Adaptive Immunity

Cellular Mechanisms and Signaling

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SITC Immunotherapy Winter School 2020

Defense reactions

- **Recognition of a threat**
  - Signaling molecules and signal receptors on innate immune cells
  - Antigen receptors and signaling molecules on adaptive immune cells
- **Processing**
  - Analysis of the received signal
  - Threshold
- **Response** (effector phase)
  - Propagation of the danger message
  - Elimination of the threat

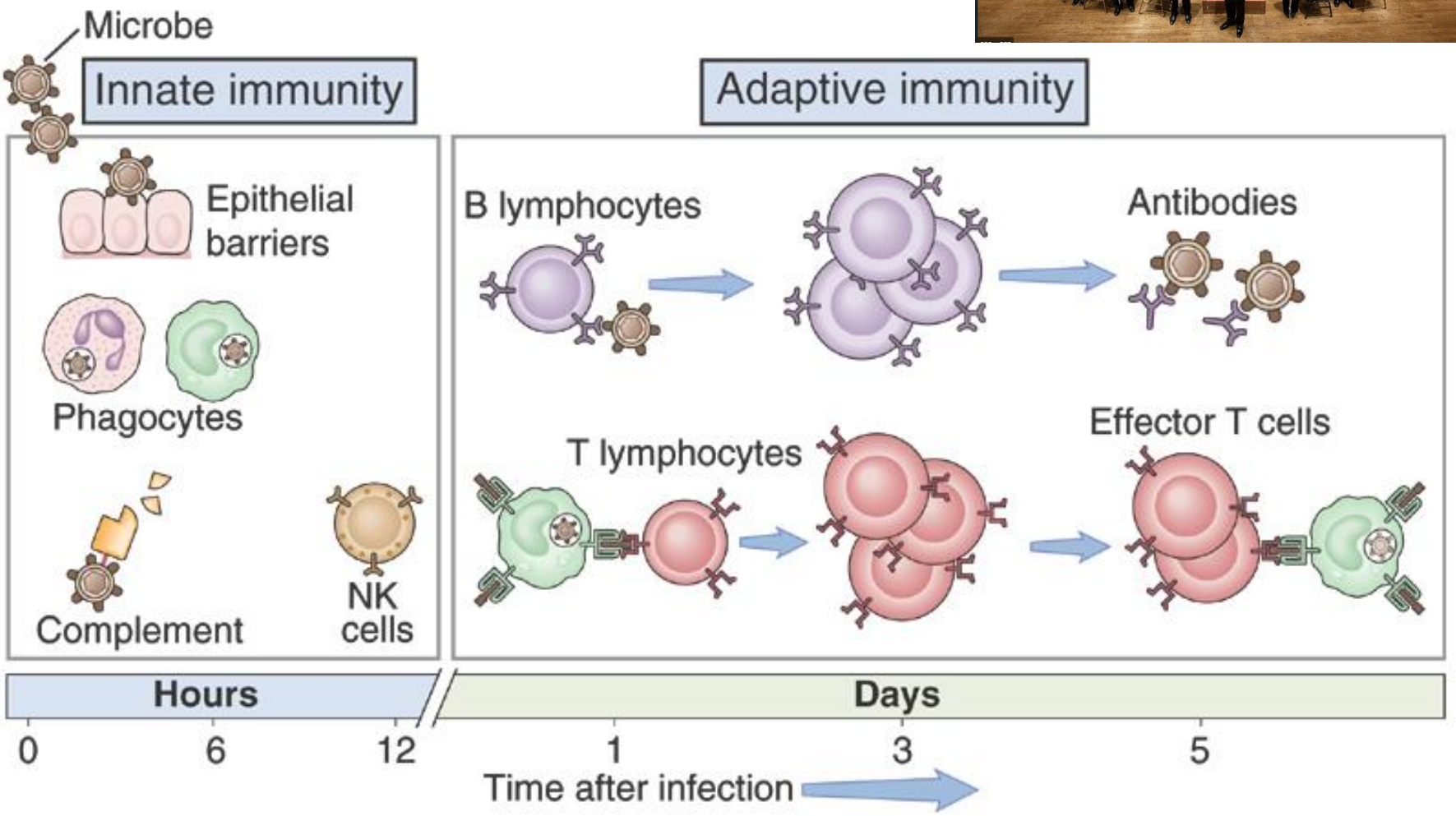
Two types of immunity

- **Innate immunity**
  - Stimulated by pathogens, signal to adaptive immunity
  - *Immediate response*
  - *Broad reactivity*
  - Players:
    - Epithelial barriers (skin, mucosa)
    - Complement system
    - NK cells
    - Phagocytes (DC and MØ)

- **Adaptive Immunity**
  - Stimulated by pathogen-derived antigens, and by innate immunity
  - *Delayed response*
  - *Narrow specificity*
  - *Two types: humoral and cellular*
  - Players:
    - B cells (antibodies)
    - T cells (CTL and Th)
    - NKT cells

A perfectly orchestrated and timed system

Pittsburgh Symphony Orchestra



Discovery of Humoral Immunity (Antibodies)

- Alexandre Yersin and *Corynbacterium diphteria* toxin (1888).
  - Observed that bacteria localized only in the throat but lesions seen throughout the body
  - Cell free filtrates made mice sick (*toxins*)
- Emil von Behring Serum from mice that recovered could transfer resistance to previously uninfected mice.
  - Mice that recovered were resistant to disease
  - Serum from mice that recovered could transfer resistance to previously uninfected mice (*antitoxins*).

The Nobel Prize in Physiology or Medicine 1901 was awarded to Emil von Behring "for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths".

Humoral Immunity

- In 1897 Rudolph Kraus discovered that immune serum precipitated the toxins (*precipitins)* and *lysed* the bacteria (*bacteriolysins*).
- Immune serum also glued bacteria together (*aglutinins)*
- 1923, Heidelberger and Avery discover that immune serum can recognize proteins or carbohydrates.
- In 1930, Karl Landsteiner ascribed all these different functions to the same family of molecules, ***antibodies***.

1930 Nobel Prize in medicine

Karl Landsteiner (1868-1943)

Antibodies

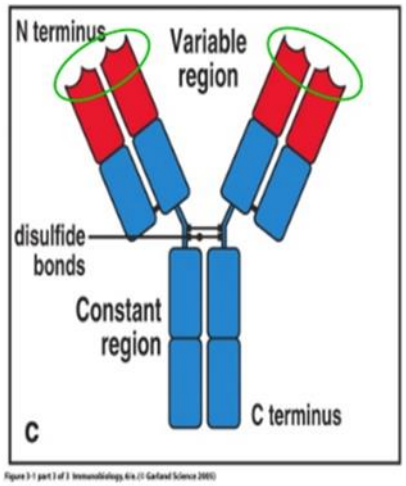
- Can be generated not only against bacteria but also against non-bacterial and totally innocuous substances (milk, eggwhite)

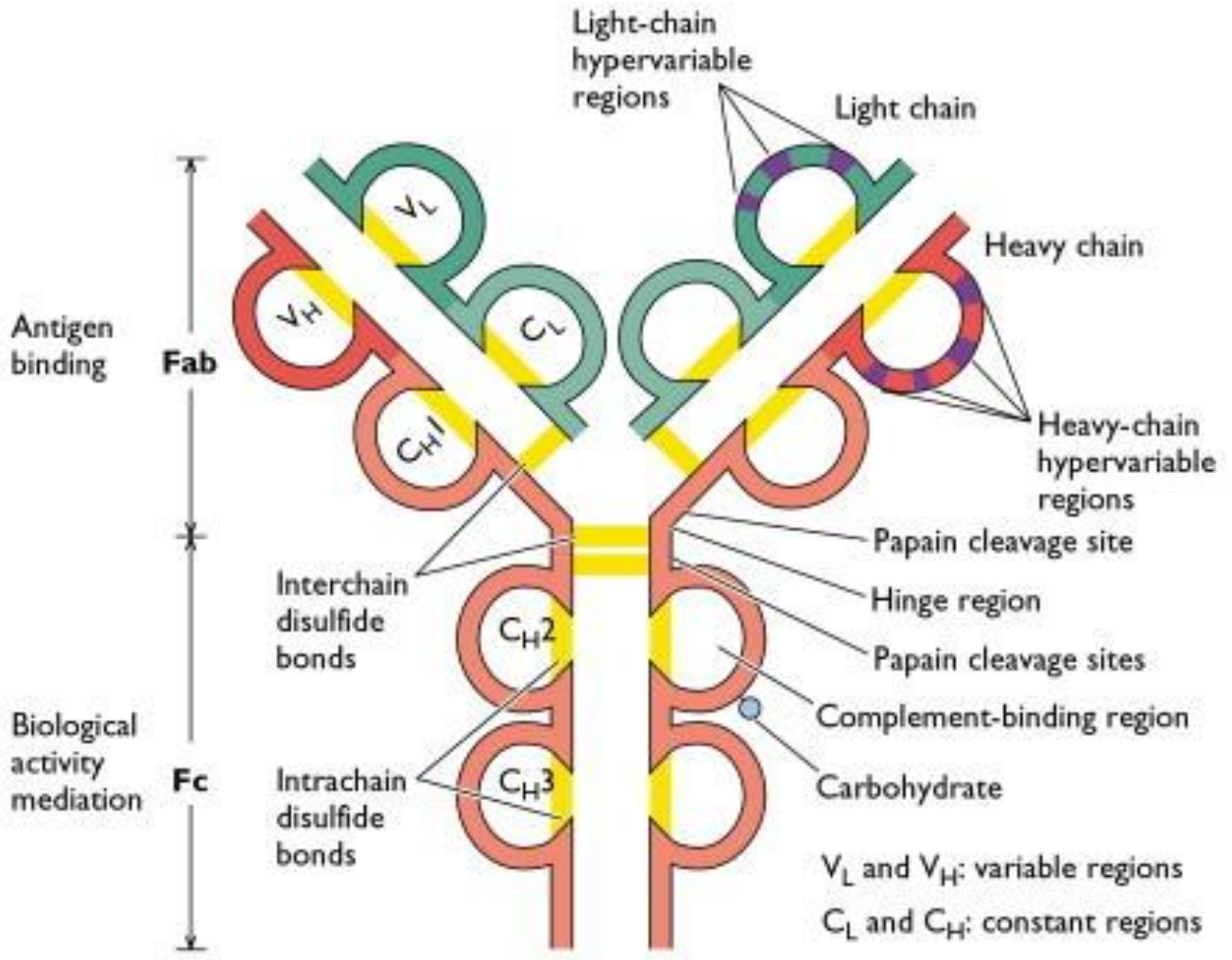
- Substances stimulating the appearance of antibodies were designated *antigens*

Gerald Edelman and Rodney Porter (1972)

The two scientists independently deciphered the structure of antibodies, which revealed how seemingly identical-looking molecules can target specifically any one of a countless number of invaders for destruction.

Secreted form of IgG, 2 heavy chains and 2 light chains, held together by S-S bonds





The Fab vs Fc

- Fab
  - Fragment that antigen binds, V regions
  - Composed of Light chain + NH2 portion of H chain
- Fc
  - Heavy chain Constant regions, no light chain
  - COOH end of H chain
  - Complement binding region
  - Interacts with Fc receptors

1984 Nobel Prize:

Niels Jerne

George Kohler

Cesar Milstein

Antibodies

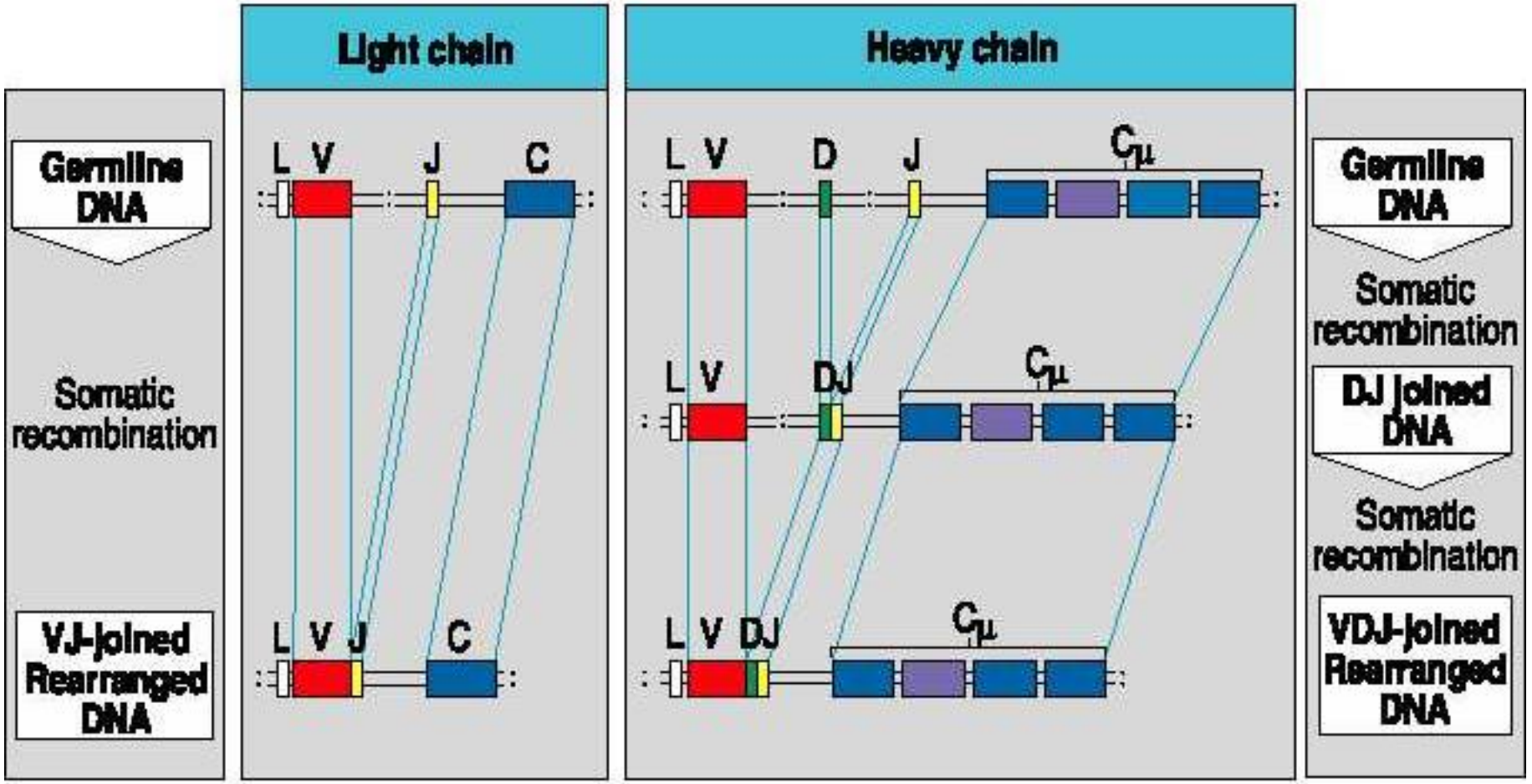
- Can be generated not only against bacteria but also against non-bacterial and totally innocuous substances (milk, eggwhite)
- Substances stimulating the appearance of antibodies were designated *antigens*
- **Diversity** and **Specificity** are observed but mechanisms remain a mystery until the late 1970s

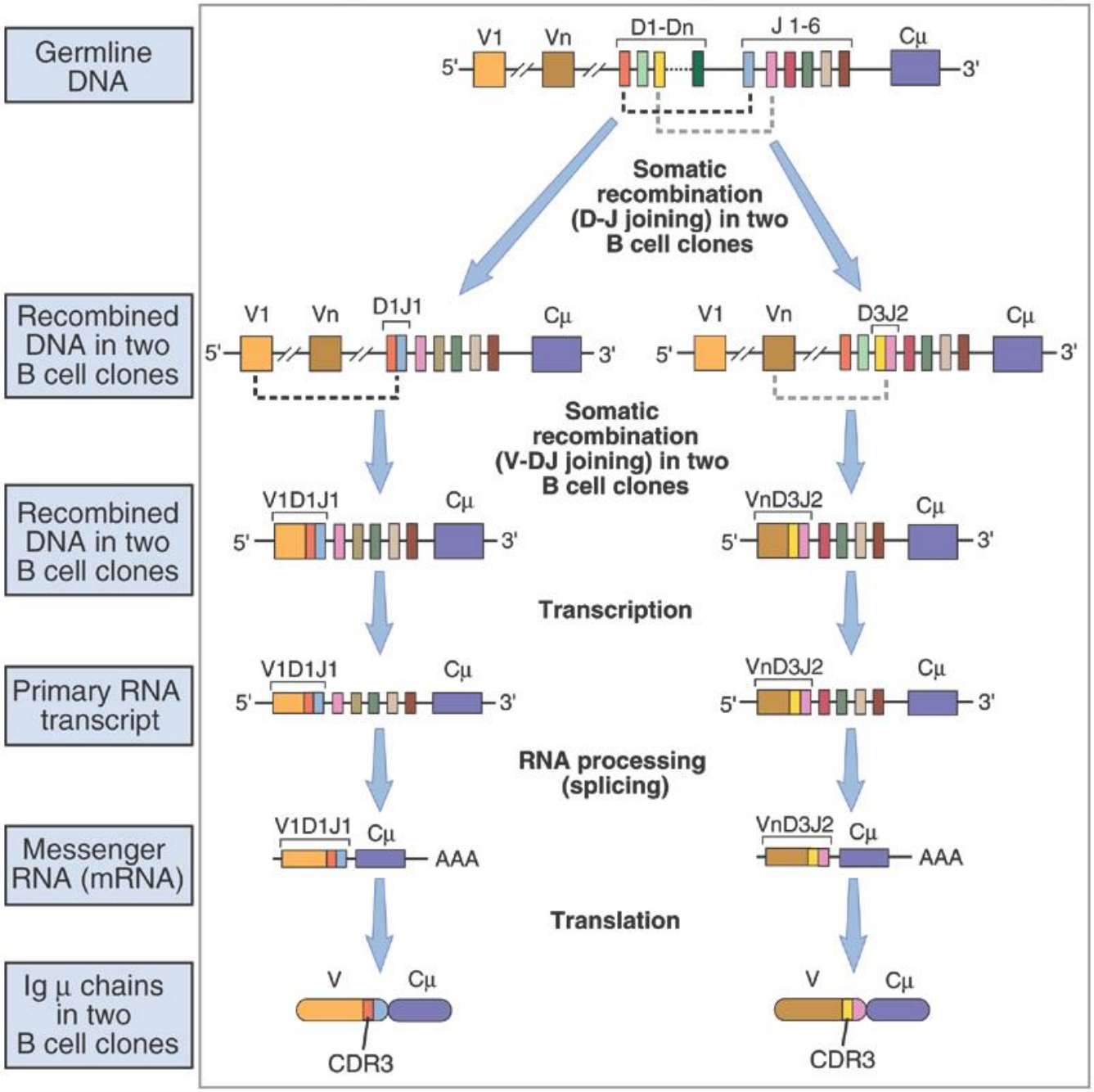
100-year old puzzle solved

Susumu Tonegawa

1987 Nobel Prize for discovering Ig gene rearrangement

V(D)J region Sequences arise from DNA recombination

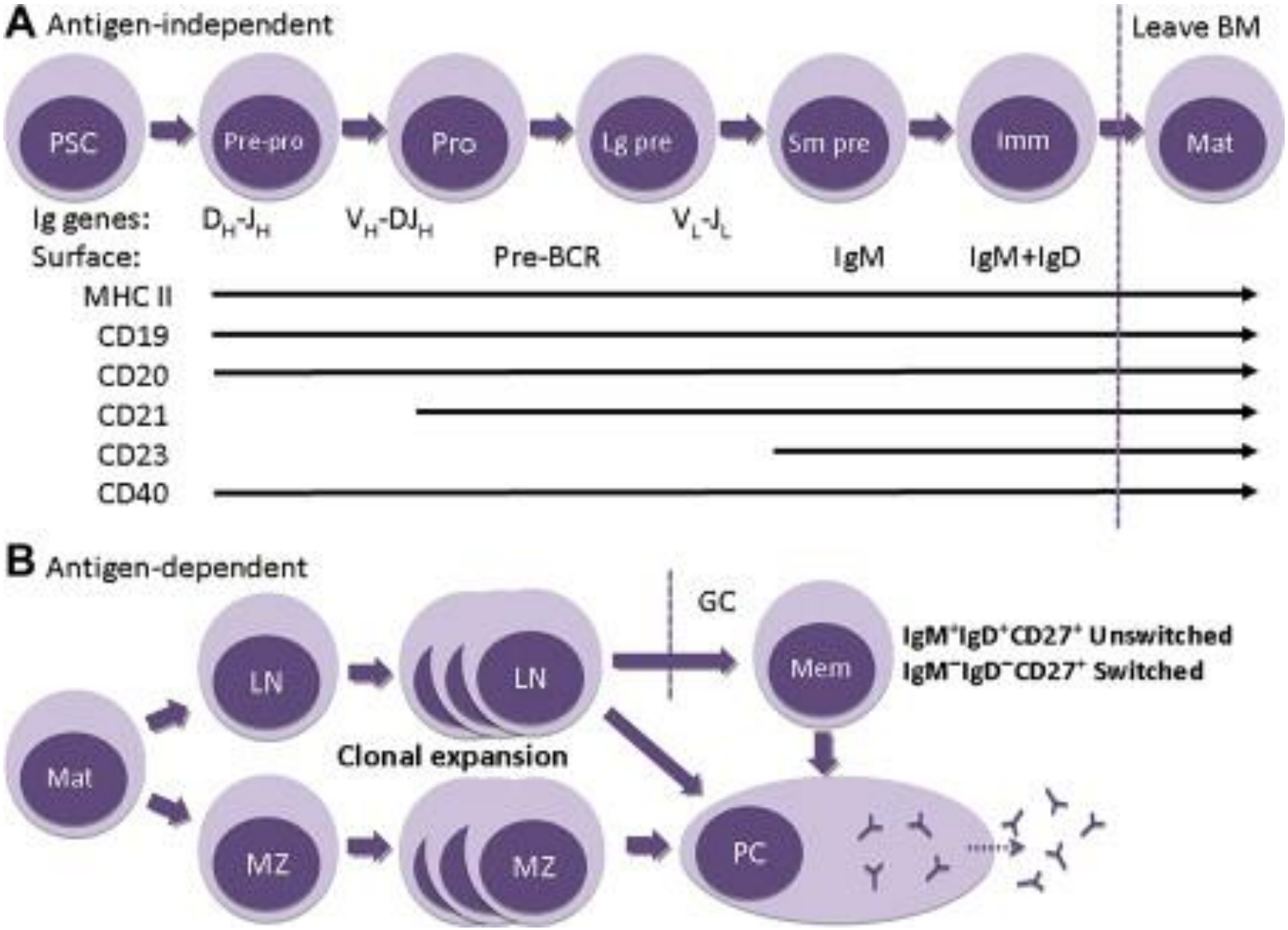




Key concepts

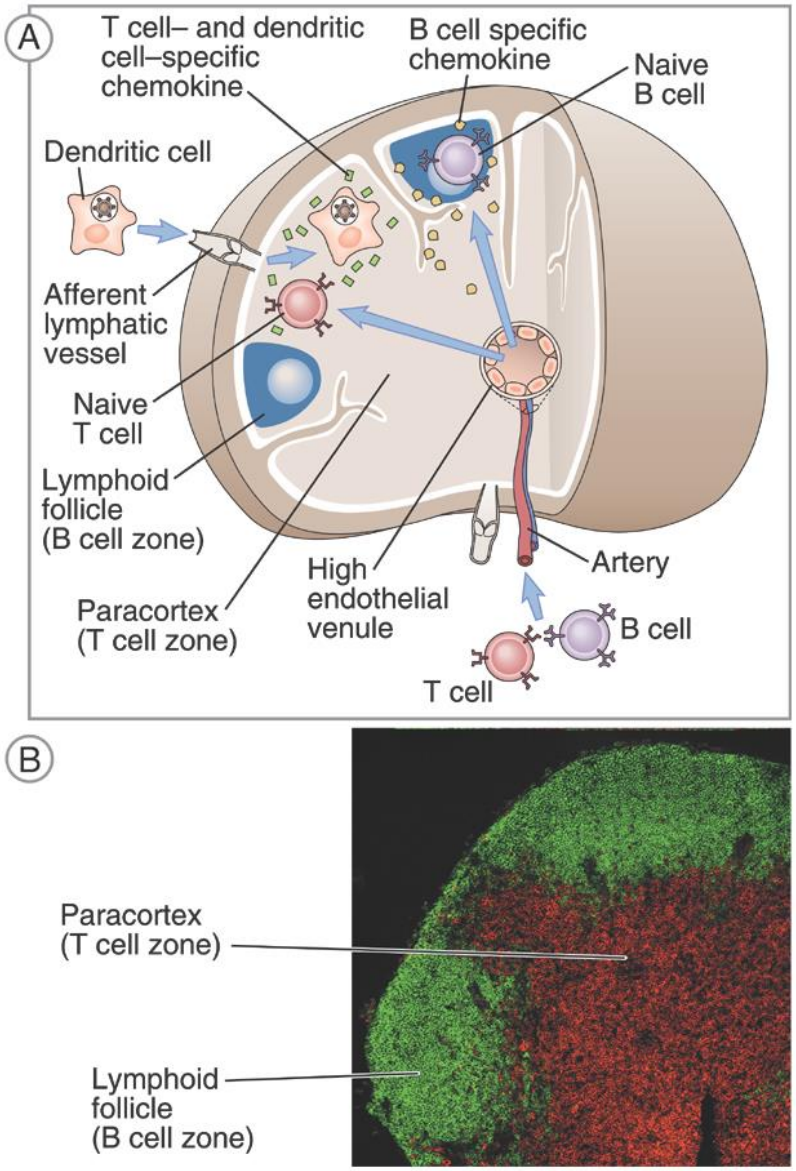
- Different choices of which V, D or J (heavy) or V:J (light) segments are recombined and made in individual B-cells.
- Productive rearrangements occur only on one chromosome (allelic exclusion).
- Each of these rearrangements and combinations has a different primary amino acid sequence.
- Each B cell thus would thus carries a different BCR with different antigen binding capabilities (idiotypes).

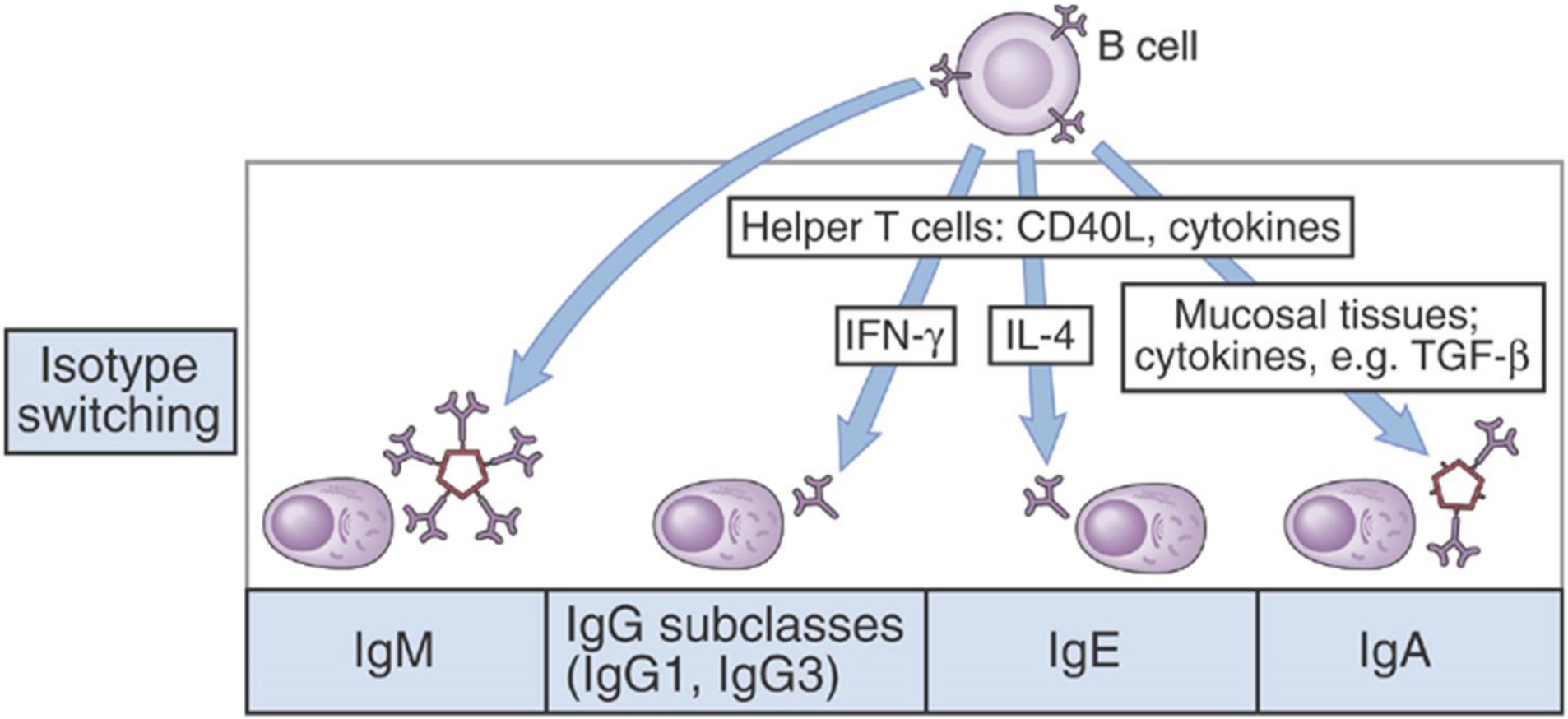
Where this all happens



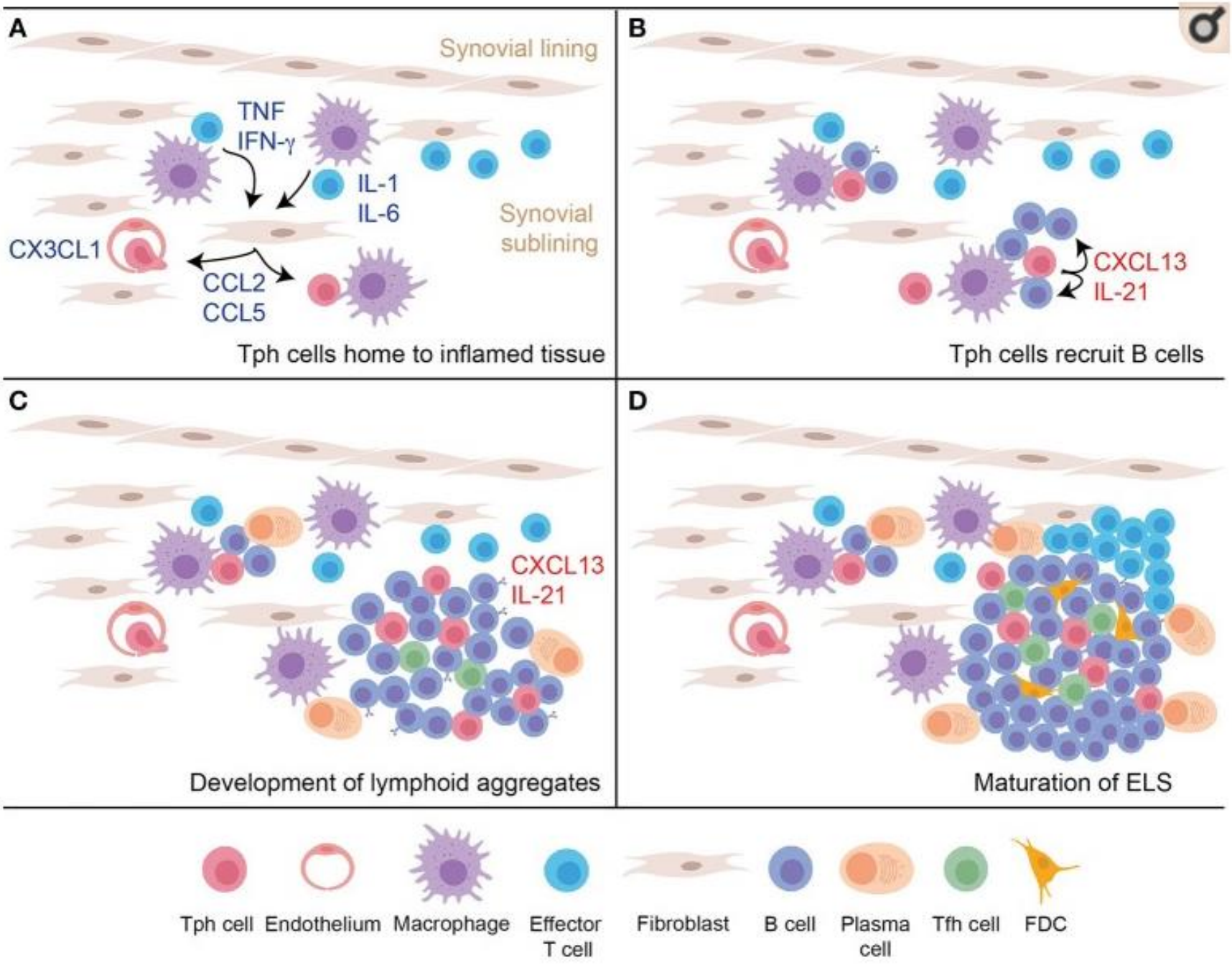
Journal of Allergy and Clinical Immunology 2010 125, S33-S40DOI: (10.1016/j.jaci.2009.09.017)

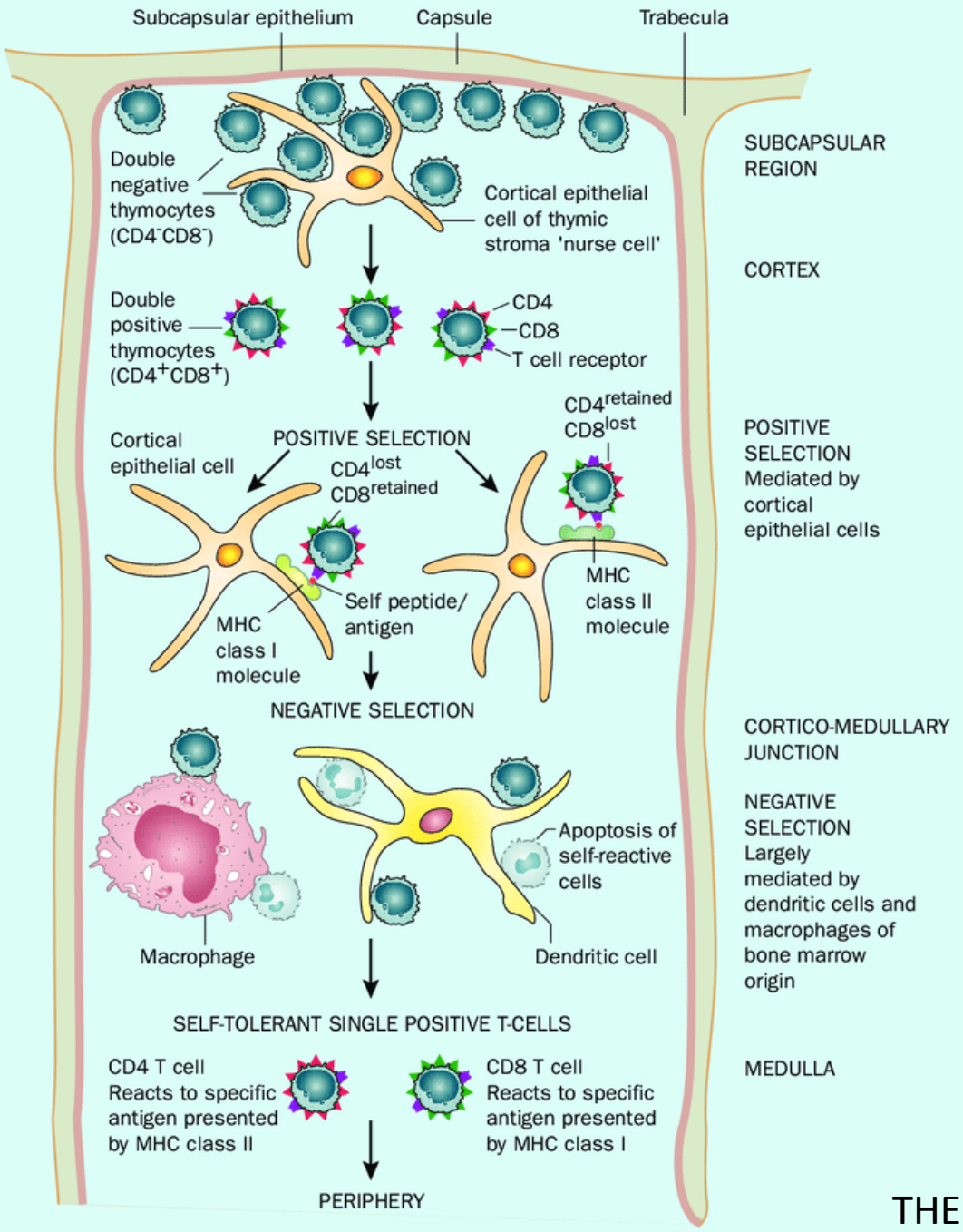
B cells need T cells (and everyone needs DC)





Principal effector functions	Complement activation	Fc receptor–dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)


A
Synovial lining
TNF
IFN-γ
IL-1
IL-6
Synovial
sublining
CX3CL1
CCL2
CCL5
Tph cells home to inflamed tissue
B
CXCL13
IL-21
Tph cells recruit B cells
C
CXCL13
IL-21
Development of lymphoid aggregates
D
Maturation of ELS
Tph cell
Endothelium
Macrophage
Effector T cell
Fibroblast
B cell
Plasma cell
Tfh cell
FDC


Subcapsular epithelium
Capsule
Trabecula
SUBCAPSULAR REGION
Double negative thymocytes (CD4⁻CD8⁻)
Cortical epithelial cell of thymic stroma 'nurse cell'
CORTEX
Double positive thymocytes (CD4⁺CD8⁺)
CD4
CD8
T cell receptor
CD4retained CD8lost
POSITIVE SELECTION
Cortical epithelial cell
CD4lost CD8retained
POSITIVE SELECTION Mediated by cortical epithelial cells
MHC class I molecule
Self peptide/ antigen
MHC class II molecule
NEGATIVE SELECTION
CORTICO-MEDULLARY JUNCTION
NEGATIVE SELECTION Largely mediated by dendritic cells and macrophages of bone marrow origin
Apoptosis of self-reactive cells
Macrophage
Dendritic cell
SELF-TOLERANT SINGLE POSITIVE T-CELLS
MEDULLA
CD4 T cell Reacts to specific antigen presented by MHC class II
CD8 T cell Reacts to specific antigen presented by MHC class I
PERIPHERY

TCR loci alpha and beta chain rearrangements

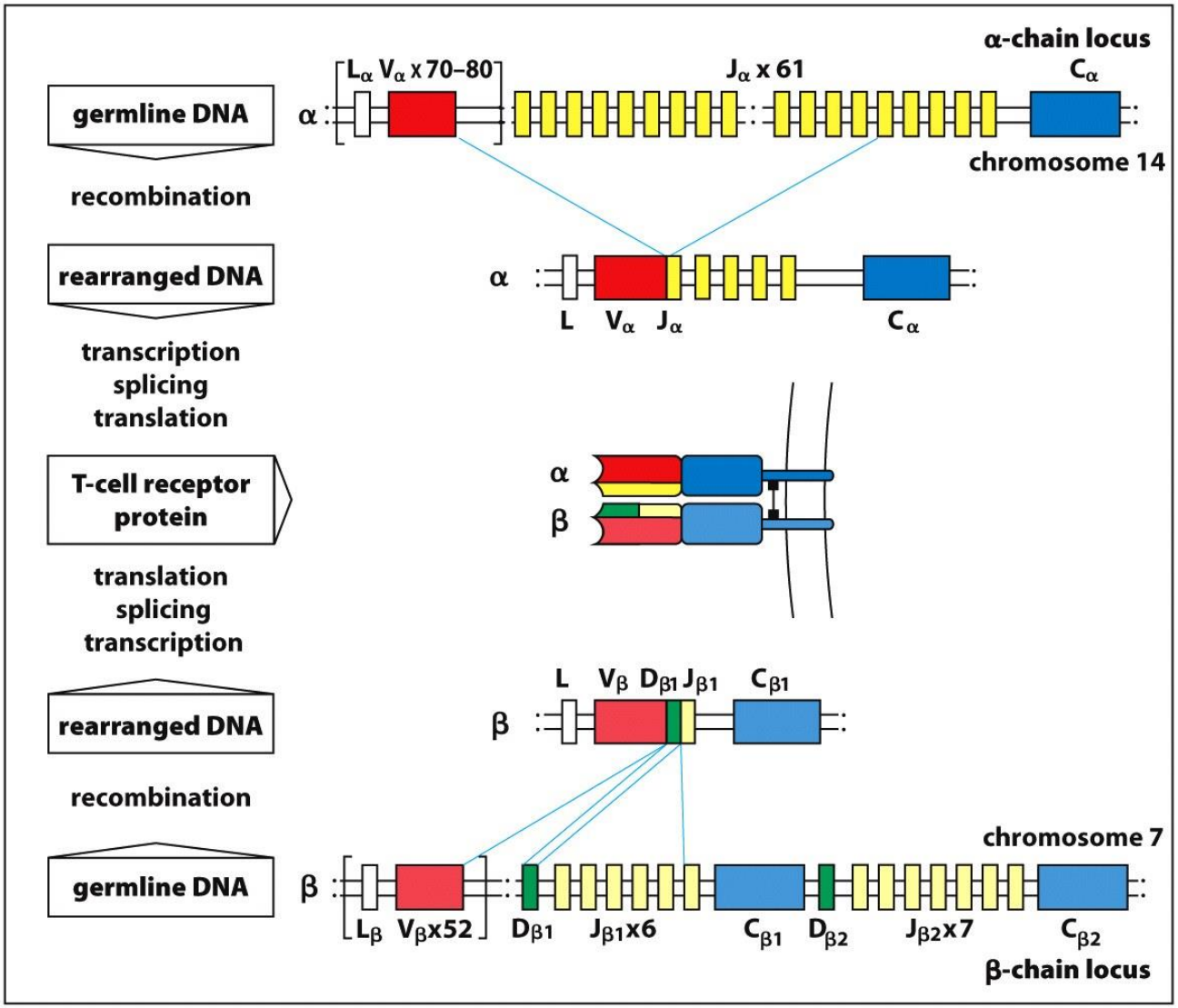


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

BCR vs TCR

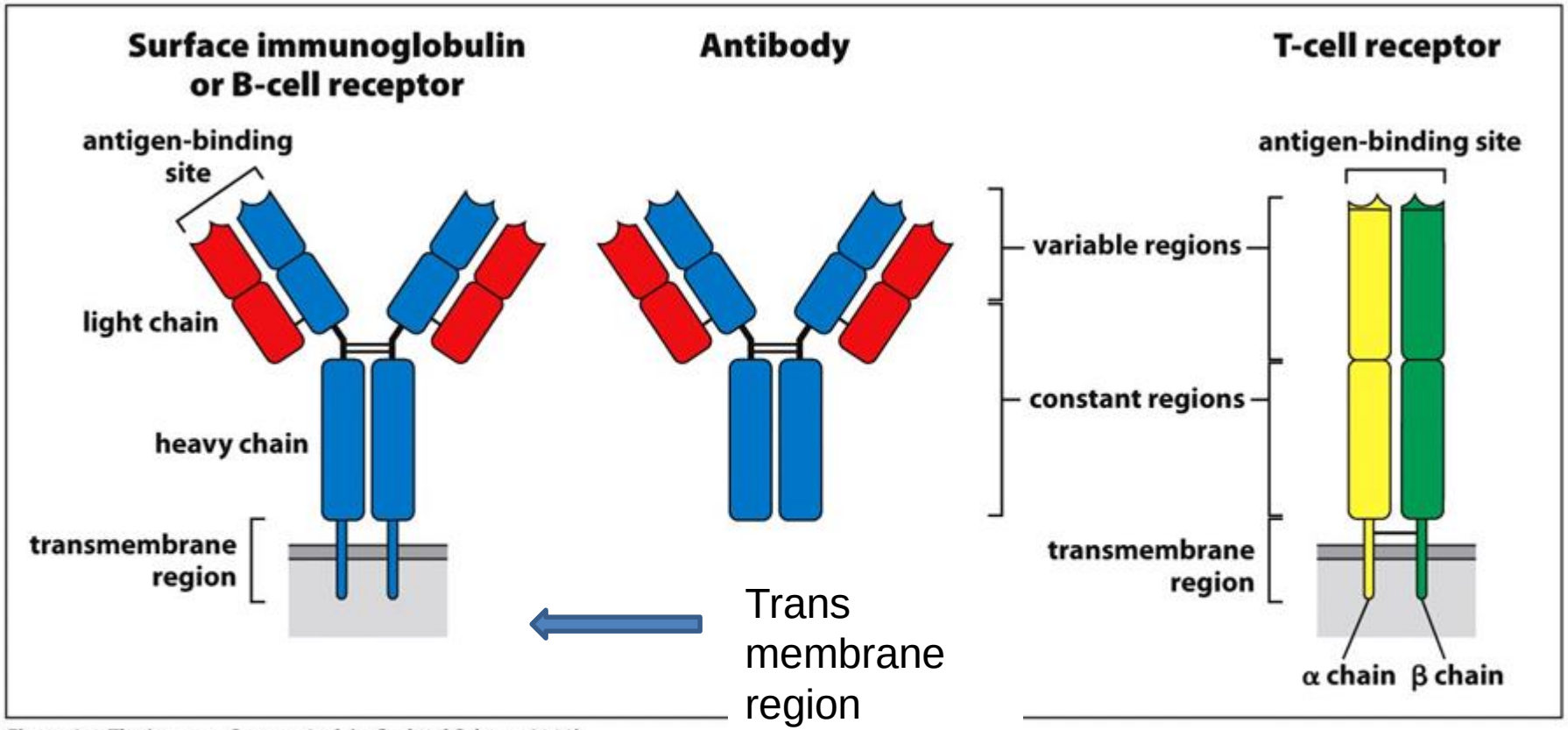
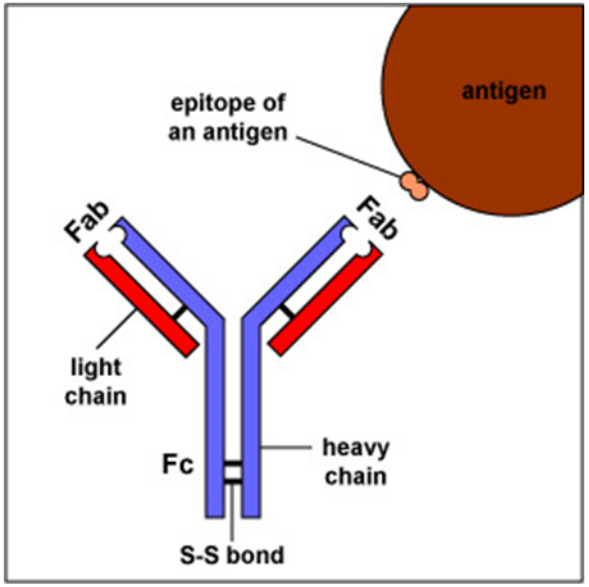
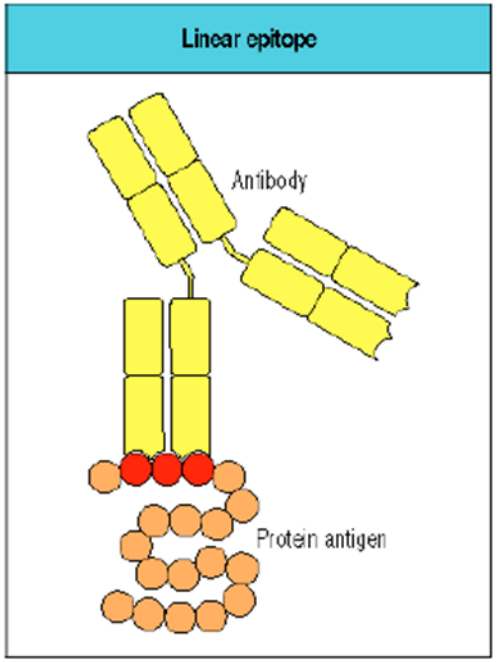


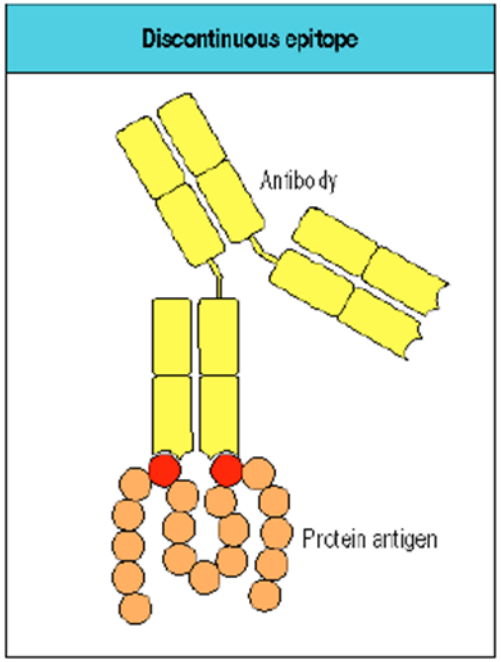
Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

Trans membrane region missing in secreted Ig

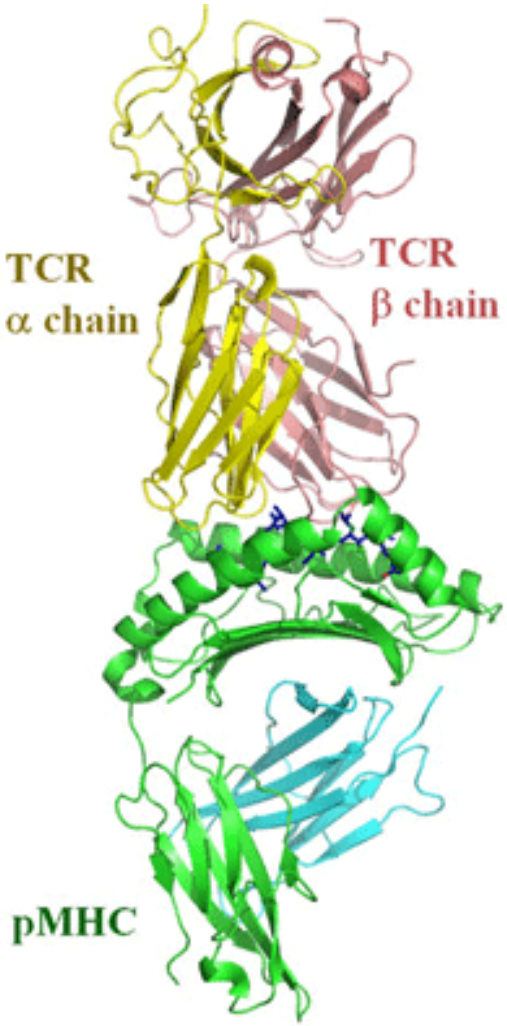
Antibody molecules only recognize a part of a large antigen, the epitope





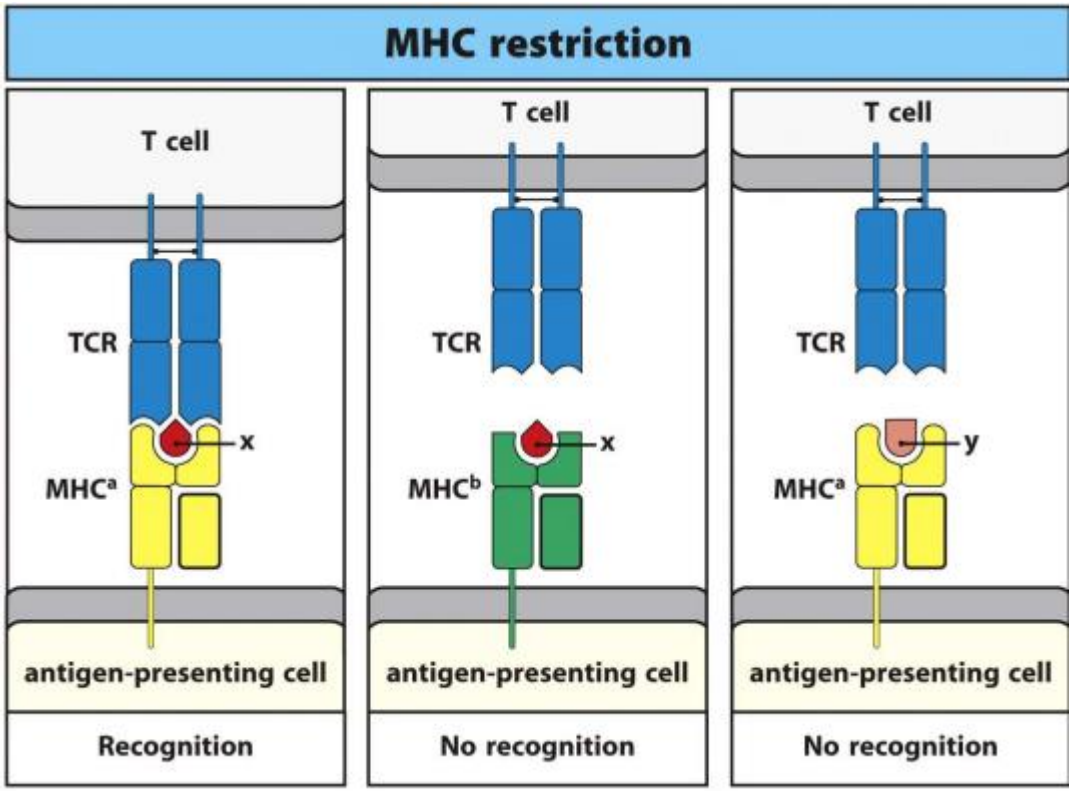


Contrast between B cell antigen recognition and T cell's need for MHC



The interaction between the TCR (yellow and salmon) the pMHCI (green and cyan)

Each (TCR/ MHC + antigenic peptide) is attached to a cell membrane
TCR shows MHC restriction



1980 Nobel Prize

Jean Dausset

Baruj Benaceraff

George Snell

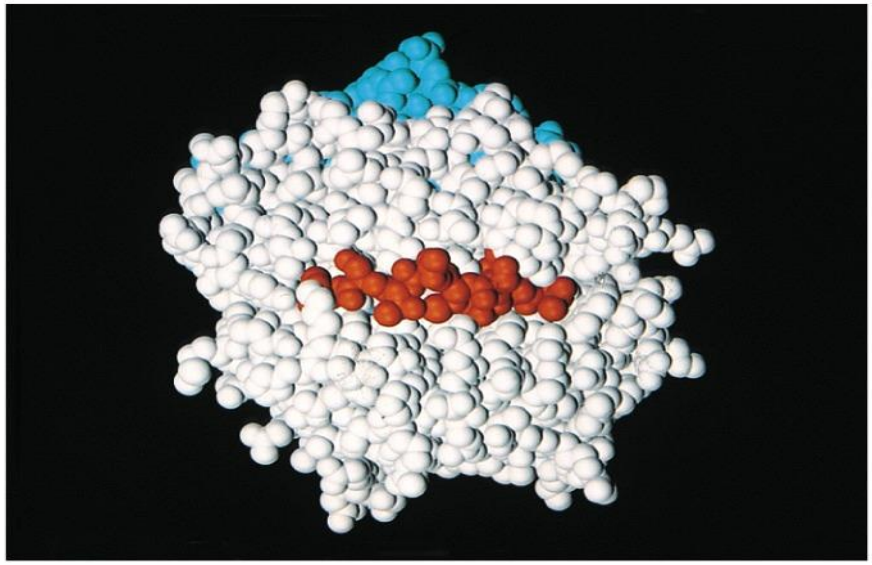
Nobel Prize in 1996 for "discovering the nature of the cellular immune defense"

Dr. Pamela Bjorkman

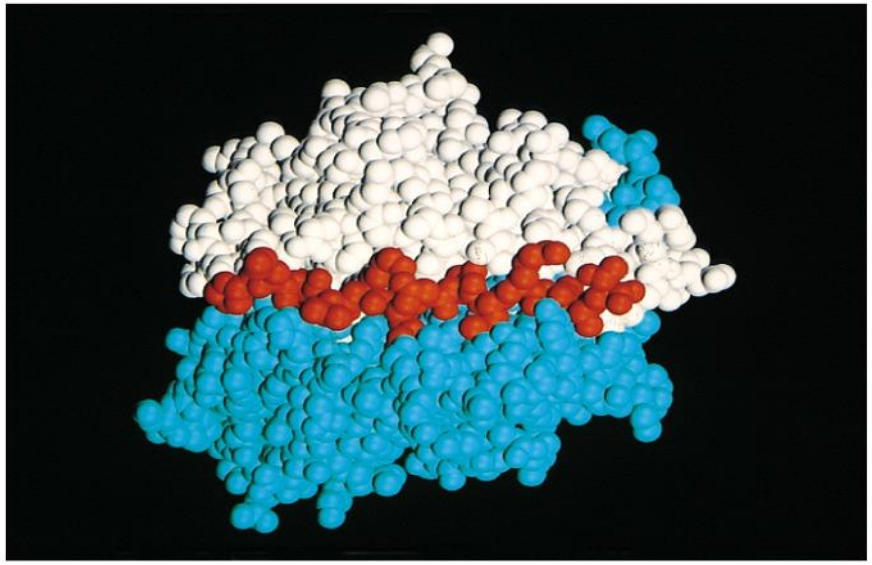
Don Wiley, 1944-2002

A picture is worth a thousand experiments

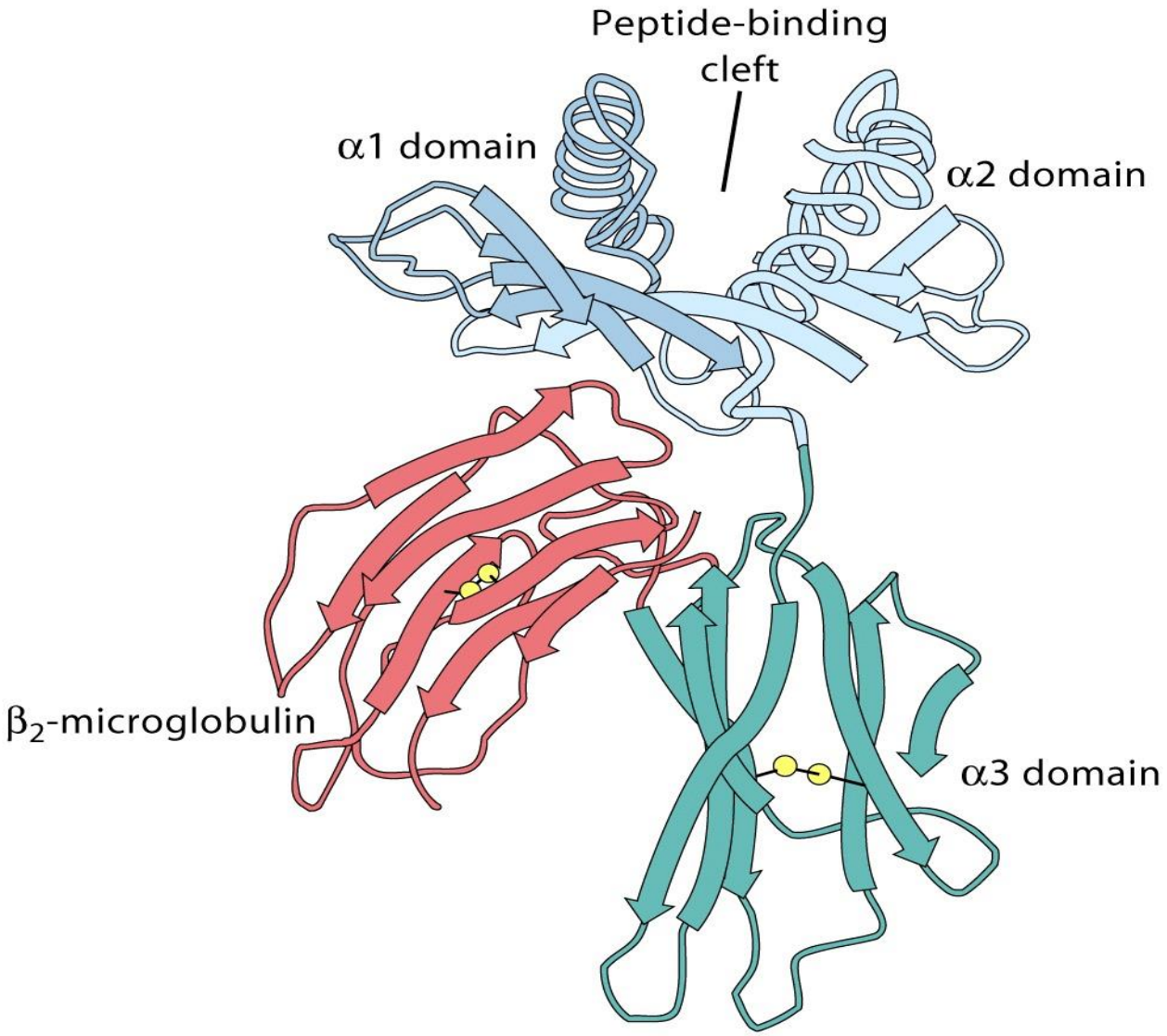
(a) **Class I MHC**

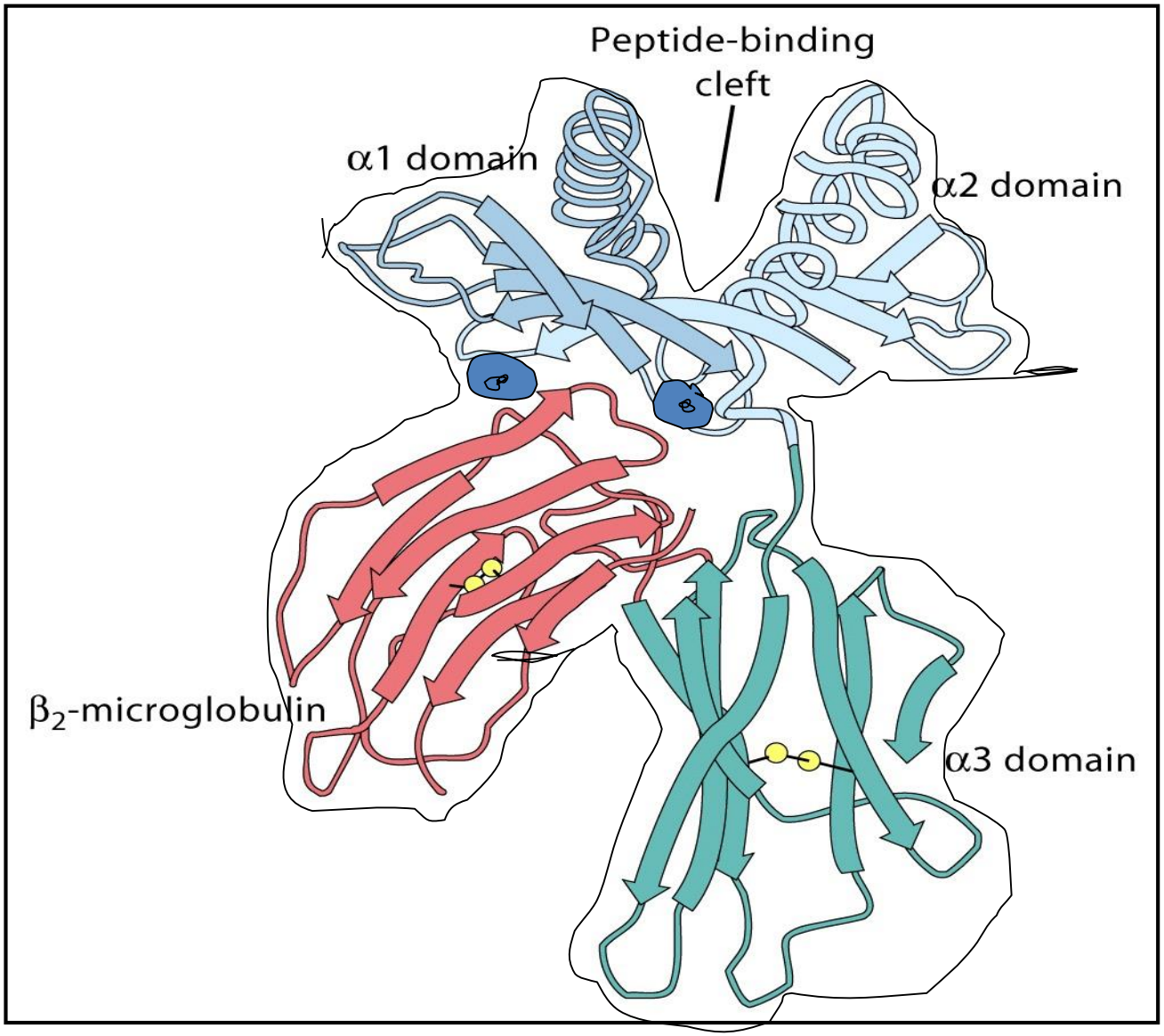


(b) **Class II MHC**

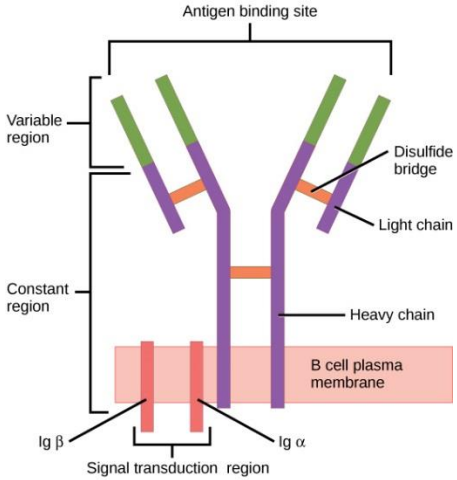


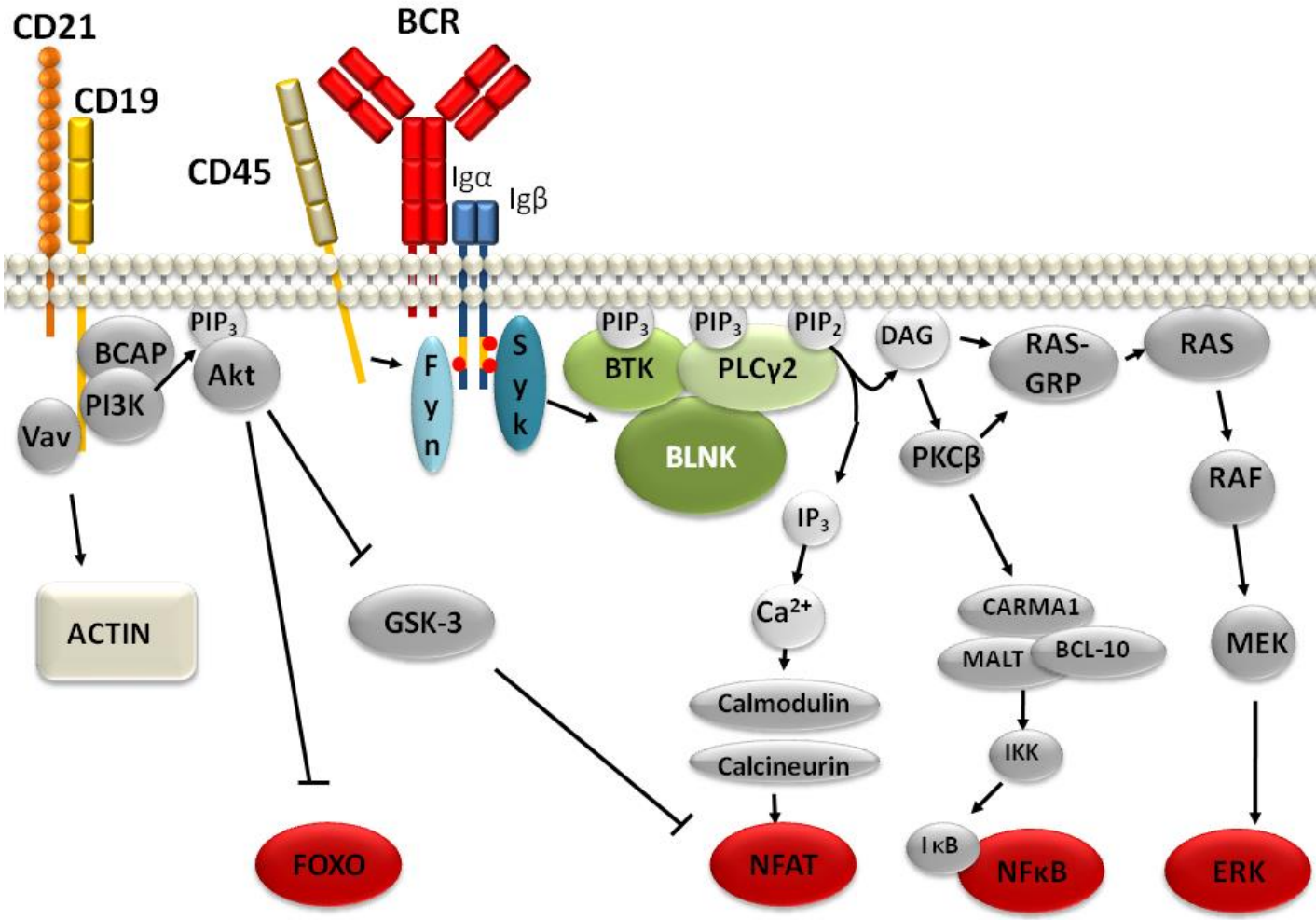
Between 1985-1995


Peptide-binding
cleft
α1 domain
α2 domain
β2-microglobulin
α3 domain

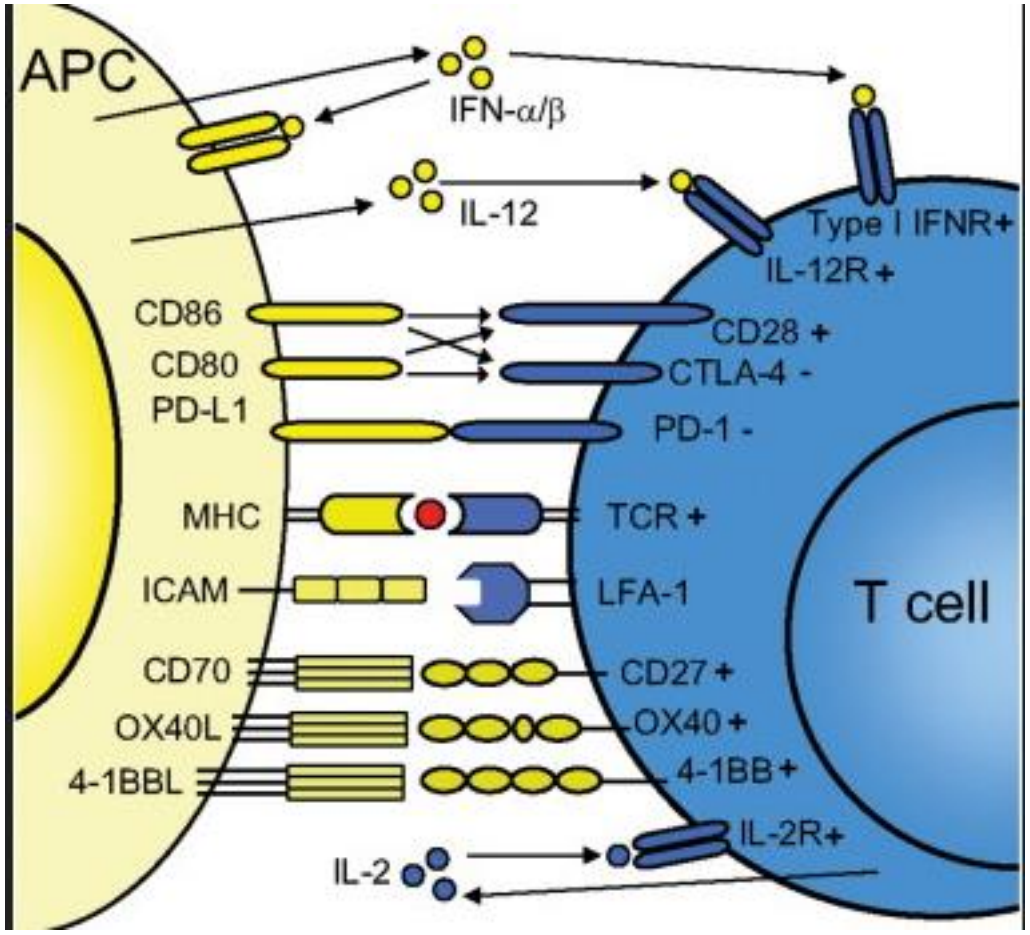

Peptide-binding
cleft
α1 domain
α2 domain
β2-microglobulin
α3 domain

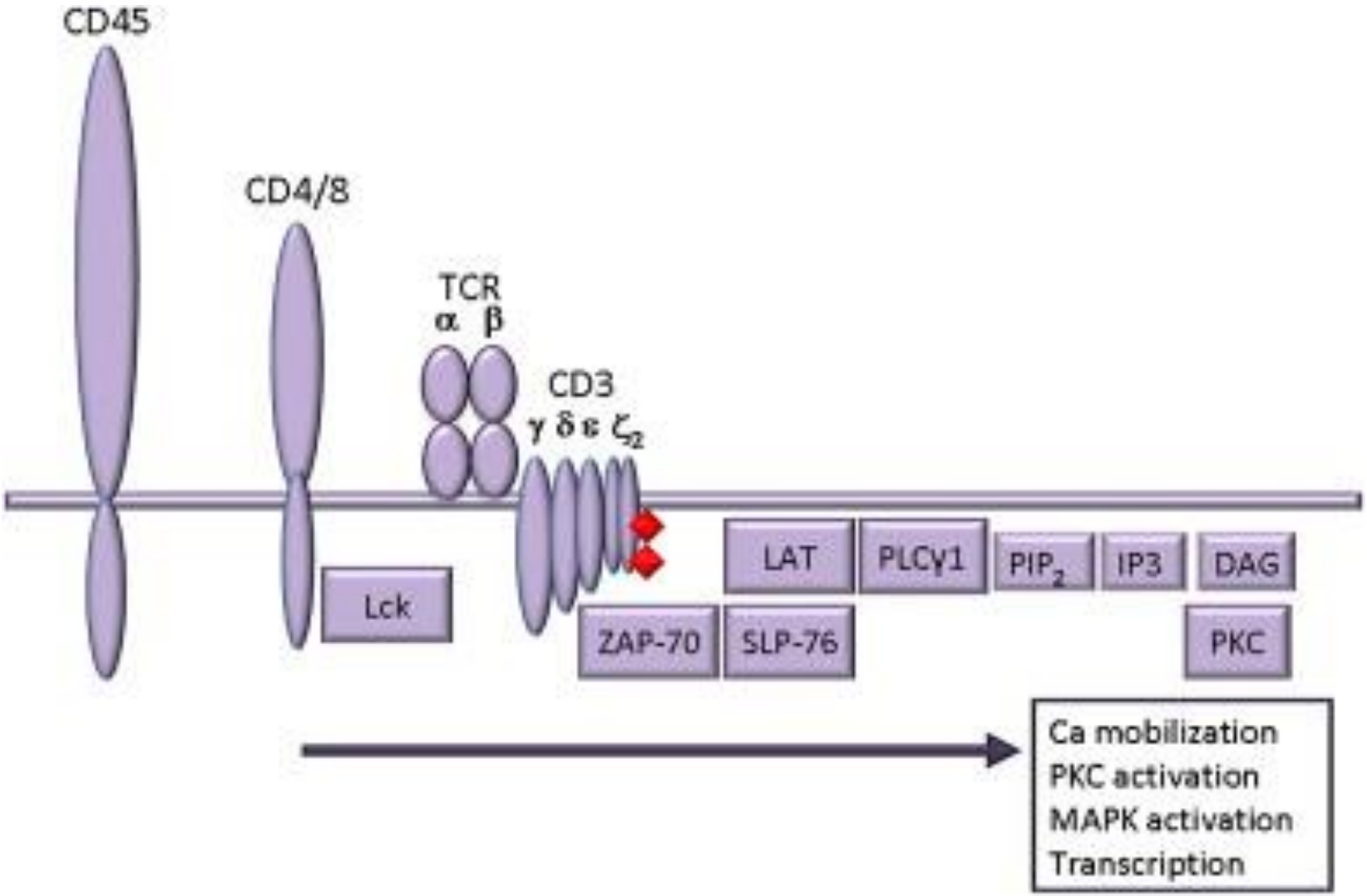
Signaling through BCR





T cell recognition of antigen





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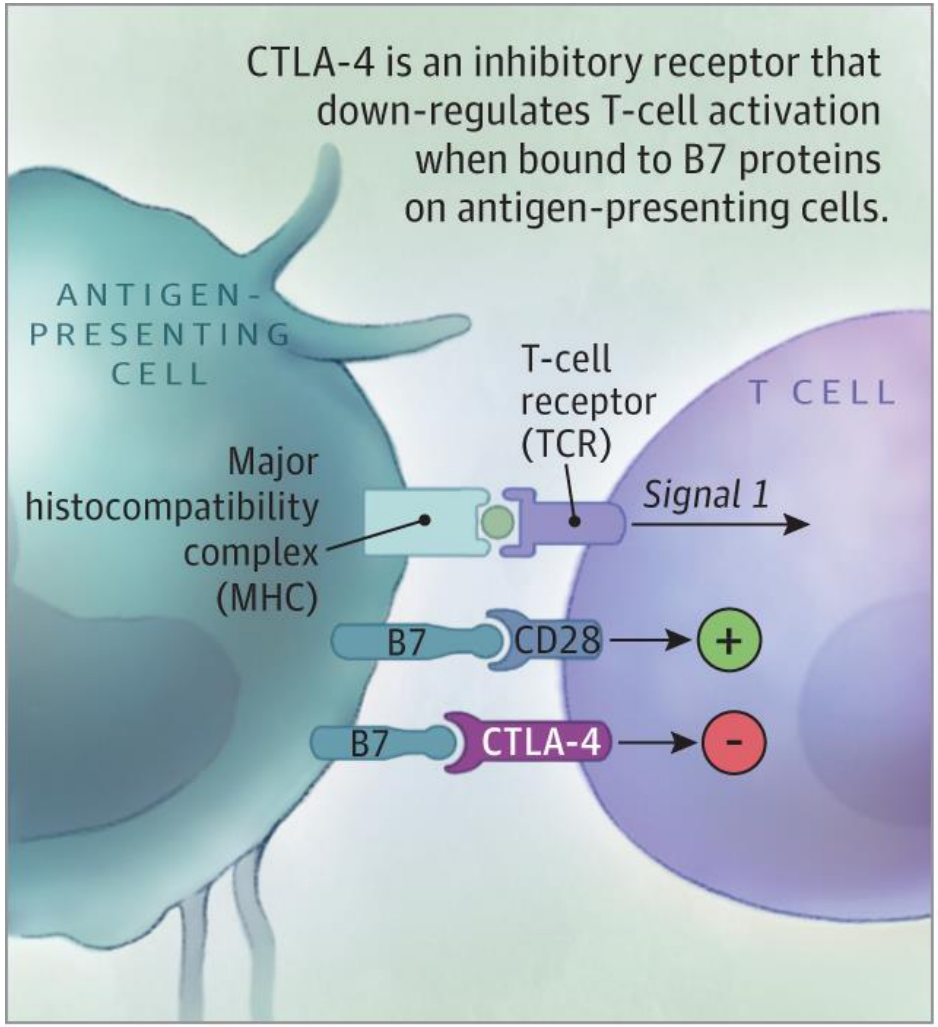
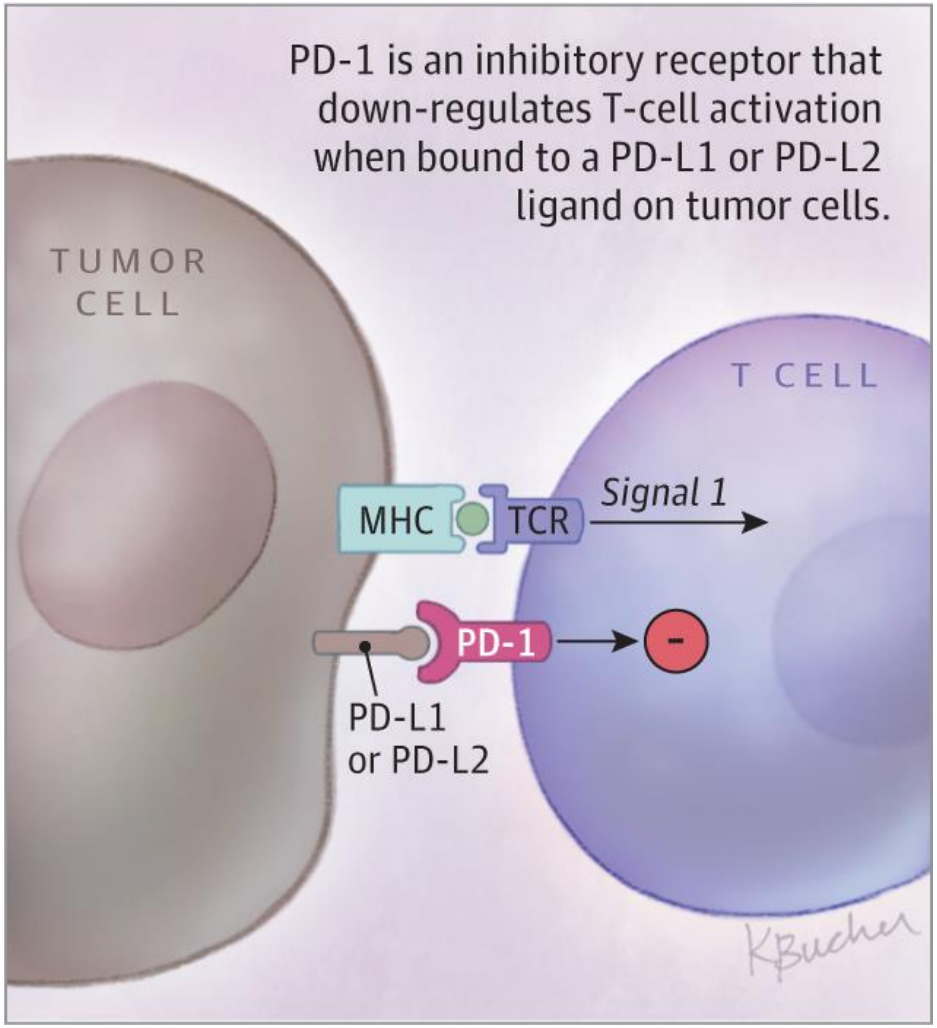
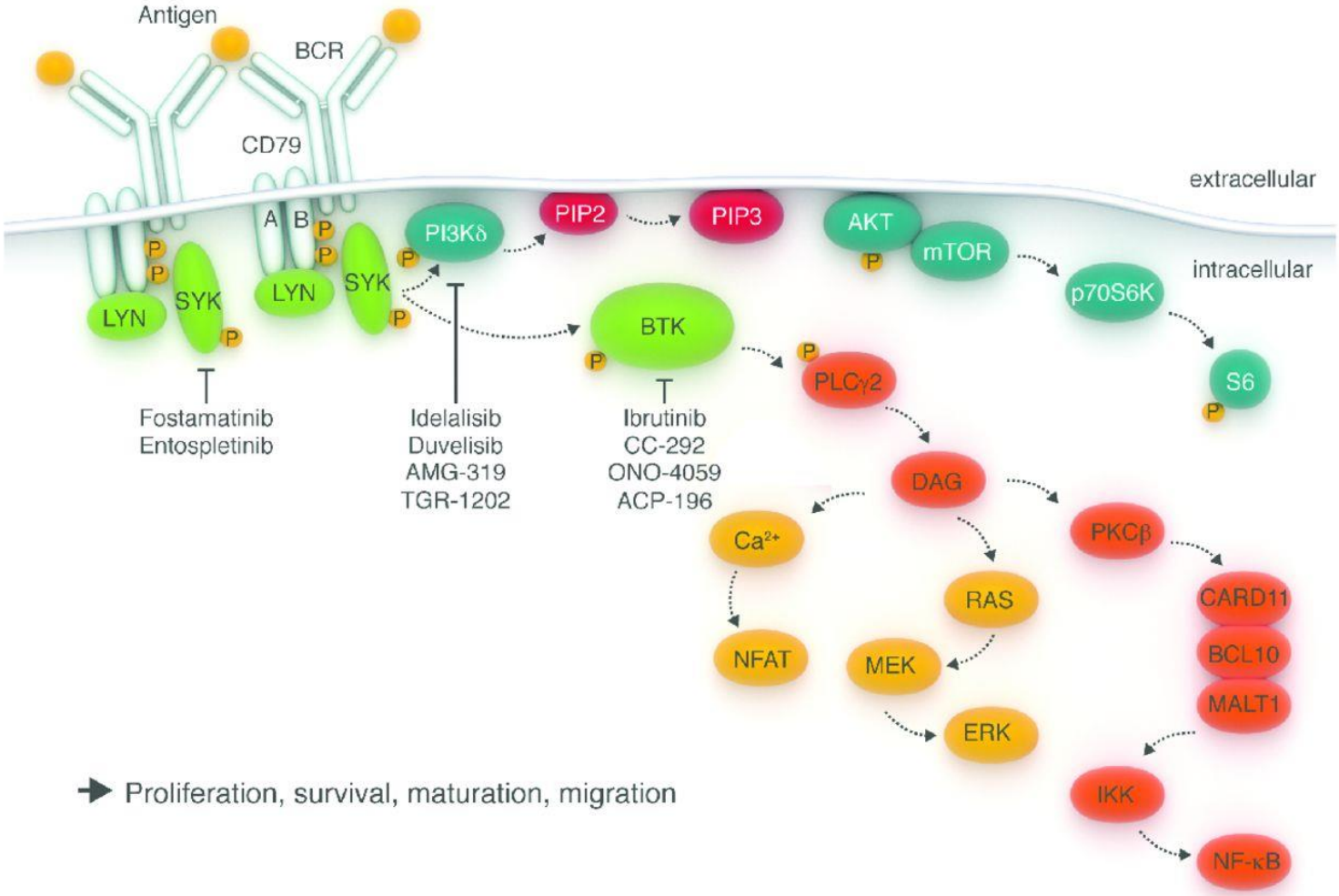

CTLA-4 is an inhibitory receptor that down-regulates T-cell activation when bound to B7 proteins on antigen-presenting cells.
ANTIGEN-PRESENTING CELL
T CELL
T-cell receptor (TCR)
Major histocompatibility complex (MHC)
Signal 1
B7
CD28
+
B7
CTLA-4
-

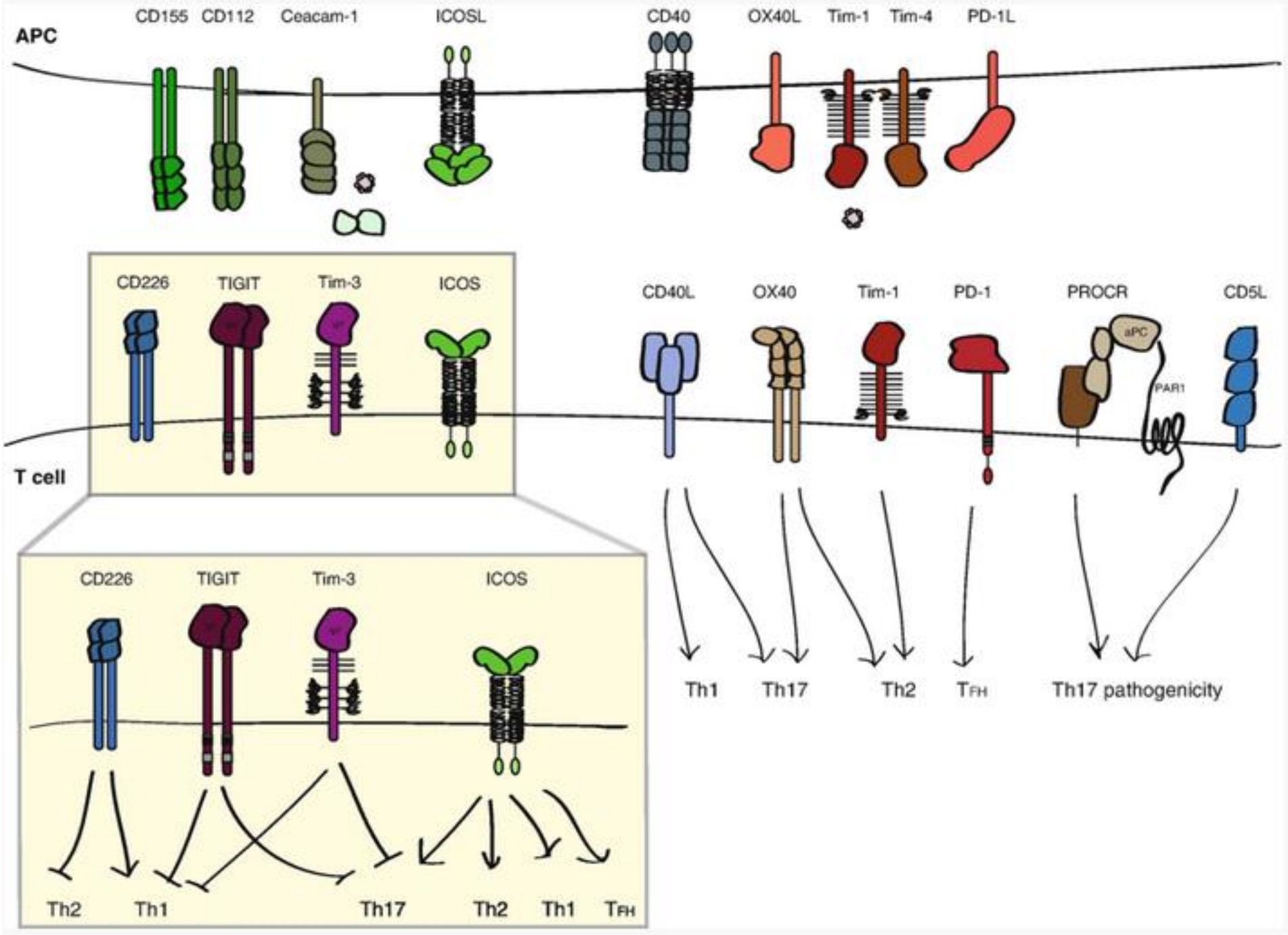

PD-1 is an inhibitory receptor that down-regulates T-cell activation when bound to a PD-L1 or PD-L2 ligand on tumor cells.
TUMOR CELL
T CELL
MHC
TCR
Signal 1
PD-1
-
PD-L1 or PD-L2
KBucher

BCR signaling and downstream pathways.

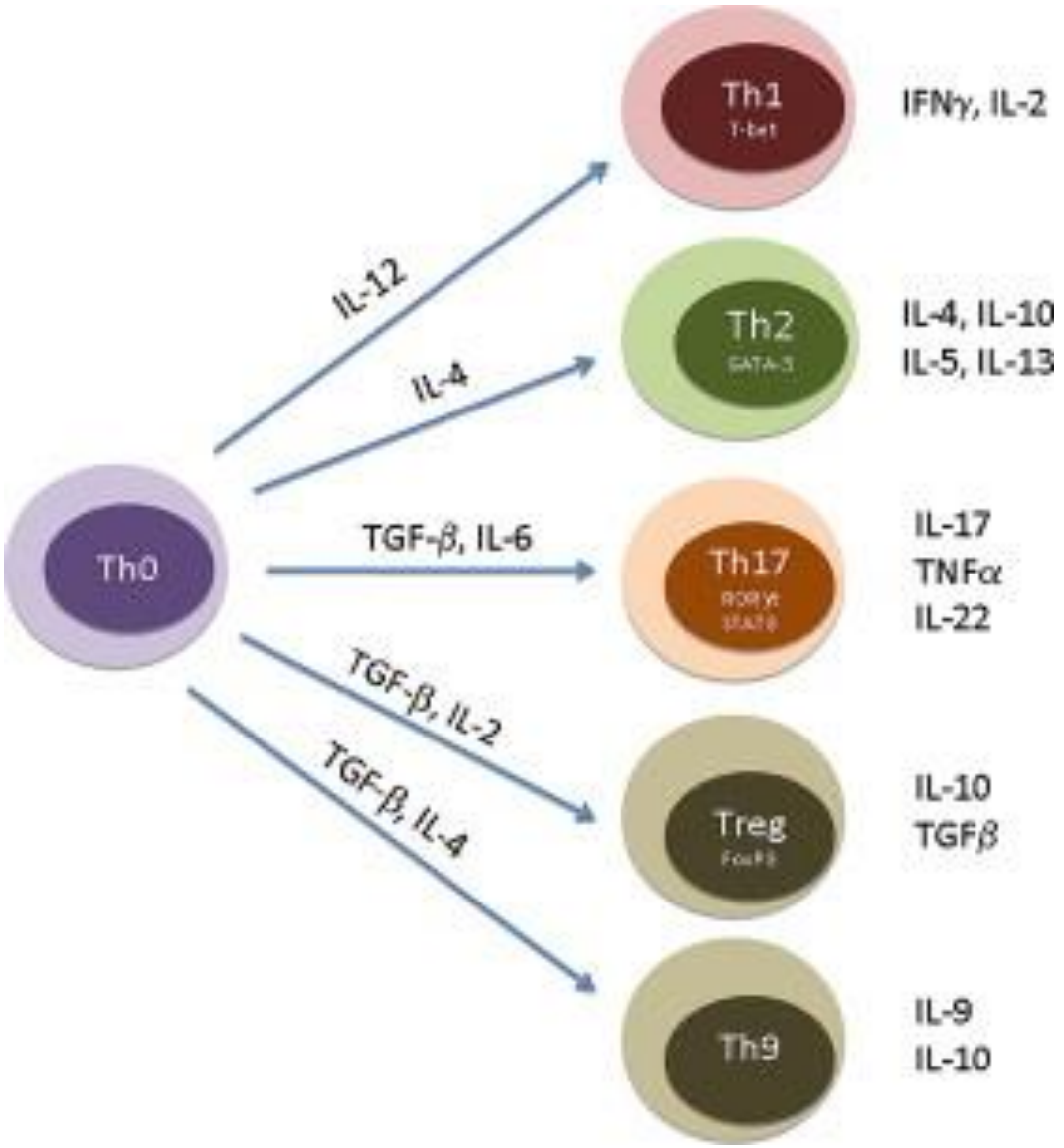


Adrian Wiestner Haematologica 2015;100:1495-1507

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation


APC
CD155
CD112
Ceacam-1
ICOSL
CD40
OX40L
Tim-1
Tim-4
PD-1L
T cell
CD226
TIGIT
Tim-3
ICOS
CD40L
OX40
Tim-1
PD-1
PROCR
CD5L
aPC
PAR1
Th1
Th17
Th2
TFH
Th17 pathogenicity
CD226
TIGIT
Tim-3
ICOS
Th2
Th1
Th17
Th2
Th1
TFH

MHC Class II restricted CD4 T helper cell subsets



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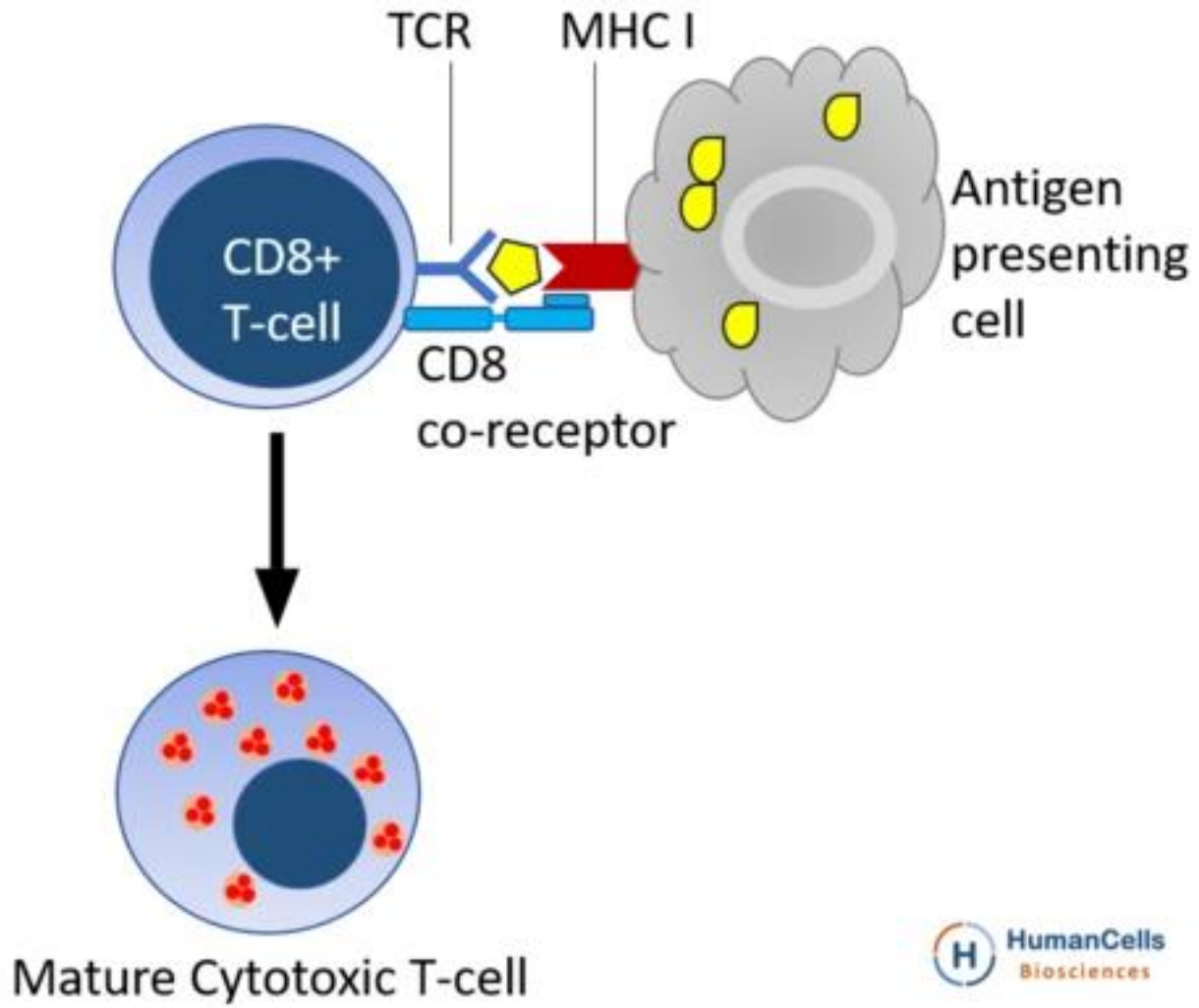
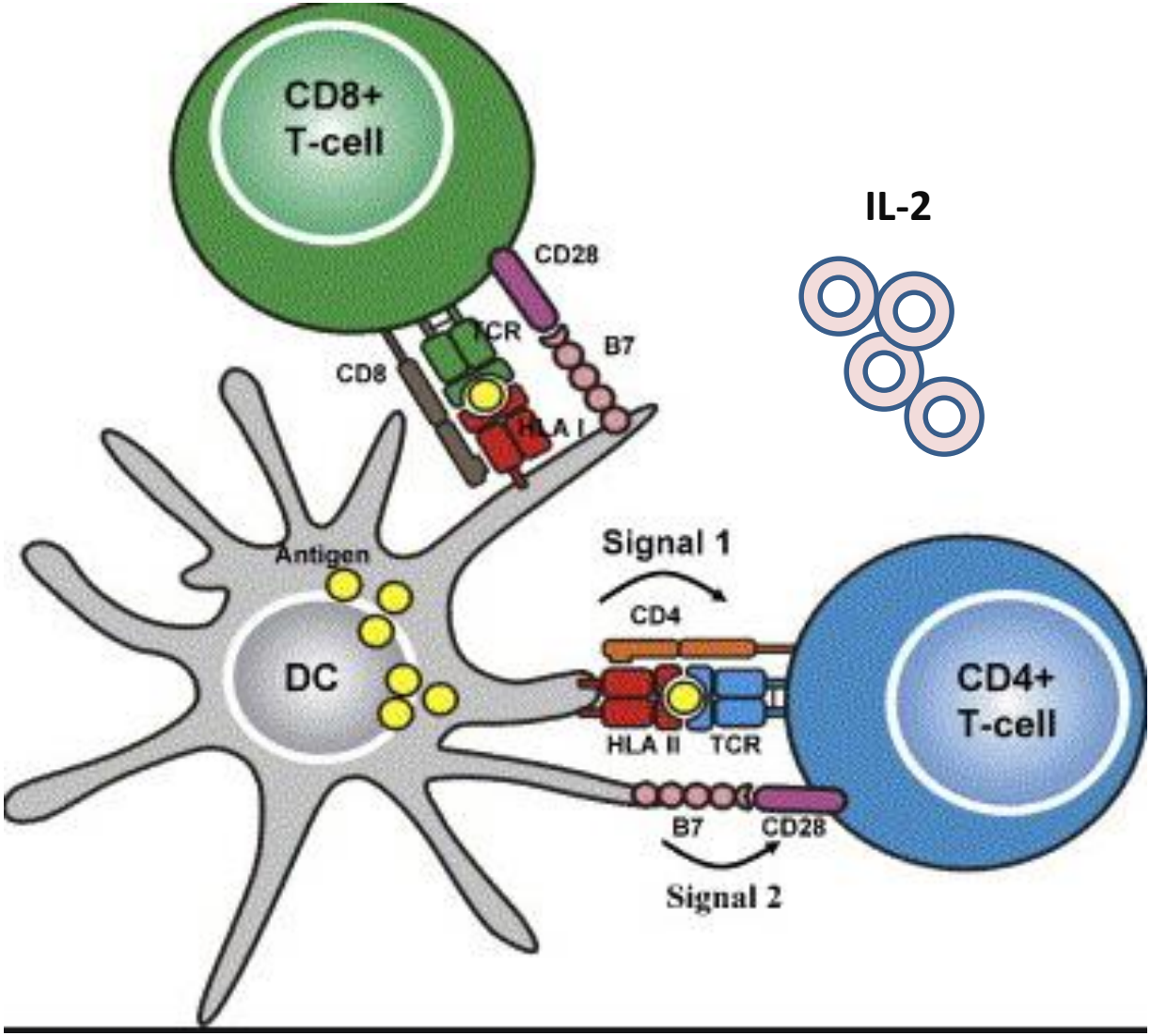
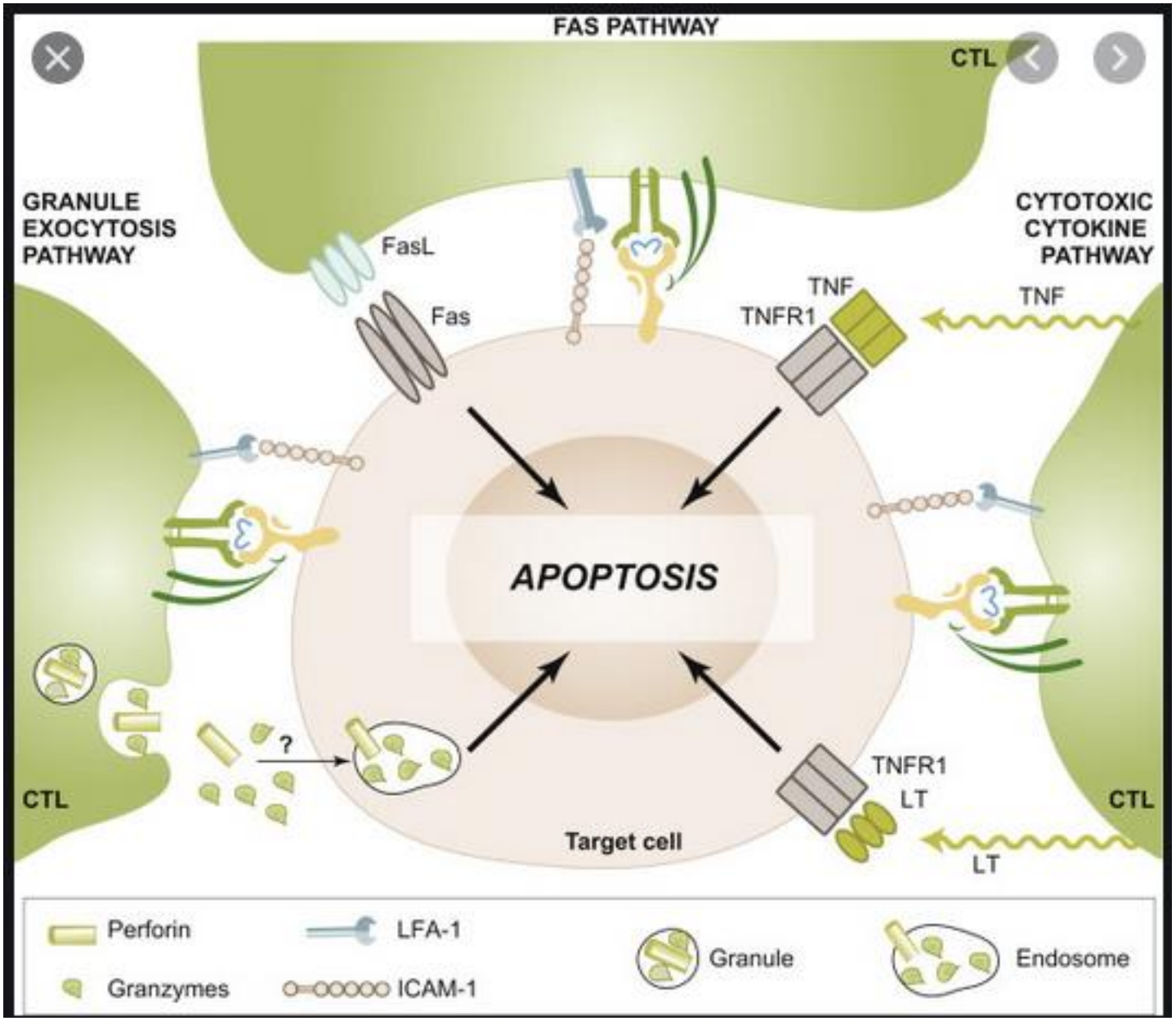
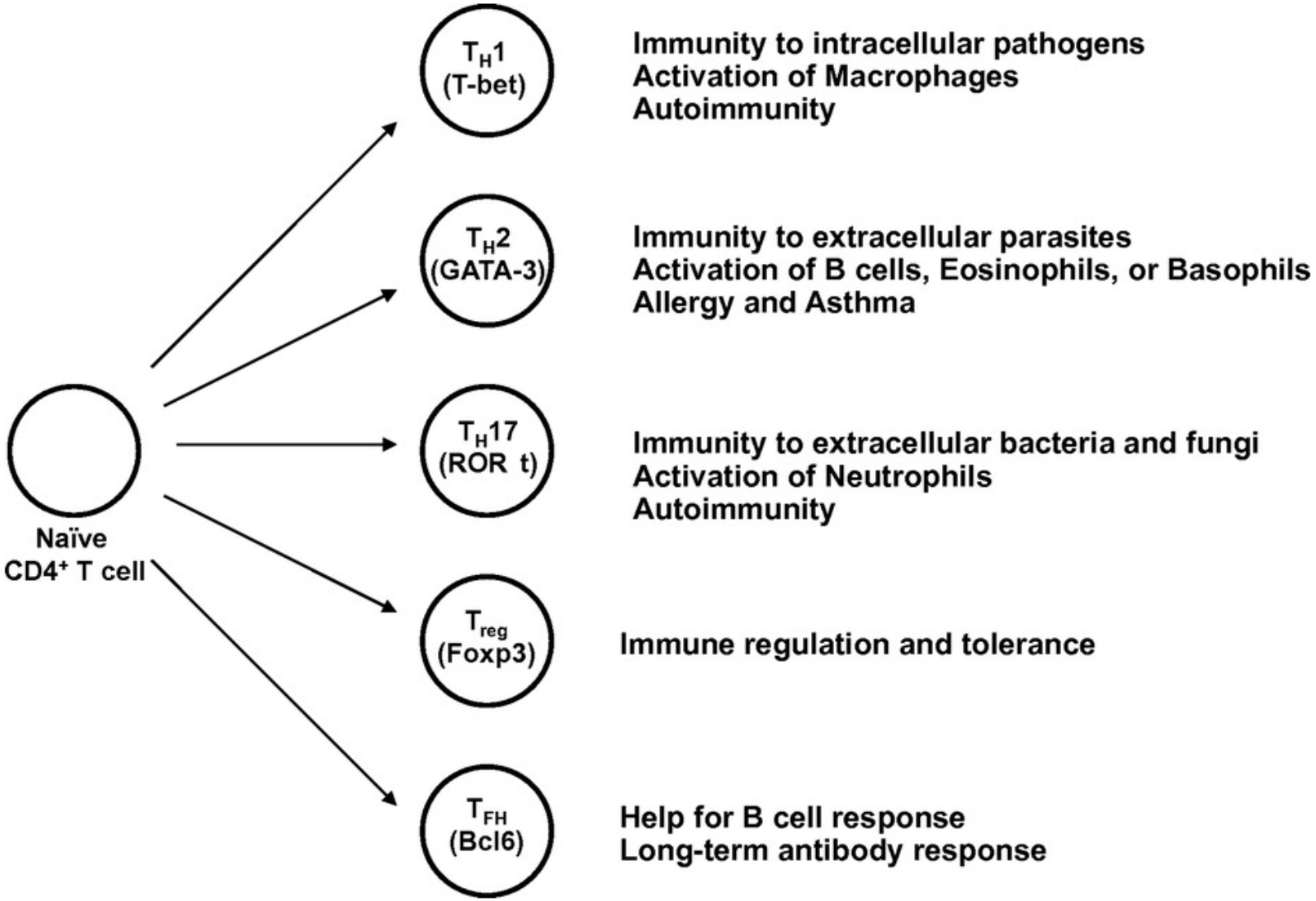
MHC Class I restricted CD8 T cells



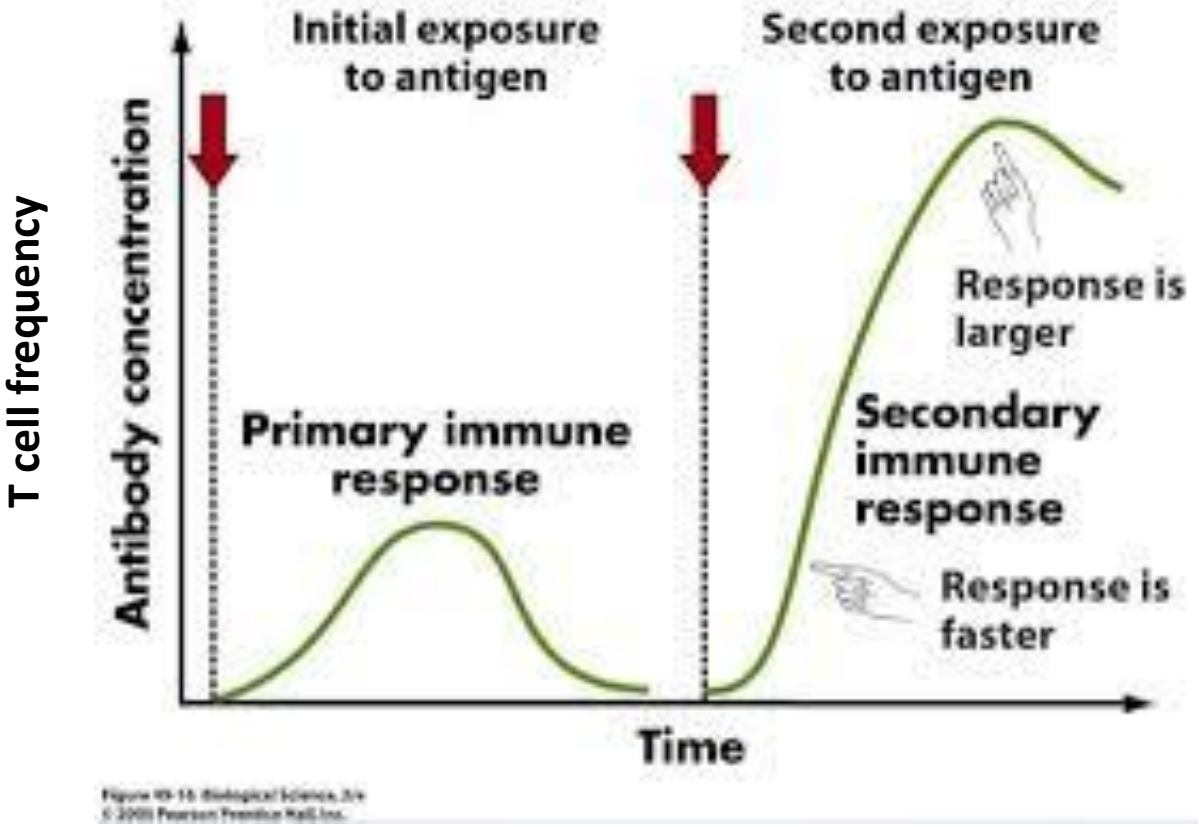
CD8 T cells need CD4 T cell help




FAS PATHWAY
CTL
GRANULE EXOCYTOSIS PATHWAY
CYTOTOXIC CYTOKINE PATHWAY
FasL
Fas
TNF
TNFR1
TNF
APOPTOSIS
?
CTL
CTL
TNFR1
LT
LT
Target cell
Perforin
LFA-1
Granule
Endosome
Granzymes
ICAM-1


Naïve
CD4+ T cell
TH1
(T-bet)
TH2
(GATA-3)
TH17
(ROR t)
Treg
(Foxp3)
TFH
(Bcl6)
Immunity to intracellular pathogens
Activation of Macrophages
Autoimmunity
Immunity to extracellular parasites
Activation of B cells, Eosinophils, or Basophils
Allergy and Asthma
Immunity to extracellular bacteria and fungi
Activation of Neutrophils
Autoimmunity
Immune regulation and tolerance
Help for B cell response
Long-term antibody response

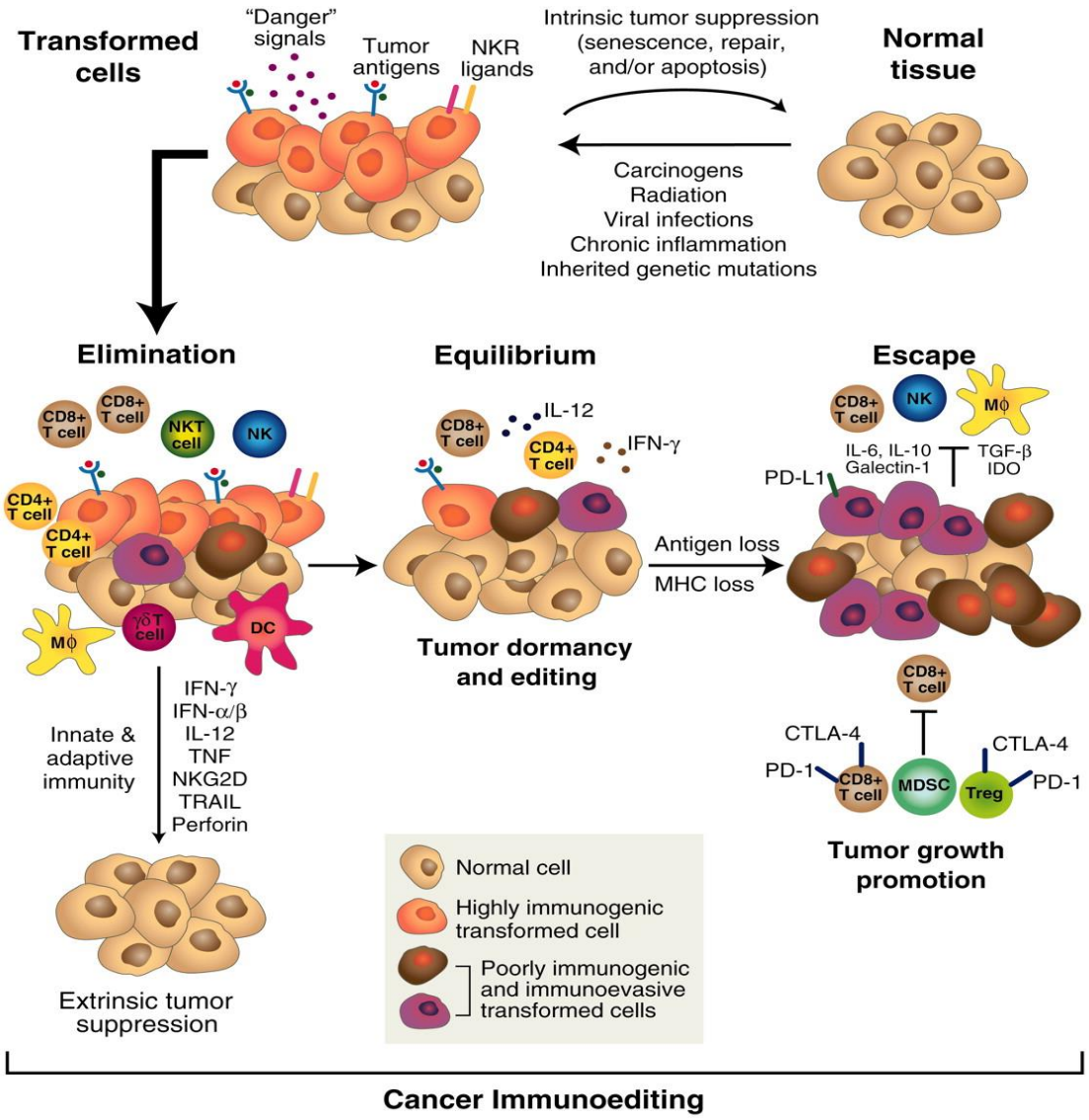
Primary vs secondary (memory) response



Summary: Adaptive Immunity

- Antigen specific and antigen driven
- Dependent on and jump-started by innate immunity
- Cellular effectors (T cells and B cells) and their soluble effectors responsible for disease elimination
- Cellular effectors directed to long term memory responsible for prevention of disease recurrence

Innate and adaptive immune symphony in tumor immunosurveillance



R D Schreiber et al. Science 2011;331:1565-1570

Recommended reading

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