



Lasso peptides siamycin I and sviceucin have anti-resistance and anti-virulence properties on Gram-positive pathogens

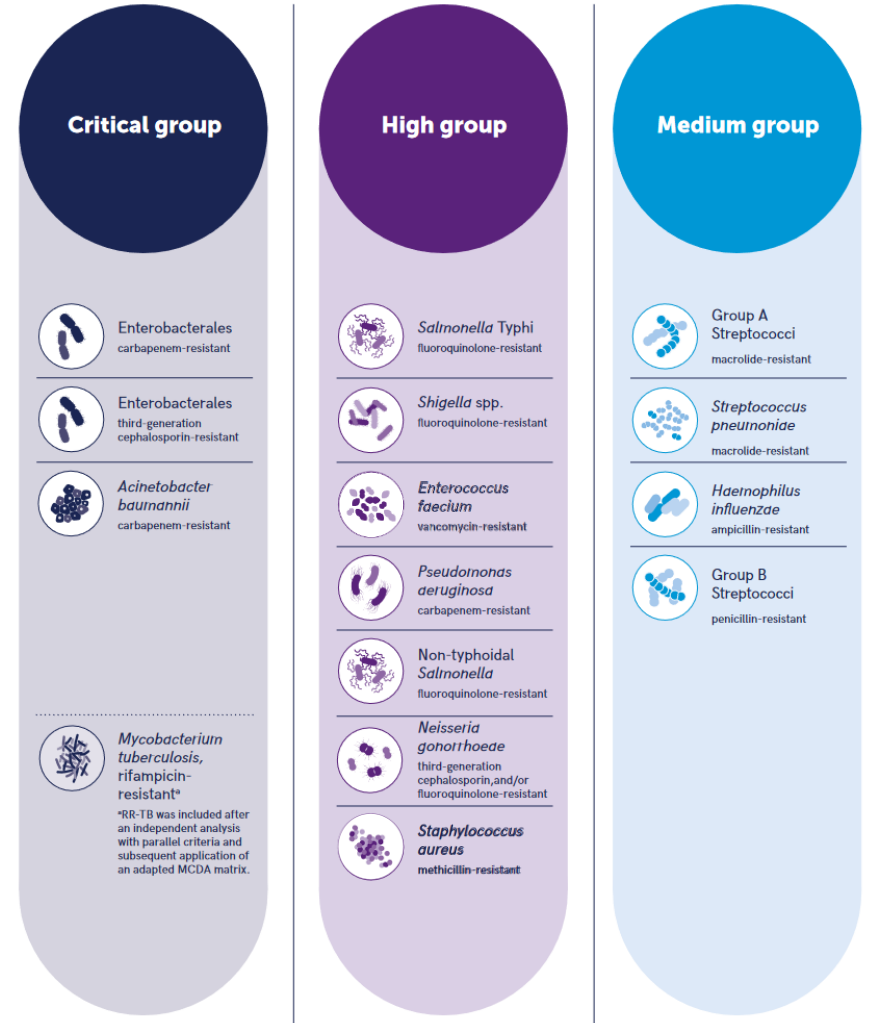
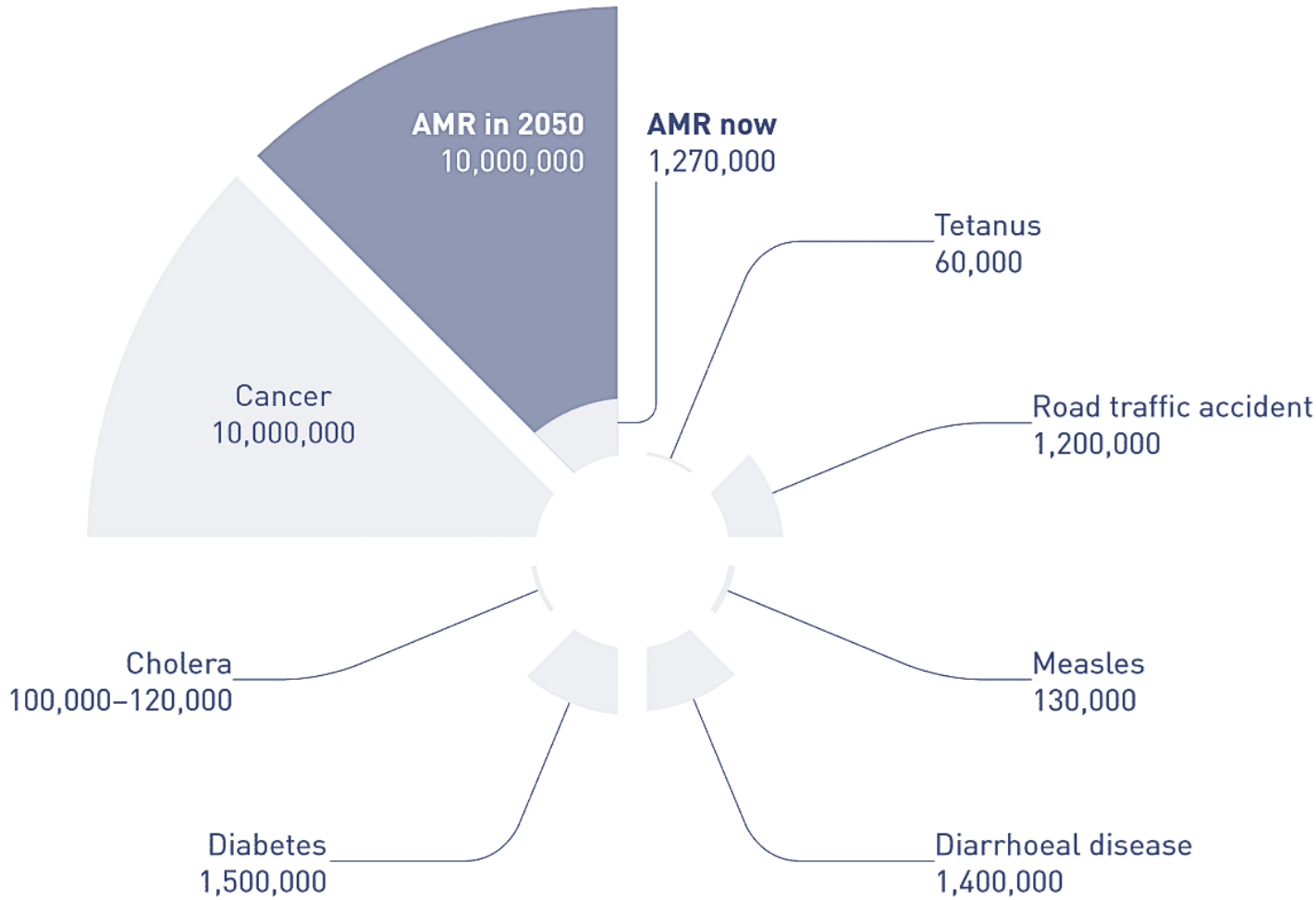
UR 4312 – Communication Bactérienne et Stratégies Anti-infectieuses

Solenn Desmadril, Benjamin Baëtz, Léa Rodrigues, Christophe Goulard, Sabrina Gueulle, Axel Hartke, Yanyan Li, **Caroline Giraud**



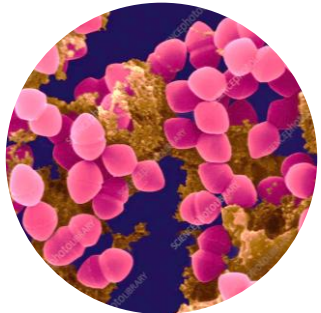
AntibioDEAL days – Rennes – 31st March 2026

Introduction





Enterococcus faecium
vancomycin-resistant



Enterococcus faecium



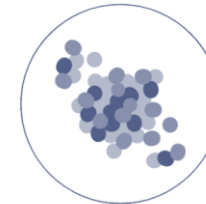
Enterococcus faecalis

Human gut microbiota commensals

Spacial and ressource competition with pathogens
Opportunistic

Pathogenicity

2nd cause of healthcare-associated infections
Intrinsic and acquired resistances to different antibiotic classes



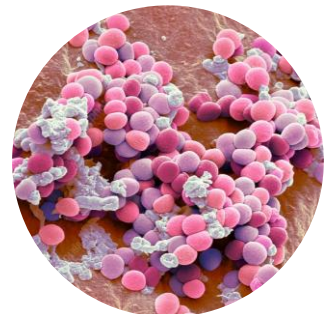
Staphylococcus aureus
methicillin-resistant

Human nasal mucosa commensal

Healthy carriers
Opportunistic

Pathogenicity

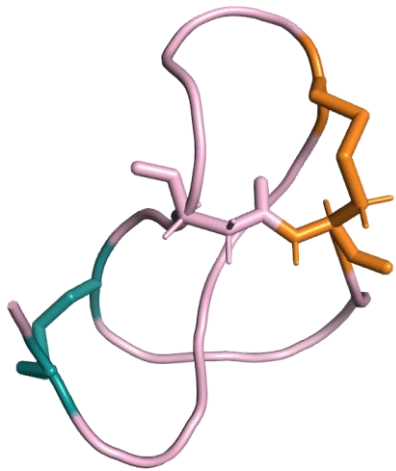
High number of virulence factors
Biofilm formation
Antibiotic resistance



Staphylococcus aureus

Type I lasso peptides (RiPPs)

Stable, can resist :
High temperatures
Low pH conditions
Protease activity

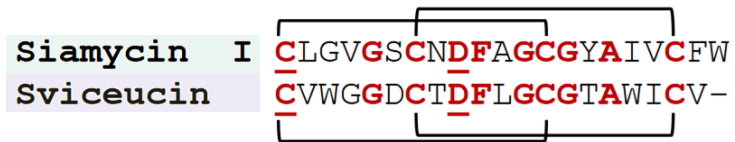


Sviceucin

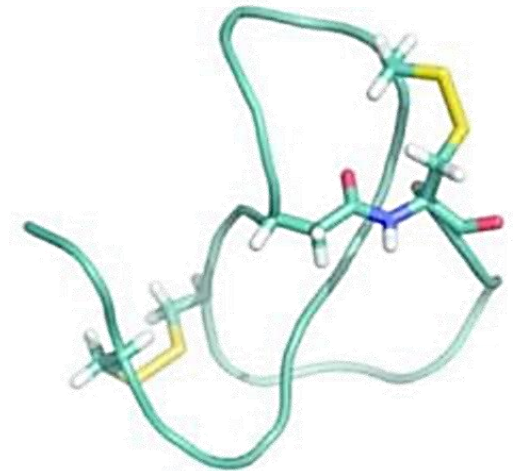
produced by *Streptomyces sviceus*

20 amino acids

21 amino acids



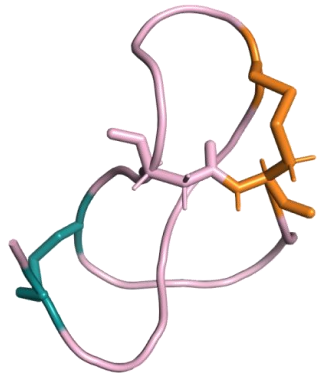
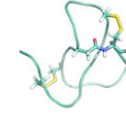
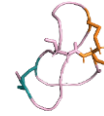
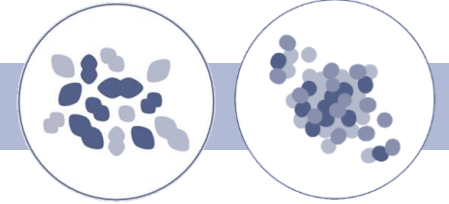
47,6 % sequence homology



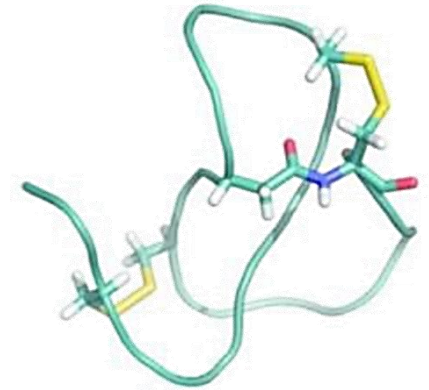
Siamycin I

produced by *Streptomyces sp.*



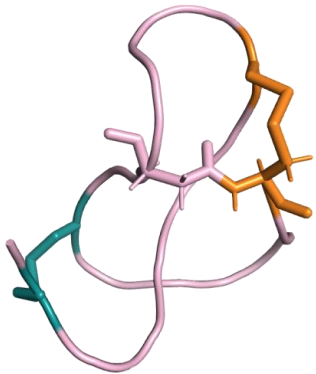
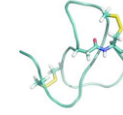
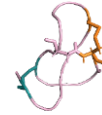
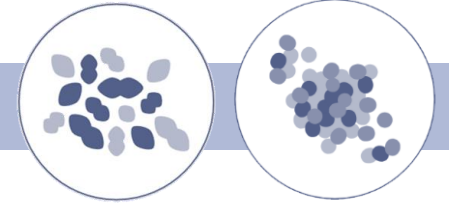


Sviveucin



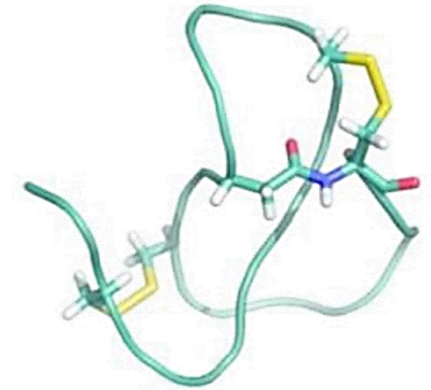
Siamycin I

Strain	Sviveucin MIC (μM)	Siamycin I MIC (μM)
<i>E. faecalis</i> V583	>10	5
<i>E. faecalis</i> JH2-2 08048	>10	5
<i>E. faecalis</i> merz96	>10	5
<i>S. aureus</i> T-SAR12 VRSA.B	>10	5
<i>E. faecium</i> 1 231 410	>10	5
<i>E. faecalis</i> HIP11704	>10	5
<i>E. faecium</i> 1 231 502	>10	5
<i>E. faecium</i> 1 230 933	>10	5
<i>S. aureus</i> T-SAR12 VRSA.A	>10	5
<i>E. faecalis</i> V583 ΔvanB	>10	5
<i>S. aureus</i> 16038 (VISA)	>10	5
<i>S. aureus</i> PR01	>40	5



Sviveucin

Strain	Sviveucin MIC (μM)	Siamycin I MIC (μM)
<i>E. faecalis</i> V583	>10	5
<i>E. faecalis</i> JH2-2 08048	>10	5
<i>E. faecalis</i> merz96	>10	5
<i>S. aureus</i> T-SAR12 VRSA.B	>10	5
<i>E. faecium</i> 1 231 410	>10	5
<i>E. faecalis</i> HIP11704	>10	5
<i>E. faecium</i> 1 231 502	>10	5
<i>E. faecium</i> 1 230 933	>10	5
<i>S. aureus</i> T-SAR12 VRSA.A	>10	5
<i>E. faecalis</i> V583 ΔvanB	>10	5
<i>S. aureus</i> 16038 (VISA)	>10	5
<i>S. aureus</i> PR01	>40	5

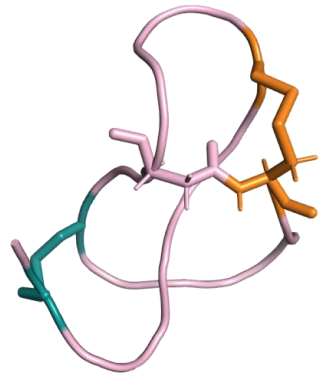
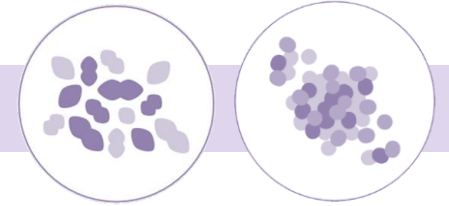


Siamycin I

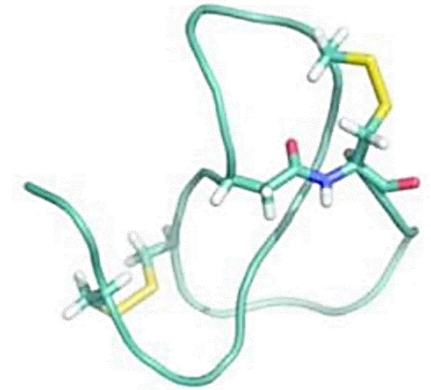
No bacteriostatic activity

Siamycin I shows bacteriostatic activity on *E. faecalis*, *E. faecium* et *S. aureus* at 5 μM

Anti-vancomycin resistance activity



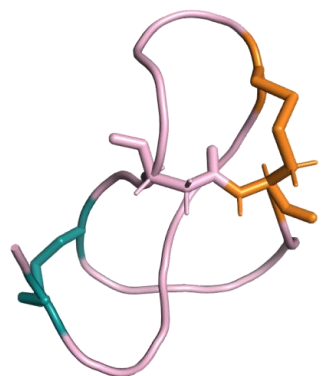
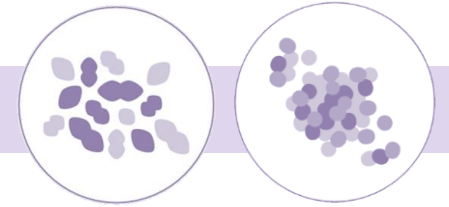
Sviceucin



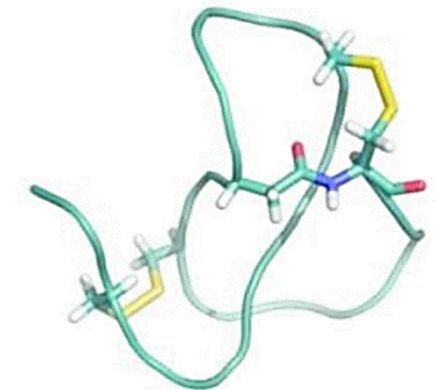
Siamycin I

Strain	Resistance type	Vancomycin MIC ($\mu\text{g/mL}$)		
		Control	Sviceucin (10 μM)	Siamycin I (2 μM)
VanB	<i>E. faecalis</i> V583	32	2	2
	<i>E. faecalis</i> JH2-2 08048	64	2	<0.5
	<i>E. faecalis</i> merz96	32	1	2
	<i>S. aureus</i> T-SAR12	64	2	2
	VRSA.B			
VanA	<i>E. faecium</i> 1 231 410	128	128	2
	<i>E. faecalis</i> HIP11704	1024	512	<0.5
	<i>E. faecium</i> 1 231 502	128	128	2
	<i>E. faecium</i> 1 230 933	512	256	2
	<i>S. aureus</i> T-SAR12	>512	>512	2
Susceptible	VRSA.A			
	<i>E. faecalis</i> V583 ΔvanB	2	2	2
	<i>S. aureus</i> 16038 (VISA)	4	4	4

Anti-vancomycin resistance activity



Sviceucin

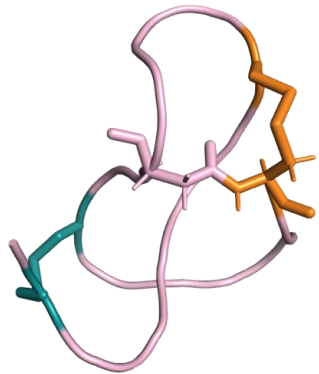
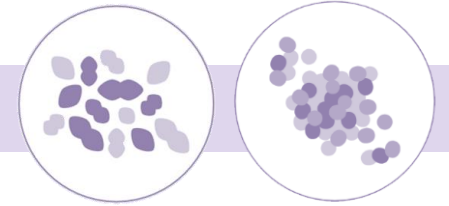


Siamycin I

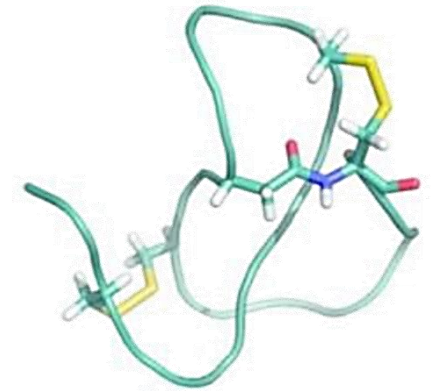
Strain	Resistance type	Vancomycin MIC (µg/mL)		
		Control	Sviceucin (10 µM)	Siamycin I (2 µM)
VanB	<i>E. faecalis</i> V583	32	2	2
	<i>E. faecalis</i> JH2-2 08048	64	2	<0.5
	<i>E. faecalis</i> merz96	32	1	2
	<i>S. aureus</i> T-SAR12 VRSA.B	64	2	2
VanA	<i>E. faecium</i> 1 231 410	128	128	2
	<i>E. faecalis</i> HIP11704	1024	512	<0.5
	<i>E. faecium</i> 1 231 502	128	128	2
	<i>E. faecium</i> 1 230 933	512	256	2
	<i>S. aureus</i> T-SAR12 VRSA.A	>512	>512	2
Susceptible	<i>E. faecalis</i> V583 Δ vanB	2	2	2
	<i>S. aureus</i> 16038 (VISA)	4	4	4

Sviceucin shows anti-vancomycin resistance activity only on VanB type strains

Anti-vancomycin resistance activity



Sviceucin



Siamycin I

Strain	Resistance type	Vancomycin MIC (µg/mL)		
		Control	Sviceucin (10 µM)	Siamycin I (2 µM)
VanB	<i>E. faecalis</i> V583	32	2	2
	<i>E. faecalis</i> JH2-2 08048	64	2	<0.5
	<i>E. faecalis</i> merz96	32	1	2
	<i>S. aureus</i> T-SAR12	64	2	2
	VRSA.B			
VanA	<i>E. faecium</i> 1 231 410	128	128	2
	<i>E. faecalis</i> HIP11704	1024	512	<0.5
	<i>E. faecium</i> 1 231 502	128	128	2
	<i>E. faecium</i> 1 230 933	512	256	2
	<i>S. aureus</i> T-SAR12	>512	>512	2
Susceptible	VRSA.A			
	<i>E. faecalis</i> V583 Δ vanB	van-	2	2
	<i>S. aureus</i> 16038 (VISA)	van-	4	4

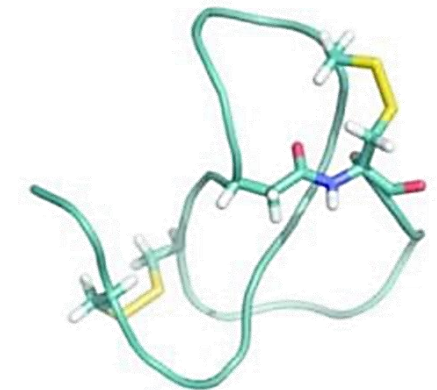
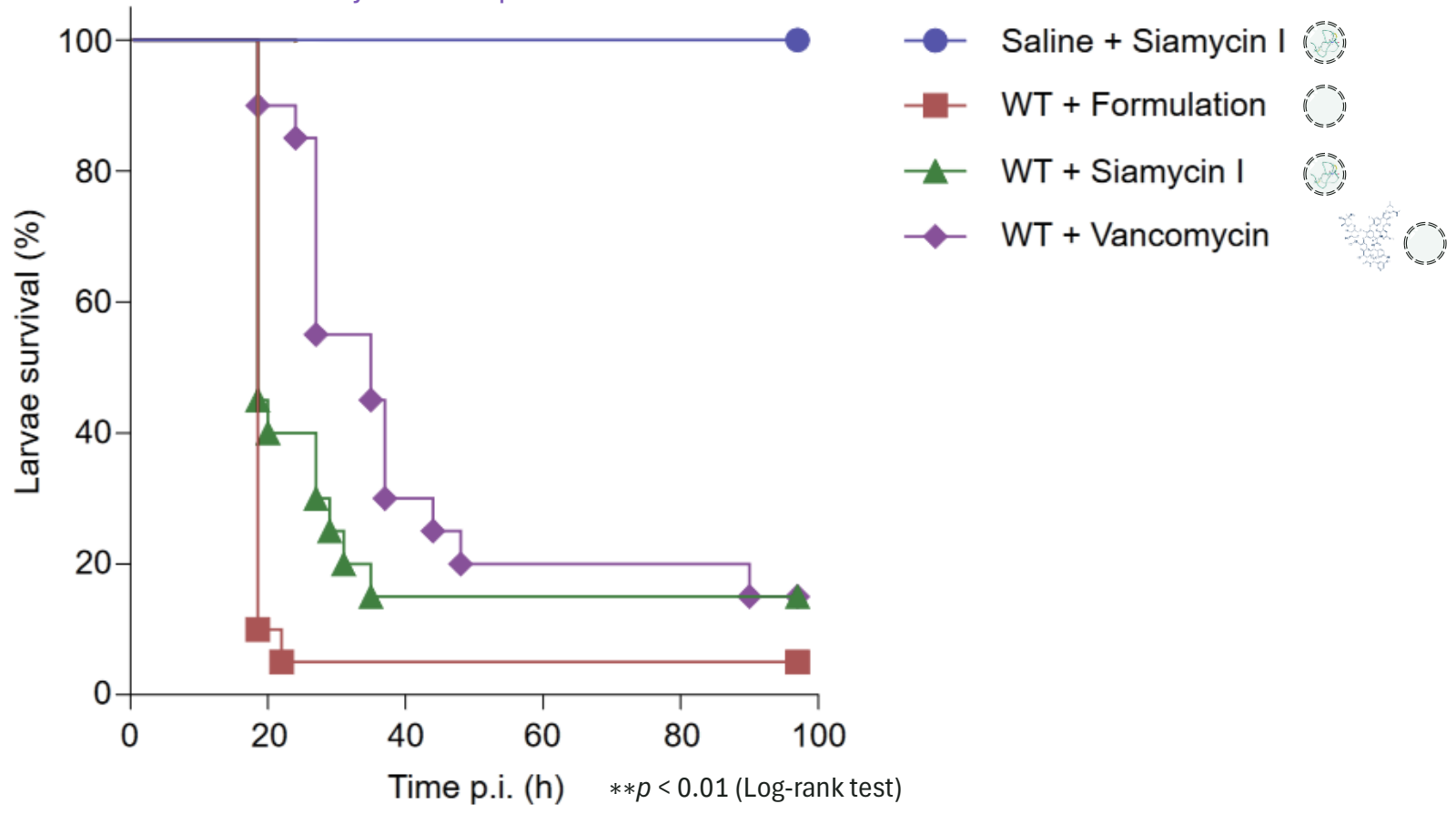
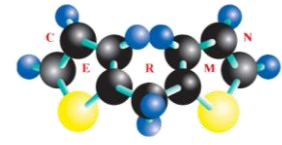
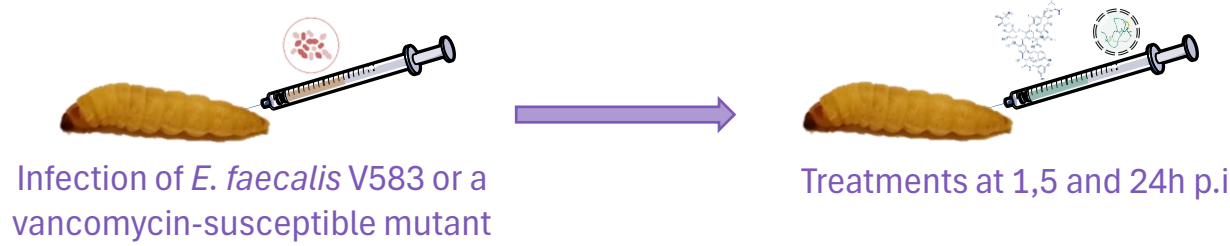
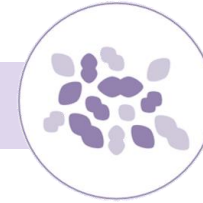
Sviceucin shows anti-vancomycin resistance activity only on VanB type strains

Sviceucin shows anti-vancomycin resistance activity only on both VanA and VanB type strains

Sources : Boudrioua et al., 2025

MIC: Minimum Inhibitory Concentration

Anti-vancomycin resistance activity

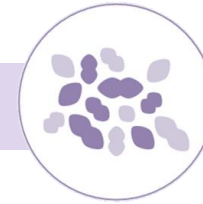


Siamycin I

Sources : Boudrioua *et al.*, 2025 ; Ségui *et al.*, 2020 ; EP 23306748.7

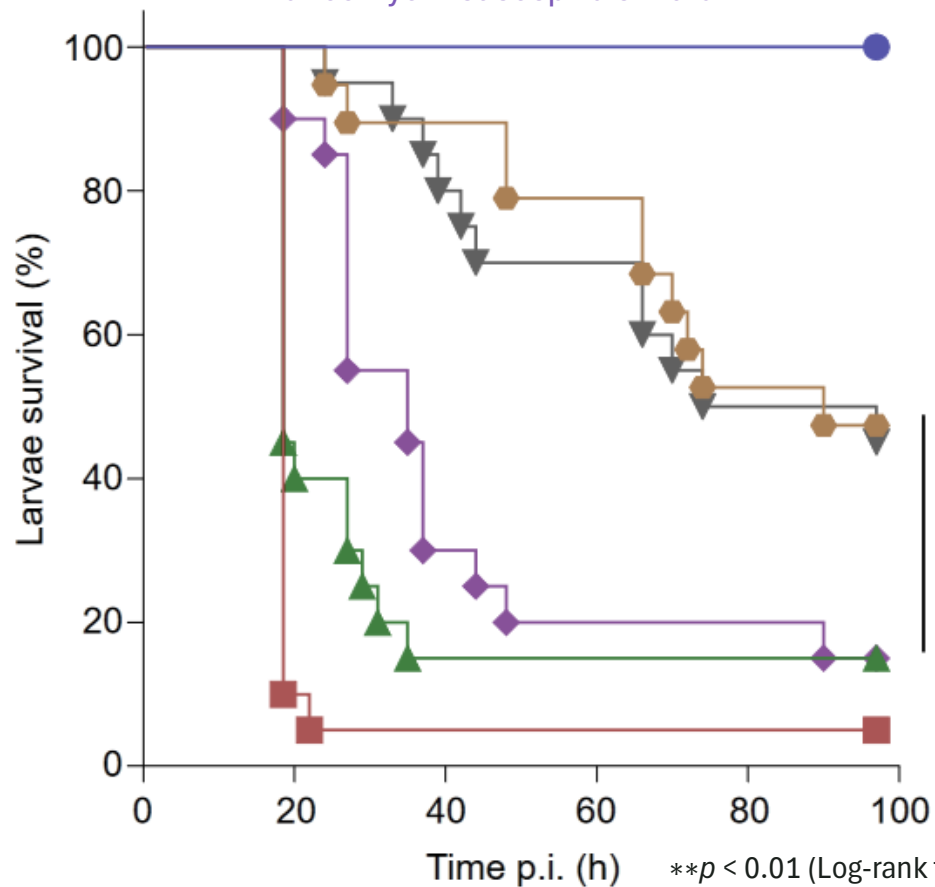
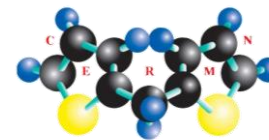
p.i: post-infection

Anti-vancomycin resistance activity

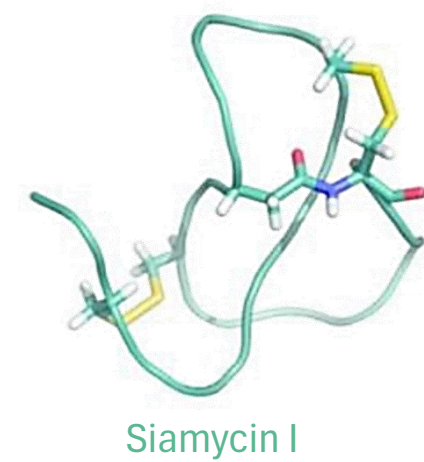


Infection of *E. faecalis* V583 or a vancomycin-susceptible mutant

Treatments at 1,5 and 24h p.i

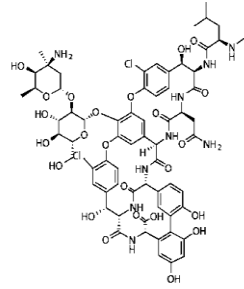
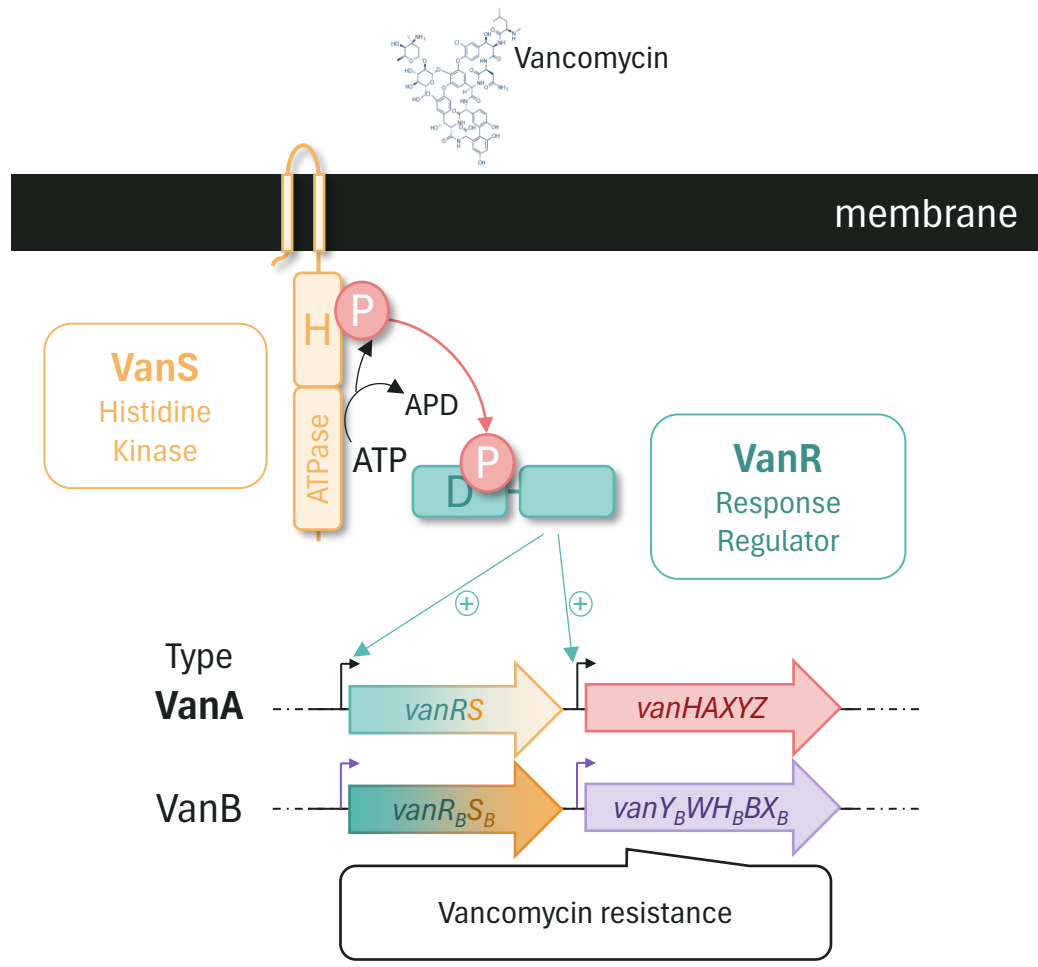
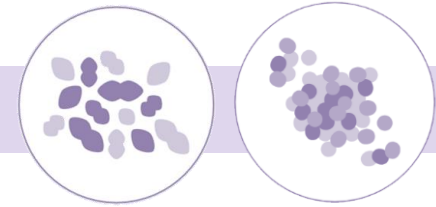


- Saline + Siamycin I
- WT + Formulation
- ▲ WT + Siamycin I
- ◆ WT + Vancomycin
- $\Delta vanB$ + Vancomycin
- ▼ WT + Vancomycin + Siamycin I



Siamycin I has an anti-vancomycin resistance activity against *E. faecalis* V583 (VanB) in the insect model *Galleria mellonella*

Anti-vancomycin resistance activity



Vancomycin
Glycopeptidic antibiotic

Used to treat MRSA infections
Resistance is *S. aureus* originates from transposon transfer from vancomycin-resistant enterococci (VRE)

Different types of resistance, including types **VanA** and **VanB** which are the most prominent in a clinical setting
Expression is regulated by a Two-Component System (TCS)

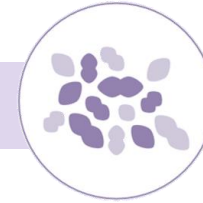
TCS : adaptation to the environment (virulence, antibiotic resistance,...)

Histidine Kinase (sensor) + Response Regulator
Not found in mammals

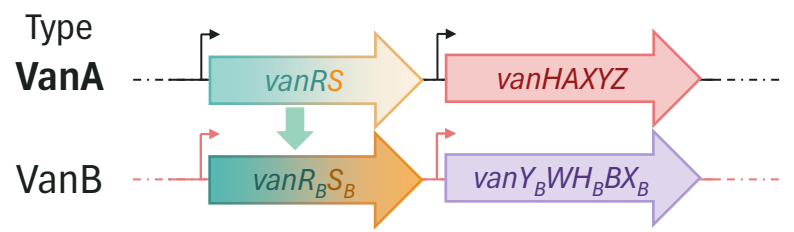
Two-Component System regulating vancomycin-resistance *van* gene clusters

Sources : Hong *et al.*, 2008

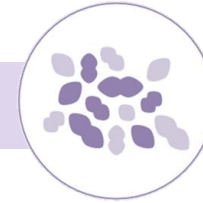
Anti-vancomycin resistance activity



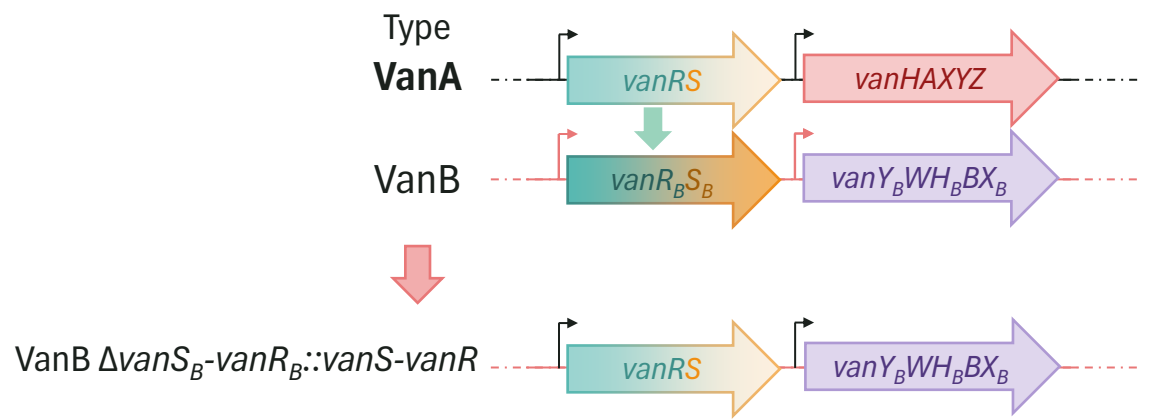
Swapping of VanA ↔ VanB genes



Anti-vancomycin resistance activity

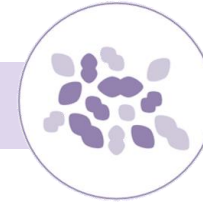


Swapping of VanA ↔ VanB genes

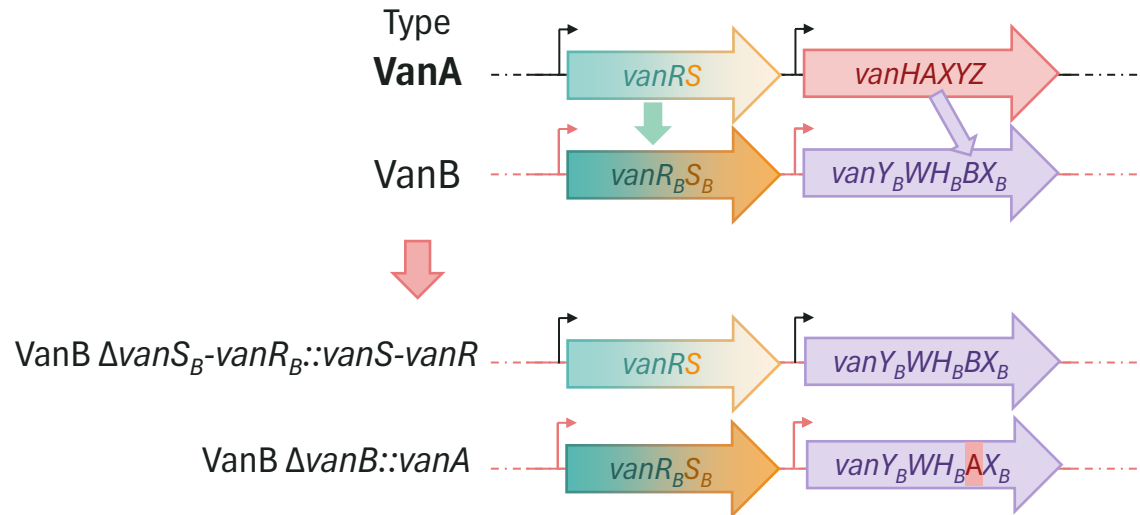


Strain	Vancomycin MIC (μ g/mL)		
	Control	Sviceucin	Siamycin I
V583	32	2	2
V583 Δ <i>vanS_B-vanR_B::vanS-vanR</i>	32	32	2

Anti-vancomycin resistance activity



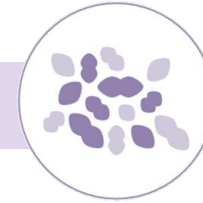
Swapping of VanA ↔ VanB genes



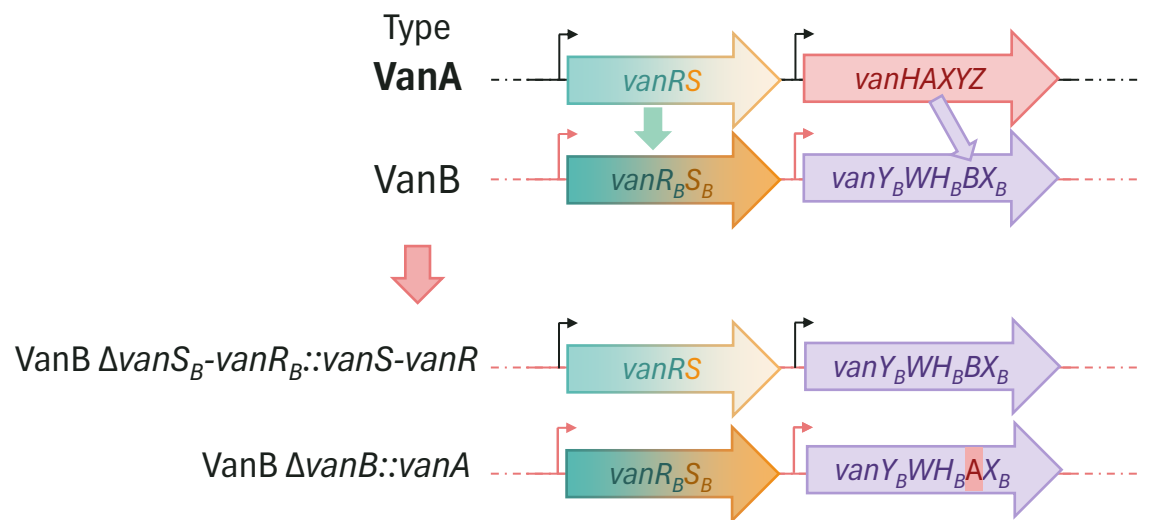
Vancomycin MIC (μg/mL)

Strain	Vancomycin MIC (μg/mL)		
	Control	Sviceucin	Siamycin I
V583	32	2	2
V583 Δ vanSB-vanRB::vanS-vanR	32	32	2
V583 Δ vanB::vanA	32	2	2

Anti-vancomycin resistance activity



Swapping of VanA ↔ VanB genes

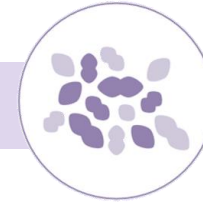


Adding a constitutively-active response regulator

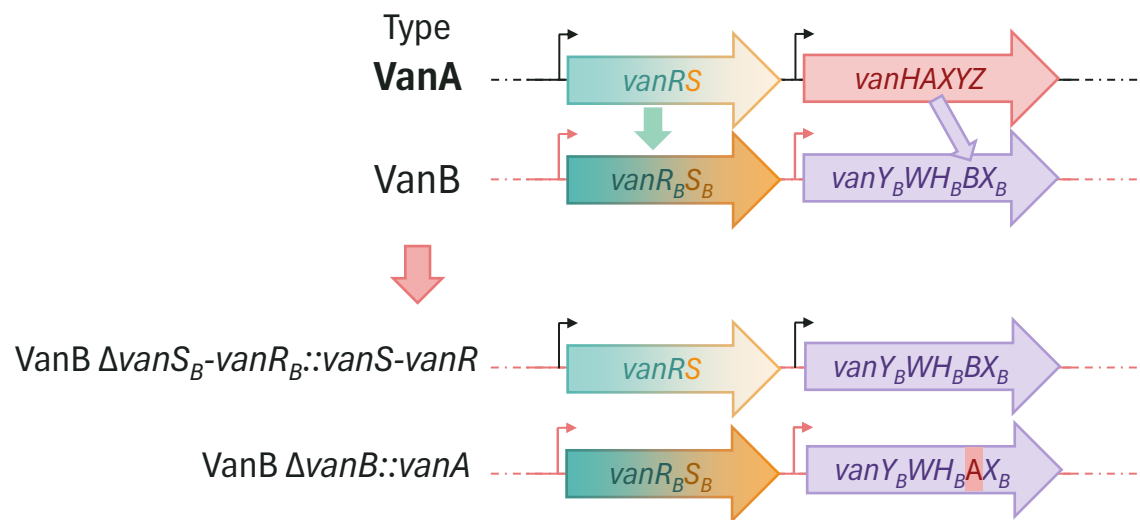


Strain	Vancomycin MIC (μg/mL)		
	Control	Sviceucin	Siamycin I
V583	32	2	2
V583 ΔvanSB-vanRB::vanS-vanR	32	32	2
V583 ΔvanB::vanA	32	2	2

Anti-vancomycin resistance activity

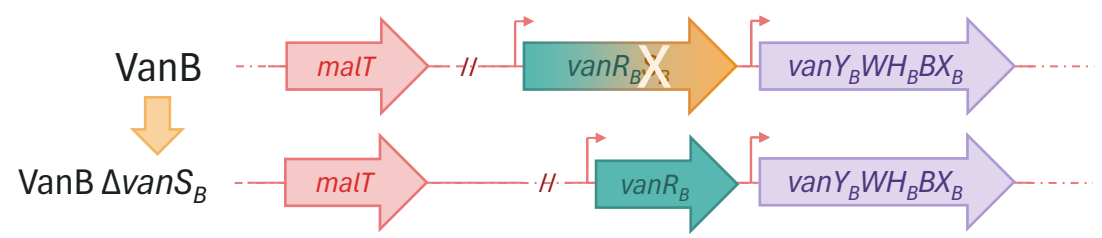


Swapping of VanA ↔ VanB genes



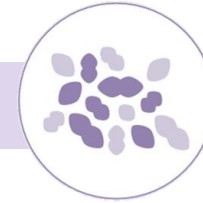
Strain	Vancomycin MIC (μg/mL)		
	Control	Svceucin	Siamycin I
V583	32	2	2
V583 $\Delta vanS_B-vanR_B::vanS-vanR$	32	32	2
V583 $\Delta vanB::vanA$	32	2	2

Adding a constitutively-active response regulator

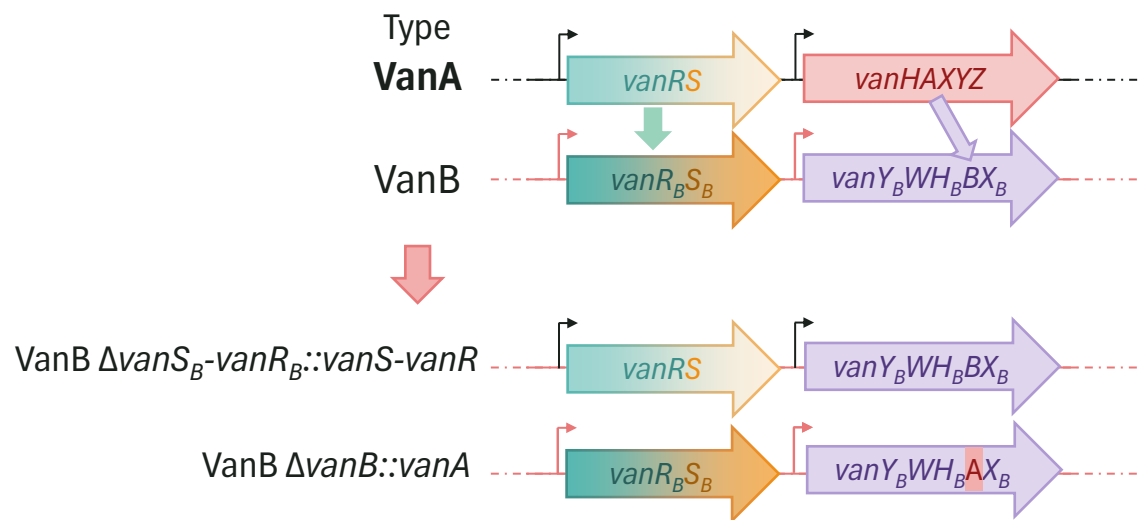


Strain	Vancomycin MIC (μg/mL)		
	Control	Svceucin	Siamycin I
V583	32	2	2
V583 $\Delta vanS_B$	2	2	2

Anti-vancomycin resistance activity

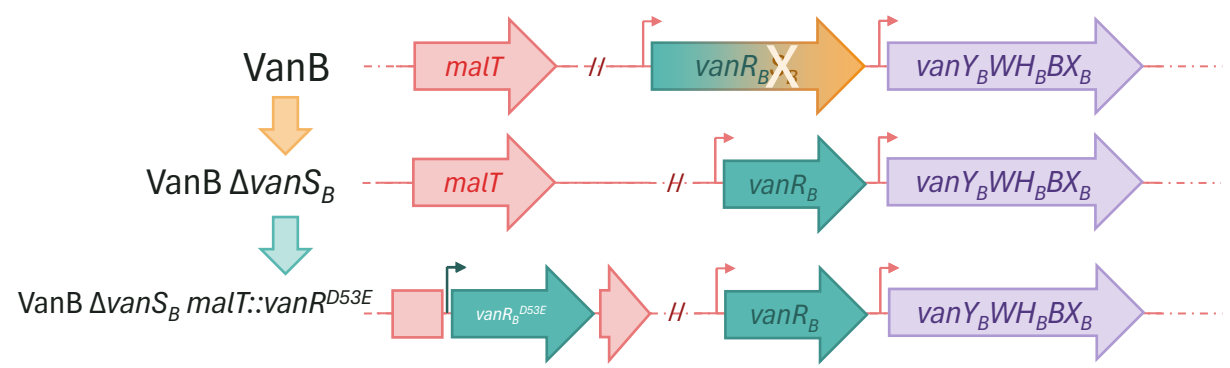


Swapping of VanA ↔ VanB genes



Strain	Vancomycin MIC (μg/mL)		
	Control	Sviceucin	Siamycin I
V583	32	2	2
V583 $\Delta vanS_B-vanR_B::vanS-vanR$	32	32	2
V583 $\Delta vanB::vanA$	32	2	2

Adding a constitutively-active response regulator

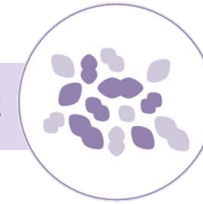


Strain	Vancomycin MIC (μg/mL)		
	Control	Sviceucin	Siamycin I
V583	32	2	2
V583 $\Delta vanS_B$	2	2	2
V583 $\Delta vanS_B malt::vanR^{D53E}$	32	32	32

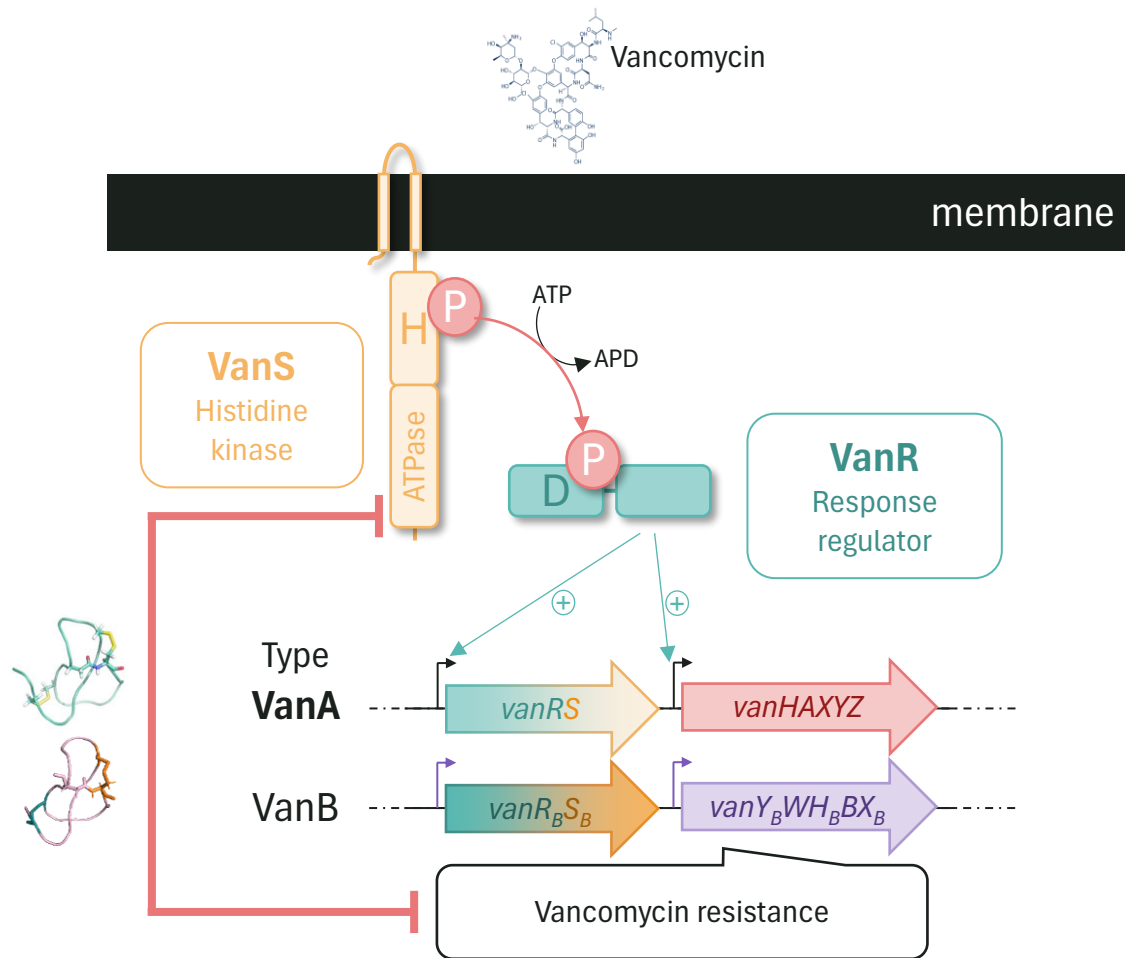
Spectrum of activity is linked to the histidine kinase

Anti-vancomycin resistance activity

Benjamin Baëtz

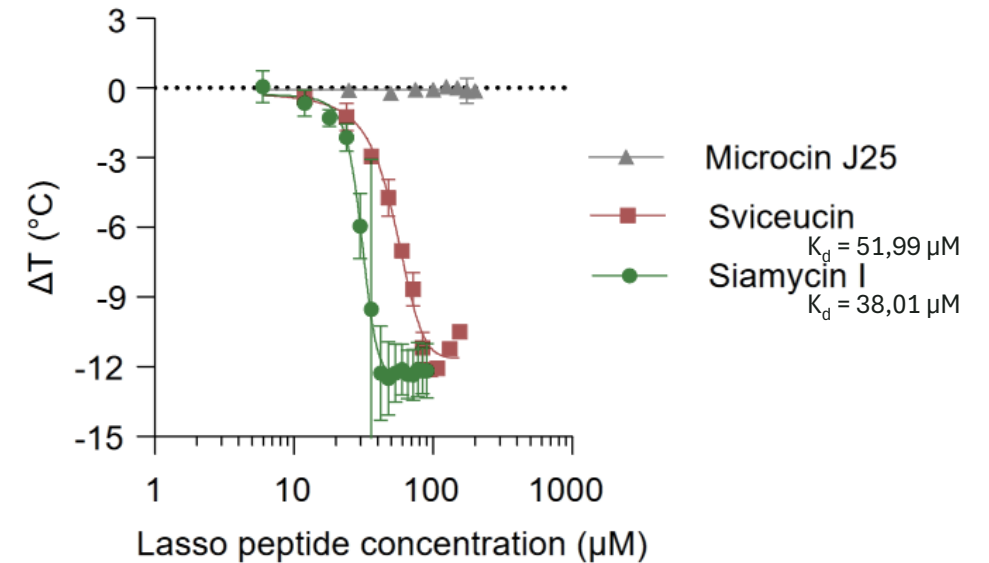


10



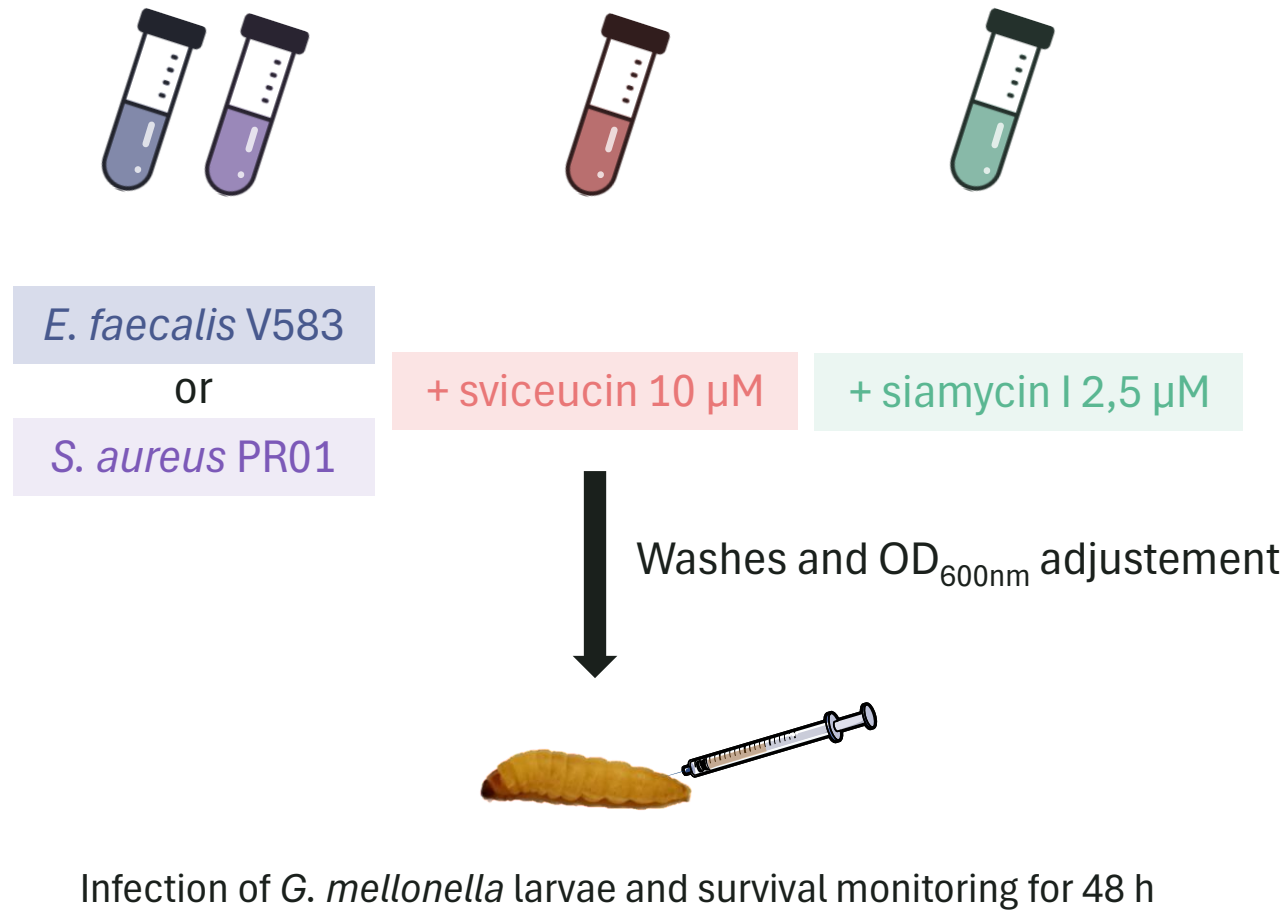
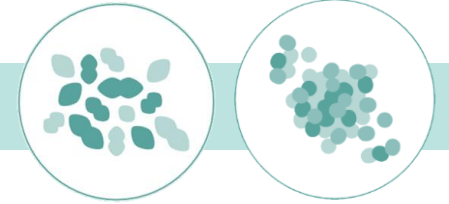
Anti-vancomycin resistance activity in *E. faecalis*, *E. faecium* and *S. aureus*

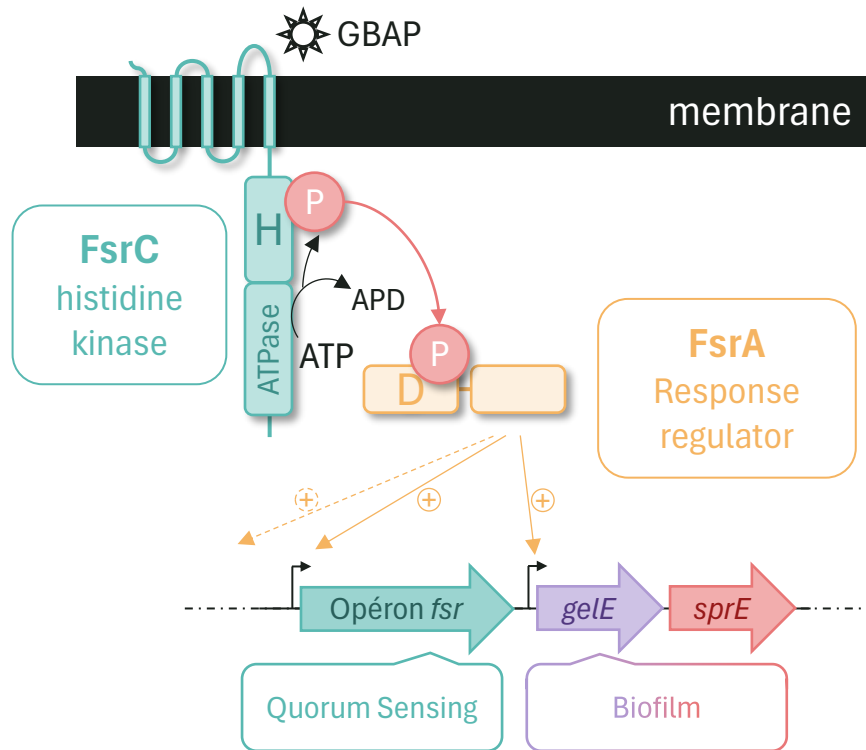
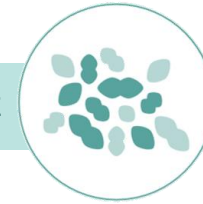
Differential Scanning Fluorimetry (DSF) of the peptide – VanS cytoplasmic domain interaction



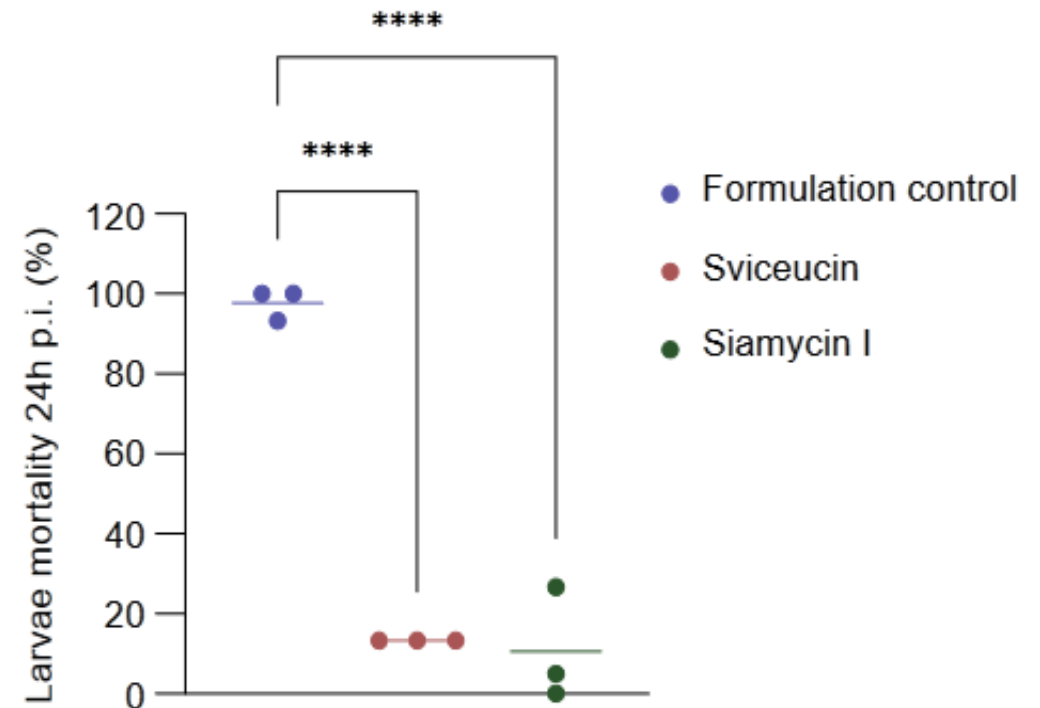
Svceucin and Siamycin interact directly with the cytoplasmic domain of the histidine kinase VanS

Anti-virulence activity

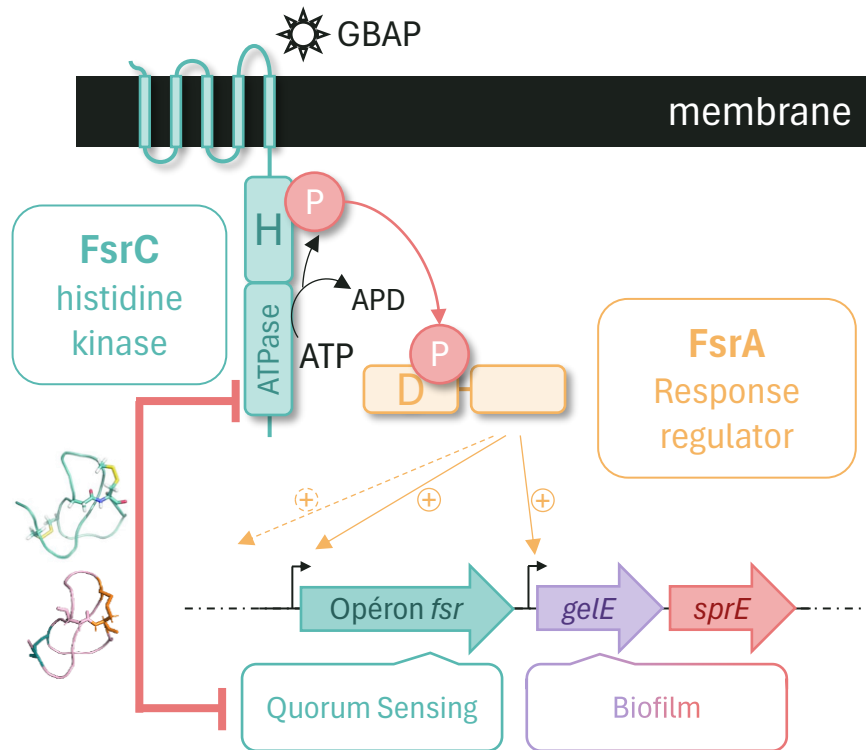
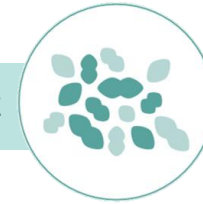




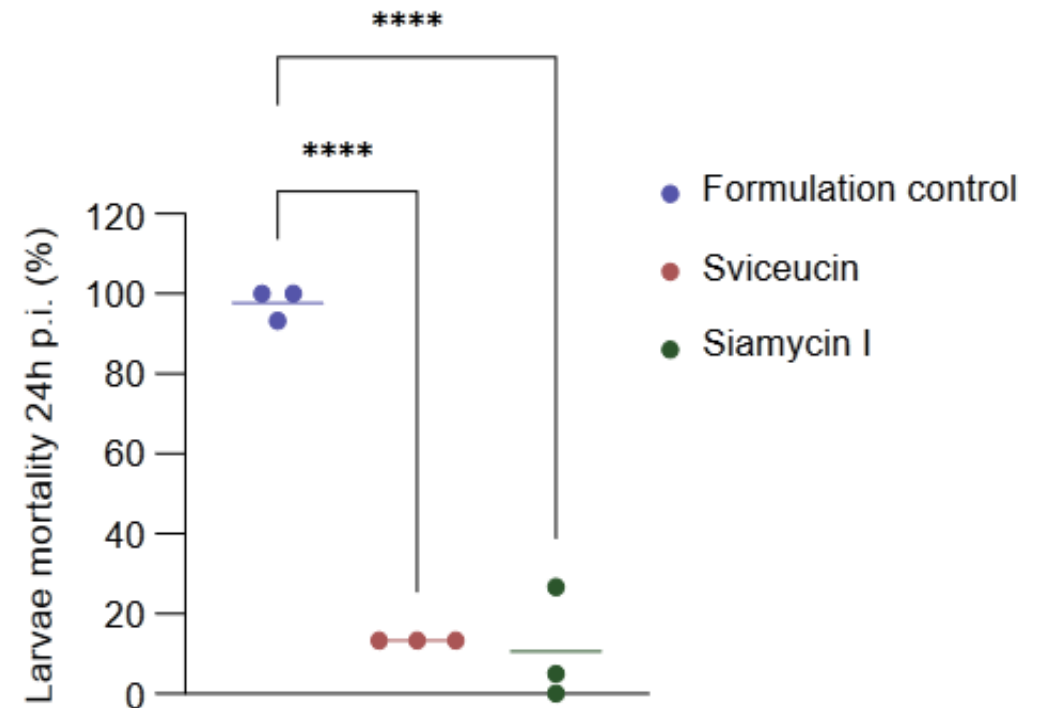
Galleria mellonella larvae mortality at 24 h post-infection with 10^6 CFU of *E. faecalis* V583 pre-incubated with or without sviceucin or siamycin I.



**** $p < 0.0001$ (Bonferroni's multiple comparisons test)



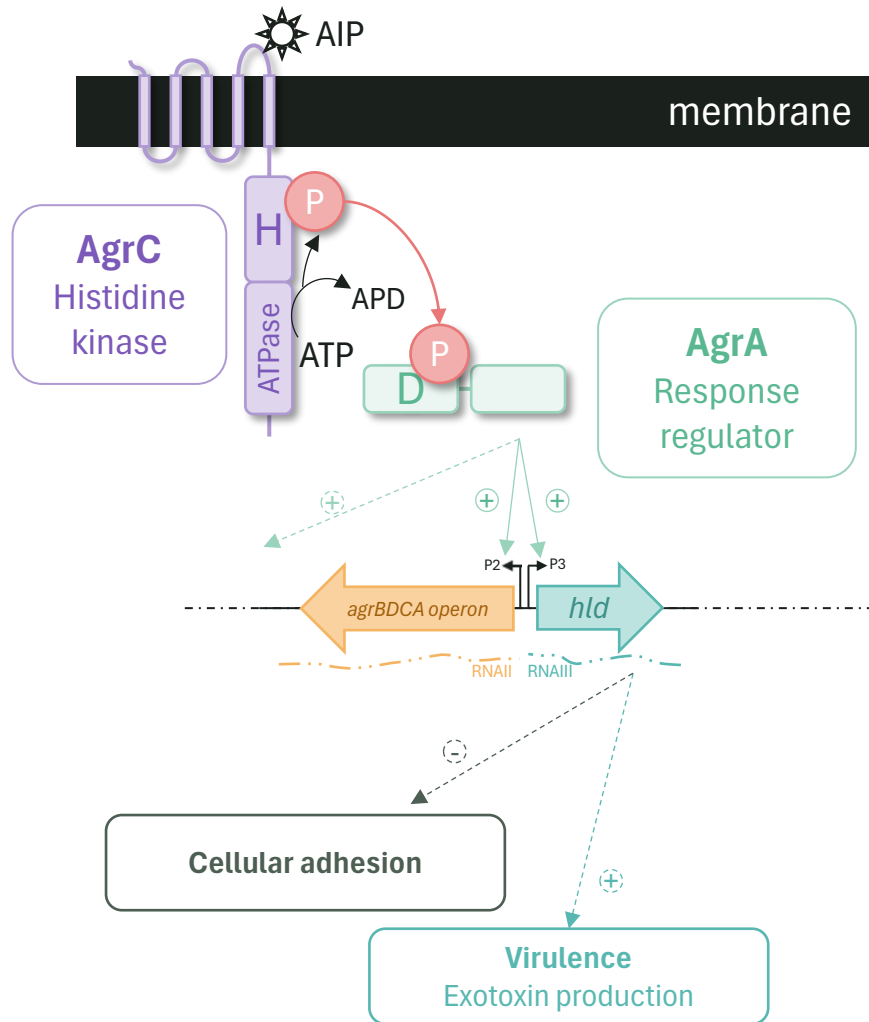
Galleria mellonella larvae mortality at 24 h post-infection with 10^6 CFU of *E. faecalis* V583 pre-incubated with or without sviceucin or siamycin I.



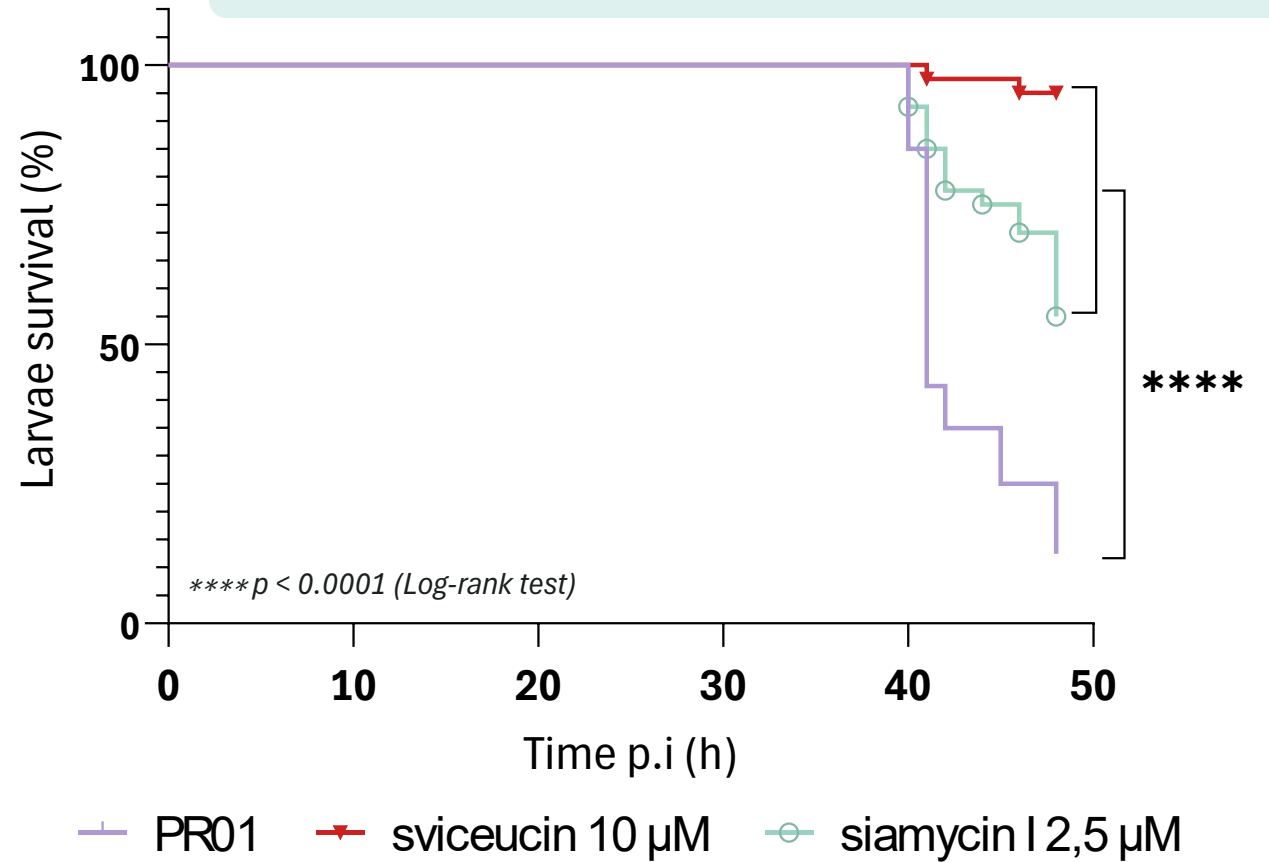
**** $p < 0.0001$ (Bonferroni's multiple comparisons test)

Svceucin and siamycin I also inhibit FrsC activity in *E. faecalis*

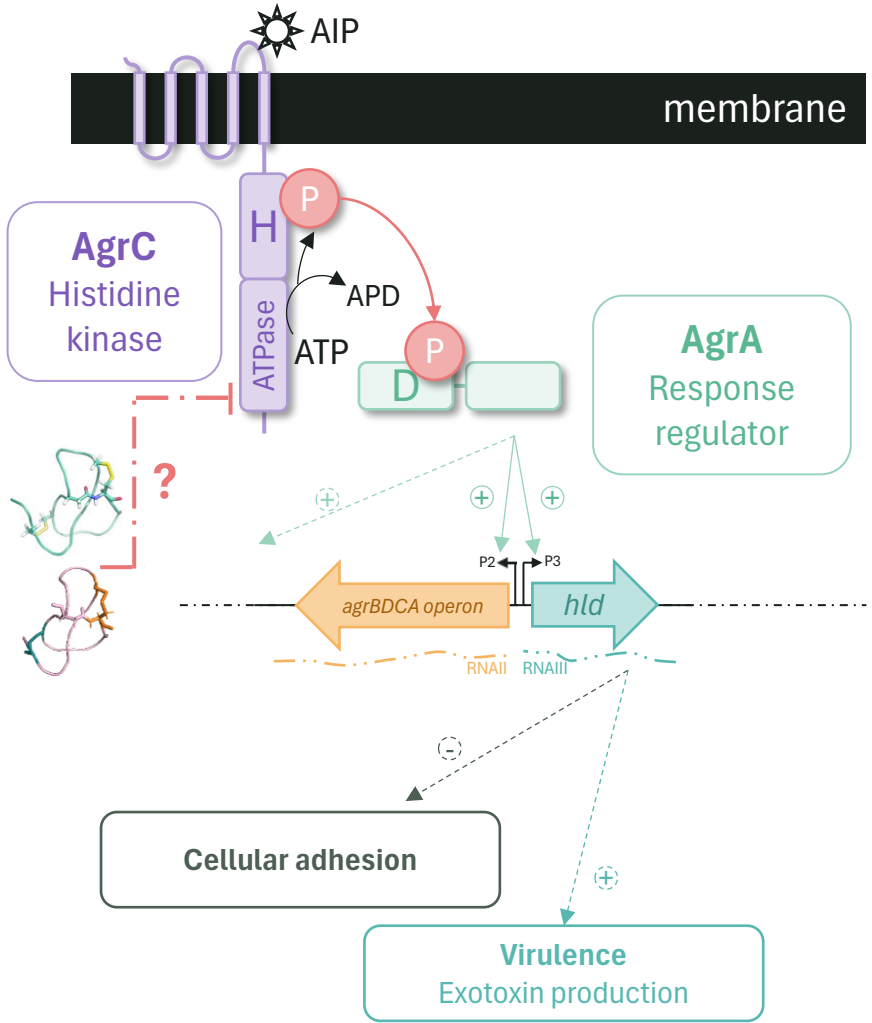
Anti-virulence activity



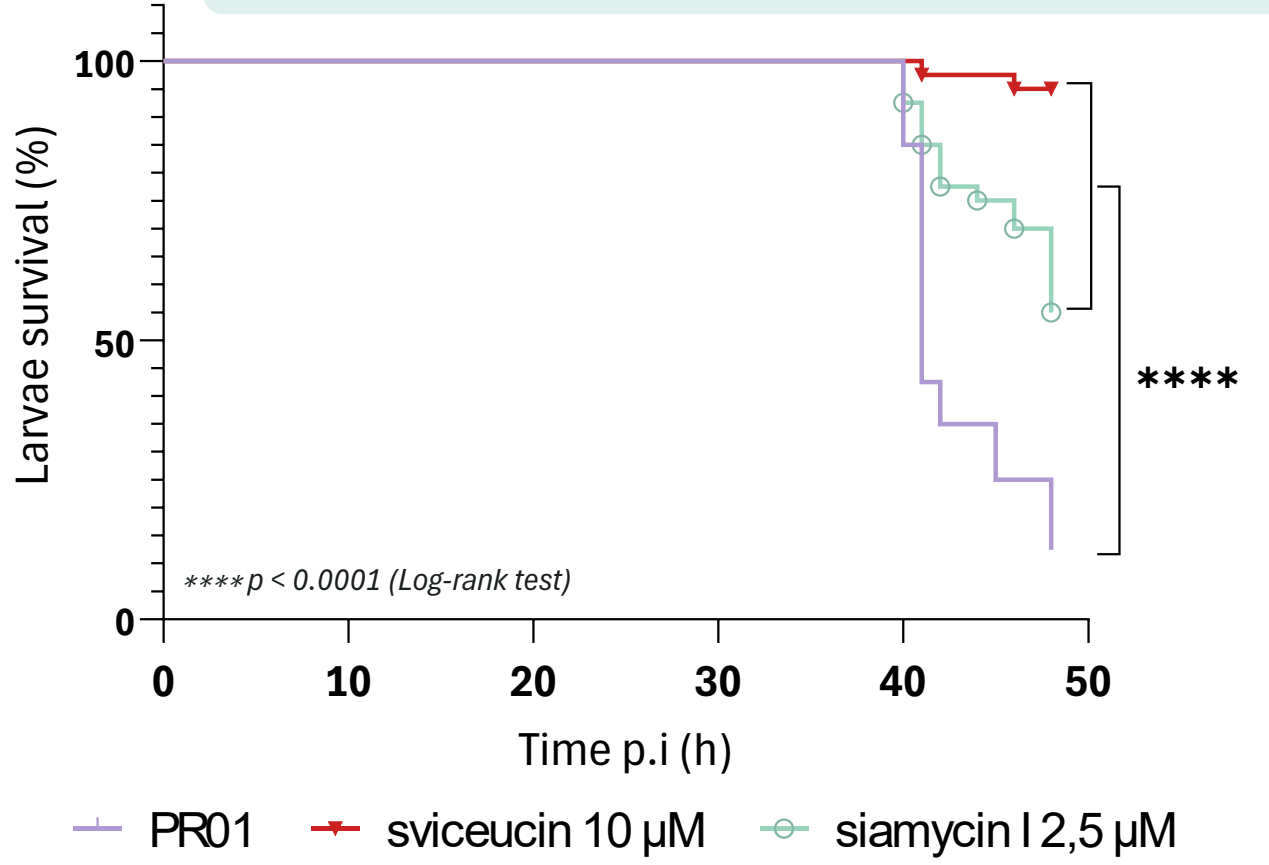
Galleria mellonella larvae survival after infection with $5 \cdot 10^6$ CFU of *S. aureus* PR01 pre-incubated with or without svceucin or siamycin I.



Anti-virulence activity



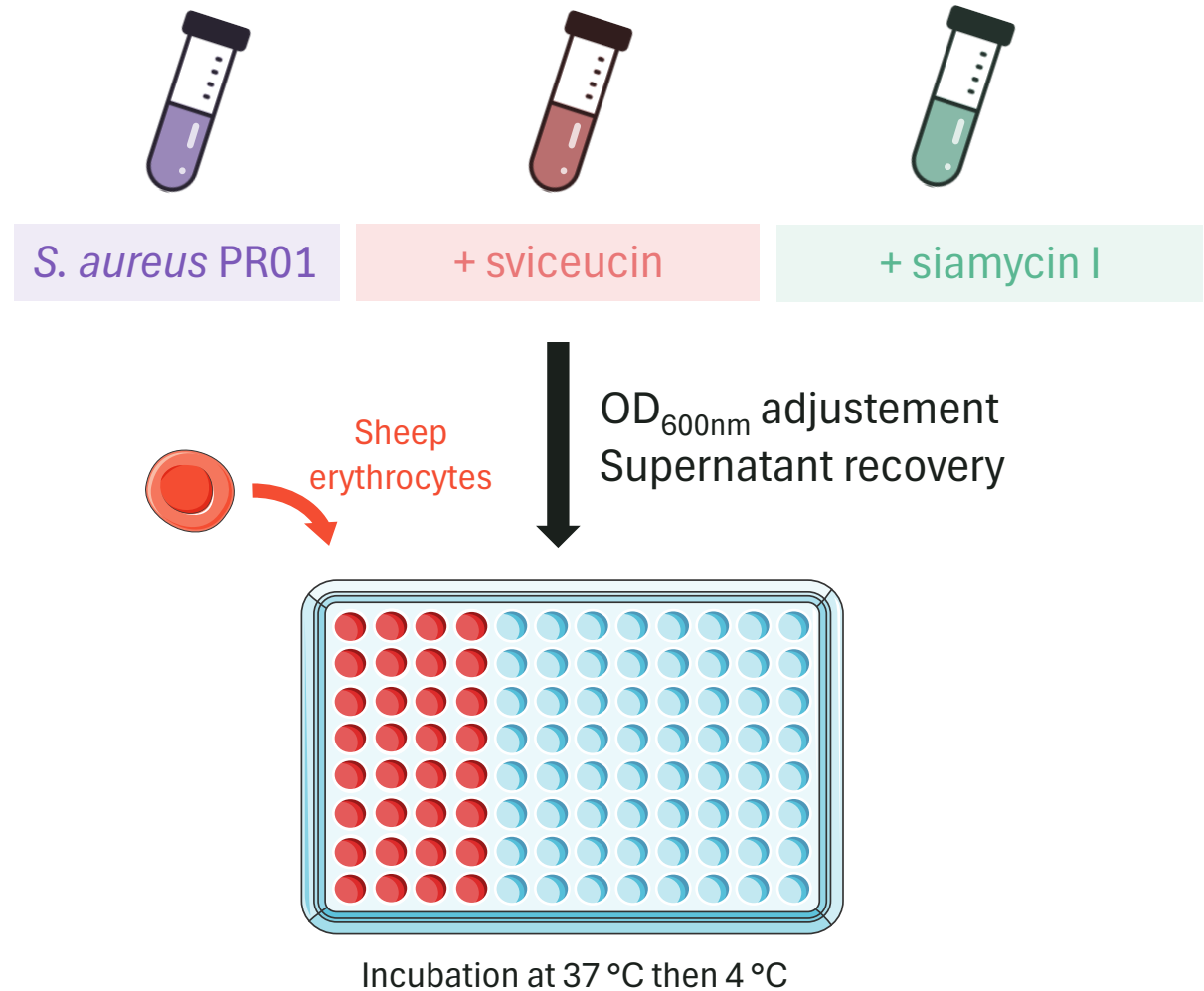
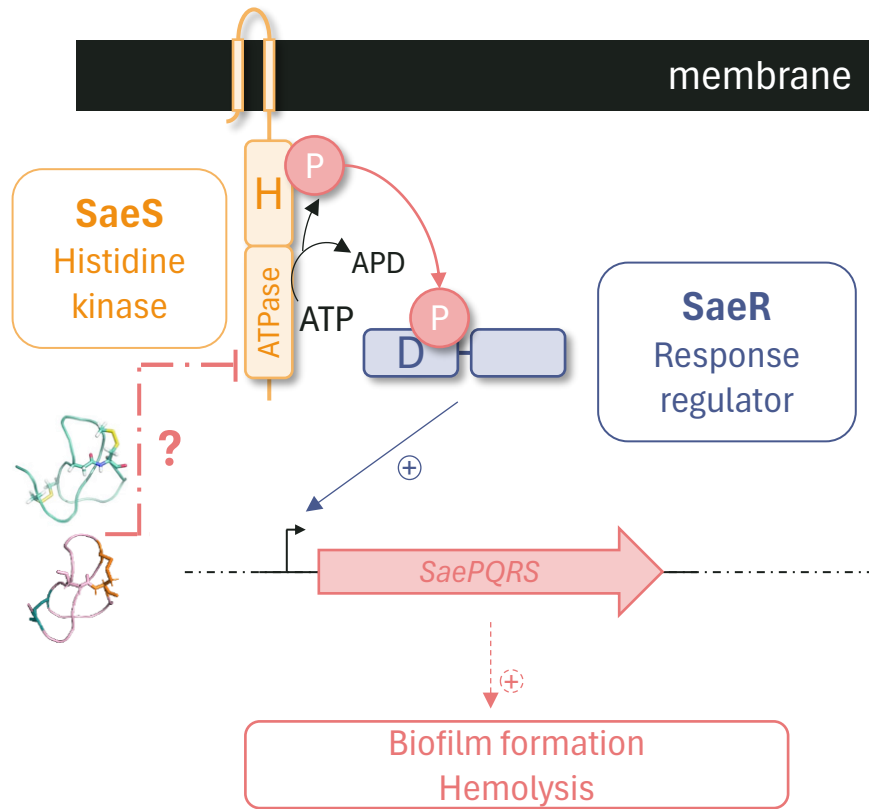
Galleria mellonella larvae survival after infection with $5 \cdot 10^6$ CFU of *S. aureus* PR01 pre-incubated with or without svceucin or siamycin I.



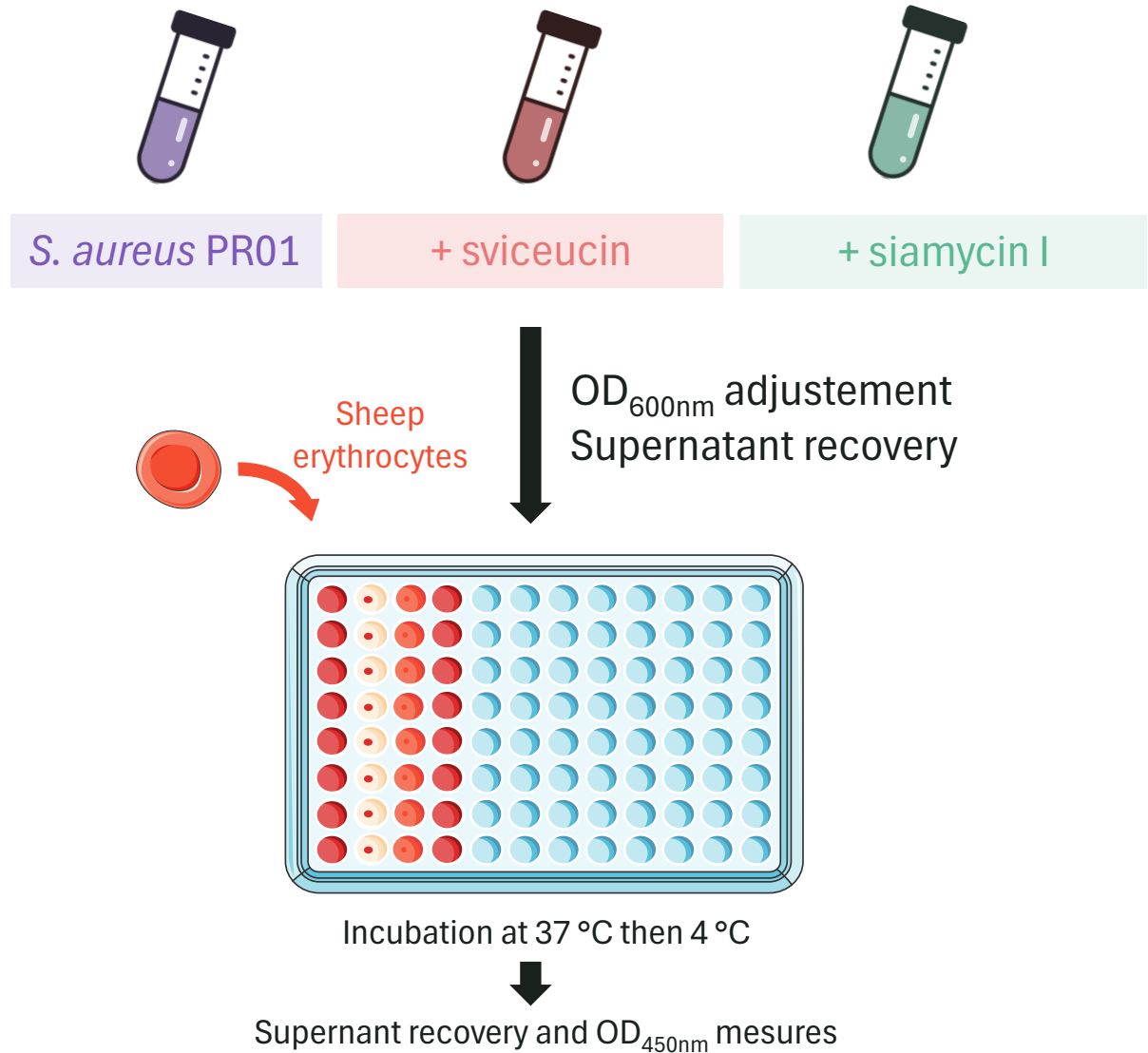
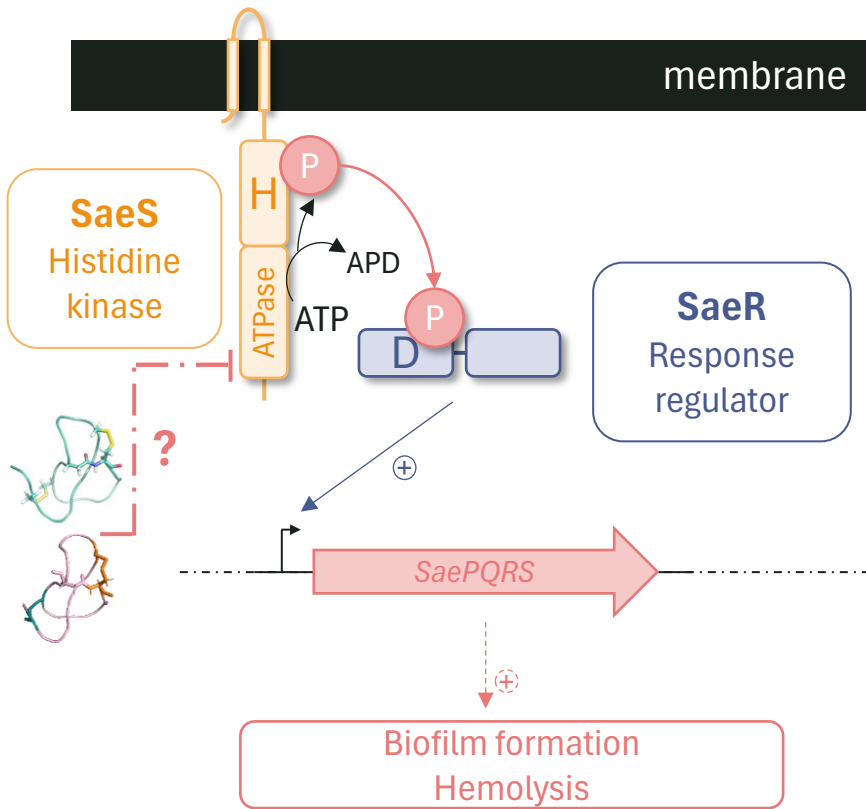
Anti-virulence activity also in *S. aureus*

Sources : Bleul et al., 2021

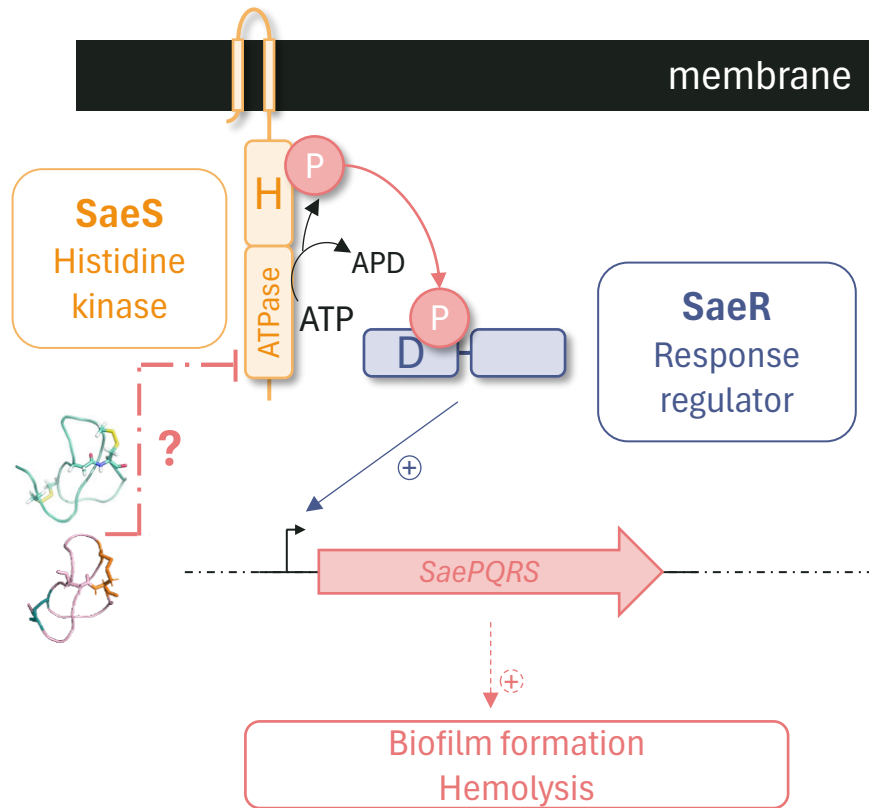
Anti-hemolytic activity



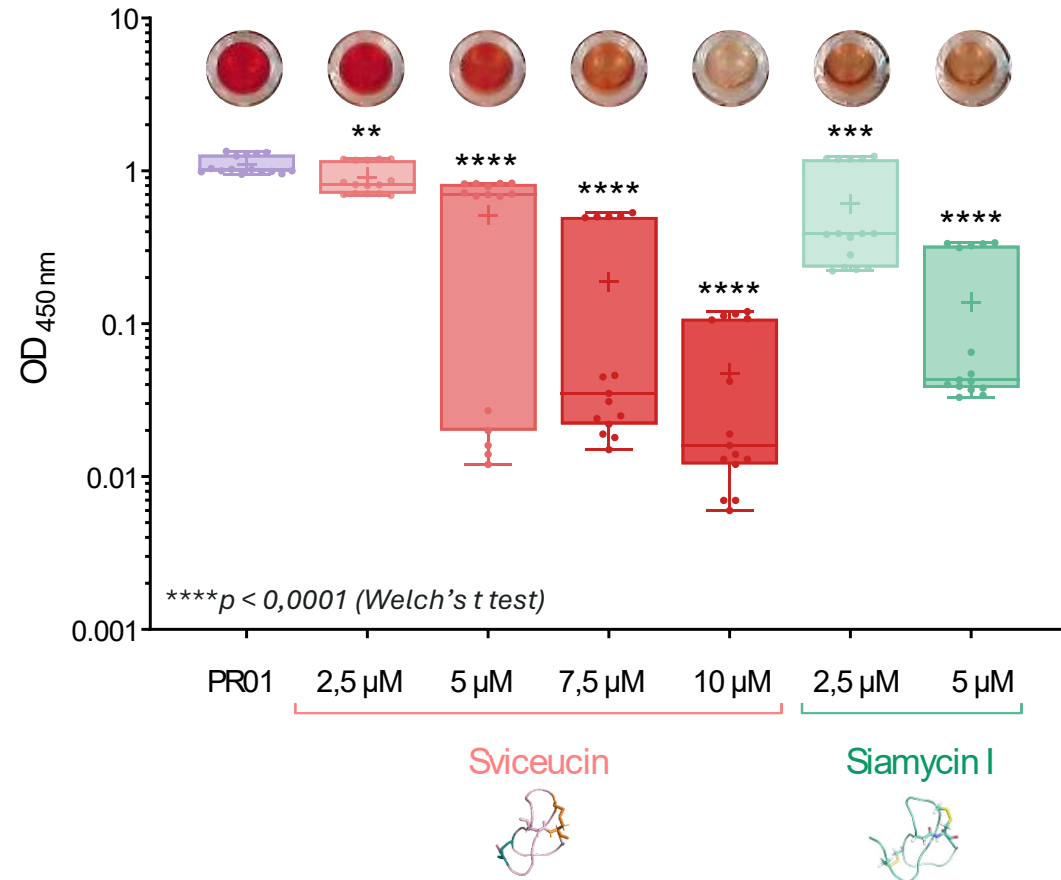
Anti-hemolytic activity

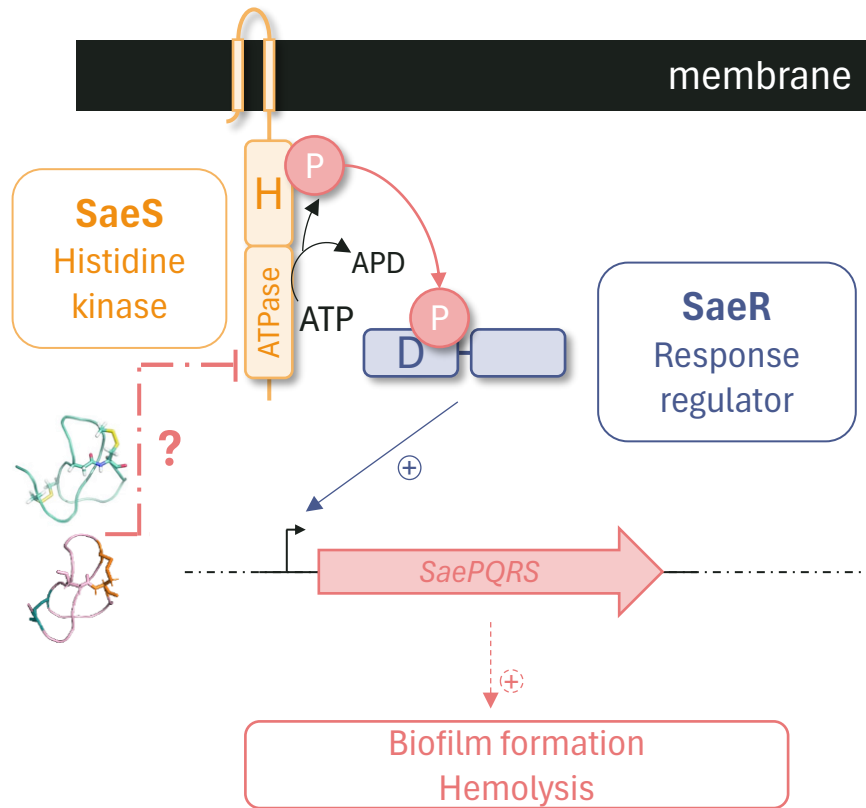


Anti-hemolytic activity

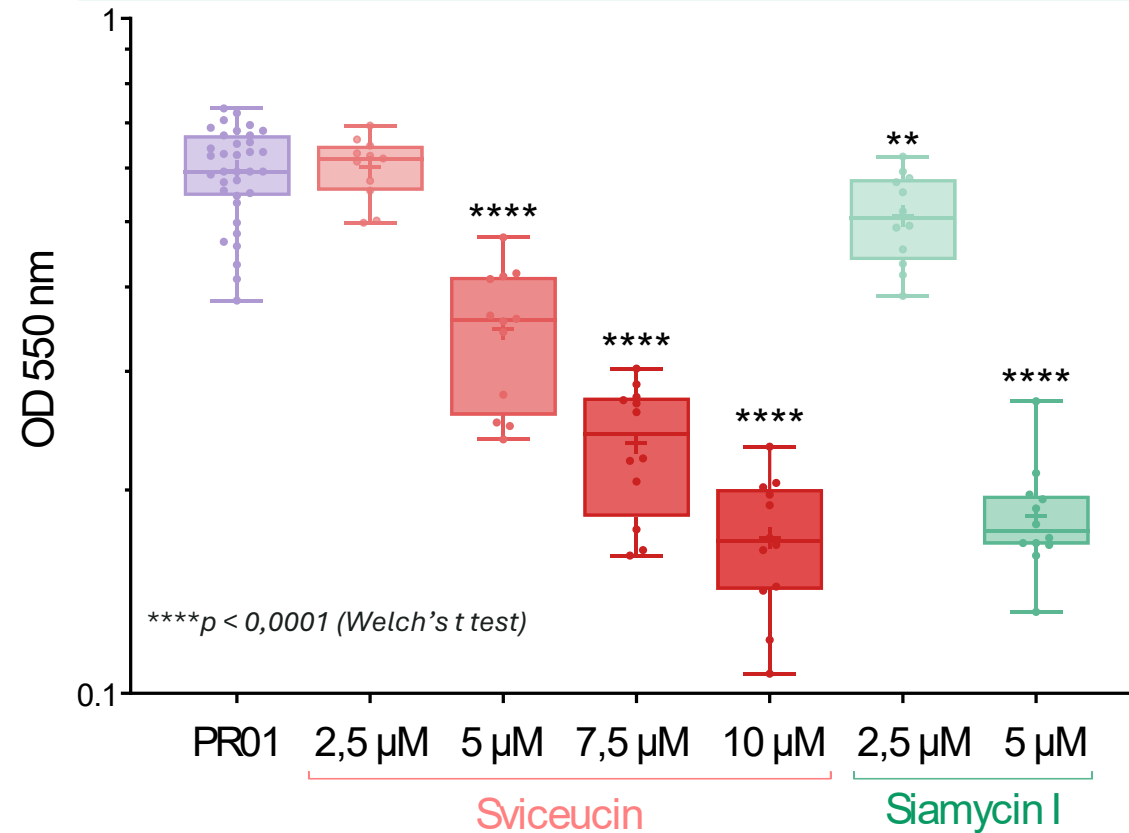


Effect of increasing concentrations of sviceucin or siamycin I on hemolysis of sheep's blood by *Staphylococcus aureus* PR01.

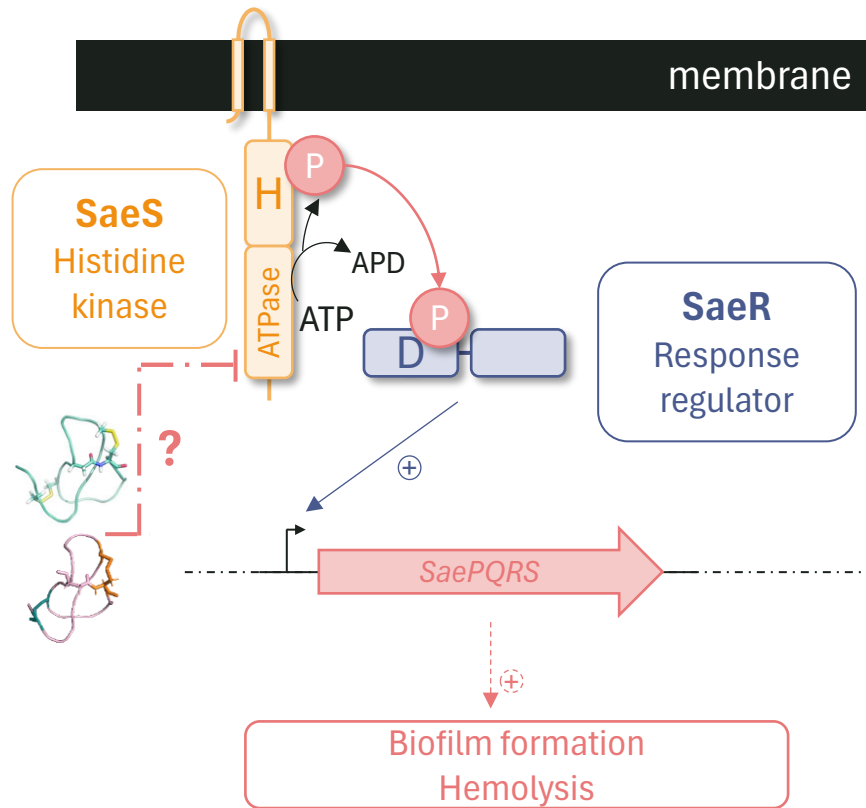




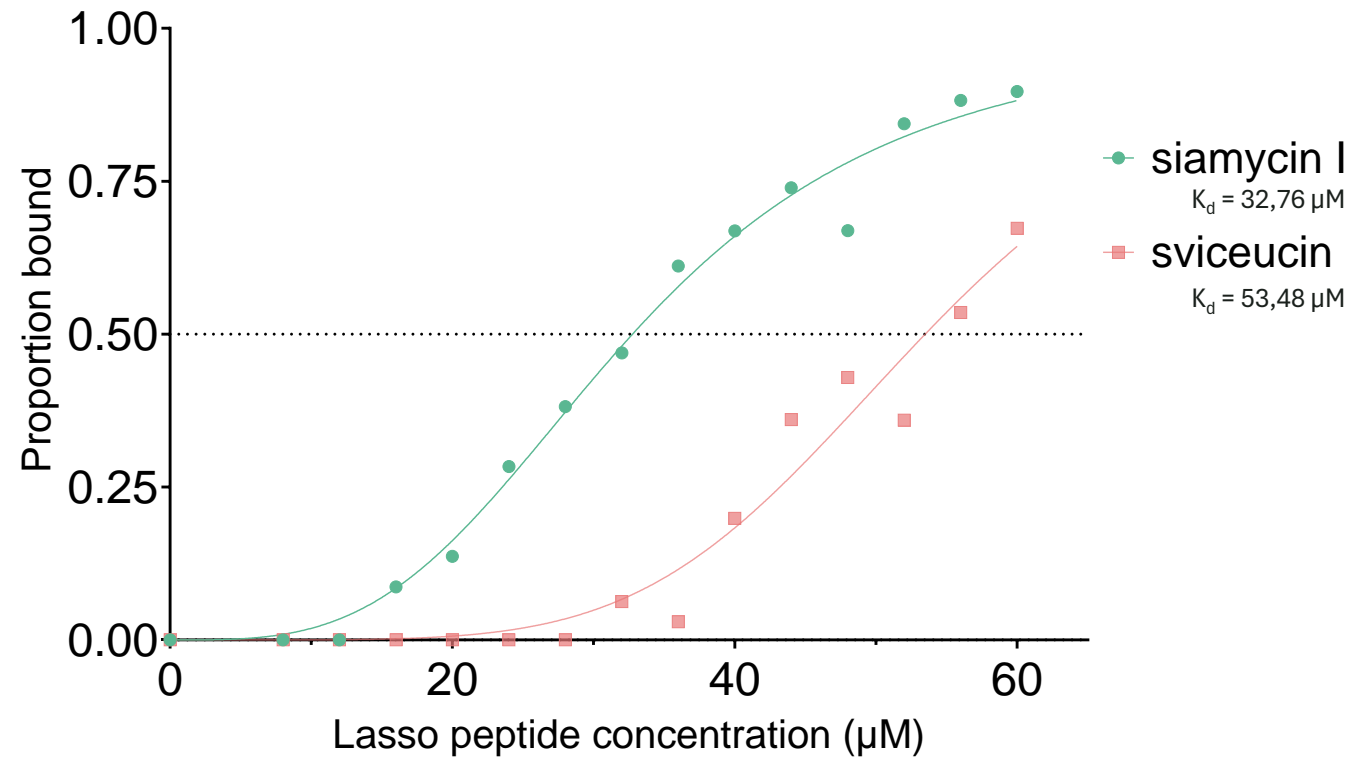
Effect of increasing concentrations of sviceucin or siamycin I on biofilm formation of *Staphylococcus aureus* PR01, determined by crystal violet assay.



Concentration-dependant biofilm formation inhibition

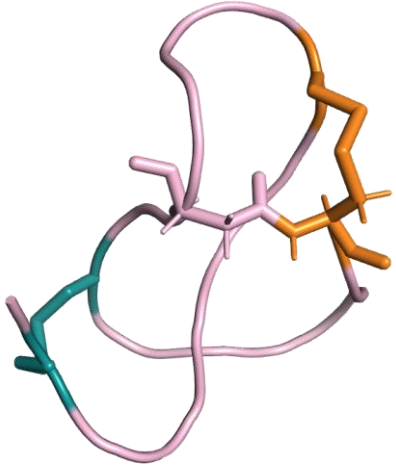


Differential Scanning Fluorimetry (DSF) of the peptide – SaeS cytoplasmic domain interaction

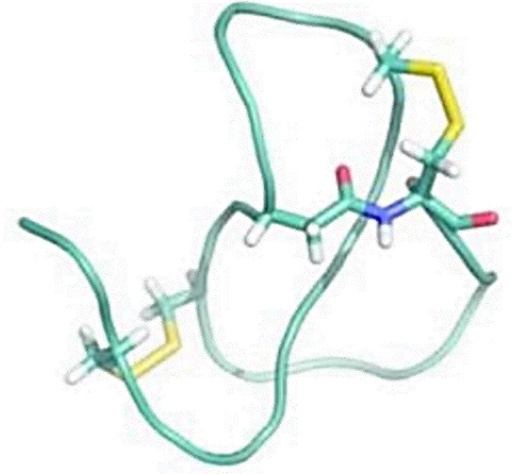


Preliminary results: Direct interaction between SaeS cytoplasmic domain and the lasso peptides

Take home message

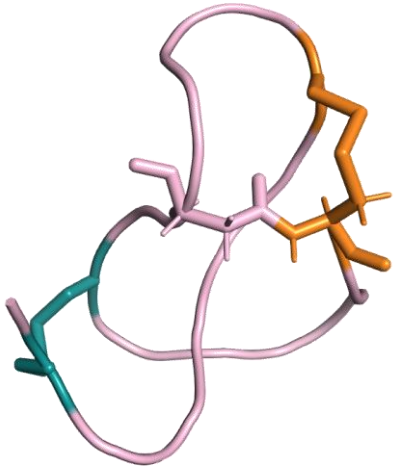


Sviceucin

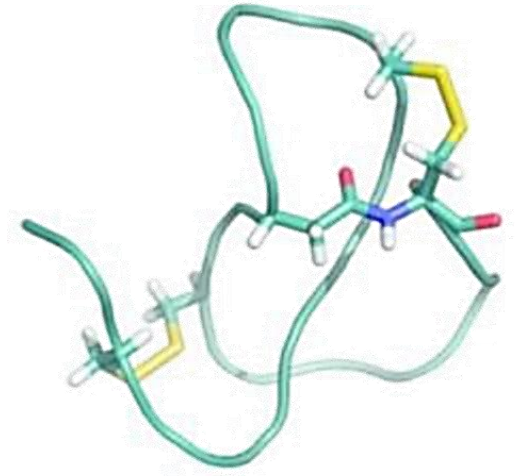
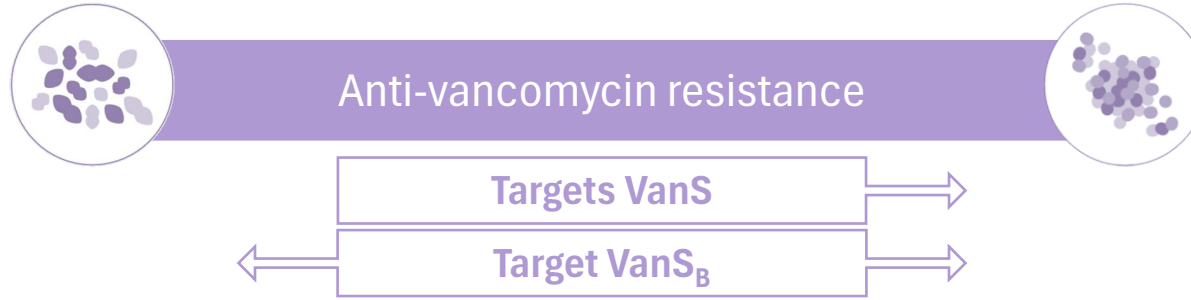


Siamycin I

Take home message

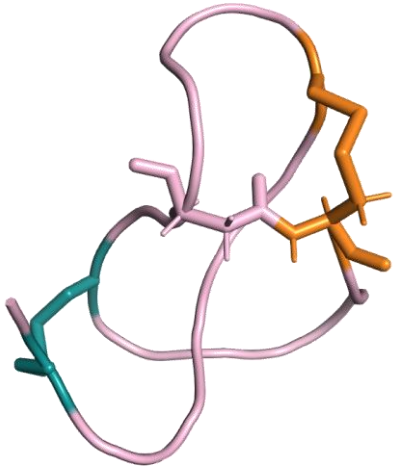


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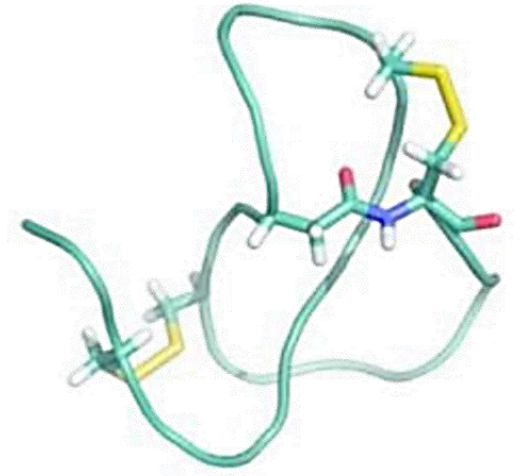
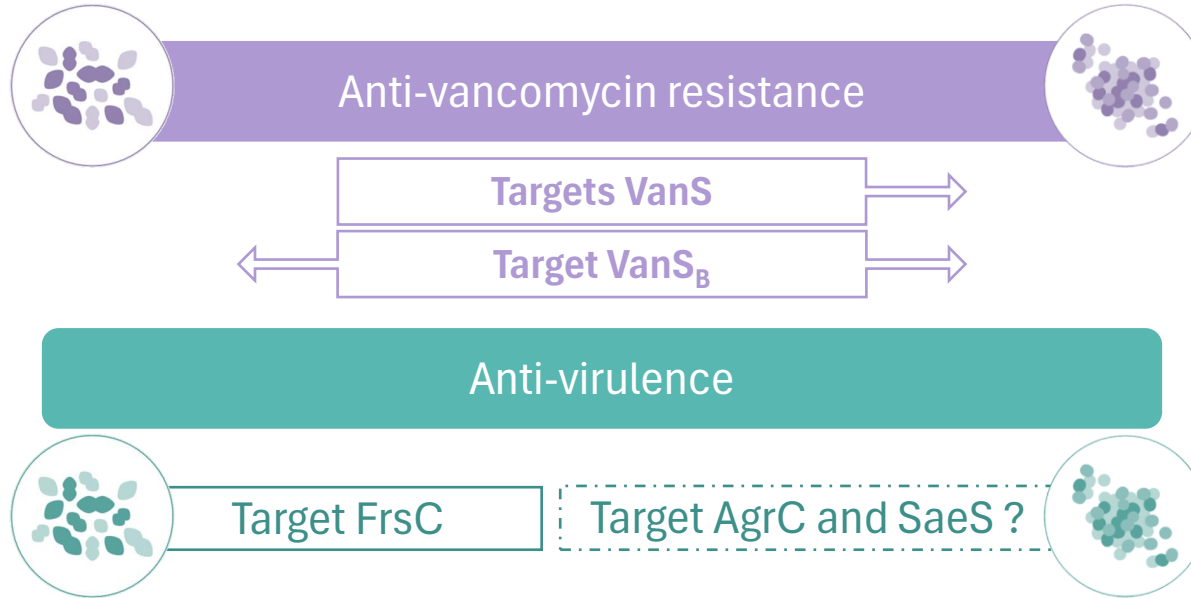


Siamycin I

Take home message

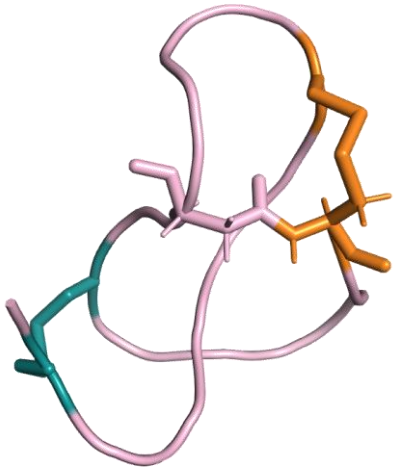


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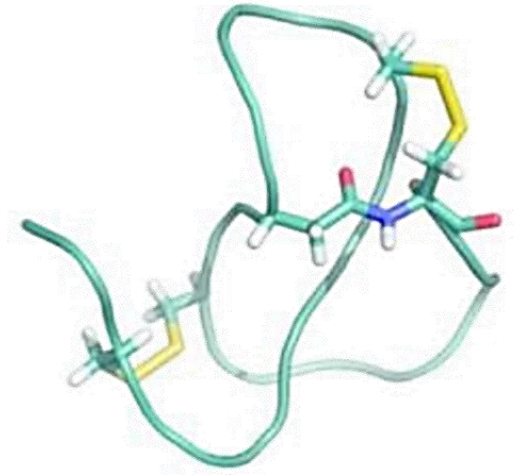
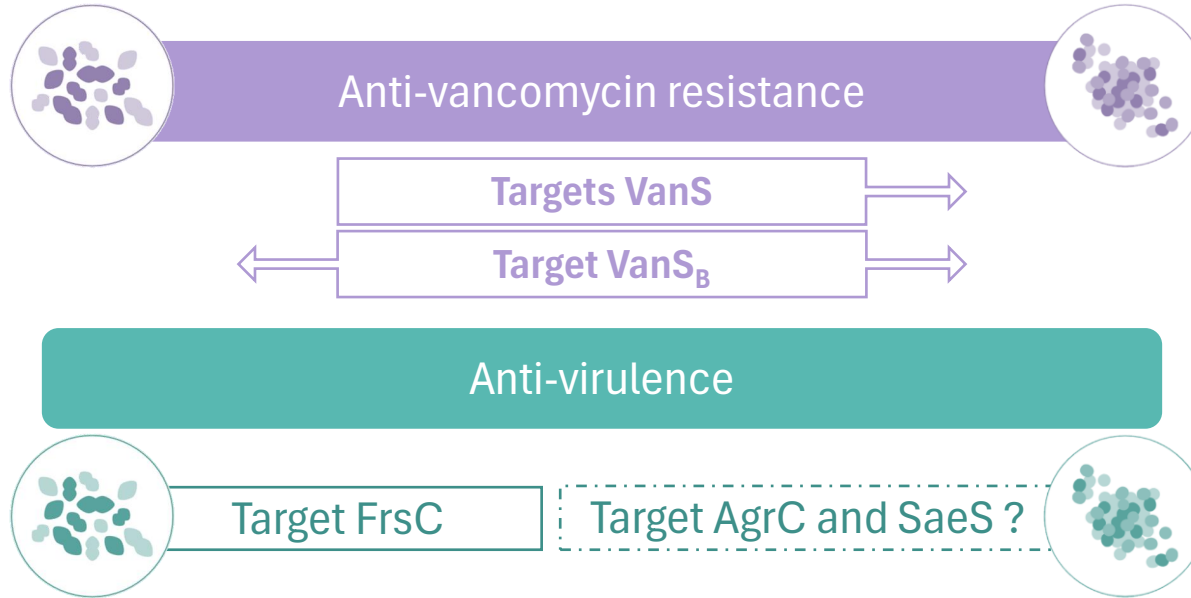


Siamycin I

Take home message



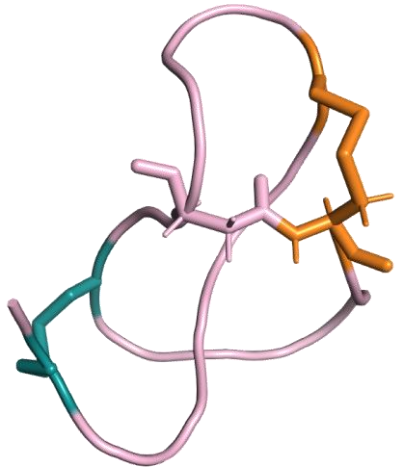
Sviceucin



Siamycin I

Inhibitory interactions with various histidine kinases

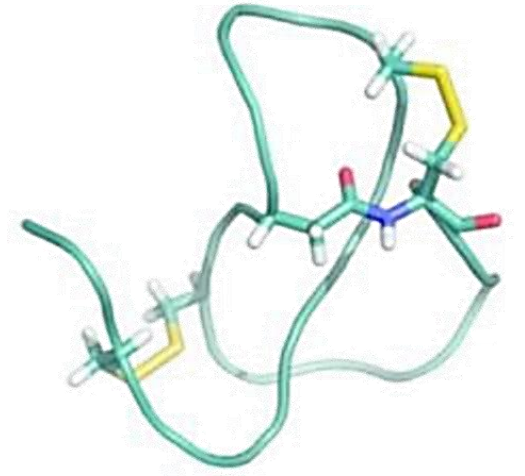
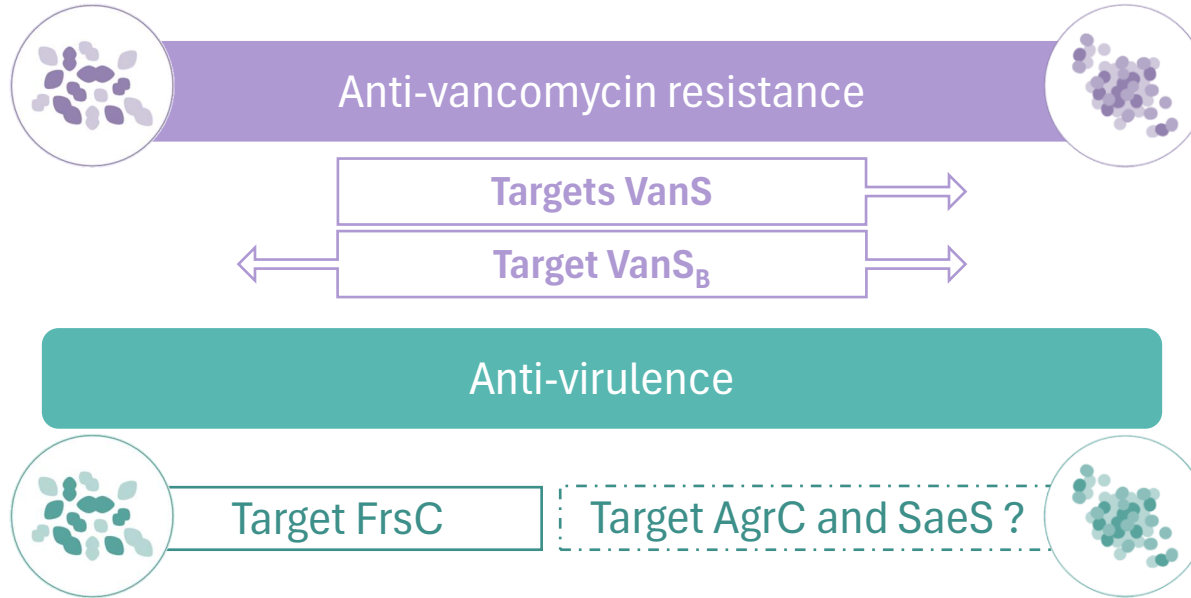
Take home message



Sviceucin



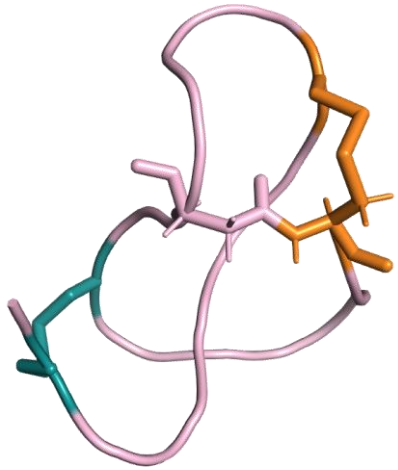
Variants



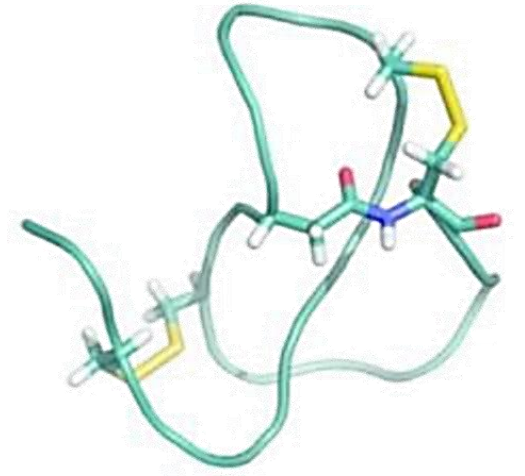
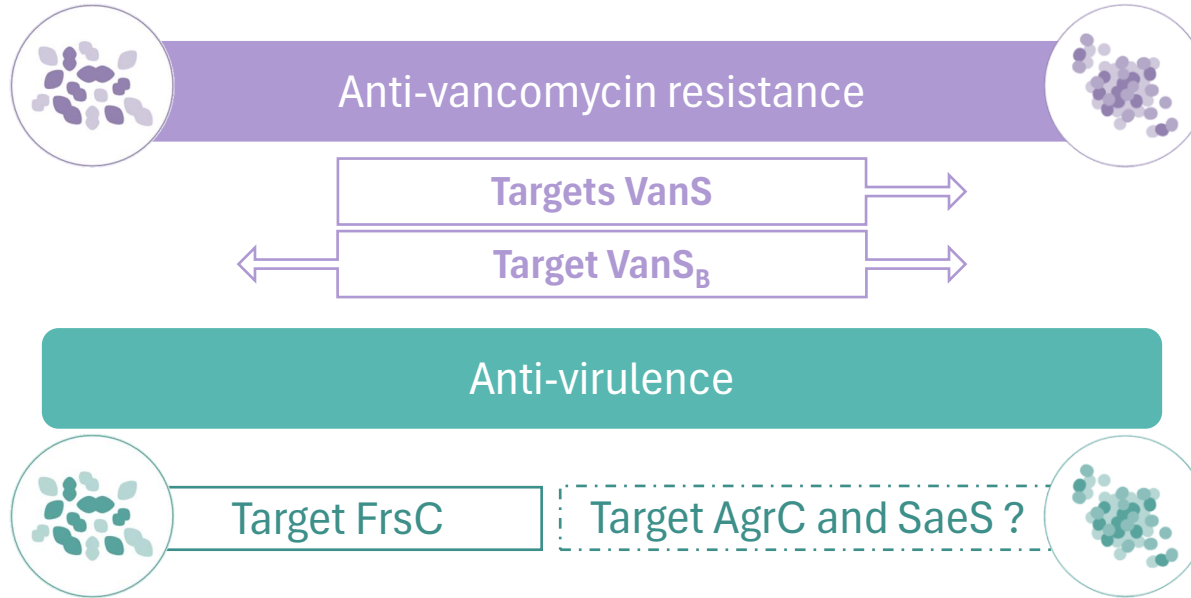
Siamycin I

Inhibitory interactions with various histidine kinases

Take home message



Sviveucin



Siamycin I

Inhibitory interactions with various histidine kinases



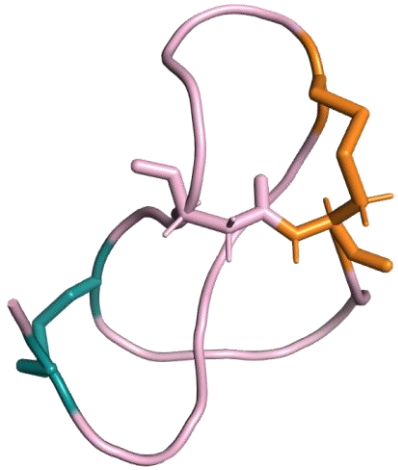
Variants

Modified activity ?

Amino acids involved in activity ?

Structure-fonction relationship

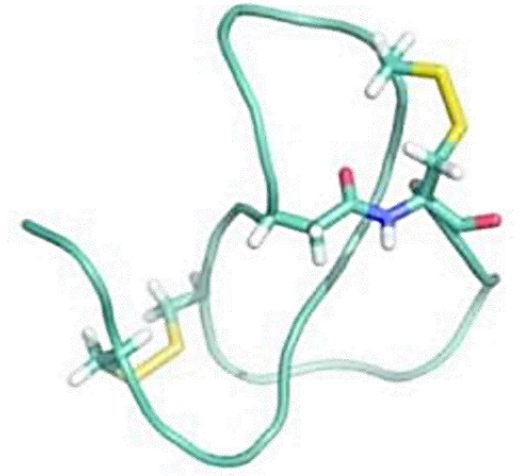
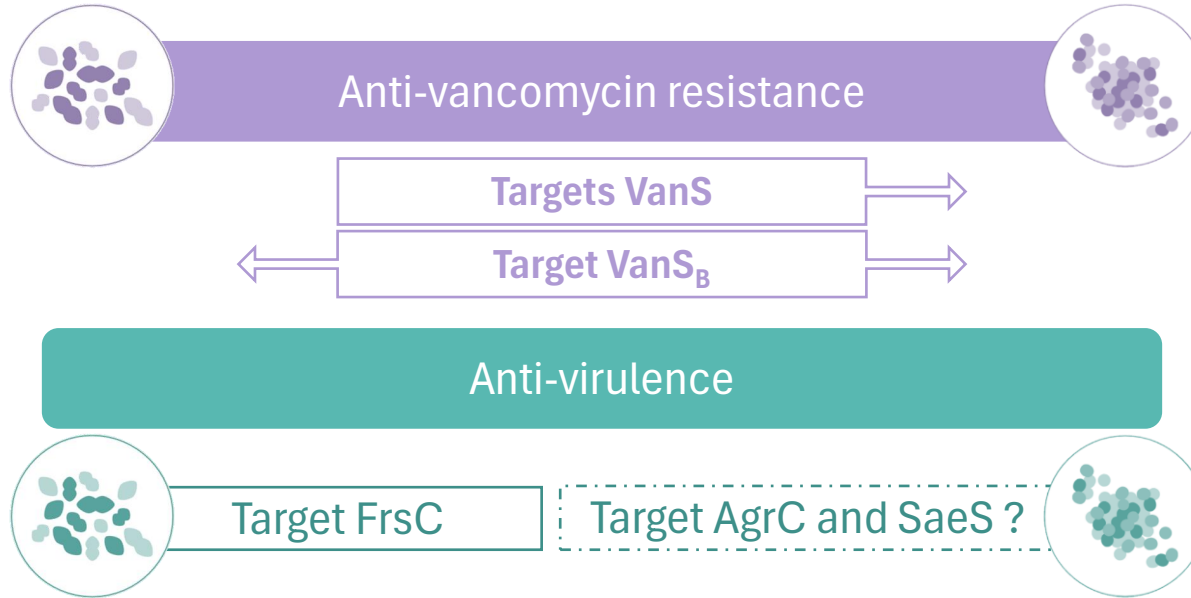
Take home message



Sviveucin



Variants



Siamycin I

Inhibitory interactions with various histidine kinases

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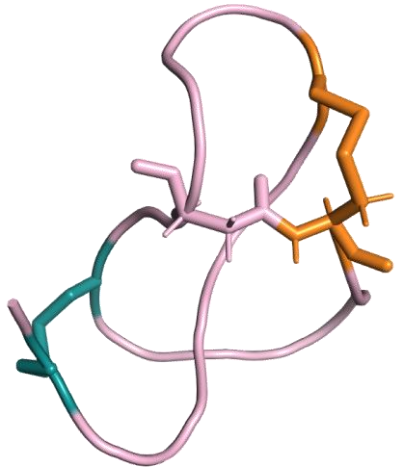


VanS mutants by error-prone PCR



Identification of interaction site

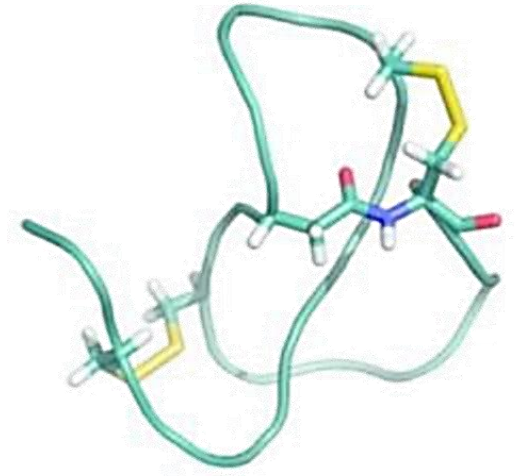
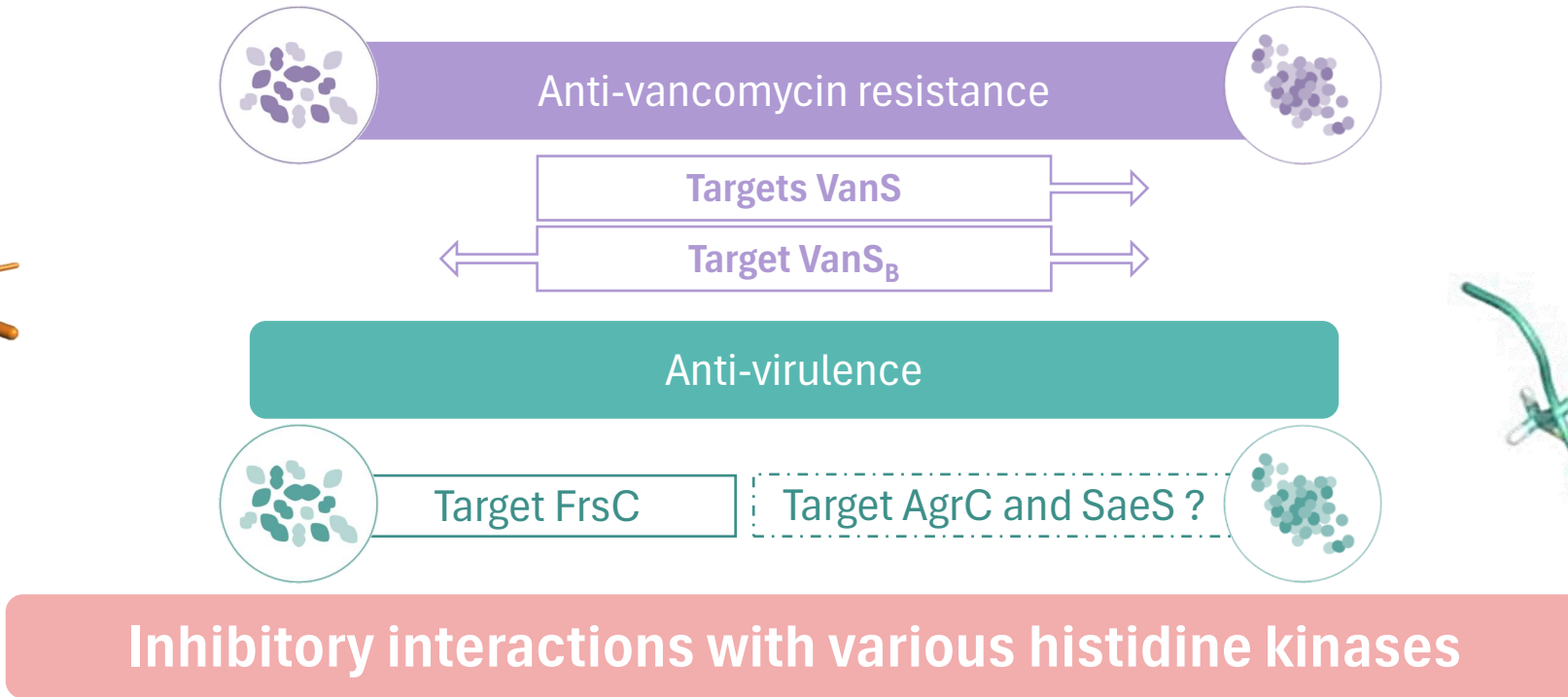
Take home message



Sviceucin

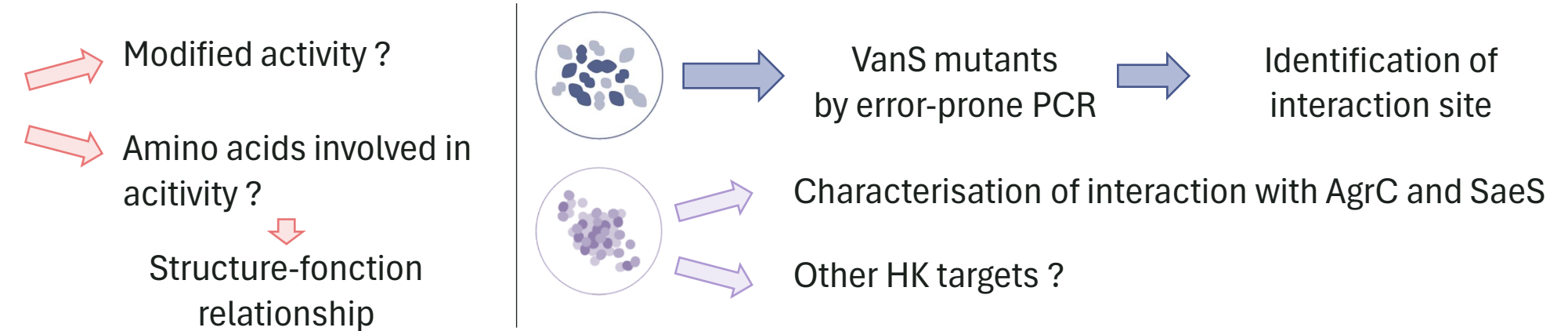


Variants



Siamycin I

Inhibitory interactions with various histidine kinases





Abdellah Benachour
 Sacha Bleux
 Eliette Bisson
 Aurélie Budin-Verneuil
 Sylvie Chevalier
 Ronan Cochelin
 Victor Combret
 Delphine Coupri
 Florie Desriac
 Marc Feuilloley
 Ismail Hasnaoui
 Claire Lallement
 Valentin Langlois
 Une Hunstad Løwø
 Alexandre Mahé
 Juliette Morice
 Cécile Muller
 Fabien Perrier
 Julie Plouhinec
 Isabelle Rincé
 Nicolas Sauvageot
 Diane Soussan
 Nicolas Verneuil



Benjamin Baëtz
 Abdelhakim Boudrioua
 Florian Couturier
 Caroline Giraud
 Sabrina Gueulle
 Axel Hartke
 Léa Rodrigues

Thank you for your attention

Peter Redder



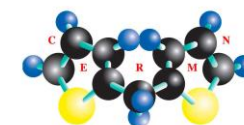
Christophe Goulard
 Johanna Sofia Kallen
 Yanyan Li
 Carine Lombard
 Marie Marugan



Isabelle Broutin



Anne-Claire Groo
 Aurélie Malzert-Fréon



Solenn Desmadril

AntibioDEAL days 2026 – Rennes – 31st March 2026





Lasso peptides siamycin I and sviceucin have anti-resistance and anti-virulence properties on Gram-positive pathogens

UR 4312 – Communication Bactérienne et Stratégies Anti-infectieuses

PhD Supervisor: Dr. Caroline Giraud



Solenn Desmadril

AntibioDEAL days – Rennes – 31st March 2026