

HOW **VIRTUAL R&D** IS LEADING TO TREATMENTS FOR NEGLECTED DISEASES

Dr Eric Chatelain,
from the Drugs for Neglected Diseases initiative,
Geneva, Switzerland,
spoke at PSWC

Eric Chatelain reports on drug development efforts to combat neglected tropical diseases such as sleeping sickness

Two children receiving the improved treatment NECT for HAT in Banda, Oriental Province, DRC



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Neglected tropical diseases (NTDs),¹ which primarily affect those living in developing countries, lie outside the world pharmaceuticals market and cause substantial economic burden.² They are among the 10 leading causes of life-years lost to disability and premature death.³ Moreover, of the 1,556 new drugs approved between 1975 and 1999, only 21 (1.3%) were specifically developed for NTDs and tuberculosis, even though they account for 11.4% of the global disease burden, demonstrating an urgent need for research and development (R&D).⁴ A more recent analysis showed some improvement in this respect, notably in terms of repurposed or reformulated treatments.⁵ Over a decade ago existing treatments for these diseases lacked efficacy, were toxic or had emerging resistance, were typically not adapted for field use, were not registered in endemic regions and were difficult for patients to access.



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Partnerships to fill the gaps

Product development partnerships (PDPs) first emerged 10 to 15 years ago, with the aim of filling gaps in the R&D pipeline by developing products that were not being developed due to a lack of lucrative market and a lack of prioritisation by governments. The Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development (TB Alliance), the Foundation for Innovative New Diagnostics (FIND) and the Sabin Vaccine Institute, among others, span different diseases and modalities (eg, therapeutics, vaccines, diagnostics). The Drugs for Neglected Diseases initiative (DNDi),⁶ a patient-needs driven, not-for-profit R&D organisation, was created to develop safe, effective, and affordable treatments for patients suffering from human African trypanosomiasis (sometimes called sleeping sickness), visceral leishmaniasis, and Chagas disease, in addition to other neglected diseases. These three diseases are caused by kinetoplastid parasites that are transmitted by the tse-tse fly, the sandfly, and the triatomine, respectively, and affect millions of people. They are typically difficult to diagnose and test for cure after treatment, or, in the case of visceral leishmaniasis and human African trypanosomiasis, fatal if untreated.

With a “virtual model” of R&D, meaning with no laboratories of its own, DNDi sets up strategic partnerships, including drug discovery consortia and clinical trial platforms, with public and private partners worldwide to fulfill its mission.⁷ Projects span from discovery and lead optimisation, pre-clinical and

clinical phases, to implementation and access. It has built the largest R&D portfolio for kinetoplastid diseases, and has delivered six treatments, including two for malaria, with its many partners. To perform clinical trials in disease-endemic countries, disease-specific clinical research platforms comprising the various stakeholders in the region and internationally (eg, clinicians, regulators, national control programmes and non-governmental organisations) were set up and local capacity reinforced through improving infrastructure and training. These platforms play a key role in defining patients’ needs and the target product profiles for new drugs, as well as overcoming the challenges of conducting clinical trials in remote areas at international GCP (Good Clinical Practice) standards.

Prime example

The improved treatment for human African trypanosomiasis is a prime example of the impact such R&D initiatives. Ten years ago, treatments for patients with the advanced stage of the disease were difficult to administer (eflornithine) or toxic (melarsoprol, which kills 5% of all patients treated with it). Nifurtimox-Eflornithine Combination Therapy (NECT),⁸ launched by DNDi and partners in 2009, was the first new treatment for human African trypanosomiasis in decades (eflornithine was approved in 1990, melarsoprol in 1949). Although still not ideal for use in remote areas, it is safer than melarsoprol and as effective as eflornithine monotherapy but with a reduced time in hospital during administration, and is more cost-effective. Furthermore, a new generation of oral treatments is currently in development, with two candidates emerging from separate research strategies. The oxaborole, SCYX-7158, is the first candidate to emerge from DNDi lead optimisation efforts, through partnerships with US biotechnology companies (Anacor Pharmaceuticals and SCYNEXIS) and academic research institutions.⁹ Its favourable pharmacokinetic characteristics give it the potential to become a one-shot oral treatment for both stages of the disease. Fexinidazole, currently being developed in partnership with Sanofi, is a rediscovered new chemical entity currently in Phase II/III clinical trials in the Democratic Republic of Congo and the Central African Republic.¹⁰ It is the result of a compound mining approach.



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Children undergoing screening process for human African trypanosomiasis (HAT) at the village level, Bandundu Province, Democratic Republic of the Congo (DRC)

Urgent need

Although there has been improvement in the R&D landscape over the past decade,⁵ there remains an urgent need for new and field-adapted treatments for NTDs, with some specific challenges:

- R&D Access to chemical diversity, know-how, knowledge, and intellectual property; and data sharing to avoid duplication of research efforts given the limited resources
- Clinical studies Clinical studies in endemic regions, often in remote areas, with recruitment and logistics challenges
- Regulatory Overcoming regulatory hurdles and the need to strengthen regulatory capacities in endemic countries (harmonisation for rapid registration in endemic regions)
- Access Equitable access and affordable treatment for all patients; pharmacovigilance.

Sustainable funding

The fragmented NTD R&D landscape a decade ago should currently be conceived within a global framework under the leadership of the World Health Organisation, and including pharmaceutical (both originator and generic) and

biotechnology companies, governments, notably those of endemic countries, academia, PDPs, non-governmental organisations and donors.

DNDi and other initiatives have demonstrated that innovative and collaborative models can work, and that it is indeed possible to make a difference for neglected patients.

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