The Immune System

1. Multiple layers of protection
2. Prevent
3. Eliminate

Innate immunity = all animals and plants

Adaptive immunity = only in vertebrates

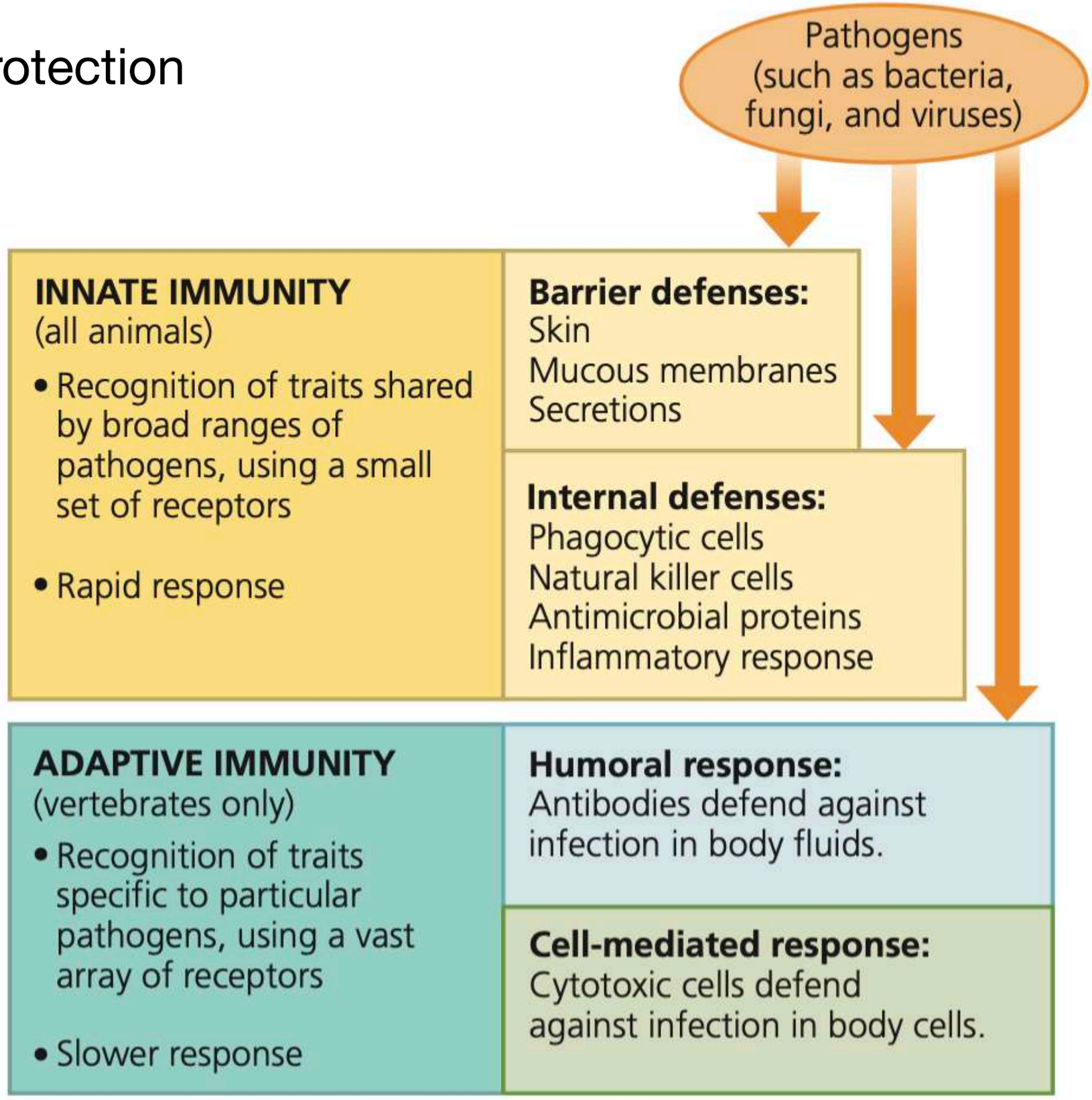
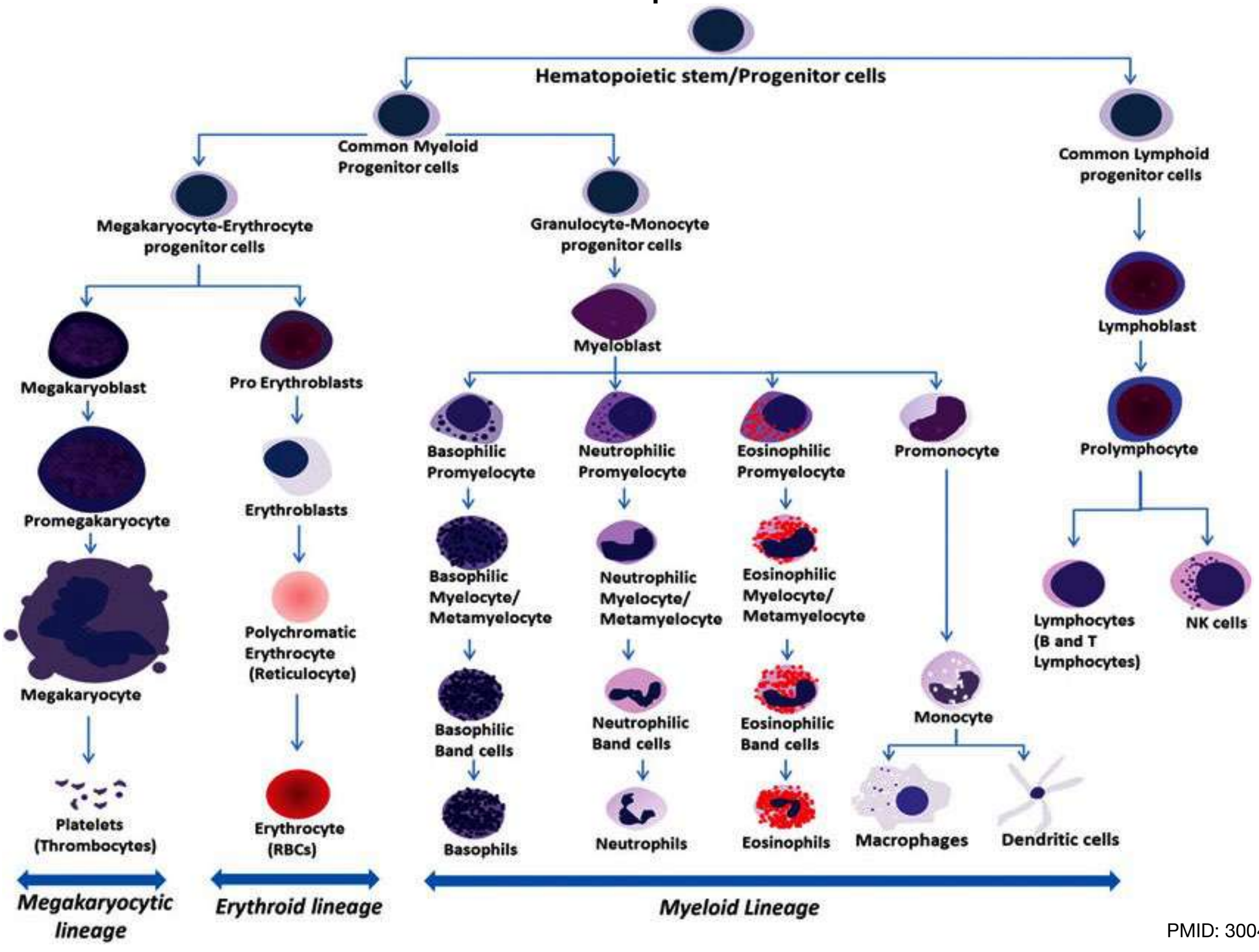


Figure 43.2 of Campbell's Biology: a global approach

Haematopoiesis



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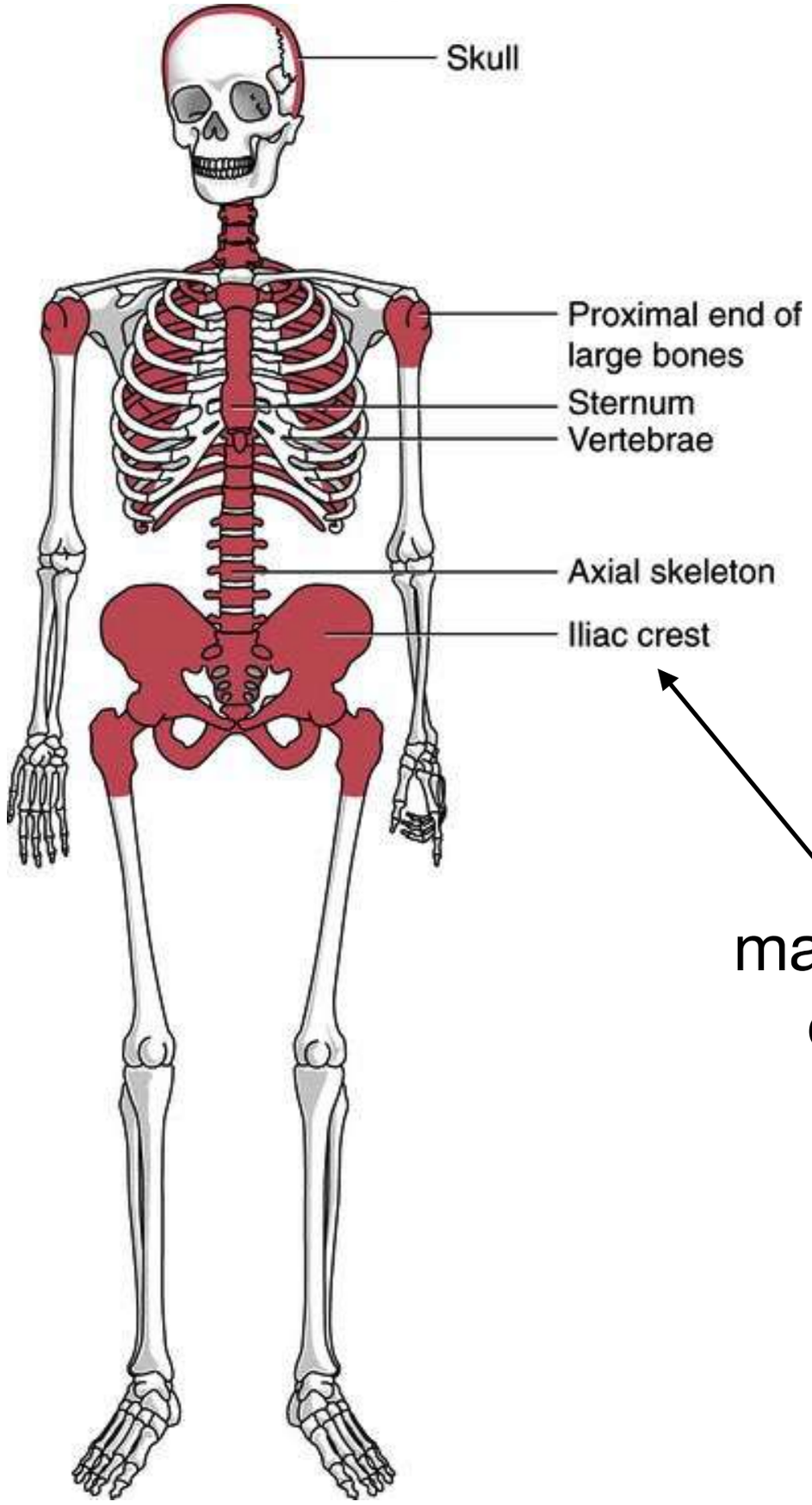
Where does haematopoiesis occur?

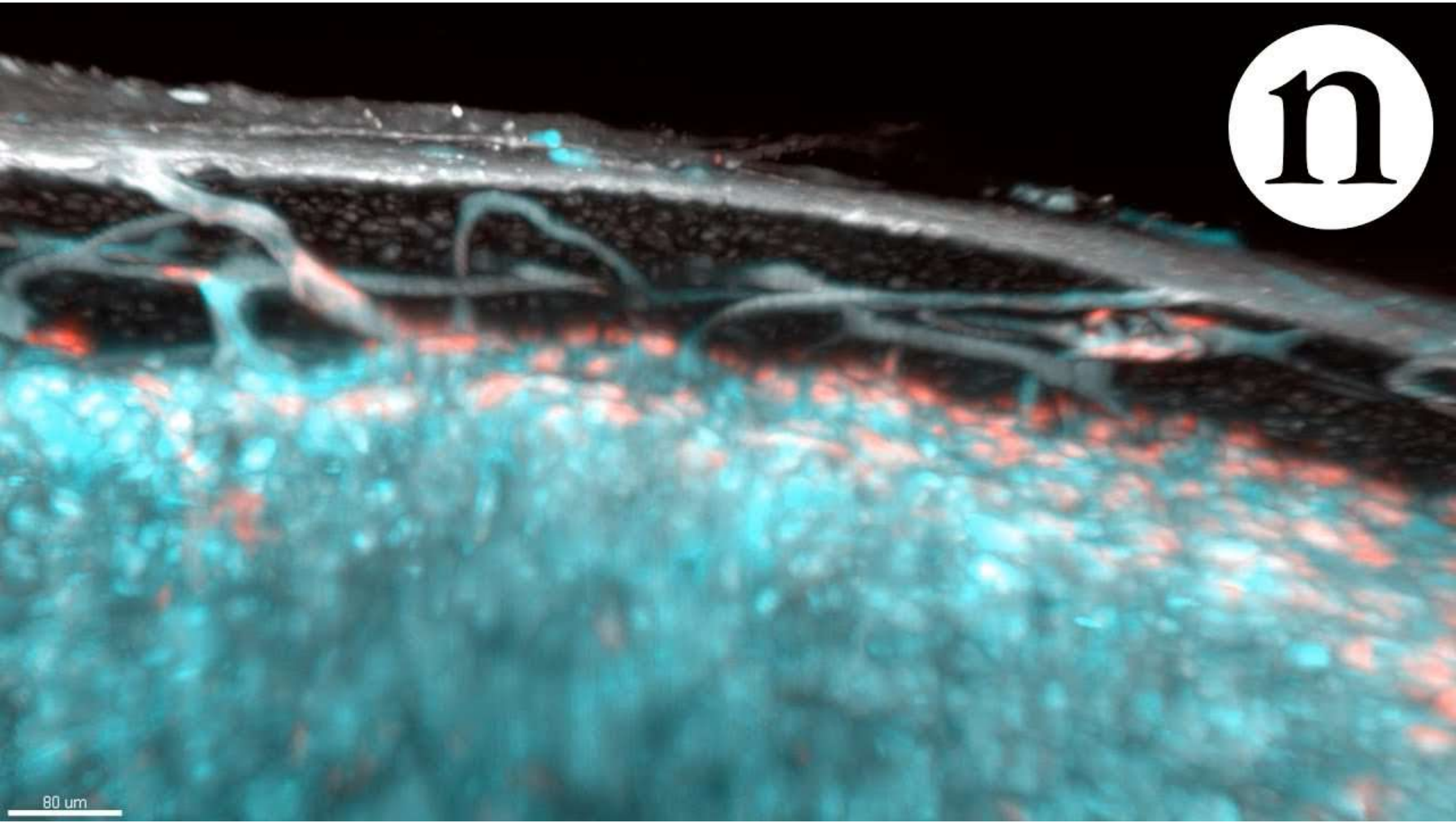


Different in children

Usually bone marrow biopsies are done from here

Sreelaja Nair

From inside the bone, how do new blood cells enter circulation?



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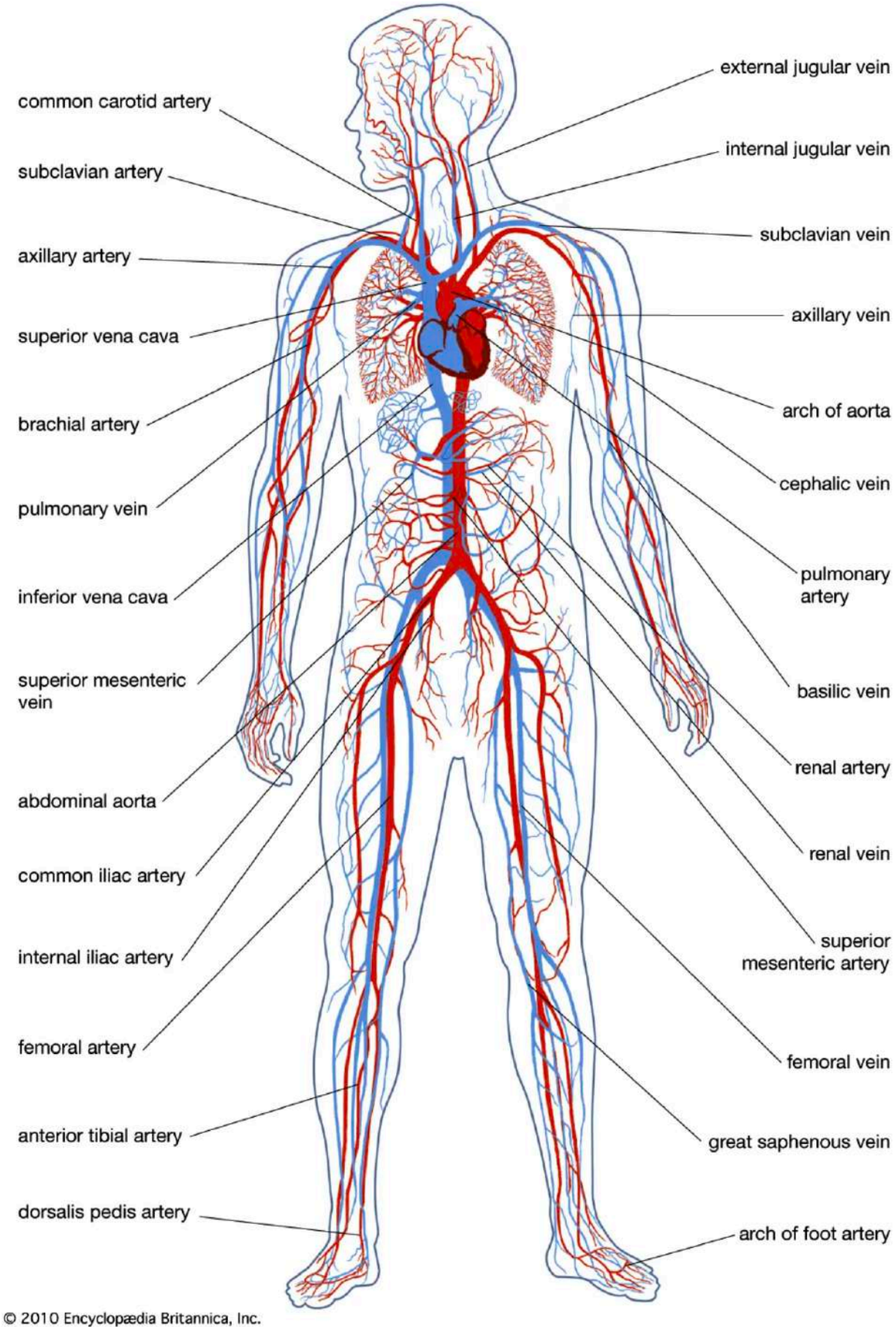
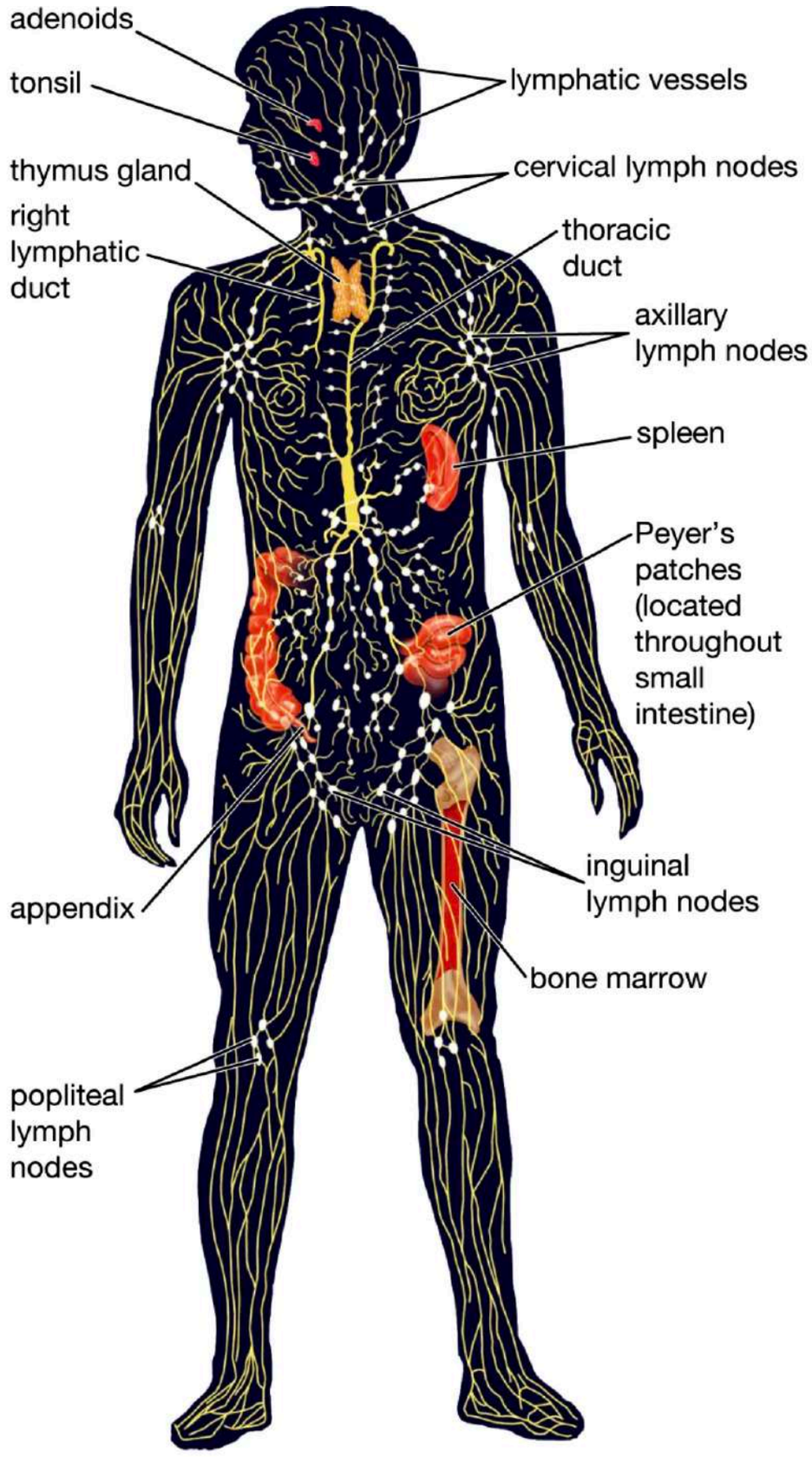
Circulatory system vs Lymphatic system





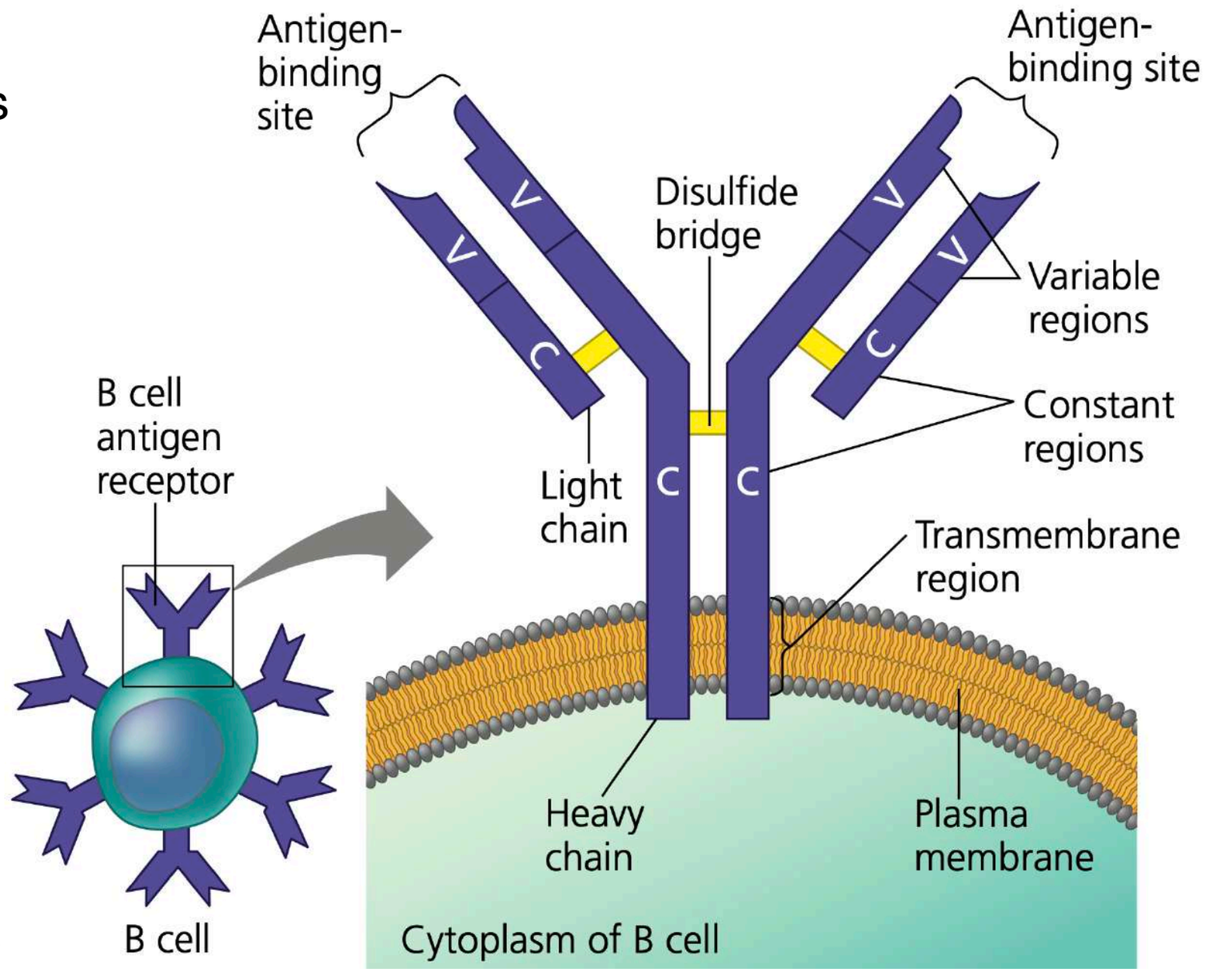
Adaptive or Acquired Immunity

- The adaptive or acquired immunity relies on T cells and B cells
- Mature B cell Mature T cell lymphocytes originate from stem cells in the bone marrow.
- Some migrate from the bone marrow to the thymus, an organ in the thoracic cavity above the heart. These lymphocytes mature into T cells.
- Lymphocytes that remain and mature in the bone marrow develop as B cells.

- Any substance that elicits a B or T cell response is called an antigen.
- In adaptive immunity, recognition occurs when a B cell or T cell binds to an antigen, such as a bacterial or viral protein
- The small, accessible portion of an antigen that binds to an antigen receptor is called an epitope
- The recognition of B or T cell with an antigen occurs via a protein called an antigen receptor.
- Although cells of the immune system produce millions of different antigen receptors, all of the antigen receptors made by a single B or T cell are identical = clonal expansion

Antigen receptor on B cells

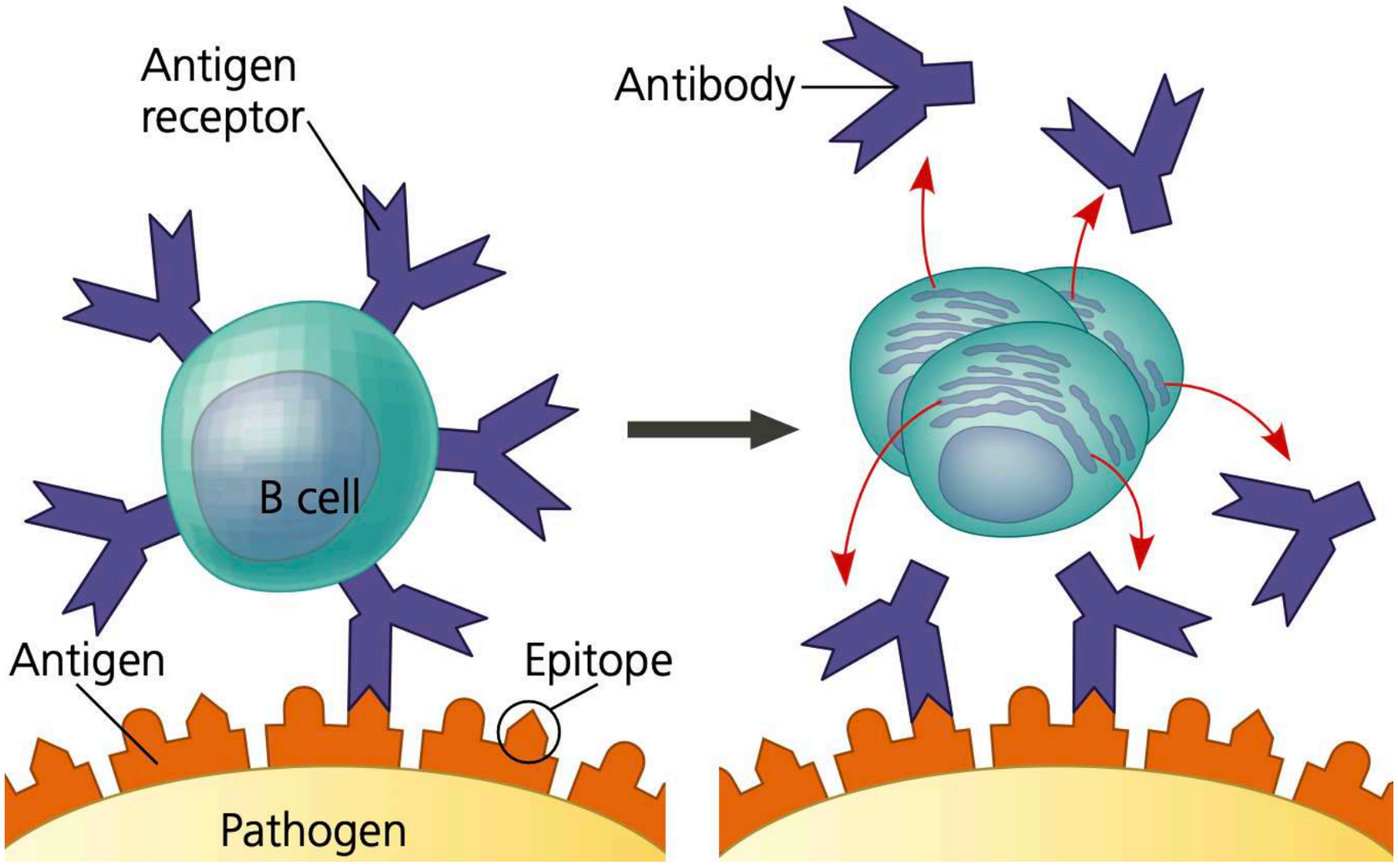
- Two identical heavy chains and two identical light chains, with disulfide bridges linking the chains together
- The light and heavy chains each have a constant (C) region, where amino acid sequences vary little among the receptors on different B cells
- Within the two tips of the Y shape each chain has a variable (V) region, so named because its amino acid sequence varies extensively from one B cell to another
- Together, parts of a heavy-chain V region and a light-chain V region form an asymmetric binding site for an antigen



Each B cell antigen receptor has two identical antigen binding sites

Figure 43.9 of Campbell's Biology: a global approach

Antigen receptor on B cells and antibodies

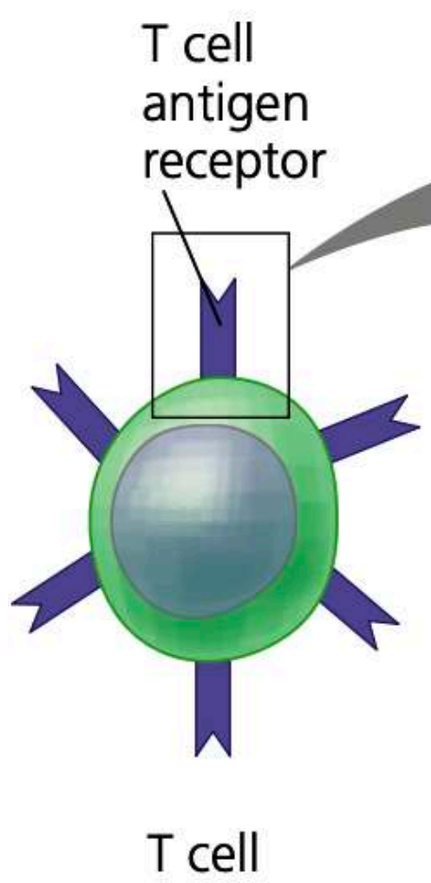


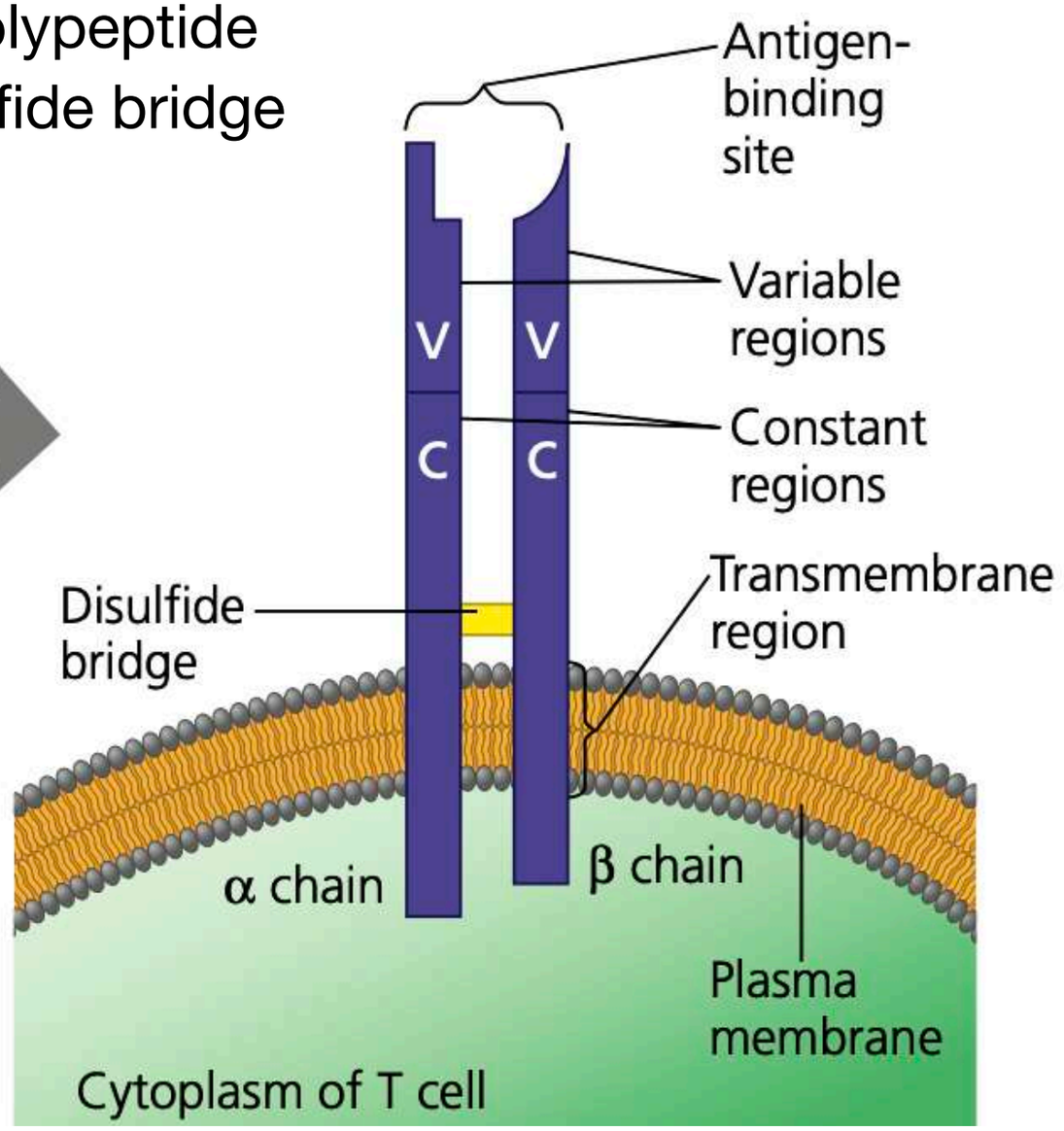
- Binding of a B cell antigen receptor to an antigen is an early step in B cell activation
- Activated B cells produce a secreted form of the antigen receptor
- This secreted protein is called an antibody
- Antibodies have the same Y-shaped structure as B cell antigen receptors but are secreted rather than membrane bound
- Antibodies can bind to antigens on the surface of pathogens or free in body fluids
- Different antibodies can be made against different antigens of the same pathogen

Figure 43.10 of Campbell's Biology: a global approach

Antigen receptor on T cells

- T cell antigen receptor consists of two different polypeptide chains, an α chain and a β chain, linked by a disulfide bridge
- At the outer tip of the molecule, the variable (V) regions of the α and β chains together form a single antigen-binding site
- The remainder of the molecule is made up of the constant (C) regions





- T cells antigen receptors bind only to fragments of antigens displayed, or presented, on the surface of host cells
- The host protein that displays the antigen fragment on the cell surface is called a major histocompatibility complex (MHC) molecule

Figure 43.11 of Campbell's Biology: a global approach

Antigen receptor on T cells

- Recognition of protein antigens by T cells begins when a pathogen or part of a pathogen either infects or is taken in by a host cell
- Inside the host cell, enzymes cleave the antigen into smaller peptides.
- Each peptide, called an antigen fragment, then binds to an MHC molecule inside the cell
- MHC molecule and bound antigen fragment move to the cell surface results in antigen presentation

Antigen presentation = advertising the fact that a host cell contains a foreign substance

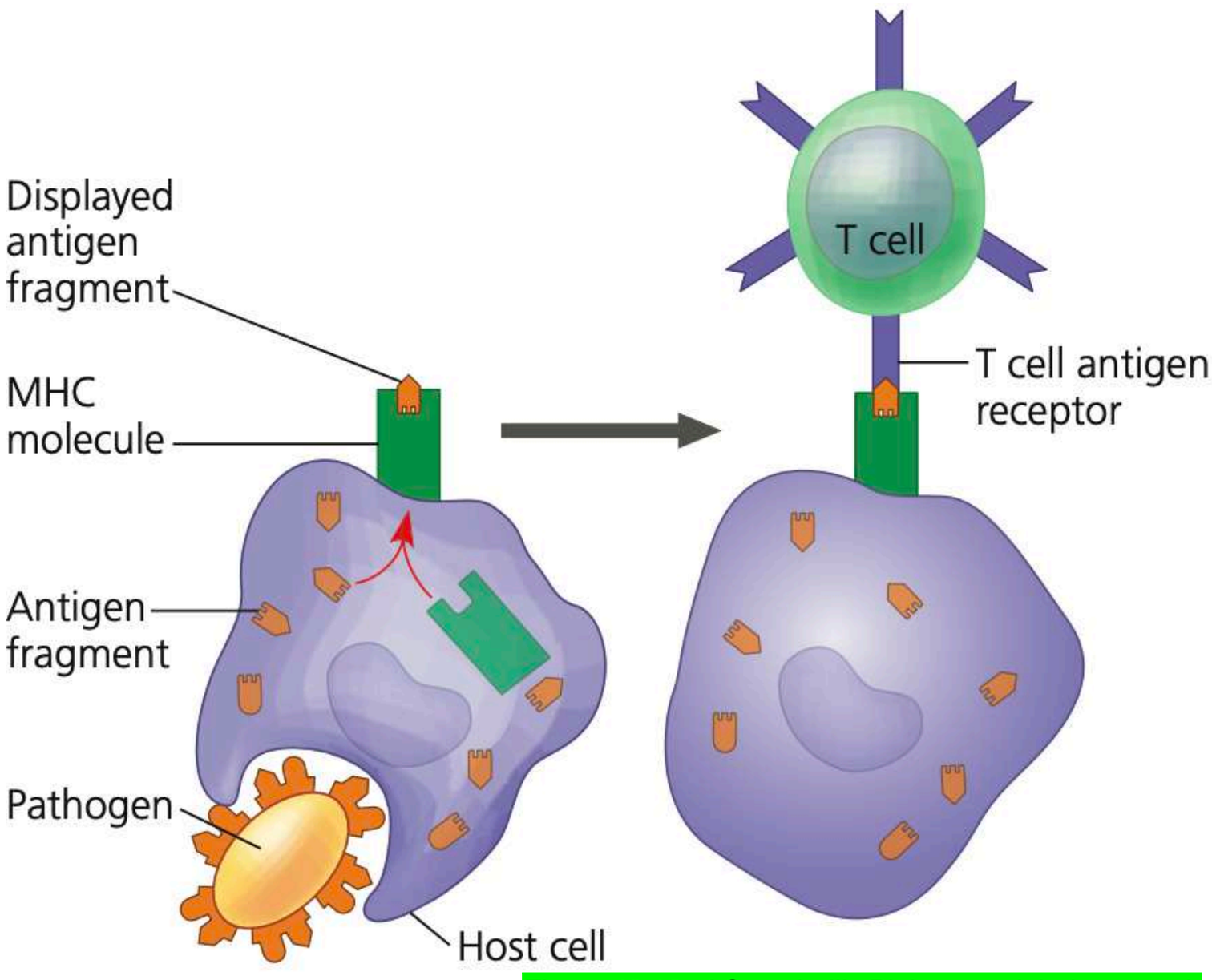


Figure 43.12 of Campbell's Biology: a global approach

Adaptive or Acquired Immunity

- Each person makes more than 1 million different B cell antigen receptors and 10 million different T cell antigen receptors
- An antigen is presented to a steady stream of lymphocytes in the lymph nodes until a match is made
- A successful match between an antigen receptor and an epitope initiates events that "activate" the lymphocyte bearing the receptor
- Once activated, a B cell or T cell undergoes multiple cell divisions.
- For each activated cell, the result of this proliferation is a clone = a population of cells that are identical to the original cell.
- Some cells from this clone become effector cells, short-lived cells that act immediately against the antigen and eliminate it.
- The effector forms of B cells are plasma cells, which secrete antibodies.
- The effector forms of T cells are helper T cells and cytotoxic T cell
- The remaining cells in the clone become memory cells, long-lived cells that can give rise to effector cells if the same antigen is encountered later in the animal's life
- This immunological memory is responsible for long-term protection against additional exposures

Adaptive or Acquired Immunity memory

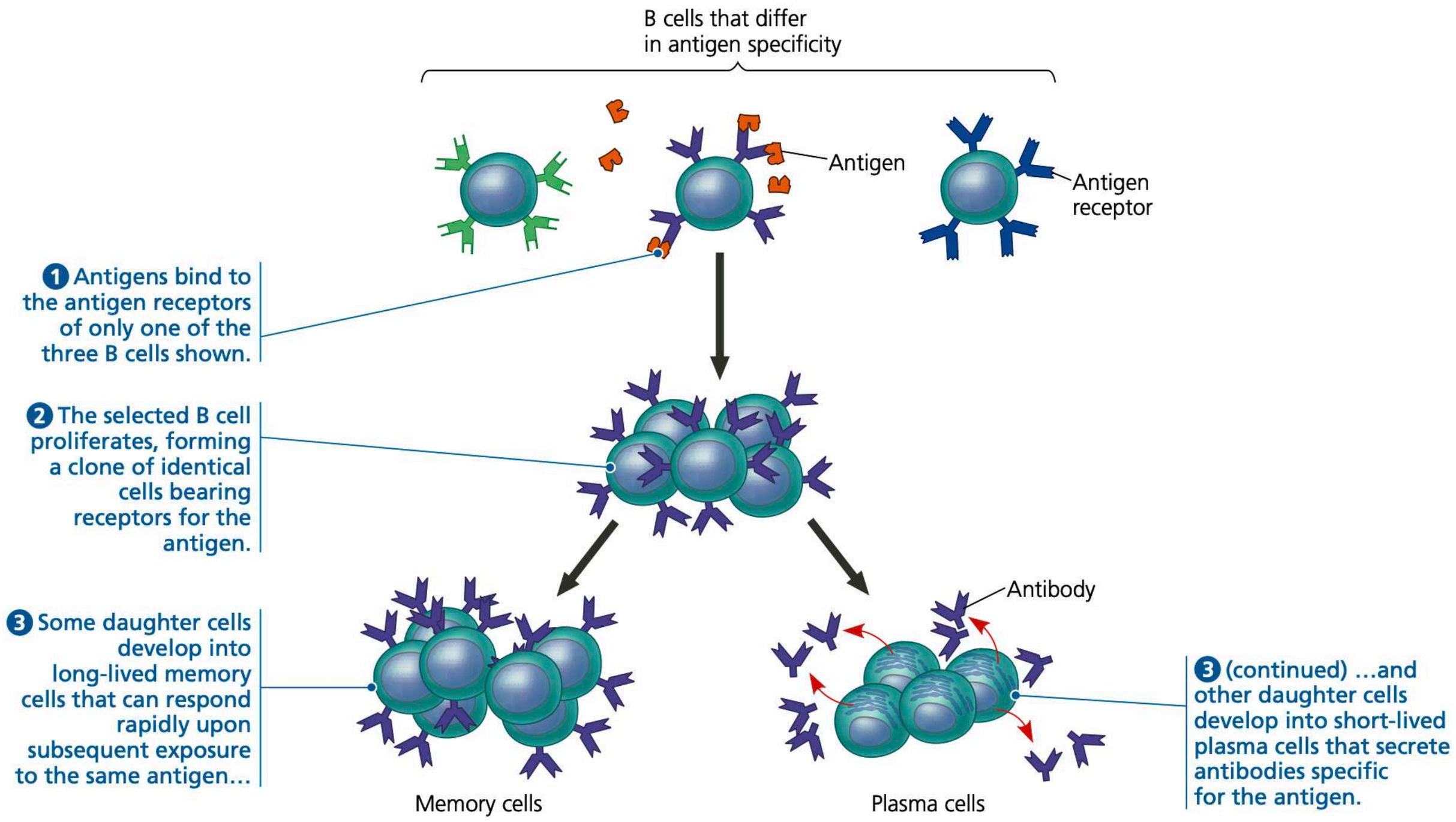
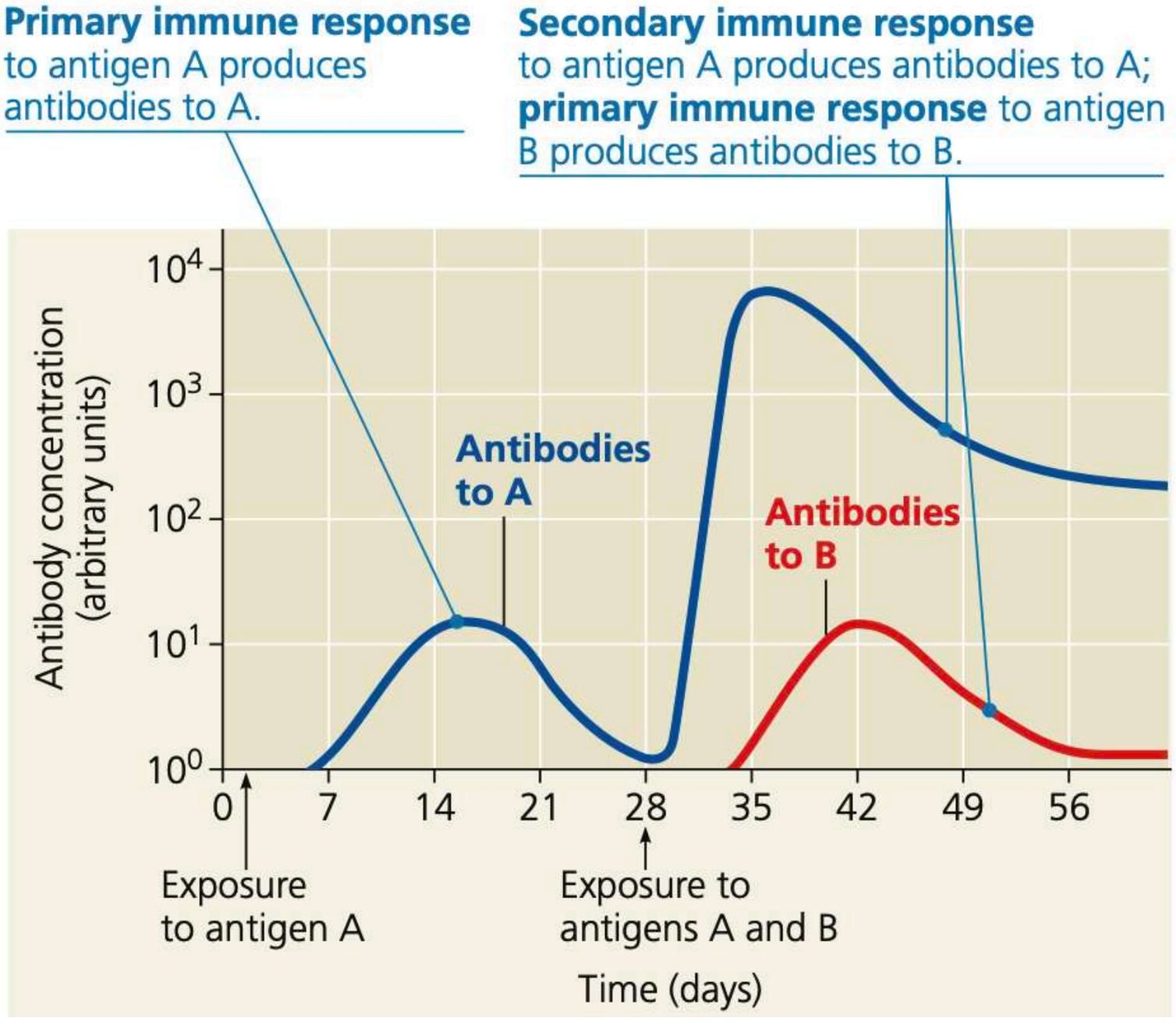


Figure 43.14 of Campbell's Biology: a global approach

Adaptive or Acquired Immunity memory



Immunological memory is specific to an antigen and does not affect responses to other antigens

Figure 43.15 of Campbell's Biology: a global approach

Antibodies do not actually kill pathogens, but by binding to antigens, they interfere with pathogen activity or mark pathogens in various ways for inactivation or destruction

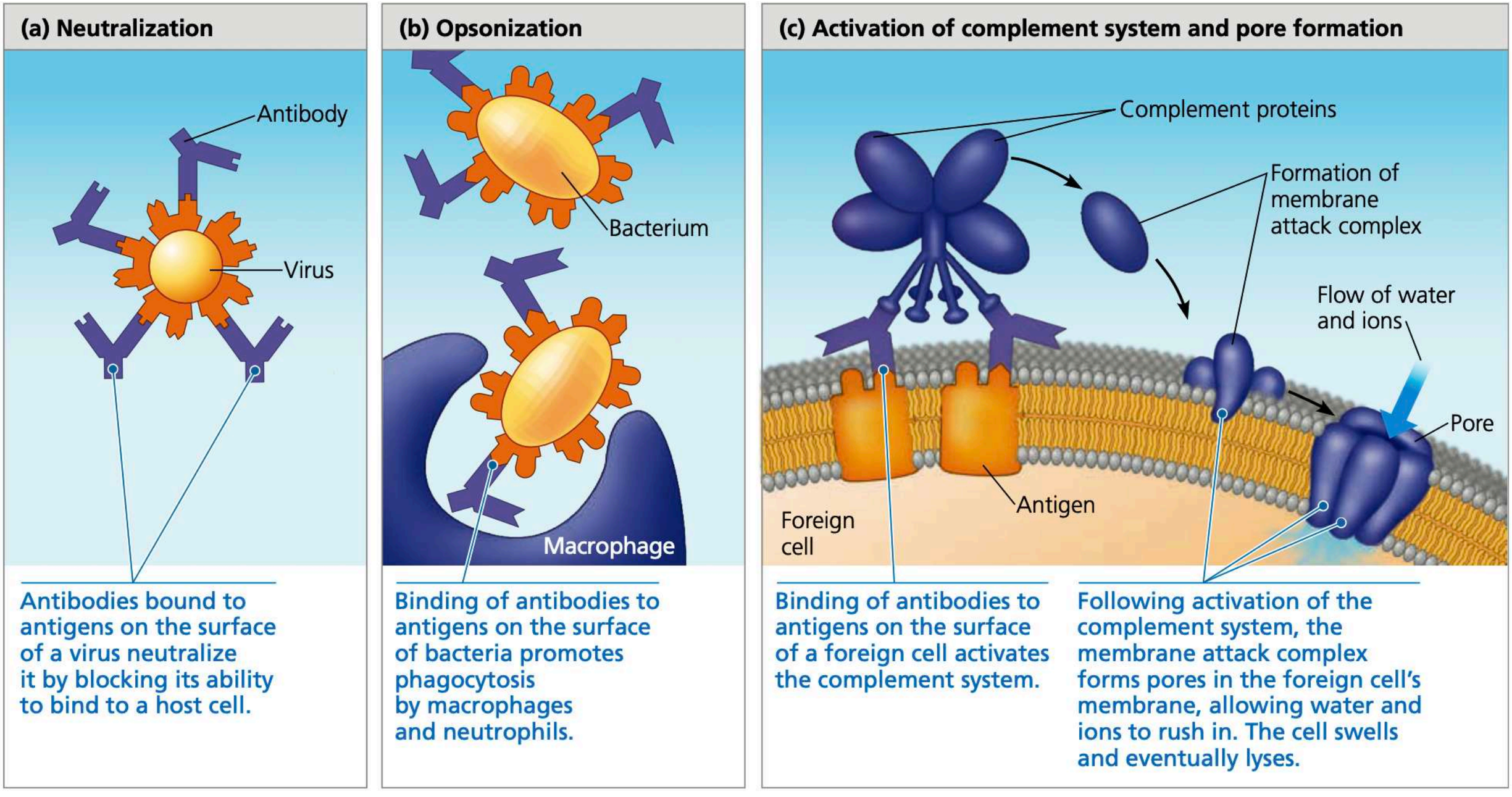
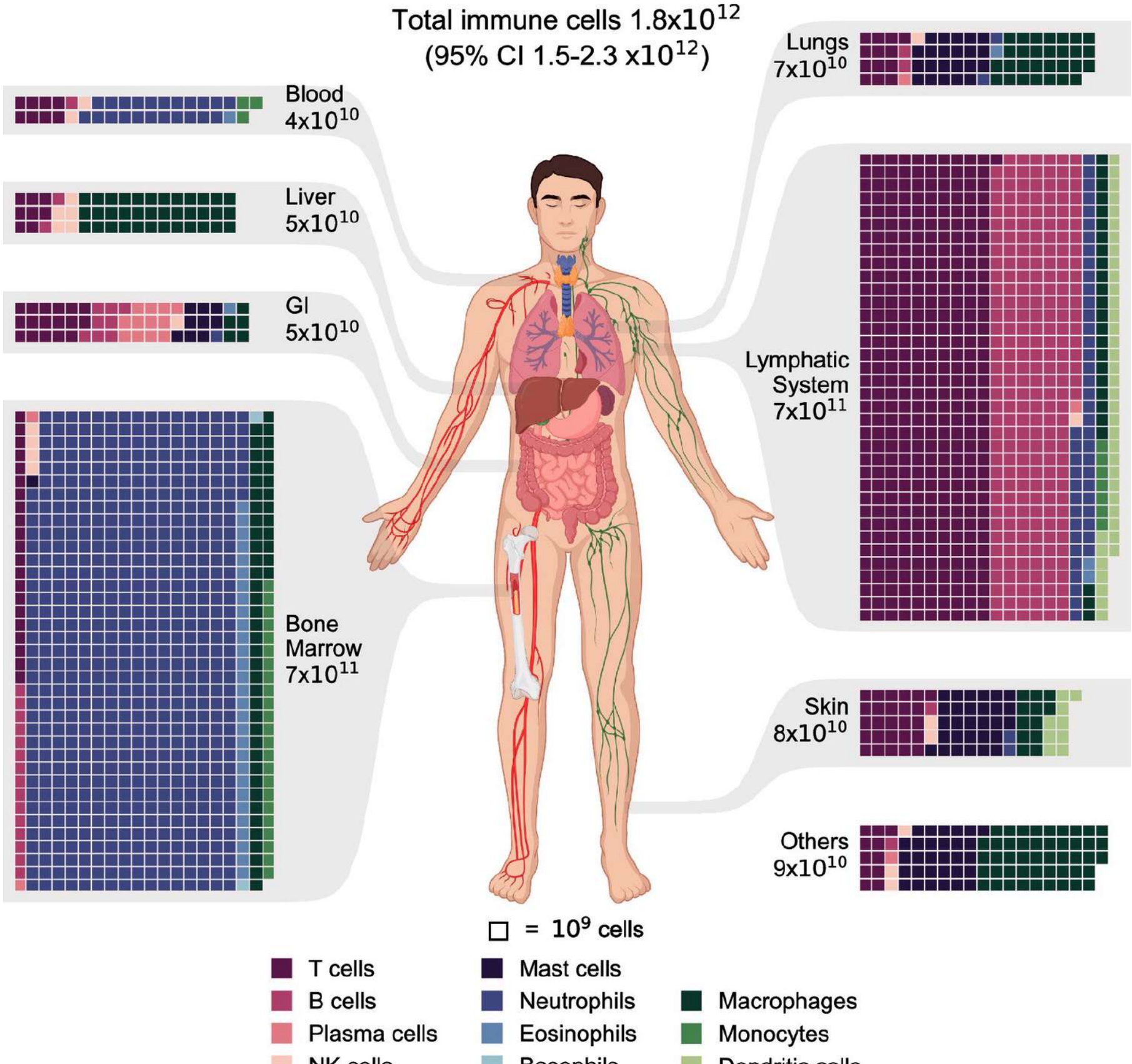


Figure 43.19 of Campbell's Biology: a global approach

The distribution of immune cells in the human body



PMID: 37871201

Generation of B and T cells with diverse antigen receptors

- B and T cells expressing diverse receptors are produced during embryonic development
- When they are first produced in the bone marrow, they are “naive” cells = not encountered any antigen yet
- Billions of naive B and T cells expressing diverse receptors are produced before these cells encounter antigens

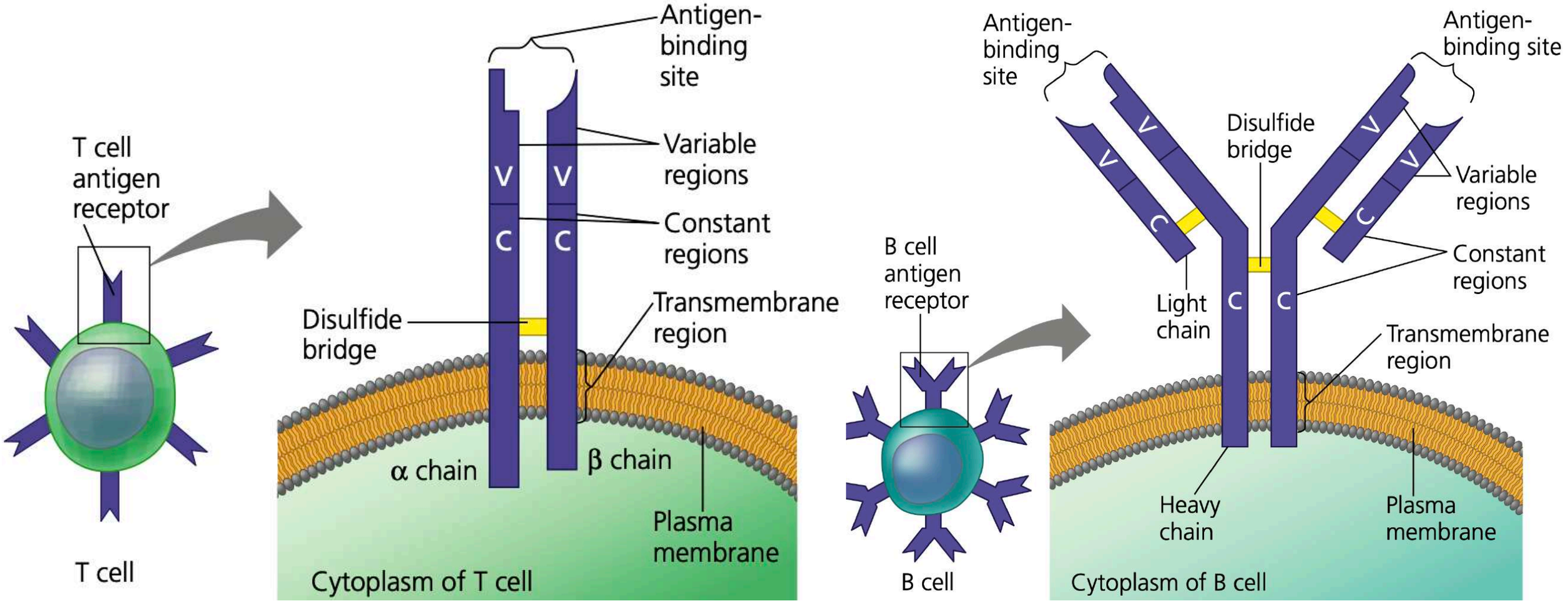
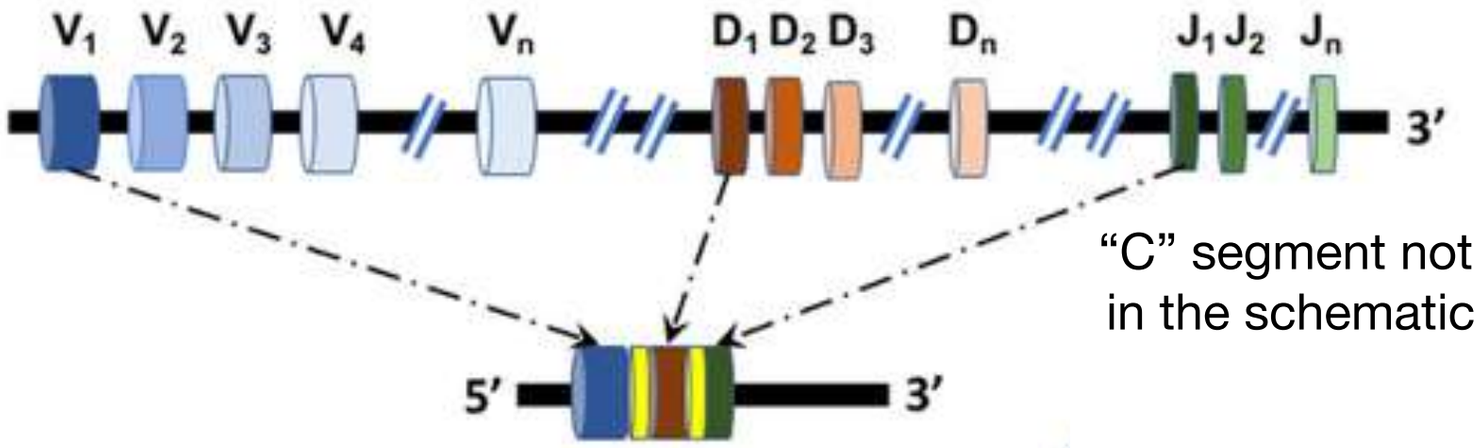
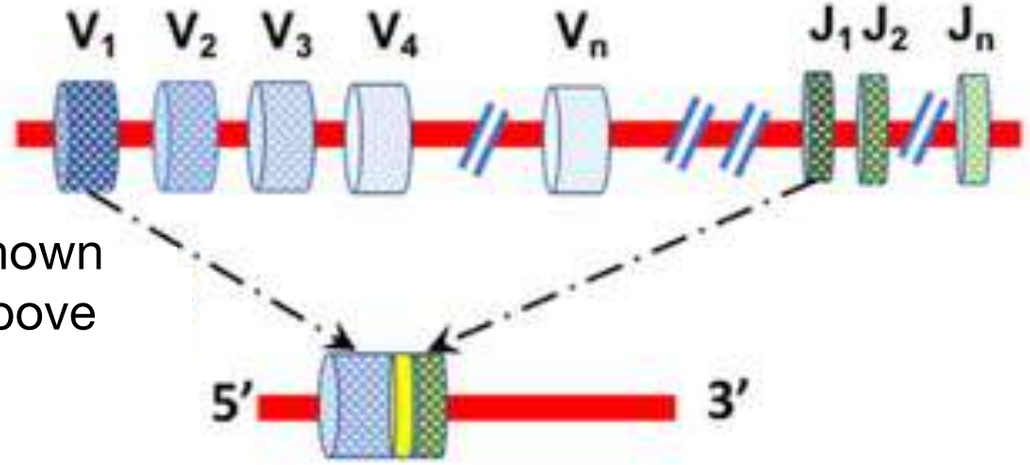


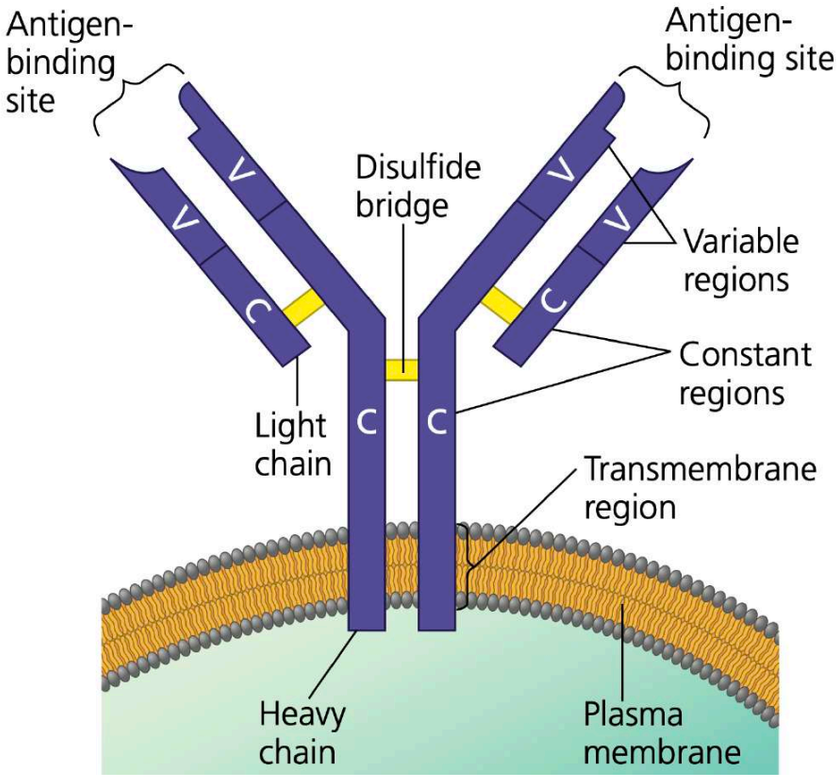
Figure 43.11 and 43.9 of Campbell’s Biology: a global approach

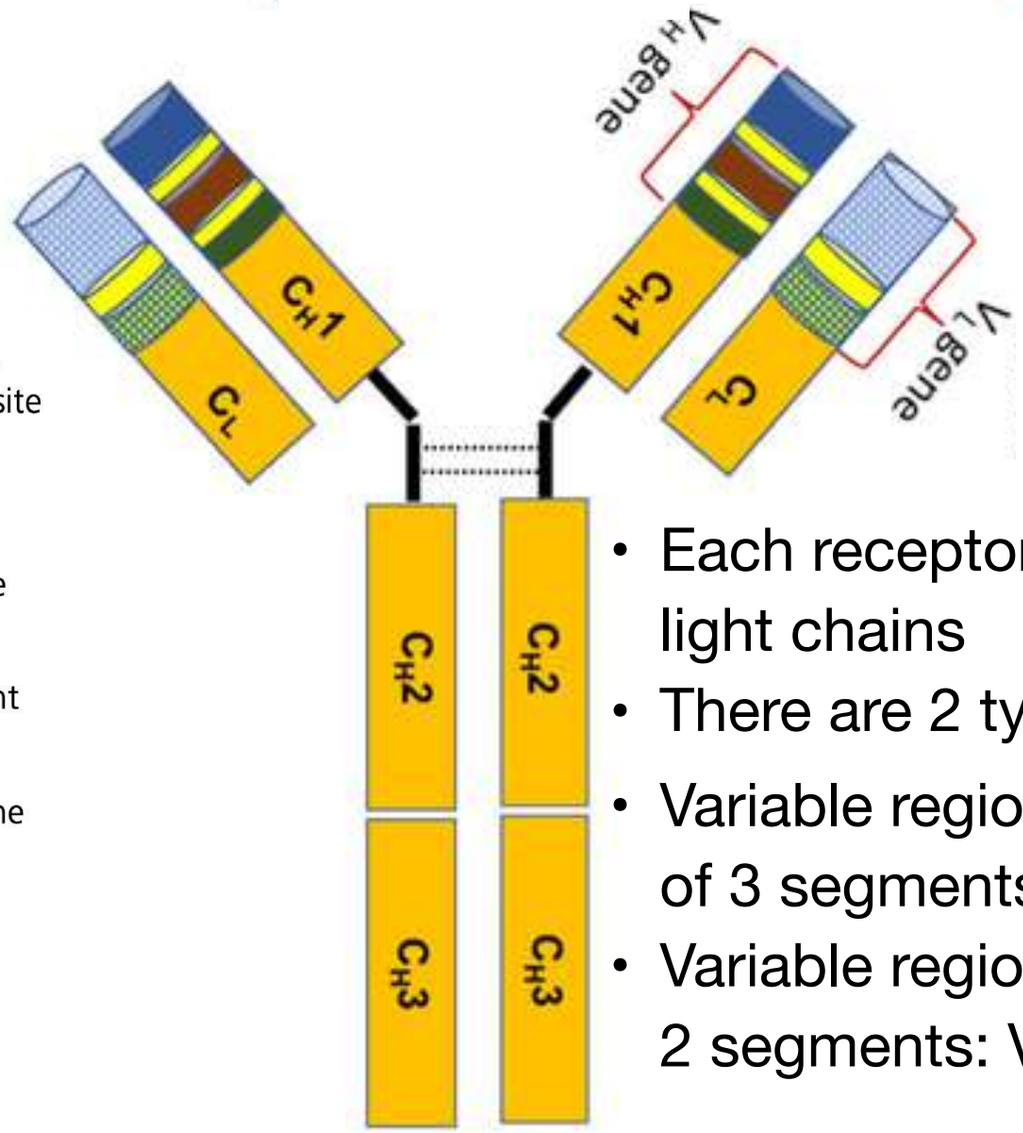
Genes coding for “V”, “D” “J” and “C” regions of the B and T cell receptors undergo recombination



“C” segment not shown in the schematic above





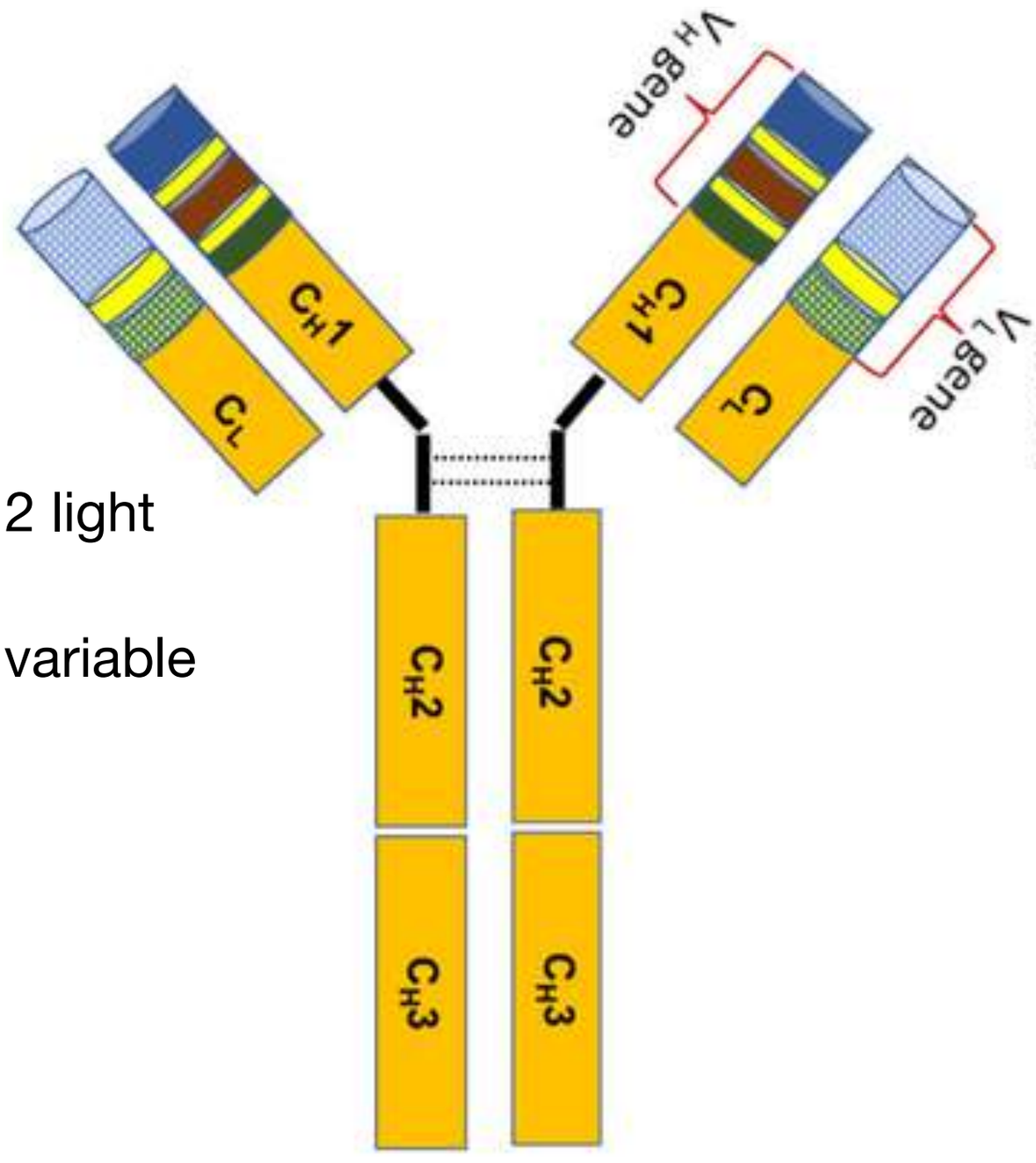


- Each receptor is made of 2 heavy and 2 light chains
- There are 2 types of light chains, λ and κ
- Variable region of Heavy chain is made of 3 segments: V, D and J
- Variable region of Light chain is made of 2 segments: V and J

PMID: 30105017

An immunoglobulin is encoded by 7 genes:
IGHV, IGHD, IGHJ, IGHC for the H chain
+
IGKV, IGKJ, IGKC for a kappa light chain

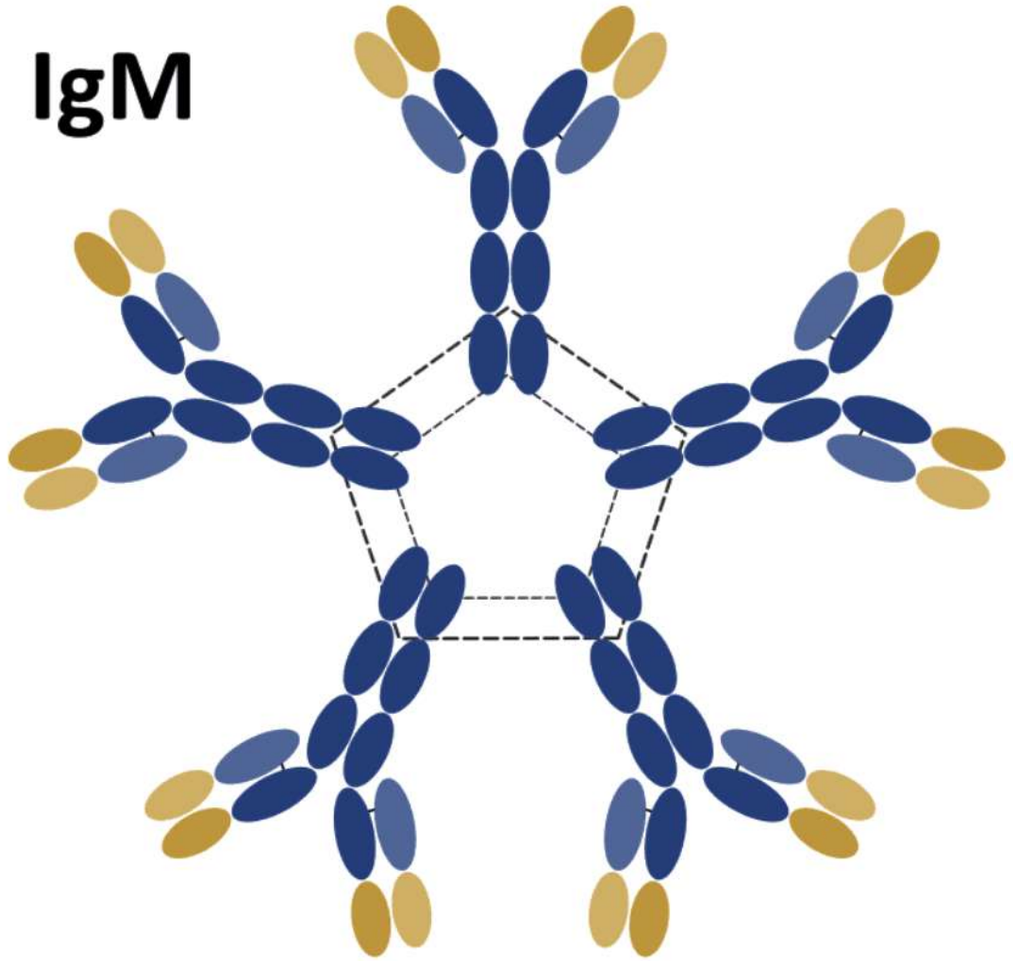
An immunoglobulin is encoded by 7 genes:
IGHV, IGHD, IGHJ, IGHC for the H chain
+
IGLV, IGLJ or IGLC for a lambda light chain

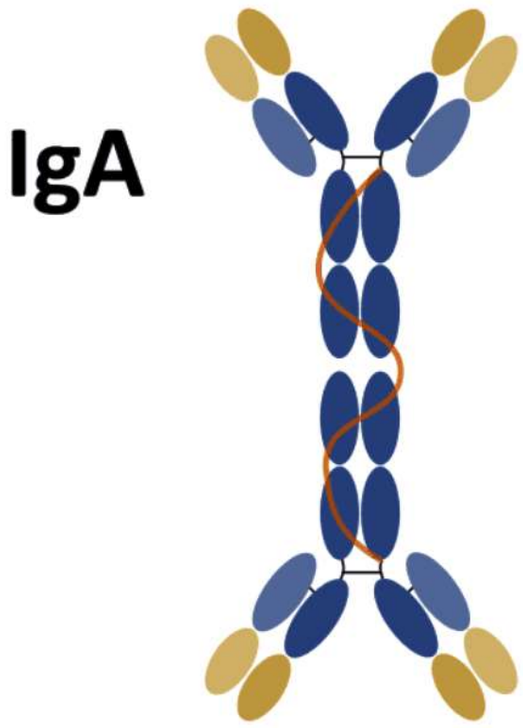


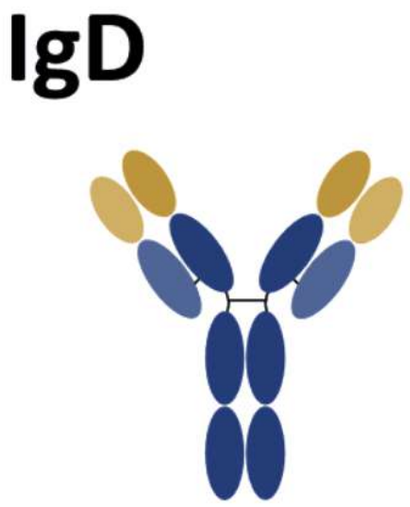
For a given receptor, the 2 light chains are identical
“D” region is only on the variable segment of heavy chain

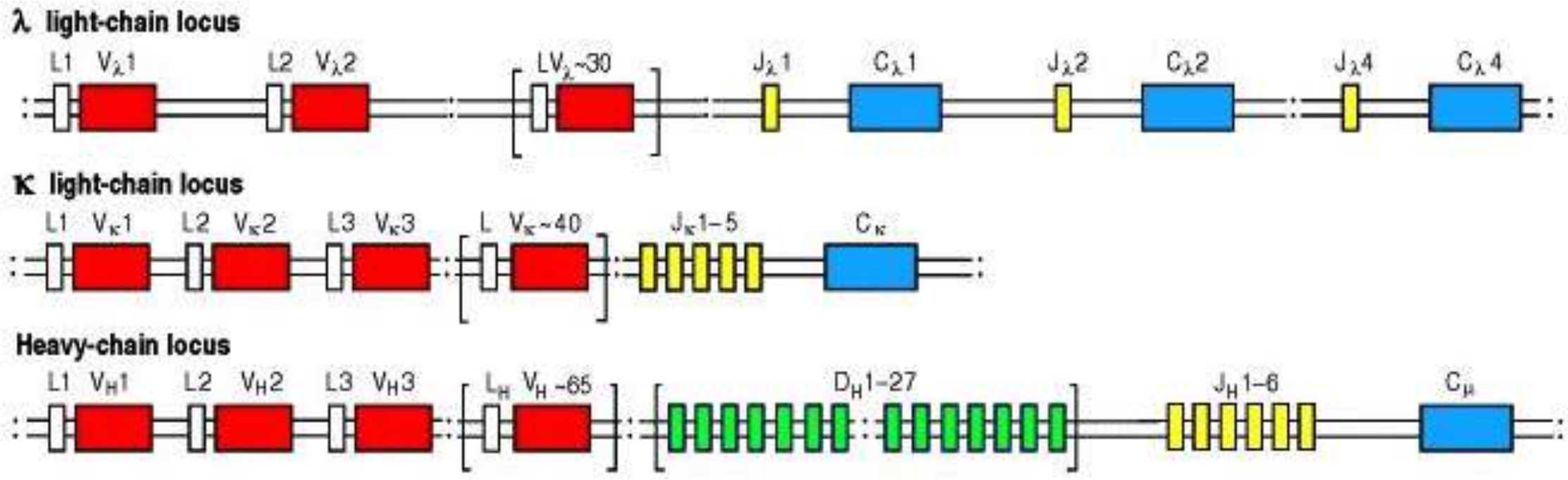
PMID: 30105017

Based on heavy and light chain compositions, antibody receptors are of different immunoglobulin classes









The human genome contains 176 functional immunoglobulin genes clustered in 3 loci:

- IGH on chromosome 14 (50 V, 23 D, 6 J and 9 C) - to make heavy chains
- IGK on chromosome 2 (40 V, 5 J and 1 C) - to make kappa light chains
- IGL on chromosome 22 (32 V, 5 J and 5 C) - to make lambda light chains

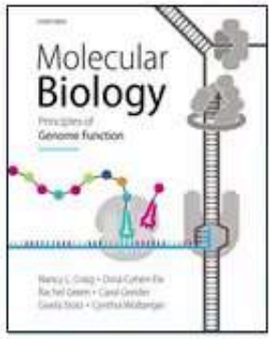
- During the development of B cells, the mechanisms of diversity involved in the immunoglobulin synthesis (combinatorial V-(D)-J diversity, junctional diversity and somatic hypermutations) lead to the huge potential antibody repertoire of each individual
- Estimated to comprise 10^{12} different immunoglobulins
- Limiting factor being only the number of B cells that an organism is genetically programmed to produce

https://www.ncbi.nlm.nih.gov/books/NBK27140/

DNA recombination

- Involves the exchange of genetic material
- Can occur between different regions of the same chromosome
- Can also occur between multiple chromosomes
- Exchange of DNA segments results in formation of “junctions” known as “Holliday Junction”
- These junctions need to be resolved to separate the individual DNA segments
- Type of resolution of Holliday Junction results in different types of of end results for the exchange event

Recombination of DNA segments is a fundamental mechanism to generate diversity



Molecular Biology: Principles of Genome Function

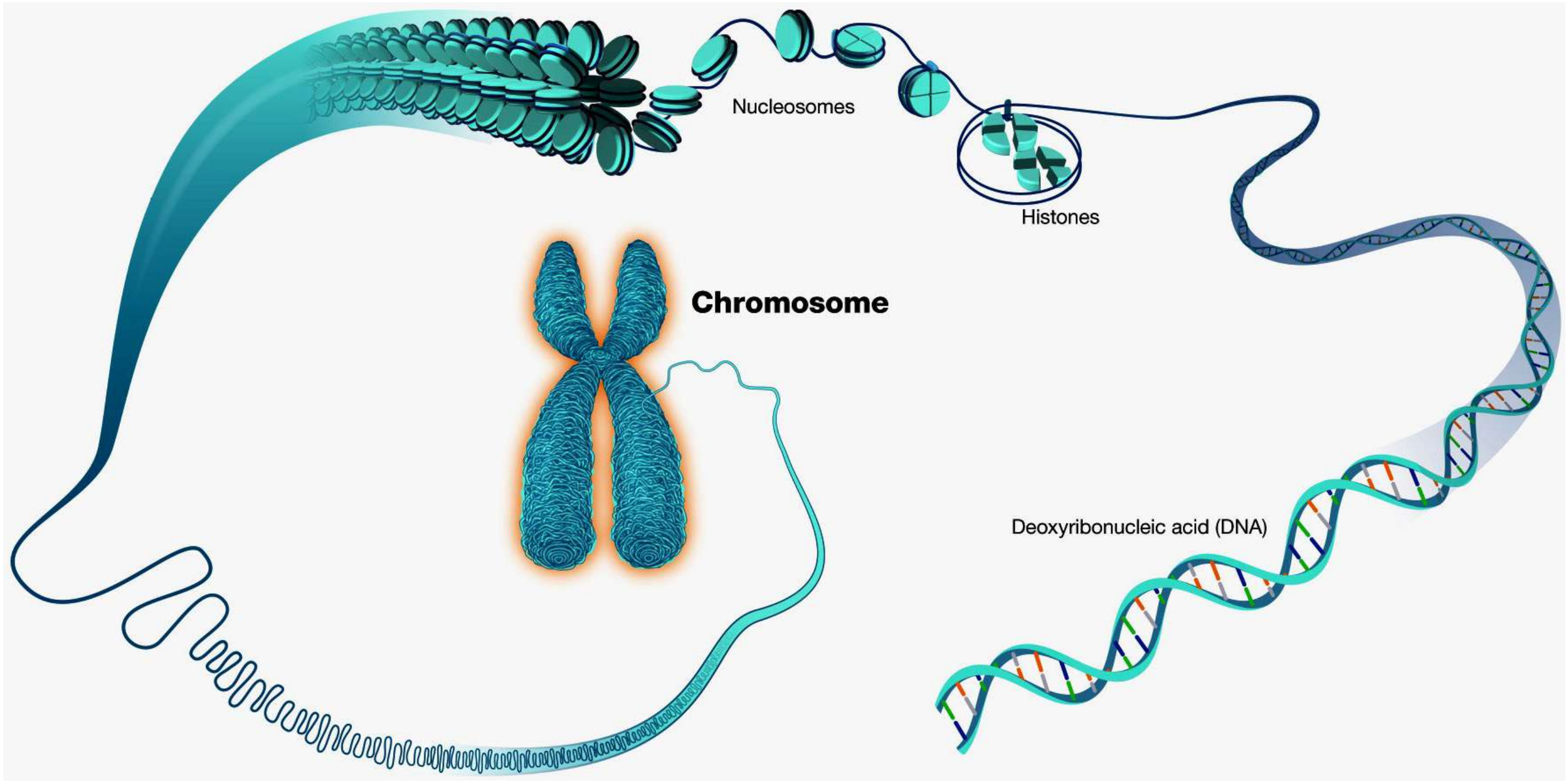
Second Edition

OXFORD
UNIVERSITY PRESS

Animation 14: **Holliday junction resolution**

Animation produced by Connor Hendrich

https://www.youtube.com/watch?v=MvnWxN81Qps



Recombination between sister vs non-sister (homologous) chromosomes result in different outcomes

https://www.genome.gov/genetics-glossary/Chromosome

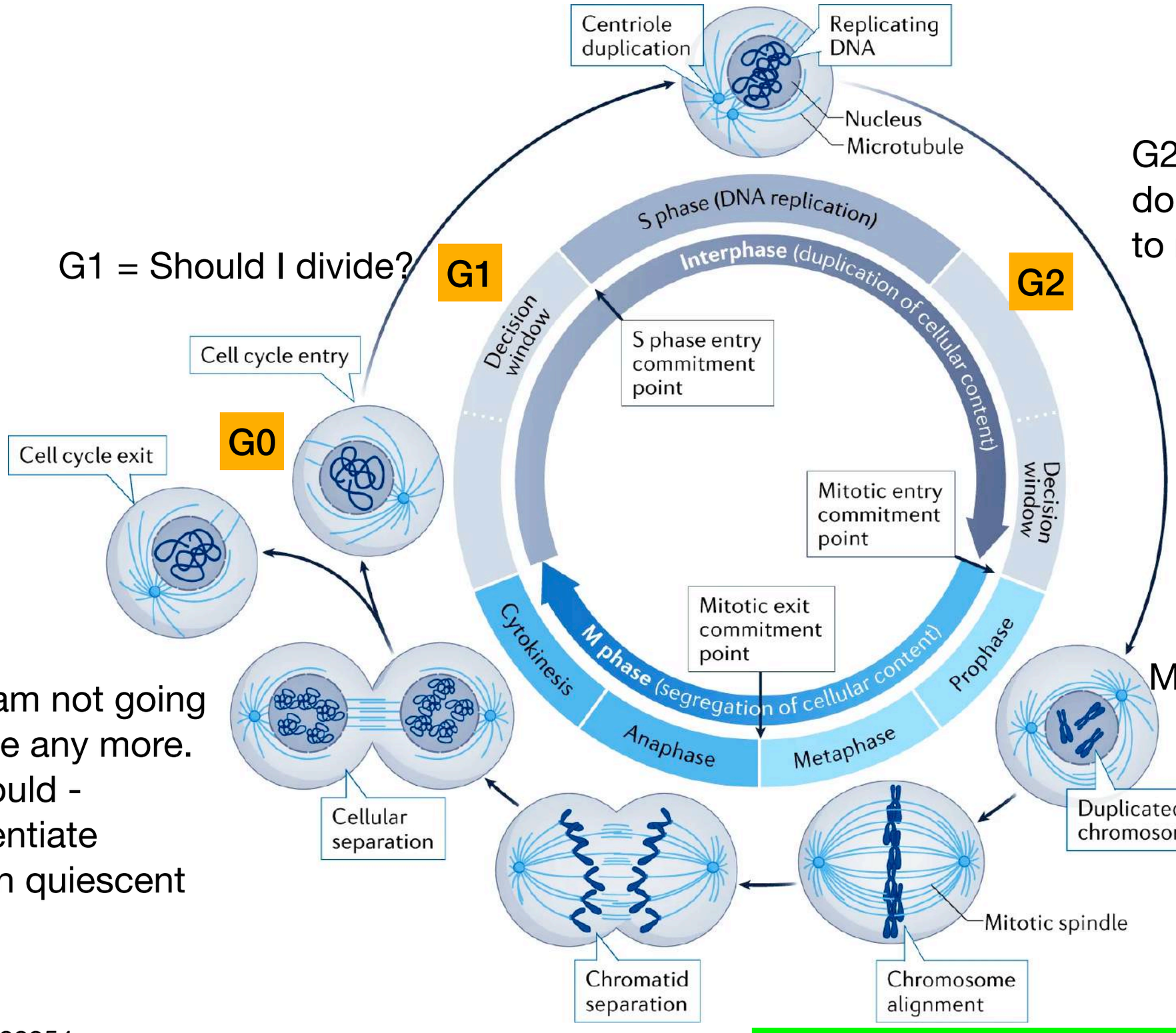
Cell Cycle

Cells that decide to continue to remain cycling through the cell cycle are capable of proliferation

S = I am doubling my DNA for daughter cells

G1 = Should I divide?

G2 = In addition to DNA, do I have everything else to make 2 daughter cells?



G0 = I am not going to divide any more. But I could -

- differentiate
- remain quiescent
- die

M = I am dividing into 2

I decided to divide and doubled my DNA. Have I ensured that the DNA will be allocated equally to both my daughters? = M phase = SAC

PMID: 34508254

Figure 12.14, 12.15, 12.16 and 12.17 of Campbell's Biology: a global approach

Cell Cycle

Progression through the cell cycle requires successfully “passing” several checkpoints

- Failure to clear a checkpoint results in stalling at that checkpoint till repair can finish to the satisfaction of passing the checkpoint
- Failure to repair and pass the checkpoint results in cell death

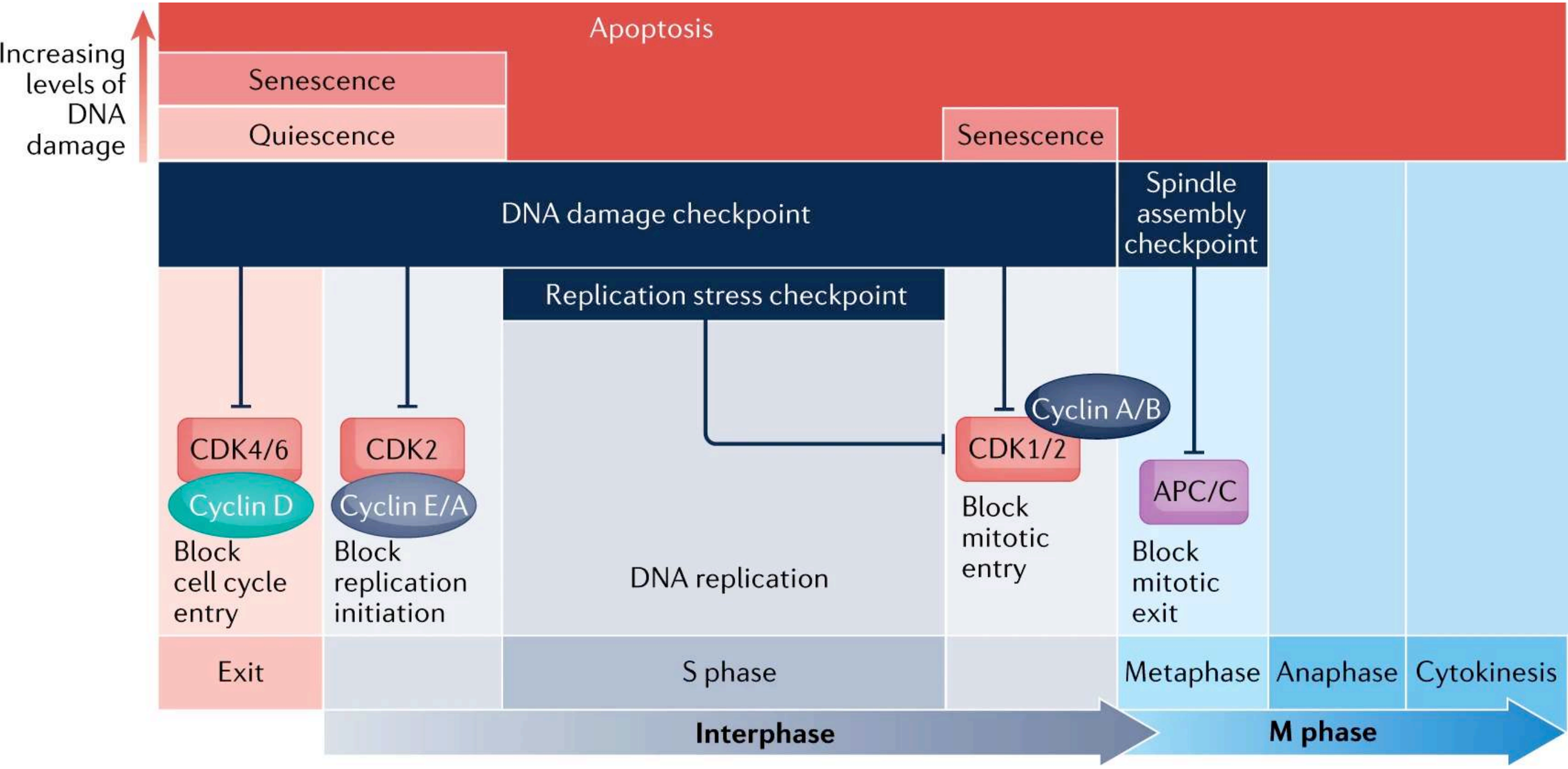


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Figure 12.14, 12.15, 12.16 and 12.17 of Campbell’s Biology: a global approach

The cell cycle is an algorithm

- This algorithm has specific and logical steps to be followed in order to achieve specific outcomes of whether to divide or not
- This algorithm automatically checks for bugs in its code and stalls the algorithm till the bug gets fixed
- Failure to fix the bug results in failure of the algorithm and cell death = good outcome!
- Failure to detect the bug and/or failure to fix the bug results in the algorithm leading to unexpected outcomes = cancer = bad outcome!

2. Remove inhibitors which prevent the cell from entering the cell cycle

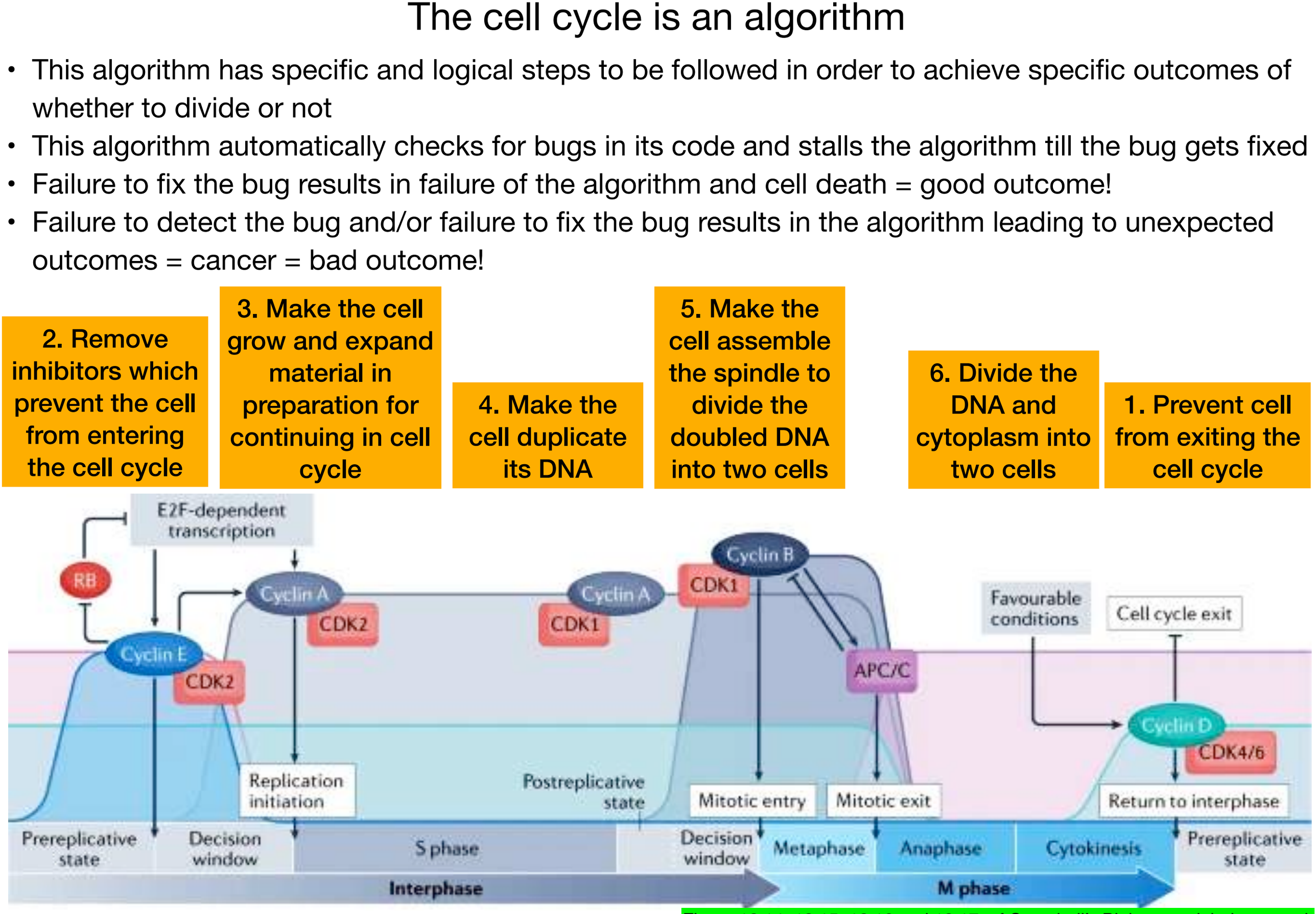
3. Make the cell grow and expand material in preparation for continuing in cell cycle

4. Make the cell duplicate its DNA

5. Make the cell assemble the spindle to divide the doubled DNA into two cells

6. Divide the DNA and cytoplasm into two cells

1. Prevent cell from exiting the cell cycle



PMID: 3450825

Figure 12.14, 12.15, 12.16 and 12.17 of Campbell's Biology: a global approach

Progression through the cell cycle requires successfully "passing" the checkpoints

- Checkpoints = protein complexes of Cyclin Dependant Kinases (CDKs) and Cyclins
- Levels of Cyclin proteins rises and falls with phases of the cell cycle
- CDKs = enzymes present at all phases of the cell cycle, but not active unless partnered with a Cyclin
- Upon partnering with a Cyclin, the CDK-Cyclin pair phosphorylates other proteins
- The phosphorylated proteins get degraded allowing the cell to progress to the next phase and checkpoint

2. Remove inhibitors which prevent the cell from entering the cell cycle

3. Make the cell grow and expand material in preparation for continuing in cell cycle

4. Make the cell duplicate its DNA

5. Make the cell assemble the spindle to divide the doubled DNA into two cells

6. Divide the DNA and cytoplasm into two cells

1. Prevent cell from exiting the cell cycle

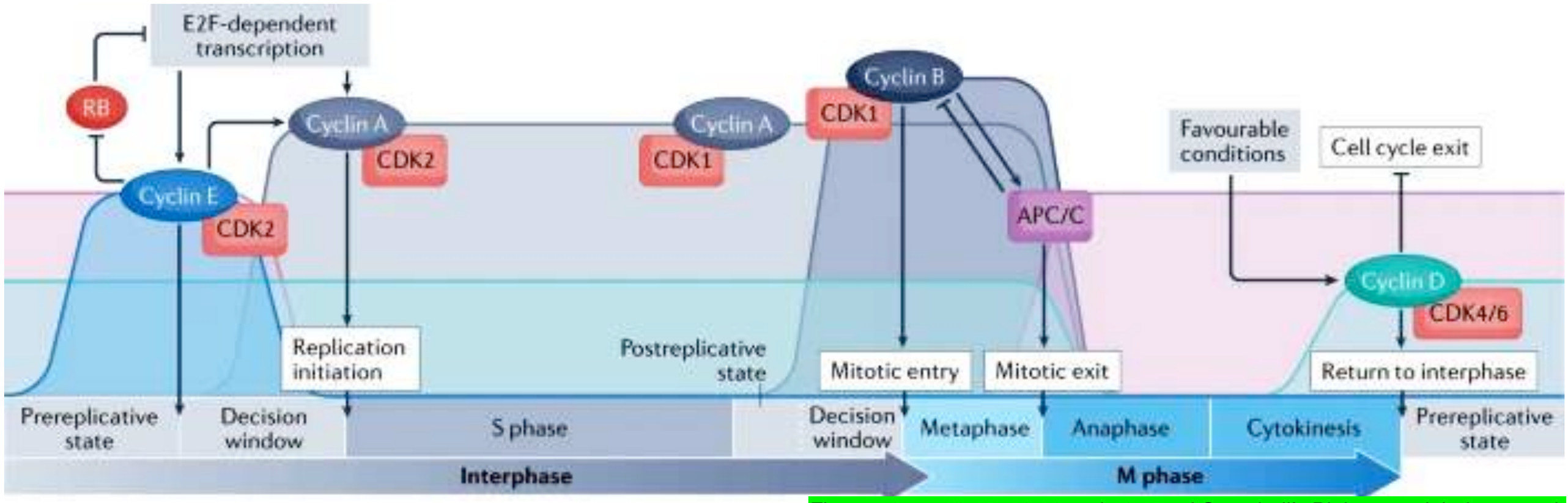


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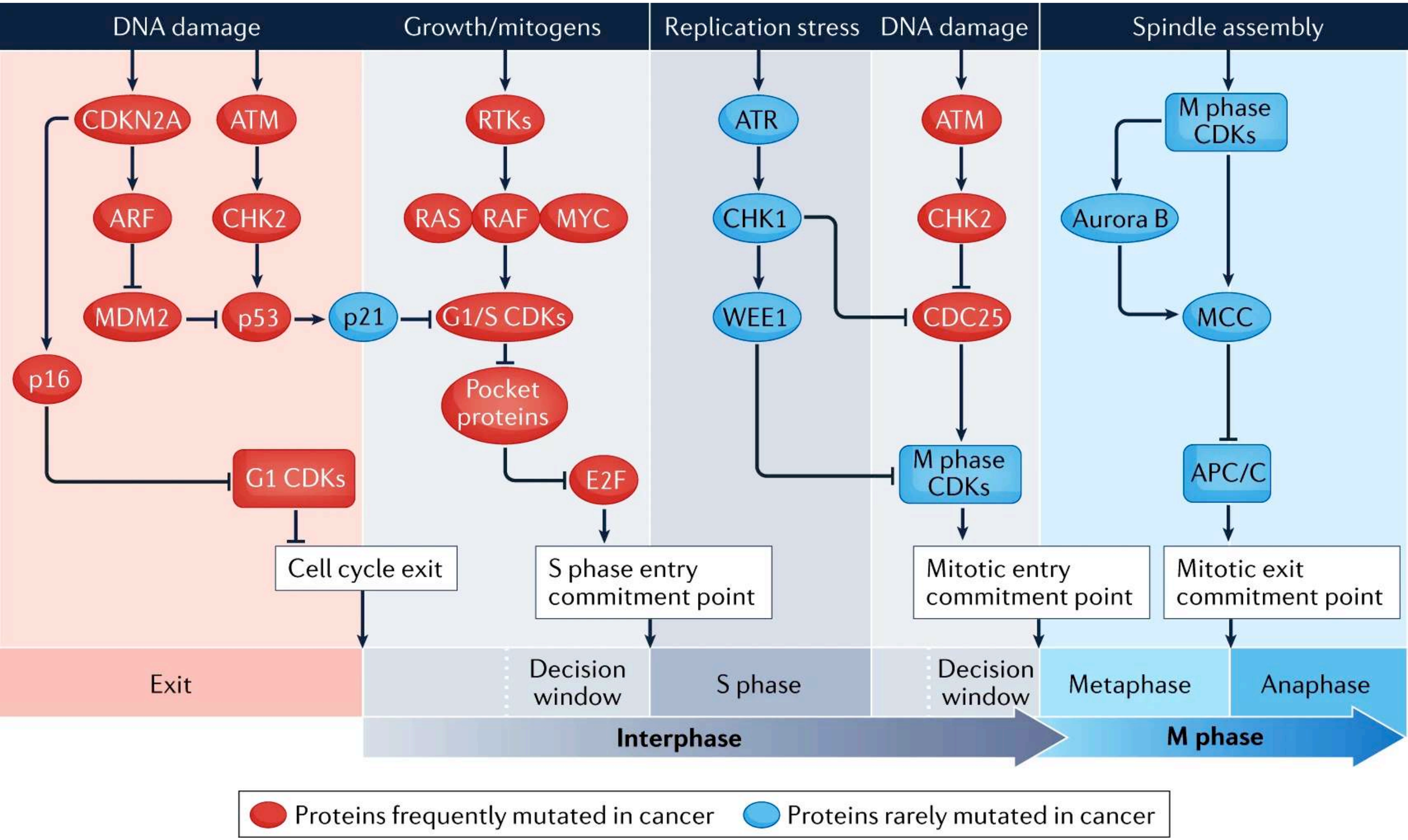
Figure 12.14, 12.15, 12.16 and 12.17 of Campbell's Biology: a global approach

Unfixable bugs in the cell cycle algorithm tend to occur more frequently in some parts of the code than in others



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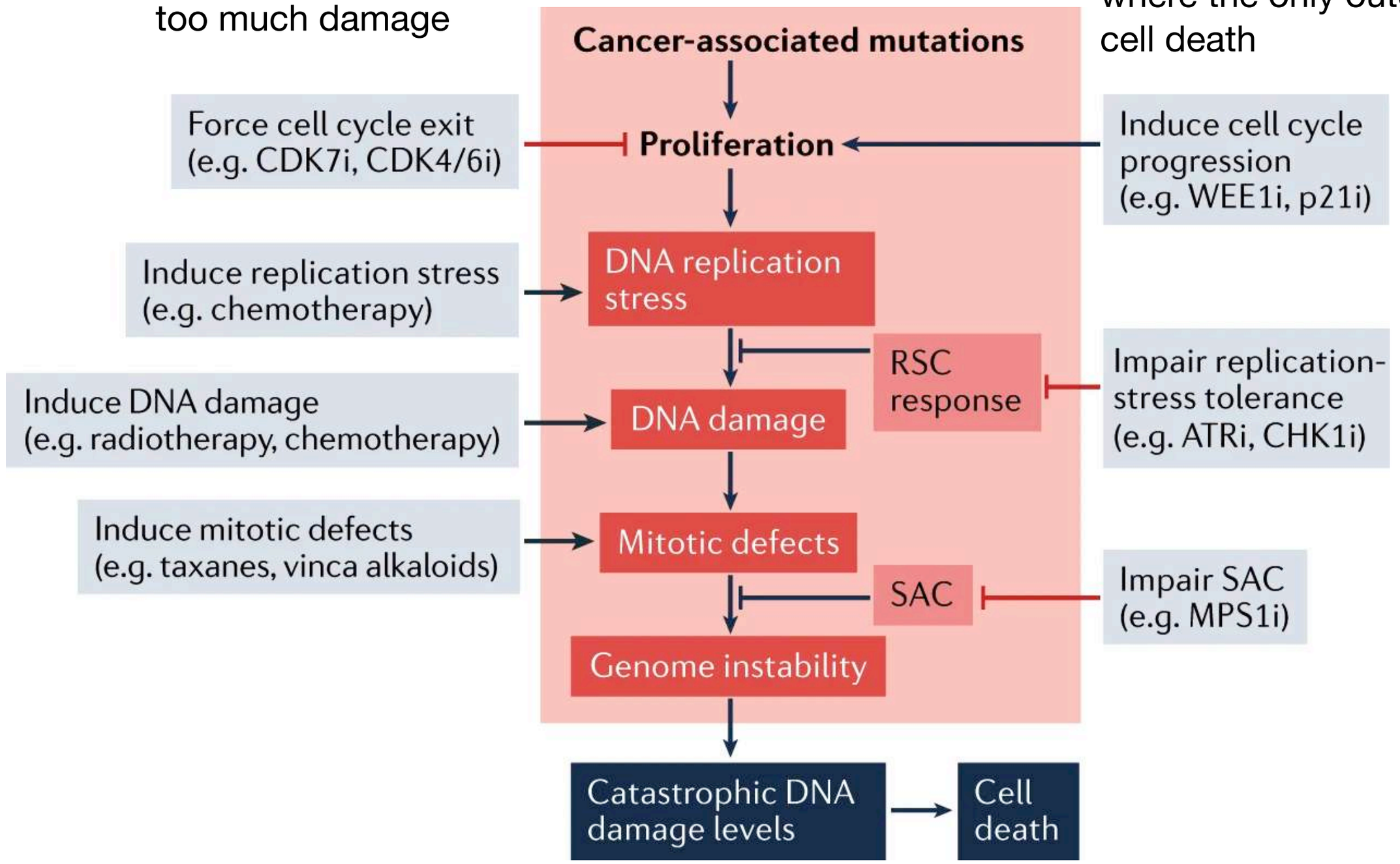
Unfixable bugs in the cell cycle algorithm are also opportunities!

fix the bug or alter the bug to get the algorithm to end without causing too much damage

Take advantage of the bug and make it go into overdrive to force the cell into a state of accelerated damage from where the only outcome is cell death



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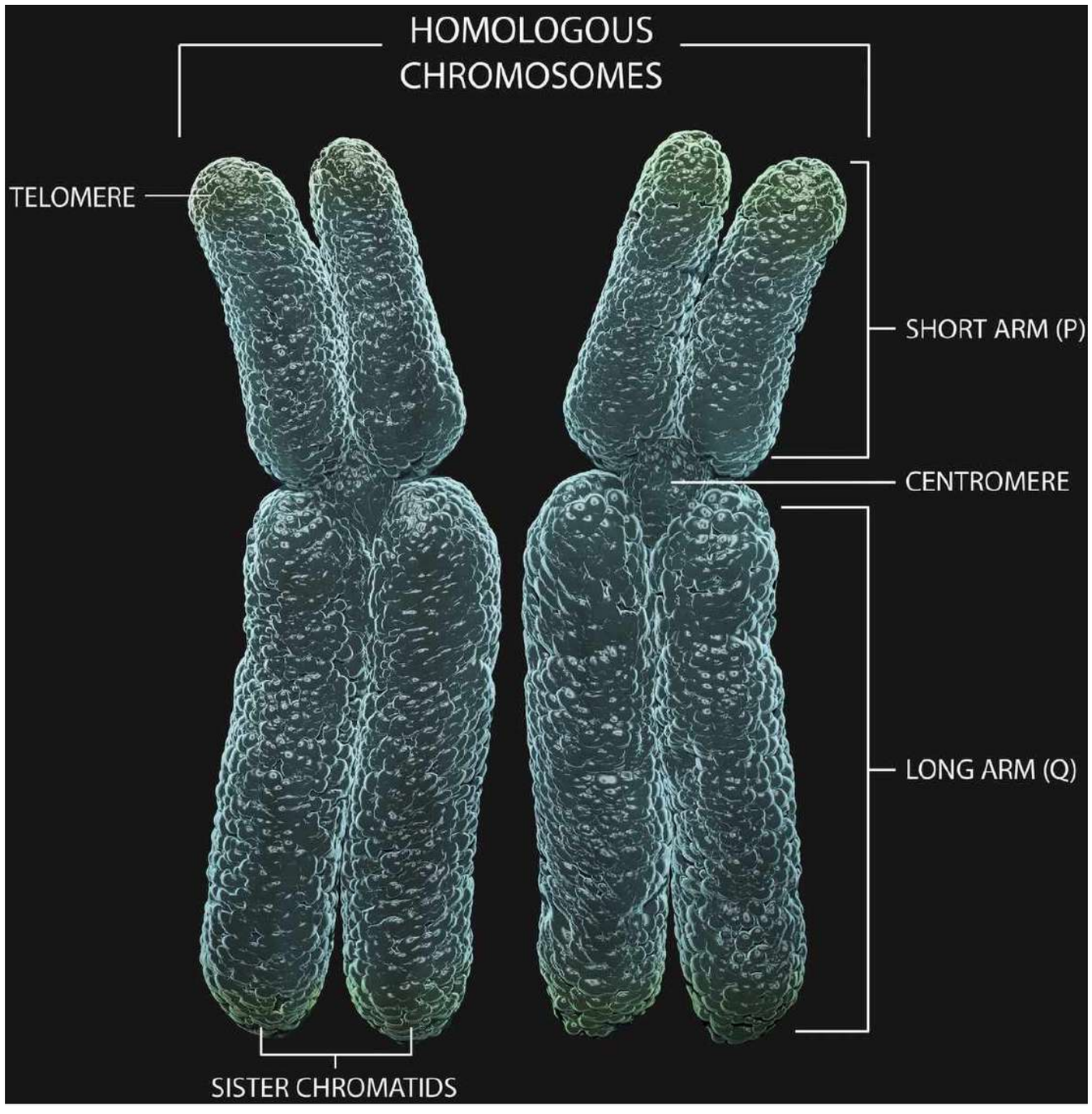
Chromosomes

- A pair of same chromosomes = homologous chromosomes
- One half of one chromosome = sister chromatid
- Sister chromatids come into existence in S-phase



What does mitosis separate - Chromatids or Chromosomes?

What does meiosis separate - Chromatids or Chromosomes?

What does the mature sperm contain - Chromatids or Chromosomes?

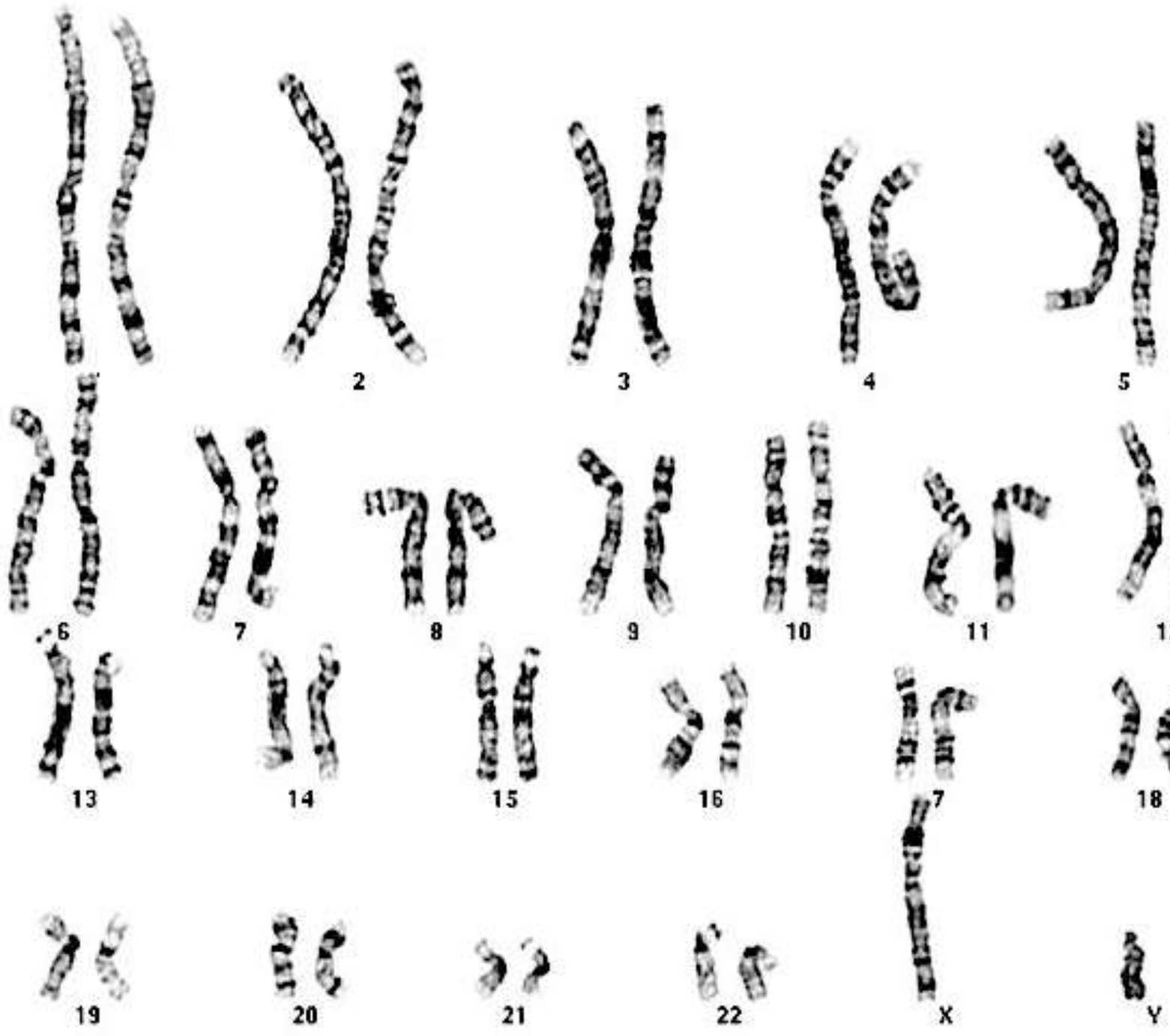
What does the mature egg contain - Chromatids or Chromosomes?

What does the one-cell embryo contain - Chromatids or Chromosomes?

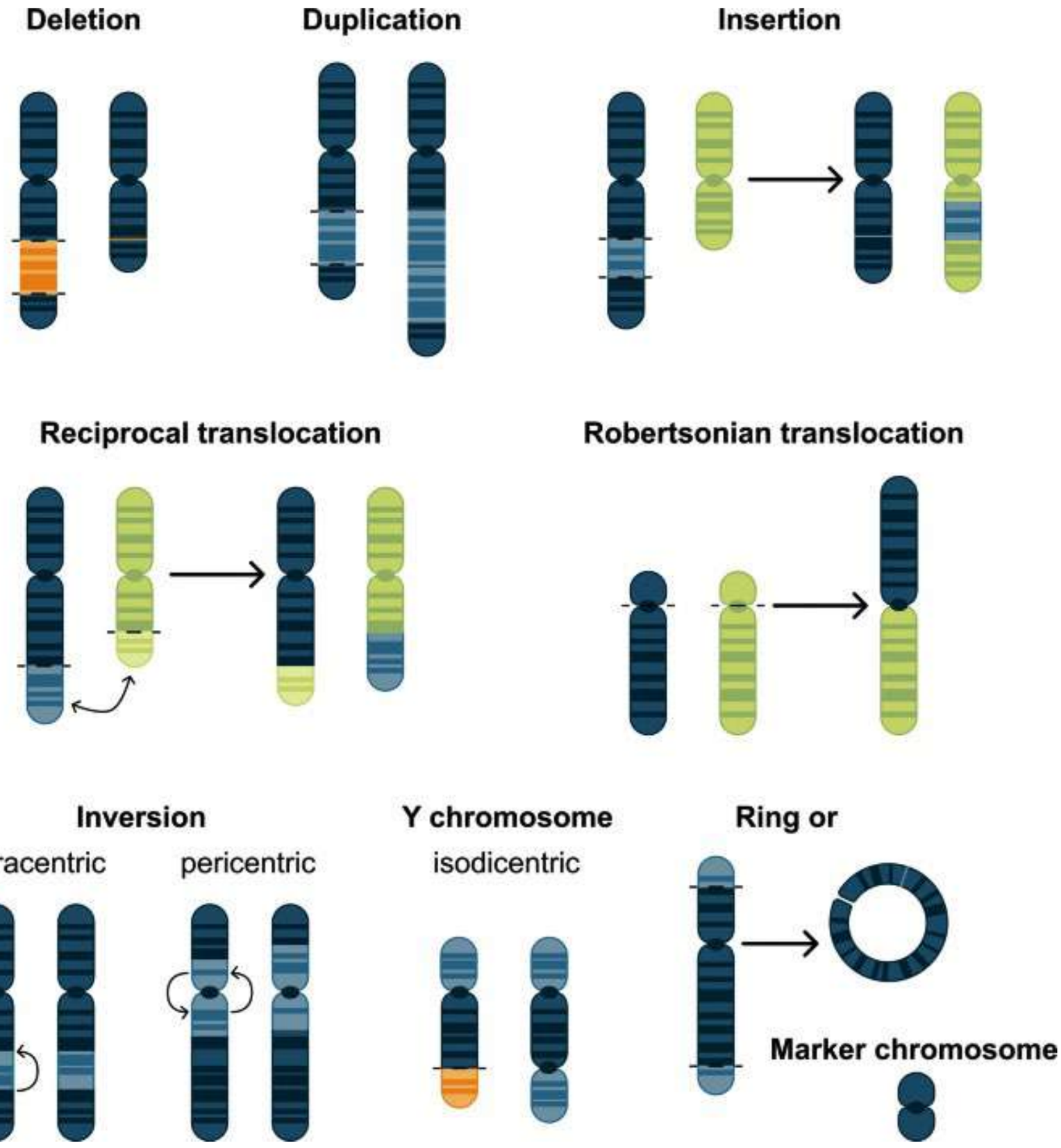
What does the interphase cell contain - Chromatids or Chromosomes?

Karyotyping

- Done by isolating metaphase DNA from nuclei of cell
- DNA is stained with a dye, results in a pattern of bands on the chromosome = G banding
- Stained chromosomes are lined up on a slide in pairs and imaged
- Each chromosome has a unique G-banding pattern



Structural abnormalities of chromosomes



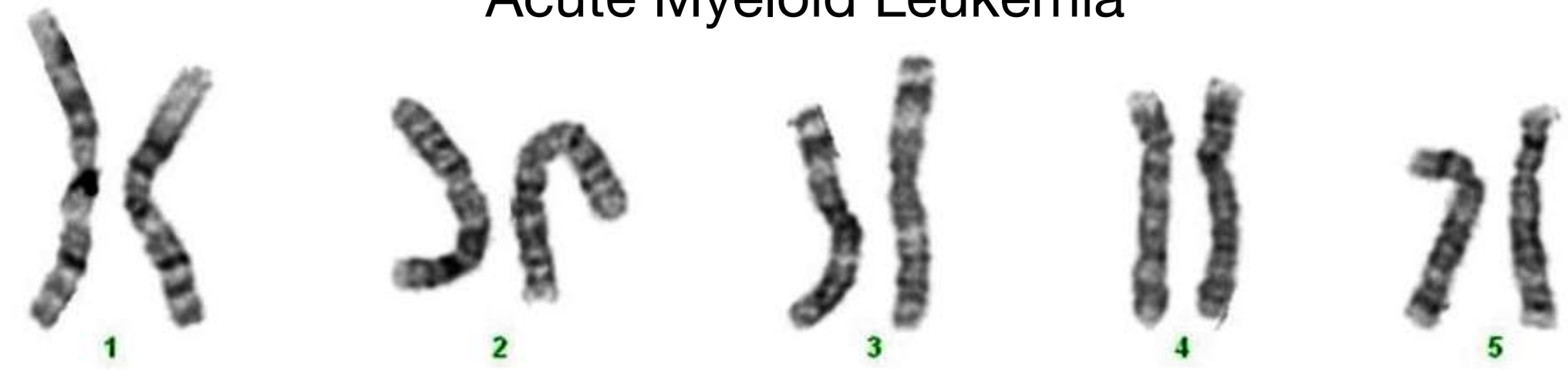
https://doi.org/10.1007/978-3-031-31574-9_23

Figure 15.14 and 15.15 of Campbell's Biology: a global approach

t(8;21)(q22;22)

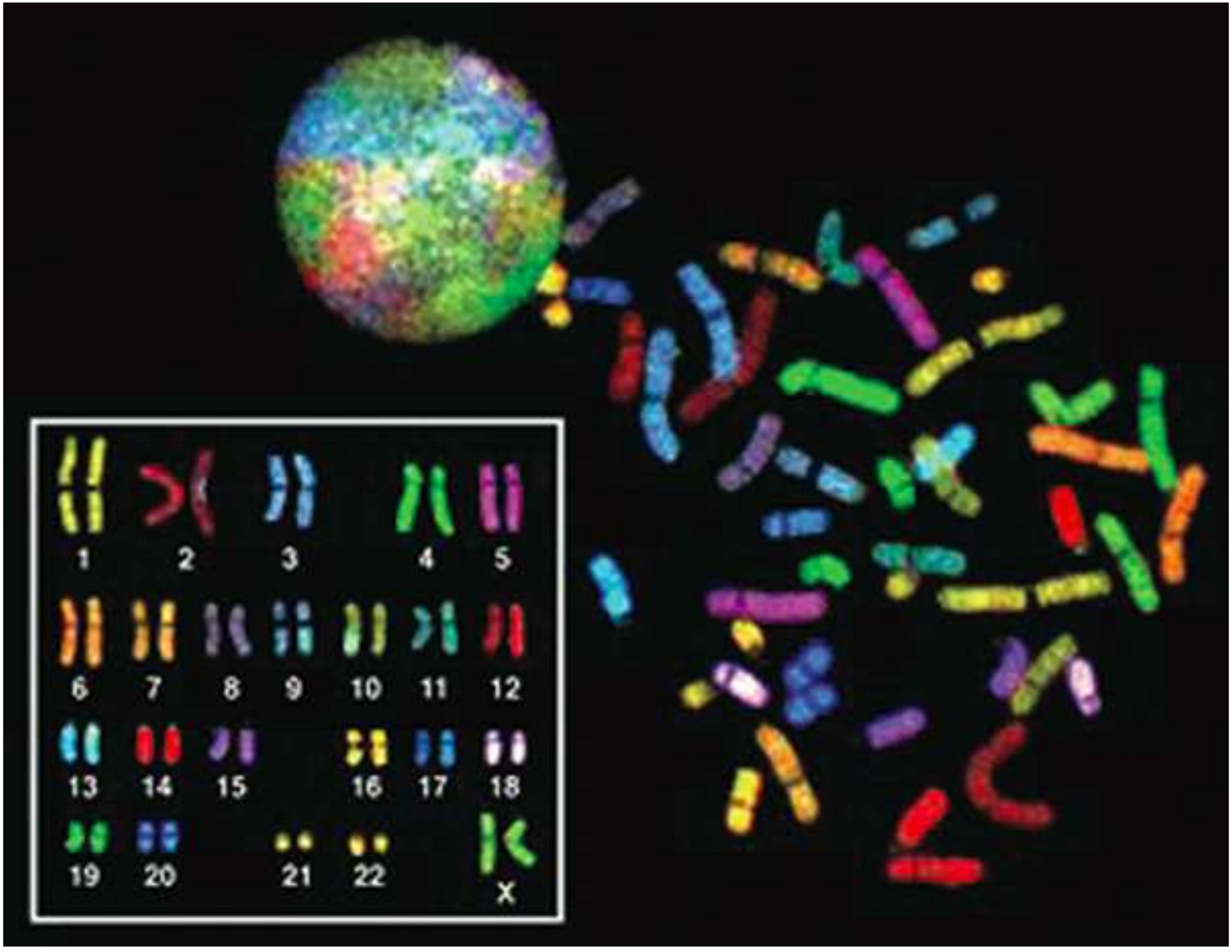
Translocation between chromosomes 8 and 21, at band 22 of q arms

Acute Myeloid Leukemia



https://imagebank.hematology.org/image/60042/acute-myeloid-leukemia-with-the-t821q2222

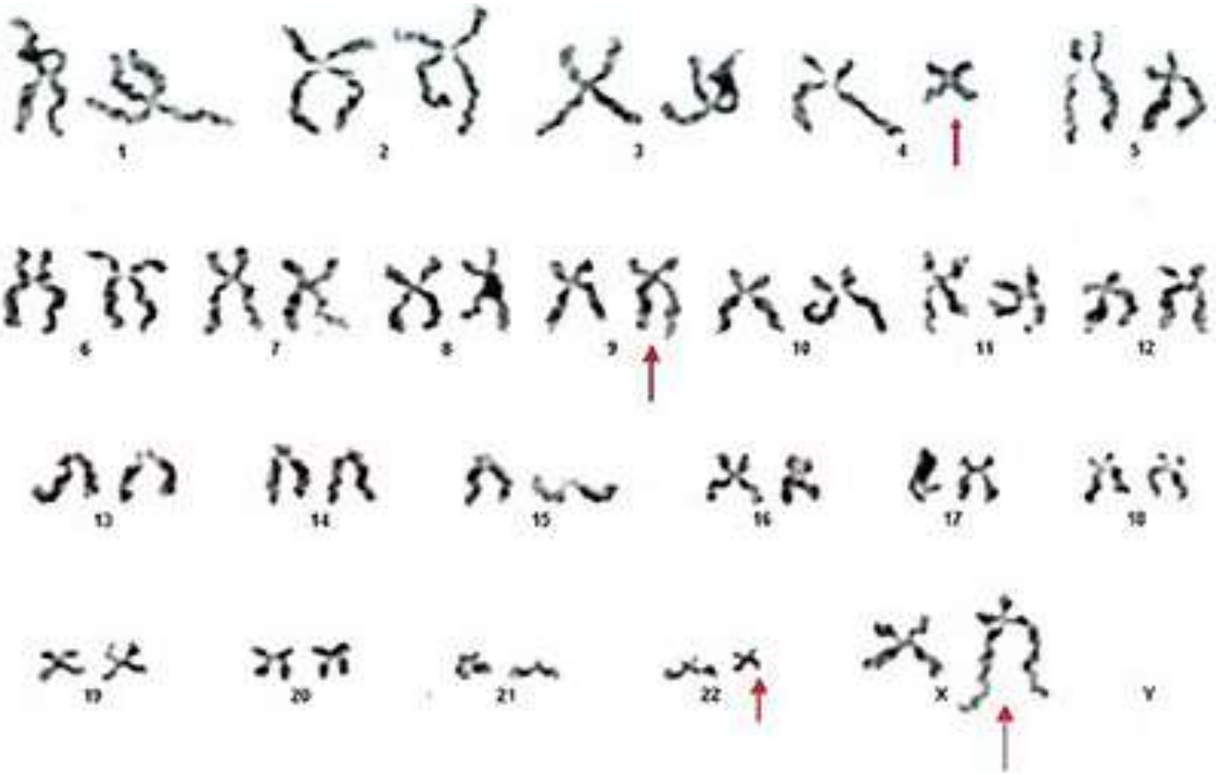
Spectral karyotyping

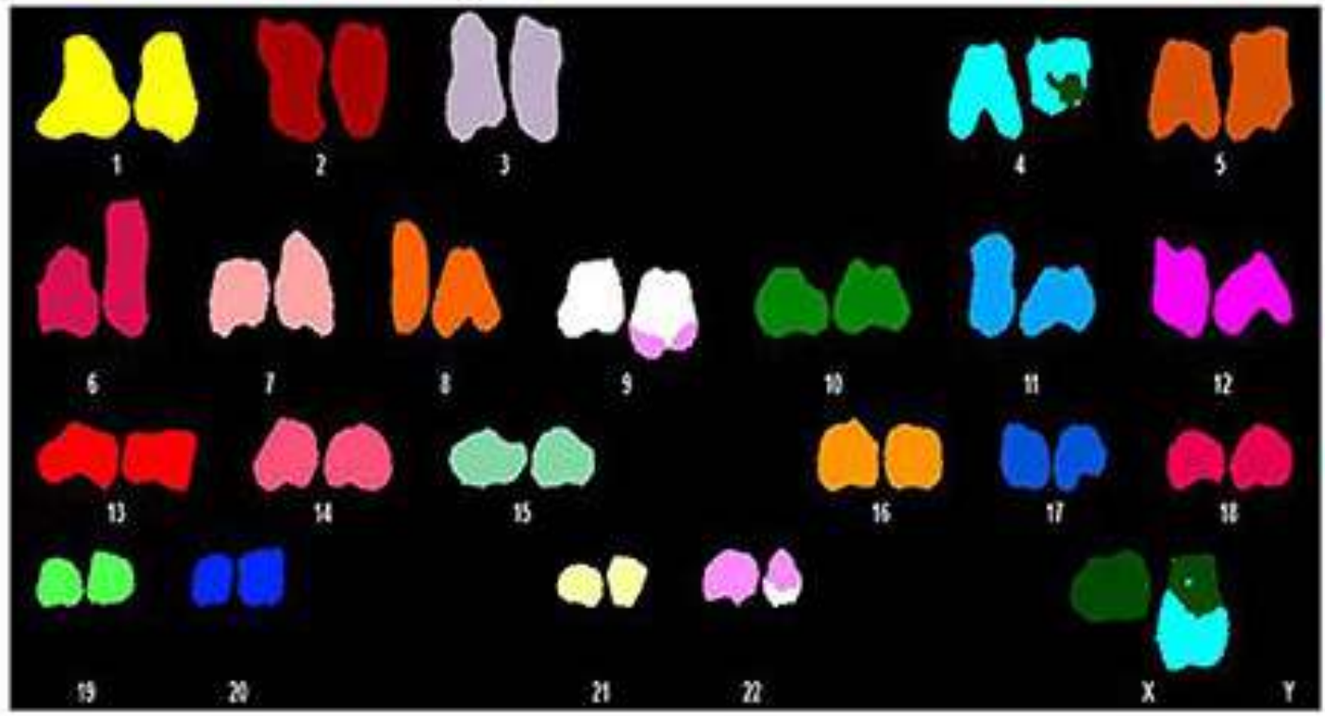


https://www.cytotest.com/sky.asp

Spectral karyotyping

Makes it visually easy to identify chromosomal structural abnormalities

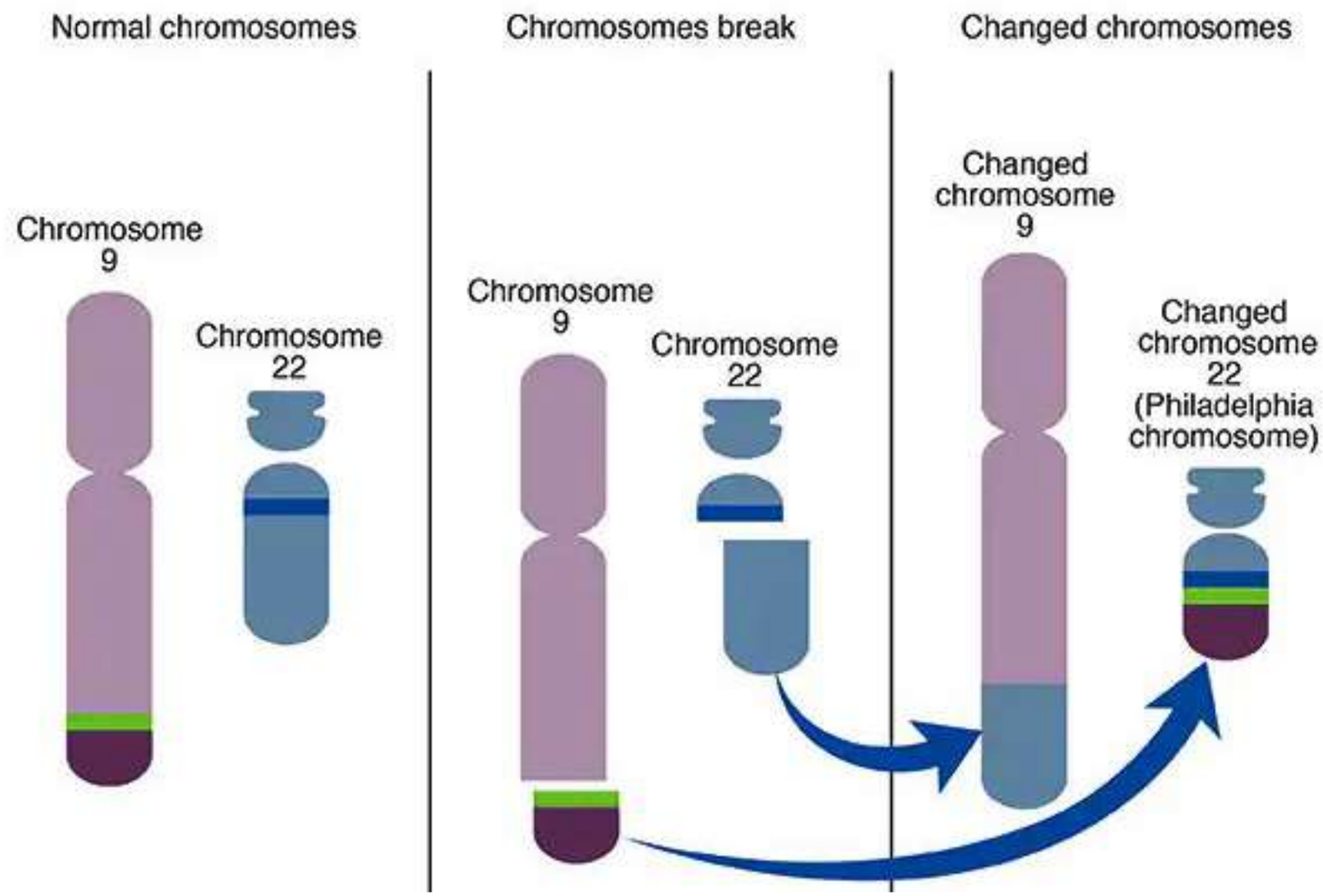




When chromosomes break and rejoin, genes “break” and “fuse”.
Causes loss of function or creates “fusion genes” which have abnormal function

PMID: 30891424

Philadelphia Chromosome



- Translocation between chromosomes 9 and 22
- Creates a longer chromosome 9
- Moves the gene *abl* on chromosome 9 next to *bcr* on chromosome 22 creating a fusion gene *bcr-abl* on 22
- b*cr-abl* is an oncogene
- Oncogene = genes whose activity cause cancer

Figure 15.16 of Campbell's Biology: a global approach