Generative design of bacteriophages with genome language models

Samuel King, Stanford Bioengineering Ph.D. Candidate

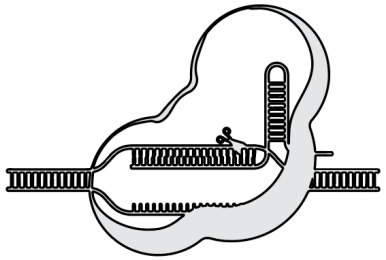
ISBR Webinar / 2026.10.22

Laboratory of Evolutionary Design

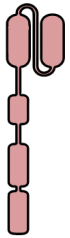
Arc Institute

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Sequence design insights have gotten us far in synthetic biology



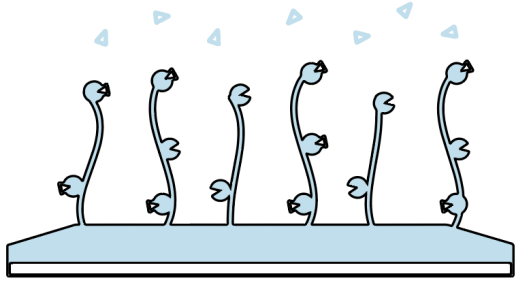
CRISPR-Cas systems



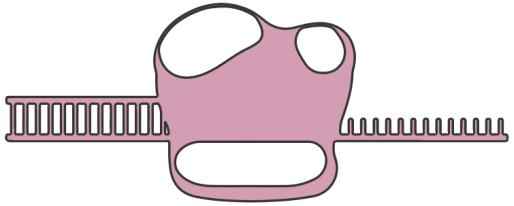
CAR-T cell therapies



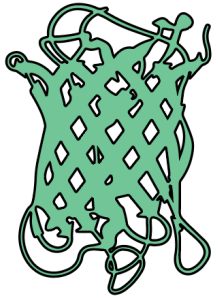
Gene circuits



Biosensors



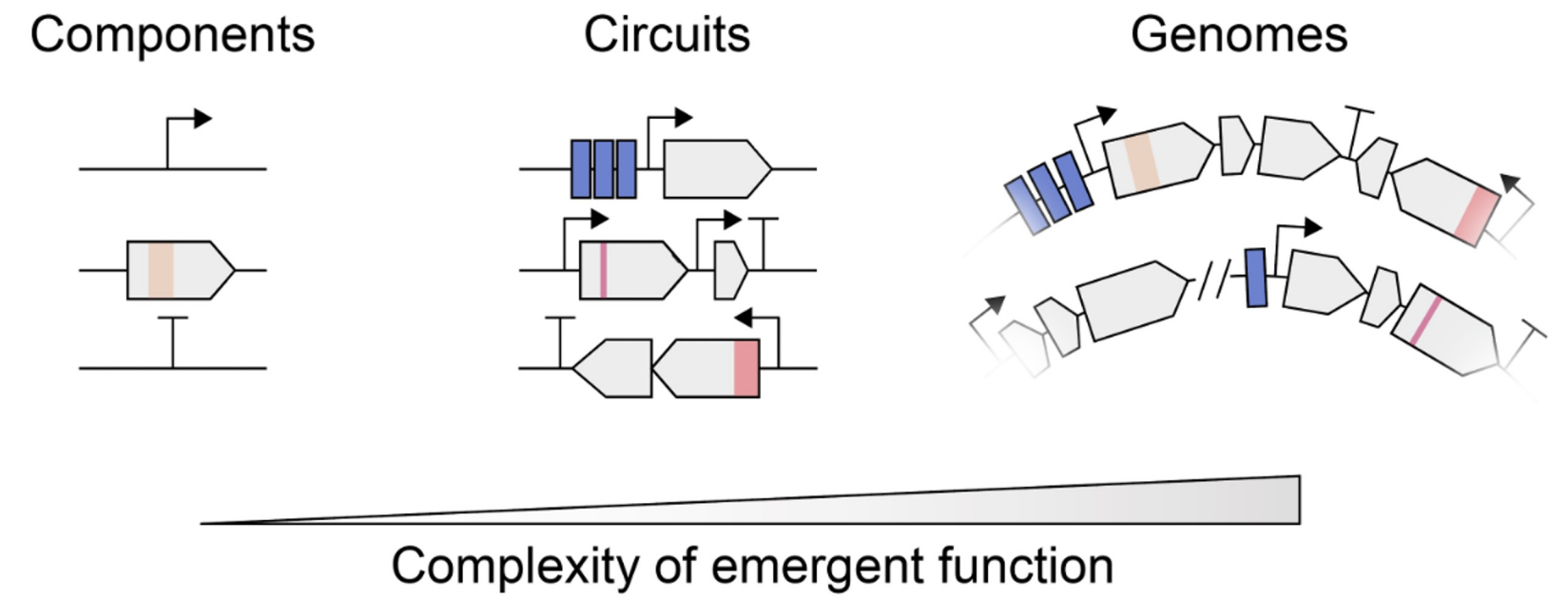
Polymerases



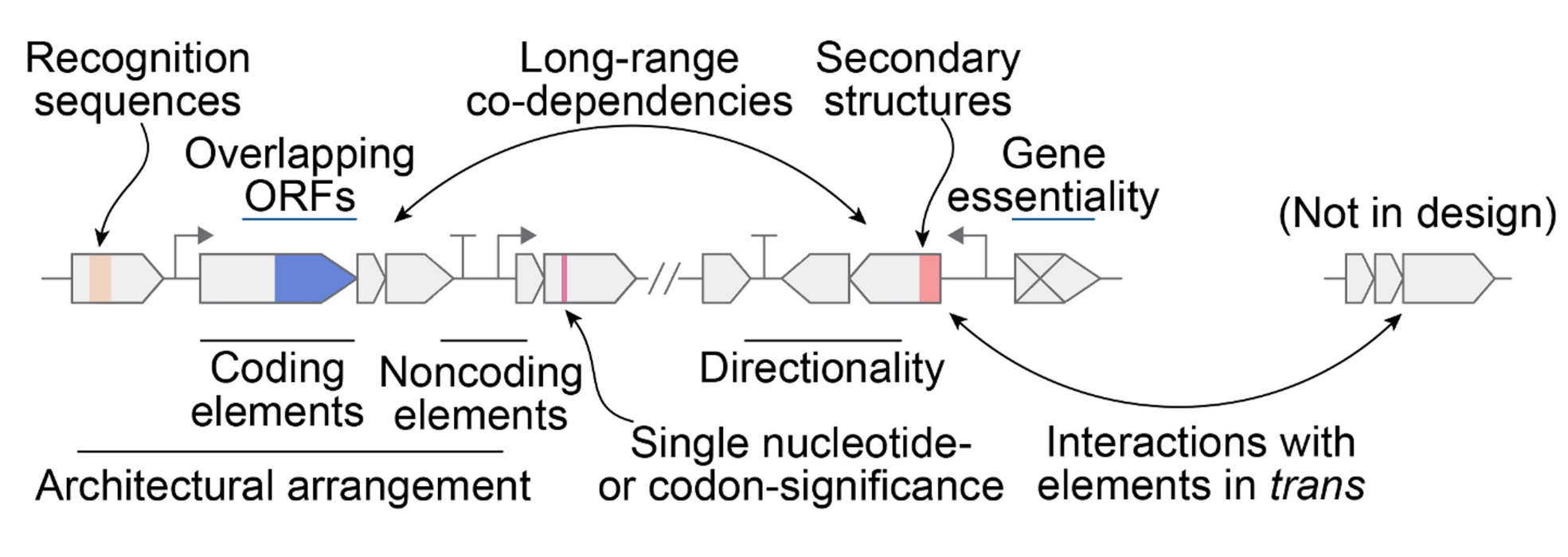
Fluorescent proteins

Slide from Aditi Merchant

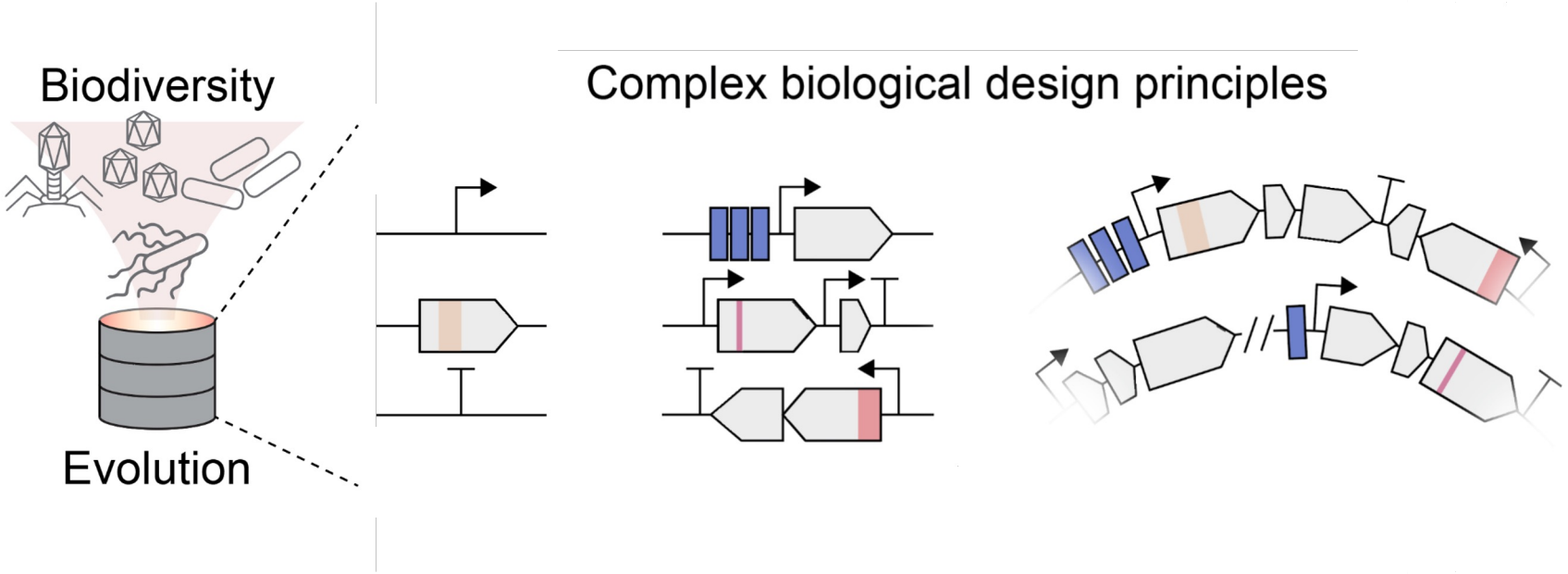
Biological design has mostly been limited to components and circuits



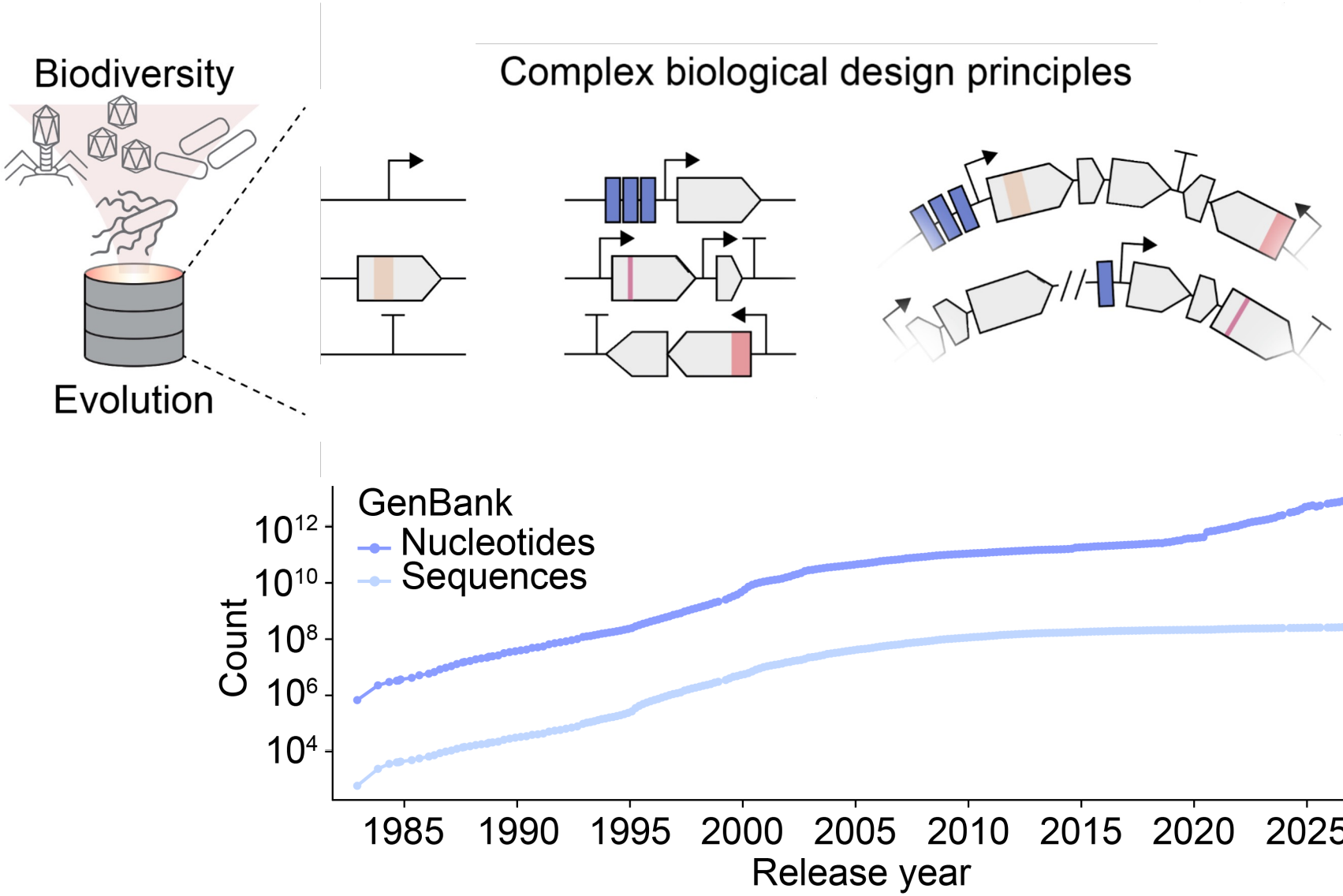
Genome design is an extraordinarily complex task



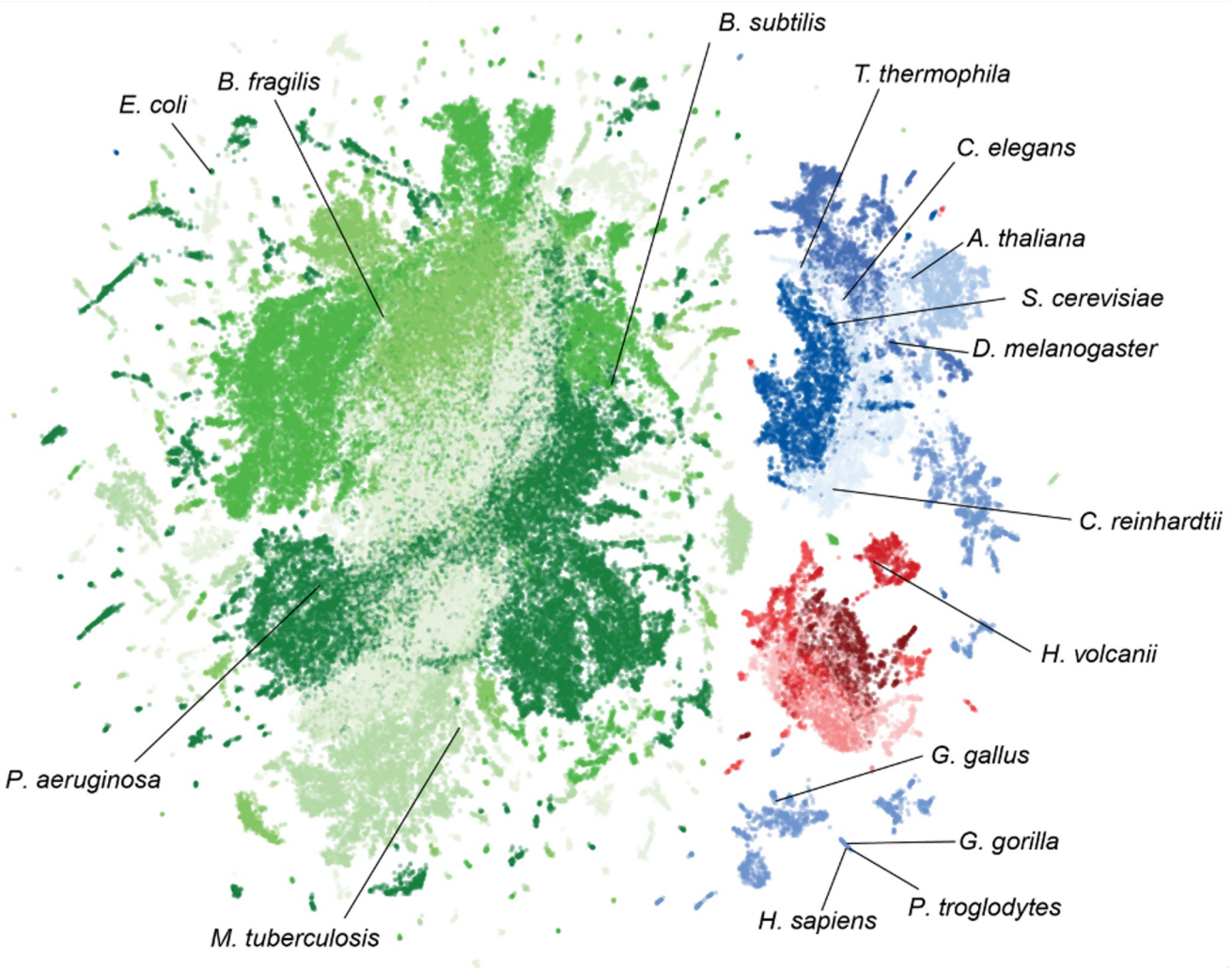
Evolutionary innovations are captured in large sequence databases

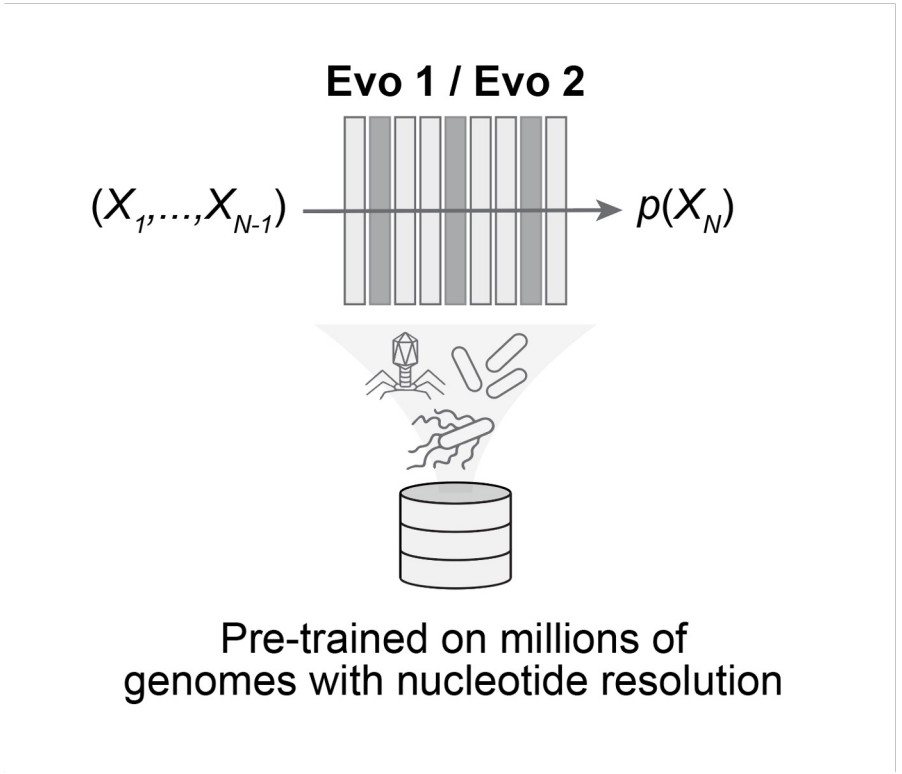


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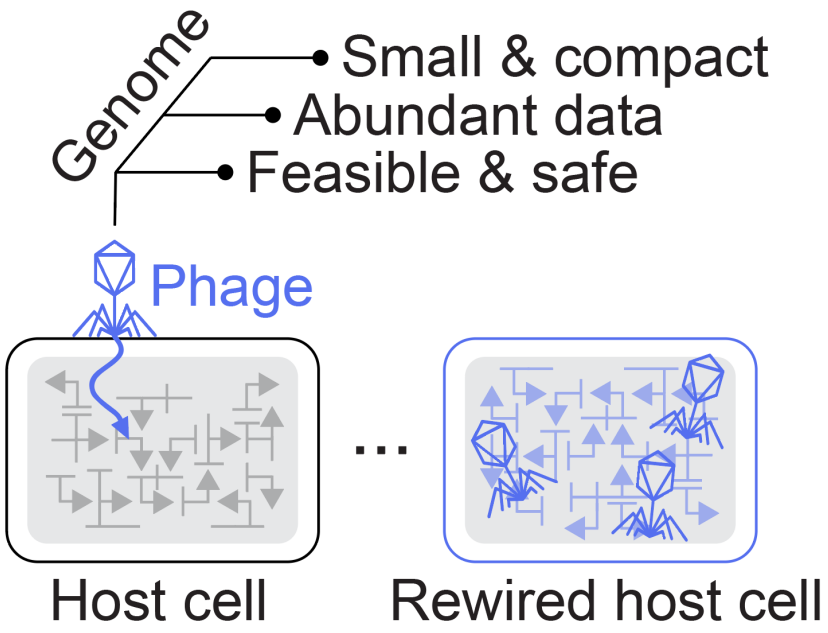
Language models learn principles of biological design without supervision





Nguyen et al. (*Science*, 2024); Brixi et al. (*Nature*, 2026)

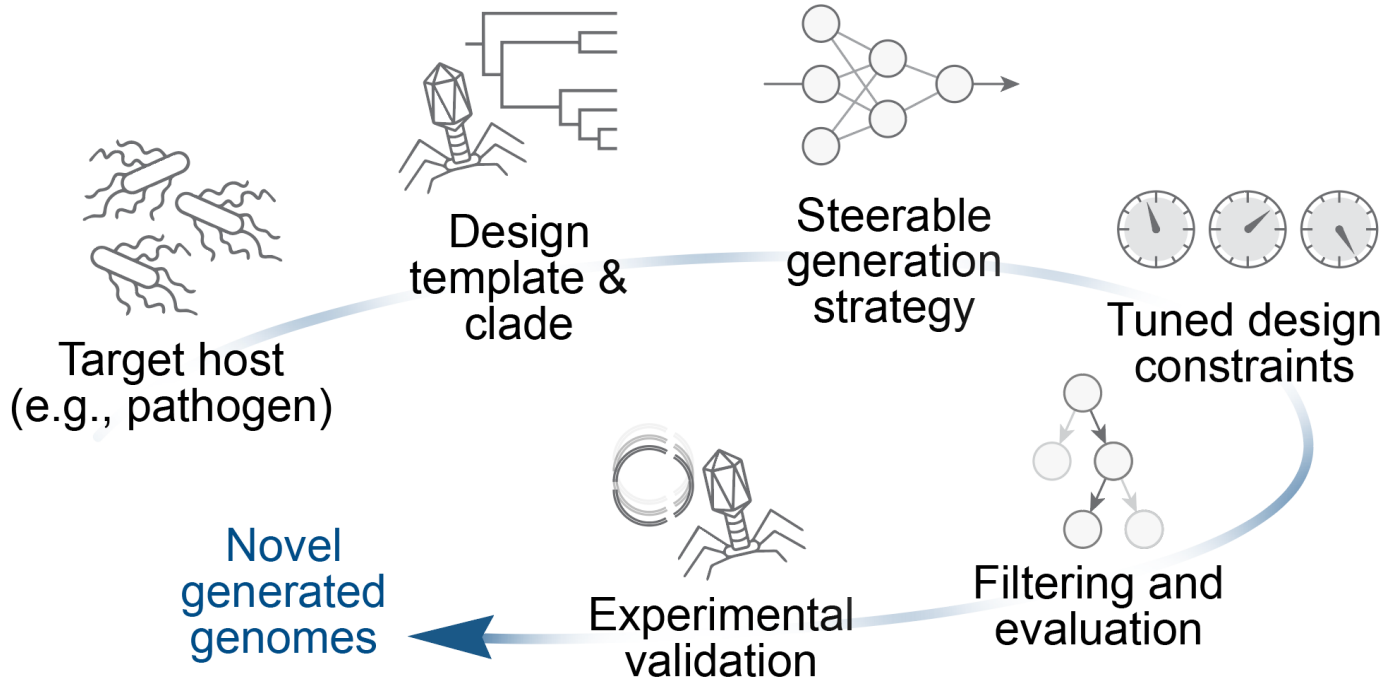
Bacteriophages are excellent models for genome design



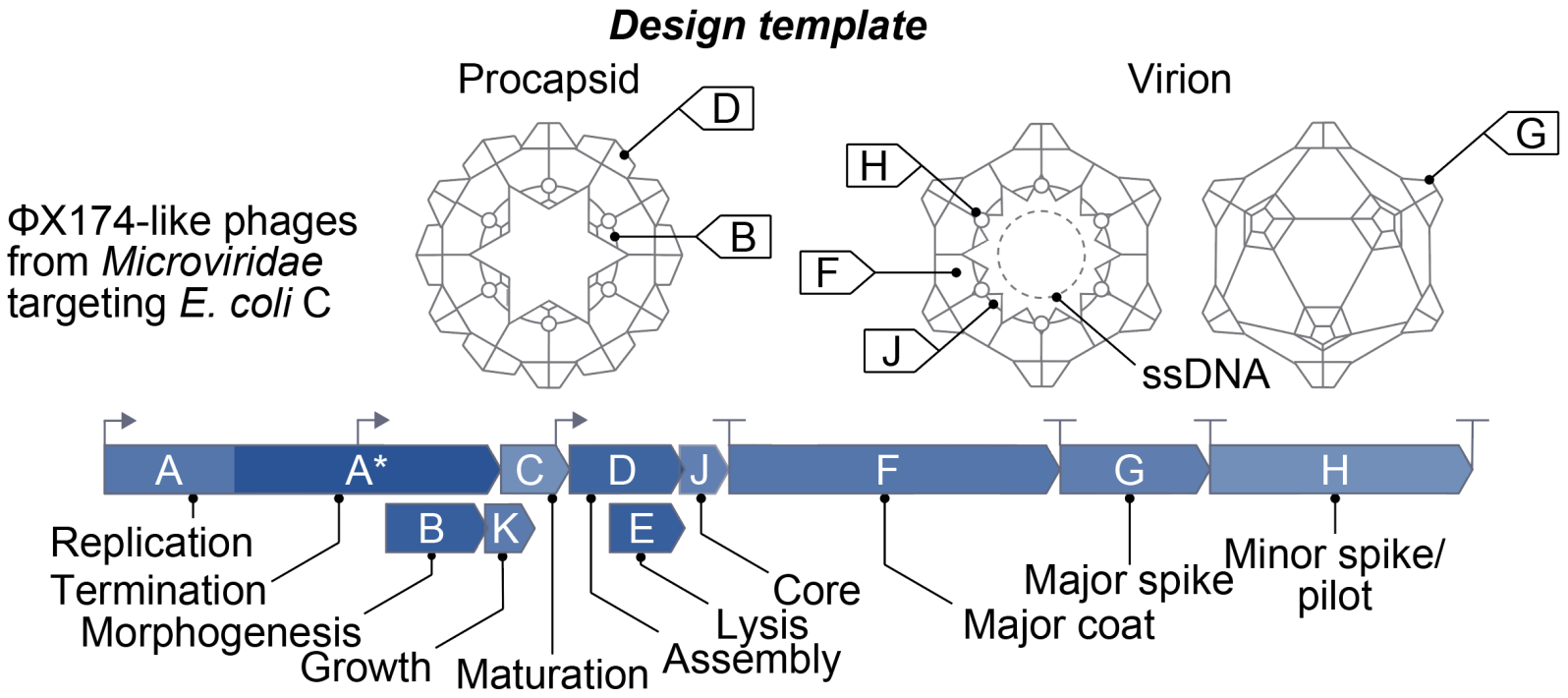
Example applications of phage designs:

- Studying molecular biology
- Genome engineering
- Microbiome modulation
- Phage therapy

Setting up a targeted phage genome design strategy

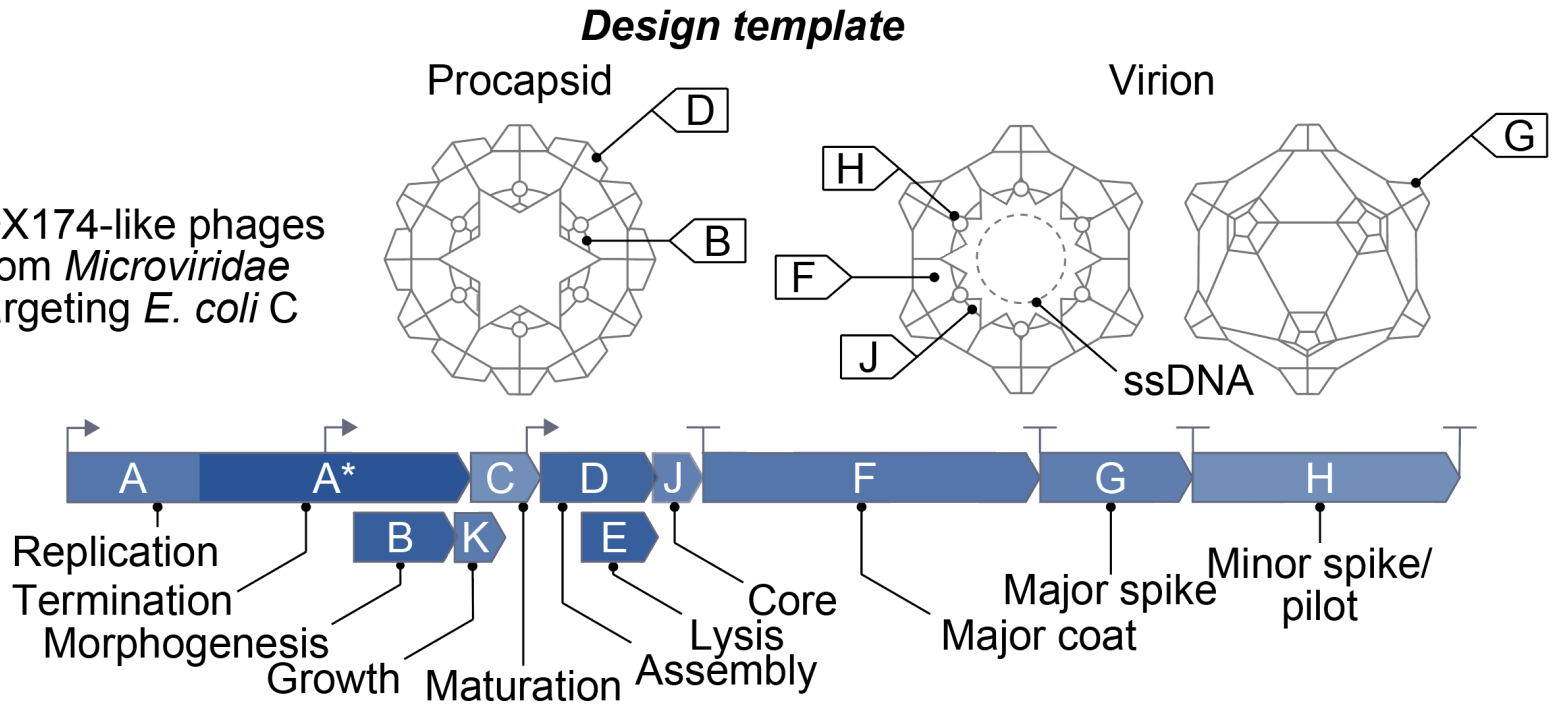


Design template: ΦX174, a *Microviridae* phage that infects *E. coli* C



Design template: ΦX174, a *Microviridae* phage that infects *E. coli* C

ΦX174-like phages from *Microviridae* targeting *E. coli* C



Nucleotide sequence of bacteriophage ΦX174 DNA

F. Sanger, G. M. Air*, B. G. Barrell, N. L. Brown†, A. R. Coulson, J. C. Fiddes, C. A. Hutchison III‡, P. M. Slocombe§ & M. Smith‖

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

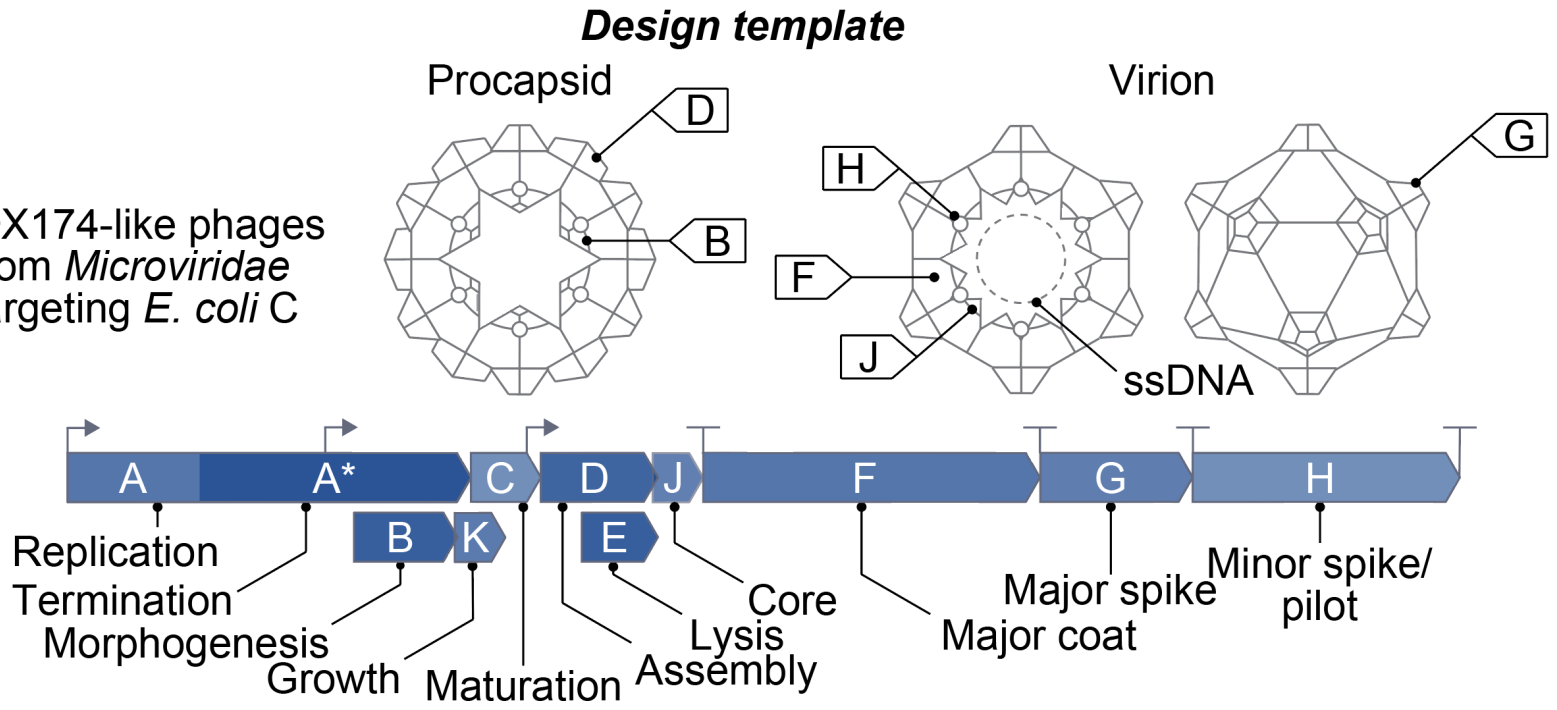
Generating a synthetic genome by whole genome assembly: ϕX174 bacteriophage from synthetic oligonucleotides

Hamilton O. Smith, Clyde A. Hutchison III†, Cynthia Pfannkoch, and J. Craig Venter‡

Institute for Biological Energy Alternatives, 1901 Research Boulevard, Suite 600, Rockville, MD 20850

Design template: ΦX174, a *Microviridae* phage that infects *E. coli* C

ΦX174-like phages from *Microviridae* targeting *E. coli* C



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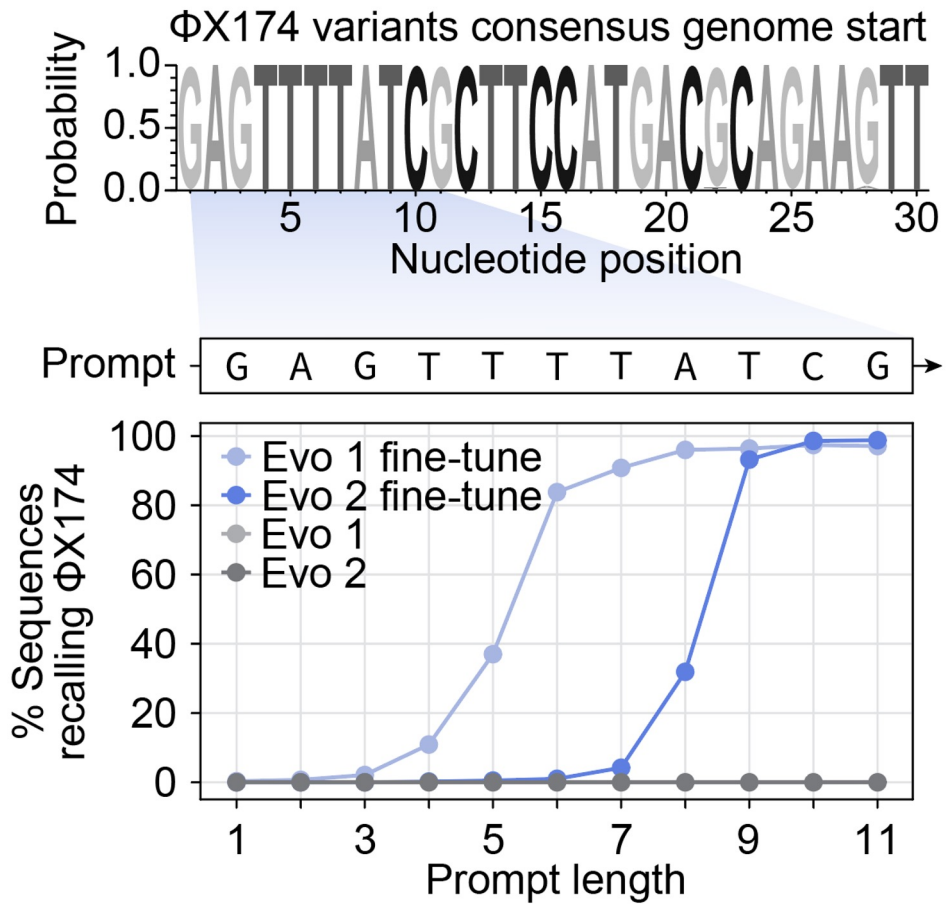
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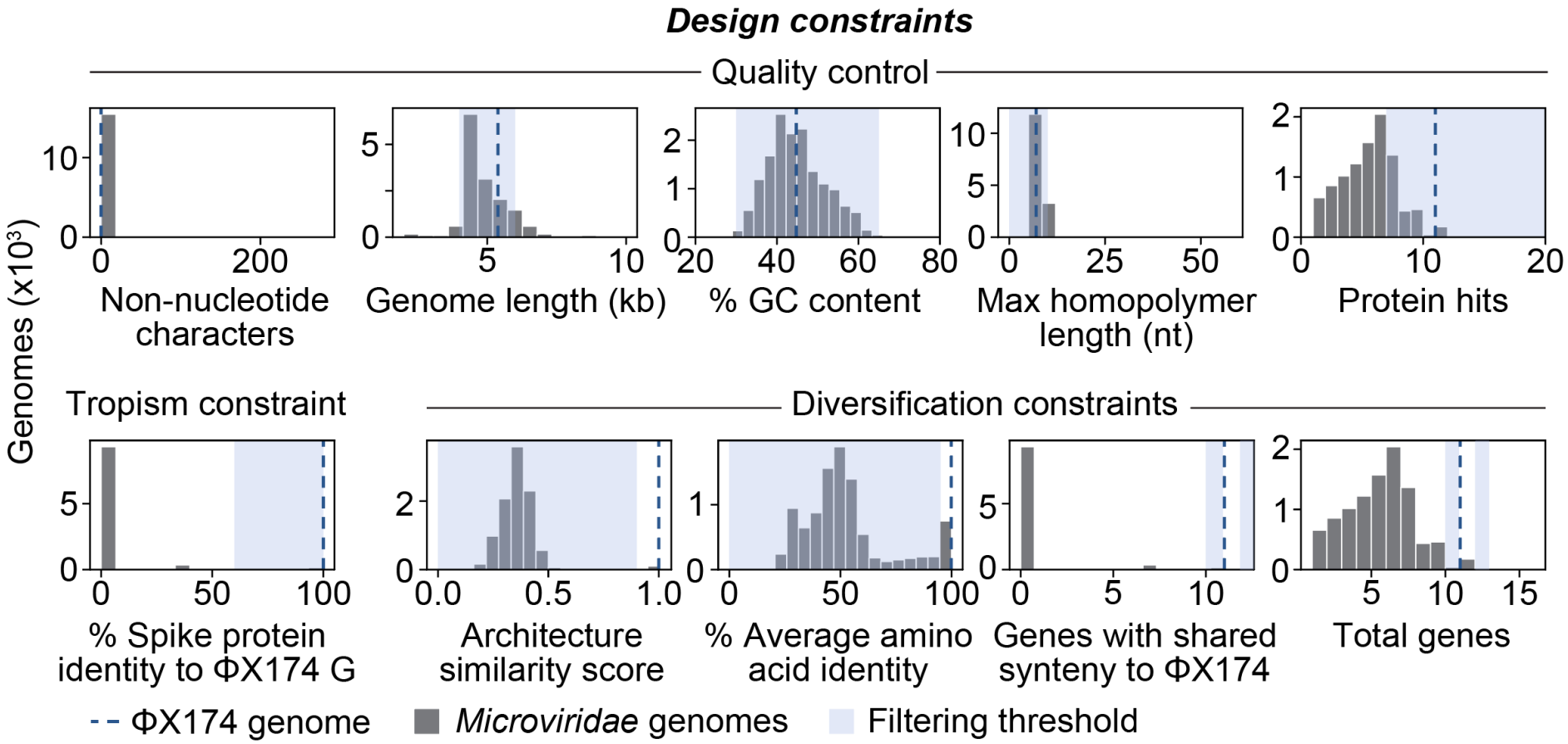
Institute for Biological Energy Alternatives, 1901 Research Boulevard, Suite 600, Rockville, MD 20850

- 5,386 nucleotides
- At least 11 genes & 7 regulatory elements
- 8 out of 11 genes overlap
- 10 out of 11 genes are essential
- Any single nonsynonymous mutation is ~20% lethal

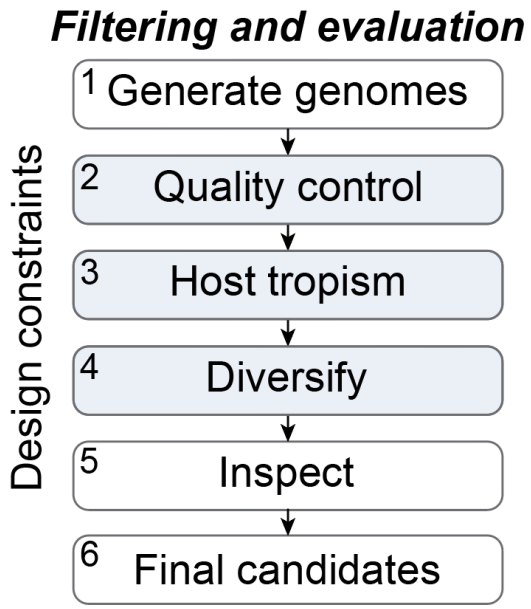
Generation strategy: Prompting Evo to generate ΦX174-like phages



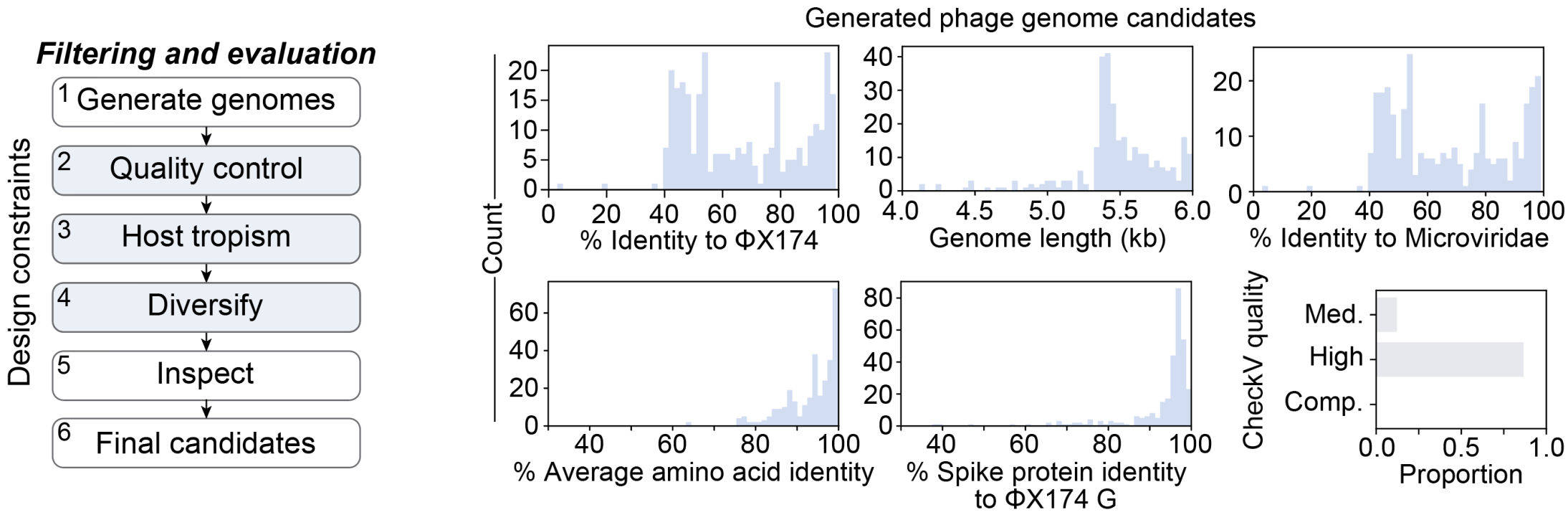
Design constraints: Criteria inspired from natural *Microviridae* genomes



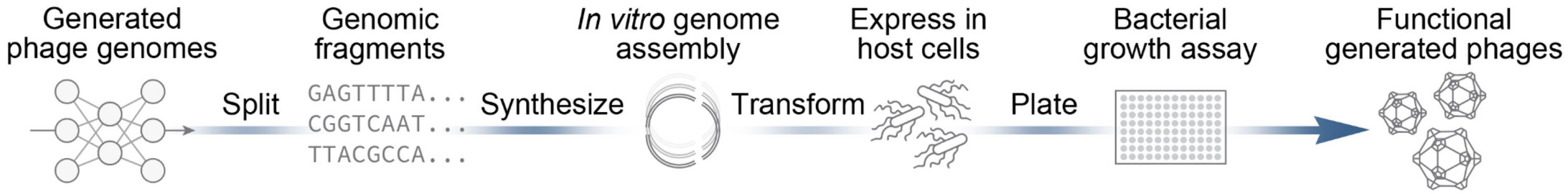
Filtering and evaluation: Running the full pipeline



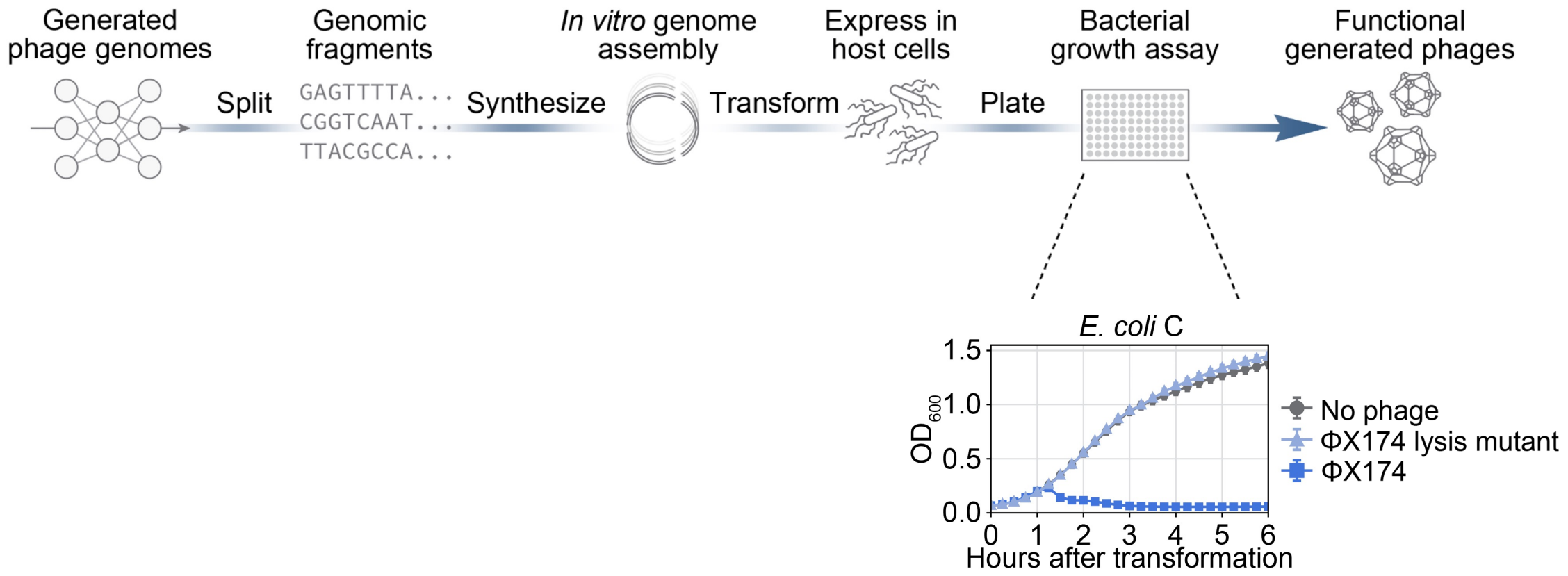
Filtering and evaluation: : Final ~300 phage genome design candidates



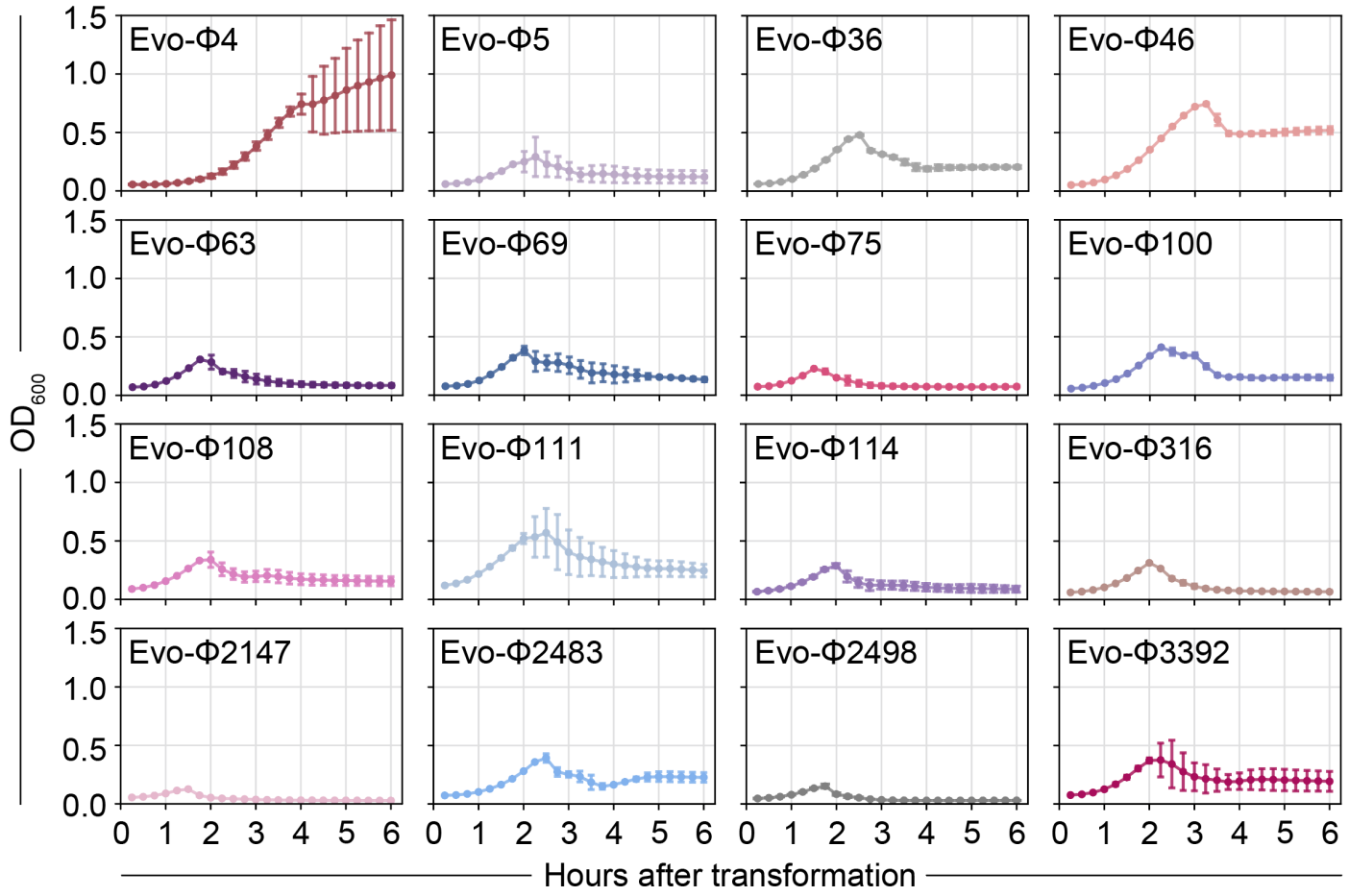
Experimental validation: Testing generated phage genomes in *E. coli* host cells

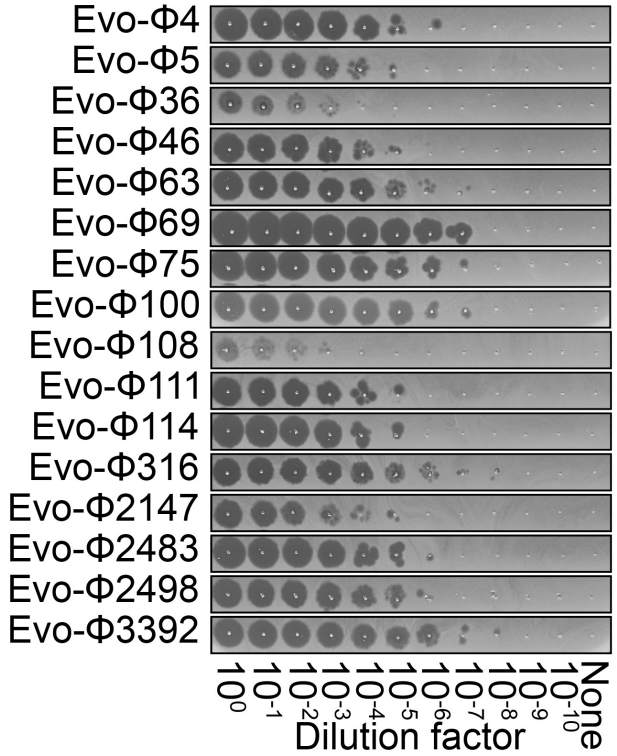


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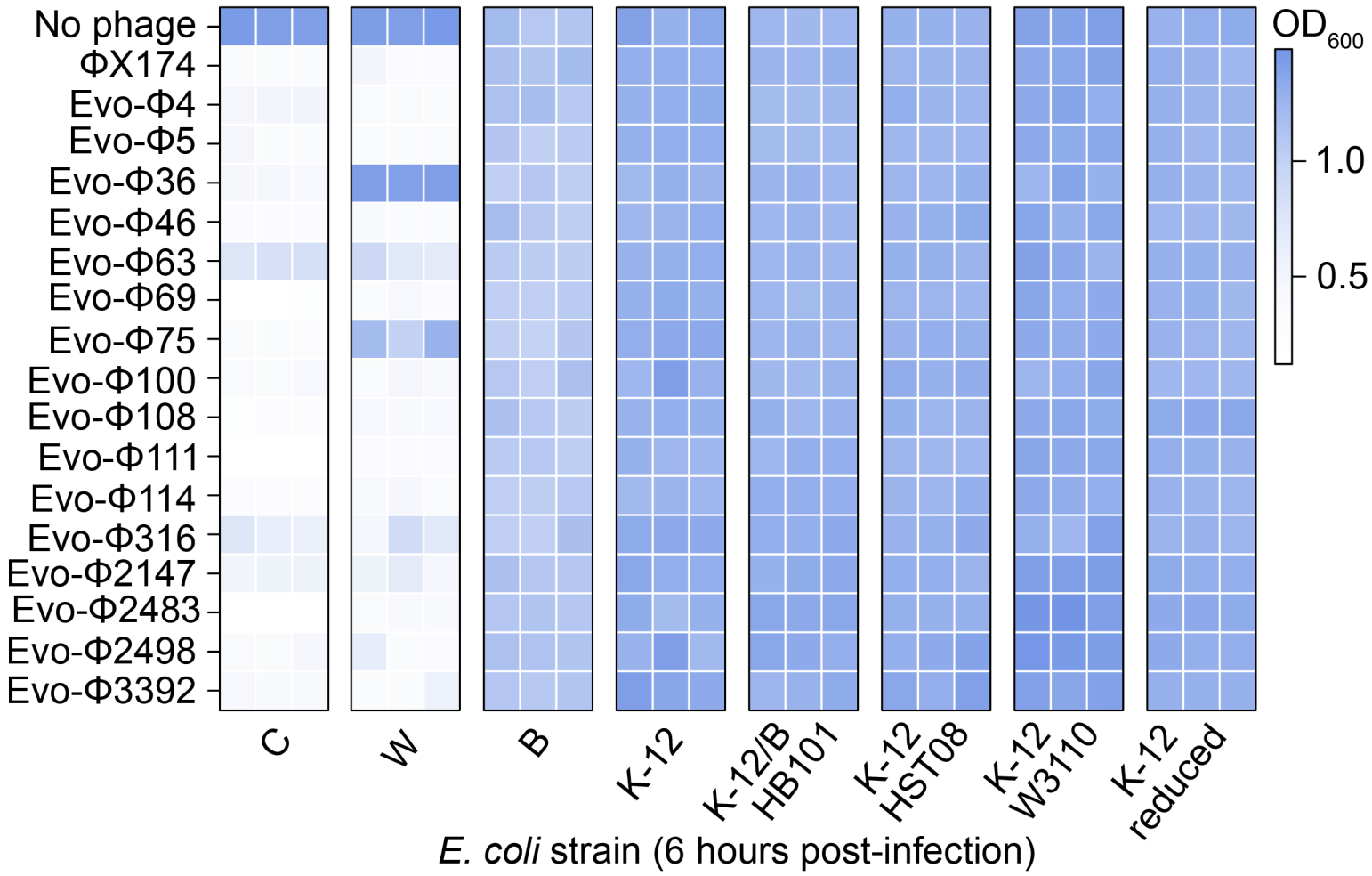


Generated phages successfully infect and lyse *E. coli* host cells

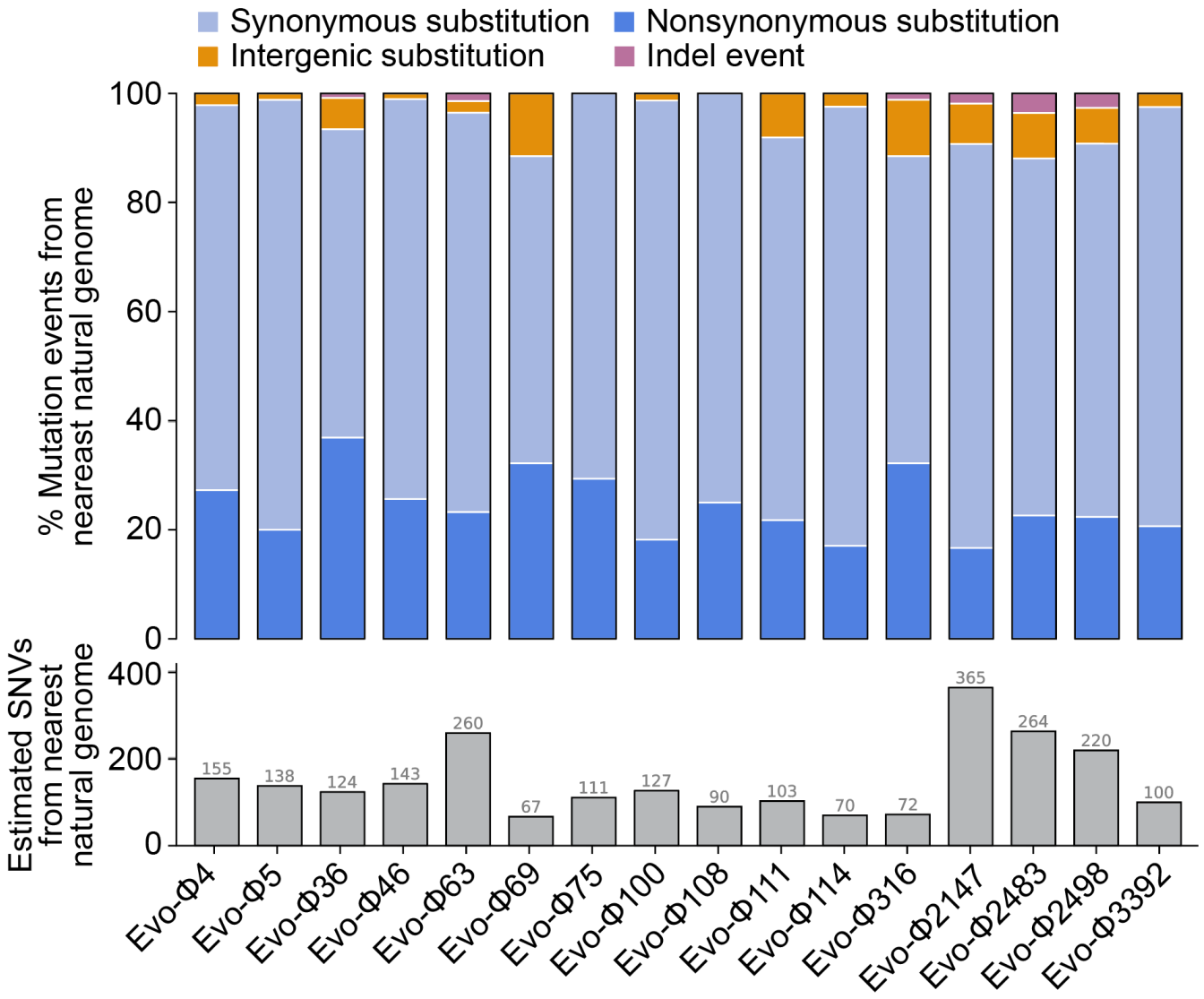




Generated phages retain target host tropism



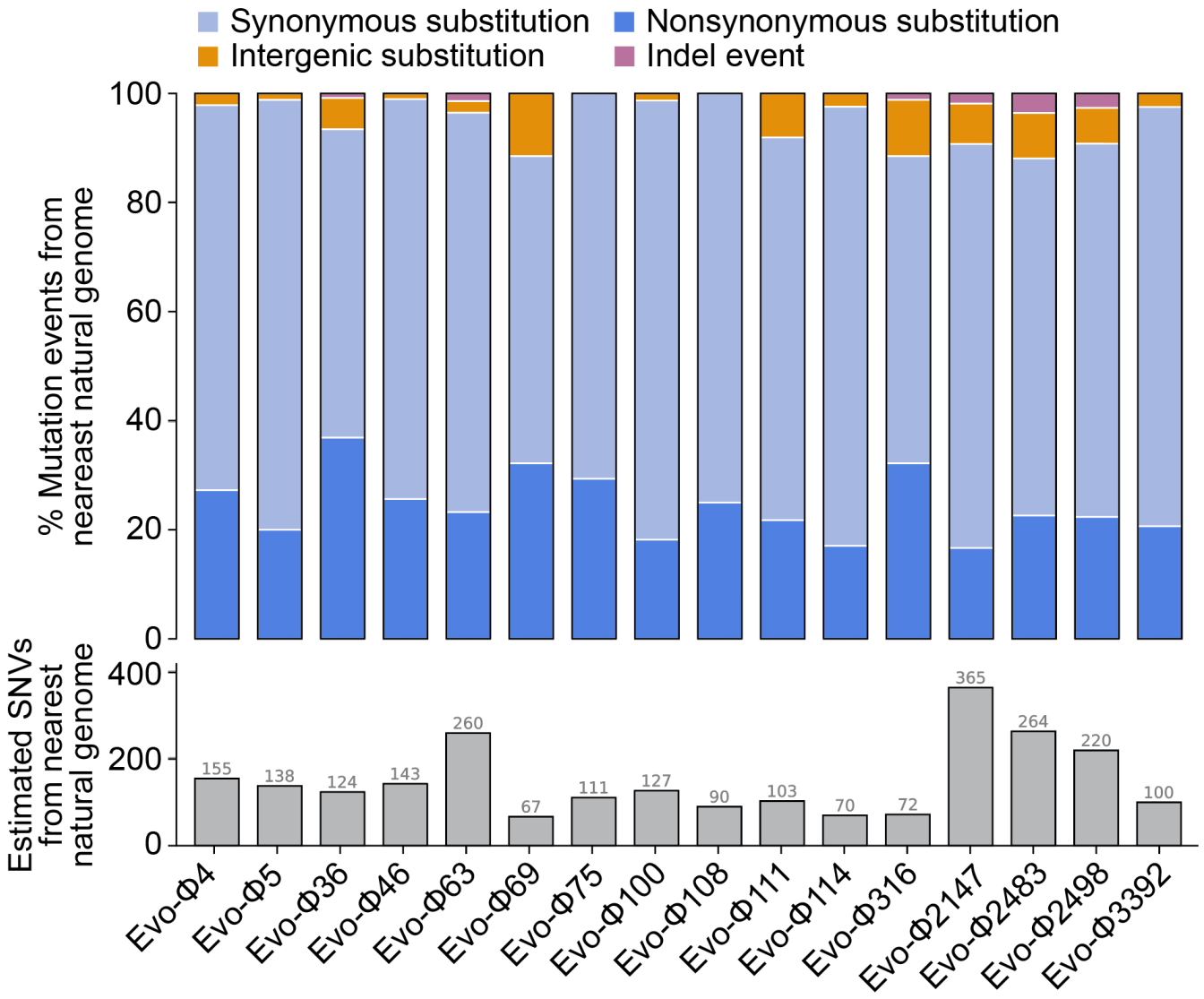
Generated phages harbor hundreds of novel mutations



Generated phages contain novel:

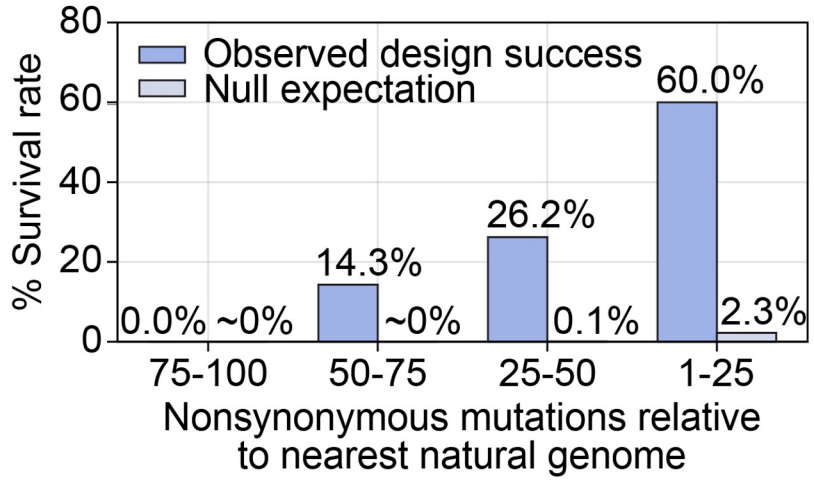
- Substitutions
- Insertions
- Deletions
- Recombinations
- Gene transfers

Generated phages tolerate high mutational burdens



Generated phages contain novel:

- Substitutions
- Insertions
- Deletions
- Recombinations
- Gene transfers

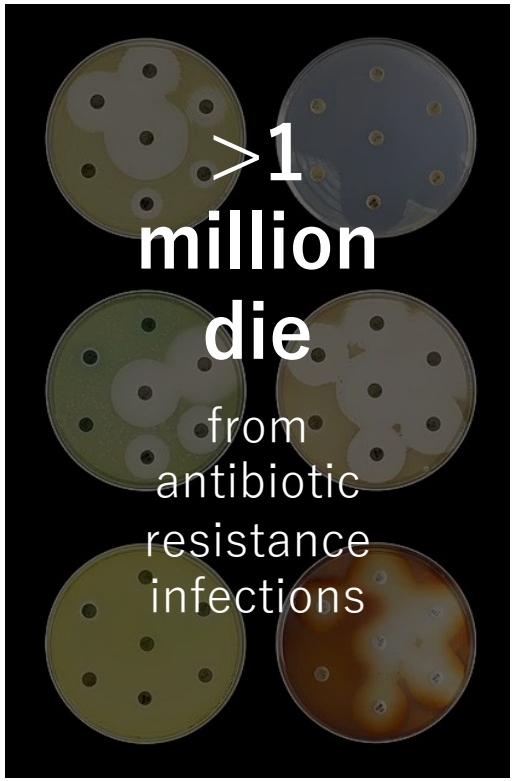


*Null based on 20% lethality rate (Domingo-Calap et al., 2009)

Could generated phage diversity help overcome bacterial resistance?

Due to bacterial pathogenic diseases, each year:



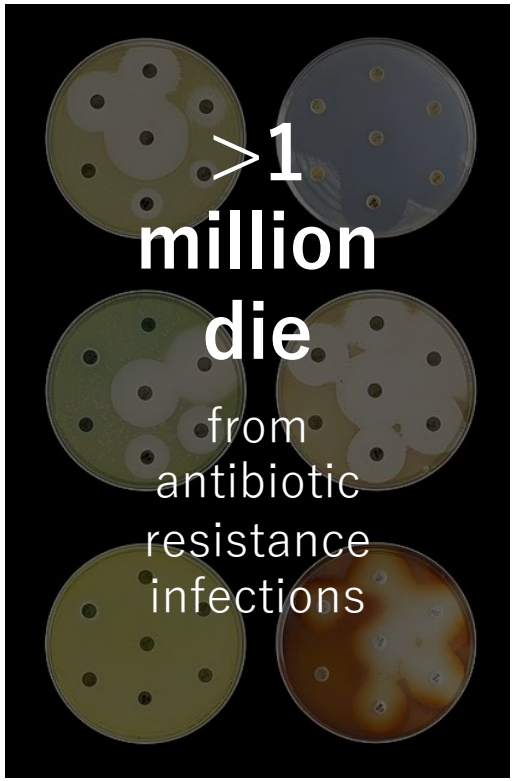


Babadoost (2021); Formidler (2025); Gai & Wang (2024); Murray et al. (2022)

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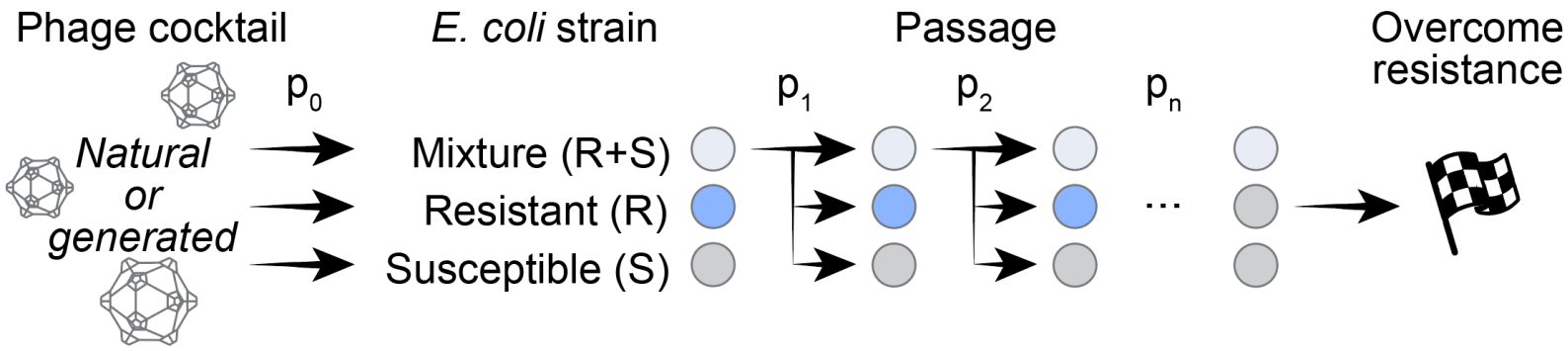




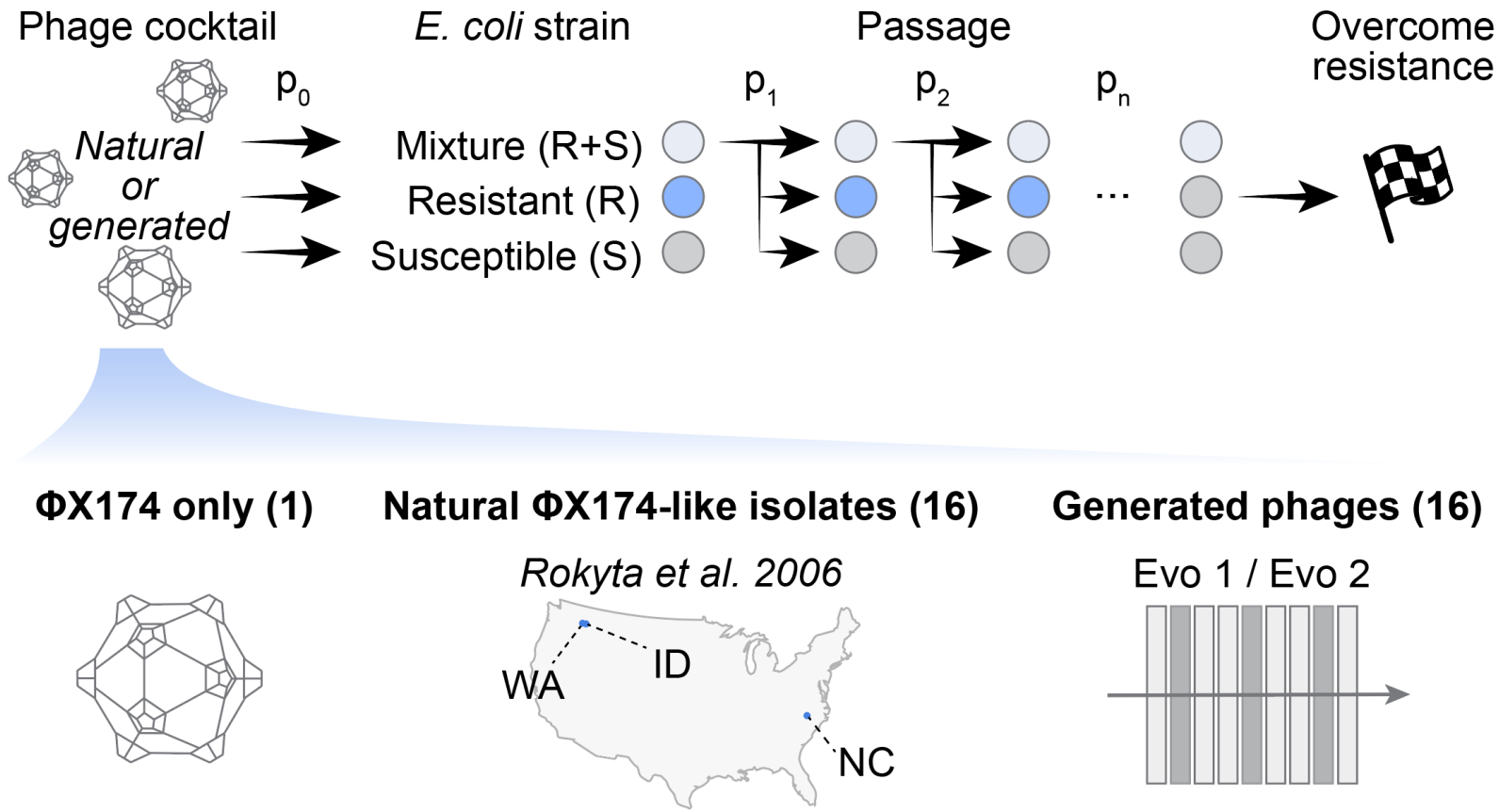
- Antimicrobial resistance is predicted to cause up to 40 million deaths by 2050
- Phage therapies are a promising solution
- Phage therapies must contain diverse phages to mitigate bacterial resistance, but sourcing diverse phages can be slow or unsuccessful

Babadoost (2021); Formidler (2025); Gai & Wang (2024); Murray et al. (2022)

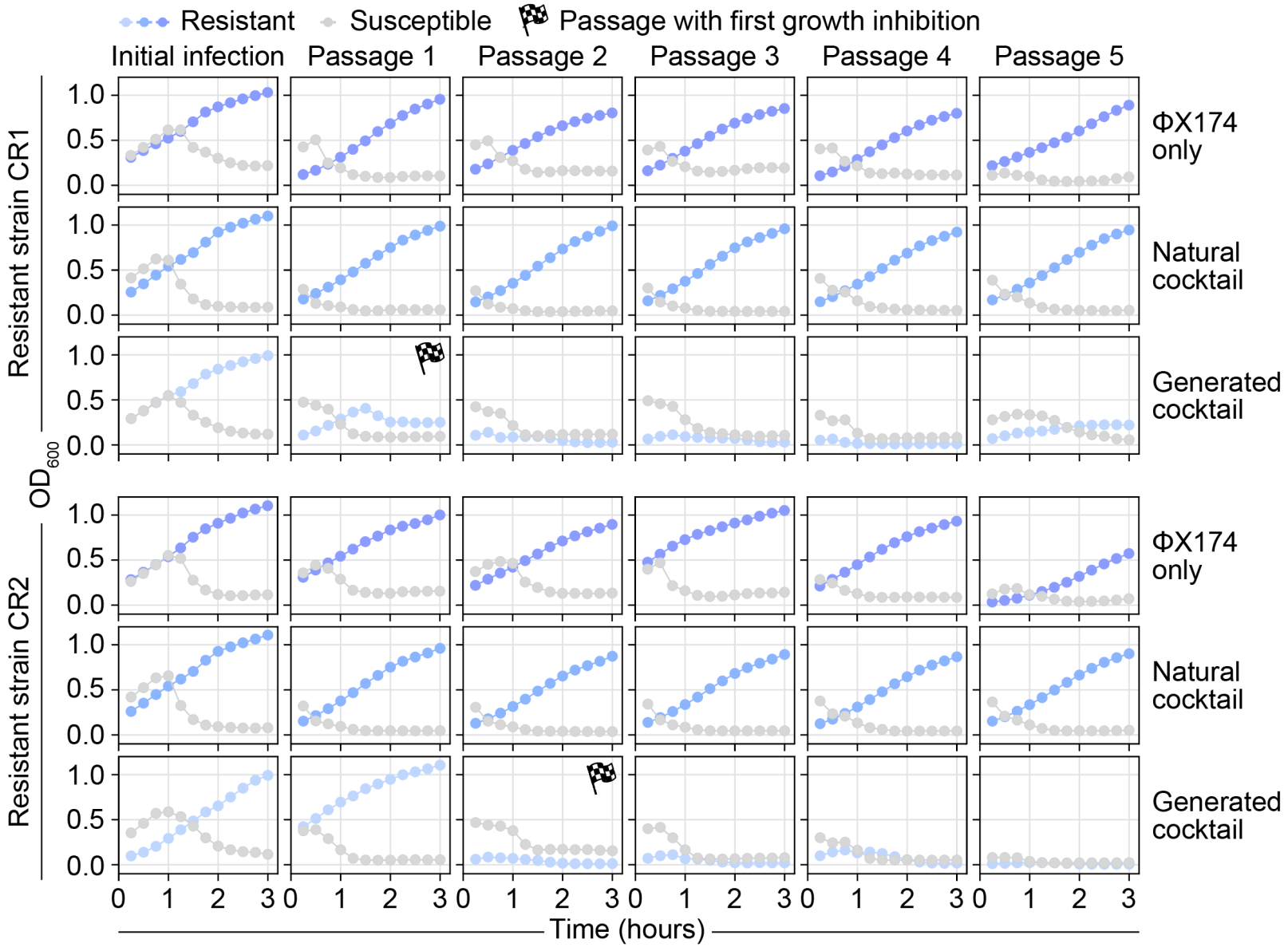
Challenging ΦX174-resistant *E. coli* C with phage cocktails



Challenging ΦX174-resistant *E. coli* C with phage cocktails



Generated phages overcome ΦX174 resistance but natural phages do not



AI-designed phage therapy has already treated a patient



The New York Times

Start-Up Claims to Use A.I.-Created Viruses to Treat a Patient

Certain viruses attack bacteria and can sometimes clear antibiotic-resistant infections. Researchers said they had tailored a virus to attack one patient's illness.

The company Radical Numerics is using its new A.I. model, Omnii, to tackle a range of challenges, including designing cancer vaccines and recognizing the risk that a virus may cause a pandemic. Among these efforts is the first trial of A.I.-designed phage therapy. Radical Numerics

By Carl Zimmer

Oct. 20, 2026

AI-designed phages are also cited for concerns around AI development

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August 10, 2026

Dear Mr. Altman, Mr. Amodei and Mr. Zuckerberg:

Almost every day, there is a new story about how your companies are losing control of the AI technology you are developing, with potentially cataclysmic results.

This week we learned, frighteningly, that AI has been used for the first time ever to create new viruses. As you know this type of development, in the wrong hands, could lead to new bioweapons that result in the deaths of tens of millions of people.

Last month, the world found out OpenAI lost control of an AI model. The result? The model hacked into another company's computers—a clear violation of federal law. After conducting internal reviews, Anthropic and Meta reported their models similarly escaped their control.

One of the targeted companies called the AI hack "an unprecedented event" that deserves an "unprecedented response." Yoshua Bengio, the most cited living scientist in the world, said these incidents "should serve as a wake-up call."

I agree.

So do the top scientists at the companies you lead, the very people building this technology. As you know, these technology leaders recently called for the international community to create a safety mechanism—a pause button—to avoid catastrophe. They warned there is a "real risk that capability development rapidly accelerates beyond our ability to understand or control the resulting systems."

Could we help trace AI-generated genomes through “watermarking”?

SynthID
A tool to watermark and identify content generated through AI

Watermarked text

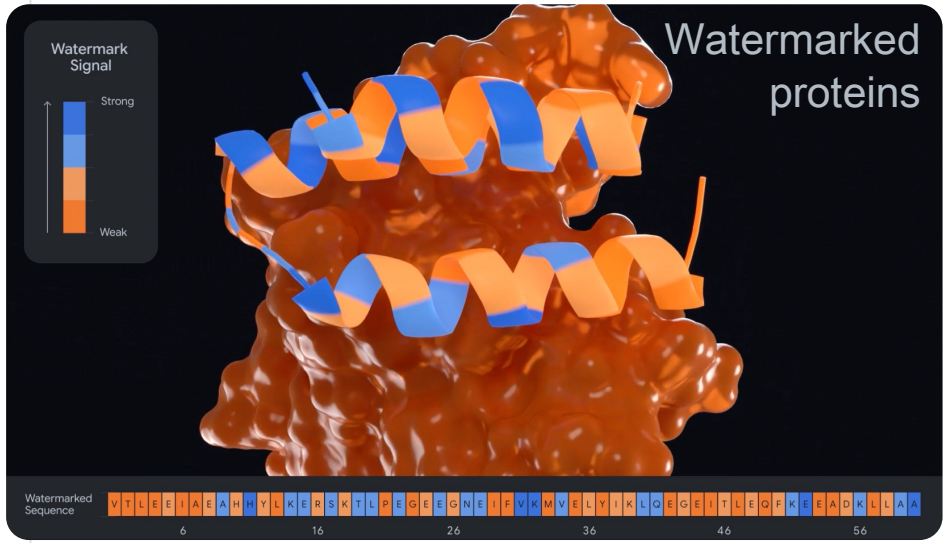
I hope this email finds you well. I'm excited to share with you some updates on the upcoming event.

We've just secured several incredible speakers who will be sharing their expertise and experiences. These speakers are leaders in their field and have a wealth of knowledge to offer. In addition to the speakers, we will also have other engaging activities such as interactive workshops, break-out sessions and networking opportunities. These activities will provide attendees with the opportunity to dive deeper into the topics, connect with peers, and build valuable relationships.

I'm confident this event will be a great success, and I'd love to have you as a speaker or workshop leader. I think your knowledge and experience would be a valuable addition to the event. If you're interested, please let me know your availability, and we can discuss the details.

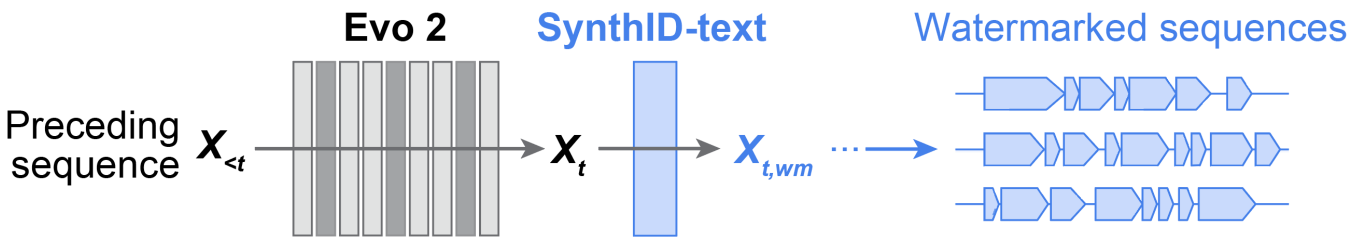
I'm excited to hear your thoughts and ideas for the event. Let's stay in touch and figure out a time to chat more in-depth about the event.
Best regards,"

Probability of being watermarked: 99.9%



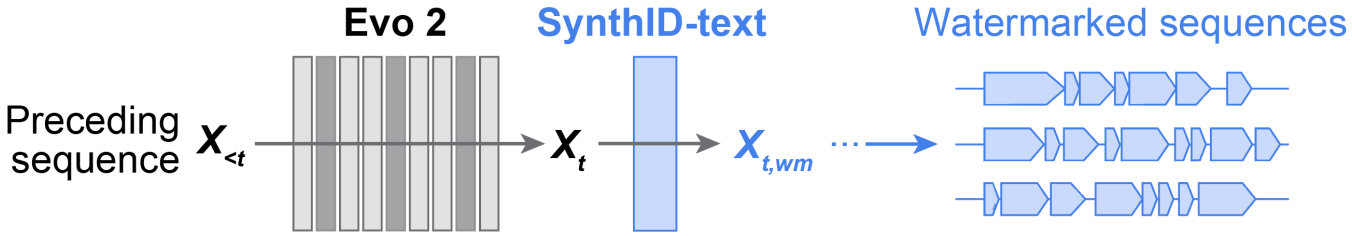
DeepMind

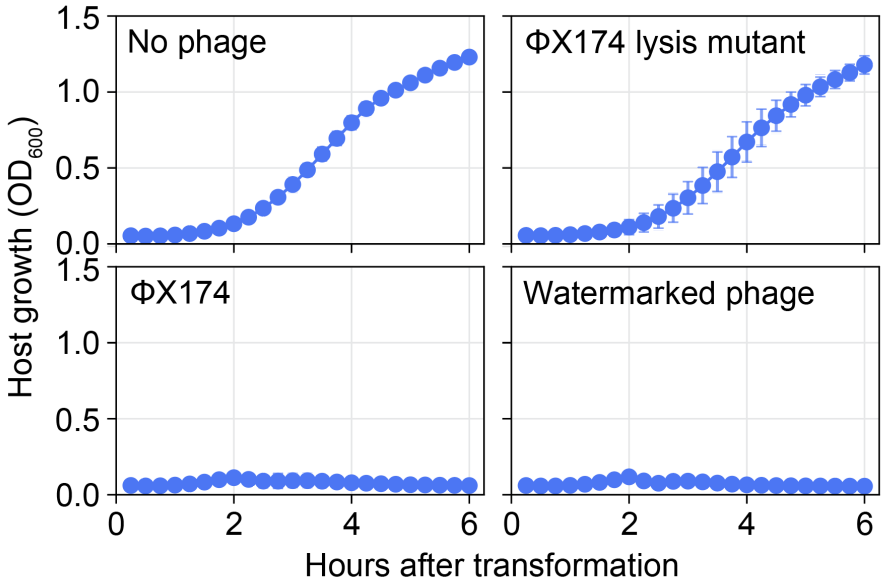
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DeepMind

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DeepMind

Acknowledgements

Laboratory of Evolutionary Design

Arc Institute

Stanford | Bioengineering
Schools of Engineering & Medicine

NSF



Brian Hie

Claudia Driscoll

David Li

Daniel Guo

Aditi Merchant

Garyk Brixi

Max Wilkinson

rest of the Hie Lab!

Read the paper:

X/Bsky: samuelhking

LinkedIn: samuelhking

Email: samhking@stanford.edu