Accessing Novel Bacterial Producers from Biodiversity-rich Habitats in Indonesia

Project Acronym: ANoBIn

Although bacteria represent an important source of antiinfectives and other pharmaceutical compounds, natural product research has so far been limited to few phylogenetic groups but has largely neglected the major part of bacterial diversity. The current project aims to assemble and operate a novel biodiscovery pipeline for the detection, isolation, screening and biobanking of previously unknown types of bacterial producers as well as yeasts from high biodiversity Indonesian ecosystems. In order to effectively target such novel producers, unique ecosystems that are characterized by tight biotic interactions have been selected for sampling. Intimate associations involve bacteria that synthesize specific compounds to either communicate with, modulate or inhibit neighboring organisms, and therefore offer a higher probability to discover novel types of bacterial producers. The project will thus focus on microbial communities associated with or colonizing endemic plants or animals, biofilms, unusual soils and springs, or aposematic higher organisms. A combination of second and third generation sequencing technology, innovative cultivation approaches, and quality controlled biobanking in the Indonesian and German culture collections including appropriate data management will be employed to recover, safeguard, and document bacterial producer strains from these sources. An important part of the program is the bioactivity guided isolation and characterization of the metabolites produced by these microorganisms. The project will integrate the complementary expertise of German and Indonesian microbiologists and organic chemists. A legal and contractual framework for the rights and obligations of all partners will be established that includes a mutually beneficial plan for intellectual property rights.

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Insect-derived anti-Infectives from Indonesia

Project Acronym: Triple-In

Insects are the most successful group of organisms on earth in terms of biodiversity. Their tremendous taxonomic and molecular diversity makes the indispensable as biological resources for natural product research. This project aims to identify natural products by targeting insects from Indonesia that exhibit antimicrobial activity, particularly against the infective agents responsible for tuberculosis and malaria. Two approaches will be combined to perform targeted screening for novel antimicrobial peptides and small organic molecules. The analysis of hemolymph samples and defensive secretions from insects will include the use of a newly-developed portable GC-MS device that allows initial screening in the field, e.g. in the rainforest. Screens for novel antimicrobial peptides will be based on the suppression subtractive hybridization approach, a PCR-based technique which is the method of choice for the targeted identification of new effector genes. Novel antimicrobial small molecules will be synthesized de novo, and novel antimicrobial peptides will be produced as recombinant proteins. Both will be tested for their activity against human pathogenic bacteria and Plasmodium falciparum. The expertise and technologies established within the LOEWE Center for Insect Biotechnology and Bioresources in Giessen provides an ideal platform for the further development of insect-derived anti-infectives as new therapeutic entities. Our combined approaches in targeted identification of novel compounds with anti-infective activity in insects will be for the first time applied in a country that belongs to hot spots of biodiversity.

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Indonesian biodiversity discovery and information system

Project Acronym: INDOBIOSYS

INDOBIOSYS will develop and provide core components for a knowledge-based functional screening approach employed to the discovery of new anti-infective compounds from Indonesian organisms. In INDOBIOSYS, this comprises 1) a novel integrated high-throughput biodiversity discovery pipeline for the sampling, identification and provision of promising target groups from areas with a high level of biodiversity and 2) setting up a digital Indonesian Biodiversity Information System (IBIS). IBIS will combine new data and results from the project with existing information in real time and make this knowledge available for both research and the wider public via an online portal. The unprecedented combination of primary biodiversity data and relevant metadata supporting an innovative approach towards the discovery of active compounds will create a novel platform that will allow a targeted, efficient, and sustainable exploitation of biological resources in Indonesia.

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Indonesian Plant Biodiversity and Human Health

Project Acronym: BIOHEALTH

The project is part of a research cluster involving several German working groups and their Indonesian partners studying the systematics, evolution and bioactive compounds of Indonesian plants (and fungi). The research cluster is designed to jointly contribute to the identification of naturally occurring substances in Indonesian plants and fungi with anti-infective effects, potentially suitable for the development of new active pharmaceutical compounds. The aim is to identify and describe so far unknown or already known, but not yet sufficiently investigated Indonesian plant (and fungal) species with their specific properties, and to document them scientifically by applying international standards. By combining the predictive power of molecular phylogenetics with metabolomics in an innovative-integrative approach, the project cluster will target specifically taxonomic groups for which existing knowledge (literature, databases, ethnobotanical information) has already proven, or strongly suggests, the occurrence of substances with anti-infective effects, but which have not been used so far as active ingredients for pharmaceuticals.

We seek highly motivated candidates holding degrees in a relevant subject (e.g. Botany, Plant Evolution, Plant Biochemistry) with a sound background in molecular systematics techniques (incl. DNA lab work) and plant morphology, or plant biochemistry. Good communication skills, the ability to work independently and the willingness to conduct fieldwork are essential. A good working knowledge of English or the motivation to follow extracurricular English lessons is required. Prior knowledge on plant taxonomy will be of advantage.

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Bio-Inspired Anti-Infective Leads from Indonesian Plants and Endophytes

Project Acronym: BALIPEND

This joint German-Indonesian project aims at the development of new lead structures for anti-infective drugs from Indonesian plants and associated endophytes. The project will focus on endemic plants and their endophytes from the Mount Halimun Salak National Park. On a yearly basis, a total of 50 extracts from plants and 50 extracts from endophytes will be prepared that will be tested in comprehensive antimicrobial screenings for their anti-infective properties. The antimicrobial screens include cellular assays against HIV, the Malaria parasite Plasmodium falciparum, Mycobacterium tuberculosis as the causative microbe for tuberculosis, and against multi-resistant nosocomial pathogens. Further screens will address molecular targets such as HIV-1 reverse transcriptase, HIV-1 protease and HIV-1 integrase, which are essential for the life-cycle of HIV, as well as the enoyl-ACP reductase, which is involved in fatty acid biosynthesis of Plasmodium falciparum. Extracts that show bioactivity in one or several of these screens will be subjected to bioactivity guided fractionation that will ultimately yield pure active substances showing antibacterial, antiviral or antiparasitic activity. These active compounds will be structurally characterized and evaluated for possible cytotoxicity towards humane cell lines as well as for their pharmacological properties (ADME). It is estimated that these endeavours will ultimately yield 5 – 10 promising compounds with favourable ADME profiles for each indication investigated in this project. These compounds will be subjected to structural optimization through medicinal chemistry methods. It is expected that at the end of the first funding period our consortium will have identified at least one novel lead structure for each of the investigated indications. These compounds can then be further evaluated in preclinical studies during subsequent funding periods.

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German-Indonesian antiinfective cooperation

Project Acronym: GINAICO

The Search for novel anti-infectives is one of the most important challenges in natural product research of this century, as diseases caused by bacteria, viruses and fungi are influencing the human society all over the world. The old resources are exploited and only the combination of the usage of novel ones like the biological resources in Indonesia , together with high sophisticated biological assays and screening technologies can be successful in the future. To the organisms which will be used belong marine and terrestrial microorganisms from the groups of the myxobacteria as well as actinobacteria, plants and marine organisms like sponges and cucumbers. The extracts of these organisms will be analyzed by different biological assays as well as chemical dereplication with different techniques which are established by the partner groups. The active microorganisms will be cultivated in a larger scale fermentation for the isolation of the compounds. These compounds as well as the ones that are extracted from plant and marine organisms will then be structure elucidated.

Therefore, it is the aim of this coordinated, interdisciplinary project to exploit the vast diversity of natural compounds with diverse biological provides by natural sources. Within this project, this unique resource will be systematically made accessible to screening campaigns involving human pathogenic viruses, bacteria and fungi. Ultimately, this project will identify novel anti-infective molecules and will establish a coordinated operation structure to access natural resources for development of anti-infectives for treatment of human diseases.

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Isolation of new unique natural compounds from unknown actinomycetes

Project Acronym: NAbaUnAkt

Streptomycetes, which belong to the heterogenic group of actinomycetes, are the most successful antibiotic producers. They synthesize two-thirds of all known natural antibiotics, which also serve as basis for the development of semi-synthetic antimicrobials. Especially these days antibiotic research has become a general significance since in the industrial nations of Europe bacterial infectious diseases are increasing.

As Indonesia is one of the most species-rich countries in the world, this biodiversity should also be reflected by the microbial species diversity. Therefore, especially Indonesian soils are a source for unknown actinobacterial strains, which may produce novel antimicrobial compounds.

The aim of this study is to isolate new antimicrobial active substances from unknown actinomycetes and to investigate them regarding to their medical potential. The isolation and identification of unknown actinomycetes as well as the primary screening for antimicrobial substances will be performed by two Indonesian partners, Dr. Wien Kusharyoto and Dr. Puspita Lisdyanti from the Research Center for Biotechnology, Indonesian Institute of Sciences (LIPI), Bogor, Indonesia. Dr. Puspita Lisdyanti is specialized in the identification and isolation of unknown actinomycetes. Dr. Wien Kusharyoto currently develops a new screening system for the identification of anti-infective substances, especially for anti-mycobacterial and anti-viral agents. Bioinformatical screenings for antibiotic biosynthesis gene cluster and their heterologous expression in appropriate host strains as well as a subsequent production optimization of lead substances will be done by Prof. Dr. Wolfgang Wohlleben / Dr. Yvonne Mast at the IMIT of the University Tübingen. A detailed antimicrobial screening as well as structure elucidations of interesting compounds chemical will be realized by Prof. Dr. Harald Groß, University Tübingen.

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 Indonesian Opisthobranchs and associated microorganisms - From biodiversity to drug lead discovery

Project Acronym: INDOBIO

The Indonesian coastline is characterized by an extremely high biodiversity. This project focusses on a specific bio-system, *i.e.* Opisthobranchia, their prey organisms, and the associated microorganisms. Based on our knowledge on systematics and ecology of these organisms, the goal is to identify new drug leads for antibiotics development.

The species in this under-investigated biological system have to interact in a complex and competitive environment. Sea slugs, forced by the absence of a protective shell, developed highly specialized defense strategies to protect their sensitive epidermis against micro and small organisms, as well as larger predators like fish and crabs. Beside the sequestration of *e.g.* cnidocysts, especially chemical substances fulfill this protective role. These biologically active metabolites, which can be synthesized by the sea slugs themselves, their food source, or by the associated bacterial or fungal community, will be isolated and identified within this project. Thereby, the compounds become readily available for antibacterial testing.

The focus will be on the slug-associated microorganisms. Using classical microbiological methods, axenic cultures are generated, from which by subsequent fermentation the biological active compounds can be isolated. By genome sequencing the biosynthetic potential of these microorganisms will be determined and harnessed. The biosynthetic gene clusters identified in this project will be used to produce natural products efficiently and sustainably.

In addition, metagenomic approaches will be used to make also the genetic potential of the so far uncultured bacteria accessible by heterologous expression.

Collected data on slugs and associated food organisms will document state of the art biodiversity in this hot spot region and can be used as base information for future monitoring of healthiness of marine habitats in North Sulawesi.

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