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Recent advancement of cyanobactins and cyanobactin prenyltransferases from 2021 to 2024

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Macrocyclic compounds have emerged in the 21st century, among which cyclic peptides are of particular interest. Cyanobactins are ribosomally synthesized and post-translationally modified peptides (RiPPs), many of which exist as cyclic peptides with a prenyl moiety, and prenylation can improve their structural stability and biological activity. This mini-review highlights the recently discovered cyanobactins and cyanobactin prenyltransferases from 2021 to 2024. Cyanobactin prenyltransferases will allow access to unique prenylated natural products for applications in drug discovery.

KEYWORDS

cyanobacterial natural products, cyanobactins, RiPPs, post-translational modification, prenyltransferases

1 Introduction

Ribosomally synthesized and post-translationally modified peptides (RiPPs) are a rapidly growing class of natural products defined by their post-translational modifications, with approximately 20 classes of RiPPs reported in 2013 and 40 classes in 2021 (Arnison et al., 2013; Montalbán-López et al., 2021). Cyanobactins are diverse RiPPs isolated from symbiotic and free-living cyanobacteria and possess diverse biological activities such as antimalarial, cytotoxicity and antimicrobial properties (Martins and Vasconcelos, 2015; Gu et al., 2019). The typical biosynthetic gene clusters of cyanobactin contain seven genes encoding precursor peptide (E protein), subtilisin-like serine protease (A/G protein), unknown function short protein (B/C protein), YcaO cyclodehydratase (D protein) and prenyltransferase (F protein) (Gu et al., 2019). The key features of cyanobactin include macrocyclization, heterocyclization (thiazole, oxazole, thiazoline and oxazoline), and prenylation (Gu et al., 2019). Only a few linear cyanobactins reported (Leikoski et al., 2013), most of them exist in the form of macrocyclic peptides.

Cyanobactin prenyltransferases are ABBA-type prenyltransferases that displace pyrophosphate group in the prenyl donor by a carbon, nitrogen or oxygen atom from the prenylated amino acid (Zheng et al., 2022; Zhang et al., 2023a). Cyanobactin prenyltransferases are highly selective for isoprenyl donors and amino acids involved in prenylation, but are relatively less selective for amino acids in macrocyclic peptides that are not involved in prenylation (Zheng et al., 2022; Zhang et al., 2023a). This feature has attracted a lot of attention from researchers because it can offer a versatile toolkit for peptide prenylation. To date, 14 cyanobactin prenyltransferases have been biochemically characterized, and one cyanobactin prenyltransferase MonF has been characterized based on genome analysis and the identification of its prenylated product, resulting in a total of 15 cyanobactin prenyltransferases (Figure 1A),

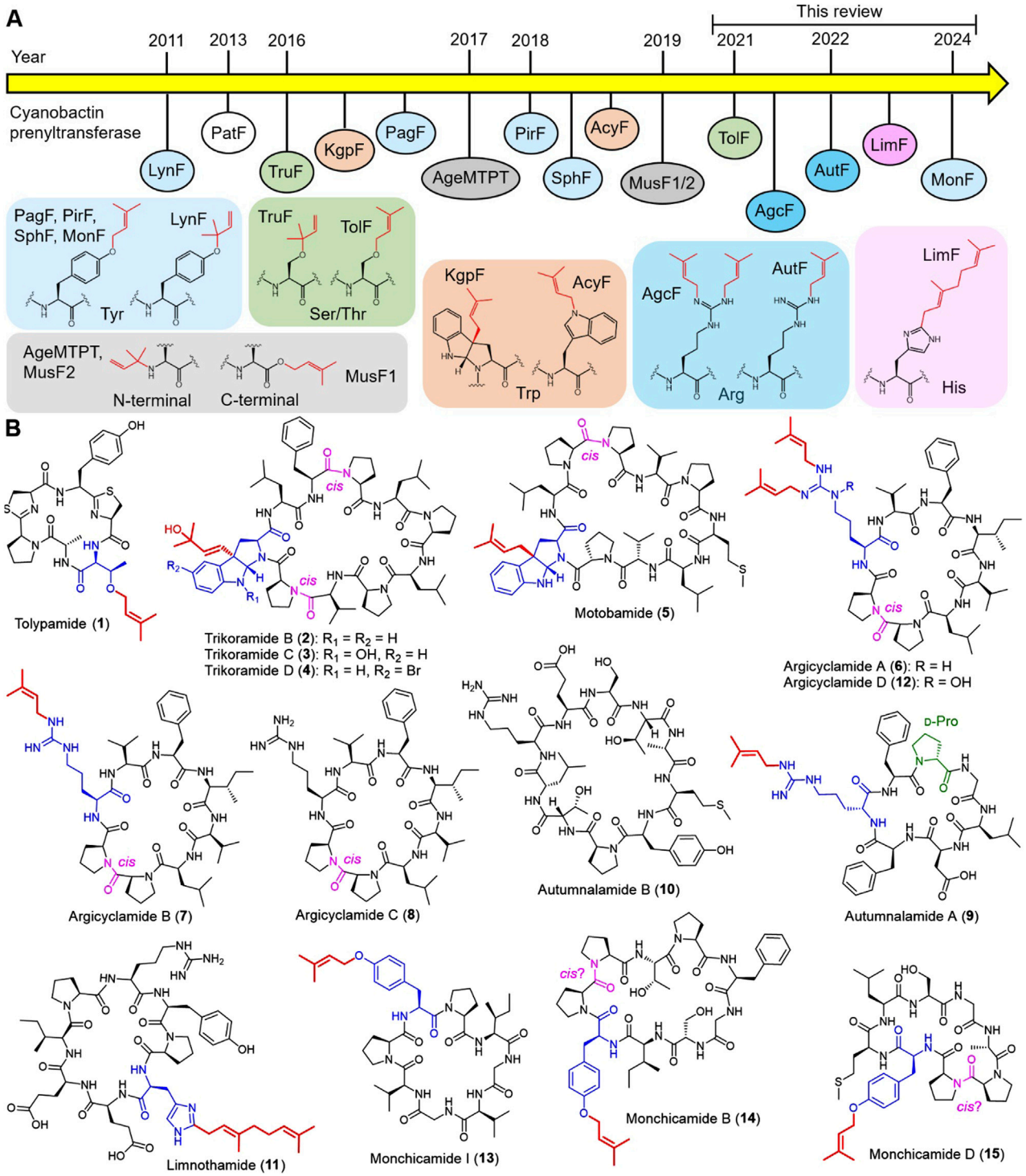


FIGURE 1
(A) Discovery timeline of cyanobactin prenyltransferases and their chemical transformations. **(B)** Structures of cyanobactins from 2021 to 2024. Prenyl groups are colored in red. Prenylated residues are colored in blue. *cis* amide bonds between Pro/Pro and Pro/X residues are colored in purple. d-amino acids are colored in green.

LynF from *Lyngbya aestuarii* (McIntosh et al., 2011; McIntosh et al., 2013), PatF from *Prochloron didemni* (Bent et al., 2013; Tianero et al., 2016), TruF from *Lissoclinum patella* (Tianero et al., 2016), KgpF from *Microcystis aeruginosa* NIES-88 (Parajuli et al., 2016; Inoue et al., 2024), PagF from *Oscillatoria agardhii* (Hao et al., 2016), AgeMTPT from *M. aeruginosa* PCC 9432 (Sardar et al., 2017), PirF from *M. aeruginosa* PCC 7005 (Estrada et al., 2018; Morita et al., 2018), SphF from *Sphaerospermopsis* sp. LEGE 00249 (Martins et al., 2018), AcyF from *Anabaena* sp. UHCC-0232 (Dalponte et al., 2018), MusF1/2 from *Nostoc* spp. PCC 7906 and UHCC 0398 (Mattila et al.,

2019), TolF from *Tolypothrix* sp. PCC 7601 (Purushothaman et al., 2021), AgcF from *M. aeruginosa* NIES-88 (Phan et al., 2021), AutF from *Phormidium autumnale* CCAP1446/10 (Clemente et al., 2022), LimF from *Limnothrix* sp. CACIAM 69days (Zhang et al., 2022), and MonF from Microcoleaceae cyanobacterium LEGE 16532 (Castelo-Branco et al., 2025). The cyanobactin prenyltransferases including (1) biosynthesis of cyanobactins and (2) discovery, biochemical characterization and bioengineering of cyanobactin prenyltransferases have been extensively reviewed elsewhere (Zheng et al., 2022; Zhang et al., 2023a). While this mini-review highlights the recently discovered prenylated cyanobactins and cyanobactin prenyltransferases from 2021 to 2024.

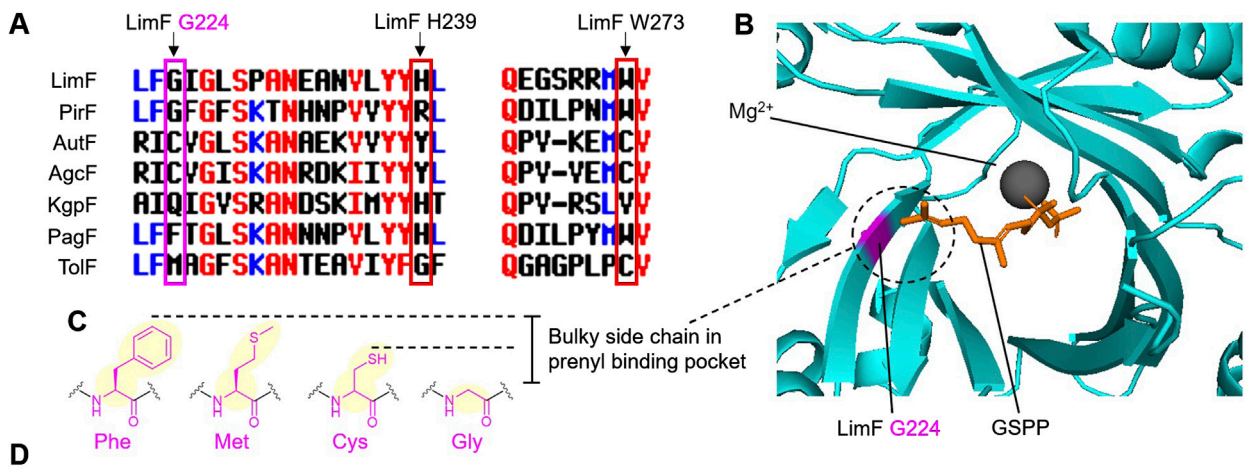
2 Discovery of cyanobactins and cyanobactin prenyltransferases from 2021 to 2024

A review published a decade ago reported a total of 57 cyanobactins (Martins and Vasconcelos, 2015), this number has not been updated since then, but a rough estimate is between 80 and 100 cyanobactins today. In 2021, a genome mining approach was used to prioritize cyanobacterial strains containing cyanobactin prenyltransferase from uncharacterized cluster in sequence-function space. This led to the isolation of tolypamide (**1**) and biochemical characterization of cyanobactin prenyltransferase TolF from *Tolypothrix* sp. PCC 7601 (Figure 1B) (Purushothaman et al., 2021). Tolypamide (**1**) showed no activity against six cancer cell lines (DU145, A549, HeLa CCL2, HepG2, and MDA-MB 231) or three bacterial strains (*Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29737 and *Pseudomonas aeruginosa* ATCC 9027). The substrate scope of TolF showed a certain degree of tolerant towards non-native peptide substrates of different lengths, sequence compositions and ring sizes. In the same year, two natural products studies reported cyanobactin-like structures without identifying their biosynthetic gene clusters. Three Trp-prenylated cyanobactins, trikoramides B-D (**2–4**) were isolated from *Symploca hydnoides* collected at Bintan Island, Indonesia (Phyo et al., 2021). Trikoramides B-D (**2–4**) possessed unique structures with additional hydroxylation or/and bromination on prenylated Trp residue (Figure 1B), but the enzymes involved in this chemical transformation are remains unknown. Trikoramides B (**2**) and D (**4**) showed cytotoxicity against acute lymphoblastic leukemia cell line (MOLT-4) with IC_{50} 5.2 and 4.7 μM, respectively. One Trp-prenylated cyanobactin, motobamide (**5**) was isolated from *Leptolyngbya* sp. collected at Okinawa, Japan (Takahashi et al., 2021). In cyclic peptides, the peptide bond geometry between two adjacent Pro residues was orientated in a *cis* conformation (Figure 1B), as observed in motobamide (**5**) where the *cis* amide bond was determined based on the (1) ^{13}C nuclear magnetic resonance (NMR) chemical shift differences between the Cβ and Cγ positions, and (2) NOESY correlations. Interestingly, two non-adjacent Pro residues in trikoramides (**2–4**) were assigned as *cis* in a similar manner. Motobamide (**5**) showed inhibitory activity against *Trypanosoma brucei rhodesiense* at IC_{50} 2.3 μM.

In the same year, LC-MS approach was used to search for prenylated cyanobactins by targeting a mass difference of 68 Da (isoprene), as this represented the mass difference between non-prenylated and prenylated cyanobactins. This led to the discovery of bis-prenylated, mono-prenylated and non-prenylated cyanobactins, argicyclamides A-C (**6–8**) and biochemical characterization of cyanobactin prenyltransferase AgcF from *Microcystis aeruginosa* NIES-88 (Figure 1B) (Phan et al., 2021). Previously, a cyanobactin prenyltransferase KgpF involved in the biosynthesis of Trp-prenylated cyanobactin, kawaguchipeptin A was characterized from the same strain (Parajuli et al., 2016). However, the putative precursor peptide AgcE was not found in the genome of *M. aeruginosa* NIES-88 (ASM157807v1), although the strain could produce both argicyclamides and kawaguchipeptins. Combining long-read and short-read re-sequencing of *M. aeruginosa* NIES-88 (ASM1970427v1) revealed argicyclamide biosynthetic gene clusters. Argicyclamides A-C (**6–8**) showed no activity against two cancer cell lines (P388 and MCF-7) but interestingly, their antibacterial activity was significantly improved based on the number of prenyl groups at Arg residue, argicyclamide A (**6**) has a MIC of 3.12–6.25 μM against *S. aureus* ATCC 12600, methicillin-resistant *S. aureus* ATCC 43300 and *Bacillus subtilis* ATCC 6051. For the substrate scope study of AgcF, several non-native peptide substrates were designed by exchanging the prenylated residue Arg to Trp, Tyr, Ser, Thr and Lys, but no prenylation activity was detected, indicating that AgcF is selective for Arg prenylation. A year later, a study involved solving the structure of the enzyme-substrate complex of LimF proposed that His167 in AgcF correlated to His172 in LimF is the catalytic residue for Arg-Nω prenylation (Zhang et al., 2022). The discovery of cyanobactin prenyltransferase AgcF expands the biocatalytic toolbox of this protein family, enabling them to catalyze prenylation on the amino acid with charged side chain. Prior to the discovery of AgcF, prenylation of this protein family are restricted to only amino acids with hydrophobic (Tyr and Trp) and uncharged side chains (Ser and Thr). The patent application on AgcF has been published (PCT/JP 2022/004501).

In 2022, cyanobactin prenyltransferase AutF was biochemical characterized from *P. autumnale* CCAP1446/10 (Clemente et al., 2022), a producer of autumnalamides A and B (**9** and **10**) (Figure 1B) (Sánchez et al., 2017). In the same year, a genome mining approach was used to explore sequence-function space of cyanobactin prenyltransferases and found an uncharacterized cyanobactin prenyltransferase LimF from *Limnothrix* sp. CACIAM 69d (Zhang et al., 2022). The NMR characterization of the *in vitro* generated product, limnothamide (**11**) confirmed a His-prenylated cyanobactin (Figure 1B). *Limnothrix* sp. CACIAM 69d was not used for the isolation of limnothamide (**11**). Among the cyanobactin prenyltransferases discovered between 2021 and 2024, LimF has the greatest potential to be developed into a biocatalyst, where LimF (1) can prenylate the His residue of any non-native peptide substrates, regardless of their length, overall sequence composition, and ring size; (2) has secondary function to prenylated Tyr residue that has not been seen in other cyanobactin prenyltransferases; (3) crystal structure in complex with substrate have been solved, PDB 7VMW and 7VMY; (4) key catalytic residues have been identified; and (5) can prenylated FDA-approved His-containing peptide/non-peptide drugs such as leuprorelin, pramlintide and cimetidine. The patent application on LimF has been published (PCT/JP 2022/038924).

In 2023, a re-visit of *M. aeruginosa* NIES-88 and found argicyclamide D (**12**) from the culture condition at 37°C without ammonium ferric citrate (iron source) supplemented in BG-11 media (Figure 1B) (Ballo et al., 2023), while argicyclamides A-C (**6–8**) were



Bulky side chain in prenyl binding pocket	Cyanobactin prenyltransferases	Prenylated position	DMAPP, C5	GPP, C10	FPP, C15
Gly (O)	LimF G224	His-C2	(-)	(+++)	(+)
Met (OOO)	LimF G224M	His-C2	(+++)	(-)	N/A
Gly (O)	LimF G224,H239G,W273T	His-C2	N/A	(+)	(+++)
Phe (OOO)	PagF F222	Tyr-O4	(+++)	(-)	(-)
Gly (O)	PagF F222G	Tyr-O4	(++)	(+++)	(+)
Gly (O)	PagF F222G,H237G,W271T	Tyr-O4	(+)	(++)	(++)
Cys (OO)	AgcF C219	Arg-Nω	(+++)	(+)	(-)
Cys (OO)	AutF C219	Arg-Nω	(+++)	(-)	N/A
Met (OOO)	TolF M231	Ser/Thr-Oβ	(+++)	(-)	(-)

FIGURE 2
(A) Sequence alignment of representative cyanobactin prenyltransferases, highlighting the active sites correlated to G224, H239 and W273 in LimF. **(B)** Complex structure of LimF-GSPP (PDB:7VMW), showing the space occupied by G224 in the prenyl binding pocket. **(C)** Bulky side chain residues that affect pocket sizes are colored in purple. **(D)** Prenylation activities. High, moderate, and low prenylation activities are indicated as (+++), (++) and (+), respectively. No reactions and not tested are indicated as (–) and N/A, respectively. Large, moderate, and small bulky side chains are indicated as (OOO), (OO) and (O), respectively.

previously isolated from the culture condition at 25°C with ammonium ferric citrate supplemented in BG-11 media.

In 2024, a genome mining approach was used to prioritize cyanobacterial strains containing cyanobactin prenyltransferase from uncharacterized cluster in sequence-function space. This led to the detection of 11 cyanobactins, monchicamides A-K, and identification of cyanobactin prenyltransferase MonF from Microcoleaceae cyanobacterium LEGE 16532 (Castelo-Branco et al., 2025). Only monchicamide I (**13**) was isolated and characterized by NMR, whereas the structures of the other cyanobactins were proposed based on LC-MS/MS data, which revealed that monchicamides B (**14**), D (**15**), F, G and K were prenylated cyanobactins. Interestingly, a *trans* amide bond between two adjacent Pro residues was proposed in the cyclic peptides of monchicamides B and D (**14** and **15**) (Figure 1B). However, if monchicamides B and D (**14** and **15**) were measured by NMR, the peptide bond between two adjacent Pro residues is most likely a *cis* geometry, and many similar *cis* amide bonds have been reported between Pro/Pro residues in cyclic peptides, such as **5-7**, noducyclamides and phakellistatins (Kwon et al., 2018; Phan et al., 2021; Takahashi et al., 2021; Mehjabin et al., 2024). Monchicamide I (**13**) showed no activity against three cancer cell lines (HepG2, HCT 116 and SH-SY5Y), four bacterial strains (*S. aureus* ATCC 29213, *B. subtilis* ATCC 6633, *E. coli* ATCC 25922 and *Salmonela typhimurium* ATCC 25241), one yeast (*Candida albicans* ATCC 10231) and three amoeba strains (*Acanthamoeba castellanii*, *Acanthamoeba polyphaga* and *Dictyostelium discoideum*).

3 Protein engineering of cyanobactin prenyltransferases from 2021 to 2024

Rational engineering of enzyme complexes in nonribosomal peptide synthetases (NRPS) and polyketide synthases (PKS) is a next-generation technology for natural products or small molecule drug discovery (Bozhüyük et al., 2024; Mabesoone et al., 2024). Many engineering studies in RiPPs have focused on the precursor peptides (Goto and Suga, 2018; Do and Link, 2023; Zhong et al., 2022). A relatively few engineering studies focused on the post-translational modification enzymes to alter or expand enzyme substrate scope (Phan and Morinaka, 2024b; Barrett et al., 2025). Cyanobactin prenyltransferases are known for their strict selectivity for the prenyl donors, with LimF and PirF only accept the GPP (C10, geranyl pyrophosphate) but not the DMAPP (C5, dimethylallyl pyrophosphate), while AutF, KgpF, PagF and TolF only accept

the DMAPP but not the GPP, but AgcF can accept both the DMAPP and GPP (Figure 2D).

In 2023, a structure-based engineering of the prenyl binding pocket size expansion was achieved in LimF (Zhang et al., 2023b). Three important active sites G224, H239 and W273 in LimF were identified (Figure 2A), particularly G224 located at the apex of the prenyl binding pocket (Figure 2B), which was thought to be the key residue in differentiating the pocket size for preference of C5 or C10 prenyl donors based on the bulky side chain of this amino acid at position 224 (Figure 2C). Mutation of G224 to Met successfully altered the prenyl donor preference from GPP to DMAPP (Figure 2D). Remarkably, the double mutant of LimF H237G,W271T achieved farnesylation accepting FPP (C15, farnesyl pyrophosphate) for the first time in cyanobactin prenyltransferases (Figure 2D). In a previous study, it was reported that the mutant PagF F222G exhibited geranylation activity (Estrada et al., 2018), and only a low farnesylation activity was detected (Zhang et al., 2023b). Interestingly, transfer of these two engineered sites in LimF H237G,W271T to PagF F222G could improve the farnesylation activity (Figure 2D) (Zhang et al., 2023b). In 2024, the mutant LimF I52A based on substrate binding pocket engineering enabled the enzyme to accept substrates with bulky chain side residue Phe preceding to the prenylated residue His, where the wild type substrate has less bulky residue Ala preceding to His (Zhang et al., 2024). Currently, the biological activities of the prenylated products catalyzed by these engineered proteins have not been evaluated. However, these engineering efforts have broadened the chemical space of cyanobactin prenyltransferases and further expanded the biocatalytic toolbox for prenylation.

4 Conclusion

Cyanobactins are a class of natural products that belong to the RiPPs. To date, RiPP is an exciting area of research for the discovery of new chemistry catalyzed by the post-translational modification enzymes (Zhong, 2023; Hubrich et al., 2022; Hubrich et al., 2024; Nguyen et al., 2024; Phan and Morinaka, 2024a; Khan et al., 2025; Kandy et al., 2025; Shi et al., 2025). Although cyanobactin system especially the subtilisin-like serine protease (A/G protein), YcaO cyclodehydratase (D protein) and prenyltransferase (F protein) has been extensively studied, there are still several aspects that can be further explored, for examples (1) unlike the A/G and D proteins, whose mechanisms have been studied (Koehnke et al., 2012; Koehnke et al., 2015; Zheng and Nair, 2023), mechanistic studies of cyanobactin prenyltrasnferases have not been performed; (2) a non-functional cyanobactin prenyltransferase PatF was found in the patellamide gene cluster (Bent et al., 2013), but its role remains unknown; (3) whether more diverse chemistries exist in the sequence-function space of cyanobactin prenyltransferases remains unclear; and (4) another open question is the logic governing the geometry of proline residues in cyclic peptides. While many cyanobactins feature a *cis* peptide bond between adjacent proline residues, the trikoramides interestingly show a *cis* configuration between non-adjacent prolines, suggesting the need for further investigation. Cyanobacteria are a rich source of natural products and biosynthetic enzymes (D'Agostino, 2023; Weiss et al., 2025), and cyanobactin prenyltransferases will allow access to unique prenylated natural products for applications in drug discovery.

Author contributions

AK: Writing – original draft, Writing – review and editing. C-SP: Writing – review and editing, Writing – original draft, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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