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Peptide-assembled nanozymes: a promising strategy to combat antimicrobial resistance

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Antimicrobial resistance (AMR) is a global health crisis that arises when microorganisms such as bacteria, fungi, viruses, and parasites evolve to resist the effects of antimicrobial drugs, rendering standard treatments ineffective.[1,2] Study indicates that the threat posed by AMR is poised to escalate dramatically in the forthcoming decades. Specifically, projections suggest a substantial increase of approximately 69.6% in AMR-associated fatalities and a notable 67.0% surge in AMR-linked deaths globally, spanning from 2022 to 2050.[3,4] This developing trend underscores the urgency of AMR as a critical global challenge demanding prompt and concerted action. At the same time, according to the World Health Organization, AMR could lead to 10 million deaths annually by 2050 if no action is taken, surpassing cancer as a leading cause of mortality worldwide.[5] The overuse and misuse of antibiotics in human medicine, agriculture, and animal husbandry have accelerated the emergence of resistant strains, creating a pressing need for innovative solutions.[6] Researchers are exploring novel antibiotics, nanozymes/nanomaterials,[7] antimicrobial enzymes (AMEs), and antimicrobial peptides (AMPs) to combat resistant pathogens. Despite these advancements, challenges remain, including the high cost of drug development, the rapid evolution of resistant strains, and the need for targeted delivery systems to minimize off-target effects.

AMPs, in particular, have gained attention for their broad-spectrum activity and low propensity to induce resistance.[8] Recently, Yuan *et al.*[9] published a study in *Nature Communications* that presents a groundbreaking approach to addressing AMR by designing peptide-assembled nanozymes that mimic the dual antifungal actions of AMPs and AMEs. This work not only advances our understanding of peptide-based nanomaterials but also offers a novel strategy for combating fungal infections, particularly those caused by *Candida albicans*.

Specifically, the authors developed a *de novo*-designed peptide nanozyme composed of a minimal heptapeptide sequence (HHHICI) that self-assembles into β-sheet helical nanotubes. These nanotubes exhibit dual enzymatic activities-phospholipase C (PLC)-like and peroxidase-like-enabled by nickel (Ni) coordination.[10] The nanozymes demonstrated remarkable antifungal efficacy, killing over 90% of *C. albicans* within 10 min by targeting the fungal cell wall, inducing lipid peroxidation, and triggering ferroptotic cell death (Figure 1A and B). This multimodal mechanism of action is a significant departure from traditional antifungal agents, which often target a single pathway and are prone to resistance. Meanwhile, the study leveraged AlphaFold2 (AF2)[11] and molecular dynamics (MD) simulations to predict and optimize the peptide sequence for self-assembly and enzymatic activity (Figure 1C and D). AF2, a deep learning-based protein structure prediction system developed by DeepMind, excels at efficiently generating atomic-level accurate spatial structures of proteins from their amino acid sequences.[12] Since its introduction, AF2 has made a significant impact in the field of protein structure prediction due to its superior performance. MD simulations, on the other hand, are a computational modeling method that relies on classical mechanics (molecular force fields) of molecules to study the structures and properties of molecular systems by numerically solving their equations of motion.[13] In this particular study, AF2 was utilized in conjunction with MD simulations to predict and optimize peptide sequences. This computational approach, combined with experimental validation, highlights the potential of integrating artificial intelligence (AI) with biomaterial design. The resulting nanozymes are highly stable, resistant to enzymatic degradation, and capable of functioning under harsh conditions, making them suitable for practical applications.

We now provide detailed interpretations of Yuan *et al.*'s[9] design of the nanozyme, as we believe that this "integrated computational and experimental" design paradigm may benefit other functional biomaterial designs. Yuan *et al.*'s[9] work exemplifies a robust synergy between computational modeling and experimental validation. AF2 predictions guided the selection

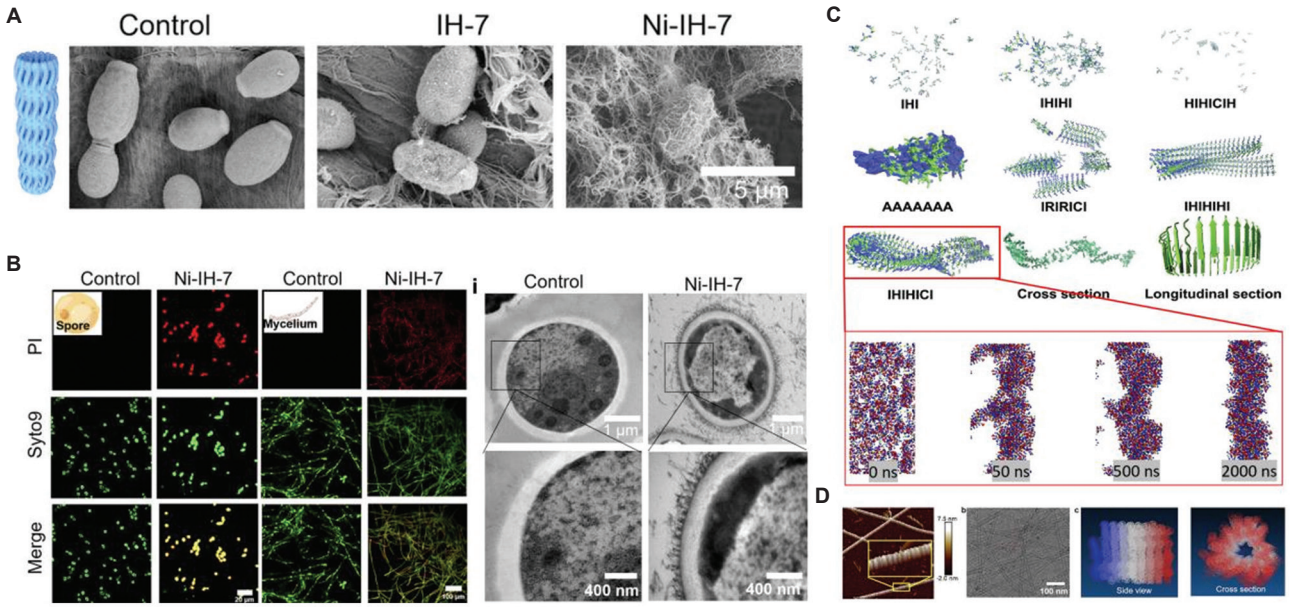

Figure 1. Overview of artificial intelligence-assisted screening of a peptide sequence that self-assembles into higher-order structures to exhibit antimicrobial enzymatic activities, efficiently killing *Candida albicans*. (A) AlphaFold2, combined with molecular dynamics simulations, ranks the "IHIHICI" amino acid sequence as the most promising candidate for forming higher-order structures. (B) Characterization of the successfully synthesized nanostructure of IHIHICI in the presence of nickel acetate. (C) Three-dimensional structure of the assembled nanotube and its effects on *C. albicans*. (D) Confocal microscopy and scanning electron microscopy confirm that the synthesized nanotube exerts antimicrobial effects by targeting the fungal cell wall. Reprinted from Yuan *et al.*[9] Copyright 2024 Authors. [https://doi.org/10.1038/s41467-024-50094-6].

of the optimal peptide sequence, whereas MD simulations elucidated the self-assembly dynamics and interactions driving nanotube formation.[14] The researchers employed AF2 to predict the three-dimensional structures of candidate peptides and screen sequences for self-assembly potential. For instance, simulations identified the heptapeptide HHHICI as optimal for forming β-sheet nanotubes. MD simulations further validated the dynamic assembly process, showing how random peptide clusters evolved into ordered tubular structures over time. These predictions reduced experimental trial-and-error and accelerated the discovery of functional sequences. Moreover, a specialized MD technique, coarse-grained MD, which reduces the system's degree of freedom by lumping multiple atoms into one pseudo-atom (often called beads) to enhance the sampling efficiency, was used to simulate the aggregation process of peptides, confirming that HHHICI exhibited the strongest assembly tendency. This approach provided insights into driving forces such as hydrogen bonding, π-π stacking, and hydrophobic interactions. To reveal the catalytic mechanism, density functional theory (DFT) calculations elucidated the role of nickel ions (Ni^{2+}) in enhancing the PLC-like activity of the nanozyme. By comparing reaction pathways with and without Ni coordination, DFT revealed that Ni reduced the energy barrier for the hydrolysis of phosphatide molecules by 0.15 eV, rationalizing the experimental observation of enhanced catalytic efficiency. DFT calculations quantified the binding energy (~0.34 eV) between HHHICI and mannan on *C. albicans* cell walls, explaining the specificity of antifungal activity. In addition, MD simulations further demonstrated how the nanotubes disrupted phospholipid membranes (e.g., 1-palmitoyl-2-oleoylphosphatidylcholine bilayers), causing structural collapse and lipid peroxidation. Free energy profiles for peptide assembly and catalytic reactions provided thermodynamic justification for the stability and activity of the nanozyme. For example, the Gibbs free energy change for PLC-like catalysis was lower in the presence of Ni, confirming its role as a cofactor.

In addition to computational modeling, multiple experimental procedures, including cryo-electron microscopy and X-ray absorption spectroscopy, validated the structural and catalytic properties of the nanozyme, ensuring high confidence in the findings.[15] This hybrid methodology accelerates the discovery of functional biomaterials by reducing trial-and-error experimentation, thereby holding immense potential for the design of other functional biomaterials.[16,17]

Besides expediting the design of functional biomaterials, the research paradigm adopted by Yuan *et al.*[9] has the added advantage of providing mechanistic insights into both the material formation process and enzymatic acclivities. The integration of quantum mechanics (i.e., DFT), MD (atomistic and coarse-grained), and continuum models allows researchers to bridge atomic interactions with macroscopic material properties. Specifically, simulations reveal molecular-level details (e.g., hydrogen bonding networks, metal coordination, and reaction intermediates) that are otherwise inaccessible experimentally. For instance, the helical β-sheet arrangement of HHHICI and its interaction with Ni^{2+} were visualized through MD and DFT, clarifying structure-function relationships. In this study, computational predictions guided experimental validation, minimizing resource expenditure on non-viable candidates.

The utilization of AI in Yuan *et al.*'s[9] work underscores the potential of AI in polymer-based biomaterial design.

The foundation of any applicable AI tool for polymer-based material design is a sufficient amount of high-quality "sequence–structure–functional relationship" data on which an AI model can be effectively trained. For amino acid polymers, such high-quality datasets are readily available due to the vast amount of accumulated data from the field of biology. For non-amino acid polymers, such as synthetic polymers, the volume of high-quality data is smaller compared to amino acid-based polymers. However, researchers are actively working to overcome this limitation by compiling data from multiple sources, such as high-throughput experimental characterization and simulation-based data generation. These efforts will significantly advance the adoption of AI in polymer-based biomaterial design.[18]

The work by Yuan *et al.*[9] has several important implications for the field of AMR and biomaterials, especially in terms of overcoming the limitations of natural AMPs and AMEs. Natural AMPs and AMEs, whereas effective, suffer from poor stability, high production costs, and susceptibility to proteolytic degradation.[19] The peptide-assembled nanozymes developed in this study address these limitations by combining the stability and cost-effectiveness of nanomaterials with the catalytic activity of enzymes.[20] This hybrid approach could pave the way for the development of next-generation antimicrobial agents. In addition, the nanozymes' ability to target multiple pathways-cell wall wall disruption, lipid peroxidation, and ferroptosis-reduces the likelihood of resistance development. This is particularly crucial for treating infections caused by drug-resistant strains of *C. albicans*, which are increasingly prevalent in clinical settings. The authors also demonstrated the practical application of these nanozymes by incorporating them into medical pads, which exhibited rapid antifungal activity. This suggests that the technology could be adapted for use in wound care, medical devices, and other clinical applications. The nanozymes' biocompatibility and lack of cytotoxicity further support their potential for human use.

While the study presents a compelling proof-of-concept, several questions remain. For instance, the long-term stability and safety of these nanozymes *in vivo* need to be thoroughly evaluated. In addition, the specificity of the nanozymes for fungal cells over mammalian cells, while promising, requires further investigation to ensure minimal off-target effects. Therefore, future directions to potentially improve the research include the following: (i) optimization of peptide sequences to enhance catalytic activity and target specificity; (ii) extending the nanozymes' efficacy to other pathogens, including bacteria and viruses, to address a wider range of AMR challenges, and (iii) evaluating *in vivo* applications to assess the therapeutic potential of these nanozymes in treating fungal infections and other microbial diseases.

Overall, Yuan *et al.*[9] have developed a novel peptide-assembled nanozyme that integrates the antimicrobial actions of AMPs and AMEs into a single, stable, and highly effective system. This work represents a significant step forward in the fight against AMR, offering a promising alternative to traditional antimicrobial agents. By combining computational design with experimental validation, the study also highlights the potential of AI-driven approaches in biomaterial innovation. As the global health community continues to grapple with the AMR crisis, such innovative strategies will be crucial in developing sustainable and effective solutions.

Author contributions

Conceptualization: MZ; Formal analysis: MZ; Investigation: HD; Project administration: MZ; Writing-original draft: HD; Writing–review & editing: JL and MZ.

All authors have approved the final version of the manuscript.

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Conflicts of interest statement

The authors declare no competing financial interest.

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