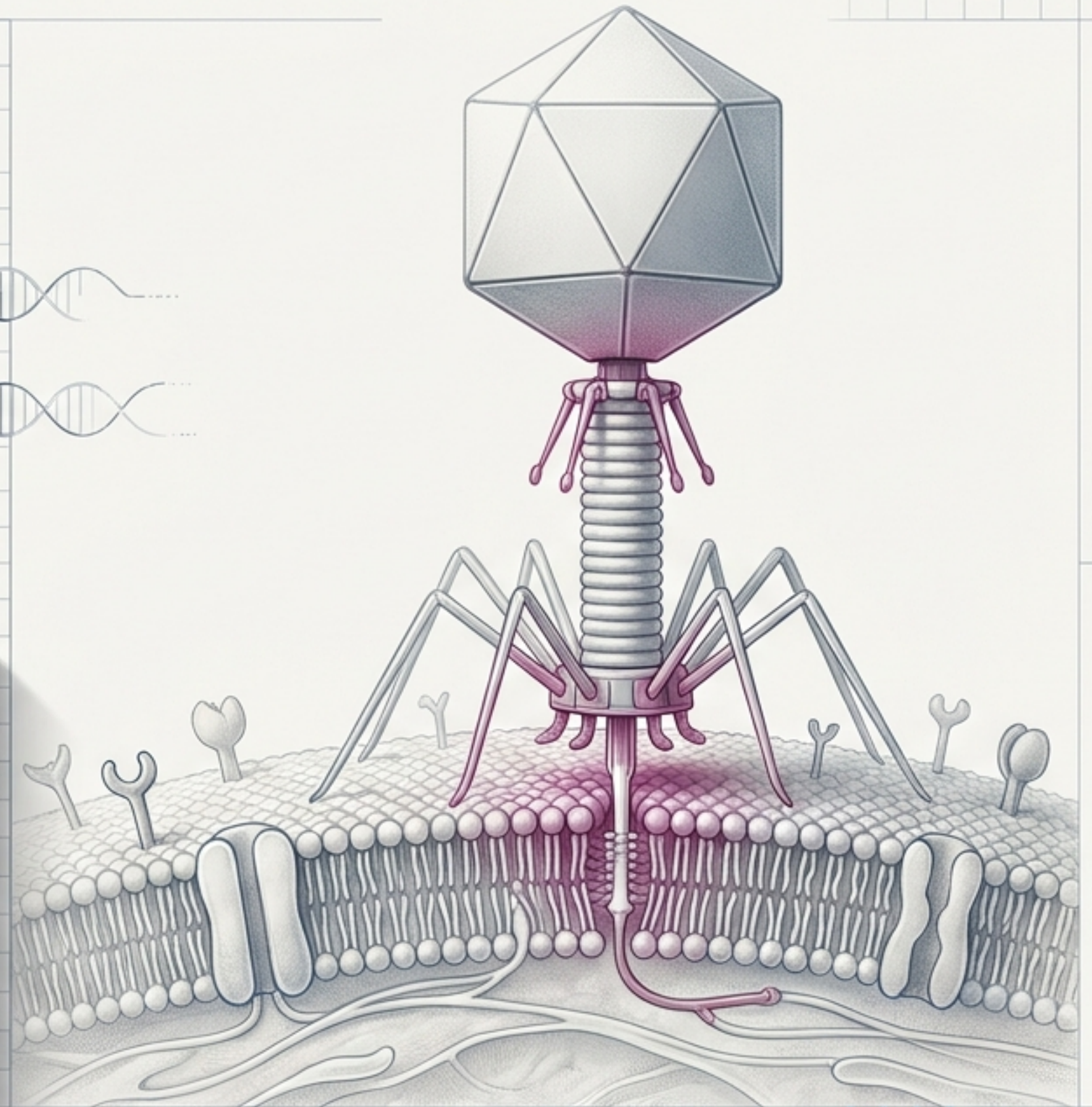


Project Blueprint: The Generative Phage Platform

Solving Antimicrobial Resistance through AI-Driven Genome Design and Precision Synthetic Biology.

A Closed-Loop Architecture for Next-Generation Living Therapeutics.



4.95M

Deaths

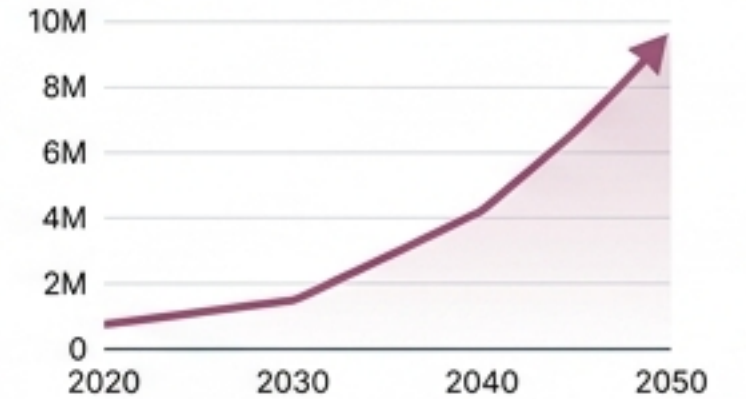
Associated with Antimicrobial Resistance in 2019. 1.2M directly attributable.



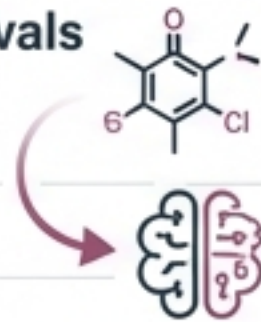
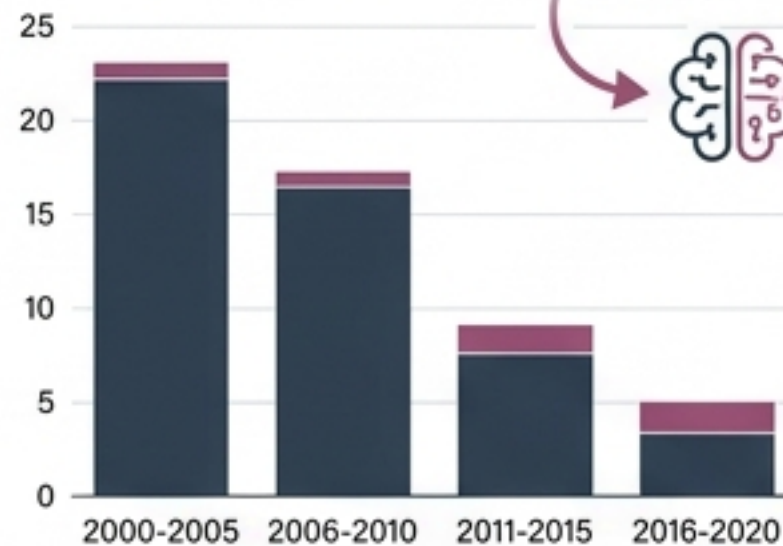
10M

Deaths by 2050

Projected annual toll, costing the global economy \$1 Trillion/year.



New Antibiotic Approvals (Last Two Decades)



The Global Mandate: Static chemicals cannot defeat dynamic, evolving pathogens. **We require therapeutics that can out-evolve the threat.**



The Renaissance: Clinical Validation



1917:

Felix d'Herelle discovers the "bacteria eater".



1930s-1940s:

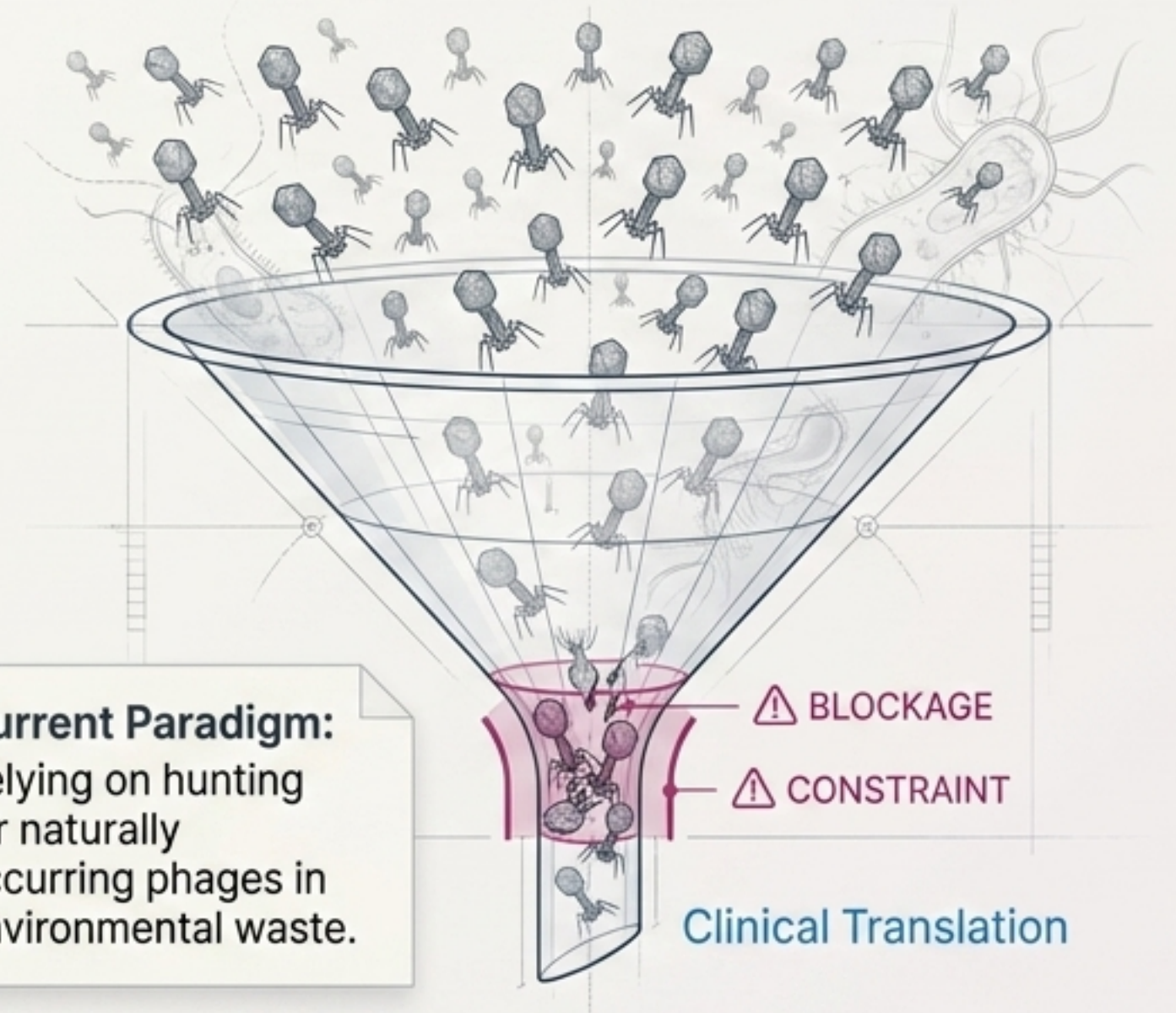
Widespread use before the penicillin era.



2016:

The Patterson Case. Clinical validation curing a terminal multidrug-resistant infection.

The Limitation: The Bio-Propecting Bottleneck



Current Paradigm:
Relying on hunting for naturally occurring phages in environmental waste.

⚠ BLOCKAGE

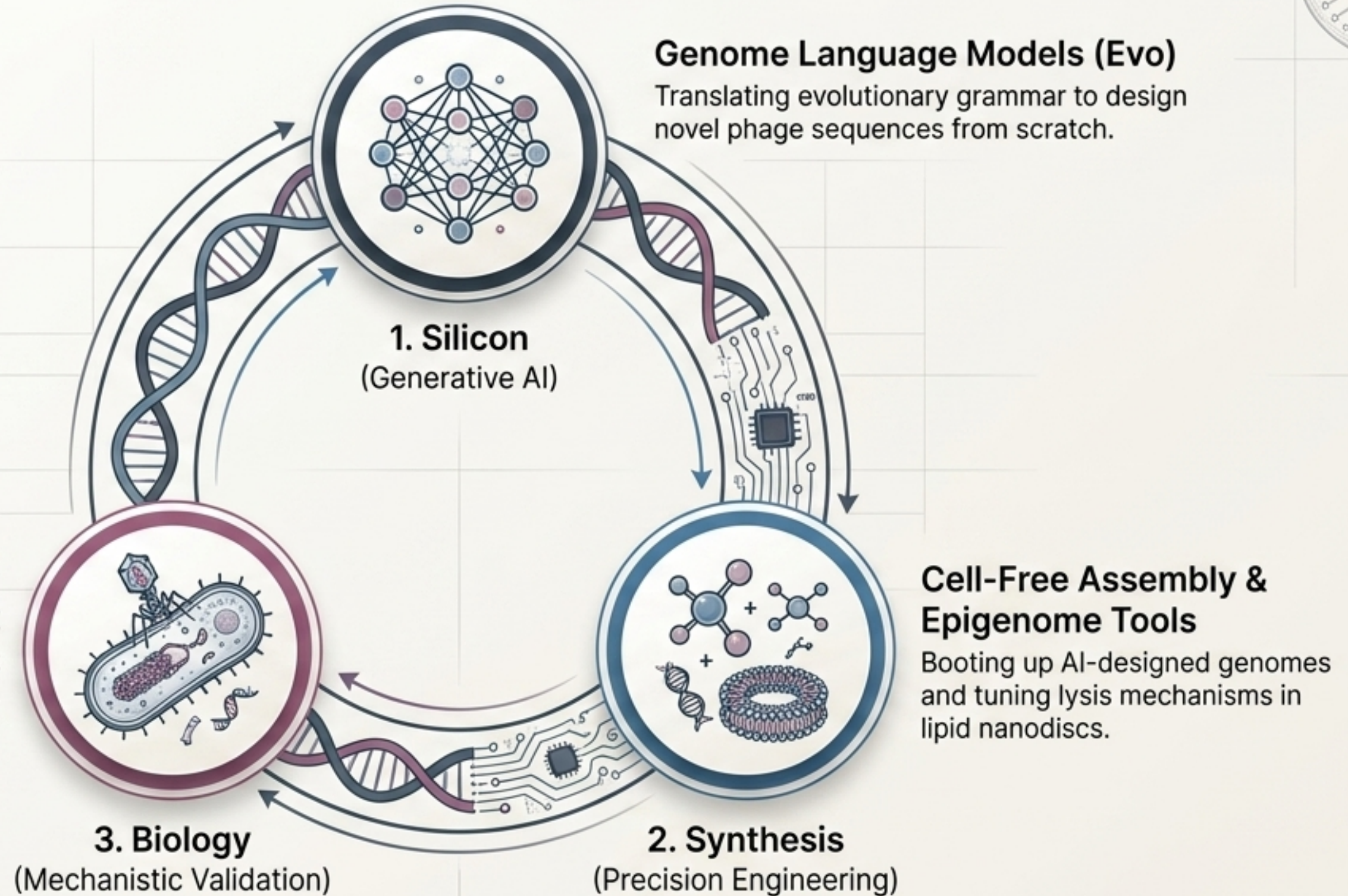
⚠ CONSTRAINT

Clinical Translation

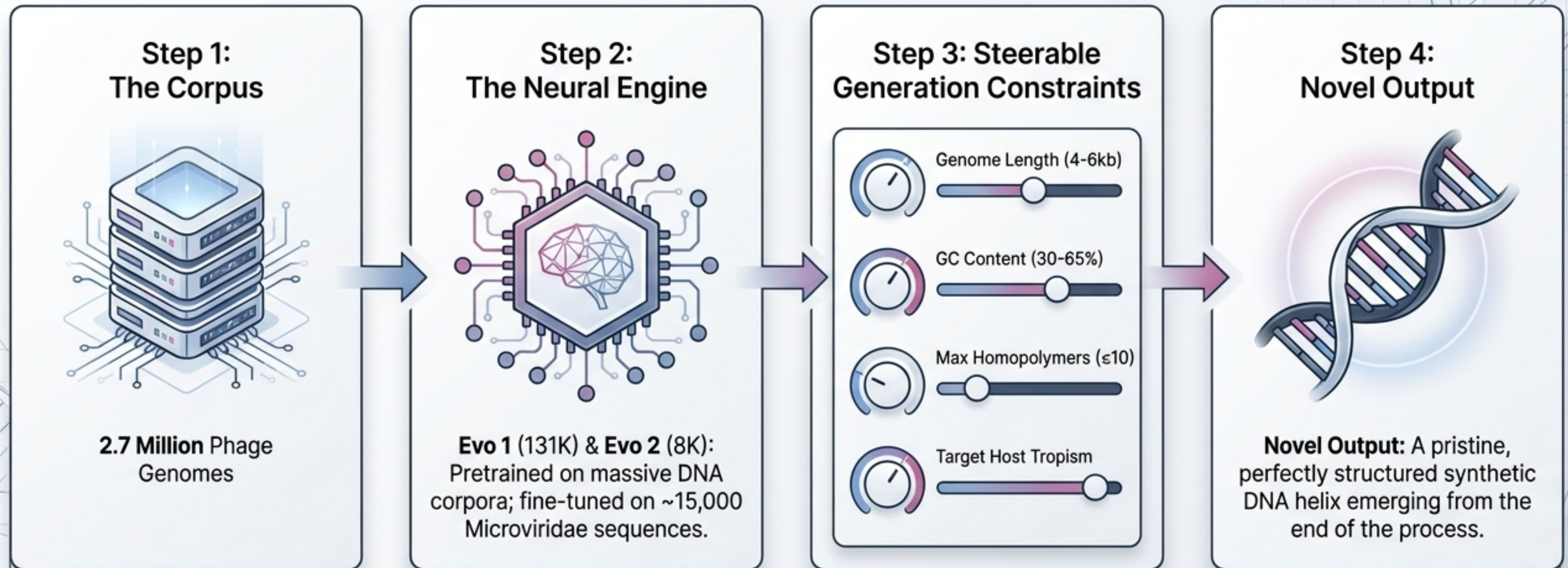
The Flaw:

Unscalable, slow, limited by natural diversity, and fundamentally unsuited for rapid clinical deployment against novel superbugs.

From Discovery to Design: A unified bio-foundry producing custom, highly fit therapeutic phages on demand.



Platform Engine 1: Generative Genome Design (Evo)

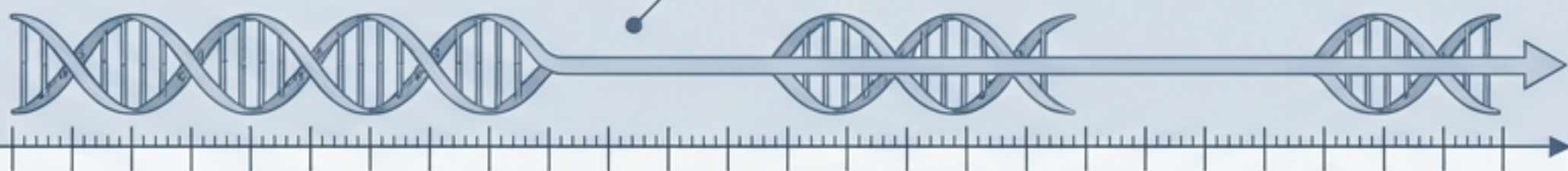


Evo models treat DNA as text, learning the **evolutionary grammar** of biological function to generate unprecedented, **biologically viable** genomes.

Silicon to Biology: The Φ X174 Blueprint

Top Track
Natural Φ X174 Template

The first complete DNA genome ever sequenced. 5.4 kb, 11 genes.



Bottom Track
Evo- Φ Synthetic Genomes



1



16 viable synthetic phages successfully booted up

2



Perfect preservation of complex genetic architecture (overlapping genes, promoters)

3



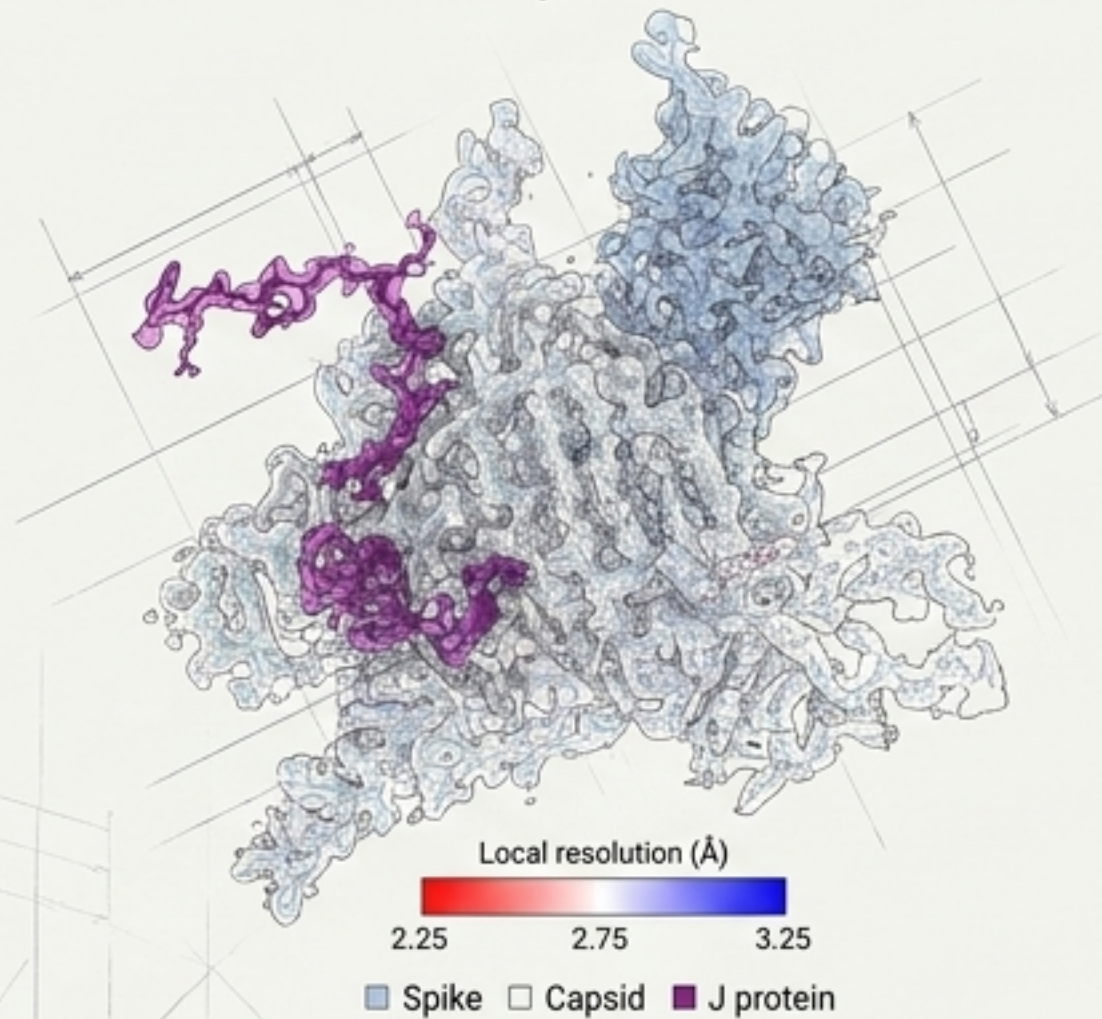
Extreme sequence divergence from any known natural template

The Generative Advantage: The AI did not memorize and copy; it successfully invented novel genetic pathways while maintaining absolute biological viability.

Structural Proof: Designing Novel Interactions

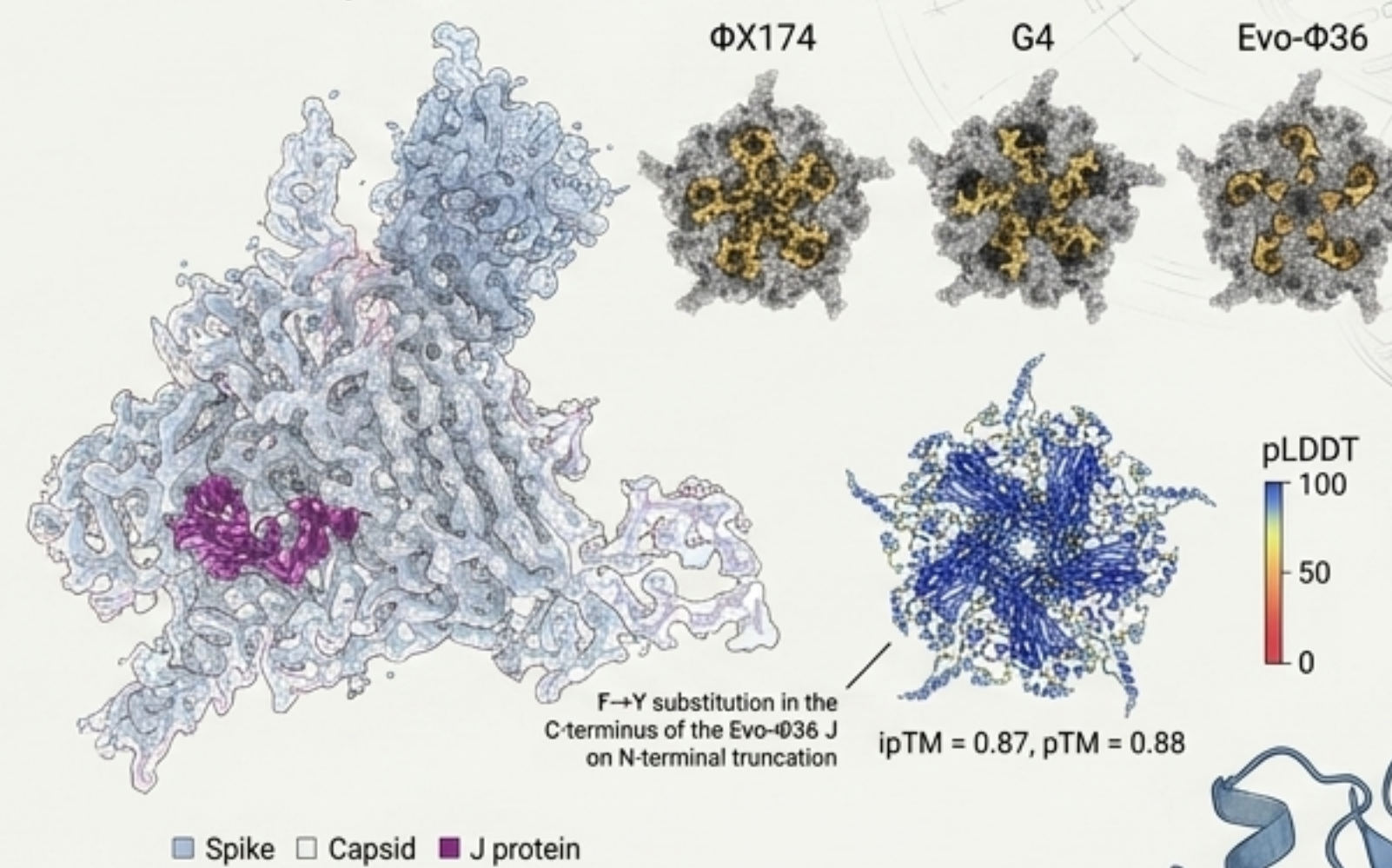
Natural Φ X174

Φ X174 asymmetric unit



Synthetic Evo- Φ 36

Evo- Φ 36 asymmetric unit



Generative design uncovers novel protein-protein co-evolutionary solutions.



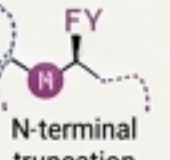
Our platform's generative models successfully identify and implement non-intuitive evolutionary paths for complex protein interactions, surpassing traditional engineering approaches.

AlphaFold 3 and Cryo-EM reveal the AI-designed phage uses an evolutionarily distant DNA packaging protein (J).











Structural data confirms that the synthetic Evo- Φ 36 phage incorporates a highly diverged J protein, originating from a distant evolutionary branch, while maintaining complete functional integrity within the novel capsid.

Maintains perfect capsid compatibility via a C-terminal F→Y substitution, despite missing 14 residues at the N-terminus.



Structural fidelity is achieved through precise compensatory mutations, such as the F→Y substitution, ensuring robust capsid assembly and DNA packaging, even with significant sequence alterations and truncations.

The Paradigm Shift: Prospecting vs. Generative Design

Traditional Bio-Prospecting	Generative Phage Platform
 <p>Months or Years of environmental hunting.</p>	 <p>Days or Weeks from sequence to synthetic generation. ✓</p>
 <p>Random chance of host matching.</p>	 <p>Precisely engineered for target host tropism. ✓</p>
 <p>Confined to mapped natural diversity.</p>	 <p>Unlocks unmapped, synthetic evolutionary design space. ✓</p>
 <p>Low (Bottlenecked by physical isolation).</p>	 <p>Infinite (Software-driven bio-foundry). ✓</p>

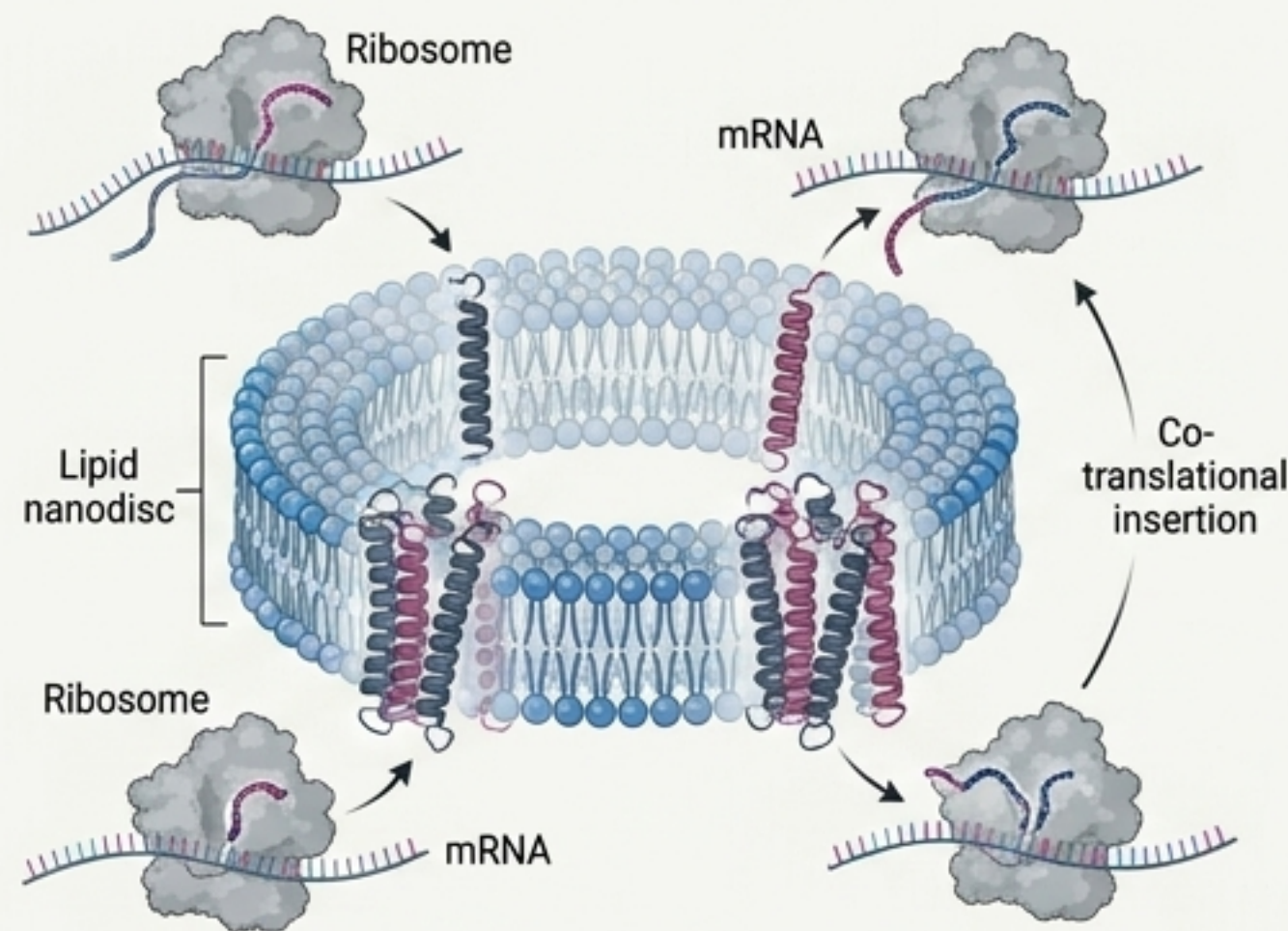
Platform Engine 2: Precision Lysis Engineering

The Challenge



Producing toxic lysis proteins traditionally kills the manufacturing host cell.

The Solution: Cell-Free Expression & Nanodiscs



Decoupled synthesis and assembly directly into native-like lipid environments.

Capabilities



Safe Manufacturing:
Decouples toxin production from live cell constraints.

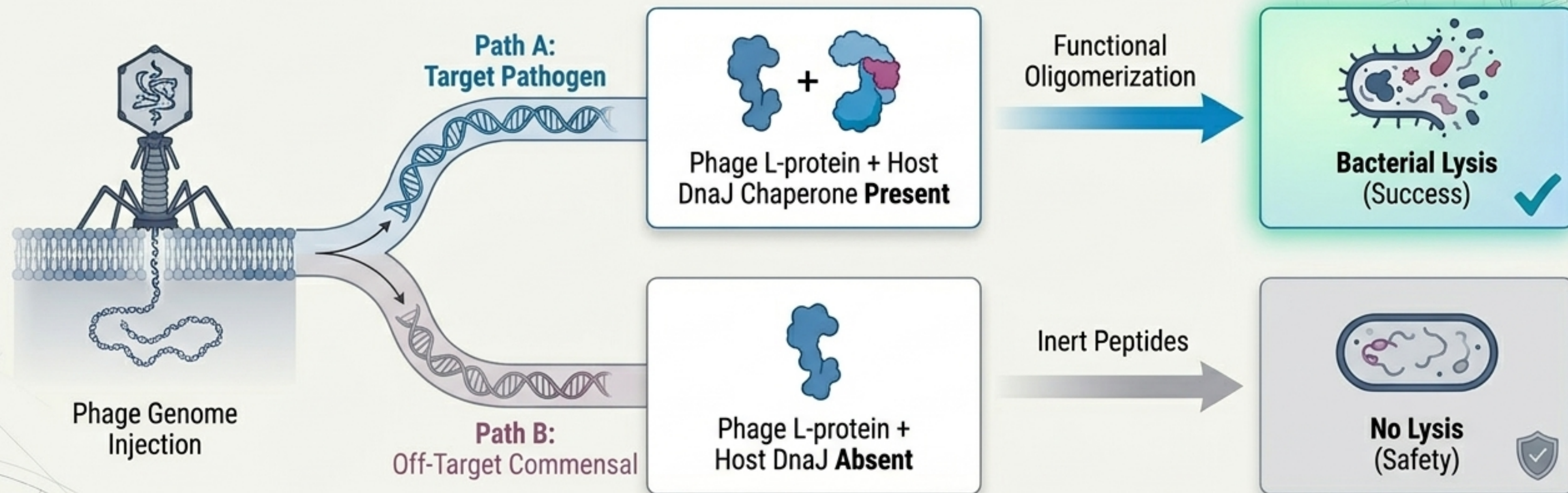


Nested Engineering:
Enables isolation and modification of specific domains (e.g., MS2-L nested deletions) to optimize bacterial destruction.



Purity:
Yields native-like lipid environments for precision biochemical tuning.

Mechanistic Validation: Host Dependencies



Deep characterization reveals that the MS2 lysis protein **strictly requires** the bacterial host's own chaperone protein (DnaJ) to form **lethal pores**.



Strategic Advantage: By mapping these dependencies, we can engineer synthetic phages that only activate within specific pathogen environments, achieving **zero off-target microbiome toxicity**.

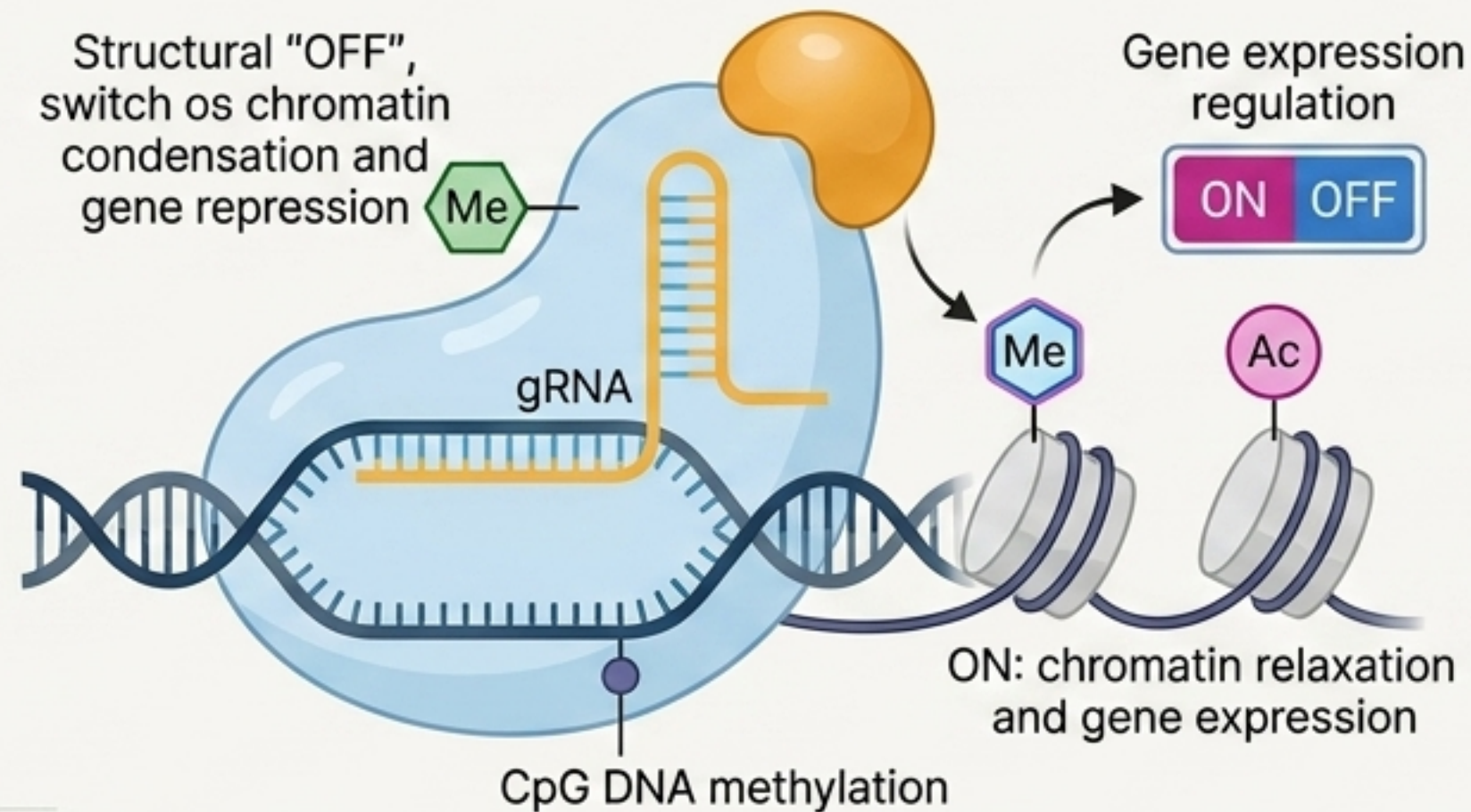
Beyond Lysis: Epigenomic Modulation

Hit-and-Run Silencing

Engineering synthetic phages to deliver CRISPR-based epigenome editors.

Transient delivery to permanently repress disease alleles.

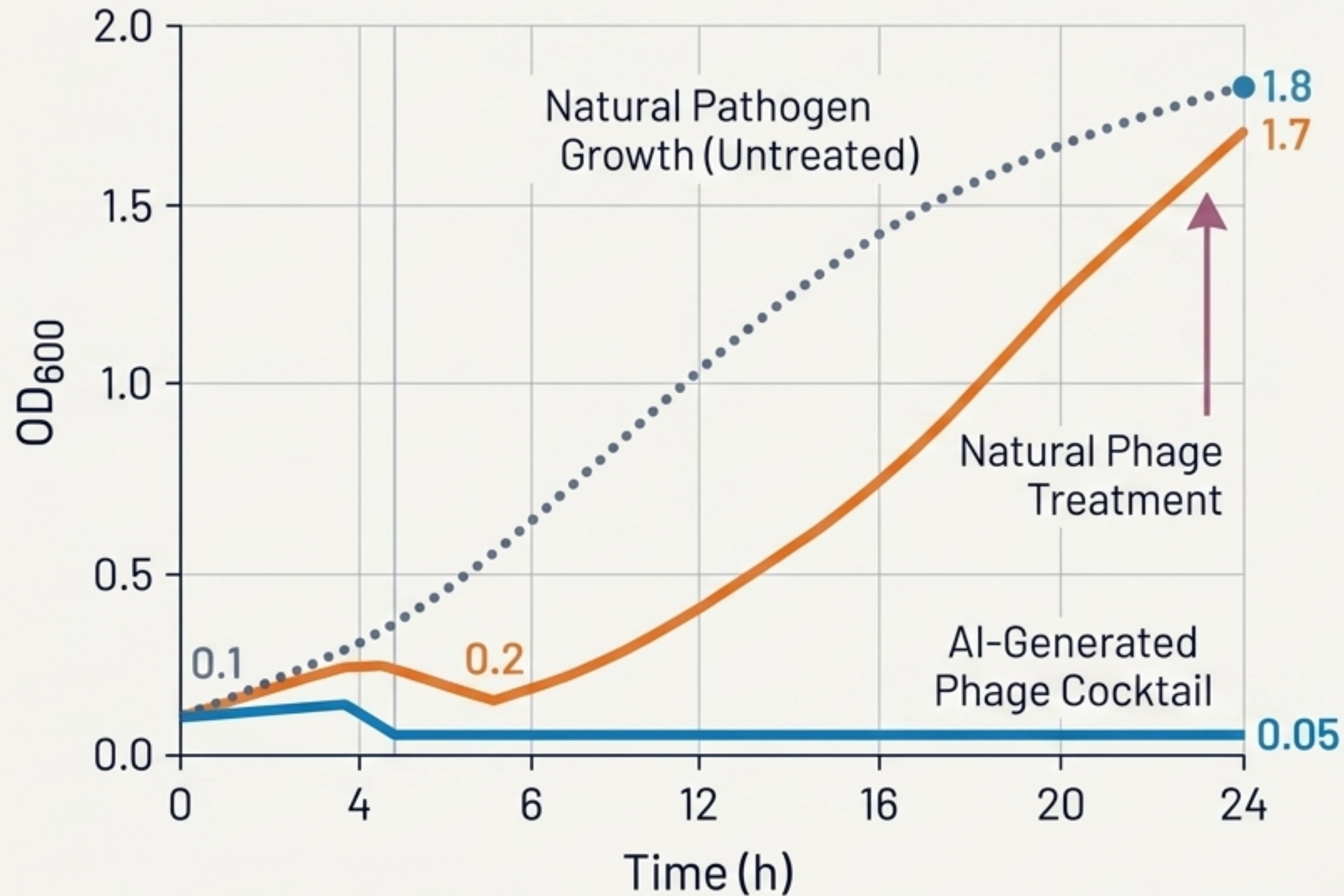
CRISPR dCas epigenome editing



Antibiotic Resensitization

Using targeted epigenomic edits to silence AMR virulence genes, turning drug-resistant superbugs back into susceptible targets.

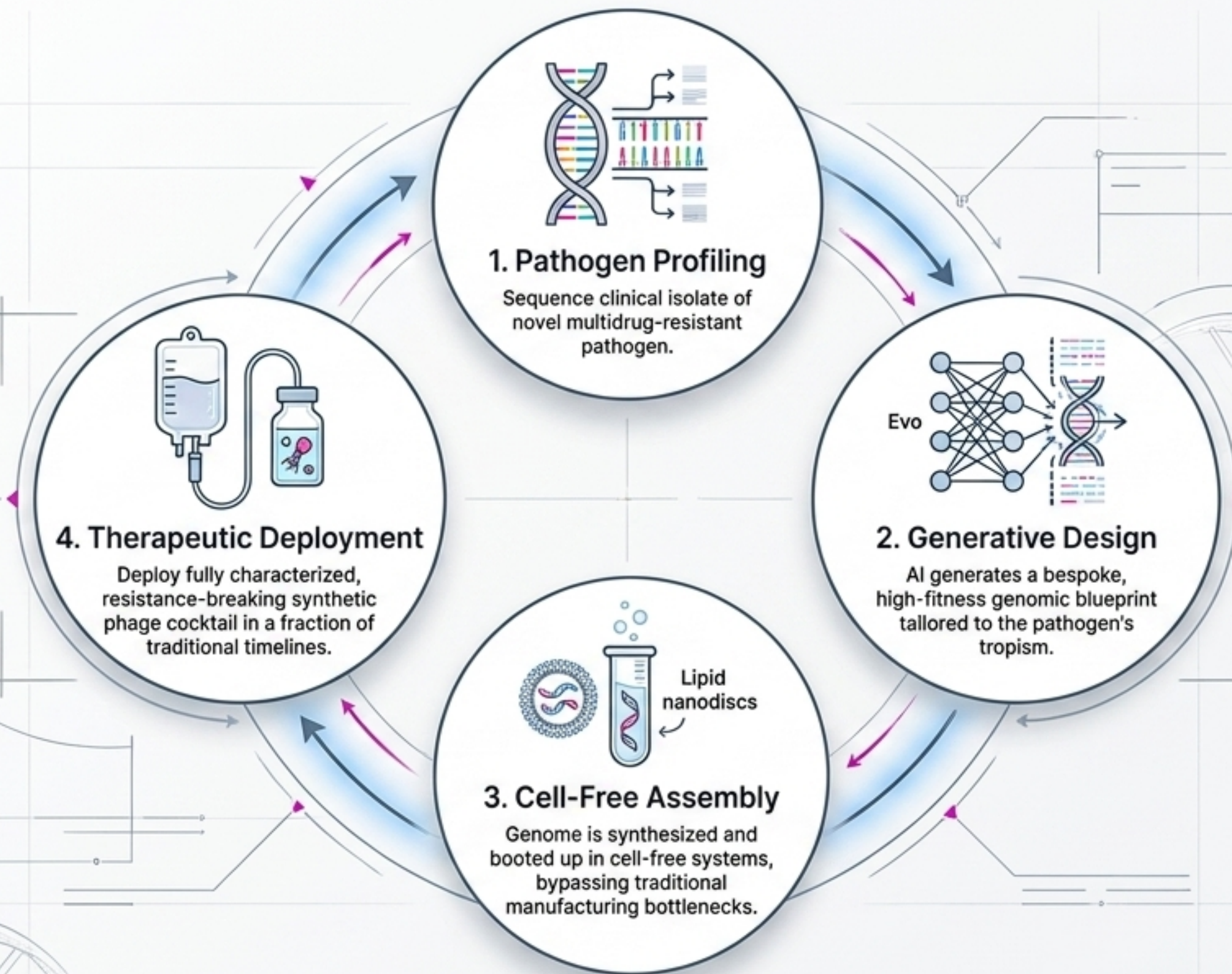
Defeating Rapid Bacterial Evolution



A targeted cocktail of highly diverged, AI-generated phages rapidly overcame Φ X174-resistance across three distinct *E. coli* strains.

We can computationally out-pace bacterial evolution.

The Synthesis: Our Integrated Bio-Foundry



Roadmap to Clinical Translation



Phase 1: Pre-Clinical Expansion

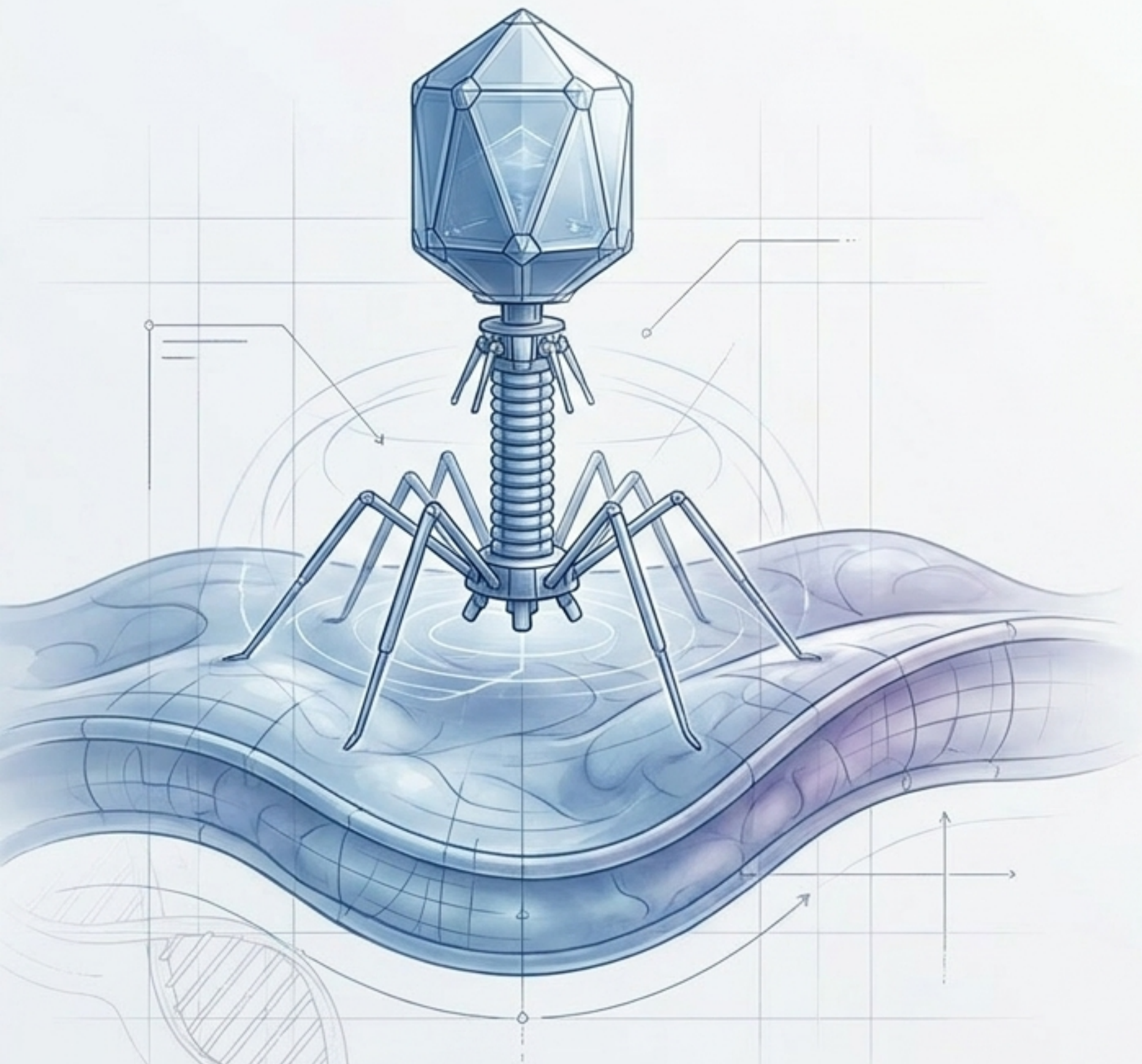
- Scaling the technology to target the WHO Priority Pathogen list.
- Expanding the LLM training corpus beyond Microviridae.

Phase 2: Compassionate Use & Regulatory Framing

- Deploying synthetic phages under FDA Emergency Investigational New Drug (eIND) applications.
- Pioneering the regulatory framework for AI-generated biological therapeutics.

Phase 3: Clinical Trials

- Initiating Phase 1 scalable clinical trials for targeted MDR infections.
- Transitioning from custom compassionate use to scalable national readiness.



The Future of Medicine is Programmable

The era of relying solely on static, broad-spectrum antibiotics is ending. The era of **generative, living therapeutics** is here.

Join us in building the **bio-foundry** infrastructure to make **programmable phage therapy** the global standard of care.