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

PhD student position 1 (available 1.10.2019): Overcoming lantibiotics resistance in bacterial pathogens: Nisin as a model system

Lantibiotics are antimicrobial peptides that are produced by Gram-positive bacteria and bactericidal against other bacteria in the low nanomolar range. Because of their high selectivity and stability, lantibiotics are considered valuable future anti-infective agents. The best-studied lantibiotic is Nisin. Various human pathogenic strains of bacteria have been found to have natural immunity to nisin, attributed to, e.g., the nisin resistance protein (NSR) or ABC transporter NsrFP. By structure-based design, hit molecules have been identified that inhibit NSR, and a structural model of NsrFP has been generated.
In this project within the DFG-funded GRK 2158 (http://www.grk2158.hhu.de/en.html), the inhibitory, physicochemical, and pharmacokinetic properties of the hits will be improved by structure-based and computer-aided drug design, analog searches, synthesis, and in vitro and in vivo testing. Furthermore, the mechanism of NsrFP will be scrutinized by molecular simulations with the aim to identify novel compounds that inhibit the transporter. Our group has a strong background in computational pharmaceutical chemistry and molecular informatics and will collaborate with the Smits, Pfeffer, Kalschauer, Stork, Pietruszka and Müller groups of the GRK 2158.

PhD student position 2 (available immediately): Functional analyses *in silico* and *in vitro* of consequences of cholestasis-associated mutations

Mutations in several genes (*ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, *MYO5B*) contribute to the development of severe forms of intrahepatic cholestasis. Since most mutations are only found in one or two families, their clinical consequences are often unknown. In particular, biological consequences of missense mutations (38-66% of mutations in ATP8B1, ABCB11, and ABCB4 in patients with severe cholestasis) are less clear.

In this project performed within the BMBF-funded Hereditary Intrahepatic Cholestasis Translational Network (HIChol), novel missense mutations will be structure-based analyzed for their potential impact on interactions with surrounding residues, substrate and cofactor binding, protein stability, structural dynamics. While molecular models have been established for *ABCB11* and *ABCB4*, and experimental structural information is (in part) available for *TJP2*, *FXR*, and *MYO5B*, a structural model of *FIC1* will be generated. In collaboration with the Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital, Heinrich Heine University Düsseldorf, results from molecular modelling and simulations will be tested for selected mutations by transfection of mutated cDNA into polarized hepatoma cell lines and HEK293 cells. Trafficking, subcellular localization, and function will then be studied. The cell culture approach will be used to optimize the predictions from molecular modelling and simulations. Results from this project will allow for classification of detected missense mutations into subgroups according to their cell biological consequences (e.g., maturation, trafficking, targeting, or function), and selected mutations will be further analyzed within HIChol.

Requirements: Ideal candidates will have a record of excellence and a strong background in computational biochemistry, molecular informatics, and computational structural biology as well as a high interest in working in an interdisciplinary research field, and profound knowledge in state-of-the-art molecular dynamics simulations (Amber) software and molecular modeling.

How to apply: Applicants should submit applications (a one-page letter of motivation *why* they are interested in the respective project and *how* they can contribute to the project's success, a current CV, and contact data of three references) by email to gohlke@uni-duesseldorf.de . **Please provide all documents as one PDF file and specify for which position you are applying.**

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