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https://doi.org/10.17952/37EPS.2024.P2055

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Nature-inspired unique antimicrobial peptides from Chilean marine sediments

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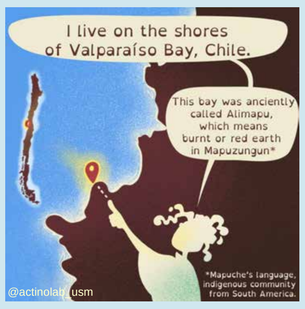
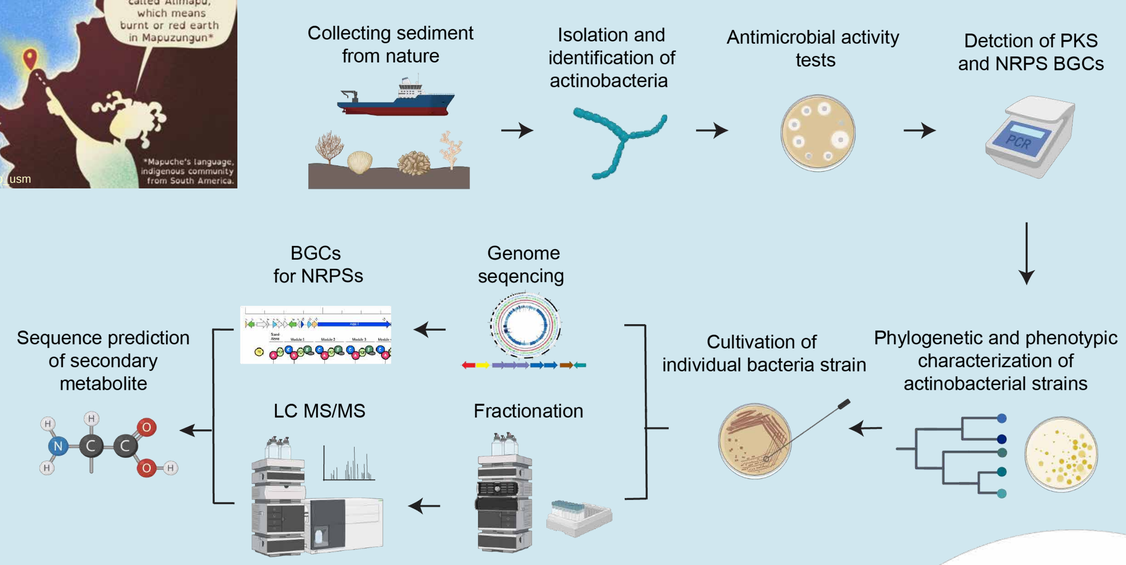
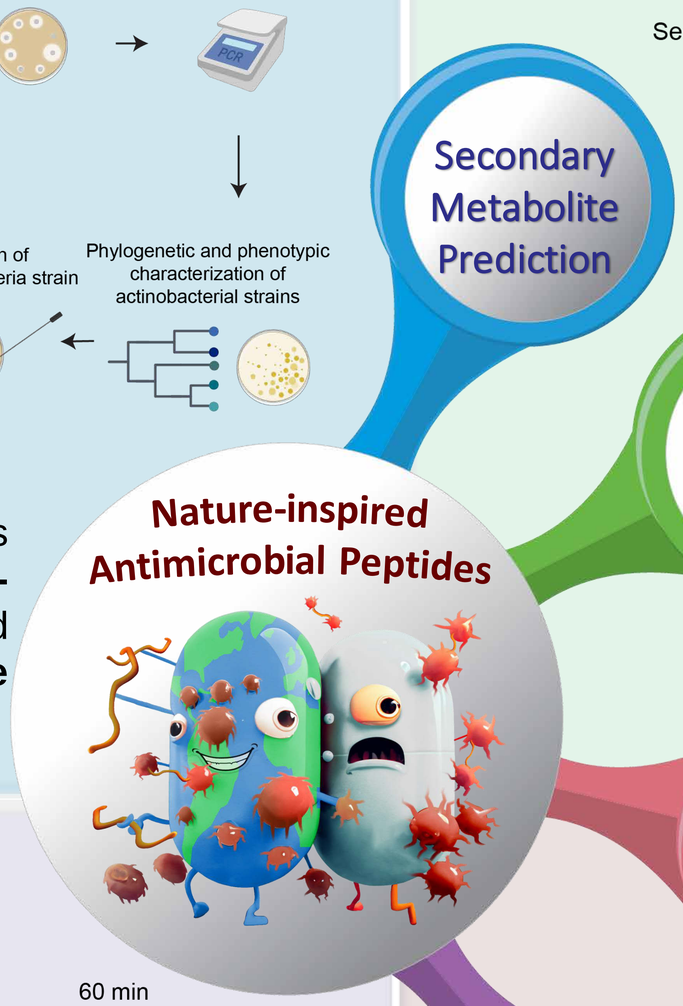
Secondary Metabolite Prediction

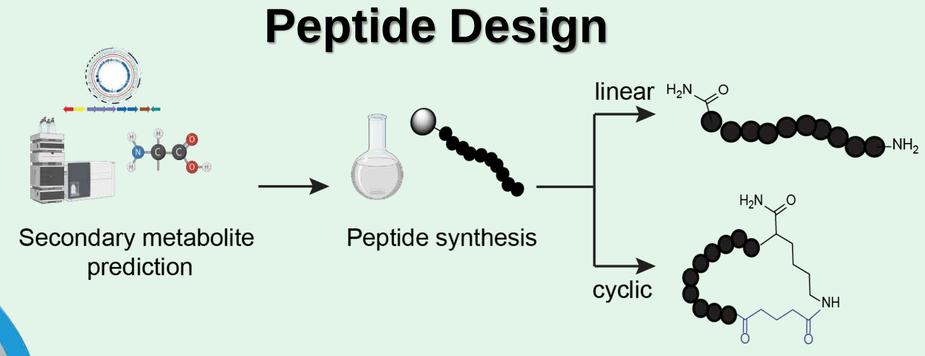




This project focuses on the discovery of AMPs from natural sources. An ambiguous cyclic **non-ribosomal peptide sequence** was predicted from ***actino*bacteria** isolated from **marine sediments in Chilean *Comau fjord***.



Peptide Design

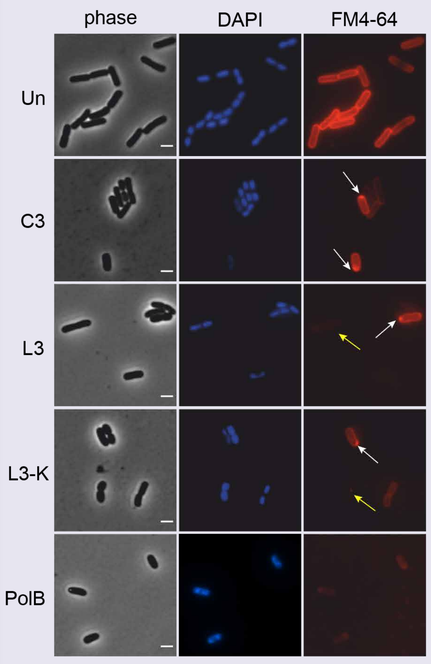


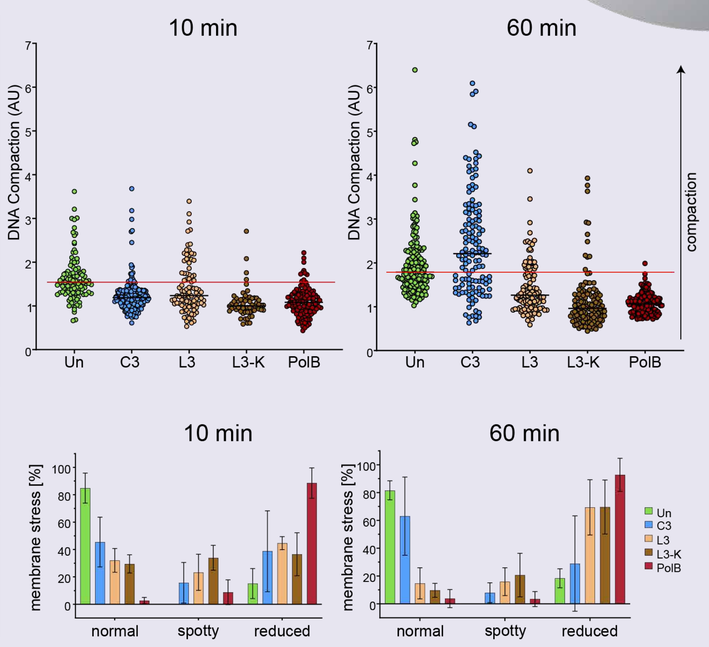
Based on ambiguous sequence three different **peptides** in their **linear and cyclic** form were **designed** and **synthesized** by automated Fmoc-based solid-phase peptide synthesis (SPPS) and manual on-resin head-to-tail cyclization.

Name	N-terminus	1	2	3	4	5	6	7	8	9	10	11
L1	free	-	$_D$A	$_D$V	$_D$A	W	$_D$D	T	$_D$D	$_D$V	-	K
C1	cyclic	-	$_D$A	$_D$V	$_D$A	W	$_D$D	T	$_D$D	$_D$V	-	K
L2	free	-	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	-	K
L2-K	free	-	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	-	-
C2	cyclic	-	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	-	K
L3	free	W	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	Y(-NO2)[1]	K
L3-K	free	W	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	Y(-NO2)[1]	-
C3	cyclic	W	$_D$A	$_D$V	$_D$A	W	Orn	T	Orn	$_D$V	Y(-NO2)[1]	K

[1] 3-Nitrotyrosine

Bioactivity Evaluation



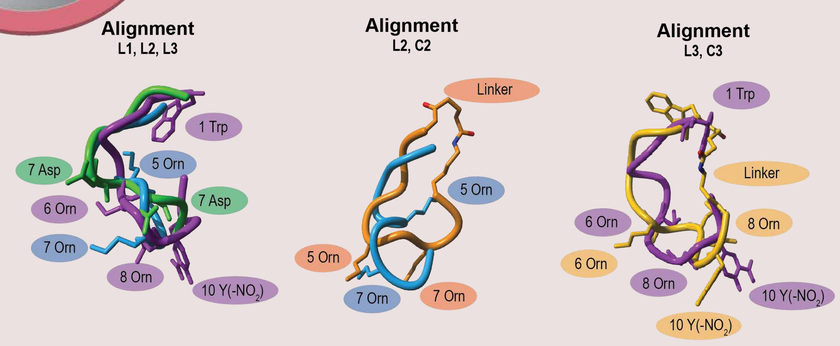


Mode of action studies performed by **live cell imaging** suggests that these peptides potentially act on the **cell membrane** *via* a **novel mechanism** allowing the passage of **small ions** resulting in the dissipation of the membrane potential.

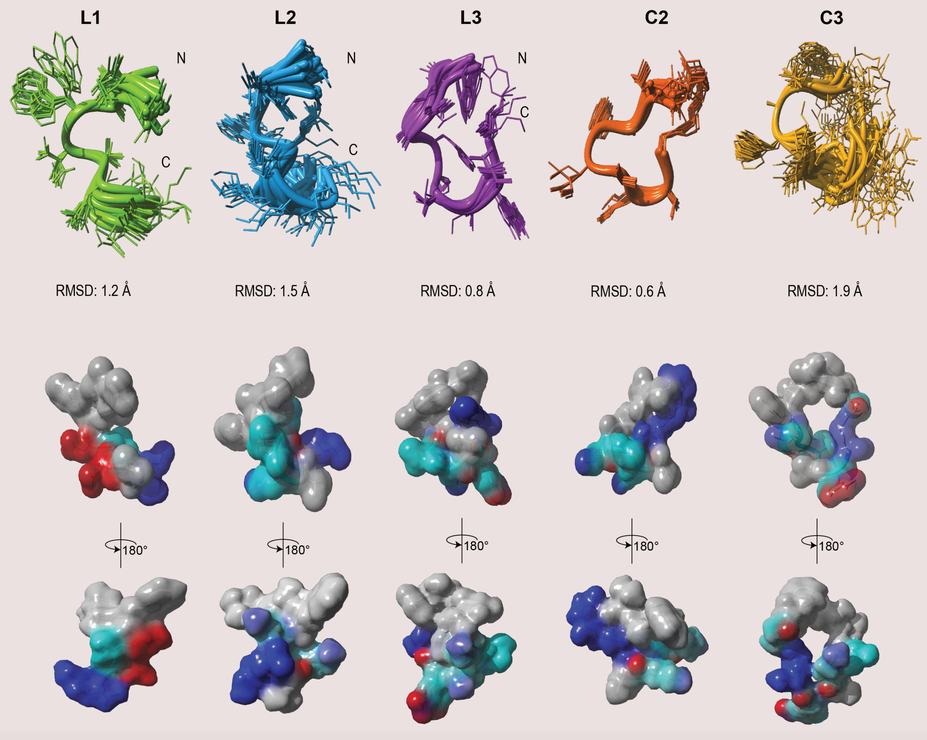
Peptide	MMC_{99} [µg/mL]								
	S. aureus			*E. coli*			*C. albicans*		
	2h	6h	24h	2h	6h	24h	2h	6h	24h
L1	>	>	>	>	>	>	>	>	>
C1	>	>	>	>	>	>	>	>	>
L2	(100)[2]	(100)[2]	>	>	>	>	50	25	25
L2-K	>	>	>	>	>	>	>	>	>
C2	>	>	>	>	>	>	>	>	>
L3	12.5	12.5	25	12.5	6.3	6.3	12.5	6.3	12.5
L3-K	25	25	25	50	25	25	25	25	12.5
C3	>	>	>	>[3]	>[3]	100	>	>	>

[1] Minimum microbicidal concentration killing ≥99% of the inoculum (MMC_{99}) at 2, 6, and 24 h of incubation in 100-fold diluted brain-heart infusion medium (BHI_{100}). Two-fold dilutions series were performed on all peptides, starting at 100 ug/mL. Peptides with a MMC_{99} of ≤100 µg/ml were repeated on two or four additional occasions (median values are reported).
[2] Just below 99% killing (98.5%) at 100 µg/mL.
[3] MMC_{99} achieved at 200 µg/mL.

Secondary Structure Analysis



Secondary structure analysis was performed by solution NMR spectroscopy using CCPN for **NMR assignment** and YASARA for **structural calculations**. The rigidity of the structures are calculated by **RMSD** values.



Beyer, L., *et al., ACS Infect Dis* **2024**, *10*, 79-92.

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