

Filarial disease, Ghana
A medical team visits a village in Kumasi, Ghana, to assess the needs of patients with lymphatic filariasis (elephantiasis).

DEVELOPING NEW TREATMENTS FOR DEBILITATING INFECTIONS

DND*i* aims to develop improved treatments for the millions of people worldwide that suffer from filarial diseases: **lymphatic filariasis** (elephantiasis) and **onchocerciasis** (river blindness). Although current treatments for these debilitating and stigmatizing illnesses help to prevent infection, health tools that rapidly cure patients are lacking.

What are filarial diseases?

Filarial diseases are caused by parasitic worms of the helminth family. While rarely fatal, these diseases affect millions of people and inflict immense hardship. Onchocerciasis is the world's second leading infectious cause of blindness and has a host of other symptoms, including skin discoloration and intense itching. The disease is contracted through the bite of an infected female blackfly. *Lymphatic filariasis* is the second cause of chronic disability worldwide and is transmitted to humans by mosquitoes. It may lead to lymphoedema (massive swelling, principally of the legs and genitals), elephantiasis (the late disfiguring stage), and hydrocele (fluid accumulation in the testes). Together, these two diseases are responsible for considerable financial and social burden on people already living in deep poverty.

Addressing R&D gaps in existing treatments

Large-scale programmes for the control of filarial diseases have been in place for over twenty years, based on the mass drug administration (MDA) of medicines donated by the pharmaceutical industry. These programmes have been successful in reducing transmission but significant R&D gaps remain. MDA programmes use microfilaricidal drugs that kill juvenile worms (microfilariae) but leave adult worms (macrofilariae) alive in the body for up to 15 years. Therefore, MDA needs to be repeated for a number of years until the adult worms naturally die out. Evidence also shows that current treatments for filarial diseases can cause neurological damage or even death for those also infected with *Loa loa* by causing sudden, massive death of juvenile *Loa loa* worms.

A safe, short-course drug that can kill adult filarial worms is therefore needed. This macrofilaricidal drug could be an essential tool for health workers in rural areas and also greatly shorten the length of MDA programmes, thus contributing to the WHO goals of eliminating lymphatic filariasis (defined as 70% of countries free of disease and 30% engaged in post-surveillance activities) and controlling onchocerciasis by 2020. New treatments are also essential for areas where *Loa loa* and other filarial diseases are co-endemic, to enable the safe treatment of co-infected patients.

DND*i* aims to register a new drug as a short course, oral macrofilaricide with potential application to treat both onchocerciasis and lymphatic filariasis, and has a two-fold strategy in place. As part of its medium term strategy DND*i* will focus on repurposing candidates used for other indications in the pharmaceutical and the animal health industries, such as emodepside, a potent drug used in veterinary medicine, which will be developed for patient use with Bayer HealthCare. The second strategy is based on partnering with other discovery initiatives on developing compounds identified from DND*i*'s screening campaign. In 2014, DND*i* began putting in place a clinical research platform for filarial diseases by expanding its existing network of partners and other platforms (see p. 50).

Without R&D for better treatments, filarial diseases will continue to exact a terrible burden on the most neglected patients.

37 million people infected with onchocerciasis

worldwide, with 99% cases in 31 African countries, and 169 million at risk

Over 120 million people infected with lymphatic filariasis glabally,

with about 40 million disfigured or incapacitated; more than 1.4 billion people in 73 countries at risk of infection

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments for onchocerciasis and lymphatic filariasis are based on repeated mass drug administration (MDA) of antiparasitic drugs through programmes directed by the WHO. WHO recommends MDA for onchocerciasis at least once yearly for 10-15 years, and for lymphatic filariasis once yearly for at least five years. The drugs used in MDA programmes are **ivermectin** for onchocerciasis; and for lymphatic filariasis, **albendazole** plus either **ivermectin** in areas where onchocerciasis is also endemic (*i.e.* African countries), or **diethylcarbamazine** (DEC) in areas where onchocerciasis is not co-endemic (*i.e.* non-African countries).

By killing microfilariae, and inducing a temporary sterilization of adult worms, MDA drugs can prevent vector-borne transmission for several months, until the adult worms produce more microfilariae larvae. However, because adult worms continue to live in the body, they eventually produce new microfilariae, often before the next MDA, thus requiring repeated MDAs for several years to decades until the adult worms die naturally.

Ivermectin is safe and has been used widely as a monotherapy in MDA programmes for onchocerciasis, killing the microfilarial stage of the parasite. However, in lymphatic filariasis and onchocerciasis patients co-infected with *Loa loa*, the sudden death of large numbers of *Loa loa* microfilariae following treatment can lead to serious adverse events, such as encephalopathy, possibly resulting in permanent brain damage and death. Furthermore, reports of a suboptimal response to ivermectin by *O. volvulus* may be a sign of developing resistance.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

DND*i*'s strategy is to develop a new compound with macrofilaricide activity for use as a safe and field-adapted macrofilaricidal drug for patient case management and possibly later MDA if needed. As a **medium-term strategy**, DND*i* is assessing emodepside, a potent antihelminthic drug used in combination with praziquantel to treat parasitic worms in cats and dogs, as a clinical candidate to treat humans.

As a **long-term strategy**, DND*i* is assessing additional opportunities through an active screening programme of drug compounds emanating from animal health/pharmaceutical companies and academic institutions, with the goal of selecting one or two candidates to move into clinical development.

Ideally a new treatment for adults and children will be a macrofilaricide (efficacious against the adult form of worms), oral, short-course treatment, well tolerated, affordable, and adapted to tropical climates.