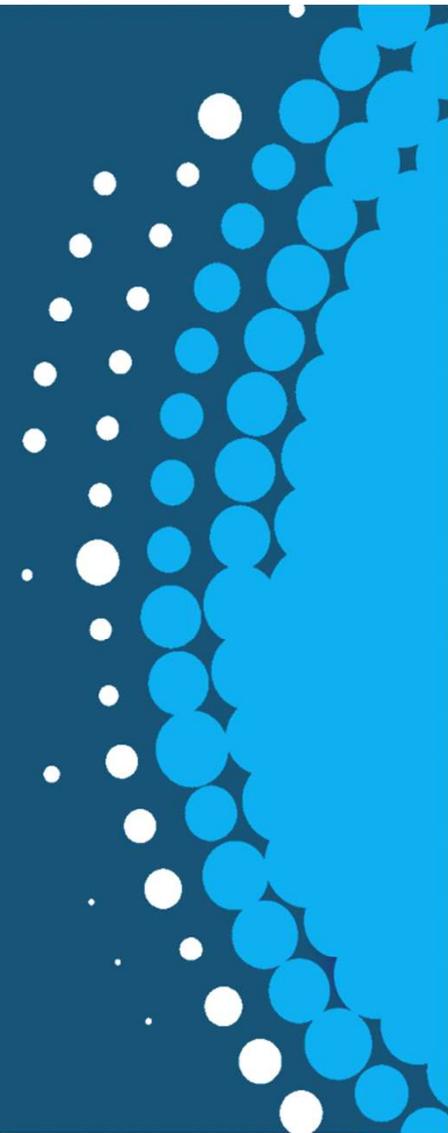


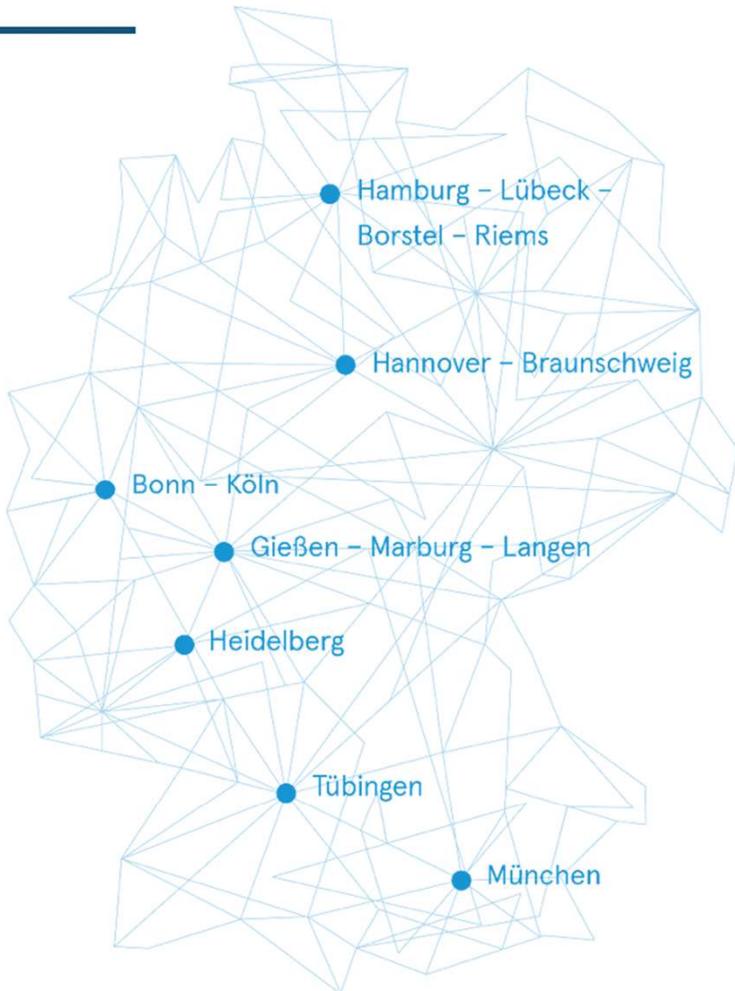


The German Center for Infection Research



DZIF member institutions and partners

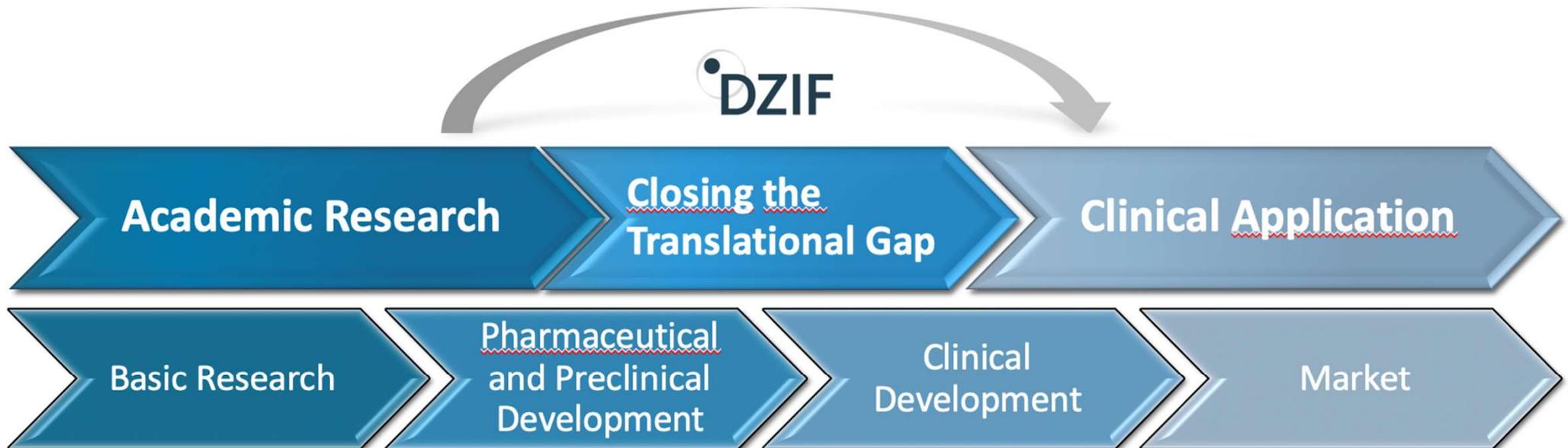
*> 10 years of
cooperation!*



- Universities
- University Hospitals
- Non-University Research Institutions
- Federal Institutions (research sections)
 - The Federal Institute for Vaccines and Biomedicines (PEI)
 - The Federal Institute for Drugs and Medical Devices (BfArM)
 - The Robert Koch Institute (RKI)
 - The Federal Research Institute for Animal Health (FLI)
 - The Bundeswehr Institute of Microbiology (IMB)

Mission

Mission: To support scientists and clinicians in developing biomedical discoveries to novel preventive, diagnostic and therapeutic products

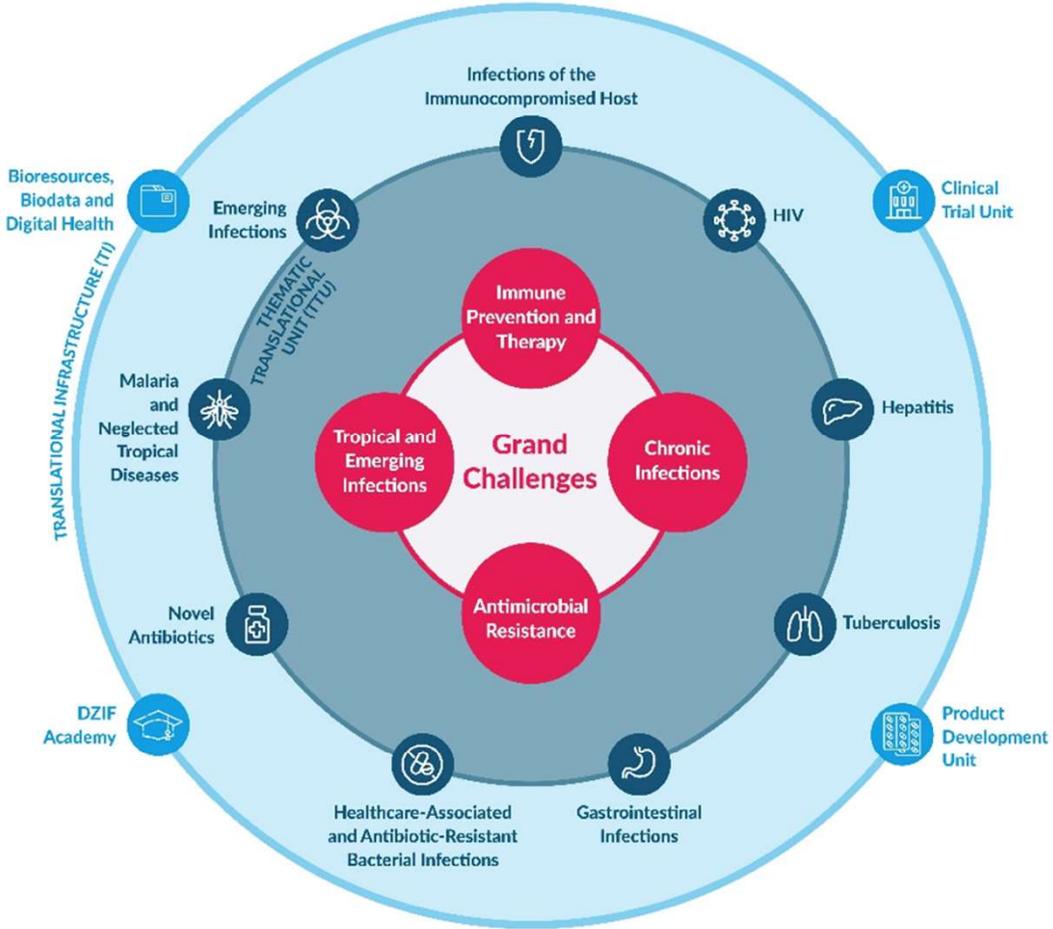


... identification of biomarkers, clinical guidelines, epidemiological data, translational infection models, platforms

External cooperations



Current DZIF overview

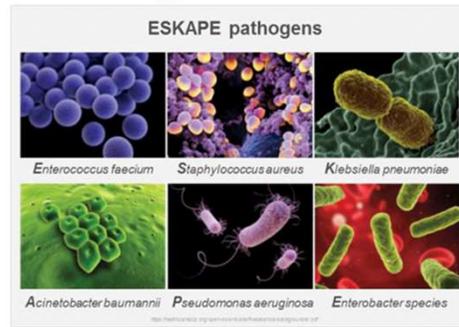
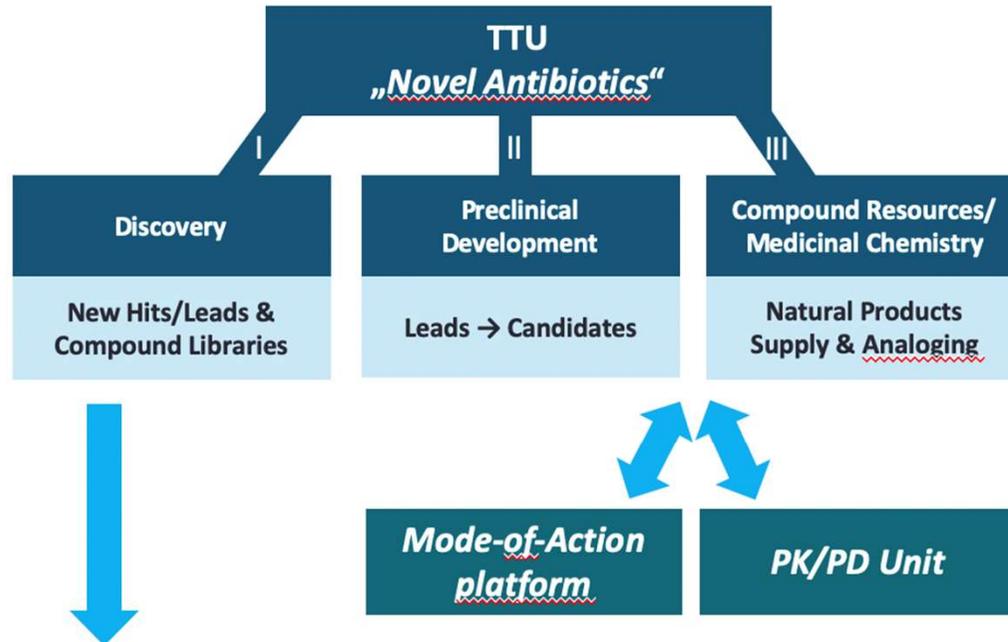


TTU NAB: Partner Sites and Discovery Resources



TTU „Novel Antibiotics“ (NAB)

HIPS HELMHOLTZ
Institute for Pharmaceutical Research Saarland



TTU NAB: Infrastructures

5 Professorships, 1 Junior Research Group



Nadine Ziemert
Tübingen

Translational Genome
Mining for Natural
Products



Marc Hübner
Bonn-Cologne

Translational
Microbiology



Ute Klarmann-
Schulz
Bonn-Cologne

Preclinical and
Clinical Development
of antiinfectives



Alexander Titz
Hannover-
Braunschweig

Medicinal Chemistry
with focus on
Natural Products



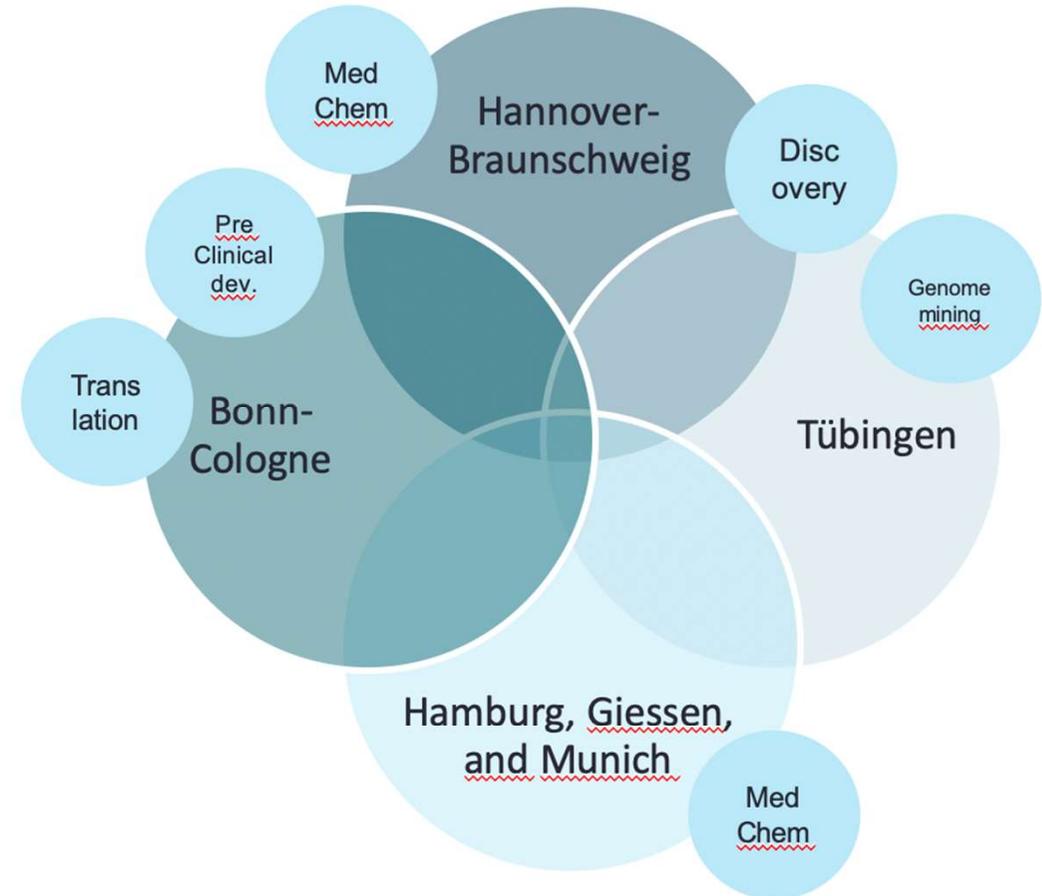
Ulrich Nübel
Hannover-
Braunschweig

Functional Genomics
of Novel Microbial
Producers

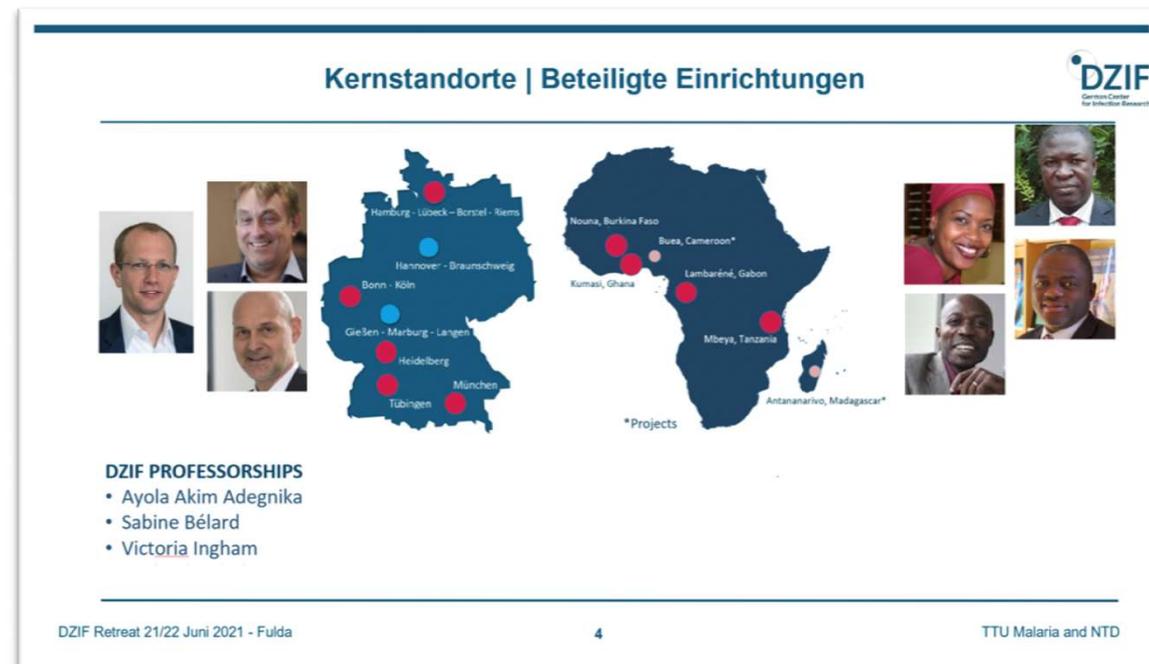


Ralph Holl
Hamburg

Medicinal Chemistry
of Novel Anti-infective
Agents



- **Malaria**
 - Epidemiology
 - Diagnostics
 - Therapy
 - Prevention (Drugs and Vaccines)
- **Neglected Tropical Diseases**
 - Diagnostics and Therapies
 - Human filarial infections
 - Schistosomiasis
- **African Partner Institutions**
 - Antimicrobial Resistance Surveillance



Kernstandorte | Beteiligte Einrichtungen

DZIF PROFESSORSHIPS

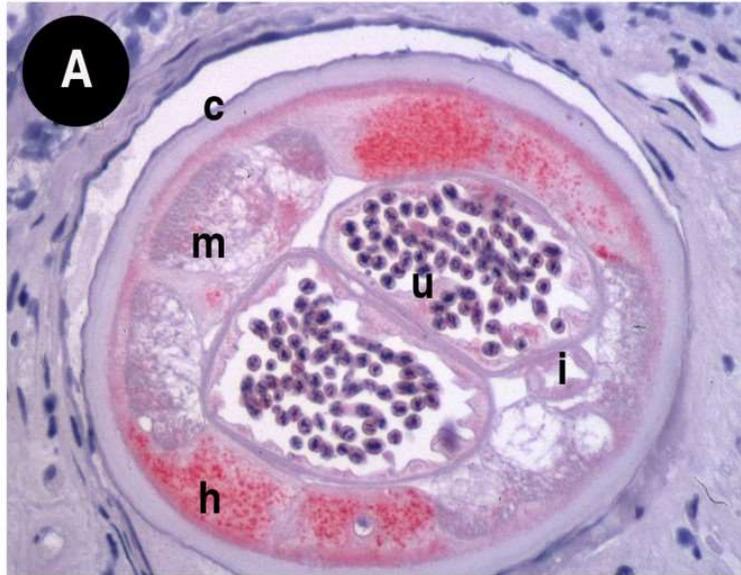
- Ayola Akim Adegnika
- Sabine Bélard
- Victoria Ingham

DZIF Retreat 21/22 Juni 2021 - Fulda

4

TTU Malaria and NTD

The slide features a map of Germany and Africa. The German map shows locations: Hamburg - Lübeck - Borstel - Riems, Hannover - Braunschweig, Bonn - Köln, Gießen - Marburg - Langen, Heidelberg, München, and Tübingen. The African map shows locations: Nouna, Burkina Faso; Busea, Cameroon*; Kumasi, Ghana; Lambaréné, Gabon; Mbeya, Tanzania; and Antananarivo, Madagascar*. Three portraits of DZIF professors are shown on the left, and three portraits of African partner institutions are shown on the right.

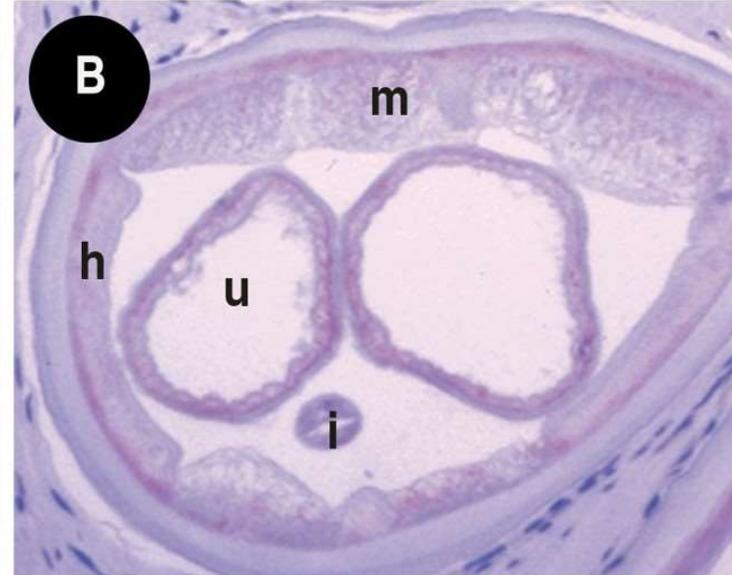


Untreated

Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis

Achim Hoerauf, Lars Volkmann, Christoph Hamelmann, Ohene Adjei, Ingo B Autenrieth, Bernhard Fleischer, Dietrich W Büttner

THE LANCET • Vol 355 • April 8, 2000



Doxycycline 100 mg/d for 6 weeks

Depletion of wolbachia endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment

Achim Hoerauf, Sabine Mand, Ohene Adjei, Bernhard Fleischer, Dietrich W Büttner

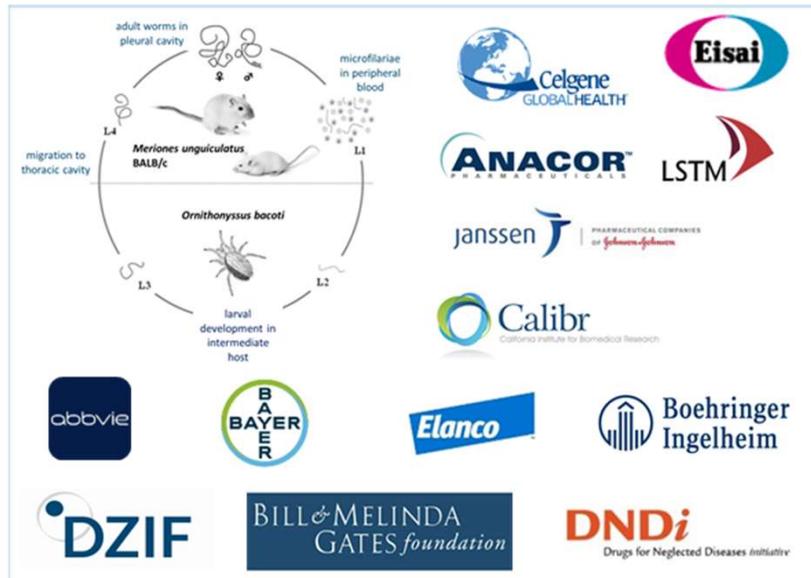
THE LANCET • Vol 357 • May 5, 2001

Preclinic



Clinical studies

- Intern. hit to lead program (>500K candidates)
- Collaboration with industry & academia
- > 450 candidates tested in the *Litomosoides sigmodontis* rodent model



Phase 1:

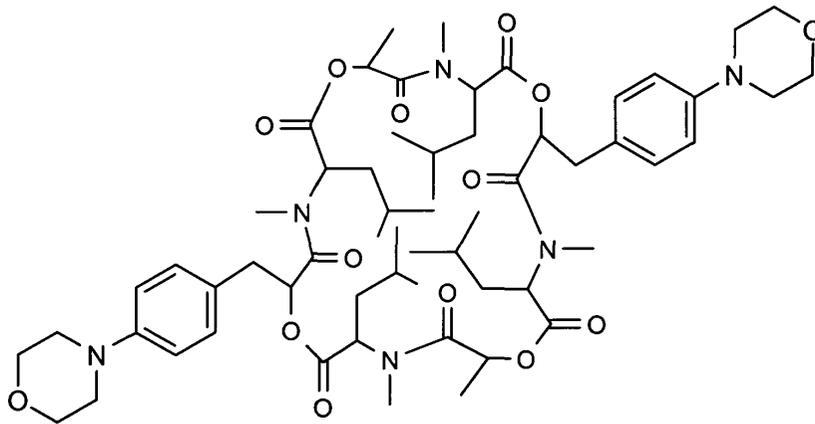
- **Corallopyronin A**
(scheduled for 2025)
- **AWZ-1066**



Phase 2:

- **Flubentylosin/ABBV-4083**
- **Emodepside**
- **Oxfendazol** (in 2024)





- Emodepside is used in combination with praziquantel (Profender) for the treatment of parasitic worms in cats and dogs
- Inhibits Ca²⁺-gated K⁺-channel Slo-1 of nematodes (Kulke et al. PLOS NTDs 2014)



Emodepside – broad activity against filarial species and life cycle stages

in vitro

| Filarial species | Life cycle stage | IC ₅₀ / EC ₅₀ |
|---------------------------------|--------------------|-------------------------------------|
| <i>Litomosoides sigmodontis</i> | Adult worms | 1 x 10 ⁻⁸ M |
| | L3 | 9 x 10 ⁻⁹ M |
| <i>Brugia malayi</i> | MF | 9 x 10 ⁻⁹ M |
| <i>Onchocerca gutturosa</i> | Adult male worms | 9 x 10 ⁻⁹ M |
| <i>Brugia pahangi</i> | Adult female worms | 4.3 x 10 ⁻⁷ M |
| | Adult male worms | 6 x 10 ⁻⁸ M |

in vivo

| Filarial species | Life cycle stage | Dose |
|---------------------------------|----------------------|-------------|
| <i>Acanthocheilonema viteae</i> | MF clearance | 100mg/kg |
| | Adult worm clearance | 100mg/kg |
| <i>Litomosoides sigmodontis</i> | MF clearance | 100mg/kg |
| | Adult worm clearance | 5x 100mg/kg |
| <i>Brugia malayi</i> | Adult worm clearance | 5x 100mg/kg |

Krücken et al. PLOS Pathog 2021

Onchocerciasis

| Concentration | Treatment duration |
|---------------|--------------------|
| 15 mg QD | 1 day |
| 30 mg QD | 1 day |
| 15 mg QD | 7 days |
| 15 mg QD | 14 days |
| 15 mg BID | 10 days |



Trichuris trichiura and hookworms



| Concentration (single dose) |
|-----------------------------|
| 5 mg QD |
| 10 mg QD |
| 15 mg QD |
| 20 mg QD |
| 25 mg QD |
| 30 mg QD |



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Emodepside for *Trichuris trichiura* and Hookworm Infection

Emmanuel C. Mrimi, M.Sc., Sophie Welsche, Ph.D., Said M. Ali, M.Sc., Jan Hattendorf, Ph.D., and Jennifer Keiser, Ph.D.



The TAKEOFF teams



Alexander Yaw Debrah
Linda Batsa Debrah
Jubin Osei-Mensah
Nana Kwame Ayisi-Boateng
Derrick Adu-Mensah
Vera Opoku
Francis Dorman
and the whole team



Samuel Wanji
Peter Enyong
Bonekeh John
Ndifor Ignatius
Nchanji Gordon Takop
Ndzeshang Bertrand
Abdel Jelil Njouendou
and the whole team



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Mwele Ntuli Malecela †
Upendo Mwingira
Abdallah Ngenya
Dennis Moshi
Winfrida John
Yusuph Mgaya
and the whole team



BMBF Research Networks for Health Innovations in Sub-Saharan Africa, Kick-Off Meeting, Tanzania 2017 photo: Pavel Desort



Inge Kroidl
Sacha Horn
Anja Feichtner
and the whole team



Achim Hoerauf
Ute Klarmann-Schulz
Janina Kuehlwein
Patricia Jebett Korir
Manuel Ritter
Angelika Kellings
Kenneth Pfarr
and the whole team



TAKeOFF2 Kickoff-Meeting, Arusha, Tanzania – June, 2023 photo: TAKEOFF TZ

SPONSORED BY THE





TAKeOFF – mission 2

Alternative strategies for elimination of LF and onchocerciasis

- Implementing alternative strategies to accelerate the elimination of LF and oncho
- **Test and Treat** trials in LF hotspots: doxycycline vs. IDA/MoxDA vs "classical" IA
- Using a Test and Treat approach in oncho to compare **doxycycline alone vs. doxycycline in combination with vector control** to accelerate elimination
- Using the capacity to conduct clinical trials, which was built during TAKEOFF1, to **carry out additional clinical trials** funded i.e. by EDCTP, DNDi, GHIT

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Federal Ministry
of Education
and Research

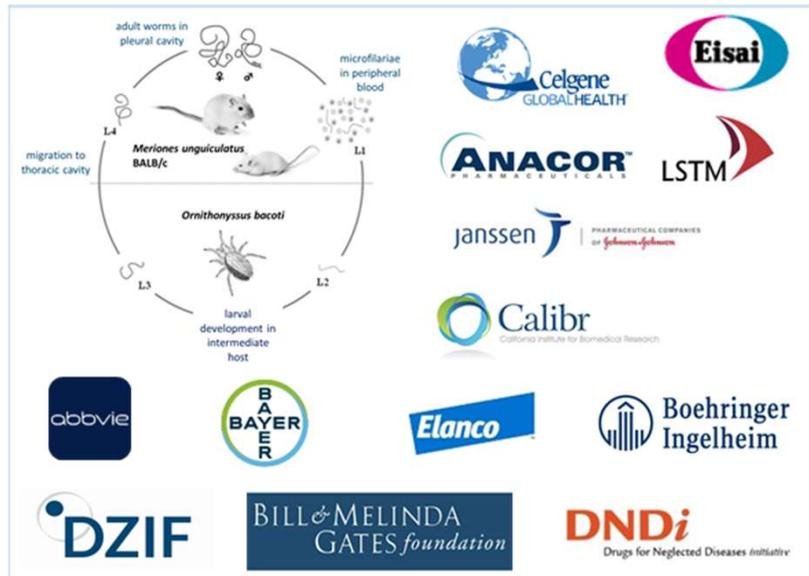


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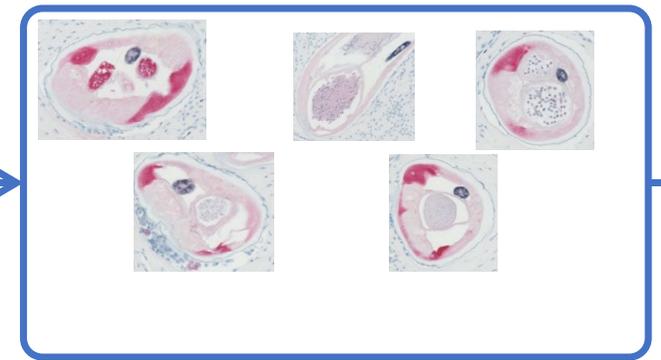
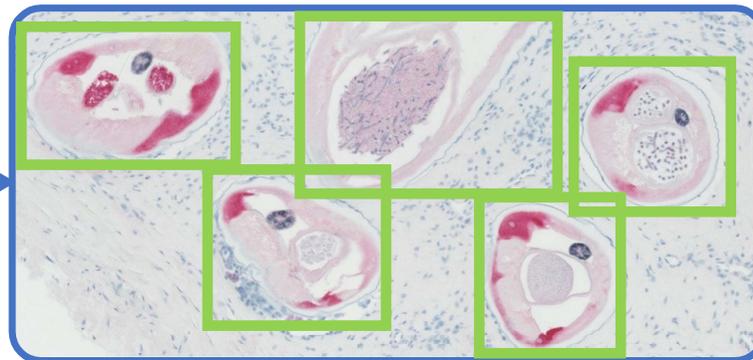
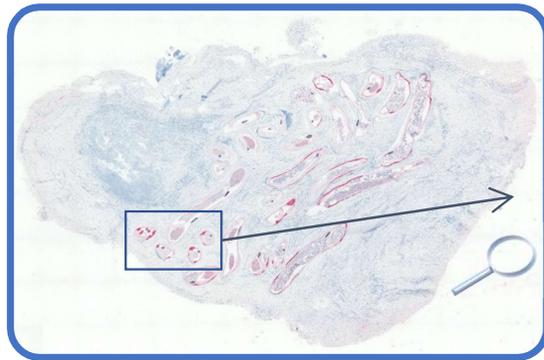
- Evaluation of treatment effect on adult worms by histological analysis of nodules (onchocercomata)
 - Time consuming process
 - Very few experts in reading the nodules
 - Two expert readers needed to assess clinical trial outcomes
- Development of an artificial intelligence (AI) tool that can be used for registration of new drugs
 - Using deep learning
 - Standardization - Less dependent on human assessors which may have a different background in nodule reading
 - Faster than manual analysis



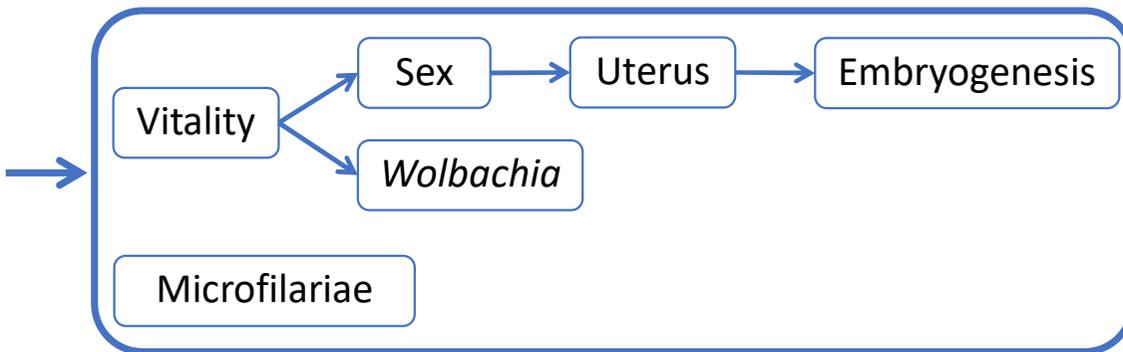
Input: Image of nodule section

Worm section detection & crops

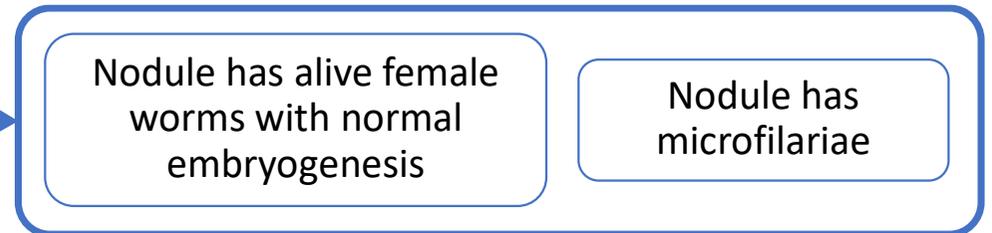
Cut worm sections & crops



Classification models



Output: joint result for the whole nodule, based on results of individual sections



In collaboration with:



- **Title:** “A clinical phase IIa randomized, ascending dose, placebo-controlled, assessor-blind, safety, tolerability and efficacy study of orally administered moxidectin in subjects with microfilaraemic *Loa loa* infection (LoloMox)”
- **Objectives:**
 - Determination of the safety and tolerability of single dose 8 mg moxidectin (MOX) in subjects infected with *L. loa* compared to ivermectin (IVM)
 - Comparison of the reduction of *L. loa* microfilarial density (MFD) after single dose MOX therapy to the reduction after single dose IVM or placebo
- **Treatment regimen** (depending on MF/ml):
 - Moxidectin 4mg
 - Moxidectin 8mg
 - Ivermectin 150 µg/kg
 - Placebo

RESEARCH ARTICLE

A randomized, open-label study of the tolerability and efficacy of one or three daily doses of ivermectin plus diethylcarbamazine and albendazole (IDA) versus one dose of ivermectin plus albendazole (IA) for treatment of onchocerciasis

Nicholas O. Opoku¹, Felix Doe², Bettina Dubben³, Nicole Fetcho⁴, Kerstin Fischer⁴, Peter U. Fischer⁴, Shelter Gordor¹, Charles W. Goss⁵, Michael E. Gyasi⁶, Achim Hoerauf³, Augustine R. Hong⁷, Eric Kanza^{1,8}, Christopher L. King⁹, Ruth Laryea¹, Daphne Lew⁵, Mahmood A. Seidu¹⁰, Gary J. Weil^{4*}

Table 5. Analysis of the effects of treatment on adult female *O. volvulus* worms adjusted for intraclass correlations for viability and fertility for multiple worms assessed within individual study participants.

| Outcome | Treatment comparison | Odds ratio (95% CI) | Adjusted P-value |
|-----------------------------------|-----------------------|---------------------|------------------|
| Fertile female <i>O. volvulus</i> | IA vs IDA1 | 1.66 (0.85–3.21) | 0.134 |
| | IA vs IDA3 | 2.23 (1.12, 4.44) | 0.023 |
| | IA vs both IDA groups | 1.91 (1.09, 3.34) | 0.023 |
| | IDA1 vs IDA3 | 1.32 (0.64, 2.85) | 0.430 |
| Living female <i>O. volvulus</i> | IA vs IDA1 | 1.41 (0.84, 2.38) | 0.192 |
| | IA vs IDA3 | 1.45 (0.92, 2.29) | 0.107 |
| | IA vs Both IDA groups | 1.44 (0.97, 2.15) | 0.068 |
| | IDA1 vs IDA3 | 1.03 (0.59, 1.79) | 0.918 |

* Mixed-effects logistic regression models were conducted in SAS using PROC GLIMMIX. Participant level random effects were included in the model to adjust for multiple worms/person.

<https://doi.org/10.1371/journal.pntd.0011365.t005>

Table 4. Nodule and adult worm data by treatment group*.

| | IA | IDA1 | IDA3 | Total |
|--|------------|------------|------------|-------|
| Total number of female worms | 198 | 274 | 300 | 772 |
| Median (IQR) female worms per participant | 4 (2,7) | 5 (2,9) | 5 (3,9) | |
| Number of living female worms (%) | 127 (64.1) | 142 (51.8) | 159 (53) | 428 |
| Number of worms evaluated for fertility*** | 180 | 261 | 281 | 722 |
| Number of fertile female worms* (%) | 41 (22.8%) | 40 (15.3%) | 34 (12.1%) | 115 |
| Number of male worms | 43 | 53 | 49 | 145 |

Acknowledgements



Achim Hoerauf
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 Cilla Riese
 Sonja Hauke
 Franziska Lenz-Plet
 Franziska Fuellmann
 and the whole team



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 Abdallah Nyenga
 Winfrida John
 and the whole team



Inge Kroidl
 Sacha Horn



Samuel Wanji
 Abdel Jelil Njouendou
 Ndzheshang Bertrand
 Fru Cho Jerome
 and the whole team



Peter Fischer
 Kerstin Fischer



Mark Taylor
 Steve Ward

Tropical Projects
 John Horton



Jonathan King



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 Ivan Scandale
 Virginie Pillet
 Karen Dequatre Cheeseman



Eric Ottesen
 Sarah Sullivan
 Charles Mackenzie



Michael Ramharter
 Tamara Nordmann
 Lidwine Badjina



Ghyslain Mombo-Ngoma



Matthias Schmid
 Waldemar Spitz



Daniel Kuehlwein
 Marcel Bergmann
 Wojciech Konieczkovicz
 Tim Hable
 Rick Kollenbroich
 Julia Poplawska



CorA team