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Targeted protein degradation as a novel therapeutic strategy against infectious diseases

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Targeted protein degradation (TPD) represents an emerging antimicrobial strategy that is predominantly still in preclinical development stages. Chimeric molecules (i.e., PROteolysis-TArgeting Chimera [PROTACs]) that can direct molecular targets for degradation by hijacking a cell's proteolytic machinery offer significant advantages over traditional small-molecule therapeutics. These include diversifying the druggable proteome by targeting previously 'undruggable' non-enzymatic and structural proteins, lowering the effective therapeutic concentration, enabling lower drug concentrations, and delaying resistance development. Recent reports of BacPROTACs that are active against *Mycobacterium tuberculosis* have set the stage to exploit TPD for antimicrobial drug development, yet despite its clear relevance to African-endemic diseases challenged by multidrug resistance—notably HIV, tuberculosis, and malaria—TPD-based infectious disease therapeutic development remains in its early stages. This review highlights the recent advances in the development and application of PROTACs as antimicrobials and provides an outlook for TPD's strategic value in addressing the growing threat posed by drug-resistant pathogens.

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Introduction

The escalating threat of drug resistance in infectious disease-causing organisms and stagnation in the clinical and preclinical pipeline represent one of the most critical global public health challenges facing humanity today [1]. This is especially evident in areas with high disease burden in Africa [2]. This highlights the desperate need for next-generation antimicrobials and innovative strategies to combat infections caused by drug-resistant pathogens.

Traditional drug discovery typically focuses on identifying small molecules that inhibit the active site of a limited number of validated protein targets. However, pathogens are particularly adept at using various resistance mechanisms to counter the growth-inhibitory effects of small-molecule antimicrobials. Targeted protein degradation (TPD) offers substantial advantages over conventional, occupancy-driven inhibition and addresses many of the challenges associated with small-molecule drugs such as low efficacy, potential toxicity, and lack of selectivity—while also offering the potential to overcome existing resistance mechanisms [3]. TPD-inducing agents do not function by blocking a protein's activity, but by leveraging the targeted cell's intrinsic proteolytic machinery to catalytically induce the destruction and elimination of a protein of interest (POI) to achieve a therapeutic effect [4,5].

The most prominent TPD modality developed in human therapeutics to date is the PROteolysis-TArgeting Chimera (PROTAC), a heterobifunctional molecule designed to independently but simultaneously bind the POI (the high-value target) and an E3 ubiquitin ligase that induces polyubiquitination of the POI, causing its proteolysis by the host ubiquitin-proteasome system (UPS) [6–10]. Within this context, PROTACs have received extensive attention in the development of new cancer treatments for humans, with one example progressing to Phase III trials [11,12].

However, the translation of human PROTAC technology to bacterial or protozoan pathogens has been slow, mainly due to the differences in their native degradation machinery and the lack of known ligands that can engage the pathogens' degradation-tagging enzymes or

proteases effectively. Yet recent studies have elegantly demonstrated that it is practically feasible to use chimeric degrader molecules to induce TPD to achieve an antibacterial effect in mycobacteria [13–15]. These foundational studies demonstrated the potential of TPD as a novel therapeutic strategy for developing new antimicrobial drugs [16–21].

This opinion piece highlights the pertinent advantages of PROTACs to anti-infective development and underlines the requirements for their development in this context. We sketch a vista of a future in which TPD platforms are poised to revolutionize the search for novel antimicrobial drugs with enhanced selectivity and a mechanism of action (MOA) capable of overcoming existing drug resistance.

Design requirements of PROteolysis-TArgeting Chimera as anti-infectious agents

The successful development of an antimicrobial PROTAC requires meeting several critical design and mechanistic criteria. The most important of these is the identification of a target POI that is essential or highly vulnerable; i.e., perturbation of its activity directly affects the targeted organism's survival. In addition, evidence that the POI acts as a substrate for the intended degradation machinery is highly beneficial.

PROTACs consist of three main components: 1) a suitable target-engaging ligand (TEL) or warhead that will interact with the high value POI of the pathogen, 2) the degradation machinery-engaging ligand (DMEL), which must recruit the relevant proteins of the degradation machinery that will be used to effect proteolysis of the POI, and 3) a flexible linker that connects the ligands (Figure 1). Importantly, since PROTACs' primary function is to transiently stabilize a ternary complex with the POI and the degradation machinery protein, it does not require either ligand to be tight-binding. However, both must be specific, and in the case of the TEL, it should ideally allow preferential binding to a surface on the POI accessible to the degradation machinery.

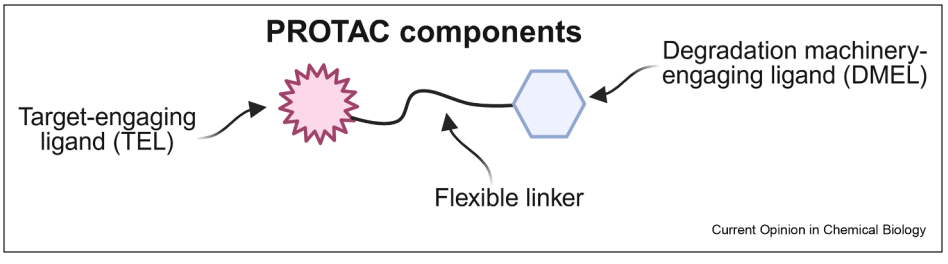
The choice of DMEL depends entirely on the targeted pathogen and the way in which the proteolytic system will be recruited (Figure 2). In eukaryotes, it can induce UPS-dependent degradation by engaging an E3 ligase that ubiquitinates the POI, or by engaging a molecular chaperone such as heat-shock protein 90 (Hsp90) to subsequently recruit the E3 ligase (the HEMTAC strategy, Figure 2) [22]. The DMEL can also bind directly to the ubiquitin-recognition receptor of the 26s proteasome (via so-called ByeTACs, Figure 2) [23,24]. In bacteria, the DMEL may similarly engage an enzyme that transfers a degradation tag (or degron) to the POI to induce its degradation by a highly conserved multimeric caseinolytic ClpC-ClpP (ClpCP) protease complex within these organisms, or directly engage such a complex. Importantly, any DMEL that acts by direct engagement with a protease must also be able to bypass its regulatory mechanisms to ensure efficient proximity-induced degradation of the POI.

The selection of the linker component of the PROTAC is a crucial design choice [26]. The linker's length, composition, and attachment points (the so-called 'linkerology') are critically important as these significantly influence both the overall physicochemical properties and the molecule's ability to promote the formation of a productive ternary complex with the POI and the degradation machinery. Most often, ideal linker parameters must be assessed individually for each POI and DMEL combination to ensure proper spatial orientation and stability of the ternary complex as these are major predictors of degradation efficiency [27].

The advantages of targeted protein degradation over traditional small-molecule antimicrobial treatments

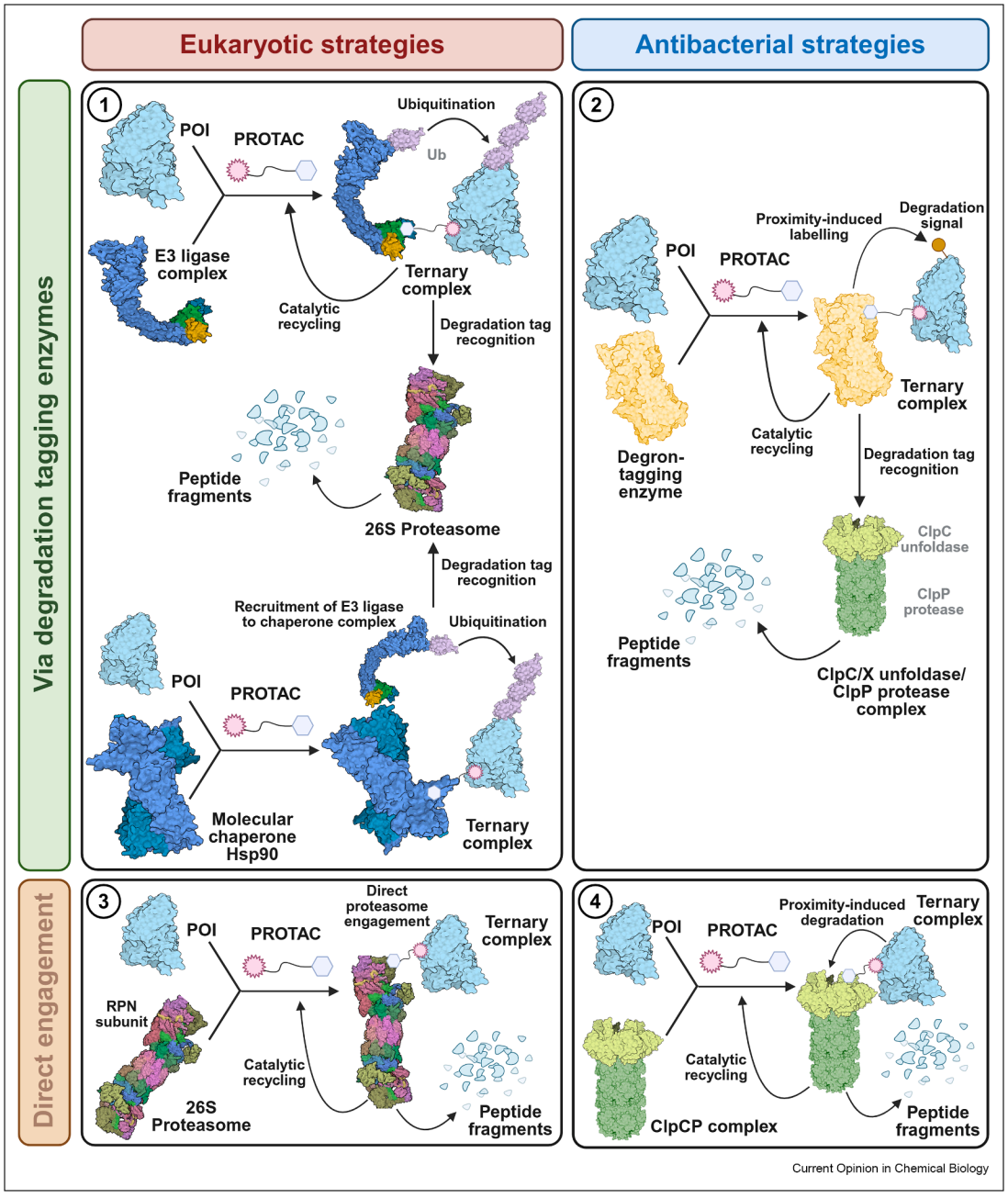
The unique catalytic, event-driven MOA of PROTACs provides several fundamental advantages over classical

Figure 1



PROTAC components. PROTACs consist of three components: 1) the target-engaging ligand (TEL) (or warhead), 2) a degradation machinery-engaging ligand (DMEL) that can either engage enzymes that tag the target protein of interest for degradation or engage a protease complex directly, and 3) a flexible linker that connects the former two components. Figure created in BioRender (https://BioRender.com/2si6zg5). PROTAC, PROteolysis-TArgeting Chimera.

Figure 2



PROTAC development strategies. Strategies for inducing TPD include the engagement of degradation-tagging enzymes that result in the target POI being tagged and directed to the protease for degradation, or alternatively, by direct engagement of the protease complexes. The method by which each of these strategies is executed depends on the pathogen; for example, there are distinct differences between the UPS-dependent tagging strategies used by eukaryotes (block ①) and the degron-tagging options used by bacteria (block ②). Moreover, the protease complexes are also different, with eukaryotic systems mainly relying on the 26S proteasome, while in bacteria unfoldase/protease complexes such as ClpCP or ClpXP are currently preferentially used for TPD. Note that in eukaryotic systems, tagging can occur by engaging the E3 ubiquitin ligase (block ①, top section), or by engaging the chaperone Hsp90, which subsequently recruits the E3 ligase for ubiquitination of the POI (block ①, bottom section). The latter strategy is especially promising for targeting pathogens (such as *P. falciparum*) for which few E3 ligase-engaging ligands are known, but for which several Hsp90 binders have been identified [25]. Protein structures were obtained from the Protein Data Bank (PDB) with codes: POI – 8GB3; ClpC – 6SFW; ClpP – 9K2K; E3 ligase – 5N4W; 26s proteasome – 5GJR; Ubiquitin – 1UBQ; Hsp90 – 8EOB. Figure created in BioRender (https://BioRender.com/qnpuori). POI, protein of interest; PROTAC, PROteolysis-TArgeting Chimera; TPD, targeted protein degradation; UPS, ubiquitin-proteasome system.

small-molecule anti-infective drugs that engage and modulate the activity of high-value targets [3].

Overcoming resistance

Since PROTACs do not rely on occupancy-driven pharmacology or high-affinity binding to the target POI but instead promote the formation of a transient ternary complex, they are not prone to point-mutation-driven resistance development, which typically reduces binding affinity as a primary resistance mechanism against traditional inhibitors [27]. Additionally, as PROTACs cause the removal of the target protein, they are also ideally suited to counter resistance mechanisms dependent on target overexpression or similar compensatory feedback mechanisms. PROTACs were found to be up to 8-fold more potent against resistant cancer cell lines and resistant viral strains, suggesting that similar resilience may apply to antibacterial PROTACs.

Expanding the 'druggable' target space

Traditional small-molecule-based drug discovery is constrained to proteins that possess a defined, accessible active site or binding pocket that can be modulated by a ligand-binding event. PROTACs, in contrast, only require a specific binding handle to interact with the POI. Consequently, they can degrade non-enzymatic and structural proteins, protein classes historically labeled 'undruggable' due to a lack of catalytic sites or binding pockets suitable for conventional inhibitors [28]. This includes transcription factors, scaffolding proteins, or proteins that act by inducing protein–protein interactions, providing opportunities to explore a larger compendium of pathogen-specific druggable targets. Moreover, known inhibitors of the target protein that were previously discarded during a classical drug discovery campaign may be reconsidered as TELs, decreasing discovery costs and enhancing development potential.

Enhanced efficacy, safety, and selectivity

The event-driven, catalytic MOA of PROTACs offers significant pharmacological advantages over conventional occupancy-driven drugs that depend heavily on maintaining specific effective concentrations. The principle of TPD translates into the potential to exhibit efficacy at lower doses, shorter treatment duration, and lower relapse rates. This, in turn, could lead to improved safety profiles and reduced toxicity. When used against pathogens, PROTACs' additional selectivity gains can be achieved by carefully selecting a DMEL component that avoids engaging the host's degradation machinery, thereby selectively inducing the degradation of pathogen-specific proteins even when starting with non-selective TELs. This may also offer avenues to reduce the impact on the host's bacterial symbionts (such as the human gut microbiome).

Targeted protein degradation application by pathogen type

Viral diseases (harnessing the host ubiquitin-proteasome system)

The application of TPD technology to combat viral infections often exploits the well-characterized human E3 ligases (like VHL and CRBN) and the human UPS that viruses typically hijack [21]. As such, the antiviral PROTAC development process largely mirrors that used for other human diseases, although differentiation has been achieved with hydrophobic tags (HyTs) that cause the POI to mimic an unfolded/misfolded state or RIBOTACs that recruit RNases to degrade the target's RNA. Some representative examples of antiviral PROTACs are listed in Table 1 and are extensively reviewed elsewhere [17,21,29,30].

Bacterial diseases (BacPROTACs)

Pursuing TPD for the development of new antibacterials requires approaches that hijack one of the various proteases involved in bacterial proteostasis, including the ClpCP protease complex. The degradation process is initiated when the N-terminal domain (NTD) of the unfoldase chaperone ClpC recognizes proteins with phospho-arginine (pArg) residues as a degradation tag (degron), introduced by a dedicated kinase (McsB) [31]. The POI is subsequently unfolded by ClpC for degradation by the proteolytic component (ClpP) [13].

BacPROTACs have been designed to specifically engage a target POI and the ClpC unfoldase in a ternary complex for proximity-induced degradation of the POI [13] (Table 1). BacPROTAC-1 linked biotin (the warhead for monomeric streptavidin, mSA) to pArg, successfully promoting selective degradation of mSA by reconstituted ClpCP from *Bacillus subtilis* and the homologous $ClpC_1P_1P_2$ from *Mycobacterium smegmatis*. However, due to the instability and poor pharmacokinetics of the pArg group, subsequent BacPROTACs used derivatives of the macrocyclic natural product Cyclomarin A (CymA) as the protease-recruiter as CymA binds the $ClpC1^{NTD}$ of mycobacteria (Figure 2). BacPROTAC-3, composed of sCym-1 and the JQ1 ligand as TEL, demonstrated selective degradation of the model protein $BRDT_{BD1}$ expressed in *M. smegmatis* cells.

Further modifications include Homo-BacPROTACs consisting of two linked $ClpC_1$ ligands to promote proximity-driven self-degradation of $ClpC_1$ [14], which

Table 1

Selected representative PROTACs currently in development as anti-infectious agents.

Pathogen	Target	PROTAC	Target-engaging ligand (TEL)	Degradation machinery-engaging l igand (DMEL)	Degradation effector	Linker extender	Linker chemistry	Ref
Hepatitis C Virus (HCV)	HCV NS3/4A protease	DGY-08-097	Telaprevir	Lenalidomide	CRBN	PEG	Amide	[43]
SARS-CoV-2	Main protease (Mpro)	Various	Various Mpro inhibitors/ligands	Thalidomide	CRBN	A	Ether	[44]
				Pomalidomide	CRBN	Piperazine–piperidine	Amide	[45]
				Lenalidomide	CRBN	PEG, alkyl	Amide, ester	[46]
				VH032	VHL	Alkyl ether	Click	[47]
				VH101	VHL	PEG	Click	[48]
H1N1 influenza virus	Neuraminidase	PROTAC 8e	Oseltamivir	VH032–CH_3	VHL	Alkyl	Amide	[49]
HIV	HIV-1 Nef	FC-14369	Hydroxypyrazole (Nef ligand)	Thalidomide	CRBN	amino alkyl acetamide	Ether	[50]
M. smegmatis	$BRDT_{BD1}$	BacPROTAC-3	JQ-1 (BRDT ligand)	sCym-1	$ClpC_1P_1P_2$	PEG	Amide	[13]
M. tuberculosis	ClpC	Homo-BacPROTACs	dCym	dCym	$ClpC_1P_1P_2$	PEG	Click	[14,15]
E. coli	CTX-M-14	NacssrA-1	Nacubactam	ssrA degron	ClpXP	Hexanoyl-Glu	Amide	[35]

PROTAC, PROteolysis-TArgeting Chimera.

showed potent bactericidal activity against drug-resistant *M. tuberculosis* (Mtb) strains (MIC <0.1 μM), and also inhibited the growth of Mtb in differentiated THP-1 macrophages [15].

Genetically engineered systems have been used to evaluate the sensitivity of specific POI targets to degradation in *M. smegmatis* [32]. The anti-TB drug pyrazinamide was shown to likely act through its activated form (pyrazinoic acid), which engages PanD and exposes a degron tag for recognition by the $ClpC_1P_1P_2$ complex [33]. A plasmid-encoded peptide expression system (Clp-interacting peptidic protein erasers, or CLIPPERs) directly engages a target POI and the homologous ClpXP complex (the latter through a native ssrA peptide-based degron tag) in *Escherichia coli* [34]. Recently, the ssrA peptide tag was linked to a TEL directed to the β-lactamase CTX-M-14 to reduce its levels in *E. coli* [35] (Table 1).

Parasitic diseases (a nascent field)

The application of PROTACs against organisms causing parasitic diseases has not been successful despite the clear potential to target parasites such as *Plasmodium falciparum*, the causative agent of malaria, the Trypanosomatids responsible for leishmaniasis, and African trypanosomiasis and Chagas disease [36], as well as related parasites such as *Toxoplasma gondii* and *Cryptosporidium* species. In malaria, multidrug resistance in *P. falciparum* is widespread and poses a significant challenge for antimalarial drug development, with current efforts focused on identifying elusive 'irresistible' chemotypes [37]. Moreover, many proteins are deemed essential for parasite survival; however, converting chemical interference of these proteins into clinical validation as druggable candidates remains difficult. This often leaves many proteins in the proteome undruggable, leading to saturation of molecules targeting the same protein. PROTACs might therefore play a role in targeting these parasites, enabling intervention on undruggable, yet essential, components beyond the existing druggable genome [38].

However, the development of antiparasitic PROTACs is faced with significant knowledge gaps regarding parasite-specific E3 ligase complexes and a limited understanding of the pathogen's protein degradation machinery. Compared to the >600 E3 ligases in the mammalian genome, the homologous family in *P. falciparum* parasites is much more restricted, with only 54 members [39,40]. No direct evidence of a VHL homolog exists in the parasite, although a functional Cullin-RING ligase complex has recently been described, providing insights into the substrates recognized by these E3 ligase complexes [41], which could potentially open new avenues for PROTACs designed specifically to target malaria parasites. Controlling protein homeostasis is crucial for *P. falciparum* parasite survival [42], and the 26S proteasome exhibits structural variations of interest to therapeutic development. Interestingly, *Plasmodium* possesses both a mammalian-like UPS and a bacterial-like caseinolytic ClpCP protease system in its apicoplast (a specialized organelle of archaebacterial origin).

Beyond malaria parasites, bioinformatic evidence suggests the presence of homologs containing the cereblon

thalidomide binding domain (CULT domain) in *Leishmania* and *Trypanosoma* species, offering a potential chemical handle for recruiting parasite CRBN E3 ligase machinery for PROTAC development in these parasites. Additional challenges in PROTAC development include target engagement *in situ*, as these parasites often reside in complex environments. For example, *P. falciparum* resides in erythrocytes, which lack an efficient UPS, and *Trypanosomatids* are compartmentalized in glycosomes, posing significant delivery challenges.

Challenges and barriers to clinical implementation

Technical challenges in PROTAC design represent the most frequently cited barrier to clinical translation. In particular, the limited range of small-molecule ligands available for engaging bacterial protease complexes currently constrains BacPROTAC development options. Moreover, while PROTACs in general face a higher optimization hurdle than monofunctional drugs to meet drug-like criteria, the limited examples of BacPROTACs provide little data on the potential specific pharmacokinetic limitations of these compounds. In this context, optimizing linker length and composition is likely to be critical for achieving appropriate pharmacokinetics and efficient ternary complex formation. Clear correlations between *in vitro* PROTAC-mediated degradation rates and the corresponding *in vivo* degradation efficiency are required to determine whether additional formulation or delivery challenges need to be addressed. For bacterial applications specifically, achieving adequate cell permeability could pose a significant hurdle and may require innovation regarding delivery systems. In the case of antiparasitic PROTAC development, similarities between human and parasitic degradation pathways could raise selectivity and toxicity concerns, requiring strategies to avoid host side effects. See Table 2 for more on potential pitfalls and mitigating actions that could be used to overcome these.

Outlook

PROTACs hold significant promise as next-generation anti-infective agents, but their translation beyond oncology remains to be proven. Advances in pathogen-specific ligase discovery, improved cell permeability in bacterial systems, and the development of PROTACs tailored to microbial proteostasis pathways will expand the range of druggable infectious targets. Opportunities include overcoming antibiotic resistance by degrading otherwise 'undruggable' or mutation-prone proteins, enabling strain-selective therapeutics, and potentially modulating host factors essential for pathogen survival, which would provide new opportunities for combination therapies with conventional inhibitors [35]. PROTACs could facilitate an immune response to infection based on their induction of the degradation of pathogen proteins into peptides that, if they reach the host, can stimulate a potent T-cell response by being presented on the cell surface via MHC (Major Histocompatibility Complex) class I [57].

Continued structural biology, chemical biology, and delivery-technology innovations suggest that PROTAC-based anti-infectives may ultimately evolve into a powerful complement to traditional antimicrobial therapeutics. The field is rapidly advancing to include computational tools for PROTAC design and modification [58,59], which will help achieve higher efficacy in ternary complex formation, thereby reducing the design–test cycles. Additionally, the pharmacological

Table 2

Potential pitfalls in applying TPD in anti-infective drug discovery, and possible actions to mitigate these.

Known pitfall	Mitigating action
E3 ligase resistance when targeting the UPS	• Expanding the repertoire of E3 ligases that can used for PROTAC design using established workflows [51,52] (especially relevant in *P. falciparum* for which little is known about available E3 ligases) • Pivoting to other degradation modalities such as lysosome and chaperone-based systems (e.g., LYTACs and HyTACs)
Resistance due to efflux of (Bac)PROTACs, especially in Gram-negative bacteria	• SAR study of (Bac)PROTAC linker length and identity may provide insight on how best to increase efflux avoidance through this component • Increase hydrophilicity, polar surface area, and solubility as compounds with these features are more likely to evade efflux [53]
Challenges in delivery of (Bac)PROTACs across low permeability membranes or to specific compartments	• The use of prodrug linkers, metabolic activation, biological carriers, or nanoparticle carriers as delivery strategies [54,55] • Employ Trojan horse strategies that hijack native transporters to introduce antibiotics [56]
For antiparasitic PROTACs, potential side effects due to off-target host degradation	• Improved understanding of similarities and differences of human and parasite UPS, especially E3 ligases.

PROTAC, PROteolysis-TArgeting Chimera; TPD, targeted protein degradation; UPS, ubiquitin-proteasome system.

constraints posed by PROTACS may be overcome by using the PROTAC knowledgebase to design molecular glues, i.e., small molecules capable of inducing TPD of a target protein by increasing its affinity for specific proteolytic machinery [5]. The PROTAC platform therefore demonstrates substantial potential for therapeutic innovation, particularly for diseases requiring long treatment durations like tuberculosis and those currently facing therapeutic failure due to the increasing prevalence of resistance.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Google's NotebookLM and elicit.com to summarize information from primary sources for an initial draft of this manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Erick Strauss reports financial support provided by the Gates Foundation and by LifeArc. Lyn-Marié Birkholtz reports financial support provided by the Gates Foundation and by LifeArc. The other authors declare that they have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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** of outstanding interest

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