EDCTP - NID Stakeholder meeting

Den Haag, 27 June 2013

Achim Hoerauf

Chair and Head,
Institute of Med. Microbiology, Immunology and Parasitology
University Bonn Medical Center
NIDs are a problem for those left behind

Intolerable burden => WHO roadmap and London declaration 2012
Additional US$2 billion is needed by 2015 to prevent and treat more than 1 billion people at risk of contracting NTDs.
Uniting to combat Neglected Tropical Diseases
Ending the neglect and reaching 2020 goals

January 30 2012
On January 30 2012, 22 partners committed to

- Sustaining and expanding programmes to help eradicate Guinea worm, eliminate 5 NTDs and control 5 NTDs by 2020.
- Advancing R&D
- Enhancing collaboration and coordination
- Supporting implementation in endemic countries
- Enhancing technical support for M&E
- Providing regular updates on progress
$784 million committed for research and programme activities

January 30 2012
Inclusion of NIDs in EDCTP 2 is an important step!

Apparently there are only three diseases on that planet!
“Harry Potter” Star Joins Global Effort to Eliminate Seven Diseases by 2020

April 13th, 2012 by Heena Patel

British actor Tom Felton, most well known in his role as “Draco Malfoy” in the Harry Potter film series, is casting up a spell to eliminate seven NTDs by 2020. As an ambassador for the END7 campaign, Felton has joined the call to help raise public awareness about these devastating diseases, which affect the lives of 1 in 6 people worldwide.

“I was inspired to support the END7 campaign when I learned how easy it was for young people to get involved,” said Felton. “By donating just a few pence, anyone can help get these treatments to people who need them most and hopefully change the future for the millions of children growing up in developing countries around the world.” Felton is referring to the 50 cents/pence it takes to treat and protect one person against all seven major NTDs for an entire year. Pills to treat these diseases are donated by pharmaceutical companies, which are administered in schools and community centers – making NTD treatment one of most cost-effective public health initiatives available today.

Since the announcement of Felton’s new role as ambassador became public on April 12, his adoring followers have already generated a ton of exposure. Popular fan sites, such as Tom Felton EU and Felt Beats, have already expressed their full support in helping Tom spread the awareness about these diseases of poverty. Great job, Team Felton!

Check out some of Felton’s tweets below:
The health burden by helminths is similar to the „big three“
<table>
<thead>
<tr>
<th>DISEASE NAME</th>
<th>CAUSATIVE AGENT</th>
<th>PREVALENCE</th>
<th>POPULATION AT RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helminth infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soil transmitted helminthiasis</td>
<td>Ascaris lumbricoides, Trichuris trichiura, hookworm</td>
<td>ascariasis: 807 million</td>
<td>ascariasis: 4.2 billion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trichuriasis: 604 million</td>
<td>trichuriasis: 3.2 billion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hookworm: 576 million</td>
<td>hookworm: 3.2 billion</td>
</tr>
<tr>
<td>Schistosomiasis (Bilharzia, snail fever)</td>
<td>Some Schistosoma spp.</td>
<td>207 million</td>
<td>779 million</td>
</tr>
<tr>
<td>Lymphatic filariasis (elephantiasis)</td>
<td>Wuchereria bancrofti, Brugia malayi, B. timori</td>
<td>120 million</td>
<td>1.3 billion</td>
</tr>
<tr>
<td>Cysticercosis</td>
<td>Taenia solium</td>
<td>50 million</td>
<td>Unknown</td>
</tr>
<tr>
<td>Onchocerciasis (river blindness, Robles’ disease)</td>
<td>Onchocerca volvulus</td>
<td>37 million</td>
<td>90 million</td>
</tr>
<tr>
<td>Fascioliasis (Distematitis)</td>
<td>Fasciola hepatica, F. gigantica</td>
<td>2.4 million</td>
<td>180 million</td>
</tr>
<tr>
<td>Dracunculusis (Guinea-worm disease)</td>
<td>Dracunculus medinensis</td>
<td>0.01 million</td>
<td>Unknown</td>
</tr>
<tr>
<td>Echinococcus (Hydatid disease)</td>
<td>Echinococcus granulosus, E. multilocularis, E. vogell, E. oligarthus</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Protozoan infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Lutzomyia, sandfly</td>
<td>12 million</td>
<td>350 million</td>
</tr>
<tr>
<td>Chagas disease (American trypanosomiasis)</td>
<td>Trypanosoma cruzi</td>
<td>8-9 million</td>
<td>25 million</td>
</tr>
<tr>
<td>Sleeping sickness (Human African trypanosomiasis)</td>
<td>Glossina, Trypanosoma brucel gambiens and T b. rhodesien</td>
<td>0.3 million</td>
<td>60 million</td>
</tr>
<tr>
<td><strong>Bacterial infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachoma (granular conjunctivitis, Egyptian ophthamia)</td>
<td>Chlamydia trachomatis</td>
<td>84 million</td>
<td>590 million</td>
</tr>
<tr>
<td>Leprosy (Hansen’s disease)</td>
<td>Mycobacterium leprae</td>
<td>0.4 million</td>
<td>Unknown</td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>Mycobacterium ulcerans</td>
<td>0.05 million</td>
<td>Unknown</td>
</tr>
<tr>
<td>Yaws (Frambesia tropica)</td>
<td>Treponema pallidum</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Viral infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue</td>
<td>Aedes aegypti, Aedes spp.</td>
<td>Unknown; as many as 50 million infected annually</td>
<td>Unknown, but increasing numbers at risk</td>
</tr>
<tr>
<td>Rabies</td>
<td></td>
<td>Unknown; 55,000 deaths annually</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Source: World Health Organization
New drugs against Schistosomiasis

• Praziquantel (PZQ)
  – Lacks activity against juvenile worms
  – Only one large formulation (large tablet, 600 mg), bitter
  – Selection of low-responding parasites in rodents and humans

Efficacy and Safety of Mefloquine, Artesunate, Mefloquine-Artesunate, and Praziquantel against *Schistosoma haematobium*: Randomized, Exploratory Open-Label Trial

Jennifer Keiser,1 Nicaise A. N’Guessan,1 Kofi D. Adoubryn,2 Kigbafori D. Siilué,2,3 Penelope Vounatsou,1,2 Christoph Hatz,1 Jürg Utzinger,1 and Eliézer K. N’Goran4,5

Table 2. Effect of Mefloquine, Artesunate, Mefloquine-Artesunate, and Praziquantel in Schoolchildren Infected with *Schistosoma haematobium*.

<table>
<thead>
<tr>
<th>Characteristic after treatment</th>
<th>Mefloquine (n = 19)</th>
<th>Artesunate (n = 20)</th>
<th>Mefloquine-artesunate (n = 18)</th>
<th>Praziquantel (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with cure</td>
<td>4 (21)</td>
<td>5 (25)</td>
<td>11 (61)</td>
<td>23 (88)</td>
</tr>
<tr>
<td>GM <em>Schistosoma haematobium</em> eggs per 10 mL of urine (range)</td>
<td>7.9 (1–694)</td>
<td>6.2 (1–267)</td>
<td>1.7 (1–73)</td>
<td>1.1 (1–5)</td>
</tr>
</tbody>
</table>
Drug efficacy against STH is species-dependent

Table 1. Summary of Observational and Case Studies Reporting the Use of Single-Dose Oral Albendazole, Mebendazole, Pyrantel Pamoate, and Levamisole Against *Ascaris lumbricoides*, *Trichuris trichiura*, and Hookworm Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parasite</th>
<th>Studies Identified and Included, No.</th>
<th>Individuals, No.</th>
<th>Overall Cure Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albendazole (400 mg)</td>
<td><em>A. lumbricoides</em></td>
<td>65</td>
<td>5126</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td><em>T. trichiura</em></td>
<td>64</td>
<td>5147</td>
<td>43.6</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>64</td>
<td>6334</td>
<td>78.4</td>
</tr>
<tr>
<td>Mebendazole (500 mg)</td>
<td><em>A. lumbricoides</em></td>
<td>12</td>
<td>2036</td>
<td>96.5</td>
</tr>
<tr>
<td></td>
<td><em>T. trichiura</em></td>
<td>12</td>
<td>3112</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>14</td>
<td>3192</td>
<td>22.9</td>
</tr>
<tr>
<td>Pyrantel pamoate (10 mg/kg)</td>
<td><em>A. lumbricoides</em></td>
<td>17</td>
<td>1208</td>
<td>87.9</td>
</tr>
<tr>
<td></td>
<td><em>T. trichiura</em></td>
<td>11</td>
<td>458</td>
<td>28.1</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>21</td>
<td>1208</td>
<td>87.9</td>
</tr>
<tr>
<td>Levamisole (2.5 mg/kg)</td>
<td><em>A. lumbricoides</em></td>
<td>3</td>
<td>202</td>
<td>91.5</td>
</tr>
<tr>
<td></td>
<td><em>T. trichiura</em></td>
<td>2</td>
<td>186</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Hookworm</td>
<td>4</td>
<td>178</td>
<td>38.2</td>
</tr>
</tbody>
</table>

Keiser et al.

Ivermectin co-administration enhances efficacy against *Trichuris*!
Efficacy and safety of mefloquine, artesunate, mefloquine-arteresunate, tribendimidine, and praziquantel in patients with *Opisthorchis viverrini*: a randomised, exploratory, open-label, phase 2 trial

Phonepasong Soukhathammavong, Peter Odermatt, Somphou Sayasone, Youthanavanh Yonghachack, Penelope Younatsou, Christoph Hatz, Kongnap Akkhavong, Jennifer Keiser

**Summary**

**Background** Praziquantel is the only drug available for treatment of *Opisthorchis viverrini*, although in-vivo studies point to activity of mefloquine, artesunate, and tribendimidine against this liver fluke. We aimed to assess the efficacy and safety of these drugs compared with that of praziquantel in patients with *O. viverrini* infection.

**Table 2: Intention-to-treat analysis of prevalence and cure rate of mefloquine, artesunate, mefloquine-arteresunate, tribendimidine, and praziquantel treatment in school children infected with *Opisthorchis viverrini* at follow-up, with Kato-Katz smear technique**

Food-borne trematodes: 750 million people at risk; 40 million people infected
HUMAN FILARIAL NEMATODE DISEASE

Onchocerciasis
‘River Blindness’ &

Lymphatic Filariasis
‘Elephantiasis’

37 million

120 million
The Global Programme to Eliminate Lymphatic Filariasis

Objectives

✓ Interrupt transmission of parasite in endemic countries
✓ Manage morbidity and prevent disability

Achieve objectives by 2020
Lymphatic filariasis:
> 120 Mio. infected

Onchocerciasis (River blindness):
> 37 Mio. infected
Control by drugs in filariasis
Mass Drug Administration (MDA)

- Diethylcarbamazine (DEC)
- Albendazole (ALB)
- Ivermectin (IVM)

- Ivermectin (IVM)
## Global Programme to Eliminate Lymphatic Filariasis: 2012

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of endemic countries</td>
<td>73</td>
</tr>
<tr>
<td>Estimated population at risk</td>
<td>1.4 B</td>
</tr>
<tr>
<td>Number of countries implementing MDA</td>
<td>53</td>
</tr>
<tr>
<td>Number of countries scaling down MDA implementation (Post MDA Surveillance)</td>
<td>12</td>
</tr>
<tr>
<td>Total number of people treated (including 153m children)</td>
<td>538.6m</td>
</tr>
<tr>
<td>Total number of people targeted for treatment</td>
<td>736.9m</td>
</tr>
<tr>
<td>Number of Countries yet to implement MDA</td>
<td>19</td>
</tr>
</tbody>
</table>

3.9 billion doses of medicines were delivered between 2000 and 2011 to a cumulative targeted population of 952 million people.
LF endemic countries not implementing MDA in 2012

AFRICA

- Angola
- Chad
- CAR
- Congo Republic
- DRC
- (South Sudan)
- Equatorial Guinea

AFRICA

- Western Sahara
- Guinea
- Eritrea
- Guinea-Bissau
- Zimbabwe
- Sudan

AFRICA

- Gabon
- Gambia
- Sao Tome and Principe

AFRICA

- New Caledonia
- Palau
- Brunei

16 (84%) are in Africa
Goal: Elimination of LF by 2020!
Some countries have stopped MDA and are in surveillance phase
-> Mf CL <1%,
   CFA <2% [95% CI!] and/or <2% sero-pos in schoolchildren 6y;
   <0.25% mosquito infection rates

But:  - Other countries have not yet started!
   - Evaluation Units sometimes too large and contain too many non-endemic spots -> cave arithmetic elimination of LF!!
An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana


Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study

Mike Y Osei-Atweneboana, Jeffrey K L Eng, Daniel A Boakye, John O Gyapong, Roger K Prichard

Thirty-month follow-up of sub-optimal responders to multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana


Phenotypic Evidence of Emerging Ivermectin Resistance in *Onchocerca volvulus*

Mike Y. Osei-Atweneboana†, Kwablah Awadzi‡, Simon K. Attah*, Daniel A. Boakye‡, John O. Gyapong*, Roger K. Prichard†

March 2011 | Volume 5 | Issue 3 | e998

Evidence for Macro cyclic Lactone Anthelmintic Resistance in *Dirofilaria immitis*

Timothy G. Geary, Catherine Bourguinat, and Roger K. Prichard
Why do we need a macrofilaricide regime NOW?

Key benefits to elimination programmes for LF and onchocerciasis

- Reduce programme timeframes
- Alternative treatment for reduced efficacy or resistance
- Usable in *Loa loa* endemic areas without risk of SAE
- Improved morbidity management
- Endgame mop-up - where elimination is the goal
New drugs
and re-purposing old treatments
Flubendazole

- 1978 discovery by Janssen group (Raemaekers et al, 1978) - Gut worm activity
- Various animal studies
- 1982 used in humans
- 2010-2013 animal studies with an oral formulation
### Table 2. Effect of flubendazole and diethylcarbamazine on adult *Onchocerca volulus* isolated from human nodules.

<table>
<thead>
<tr>
<th>Status of parasites</th>
<th>2 months post-Rx</th>
<th>3 months post-Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEC†</td>
<td>FLUB†</td>
</tr>
<tr>
<td>Degenerated adults</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Intact adult worm</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>Females with empty uteri</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Females with only oocytes</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Reduction in dermal microfilariae†</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

†DEC (100 mg) was administered twice daily for 14 days and 750 mg FLUB was injected intramuscularly once a week for five doses.

‡There was no significant ocular or skin pathology related to microfilarial death in those receiving FLUB. The only significant post-FLUB treatment reactions were associated with inflammation at the injection site. Dermal microfilarial loads stayed at pretreatment levels in the FLUB-treated individuals for approximately 6 months.

DEC: Diethylcarbamazine; FLUB: Flubendazole; Post-RX: After last treatment with flubendazole.

Data taken from [6] and [Mackenzie CD, Martinez-Palomo A. Unpublished Data].
Flubendazole Macrofilaricide (Helminth)

- **Target disease**: Helminth infections
- **Partners**: Johnson & Johnson, USA; Michigan State University, USA; Abbott Laboratories, USA; University of Buea, Cameroon
- **Leadership**: Discovery & Preclinical Director: Rob Don; Project Manager: Ivan Scandale
- **Start date**: April 2011
- **Funding**: Bill & Melinda Gates Foundation, USA; Department for International Development (DFID), UK; Federal Ministry of Education and Research (BMBF through KfW), Germany; Médecins Sans Frontières/Doctors without Borders, International/Norway; Spanish Agency for International Development Cooperation (AECID), Spain; Swiss Agency for Development and Cooperation (SDC), Switzerland

**Objective**: Determine the potential of flubendazole as a pre-clinical macrofilaricide candidate for mass drug administration for preventive treatment of onchocerciasis and lymphatic filariasis in *Loa loa* co-endemic regions.

This project aims to develop flubendazole as a safe, highly efficacious, and fieldusable macrofilaricidal drug candidate for Onchocerciasis-*Loa loa* co-infections. If flubendazole meets the criteria specified for pre-clinical development, the project will also support the necessary studies required to draft an Investigational Medicinal Product Dossier (IMPD) followed by submission and subsequent approval of the IMPD.

In 2011, activities to extensively characterize the flubendazole API (active pharmaceutical ingredient) were conducted and four different formulation strategies to enhance its bioavailability were tested. The amorphous solid dispersion (ASD) formulation achieved sustained plasma levels of flubendazole and will be used for pre-clinical development. The safety profile of flubendazole is not yet defined, in particular with respect to genotoxicity. However, embryotoxicity has been observed at concentrations above 0.25 μg/mL and such levels are achieved with the ASD formulation in vivo. Therefore, embryotoxicity is likely to be observed with flubendazole, which could be a limiting factor for its development as a mass drug administration programme. It will be essential to confirm these results in in vivo reproductive toxicology studies. In 2012, DNDi will conduct IMPD-enabling safety studies, develop an oral formulation suitable for human clinical use and conduct more extensive PK/PD studies to guide/refine the selection of human therapeutic doses.
Wolbachia endosymbionts of filarial nematodes

- symbionts in some filarial species: 

  **NOT** *Loa loa*, *O. flexuosa*, *A. viteae*, *Setaria* spp.

- vertical transmission via oocytes
- found in hypodermis and embryos of filariae
- associated with blindness in murine onchocerciasis (St. Andre et al., 2002)
“Re-purposing” of registered drugs is a time saver!

Hoerauf et al., Lancet 2000, 2001

Untreated

Doxycycline 100 mg/d for 6 weeks
Results: LF

- Microfilariae: significant reduction of *Wolbachia* (>90%) in doxycycline treated groups
- Reduction in *Wolbachia* led to sterility of adult worms
- Ultrasonography: reduction of no of worm nests (FDS)
  - 90% of male patients without scrotal worm nests => macrofilaricidal effect

- 8 weeks doxy: Taylor, Lancet 2005
- 6 weeks doxy: Debrah, PLoS Pathog 2006
- 4 weeks doxy: Debrah, TMIH 2007
- (3 weeks doxy: Turner, Clin Infect Dis. 2006 + IVM/ALB => not macrofilaricidal)
- 3 weeks doxy: Mand, AJTMH 2009 + DEC single dose
Role of *Wolbachia* in lymphatic pathology

- Lymphatic dilation is reduced following doxycycline
Role of *Wolbachia* in lymphatic pathology

- Lymphatic dilation is reduced following doxycycline
Figure 4. Pretreatment Plasma Levels of sVEGFR-3 in Filaria-Infected Patients and Endemic Controls

Plasma concentrations (mean ± SD) of sVEGFR-3 were measured using a commercial kit from plasma of lymphedema patients (n = 26), microfilaremics (n = 76), and endemic controls (n = 23, who did not have filarial infection). Mean plasma levels of sVEGFR-3 were significantly elevated in the microfilaremics (p = 0.0006) and lymphedema patients (p = 0.0012) compared to endemic controls (Student t-test with Bonferroni/Dunn correction). sVEGFR-3 was also significantly elevated in lymphedema patients (p = 0.0024) compared to microfilaremics patients.
Lymphedema: Characteristics

Swelling is not reversible overnight

Stage 2: shallow skin folds

Stage 3: knobs

Stage 4: knobs and deep skin folds

Stage 5: knobs, deep skin folds and mossy lesions

Stage 6: patients are unable to perform daily activities

Stage 7:
Doxycycline improves conditions of LE patients

Improvement manifests as:
- improvement in skin texture
- reduction of knobs
- fewer entry lesions

Debrah et al., PLoS Pathogens 2006
Before doxycycline

After doxycycline


GAELF ENDORSE DOXY FOR MORBIDITY MANAGEMENT
Current recommendations for doxycycline treatment in onchocerciasis and LF

- **Onchocerciasis**
  - Doxy 200 mg/d for 6 weeks if macrofilaricidal effect is wanted
  - Doxy 200 mg/d for 4 weeks or 100 mg/d for 5 weeks if only worm sterility is wanted

- **Lymphatic filariasis**
  - Doxy 200 mg/d for 6 weeks if LE or hydrocele is to be treated in addition to macrofilaricidal effect
  - Doxy 200 mg/d for 4 weeks (future: 100 mg/d -> new studies!) if focus is on the macrofilaricidal effect

Hoerauf, Curr Opin Infect Dis 2008,
Taylor-Hoerauf-Bockarie Lancet 2010
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Hoerauf, Curr Opin Infect Dis 2008,
Taylor-Hoerauf-Bockarie Lancet 2010
Wolbachia is essential for:

Development
- Larval development
- Embryogenesis

PROPHYLAXIS
TRANSMISSION BLOCKING

Adult worm longevity (10-14 years)
- Adults depleted of Wolbachia die 1-2 years later

MACROFILARICIDAL

Disease pathogenesis
- Inflammatory SAE
- Clinical disease

CLINICAL CASE MANAGEMENT
DOXY adopted by OEPA to shorten MDA timeframe

Transmission status
- ELIMINATED: 15%
- INTERRUPTED: 21%
- SUPPRESSED: 43%
- ONGOING: 21%

Regional population at risk: 470,222
Population no longer at risk: 81,923
Population under PTS: 116,772
Eligible for treatment: 323,077
A·WOL MODE OF ACTION **AVOIDS** RAPID MACROFILARICIDE = EXPLODING NODULES & SCROTAL INFLAMMATORY LESIONS
A·WOL mode of action AVOIDS direct anti-helminth drug issues

- SAFE macrofilaricidal kinetics
  - GAELF do not want a rapid macrofilaricide
  - = Scrotal inflammatory lesions
- Cysticercosis – *Taenia solium*

Microfilaricidal SAE (parasite and *Wolbachia* mediated)
- **Diethylcarbamazine** rapid microfilaricidal activity and Mazzotti reaction prevent use in Africa (Oncho/Loa SAE)
- **Ivermectin** – SAE in *Loa loa* co-infection
The principle of *Wolbachia* depletion allows high(er)-throughput approaches using insect cells

*Wolbachia*-infected insect cell line  cured cells
A·WOL Screening Funnel

Wolbachia cell assay in vitro

7 day assay qPCR readout

5 day assay qPCR, motility

7-14 day treatment Dose/regime reduction 35 day readout

25 day treatment Dose/regime reduction 2 & 8 month readout

Phase II trials: 6, 12, 24 month follow-up
Drug library screening

**Anti-infective library screening:**
1000’s drugs
Anacor Pharmaceuticals
Pfizer
Abbott
TB alliance
AstraZeneca

**Diversity library screening:**
Bio-focus: ‘Softfocus’ library – 10,000
SIMM (Shanghai): natural product library
50,000
MMV: 500,000 compounds
BROAD: DOS library – 10,000
A-WOL’s GOALS

1) To find a new anti-Wolbachia treatment compatible with MDA programmes for onchocerciasis and lymphatic filariasis.
   - Shorter treatments (weeks to 7 days or less)
   - Safe in pregnancy and children

2) To find the best regime with existing antibiotics for use in restricted settings (eg. on drug-resistant parasites, *Loa loa* co-endemic areas, MDA end game = IDA TEST & TREAT).
Loa loa - the tropical eye worm
Map of the estimated prevalence of eye worm history in Africa. ~300 MILLION AT RISK

doi:10.1371/journal.pntd.0001210
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001210
Map of the predictive probability that the local prevalence of eye worm history exceeds 40%.

~15 MILLION AT RISK OF SAE

doi:10.1371/journal.pntd.0001210
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001210
A·WOL - Product Portfolio Timeline

2012: DOXYCYCLINE – restricted populations
  • Drug resistant parasites
  • *Loa loa* co-endemic areas (avoids SAE),
  • Reduced timeframe for MDA, e.g. OEPA Venezuela
  • End-game mop-up to meet elimination criteria; test & treat.

2013: Optimized combination and improved monotherapy with registered 2nd generation A·WOL drugs with delivery from weeks to days

2015: Optimized regimes of 2nd generation A·WOL drugs in combination with A·FIL drugs

2017: Pre-clinical candidates of 3rd generation A·WOL drugs

2020: A·WOL 3rd generation clinical candidate - Phase III trial
Progress towards a vaccine against river blindness

EMCF river blindness programme

NIH funded projects

EU DG Research funded contracts


First *O volvulus* recombinant antigens produced

*Brugia malayi* mouse model

*O volvulus* mouse chamber model

*O ochengi* bovine model

*Litomosoides sigmodontis* mouse model

Protective immunity induced by 15 recombinant proteins

Role of T regulatory cells in expression of protective immunity

Protective immunity induced by *Lg* DNA vaccines and synthetic peptides

Protective immunity induced by recombinant *Ov* and *Bm* antigens

Consensus on priority testing of vaccine candidates
Progress towards a vaccine against river blindness

- **EMCF river blindness programme**
- **NIH funded projects**
- **EU DG Research funded contracts**

1985 - 2020

- First *O volvulus* recombinant antigens produced
- *Brugia malayi* mouse model
- *O volvulus* mouse chamber model
- *O ochengi* bovine model
- *Litomosoides sigmodontis* mouse model
- Protective immunity induced by recombinant proteins
- Role of T regulatory cells in expression of protective immunity
- Protective immunity induced by *Lg* DNA vaccines and synthetic peptides
- Protective immunity induced by recombinant *Ov* and *Bm* antigens
- Consensus on priority testing of vaccine candidates
- cGMP manufacturing of vaccines

First RB vaccine candidates ready for Phase I, first-in-human safety trials
## The vaccine candidates

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Location</th>
<th>In vitro killing</th>
<th>In vivo L3 killing</th>
<th>In vivo Adult killing</th>
<th>In vivo Mf killing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI</td>
<td>ES, Surface, all stages</td>
<td>Ov L3 94% neutrophils</td>
<td>Ov 37% (recom prot)</td>
<td>Ls 50% (recom prot)</td>
<td>Ls &gt;85% (DNA) Ls &gt;85% (syn pep)</td>
</tr>
<tr>
<td>RAL2</td>
<td>ES, surface, all stages</td>
<td>Ov L3 100% neutrophils</td>
<td>Ov &gt;44% (recom prot)</td>
<td>Bm &gt;60% (recom prot)</td>
<td>Bm &gt;90% (recom prot) Ls &gt;90% (DNA)</td>
</tr>
<tr>
<td>Ov103</td>
<td>Surface, all stages</td>
<td>Ov L3 100% neutrophils</td>
<td>Ov &gt;40% (recom prot)</td>
<td>Bm &gt;40% (recom prot)</td>
<td>Ov Mf 93% neutrophils</td>
</tr>
</tbody>
</table>

ES, excreted-secreted and includes immuno-modulators
Ov, *Onchocerca volvulus*
Ls, *Litomosoides sigmodontis*
Bm, *Brugia malayi*
Transatlantic Product Development Partnership for a River Blindness Vaccine

Lindsley F Kimball Research Institute
Thomas Jefferson University
Louisiana State University
Baylor College of Medicine

University of Edinburgh
University of Liverpool
Imperial College, London
Muséum national d’Histoire naturelle, Paris
University Hospital of Bonn
Eberhard Karls University, Tuebingen

Kwame Nakrumah University, Kumasi
Université de Lomé, Togo
Institut de Recherche Agricole pour le Developpement, Ngaoundéré
University of Buea
What the vaccine will do
Prevent new infections with L3
Reduce adult worm burden
Reduce microfilaria production/survival/burden
Reduce morbidity
Reduce transmission potential
Allow a diminished usage of drugs
Forestall development of drug resistance

How it will be used
In children
In integrated control strategies that may include
Pregnant and breast-feeding women
Communities co-endemic for Loa loa
Populations where ivermectin alone will not lead to elimination
Summary - needs for filariasis

- Develop new macrofilaricidal drugs
  - Surrogate animal models are in place
  - Ideally compatible with MDA (incl. children)
- Implement existing macrofilaricidal drugs, e.g. doxycycline
  - ("Mopping-up" scenarios)
  - Test & treat strategies
  - Lymph edema case management
- Define and validate biomarkers (through study samples)
- Vaccine (s)
- Integration with control of other NTDs, e.g. STH and schisto
  - Research questions needed to avoid simple subsistence payments for existing programs
Points to consider - NIDs in general

- Impact of money spent on new drugs/new delivery systems is huge -> endgame strategies (test & treat) may become feasible
- Re-purpose „old drugs“ for test & treat strategies
- Combinations of drugs not thoroughly tested in trials
- Phase III trials (only or mainly) on top of existing programmes
- Different diseases may have different priorities for R&D and implementational research
- Diagnostics: trials as a source for defined biomarkers
- Co-infection with „big three“ (only) where appropriate

- Recommendation: money should be ringfenced for NIDs