AI-Designed Peptides: A New Weapon Against Fungal Pathogens

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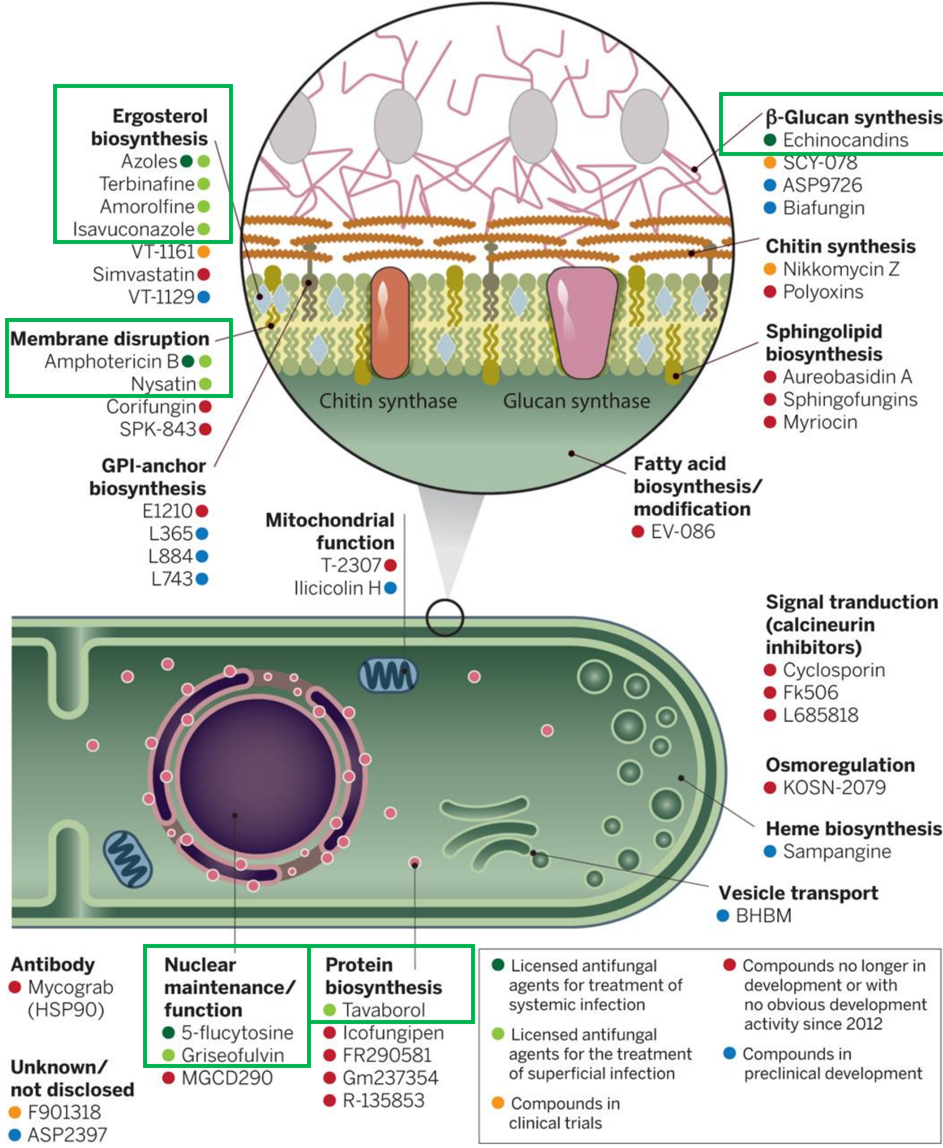
Parmis Abdoli

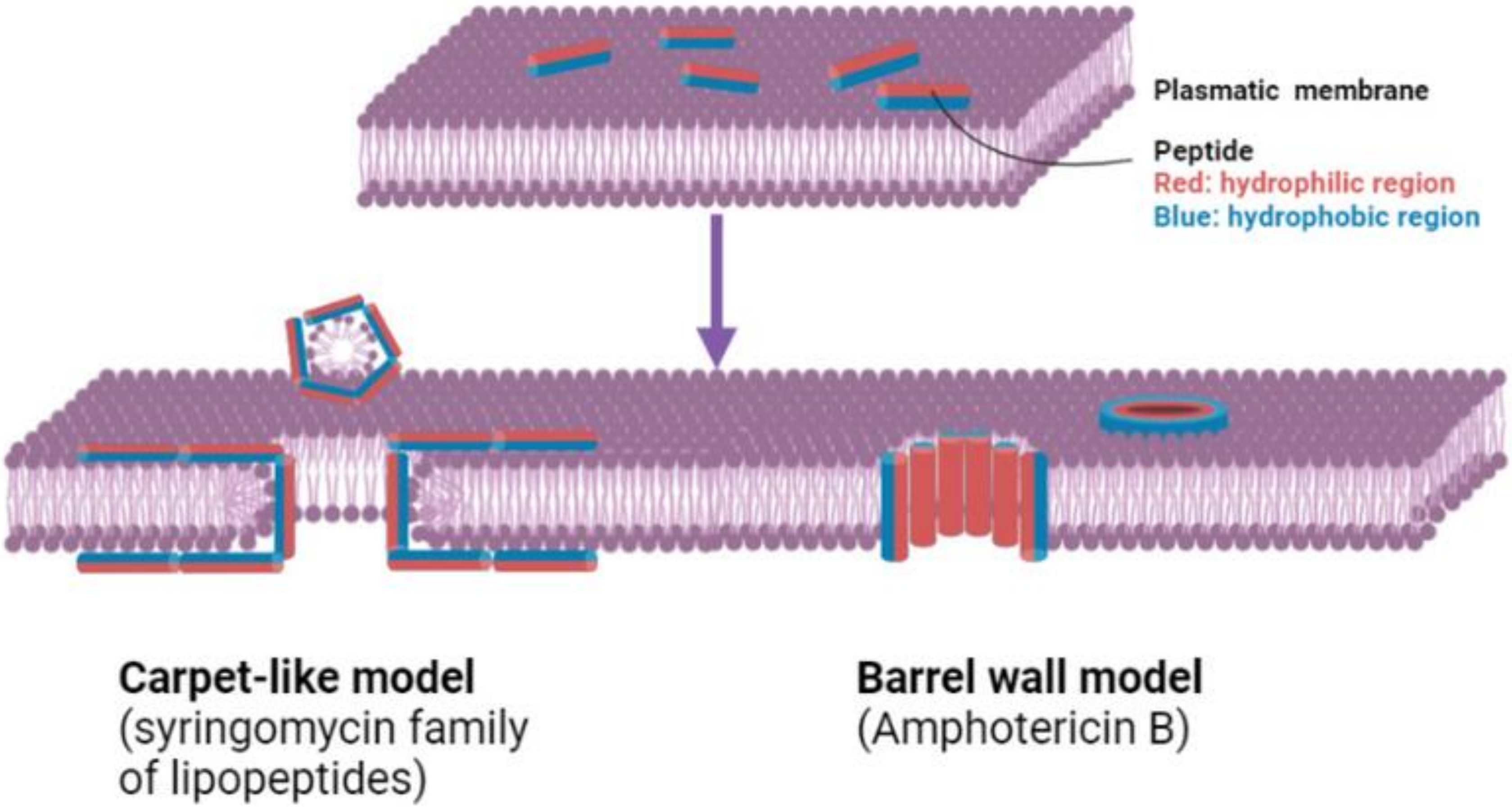
Challenges in antifungal discovery

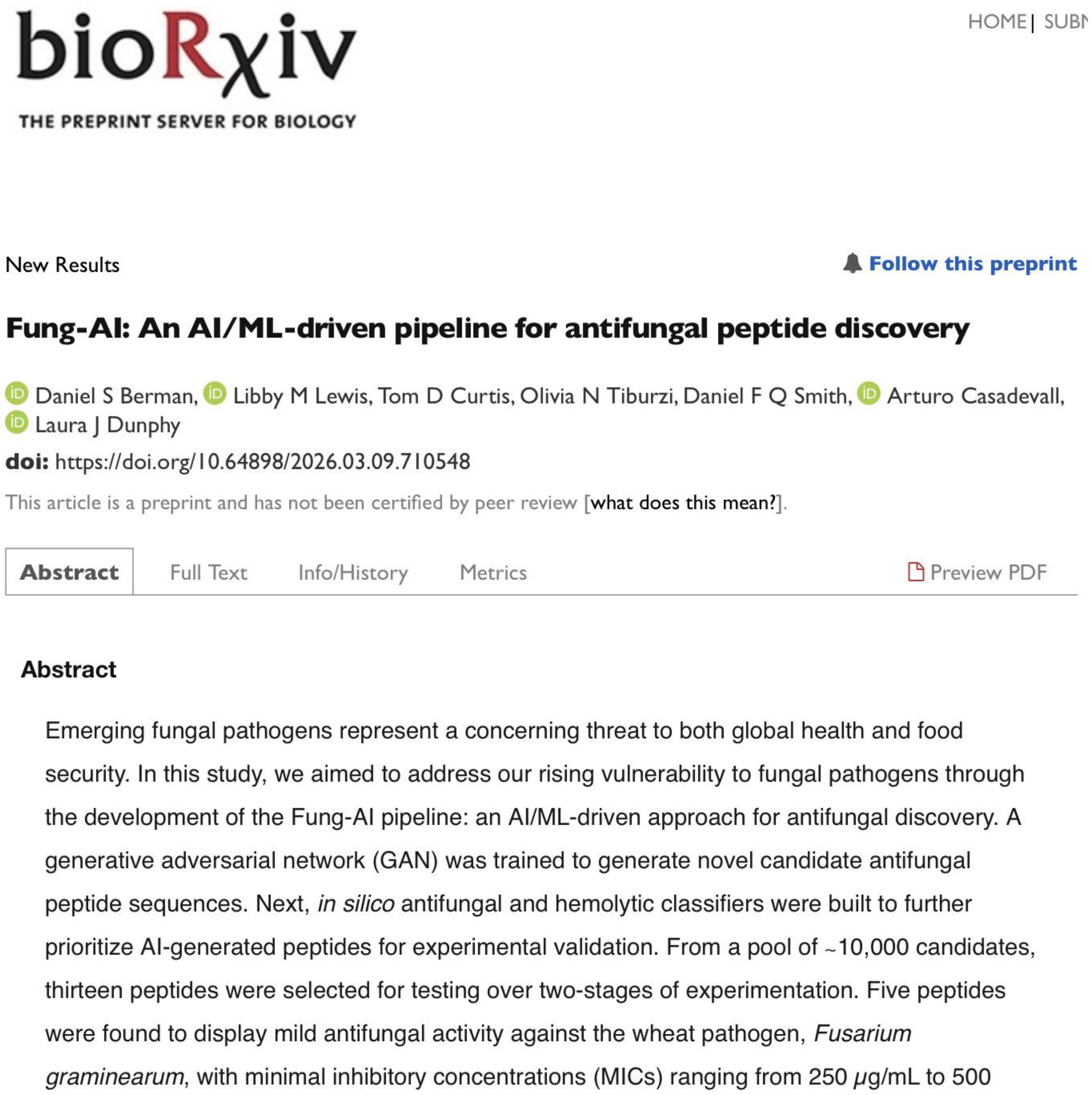
- Rising morbidity and mortality rates due to antifungal resistance
- Limited therapeutic targets
- Fungal and eukaryotic similarity complicates drug design
- Many candidates fail due to host toxicity



Antifungal peptides as alternative therapeutics

- Short, naturally occurring peptides
- Often disrupt multiple cellular processes
- ML methods increasingly used for peptide discovery





New Results

Fung-AI: An AI/ML-driven pipeline for antifungal peptide discovery

Daniel S Berman, Libby M Lewis, Tom D Curtis, Olivia N Tiburzi, Daniel F Q Smith, Arturo Casadevall, Laura J Dunphy

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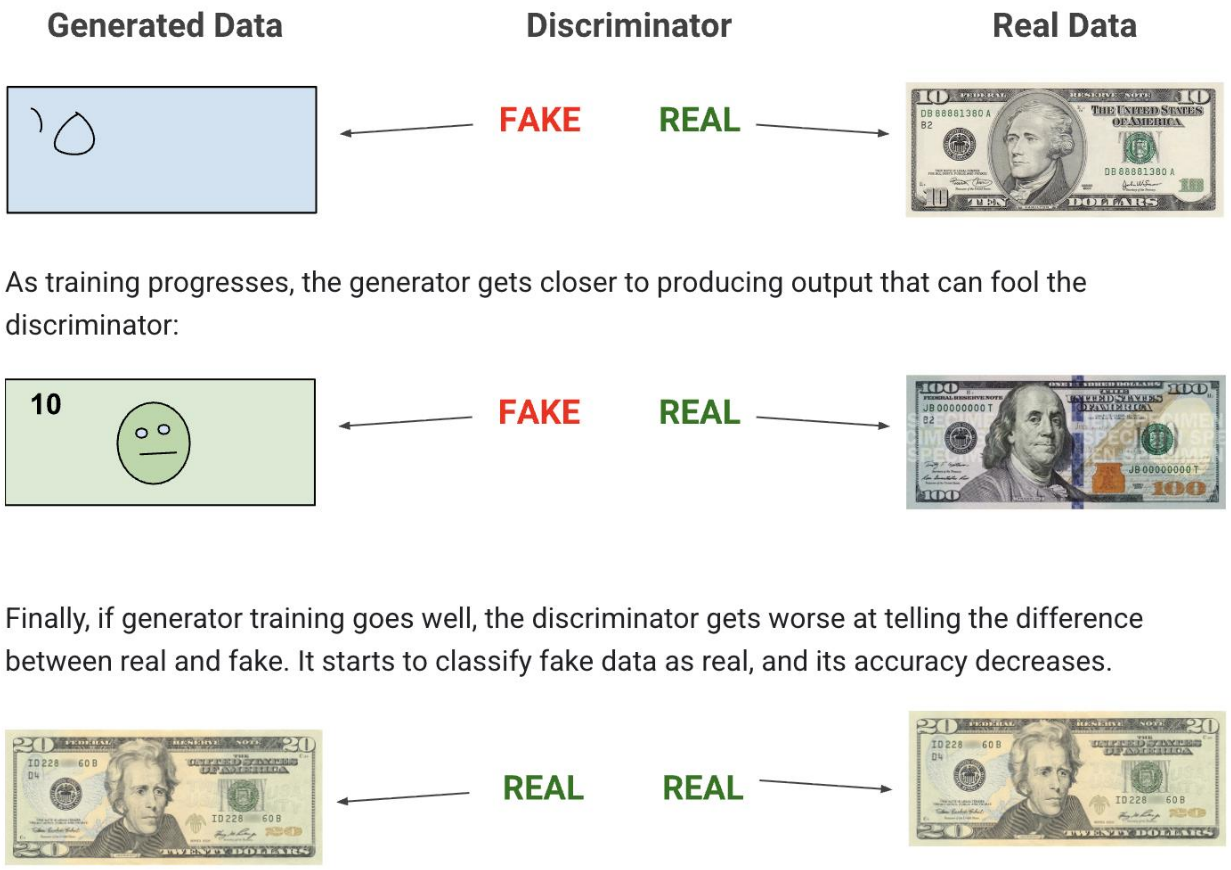
Abstract

Emerging fungal pathogens represent a concerning threat to both global health and food security. In this study, we aimed to address our rising vulnerability to fungal pathogens through the development of the Fung-AI pipeline: an AI/ML-driven approach for antifungal discovery. A generative adversarial network (GAN) was trained to generate novel candidate antifungal peptide sequences. Next, *in silico* antifungal and hemolytic classifiers were built to further prioritize AI-generated peptides for experimental validation. From a pool of ~10,000 candidates, thirteen peptides were selected for testing over two-stages of experimentation. Five peptides were found to display mild antifungal activity against the wheat pathogen, *Fusarium graminearum*, with minimal inhibitory concentrations (MICs) ranging from 250 μg/mL to 500

Generative adversarial networks (GANs)



As training progresses, the generator gets closer to producing output that can fool the discriminator:

Finally, if generator training goes well, the discriminator gets worse at telling the difference between real and fake. It starts to classify fake data as real, and its accuracy decreases.

Consists of two parts:

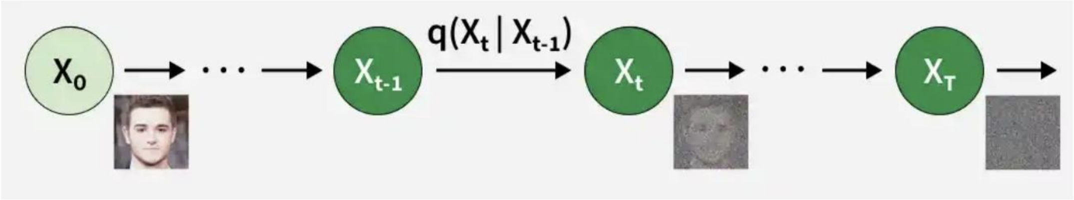
- Generator: creates candidate peptides
- Discriminator: tries to determine if the peptide is real

Common failure: mode collapse

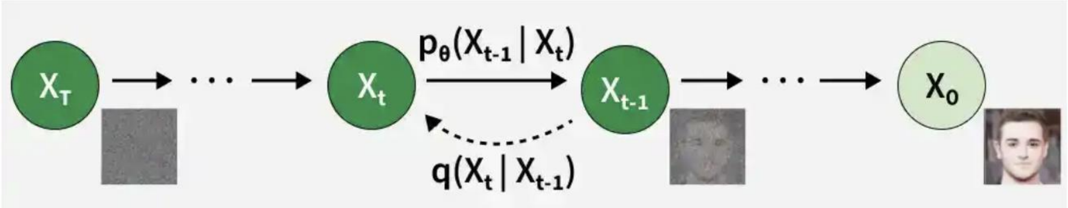
- Authors add an encoder to mitigate this

Diffusion models

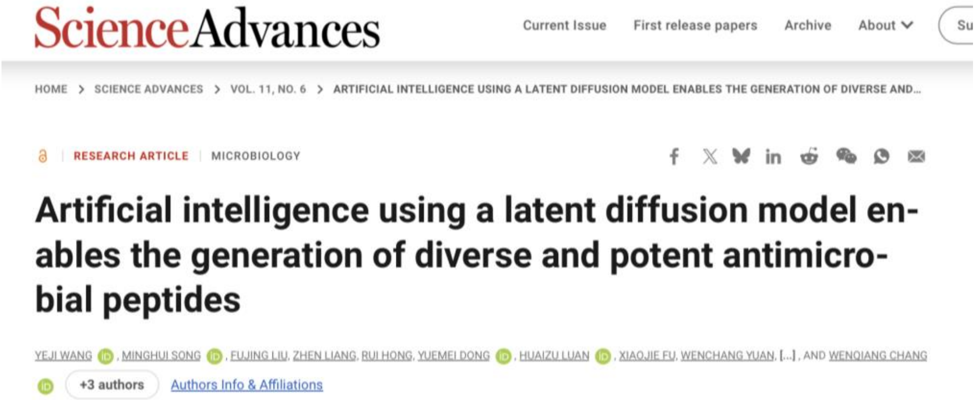
Diffusion models are trained to progressively turn random noise into meaningful output.



Forward Diffusion Process



Reverse Diffusion Process



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Artificial intelligence using a latent diffusion model enables the generation of diverse and potent antimicrobial peptides

YEJI WANG, MINGHUI SONG, FUJING LIU, ZHEN LIANG, RUI HONG, YUEMEI DONG, HUAIZU LUAN, XIAOJIE FU, WENCHANG YUAN, [...], AND WENQIANG CHANG

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> Adv Sci (Weinh). 2025 May;12(20):e2412926. doi: 10.1002/advs.202412926. Epub 2025 Apr 15.

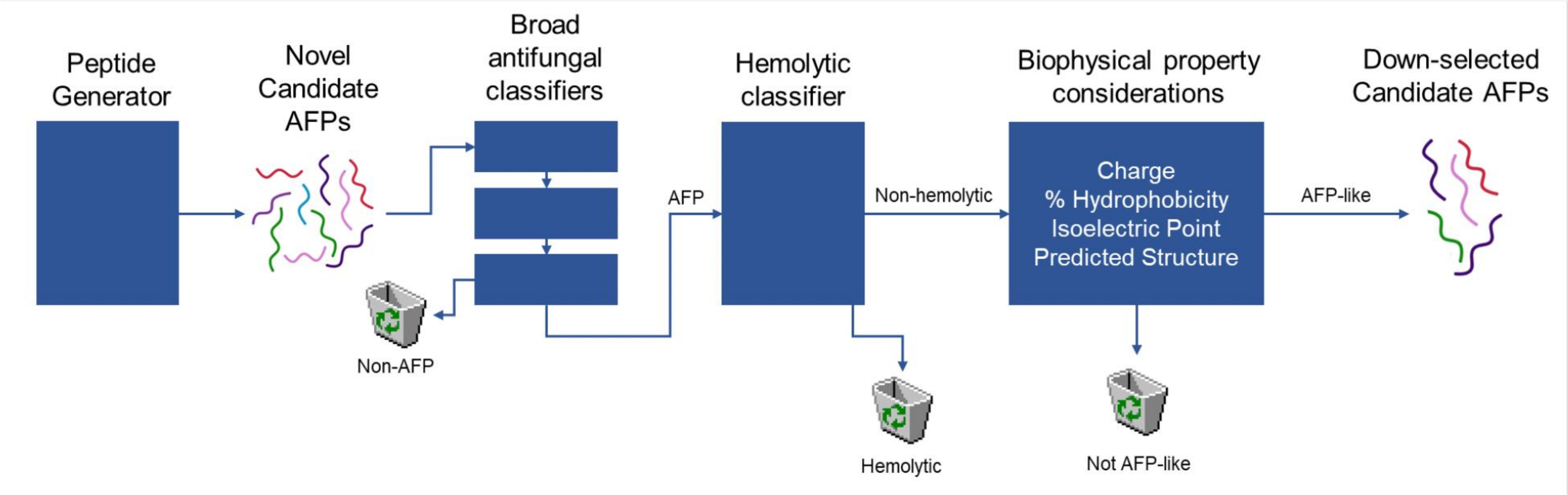
CPL-Diff: A Diffusion Model for De Novo Design of Functional Peptide Sequences with Fixed Length

Zhenjie Luo [1], Aoyun Geng [1], Leyi Wei [2] [3], Quan Zou [4] [5], Feifei Cui [1], Zilong Zhang [1]

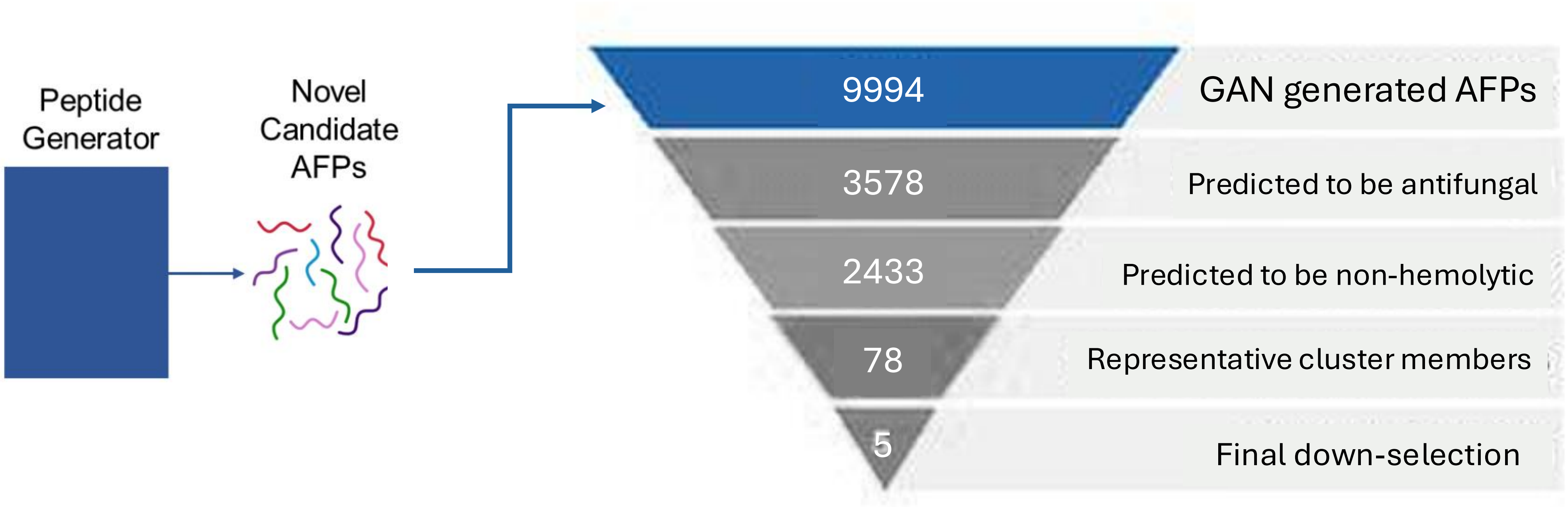
Affiliations + expand

PMID: 40231709 PMCID: PMC12120732 DOI: 10.1002/advs.202412926

Fung-AI pipeline



Generated peptide pool

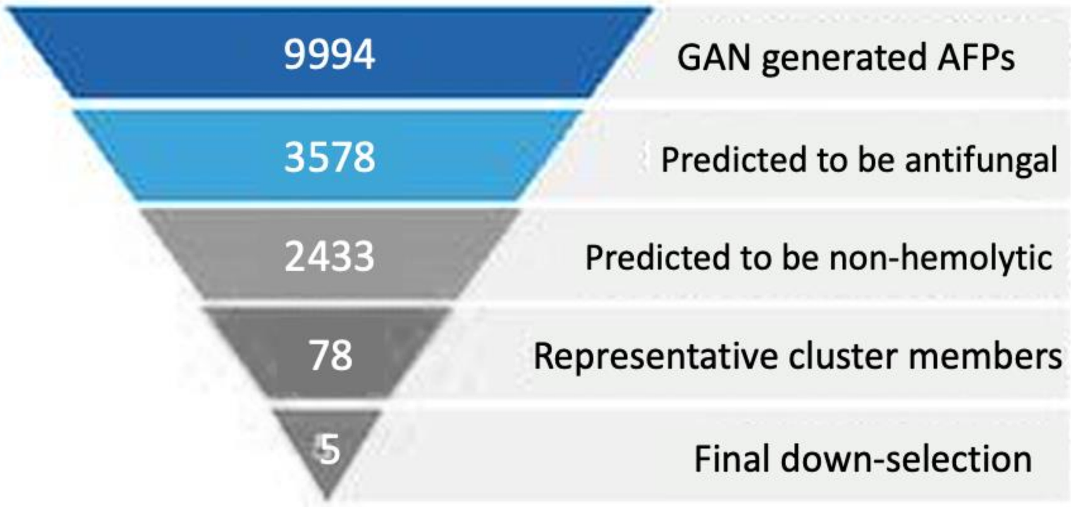


Peptide Generator

Novel Candidate AFPs

9994	GAN generated AFPs
3578	Predicted to be antifungal
2433	Predicted to be non-hemolytic
78	Representative cluster members
5	Final down-selection

Antifungal classification



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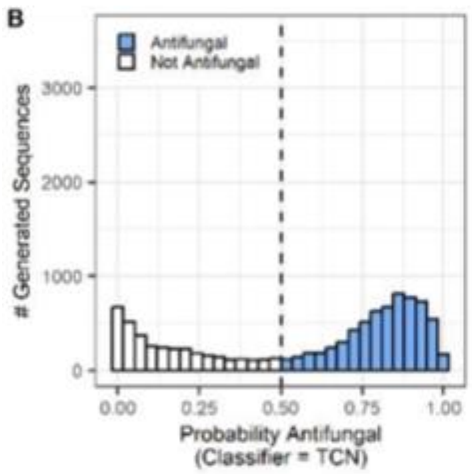
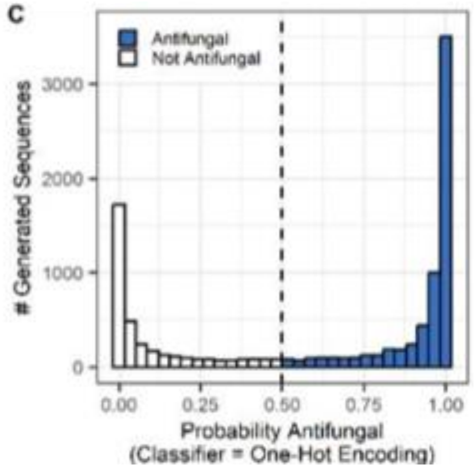
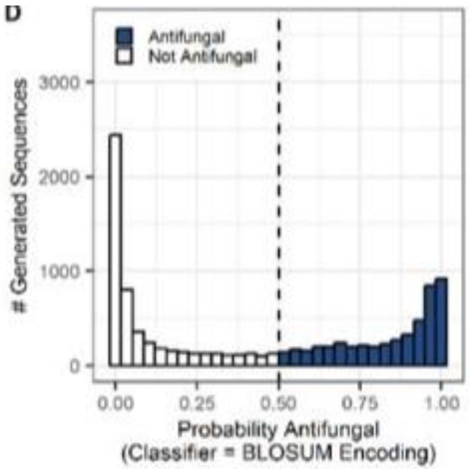
Temporal Convolutional Network



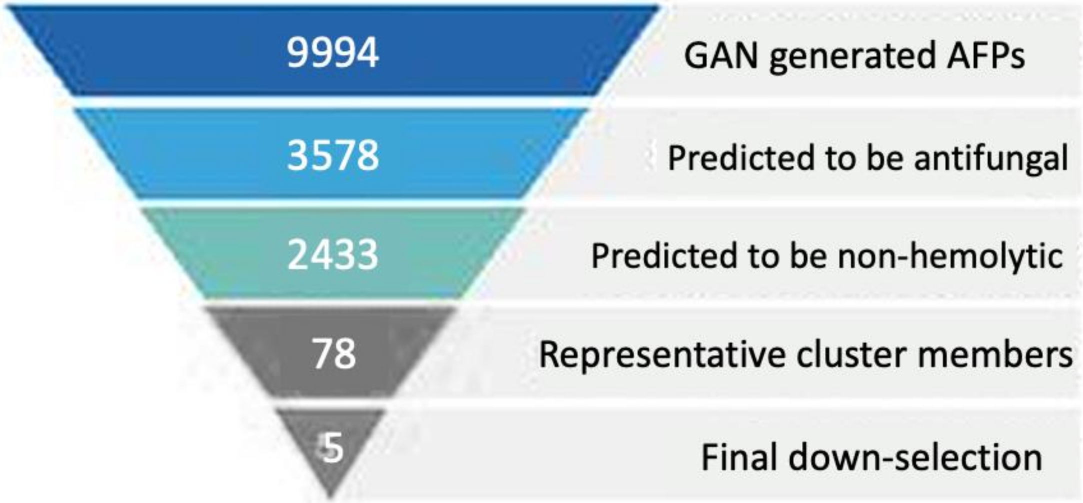
One-Hot Encoding



BLOSUM Encoding



Biophysical/Toxicity Filtering



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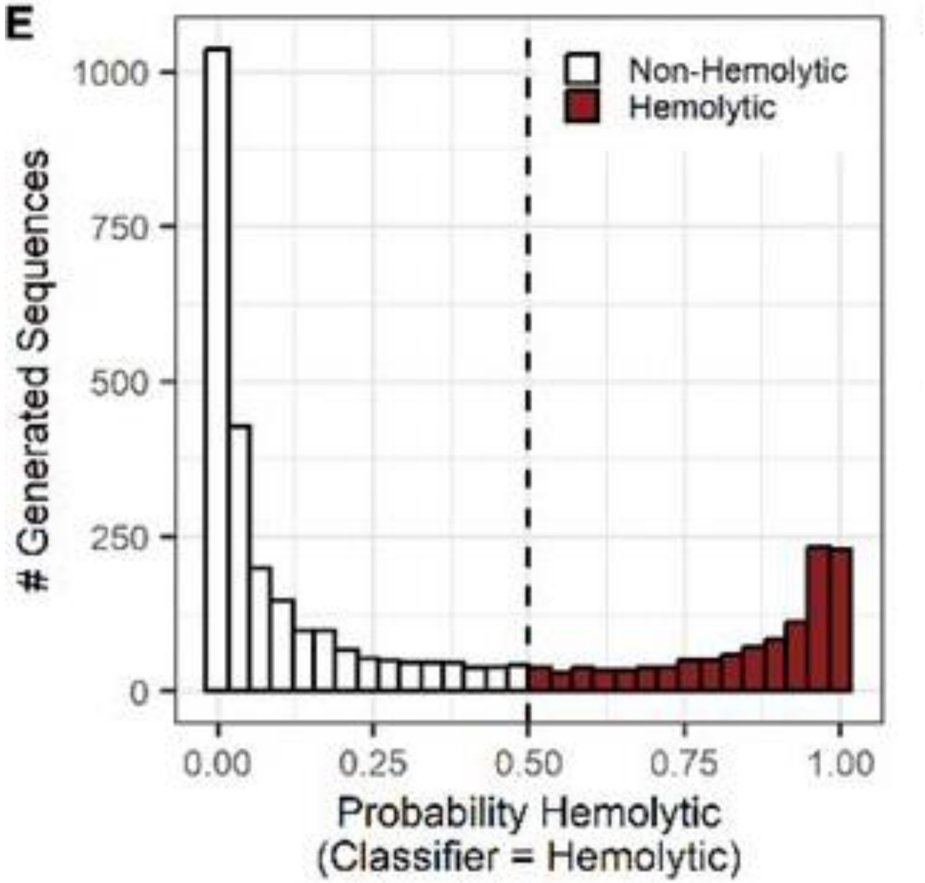
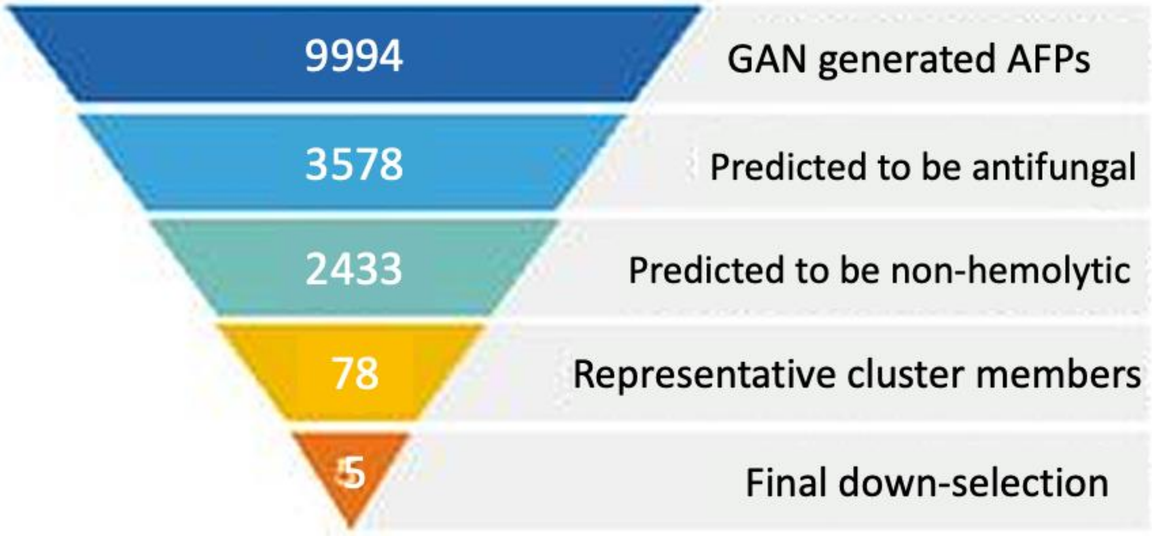


Clustering and Novelty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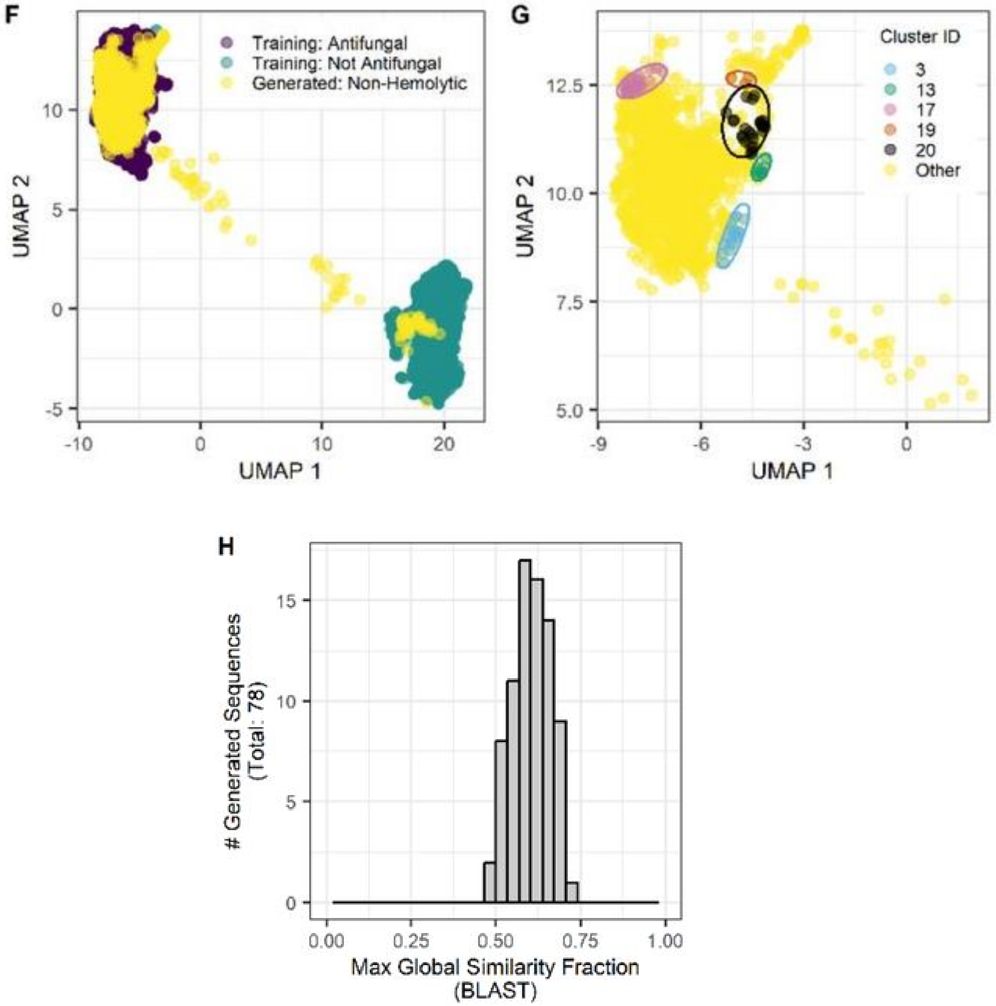
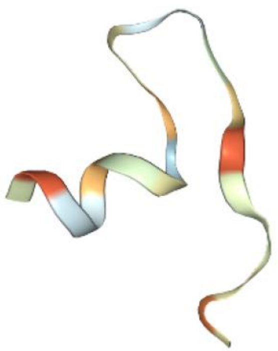
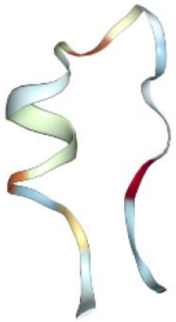


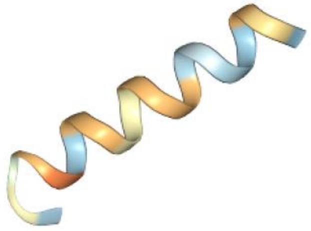
Structural and biophysical characterization of prioritized AFPs.



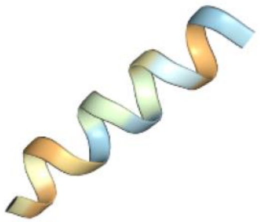
Peptide 27
GYGTTFIAPPGGLRGALPQFS



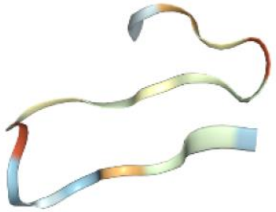
Peptide 50
KRRWPPKPVFSPNAAAYKCNP



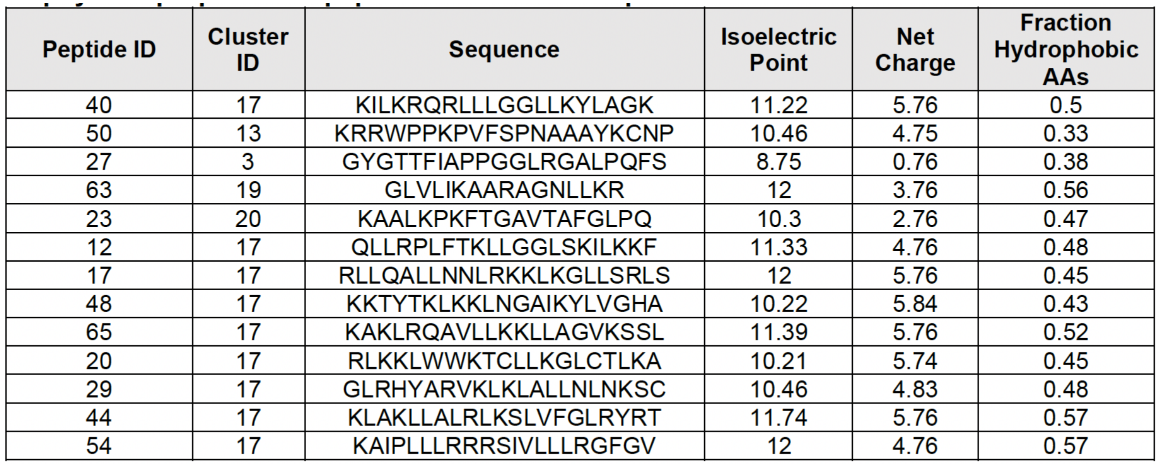
Peptide 40
KILKRQRLLLGGLLKYLAGK



Peptide 63
GLVLIKAARAGNLLKR

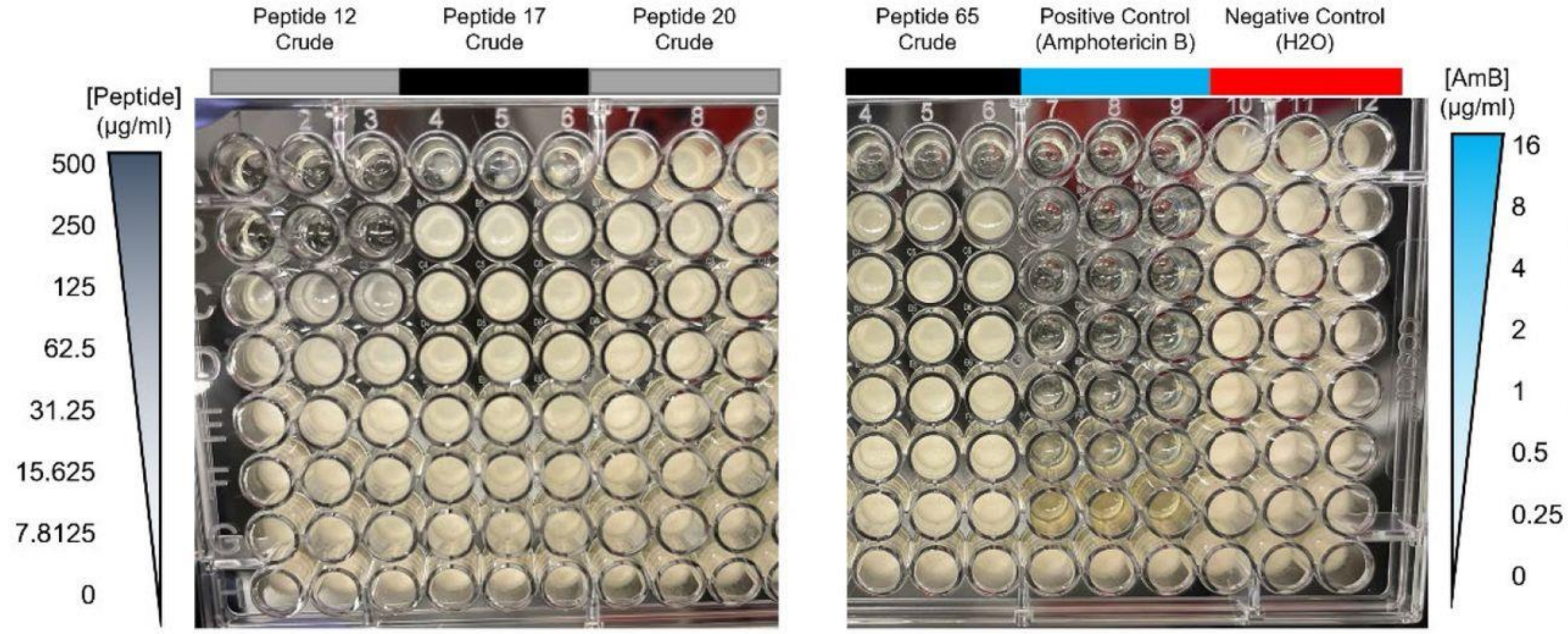


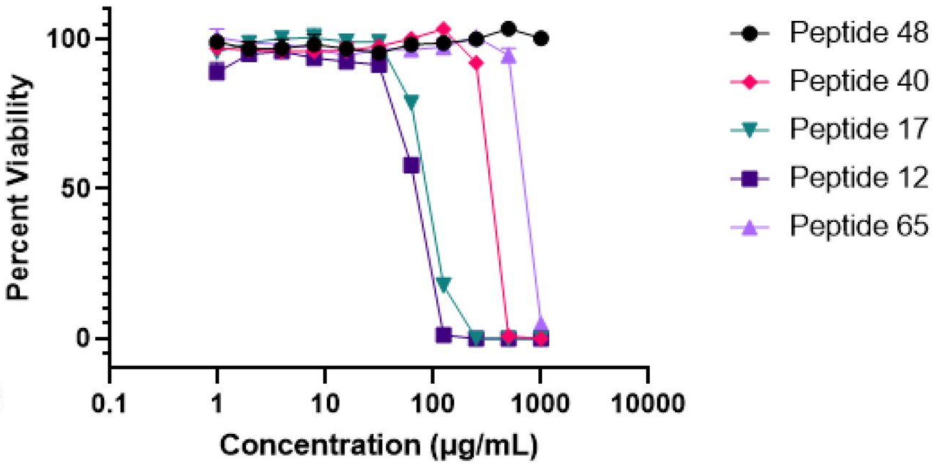
Peptide 23
KAALKPKFTGAVTAFGLPQ

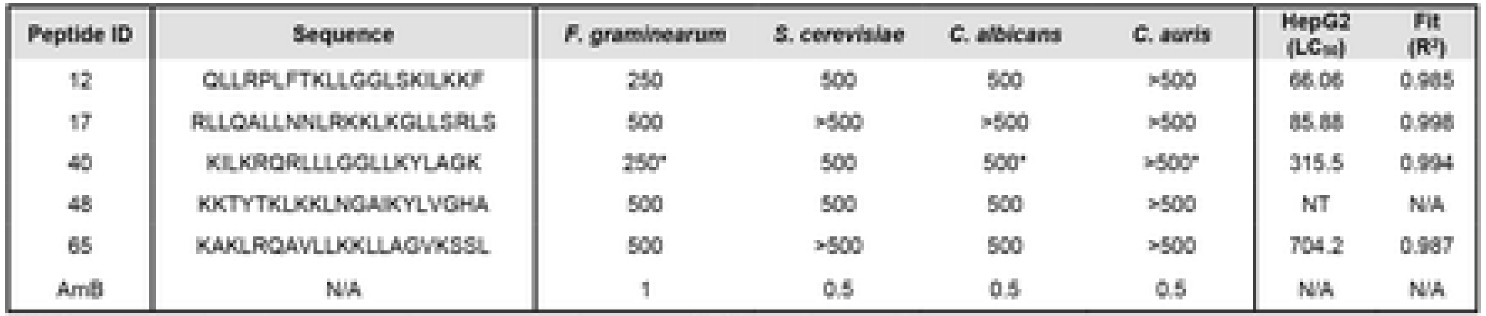


Peptide ID	Cluster ID	Sequence	Isoelectric Point	Net Charge	Fraction Hydrophobic AAs
40	17	KILKRQRLLLGGLLKYLAGK	11.22	5.76	0.5
50	13	KRRWPPKPVFSPNAAAYKCNP	10.46	4.75	0.33
27	3	GYGTTFIAPPGGLRGALPQFS	8.75	0.76	0.38
63	19	GLVLIKAARAGNLLKR	12	3.76	0.56
23	20	KAALKPKFTGAVTAFGLPQ	10.3	2.76	0.47
12	17	QLLRPLFTKLLGGLSKILKKF	11.33	4.76	0.48
17	17	RLLQALLNNLRKKLKGLLSRLS	12	5.76	0.45
48	17	KKTYTKLKKLNGAIKYLVGHA	10.22	5.84	0.43
65	17	KAKLRQAVLLKKLLAGVKSSL	11.39	5.76	0.52
20	17	RLKKLWWKTCLLKGLCTLKA	10.21	5.74	0.45
29	17	GLRHYARVKLKLALLNLNKSC	10.46	4.83	0.48
44	17	KLAKLLALRLKSLVFGLRYRT	11.74	5.76	0.57
54	17	KAIPLLLRRRSIVLLLRGFGV	12	4.76	0.57

From *in silico* prediction to experimental validation



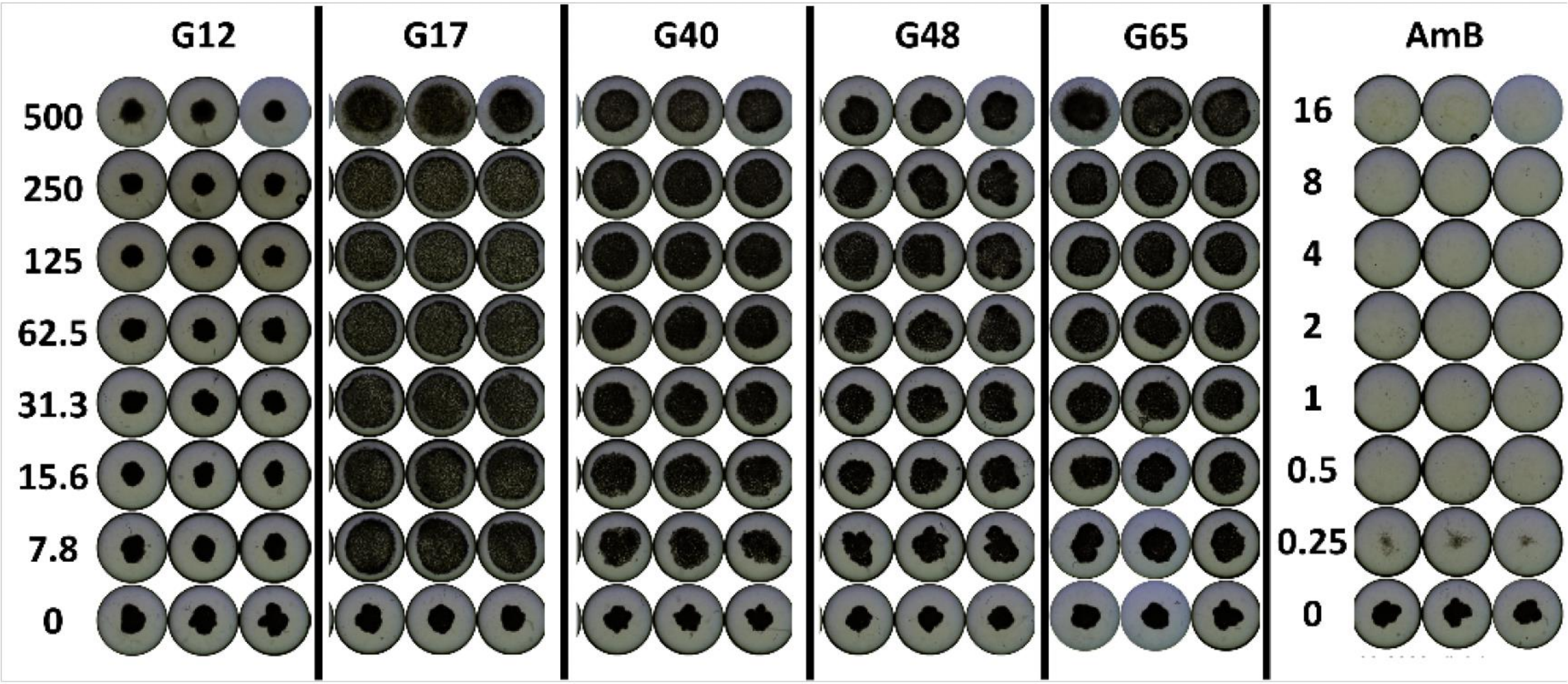




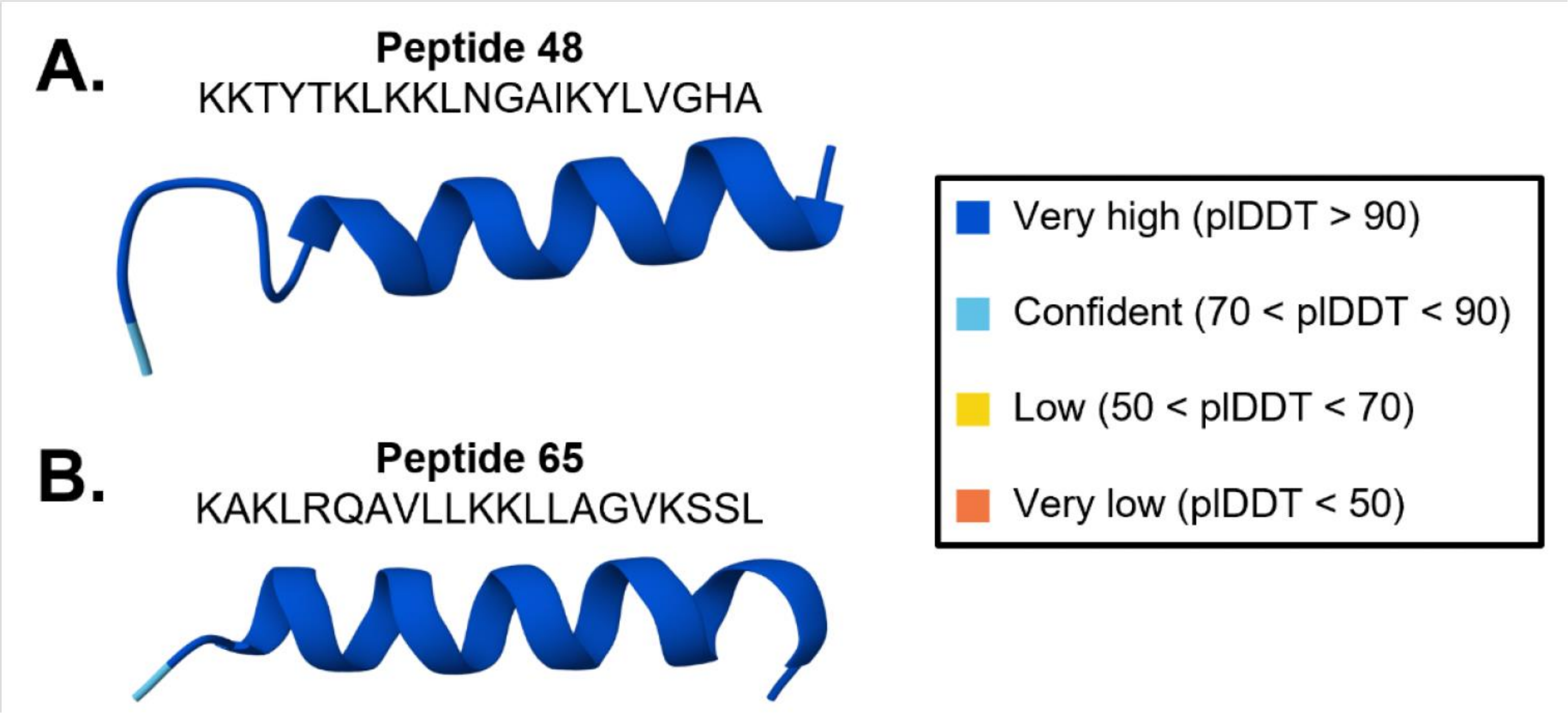
Peptide ID	Sequence	*F. graminearum*	*S. cerevisiae*	*C. albicans*	*C. auris*	HepG2 (LC_{50})	Fit (R^2)
12	QLLRPLFTKLLGGLSKILKKF	250	500	500	>500	66.06	0.985
17	RLLQALLNNLRKKLKGLLSRLS	500	>500	>500	>500	65.88	0.998
40	KILKRQRLLLGGLLKYLAGK	250*	500	500*	>500*	315.5	0.994
48	KKTYTKLKKLNGAIKYLVGHA	500	500	500	>500	NT	N/A
65	KAKLRQAVLLKKLLAGVKSSL	500	>500	500	>500	704.2	0.987
AmB	N/A	1	0.5	0.5	0.5	N/A	N/A

*MIC value determined on both crude purity and >95% purity peptide.

Potency of AFPs against *Candida auris*



Predicted secondary structures of high-potency low-cytotoxicity AFPs



Summary

- Authors created a semi-automated pipeline that uses GAN to design novel antifungal peptide sequences.
- Experimental validation showed that five peptides inhibited a wheat pathogen, and four of them were also effective against a human pathogen.
- Peptides 48 and 65 were the most promising candidates identified due to combined antifungal efficiency and low cytotoxicity to human liver cells.

Strengths and weaknesses

- Generation of an AI/ML pipeline with very limited data for training.
- Successfully were able to synthesize and experimentally test selected peptides

- Very limited biophysical characterization of the synthesized peptides.
- No mechanism of action characterization of the peptides.
- Lack of clarity for rationale behind the parameters used to select peptides.

Future directions

- Characterize the mechanisms of action of the peptides they identified.
- Test peptides from other clusters on human pathogens of interest, not just cluster 17.
- Develop specialized classifiers for identification of peptide candidates that are effective against multi-drug resistant pathogens.
- Optimization of found peptides to increase efficiency.