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LPL1 Derived Immune Enhancing Peptides: A New Tool against MRSA&Co.

Technology Description

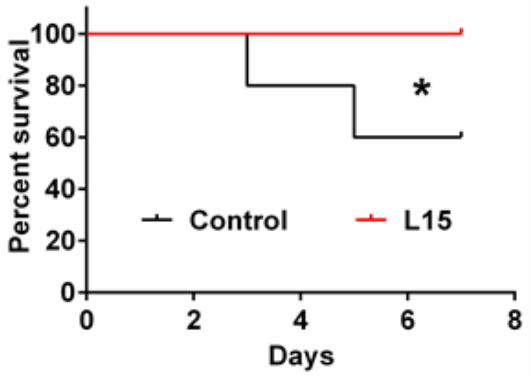

Figure 1: Mice treated with L15 before systemic MRSA-infection show a significant survival advantage.

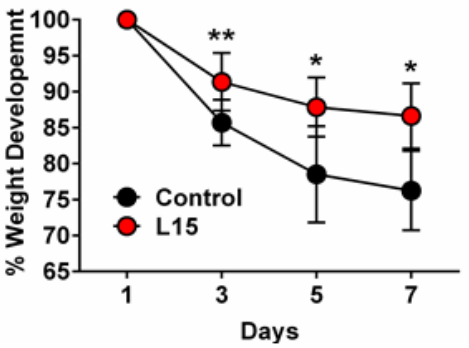

Figure 2: L15 also shields against deadly weight loss in this animal model.

A recently published study estimates nearly 5 million deaths worldwide associated with antimicrobial resistance (AMR) for the year 2019, 1.27 million deaths being directly attributable to bacterial AMR[1]. And *Staphylococcus aureus* is listed under the six leading pathogens for deaths associated with (AMR), thus new drugs especially against MRSA are utterly required.
A peculiar example of the dangers of *S. aureus*-infection is septic arthritis, a debilitating joint disease, that causes permanent joint dysfunction in almost 50% of the patients[2].

Here we present two sub fragment-peptides, L13 and L15, derived from the protein Lpl1 (lipoprotein-like lipoprotein 1) in *Staphylococcus aureus*, that show strong protective activity against MRSA in animal models of septic arthritis. These sub fragments are countering the role of Lpl1 in the invasion of human cells by *S. aureus*[3]. First data point to a strong shielding effect of our peptides against systemic infection in a mouse model of septic arthritis[3,4].

Treatment with L15 renders a strong survival advantage compared to animals treated with PBS as control (please refer to Fig. 1 and 2). NMRI mice were intraperitoneally treated with L15 or PBS (control) starting two hours before intravenous inoculation with *S. aureus* Newman strain. Treatment with L15 was then continued every day.

Innovation

- Use of L13 and L15 as substitutes for antibiotics or co-factors in treatments against MRSA-infection.
- Use in cancer treatment also possible.
- L13 and L15 are stable, water soluble, non-hemolytic, and less cytotoxic than geldanamycin, a known Hsp90 inhibitor.

Market Potential / IP Status

Methicillin-resistant *S. aureus* was the only one pathogen–drug combination in 2019 with more than 100 000 deaths worldwide and 3.5 million DALYs attributable to resistance[1].

EKUT filed a priority application with the European Patent Office, Priority date 2021-12-22

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PROOF OF CONCEPT

Blocking the Invasion by *Staphylococcus aureus*

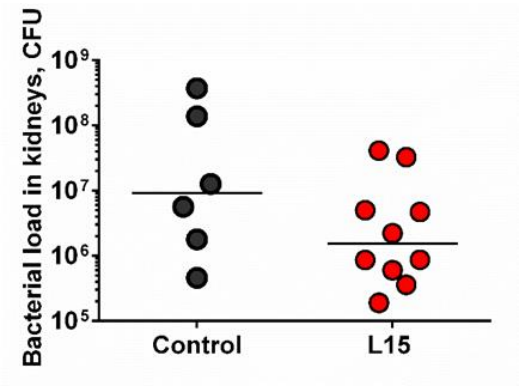

Figure 3: L15 treatment dampens systemic *S. aureus* infection in mice.

There is a significant reduction of bacterial load in kidneys of mice on day 7 post-infection. Control animal received only PBS. On day 7 after inoculation with *S. aureus* animals were sacrificed and bacterial load in kidneys determined.

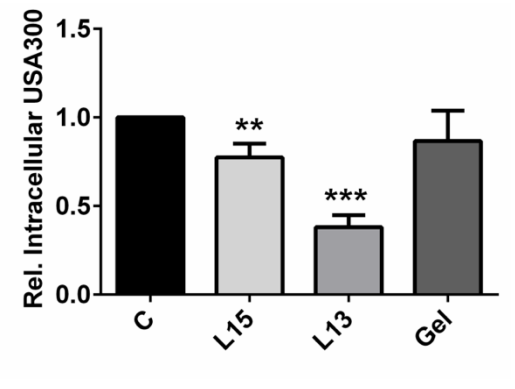

Figure 4: L15 significantly reduces intracellular invasion

Pre-treatment with L15 and L13 reduces the phagocytosis of *S. aureus* USA300 by primary human CD14+ monocytes, while geldanamycin (Gel) shows no such effect.

Validation in a Second Animal Model

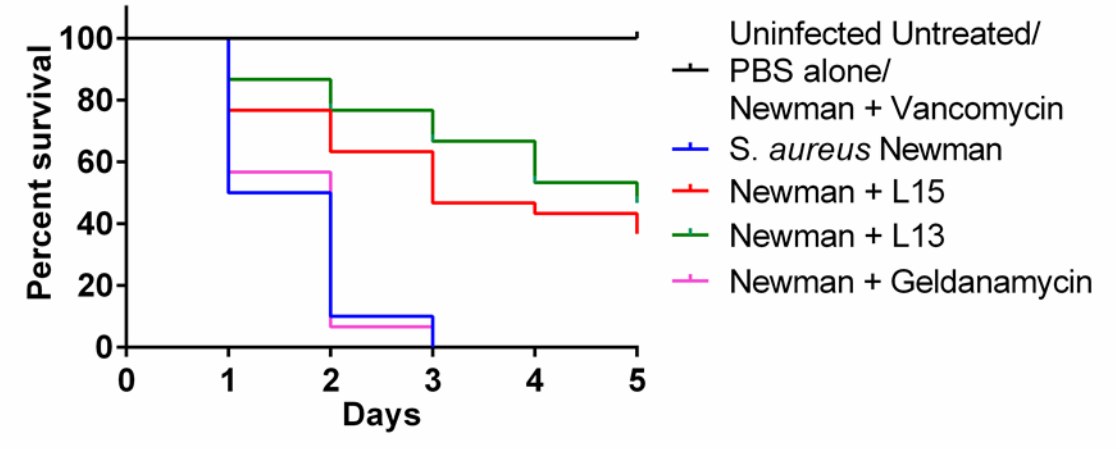

Figure 5: L15 and L13 partially (~ 40 %) protects larvae from killing by S. aureus.

Larvae of *Galleria mellonella* were treated the same way as described for the experiments with mice. Although the peptides do not provide 100% protection against larval infection with *S. aureus*, they do reduce the virulence of this pathogen. For this reason, they have the potential to be used effectively either alone or in combination with other drugs.

REFERENCES

1 Antimicrobial Resistance Collaborators, The Lancet, January 19, 2022, DOI: https://doi.org/10.1016/S0140-6736(21)02724-0

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3 Ammanath et al., From an Hsp90 - binding protein to a peptide drug, microLife, Volume 4, 2023, uqac023, https://doi.org/10.1093/femsml/uqac023

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