HIV Cure-Related Research Strategies

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.

Module Outline

- Key timeline events
- Research process overview
- Research ‘dam’ analogy
- Stem cell transplantations
- Early ART
- Draining the ‘reservoir’
- Reinforcing the ‘dam’
- Making cells stronger
- Putting different strategies together

research strategies

Key timeline events

HIV cure is **rare**.

research strategies

HIV Cure is Rare: Elimination and Durable ART-Free Suppression

2009 — **TIMOTHY RAY BROWN**

THE BERLIN PATIENT

2010 — **VISCONTI/SPARTAC/CHAMP**

POST TREATMENT CONTROL

2019 — **ADAM CASTILLEJO**

THE LONDON PATIENT

2020 — **LOREEN WILLENBERG**

THE SAN FRANCISCO PATEINT.

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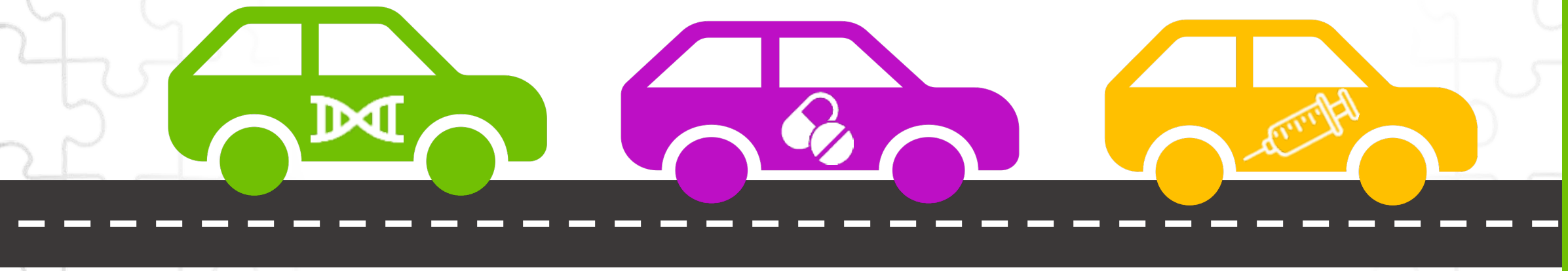
Hutter et al., N Engl J Med 2010; Gupta et al., Nature 2019; Gupta et al, Lancet HIV 2019; Jiang et al., Nature 2020

SLIDE CREDIT: Sharon Lewin, Singapore AIDS Conference 2020

Overview of the Research Process

Overview of Research Process



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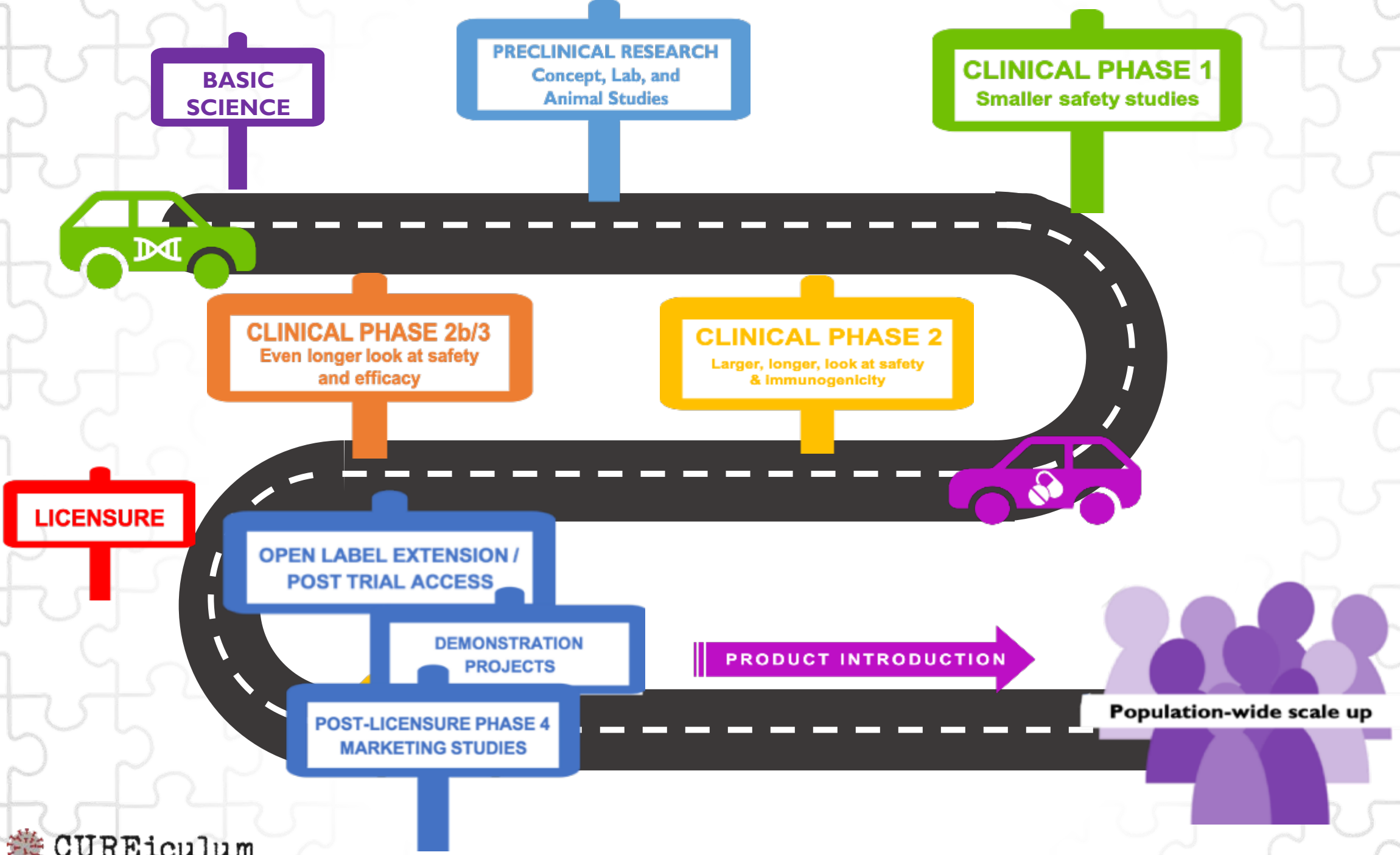

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Why is HIV so hard to cure?

So few cells harbor HIV in people on antivirals medications and these cells appear normal to our immune system

Research ‘dam’ analogy

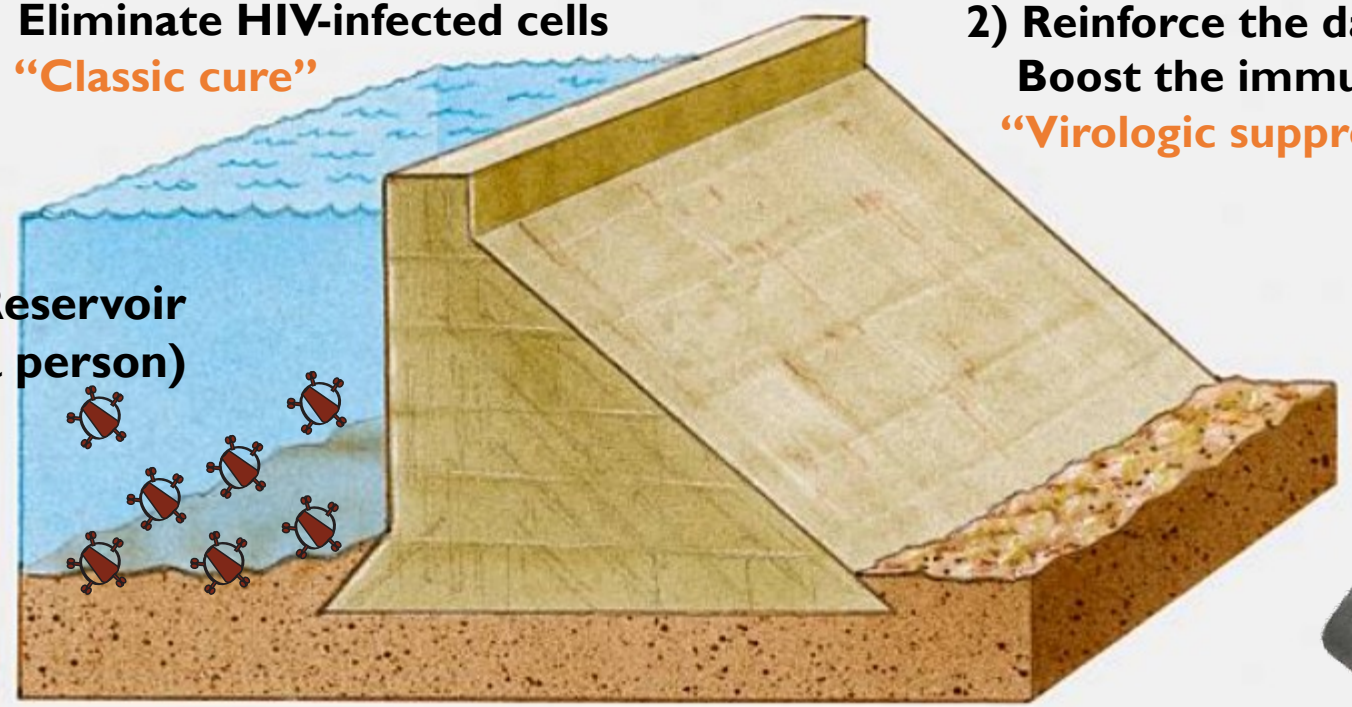
How Can We Prevent HIV From Rebounding Off Therapy?

R. Brad Jones

1) Drain the HIV reservoir
Eliminate HIV-infected cells
"Classic cure"

2) Reinforce the dam
Boost the immune response to HIV
"Virologic suppression off ART/remission"

HIV Reservoir
(in a person)



SLIDE CREDIT: Jones RB. The Newest Science in Cure and Vaccine. Plenary Presentation Main IAS 2018 Conference.

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Strategies Towards HIV Cure

R. Brad Jones

Latency reversal– **reactivate latent HIV** with drugs and kill with immune system

Gene therapy to **delete HIV** out of cells

Gene therapy to make cells **resistant to HIV**

Vaccines / Immunotherapies – **enhance immune responses** to control virus

'Block and lock' – **permanently silence** HIV expression (force into deeper latency)

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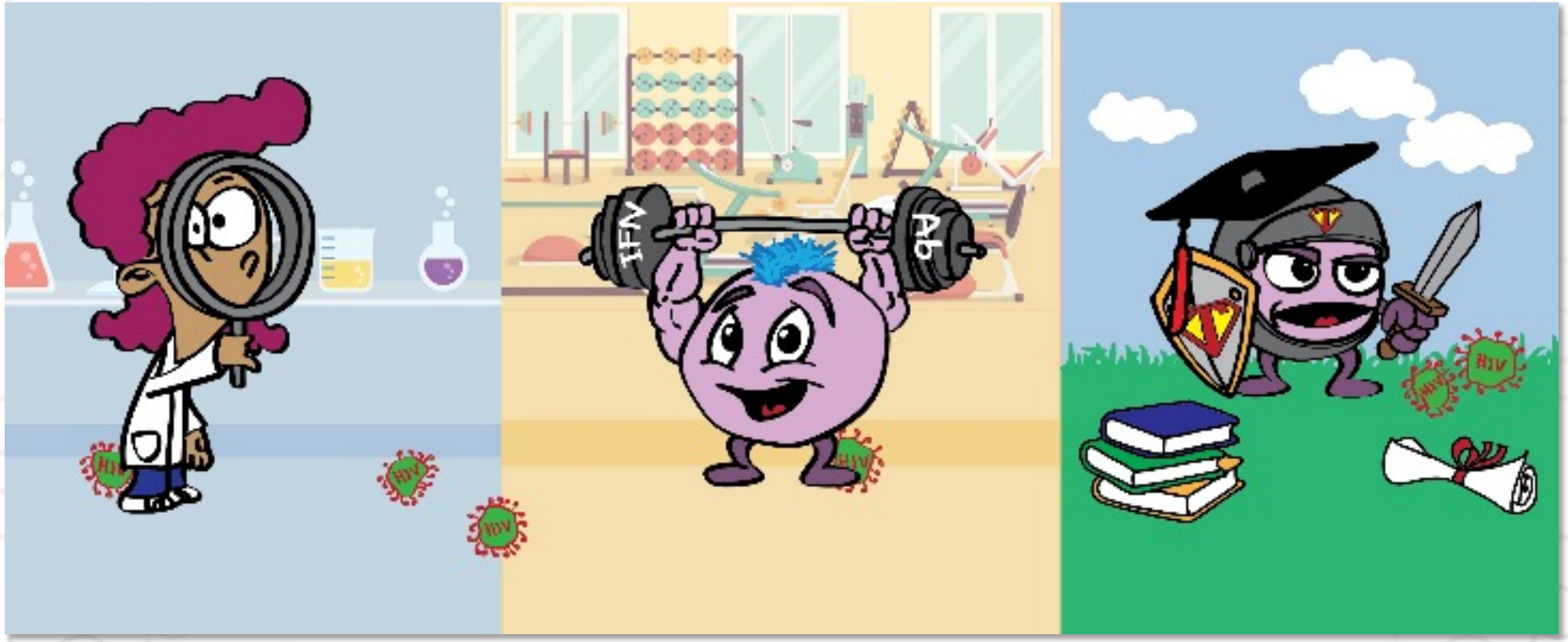
SLIDE CREDIT: Jones RB. The Newest Science in Cure and Vaccine. Plenary Presentation Main IAS 2018 Conference.

HIV Cure-Related Research Strategies Under Investigation



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Cartoon Credit: BEAT-HIV Collaboratory

Slide Credit: Nicolas Chomont

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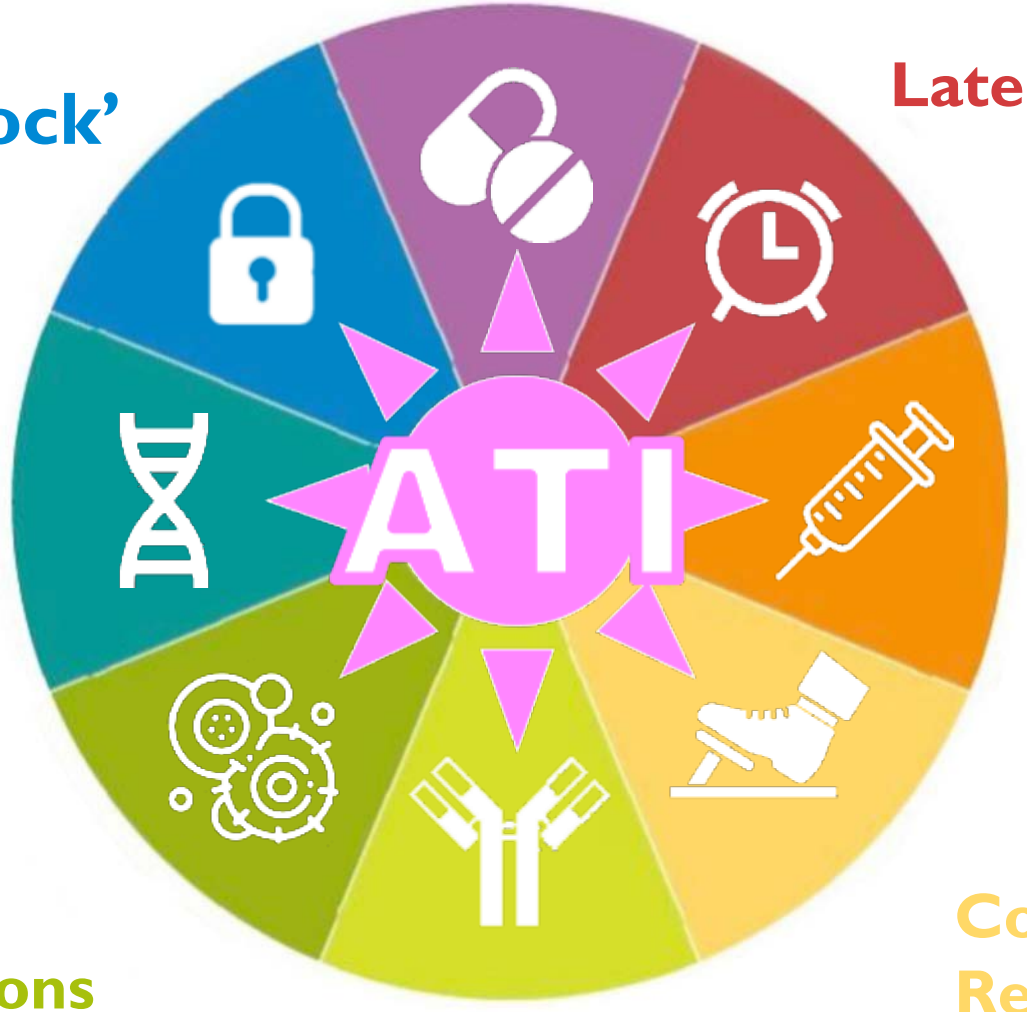
Early Antiretroviral Treatment

‘Block and Lock’

Latency Reversal Agents



Cell & Gene Therapy

Immunotherapy Strategies

Stem Cell Transplantations

Co-Inhibitory Receptors

Broadly Neutralizing Antibodies

Stem Cell Transplantations

13 years 7 months

Timothy Ray Brown
"The Berlin Patient"
March 11, 1966 – September 29, 2020

Donor: CCR5 Δ32 homozygous
Recipient: CCR5 Δ32 heterozygous

Acute myelogenous leukemia

Two stem cell transplants

Total body irradiation
full intensity conditioning
T cell depletion with ATG

Mild GVHD* / 100% chimerism

5 years

Adam Castillejo
"The London Patient"

+

Donor: CCR5 Δ32 homozygous
Recipient: CCR5 Wild Type

Hodgkins lymphoma

One stem cell transplant

No irradiation
reduced intensity conditioning
T cell depletion with aCD52

Mild GVHD* / 100% chimerism

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**GVHD = Graft Vs. Host Disease*

Timing of ART Initiation Following HIV Infection

Caroline Tiemessen

Effects of early ART

Reduced immune activation

Limited virus escape/diversity

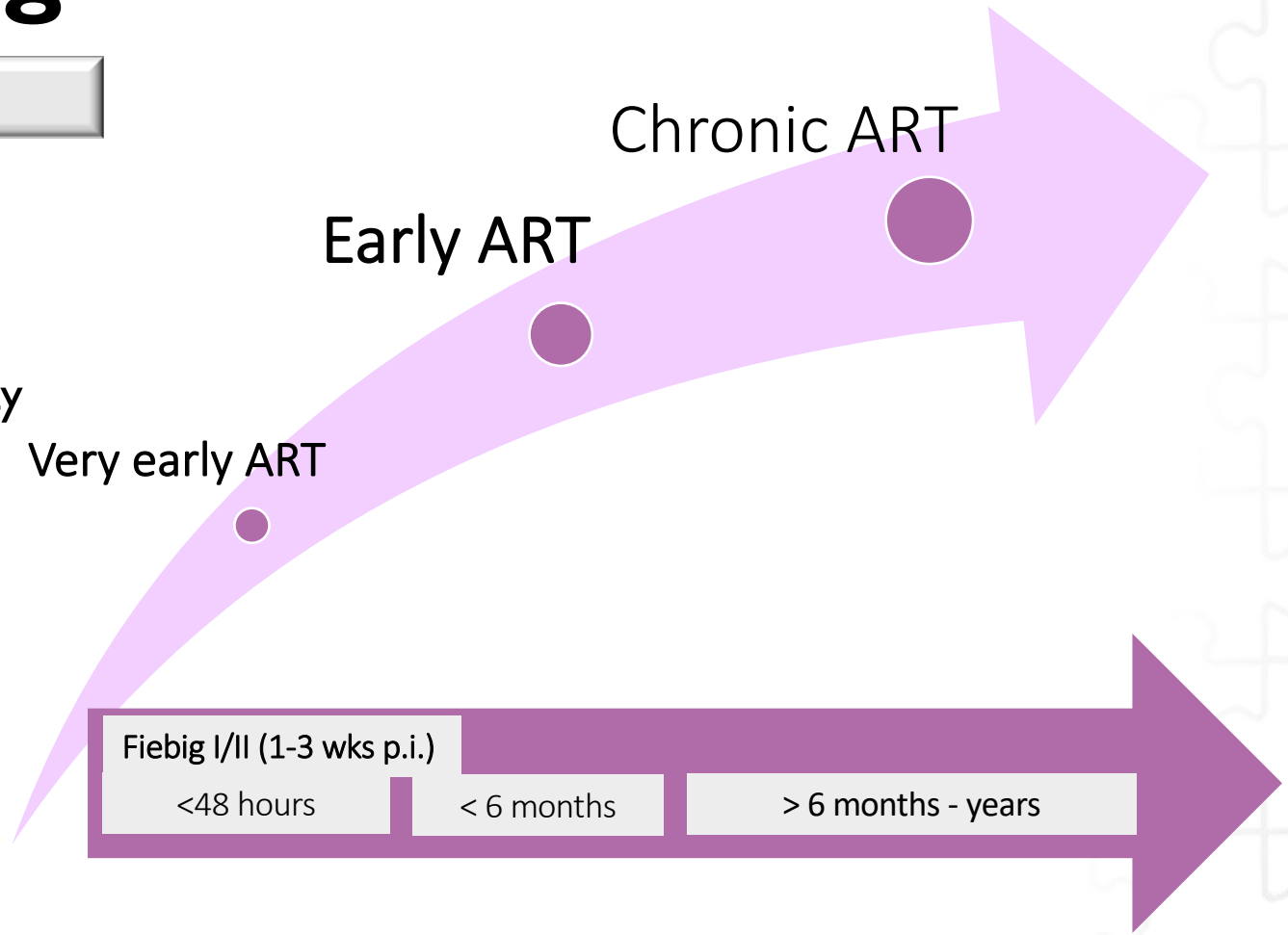
Reduced morbidity and mortality

Better control on ART

No seroconversion, lack of adaptive immune responses

Smaller reservoirs

Preserved immunity



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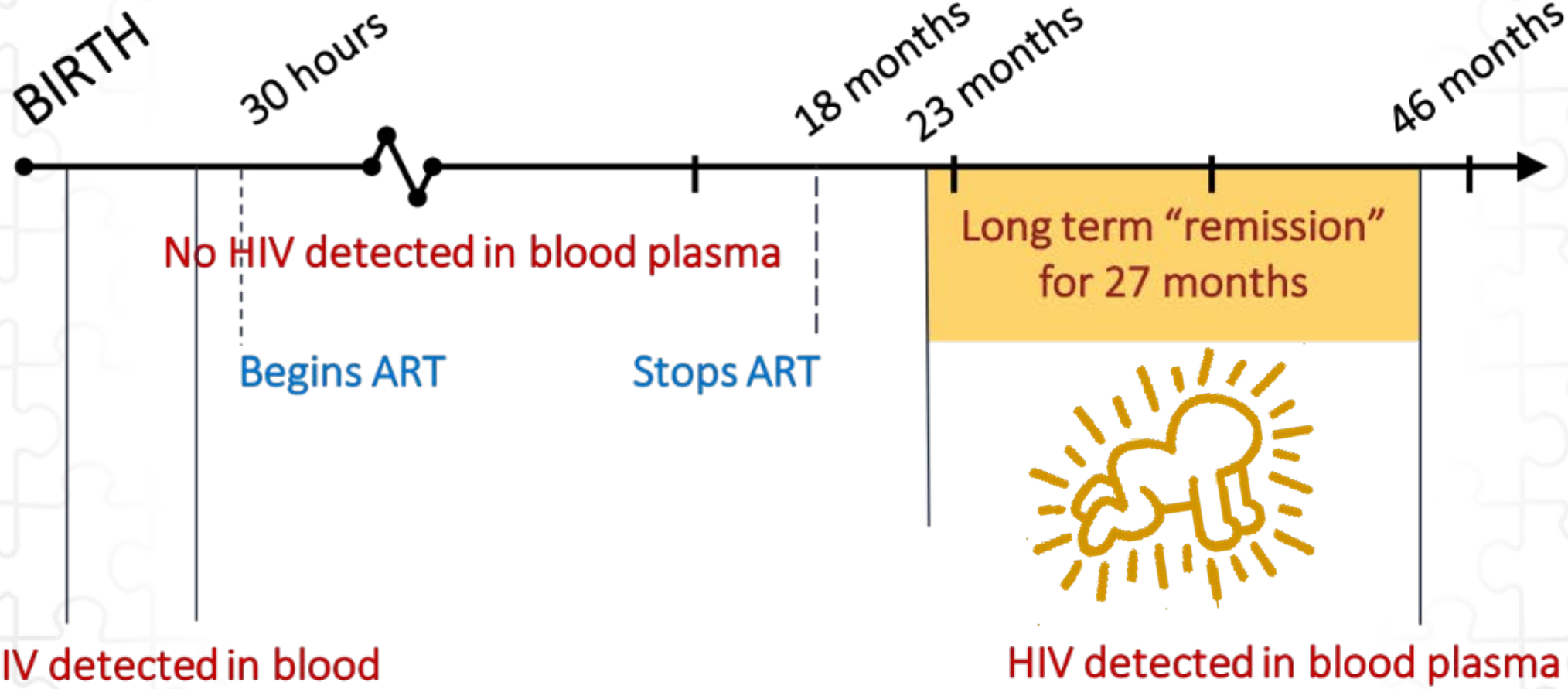
SLIDE CREDIT: Tiemessen CT. Post-Treatment Control. Community Cure Workshop. Saturday July 21, 2018.

The Mississippi Child



Persaud et al 2013 NEJM; Luzuriaga et al 2015 NEJM

Draining the ‘reservoir’

Latency-Reversing Agents

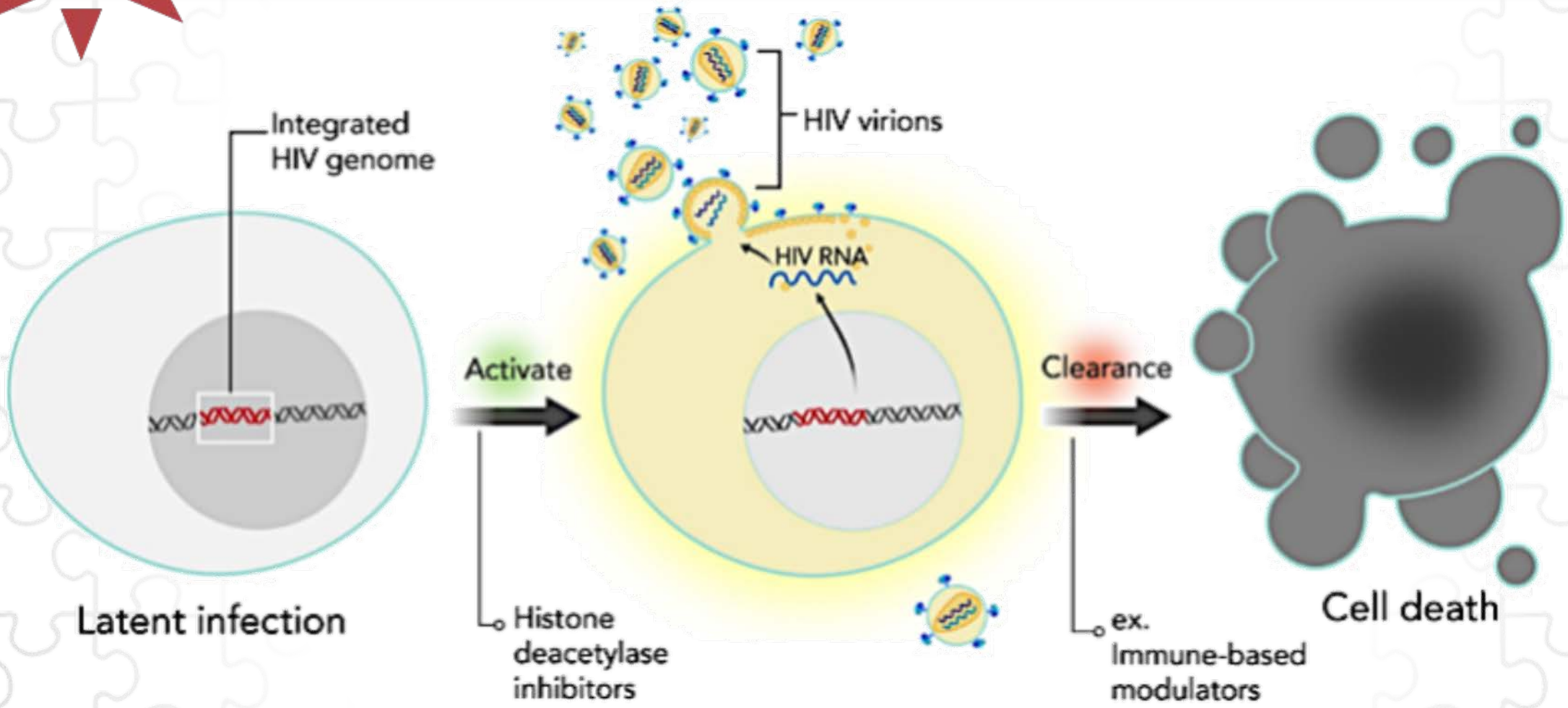


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

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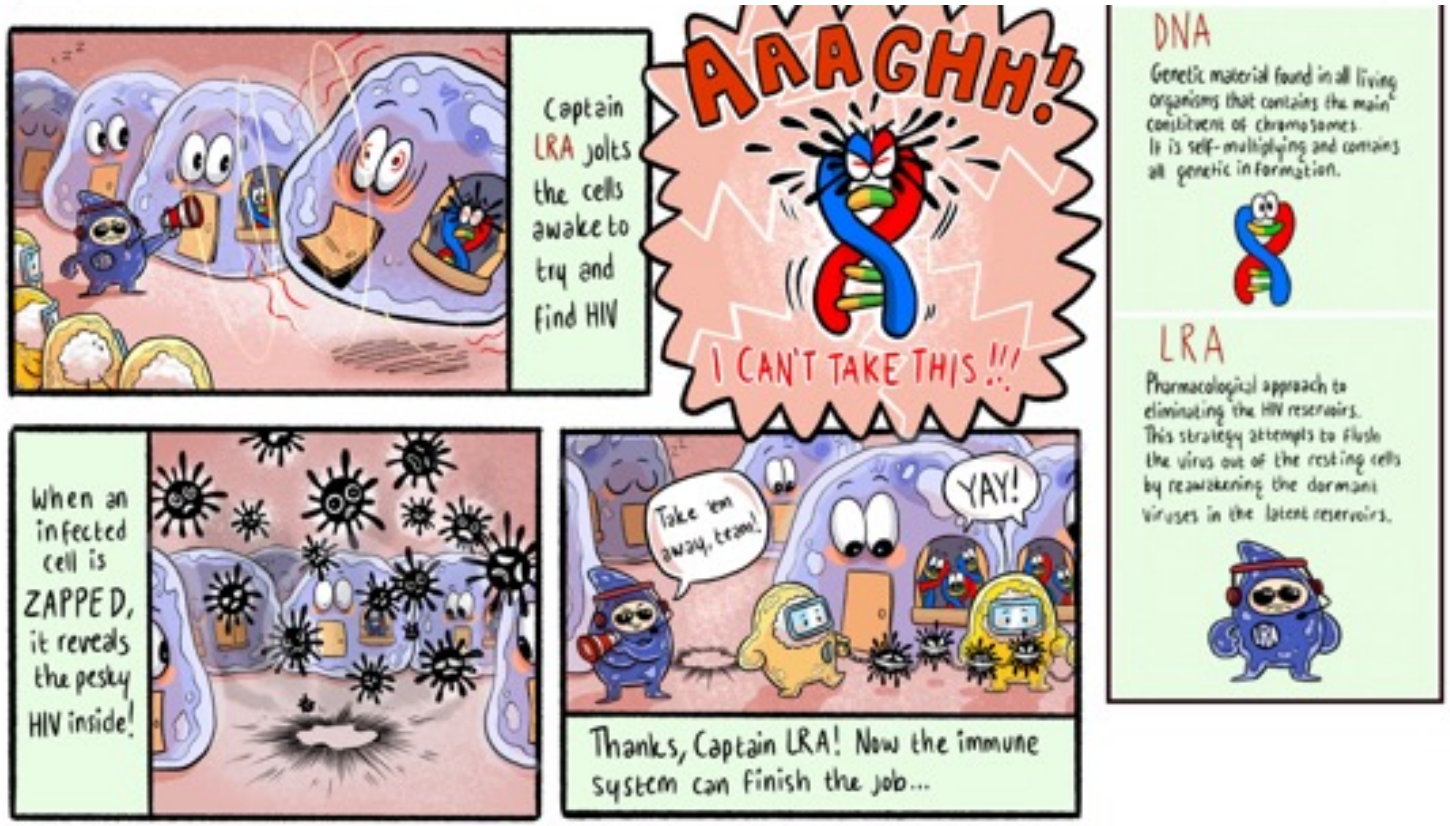
CAPTAIN LRA SAVES THE DAY!



Story by Eric Lee, Matylda Mai & Jazmin Guzman
(Pencils) (Inks) (colors)

Y4C

Visual Art Credit:
Eric (Yi-Hao) Lee, Jasmin Guzman, and Matylda McCormack-Sharp

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The "Block and Lock" Approach

Block & Lock

Transcription inhibitor

Sleeping beauty keeps on sleeping
She never wakes up for the prince

[1]Kessing, Cell Report 2017; [2]Ahlenstiel, Mol Ther Nucleic Acid 2015

SLIDE CREDIT: Ananworanich, A. Overview of Ongoing Cure Research Globally. Community Cure Workshop. Saturday July 21, 2018.

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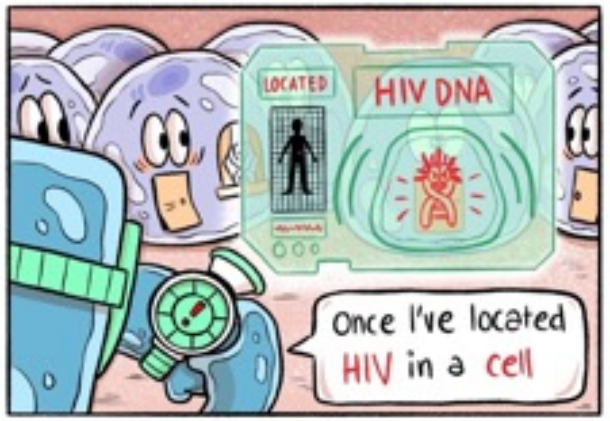
AGENT BLOCK 'N` LOCK



KEY

Immune System

(Includes CD4 T lymphocyte cells)

A System of cells, tissues and organs within the body that help fight off infections and diseases

HIV

(Human Immunodeficiency Virus)

A virus that enters and attacks the cells that help to fight off infections, making the body highly susceptible to diseases and infections

DNA

Genetic material found in all living organisms that contains the main constituent of chromo somes. It is self-multiplying and contains all genetic info

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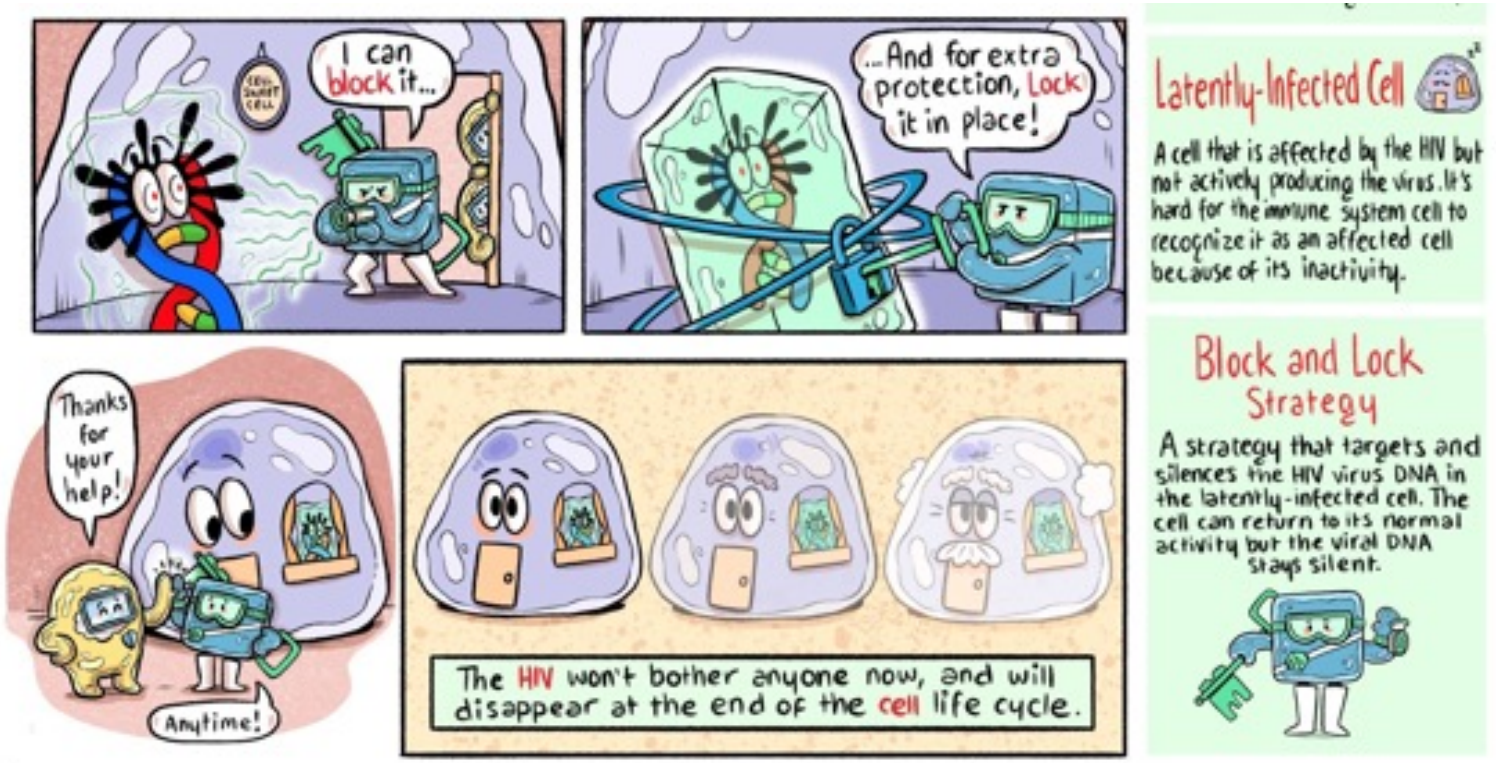

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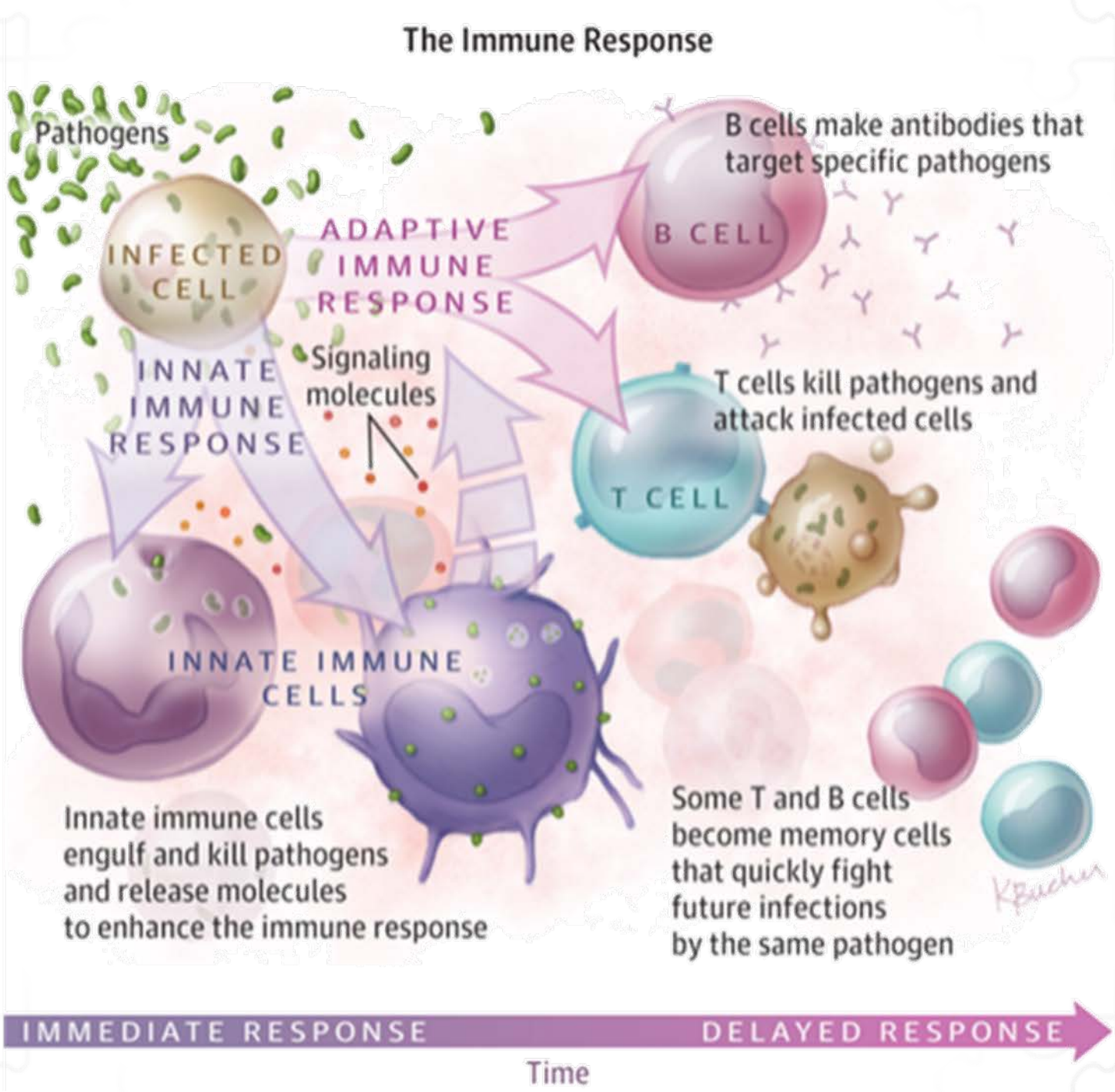
YOUTH4 CURE

UCSF Center for AIDS Prevention Studies
Division of Prevention Sciences

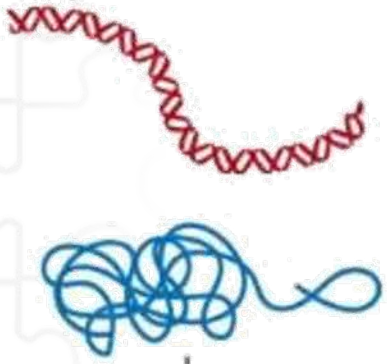
Visual Art Credit:
Eric (Yi-Hao) Lee, Jasmin Guzman, and Matylda McCormack-Sharp

Reinforcing the ‘dam’

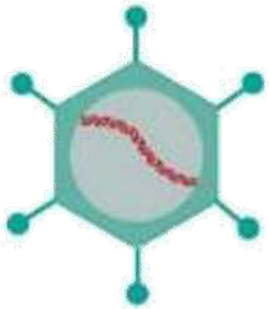


Types of HIV Therapeutic Vaccines

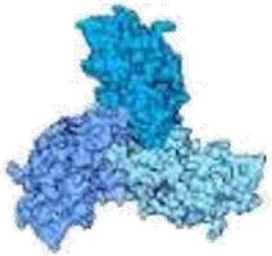
1. DNA and RNA vaccines



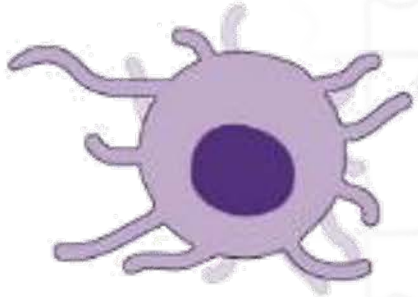
2. Viral vector vaccines



3. Protein or peptide vaccines



3. Dendritic cell vaccines



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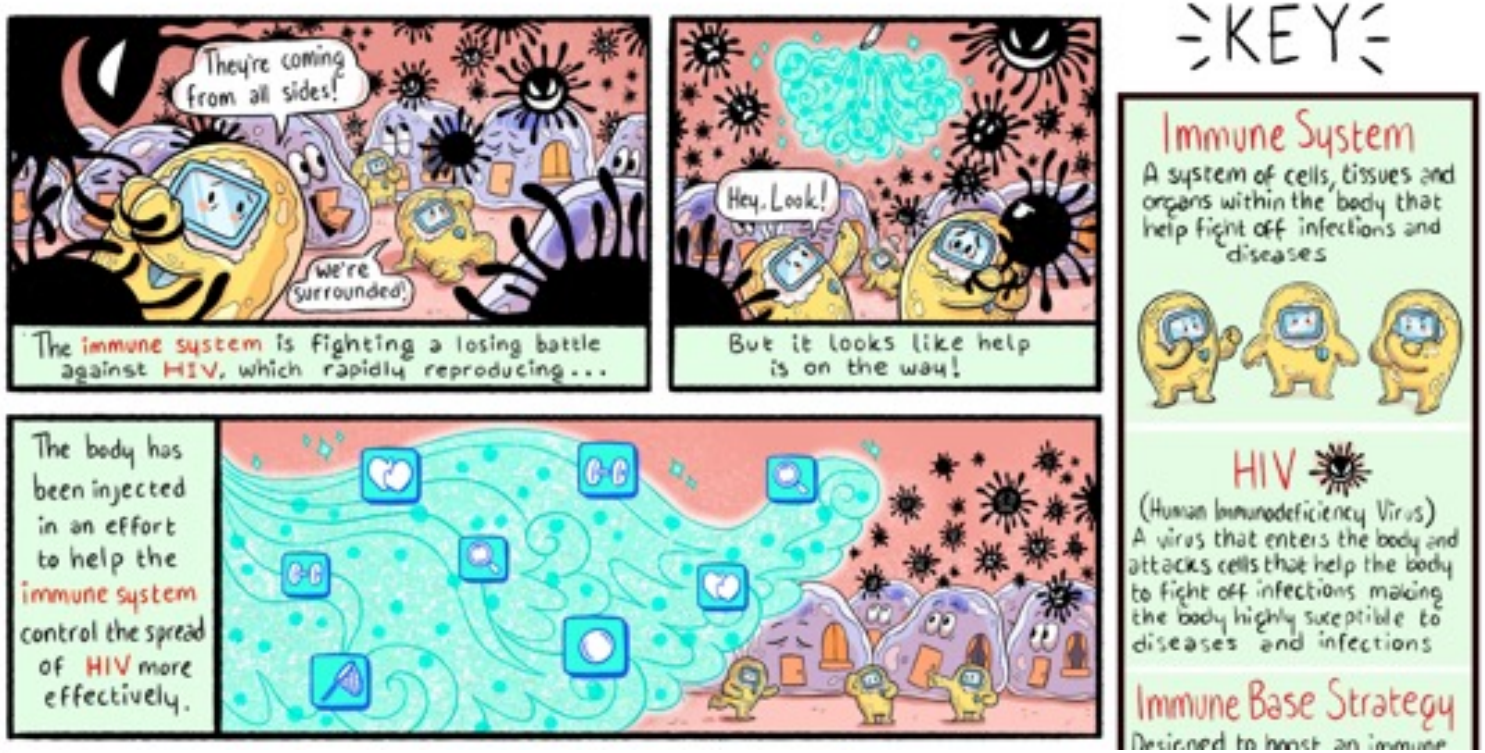
IMMUNOTEAM: POWER UP!



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Immune Base Strategy
Designed to boost an immune

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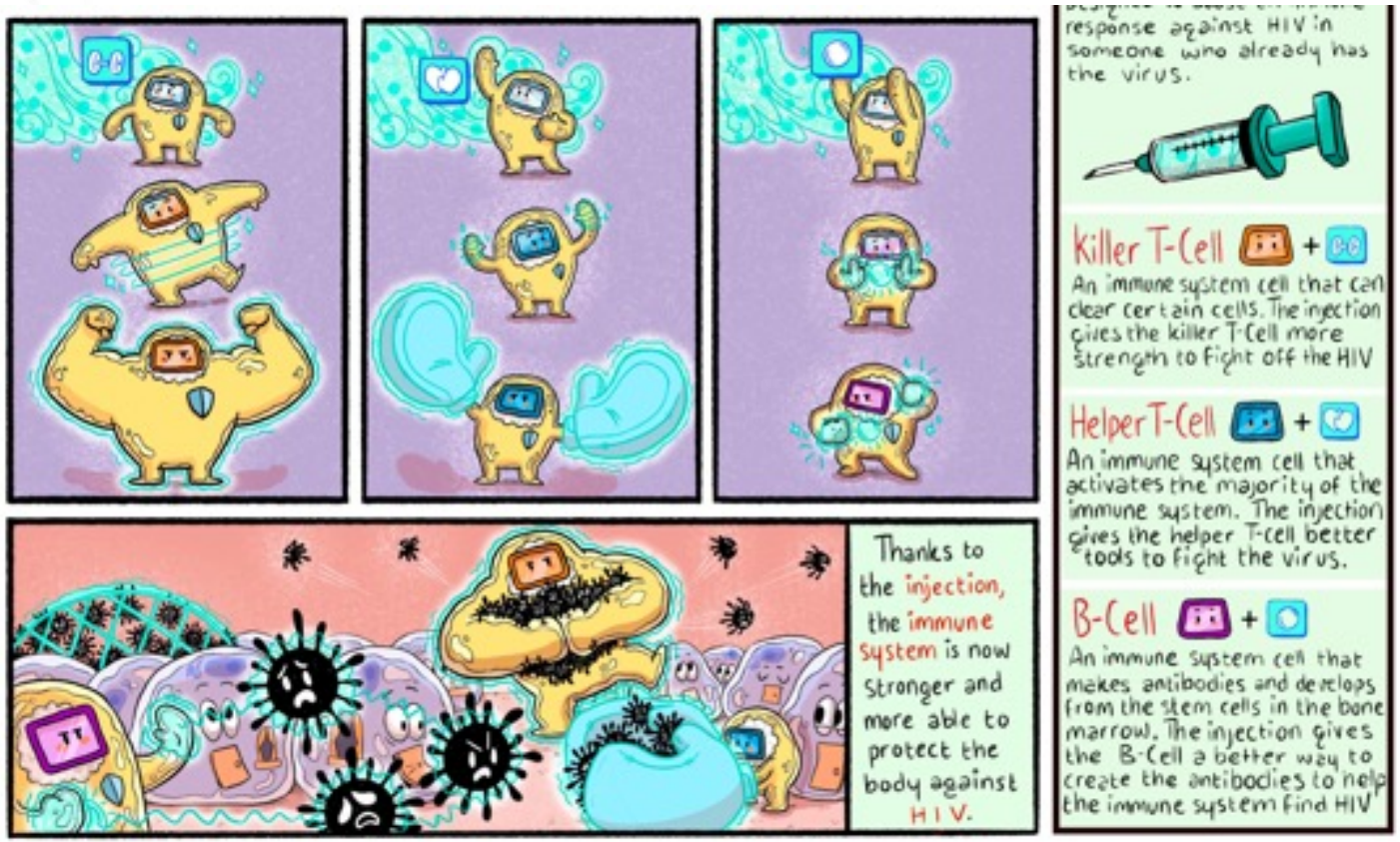

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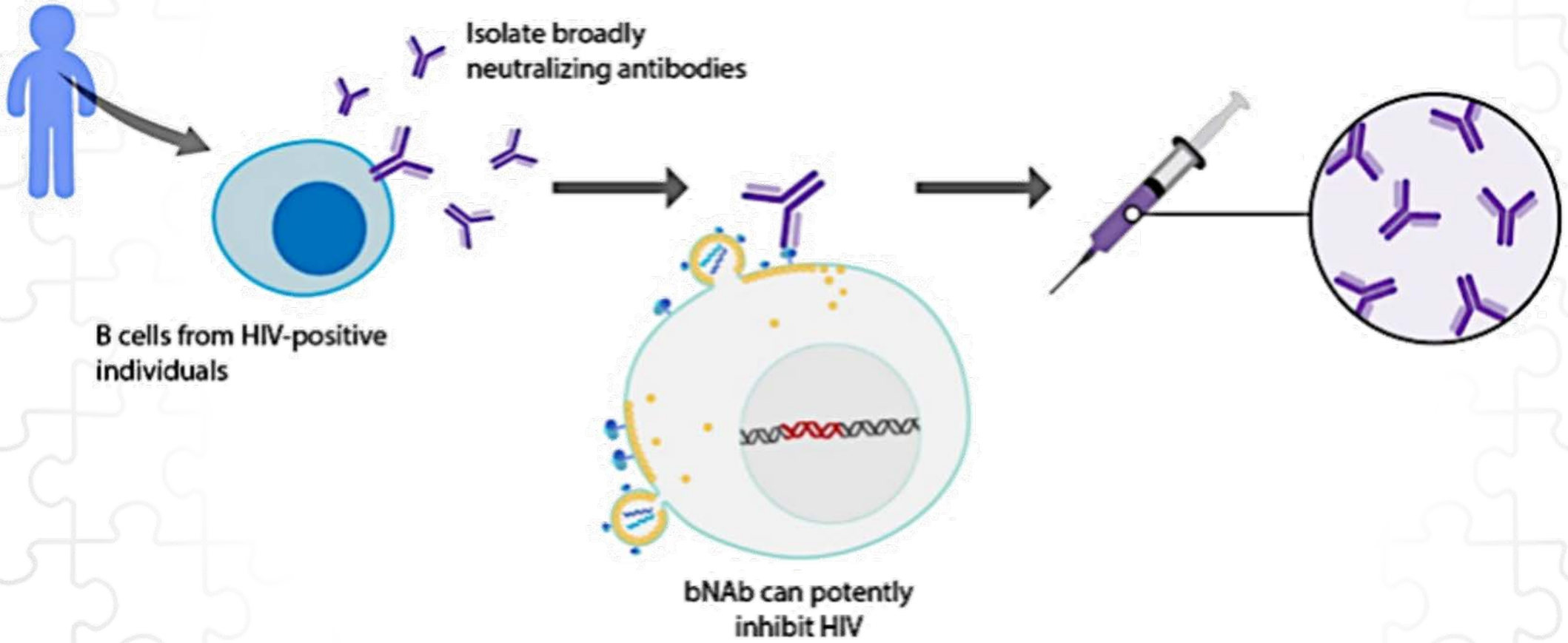
Passive Immunization: Broadly Neutralizing Antibodies



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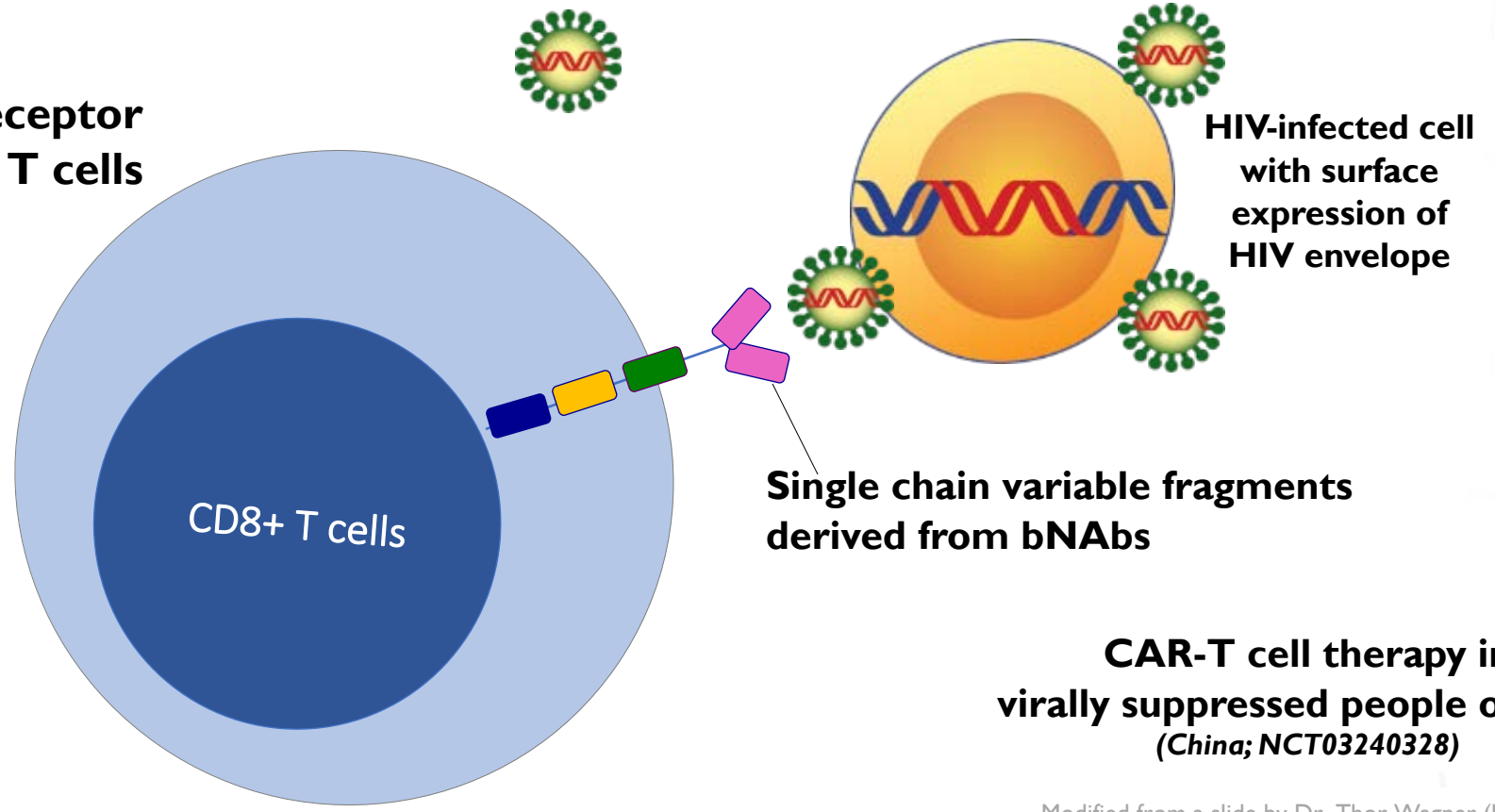
Genetic Engineered T cells: Creating Super T Cells

Chimeric Antigen Receptor (CAR) T cells



'Super T cell'

CAR-T cell therapy in virally suppressed people on ART
(China; NCT03240328)

Modified from a slide by Dr. Thor Wagner (U Washington)
Hale and Wagner, Mol Ther 2017; Ali, J Virol 2016; Liu, J Virol 2016; Hale, Mol Ther 2017

SLIDE CREDIT: Ananworanich, A. Overview of Ongoing Cure Research Globally. Community Cure Workshop. Saturday July 21, 2018.

Making cells stronger

What is Cell and Gene Modification?

- A branch of **Regenerative Medicine**, an emerging field that involves the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function".

- **Gene therapy** is the delivery of therapeutic gene into a patient's cells to treat disease.

- **Cell therapy** is the delivery of intact, living cells into a patient to treat disease.

- Combination **Cell/Gene Modification** approaches that seek to insert genes into a patients' own cells to control or kill HIV are in clinical trials now.

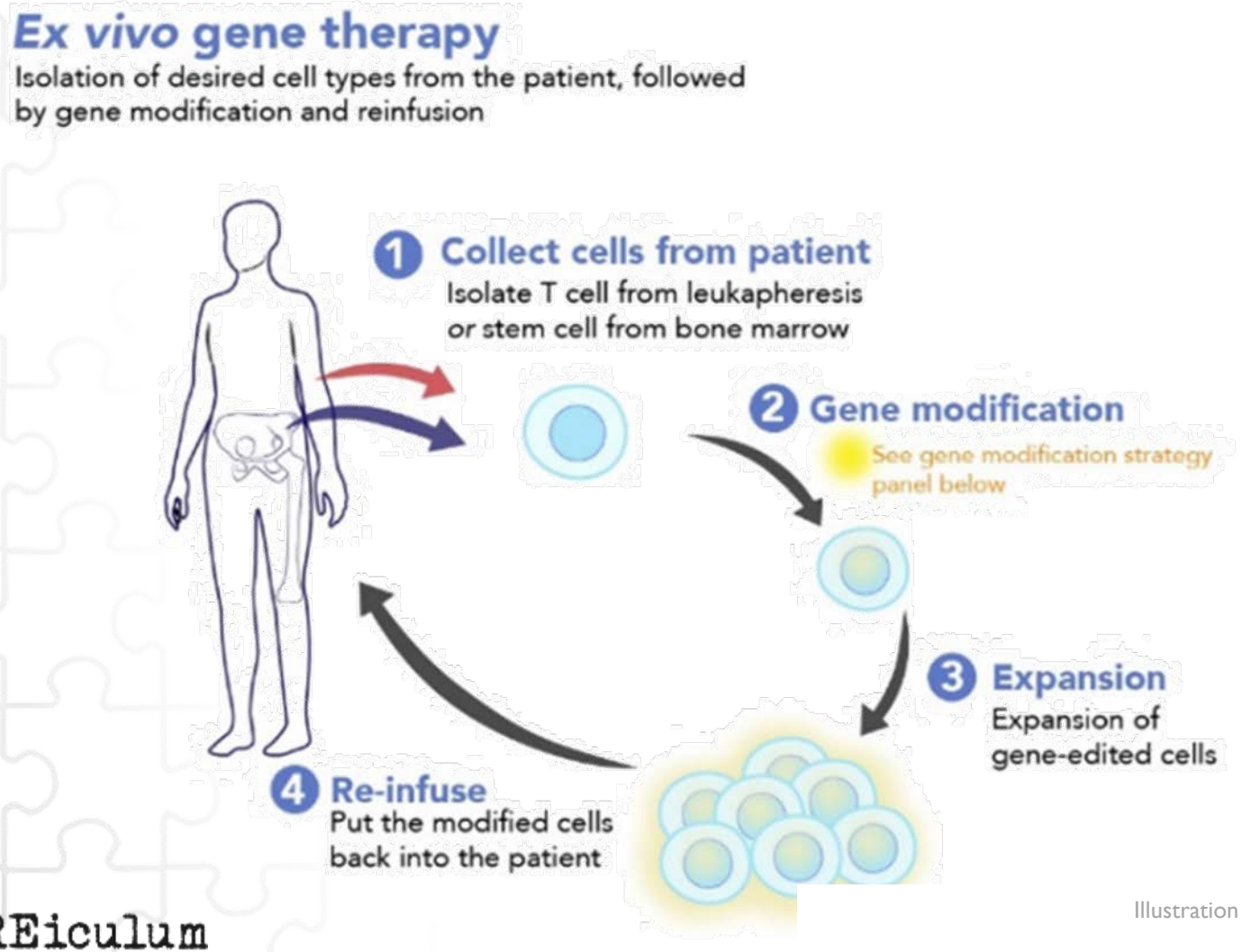
Somatic versus Germline Modification

	SOMATIC	GERMLINE
THERAPY	medicine & research 	 He Jiankui's experiments
ENHANCEMENT	Plastic surgery 	 Designer babies

Cell and Gene Modification

Scheufele DA et al. U.S. Attitudes on Human Genome Editing. *Science* 2017; 357 (6351): 553 – 4.

Modification Occurring Outside the Body '*Ex Vivo*'



Outside of the body

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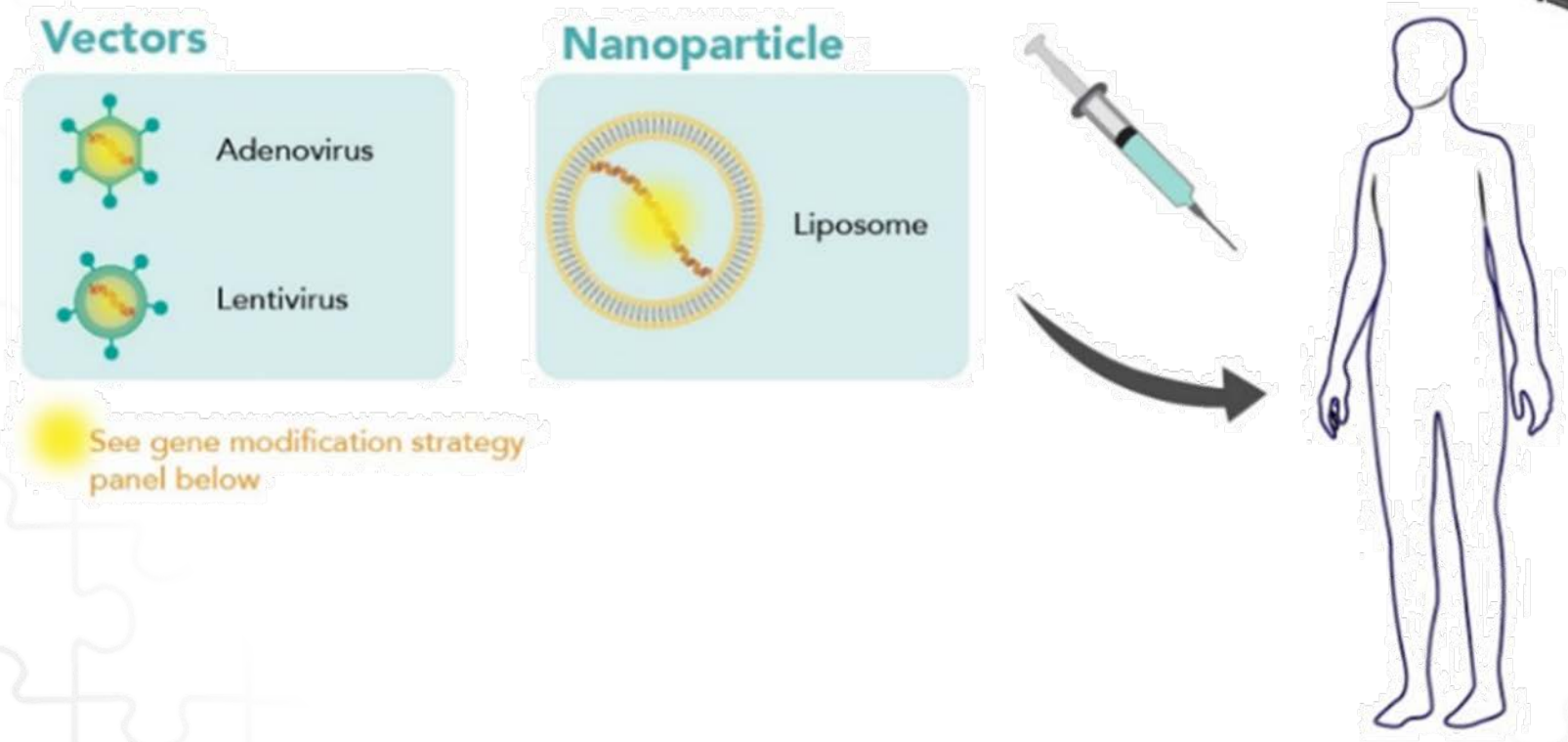
Modification Occurring Inside the Body '*In Vivo*'

Inside of the body



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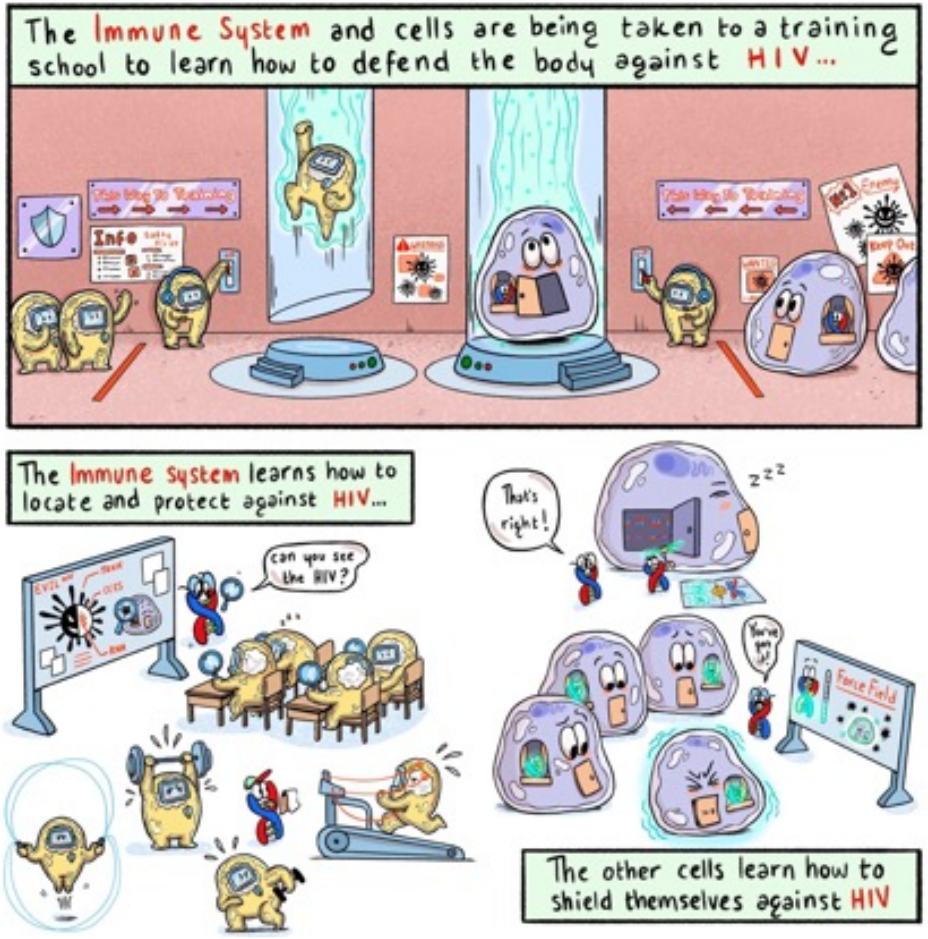
IMMUNOTEAM: DEFEND 'N' ASSIST



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DNA
Genetic material found in all living organisms that contains the main constituent of chromosomes. It is self-multiplying and contains all genetic info

Gene Editing
There are two main forms:
1. Cells are taken out of the body to have some of their genetic characteristics modified.
2. Genes in the cells are modified

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Treatment Action Group

Research Towards an HIV Cure (Trials)

TAG
Treatment Action Group

Research Toward a Cure June 15, 2021

Table 1. Current Clinical Trials

Trial	Trial Registry Identifier(s)	Sponsor(s)	Phase	Estimated End Date/Interim Results
ADOPTIVE IMMUNOTHERAPY				
alloRESIST: Evaluate the safety, immunologic, and virologic responses of donor derived HIV-specific T-cells in HIV+ individuals following allogeneic bone marrow transplantation	NCT04248192	Catherine Bollard, Children's Research Institute	Phase I	April 2024
HST-NEETs: HIV-1 specific T-cells for HIV-infected individuals	NCT03485963	Children's Research Institute	Phase I	December 2021
ANTIBODIES				
VRC01 (analytical treatment interruption in HVTN 703/HPTN 081 AMP trial participants)	NCT04860323	HIV Vaccine Trials Network	N/A	November 2022
VRC01 (analytical treatment interruption in HVTN 704/HPTN 085 AMP trial participants)	NCT04801758	HIV Vaccine Trials Network	N/A	June 2022
GSK3810109A (broadly neutralizing antibody formerly named N6-LS)	NCT04871113 (not yet open for enrollment)	ViiV Healthcare	Phase IIa	October 2023
10-1074-LS + 3BNC117-LS in primary HIV infection	NCT04319367 (not yet open for enrollment)	Imperial College London	Phase II	March 2025

- List of trials and pipeline report

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https://www.treatmentactiongroup.org/cure/trials/

research strategies

Putting different strategies together

Combination Approaches

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Questions for Discussion

ACKNOWLEDGMENTS

We wish to thank AIDS Treatment Activists Coalition for the funding to complete this module

Their caring support of the CUREiculum 2.0. will make a difference in the lives of thousands. of people living with HIV










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