Pre-clinical development of Corallopyronin A – a natural product active against helminths, STIs and Staphylococci

Kenneth Pfarr[1,10], Andrea Schiefer[1,10], William Shafer[2], Jennifer Edwards[3], Tim Becker[4], Gabriele Bierbaum[1], Stefan Kehraus[4], Miriam Grosse[5], Rolf Jansen[5], Silke Alt[6], Gabriele König[7], Alexandra Ehrens[1], Tanja Schneider[8], Marc P. Hübner[1,10], Rolf Müller[9,11], Karl Wagner[4,10], Thomas Hesterkamp[6], Marc Stadler[5,11], Achim Hoerauf[1,10*]

[1]Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn
[2]Emory Antibiotic Resistance Center, Emory University School of Medicine, Atlanta, USA
[3]Nationwide Children's Hospital; Department of Pediatrics, Ohio State University, Columbus, USA
[4]Department of Pharmaceutical Technology and Biopharmacy, University of Bonn
[5]Department Microbial Drugs, Helmholtz Centre for Infection Research, Braunschweig
[6]Translational Project Management Office (TPMO), German Center for Infection Research
[7]Institute for Pharmaceutical Biology, University of Bonn
[8]Institute for Pharmaceutical Microbiology, University of Bonn
[9]Department Microbial Natural Products, Helmholtz Institute for Pharmaceutical Research Saarland
[10]German Center for Infection Research (DZIF), partner site Bonn-Cologne
[11]German Center for Infection Research (DZIF), partner site Braunschweig-Hannover

*Corresponding Author

Corallopyronin A (CorA) inhibits bacterial DNA-dependent RNA polymerase and has a different binding site to rifampicin. Thus, it is effective against rifampicin-resistant *Staphylococcus aureus*. We have shown that CorA kills Gram-negative *Wolbachia* endobacteria of filarial nematodes, causative agents of onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis). Depleting the essential endosymbionts results in worm sterility and slow adult worm killing. Within DZIF we demonstrated CorA activity against *Neisseria gonorrhoeae* and multi-resistant *S. aureus.* At 4x MIC no spontaneous CorA resistance in *N. gonorrhoeae* could be detected, predicting a frequency of mutation of $\leq 10^{-10}$. We have also shown CorA activity against established *S. aureus* biofilms and their formation. Furthermore, CorA has excellent biodistribution into bone. We have received funding to investigate CorA as a new antibiotic class for treating osteomyelitis and *S. aureus* biofilms.

In support of CorA as a novel solution to several targets of the WHO Priority Pathogen List for which new antibiotics are needed, we have conducted standard non-GLP ADMET studies. *In vitro* toxicity tests (off-target, AMES, micronucleus, hERG, phototoxicity) demonstrated that

CorA is nontoxic and pharmacologically safe; supported by non-GLP *in vivo* toxicity studies in rats and dogs in which the maximal tolerated dose (MTD) in both species was 1000 mg/kg CorA, causing mild symptoms. Results of the 7-day repeated dose studies in rats and dogs that will form the basis for the design of the regulatory-conform GLP toxicity and safety pharmacology studies will be presented.

CorA drug substance is heterologously produced using genetically modified *Myxococcus xanthus*. In preparation for GMP manufacturing, the first scale up to industrial scale ($15m^3$) was achieved in 2022 at Bio Base Europe Pilot Plant (Ghent, Belgium). The Helmholtz Centre for Infection research, Braunschweig performed the DSP of this large amount of material, achieving 90-95% HQ-RGM material. Using amorphous solid dispersion (ASD) formulation principles, two solid oral formulations were developed with increased stability (>3 months at 30 °C, >6 months at 5 °C) and oral bioavailability (mouse >59%, rat >100%, dog >53%) compared to neat CorA. After finalization of the pre-clinical work, we plan to enter the clinical phase I in 2024/2025.