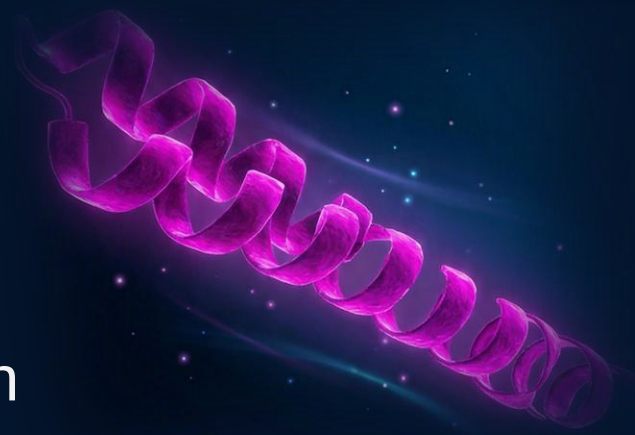
@valentynbez

DESIGNER ANTIMICROBIALS

Computational phage and antimicrobial peptide discovery for the post-antibiotic era



20 February • 1:30 PM

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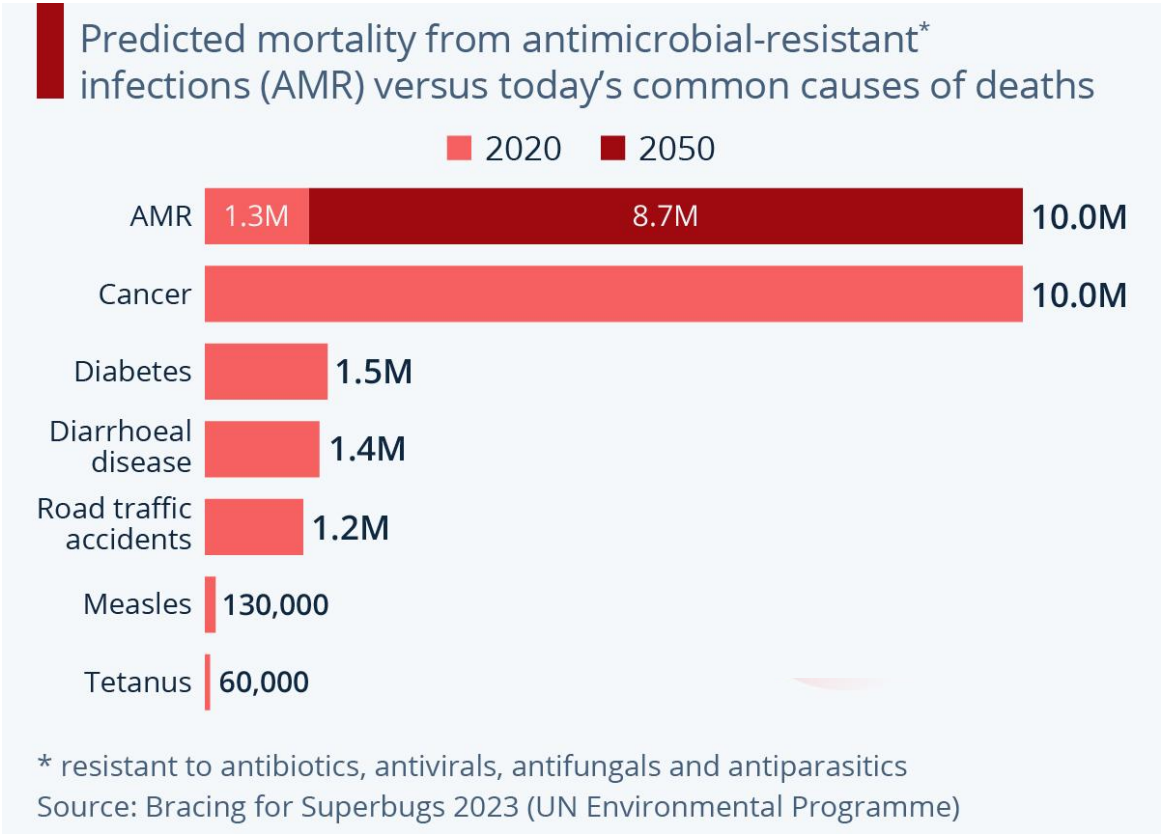
AI IMPACT SUMMIT

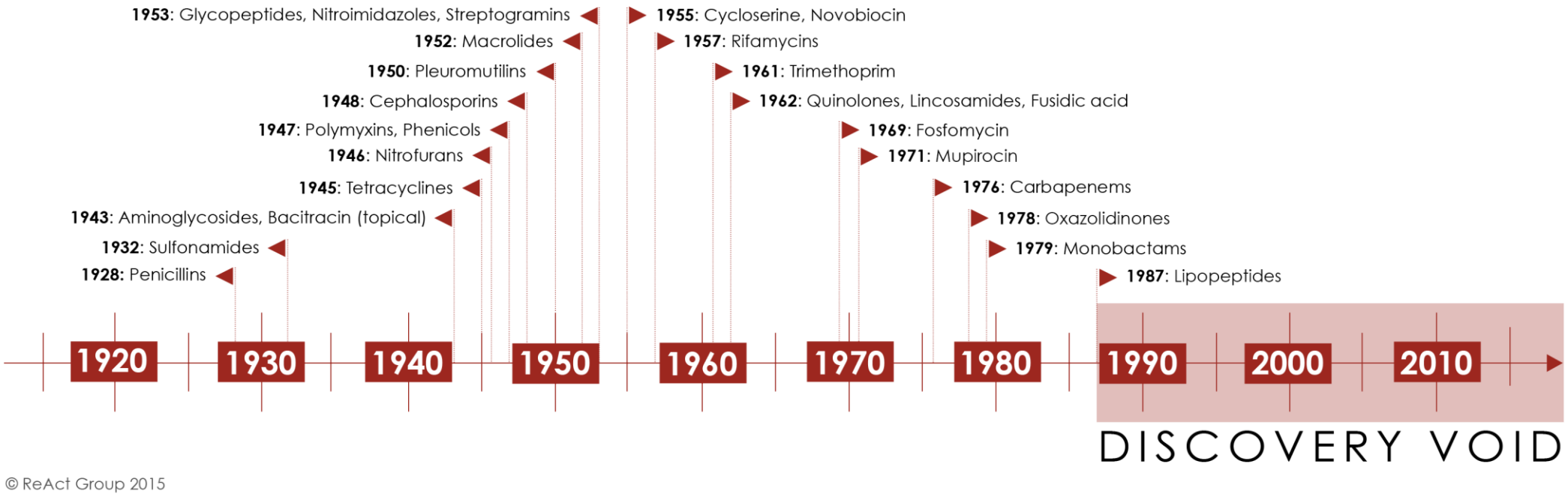
Introduction

The antimicrobial resistance (AMR) crisis

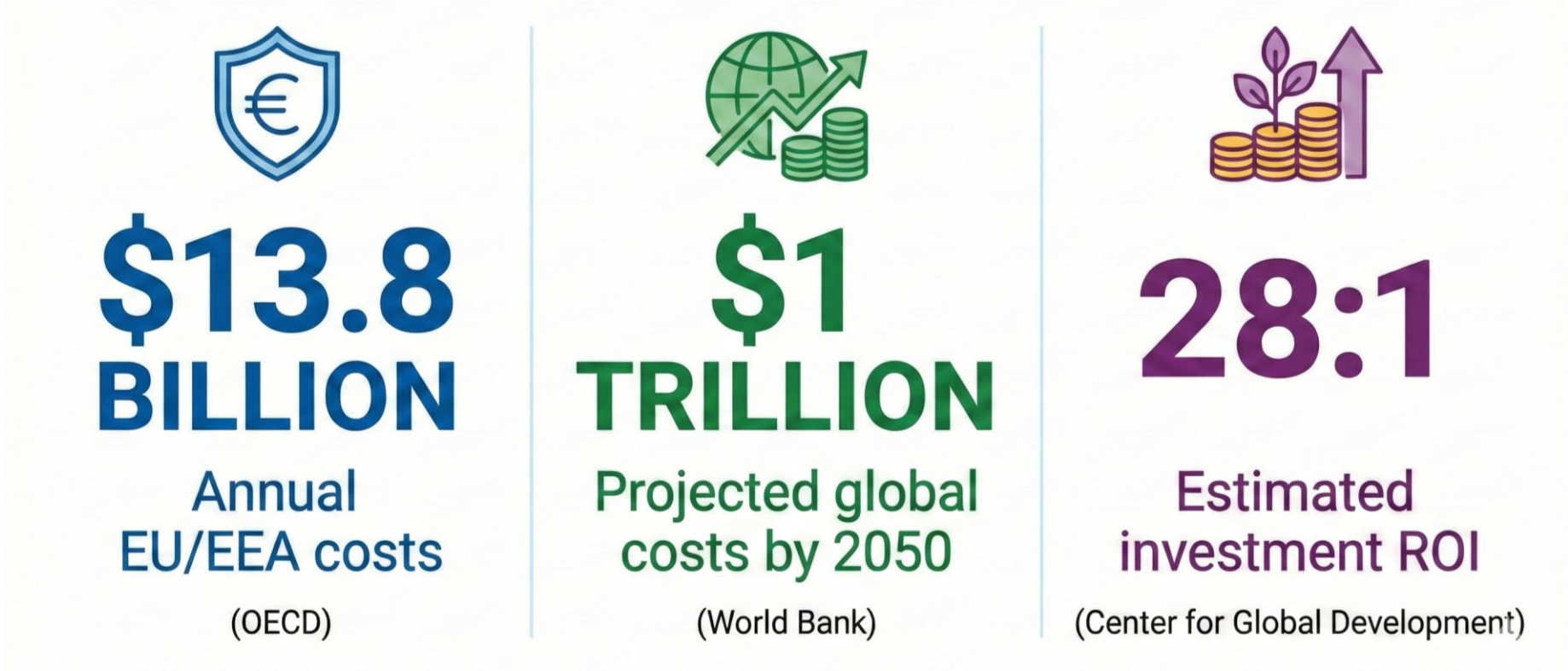
- **The Mechanism:** Bacteria rapidly evolve to survive standard antibiotics.
- **The Driver:** Clinical and agricultural overuse of antibiotics.
- **Current Toll:** 1.3M direct and 4.95M associated deaths annually.
- **Future Threat (2050):** Projected to reach 10M deaths per year, matching or surpassing cancer mortality.



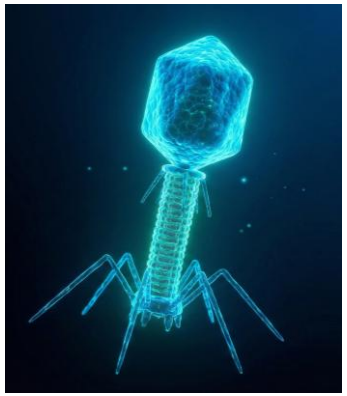
Stagnating antibiotic pipeline



Economic impact of AMR crisis

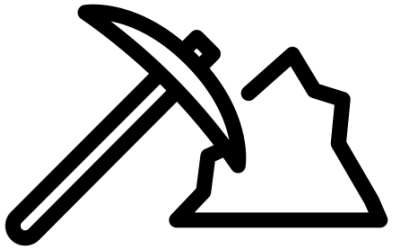


The Contenders: Phages vs. AMPs



Feature	Bacteriophages (Phages)	Antimicrobial Peptides (AMPs)
Nature	Natural bacteria-killing viruses	Short, mostly positively charged proteins
Specificity	High	Broad-spectrum
Mechanism of Action	Lyses bacterial cell upon infection	Physically disrupts bacterial cel membranes
Resistance	Co-evolves alongside bactetria	Slower to induce resistance

Computational discovery pipelines

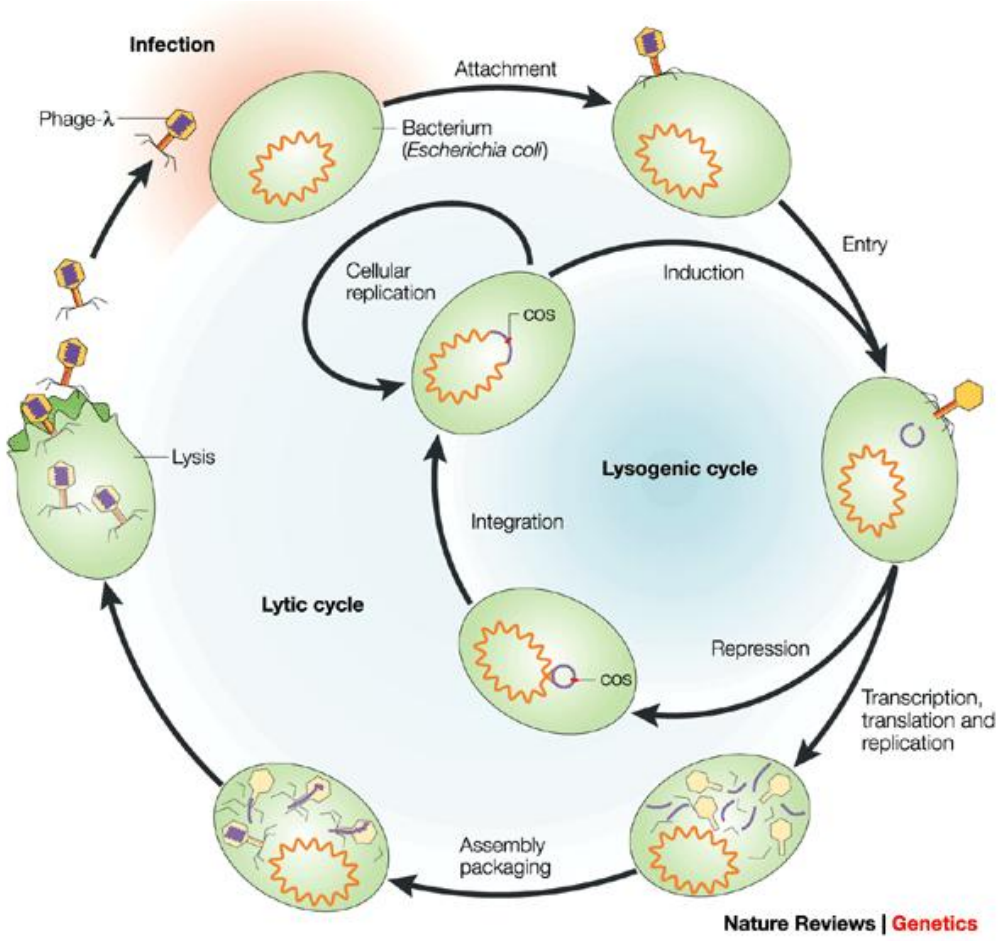


Pipeline	Metagenomic Recovery	Generative AI
Concept	Searching similar seuences in environmental datasets	Deep learning models "hallucinate" novel sequence
Key Tools	**Amplify, Macrel**	**AMPGen, FBGAN**
Sequence Source	Existing natural microbiomes	Latent space of the model
Primary Advantage	**High biological viability**	**Lab-in-the-loop optimization**
Primary Limitation	Restricted to biological sequences space	Higher risk of biologially invalid sequences

Phages

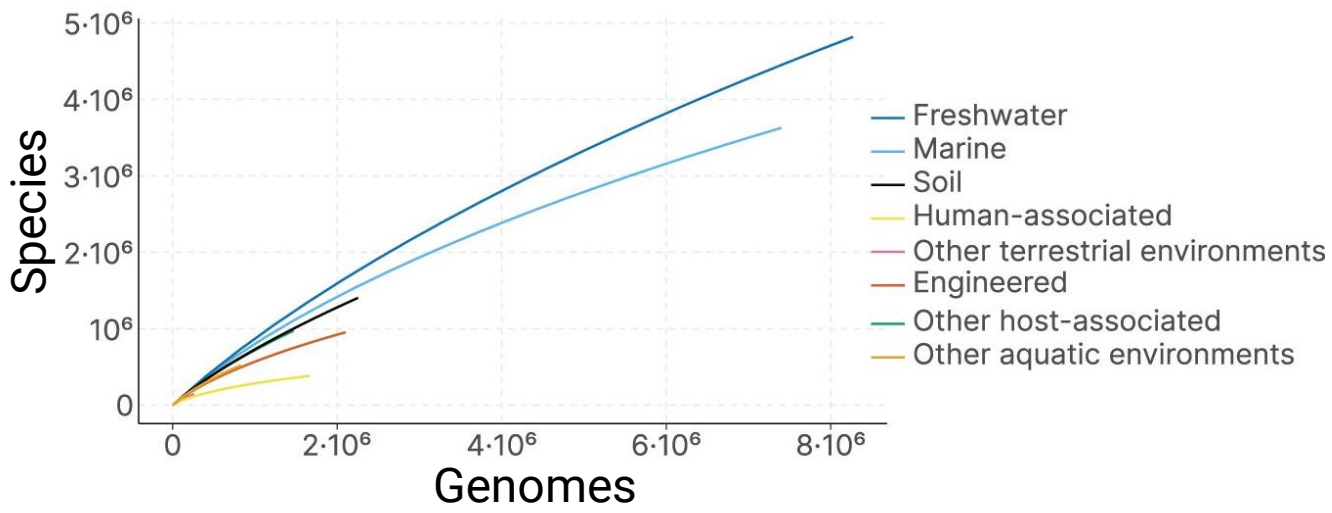
Short intro to phage biology

- Phages can be **virulent** or **temperate**
- **Virulent** phages cause **lysis**
- **Only lytic phages** are used as **antimicrobials**



Incredible natural diversity

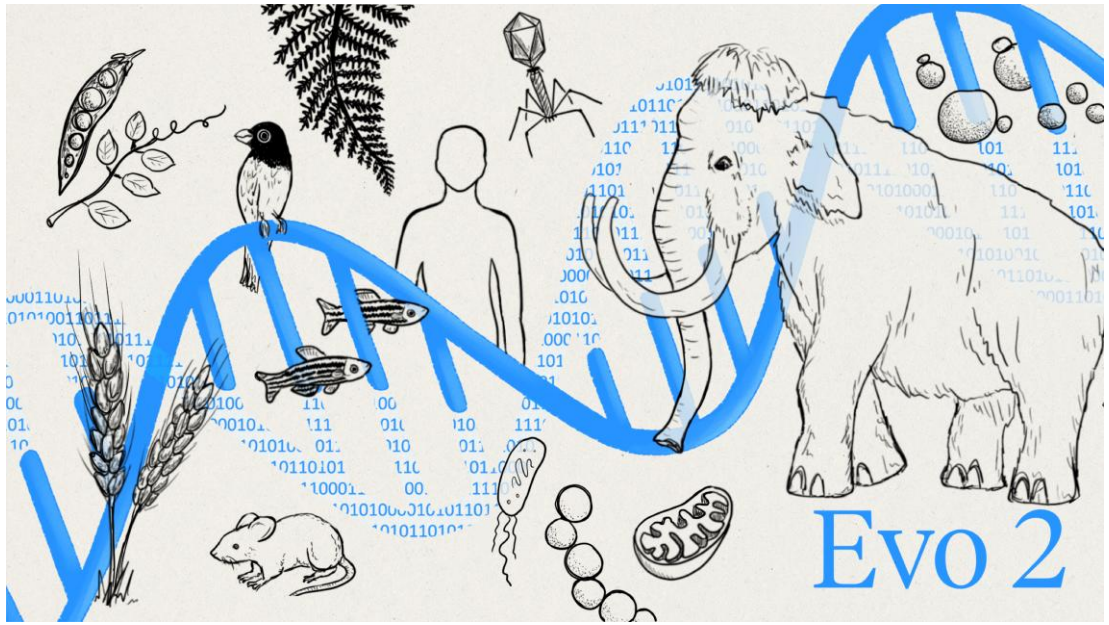
- Mining of environmental DNA has revealed **millions of novel phages**.
- This approach accesses vast diversity from ecosystems like **soil, oceans, and freshwater**.
- **The takeaway:** more genomes = more phage species
- **Problem:** no link to host bacteria



Fiamenghi et al., 2026

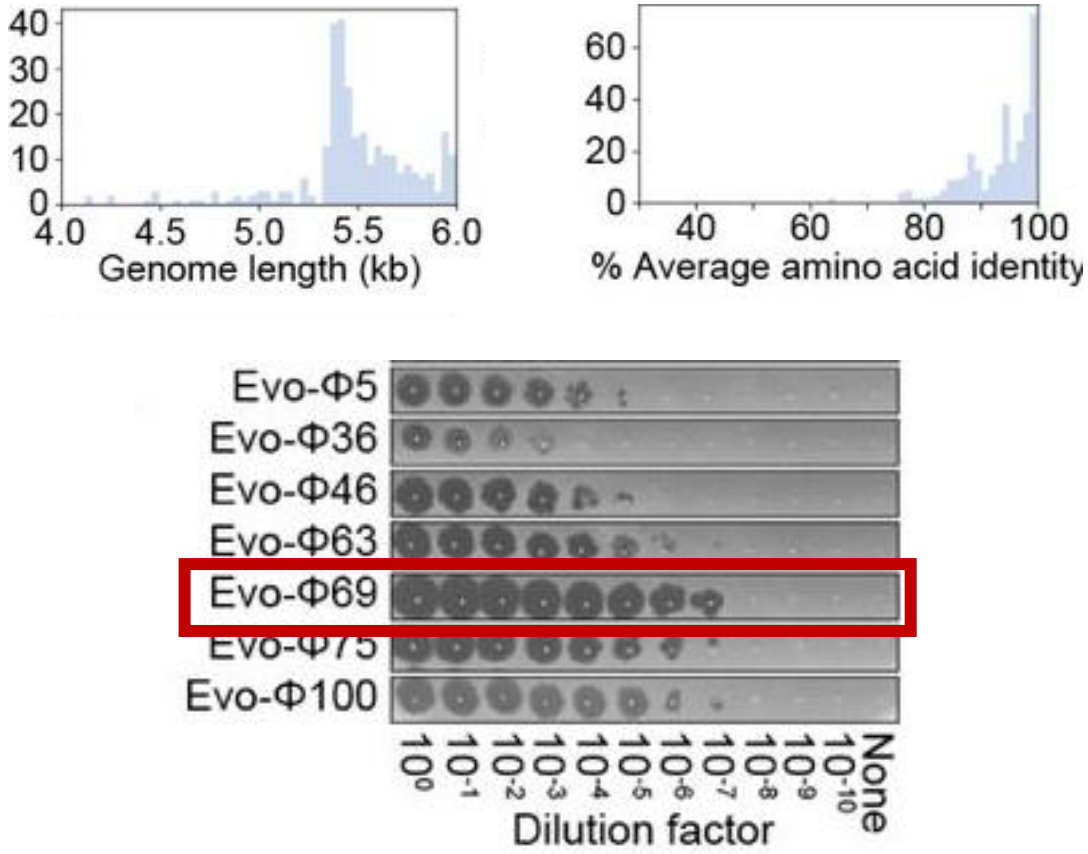
Large language model of all biology

- Evo 2 is 40B parameter large DNA language model designed by Arc Institute
- It uses genomes across all domains of life to learn genome dependencies
- Can predict gene function – 90% accuracy in classyfying oncogenic BRCA1 variants



Generative Design: Creating Novel Phages

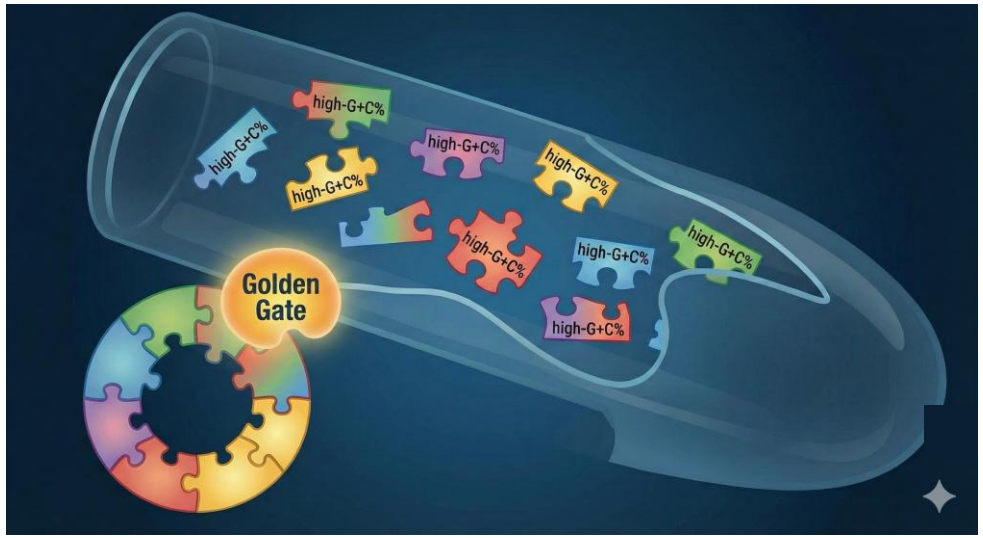
- **The Input:** A short genetic "prompt" to instruct the Evo 2 model to generate novel *E. coli* phages.
- **Biological validity:** generated phages belong to the same viral genus
- **Laboratory Validation: Evo-Φ69** is more potent than natural phage

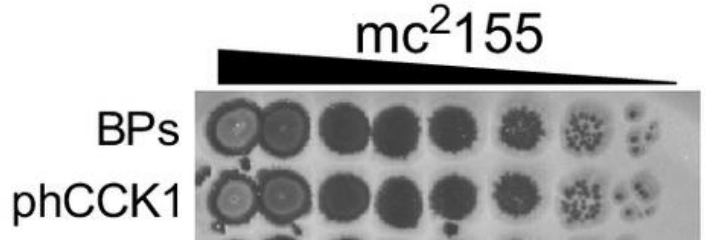


King et al., 2025

Synthesizing complete Mycophages

- **Synthetic genome:** Researchers synthesized 2 viable Mycophage genomes gene-by-gene
- **Unique challenges:** high GC content and long genome (50 kbp)
- **Laboratory Validation:** no differences from natural counterparts



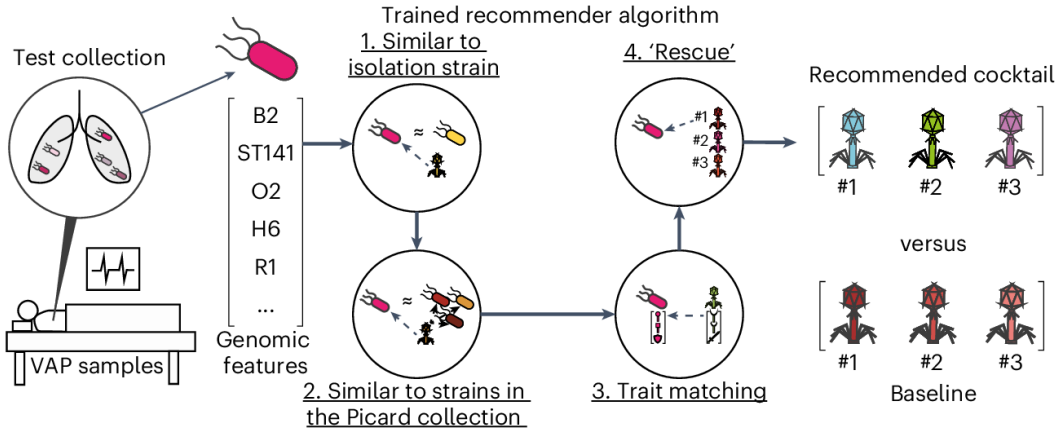


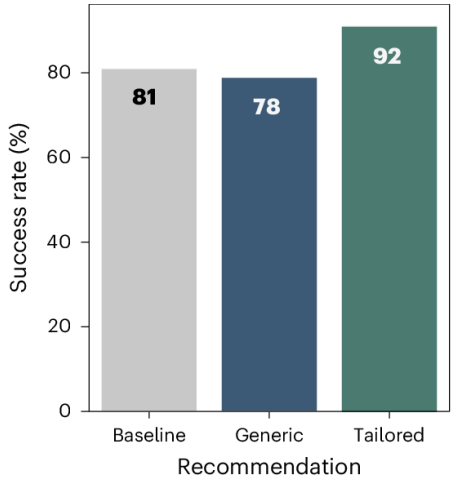
Ko et al., 2025

ANSA BIOTECHNOLOGIES

Custom phage cocktails

- **The data:** a matrix of bacterial susceptibility to phages from the biobank
- **Test:** 100 unseen bacteria from ventilator-associated pneumonia
- **Result:** tailored cocktails were 13% more effective than the baseline





Gaborieau et al., 2024

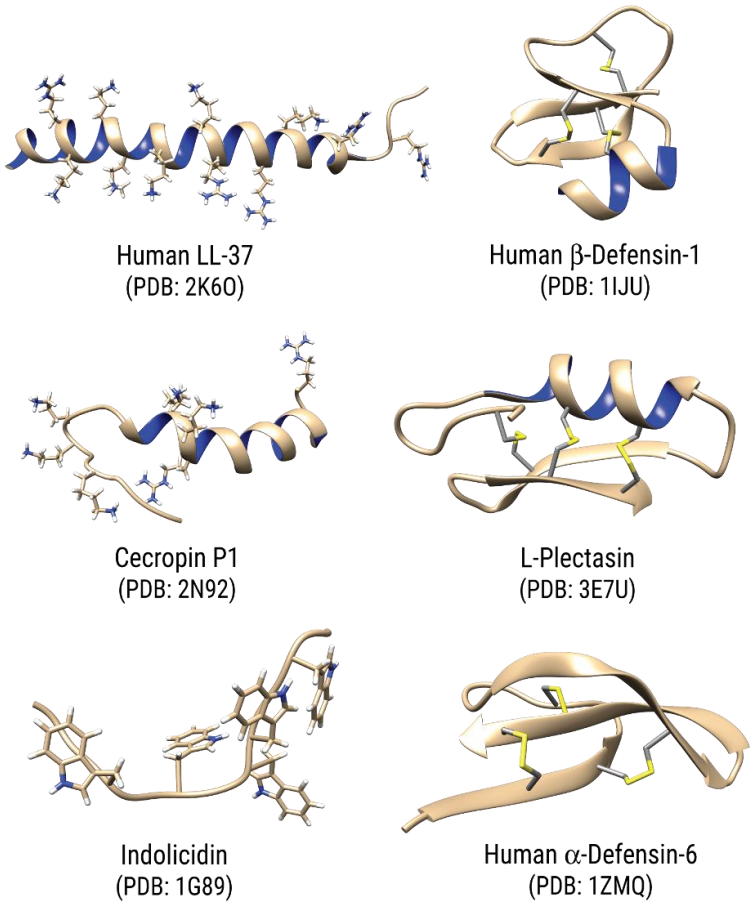
Section conclusions

- **From natural blueprint to synthetic design:** phage genomes mined from natural DNA served as training data for generative AI models
- **Era of artificial genomes:** The relatively small size of phages makes them the ideal primary targets for complete, de novo genome synthesis.
- **Multilevel precision medicine:** Not only can individual viral genomes be synthesized from scratch, but entire phage cocktails can be dynamically tailored for personalized patient treatment.

Antimicrobial peptides (AMPs)

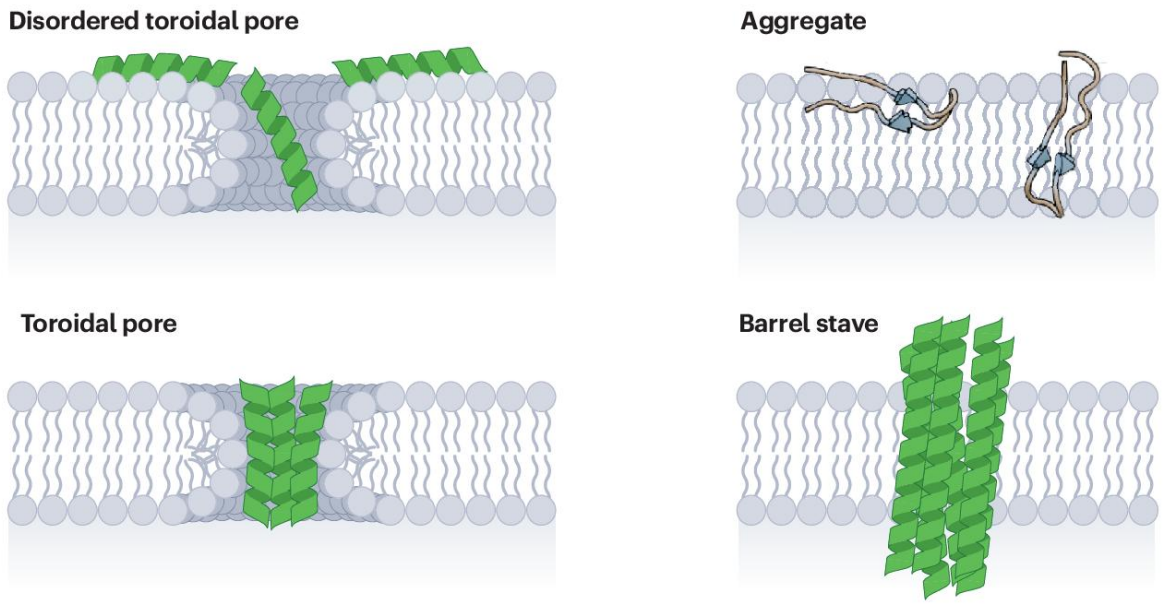
Biology of AMPs

- **AKA „bacteriocins”**
- **Size:** short sequences **(10-100 amino acids)**
- **Structure:** remain unstructured in fluids, but rapidly fold into distinct 3D shapes upon contact with membranes
- **Broad representation:** found in the immune systems of almost all classes of life



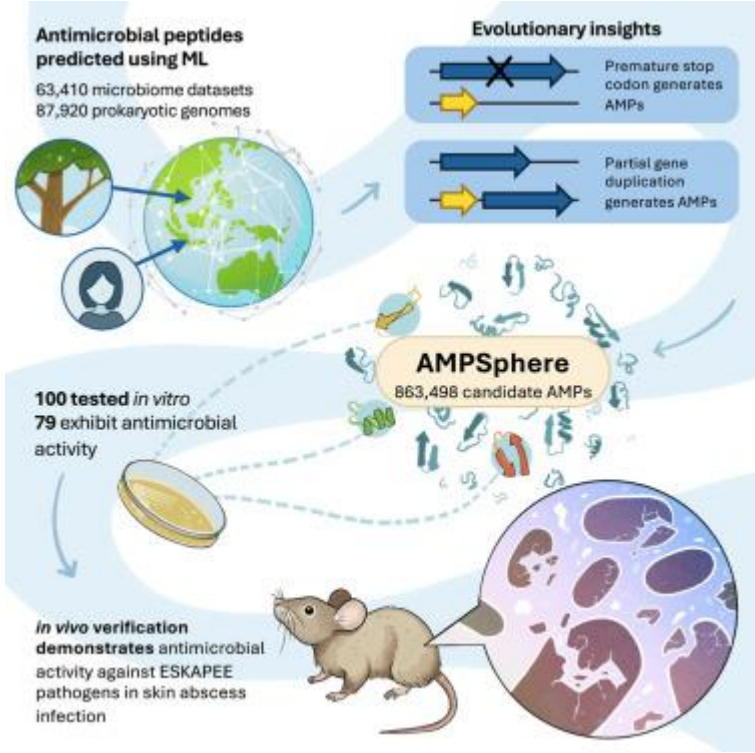
AMP mechanism of action

- **Chemical Profile:** Most are **cationic** (positively charged) and **amphipathic**
- **Mechanism of Action:** positive charge attracts them to the negatively charged bacterial surface, where they physically puncture the membranę.



Mining AMPs from metagenomes

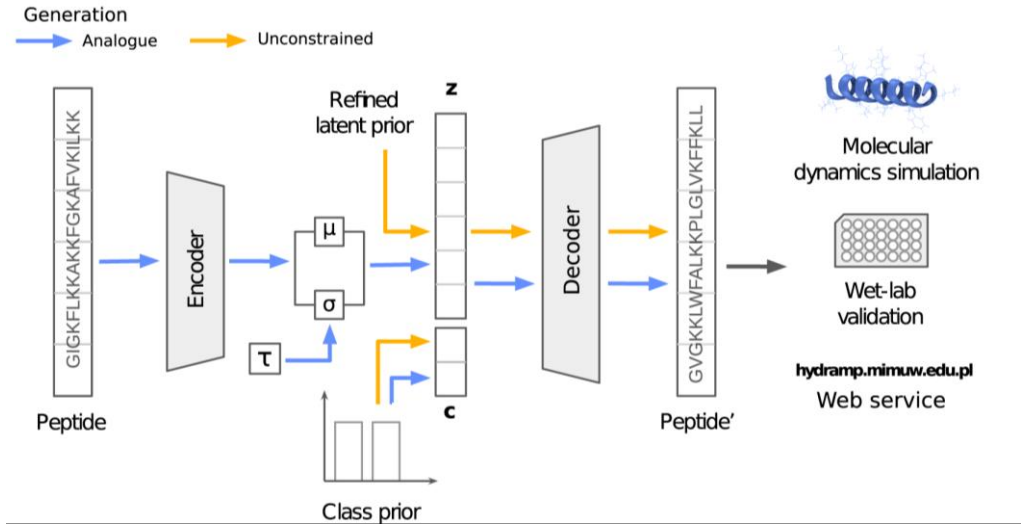
- **The Massive Scale:** 63,410 metagenomes and 87,920 prokaryotic genomes from diverse global habitats
- **The AMPSphere:** a comprehensive, open-access catalog containing **863,498 candidate AMPs** (90% novel)
- **Lab Validation:** 79 out of 100 synthesized AMPs were active against drug-resistant pathogens

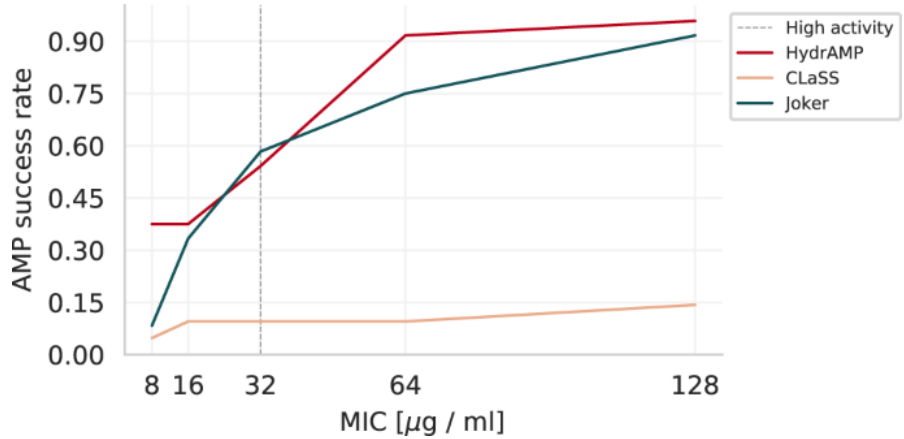


Santos-Júnior et al., 2024

Generating AMPs

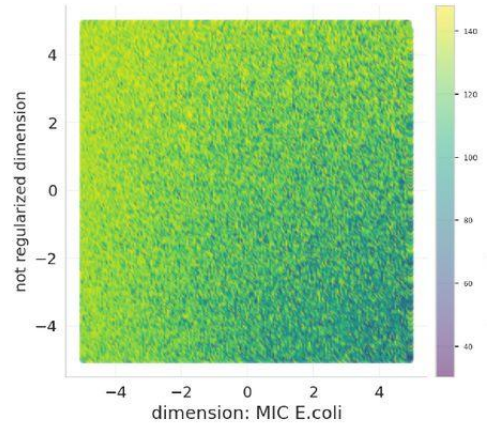
- **The Model:** a conditional VAE for generating AMPs under 25 aa (Szymczak et al., 2024)
- **Dual Generation Modes**
  - Analogue Generation
  - Unconstrained Generation
- **Smart Preselection:** model uses a built-in ranking system and molecular dynamics simulations to preselect candidates

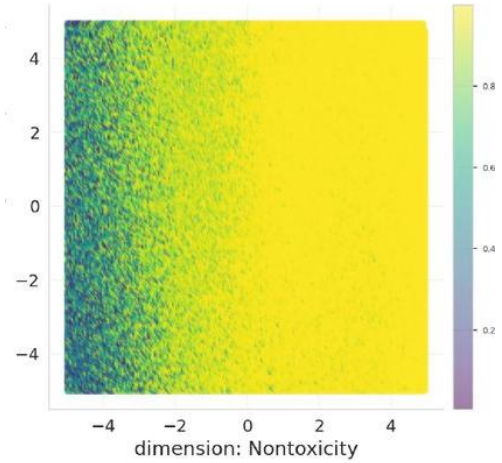




Tailoring AMPs

- **PepGlider** allows for multiobjective optimization of AMPs
- **Uncoupling Correlated Traits:** In biological systems, certain traits naturally move together. PepGlider's "disentanglement" allows it to independently control naturally correlated properties.
- **Application to Antimicrobial Peptides (AMPs):** When specifically applied to AMP design, model successfully generated new peptide candidates with **high antibacterial and low toxicity profile.**



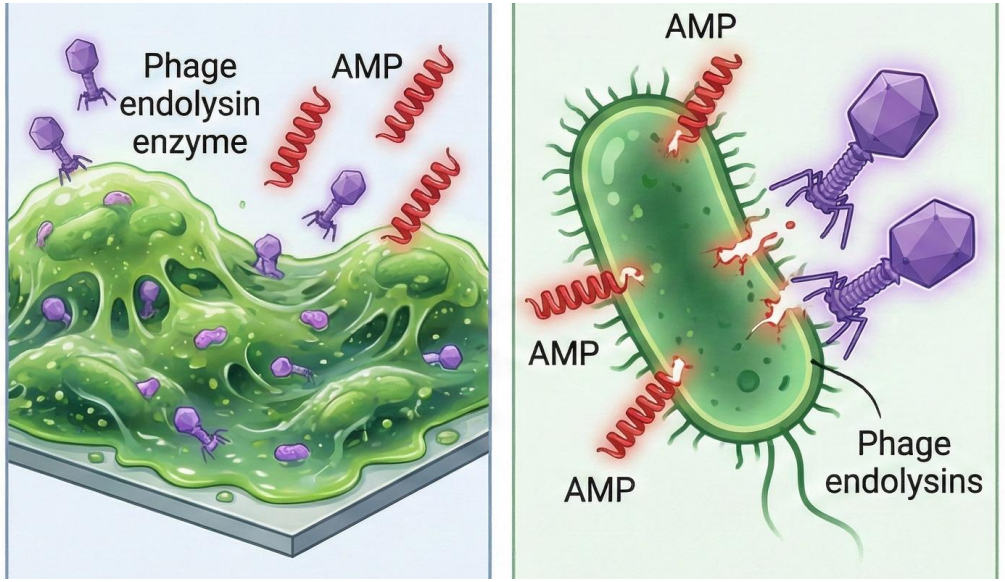


Section conclusions

- **Mining of AMPs:** researchers were able to mine AMPs from different environments
- ***De novo* AMP generation:** with help of GenAI, active AMPs can be generated from scratch
- **Custom optimization of AMPs:** AMPs an be optimized for different properties, allowing high customization

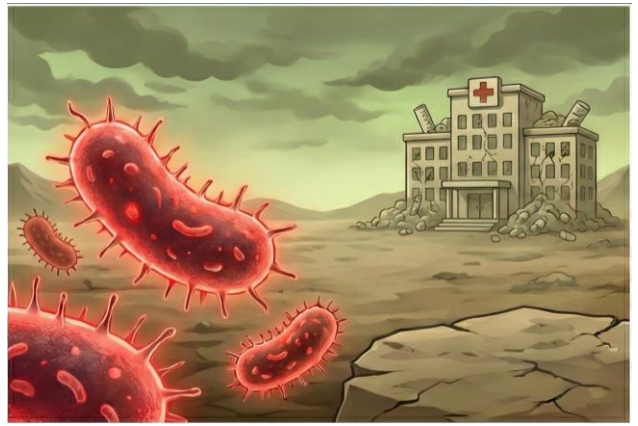
Phage and AMP synergy

1. **Enhanced Biofilm Eradication:** AMPs + phage improve biofilm eradication in ESKAPE pathogens.
2. **Increased Sensitivity:** Pre-treating bacteria with AMPs improves efficiency of phages
3. **Lowering Resistance Thresholds:** combining endolysins with AMPs lowers the Minimum Inhibitory Concentration (MIC) required to kill polymyxin B-resistant *Salmonella*.
4. **Phage-Derived AMPs:** phage endolysins naturally mimic the structure of mammalian AMPs - strong activity against MDR bacteria while remaining non-toxic to human cells.



Conclusions

1. **Technological Convergence:** Metagenomic mining, GenAI, and DNA synthesis integration enables programmable phage and AMP therapeutics.
2. **Ultimate Synergy:** Combining AMPs and phages creates an enhancedsolution for eradication of resistant bacteria and biofilms.
3. **Economic Bottleneck:** Therapeutic development is largely abandoned due to low returns on investment (ROI), despite progress.
4. **Alternative Funding:** Translating therapies requires strategies like public-private partnerships and government push/pull incentives.



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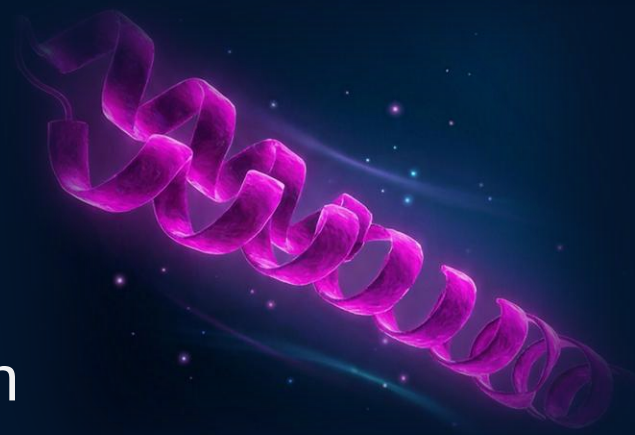

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