Treatment Options for Carbapenem Resistance AND Antimicrobial Peptide Design with AI

Önder Ergönül	SoM, Infectious Diseases and Clinical Microbiology
Füsun Can	SoM, Medical Microbiology
Anı Akpınar	KUISCID, Molecular Biology and Genetics
Özlem Keskin	CE, Chemical&Biological Engineering
Attila Gürsoy	CE,Computer Engineering
Alireza Noroozi	CE, Computer Engineering

Koç University

Fig. 2. Pathogens prioritized in the 2024 BPPL update as compared with the 2017 BPPL

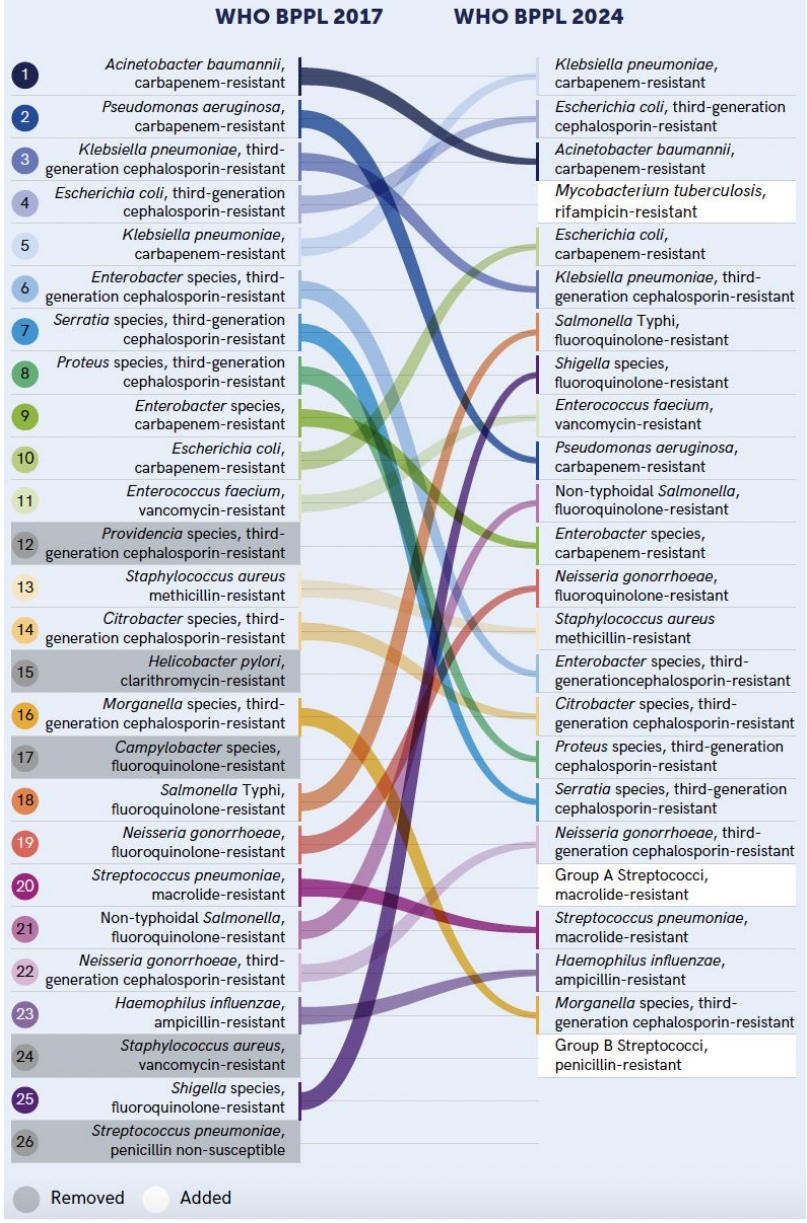
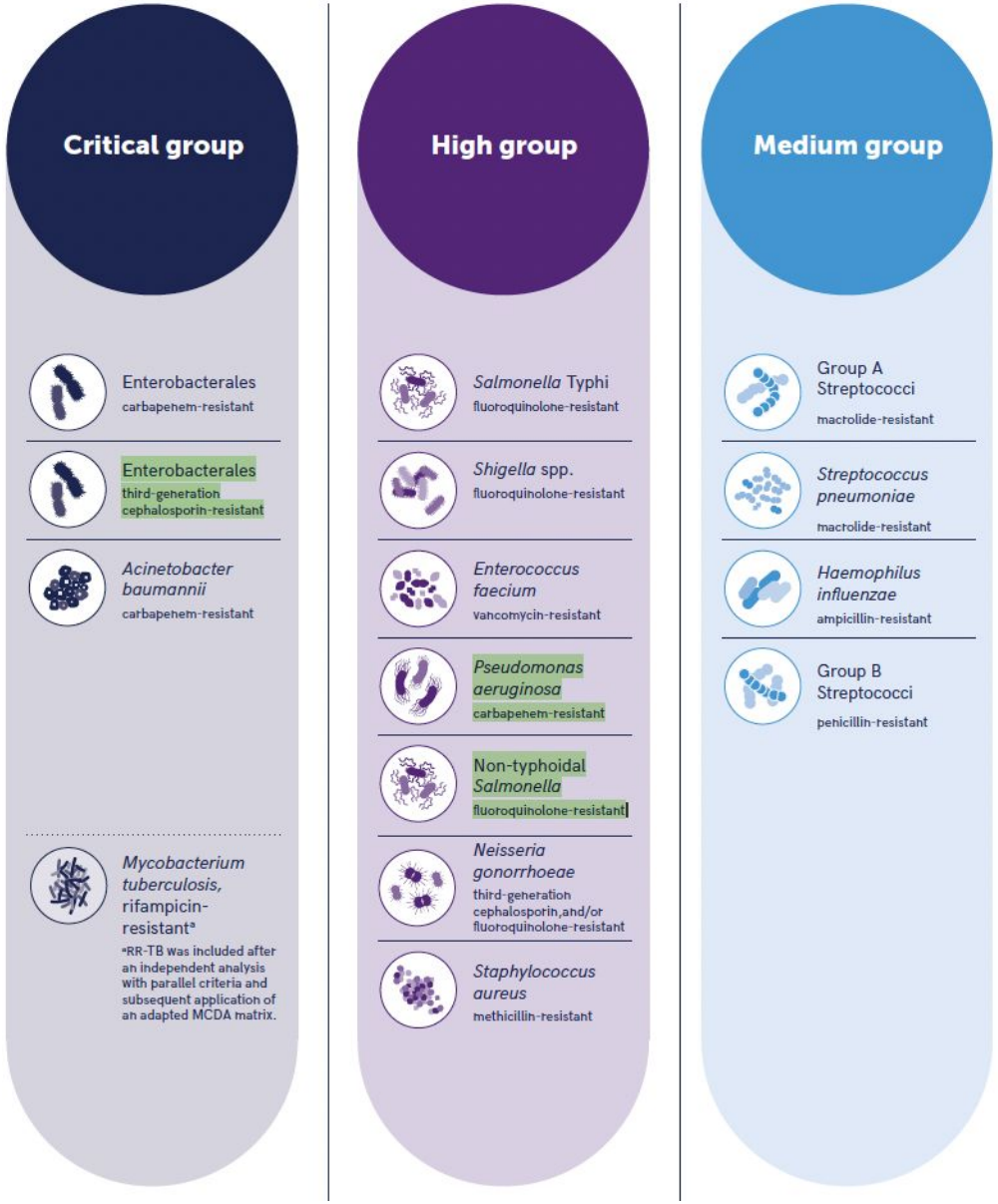
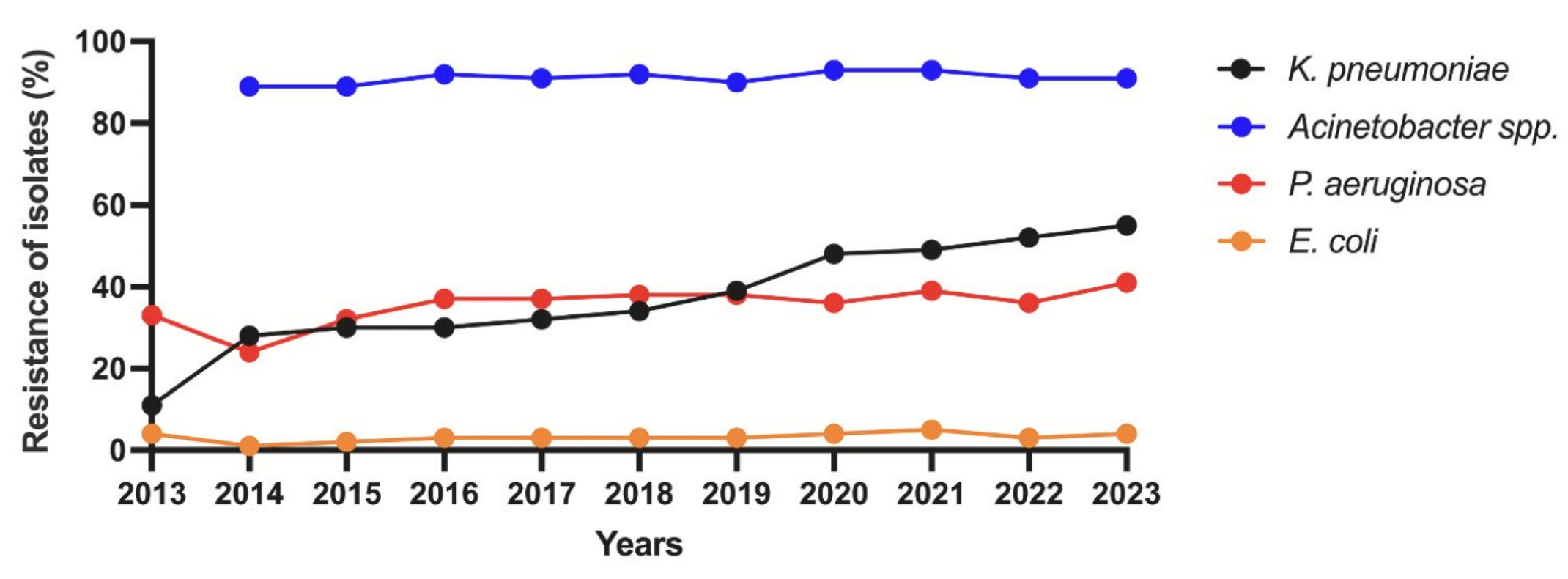


Fig 4. WHO Bacterial Priority Pathogens List, 2024



Increasing Antimicrobial Resistance in Türkiye



Alhan Ö, Özger HS, Karatuna O, Azap ÖK, Madran B, Keske Ş, Çınar G, Akdemir İ, Ergönül Ö. Antibiotic resistance in Türkiye: what has been done and what needs to be done urgently? Clin Microbiol Infect. 2025

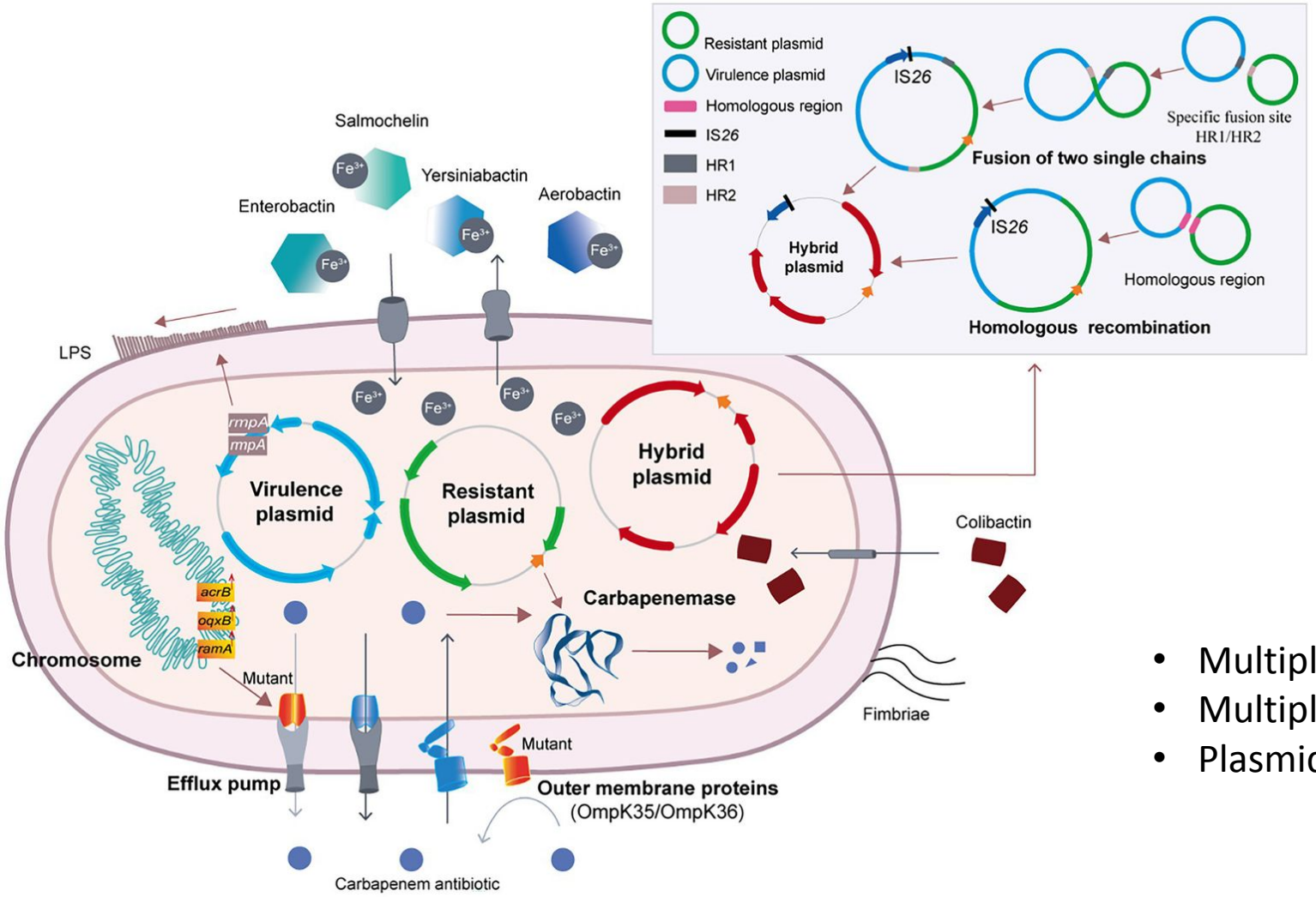
Nightmare Scenario
High resistance + hypervirulence

These strains combine:

- **Carbapenem resistance** (e.g., *blaKPC*, *blaNDM*, *blaOXA-48*)
- **Hypervirulence genes** (e.g., *rmpA*, *iucA*, *ybtA*)

This makes them both harder to treat and more capable of causing severe, rapidly progressing infections.

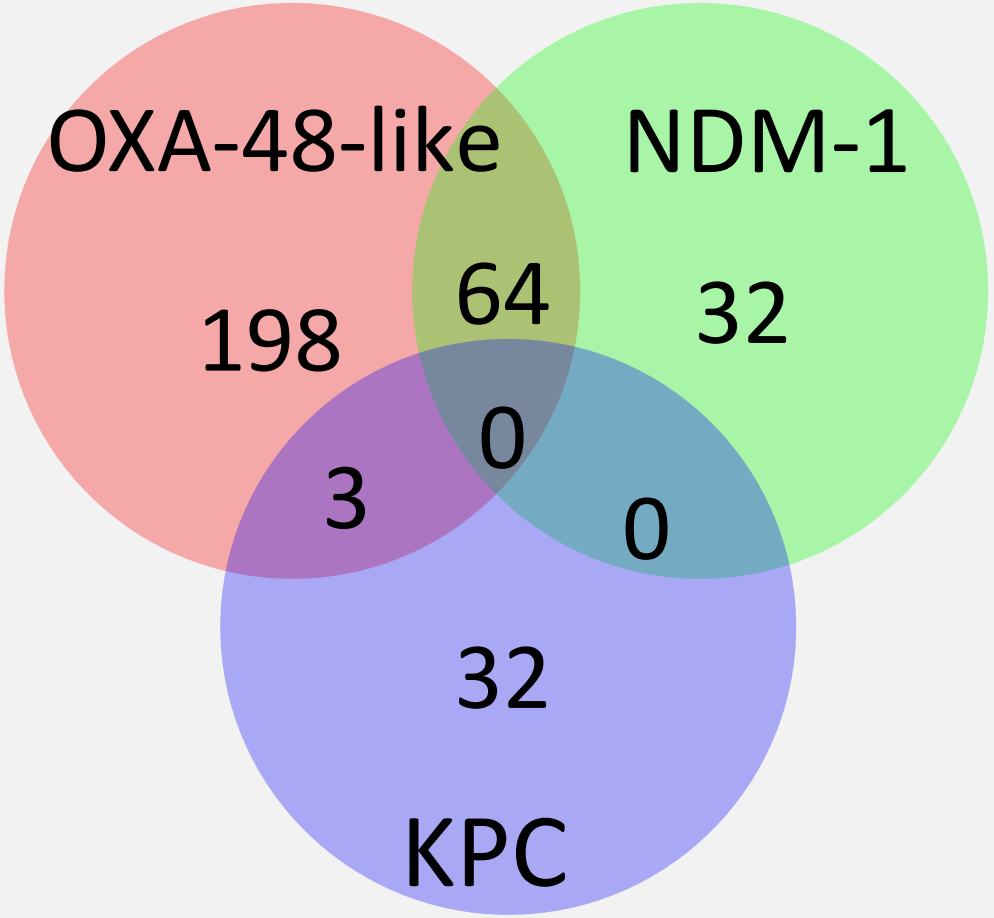
Carbapenem-resistant *Klebsiella pneumoniae* is a global threat



(Han et al., 2022, Front Microbiol)

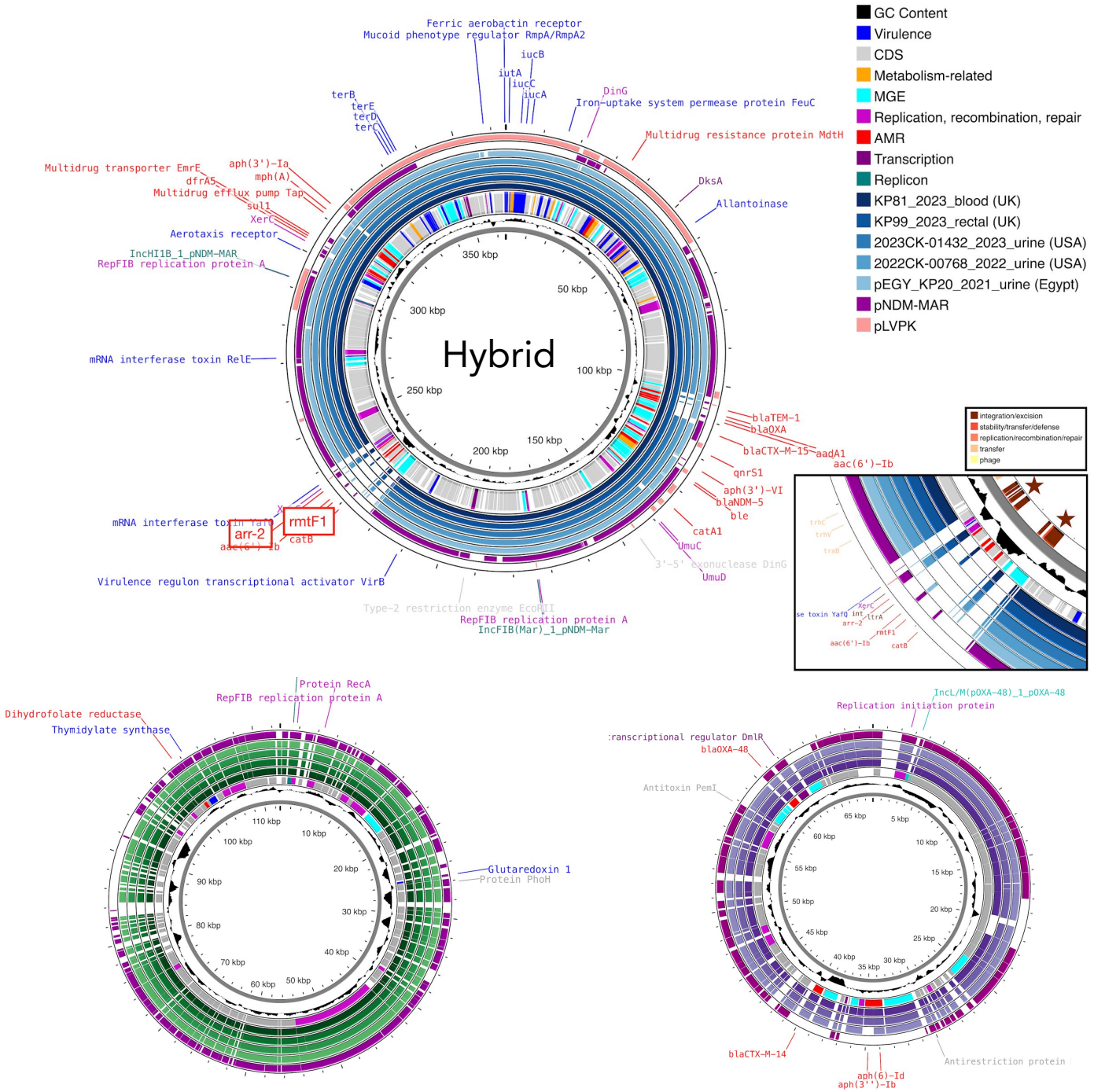
- Multiple virulence factors
- Multiple antibiotic resistance mechanisms
- Plasmids for transfers

Molecular Features of Carbapenem Resistant *Klebsiella pneumoniae*, n=427



Specific subtype, ST147, is disseminating in Türkiye that carries a hybrid plasmid with multiple virulence and AMR factors, including NDM-5

All in a single isolate!



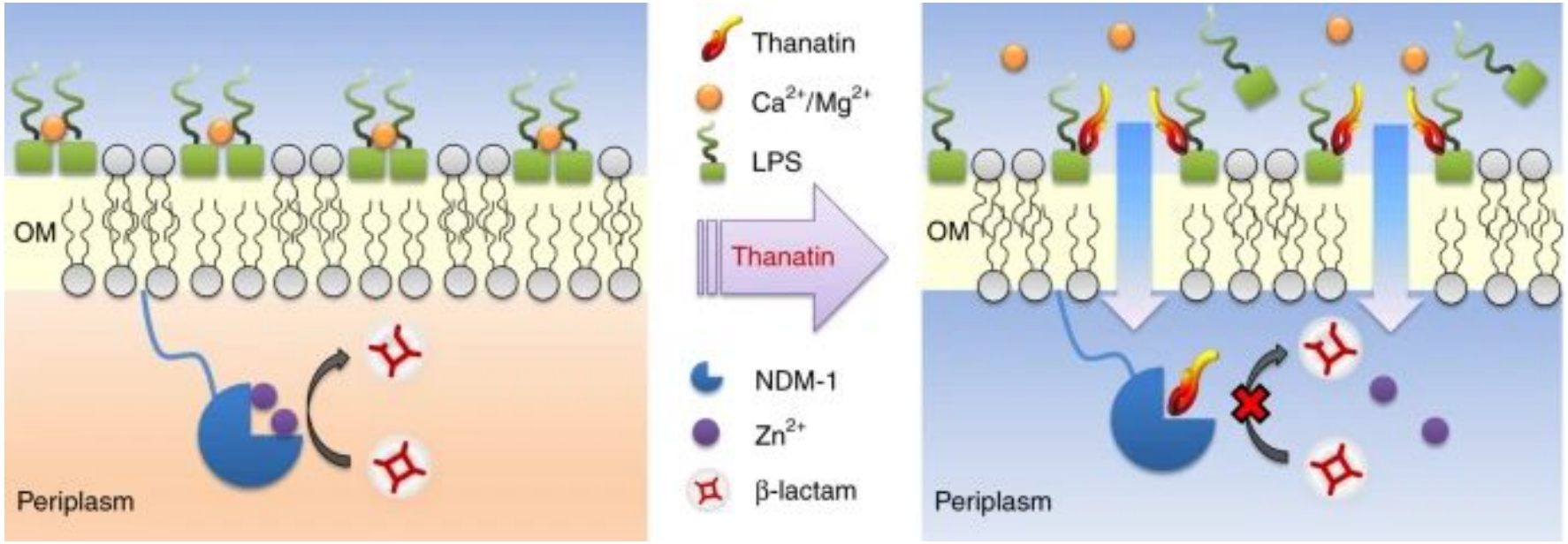
Antimicrobial Peptides (AMP)

- short peptides made by many organisms, including humans, animals, plants, and microbes
- 10-50 amino acids
- they can act against drug-resistant bacteria

LL-37 *human cathelicidin*

LLGDFFRKSKEKIGKEFKRI
VQRIKDFLRNLVPRTES

PDB 2K6O • α-helical amphipathic peptide



Bo Ma et al., *Nature Communications* **volume 10**,(2019)

spined soldier bug

GMTEYKLVVVGAVGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGET
CLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIK
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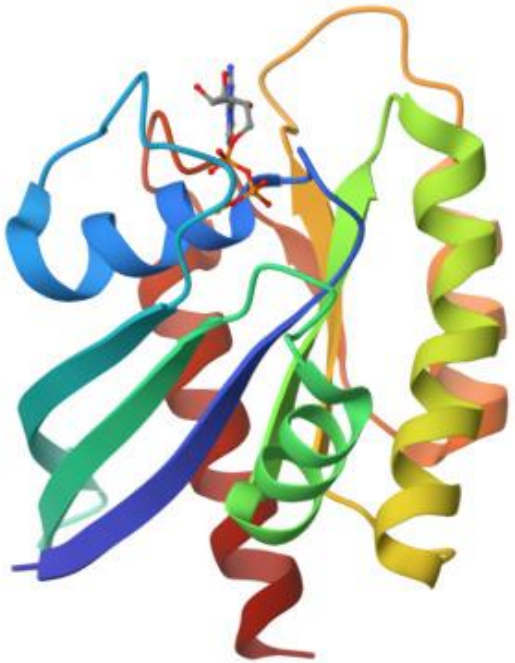
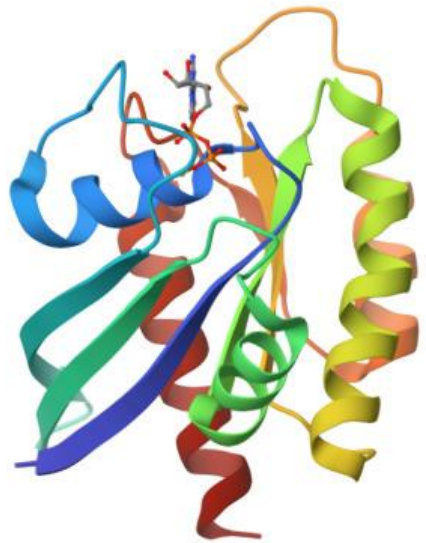
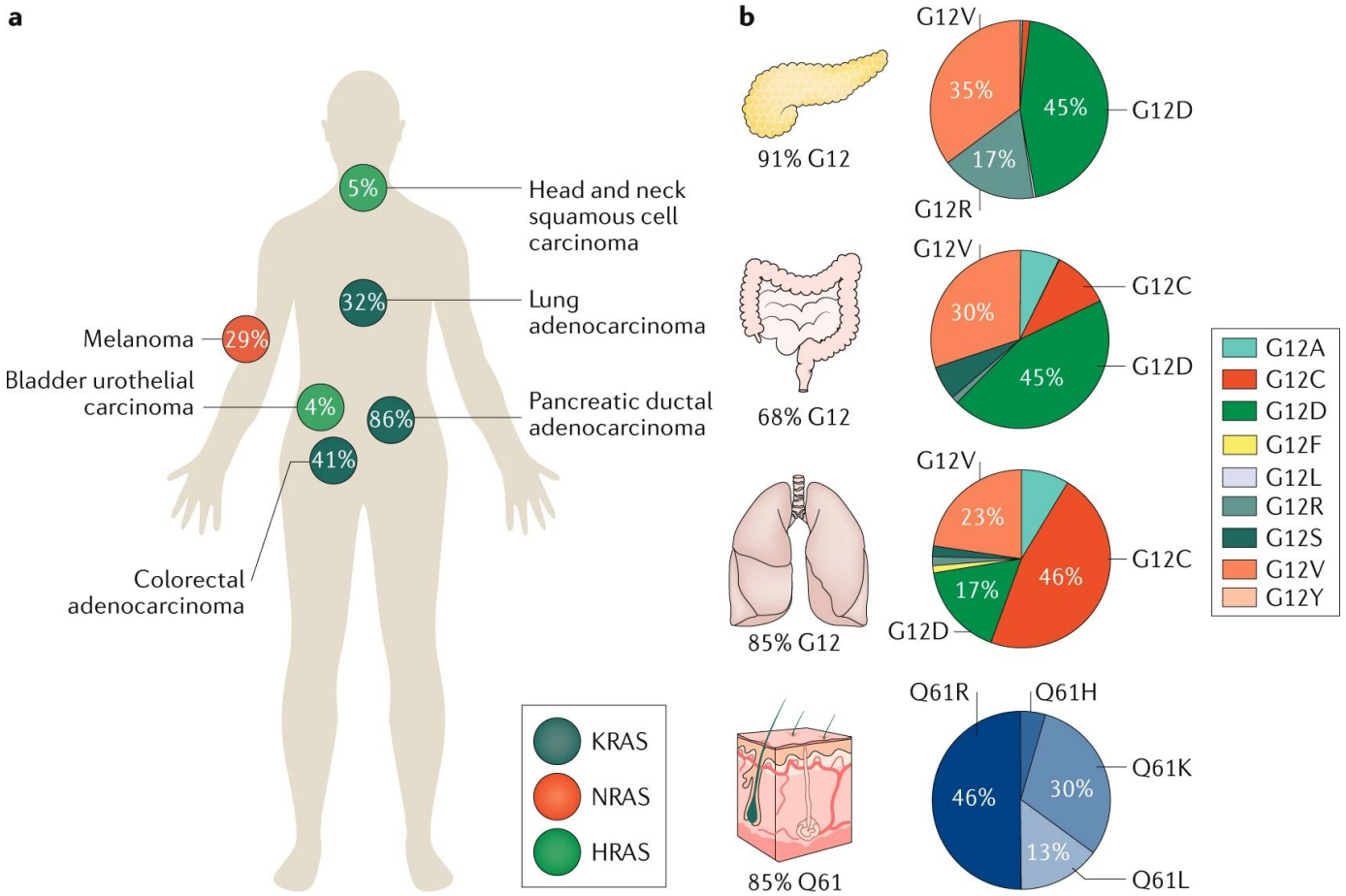
VDDAFYTLVREIRKHKE



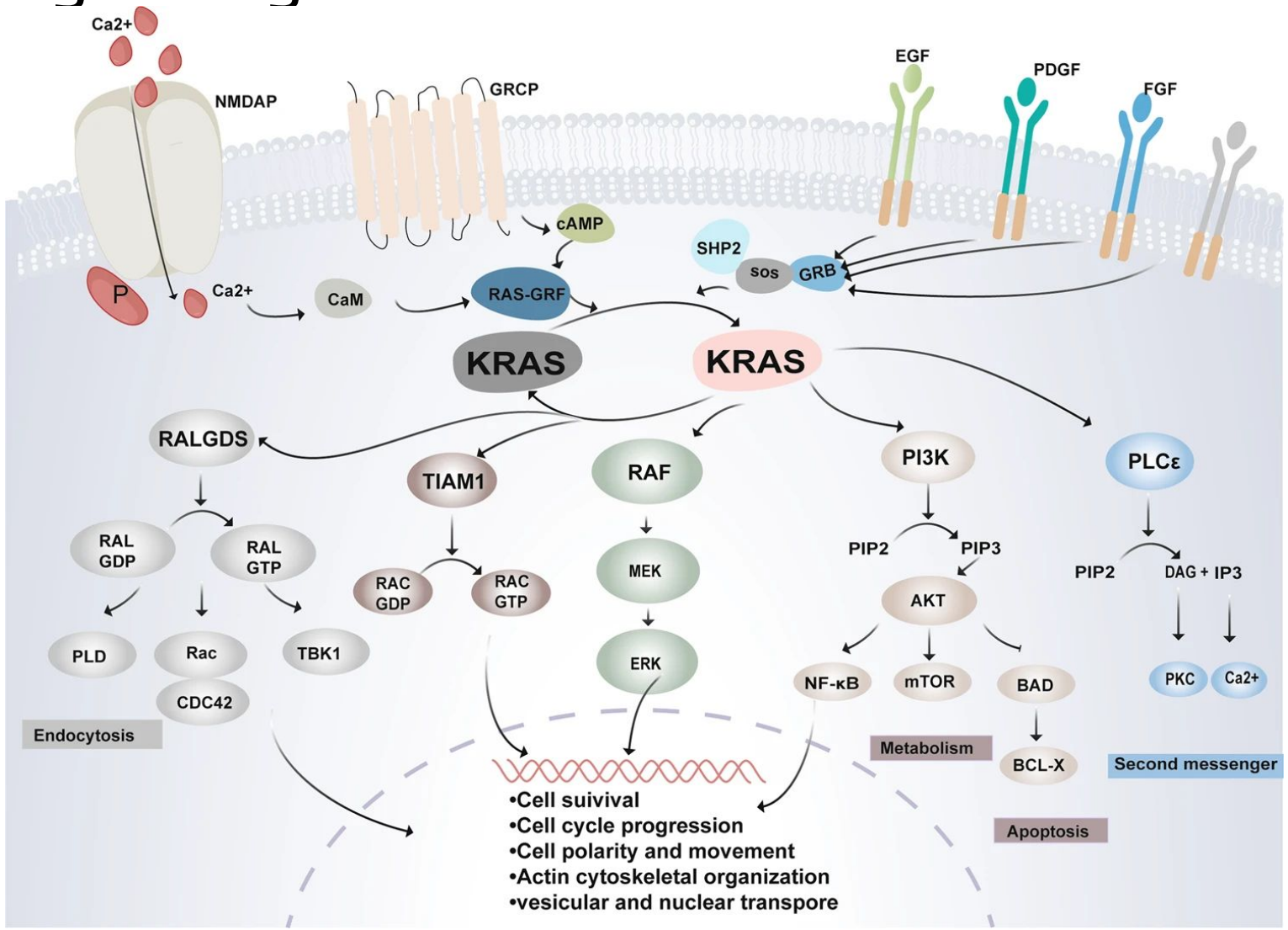
KRAS – most mutated protein in cancer





Moore, A.R., Rosenberg, S.C., McCormick, F. *et al.* RAS-targeted therapies: is the undruggable drugged?. *Nat Rev Drug Discov* **19**, 533–552 (2020)

KRAS signalling

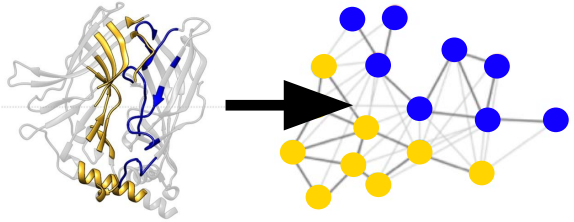


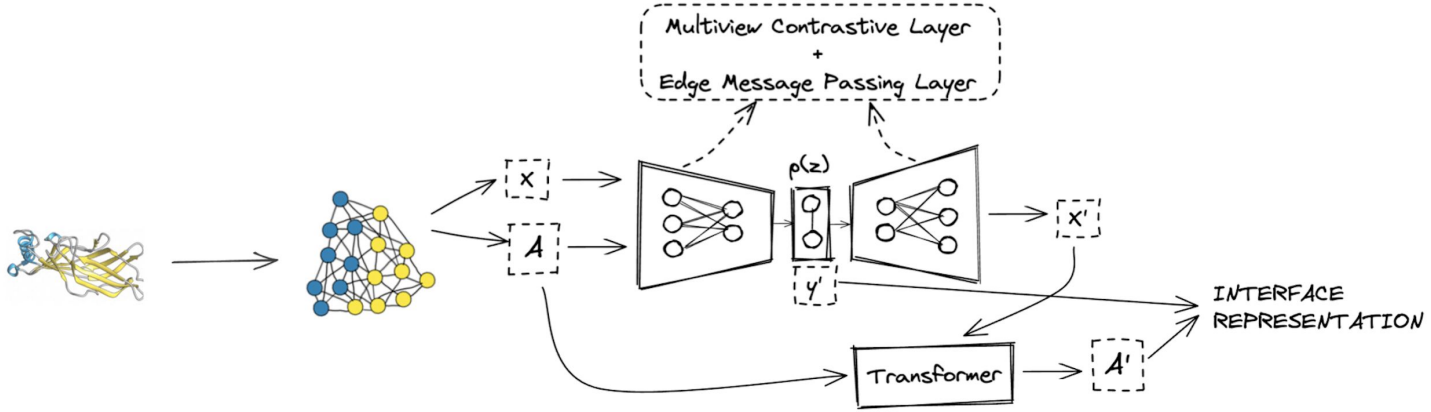
Signal Transduction and Targeted Therapy (*Sig Transduct Target Ther*)

http://www.cellsignal.com

Multiview Contrastive Representation Learning and Protein-Protein Interaction Prediction

- *Nodes:* residue type, polarity, residue charge, relative ASA, PP, backbone dihedral angles - Phi (φ) and Psi (ψ)
- *Edges:*
  - Sequential edges, Radius edges, K-nearest edges





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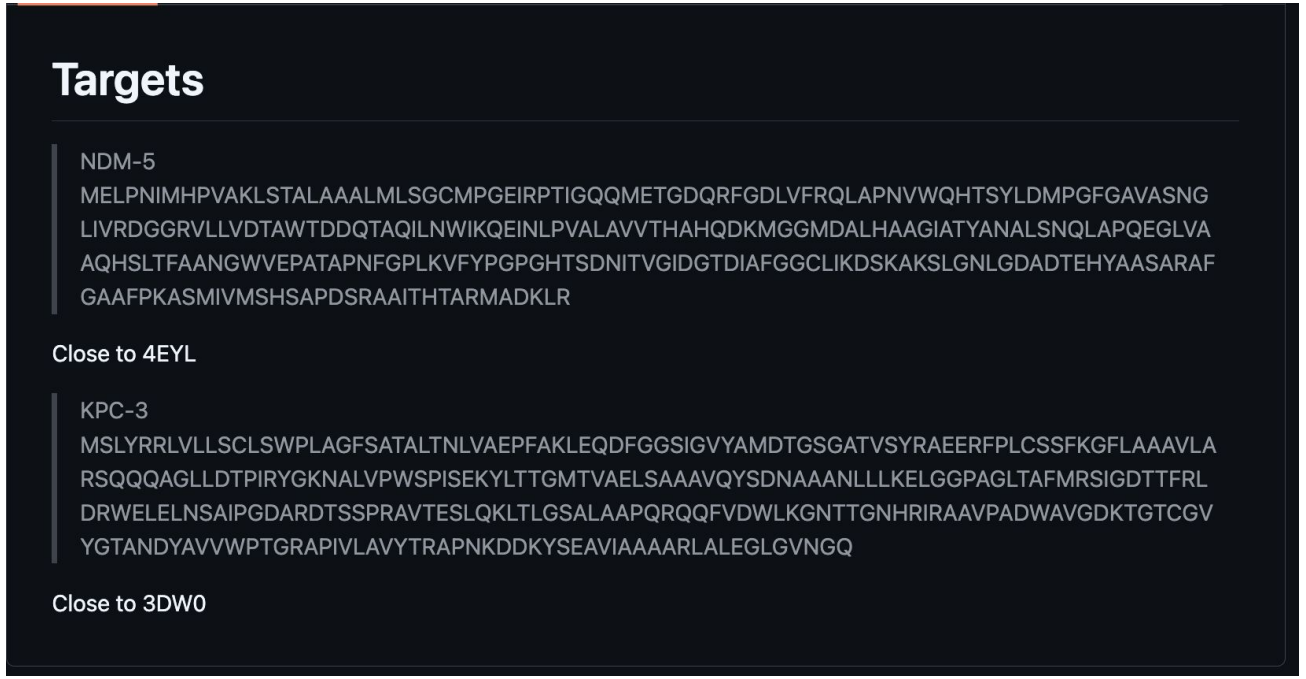
MACHINE LEARNING AND DEEP LEARNING | March 25, 2024

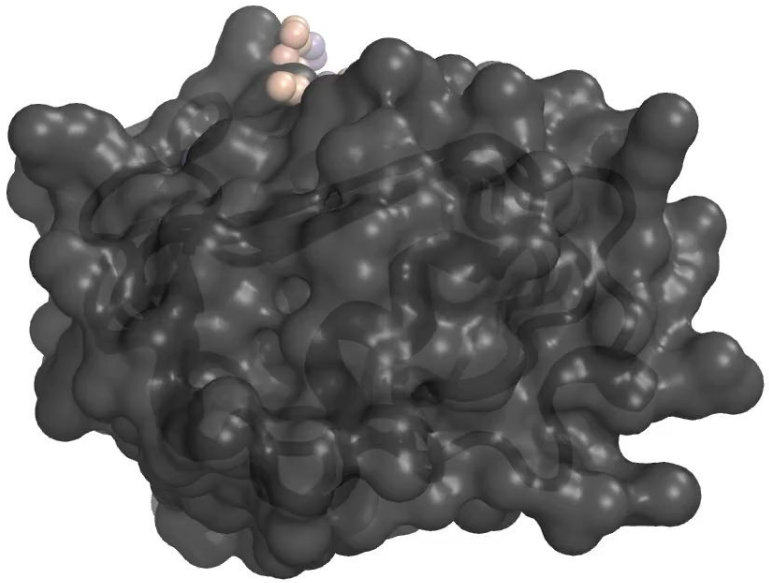
ProInterVal: Validation of Protein–Protein Interfaces through Learned Interface Representations

Damla Ovek, Ozlem Keskin, and Attila Gursoy*

Can we design target-specific AMPs using Generative AI

- Two AMR-related targets identified
  Goal: design **binders that also behave as antimicrobial peptides**
- Challenge:
  - Short peptides
  - Need high activity
  - Low toxicity
  - Good stability

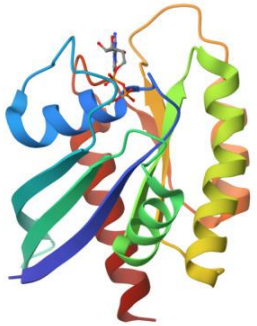


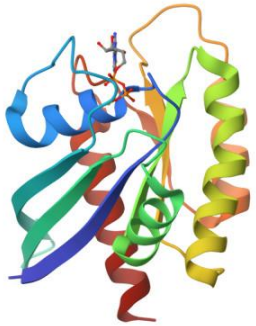


https://www.bakerlab.org/2023/07/11/diffusion-model-for-protein-design/

Protein Structure Prediction (Folding)
Protein Design (inverse folding)

GMTEYKLVVVGAVGVGKSALTIQLIQNHFV
DEYDPTIEDSYRKQVVIDGETCLLDILDTAG
QEEYSAMRDQYMRTGEGFLCVFAINNTKS
FEDIHHYREQIKRVKDSEDVPMVLVGNKC
DLPSRTVDTKQAQDLARSYGIPFIETSAKT
RQGVDDAFYTLVREIRKHKE





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FEDIHHYREQIKRVKDSEDVPMVLVGNKC
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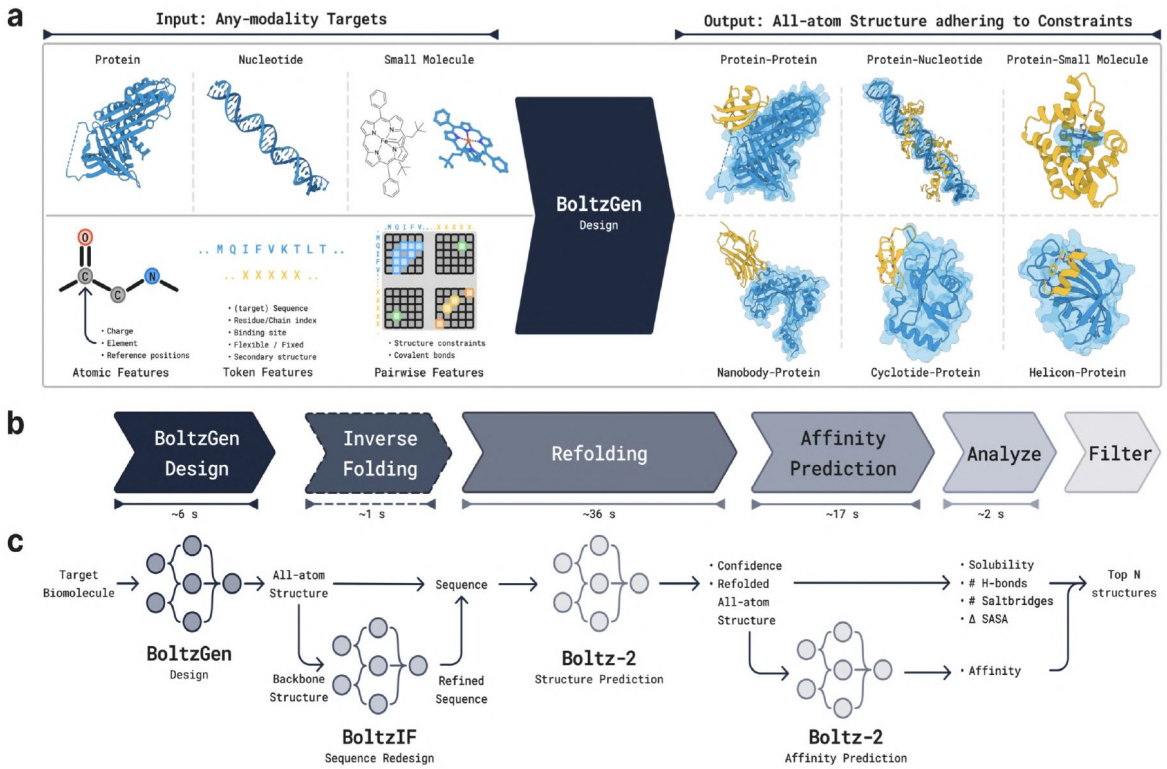
RQGVDDAFYTLVREIRKHKE

[Nobel Prize in Chemistry 2024]

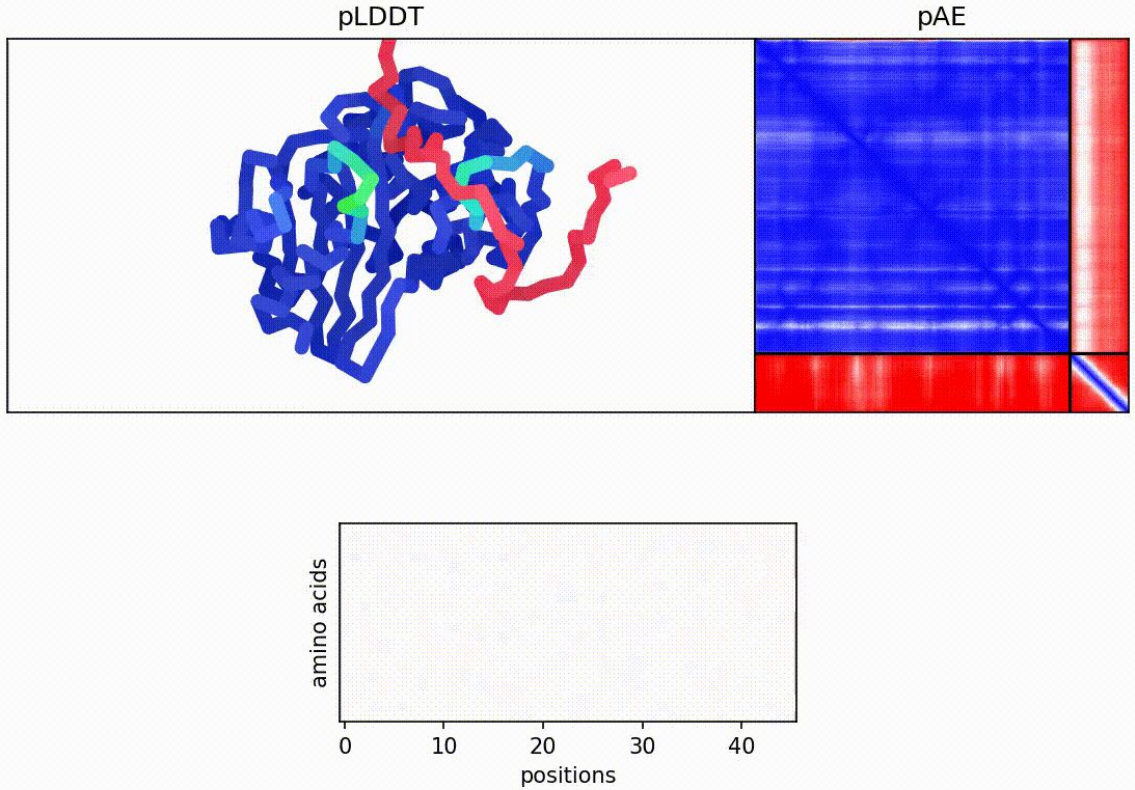
Boltzgen

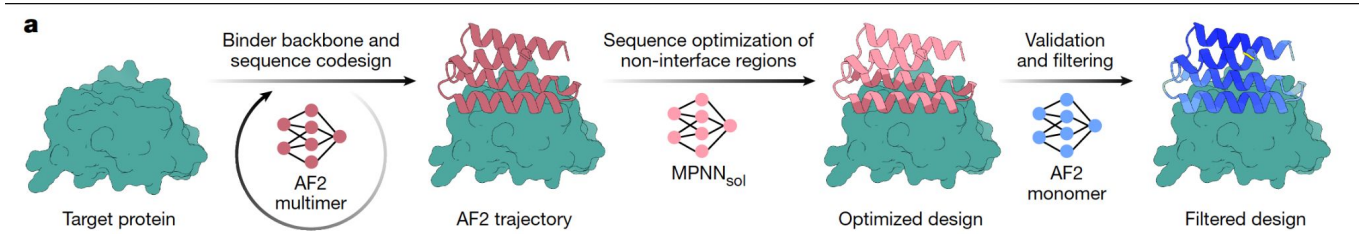
https://boltz.bio/boltzgen



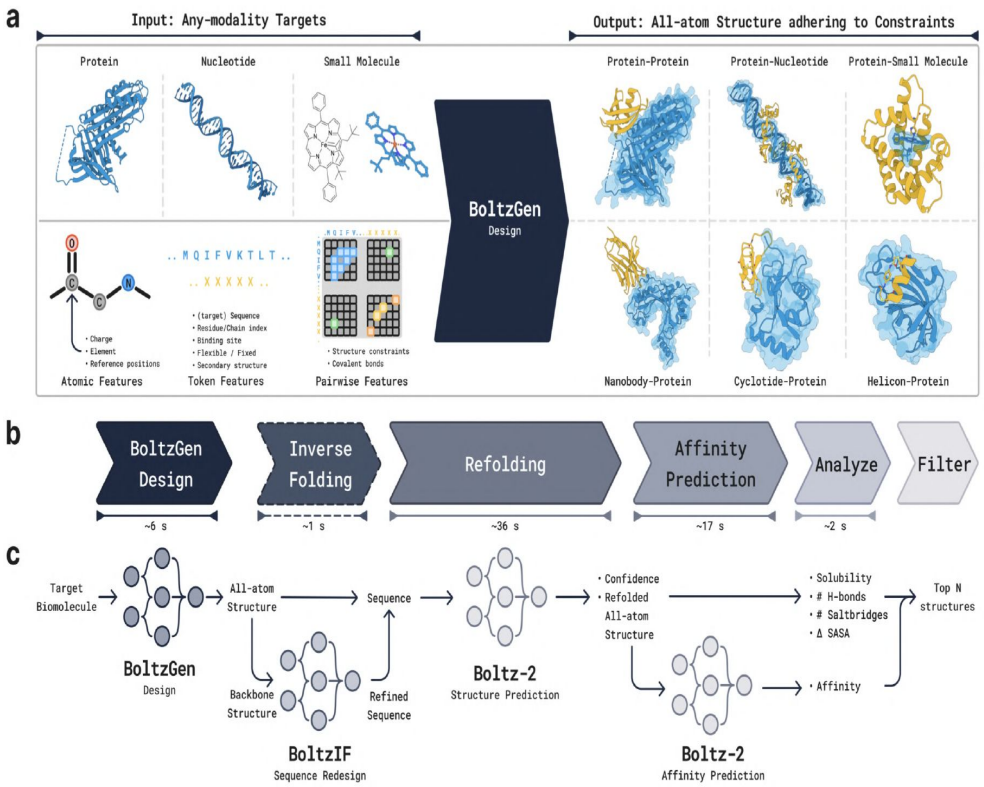
BindCraft

Nature **volume 646**, pāges483–492 (2025)





Can we use protein design pipelines for AMP design



SoTA Protein Design

Design approach

Use boltzgen to design binders with targets

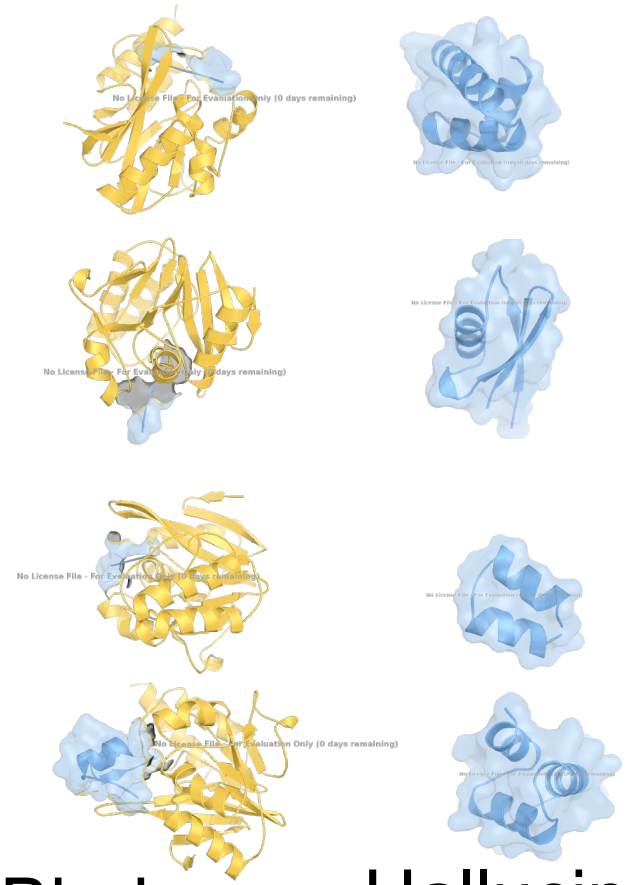
- Filter by Toxin, Macrel, AMPScanner.

Hallucination

Without targets

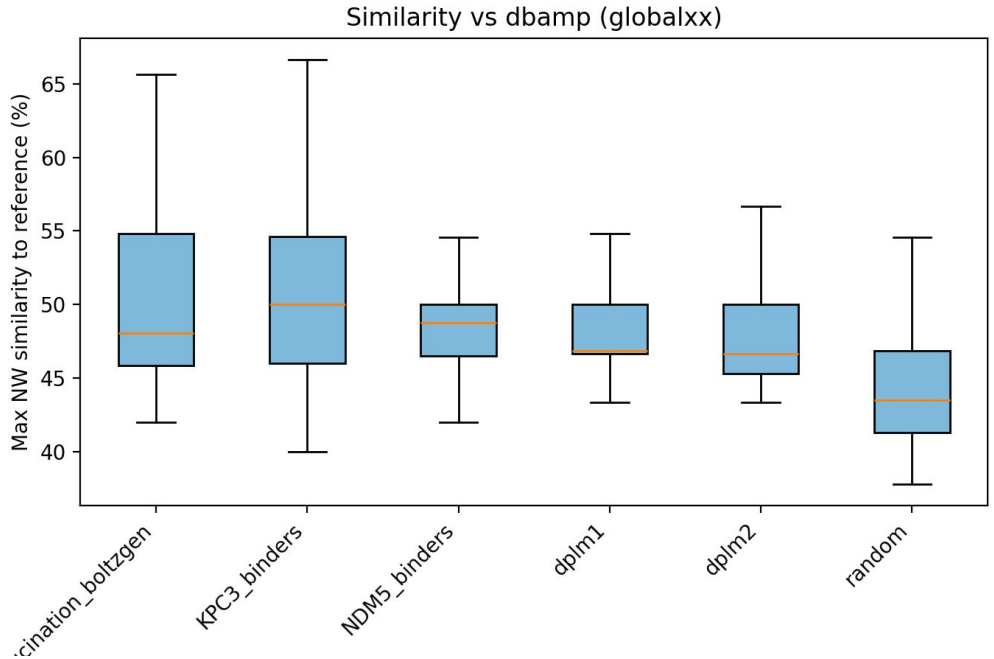
- Input xxxxxxxx to get AMPs.
- Run boltz2, Af2 to get affinity bindings to specific target(NDM).
- Filter by Toxin, Macrel, AMPScanner.

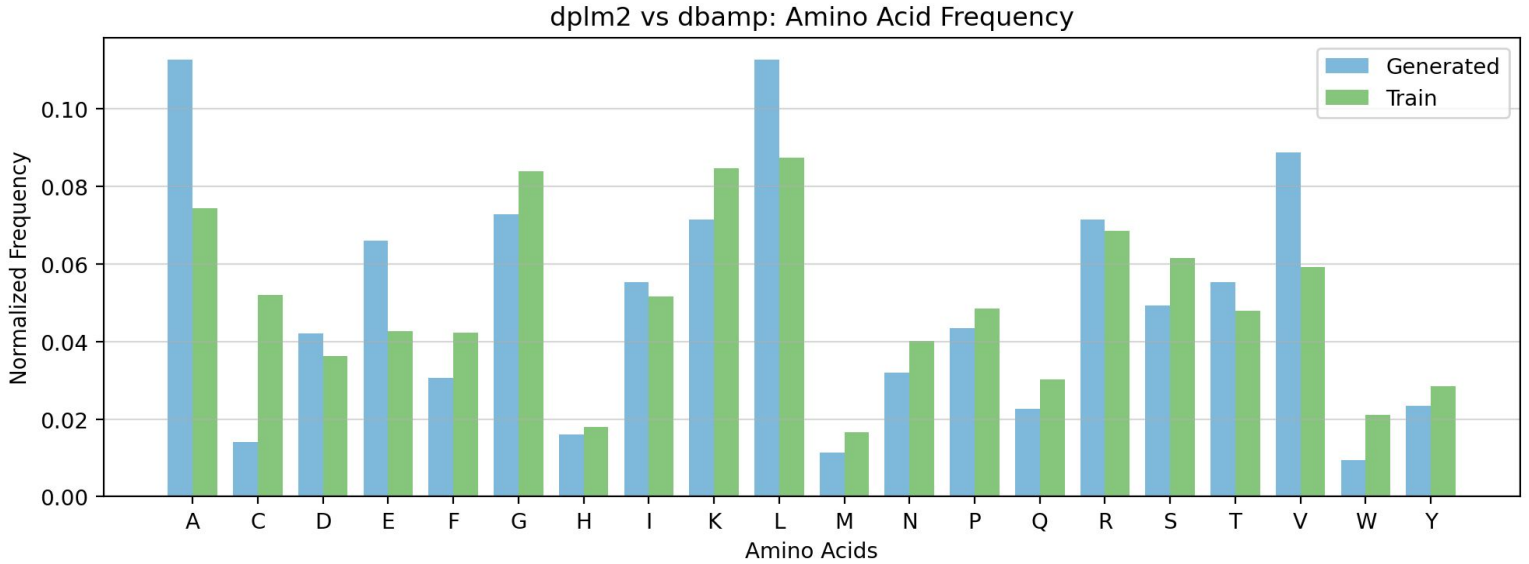
With targets – less AMP like, better binding
Without targets – more AMP like, worse binding



Binders

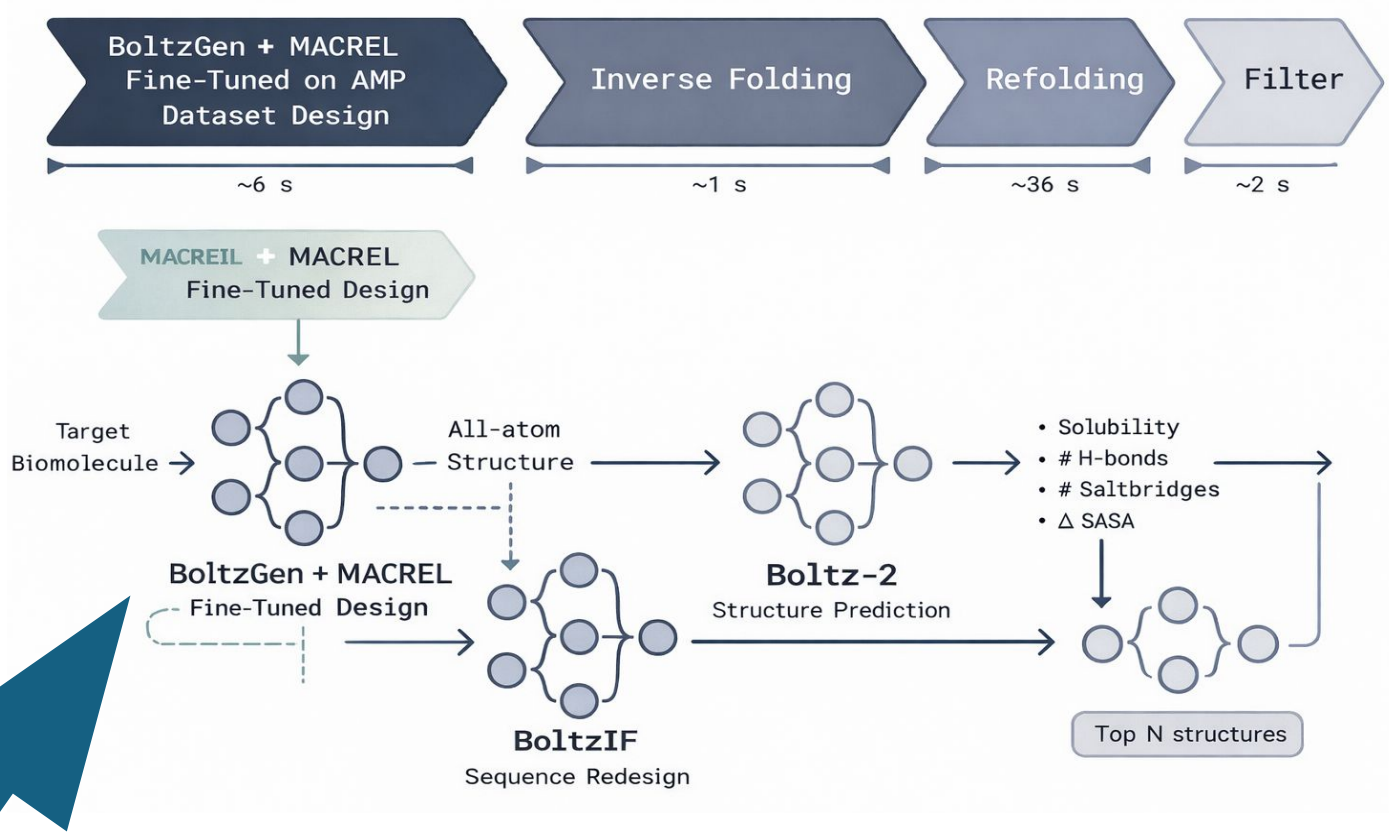
Hallucinations

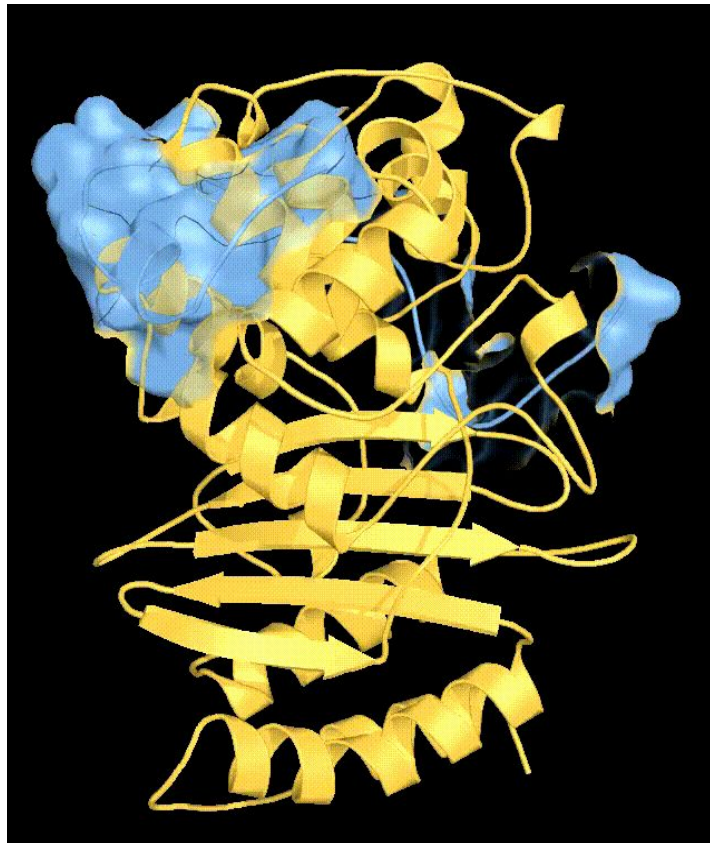




New AMP Design Pipeline:

- Conditioned generation using AMP classifiers (MACREL)
- Generated binders under AMP-activity constraints





Team

Fusün Can, SOM

Önder Ergönül SOM

Alireza Noroozi, MS student CE

Ani Akpinar, Research Sci. SOM

Özlem Keskin, CE

Attila Gürsoy, CE

Erkmen Erken MBGE CS DM

Eylül Sevinç MBGE CS DM

Thank you

ID & CM

Füsun Can
Şiran Keske
Mert Kuşkucu
Lal Sude Gücer
Cansel Vatansever
Fatihan Pınarlık
Jale Boral
Nazlı Ataç
Güz Ekinci
Francis K. Cooper
Anı Akpınar
Pelin İrkören
Bahar Madran

kuiscid@ku.edu.tr

https://twitter.com/kuiscid

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https://www.linkedin.com/company/ku-is-cid