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

PART A

Title of the project: Lead structure optimisation of new gram-negative antibiotics

Helmholtz Centre and institute: Helmholtz Zentrum München, German Research Center for Environmental Health (GMBH) (HMGU), Institute of Medicinal Chemistry (IMC)

Project leader: Dr. Gerrit Jürjens in cooperation with Prof. Plettenburg

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Description of the project (max. 1 page)**:**
Already today the annual direct economic burden of nosocomial infection in China is estimated to be $1.5-2.3 bln (¥10-15 bln). Currently 10.000 to 15.000 of the 400.000 to 600.000 nosocomial infections each year in Germany result in death. A significant rise in case numbers is expected, the Wellcome Trust in London estimated that antimicrobial resistance in China could cause 1 million premature annual deaths by 2050. If one takes a closer look at the resistance patterns of the critical ESKAPE strains it is obvious, that our arsenal of effective antibiotics against the pathogens is dwindling. In the past 30 years, only two novel classes of antibiotics were discovered: the oxazolidinones and the lipopeptides – both classes exclusively active against gram positive bacteria. Unfortunately, four of the six dangerous ESKAPE strains are gram negative pathogens and in this case the situation looks significantly bleaker: *Pseudomonas aeruginosa* for instance can pose severe problems, often being resistant towards all known antibiotics besides the toxic colistin. Therefore, the demand for novel treatments against gram-negative pathogens will probably rise significantly in the next few years and failure to identify novel methods of treatment may result in a dramatic increase of nosocomial infection mortality.

Resistance to certain antibiotics is often directly linked to transport mechanisms of the bacterial membranes. Unlike the passive transport over eukaryotic membranes, antibiotics are usually transported via porins and other protein channels over the membranes in gram-negative bacteria. This transport is also the crux in antibiotic research. Addressing additional transport mechanisms and preventing efflux is often the key to breaking resistance or preventing a frequent occurrence of resistance. Altering molecular structure to tackle transport issues may allow transforming impermeable natural products into potential antibiotic candidates.

Several potential antibiotic compounds with these transport problems will be evaluated and synthesized by the researcher. The scientist will alter the chemical structure in order to overcome these issues, either by changing physicochemical properties or by introduction of different structural motifs which allow new transport mechanisms of the molecule into the

pathogen. Efficacy, physicochemical properties and ADME properties of these compounds will be determined in the facilities of the IMC by the prospective researcher and be the starting point for evaluation of a potential antibiotic lead candidate. The newly-founded IMC provides an excellent infrastructure for organic synthesis and medicinal chemistry. It has close collaborations with other HMGU facilities which allow access to further biological testing as well as contacts with industrial antibiotic research groups.

Since complex natural products are usually the starting point in antibiotic research the prospective researcher should have a strong background in complex multistep organic synthesis, modern synthetic methodology and ideally a fundamental understanding of medicinal chemistry. Knowledge in the field of microbiology and the handling of highly polar organic compounds is a bonus.

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**
We are looking for a highly motivated postdoctoral candidate with profound experience in synthesis of complex organic molecules and a deep interest in medicinal chemistry related questions who will join our young team to contribute to the project sketched above. This exciting project will offer the chance to work in a highly interdisciplinary team located in a modern medicinal chemistry environment.
In our past, we had good experiences with researchers from institutes in Hong Kong and Shanghai but are also open for other excellent candidates. We are interested in candidates from institutes with a strong organic synthetic background for a long-term partnership between the IMC and the respective institute.

Required qualification of the post-doc:

- PhD in organic chemistry
- Profound experience in modern multi-step organic synthesis (e.g. stereoselective synthesis, modern transition metal-based catalysis)
- Basic knowledge in medicinal chemistry