

Journey into science and HIV-1 cure strategies research

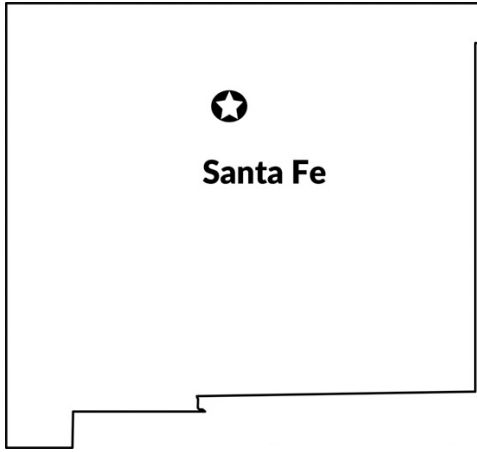
Emily, PhD in Microbiology & Immunology

Masters in Clinical Investigation

STEM Cap – Science Right Now

Feb 2023





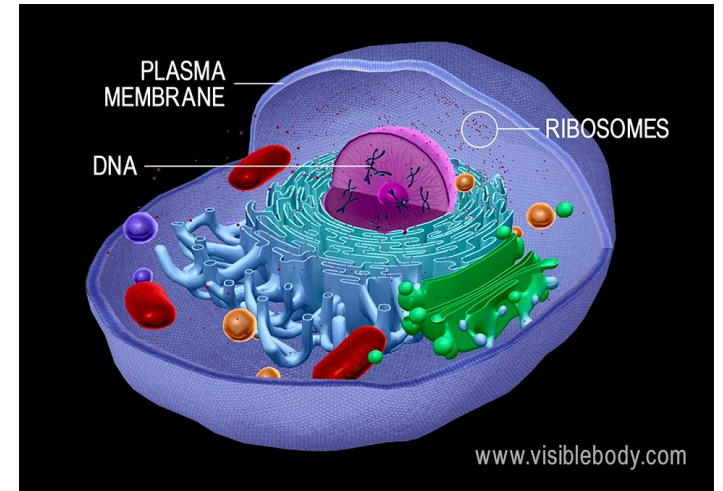
Who am I?

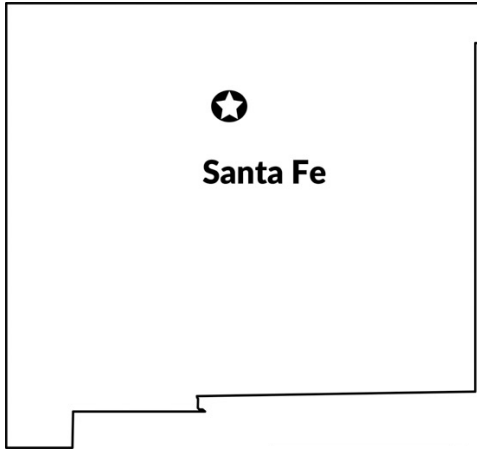


Went to public
high school



Biology – What is it?





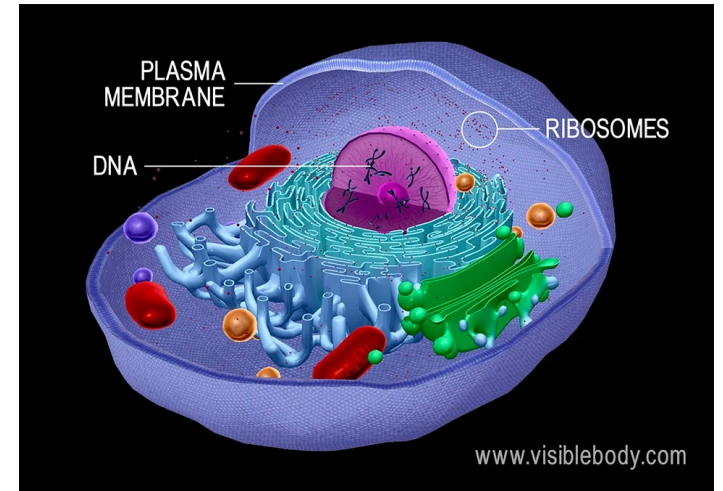
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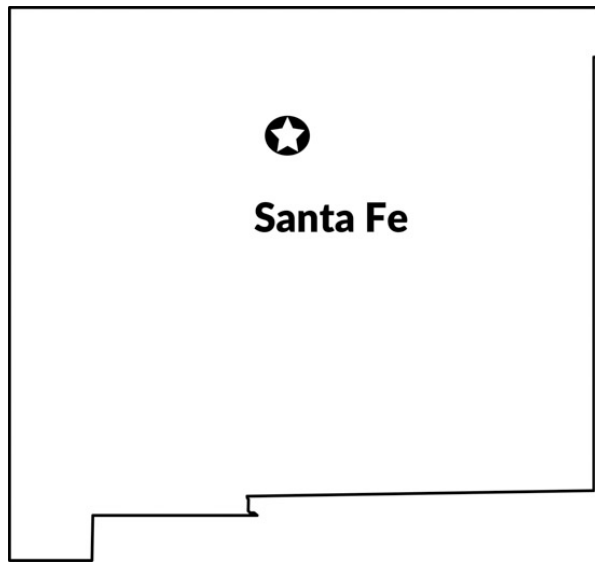


Biology – What is it?



The study of living
organisms

Who am I?



Graduated from public
high school



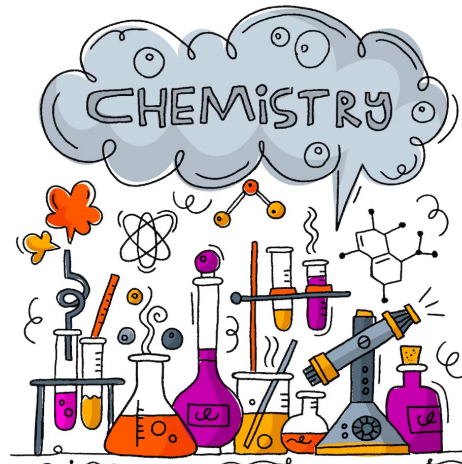
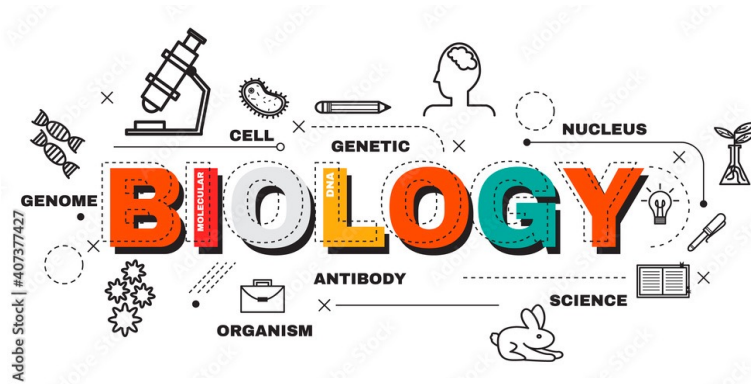
Went to college at UNM



?

I studied many subjects during college

Science



designed by freepik

Dance



Portuguese

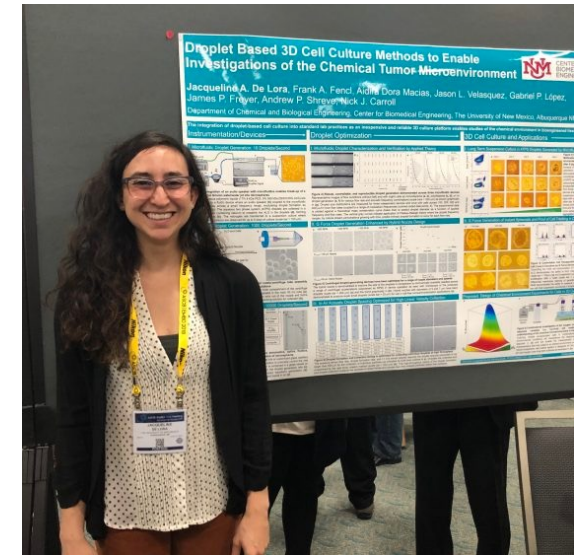
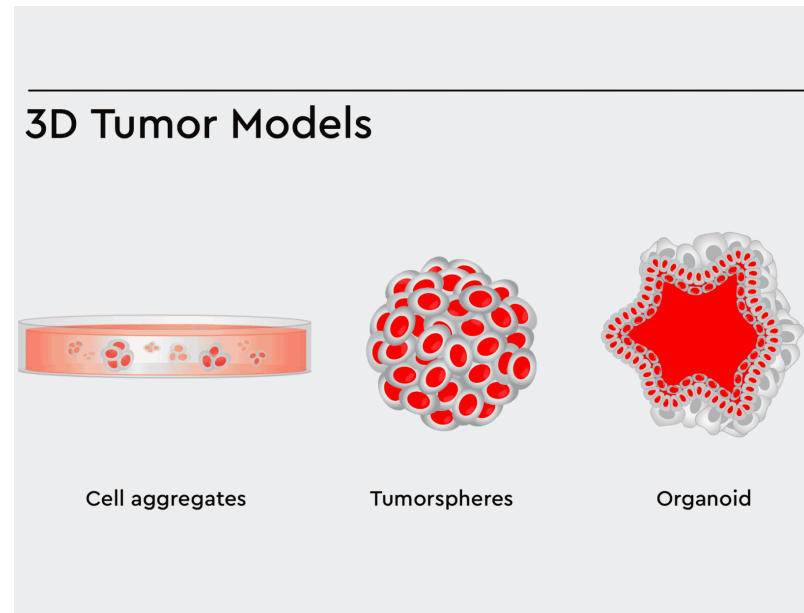
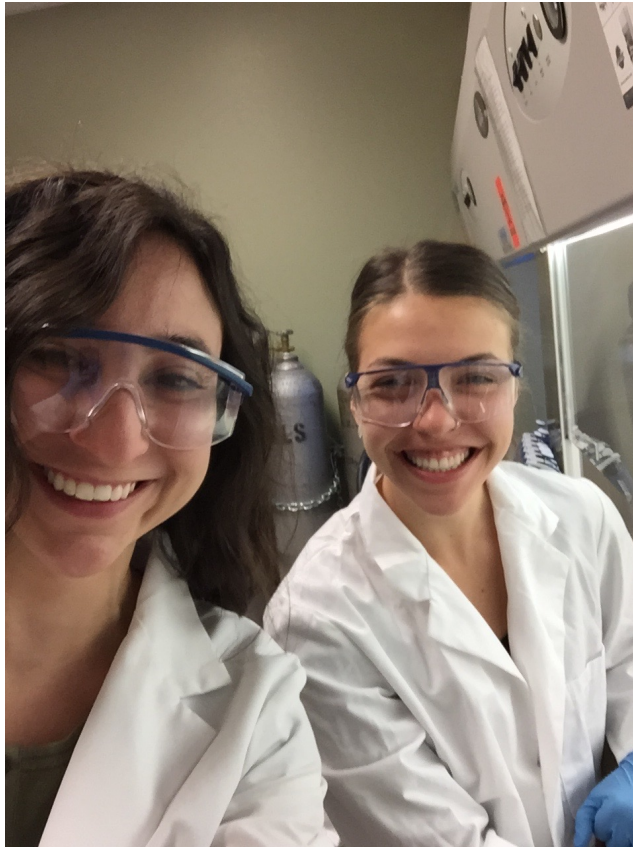


Bachelors of Science
in Biology



Finding a science research mentor

Studied the 3 dimensional tumor microenvironment



Encouraged me to go to grad school after working in several laboratories for two years

Excited about science research

Science research allows you to ask questions and figure out the answer

Why do people get sick?

Why do some viruses or bacteria cause disease?

How do we develop treatments?

How does our immune system work?



Getting a PhD in Microbiology and Immunology



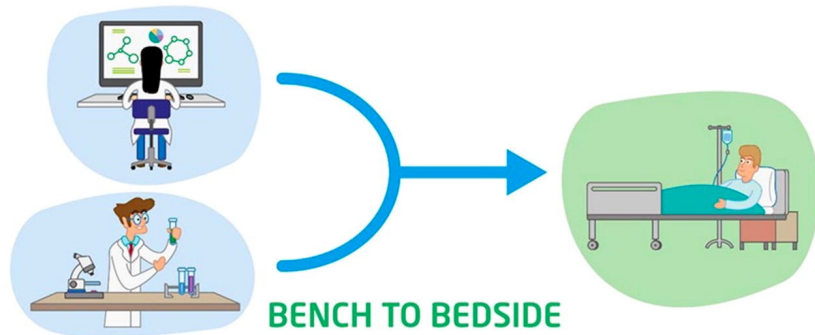
HEALTH
UNIVERSITY OF UTAH



Studying HIV-1, immune system,
and therapeutics

Getting a PhD in Microbiology and Immunology

Masters of Science in Clinical Investigation



Studying HIV-1, immune system,
and therapeutics

Outline

1. Immune System

2. HIV Background

3. Research on HIV cure strategy



The Immune System

- What ways does your body react when you get sick?



fever



fatigue



inflammation

- The immune system is activated to help defend your body
 - Heat and chemicals produced!

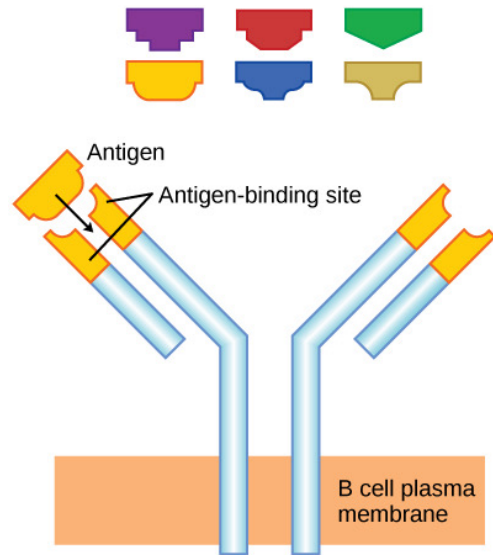
What is the Immune System?



- Defends you from harmful invaders (viruses, parasites, bacteria)
- Recognizes and attacks the invader
- Involves immune cells

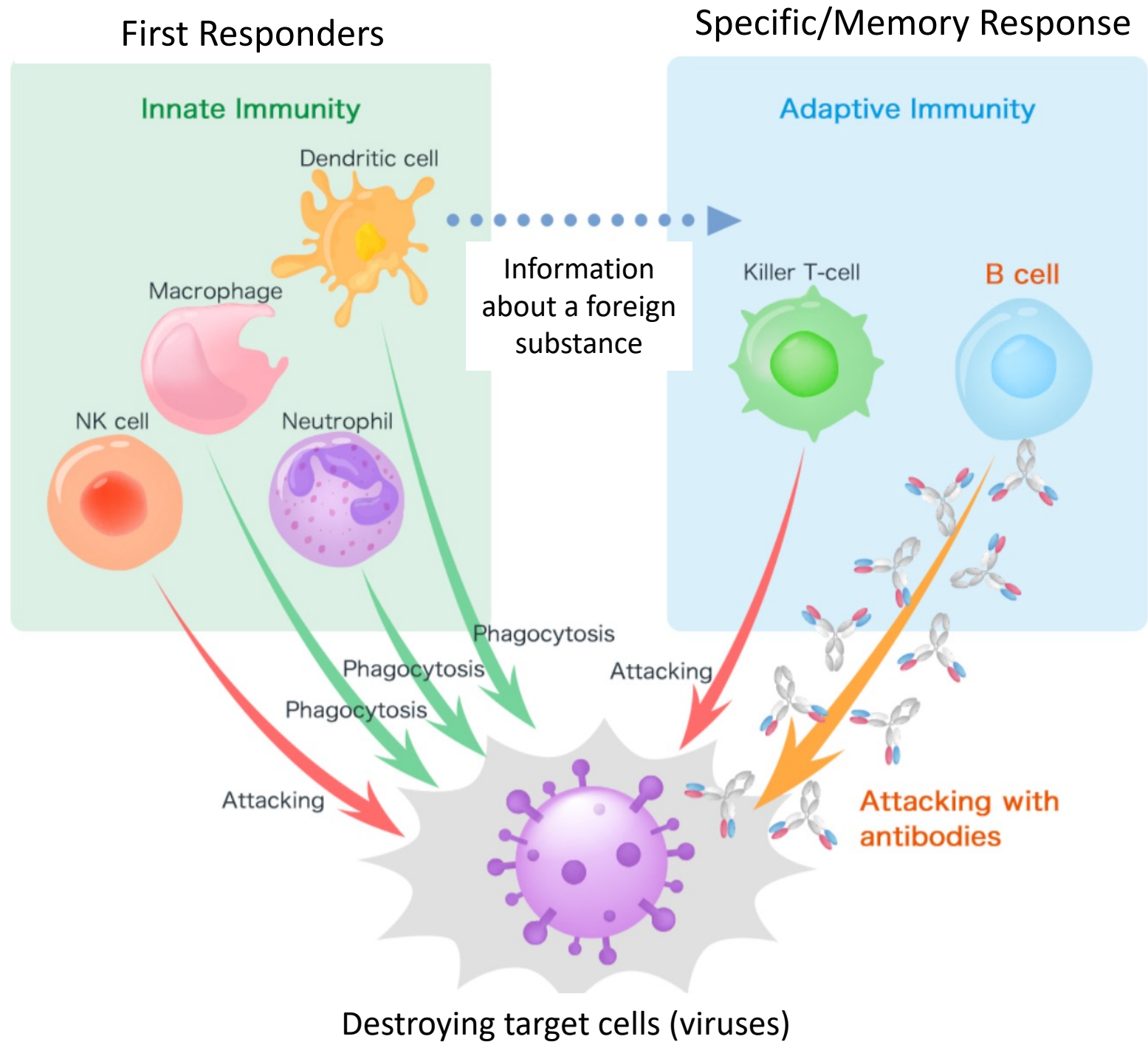
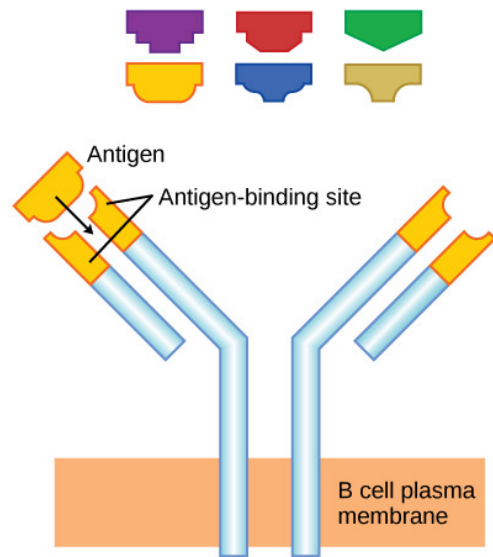
The immune system has two arms

Antigens: stimulate immune response

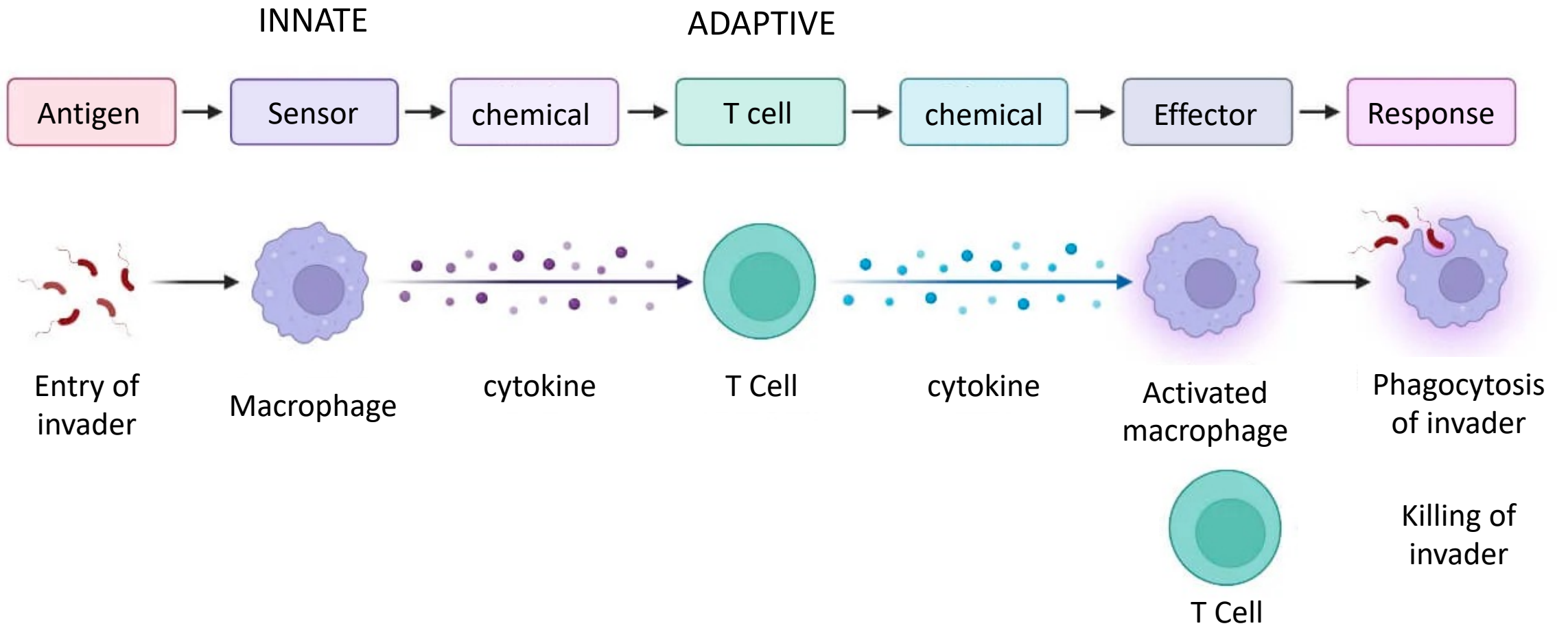


The immune system has two arms

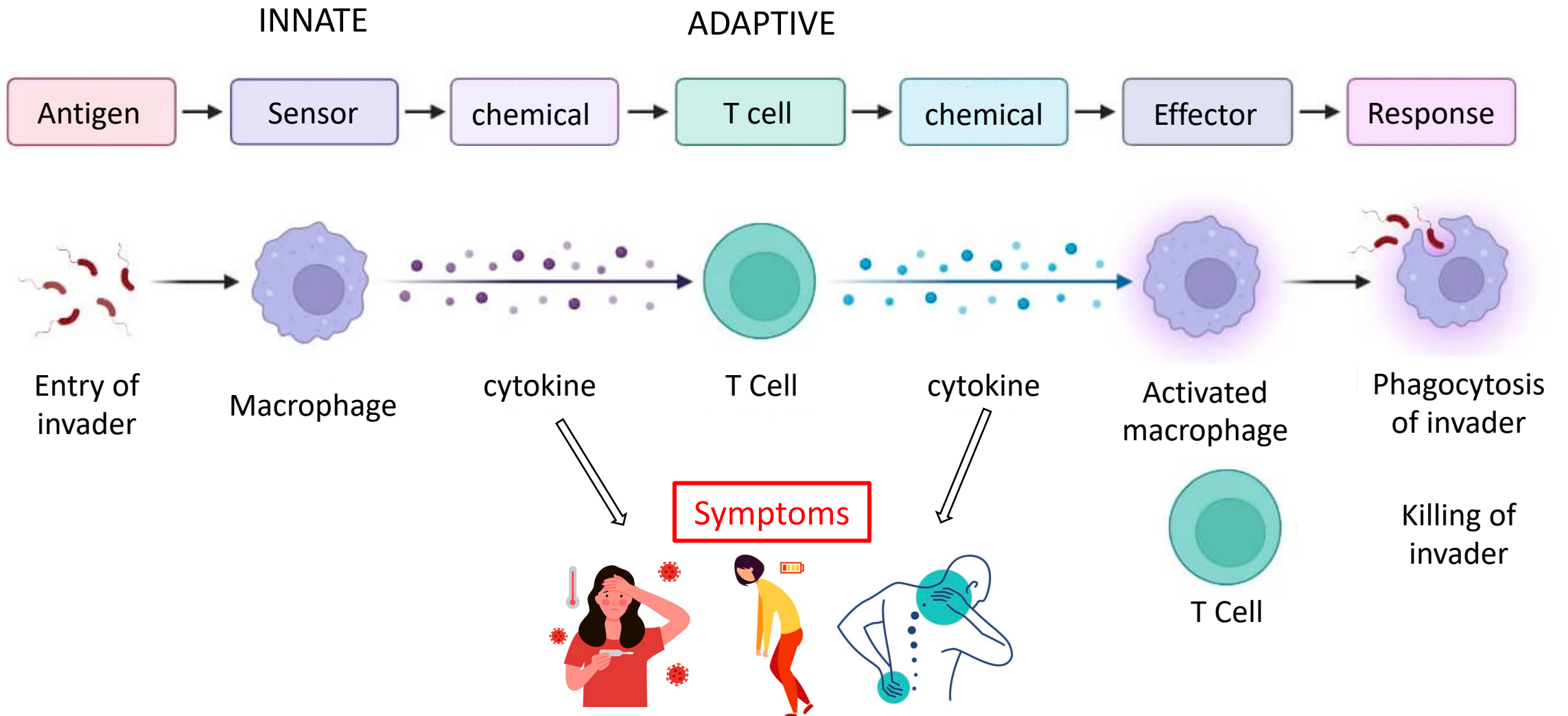
Antigens: stimulate immune response



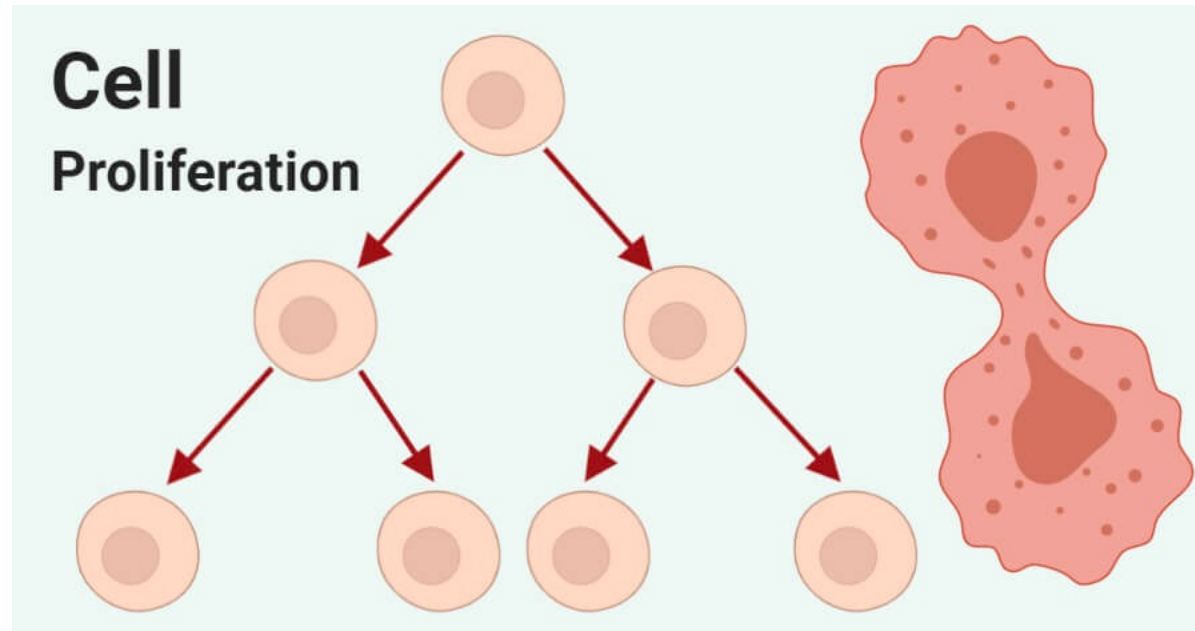
The immune response is coordinated



The immune response is coordinated



Antigens and chemicals cause T & B cell proliferation

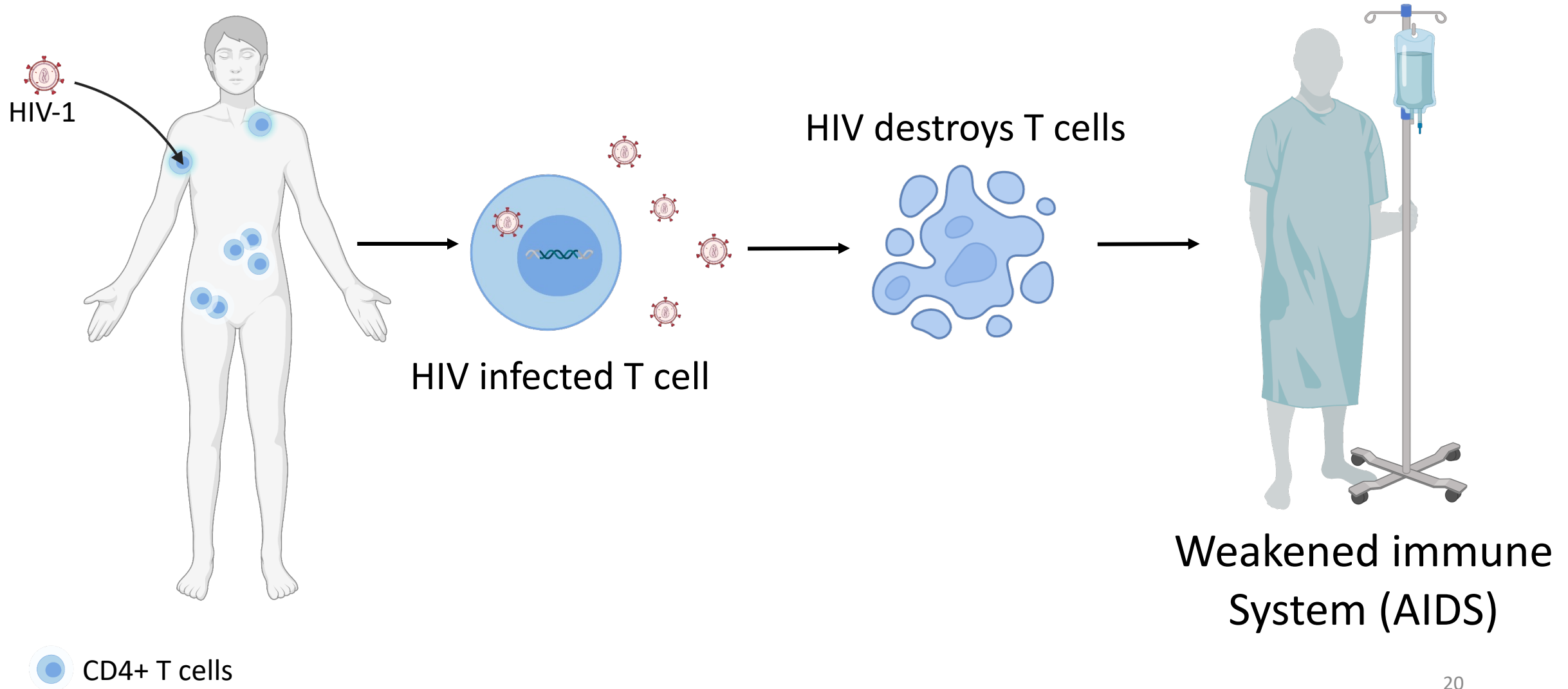


What happens during a viral infection with HIV?

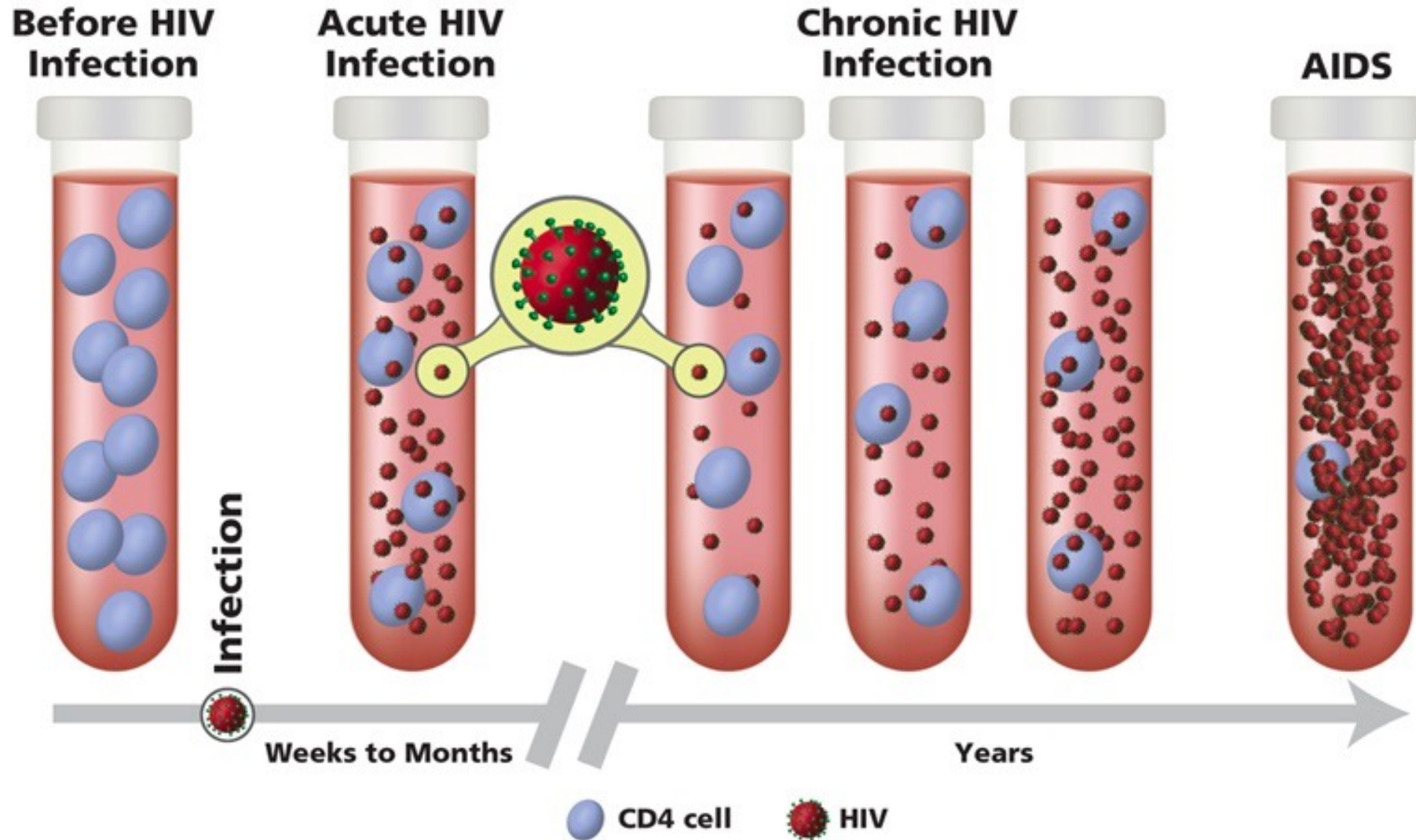
What happens during a viral infection with HIV?

What is
immunodeficiency?

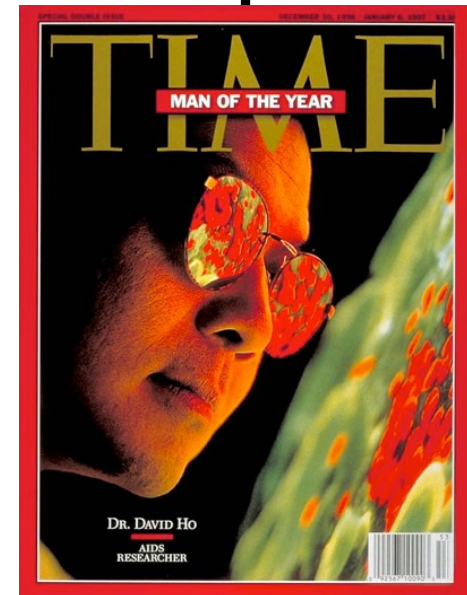
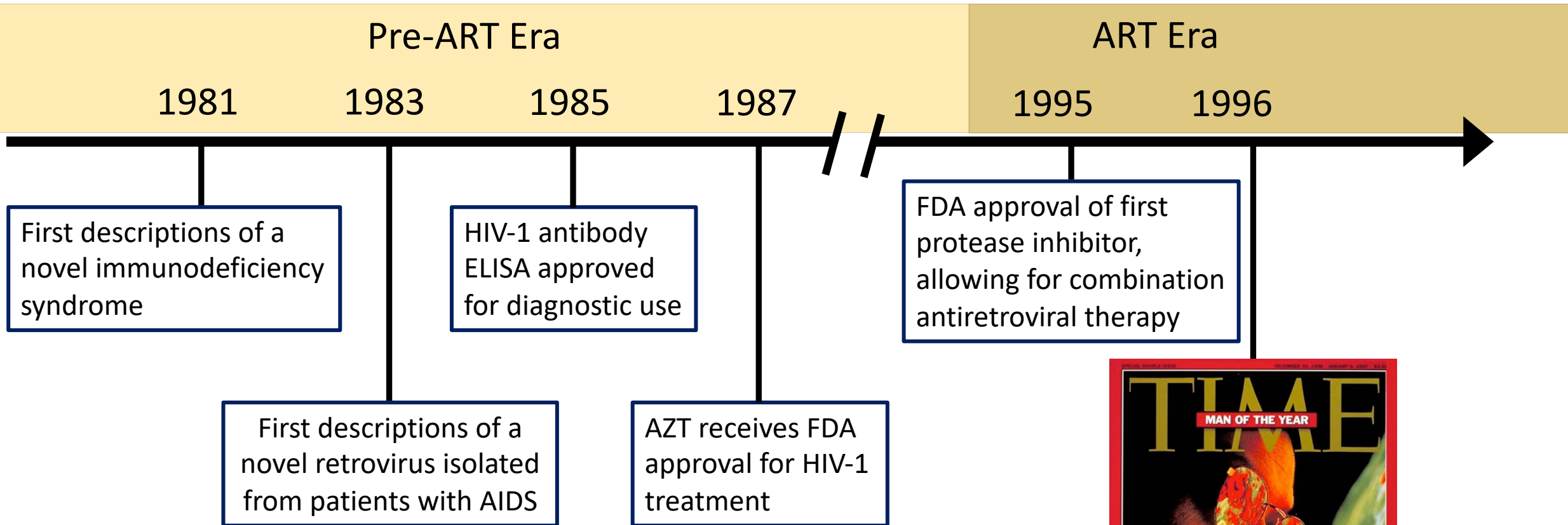
HIV-1 attacks the body's immune system



HIV Progression

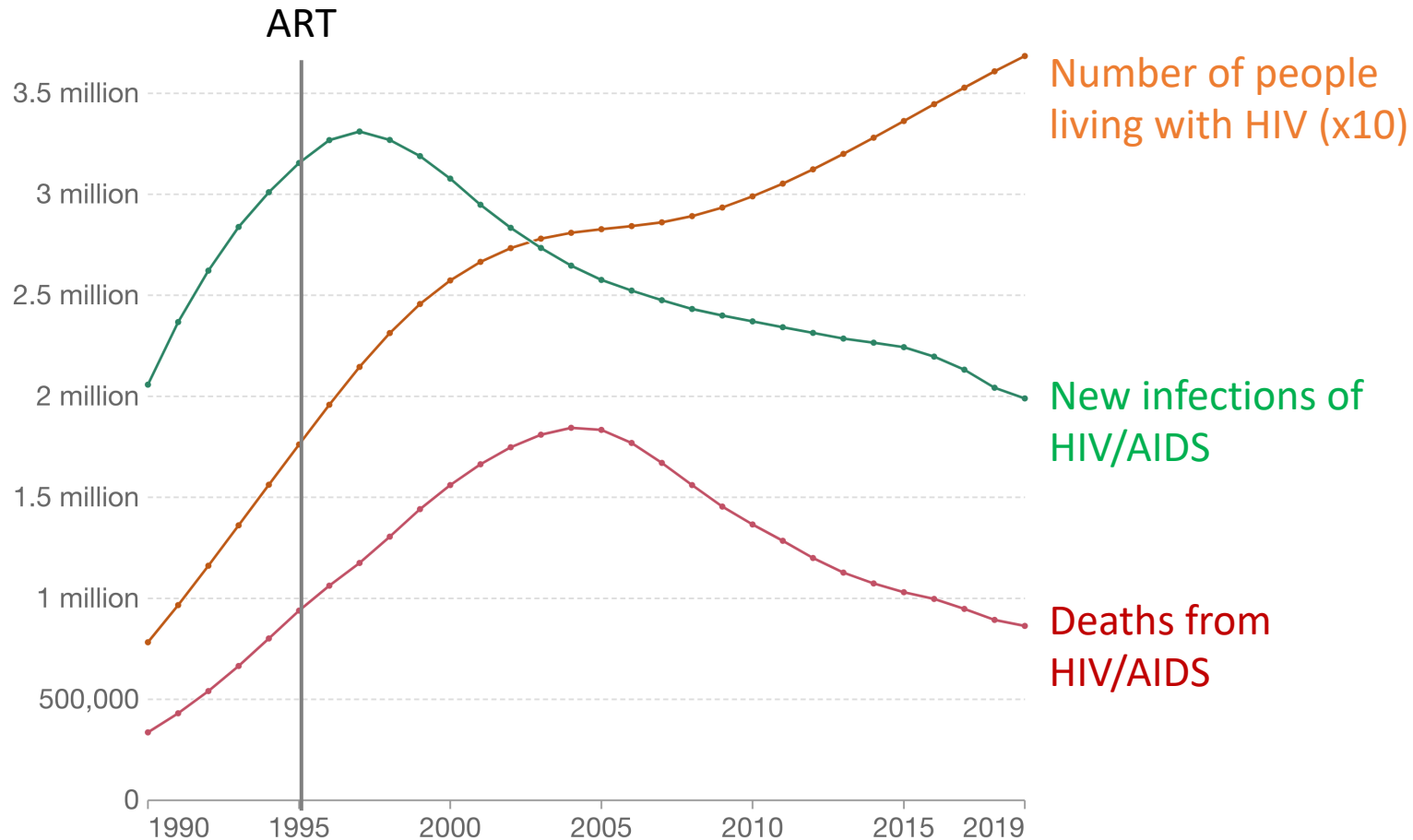


HIV Time Line (US)



ART = Anti-Retroviral Therapy

HIV: Current global health concern



Worldwide (2021)

- 38.4 million people living w/HIV
- 1.5 million acquired HIV-1
- Take ART for life
- \$400,000 per person for life

Increased risk for:

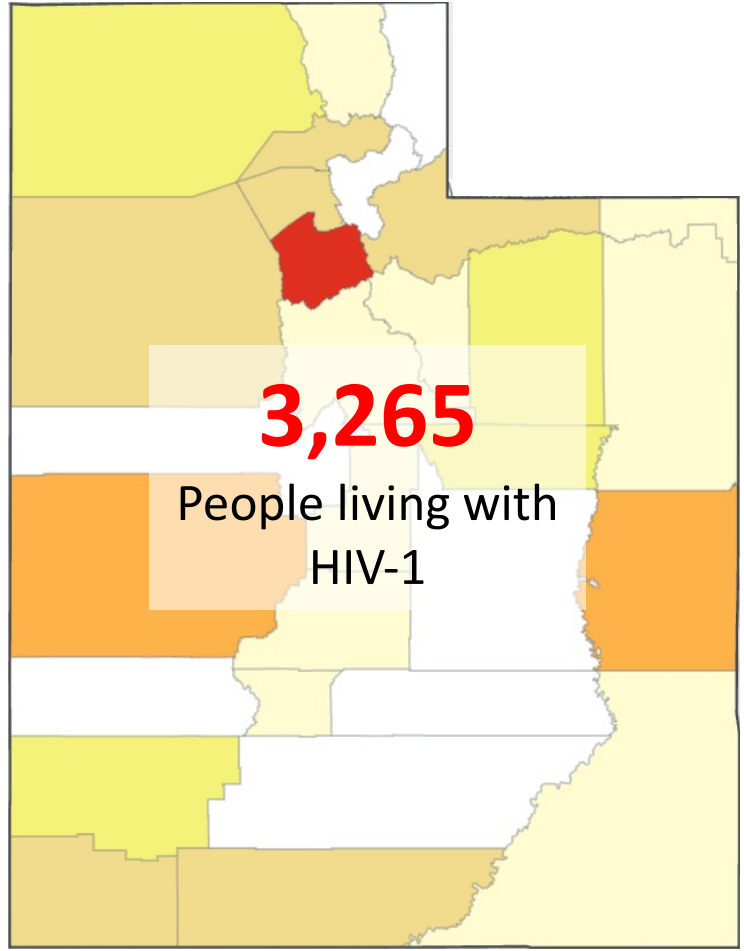
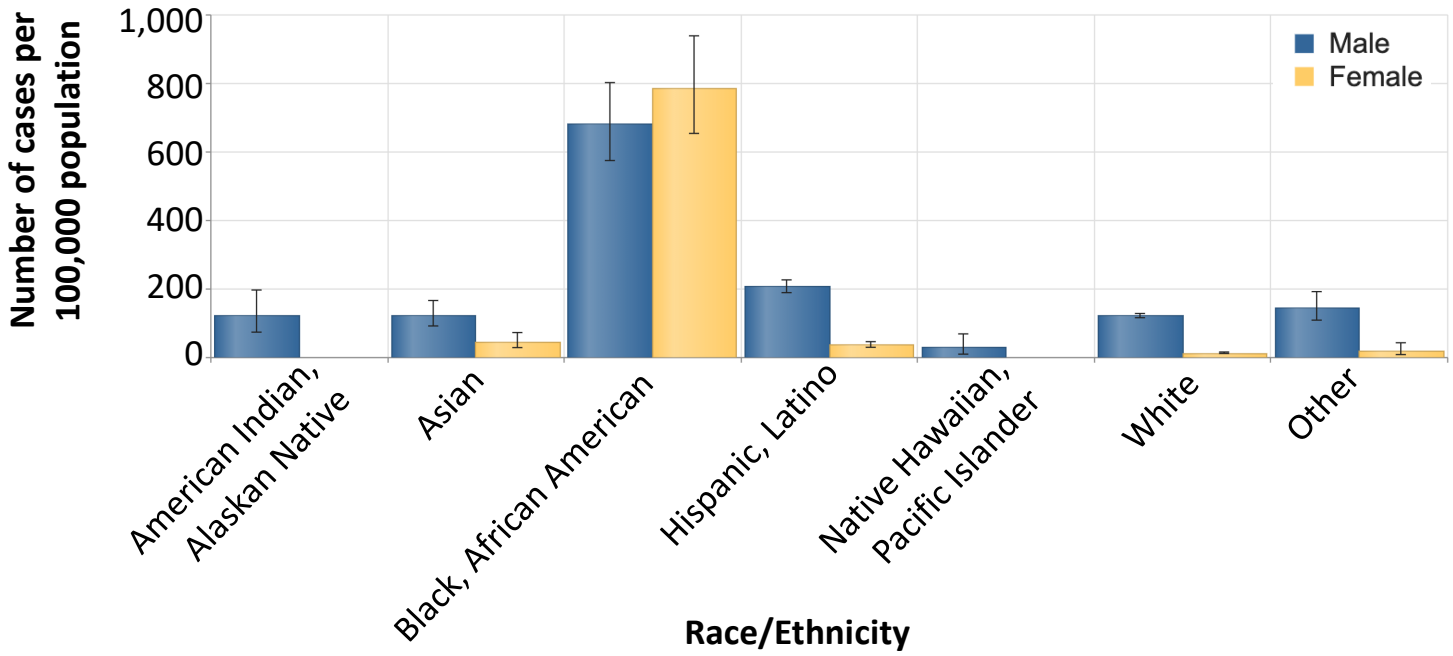
- Brain disorders
- Heart disease
- Cancers

Source: IHME, Global Burden of Disease (2019)

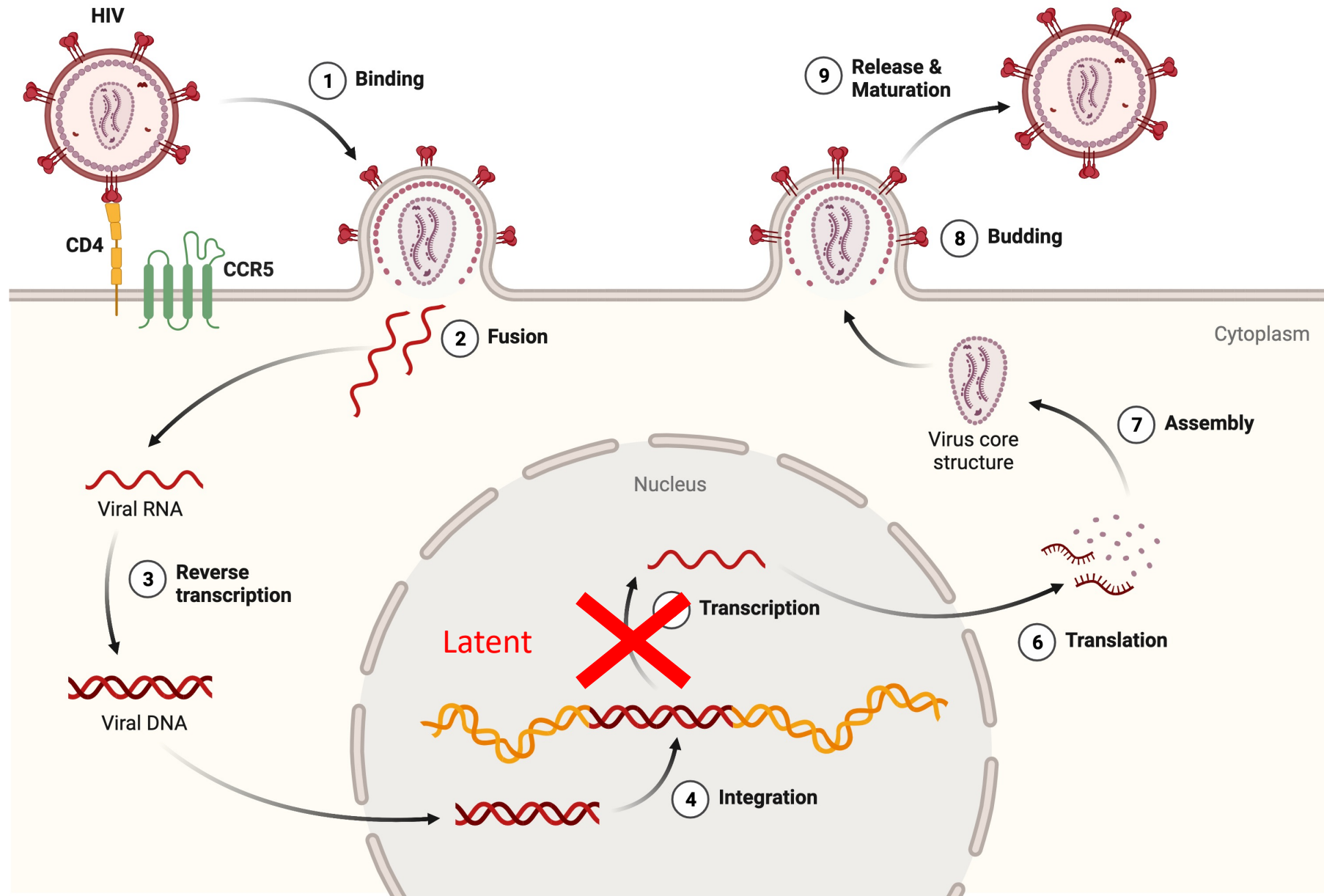
CC BY

HIV in Utah disproportionately affects ethnic/racial minorities

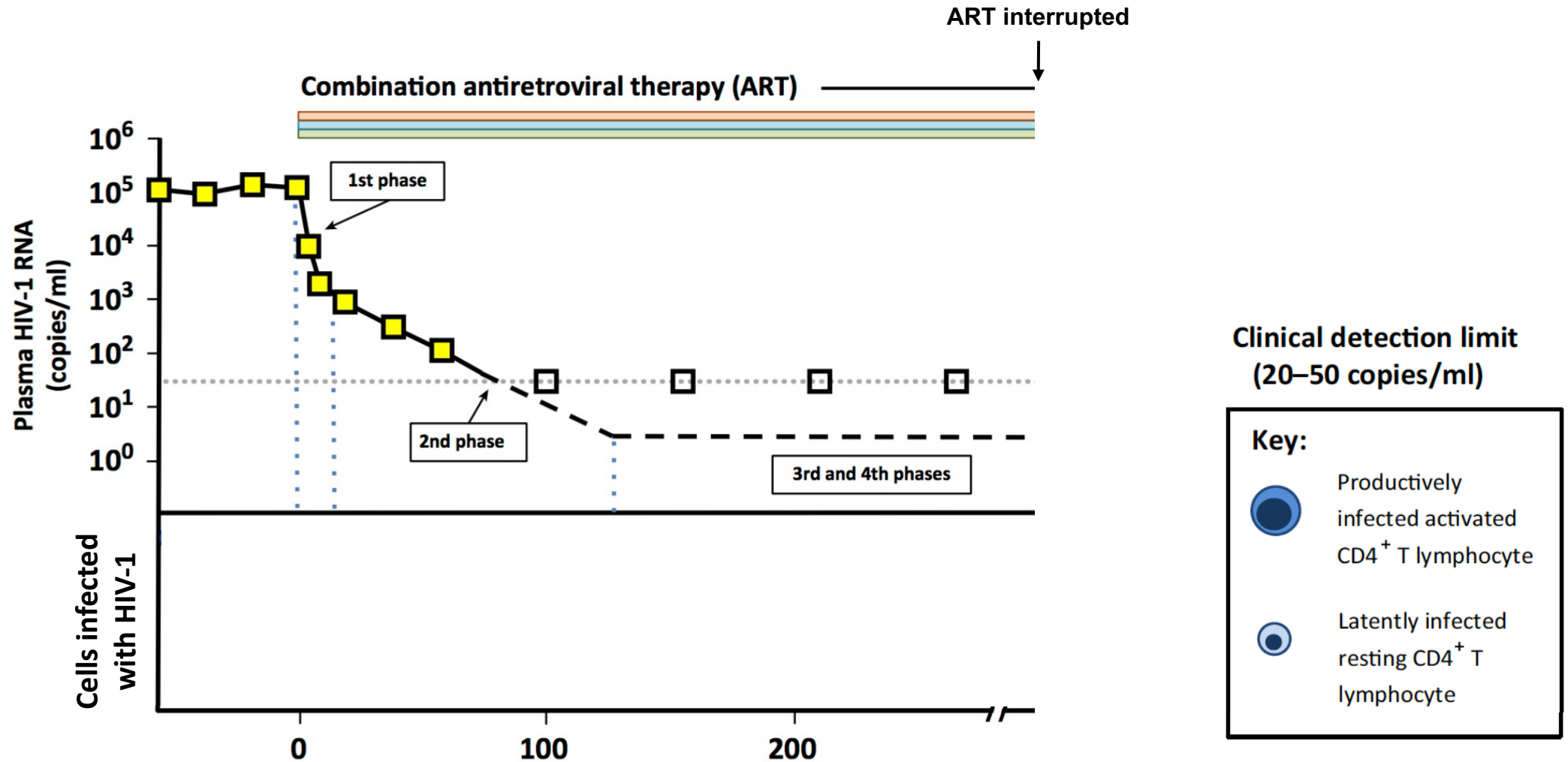
Rates of Persons Living with Diagnosed HIV-1 per 100,00 by Race/Ethnicity and Sex, 2019



HIV targets and destroys CD4⁺ T cells

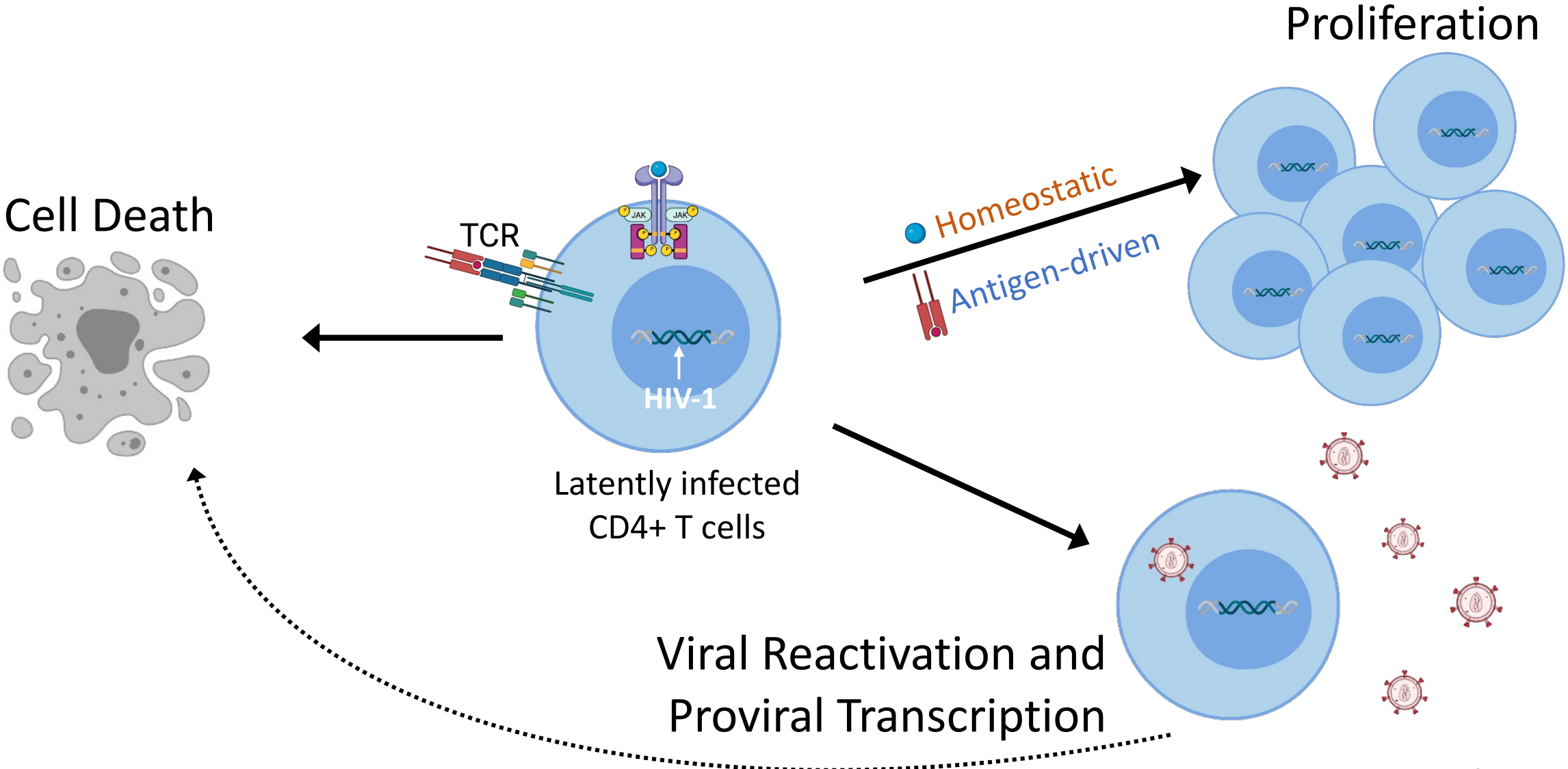


Antiretroviral therapy (ART) does not eliminate latently HIV infected T cells



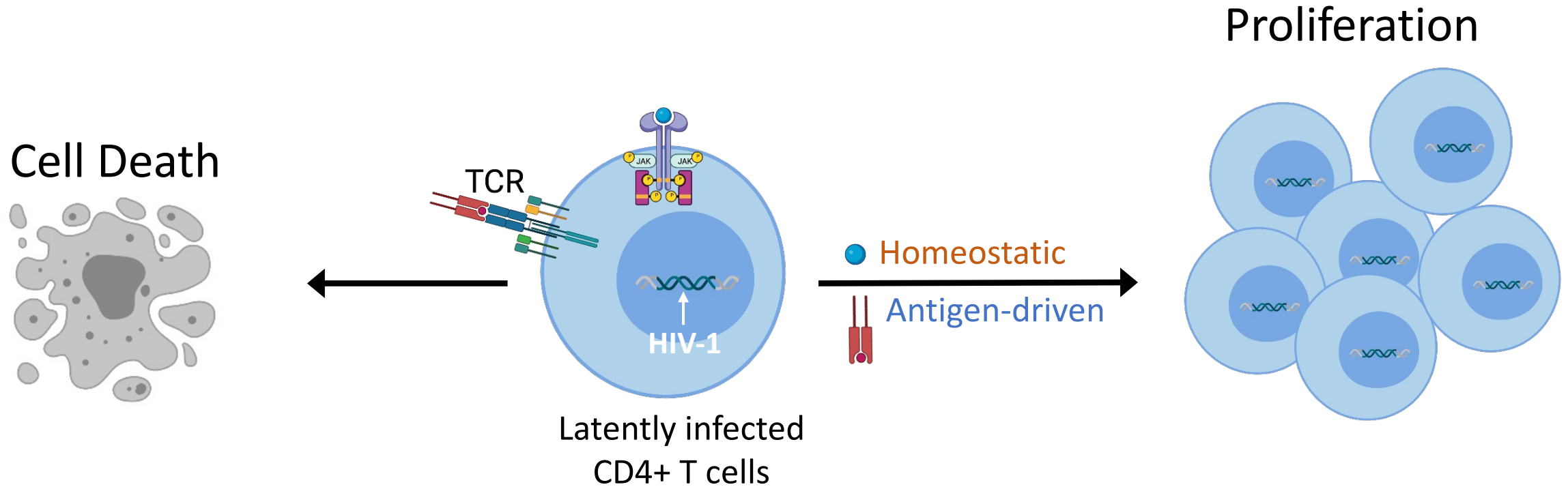
Latently infected cells must be eliminated to achieve a cure

Latently infected cells are maintained by proliferation and death

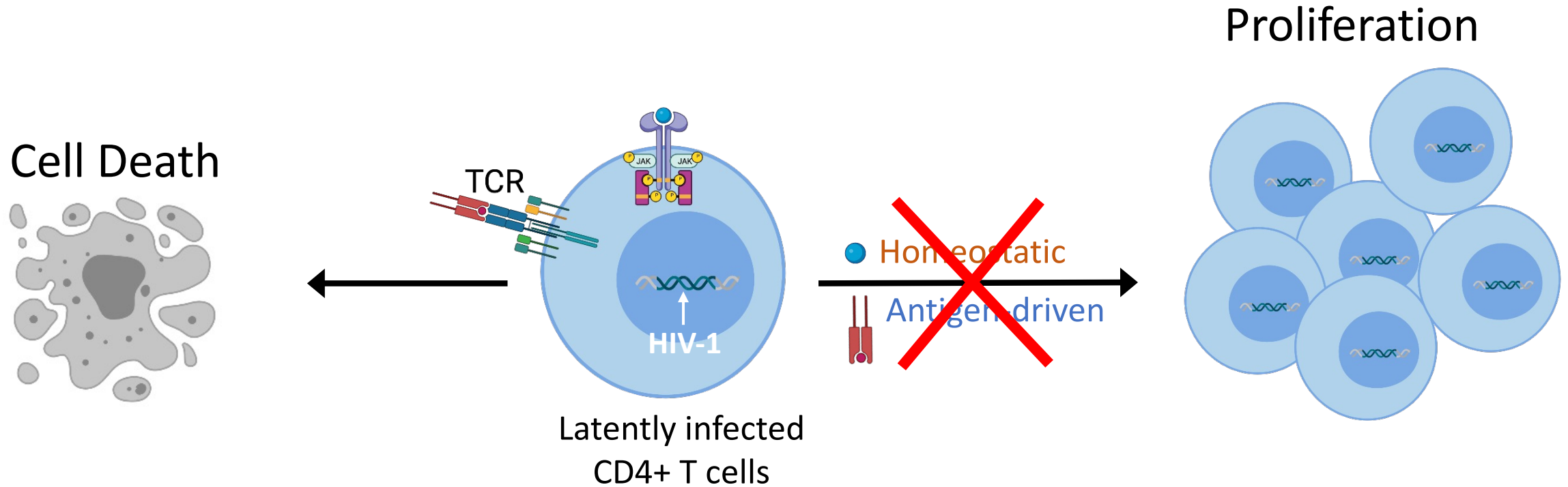


Adapted from Reeves et al, Sci Rep 2017 and Adam Spivak

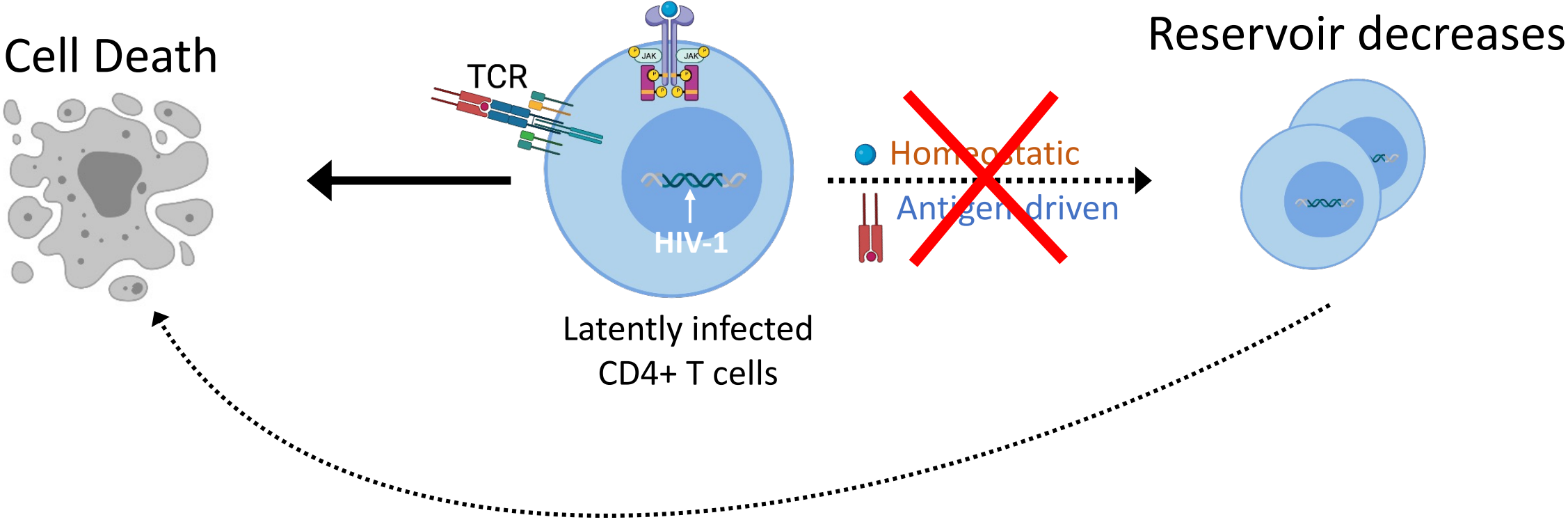
The size of the latent reservoir is stable over time:
Maintained by **antigen-driven** & **homeostatic** proliferation



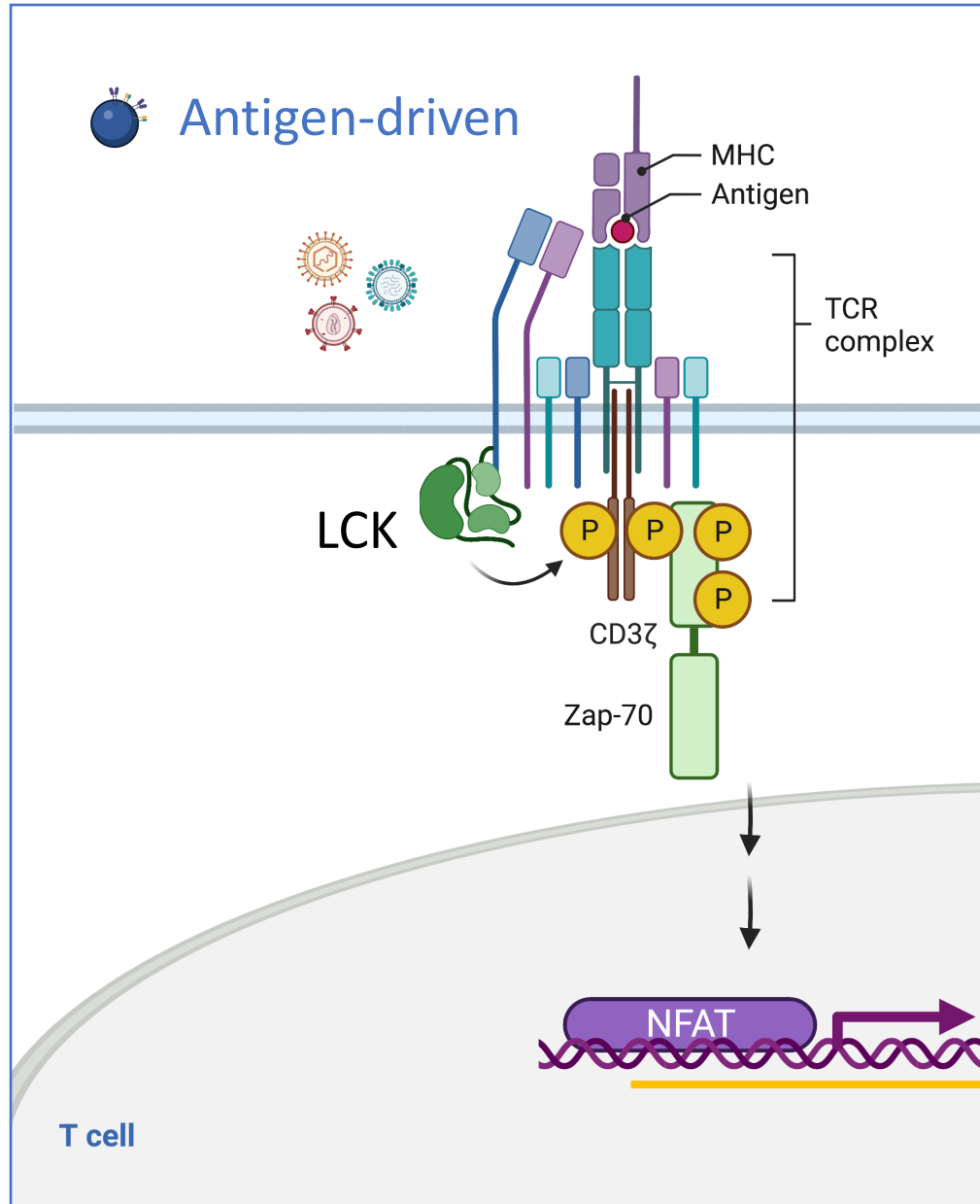
Blocking proliferation to target the latent HIV-1 reservoir



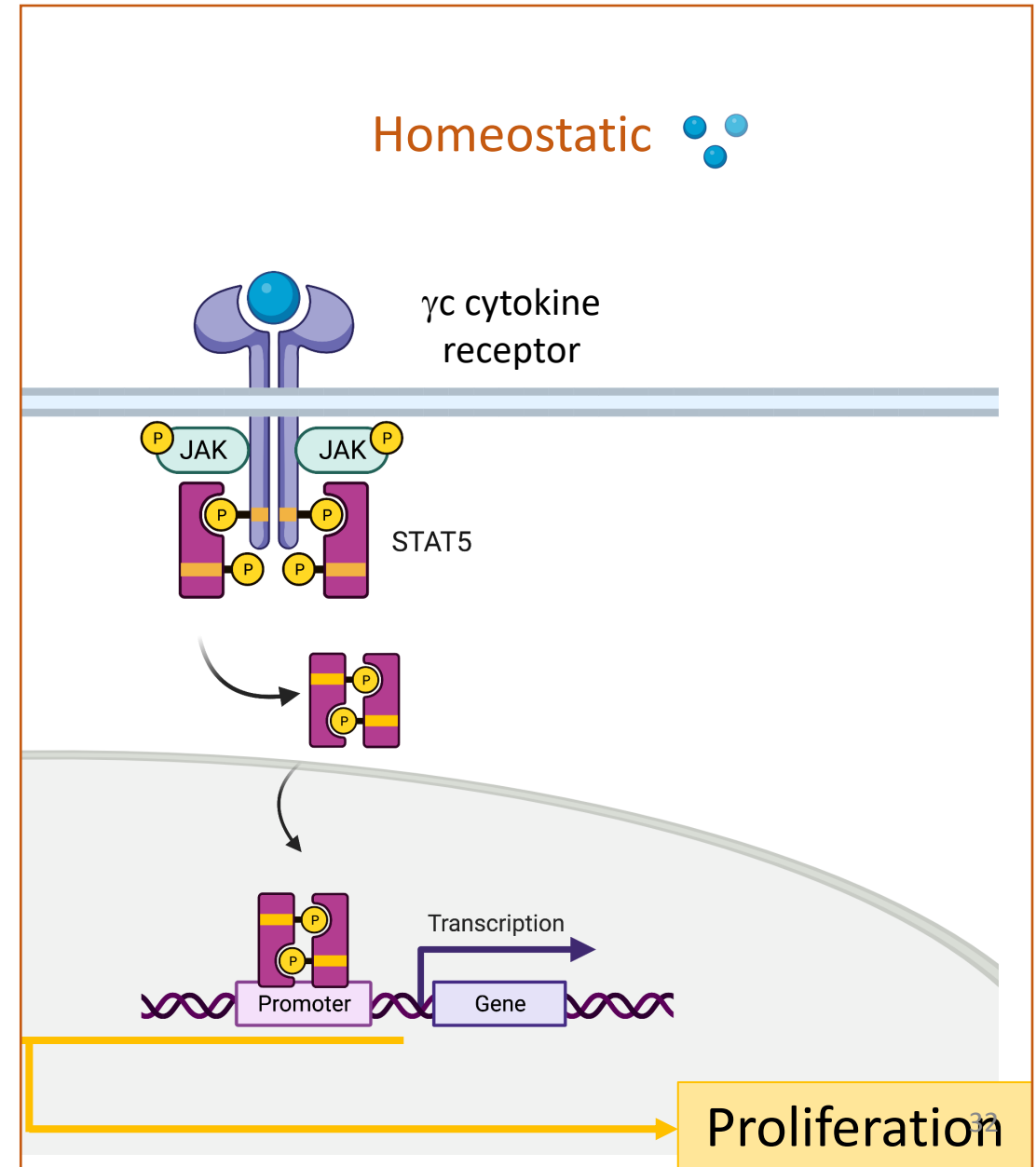
Blocking proliferation to target the latent HIV-1 reservoir



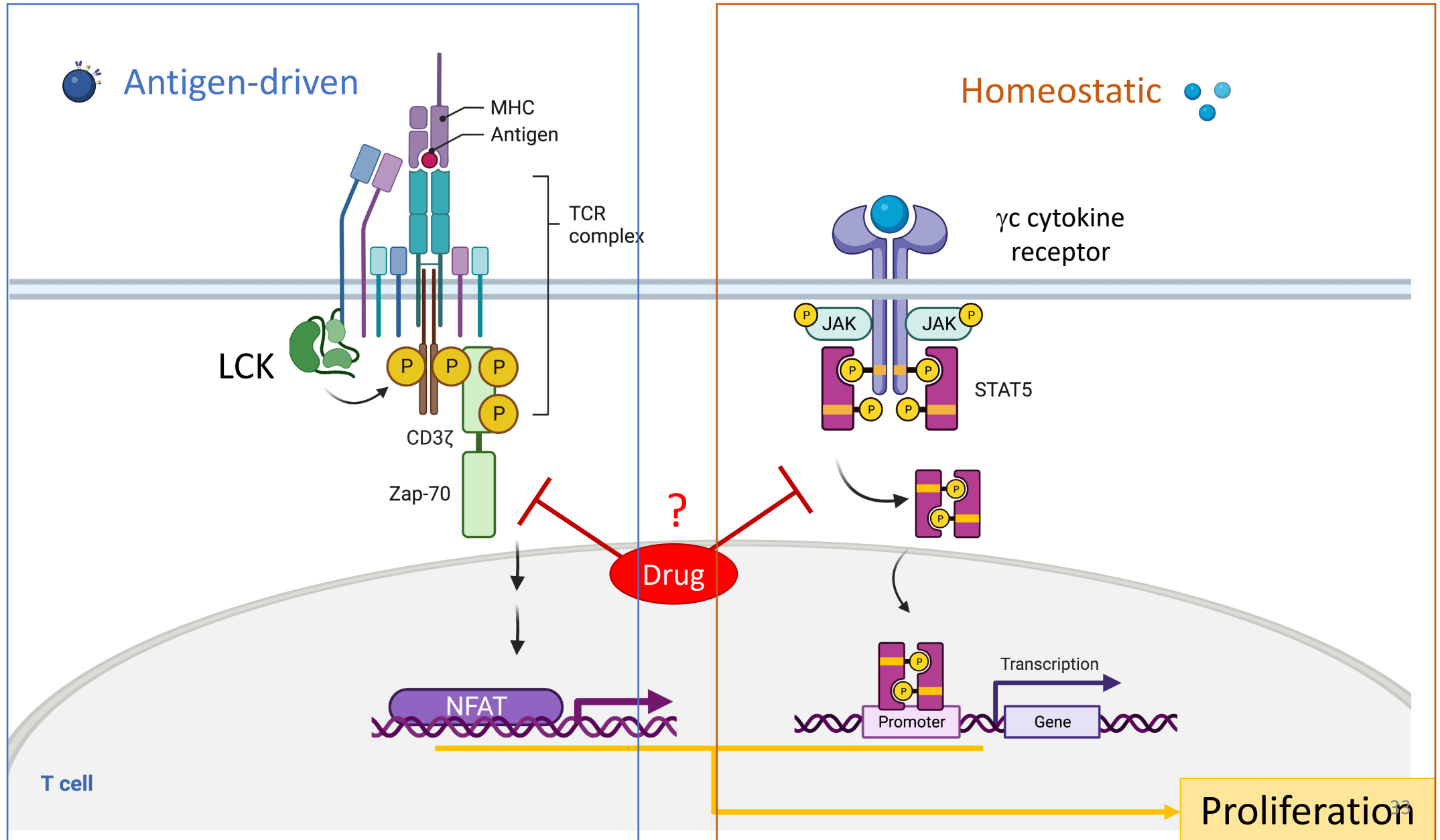
Identify drugs that block antigen-driven and homeostatic proliferation



Identify drugs that block antigen-driven and homeostatic proliferation



Identify drugs that block antigen-driven and homeostatic proliferation



Screening anti-proliferative therapeutics to block **antigen-driven** and **homeostatic** proliferation

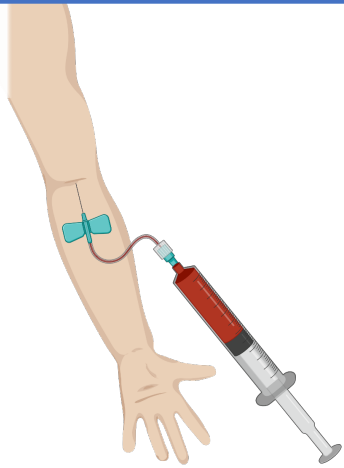
- 129 **FDA-approved** cancer drugs:

Drug target	Drug
ALK	Crizotinib, Ceritinib, Alectinib, Brigatinib
BCR–Abl	Bosutinib, Dasatinib, Imatinib, Nilotinib, Ponatinib
B-Raf	Vemurafenib, Dabrafenib
BTK	Ibrutinib
CDK family	Palbociclib, Sorafenib, Ribociclib
c-Met	Crizotinib, Cabozantinib
EGFR family	Gefitinib, Erlotinib, Lapatinib, Vandetanib, Afatinib, Osimertinib
JAK family	Ruxolitinib, Tofacitinib
MEK1/2	Trametinib
RET	Vandetanib
Src family	Bosutinib, Dasatinib, Ponatinib, Vandetanib

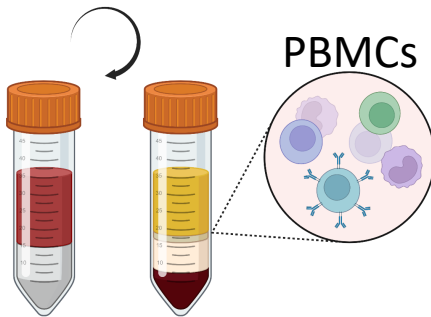
Ex vivo model of homeostatic and antigen-driven proliferation

Cell Isolation

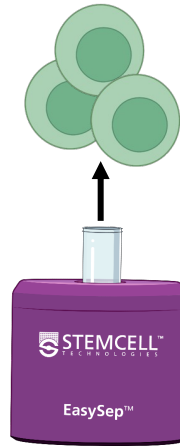
Proliferation Assay



Draw 180 mL blood from uninfected donor

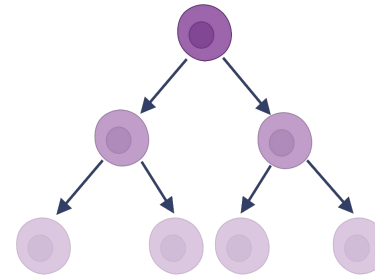


Spin and collect immune cells



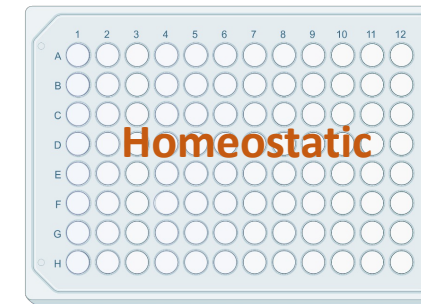
Isolate CD4⁺ T cells

Cell trace violet

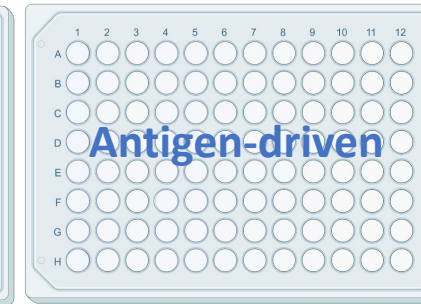


Stain cells with proliferation dye

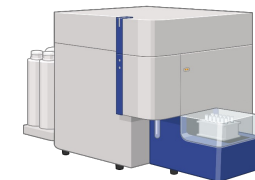
Day 0: Plate cells with drugs



2 hour: Stimulate cells



Day 7: Flow Cytometry
Viability, Activation (CD69), Proliferation

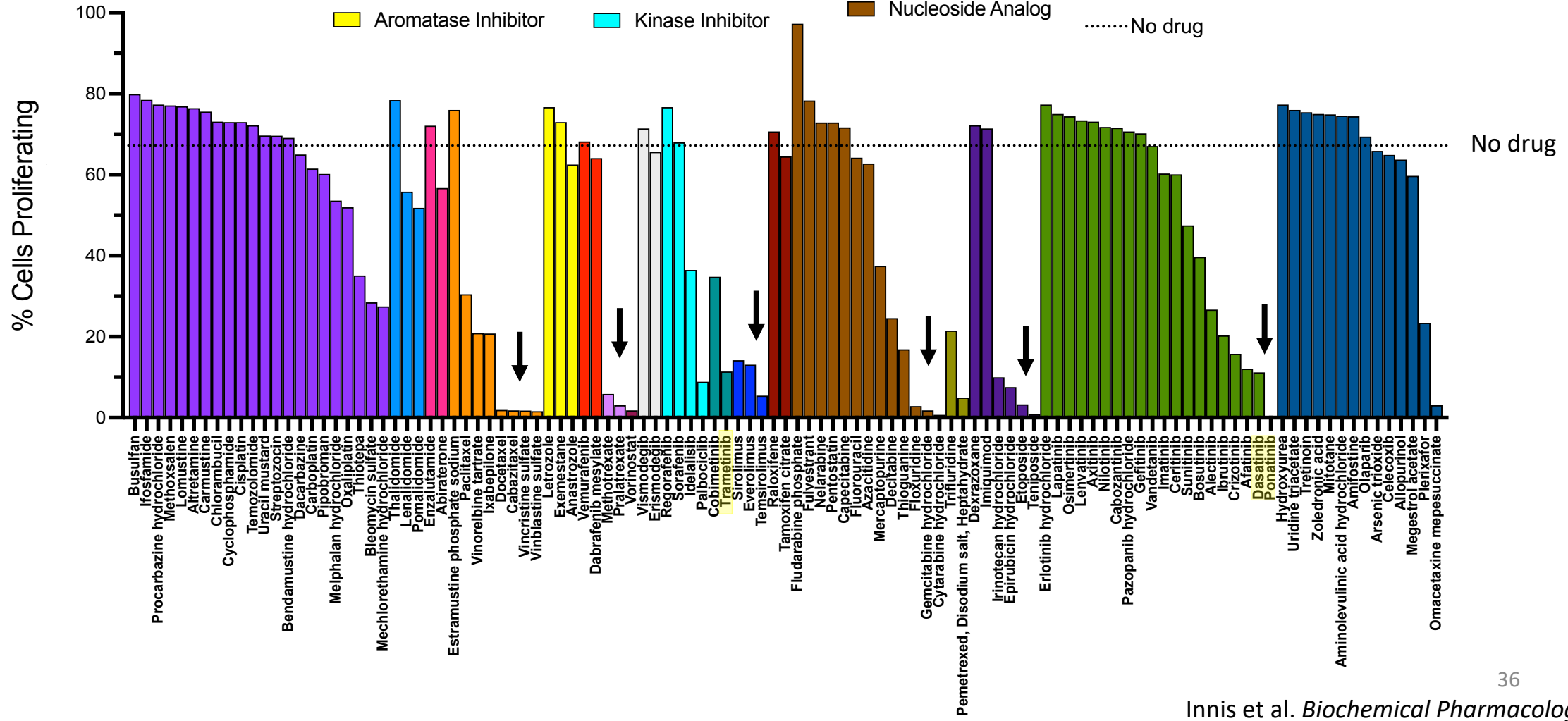
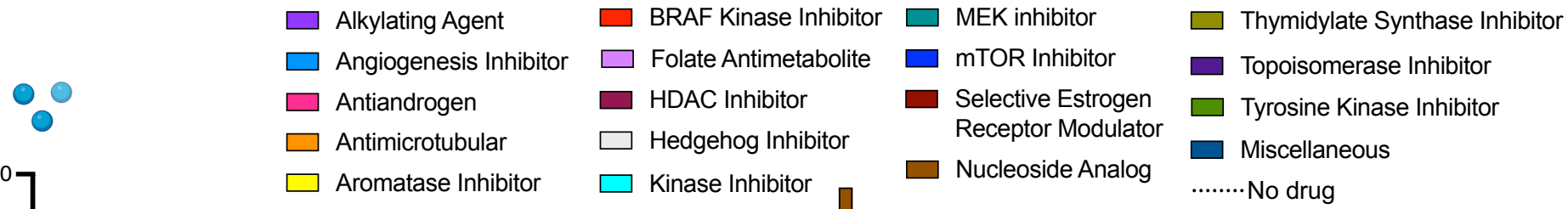


Homeostatic
Antigen-driven



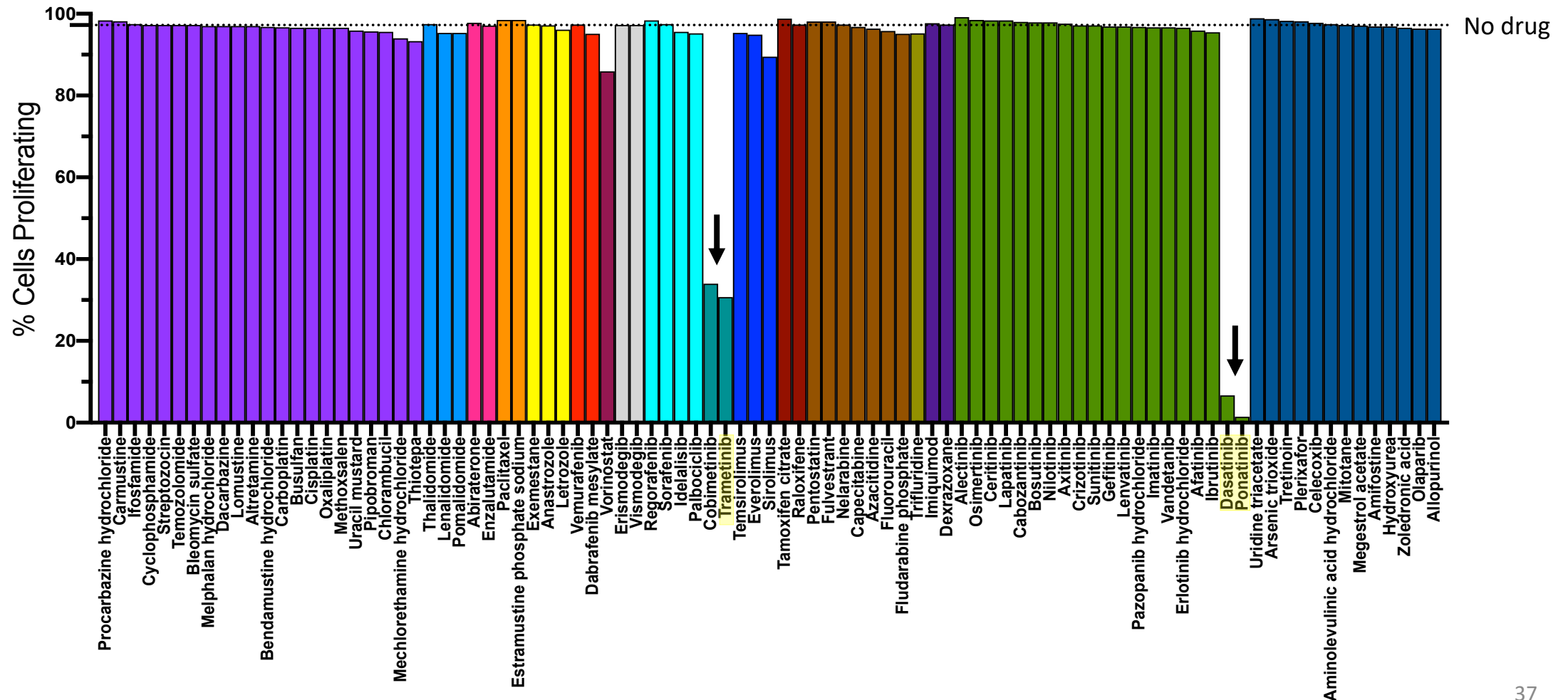
Screening for FDA approved antiproliferative agents

Homeostatic



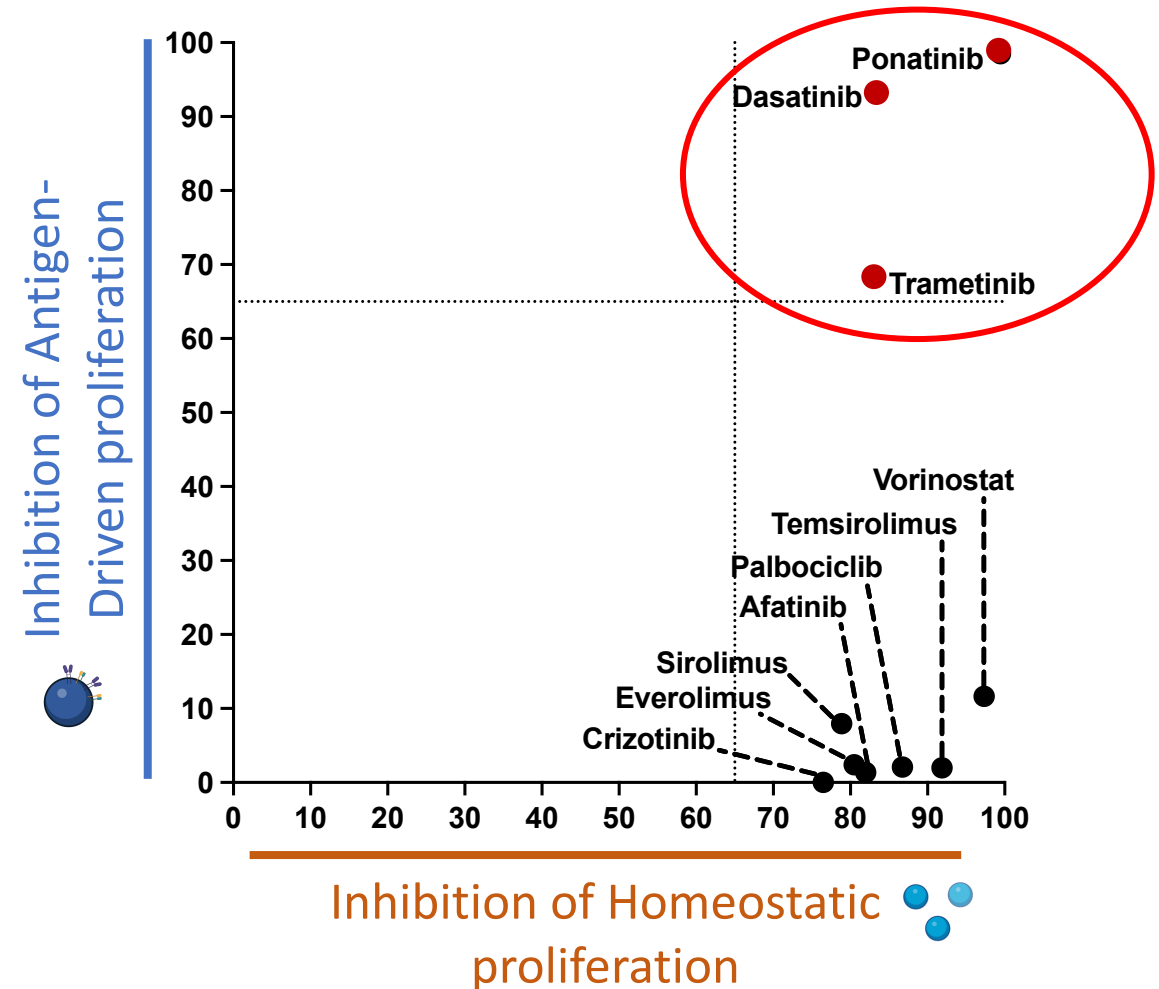
Screening for FDA approved antiproliferative agents

Antigen-driven 

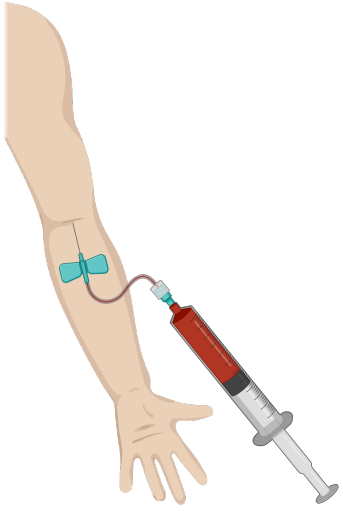


Ponatinib, dasatinib and trametinib inhibit BOTH antigen-driven and homeostatic proliferation in T cells

- **Ponatinib & Dasatinib:** Leukemia
- **Trametinib:** Melanoma

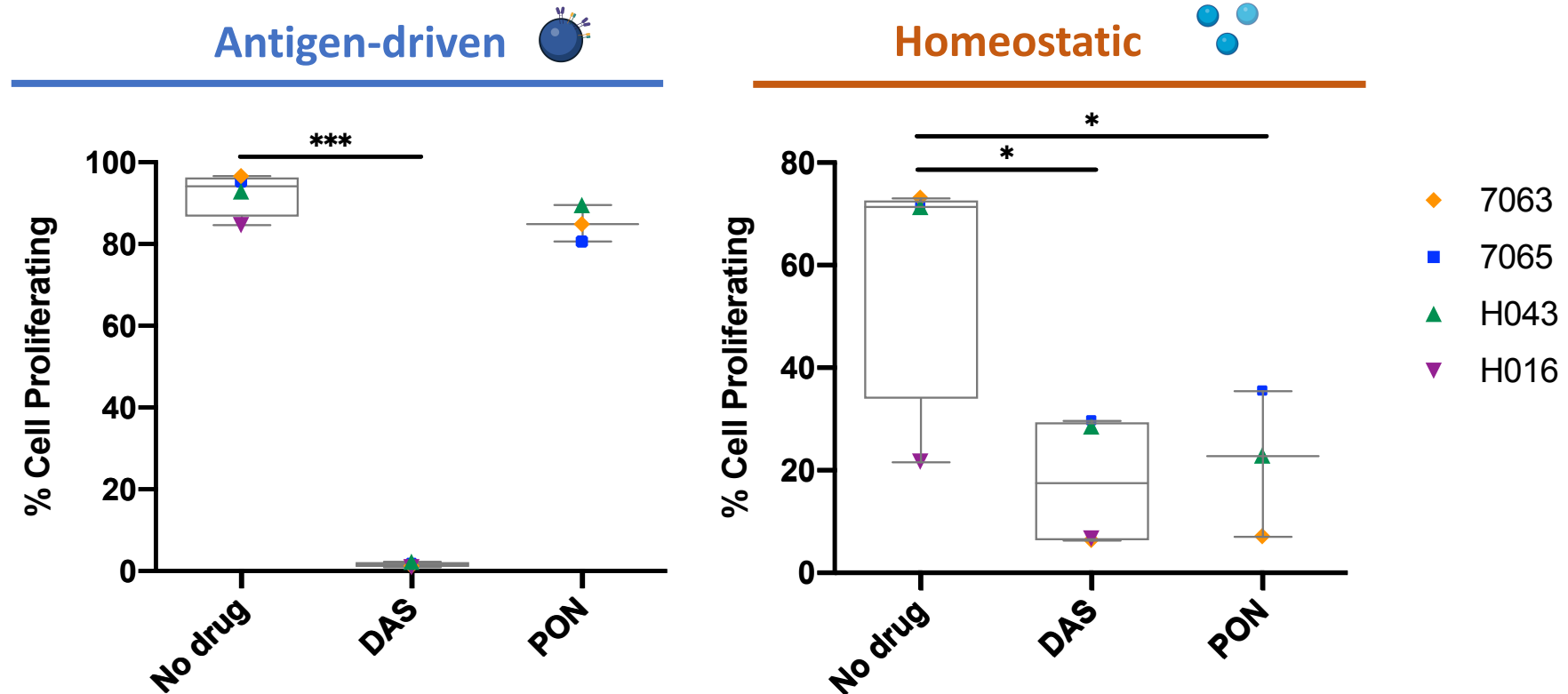


Dasatinib blocks **antigen-driven** and **homeostatic** proliferation in T cells from people living with HIV



Draw 180 mL
blood from **people
living with HIV**

Dasatinib blocks antigen-driven and homeostatic proliferation in CD4⁺ T cells from people living with HIV

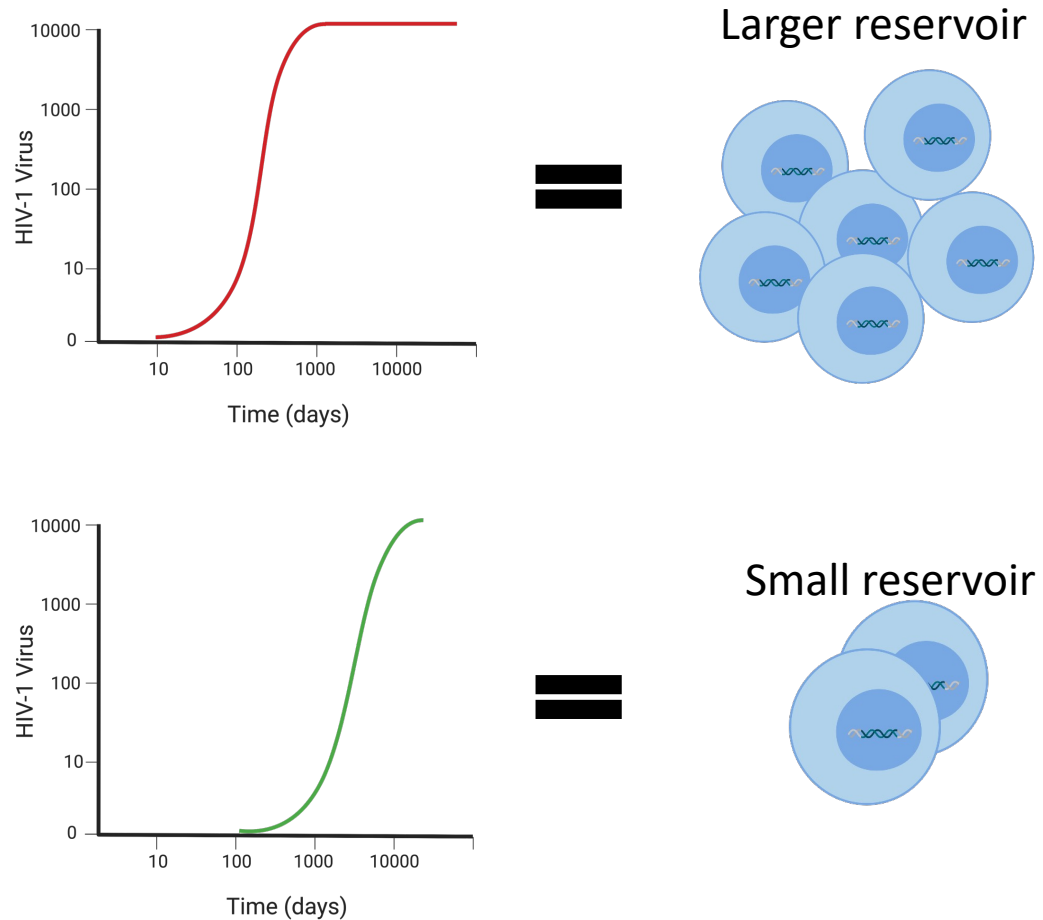


DAS = dasatinib
PON = ponatinib

Dasatinib blocks **antigen-driven** and **homeostatic** proliferation in CD4⁺ T cells from people living with HIV

What is the effect of dasatinib on the latent HIV reservoir?

Measuring the effect of dasatinib on latent HIV: time to rebound

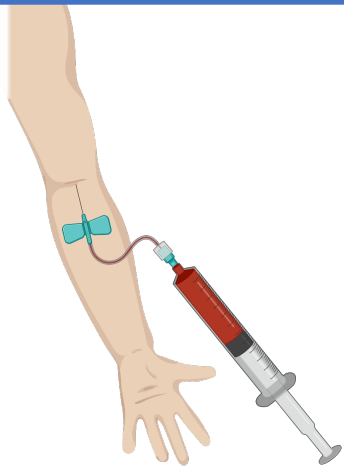


100 day delayed time to detection
= 10-fold reservoir reduction

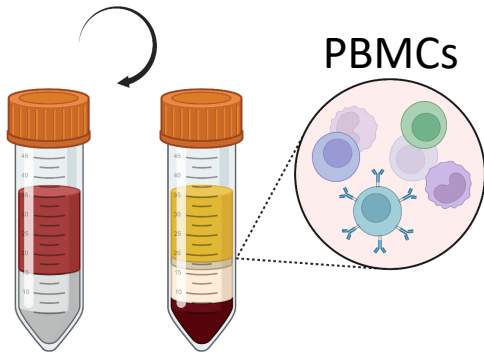
**Delayed time to rebound =
smaller reservoir size**

Measuring the latent HIV reservoir outside the body

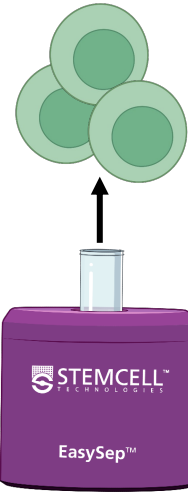
Cell Isolation



Draw 180 mL
blood from
**participant living
with HIV**

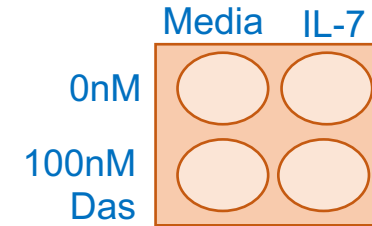


Centrifuge and
collect immune
cells



Isolate memory
CD4⁺ T cells

Day 0: Plate cells with dasatinib
NO Antiretroviral therapy



Day 3:

Day 11:

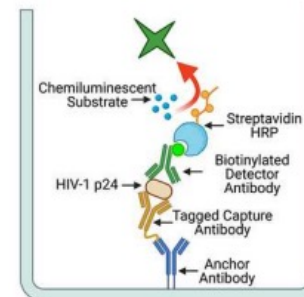
Day 15:

Day 19:

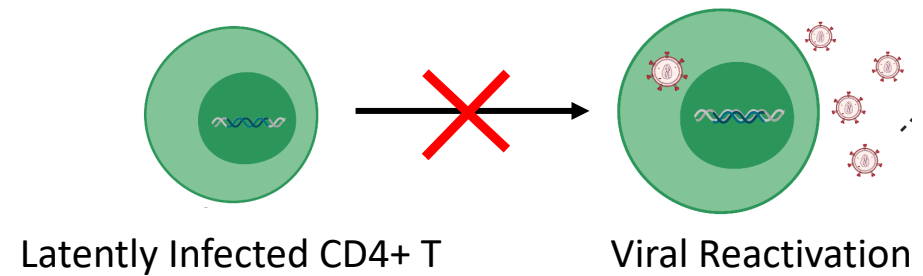
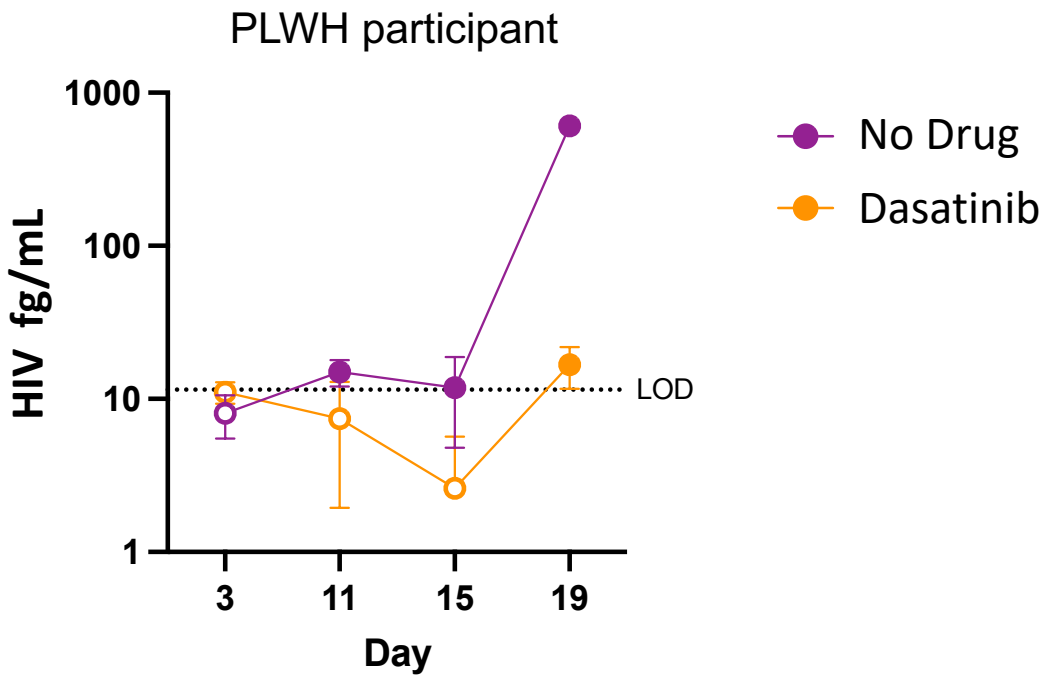


Extract supernatant

HIV Protein quantification via ELISA



Dasatinib blocks spontaneous reactivation of HIV from T cells from people living with HIV (PLWH)

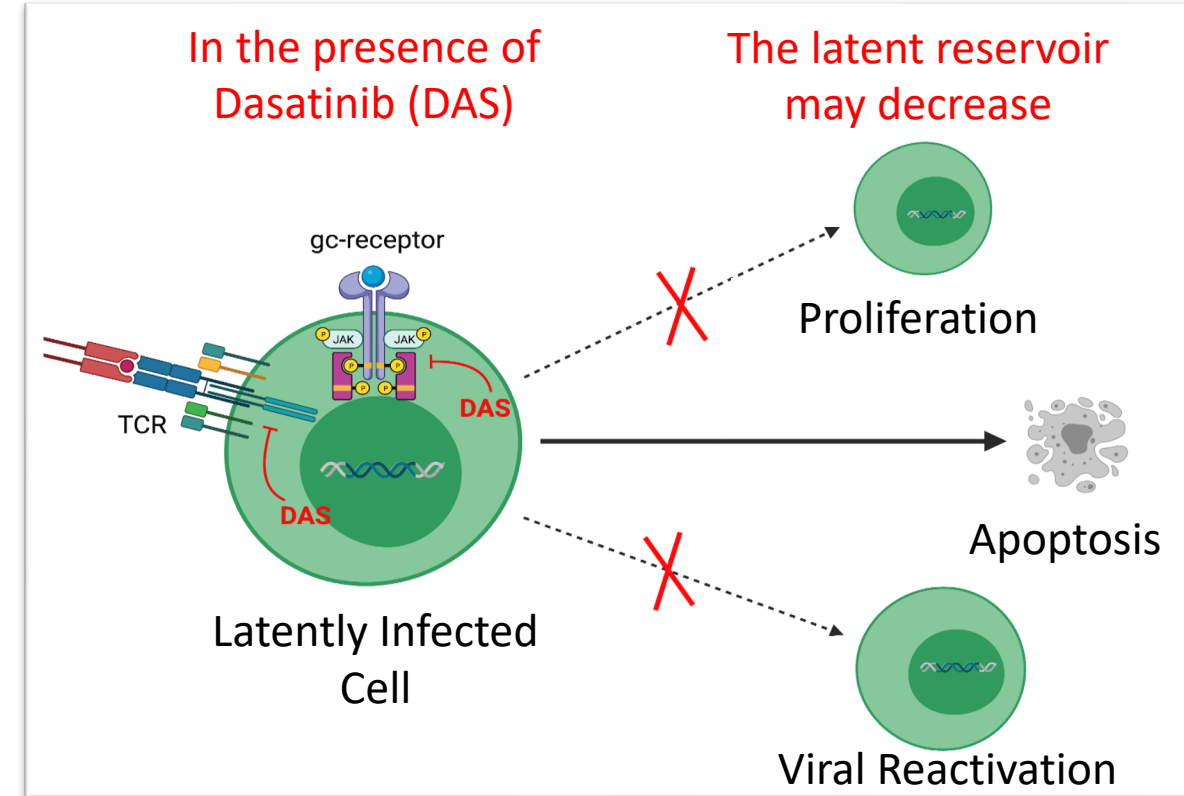
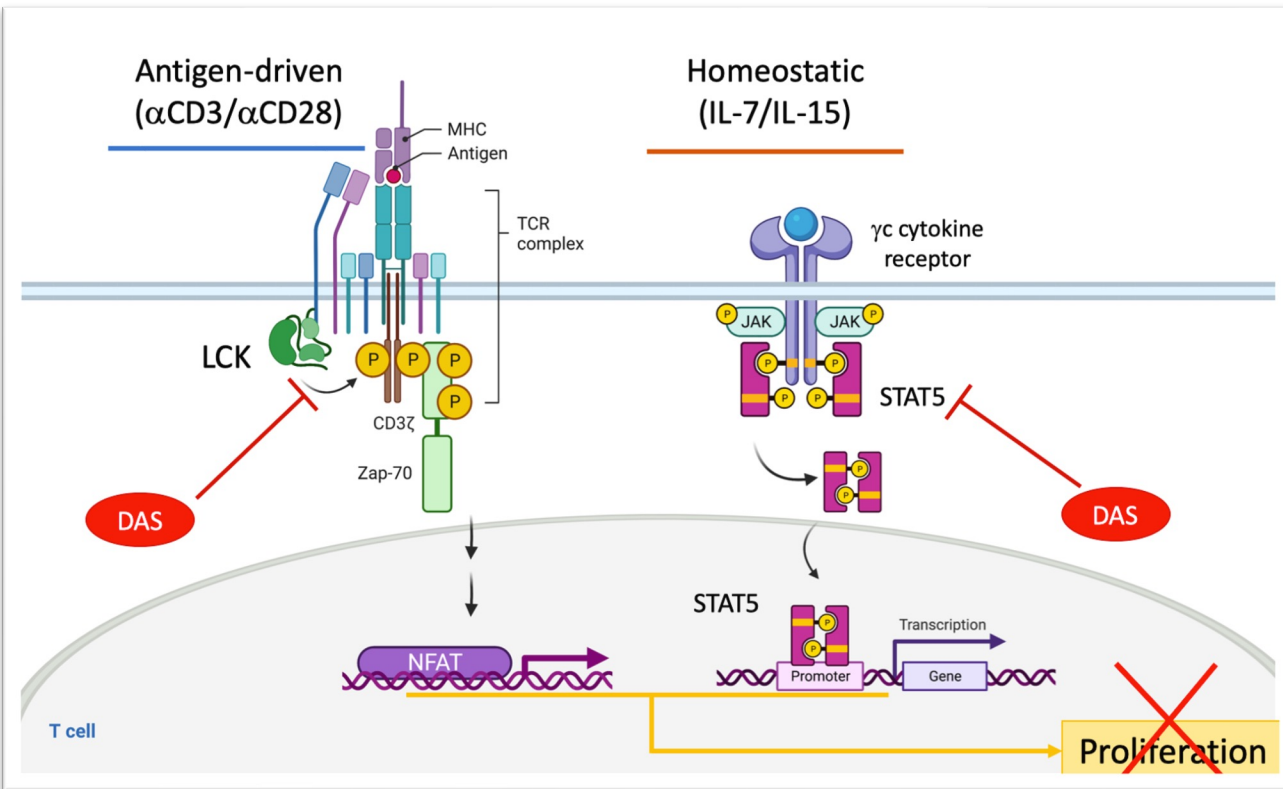


Delayed time to rebound = smaller reservoir size

Conclusions: Dasatinib for HIV-1 reservoir reduction

Dasatinib blocks **antigen-driven** & **homeostatic** proliferation

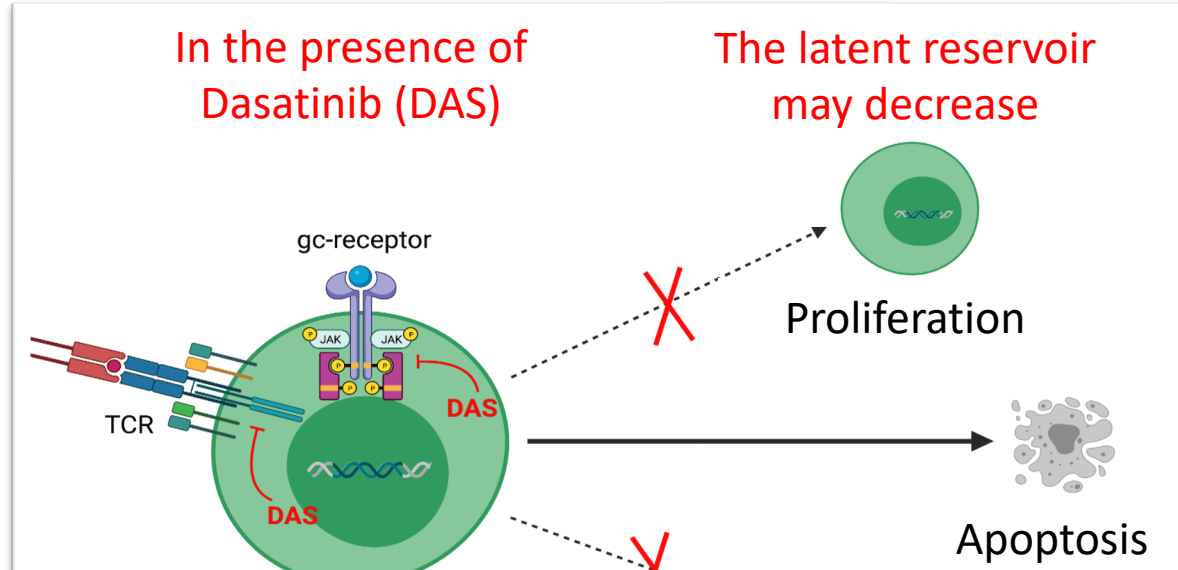
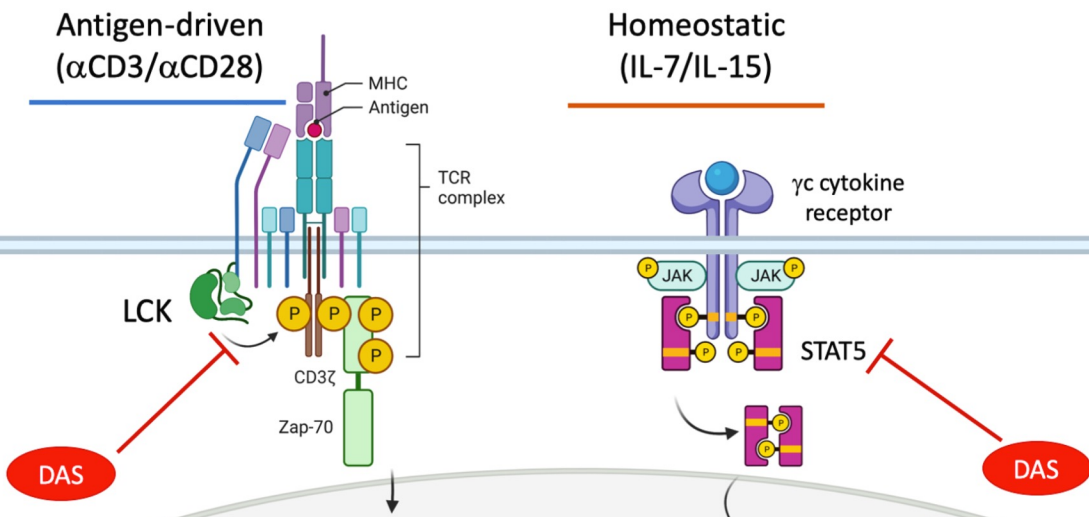
Blocks viral reactivation and prevents expansion of the latent reservoir



Conclusions: Dasatinib for HIV-1 reservoir reduction

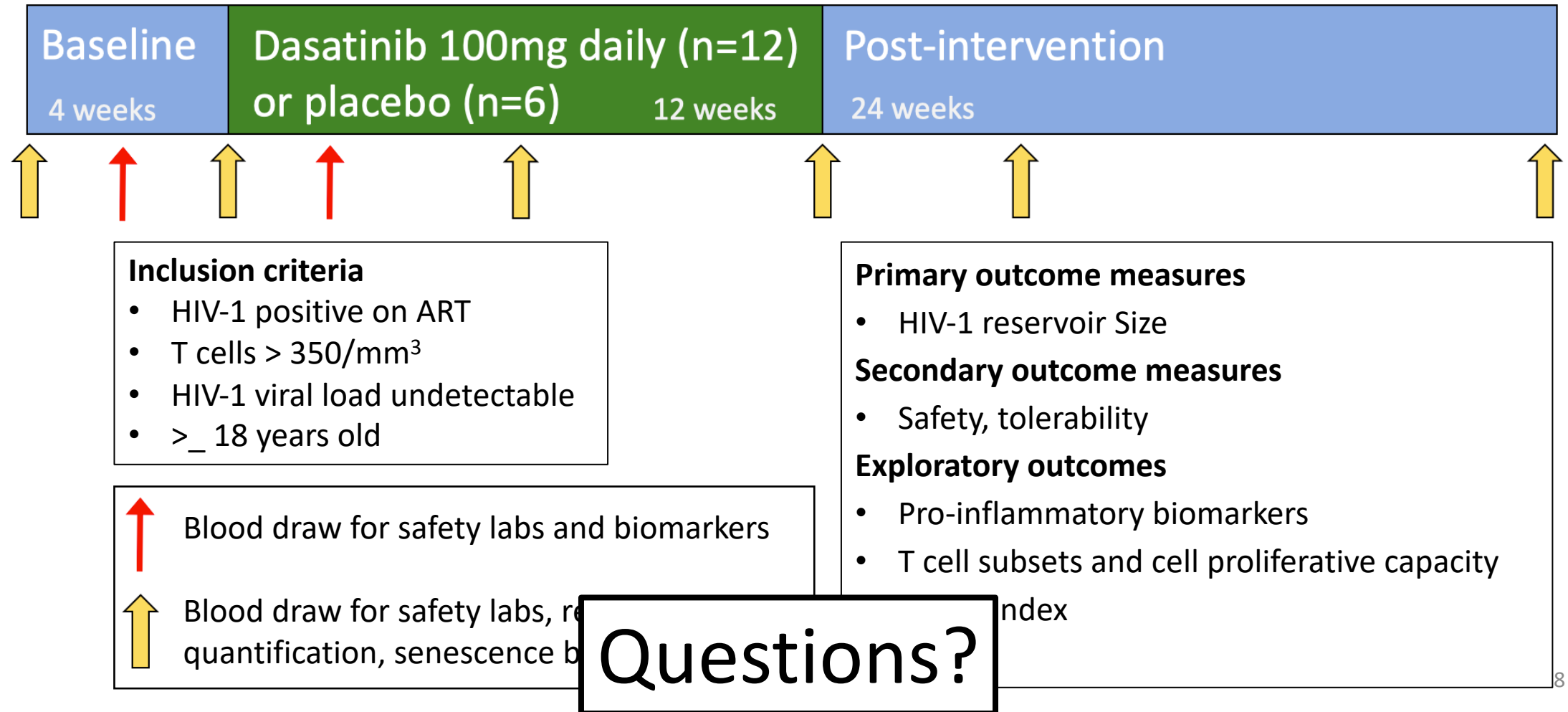
Dasatinib blocks **antigen-driven** & **homeostatic** proliferation

Blocks viral reactivation and prevents expansion of the latent reservoir



Screen and identify cancer drugs that can target HIV infected cells and be used in human clinical trial.

Future Directions: Clinical Trial of Dasatinib for HIV reservoir reduction in people living with HIV



Still no cure for HIV, but there is prevention!

- What is pre-exposure prophylaxis (PrEP)?
 - ART administration in high-risk HIV-negative individuals to prevent infection
- Managing patients on PrEP
 - Currently two FDA-approved regimens (FTC / TDF or FTC / TAF)
 - One pill once a day
 - Baseline and 3 month STD / HIV testing

Being a scientist is exciting but challenging



Experiments often don't work out the way you think they will!

You learn how to fail a LOT and continue moving forward

You need good mentors and collaborators to work with

What skills or characteristics makes a good scientist?



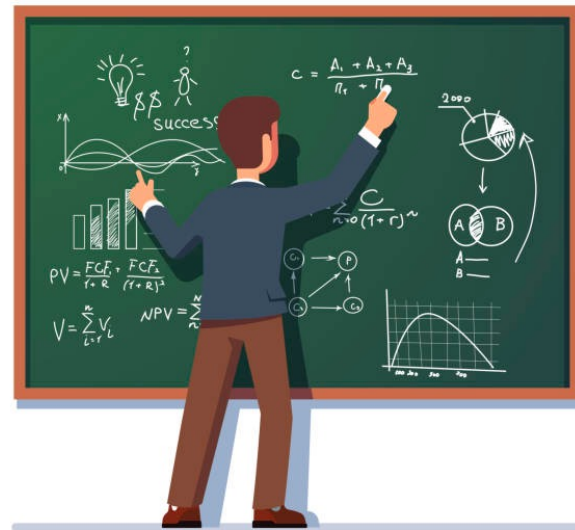
What can you do with a PhD in microbiology and immunology?

What can you do with a PhD in microbiology and immunology?

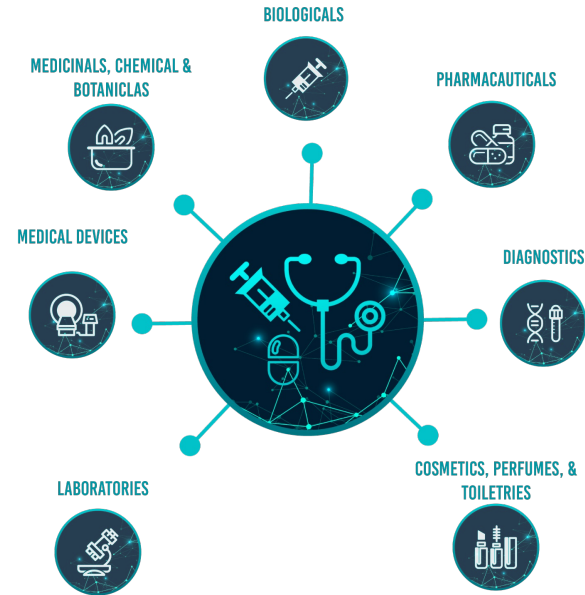
Laboratory Scientist



Educator/Teacher



Biotech/Pharma



Communication



Thanks for listening! Questions?