

## MINI REVIEW

# Harnessing Gram-negative bacteria for novel anti-Gram-negative antibiotics

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**Abstract**

Natural products have proven themselves as a valuable resource for antibiotics. However, in view of increasing antimicrobial resistance, there is an urgent need for new, structurally diverse agents that have the potential to overcome resistance and treat Gram-negative pathogens in particular. Historically, the search for new antibiotics was strongly focussed on the very successful Actinobacteria. On the other hand, other producer strains have been under-sampled and their potential for the production of bioactive natural products has been underestimated. In this mini-review, we highlight prominent examples of novel anti-Gram negative natural products produced by Gram-negative bacteria that are currently in lead optimisation or preclinical development. Furthermore, we will provide insights into the considerations and strategies behind the discovery of these agents and their putative applications.

## INTRODUCTION – THE IMPORTANCE OF NATURAL PRODUCTS AS ANTIBIOTICS

Beginning with the development of salvarsan in the early 20th century (Ehrlich, 1913), small molecule antibiotics have become one of the pillars of modern medicine. These drugs gave humankind the ability to treat and cure a wide range of bacterial infections and paved the way for many modern medical procedures (Hutchings et al., 2019). However, this progress is jeopardised by the rise of antimicrobial resistances (AMR) against more and more classes of antibiotics, leading to increasing numbers of deaths that are associated with or directly attributed to AMR (Murray et al., 2022; O'Neil, 2014; Ventola, 2015). Therefore, the discovery and development of novel antibiotics with new chemical scaffolds and molecular targets are needed, in particular with activity against Gram-negative bacteria (Walesch et al., 2022).

Although the first antibiotics were of synthetic nature (Ehrlich, 1913; Otten, 1986), the discoveries and

subsequent use of penicillin and streptomycin shifted the focus of antibiotic discovery towards natural products from microbes (Abraham et al., 1941; Fleming, 1929; Waksman & Schatz, 1945; Walesch et al., 2022). The ongoing relevance of microbial natural products as antibiotics is attested by the fact that more than two thirds of antibiotics that were approved between 1981 and 2019 are natural products or derivatives thereof (Newman & Cragg, 2020). When taking into account antibiotics that are currently marketed in the United States for the systemic treatment of non-mycobacterial infections, 18 out of 22 antibiotic classes are natural product-based (Walesch et al., 2022). Compared to synthetic compounds, microbial natural products are believed optimised through evolution to facilitate microbial competition for nutrients and habitats. Therefore, their structural diversity and physico-chemical properties are optimised to penetrate cell walls and selectively inhibit bacteria or other cells (Hutchings et al., 2019; Lakemeyer et al., 2018; Laraia & Waldmann, 2017; Wright, 2017).

Bacteria deserve a special place among microbial natural products producers. According to the latest

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version of the MIBiG database, the structural and biosynthetic diversity of bacterial natural products exceeds that of the compounds produced by fungi (Terlouw et al., 2023). Furthermore, the organisation of the genes responsible for the production of natural products are mostly clustered in biosynthetic gene clusters (BGCs) facilitating genetic manipulations to study and optimise the production of such compounds (Bode & Müller, 2005). Bacteria can be isolated from diverse habitats ranging from marine to soil and from permafrost to desert environments. In these complex ecosystems, bacteria may live independently or as symbionts and their natural products play a key role fulfilling a broad range of biological functions, e.g., cooperation and communication, defence mechanisms and predation (Figure 1). A vast majority – more than 99% – of bacteria have not been cultivated, thus providing an immense potential to discover novel natural products (Crits-Christoph et al., 2018; Locey & Lennon, 2016).

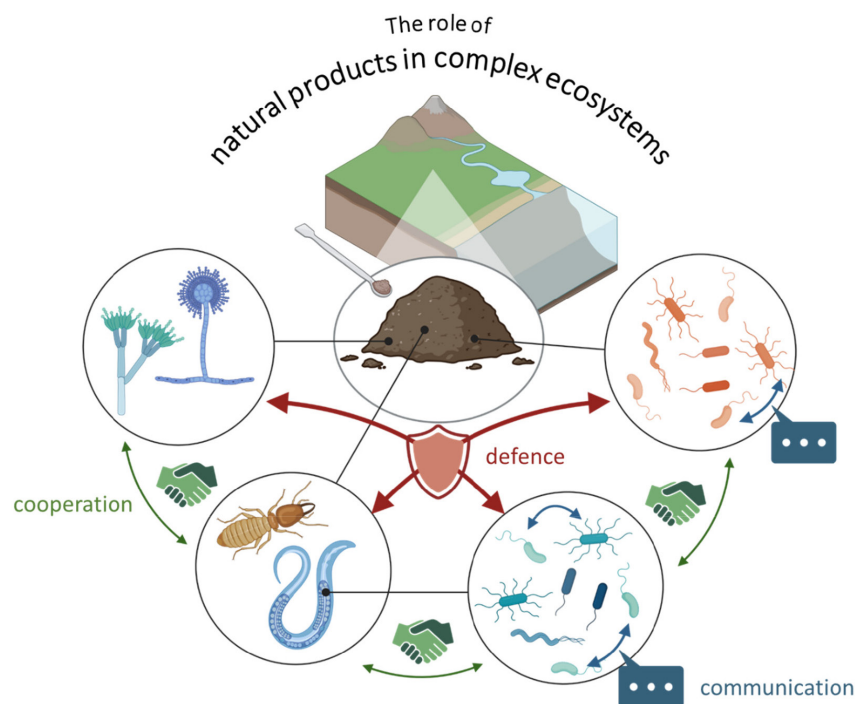
Hitherto, the majority of bacterial natural products listed in the NPAtlas database was discovered from Actinobacteria (Figure 2) (van Santen et al., 2022). Especially the genus *Streptomyces* was extremely fruitful for the discovery of clinically relevant antibiotics and anti-cancer agents (Katz & Baltz, 2016; Newman & Cragg, 2020). However, the bias towards soil-dwelling Actinobacteria and the resulting under-sampling of other phyla underestimated the potential of other natural products producers (Hutchings et al., 2019). For example, the phyla Cyanobacteria, Proteobacteria, Firmicutes or Bacteroidetes are less explored than Actinobacteria and harbour more genera with less reported natural products (Figure 2) (van Santen et al., 2022; Walesch et al., 2022; Wright, 2017). In this

mini-review, we exemplarily highlight three different discovery approaches that were recently applied to generally underrepresented Gram-negative producer strains, which yielded novel anti-Gram negative antibiotics that are currently listed in preclinical development stages by the WHO, which comprise agents in lead optimisation, preclinical candidates applying Good Laboratory and Good Manufacturing Practices (GLP and GMP) and agents in Clinical Trial Application and Investigational New Drug-enabling studies (CTA/IND) (Antimicrobial Resistance Division, 2024).

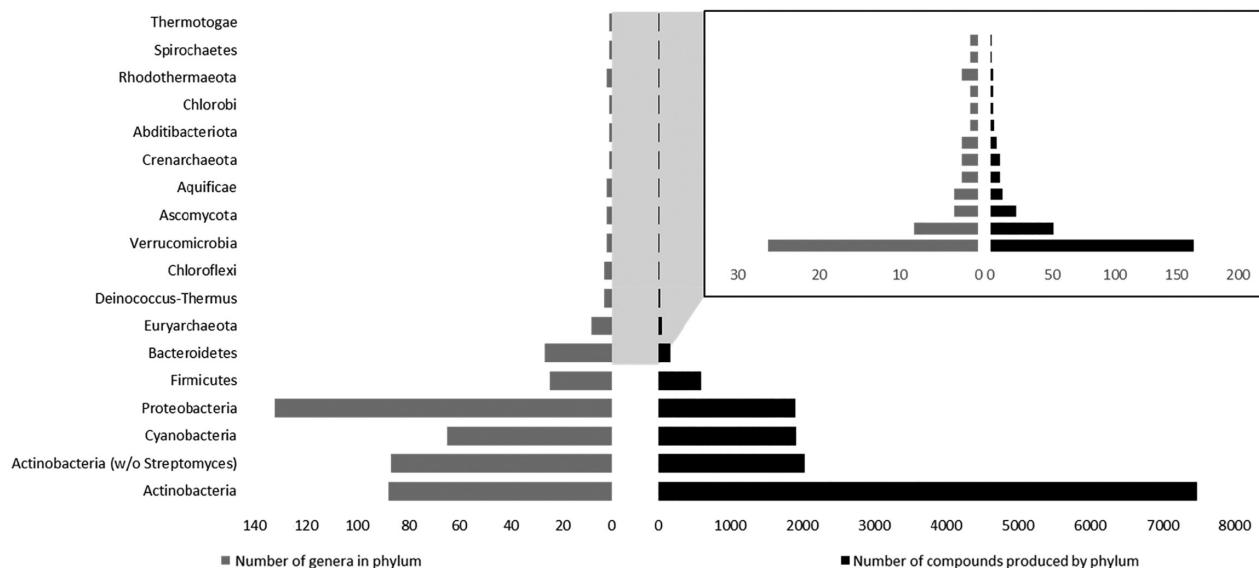
## MAIN – GRAM-NEGATIVE BACTERIA PRODUCING ANTI-GRAM-NEGATIVE ANTIBIOTICS – APPROACHES/HABITATS

### Predator approach

*Myxococcota* (or myxobacteria) are rod-shaped Gram-negative bacteria that grow in terrestrial and aquatic habitats all around the world (Mohr, 2018). They demonstrate a sophisticated and social life-style including coordinated swarming on flat surfaces, cooperative predation of other microorganisms and the formation of multicellular fruiting bodies upon starvation (Munoz-Dorado et al., 2016; Reichenbach, 1999). Furthermore, myxobacteria have the largest bacterial genomes with up to 16 Mbp (Han et al., 2013; Pal et al., 2021), harbouring a great potential to produce secondary metabolites (Garcia et al., 2024; Zaburanyi et al., 2016).



**FIGURE 1** Microorganisms live in diverse habitats and ecosystems, as individuals, in competition or in symbiosis. Natural products are used as a means of communication, cooperation, inhibition, defence and predation. Exemplified by the cooperation of termites and fungi and of bacteria and nematodes, in defence of other microorganisms. Created in BioRender. Birkelbach, J. (2024) BioRender.com/x25z927



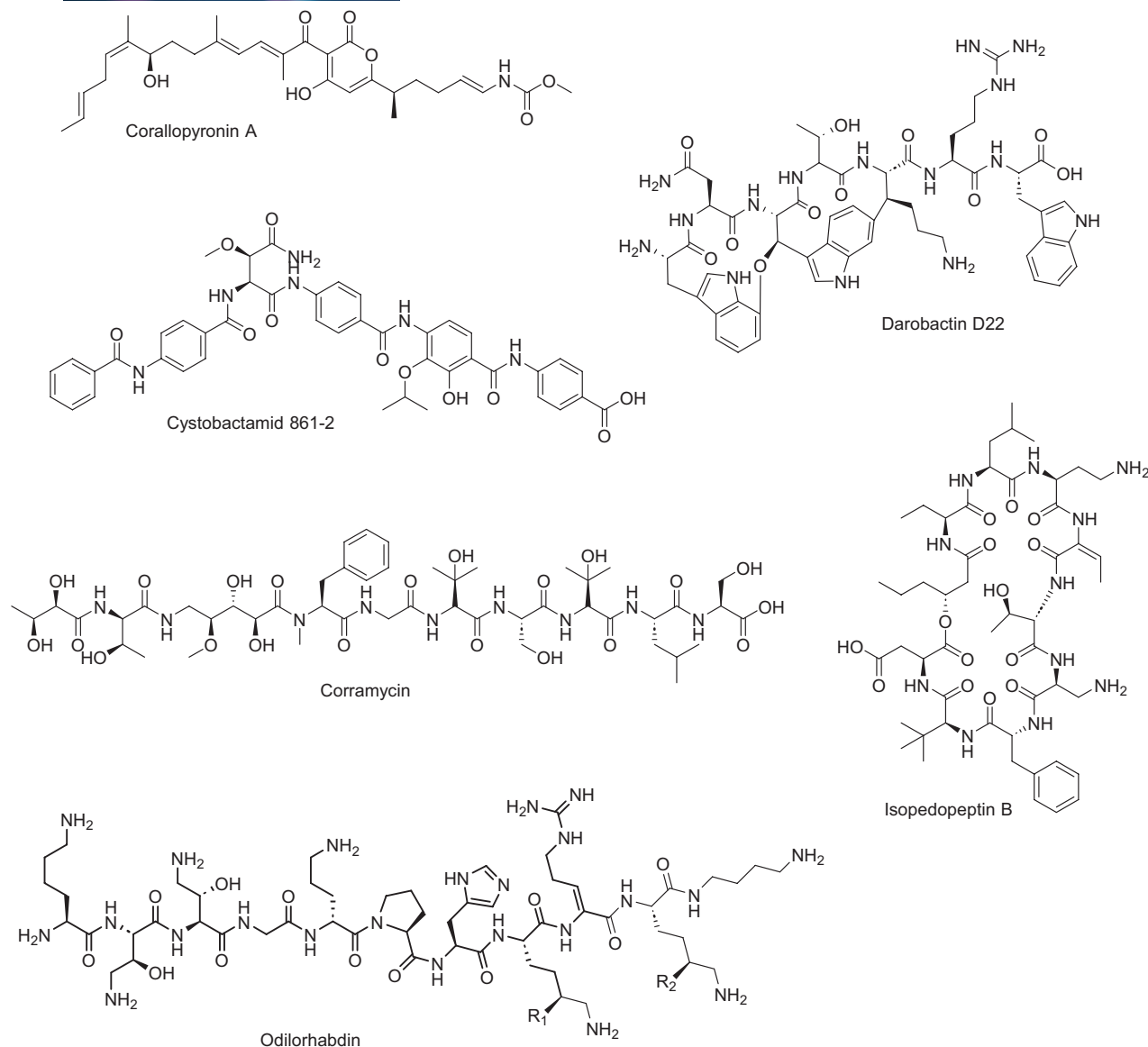
**FIGURE 2** The number of bacterial natural products produced per phylum (left) versus the number of validly described genera per phylum (right) reported in the NPAtlas database (van Santen et al., 2022). Inset shows phyla that produce <200 reported natural products.

The potential value of myxobacteria as producers of antibiotics was first discussed in the middle of the past century, based on their ability to lyse other microbes (Oxford, 1947; Singh, 1947). Further research showed the ability of myxobacteria to lyse human pathogenic bacteria and to produce substances with antibacterial properties (Mathew & Dudani, 1955; Noren & Raper, 1962). Arguably, due to the comparably difficult (large scale) cultivation of most *Myxococcota* in the laboratory (Mohr, 2018), it took until the late 1970s before ambrucitin was isolated as the first natural product from a myxobacterium (Ringel et al., 1977). Since then, myxobacteria have proven themselves as a fruitful source of natural products with diverse chemical scaffolds displaying a wide range of biological activities (Herrmann et al., 2017). As of 2023, more than 800 natural products, belonging to ~170 chemical scaffolds were isolated from myxobacterial cultivation extracts (Wang et al., 2024). Among the many natural product scaffolds from myxobacteria with antibacterial activities, three compounds or compound classes are currently in preclinical development for their activities against Gram-negative bacteria, coralopyronin A, cystobactamids and corramycins (Figure 3).

Although coralopyronin A (Figure 3) and its antibacterial activities against a range of Gram-positive and -negative bacteria was already described in the 1980s (Irschik et al., 1985; Jansen et al., 1985), its development as antibiotic seemed unlikely, due to low production titres in the original producer *Coralococcus coraloides* and a poor yield in chemical synthesis (Krome et al., 2022). This changed with the implementation of a heterologous expression system of coralopyronin in *Myxococcus xanthus*, which increased the production of coralopyronin A greatly (Pogorevc et al., 2019; Sucipto

et al., 2017). Coralopyronin A displays potent activity against Gram-negative bacteria like *Neisseria gonorrhoeae*, *Chlamydia* spp., *Rickettsia* spp. and *Wolbachia* spp. (Miethke et al., 2021). As a preclinical candidate it is currently developed for the treatment of filarial worm infections, by targeting their *Wolbachia* endosymbionts and has shown its efficacy in rodent infection models (Ehrens et al., 2022; Krome et al., 2022; Schiefer et al., 2020). The mode of action of coralopyronin A is the inhibition of the DNA-dependent RNA polymerase (Mukhopadhyay et al., 2008). As its binding site at the 'switch region' of the enzyme is distinct from the binding sites of other RNA polymerase inhibitors, coralopyronin A does not show cross-resistance with other antibiotics (Krome et al., 2022; Shima et al., 2018).

The antibacterial cystobactamids (Figure 3) were discovered in the cultivation extracts of *Cystobacter velatus* Cbv34 in the course of a screening campaign of a biodiverse collection of myxobacteria (Baumann et al., 2014; Herrmann et al., 2016). They are unusual peptides, featuring several *para*-aminobenzoic acids and display activity against Gram-positive and Gram-negative bacteria (Baumann et al., 2014). The molecular target of cystobactamids, the bacterial type IIa topoisomerase was found through investigation of the self-resistance mechanisms of the producing *Cystobacter* strain (Baumann et al., 2014). Obviously, cystobactamids target a different binding site in bacterial gyrases as the quinolone antibiotics, as they show a low to no cross-resistance with this scaffold (Baumann et al., 2014; Hüttel et al., 2017). In the past years cystobactamids have progressed to the lead optimisation phase, as the implementation of a heterologous expression system and a total synthesis route have led to the development of derivatives with highly improved properties *in*



**FIGURE 3** Chemical structures of corallopyronin A, cystobactamid 861-2, corramycin, isopedopeptin B, odilorhabdin and darobactin D22.

*vitro* and *in vivo* (Elgaher et al., 2020; Groß et al., 2021; Moeller et al., 2019; Moreno et al., 2015; Testolin et al., 2020). Interestingly, the albidins, originally isolated from the Gram-negative bacterium *Xanthomonas albilineans*, have a similar scaffold and antibacterial activities to the cystobactamids (Cociancich et al., 2015). Due to their unique scaffold the cystobactamids and albidins are currently in lead optimisation, which yielded derivatives with improved antibacterial properties and a better understanding of their modes of action and resistance mechanisms (Kleebauer et al., 2021; Michalczyk et al., 2023; Risch et al., 2024; Saathoff et al., 2023; Zborovsky et al., 2021).

Corramycins (Figure 3) are linear peptides with activity against *E. coli* that were first found in cultivation extracts of *Coralloccoccus coralloides* (Couturier

et al., 2022). Lead optimisation by organic synthesis was used to develop a corramycin derivative with a more than 300-fold increased activity against Gram-negative bacteria, displaying promising activities against *K. pneumoniae* and *A. baumannii* (Renard et al., 2023). Inactivation of the warhead by phosphorylation was identified as a mechanism of self-resistance in the producing myxobacteria (Adam et al., 2024). Although the mechanism of action of corramycins has not been elucidated yet, it can be assumed that it inhibits bacterial growth by a novel molecular target, as it shows no cross-resistance with known antibiotic classes (Couturier et al., 2022; Renard et al., 2023). Moreover, corramycins have shown their *in vivo* efficacy in a range of rodent infection models (Couturier et al., 2022; Renard et al., 2023).



## Resistance-based isolation approach

Antibiotic producing bacteria obviously require self-resistance mechanisms to protect themselves against the toxicity of the natural product they produced to affect their opponent.

To exploit self-resistance mechanisms, Thaker et al. successfully developed the resistance-guided cultivation approach selecting for glycolipopetide-resistant actinomycetes to screen for the production of new glycolipopeptides (Thaker et al., 2013, 2014). Bjerketorp et al. adapted and extended this approach on the screening of soil isolates selecting for environmental multi drug resistance (MDR) bacteria (Bjerketorp et al., 2021). Therefore, the combination of several antibiotics from different chemical classes was used to screen for natural product producers with multiple self-resistance mechanisms and thus the capacity to produce several antibacterial compounds. Furthermore, it enabled the isolation of low-abundant underexplored natural product producers present in soil-samples (Bjerketorp et al., 2021), which would have proven difficult without the selection bias.

This approach led to the isolation of several MDR *Pedobacter* spp., which are Gram-negative bacteria belonging to the phylum *Bacteroidota* and the family *Sphingobacteriaceae* (Bjerketorp et al., 2021). Nord et al. discovered the lipodepsipeptide isopedopeptin scaffold, which shows low micro-molar activity against WHO top priority pathogens including colistin resistant strains (Nord et al., 2020). Membrane disruption is proposed as one mode of action (MoA) of isopedopeptins, which is corroborated by the structural similarity to bacterial lipopolysaccharide (LPS)-binding pedopeptins (Hirota-Takahata et al., 2014; Kozuma et al., 2014). However, the discrepancy with the MIC suggests additional MoAs. Currently, isopedopeptin B (ULT3, Figure 3) is in CTA/IND studies showing good anti-Gram-negative activity and acceptable cytotoxicity. Although it is expected to discover similar antibiotics compared to the ones the isolates are resistant to, the extended resistance-based approach facilitated the isolation of underrepresented natural products producers, thereby the discovery of novel antibacterial compounds.

## Endosymbiont approach-*Xenorhabdus* and *Photorhabdus* as a promising source of new anti-Gram-negatives

In addition to bacterial species that have long been studied for the discovery of novel antibiotics, such as *Actinomyces* or *Myxococcota* (Müller & Wink, 2014), entomopathogenic bacteria have become a focus of research interest due to their complex lifestyle (Chaston

et al., 2011), which is mainly feasible due to the production of bioactive secondary metabolites that have a positive influence on persistence in the host (Cimen et al., 2022; Shi et al., 2022). In particular, studies have shown that the  $\gamma$ -proteobacteria *Xenorhabdus* and *Photorhabdus* spp., that live in mutualistic symbiosis with nematodes, provide antibiotic candidates with promising anti-Gram-negative activity against difficult-to-treat pathogens (Chaston et al., 2011; Walesch et al., 2022). *Xenorhabdus* spp. primarily infect nematodes of the genus *Steinema*, whereas *Photorhabdus* spp. mainly infect *Heterorhabditis* spp. (Clarke, 2008; Forst, 2002; Poinar, 1966; Poinar & Thomas, 1967; Waterfield et al., 2001). Although they use functionally different approaches, both infect the intestinal tract of their host and are able to overcome or suppress the immune system of their hosts (Chaston et al., 2011; Clarke, 2008), or kill it by producing insecticides (Proschak et al., 2014; Sergeant et al., 2006). Furthermore, both are producing many antimicrobial compounds to prevent the growth of antagonistic microorganisms allowing the persistence in the intestinal tract of their nematode host (Blackburn et al., 2016; Hu et al., 2006; Muangpat et al., 2017, 2020; Sajnaga & Kazimierczak, 2020; Wenski et al., 2020; Zhou et al., 2013). Recently, two promising novel antibacterial classes were discovered from these two endopathogenic bacteria: the odilorhabdins (Racine & Gualtieri, 2019) and the daropeptides (Ma et al., 2024), consisting of darobactins and dynobactin (Figure 3). Both classes exhibit strong anti-Gram-negative activity against, e.g., *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* strains including clinical isolates (Chaston et al., 2011; Imai et al., 2019; Ma et al., 2024; Pantel et al., 2018).

## Odilorhabdins

The discovery and development of odilorhabdins was largely driven by the start-up Nosopharm (Racine & Gualtieri, 2019). In a comprehensive screening of various *Xenorhabdus* strains, the first odilorhabdins (Pantel et al., 2018) were isolated from *X. nematophila* using a traditional bioactivity-guided approach, subsequently identifying the chemical structure and mode of action. Odilorhabdins represent a new class of broad-spectrum antibiotics. These compounds target the 30S ribosomal subunit of Gram-negative and Gram-positive bacteria on a binding site not exploited by currently marketed antibiotics, thus they have a reduced risk of cross-resistances (Pantel et al., 2018). Additionally, they conducted extensive derivatisation using chemical total synthesis to enhance antibacterial activity, particularly against *E. coli* and *K. pneumoniae* strains (Sarciaux et al., 2018). This led to the development of a frontrunner molecule, NOSO-502 (Racine

et al., 2018; Sarciaux et al., 2018), which is supposedly nearing clinical phase I studies for the treatment of critical urinary tract infections (UTIs) (Lanois-Nouri et al., 2022; Präve et al., 2024; Racine et al., 2018; Racine & Gualtieri, 2019).

## Darobactins

The first native darobactins were discovered after the bioactivity screening of *Photorhabdus* extracts (Imai et al., 2019). The bioactivity-guided approach resulted in the isolation of darobactin A (DA) from *P. khanii*, a novel anti-Gram-negative agent that is a ribosomally synthesised and post-translationally modified peptide (RiPP). Darobactins target the outer membrane protein BamA, part of the BamABCDE complex, preventing the incorporation and proper folding of outer membrane proteins into the cell membrane, thereby selectively killing Gram-negative bacteria (Haysom et al., 2023; Imai et al., 2019; Kaur et al., 2021). Through binding on BamA, a novel antibacterial target, darobactins have a strongly reduced risk of cross-resistance with currently used antibiotic classes.

Ongoing studies have focused on the heterologous production and total synthesis of native and artificial derivatives of darobactin A in *E. coli* by engineering the biosynthetic gene cluster (BGC) to produce optimised darobactin derivatives with modifications in the core peptide (Böhringer et al., 2021; Groß et al., 2021; Lin et al., 2022; Nesic et al., 2022; Seyfert et al., 2022; Wuisan et al., 2021). This has resulted in derivatives such as D22 (Figure 3) and D69, which exhibit up to 128-fold enhanced *in vitro* anti-Gram-negative activity against pathogens classified as critical prioritised by the WHO, such as carbapenem-resistant *A. baumannii* (CRAB), comparable to last-resort antibiotics like colistin (Seyfert et al., 2022; Seyfert et al., 2023; World Health Organisation, 2018). Despite these advancements, both the total synthesis routes and the biotechnological production in alternative production hosts currently suffer from relatively low yields (Seyfert et al., 2023), which must be addressed to bring these highly promising agents into clinical development.

## Outlook

The approaches described here, the predator approach, the resistance approach and the endosymbiont approach, led to promising anti-Gram-negative agents produced by Gram-negative bacteria. Exemplary compounds such as cystobactamids, corramycins, coralporonin A, isopedopeptins, darobactins and odilorhabdins and their bioengineered or synthetic

derivatives, respectively, are currently in development to prove their *in vivo* efficiency or have done so already (Couturier et al., 2022; Ehrens et al., 2022; Nord et al., 2020; Racine et al., 2018; Renard et al., 2023; Schiefer et al., 2020; Seyfert et al., 2023; Seyfert et al., 2023; Testolin et al., 2020). Those compounds, as well as other natural products in general, could be further optimised and their underlying biosynthesis investigated in more detail to allow for synthetic biology and evolution-inspired bioengineering techniques (Bozhüyük et al., 2024; Präve et al., 2024). Moreover, novel bioinformatically guided tools could allow for the modification of the chemical structure, to, e.g., enhance target binding or alter the pharmaceutical properties (Ndagi et al., 2020; Wang et al., 2022). The discovery approaches described here, which aimed at identifying compounds with new target sites, unknown chemistry and exhibiting no cross-resistances with marketed antibiotics, emphasise their potential for the development of novel molecules against Gram-negative bacteria. Further approaches such as high-throughput elicitor screening and the well-established OSMAC approach enable the identification of additional antibacterial molecules. Those approaches can be used to investigate already cultivated but also uncultivated bacterial species, living in mostly underexplored habitats to discover novel chemistry to fight the AMR crisis (Bader et al., 2021; Claesen et al., 2020; Crits-Christoph et al., 2018; Donia et al., 2014; Gavriilidou et al., 2022; Hegemann et al., 2023; Locey & Lennon, 2016; Nett et al., 2009; Nichols et al., 2010). As highlighted in Figure 2, e.g., *Pseudomonas*, *Burkholderia*, Cyanobacteria and Firmicutes species are further examples of underexplored yet promising natural products producers, which harbour the potential for the discovery of future antibiotic agents (Hegemann et al., 2023; van Santen et al., 2022; Walesch et al., 2022; Wright, 2017).

## AUTHOR CONTRIBUTIONS

**Joy Birkelbach:** Conceptualization; writing – original draft; writing – review and editing; visualization. **Carsten E. Seyfert:** Conceptualization; writing – original draft; writing – review and editing. **Sebastian Walesch:** Conceptualization; writing – original draft; writing – review and editing. **Rolf Müller:** Conceptualization; writing – review and editing; project administration; supervision.

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## CONFLICT OF INTEREST STATEMENT

C.E.S. and R.M. are inventors of the patent application WO 2022/175443 A1.

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