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Antibacterial PROTACs: the road ahead for next-generation antibiotics?

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The discovery of antibiotics revolutionized modern medicine, enabling the treatment of once-deadly bacterial infections. However, the rise of antibiotic-resistant bacteria has severely limited their effectiveness, making antimicrobial resistance (AMR) a major global health challenge. Developing new antibiotics with novel mechanisms of action is notably difficult. A promising approach is targeted protein degradation (TPD), a technology that has transformed drug discovery and shown success in cancer, neurodegenerative diseases, and immunology. In this review, we explore the potential of TPD to create next-generation antibacterials, its advantages over conventional antibiotics, and current research on prokaryotic protein degradation systems and BacPROTAC molecules.

Introduction

Antibiotics are among the most successful drugs in the history of medicine and we are currently in the so-called 'modern antibiotic era', which began during the 20th century thanks to the work of Paul Ehrlich and Alexander Fleming and the discovery of salvarsan, prontosil, and penicillin.[(p1)] Modern medicine has a massive arsenal of antibiotics available to treat different pathological conditions; however, these drugs are gradually becoming ineffective because of the emergence of drug-resistant pathogenic strains. According to the WHO, AMR is 'one of the top 10 global public health threats facing humanity and requires a global, coordinated action plan to address'. AMR was estimated to have contributed to the deaths of 4.95 million people in 2019 and is projected to cause up to 8.2 million deaths per year by 2050.[(p2)] For comparison, cancer currently causes around 10 million deaths worldwide each year,[(p3)] whereas autoimmune diseases affect hundreds of millions of people globally.[(p4)] This highlights the potential magnitude of the AMR threat. It is believed that AMR is inevitably pushing humanity into the 'post-antibiotic' era and is expected to have a higher global burden than HIV or malaria.[(p5)] Thus, both WHO and the G7 Finance Ministers have highlighted the need 'to take additional specific and appropriate steps to address the antibiotic market failure. . .and bring new drugs to market where they meet identified public health needs'.[(p6)] However, developing a new antibiotic, specifically new chemotypes or classes endowed with an innovative mechanism of action, is difficult,[(p7)] with an estimated failure rate of 95%, and costs of hundreds of millions of dollars.[(p8)] Between January 2013 and December 2022, only 19 new antibiotics were approved by regulatory agencies worldwide.[(p9)] However, the preclinical antibacterial pipeline is characterized by a high level of diversity and intriguing concepts, with a remarkable 70% of new projects targeting novel pathways or presenting new mechanisms of action.[(p10)] For instance, a fascinating example of a new class of antibiotic was recently reported to kill antibiotic-resistant strains of *Acinetobacter baumannii*, through a previously unknown mode of action.[(p11),(p12)] Another example is the lasso peptide antibiotic lariocidin and its

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internally cyclized derivative lariocidin B, both of which exhibit broad-spectrum activity against a range of bacterial pathogens. These compounds inhibit bacterial growth by binding to the ribosome and interfering with protein synthesis.[p13]

The process of discovery and development of new antibiotics could benefit from the application of innovative approaches, such as the identification of proximity-induced modulators, including molecular glues,[p14] and proteolysis-targeting chimeras (PROTACs), which are able to trigger TPD *in vivo*.[p15] The latter, based on designing heterobifunctional molecules able to direct target proteins to the proteasome, has recently revolutionized drug discovery, leading to the identification of new hit and lead compounds, as well as clinical candidates.[p16] Over the past decade, this design strategy has yielded outstanding results in several pathological conditions, from cancer[p17],[p18],[p19] to neurodegenerative disorders,[p20],[p21] to infectious diseases[p22],[p23],[p24] and immunology.[p24],[p25],[p26] Several heterobifunctional degraders have advanced into clinical evaluation. Among them, vepdegestrant (ARV-471), an estrogen receptor degrader developed by Arvinas and Pfizer, is being investigated for the treatment of hormone receptor-positive breast cancer; CC-94676, an androgen receptor degrader developed by Bristol Myers Squibb, is under evaluation for metastatic castration-resistant prostate cancer; and BGB-16673, a Bruton's tyrosine kinase (BTK) degrader developed by BeiGene, is being assessed in patients with relapsed or refractory B cell malignancies. All three compounds are in advanced Phase III clinical trials, underscoring the clinical maturity of the PROTAC modality.[p26]

PROTACs offer several benefits over classical anti-infective small-molecule drugs in terms of toxicity, selectivity, and resistance, and the possibility to (i) target proteins generally considered as 'undruggable'; (ii) recycle discarded molecules; and (iii) open new possibilities for combination therapies.[p22],[p27],[p28]

However, although from a purely conceptual point of view PROTAC technology is easily transferable from eukaryotic to prokaryotic cells, the differences in basic biology and in the protein degradation processes make its application in the antibacterials field more complex. Indeed, with the exception of *Actinobacteria*, bacteria lack the ubiquitin–proteasome disposal system characteristic of eukaryotic cells, instead relying on a set of conserved degradative proteases for proteome maintenance and protein quality control.[p29] The main proteases, which are organized in oligomeric protein machineries, are caseinolytic protease P (ClpP), Lon, Filamenting temperature-sensitive protein H (FtsH), Heat shock locus U and V protease complex (HslUV), High-Temperature Requirement protein A (HtrA), and the Tail-specific protease (Tsp).[p30] In general, these complexes have two major components, an ATPase that provides energy for polypeptide chain unfolding and translocation, and a proteolytic domain responsible for hydrolysis of peptide bonds. ClpP is widely conserved across the bacterial kingdom and is an ATP-dependent serine protease with a classic Asp-His-Ser catalytic triad, which has an essential role in protein degradation and the proteome maintenance.[p31],[p32] ClpP oligomerizes into a homotetradecamer and cooperates with AAA^+ unfoldases, such as ClpX, ClpA, or ClpC.[p33] This association is crucial to the degradation process. In fact, ClpP alone can degrade only unstructured proteins and short peptides; to degrade larger proteins, it needs to be associated with an unfoldase. ClpX is the best conserved ClpP partner and is found in most bacteria.[p34],[p35] ClpA and ClpC are present in general in Gram-negative or Gram-positive bacteria, respectively.[p35]

Whereas eukaryotic proteasome recognizes a polyubiquitinated residue as the degradation signal (Figure 1a), bacteria can recognize different degradation signals (degrons), typically located at the N- or C-terminal ends of target proteins, and which can vary in size from single amino acids to short peptides, to post-translational modifications, including binding with a small protein.[p30]

Degrons can interact directly with unfoldases or with adaptor proteins, which help to deliver substrates to proteolytic complexes.[p29],[p36] An example is the ssrA tag, an 11-residue peptide (AANDENYALAA) that directs proteins toward degradation by the ClpXP complex (Figure 1b).[p37] This system, largely conserved among prokaryotes, has a prominent role in protein quality control in bacterial cells.[p38] The degron is added via a complex mechanism involving a transfer-mRNA (tmRNA), referred to as 'trans-translation' and rescuing stalled ribosomes (i.e., processing aberrant mRNAs) and preventing the accumulation of abnormal proteins.[p39]

The recently published cryo-electron microscopy (EM) structures of recognition and intermediate complexes between ClpX and ssrA [Protein Data Bank (PDB) IDs 6WRF and 6WSG, respectively) represent the first visualizations of the interaction of ClpX with a degron and could serve as an interesting starting point for the design of heterobifunctional molecules (Figure 2). Recently, it was reported that phosphorylated arginine (pArg) residues act as degradation signals in Gram-positive bacteria and *Mycobacteria*. These residues are recognized by highly specific receptor sites located in the N-terminal domain of ClpC ($ClpC_{NTD}$) (Figure 1C).[p40] For in-depth discussions regarding the bacterial protein degradation machinery, readers are referred to other reviews.[p30],[p41]

Lon is a serine protease that contains a Lys-Ser catalytic dyad and, in contrast to ClpP, does not require an association with an unfoldase, given that it contains both the proteolytic and ATPase domains.[p42] FtsH is a Zn^{2+}-dependent membrane-anchored metalloprotease that is also able to degrade ssrA-tagged proteins.[p43] By contrast, HslUV is a threonine protease.[p44] HtrA, also known as DegP in *Escherichia coli*, is a serine endoprotease that represents one of the most abundant proteins in the bacterial periplasm, having a crucial role in the maintenance of proteins in the cell envelope of diderm bacteria (e.g., ensuring that only properly folded β-barrel outer membrane proteins are included in the outer membrane). Interestingly, DegP displays dual chaperonin/protease activity, one or the other activity being predominant based on several factors (stress conditions, temperature, and a reducing environment).[p45],[p46] Given that it is located in the periplasm, where ATP is not available, DegP-mediated protein degradation does not require other partner proteins (such as unfoldases) and occurs in an ATP-independent manner.[p47]

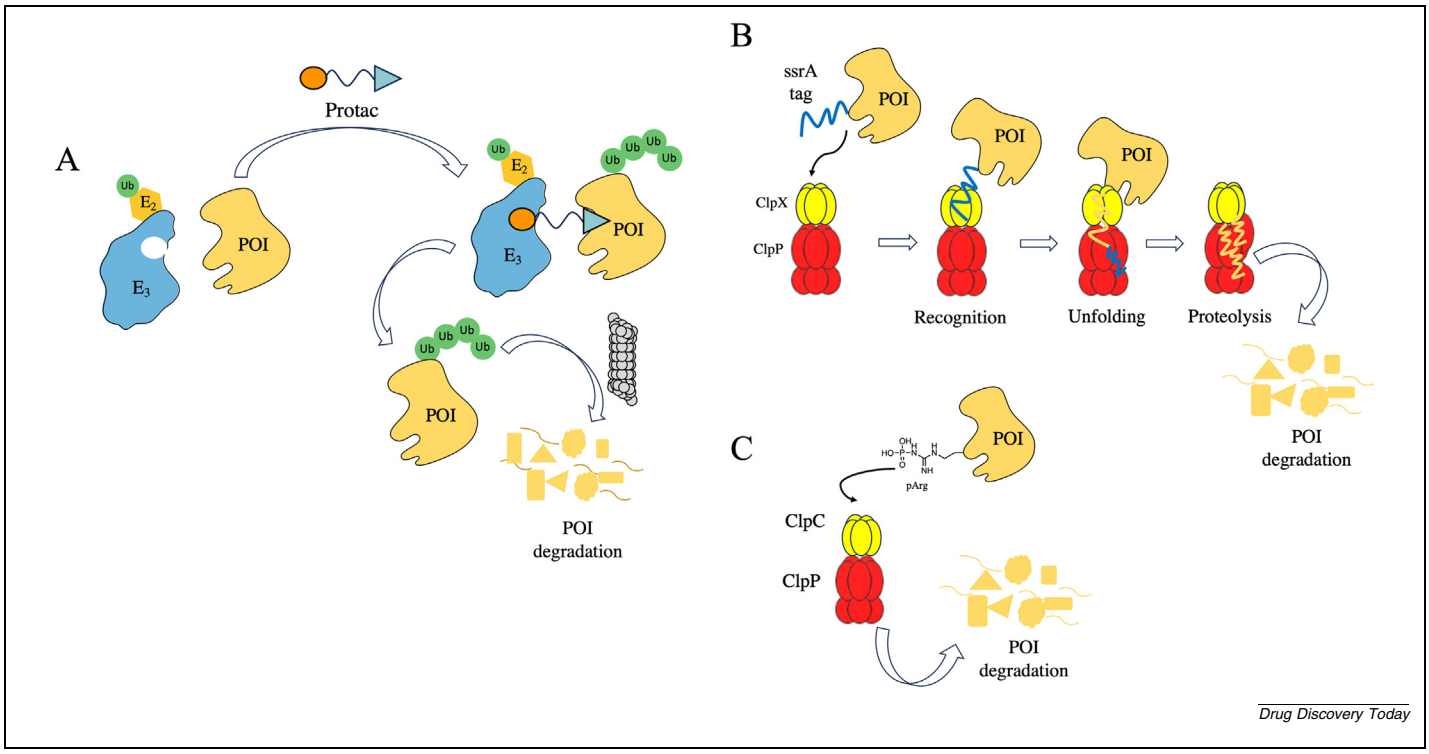

FIGURE 1

Mechanisms of targeted protein degradation in eukaryotic and bacterial systems. **(a)** Classic mechanism of action of proteolysis-targeting chimeras (PROTACs). PROTACs induce the formation of ternary complexes between E3 ligase and the protein of interest (POI). Polyubiquitination of POI leads to proteasome-mediated POI degradation; **(b)** Degradation of ssrA-tagged polypeptides by ClpXP protease. SsrA-tag is recognized by ClpX, leading to the unfolding of the polypeptide chain. Unfolded protein is then translocated into the ClpP chamber, where the peptide is completely degraded; **(c)** Bacterial protein degradation mediated by the recognition of the pArg residue by the ClpC protease.

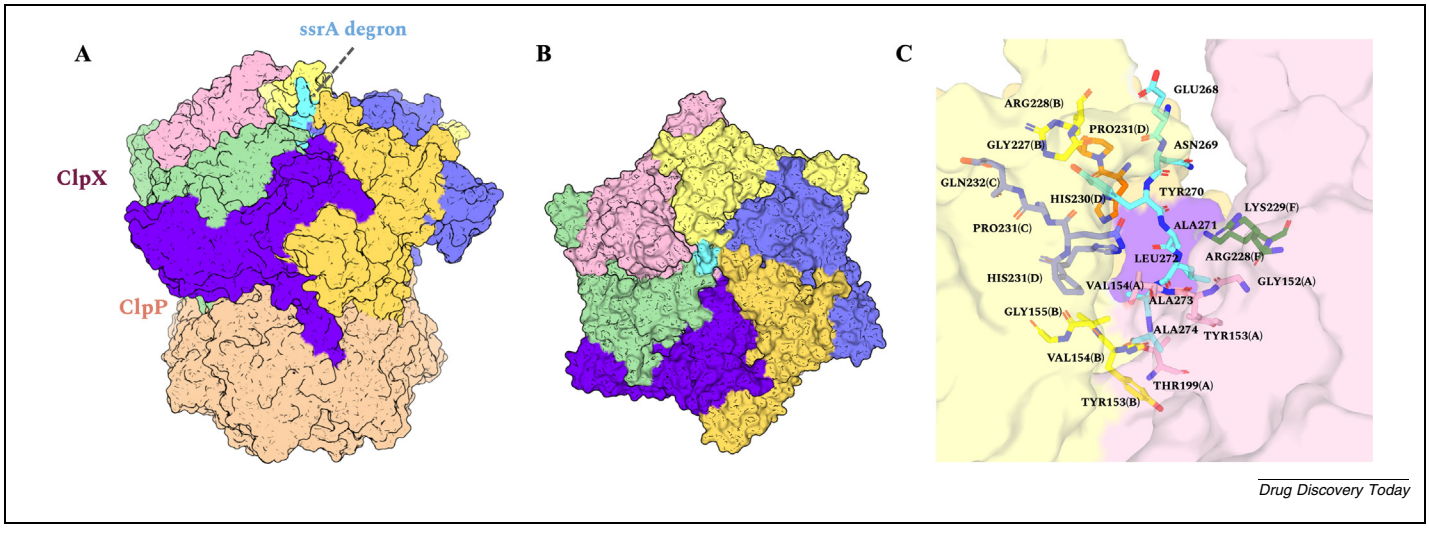

FIGURE 2

Cryo-electron microscopy structure of the recognition complex formed by ClpXP and the ssrA degron [Protein Data Bank (PDB) ID 6WRF]. **(a)** Frontal view. ClpX monomers are in different colours, whereas the entire ClpP ring is orange. The ssrA degron is in cyan. **(b)** Upper view of ClpX and ssrA. **(c)** The ssrA binding site. The degron residues and residues lining the ClpX pocket are showed as capped sticks and are labeled. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Development of BacPROTACs

Although PROTACs are being developed for a range of human diseases, limited PROTAC-like approaches have been applied in antibacterial drug discovery.[p22] Well-established approaches, such as hydrophobic tagging, have been considered in the inhibition of bacterial dihydrofolate reductase (DHFR).[p48] Indeed,

the first proof of concept of possible TPD in bacterial cells was obtained in 2012, when the hydrophobic tag triBoc Arginine was conjugated to trimethoprim, a DHFR inhibitor, resulting in DHFR degradation in *E. coli*.[p48] Another example of protein degradation in bacteria was obtained with pyrazinamide.[p49] This molecule is a prodrug that, in *Mycobacterium tuberculosis* (*Mtb*), is converted by the *pncA*-encoded pyrazinamidase into pyrazinoic acid that binds, albeit weakly, to PanD aspartate decarboxylase, inducing its degradation via the protease ClpC1P. In this case, the mode of action is similar to the anti-cancer drug fulvestrant, which promotes degradation of estrogen receptors via the proteasome.[p50]

Recent studies showed that, even though bacteria do not harbor the E3 ligase-proteasome system, it is possible to design PROTACs that directly engage bacterial proteases.[p51] Following this discovery, in a groundbreaking study, Morreale *et al.* designed heterobifunctional small molecules, named BacPROTACs, which are able to reprogram Clp proteases to degrade different proteins in Gram-positive bacteria and *Mycobacteria*.[p23] As an initial proof of concept, by using monomeric streptavidin (mSA) as a model protein, the authors demonstrated that a bifunctional molecule **1** was able to induce protein degradation in *Bacillus subtilis* (Figure 3a).

Compound **1** was designed using pArg, mimicking the bacterial degradation tag, and biotin, a specific ligand of streptavidin, connected via a linker. The linker attachment points were determined on the basis of available crystal structures (Figure 4a).[p40],[p52] Compound **1** was able to engage both targets (mSA K_D = 3.9 μM, $ClpC_{NTD}$ K_D = 2.8 μM) to form a stable ternary complex. Interestingly, significant mSA degradation was obtained at 100 μM of

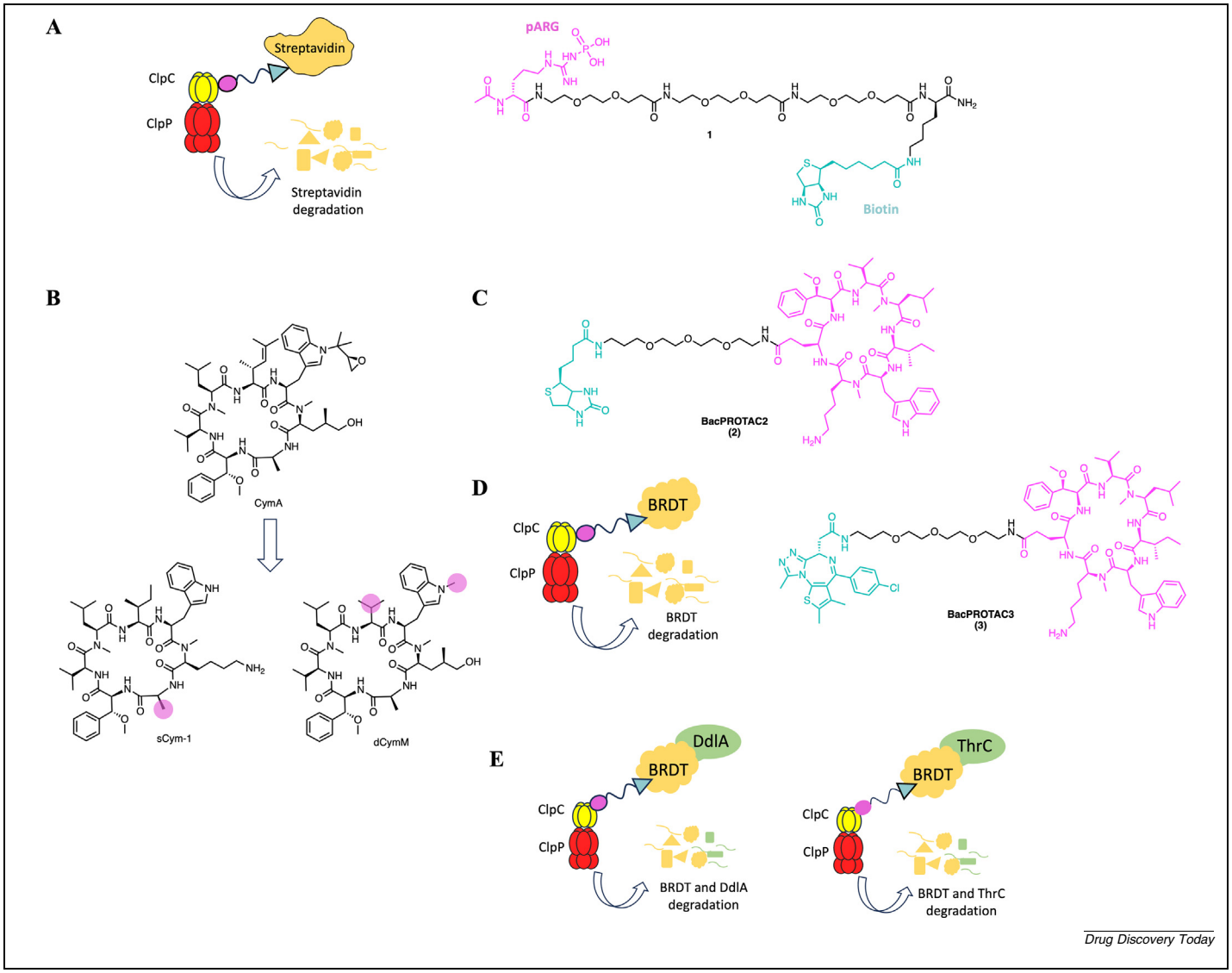

FIGURE 3

Design and proof-of-concept applications of BacPROTACs. **(a)** Schematic of ClpC–ClpP-induced streptavidin degradation and the structure of BacPROTAC **1**; the pArg residue is purple, whereas the biotin residue, the streptavidin-recruiting element, is cyan. **(b)** Structure of cyclomarin A (CymA) and analogs used for the design of BacPROTACs; linking attachment points are in purple. **(c)** Structure of BacPROTAC2 **2**; the sCym and biotin residues are in purple and cyan, respectively. **(d)** Schematic of ClpC–ClpP-induced BRDT degradation and structure of BacPROTAC3 **3**: the CymA analog is in purple, whereas the analogue reporting distomer JQ1 residue, the BRDT-recruiting element, is in cyan. **(e)** Schematic of ClpC–ClpP-induced BRDT-fused proteins, namely DdlA and ThrC, degradations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

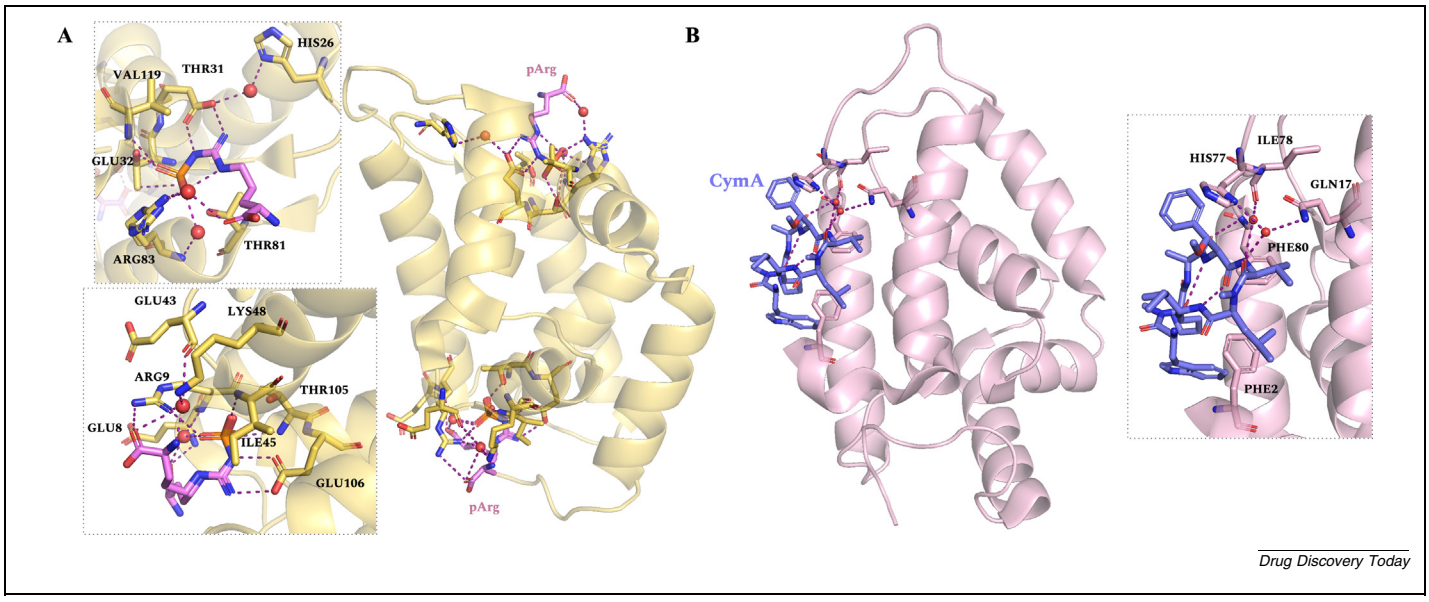

FIGURE 4

Structural basis of ClpC N-terminal domain recognition by pArg and cyclomarin A analogs. **(a)** X-ray structure of the ClpC N-terminal domain with bound pArg [Protein Data Bank (PDB) ID 5hbn]. The phospho-arginines (magenta) and interacting residues are shown as capped sticks and are labeled in the insets. Hydrogen bonds are shown as dashed lines and water molecules as red spheres. **(b)** X-ray structure of the ClpC1 N-terminal domain bound to a CymA analog (PDB ID 7AA4). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

compound **1**, a concentration higher than the measured affinities for the individual targets. Analogs with shorter linkers between the pArg and biotin moieties have been synthesized and, unexpectedly, their degradation efficiency was not significantly affected. This suggests that the linker length is not a crucial determinant for ClpCP to engage with streptavidin. This is surprising considering how linker length could affect PROTAC efficiency.[(p23),(p53)] Interestingly, structural characterization of the formed ternary complex revealed that BacPROTACs induce a structural reorganization from the inactive ClpC decamer to a highly ordered tetramer of ClpC hexamers.

Numerous issues, such as the poor chemical stability of pArg, and the limited ability to cross bacterial cell walls, severely limit the use of pArg-based BacPROTACs; therefore, a 'second generation' of BacPROTACs was developed by replacing the pArg moiety with Cyclomarin A (CymA), a $ClpC1_{NTD}$-directed antibiotic able to cross cell membranes.[(p54)] Interestingly, CymA binds to a hydrophobic pocket located in a different position to the pArg-binding site, a pocket highly conserved in ClpC1 mycobacterial protease but absent in Gram-positive ClpC proteins (Figure 4b). Given that CymA is a cyclic polypeptide comprising several nonproteinogenic amino acids, a series of analogs were synthesized and evaluated. Among these, the new derivative sCym-1 showed high affinity toward $ClpC1_{NTD}$ (K_D = 0.81 μM) and retained the same binding mode of the parent CymA (Figure 3b). Consequently, novel BacPROTAC **2** was prepared by replacing pArg with sCym (Figure 3c). It demonstrated the ability to degrade mSA, highlighting the possibility of building $ClpC1_{NTD}$-recruiting BacPROTACs using CymA analogs. To further demonstrate the broad applicability of the approach, the authors prepared different BacPROTACs to target the bromodomain testis-specific fusion proteins ($BRDT_{BD1}$), using chemically simpler CymA analogs as degrons and exploiting different linker attaching points. The classic analogue reporting distomer JQ1 has been used as the protein-of-interest (POI)-recruiting element and, among the different BacPROTACs synthesized, BacPROTAC **3** induced highly selective $BRDT_{BD1}$ degradation in *Mycobacterium smegmatis* at a 1 μM concentration by recruiting ClpC1P1P2 (Figure 3d).

Interestingly, analogue reporting distomer JQ1 induced only partial $BRDT_{BD1}$ degradation and only at the highest concentration used (100 μM). The authors also showed how BacPROTACs can be used to degrade BRDT fusion proteins, highlighting the potentiality of this technology to mitigate antibiotic resistance. Indeed, BacPROTACs were shown to be able to degrade two proteins responsible for antibiotic resistance. First, BacPROTAC **3** was used to degrade D-alanylalanine synthase, an essential component of the peptidoglycan biosynthetic pathway, the overexpression of which is correlated with D-cycloserine (DSC) resistance in *M. smegmatis*.[(p55)] Remarkably, BacPROTAC **3** fully restored DSC sensitivity. The authors then focused on a second target, threonine synthase (ThrC), a crucial enzyme in threonine biosynthesis.[(p56)] BacPROTAC **3** showed the ability to degrade ectopically expressed $BRDT_{BD1}$-ThrC in *M. smegmatis*, inducing an auxotrophic phenotype not reverted by the addition of L-threonine (Figure 3e).

In a subsequent work, Clausen and co-workers used desoxycyclomarin C (dCym), a CymA mimic, to develop extremely potent Homo-BacPROTACs to kill *Mtb*.[(p57)] To this end, such bifunctional compounds target the cellular protein quality control system by inducing degradation of ClpC1 and its guardian protein, ClpC2. Indeed, by examining the effects of different antibiotics on the activity of Clp proteases, the authors discovered that peptide antibiotics, such as dCym and ecumicin, mimicking a misfolded protein, bind to a conserved site, and permanently activate the protease, causing unselective massive perturbation

of the proteome. The authors observed that treatment of *Mtb* cells with dCym resulted in upregulation of ClpC2, whereas treatment with an ecumicin derivative led to upregulation of ClpC3. These two proteins, highly homologous to the $ClpC1_{NTD}$ domain, work as ClpC1 'guardians' because binding to small molecules that mimic misfolded proteins, such as dCym and ecumicin, can reduce the intracellular concentration of antibiotics that target ClpC1. The protective effects of ClpC2 were also confirmed in a parallel study from the Weber-Ban group.[p58] Therefore, the new class of Homo-BacPROTACs designed containing two dCym head, have a double function: (i) inducing ClpC1 degradation; and (ii) targeting and eliminating ClpC2 to counteract its protecting activity (Figure 5a). By using Trp6 or Val7 as linker attachment points, the designed HomoBacPROTACs **4** and **5** (Figure 5b) were able to induce degradation of both proteins and to inhibit *Mtb* growth ~100-fold more efficiently compared with the natural monomeric cyclic peptide. However, when *Mtb* H37Rv was treated to assess potential resistance development, the formation of four spontaneous resistant clones, with an F80V mutation able to reduce the affinity of dCym for ClpC1, was observed. In a subsequent paper, the authors explored the structure–activity relationships of Homo-BacPROTACs[p59] and, interestingly, showed that both enantiomers and monomers did not induce any degradation.

Recently, a new class of BacPROTACs was developed to degrade the CTX-M-14 β-lactamase by redirecting the ClpXP protease complex.[p60] CTX-M-14 is an extended-spectrum β-lactamase belonging to the CTX-M family, a group of enzymes that confer resistance to various antibiotics, particularly penicillins and cephalosporins.[p61] These BacPROTACs were designed using nacubactam, a known β-lactamase inhibitor,[p62] covalently linked to a degron through a series of different linkers (Figure 6). Among the various compounds obtained, NacssrA-1 was shown to degrade sCTX-M-14 (an engineered nascent CTX-M-14 lacking the signal peptide) in *E. coli* after 1 h of incubation, achieving maximal activity at 10 mM. Interestingly, at 100 mM, the degradation effect was comparable to that observed at 10 mM, consistent with a cell-recall effect.

Moreover, overexpression of CTX-M-14 renders *E. coli* resistant to cefotaxime. Remarkably, the BacPROTACs were able to resensitize the bacteria by promoting degradation of CTX-M-14, whereas the inhibitor nacubactam alone could not achieve the same effect. This highlights the potential of BacPROTAC technology to overcome bacterial resistance.

Concluding remarks

TPD, and especially PROTAC technology, has revolutionized drug discovery and has become an increasingly relevant approach in discovery projects in both academic and industrial research programs.[p16] This is certainly the result of the significant success obtained by these molecules, and the high expectations surrounding ongoing clinical trials, especially for ARV-471 and ARV-110.[p16] However, PROTACs that have successfully

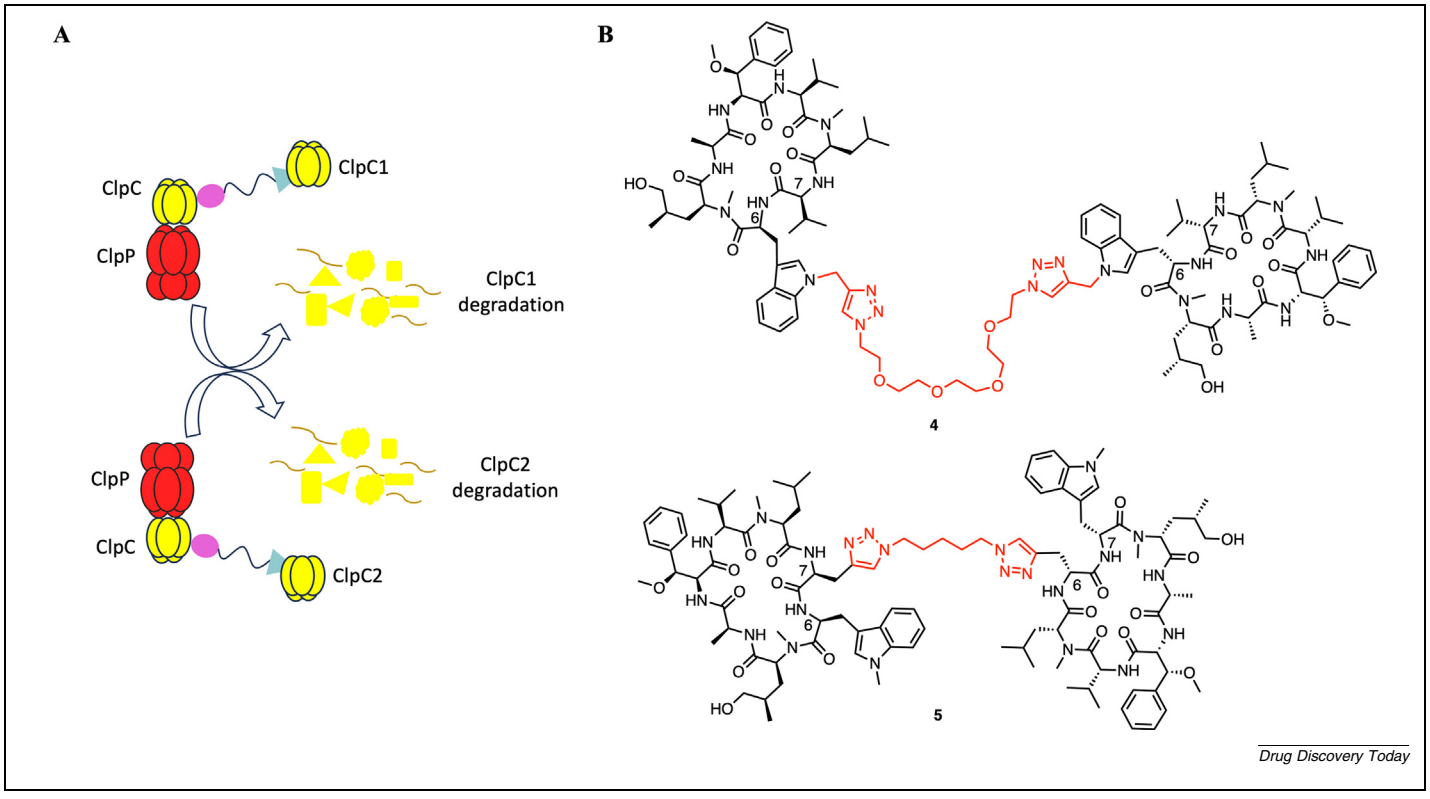

FIGURE 5

Homo-BacPROTAC-mediated degradation of ClpC1 and ClpC2. **(a)** Mechanism of action of HomoBacProtac. **(b)** Chemical structure of HomoBacProtac **3** and **4**. Triazole-based linkers are in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

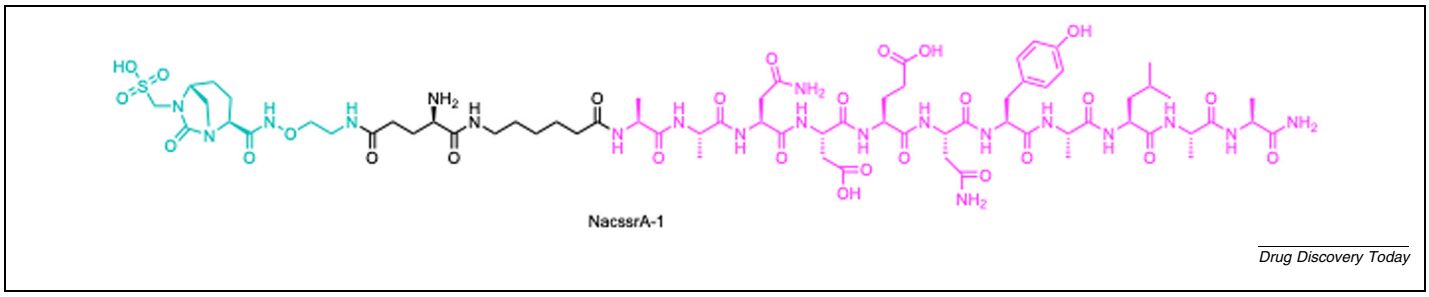

FIGURE 6

Chemical structure of the CTX-M-14-degrader NacssrA-1. The protein-of-interest (POI) recruiter is in green, whereas the ssrA ClpXP- binder is in magenta. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

advanced to clinical trials are primarily directed against cancer-related proteins[p17] and promising results have also been obtained in the development of PROTACs directed against viruses.[p63]

The application of this technology to antibacterial drug discovery remained unexplored until 2022, when Morreale *et al.* established the first proof of concept for antibacterial PROTACs. This groundbreaking work is expected to stimulate broader investment in PROTAC-based discovery of antibiotics suitable for clinical development.[p23] Although BacPROTACs are not the first agent to kill bacteria through protein degradation,[p48],[p49] the compounds developed by Morreale *et al.* might truly represent the turning point of PROTACs as antibacterials. Indeed, these molecules have been shown to degrade different proteins in multiple bacterial types.

Nevertheless, this approach, and the design of additional antibacterial PROTAC compounds, has several limitations. First, the presence of the bacterial wall and, more specifically, the outer membrane of Gram-negative bacteria, might limit BacPROTAC cell permeability and uptake. Indeed, this is why the observed apparent protein degradation in whole-cell assays is less pronounced than that observed in classical biochemical assays.[p23] In addition, there are significant issues associated with the physicochemical and drug-likeness properties of such complex molecules, especially in terms of high molecular weight, elevated number of hydrogen bond donors/acceptors, large total polar surface area, and low solubility. However, these problems are common to almost all PROTACs; therefore, generalized conclusions cannot be drawn and each case must be evaluated individually, with the hope that medicinal chemistry strategies might be established to successfully address these limitations.[p64]

Other concerns relate to the effect that these compounds might have on eukaryotic cells and on the host; this is particularly important when using CymA as a Clp-recruiter, given that CymA shows strong anti-inflammatory activity *in vitro* and *in vivo*.[p65] Moreover, ClpP is present also in mitochondria, where it is involved in the degradation of several enzymes of the electron transport chain.[p66] These considerations underscore the necessity to target more prokaryote-specific proteasome components.

The development of BacPROTACs could parallel that of 'classic' PROTACs. Indeed, although the first paper regarding this concept was published back in 2001,[p67] the actual expansion of the PROTAC approach occurred only in 2015, when it was discovered that small molecules, such as thalidomide-based compounds, could be used for harnessing cereblon (CRBN) E3 ligase.[p68],[p69] Subesequently, the von Hippel-Lindau (VHL) ligase was identified and successfully targeted[p70] and, over the years, numerous ligases have been reprogrammed to induce protein degradation, with remarkable results.[p71] Similarly, the discovery of nonpeptidic/peptidomimetic small molecules capable of recruiting Clp and other degrading systems could be the turning point in BacPROTAC development. Beyond Clp, the only successfully protease targeted up to now, it is of crucial importance to target other proteases, such as Lon, which also does not need to associate with other proteins to function properly. In this context, it is important to discover novel bacterial protease activators that can be used in the design of heterobifunctional molecules.

Given their distinct mechanism of action, BacPROTACs could open new therapeutic avenues across multiple bacterial species, particularly the WHO critical-priority carbapenem-resistant *Enterobacterales* (including *Klebsiella pneumoniae* and *E. coli*) and *A. baumannii*. PROTACs offer intriguing prospects in antibacterials because prokaryotes exhibit substantial diversity in degrons and proteolytic machineries, and the set of potential targets is almost unlimited. This could enable PROTACs with tailored activity spectra, either by degrading host-specific bacterial proteins (sparing the healthy microbiota and limiting antibiotic-induced dysbiosis) or by degrading factors that drive resistance or virulence (e.g., biofilm formation or secretion of host-damaging toxins), thereby disarming pathogens or restoring the efficacy of existing antibiotics in rational combinations. Furthermore, periplasmic proteases found in diderm bacteria (e.g., DegP) could also be exploited to induce the degradation of proteins with key roles in the proteostasis of the cell envelope, including those involved in peptidoglycan synthesis or lipopolysaccharide biogenesis and transport.

All these considerations open exciting possibilities for medicinal chemists, from the identification of new targets to the design of novel hits suitable for lead optimization, and the identification of clinical candidates. This approach holds significant promise for the development of potent, selective, and drug-like antibacterial agents, whose potential was demonstrated in the studies discussed herein. Such molecules could represent the

long-awaited next generation of antibiotics, capable of effectively counteracting the growing threat of AMR.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Andrea Milelli: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Simone Raimondi:** Writing – original draft, Formal analysis. **Somayeh Asgharpour:** Writing – original draft, Formal analysis. **Jean-Denis Docquier:** Writing – original draft. **Francesca Spyrakis:** Writing – original draft.

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Data availability

Data will be made available on request.

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