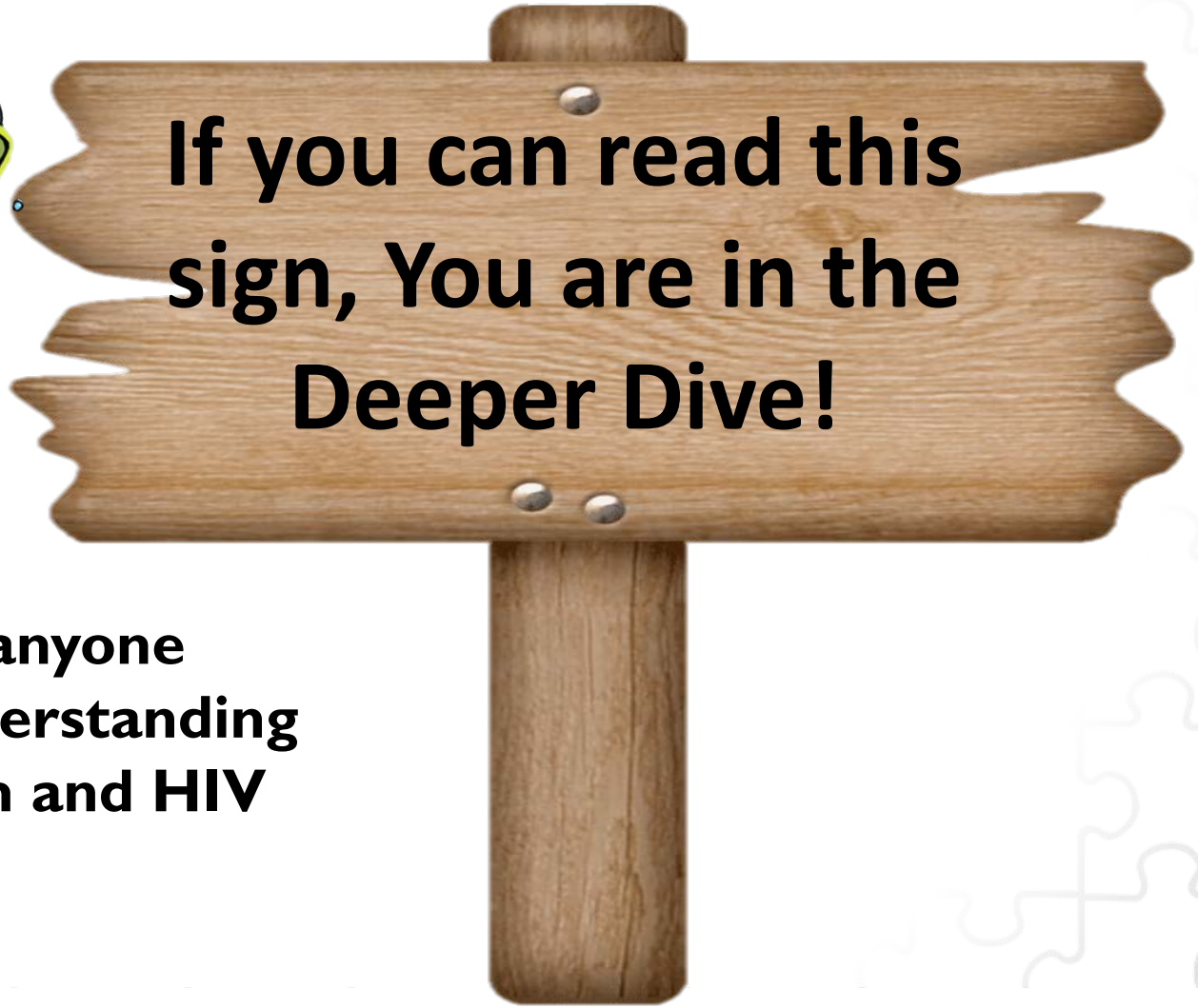
Introduction to HIV Cure-Related Research

DEEPER DIVE

CUREiculum

This research training curriculum is a collaborative project aimed at making the science of HIV cure-related research accessible to the community and the HIV research field.



This module is for anyone exploring a deeper understanding of the immune-system and HIV

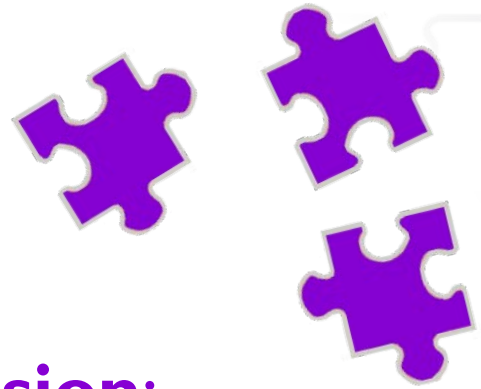
Why take a deeper dive?

- Following set of slides afford greater detail on some of the complex interaction between HIV and our immune system.
- Designed by **community for community**
- Hope it will lead to meaningful community-centered conversations

6 modules:

1. **Introduction to HIV cure-related research**
2. **Analytical treatment interruptions (ATIs)**
3. **HIV persistence**
4. **HIV cure-related research strategies**
5. **Ethics of HIV cure-related research**
6. **Community, patient & stakeholder engagement**

Glossary of Key Terms



Antiretroviral (ART)-free HIV suppression:

Control of virus in the absence of HIV treatment
(also: 'post-treatment control' or 'ART-free durable control')

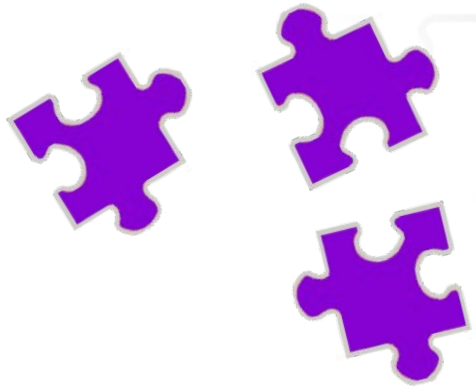
Latency:

The ability of a virus to stay dormant (inactive) within a cell

Provirus:

A virus' genetic material that has become integrated inside the DNA (deoxyribonucleic acid) of a cell

Glossary of Key Terms



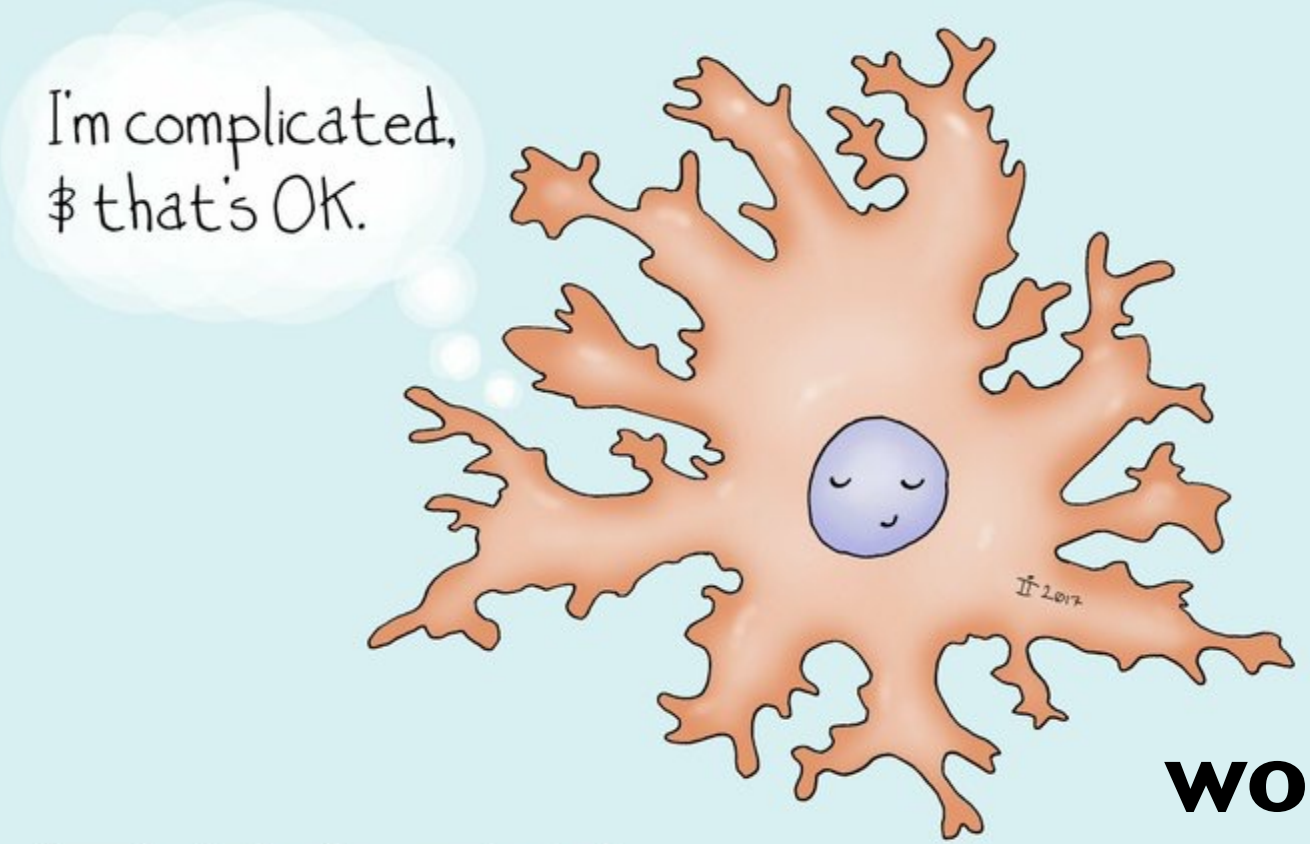
Reservoirs:

Cells and compartments in the body where HIV can hide and not be found, even in the presence of antiretroviral therapy

Viral rebound:

When a person has detectable levels of HIV in the blood after a period of having undetectable levels

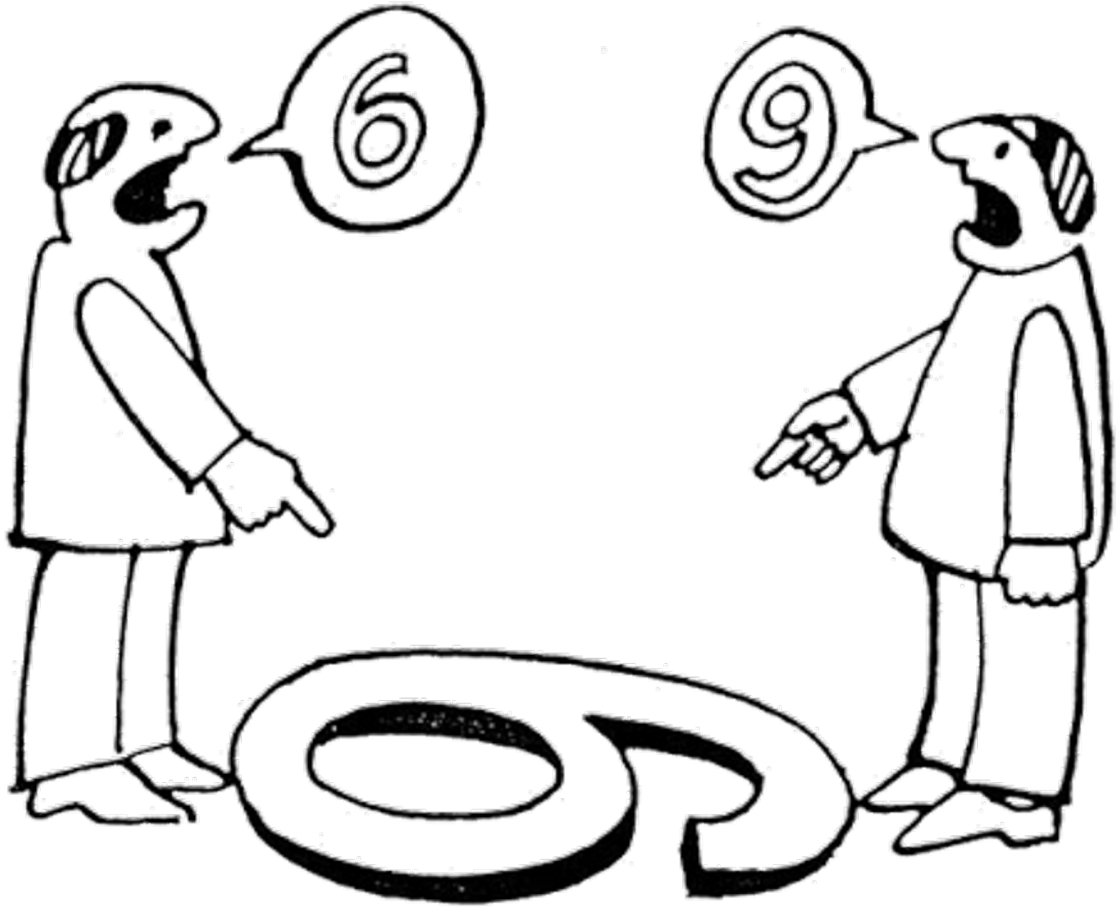
Understanding HIV cure-related research can be complicated…



…but we are working hard to help you understand it!

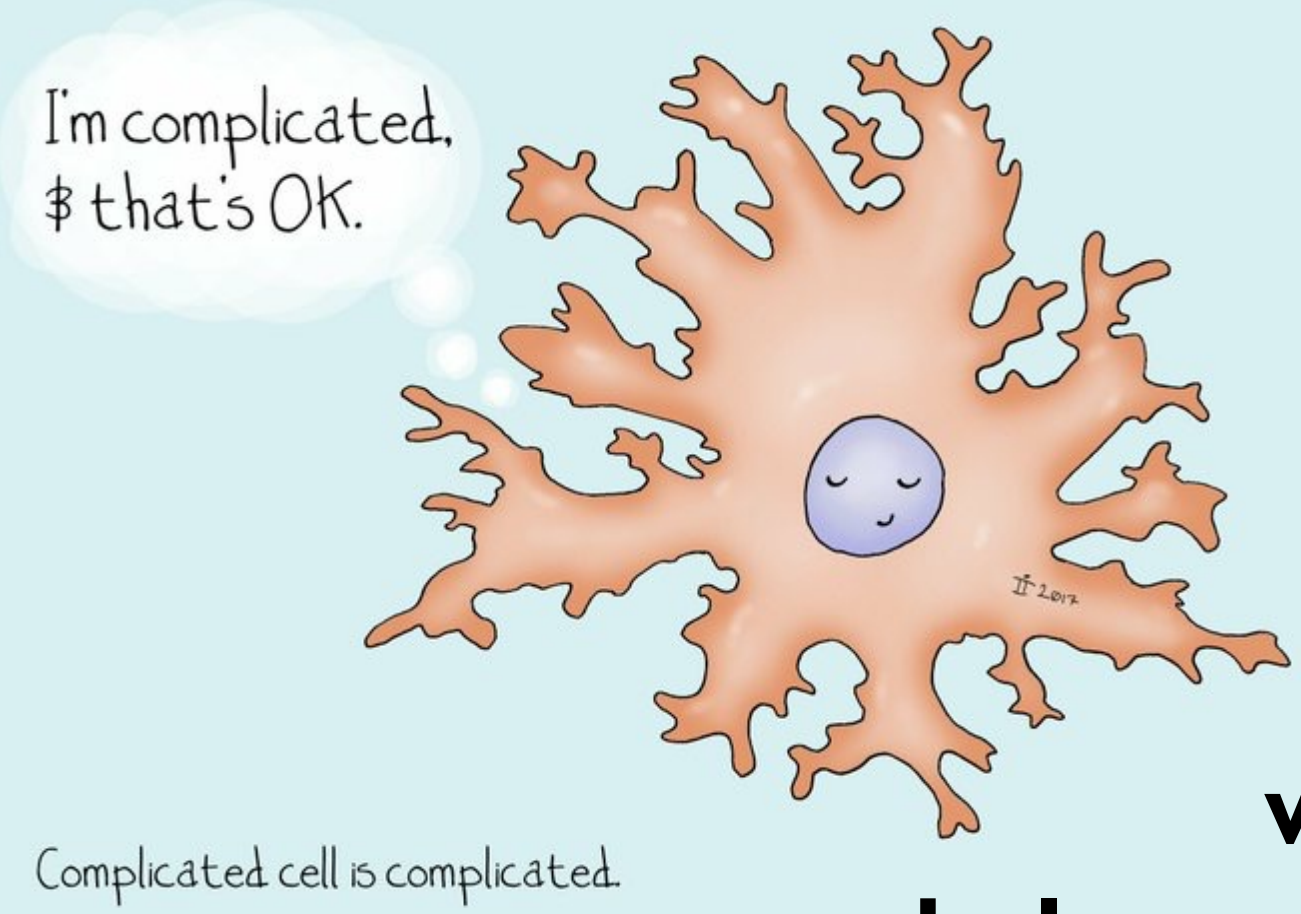
https://twitter.com/cartoon_neuron/status/997479403478224897

Perception plays a role in HIV cure research because every individual comes with their own views and experiences.



Introduction

Understanding HIV cure-related research can be complicated…



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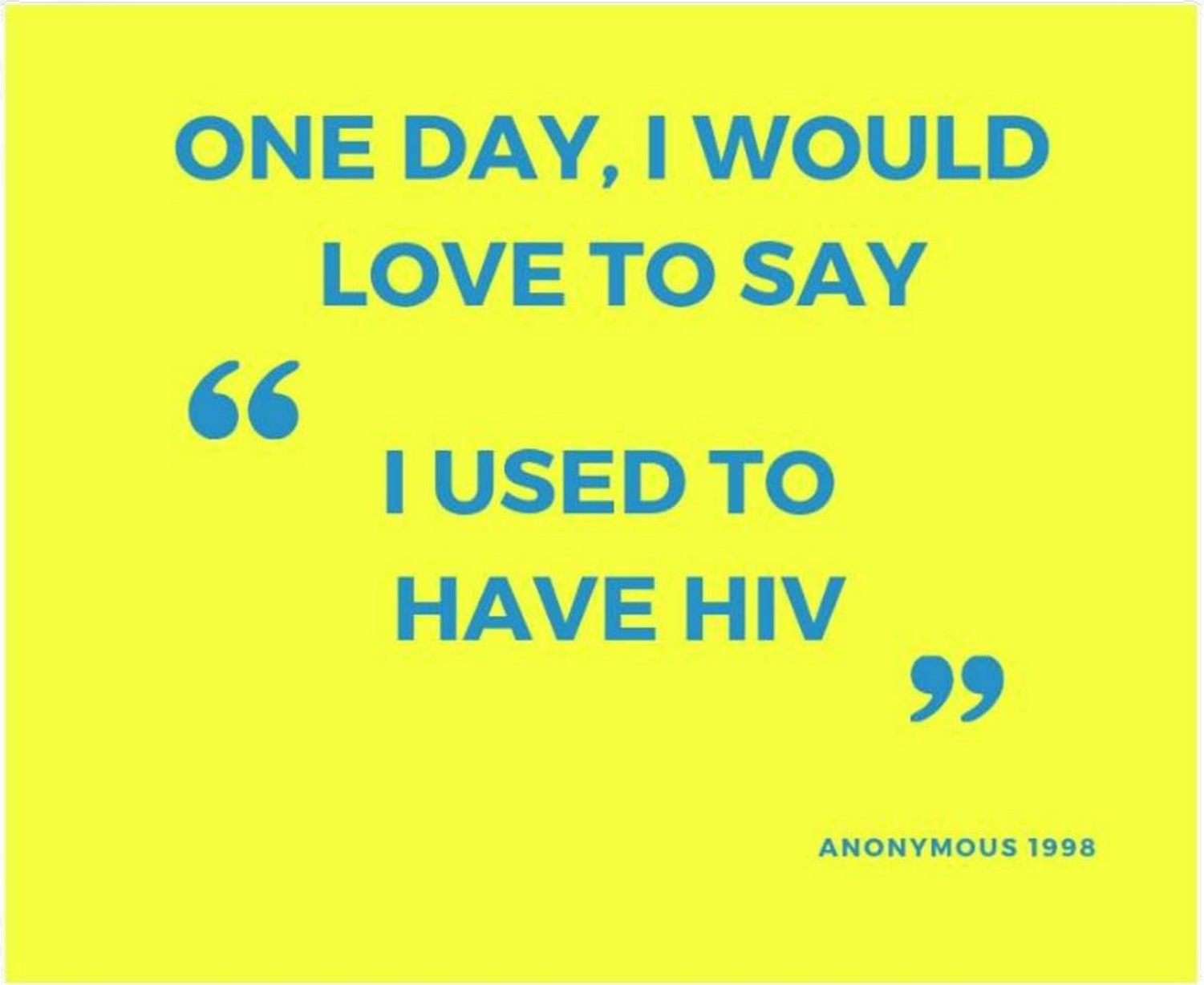
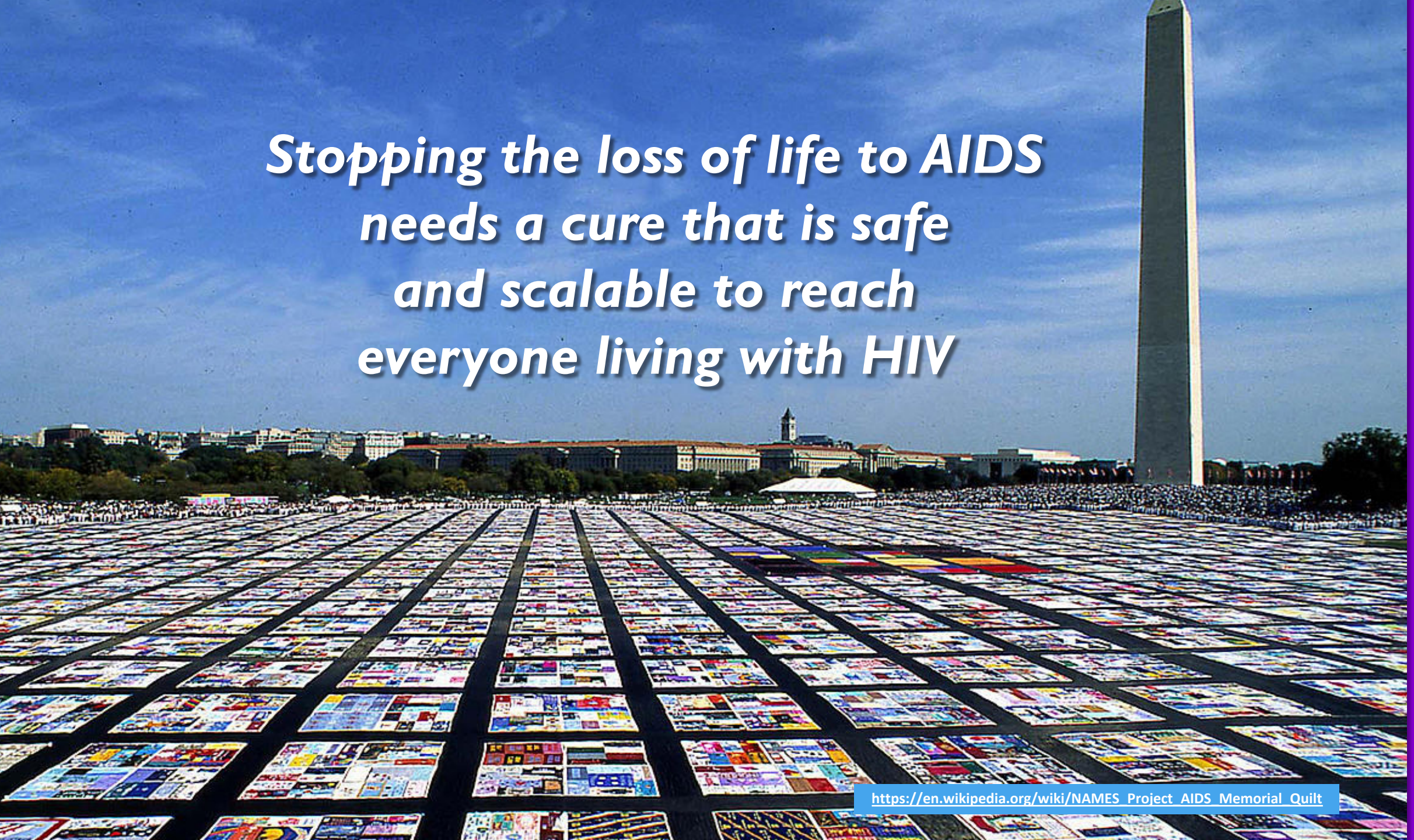

ONE DAY, I WOULD
LOVE TO SAY
“
I USED TO
HAVE HIV
”
ANONYMOUS 1998

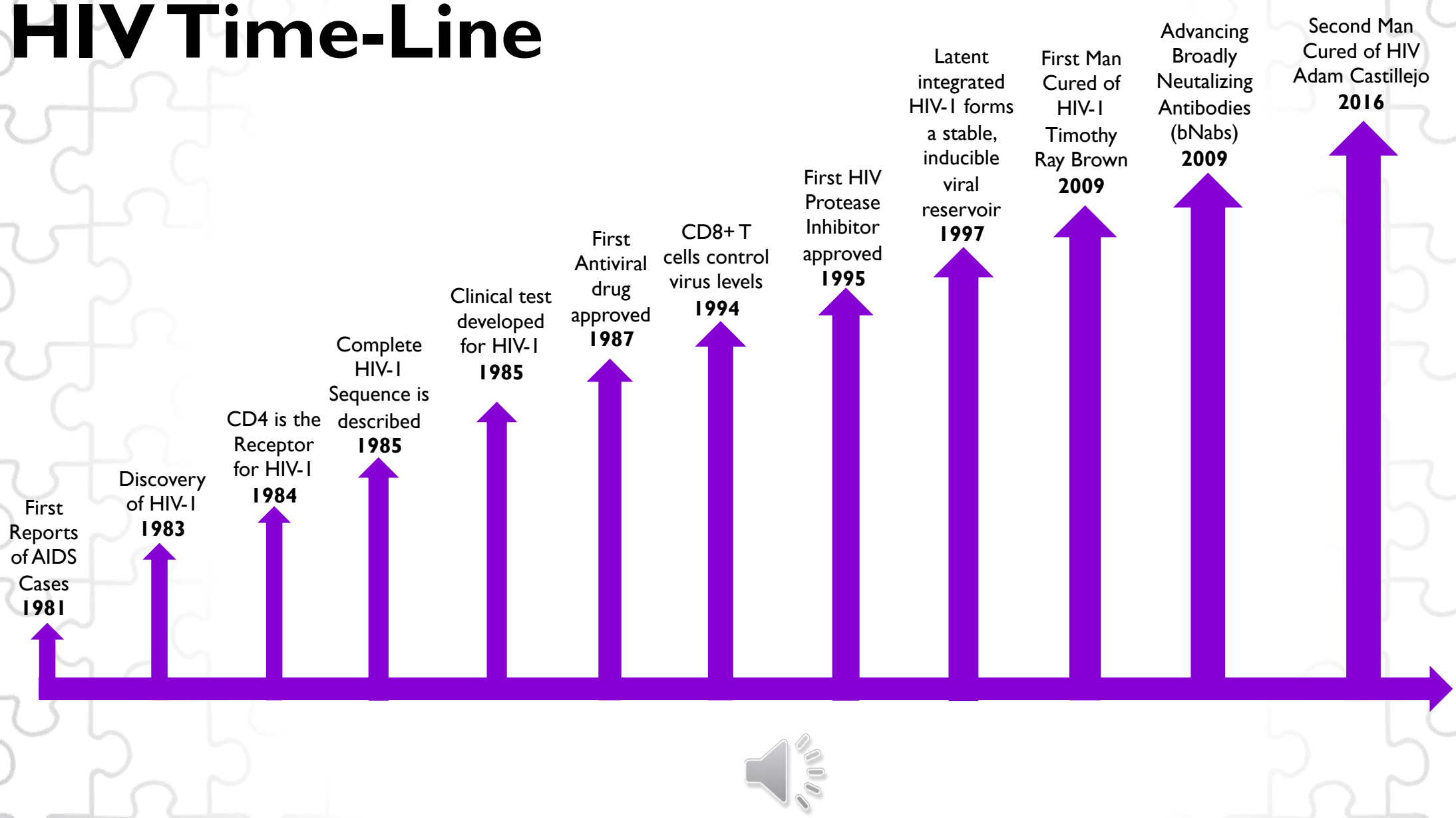


Stopping the loss of life to AIDS needs a cure that is safe and scalable to reach everyone living with HIV

https://en.wikipedia.org/wiki/NAMES_Project_AIDS_Memorial_Quilt

HIV Time-Line

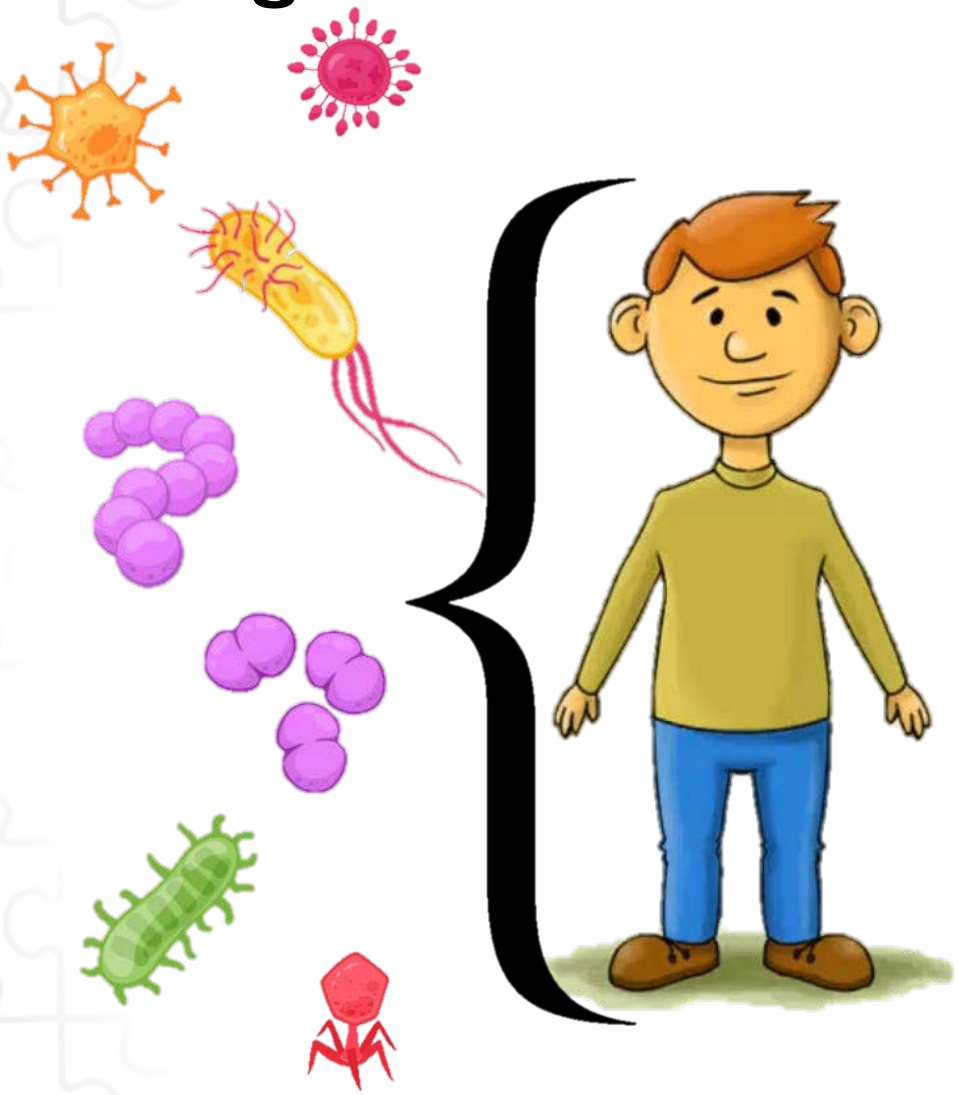
HIV Time-Line



https://www.nature.com/collections/mghkkdjlgx/timeline/

Our Immune System

Pathogens



Immune System

* Made up of....
  - ~ Organs
  - ~ Tissues
  - ~ Cells
  - ~ Molecules
* Can....
  - ~ Identify a threat
  - ~ Mount an attack
  - ~ Eliminate a pathogen
  - ~ Remember

  .... In 10 days!
* Prolonged reactions....

⬇

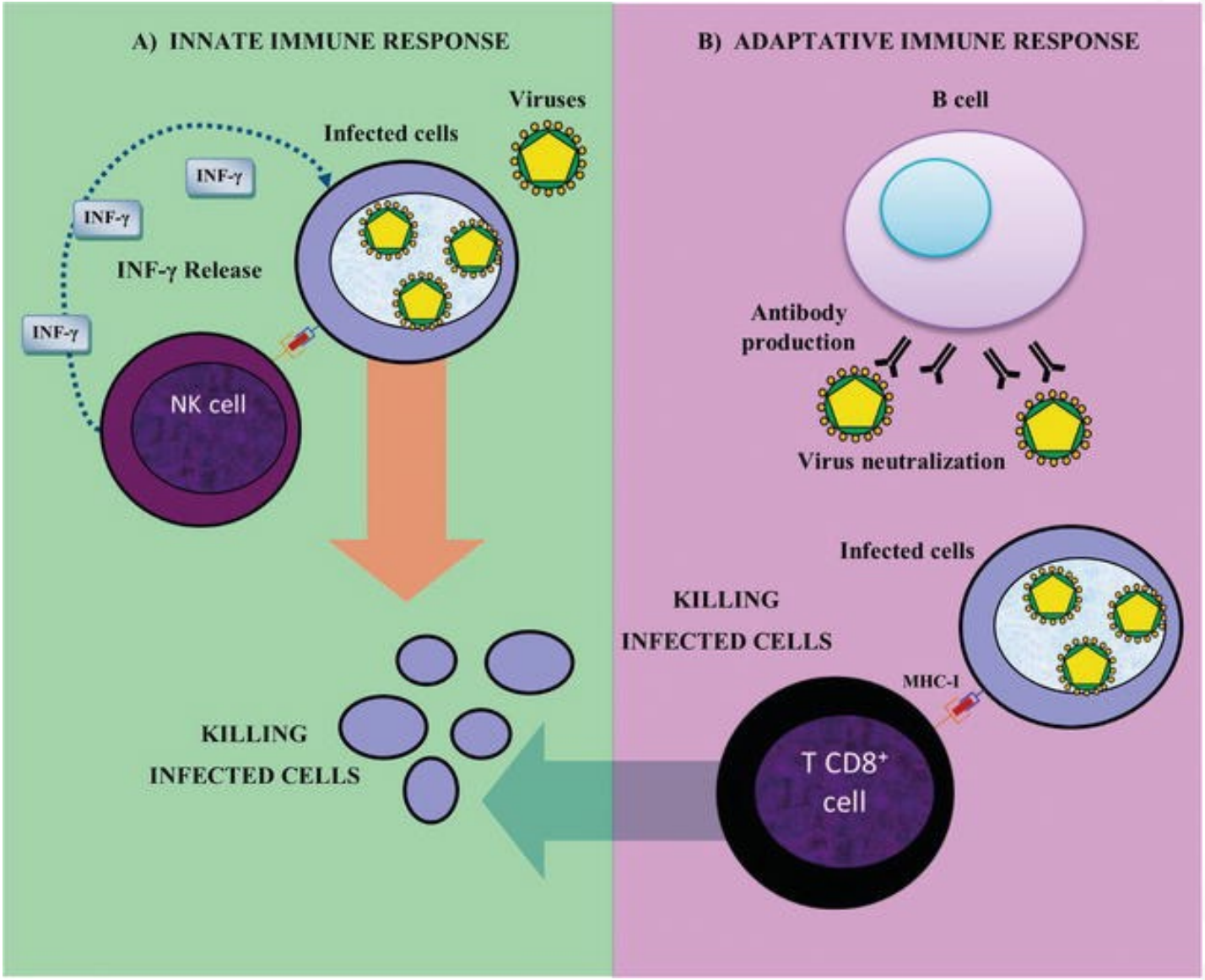
Chronic Inflammation

Two main arms of the immune system.

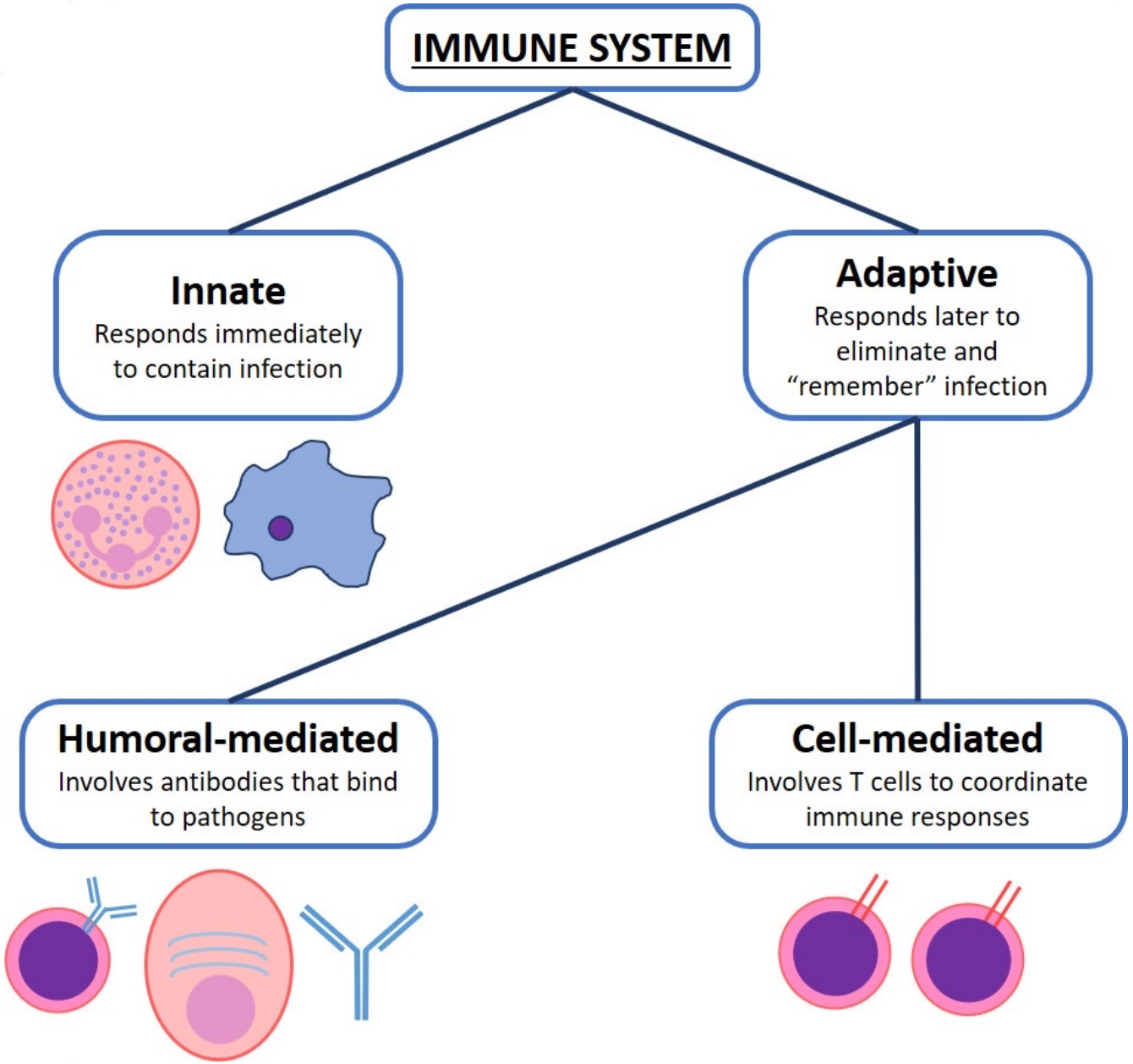
Vertebrate Immunity		
Innate Immune System		Adaptive Immune System
Physical Barriers	Internal Defenses	
• Skin, hair, cilia • Mucus membranes • Mucus and chemical secretions • Digestive enzymes in mouth • Stomach acid	• Inflammatory response • Complement proteins • Phagocytic cells • Natural killer (NK) cells	• Antibodies and the humoral immune response • Cell-mediated immune response • Memory response

https://courses.lumenlearning.com/os-conceptsofbio/chapter/innate-immunity/

Two arms of the immune system.



https://www.intechopen.com/books/physiology-and-pathology-of-immunology/physiology-and-pathology-of-innate-immune-response-against-pathogens

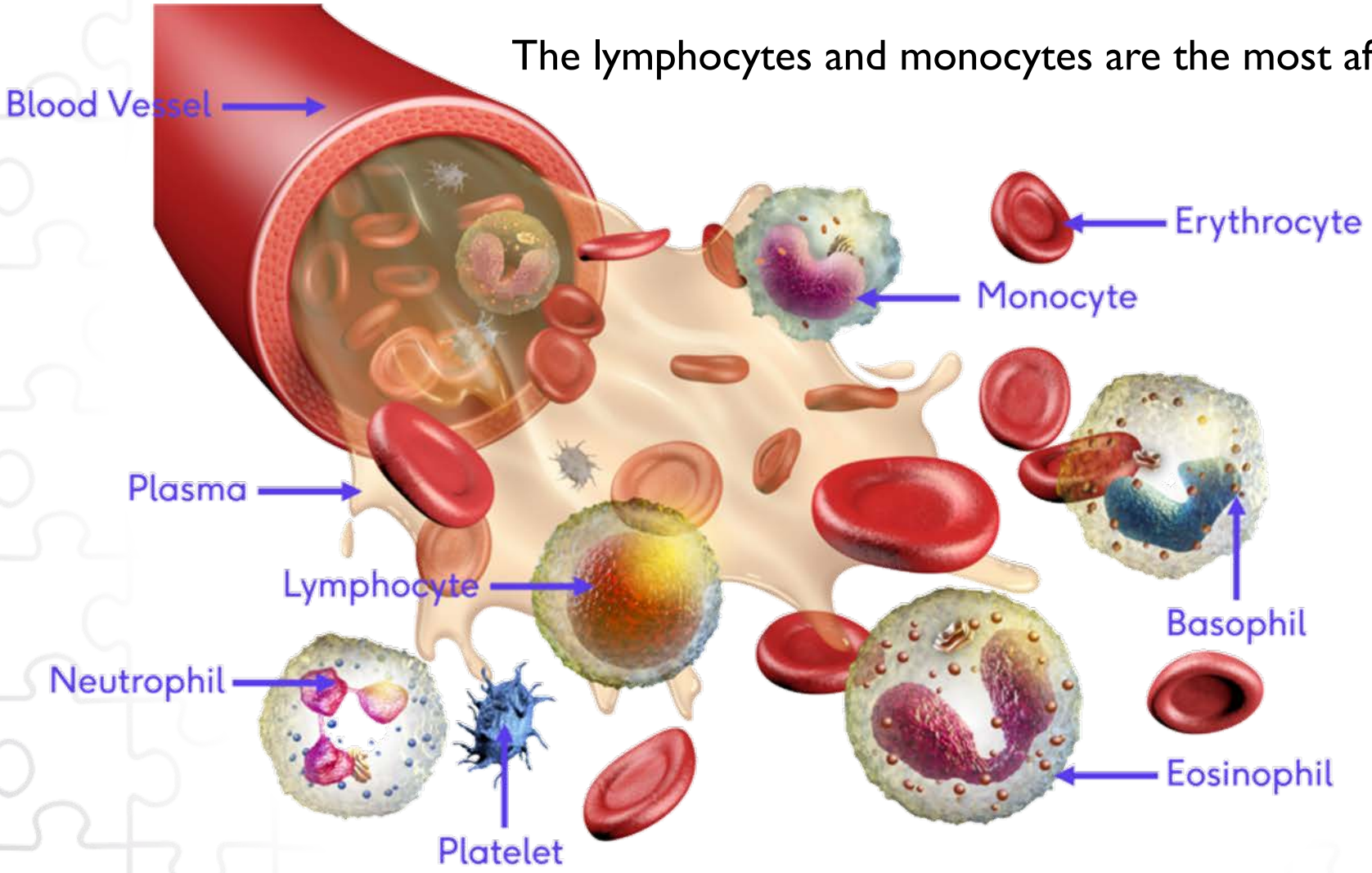


https://theactivescientist.com/journal-club-001/

What are the key components of the immune system?

Components of the Peripheral Blood System

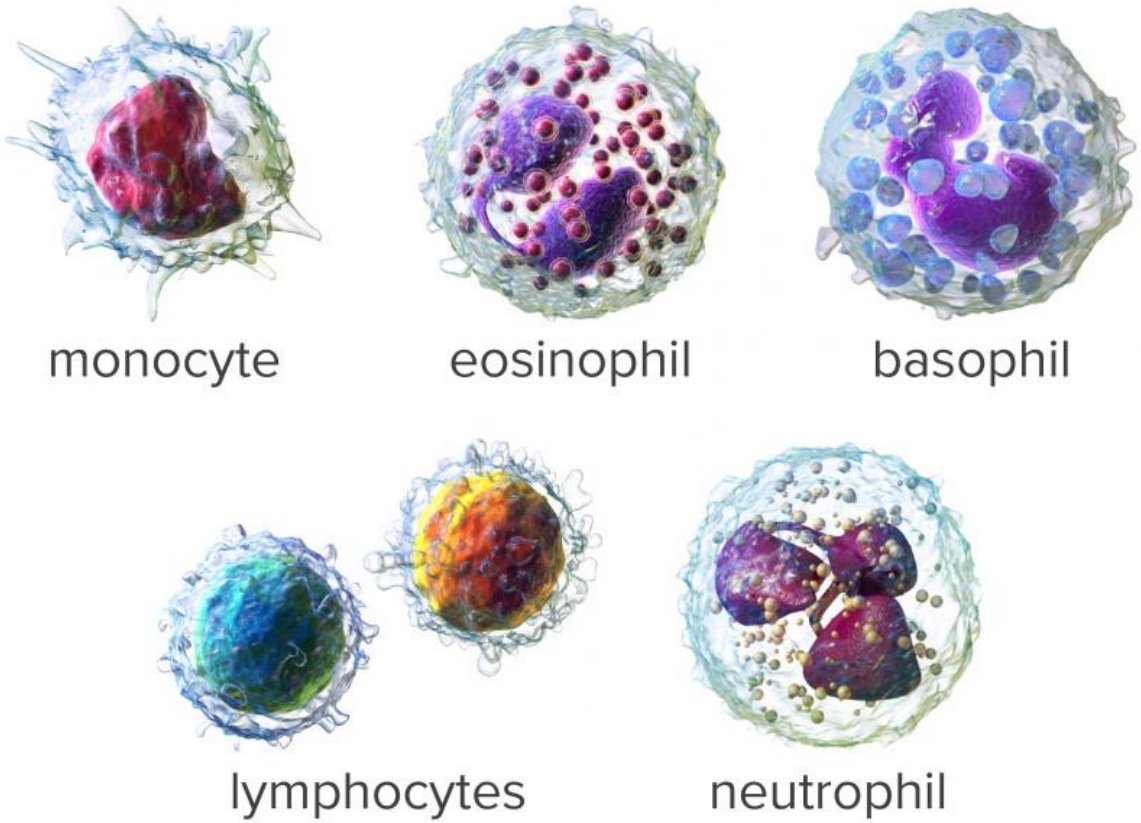
The lymphocytes and monocytes are the most affected by HIV



https://www.physio-pedia.com/images/thumb/5/55/Blood_with_description.png/1000px-Blood_with_description.png

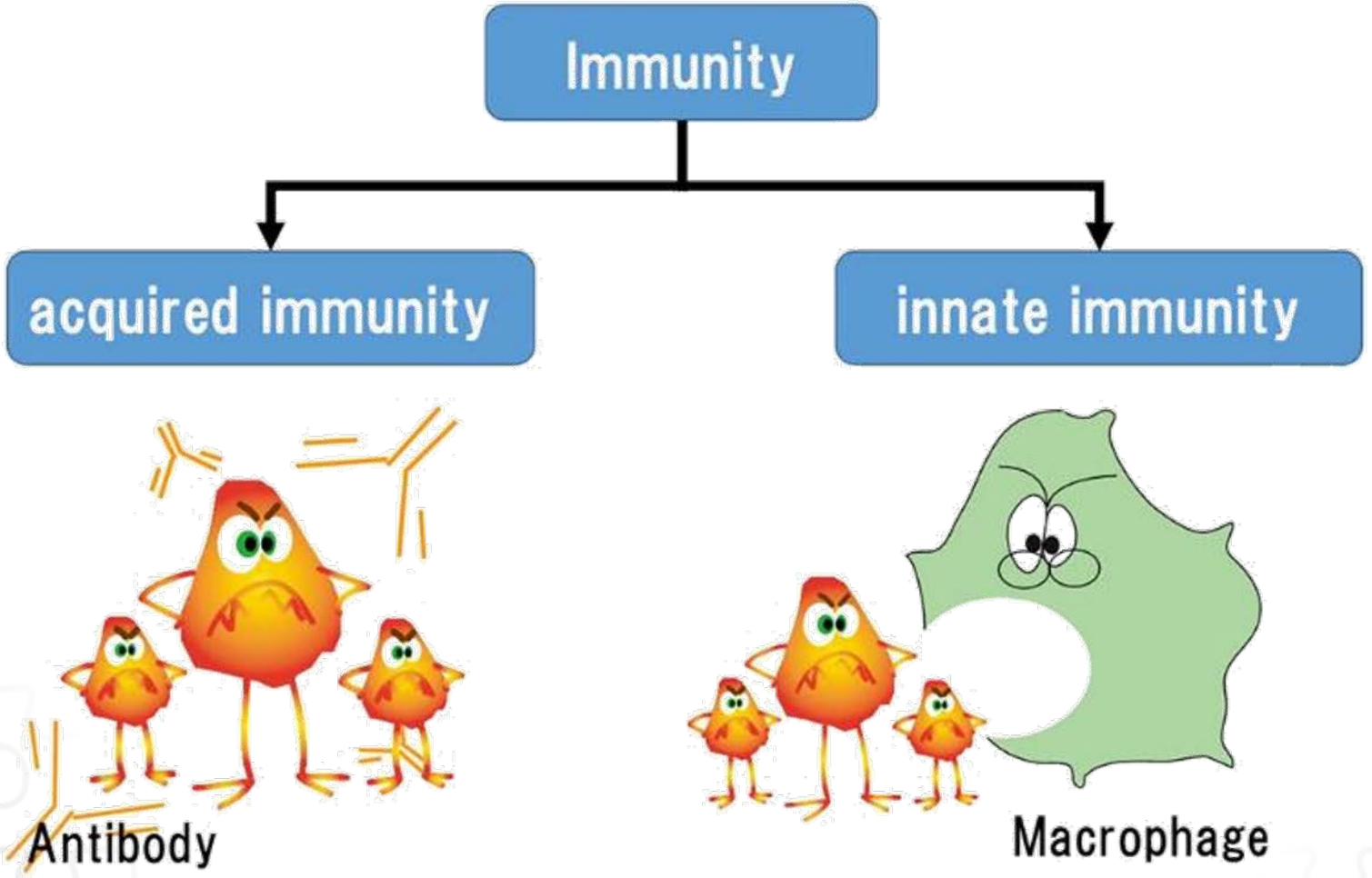
MEDICALNEWSTODAY

White Blood Cells



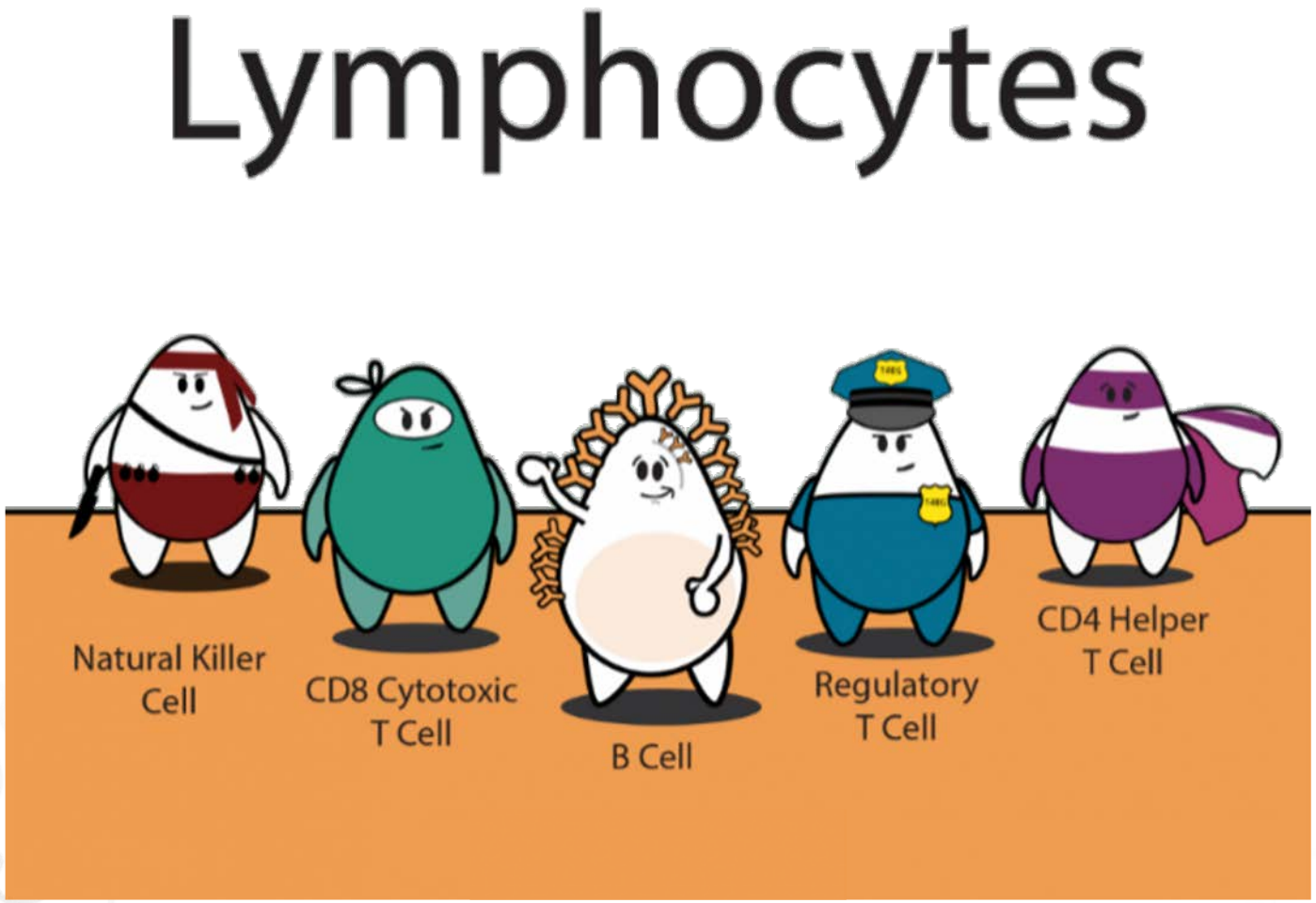
https://www.medicalnewstoday.com/articles/327446

A glimpse at the adaptive (acquired) & the innate arms of the immune system



https://www.macrophi.co.jp/english/lps/4-1.html

A functioning immune system requires all cells working together



https://cellcartoons.net/lymphocytes/

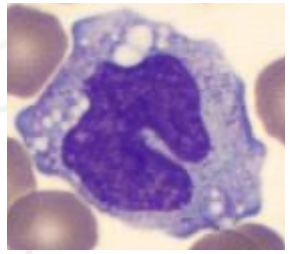
The CD4 T cell is an important player in a ‘League of Superhero Immune Cells’

Monocytes and macrophages are a type of white blood cell that love to eat (phagocytize) pathogens with their ferocious appetites

These cells can act as a reservoir of HIV

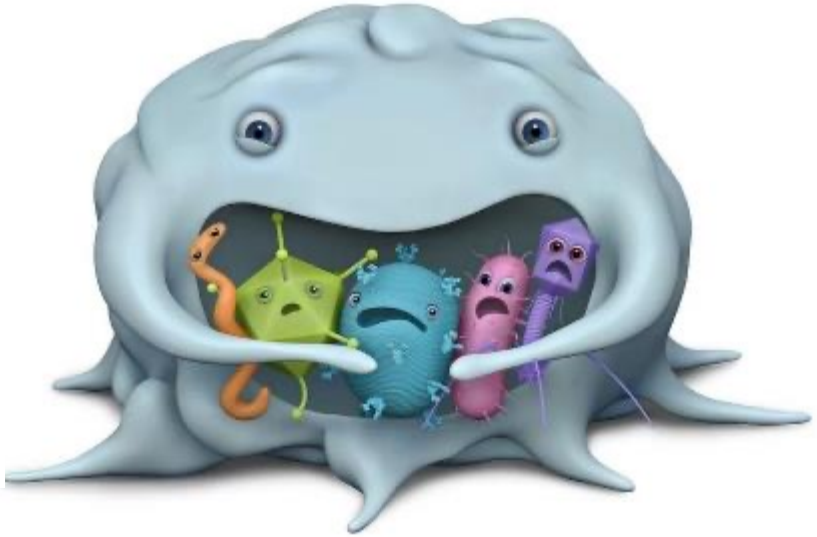
They express both CD4 and CCR5

Monocyte



Monocyte

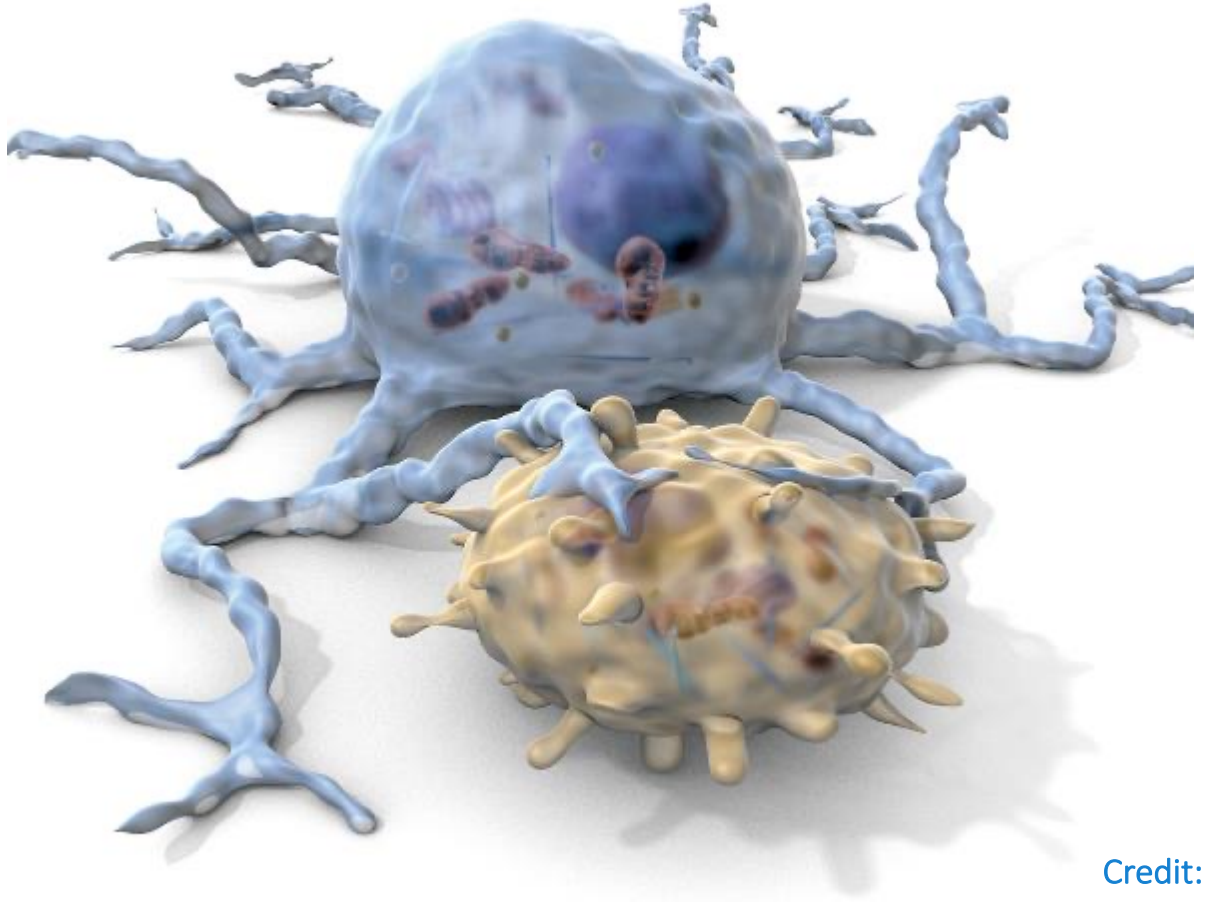
Macrophage



phagocytize

https://justinroot.com/immune-cartoon/
https://www.melissalogies.com/3d?lightbox=dataItem-jd85i38s

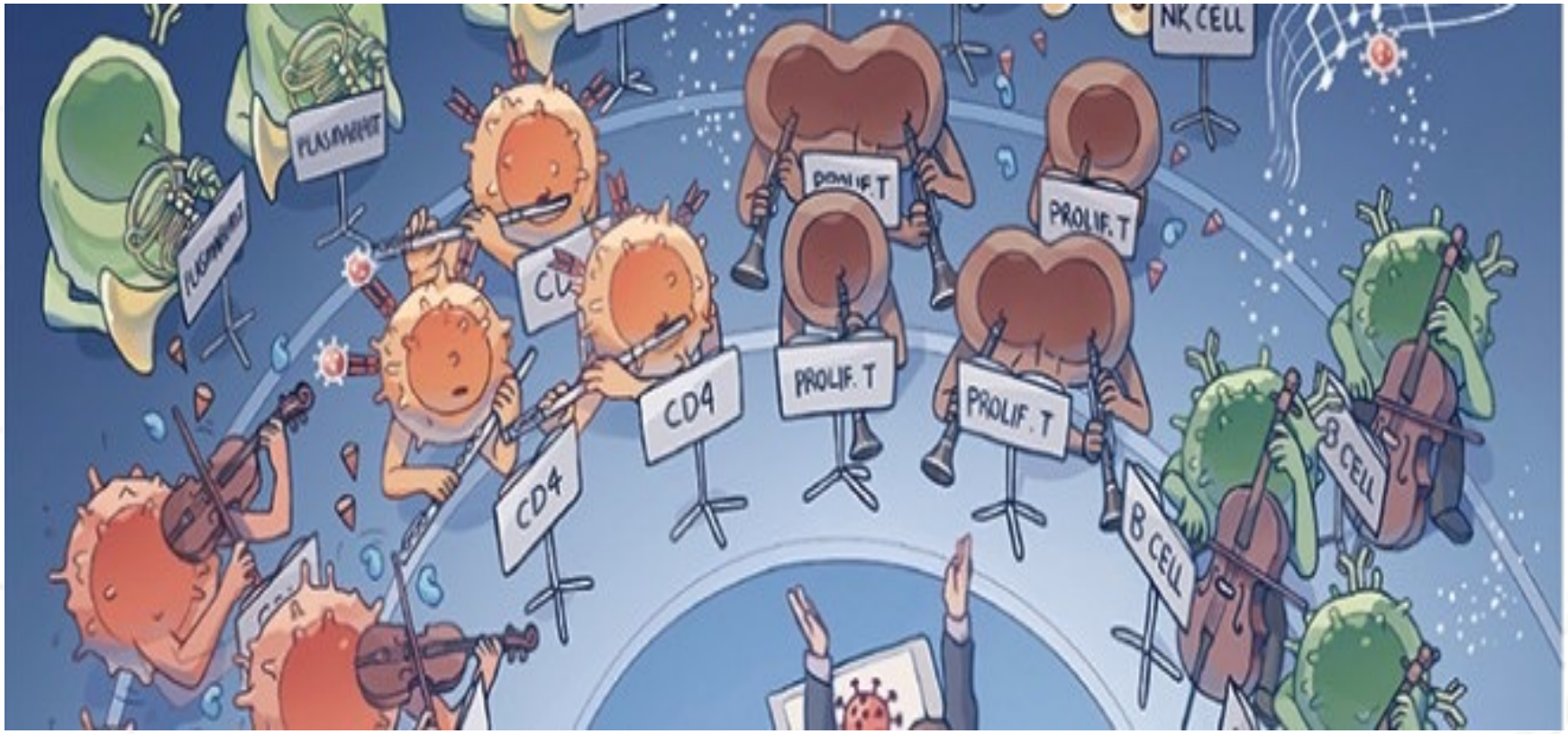
A Dendritic Cell (blue) Engages a T cell (yellow)



Credit: C. BICKEL/*SCIENCE*

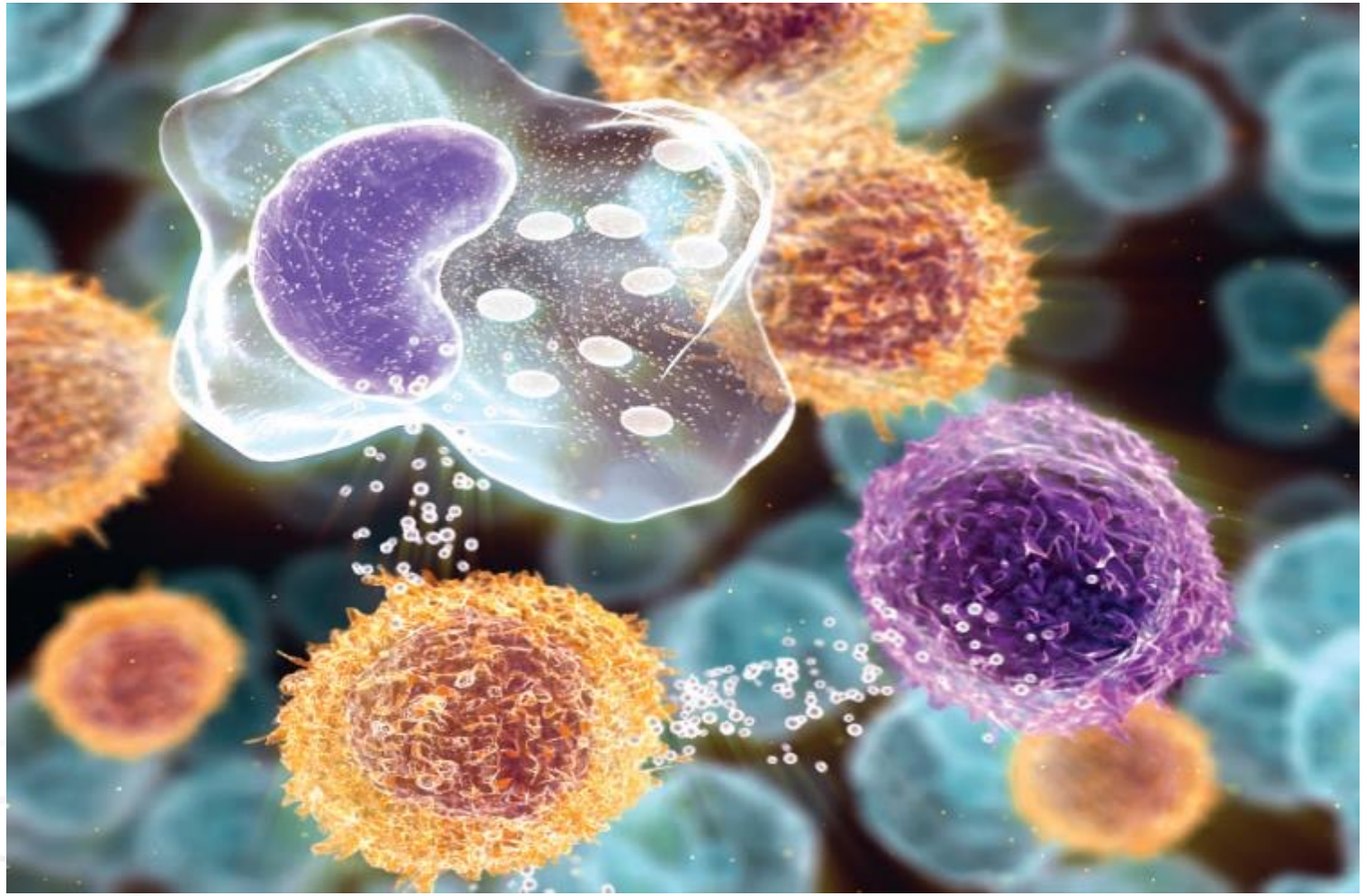
https://science.sciencemag.org/content/346/6209/597.1

All the cells of the immune system work in perfect concert together under normal conditions making music for our ears



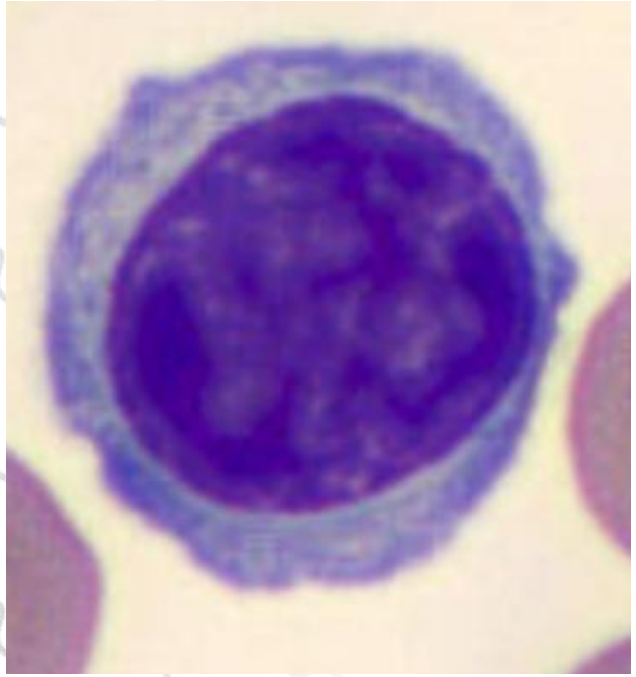
https://www.ragoninstitute.org/understanding-the-score-a-dynamic-interrogation-of-acute-hiv-infection/

Cells communicate through chemical signals much like we do through words



https://scienmag.com/new-clues-found-to-immune-systems-misfiring-in-autoimmune-diseases/

Lymphocyte



Lymphocytes

B cells & T cells

Immense Immunology Insight

Count
20% - 40% in peripheral blood

Round nucleus
- Large
- Dark staining

Scanty cytoplasm
- Thin rim around the nucleus
- Pale eosinophilic
- Barely visible

Killing strategy
Coming soon!

To be continued...

https://www.alignable.com/sweetwater-tn/lifes-many-blessings/what-is-a-helper-t-cell-jul-2018

B CELL

IMMENSE IMMUNOLOGY INSIGHT

Count
20% of total lymphocytes

War strategy

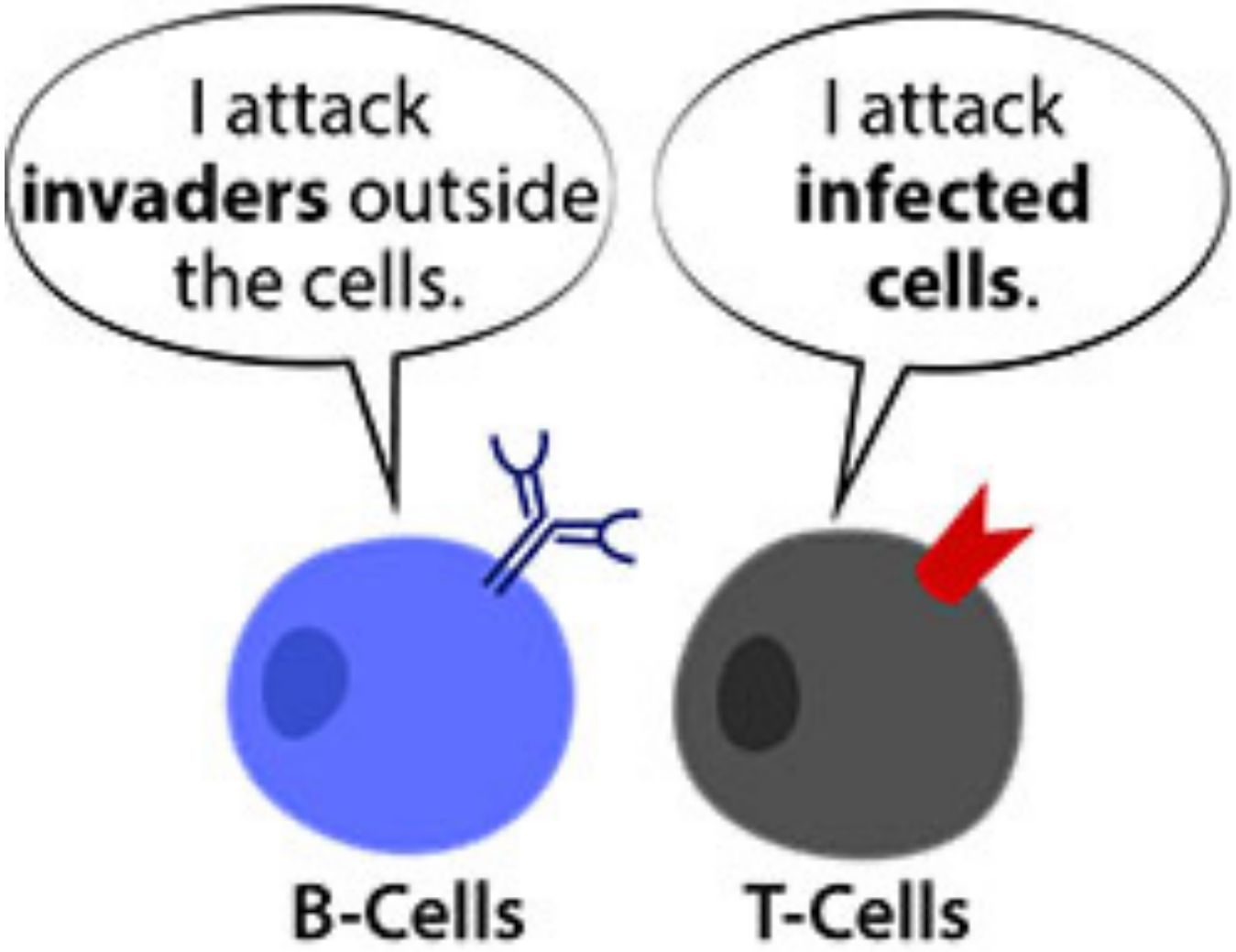
① Recognize enemy (B cell receptor)

② Recieve signal for activation:
- Show antigen to CD4 T cells (Antigen presentation)
- Recognize multiple crosslinking (Thymus independent activation)

③ Transform into:
- Plasma cell (Secretes antibodies)
- Memory B cell (For faster recognition of the same enemy in the future)

https://www.alignable.com/sweetwater-tn/lifes-many-blessings/what-is-a-helper-t-cell-jul-2018

Unique differences between B and T cells.



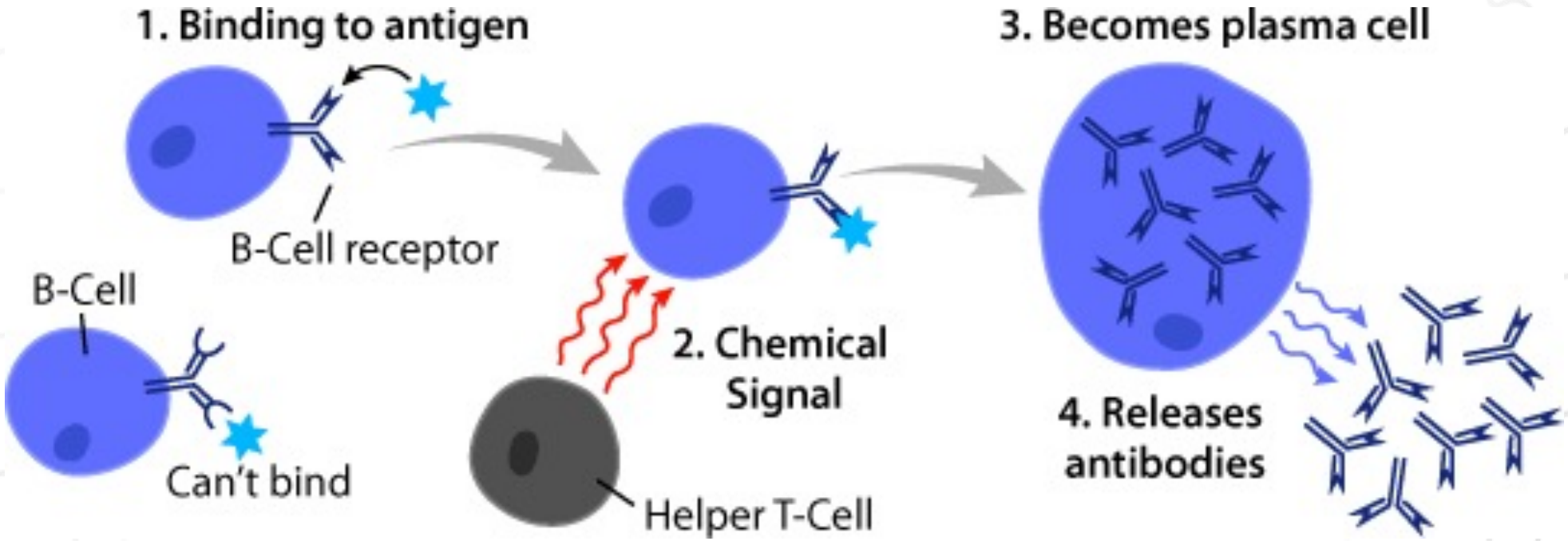
https://askabiologist.asu.edu/b-cell

T and B Lymphocyte distribution in different organ systems

Lymphoid Organ	T Lymphocytes (%)	B Lymphocytes (%)
Thymus	100	0
Bone marrow	10	90
Spleen	45	55
Lymph nodes	60	40
Blood	70	30

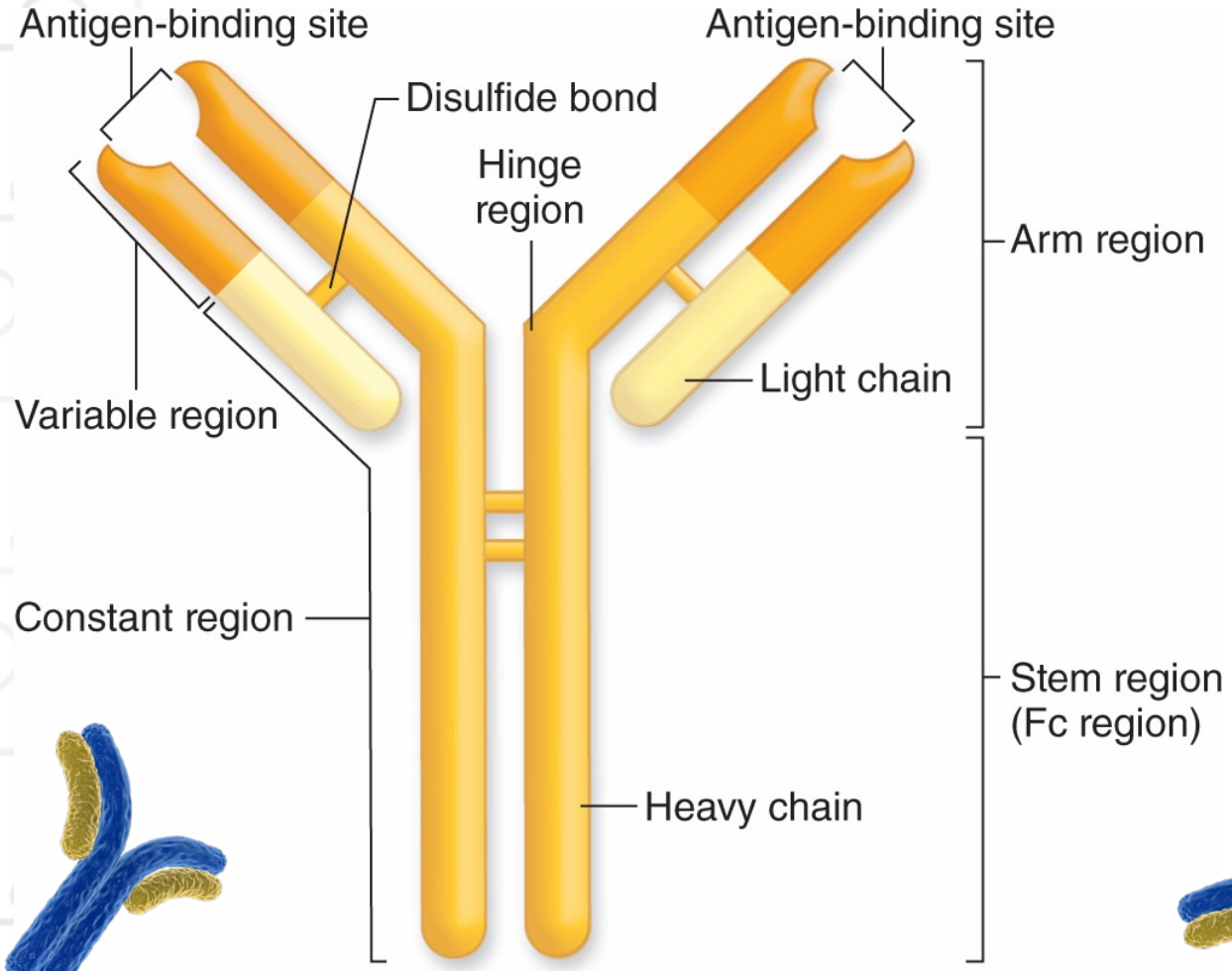
https://basicmedicalkey.com/the-immune-system-lymphoid-organs/

T helper cells provide an important link to B cells.

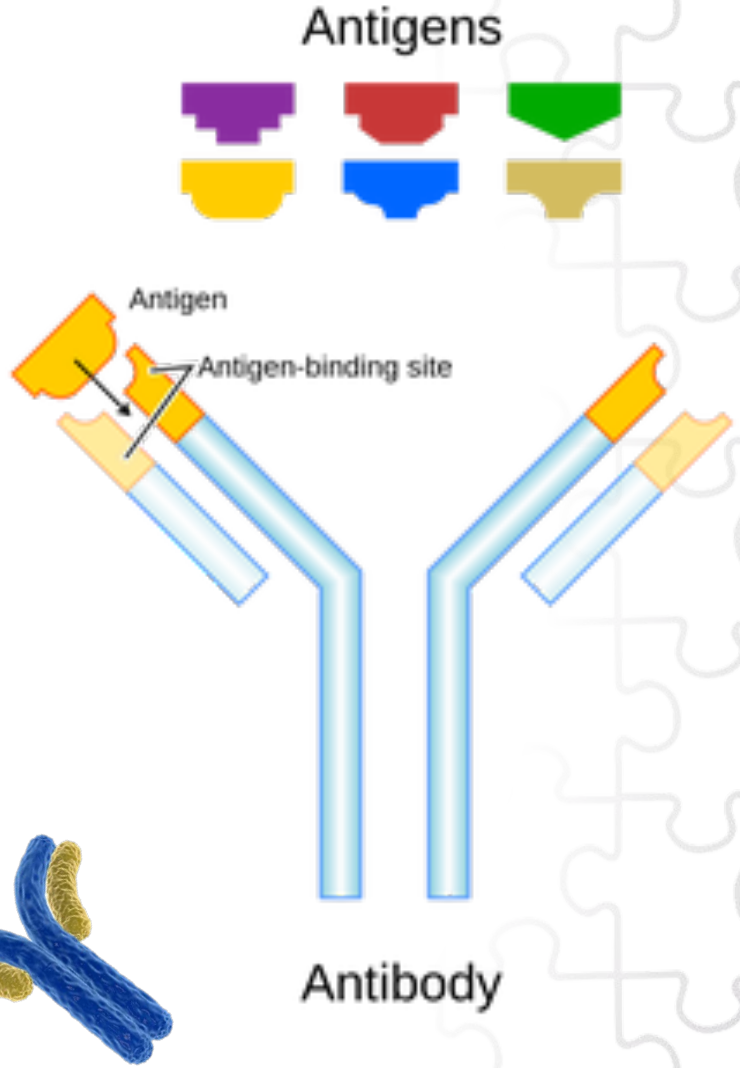


https://askabiologist.asu.edu/b-cell

Immunoglobulin G (IgG)



https://basicmedicalkey.com/the-immune-system-lymphoid-organs/



https://en.wikipedia.org/wiki/Antibody

Introduction

CUREiculum

HELPER T CELL

IMMENSE IMMUNOLOGY INSIGHT

Expresses
CD4 glycoprotein
(CD4+ T cells)

Warrior types

TH1 cells
Activates:
- Macrophages
- Killer T cells
- B cells

Secretes:
- IFN - γ
- IL - 2
- TNF - α

TH2 cells
Activates:
- Eosinophils
- Mast cells
- Basophils

Secretes:
- IL - 4
- IL - 5
- IL - 13

TFH cells
Activates B cells for:
- Isotype switching
- Affinity maturation

TH17 cells
Recruits:
- Neutrophils

Secretes:
- IL - 17

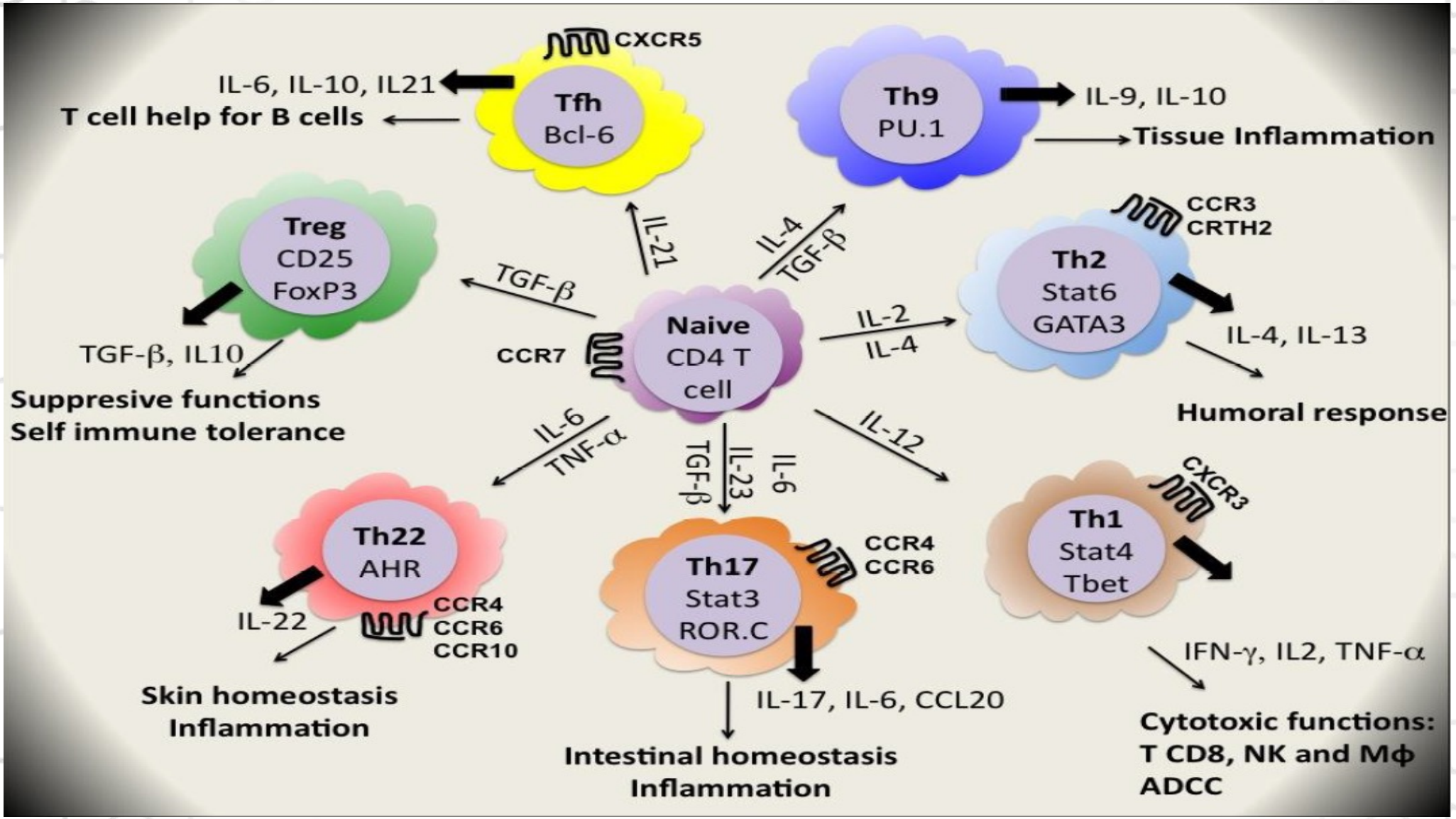
Treg cells
Inhibits dendritic cells:
- Prevents autoimmunity
- Supresses T cell

ronwendyheal.com

#AskStorm

https://www.alignable.com/sweetwater-tn/lifes-many-blessings/what-is-a-helper-t-cell-jul-2018

The many functions of CD4 T Helper Cells.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185763/

"I am a killer T cell"

Expresses
CD8 glycoprotein
(CD8+ T cells)

① Recognize antigen combined with class I MHC (altered self cells)

② Recieve signal for activation:
- With CD4 T cell help: Cytokines (IL-2)
- Without help: Activation by potent APCs

③ Releases cytotoxic proteins:

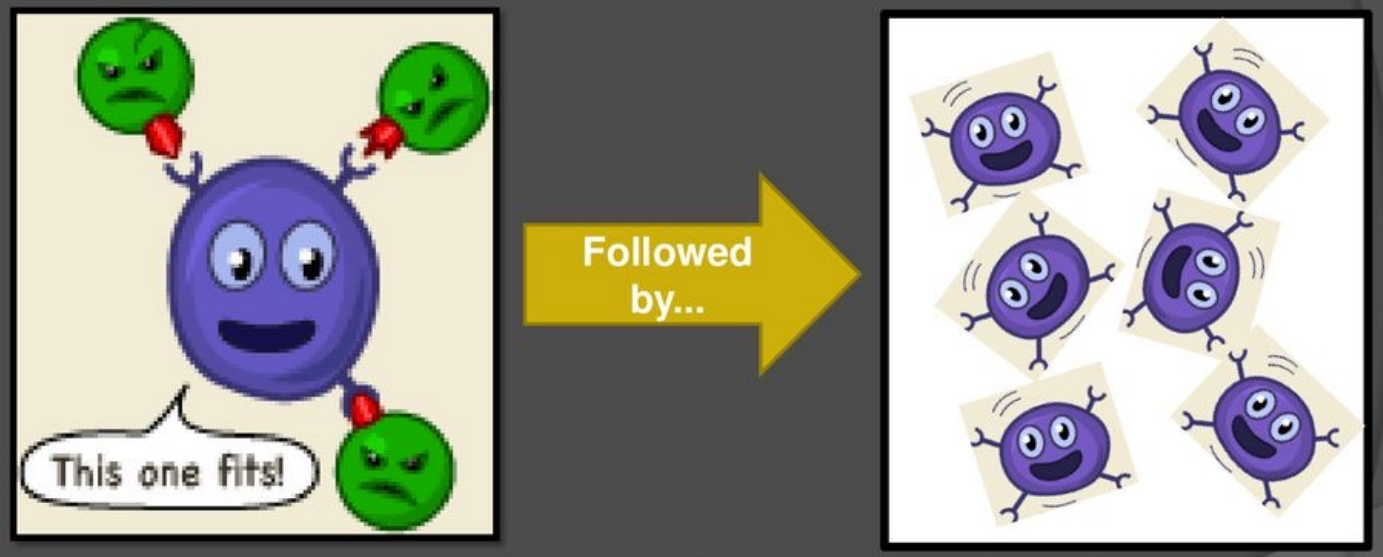
- Perforin: Forms a pore for delivery of granzymes
- Granzymes: Programmes cell to die (Induces apoptosis)
- Granulysin: Stabs the cell (Creates holes in target membrane & destroys it)

https://www.alignable.com/sweetwater-tn/lifes-many-blessings/what-is-a-helper-t-cell-jul-2018

- The selection of the correct B and T lymphocytes is known as clonal selection

Clonal Selection

Clonal Expansion



- To become effective at fighting the pathogen the lymphocytes must increase in number, this is clonal expansion

https://slideplayer.com/slide/14473568/

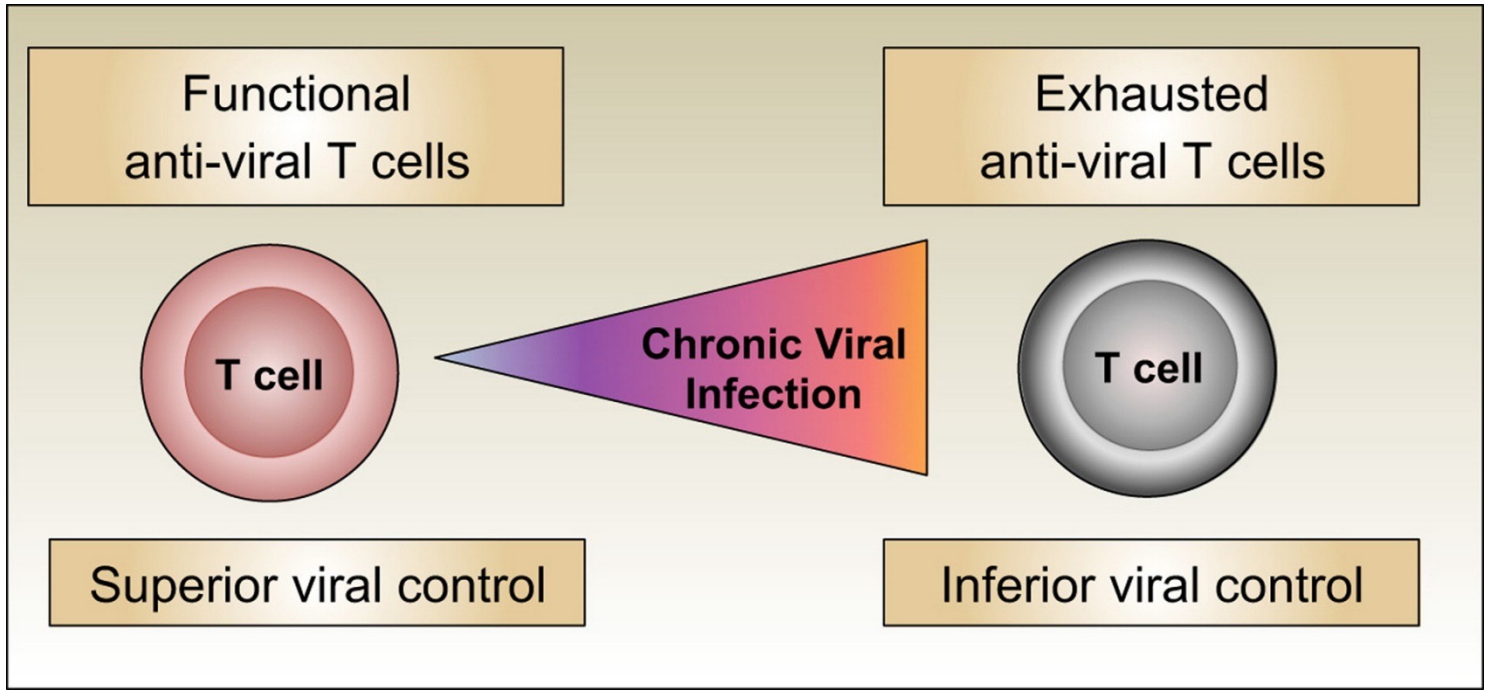
A sample of some important cytokines.

GM-CSF, M-CSF	Growth and differentiation factors for leukocyte progenitor cells in bone marrow
TNF-α, TGF-β, IL-1	Stimulation of inflammation and fever
IL-12	Stimulation of growth in T lymphocytes and NK cells
IL-2, IL-4	Growth factors for T helper cells and B lymphocytes
IL-5	Eosinophil proliferation, differentiation, and activation
Interferon-γ, IL-4	Activation of macrophages
IL-10	Inhibition of macrophages and specific adaptive immune responses
Interferon-α, interferon-β	Antiviral activity
IL-8	Chemokine for neutrophils and T lymphocytes

[a]GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; TGF, transforming growth factor; TNF, tumor necrosis factor.

https://basicmedicalkey.com/the-immune-system-lymphoid-organs/

The effect T cell exhaustion in fight against HIV.



https://www.sciencedirect.com/science/article/pii/S0042682214005820

Why Do We Love Dendritic Cells so Much?

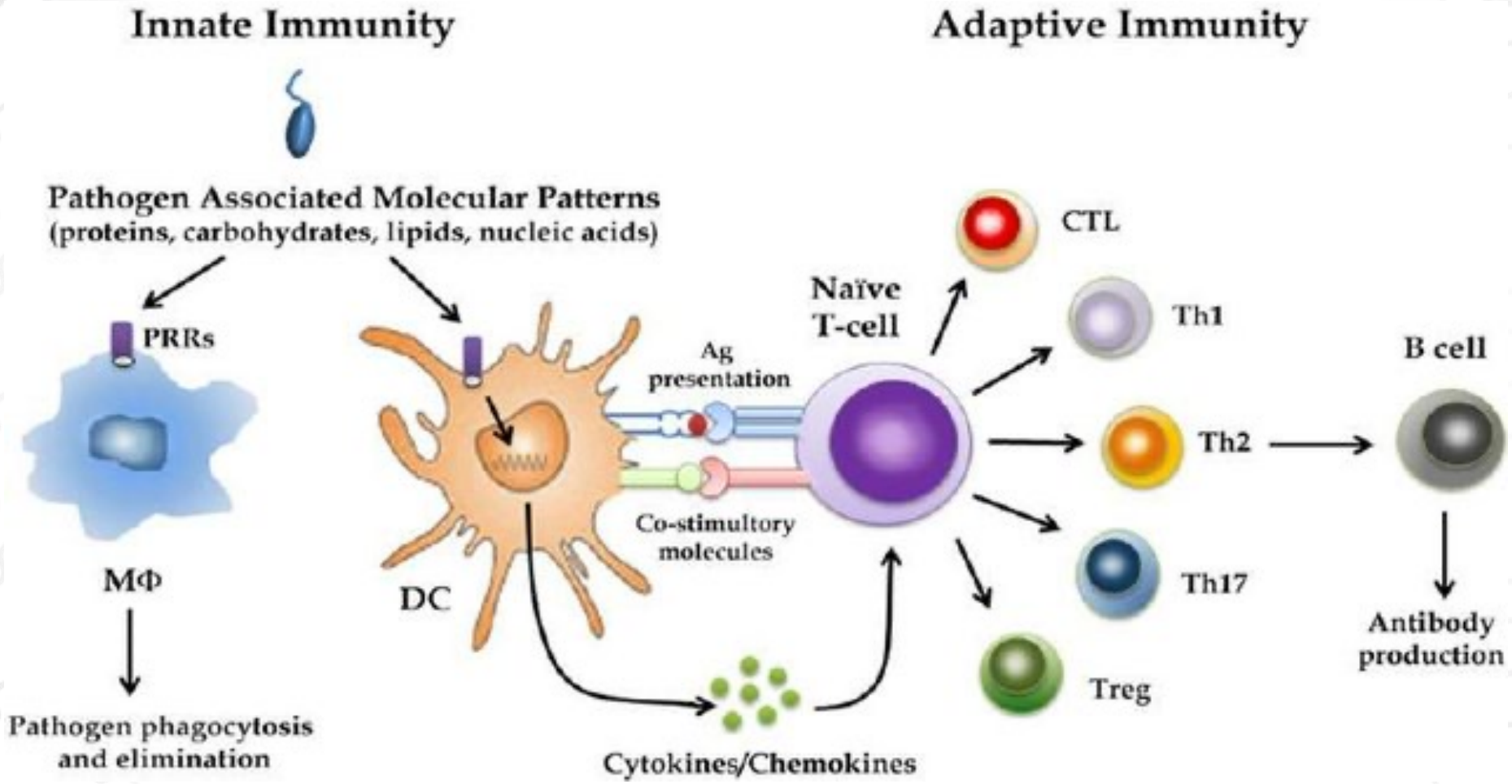
- Present antigens to the adaptive immune system
- Act as messenger cells

WHERE ARE DENDRITIC CELLS FOUND?

Most of the dendritic cells are found in the tissues of the external environment, such as skin contact (in this area Dendritic cells are also called *Langerhams Cells*) and also found in the nose, lungs and digestive tract.

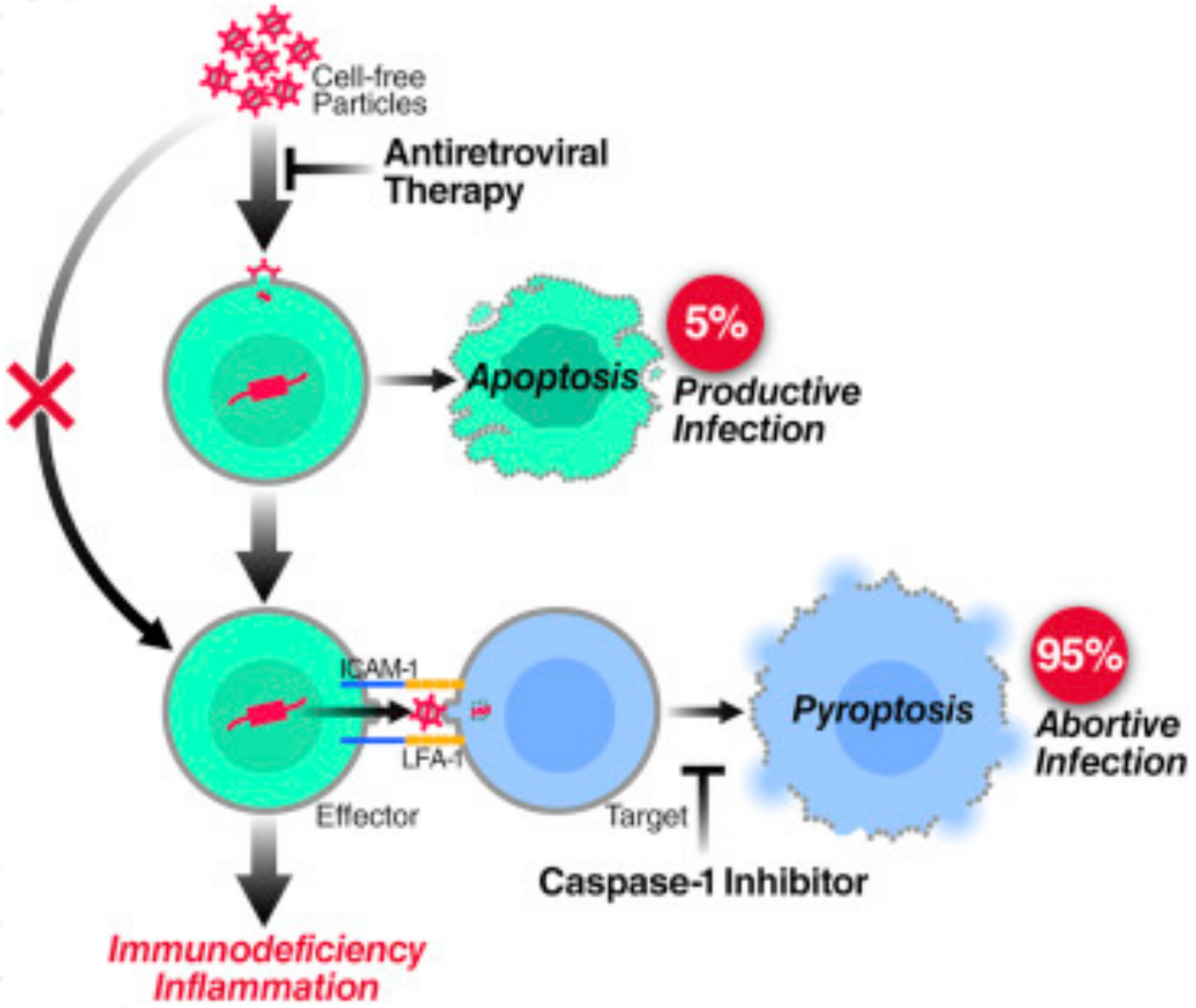
https://en.wikipedia.org/wiki/Dendritic_cell

The important role of dendritic (DC) cells.



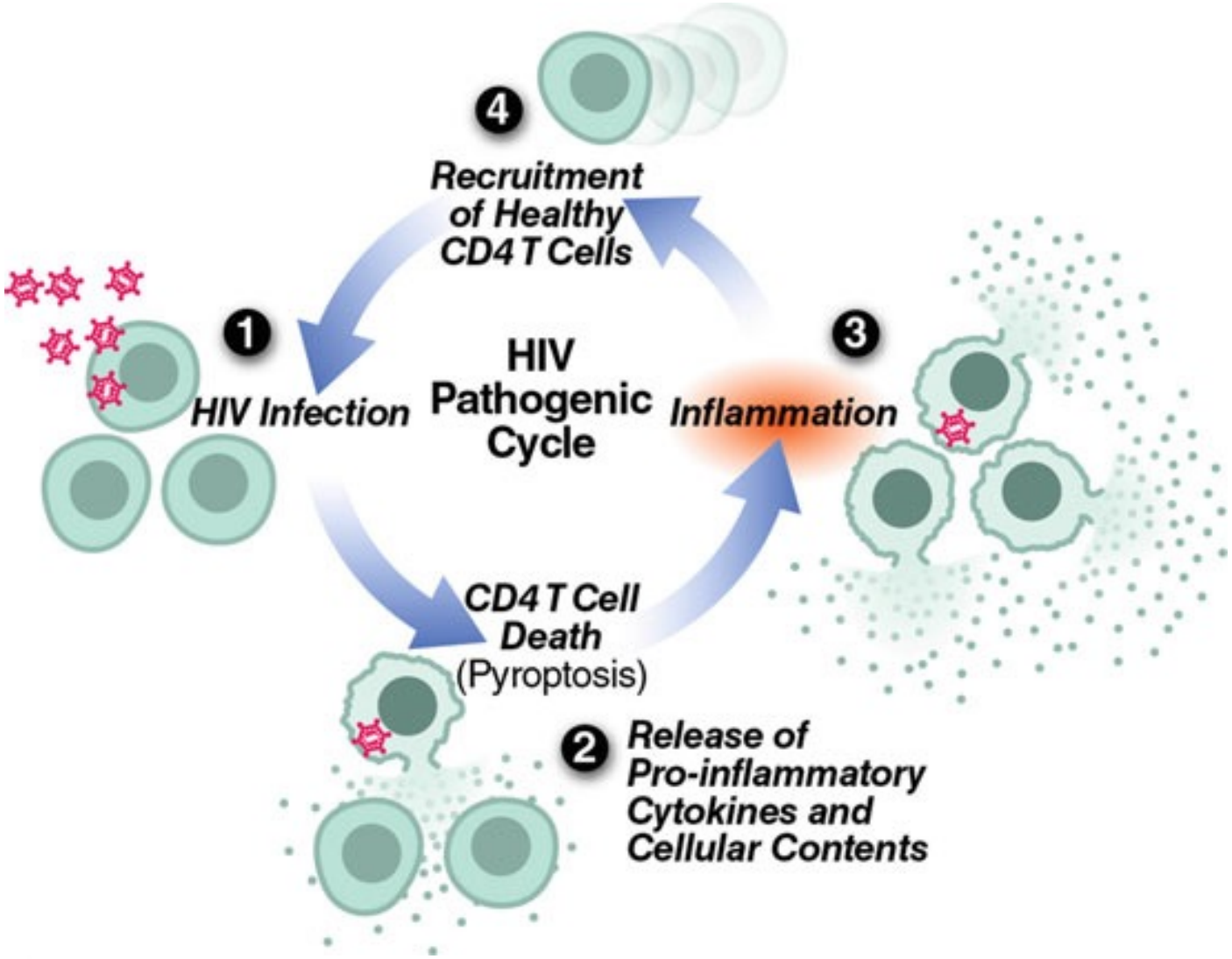
https://www.researchgate.net/publication/256257651_Pathogen_Strategies_to_Evade_Innate_Immune_Response_A_Signaling_Point_of_View/figures?lo=1

Two of three ways HIV causes the death of CD4 T Helper Cells.



https://www.sciencedirect.com/science/article/pii/S2211124715008827

The role of HIV and pyroptosis in the death of CD4 T Helper Cells.



https://link.springer.com/referenceworkentry/10.1007%2F978-1-4614-9610-6_392-1

Cell mediated killing of HIV infected cells.

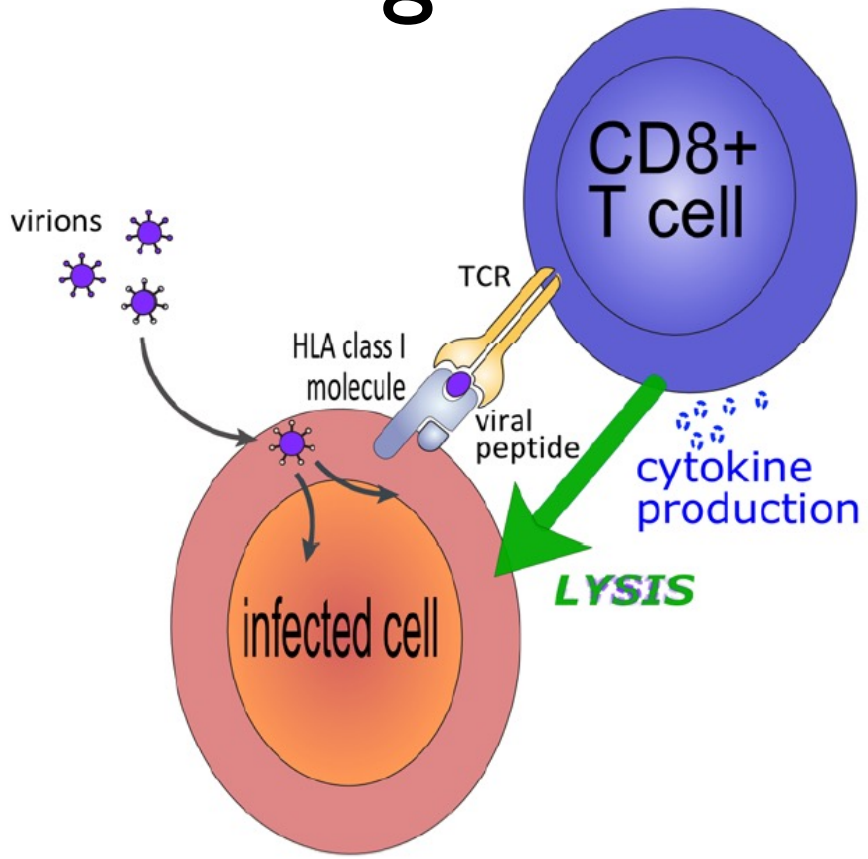


Figure 1. CD8+ T cells recognise virally infected cells via their T cell receptor (TCR). The TCR binds complexes of viral peptides and HLA class I molecules at the surface of virus-infected cells. Following CD8+ T cell recognition of the infected cell, the CD8+ T cell effector mechanisms are triggered. CD8+ effector mechanisms can be lytic (killing of the infected cell) and/or non-lytic (secretion of cytokines such as IFNg and TNFa which reduce the probability of cell infection and viral production).
doi:10.1371/journal.pcbi.1002381.g001

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3285570/

Why do we think a cure for HIV is possible?

Loreen Willenberg: An Exceptional Elite Control

- Exceptional **spontaneous response**

Test	Cell number	Cell type	Intact virus
Sequencing	>1.5 billion cells	PBMC	No
Viral outgrowth	340 million cells	Resting CD4	No
Intact DNA (PCR)	14 million cells	Resting CD4	No
	4 million cells	GI tract	No

Loreen Willenberg

Article

Distinct viral reservoirs in individuals with spontaneous control of HIV-1

https://doi.org/10.1038/s41586-020-2651-8
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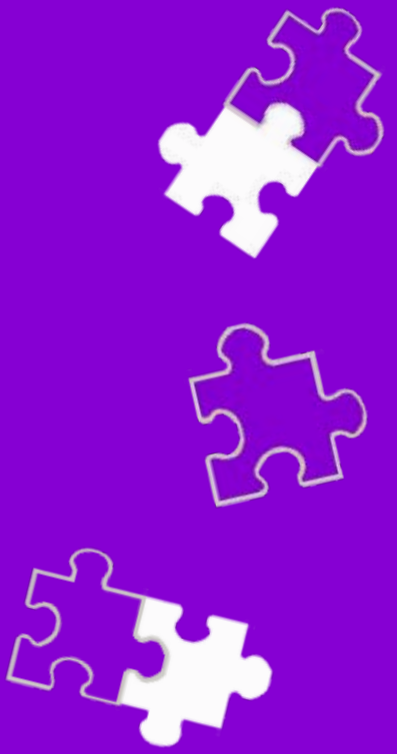
Check for updates

Chenyang Jiang[1,2,15], Xiaodong Lian[1,2,15], Ce Gao[1,15], Xiaoming Sun[1], Kevin B. Einkauf[1,2], Joshua M. Chevalier[1,2], Samantha M. Y. Chen[1], Stephane Hua[1], Ben Rhee[1,2], Kaylee Chang[1], Jane E. Blackmer[1], Matthew Osborn[1], Michael J. Peluso[3], Rebecca Hoh[3], Ma Somsouk[3], Jeffrey Milush[3], Lynn N. Bertagnolli[4], Sarah E. Sweet[4], Joseph A. Varriale[4], Peter D. Burbelo[5], Tae-Wook Chun[6], Gregory M. Laird[7], Erik Serrao[8,9], Alan N. Engelman[8,9], Mary Carrington[1,10], Robert F. Siliciano[4,11], Janet M. Siliciano[4,11], Steven G. Deeks[3], Bruce D. Walker[1,11,12,13], Mathias Lichterfeld[1,2,14] & Xu G. Yu[1,2]✉

How can HIV medications be helpful to a cure?



HIV Life Cycle and Drug Targets

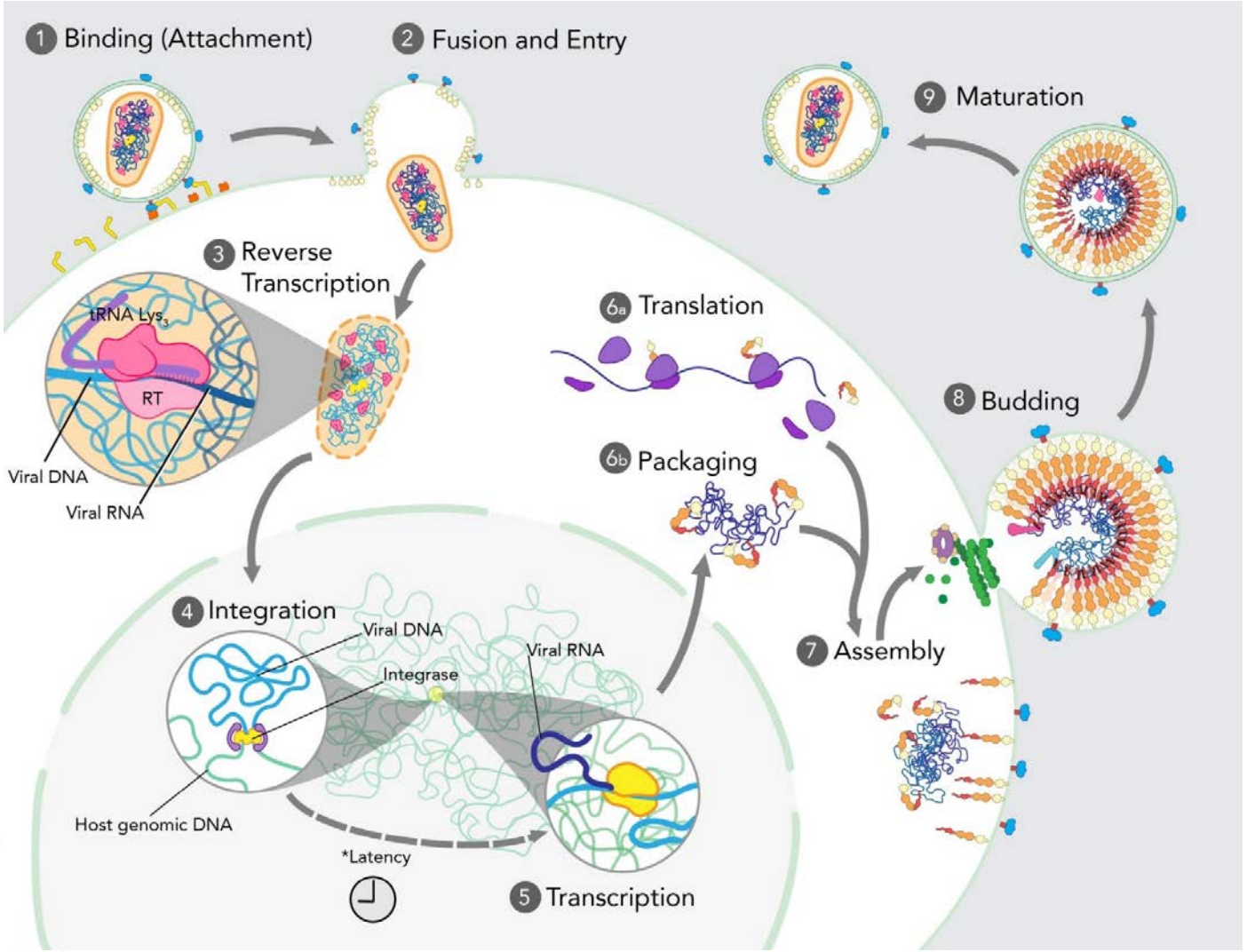
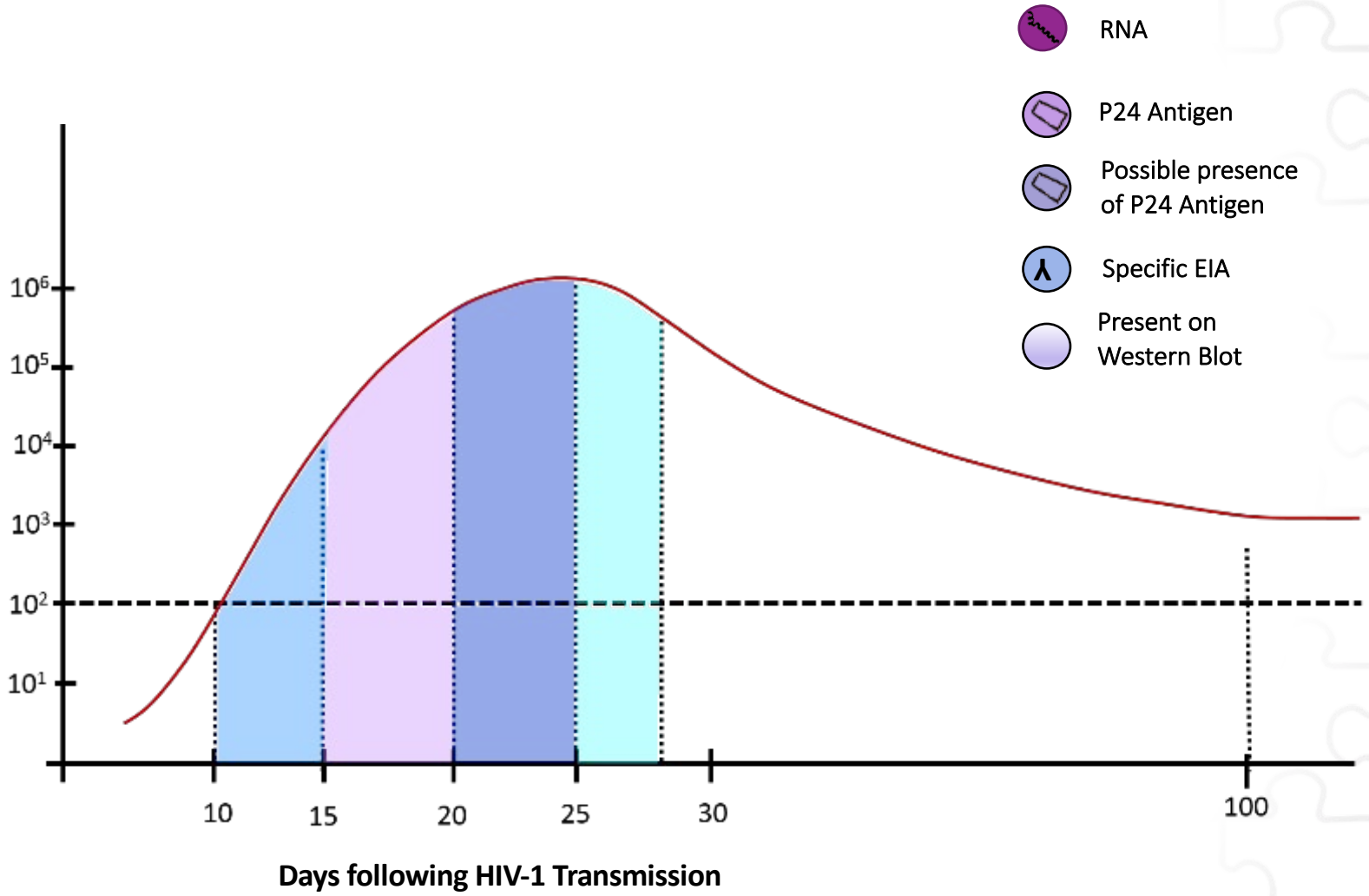
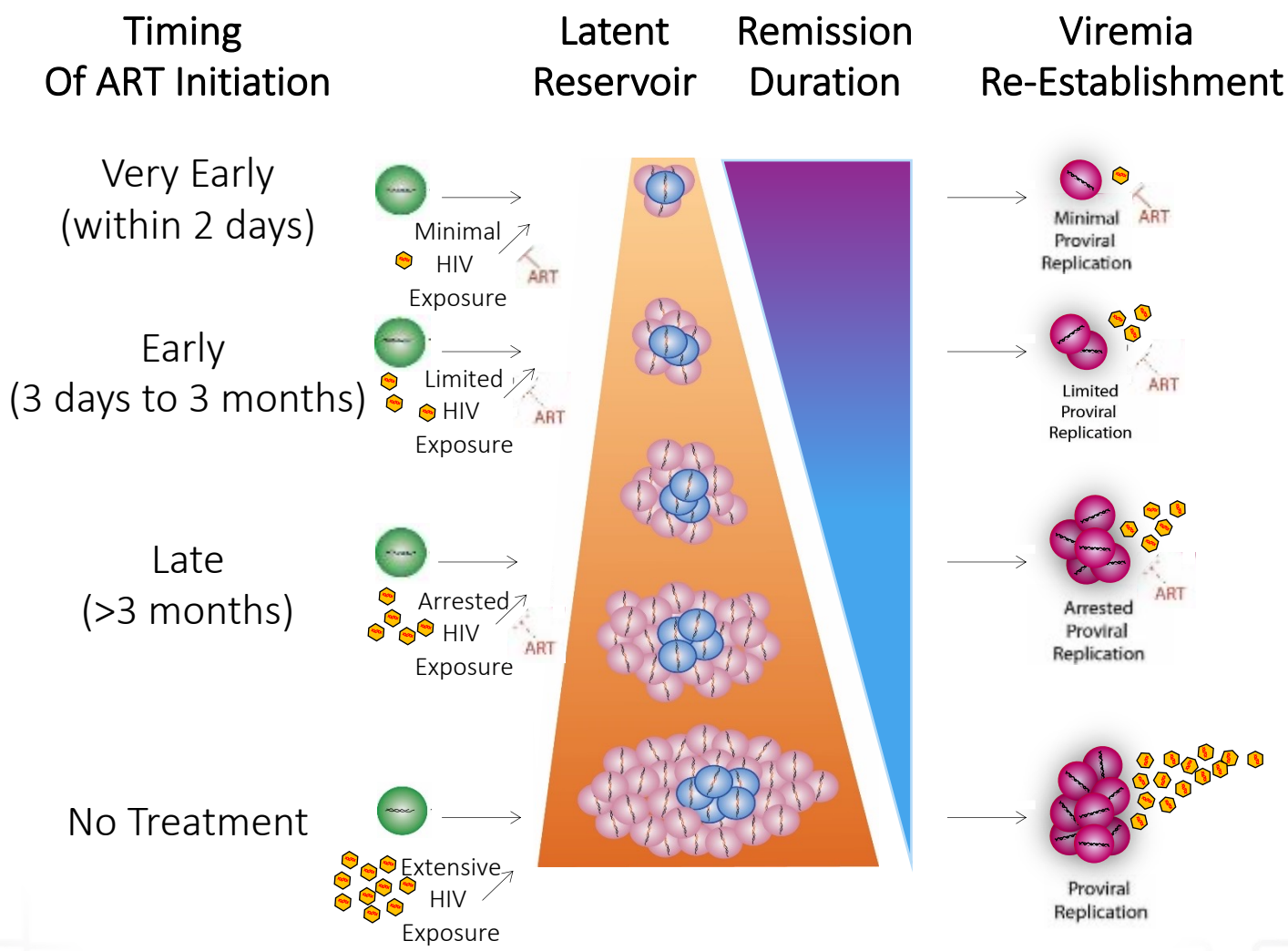


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

What are the Fiebig Stages?

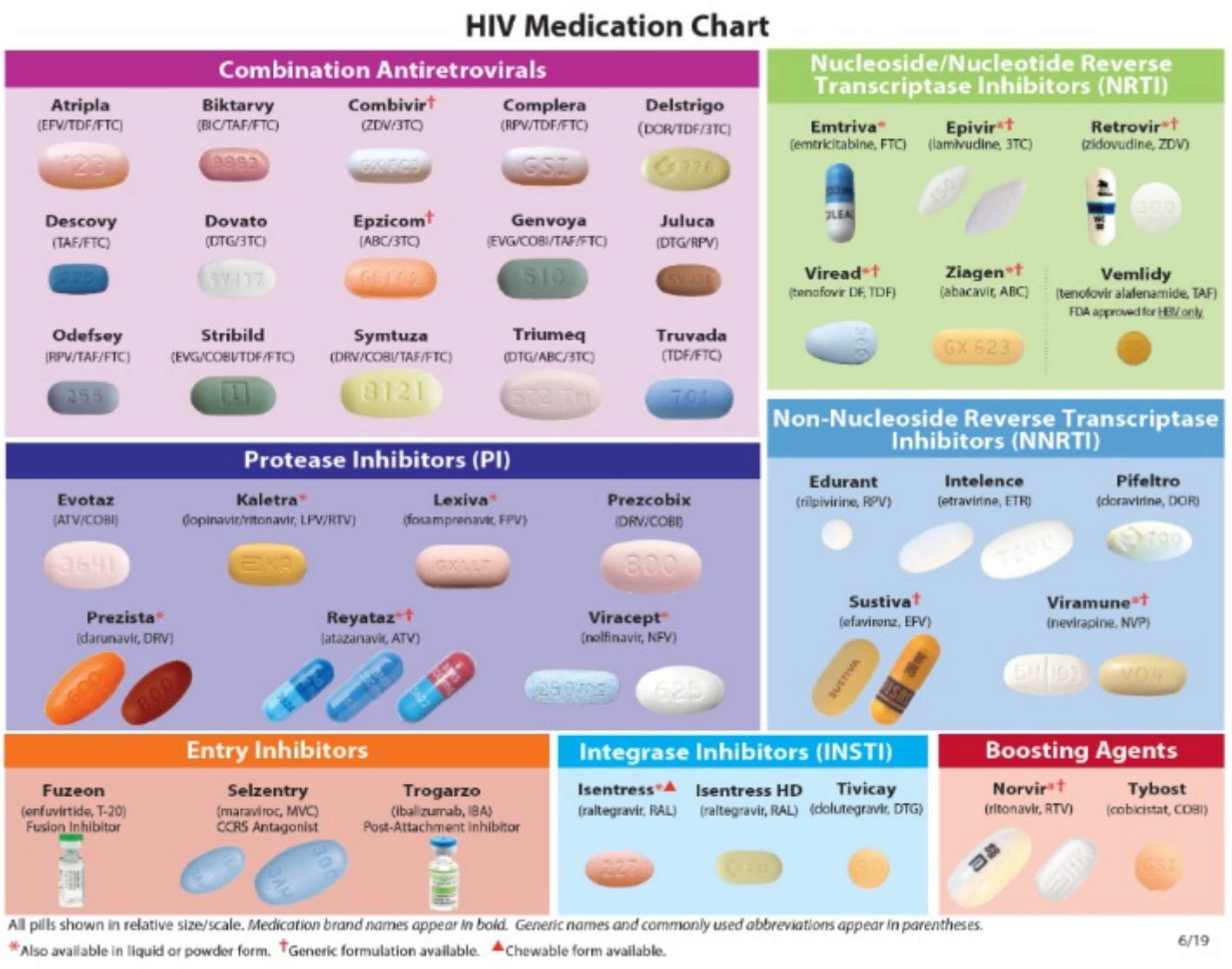


Early ART in Infants



Rainwater-Lovett et al 2015 *Curr Opin HIV AIDS*

Common Medications Used to Treat HIV

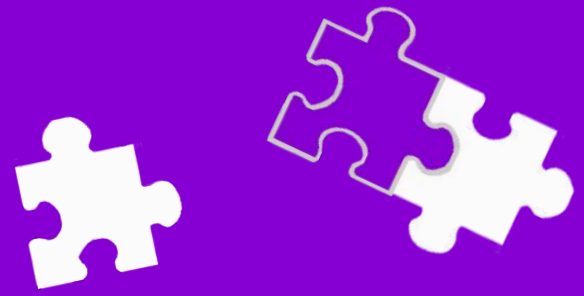


https://aidsetc.org/resource/hiv-medication-chart-pad

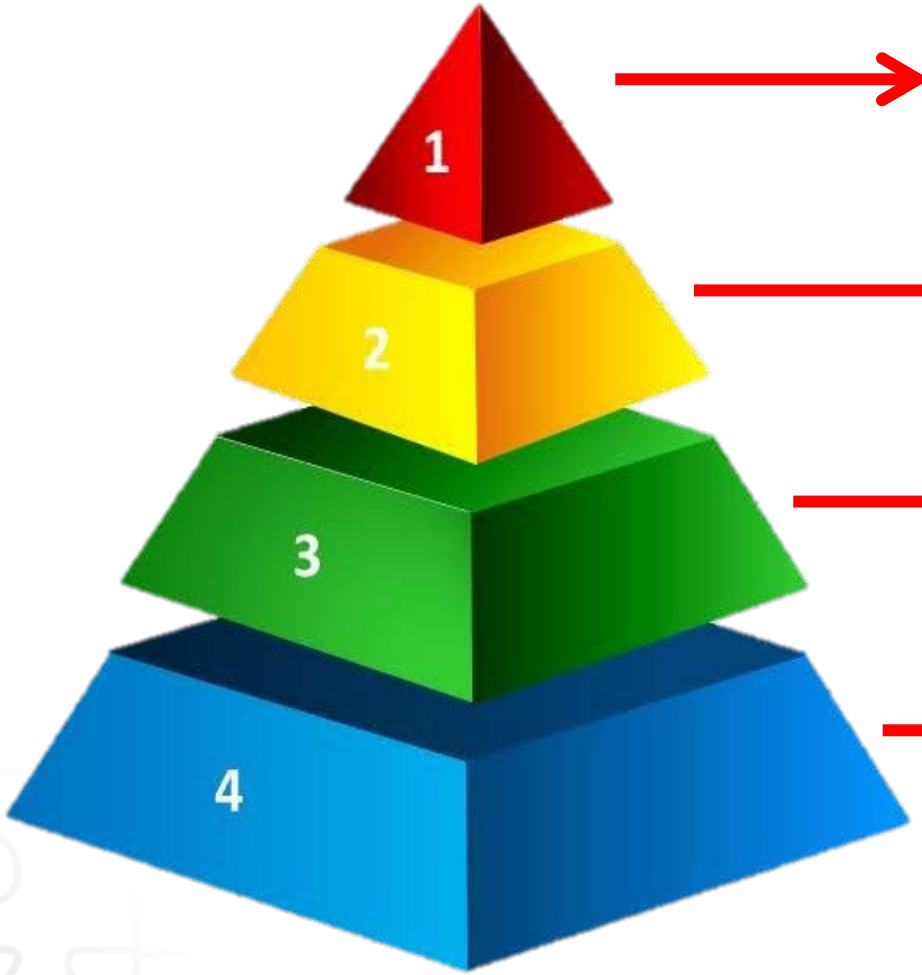
CUREiculum

Introduction

What has been the pathway to an HIV cure?



Stages of Clinical Research



Studies with cells in culture.

Studies in animal models.

Pre-clinical studies looking at safety.

Larger clinical studies looking at efficacy.

HIV Cure-Related Research

Bench Science

Understanding Persistence & Immune control

- Viral subtype
- Genetics
- Tissues
- Intervention Mechanism
- Analysis of preliminary work

Intervention Trials

Animal & Human Studies

Single or Combination Interventions

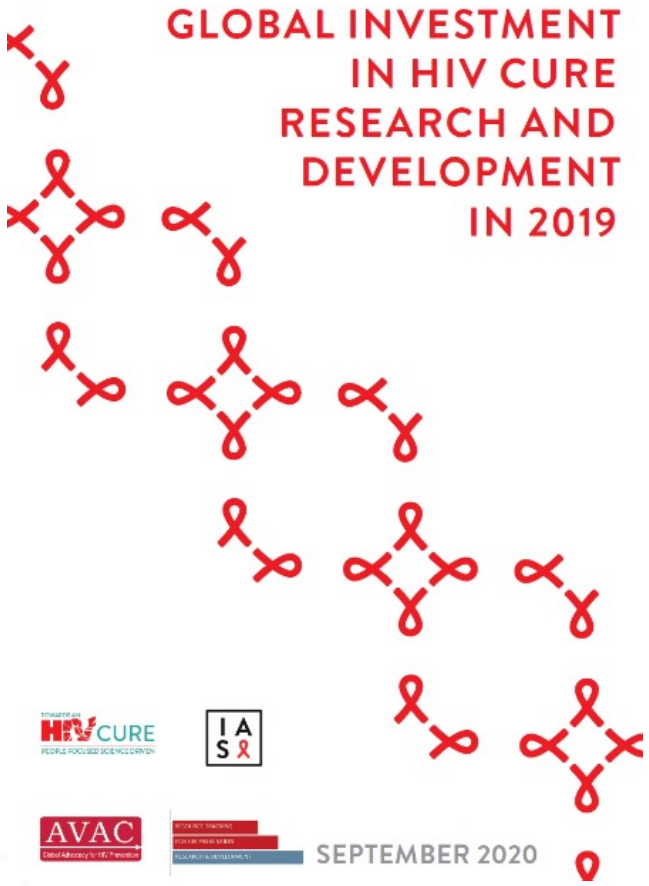
- Early ART
- Latency modifying agents
- Immune Therapies
- Cell & Gene Therapies

Ethics & Social-Behavioral Sciences

- Decision-making
- Perceptions of risks and benefits
- Attitudes about research
- Individual and societal impact

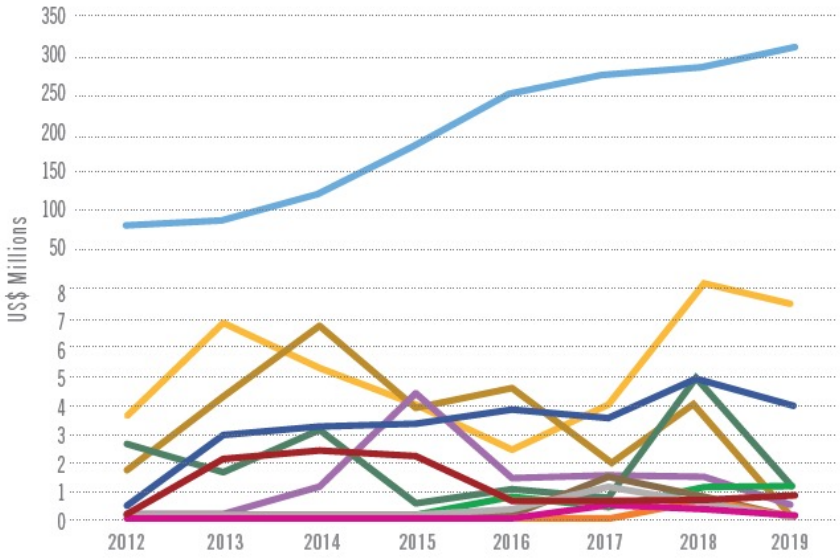
Adapted from Jintanat Ananworanich, Community HIV Cure Workshop, AIDS 2018

Global Investment in HIV Cure R & D (2019)



HIV Cure R&D Investments by Country, 2012–2019

	2012	2013	2014	2015	2016	2017	2018	2019
Australia	2.6	1.6	3.1	0.5	1.0	0.7	5.0	1.1
Canada	0.4	2.9	3.2	3.3	3.8	3.5	4.9	4.0
Cuba	0	0	0	0	0	0.5	0.4	0.1
European Commission	1.6	4.2	6.7	3.8	4.5	2.0	4.0	0
France	3.5	6.8	5.2	3.9	2.3	3.9	8.2	7.5
Germany	0	0	0	0	0.7	0.3	1.2	1.1
Italy	0	0	0	0	0	1.4	0.5	0
Spain	0	0	0	0	0	0	0.8	0
Switzerland	0.03	2.0	2.3	2.1	0.5	0.5	0.6	0.9
The Netherlands	0	0	0	0	0.2	1.0	0.4	0
United Kingdom	0.03	0.03	1.0	4.3	1.3	1.4	1.6	0.7
United States	79.4	85.9	120.4	183.2	252.1	273.6	296.0	312.8



Global investment:

approximately ***US $323.9 million***

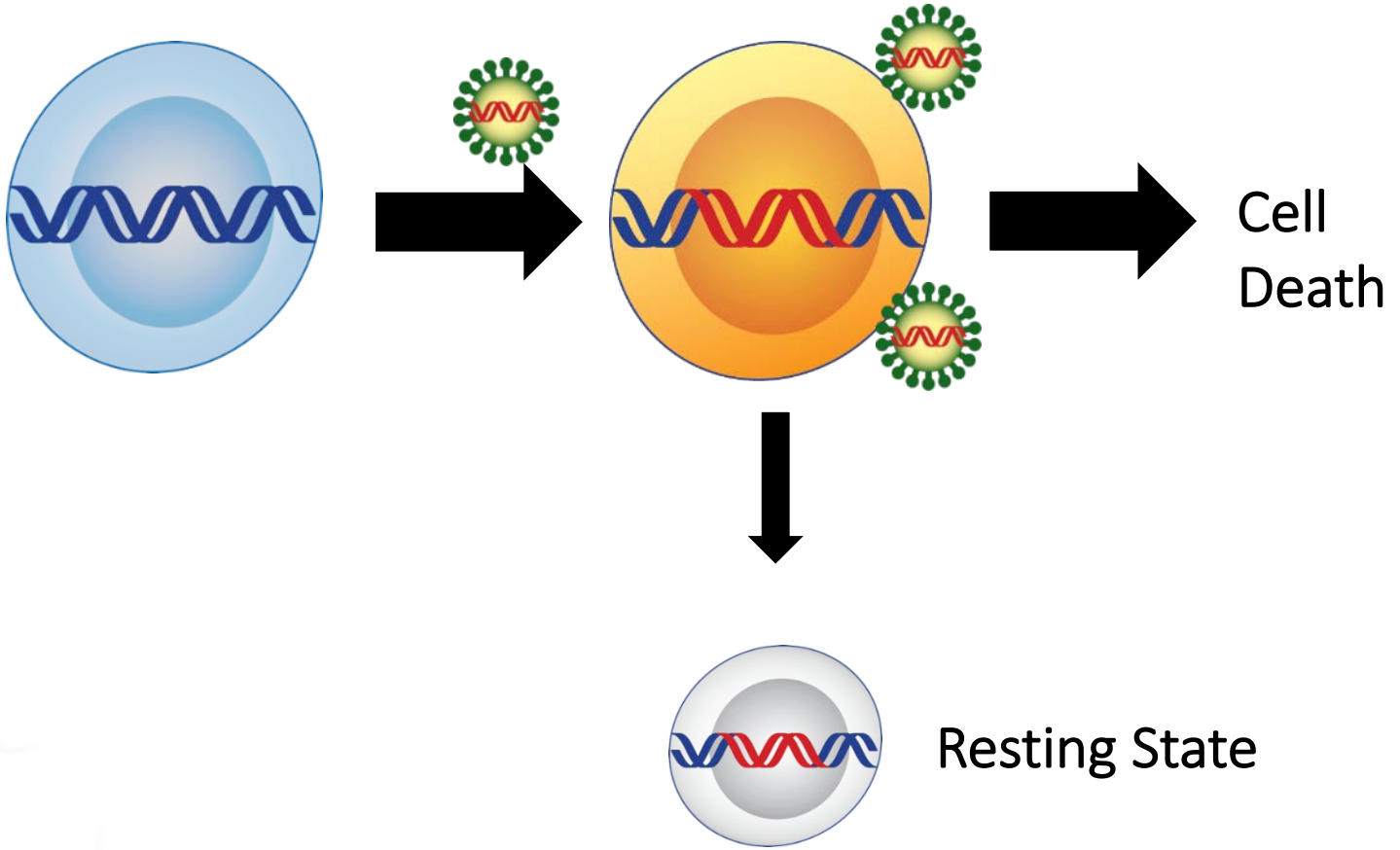
https://www.avac.org/blog/new-report-global-investment-hiv-cure-research-and-development

Why is it difficult to cure HIV?

Why is HIV **so hard** to cure?

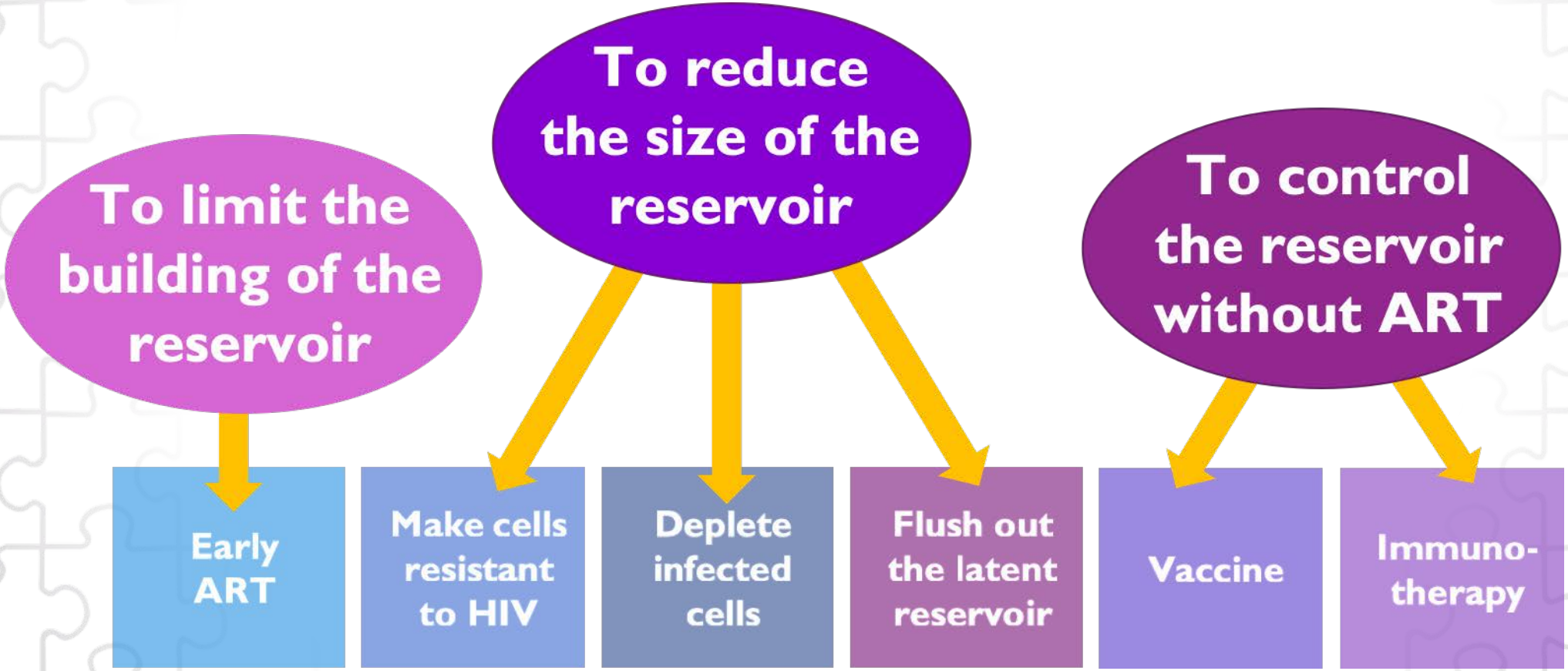
- HIV enters a cell and integrates into the cell's DNA
- **Most** cells recognize infection – causing cell death
- **A few** infected cells become "long-lived" memory cells or "resting memory" cells
- The collection of long-lived memory cells is called the **Latent Reservoir** = main barrier to curing HIV

Establishing the Reservoir



What pathways are currently being explored?

HIV Cure-Related Research Strategies Under Investigation



Slide Credit: Nicolas Chomont

Latency Reversing Agents

Image credit: The Economist, July 11

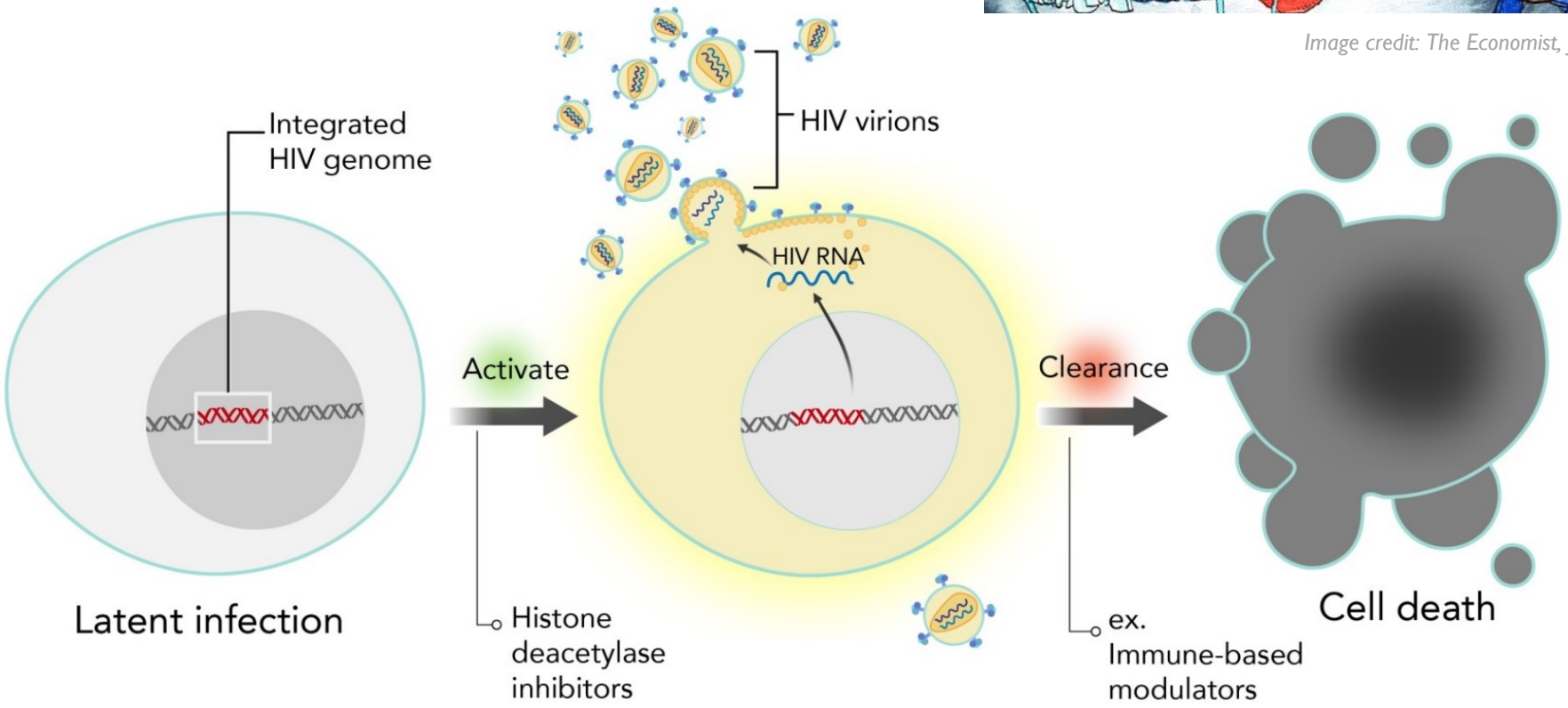
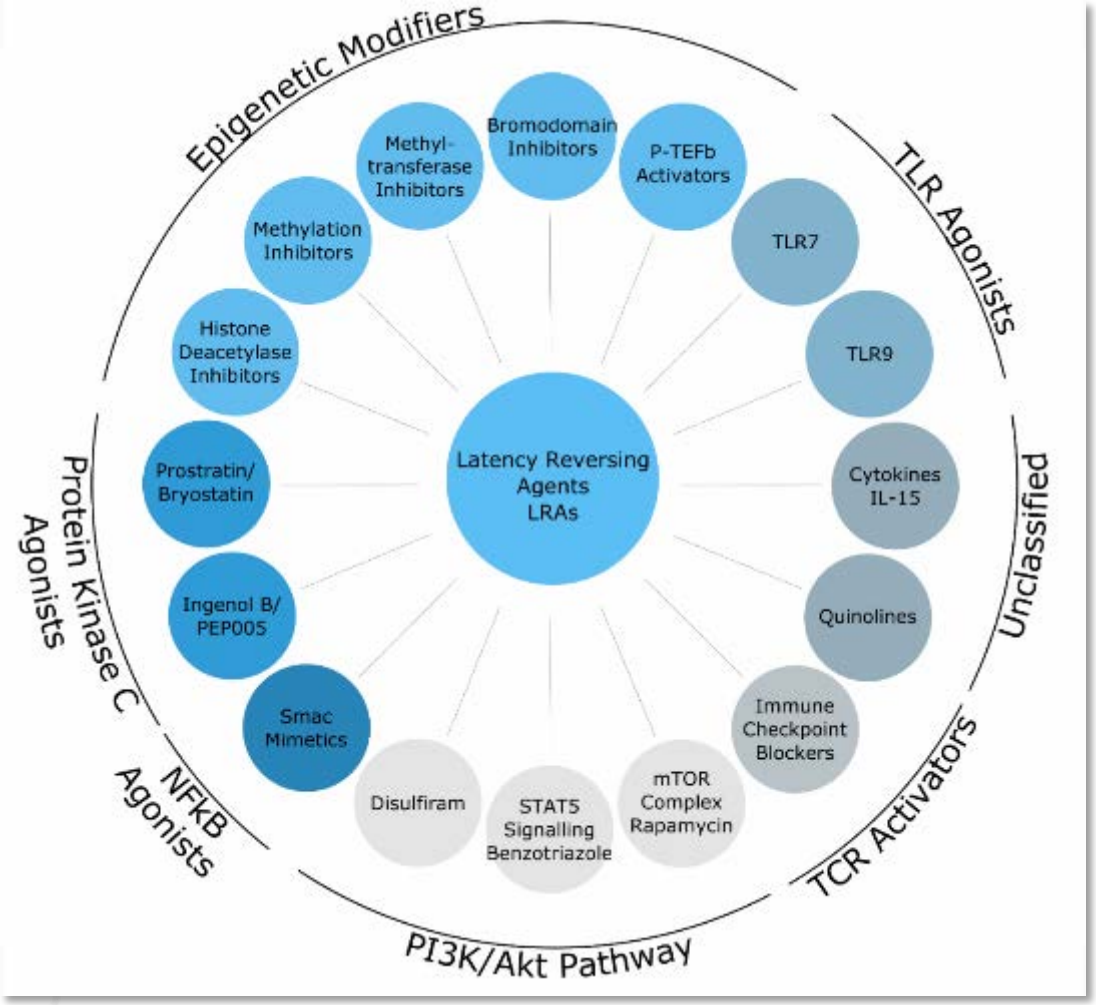


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Latency-Reversing Agents

Sharon Lewin

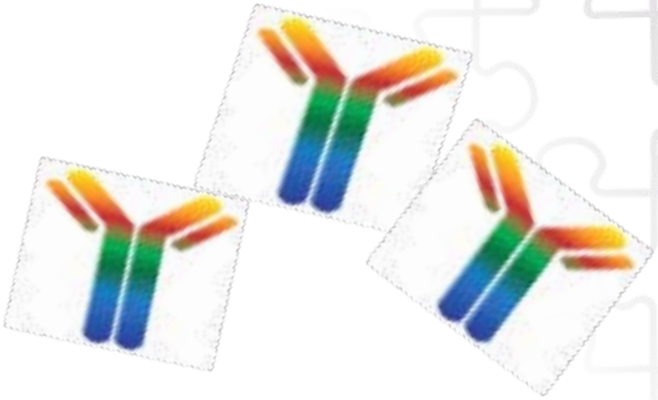


- None are HIV specific
- None are as potent as T-cell activation
- Unclear if virus is coming from all cells or just a few
- Still need better latency-reversing agents

Kim, Anderson and Lewin. *Cell Host Microbe* 2018

Lewin SR. Why Should We 'Shock and Kill'. Community Cure Workshop. Saturday July 21, 2018.

Broadly Neutralizing Antibodies



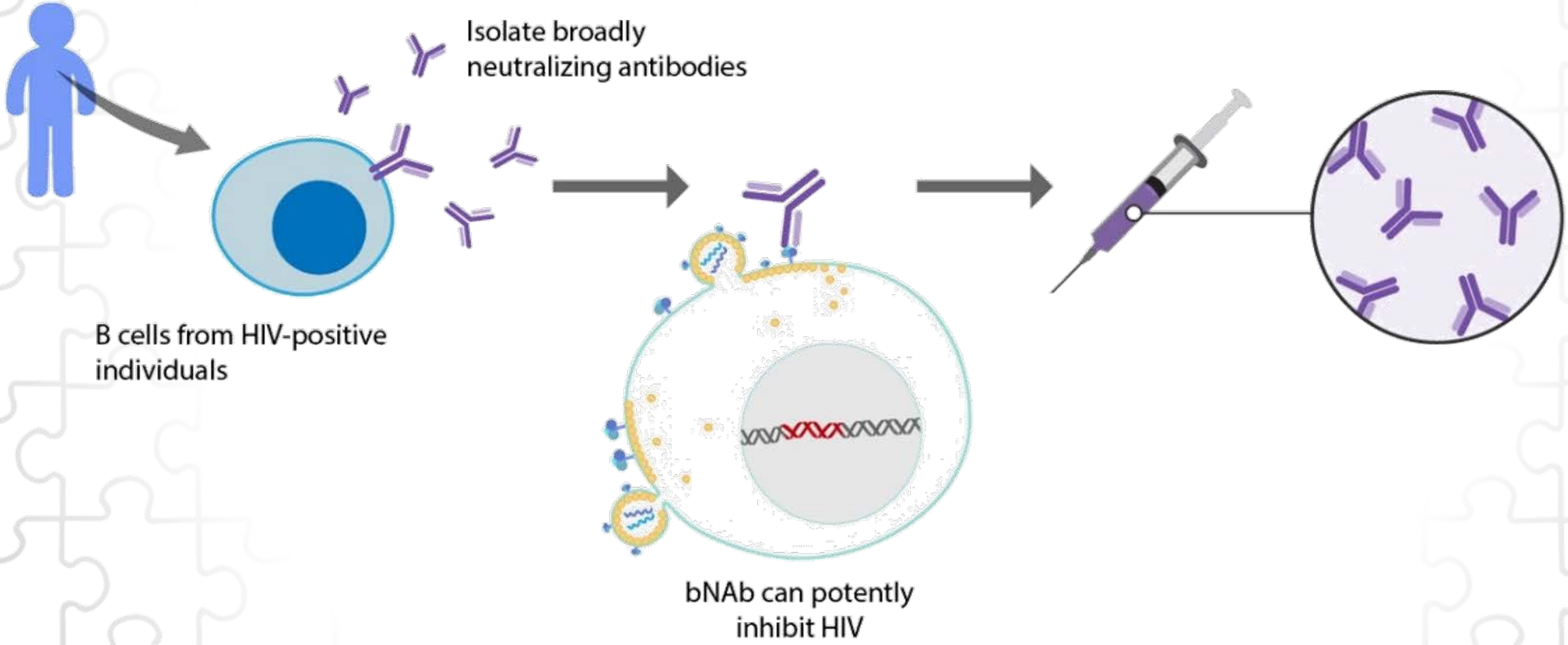
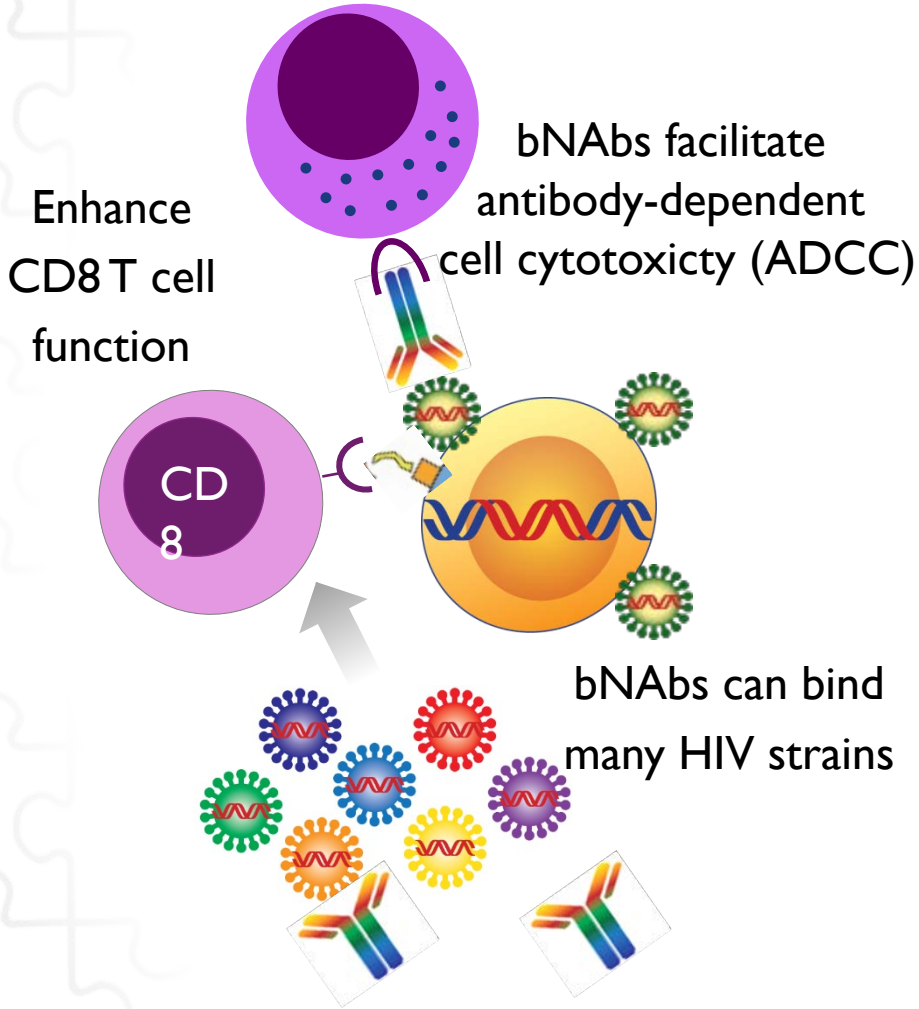


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Broadly Neutralizing Antibodies (bNAbs)



Main obstacle

- Pre-existing resistance

Strategies

- Broad and potent
- Multiple
- Tri-specific
- Long-acting
- Novel delivery platforms
- Early administration
- Combine with other agents

Kong, J Virol 2015; Barr, NEJM 2016; Scheid, Nature 2016; Caskey, Nature Med 2017; Hessell, Nature Med 2016; Liu, Science 2016; Nishimura, Nature 2017; Pardi, Nature Communications 2017; Gardner, Nature 2015; Pitman, Lancet 2018

Immune-Based Strategies

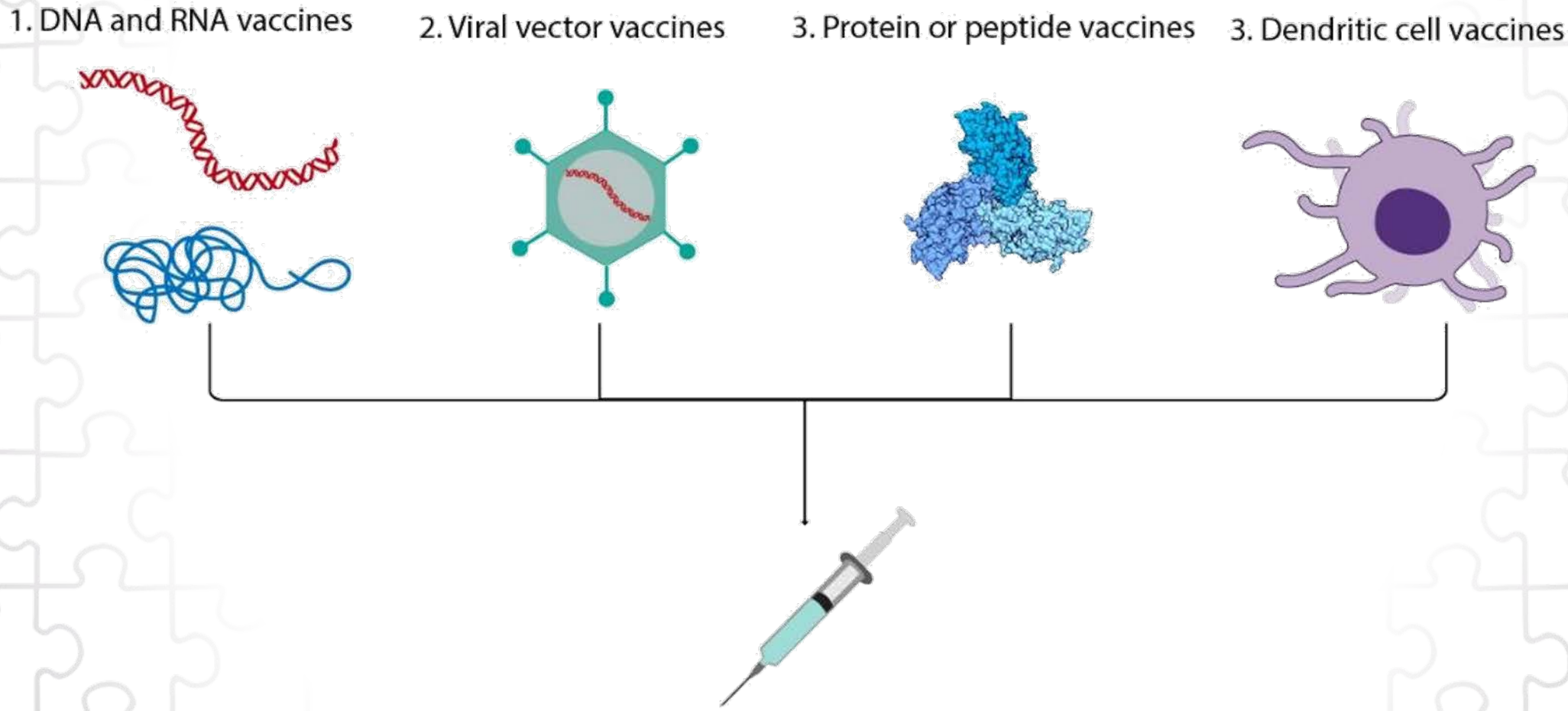
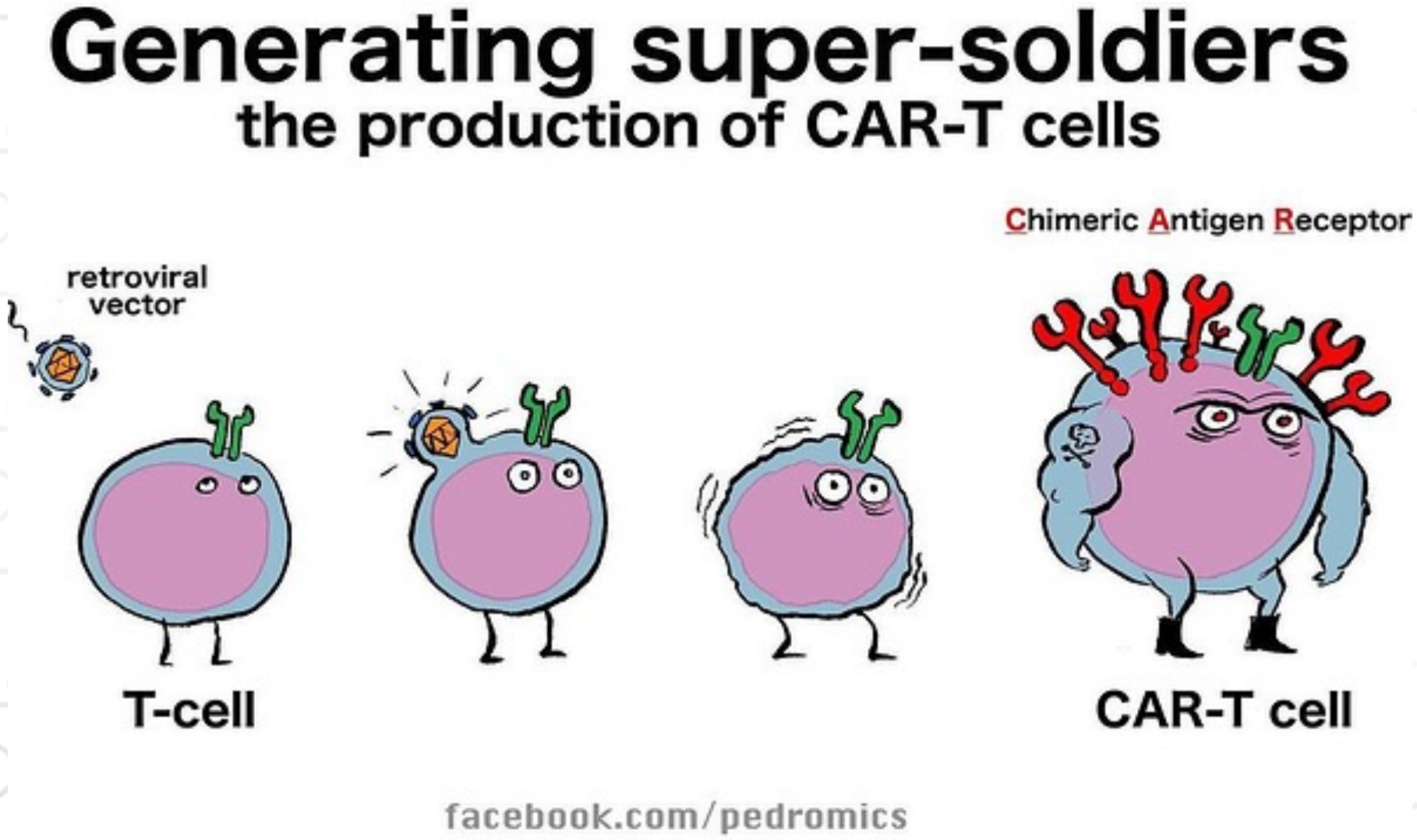


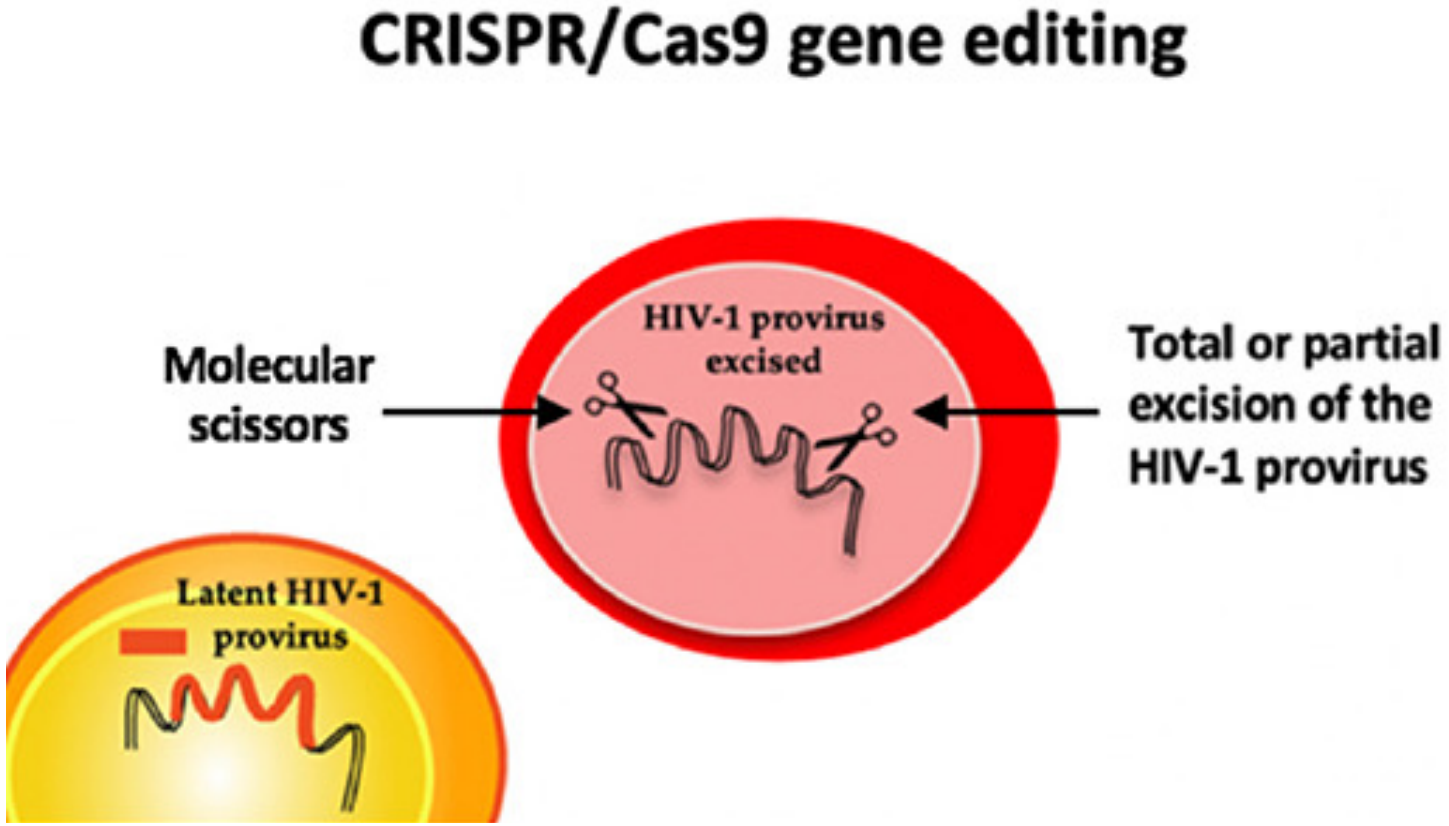
Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Chimeric Antigen T cells (CAR-T cell)



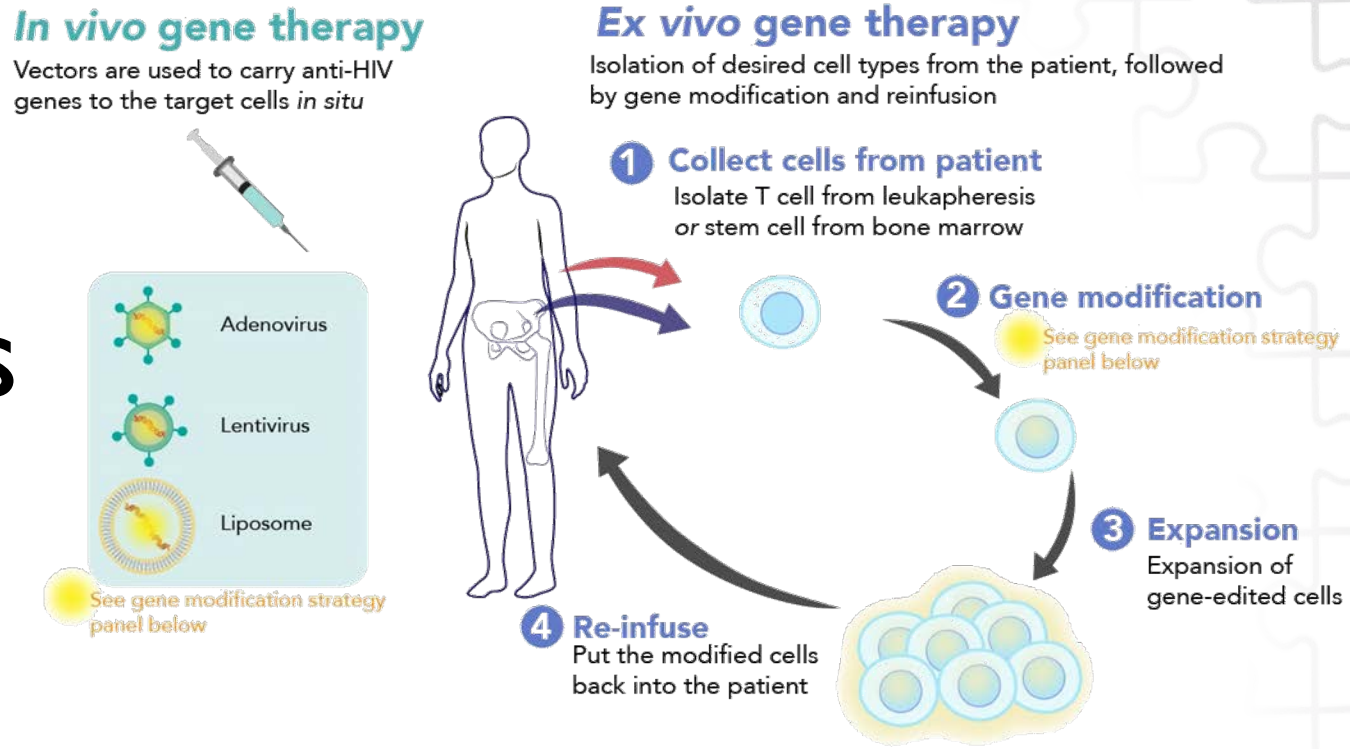
https://blog.seracare.com/ngs/aacr-2019-day-one-highlights-next-generation-car-t-cells?utm_medium=social&utm_source=facebook

Cell & Gene Approaches



https://www.frontiersin.org/articles/10.3389/fcimb.2020.00424/full

Cell & Gene Approaches



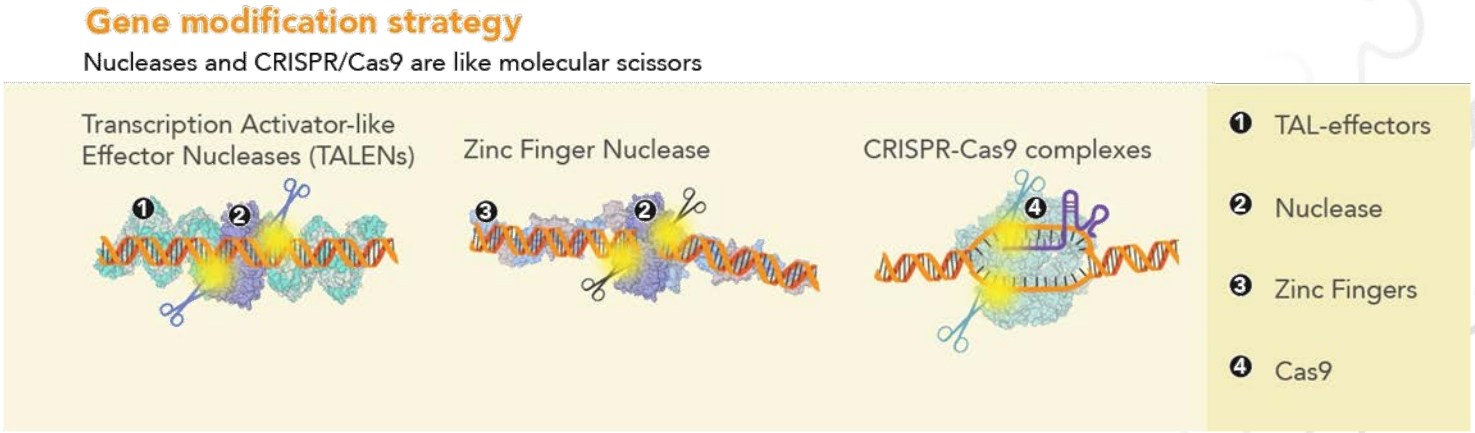
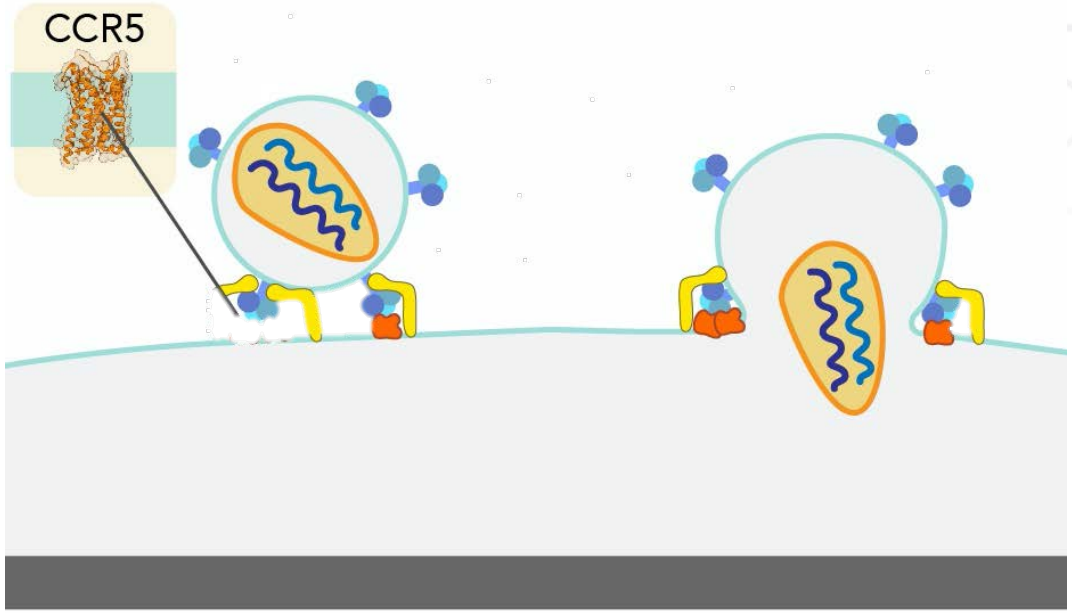
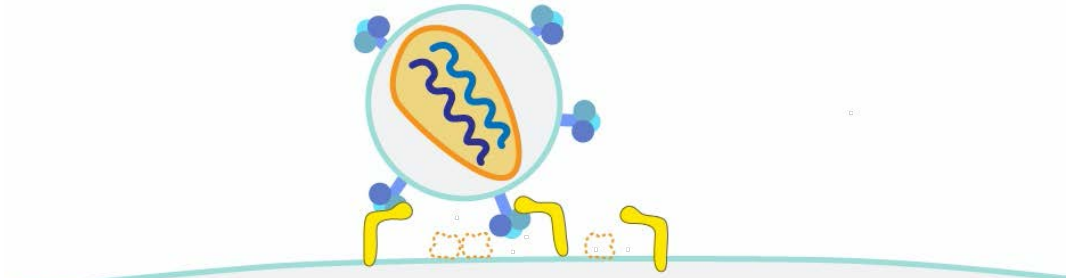


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Cell & Gene Approaches



Use gene therapy techniques to disable the gene that encodes CCR5 receptor



Modified CCR5 receptors cannot bind to HIV, blocking fusion with host cell

Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Cell & Gene Approaches

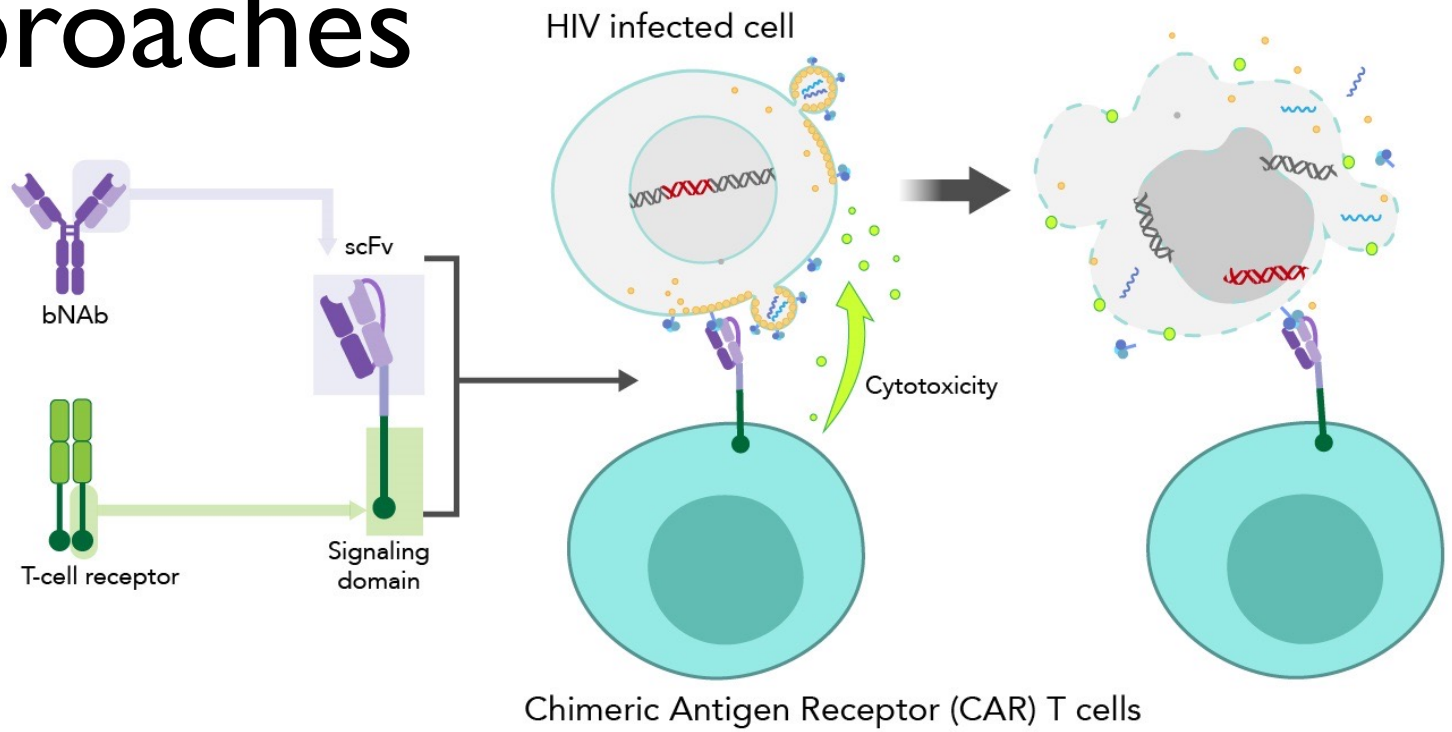


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Useful Video Links

- **Understanding Apoptosis and Pyroptosis:**
  https://www.yotube.com/watch?v=vKi95jdJLhs
- **Khan Academy - How HIV Kills So Many CD4 T Cells**
- https://www.youtube.com/watch?v=vKi95jdJLhs
- **Khan Academy - How HIV infects us 1: mucous membranes, dendritic cells, and lymph nodes.**
- https://www.youtube.com/watch?v=QEvjvpvLxmQ
- **What is CAR T-Cell Therapy?**
- https://www.youtube.com/watch?v=LNX-ywebx-0
- **HIV: Basic Function Of The Immune System**
  https://www.youtube.com/watch?v=YUNVGCQVe2g
- **HIV Infection Stages, Pathology And Treatment**
  https://www.youtube.com/watch?v=horX8xLVpCg
- **HIV Infection Mechanism – Dendritic Cells**
  https://www.youtube.com/watch?v=ZroXIBg8keA
- **Understanding HIV Reservoirs**
  https://www.youtube.com/watch?v=XkQqE02gbVc
- **Understanding Broadly Neutralizing Antibodies**
  https://www.youtube.com/watch?v=Dr7werW5Or4&t=26s

Useful Video Links (cont'd)

- **Gene Editing explained**
  https://www.youtube.com/watch?v=E8vi_PdGrKg
- **CAR-T Cells in cancer**
  https://www.youtube.com/watch?v=OadAW99s4Ik
- **Live Cell Imagine T cells with Macrophages**
  https://www.youtube.com/watch?v=SkT1ZxsVSGM
- **Cytotoxic T cell function**
- https://www.youtube.com/watch?v=WdCiaIS2LV4

ACKNOWLEDGMENTS

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AIDS ACTION BALTIMORE

TAG Treatment Action Group








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