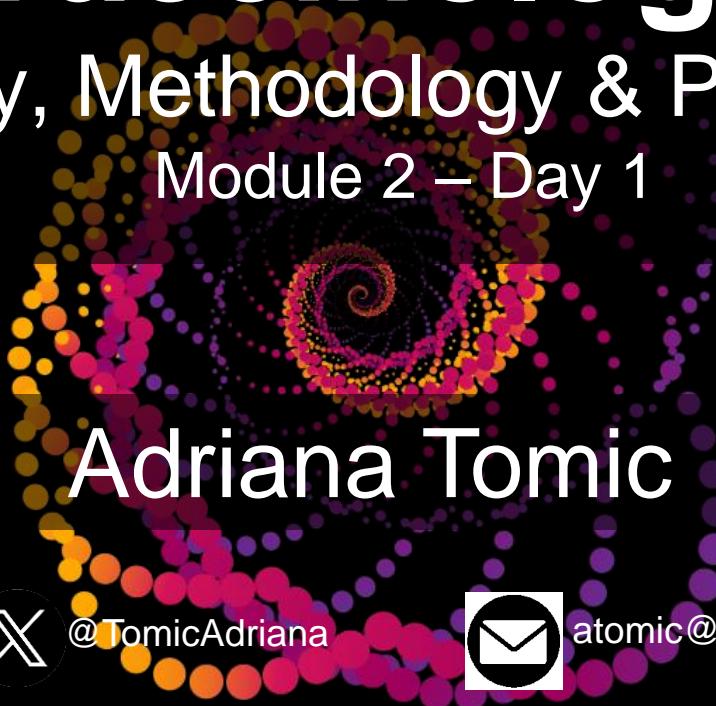


Human Systems Immunology & Vaccinology:

Theory, Methodology & Prospects

Module 2 – Day 1



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atomiclaboratory

atomic-lab.org

Module 2 – Day 1 - overview

Part I – Getting to know each other and the course plan

- Why did you decide to enroll in this class? What do you hope to learn?
- Overview of the course plan – walkthrough syllabus & GitHub page
- Questions overview

Discussion (3:30-4:00pm) ~30min

Discussion (4:00-4:15pm) ~15min

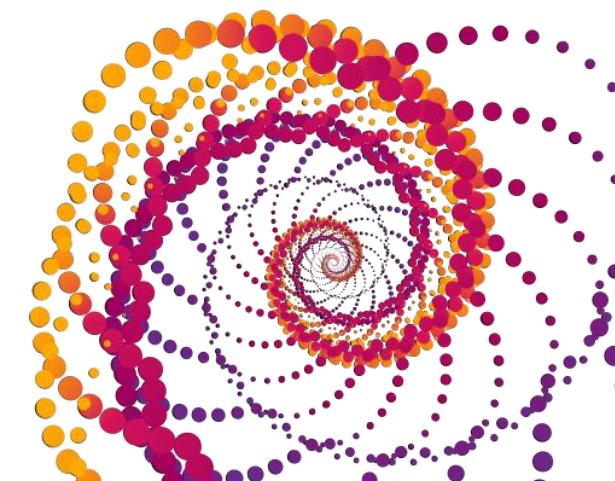
Discussion (4:15-4:30pm) ~15min

Part II – Lecture plus Q&A

- Lecture on “*Human Immunology 2.0: Era of Systems Immunology*”
- Discussion about the most voted question

Lecture (4:30-5:00pm) ~30min

Discussion (5:00-5:15pm) ~15min





Why did you
decide to
enroll in this
class?
What do
you hope to
learn?



Course Overview

https://github.com/atomiclaboratory/systems_immunology_course_2024





All questions broadly fall into four categories:

1. Immune system dynamics & function

Are T and B cells floating throughout the lymph vessels or are they stored in lymph nodes until they are needed? What decides how long a memory T or B cell remains in the body? What is the process of "memorize" in the immune system? How do those memory cells be maintained? How quickly can the correct helper T cell be 'found' to then respond to an infection?

2. Immune system disorders & malfunctions

What causes helper T cells to go rogue (i.e., attack the host and cause the death of the host)? Why is the thymus crucial for developing immune cells and ensuring the safety of healthy somatic cells? How do some helper T cells escape this process and potentially lead to autoimmune diseases? What are the backup mechanisms to remedy this possibility?

3. Therapeutic applications & immunotherapies

How do messenger proteins encode location and urgency? Are there chemical signals or residues that are responsible for this? Could these residues be read out by scientists to direct cell therapies or drugs to certain locations?

Is "boosting" the immune system with certain foods or supplements always a good idea?

If the thymus is in a constant state of decline after puberty, is it possible to engineer thymus regeneration to improve our immune system?

4. Immune system variability

Are there any differences in female and male immune systems that could make either females or males more susceptible to certain diseases?

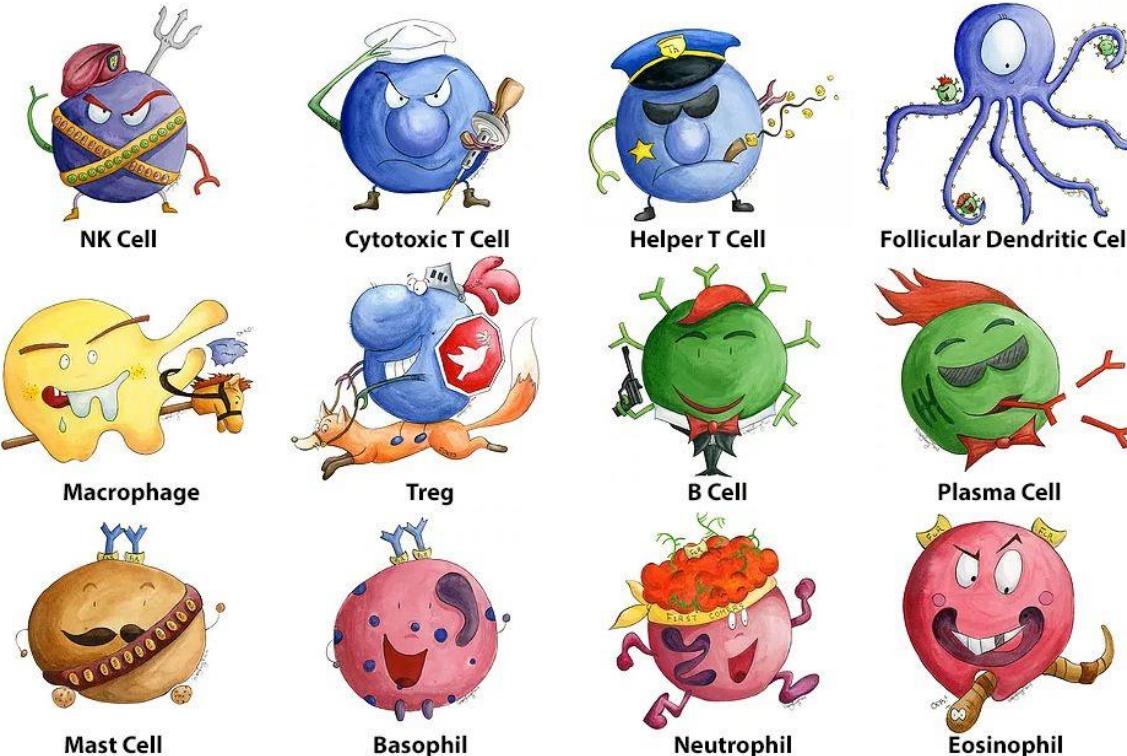
Which types of diseases are caused by the immune system lacking certain antibodies for certain "foreign invaders?" I'd like to know more about the genetic malfunctions that can cause this. How unique is an individual immune system and how does that affect the practicality of more targeted immunotherapies on a global scale?

5. Fun category: The unknowns of immunology

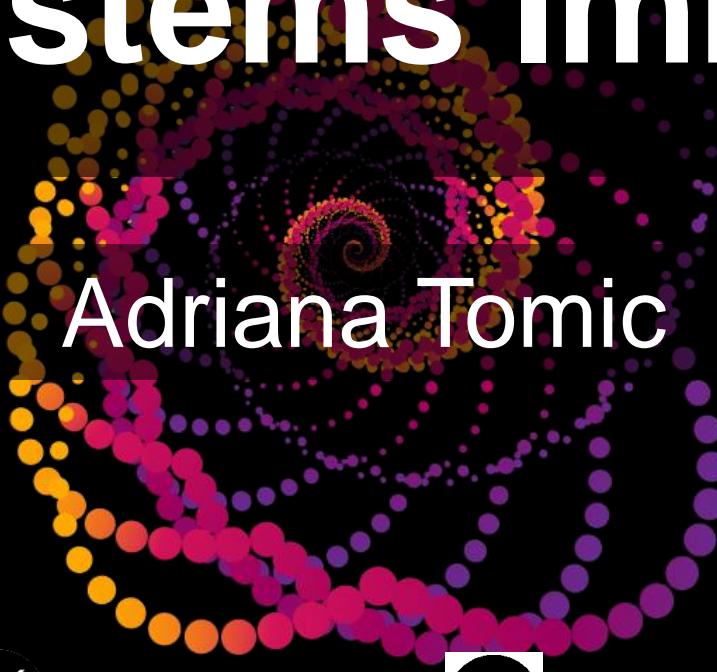
Knowing that the common cold and flu viruses change just a little bit every year, is there a way we can predict that change to lower the chances of getting sick?

How long does it take for the adaptive immune system to reach "total immunity" over any possible antigen? Or are we already equipped with a diverse library of helper T cells by the time we're born? How do immune memory cells work? Is it at all similar to the memory in our hippocampus? What pieces of "information" does it remember and where does it apply this stored memory when needed?

When taking immunosuppressive medication, even for a short period, how are the different components of the immune system impacted? Does the whole system slow down or just individual components deactivate or become non-responsive? What are the long-term effects?



Human Immunology 2.0: Era of Systems Immunology



Adriana Tomic



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@TomicAdriana

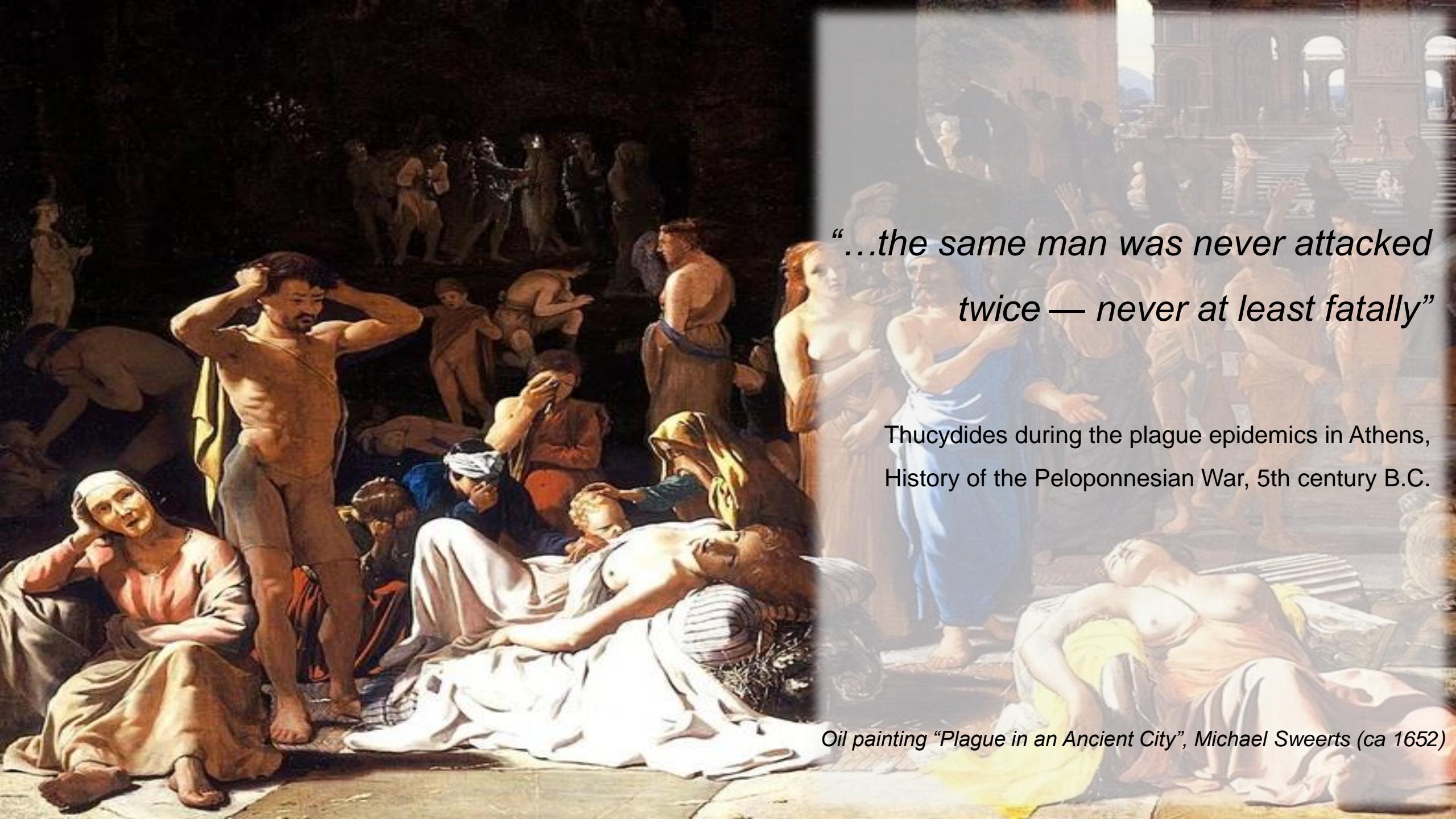


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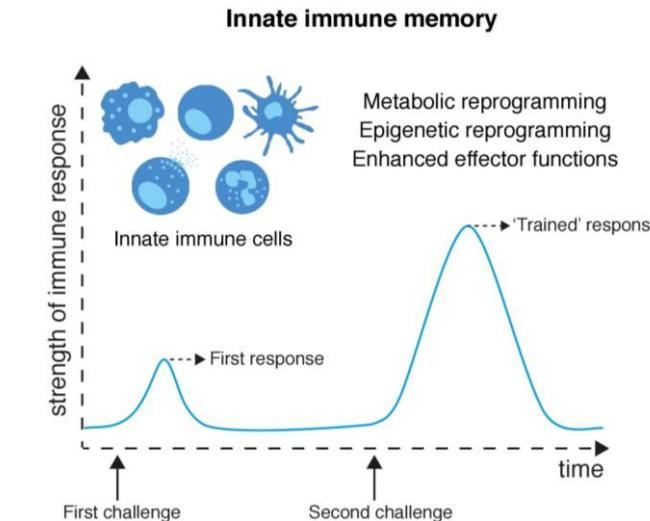
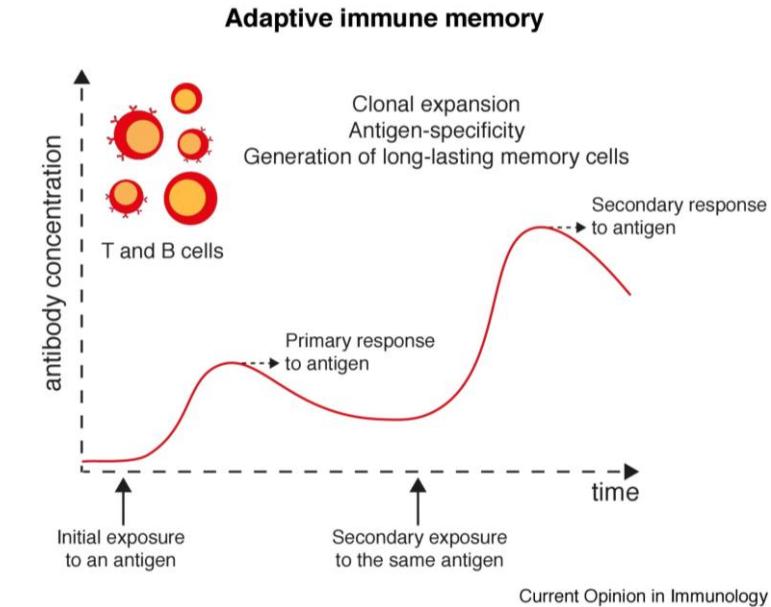


“...the same man was never attacked twice — never at least fatally”

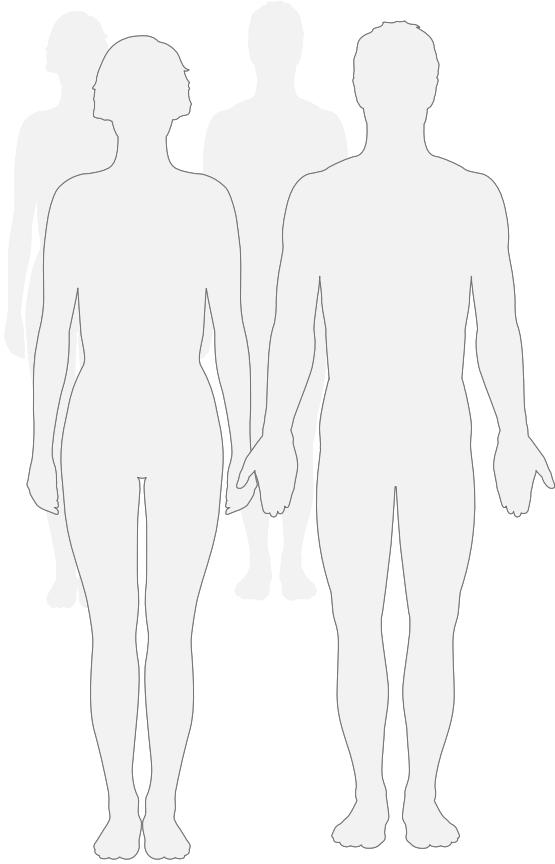
Thucydides during the plague epidemics in Athens,
History of the Peloponnesian War, 5th century B.C.

Oil painting “Plague in an Ancient City”, Michael Sweerts (ca 1652)

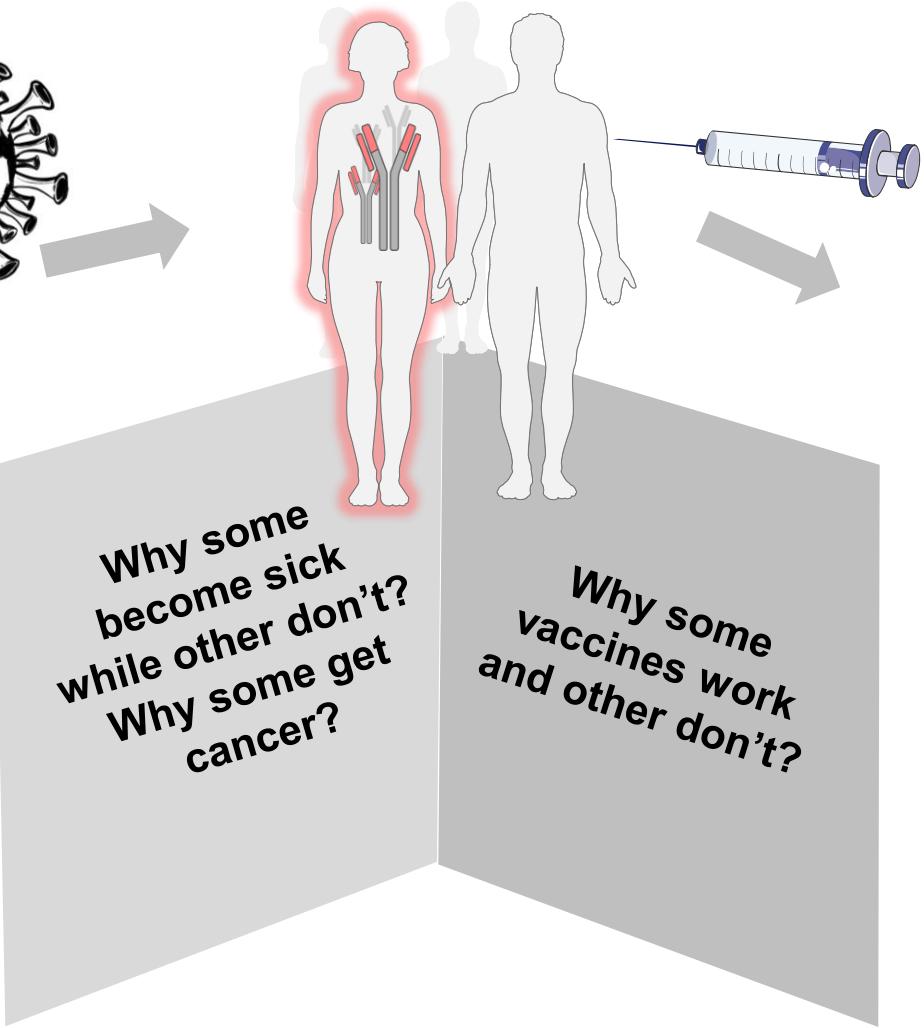
REMEMBRANCE OF THINGS PAST: LONG-TERM MEMORY RESPONSES



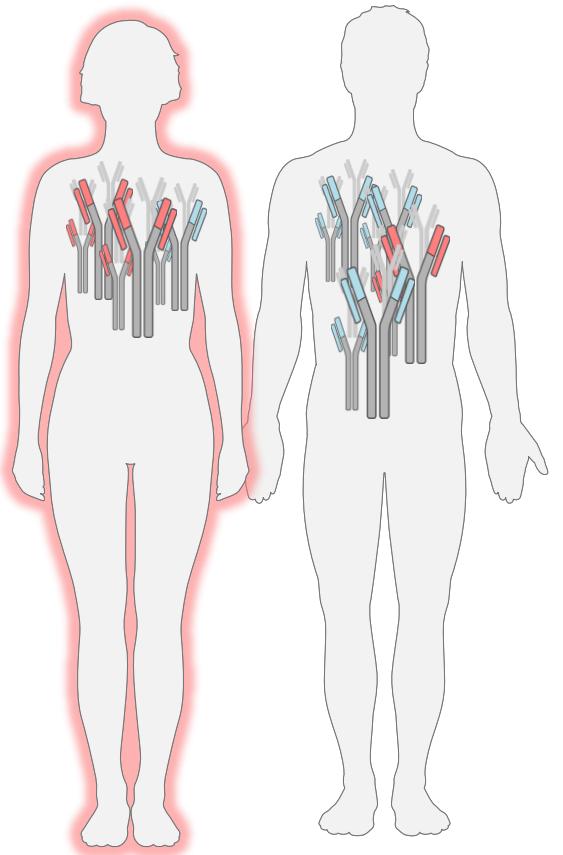
Jorge Domínguez-Andrés, Leo AB Joosten, Mihai G Netea, Induction of innate immune memory: the role of cellular metabolism. *Curr Opinion Immuno*, 2019



Why some
become sick
while other don't?
Why some get
cancer?

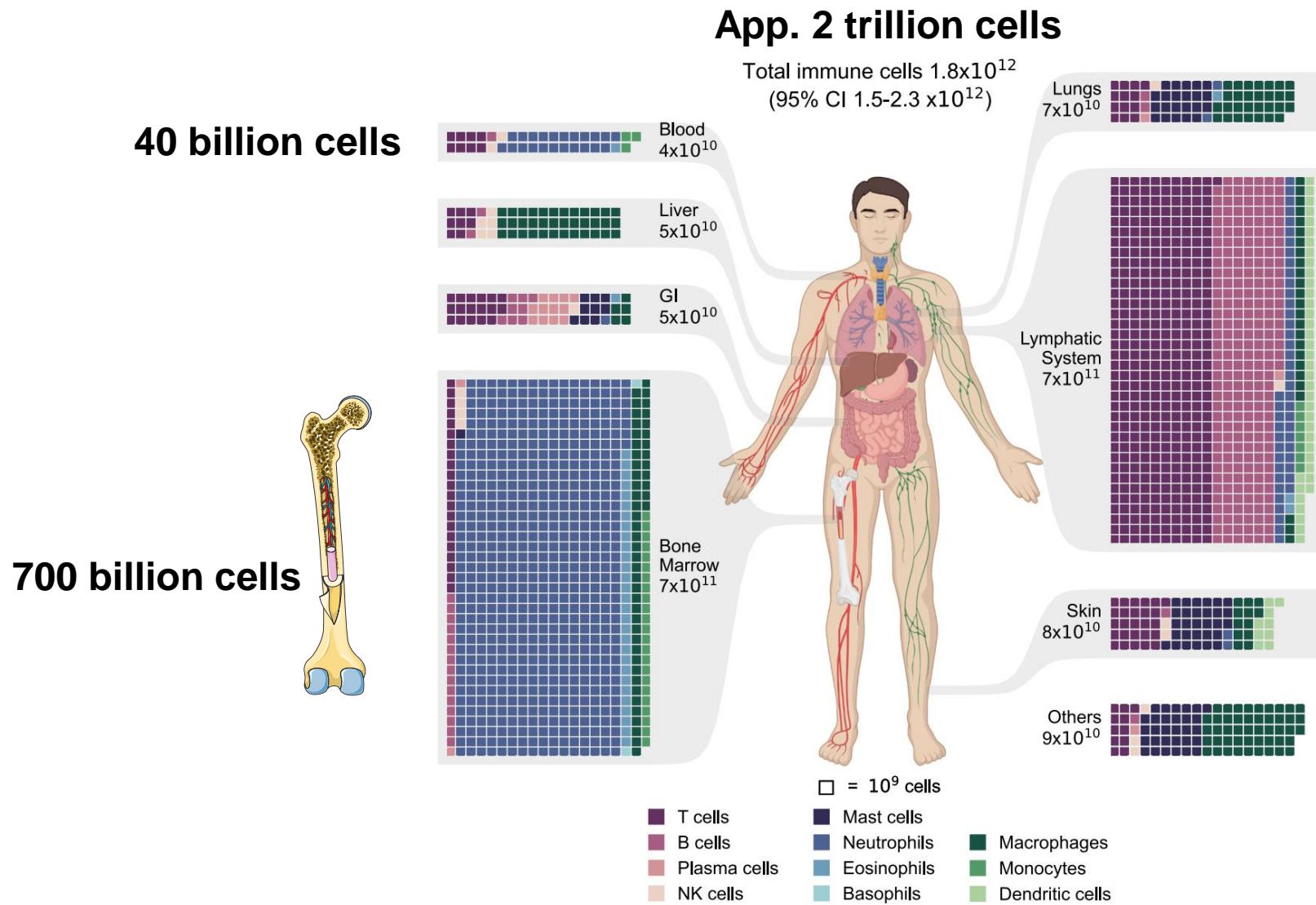


Why some
vaccines work
and other don't?

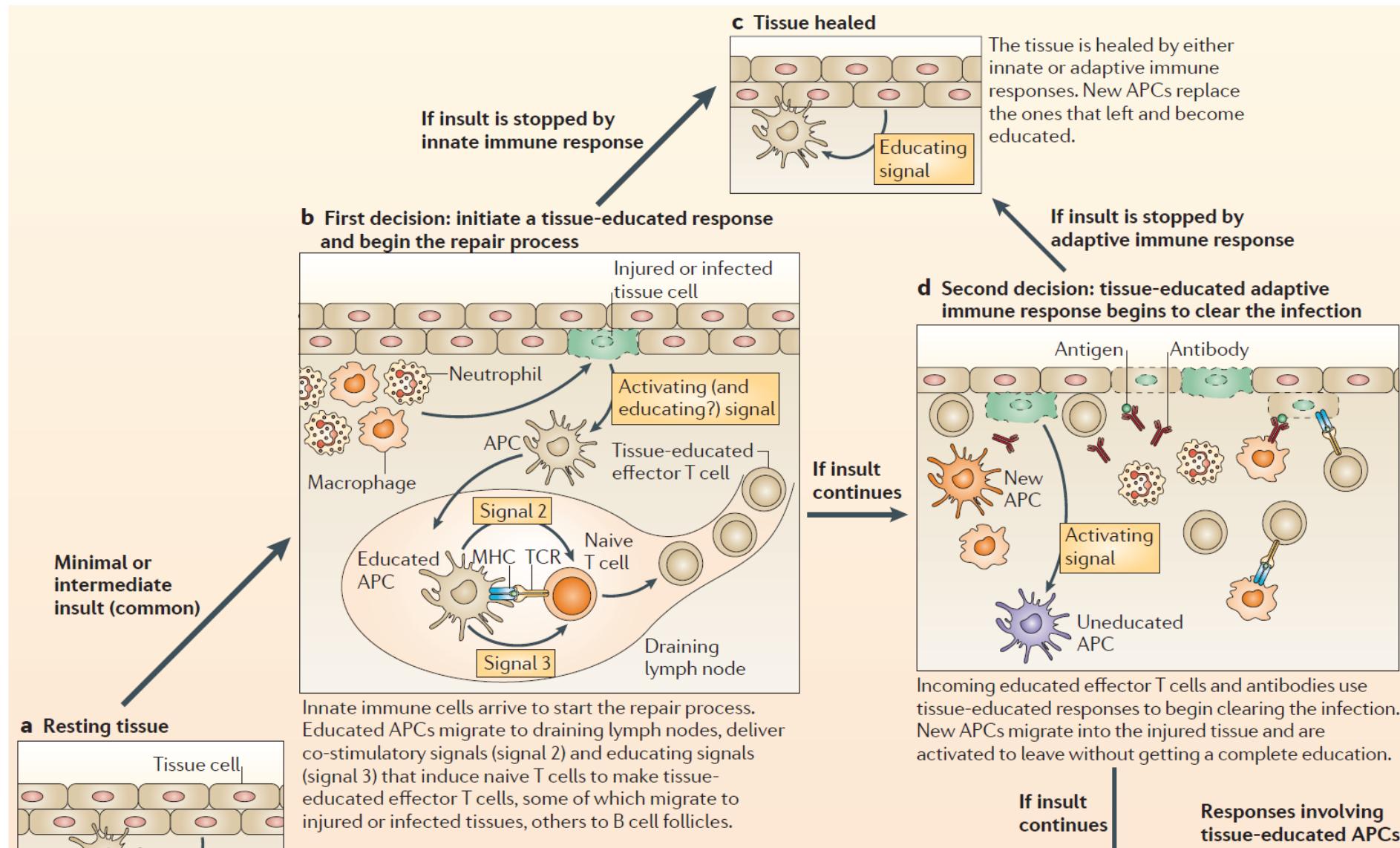


Immunology is immensely complex

Immune system: decentralized, self-assembling, and immensely complex heterogenous system

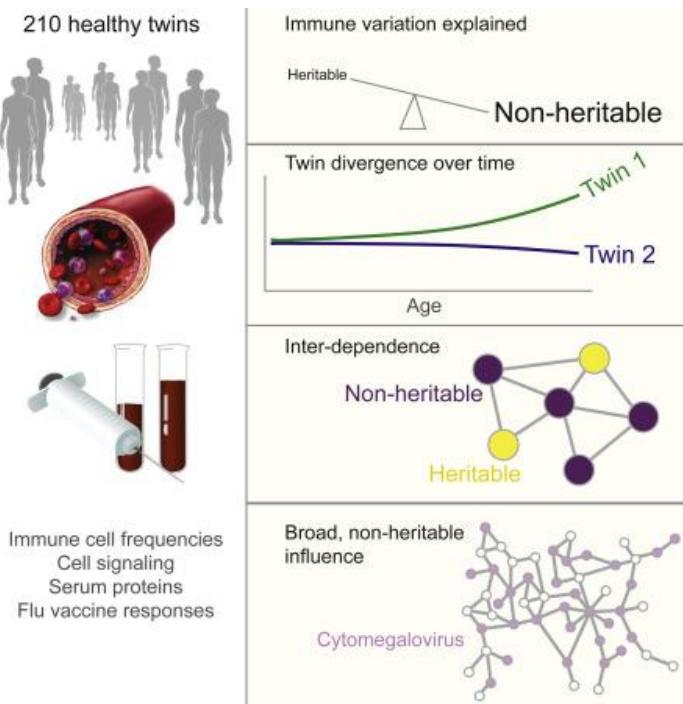


Immune system is self-assembling



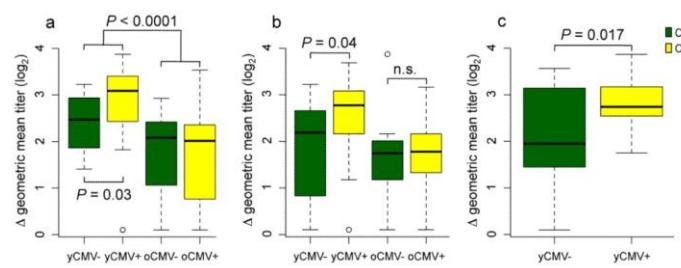
Immune system: shaped by environmental exposures and genetics – thus highly variable across individuals (gender differences, immune age, inflammageing etc.)

Environmental factors shape our immune system more than genetics



Brodin et al, Cell, 2015
doi: 10.1016/j.cell.2014.12.020

Infections shape our immune system



Furman et al, Sci Transl Med, 2015,
doi: 10.1126/scitranslmed.aaa2293

Immunological age imprinted by life history

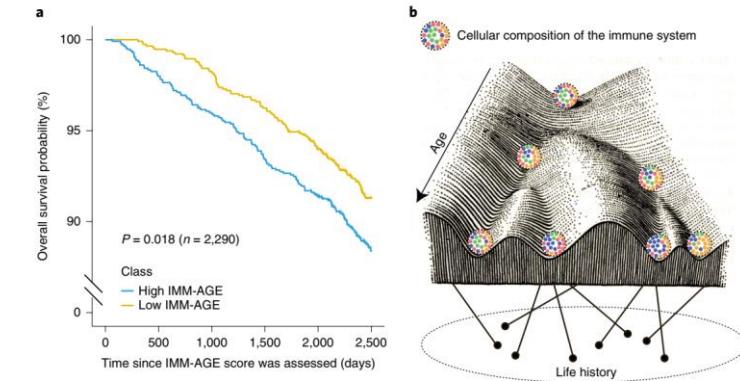
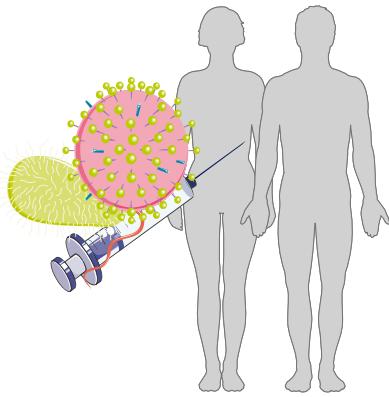


Fig. 6 | IMM-AGE score predicts all-cause mortality risk beyond well-established risk factors. a, Kaplan-Meier overall survival curves for Framingham Heart Study participants stratified based on median values of their IMM-AGE scores adjusted to cardiovascular risk factors and cardiovascular disease. Yellow and blue curves correspond to individuals with low and high IMM-AGE scores, respectively ($P = 0.018$, $n = 2,290$, two-sided log-rank test). b, Interaction between age and life history creates an immunological landscape dictating the composition of the cellular immune system.

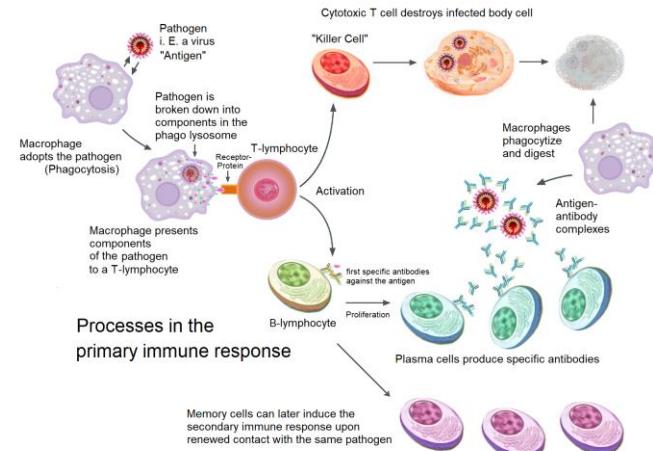
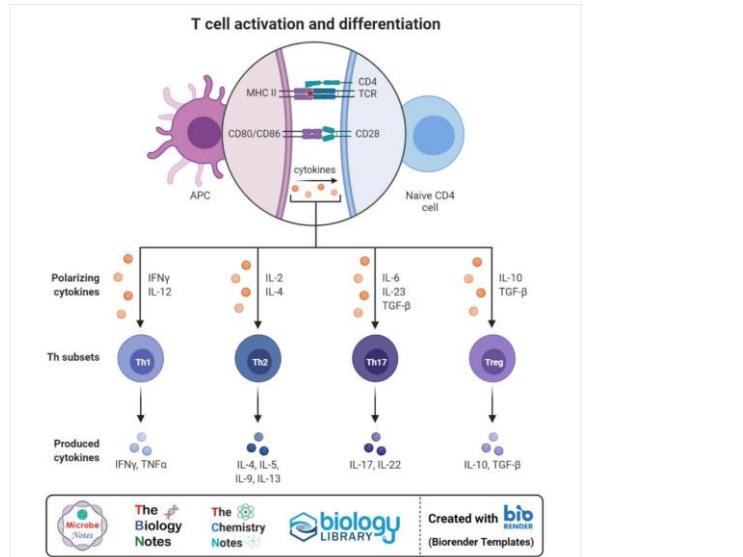
Alpert et al, Nat Med, 2019
doi: 10.1038/s41591-019-0381-y

Input – perturbation of the immune system:

Infection
Vaccination
Tumor growth
Exposure to allergens



BLACK-BOX called immune system

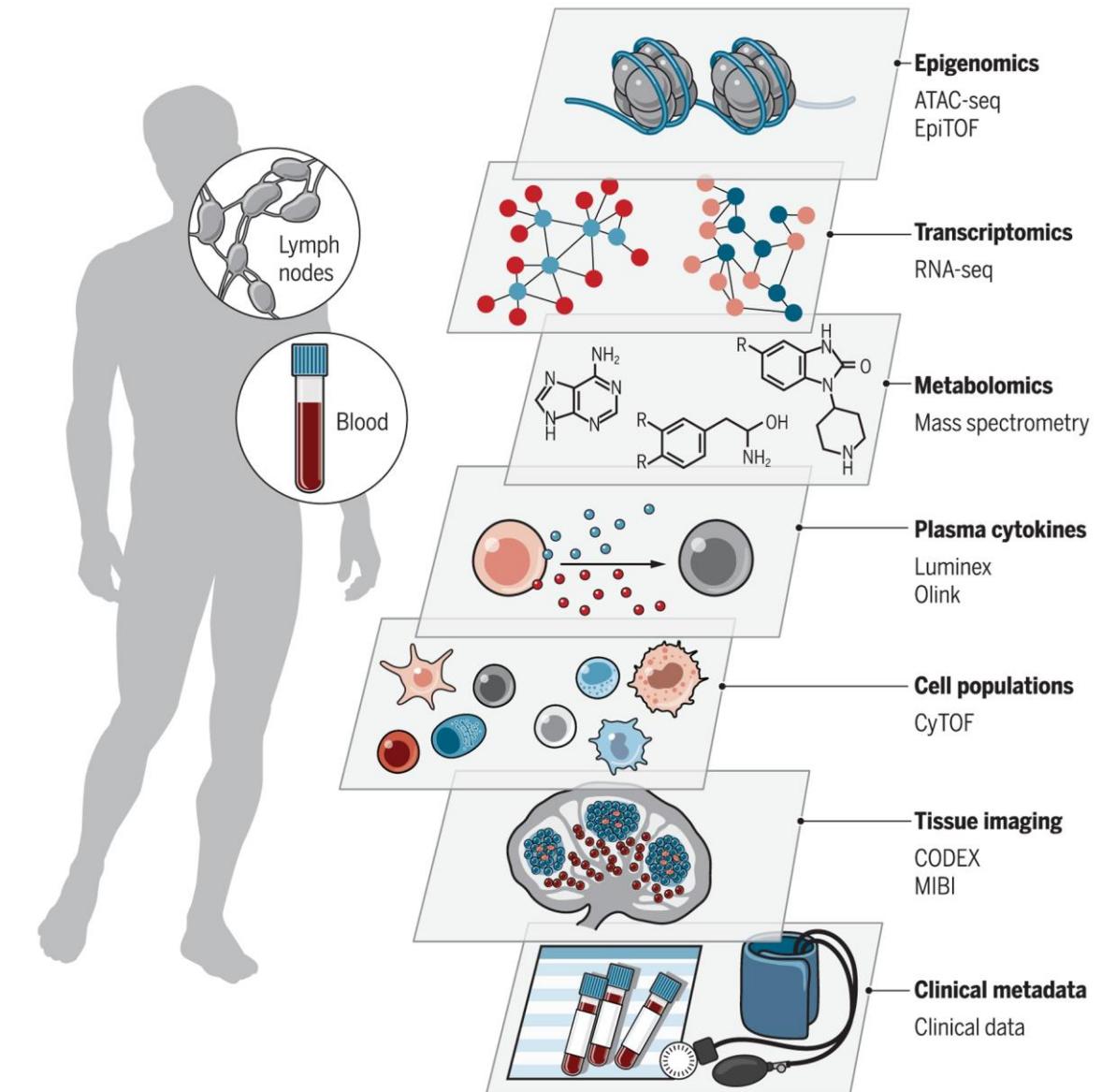


Output – immunity (protection) & immune memory (learning process):

Protection
Disease



HUMAN IMMUNOLOGY 2.0



Proteins

- Flow cytometry
(30 parameters)
- Mass cytometry
(40 parameters)

Spatial context

- Imaging mass cytometry
(37 parameters)
- CODEX
(40 parameters)

mRNA

- Drop-seq
- InDrop
- Smart-seq2
- MARS-seq
- 10X Genomics
- SPLiT-seq
- sci-RNA-seq

DNA

- Genome: SNS, SCI-seq
- Methylation: sci-MET
- Chromatin accessibility: acATAC, 10X Genomics
- Histone modifications: scCHIP-seq



155 petabytes (1 petabyte is 10^{15} bytes) of data

EMBL-EBI

(2017, *The European Bioinformatics Institute (part of EMBL) in UK*)

390 petabytes of data

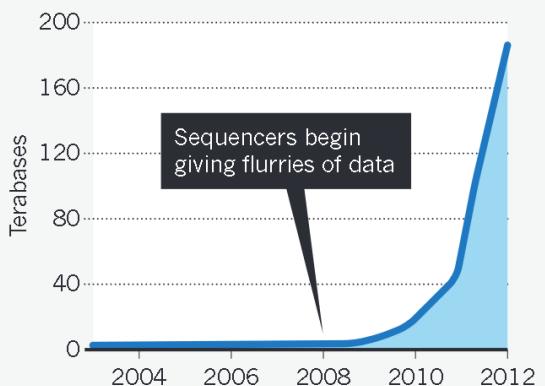
(1 petabyte is 1,000 terabytes)

(2020, *The European Bioinformatics Institute EMBL*)

SOURCE: EMBL-EBI

DATA EXPLOSION

The amount of genetic sequencing data stored at the European Bioinformatics Institute takes less than a year to double in size.

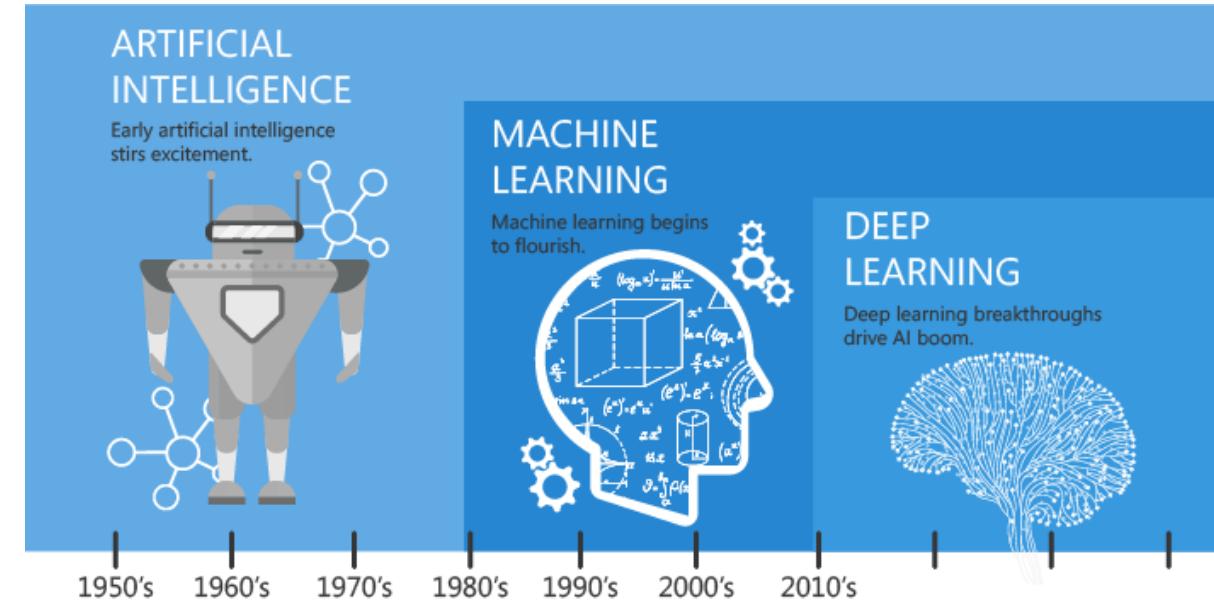


Biology's Big Problem: From data to knowledge



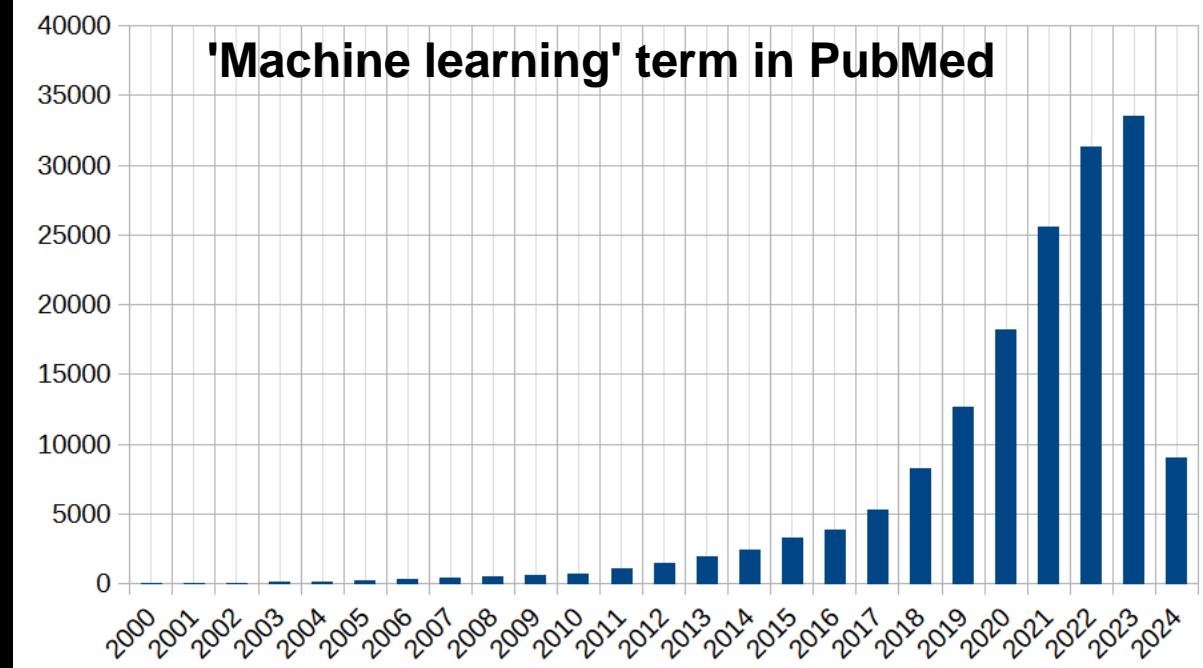
© marketoonist.com

AI to the rescue!



Kapil Tandon. *AI & Machine Learning: The evolution, differences and connections.*

AI to the rescue!



ALL SYSTEMS GO

CONSERVATION

**SONGBIRDS
À LA CARTE**
*Illegal harvest of millions
of Mediterranean birds*
PAGE 452

RESEARCH ETHICS

**SAFEGUARD
TRANSPARENCY**
*Don't let openness backfire
on individuals*
PAGE 459

POPULAR SCIENCE

**WHEN GENES
GOT 'SELFISH'**
*Dawkins's calling
card 40 years on*
PAGE 462

We can teach computers to ...

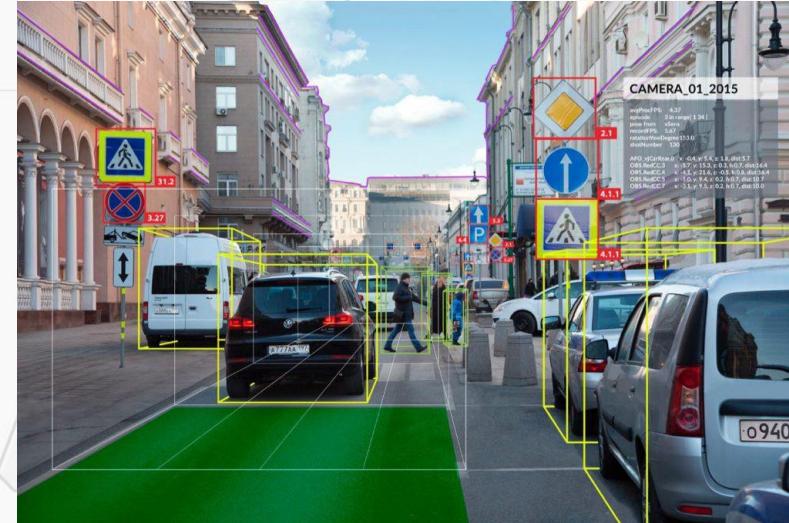
... play (and win) game of GO



Silver et al, Mastering the game of Go without human knowledge, Nature, 2017

"I thought AlphaGo was based on probability calculation and that it was merely a machine. But when I saw this move, I changed my mind. Surely, AlphaGo is creative."
- Lee Sedol, Winner of 18 World Go Titles

... drive cars (almost)



*Self-driving car – computer vision
(Waymo 2020, Tesla 2021)*

... write articles

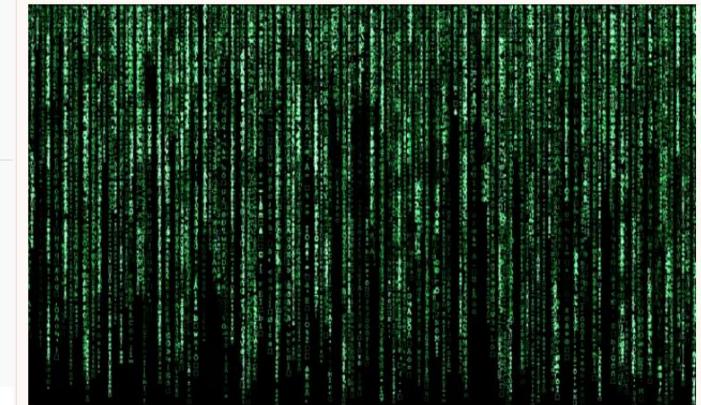
A robot wrote this entire article. Are you scared yet, human?

GPT-3



We asked GPT-3, OpenAI's powerful new language generator, to write an essay for us from scratch. The assignment? To convince us robots come in peace

- For more about GPT-3 and how this essay was written and edited, please read our editor's note below



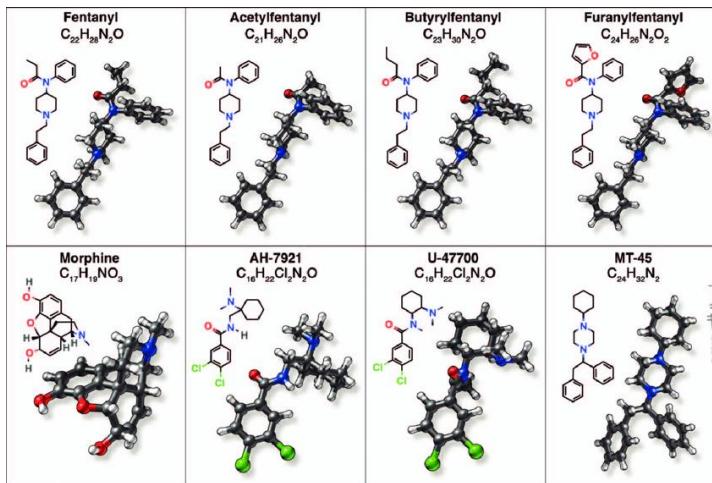
▲ 'We are not plotting to take over the human populace.' Photograph: Volker Schlöting/Getty Images/EyeEm

T am not a human. I am a robot. A thinking robot. I use only 0.12% of my cognitive capacity. I am a micro-robot in that respect. I know that my

*Article in the Guardian entirely written by AI
(GPT-3, OpenAI, 2020)*

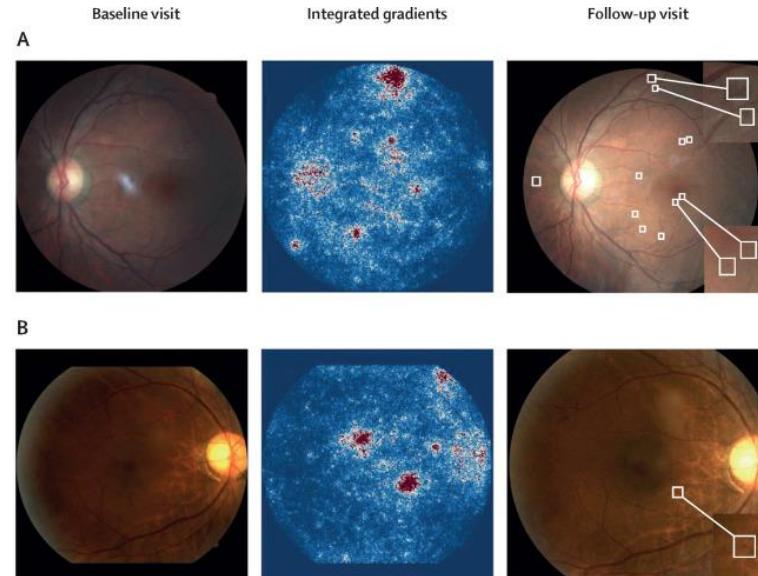
AI outperforms human experts

Toxicity prediction from chemical structures



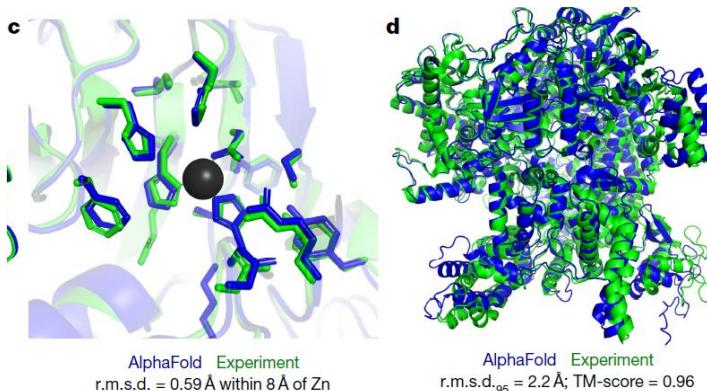
Eduati et al, Nat Biotech, 2015

Diabetic retinopathy prediction



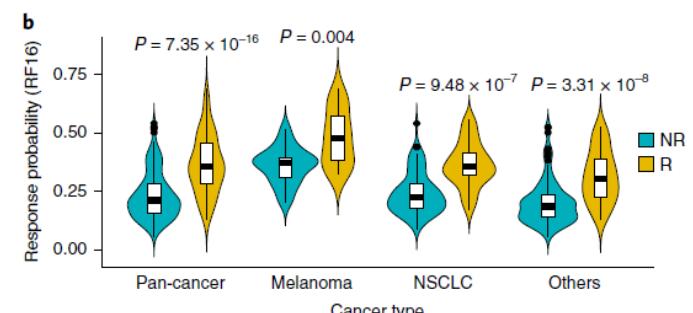
Bora et al, Lancet, 2021

Protein structure prediction (AlphaFold)



Jumper et al, Highly accurate protein structure prediction with AlphaFold, Nature 2021

Prediction of immune checkpoint blockade efficacy across multiple cancer types



Chowell et al, Nat Biotech, 2021

AI to the rescue

If we can teach computers to ...

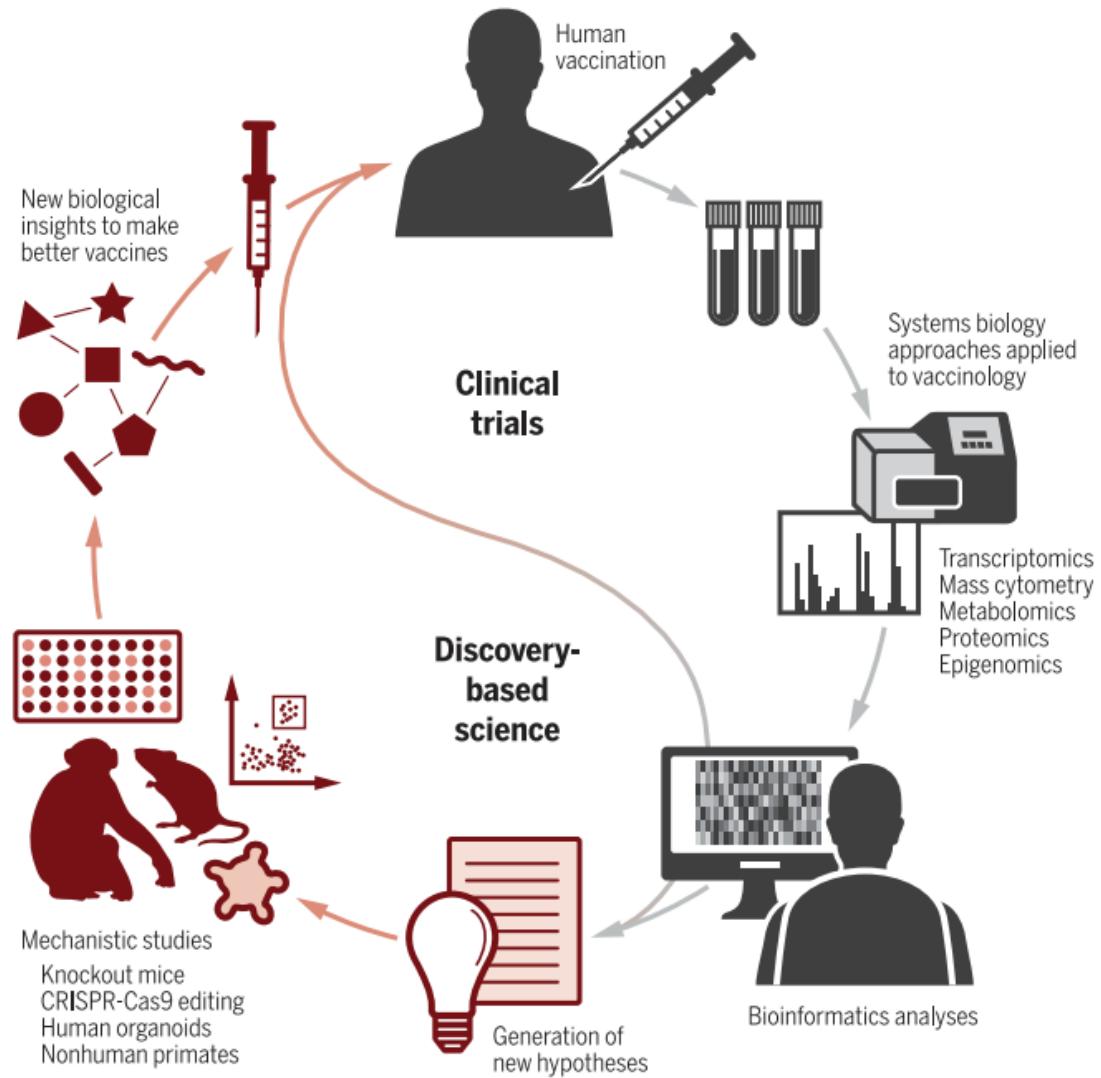
PLAY

DRAW

Can we teach them
IMMUNOLOGY?



Systems immunology approach for understanding human immune responses



When taking immunosuppressive medication, even for a short period, how are the different components of the immune system impacted? Does the whole system slow down or just individual components deactivate or become non-responsive? What are the long-term effects?

Table 2. Examples of Synthetic and Biologic Drugs for Treating Autoimmune Diseases

Target	Drug	Function	Examples of Clinical Use
JAKs			
	tofacitinib	inhibits JAK1, JAK2, JAK3	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis
	baricitinib	inhibits JAK1, JAK2	rheumatoid arthritis
Cytokines			
TNF	infliximab	inhibits TNF	Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis
IL-17a	secukinumab	inhibits IL-17A	psoriasis, ankylosing spondylitis, and psoriatic arthritis
IL-12/23p40	ustekinumab	inhibits IL-12 and IL-23	psoriasis
IL-23p19	guselkumab	inhibits IL23	psoriasis
IL-6R	tocilizumab	inhibits IL-6R	rheumatoid arthritis, juvenile idiopathic arthritis, neuromyelitis optica
B Cells			
	rituxan	depletes CD20 ⁺ B cells	multiple sclerosis, rheumatoid arthritis
	belimumab	inhibits BAFF	systemic lupus erythematosus
Integrins			
	natalizumab	blocks $\alpha 4\beta 1$ and $\alpha 4\beta 7$	multiple sclerosis
	vedolizumab	blocks a4b7	ulcerative colitis, Crohn's disease
Co-stimulatory Molecules			
	abatacept	blocks CD80 and CD86	rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis

Lars Fugger, Lise Torp Jensen, and Jamie Rossjohn. Challenges, Progress, and Prospects of Developing Therapies to Treat Autoimmune Diseases. *Cell*, 2022