University of Münster, Germany

Graduate School of Natural Products (GS-NP)

Graduate School Scholarship Program 2024

of the German Academic Exchange Service DAAD

Advertisement of two positions for PhD thesis

The University of Münster, Germany, offers excellent research opportunities within a strong interdisciplinary environment. The *Graduate School of Natural Products GS-NP* (https://www.uni-muenster.de/GSNP/) represents a highly interdisciplinary program among the faculties of Chemistry and Pharmacy, Biology and Medicine to strengthen cutting-edge research on Natural Products (NP) and combines more than 20 individual research groups. This structured doctoral program offers interested PhD students a variety of opportunities for scientific research and exchange, extended training and discussions in the field of NP. The program simultaneously pools the expertise of the different research groups and offers diverse interdisciplinary and strongly international opportunities within the different, well-equipped laboratories, each with different scientific expertise.

GS-NP together with German Academic Exchange Service (DAAD) provides two additional scholarships starting in 2024 for a maximum of 4 years. The attractive scholarships include monthly payments of approximately € 1,300, travel allowance, payments towards health insurance, a special research allowance, and a preparatory German language course (if needed).

Successful candidates should have an excellent academic profile and must have completed their studies with a master's (M.Sc.) degree or equivalent.

Applicants should perform research on one of the four research topics indicated below, which give the framework for the work. Own ideas and modifications of the respective framework subjects by the applicants are strongly encouraged and should be displayed within a two-page research proposal together with the formal application.

Please note: Four framework topics are suggested by GS-NP but only two projects will be granted, depending on the quality of the submitted applications and background of the applicants in regard to the respective projects. Every applicant can only apply for one project.

For more information on the scientific background of the projects and the respective principal investigators please check the information given on the GS-NP homepage (https://www.uni-muenster.de/GSNP/).

Framework topic #1: Discovery of novel anti-trypanosomatid drug candidates

Framework topic #2: Characterization of herbal urologicals with a focus on potential immunomodulatory properties and host cell-based defense mechanisms

Framework topic #3: Pattern Recognition Receptors as Targets for Natural Products

Framework topic #4: Role of lipid droplets in synthesis and/or storage of natural products

For formal application, a letter of motivation is required. Additionally, please provide detailed research ideas and how to plan and to develop the favoured project within the given framework (two pages maximum). Please also provide a one-page timeline for your planned research, including information about possible field studies or studies outside Germany. Your project proposal, your individual ideas and scientific visions will be evaluated by GS-NP reviewers.

Additionally, the Bachelor and Master degree certificates, and documents certifying knowledge of English language (level B2) should be provided with the application.

Furthermore, one letter of recommendation by a professor of applicant's home university is required. Only the DAAD form should be used - download here:
http:///www.daad.de/imperia/md/content/de/foerderung/recommendation.pdf or:
https://www.daad.de/medien/deutschland/stipendien/formulare/recommendation.doc

Applicants should ask a professor of their home university to fill in and send the letter of recommendation directly to GS-NP (E-mail: gsnp@uni-muenster.de).

Applications should be sent no later than November 30th 2023, electronically by E-mail to the University of Münster, Graduate School of Natural Products, gsnp@uni-muenster.de (please combine in your application all individual attachments to one pdf file).

Framework Topic #1

Discovery of novel anti-trypanosomatid drug candidates

Trypanosomiasis and *Leishmaniasis* are among the 20 *Neglected Tropical Diseases* recognized by the World Health Organization, rendering a strong medical need for the development of anti-trypanosomatid drugs. The major aim of the proposed project is the discovery of highly active *dual inhibitor*s of the parasites' dihydrofolate reductase (DHFR) and pteridine reductase 1 (PTR1) as potential drug candidates against trypanosomatid infections.

We will apply a sophisticated virtual screening approach, which represents a step forward with regard to the prediction of activity and specificity within a broad chemical space. Since proteins are flexible and show a dynamic behavior, they have to be regarded as dynamic entities in order to address their specific function. To tackle this challenge, we will apply a fully automated combination of three-dimensional pharmacophore models and molecular dynamics simulations to build more realistic models and enhance virtual screening performance. The most promising hits will be retrieved from commercial sources and tested experimentally in biochemical assays with the option for subsequent in-vivo testing.

Principal Investigators: Prof. Dr. Marcel Bermúdez (m.bermudez@uni-muenster.de), Prof. Dr. Thomas Schmidt (thomschm@uni-muenster.de)

Framework Topic #2

Characterization of herbal urologicals with a focus on potential immunomodulatory properties and host cell-based defense mechanisms

Uncomplicated urinary tract infections (UTIs) are one of the most common bacterial infections and are a serious global health problem affecting millions of people each year. Statistically, more than 50% of all women experience a symptomatic UTI at least once in their lifetime, requiring antibiotic treatment. More than 25 % of all women suffer from recurrent symptomatic episodes despite antibiotic treatment. Antibiotic treatment of uncomplicated UTIs is often still effective, but recurrent symptomatic episodes combined with prolonged low-dose antibiosis often result in problematic side effects, such as selection of antibiotic-resistant pathogens, destruction of the patient's normal microbiota, gastrointestinal side effects, and allergic reactions (Foxman, 2014; Flores-Mireles et al., 2015; Klein & Hultgren, 2020). Against this background and due to the increasing frequency of (multi-)resistance development in uropathogenic *E. coli* (UPEC), there is a great demand for the establishment of alternative treatment strategies.

Many medicinal plants used in UTI treatment have not yet been comprehensively tested for their mode of action. Although various herbal extracts used in traditional medicine seem to alleviate the symptoms of UTIs and have a positive effect on eliminating the infection, the exact mechanisms underlying these observations are still unclear. Whereas antibacterial and antiadhesive effects have been described for some herbal compounds, other herbal urologicals seem not to act on the uropathogens, but reduce the susceptibility of the host cells to UPEC infection. We currently lack systematic analyses of their effect on host cell functions that counteract bacterial infection in the context of innate immune defense or other mechanisms of infection resistance. This might involve, for example, the expression of host defense proteins, the regulation of other components of the innate immune response, and cellular mechanisms involved in intracellular transport and membrane function.

Principal Investigators: *Prof. Dr. Ulrich Dobrindt (dobrindt@uni-muenster.de), Prof. Dr. Ursula Rescher (rescher@uni-muenster.de), Prof. Dr. Andreas Hensel (ahensel@uni-muenster.de)*

Framework Topic #3

Pattern Recognition Receptors as Targets for Natural Products

Microorganisms or damaged cells release molecules (Pathogen-Associated Molecular Patterns/PAMPs and Damage-Associated Molecular Patterns/DAMPs) that often bind to the same Pattern recognition receptors (PRRs), initiating and regulating immune responses. *Formyl peptide receptors* (FPR) and *Toll-like receptors* (TLR) are among the most important PRRs and represent the first barrier in immune response. Both protein families bind and can be modulated by a broad spectrum of ligands from natural origin including small peptides, lignans, terpenes, and sesquiterpene lactones among others. Interestingly, the signaling via FPRs and TLRs can be very diverse, with divergent signaling behavior depending on the type of the recognized ligand. This so-called *biased signaling* is an emerging field of research, which focuses mostly, but not exclusively on G protein-coupled receptors (e.g. FPRs).

The major aim of the proposed project is to decipher biased signaling mechanisms at PPRs, namely FPRs and TLRs. We will study by which mechanisms natural products deliver their highly specific functionality. Therefore, we will analyze the chemical space of natural products binding to those receptors and link chemical structures to their pharmacological profile. We will further identify natural products as biased ligands and use them as pharmacological tools to dissect physiological roles of distinct signaling pathways in inflammation.

Principal Investigators: Prof. Dr. Marcel Bermúdez (m.bermudez@uni-muenster.de), Prof. Dr. Ursula Rescher (rescher@uni-muenster.de)

Framework Topic #4

Role of lipid droplets in synthesis and/or storage of natural products

Lipid droplets, also referred to as oleosomes or oil bodies, are ubiquitous subcellular structures found primarily in the seeds of many plants as storage sites for triacylglycerol (plant oil) and are also known as the main constituent of vegan milk products. However, recent results indicate that LDs are also hot spots for the synthesis of hydrophobic secondary metabolites and their storage. This could be especially true in species that produce high amounts of such metabolites such as ginger (α-zingiberene), curcuma (curcumin), and rosemary (ursolic acid).
The goal of this project is to answer the question what type of secondary metabolites are stored in lipid droplets, which enzymes are involved in their synthesis, and if these are localized on the lipid droplet surface. Furthermore, the project aims to resolve if these secondary metabolites are stored in distinct lipid droplets separate from triacylglycerol, and whether they require a specific set of proteins for packaging and shielding. Subsequent biotechnological approaches could lead to the production of these compounds in yeast or suitable plant species to increase their production, and to study their bioactivity in plants, mammals and microorganisms.

Principal Investigators: Prof. Dr. Till Ischebeck (till.ischebeck@uni-muenster.de), Prof. Dr. Bodo Philipp (bodo.philipp@uni-muenster.de), Prof. Dr. Dirk Prüfer (dpruefer@uni-muenster.de)