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# Striving to eliminate lymphatic filariasis and onchocerciasis



A *Wuchereria bancrofti* worm; responsible for lymphatic filariasis.  
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Around the world millions of people suffer from lymphatic filariasis and onchocerciasis. Despite years of research, and some improvements, more effective treatments are still required. Professor Drs Marc Hübner and Achim Hoerauf of the University Hospital Bonn, outline the difficulties that remain.



**Professor Dr Marc P Hübner**  
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Professor Dr Marc Hübner's research primarily covers the identification and preclinical testing of new therapies against parasitic helminths, which is done in close collaboration with partners from industry and non-profit organisations. His lab studies protective immune responses against filariae, impact of filarial infections on non-communicable diseases such as type 2 diabetes, and conducts studies with filariasis patients with partners in Cameroon.



**Professor Dr Achim Hoerauf**  
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Professor Dr Achim Hoerauf is internationally renowned for his work in tropical medicine, specifically, for pioneering a new drug treatment for filariasis. The new treatment exploits the symbiosis between the filarial nematodes and bacterial endosymbionts called *Wolbachia*, which are susceptible to some classes of antibiotic. The feasibility of delivering a safe macrofilaricidal drug has sparked the development of macrofilaricidal research programmes by the Gates Foundation and DNDi.

Despite years of research and directives from the World Health Organization, lymphatic filariasis (LF – most commonly presented as elephantiasis) and onchocerciasis (usually known as river blindness) continue to blight the lives of millions of people in tropic and subtropic regions. While improvements have been seen in LF, effective treatments for onchocerciasis remain stubbornly elusive and require further funding and targeted research.

Here Professor Dr Marc Hübner and Professor Dr Achim Hoerauf, of the Institute of Medical Microbiology, Immunology and Parasitology at University Hospital Bonn, discuss the history of the fight against these two diseases and detail what more needs to be done to bring them under close control, alleviating the suffering of millions.





Elephantiasis of the leg due to lymphatic filariasis. Luzon, Philippines.

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Yemen and at the border of Brazil and Venezuela. Both of these infections are vector-borne and the vectors transmit the infective L3 larvae during blood feeding which, upon entering the human host, migrate through the body and undergo further development into adult worms by moulting. The adult worms reside either in the lymphatics (LF) or in subcutaneous nodules (onchocerciasis). Finally, their progeny, first-stage larvae known as microfilariae (Mf), are released into the surrounding tissues and vessels from where they can be taken up by the vectors, thus perpetuating the life cycle.

Vector control has proved to be an important tool to reduce the spread of filarial infections in tackling these diseases. No vaccine is available despite decades of research, but in the case of onchocerciasis, a vaccine based on recombinant antigens developed by The Onchocerciasis Vaccine for Africa (TOVA) consortium will hopefully enter clinical testing in the near future.

### The long and winding road

Although lymphatic filariasis (LF) and onchocerciasis have been targeted for global elimination, these infections caused by parasitic worms are still a major public health problem across the tropics and subtropics. They are included in the World Health Organization's (WHO) list of neglected tropical diseases and were responsible for around 51.4 million lymphatic filariasis (LF) and 21 million onchocerciasis infections as of 2018 and 2017, respectively. Although the LF figure represents a 74% decline since 2000, decades of research, and a long history of campaigns to control and eliminate filarial infections, these diseases remain of public health importance in the tropics and subtropics; treatment options remain limited and drugs that completely clear the infections, and can be used on a large scale, are still unavailable.

LF can be transmitted by four different parasite mosquito species in Africa, India and a number of regions in Southeast Asia, whilst onchocerciasis is transmitted by parasitic blackflies and is endemic mostly in sub-Saharan Africa, with small foci in



Onchocerciasis patient: Nodule containing the adult filiriae. Image © Prof. Dr. Achim Hoerauf/ University of Bonn.

Onchocerciasis patient: skin pathology (sowda).  
Image © Prof. Dr. Achim Hoerauf/ University of Bonn.



LF may manifest in a variety of clinical symptoms, the most well-known being elephantiasis, and filarial lymphedema clusters in families, appearing to have a genetic disposition. It is initially dependent on the presence of adult worms in the lymphatics which induce the release of vascular endothelial growth factors causing dilation of lymphatic vessels and impairing the flow of the host's lymph fluid.

By contrast, *Onchocerca volvulus* adult worms reside in subcutaneous nodules, also known as onchocercomata, while their Mf migrate through the skin and may invade the eye. The killing of Mf, either through drugs or naturally via the host's immune response, may lead to a rapid release of filarial and bacterial antigens, which in turn can cause severe inflammatory responses and lead to keratitis, chorioretinitis, optic atrophy, and neuritis, and over time, to vision loss (river blindness) or dermatitis depending on the location of the dying Mf.

Onchocerciasis patient: Nodule containing the adult filiriae.  
Image © Prof. Dr. Achim Hoerauf/ University of Bonn.

### Progress... to an extent

Over the last two decades, the WHO has seen significant progress in the development of novel treatment strategies for human filarial infections, particularly with LF, and a mass drug administration (MDA) with ivermectin (IVM), diethylcarbamazine citrate (DEC), and albendazole (ALB) – together known as IDA – has consistently demonstrated a higher efficacy than monotherapies and a safe profile for the disease.



However, IDA bears safety concerns in onchocerciasis and loiasis patients and is not significantly reducing the fertile viable adult worms in onchocerciasis. Thus, treatment options for onchocerciasis remain limited and macrofilaricidal therapies are still unavailable for MDA. The preclinical and clinical developmental pipeline contains only a few novel treatment options and recent setbacks of two promising candidates have again highlighted the high attrition rate of (pre)clinical development.

As such, it is imperative that the filarial community continues to improve the preclinical phase with novel technologies and the identification of new treatment options. In addition, close co-operation of academia, pharmaceutical companies, NGOs, and local stakeholders will be essential to develop, produce, and adopt novel treatment strategies to eliminate human filarial infections.

### Challenges in drug development – the example of onchocerciasis

Public health initiatives by the WHO, national governments, and international consortia have contributed to a tremendous reduction in the overall disease burden of onchocerciasis and LF on a population level. However, despite decades of research, the availability of curative therapeutic options remains low as DEC, IVM, and ALB continue to be the drugs of choice for filarial diseases.

Despite the recent success of the IDA triple therapy for LF, the application of this new treatment regimen remains limited to countries that are not co-endemic for onchocerciasis or loiasis. Therefore, as the focus shifts from overall reduction of the disease burden to elimination of filarial infections on a regional level, the limitations of the currently available drugs will be exacerbated.

Adult Black Fly (*Simulium yahense*) with (*Onchocerca volvulus*) emerging from the insect's antenna. The parasite is responsible for the disease known as River Blindness in Africa. Sample was chemically fixed and critical point dried, then observed using conventional scanning electron microscopy.

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The development and, importantly, the production and distribution of macrofilaricidal drugs may help to close the gaps in coverage of the currently available treatment options. Currently, doxycycline is the only well-tolerated macrofilaricidal treatment available for onchocerciasis and LF, and its use was incorporated into elimination strategies to specifically treat Mf-positive people in areas where transmission has been largely interrupted in Venezuela and Brazil. However, daily doxycycline treatment for four or six weeks – and the contra-indication for pregnant and breast-feeding women as well as children below the age of eight years – hampers the broader implementation of doxycycline to achieve the elimination of LF and onchocerciasis in sub-Saharan Africa and confines its use to individual therapy. Thus, the WHO highlighted the need for new macrofilaricidal treatments.

While a number of candidates are at various stages of clinical trials, two highly promising candidates were terminated in 2023 due to a lack of efficacy in onchocerciasis patients and safety issues in healthy volunteers, providing clear reminders that drugs often fail at this development stage with an estimated failure rate of up to 80%. In filarial diseases, the indirect mode of action (anti-*Wolbachia*) may be preferred due to its low risk of parasite-related adverse events (reaction to the Mf) or slow killing of adult worms. However, the two promising candidates failed due to toxicity in one and a lack of efficacy in the other, so that only doxycycline remains as a proven and used anti-wolbachial treatment of filariasis. By contrast, direct-acting drugs have been successfully in use for decades in the veterinary field, and the two remaining direct-acting candidates, emodepside and oxfendazole, currently undergoing Phase 2 trials are originally veterinary drugs and appear safe to date. Therefore, host toxicity rather than effectiveness against the parasite may be the major limitation. Ultimately, toxicity and disease-specific issues are tightly linked through the safety margin of a drug candidate in humans.

Importantly, both drug candidates, oxfendazole and emodepside, are pan-nematode drugs, i.e. they are expected to be effective against intestinal worms as well as tissue-dwelling filariae. Moreover, oxfendazole is a promising macrofilaricidal drug candidate for loiasis, which cannot be treated by doxycycline, as it does not have the endosymbiotic *Wolbachia* bacteria. Thus, oxfendazole is currently tested by the eWHORM consortium against three filarial diseases, onchocerciasis, loiasis and mansoniellosis as well as the human whipworm *Trichuris trichiura* in four African countries. The only “novel” candidate is the anti-*Wolbachia* compound Corallopyronin A, which is in preparation for phase 1 clinical trials and based on animal model results expected to shorten the treatment time to 14 days and to provide a prominent macrofilaricidal effect. Of note, Corallopyronin A was also shown to be effective against resistant *Staphylococcus aureus*, as well as *Neisseria gonorrhoeae* and *Chlamydia*.

Thus, there is a clear need to continue drug pipelines and improve preclinical research and development of novel macrofilaricidal drugs to account for the high attrition rates in preclinical and clinical development of drugs. The recent challenges in the clinical trials of the failed candidates present an excellent opportunity to revisit the preclinical data and extract valuable insights. By keeping the research active, we can leverage innovative methods, enhance our understanding of parasitic infections, and reduce the risk of similar setbacks in the future.

One particular field that has so far been underutilised in filarial research is the organoid and organ-on-a-chip technologies. However, both technologies are advancing rapidly and may drastically change the preclinical phase of drug development. Even though the size of filariae and chronic nature of filarial infections pose challenges for the incorporation of *in vitro* organ/ organoid technologies, it is clear in the face of the high attrition rate of clinical and preclinical development that any potential

improvement of the developmental pipeline is worth pursuing. One such improvement could be the implementation of artificial intelligence (AI)-based drug discovery and pharmacokinetic modelling.

## Considerations for the future of filarial disease elimination

Developing a drug from initial screening (discovery) to the bedside (access) is a long, risky, and complicated process that no single research group can manage alone. Funding needs are enormous but have been provided so far by the Gates Foundation, EDCTP, The German Ministry for Research and Technology (formerly BMBF, now BMFTR), and GHIT Fund, to name a few. It is essential that fundings are maintained to ensure that the progress in elimination made so far is kept and the goal of elimination is reached. While a number of candidates initially developed for filarial infections either by single entities or in partnerships were discontinued or put on hold due to lack of prioritisation within a global health environment, recent setbacks have highlighted why a reliance on a limited number of compounds may seem fiscally sound in the short term, but can be counter-productive in the face of the high attrition rates associated with the development process. It is clear that a small number of candidates limits the effectiveness of such a process, and preclinical development of new drug candidates or combinations of existing drugs needs to continue in order to find and apply new macrofilaricidal treatments in a timely manner.

One important gap for both existing treatments and newly developed drugs is the absence of formulations appropriate for use in young children. This requires not only the determination of safety or efficacy of a given treatment in clinical trials, but also the development of age-appropriate formulations. Children process drugs differently, often requiring different dosages but also specific

formulations with improved texture, taste, and size, which is crucial for the treatment's effectiveness. Moxidectin, for example, is only registered for use in children over 12 years old. However, safety and pharmacokinetic (PK) studies for moxidectin in children below the age of 12 have been completed, supporting development of a paediatric formulation of moxidectin. As MDA programmes transition towards the elimination of diseases, a high or near universal coverage (including children) becomes essential to prevent resurgence once MDA has been discontinued.

The launch of the new Global Onchocerciasis Network for Elimination (GONE) in 2023 and recent pledge of \$777m (~£574m) at the 2023 meeting of the Reaching the Last Mile (RLM) Forum held during the United Nations Climate Change Conference in 2023 may help to overcome some of the financial limitations that have plagued the development of new macrofilaricidal compounds. However, even if the available amount of money increases, it is important that we as a community use the available funds effectively.

Establishing and maintaining partnerships between researchers, pharmaceutical companies, non-governmental organisations (NGOs), funders, local stakeholders, and patients is essential to facilitate the effective development, production, distribution, and uptake of a newly developed compound or treatment strategy.

[The long and winding road towards new treatments against lymphatic filariasis and onchocerciasis.](#)

[Corallopyronin A for short-course anti-wolbachial, macrofilaricidal treatment of filarial infections.](#)

[Oxfendazole mediates macrofilaricidal efficacy against the filarial nematode \*Litomosoides sigmodontis\* in vivo and inhibits \*Onchocerca spec.\* motility in vitro.](#)