Applications are invited for **a PhD student position available 1.10.2022** in the Computational Pharmaceutical Chemistry & Molecular Bioinformatics group (Prof. Dr. Holger Gohlke; http://cpclab.uni-duesseldorf.de) at the Heinrich-Heine-University, Düsseldorf, Germany.

Topic: Integrative modeling using nisin as a model system to overcome lantibiotic resistance in bacterial pathogens

Nisin is a bactericidal peptide produced by certain Gram-positive bacteria, such as Lactococcus spp., the best-studied lantibiotic, and, as such, a model system to understand and overcome lantibiotic resistance in bacterial pathogens. Lantibiotic resistance often occurs in human pathogenic bacterial strains (including *Streptococcus agalactiae*) that do not produce nisin themselves. Resistance is mediated by the operon-encoded proteins NSR, a serine protease, NsrFP, an ABC transporter, and NsrRK, a two-component system. Furthermore, to gain immunity against nisin, the producing *Lactococcus* spp. expresses, among other proteins, the ABC transporter NisFEG.

In previous work and applying integrative modeling in tight collaboration with experimental groups of the GRK, we succeeded in generating a model of the SaNSR/nisin complex,(1, 2) identified the first small-molecule inhibitors of SaNSR by virtual screening (3) and performed initial lead optimization, as well as characterized the nucleotide-binding domain SaNsrF.(4) In so far unpublished work, we generated structural models of SaNsrP and NisEG, using ab initio modeling, coevolutionary information, and experimental data, as a basis to scrutinize their molecular functions.

The overarching goal of the upcoming PhD project is to overcome lantibiotic resistance, specifically nisin resistance, in bacterial pathogens by means of structural and mechanistic approaches. Here, *computer-assisted molecular modeling and simulation approaches* performed in our group will be closely interlinked with biochemical/structural biological (performed in the group of Prof. S. Smits) and medicinal chemistry (performed in the group of Prof. H. Stark) work, as has been successfully applied up to now. Specifically, we will optimize small-molecule inhibitors of SaNSR and elucidate the molecular mechanisms of NsrFP and NisFEG.

Requirements: Ideal candidates will have a record of excellence and a strong background in computational biochemistry/chemistry or structural bioinformatics, a high interest in working in an interdisciplinary collaboration, and profound knowledge in state-of-the-art molecular dynamics simulations (Amber) software, molecular modeling (including protein-ligand and protein-protein-complex structure predictions and evaluations), and medicinal chemistry.

How to apply: Applicants should submit application documents as listed here https://www.grk2158.hhu.de/positions-for-doctoral-students by email to gohlke@uni-duesseldorf.de AND grad2158@uni-duesseldorf.de.

Detailed **information about living and studying in Düsseldorf** is provided here: http://www.uni-duesseldorf.de/home/leben-in-duesseldorf.html

Recommended literature

1. Khosa S, Frieg B, Mulnaes D, Kleinschrodt D, Hoeppner A, Gohlke H, et al. Structural basis of lantibiotic recognition by the nisin resistance protein from Streptococcus agalactiae. Sci Rep. 2016;6:18679.
2. Mulnaes D, Porta N, Clemens R, Apanasenko I, Reiners J, Gremer L, et al. TopModel: Template-Based Protein Structure Prediction at Low Sequence Identity Using Top-Down Consensus and Deep Neural Networks. J Chem Theory Comput. 2020;16(3):1953-67.
3. Porta N, Zaschke-Kriesche J, Frieg B, Gopalswamy M, Zivkovic A, Etzkorn M, et al. Small-molecule inhibitors of nisin resistance protein NSR from the human pathogen Streptococcus agalactiae. Bioorg Med Chem. 2019;27:115079.
4. Furtmann F, Porta N, Hoang DT, Reiners J, Schumacher J, Gottstein J, et al. Characterization of the nucleotide-binding domain NsrF from the BceAB-type ABC-transporter NsrFP from the human pathogen Streptococcus agalactiae. Sci Rep. 2020;10(1):15208.