Novel treatments offer hope for neglected tropical diseases

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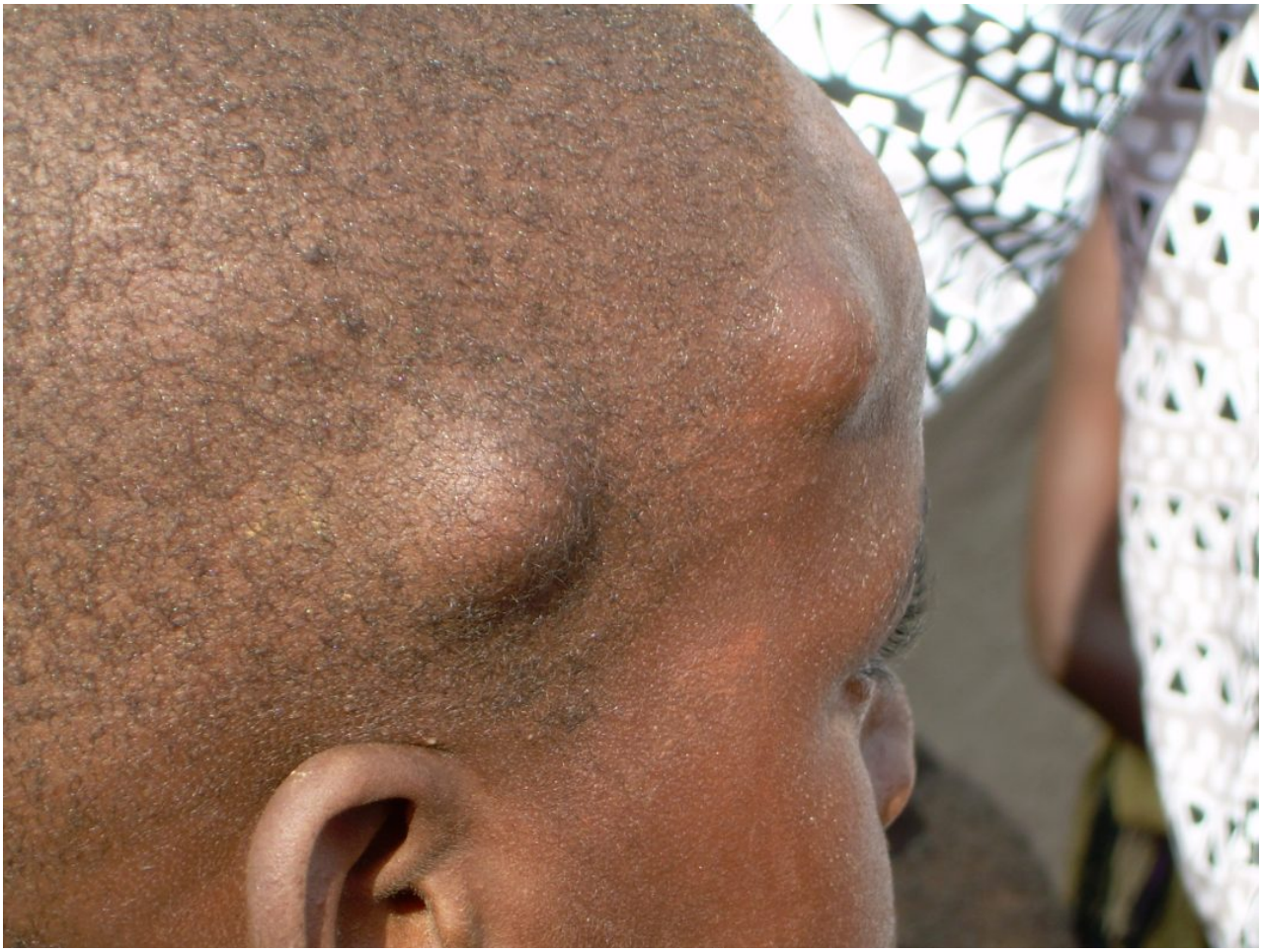

Worm nodules containing Onchocerca volvulus, the filarial species causing river blindness if not treated, on the head of a 5 year-old boy Image: © Achim Hoerauf

Researchers at the Institute of Medical Microbiology, Immunology and Parasitology (IMMIP) at the University of Bonn are pioneering innovative treatment strategies for neglected tropical diseases that hold promise for more effective and sustainable solutions.

This interview with Professors Achim Hoerauf and Marc Hübner explores their groundbreaking work, focusing on the development of novel drugs and the importance of collaborative partnerships in tackling these devastating diseases

Neglected tropical diseases (NTDs) affect millions worldwide. Parasitic diseases caused by filarial worms can lead to debilitating conditions, including blindness, skin disfigurement, and lymphedema. While current mass drug treatments offer some relief,

they primarily target the larval stage of the parasite, requiring repeated administration over many years and failing to address the adult worms responsible for long-term pathology.

The quest for effective treatments

Why research neglected tropical diseases, particularly onchocerciasis and lymphatic filariasis?

Professor Hoerauf's research initially focused on the immune response to filarial worms, with the goal of vaccine development. However, the sheer number of parasite antigens proved a major obstacle. This challenge led to a crucial shift in research direction: the discovery of the essential role of Wolbachia, bacterial endosymbionts, within the filarial worms.

This breakthrough led to the development of doxycycline treatment, which targets these endosymbionts, effectively sterilising and slowly killing the adult worms. Although a significant advance, the 4-6-week treatment duration spurred the search for more efficient alternatives. "We started doing a lot of other work trying to find second-generation antibiotics," explains Professor Hoerauf, "and anti helmintics that do that job in a much shorter time."

Professor Hübner's interest in parasitology began with a fascination for the immunomodulation parasites employ. He explains how these parasites, especially helminths, can suppress the host's immune system to survive. His initial research explored the impact of helminth infections on sepsis, demonstrating a protective effect.

This work expanded to investigate the influence of these infections on other conditions, such as type 1 diabetes and even diet-induced obesity, where similar immunomodulatory benefits were observed. "Subsequently, we continued to investigate this in humans," Professor Hübner notes, referring to a clinical trial in Cameroon examining the effect of filarial infections on diabetes development. However, he also points out that especially those infected individuals where this immunomodulation is not successful develop pathology, prompting him to explore new drug candidates that target the adult worms directly. "And so in 2014, I began identifying new drug candidates," he explains, "since, as was previously mentioned, we do not have drugs that can kill the adult worms with a short-term treatment."

Rivers like this one harbor breeding sites for the vector Simulium damnosum. Image: © Achim Hoerauf

Summarising current treatment options available for filarial diseases and the major limitations of existing therapies

Current treatment for onchocerciasis and lymphatic filariasis primarily relies on mass drug administration (MDA) of medications like ivermectin, diethylcarbamazine and albendazole. While these drugs temporarily reduce the larval stages of the parasite (microfilariae), reducing transmission and alleviating some symptoms, they fail to eliminate the adult worms, which can survive for over a decade within the human host. “In principle, you would have to make sure that during the whole lifetime of the worm, you give the drugs in order to wipe out the disease,” Professor Hoerauf emphasises. This necessity for repeated, long-term treatment poses a significant logistical challenge, especially in remote and resource-limited settings. Furthermore, these MDA administrations are ineffective against other filarial diseases, such as loiasis and mansonellosis.

Professor Hübner points out that these diseases, while not currently classified as neglected tropical diseases by the WHO, still impact millions and can cause significant morbidity. He also highlights a critical safety concern: “If patients have a very high microfilarial load of Loa loa, diethylcarbamazine and ivermectin can, by quickly killing microfilariae, induce encephalitis.”

This risk of severe, even fatal, reactions in co-infected individuals makes MDA administration complex and requires careful consideration of local disease prevalence.

Innovative treatment strategies

Can you explain one or two of the most promising approaches being investigated in your lab and what makes them unique?

The IMMIP research team is pursuing several promising avenues for novel treatments. One approach focuses on developing second-generation antibiotics that target the Wolbachia endosymbionts with improved efficacy and shorter treatment durations. Professor Hoerauf discussed the challenges of drug development, emphasising the high attrition rate and the need for long-term funding commitments. He highlights the potential of Corallopyronin A, a new drug candidate currently in development for first in human studies with promising pharmacokinetic properties.

Another strategy involves repurposing existing veterinary drugs for human use. Professor Hübner explains that several drugs used for decades in animals have shown efficacy against filarial worms in preclinical models. These drugs, having already undergone extensive safety testing in animals, offer a potential shortcut to human trials. Emodepside and oxfendazole are two such candidates currently being investigated in human filariasis patients. “Within our eWHORM consortium, an EDCTP3 EU project, we investigate oxfendazole as a pan-nematode drug candidate against three different filarial and one soil-transmitted helminth species,” says Professor Hübner. Using an adaptive, innovative clinical trial design the drug is tested against multiple diseases, potentially accelerating the development process and reducing costs.

Challenges and collaborations

What are the biggest challenges you face in translating these new treatment approaches?

Translating promising research into effective treatments faces significant hurdles.

Professor Hoerauf points to the high attrition rate in drug development as a major challenge. “Out of these 500,000,” he explains, referring to the initial number of compounds screened in vitro, “if five, a handful, would make it into clinical trials and one to the market, we would see it as a big success.” This high failure rate demands sustained funding and long-term commitment from both researchers and funders. “If you have a funding agency that gives you just a pop-up three-year project,” he cautions, “it will never work.” Securing funding for Phase III clinical trials, which are particularly expensive, is another significant obstacle. “Phase 3 incurs massive costs,” Professor Hoerauf notes, “due to the large number of patients, along with all the regulatory issues regarding drug procurement and so forth.” Navigating the intricate regulatory landscape adds further difficulty.

Professor Hoerauf stresses the need for innovative funding mechanisms, such as Priority Review Vouchers, to incentivise pharmaceutical companies to invest in NTD drug development. “This is a very attractive pull mechanism, but it is only to be used for really a new chemical entity.”

Discussing the importance of interdisciplinary collaborations and partnerships in research programmes Collaboration is fundamental to advancing NTD research and building sustainable solutions. Professor Hübner emphasizes the importance of interdisciplinary teams, bringing together diverse expertise. “You need a lot of expertise and different expertise. It’s not enough to have some parasitologists,” he explains. These collaborations started with the colleagues of the Liverpool School of Tropical Medicine and extend to industry partners, who provide crucial expertise in drug development and “allow us to use their drug libraries,” says Professor Hübner.

Critically, collaboration with African research institutions is essential for building capacity and fostering long-term sustainability in endemic countries. Professor Hübner notes that this investment in local expertise is vital for tackling these complex challenges.

Finally, the support of organisations like DNDi, the Gates Foundation, and the German Center for Infection Research (DZIF) provides essential funding and expertise, further enabling researchers to advance the field.

The Future of Filarial Disease Treatment

In the future, how do you envision the future of filarial disease treatments?

Professor Hübner anticipates a shift from mass drug administration (MDA) to individual treatment approaches as disease prevalence decreases. “So just due to the fact that we’ll have less and less patients, and then also from the cost-benefit, it just makes sense to do the individual treatment”, he explains. Hübner envisions new drugs that not only prevent transmission but also clear existing infections, offering the potential for true elimination. “And we may also have then a pan-nematode drug…that does not only clear filarial infections, but also soil-transmitted helminth infections,” he adds.

Professor Hoerauf stresses the potential impact of changing global health funding priorities, particularly regarding USAID. However, the success is fragile and depends on continued international support, as even short interruptions in control measures can reverse the progress made over the past decades. He suggests that a shift towards national health insurance schemes in endemic countries could create a more sustainable model for providing access to curative treatments. He emphases the importance of adhering to the UN Sustainable Development Goals, which commit nations to ensuring health coverage for all their citizens: “This is part of the UN Sustainable Development Goals. If you read 3.8, that no one should be left behind with regard to health coverage, all the countries that have signed the UN Charter actually signed that they take responsibility for their populations to get the drugs needed.”

Conclusion

The research being conducted at IMMIP offers a beacon of hope for millions affected by neglected tropical diseases. The development of novel treatments targeting the adult filarial worms, combined with innovative clinical trial designs and strong collaborative partnerships, is paving the way for more effective and sustainable solutions. While challenges remain, the dedication and expertise of researchers like Professors Hoerauf and Hübner, along with the support of funders and partners, are driving progress towards a future free from the burden of these debilitating diseases.

The Corallopyronin A team, led by Prof. Dr. Achim Hörauf, has succeeded in acquiring funding for the further preclinical development of the antibiotic corallopyronin A. In partnership with the Japanese pharmaceutical company Eisai, the Helmholtz Centre for Infection Research Braunschweig/Saarbrücken and the University of Bonn, the team has put together a research program to successfully take corallopyronin A into clinical phase 1.

Please have a look at the links below :

- https://www.ghitfund.org/newsroom/press/detail/433/en
- https://www.dzif.de/en/new-antibiotic-against-river-blindness-and-lymphatic-filariasis-pathogens
- https://www.uni-bonn.de/de/neues/neues-antibiotikum-gegen-erreger-der-flussblindheit-und-lymphatischen-filariose
- https://idw-online.de/de/image392518

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