

2017 Helmholtz – OCPC – Programme for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project: Deciphering and remoulding the biosynthesis of active and promising compounds from actinomycetes

Helmholtz Centre and institute: Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), a joint institute of Helmholtz Centre for Infection Research and Saarland University, Department Microbial Natural Products

Project leader: Prof. Dr. Rolf Müller

Web-address: https://www.helmholtz-hzi.de/en/research/research_topics/anti_infectives/microbial_natural_products/our_research/

Description of the project:

Natural products contribute greatly to human health via providing useful compounds as drugs/leads combating various diseases. We have isolated several active compounds from actinomycetes, such as polypeptides containing novel amino acids from a marine actinomycete, which displayed potent anti-tumor and anti-BCG activities. We are intending to spend efforts on their biosynthesis and structure modification due to the potential novelty in chemistry, biosynthesis and activities. This project includes several topics as follows:

1. Confirmation of the corresponding biosynthetic gene cluster. According to retro-biosynthetic analysis, all candidate clusters will be predicted from the genome of the producer strain and then gene deletion experiments will be employed to confirm the corresponding gene cluster. The boundaries of the cluster will be determined by further gene knockouts.
2. Characterization of the biosynthesis. After the confirmation of the gene cluster, a hypothetic biosynthetic pathway will be proposed via bioinformatic analysis. Next, genetic manipulations on these genes will be performed to revise and verify the pathway. The elucidation of the biosynthesis pathway of the novel building block is one of the top aims in this project requiring gene knockout/complementation as well as *in vitro* enzymatic assays of key enzymes in its pathway.
3. Heterologous expression. Based on the characterized cluster, we aim to express the compounds in heterologous hosts, which might facilitate the engineering of the pathway as well as compound isolation.
4. Structure diversification. Three distinct ways might be employed to diversify compound structures: (1) To improve the production of small portion of analogs (detected level) in

the producer via heterologous expression and synthetic biology; (2) To obtain the intermediates in tailoring gene deleted mutants; (3) To produce new analogues via alteration of the substrate specificity of enzymes responsible for building block incorporation; (4) To introduce various modified unusual units via engineering its sub-pathway or via feeding chemically synthesized substrates into the sub-pathway broken mutant.

In summary, our goal is to elucidate new chemistry from nature and to produce novel compounds with better activities based on the acquired knowledge.

Description of existing or sought Chinese collaboration partner institute:

We have built a long-term partnership with Prof. Lixin Zhang from Institute of Microbiology, Chinese Academy of Sciences and achieved milestones in terms of co-published papers.

Now we are collaborating on heterologous expression of griselimycin and the biosynthesis of proximicin. Griselimycin is a naturally occurring antibiotic with anti-TB activity produced by *Streptomyces* and proximicins are novel aminofuran containing compounds with potent anti-cancer cell and anti-TB activities produced by *Verrucosisspora*. In this cooperative project, we will exploit creativity on both sides to improve the production and modification of griselimycin via heterologous expression, and to fully understand novel chemistries concealed in biosynthesis pathway of proximicins.

Required qualification of the post-doc:

- A PhD on natural products 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

PART B

Documents to be provided by the post-doc:

- Detailed description of the interest in joining the project (motivation letter)
- Curriculum vitae, copies of degrees
- List of publications
- 2 letters of recommendation

PART C

Additional requirements to be fulfilled by the post-doc:

- Max. age of 35 years
- PhD degree not older than 5 years
- Very good command of the English language
- Strong ability to work independently and in a team