



Lugdunin: A New Class of Antibiotics Against Gram-Positive Bacteria

Technology Description

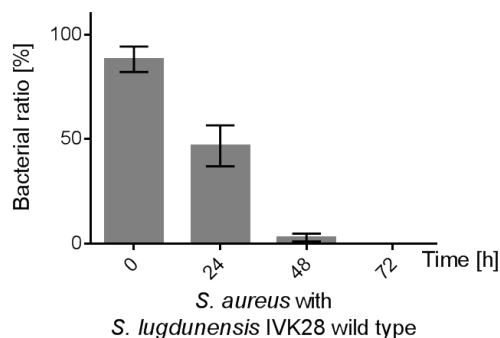
Biological activity of Producer Strain:

Elimination of *S. aureus* USA 300

- in vitro
- in vivo (mouse)

Pure Antibiotic

- from chemical synthesis
- Stable in preliminary toxicity assays



S. aureus is overgrown by *S. lugdunensis* IVK28 wild type on agar plates inoculated at ratios of ~ 90:10.

Among Gram-positive bacteria are some of the most dangerous pathogens like Methicillin-resistant *Staphylococcus aureus* (MRSA) that is responsible for a high percentage of hospital-acquired and deadly infections.

We identified and isolated a previously unknown class of cyclic peptides (Fibupeptides) from the human commensal *Staphylococcus lugdunensis* (strain IVK28) with high potential as new antibiotics. The main compound Lugdunin shows very high efficacy against MRSA and other highly-resistant species like vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (VRE), *Streptococcus pneumoniae* and *Listeria monocytogenes*¹. Lugdunin shows protonophore activity, leading to the disruption of bacterial membrane potential and energy loss. It is probably the first protonophore described from the human microbiome.

Industrial production of "Fibupeptides" is possible via newly established chemical synthesis or fermentative routes².

Furthermore, the naturally human-associated bacterial antibiotic producer (*S. lugdunensis* IVK28 wild type) could be used as a probiotic cure before patients enter hospitals.

Innovation

High activity against a wide range of Gram-positive pathogens. Resistance development has not been observed in MRSA – possibly due to the lack of transporters necessary for clearance³.

Market Potential

The "MRSA-burden" in the EU amounts to one fifth of all disability-adjusted life-years caused by antibiotic-resistant bacteria – 150.000 infections and 8000 deaths per year⁴.

Applications

Human and veterinary medicine: Potential use of Fibupeptides as drugs against MRSA, but also a broader spectrum of Gram-positive bacteria. Use of producer strain as a probiotic. Efficiency of pure Lugdunin against atopic dermatitis already shown in a mouse model.

Advantages

Selective and complete killing of pathogenic bacteria even in the non-growing state. Synergistic activity with human AMPs.

Low toxicity: First data point to a low cytotoxic potential against human cells. General microbiome composition remains stable

IP Status

EP 3 072 899 B1, validated in GB, FR, DE, ES, IT; US10774113 granted; JP - application pending

CONTACT

Dr. Rolf Hecker
Eberhard Karls Universität Tübingen
Technology Transfer Office
Keplerstraße 2
72074 Tübingen · Germany

+49 7071 29 72639
r.hecker@uni-tuebingen.de
www.technologietransfer.uni-tuebingen.de

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Dr. Bernhard Krismer
Eberhard Karls Universität Tübingen

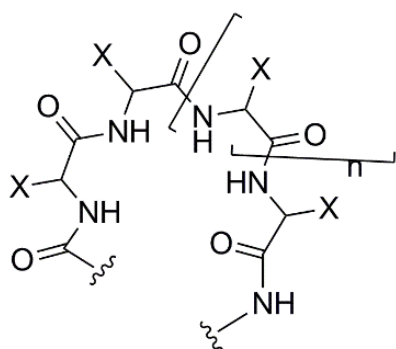
Auf der Morgenstelle 28
72076 Tübingen · Germany

+49 7071 29 74640
b.krismer@uni-tuebingen.de

SCIENTIST

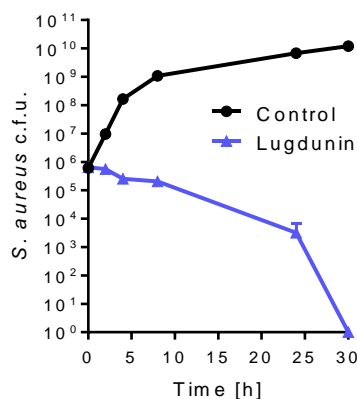
PROOF OF CONCEPT

Overall Structure of Lugdunin (C₄₀H₆₂N₈O₆S) and Activity against Pathogens



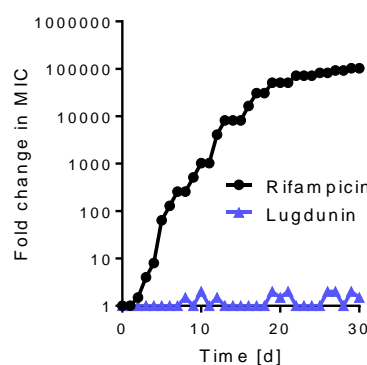
Organism and strain	Resistance	Lugdunin MIC (µg/mL)
<i>Staphylococcus aureus</i> USA300 (LAC)	MRSA	1.5
<i>Staphylococcus aureus</i> USA300 (NRS384)	MRSA	1.5
<i>Staphylococcus aureus</i> Mu50	GISA	3
<i>Staphylococcus aureus</i> SA113		3
<i>Staphylococcus aureus</i> RN4220		3
<i>Enterococcus faecium</i> BK463	VRE	3
<i>Enterococcus faecalis</i> VRE366	VRE	12
<i>Listeria monocytogenes</i> ATCC19118		6
<i>Streptococcus pneumoniae</i> ATCC49619		1.5

Bactericidal Mode of Action



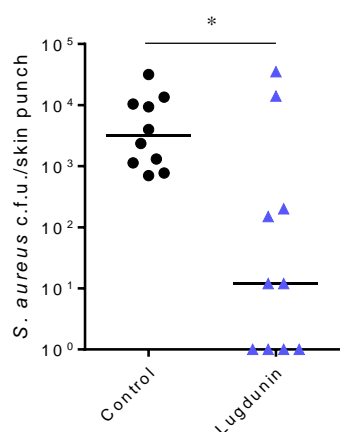
Lugdunin kills highly pathogenic *S. aureus* (MRSA) after a single-dose treatment, demonstrating the compound's bactericidal mode of action.

No Resistance Development



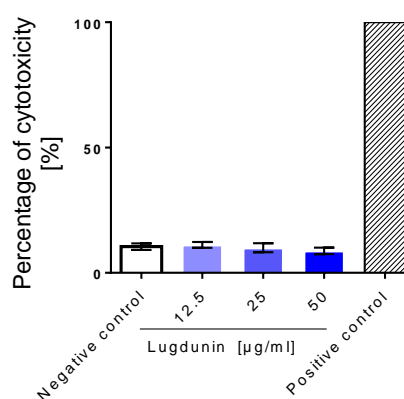
Furthermore, *S. aureus* does not select for spontaneous resistance when lugdunin is applied at subinhibitory concentrations over 30 days.

Efficacy in an Animal Model



Topical application of the antibiotic leads to eradication of *Staphylococcus aureus* in an animal model (mouse). (* P < 0.05)

No Toxicity on Human Neutrophils



Determination of potential cytotoxic effects on neutrophil granulocytes shows no significant effect (monitored after 3 h of incubation by the release of lactate dehydrogenase (LDH)).

REFERENCES

- Zipperer et al., Nature 535:511-516, 2016; doi:10.1038/nature18634
- Saur JS, et al., J Med Chem. 2021 Apr 8;64(7):4034-4058 doi: 10.1021/acs.jmedchem.0c02170
- Krauss et al., Antimicrob Agents Chemother 2020 Dec 16;65(1):e01734-20. doi: 10.1128/AAC.01734-20
- Cassini et al., The Lancet Infectious Diseases 19, ISSUE 1: 56-66, January 01, 2019; doi: https://doi.org/10.1016/S1473-3099(18)30605-4