



2023 Helmholtz – OCPC – Programme for the involvement of postdocs in bilateral collaboration projects

PART A

Evaluation of cytochalasans as anti-infective lead structures

<insert the title of the project here>

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Description of the project (max. 1 page):

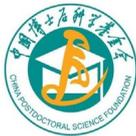
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1. General

The proposed project is associated with the DFG-funded Researchers Group “**CytoLabs**” <https://www.cytolabs-dfg.info/>. This multidisciplinary project deals with the evaluation of cytochalasans.

These are fungal metabolites that exhibit profound biological effects on cells. They are known to bind to actin, the key protein component of the eukaryotic cytoskeleton, and by inhibiting actin assembly they can change the structure and mobility of cells. Since cytochalasans are also involved in bacterial biofilm inhibition, and some are known to possess antiviral activities, the project also investigates new molecular targets for cytochalasans and the ecological role these compounds have in inter-species interactions.

The CytoLabs project aims to understand these effects in vivo and in vitro, and to produce new and known cytochalasans by chemical synthesis, biosynthetic engineering, and fermentation. Our own contributions to this project are a) the provision of new and known cytochalasans from rare and new



fungal species, **b)** the design of biotechnological production processes to access material for semi-synthesis and **c)** the general biological characterization of the natural and synthetic derivatives that will be pooled in a library. While we are performing the assays for evaluation of antimicrobial, nematocidal, anti-biofilm and cytotoxic effects ourselves, we have a particular strong collaboration with the HZI departments of cell biology (Profs. Rottner and Stradal) who are in charge of evaluating the actin effects in-depth.

Another task of our team is to produce the new cytochalasins provided by partners such as Russell Cox (Leibniz-University Hannover) or Prof. Christine Beemelmans (HIPS Saarbrücken) in up to gram scale for further evaluation, using mutasynthesis, precursor-directed biosynthesis or heterologous expression. For instance, we are currently evaluating the genomes of Xylariales for biosynthetic gene clusters encoding for cytochalasin production

2. Work program of the Postdoc candidate

During the first stage of the project, we have gathered various new compounds from fungal fruitbodies and cultures and made them available to the consortium. We have also studied extracts of newly obtained cultures using HPLC-DAD/MS dereplication techniques, from which we observed numerous potentially new cytochalasan derivatives.

We have also received some requests from the chemists and biochemists to provide larger amounts of certain compounds from wild type strains as well as from GMO strains that were generated using synthetic biotechnology approaches. The candidate will participate in regular project meetings with the scientists mentioned in 1) and their co-workers and will therefore get a good overview about the interactions in this project.

The postdoc is supposed to assist our team in the optimization of biotechnological production processes and the corresponding downstream processing procedures (MPLC prep. HPLC, using different methods of reversed phase and normal phase chromatography). He/she will also learn the preparative isolation of the compounds and can also participate in their biological characterization or the structure elucidation, if this appears practical.

The strains to be selected for intensified evaluation have already been subjected to a preliminary analysis of their metabolite profiles and fermentation conditions and the project work can start immediately. Our lab has a very strong record with integration of international guests who have mostly become productive after a rather short period of time..

Moreover, we are continuously recruiting BSc and MSc candidates who will work under supervision of the postdocs and help them to achieve their goals during their thesis work. The candidate postdoc selected for the current project will also be able to supervise such students, thereby gaining important experience for his/her future career.

We expect that at least 2-3 papers will result from the project work that deal with the discovery of novel anti-infective molecules or with the optimization of the biological activities and selectivity.

Literature

- Pourmoghaddam MJ et al. (2021) Mycol Prog. 22:65.
- Garcia KYM et al. (2022) J Fungi 8:560
- Matio Kemkuignou B et al. (2022). MycoKeys 90:85-118.
- Kuhnert E et al. (2021) Stud Mycol 99:100118.
- Lambert C et al. (2021) J Fungi 7:131.
- Wang C et al. (2020) Chemistry Eur J 26:13578-13583
- Wang C et al. (2019) Org Lett 21:8756-8760.



Description of existing or sought Chinese collaboration partner institute (max. half page):

We do not currently have an active collaboration with a Chinese institution, also due to the COVID restrictions. However, we are planning to enhance our interactions in the future again, now that travelling has become easier again. Marc Stadler has previously worked with leading Chinese researchers during his time at Bayer (collaboration with IMM, Beiing and Kunming Institute of Botany since 1997) and later on (2013/14) in the State Key Lab of Microbiology, Beijing, as Visiting Professor. He continuously publishes papers with Chinese mycologists and chemists and has various good contacts even in other regions of China, such as Yunnan (Kunming Institute of Botany) and in the Ghuizou, Wuhan, Shandong and Shanghai areas. It will thus be no problem to integrate the present project in the plans to increase and strengthen the collaboration with Chinese researchers

Required qualification of the postdoc:

- PhD in Biotechnology biology or natural product chemistry.....
- Experience with the isolation and characterization of fungi the fermentation of fungi and the characterization of their secondary metabolites are mandatory.
- Additional skills in HPLC-MS analytics, structure elucidation of natural products (NMR spectroscopy) or with performance of cellular bioassays is helpful but not mandatory because these skills are already well-represented in our team, which currently comprises 17 PhD students and postdocs from 12 countries.
- Language requirement: Fluent English