

**Name of PI:**

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**Title of PhD Project:**

Combating the resistance against lantibiotics: Nisin as a model system

**Abstract:**

Bacterial infections are one of the most common diseases which can be treated by antibiotics. Since several years the need for new antibiotics is rising due to emerging resistance against them. One possible novel antibiotic are antimicrobial peptides called lantibiotics. These are highly potent peptides produced by some Gram-positive bacteria. Nisin is such a lantibiotic and consists of 34 amino acids. Due to intermolecular thio ether-bridges the molecule is very stable and not susceptible for proteases. In *Streptococcus agalactiae* however a gene cluster consisting of five proteins causes resistance against nisin. The proteins are upregulated and over expressed within *S. agalactiae* whenever nisin is found in the exterior. The protein NSR is membrane anchored and cleaves nisin by which the activity is reduced 100-fold. We recently determined the X-ray structure of NSR and its substrate specificity. Besides this protein also an ABC transporter is expressed, NsrFP, which expels nisin once it reaches the cellular membrane. Our goal is to understand the exact mechanism of lantibiotic resistance and to identify a compound or compound class, which specifically interferes with the function of this resistance operon. That way, nisin will be able to reach and penetrate the pathogenic bacteria.

**Suggested Reading:**

Khosa S, Lagedroste M, and Smits SHJ (2016) Protein defence systems against the lantibiotic nisin: Function of the immunity protein NisI and the resistance protein. NSR *Frontiers Microbiology*. - Antimicrobials, Resistance and Chemotherapy (volume 7 article 504).

Khosa S, Hoepfner A, Gohlke H, Schmitt L, Smits SHJ (2016) Structure of the Response Regulator NsrR From *Streptococcus agalactiae*, which is Involved in Lantibiotic Resistance. *PLOS ONE* 11:e0149903.

Khosa S, Frieg B, Mulnean D, Kleinschrodt, D, Hoepfner A, Gohlke H, Smits SHJ (2016) Structural basis of lantibiotic recognition by the nisin resistance protein from *Streptococcus agalactiae*. *Scientific Reports* 6:18679.

Khosa S, Alkhatib Z, and Smits SHJ (2013) NSR from *Streptococcus agalactiae* confers resistance against nisin and is encoded by a conserved nsr operon. *Biological Chemistry* 394:1543-1549.

Draper LA, Cotter PD, Hill C, and Ross RP (2015) Lantibiotic Resistance. *Microbiol Molecular Biology Review* 79:171-191.