FRED HUTCH

UNIVERSITY of WASHINGTON

Transform from within: Gene Editing for HIV Cure

Bish (Biswajit) Paul
bishp@uw.edu
Doctoral Candidate, Kiem Lab
UW Molecular Cellular Biology PhD program

Scholars' Studio

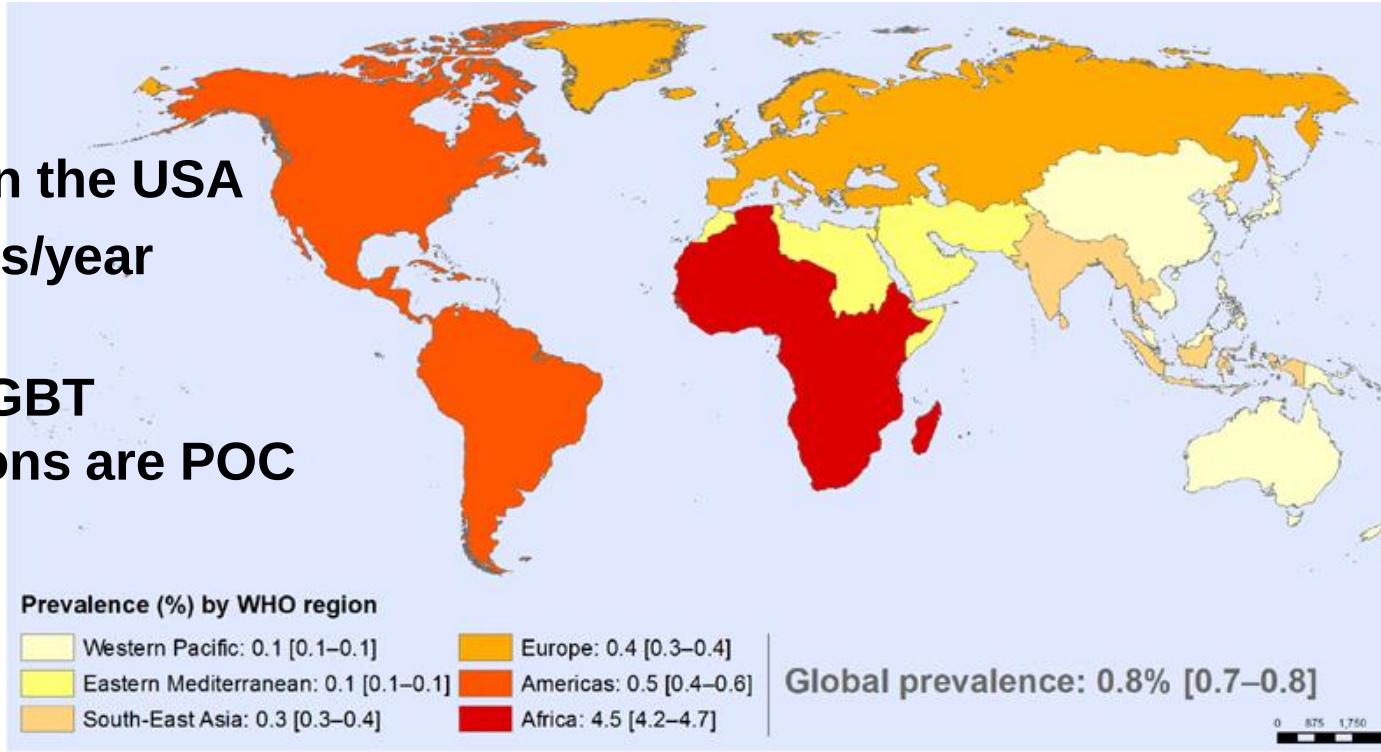
HIV infection: a persistent & devastating problem

Worldwide Infections: 78 million
Deaths: 39 million

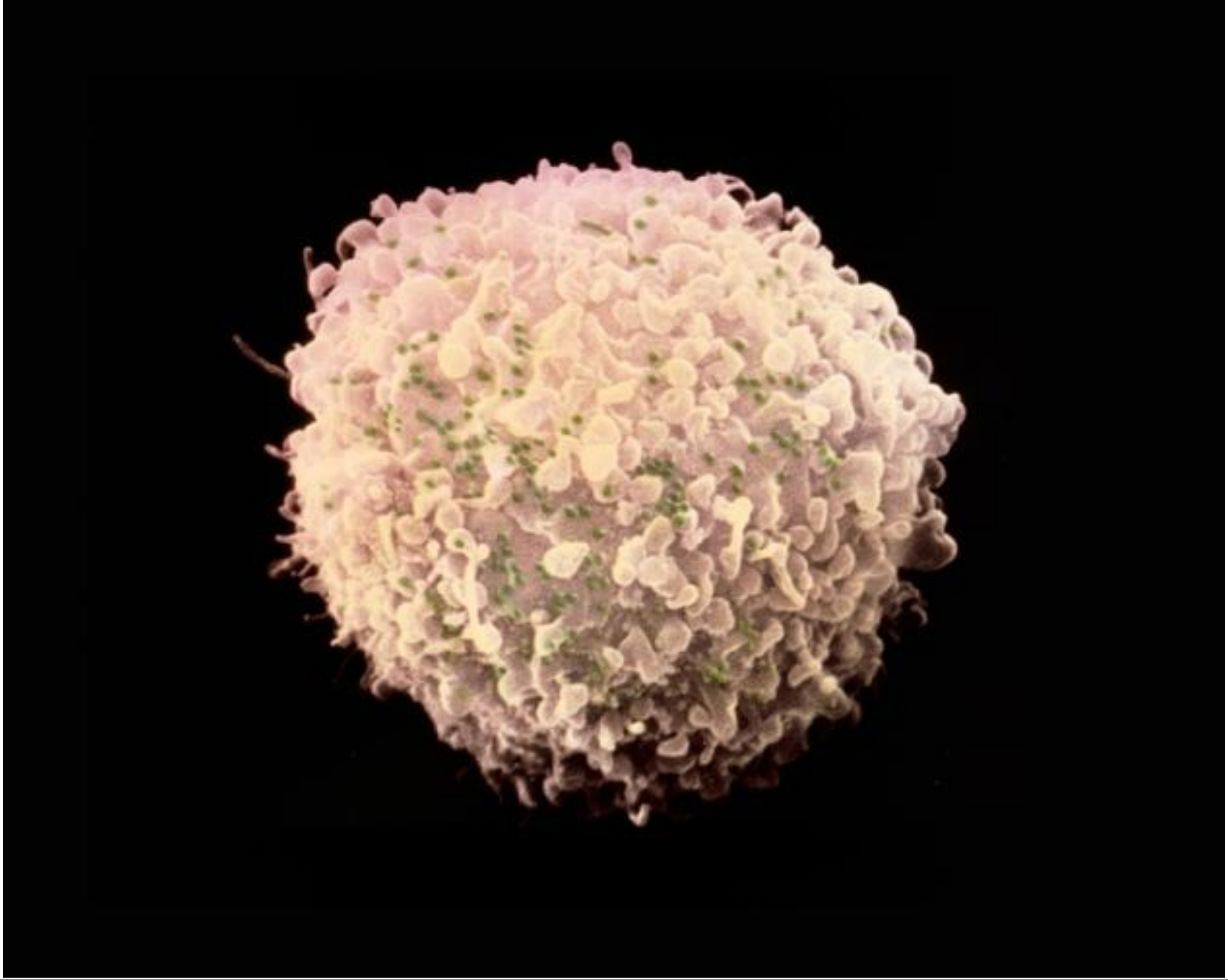
1.2 million infected in the USA

50,000 new infections/year

>50% infected are LGBT
>44% of new infections are POC

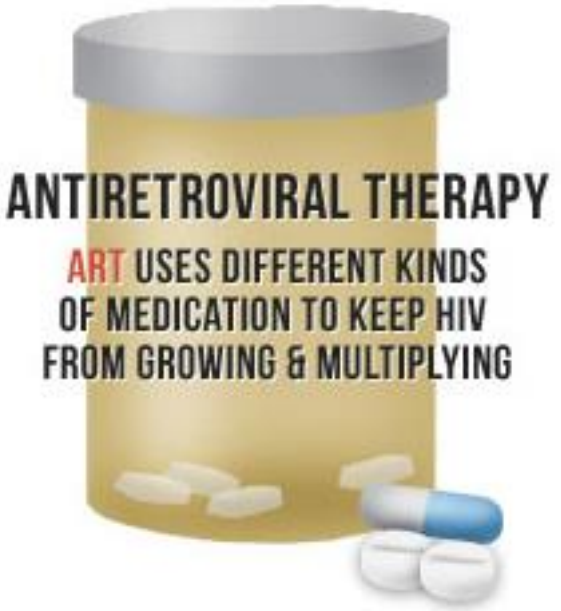


Sources: World Health Organization; Centers for Disease Control



Limitations of Anti-retroviral Therapy to treat HIV infection

Combination of 3 or more drugs.



Drug therapy has limitations:

1. Adherence
2. Side effects of drugs & Morbidity
3. Treatment costs per patient over their lifetime: USA $450,000 -700,000
4. Potential viral resistance
5. Never Cured

Source: Centers for Disease Control

Is it time to re-think how we treat diseases?

Current Model of Treatment:

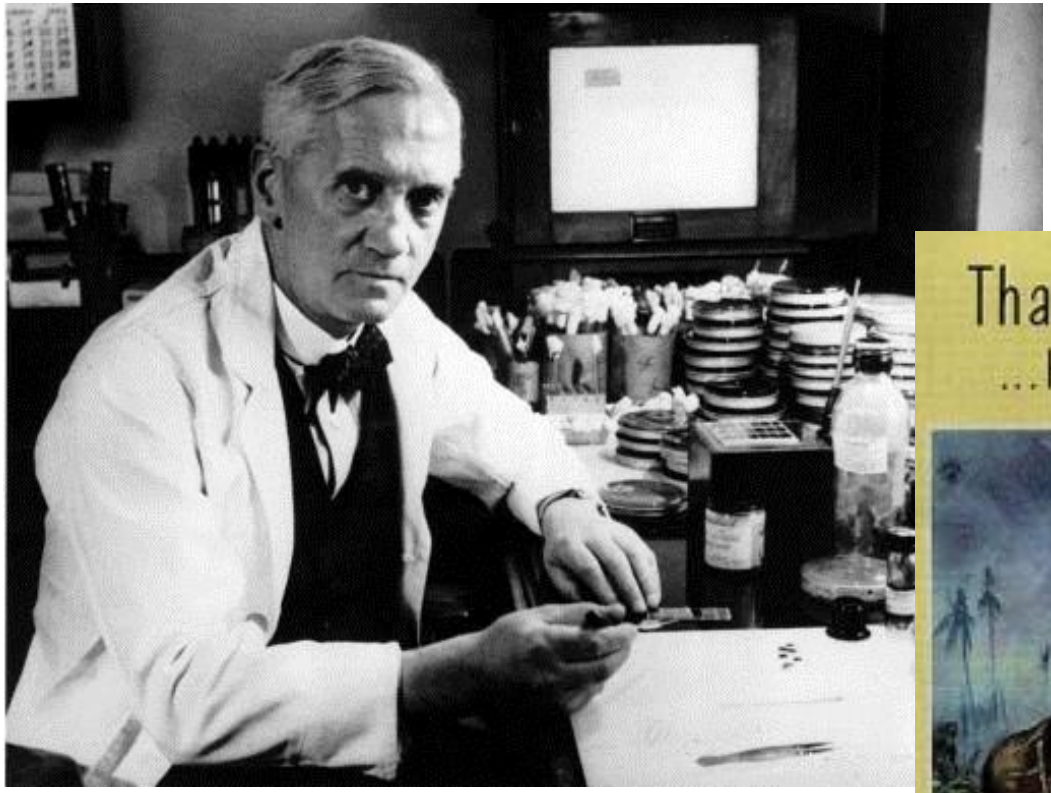
Identify Disease

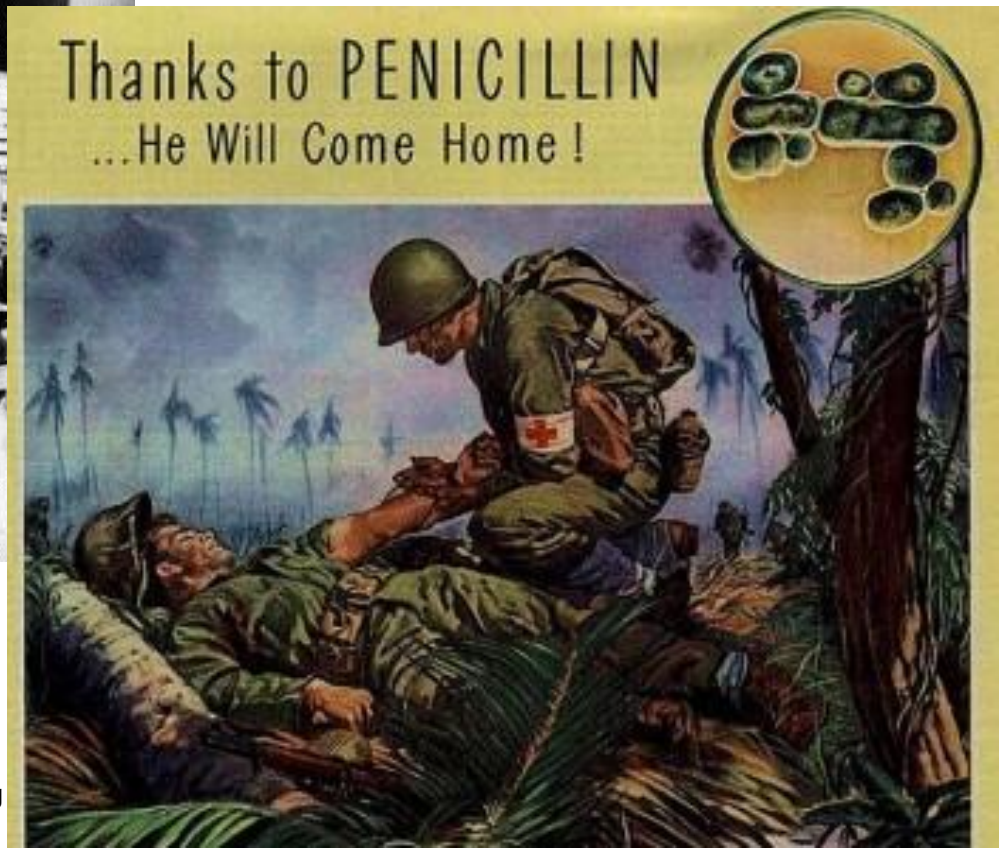
Model it in animals/ humans

Screen hundreds or thousands of drug molecules

Ameliorate symptoms of disease

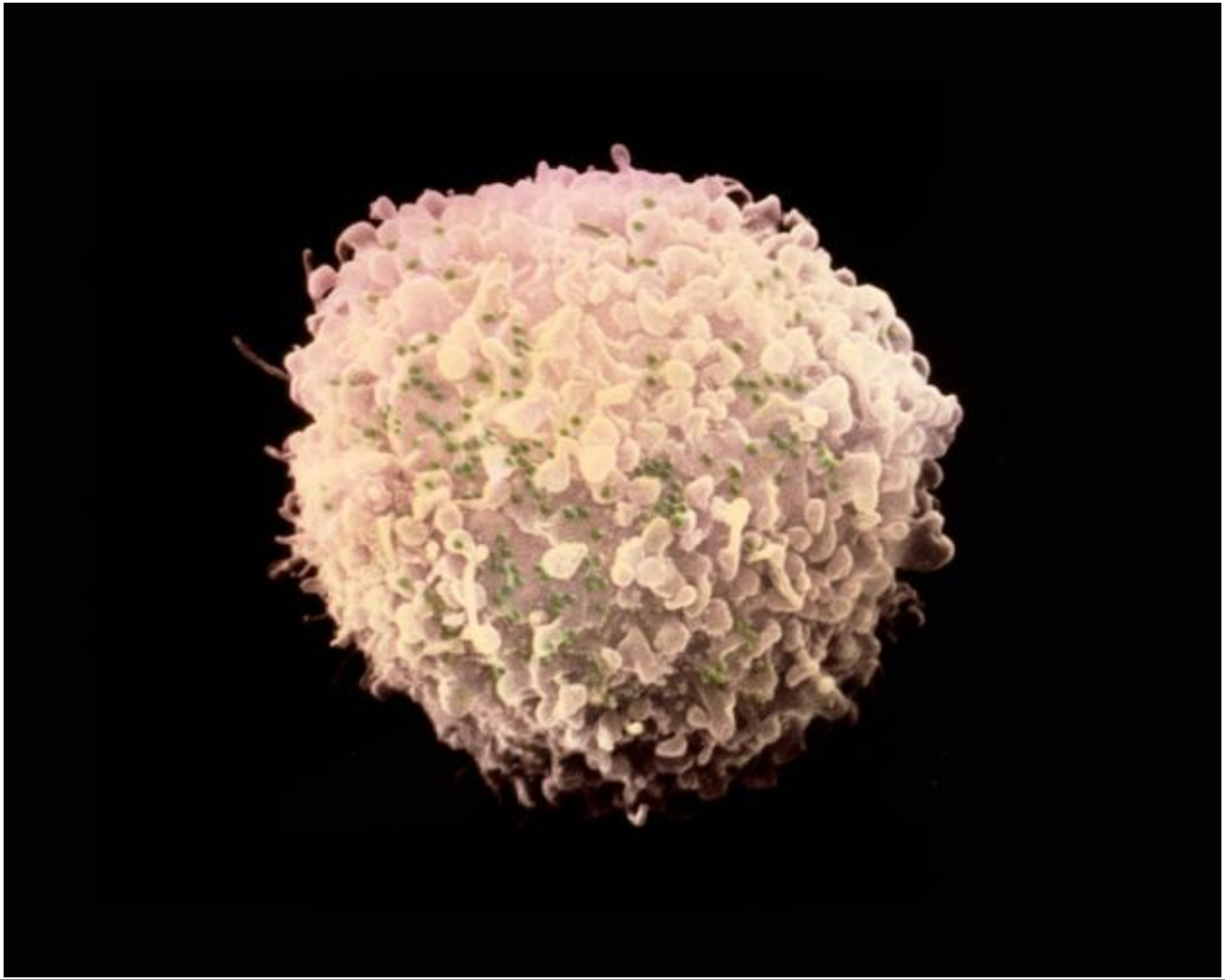
Is it time to re-think how we treat diseases?



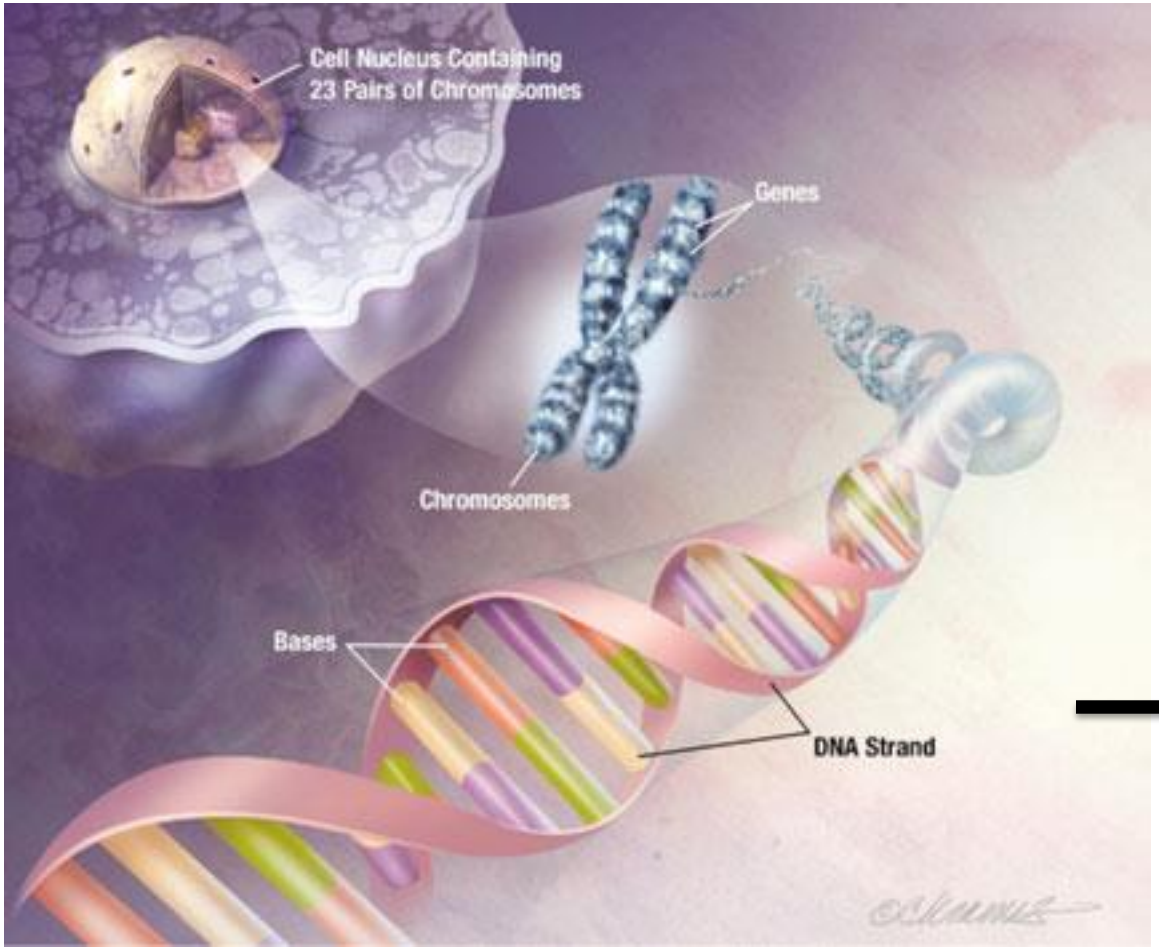


https://upload.wikimedia.org/wikipedia/commons/4/4c/Alexander_Fleming.jpg
http://www.xenex.com/sites/default/files/xenex-blog-penicillinWWII.jpg

Could we transform the cell itself?



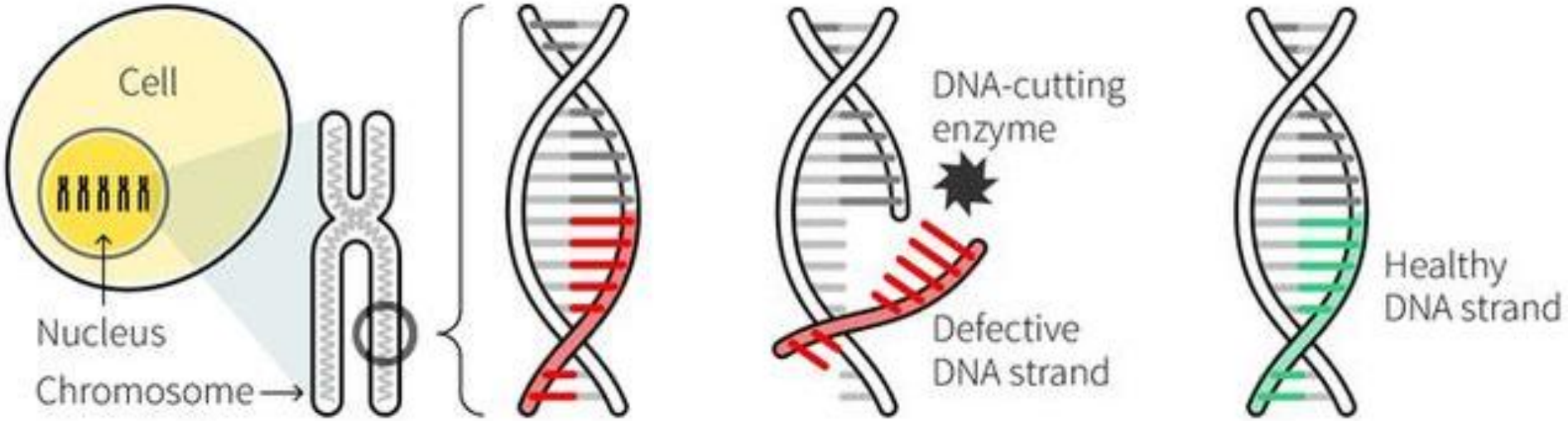
A Paradigm Shift: Cellular therapies to treat diseases



http://www.livingwithcah.com/sections/Genetics/genetics.jpg
http://blogs.discovermagazine.com/crux/files/2015/11/DNA_edits.jpg

Gene Editing to treat diseases

CUT & *PASTE* using Molecular Scissors



https://agenda.weforum.org/wp-content/uploads/2015/11/CRISPR.jpg

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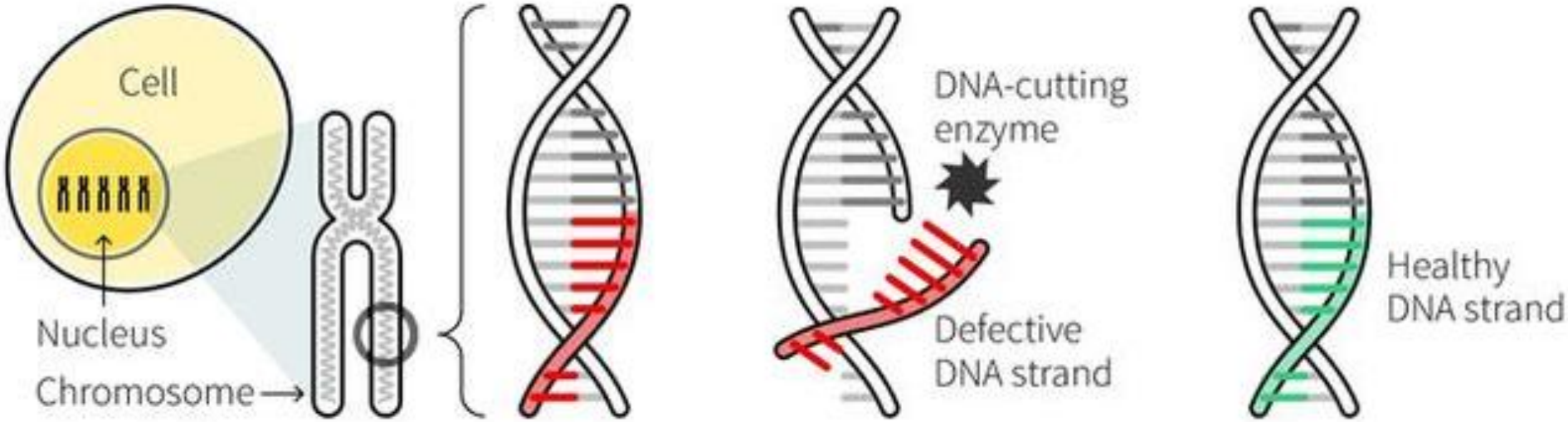
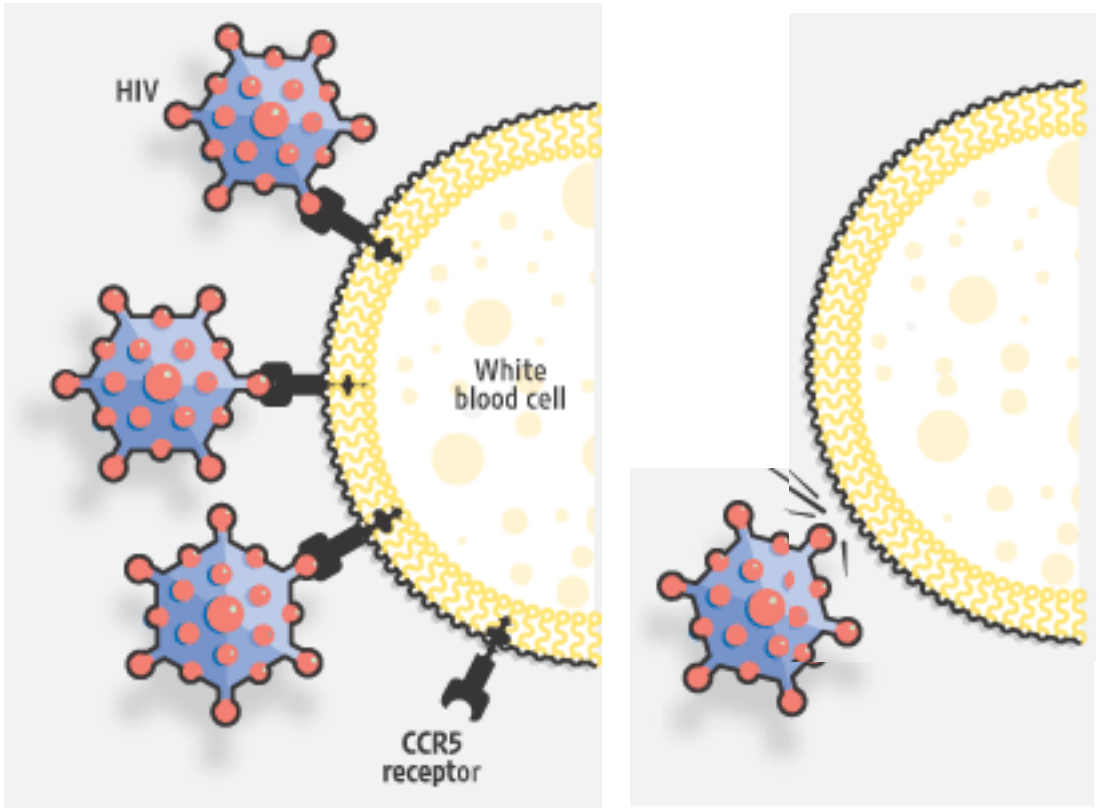


Nuclease = DNA-cutting enzyme

Ex: CRISPR, megaTAL

https://agenda.weforum.org/wp-content/uploads/2015/11/CRISPR.jpg

Gene Editing to treat HIV: elimination of CCR5



CCR5 co-receptors on the surface of T-cells are used by HIV for cellular entry

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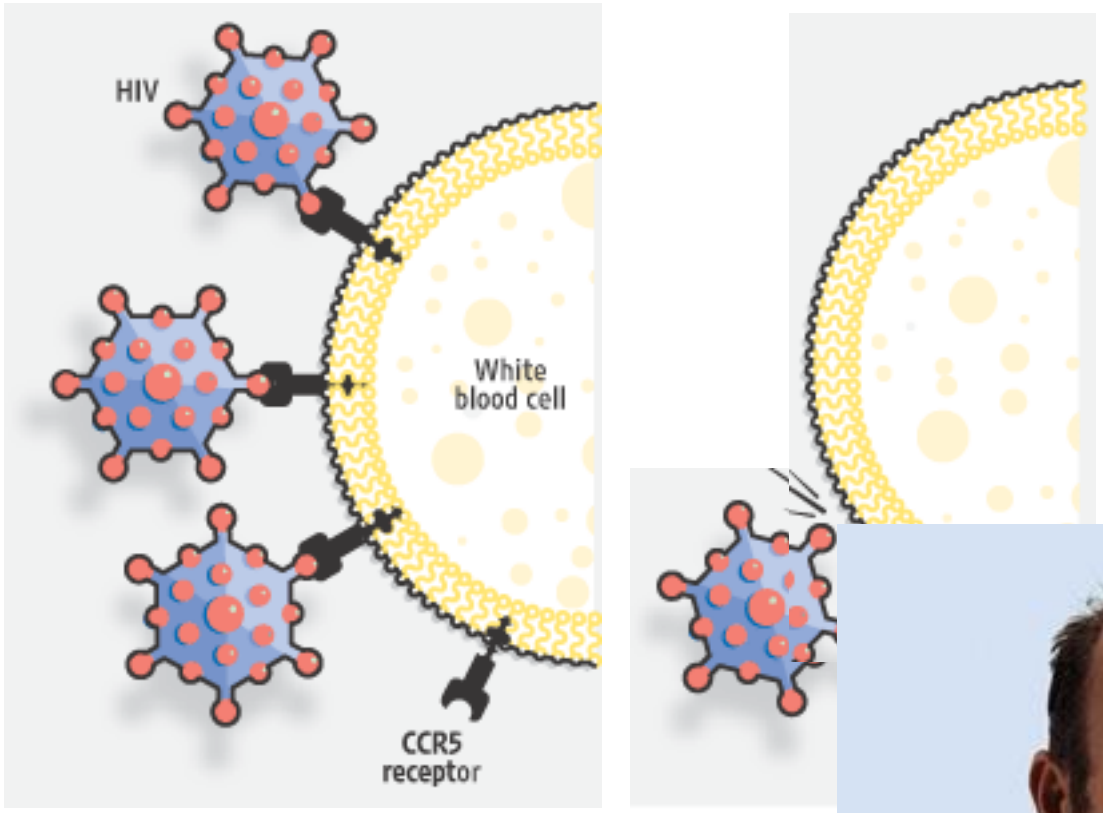

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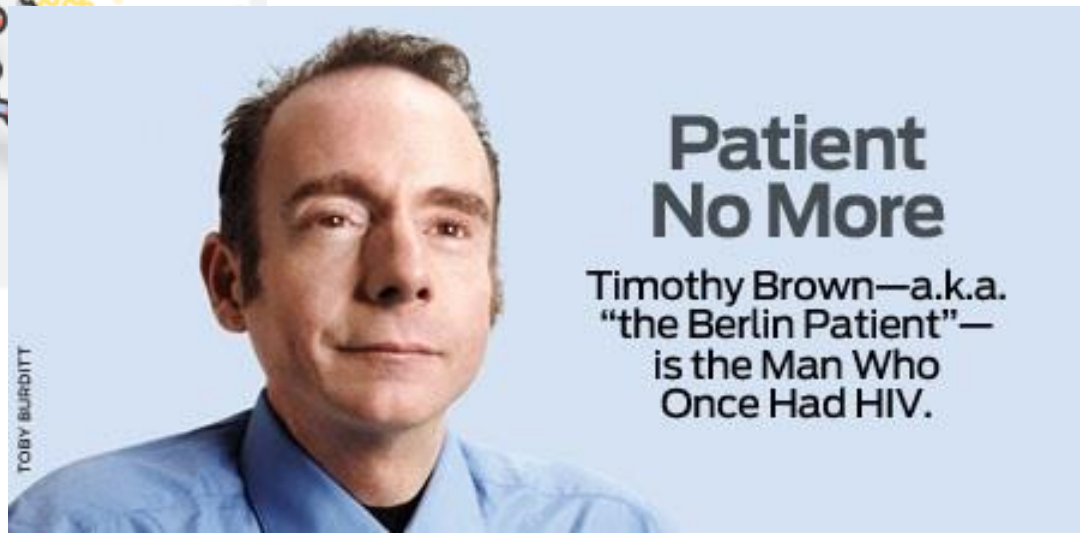

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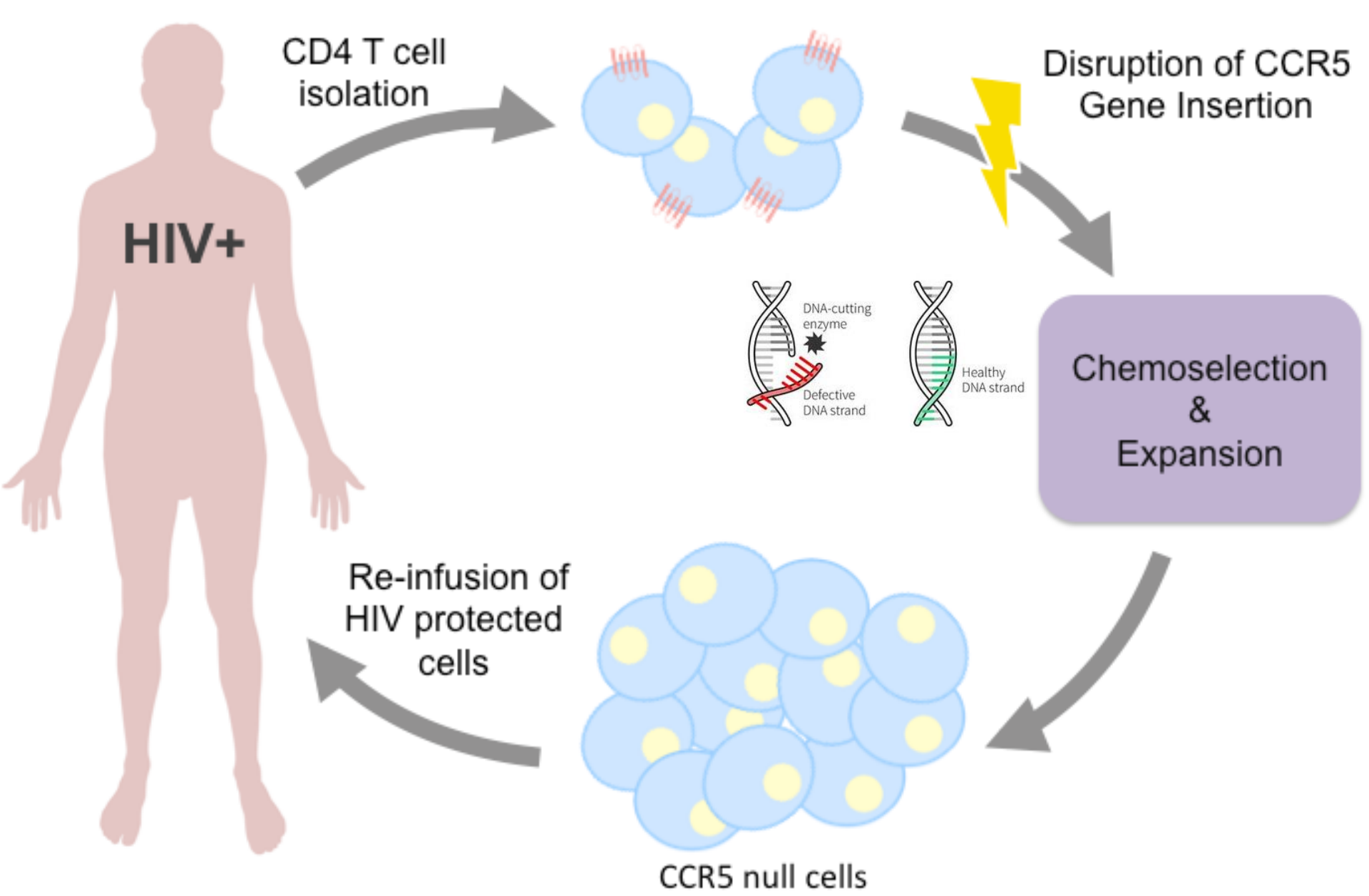
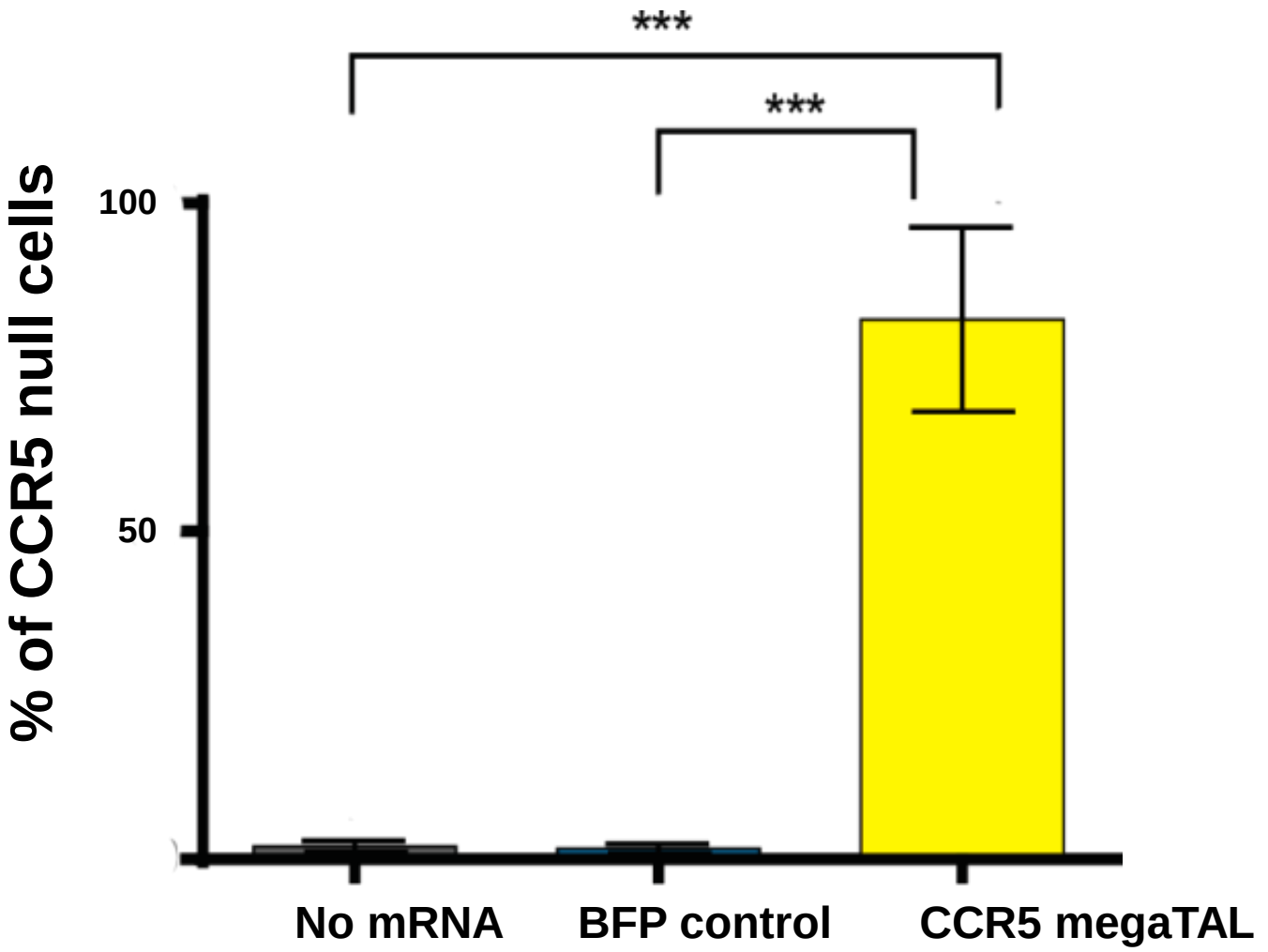
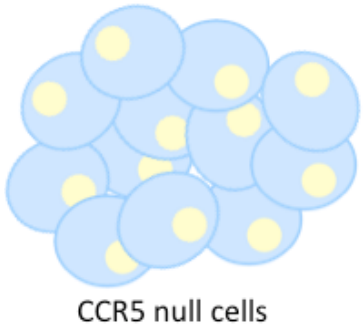

HIV+
CD4 T cell isolation
Disruption of CCR5 Gene Insertion
DNA-cutting enzyme
Defective DNA strand
Healthy DNA strand
Chemoselection & Expansion
Re-infusion of HIV protected cells
CCR5 null cells

CCR5-megaTAL nuclease eliminates CCR5 receptor

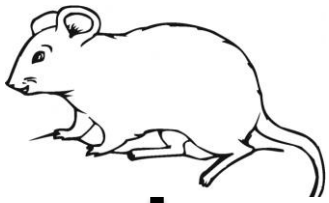


~ 80% CCR5 disruption

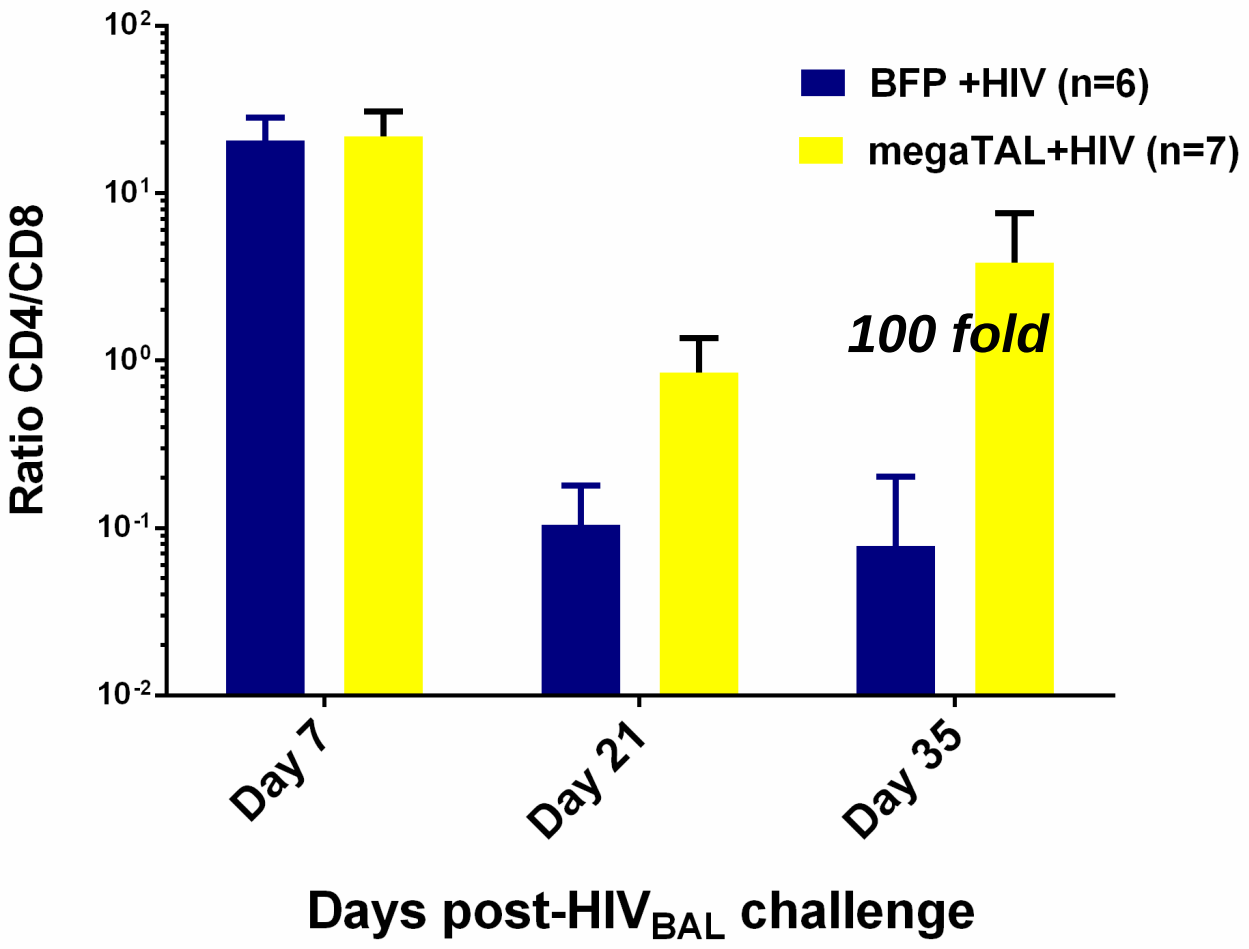
CCR5-megaTAL treatment protects against HIV



Infusion into 'humanized' mice



Challenge with HIV



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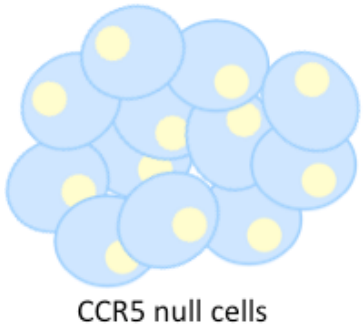

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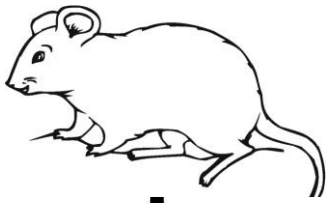

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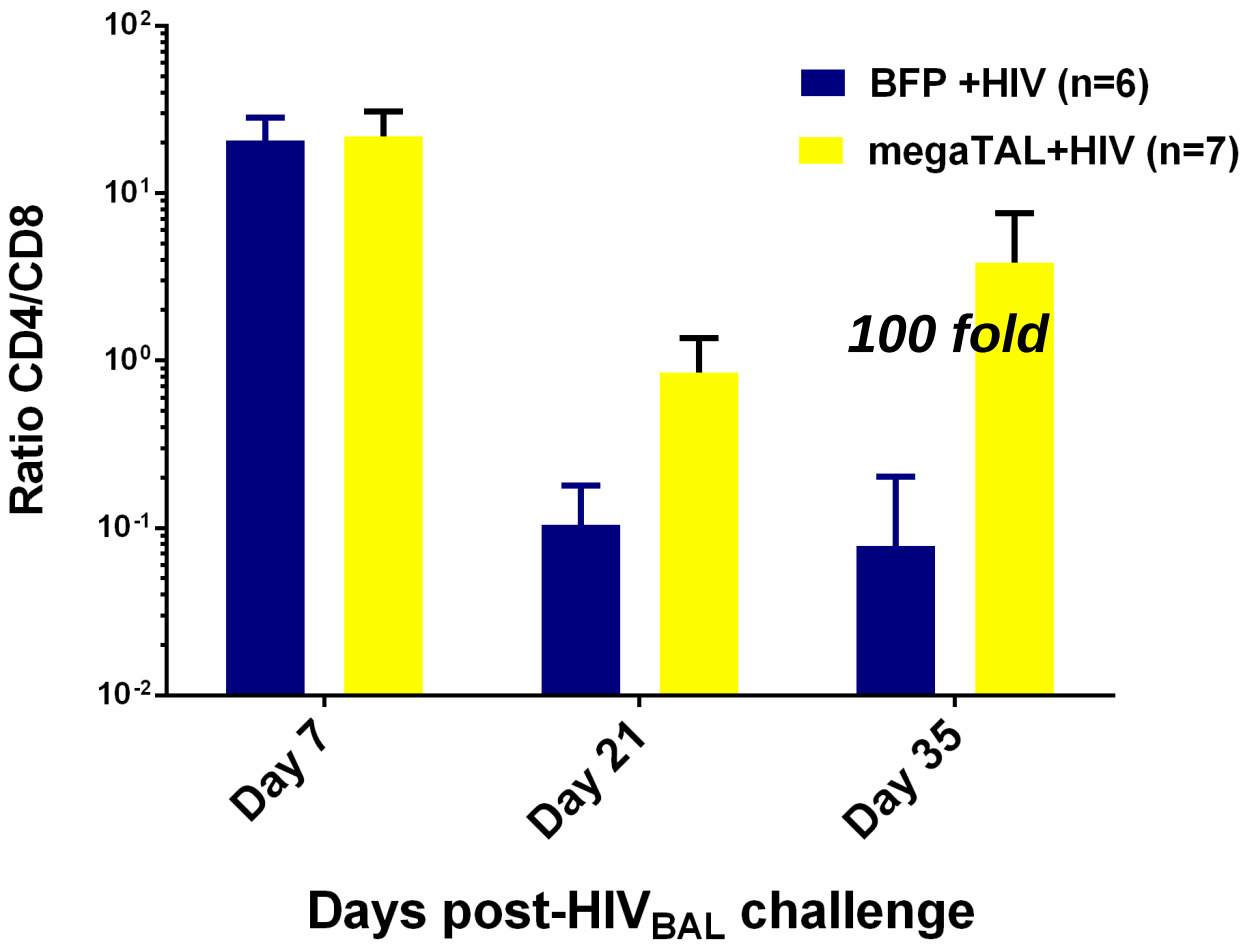
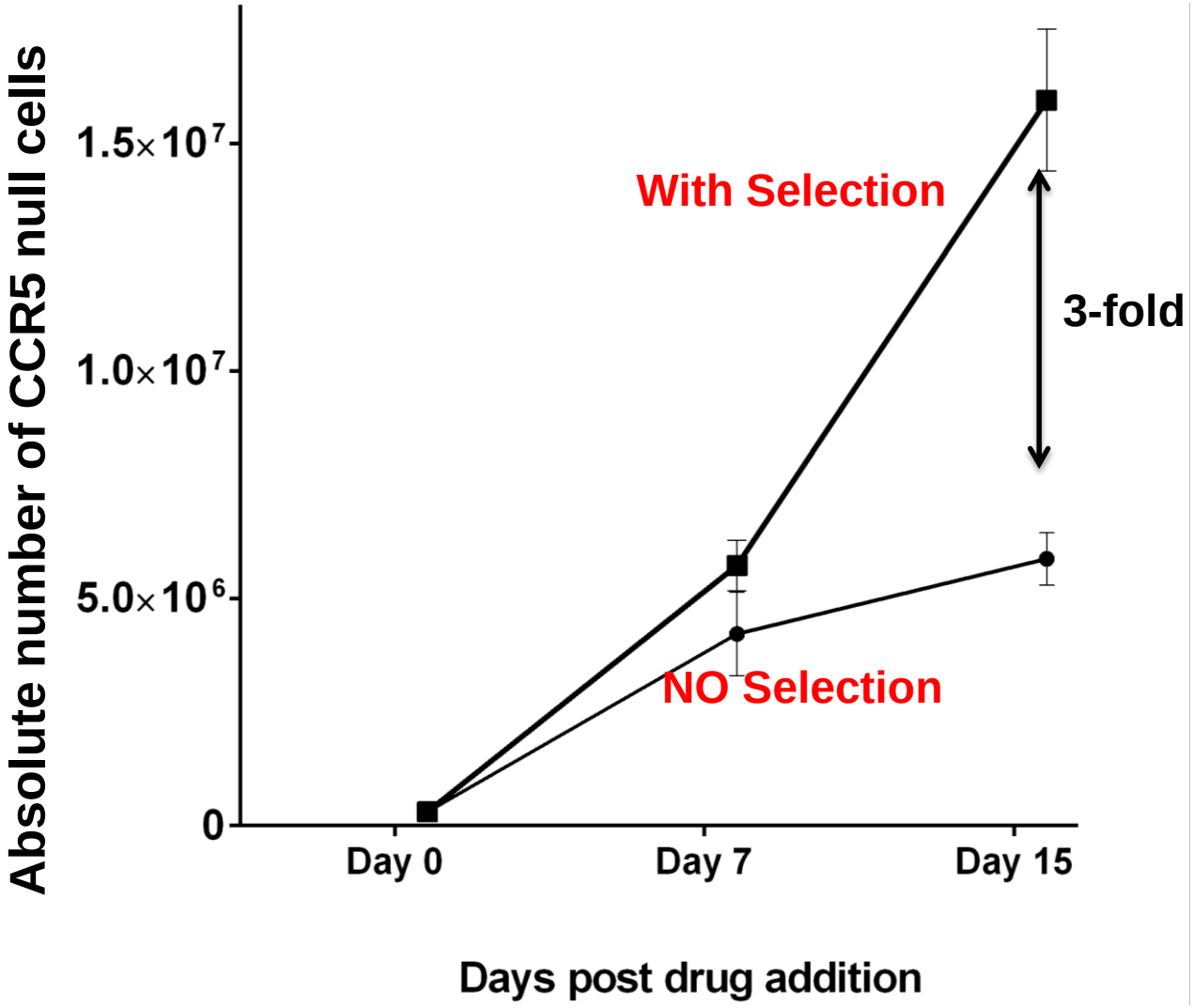


CCR5-null cells can be preferentially expanded

Selection
&
Expansion



Summary

Gene & Cell therapies are a paradigm shift in medicine and can be used to treat monogenic diseases.

HIV uses the CCR5 co-receptor present on the surface of $CD4^+$ T-cells to enter the cell and infect it.

The CCR5-megaTAL nuclease (DNA-cutting enzyme) eliminates this receptor in >80% of human $CD4^+$ T-cells.

These modified $CD4^+$ T-cells preferentially survive during active HIV infection modeled in a mouse.

We can use an FDA approved drug to preferentially select and expand these modified CD4+ T-cells.

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- Name: **Bish (Biswajit) Paul**
- Department: **Fred Hutch/ MCB**
- Contact Information: **bishp@uw.edu**

- Bish is a scientist and community leader whose work straddles science, education and outreach, and LGBTQ advocacy.
- As a gay, immigrant scientist-of-color, he is passionate about increasing diversity in STEM, especially in leadership positions.
- He is also a Pacific Science Center Science Communication fellow, a Bellevue College Teaching fellow, a documentary filmmaker, a foodie, and an avid hiker.