# AMP-BindGen: Guided Protein Design for Antimicrobial Peptides and Targeted Inhibitors Against AMR

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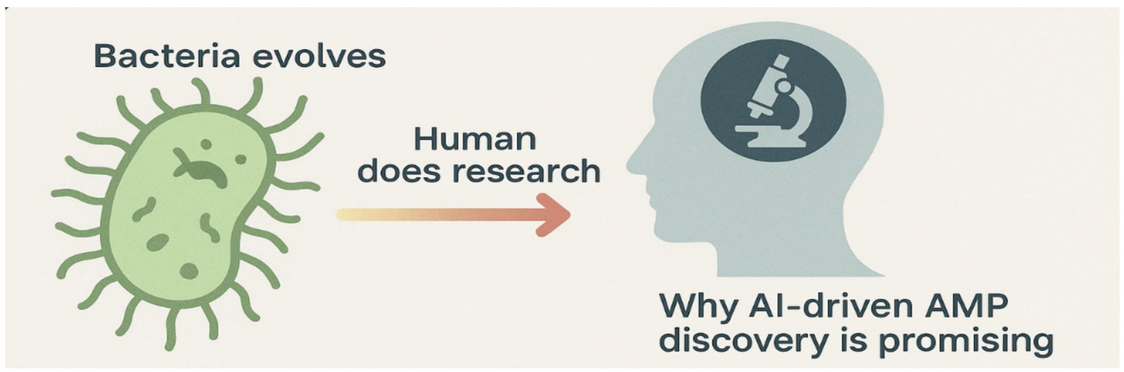
## Motivation

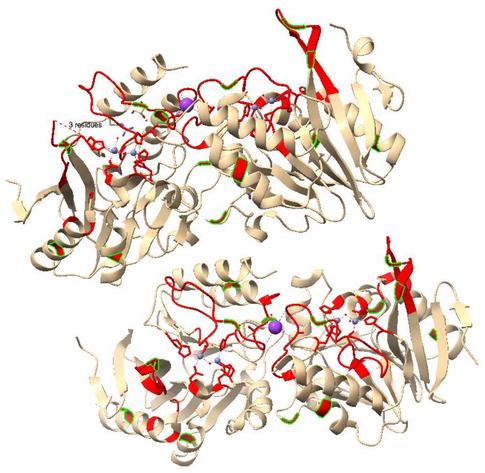
Antimicrobial resistance (AMR) poses a critical global health threat, demanding rapid discovery of novel antimicrobial peptides (AMPs).




## Key Mission

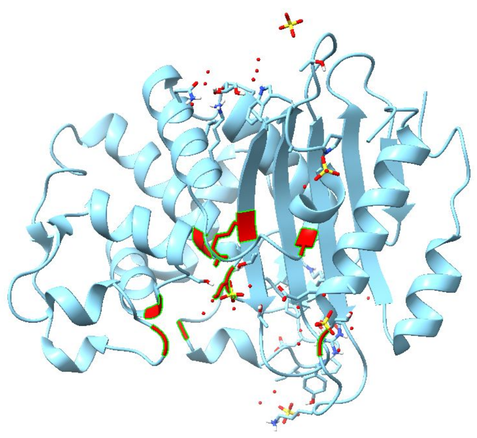
**Antimicrobial peptides (AMPs)** are a promising alternative to conventional antibiotics due to their broad-spectrum activity, rapid mechanism of action, and lower propensity for inducing resistance. As antimicrobial resistance (AMR) continues to threaten global health, the discovery and design of novel AMPs has become increasingly important. In this work, we focus on two biologically relevant targets derived from **antimicrobial resistance genes**, aiming to design effective AMP candidates using AI-driven generative models. The designed peptides are currently in the **activity testing stage**, where their antimicrobial efficacy is being experimentally evaluated.

## Targets



NDM-5

- **NDM-5 and KPC-3 are clinically important carbapenemases.**
- They enable *K. pneumoniae* to resist last-line β-lactam antibiotics.
- **Targeted peptide-like binders** could inhibit or destabilize these enzymes.
- This may **restore bacterial susceptibility to antibiotics**.



KPC-3

## Method

### Pipeline

**0 Epitope**
Map the catalytic cleft from inhibitor co-crystals onto NDM-5 / KPC-3 sequences.

**1 BoltzGen**
Generate 12–45 aa peptides conditioned on those hotspot residues (sequence-only target).

**2 AMP models**
Score every sequence with AMPScanner, Macrel, HydrAMP, APEX, and ToxinPred3.

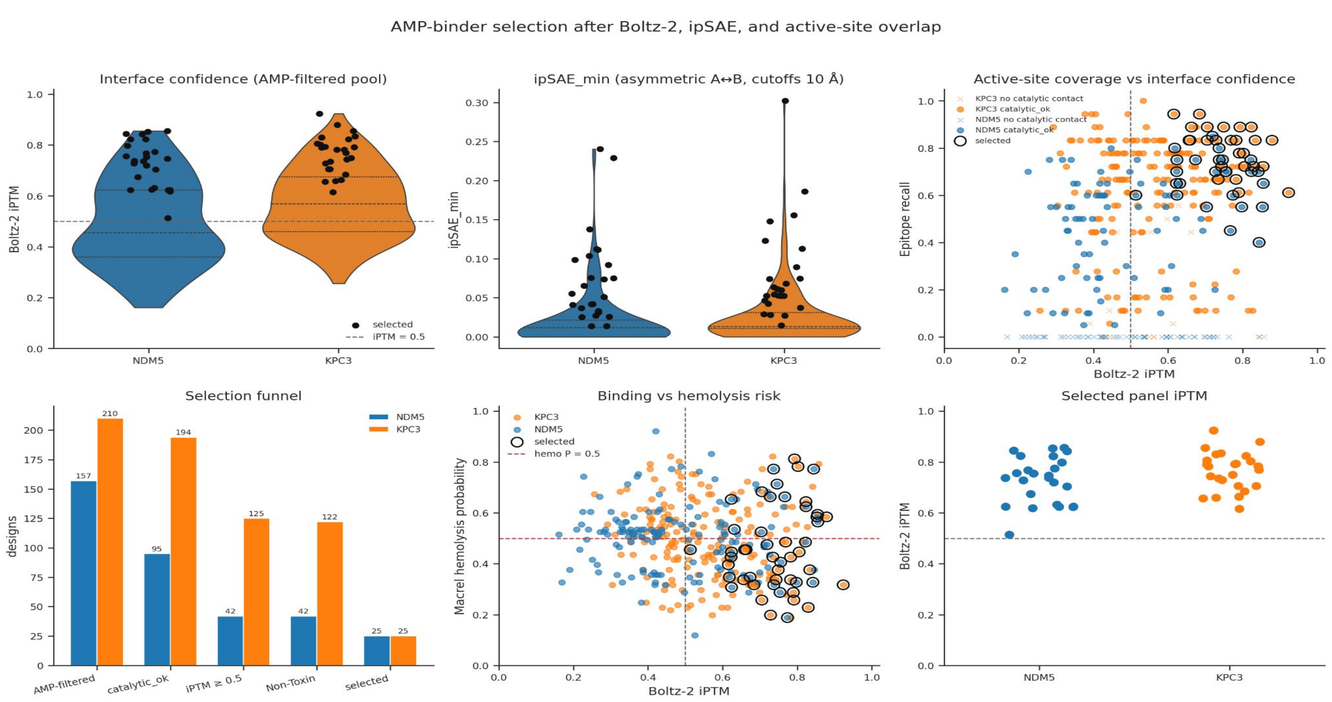
**3 AMP filter**
Keep AMP-positive, developable peptides (length, liabilities, aggregation).

**4 Boltz-2**
Refold each complex; require catalytic-site contact and interface confidence.

**5 Select 25**
Weighted rank + pairwise identity < 80% – wet-lab panel of 25 per target.

## Results

Overview of the AMP-binder screening and selection pipeline for NDM-5 and KPC-3. Candidate peptides are evaluated by Boltz-2 interface confidence (ipTM), ipSAE_min, catalytic-site coverage, and predicted hemolysis risk. The selection funnel shows progressive filtering from AMP-positive designs to candidates satisfying catalytic-site contact, ipTM, and non-toxicity criteria, followed by composite ranking and diversity-aware selection of 25 candidates per target. Black-outlined points indicate the final selected peptides, which show strong interface confidence while maintaining active-site engagement and favorable predicted safety profiles.




Composite rank_score weights — within-target percentiles

Higher-is-better metrics enter as percentile rank; lower-is-better metrics are inverted. toxin_safe is 1 if ToxinPred = Non-Toxin. Weights are divided by 11.4 so rank_score is in [0, 1].

| Metric | Weight | Direction | Role |
|---|---|---|---|
| Boltz-2 IPTM | 2.5 | higher | Interface confidence (dominant) |
| ipSAE_min (A ↔ B) | 1.5 | higher | PAE-based interface; tie-breaker here |
| epitope_recall | 1.5 | higher | Fraction of active site contacted |
| n_catalytic_contacts | 1.0 | higher | Depth of catalytic-core contacts |
| ToxinPred non-toxin | 1.0 | higher | Safety bonus |
| interface_precision | 0.8 | higher | Focus on epitope vs elsewhere |
| Macrel P(hemolytic) | 0.8 | lower | Prefer NonHemo; do not empty the panel |
| pDockQ | 0.6 | higher | Docking-quality proxy |
| AMPScanner P(AMP) | 0.4 | higher | Soft; pool already AMP-gated |
| aggregation_proxy | 0.4 | lower | Developability |
| Macrel P(AMP) | 0.3 | higher | Soft AMP score |
| delivery_proxy | 0.3 | higher | Cationic + amphipathic OM proxy |
| n_liabilities | 0.3 | lower | Synthesis flags |

Composite ranking scheme used for peptide candidate selection. Candidate peptides are ranked within each target using a weighted combination of interface confidence, catalytic-site engagement, AMP activity, toxicity, docking quality, and developability metrics. Higher-is-better metrics are percentile-ranked, while lower-is-better metrics are inverted before computing the final normalized rank score.