2026 Helmholtz – OCPC – Programme

for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project:

Selective Inhibition of the Zinc Metalloprotease LasB as a Novel Antivirulence Strategy for *P. aeruginosa* Burn-Wound Infections

Helmholtz Centre and/or institute:

Helmholtz Centre for Infection Research (HZI), Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS)

Project leader:

Dr. Jörg Haupenthal

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Department: (at the Helmholtz centre or Institute)

Drug Design and Optimisation

Programme Coordinator (Email, telephone and telefax)

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Description of the project (max. 1 page)**:**

Pseudomonas aeruginosa is a major opportunistic Gram-negative pathogen and a leading cause of severe infections in immunocompromised patients. In particular, burn wound infections caused by *P. aeruginosa* are associated with high morbidity and mortality due to rapid tissue destruction, impaired wound healing, and increasing antimicrobial resistance. Despite intensive antibiotic treatment, clinical outcomes remain poor, highlighting burn-wound infections as an unresolved medical problem with a high unmet need for alternative therapeutic strategies.
One promising antivirulence target is the secreted zinc-dependent metalloprotease LasB (elastase), a key virulence factor of *P. aeruginosa*. LasB degrades host extracellular matrix proteins, disrupts epithelial barriers, and severely impairs immune responses and tissue regeneration. Importantly, LasB inhibition does not directly affect bacterial viability, thereby reducing selective pressure for resistance development.
Our group has established a comprehensive LasB inhibitor program and generated a focused library of highly potent small-molecule inhibitors. Building on this strong foundation, we aim to

evaluate their therapeutic potential in burn wound infections caused by *P. aeruginosa*. To this end, we will establish and apply complementary in vitro, ex vivo, and in vivo models that reflect clinically relevant aspects of *P. aeruginosa* burn-wound infections. The proposed work packages (WPs) are outlined below:

WP1: Compound selection and in vitro validation. From the existing inhibitor collection, ten compounds will be selected, prioritizing molecules containing a phosphonate moiety as the preferred zinc-binding group. These compounds will be evaluated in cell-based infection models using human skin-derived cell lines (HaCaT keratinocytes and NHDF fibroblasts). Experiments will be performed in the presence of clinically relevant *P. aeruginosa* isolates (our department maintains a well-characterized collection of more than 150 clinical isolates). Using the Cellwatcher system (PHIO), we will monitor real-time cytotoxic effects of pure LasB as well as bacterial infection and assess the ability of LasB inhibitors to prevent or reverse host-cell damage. Additionally, we will examine the transepithelial electrical resistance (TEER) of skin cells in presence and absence of LasB or the pathogen ± LasB inhibitors.
WP2: **Ex vivo tissue exposure experiments**. The compounds selected for WP1 will be evaluated using burned and LasB-treated human skin samples. Following topical treatment with the selected compounds, cryosection analyses will be performed to assess compound penetration, distribution, and local efficacy in human skin tissue.
WP3: In vivo pharmacokinetics studies. The five most effective compounds from WPs1+2 will be advanced to in vivo pharmacokinetic (PK) cassette studies in mice in collaboration with the HZI PK/PD Unit and our collaboration partner Prof. Guo Yu. Oral and topical administration routes will be evaluated to determine compound exposure in skin tissue.
WP4: In vivo efficacy in a burn wound infection model. To evaluate in vivo efficacy, a burn wound infection model in *Galleria mellonella* will be established based on published protocols. Larvae will be subjected to standardized burn injuries, infected with selected clinical *P. aeruginosa* isolates, and subsequently treated with the five lead LasB inhibitors. Therapeutic efficacy will be assessed using survival as the primary endpoint. We intend to test the most promising compound in a murine burn-wound infection model (collaboration Prof. Guo Yu).

This project will provide a comprehensive evaluation of LasB inhibitors as novel anti-virulence therapeutics for burn-wound infections. By combining strong chemical starting points with clinically relevant infection models, the project aims to lay the foundation for further translational development of LasB inhibitors and to establish a sustainable international collaboration in the field of anti-infective research.

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

We are delighted to have identified Prof. Guo Yu (Professor, Associate Dean of the School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University) as an interested collaboration partner. She will primarily drive the project forward in the area of in vivo PK profiling and PD models.

Required qualification of the postdoc:

- PhD in biology, pharmacy, or related
- Experience with establishment and conduction of biochemical assays to evaluate inhibitors of enzymes/proteins, ex vivo experiments, working with S2 pathogens
- Additional skills in scientific writing (papers, reports), use of MS Office
- Language requirement English