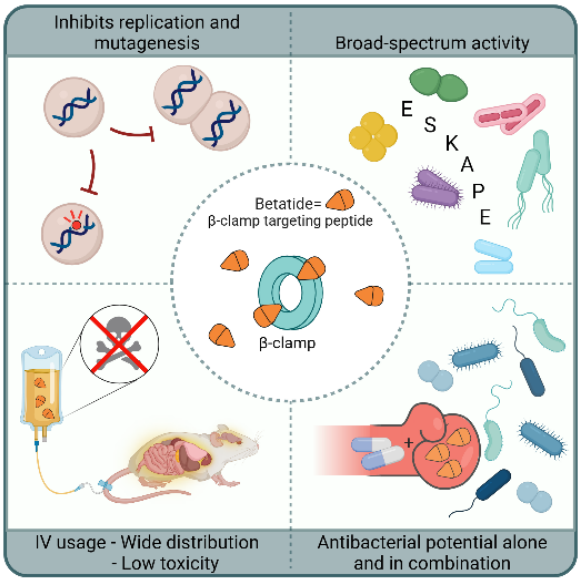
Novel antibiotic peptides in the fight against AMR

Caroline K. Søgaard and Marit Otterlei
Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Science
NTNU Norwegian University of Science and Technology, NO-7491 Trondheim, Norway.

New antibiotics with new targets and modes of action are urgently needed to combat antimicrobial resistance (AMR). We are developing cell-penetrating β-clamp targeting peptides (betatides). These rapidly bactericidal peptides inhibit replication and mutagenesis in both G+ and G- bacteria, including multi-drug resistant ESKAPE species. Bacteria also have difficulty in evolving resistance to these peptides, they enhance the efficacy of other antibiotics and reduce the ability to develop resistance to them. The peptides are widely distributed in all organs and tissues and have low toxicity (1-4). That´s why we believe Betatides can be used broadly, in combination or alone when conventional therapies don´t work.



An anti-cancer peptide containing an interaction motif for the mammalian DNA sliding clamp PCNA was accidentally discovered to have antibacterial activity due to its interaction also with the bacterial β–clamp (1). This peptide was recently shown to have a favorable toxicity profile in a Phase I study (5). We are currently designing and testing 2nd generation peptides.

We already have several peptide candidates with improved antibacterial activity, the same mode of action and the same, low toxicity profile as the anti-cancer peptide. We aim to select a new lead and demonstrate systemic proof-of-concept by 2024.

1. Nedal et al. Peptides containing the PCNA interacting motif APIM bind to the beta-clamp and inhibit bacterial growth and mutagenesis. Nucleic acids research. 2020; 48(10):5540.
2. Nepal et al. Broad-Spectrum Antibacterial Peptide Kills Extracellular and Intracellular Bacteria Without Affecting Epithelialization. Front Microbiol. 2021;12:764451.
3. Sumabe et al. Nucleoside Analogues Are Potent Inducers of Pol V-mediated Mutagenesis. Biomolecules. 2021;11(6).
4. Raeder et al. Novel Peptides Targeting the beta-Clamp Rapidly Kill Planktonic and Biofilm Staphylococcus epidermidis Both in vitro and in vivo. Front Microbiol. 2021;12:631557.
5. Lemech et al. ATX-101, a cell-penetrating protein targeting PCNA, can be safely administered as intravenous infusion in patients and shows clinical activity in a Phase 1 study. Oncogene. 2022, Epub 23rd Des.