Transplantation

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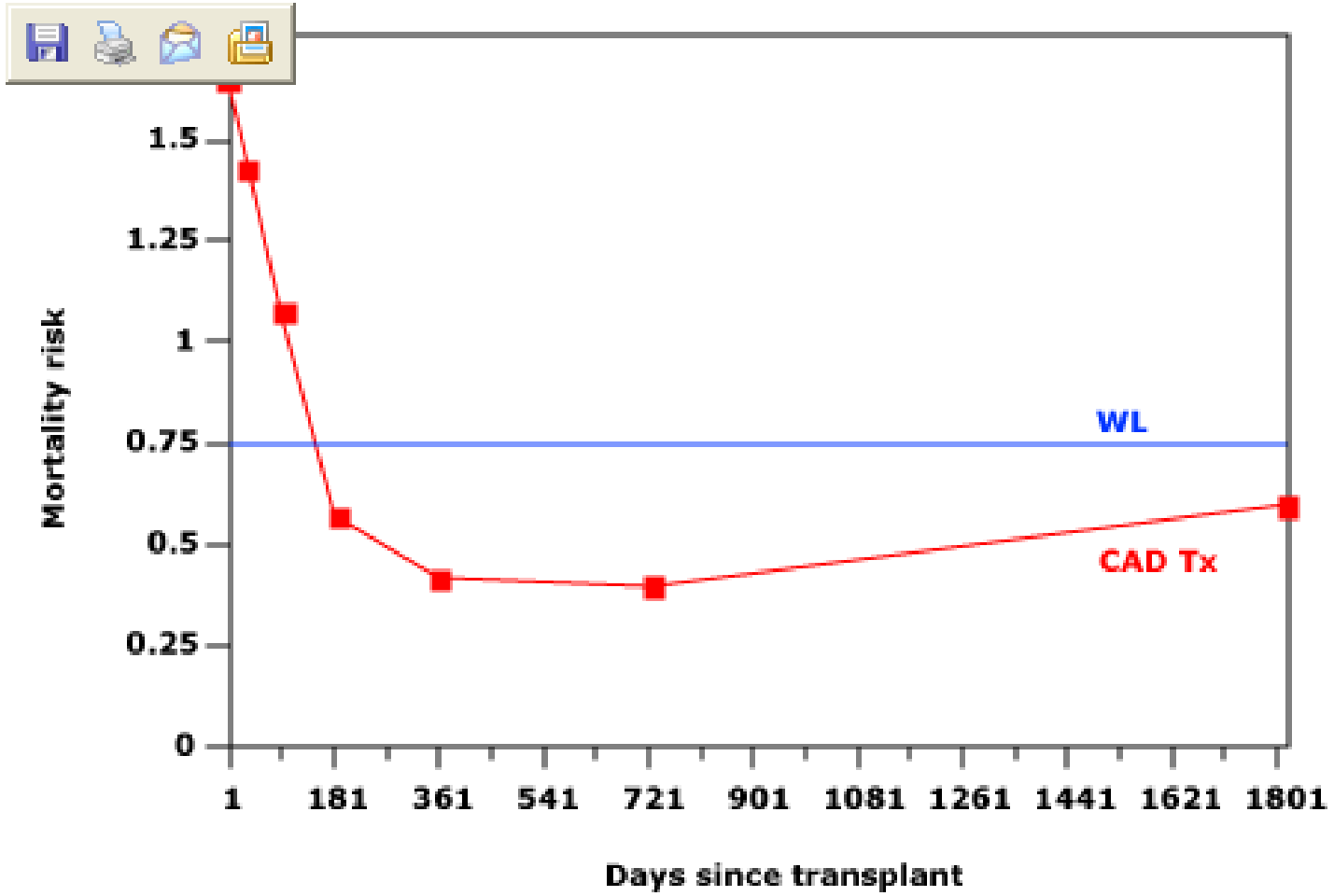
"I know so much that I don't know where to begin."

You have been on dialysis for 3 years, a cadaver transplant is offered to you. Do you accept?

A. No
B. Yes, because I love immunology
C. Yes, because I dislike dialysis
D. Yes, because I'll live longer

Mortality risk of recipients of cadaveric renal transplants vs. wait-listed patients with ESRD who were on dialysis for at least 2 years



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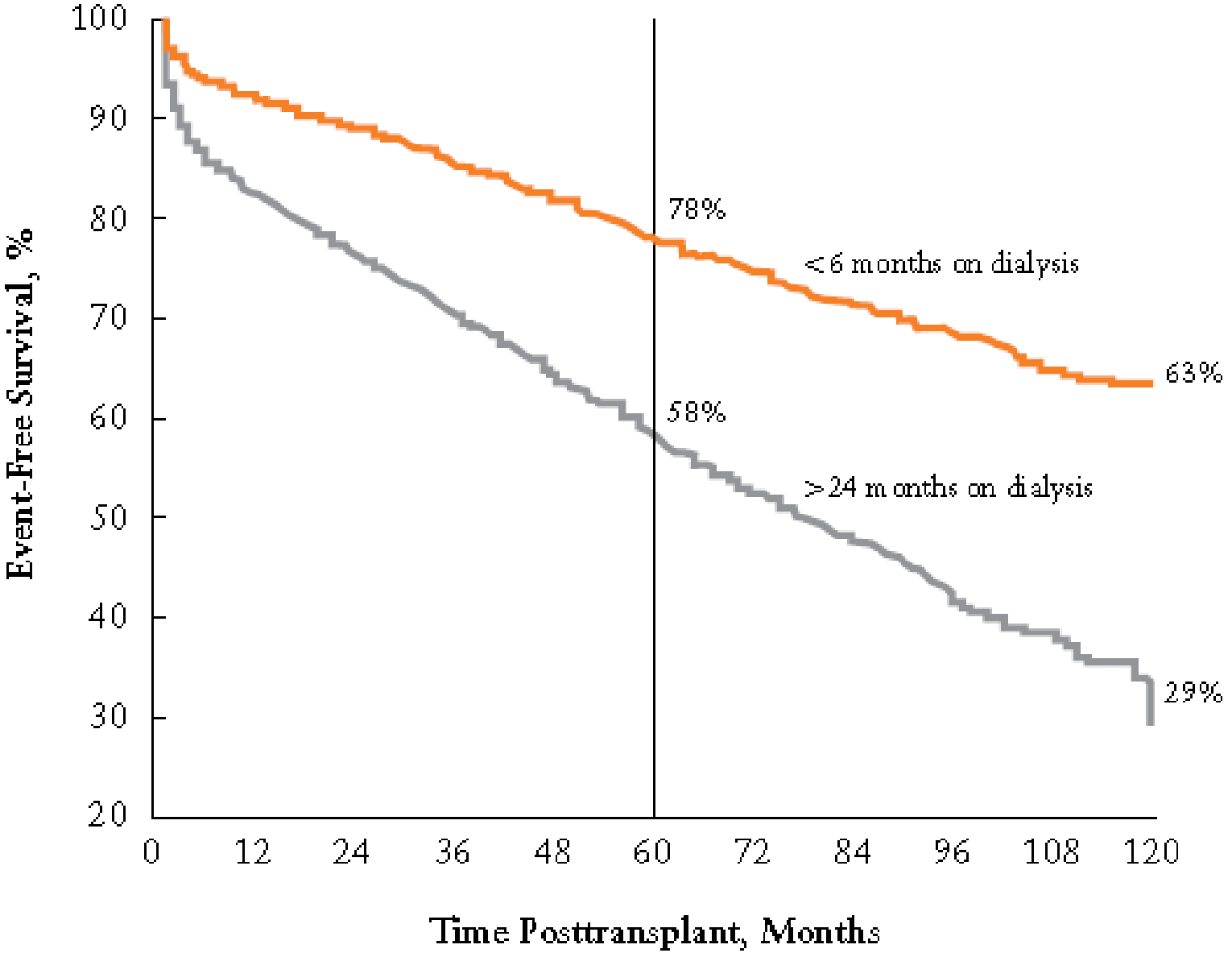
If you were getting a transplant, at what point would you like to get it?

- No dialysis
- HD x 6 months
- HD x 1 yr
- HD x 5 yr



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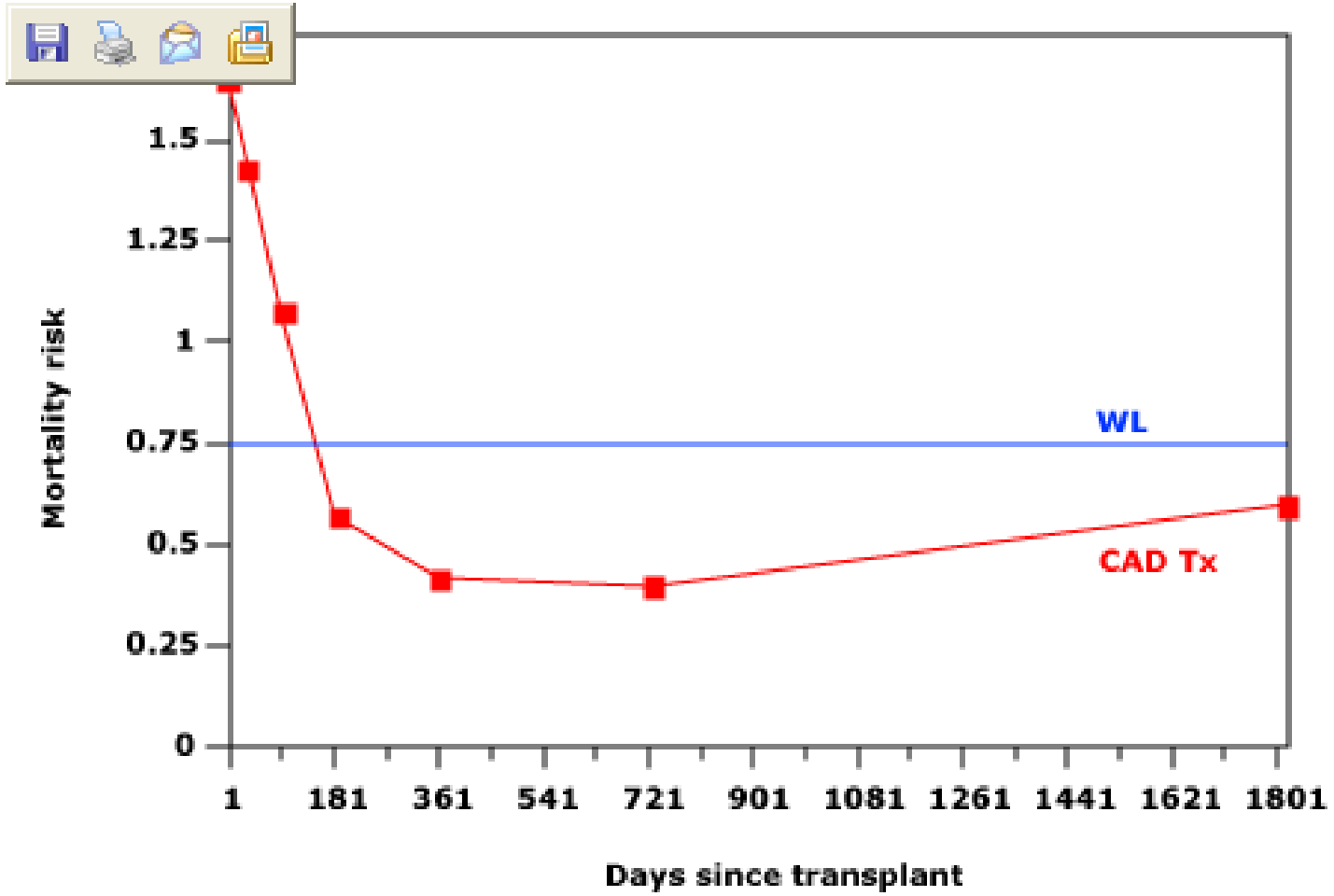
If your life expectancy was 6 months, and you were offered a transplant, would you accept?

- Yes
- No

Mortality risk of recipients of cadaveric renal transplants vs. wait-listed patients with ESRD who were on dialysis for at least 2 years



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If you were given the option between taking a living donor kidney versus a deceased donor kidney, which one would you pick?

A. Living donor
B. Deceased donor

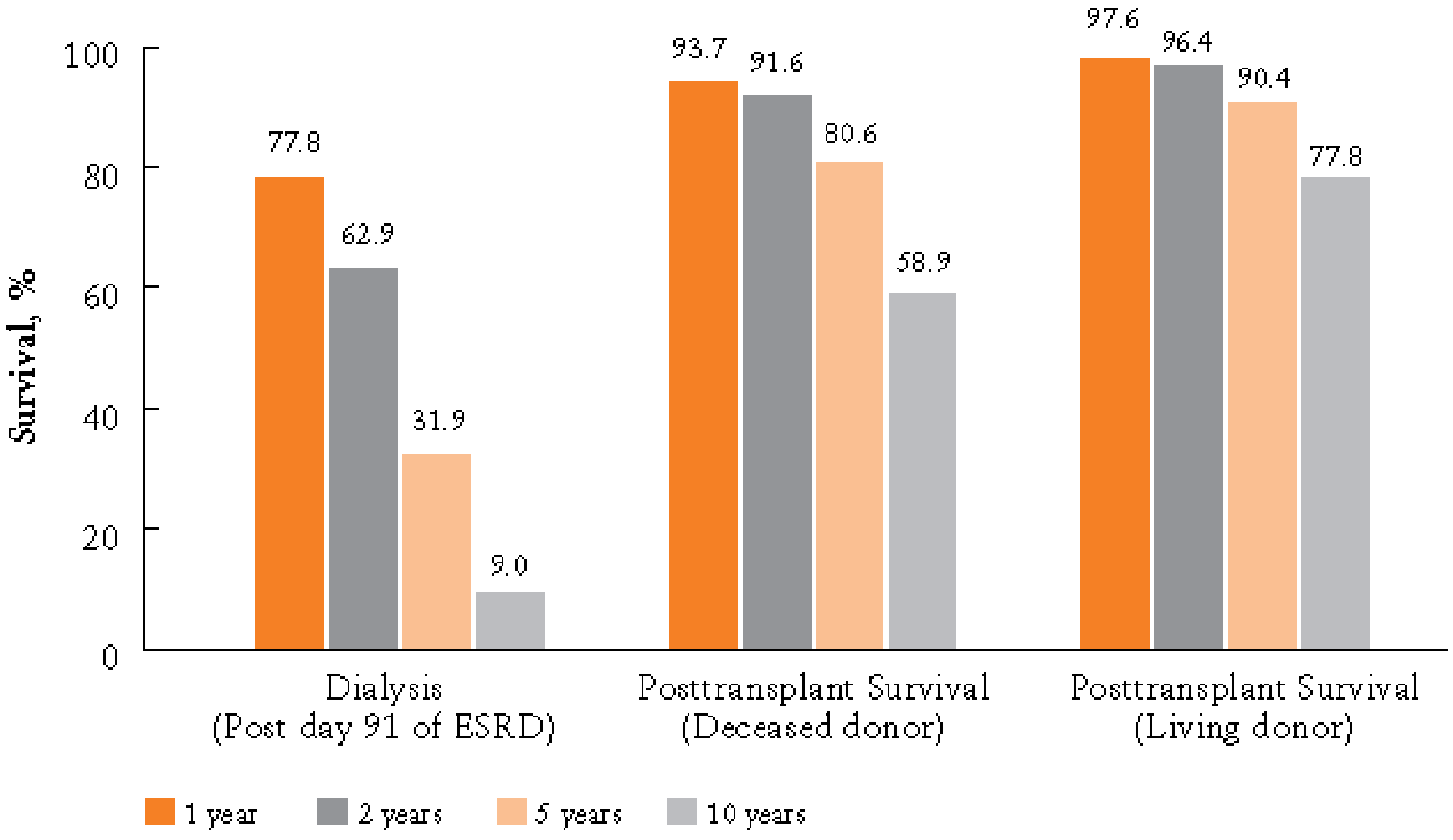
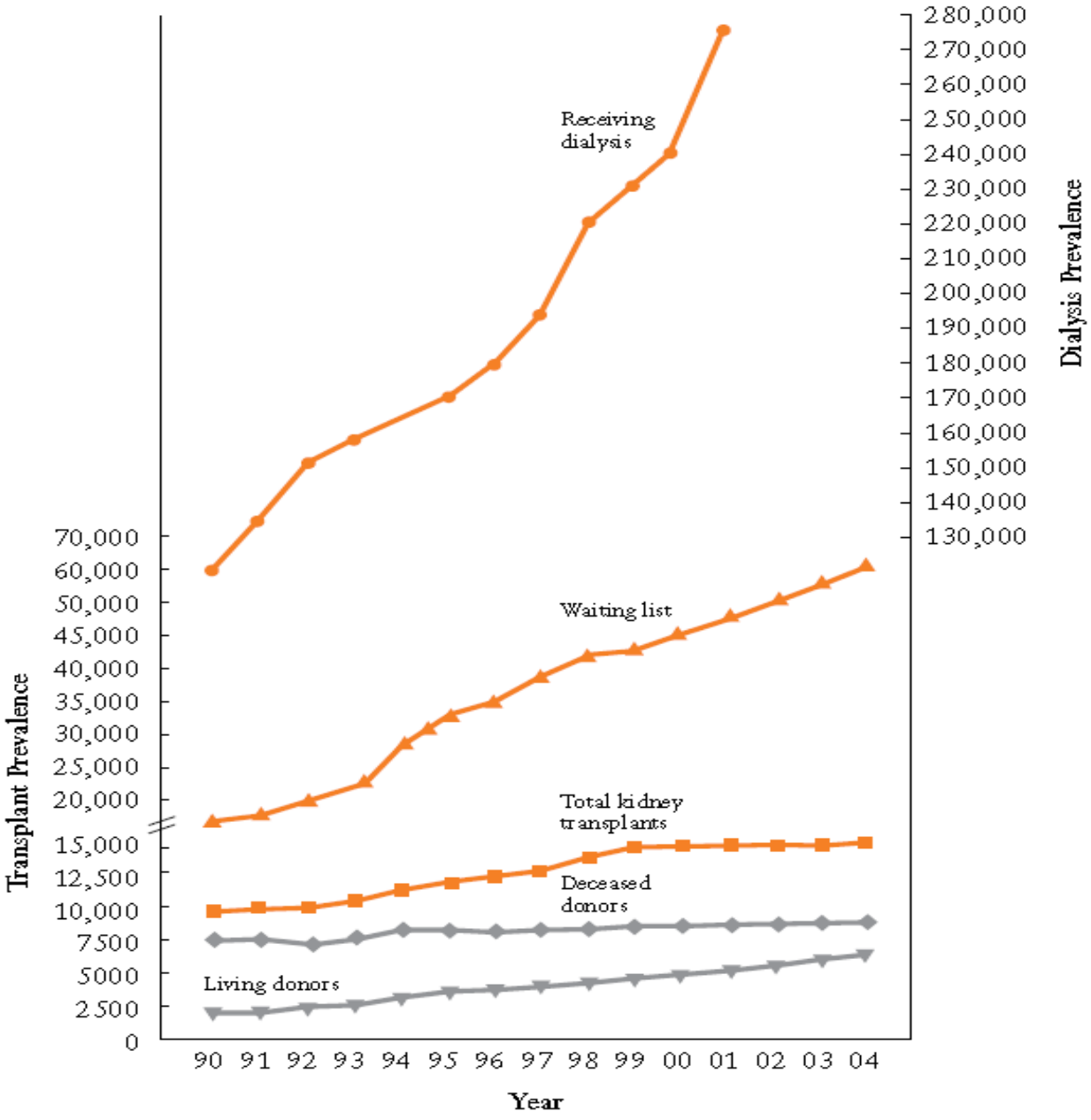

Survival, %
100
80
60
40
20
0
77.8
62.9
31.9
9.0
93.7
91.6
80.6
58.9
97.6
96.4
90.4
77.8
Dialysis
(Post day 91 of ESRD)
Posttransplant Survival
(Deceased donor)
Posttransplant Survival
(Living donor)
1 year
2 years
5 years
10 years

Figure 8. ESRD Patients Receiving Dialysis, on the Waiting List, or Transplanted, 1990-2004[18,19]



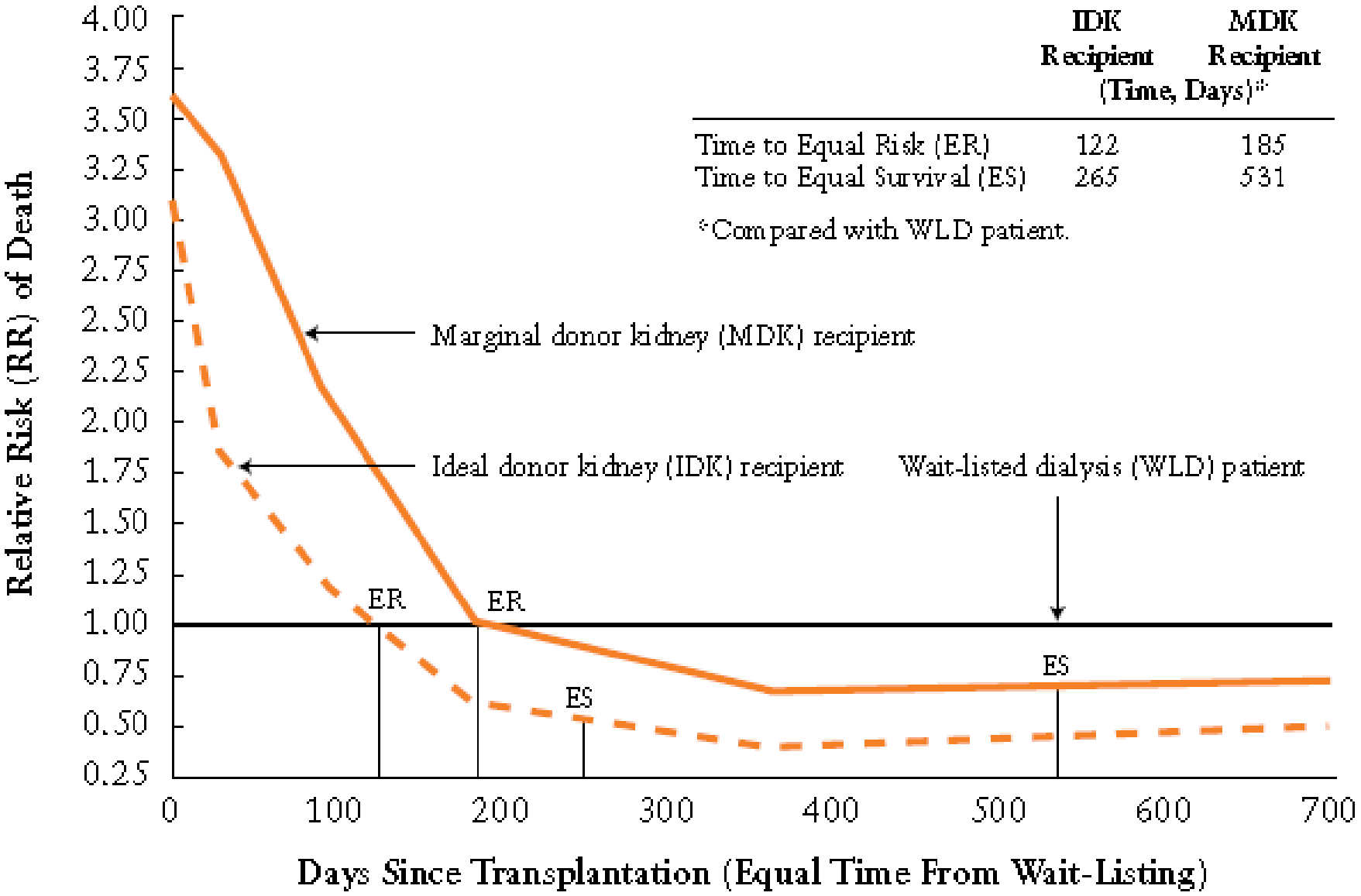
Adapted from United States Renal Data System. *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Available at: http://www.usrds.org/. Accessed January 14, 2005, and The United Network for Organ Sharing. Available at: http://www.unos.org. Accessed December 23, 2004.

Extended criteria donors

- Age > 60
- Age 50-59 + 2 of the following
  - Cr > 1.5
  - HTN
  - Cerebrovascular death

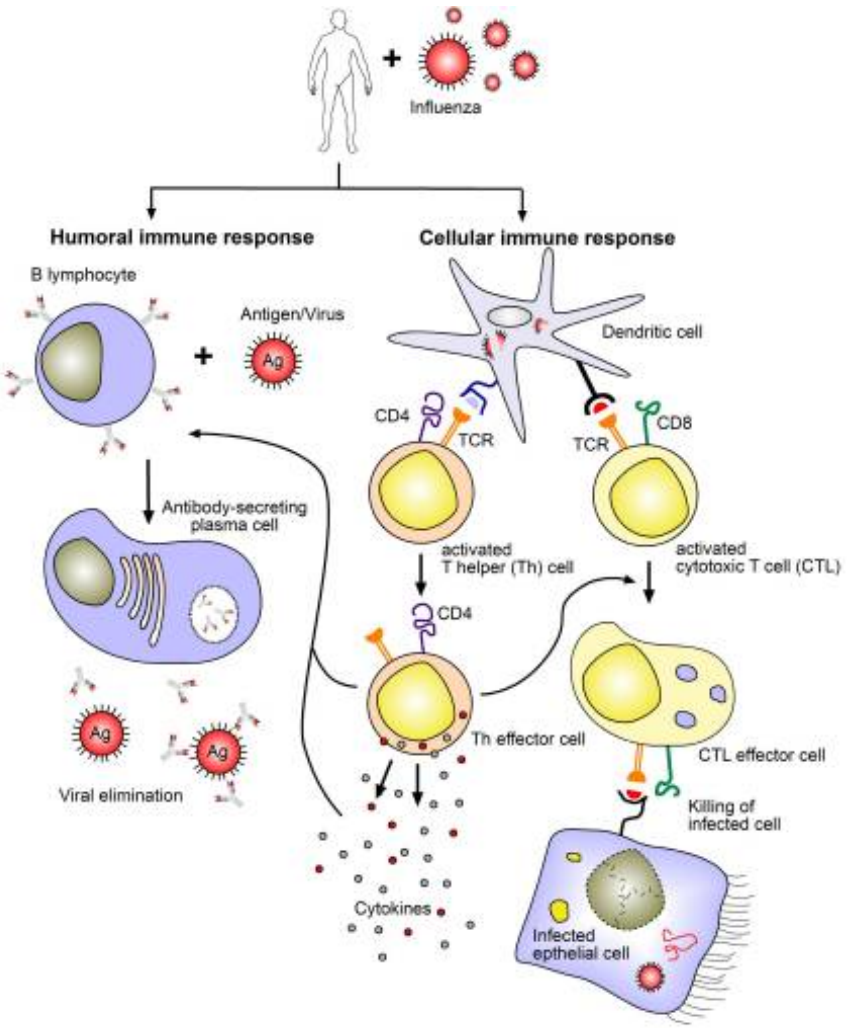
You have the option of remaining on HD or taking an ECD kidney…..which one would you pick?

A. HD
B. ECD kidney

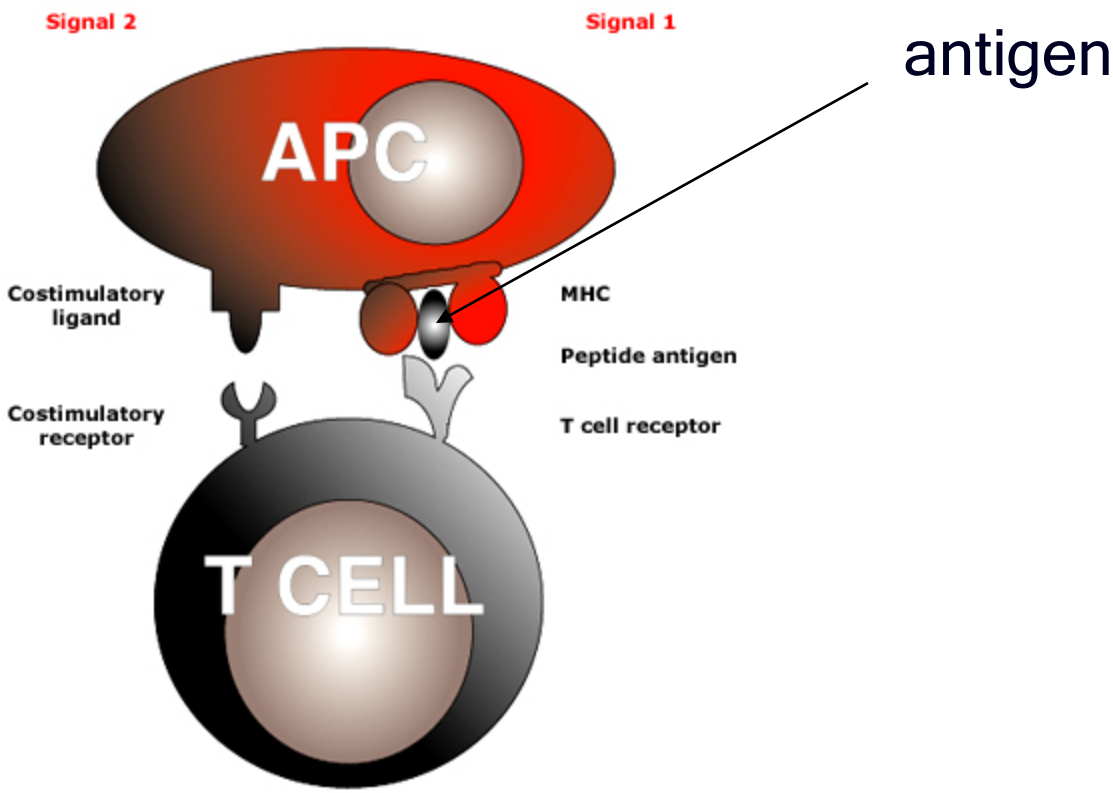


Adapted with permission from Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol.* 2001;12:589-597.

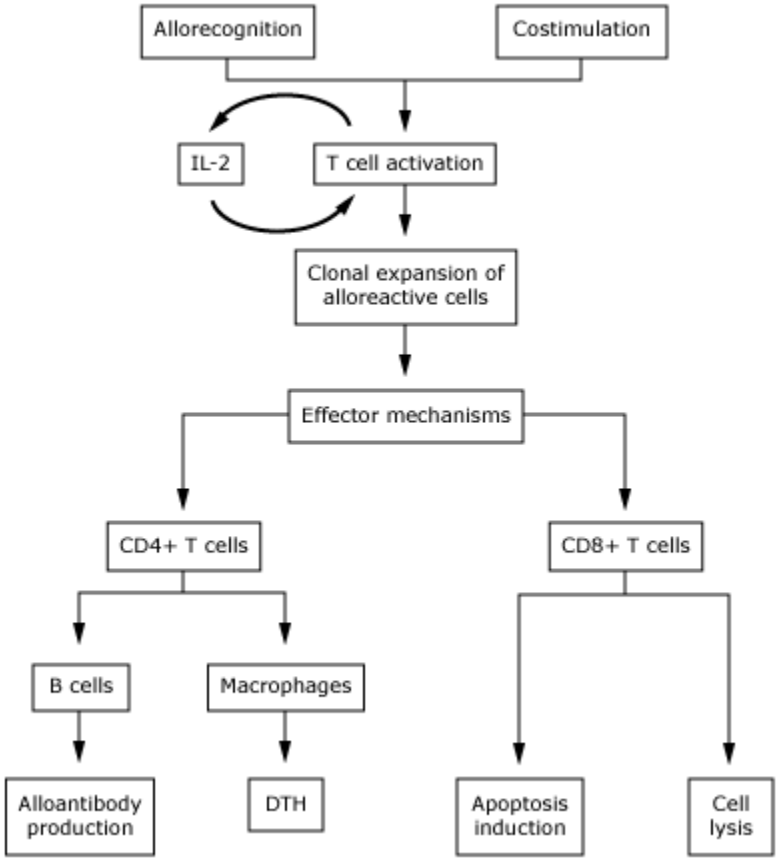
Transplant Immunology for non-transplant nephrologists


Influenza
Humoral immune response
Cellular immune response
B lymphocyte
Antigen/Virus
Ag
Dendritic cell
CD4
TCR
TCR
CD8
Antibody-secreting plasma cell
activated T helper (Th) cell
activated cytotoxic T cell (CTL)
CD4
Th effector cell
CTL effector cell
Killing of infected cell
Ag
Ag
Viral elimination
Cytokines
Infected epthelial cell

STEP 1 = Ag + APC meets T cell



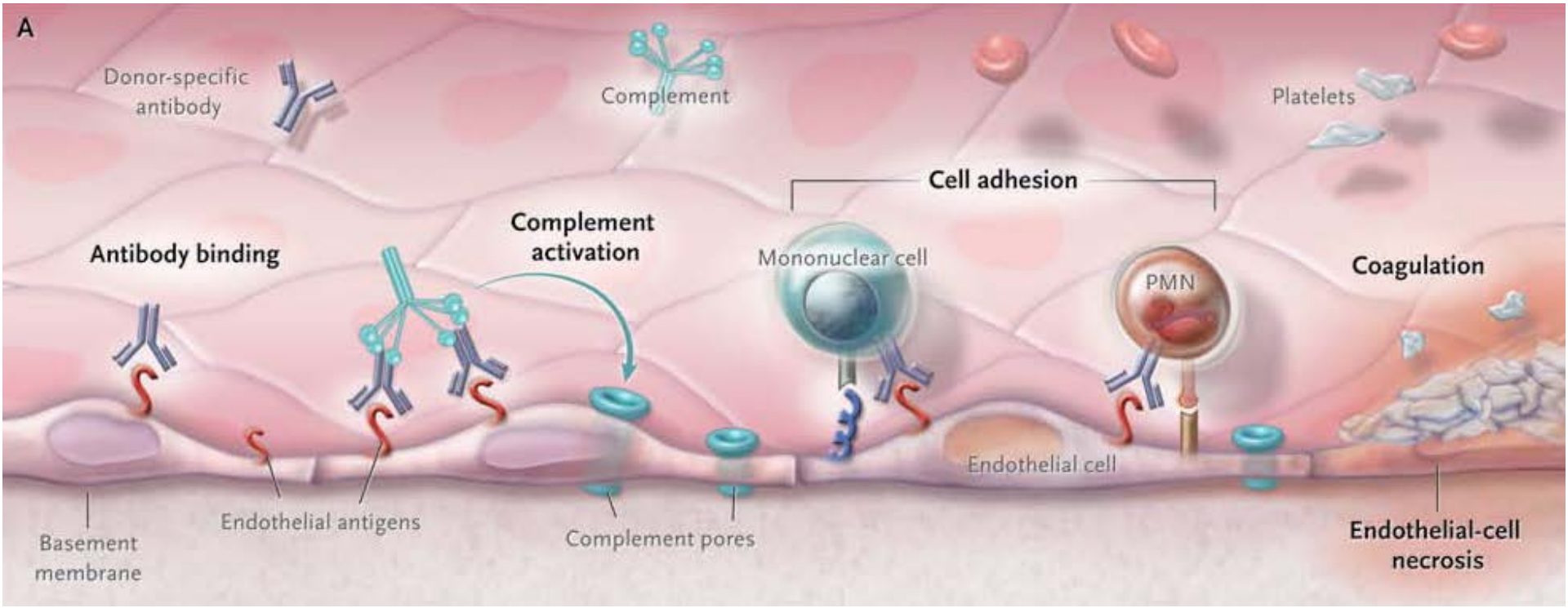
STEP 2 = T cell activation



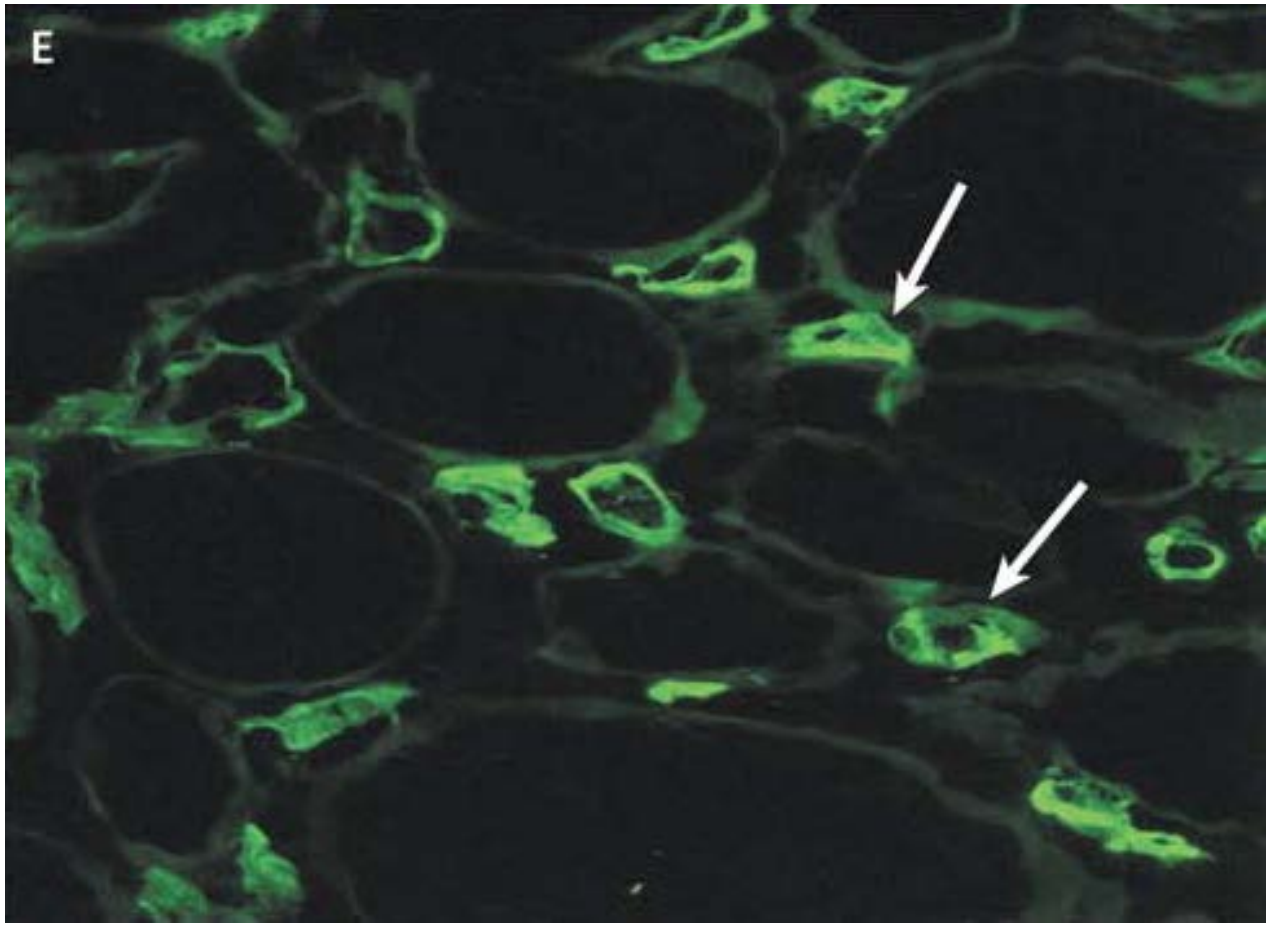
STEP 3 = Acute Rejection

1. Acute Humoral rejection: B
2. Acute Cellular rejection: T

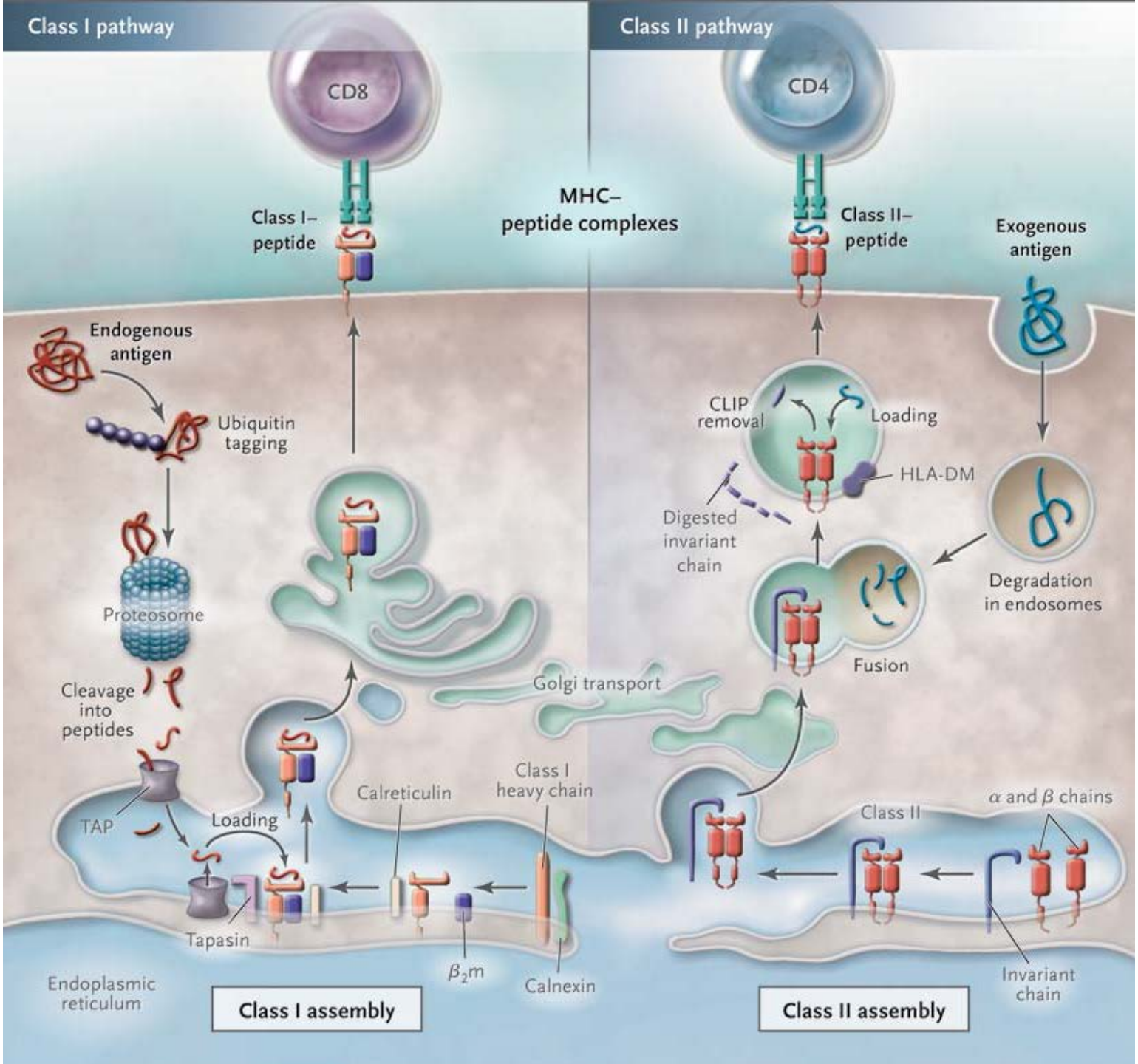
STEP 3 = Acute Humoral rejection: B

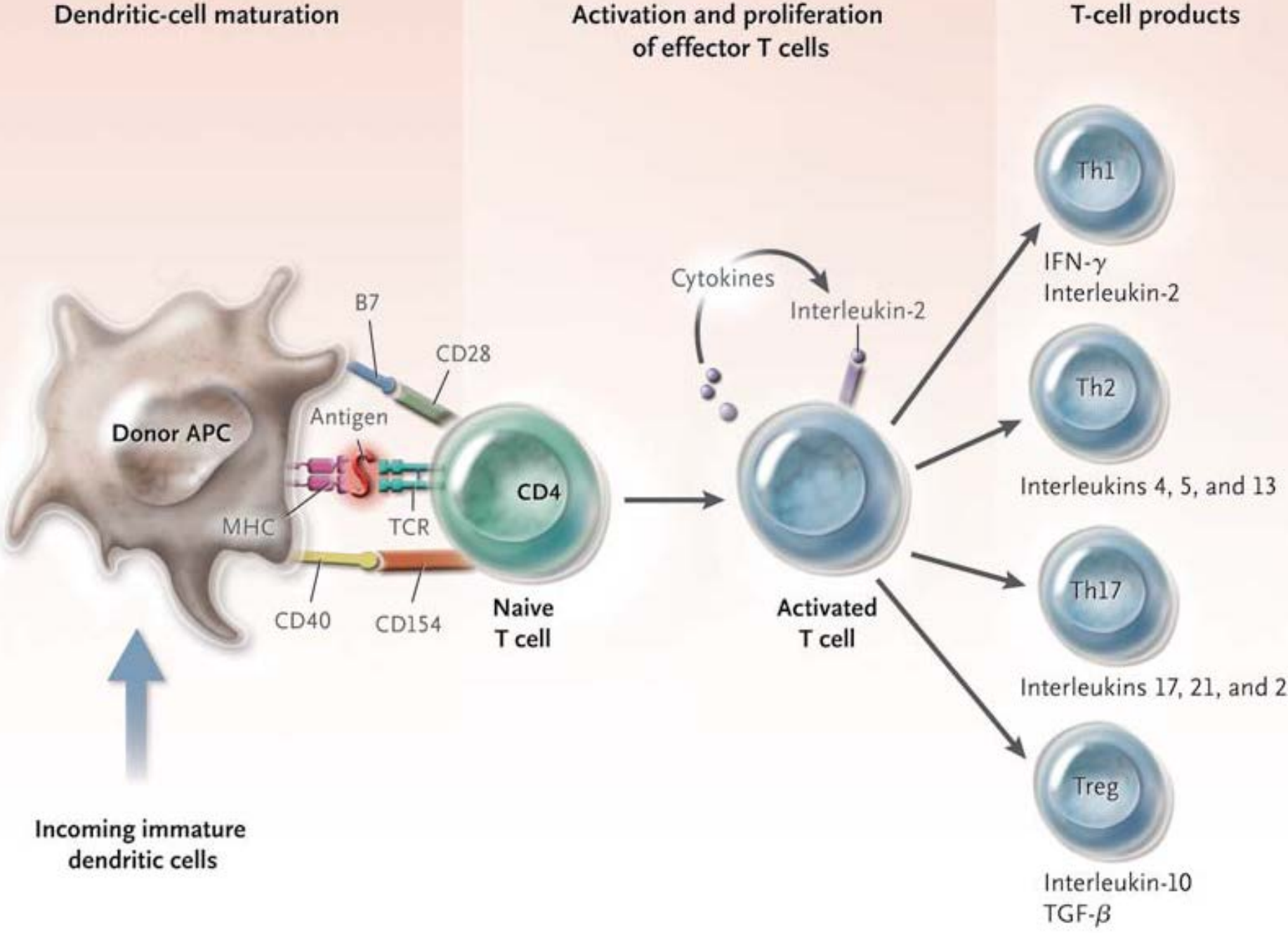


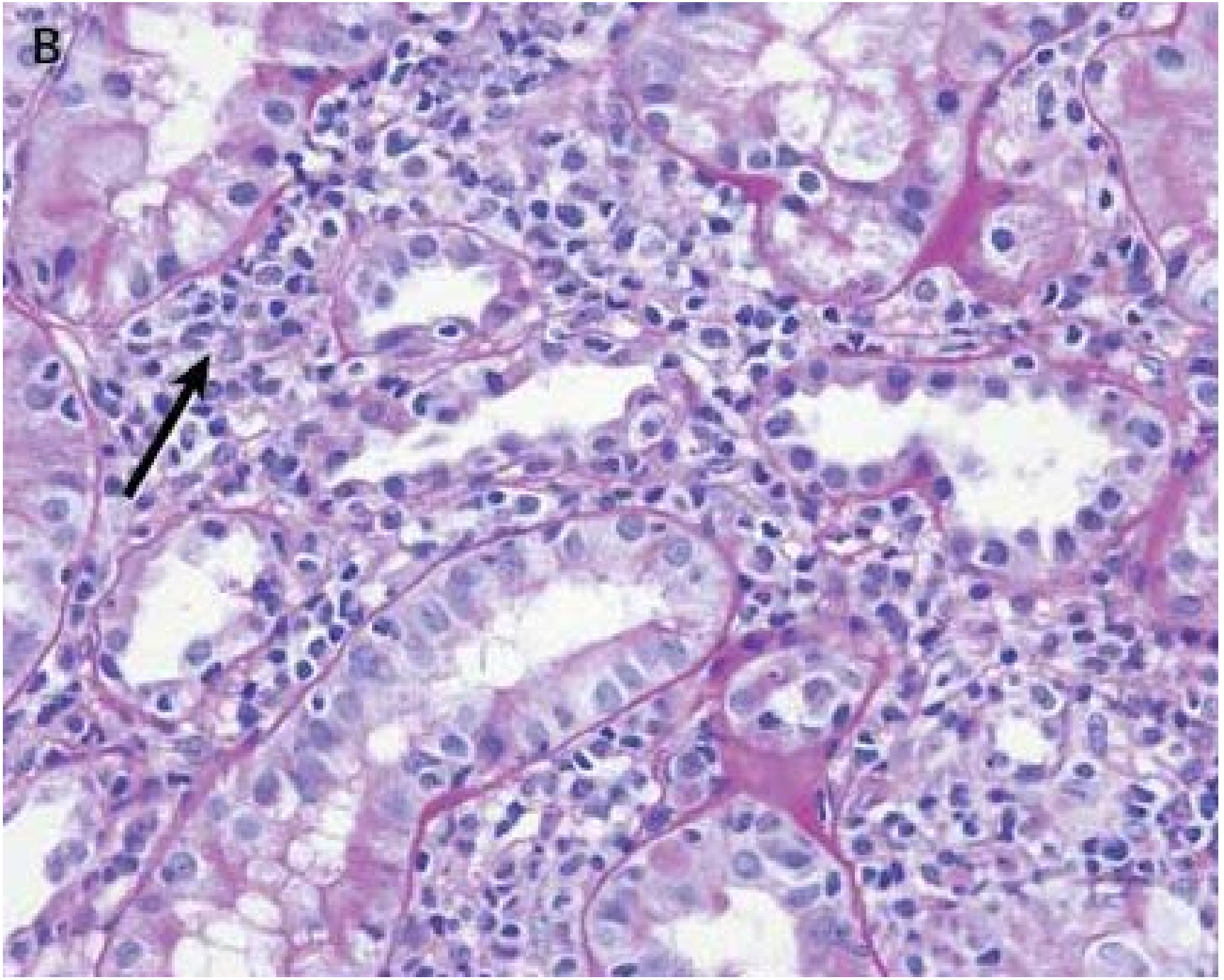
STEP 3 = Acute Humoral rejection: B

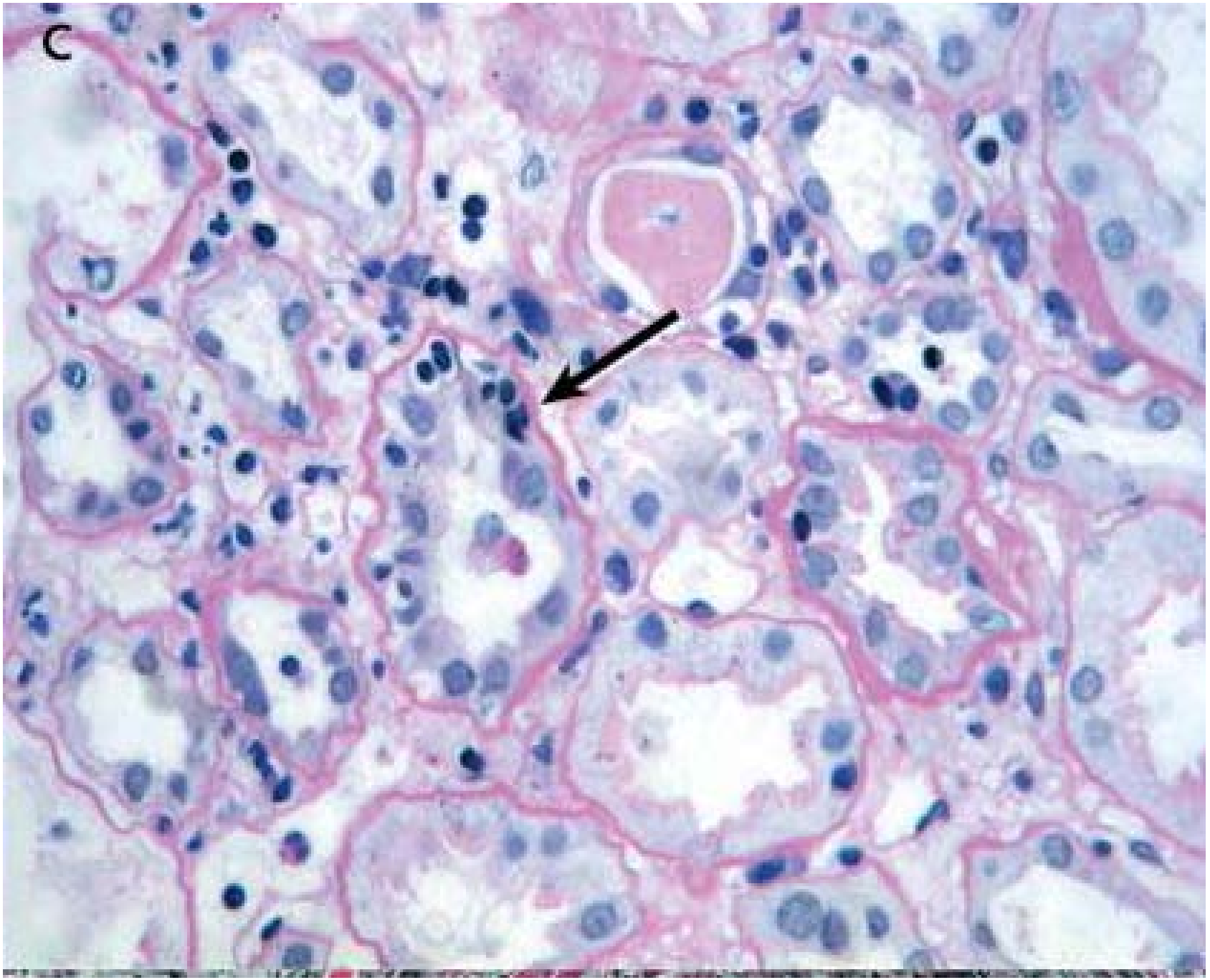


STEP 3 = Acute cellular rejection: T


Class I pathway
Class II pathway
CD8
CD4
MHC–
peptide complexes
Class I–
peptide
Class II–
peptide
Exogenous
antigen
Endogenous
antigen
Ubiquitin
tagging
CLIP
removal
Loading
HLA-DM
Digested
invariant
chain
Degradation
in endosomes
Proteosome
Fusion
Golgi transport
Cleavage
into
peptides
Class I
heavy chain
Calreticulin
α and β chains
Class II
TAP
Loading
Tapasin
β2m
Calnexin
Invariant
chain
Endoplasmic
reticulum
Class I assembly
Class II assembly


Dendritic-cell maturation
Activation and proliferation of effector T cells
T-cell products
Donor APC
B7
CD28
Antigen
MHC
TCR
CD4
CD40
CD154
Naive T cell
Incoming immature dendritic cells
Cytokines
Interleukin-2
Activated T cell
Th1
IFN-γ
Interleukin-2
Th2
Interleukins 4, 5, and 13
Th17
Interleukins 17, 21, and 2
Treg
Interleukin-10
TGF-β


B

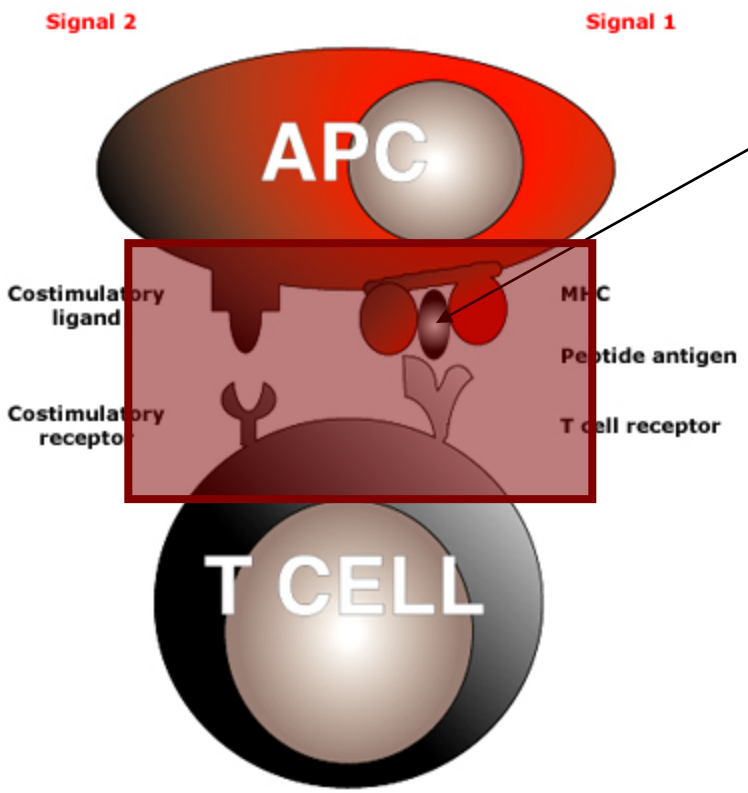

C

STEP 3 = Acute cellular rejection: T

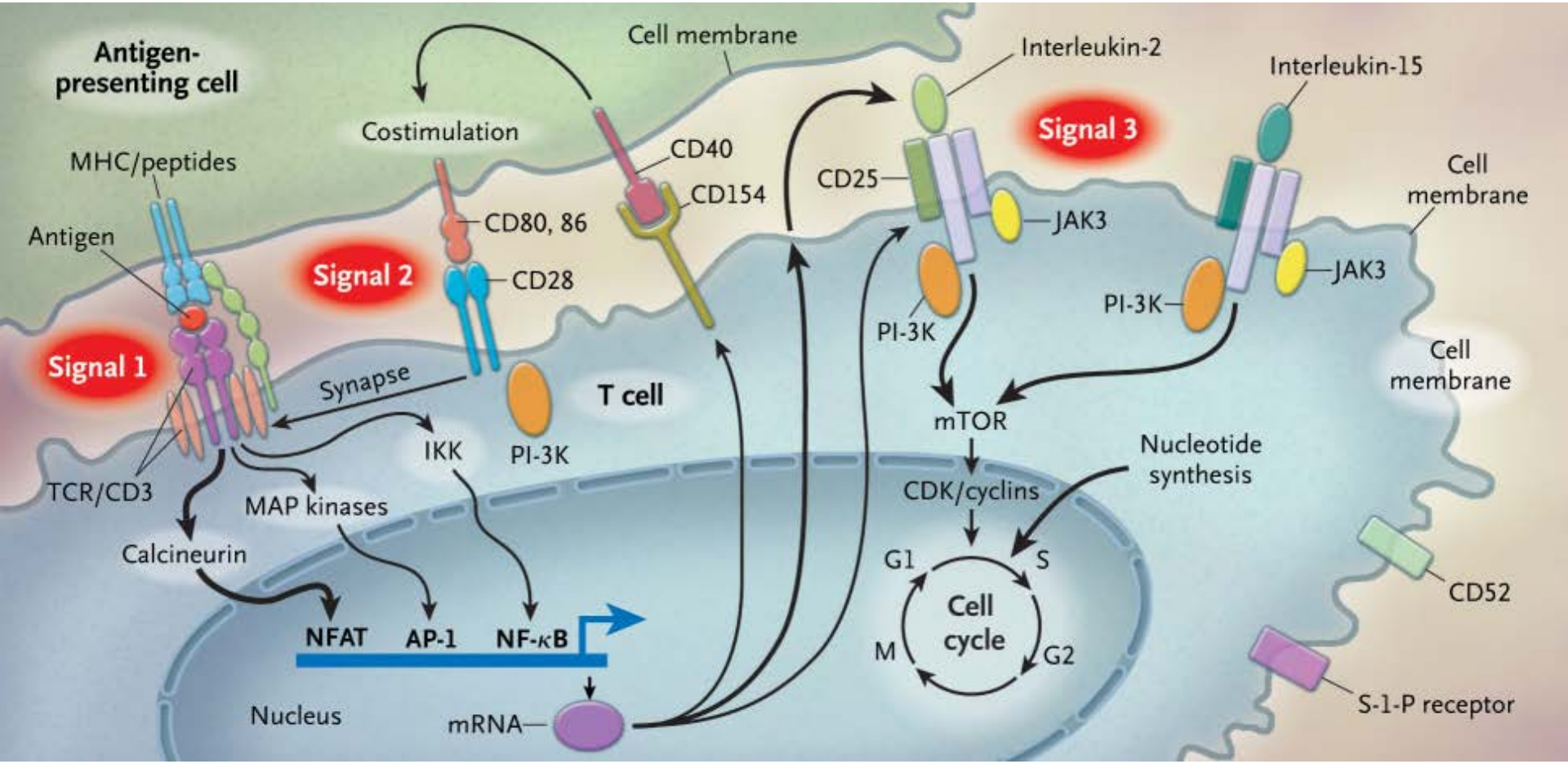
Table 1. Acute T-Cell–Mediated Rejection.*

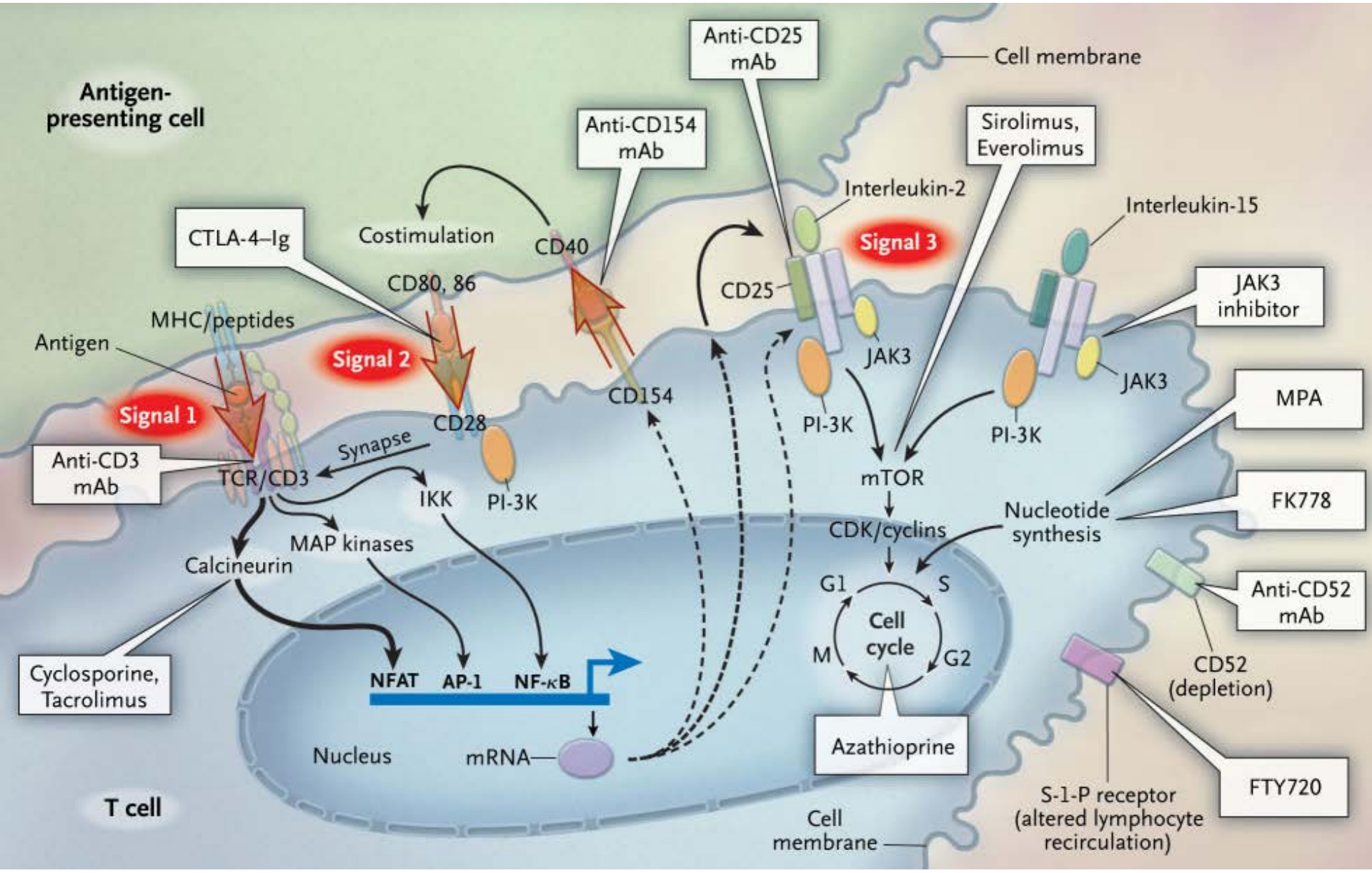
Banff Grade	Description
IA	Interstitial infiltration, with >25% of parenchyma affected (mononuclear-cell–infiltration inflammation score, 2 or 3) and foci of tubulitis (tubulitis score, 2)
IB	Interstitial infiltration; same as grade IA for infiltration but with foci of severe tubulitis (tubulitis score, 3)
IIA	Mild-to-moderate intimal arteritis (vasculitis score, 1)
IIB	Severe intimal arteritis comprising >25% of the luminal area (vasculitis score, 2)
III	Transmural arteritis or arterial fibrinoid change and necrosis of medial smooth-muscle cells with accompanying lymphocytic inflammation (vasculitis score, 3)

STEP 1 = Ag + APC meets T cell



antigen


Antigen-presenting cell
Cell membrane
Costimulation
MHC/peptides
CD40
CD154
Interleukin-2
Interleukin-15
Signal 3
CD25
JAK3
Cell membrane
CD80, 86
Antigen
Signal 2
CD28
PI-3K
JAK3
PI-3K
Signal 1
Synapse
T cell
Cell membrane
mTOR
IKK
PI-3K
Nucleotide synthesis
TCR/CD3
MAP kinases
CDK/cyclins
Calcineurin
G1
S
CD52
Cell cycle
NFAT
AP-1
NF-κB
M
G2
Nucleus
mRNA
S-1-P receptor


Antigen-presenting cell
Anti-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
CTLA-4–Ig
Costimulation
CD40
Signal 3
CD80, 86
CD25
JAK3 inhibitor
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
CD154
MPA
Signal 1
CD28
PI-3K
PI-3K
Anti-CD3 mAb
Synapse
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
MAP kinases
CDK/cyclins
Calcineurin
G1
S
Cell cycle
M
G2
Anti-CD52 mAb
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
CD52 (depletion)
Nucleus
mRNA
Azathioprine
FTY720
T cell
S-1-P receptor (altered lymphocyte recirculation)
Cell membrane

Induction

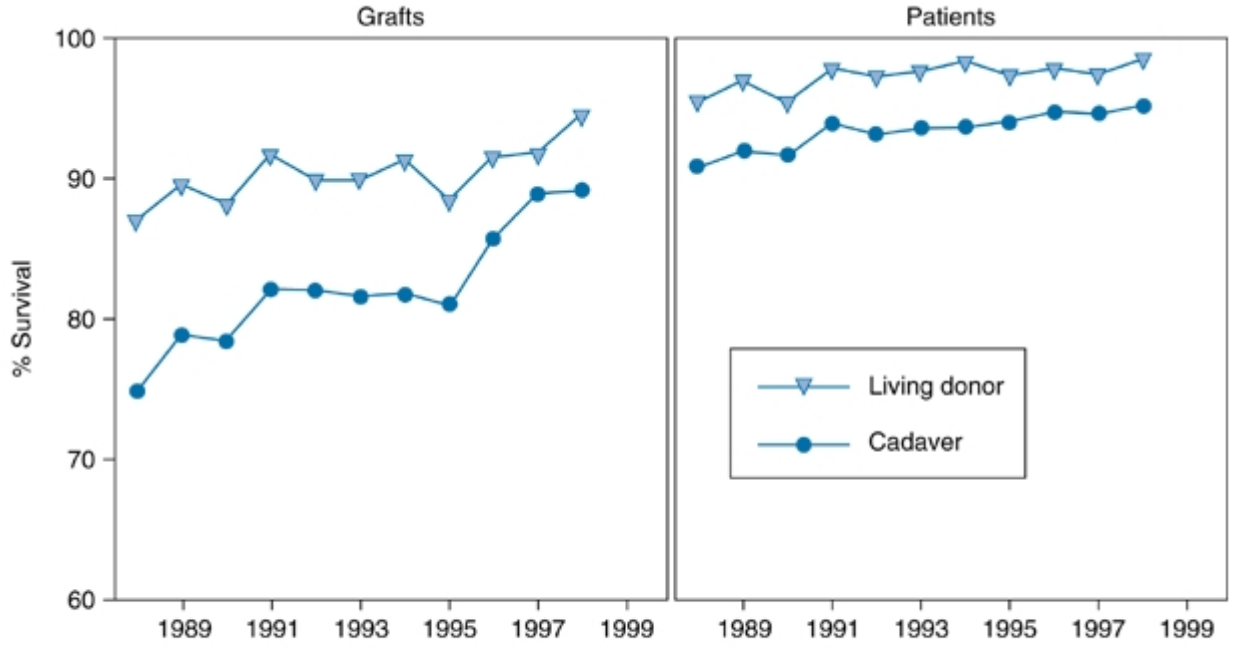
High dose conventional agents	Antibody induction
Calcineurin inhibitor: Cyclosporine or tacrolimus	Alemtuzumab (CD52)
Corticosteroid	ATG
Antimetabolite: Mycophenolate mofetil or azathioprine	Basiliximab (IL-2R)

Maintenance

- Cellcept 1g BID
- Prograf
- Steroid free

Are kidney transplants (and patients) surviving longer than in the 1980s?

A. Of course
B. Absolutely
C. Yes



(From USRDS: USRDS 2001 Annual Data Report: NIH and NIDDK, Bethesda, MD, 2002.)

Questions?