
Engineering Immunity
Controlling the where, when
and how long of vaccine delivery
Darrell J. Irvine
hhmi
Scripps
Research

Luck is when preparation meets opportunity

– Neil Peart





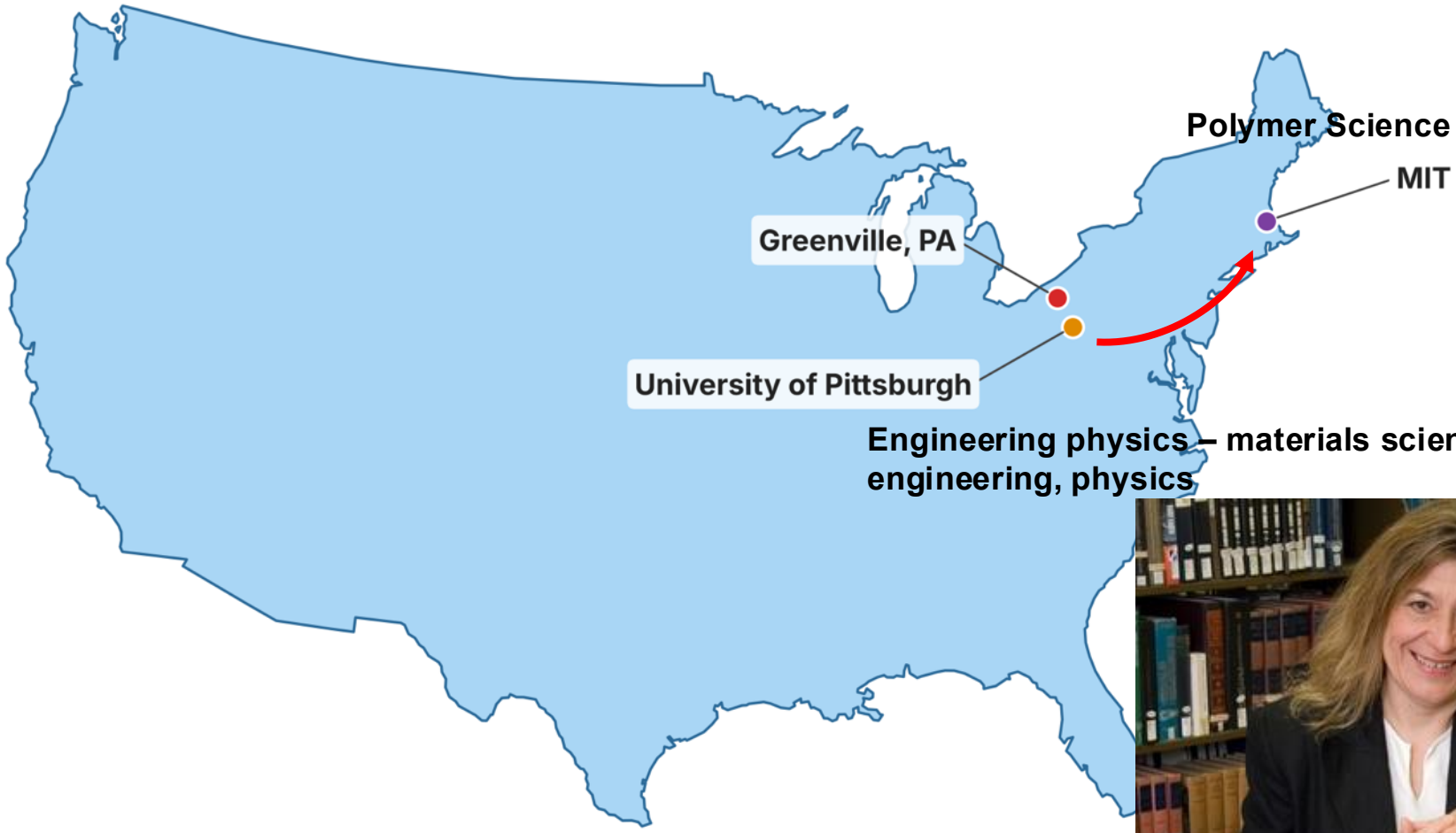
Engineering physics – materials science, electrical engineering, physics



Anna Balazs

Luck is when preparation meets opportunity

– Neil Peart





Anne Mayes



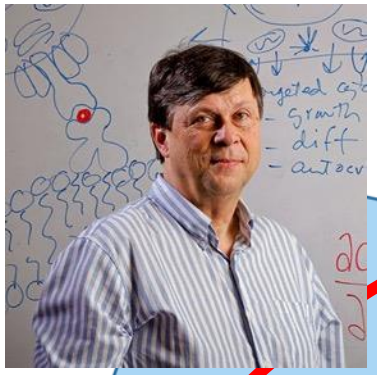
Linda Griffith



Anna Balazs

Luck is when preparation meets opportunity

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Mark Davis



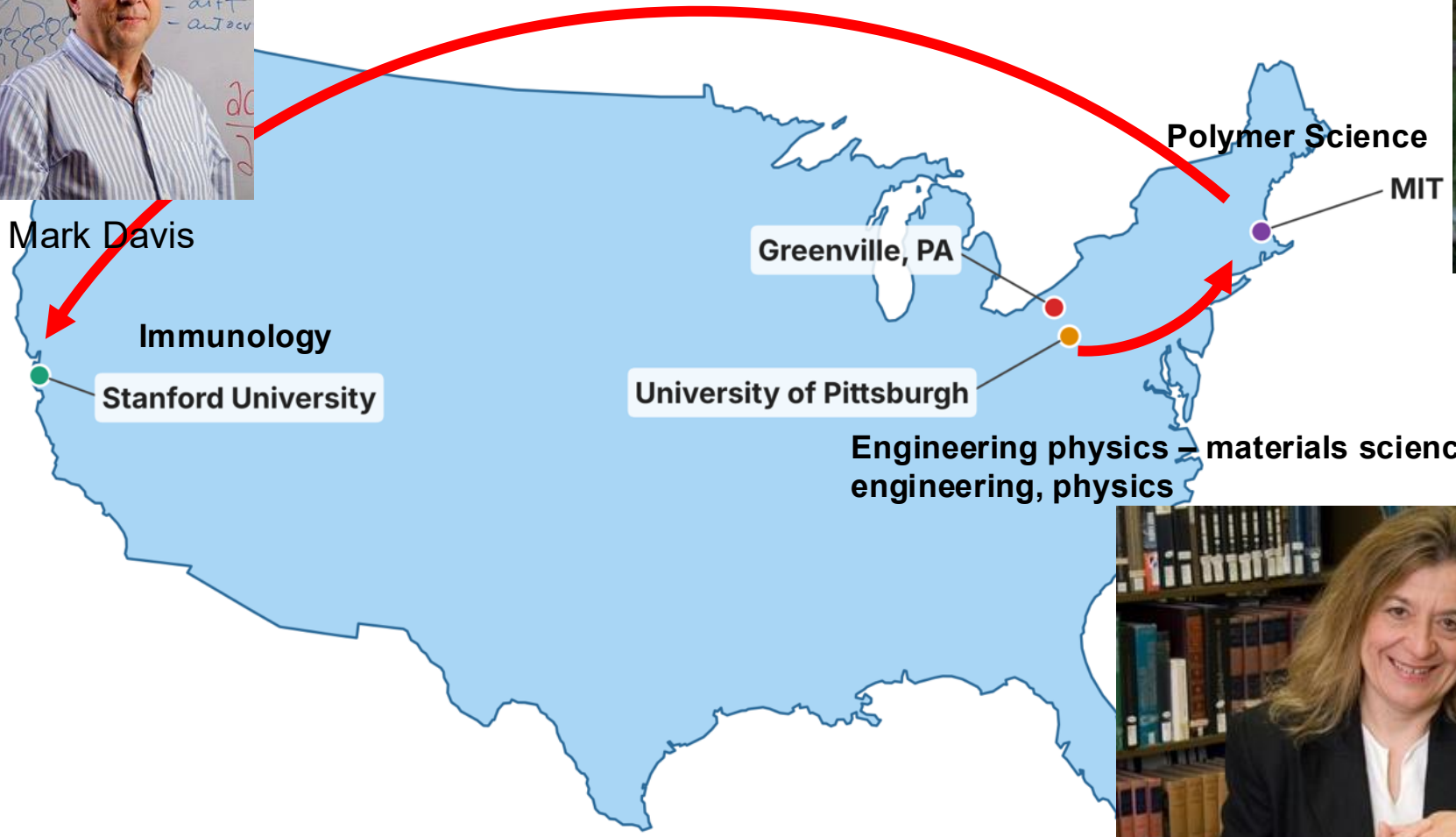
Anne Mayes



Linda Griffith



Anna Balazs



Luck is when preparation meets opportunity

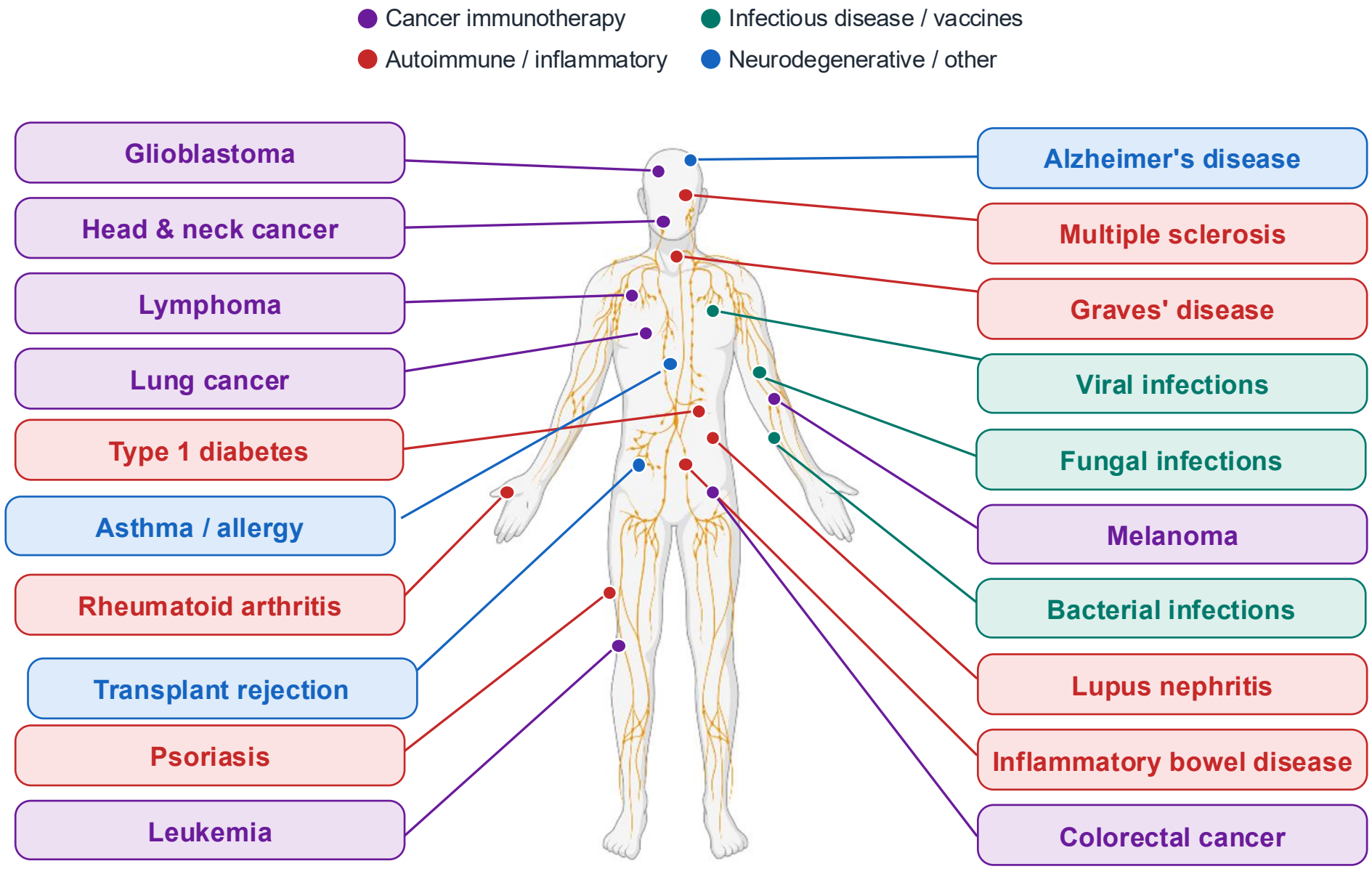
– Neil Peart



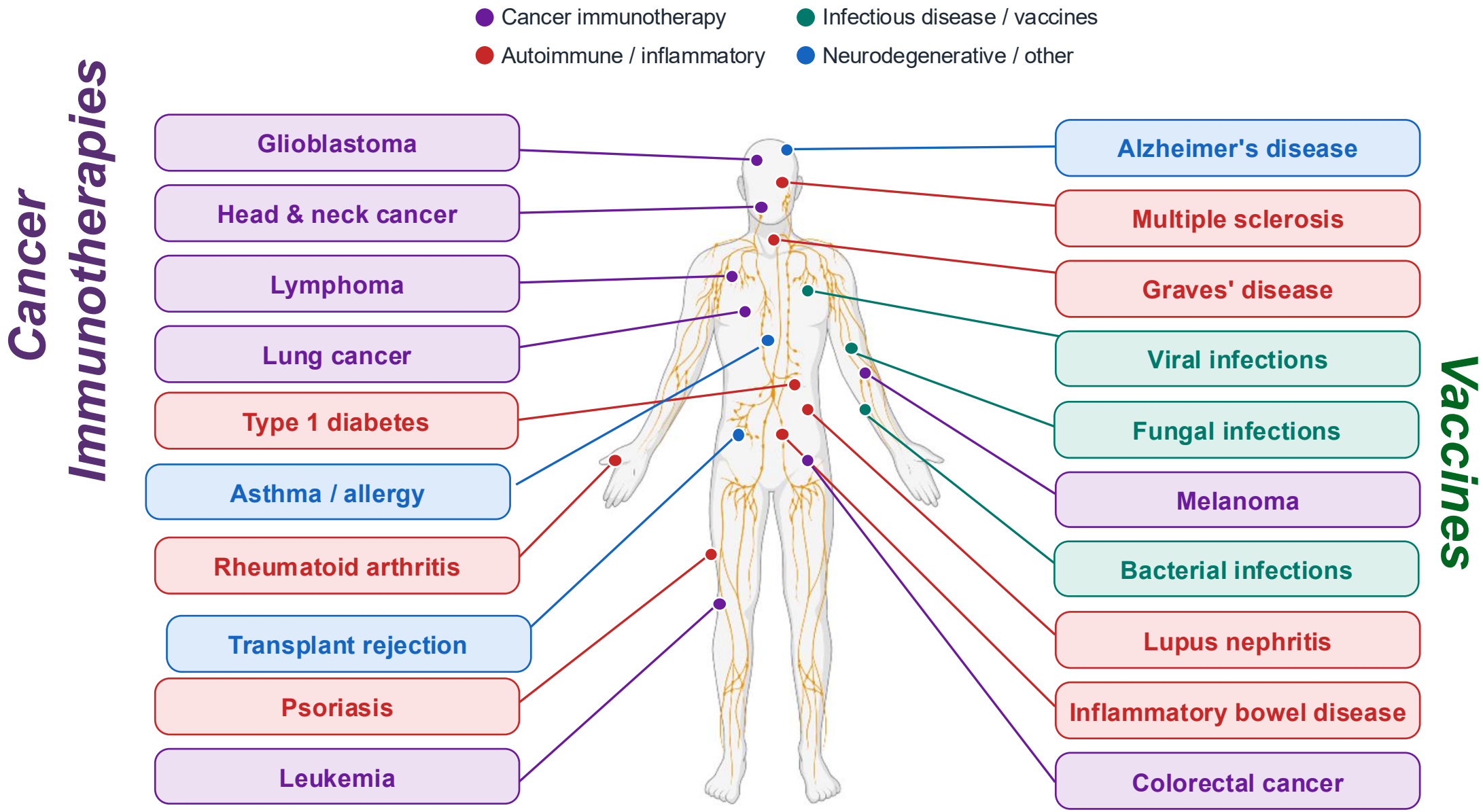
Bioengineering Immunology

Engineering Immunity

The immune system plays critical roles in health and disease

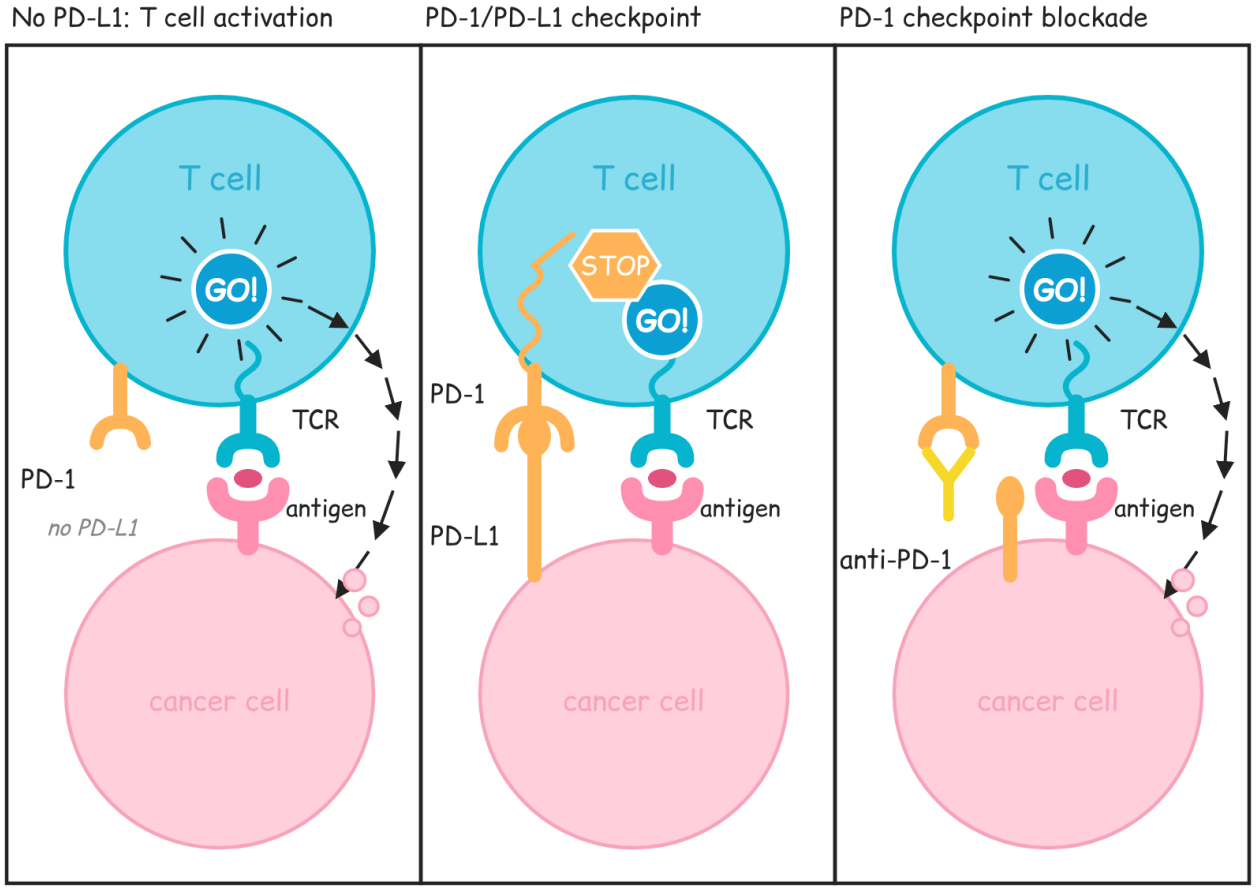


…and this has motivated the development of medicines that act on or through the immune system



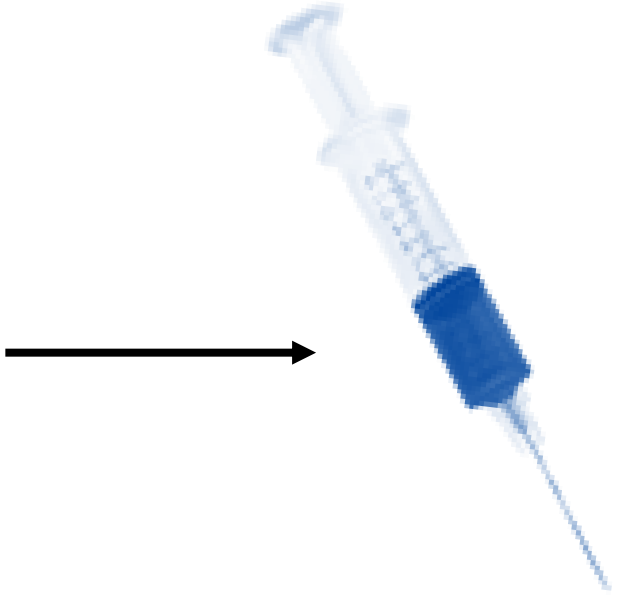
Most immunotherapy drugs are developed by identifying a signal that needs to be turned on or blocked on a specific subset of immune cells

Example: The most common cancer immunotherapy – “checkpoint blockade”



The drug!





Schematic modified from: https://www.ucir.org/therapies/checkpoint-blockade

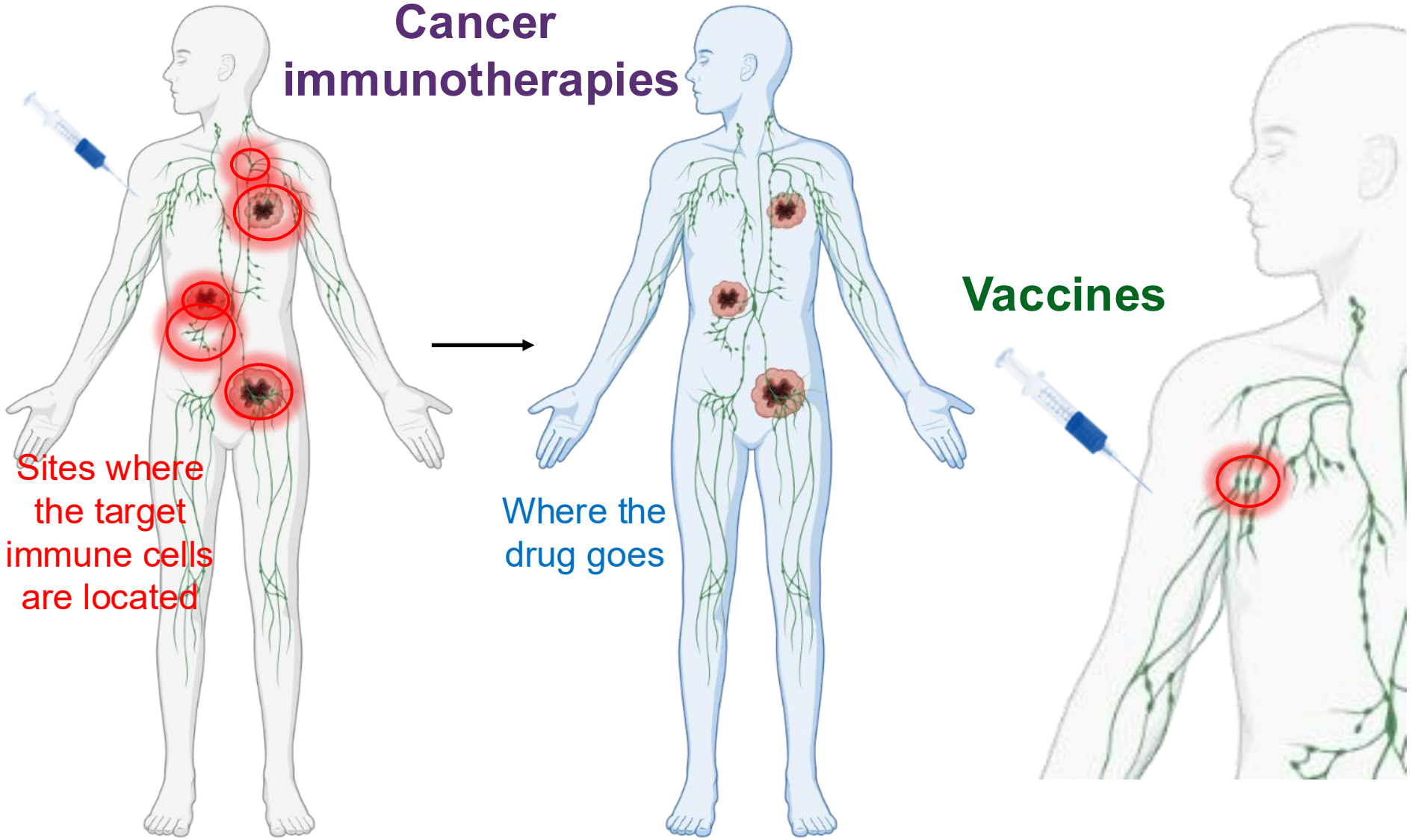
However, much less design goes into how we deliver the drug to the patient

But for a **drug** to be an effective **therapy**, it must be in the <u>right place for the right time</u>:

(1) Reach the cells/ tissues where it is needed

(2) Avoid stimulating cells it shouldn't!

(3) Persist for the right duration



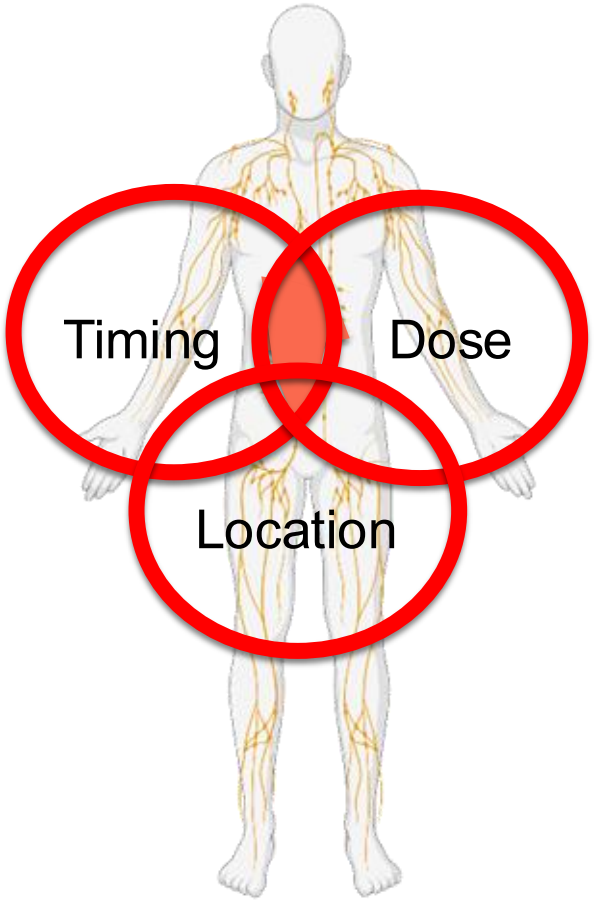
Graphic made with biorender.com

Key theme of our work:

Engineering the where, when, and how much of immune stimulation

Vaccines

- single-shot vaccine technologies
- vaccines that home to lymph nodes
- next-generation vaccine adjuvants
- “smart” mRNA vaccines



Basic research in the lab

Translation to the Clinic

Cancer immunotherapy

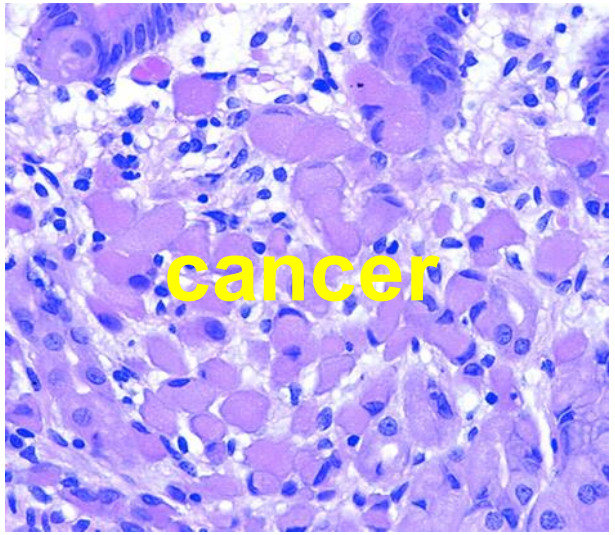
- Designing immune cell-targeted cytokines
- Engineering immune cells directly in the body
- Targeting therapeutics to tumors
- Cancer vaccines

Today's talk:



Zanetti et al. *PLoS pathogens* (2006)

- What is a vaccine?
- Solving a vaccine mystery
- A new way to dose vaccines that may help us reach an HIV vaccine



J Med Genet 2010;**47**:433-435

- Applying technology from HIV vaccines to attack cancer

What makes up a vaccine?

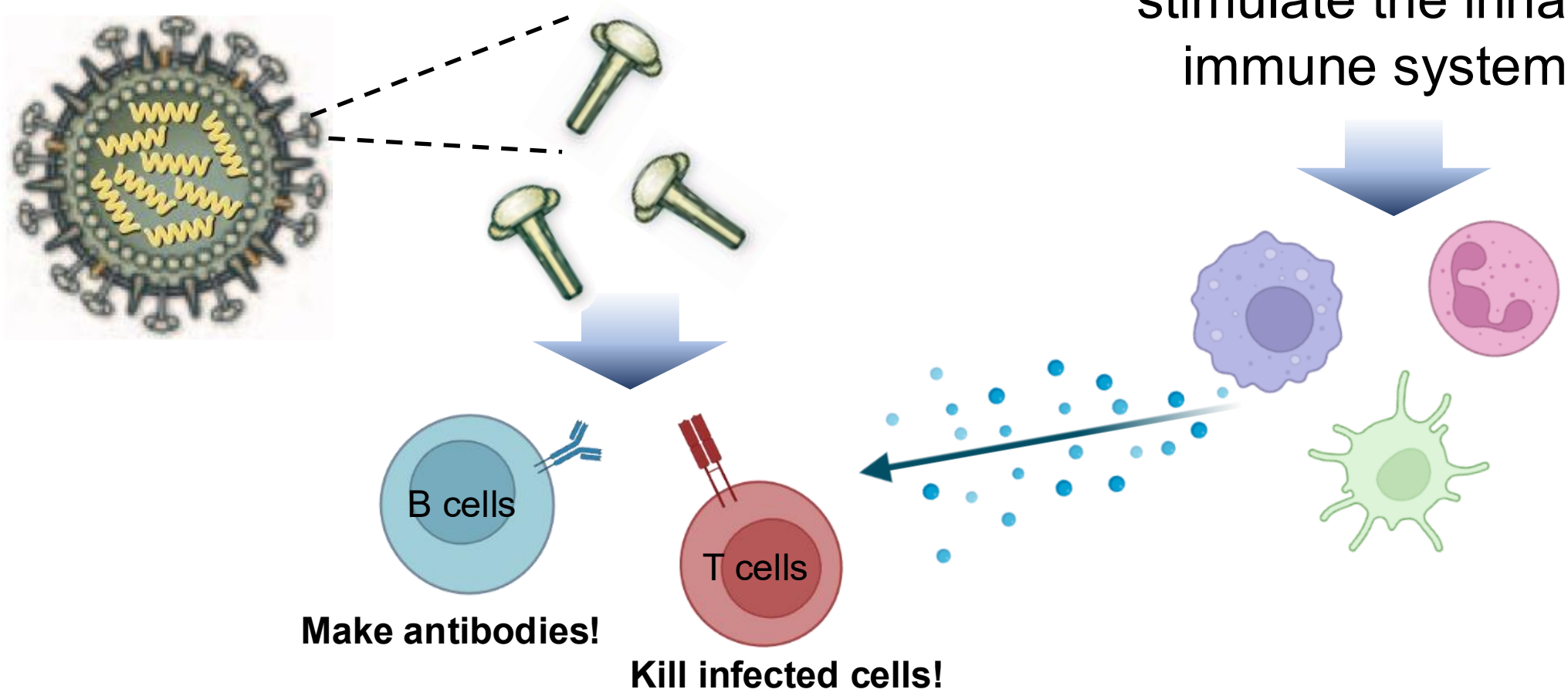
antigen

What the immune system must recognize for protective immunity

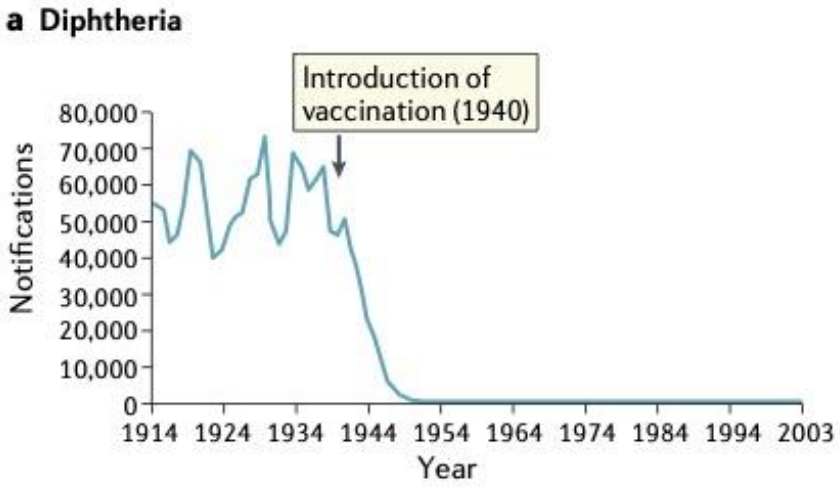
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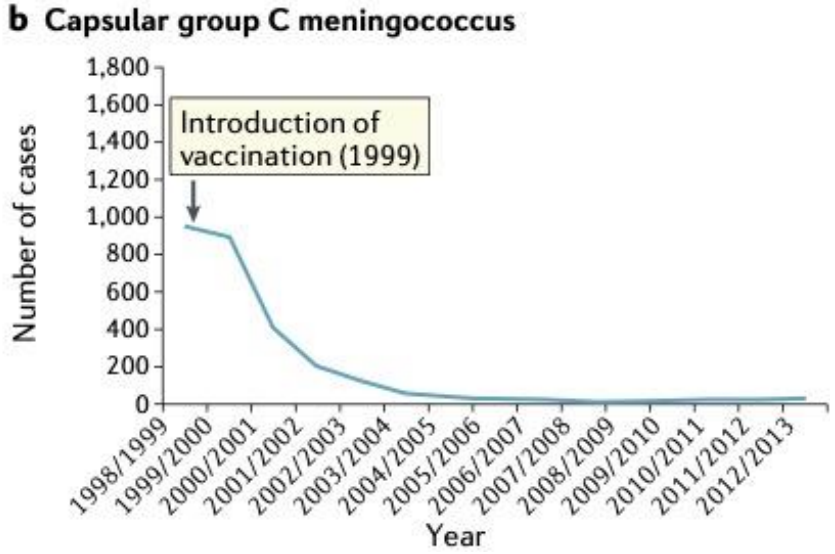
adjuvant

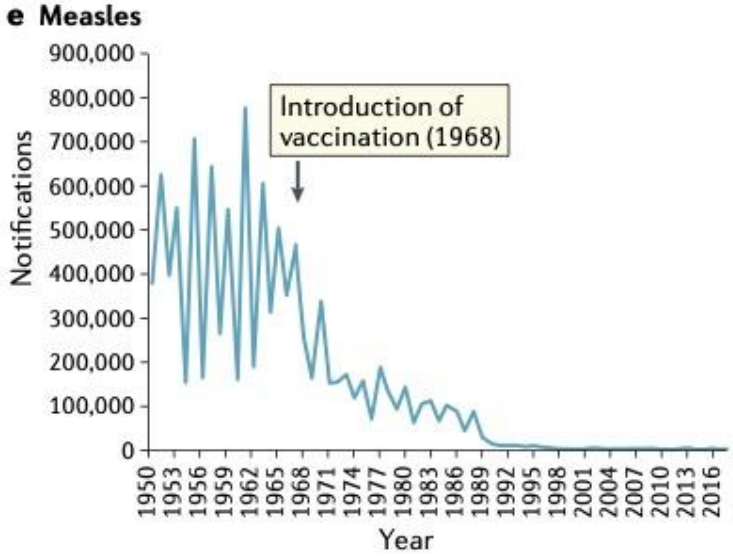
Added to the vaccine to stimulate the innate immune system



the power of vaccines for improving global health



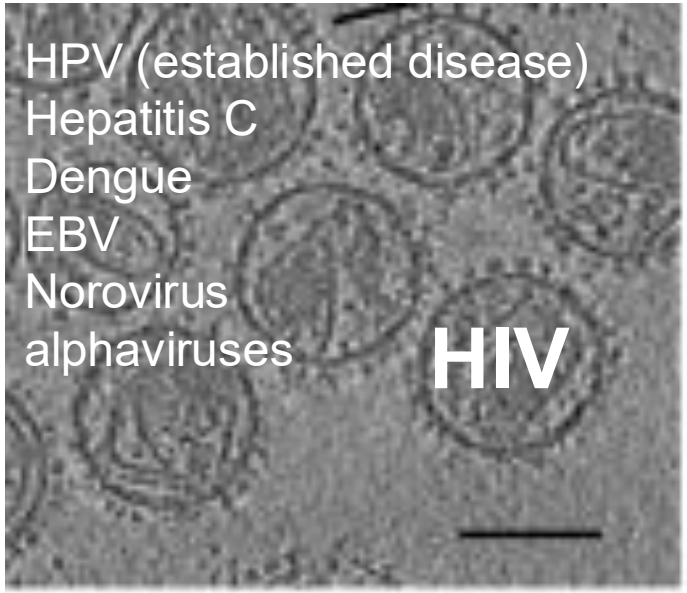




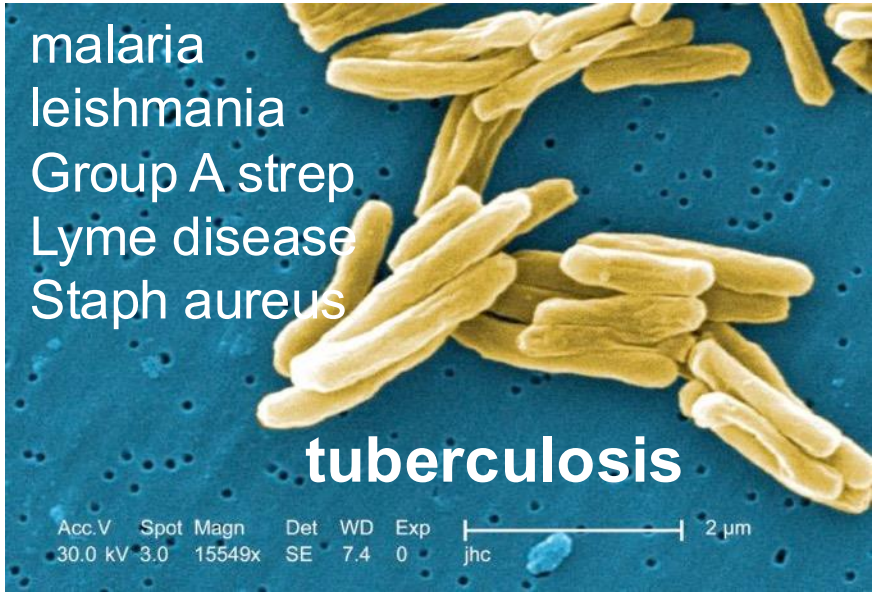
Disease	Pre-vaccine Cases: 20th century	Deaths in 2002
Smallpox	4.81 million	0
Diphtheria	17.60 million	2
Tetanus	0.13 million	13
Mumps	1.52 million	236
Pertussis	1.47 million	6632
Rubella	4.77 million	20

Pollard and Bijker *Nat. Rev. Immunol*. 2021; Nabel *NEJM* (2013)

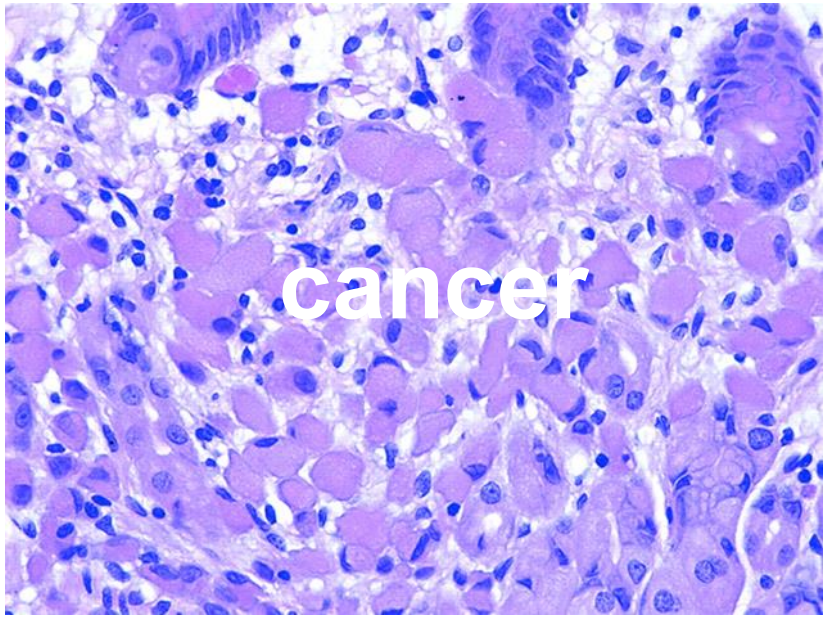
However, many diseases remain unsolved challenges for vaccination:



Zanetti et al. *PLoS pathogens* (2006)



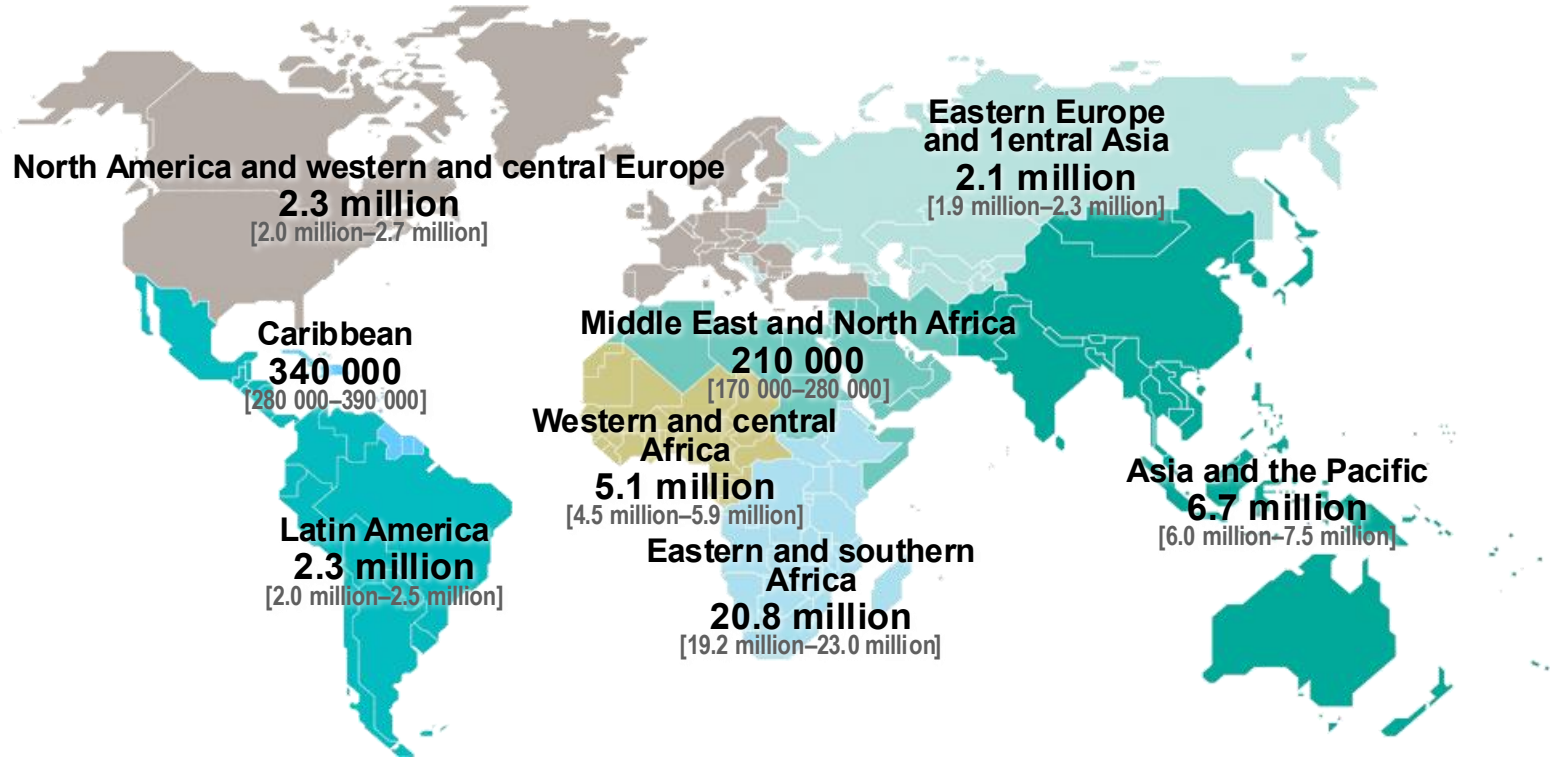
Tuberculosis bacteria
Photo: Janice Haney Carr,Public Health Information Library



J Med Genet 2010;**47**:433-435

The global HIV epidemic and HIV vaccine challenge

Adults and children estimated to be living with HIV | 2023



1.3 MILLION

people were newly infected with HIV in 2023

39.9 MILLION

people were living with HIV in 2023

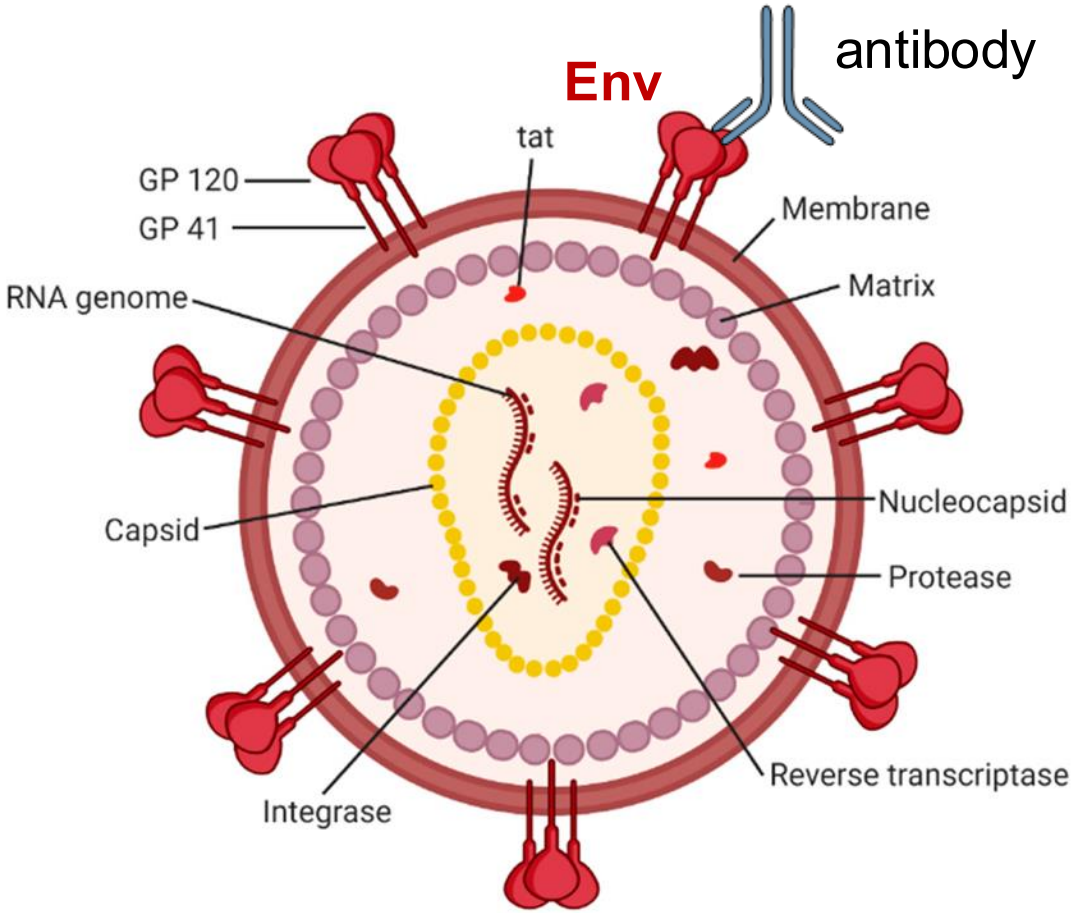
630 THOUSAND

people died of AIDS-related illnesses in 2023

UNAIDS

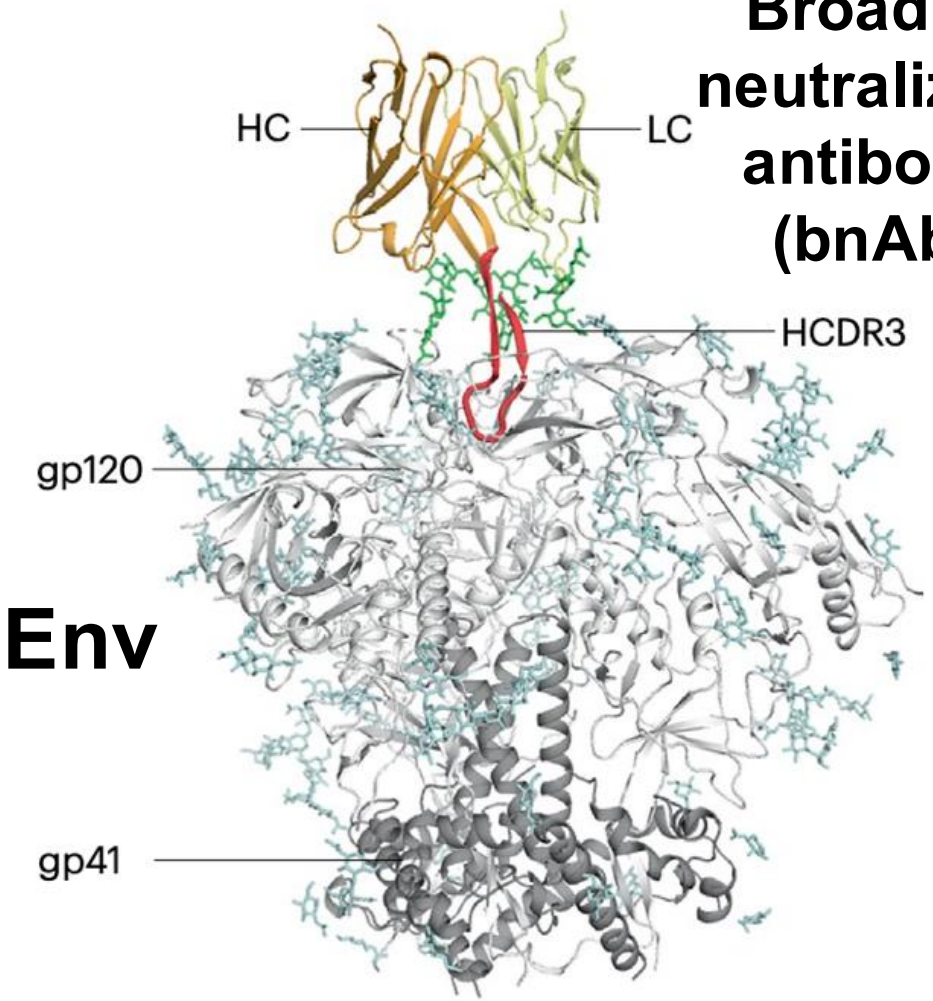
The global HIV epidemic and HIV vaccine challenge

HIV Env: the target for protective antibody responses



Rossi et al. *Life* 2021

Broadly-neutralizing antibody (bnAb)

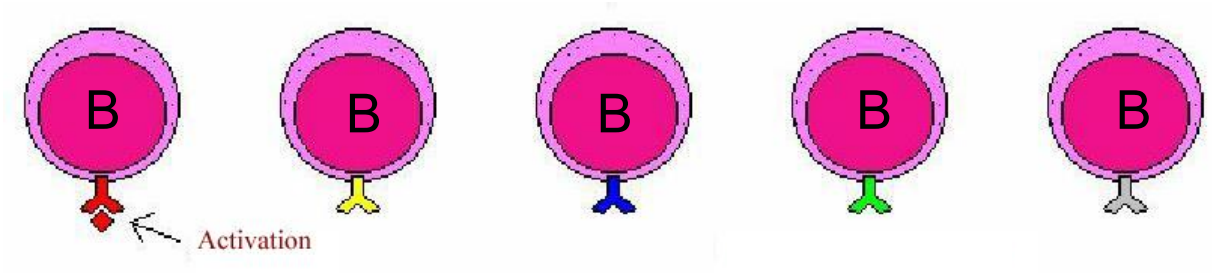


Klasse et al. *Nat. Rev. Microbiol*. 2025;
Haynes et al. *Nat. Rev. Immun*. 2022
Klasse et al. *Cell Host & Microbe* 2020

Anatomy of vaccine immunology

B cell responses – e.g., for protective antibodies against infection

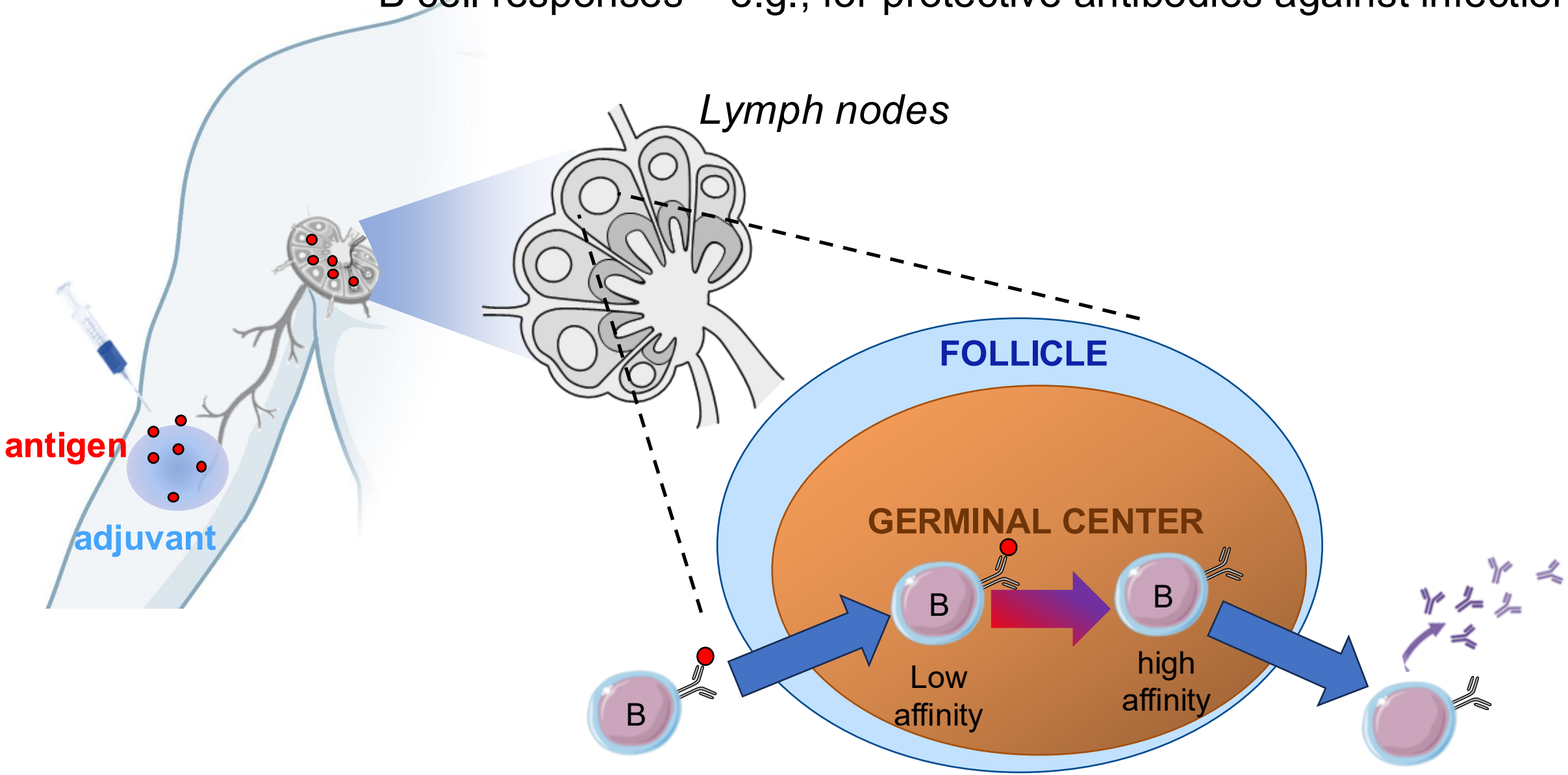
Each of us has millions of B cells that each express a unique antibody receptor:



http://doctor-jones.co.uk/Immunology/Tutorial/Clonal%20Selection%20Theory%20-%20larger%20image.jpg

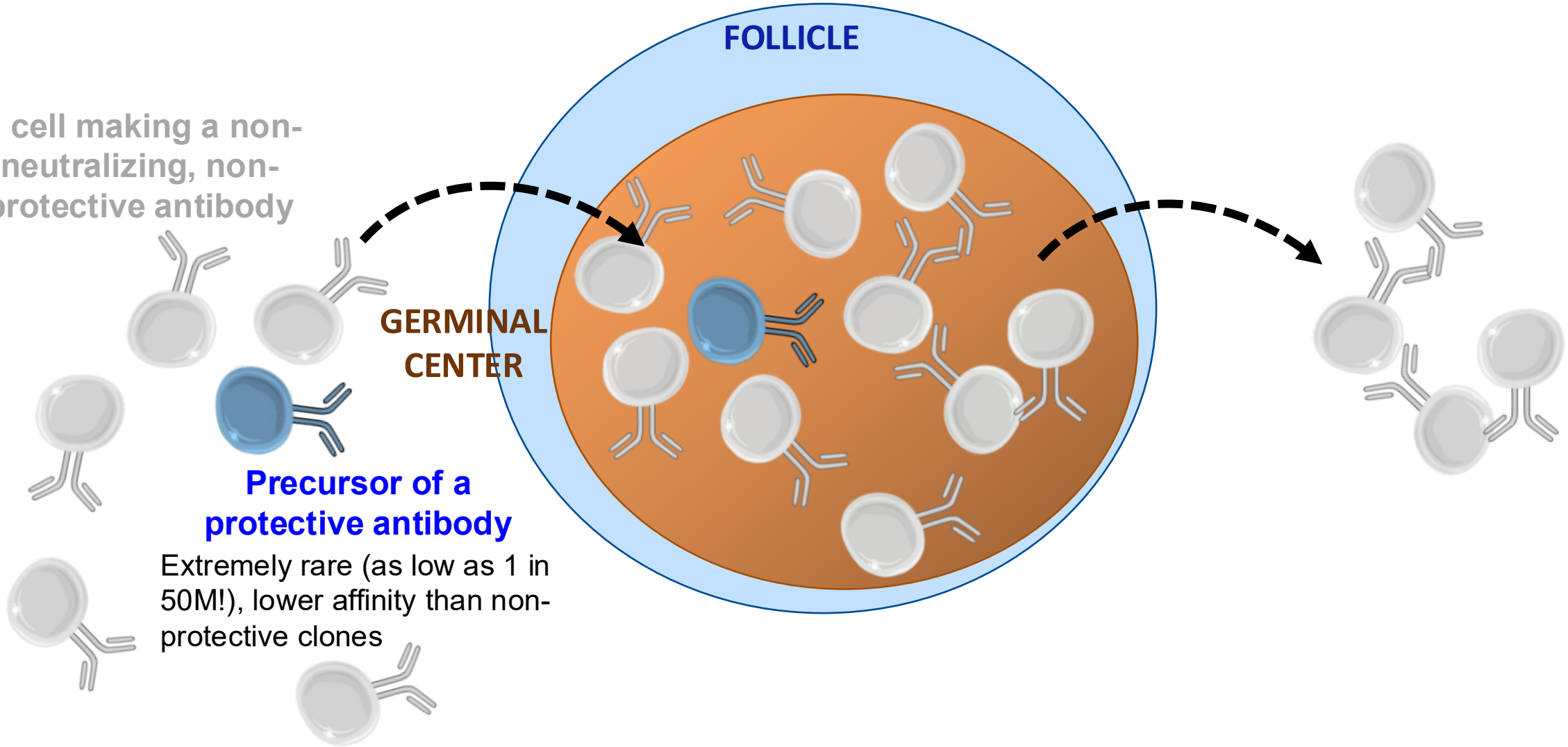
Anatomy of vaccine immunology

B cell responses – e.g., for protective antibodies against infection



A key challenge in HIV vaccine design:

Precursor B cells with the right genetics to generate bnAbs are very rare and can be readily outcompeted in germinal centers



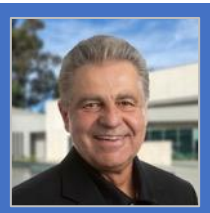
The Scripps Consortium for HIV/AIDS Vaccine Development



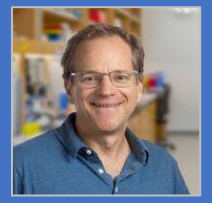
Dennis Burton
Scripps Research



Ian Wilson
Scripps Research



Rich Wyatt
Scripps Research



Bill Schief
Scripps Research



Bryan Briney
Scripps Research



Andrew Ward
Scripps Research



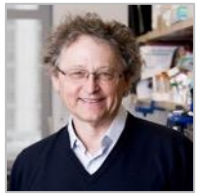
Lars Hangartner
Scripps Research



James Paulson
Scripps Research



Devin Sok
IAVI / Scripps Research



Michel Nussenzweig
Rockefeller University



Shane Crotty
LJI



Bruce Walker
Ragon Institute



Rafi Ahmed
Emory University



Facundo Batista
Ragon Institute



Max Crispin
University of Southampton



Gunilla Karlsson Hedestam
Karolinska Institutet



Peter Gilbert
Fred Hutchinson CRC



Daniel Kaufmann
University of Lausanne



Penelope Moore
University of the Witwatersrand



Guido Silvestri
Emory University



Bali Pulendran
Stanford University



Leonidas Stamatatos
Fred Hutchinson CRC



Darrell Irvine
MIT



Julie McElrath
Fred Hutchinson CRC



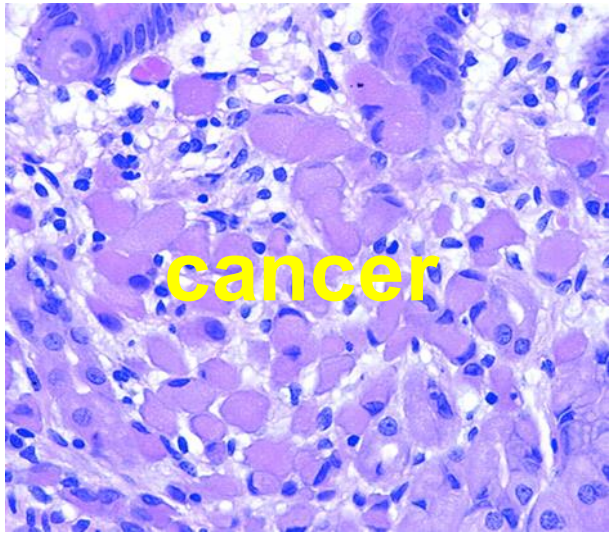
Sangeetha Sagar
IAVI

Today's talk:



Zanetti et al. *PLoS pathogens* (2006)

- What is a vaccine?
- **Solving a vaccine mystery**
- A new way to dose vaccines that may help us reach an HIV vaccine

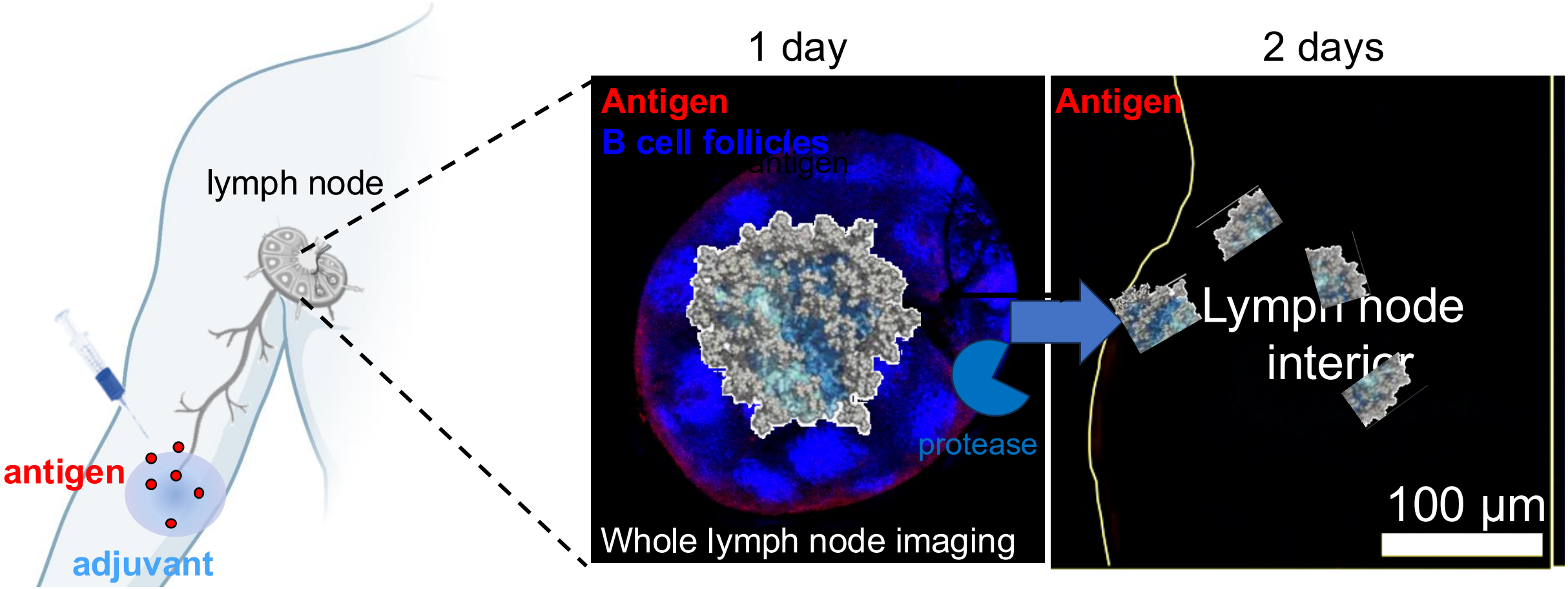


J Med Genet 2010;**47**:433-435

- Applying technology from HIV vaccines to attack cancer

A vaccine mystery:

Antigen often clears very rapidly in a primary immunization

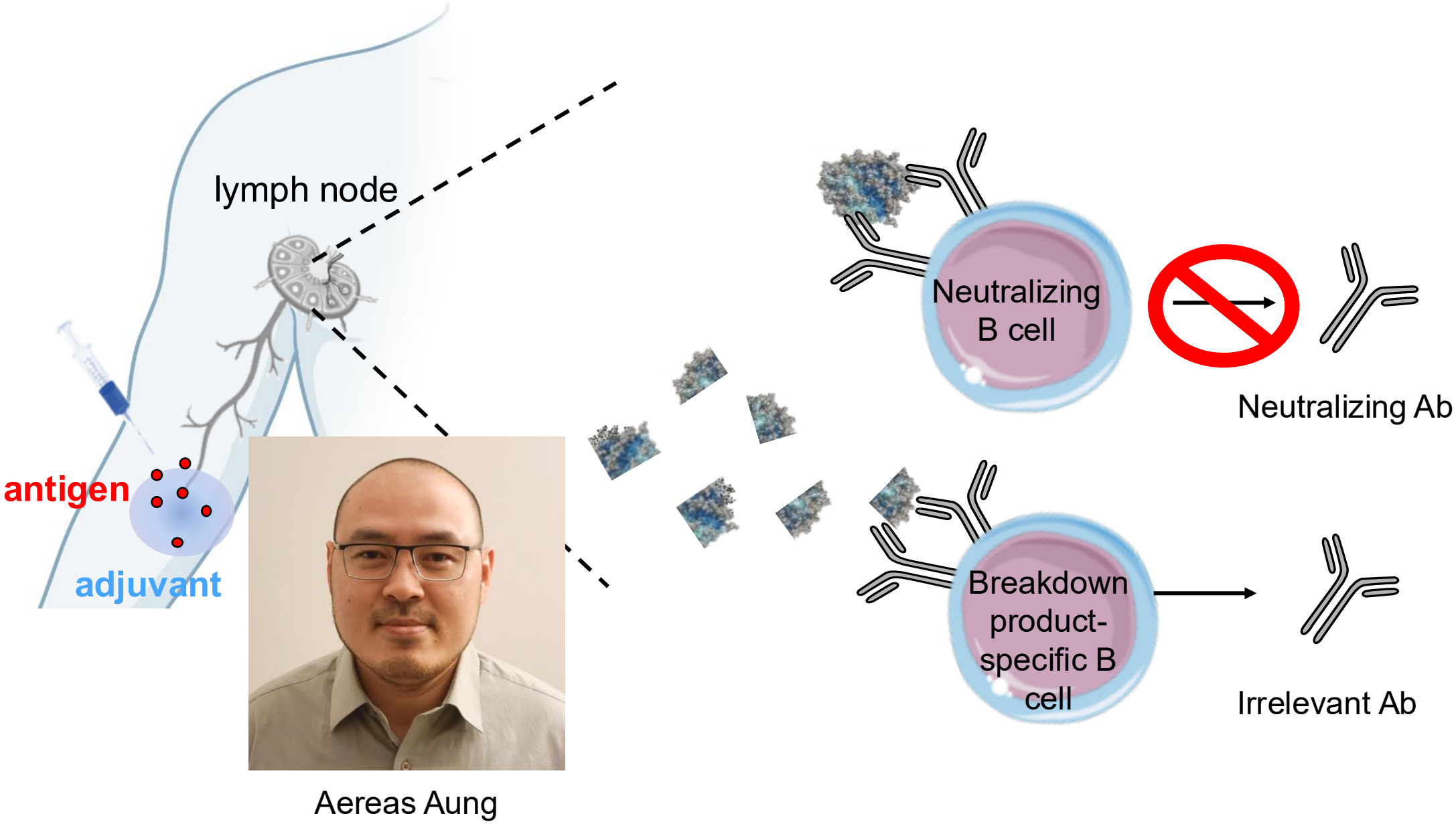


Potential mechanisms of antigen clearance:

1. Carried away by lymph?
2. Internalized by cells in the lymph node?
3. Extracellular breakdown?

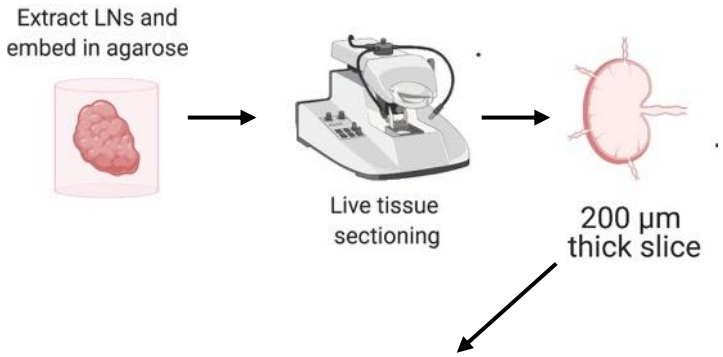
A vaccine mystery:

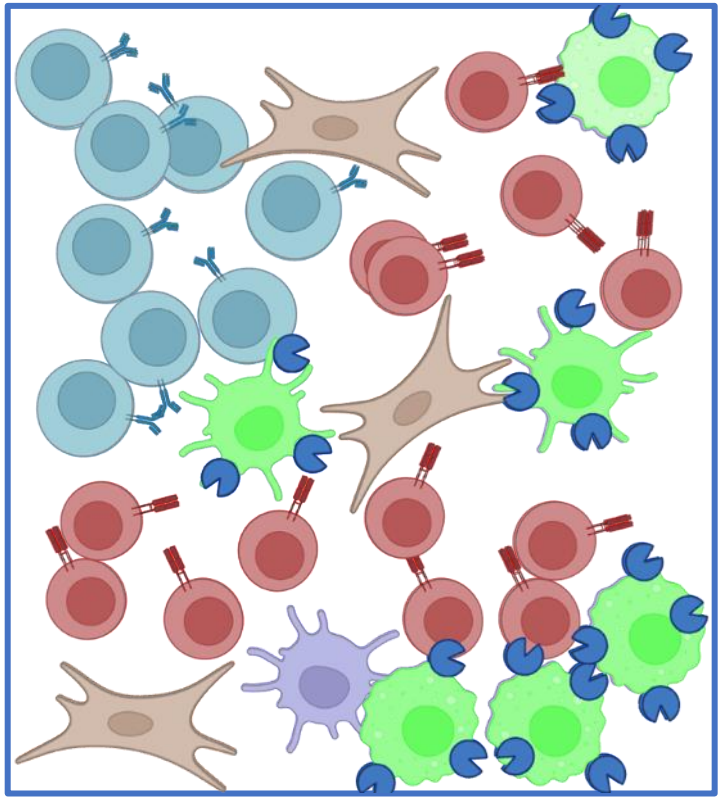
Antigen often clears very rapidly in a primary immunization



Aereas Aung

Visualizing protease activity in lymph nodes



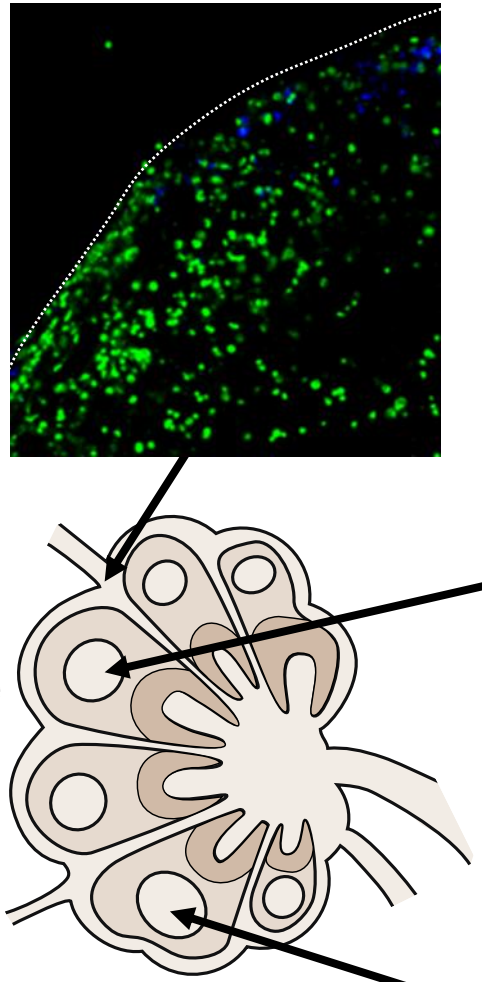


Non-stick
Fluorescent
peptide

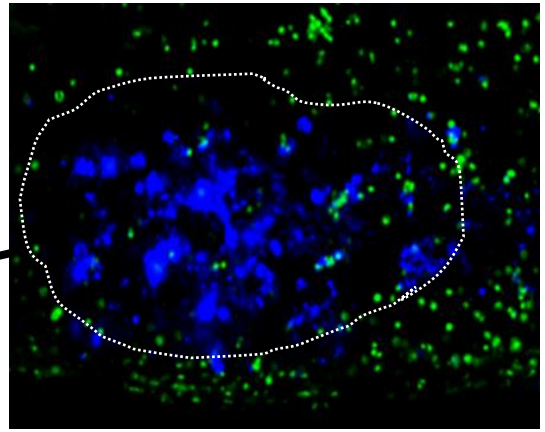
protease

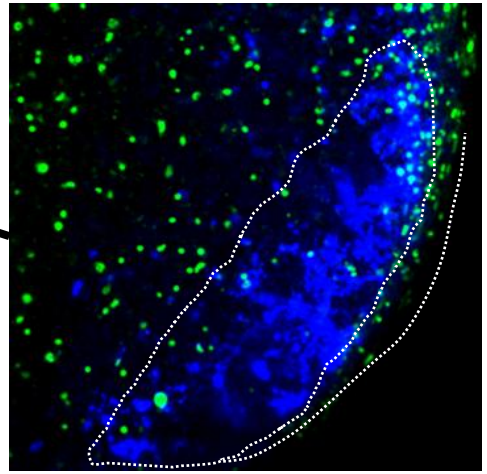
sticky
Fluorescent
peptide

microscope



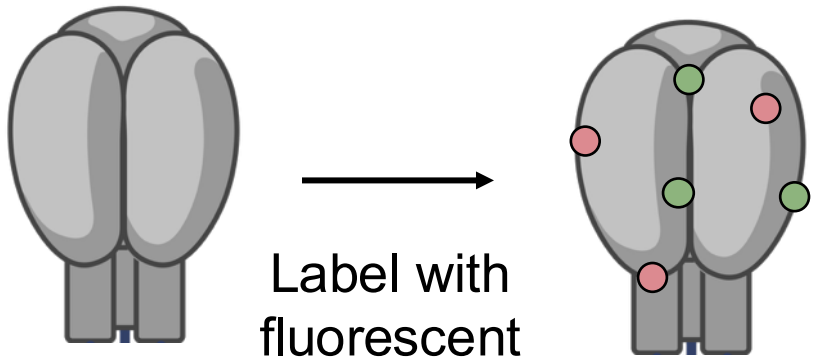
Protease+ cells
follicles



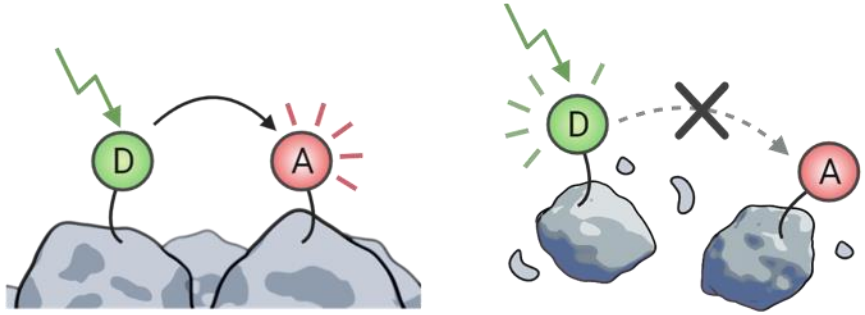


If proteases are active in the lymph node, what happens to our vaccine antigen?

Env antigen

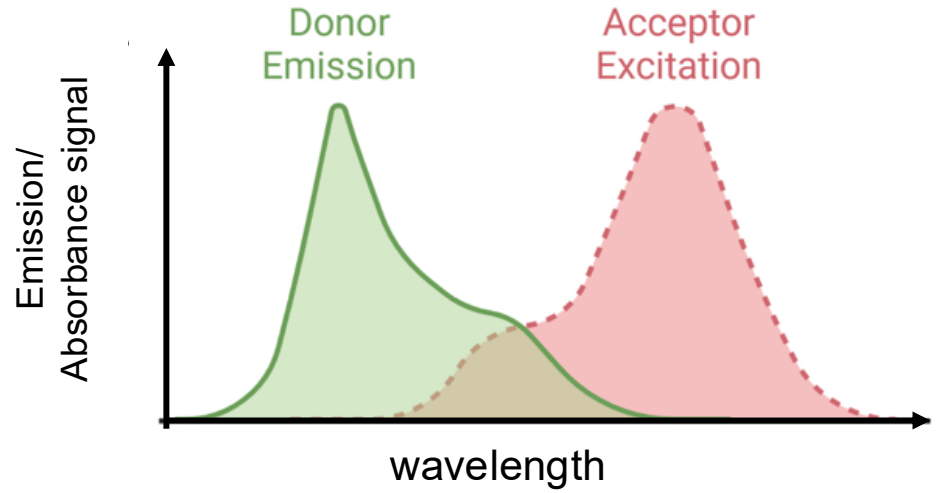


Label with fluorescent dyes



Intact Antigen
= FRET

Degraded Antigen
= No FRET



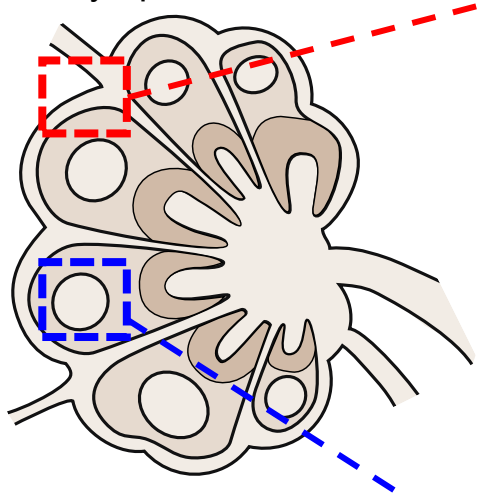
FRET = fluorescence resonance energy transfer

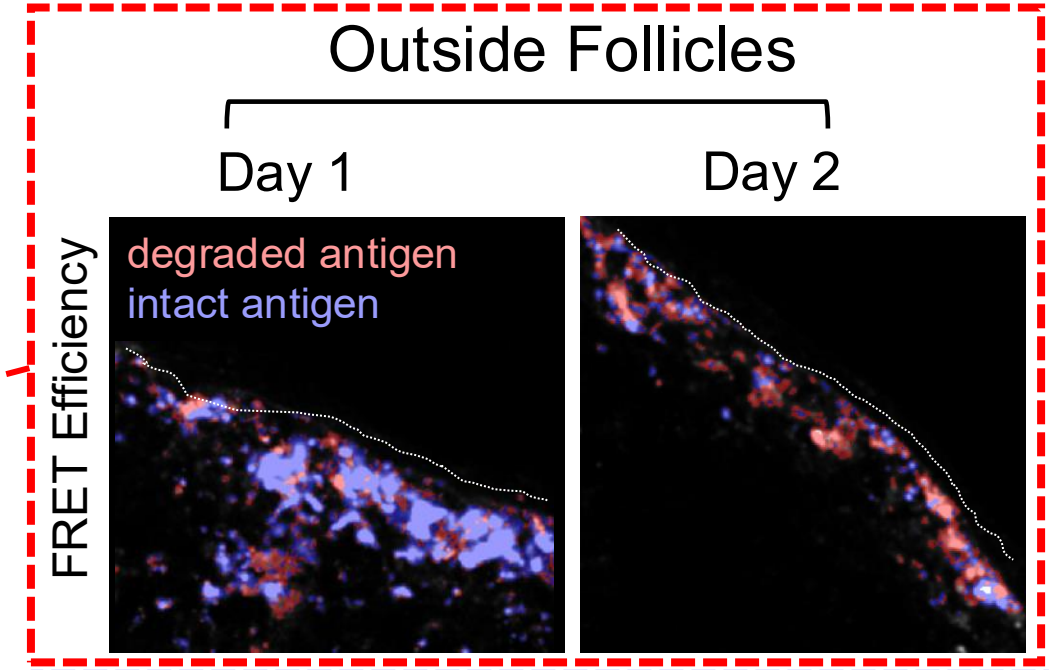
Visualizing the fate of vaccines in lymph nodes

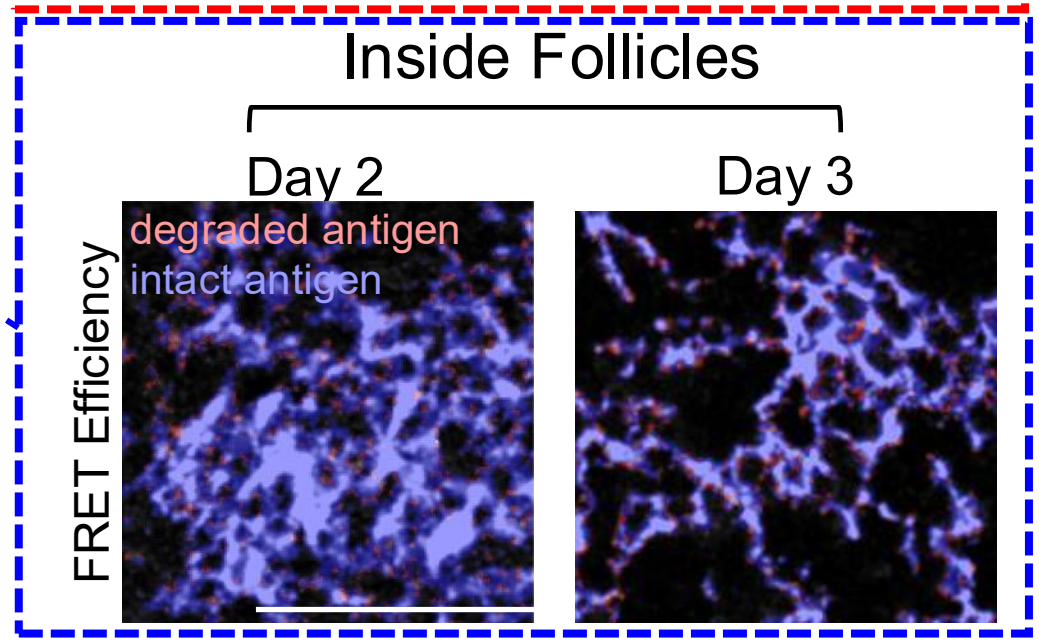


immunize

Image draining lymph node





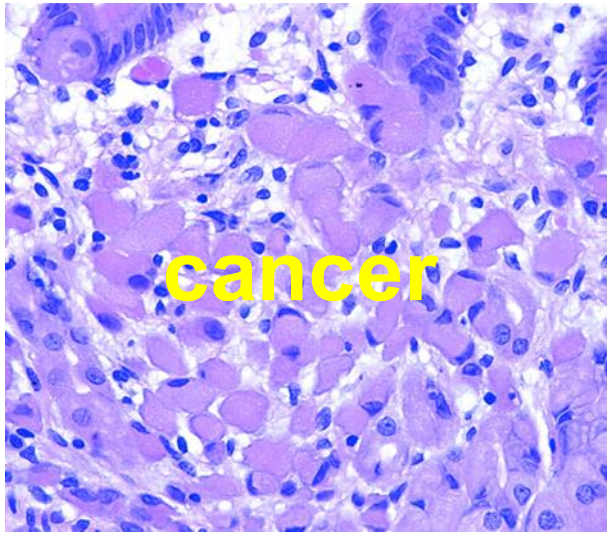


Aung et al. *Science* 2023

Today's talk:



Zanetti et al. *PLoS pathogens* (2006)



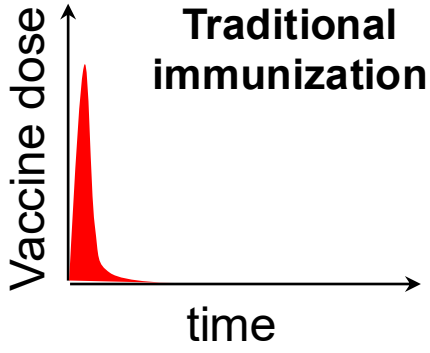
J Med Genet 2010;**47**:433-435

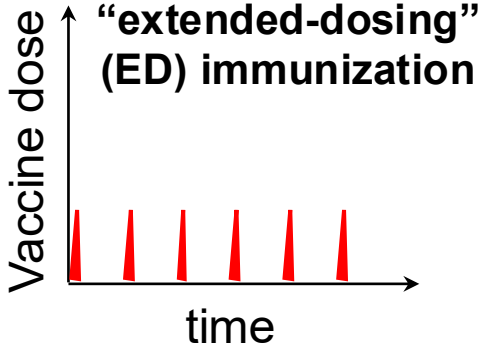
- What is a vaccine?
- Solving a vaccine mystery
- **A new way to dose vaccines that may help us reach an HIV vaccine**

  Idea: targeting vaccine antigens to B cell follicles should maximize productive antibody responses

- Applying technology from HIV vaccines to attack cancer

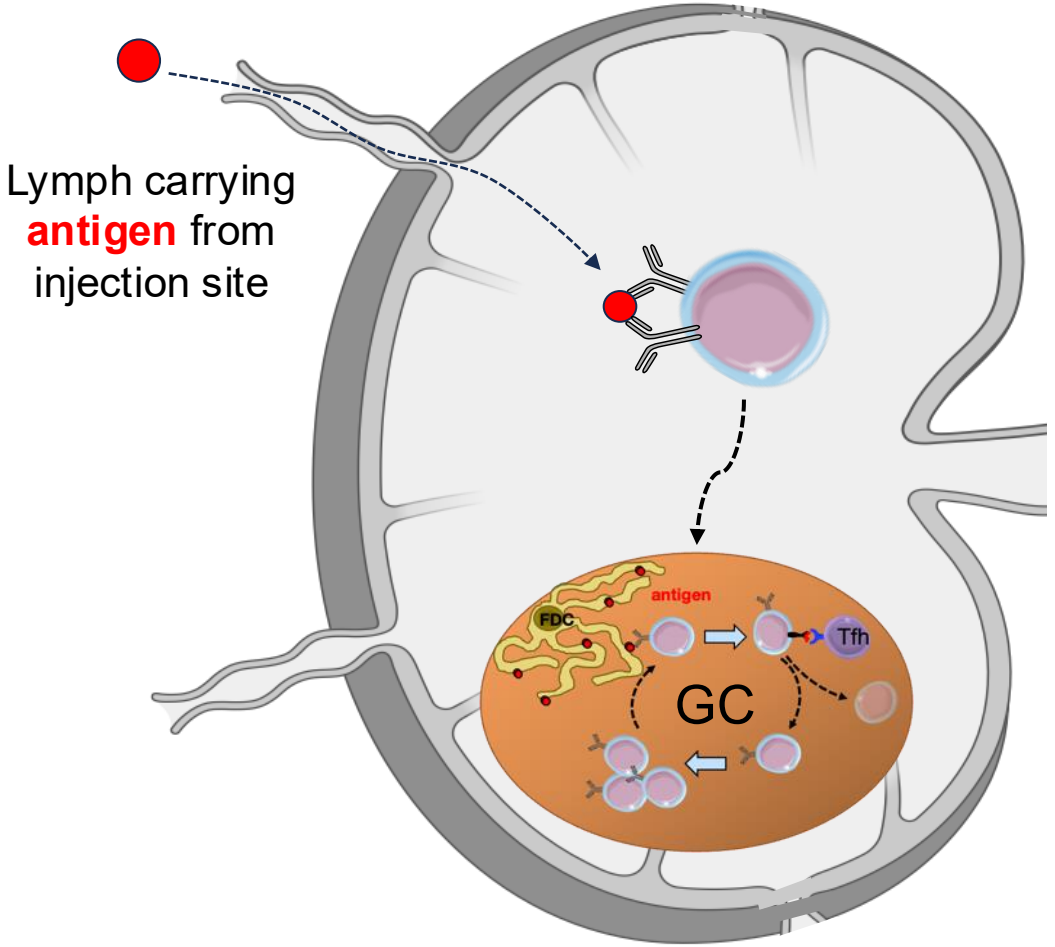
“Extended dosing” immunization to target antigen to B cell follicles





(Total dose of antigen the same in each case)

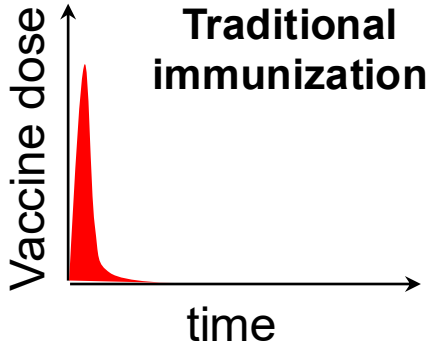
(i) Initial antigen arrival in lymph node activates B/T cells and GCs initiate

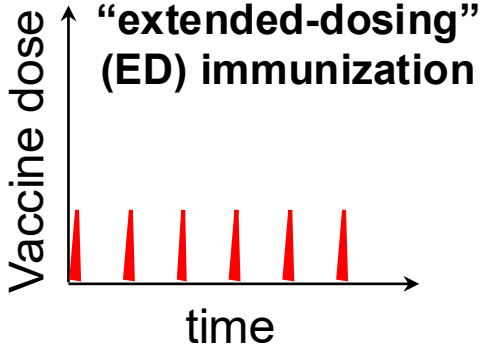




Mariane Melo

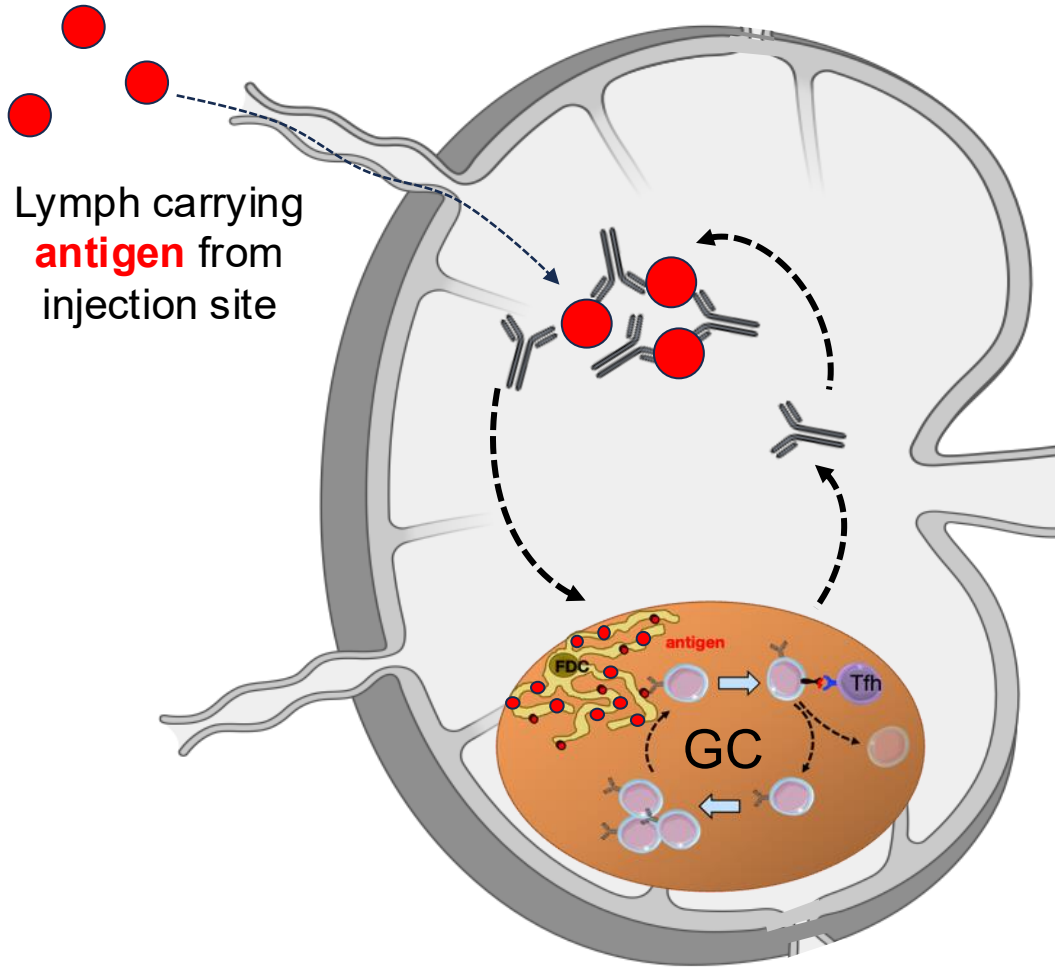
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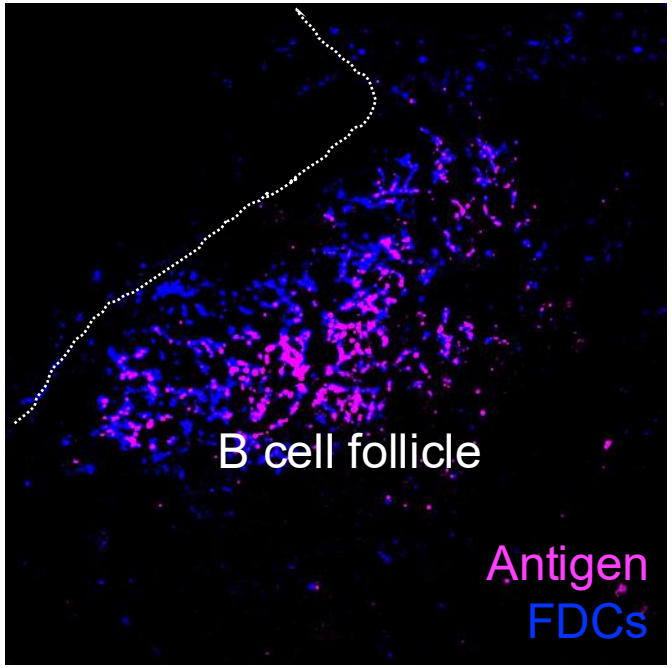
(Total dose of antigen the same in each case)

(ii) antigen continuing to arrive in LN 7-10 days later captured in immune complexes (ICs) and captured on FDCs, fueling GC reaction

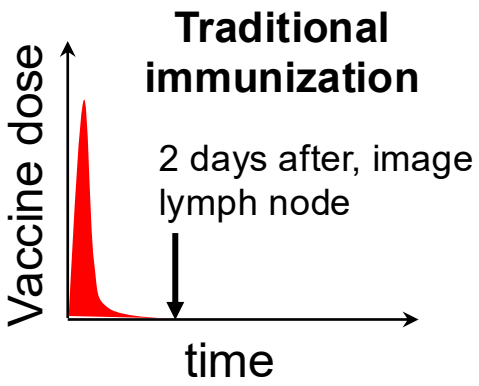


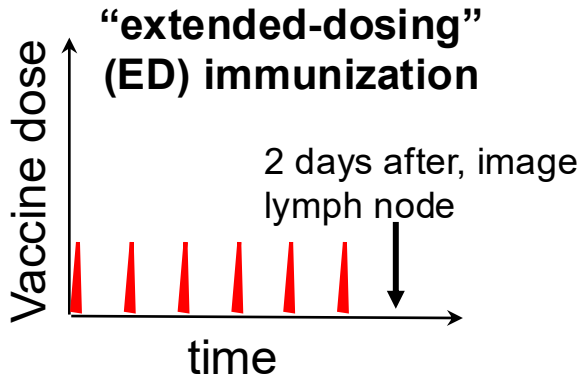


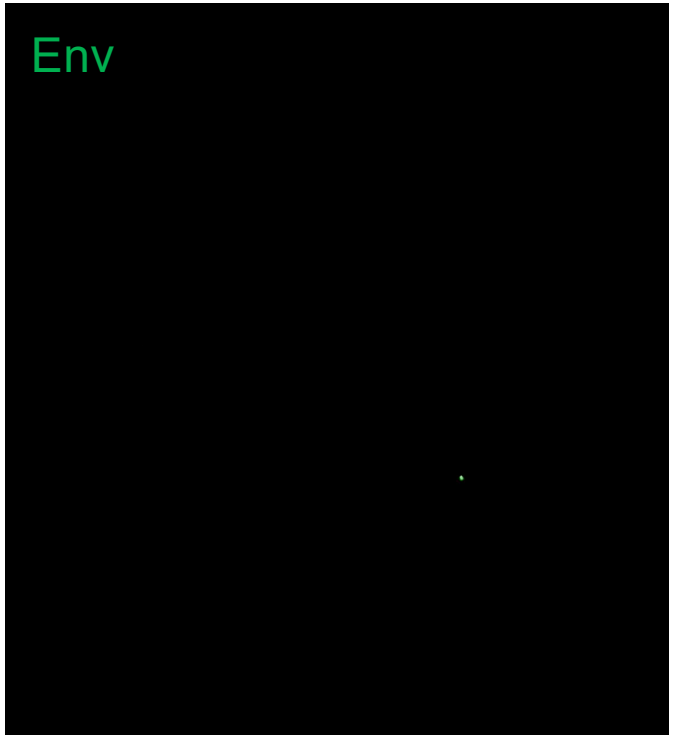
Mariane Melo

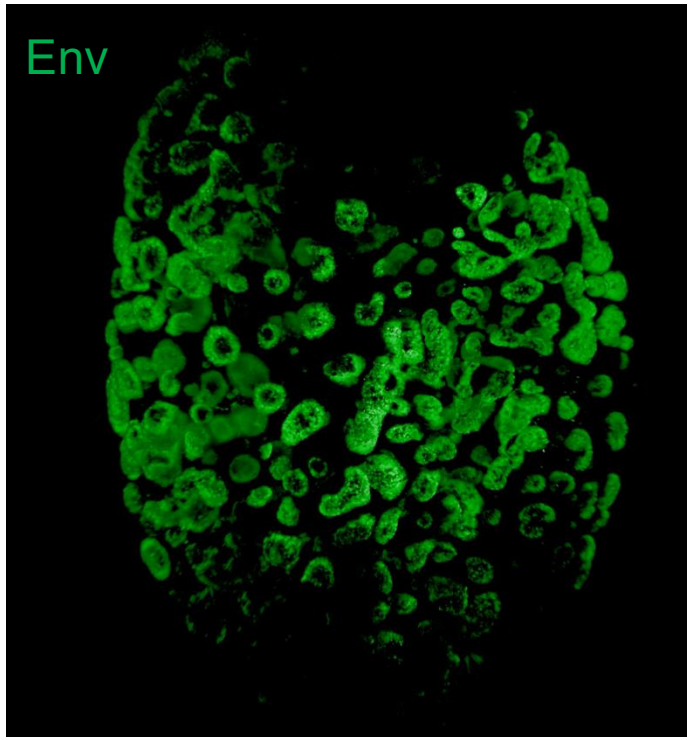


Imaging whole lymph nodes following immunization
with **fluorescently-labeled HIV Env antigen**:









5X bigger germinal centers

20X more "on target" B cells

10X greater neutralizing antibody titers

In collaboration with lab of Shane Crotty, LJI: Cirelli et al. *Cell* 2019

Luck is when preparation meets opportunity

– Neil Peart

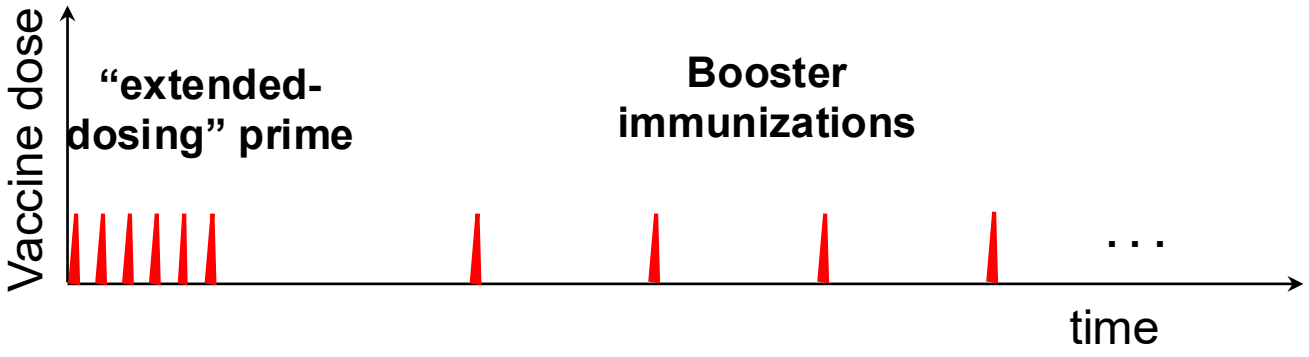


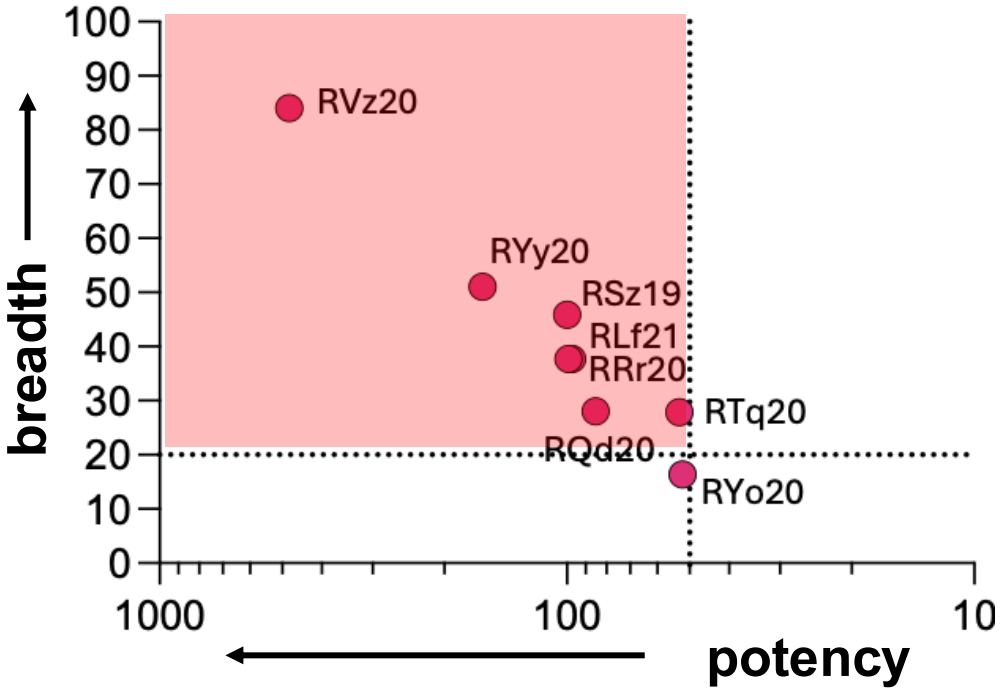
Bioengineering Immunology

Engineering Immunity

3 Studies published this past summer reported first induction of broadly neutralizing antibodies in outbred animals– all using extended-dosing priming!

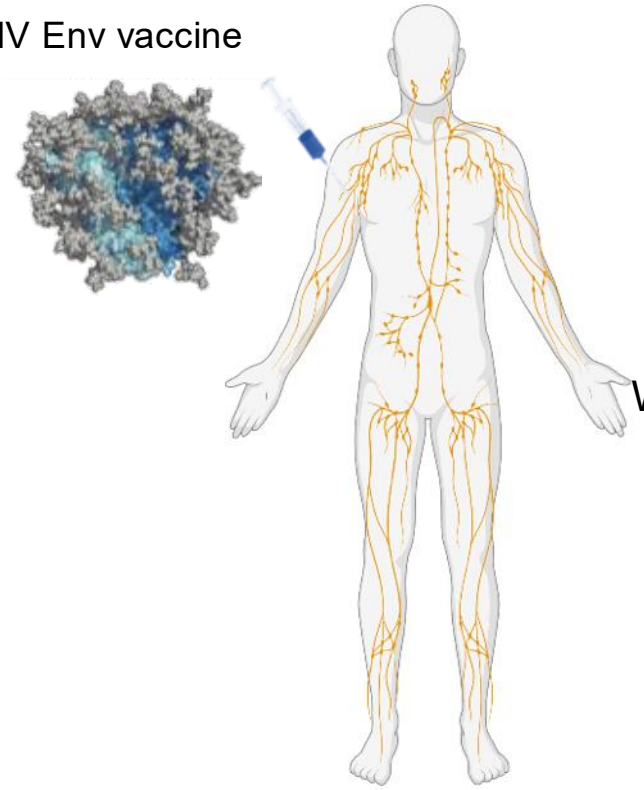
Guenaga et al. *Nature* 2026 (Rich Wyatt's lab)
Steichen, Madden et al. *Nature* 2026 (Bill Schief's lab)
Marchitto et al. *Nature* 2026 (George Shaw's lab)

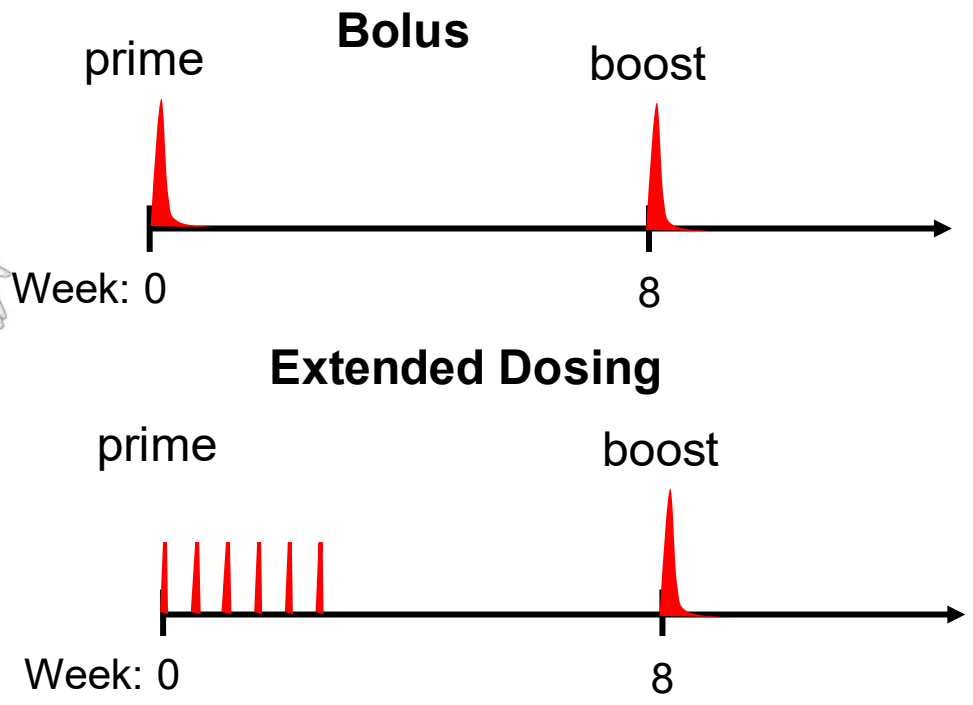




Testing extended-dosing immunization in humans

HIV Env vaccine





Extended dosing led to:

~10X more memory T cells

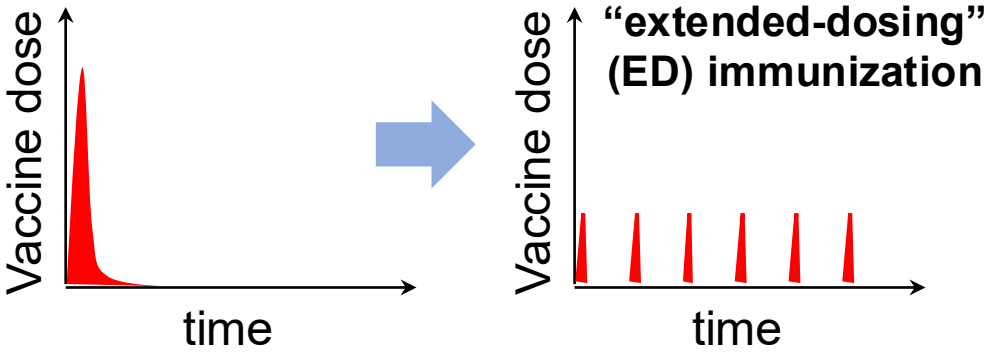
~20X more memory B cells

~20X greater antibody titers

Clinicaltrials.gov: NCT06033209

Pause for reality check:

“Extended Dosing” makes vaccines much more effective…



“extended-dosing” (ED) immunization

But…



What makes up a vaccine?

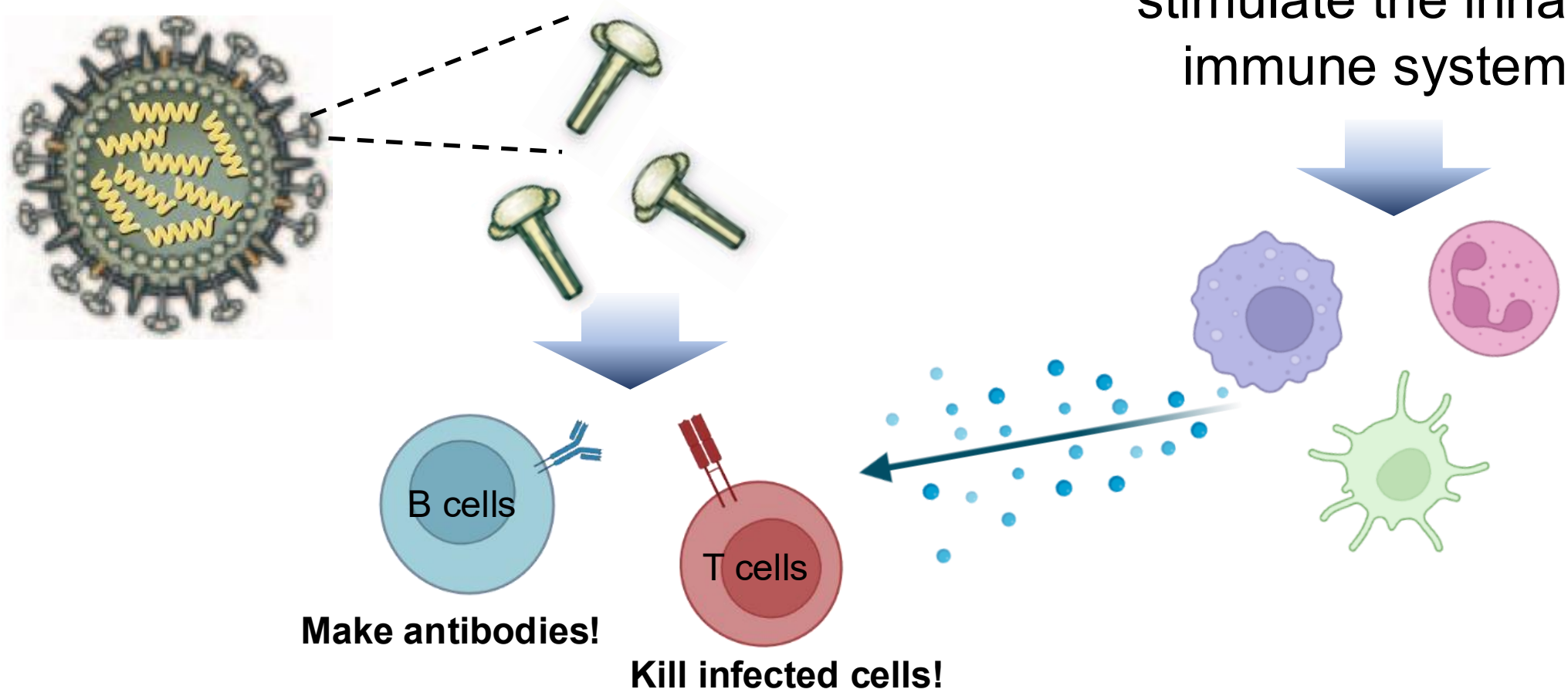
antigen

What the immune system must recognize for protective immunity

+

adjuvant

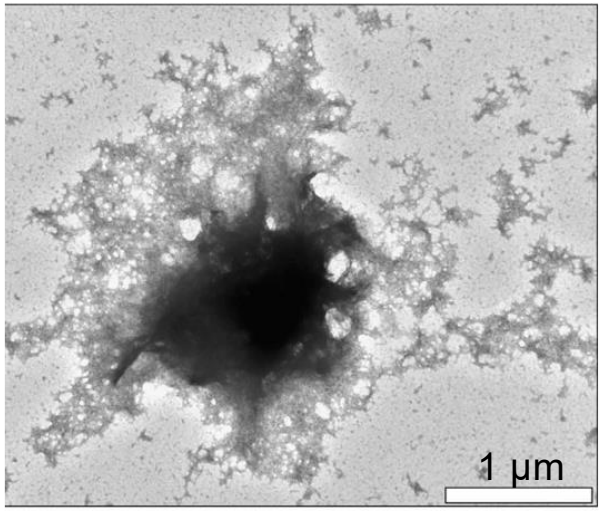
Added to the vaccine to stimulate the innate immune system



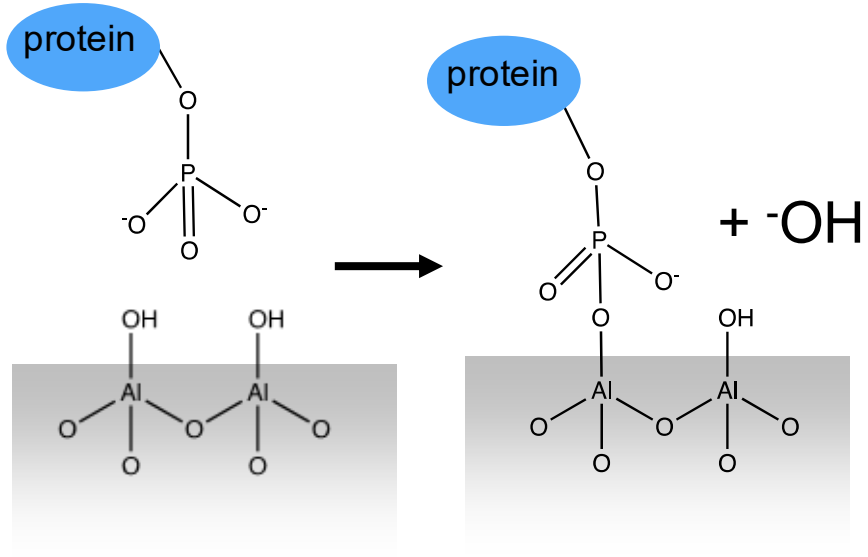
Engineering immunogen anchoring on alum via phosphoserine (pSer) tags

The most common vaccine adjuvant: alum





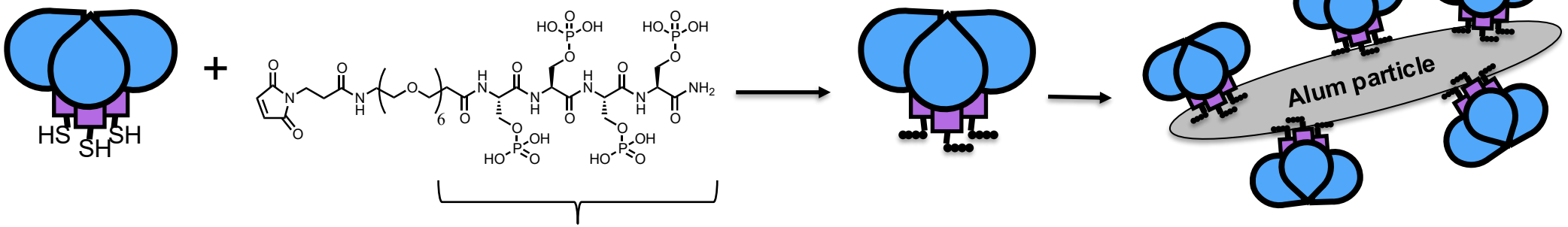
Mold et al. *Scientific Reports* (2016)





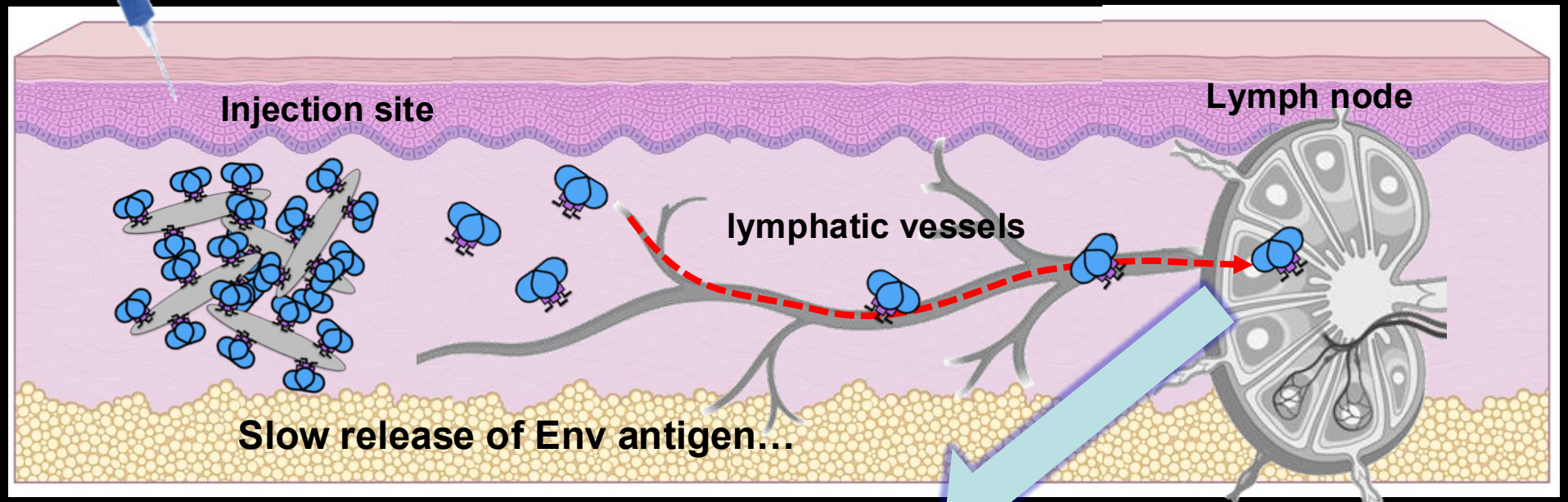
Tyson Moyer

HIV Env antigen

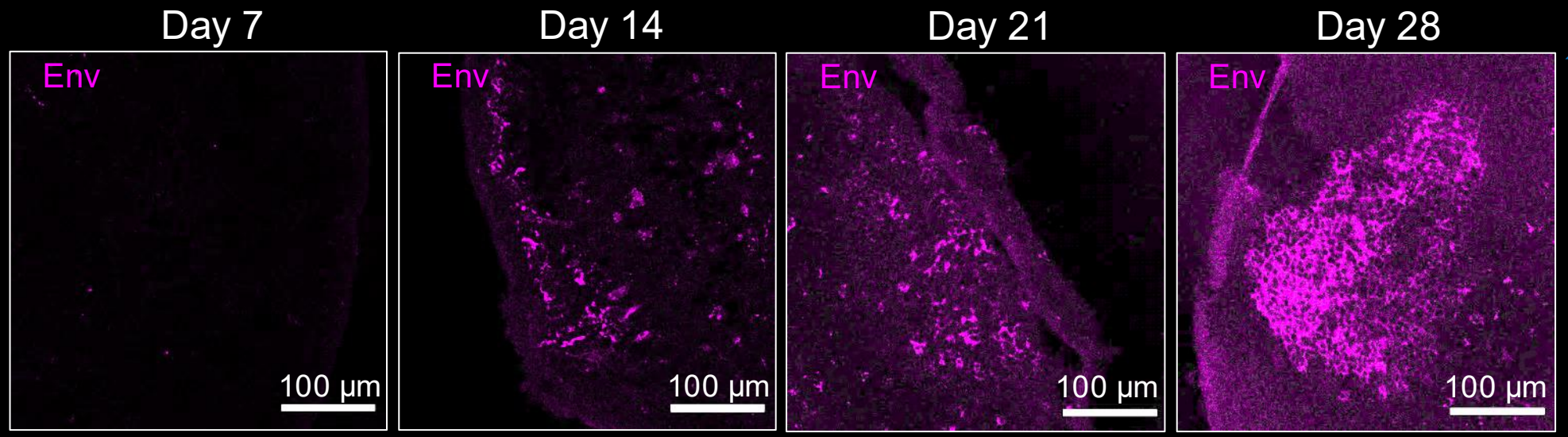


Phosphate tag

Moyer et al. *Nat. Med*. 2020;
Rodrigues et al. *Sci. Adv*. 2021



5X bigger germinal centers



10X greater neutralizing antibody titers

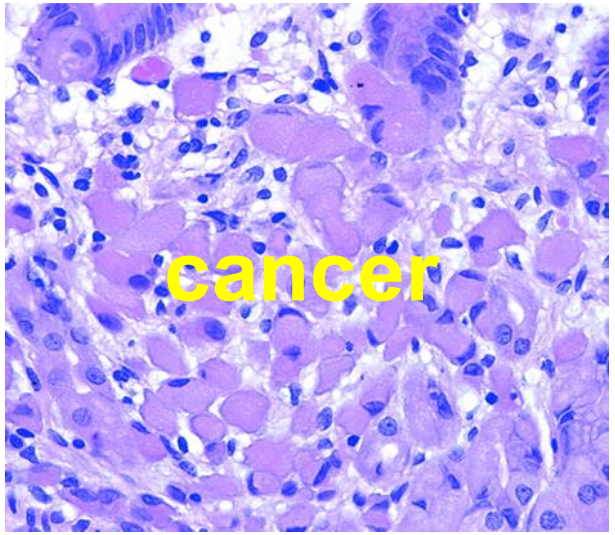
Rodrigues, Zhang et al. *Sci. Transl. Med.* 2025

Today's talk:



Zanetti et al. *PLoS pathogens* (2006)

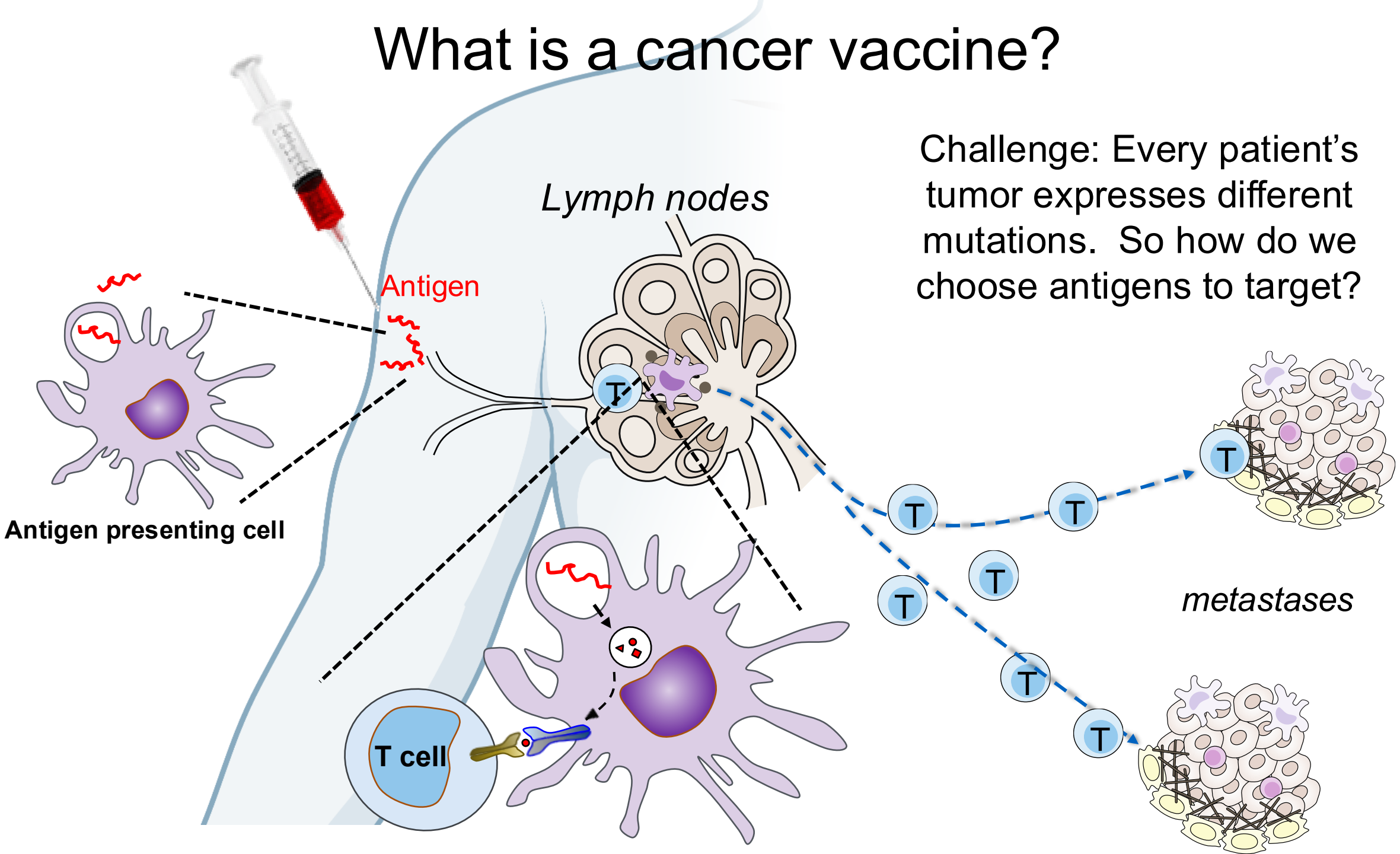
- What is a vaccine?
- Solving a vaccine mystery
- A new way to dose vaccines that may help us reach an HIV vaccine



J Med Genet 2010;**47**:433-435

- **Applying technology from HIV vaccines to attack cancer**

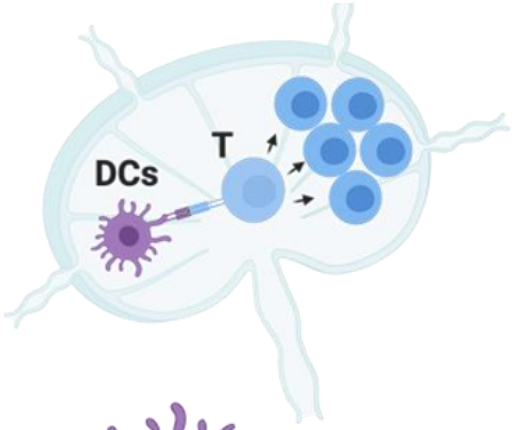
What is a cancer vaccine?



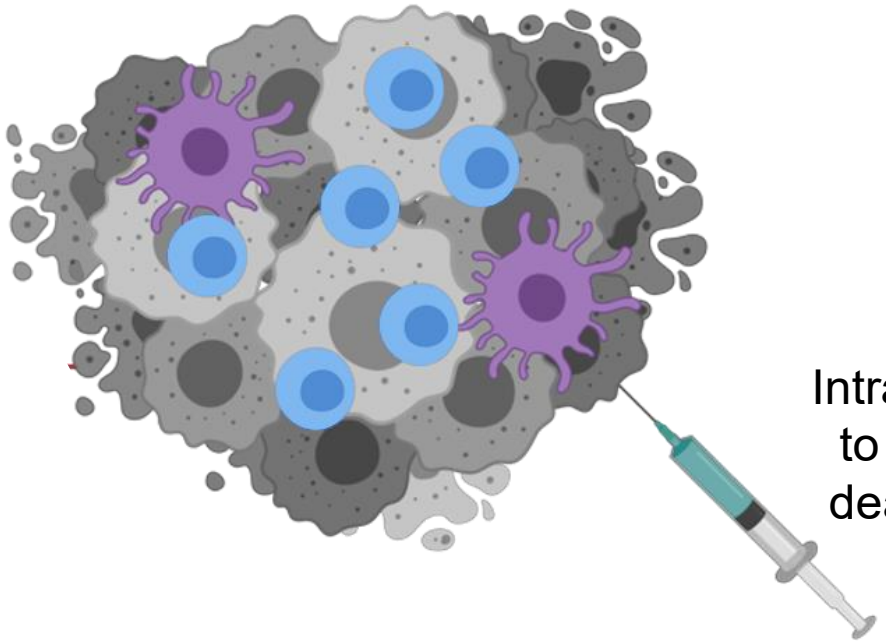
Challenge: Every patient's tumor expresses different mutations. So how do we choose antigens to target?

A potential solution?: Use the tumor itself as a vaccine

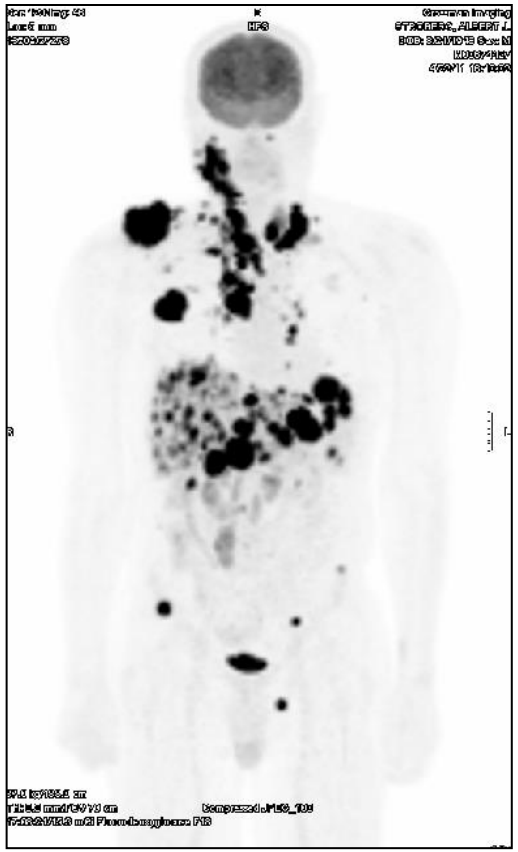
Lymph node



antigen presenting cells

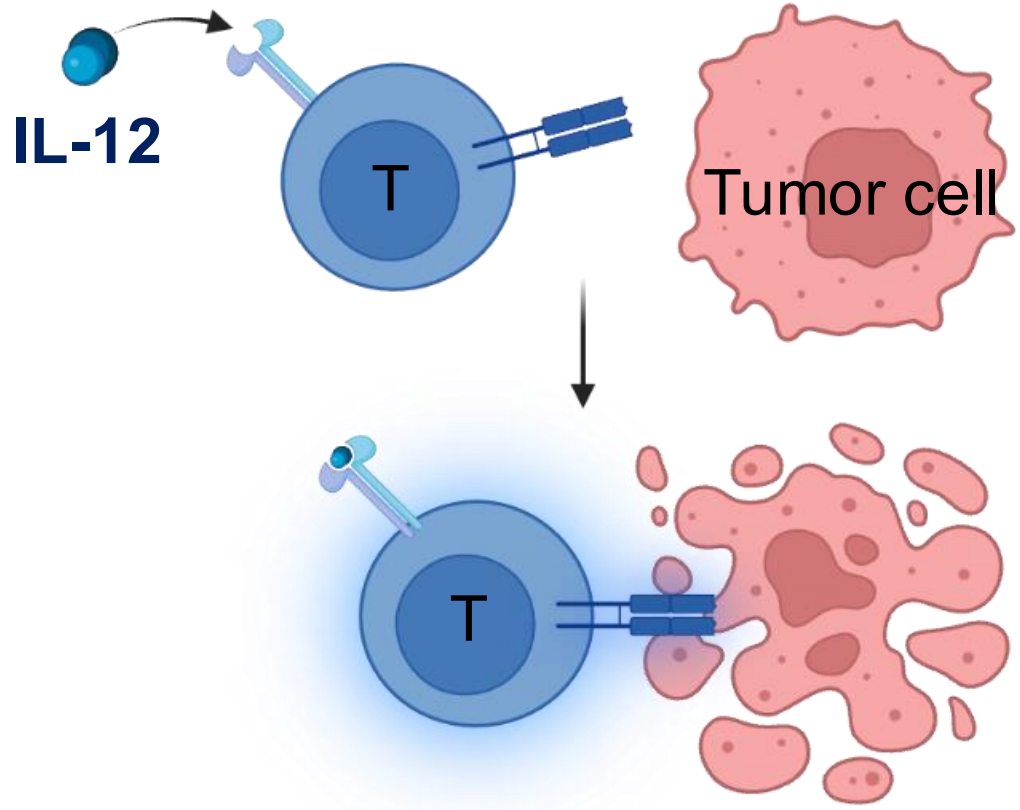


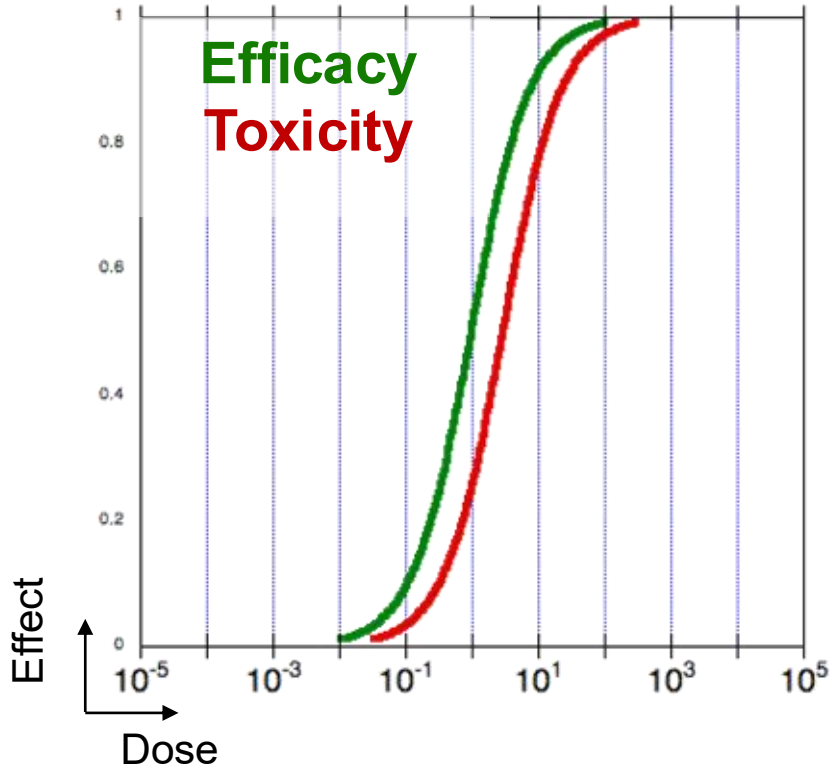
Intratumoral treatment to induce tumor cell death and release of antigens



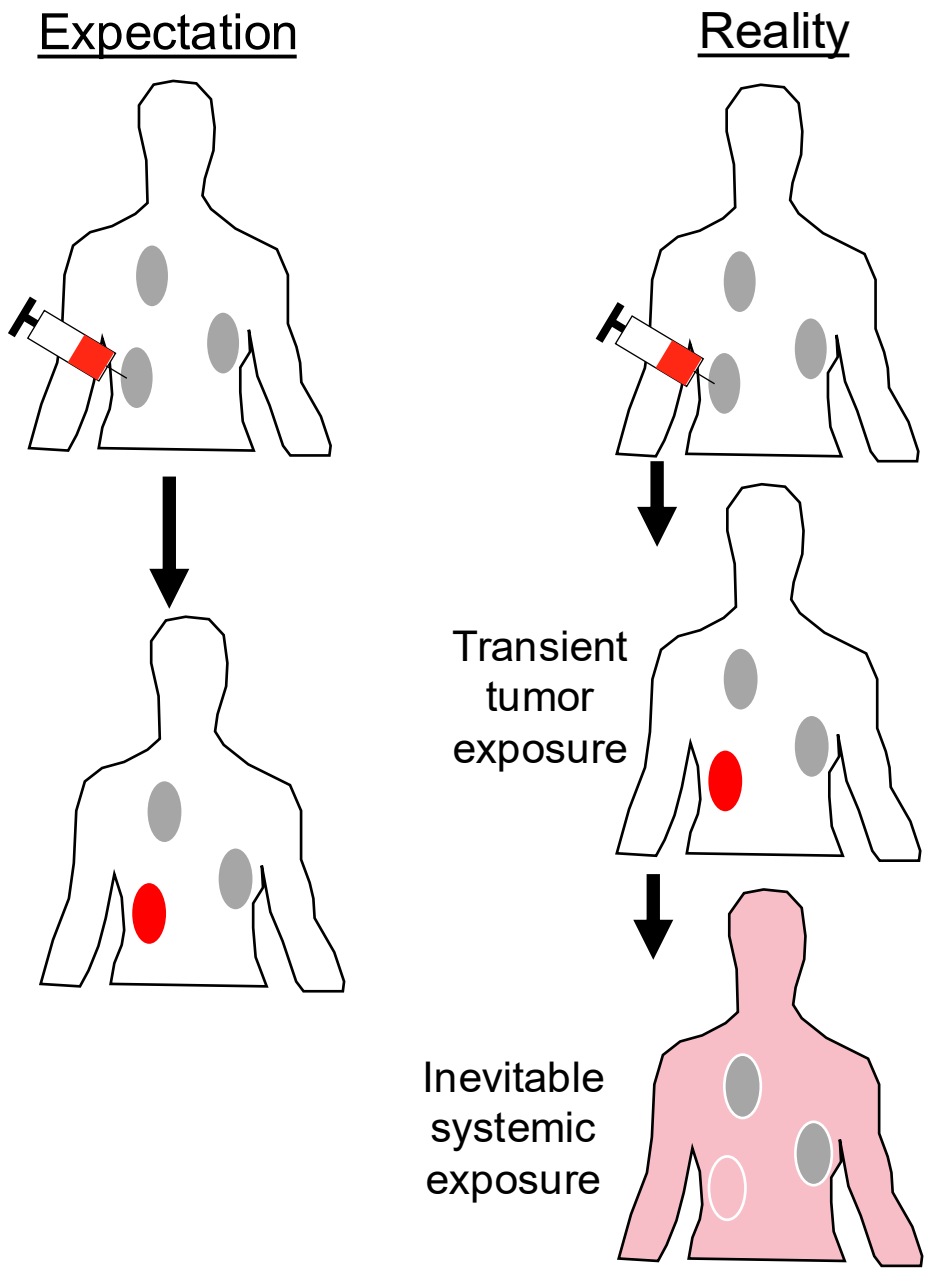
How do we start the cascade for a tumor-as-vaccine concept? One strong, but complicated candidate: interleukin-12 (IL-12)

IL-12 stimulates T cell killing:



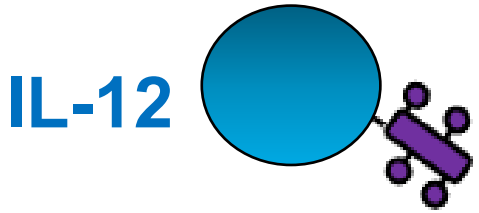


Intratumoral drug delivery as a solution to the toxicity of IL-12?



Alum anchoring as a strategy for localized immunotherapy

Phosphate-tagged IL-12:



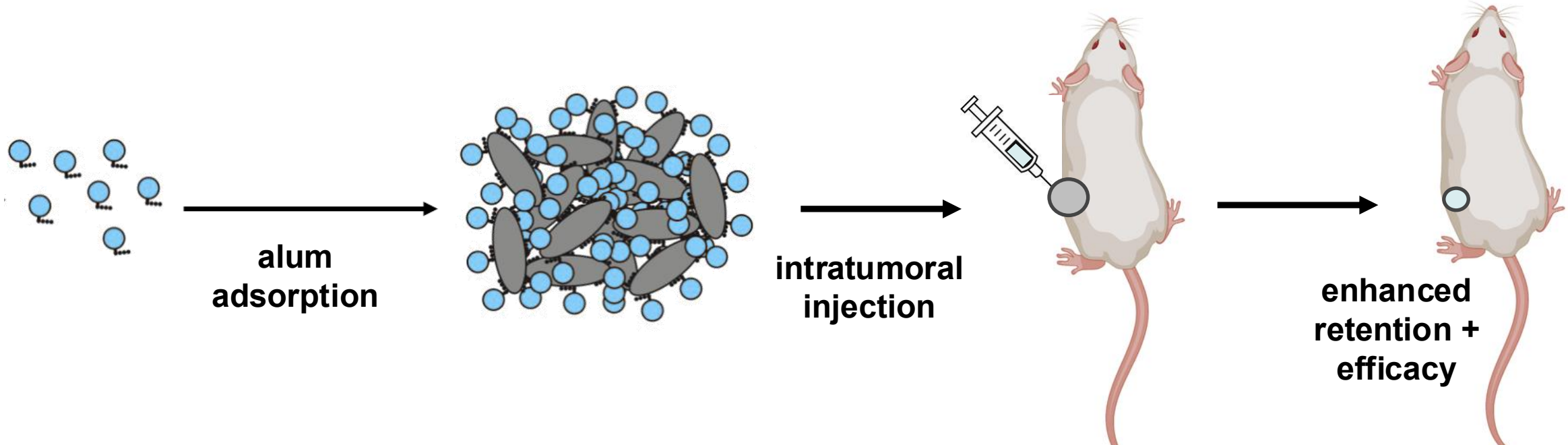
ABP = alum-binding peptide
(phosphoserine peptide)



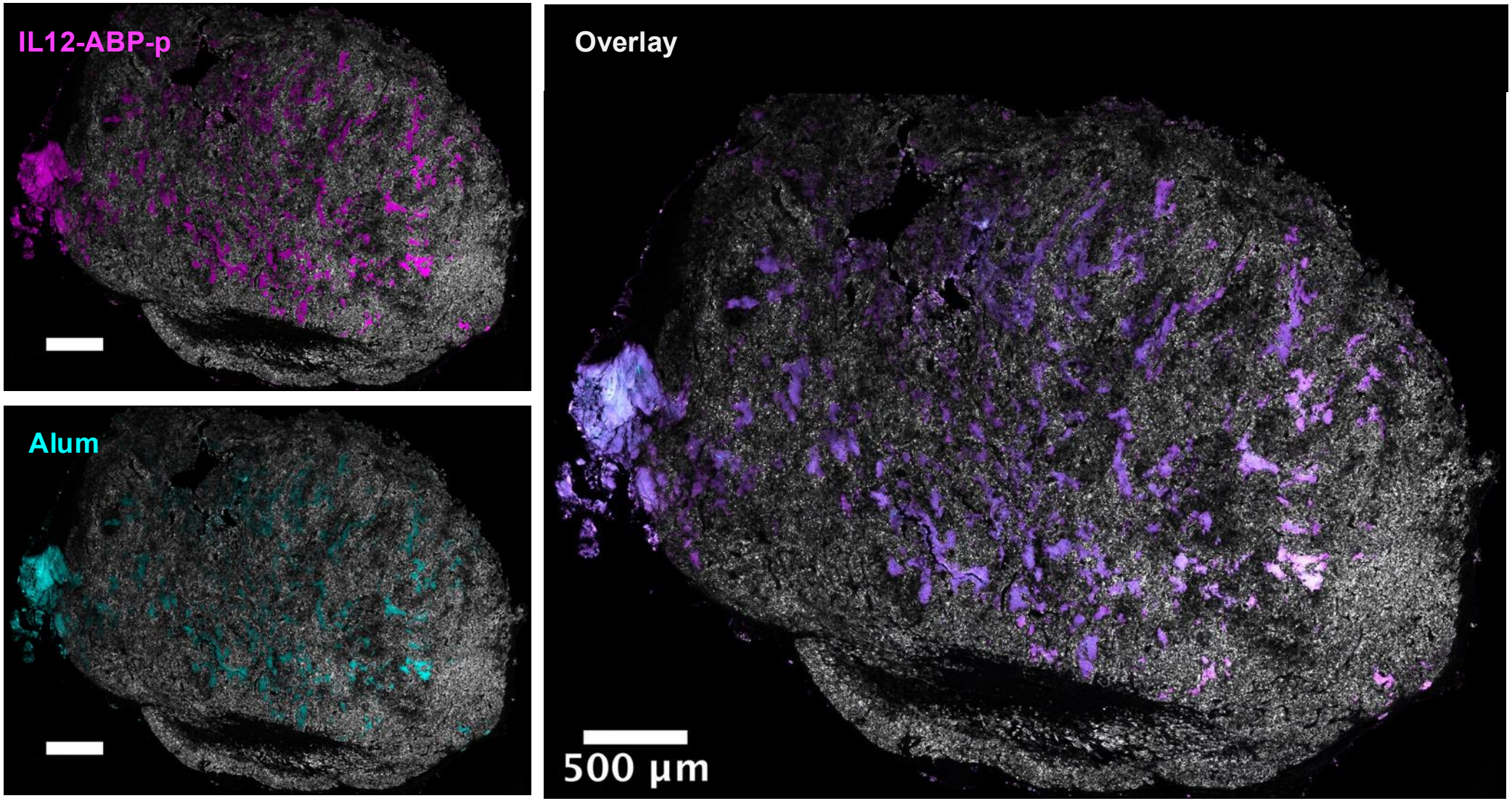
Yash Agarwal



Dane Wittrup

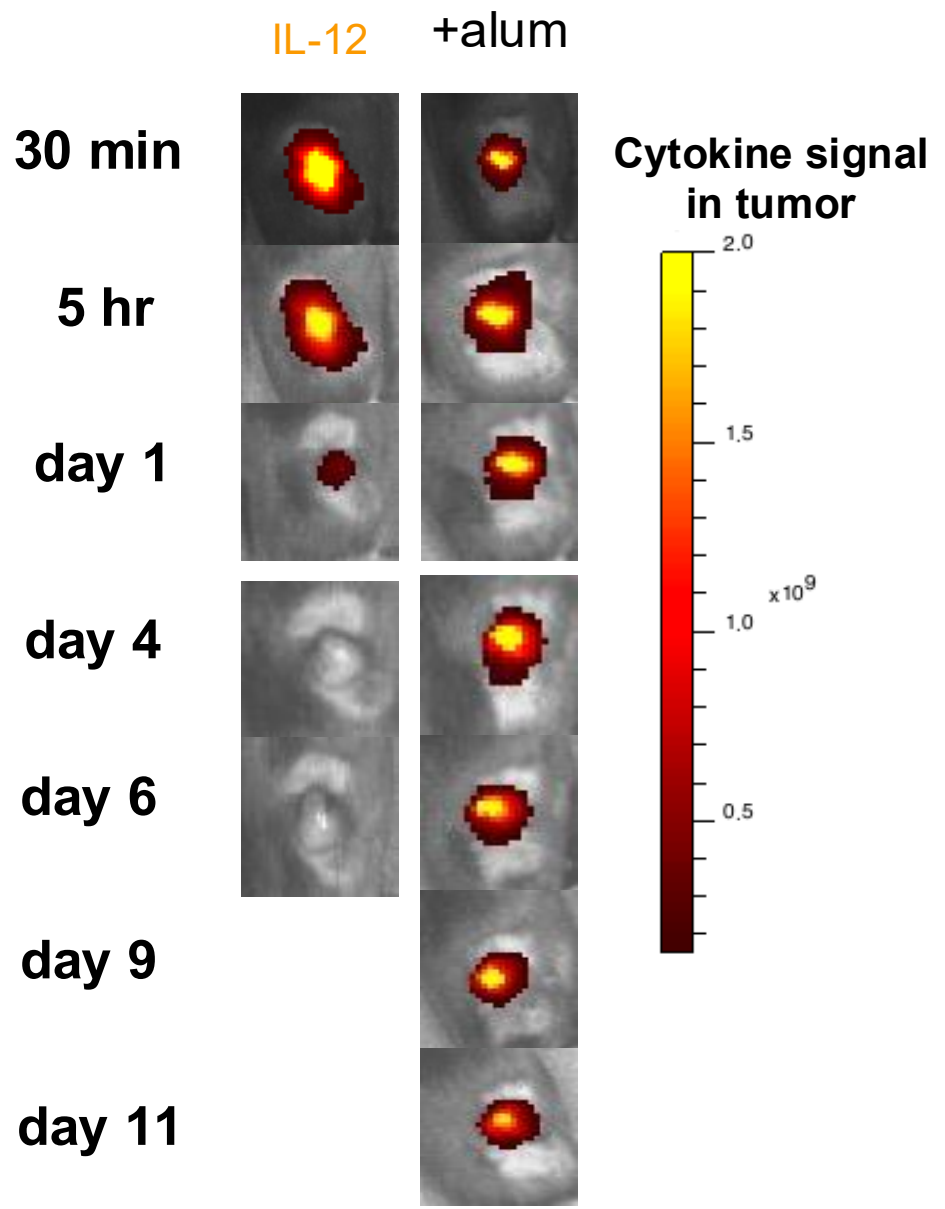


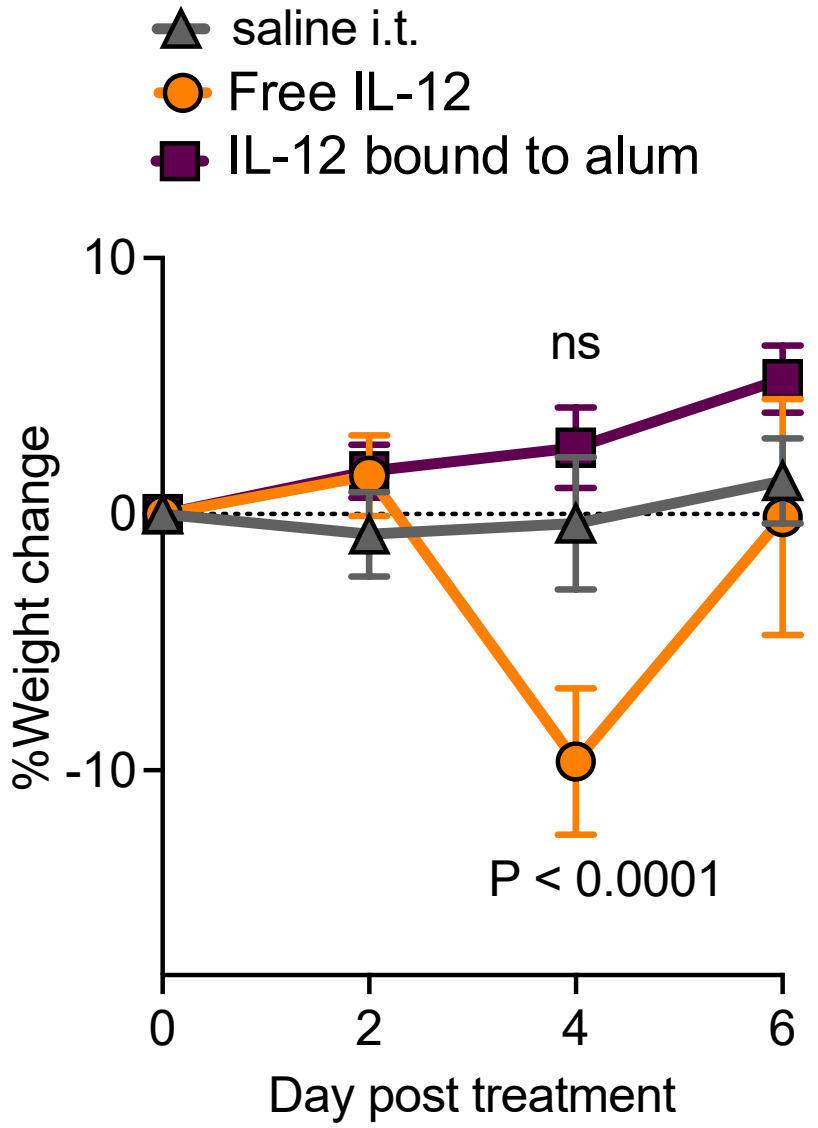
Alum-bound cytokine readily distributes throughout the tumor bed



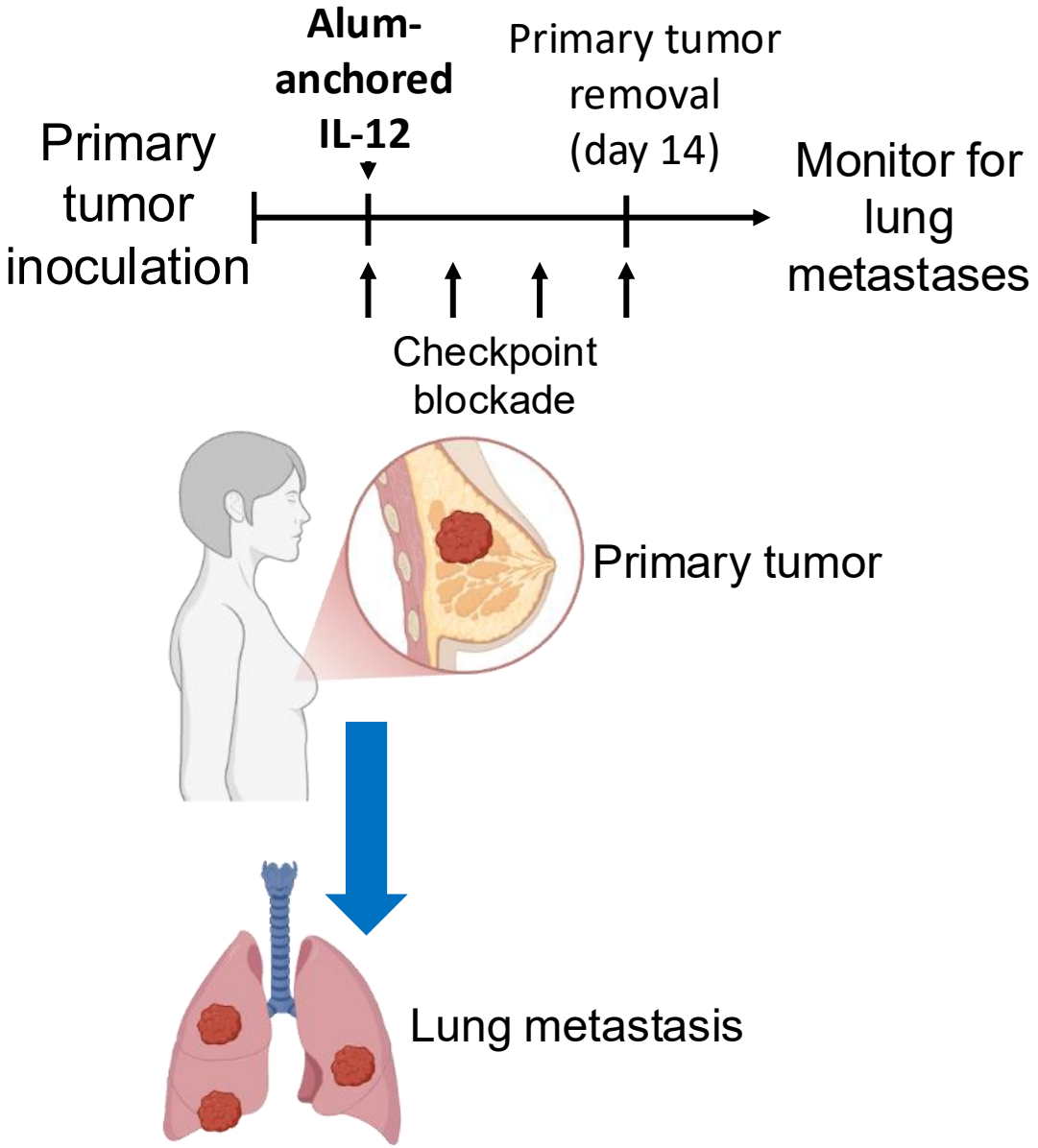
Yash Agrawal

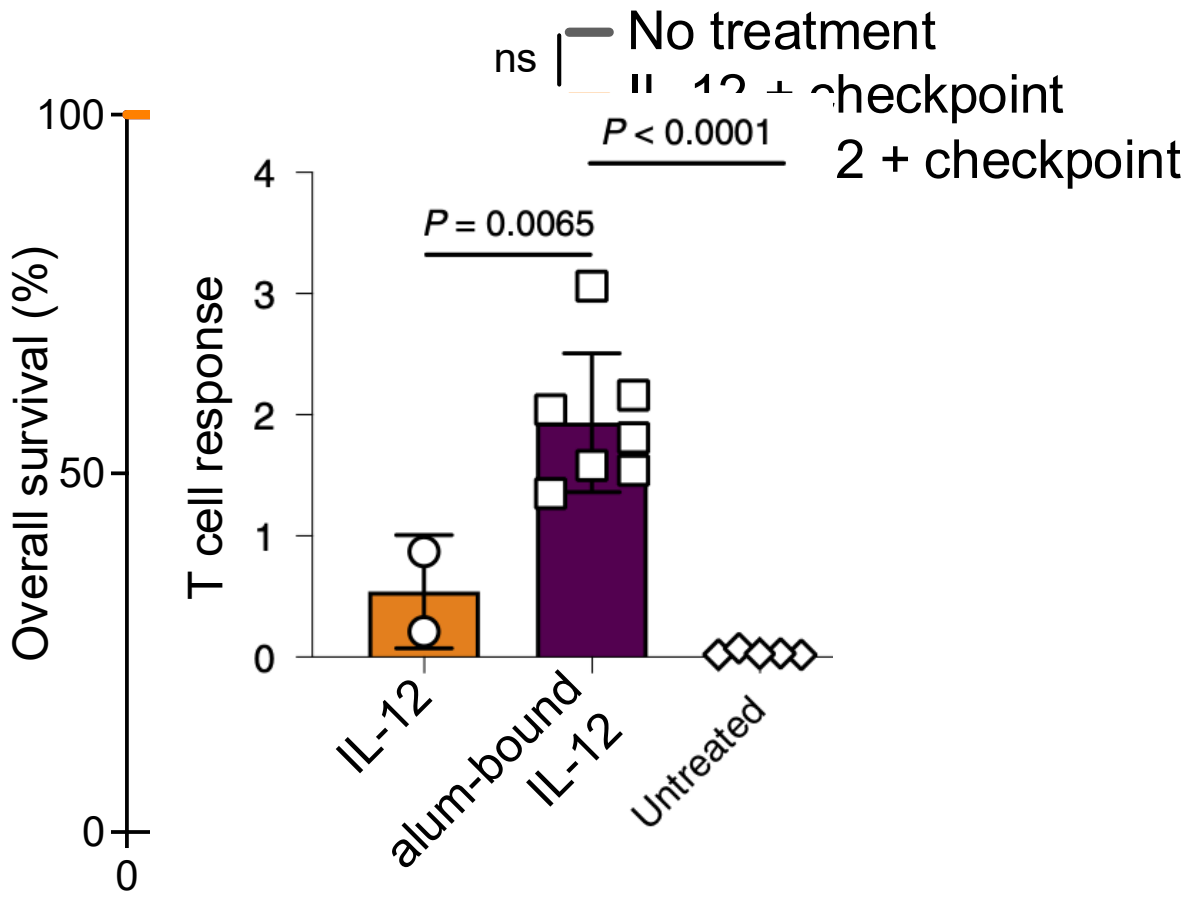
Alum-anchoring improves intratumoral retention and limits systemic exposure





Alum-anchored IL12 stimulates systemic immunity





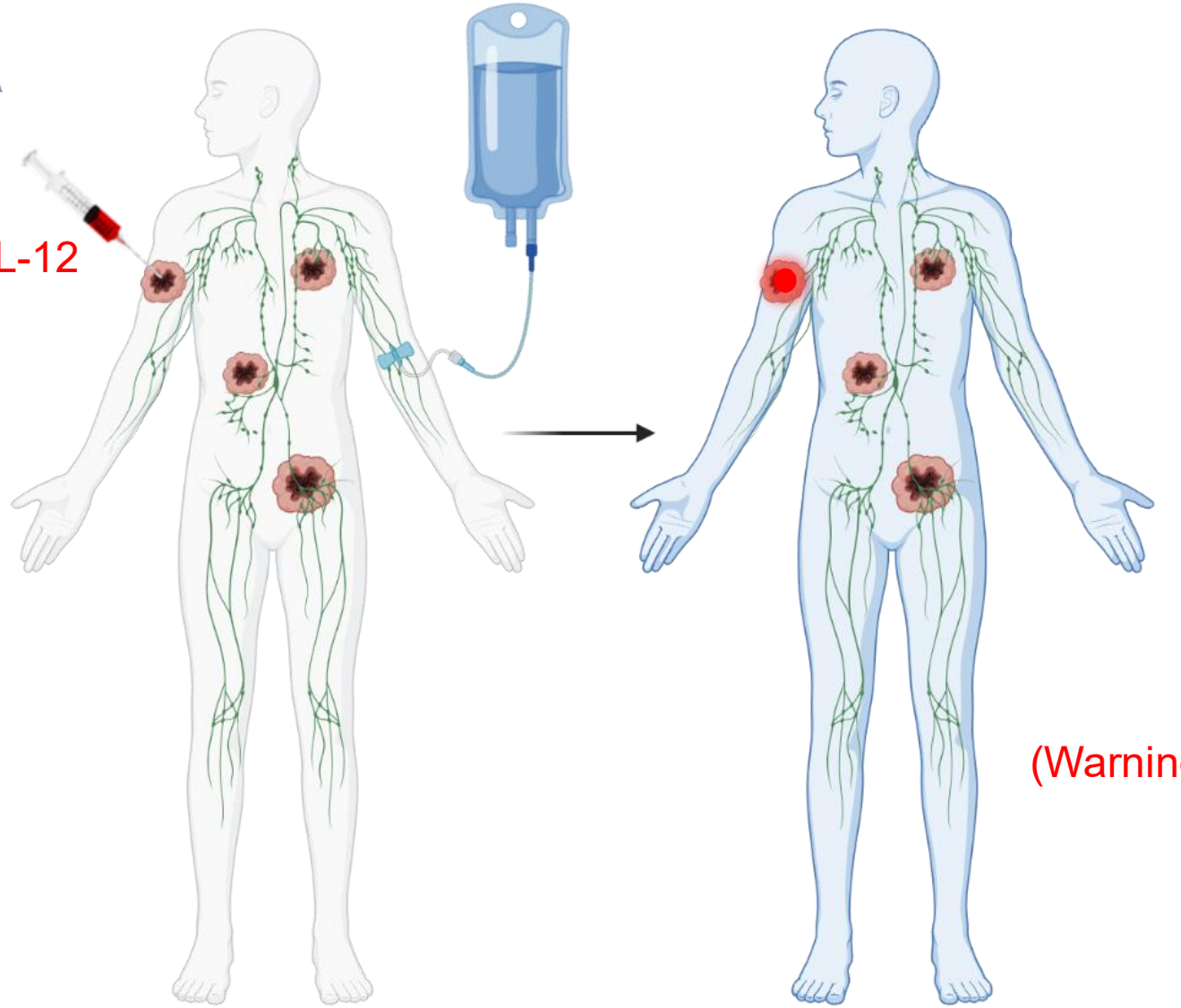
Agarwal et al. *Nat. Biomed. Eng*. 2022

Translating alum-anchored immunotherapy into patients

ANKYRA

Checkpoint blockade

Alum-anchored IL-12



(Warning: next slide is graphic)

Key Takeaways

Timing and Location matter a lot for drugs acting on the immune system

Controlling these factors may be critical for next-generation immunotherapies and vaccines to reach their potential while remaining safe

Interdisciplinary science (which Scripps does really well) is key!

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