MAX KADE FOUNDATION SCHOLARSHIP APPLICATION

Through the generosity of the Max Kade Foundation, the Department of Life Sciences is able to provide three scholarships (incl. travel costs) to enable students from Leipzig University to participate in the 2019 Vanderbilt Program.

Recipients are selected on the basis of (1) academic merit, and (2) strength of application and motivation. German majors and minors will receive preference.

For your application to be accepted, please complete the program application or be accepted to the program by the application deadline, Monday, February 25, 2019.

Date: ______________
Name: _________________________________________________________________
Email address: ___________________________________________________________
Home address: ___________________________________________________________

3. Current Academic Status

Bachelor: ___________   Master: _______________  PhD-Student:_________________
Graduation Term/Year: _______

Research Project
I am interested in following research project:

☐ Arrestin interaction with SRC family kinases.
  Prof. Dr. Vsevolod Gurevich, Dr. Sandra Berndt (Department of Pharmacology)

☐ Investigating evolutionary and energetic constraints on membrane proteins through computational structural biology
  Prof. Dr. Jens Meiler, Hope Woods (Center for Structural Biology, Chemical Biology)

☐ Rosetta homology modeling and docking of allosteric modulators to the Y1 receptor.
  Prof. Dr. Jens Meiler, Oanh Vu (Center for Structural Biology, Chemical Biology)

Final Reflection Essay / Report
Awardee agrees to send a 1-2 page reflection essay in English on his/her experience and thank any donor who helped support studies.

Checklist of materials to be returned to Anett Albrecht (albrecht@uni-leipzig.de) by February 25th:
  ___ completed application form
  ___ CV
  ___ (unofficial) transcript
  ___ letter of motivation
ARRESTIN INTERACTION WITH SRC FAMILY KINASES.

Arrestins were shown to signal through the non-receptor tyrosine kinase Src, a member of Src family kinases (SFKs). SFKs are involved in the regulation of cell morphology, proliferation and survival, representing important pharmacological targets. SFK contain three homology domains (SH3, SH2, and kinase domain). The molecular mechanism of the interaction of arrestins with SFKs is unclear. Here we investigate the interaction of all SFKs with free arrestin-2 and -3. SH3 domain was shown to serve as the major binding element of SFKs. We performed pull down assays with SH3 domains of all SFKs and detected significant differences in arrestin interaction. To identify interaction sites, we used peptide array with immobilized arrestin-3 peptides and NMR spectroscopy. We used NMR titrations to measure the affinity of this interaction. The computational analysis and visualization by MD simulation of this protein-protein interaction is done in collaboration with the University of Leipzig, in the group of Dr. Peter Hildebrand. During the research stay, the student from the Hildebrand group will visualize the interaction of full length arrestin-2 and arrestin-3 with the different SH3 domains of all SFKs, based on the generated experimental data. These findings will be compared to the MD simulation with the isolated peptides of the different arrestins, which are already in preparation within the collaboration and will be done in the next month. The generated results will be used to propose a binding and activation mechanism of the SFKs by arrestins during the exchange. Within the last weeks the manuscript preparation can begin.

Laboratory Principal Investigator:    Graduate Student in host Laboratory:
Prof. Vsevolod Gurevich / Tina Iverson     Dr. Sandra Berndt

Collaborating Principal Investigator at Partner Institution:
Prof. Dr. Hildebrand / Prof. Dr. Beck-Sickinger

INVESTIGATING EVOLUTIONARY AND ENERGETIC CONSTRAINTS ON MEMBRANE PROTEINS THROUGH COMPUTATIONAL STRUCTURAL BIOLOGY

Membrane proteins (MP) are responsible for many essential cellular processes like signal transduction and ion-transport. Despite this, experimental challenges limit our ability to fully understand the membrane environment and have greatly hindered our ability to accurately characterize MP energetics. One facet of MPs is the process of folding within the membrane environment and membrane insertion may be energetically costly. Specifically, alpha-helical membrane insertion is typically facilitated by dedicated transporters called translocons. These transporters are aided by electrostatic interactions between the transmembrane side chains of the MPs and hydrophobic lipids of the membrane. The transmembrane region of a single membrane-spanning helix largely consists of hydrophobic residues that favorably interact with the lipid environment. Despite this hydrophobic preference, many polar residues are often also embedded within the membrane. These residues are often linked to function; however, some evidence suggest there is evolutionary pressure on maintaining the marginal stability of certain transmembrane helices. To gain a better understanding of the balance between function, stability, and regulation of membrane proteins we are investigating rhodopsin, one of the most well characterized G-protein coupled receptors. This project will consist of building a model of an alternative topological state of rhodopsin using the Rosetta software suite. The stability and dynamics of this model will be analyzed using various Rosetta and molecular dynamics tools.

Laboratory Principal Investigator:    Graduate Student in host Laboratory:
Prof. Dr. Jens Meiler     Hope Woods

Collaborating Principal Investigator at Partner Institution:
Prof. Dr. Hildebrand / Prof. Dr. Beck-Sickinger
The human neuropeptide Y (NPY) receptor family (Y1R, Y2R, Y4R, and Y5R) are comprised of G-protein coupled receptors (GPCR) that can be potential targets for obesity treatments. Their ligand neuropeptides—ligand neuropeptide Y (NPY), polypeptide YY (PYY), and pancreatic polypeptide (PP)—have been shown to play critical roles in regulating satisfaction after food intake and energy homeostasis [1]. As non-specific targeting this protein family could disrupt the metabolism of bone tissues, selective modulation of only peripheral NPY receptors would promote obesity therapeutic effects without deteriorating bone health [3]. Furthermore, efforts in developing mimetics of NPY might face challenges of peptide drugs such as bioavailability and stability. For those two reasons, we are especially interested in designing drug candidate as small molecules that exhibit high selectivity toward Y4R. Previous high-throughput screening (HTS) study has isolated a set of positive allosteric modulators for Y4R [2]. In this internship, the interaction of those lead compounds and Y4R will be investigated further computationally using Rosetta and BCL. Various small molecule modulators will be docked to homology models of Y4R, and mutagenesis data (provided by the Beck-Sickinger) lab will be used as the filter to select the most plausible binding poses of the ligands.

Methods: Comparative modeling and ligand docking using Rosetta and BCL, using text editing tools and BASH commands/scripts in Linux/Unix working environment, performing data analysis and visualization using Python, and running computational jobs on High Performance Computing cluster ACCRE.

References