Corallopyronin A – a natural antibiotic against helminths, STI and Staphylococci

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University Hospital Bonn
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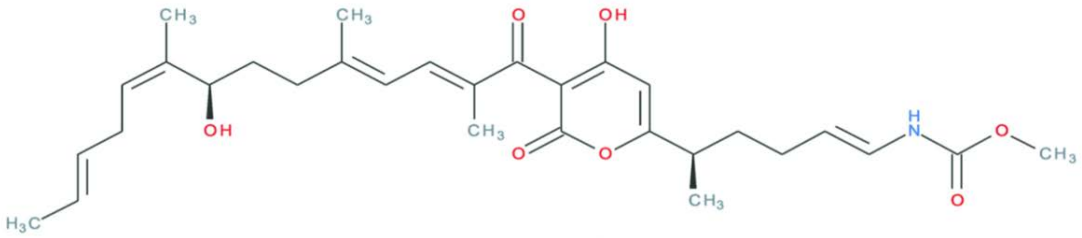
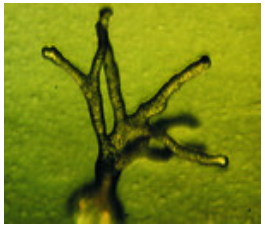
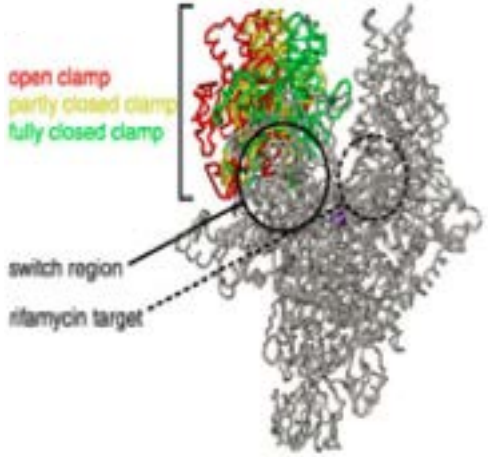
Background: Corallopyronin A (CorA)





Corallococcus coralloides

- **Produced by *Corallococcus coralloides***
  - Soil Myxobacteria
- **Inhibits bacterial DNA dependent RNA polymerase**
- **Novel MoA: different from rifamycins**
  - Effective against rifampicin-resistant *S. aureus*
- **Effective against Gram-positive bacteria**
  - *E. coli* ΔtolC mutants are sensitive

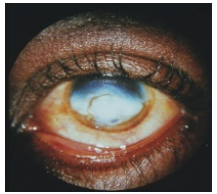


Primary Indication: Treatment of Filariasis

(Lymphatic filariasis & Onchocerciasis)

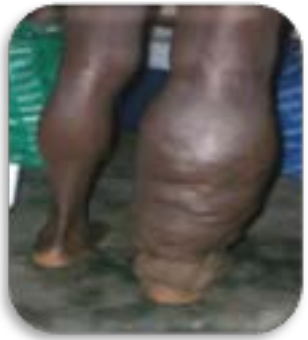
Caused by filarial nematodes

- **Lymphatic filariasis** (elephantiasis, 51 million infected*)
- **Onchocerciasis** (river blindness, 21 million infected*)

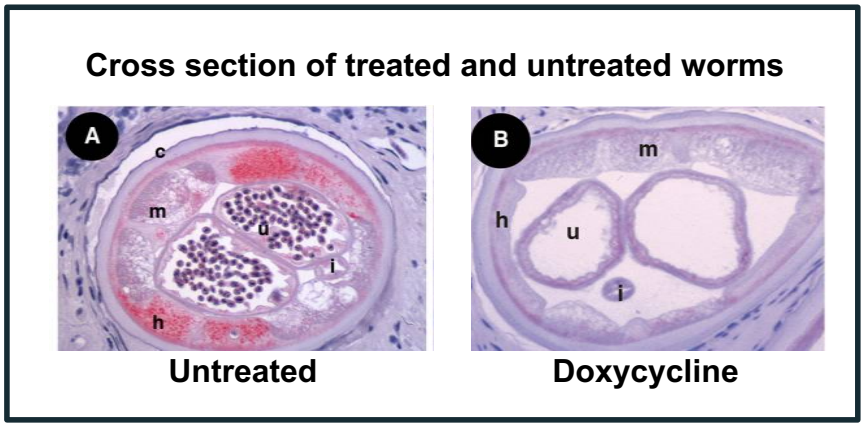


River blindness

- **CorA has efficacy against *Wolbachia* bacterial endosymbionts of filariae**
  - *In vivo* depletion of *Wolbachia* → blocked development, worm death



Elephantiasis



*World Health Organization (2020). Ending the neglect to attain the Sustainable Development Goals – A road map for neglected tropical diseases 2021–2030 (Geneva: World Health Organization).

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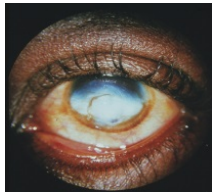

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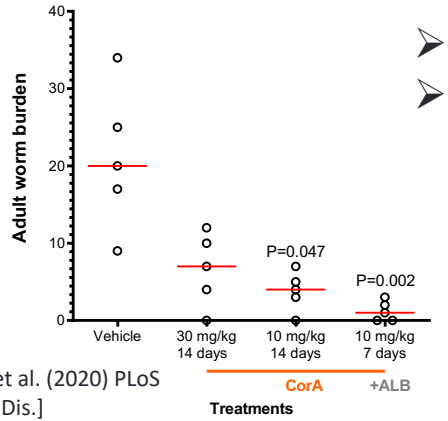
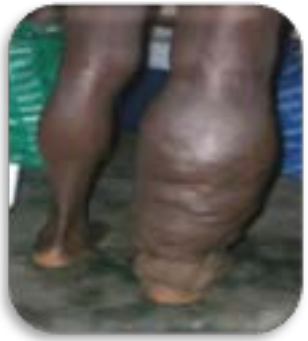


[Schiefer et al. (2020) PLoS Negl Trop Dis.]

- **Kills adult worms**
- **Better efficacy than the comparator substances**

	Minimal effective dose gerbil
Doxycycline	100 mg/kg QD 28 days
CorA	30 mg/kg BID 14 days
CorA + Albendazole	10 mg/kg BID + ALB 7 days



Elephantiasis

Patents:
US 9 168 244
US 9 687 470
EP 12 721 456.7

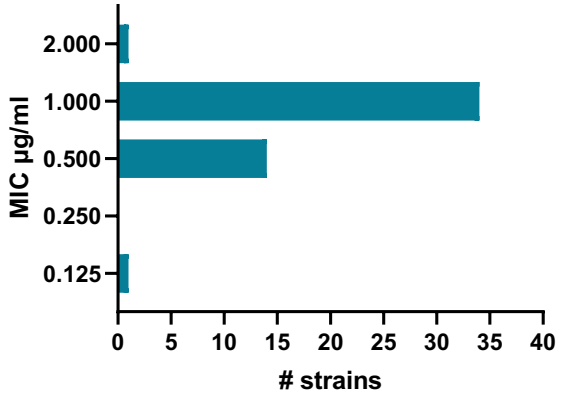
*World Health Organization (2020). Ending the neglect to attain the Sustainable Development Goals – A road map for neglected tropical diseases 2021–2030 (Geneva: World Health Organization).

DZIF

Secondary Indication: Treatment of gonorrhea

➢ **CorA is effective against *Neisseria gonorrhoeae***

Activity vs. *N. gonorrhoeae* strains

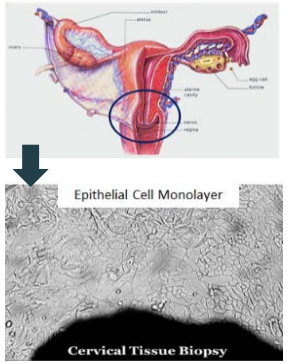


- 50 CDC and 14 WHO *N. gonorrhoeae* MDR/XDR strains
- **No spontaneous resistance selected at 4X MIC**
  - **Predict a frequency of mutation $\leq 10^{-10}$ (clinical strains)**

Activity vs. WHO *N. gonorrhoeae,* primary cervical epithelial cells

	µg/mL to cure Pex cells after 48 hrs	
Strain	CorA	Ceftriaxone
1291	0.5	0.5
WHO-M	1	0.5
WHO-X	2	R
WHO-Y	1	R
WHO-Z	1	R

[Edwards et al. (2022) mSphere]

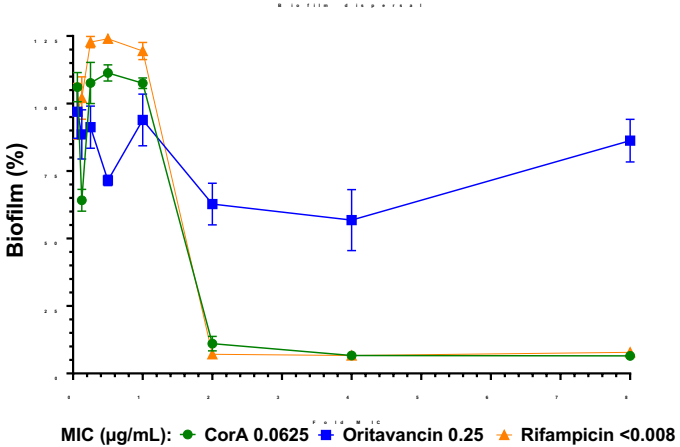


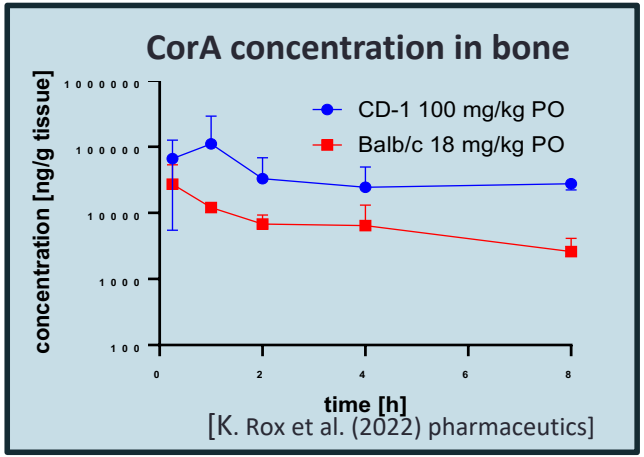
Collaboration with leaders in gonorrhoeae research:

- 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

Secondary Indication: Treatment of *S. aureus* /MRSA

- **Alternative antibiotic to treat antimicrobial resistant strains:**
  - Active against rifampicin-resistant *Staphylococcus aureus,* MRSA and VISA
  - *S. aureus* CorA rate of mutation is lower than rifampicin CorA: $1.7x10^{-8}$ vs Rifampicin: $1.0x10^{-7}$
- **CorA has good activity against *S. aureus* biofilm formation and disperses biofilms**
- **Good PK biodistribution into bone ➔ osteomyelitis**





[K. Rox et al. (2022) pharmaceutics]

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

***In vitro* and *in vivo* safety data**		**Conclusion**
Off target profiling		A3, PPARγ, COX1; EC_{50} = 170-850X higher than CorA EC_{50} = 0.016 µM against *Wolbachia in vitro*
Cyp inhibition		No inhibition of six recombinant human CYPs; inhibition of 2CP
CYP 3A4 induction via PXR		Minimal inducer: 12 µM CorA vs 1.5 µM 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 µM)
Liver toxicity		No toxicity in hepatocytes from rats or humans (200µM)
Non-GLP hERG		Predicted IC_{50} = > 10 µM
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		**NOEL**: 150 mg/kg bw/d; Predicted **HED** = 4 mg/kg.

- **CorA has no relevant safety issues**
- **Next: GLP toxicity in Q4/2023-Q2/2024**

Development strategy: hybrid approach

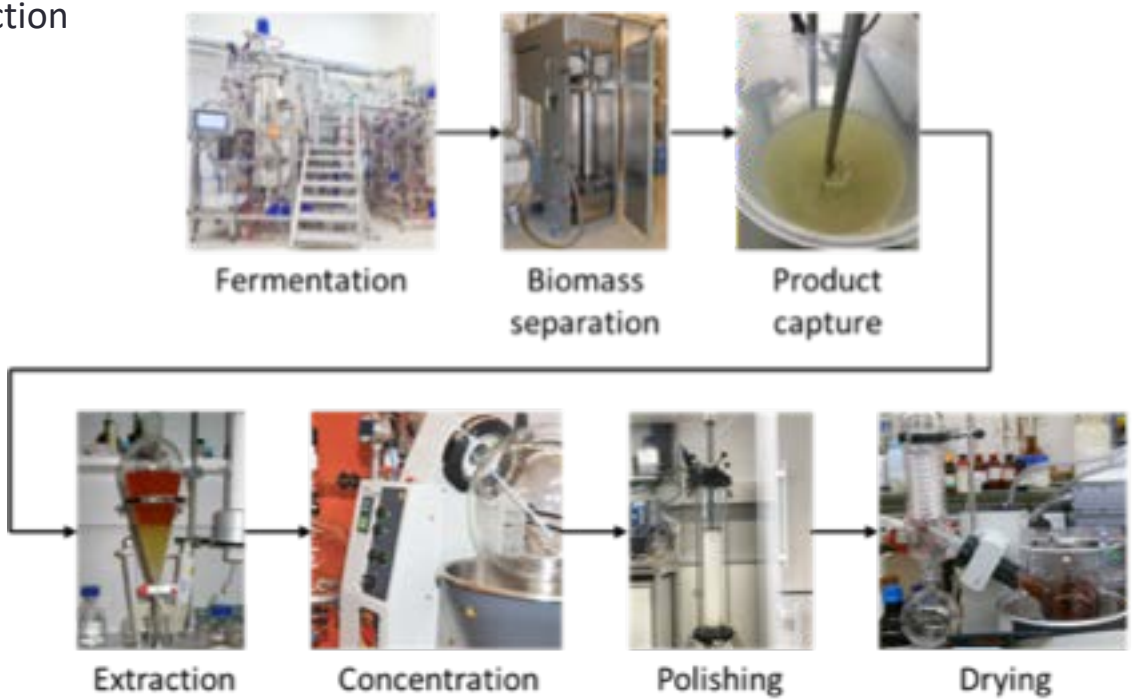
- **Public health funding for filarial indication until Phase I**
  - At clinical proof-of-concept we would partner with
    - public health branch of a major pharmaceutical company (currently Eisai)
    - public-private-partnership (DNDi)

- **Commercial market for staphylococci indications**
  - In parallel development for ABSSI infections and bone/ prosthetic infections
    - CABP infections offer another route to market
  - Founding a spin-off company for investments

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

Stable production of HQ-RGM (90%-95%) in multi-gram scale

- In-house 150 L/ 350 L scale production
- Average yield USP ~ 80 mg/L
- Average yield DSP ~ 70 % yield

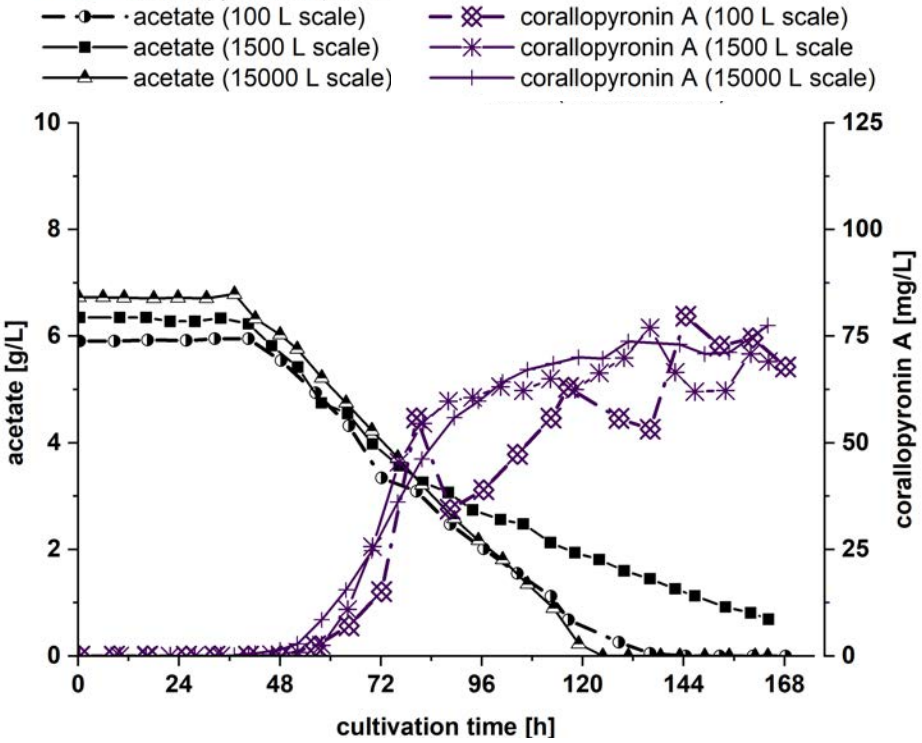


Upstream and downstream processing of CorA

Scale up to kg range

- USP successfully scaled up to 15m³
  - Titers equivalent to those observed at HZI

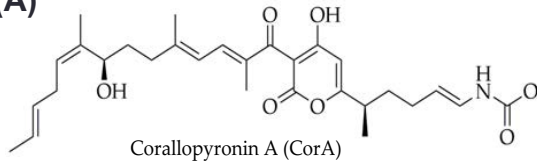
➡ **Next: GMP production for GLP toxicity and clinical trial material at Phyton (Germany/Canada)**



CorA formulation – amorphous dispersion

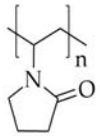
Neat-CorA

(A)



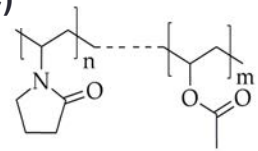
Corallopyronin A (CorA)

(B)

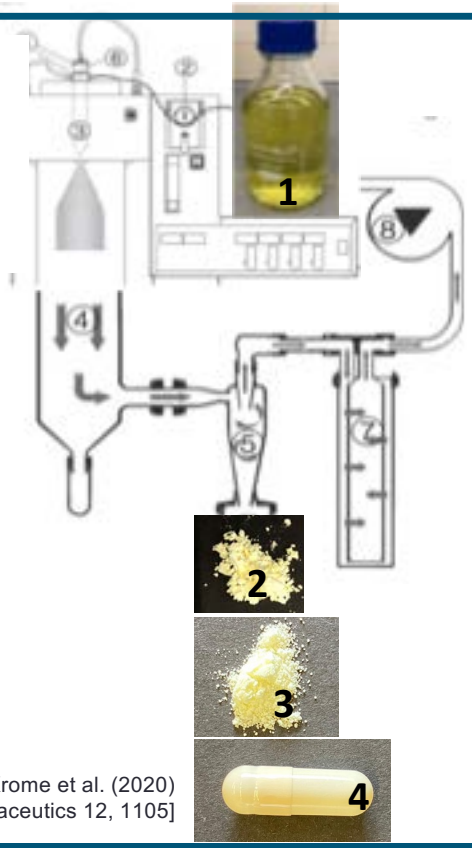


Povidone (PVP)

(C)



Copovidone (PVP/VA)



Step 1: Preparation of CorA and polymer solution. Drug load 20%.
Step 2: Spray drying.
Step 3: Dry granulation, milling, and sieving (125-249 µm).
Step 4: Free flowing powder filled into gastro resistant capsules (HPMC-AS)

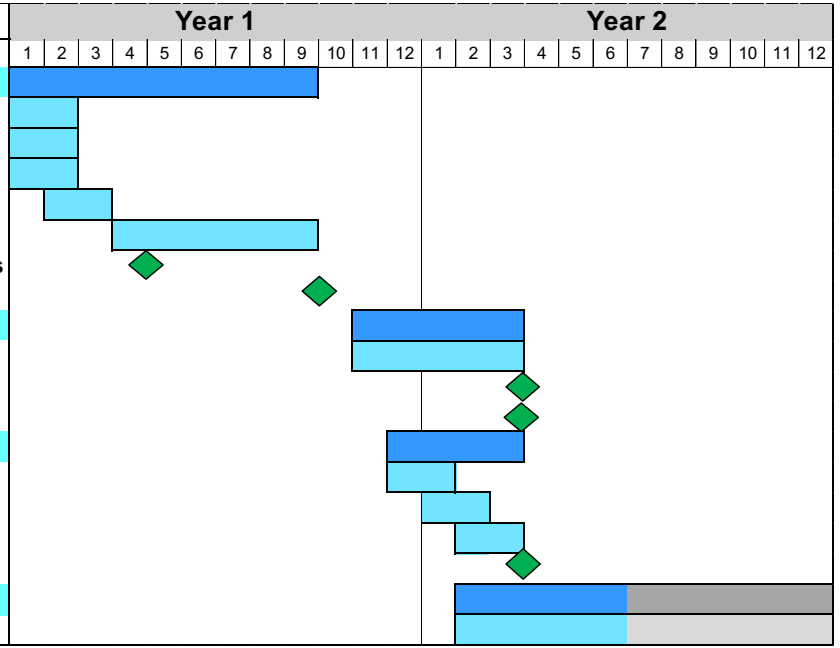
CorA embedded in PVP or PVP/VA

- **Improved oral bioavailability in mouse, rat and dog** [F from 5% to 35%-60%]
- **Improved stability** [stable >3 months at 30 °C, >6 months at 25°C]
- **Formulation Patent EP 20 172 409.3; GMP compatible**

[Krome et al. (2020) Pharmaceutics 12, 1105]

EKFS work program: Production of CorA clinical trial material

WP and M	Item
1	Transfer of trial form manufacturing process to CMO
1.1	Implementation of spray drying process
1.2	Implementation of dry granulation step
1.3	Implementation of hard capsule filling
1.4	Implementation of DP analytics
1.5	Initiation of stress stability
M1	Tech transfer of oral formulation to CMO & production of test batches
M2	Stress stability test of test batches
2	Compilation of the DP related IMPD
2	Compilation of the DP related IMPD
M3	Filing of IMPD for IMP
M4	Phase 1 trial application
3	Manufacturing of IMP
3.1	GMP-manufacturing of IMP
3.2	Packaging of IMP
3.3	Labeling of IMP
M5	Production of clinical trial material for phase 1
4	Initiation of concurrent stability
4	Start of concurrent stability test of IMP for 12 months



- Start of the project: identification of suitable CMOs for the production of IMP
- EU-tendering process
- Production of drug substance and GLP toxicity package in parallel

DZIF partners and external advisors

Qualified Person
J. Thumann

Production
- Fermentation and DSP:
  HZI, MWIS, Braunschweig: M. Stadler, R. Jansen, M. Große, B. Sandargo
- Heterologous producer:
  HZI, MINS, Saarbrücken: R. Müller
- CMO: Bio Base Europe Pilot Plant, Belgium

Efficacy studies
- Filarial Indication:
  IMMIP: M. Hübner, A. Ehrens, H. Neufeld, U. Klarmann-Schulz, T. Aden, M. Fendler, M. Koschel
- Gonococcal Indication:
  Emory Antibiotic Resistance Center, Atlanta: W. Shafer
  Nationalwide Children´s Hospital, Ohio: J. Edwards
  WHO Collaborating Centre for Gonorrhoea, Sweden: M. Unemo
- Mycobacteria Indication:
  Universidad Pontificia Bolivariana, Medellín, Colombia: J. Robledo
- Staphylococcal Indication:
  Uni BN: T. Schneider, G. Bierbaum, C. Szekat
  HZI: K. Rox , E. Medina, H. Schrey, M. Müsken

Corallopyronin A
- Project leader: A. Hörauf
- Project management: A. Schiefer, K. Pfarr

Project Supervision
- TPMO: T. Hesterkamp, S. Alt, M. Steindorf
- Project Advisory Group (PAG):
  H. Rübsamen-Schaeff, AiCuris, Advisor
  R. Lehnert, Regulator at BfArM
  J. Reinhard-Rupp, Head of Merck Global Health - Advisor
  D. Busch, Chairman of the DZIF Executive Board
  T. Jäger, DZIF Managing Director

Formulation
Uni BN: K. Wagner, S. Kehraus, T. Becker, J. Heitkötter

Toxicological Consulting
I. Stammberger

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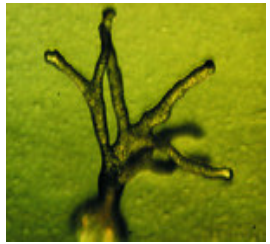
Project summary - Corallopyronin A (CorA)

- **CorA is a natural product of *Corallococcus coralloides* that is heterologously expressed in *Myxococcus xanthus***

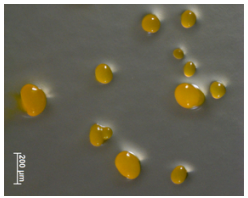
- **A bacterial RNA polymerase inhibitor with novel MoA in preclinical development:**
  - **As antifilarial drug to treat onchocerciasis**
    - Adulticidal activity with 10-14 day treatment
  - **As antibacterial drug to treat *Neisseria gonorrhoeae* and *Staphylococcus aureus* infections**
    - Effective vs. MDR/XDR clinical strains
    - Depletes established biofilms and prevents biofilm formation
    - Medium (*S. aureus*) to no (*N. gonorrhoeae*) resistance selection

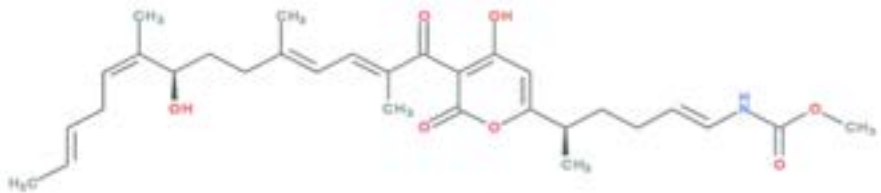
- **USP & DSP process established for 15,000 L bioreactor (industrial scale!)**
- **GLP appropriate oral formulations developed**
- **GMP-compliant Master Cell Bank (MCB) is available**
- **No prohibitive safety issues**

- **Phase I clinical trials scheduled for 2025/2026**

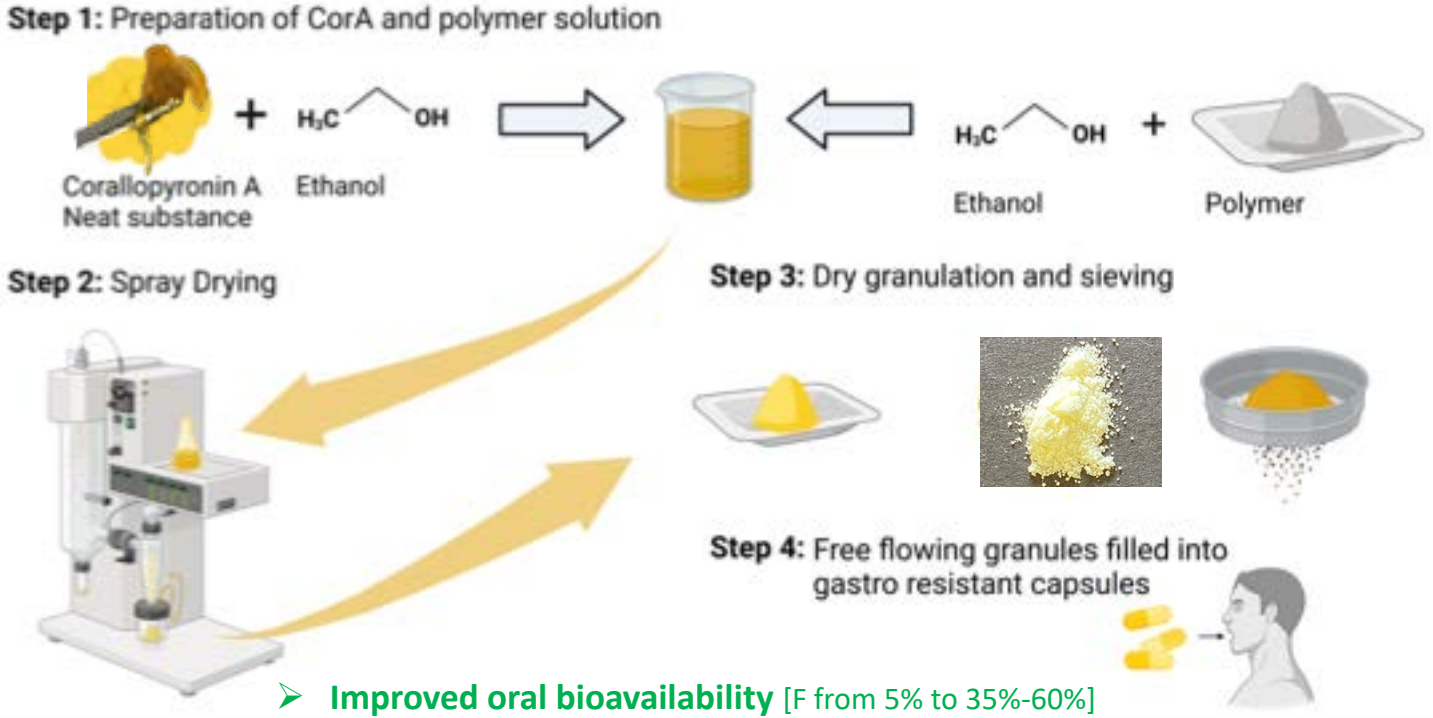


Corallococcus coralloides





CorA formulation process– amorphous dispersion



- **Improved oral bioavailability** [F from 5% to 35%-60%]

Improved stability [stable >3 months at 30 °C, >6 months at 25°C]

Formulation Patent EP 20 172 409.3