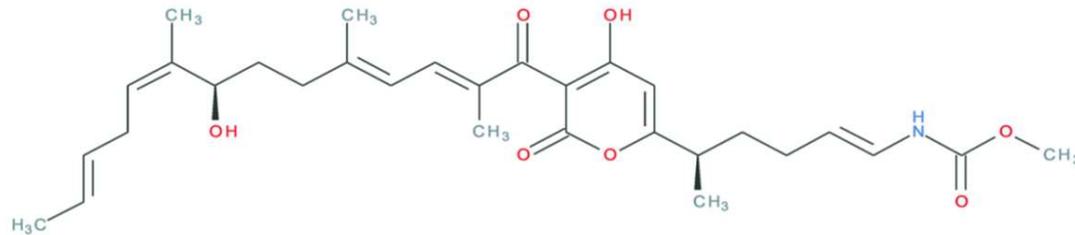


# Corallopyronin A- a new natural compound against filariae, STI and staphylococci on its way to phase 1

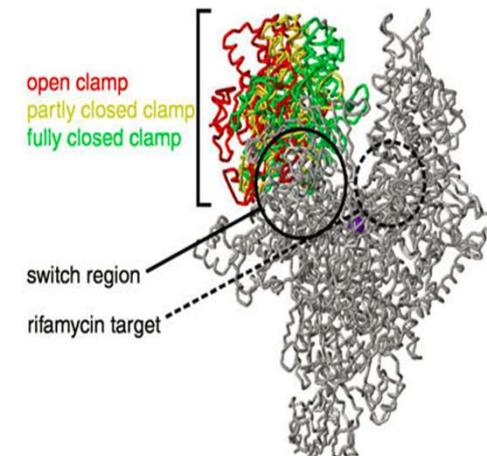
Institute for Medical Microbiology, Immunology and Parasitology (IMMIP)  
German Center for Infection Research (DZIF), partner-site Bonn-Cologne  
University Hospital Bonn  
Bonn, Germany

## Background: Corallopyronin A (CorA)



*Corallococcus coralloides*

- **Produced by *Corallococcus coralloides***
  - Soil Myxobacteria
- **Inhibits bacterial DNA dependent RNA polymerase**
- **Novel MoA: different from rifamycins**
  - Switch region – blocks entrance of DNA template
  - Effective against rifampicin-resistant *S. aureus*
- **Effective against Gram-positive bacteria**
  - *E. coli*  $\Delta$ tolC mutants are sensitive



# Primary Indication: Treatment of Filariasis

(Lymphatic filariasis & Onchocerciasis)

## Caused by filarial nematodes

- **Lymphatic filariasis** (elephantiasis, 51 million infected)
- **Onchocerciasis** (river blindness, 21 million infected)
- **CorA has efficacy against *Wolbachia* bacterial endosymbionts of filariae**
  - *in vivo* depletion of *Wolbachia* → blocked development, worm death



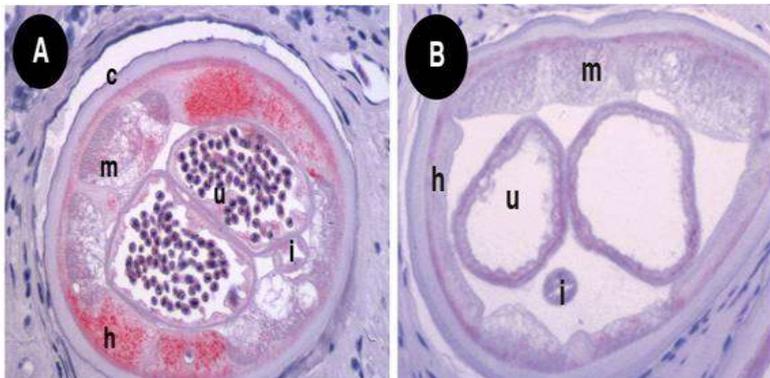
River blindness



Elephantiasis

Untreated

Doxycycline



[Hoerauf et al. (2000) Lancet 355,1242-1243]  
[Hoerauf et al. (2001) Lancet 357, 1415-1416]  
[Turner et al. (2006) Clin Infect Dis 42, 1081-1089]  
[Debrah et al. (2007) Trop Med Int Health 12, 1433-1441]  
[Hoerauf et al. (2008) Med Microbiol Immunol 197, 295-311]  
[Mand et al. (2009) Am J Trop med Hyg 81, 702-711]  
[Debrah et al. (2011) J Parasitol Res 2011]  
[Klarmann-Schulz et al. (2017) PLoS Negl Trop Dis]

# Primary Indication: Treatment of Filariasis

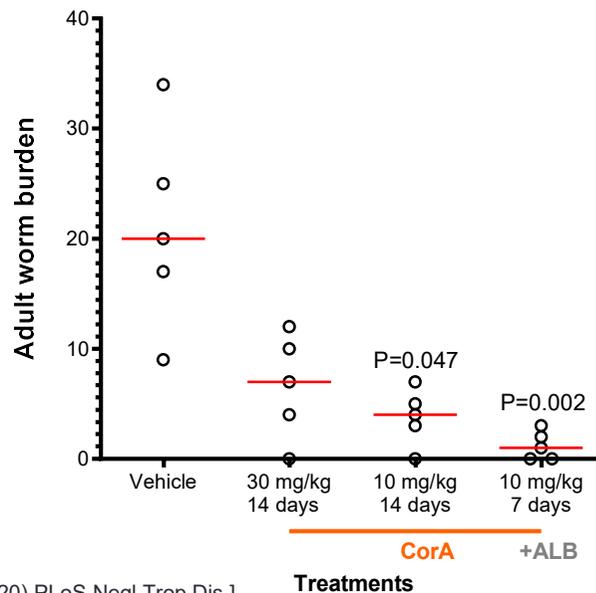
(Lymphatic filariasis & Onchocerciasis)

- **CorA has efficacy against *Wolbachia* bacterial endosymbionts of filariae**
  - *in vivo* depletion of *Wolbachia* → blocked development, worm death
  - Kills adult worms
  - Better efficacy than the comparator substances



River blindness

Elephantiasis



Prediction of HED according to FDA  
(Guidance for Industry 07/06/05)

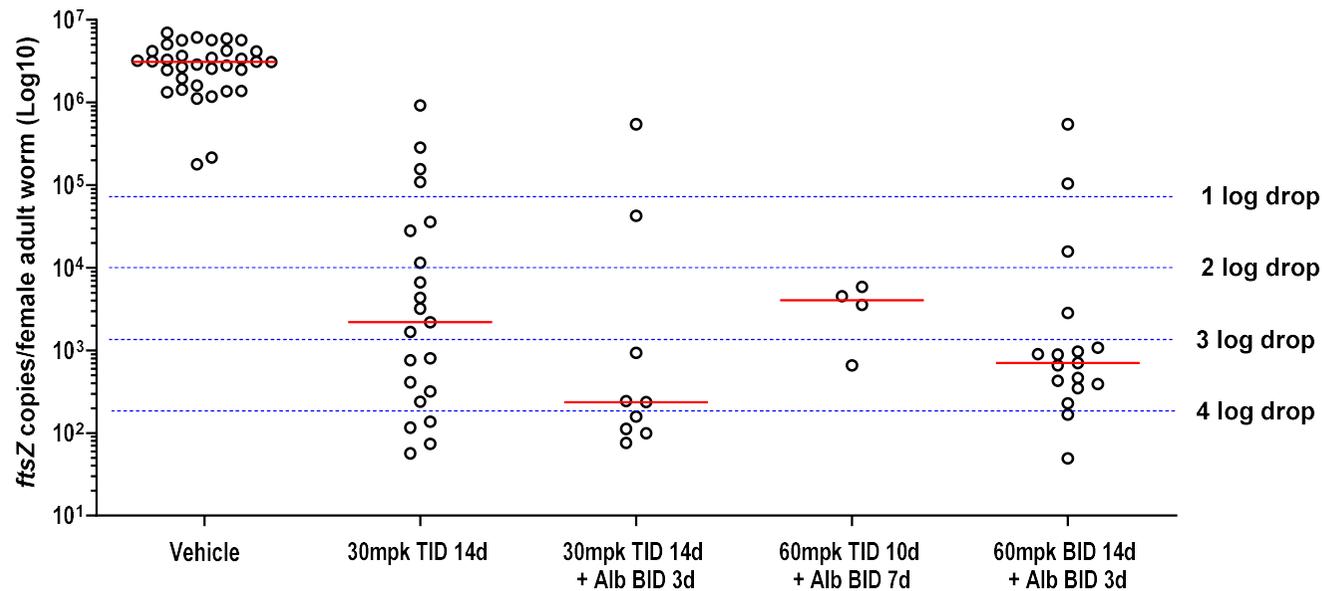
Minimal effective dose	Human
Jird therapy: 30 mg/kg BID 14 days	4 mg/kg
Jird therapy: 10 mg/kg BID + ALB 10 days	1.4 mg/kg
Mouse prophylaxis: 18 mg/kg QD 14days	1.5 mg/kg

[Schiefer et al. (2020) PLoS Negl Trop Dis.]

# Primary Indication: Treatment of Filariasis

(Lymphatic filariasis & Onchocerciasis)

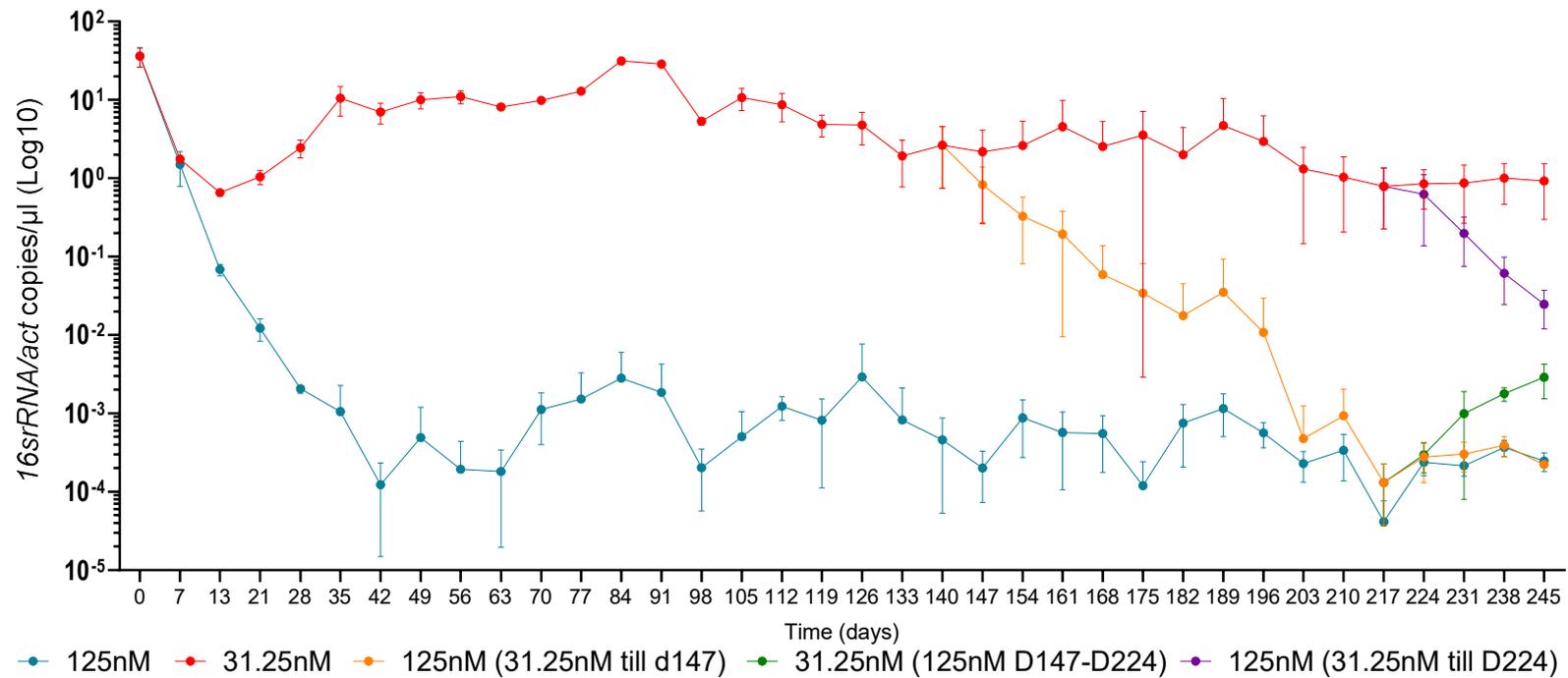
- **CorA has efficacy against *Wolbachia* bacterial endosymbionts of filariae**
  - Combination with albendazole improves drug efficacy & allows shorter treatment regimens and lower doses
  - Improved efficacy with TID treatment argues for the development of a slow release formulation to achieve shorter treatment regimens and/or lower doses





# Primary Indication: Treatment of Filariasis

(Lymphatic filariasis & Onchocerciasis)



**No selection of CorA-resistant *Wolbachia* endobacteria in C6/36 insect cells**

# Non-GLP *in vitro* and *in vivo* toxicity

<i>In vitro</i> and <i>in vivo</i> safety data	Conclusion
Off target profiling	A3, PPAR $\gamma$ , COX1; EC <sub>50</sub> = 170-850X higher than CorA EC <sub>50</sub> = 0.016 $\mu$ M against <i>Wolbachia in vitro</i>
Cyp inhibition	No inhibition of six recombinant human CYPs; inhibition of 2CP
CYP 3A4 induction via PXR	Minimal inducer: 12 $\mu$ M CorA vs 1.5 $\mu$ M Rifampicin, DDI unexpected
Non-GLP Micronucleus	No induction of chromosomal damage, no genotoxicity
Non-GLP AMES (5 strains)	No evidence of genotoxicity
Phototoxicity	No phototoxicity up to limit of solubility (38 $\mu$ M)
Liver toxicity	No toxicity in hepatocytes from rats or humans (200 $\mu$ M)
Non-GLP hERG	Predicted IC <sub>50</sub> = > 10 $\mu$ M
MTD rat	1000 mg/kg; mild clinical symptoms
MTD dog	1000 mg/kg; moderate, transient symptoms
7d repeated-dose rat: 0, 250, 1000 mg/kg/d	250 mg/kg/d, no effects seen
7d repeated-dose dog: 0, 150, 450, 750 mg/kg/d	<b>NOEL</b> : 150 mg/kg bw/d; Predicted <b>HED</b> = 4 mg/kg (filariae).

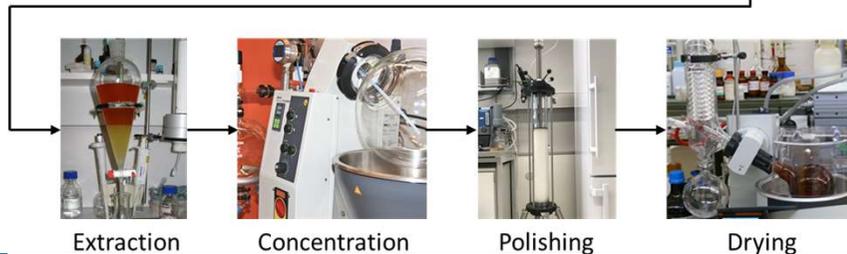
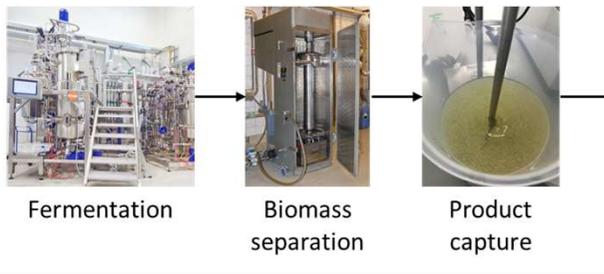
➤ **CorA has no relevant safety issues**

➤ **Next: GLP toxicity in Q4/2023-Q2/2024**

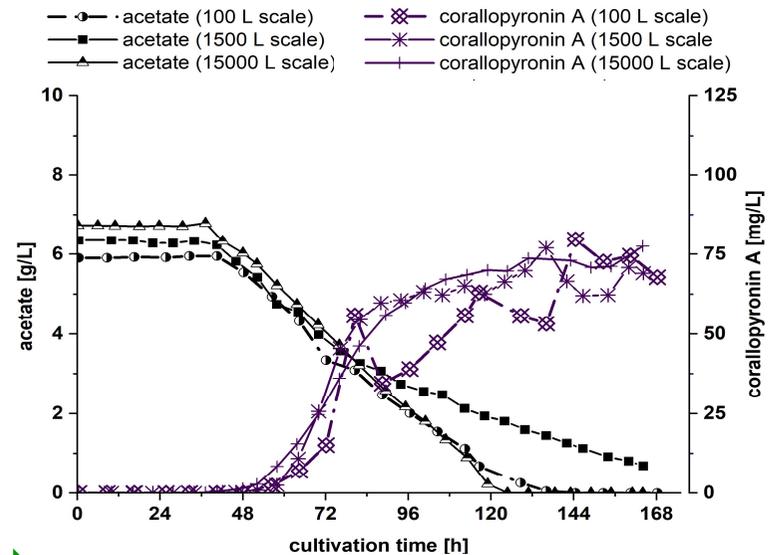
# Production process of high quality research grade material (HQ-RGM) at HZI

## Stable production of HQ-RGM (>90% purity) in multi-gram scale

- ⇒ USP upscaled to 15 m<sup>3</sup>
  - ⇒ Average yield USP ~ 80 mg/L
  - ⇒ Average yield DSP ~ 70 % yield



### Heterologous production in *M. xanthus*



➔ Next: GMP production for GLP toxicity and clinical trial material at Phytion Biotech



# IP landscape

- University of Bonn has the freedom to Licence 4 granted patents and 1 patent-pending
- Licensing agreement between HZI and University of Bonn
- Freedom to operate for a licensing Partner

Title	Patent	Granted in	Validated in
Compounds for use in the treatment of filariasis	US 9168244 B2	2015	US
Compounds for use in the treatment of filariasis	EP 2704708 B1	2017	DE, GB, NL, CH, IT, ES, FR and HR
Compounds for use in the treatment of filariasis	US 9687470 B2	2017	US
Production of Myxopyronin and of its derivatives	EP 2 994 535	2018	DE, GB, NL, CH, IT, ES and FR
Solid and liquisolid formulations of Corallopyronin A	PCT/EP2021/061310	PCT/EP2021/061310	

## Secondary Indication: Treatment of *Staphylococcus aureus*

- Active vs. 34 *Staphylococcus* spp., incl. rifampicin-resistant *S. aureus*, MRSA, VISA, and *S. epidermis* strains (MICs 0.1-1 µg/mL)
- *S. aureus* CorA rate of mutation is lower than rifampicin
- CorA has good activity against *S. aureus* biofilm formation and established biofilms
- Good PK biodistribution into bone → osteomyelitis

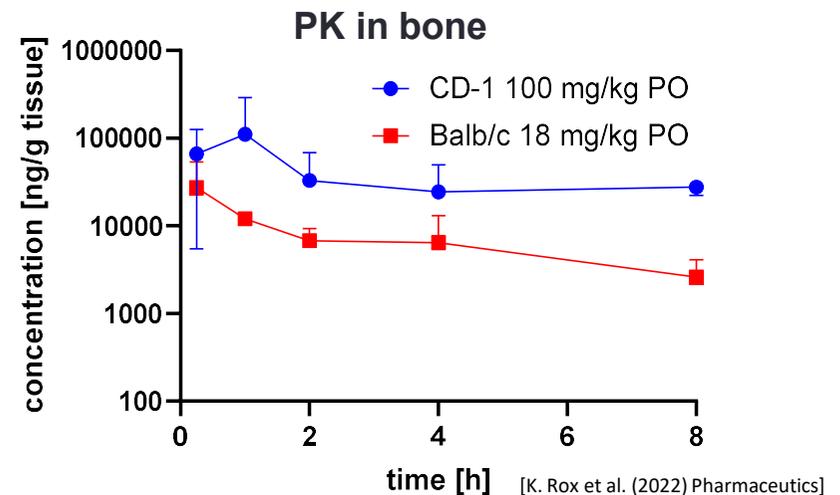
### Mutation frequency SH1000:

Rifampicin:  $2.1 \times 10^{-8}$

CorA:  $7.7 \times 10^{-9}$

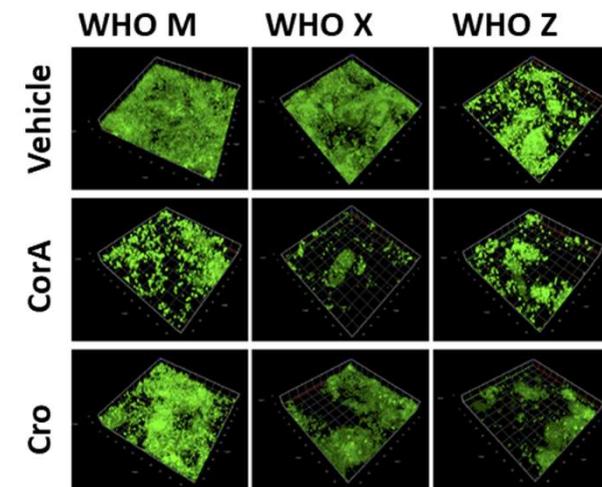
Only 5 potential mutation sites or CorA in the switch region vs. 16 for rifampicin in the active site.

[Balansky et al. (2022) Antibiotics 11]



## Secondary Indication: Treatment of gonorrhoea

- CorA is effective vs. 50 CDC and 14 WHO *Neisseria gonorrhoeae in vitro* (MIC = 0.125-2 µg/mL)
- CorA has activity vs. 4 WHO strains in primary cervical cells (MIC 1-2 µg/mL)
- Effective against *N. gonorrhoeae* biofilms
- No spontaneous resistance selected at 4X MIC
  - Mutation frequency predicted  $\leq 10^{-10}$
  - Three-step resistance needed for MIC of 32
    - Requires mutation in efflux repressor as 1<sup>st</sup> step



Collaboration with leaders in gonorrhoeae research:

- Prof. Dr. William Shafer: Emory Antibiotic Resistance Center, Emory School of Medicine
- Prof. Dr. Magnus Unemo: WHO Collaborating Centre for Gonorrhoea and Other STIs, Sweden
- Prof. Dr. Jennifer Edwards: Center for Microbial Pathogenesis, Nationwide Children's Hospital

[Edwards et al. (2022) mSphere]

## Development plan

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- **Primary indication, onchocerciasis/lymphatic filariasis**
  - Complete GLP-Tox in dogs (2024)
  - Establish GMP production at Phyton Biotech (2023+2024)
  - Seek public funding
  - Produce GMP drug substance
  - Contract GMP company to produce clinical trial material (2025)
  - Phase I study by 2026 to generate data in human
    - De-risk the project
    - Find partner for further development
      - Noncommercial
      - Commercial (Licensing, spin-off company)
- **Secondary indications**
  - *S. aureus* biofilm and osteomyelitis (DZIF funded)
  - *N. gonorrhoeae*: seek public funding

# DZIF partners and external advisors

