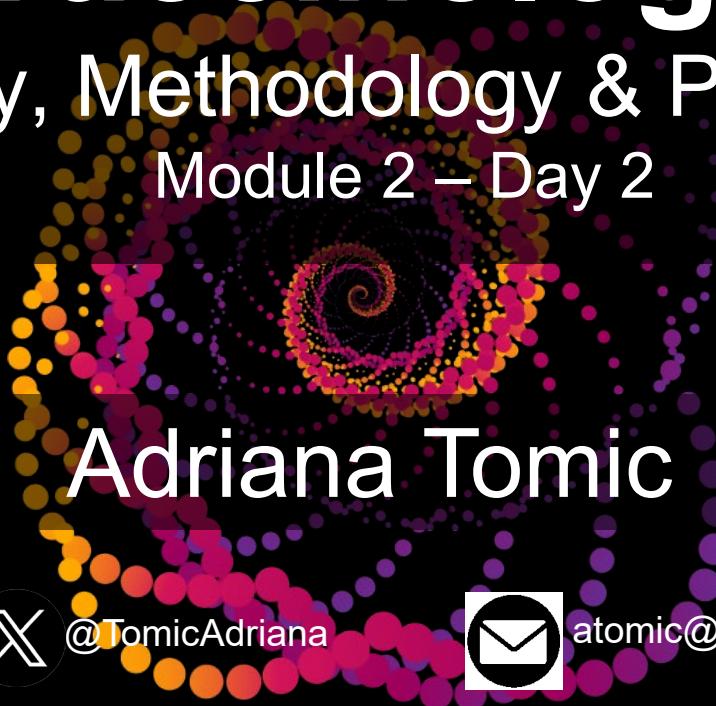


Human Systems Immunology & Vaccinology:

Theory, Methodology & Prospects

Module 2 – Day 2



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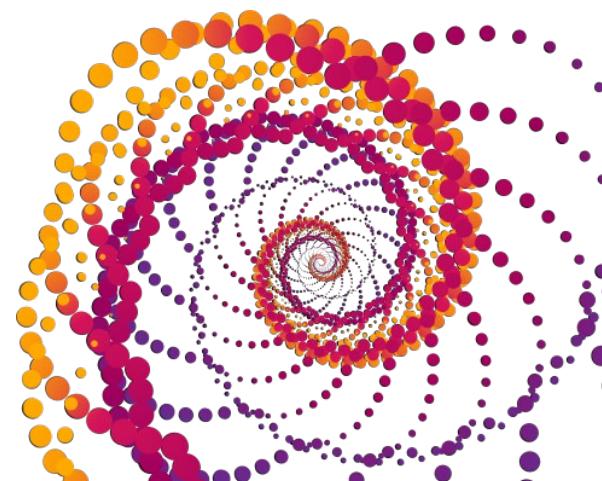
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Module 2 – Day 2 - overview

Part I – Lecture and Q&A

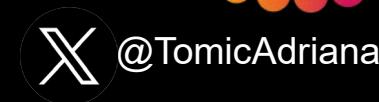
Part II – Team-specific tasks

- Teams selection *Activity (4:15-4:45pm) ~30min*
 - Overview of the team-specific tasks *Discussion (4:45-5:15pm) ~30min*



Bridging Science and Practice in Human Systems Immunology

Adriana Tomic



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Biological processes are
COMPLEX



Biological processes are
COMPLEX

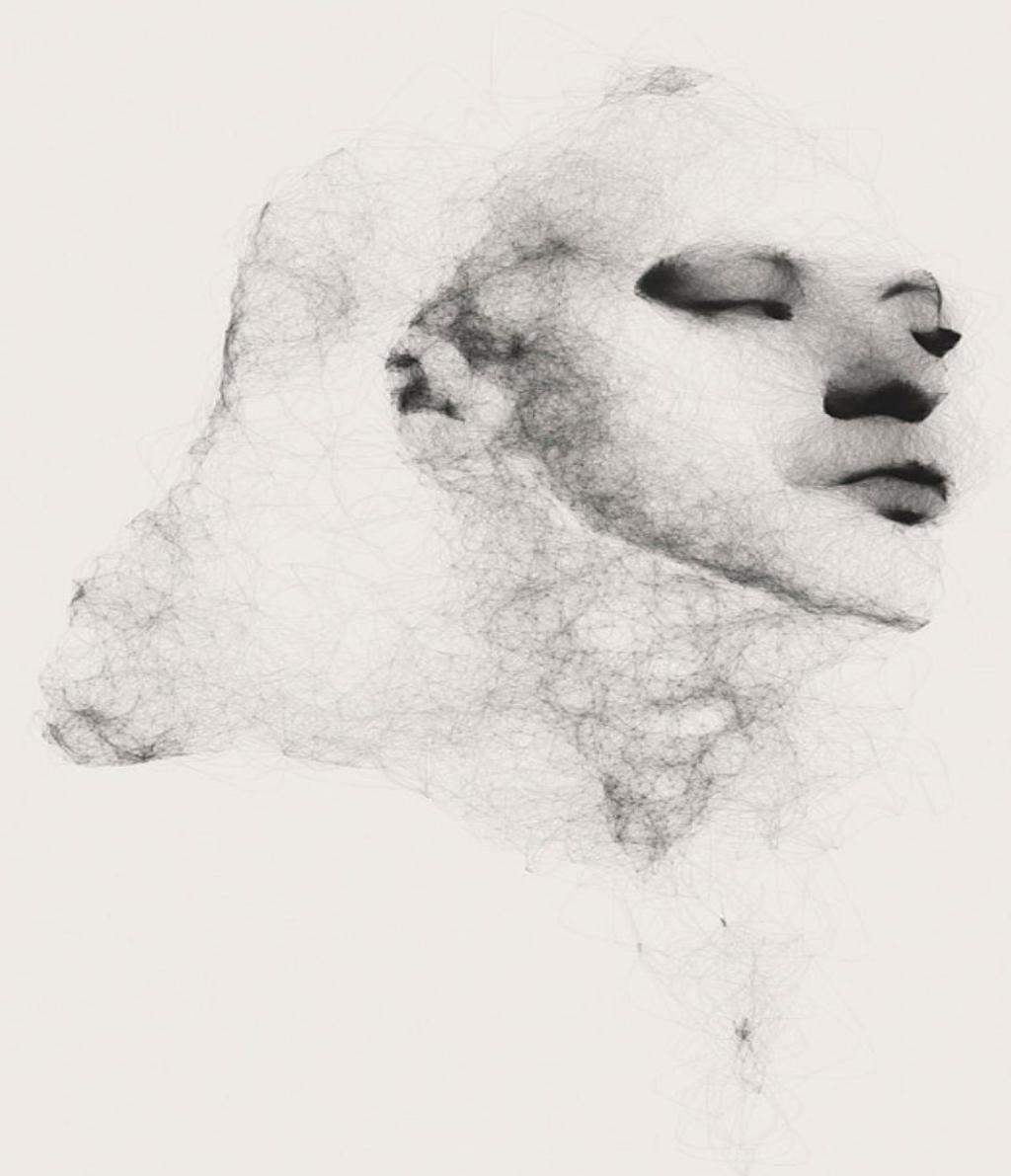
We need a
**DIFFERENT
PERSPECTIVE**



Biological processes are
COMPLEX

We need a
**DIFFERENT
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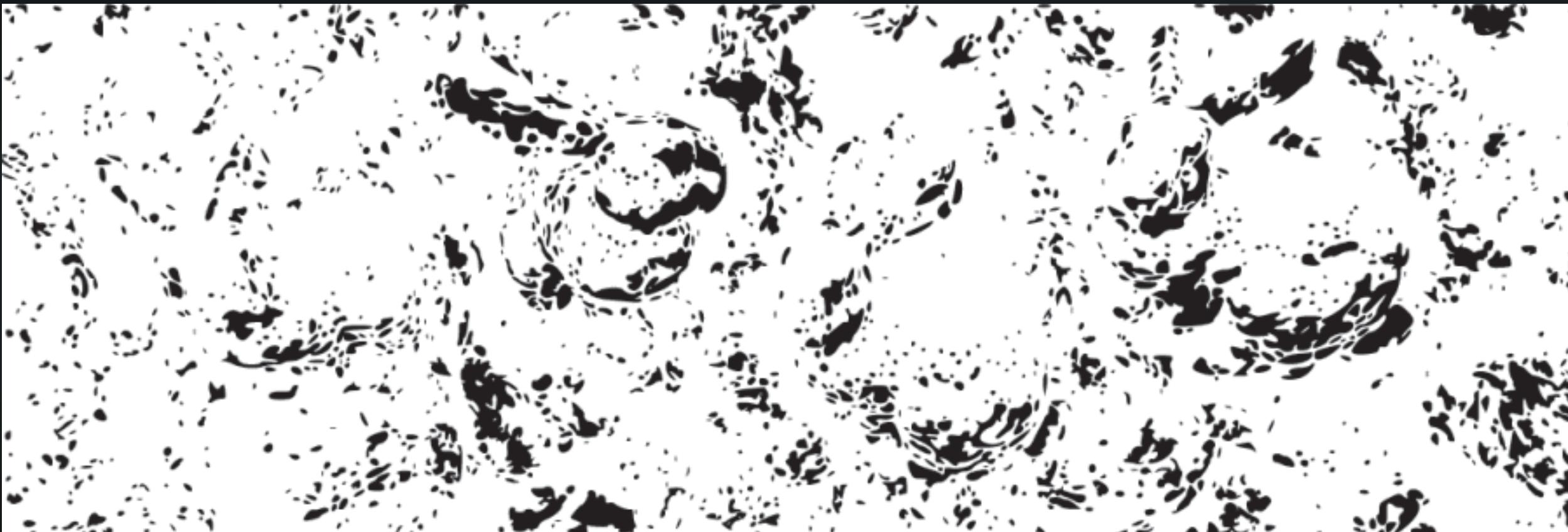
It is time for
**SYSTEMS
IMMUNOLOGY**



Diana Lange, OpenProcessing; <https://www.diana-lange.de/>

Systems immunology provides a holistic understanding of the immune system

Gestalt: Emergence



Niloy J. Mitra, Hung-Kuo Chu, Tong-Yee Lee, Lior Wolf, Hezy Yeshurun, Daniel Cohen-Or, Emerging images.

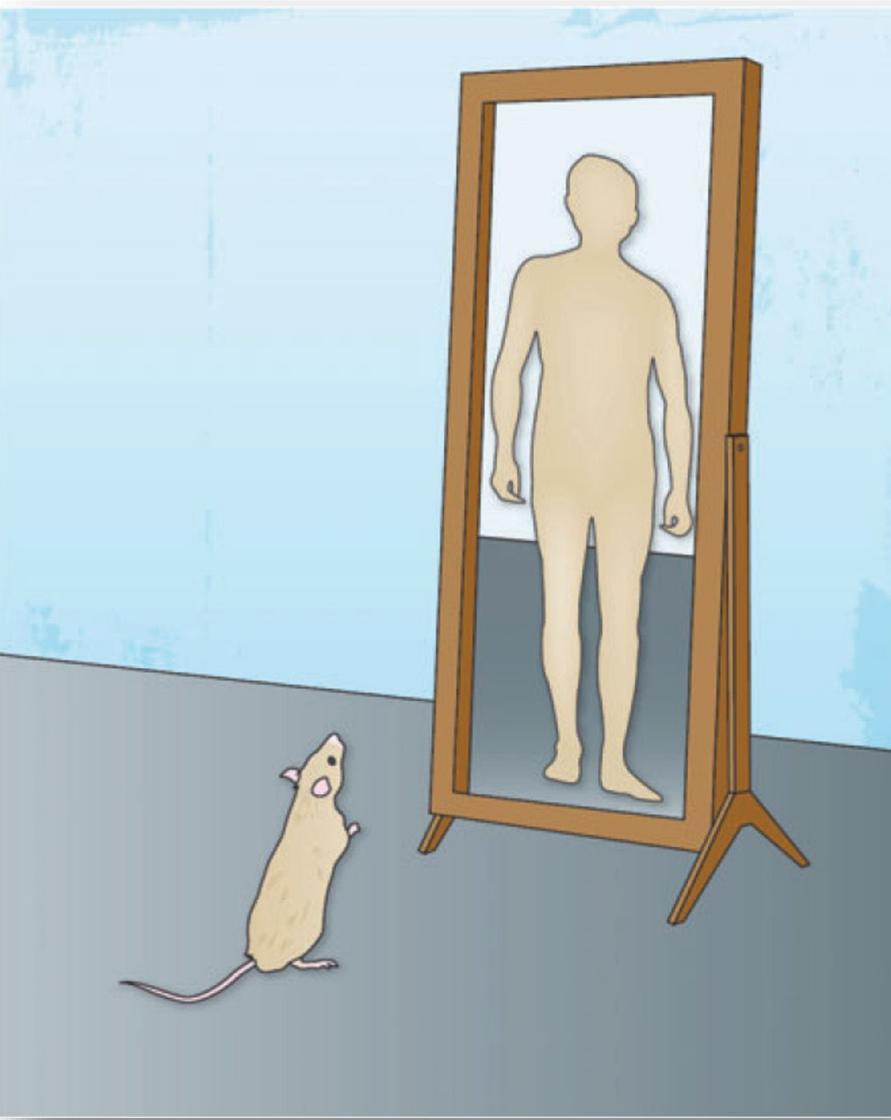
Immunology: Standing on the shoulders of ... mice



Table 1. Animal models have enabled many Nobel Prize-winning discoveries in immunology. Nobel Prize in Medicine or Physiology award dates are in chronological order.

Discovery	Animal model
Development of antitoxins against diphtheria and tetanus: Emil von Behring (1901 Nobel Prize) and Kitasato Shibasaburo	Guinea pigs, goats, horses, mice
Discovery of phagocytes and their role in innate immunity: Elie Metchnikoff (1908 Nobel Prize)	Starfish
Methods for standardization of antibody activity in immune sera, description of neutralizing and complement-depending effect of antibodies, and enunciation of the "side-chain" theory of the formation of antibodies: Paul Ehrlich (1908 Nobel Prize)	Guinea pigs, horses
Discovery of anaphylaxis reactions: Charles Richet (1913 Nobel Prize)	Dogs
Discovery of immunological tolerance: Peter Medawar and MacFarlane Burnet (1960 Nobel Prize)	Mice
Discovery of major histocompatibility genes: Baruj Benacerraf, Jean Dausset, and George Davis Snell (1980 Nobel Prize)	Mice
Method for generating monoclonal antibodies: Cesar Milstein and George Kohler (1984 Nobel Prize)	Mice
Discovery of mechanism of generating antibody diversity: Susumu Tonegawa (1987 Nobel Prize)	Mouse embryo
Invention of organ transplantation techniques: Joseph Murray and Donnall Thomas (1990 Nobel Prize)	Dogs
Discovery of the role of major histocompatibility complex (MHC) molecules in mediating detection and killing virally infected cells: Peter Doherty and Rolf Zinkernagel (1996 Nobel Prize)	Mice
Discovery of dendritic cells: Ralph Steinman (2011 Nobel Prize)	Mice
Discovery of the role of Toll-like receptors in innate sensing: Bruce Beutler and Jules Hoffman (2011 Nobel Prize)	Mice, fruit flies
Discovery of cancer immunotherapy by inhibition of negative immune regulation: James Allison and Tasuku Honjo (2019 Nobel Prize)	Mice

But humans are not mice – 80 million years of evolution apart

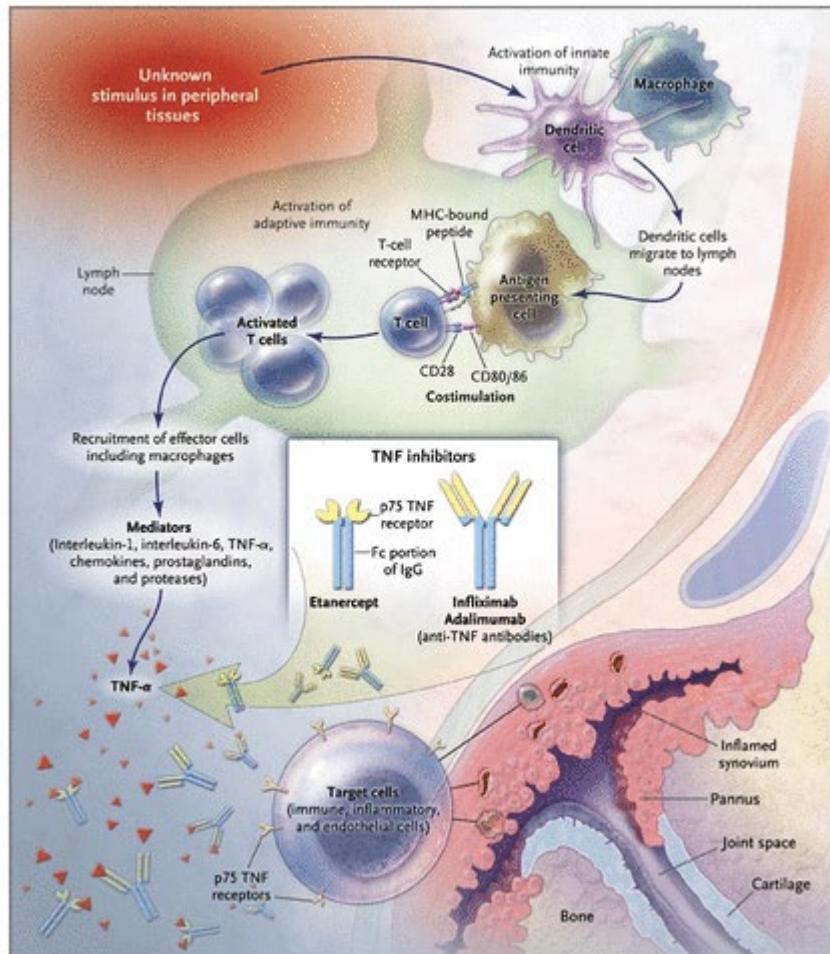


	<i>Mus musculus</i>	<i>Homo sapiens</i>
Evolutionary divergence		~65 to 80 million years
Genome		~3.1 billion base pairs ~30,000 protein-coding genes On average, 85% of protein-coding sequences are identical Only 50% of non-protein-coding regions are similar
Size	Weight: ~20 to 30 g; length: 7.5 to 10 cm	Weight: ~62 kg; height: 163 cm (females), 176 cm (males)
Some differences in the innate immune system	TLR7 on pDCs, myeloid DCs (150) TLR9 on myeloid cells, pDCs and B cells (150) TLR10: pseudogene (150) MyD88 knockout mice: impaired immunity to bacteria, viruses, and parasites (150)	TLR7 only on pDCs and B cells (150) TLR9 only on pDCs and B cells (150) TLR10: widely expressed (150) MyD88 mutant humans: susceptible to invasive pathogenic bacterial infections, but normal immunity to many bacteria, viruses, fungi, and parasites (151)
Some differences in the adaptive immune system	Ig subclasses: IgA, IgD, IgE, IgG1, IgG2a*, IgG2b, IgG3, IgM (152) *absent in C57BL/6, /10, SJL, and NOD mice, which have IgG2c Ig CDR-H3 region: shorter, less diverse (153) Effect of γ_c deficiency: loss of T, NK, and B cells (154)	Ig subclasses: IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, IgM (152) Ig CDR-H3 region: longer, more diverse (153) Effect of γ_c deficiency: loss of T, NK, but normal B cells (154)
	Effect of IL-7R deficiency: blocks T and B cell development (154, 155)	Effect of IL-7R deficiency: only blocks T cell development (154, 155)

Pulendran B and Davis M. Science, 2020

Development of successful therapies

Tumor necrosis factor (TNF) inhibitors for rheumatoid arthritis



Scott, D.L. and Kingsley, G.H. Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis. NEJM, 2006

Checkpoint inhibitors (anti-CTLA4 and anti-PD-1) as a tumor therapy

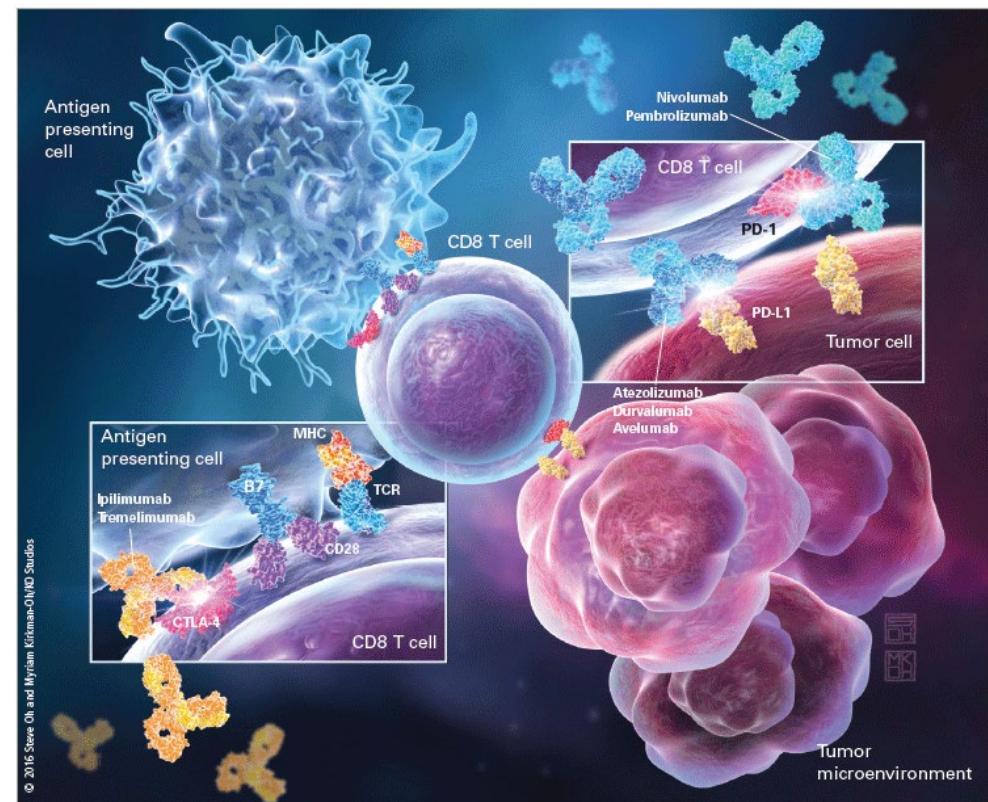


Figure. Immune Checkpoint Inhibition Mechanisms of Action Relevant to Lung Cancer Immunotherapy—T cells express CTLA-4 antigens on their cell surfaces, which downregulate T-cell function. Anti-CTLA-4 antibodies can bind to CTLA-4 on T cells and reverse this T-cell activation downregulation. PD-1 proteins on T cells bind to PD-L1 and PD-L2 ligands on cancer cell and antigen presenting cell surfaces, preventing T-cell activation and cell-mediated antitumor immune responses. Anti-PD-1 antibodies bind to PD-1, preventing interaction with its ligands; anti-PD-L1 antibodies bind to PD-L1 and/or PD-L2, preventing interaction with PD-1. CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; MHC = major histocompatibility complex; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

TGN1412 (CD28-Super agonist mAb): The horror

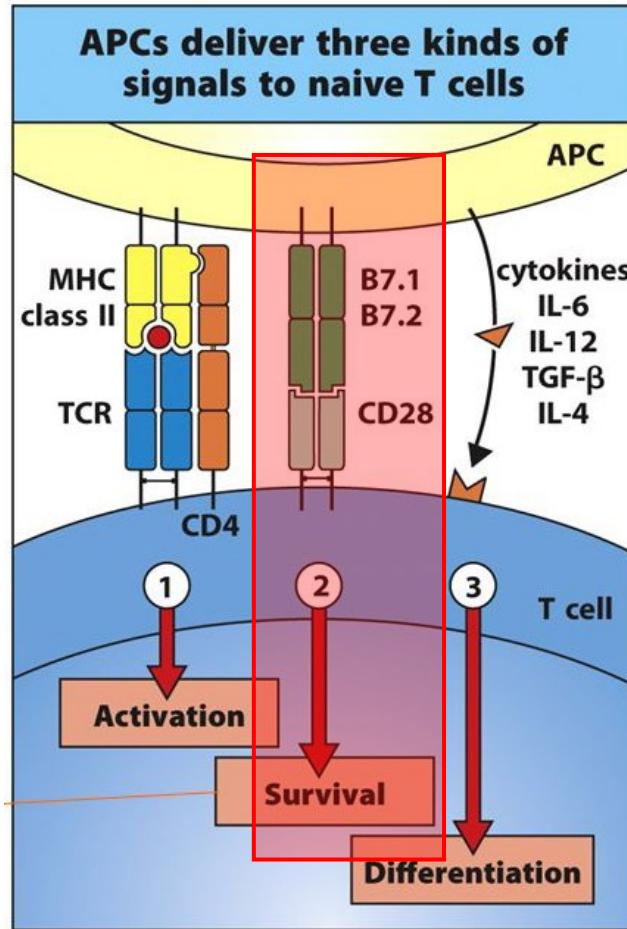


Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

TeGenero, 2006, clinical trial in 6 healthy subjects
– within 90min of injection all 6 volunteers had a severe cytokine storm and multi-organ failure



Could this horror be avoided? Well even monkeys are not human!



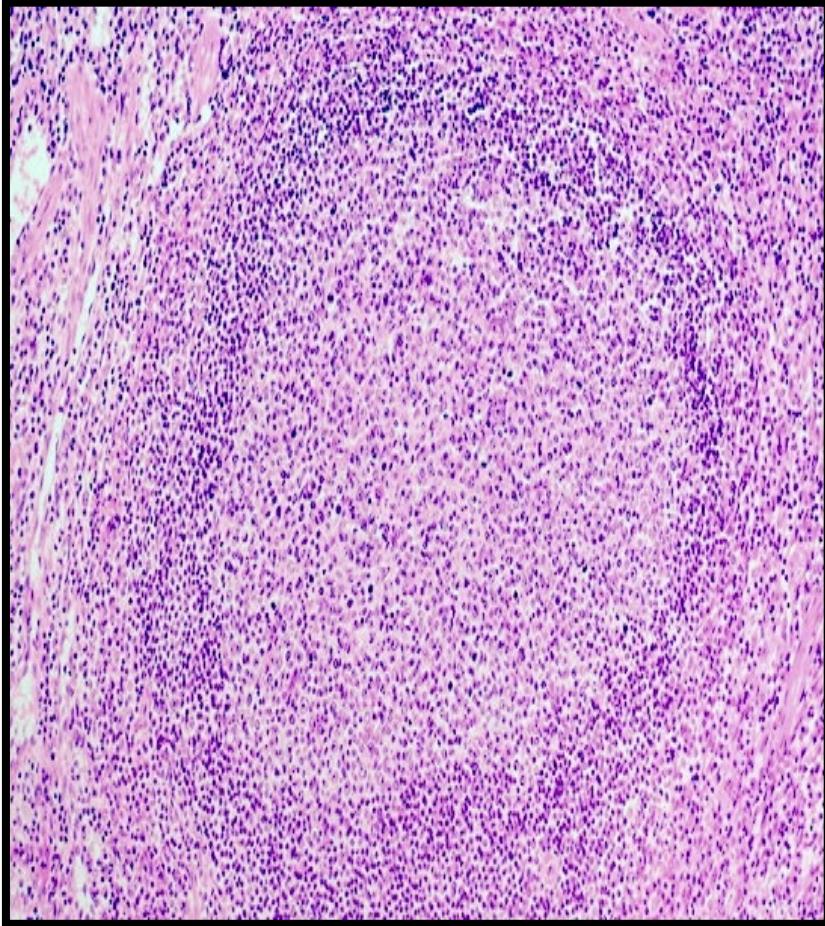
Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4⁺ effector memory T-cells

Eastwood et al, BJP, 2010

In vitro data revealed that the CD4+ effector memory T-cells of *Macaca fascicularis*, the species of primate used for pre-clinical safety testing of TGN1412, lack CD28 expression. Since CD28 is the target of the TGN1412 antibody, *M. fascicularis* effector T-cells could not be stimulated by the drug

Functionality of CD8+ T cells

Tissue



Germinal center

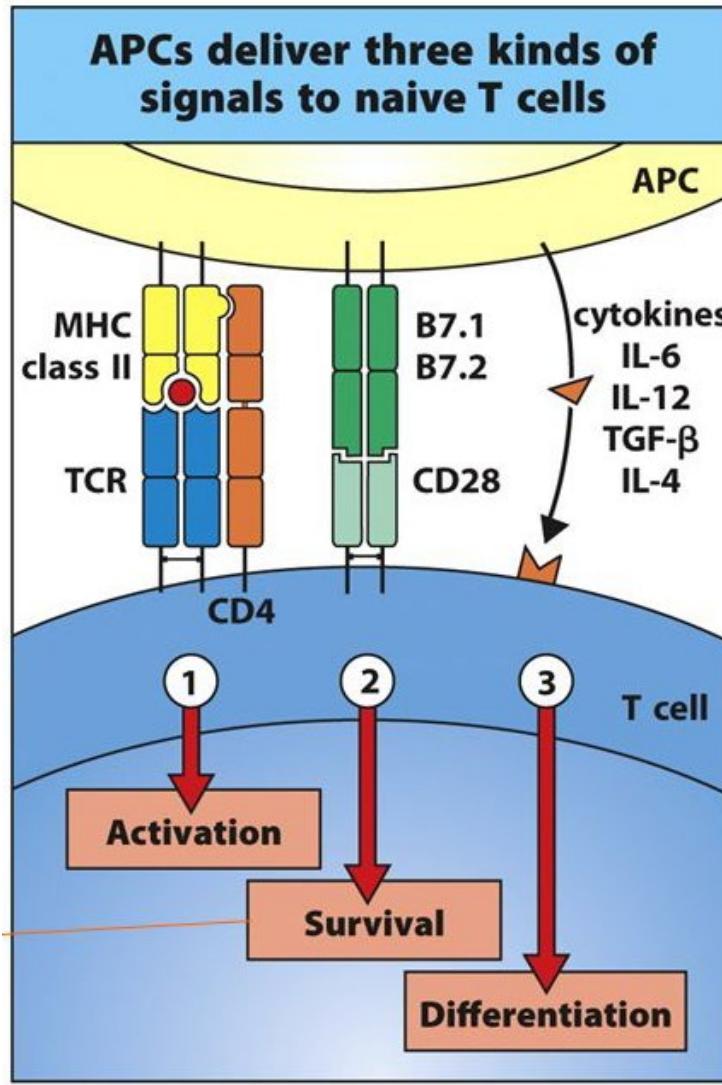


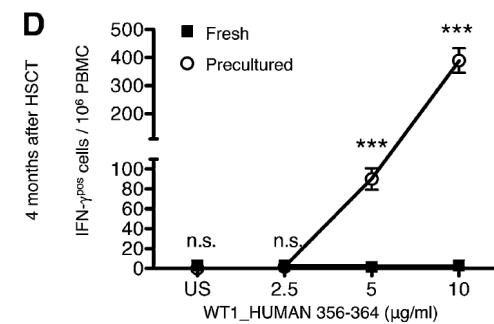
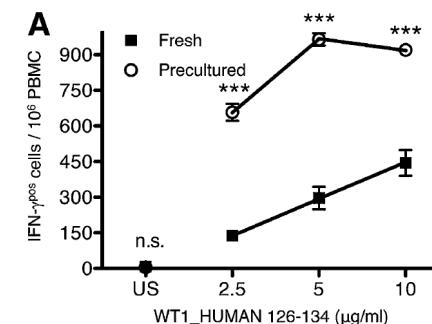
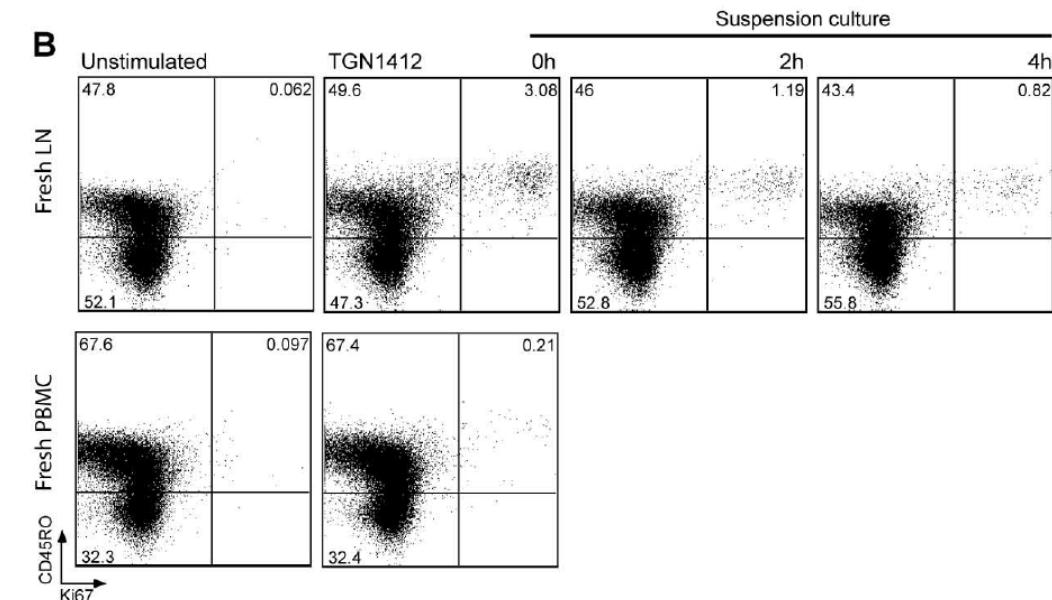
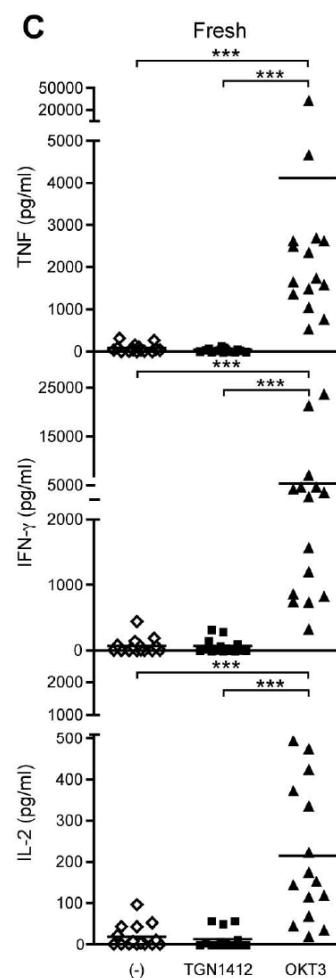
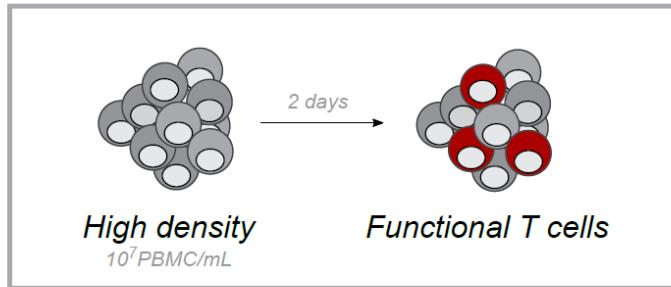
Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

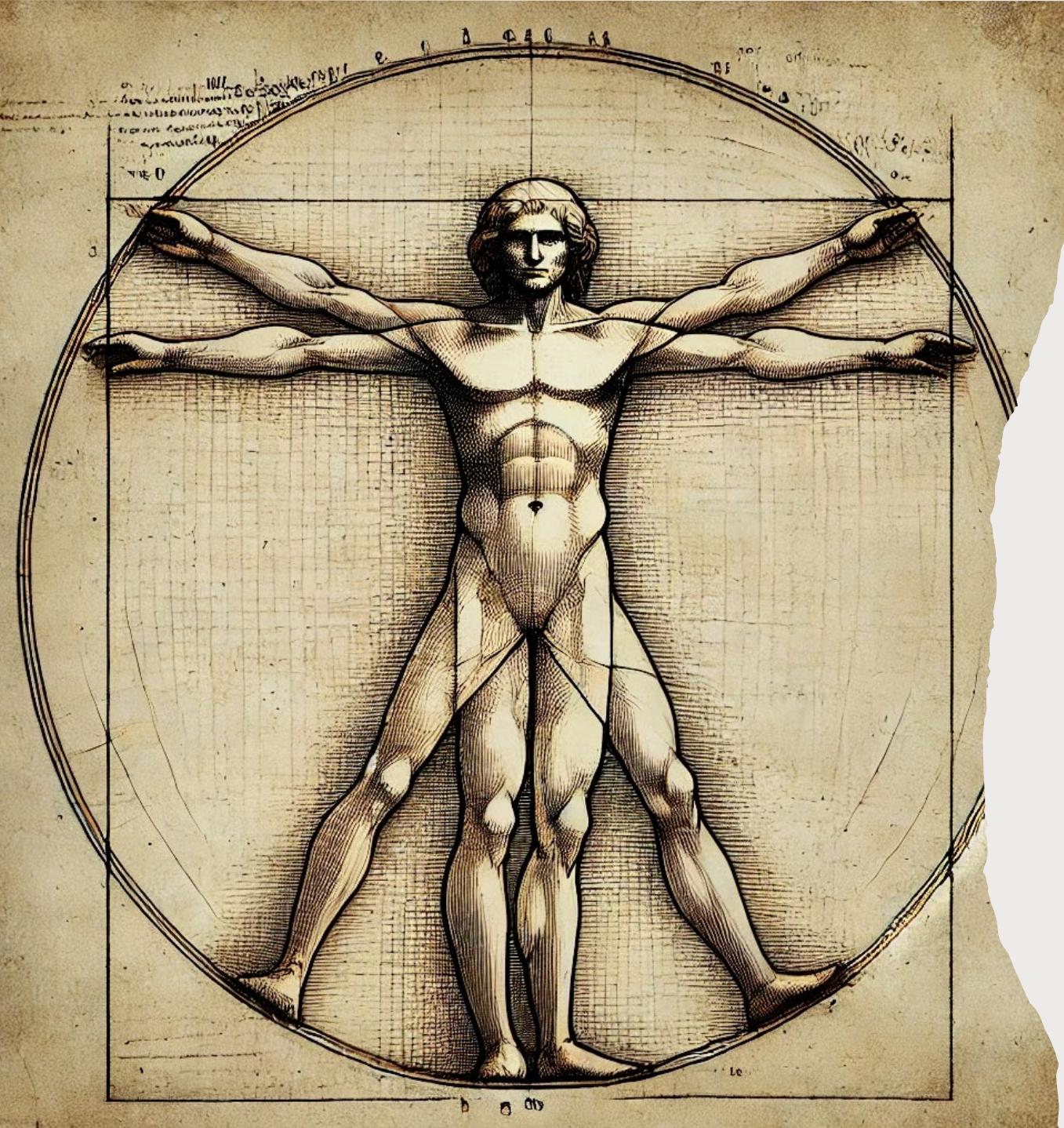
Blood



Could this horror be avoided? Circulating T cells are not functional!

RESTORE protocol (Romer et al. Blood, 2011)

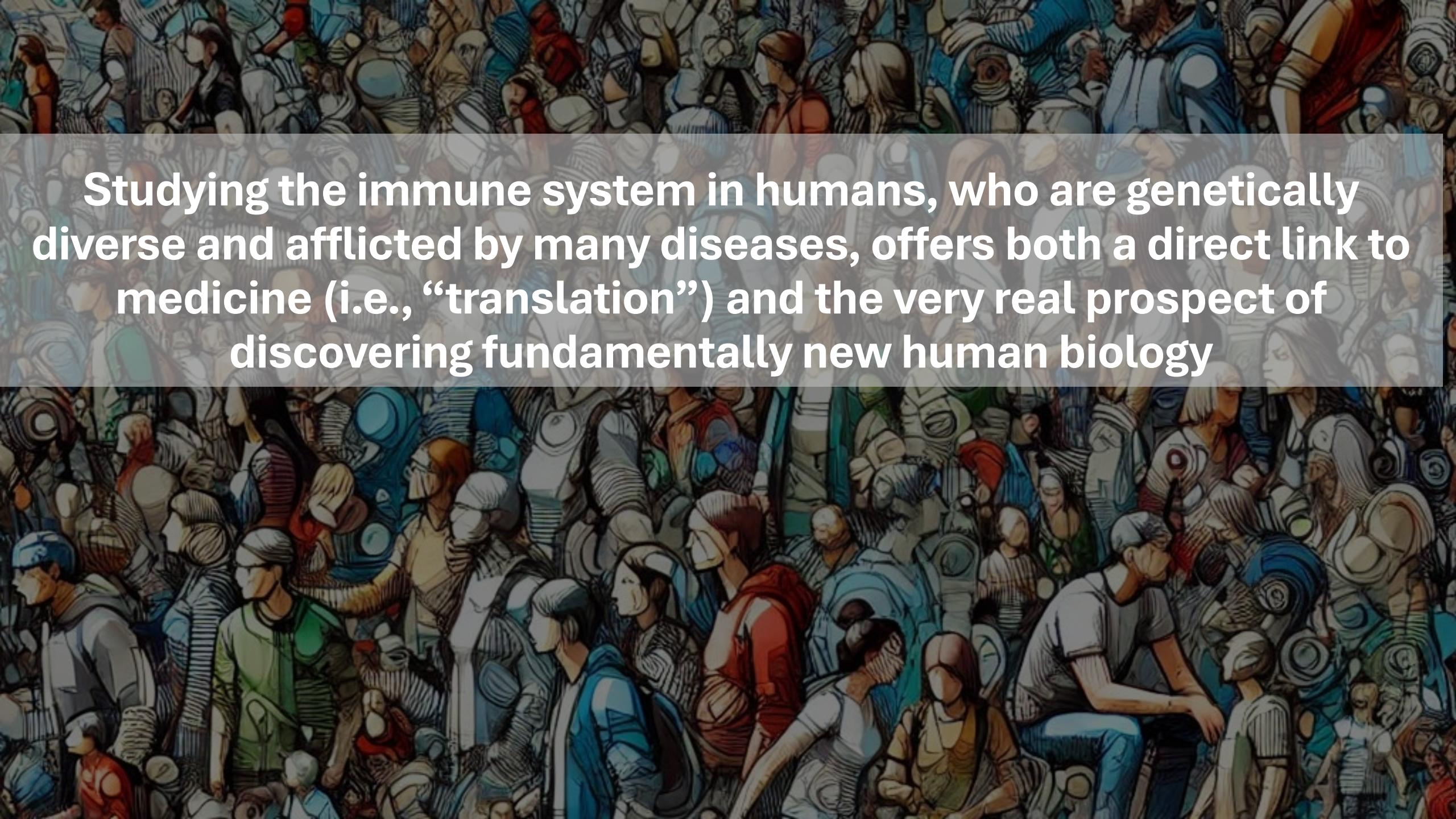




Solution: Using the ultimate animal model

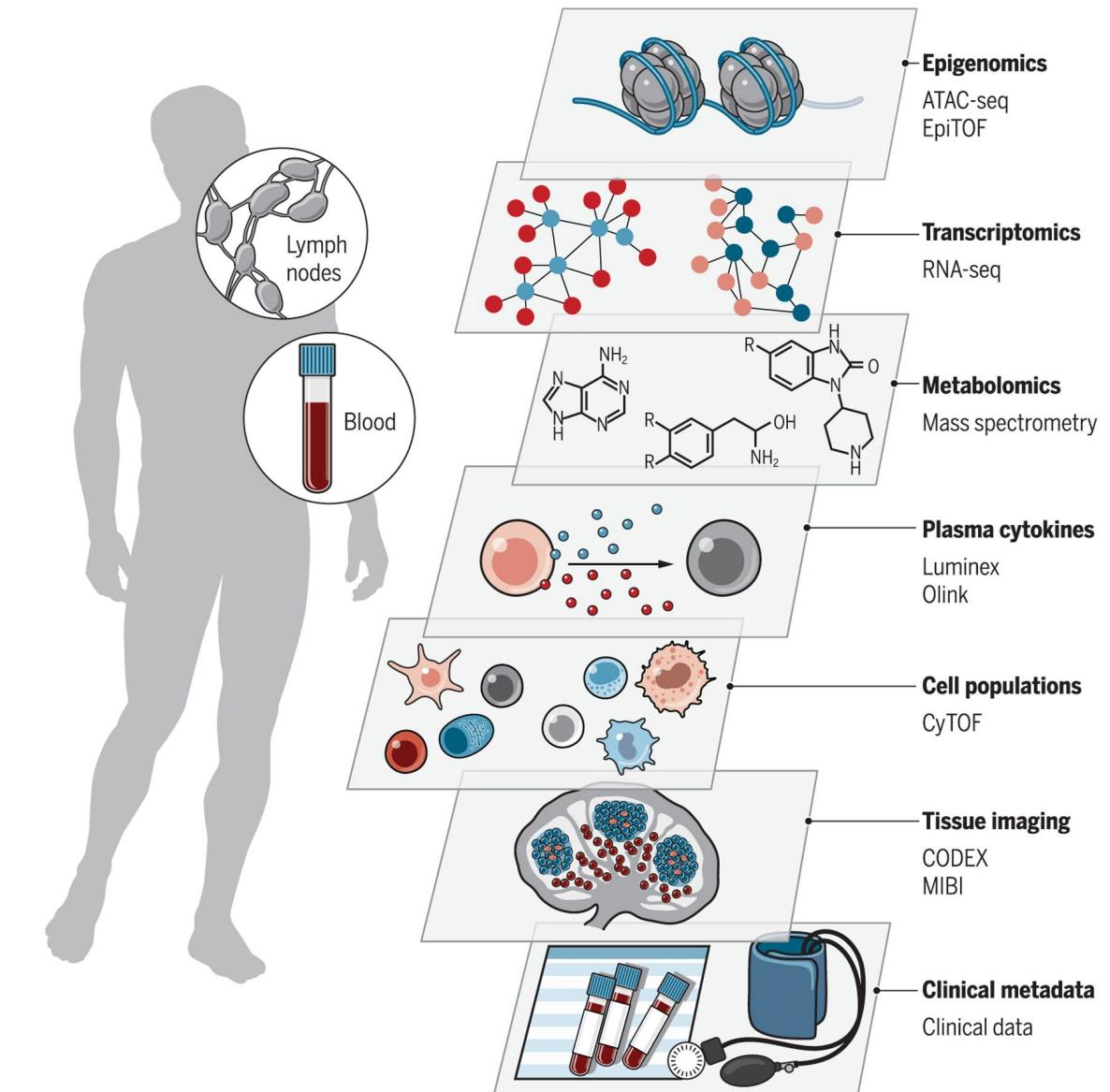
“We don’t have to look for a model organism anymore. Because we are the model organisms.”

Sydney Brenner 2008



Studying the immune system in humans, who are genetically diverse and afflicted by many diseases, offers both a direct link to medicine (i.e., “translation”) and the very real prospect of discovering fundamentally new human biology

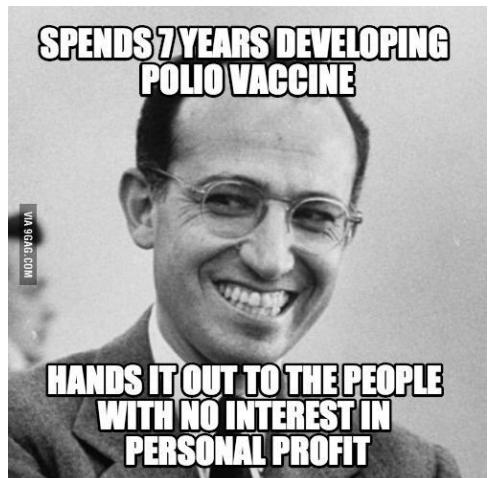
HUMAN SYSTEMS IMMUNOLOGY



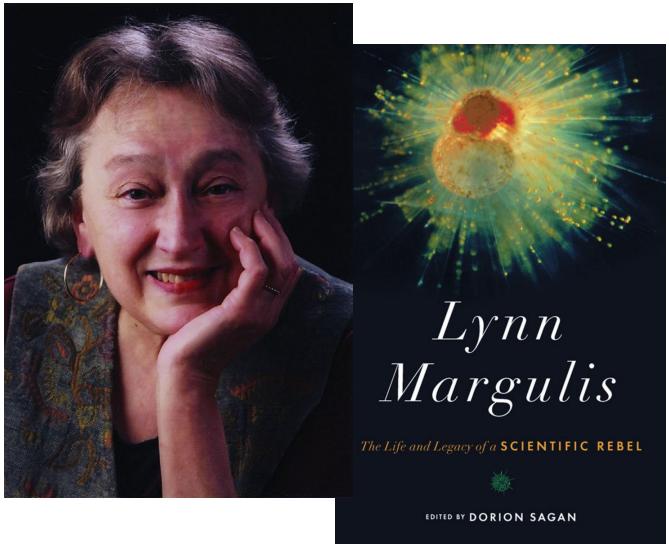
Pulendran B and Davis M. Science, 2020

6 TEAMS

TEAM 1: JONAS SALK



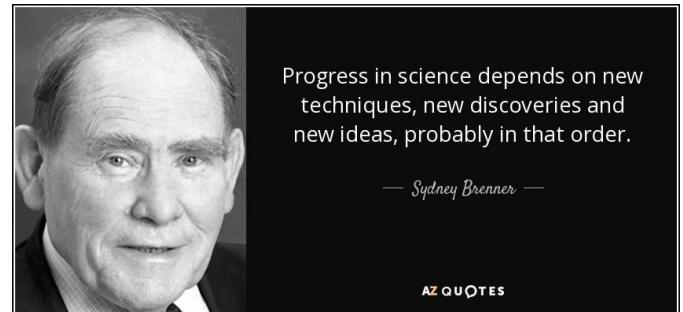
TEAM 3: LYNN MARGULIS



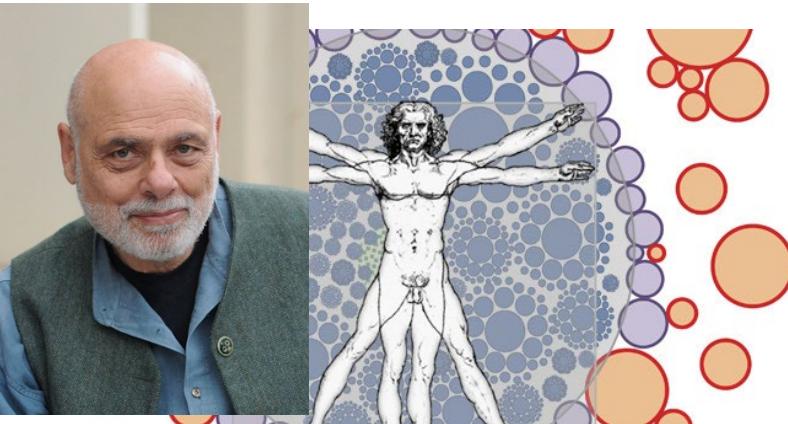
TEAM 5: POLLY MATZINGER



TEAM 2: SYDNEY BRENNER



TEAM 4: IRUN COHEN



TEAM 6: DENIS NOBLE

