

Novel Targets for Immunosuppression in Clinical Trial



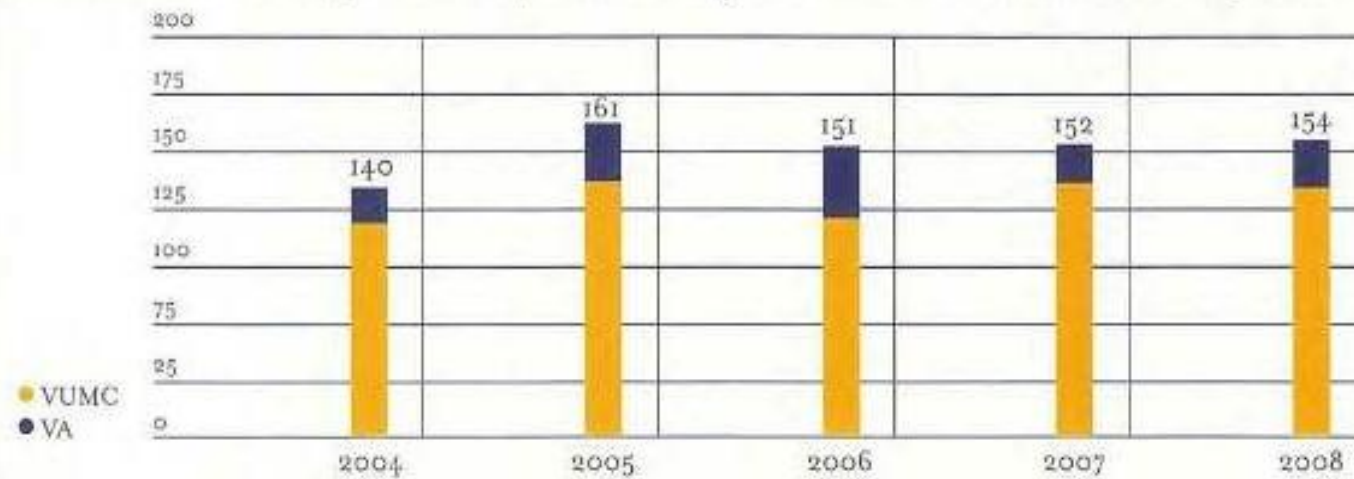
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VANDERBILT UNIVERSITY
MEDICAL CENTER

1 Total Transplants, Vanderbilt/Nashville VA Kidney/Pancreas Transplant Program

Total Number of Transplants Kidney/Pancreas Program, Vanderbilt/Nashville VA, 2004 – 2008



Adult Kidney Transplants VUMC/VA

| | 2004 | 2005 | 2006 | 2007 | 2008 |
|----------------|------|------|------|------|------|
| Deceased Donor | 60 | 62 | 58 | 85 | 85 |
| Living Donor | 61 | 83 | 71 | 55 | 54 |
| Total | 121 | 145 | 129 | 140 | 139 |

Pediatric Kidney Transplants

| | 2004 | 2005 | 2006 | 2007 | 2008 |
|----------------|------|------|------|------|------|
| Deceased Donor | 2 | 3 | 2 | 1 | 2 |
| Living Donor | 6 | 6 | 7 | 4 | 3 |
| Total | 8 | 9 | 9 | 5 | 5 |

Adult Pancreas Transplants

| | 2004 | 2005 | 2006 | 2007 | 2008 |
|-------|------|------|------|------|------|
| SPK | 4 | 5 | 12 | 5 | 9 |
| PAK | 7 | 2 | 1 | 2 | 1 |
| Total | 11 | 7 | 13 | 7 | 10 |

SPK – Simultaneous Pancreas Kidney

PAK – Pancreas After Kidney

2 VUMC/Nashville VA Patient and Graft Survival

Vanderbilt Adult

| | 1 Year | 3 Year |
|---------------------------------|--------|--------|
| Patient Survival | 98% | 94% |
| Graft Survival – Deceased Donor | 93% | 84% |
| Graft Survival – Living Donor | 95% | 93% |

Vanderbilt Pediatric

| | 1 Year | 3 Year |
|---------------------------------|--------|--------|
| Patient Survival | 94% | 94% |
| Graft Survival – Deceased Donor | 80% | 75% |
| Graft Survival – Living Donor | 92% | 85% |

Nashville VA

| | 1 Year | 3 Year |
|---------------------------------|--------|--------|
| Patient Survival | 98% | 96% |
| Graft Survival – Deceased Donor | 91% | 88% |
| Graft Survival – Living Donor | 100% | 100% |

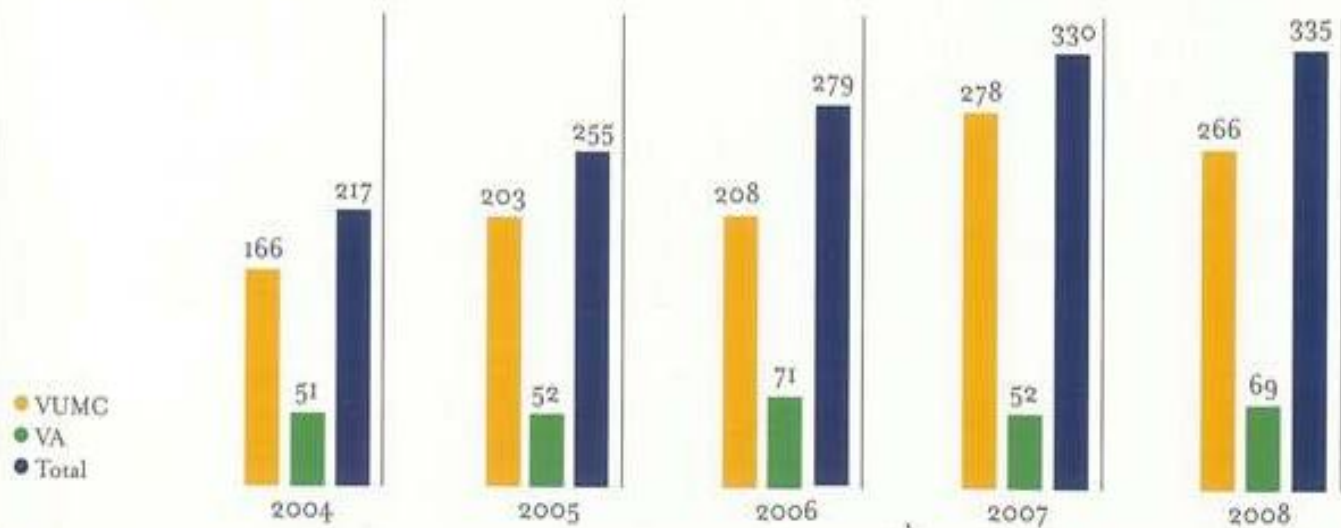
Scientific Registry of Transplant Recipients (SRTR)

www.ustransplant.org

Release Date January 2009

3 Total Waitlist Additions, Vanderbilt/Nashville VA Kidney/Pancreas Transplant Program

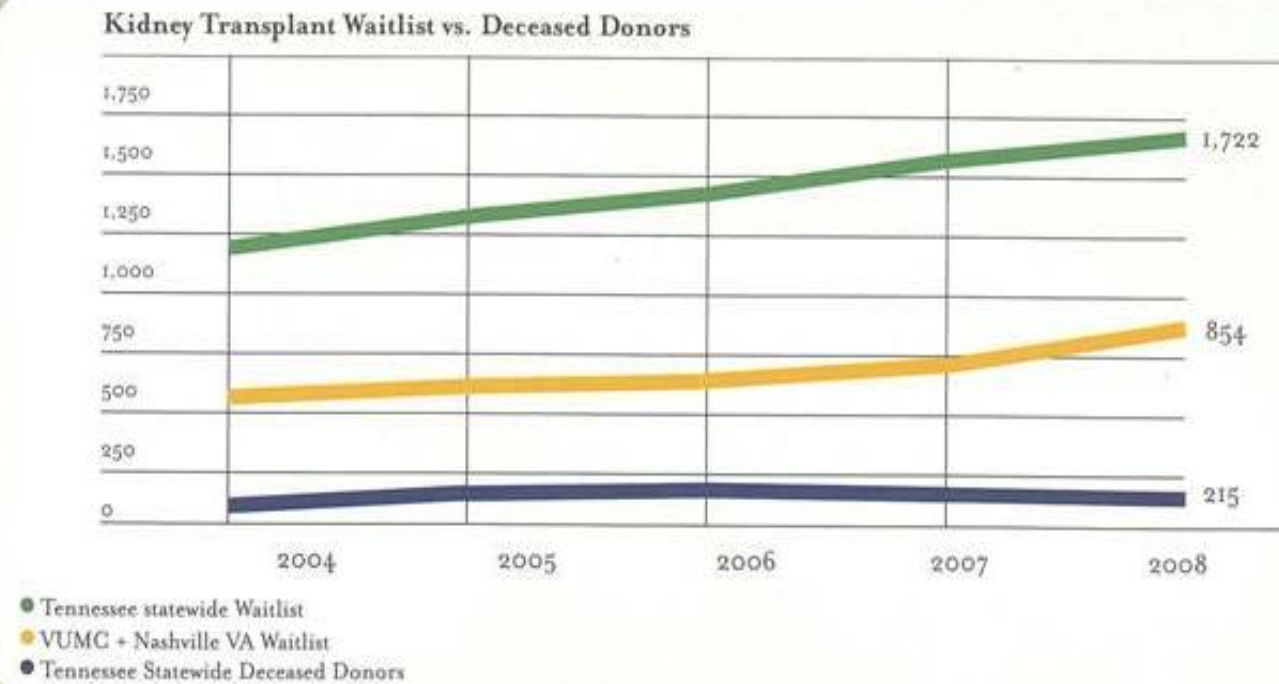
Total Number of Waitlist Additions Kidney/Pancreas Program, Vanderbilt/Nashville VA, 2004 – 2008



4 Median Waiting Time for Deceased Donor Kidney Transplant, VUMC

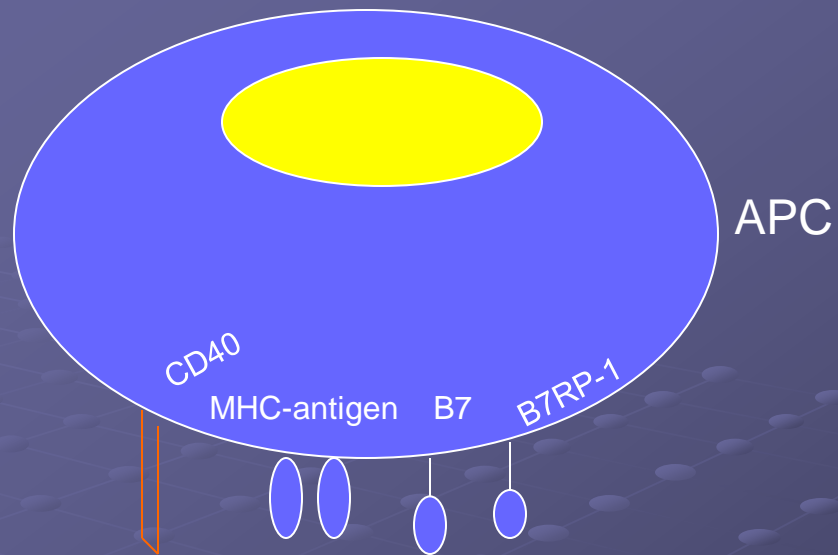
| Calendar Year | Median (Days) |
|---------------|---------------|
| 2008 | 561 |
| 2007 | 415 |
| 2006 | 548 |
| 2005 | 292 |
| 2004 | 609 |

5 Patients Waiting for a Kidney Transplant vs. Deceased Donor Kidneys Available

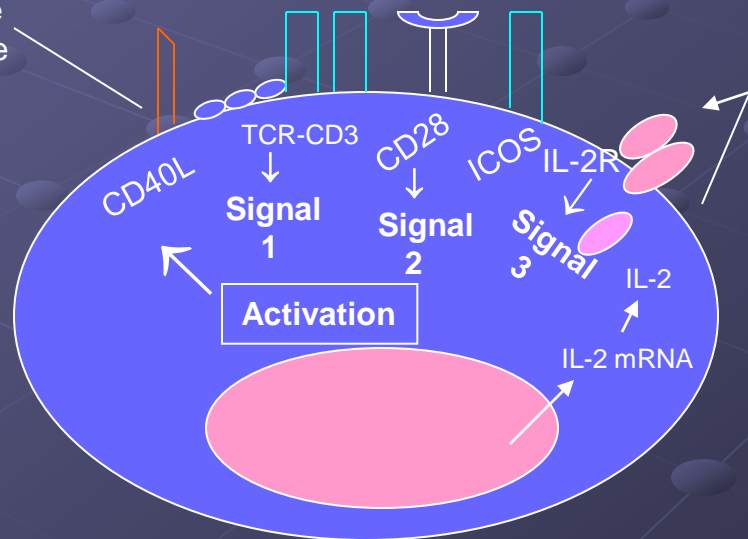


New Immunosuppressive Transplant Medications

- ISA 247 - CNI
- Lea29Y – Co Stimulatory Blockade
- Efalizumab - Co Stimulatory Blockade
- AEB – PKC Inhibition
- CP690550 – JAK3 Inhibition
- KRP – 203 Lymphocyte Trafficking Inhibition

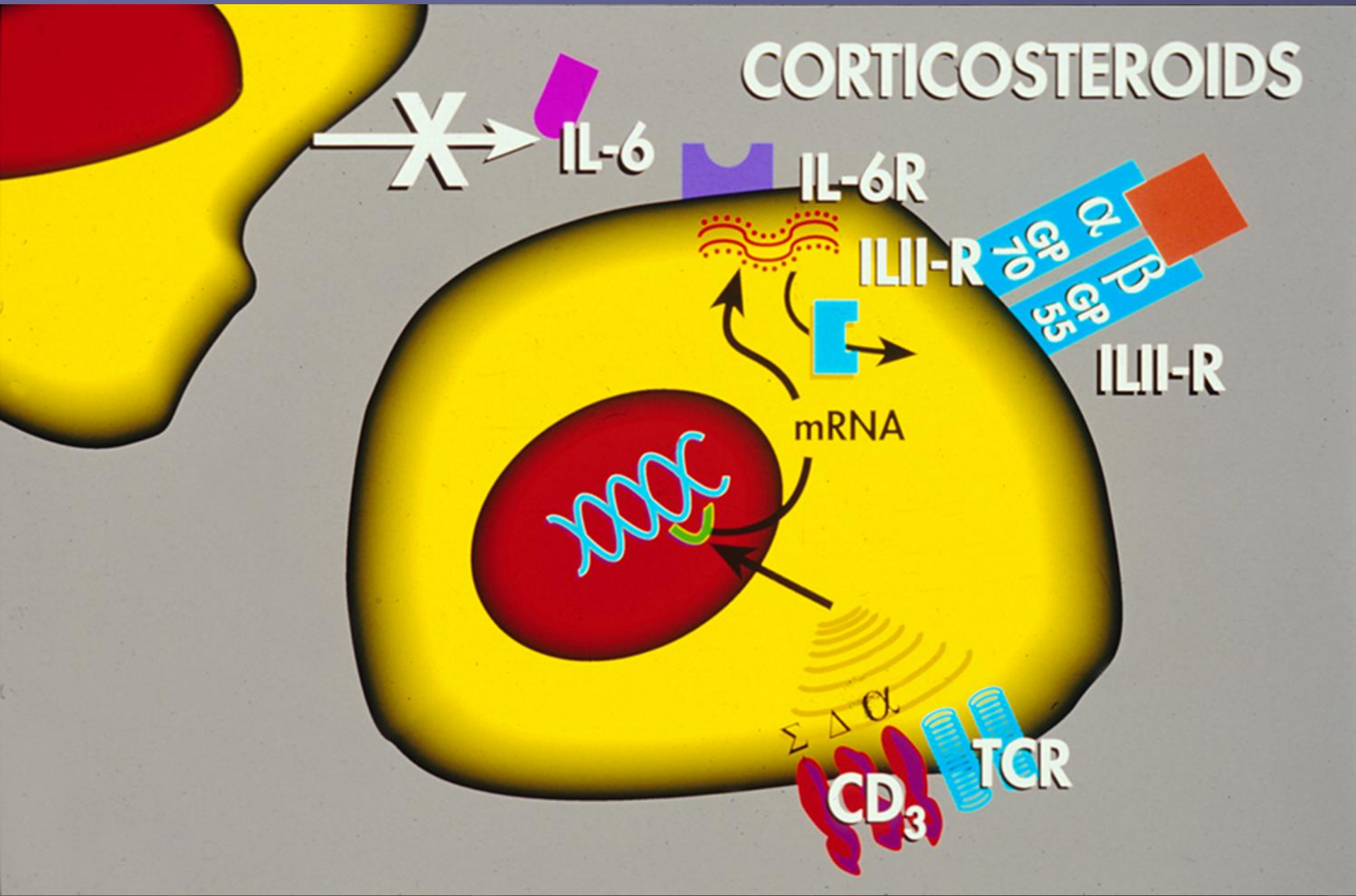


Immune
synapse

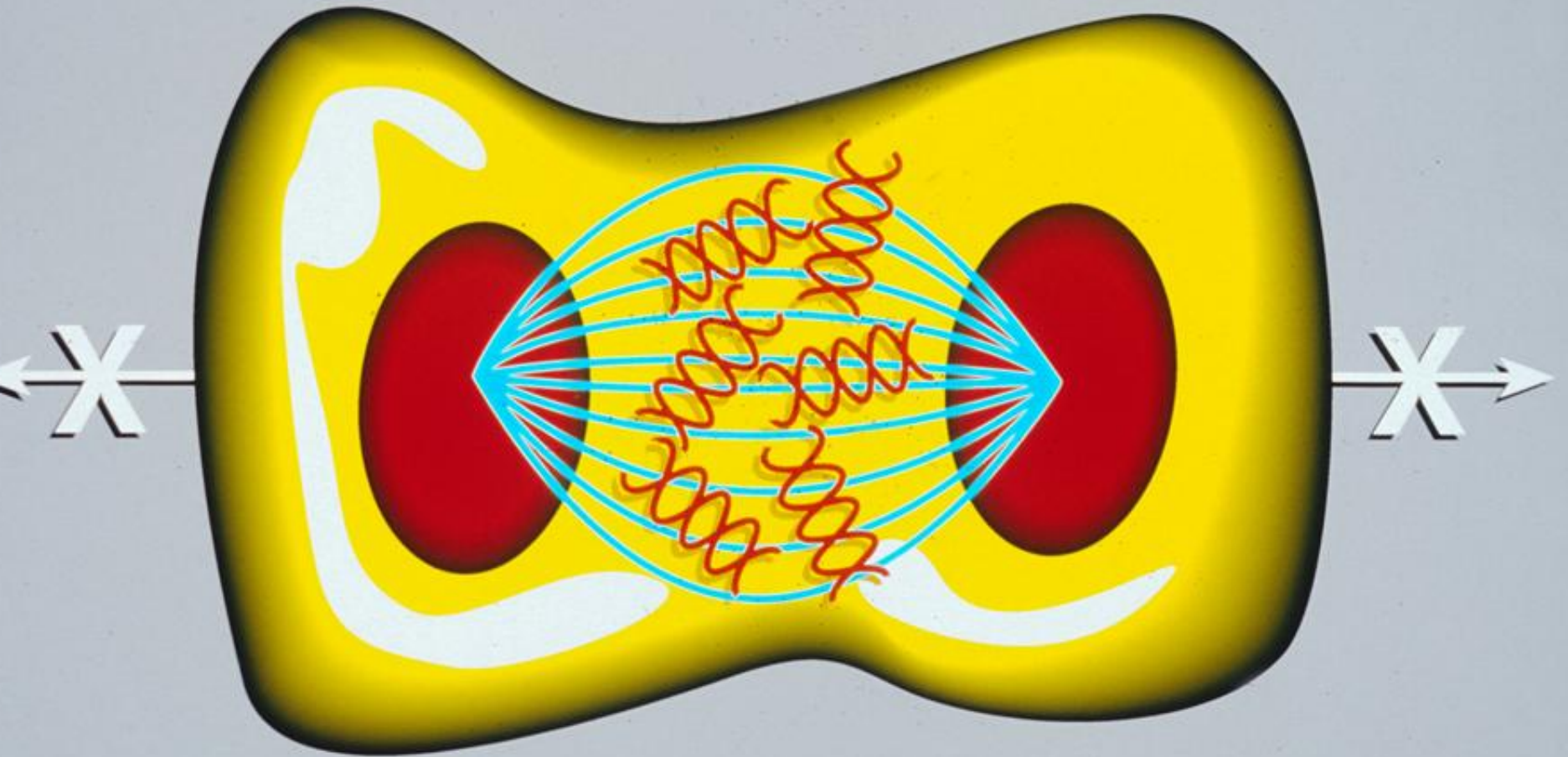


Naïve T cell

CORTICOSTEROIDS

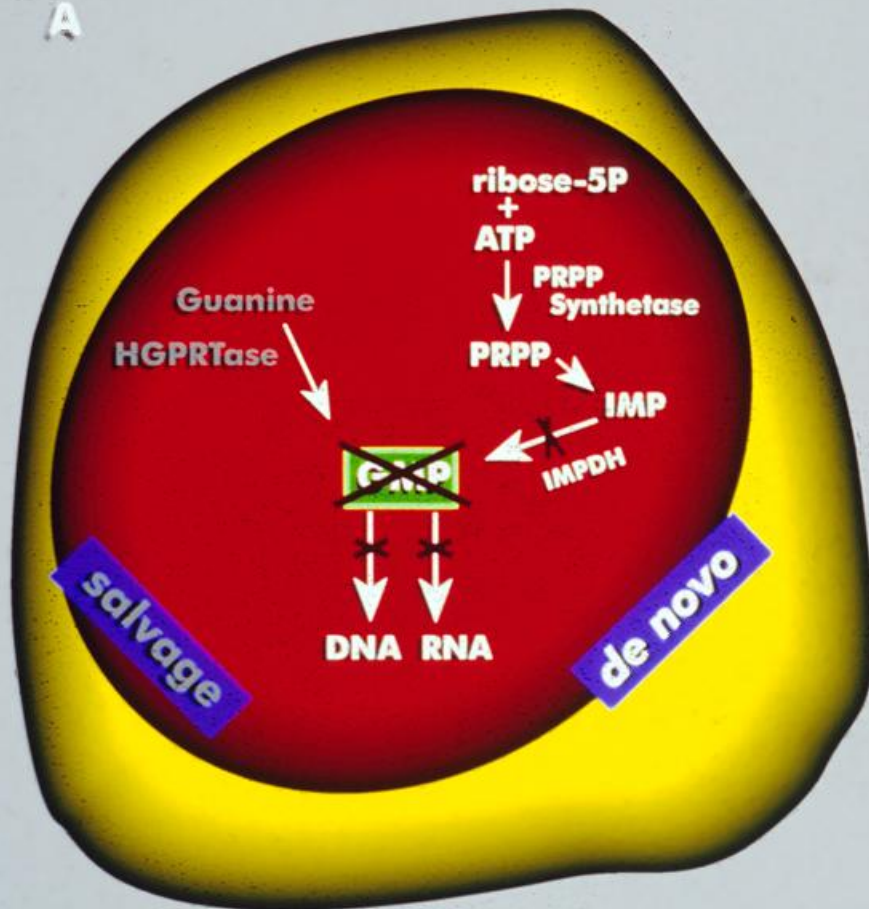


Antimetabolites - Azathioprine, Mycophenolate
Mofetil, Brequinar



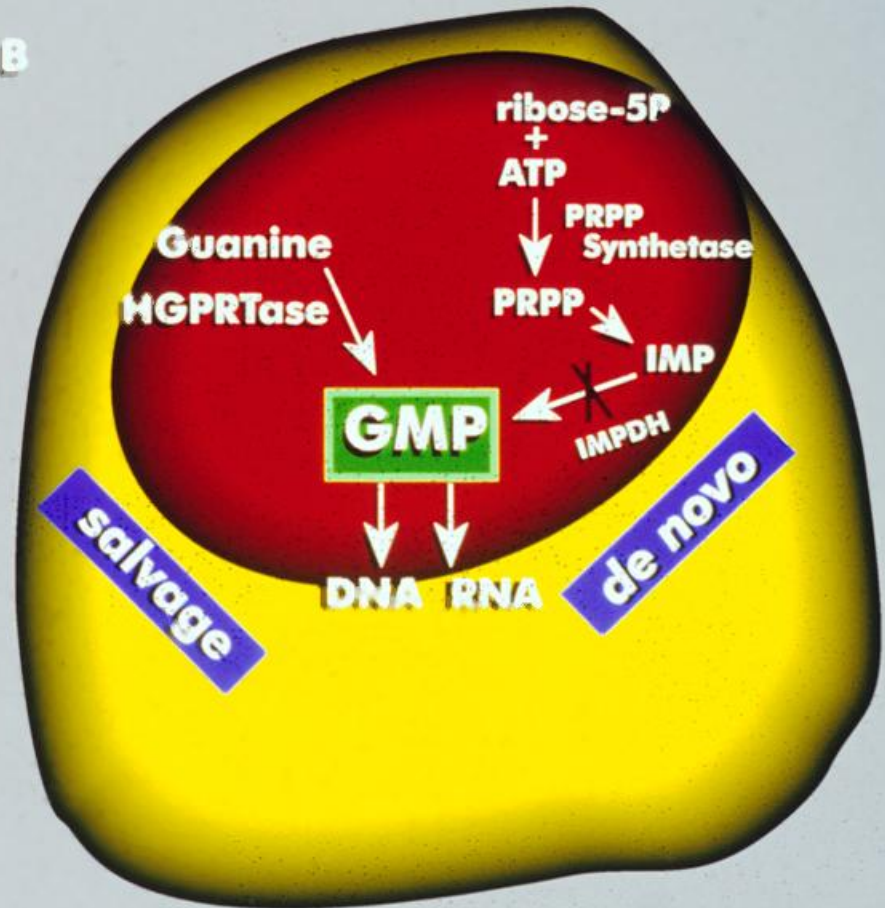
Mycophenolate Mofetil

A

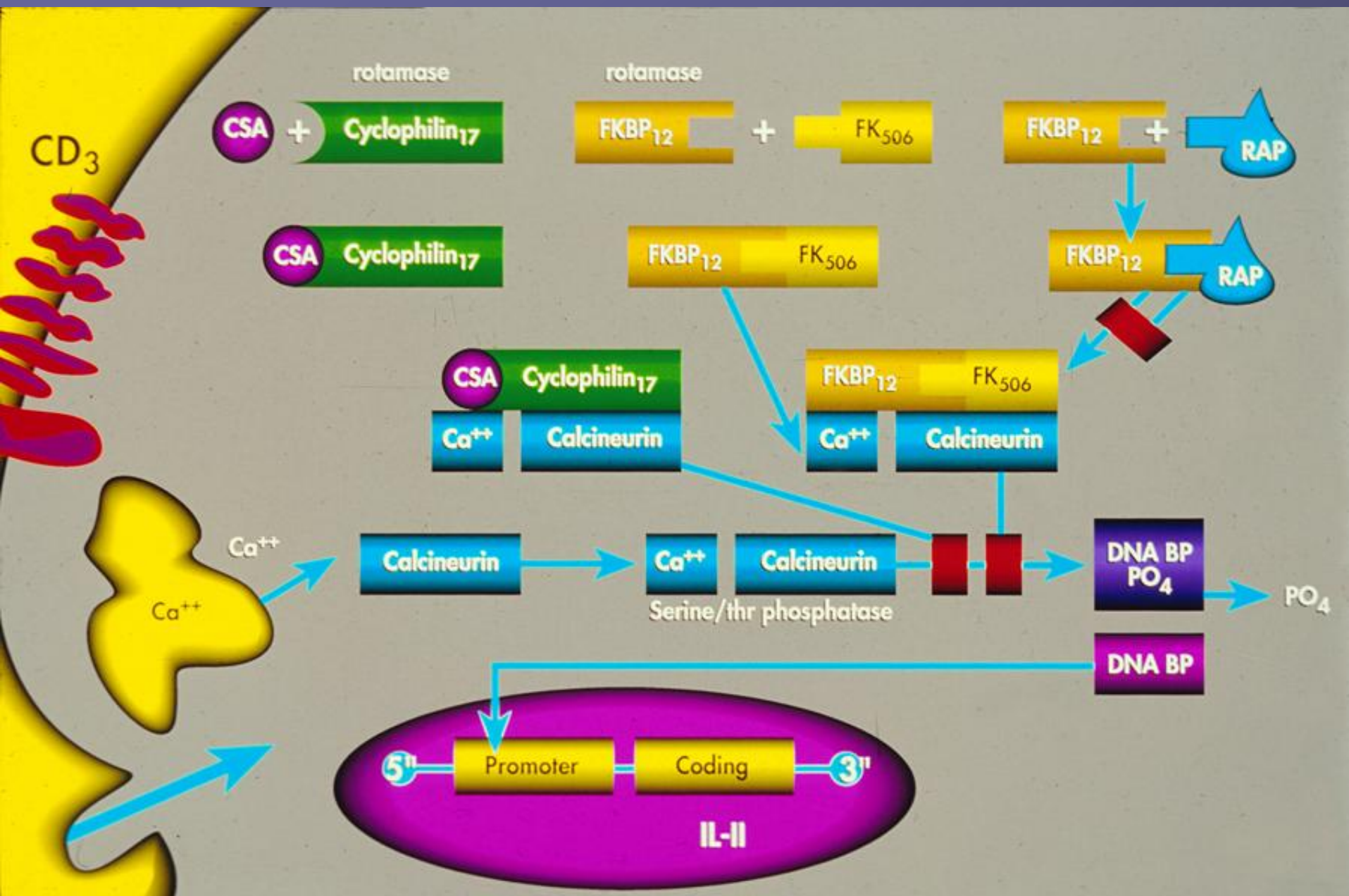


Lymphocyte

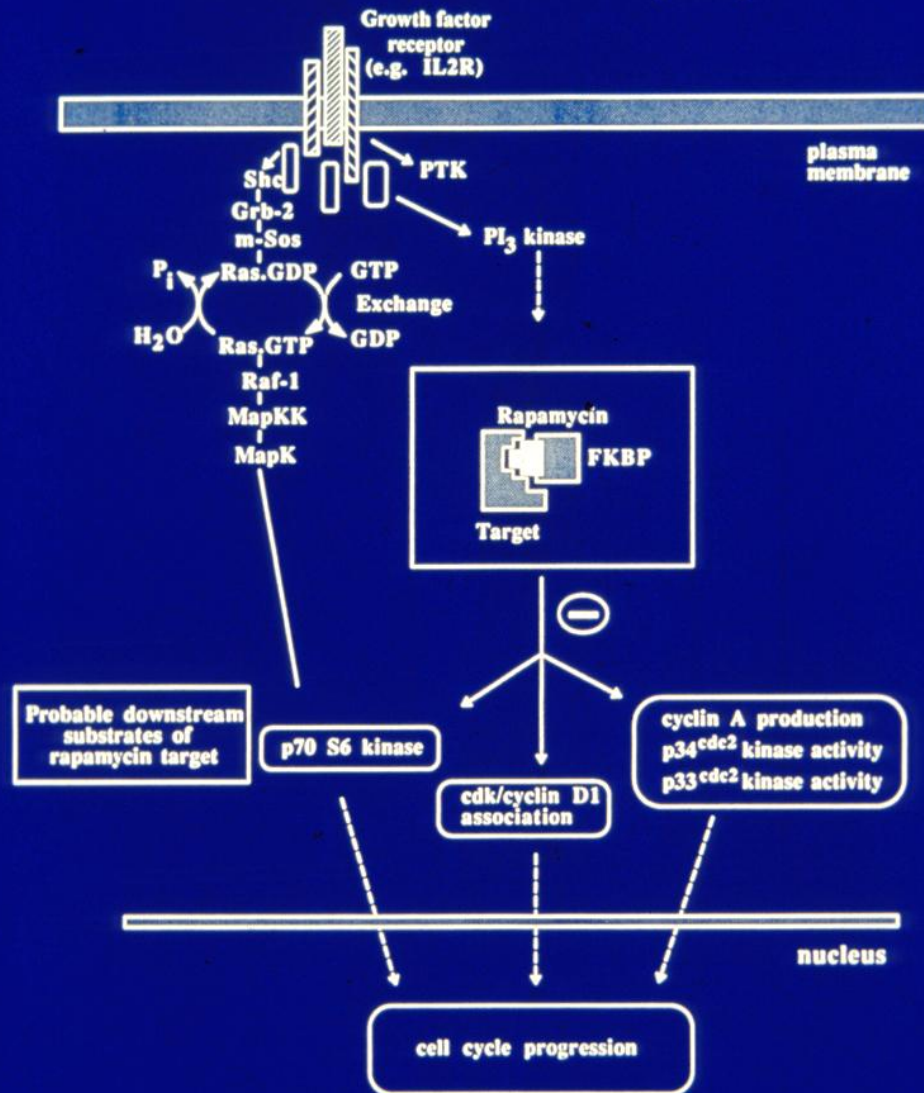
B



Parenchymal Cell



Mechanism of Action of Rapamycin



Calcineurin Inhibition

ISA 247

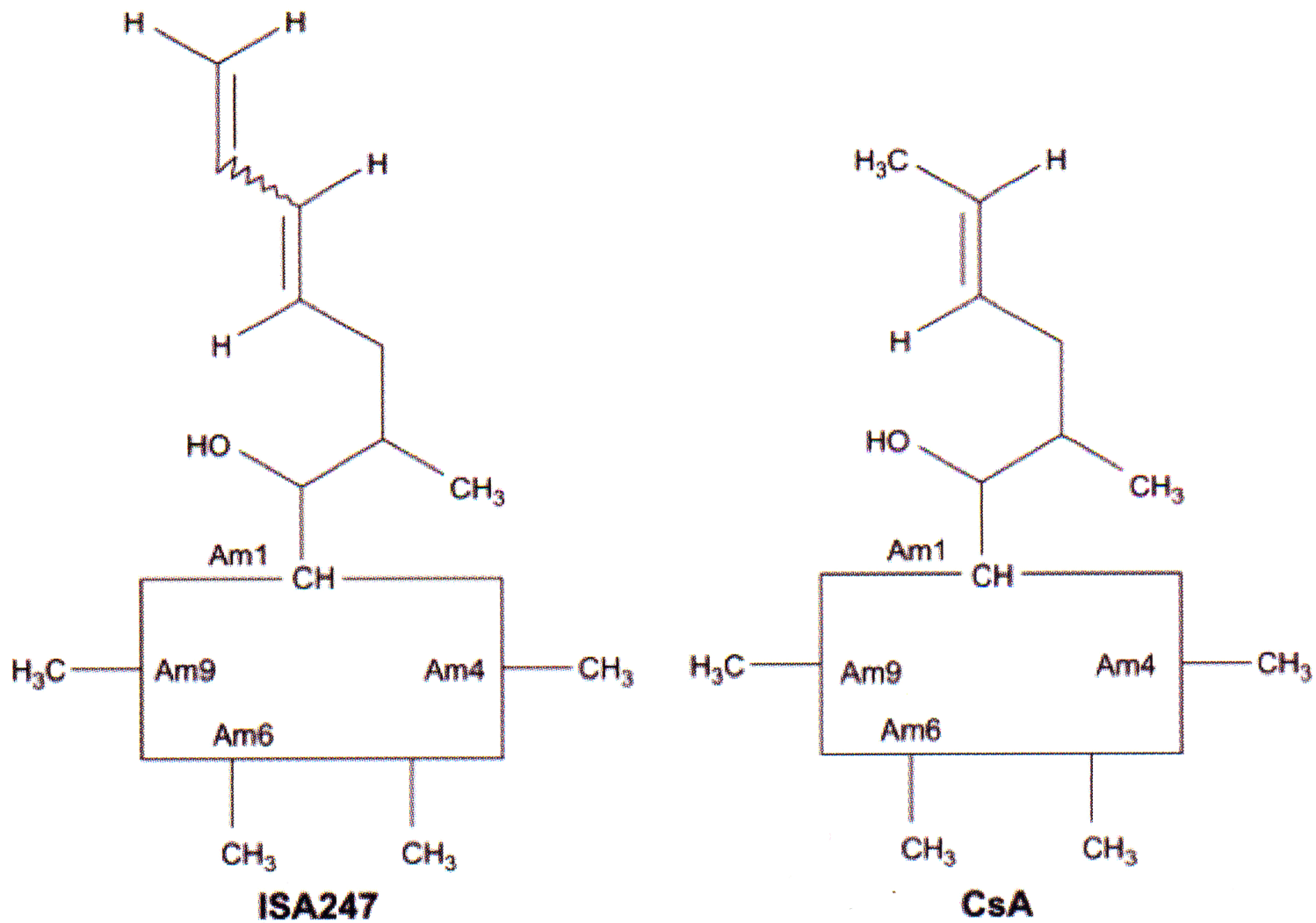
- Oral analogue of CS
- Modification of the functional group on AA I
- More potent CNI than CSA
- No nephrotoxicity in animals
- Prolongs organ transplants in animals
- Phase III Psoriasis trial underway

Aspeslet et.al. Trans Proc. 33:2001

Stadler et al. J Heart Lung Trans. 22:2003

Gregory et al. Transplantation 78:2004

Structure of ISA 247 and cyclosporine A

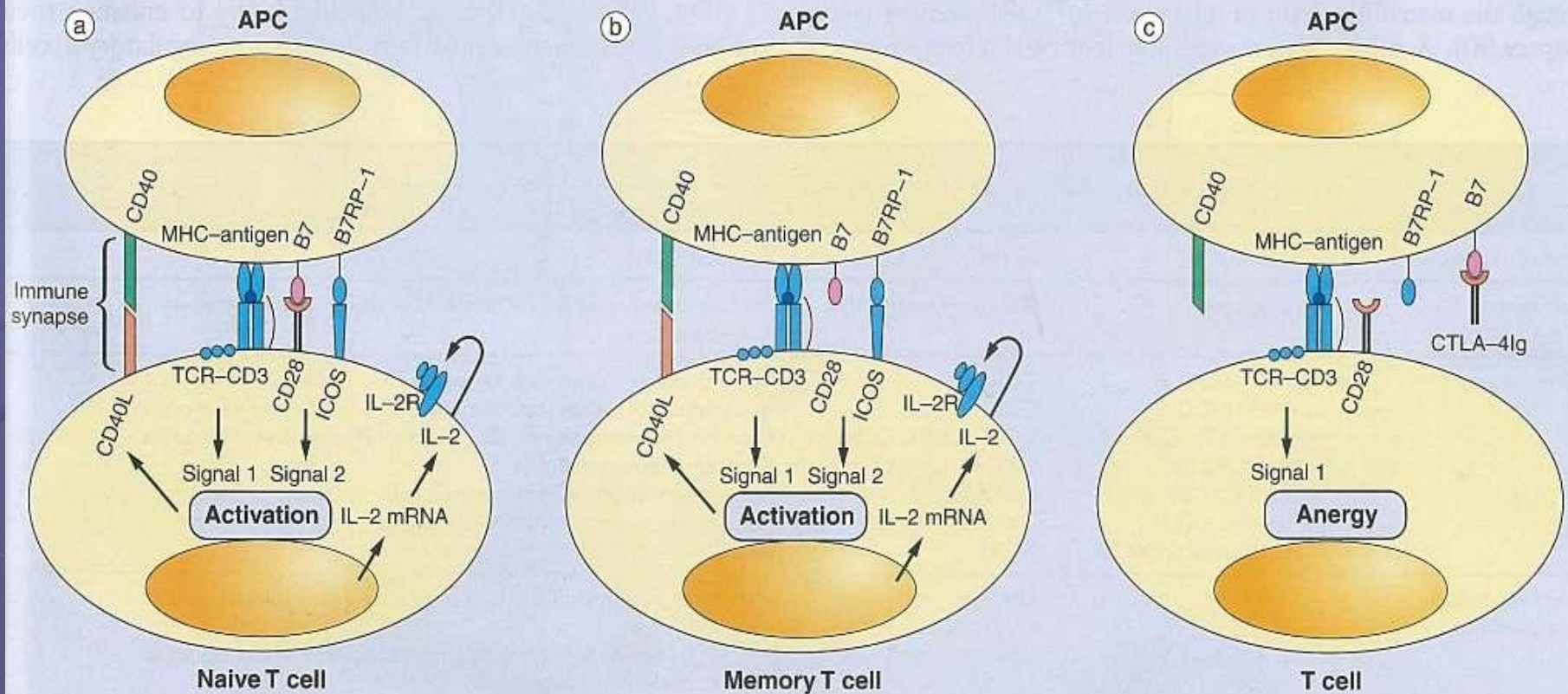


CNI

ISA 247

- 6 month phase II renal transplant study (n=120).
- ISA 247 (0.4, 0.6, 0.8 mg/lg 2x/d) vs. TAC, IL2R-ab Induction, Maintenance: MMF + Steroids
- AR 14%, 12%, 0% ISA 247 v
14% TAC

Costimulation in Tcell activation



Interference with Adhesion Molecule Directed Signal Two

- CD 154 - C40 Pathway
- CD 28 - CD80/86 Pathway
- LFAI – ICAM Pathway

CD 154 – CD 40 Pathway

- Humanized moab directed to D 154
- proof of principle in non-human primates

Kirk et al. Nat Med 5:1999

CD 154 – CD 40 Pathway

- **Phase 1 human trial of Hu5C8 – humanized α CD 154 MOAB**
 - **Short course of steroids**
MMF
CNI free
 - **Halted because of thromboembolic events**
Kirk et al. AJT 1:2001; Andre et al. Nat Med 8:2002.
 - **Complication not epitope specific, other α CD 154 MOABs had same complication**

CD 154 – CD 40 Pathway

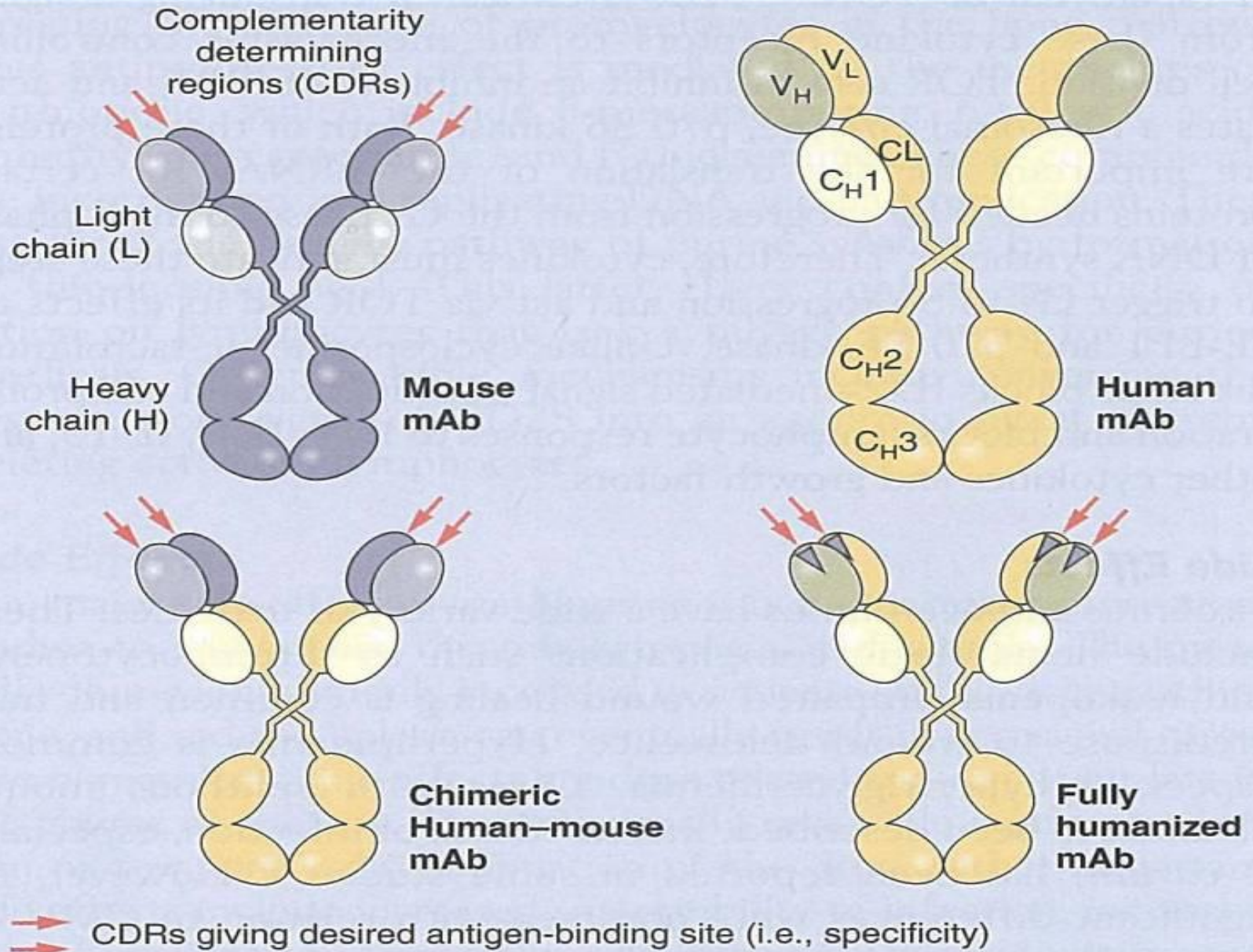
MOAB targetting CD 40 have not been shown to be procoagulant and may be prepared for study

CD 28 – CD 80/86 Pathway

- 1st studied reagent CTLA4Ig
 - fusion protein
 - extra cellular domain of CTLA4
 - Fc portion of human Ig
- Excellent pre clinical results but less spectacular non-human primate data

Sayegh and Turkha NEJM 338:1998

Chimeric versus humanized monoclonal antibodies



CD28 – CD80/86

- LEA 29Y (Belatacept)
 - Leucine 104 → Glutamate
 - Alanine 29 → Tyrosine
- 2nd generation CTLA4Ig
- Substitutions increase theoretic efficacy
 - 2 fold ↑ binding to CD 80
 - 4 fold ↑ binding to CD 86
 - 10 fold ↑ T cell function inhibition

CD28 –CD 80/86 Pathway

LEA 29Y Phase II Human Trial

- n = 218
- 3 Arms
 - High Dose LEA 29Y
 - Low Dose LEA 29Y
 - CSA Control
- Induction: basiliximab
- maintenance: MMF + Seroids
- Results:
 - a) AR similar
 - b) GFR, CAN rate, metabolic complications favored LEA 29Y

CD28 – CD 80/86 Pathway

LEA29Y

- Phase III in ECD kidneys are in standard donor recipients.
- Conversion trial (CNI)
- Rapid steroid withdrawal trial
(thymoglobulin + LEA 29 Y + either MMF or mTOR I)

Phase III Pivotal Trials of Belatacept (LEA 29Y)

- Two critical international, randomized, prospective, multicenter outcomes trials
- Benefit- standard criteria donors-Vincenti et al AJT 10:535-546,2010.
- Benefit extended-extended criteria donors-Durrbach et al AJT 10:547-557.2010.
- Three year follow-Pestana et al AJT 11:630-639,2012.

Phase III Pivotal Trials of Belatacept (LEA 29Y)

Results

- Equal graft and patient survival as much as 3 years later
- Small increase in early easily reversible biopsy proven rejection
- A few cases of lymphoma in EBV negative recipients
- Received FDA Approval 2011

CD28 – CD 80/86 Pathway

LEA 29 Y

- After periop induction LEA 29 Y administered monthly
- Parental administration reduces non-adherence to daily pill regimens
- A subcutaneous preparation would increase patient acceptance.

Belatacept Issues

- Use only in EBV negative recipients
- Monthly IV infusion: positive- no issues of adherence; Neg- needs arrangement and payment
- Still determining how best to use- trial for conversion and for RX of *IFTA* about to begin

LFA I – ICAM Pathway

Efalizumab – Humanized moab α CD11a

- LFA I – 2 chain heterodimer β 2 integrin (α + β Chain)
- α chain = CD 11a
- β chain = CD 18
- Approved for use in psoriasis

LFA I – ICAM Pathway

Efalizumab Phase I/II human Trial

- Full dose CSA + MMF _ steroids v. half dose CSA + mTOR I + steroids
2 Doses of efalizumab (0.5 or 2.0 mg/kg)
q week x 12 weeks
- AR at 6 mos 11% (4/38)
- Full dose CSA + high efalizumab
abandoned because of 3 cases PTLD

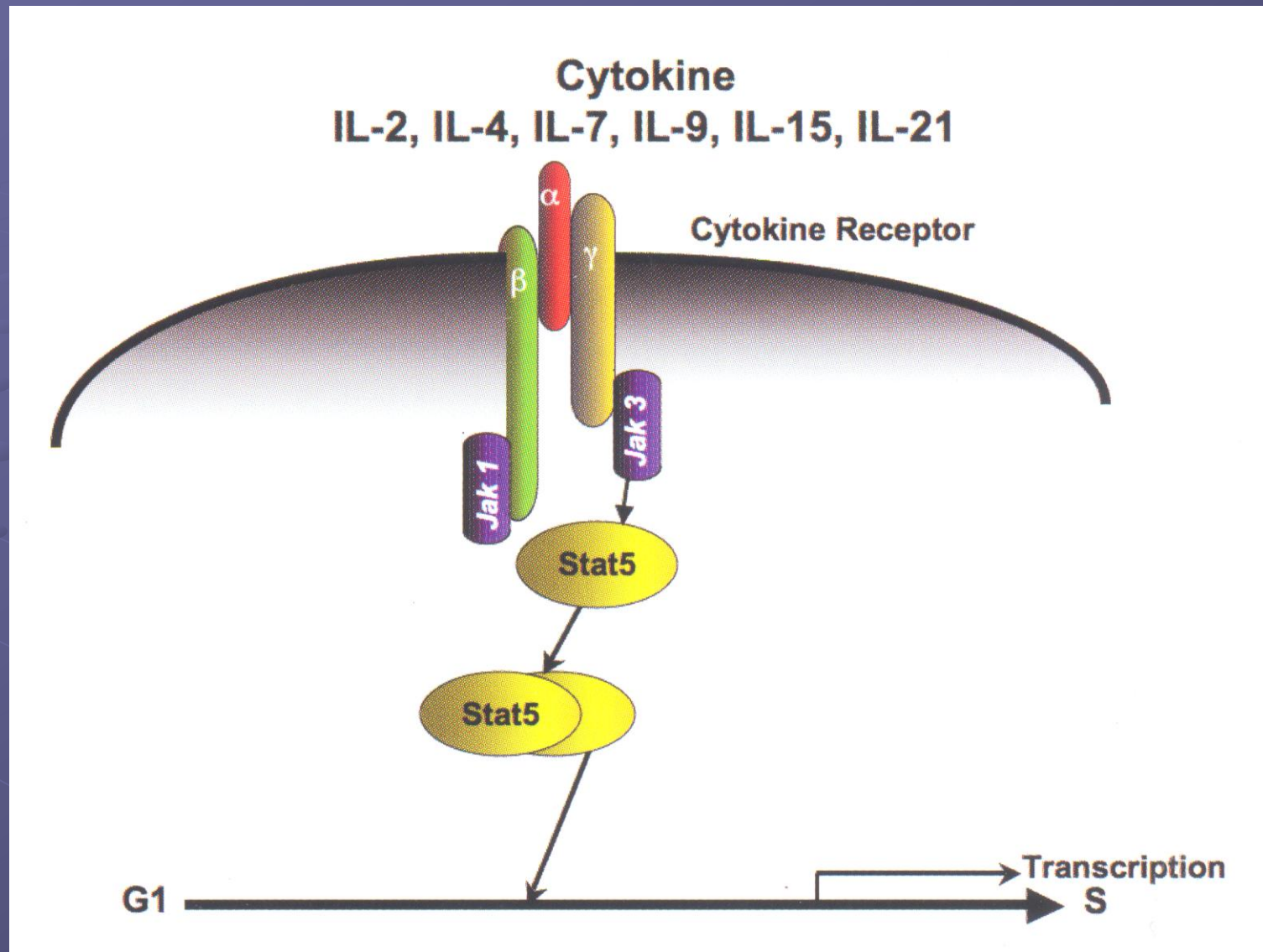
Intracellular Signalling

- Protein Kinase C Signalling Couples T cell receptor engagement to downstream activation (Signal One)
and
Costimulation (CD28) to gene activation (Signal two)

Protein kinase C (PKC) isoenzymes

| Isoform | Predominant Tissue Expression | PKC Knockout Phenotype |
|-------------------------------------|-------------------------------|---|
| Conventional © PKC subfamily | | |
| α | Ubiquitous, high in T cells | T-cell defect |
| β | Ubiquitous, high in B cells | Neutrophil, B-, and mast-cell defects |
| γ | Brain | Not determined |
| Novel (n) PKC subfamily | | |
| δ | Ubiquitous, high in T cells | Hyperproliferative B and mast cells; B-cell anergy defect |
| ϵ | Ubiquitous, high in T cells | Macrophage defect |
| η | Ubiquitous, high in T cells | Not determined |
| θ | T cells, platelets, monocytes | T-cell signaling defect |
| Atypical (a) PKC subfamily | | |
| ζ | Ubiquitous | B-cell signaling defect |
| τ | Ubiquitous | Not determined |

Site of action of the JAK 3 inhibitors.



Intracellular Signalling

- PKC α, β, θ important in Lymphocyte Signaling
- PKC θ T cell restricted, mediates transcription factor protein-1 & Nf κ B (on ko mice)

Table 1: Small molecules in clinical trials

Table 1: Small molecules in clinical trials

| Drug | Pathway | Phase of Study | Maintenance Regimen | Results/1° Endpoint |
|----------------------|---------------------------------------|----------------|--|---|
| ISA247 (Isotechnika) | Calcineurin inhibitor (signal one) | Phase II | Three dose levels of ISA247 versus Tac. All patients are treated with MMF + CS | 1° Endpoint: similar efficacy and renal function in all treatment groups |
| AEB07 (Novartis) | Protein kinase C (signal one and two) | Phase II | AEB + Everolimus + CS | 1° Endpoint: acute rejection |
| | | Phase II | AEB + Tac + CS with Tac withdrawal at 3 months versus Tac + MPS + CS | Study halted because of an increase in acute rejection after Tac withdrawal. |
| | | Phase II | AEB + MPS + CS versus Tac + MPS + CS | Study halted due to increase in acute rejection |
| CP 690,550 (Pfizer) | Janus kinase 3 (signal three) | Phase Iia | CP 690,550 15 mg or 30 mg bid + MMF + CS versus Tac + MMF + CS | Comparable efficacy between all treatment groups. More infections in high CP690, 550 group. |
| | | Phase IIb | Clinical trial in progress with 2 doses CP 690,550 15 mg and 10 mg bid with MMF + CS | 1° Endpoint: acute rejection |

CS = corticosteroids; Tac = tacrolimus; MPS = mycophenolic sodium; MMF = mycophenolate mofetil.

Intracellular Signalling

AEB

- oral low MW inhibitor of PKC isoforms
- inhibits T cell activation and IL 2 synthesis
- little effect on NFAT
- No effect on cytokine directed cell proliferation-(signal three)

Intracellular Signaling

AEB Preclinical

- Prolonged heart and kidney grafts

Bruns et al AJT 6:2006

Wagner et al. AJT 6:2006

- Prolonged Kidney transplantation in cynomolgus monkey

Bigaud et al AJT 6:06

Intracellular Signaling

3 Phase II human AEB Trials

1. 12 mos. 3 Arms – AEB + TAC; AEB + reduced TAC; MMF + TAC- induction α IL2 R maintenance: steroids + MMF
2. 12 mos. 2 ARMS – AEB vs TAC; Induction α IL2 R - maintenance : steroids + MPA
3. 12 mos. 2 ARMS – AEB vs CSA- Induction - IL2 R , maintenance: mTor I + steroids

Intracellular Signaling from the Cytokine Receptor

CP690550

- JAK 3 inhibitor
- JAK 3 resistant to hematopoietic cells
- JAK 3 associates with common α chain of cytokine R for IL2, 4, 7, 9, 11, 21
- Dimerizes STAT 5 after phosphorylation, then can traverse nucleus and activate gene regulation of cell division

Intracellular Signaling from the Cytokine Receptor

CP690550

Preclinical Studies

- Murine heart transplant (Changelian et al., Science 302:2003)(Kudlacz et al., AJT 4: 2004)
- Non-human primate studies- good graft survival, no nephrotoxicity ↑ polyoma, anemia, GI sx (Borie et al. Transplantation 79:2005)

Intracellular Signaling from the Cytokine Receptor

CP690550

Phase II human Kidney transplant Trial

- 3 ARMS: 15mg CP690550 BID vs. 30mg. CP690550 BID vs. TAC BID
- Induction IL2R ab
- Maintenance: MMF + Steroids
- Results
 - Comparable AR
 - 100% pt and graft survival
 - No PTLD
 - CMV & polyoma in high dose group
- Study into 2 yr extension
- 2nd phase II against CSA underway

Lymphocyte Trafficking

- Selective agonist at G protein coupled Sphingosine 1-phosphate receptor
- Thought to avoid FTY 720 side effects
- Prolonged rodent heart transplants

Kahan et al. AJT 7: 2007

Shimizu et al. Circulation 111:2005

Lymphocyte Trafficking

FTY 720

- 2, Phase III renal Transplant trials showed no benefit
- Important side effects
 - Bradycardia
 - Macular edema
- Studies in transplant abandoned

Tedesco – Silva et al. Transplantation 82: 2006

Salvadori et al. AJT 6:2006