Effects Of Long-term ART On The HIV Reservoir

2023 Pre-CROI Community HIV Cure Research Workshop

FRED HUTCH

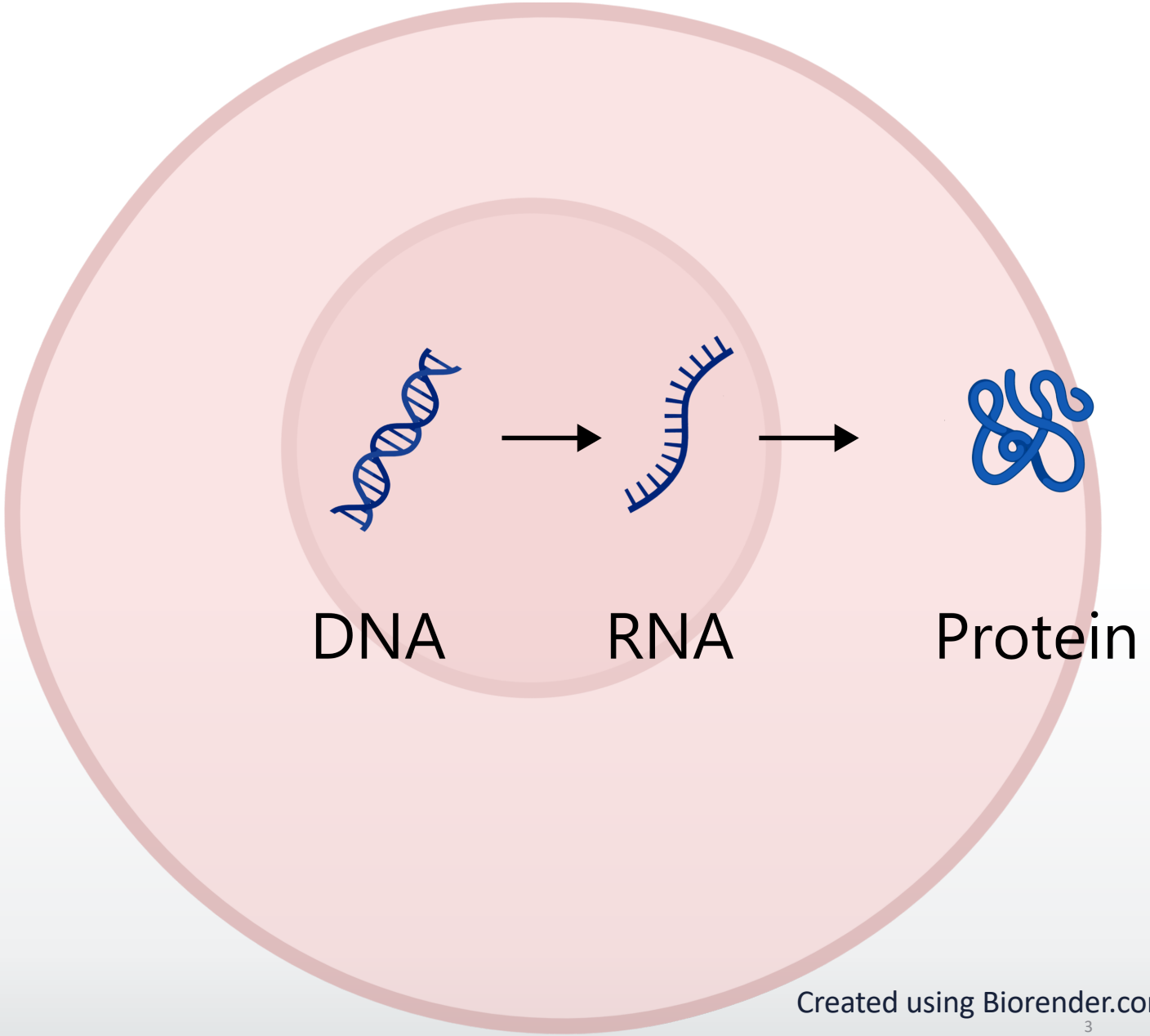
Jared Stern

Overview

- **Key question(s)** of the research
  - How does HIV persist in people on suppressive antiretroviral therapy (ART) and how does ART change the composition of the HIV reservoir over time?
- **Key findings** and take-home messages
  - HIV can establish a chronic infection of T-cells (reservoir) with some viruses being more active than others
  - On ART, active HIV-infected cells are cleared faster than inactive cells
  - The HIV reservoir becomes less active over time on ART
- How does this work **relate to an HIV cure?**
  - A less active reservoir affects how well cure strategies may work depending on their approach
  - Differences in the composition of the HIV reservoir may require tailoring of cure interventions

The Central Dogma of Biology

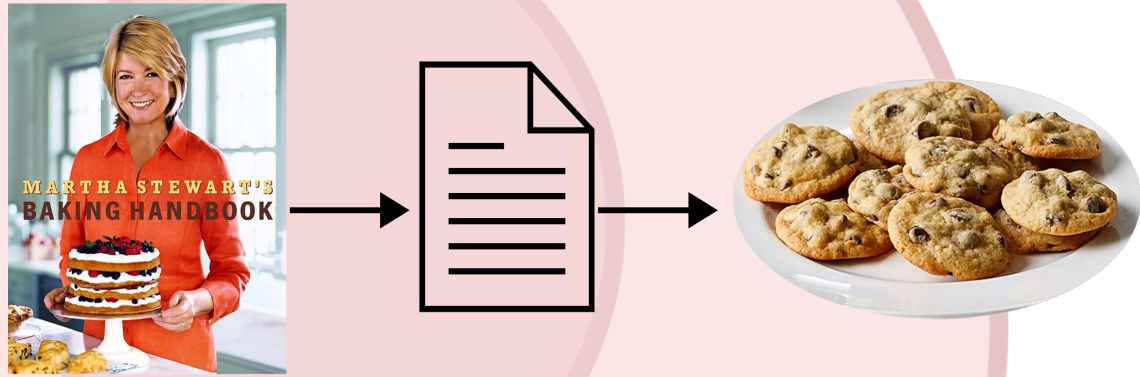
- Deoxyribonucleic acid (DNA) is the genetic code to produce everything our cells – and bodies – need.
- Ribonucleic acid (RNA) is the message **transcribed** from DNA
- RNA is **translated** into proteins necessary for cellular functions



Created using Biorender.com

The Central Dogma of Biology

- Deoxyribonucleic acid (DNA) is the genetic code to produce everything our cells – and bodies – need.
- Ribonucleic acid (RNA) is the message **transcribed** from DNA
- RNA is **translated** into proteins necessary for cellular functions

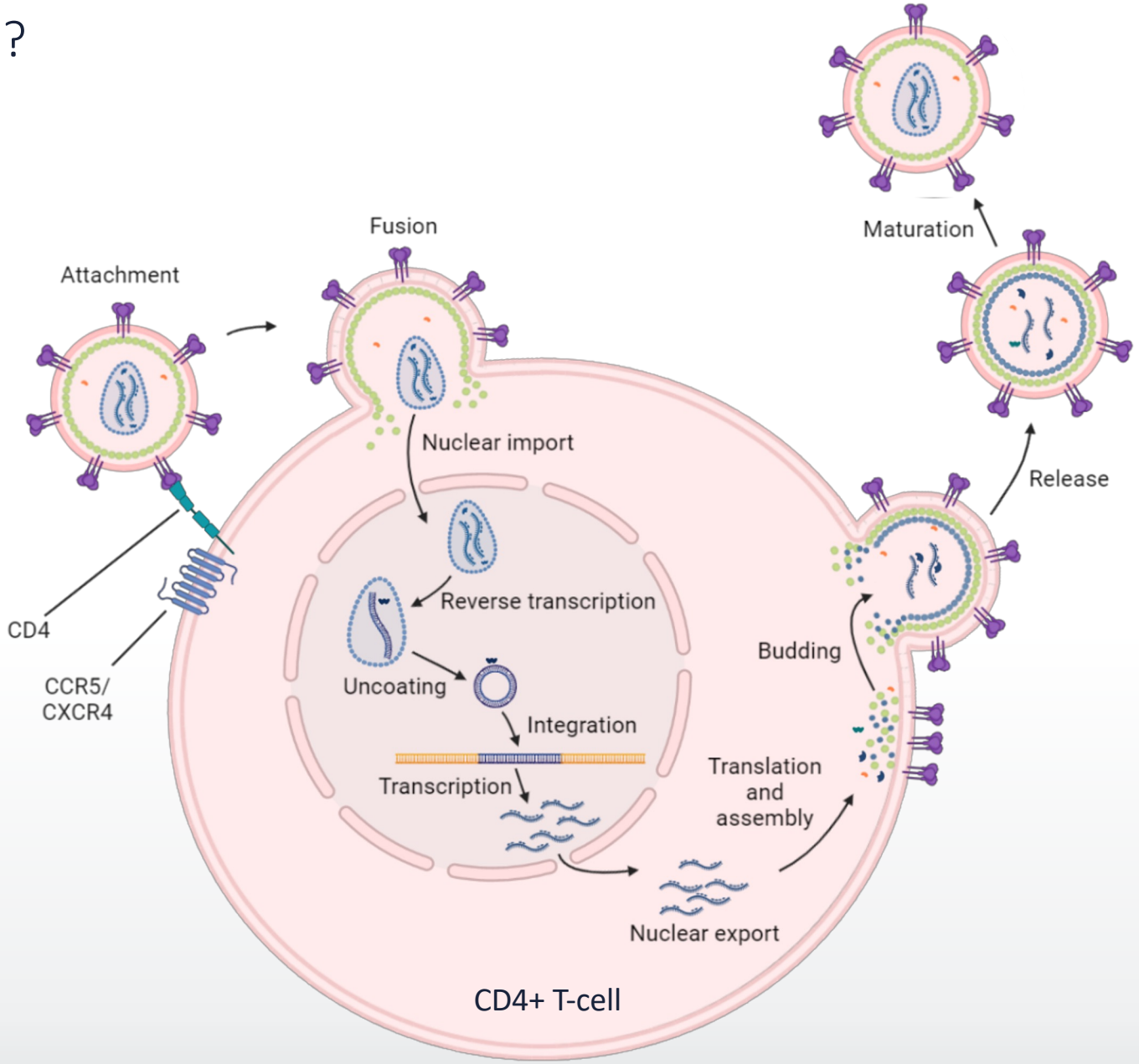


DNA RNA Protein

FRED HUTCH

What makes HIV such a Retro- virus?

- HIV's genome is made of RNA and is **reverse transcribed** into DNA
- The new HIV DNA genome is **integrated** into the host cell's DNA
- As HIV goes from RNA ➔ DNA ➔ RNA ➔ protein, it goes **against the central dogma** of biology, hence "**retro"virus**
- All currently licensed ART, except for lenacapavir (capsid inhibitor), act pre-integration
- Once a cell has an integrated viral genome (provirus), it will remain infected until it dies



Created using Biorender.com

What makes HIV such a Retro- virus?

- HIV's genome is made of RNA and is **reverse transcribed** into DNA
- The new HIV DNA genome is **integrated** into the host cell's DNA
- As HIV goes from RNA ➔ DNA ➔ RNA ➔ protein, it goes **against the central dogma** of biology, hence "**retro"virus**
- All currently licensed ART, except for lenacapavir (capsid inhibitor), act pre-integration
- Once a cell has an integrated viral genome (provirus), it will remain infected until it dies

Youtube

The Human Genome

- The human genome is 3,117,275,501 base pairs (bp) long
- The King James Bible is 3,116,480 letters long
- The HIV genome is 9,800 bp long
- ~10% of the human genome are endogenised retroviruses (ERVs)

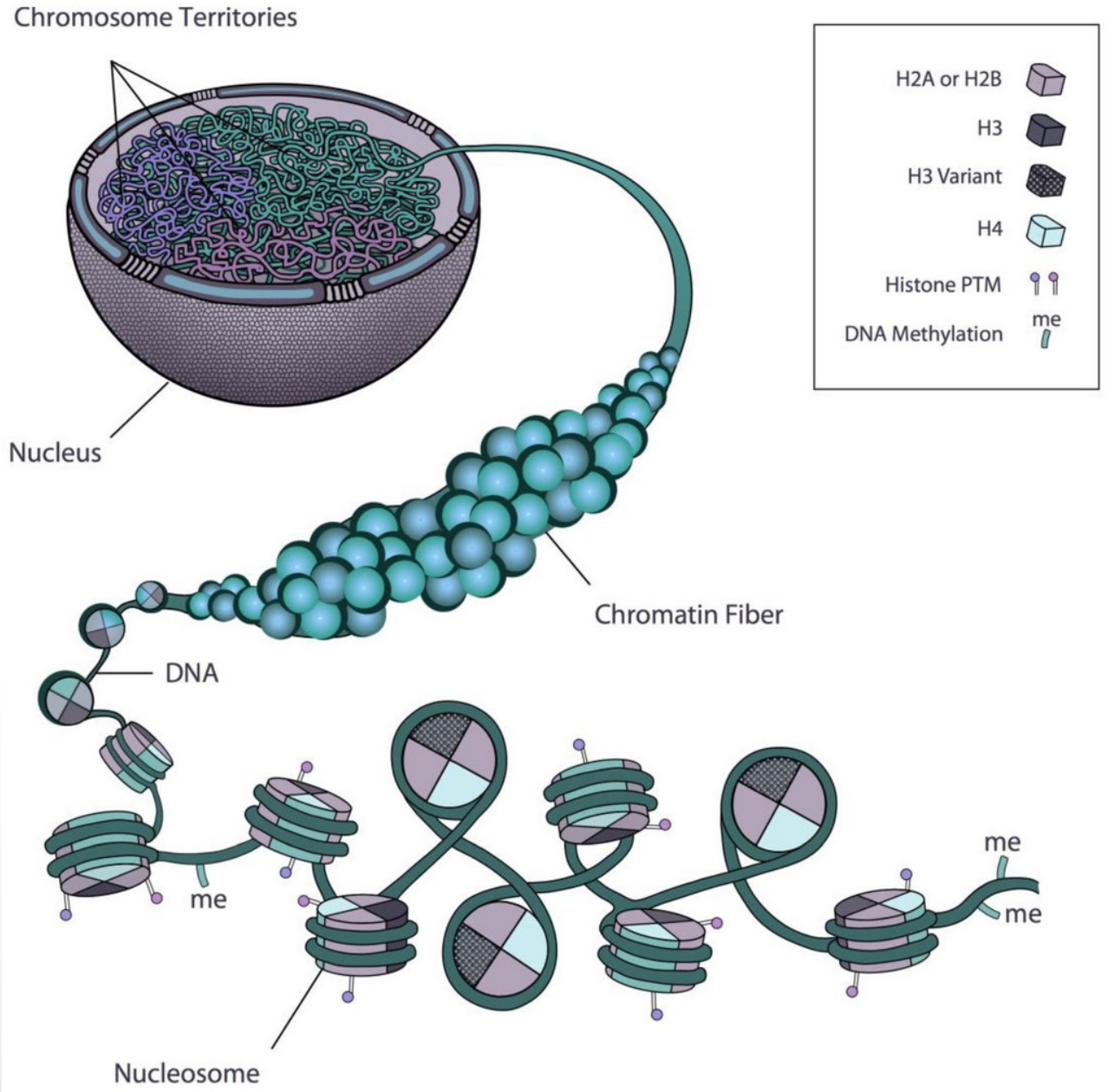


Fig 1. Rosa and Shaw, 2013 10.3390/biology2041378

The Human Genome

- Only 1% of the human genome are **genes** encoding for proteins
- Because of its considerable length, DNA is a highly organized structure **supercoiling** around itself to form chromosomes
- In order to read genes, DNA needs to be in a relaxed and open state
- Actively transcribed genes are located in the nuclear periphery
- HIV tends to integrate into actively transcribed genes, but not always
- The site of HIV integration can impact the viral activity of infected cells

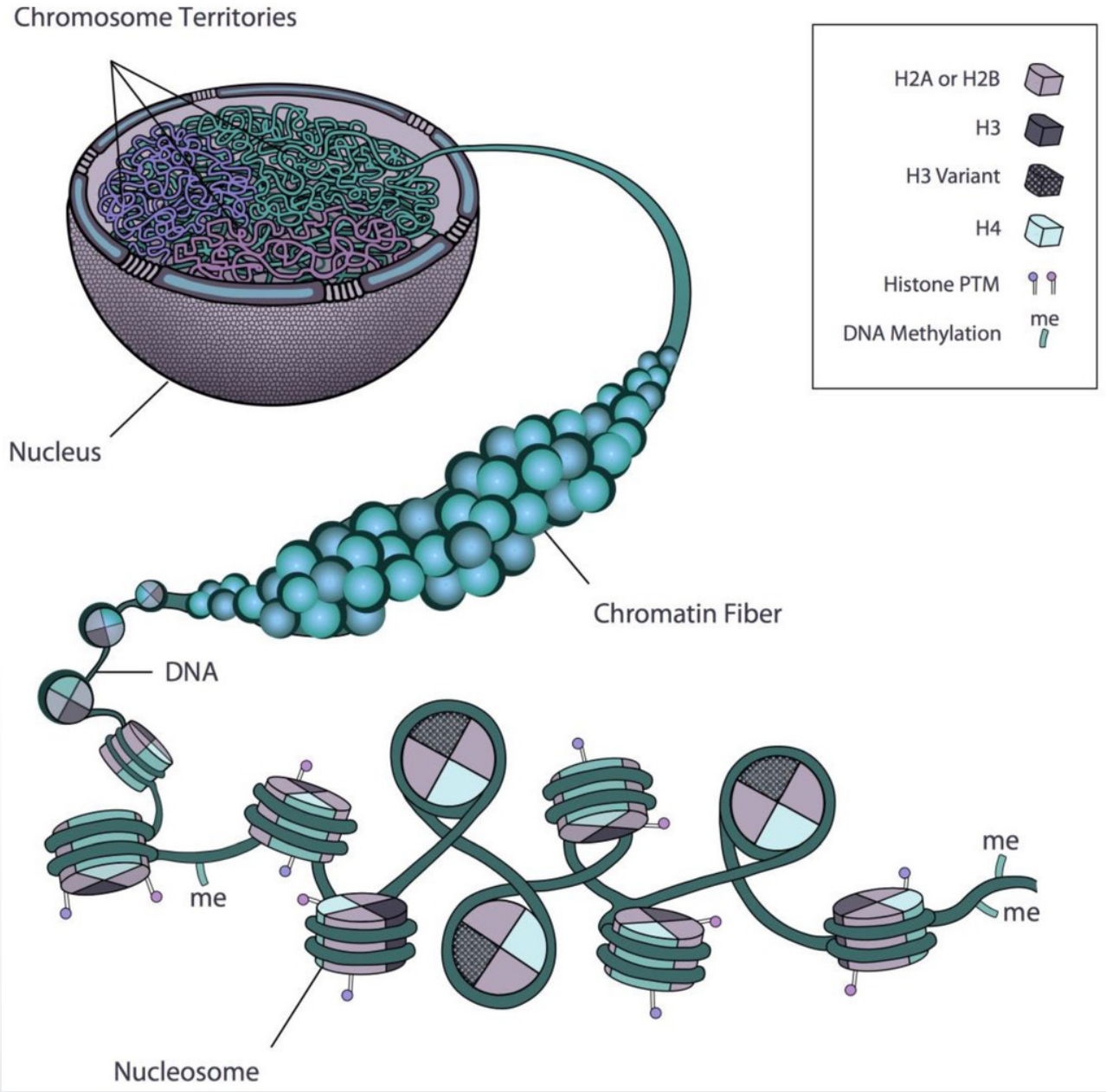
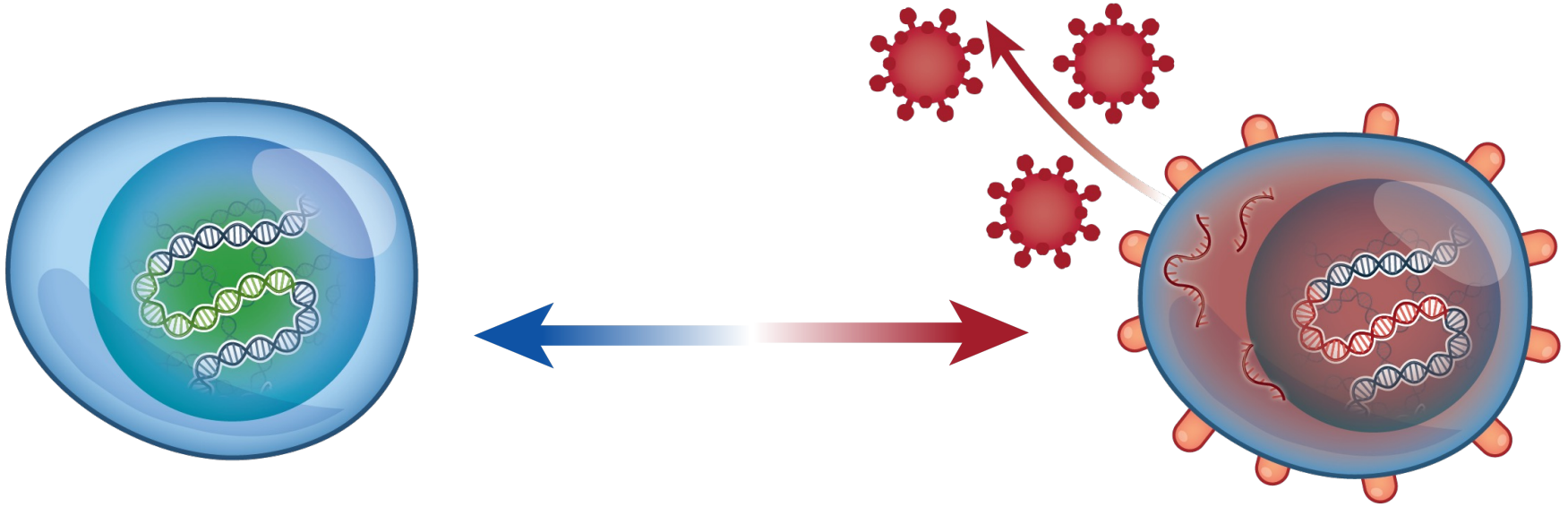


Fig 1. Rosa and Shaw, 2013 10.3390/biology2041378

HIV Latency – Not All Proviruses Are Made Equally

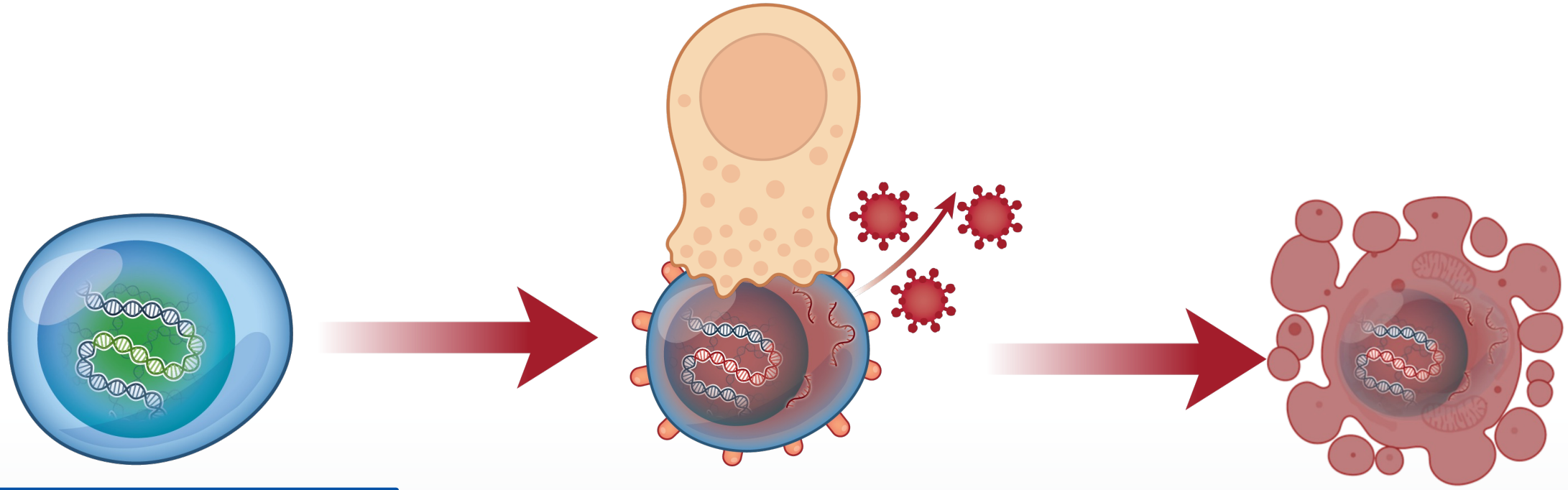


Latent infection
DNA positive
RNA negative
HIV protein negative

Productive infection
DNA positive
RNA positive
HIV protein positive

Courtesy of Sharon Lewin

Productive Infection is Required for Clearance of Infected Cells



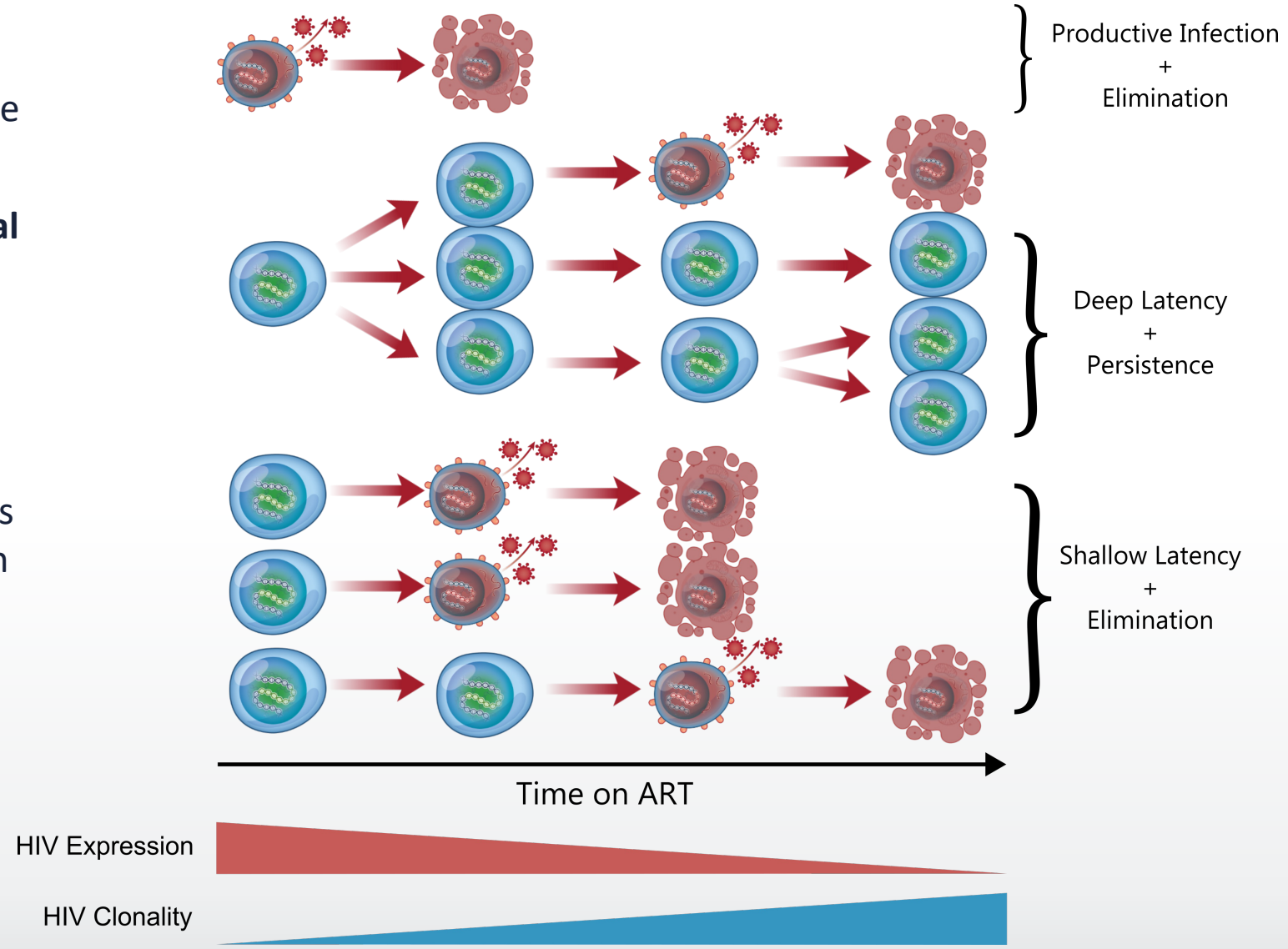
Latent infection
DNA positive
RNA negative
HIV protein negative
Cell Survival

Productive infection
DNA positive
RNA positive
HIV protein positive
Cell Death

FRED HUTCH

The HIV Reservoir Becomes Increasingly Latent Over Time on ART

- On ART, proviruses that are more active are cleared rapidly
- The HIV reservoir persists on ART by **clonal expansion**
- Viruses that can remain latent during cell division avoid clearance by the immune system
- This means that the HIV reservoir becomes increasingly **clonal** and **latent** over time on ART



FRED HUTCH

Summary

- ART is highly effective at preventing cells becoming infected with HIV, but it is **ineffective against cells already infected with HIV**
- HIV uses unique biology to **integrate** its genome into the host cell's DNA, thus the virus persists for as long as an infected cell survives
- HIV integration is somewhat random, but there are preferences for **actively transcribed genes**
- For infected cells to be cleared, viral expression is necessary
- HIV can establish a **latent** state of infection where it remains inactive in a cell and is hidden
- Proviruses that are more latent are able to be hidden and survive longer in people with HIV
- The HIV reservoir becomes **more latent over time** on ART
- Though the HIV reservoir decreases on ART, this is counteracted by division of infected cells by **clonal expansion**
- The HIV reservoir becomes **more clonal over time** on ART

Major Outstanding Research Questions

- What determines if a cell will be latent or productively infected?
- What determines if a cell will switch from being latent to productive?
- What makes one cell undergo clonal expansion and not another?
- Can HIV itself make infected cells divide and survive better?
- Should a cure make HIV less latent (less hidden, more easily cleared) or more latent (more hidden, but less likelihood of virus being made)?
- Is long ART enough to enrich for a deeply latent HIV reservoir that doesn't rebound when ART is stopped?