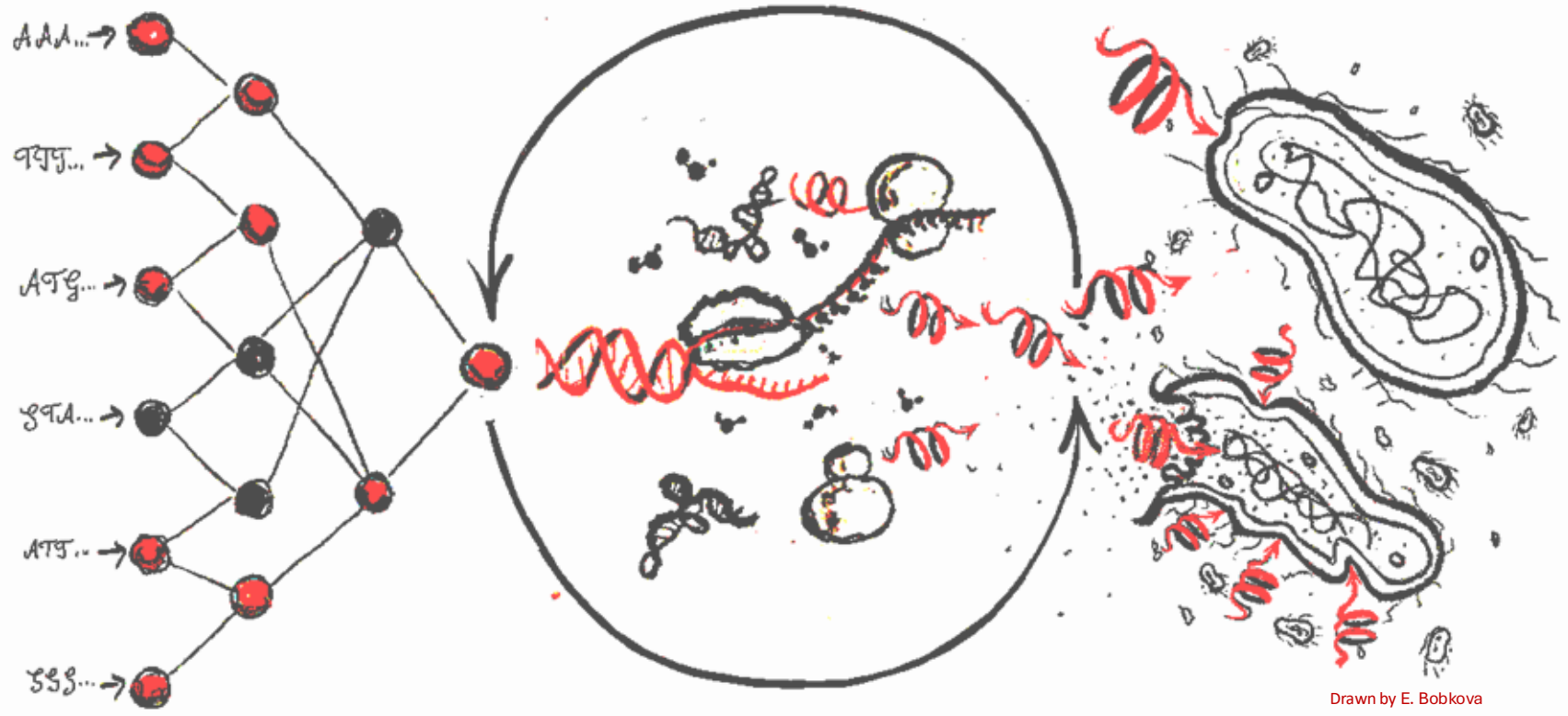
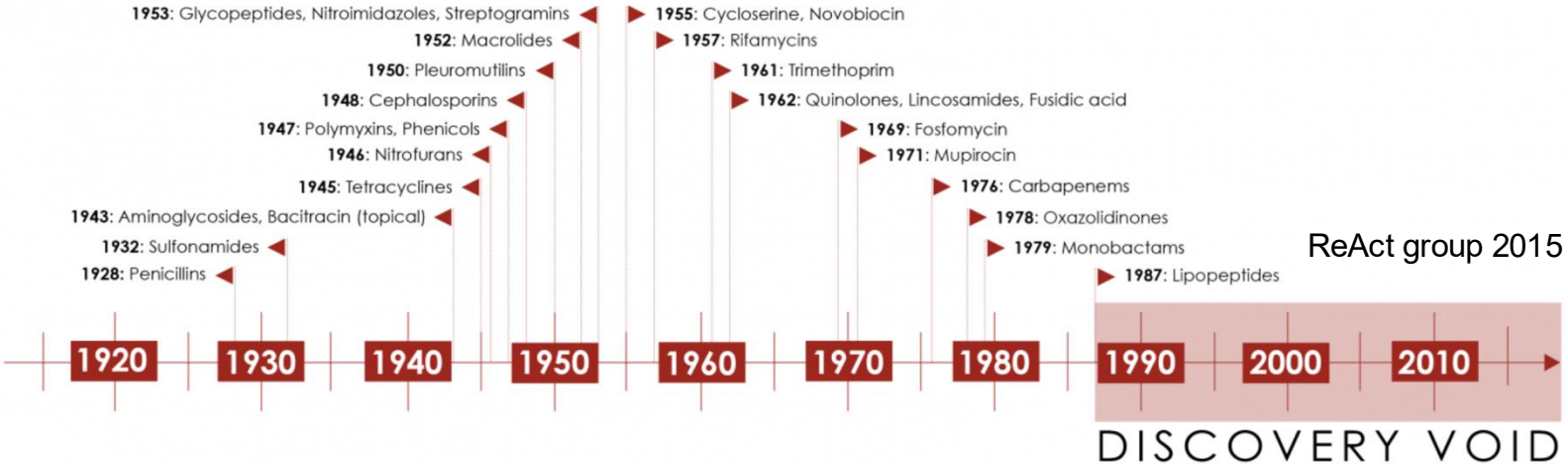


De novo antimicrobial peptides by integrating deep learning and synthetic biology

Amir Pandi

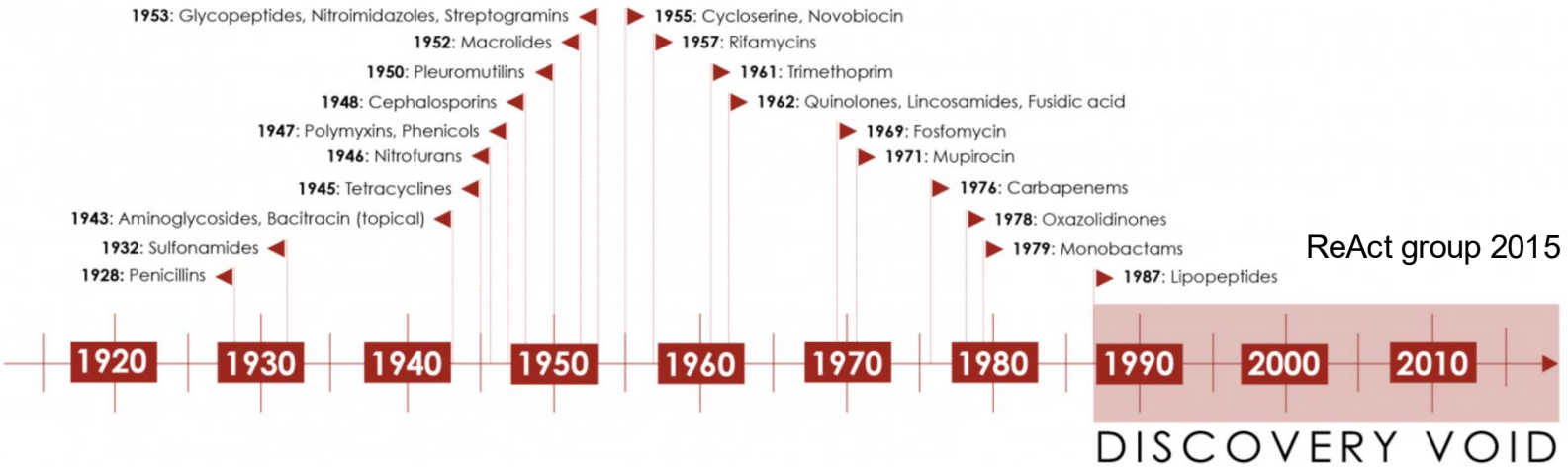
AI for Drug Discovery and Development, January 23rd, 2026

The shortage of new antibiotics, combined with rising antimicrobial resistance, a critical global health threat of the 21st century



ReAct group 2015

The shortage of new antibiotics, combined with rising antimicrobial resistance, a critical global health threat of the 21st century



ReAct group 2015

- **7.7 million** deaths yearly from bacterial infections:
  - **4.95 million** linked to drug-resistant pathogens.
  - **1.27 million** directly caused by antibiotic-resistant bacteria.

Okeke, I. N. *et al. Lancet* (2024)

- By 2050, antimicrobial resistance (AMR) could cause **10 million** deaths per year globally

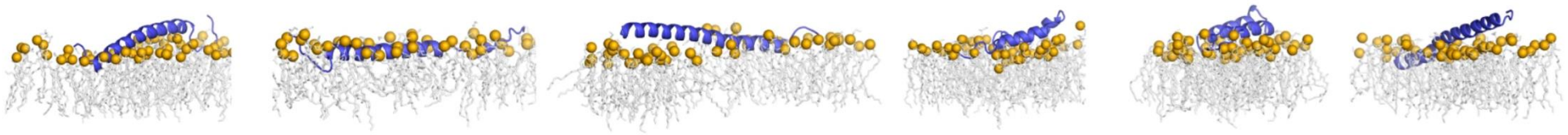
AMR collaborators *Lancet* (2022)

Antimicrobial peptides (AMPs) offer a promising solution: low propensity for resistance and great potential in therapies, food and biomaterials

Unmodified ribosomal antimicrobial peptides (AMPs)

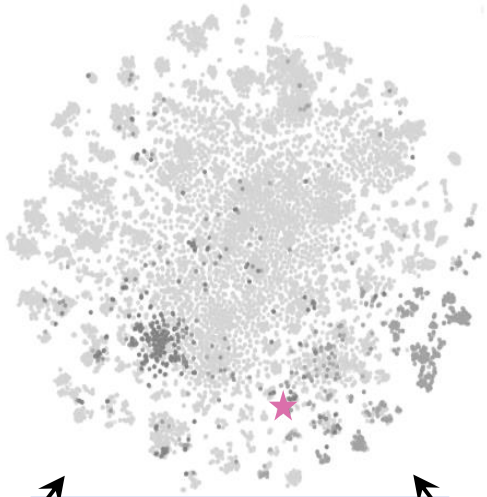
- Low emergence of resistance
- > 3000 AMPs discovered across all domains of life
- Ease of development (natural amino acid subunits)

Lazzaro *et al.,* Science, 2020

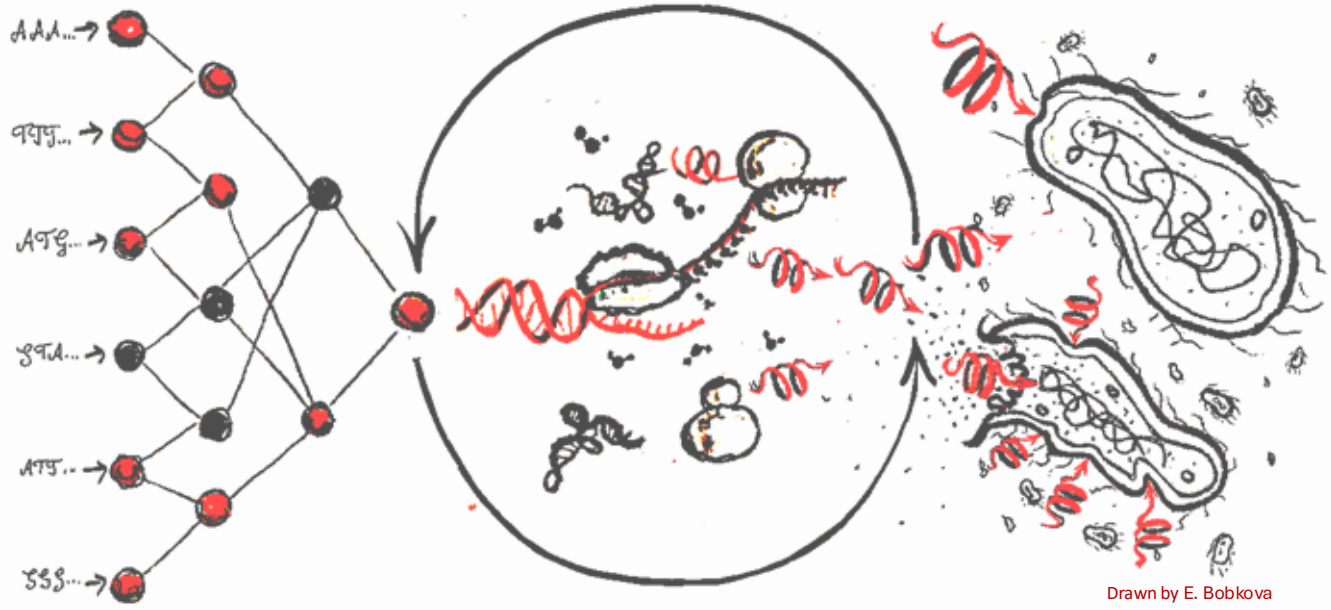


Design of *de novo* antimicrobial peptides (AMPs) to tackle antimicrobial resistance

Generate new AMPs
by deep learning

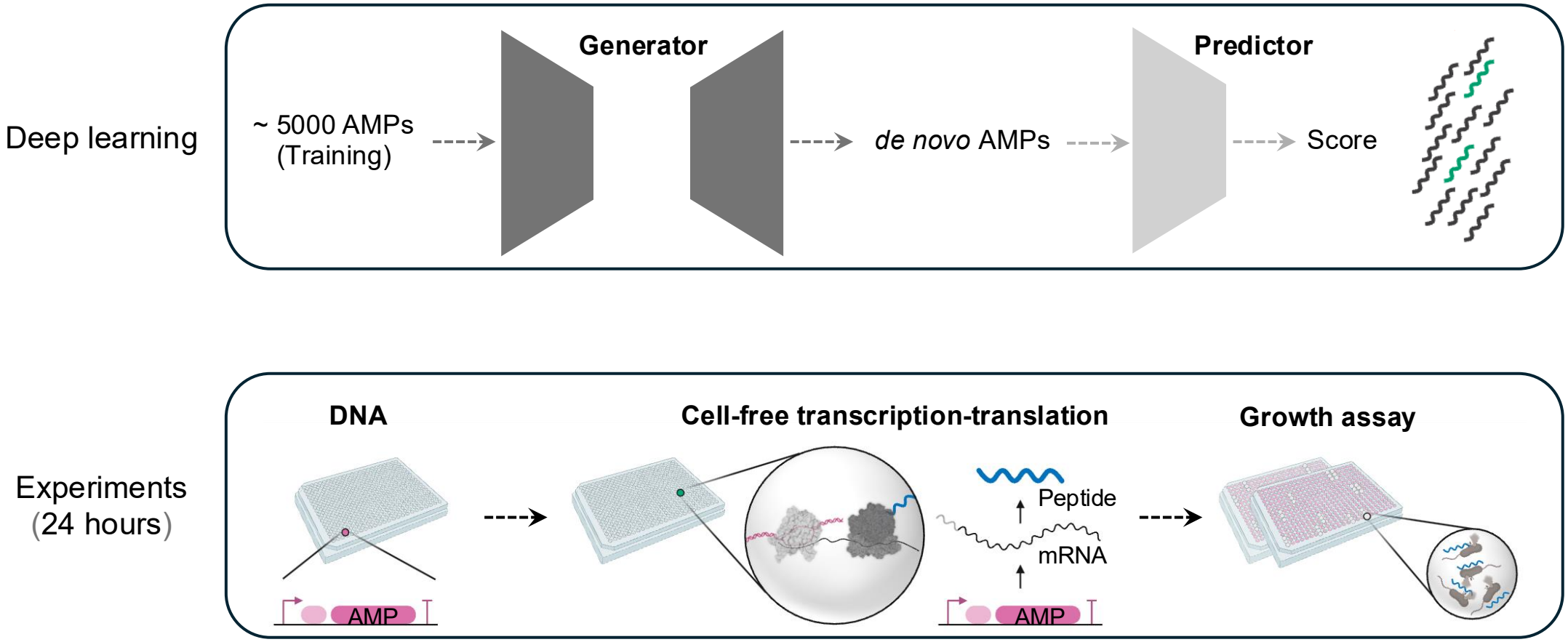


Massive sequence space



Drawn by E. Bobkova

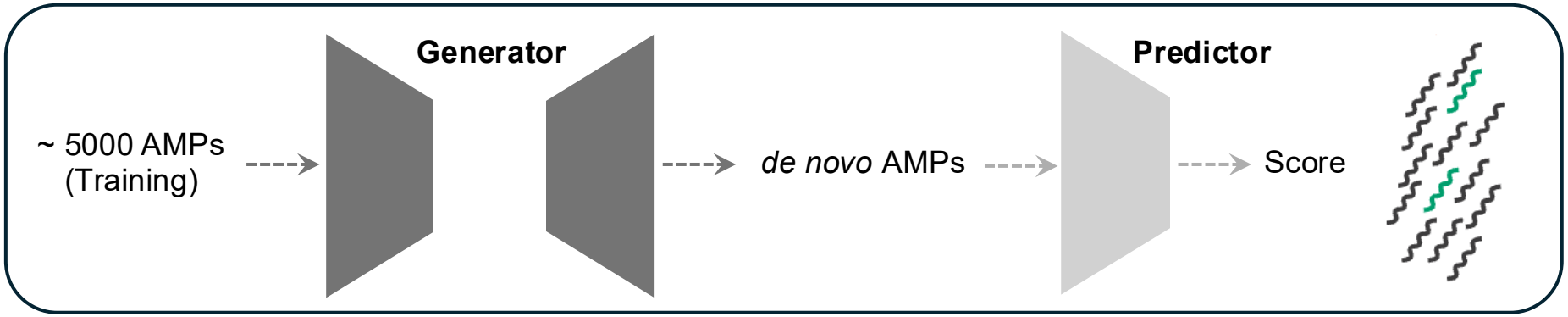
Combination of deep learning and cell-free biosynthesis enables rapid development of de novo AMPs



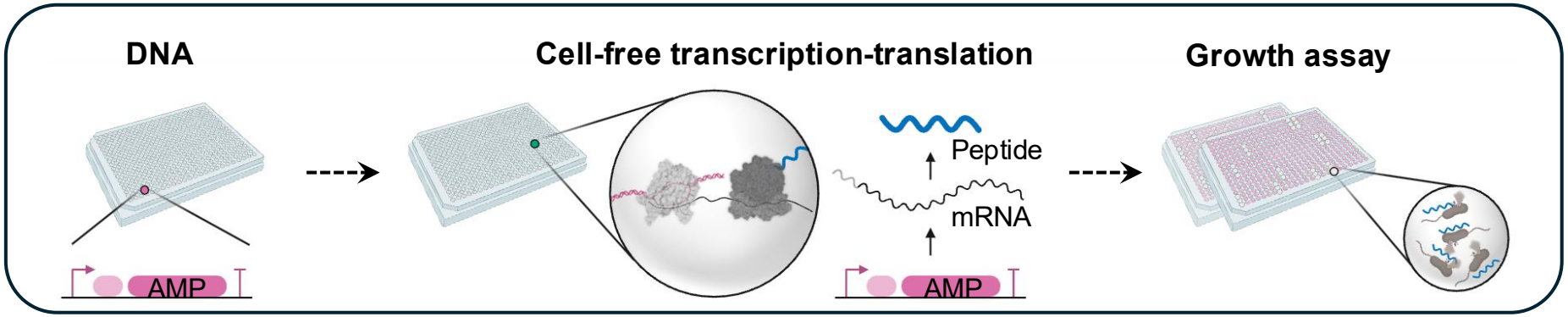
Pandi *et al*. Nature Communications (2023)

Combination of deep learning and cell-free biosynthesis enables rapid development of de novo AMPs

Deep learning



Experiments
(24 hours)
500 AMPs

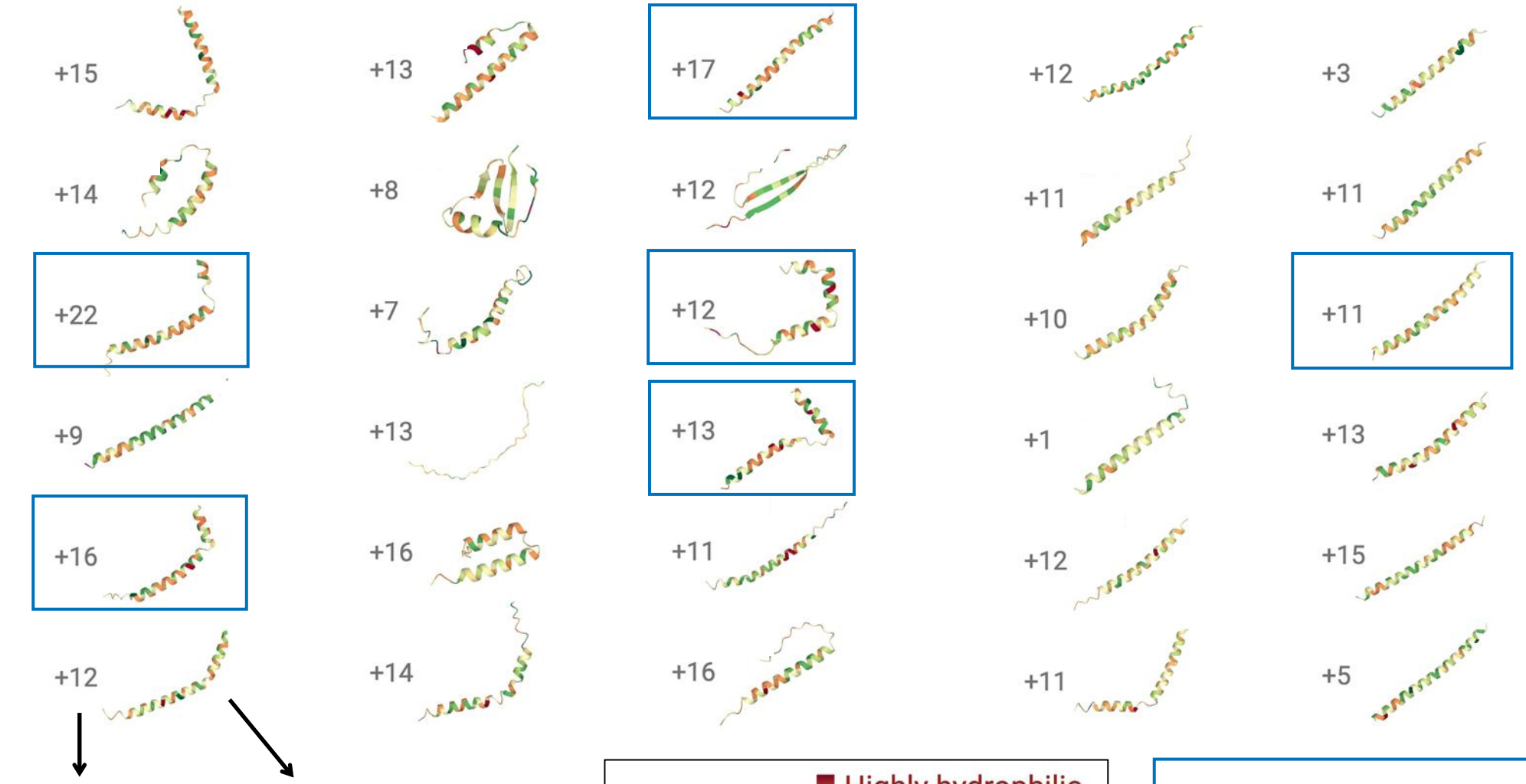


30 *de novo* AMPs

**In 5 rounds, total of 500 AMPs tested,
with success rates of 0 (round 1) to 12.6% (round 5)**

Pandi *et al*. Nature Communications (2023)

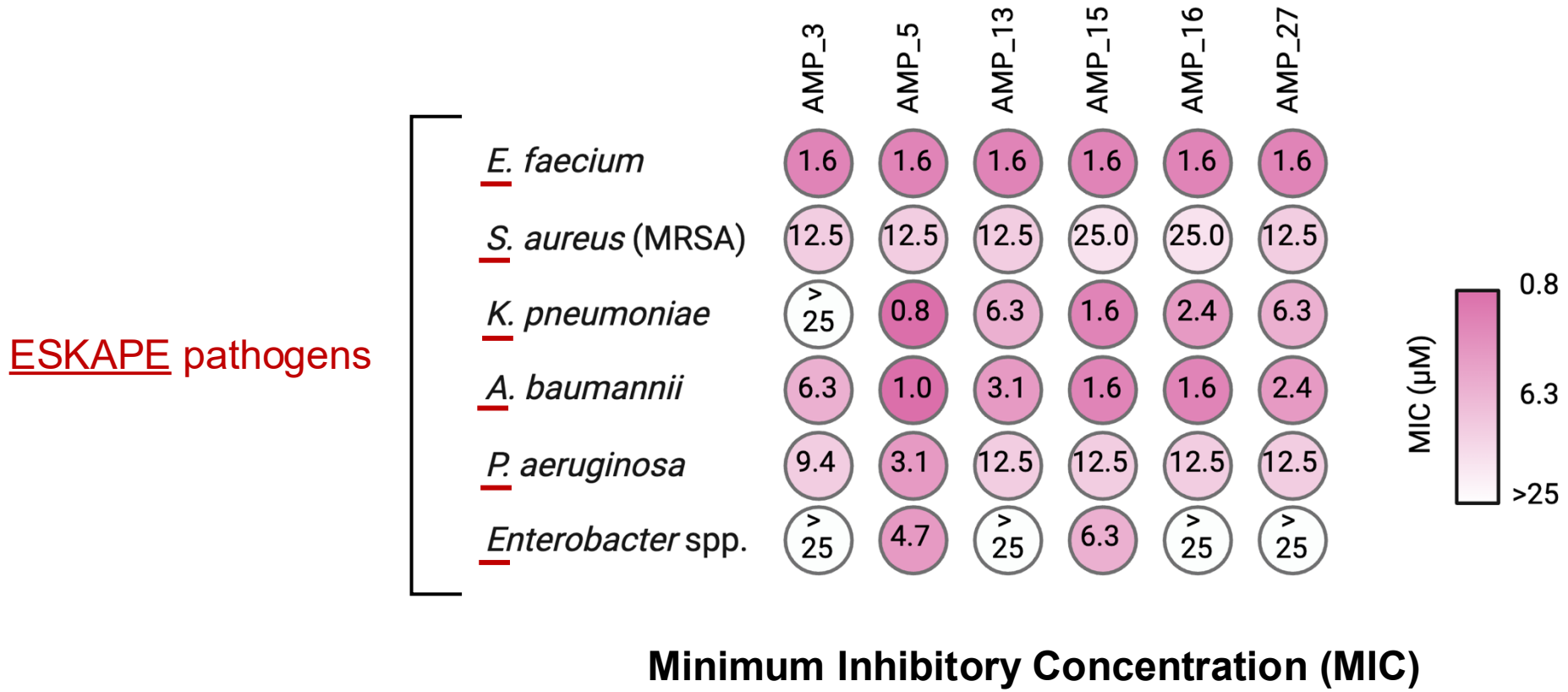
30 *de novo* AMPs were identified out of 500 candidates screened experimentally



Low toxicity & broad-band activity against ESKAPE pathogens *in vitro*

Pandi *et al*. Nature Communication 2023

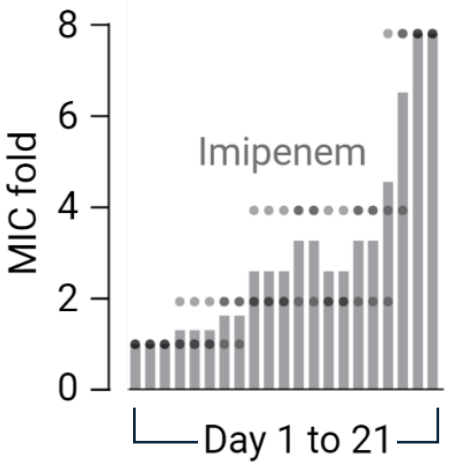
Six *de novo* AMPs showed broad-spectrum activity *in vitro*



Pandi *et al*. Nature Communications (2023)

E. coli did not evolve resistance against *de novo* AMPs, *in vitro*

21 days daily passage with fresh media and AMP



Pandi *et al*. Nature Communications (2023)

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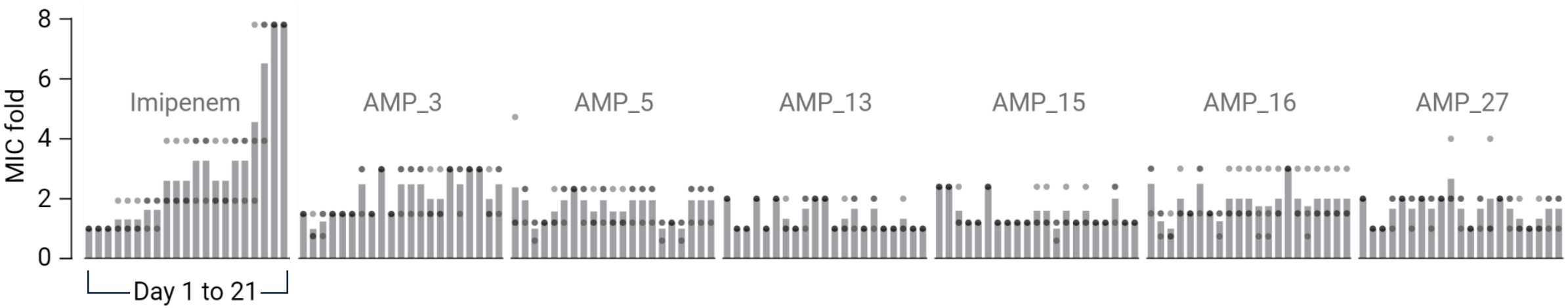

Pandi *et al*. Nature Communications (2023)

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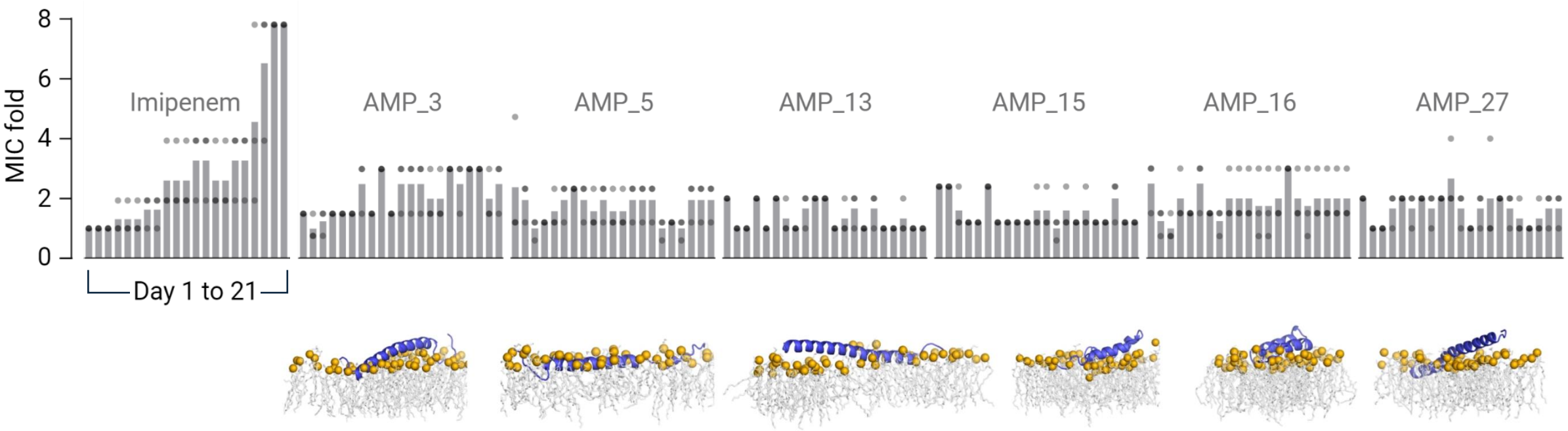


All-atom molecular dynamics simulation for 1 μs

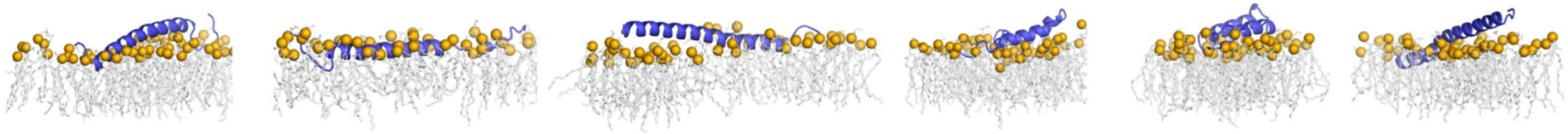
Pandi *et al*. Nature Communications (2023)

Limitations of (unmodified ribosomal) AMPs

Protease instability

Lack of antimicrobial specificity

Simple mode of action



Methods and features to put antimicrobial peptides (AMPs) into effect

	Challenges	Solutions
Methodological	• Datasets and models • Expression of de novo peptides • AMP synthesis/purification	
AMP features	• Protease stability • Pathogen specificity • Mechanism of action	

Methods and features to put antimicrobial peptides (AMPs) into effect

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Methodological	• Datasets and models • Expression of de novo peptides • AMP synthesis/purification	---------→ • Codon language AI for DNA design
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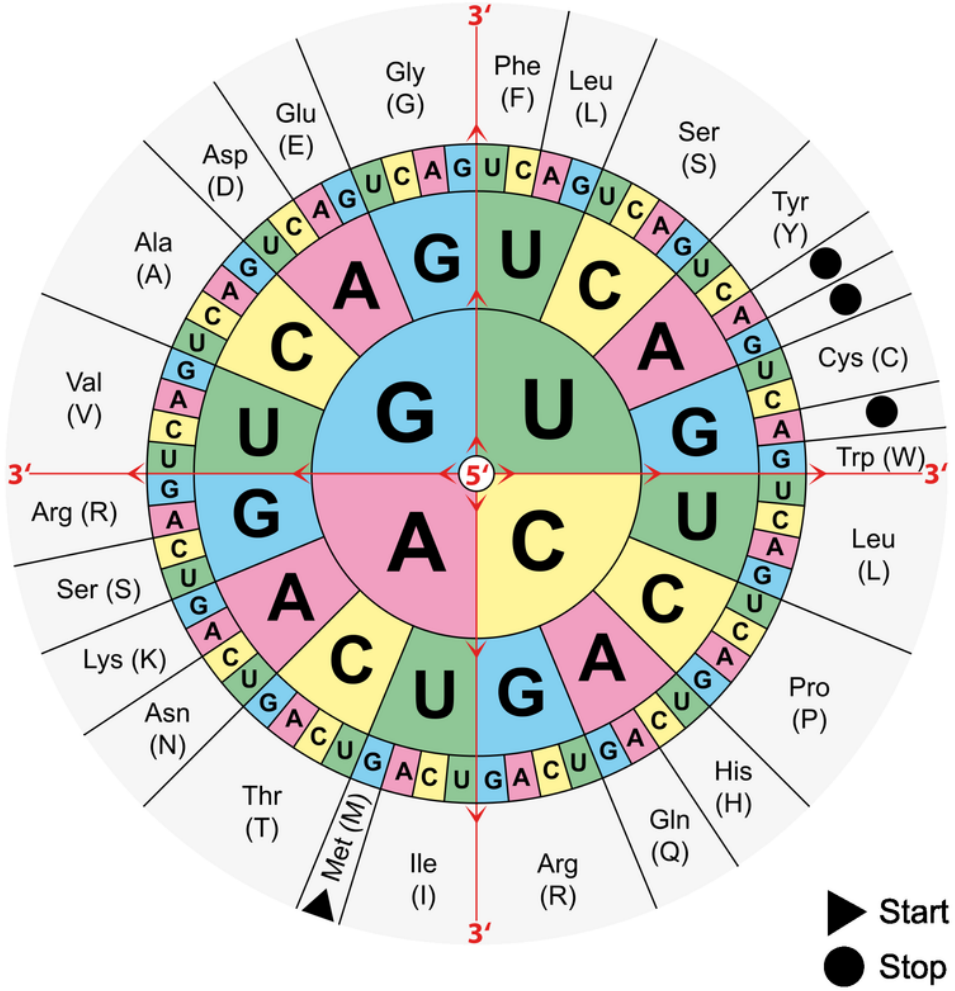
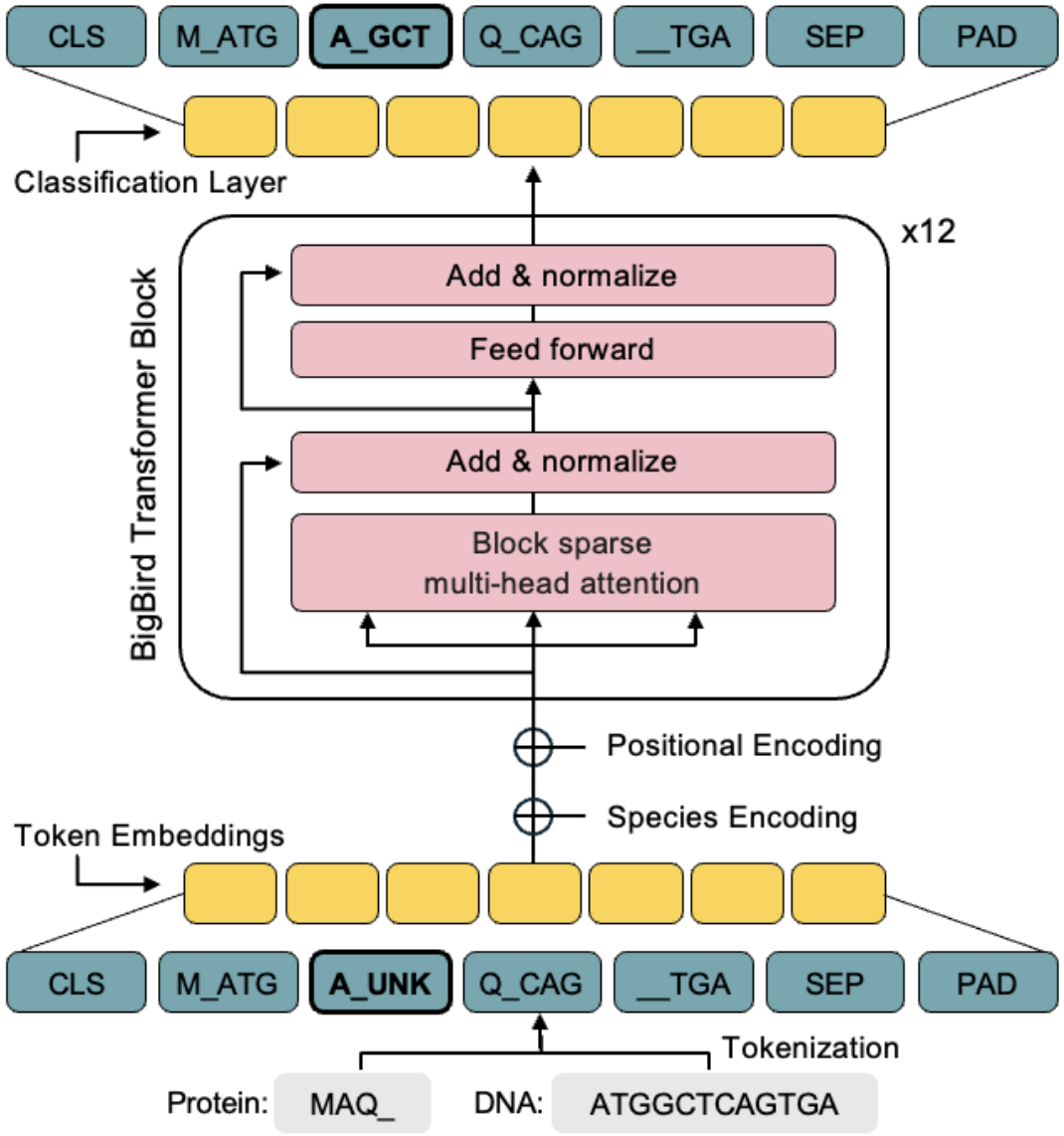
Codons are universal but degenerate: different species have varied preferences

Importantly, de novo proteins/peptides do not have a natural DNA



CodonTransformer: A multispecies context-aware neural network for codon optimization



Fallahpour *et al*. Nature Communications (2025)

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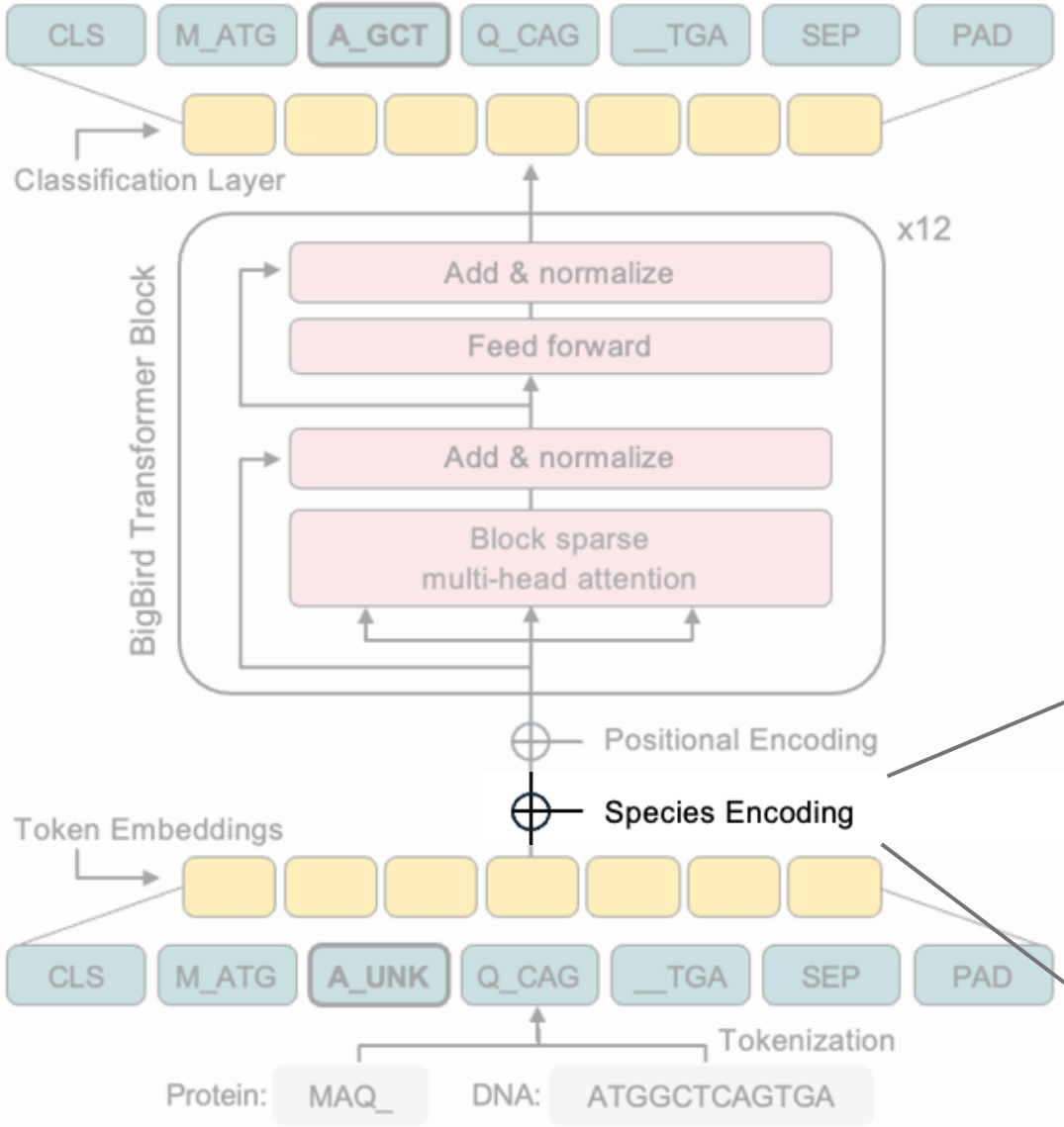

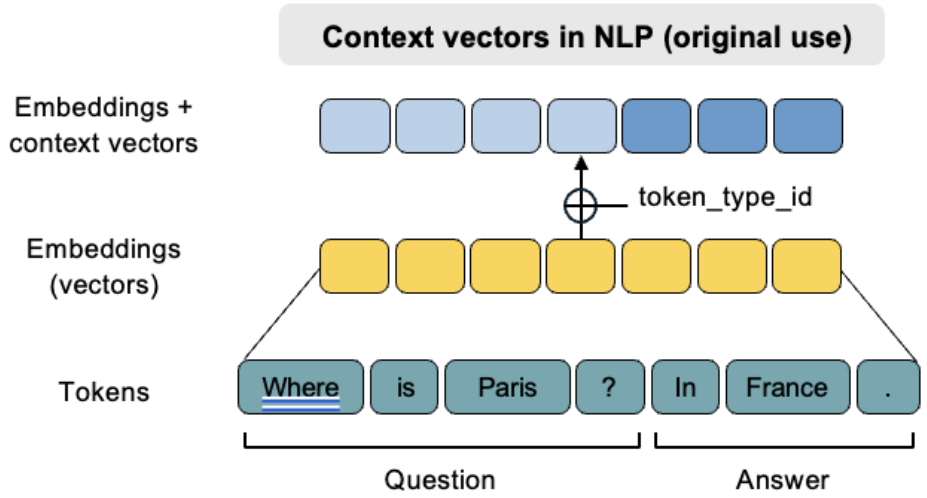

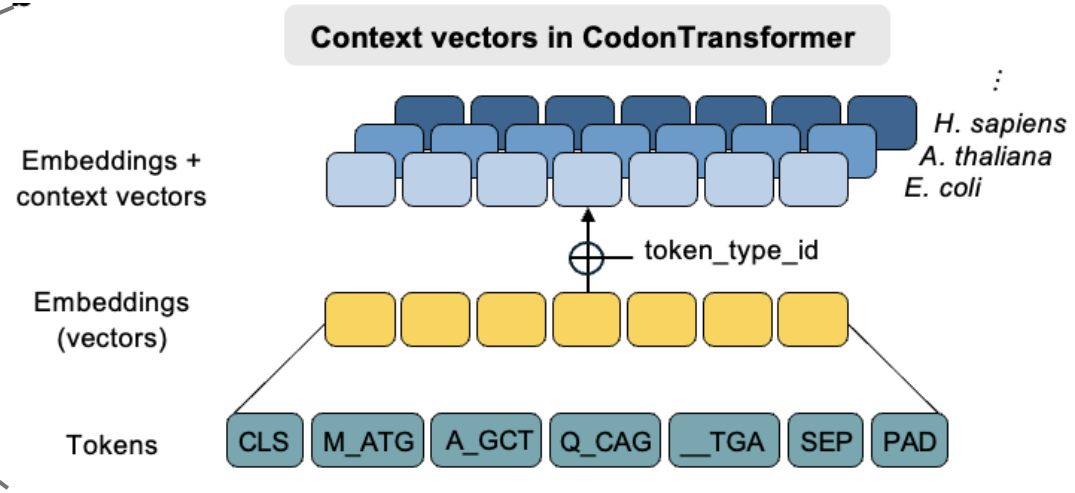

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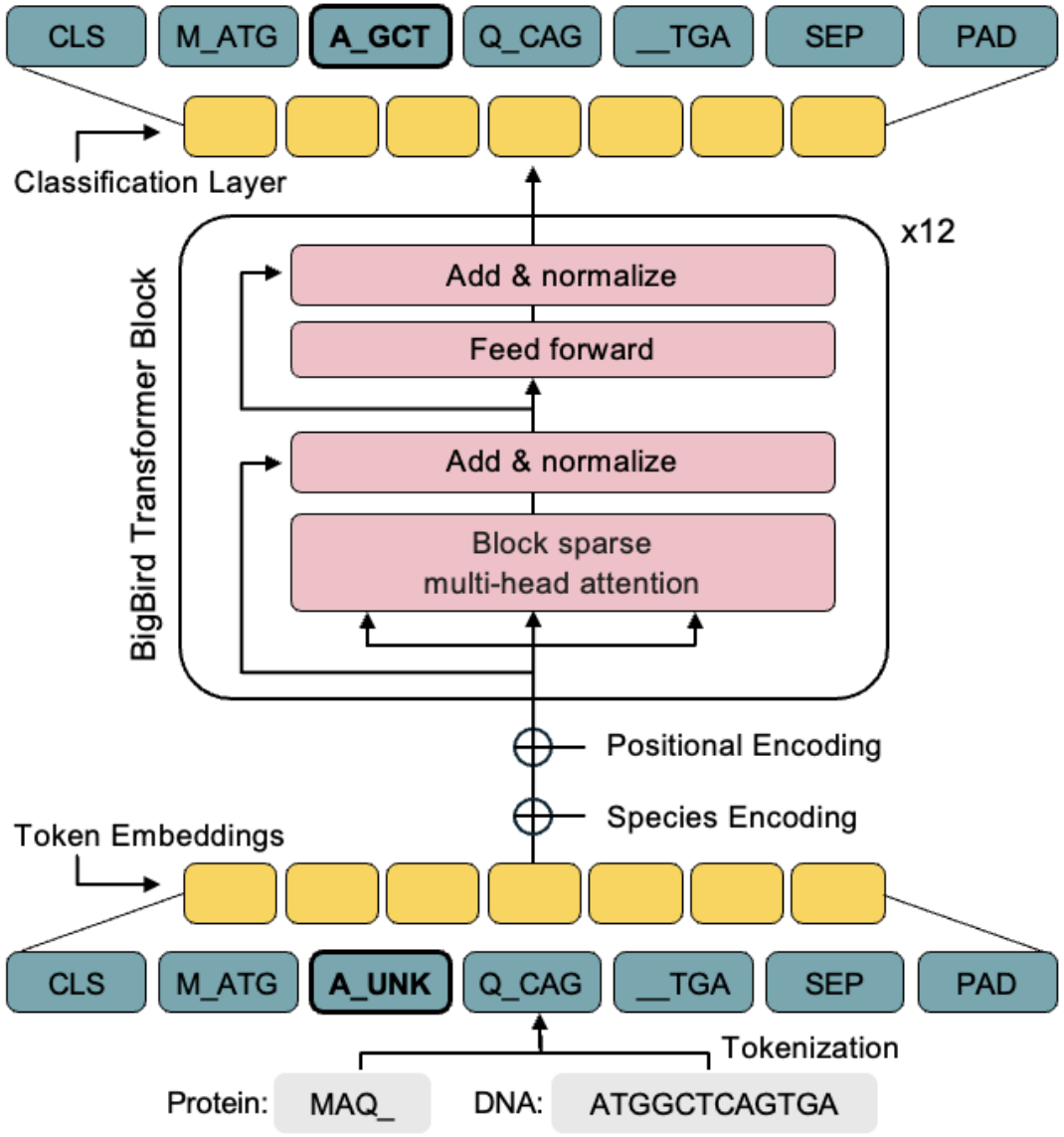
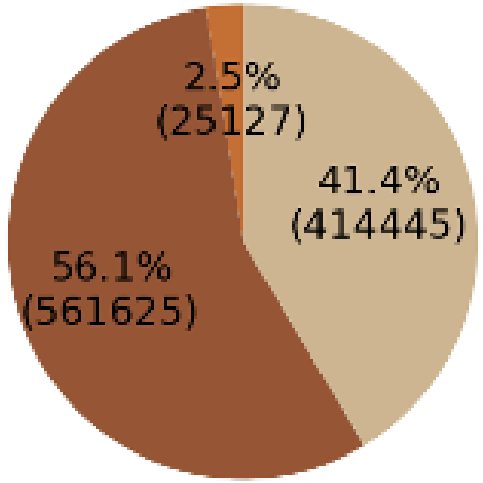
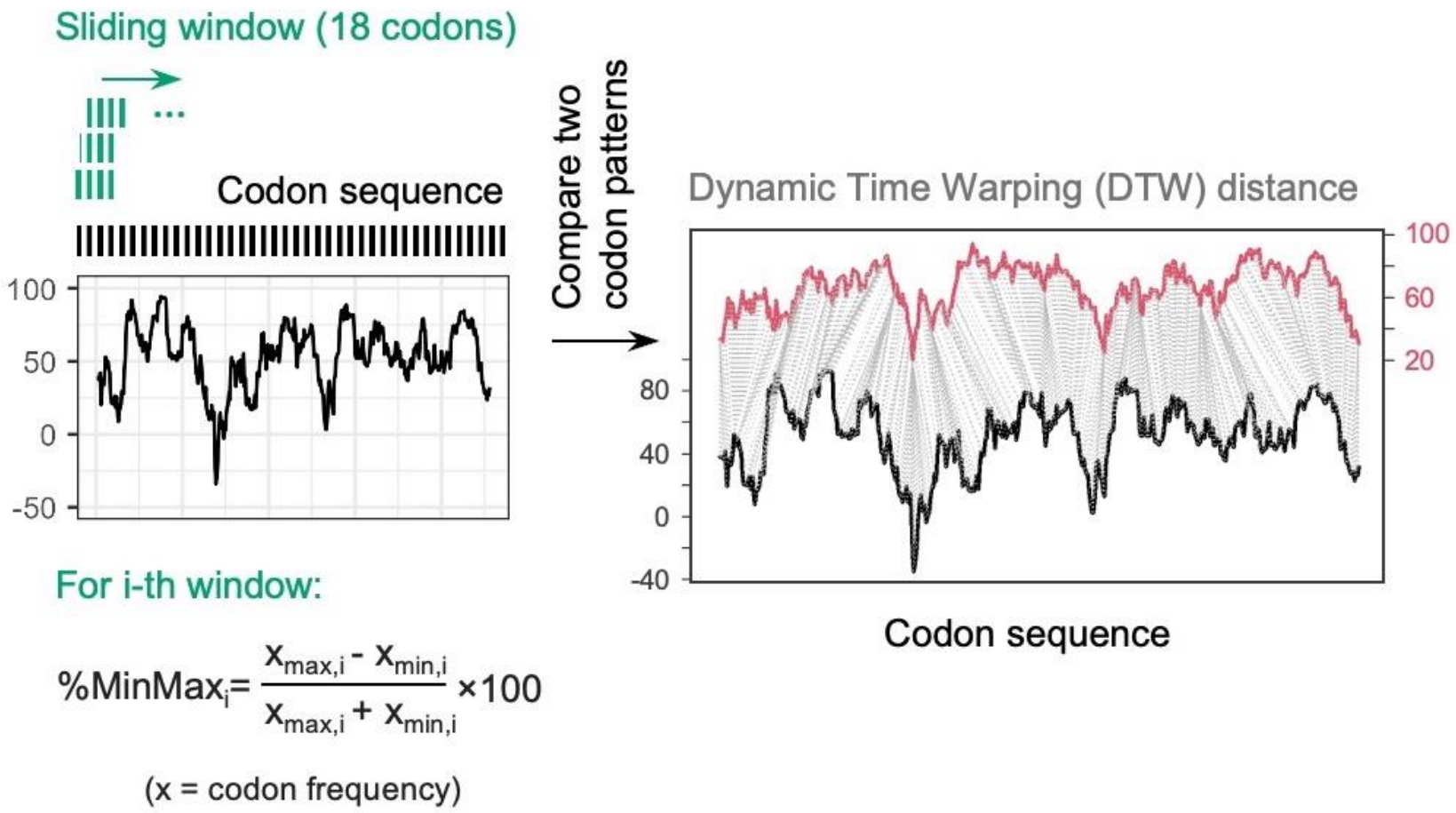




Base model Training with ~ 1 million genes
(Archaea, Eukarya, Bacteria)

Fallahpour *et al*. Nature Communications (2025)

CodonTransformer generates natural-like DNA sequence patterns



Fallahpour *et al*. Nature Communications (2025)

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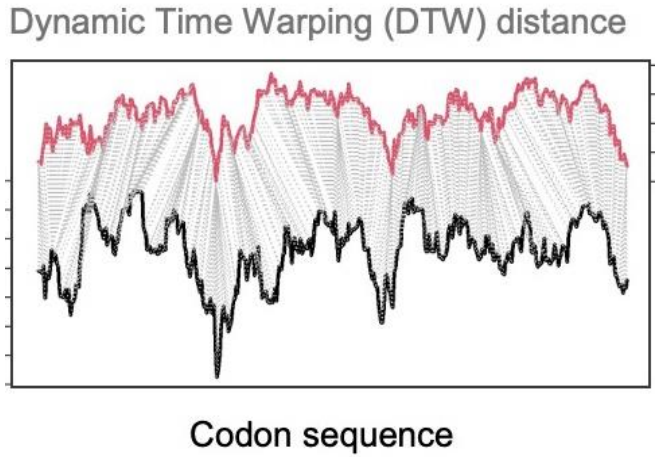

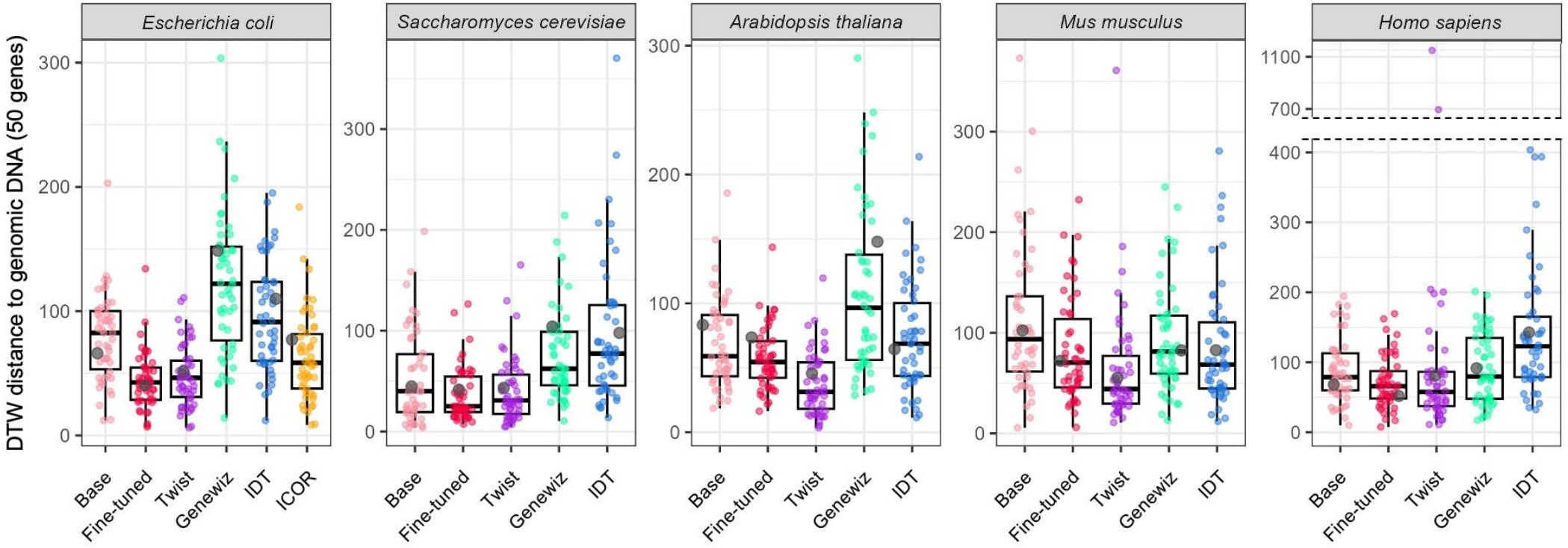

Fallahpour *et al*. Nature Communications (2025)

Methods and features to put antimicrobial peptides (AMPs) into effect

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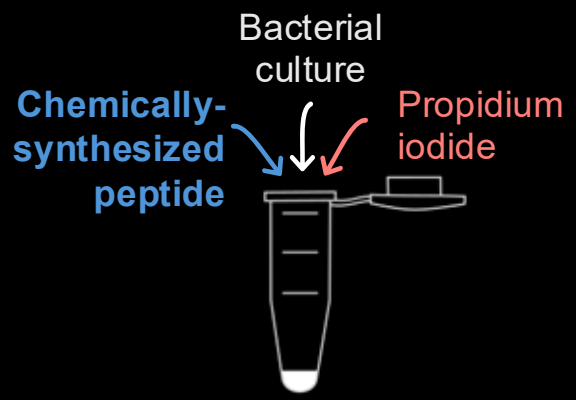
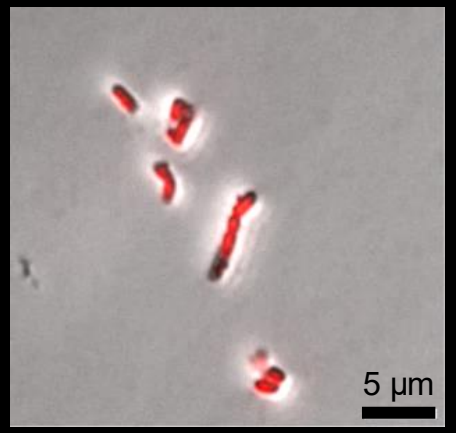
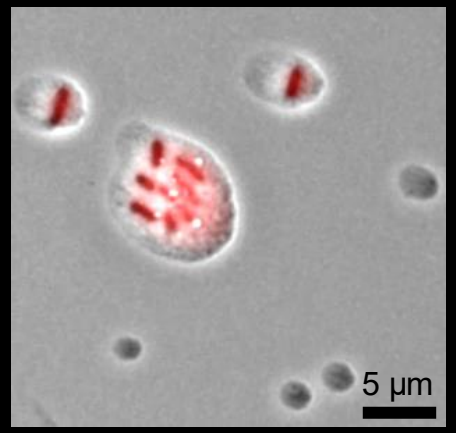
AMP features	• Protease stability • Pathogen specificity • Mechanism of action	------→ • Discovery of a new feature

Discovery of a novel AMP feature





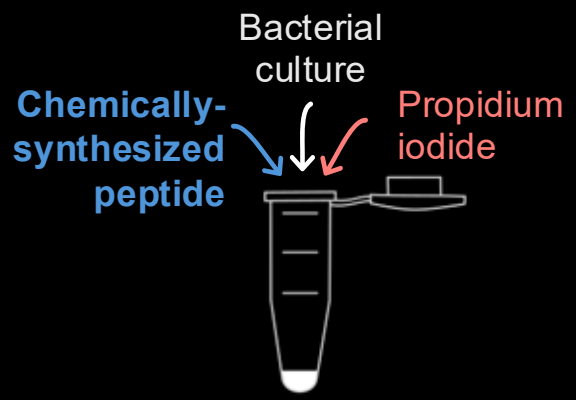


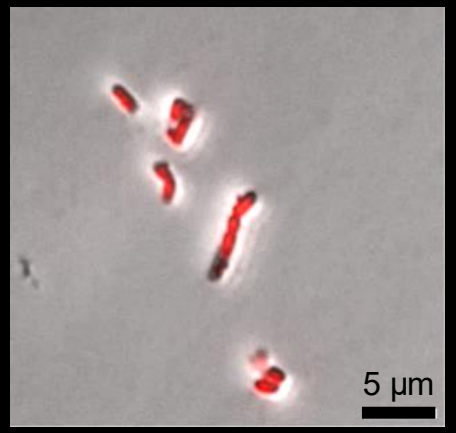
→ Forms droplets *in vitro*, engulfs and kills bacteria

Patent application PCT/EP2025/065003

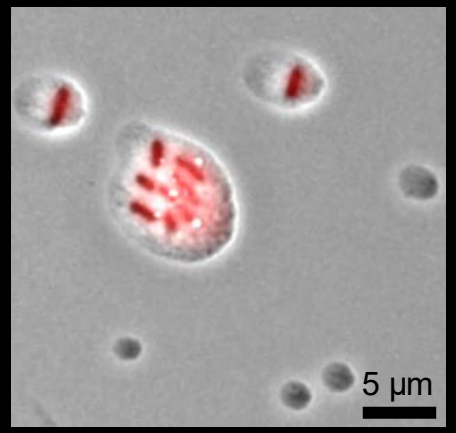
Discovery of a novel AMP feature

Liquid-liquid phase separation (LLPS)



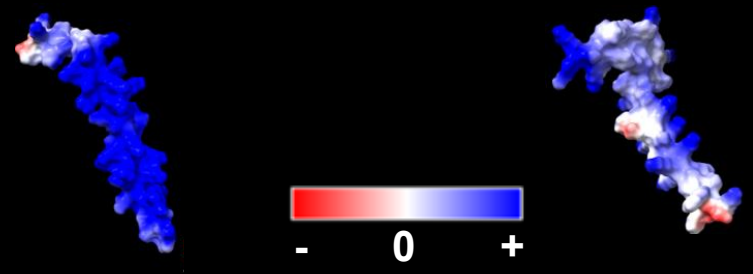


AMP without LLPS



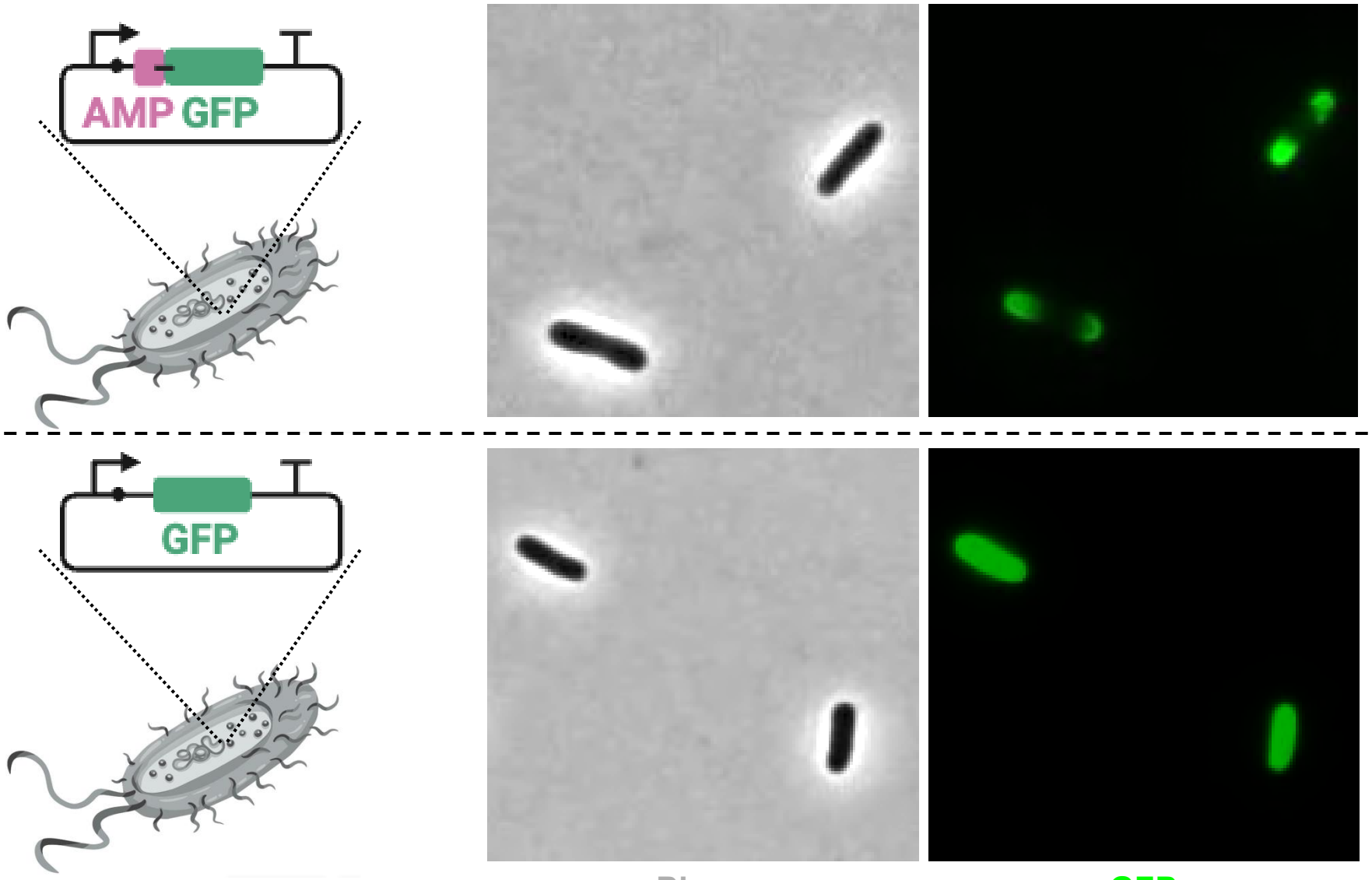
L1AMP (with LLPS)

→ Forms droplets *in vitro*, engulfs and kills bacteria



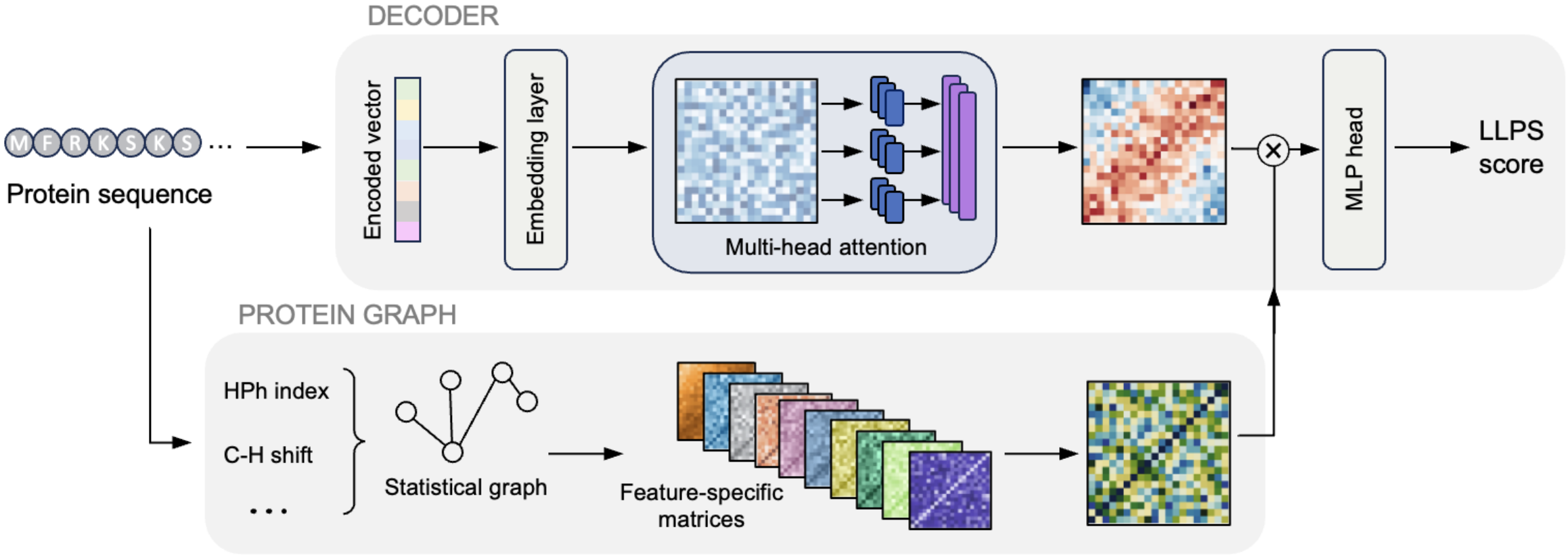
Patent application PCT/EP2025/065003

L1AMP phase-separates when expressed in *E. coli* fused to GFP

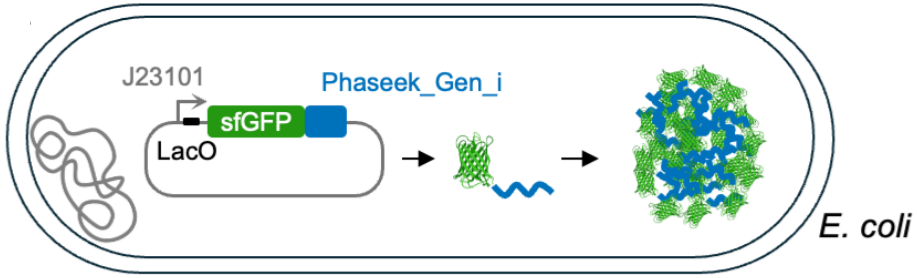


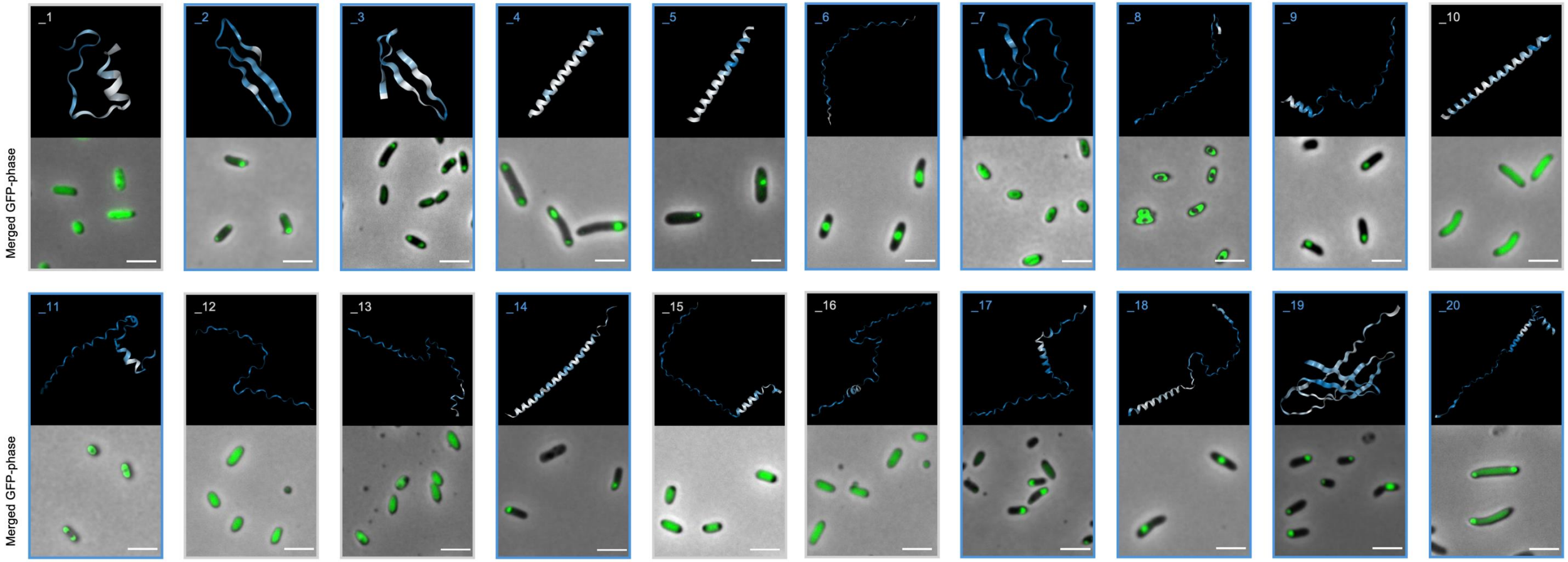
Patent application PCT/EP2025/065003

Phaseek: a hybrid model for multiscale prediction of protein liquid-liquid phase separation



Phaseek can be used to generated new phase-separating peptides



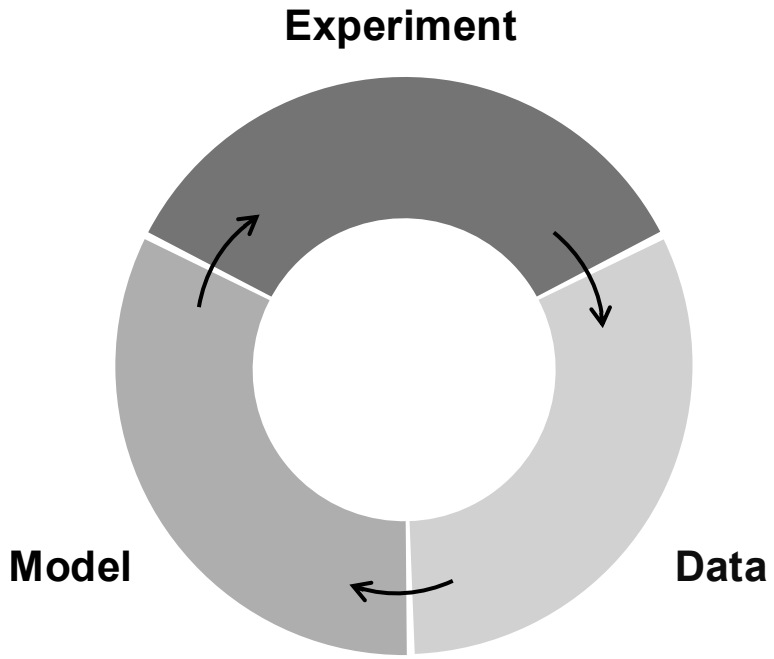


Unpublished results, patent in process.

Methods

- Experimental methods
  - Cell-free biosynthesis
  - Phage display
- Computational models
  - Neural networks

Fundamental **understanding** and **applications**



Protease stability

Antimicrobial specificity

Mode of action

- Inspired by the natural examples
- Learning their underlying language
- Inexhaustible design of candidates with “tailored properties” that nature did not have the selective pressure to explore.

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C. Diehl
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B. Fallahpour
V. Gureghian
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H. Teimouri
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Tobias Erb

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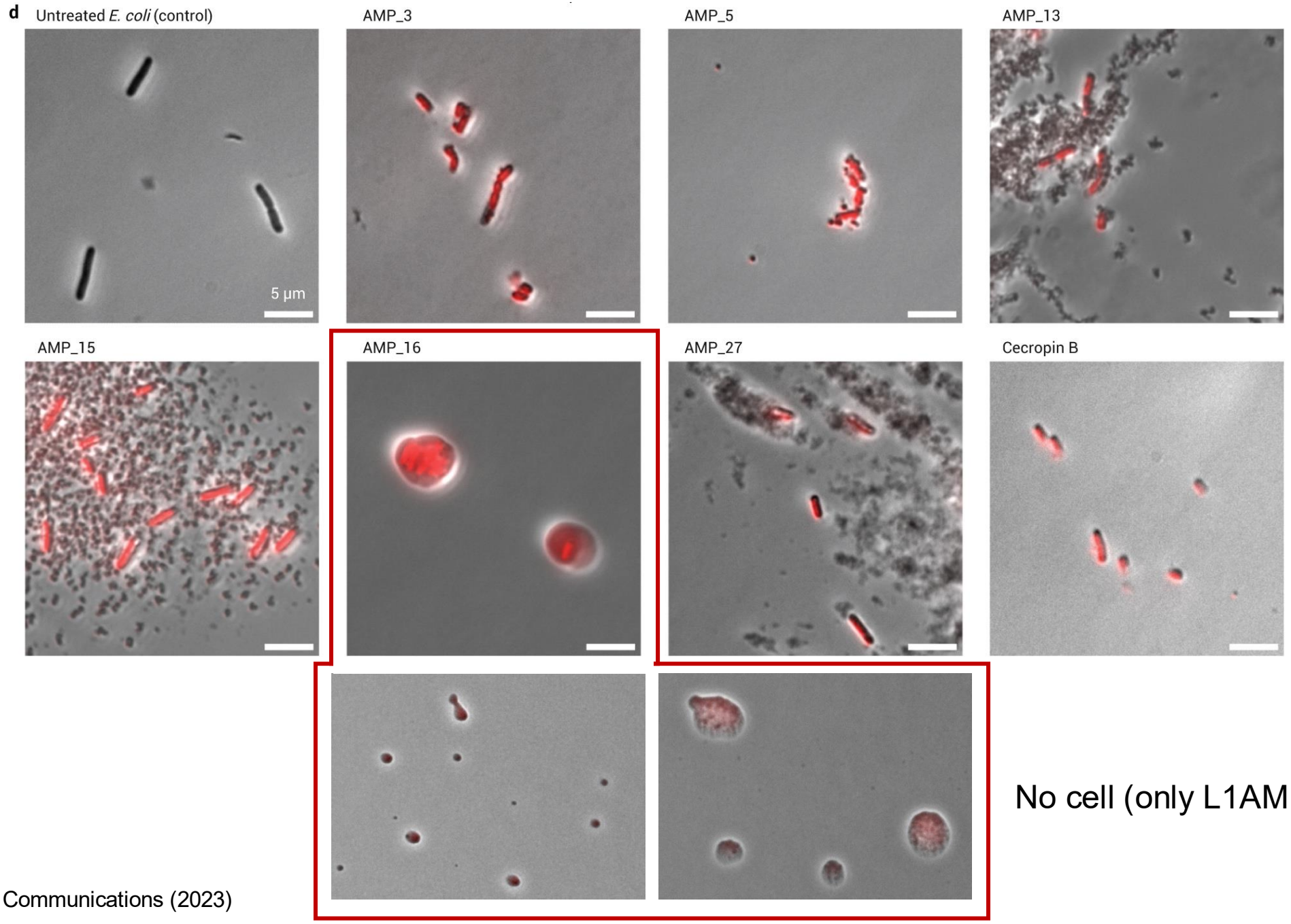
Bundeswehr Institute for Microbiology, Munich
Dr. H von Buttlar, Dr. D Adam, P Braun

Funding:



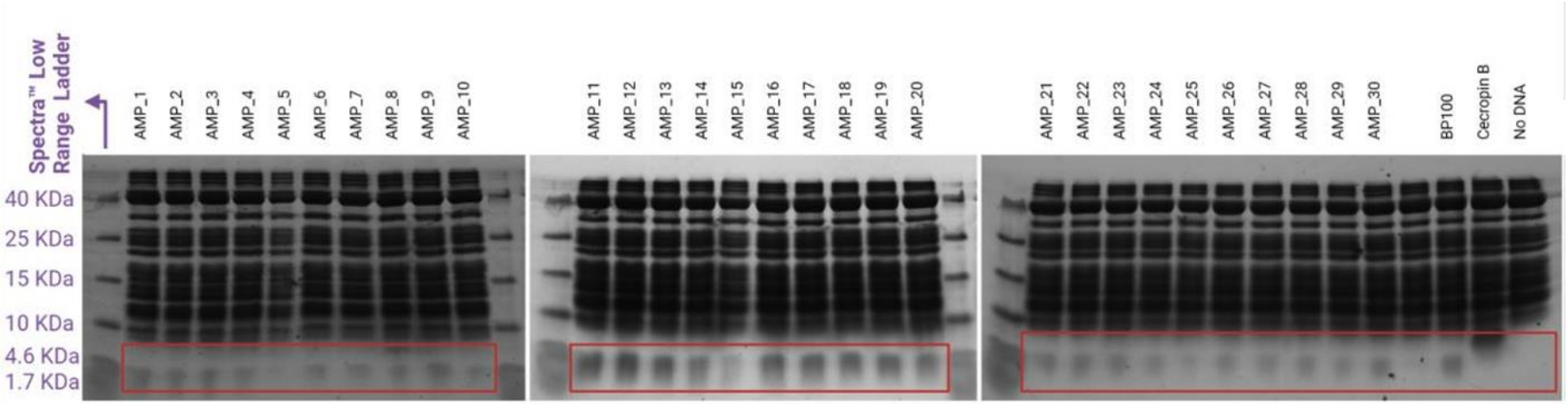
No cell (only L1AMP)

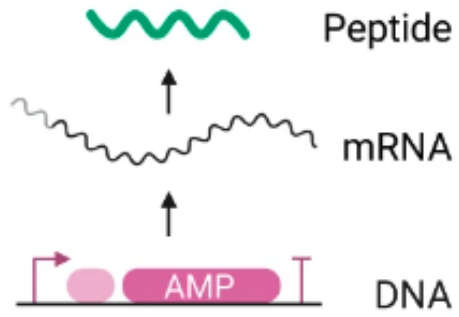
Pandi *et al*. Nature Communications (2023)

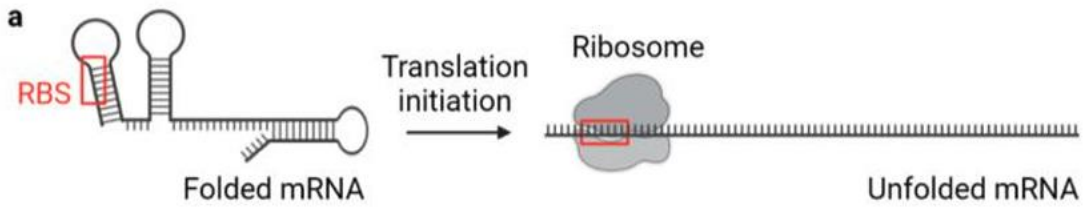
Supplementary Table 4: Rounds of AMP generation, filtering, and prioritization with different models/approaches and numbers.

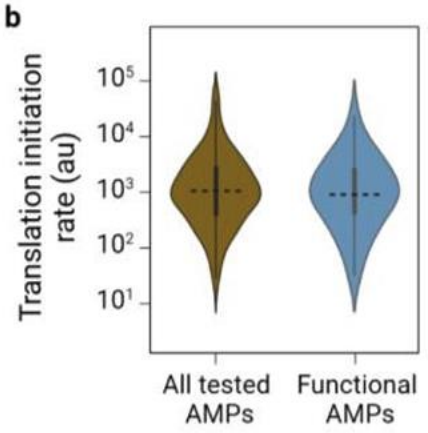
	round 0	round 1	round 2	round 3	round 4
Generator	VAE_v0	VAE_v0	VAE_v1	VAE_v1	VAE_v2
Sampling	Optimized Cecropin B*	random	random	random	random
Regressor	CNN reg_v0	CNN reg._v0	CNN reg._v1	CNN reg._v2 + Toxicity classifier	CNN reg._v2 + RNN reg._v0
All generated peptides	100	100,000	100,000	200,000	150,000
Viable peptides	100	9,220	9,117	18,218	29,457
MIC-predicted and experimentally tested	50	50	150	100	150
Functional peptides discovered	0	2	9	0	19
Efficiency (%)	**0**	**4**	**6**	**0**	**12.6**

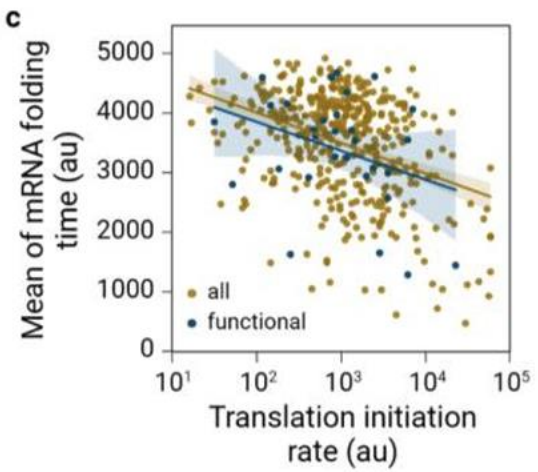
Pandi *et al*. Nature Communications (2023)



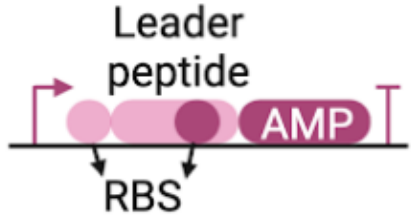


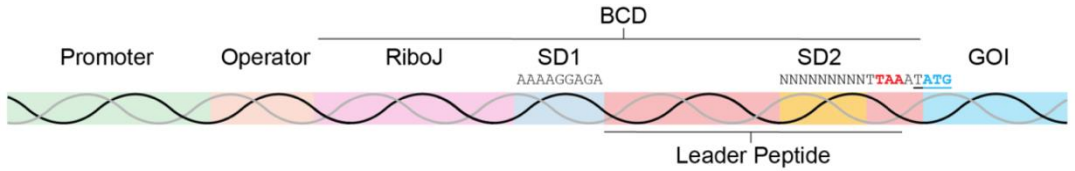






New design for improved peptide expression

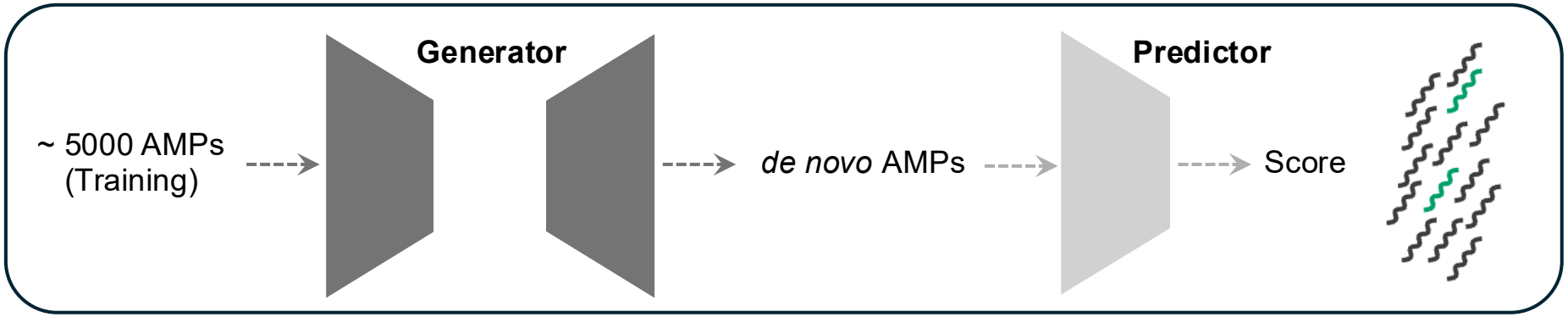




Pandi *et al*. Nature Communications (2023)

Combination of deep learning and cell-free biosynthesis enables rapid development of de novo AMPs

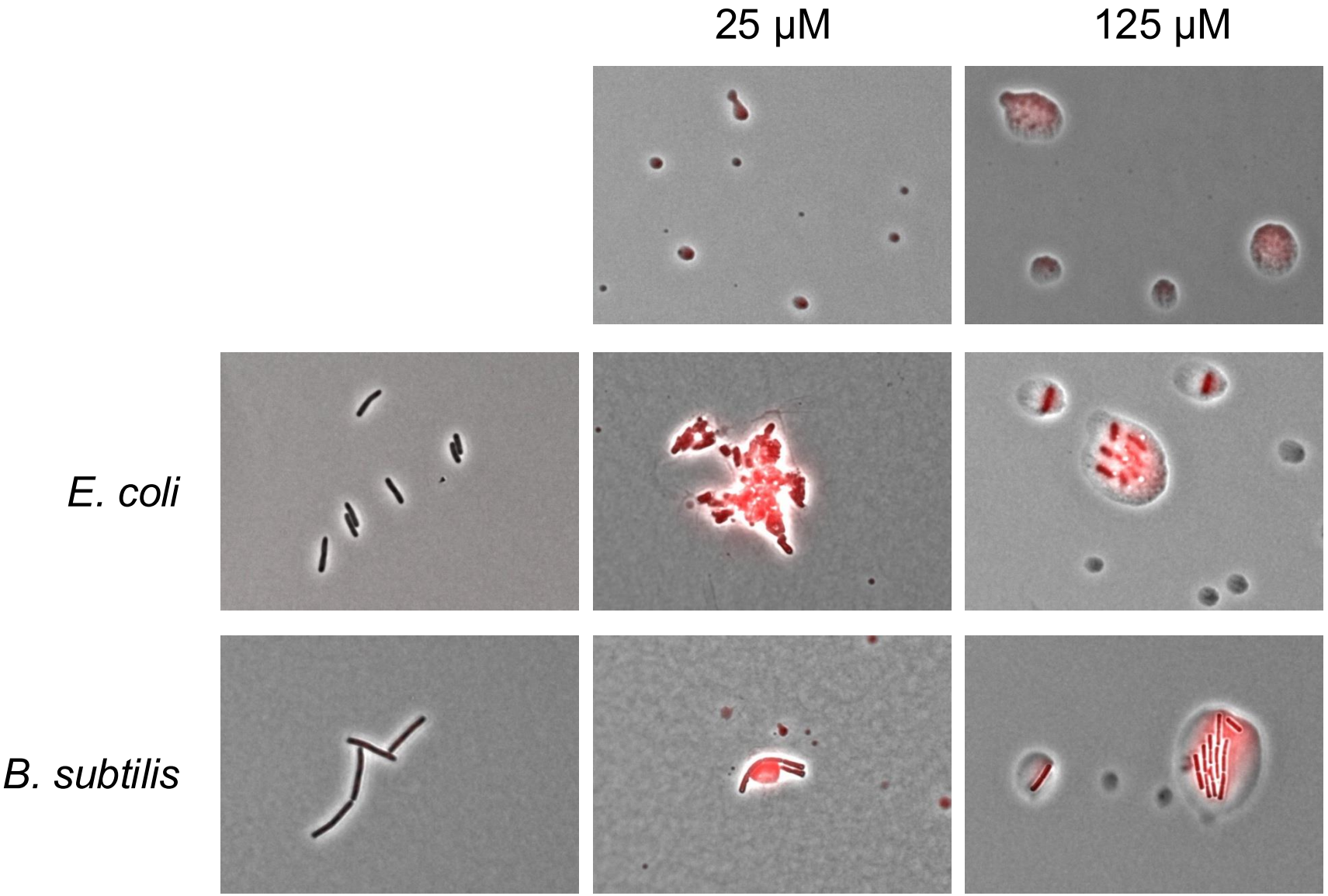
Deep learning



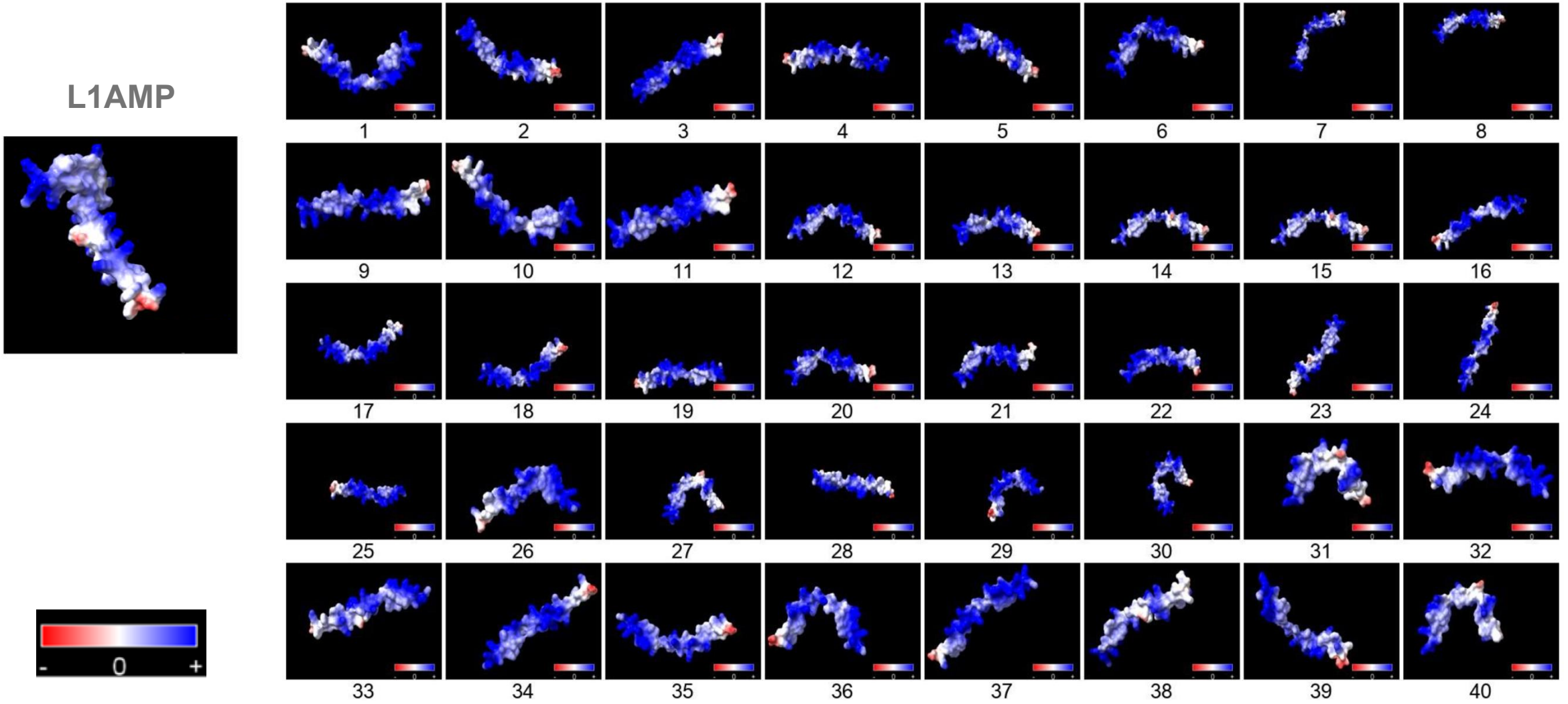
	Chemical synthesis	Cell-free biosynthesis	Cell-based biosynthesis
Cost	**High**	Moderate	Inexpensive
Speed	**Slow**	Fast	Moderate
Purity	**Good**	Low	Good

Pandi *et al*. Nature Communications (2023)

LLPS and bacterial killing by chemically synthesized AMP

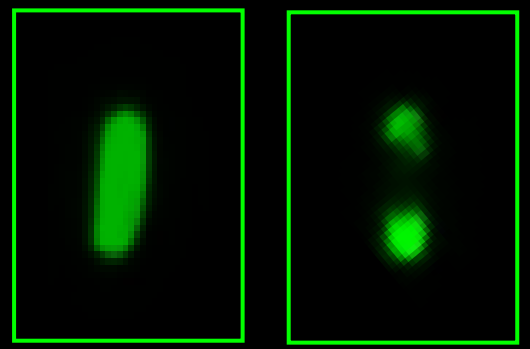


40 *de novo* AMPs were generated from L1AMP using the generative model



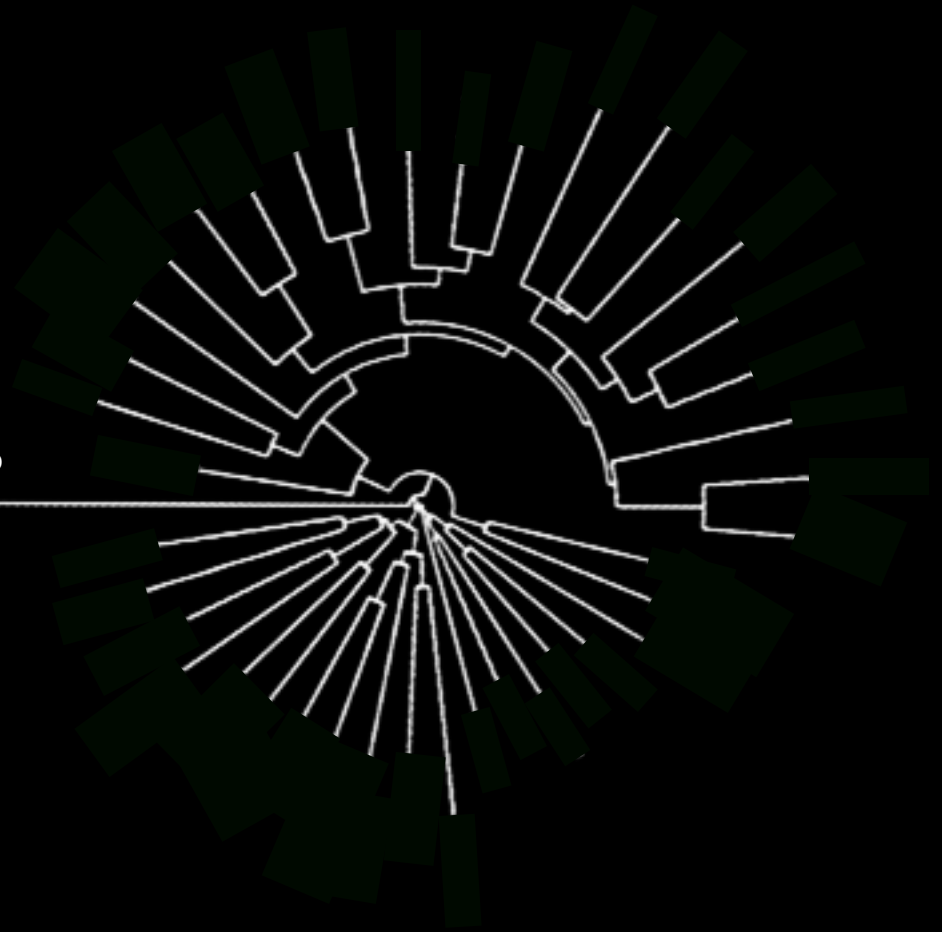
Discovery of a novel AMP feature

40 peptides

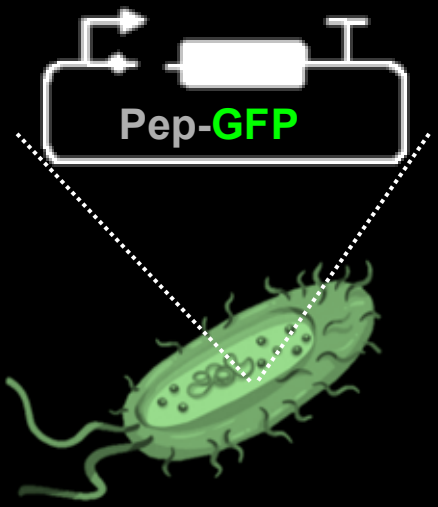


GFP
(no peptide fusion)

L1AMP

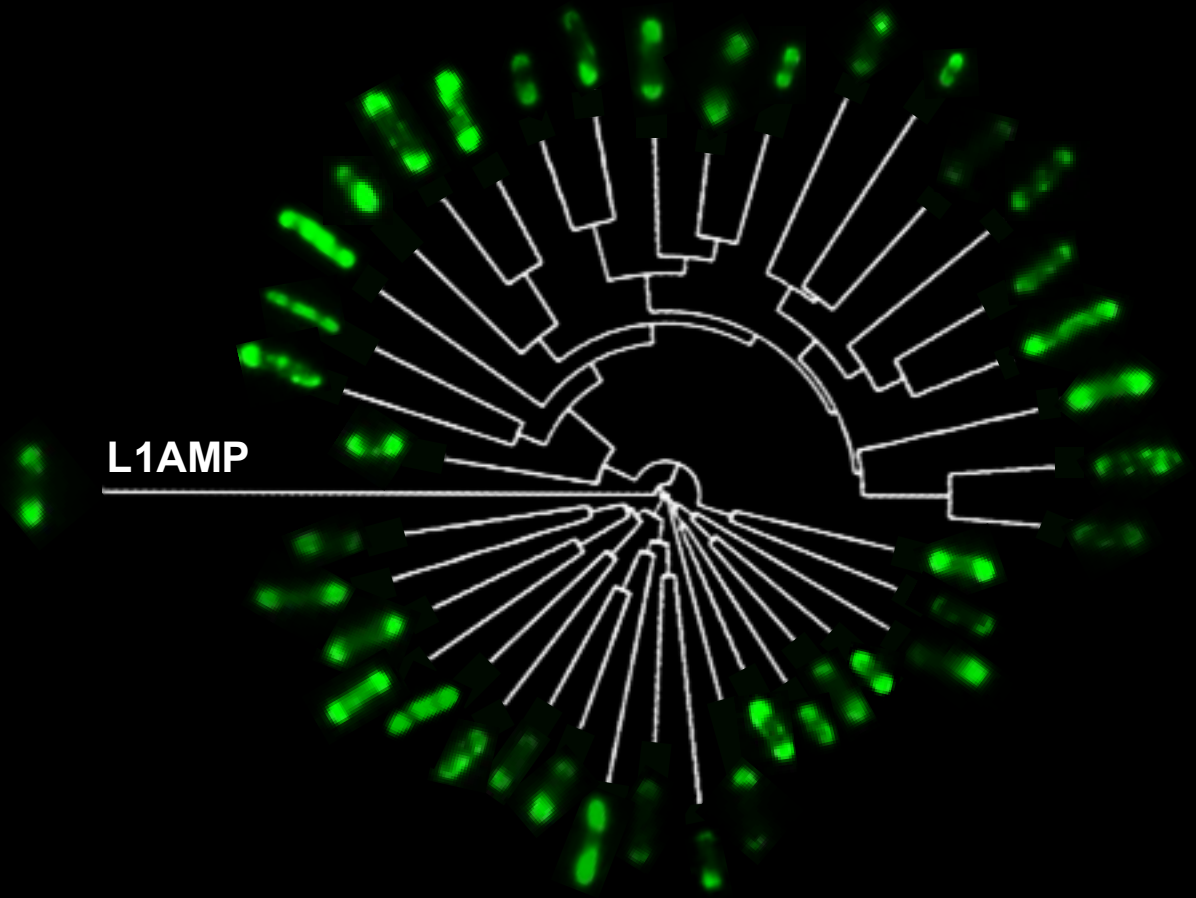


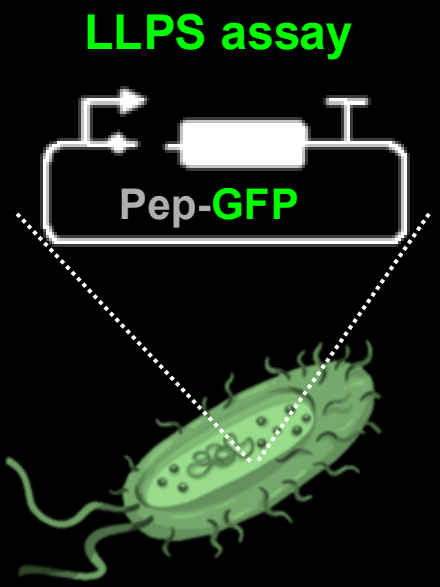
LLPS assay



Discovery of a novel AMP feature

40 peptides



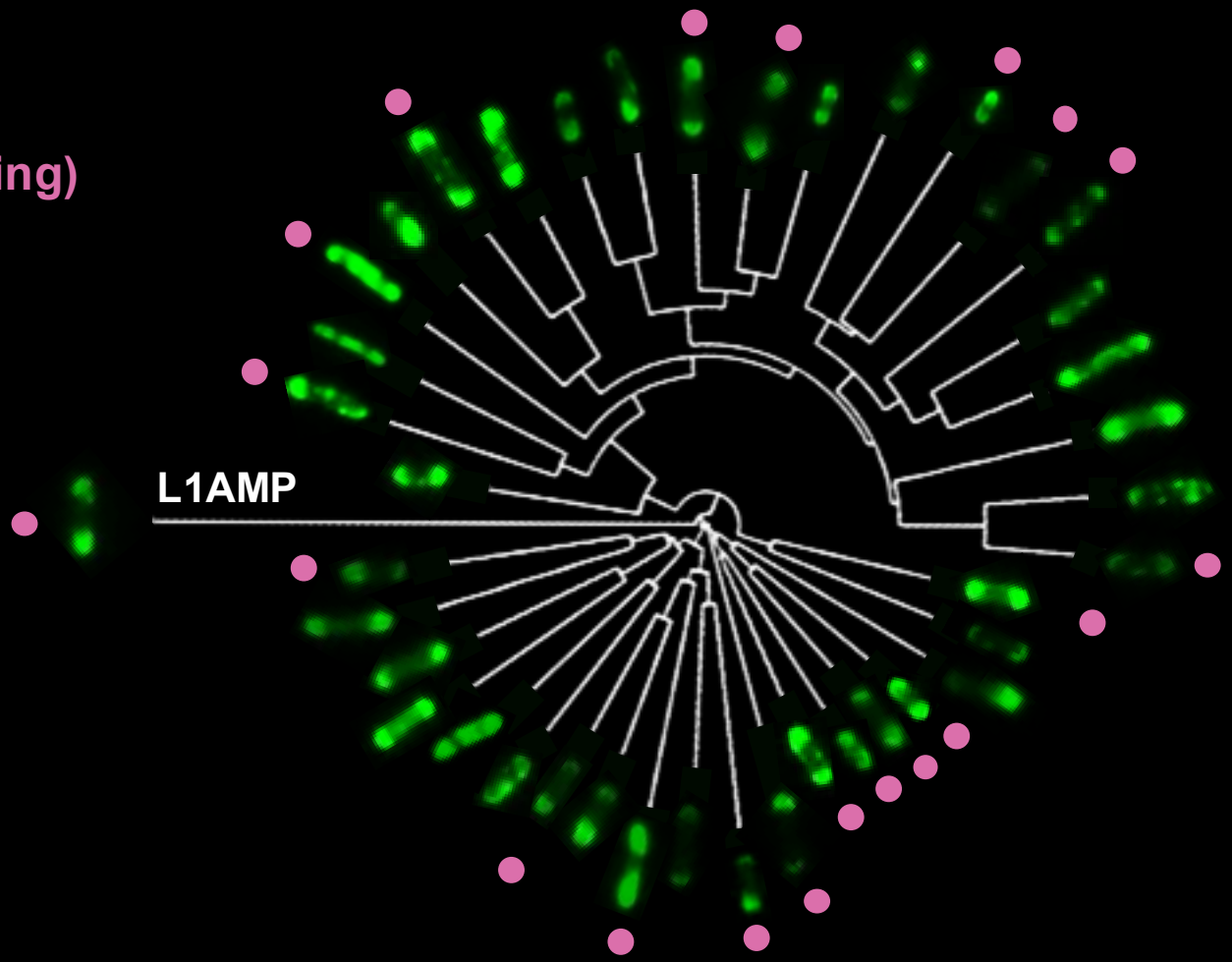


L1AMP-derived peptides show LLPS behavior

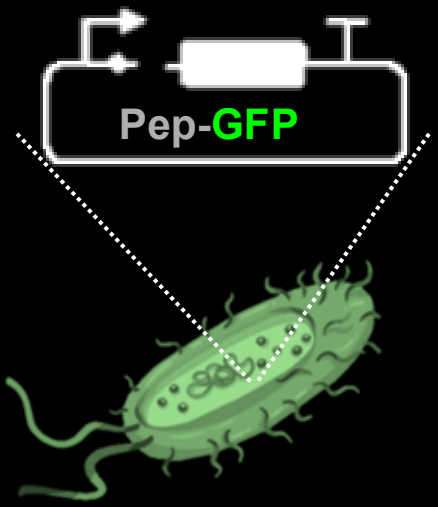
Discovery of a novel AMP feature

40 peptides

AMP activity
(Cell-free screening)

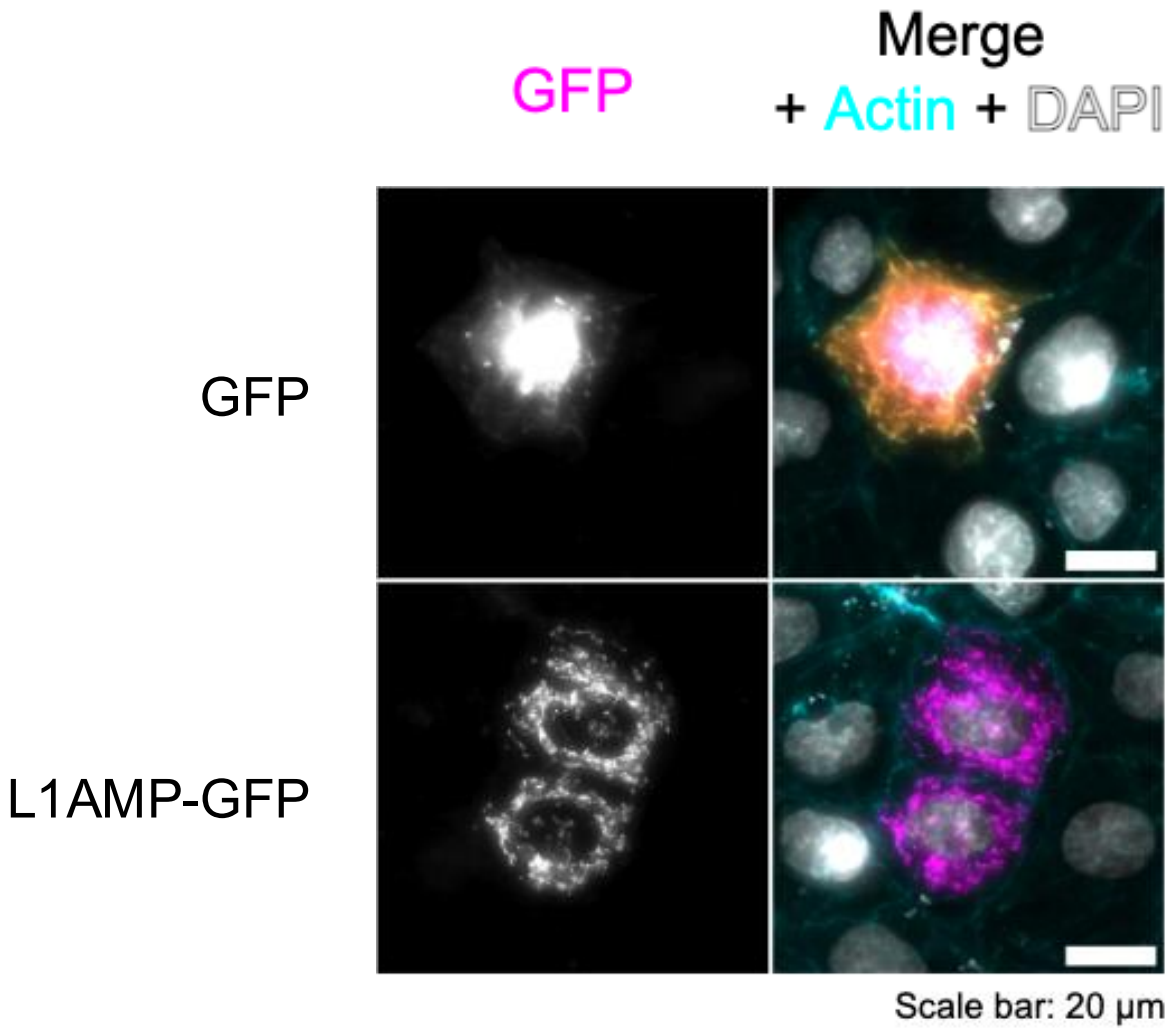


LLPS assay



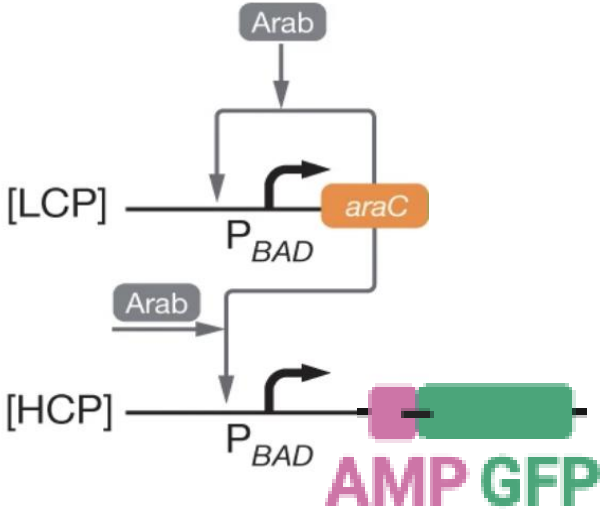
19 show both LLPS and antimicrobial behaviors

L1AMP phase-separates in human cells (TC7)



Thomas Petit, Alice LEBRETON lab
(ENS Paris)

Different expression levels of L1AMP-GFP



Daniel *et al*. 2013 *Nature*