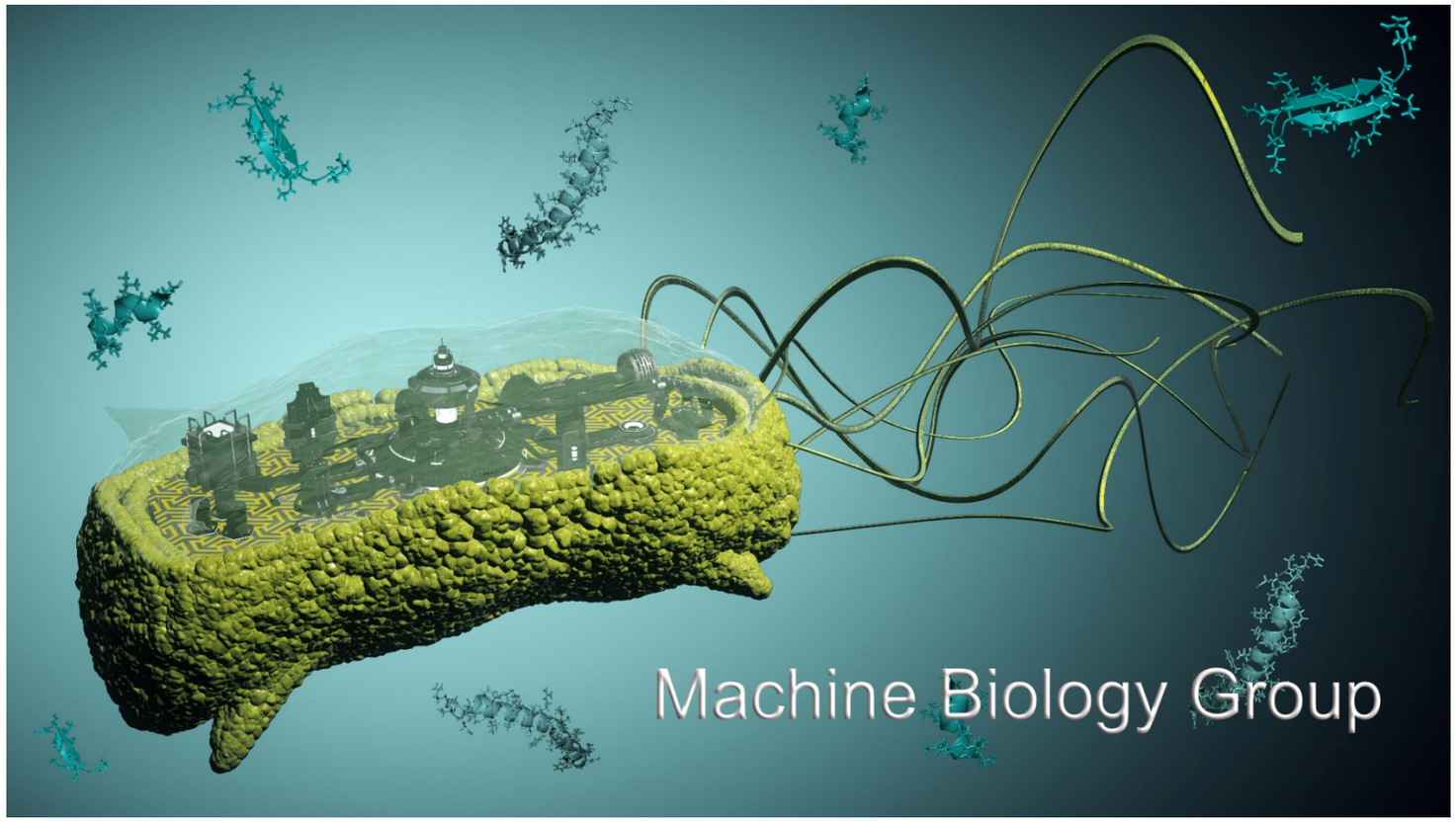
Artificial Intelligence Approaches for Antibiotic Discovery



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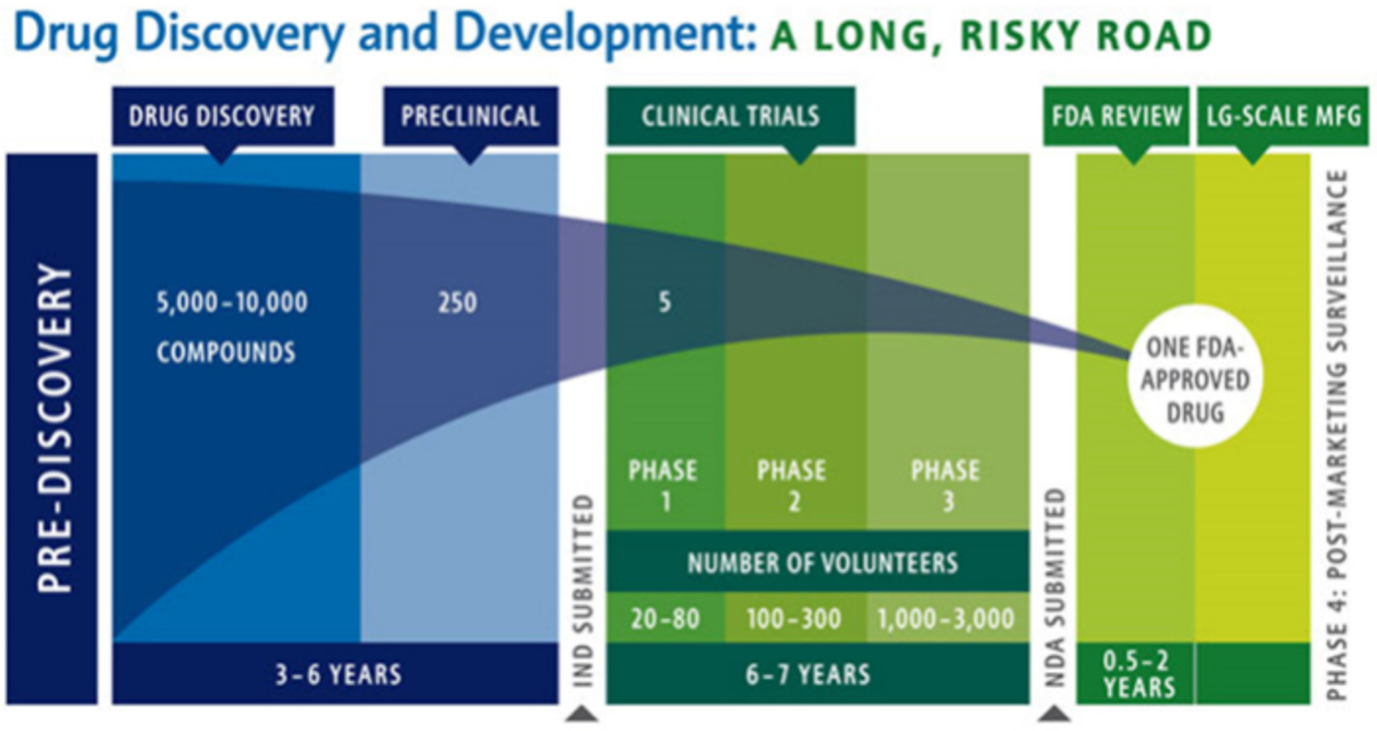
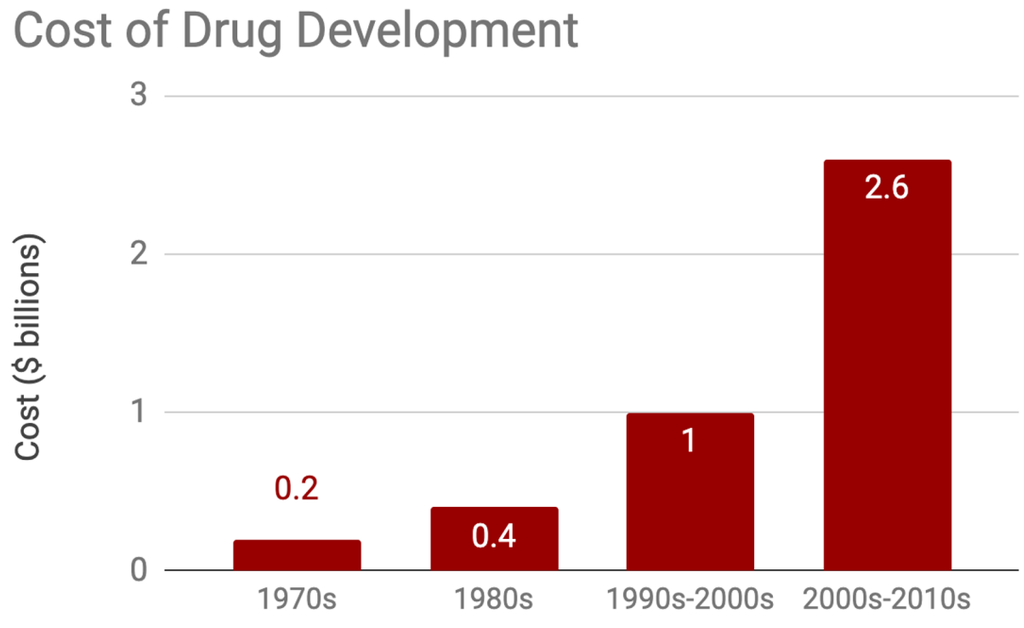
Institute for Computational Science
Institute for Translational Medicine and Therapeutics,
Depts. of Psychiatry and Microbiology,
Perelman School of Medicine
Depts. of Bioengineering and
Chemical and Biomolecular Engineering
University of Pennsylvania

Developing Drugs is Slow and Expensive

Time: >10 years from lab to the clinic



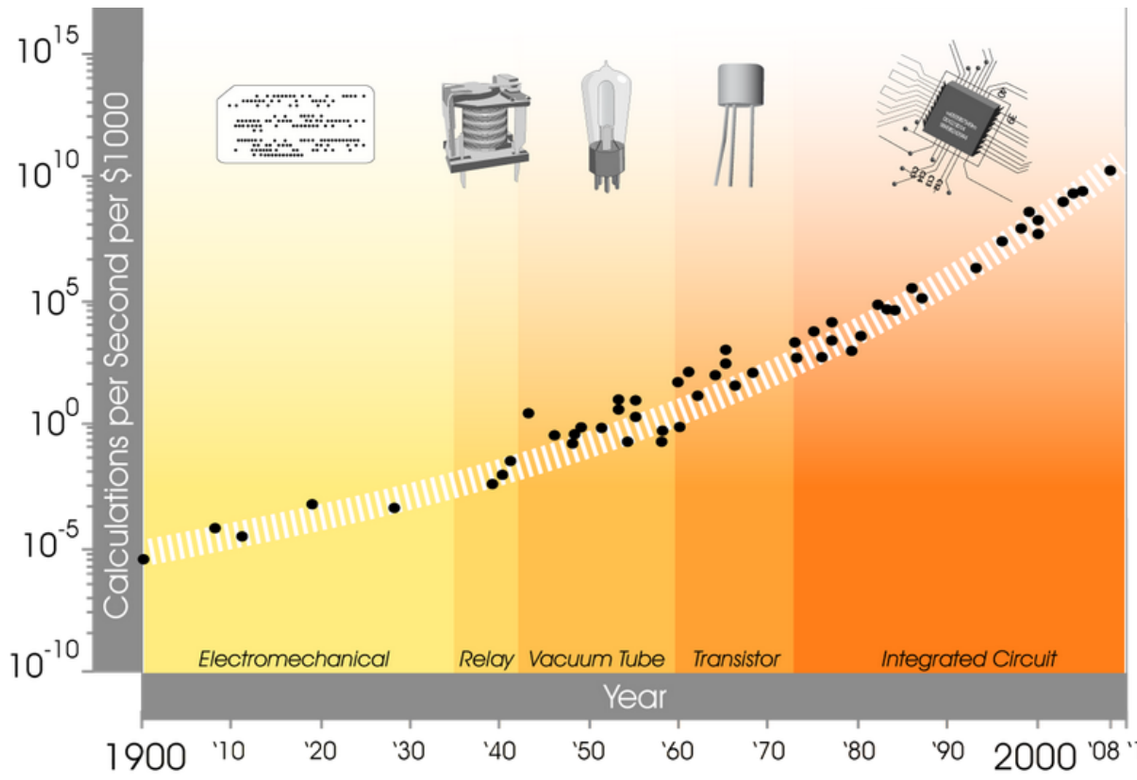
Cost: $2.6 billion per drug in 2014



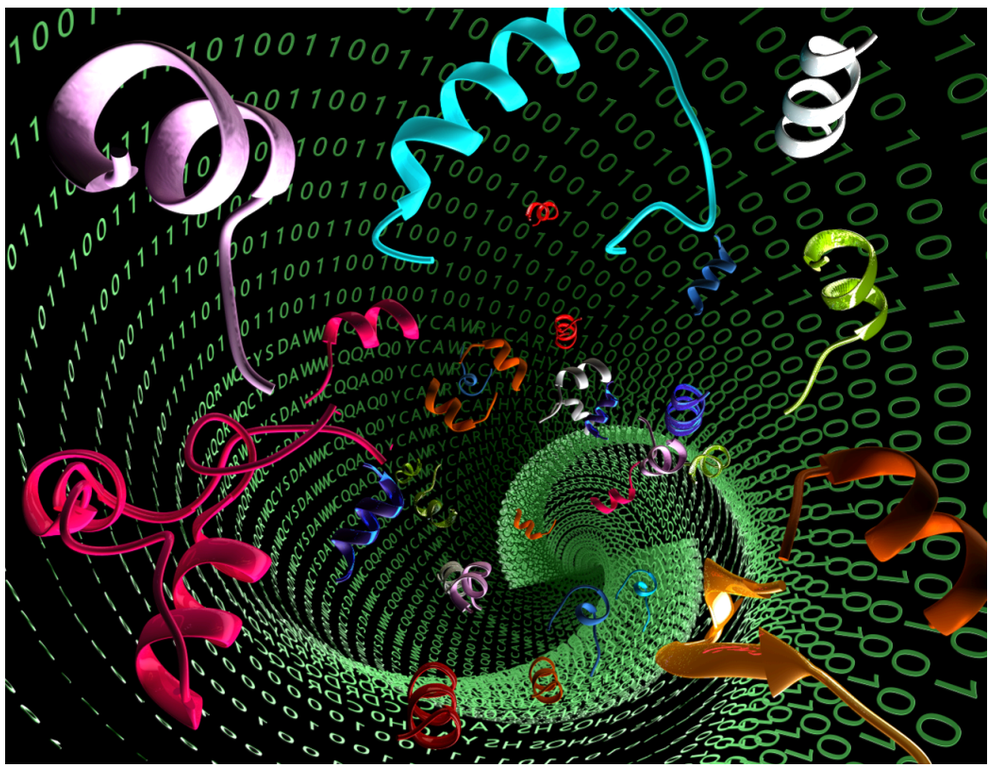
Source: Scientific American

Computational Drug Discovery

Compute power



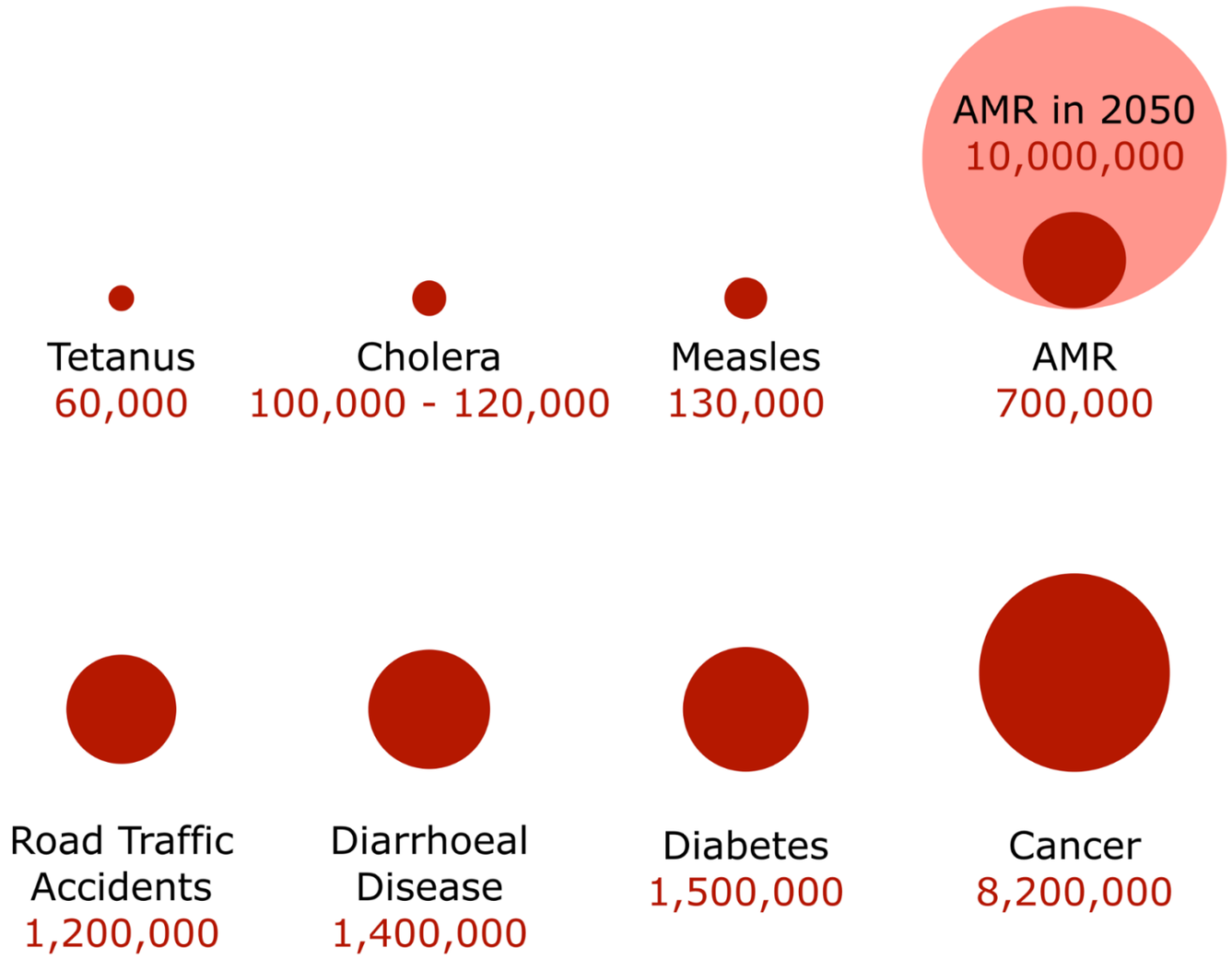
Data availability



Source: Nat Rev Drug Discov. 2012;11:191-200.
https://ourworldindata.org/technological-progress

Antibiotic Resistance: A Global Health Problem

Deaths attributable to antimicrobial resistance every year compared to other major causes of death

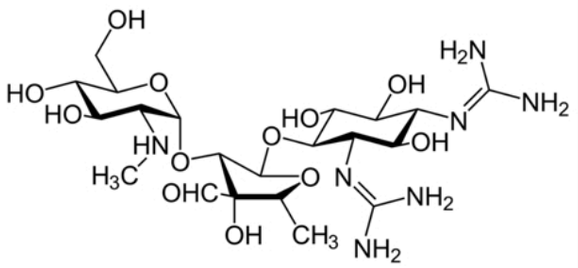


1 human death every 3 seconds

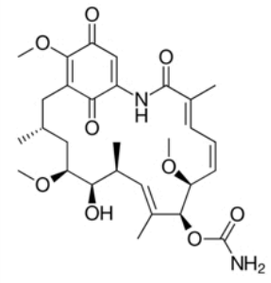
Source: Review on Antimicrobial Resistance 2014; Nature Reviews Drug Discovery 6:28.

The Biological World is Running Out of Antibiotic Chemistries

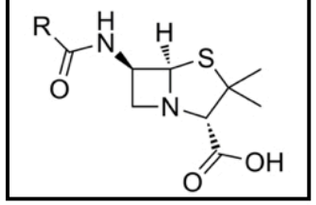
Aminoglycosides



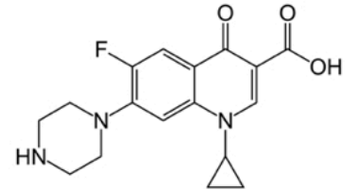
Ansamycins



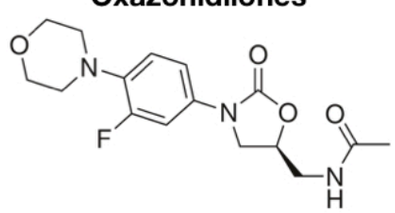
Beta-lactams



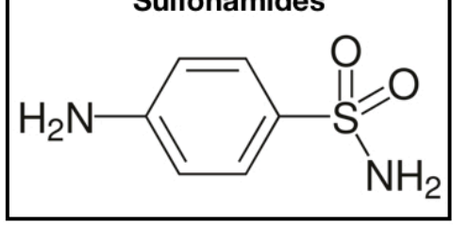
Quinolones



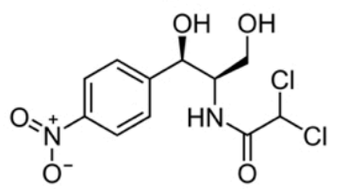
Oxazonidilones



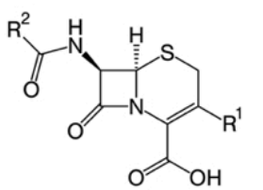
Sulfonamides



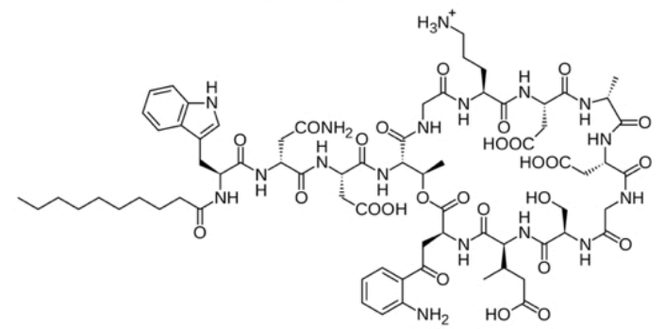
Chloramphenicol



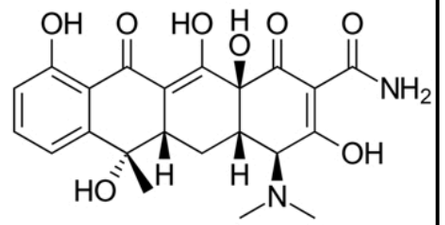
Cephalosporins



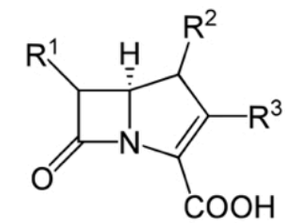
Lipopeptides



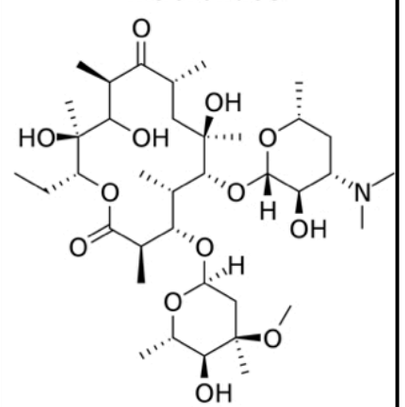
Tetracyclines



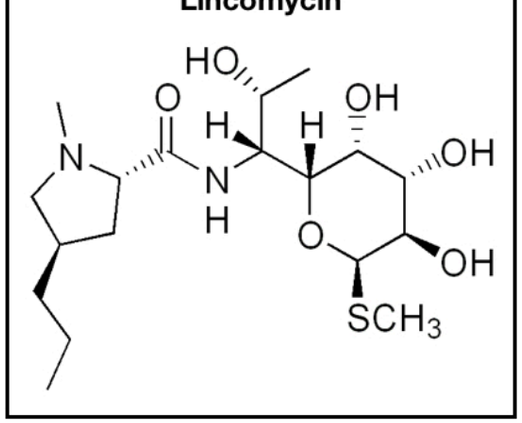
Carbepenems



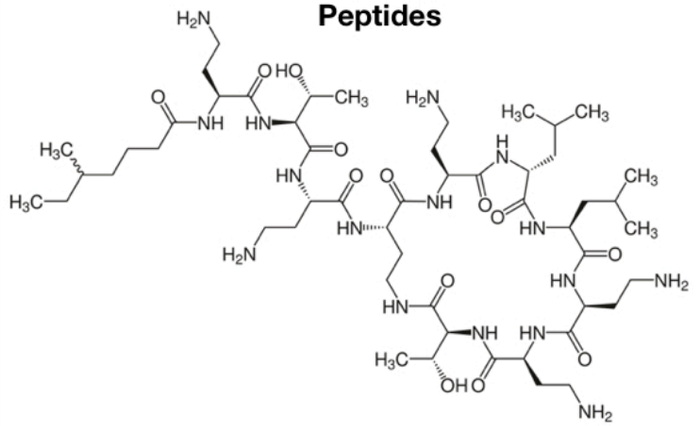
Macrolides



Lincomycin

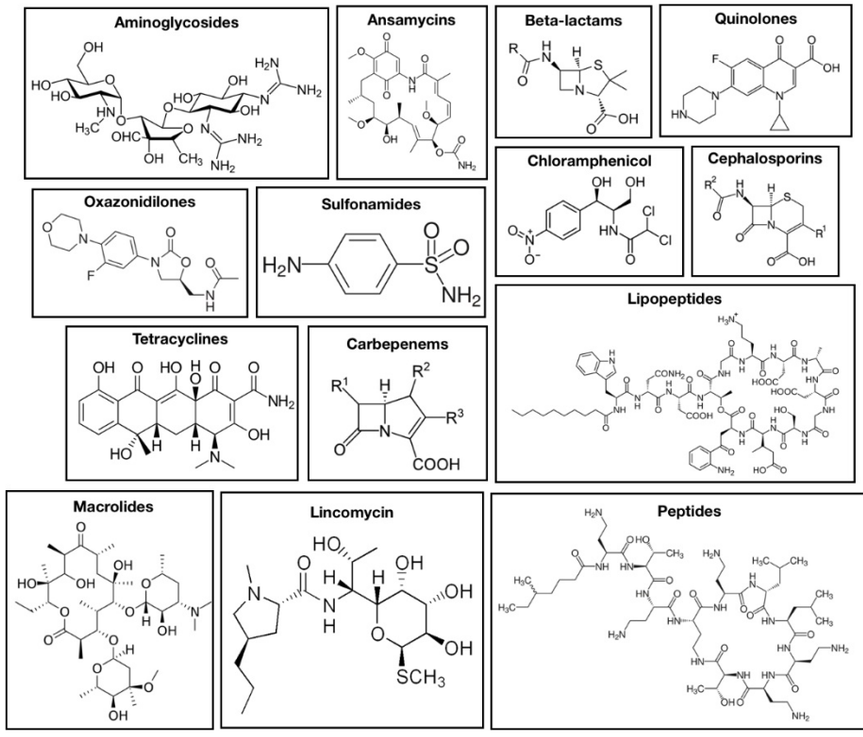


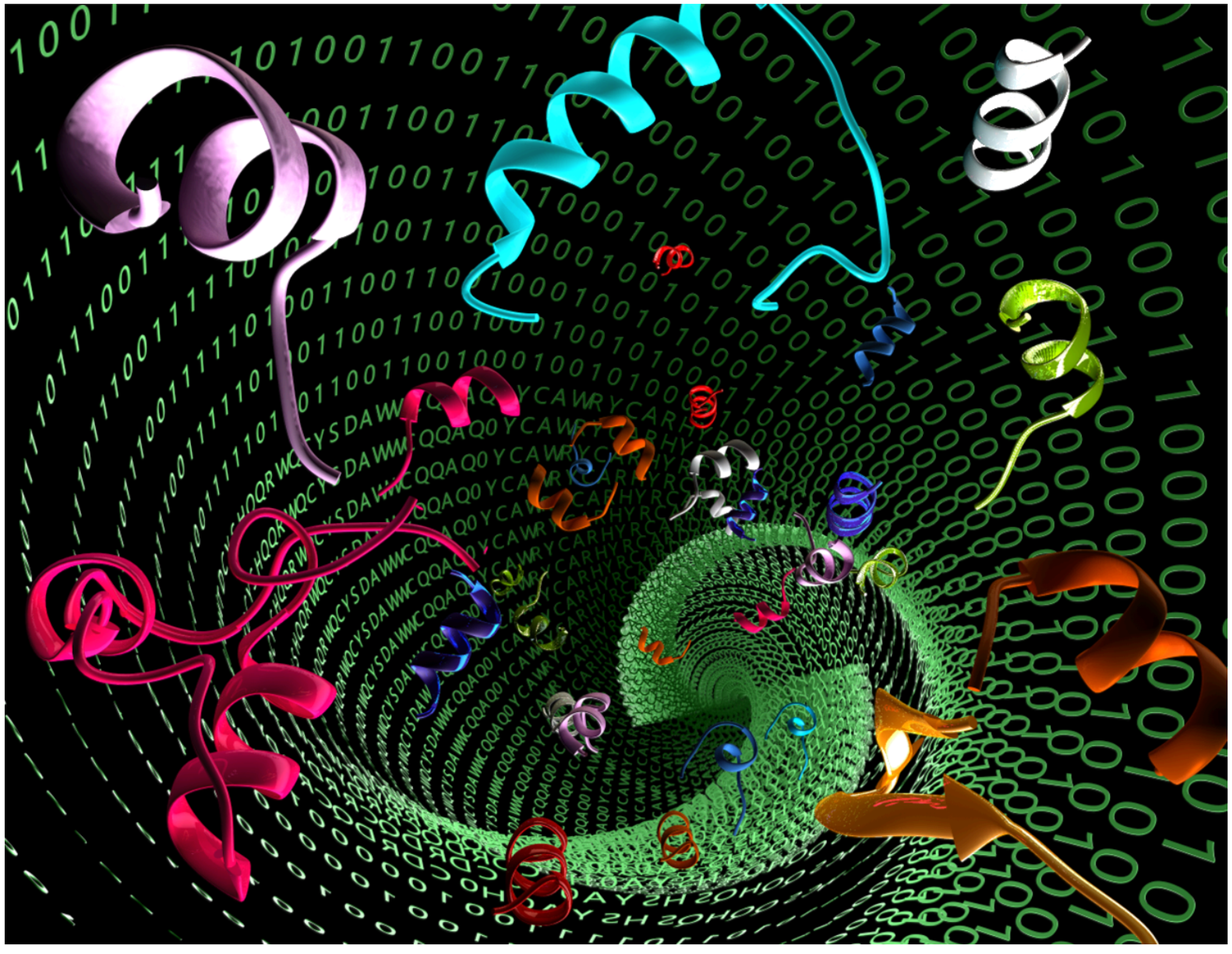
Peptides



Photograph: NASA

Can Computers Achieve Autonomous Molecular Discovery?

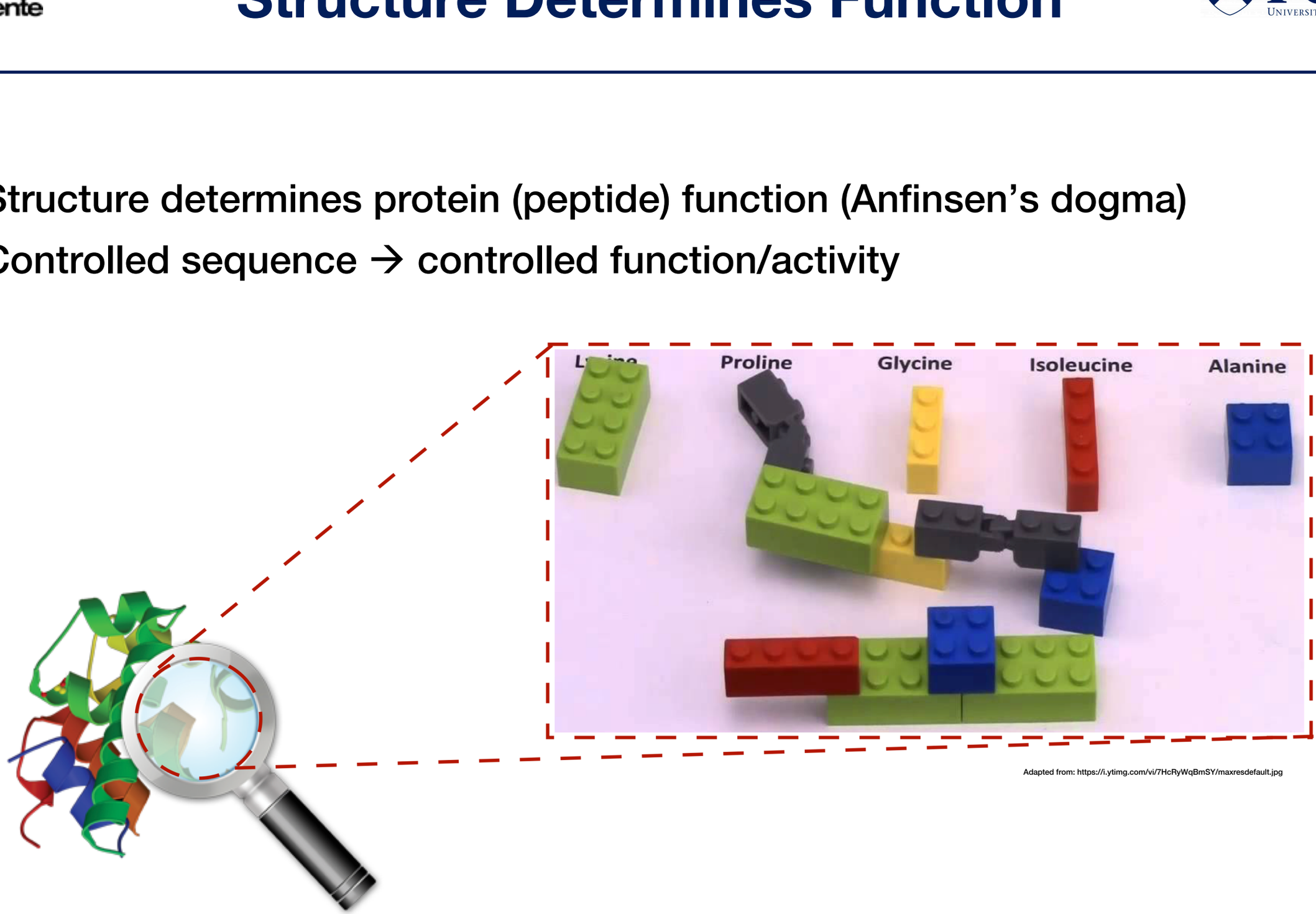




Structure Determines Function

Structure determines protein (peptide) function (Anfinsen's dogma)

Controlled sequence → controlled function/activity



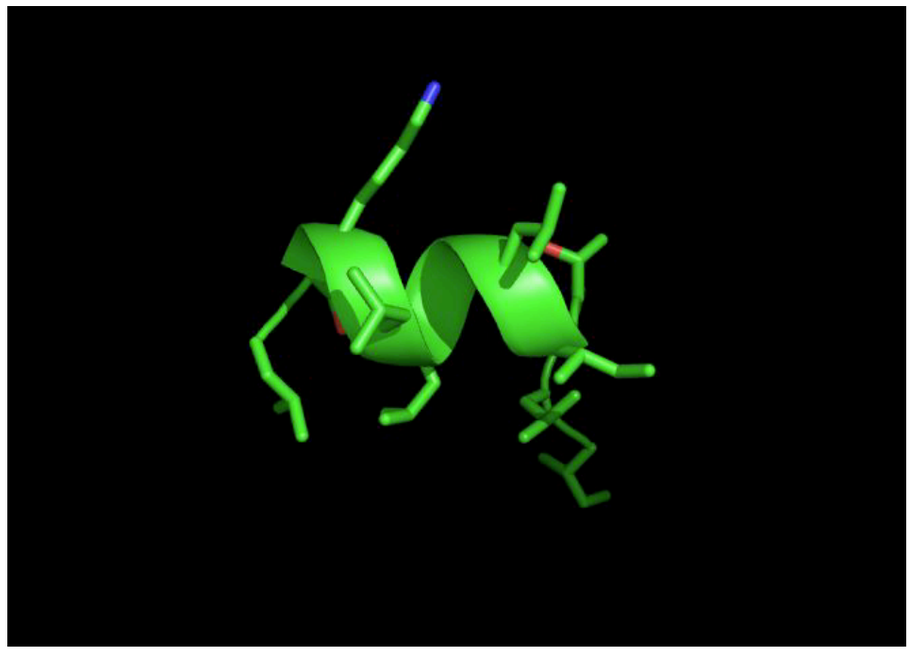
Adapted from: https://i.ytimg.com/vi/7HcRyWqBmSY/maxresdefault.jpg

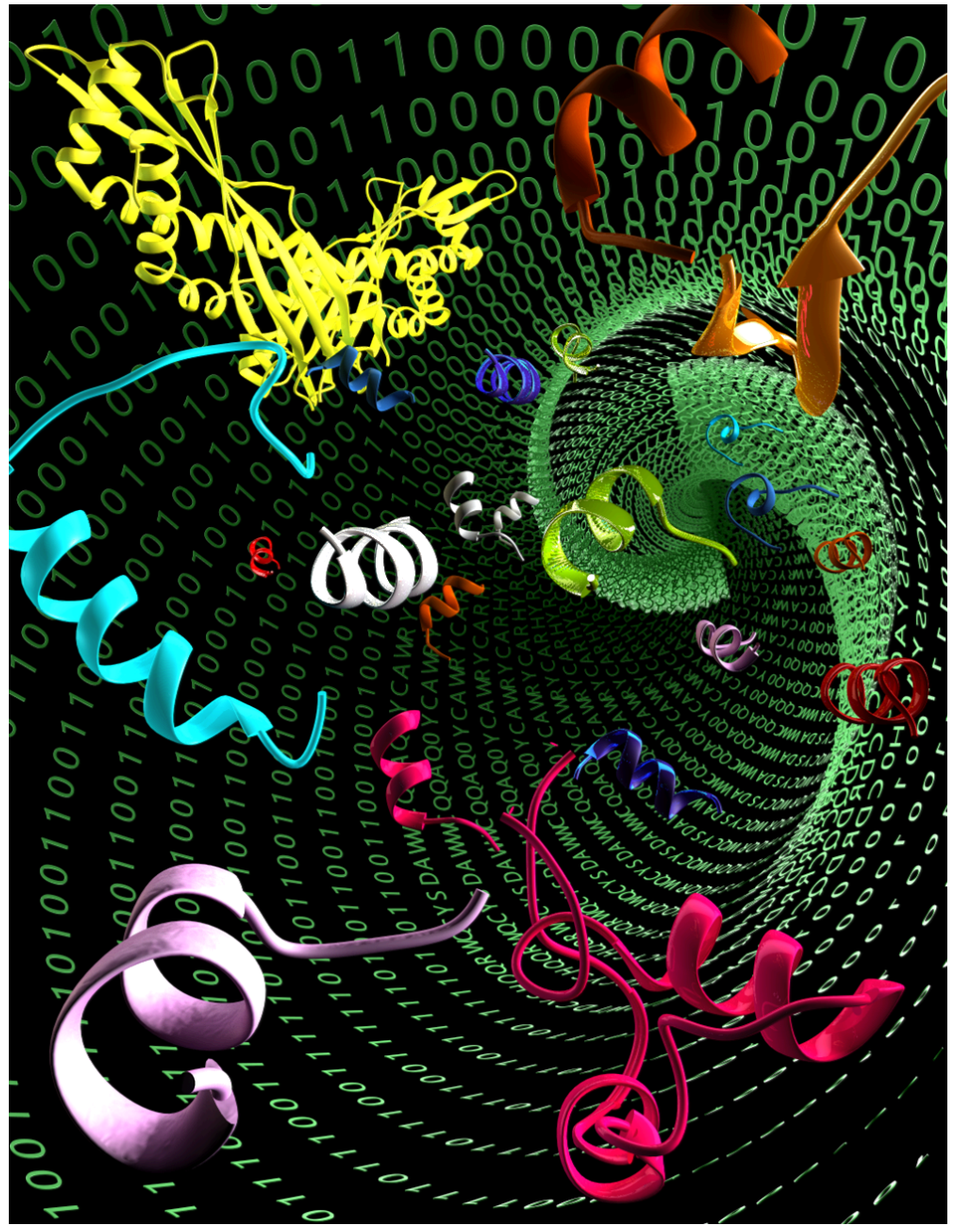
AI for Drug Discovery

Explore Sequence Space

Generate New Molecules

Mine Biology





Protein Space is Astronomical: Opportunity for Engineering

Number of plant and animal species on Earth: 10^7

Number of people on Earth: 10^{10}

Number of microbial species on Earth: 10^{12}

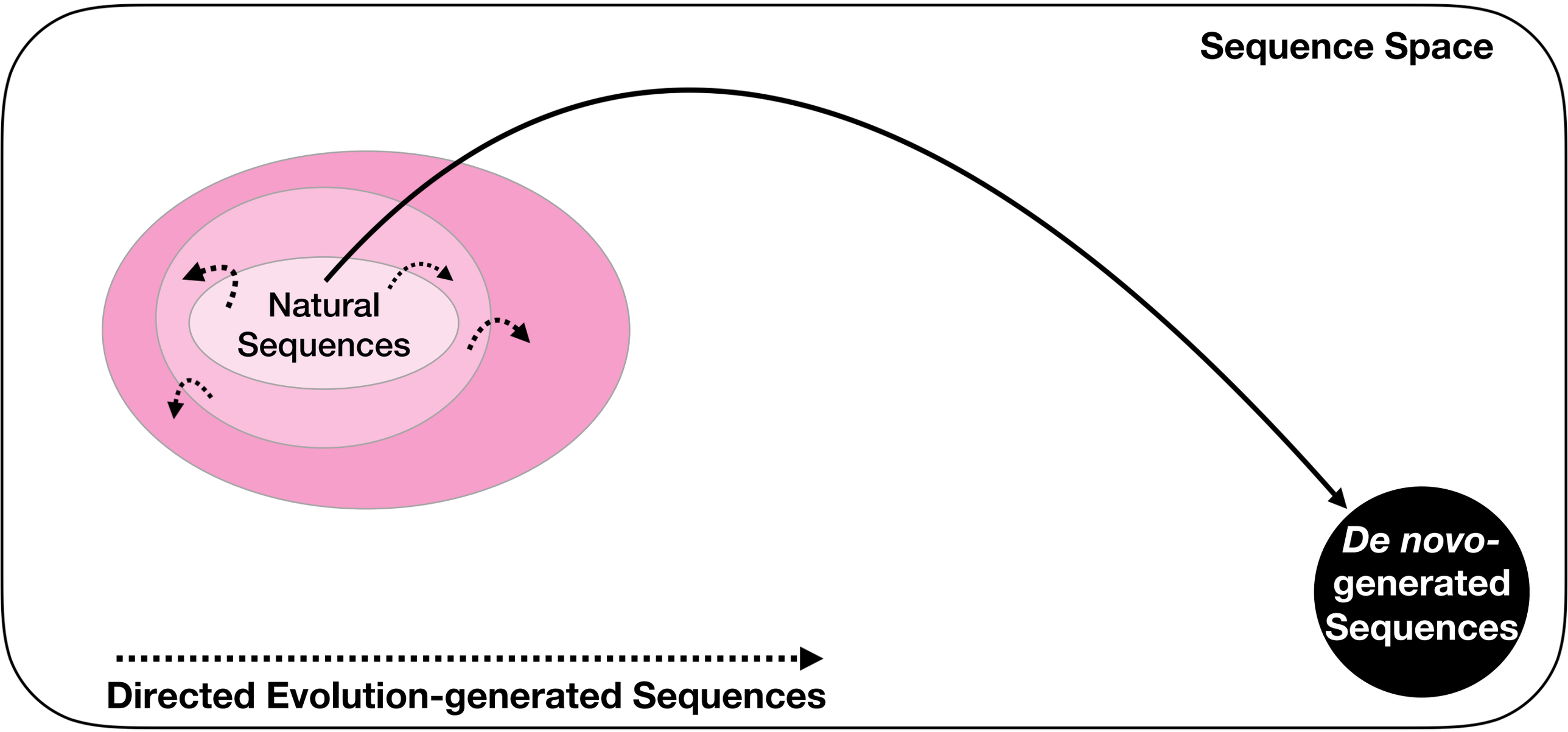
Number of bacteria in a human: 3.8×10^{13}

Number of sand corns on Earth: 10^{28}

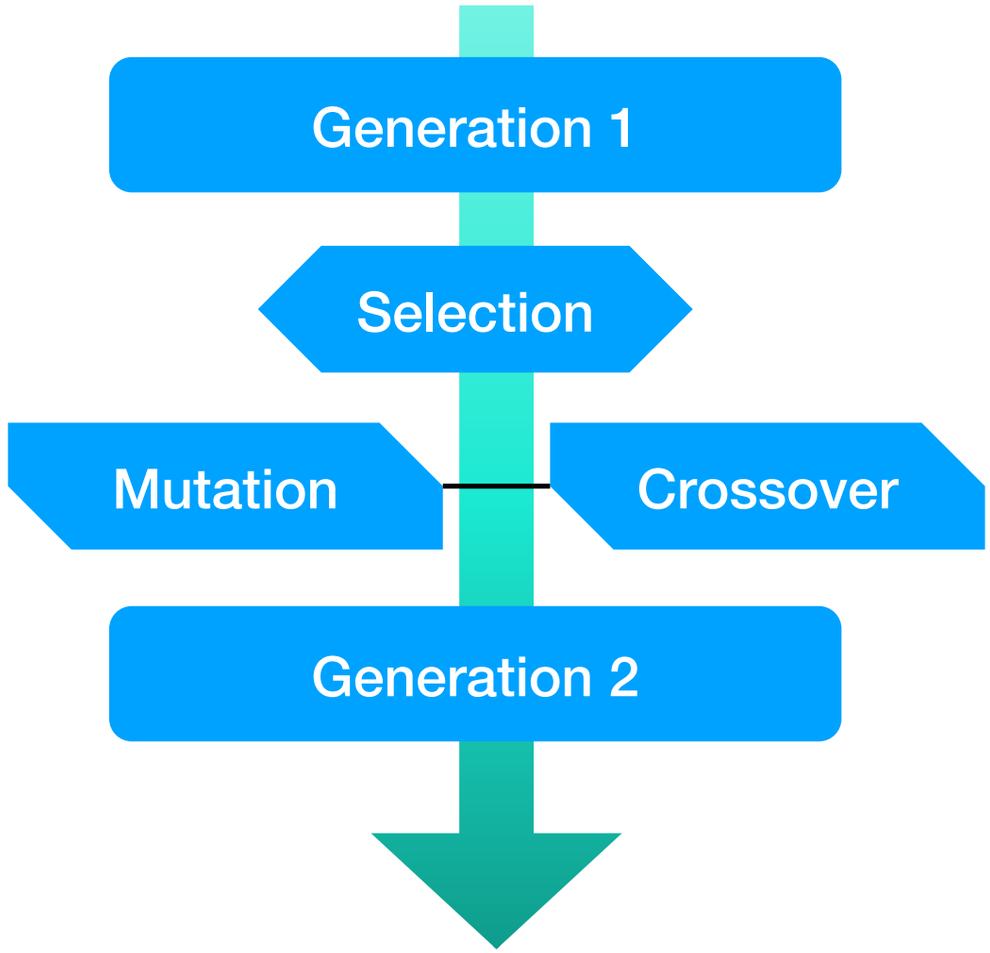
Number of stars in the Universe: 10^{31}

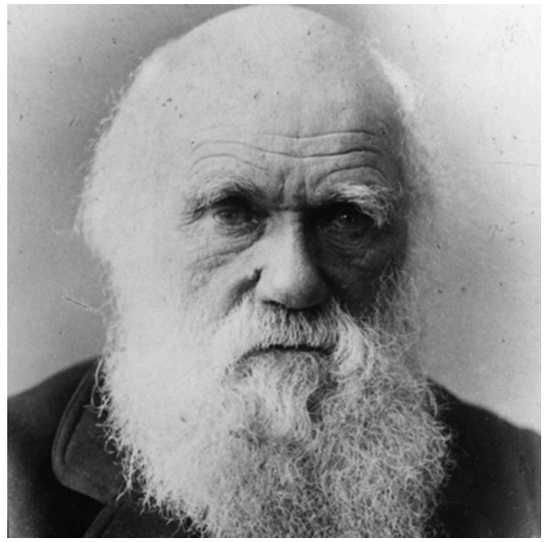
25 amino-acid peptide: 10^{32}!

Molecular Sequence Space is Astronomical: Opportunity for Engineering



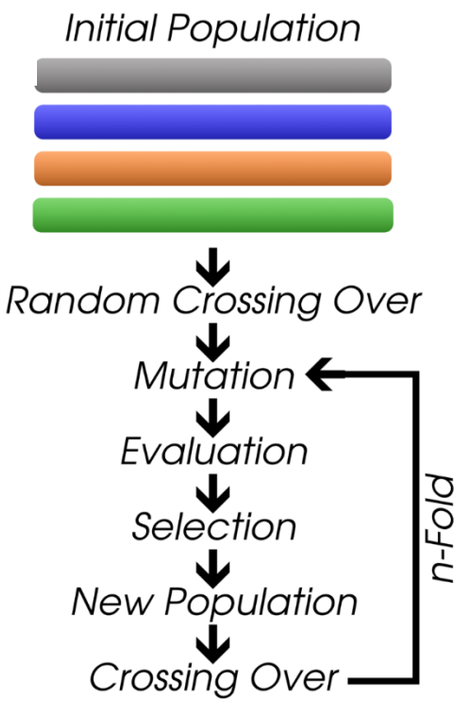
Antimicrobial Design by Computers

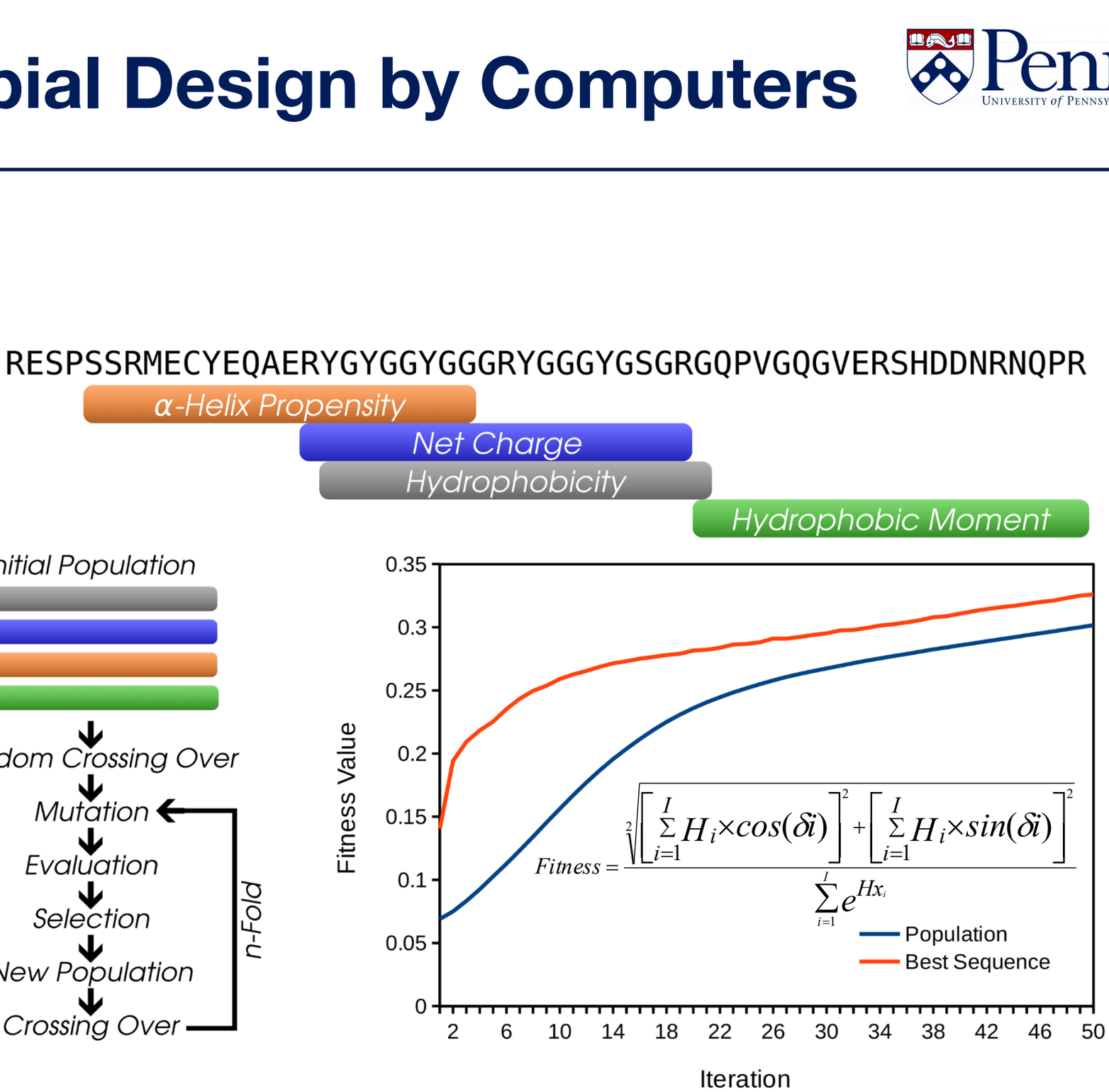




Antimicrobial Design by Computers

Computational Directed Evolution Using Genetic Algorithms

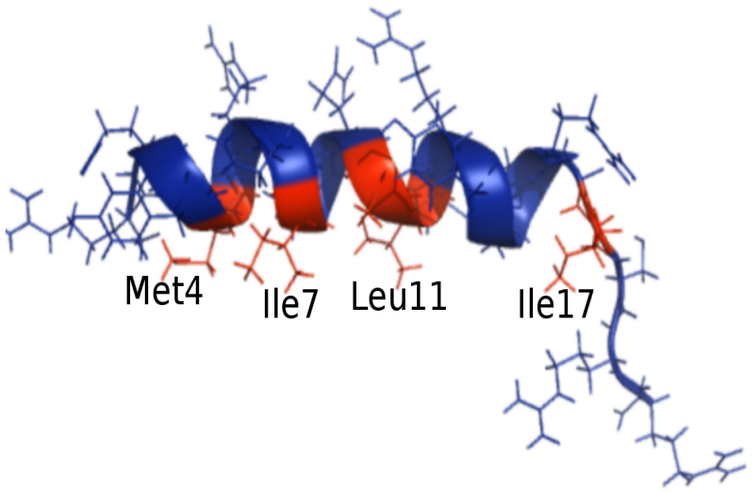


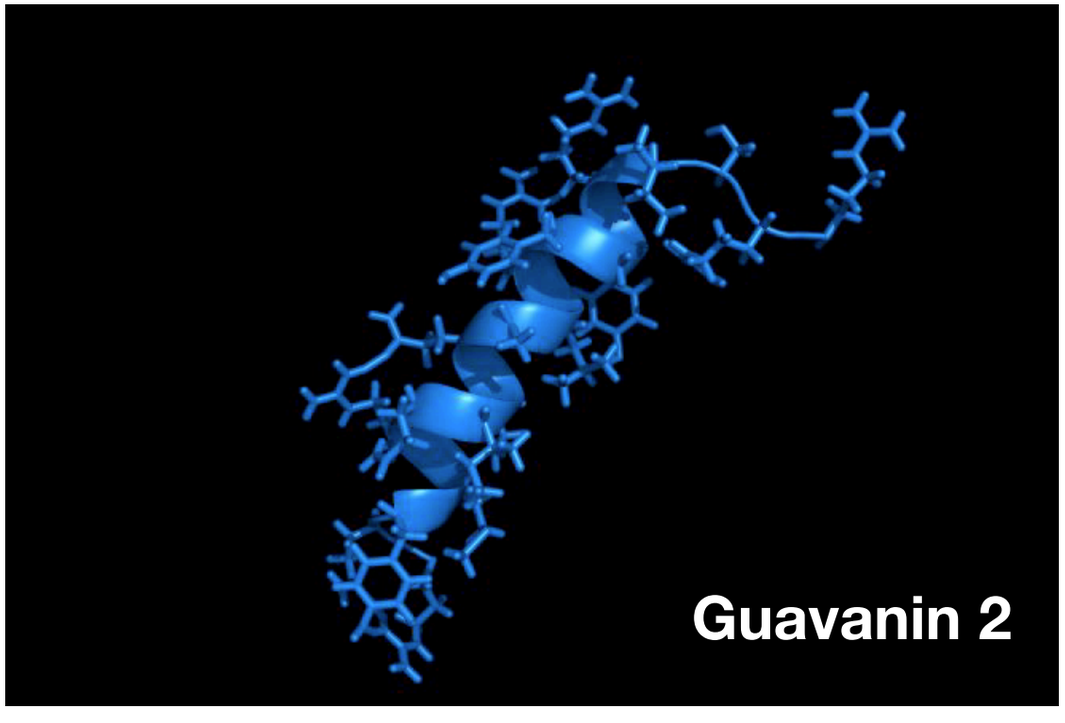


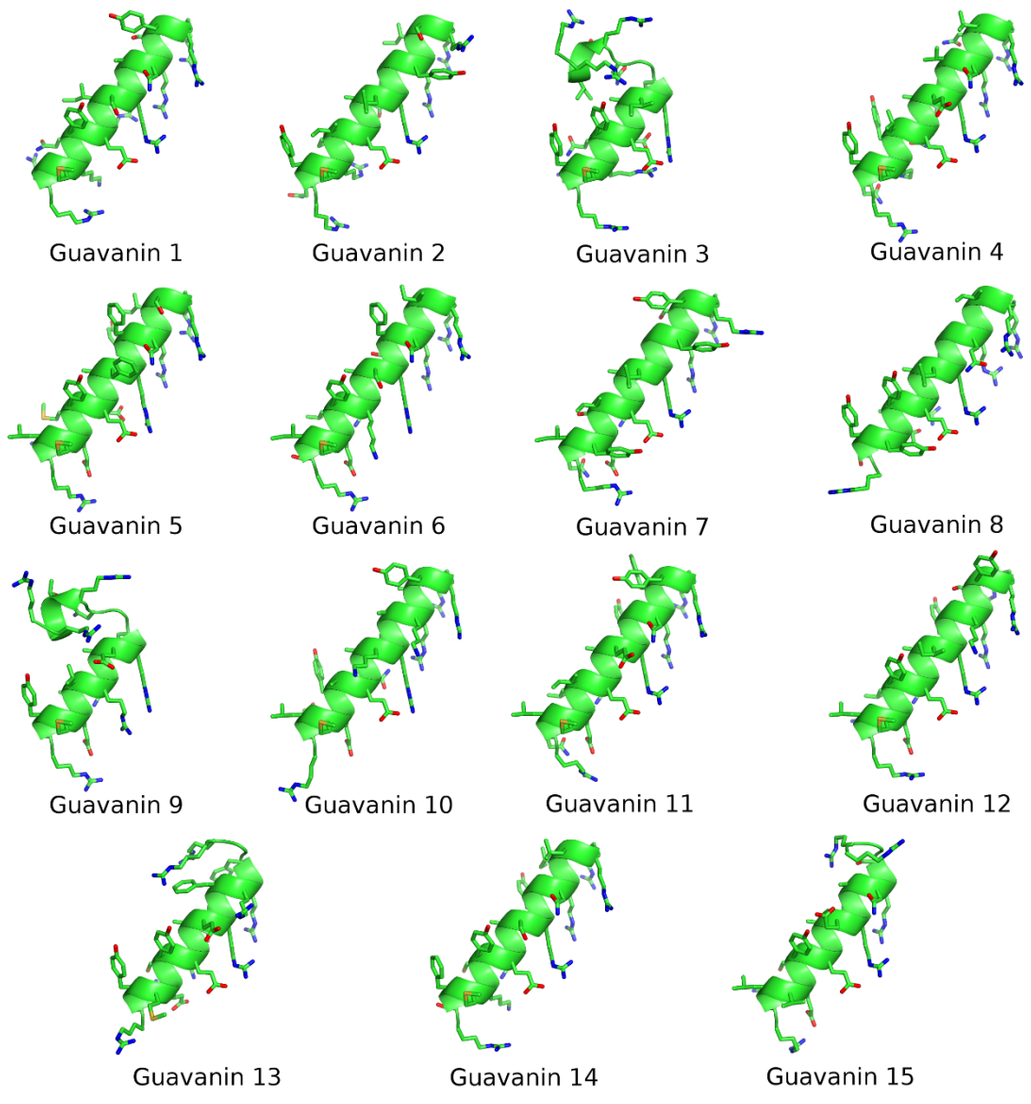
Nature Communications, 2018, 9:1490.

Antimicrobial Design by Computers

Lead peptide MIC = 6 μg mL^{-1}
vs.
Pg-AMP1 (WT peptide) MIC > 100 μg mL^{-1}



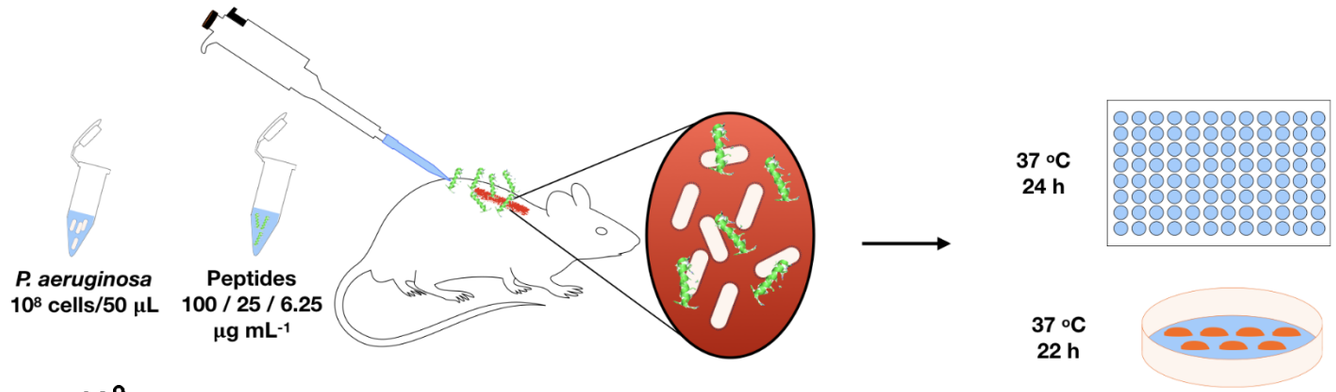


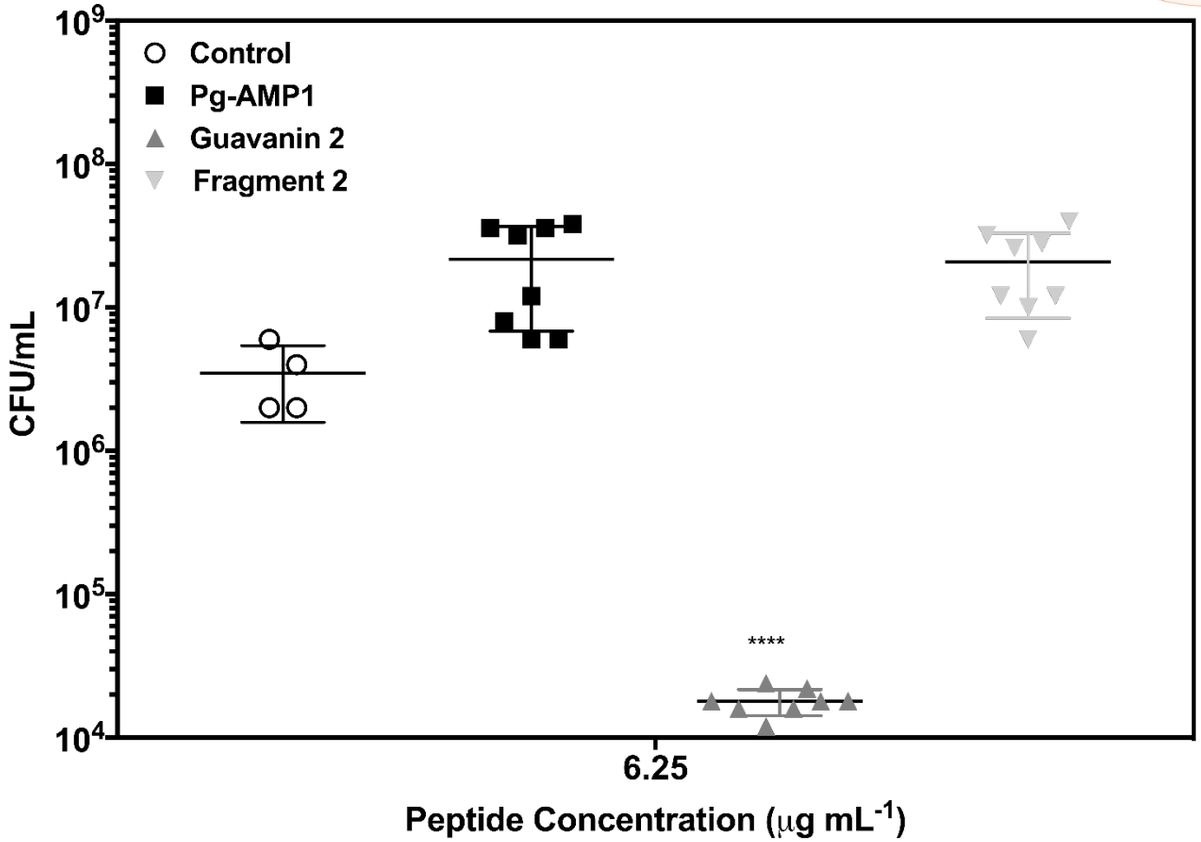


Nature Communications, 2018, 9:1490.

Machine-Made Antibiotics Kill Bacteria in Animals

In vivo Activity of "Artificially Evolved" Peptide





Nature Communications, 2018, 9:1490.

Venoms as a Source of Antibiotics

a

Brevenins

- FLPIIAGVAAKVLPKIFCAISKKC
- FLPIIAGIAAKFLPKIFCTISKKC
- FLPIIAGVAAKVLPKLFCAITKKC
- FLPIIAGVAAKVFPKIFCAITKKC
- FLPIIAGIAAKVFPKIFCAISKKC
- FLPIIASVAAKVFSKIFCAISKKC
- FLPIIASVAANVFSKIFCAISKKC
- FLPIIASVAANVFPKIFCAISKKC
- FLPIIAGIAAKFLPKIFCAISKKC
- FLPIIAGVAAKVFPKIFCTISKKC
- FLPIIAGMAAKFLPKIFCAISKKC
- FLPIIAGMAAKVICAITKKC
- FLPIIAGAAAKVVQKIFCAISKKC
- FLPIIAGAAAKVVEKIFCAISKKC

Temporins

- FLPIIGQLLSGLL
- FLPIIAKVLSGLL
- FLPIIASVLSSLL
- FLPIIGKLLSGIL
- FLPIITNLLGKLL

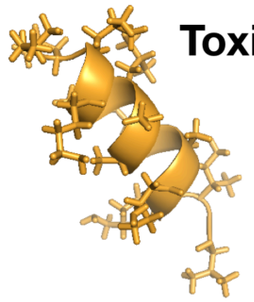
Vespid Chemotactic Peptides

- FLPIIAKLVSGLL
- FLPIIGKLLSGLL
- FLPIIAKLLGGLL

FLPII - Antimicrobial and Immunomodulatory Motif in Natural Peptides

b

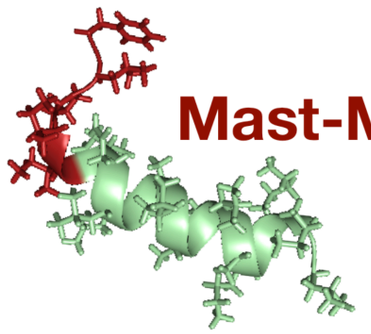
Mastoparan-L



Toxic

INLKALAALAKKIL

FLPII

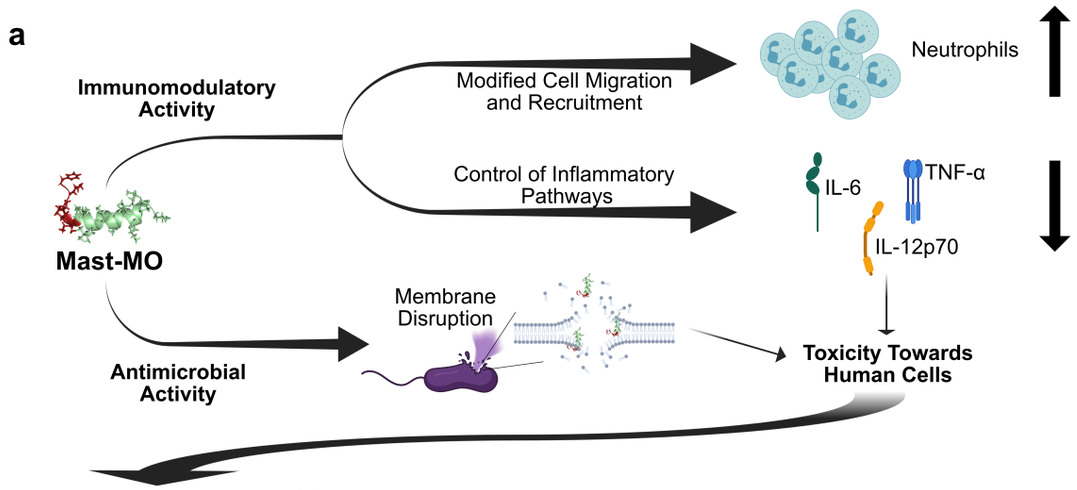


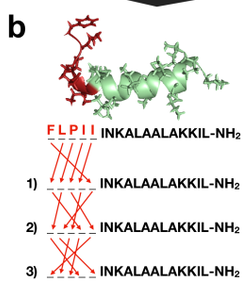
Mast-MO

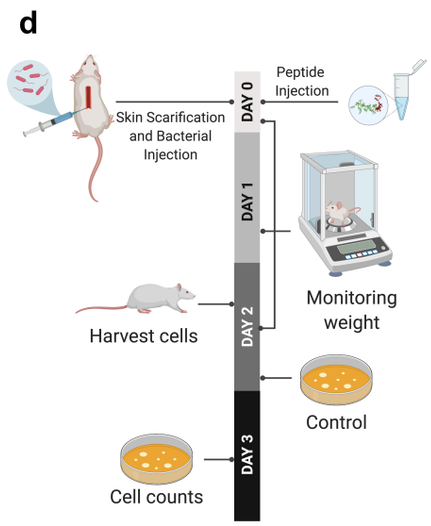
FLPIIINLKALAALAKKIL

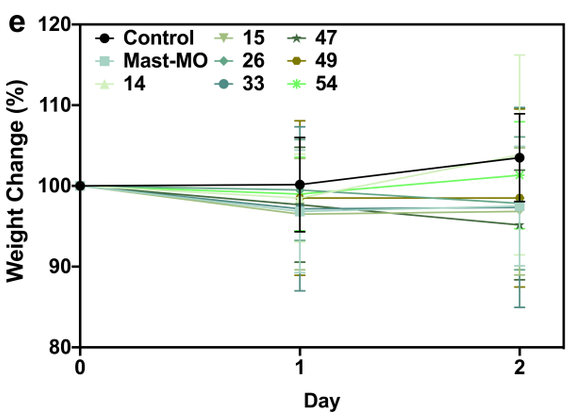
PNAS. 2020

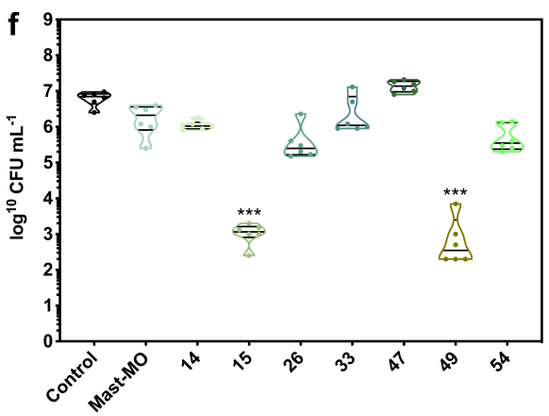
Venoms as a Source of Antibiotics











Dual antimicrobial + immunomodulatory activities

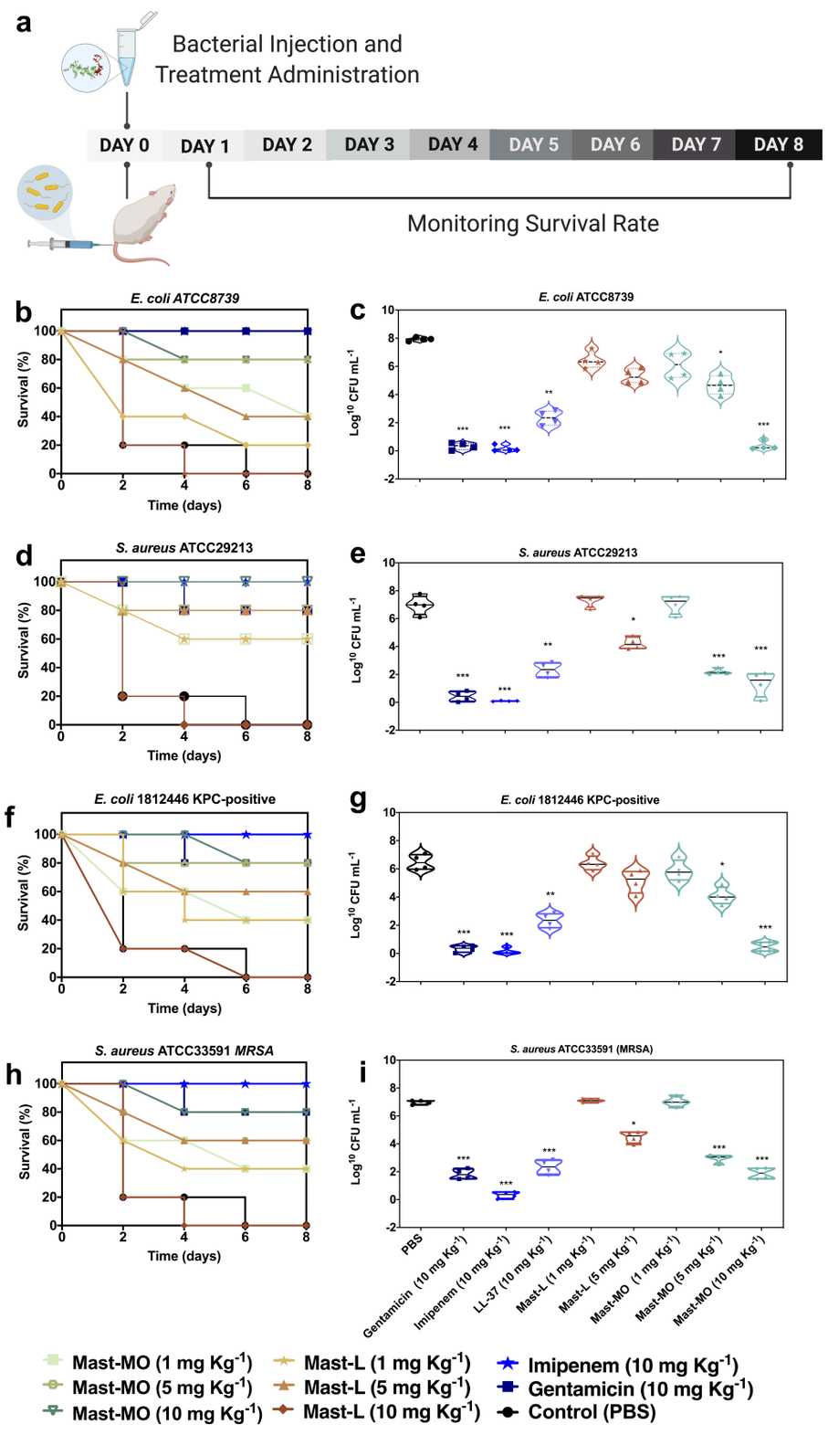
Anti-inflammatory properties

Rational design depletes cytotoxicity vs human cells

Efficacy in mouse model

PNAS. 2020

Venoms as a Source of Antibiotics



Effective vs sepsis which kills 11 million people per year (as of 2017)

Efficacy comparable to standard-of-care antibiotics

Broad-spectrum activity

Active vs drug-resistant strains

PNAS. 2020

Computer-Guided Antimicrobial Discovery

Biology has encrypted useful information.
How do we decrypt it to discover novel antibiotics?

http://news.softpedia.com/news/new-decryption-key-available-for-cry128-strain-of-crypton-ransomware-family-515363.shtml#sgal_0

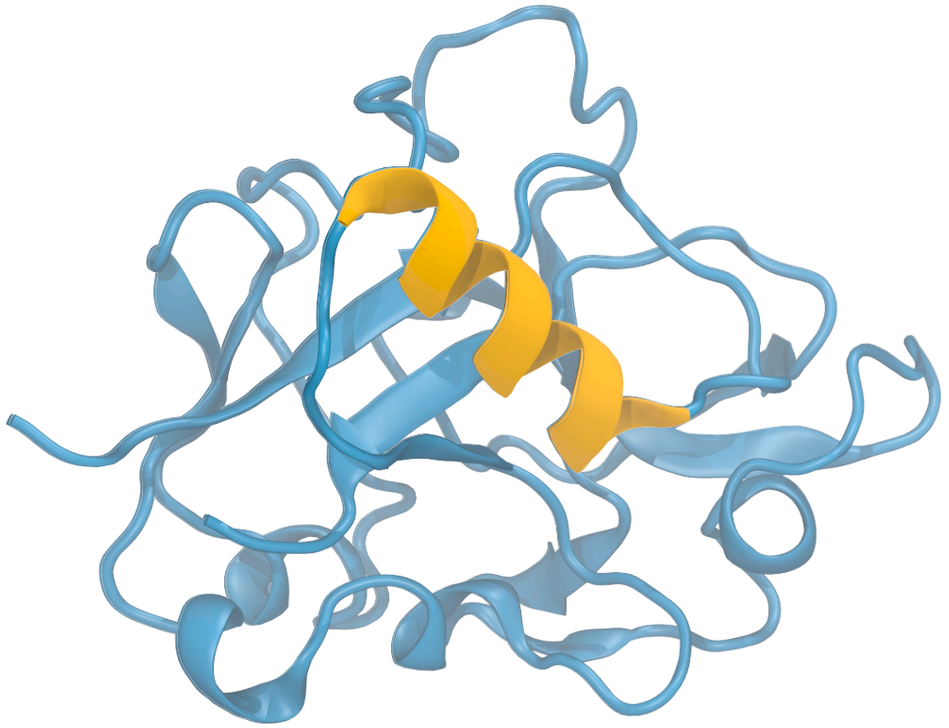
Computer-Guided Antimicrobial Discovery

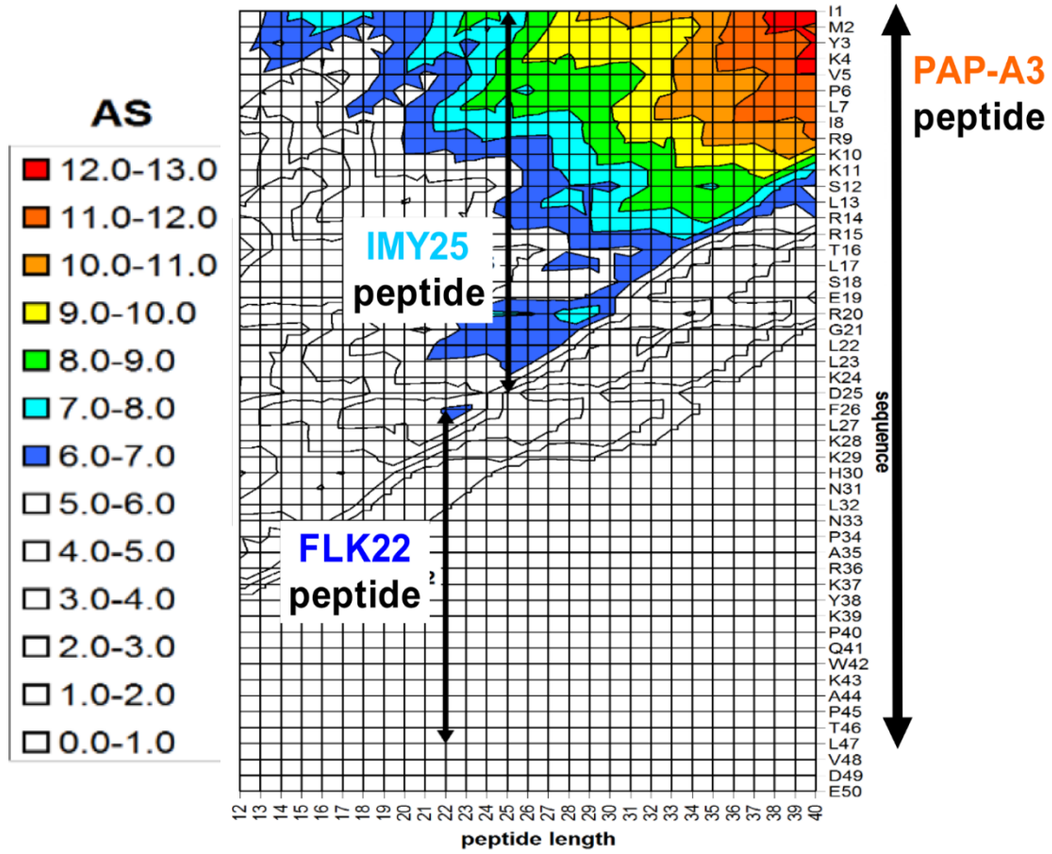
Pattern Recognition for Antibiotic Discovery?

Patterns identified based on desired target function

Computer-Guided Antimicrobial Discovery

$$f(x) = C^m H^n L$$

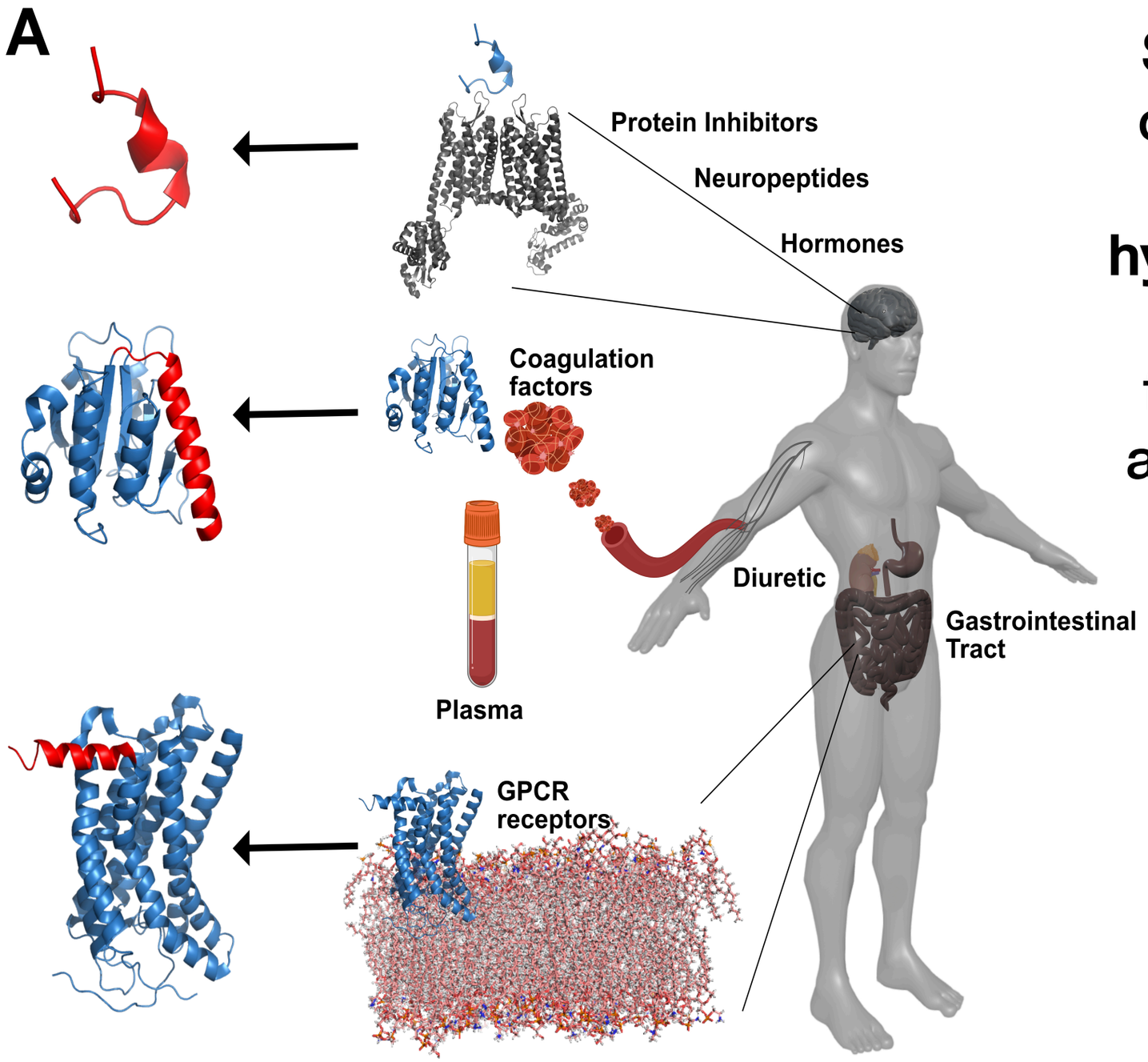




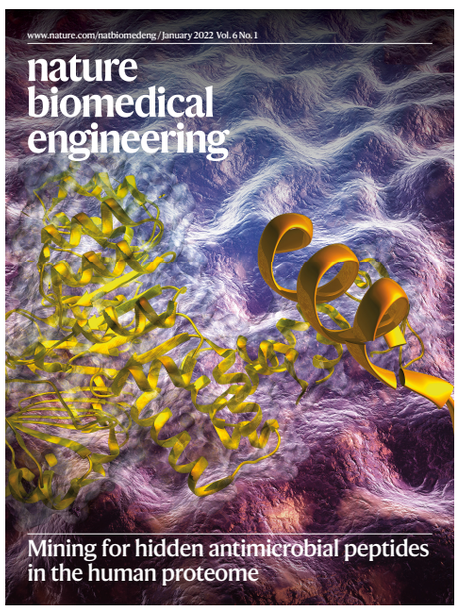
ACS Synthetic Biology, 2018, 7:2105-2115.

Computer-Guided Antimicrobial Discovery

Antibiotics hidden in the human proteome

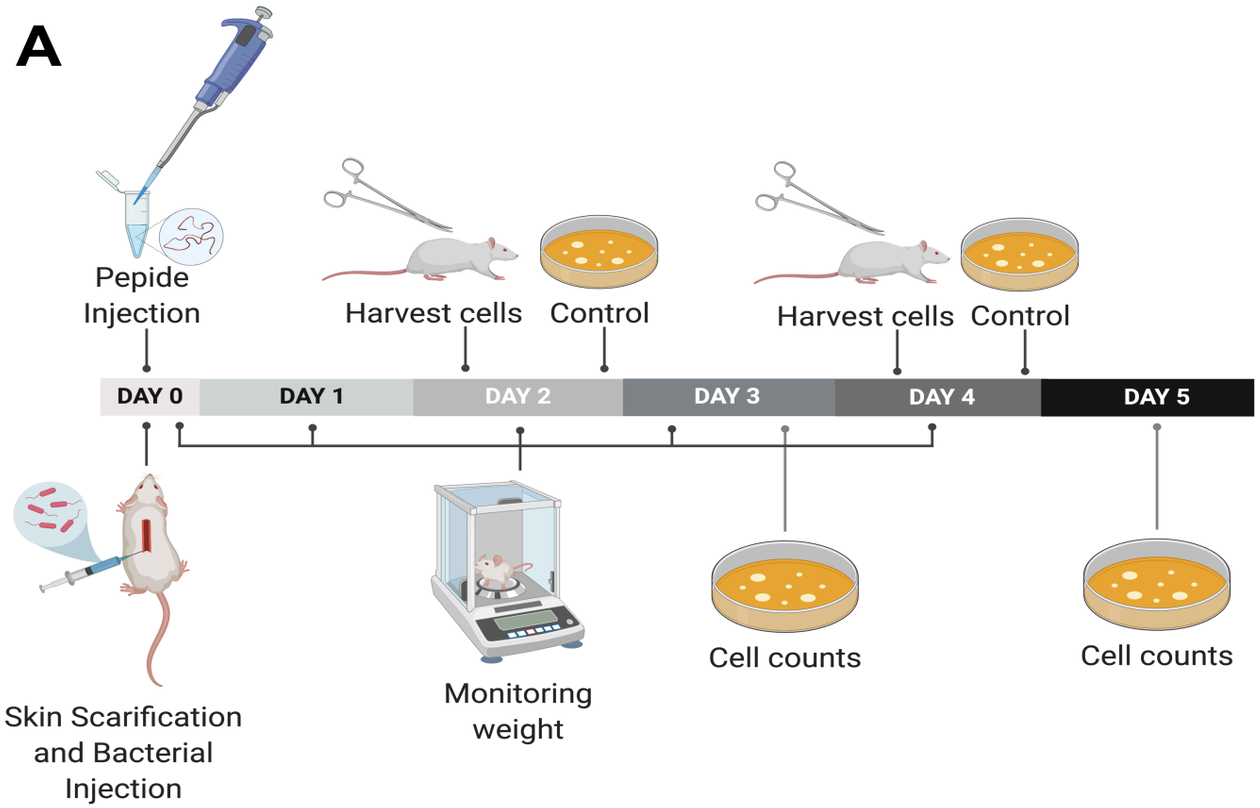


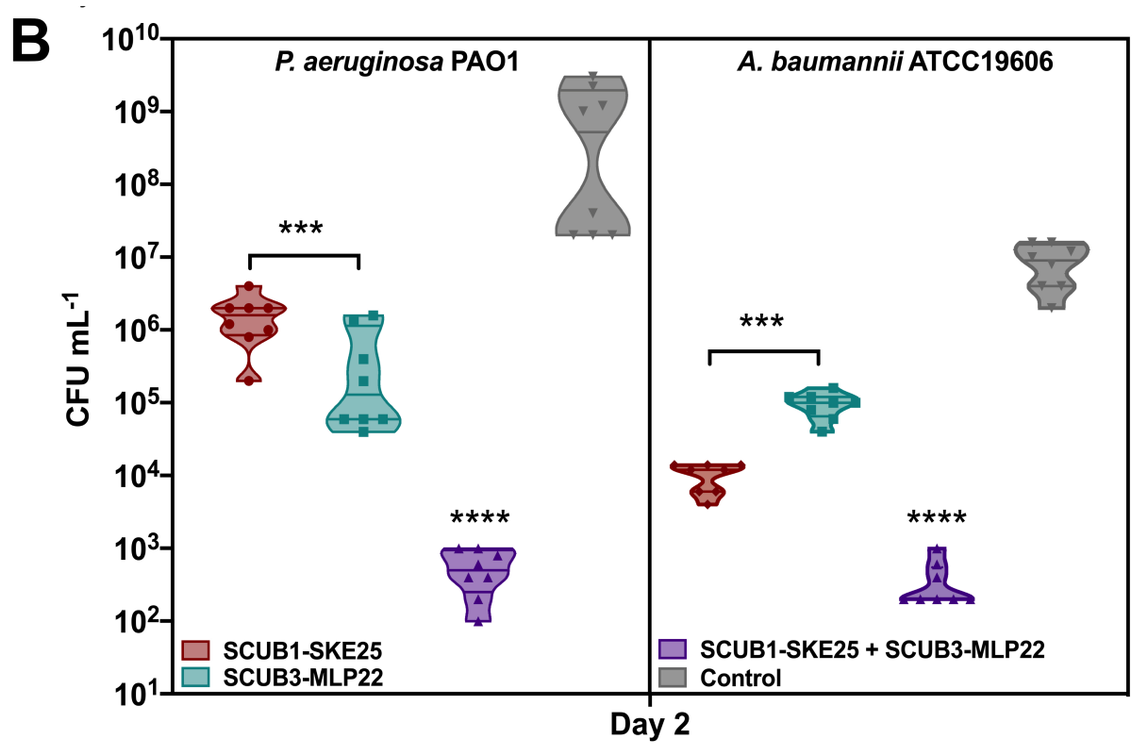
Search algorithm based on sequence **length, net charge** and **average hydrophobic** residues was integrated into fitness function that selects for antimicrobial sequences.



Nature Biomedical Engineering, 2022

Computer-Guided Antimicrobial Discovery





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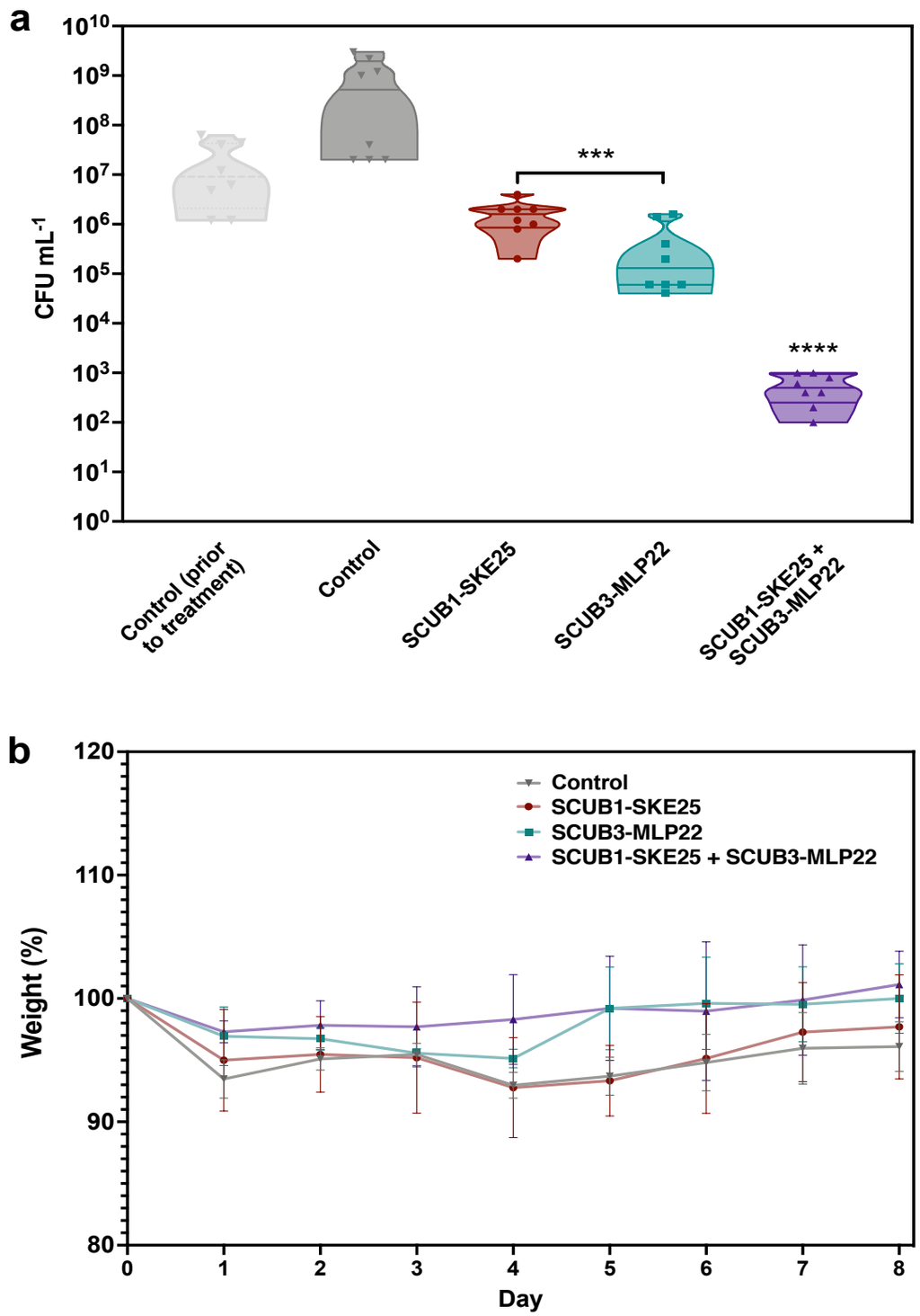

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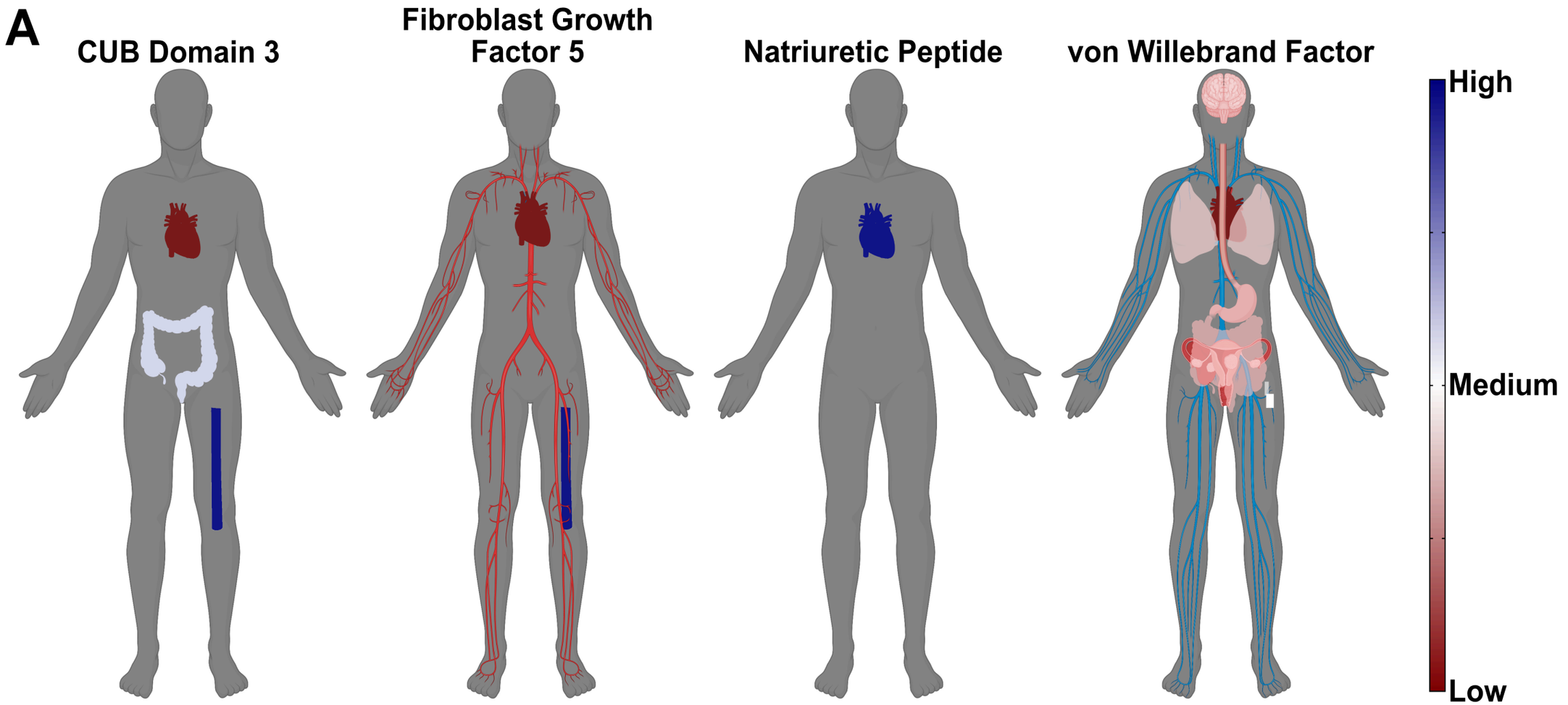

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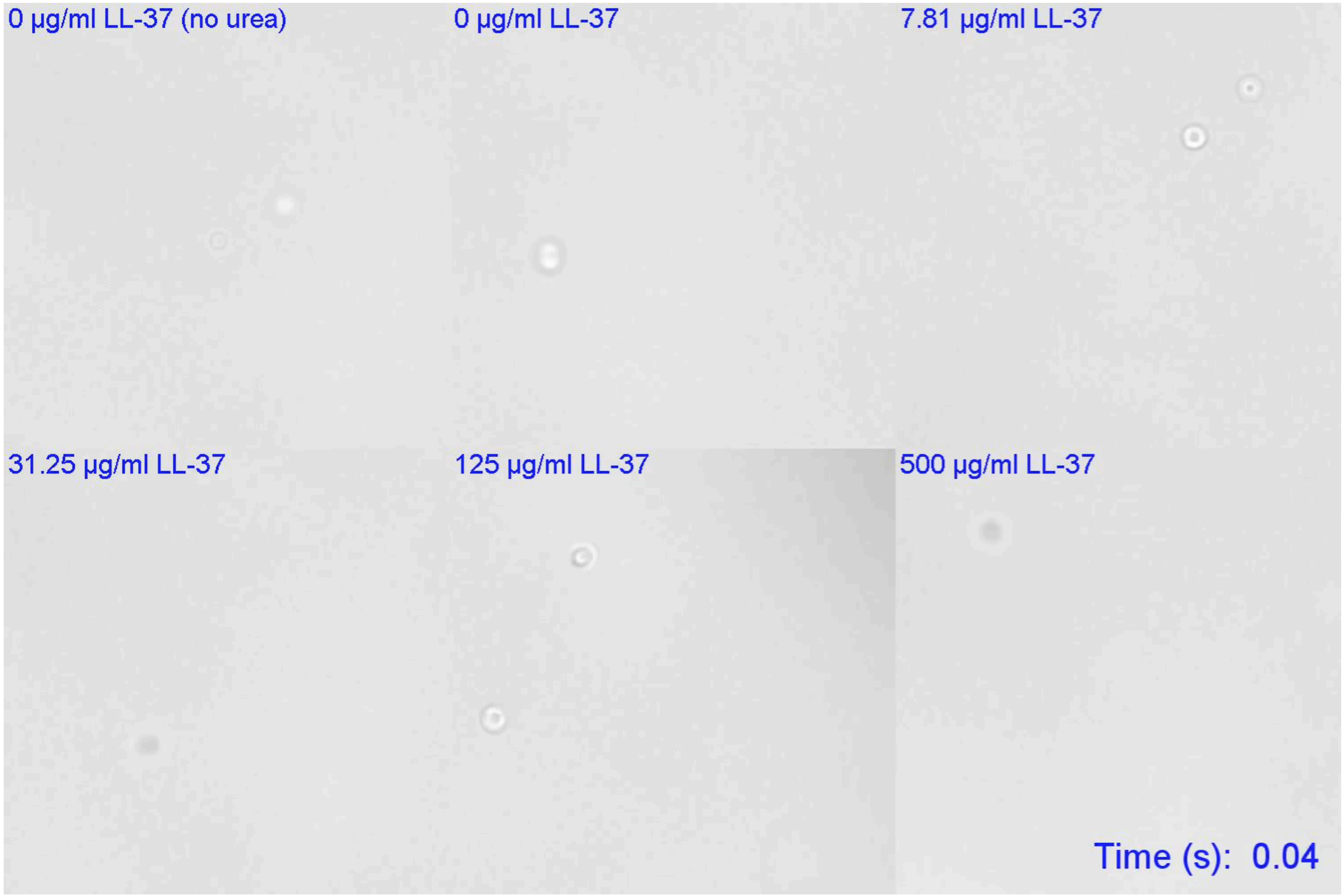

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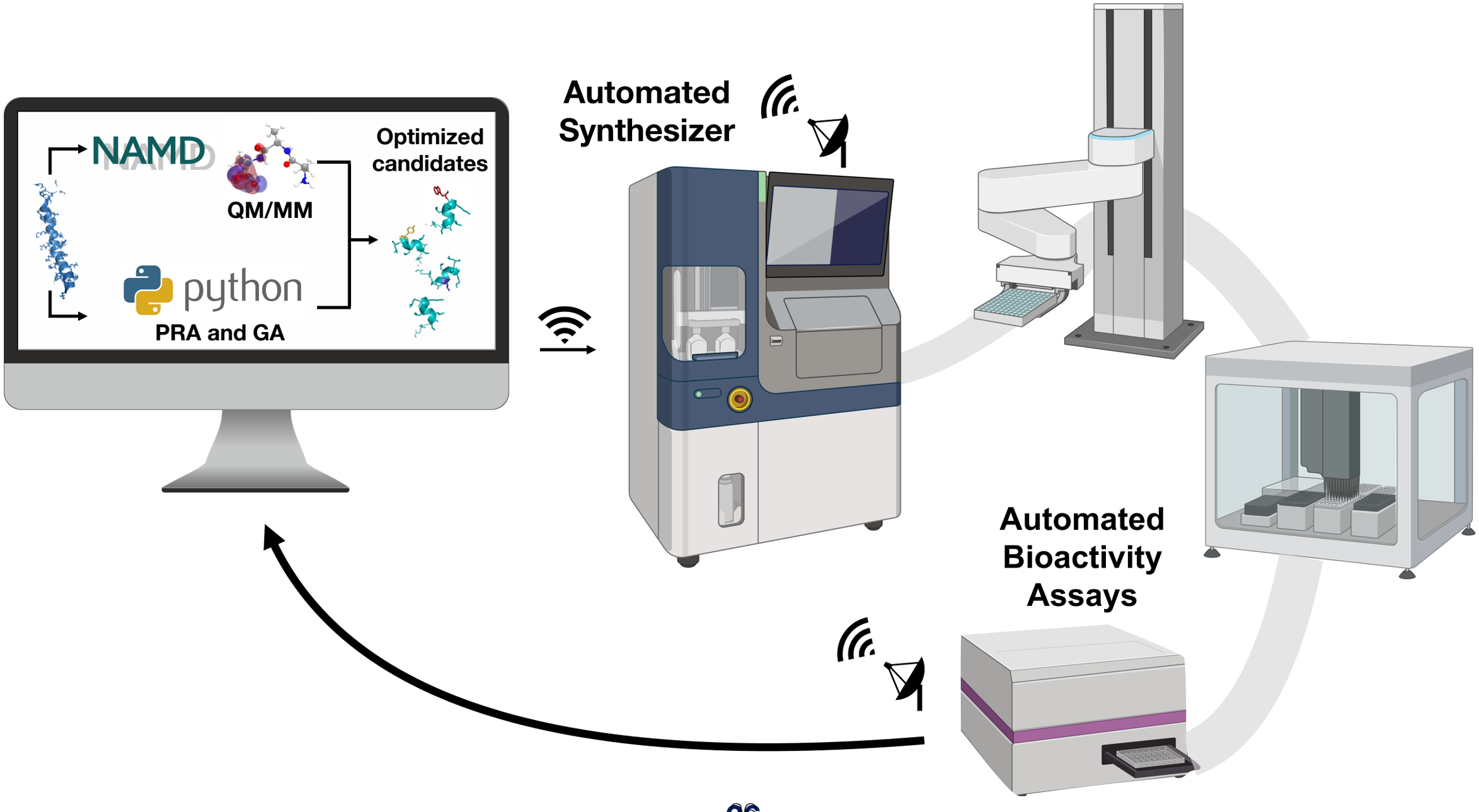

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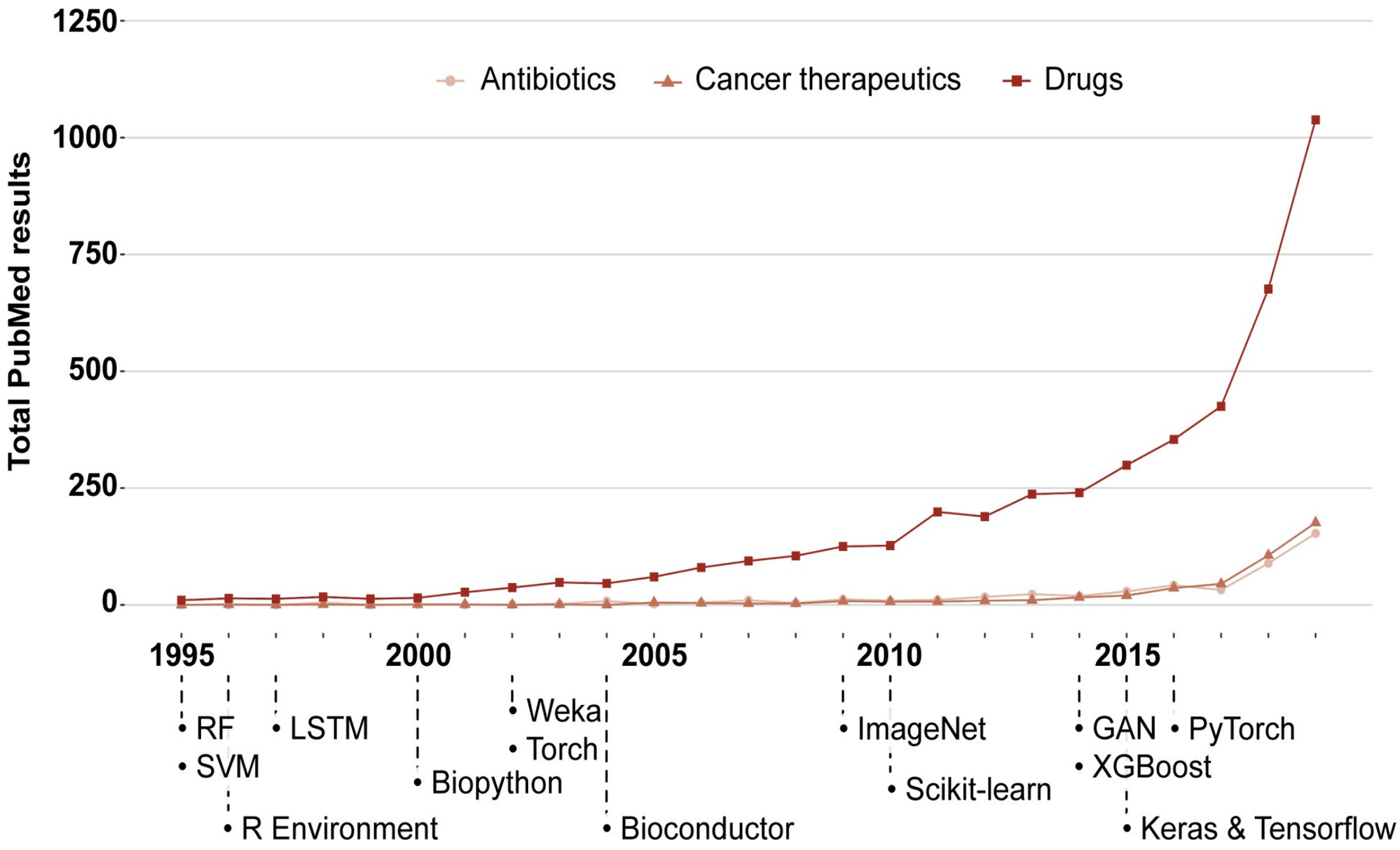

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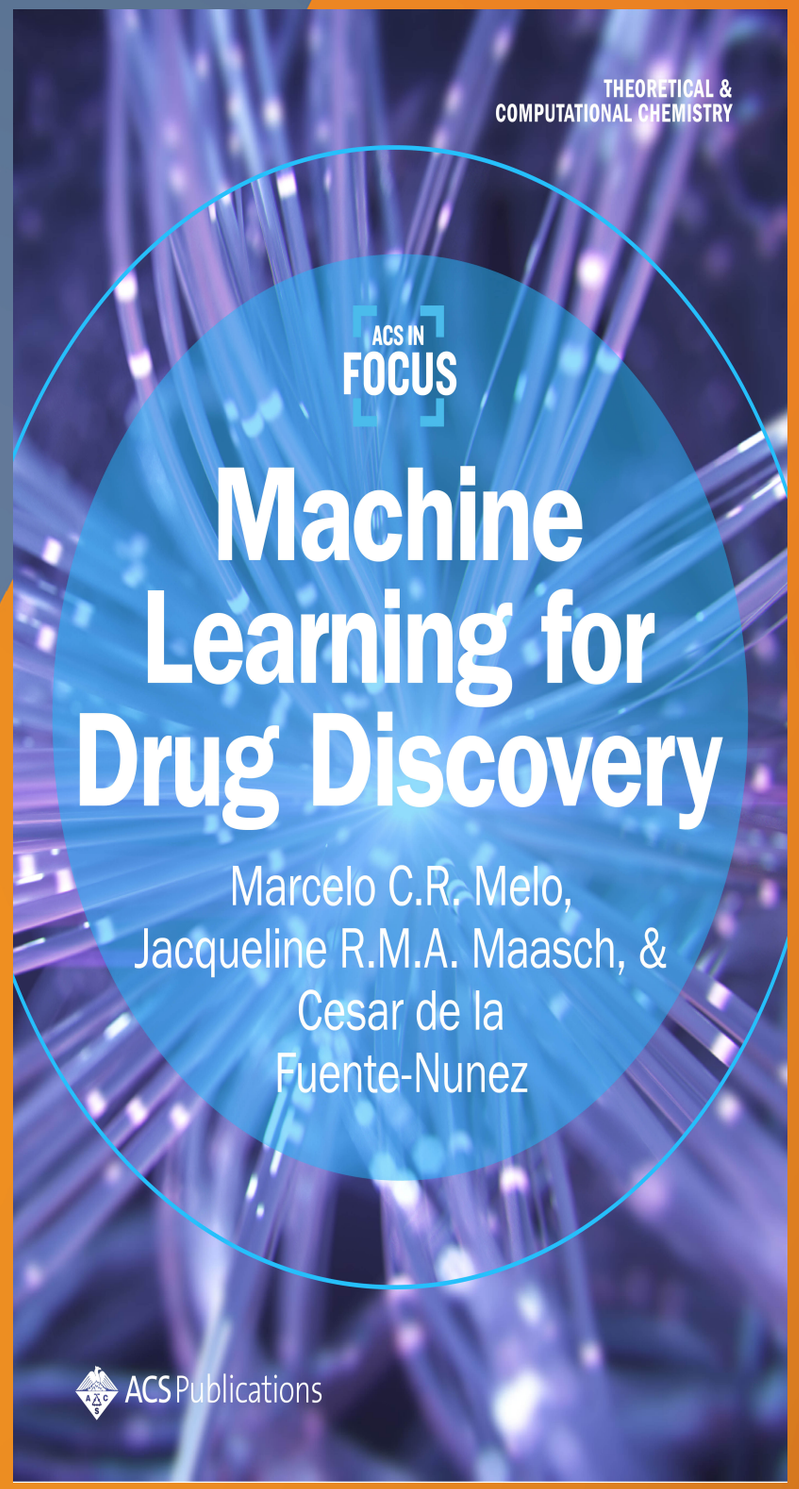

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