Adaptive Immunity

Cellular Mechanisms and Signaling

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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

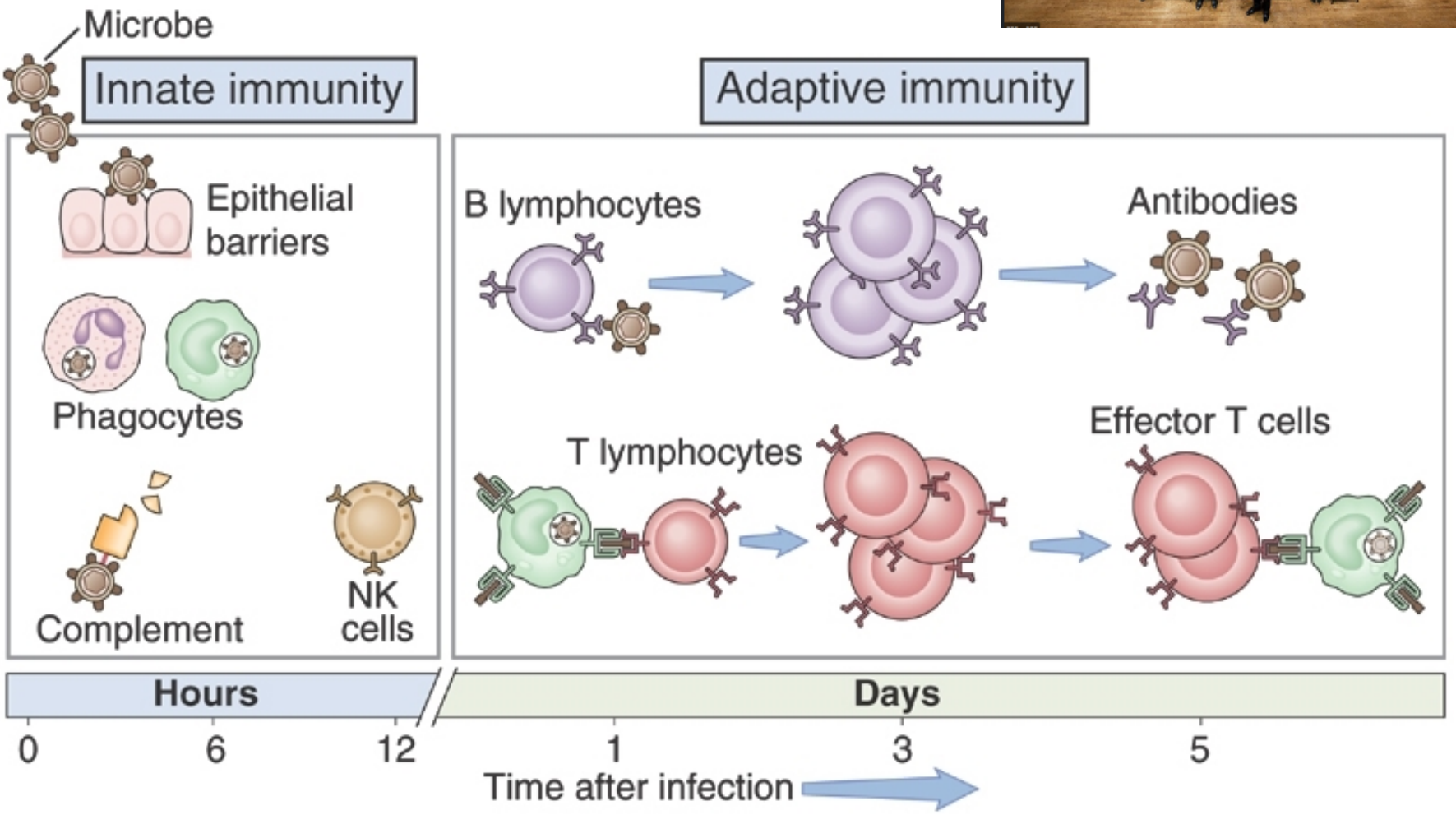
Two types of immunity

- **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

Perfectly orchestrated and timed system

Pittsburgh Symphony Orchestra



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Discovery of Humoral Immunity

- 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

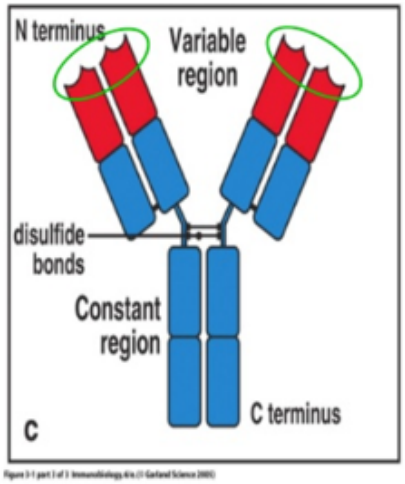
- Can be generated not only against bacteria but also against non-bacterial and totally innocuous substances (milk, eggwhite)

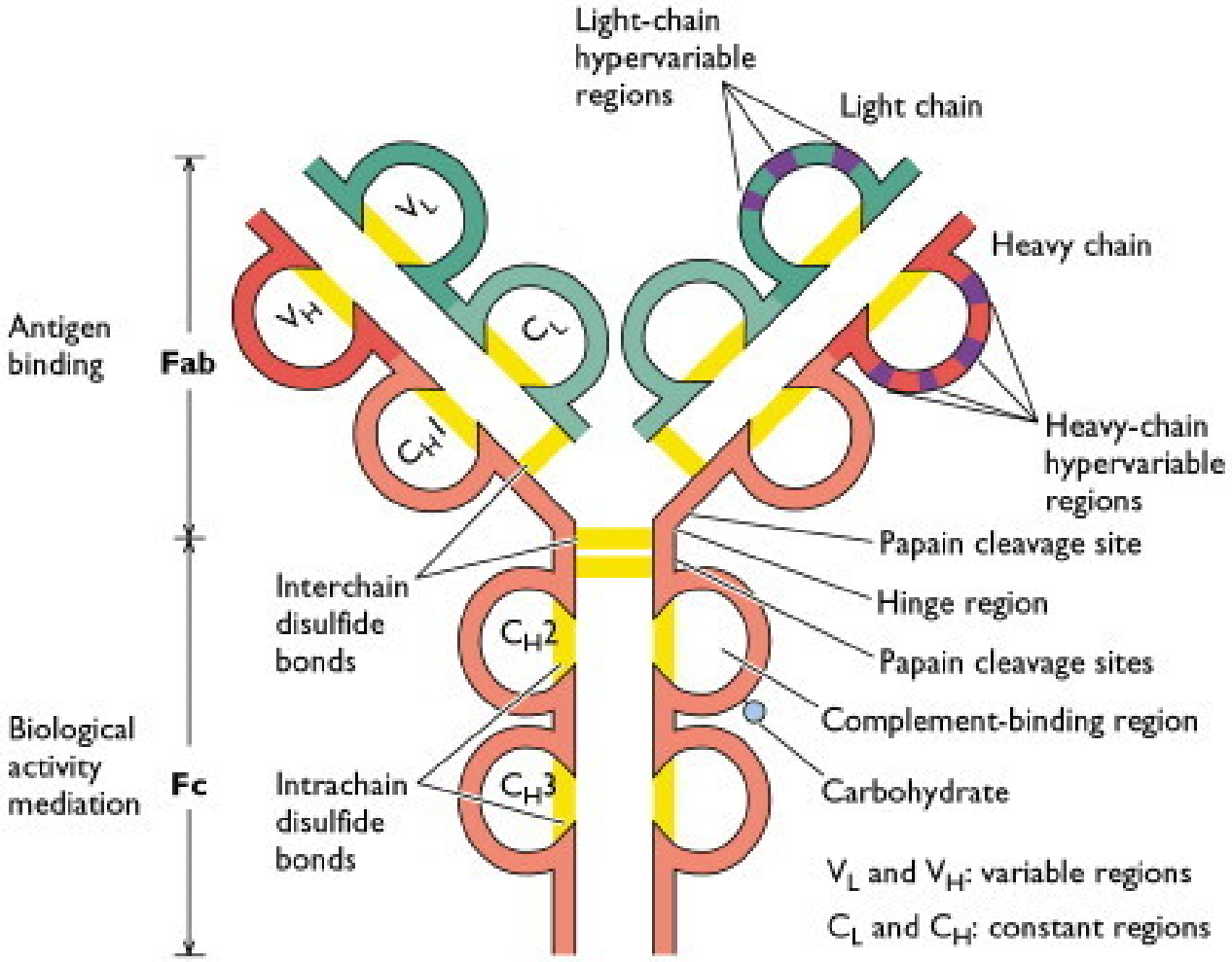
- Substances stimulating the appearance of antibodies were designated *antigens*

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





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*

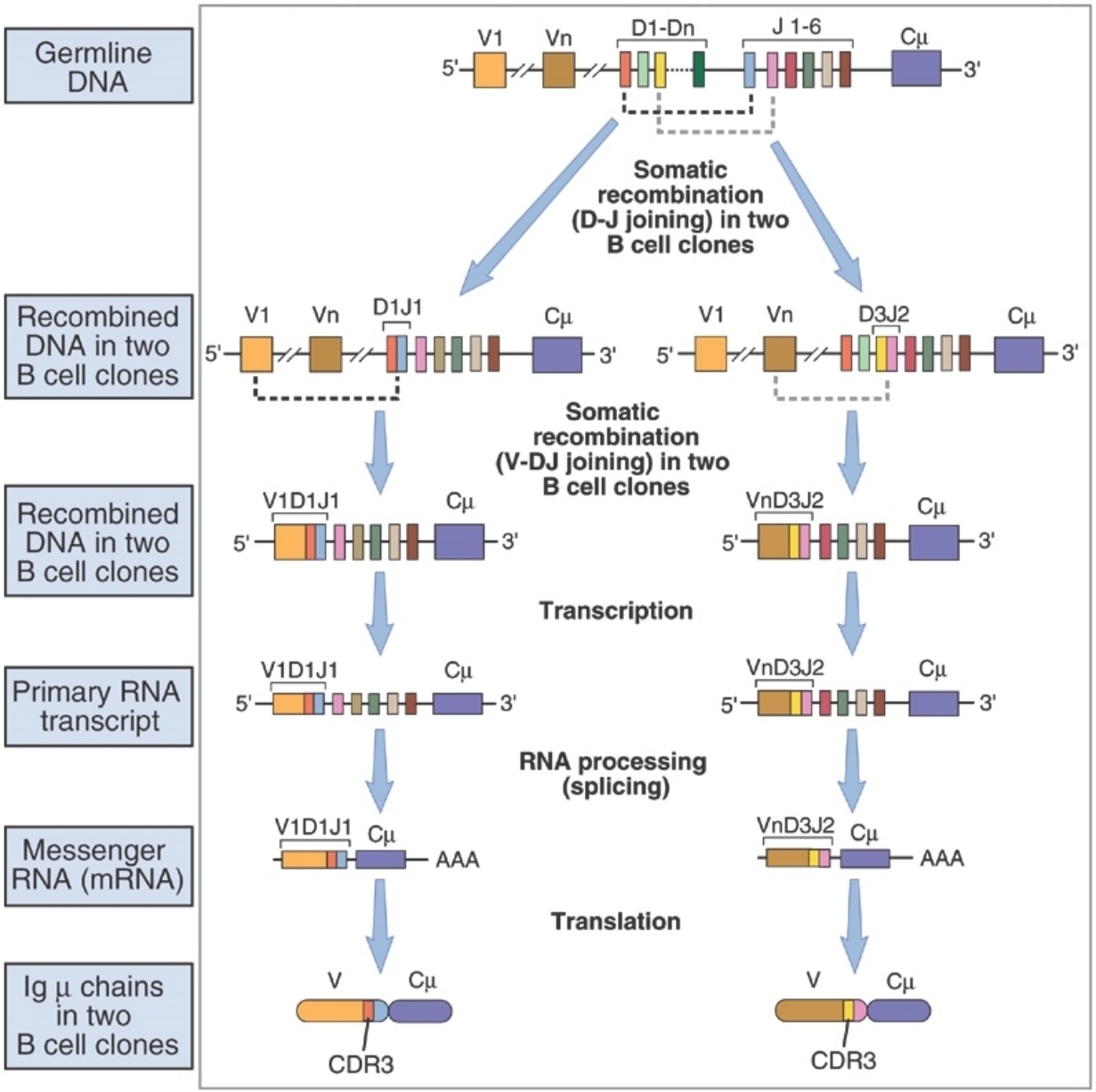
- **Diversity** and **Specificity** are observed but mechanisms remain a mystery until the late 1970s

100-year old puzzle solved

Susumu Tonegawa

1987 Nobel Prize for discovering Ig gene rearrangement

DNA recombination



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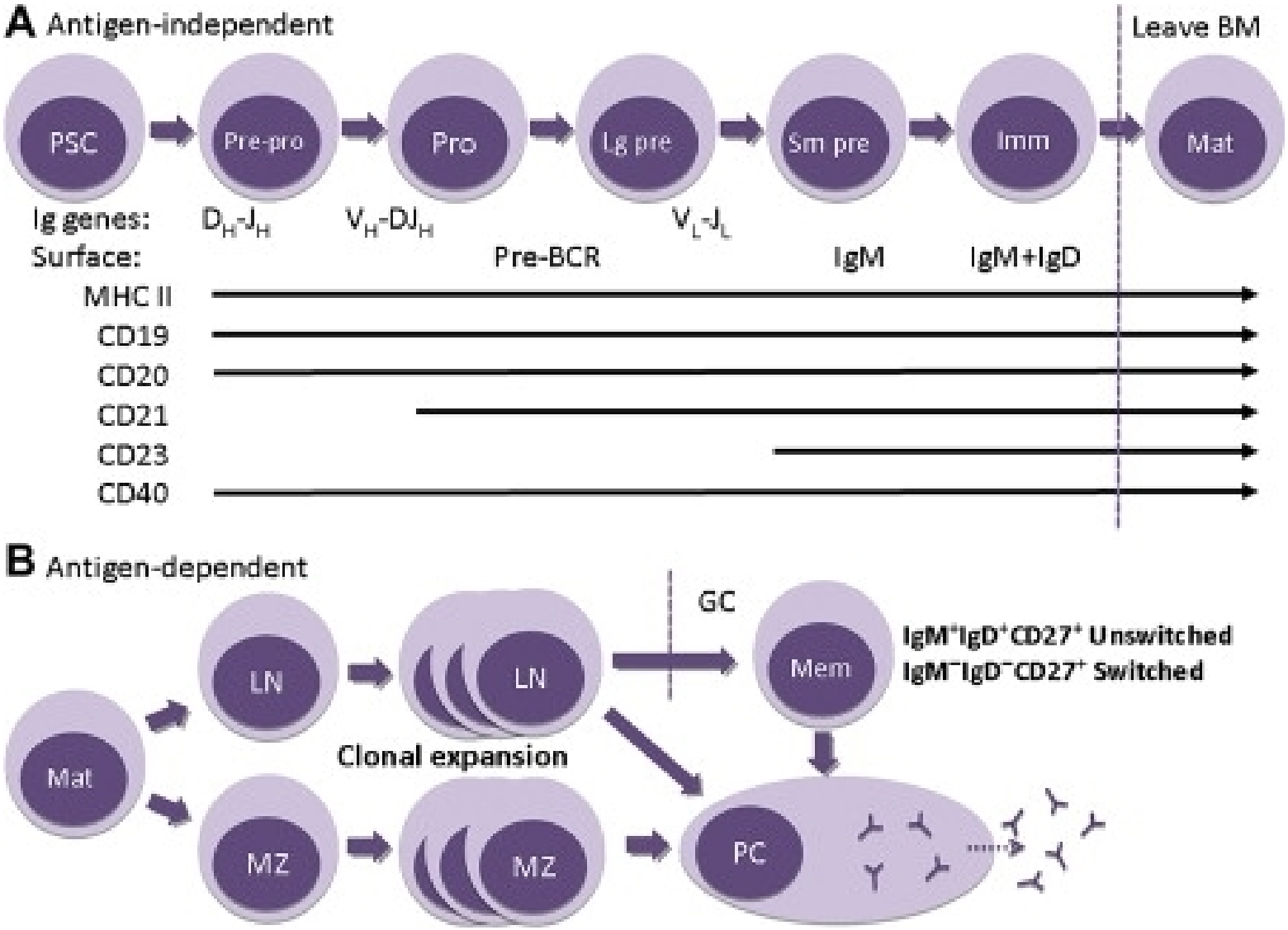
Key concepts

- 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 carries a different BCR with different antigen binding capabilities (idiotypes).

Where this all happens



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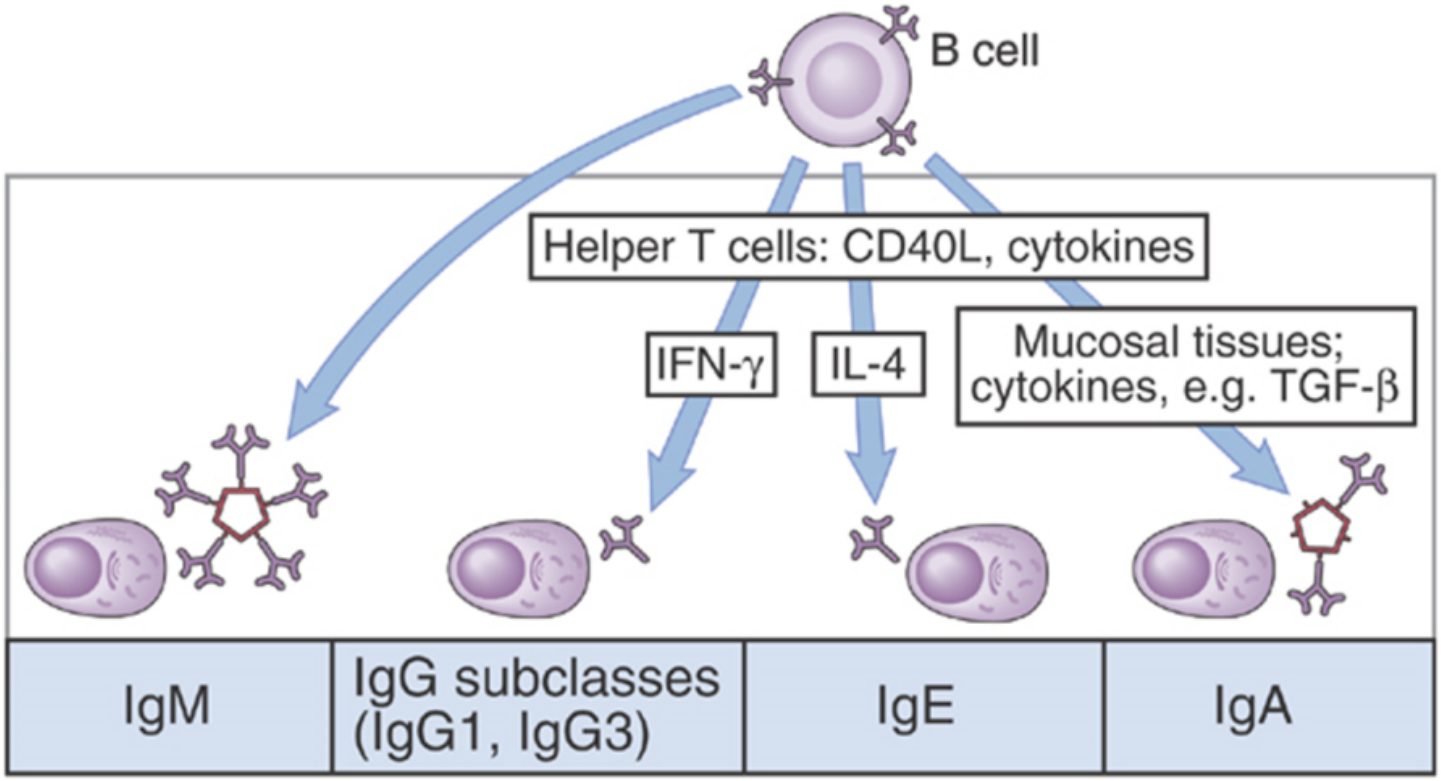
B cells need T cells



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)

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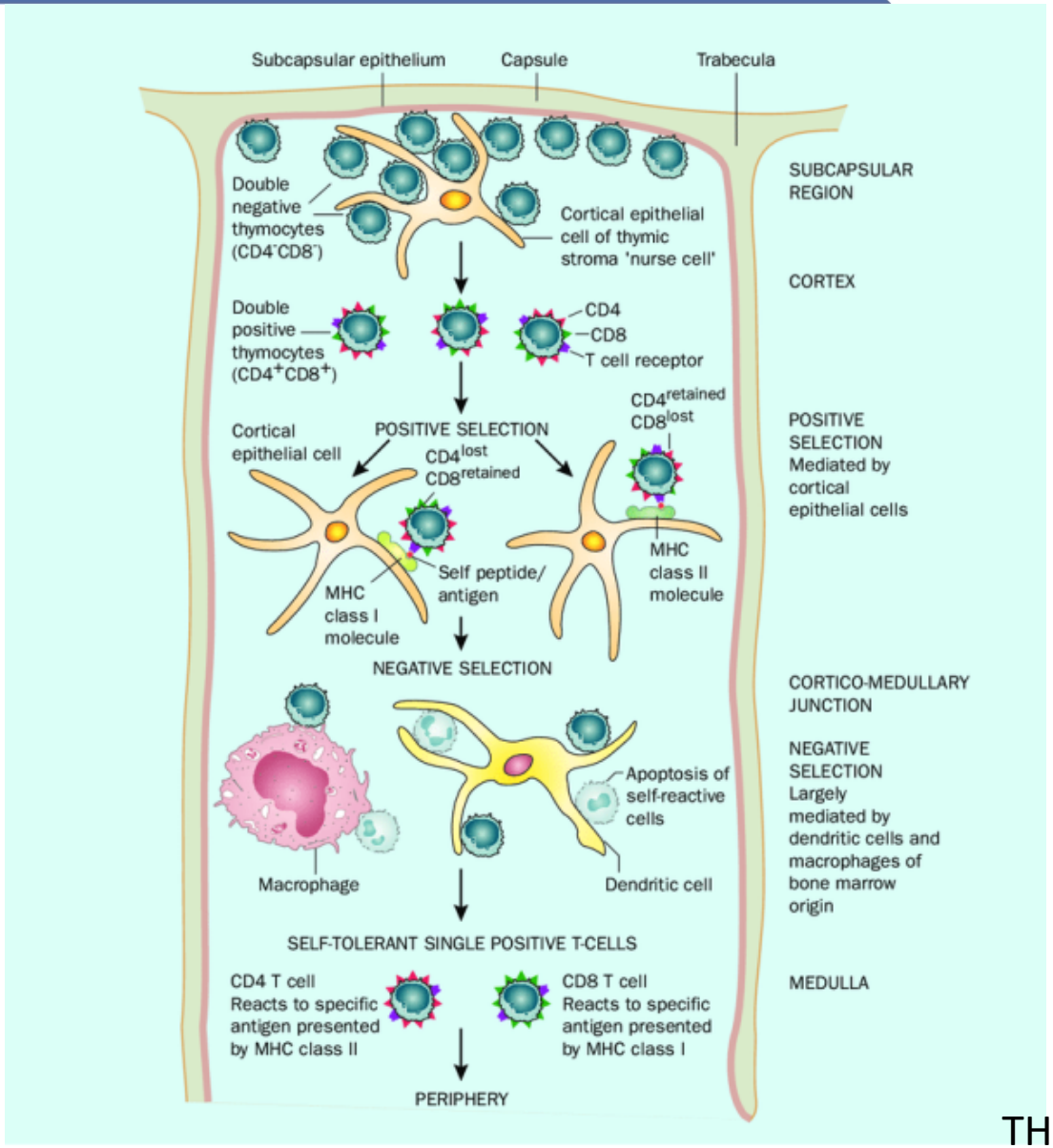
T cells develop in the thymus from BM precursors



THE LANCET • Vol 357

TCR rearrangements

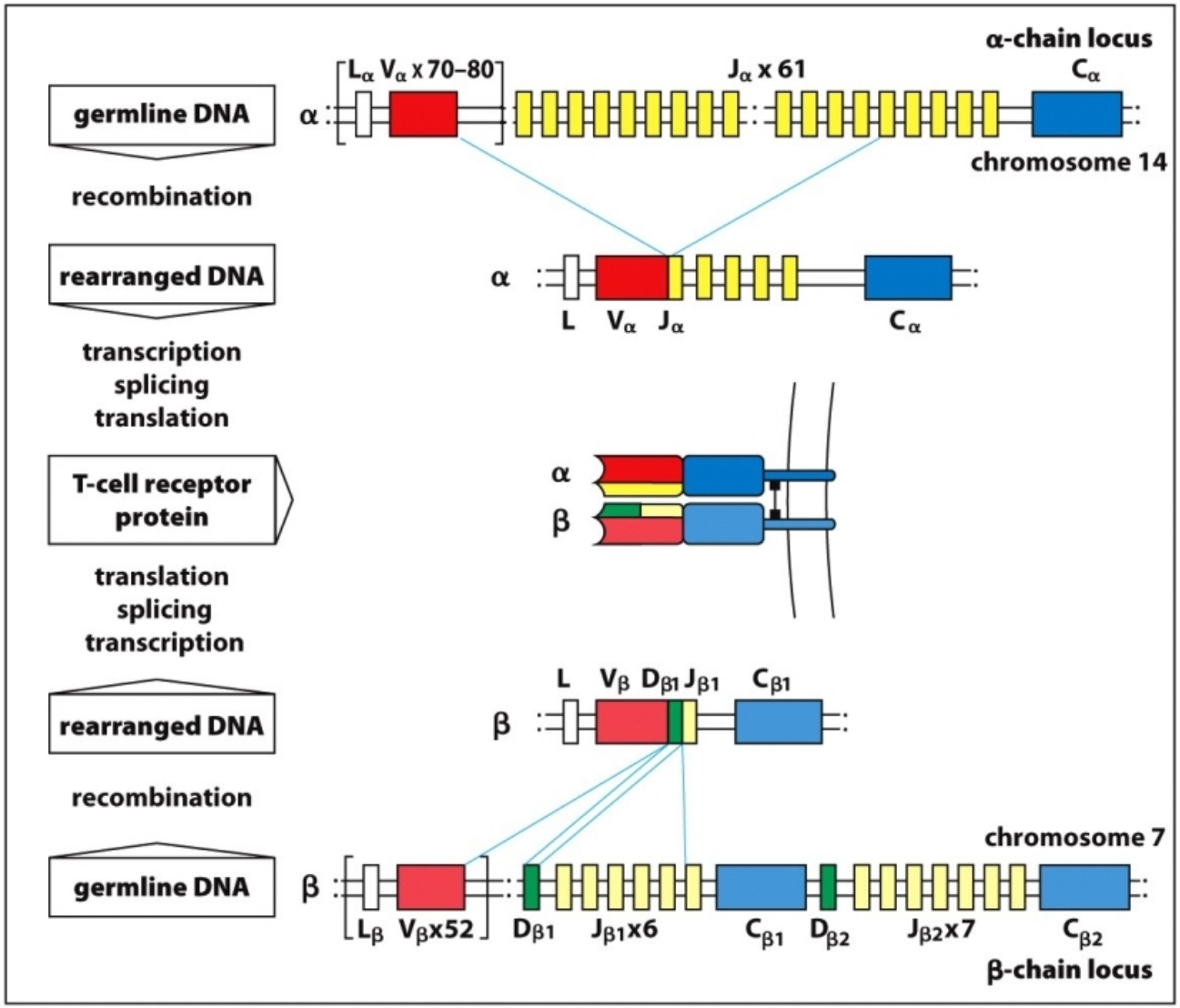


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

BCR vs TCR

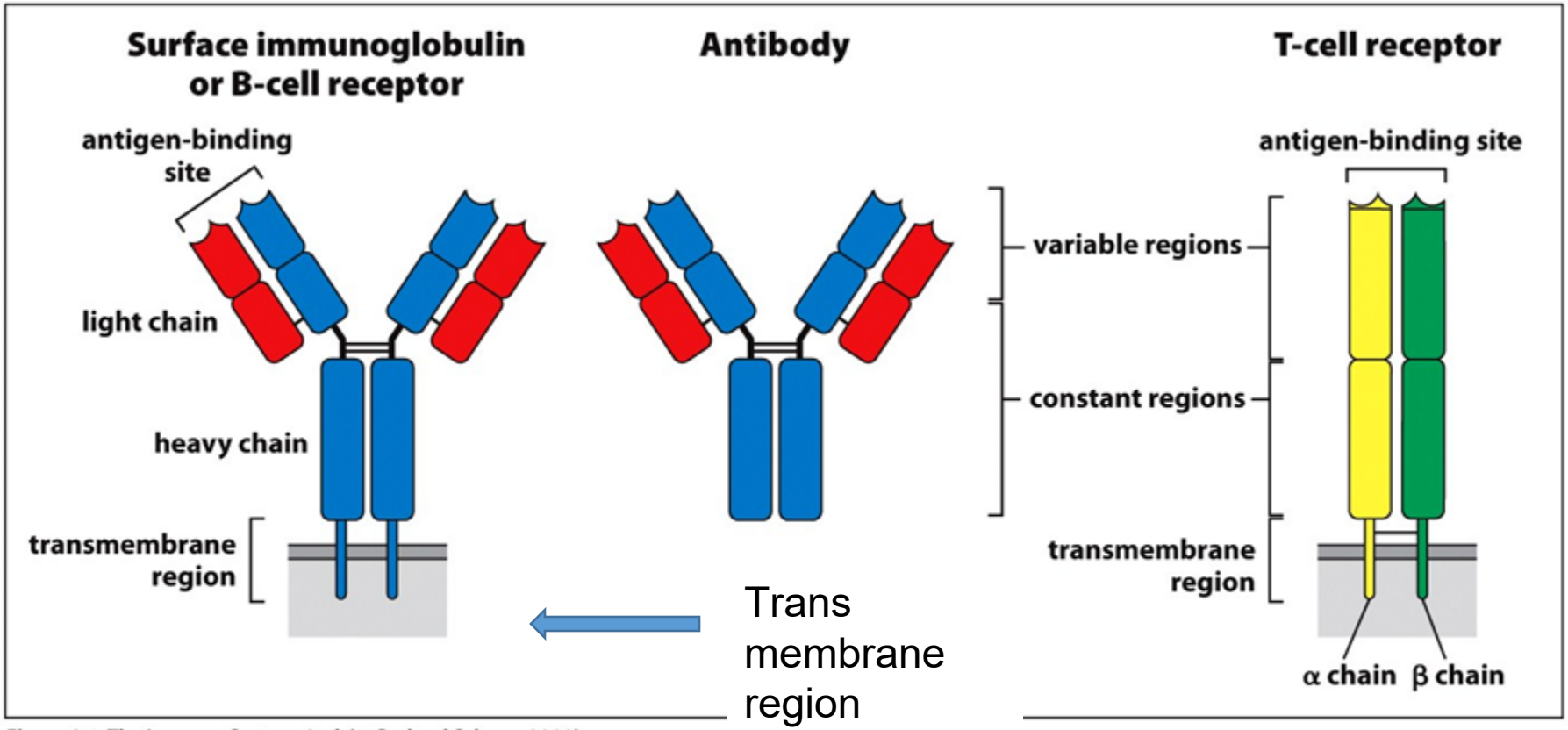
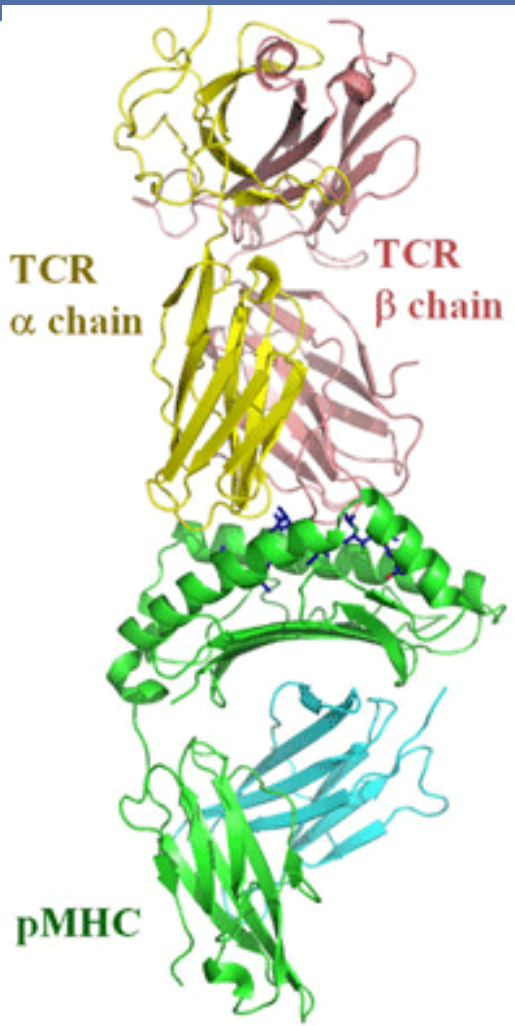


Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

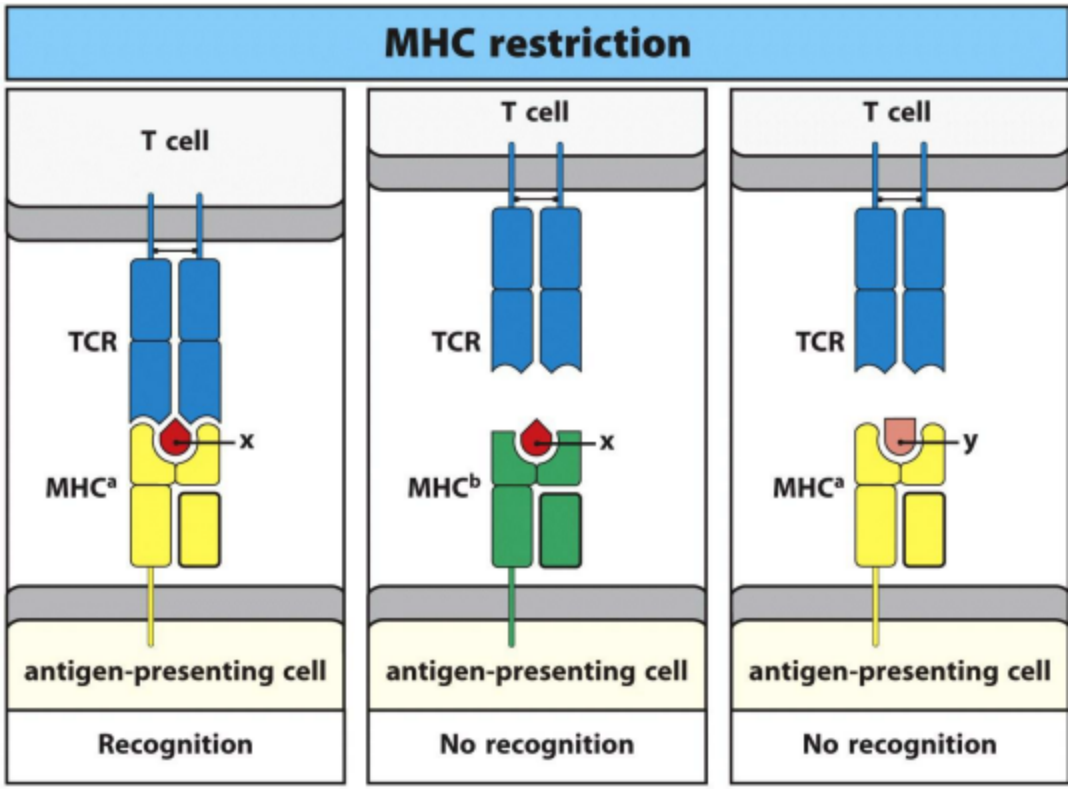
Trans membrane region missing in secreted Ig

Contrast between B cell and T cell antigen recognition



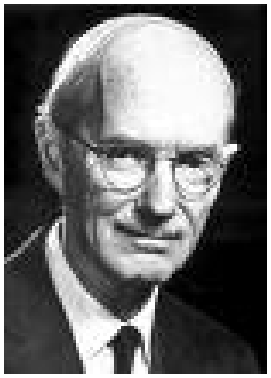
The interaction between the TCR (yellow and salmon) the pMHCI (green and cyan)

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

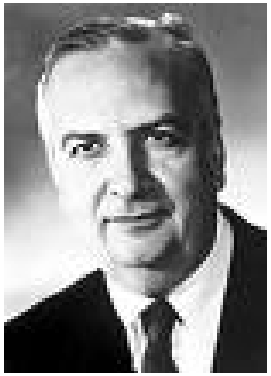


1980 Nobel Prize

Jean Dausset



George Snell



Baruj Benaceraff

1996 Nobel Prize

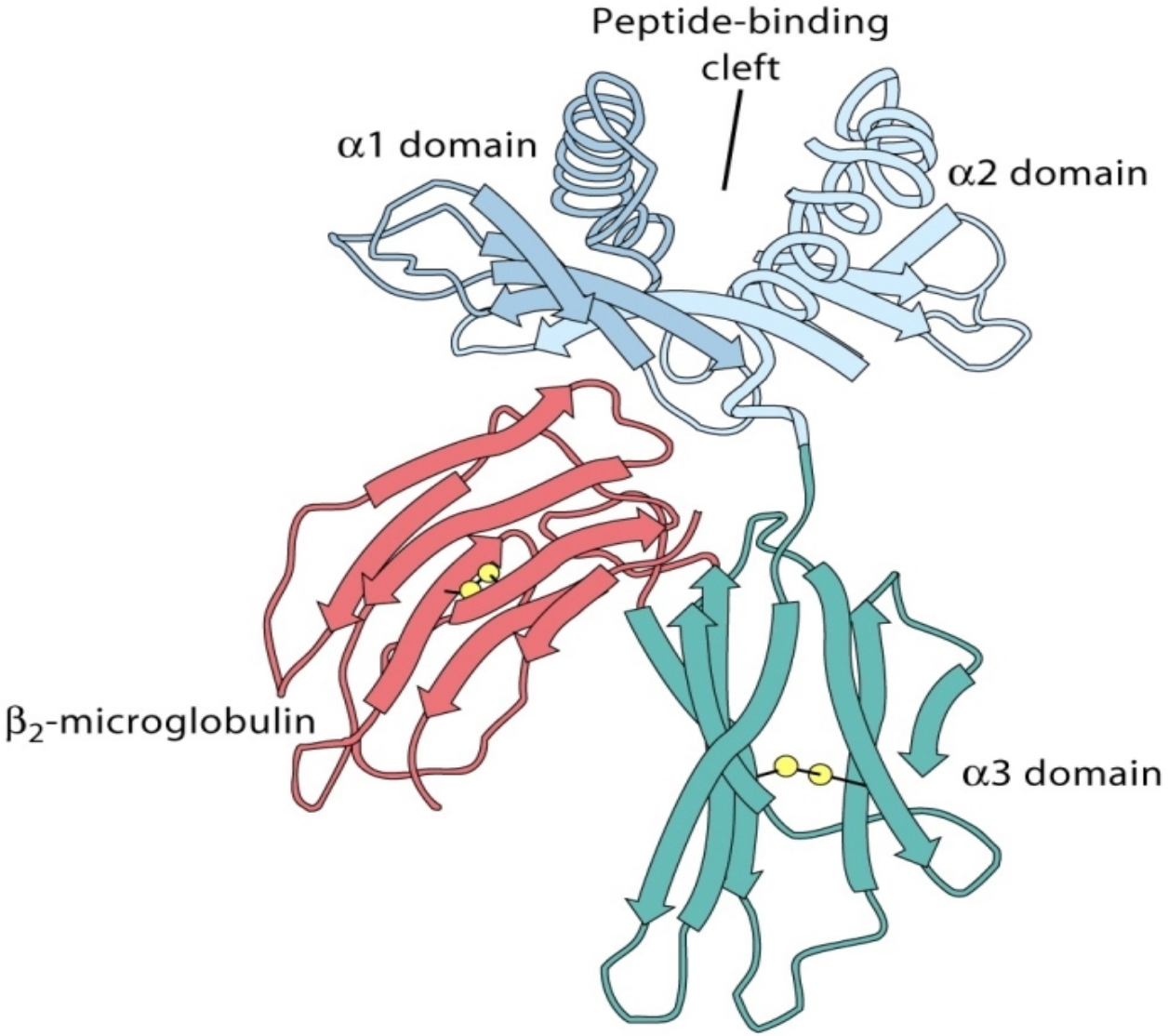
Society for Immunotherapy of Cancer

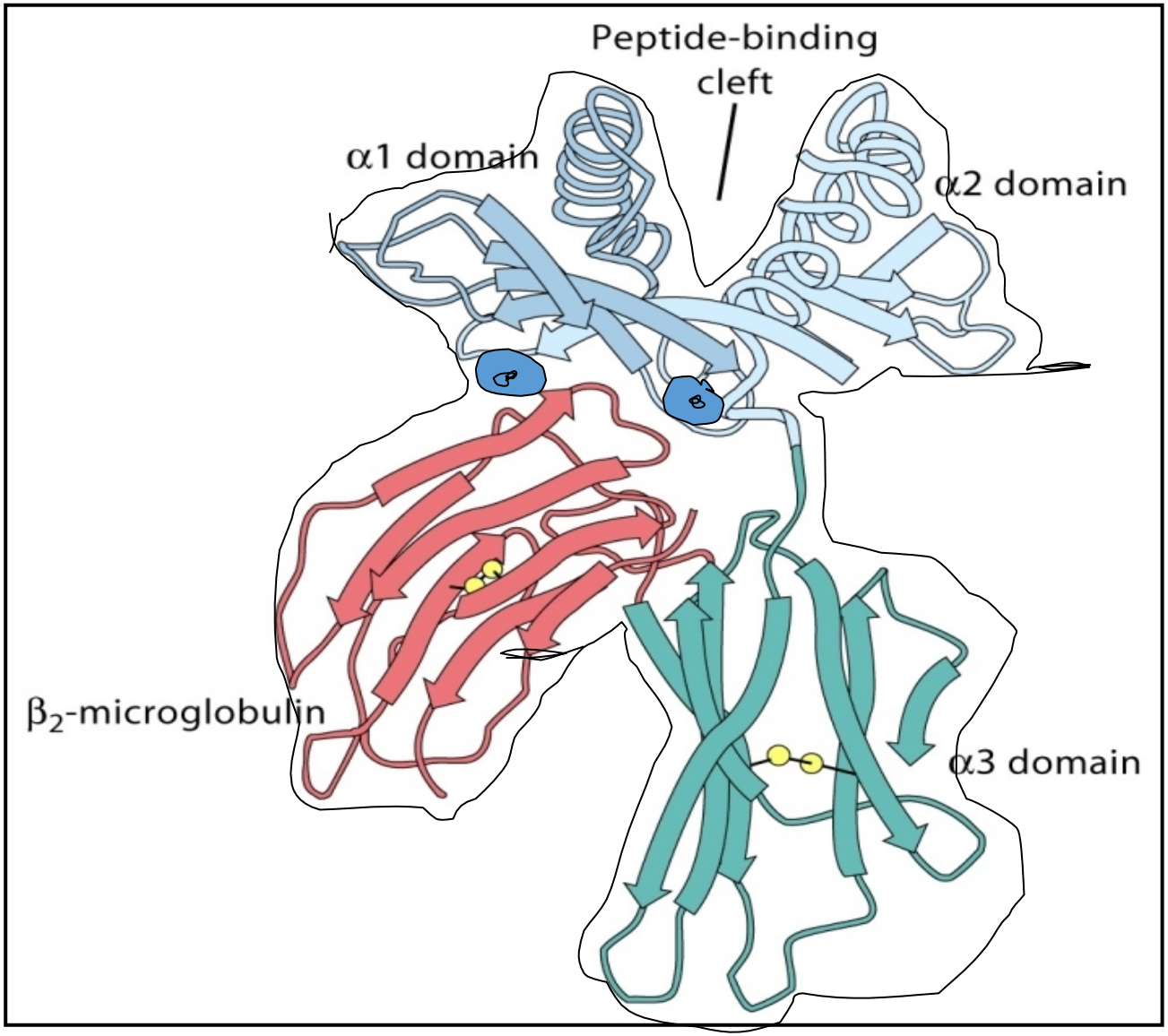
“for discovering the nature of the cellular immune defense”

Peter Doherty and Rolf Zinkernagel

Dr. Pamela Bjorkman

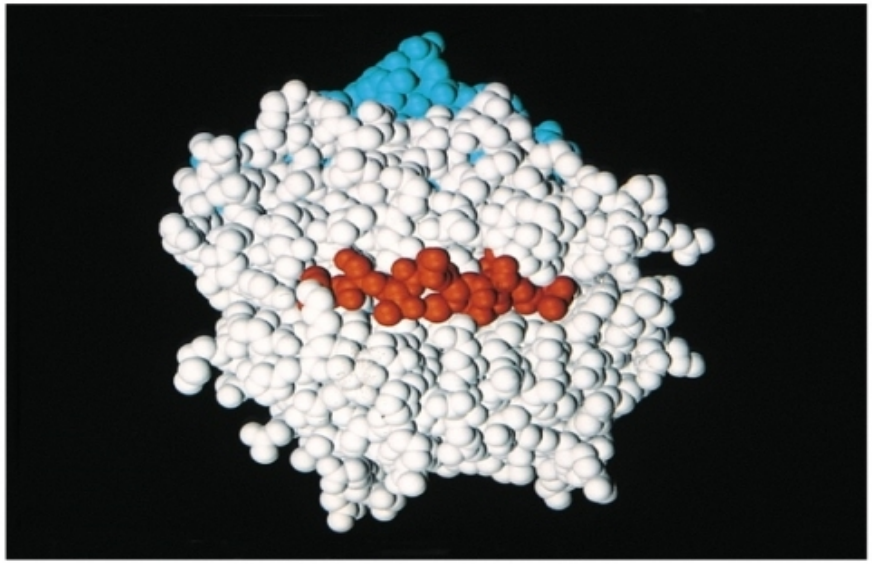
Don Wiley, 1944-2002


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

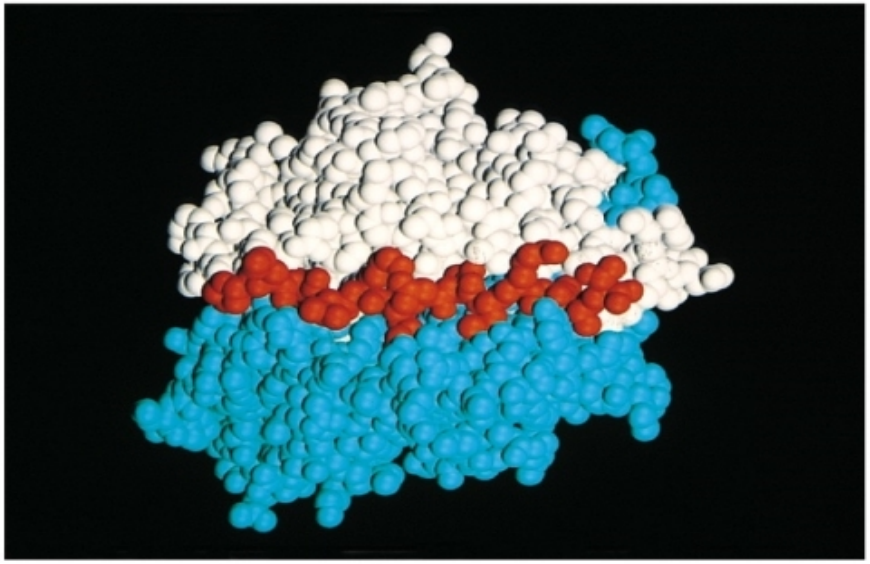

Peptide-binding
cleft
α1 domain
α2 domain
β2-microglobulin
α3 domain

A picture is worth a thousand experiments

(a) **Class I MHC**

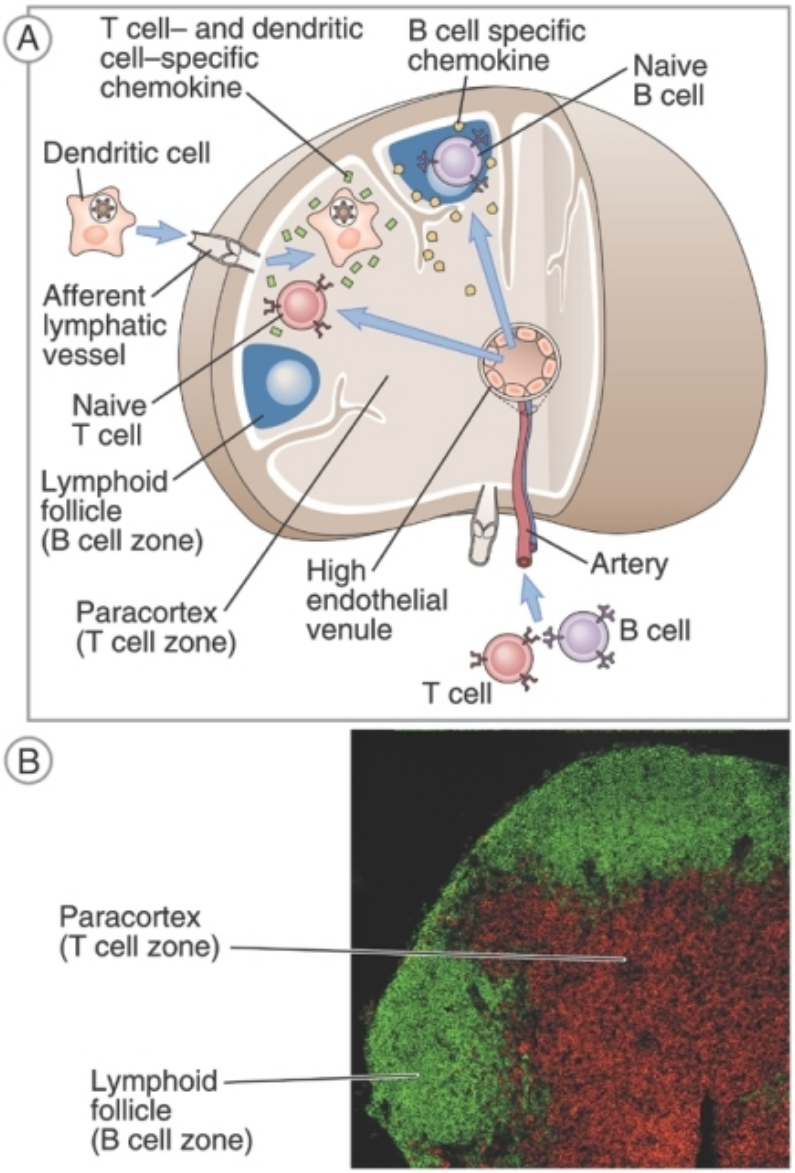


(b) **Class II MHC**



Everyone needs dendritic cells

Society for Immunotherapy of Cancer



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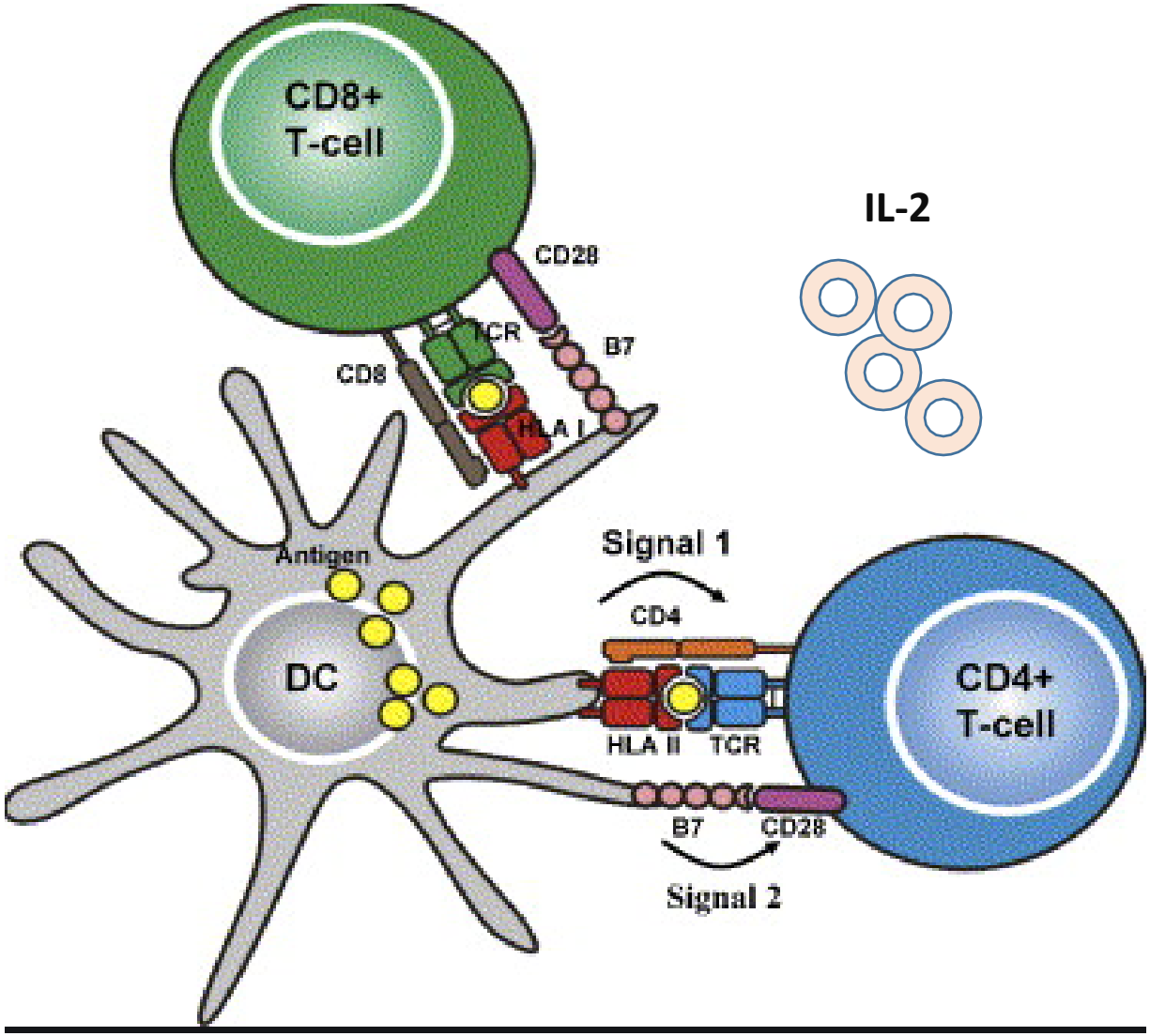
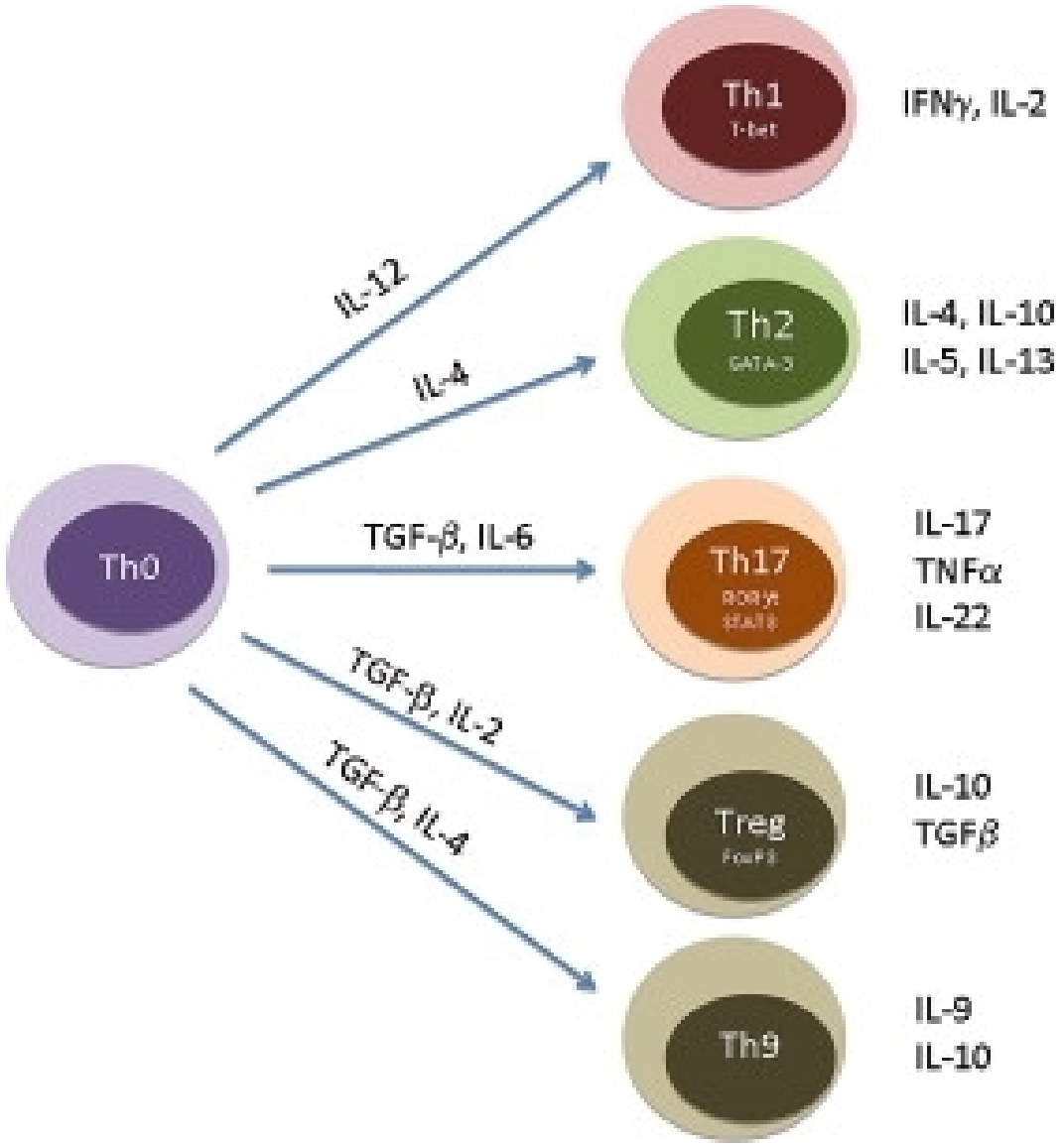
CD8 T cells need CD4 T cell help



CD4 T helper cell subsets



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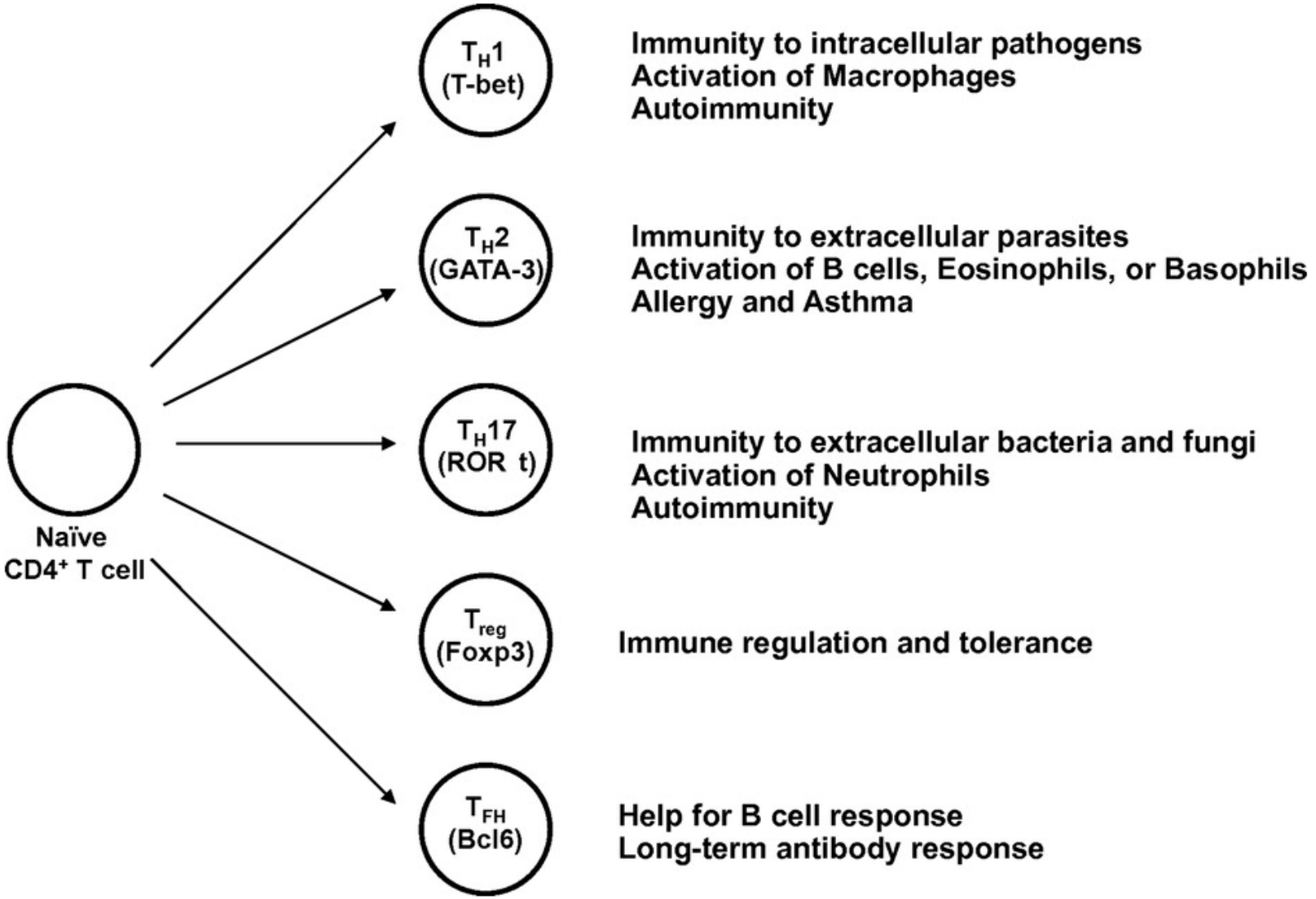
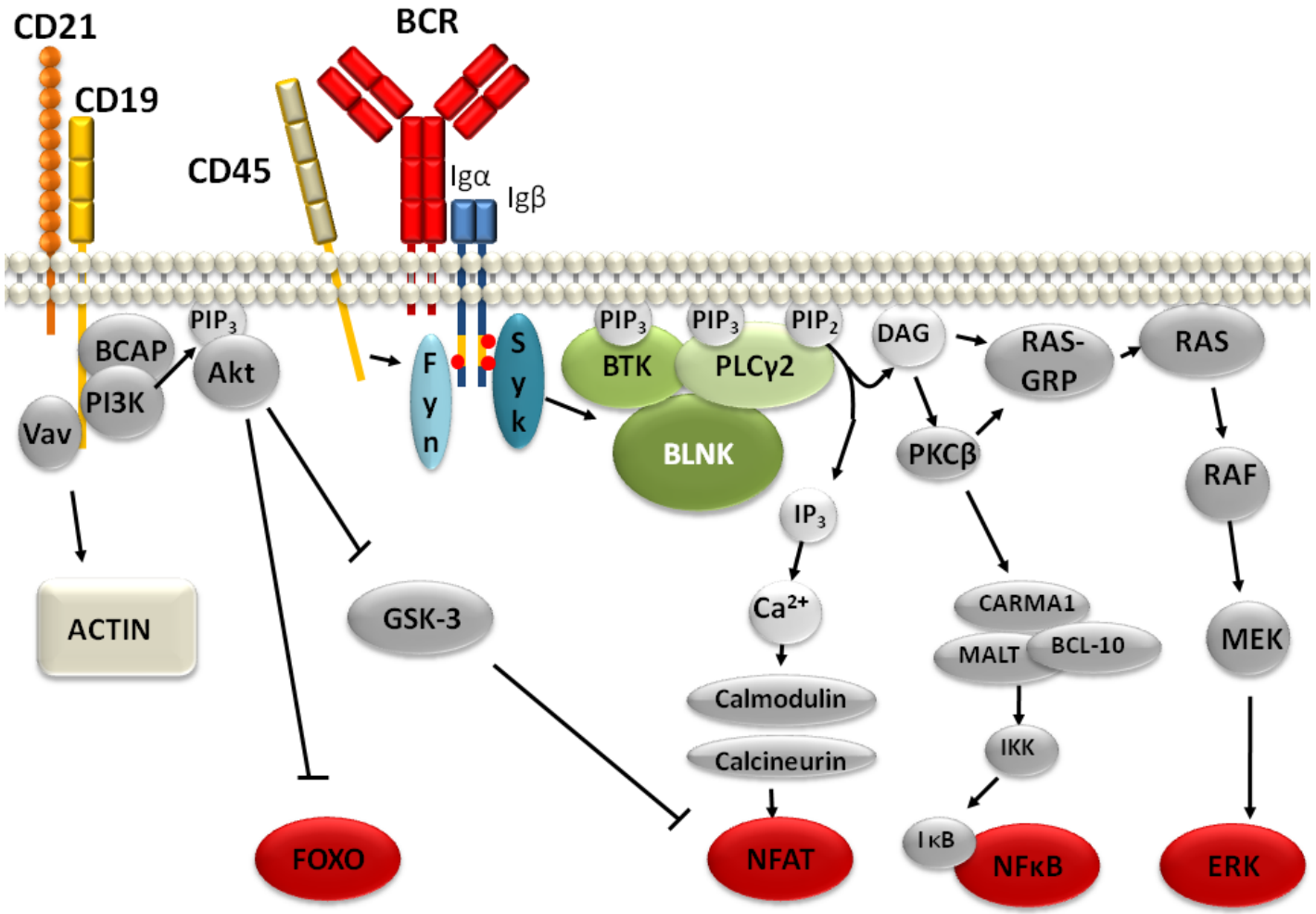
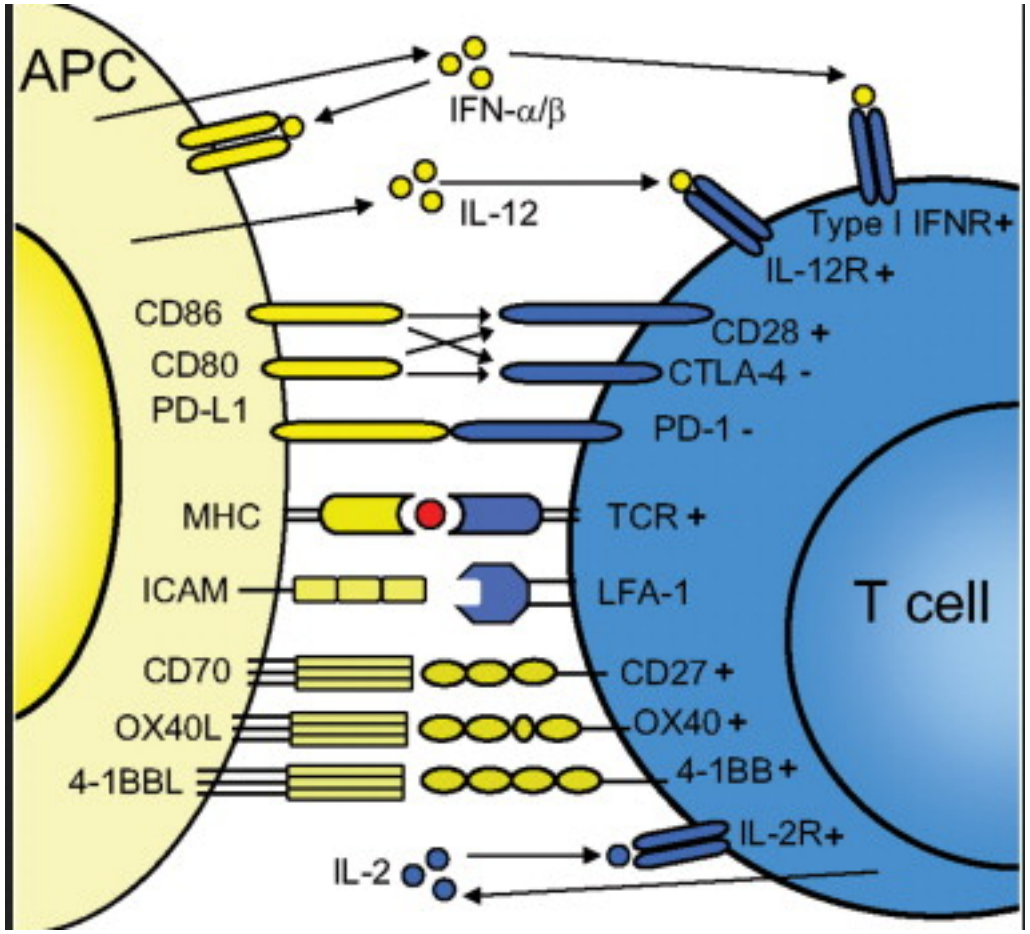

Naïve
CD4+ T cell
TH1
(T-bet)
TH2
(GATA-3)
TH17
(ROR t)
Treg
(Foxp3)
TFH
(Bcl6)
Immunity to intracellular pathogens
Activation of Macrophages
Autoimmunity
Immunity to extracellular parasites
Activation of B cells, Eosinophils, or Basophils
Allergy and Asthma
Immunity to extracellular bacteria and fungi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

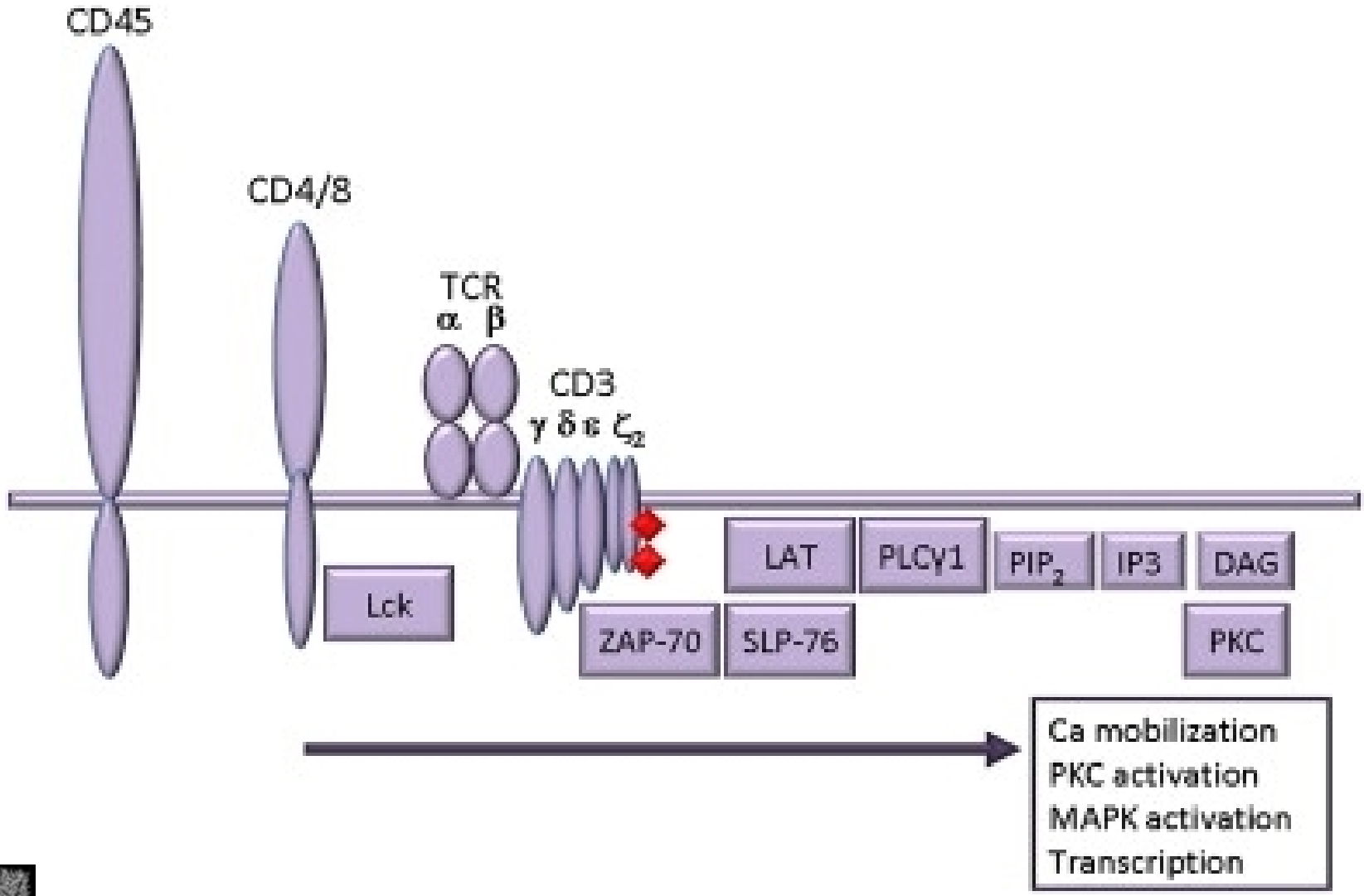
Signaling through BCR



T cell recognition of antigen



Signaling through the TCR



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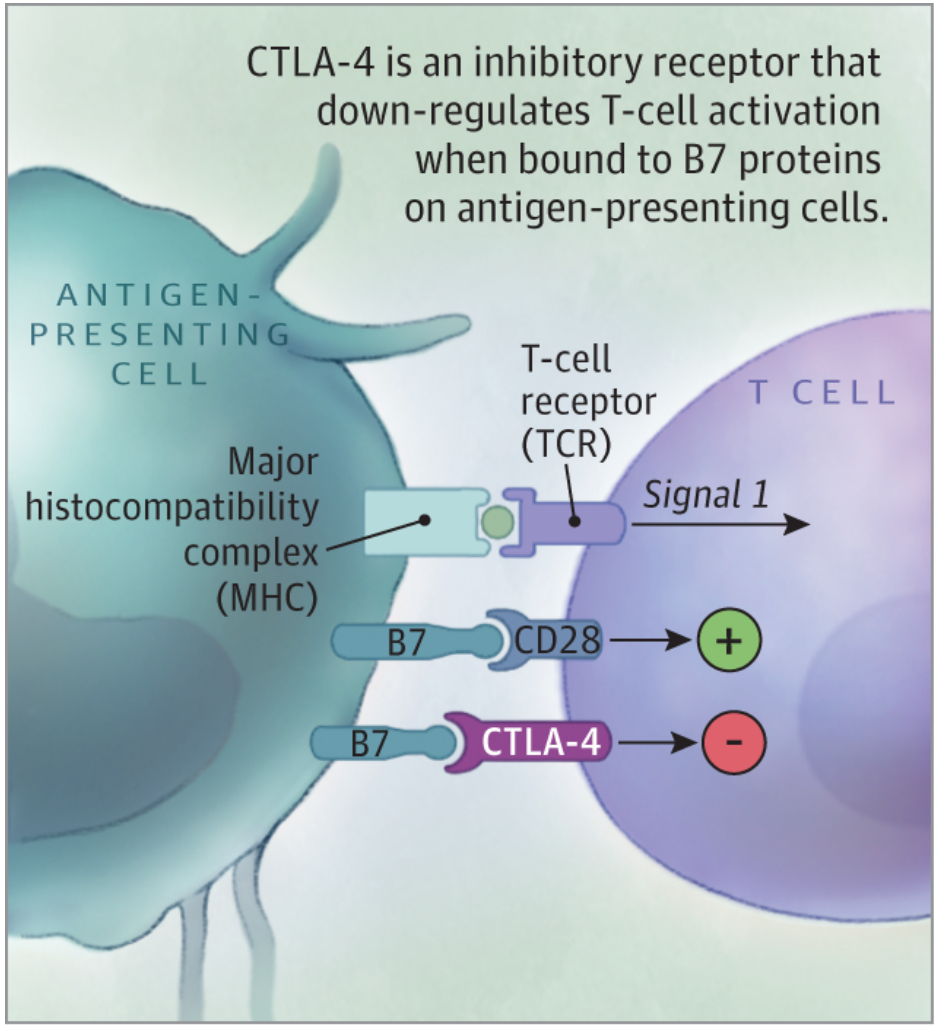
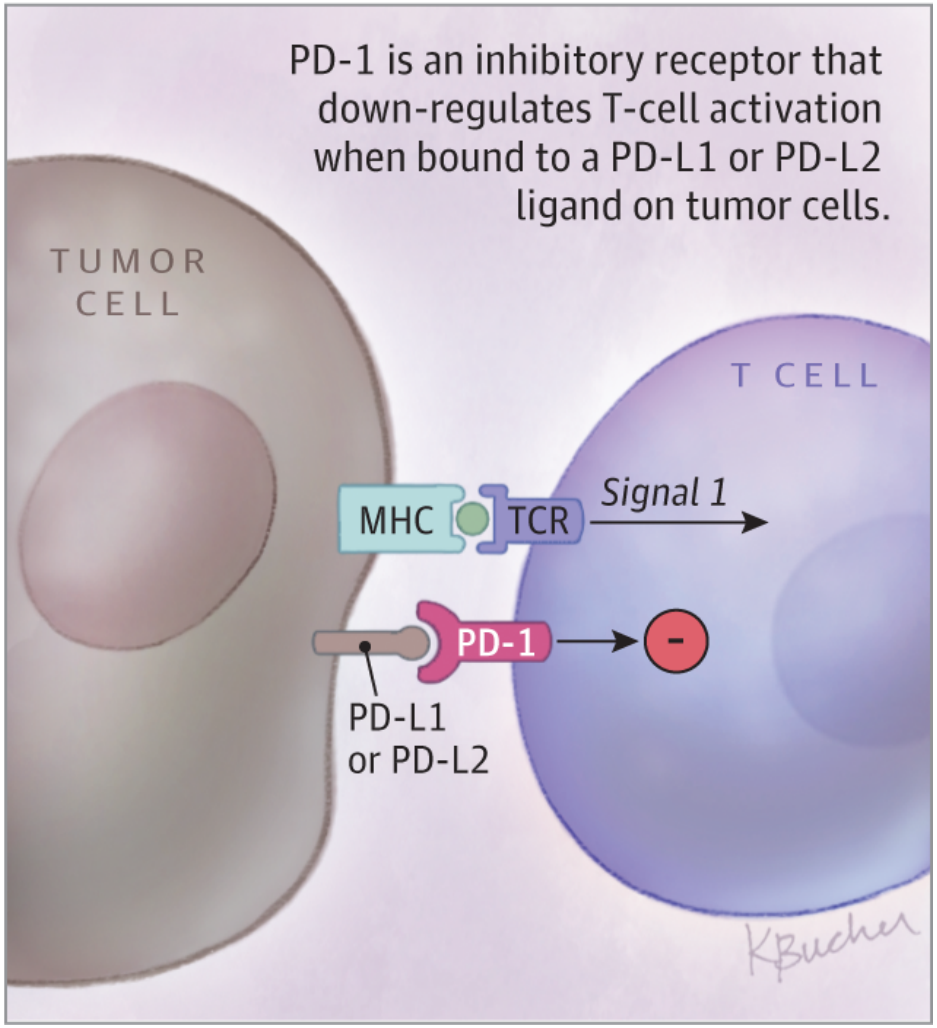
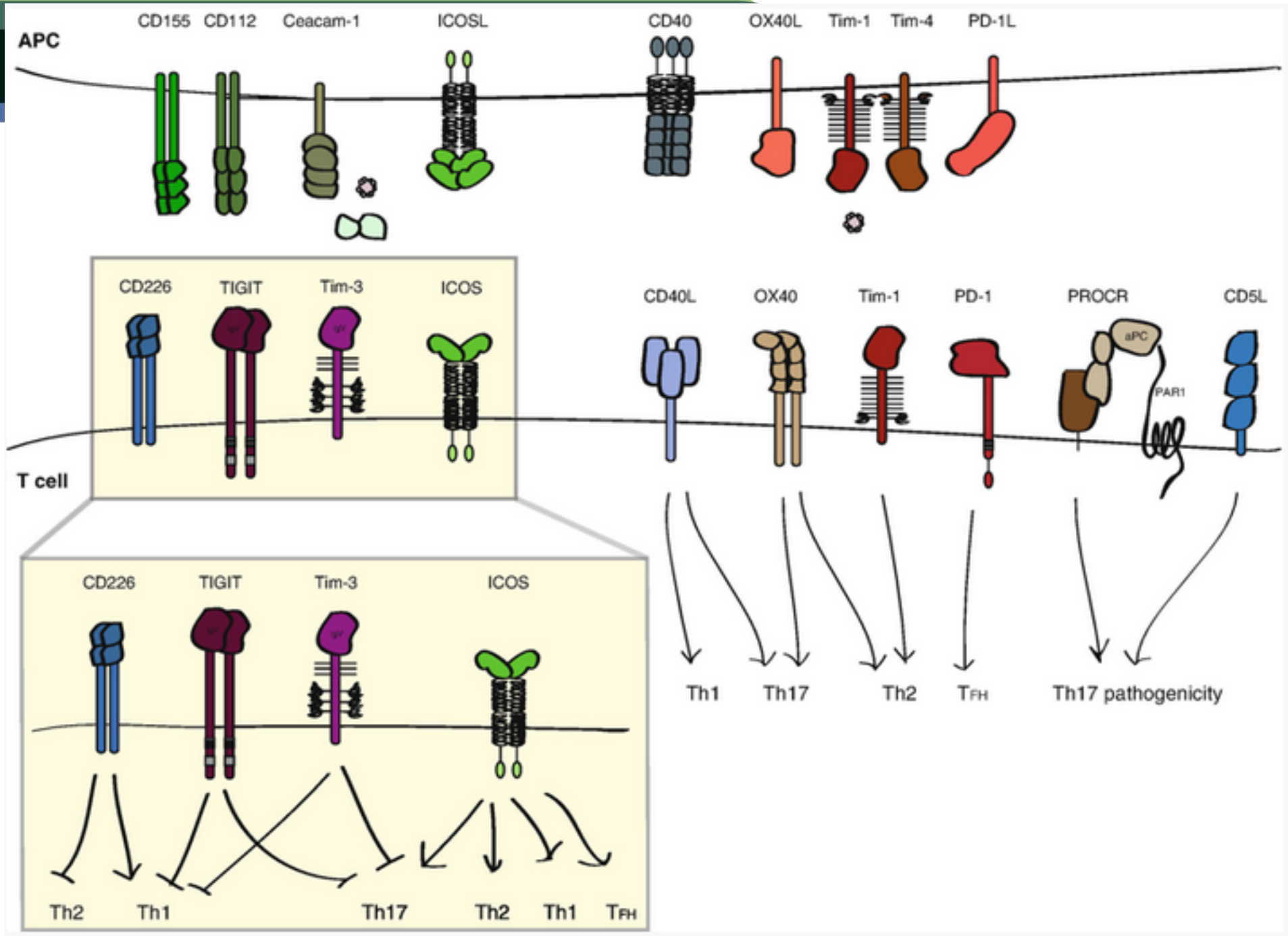

CTLA-4 is an inhibitory receptor that down-regulates T-cell activation when bound to B7 proteins on antigen-presenting cells.
ANTIGEN-PRESENTING CELL
T CELL
T-cell receptor (TCR)
Major histocompatibility complex (MHC)
Signal 1
B7
CD28
+
B7
CTLA-4
-


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


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

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 are responsible for prevention of disease recurrence

Recommended reading

- Malissen B and Bongrand P. Early T cell activation: integrating biochemical, structural and biophysical cues. Annu. Rev. Immunol. 2015. 33:539-61

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