The Adaptive Immune System: Function, Vaccination, and Disease

Zane H. Boyer

MacMillan Research Group

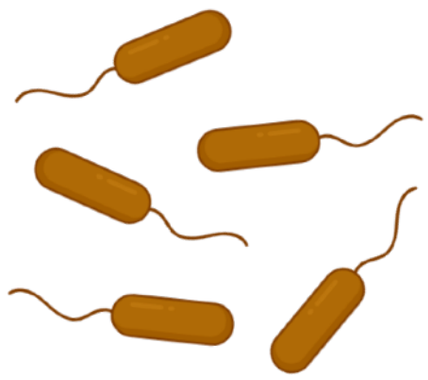
Group Meeting

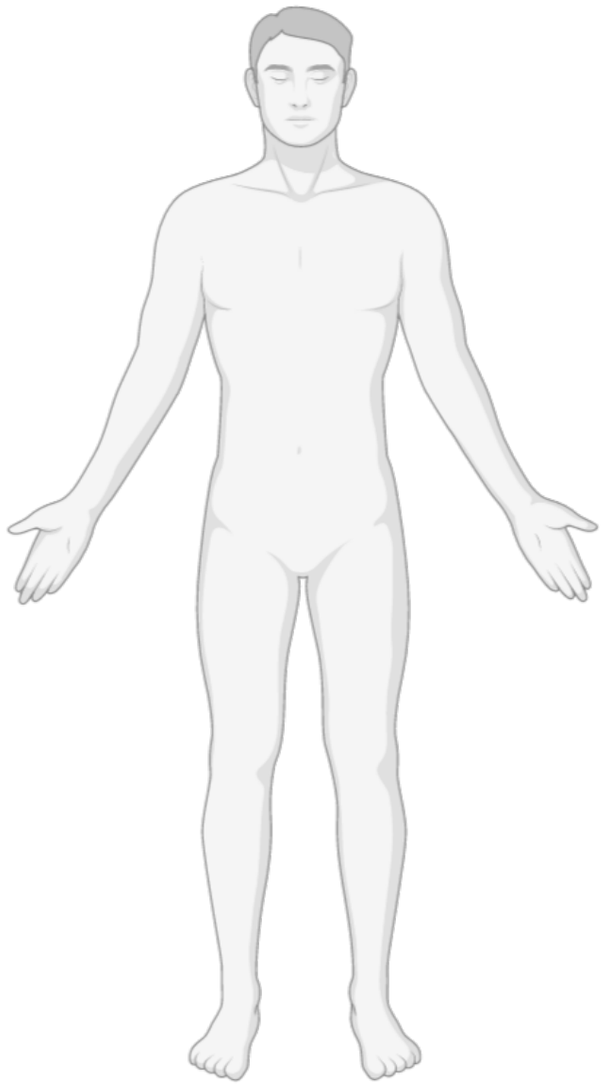
February 20, 2024

Our Bodies' Constant Fight Against Disease

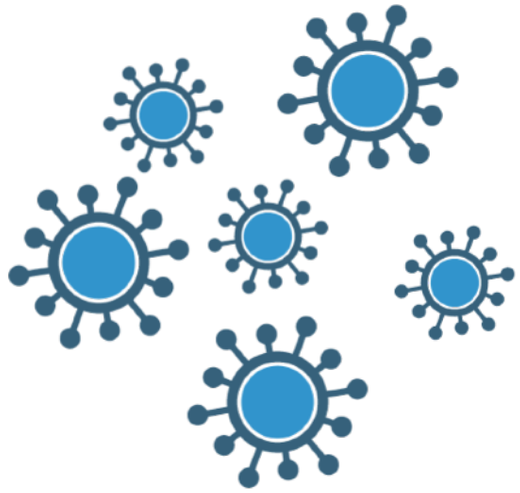
Destruction of pathogens and mutated cells

Bacteria



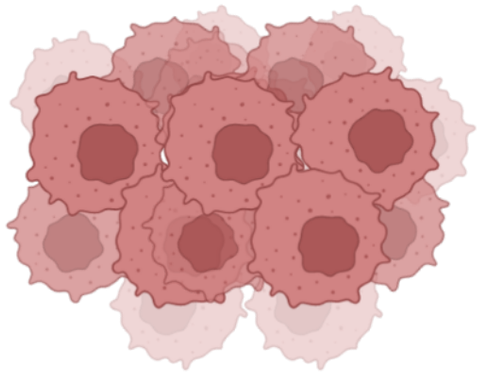


Viruses



Parasites

Cancerous cells



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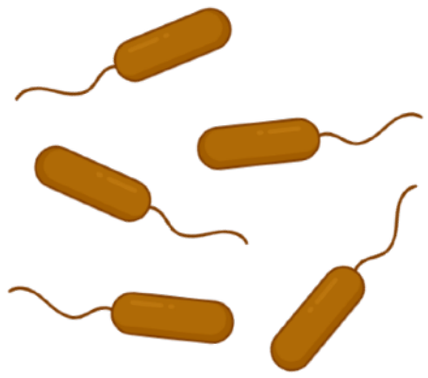

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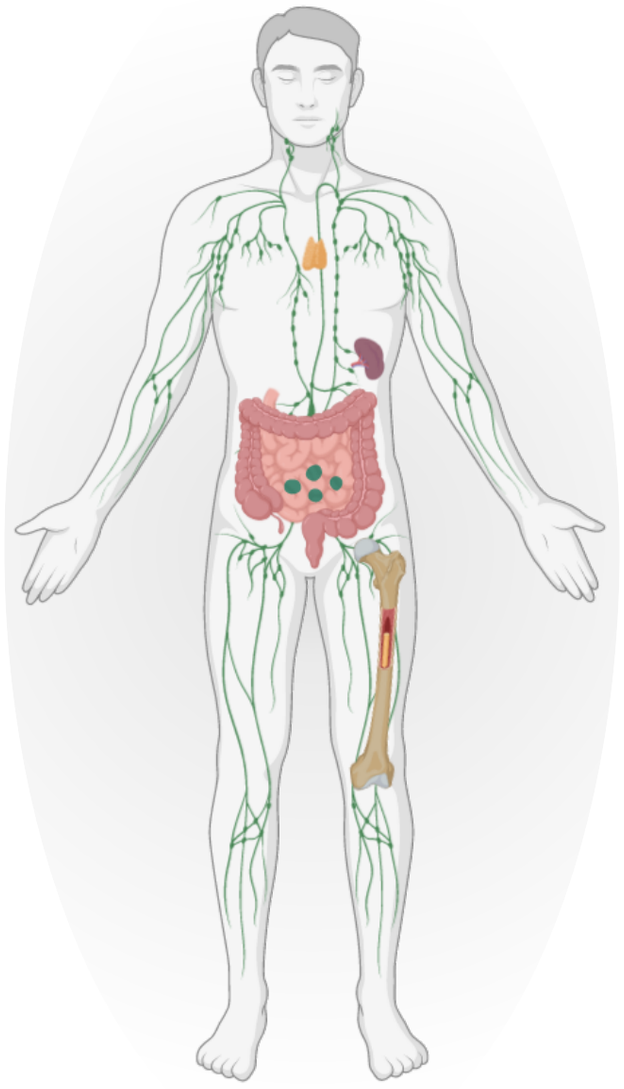

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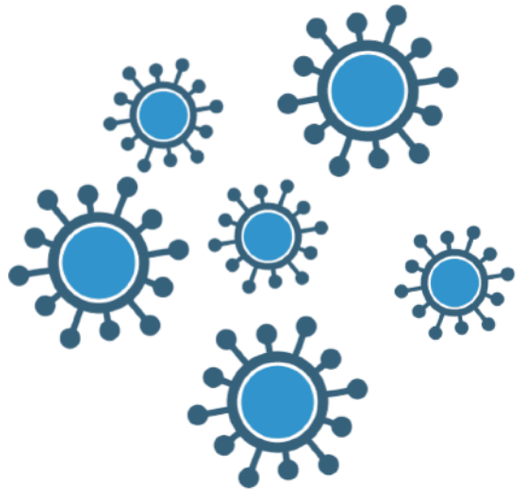

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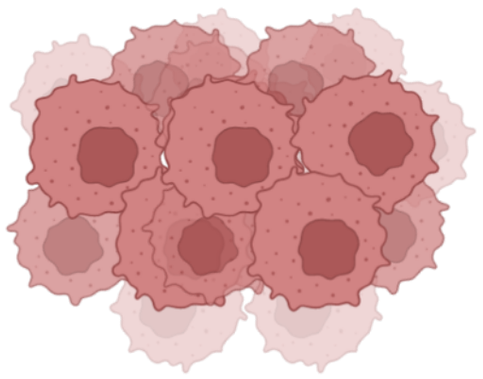
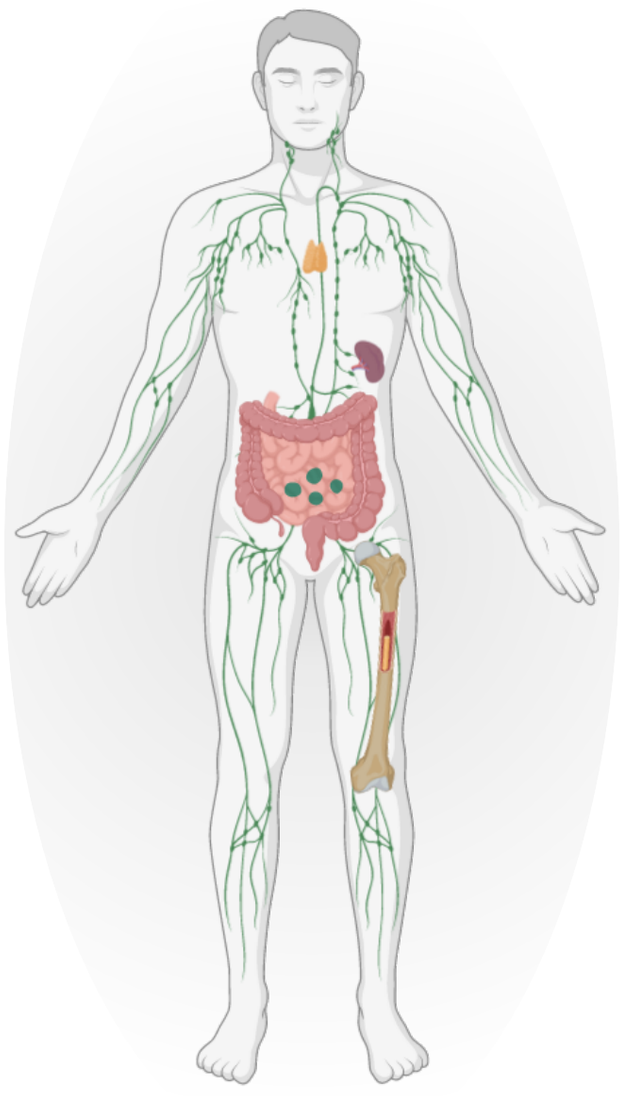


The immune system works to maintain homeostasis and destroy pathogens

Our Bodies' Constant Fight Against Disease

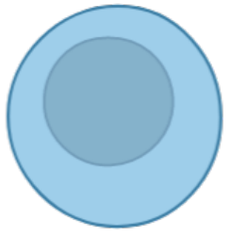
Destruction of pathogens and mutated cells



Cells of the Immune System

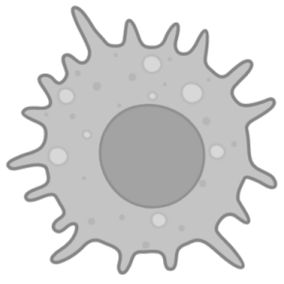
T cell

B cell

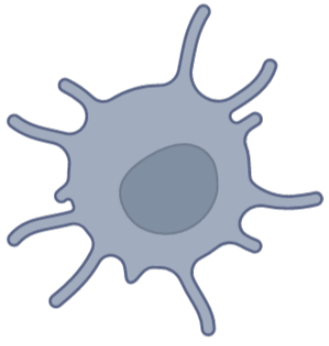


NK cell

Macrophage

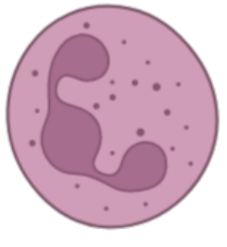


Dendritic cell

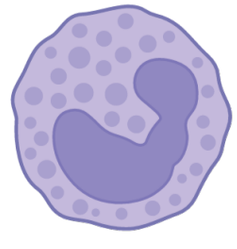


Eosinophil

Neutrophil



Basophil



Our Bodies' Constant Fight Against Disease

Adaptive and innate immune cells

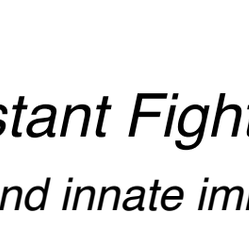
Adaptive Immune Cells

T cell

B cell

Innate Immune Cells

NK cell

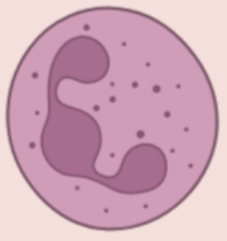


Macrophage

Dendritic cell

Eosinophil

Neutrophil



Basophil

Our Bodies' Constant Fight Against Disease

Adaptive and innate immune cells

Adaptive Immune Cells

Specific immunity

Recognizes unique peptide or antigen motifs unique to a pathogen

T cell

B cell

Innate Immune Cells

Non-specific immunity

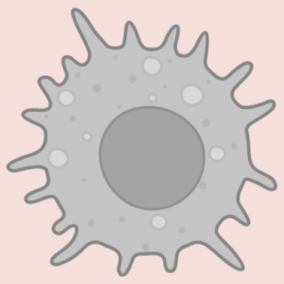
Not specific to any pathogen

Responds to variety of pathogen motifs, can be activated by peptides, nucleotides

First line of defense against infections and mutations

NK cell

Macrophage



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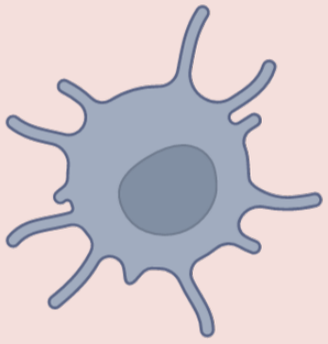

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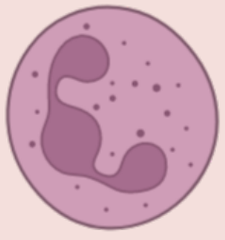

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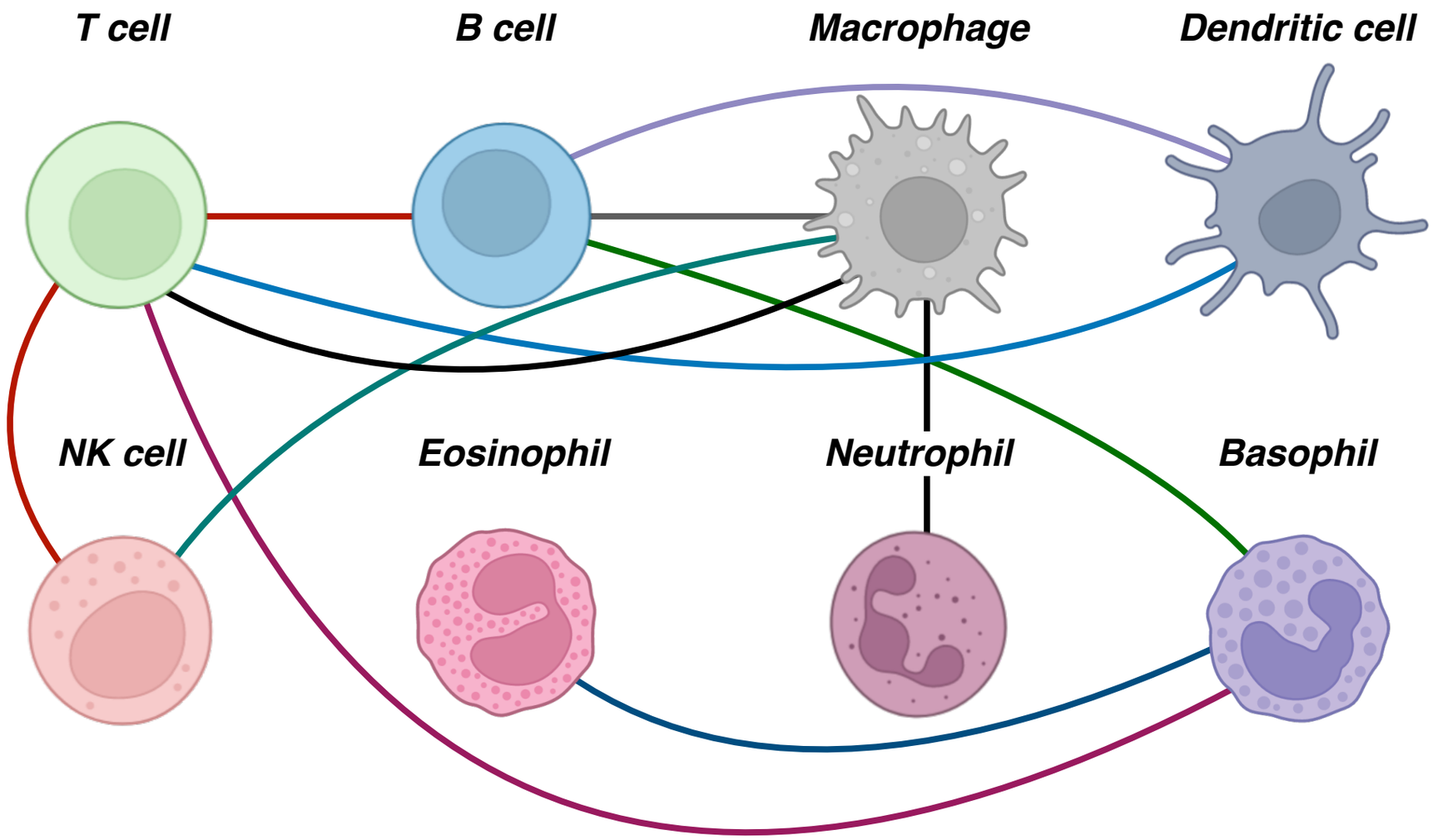
Adaptive and innate immune cells

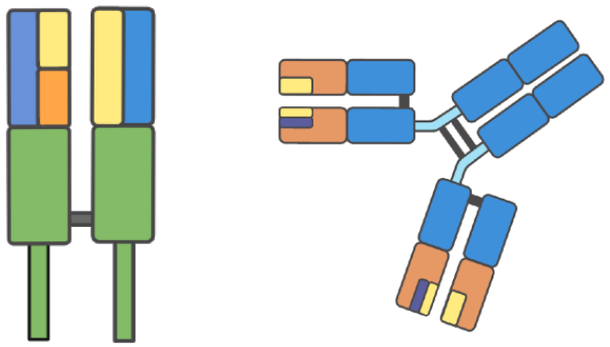


Immune cells work in tandem to generate tailored immune response

Adaptive Immune System

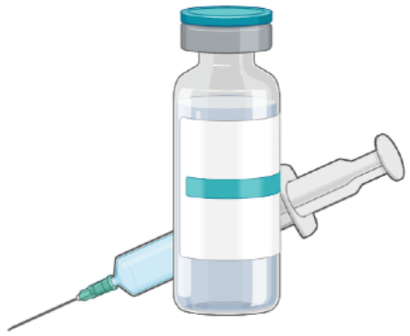
Enabling aspects and failures of adaptive immunity

Ultra-specific targeting



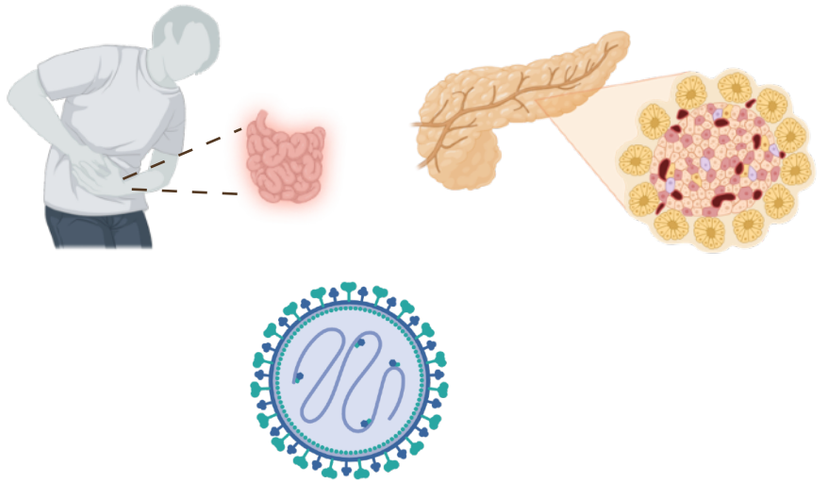
Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines



Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases



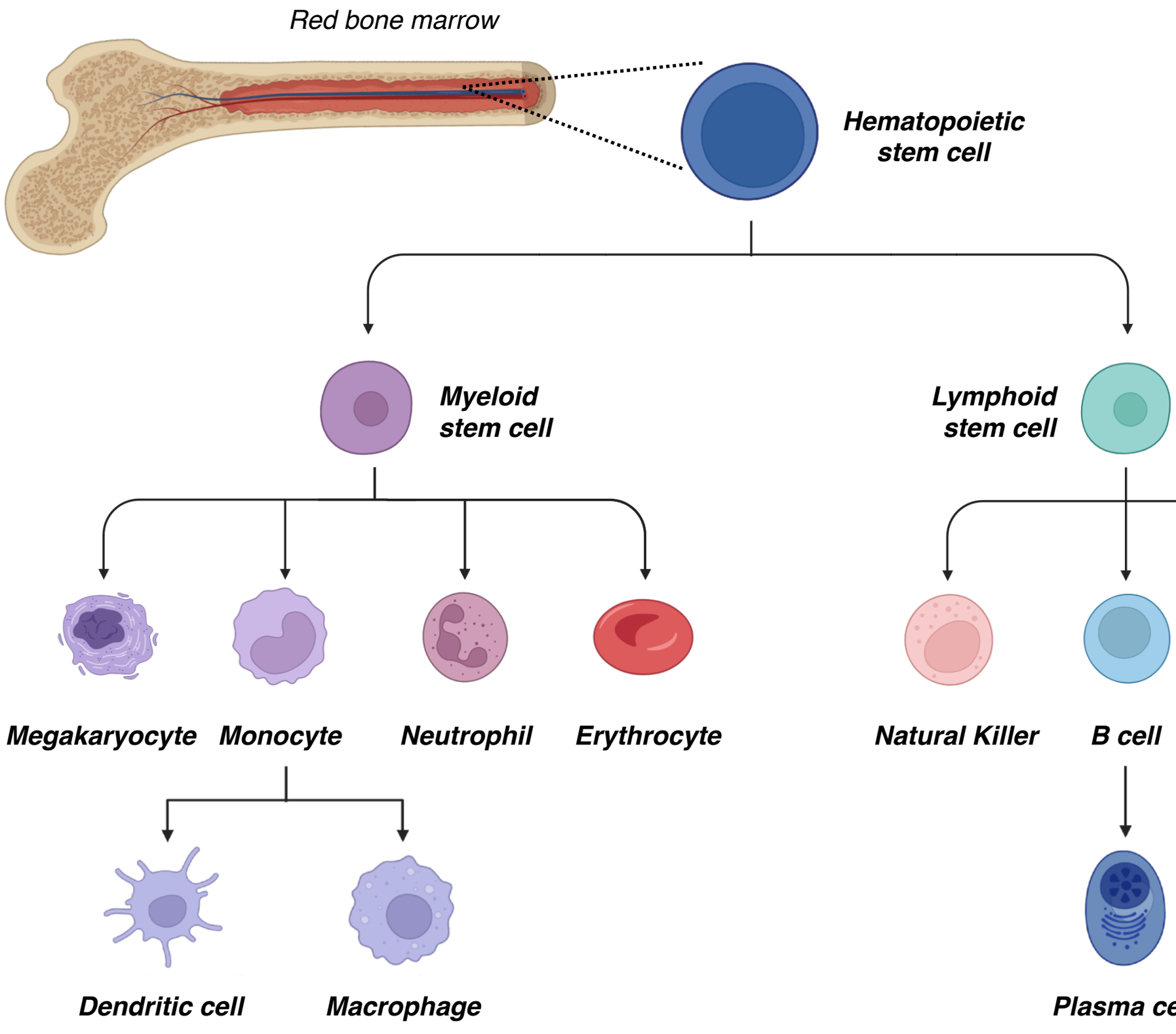
Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

Adaptive Immune System

Outline

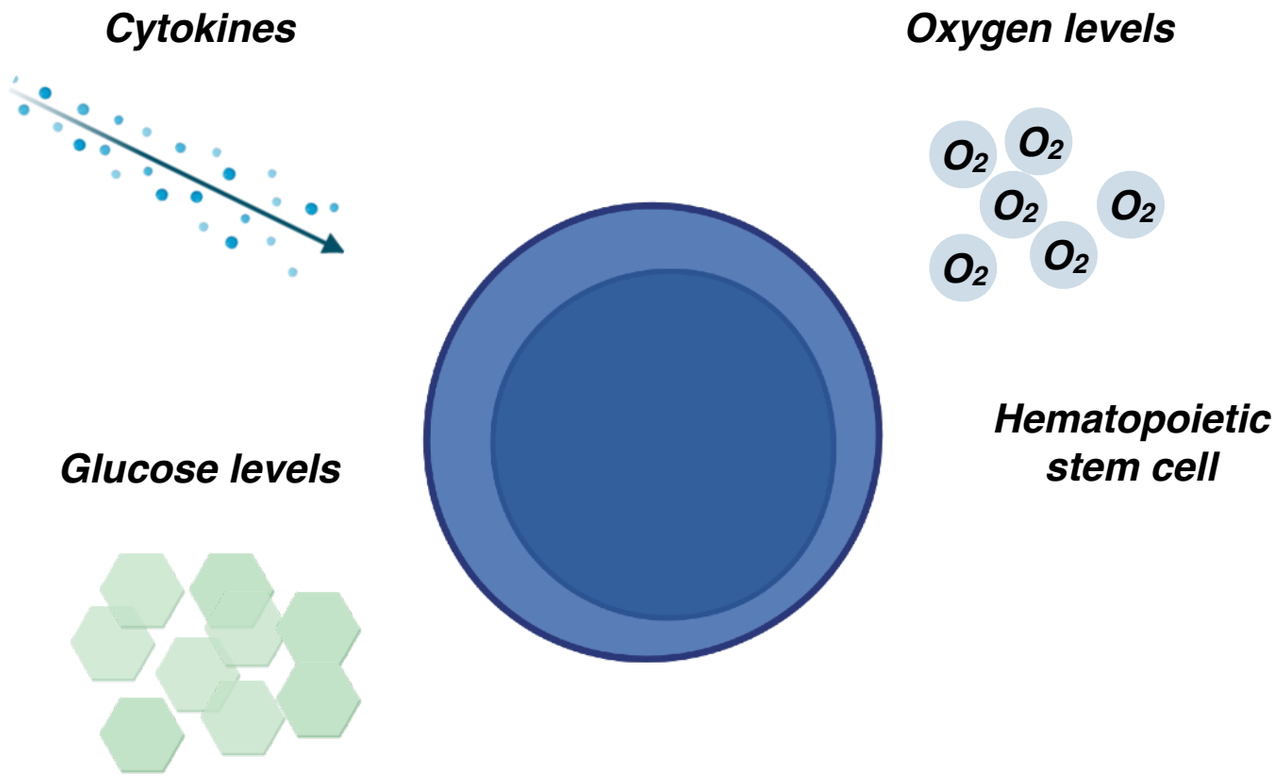
- *Biological development of T and B cells and their receptors*
- *A timeline of vaccine discoveries and developments*
- *How vaccination primes our immune system*
- *Contrasts between vaccine types targeting poliovirus*
- *Autoimmunity and pathogens of adaptive immune cells*

Biological Development of T and B Cells



Biological Development of T and B Cells

HPSC differentiation



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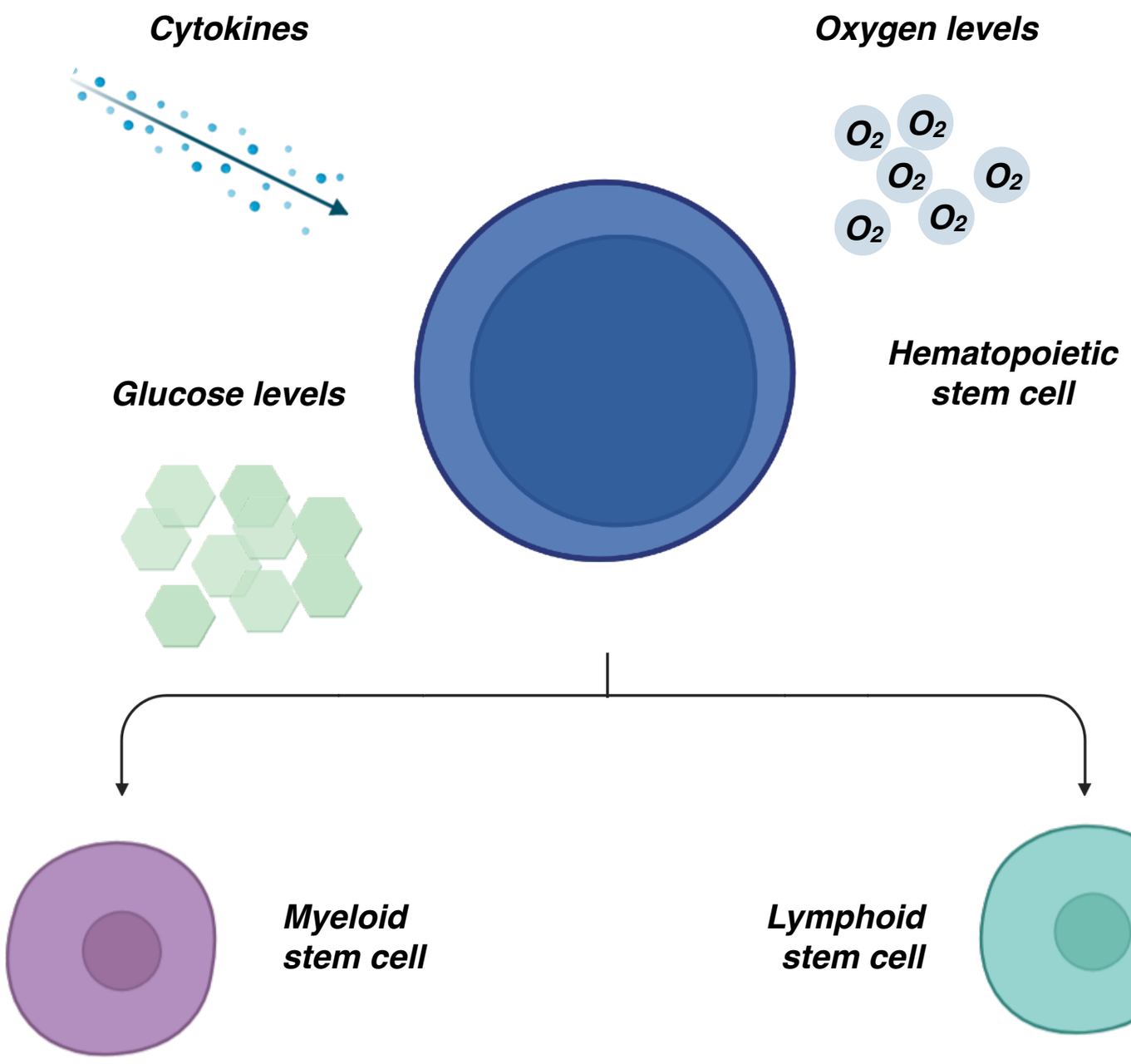
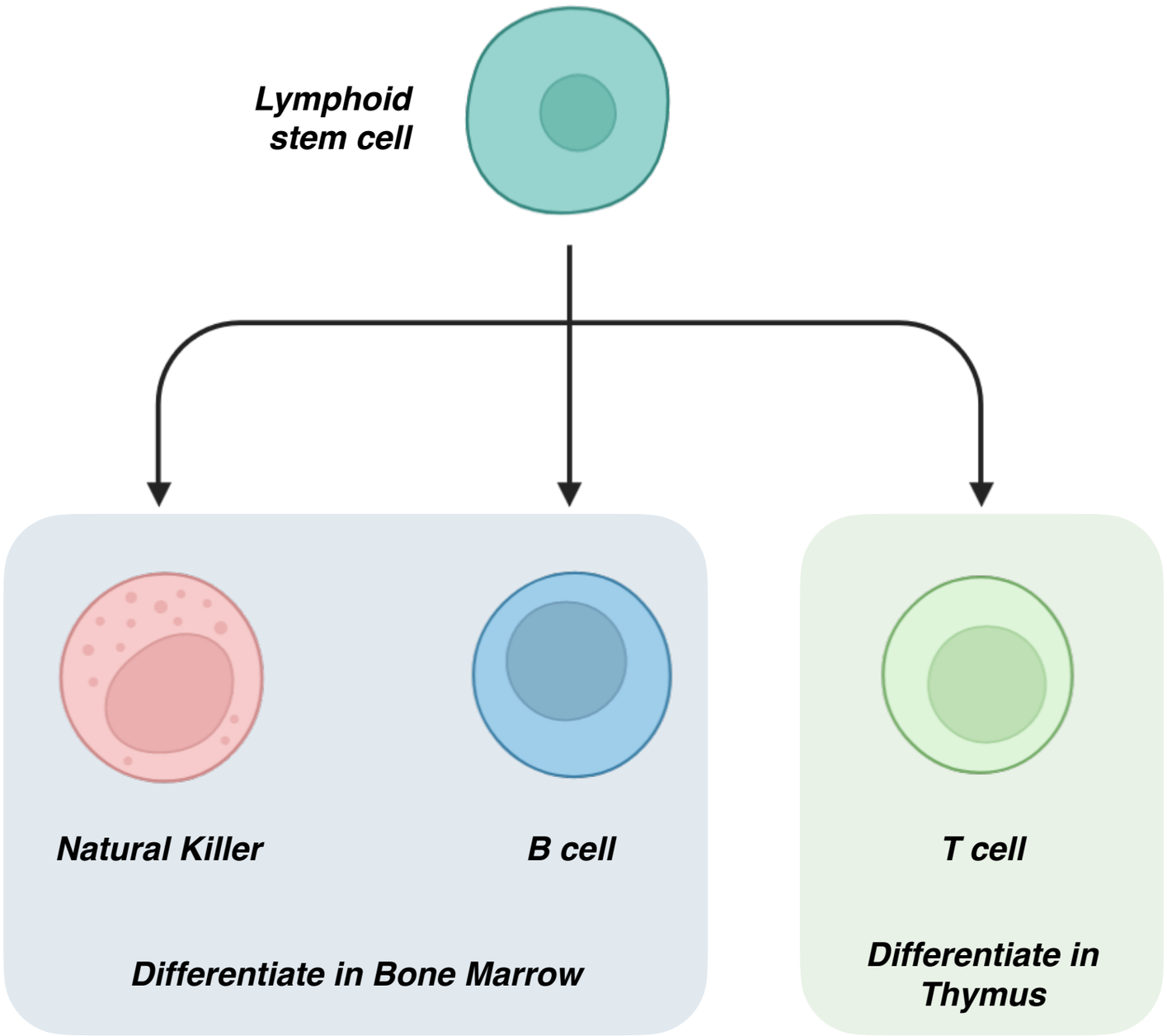


Various chemical signals induce initial differentiation of HPSCs

Biological Development of T and B Cells



Differentiation is determined by organ location of lymphoid precursors

Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

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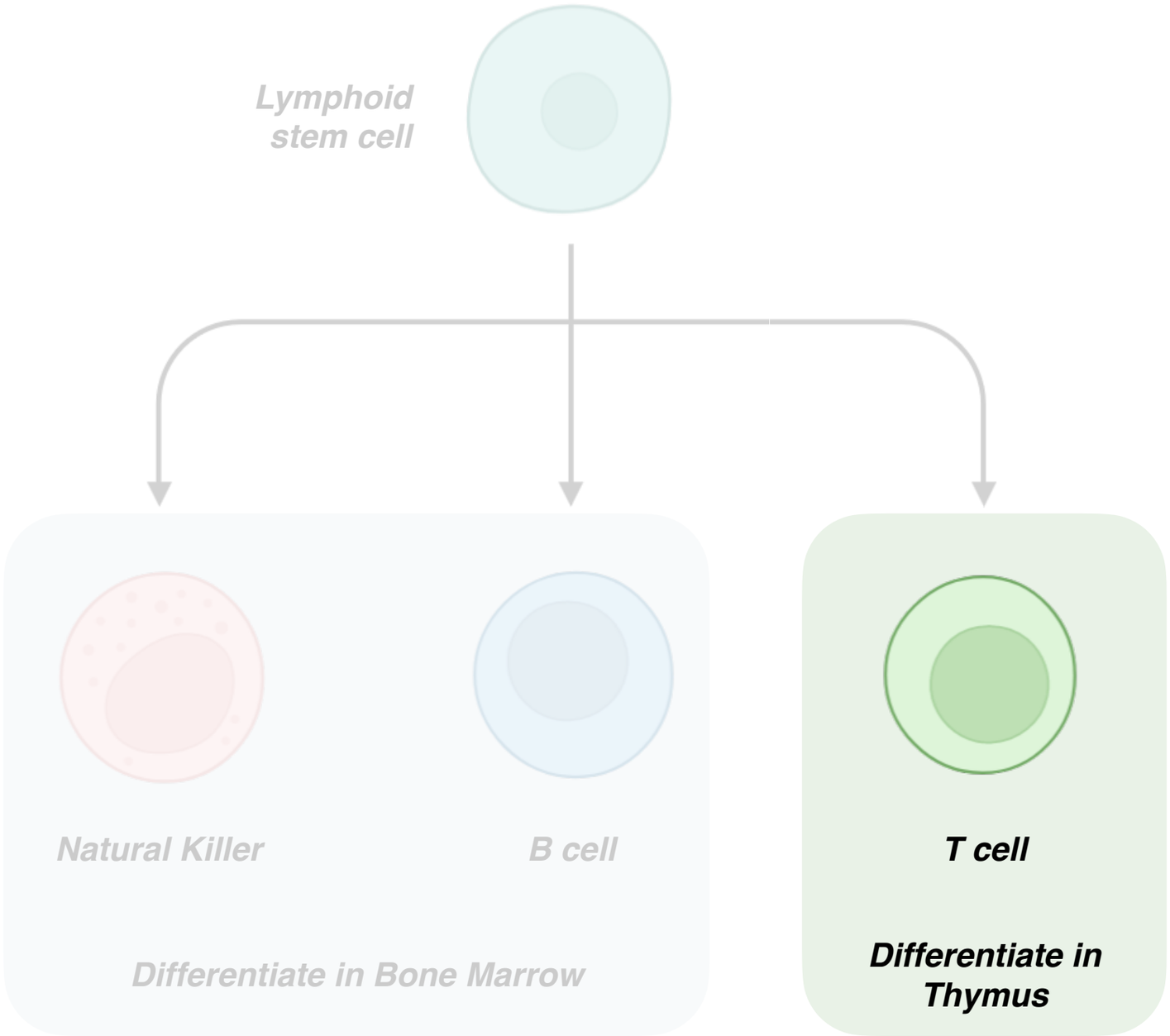

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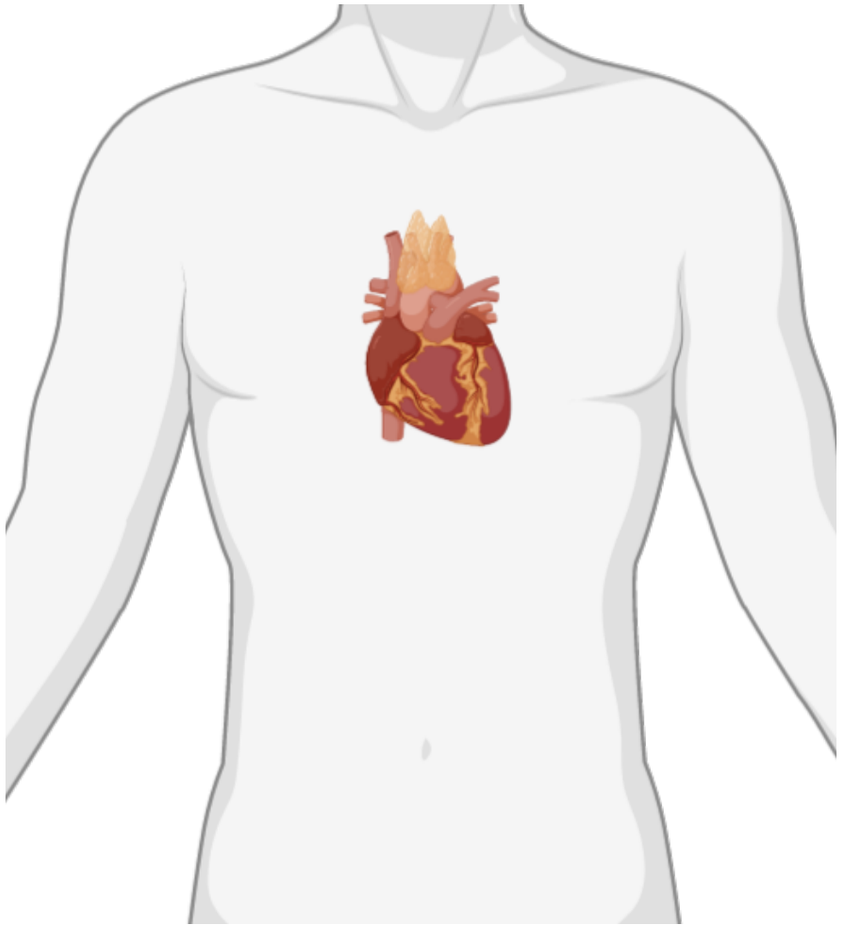
T Cell Development in the Thymus



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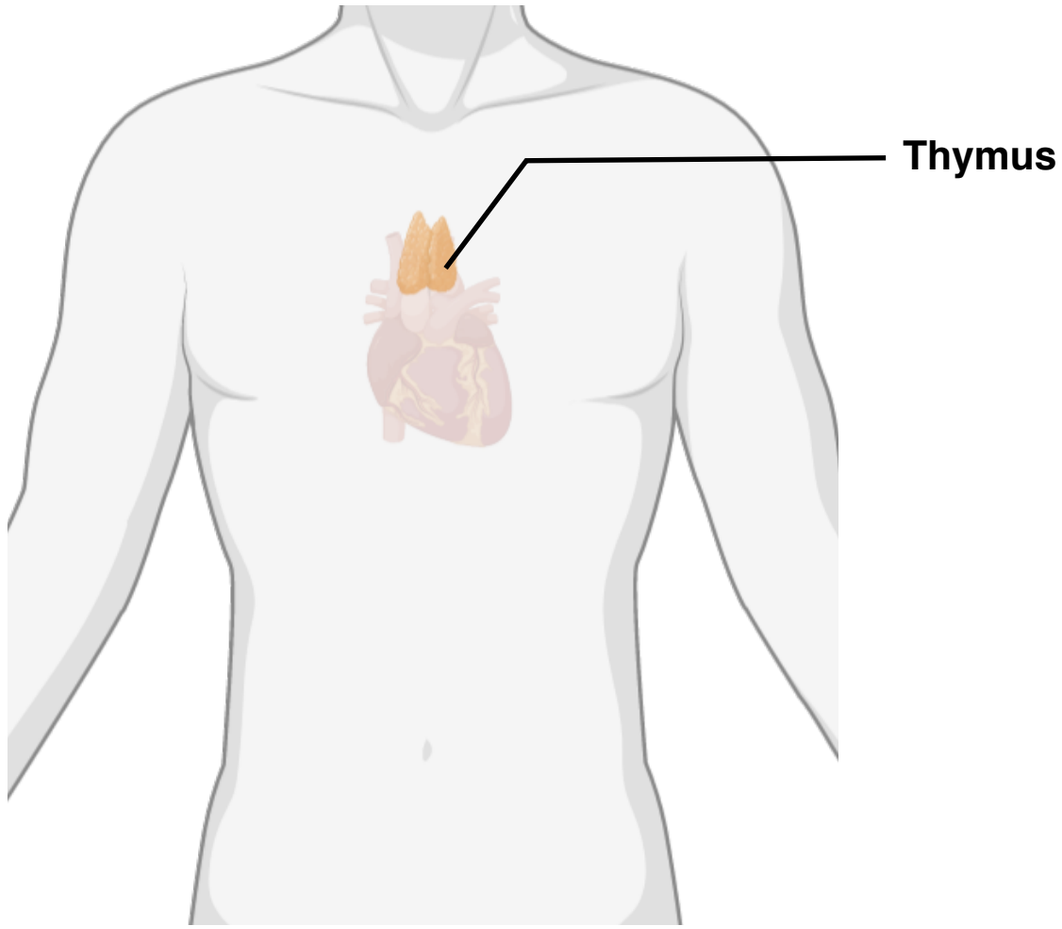

The thymus is a small gland that resides upon the heart

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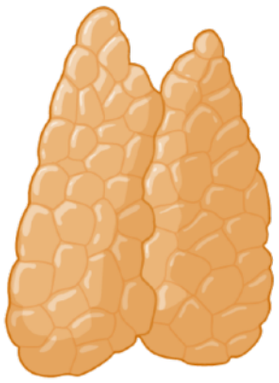

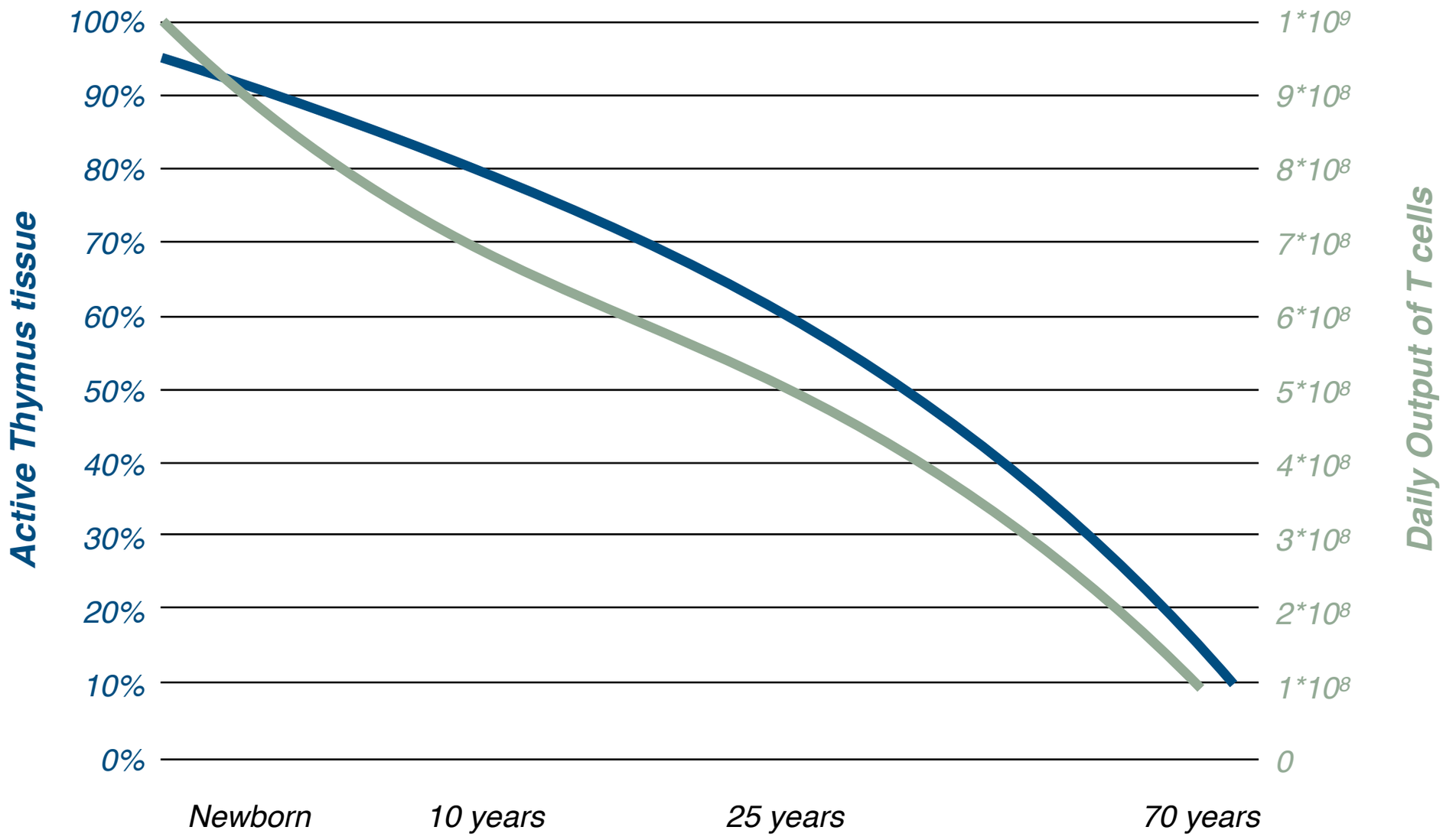

Most thymus activity occurs in early years of life

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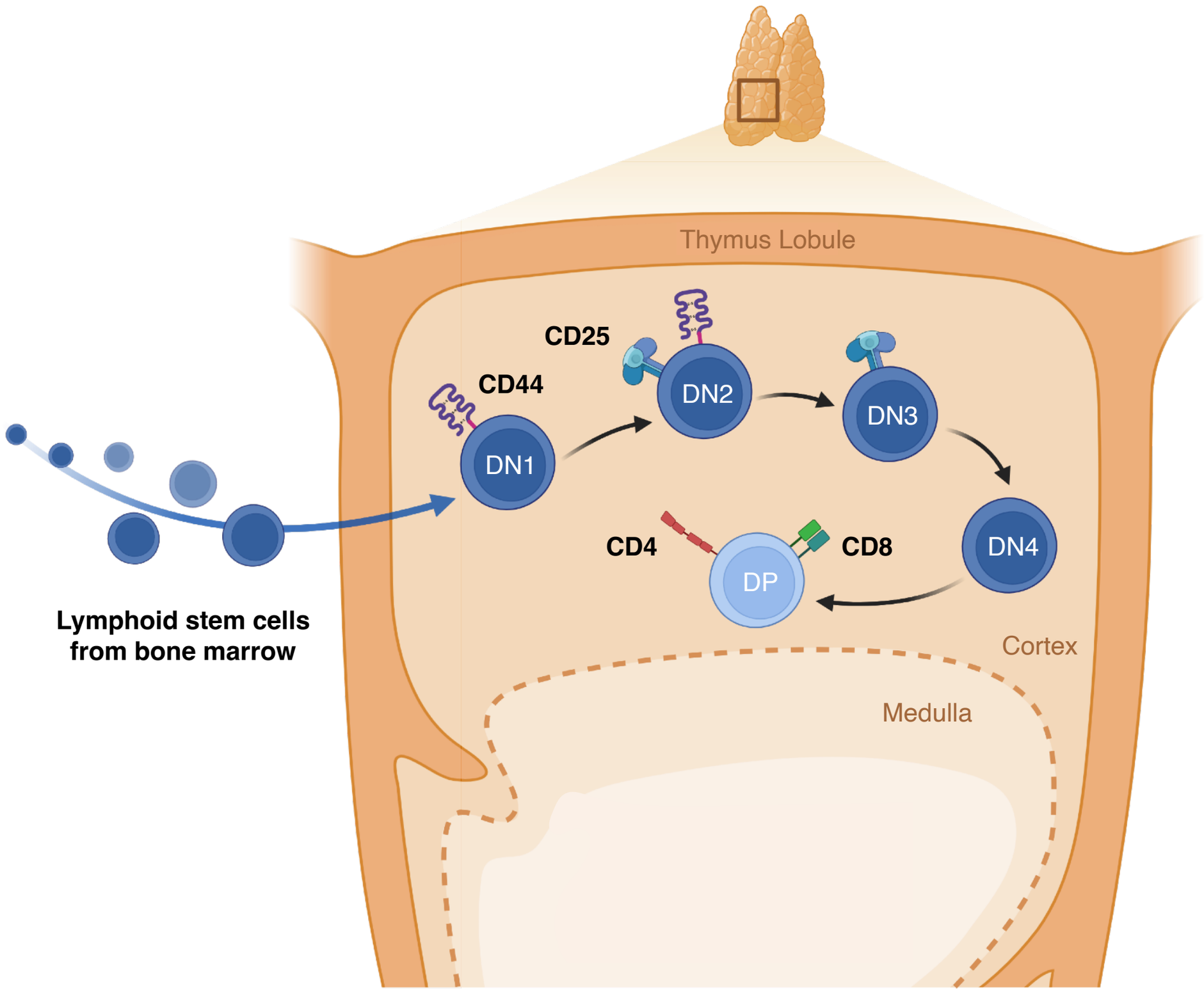

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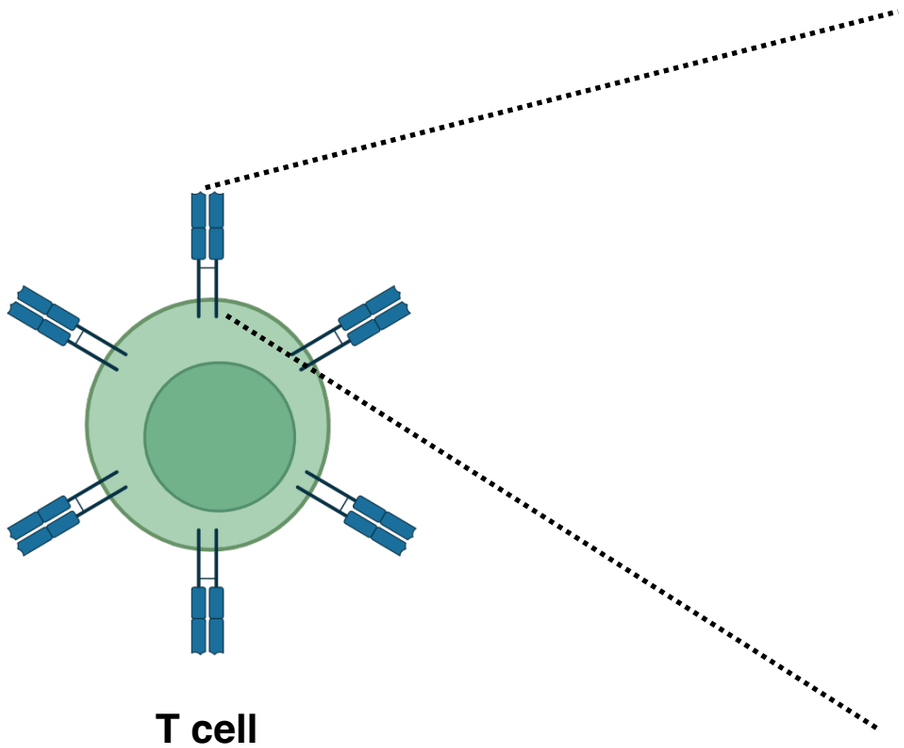
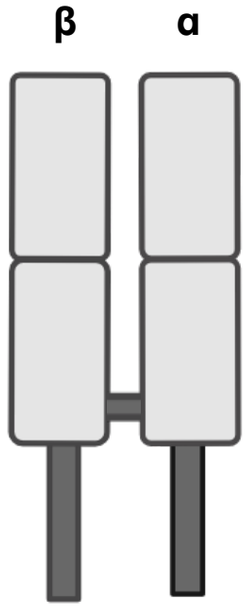
How Do T Cells Become so Specific?

V(D)J recombination and positive selection

By Double Positive stage, T cells have complete TCRs





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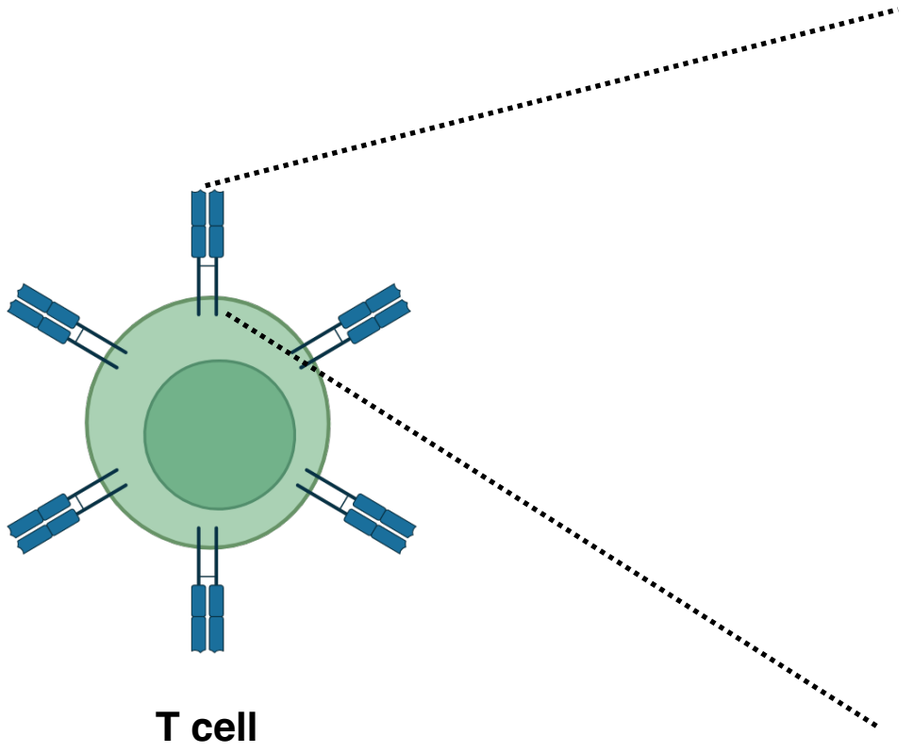

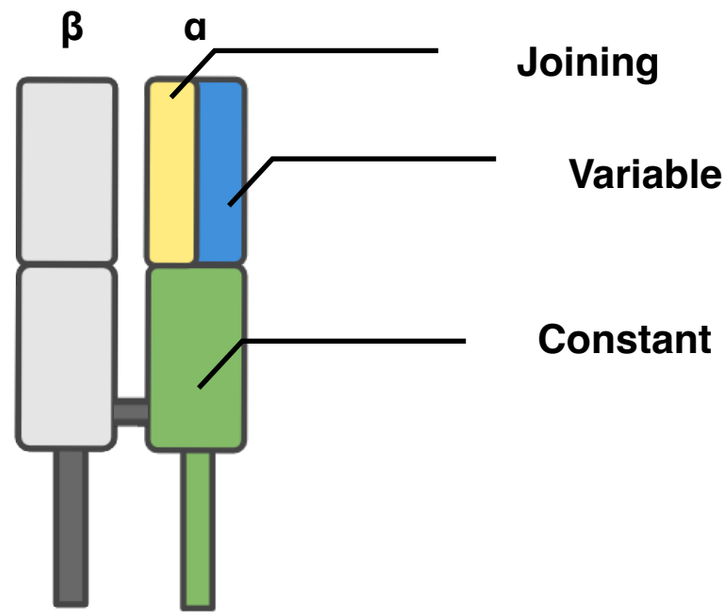

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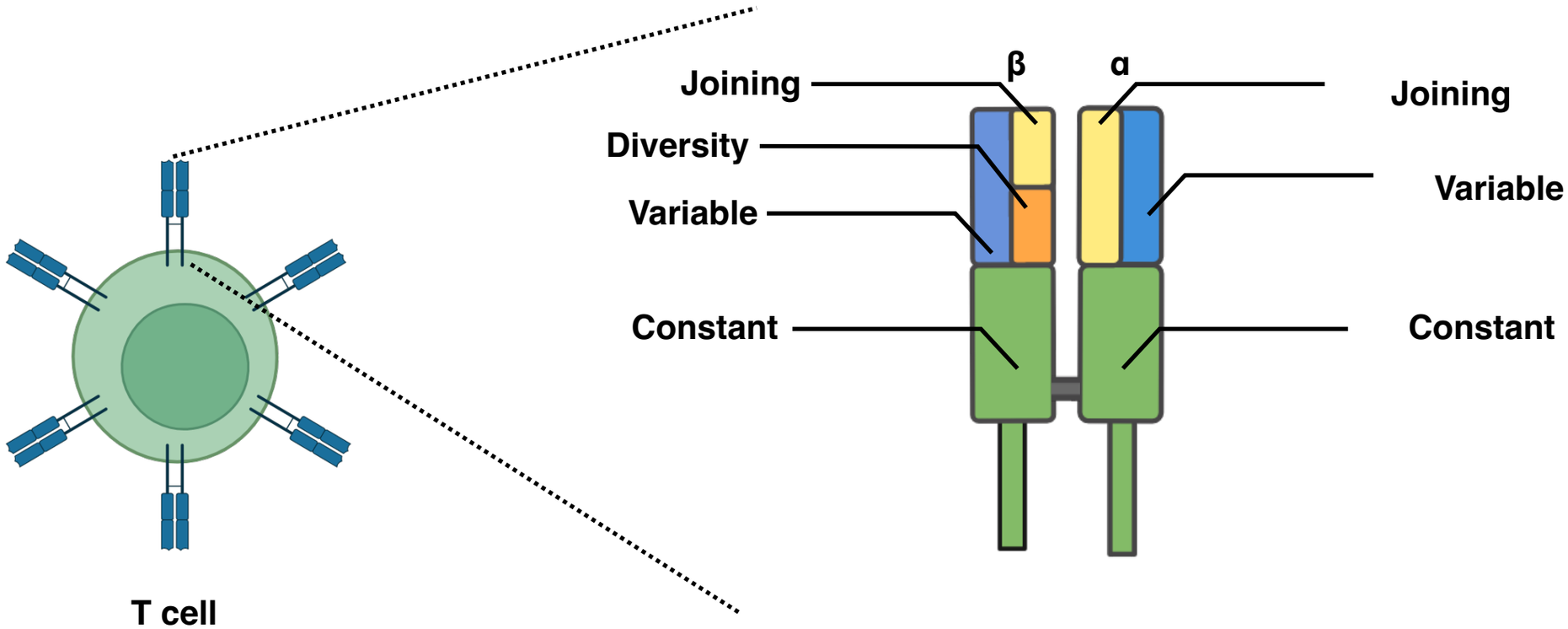

Variable components of both chains enable TCR specificity, diversity

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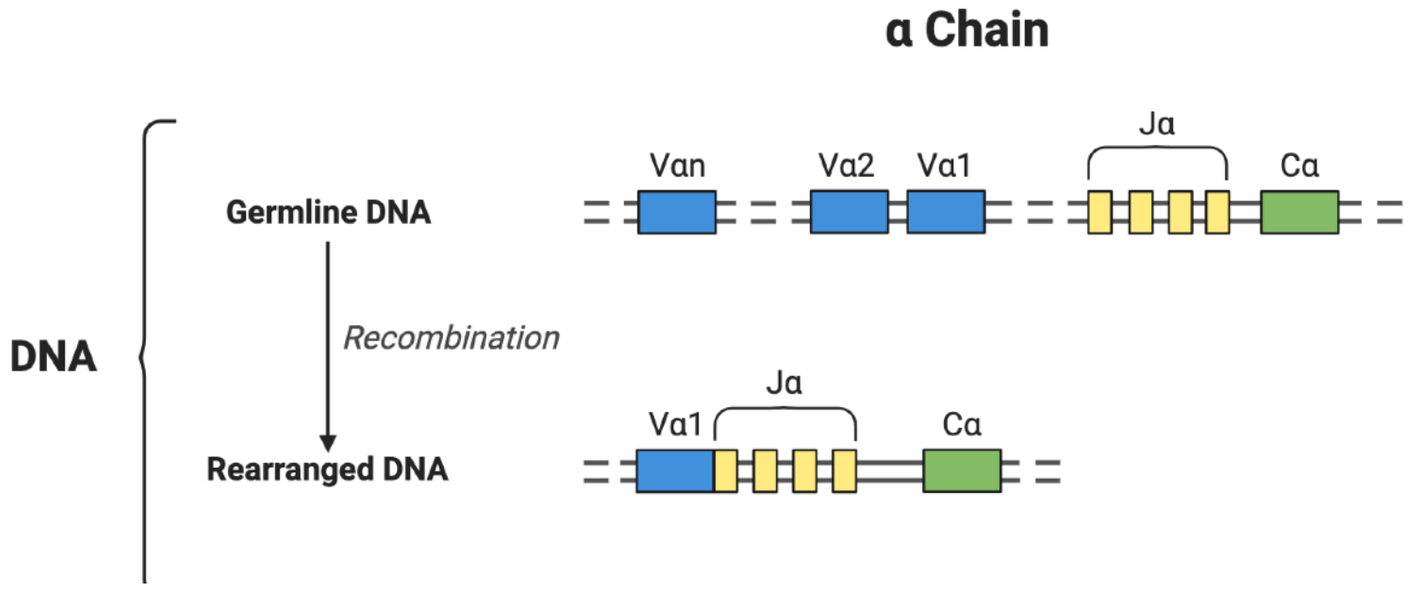

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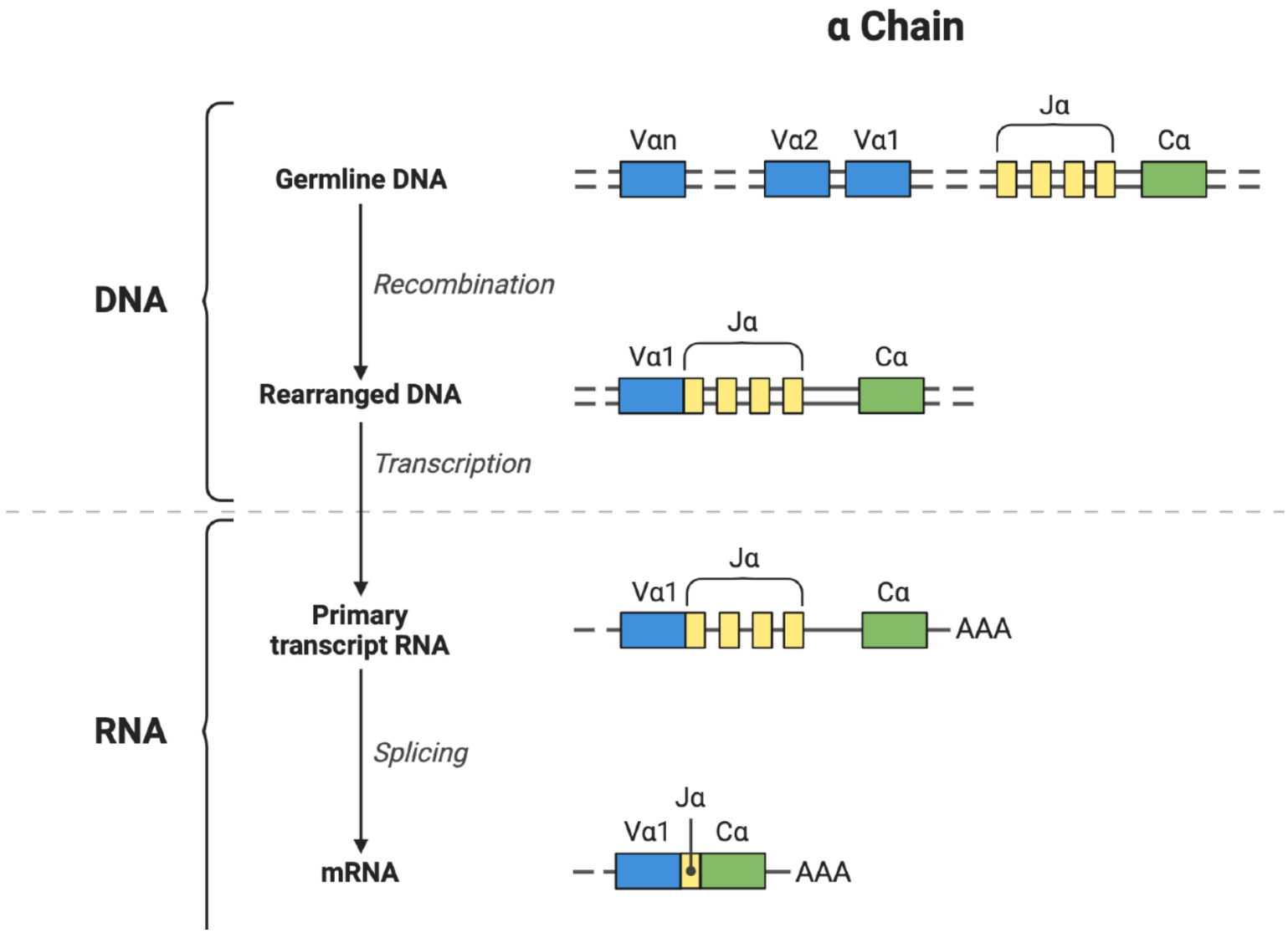

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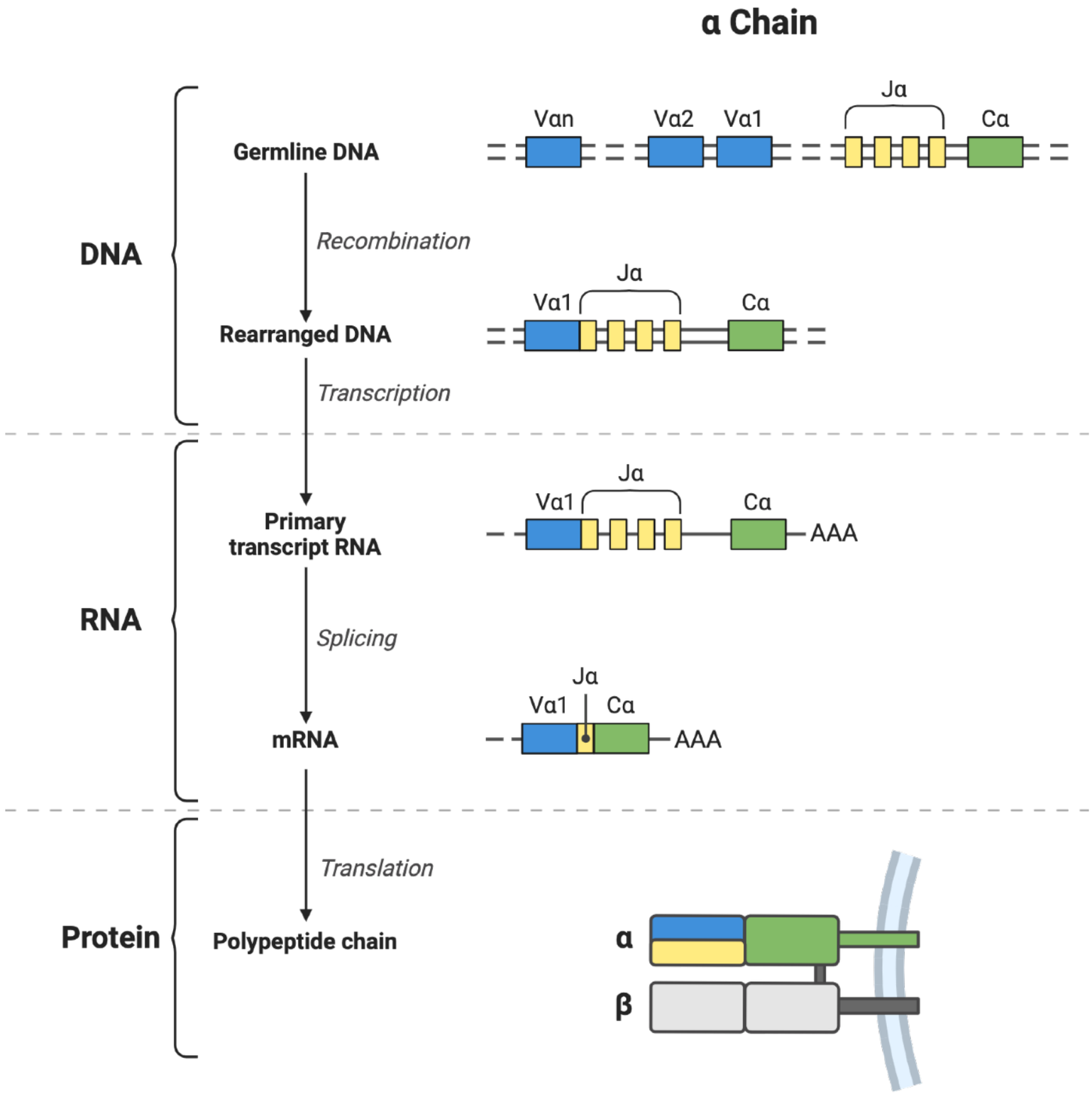

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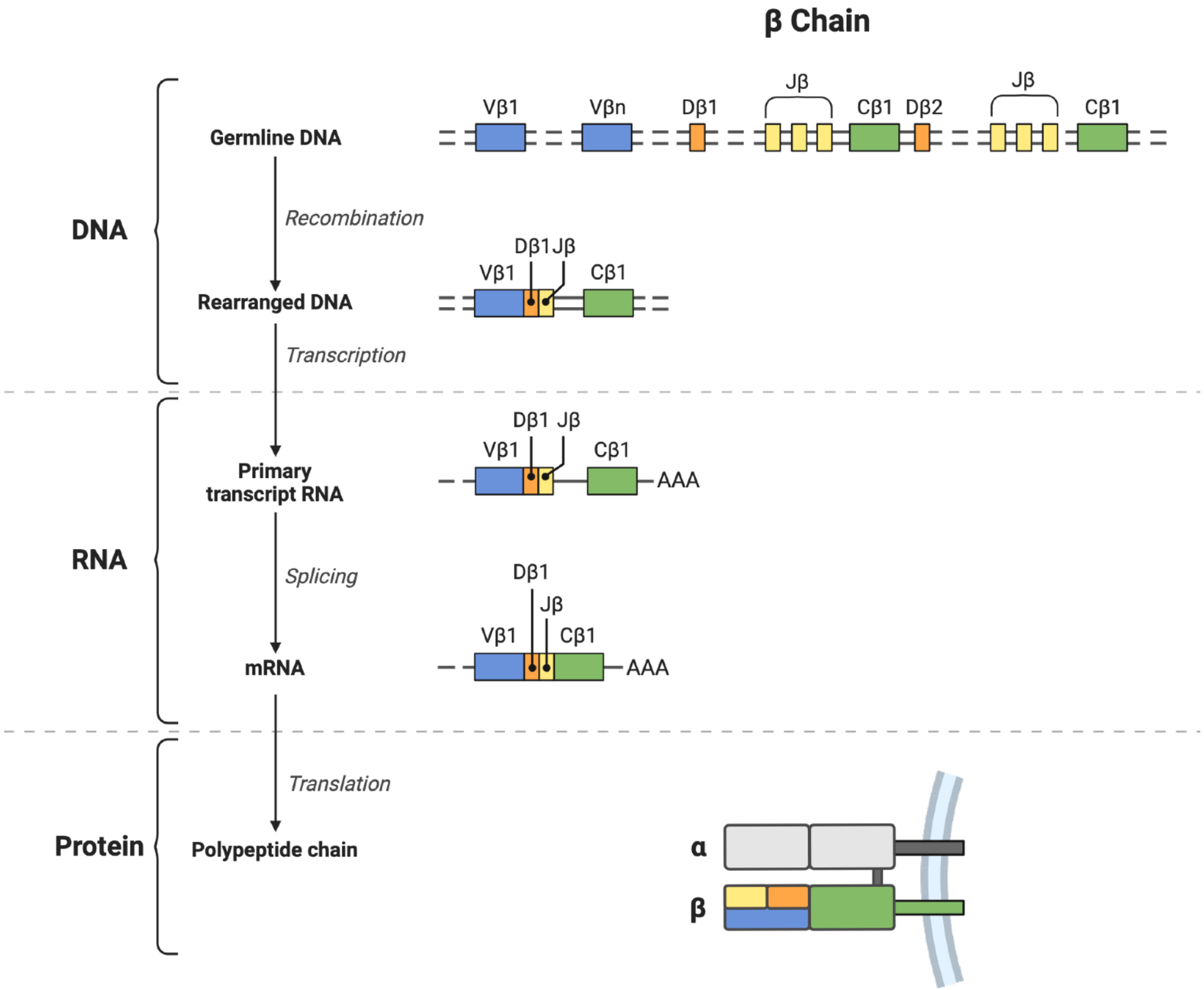

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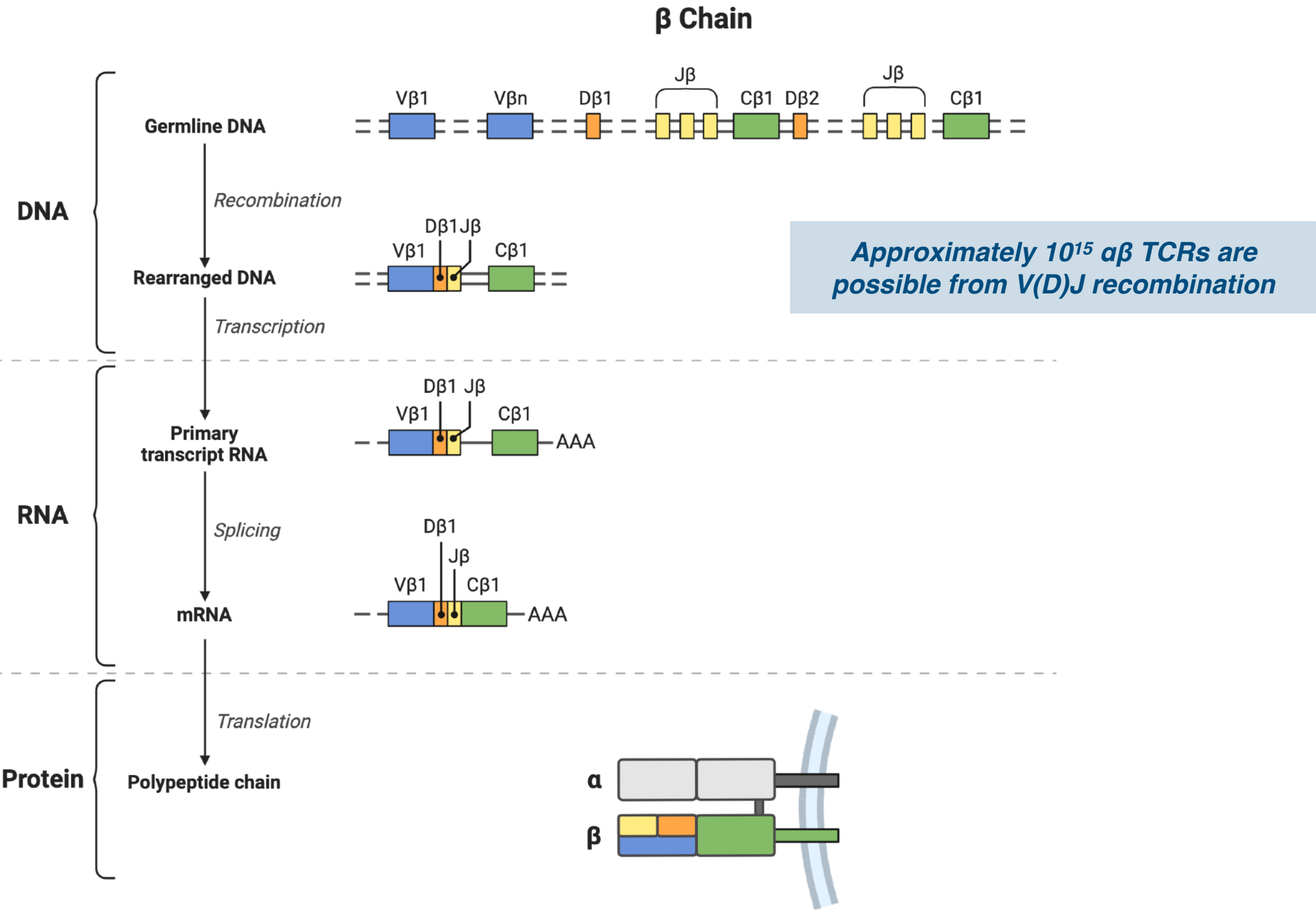

Approximately 10^{15} αβ TCRs are possible from V(D)J recombination

Lythe, G., et al. *J. Theor. Biol.* **2016**, *389*, 214-224.

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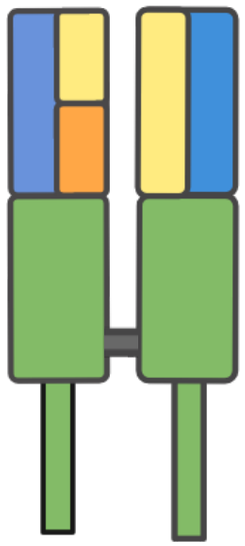
V(D)J recombination and positive selection

TCR



Approximately 10^{15} αβ TCRs are possible from V(D)J recombination

T cells expressing various recombined TCRs are tested by thymus cells

T cells expressing TCRs that bind MHC proteins are stimulated and enabled to progress

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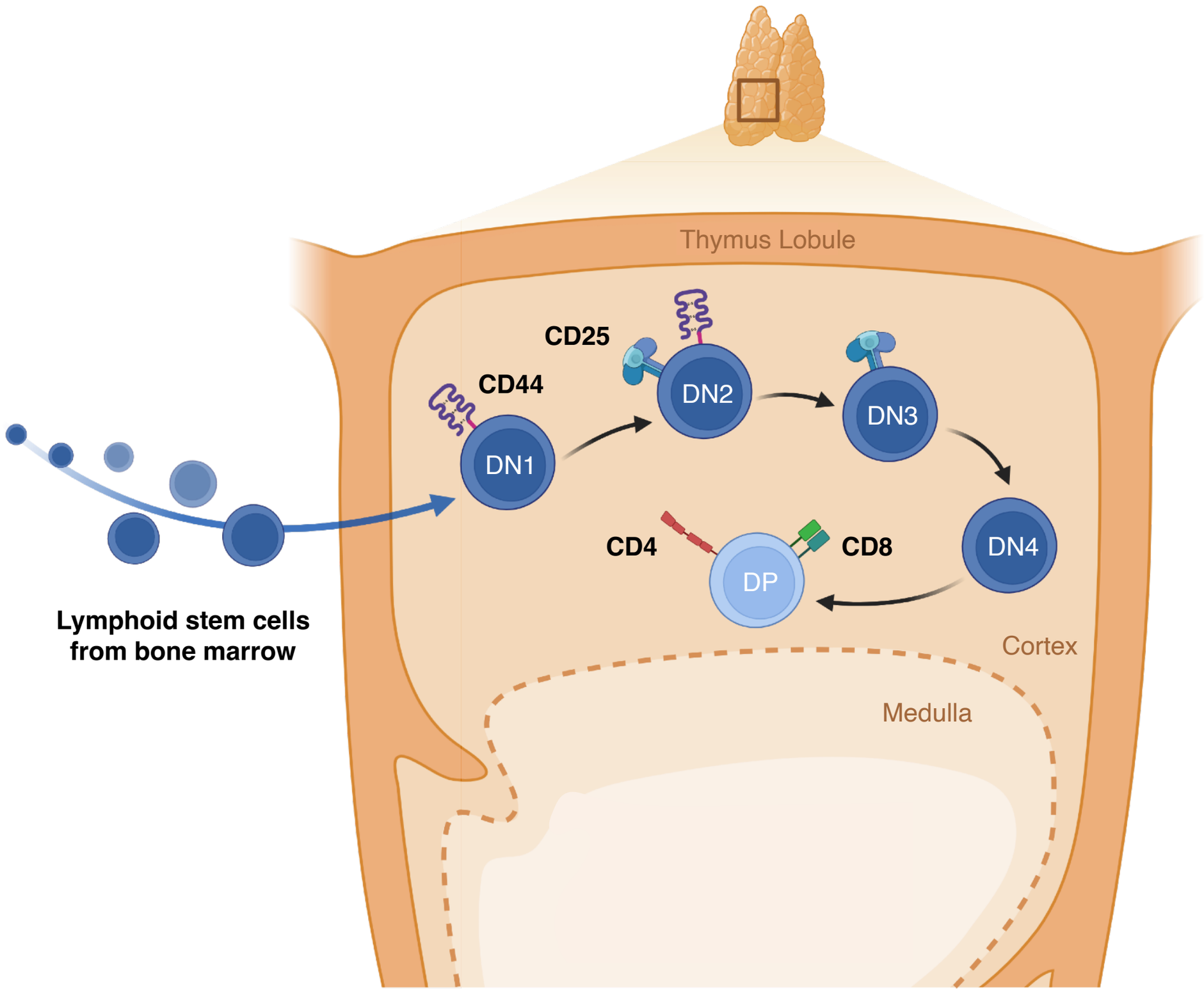
T Cell Development in the Thymus



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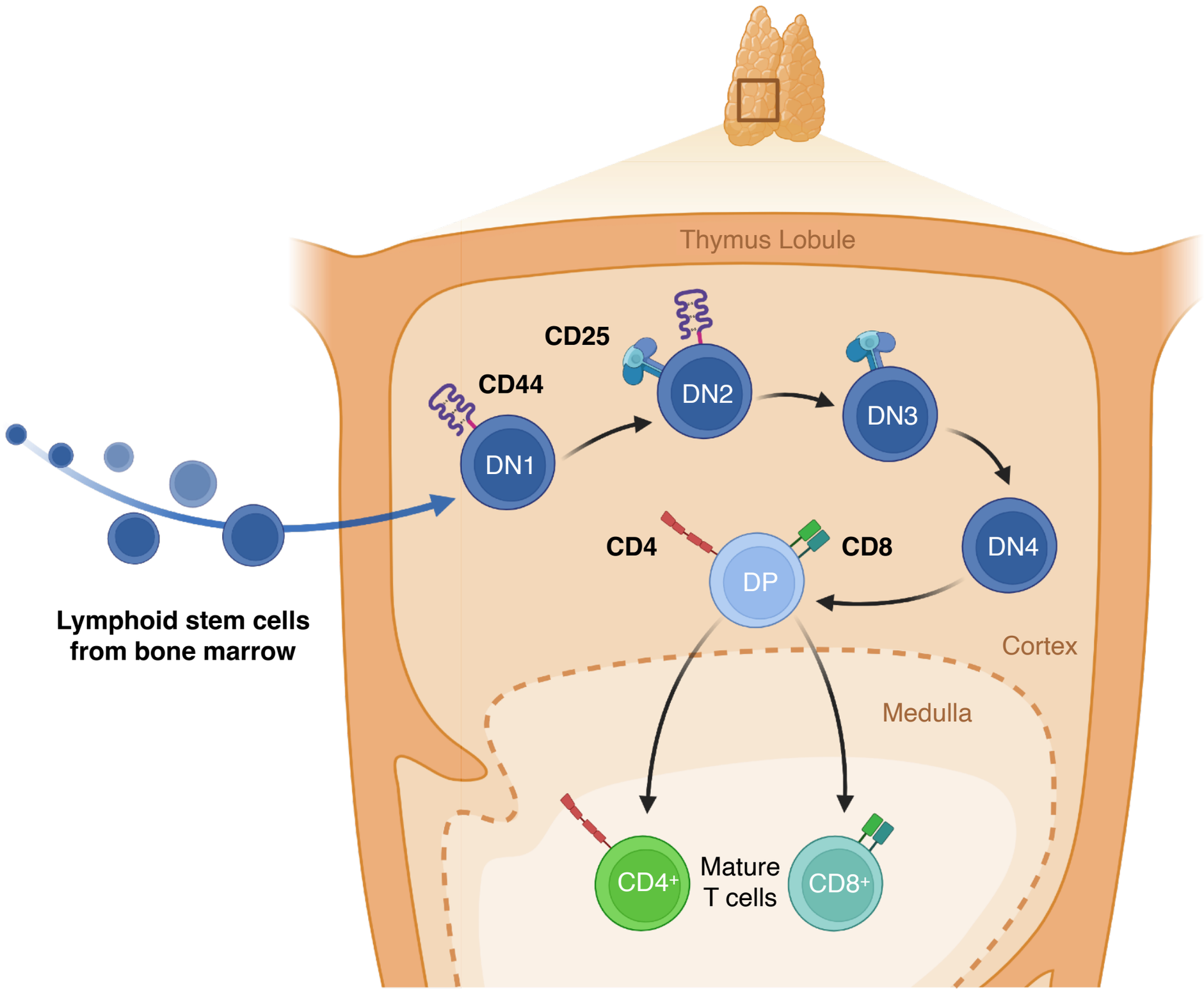

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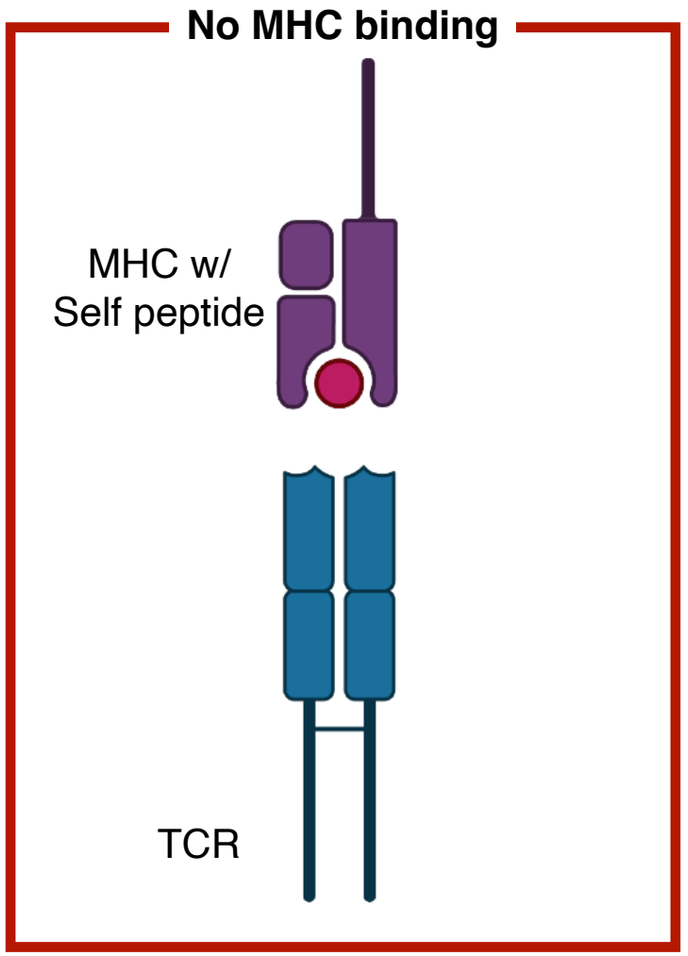
Negative Selection of TCRs



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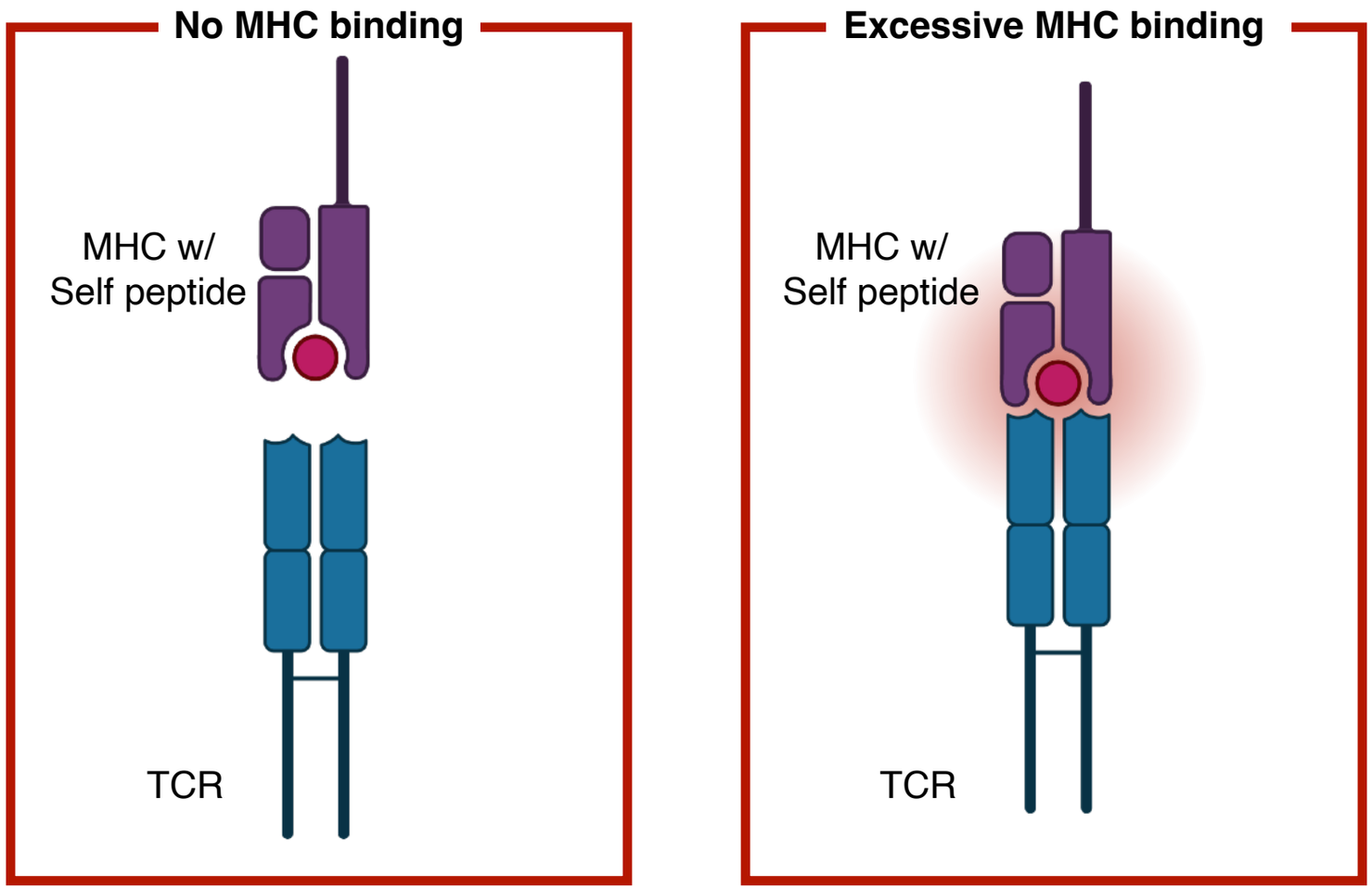
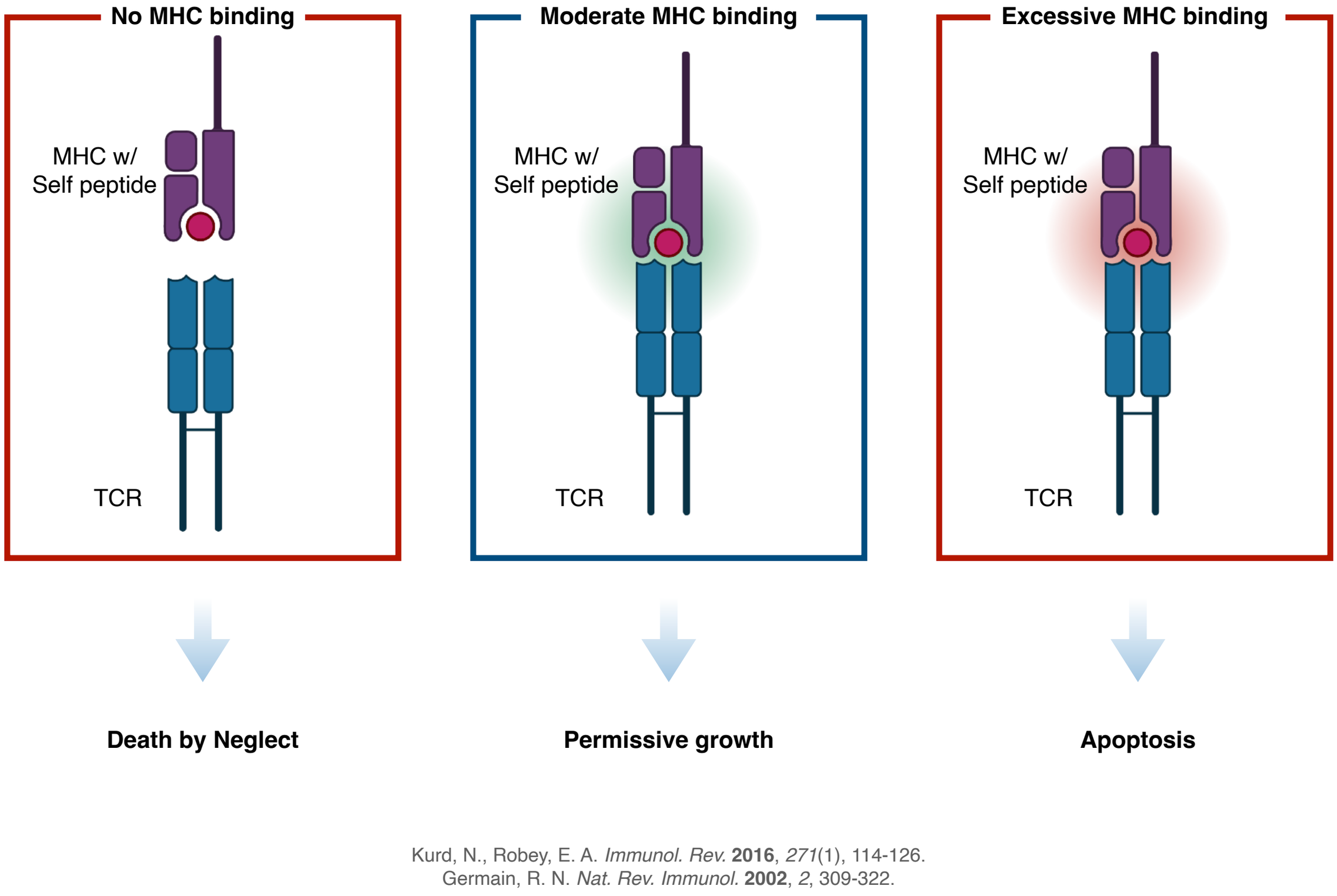
Germain, R. N. *Nat. Rev. Immunol.* **2002**, *2*, 309-322.

Negative Selection of TCRs



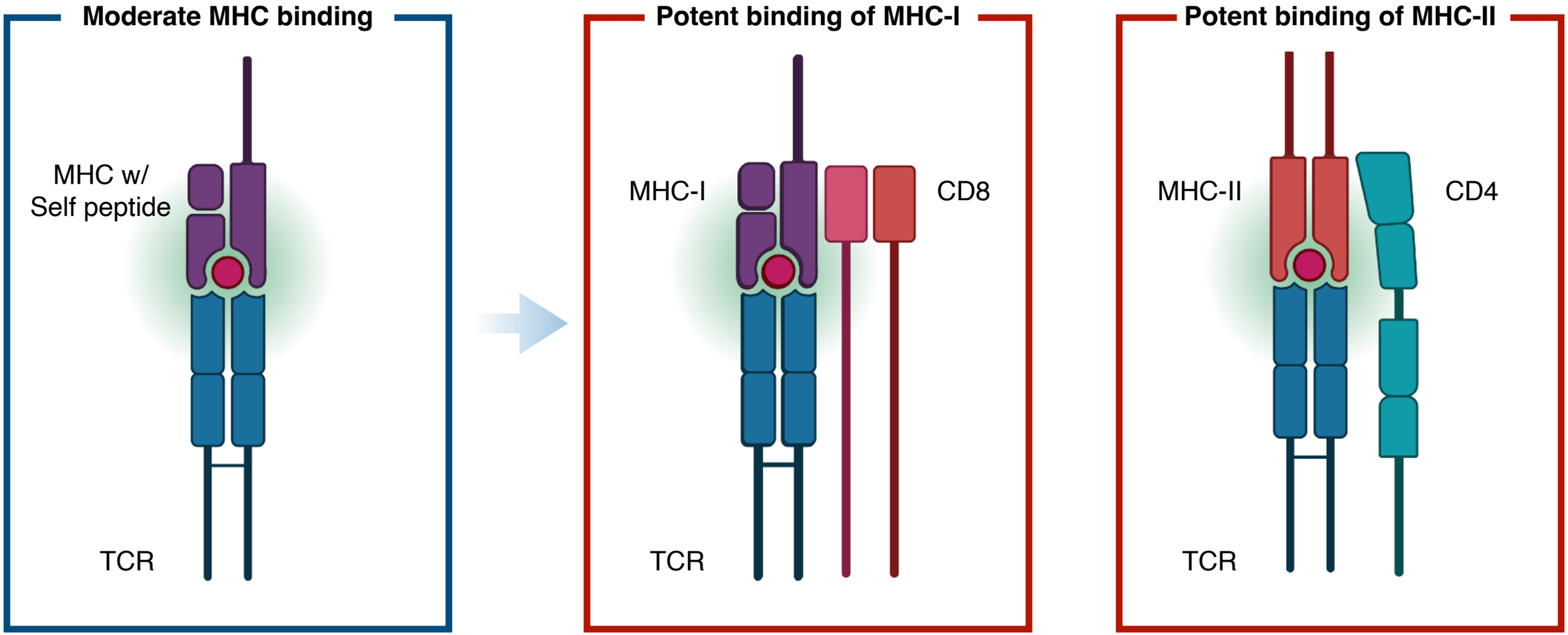
Kurd, N., Robey, E. A. *Immunol. Rev.* **2016**, *271*(1), 114-126.
Germain, R. N. *Nat. Rev. Immunol.* **2002**, *2*, 309-322.

Negative Selection of TCRs



Kurd, N., Robey, E. A. *Immunol. Rev.* **2016**, *271*(1), 114-126.
Germain, R. N. *Nat. Rev. Immunol.* **2002**, *2*, 309-322.

Positive Selection of TCRs



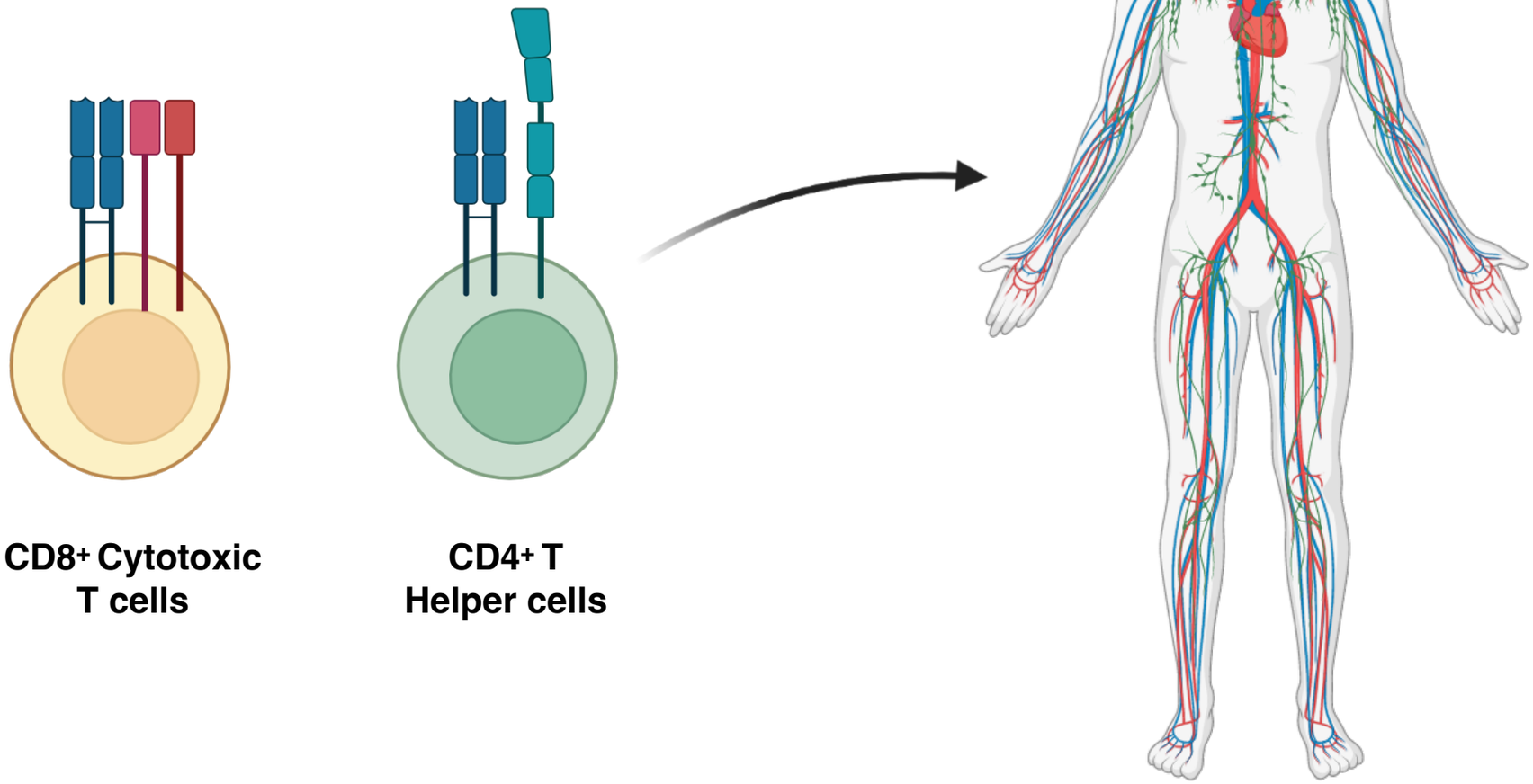
Double positive CD4+ CD8+ T cells

CD8+ Cytotoxic T cells

CD4+ T Helper cells

Kurd, N., Robey, E. A. *Immunol. Rev.* **2016**, *271*(1), 114-126.
Germain, R. N. *Nat. Rev. Immunol.* **2002**, *2*, 309-322.

Mature T Cells Exit the Thymus



CD8+ Cytotoxic T cells

CD4+ T Helper cells

Mature, naive T cells enter circulatory and lymphatic systems

Kurd, N., Robey, E. A. *Immunol. Rev.* **2016**, *271*(1), 114-126.
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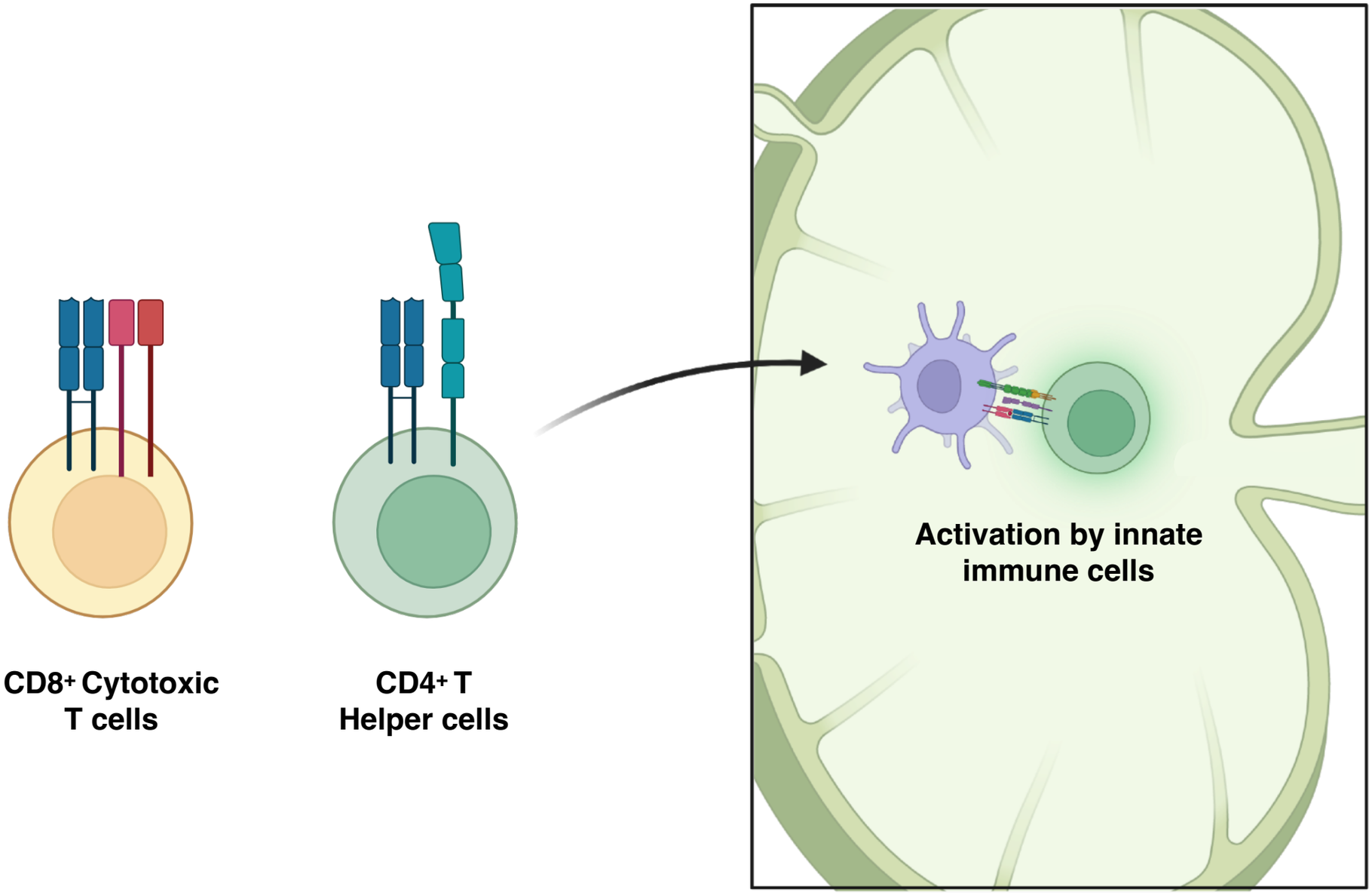

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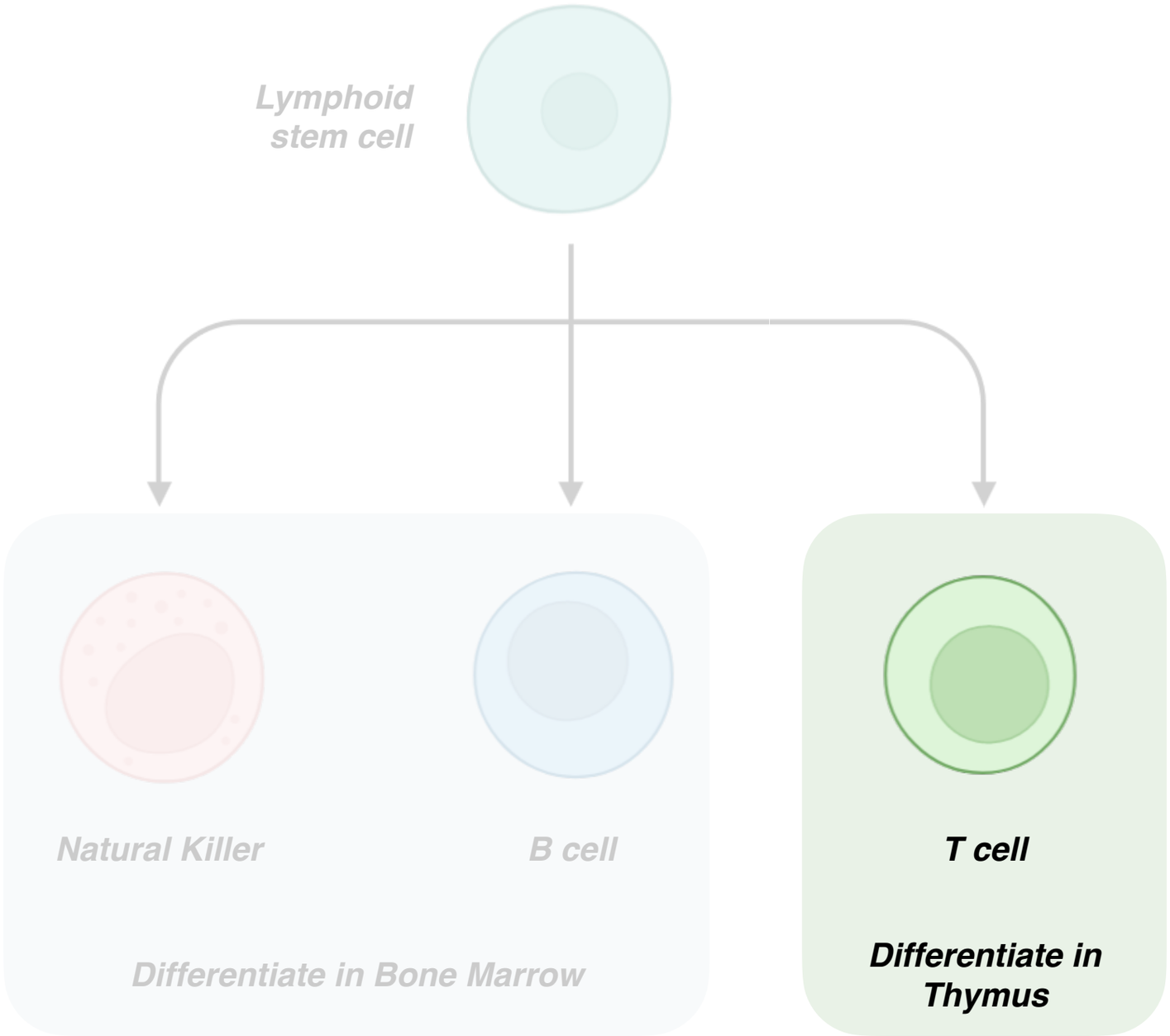
Germain, R. N. *Nat. Rev. Immunol.* **2002**, *2*, 309-322.

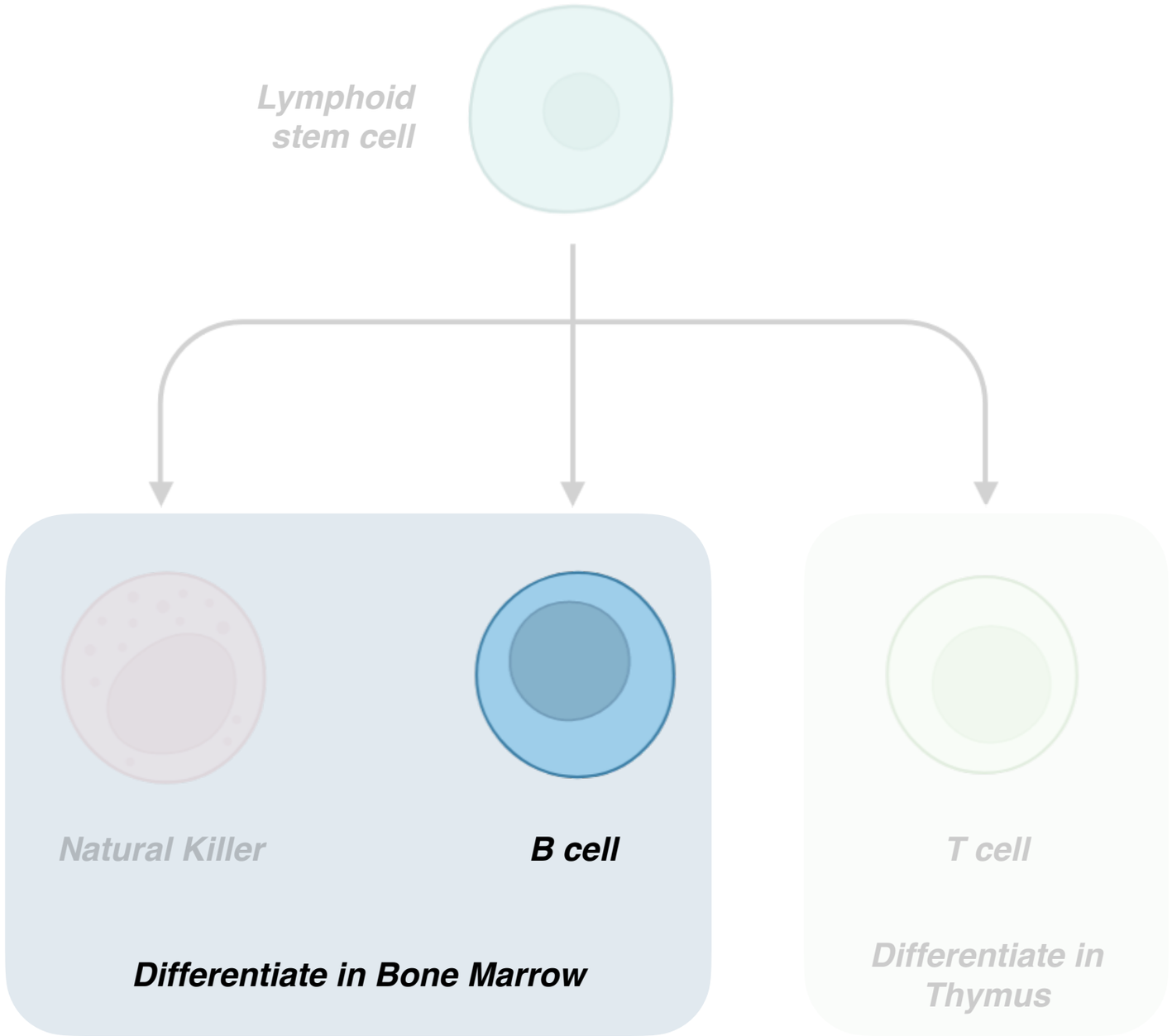
Biological Development of T and B Cells



Differentiation is determined by organ location of lymphoid precursors

Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

Biological Development of T and B Cells



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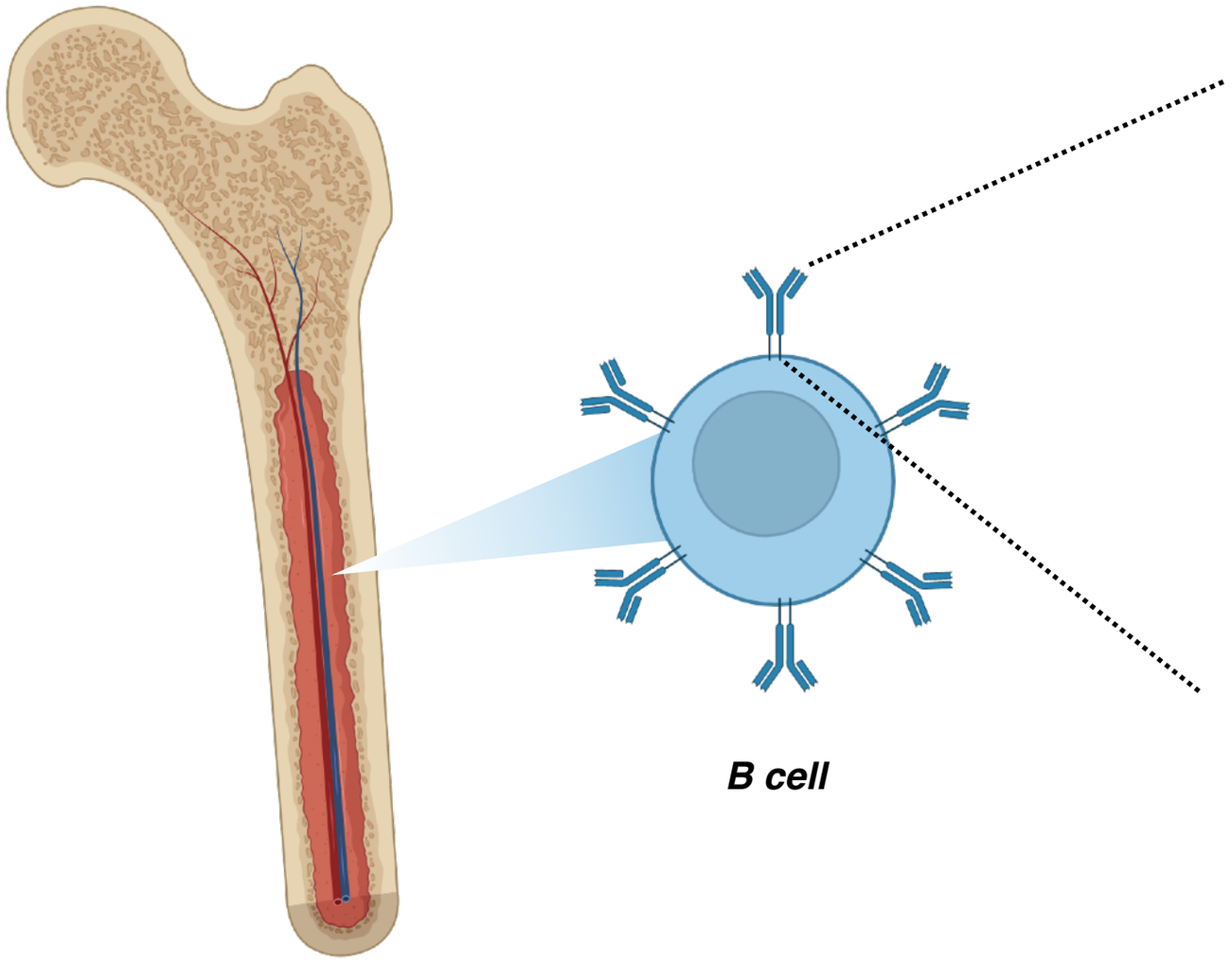
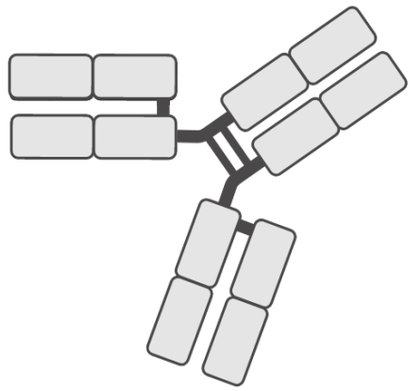
B Cell Development



Red bone marrow

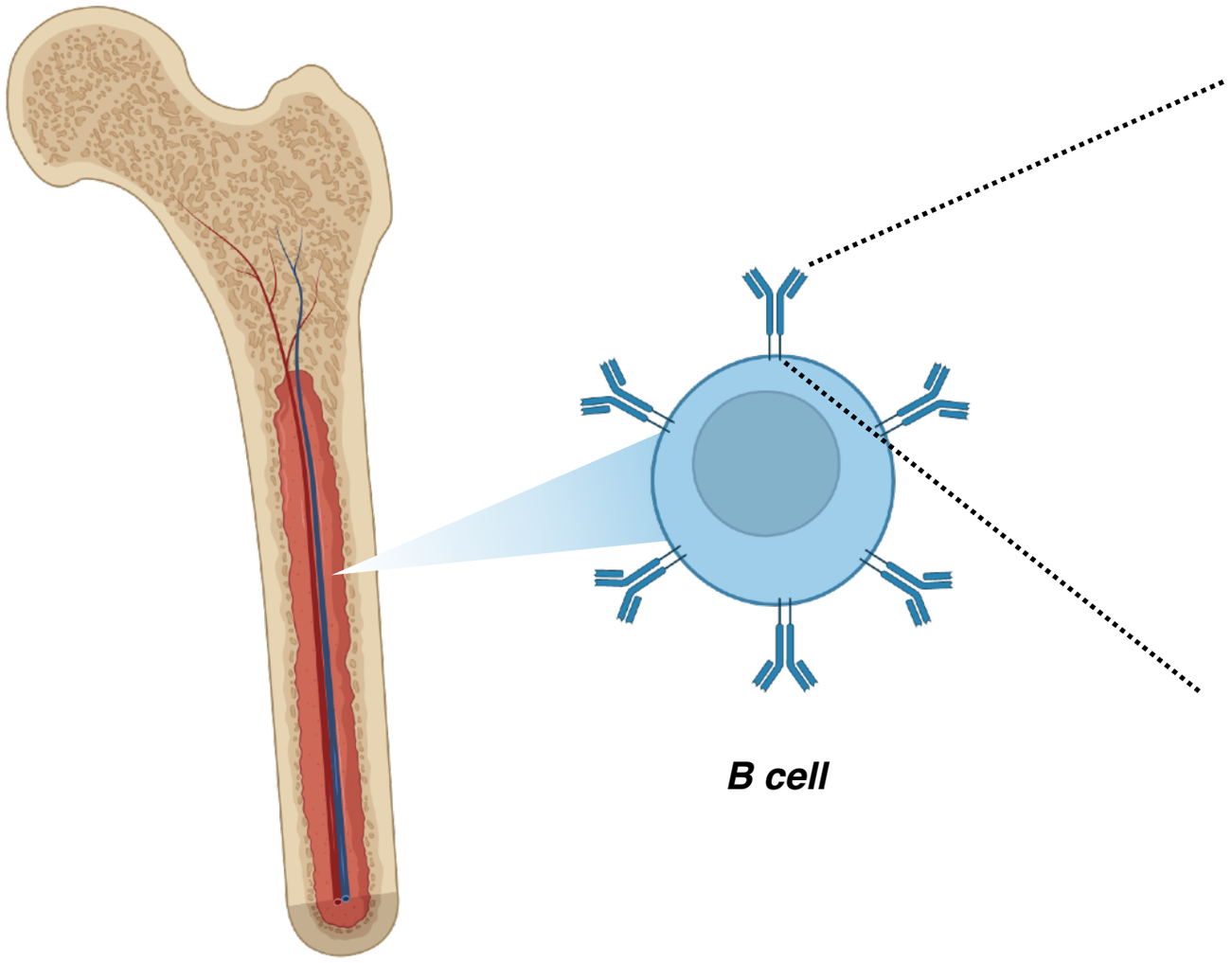
B cell



Immunoglobulin B cell receptor (BCR)

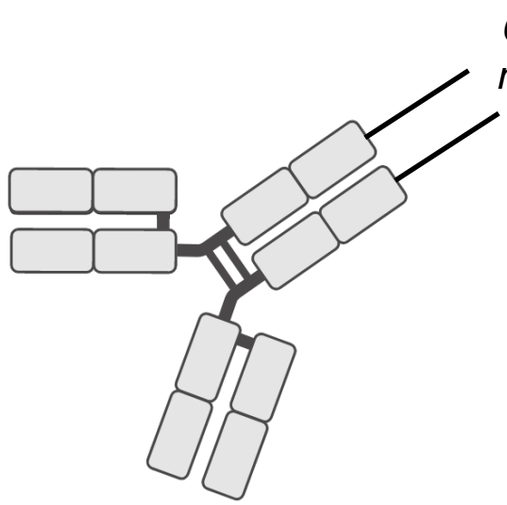
Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

B Cell Development



Red bone marrow

B cell

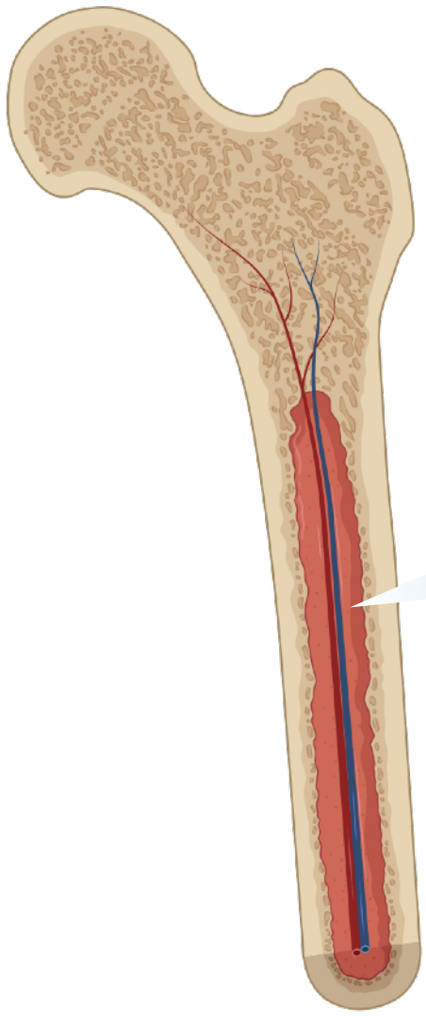


Can be anchored to membrane (BCR) or soluble (Ab)

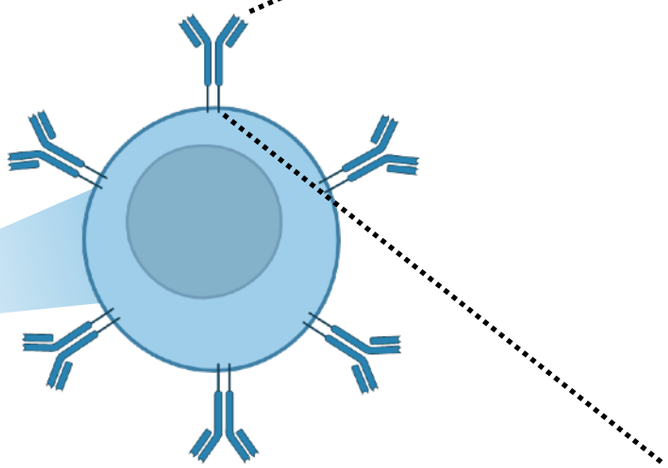
Immunoglobulin B cell receptor (BCR)

Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

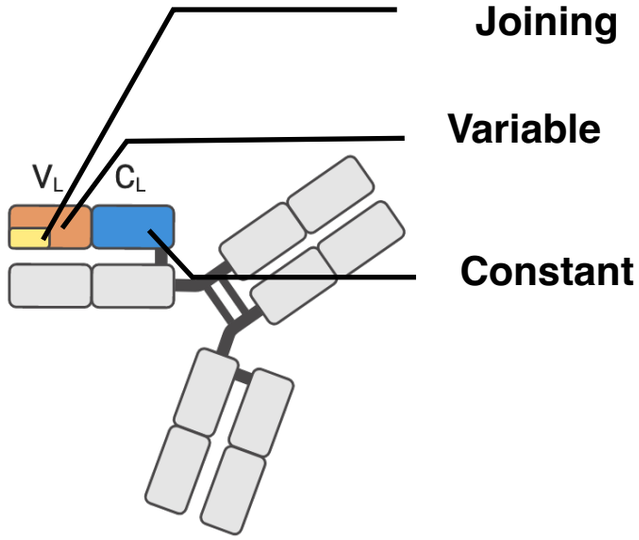
B Cell Development



Red bone marrow



B cell

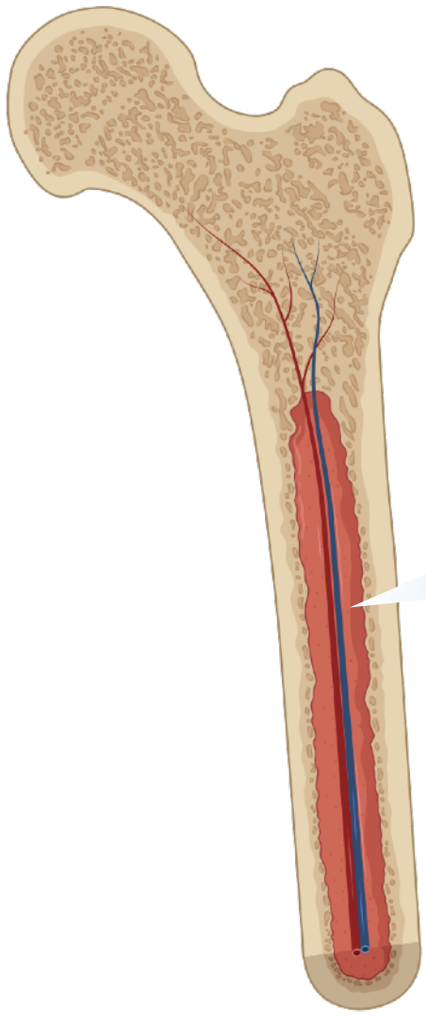


Immunoglobulin B cell receptor (BCR)

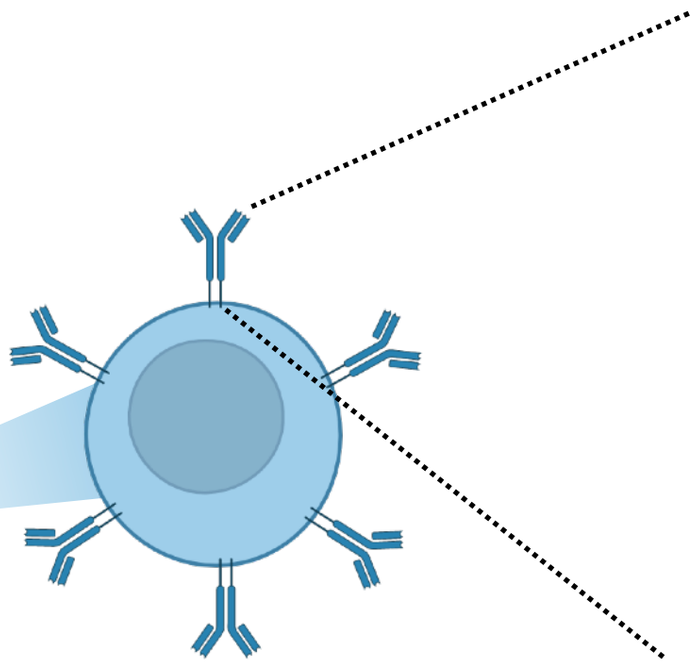
Ig light chain is analogous to TCRα

Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

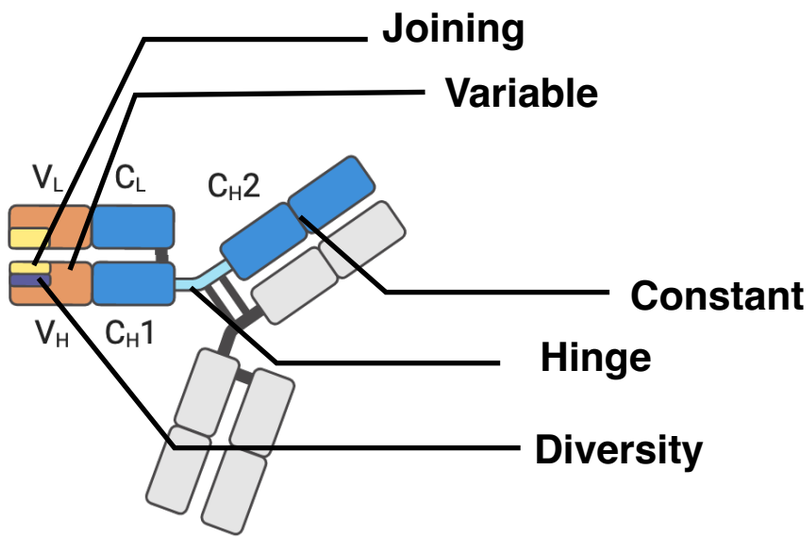
B Cell Development



Red bone marrow



B cell

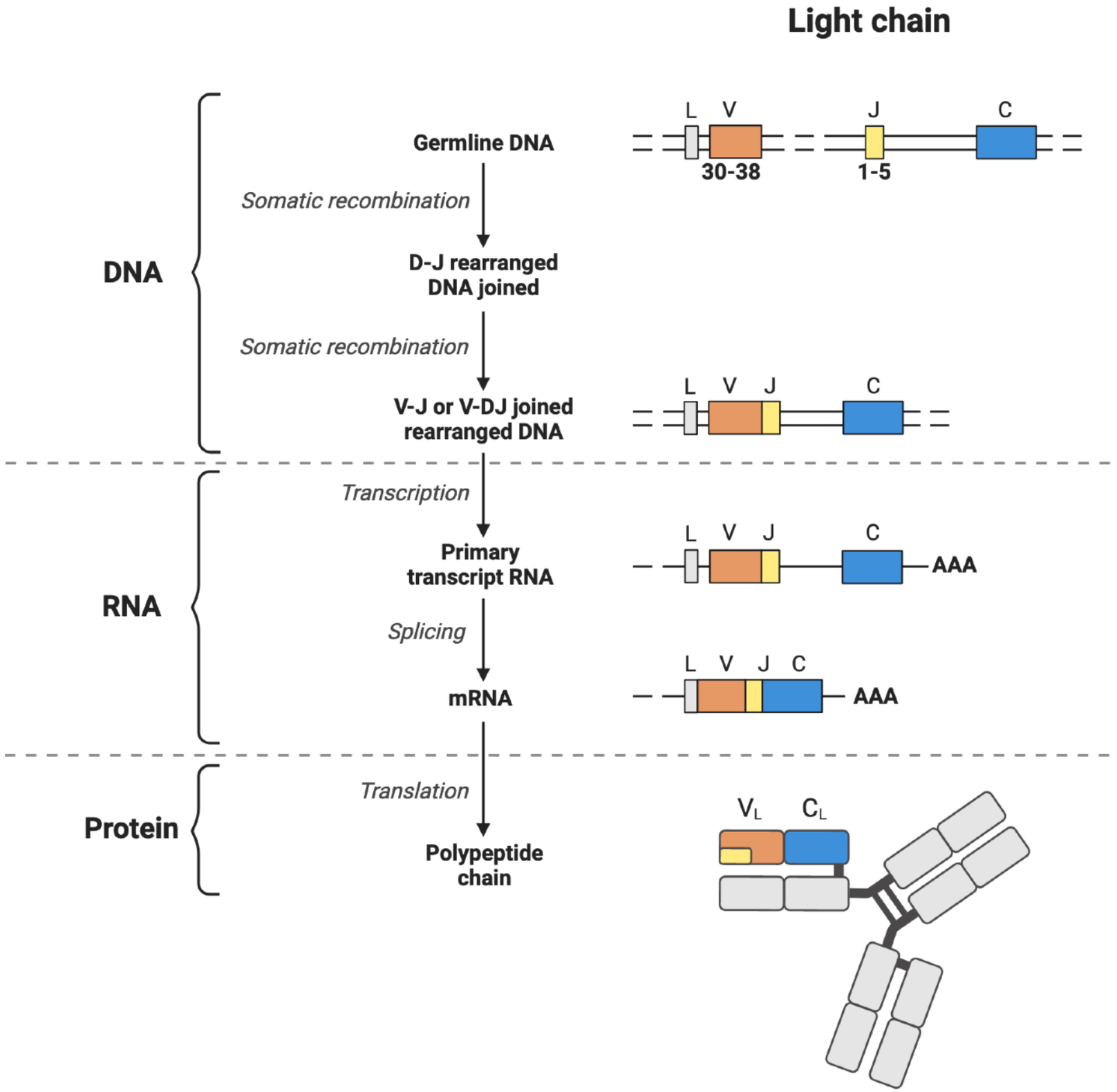


Immunoglobulin B cell receptor (BCR)

Ig heavy chain is analogous to TCRβ

Lai, A. Y., Kondo, M. *Semin. Immunol.* **2008**, *20*(4), 207-212.
Rizzani, R., et al. *Int. J. Mol. Sci.* **2020**, *21*(22), 8806

How Do B Cells and Antibodies Become so Specific?



Alberts, B., Johnson, A., Lewish, J., et al. *Mol. Biol. of the Cell 4th Ed.* **2002**, *Garland Science*.

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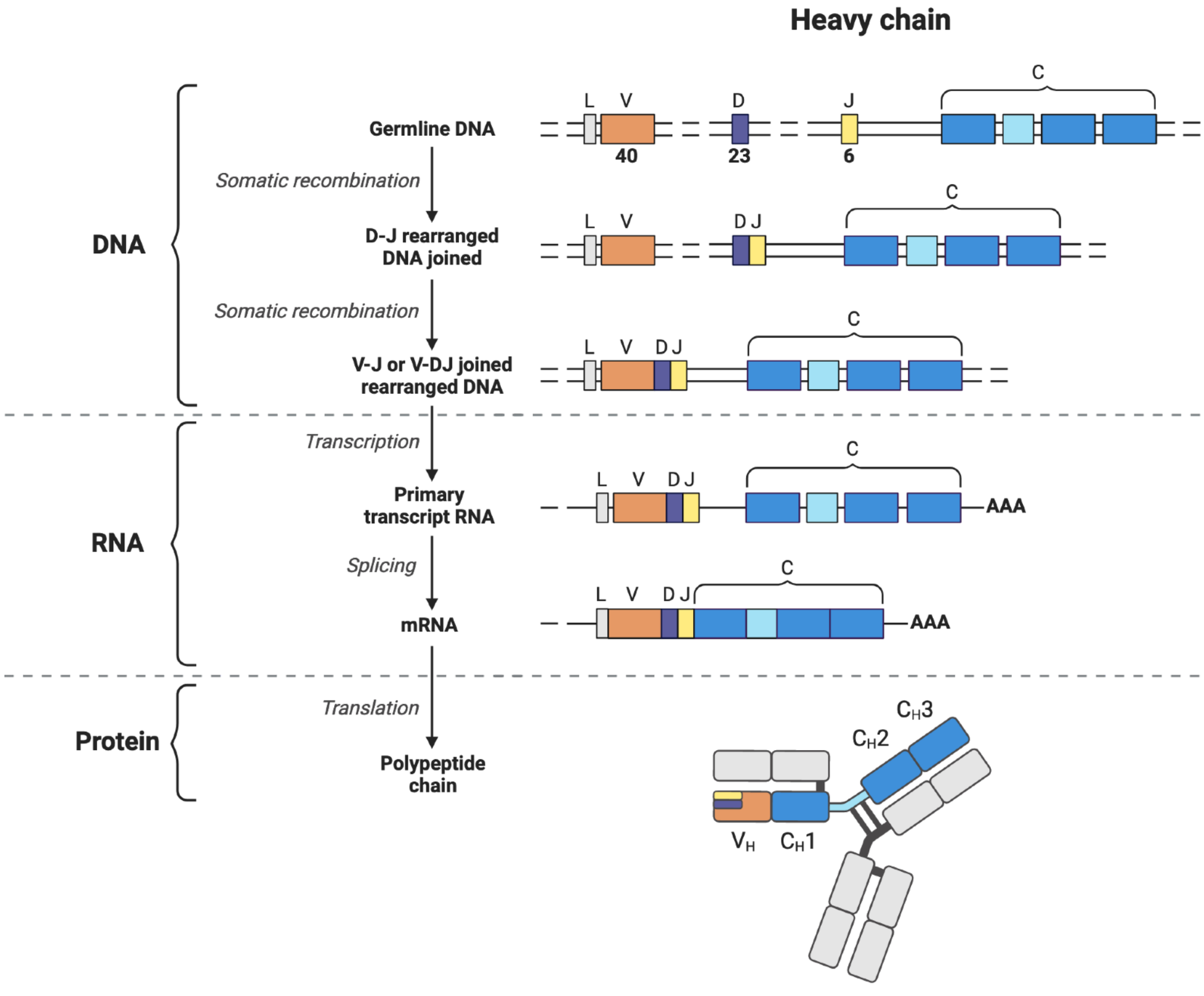

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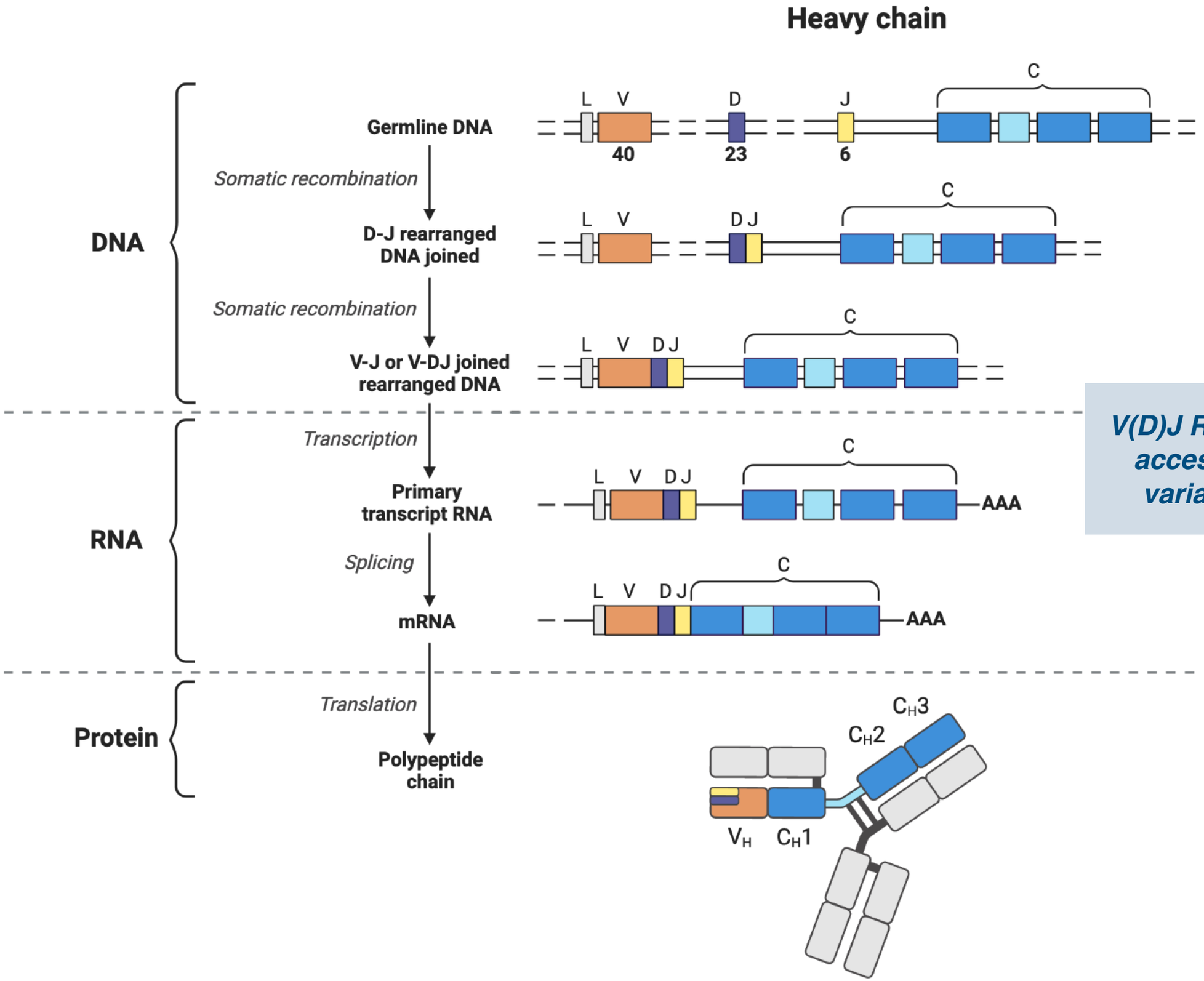
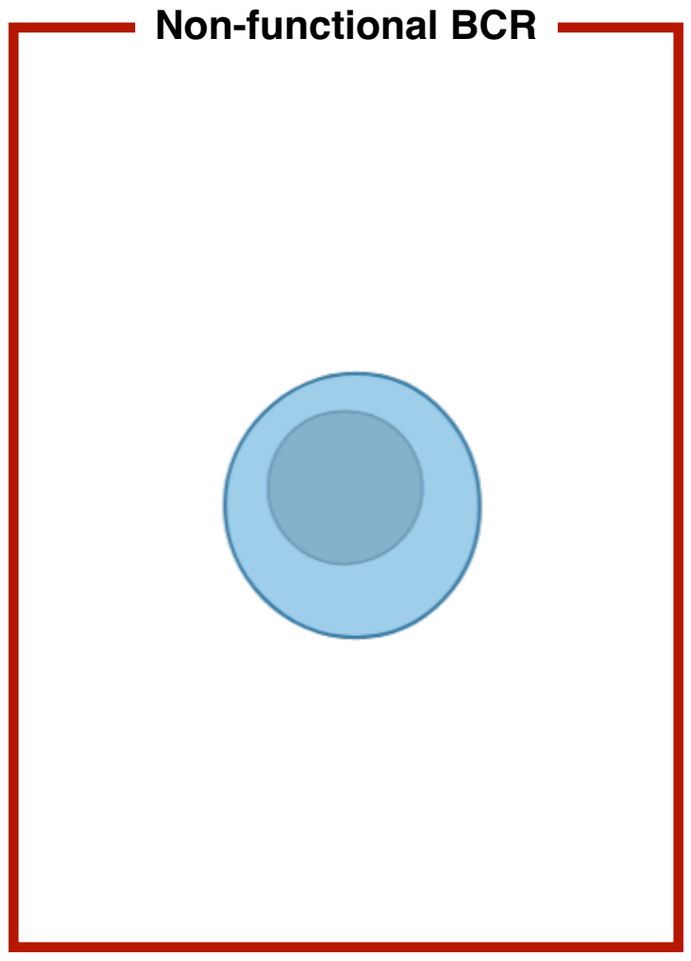


V(D)J Recombination grants access to ~10^{12} antibody variable fragments (Fv)

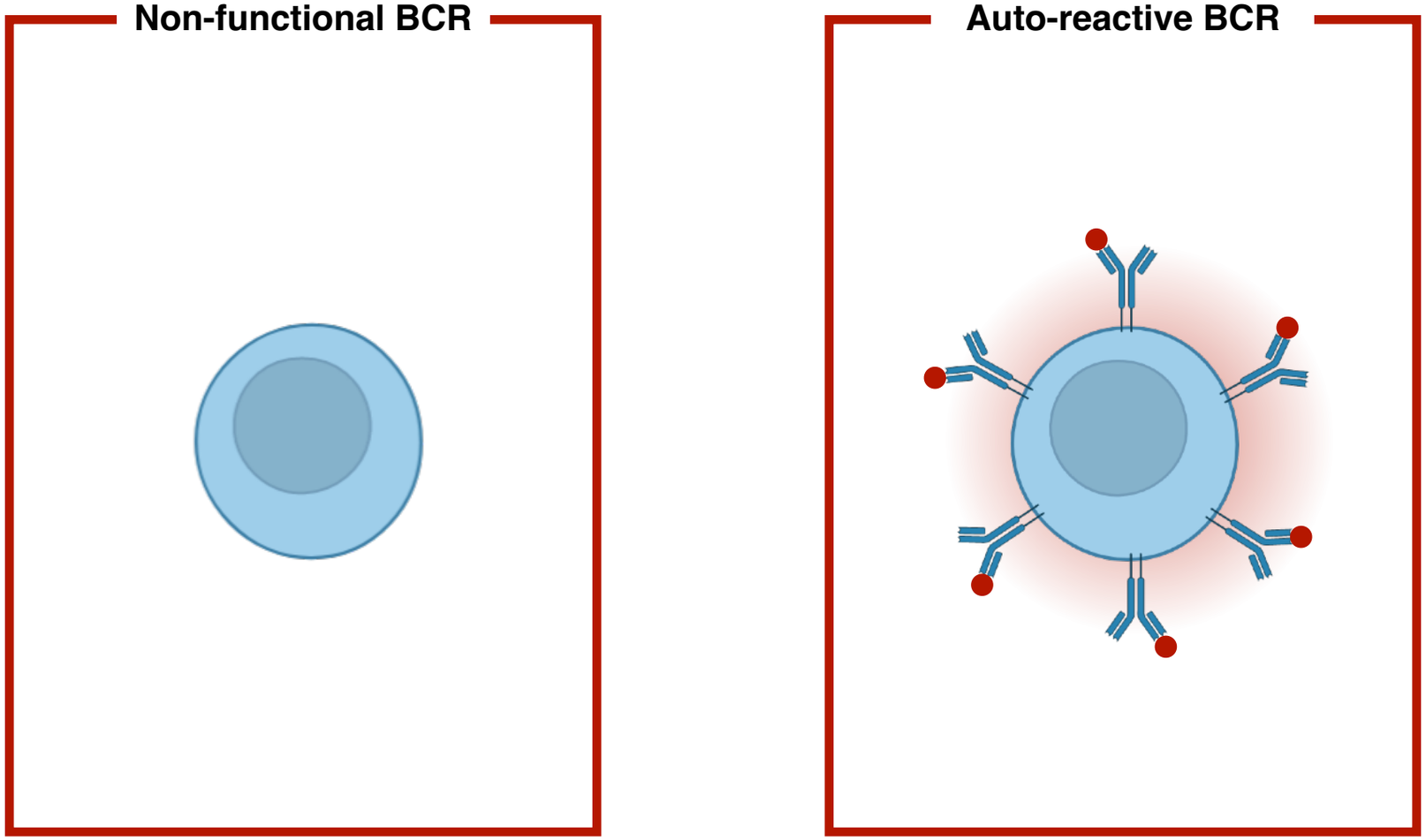
Alberts, B., Johnson, A., Lewish, J., et al. *Mol. Biol. of the Cell 4th Ed.* **2002**, *Garland Science*.

Positive and Negative Selection of BCRs



Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

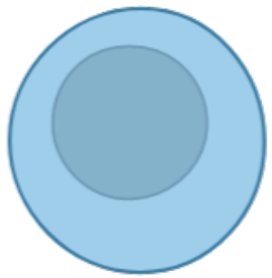
Positive and Negative Selection of BCRs



Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

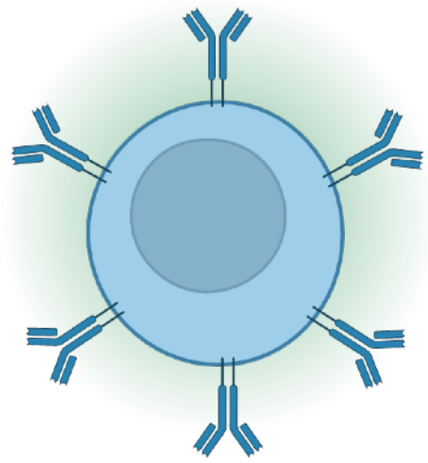
Positive and Negative Selection of BCRs

Non-functional BCR



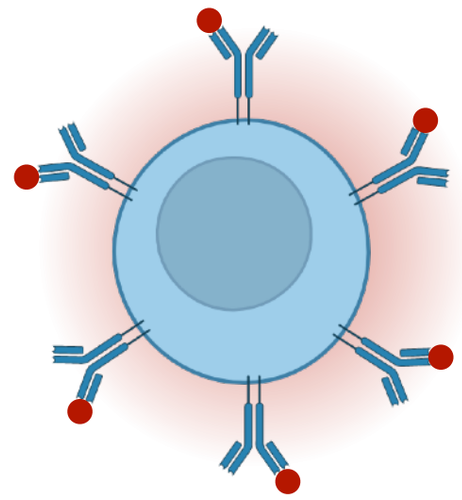
Lack of PI3K signaling leads to cell death

Innocuous BCR



Tonic PI3K signaling promotes survival, development

Auto-reactive BCR

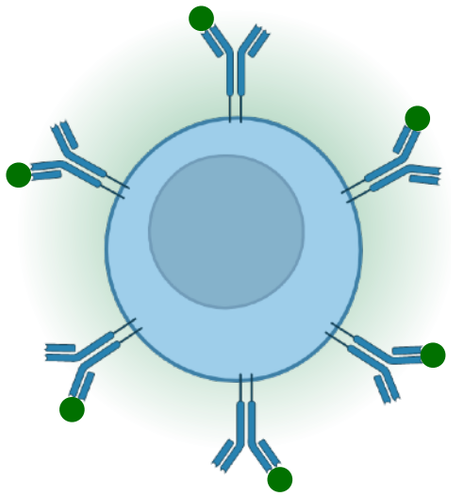


Triggered somatic hypermutation or cell death

Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

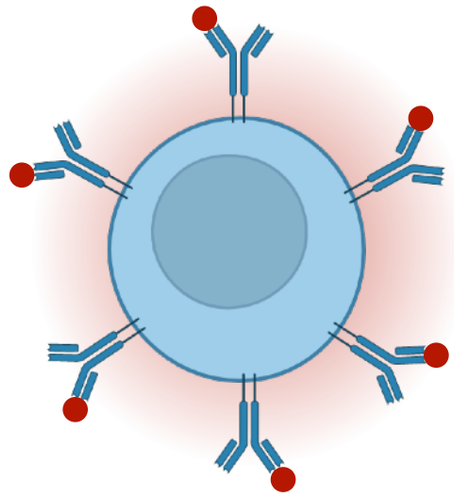
Somatic Hypermutation: Further Diversification of Immunoglobulins

In blood or lymph



Binding of foreign antigens
triggers hypermutation

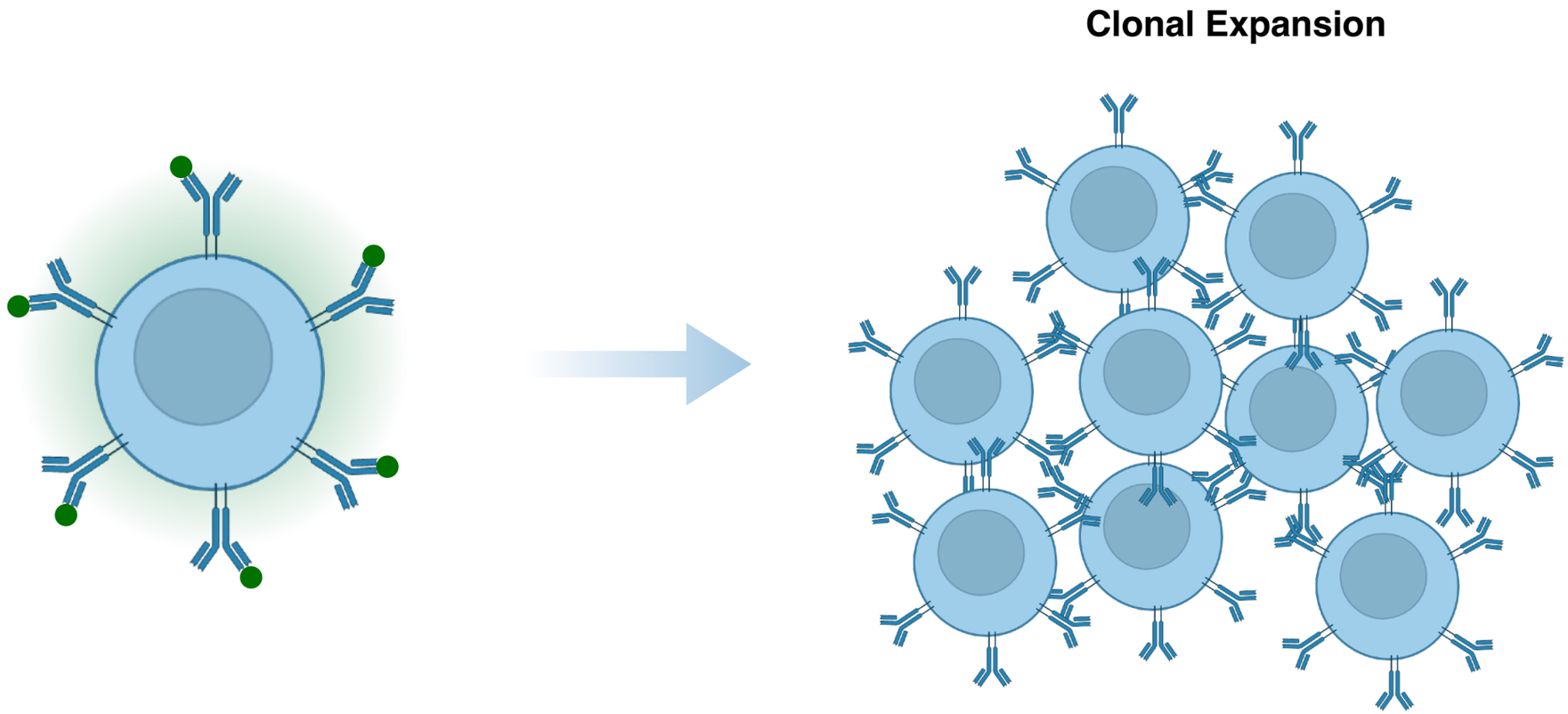
In bone marrow



Binding of self antigens can
trigger hypermutation

Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

Somatic Hypermutation: Further Diversification of Immunoglobulins



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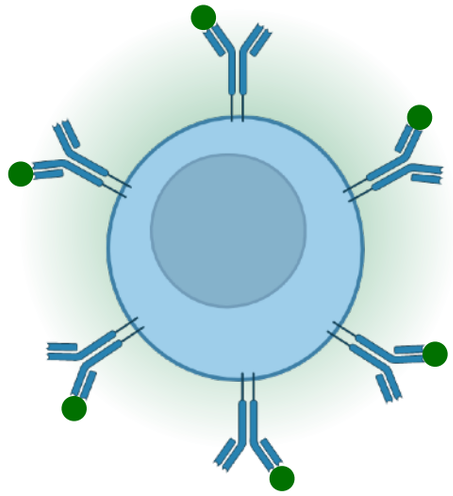
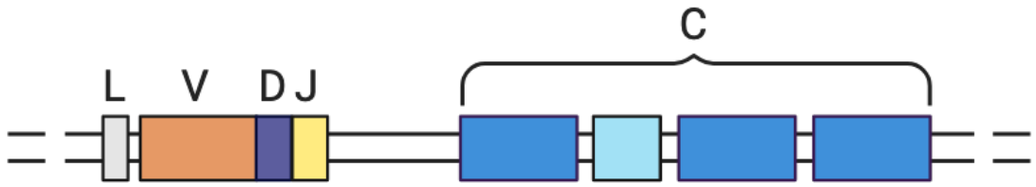
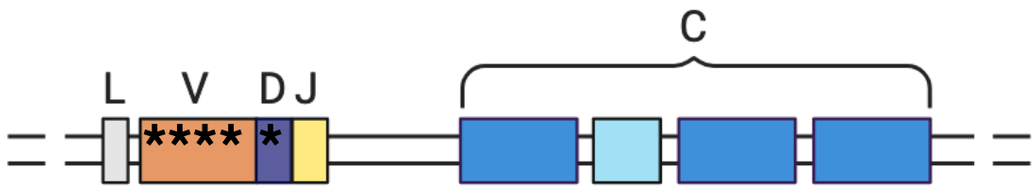


Heavy Chain DNA Locus



Replication with 10^6 fold more frequent mutations



Accumulated mutations in variable region

Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

Somatic Hypermutation: Further Diversification of Immunoglobulins

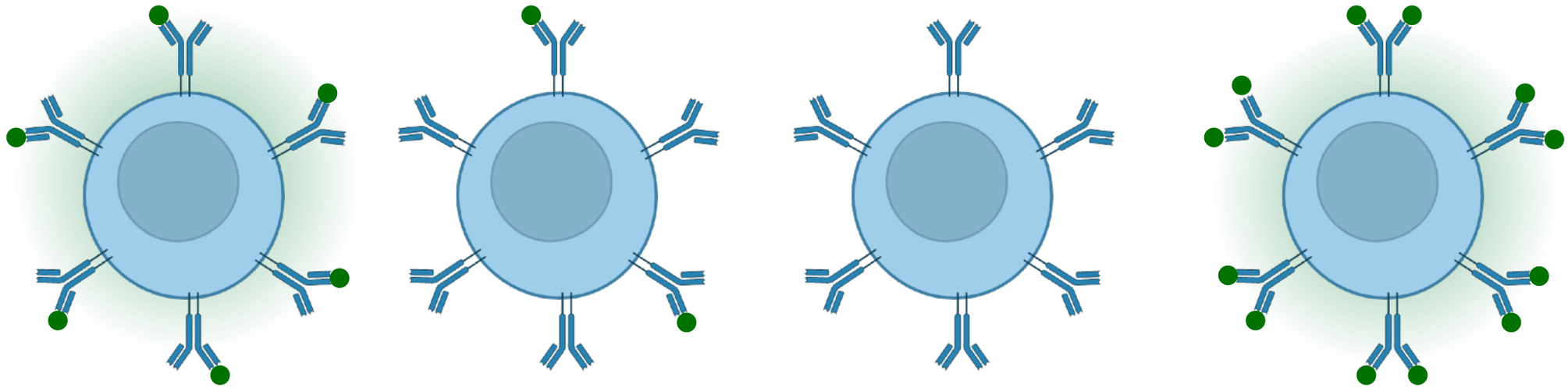
Hypermutated B cells

Moderate binding

Low binding

No binding

High binding

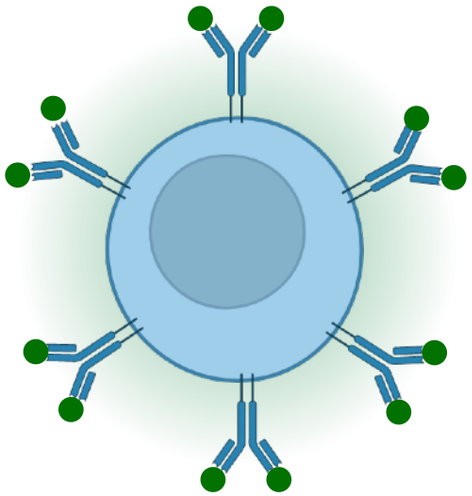


Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

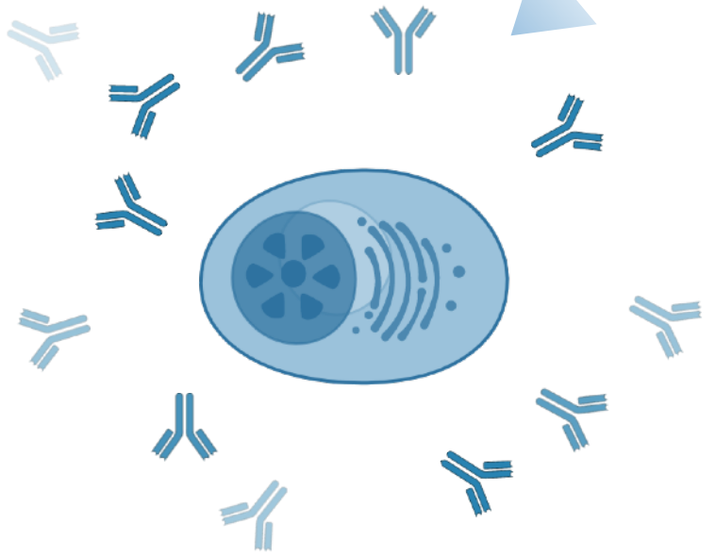
Somatic Hypermutation: Further Diversification of Immunoglobulins

Hypermutated B cells

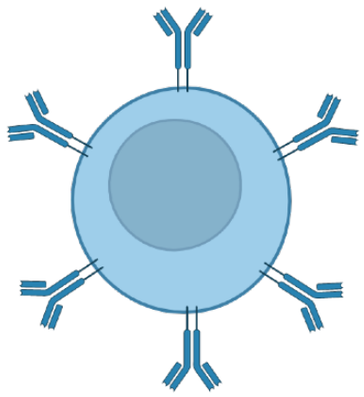
High binding



Plasma cells



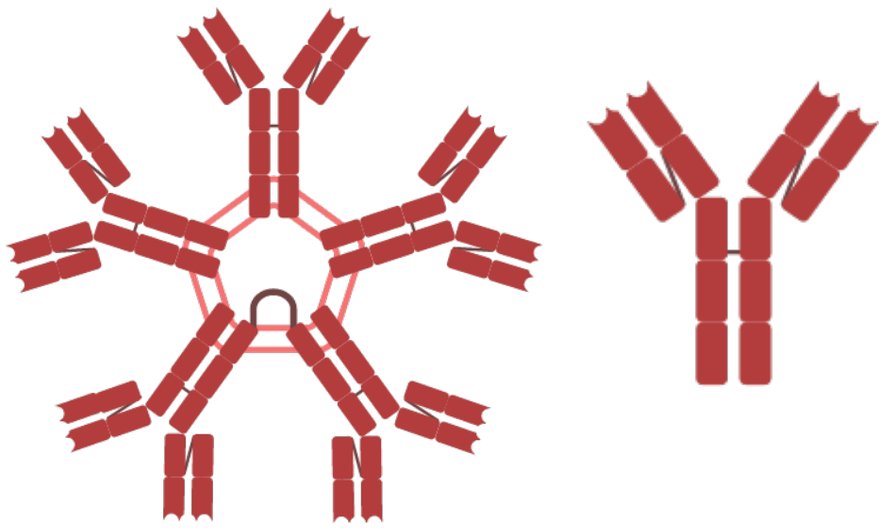
Memory B cells



Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

Affinity Maturation

IgM as Dominant Isotype



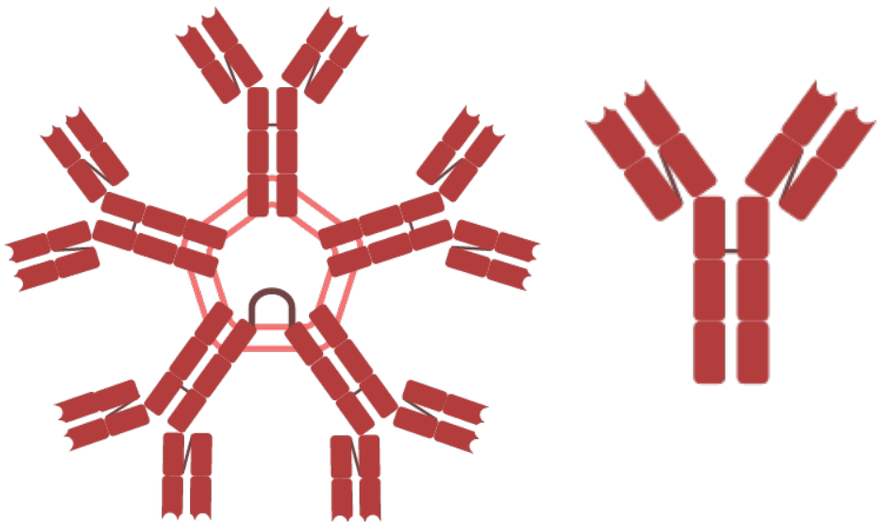
IgM Pentamer
(humoral)

IgM Monomer
(membrane bound)

Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

Affinity Maturation

IgM as Dominant Isotype

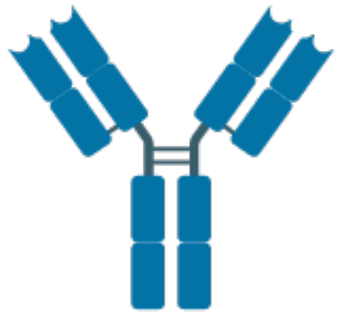


IgM Pentamer
(humoral)

IgM Monomer
(membrane bound)

Naturally lower affinity, less potent at promoting innate immunity

IgG as Dominant Isotype



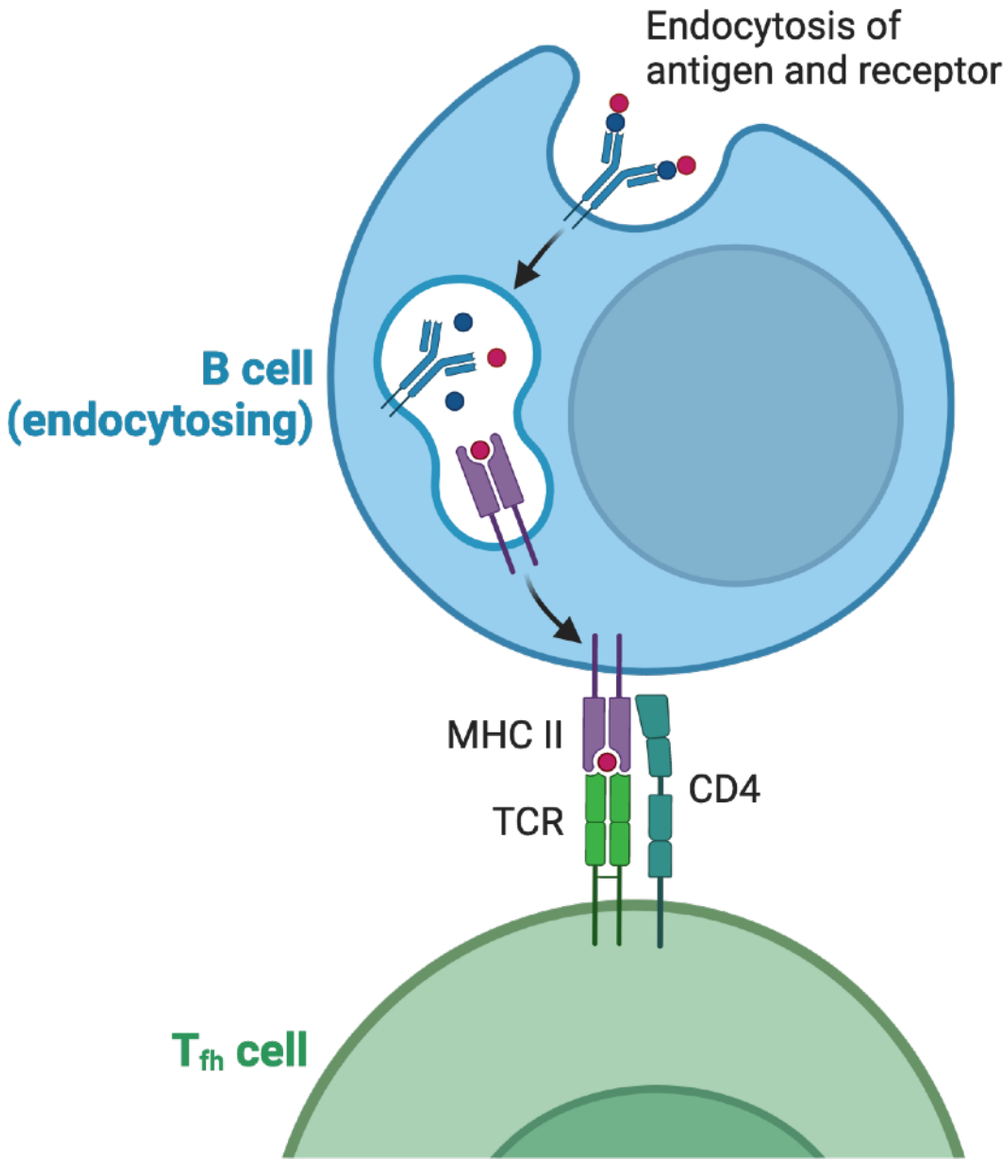
IgG Monomer (humoral
and membrane bound)

Naturally higher affinity, more potent at promoting innate immunity

Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

Affinity Maturation

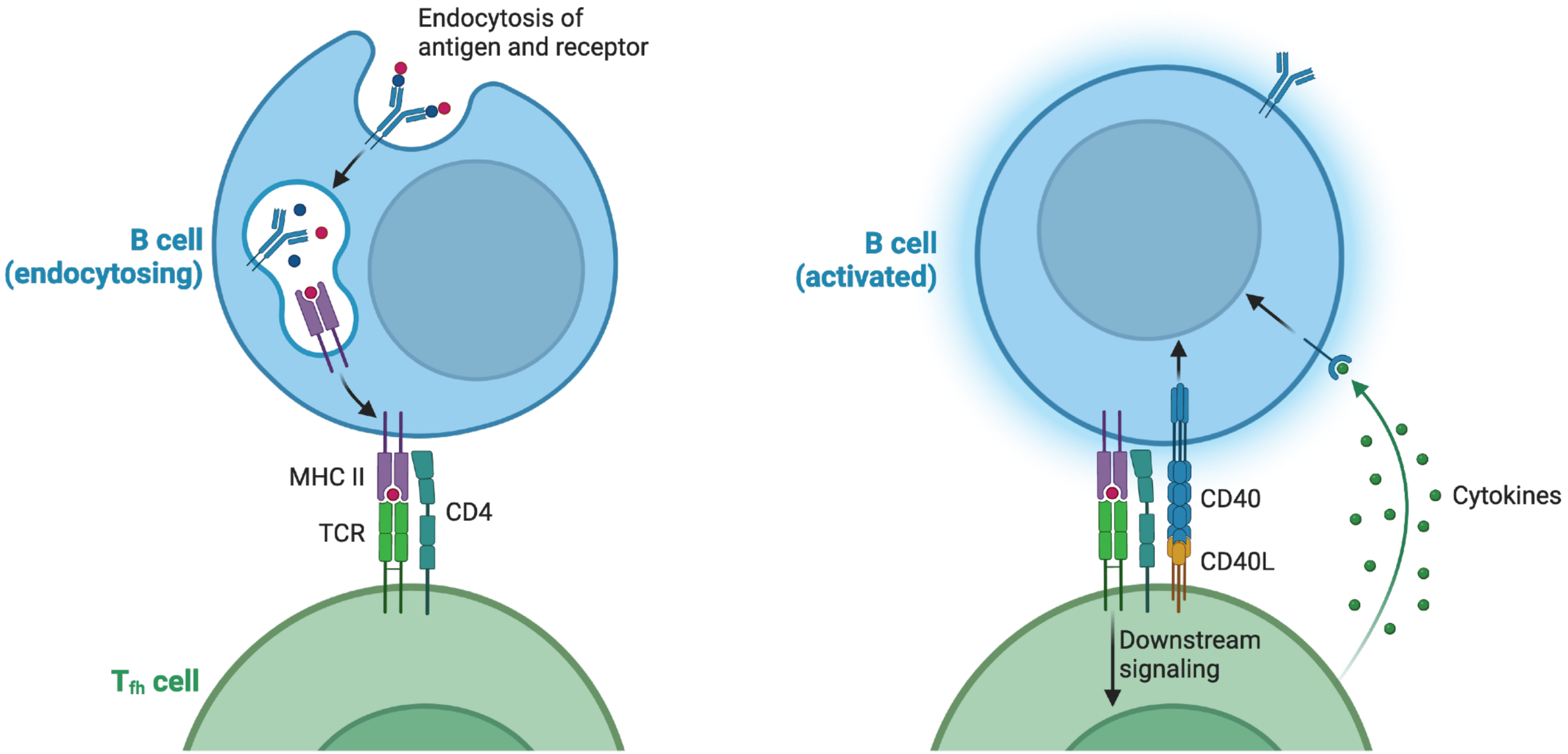
T_{fh} cell recognizes a peptide generated from antigen recognized by BCR



Nemazze, D. *Nat. Rev. Immunol*. **2017**, *17*, 281-294.

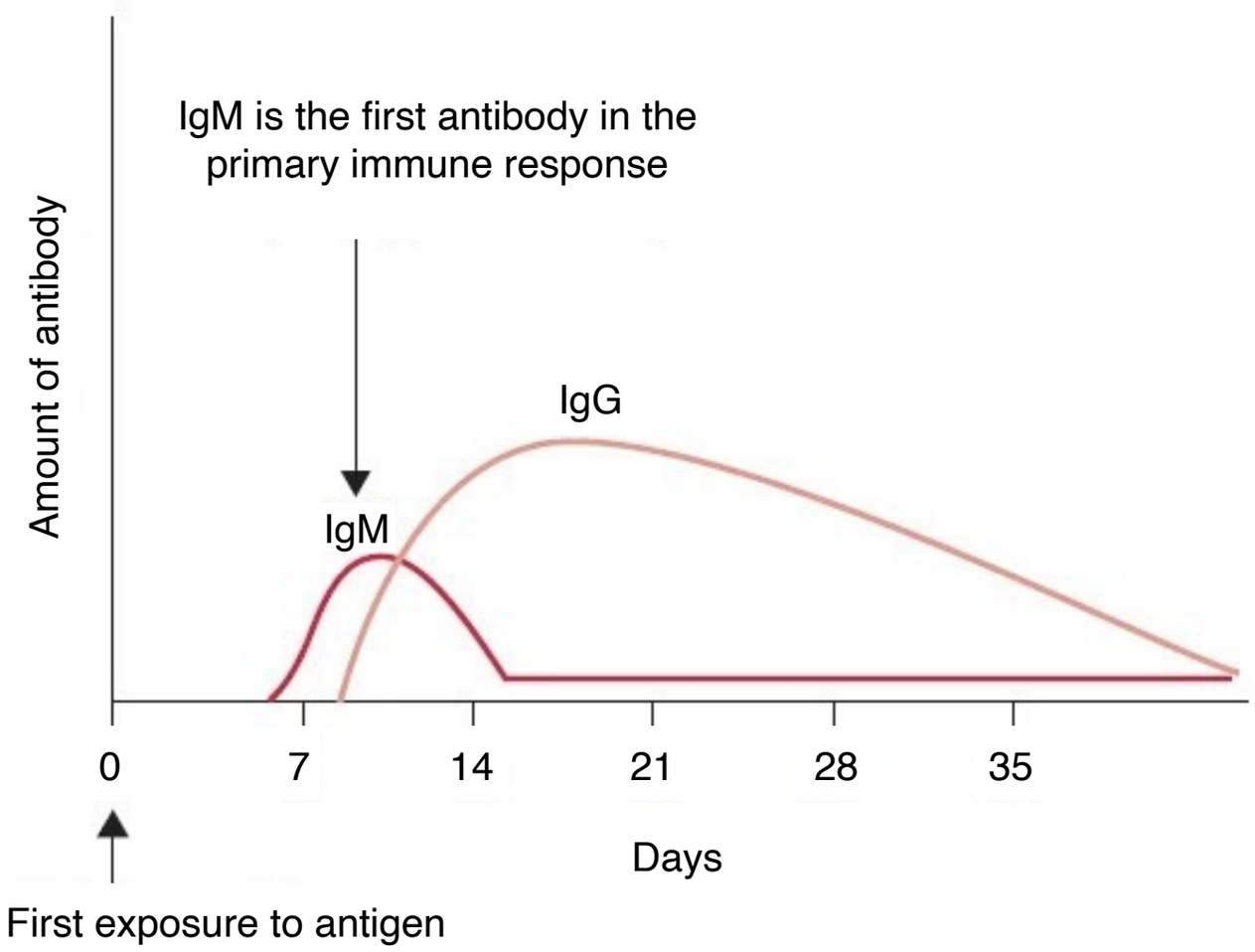
Affinity Maturation

T_{fh} cell recognizes a peptide generated from antigen recognized by BCR → **Naive B cell and T_{fh} cell interact, initiate B cell activation, affinity maturation**



Nemazze, D. *Nat. Rev. Immunol.* **2017**, *17*, 281-294.

Affinity Maturation

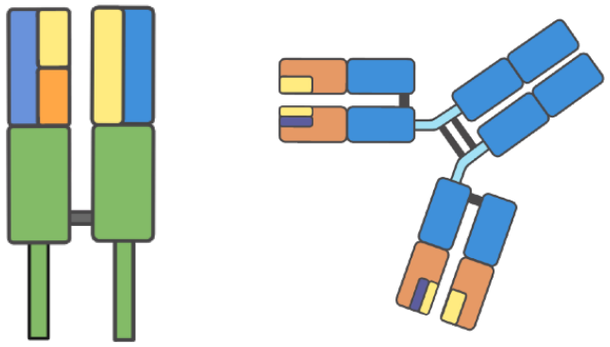


Parija, S. C. *Microbiology and Immunology 2nd Ed.* **2012**.

Adaptive Immune System

Enabling aspects and failures of adaptive immunity

Ultra-specific targeting



Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines

Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

Adaptive Immune System

Enabling aspects and failures of adaptive immunity

Ultra-specific targeting

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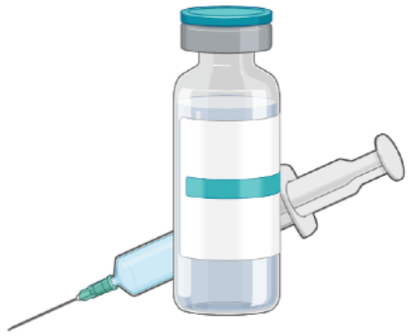
Vaccines



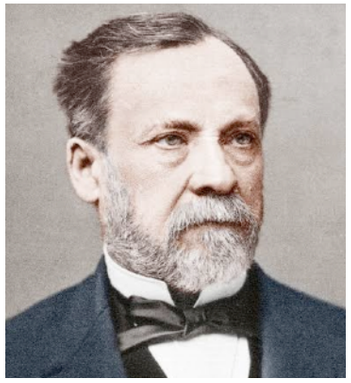
Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

A Timeline of Vaccine Development

Benjamin Jetsy infects sons and wife with cowpox pus during smallpox epidemic



Louis Pasteur proposes germ theory, generates first attenuated vaccines

1774

1877-1885

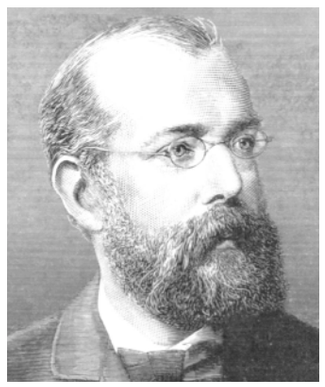
12th Century

1786

1882

Variolation was developed in Turkey Africa, China, Europe

Edward Jenner inoculates child with cowpox, demonstrates immunity to smallpox



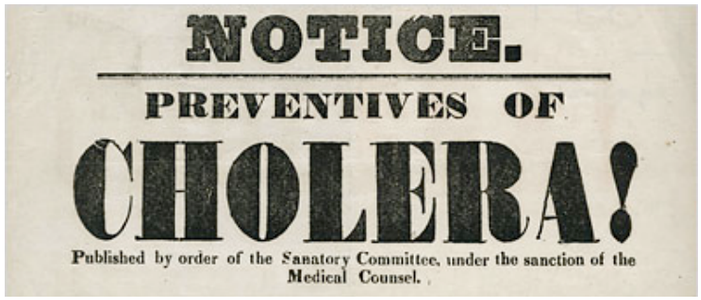
Robert Koch identifies M. tuberculosis *as cause of tuberculosis*

immunize.org

A Brief History of Vaccines. The World Health Organization.

Pead, P. J. *Lancet*. **2006**, *368*(9554), 2202.

A Timeline of Vaccine Development

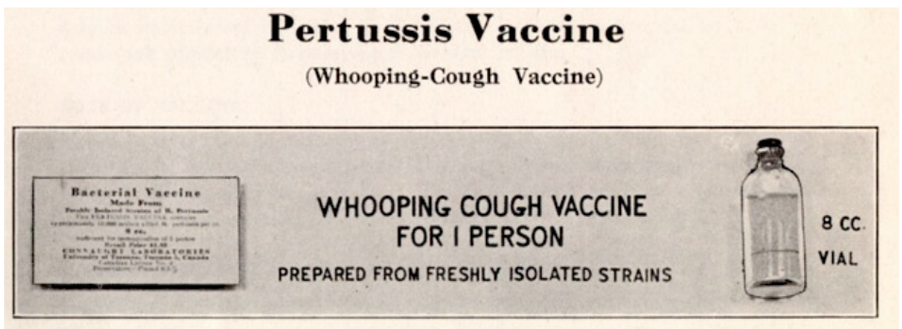


Cholera and typhoid vaccines invented

1896

1915

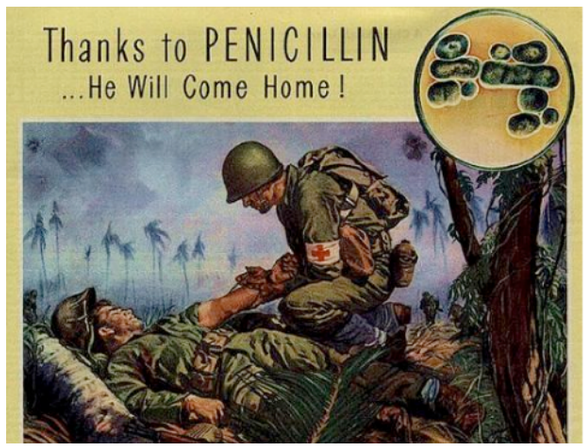
First inactivated vaccine



Influenza pandemic kills 50 million people, promotes flu vaccine research

1918

1940s



Flu and DTaP vaccines created, penicillin became mass produced, smallpox was eradicated in the US

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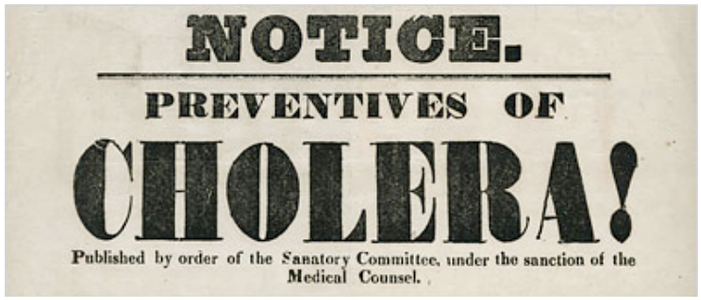

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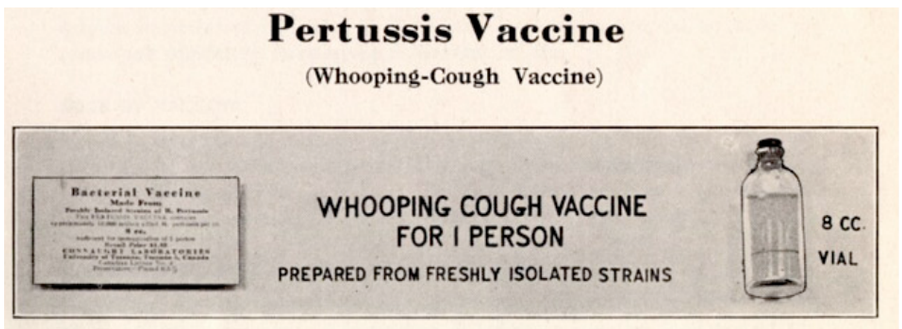

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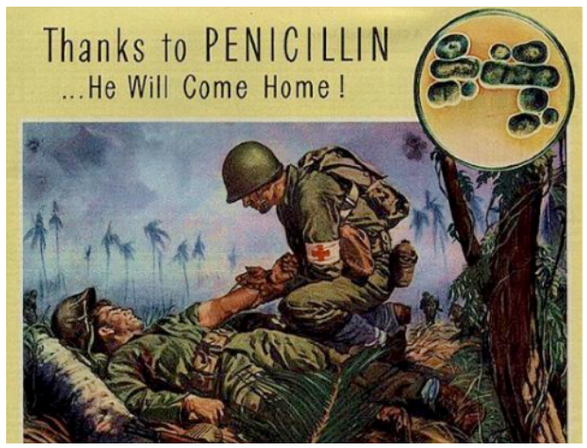

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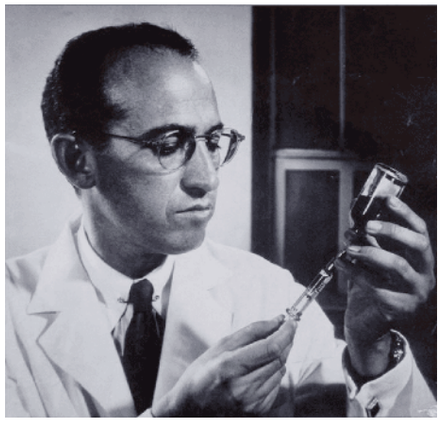


1955

First polio vaccine licensed

1966-1967

Global and US smallpox and measles eradication programs launched

1991

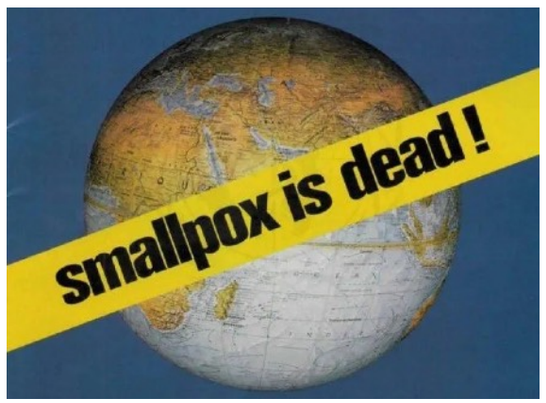
Last case of wild polio in western hemisphere

1961-1963

Trivalent live oral polio vaccine, numerous measles vaccines developed

1980

Smallpox is eradicated



2006

First "cancer" vaccine approved by FDA

GARDASIL®9

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A Brief History of Vaccines. The World Health Organization.

Pead, P. J. *Lancet*. **2006**, *368*(9554), 2202.

A Timeline of Vaccine Development

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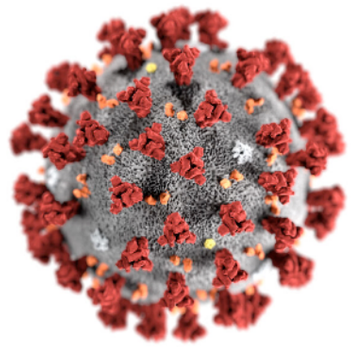
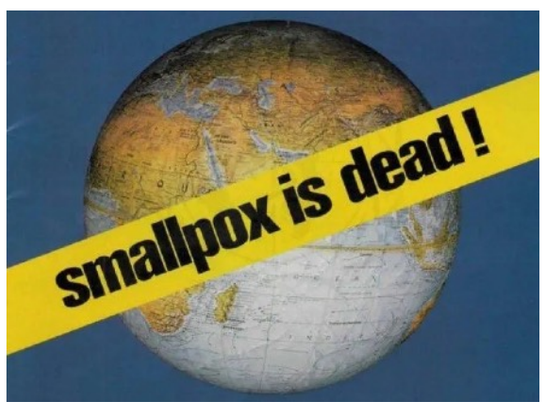


Covid-19 Pandemic Declared

March 11, 2020

1980

Smallpox is eradicated



2006

First "cancer" vaccine approved by FDA

GARDASIL®9

August 23, 2021

First mRNA vaccine, targeting SARS-CoV-2, approved

COMIRNATY®
(COVID-19 Vaccine, mRNA)

immunize.org

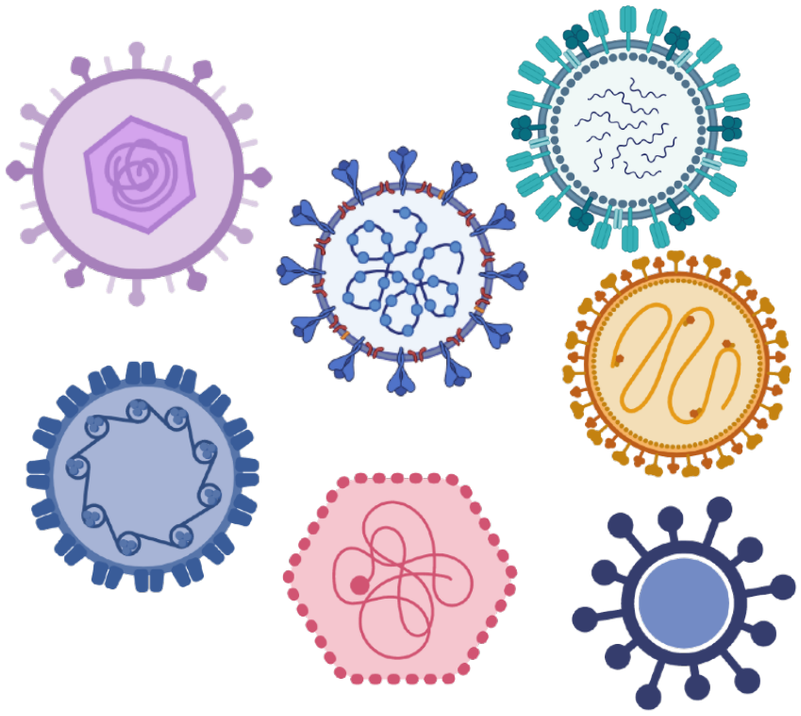
A Brief History of Vaccines. The World Health Organization.

Pead, P. J. *Lancet*. **2006**, *368*(9554), 2202.

Vaccines: Frontline Protection from Viral and other Diseases

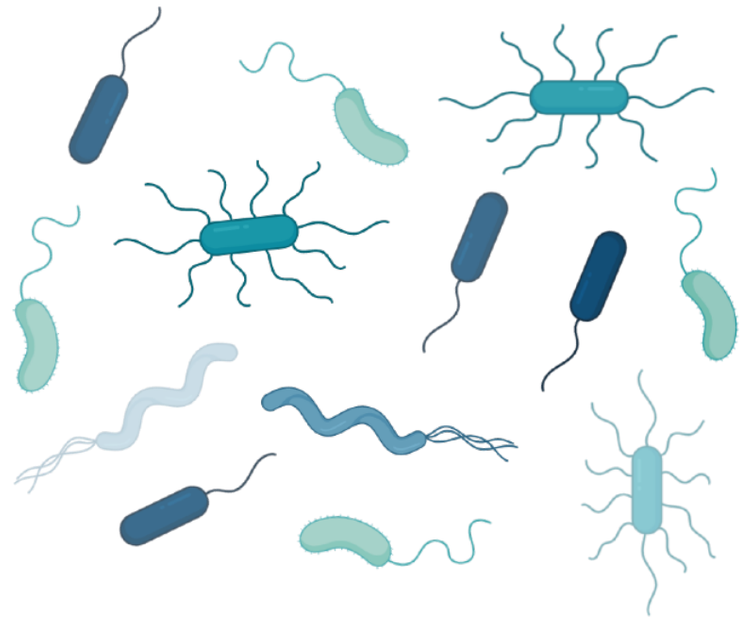
Vaccine preventable pathogens

Viruses



Varicella, Influenza, Hepatitis A/B, HPV, Measles, Mumps, Rubella, Poliovirus, Rotavirus, RSV, Rabies, Smallpox, Yellow Fever, Dengue, Shingles

Bacteria



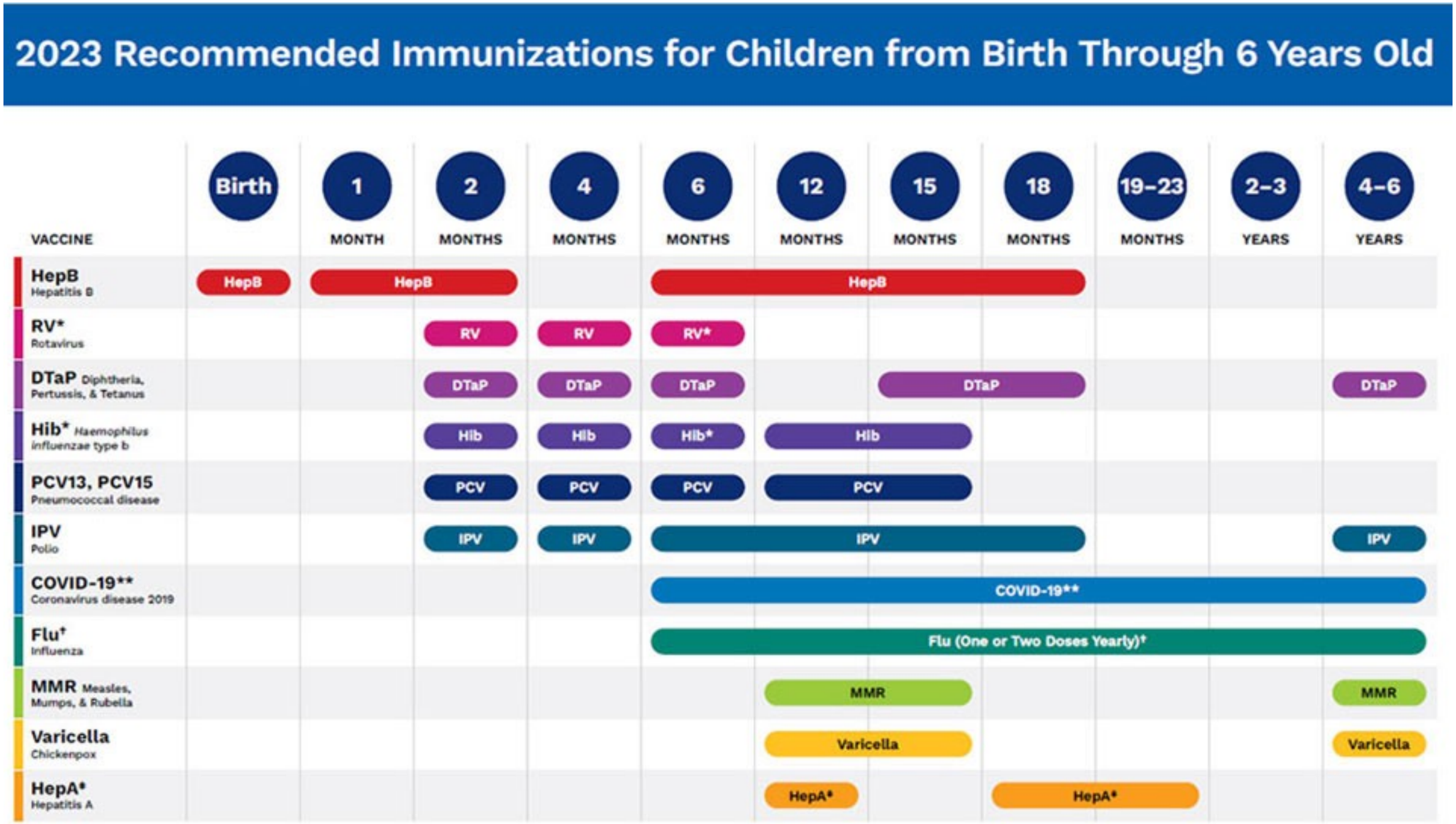
Diphtheria, HiB, Meningococcal, Clostridium tetani, Bordetella pertussis, Mycobaterium tuberculosis

>20 Vaccine preventable viruses and bacteria

Diseases & the Vaccines that Prevent Them. CDC. **2024**.

Vaccines: Frontline Protection from Viral and other Diseases

Vaccine preventable pathogens

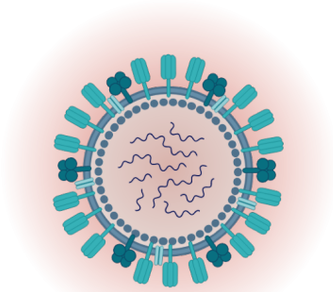


Recommended Immunizations. CDC. **2023.**

Vaccines: Frontline Protection from Viral and other Diseases

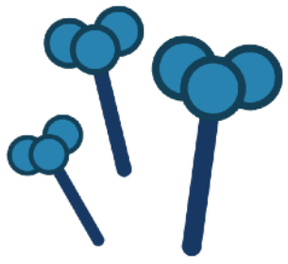
Classes of vaccine

Traditional Vaccines



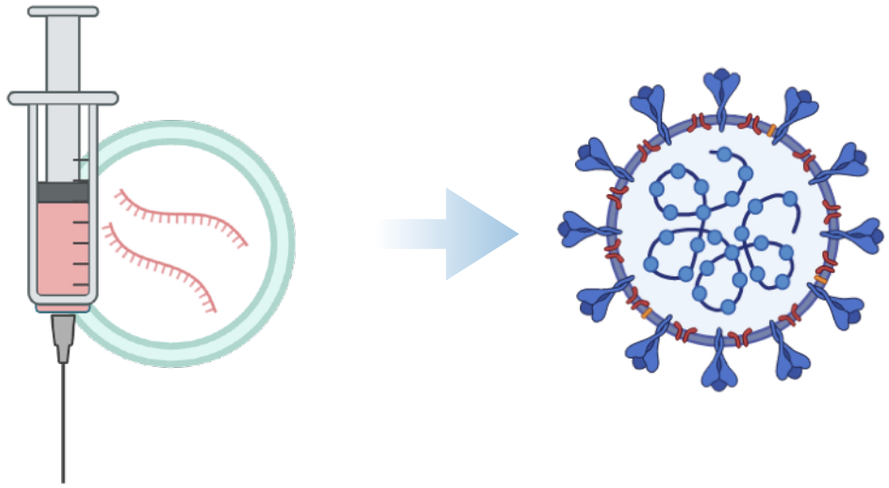
Inactivated (killed)
e.g. HepA, Flu, Polio

Live attenuated
e.g. MMR, Rotavirus,
Smallpox, Chickenpox



Subunit/Toxoid
HepB, HPV, Diphtheria,
Tetanus, Meningococcal

RNA Vaccines



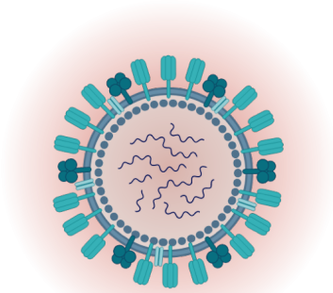
mRNA vaccine against SARS-CoV-2

US Department of Health and Human Services.

Vaccines: Frontline Protection from Viral and other Diseases

Classes of vaccine

Traditional Vaccines



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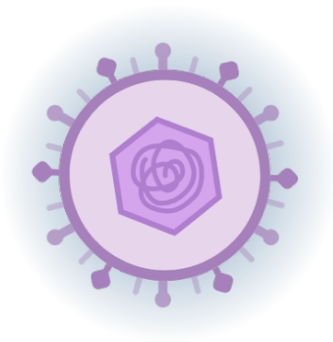

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e.g. MMR, Rotavirus,
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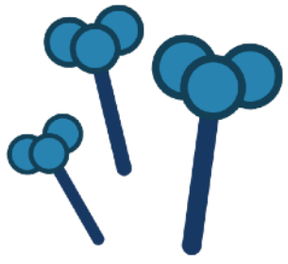

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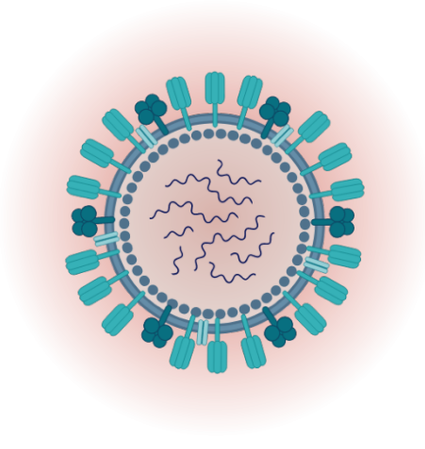
Vaccines: Frontline Protection from Viral and other Diseases

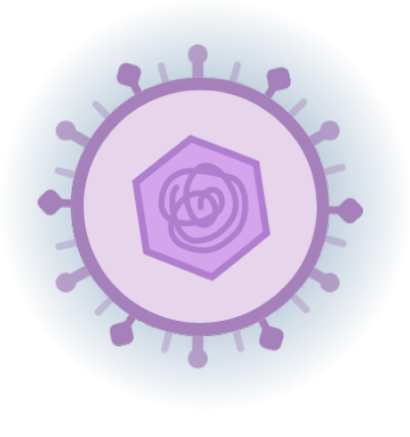


Inactivated Vaccines

- *Inactivated with heat or chemicals (ethylenimine, formaldehyde)*
- *Incredibly safe, cannot cause infection*
- *Stable, easily mass produced*
- *Primarily function through initial BCR activation*
- *Weaker immune activation*
- *Requires numerous doses*

US Department of Health and Human Services.

Vaccines: Frontline Protection from Viral and other Diseases

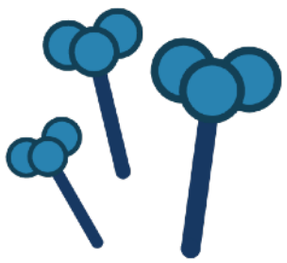


Live Attenuated Vaccines

- *In vitro viral passaging results in mutations depleting viral dangers*
- *Target macrophages and dendritic cells*
- *Potent, provide long lasting immunity*
- *Require refrigeration to remain stable*
- *Attenuated virus can regain pathogenicity, can rarely cause disease outbreaks*

US Department of Health and Human Services.

Vaccines: Frontline Protection from Viral and other Diseases



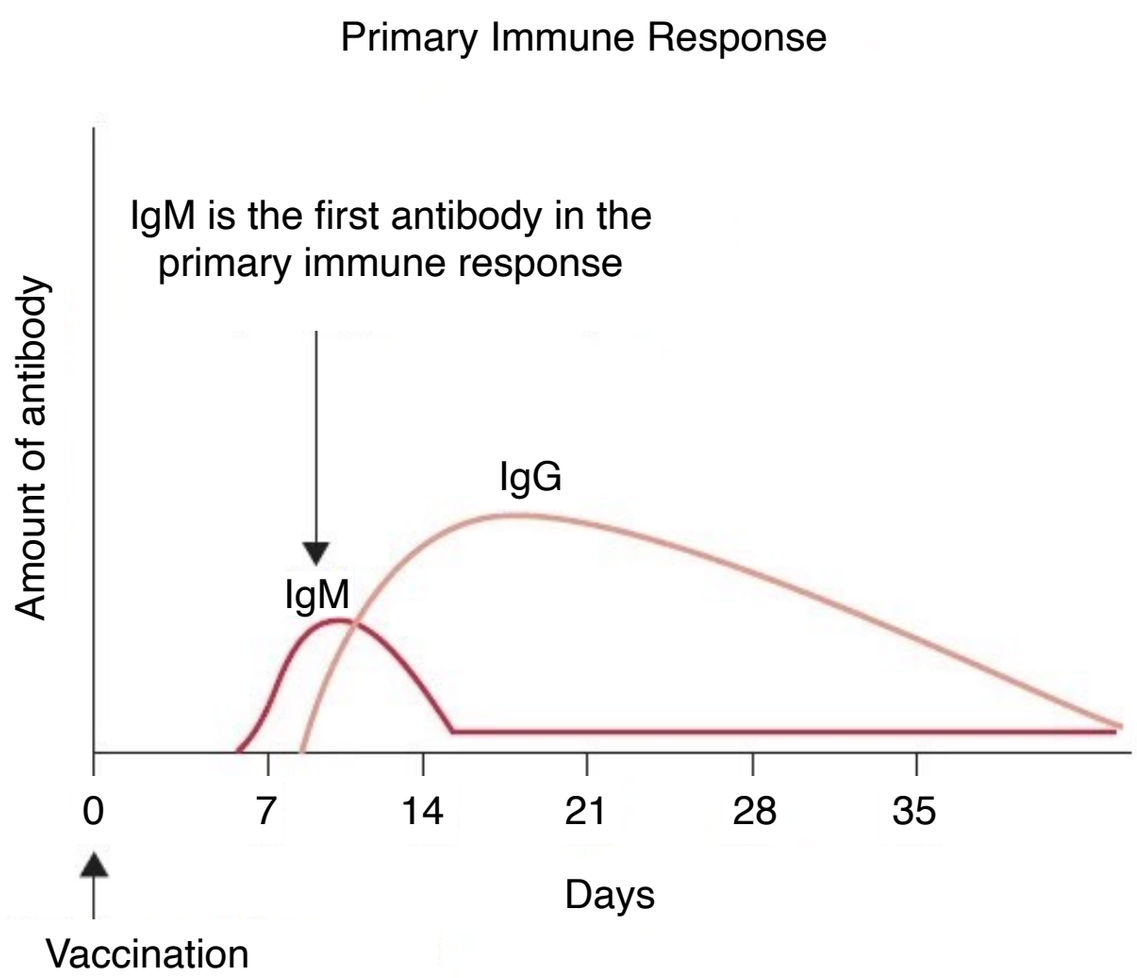
Subunit/Toxoid Vaccines

- *Viral or bacterial proteins or inactivated toxins promote immunity*
- *Targets APCs and BCR*
- *Often long lasting immunity, very safe*
- *Require adjuvant to boost immune response*
- *Requires optimization of adjuvant and subunit to promote proper immunity*

US Department of Health and Human Services.

Vaccines: Frontline Protection from Viral and other Diseases

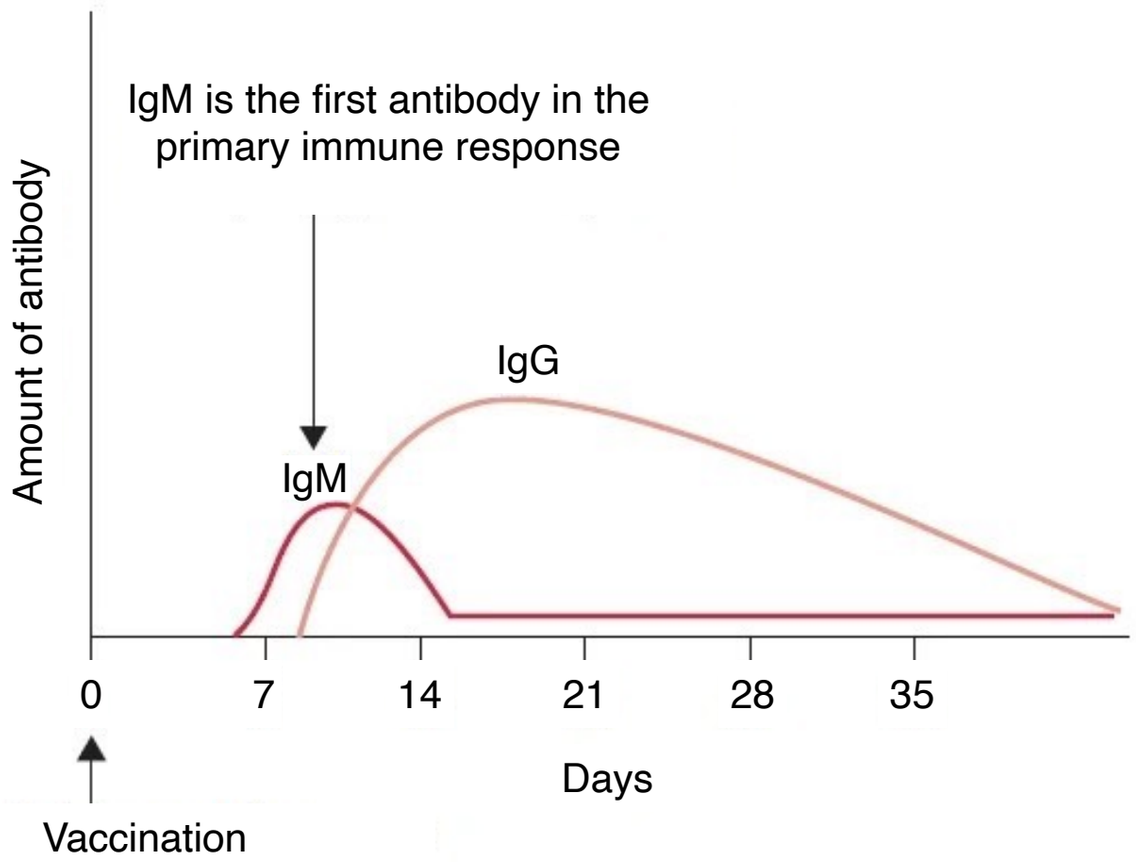
Distinctions between vaccine types



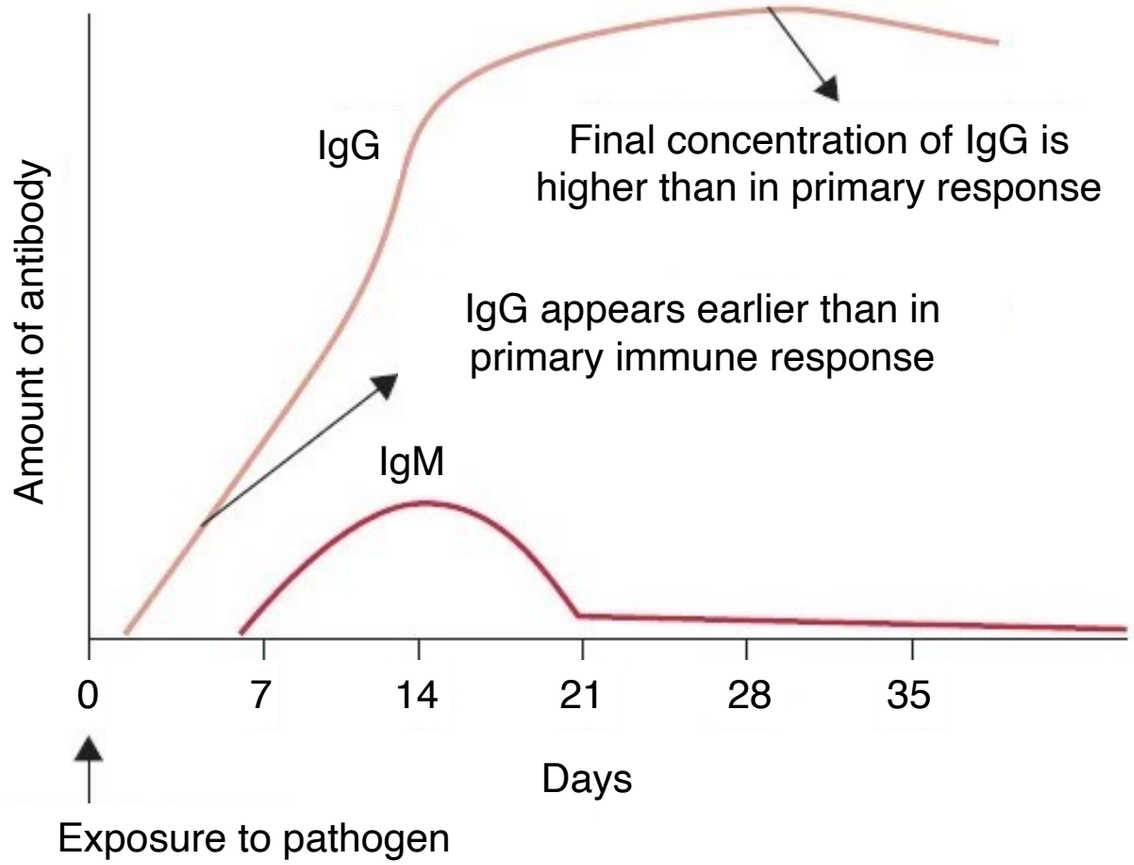
Vaccines: Frontline Protection from Viral and other Diseases

Distinctions between vaccine types

Primary Immune Response

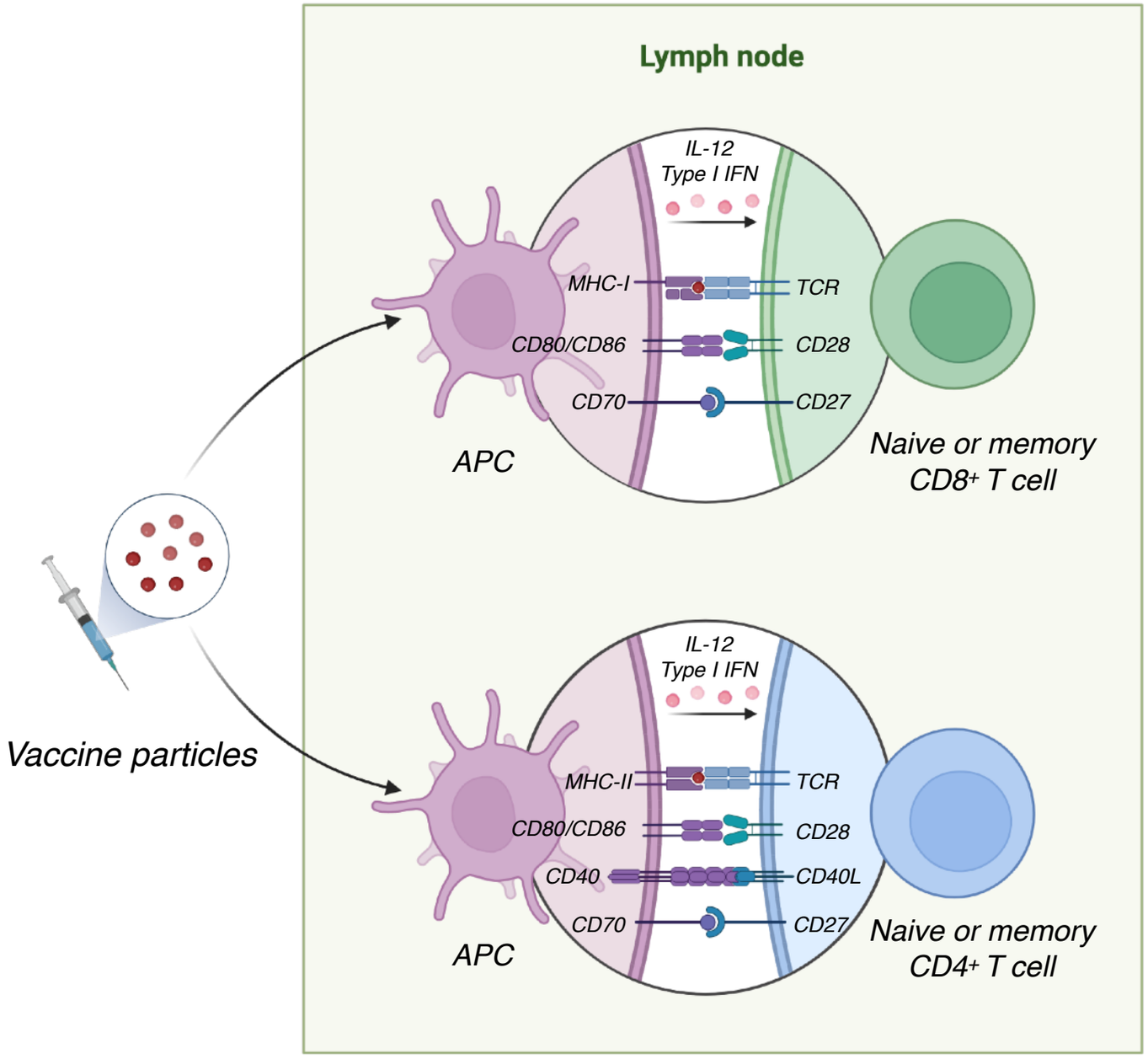


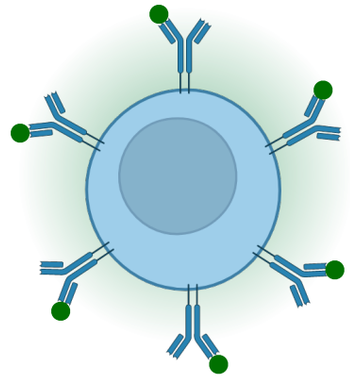
Secondary Immune Response



Vaccines: Frontline Protection from Viral and other Diseases

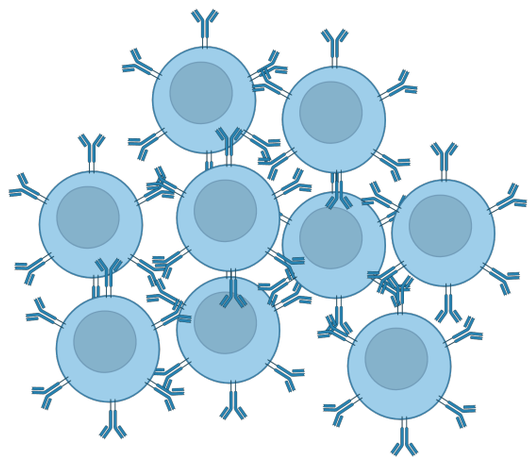
Vaccination mechanism





Mature B cell
binds antigen

Co-activation by T cell
targeting antigen



Clonal expansion, somatic
hypermutation, class switching

Vaccines: Frontline Protection from Viral and other Diseases

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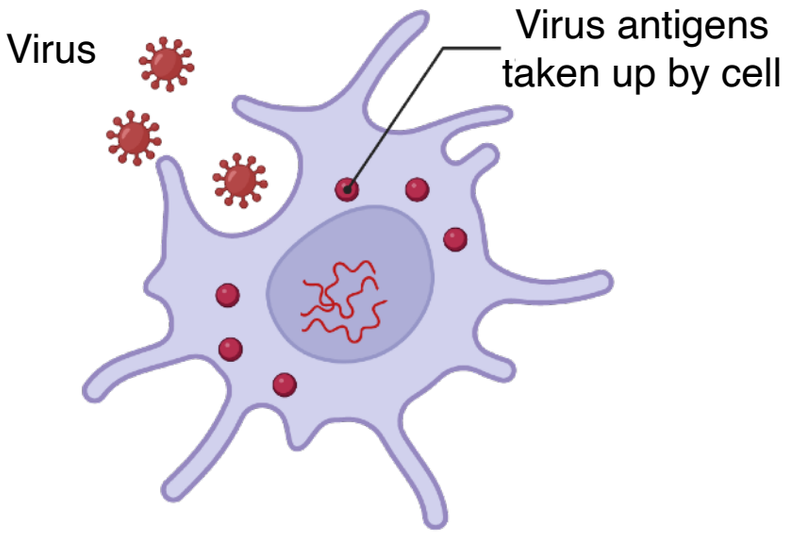
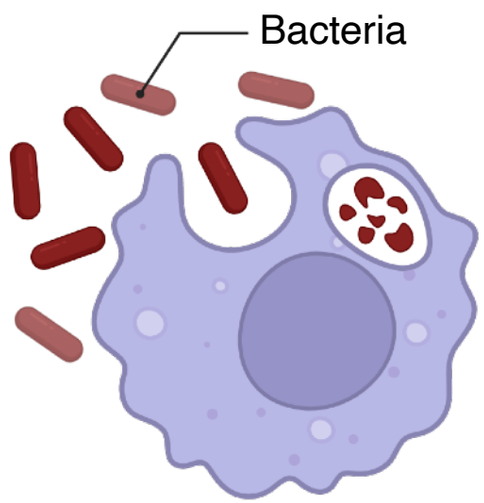
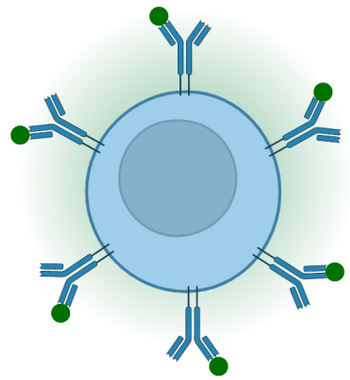


Virus infecting
dendritic cell



Bacteria infecting
macrophage

Viral vaccines often target DCs first while bacterial vaccines target macrophages



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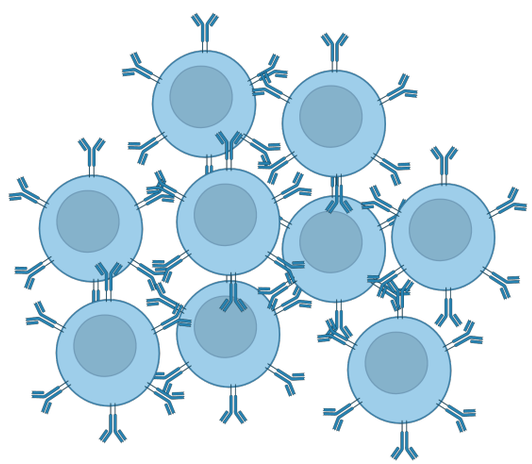

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Vaccines: Frontline Protection from Viral and other Diseases

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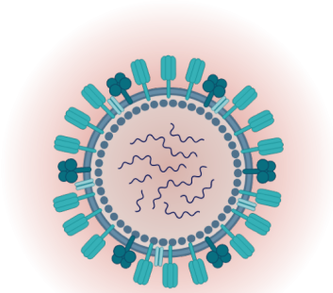

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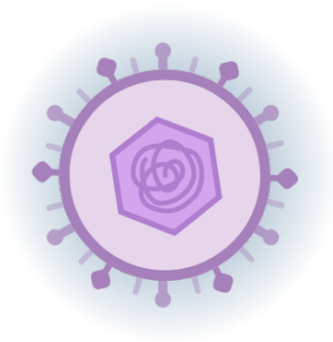

Live attenuated
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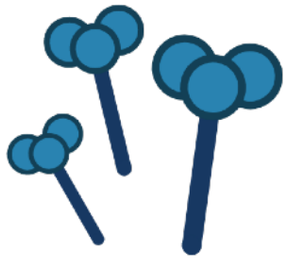

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RNA Vaccines

mRNA vaccine against SARS-CoV-2

US Department of Health and Human Services.

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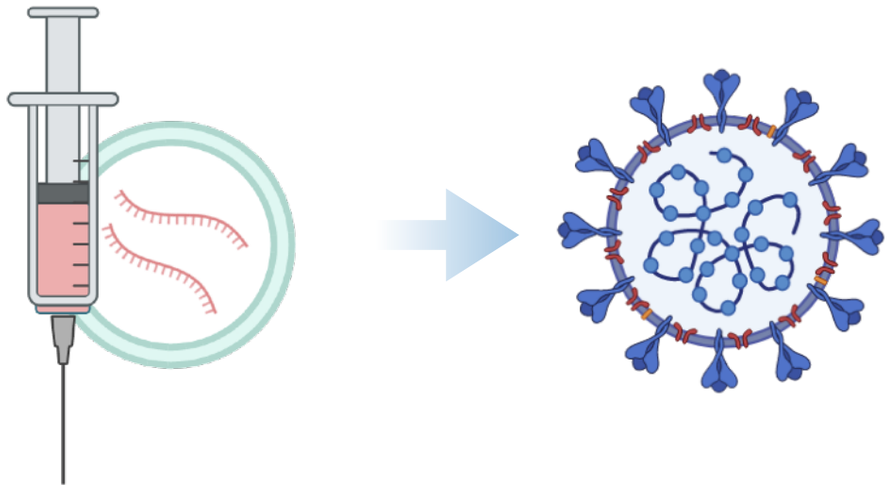

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US Department of Health and Human Services.

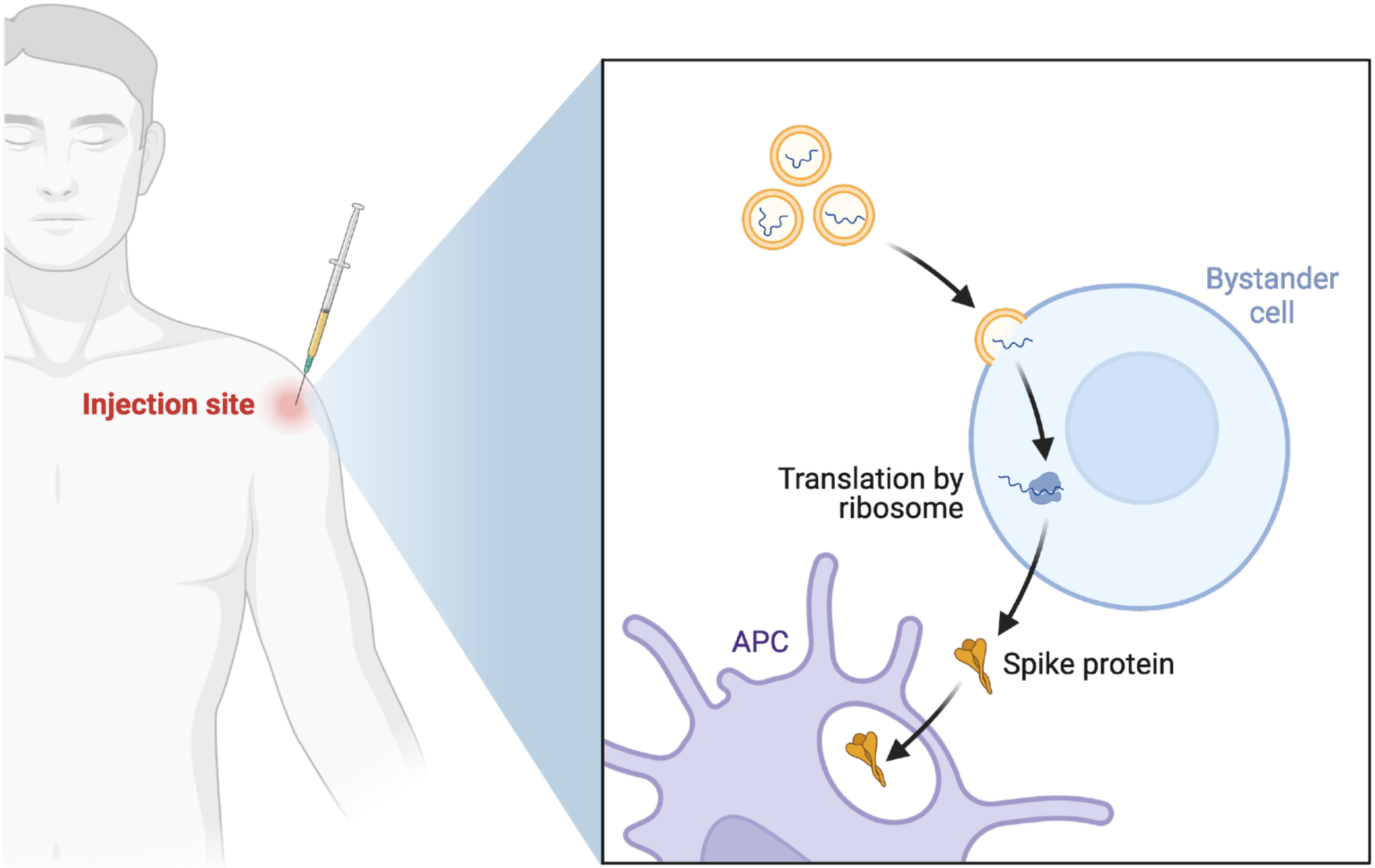
The New York Times

New Pfizer Results: Coronavirus Vaccine Is Safe and 95% Effective

The company said it planned to apply for emergency approval from the Food and Drug Administration "within days."

Vaccines: Frontline Protection from Viral and other Diseases

mRNA vaccine function



Vaccines: Frontline Protection from Viral and other Diseases

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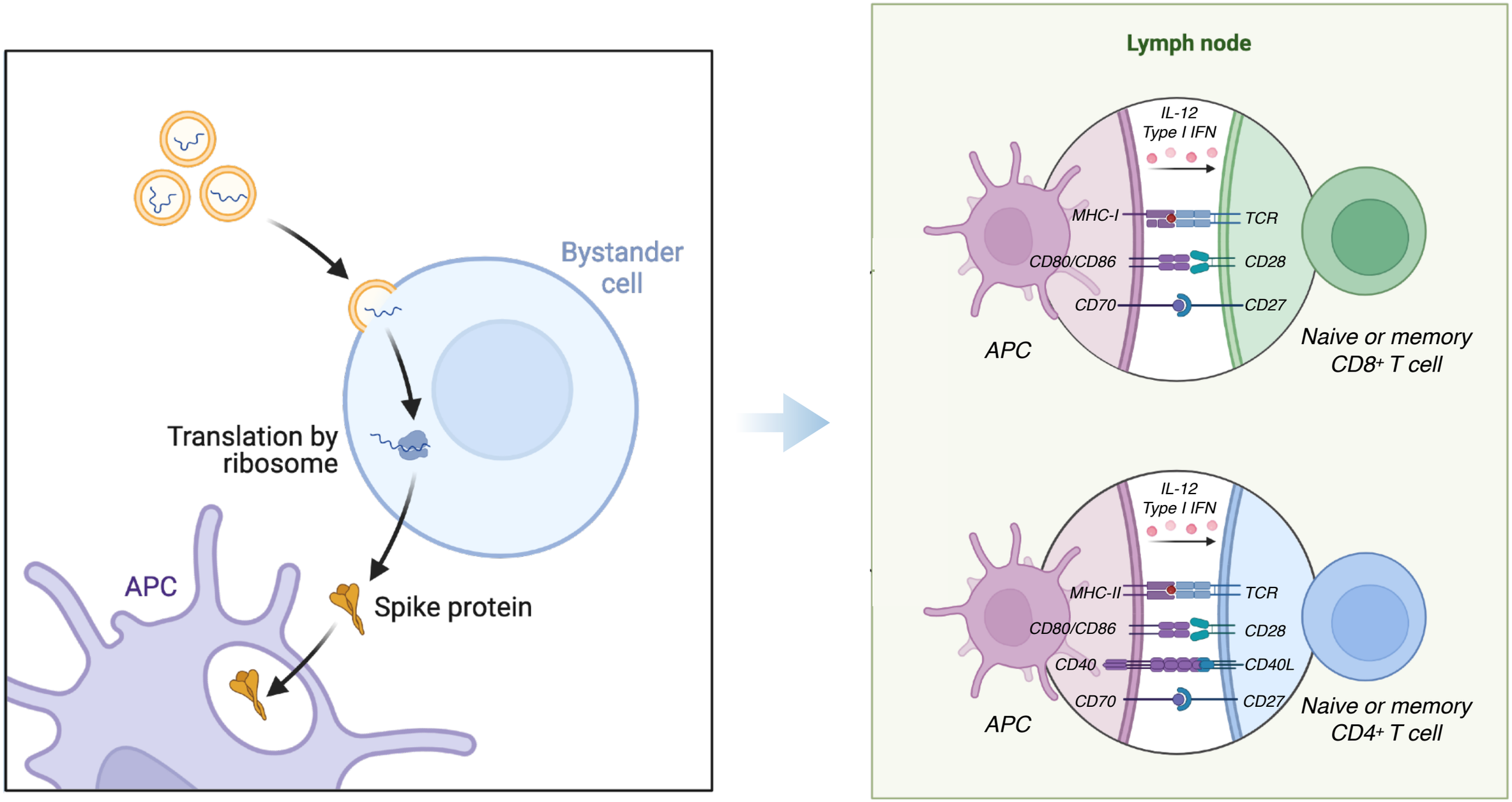

Vaccines: Frontline Protection from Viral and other Diseases

Why are certain types of vaccines used instead of others?

Case Study: Polio Inactivated and Live Vaccines

Before widespread immunization, Polio caused 500,000 deaths or paralyzes per year

Mehndiratta, M. M. *Neurohospitalist*. **2014**, *4*(4), 223-229.

History of Polio Vaccination. The World Health Organization.

Case Study: Polio Inactivated and Live Vaccines

Only two countries with endemic poliovirus as of 2020

Mehndiratta, M. M. *Neurohospitalist*. **2014**, *4*(4), 223-229.
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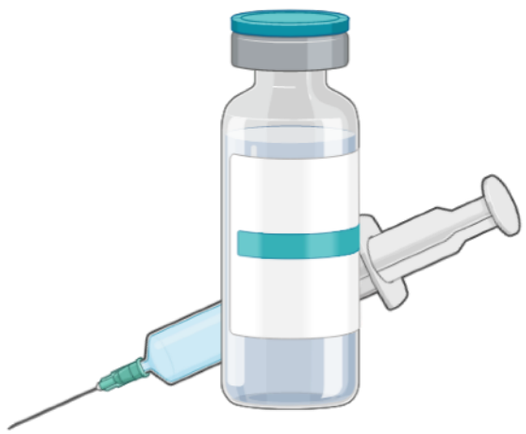
Case Study: Polio Inactivated and Live Vaccines

Inactivated poliovirus vaccine (IPV)

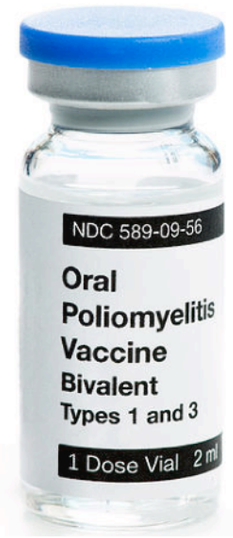


Contains inactivated version of all 3 polio strains

Promotes immunity in bloodstream, prevents disease but less effective at infection prevention

Cannot cause paralysis

Oral Poliovirus Vaccines (OPVs)



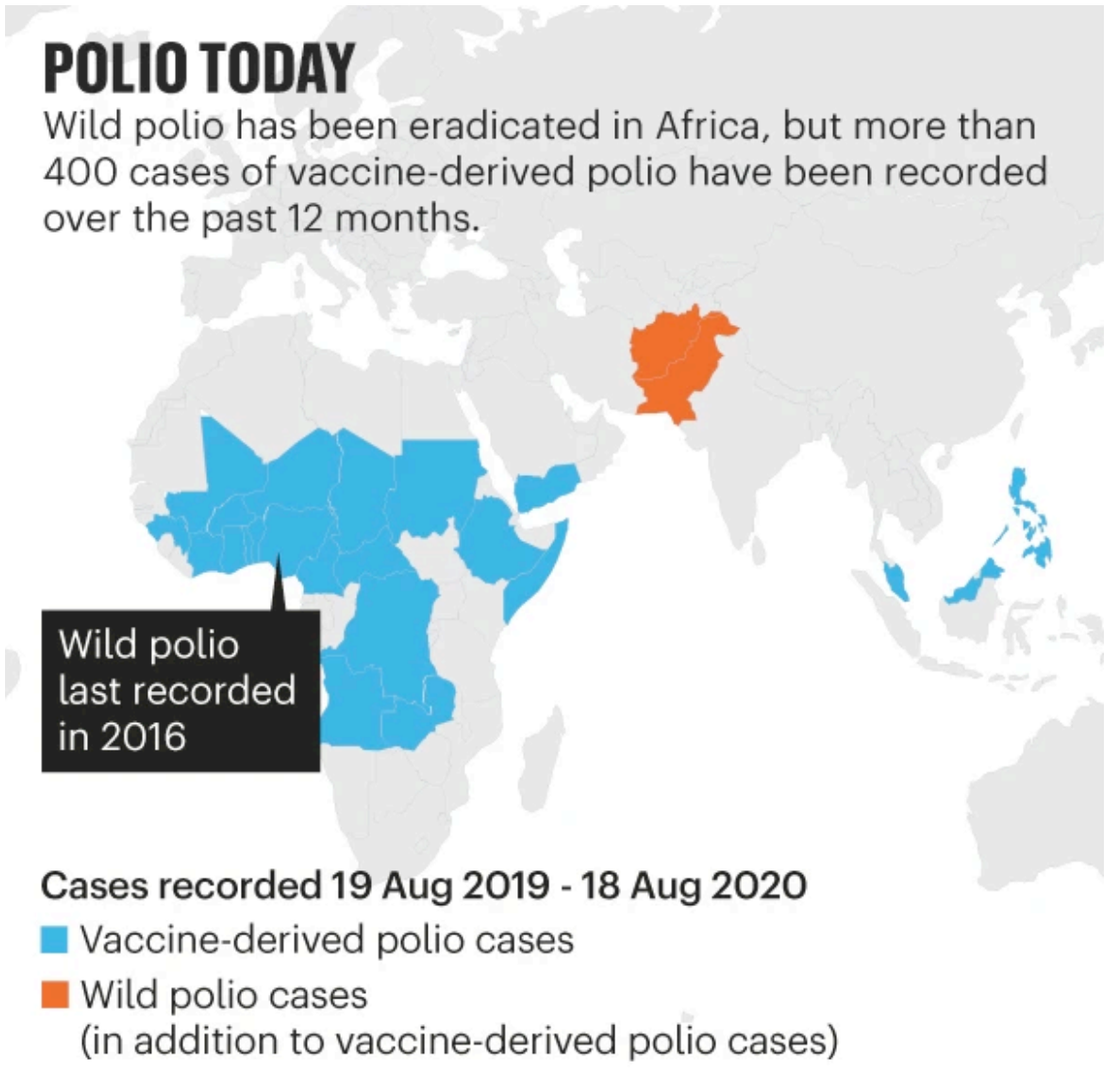
Contains attenuated version of 1-3 polio strains

Promotes immunity in intestine, prevents paralysis and transmission

Attenuated virus mutates and causes paralysis, infectious disease in 1 out of 2.4 million cases.

Watson, C. *Nature.* **2023**, *620*, 706-707.
Polio Vaccine. Children's Hospital of Philadelphia. **2024**.

Case Study: Polio Inactivated and Live Vaccines



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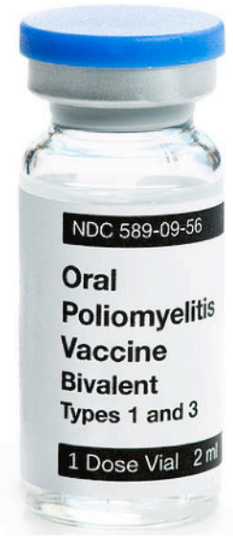

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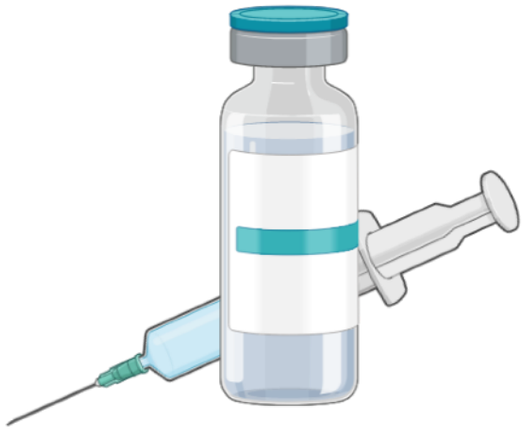
Gugliemli, G. *Nature*. **2020**.

Case Study: Polio Inactivated and Live Vaccines

Why is OPV used anywhere?

Case Study: Polio Inactivated and Live Vaccines

Inactivated poliovirus vaccine (IPV)



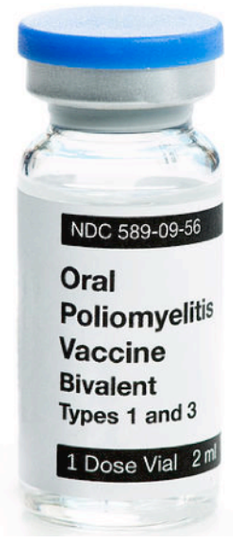
Cost per dose: $2.74

Administration cost per dose: $1.78

Total cost per dose: $4.52

Protects individual

Oral Poliovirus Vaccines (OPVs)



Cost per dose: $0.13

Administration cost per dose: $0.95

Total cose per dose: $1.08

Protects community

Socioeconomic factors play large role in vaccine usage, availability

Thompson, K. M., Kalkowsa, D. A. *Risk. Anal.* **2021**, *41*(2), 349-363.

Case Study: Polio Inactivated and Live Vaccines

Novel Oral Poliovirus Vaccines (nOPVs)

Novel gene editing and analysis enabled next generation vaccines

Approved in March 2021, over one billion doses administered

Used in controlling vaccine derived polio outbreaks

Macklin, G. R. *Vaccine*. **2023**, *41*, A122-A127.

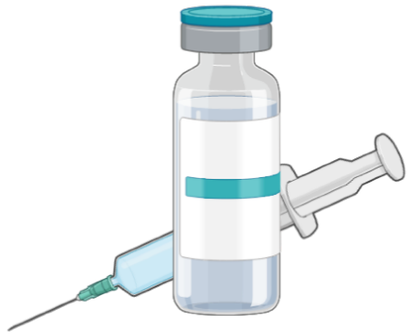
Adaptive Immune System

Enabling aspects and failures of adaptive immunity

Ultra-specific targeting

Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines



Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases

Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

Adaptive Immune System

Enabling aspects and failures of adaptive immunity

Ultra-specific targeting

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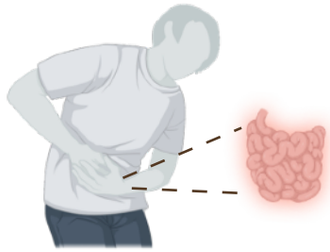
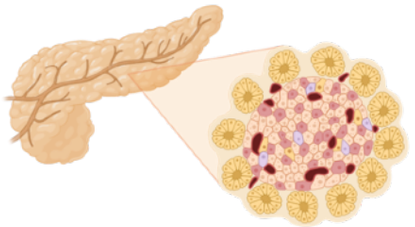
Adaptive immune diseases



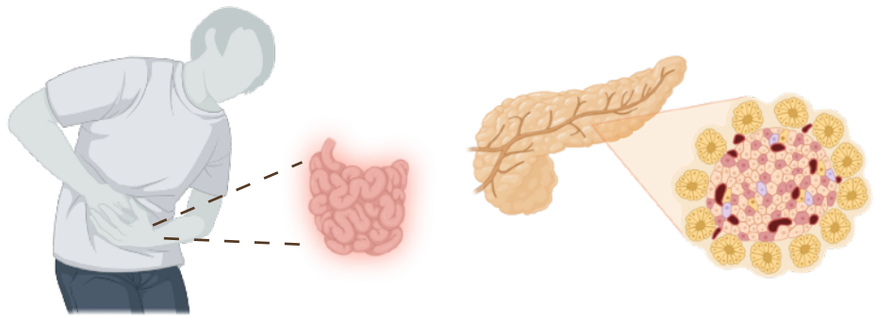


Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

Autoimmune diseases



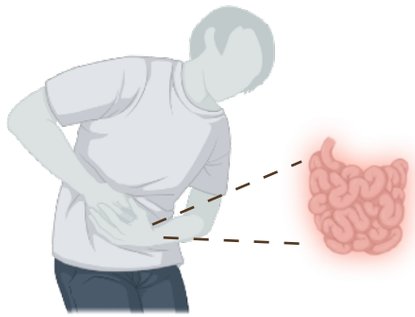
Celiac *Type 1 Diabetes*

Immune cells recognize and target self antigens

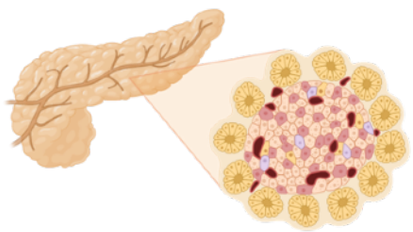
Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

Autoimmune diseases



Celiac

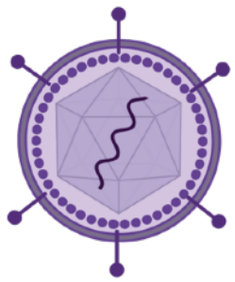


Type 1 Diabetes

Immune cells recognize and target self antigens

Pathogens of immune cells

Measles



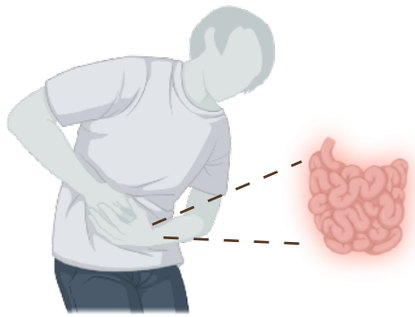
HIV

Pathogens evolved to target immune cells and evade neutralization

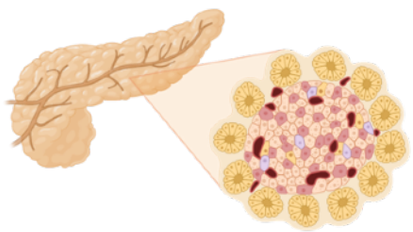
Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

Autoimmune diseases



Celiac



Type 1 Diabetes

Immune cells recognize and target self antigens

Pathogens of immune cells

Measles

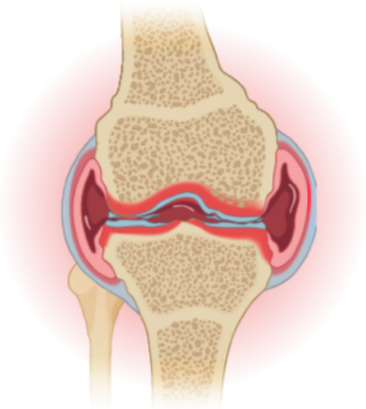
HIV

Pathogens evolved to target immune cells and evade neutralization

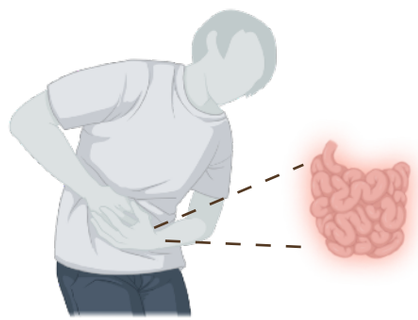
Autoimmune Diseases

Dysfunction of the adaptive immune system

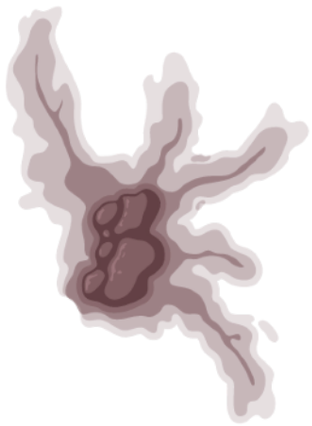
Rheumatoid Arthritis



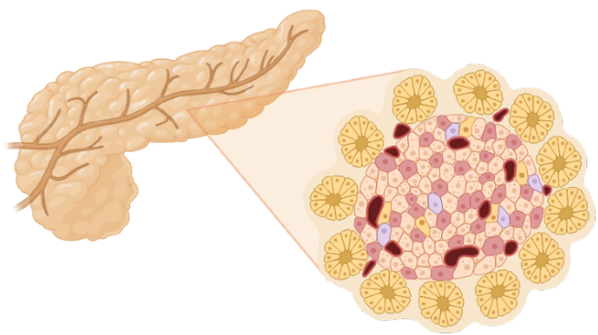
Celiac Disease



Multiple Sclerosis



Type 1 Diabetes

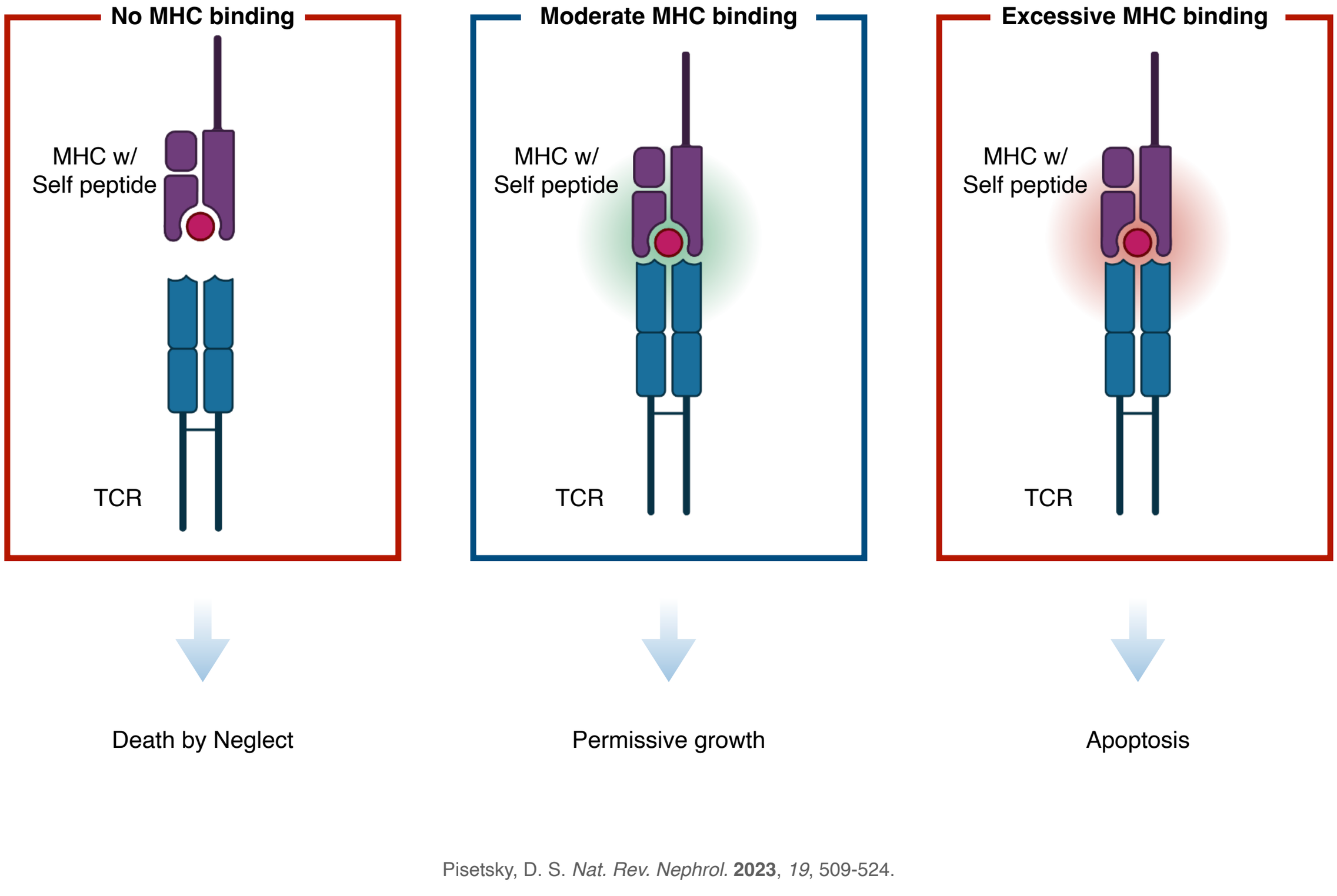


Wide variety of autoimmune diseases resulting from immune targeting of distinct tissues, organs, or non-specific self proteins

Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.

Autoimmune Diseases

Dysfunction of the adaptive immune system



Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.

Autoimmune Diseases

Dysfunction of the adaptive immune system

Autoimmune diseases

No MHC binding

MHC w/
Self peptide

TCR

Death by Neglect

Moderate MHC binding

MHC w/
Self peptide

TCR

Permissive growth

Excessive MHC binding

MHC w/
Self peptide

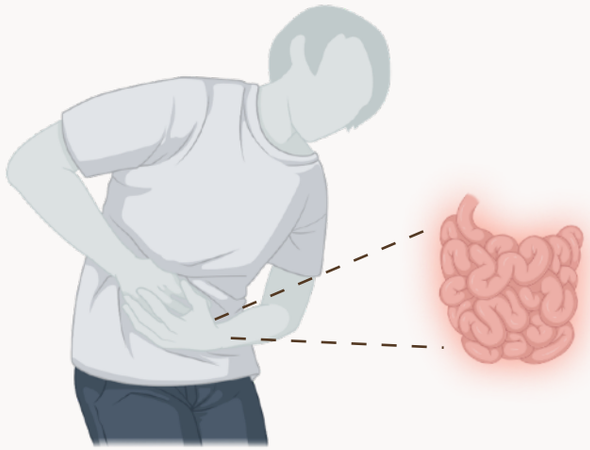
TCR

Permissive growth

Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.

Celiac Disease

Dysfunction of the adaptive immune system



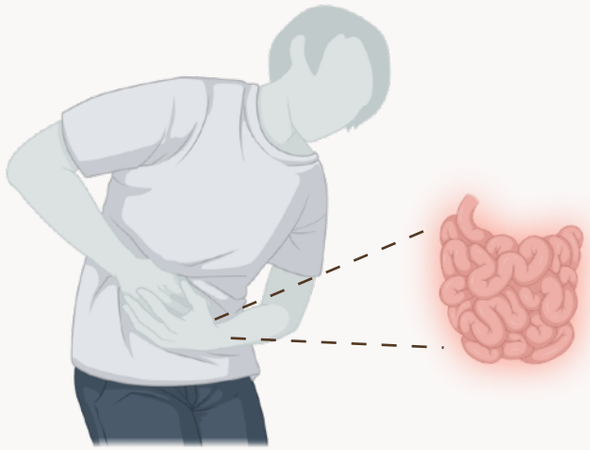
Celiac Disease

- *Autoimmune disease in small intestine*
  - *Affects 1% of world populations*
- *Results in malabsorption of nutritions and vitamins, as well as anemia, osteoporosis, infertility, cancer, etc.*

Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.
Kochhar, G. S. *et al*. *Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Celiac Disease

Dysfunction of the adaptive immune system

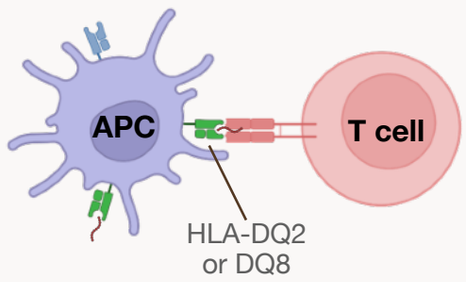


Celiac Disease

- *Autoimmune disease in small intestine*
  - *Affects 1% of world populations*
- *Results in malabsorption of nutritions and vitamins, as well as anemia, osteoporosis, infertility, cancer, etc.*

Genetic Predisposition

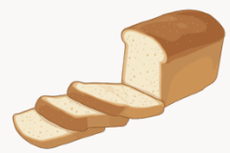
- *HLA-DQ2 or/and HLA-DQ8+ at MHC on antigen-presenting cells*



+

Environmental Factors

- *Intake of indigestible gluten, such as wheat, barley, rye, etc.*



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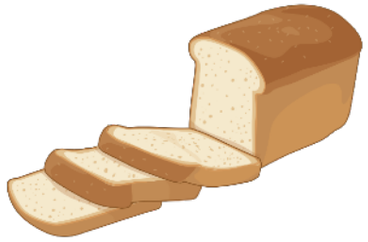
Dysfunction of the adaptive immune system



Gluten-containing food

Small intestinal lumen

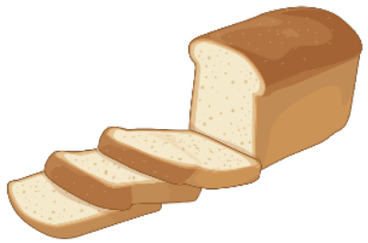
Small intestinal lamina propria

Normal conditions

Kochhar, G. S. *et al*. *Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Celiac Disease

Dysfunction of the adaptive immune system



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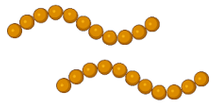

Gliadin — PQ rich peptides

Small intestinal lumen

Small intestinal lamina propria

Normal conditions

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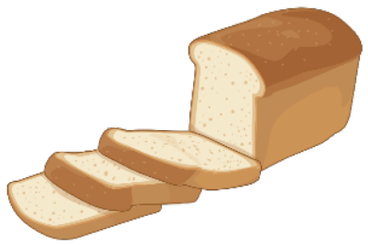
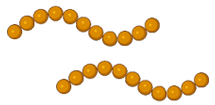
Celiac Disease

Dysfunction of the adaptive immune system



Gluten-containing food



Gliadin — PQ rich peptides

Small intestinal lumen

Small intestinal lamina propria

Transglutaminase

TG2

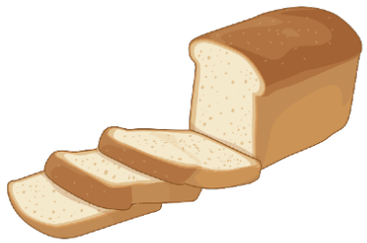
Deamidated gliadin

Normal conditions

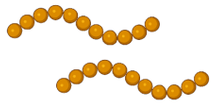
Kochhar, G. S. *et al. Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Celiac Disease

Dysfunction of the adaptive immune system



Gluten-containing food



Gliadin — PQ rich peptides

Small intestinal lumen

Small intestinal lamina propria

Transglutaminase

TG2

Deamidated gliadin

Disease conditions

HLA-DQ2/DQ8+
Antigen-presenting cell

APC

T cell

Activated T cell

Kochhar, G. S. *et al. Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Celiac Disease

Dysfunction of the adaptive immune system

Gluten-containing food

Gliadin — PQ rich peptides

Small intestinal lumen

Transglutaminase

TG2

Deamidated gliadin

HLA-DQ2/DQ8+
Antigen-presenting cell

APC

T cell

Disease conditions

Immunological response

Small intestinal lamina propria

Cytotoxic T cell

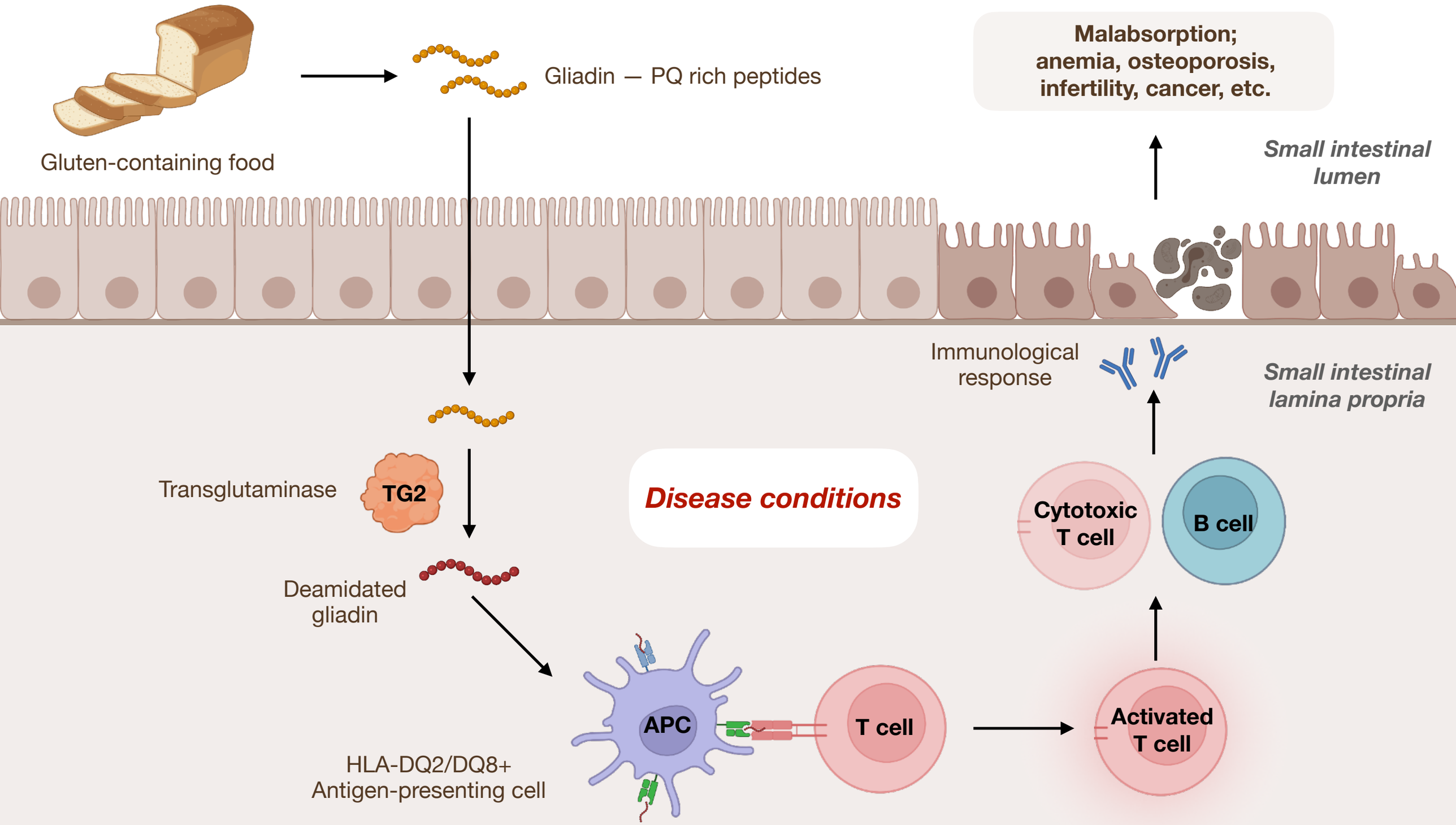
B cell

Activated T cell

Kochhar, G. S. *et al. Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Celiac Disease

Dysfunction of the adaptive immune system



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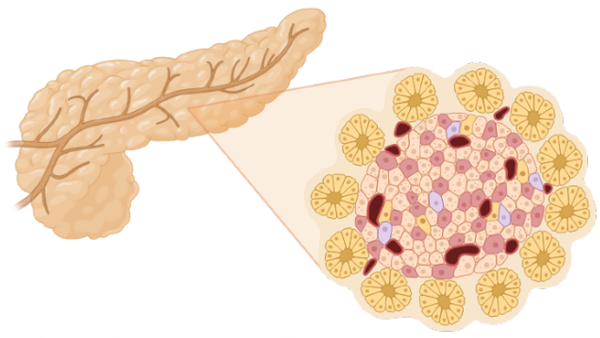
Kochhar, G. S. *et al. Cleve. Clin. J. Med.* **2016**, *83*, 217-227.

Type 1 Diabetes

Dysfunction of the adaptive immune system



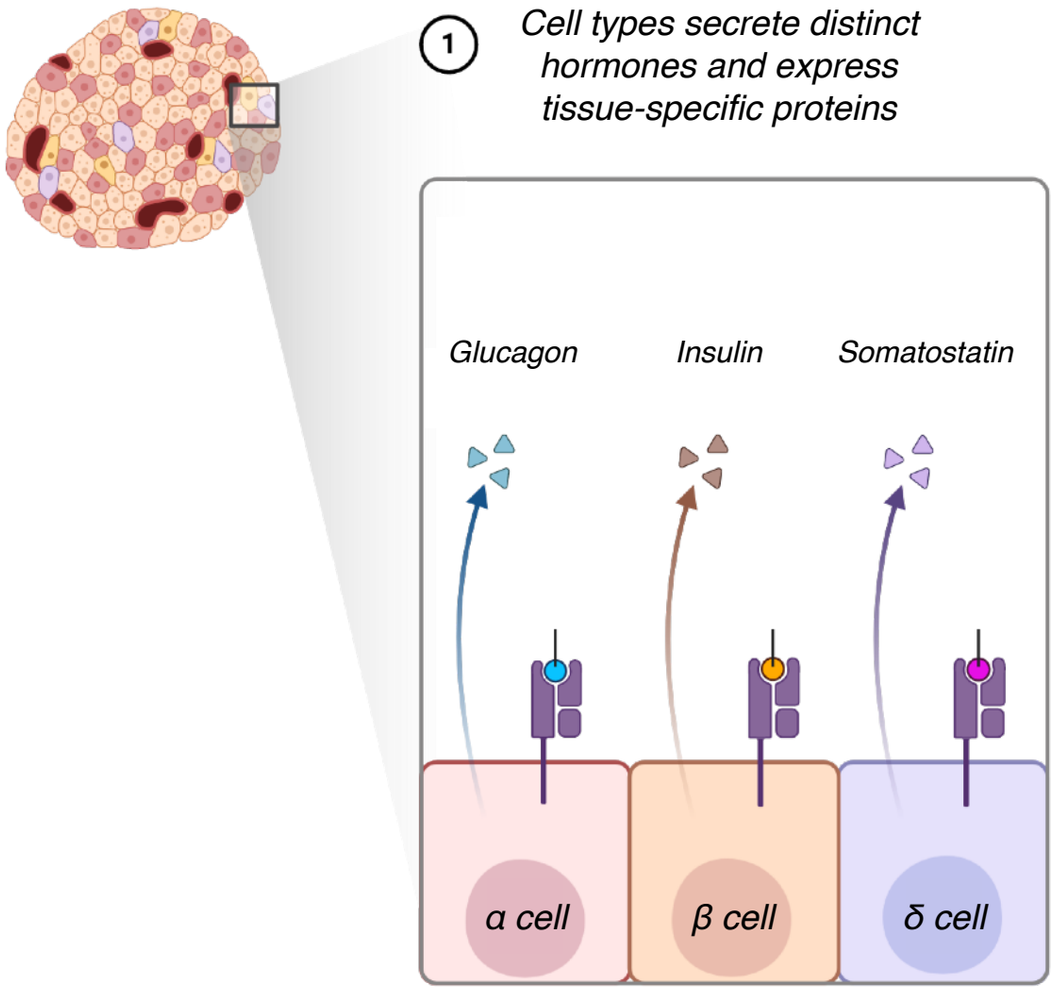
Autoimmune disease of the pancreas

The Growing Global Burden of T1D. Juvenile Diabetes Cure Alliance. **2022**.
Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.
Choy, E. H. S., Panayi, G. S. *NEJM*. **2001**, *344*, 907-916.

Type 1 Diabetes

Dysfunction of the adaptive immune system

Islets of Langerhans in the pancreas



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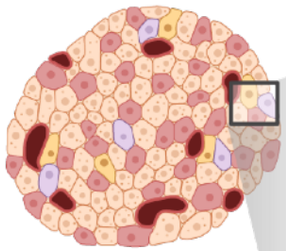
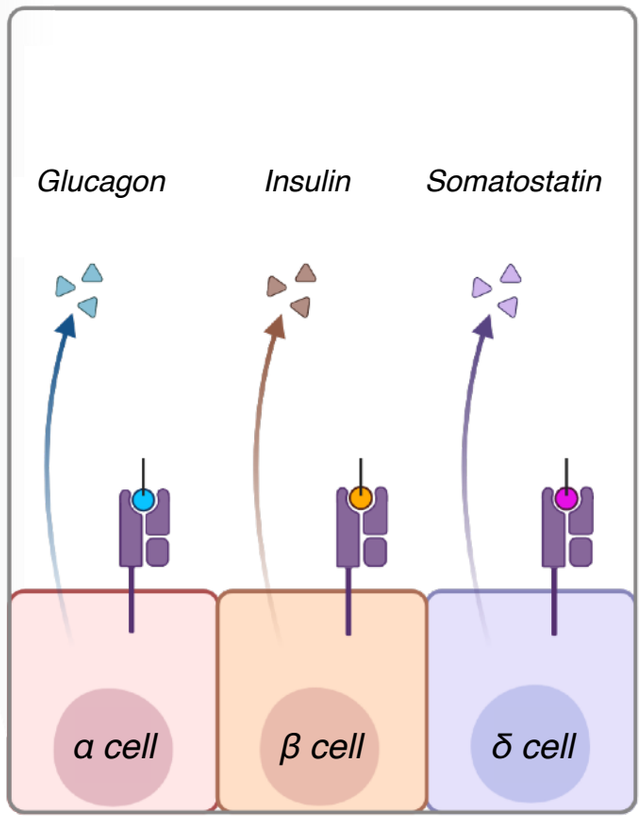
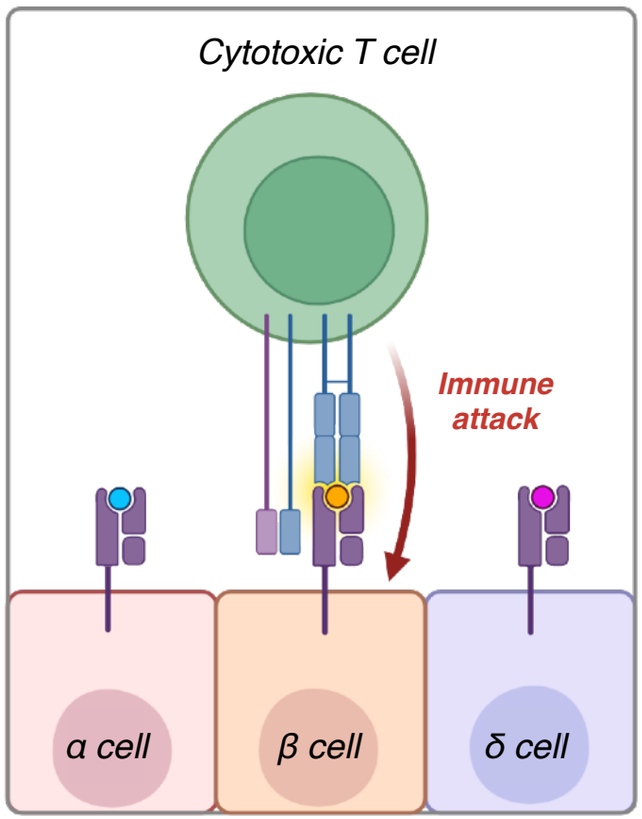


1 *Cell types secrete distinct hormones and express tissue-specific proteins*



2 *In **type 1 diabetes**, a T_{eff} cell recognizes peptides from **β cell** proteins and kills the β cell.*



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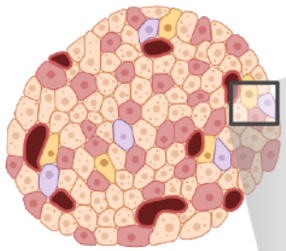

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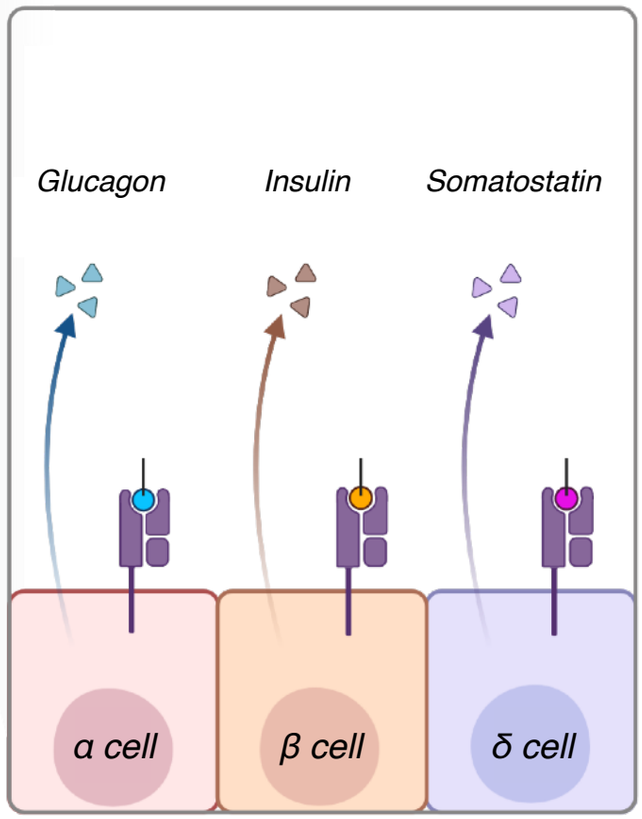

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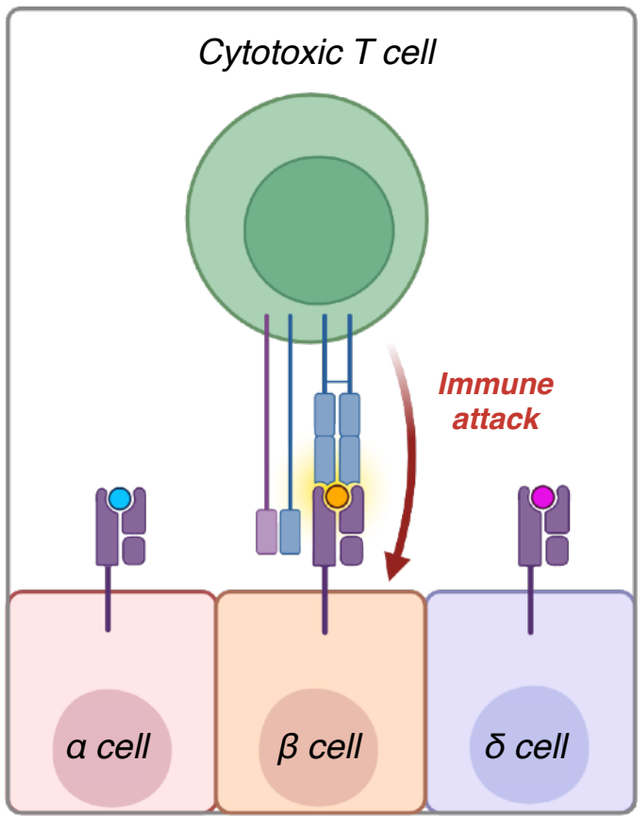
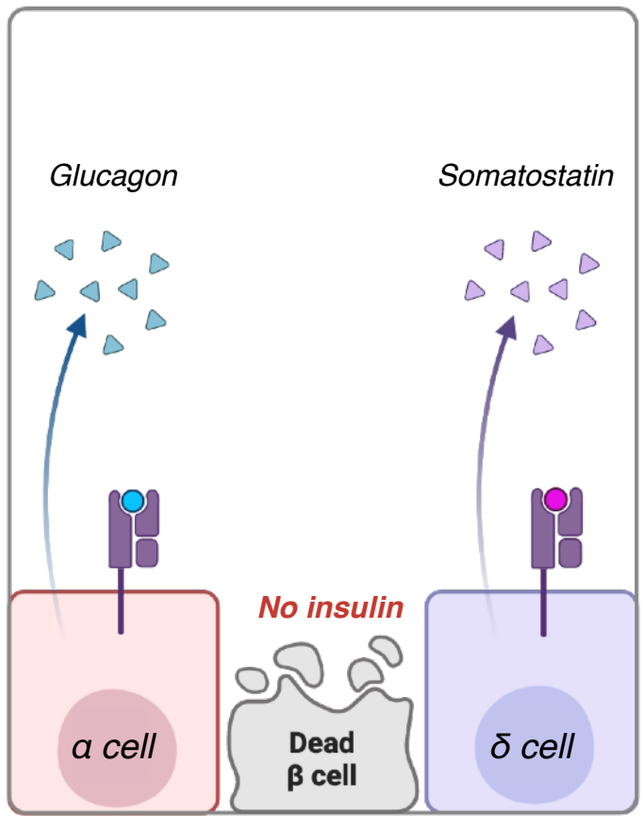


3 *Glucagon and somatostatin are produced by α and δ cells, but no insulin is produced*



Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.
Choy, E. H. S., Panayi, G. S. *NEJM*. **2001**, *344*, 907-916.

Treatments for Autoimmune Diseases

Dysfunction of the adaptive immune system

Physical Therapy	***Surgery***	***Medication***	***Hormone replacement***
			
For rheumatoid arthritis	*For Crohn's disease*	*Analgesics, anti-inflammatory, Corticosteroids*	*Insulin for diabetes*

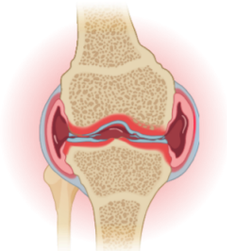
A variety of treatments exist, but no cures, indicating need for further research into adaptive immunity

Pisetsky, D. S. *Nat. Rev. Nephrol.* **2023**, *19*, 509-524.
Choy, E. H. S., Panayi, G. S. *NEJM*. **2001**, *344*, 907-916.

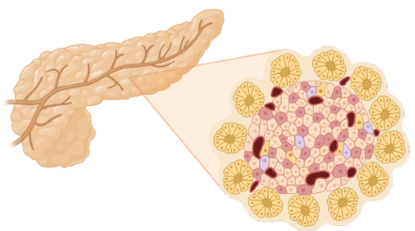
Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

Autoimmune diseases



Arthritis



Type 1 Diabetes

Immune cells recognize and target self antigens

Pathogens of immune cells

Measles

HIV

Pathogens evolved to target immune cells and evade neutralization

Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

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Pathogens evolved to target immune cells and evade neutralization

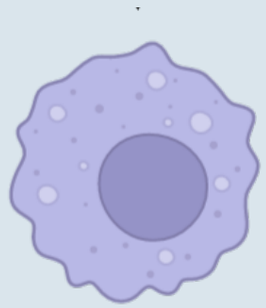
Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

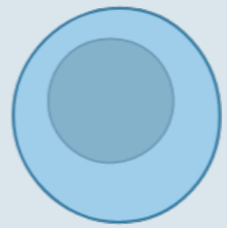
Measles

Targets CD150 surface marker

Dendritic cell



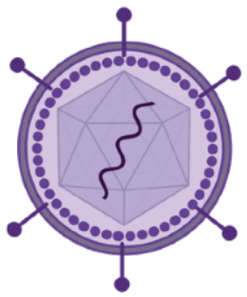
Macrophage



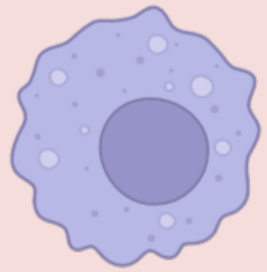
B cell

T cell

HIV



Targets CD4, CCR5 surface markers



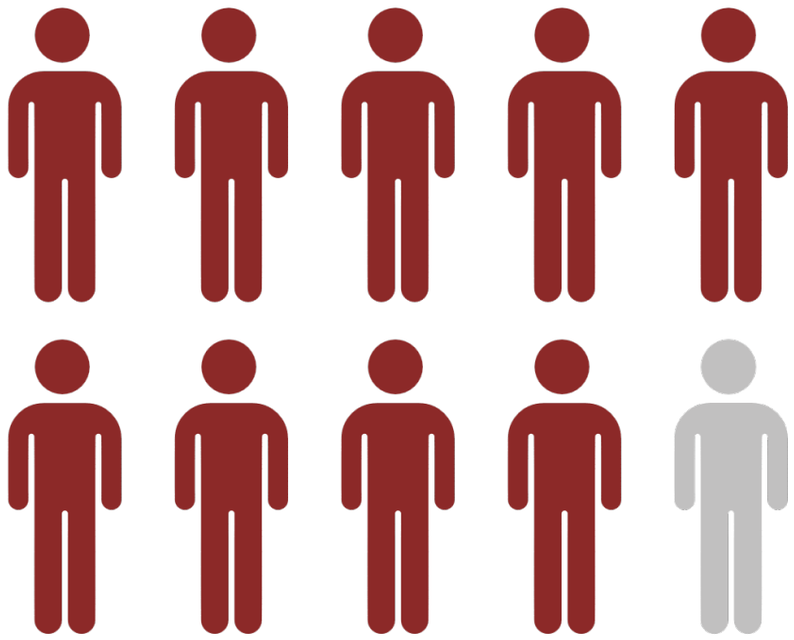
Macrophage

CD4⁺ T cell

Adaptive Immune Diseases

Failures and pathogens of adaptive immune cells

Measles



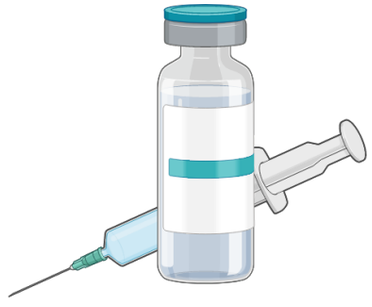
Extremely transmissible

90% of exposed unvaccinated people develop disease

3% of patients die or experience brain damage

Many severe effects occur after recovery from measles

97% Effective Vaccine



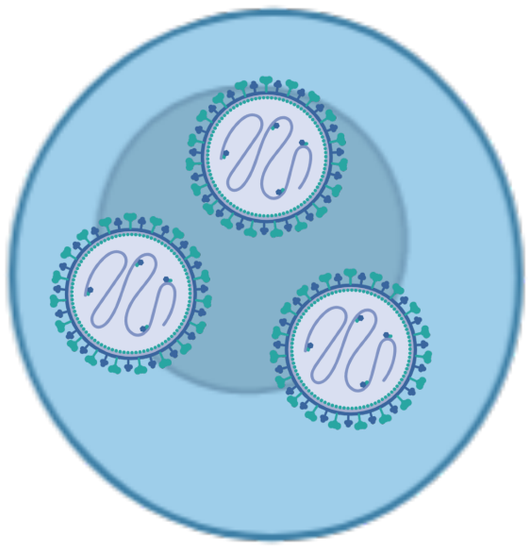
No treatment

Hagen, A. *American Society for Microbiology*. **2019**.

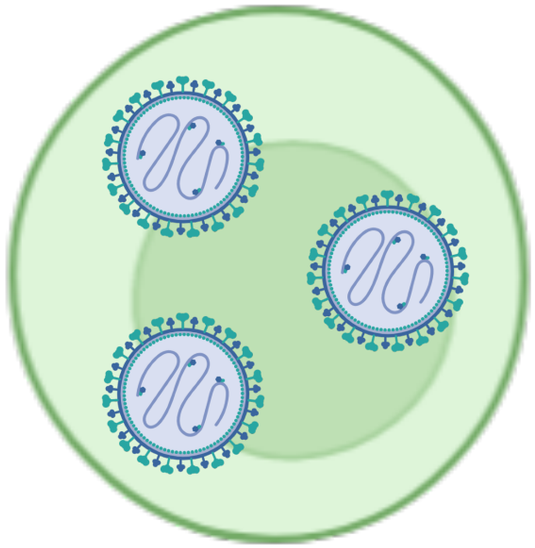
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Measles infected memory B cell



Measles infected memory T cell



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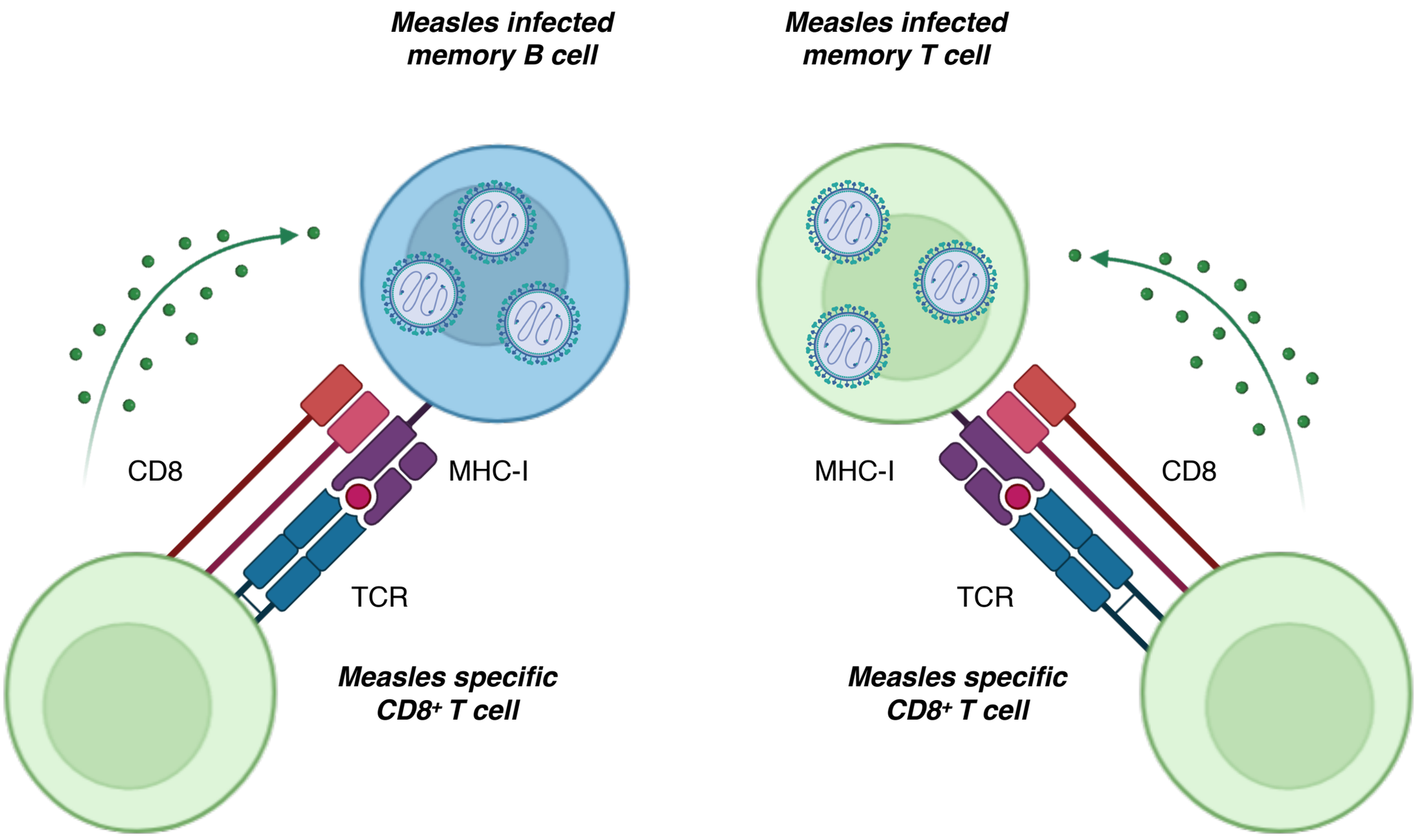
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells



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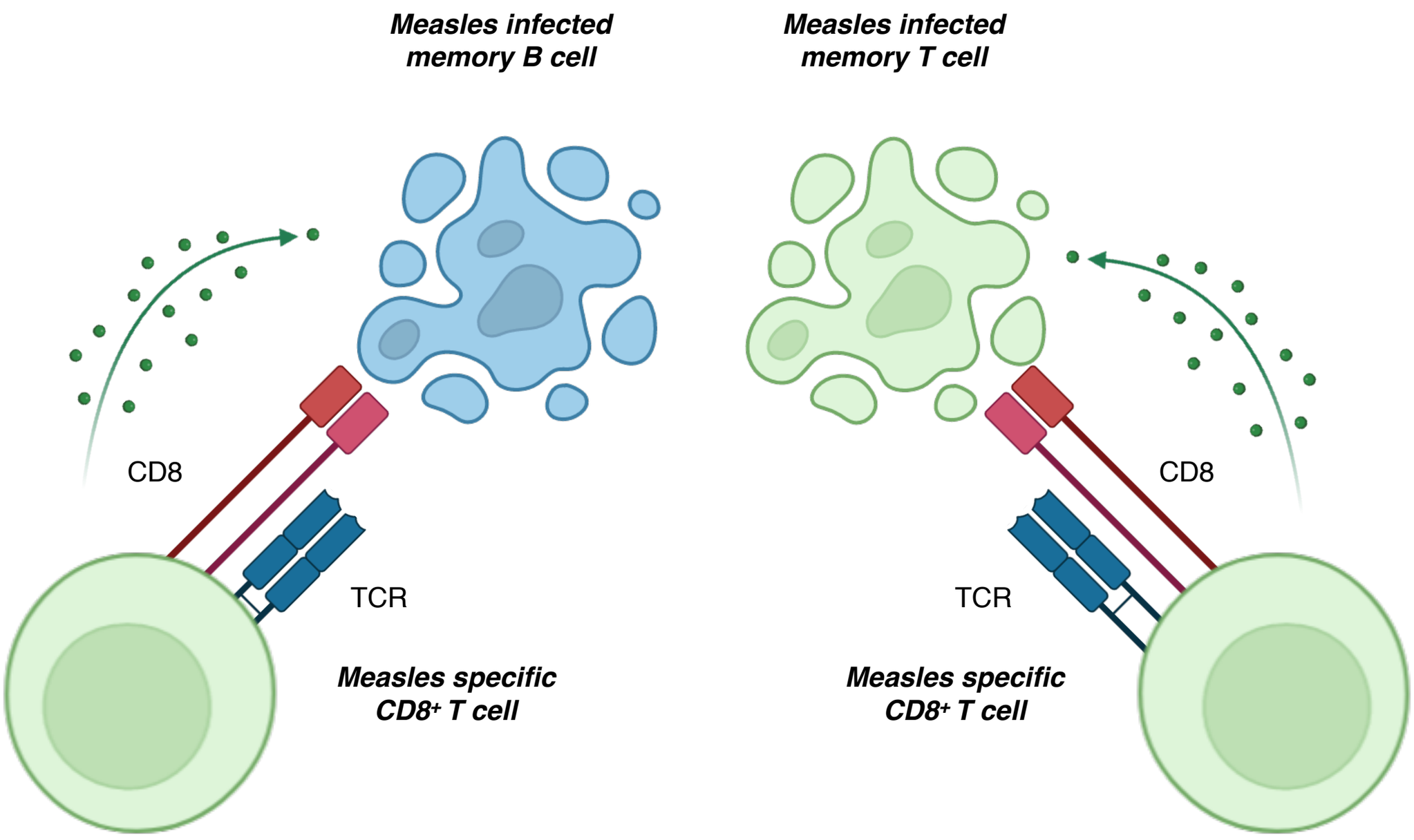
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells



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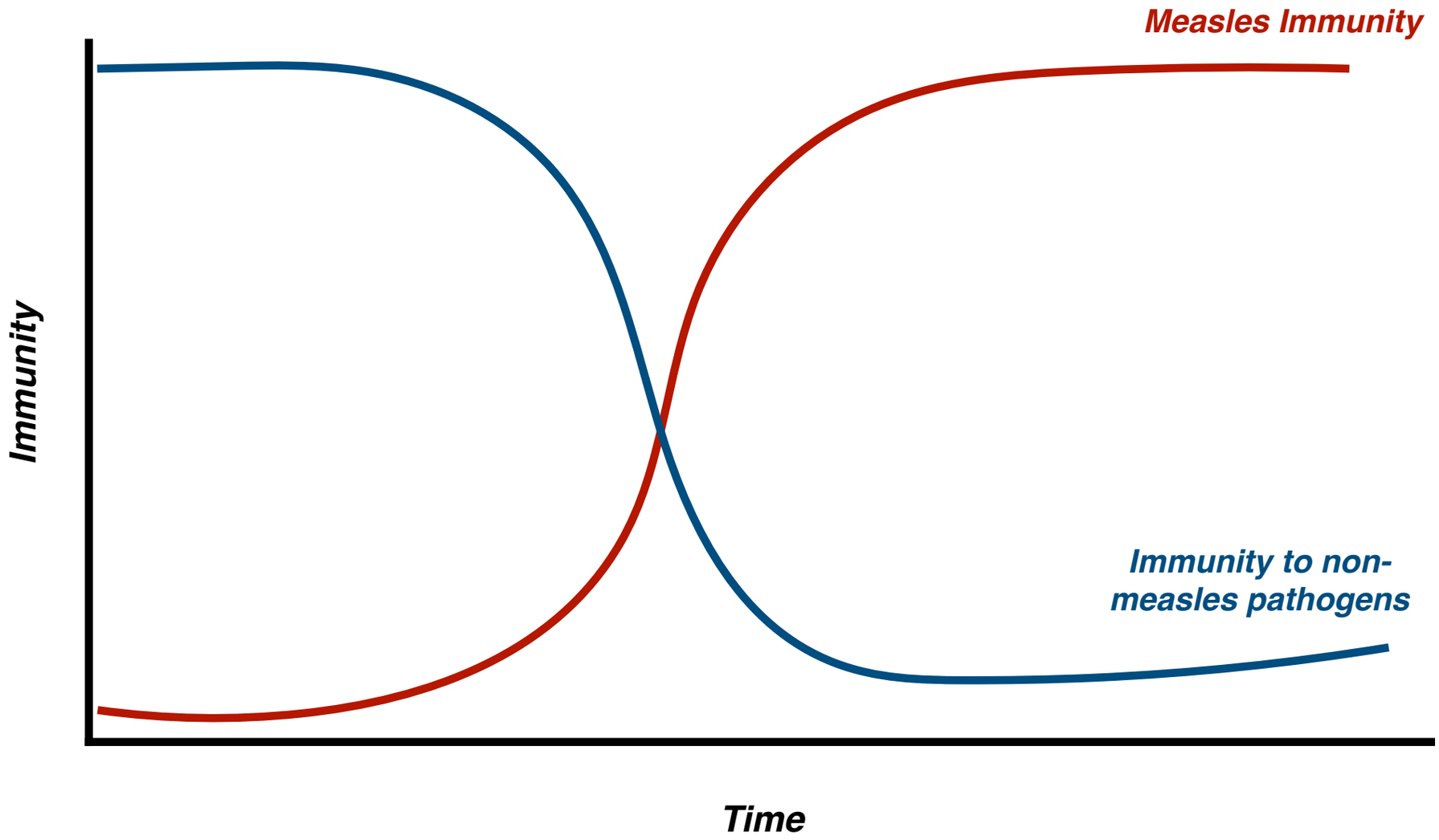
Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells



Recovery from measles provides lifelong immunity to measles, deteriorates immunity to all other pathogens

Hagen, A. *American Society for Microbiology*. **2019**.

Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Five years to recover healthy levels of immunity

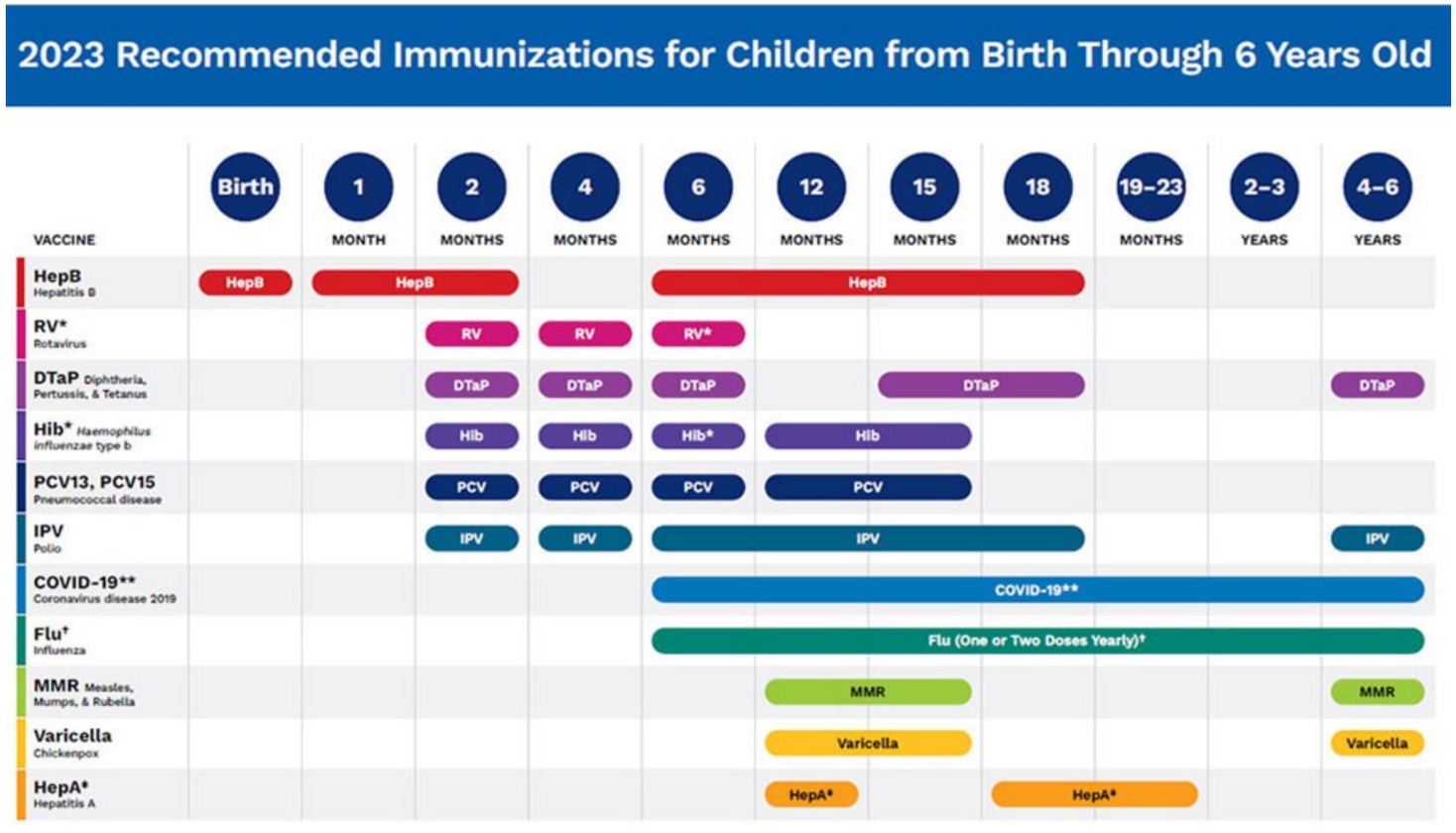
Hagen, A. *American Society for Microbiology*. **2019**.

Measles and Immune Amnesia

Failures and pathogens of adaptive immune cells

Five years to recover healthy levels of immunity

Repeated immunization



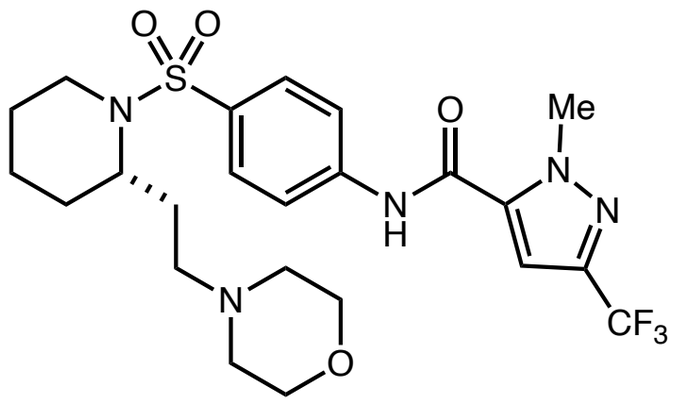
Highlights necessity of measles vaccination in all communities

Hagen, A. *American Society for Microbiology*. **2019**.

Measles and Immune Amnesia

Future therapies

Measles polymerase inhibitor



Benefits

Can decrease immune amnesia, other measles symptoms

Helps prevent lethal bacteria superinfection

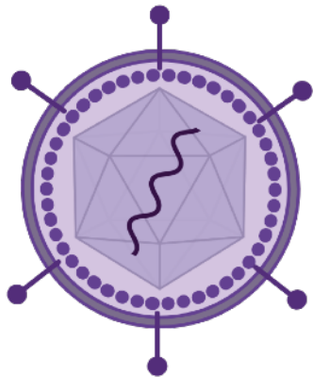
Best applied before or at peak viral titer

Cox, R. M., et al. *Nat. Commun.* **2024**, *15*, 1189.
Krumm, S. A., et al. *Sci. Transl. Med.* **2014**, *6*(232), 52.

Human Immunodeficiency Virus

Pathogenesis of HIV

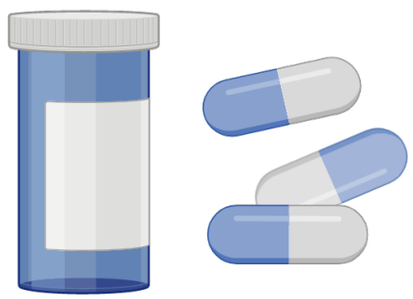
Human Immunodeficiency Virus



AIDS pandemic led to ~40 million deaths over past four decades

No vaccine available

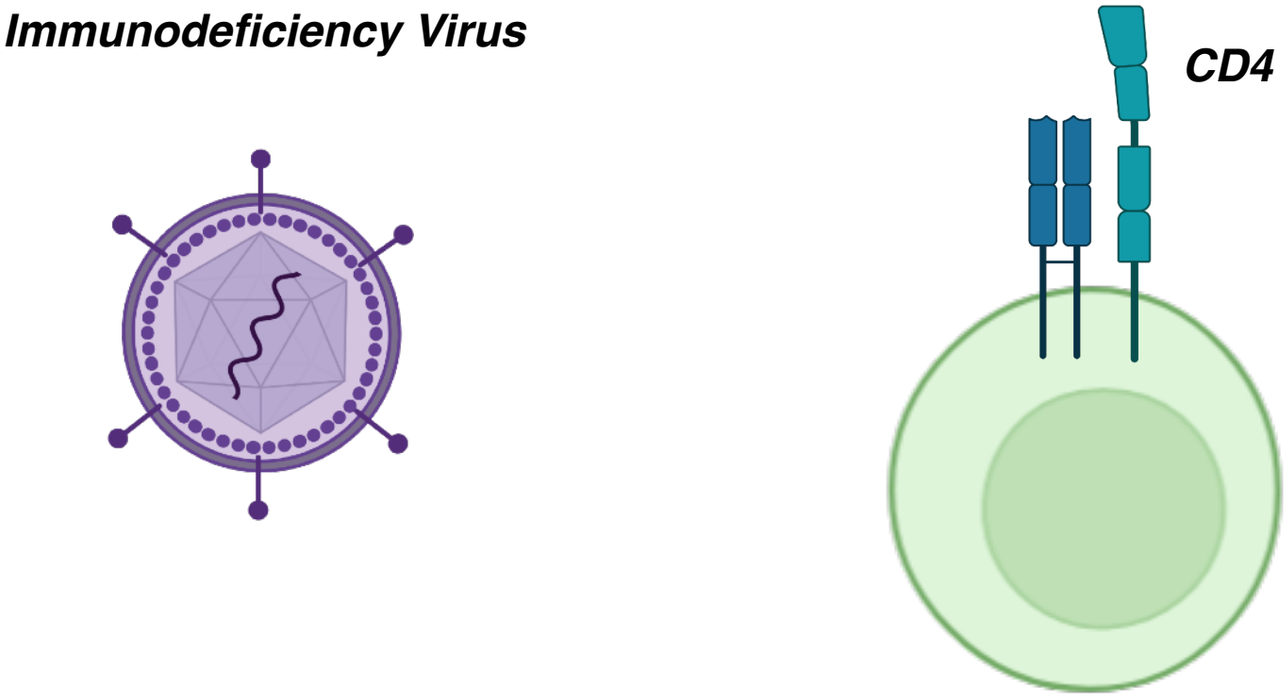
Numerous antiretroviral therapies



Bekker, L., et al. *Nat. Rev. Dis. Primers.* **2023**, *9*, 42.
Vijiyan, K. K. V., et al. *Front. Immunol.* **2017**, *8,* 580.

Human Immunodeficiency Virus

Pathogenesis of HIV



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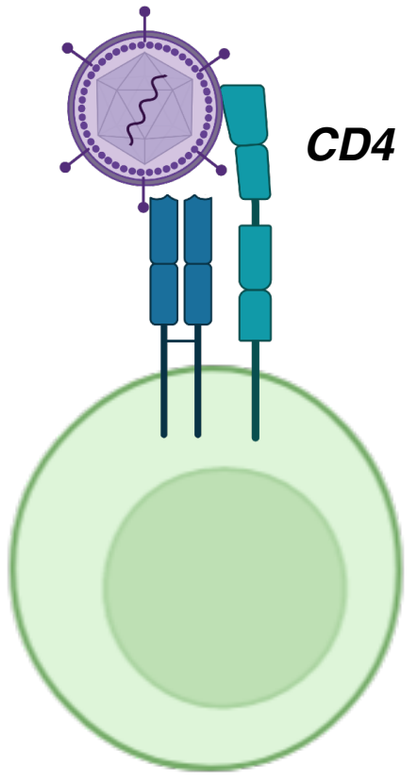

CD4⁺ T cell

Binding of CD4 enables HIV entry into T cells

Bekker, L., et al. *Nat. Rev. Dis. Primers.* **2023**, *9*, 42.

Human Immunodeficiency Virus

Pathogenesis of HIV

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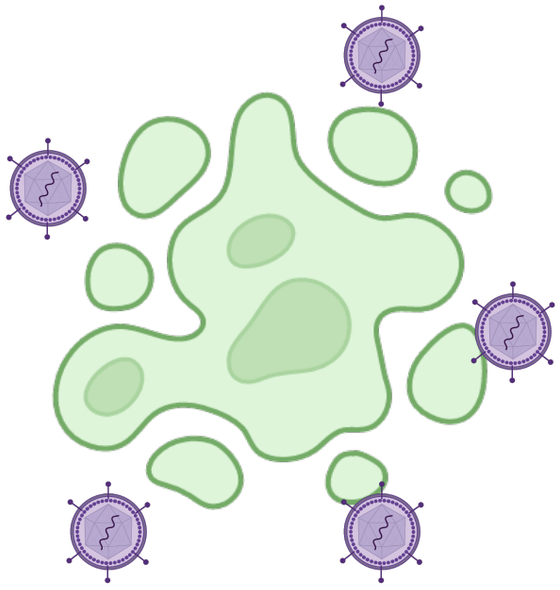
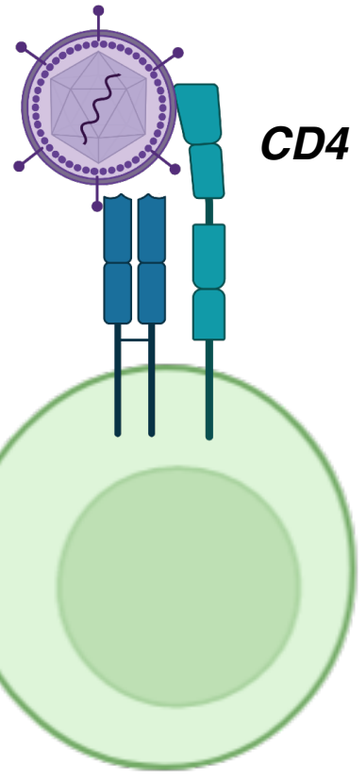


Caspase triggered apoptosis



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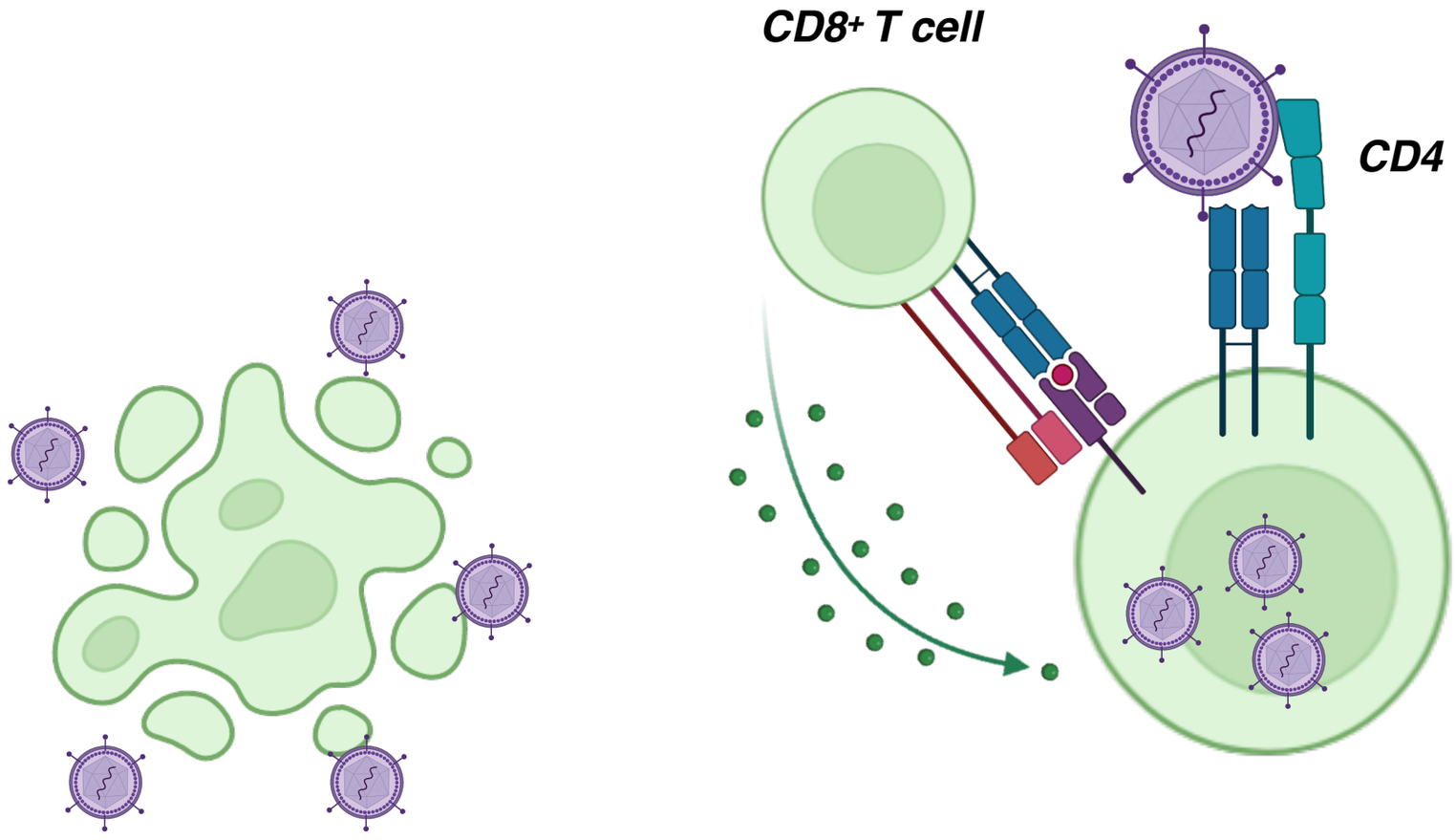

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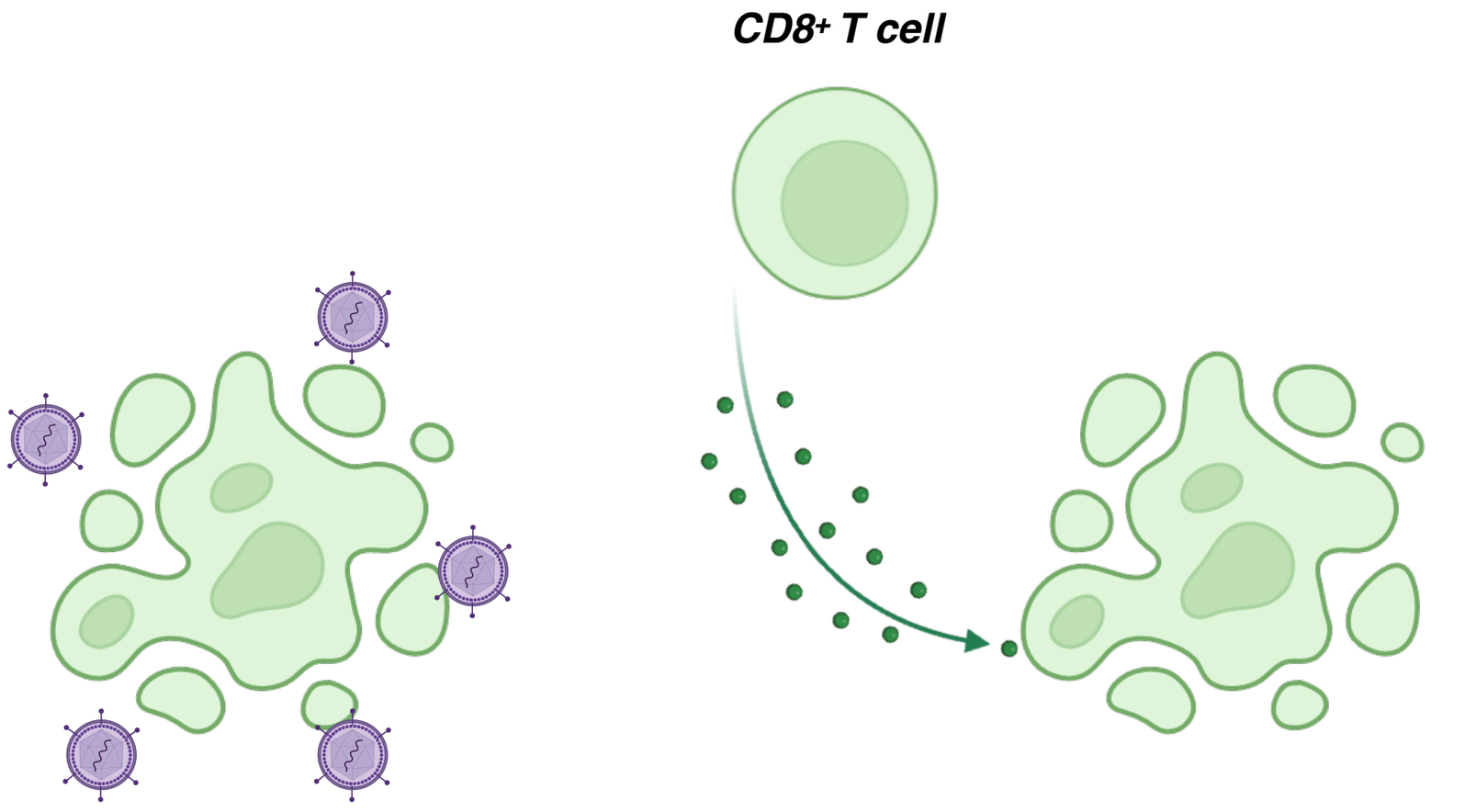
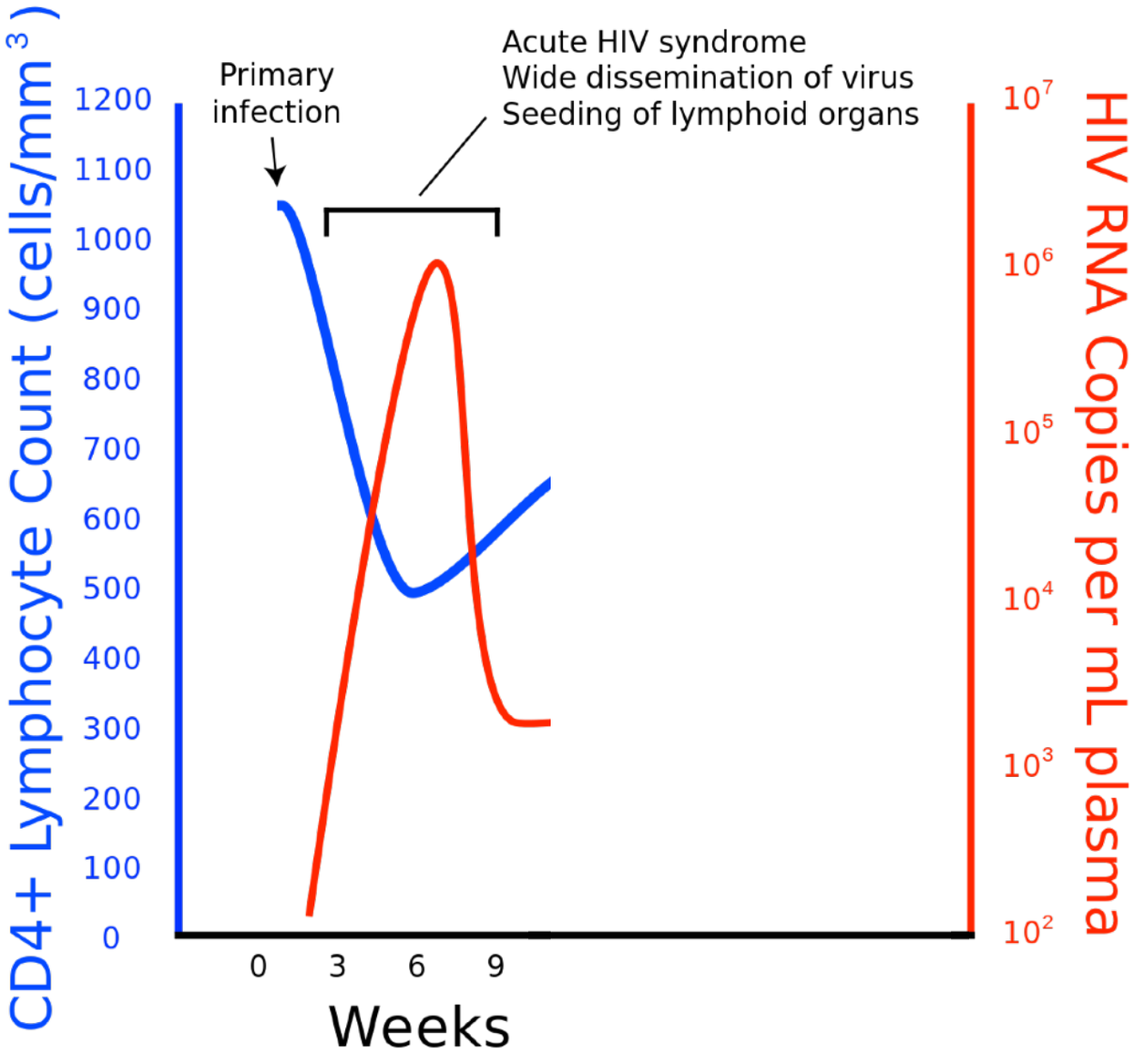


Bekker, L., et al. *Nat. Rev. Dis. Primers.* **2023**, *9*, 42.

Human Immunodeficiency Virus

HIV progression to AIDS



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Human Immunodeficiency Virus

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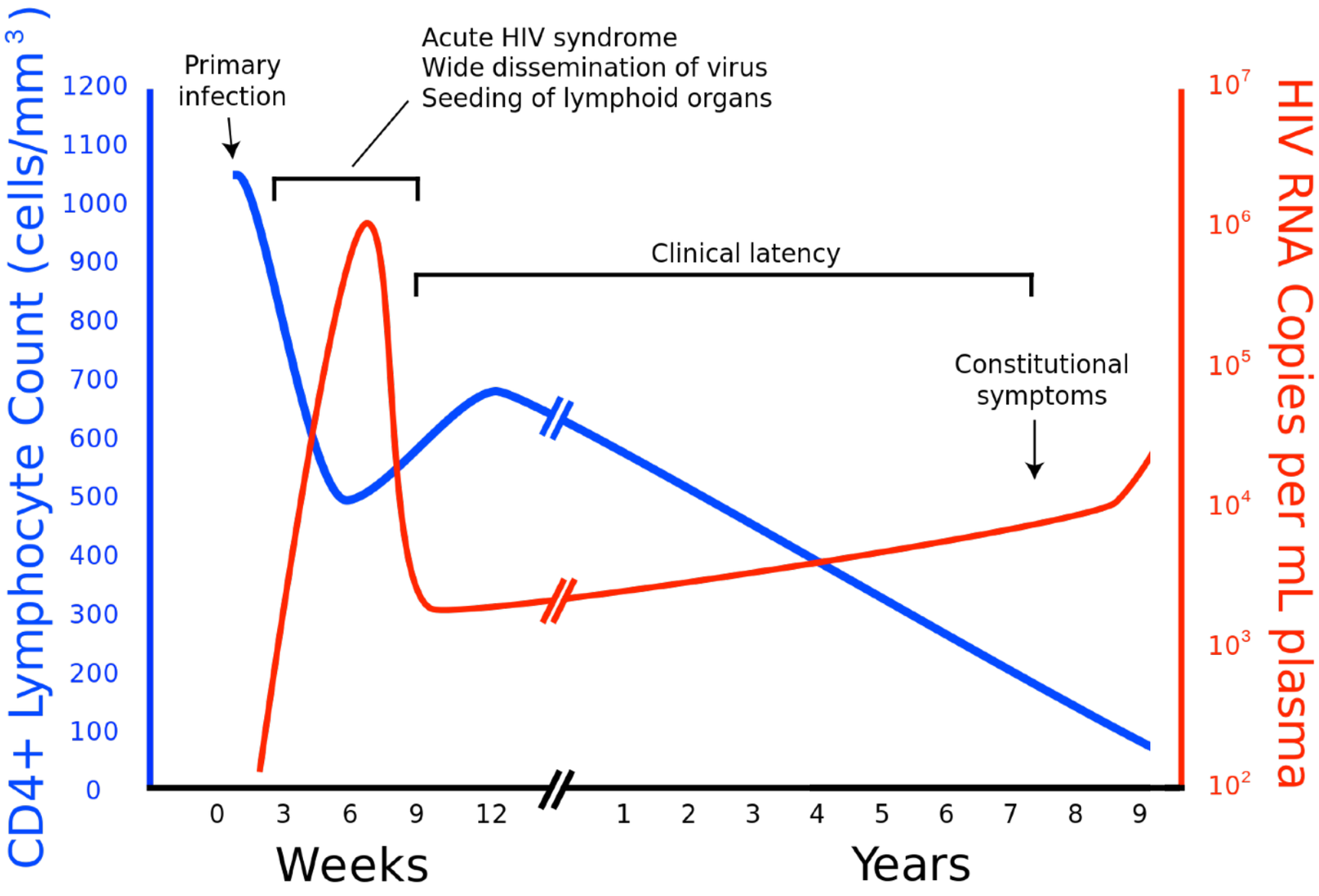

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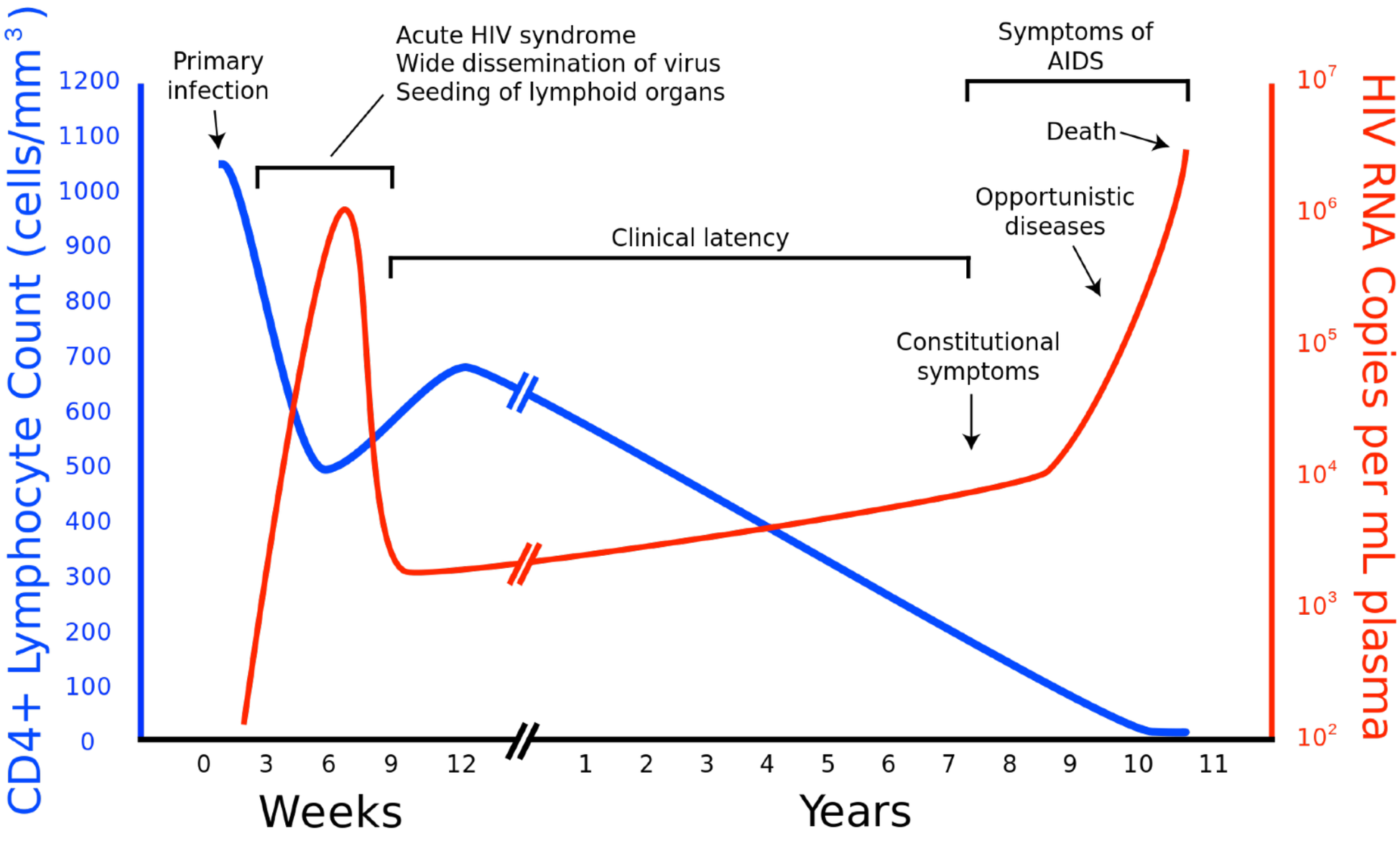


Bekker, L., et al. *Nat. Rev. Dis. Primers.* **2023**, *9*, 42.

Human Immunodeficiency Virus

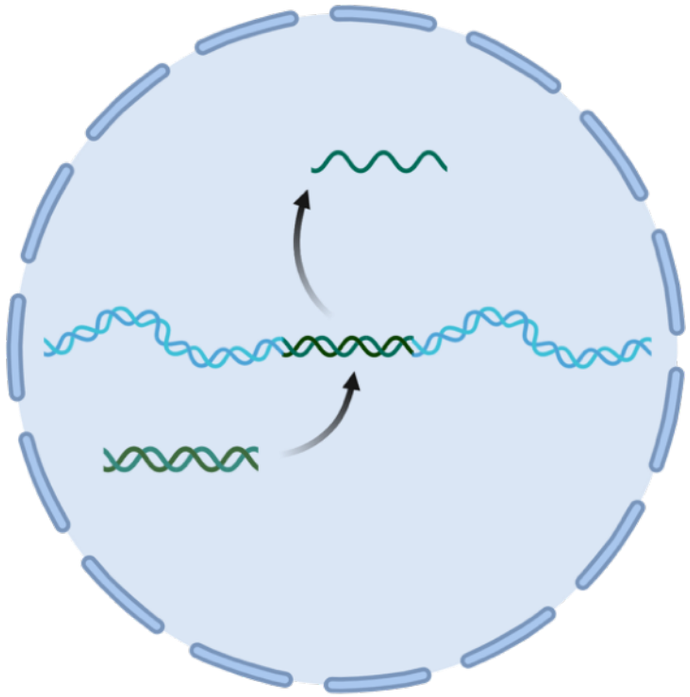
HIV progression to AIDS

Combination Anti retroviral therapy

Reduced risk of transmission by 96%

Can prolong life from ~2 years to >40 years

HIV Reverse Transcription into genome



Severely hinders possible curative treatments

Leads to lifelong infection with HIV

Bekker, L., et al. *Nat. Rev. Dis. Primers.* **2023**, *9*, 42.
Cohen, M. S., et al. *NEJM*. **2011**, *365*, 493-505.

Human Immunodeficiency Virus

HIV progression to AIDS

Currently no vaccine for HIV

Phase I trial has begun in the US and South Africa

CMV viral vector will deliver HIV material to prevent establishment of HIV infections

Further vaccine research may enable greater control of HIV in lower income nations

News Releases, *NIH.* **2023.**

Adaptive Immune System

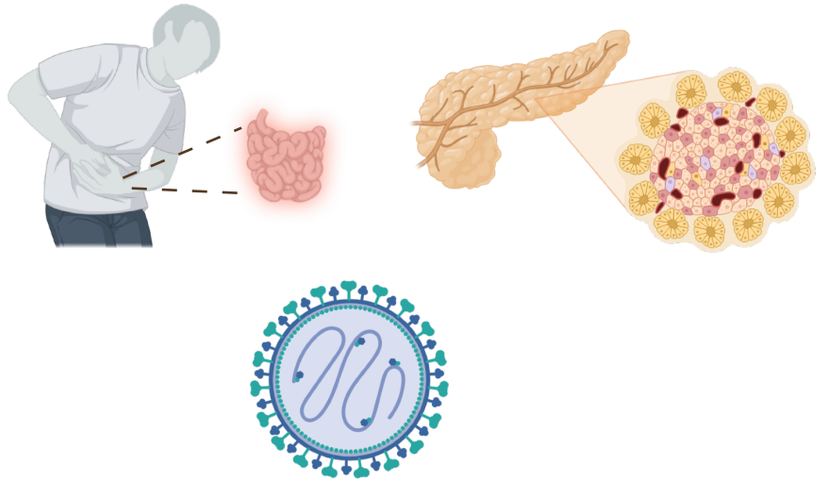
Ultra-specific targeting

Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines

Vaccines use adaptive immunity to grant long term protection from pathogens

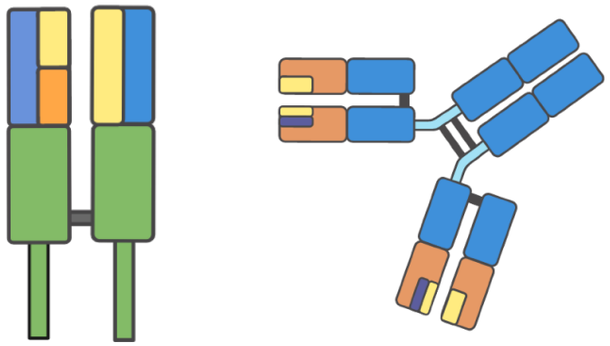
Adaptive immune diseases



Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens

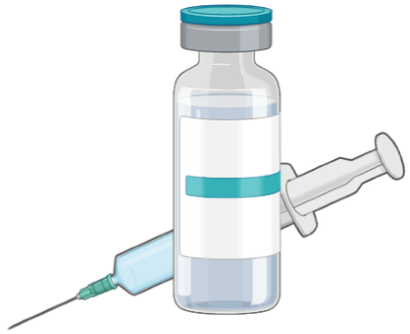
Questions?

Ultra-specific targeting



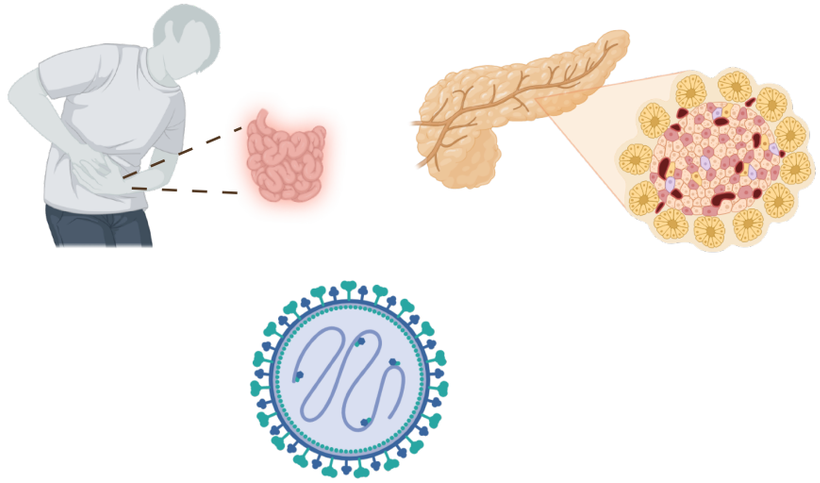
Selective T cell receptors and antibodies enable adaptive immune specificity

Vaccines



Vaccines use adaptive immunity to grant long term protection from pathogens

Adaptive immune diseases



Adaptive immune cells can trigger autoimmune diseases and be targets of pathogens