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Letter

Discovery of Paenibacillaceae Family Gram-Negative-Active Cationic Lipopeptide Antibiotics Using Evolution-Guided Chemical Synthesis

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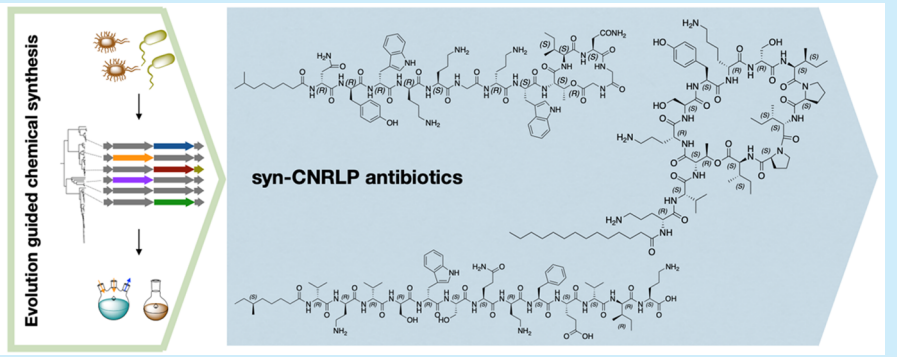

ABSTRACT: Cationic nonribosomal lipopeptides (CNRLPs) from *Paenibacillus* spp. have been a rewarding source of Gram-negative-active antibiotics. Here we systematically screened sequenced bacterial genomes for CNRLP biosynthetic gene clusters (BGCs) that we predicted might encode additional Gram-negative-active antibiotics. Total chemical synthesis of the bioinformatically predicted products of seven such BGCs led to our identification of new laterocidine, tridecaptin, and paenibacterin-like antibiotics with potent activity against both multiple-drug-resistant Gram-negative and Gram-positive pathogens.

Infections caused by antibiotic-resistant bacteria represent a serious and growing public health risk.[1] Gram-negative bacterial pathogens are of particular concern as they are responsible for ∼75% of deaths from antibiotic-resistant infections.[2] Many of the Gram-negative-active antibiotics that are currently in clinical use are based on metabolites that were originally found as products of bacteria grown in monoculture in the laboratory. Extensive use of these antibiotics has led to a rapid rise in resistant strains around the world. The increased appearance of bacterial pathogens that are resistant to our current arsenal of antibiotics necessitates the development of new antibiotics that are capable of killing antibiotic-resistant pathogens.[3]

Cationic nonribosomal lipopeptide (CNRLP) antibiotics are a small family of Gram-negative-active *N*-acylated cyclic and linear lipopeptide natural products that contain multiple positively charged amino acids (i.e., arginine, histidine, lysine, ornithine, and 2,4-diaminobutyric acid).[4] Many CNRLPs are particularly appealing from a clinical development standpoint because they show limited to no cross resistance with antibiotics that are currently in use in human pharmacotherapy. *Bacillus* and *Paenibacillus* spp. fermentation broths have traditionally been a rich source of CNRLPs, suggesting that these species are likely in continuous competition with Gram-negative bacteria in the environment.[5] The *Paenibacillus* spp.-produced CNRLP, colistin, is used as the last line of therapy against infections caused by multiple-drug-resistant (MDR) Gram-negative pathogens.[6] A number of additional *Bacillus*- and *Paenibacillus* spp.-derived CNRLPs are in early stage clinical development (e.g., laterocidine, tridecaptin, and paenibacterin).[5] The early stages of most antibiotic development programs include the synthesis of a large number of analogues in an effort to identify compounds with improved activity. A number of synthetic efforts have been made to optimize CNRLPs. These studies have largely centered on changing the N-terminal lipid, substitution of nonproteinogenic cationic amino acids, and changing the cyclization type.[7−11] So far none of these studies have succeeded in dramatically changing the potency and spectrum of these antibiotics. In the case of natural products, not only is it possible to imagine generating improved analogues by random synthesis (Figure 1), it is also possible to find inspiration from nature by studying naturally occurring congeners.

Here we hypothesized that natural niche competition between Paenibacillaceae bacteria and environmental Gram-

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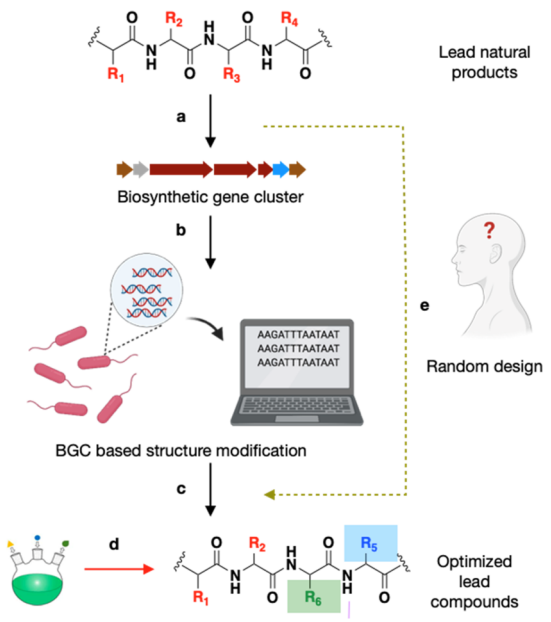

Figure 1. Evolution-guided antibiotic improvement. The BGC of a known antibiotic of interest (a) is used to identify related BGCs from among sequenced bacterial genomes (b). The bioinformatically predicted products of these BGCs (c) are synthesized to produce novel congeners (d). The traditional approach for improving a natural product has largely relied on random design (e).

negative bacteria might have led to the evolution and selection of biosynthetic gene clusters (BGCs) that encode natural analogues (i.e., congeners) of CNRLPs that differ in potency, spectrum of activity, and/or resistance profile. Each of these is important for an antibiotic's ecological role and are critical factors in the successful development of a new antibiotic. The true biosynthetic potential of bacteria for producing Gram-negative active CNRLPs is undoubtedly yet to be uncovered due to the silencing of BGCs in laboratory fermentation studies and difficulties with culturing environmental bacteria. A bioinformatic search of sequenced bacterial genomes for BGCs that we predicted might encode congeners of CNRLP antibiotics identified BGCs related to three families of Gram-negative active natural products: laterocidines, tridecaptins, and paenibacterins.[4,12−14] To circumvent potential problems associated with the fact that most bacterial BGCs are silent in laboratory fermentation studies, we chemically synthesized the products of the seven BGCs that were bioinformatically predicted to generate novel CNRLP structures. Among these synthetic bioinformatic natural products (syn-BNPs)[15] we identified CNRLP analogues with improved Gram-negative activity, increased broad-spectrum activity, and differences in activity against antibiotic-resistant pathogens. With the dramatic increase in publicly available bacterial genome sequence data, we believe that the use of BGC encoded information as a guide for synthetic derivatization studies should be applicable to improving an ever-increasing number of bioactive natural products.

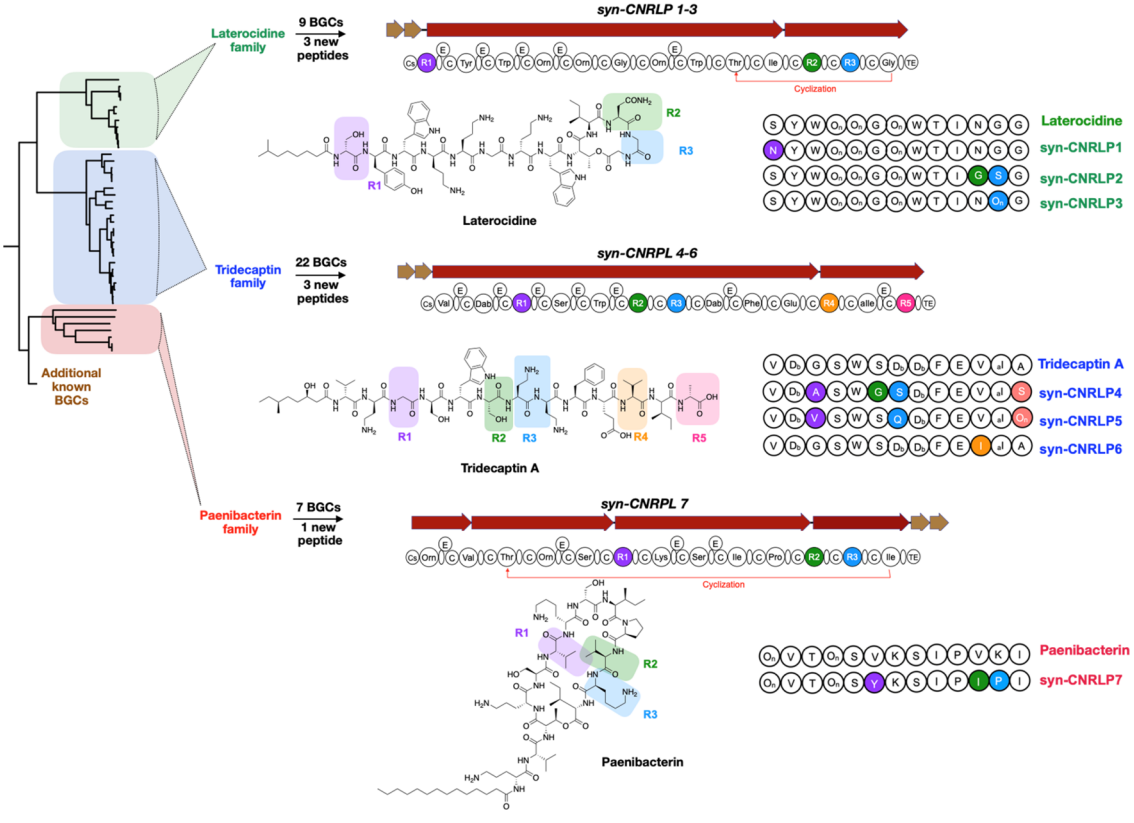

Figure 2. Discovery of CNRLP congener BGCs. A phylogenetic tree of Cs (condensation starter) domains was used to guide the discovery of BGCs that are related to the biosynthesis of the Gram-negative CNRLPs laterocidine, tridecaptin, and paenibacterin. The linear peptide product of each potential CNRLP congener BGC were bioinformatically predicted based on an A-domain substrate specificity analysis. Amino acids that differ from the predicted NRP product of a sequenced BGC are color coded on both the parent antibiotic structures and the bubble diagrams of predicted linear peptides. Nonproteinogenic amino acid codes: O_n: ornithine, aI: allo-isoleucine; D_b: 2,4-diaminobutyric acid.

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Table 1. MIC Values of Syn-CNRLPs against *E. coli* and the ESKAPE Pathogens[a]

	Gram-positive		Gram-negative				
	E. faecium	*S. aureus*	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*	*E. cloacae*	*E. coli*
CNRLP	MIC μg/mL						
laterocidine	>128	>128	2	0.5	2	1	0.5
syn-CNRLP1	>128	>128	2	0.25	4	1	1
syn-CNRLP2	64	128	2	2	4	4	1
syn-CNRLP3	>128	>128	2	4	4	1	2
tridecaptin A	64	128	1	4	64	2	1
syn-CNRLP4	>128	>128	1	2	>128	2	2
syn-CNRLP5	2	8	2	1	>128	8	2
syn-CNRLP6	>128	>128	1	2	>128	2	1
paenibacterin	8	16	8	8	8	4	4
syn-CNRLP7	2	8	8	16	64	16	32

[a]The MIC values were measured in duplicate.

Although individual CNRLP antibiotics differ significantly in peptide sequence and cyclization mode (e.g., linear peptides, small and large macrocycles, and cyclization using different nucleophiles), all CNRLPs contain an N-terminal lipid tail that is installed by a nonribosomal peptide synthetase (NRPS) condensation starter (Cs) domain.[16,17] By definition, CNRLP antibiotics contain multiple positively charged amino acids and have historically been relatively large (i.e., longer than 5 amino acids in length) NRP peptides. We used these common features to facilitate our search for CNRLP BGCs from sequenced genomes. We began the search for new CNRLP antibiotics by collecting NRPS BGCs from ∼10 000 sequenced bacterial genomes. A total of 15 254 of these BGCs were predicted to contain a Cs domain. Among these, 4253 BGCs were predicted to encode peptides with five or more residues, and 395 of these were predicted to contain two or more positively charged amino acids. To help guide our CNRLP discovery studies, we generated a phylogenetic tree of Cs domains from these 395 BGCs (Figure S1). In this tree, Cs domains from BGCs that are predicted to encode similar CNRLP structures grouped closely together, as would be expected for congener BGCs that arise from a common ancestor. This organization provided a simple means by which we could identify BGCs that were predicted to encode congeners of Gram-negative active CNRLP antibiotics. Uncharacterized BGCs that were associated with Cs domains that fell into the same clade as a Cs sequence from a known CNRLP BGC were examined in detail for the potential to encode a novel CNRLP congener. This analysis identified three CNRLP families that contained a number of uncharacterized sequenced BGCs: nine laterocidine BGCs, twenty-two tridecaptin BGCs, and seven paenibacterin BGCs (Figure 2).

NRPs are produced by sets of multidomain modules that extend the growing peptide by one amino acid per module. A canonical module is composed of an adenylation (A), a condensation (C), and a thiolation (T) domain, which select the amino acid substrate, create the new peptide bond, and carry the growing peptide, respectively.[18] The specific building block incorporated by a module can be predicted based on 10 amino acids that line the A-domain substrate-binding pocket (i.e., an A-domain signature sequence).[19] As NRPS tailoring enzymes are only rarely seen in characterized CNRLP biosynthetic pathways, the linear peptide structure encoded by a CNRLP BGC can be determined, in most cases, based solely on the A-domain substrate specificity analysis for each module in the BGC.

To determine the linear peptides produced by the 38 congener CNRLP BGCs, we identified, in sequenced bacterial genomes, each A-domain substrate-binding pocket in these BGCs was compared to publicly available A-domain signature sequence databases. We also compared them to a manually curated collection of A-domain signature sequences that we generated specifically from characterized CNRLP BGCs (Tables S1−S7). Due to taxonomic variation in A-domain signature sequences, we expected this manually curated, CNRLP-specific database to provide more accurate predictions of the peptide structures that are produced by CNRLP BGCs than is achieved using existing generic A-domain signature sequence databases. Based on our analysis most predicted CNRLP congener BGCs were determined to encode peptides that are identical to previously characterized natural products; however, seven BGCs were predicted to encode novel linear peptides. These included three laterocidine, three tridecaptin, and one paenibacterin congener BGCs (Figures 2 and S1). The linear peptide products of these BGCs were each predicted to differ from any previously characterized antibiotic in these families by one to three amino acids (Figure 2).

Although the natural products encoded by these CNRLP BGCs could theoretically be identified in fermentation broths of the bacteria in which they are found, this is a resource-intensive process and often of only limited utility, because the majority of BGCs are not activated in laboratory-based fermentation studies. With the increasing accuracy of bioinformatic algorithms for predicting natural product structures encoded by BGCs, we believed that the most straightforward method for accessing the small molecules encoded by this collection of CNRLP congener BGCs was through total chemical synthesis (Supplementary Scheme 1). The bioinformatically predicted linear peptide produced by each CNRLP BGC was therefore generated by Fmoc-based solid phase peptide synthesis (SPPS).[20] Peptides were then N-terminally acylated and either released as linear products (tridecaptins) or cyclized through the C-terminus using a nucleophilic amino acid side chain. The specific amino acid side chain that was used in a cyclization reaction was chosen to mimic the analogous structures seen in each specific CNRLP family. In the same vein, the structure of the specific N-terminal lipid used in each synthesis was based on the lipid most commonly seen in that family (laterocidines: 7-

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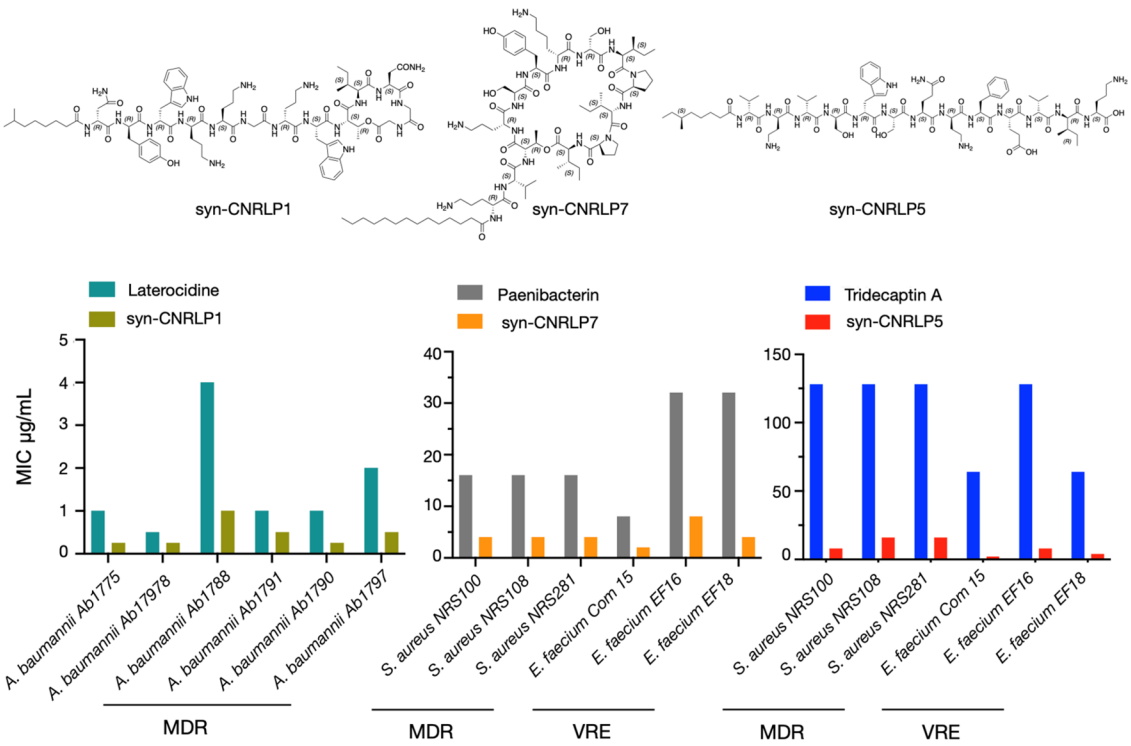

Figure 3. Antibacterial activity (MIC in μg/mL) of syn-CNRLPs and the parent natural product in each family against antibiotic-resistant pathogens.

methyloctanoic acid, tridecaptins: (*S*)-6-methyloctanoic acid, paenibacterins: myristic acid). The resulting laterocidine-, tridecaptin-, and paenibacterin-related structures were named syn-CNRLP1, -2, and -3, syn-CNRLP4, -5, and -6, and syn-CNRLP7, respectively (Figure 2, Figures S2−S9). Each deprotected peptide was purified by semipreparative HPLC (Figures S10−S16), and its structure was confirmed by HRMS as well as 1D and 2D NMR spectroscopy (Figures S17−S51, Tables S10−S16).

Synthetic CNRLPs (syn-CNRLP1 through -7) were tested for antibacterial activity against *Escherichia coli* as well as the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) (Table S8). Consistent with previously characterized CNRLPs, all seven syn-CNRLPs were active against Gram-negative bacteria. When compared to the activity of three parent CNRLP antibiotics that we synthesized in parallel as controls (i.e., laterocidine, tridecaptin A, and paenibacterin), the seven new BGC-predicted synthetic congeners showed differences in potency as well as spectrum of activity (Table 1, Table S9).

The three laterocidine congeners (syn-CNRLP1, -2, and -3) that we synthesized differ from laterocidine by one or two amino acids each. They all showed selective potent activity against Gram-negative bacteria with MICs ranging from 0.25 to 4 μg/mL, which is similar to the activity of the parent natural product laterocidine. One exception was that syn-CNRLP1 was more potent than laterocidine against the *A. baumannii* strain used in our screen. Subsequent screening of a larger collection of MDR *A. baumannii* clinical isolates found this was a general trend (Figure 3, Table S9). In fact, syn-CNRLP1 was more active against all of the *A. baumannii* strains that we tested (Figure 3, Table S9). Structurally, syn-CNRLP1 differs from laterocidine by the exchange of the exocyclic serine at position 1 for an arginine.[4] In contrast, syn-CNRLP2 and -3, which both showed a 4- to 8-fold increased MIC against *A. baumannii*, both contain changes to the amino acids in the laterocidine pentapeptide macrocycle (Table 1). In the future, further optimization of the exocyclic portion of laterocidine could potentially provide an even more potent *A. baumannii*-active antibiotic.

Paenibacterin is a broad-spectrum lipopeptide antibiotic that was originally isolated from cultures of *Paenibacillus thiaminolyticus* OSY-SE.[13,21] Up to now, only one naturally occurring paenibacterin structure had been reported from the analysis of bacterial culture broths. Syn-CNRLP7 differs from paenibacterin by three amino acids, which results in a shift in spectrum of activity. Syn-CNRLP7, like paenibacterin, is a broad-spectrum antibiotic with activity against both Gram-positive and Gram-negative pathogens in the panel of strains we screened. When compared to paenibacterin, syn-CNRLP7 showed a general reduction in Gram-negative antibacterial activity but an improvement in activity against both wild-type and MDR *S. aureus* and vancomycin-resistant *Enterococcus* (VRE) pathogens (MICs range from 2 to 8 μg/mL) (Figure 3, Table S9). Although this broad-spectrum activity is interesting, it is tempered by the fact that, as is the case for paenibacterin itself, syn-CNRLP7 has generally weaker Gram-negative activity than is seen with other syn-CNRLPs we generated.

The three tridecaptin A congeners that we generated (syn-CNRLP4, -5, and -6) differ from tridecaptin A by one to three amino acids. These are the first reported cases of changes at positions 3, 6, and 7 in a tridecaptin congener. Unlike known tridecaptin congeners (i.e., tridecaptins A, B, C, and M), which show activity only against Gram-negative pathogens,[22−24] one of the tridecaptin congeners we synthesized, syn-CNRLP5, showed broad-spectrum activity. It was active against both Gram-negative and Gram-positive ESKAPE pathogens, with

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MICs ranging from 1 to 8 μg/mL. In contrast, syn-CNRL4 and -6, like tridecaptin A itself, were specifically active against Gram-negative bacteria. Syn-CNRL5 is active against not only wild-type strains but also MDR Gram-positive pathogens (Figure 3). Against VRE clinical isolates its MIC ranged from 2 to 8 μg/mL, and against MDR *S. aureus* strains its MIC ranged from 8 to 16 μg/mL. In both cases this is significantly better than tridecaptin A, which has an MIC of 128 μg/mL against these same strains (Figure 3, Table S9). To the best of our knowledge, syn-CNRL5 is the first natural or synthetic tridecaptin analogue with potent Gram-positive activity.[7,22−24]

Bacteria have been a rich resource of Gram-negative-active CNRLP antibiotics. Here we systematically screened sequenced bacterial genomes for uncharacterized BGCs that we predicted would encode congeners of Gram-negative-active CNRLP antibiotics. This led to our identification of seven CNRLP BGCs that were bioinformatically predicted to encode previously unreported laterocidine-, tridecaptin-, and paenibacterin-like antibiotics. Through total chemical synthesis of the structures that each of these BGCs was bioinformatically predicted to encode, we identified CNRLPs with improved activity against Gram-negative pathogens as well as improved broad-spectrum antibacterial activity. The identification of additional evolutionarily selected analogues within each of these natural product families adds to the arsenal of structures that are available to explore in the effort to develop novel CNRLP-based therapeutics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01879.

Experimental methods, overall synthetic scheme, syn-CNRLP domain prediction tables, syn-CNRLP biosynthetic pathways, and syn-CNRLP NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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