

SPOKESPERSONS

Coordinator / Spokesperson

Prof. Dr. Annette Beck-Sickinger
Leipzig University, Faculty of Life Sciences
Institute of Biochemistry
Email abeck-sickinger@uni-leipzig.de

Vice spokesperson

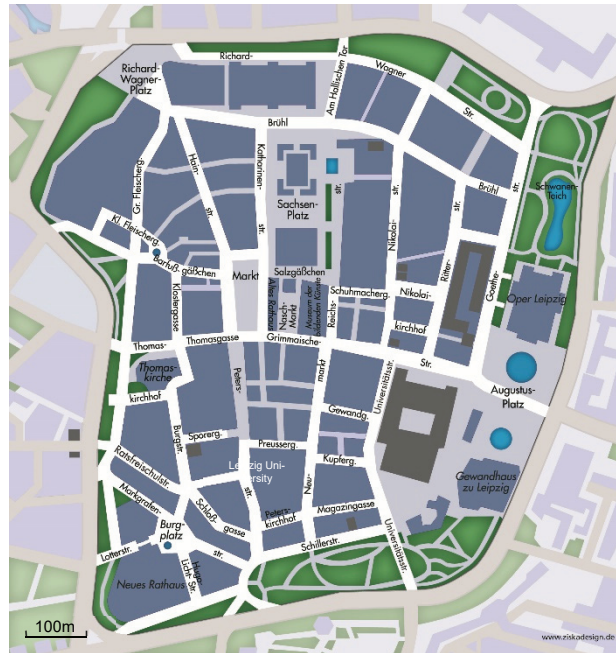
Prof. Dr. Torsten Schöneberg
Leipzig University, Faculty of Medicine
Rudolf Schönheimer Institute of Biochemistry
E-Mail schoberg@medizin.uni-leipzig.de

Head of IRTG

Daniel Huster
Leipzig University, Faculty of Medicine
Institute of Medical Physics and Biophysics
E-Mail daniel.huster@medizin.uni-leipzig.de

Office / Transfer

Anett Albrecht
Leipzig University, Faculty of Life Sciences
Institute of Biochemistry
Email albrecht@uni-leipzig.de



PARTICIPATING INSTITUTIONS



UNIVERSITÄT
LEIPZIG



MDC
MAX-DELBRÜCK-CENTRUM
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MARTIN-LUTHER-UNIVERSITÄT
HALLE-WITTENBERG

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Biochemistry, Structural Biology, Biophysics, Research areas Bioinformatics, Bioorganic Chemistry, Molecular Pharmacology

C Coordinating university
Leipzig University
Faculty of Life Sciences
Institute of Biochemistry
Brüderstrasse 34, 04103 Leipzig

Phone 0341 – 97 36902
E-Mail sfb1423@uni-leipzig.de
Web research.uni-leipzig.de/sfb1423

Collaborative Research Center 1423

Structural Dynamics of GPCR Activation and Signaling

Leipzig University

ABOUT US

The SFB1423 is a 4-year research institution funded by the German Research Foundation (DFG) and involving four funding institutions: Leipzig University, Martin Luther University Halle-Wittenberg, Charité – Universitätsmedizin Berlin and the Max Delbrück Center for Molecular Medicine.

Researchers from biochemical, biomedical and computational science contexts are working together across the boundaries of their respective institutions and disciplines to achieve a comprehensive understanding of the effects of structural dynamics on the function of the GPCR. Special research projects are carried out in 17 subprojects, which are evaluated every four years by the DFG in order to ensure the quality of the research in the long term.

RESEARCH FOCUS

Cells communicate with each other and with their environment via receptors. The G-protein coupled receptors (GPCRs) are the largest group of membrane receptors and occur in almost all living organisms. The aim of this CRC is to understand the structural dynamics of ligand binding, signal transduction, and downstream control of G protein- and arrestin-signaling pathways using native ligands as well as artificial probe molecules in conjunction with hybrid methods of structural biology including NMR, X-ray (conventional and serial protein X-ray crystallography at synchrotrons and free electron lasers), cryo-electron microscopy, mass spectrometry and computational methods (molecular modeling and dynamics). Phenomena such as biased signaling are tackled using assays that target specific signaling pathways. Results are tied in with a phylogenetic analysis of GPCRs, arrestins and G proteins. One goal of the CRC is to clarify the dynamic structural states of these GPCRs in order to understand their functions. This could lead to the development of novel therapeutics for this class of GPCRs.

GRADUATE SCHOOL OF THE SFB1423

The goal of the Integrated Research Training Group (IRTG) is a program that addresses all aspects of GPCR research. The profile will qualify graduates for an independent career in various academic and industrial areas. The doctoral researchers are expected to spend about 5-10% of their time on qualification, covered by this program. The main pillars of the program include scientific modules, annual summer schools, (international) laboratory rotations, and professional skills workshops. One lab rotation can be performed at VU for which a period of several months is suggested. We will work to establish formal rules for dual doctoral programs so that doctoral researchers will benefit from this approach and may earn a doctorate from both, VU and LU.

PROJECT GROUPS

Project group A

Subprojects that aim to determine GPCR structure and function the determination of GPCR structures are summarized in the Project Group A. This includes important targets and their structural elucidation via different methods such as protein X-ray crystallography, high-resolution solid-state and solution NMR spectroscopy, as well as cryo-EM. A01 to A04 focus on different peptide-binding class-A (rhodopsin-like) GPCRs, whereas A05 and A06 address aGPCRs to understand their structure and function. A07 develops new tools to enable and to improve molecular modeling of GPCRs in complex with extracellular ligands and intracellular signaling proteins. For an accurate and deep understanding of allostery in GPCRs such structural (atomic) knowledge of the interplaying partners in a GPCR/ligand/effecter system is obligatory. The number of crystallized – mostly aminergic GPCRs – has been increased dramatically over the last decade, but for peptide receptors structural information is still fragmentary available, yet.

Project group B

GPCR activity is modulated by distinct signals that lead to the stabilization of the active receptor conformation(s). This will be studied and analyzed by the projects grouped in group B. Projects B01 to B04 address the function of specific ligands in peptide GPCRs to elucidate the possibilities and mechanisms of receptor activation as well as its physiological consequences, whereas B05 and B06 address similar issues on aGPCRs. Selective and biased peptide and non-peptide ligands as well as allosteric modulators will be studied and mutagenesis and genetically encoded crosslinkers will be used at the receptor side. *Drosophila* (B06) and *C. elegans* (B03/C04) as “easy to manipulate” model organisms will be included for studying the relevance of receptor dynamics in *in vivo* settings.

Project group C

GPCR transmit signals to different transducers, e.g. they activate several classes of G proteins and recruit arrestins after phosphorylation. However, the N terminus of GPCR with large ectodomains may also function as signal itself (trans-signaling) suggesting a new concept in GPCR signal transduction (C04). Projects grouped in C will investigate how the modulation of signal selectivity is performed on a molecular level and which are the consequences. Most recent evidence indicates that biased ligands elicit divergent structural changes in the ligand binding pocket which are allosterically translated to the intracellular transducer binding site, thus leading to biased signaling. The structural dynamics of biased signaling will be studied at M2 receptor, as it is by far the best-studied receptor in terms of allosteric modulation (C05). The prototypical β -adrenergic receptors have been well-characterized in diverse signaling pathways being an ideal model for studying signaling selectively not only at the cell membrane but also in intracellular compartments (C03). C01 uses computational approaches to identify possible receptor G-protein/arrestin binding motifs conserved during evolution in sequence and space.

Projects

A01	Structural elucidation of neuropeptide GPCRs	Dr. Patrick Scheerer
A02	Investigation of the structure and dynamics of the ghrelin/GHS receptor complex	Prof. Dr. Daniel Huster Prof. Dr. Peter Hildebrand
A03	Characterizing the molecular interactions of Y1 and Y2 receptors with NPY	Dr. Peter Schmidt Prof. Dr. Andrea Sinz
A04	Characterizing the molecular interaction between the Y receptor and arrestin	Prof. Dr. Annette Beck-Sickinger Prof. Dr. Daniel Huster
A05	Structures of adhesion GPCR by cryo-electron microscopy	Dr. Patrick Scheerer Prof. Dr. Christian M.T. Spahn Prof. Dr. Torsten Schöneberg
A06	Enzymology of autoproteolysis and signaling function of the GAIN domain in adhesion GPCRs	Prof. Dr. Norbert Sträter Prof. Dr. Tobias Langenhan
A07	Innovative Rosetta algorithms for comparative modeling and docking of GPCRs	Prof. Dr. Jens Meiler
B01	Molecular mechanisms of allosteric modulators at Y-receptors	Prof. Dr. Annette Beck-Sickinger
B02	Melanocortin 4 receptor signaling revisited: from ligand/receptor interphase to signaling modulation	Prof. Dr. Heike Biebermann PD Dr. Patrick Kühnen
B03	Role of extracellular loop interactions in NPY receptor activation	Dr. Anette Kaiser
B04	Mapping binding sites of NPY peptides on the Y5 receptor using genetically encoded crosslinkers	Prof. Dr. Irene Coin
B05	Structural consequences of adhesion GPCR activation	Prof. Dr. Dr. Ines Liebscher
B06	Dynamic modulation of adhesion GPCR function through complex formation	Dr. Nicole Scholz
C01	Evolution of functional selectivity in GPCR signal transduction	Prof. Dr. Peter Stadler Prof. Dr. Peter Hildebrand
C03	Microscopic methods to study how GPCR dynamics and localization impact signaling specificity	Dr. Paolo Annibale Prof. Dr. Martin Lohse
C04	The neglected receptor N terminus – signal filter, signal integration, trans-signaling of adhesion GPCR	Dr. Simone Prömel Prof. Dr. Torsten Schöneberg
C05	Structural dynamics of allosteric coupling in GPCRs	Dr. Andreas Bock Prof. Dr. Irene Coin
Z03	Peptide synthesis and membrane protein (GPCR) expression	Dr. Patrick Scheerer Prof. Dr. Annette Beck-Sickinger
Z04	Computational models of structure, dynamics and evolution of GPCRs	Prof. Dr. Jens Meiler Prof. Dr. Peter Stadler Prof. Dr. Peter Hildebrand

