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HIGHLIGHT

Protein degradation-based anti-infective drug research



KEY WORDS

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Drug resistance;
Targeted therapy

1. Background of anti-infective drug research

In the realm of anti-infective research, the escalating challenge of pathogen drug resistance has rendered many conventional drugs ineffective. The rise of bacterial drug resistance, malaria drug resistance, and viral mutations has urged the scientific community to innovate. Protein degradation-based drug technologies have emerged as a novel strategy, offering a distinct approach to combat infections by specifically eliminating key pathogen proteins, thereby circumventing the limitations of traditional drugs. This review highlights recent advances in targeted protein degradation (TPD)-based approaches against bacterial^{1,2}, malarial³, and viral infections^{4–7}.

2. Protein degradation-based antimicrobial drug research

The development of antimicrobial drugs is confronted with the rapid evolution of bacterial resistance. Conventional drugs often face the challenge of bacterial drug resistance, which can be attributed to various mechanisms such as enzymatic hydrolysis of drugs, alteration of target proteins, and enhanced drug efflux. The protein degradation-based approach aims to hijack the bacterial endogenous protease system to achieve specific degradation of

target proteins, but this strategy is not without its challenges. These include the difficulty of penetrating bacterial barriers, the unclear activation mechanisms of proteases, and the regulation of substrate selectivity.

In 2022, Markus Kaiser & Tim Clausen's research group¹ addressed the challenge of whether small-molecule adapters could reprogram bacterial endogenous protease systems, specifically the ClpCP protease system, to induce the degradation of non-native substrates and bypass traditional resistance mechanisms. They designed bifunctional BacPROTACs, which bind to target proteins (such as BRDT BD1 and DdIA) at one end and to the N-terminal domain of ClpC (ClpC NTD) at the other, forming a “target protein–BacPROTAC–ClpC” ternary complex. This design induces target protein degradation (TPD). Utilizing structural biology techniques such as cryo-EM, they revealed the mechanism of ClpC activation. Their experiments demonstrated that BacPROTACs could effectively degrade model proteins *in vitro*, with degradation efficiency dependent on ClpC's ATPase activity and substrate disordered structure. For instance, BacPROTAC-1 showed significant degradation capability. Additionally, BacPROTACs based on CymA exhibited high efficiency in degrading the BRDT BD1 fusion protein in *Mycobacterium smegmatis*, with BacPROTAC-4 showing a binding affinity of 0.2 $\mu\text{mol/L}$ for ClpC1 NTD and a 15-fold improvement in degradation efficiency *in vivo*. These compounds also restored the sensitivity of mycobacteria to D-cycloserine and induced threonine auxotrophy by degrading the essential enzyme ThrC, thereby demonstrating their antimicrobial potential. Notably, BacPROTAC-3 reduced BRDT BD1 protein levels by over 70% in mycobacteria without significant off-target effects.

In 2023, Tim Clausen's research team² focused on the development of novel antimicrobial strategies by reprogramming the endogenous ClpC1P2 protease system in bacteria. They explored the mechanisms of action of natural antibiotics such as Cymarin A, as well as the regulatory role of bacterial protective

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proteins like ClpC2/ClpC3. Designing bifunctional homo-BacPROTACs (HBPs), they connected two Cymarin A molecules to simultaneously target ClpC1 and protective protein ClpC2, inducing their synergistic degradation and overcoming bacterial defense mechanisms. Their research revealed that Cymarin A and its analogs bind to the N-terminal domain of ClpC1 (ClpC1 NTD) *via* a mechanism mimicking misfolded proteins, thereby inducing ClpC1 oligomerization and activating protease activity. This leads to proteostasis collapse in bacteria. Furthermore, they demonstrated that HBPs could simultaneously induce the degradation of ClpC1 and ClpC2, achieving a 115- to 150-fold reduction in the minimum inhibitory concentration (MIC) for *Mycobacterium tuberculosis* compared to Cymarin A alone, while maintaining efficient bactericidal activity in ATP-starved dormant bacteria. Their studies also indicated that the frequency of resistance mutations against HBPs was lower than that of conventional antibiotics, with mutations primarily concentrated in the drug-binding region of ClpC1 NTD, providing valuable insights for the design of next-generation drugs (Fig. 1).

The protein degradation-based approach has shown significant potential in antimicrobial research. By hijacking bacterial endogenous protease systems and utilizing bifunctional small molecules or bivalent molecules, specific degradation of target proteins has been achieved, offering a new strategy to overcome bacterial drug resistance. However, several challenges remain. The activation mechanisms of certain bacterial protease systems are not yet fully understood, necessitating further research to optimize drug design. The cell membrane permeability of drugs needs to be improved, particularly for bacteria with complex cell wall structures. Additionally, most current studies are limited to *in vitro* models and preliminary *in vivo* models, and the clinical application prospects of these drugs require validation through more extensive *in vivo* experiments and clinical trials. Future research directions should focus on exploring novel protease targets, developing protein degradation molecules with higher specificity and efficiency, and intensive study the pharmacokinetics and pharmacodynamics of these molecules in complex biological environments to accelerate their clinical translation.

3. Protein degradation-based antimalarial drug research

Malaria remains a global health threat, and the growing resistance of Plasmodium to conventional antimalarial drugs like artemisinin has necessitated the development of novel antimalarial agents with innovative mechanisms of action. In 2023, Laura A. Kirkman & Gang Lin's research group³ targeted the specific scientific question of whether a dual-pharmacophore Artezomib (ATZ), combining artemisinin and proteasome inhibitors (PIs), could hijack the Plasmodium ubiquitin–proteasome system (UPS) to achieve synergistic bactericidal effect and overcome single-drug resistance.

The research encounters several challenges, including the unclear mechanism of drug synergism between artemisinin and PIs, the need to design dual-functional molecules capable of evading mutations such as K13 in Plasmodium and β -subunit mutations in proteasomes (*e.g.*, β 5A49S, β 6A117D) that cause PI resistance, and the requirement for ATZs to be efficiently activated within Plasmodium to covalently modify target proteins while avoiding toxicity to host cells.

To address these challenges, Kirkman & Gang Lin's team³ designed ATZ molecules by linking artemisinin analogs (ART1) with PIs (PI01) *via* amide bonds. They utilized the heme in Plasmodium to activate the ART component, which covalently labels target proteins. Subsequently, the PI component inhibits proteasome activity, inducing the degradation of labeled proteins. They constructed an ATZ-PI probe to track the covalent modification sites of ATZs within Plasmodium using click chemistry and verify the hijacking of the UPS post-ATZ activation. Additionally, they generated a dual-resistant Plasmodium model (*e.g.*, Dd2 β 6A117D K13R539T) to evaluate the ability of ATZs to overcome dual resistance. Structural biology techniques such as X-ray crystallography and cryo-EM were employed to elucidate the binding modes of ATZs with proteasomes and observe proteasome oligomerization. Quantitative proteomics *via* LC–MS/MS identified ATZ-covalent modification targets and degradation products, analyzing UPS pathway changes. Microbiological assays, including *in vitro* ring-stage survival assays (RSA), mouse models for antimalarial efficacy and relapse inhibition, assessed the therapeutic potential and resistance inhibition of ATZs.

Mechanistically, ATZs activate a “tagging-degradation” dual mechanism. The PI component engages in long-distance interactions with the proteasome active site, enabling ATZs to overcome PI resistance caused by β -subunit mutations, enhancing killing efficiency against artemisinin-resistant strains (*e.g.*, Cam3.1R539T) by over tenfold. Regarding resistance overcoming, ATZ4 demonstrated a ≥ 5 -fold increase in killing efficacy against PI-resistant strains (Dd2 β 5A49S, Dd2 β 6A117D) compared to PI01, while maintaining high activity against dual-resistant strains (Dd2 β 6A117D K13R539T) with EC₅₀ changes ≤ 2.9 -fold. *In vivo* efficacy confirmation showed that ATZ4 inhibited relapse of the artemisinin-resistant strain (Pb K13R551T) in mouse models, reducing parasite burden by $>3 \log_{10}$ at a dose of 25 mg/kg, surpassing the efficacy of artemisinin monotherapy. Specificity validation revealed that ATZs exhibit 30–300 times lower inhibitory activity against human proteasomes (hu c-20S, hu i-20S) than against Plasmodium proteasomes, indicating favorable selectivity.

To sum up, the development of Artezomibs has opened new avenues for antimalarial drug research. By hijacking the UPS of Plasmodium, these agents achieve synergistic bactericidal effects and overcome drug resistance. However, current research has limitations. The distribution and metabolic processes of ATZs within Plasmodium are not yet fully understood. Long-term toxicity and potential side effects in complex biological environments require further evaluation. While mouse models have shown promise, the actual efficacy and safety of these drugs in humans need validation through large-scale clinical trials. Future research should delve deeper into the pharmacokinetic properties of ATZs, optimize molecular structures to enhance stability and bioavailability, further explore their mechanisms of action across different stages of the Plasmodium life cycle, and conduct more clinical studies to facilitate clinical application.

4. Protein degradation-based antiviral drug research

4.1. Scientific challenges in antiviral research

The development of antiviral drugs faces significant hurdles due to the genetic diversity and mutation-prone nature of viruses such as

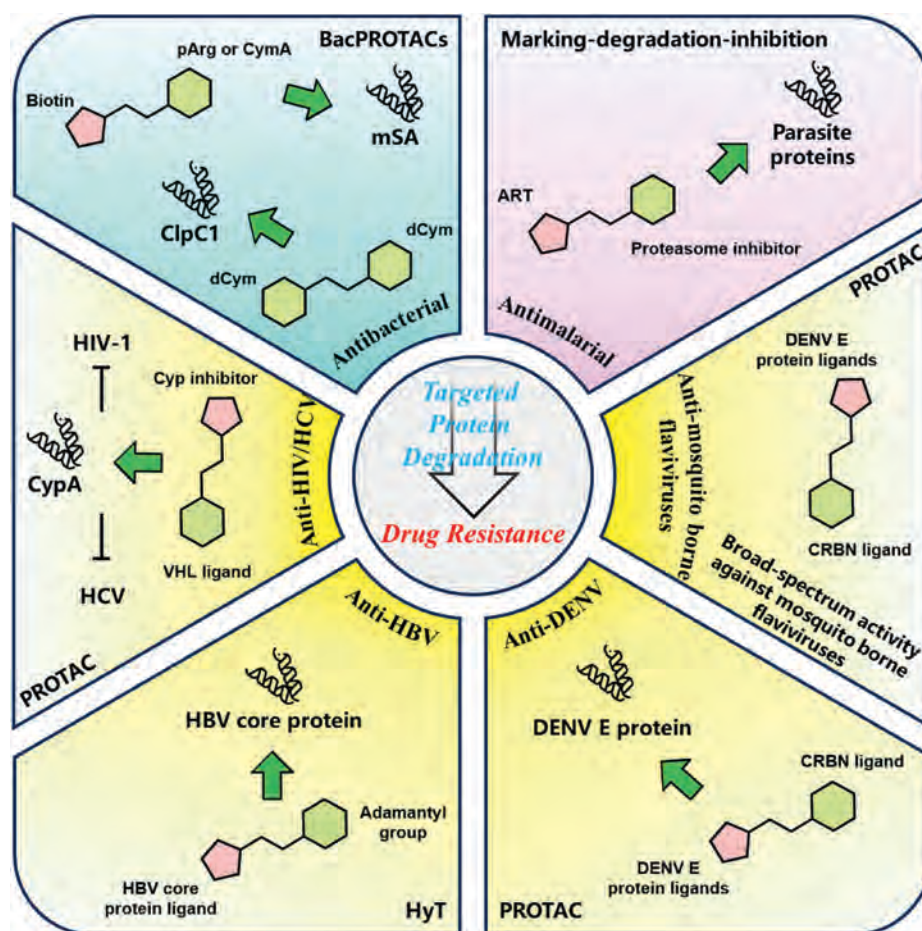


Figure 1 Typical cases of using TPD technology to overcome drug resistance in the fields of anti-infection (including bacteria, malaria parasites, and viruses).

mosquito-borne flaviviruses (*e.g.*, dengue virus, Zika virus), hepatitis B virus (HBV), HIV-1, and HCV. Traditional antiviral drugs often have narrow spectra and are prone to resistance. In 2024, Priscilla L. Yang's research team addressed the challenge of whether flavivirus envelope protein (E protein) could be targeted for degradation using protein degradation technology to develop broad-spectrum antiviral agents with high resistance barriers⁴. The specific scientific questions included: designing bifunctional PROTAC molecules capable of simultaneously binding to E protein and E3 ubiquitin ligase; determining whether E protein degradation could inhibit both viral entry and particle formation; and assessing the broad-spectrum activity of these molecules against multiple flaviviruses.

In the same year, Priscilla L. Yang's research group⁵ focused on the limitations of traditional inhibitors targeting the E protein of dengue virus (DENV), including insufficient efficacy and drug resistance. They explored whether E protein could be developed into a degradable target through the application of TPD technology to enhance antiviral activity and overcome drug resistance. The specific scientific questions were: how to couple known E protein inhibitors (GNF-2, CVM-2-12-2) with E3 ubiquitin ligase ligands to achieve ubiquitination and degradation of E protein; whether the degraders could simultaneously inhibit viral entry and particle formation; and whether these molecules possessed broad-spectrum activity against multiple DENV serotypes.

Also in 2024, Peng Zhan's research team⁶ tackled the challenges of treating chronic hepatitis B, where the persistence of covalently closed circular DNA (cccDNA) and drug resistance pose significant hurdles. They investigated whether hydrophobic tagging (HyT) technology could be employed to develop novel small-molecule degraders capable of specifically degrading the hepatitis B virus core protein (HBc) to inhibit viral replication and overcome drug resistance. The specific scientific questions included: how to couple HBc ligands with hydrophobic tags to induce protein degradation; whether the degraders acted *via* the autophagy–lysosome pathway; and their efficacy against drug-resistant mutants.

Similarly, in 2024, Greg J. Towers & David L. Selwood's research group⁷ addressed the issue of traditional antiviral drugs targeting viral proteins, which are prone to resistance and have narrow spectra. They focused on cyclophilin A (CypA), a common host factor for HIV-1 and HCV, as a potential broad-spectrum antiviral target. The study explored whether macrocycle-based PROTACs (Cyp-PROTACs) could be designed to specifically degrade CypA and inhibit viral replication. The specific scientific questions were: how to couple macrocyclic CypA inhibitors with E3 ubiquitin ligase ligands to form degraders; whether Cyp-PROTACs could selectively degrade CypA in cells and primary cells; and their antiviral activity and resistance advantages against HIV-1 and HCV.

4.2. Strategies and technologies in protein degradation-based antiviral drug research

Priscilla L. Yang's team⁴ designed bifunctional PROTAC molecules, with one end being E protein fusion inhibitors (GNF-2, 2-12-2) and the other end being CRBN ligands (thalidomide analogs), connected *via* linkers to induce ubiquitination and degradation of E protein. They constructed virus-like particle (VLP) models and CRBN knockout cell lines to verify the specificity and CRBN dependency of degradation. Using point-mutant virus strains (*e.g.*, E-F193L/M196V), they assessed the tolerance of PROTACs to resistant mutations. Structural biology techniques such as X-ray crystallography were employed to resolve the binding modes of E protein and β OG, guiding PROTAC design. Western blotting was used to detect E protein degradation efficiency, and plaque formation assays evaluated antiviral activity. Infections with multiple flaviviruses (dengue, Zika, Japanese encephalitis, etc.) validated the broad-spectrum activity of PROTACs.

Additionally, Priscilla L. Yang's team⁵ also designed bifunctional PROTACs, using GNF-2 or CVM-2-12-2 as E protein-binding ligands and connecting thalidomide derivatives (CRBN ligands) *via* amide or PEG linkers to induce ubiquitination and degradation of E protein. They constructed CRBN knockout cell lines and VLP models to verify the CRBN dependency of degradation and its impact on viral particle formation. Cell thermal shift assays (CETSA) and proteomic analyses confirmed the direct binding of degraders to E protein and assessed off-target effects. Drug chemistry involved designing compounds based on structure-based docking (Schrödinger Glide) and synthesizing degraders like ZXH-2-107 (derived from GNF-2) and ZXH-8-004 (derived from CVM-2-12-2) through amide bond formation. Western blotting quantified E protein degradation efficiency, and plaque formation assays measured antiviral activity (EC_{90}). Infections with multiple DENV serotypes (DENV1-4) validated broad-spectrum activity, and proteomic analyses (mass spectrometry) assessed degrader selectivity.

Peng Zhan's team⁶ employed sulfonamide benzoic acid (SBA) compounds like NVR 3-778 as a scaffold, connecting adamantyl hydrophobic tags *via* amide bonds to design bifunctional HyT degraders (*e.g.*, HyT-S7) that induce HBc ubiquitination and degradation. They optimized linker length and hydrophobic groups using structure-activity relationships (SAR) to screen for efficient degraders. CETSA, surface plasmon resonance (SPR), and molecular dynamics simulations validated the binding modes and mechanisms of degraders with HBc. Drug chemistry involved synthesizing a series of HyT degraders based on the co-crystal structure of HBc and NVR 3-778 (PDB: 5T2P), optimizing the carbon chain length and ring structure of the adamantyl linker. Western blotting assessed HBc degradation efficiency, and real-time quantitative PCR measured HBV DNA replication levels to evaluate antiviral activity. Proteomic analyses using data-independent acquisition (DIA) examined protein expression changes post-degrader treatment, and autophagy inhibitors (*e.g.*, 3-MA, HCQ) verified the degradation pathway.

Greg J. Towers & David L. Selwood's team⁷, using sanglifehrin A-derived macrocyclic compound TWH106 as a scaffold, connected VHL ligands (Me-VH032) *via* amide bonds or click chemistry to construct bifunctional PROTACs (CG167 and RJS308) that induce CypA ubiquitination and degradation. They optimized linker length and connection sites using SAR to enhance the formation efficiency of the ternary complex between

PROTACs, CypA, and VHL. SPR, proteomics, and viral infection experiments validated the binding specificity, degradation mechanisms, and antiviral activities of PROTACs. Drug chemistry involved synthesizing macrocyclic scaffolds *via* Heck cross-coupling reactions and connecting VHL ligands using CuAAC click chemistry to optimize PROTAC stereochemistry and yield. SPR measured compound binding affinities (K_D values) with CypA/CypB, size-exclusion chromatography (SEC) verified ternary complex formation, and Western blotting assessed CypA degradation efficiency. Viral infection experiments in U87 cells, Jurkat T cells, primary CD4⁺ T cells, and Huh7 cells evaluated antiviral activity using fluorescence-labeled viruses and replicon systems, with flow cytometry and RT activity assays quantifying infection efficiency.

4.3. Achievements in protein degradation-based antiviral drug research

Priscilla L. Yang's team⁴ demonstrated that PROTACs induce E protein degradation *via* the CRL4–CRBN ubiquitination pathway, reducing E protein levels by over 95% in Huh7.5 cells in a proteasome-dependent manner. The antiviral efficacy against dengue virus (EC_{90}) was enhanced 4–10 times compared to parent inhibitors, and activity was lost in CRBN knockout cells, confirming the necessity of the degradation mechanism. PROTACs showed broad-spectrum activity against ZIKV, JEV, WNV, YFV, with EC_{90} values in the low μ mol/L range, representing a 2–10 times improvement over parent inhibitors. Among them, GNF-2-deg exhibited significant activity against YFV.

Priscilla L. Yang's team⁵ confirmed that ZXH-8-004 degraded E protein in a CRBN-dependent manner in Huh7.5 cells, reducing E protein levels by over 90% within 24 h without affecting ABL kinase. ZXH-8-004 showed an EC_{90} of 1.7 μ mol/L against DENV2, an 8-fold improvement over the parent inhibitor CVM-2-12-2 (13.3 μ mol/L), and was effective against DENV1-4. Sensitivity to single-mutant viruses (*e.g.*, E-F193L) remained unchanged, while degradation efficiency decreased for double-mutant strains (E-F193L/M196V), indicating high barriers to single-mutation escape. Proteomics revealed that ZXH-8-004 primarily degraded E protein and known CRBN substrates (ZFP91, GSPT1), with GSPT1 degradation potency 80 times lower than that of selective degraders, suggesting limited off-target effects.

Peng Zhan's team⁶ developed HyT-S7, which showed optimal activity with a linker containing seven carbon atoms in the adamantyl group. It exhibited an EC_{50} of 0.46 μ mol/L for inhibiting HBV DNA *in vitro* and a DC_{50} of 3.02 ± 0.54 μ mol/L for degrading HBc, with significantly reduced cytotoxicity ($CC_{50} = 28.84$ μ mol/L). HyT-S7 induced HBc degradation *via* the autophagy–lysosome pathway, as autophagy inhibitors (3-MA, HCQ) reversed the degradation effect, and proteomics showed altered expression of autophagy-related proteins (*e.g.*, LC3B, p62). HyT-S7 was effective against 11 drug-resistant mutants, including highly resistant P25G and T33N, maintaining degradation efficiency comparable to wild-type strains. In contrast, traditional capsid assembly modulators like GLS4 showed significantly reduced activity against mutants. CETSA and SPR confirmed direct binding of HyT-S7 to HBc ($K_D = 0.78$ μ mol/L), and molecular dynamics simulations indicated that the adamantyl group mimicked protein misfolding, enhancing hydrophobic interactions with HBc to stabilize the degradation complex.

Greg J. Towers & David L. Selwood's team⁷ showed that CG167 and RJS308 degraded CypA in Jurkat cells in a dose- and

time-dependent manner, with DC_{50} values of 123 and 284 nmol/L, respectively. Degradation relied on the VHL-E3 ligase pathway and could be inhibited by MLN4924 and VHLi. Proteomics revealed that PROTACs selectively degraded CypA with minimal effects on other cyclophilins (e.g., CypB, CypE), maintaining selectivity in primary $CD4^+$ T cells and macrophages. In primary $CD4^+$ T cells, Cyp-PROTACs demonstrated superior inhibitory activity against HIV-1 compared to the non-PROTAC inhibitor TWH106, especially at low concentrations (1 μ mol/L) and under pre-treated wash-out conditions. Similarly, in HCV replicon systems, PROTACs showed enhanced inhibitory effects at 1 μ mol/L, dependent on the VHL mechanism. By degrading CypA rather than competitive inhibition, PROTACs potentially avoid viral resistance caused by target protein mutations, offering a new strategy for broad-spectrum antiviral agents.

Protein degradation-based antiviral drug research has shown unique advantages in addressing viral genetic diversity and drug resistance^{8–10}. By hijacking host or viral protein degradation systems, specific degradation of viral key proteins or host auxiliary factors has been achieved, leading to significant outcomes in various viral models. However, challenges remain. The degradation efficiency and selectivity of certain degraders need further improvement, particularly when confronting complex viral environments and multiple drug-resistant mutants. The pharmacokinetics and toxicology of degraders *in vivo* are not yet fully understood, and their safety and efficacy require deeper research. Most current studies are limited to *in vitro* models and preliminary *in vivo* models, and the clinical application prospects of these drugs need validation through more extensive *in vivo* experiments and clinical trials. Future research directions should focus on exploring novel viral targets and host auxiliary factors, developing protein degradation molecules with higher degradation efficiency and selectivity, and intensive study the mechanisms of action and pharmacokinetic properties of these molecules in complex biological environments to accelerate their clinical translation.

5. Summary and outlook

In summary, protein degradation-based anti-infective drug research has made significant progress in antimicrobial, antimalarial, and antiviral fields, offering new strategies to address pathogen drug resistance. Antimicrobial, antimalarial, and antiviral research share similarities in the application of protein degradation technologies, all aiming to achieve specific clearance of target proteins by hijacking the protein degradation systems of pathogens or hosts. However, they also have distinct features. Antimicrobial research focuses on reprogramming bacterial endogenous protease systems, antimalarial studies target the hijacking of the Plasmodium UPS, and antiviral research involves the degradation of viral key proteins or host auxiliary factors. Future research should strengthen cross-disciplinary collaboration and exchange^{11,12}, drawing on the successful experiences of protein degradation technologies across different fields to further optimize and innovate drug design strategies. Additionally, in-depth studies on the mechanisms of protein degradation technologies in diverse pathogens and host environments are needed to enhance drug specificity and efficiency while reducing off-target effects and toxicity. Clinical trials should be intensified to promote the clinical translation and application of protein degradation-based drugs, providing more effective and safer drug

options for anti-infective treatments and addressing the growing challenge of infectious diseases to safeguard human health.

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Author contributions

Dazhou Shi: Writing - original draft, review & editing. Shujing Xu: Writing - review & editing, conceptualization. Xu Deng: Formal analysis. Yundong Sun: Conceptualization, validation. Peng Zhan: Writing-review & editing, supervision, funding acquisition, conceptualization.

Conflicts of interest

The authors declare no conflicts of interest.

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