For our interdisciplinary research group Biostructural Interactions at the Friedrich Schiller University Jena, Germany we are looking for

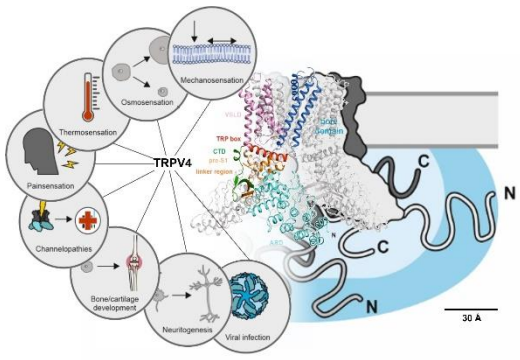
three PhD/PD candidates

All positions are fully funded. Successful applicants are invited to join the Jena School of Microbial Commuication (JSMC) graduate school or the International Research Training Groups of the respective DFG-funded Cluster of Excellence and Collaborative Research Centers (EXC2051 – Balance of the Microverse; CRC1507 - Membrane-associated Protein Assemblies, Machineries, and Supercomplexes; CRC1127 – Chemical Mediators in Complex Biosystems; CRC1278 - Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies) or the International Max Planck Research School of the MPI for Chemical Ecology.

For all projects, we seek team players that are enthusiastic about science and making new discoveries. We are particularly interested in getting to know people fascinated by protein structural dynamics and how it ties into (patho)physiology and cellular organization. Successful candidates will have an MSc (or PhD) in Biochemistry, Chemistry, Molecular Biology, Biophysics, Pharmacy or a related discipline. The laboratory language is English, German skills are not required, but we will support you in taking language classes if this is of interest. Successful applicants will join a vibrant scientific community at the Friedrich Schiller University Jena. We will actively support you in regularly visiting workshops and conferences and, if desired, will enable long-term stays with our national and international collaboration partners to extend your methodology portfolio.

For more information please visit our website: www.hellmich-group.de or contact Prof. Dr. U. Hellmich ute.hellmich@uni-jena.de. To apply, please send a motivation letter, CV, short summary of MSc thesis (PhD applicants) or PhD (PD applicants) and the names of two recommenders. Positions are available immediately and will be filled as soon as possible.

Project 1: Structural Dynamics and Functional Regulation of TRPV Ion Channels in health and disease (PhD or PD, up to 3.5 years)



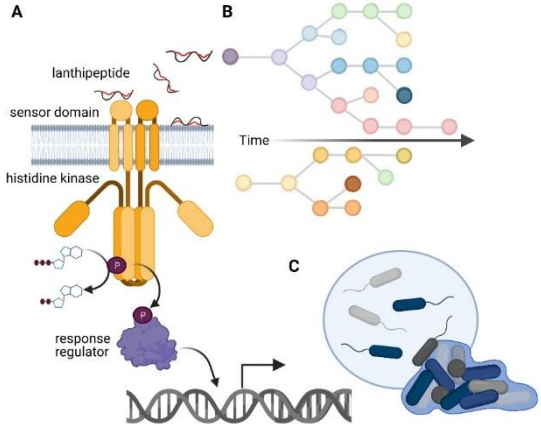
Transient receptor potential (TRP) channels have garnered significant attention as important pharmacological targets in recent years due to their role as cellular polymodal sensory hubs and their involvement in numerous diseases. Nonetheless, their integration into larger cellular signaling networks remains challenging. A detailed molecular description is particularly hampered by the absence of the large intrinsically disordered regions that act as interaction hubs for regulatory proteins and lipids from the currently available TRP channel structures. TRPV4 (vanilloid 4) is a ubiquitously expressed homotetrameric cation channel that plays important roles in temperature, osmo- and mechano-sensation. More than 60 described point mutants lead to severe skeletal and neuronal pathologies, so-called channelopathies. The disease mutations cluster mainly in the channel N-terminus comprised of an ankyrin repeat domain and a 150 amino acid intrinsically disordered region. In this project, we will investigate the conformational ensemble of the TRPV4 N-terminus and the central role of TRPV4 as a cellular signaling hub and coordinator of dynamic, multivalent protein interactions in the plasma membrane using an integrated structural biology and cell biological approach. The intrinsically disordered termini of other TRPV channels and their interaction with regulatory partners will

also be investigated.

Methodologies (also in collaboration with expert partners): Membrane protein biochemistry, intrinsically disordered proteins, NMR spectroscopy (solution/solid-state), cryoEM, X-ray crystallography, SAXS, HDX-MS, XL-MS, Fluorescence spectroscopy, super-resolution microscopy, CLEM, human cell culture, MD simulations

This project is a close collaboration with partners at the Max-Planck Institute for Biophysics, Frankfurt, the University of Frankfurt and the University of Mainz and the Johns Hopkins University Department of Neurology.

Project 2: Structural Dynamics of Membrane Proteins involved in Microbial Communication (PhD or PD, up to 3.5 years)

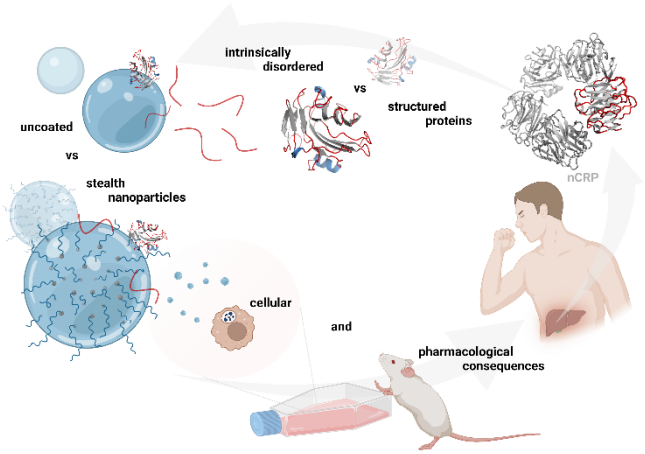


As bacteria explore new habitats, go to war with competitors, collaborate against common enemies or stably coexist within complex communities, they rely heavily on intra- and interspecies communication and precise molecular scouting of their environment. So-called two-component systems (TCS) as archetypical molecular communication modules play important roles in quorum sensing and enable bacteria to probe and react to environmental cues (e.g. redox state, nutrients, pH). Prototypical TCS consist of (i) a membrane bound histidine kinase (HK) with an extracellular sensor domain, a transmembrane region and an intracellular kinase domain as well as (ii) a soluble response regulator that acts as a dedicated transcription factor. When a ligand binds to the extracellular sensor domain of the HK, the signal is transmitted into the intracellular domain in an as of yet unspecified manner, resulting in the stimulus-dependent autophosphorylation of the intracellular kinase domain. The phosphate group is then transferred from the HK to the soluble response regulator, leading to DNA binding and induction of gene transcription. We can functionally purify the HK of interest into lipid nanodiscs. The next steps are the structural characterization, and the elucidation of allosteric pathways across the membrane between sensor and kinase domain and the elucidation of the structure and molecular mechanism of the bacterial proteins involved in modifictions of infochemicals involved in interspecies microbial crosstalk.

Methodologies (also in collaboration with expert partners): Biochemistry, Microbiology (BLS1/BSL2), functional assays (incl. ^{32}P labeling), cryoEM, SAXS, HDX-MS, MD simulations, organic synthesis/natural product isolation, co-evolution of receptor and substrate, bioinformatics

This project is a close collaboration with the Max-Planck Institute for Chemical Ecology and the Leibniz Institute for Natural Product Research and Infection Biology (Hans-Knöll-Institute) in Jena and partners at the Universities of Würzburg and Frankfurt.

Project 3: Intrinsically disordered proteins on complex surfaces – new therapeutics for sepsis and beyond (PhD or PD, up to 3.5 years)



Despite the successful use of nanoparticles in various medical applications, the molecular basis of nanoparticle/host interactions in inflammatory diseases needs to be established. Controlling and beneficially engineering the interactions that determine the cellular fate and the organismic (patho)physiological responses is of fundamental interest for the medical application of nanoparticles. Polymer-based nanoparticles with "stealth" properties were developed to avoid undesired interactions with immunocompetent cells. However, the behavior of these nanoparticles in the altered serum conditions found in patients fighting systemic infections such as sepsis remains poorly studied, in particular with regard to the molecular mechanisms of biomolecular interactions, cellular uptake, distribution and immunomodulatory effects of nanoparticles.

Sepsis is a severe medical condition threatening millions of lives every year. One of the most important clinical markers for inflammation and infection is C-reactive protein (CRP), whose serum levels can rise >100-fold during infection. High serum levels of CRP are correlated with a poor prognosis in sepsis. Based on our preliminary data that show that CRP readily interacts with nanoparticles leading to different immune-modulatory properties, CRP is a prime candidate to study the molecular details of protein-polymer-based nanoparticle interaction and their downstream consequences, *e.g.* targeting and cellular responses. Importantly, both full-length CRP and peptides corresponding to its intrinsically disordered regions (IDRs) can have either pro- or anti-inflammatory effects. IDRs are prone to conformational rearrangements upon surface interaction and could therefore be responsible for distinct inflammatory responses to nanoparticle-bound CRP. While structural disorder is prevalent in >40% of the human proteome and intrinsically disordered proteins (IDPs) are remarkably versatile biomolecular interaction partners, the effects of (dis)order on protein interactions with (stealth) nanoparticles in general is largely unknown.

Here, we will investigate the molecular interactions between nanoparticles and selected proteins including CRP to establish structure-property relationships. We aim to identify general as well as nanoparticle- and protein-specific structural and physicochemical features governing the interaction of proteins with nanoparticles for therapeutic purposes. The influence of the varying properties of these stealth nanoparticles on the molecular responses of immune cells during health and inflammation will be studied *in vitro* and *in vivo*.

Methodologies (also in collaboration with expert partners): Protein biochemistry, functional assays, NMR spectroscopy, cryoEM and TEM, bioinformatics, super-resolution microscopy, work with patient samples and mice (in collaboration).

This project is a close collaboration with partners at the University Hospital Jena, and experts in polymer chemistry, cell biology, pharmacy, and high-resolution microscopy from the faculties of chemistry, biology and physics at the University of Jena.