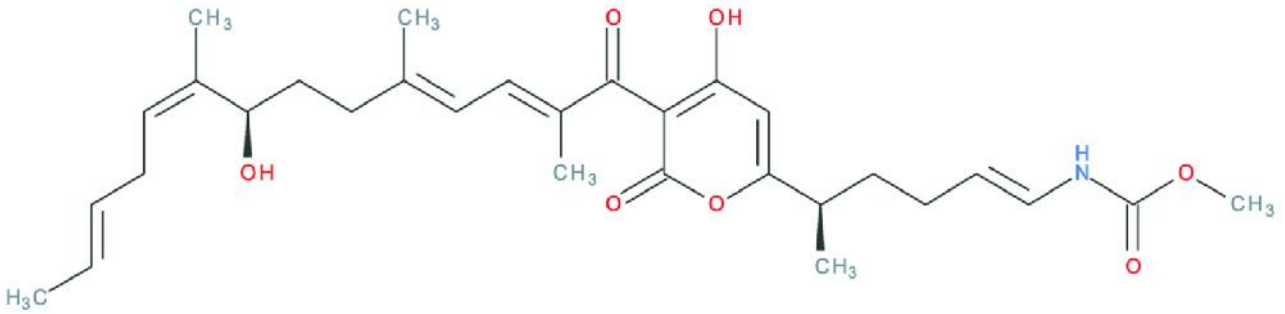
Corallopyronin A – an antibiotic active against Helminths, *Staphylococci* and STIs



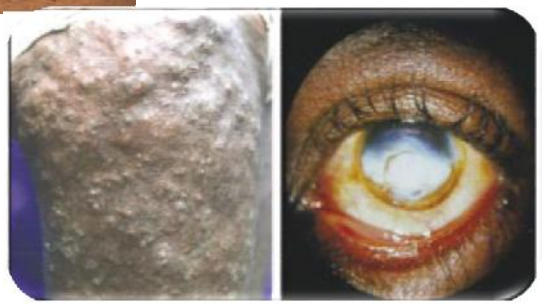
Corallopyronin A

Prof. Dr. med. Achim Hoerauf

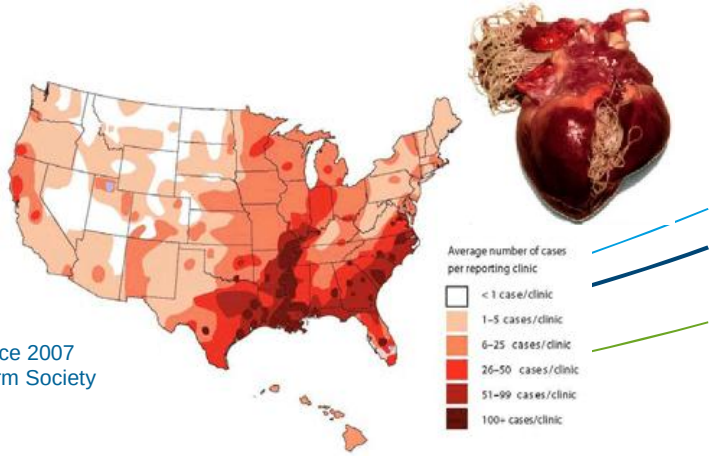
Filariasis in humans and dirofilariasis in pets

- Caused by nematodes, transmitted via blood sucking insects

- Human filariasis
  a) Lymphatic filariasis (elephantiasis):
    - 70 million infected (2000: 120 m infected)
    - ~40% have disease
  b) Onchocerciasis (river blindness):
    - 37 million infected
    - ~50% have skin disease or vision impairment

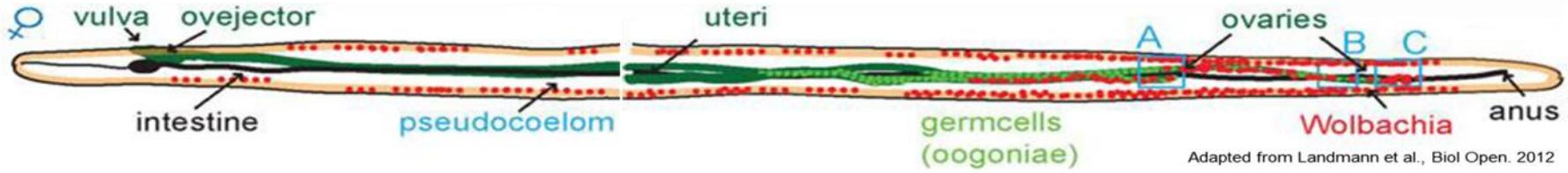


- Animal dirofilariasis (heartworm disease):
    - Infect more than 30 animal species
    - Large companion animal market
    - Endemic in all states of the USA, especially in the South
    - USA is 90% of the total market, spending $1.3 billion annually (2011) [FTC Staff Report, 2015]



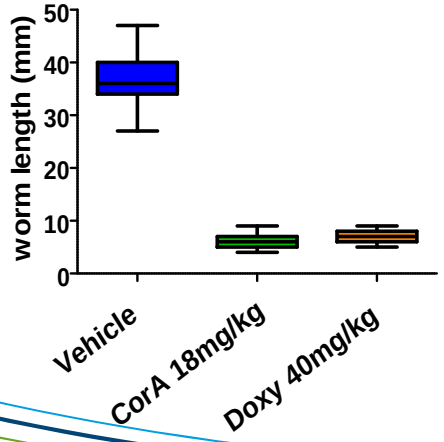
Heartworm Incidence 2007
American Heartworm Society

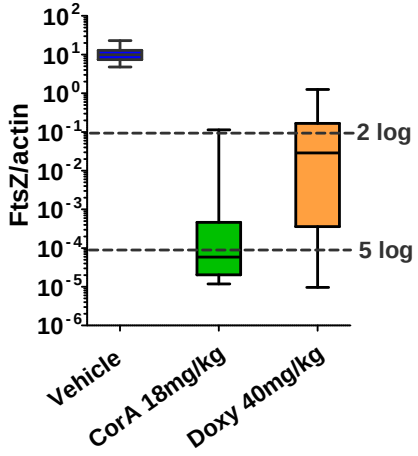
Corallopyronin A targets *Wolbachia* endobacteria

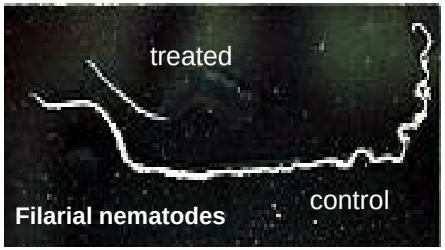


- All worms harbor the bacterial endosymbiont *Wolbachia*
  - Essential for worm development, fecundity and survival

- Corallopyronin A (CorA) has efficacy against *Wolbachia*
  - *in vivo* results: depletion of >98% of *Wolbachia* → blocked larval development





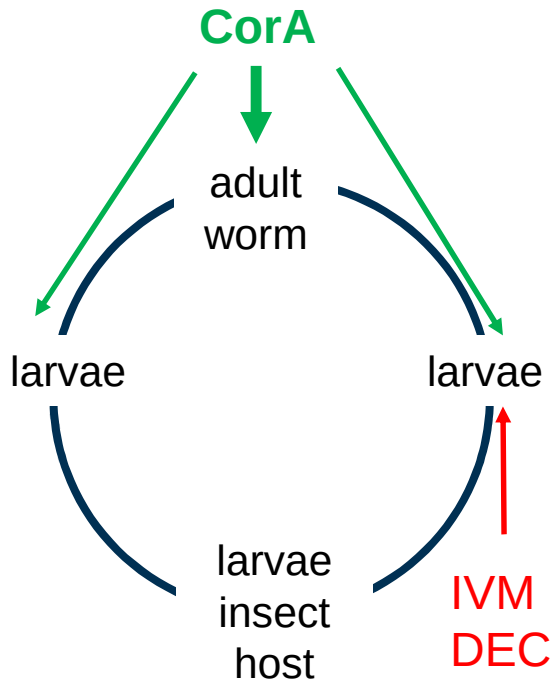


Existing solutions – promising alternative CorA

Current treatment in humans:

a) Target: nematodes
- Diethylcarbamazine and Ivermectin against larvae
  - Populations in endemic regions
  - Treatment for many years
  - Possible resistance / low performance of drug

b) Target: *Wolbachia*
- Doxycycline
  - Treatment time too long
- Rifampicin
  - Concern of resistance in *M. tuberculosis* if used for other indications



Promising alternative: CorA

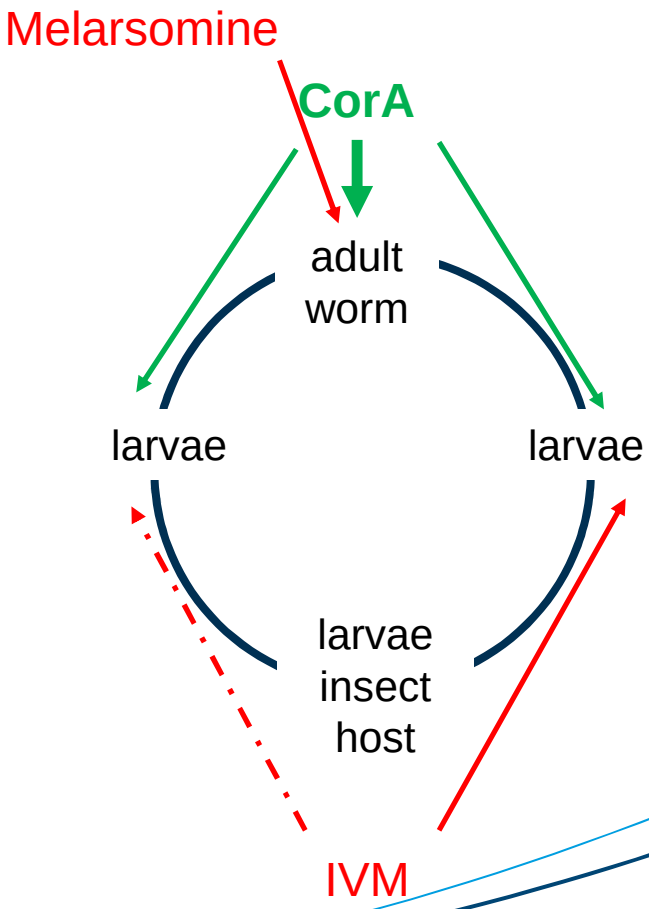
Existing solutions – promising alternative CorA

Current treatment in dogs:

a) Targets adult worms: melarsomine
- Severe side effects possible
- High mortality rate (5-30%)

b) Targets larvae: ivermectin
- Drug-resistance has been described
- Harmful to some species of dogs

Promising alternative: CorA



CorA – a preclinical development candidate

- MoA: binds RNAP
  - Active against rifampicin-resistant *S. aureus* and MRSA

- Active against intracellular bacteria (Chlamydia, Gonococci)

→ Drug against sexually transmitted infections (STIs)

- Small spectrum antibiotic
  - Good efficacy against Gram-positive
  - Ineffective against *Mycobacterium* spp.
  - Ineffective against Gram-negative

→ Less alteration of gut microbiome expected

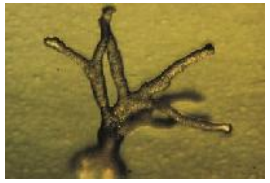
- Two internationally used rodent models [Gates foundation / DNDi]
  - Excellent oral bioavailability in mice and jirds
  - Human anticipated therapeutic dose 100-200 mg

- <u>Preclinical data available:</u>
  - Plasma stability and protein binding

→ **Cytochrome P450**

  - Stability in Simulated Intestinal Fluid
  - Stability in hepatocytes and microsomes
  - Microsome metabolite profiling
  - Permeability in Caco2 cells
  - UGT phenotyping
  - Off target profiling
  - PK profile

Preparing CorA for GMP manufacturing



Corallococcus coralloides

Initial yields: <2 mg/L

Myxococcus xanthus

Current yields: >100 mg/L

Fermentation

- Heterologous expression in *M. xanthus* (intra-DZIF collaboration project with HZI)
  - Current yields: 100 mg/L
  - Further strain optimization, goal: 300 mg/L
- Improvements of the down-stream process
  - DSP without HPLC
  - Current CorA purity: 90%-95% per NMR
  - Goal: 95% (pending BfArM scientific advice)
- Approaching CMO to manufacture GMP-quality material (DZIF funding)
  - Goal: GMP CorA by 2020 for phase I

Corallopyronin A – risks and bottlenecks

- Cost of goods:
  - Intermediate goal: 3000 $/kg
  - Long-term goal: 100-200 $/kg

- Development of an oral formulation

IP Status

University of Bonn owns 3 patents:

Compounds for use in the treatment of filariasis

- **US 9168244 B2** granted 2015
  Therapeutic treatment of filariasis/dirofilariasis in humans/animals

- **US 9687470 B2** granted 2017
  Prevention of filariasis/dirofilariasis in dogs and humans

- **EP 2704708 B1** granted 2017, validated in DE, GB, NL, CH, IT, ES, FR, HR
  Prevention and treatment of filariasis/dirofilariasis in humans/animals

Helmholtz Centre for Infection Research pat. pending:

- **WO 2014/181000 A1** Production of myxopyronin and of its derivatives and know how on the manufacturing process
  - License agreement currently under negotiation between both DZIF partners

Partnering proposition

We continue development of CorA for public health indication up to clinical PoC (phase IIa)

- Co-dvpt opportunity for industrial partner
- Established clinical study sites in Ghana and Cameroon
- Resource requirement € 7-9m (2019-2022)
- Funded in part through federal and philanthropic funders

Advanced, de-risked project may be licensed within filariasis indication for drug approval and transferable priority review voucher (FDA)*

Advanced, de-risked project may be licensed outside public health indication for dvpt for commercial markets (e.g. staphylococcal infections, STIs)

Separately we are seeking a vet med partner to develop product for veterinarian markets (dirofilariasis)

* https://www.fda.gov/downloads/Drugs/Guidances/UCM080599.pdf

Thank you for your attention!

Scientists involved in the CorA Project

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Q6. What is a priority review voucher and when is it awarded?

The term *priority review voucher* is defined in section 524(a)(2) of the FD&C Act. It refers to a voucher issued by the FDA to the sponsor of a tropical disease product application at the time of approval of the application that entitles the holder of such voucher to designate a single human drug application submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act (see section 524(a)(2) of the FD&C Act) as qualifying for a priority review. Such a subsequent application would not have to meet the usual requirements for a priority review. (See Question 13.)

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