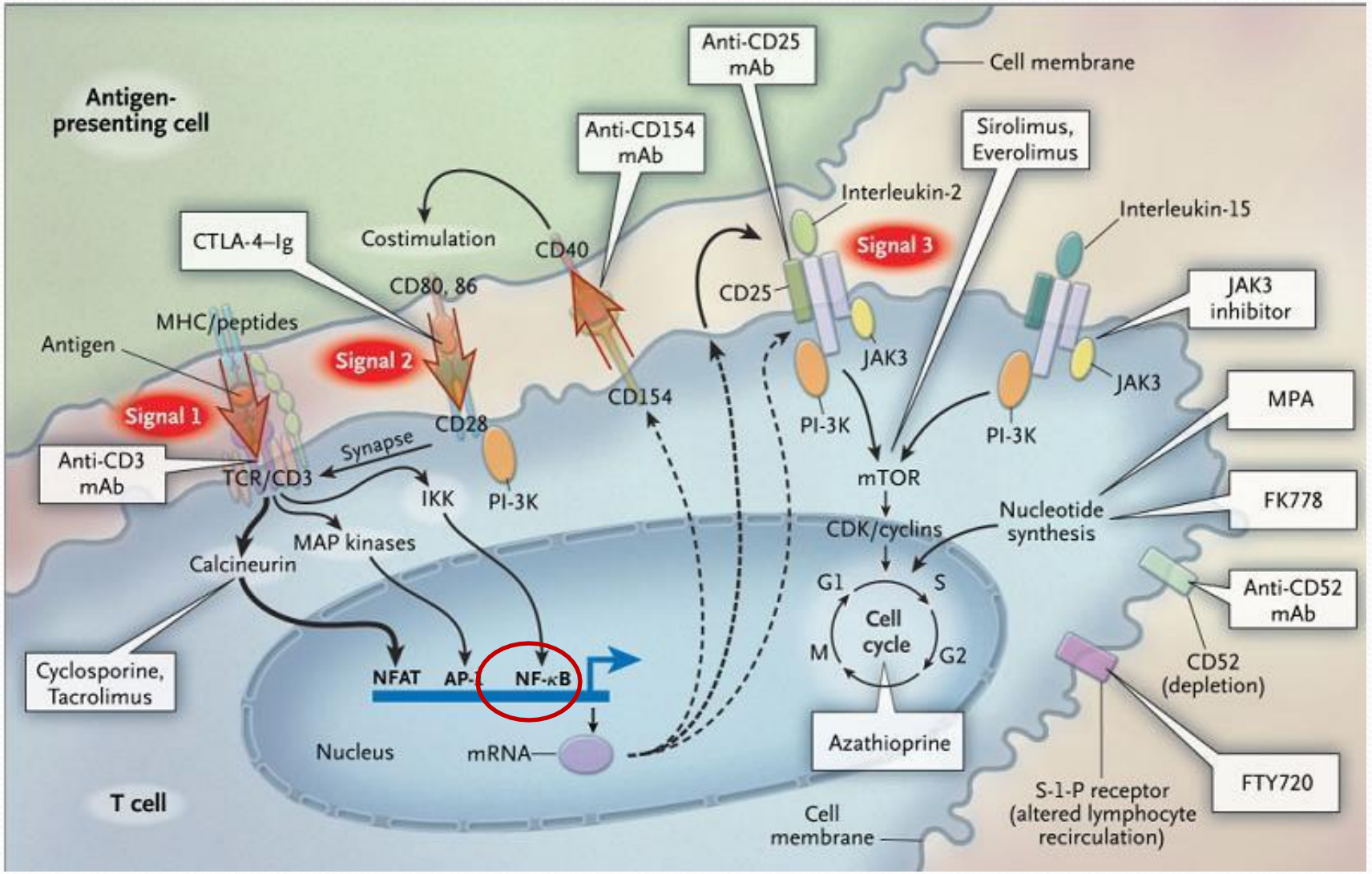
- Induction:
- Corticosteroids
- Anti-thymocyte globulin (ATG)
- IL-2 receptor antagonists
- Maintenance:
- Corticosteroids
- Calcineurin inhibitors (CNIs)
- mTOR inhibitors
- Antimetabolites

Immunosuppressive Medications

- Treatment of Rejection:
- Corticosteroids
- Anti-thymocyte globulin
- Intravenous Immunoglobulin (IVIG)
- Rituximab
- Plasmapheresis

Corticosteroids

- Used for induction, maintenance and treatment of rejection.
- Mechanism of action:
- Inhibit function of dendritic cells.
- Inhibit translocation to nucleus of NF-κB.
- Suppress production of IL-1, IL-2, IL-3, IL-6, TNF-α, and γ-IFN.
- Adverse effects numerous and well-known.



Halloran, *N Eng J Med*, 2004;351:3715

Corticosteroids

- Component of >80% of transplant protocols.
- Given IV at high doses (250-500 mg/day) for induction or treatment of rejection.
- Tapered to maintenance dose of 5-10 mg/day in early post-transplant phase.
- Should NOT be tapered off: increased risk of rejection and graft loss!
- Steroid free regimen: overall some benefits but graft survival likely worse.

Anti-thymocyte Globulin (Thymoglobulin®)

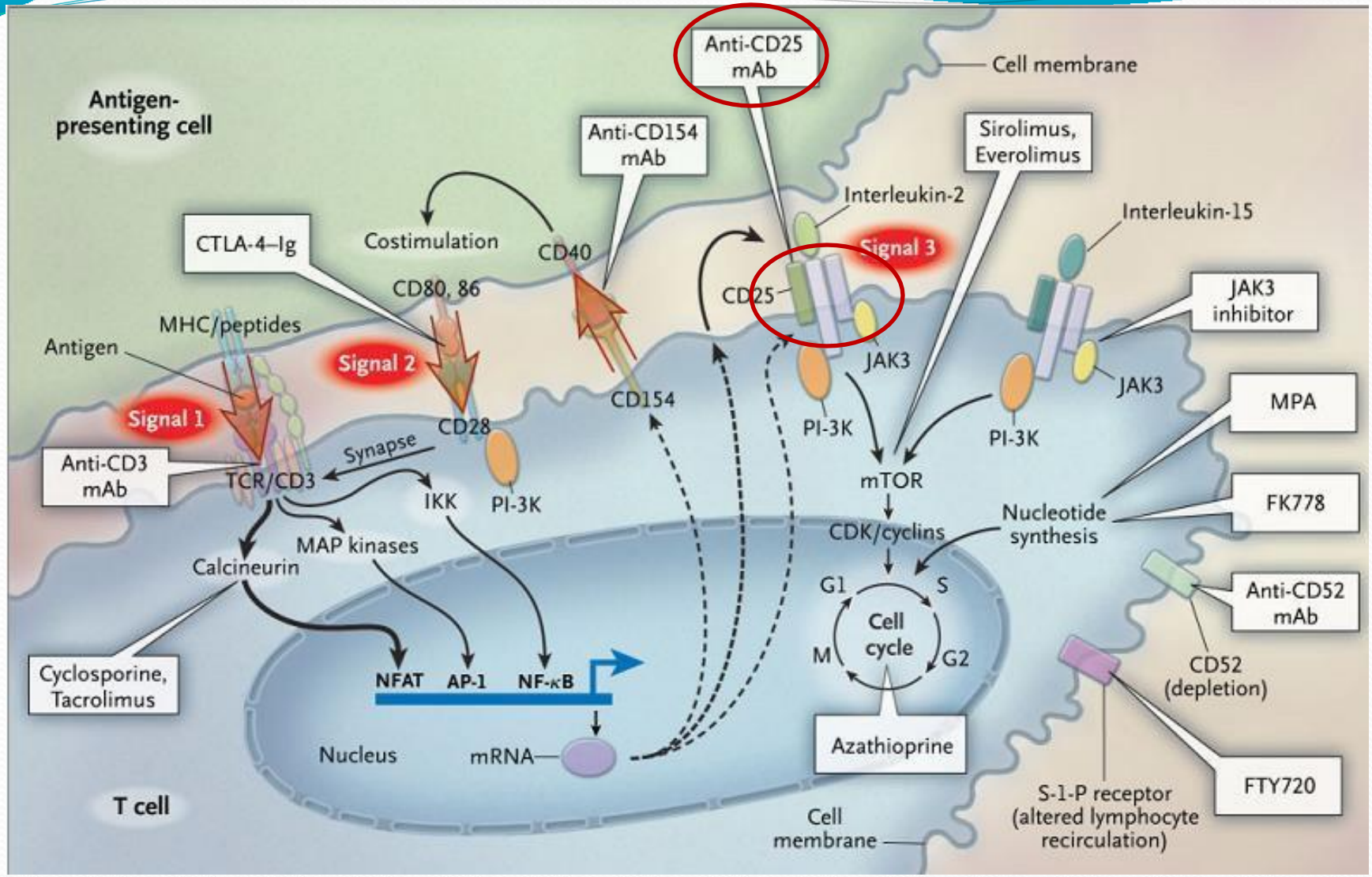
- Used for induction and treatment of rejection.
- Prepared by immunization of rabbits with human lymphoid tissue.
- Causes depletion of peripheral blood lymphocytes.
- Administered generally via central line for 3-10 days.
- Premedication required: acetaminophen, corticosteroids and antihistamine.

Anti-thymocyte Globulin: Adverse Effects

- Infusion-related reactions: chills, fevers, arthralgias.
- Lymphopenia.
- Thrombocytopenia.
- Prolonged immunosuppression: increased risk of opportunistic infections (PCP, CMV, fungal).
- Possibly increased risk of BK virus nephropathy.

IL-2 Receptor Blockers

- Basiliximab (Simulect®) and Daclizumab (Xenapax®).
- Block CD25 (IL-2 receptor) on activated T cells.
- Used for induction only.
- Almost no side effects, but also much less potent.

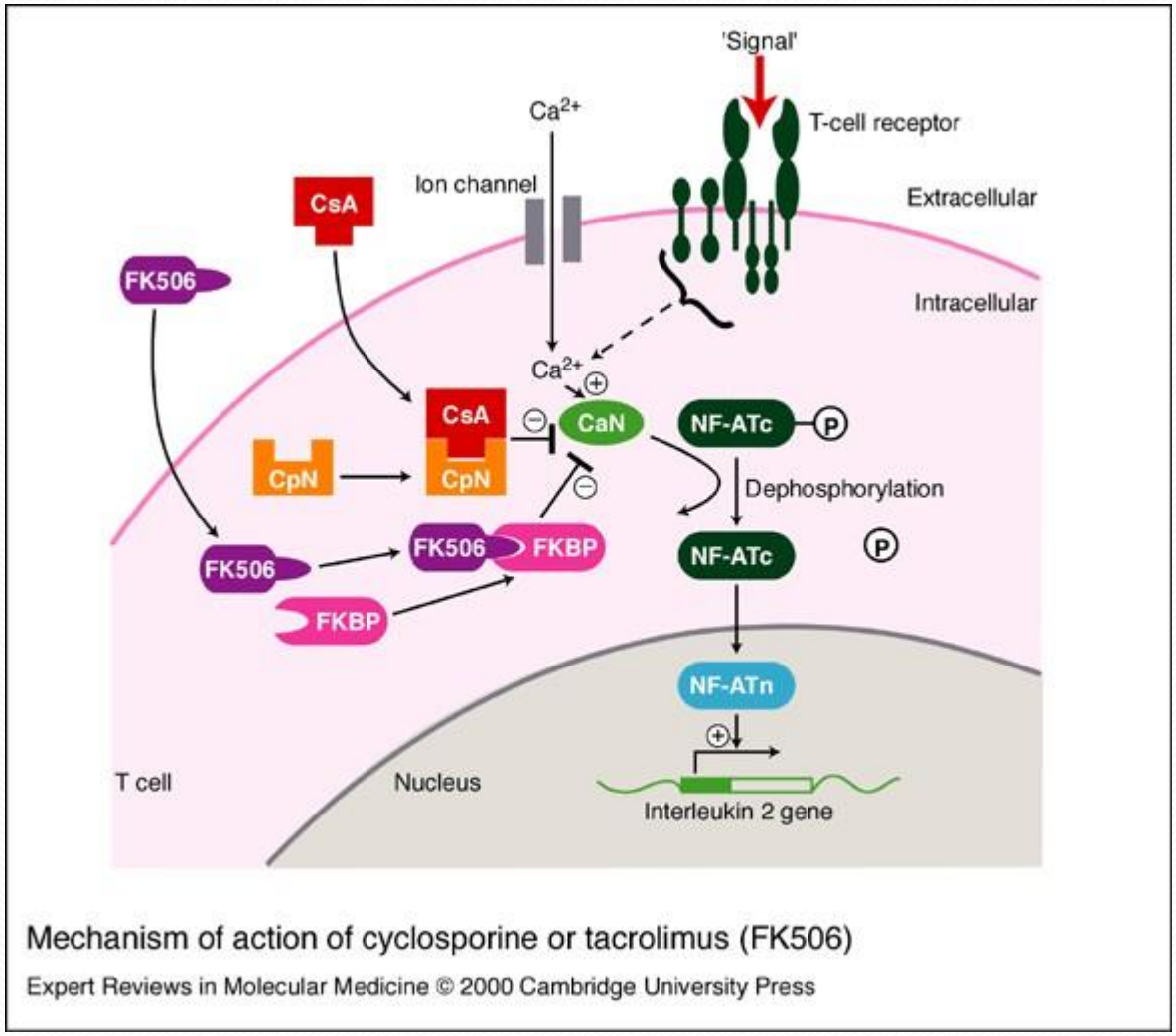


Halloran, *N Eng J Med*, 2004;351:3715

Calcineurin Inhibitors

- Used for maintenance immunosuppression.
- Two agents in clinical practice:
- Cyclosporine (Sandimmune®, Gengraf®, Neoral®, generic; CysA)
- Tacrolimus (Prograf®, generic; FK506).
- Generics NOT clinically therapeutically equivalent.
- At present are key to maintenance immunosuppression and a component of the majority of transplant protocols.

Calcineurin Inhibitors: Mechanism of Action



Mechanism of action of cyclosporine or tacrolimus (FK506)

CsA: Cyclosporine

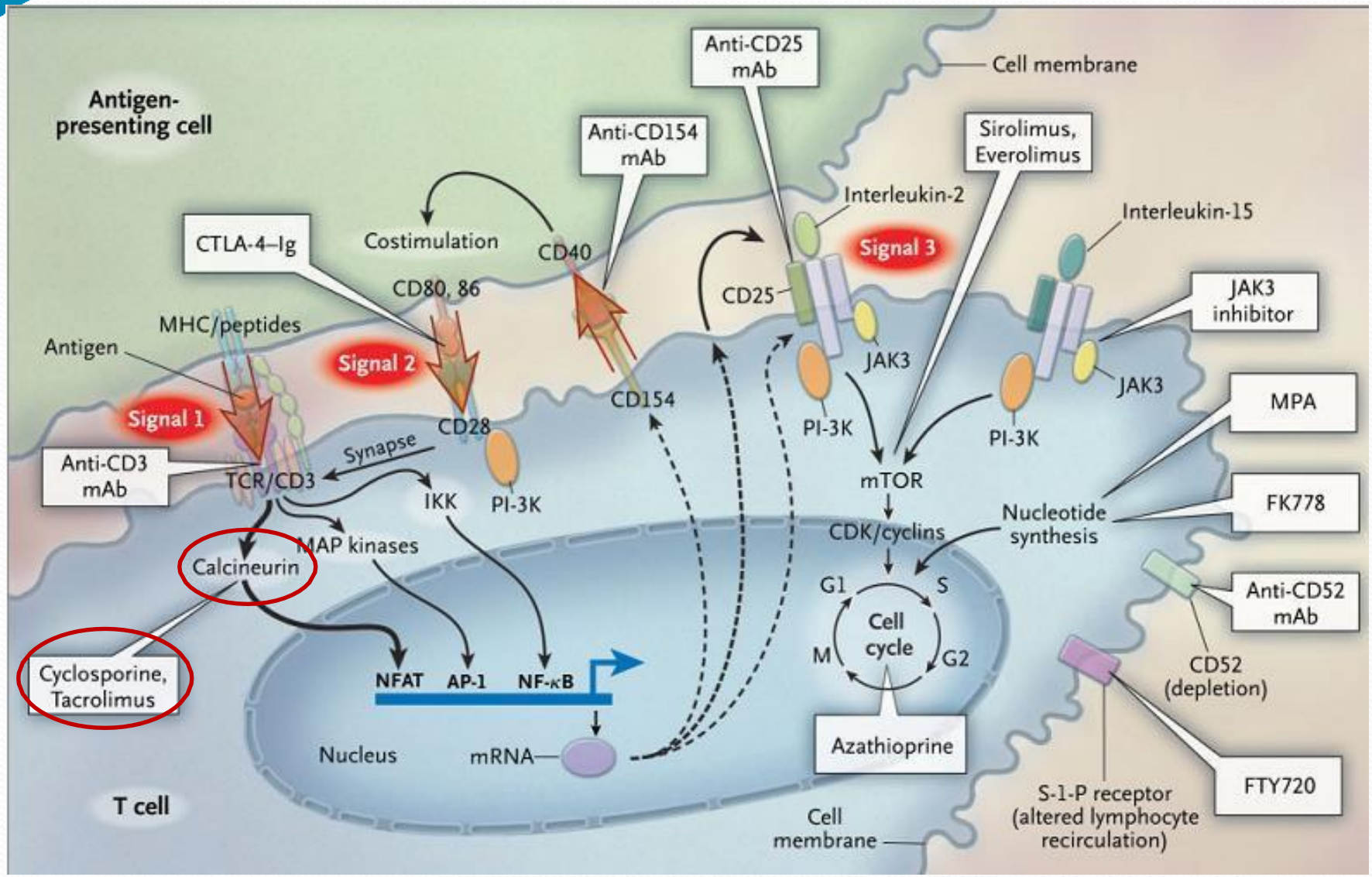
FK506: Tacrolimus

FKBP: FK Binding Protein

CpN: Cyclophilin

NF-AT: Nuclear Factor of Activated T-cells (c-cytosolic component; n-nuclear component).

Stepkowski, *Expert Rev Mol Med*, 2000;2(4):1



Halloran, *N Eng J Med*, 2004;351:3715

Calcineurin Inhibitors: Dosing and Monitoring

- Both medications are generally dosed twice per day, 12 hrs apart.
- Trough levels monitored: check approximately 12 hrs after last dose.
- In some cases C2 levels might be checked 2 hrs after administration.
- Cyclosporine is 35-40% bioavailable, tacrolimus approximately 25%.
- Oral to IV conversion 3-4:1.
- Both are metabolized by cytochrome P450 3A4 & 3A5.

Calcineurin Inhibitors: Interactions

Drug interactions with cyclosporine and tacrolimus

Increase cyclosporine or tacrolimus blood levels	Decrease cyclosporine or tacrolimus blood levels	Increase cyclosporine or tacrolimus nephrotoxicity
Ketoconazole	Anticonvulsants: phenytoin, phenobarbital (phenobarbitone), carbamazepine, others	Amphotericin B
Fluconazole		Aminoglycosides
Erythromycin		Cisplatin
Diltiazem	Antibiotics: rifampin (rifampicin), rifabutin	
Verapamil		
Nicardipine	Nonsteroidal anti-inflammatory drugs	
Metoclopramide		
Methylprednisolone		
Sirolimus (increases cyclosporin levels)		

Halloran, from Johnson (ed.), *Comprehensive Clinical Nephrology*, Mosby Elsevier, 2003.

Calcineurin Inhibitors: Interactions

- Drugs to use with caution:
- NSAIDs—avoid.
- Amphotericin B & Aminoglycosides– worsened nephrotoxicity.
- ACEi & ARBs– use with caution.
- Statins– avoid lovastatin, start others at lowest possible dose.

Calcineurin Inhibitors: P-Glycoprotein

- P-Glycoprotein (P-gp, also known as MDR1) is an ABC-transporter found among other places, in the intestine.
- It is thought to have evolved as a defense mechanism against harmful substances.
- It acts as an efflux pump for many substances including drugs (CNIs, colchicine, some cancer chemotherapeutic agents, digoxin, corticosteroids, antiretrovirals).
- Decreased P-gp expression, such as in diarrhea, leads to elevated drug levels.

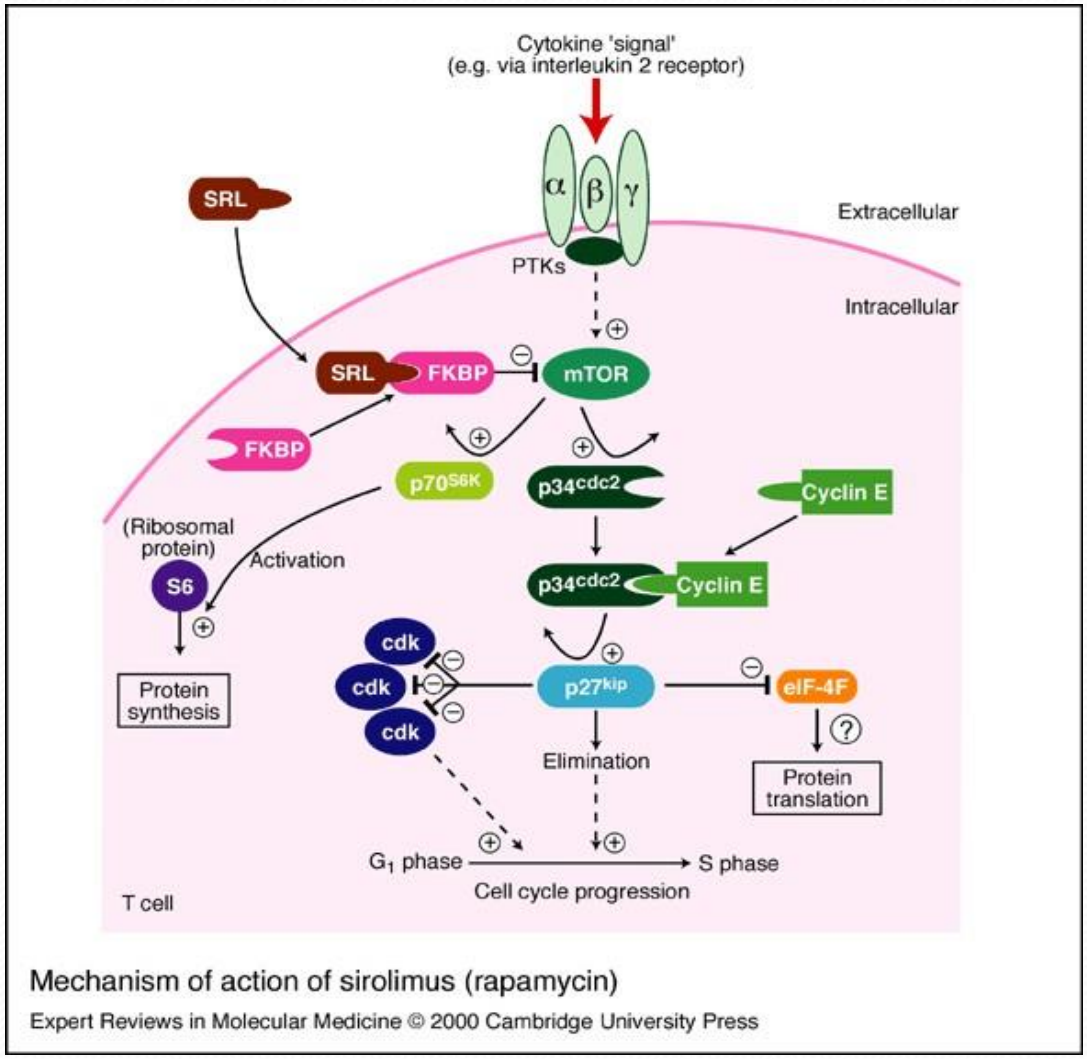
Calcineurin Inhibitors: Adverse Effects

- Nephrotoxicity:
- Functional decrease in blood flow from afferent arteriolar vasoconstriction.
- Thrombotic microangiopathy (rare).
- Chronic interstitial fibrosis.
- Hyperkalemia, hypomagnesemia and type IV renal tubular acidosis.
- Cyclosporine thought to be more nephrotoxic.

mTOR Inhibitors

- Target site is the mammalian target of rapamycin (mTOR), a key regulatory kinase in cell division.
- Sirolimus (Rapamune®) only available mTOR inhibitor in the US.
- Administered once daily, 24-hour trough levels monitored.
- Also metabolized by P450 3A system, with interactions similar to the CNIs.

Sirolimus: Mechanism of Action



Mechanism of action of sirolimus (rapamycin)

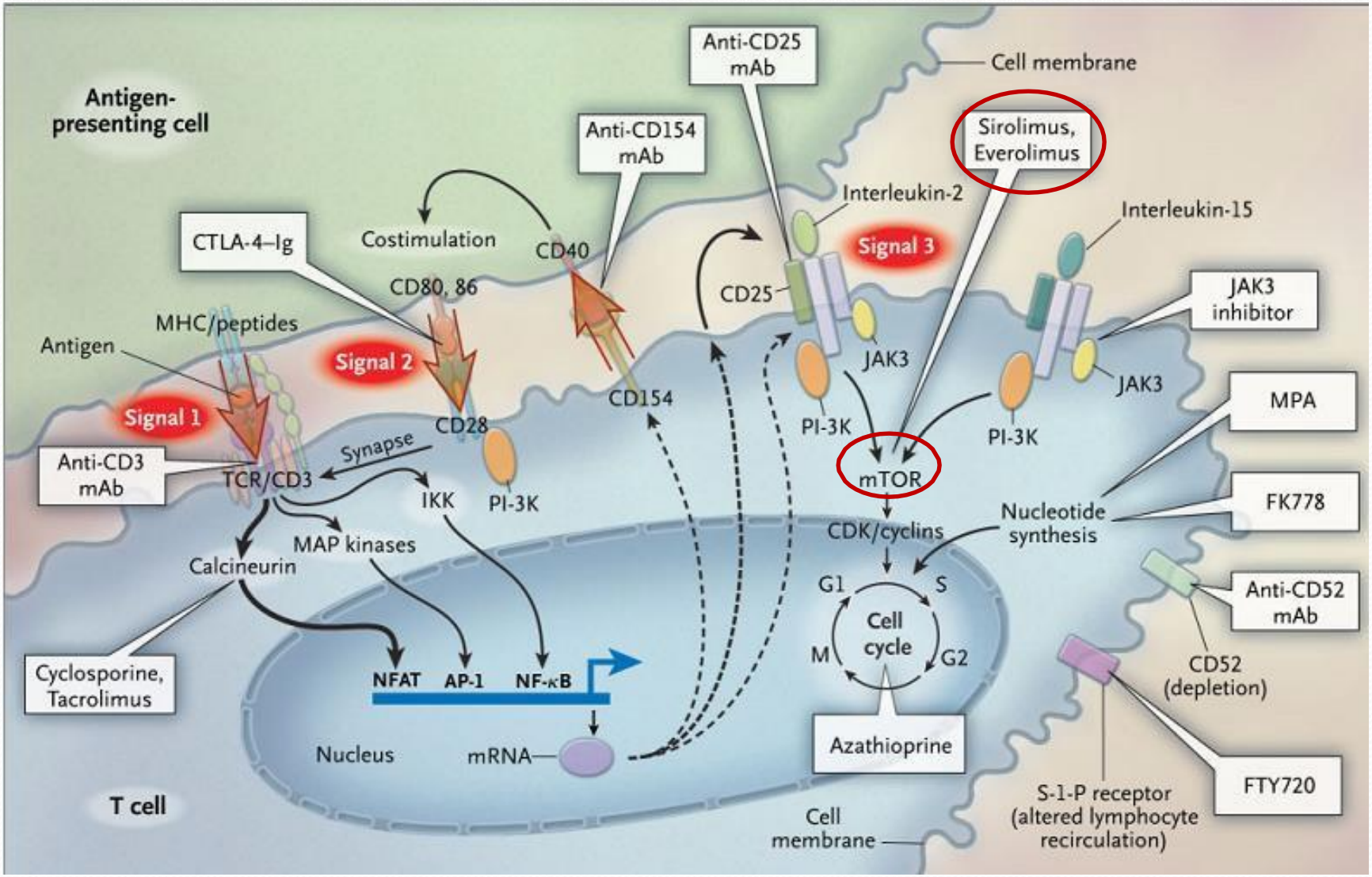
SRL: Sirolimus

FKBP: FK Binding Protein

mTOR: Mammalian target of rapamycin

Cdk: cyclin-dependent kinase

Stepkowski, *Expert Rev Mol Med*, 2000;2(4):1



Halloran, *N Eng J Med*, 2004;351:3715

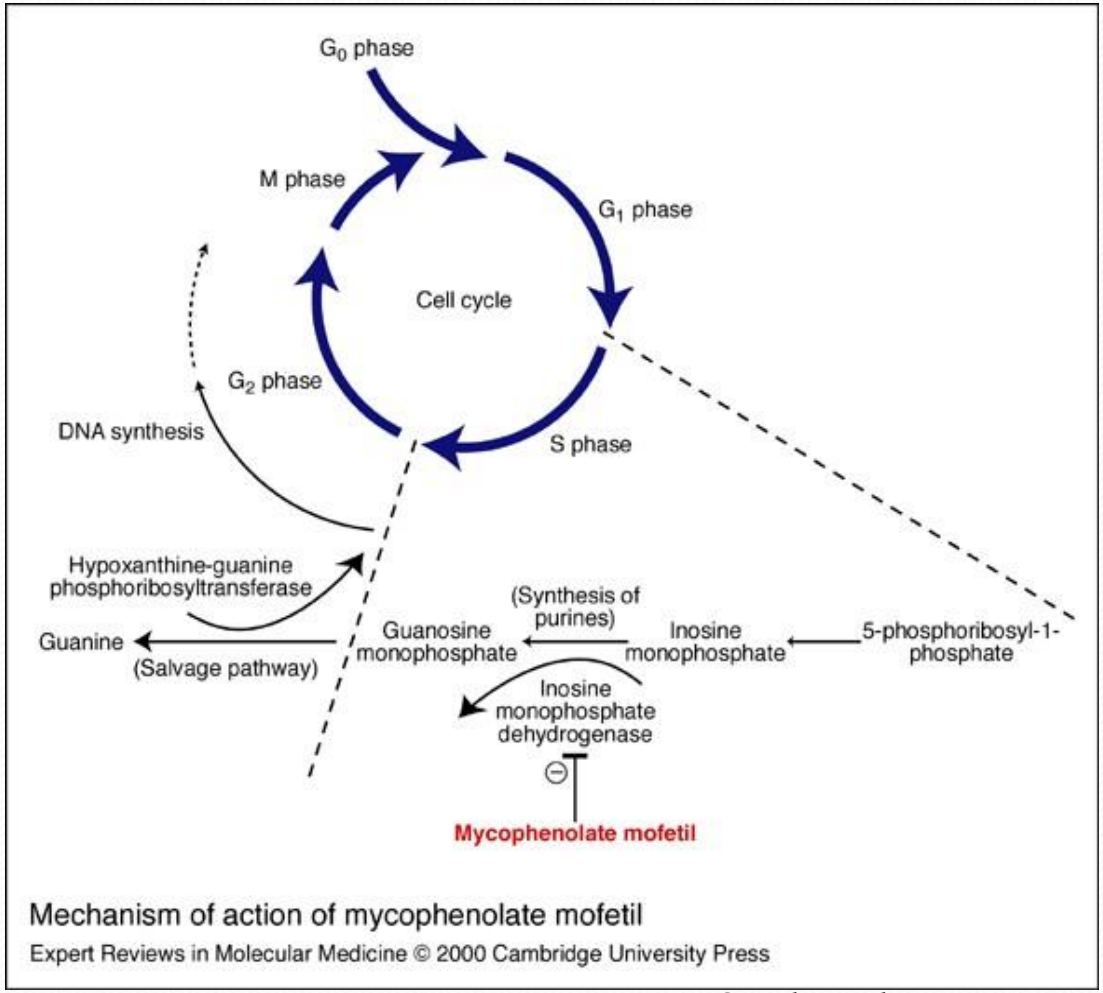
Sirolimus: Adverse Effects

- Nephrotoxicity:
- Delays recovery from ATN.
- Potentiates cyclosporine nephrotoxicity.
- Induces proteinuria.
- Tubulotoxic.
- Impairment of wound healing.
- Dyslipidemia (increased LDL and TGs).
- Pneumonitis.
- Cytopenias and anemia.

Antimetabolites

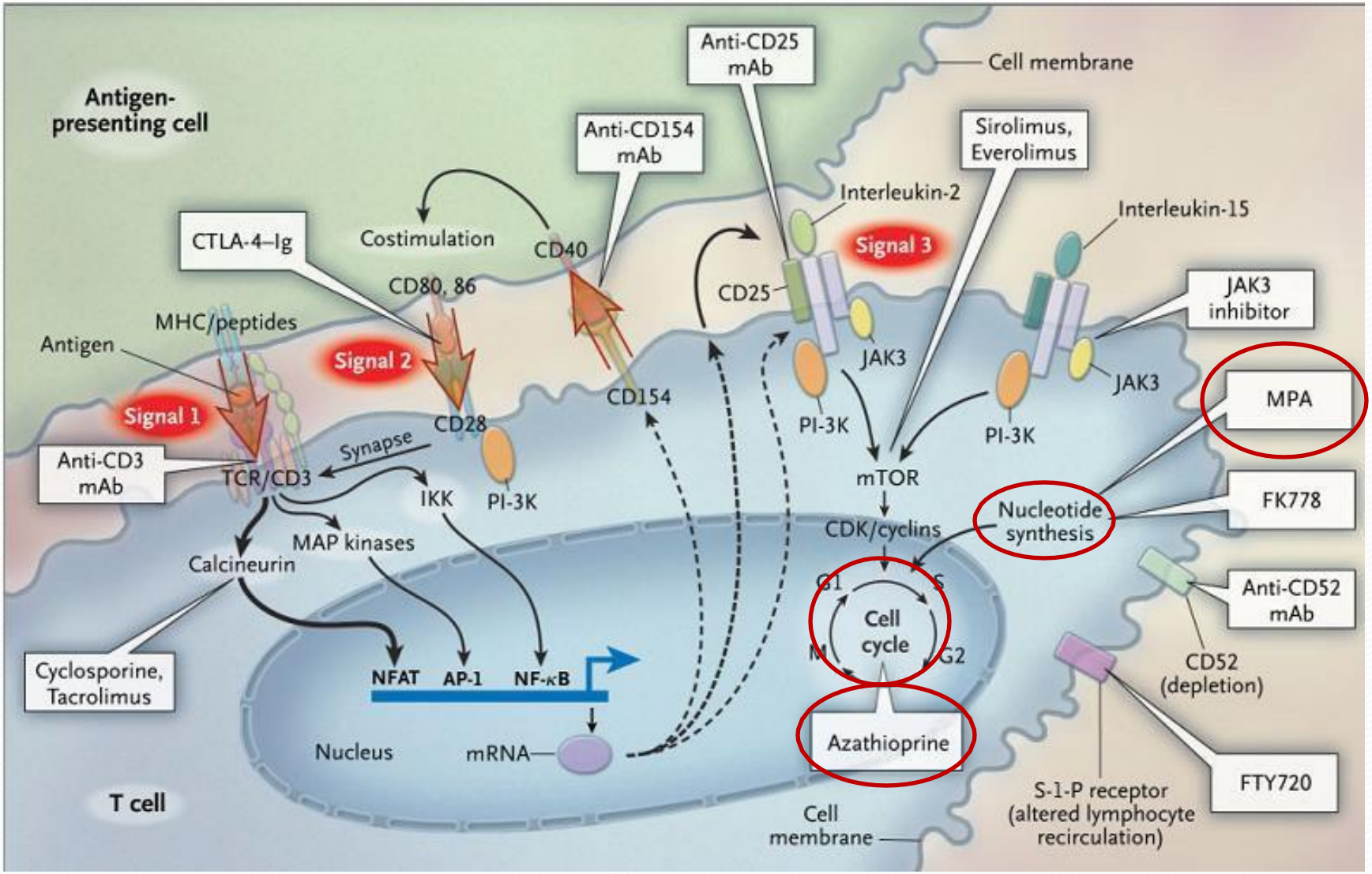
- Azathioprine (Imuran®, generic) is a purine analogue that is incorporated into RNA and inhibits cell replication.
- A mainstay of transplantation for 30 years, it has largely been replaced by the below drugs.
- Mycophenolate mofetil (Cellcept®) and enteric-coated mycophenolate sodium (Myfortic®) are prodrugs of mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase (IMPDH).

Mechanism of Action: MPA Prodrugs



Mechanism of action of mycophenolate mofetil

Stepkowski, *Expert Rev Mol Med*, 2000;2(4):1



Halloran, *N Eng J Med*, 2004;351:3715

Antimetabolites: Adverse Effects

- Azathioprine:
- Bone marrow suppression.
- Hepatitis.
- Azathioprine is inactivated by xanthine oxidase, therefore ***should not be used in combination with allopurinol***.
- MPA prodrugs:
- GI toxicity: diarrhea, nausea, esophagitis.
- Leukopenia and anemia.
- Not different between formulations.

Antimetabolites: Interactions

- Azathioprine:
- Allopurinol
- Other marrow suppressive drugs
- MPA prodrugs:
- Cyclosporine
- Antacids
- Cholestyramine
- Ferrous sulfate
- OK to use with allopurinol

Intravenous Immune Globulin

- Used primarily for treatment of antibody-mediated rejection.
- Mechanism of action:
- Reduction of alloantibodies through suppression of antibody formation.
- Increased catabolism of circulating antibodies.
- Adverse effects:
- Infusion-related reactions (myalgias, headaches).
- Severe headache & aseptic meningitis.
- Autoimmine hemolytic anemia.
- Sucrose-based IVIG can cause ARF.

Rituximab

- Used in the treatment of antibody-mediated rejection.
- Monoclonal antibody directed at CD20 antigen on B lymphocytes.
- Causes rapid and sustained depletion of B lymphocytes.
- Does not have direct activity against plasma cells and memory B cells, which do not express CD20.
- Adverse events: infusion reactions, and increased susceptibility to infection.

Other Agents

- OKT3
  - Used for induction and treatment of rejection, now largely replaced by anti-thymocyte globulin.
  - Monoclonal antibody against CD3
  - Severe infusion reactions (pulmonary edema & capillary leak syndrome).
- Alemtuzumab (Campath-1H®)
  - Monoclonal anti-CD52 antibody
  - Toxicities include bone marrow suppression and severe infections
- Leflunomide (Arava®)
  - Dihyroorotate dehydrogenase (DHODH) inhibitor.
  - Used in certain clinical settings as an adjunct immunosuppressive.

Common Complications of Transplantation

- Early complications
  - Surgical complications
  - Delayed or slow graft function
  - Lymphocele
- Acute rejection
  - Acute cellular rejection
  - Antibody-mediated rejection
- Infectious complications
  - Cytomegalovirus
  - BK virus
  - Others
- Malignancy
- Chronic allograft dysfunction

Surgical Complications

- Graft thrombosis:
  - Caused by thrombosis of donor renal artery or vein.
  - Usually happens in first week.
  - Diagnosed by ultrasound with doppler studies.
  - Almost always requires explant of kidney.
- Urine leak:
  - Elevated creatinine.
  - May or may not have abdominal pain.
  - Diagnose with nuclear medicine scans (DTPA or MAG3).
  - Surgical repair and/or relief of obstruction.

Delayed Graft Function

- Need for dialysis in the first week after transplantation.
- Causes:
- ATN from prolonged cold ischemia.
- Acute rejection.
- Recurrent disease.
- Usually requires biopsy for diagnosis and management.

Lymphocele

- Collection of lymph caused by leakage from iliac lymphatics.
- Presents several weeks post-operatively.
- Symptoms:
- Compression of kidney, ureter, bladder: obstructive uropathy and ARF.
- Compression of iliac vessels: unilateral lower extremity edema and DVT.
- Abdominal mass.
- Treatment is surgical.

Acute Rejection

- May present with ARF or proteinuria.
- Diagnosis made by biopsy.
- Pathology is reported according to Banff classification.
- Acute cellular rejection: treat with steroids or ATG based on severity
- Antibody-mediated rejection: may require steroids, ATG, rituximab, IVIG or plasmapheresis based on severity and setting.

Diagnostic criteria for acute antibody-mediated rejection (AHR)

1. **Morphologic evidence of acute tissue injury/ acute tubular injury**
   - **neutrophils and/or mononuclear cells in PTC and/or glomeruli and/or capillary thrombosis fibrinoid necrosis/intramural or transmural inflammation in arteries**
2. **Immunopathologic evidence for antibody action C4d and/or (rarely) immunoglobulin in PTC Ig and complement in arterial fibrinoid necrosis**
3. **Serologic evidence of circulating antibodies to donor HLA or other anti-donor endothelial antigen**

Cases that meet only two of the three numbered criteria are considered suspicious for AHR. Acute cellular rejection may also be present.

Colvin RB. J Am Soc Nephrol 18: 1046–1056, 2007

Diagnostic Criteria for Acute AMR

- **Characteristic histologic features including:**

Grade 1

1) glomerulitis/capillaritis
2) margination of neutrophils in the PTC
3) fibrin thrombi
4) interstitial hemorrhage

Grade 3

5) severe or necrotizing vasculitis

- **Diffuse, linear C4d staining in the PTC**

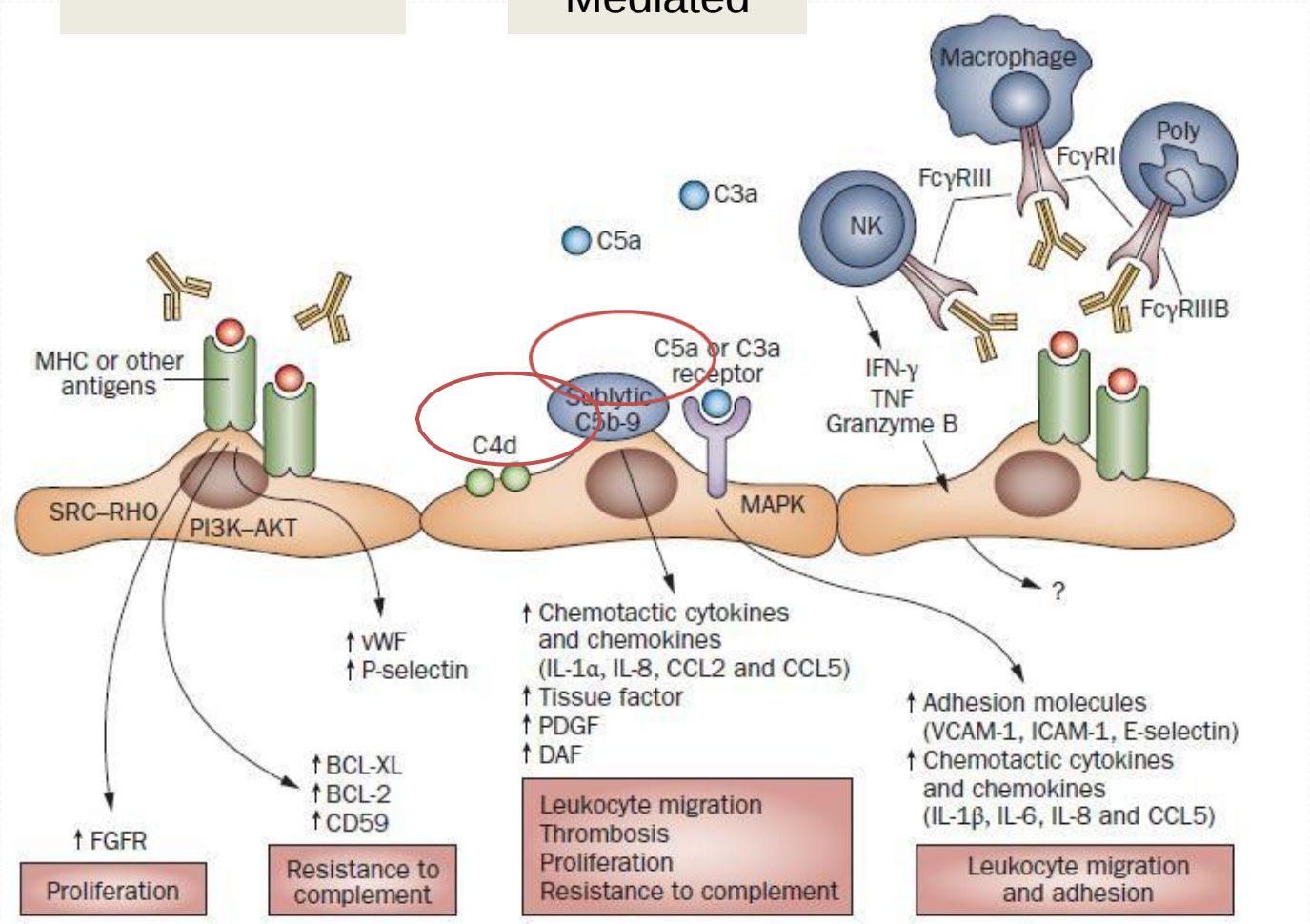
- **Identification of DSA**

Three Pathways to Antibody-Mediated Injury

Antibody Alone

Complement Mediated

Cell Mediated (FcR)



Farkash and Colvin, Nat Rev Nephrol 8:255, 2012

AMR Treatment

- ***Suppression*** of T cell response
- ***Elimination*** of circulating Ab
- ***Inhibition*** of Ab
- ***Suppression/Depletion*** of B cells

Therapeutic Options For The Treatment Of AMR

Antibody Reduction

Plasmapheresis/IA
IVIg

B-cell Modulation

Splenectomy
Anti-CD20
Cytoxan
Bortezomib

Immunomodulation

IVIg
ATG
IL-2R blockers
Fk 506, Rapamycin
MMF/DSG
CAMPATH?

Complement Inhibition

Eculizumb

Suppression of T-cell Response

Depletional Antilymphocyte Ab (rATG)

- Has multiple anti-T cell Ab specificities, costimulatory pathways, cell adhesion molecules, cell surface molecules expressed on B cells and plasma cells.
- Usually used as adjuvant therapy in AMR
- Used for severe or steroid resistant ACR
- FDA approved for Kidney transplant rejection

Steroids

- inhibits IL-1,IL-2, IL-6 production, T-cell proliferation, cytokine gene transcription & antigen presentation

MPA

- Prevents proliferation of T & B-cells
- FDA approved for kidney

CNI

- Both CsA & Tac inhibit T & B-cell activation and proliferation
- FDA approved for kidney, liver, heart

Singh et al, Transplantation Review, 2009
Samaniego et al, Nature Clinical Practice, 2006
micromedex

Elimination of Circulating Ab

Plasmapheresis

- Fast, effective method of eliminating DSA
- Used in combination with other therapies
- Adverse effects:
  - Nonselective removal of proteins, bleeding diatheses, volume contraction, requires replacement fluid (albumin), allergic reactions, bld borne pathogens, need HD access
- Dose:
  - 1-1.5 total plasma volume QD or QOD (3 to 6 treatments), followed by maintenance PP
  - Decision to stop PP should be based on:
    - elimination of donor-directed HLA antibody
    - establishment of good graft function
    - graft failure
- Cost: 18000NT per treatment

Apheresis Guidelines

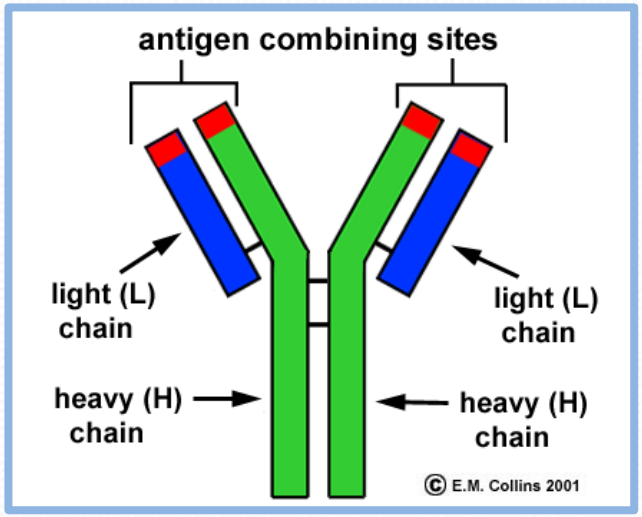
considered a therapeutic option when AMR has been confirmed by Bx and/or + DSA & immunosuppressive treatment has not been effective.

Singh et al, Transplantation Review, 2009
Apheresis Guidelines, 2009

Cytomegalovirus

- Most common viral infection after transplantation.
- Various degrees of severity:
  - Asymptomatic CMV viremia
  - CMV syndrome (viremia plus constitutional symptoms)
  - CMV end-organ or invasive disease (hepatitis, gastritis, colitis, pneumonitis)
- Risk factors:
  - Use of antibody induction
  - Donor seropositive, recipient seronegative status

Inhibition of Antibody



Immune Globulin

Highly purified IgG from large pools of human plasma diluted in sterile water +/- glucose, sodium.

Non-FDA labeled use

- Action:
  - immunomodulatory effects on T cells, macrophages, cytokine synthesis, B-cell function & regulatory action on complement system
  - Down regulates antibody/blocks HLA Ab from binding to targets
  - T & B cell suppression
- Adverse effects:
  - Arthralgias, mylagias, HA, HTN, hypotension, MI, Hypercoagulability, allergic reactions, volume overload, AKI
- Dose:
  - T ½ = 3 weeks
  - Range 100 mg/kg to 2 gm/kg
  - 20,000NT for 100mg/kg dose

Singh et al, Transplantation Review, 2009
Micromedex

Cytomegalovirus

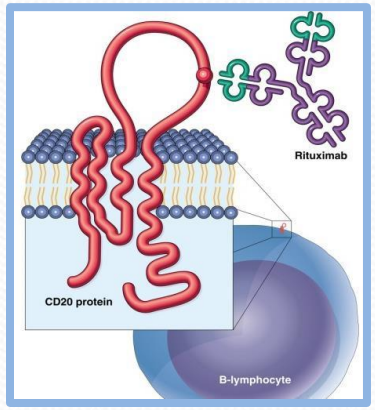
- Clinical presentation:
- Asymptomatic (detected on screening)
- Neutropenia
- Malaise & constitutional symptoms
- GI CMV: gastritis, colitis, esophagitis
- Clinical hepatitis, pneumonitis
- Prophylaxis:
- All patients at risk (D+/R+, D-/R+ or D+/R-) receive valganciclovir prophylaxis for 4.5-6 months.
- “Preemptive” strategy with CMV PCR monitoring.

Suppression/Depletion of B-cells

Rituximab

Genetically engineered chimeric MoAb w/ mouse fused with human IgG.

- Indication:
  - FDA approved for Non-hodgkin's Lymphoma, rheumatoid arthritis. Use for AMR is off label.
- Action:
  - binds to the CD20 antigen located on pre-B & mature B lymphocytes: mediates B cell lysis
  - Depletes CD19 & CD20 (Chemical splenectomy)
  - No effect on plasma cells
- Adverse effects:
  - Infusion and hypersensitivity reactions, cytopenias, fever, infection risk including association with BK
- Dose
  - 375 mg/m^2 BSA IV
  - Duration of treatment ?
  - 50000NT/500mg



Singh et al, Transplantation Review, 2009
Micromedex

Depletion of Plasma cell

Bortezomib

Reversible proteasome inhibitor

- Indication: FDA approved for multiple myeloma. Use for AMR is off label.
- Dose: 1.3 to 1.5 mg/m^2 IV day 1, 4, 8, 11.
- Adverse effects:
  - Neuropathy, plt, WBC, GI symptoms
- Cost ~50-60K NT per injection

UW experience:

used in kidney, liver and pancreas AMR

Steroids + PP + IVIG + Bortezomib +/- ATG

Everly et al, Transplantation, 2008
Djamali et al, Clinical Transplants, 2009
Sollinger et al, WTC Abstract 2010

Complement Inhibition

Eculizumb

- Recombinant humanized monoclonal IgG antibody produced from murine myeloma cells that inhibits the cleavage of C5
- Indication: PNH, atypical HUS
- Blocks graft injury in presence of DSA, may suppress plasma cells.
- Adverse effects:
  - Risk of neisseiria meningitis, need immunization
- Mayo monitored DSA, B & T flow CM, protocol Bx.
- Dose:
  - 600 mg IV injection qw to q2w
  - Duration of therapy unknown
  - Cost $5000 for 300 mg vial

Eculizumab

- Directed against complement protein C5. inhibiting conversion of C5 to C5b and preventing formation of the membrane attack complex (C5–9).
- Prior vaccination against meningococcus and pneumococcus is necessary.

- Desenti J. AJT 2009.

Antibody Reduction Therapy

- **High dose IVIG (1-2 gms/kg)**
  - **Mechanism:**
    - **Anti-idiotypic networks probably important**
    - **Many putative immunomodulatory pathways identified**
  - **Advantages:**
    - **In vitro test for predicting efficacy**
    - **Ease of administration?**
  - **Disadvantages:**
    - **Non-responders**
    - **Different techniques required to follow DSA titers**
    - **Less rapid Ab removal, unproven for high-titer DSA**
    - **Toxicity & batch-to-batch variability**
    - **Unproven for ABOi Tx**

Antibody Reduction Therapy

- **Plasmapheresis/Low Dose IVIg (100 mg/kg)**
  - **Mechanism:**
    - **Rapid reduction in anti-HLA or isoagglutinin Ab**
    - **Induces donor specific unresponsiveness (HLA) or accommodation (ABOI)**
  - **Advantages:**
    - **Predictable kinetics of plasmapheresis**
    - **No evidence of "nonresponders"**
    - **Able to easily follow DSA levels during/after therapy**
  - **Disadvantages:**
    - **DSA may rebound between treatments or if discontinued**
    - **Treatment may be prolonged and immunosuppressive**
    - **Expensive and resource intensive**

Cytomegalovirus

- CMV PCR assays have largely replaced pp65 antigenemia for diagnosis.
- Low-level viremia can be treated with full-dose oral valganciclovir (900 mg bid, dose-adjusted for renal function).
- High-grade viremia or invasive disease requires 2-4 week course of IV ganciclovir, which may be followed by oral valganciclovir.
- Ganciclovir-resistant cases might require foscarnet or cidofovir.

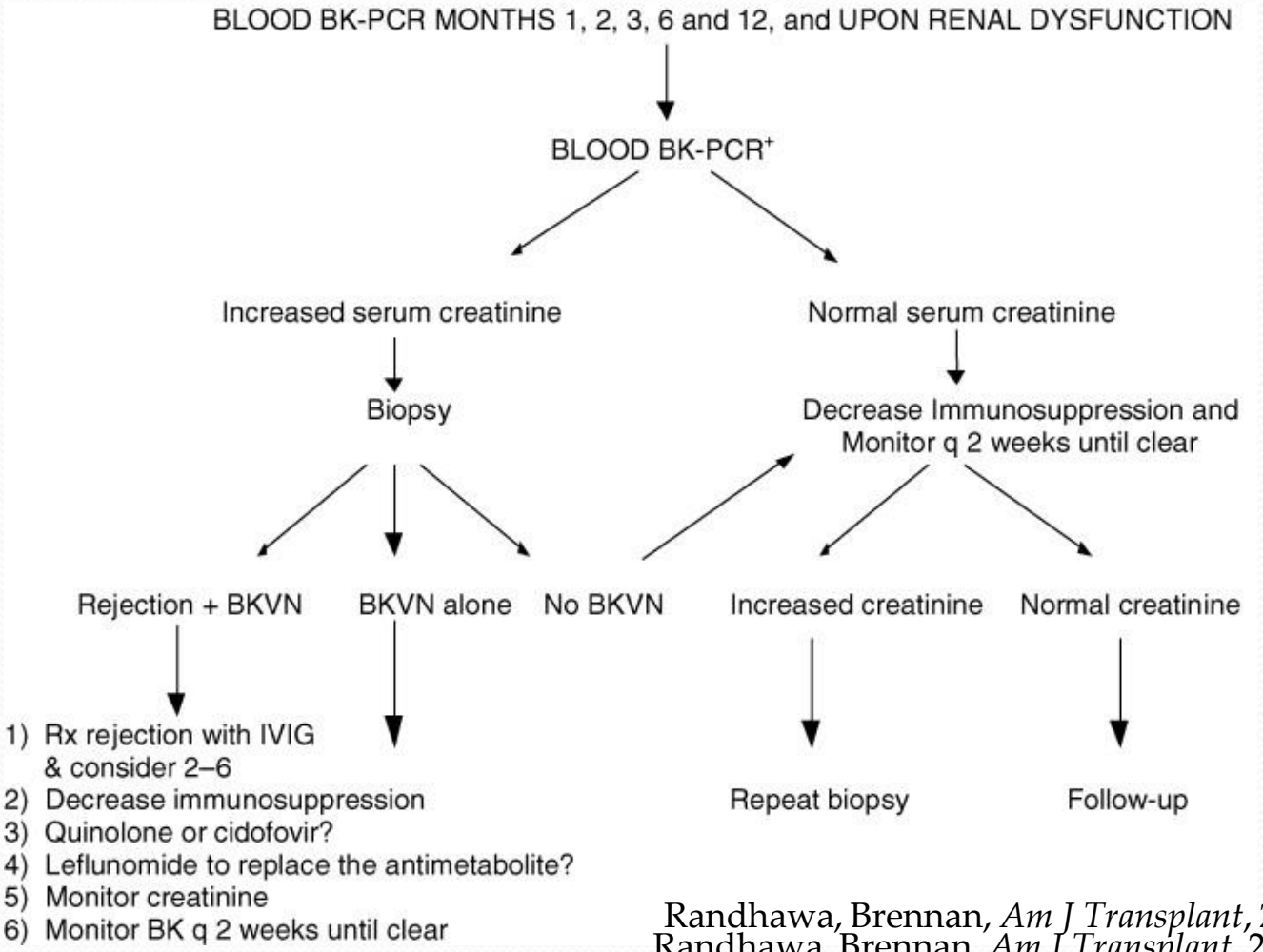
BK Virus Disease

- BK virus is a member of the polyomavirus family.
- An increasingly important cause of allograft failure.
- Latent in genitourinary tract and reactivated by immunosuppression.
- Usually presents in first year after transplantation.
  - Asymptomatic viruria or viremia
  - BK-associated interstitial nephritis
  - BK virus nephropathy

BK Virus Disease

- Screening is by BK viral PCR in blood or urine.
- Presence of BK virus titers >10,000 is suggestive but not diagnostic of BK nephropathy.
- Diagnosis can only be established by biopsy.
- Options for therapy:
- Judiciously reduce immunosuppression
- Use of leflunomide
- IVIG (especially in simultaneous rejection & BK nephropathy).

BK Virus Monitoring Algorithm



Randhawa, Brennan, *Am J Transplant*, 2006;6:2000

Randhawa, Brennan, *Am J Transplant*, 2006;6:2000

Other Infections

- Transplant patients have increased susceptibility to all other common infections.
- Opportunistic infections can also be seen:
- *Pneumocystis jirovicii* pneumonia
- *Candida* infection
- Toxoplasmosis
- Nocardiosis
- *Cryptococcus* infections

Malignancy

- Recipient of organ transplants are at higher risk of developing malignancy.
- May be related to impaired immune surveillance as a result of immunosuppression.
- Skin cancer most common: sun protection ***mandatory***.
- Routine cancer screening.
- Specific malignancies:
  - Kaposi sarcoma
  - Post-transplant lymphoproliferative disorder (PTLD)

Chronic Allograft Dysfunction

- Persistent rise in serum creatinine and worsening GFR over weeks to months is termed chronic allograft dysfunction.
- Histological counterpart is chronic allograft nephropathy (CAN).
- Characterized by nonspecific interstitial fibrosis and tubular atrophy.
- Usually irreversible and will lead to allograft failure and need for dialysis or retransplantation.

Chronic Allograft Dysfunction: Why Do Grafts Fail?

- Chronic low-grade immune injury
- Long-standing hypertension
- Recurrent disease (diabetic nephropathy or glomerulonephritis)
- Repeated episodes of acute rejection
- Donor disease
- Calcineurin inhibitor nephrotoxicity

Thank you for your time and attention