



2023 HGF – OCPC – Programme

for the involvement of postdocs in bilateral collaboration projects

Part A

Title of the project:

Genome Mining of Myxobacteria with Systematic Heterologous Expression of Biosynthetic Gene Clusters

Helmholtz Centre and institute:

Helmholtz Centre for Infection Research

Project leader:

Rolf Müller

Contact Information of Project Supervisor:

Rolf.Mueller@helmholtz-hips.de, +49 68198806-3001

Web-address:

<https://www.helmholtz-hips.de/en/research/people/person/prof-dr-rolf-mueller/>

Institute:

Helmholtz Institute for Pharmaceutical Research Saarland, Department Microbial Natural Products

Programme Coordinator (Email, telephone)

Helmholtz Centre for Infection Research (HZI)

Scientific Strategy

Birgit Grün

Phone: +49 531 6181-5006

Email: birgit.gruen@helmholtz-hzi.de



Description of the project (max. 1 page):

The demand for novel small-molecule drugs is on a continuous regarding a number of different pathologies, especially infections diseases. Myxobacteria are a prolific source for secondary metabolites with diverse structures and intriguing biological activities. However, compared to the numbers of biosynthetic gene clusters (BGCs) predicted in the genomes of myxobacteria, the number of discovered myxobacterial compounds is still limited. To explore the underexploited biosynthetic potential of myxobacteria, promising myxobacterial strains have been whole-genome sequenced with PacBio sequencing technology and cosmid genomic DNA libraries have been constructed. Each cosmid library has been end-sequenced to facilitate the positioning of individual cosmid clones based on the high-quality genome data obtained from PacBio sequencing. The genome data will be analyzed according to our genome analyzing pipeline, allowing us to predict the biosynthetic potential for secondary metabolites. All BGCs will be categorized into different groups based on criteria such as potential compound class, novelty, key biosynthetic genes, and BGC size, which will help us to prioritize the BGCs for heterologous expression in well-studied host strains. The BGCs which are covered by more than one cosmid will first be assembled by gene recombineering technologies such as Red/ET. Different gene engineering strategies will be employed to improve the success rate for BGC heterologous expression (e.g. promoter exchange or transcription regulator engineering). State-of-the-art analytic methods and instruments at HIPS will facilitate the discovery, isolation and structure elucidation of novel compounds from heterologous host strains. If interesting moieties with unknown biosynthesis origin are found, the biosynthetic pathways of isolated compounds will be elucidated by comprehensive *in vivo* and *in vitro* studies. Finally, the bioactivity of compounds against various pathogens and cancer cell lines will be tested and their mode-of-action will be analyzed. This project includes the following topics:

1. Heterologous expression of BGCs from myxobacteria.
 2. Isolation, purification, and structure elucidation of compounds produced by heterologous expression.
 3. Characterization of the biosynthetic pathways of compounds discovered in this study.
 4. Bioactivity testing and mode-of-action analysis of compounds discovered in this study.
- In summary, our final goal is to learn about new chemistry from nature and to produce novel compounds with improved activities based on the acquired knowledge.

Description of existing or sought Chinese collaboration partner institute (max. half page, not mandatory):

Helmholtz International Labs. In cooperation with the Chinese Shandong University, an interdisciplinary research team at the Helmholtz International Lab will work on the development of antibacterial and antiviral strategies that should ultimately lead to innovative drug candidates.



Required qualification of the post-doc:

- A PhD in natural product research or a related field
- Extensive hands-on experience in genetics and biochemistry
- Experience in writing publications, conference papers and research proposals
- Fluency in spoken and written English and excellent oral and written communication skills
- Planning and organisational skills, prioritisation of multiple tasks, meeting strict deadlines
- Demonstrated project and laboratory management skills in multiple tasks
- Capability of creative and critical thinking, independent thought and experimentation, decision making, problem solving with discretion, self-motivation and curiosity.