HIV Cure-Related Research Strategies

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This research training curriculum is a collaborative project aimed at making the science of HIV cure-related research saccessible 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

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Key timeline events

HIV cure is **rare**.

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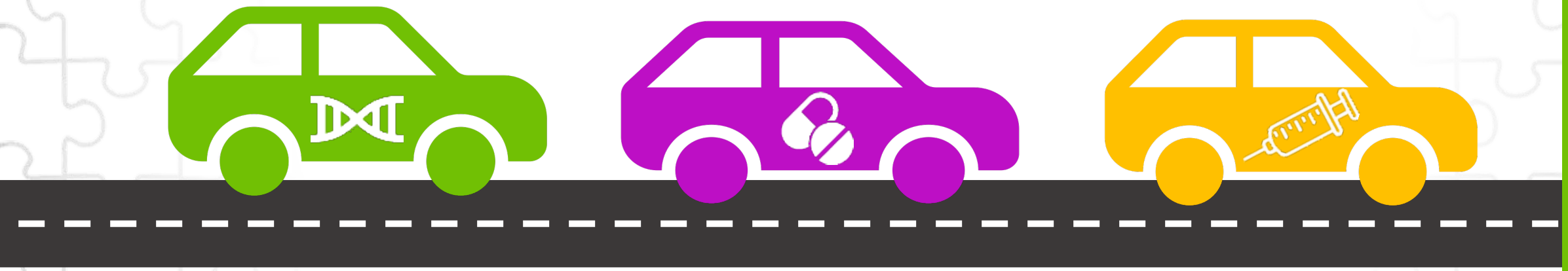
Hutter et al., N Engl J Med 2010; Gupta et al., Nature 2019; Gupta et al, Lancet HIV 2019; Jiang et al., Nature 2020

SLIDE CREDIT: Sharon Lewin, Singapore AIDS Conference 2020

Overview of the Research Process

Overview of Research Process



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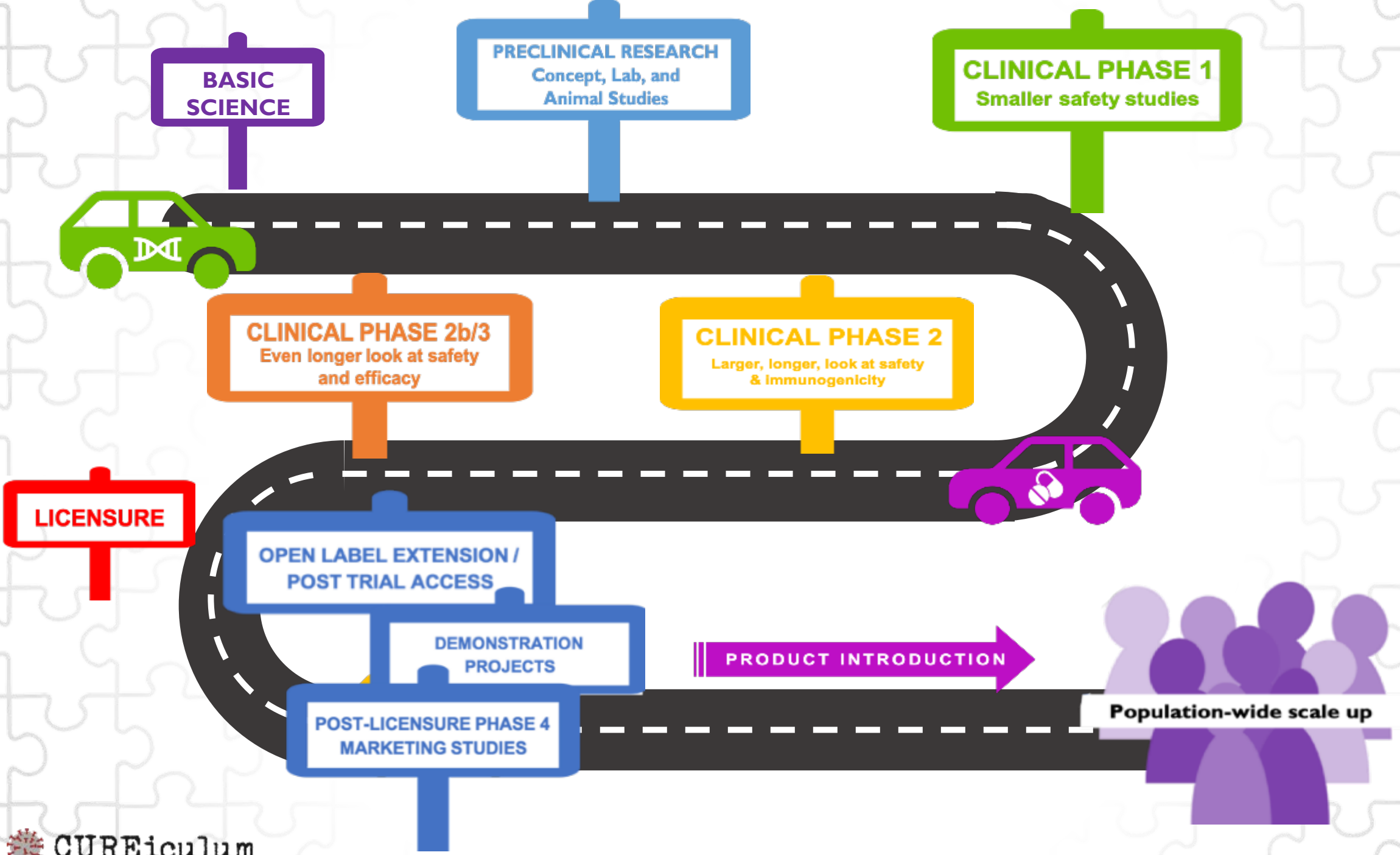

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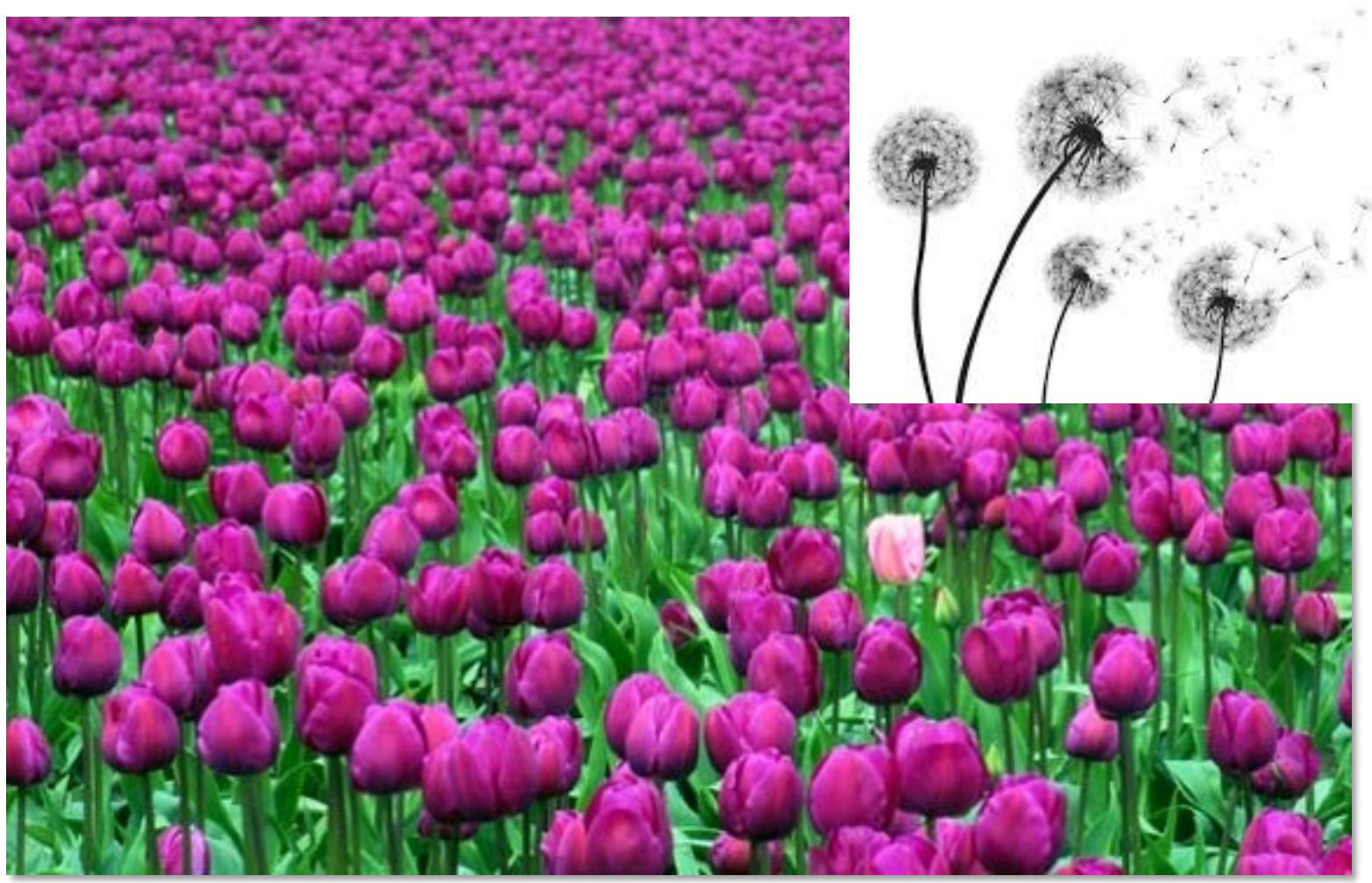
Why is HIV so hard to cure?



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

Research ‘dam’ analogy

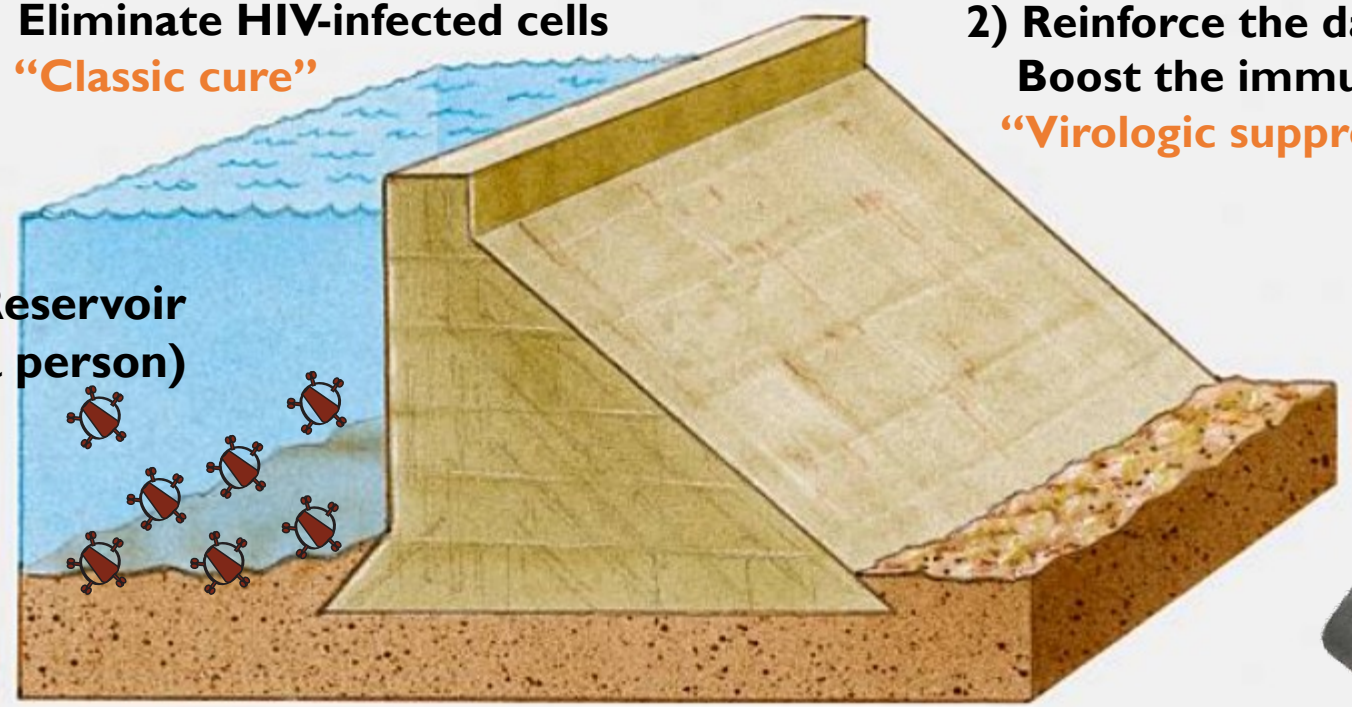
How Can We Prevent HIV From Rebounding Off Therapy?

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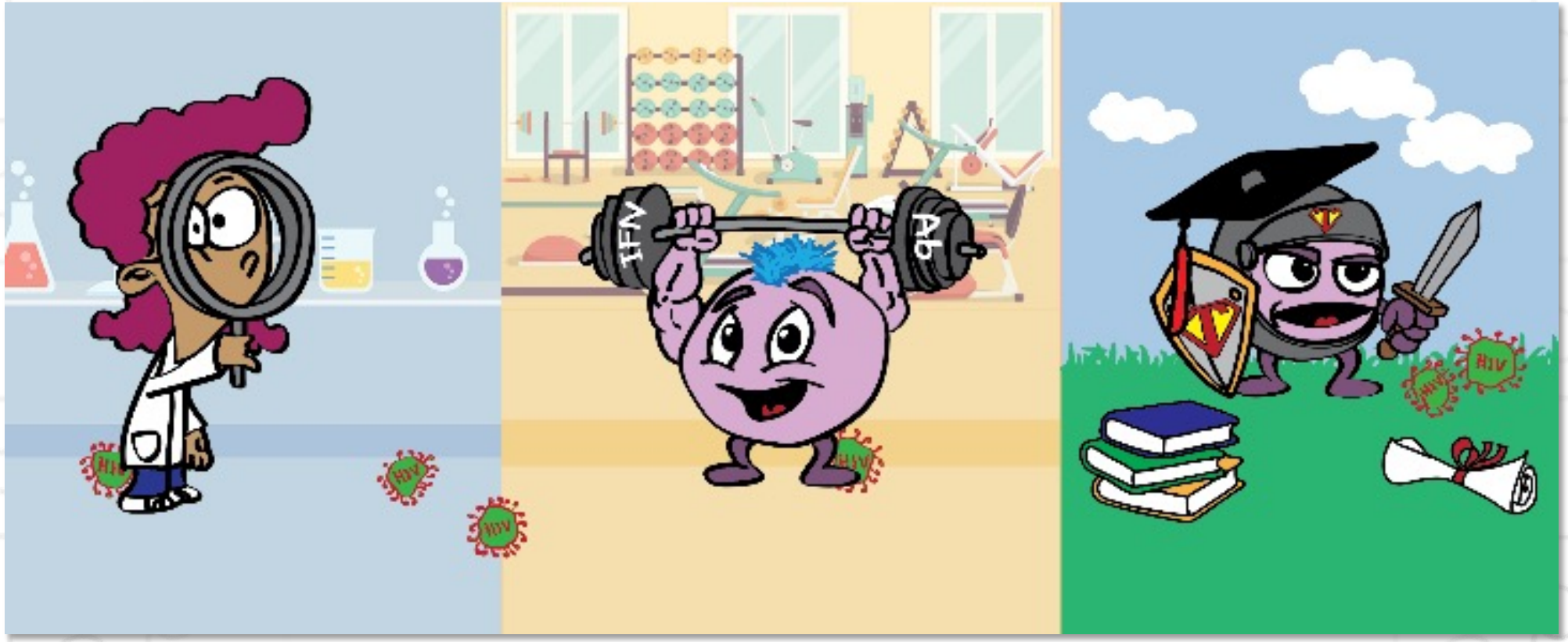
SLIDE CREDIT: Jones RB. The Newest Science in Cure and Vaccine. Plenary Presentation Main IAS 2018 Conference.

HIV Cure-Related Research Strategies Under Investigation



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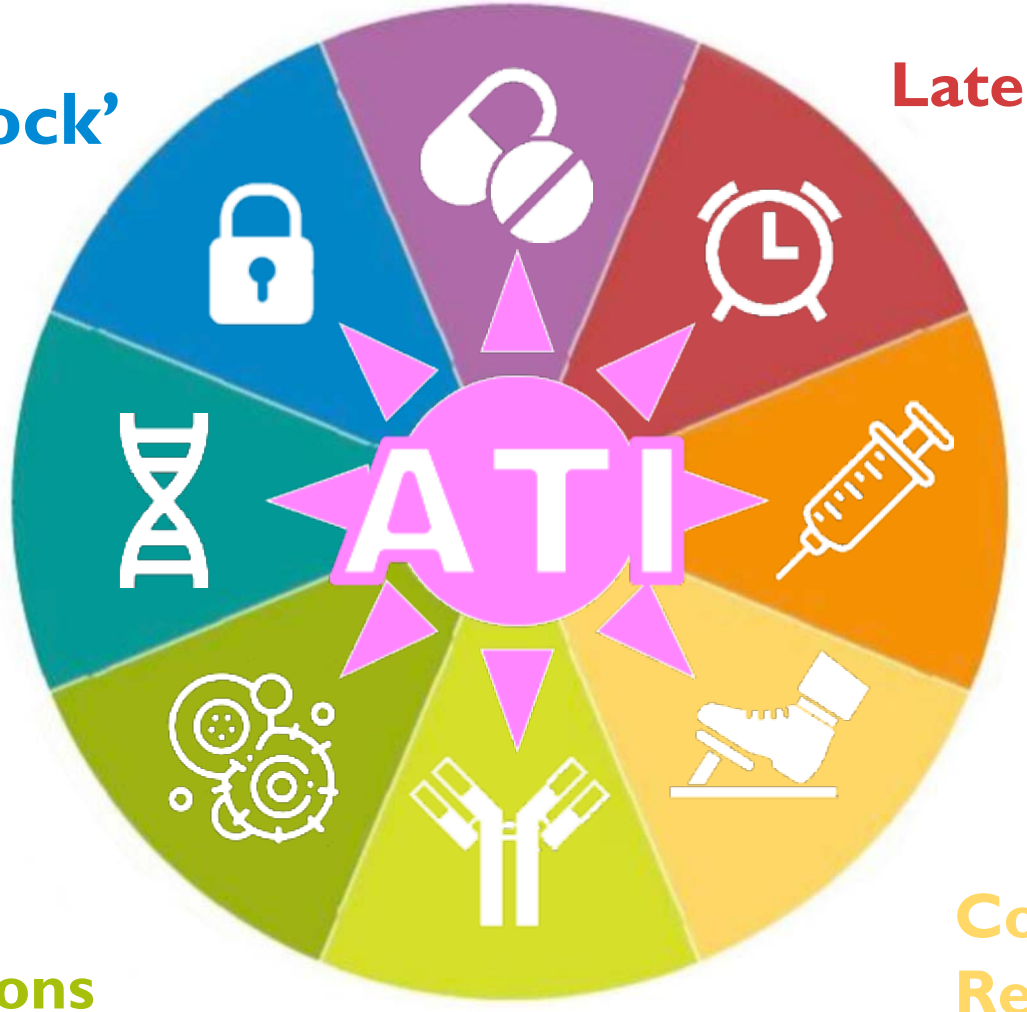
Cartoon Credit: BEAT-HIV Collaboratory

Slide Credit: Nicolas Chomont

Early Antiretroviral Treatment

‘Block and Lock’

Latency Reversal Agents



Cell & Gene Therapy

Immunotherapy Strategies

Stem Cell Transplantations

Co-Inhibitory Receptors

Broadly Neutralizing Antibodies

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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*

A Realistic Appraisal of the Role of Stem Cell Transplantation in the "Cure" of HIV Infection

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- A reasonable approach for HIV-infected individuals who require stem transplantation for the treatment of leukemia/lymphoma and related diseases.
- The risk, morbidity, and expense for the average HIV-infected individual who is virally suppressed on ART outweighs the potential benefit.
- Not scalable for the tens of millions of people infected with HIV.
- If we could maintain HIV-uninfected patients with leukemia in complete long-term remission (without "cure") with a single pill per day, would we be doing stem cell transplantations in them? Consider Gleevec for chronic myeloid leukemia.

ICISTEM

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- International collaboration to study potential HIV cure by stem cell transplants in Europe
- Looking at the reservoir of virus in people with HIV **who either had** or **may get** an allogeneic stem cell transplant
- Special laboratories with the highly sensitive tests to measure the reservoir and the quality of the immune system

Unfortunately, stem cell transplants are dangerous procedures which come with a high rate of death.

People who do not have a disease requiring a transplantation therefore *cannot join this study.*

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Timing of ART Initiation Following HIV Infection

Caroline Tiemessen

Effects of early ART

Reduced immune activation

Limited virus escape/diversity

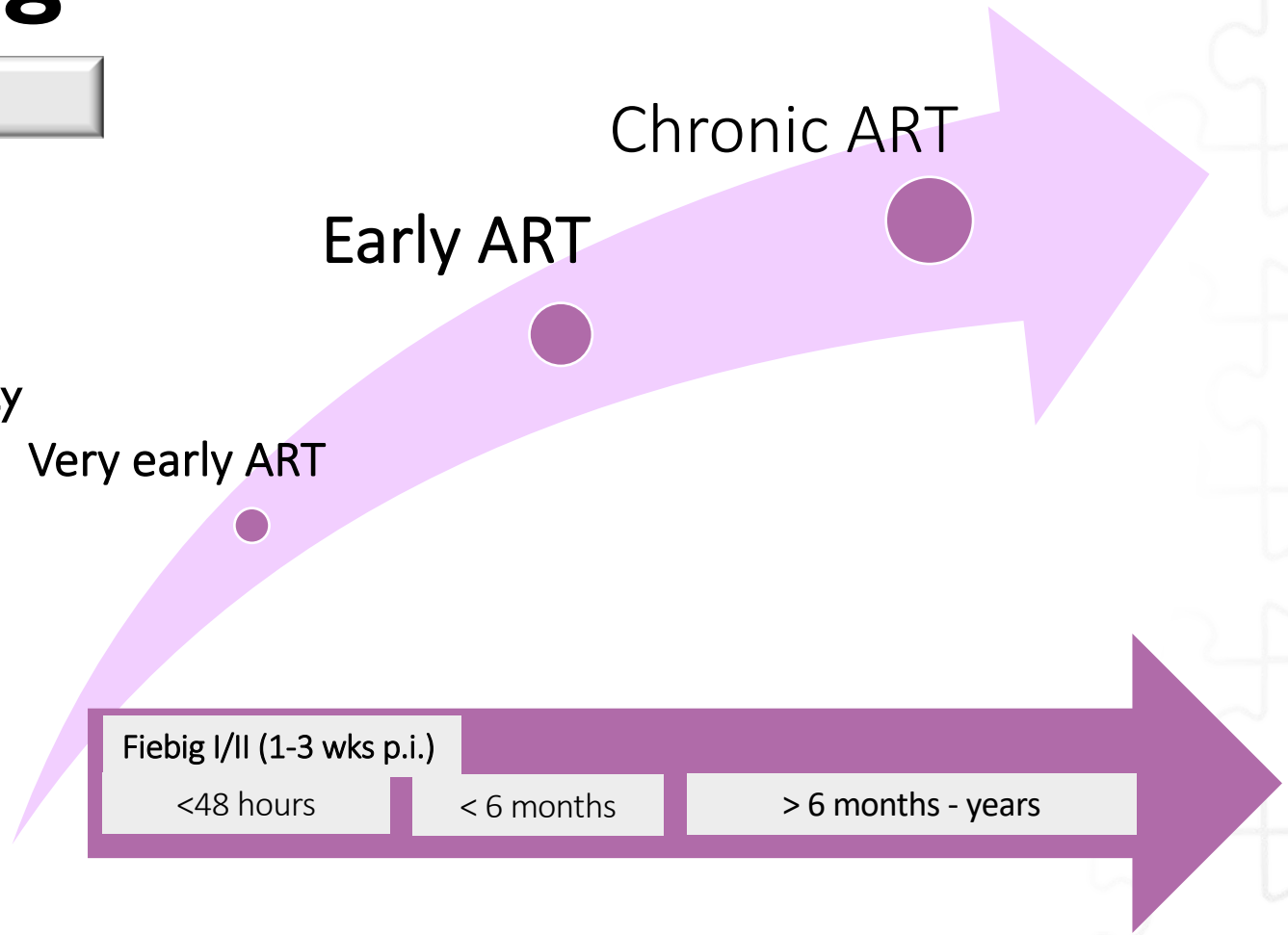
Reduced morbidity and mortality

Better control on ART

No seroconversion, lack of adaptive immune responses

Smaller reservoirs

Preserved immunity



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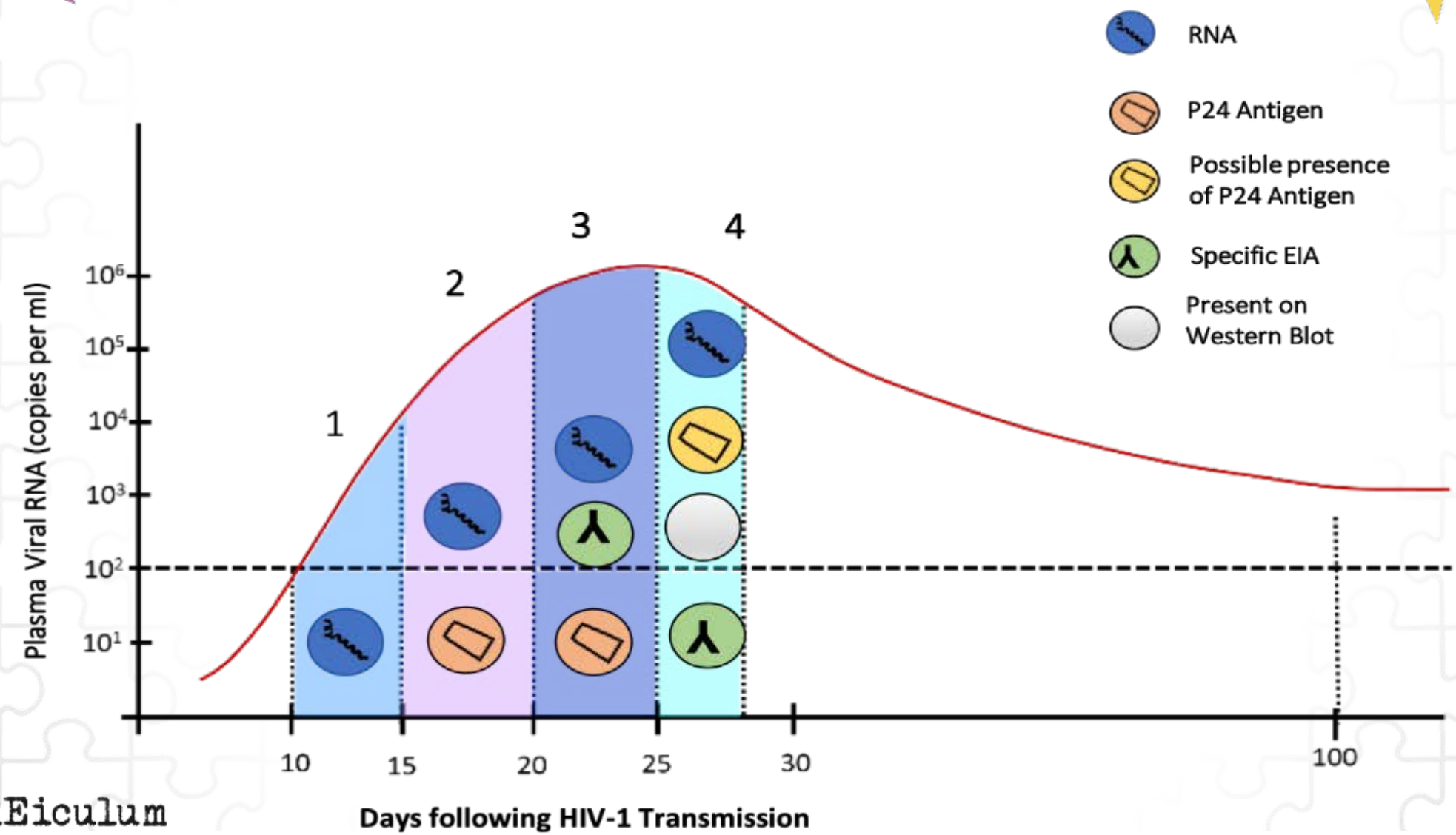
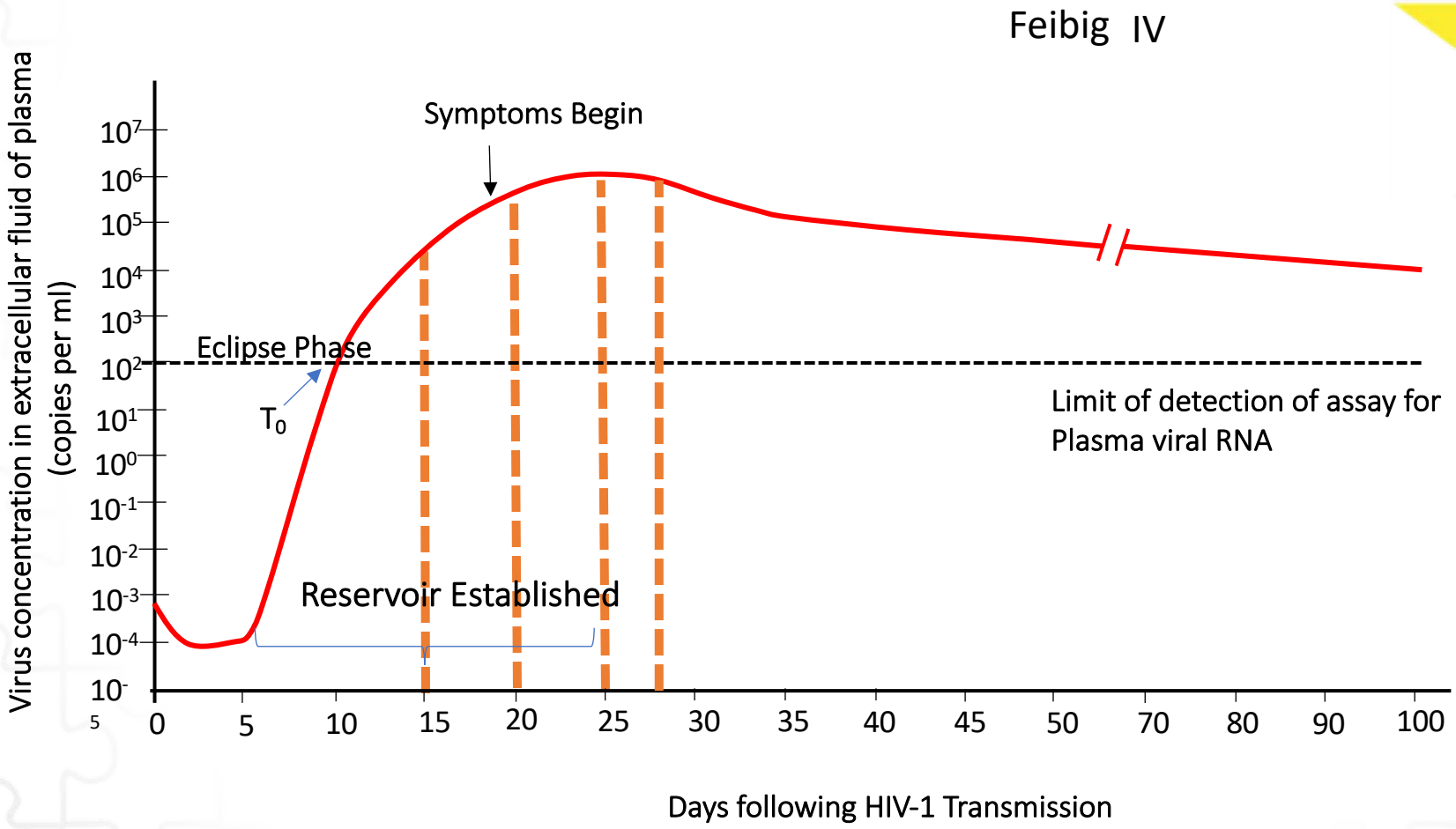
SLIDE CREDIT: Tiemessen CT. Post-Treatment Control. Community Cure Workshop. Saturday July 21, 2018.

What are the Fiebig Stages?

Go Deeper



What is the Definition of Early?



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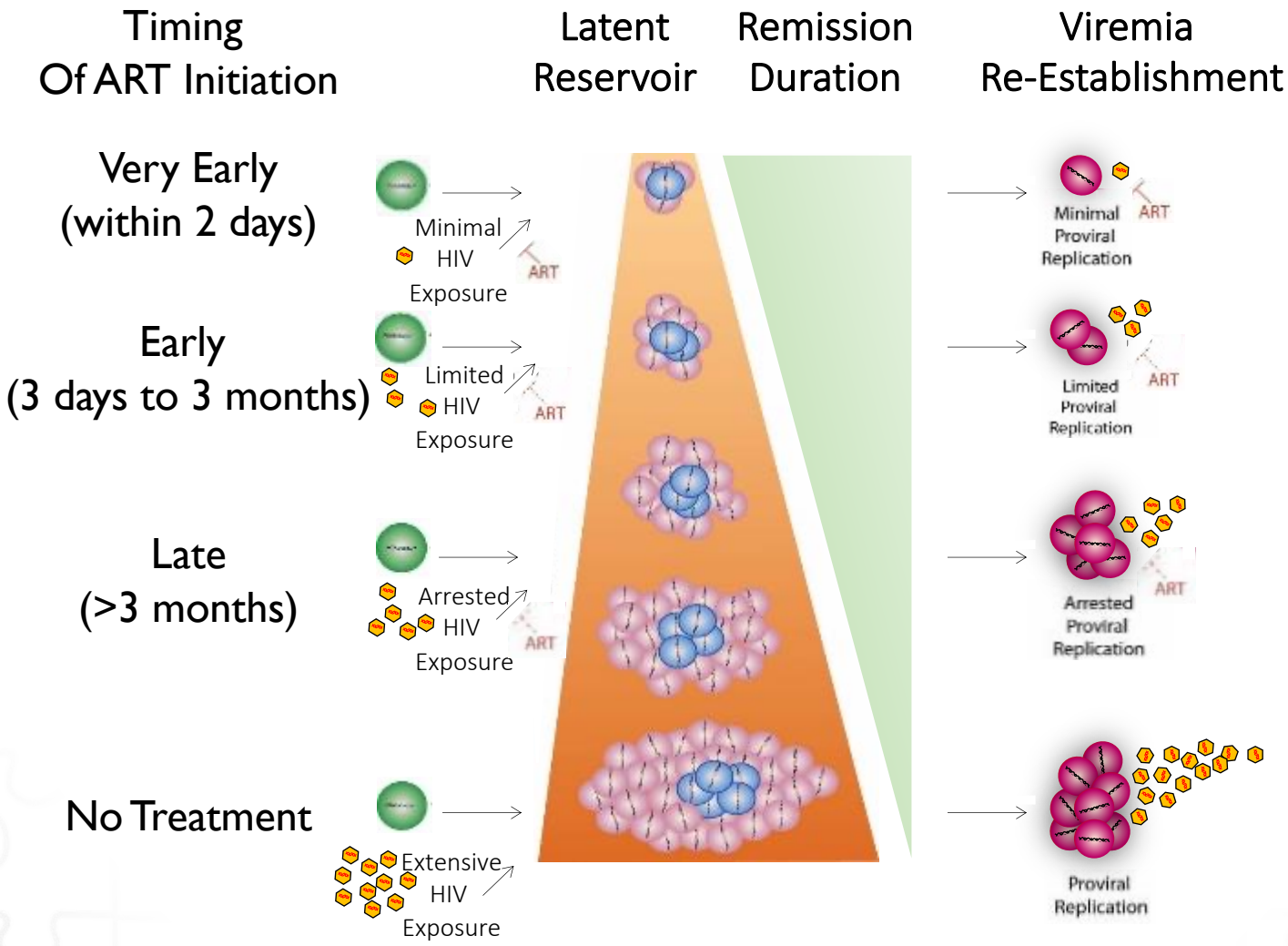
Adapted from McMichael AJ, *Nature Reviews Immunology*, 2010

Early ART in Infants



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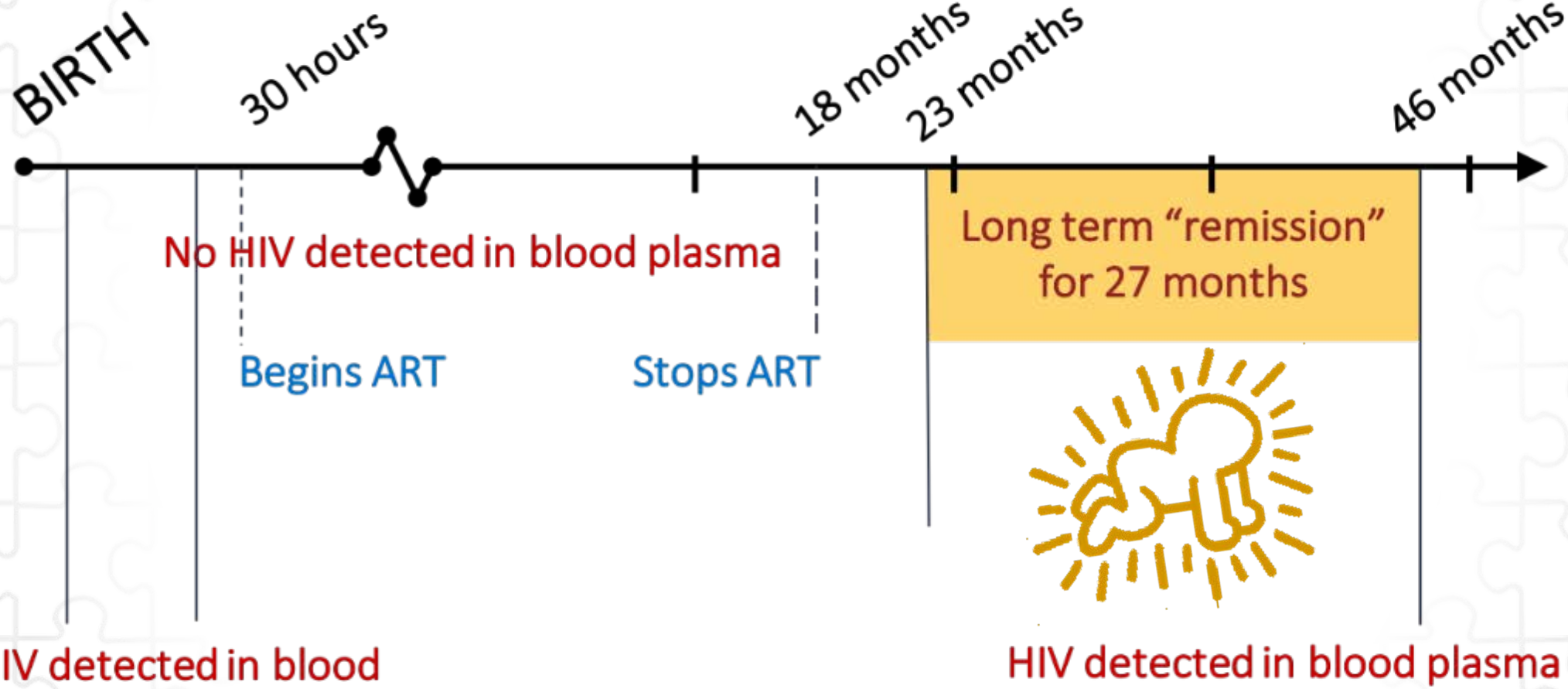
Rainwater-Lovett et al 2015 *Curr Opin HIV AIDS*

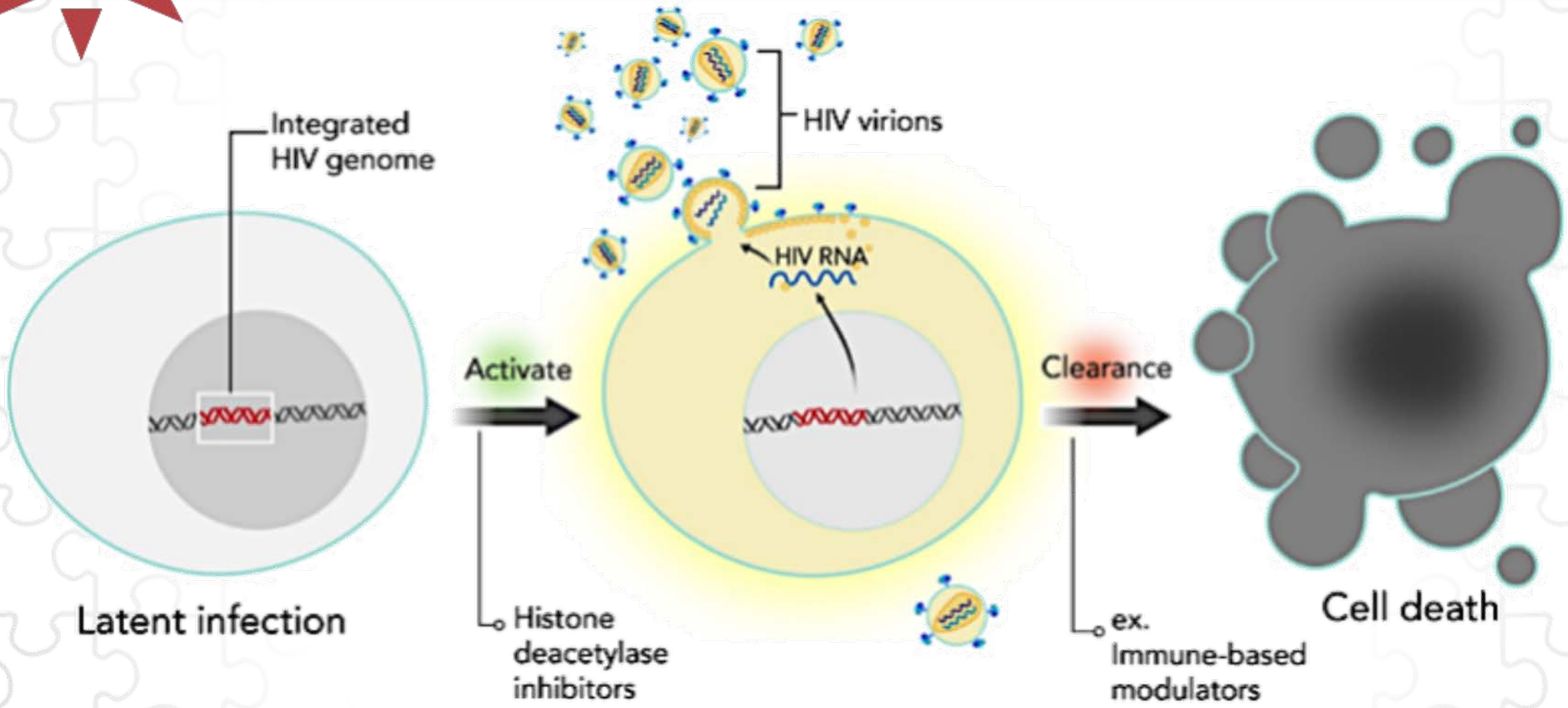
The Mississippi Child



Persaud et al 2013 NEJM; Luzuriaga et al 2015 NEJM

Draining the ‘reservoir’

Latency-Reversing Agents



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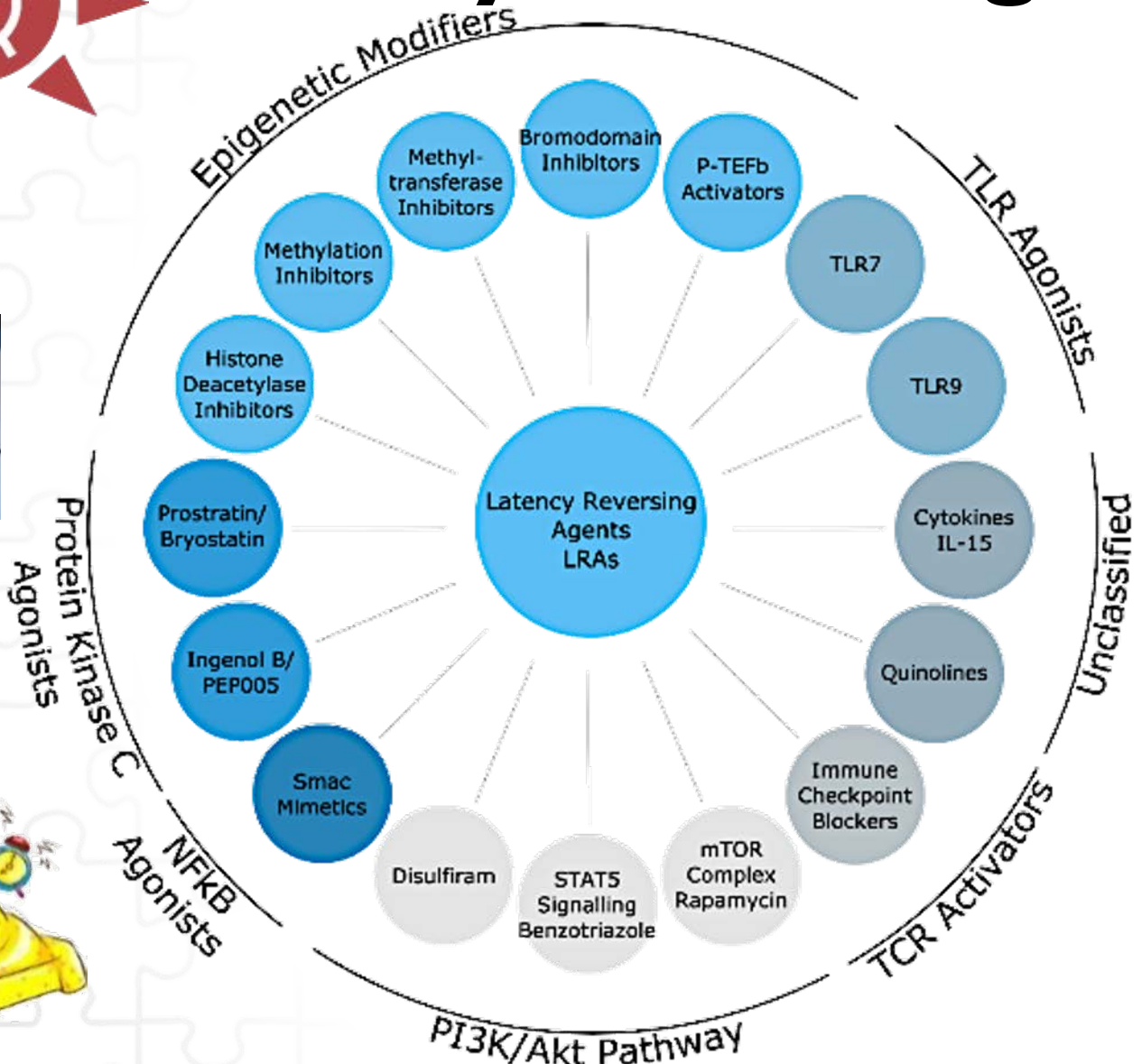
Latency-Reversing Agents

Sharon Lewin

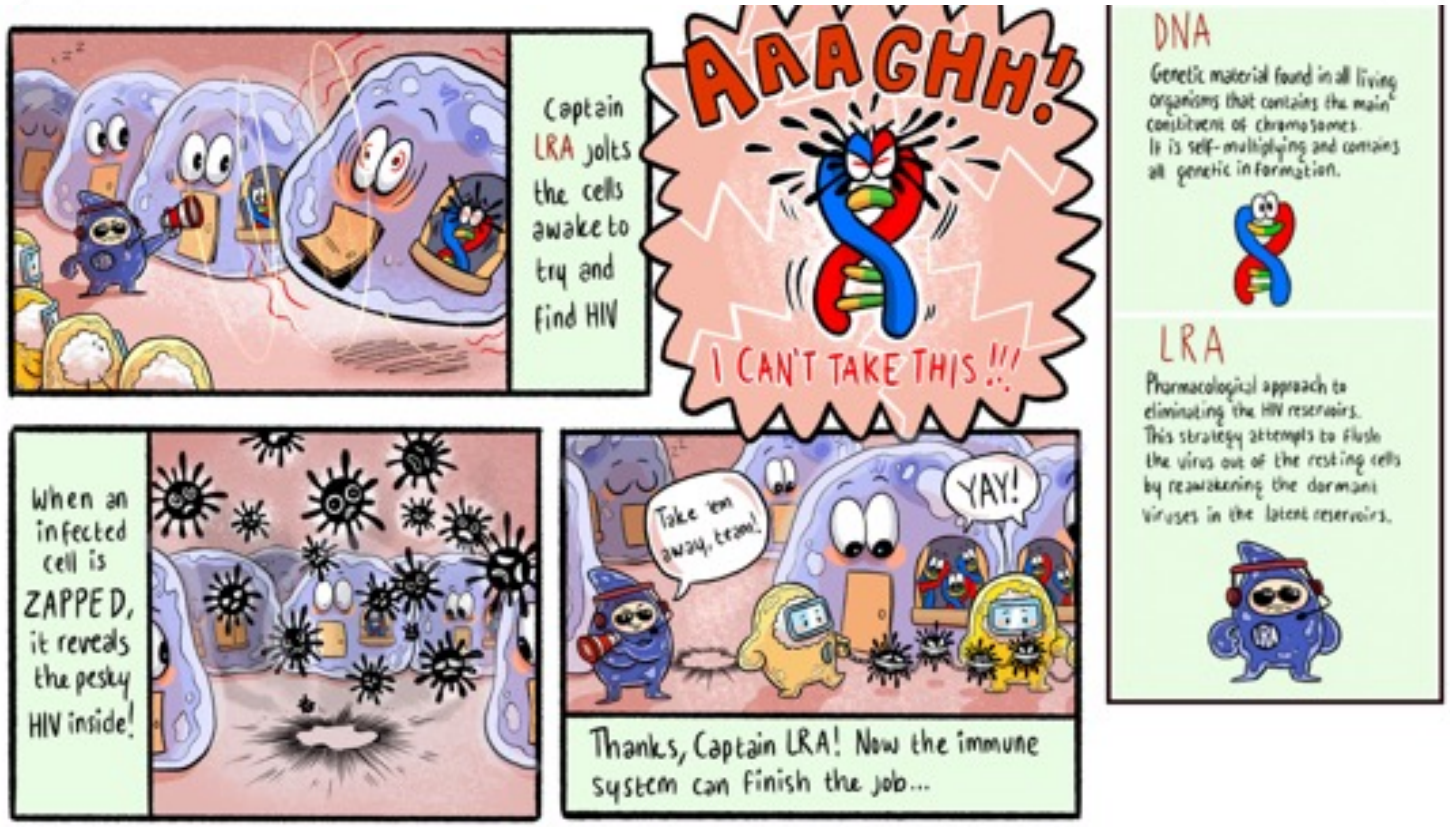


- None are HIV specific
- None are as potent as T-cell activation
- Unclear if virus is coming from all cells or just a few
- Still need better latency-reversing agents

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

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

CAPTAIN LRA SAVES THE DAY!



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

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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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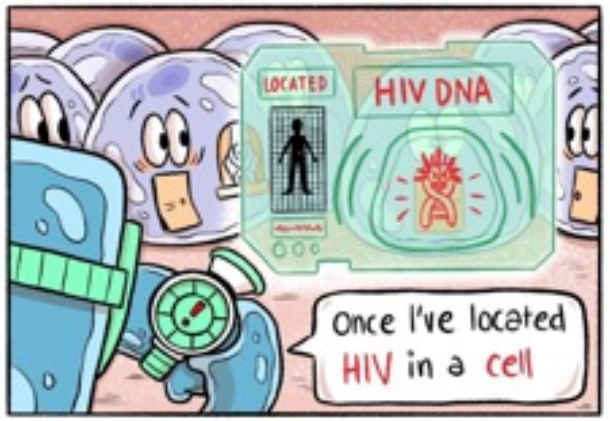
AGENT BLOCK 'N` LOCK



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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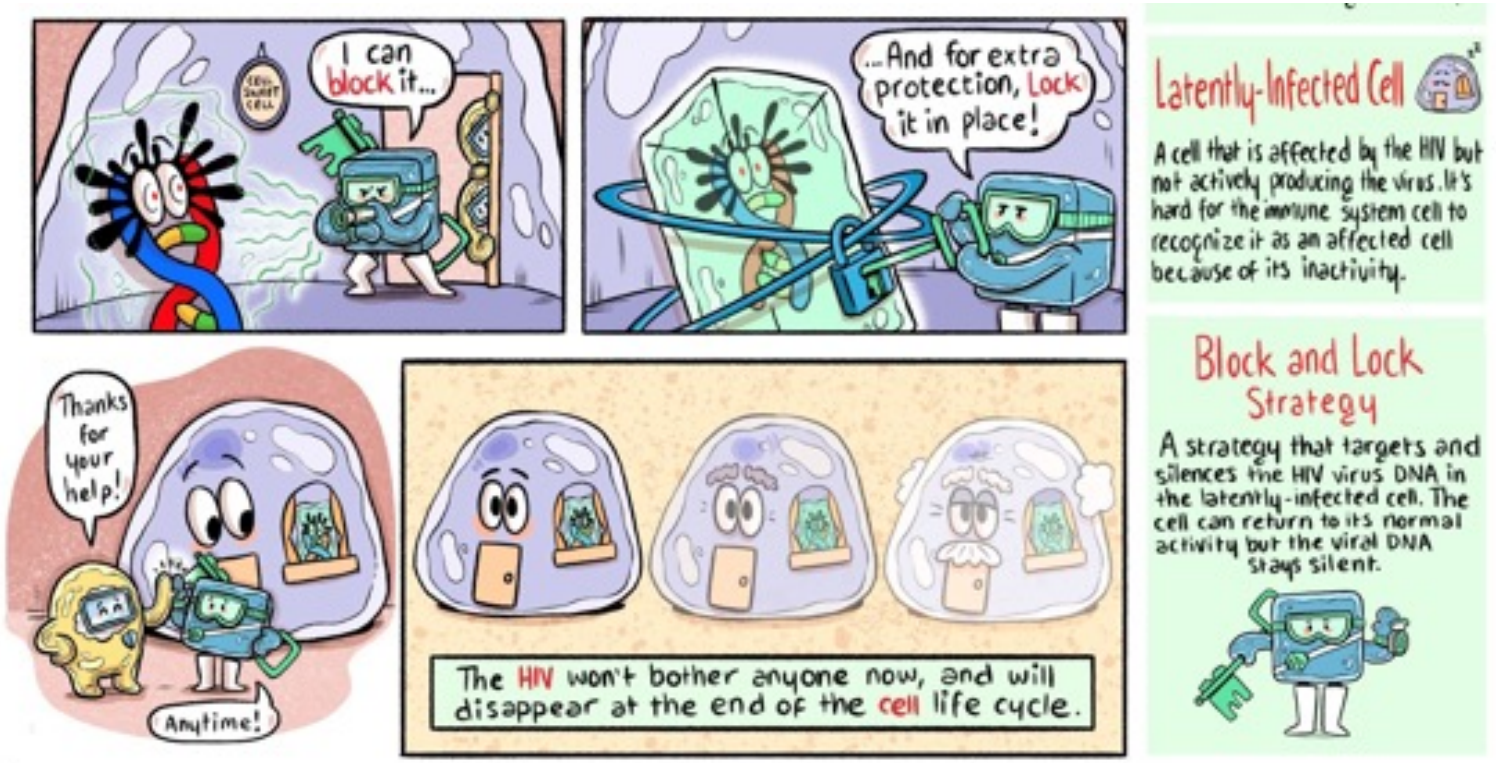

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YOUTH4 CURE

UCSF Center for AIDS Prevention Studies
Division of Prevention Sciences

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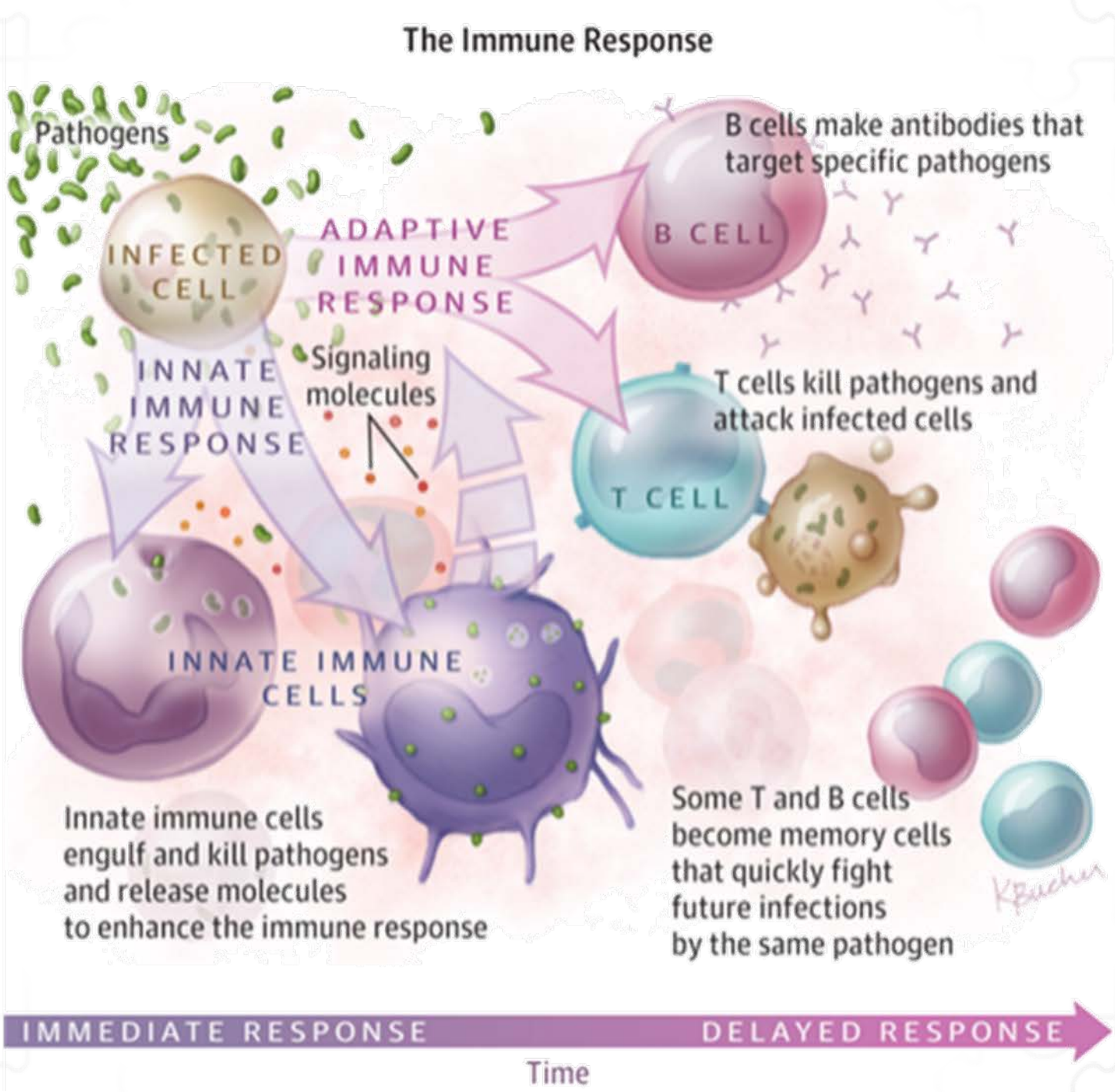
Eric (Yi-Hao) Lee, Jasmin Guzman, and Matylda McCormack-Sharp

Reinforcing the ‘dam’



Immunological Approaches

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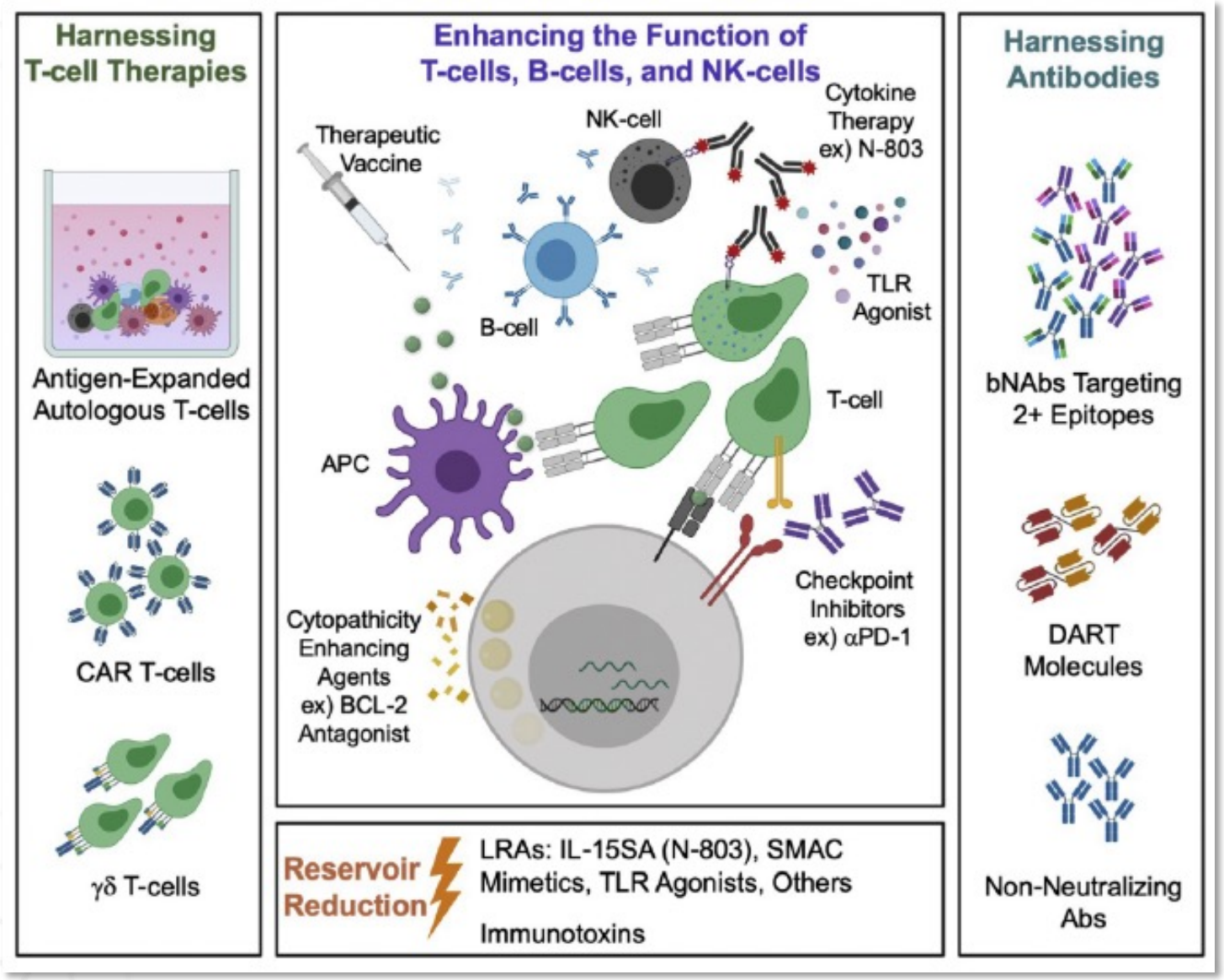

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Ward A, Mota TM, Jones RB. Immunological Approaches to HIV Cure. *Semin Immunol* 2020.

Targeting Virus *vs.* Improving Immune System

Very early ART

Broadly neutralising antibodies (bNAbs)

Latency reversal

T-cell vaccines

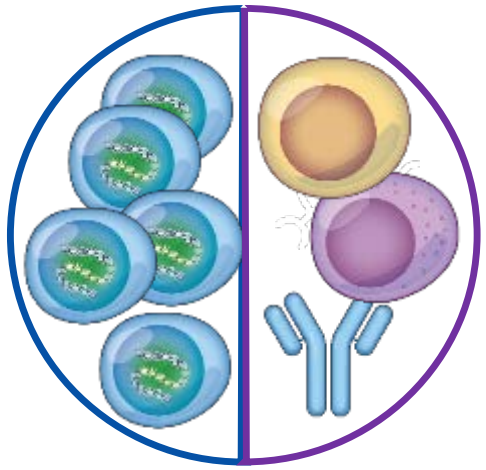
Pro-apoptotic drugs

Immunomodulation

Immunotoxins

CAR T-cells

Latency silencing



Gene editing

Gene editing

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SLIDE CREDIT: Sharon Lewin, AIDS 2020

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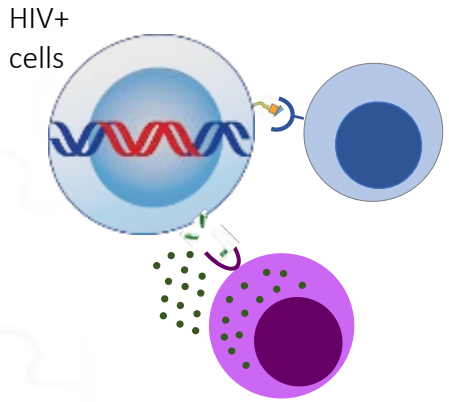
Improve CD8+ T Cell Clearing of HIV-Infected Cells

***CD8+ T cells help clear cells with the virus**

Therapeutic Vaccines



- ChAdV63/MVA (HIVconsv)[1]
- Ad26/MVA or protein[2]
- DNA/MVA[3]
- Dendritic cell+/-LRA[3]

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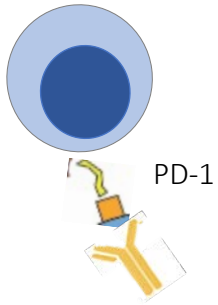
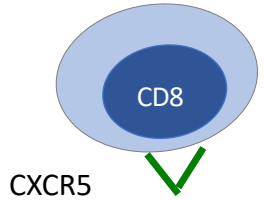
Immune Checkpoint Blockers



- In people with cancer/HIV[5]
- Anti-PD1 or PDL1
- Anti-CTLA-4

T-Cell Trafficking



- IL-15 superagonist[6]

Anti-inflammation

- mTOR inhibitors[7]

www.treatmentactiongroup.org; www.clinicaltrials.gov :[1]NCT02336074; [2]NCT02919306/[3]NCT02972450;[4]NCT02707900/NCT02767193 [5]NCT02408861/NCT02595866; [6]NCT02191098; [7]NCT02440789/NCT02990312

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

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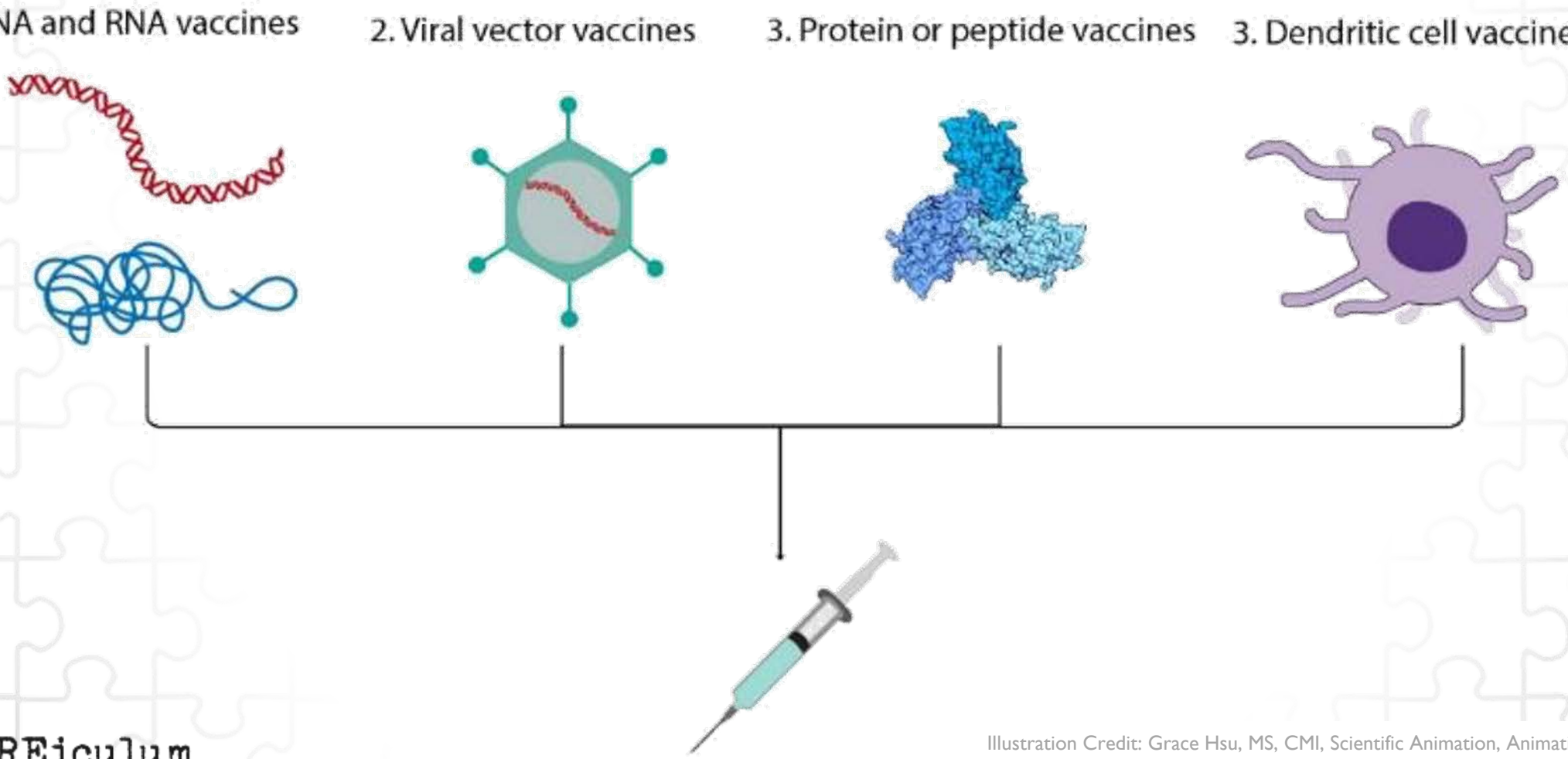
Types of HIV Therapeutic Vaccines



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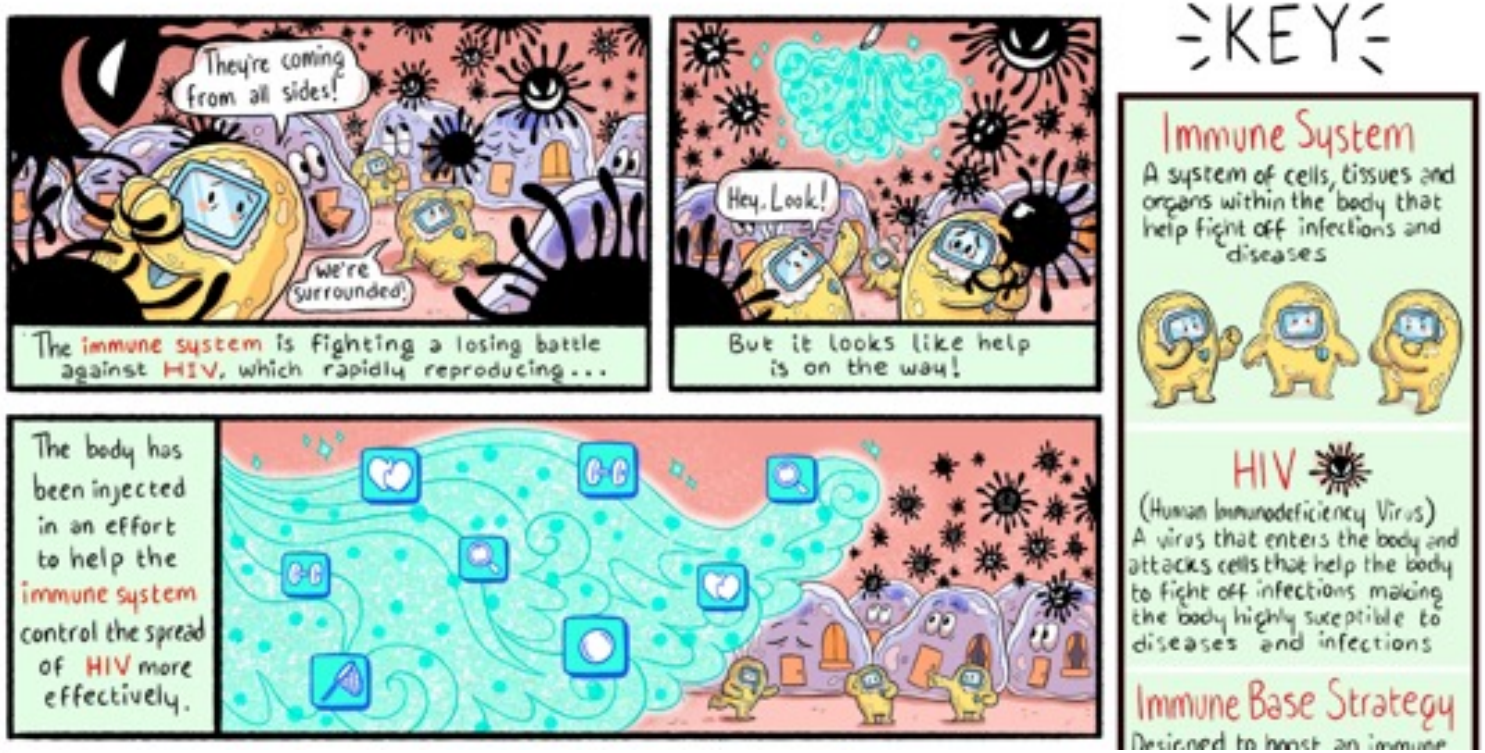
IMMUNOTEAM: POWER UP!



KEY

Immune System
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 the body and attacks cells that help the body to fight off infections making the body highly susceptible to diseases and infections

Immune Base Strategy
Designed to boost an immune

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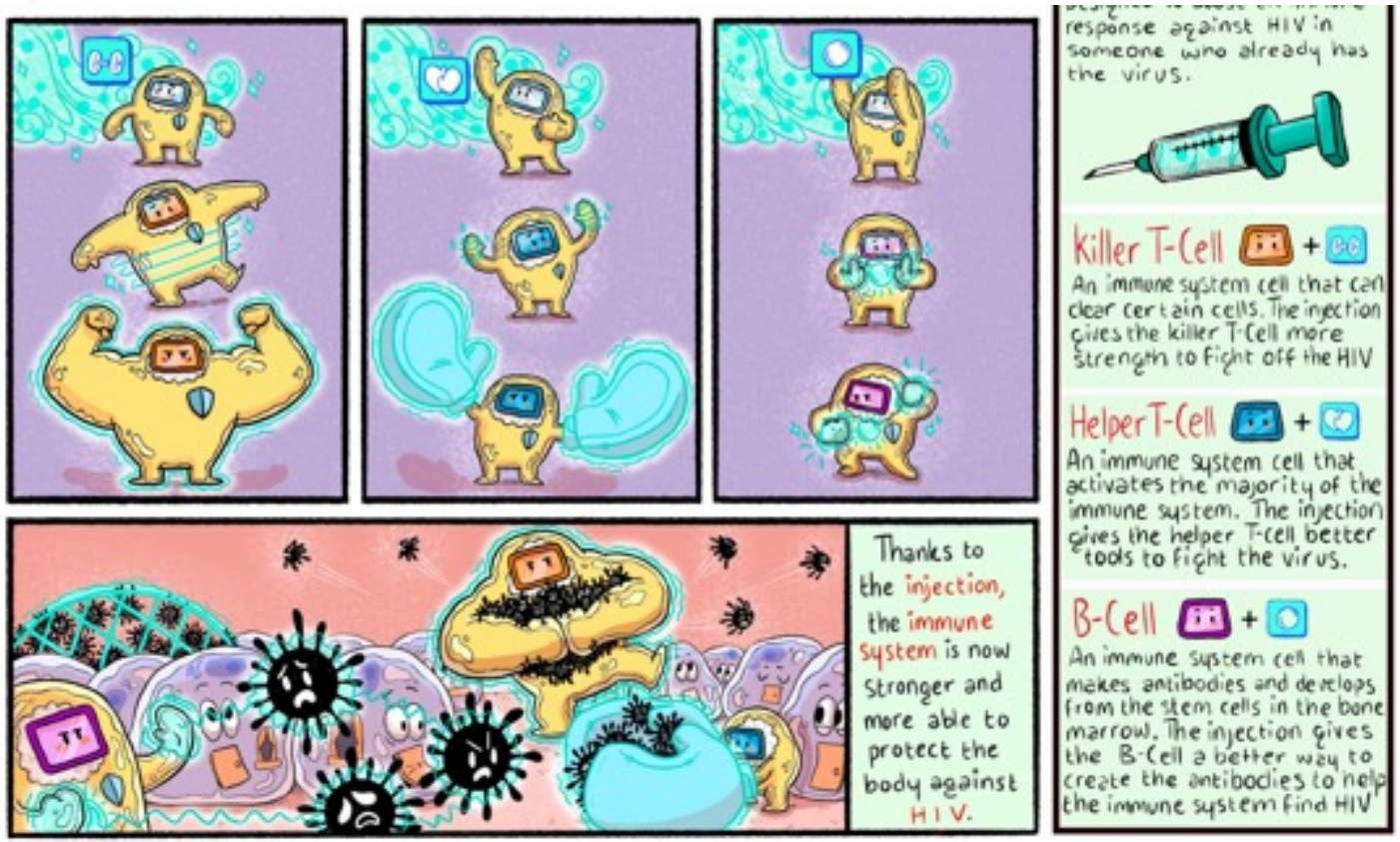

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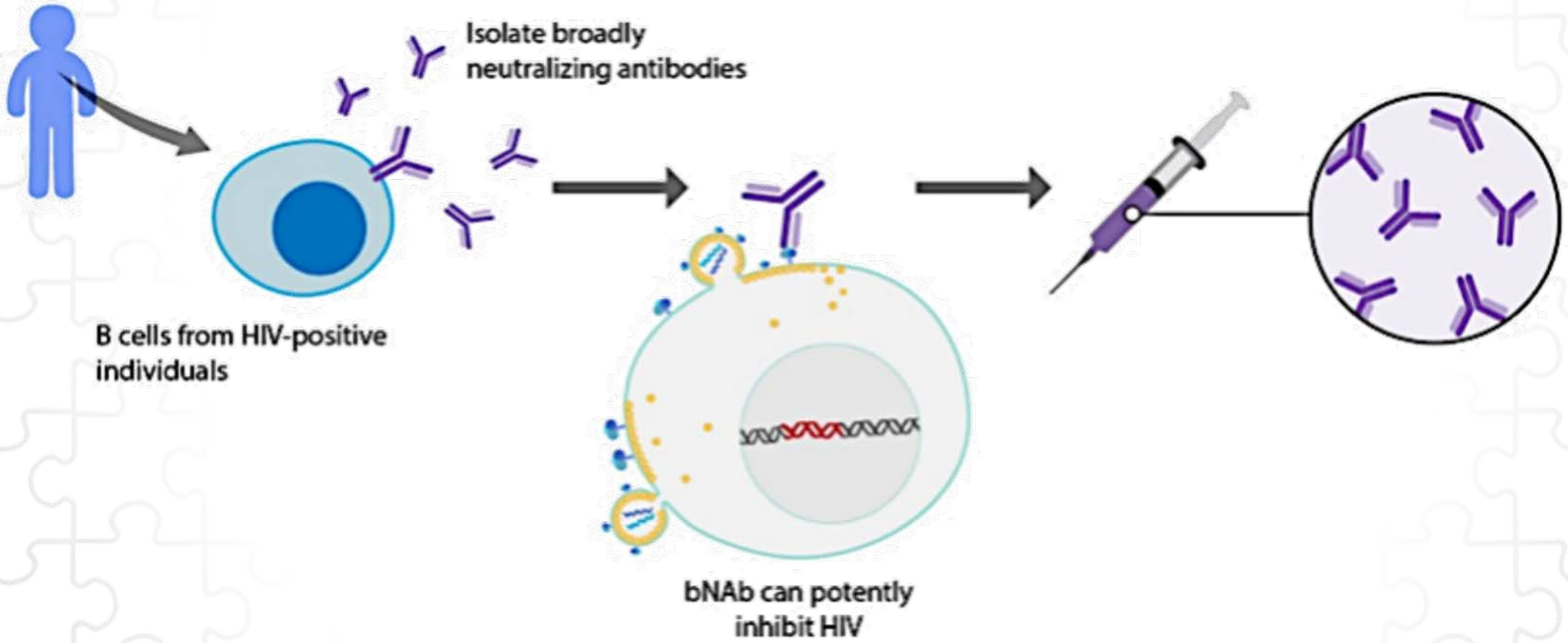
Passive Immunization: Broadly Neutralizing Antibodies



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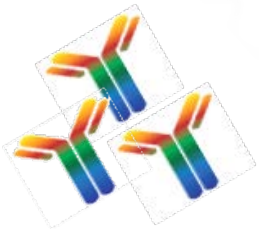
Broadly Neutralizing Antibodies (bNAbs)



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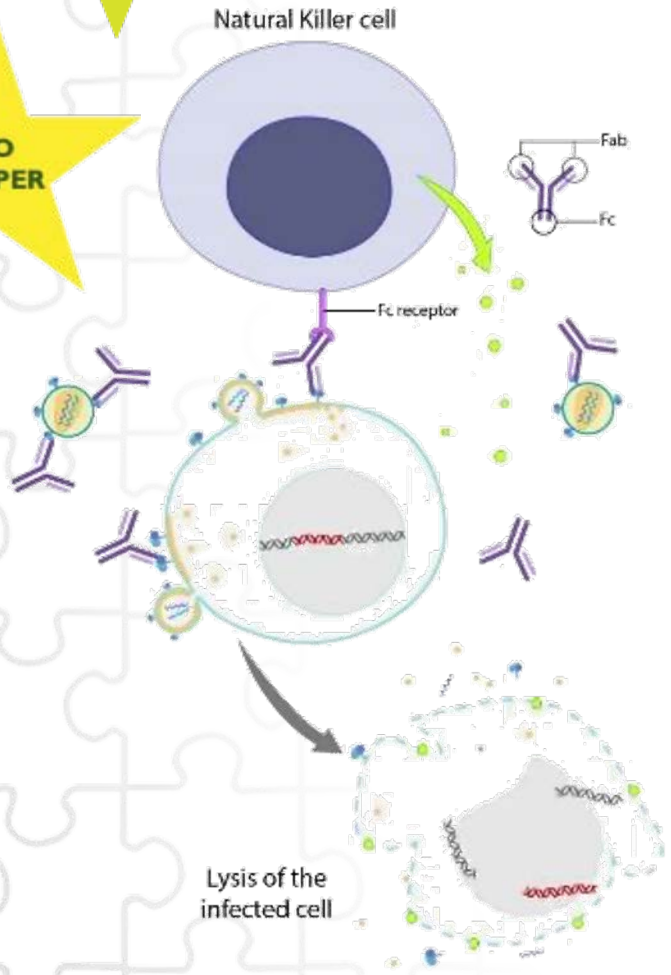

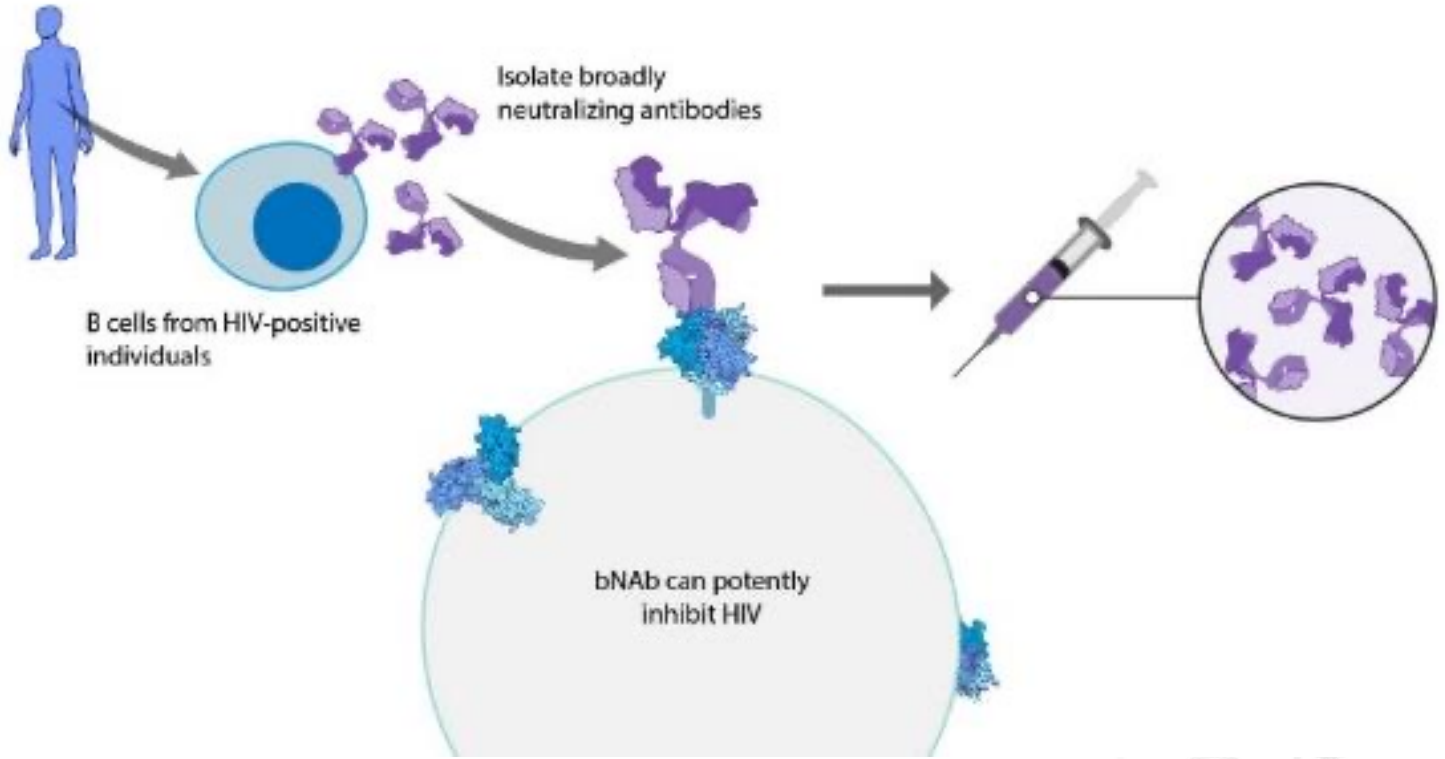

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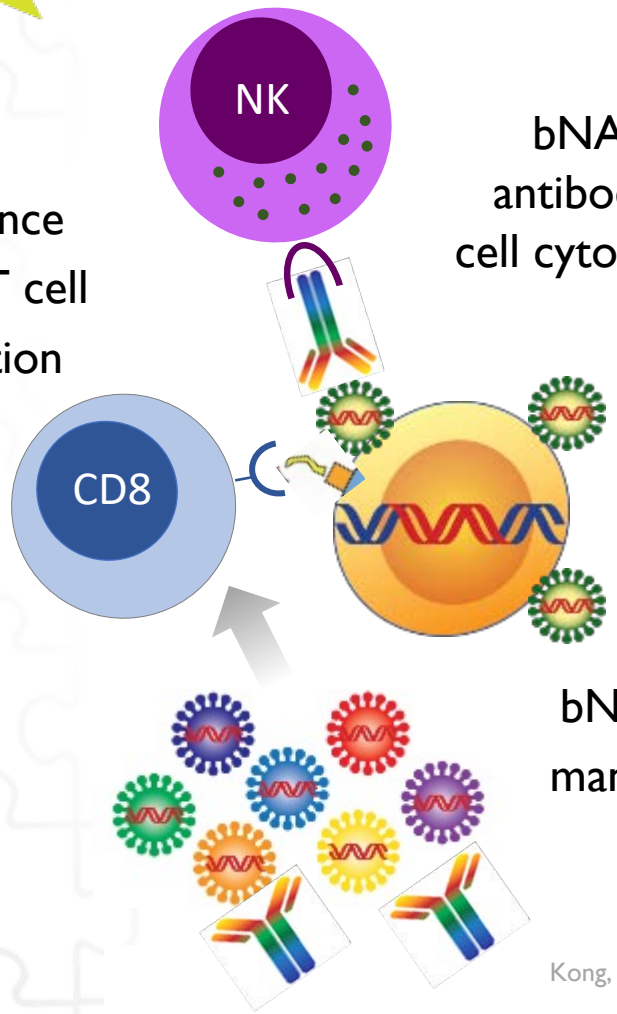
Broadly Neutralizing Antibodies (bNAbs)



Enhance CD8 T cell function

bNAbs facilitate antibody-dependent cell cytotoxicty (ADCC)

bNAbs can bind many HIV strains

Main obstacle

- Pre-existing resistance

Strategies

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

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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

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

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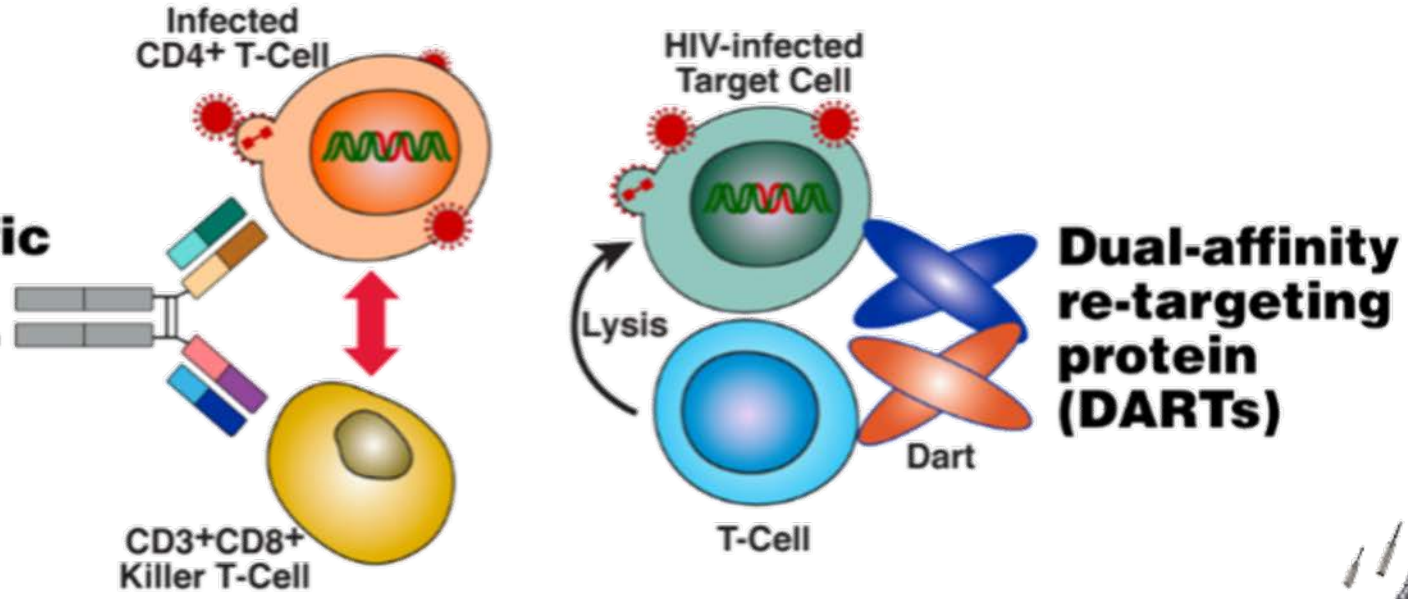
Bi-functional Antibodies (e.g., Bind HIV and CD3/CD8)



Two-headed figure analogy

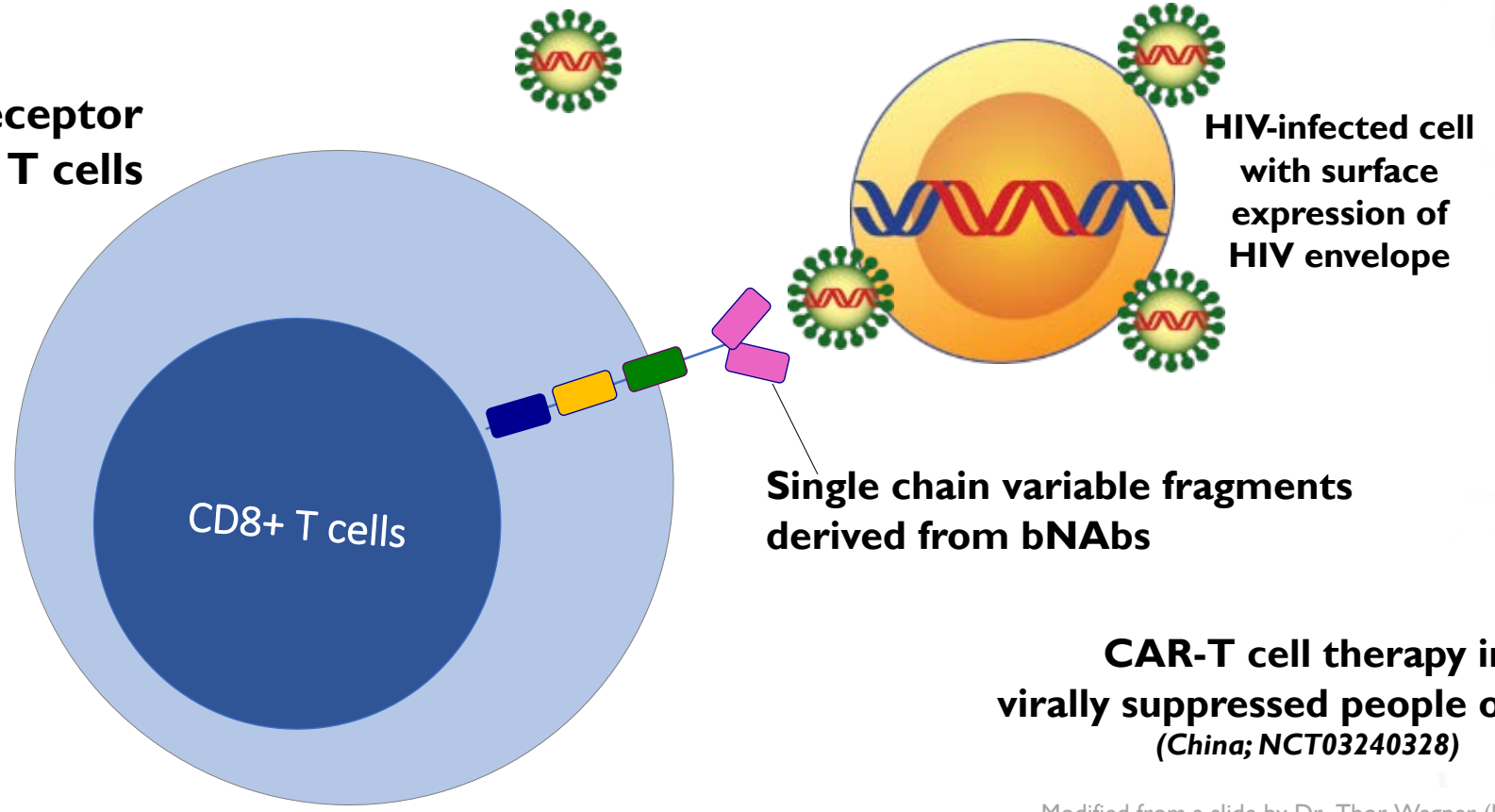
- Antibody platforms exist and entered clinical trials (for cancer)
- For HIV-1: *In vitro* proof-of-concept

Hammer-screwdriver combo analogy

Courtesy of John Mascola

Genetic Engineered T cells: Creating Super T Cells

Chimeric Antigen Receptor (CAR) T cells



'Super T cell'

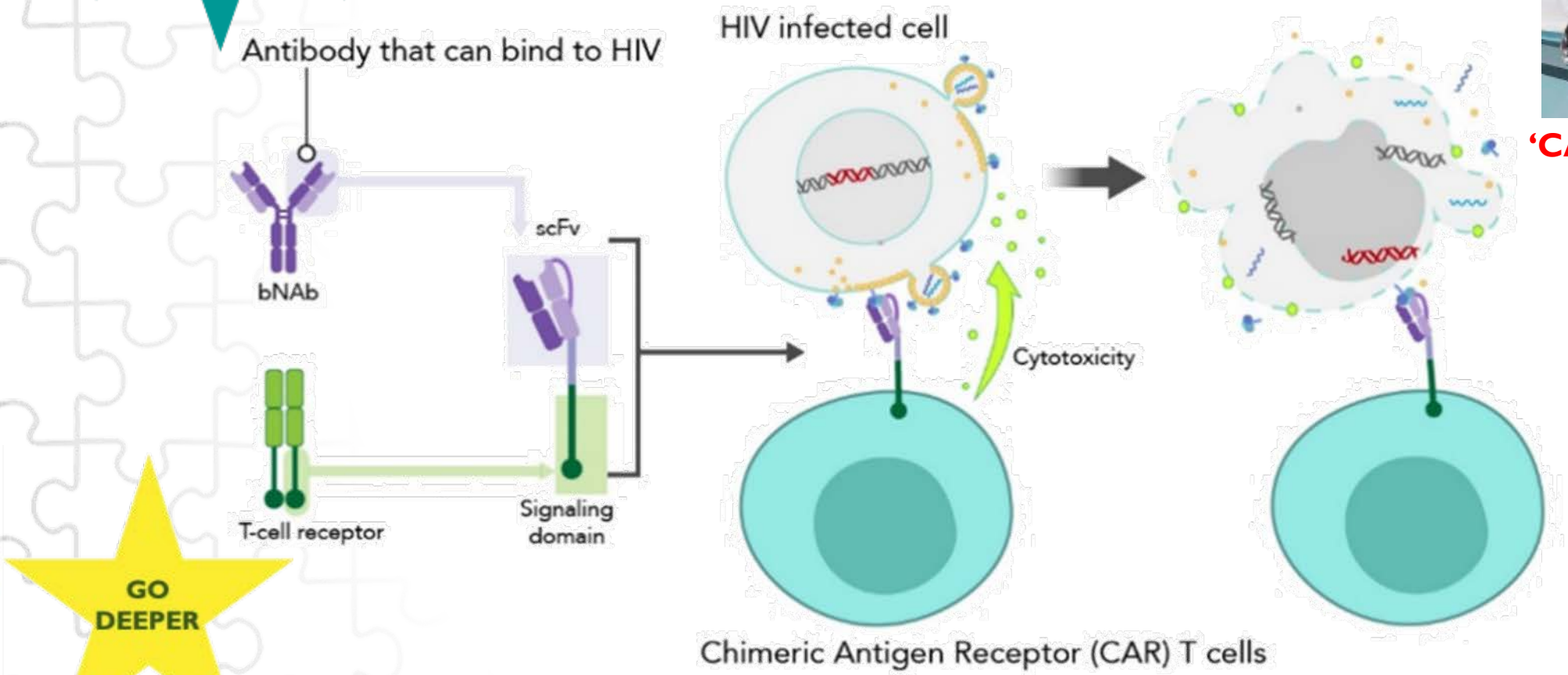
CAR-T cell therapy in virally suppressed people on ART
(China; NCT03240328)

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.

Chimeric Antigen Receptor (CAR) T Cells

'CAR' [T-cell] of the future analogy'



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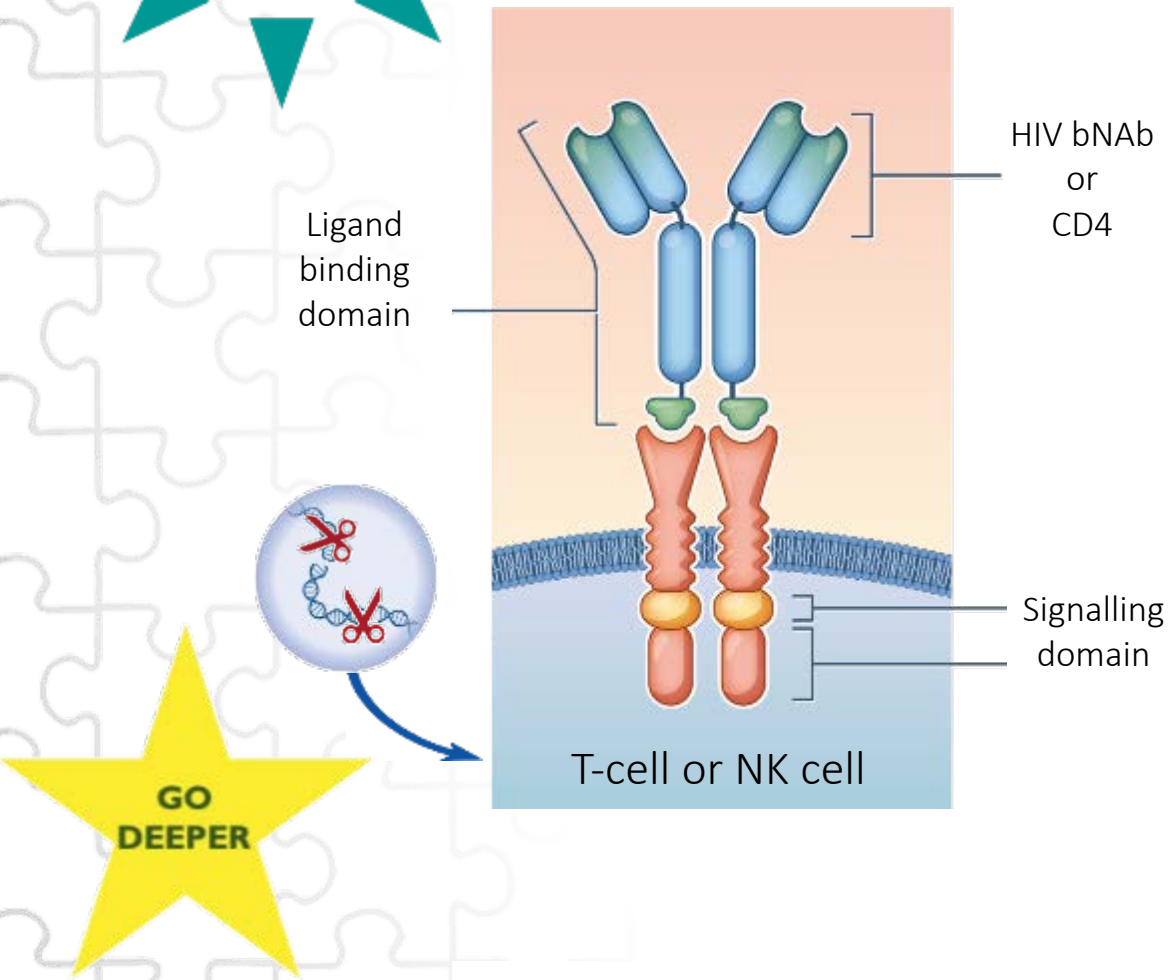
Chimeric Antigen Receptor (CAR) T Cells



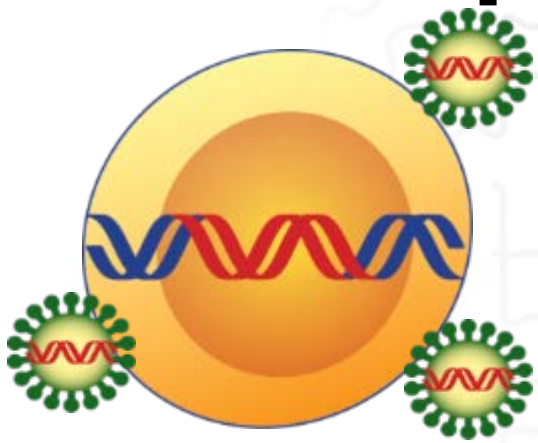
- Autologous T-cells or NK cells undergo gene editing to express a CAR to bind and kill cells that express HIV envelope [1-4]
- CAR T-cells for HIV tested in mice, macaque models and in clinical trials in China (x3) and the US (x1)[5]
- Major challenges include toxicity (potentially preventable), delivery to tissue sites and low expression of HIV envelope on ART

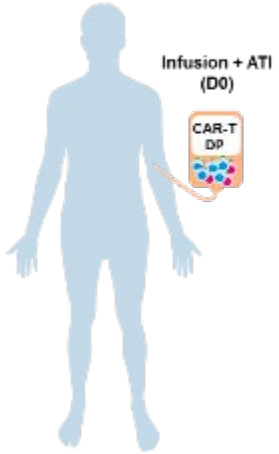
1 Deeks et al., Mol Ther 2002; 2 Sung et al., Mol Ther 2018; 3 Herzig et al., Cell 2019; 4 Anthony-Gonda Sci Transl Med 2019; 5 clinical trials.gov

Anti-HIV duoCAR-T cell therapy

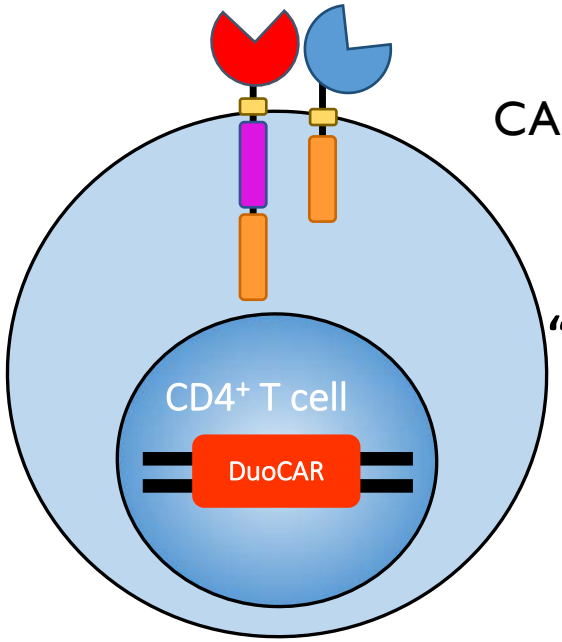
The new kid on the block!

1. **Protects** CD4⁺ T cells
2. **Dual targeting** of HIV⁺ cells via the Env glycoprotein
3. **Activation** of duoCAR-T cells
4. **Clearance** of HIV⁺ cells





DuoCAR-T Cells for HIV Infection
PI: Steven Deeks, MD
Collaborator: Caring Cross
US, NCT04648046



CAR **blocks** HIV entry

"Licensed to clear"
CD8⁺ T cell

DuoCAR-T cell approach

*"**Protecting** T cells against **HIV** using **Two CARs, One Cell**"*

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SLIDE CREDIT: Kim Anthony-Gonda, Boro Dropulic 2021

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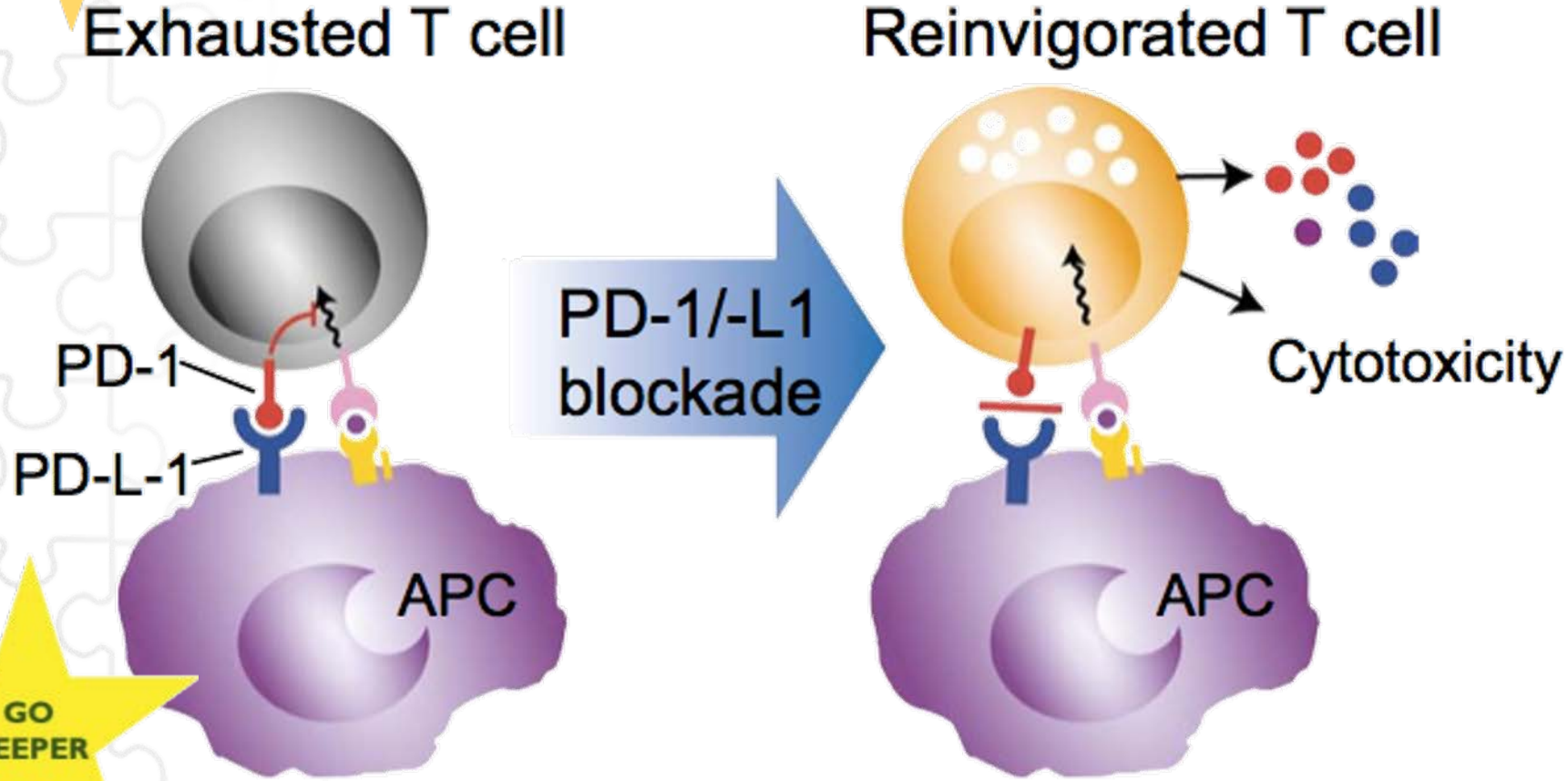
Immune Checkpoint Blockers



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Stephen Mason, Bristol-Myers Squibb.
The potential role of PD-1/PD-L1 blockade in HIV Remission & Cure.
Community Cure Workshop, February 22, 2015 Seattle, WA

Making cells stronger

What is Cell and Gene Modification?

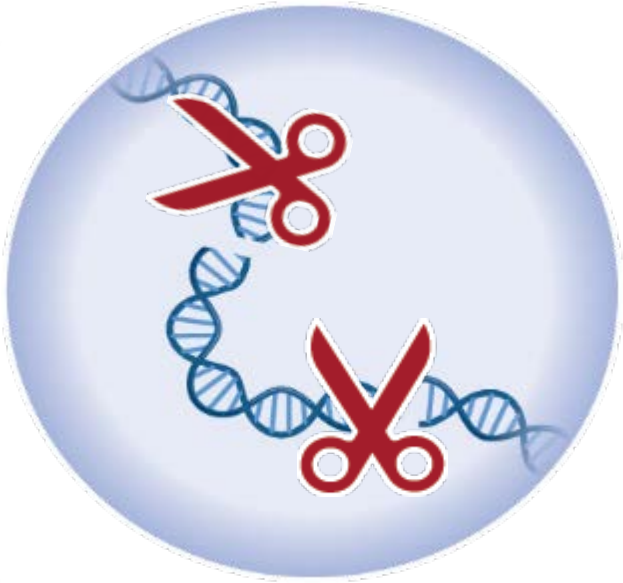
- A branch of **Regenerative Medicine**, an emerging field that involves the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function".

- **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.

Gene Modification: Targets and Strategies



Attack: enhance anti-HIV immune responses

Protect: engineer uninfected cells to be resistant to HIV

Purge: directly eliminate the virus itself

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Delivery of gene therapy a major challenge:

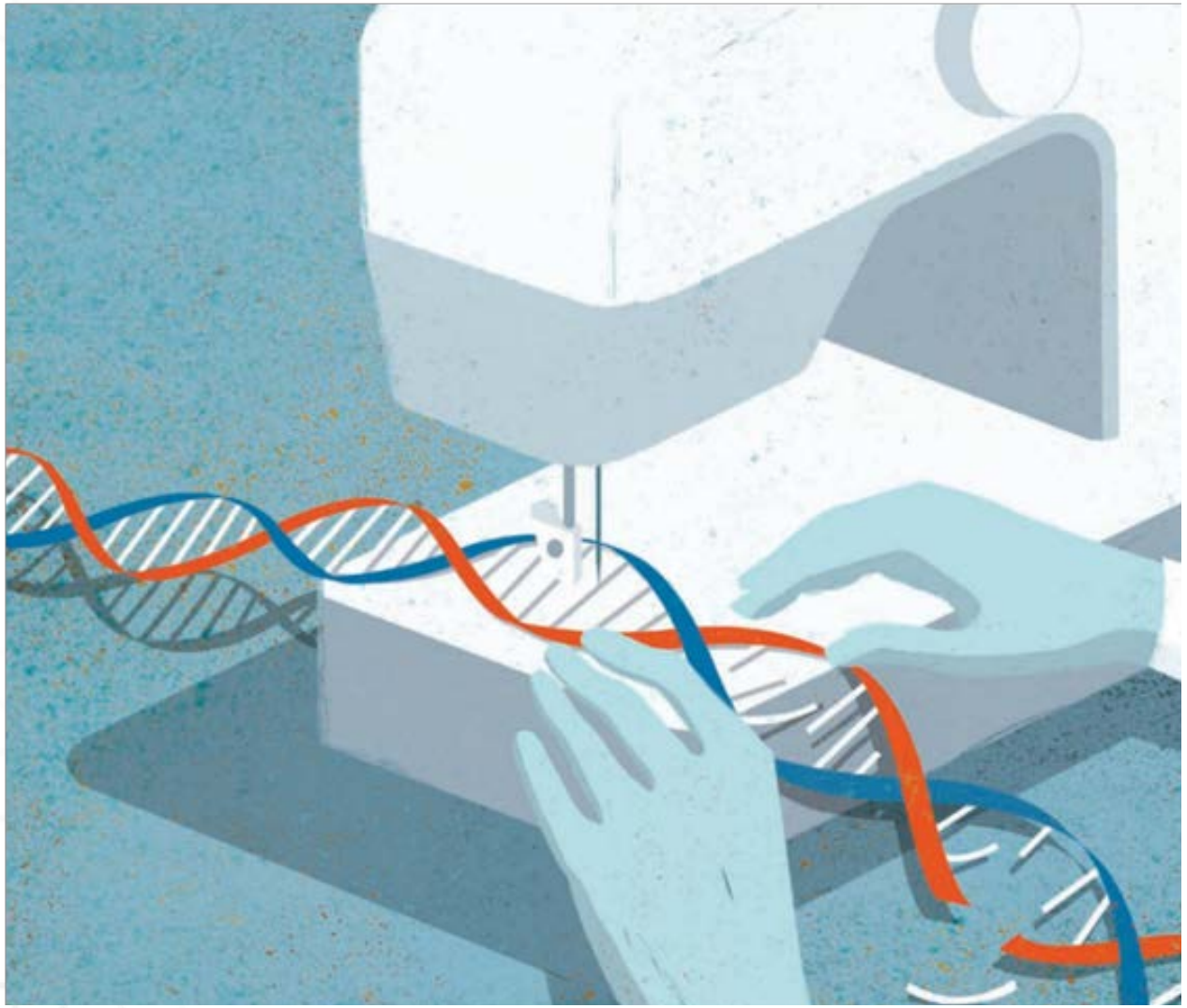
- ***ex vivo*** (gene editing of cells outside the body) or ***in vivo*** (gene editing in the body)

Lewin, CROI 2020
Slide Courtesy of Paula Cannon

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.

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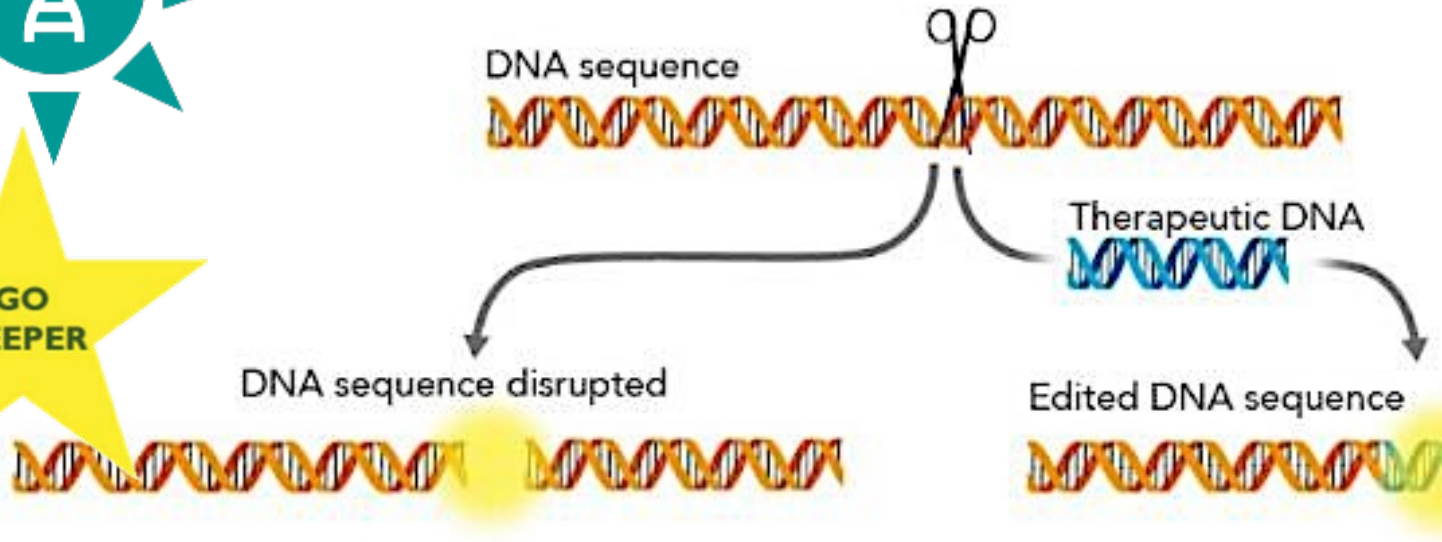
Gene modification strategies



Gene editing for HIV Cure: example of site-specific platforms

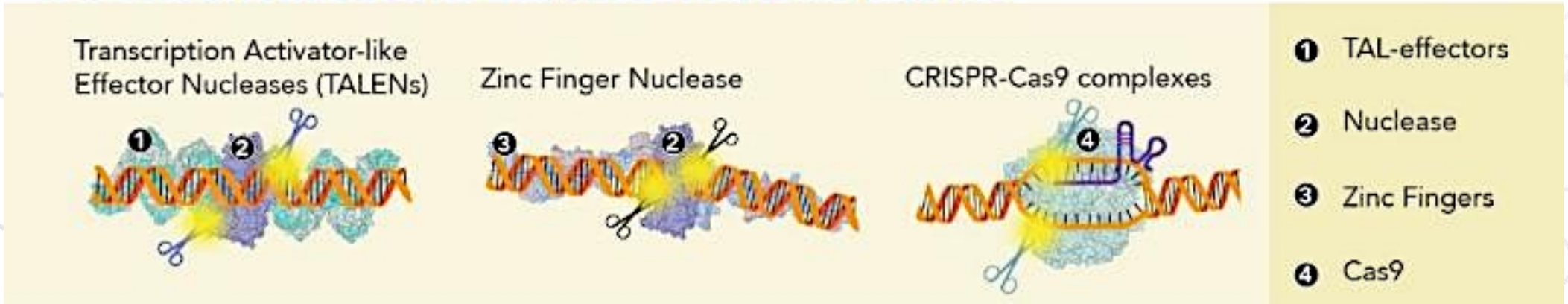
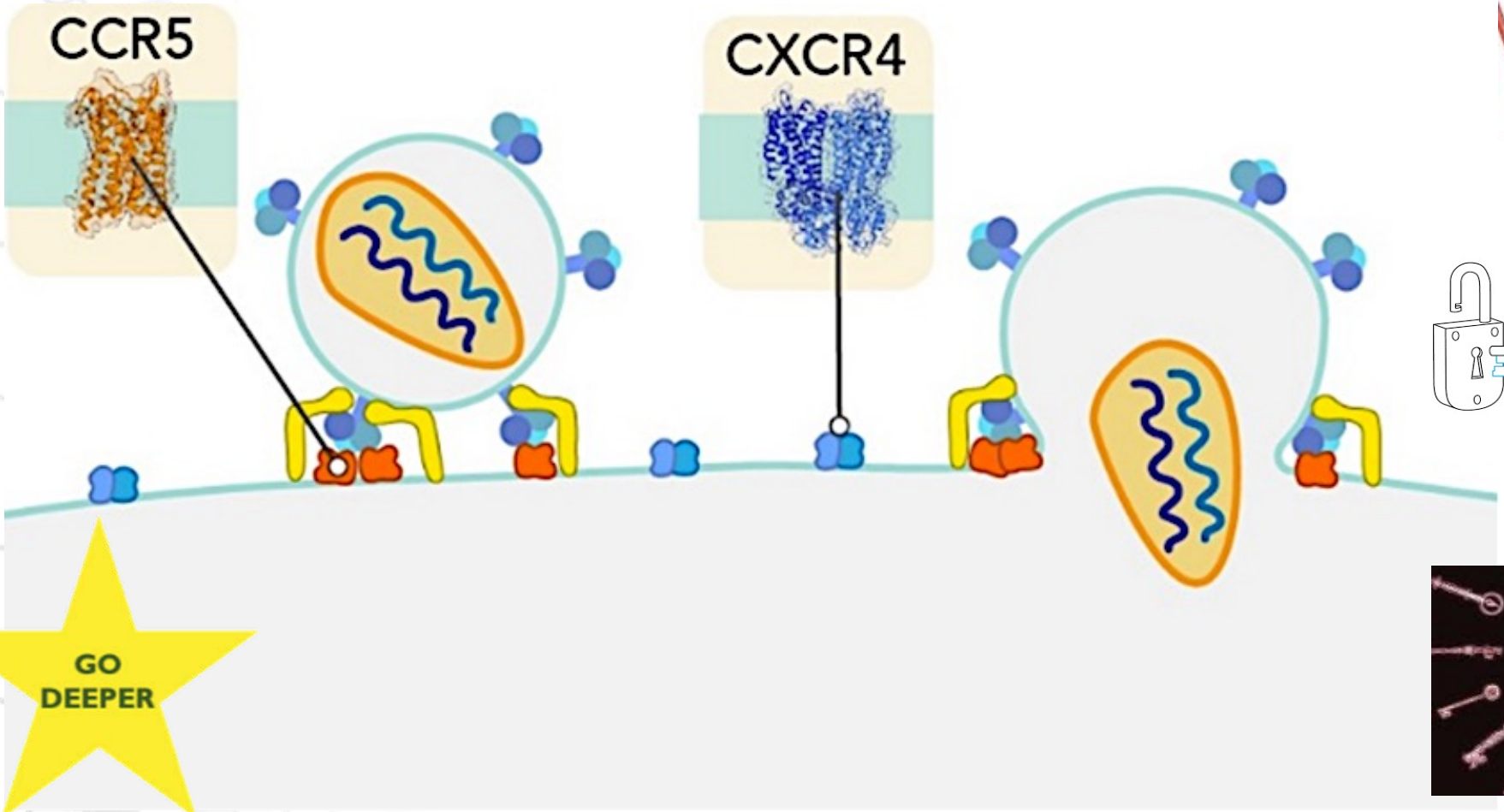
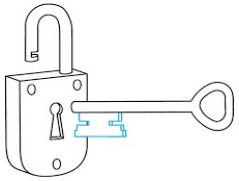


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Prevent HIV from Entering Cells

'Tinkering with the Lock & Key'





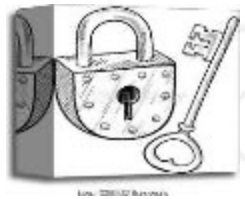


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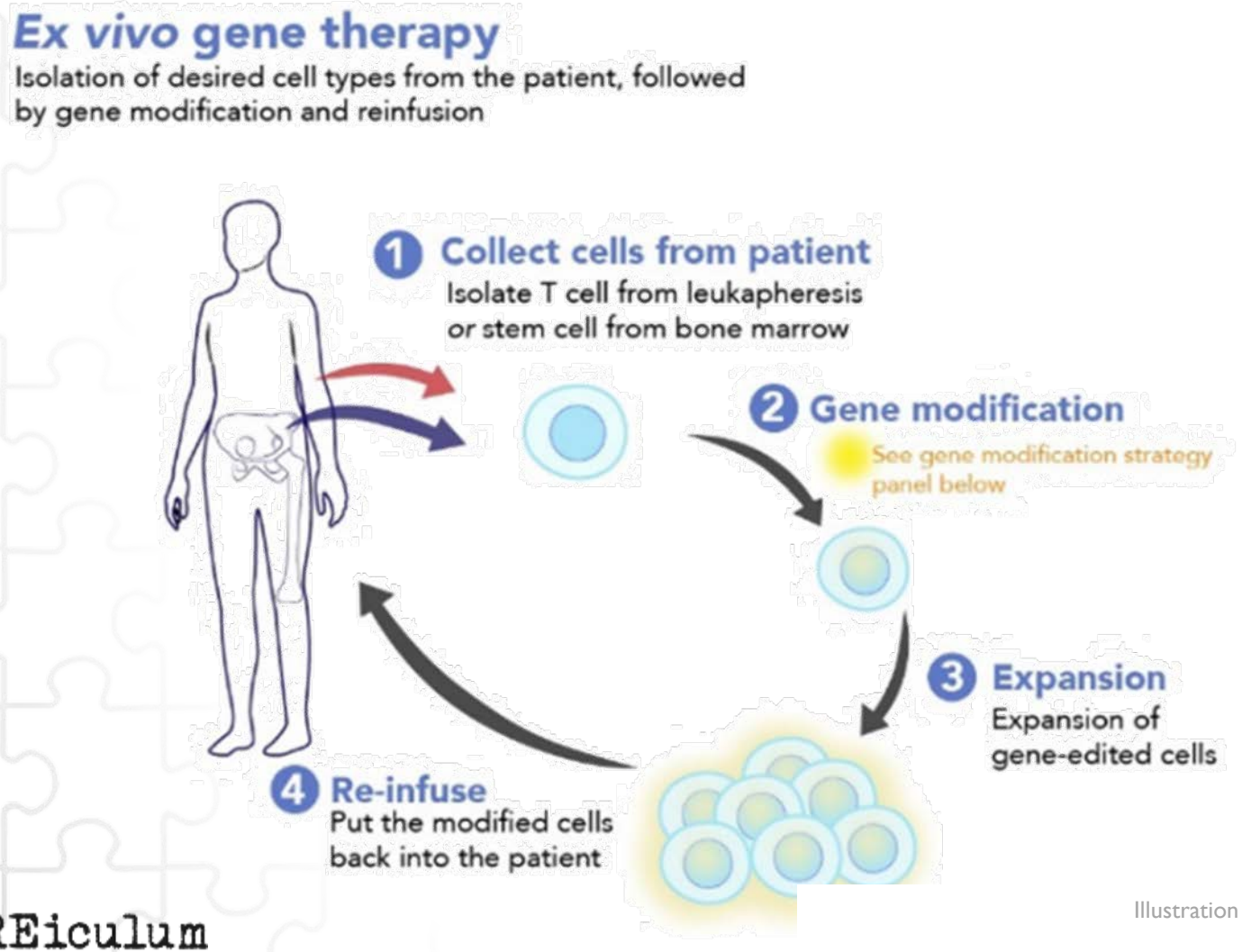
Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Modification Occurring Outside the Body '*Ex Vivo*'



Outside of the body

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

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Modification Occurring Inside the Body '*In Vivo*'

Inside of the body

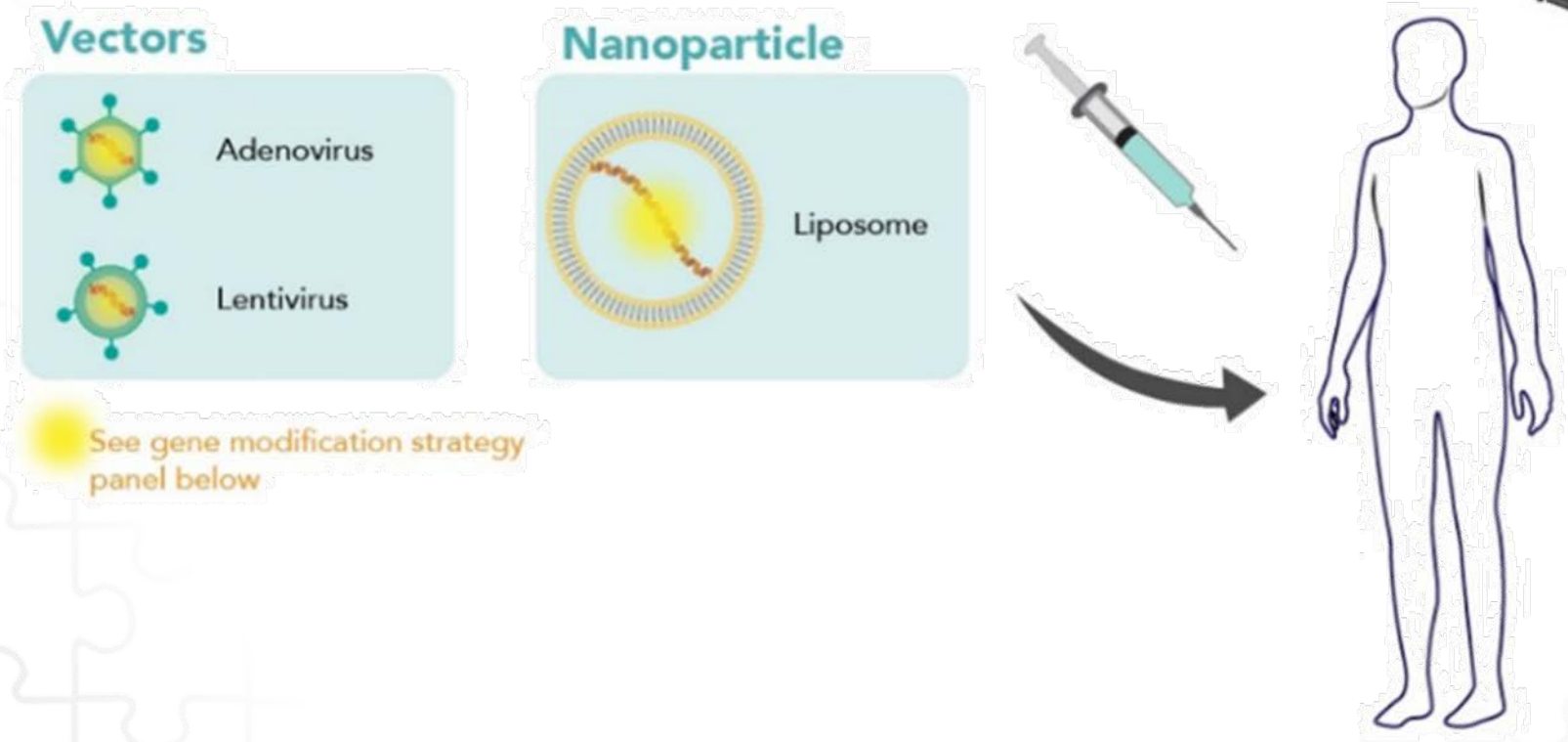

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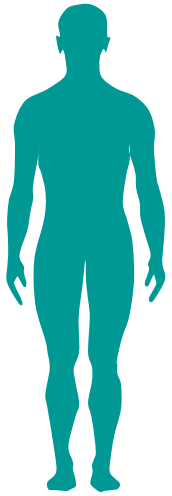
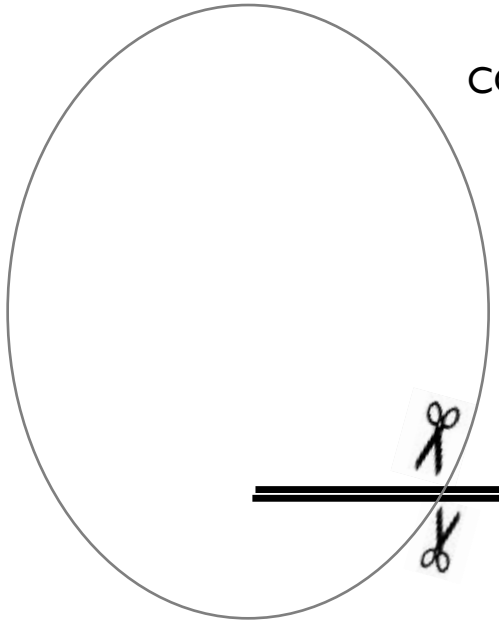
Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Gene Modifications to Make Cells Resistant to HIV

Leukapharesis
CD4+ T-cell isolation



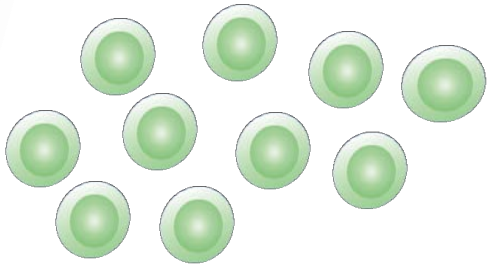
CCR5-



CCR5+

Gene modification strategy

Re-infuse



Strategies

- Use stem cells
- Conditioning therapies
- CCR5 and other anti-HIV genes
- Newer editing technologies

- **People with HIV/no cancer**
  - SB-728mR-T+cyclophosphamide[1]
  - shRNA-modified stem cells[2]
- **People with HIV and cancer**
  - Stem cells gene-modified to encode multiple anti-HIV RNAs[3]
  - CRISPR CCR5 modified CD34+ cells[4]

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Tebas P, NEJM 2014

www.treatmentactiongroup.org; www.clinicaltrials.gov : [1]NCT02388594; [2]NCT03517631; [3]NCT02343666/NCT02337985; [4]NCT03164135

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

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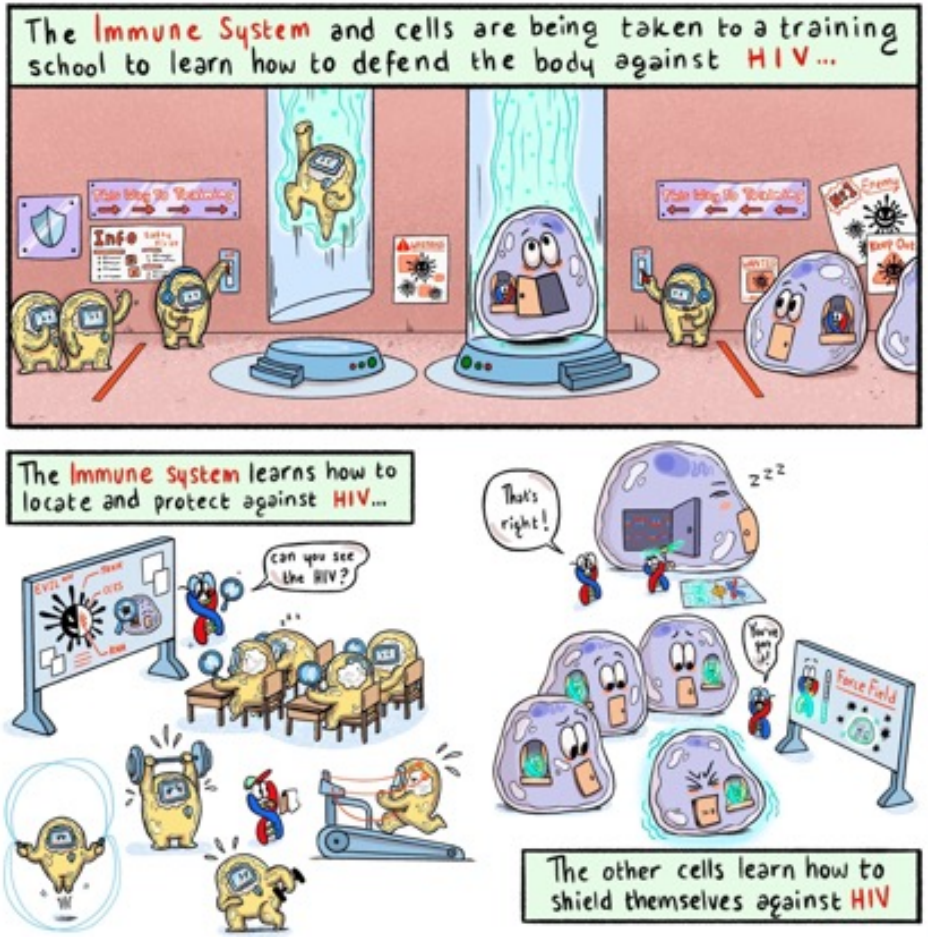
IMMUNOTEAM: DEFEND 'N' ASSIST



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

YOUTH4 CURE

UCSF Center for AIDS Prevention Studies
Division of Prevention Sciences

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

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/

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Landscape Analysis of HIV Cure-Related Trials

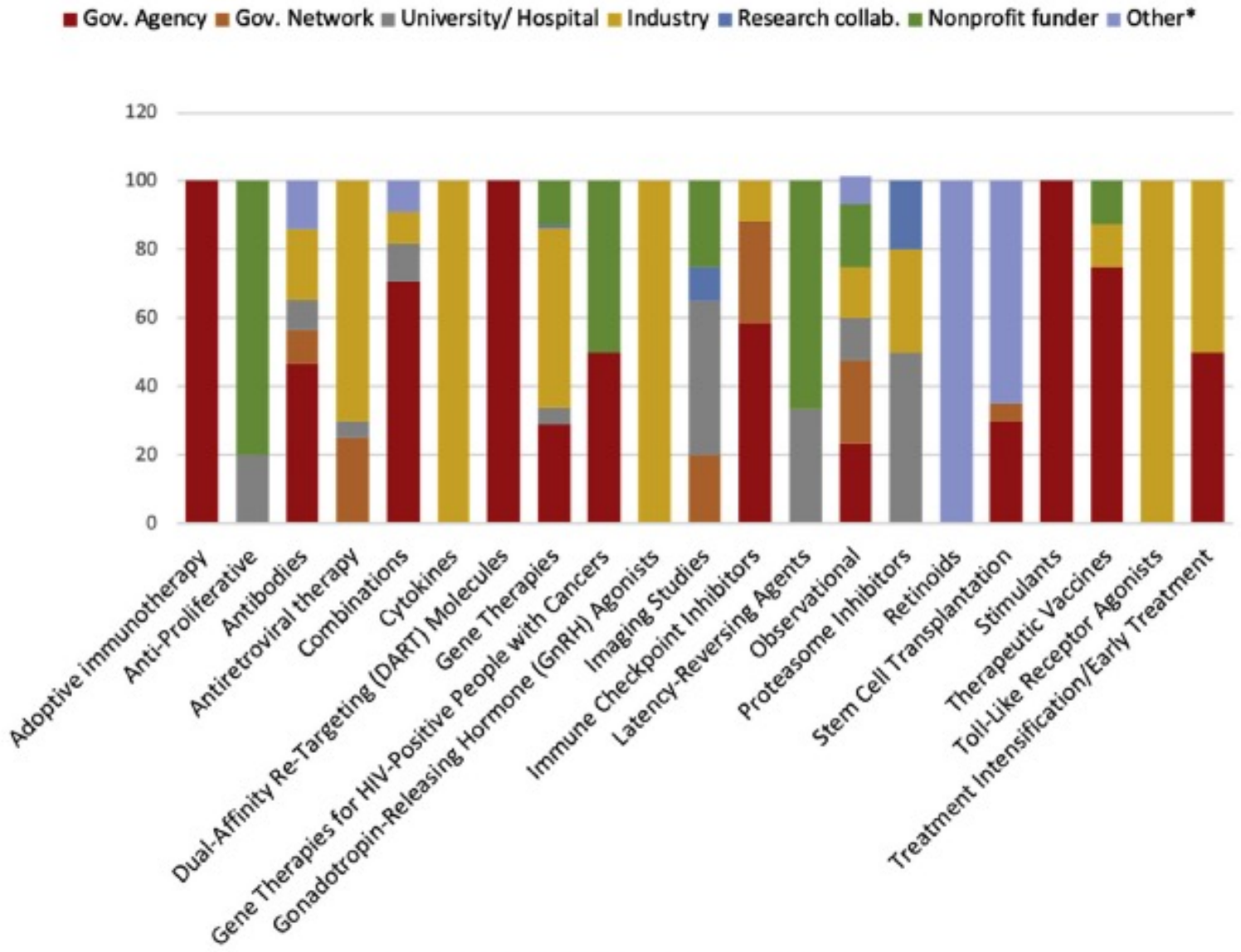

Fig. 4. Mean per-category funding by funder category.

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Barr L, Jefferys R. A Landscape Analysis of HIV Cure-Related Clinical Research in 2019. Journal of Virus Eradication 2020; 6(4): 100010

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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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