



2025 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

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Description of the project:

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 genomic DNA libraries that were constructed to achieve high quality sequences. 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 will first be assembled by various technologies including recombineering and gene synthesis. Different gene engineering and BGC transfer 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. Promising compounds with unknown biosynthesis origin are constantly 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:

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. Additional collaboration partners are welcome, e.g. CAS microbiology, Chinese Pharmaceutical University.

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



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- Capability of creative and critical thinking, independent thought and experimentation, decision making, problem solving with discretion, self-motivation and curiosity.