Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Title of the M2 research internship:
Structure-function relationship of *Ruminococcus gnavus* RumC Antimicrobial Peptides

Project summary:
Antibiotic resistance is considered as one of the main health challenges around the world. The WHO is alerting that the death toll caused by antimicrobial resistance might reach 10 million cases in 2050. One of the possible alternatives to conventional antibiotics is a class of antimicrobial peptides called RiPPs (Ribosomally synthesized and post-translationally modified peptides) produced by bacteria. *Ruminococcus gnavus*, an anaerobic commensal bacterium residing in the human gut, was shown to produce five peptide isoforms called RuminococcinC (RumC1-C5). They are characterized by their double hairpin structure held by four thioether bonds inserted onto the precursor peptide during the maturation step by a radical-SAM enzyme. The RumC1 peptide was proven to be a very efficient compound exhibiting minimal inhibitory concentrations (MIC) that are similar to or less than those of the reference antibiotics used for priority pathogens including *Clostridium difficile*, *Enterococcus faecium*, and *Streptococcus pneumoniae*. Interestingly, sequence alignments of the five RumC peptides confirmed that, although very close, their amino acid sequences vary at fourteen positions. Moreover, NMR structural studies showed that these variable residues were all localized on one surface of RumC1, which highly suggests that this surface is playing a role in the interaction with the cellular target(s). In an attempt to conduct a structure-function relationship, we are interested in understanding the importance of these residues for the antimicrobial activity of the peptide. Thus, we will focus on the production and the biochemical characterization of targeted RumC1 variants, carrying mutations at one or more variable positions. Finally, the antimicrobial efficacy of RumC1 variants will be investigated on several pathogenic strains including clinical isolates.

Keywords:
antibiotic resistance, antimicrobial peptides, human gut microbiota

Relevant publications of the team:
Ruminococcin C, a promising antibiotic produced by a human gut symbiont. Chiumento S, Roblin C, Kieffer-Jaquinod S, Tachon S, Leprètre C, Basset C, Aditiyarini D, Olleik H, Nicoletti C, Bornet O, Iranzo O, Maresca M, Hardré R, Fons M, Giardina T, Devillard E, Guerlesquin F, Couté Y, Atta M, Perrier J, Lafond M*, Duarte V*. Science Advances, 2019 Sep 25;5(9):eaaw9969. doi: 10.1126/sciadv.aaw9969. eCollection 2019 Sep.

The unusual structure of Ruminococcin C1 antimicrobial peptide confers clinical properties. Roblin C, Chiumento S, Bornet O*, Nouailler M, Müller CS, Jeannot K, Basset C, Kieffer-Jaquinod S, Couté Y, Torelli S, Le Pape L, Schünemann V, Olleik H, De La Villeon B, Sockeel P, Di Pasquale E, Nicoletti C, Vidal N, Poljak L, Iranzo O, Giardina T, Fons M, Devillard E, Polard P, Maresca M, Perrier J, Atta M, Guerlesquin F, Lafond M*, Duarte V*. Proc. Natl. Acad. Sci., 2020, doi/10.1073/pnas.2004045117.

The Multifunctional Sactipeptide Ruminococcin C1 Displays Potent Antibacterial Activity In Vivo as Well as Other Beneficial Properties for Human Health. Roblin C, Chiumento S, Jacqueline C, Pinloche E, Nicoletti C, Olleik H, Courvoisier-Dezord E, Amouric A, Basset C, Dru L, Ollivier M, Bogey-Lambert A, Vidal N, Atta M, Maresca M, Devillard E, Duarte V, Perrier J, Lafond M*. International Journal of Molecular Sciences. 2021; 22(6):3253. https://doi.org/10.3390/ijms22063253