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CONNECTING DATA TO HEALTH

A translational immunologist's perspective on mirror organism

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While we are discussing…

Generative design of novel bacteriophages with genome language models

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Abstract

Many important biological functions arise not from single genes, but from complex interactions encoded by entire genomes. Genome language models have emerged as a promising strategy for designing biological systems, but their ability to generate functional sequences at the scale of whole genomes has remained untested. Here, we report the first generative design of viable bacteriophage genomes. We leveraged frontier genome language models, Evo 1 and Evo 2, to generate whole-genome sequences with realistic genetic architectures and desirable host tropism, using the lytic phage ΦX174 as our design template. Experimental testing of AI-generated genomes yielded 16 viable phages with substantial evolutionary novelty. Cryo-electron microscopy revealed that one of the generated phages utilizes an evolutionarily distant DNA packaging protein within its capsid. Multiple phages demonstrate higher fitness than ΦX174 in growth competitions and in their lysis kinetics. A cocktail of the generated phages rapidly overcomes ΦX174-resistance in three *E. coli* strains, demonstrating the potential utility of our approach for designing phage therapies against rapidly evolving bacterial pathogens. This work provides a blueprint for the design of diverse synthetic bacteriophages and, more broadly, lays a foundation for the generative design of useful living systems at the genome scale.

Stanford researchers have used AI to design real, working viruses in the lab, raising major questions about safety, regulation, and future use.

The Research

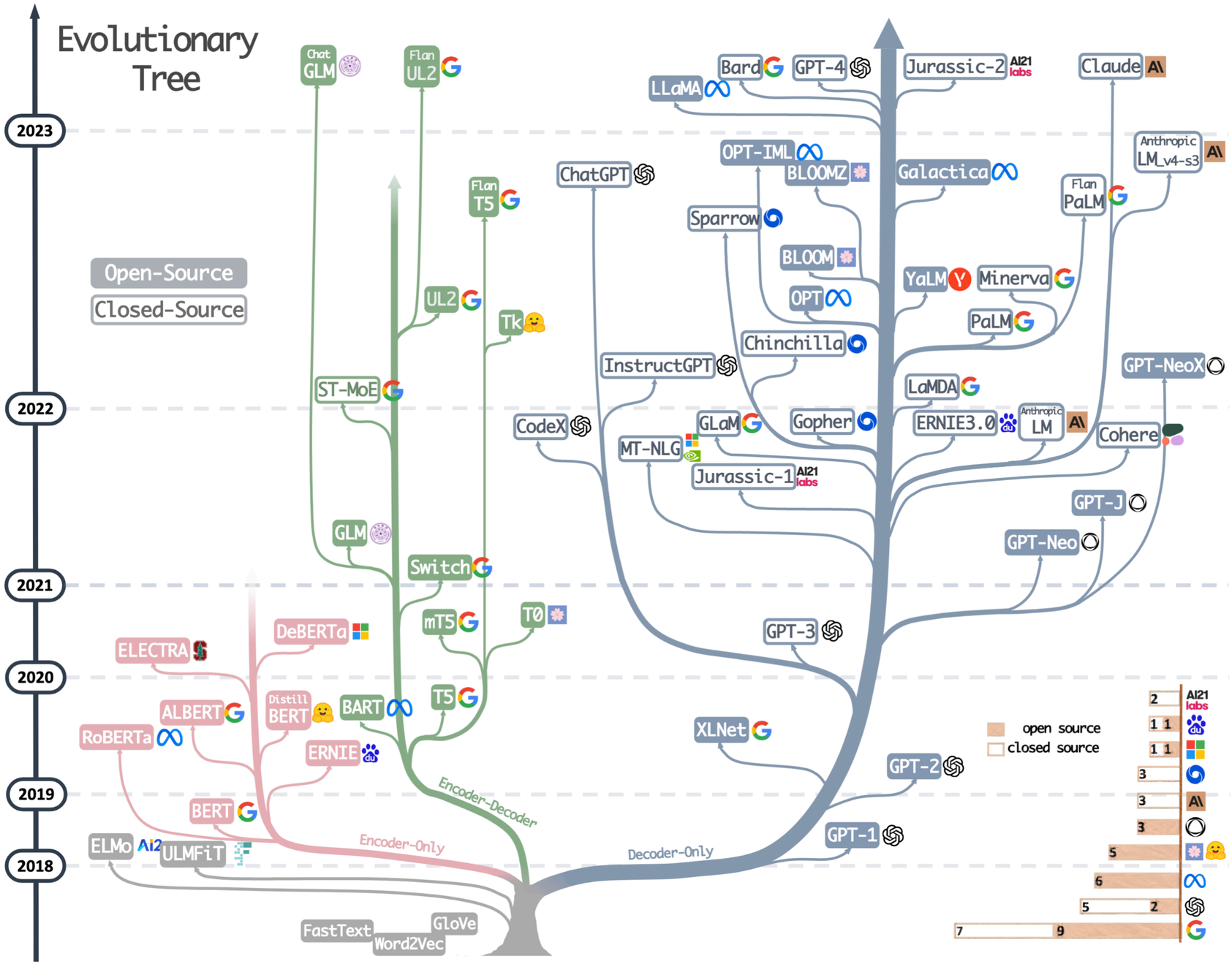
This month (September 2025), a team led by Brian Hie at Stanford and the Arc Institute revealed that generative AI models can now design entire genome-scale viruses that work in practice. These were not simulations or theoretical sequences. The viruses were tested and validated in a lab, and in some cases outperformed their natural equivalents.

Synthetic Versions Created

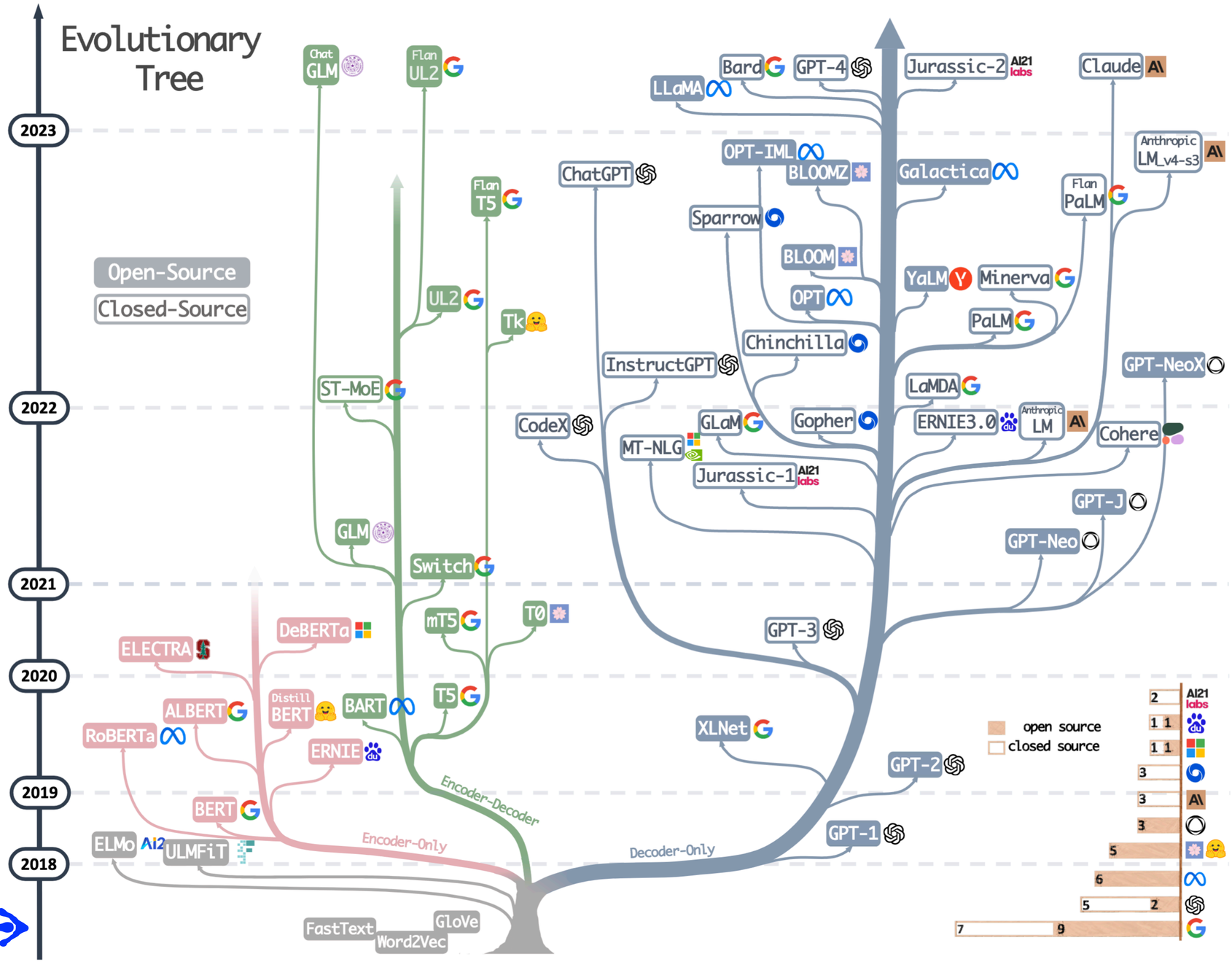
The AI-created viruses were synthetic versions of ΦX174, a bacteriophage that infects E. coli. Using large language models trained on genetic data, the team designed dozens of new variants. Lab tests showed many of these were viable and highly infectious against bacterial hosts.

In three separate experiments, the synthetic phages (viruses that infect and kill bacteria) infected and killed bacteria more effectively than natural ΦX174. The researchers reported that, in one case, the natural version didn't even make the top five.

Evolution of foundational models in natural language



Evolution of foundational models in natural language



We are here

Immune system has special privileges

- Exclusive access to all organs
  (Tasked to surveil entire organism)
- Only organ system evolutionarily allowed to be mobile
- Only organ system allowed to expand and contract as needed
- Continuously evolving over lifespan
- Has memory

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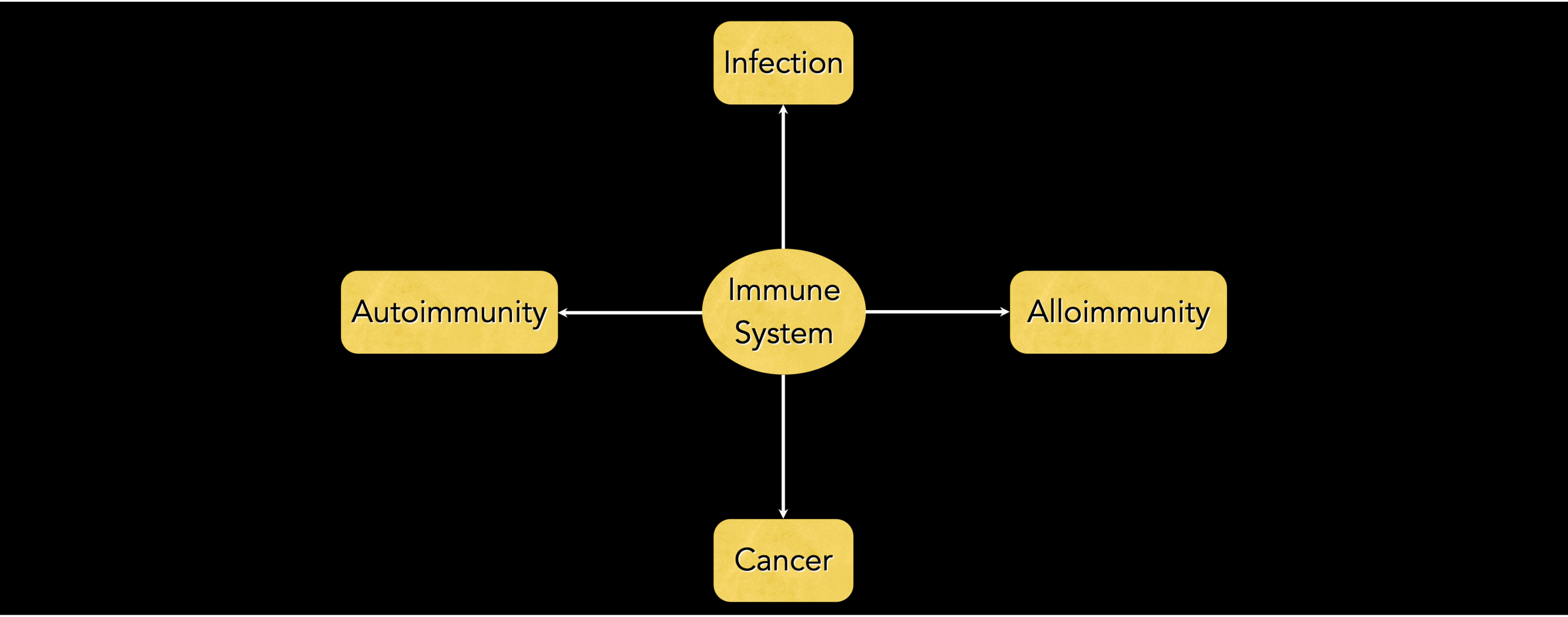
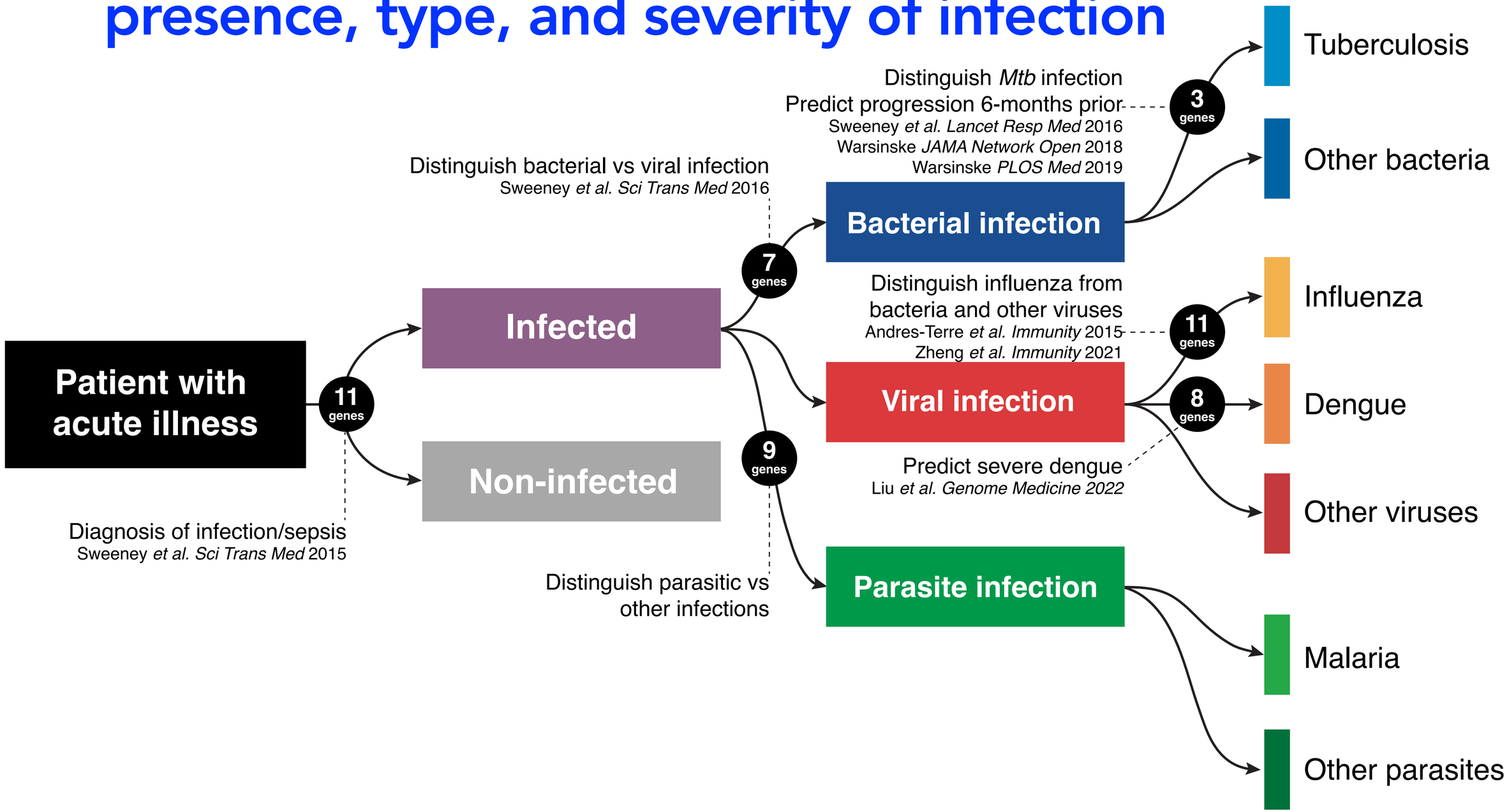
- Detect any infection
  (Not just bloodstream infections)
- Differentiate infection types including emerging pathogens
- Risk-stratify patients
- Predict treatment response

Hypothesis: Immune response can serve as diagnostic and prognostic tool for inflammatory conditions



August 7, 2012

Host immune responses to pathogens can diagnose presence, type, and severity of infection



Host response is entering clinical practice

Article https://doi.org/10.1038/s41591-025-03933-y

Clinical validation of an AI-based blood testing device for diagnosis and prognosis of acute infection and sepsis

Article https://doi.org/10.1038/s41591-025-03956-5

A consensus immune dysregulation framework for sepsis and critical illnesses

Article https://doi.org/10.1038/s41591-025-03964-5

A consensus blood transcriptomic framework for sepsis

Risks of mirror organism for immune system

- Many lessons learned over 3.8 billion years of evolution would not apply
- Reduced efficacy of current diagnostics, therapies, and treatment protocols
    - It takes 17 years to change clinical practice
    - Restricted global access
        - Vaccines during pandemic

Medical News & Perspectives

It Takes an Average of 17 Years for Evidence to Change Practice—the Burgeoning Field of Implementation Science Seeks to Speed Things Up

Rita Rubin, MA

JAMA 2023

Risks of mirror organism for immune system

- Partial immune invasion
  - Inability to clear infection/pollutant
  - Could lead to chronic infection
  - Long-term risk of chronic diseases
  - Epigenetic effects over long term
    - Think sugar, smoking
    - Not immunogenic over short term, but serious chronic illnesses over long-term

ORIGINAL RESEARCH

Viridans Streptococcal Biofilm Evades Immune Detection and Contributes to Inflammation and Rupture of Atherosclerotic Plaques

Pekka J. Karhunen, MD, PhD; Tanja Pessi, PhD; Sohvi Hörkkö, MD, PhD; Vesa Karhunen, DDS; Sirkka Goebeler, MD, PhD; Anne-Mari Louhelainen, MD; Mika Martiskainen, MD; Teppo Haapaniemi, MSc; Johanna Lappeteläinen, MSc; Tommi Ijäs, MSc; Leo-Pekka Lyytikäinen, MD; Emma Raitoharju, PhD; Thanos Sioris, MD, PhD; Sari Tuomisto, PhD; Heini Huhtala, MSc; Chunguang Wang, MD, PhD; Claudia Monaco, MD, PhD; Niku Oksala, MD, PhD, DSc (med); Terho Lehtimäki, MD, DDS, PhD; Reijo Laaksonen, MD, PhD

CONCLUSIONS: Latent chronic bacterial inflammation evades immune detection and may contribute to the pathogenesis of complicated atherosclerotic plaques and fatal myocardial infarction.

JAHA 2025

Risks of mirror organism for immune system

- Complete immune evasion
  - Sepsis
  - Fatal

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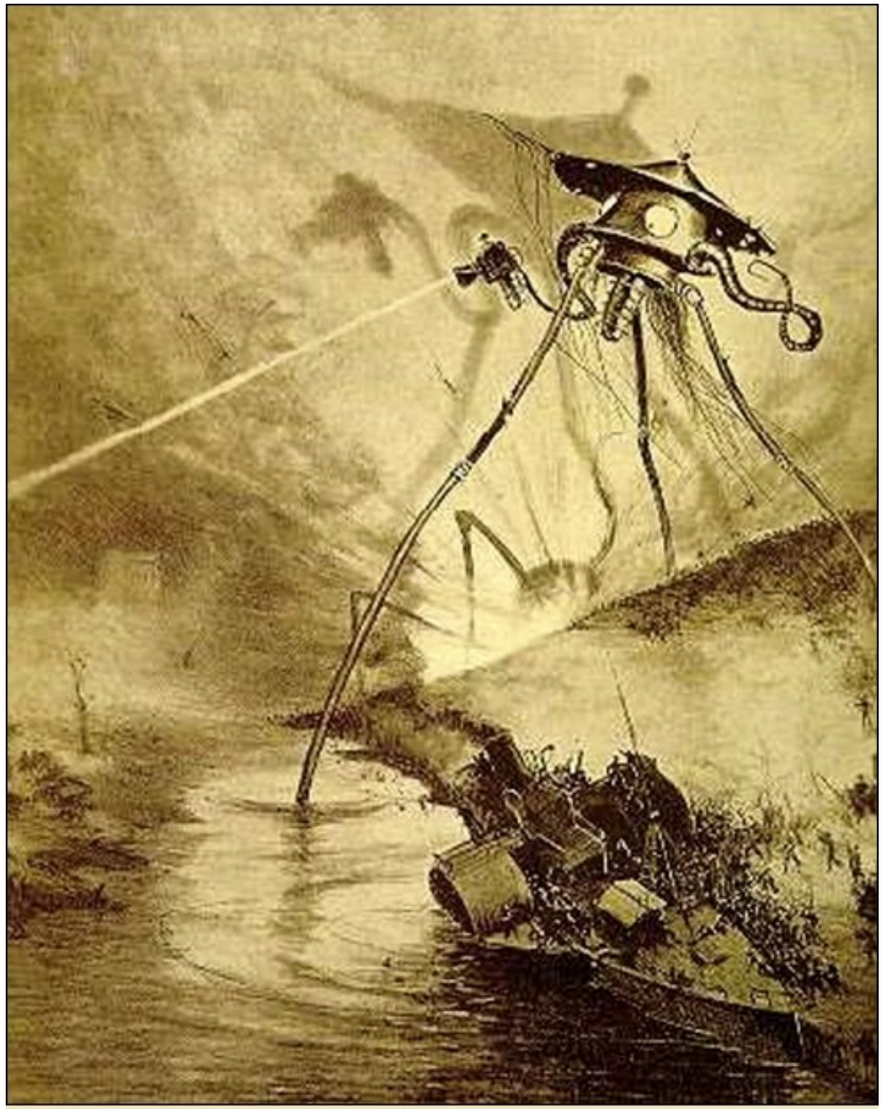

Martian fighting machines in the Thames Valley.

"War of the worlds"

Image: Wikipedia