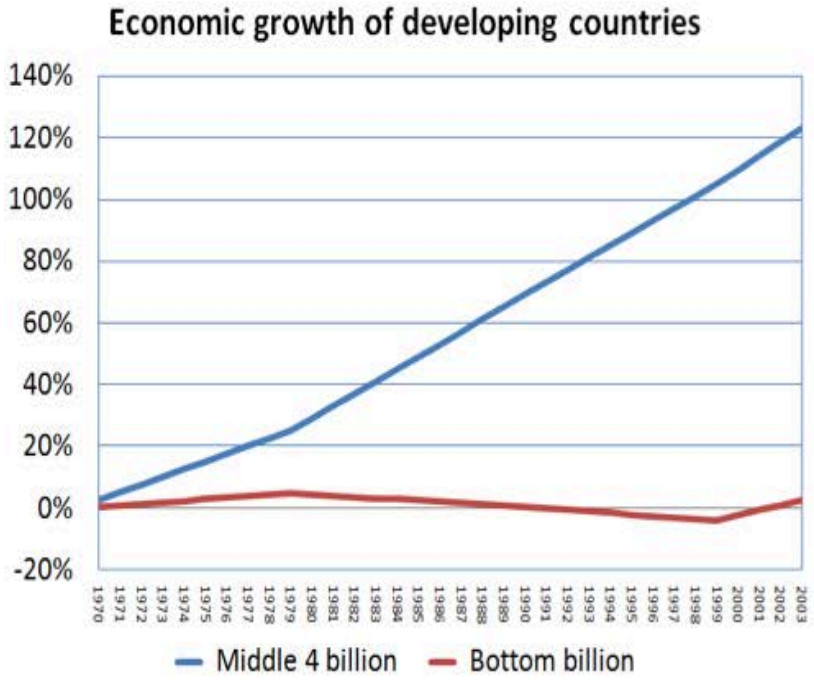
EDCTP - NID Stakeholder meeting

Den Haag, 27 June 2013

Achim Hoerauf

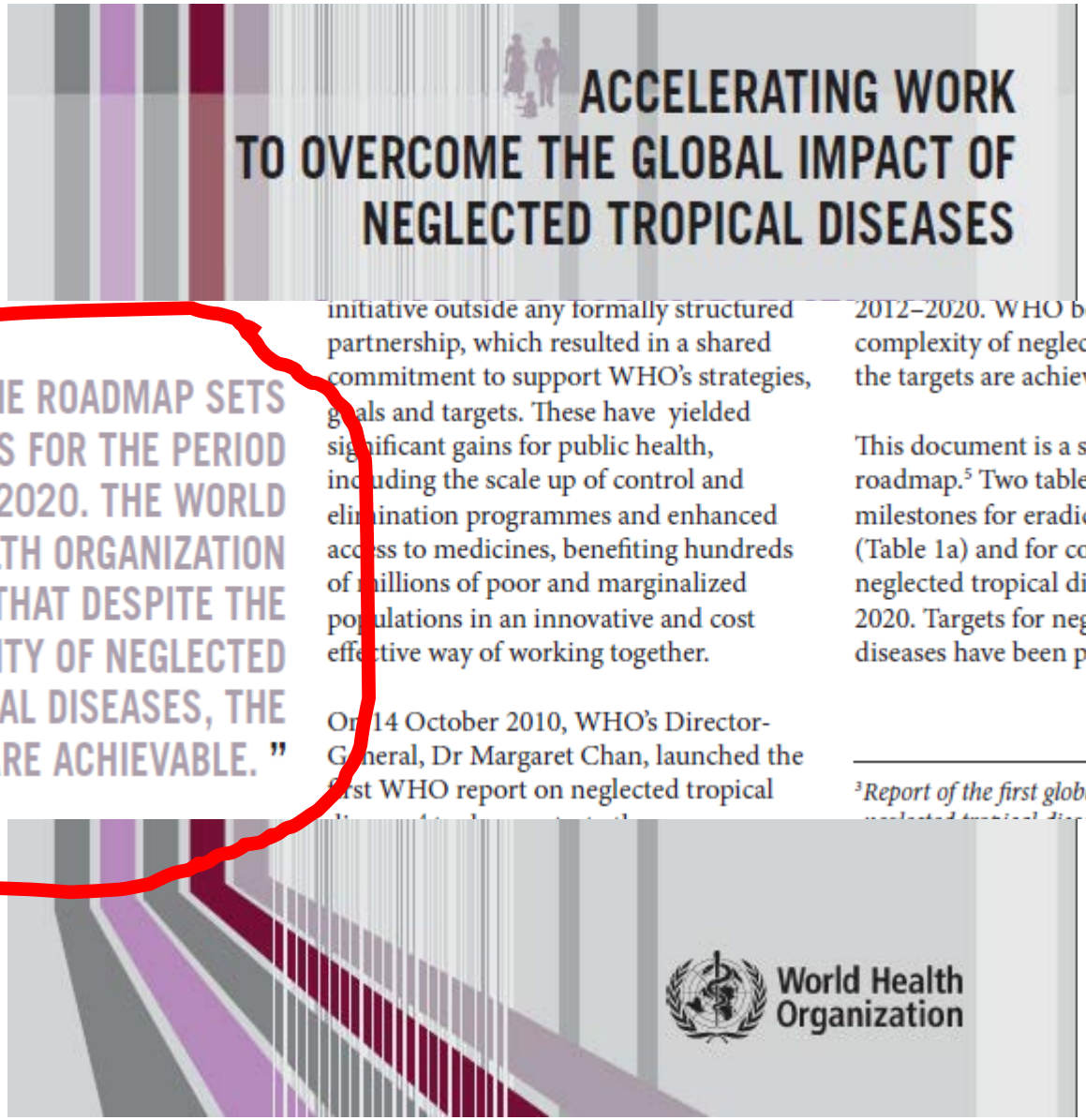
Chair and Head,
Institute of Med. Microbiology, Immunology and Parasitology
University Bonn Medical Center

NIDs are a problem for those left behind



Intolerable burden => WHO roadmap and London declaration 2012

Roadmap targets are achievable



"THE ROADMAP SETS TARGETS FOR THE PERIOD 2012–2020. THE WORLD HEALTH ORGANIZATION BELIEVES THAT DESPITE THE COMPLEXITY OF NEGLECTED TROPICAL DISEASES, THE TARGETS ARE ACHIEVABLE."

But.....

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

UNITING TO COMBAT NEGLECTED TROPICAL DISEASES

Ending the Neglect & Reaching 2020 Goals

LONDON DECLARATION ON NEGLECTED TROPICAL DISEASES

- Endorsers:

Abbott

AstraZeneca

Bayer

Becton Dickinson

Bill & Melinda Gates Foundation

Bristol-Myers Squibb

CIFF

DFID

DNDi

Eisai

Gilead

GlaxoSmithKline

Johnson & Johnson

Lions Clubs International

Merck KGaA

MSD

Mundo Sano

Novartis

Pfizer

Sanofi

USAID

World Bank

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

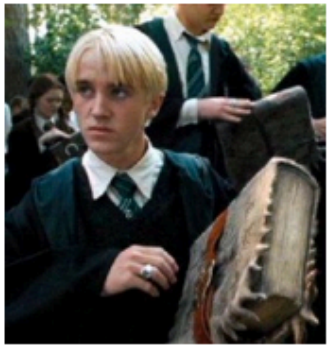
$784 million committed for research and programme activities

January 30 2012

Inclusion of NIDs in EDCTP 2 is an important step!

“Harry Potter” Star Joins Global Effort to Eliminate Seven Diseases by 2020

April 13th, 2012 by Heena Patel Leave a reply »



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 of 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:

WE’RE ON A MISSION TO SEE THE END OF 7 DISEASES BY 2020

They devastate the lives of 1 in 6 people worldwide. But the great news is that with your help we can actually end this suffering. Helping is easy - just 'like' our page & share it!

CATEGORIES

Select Category

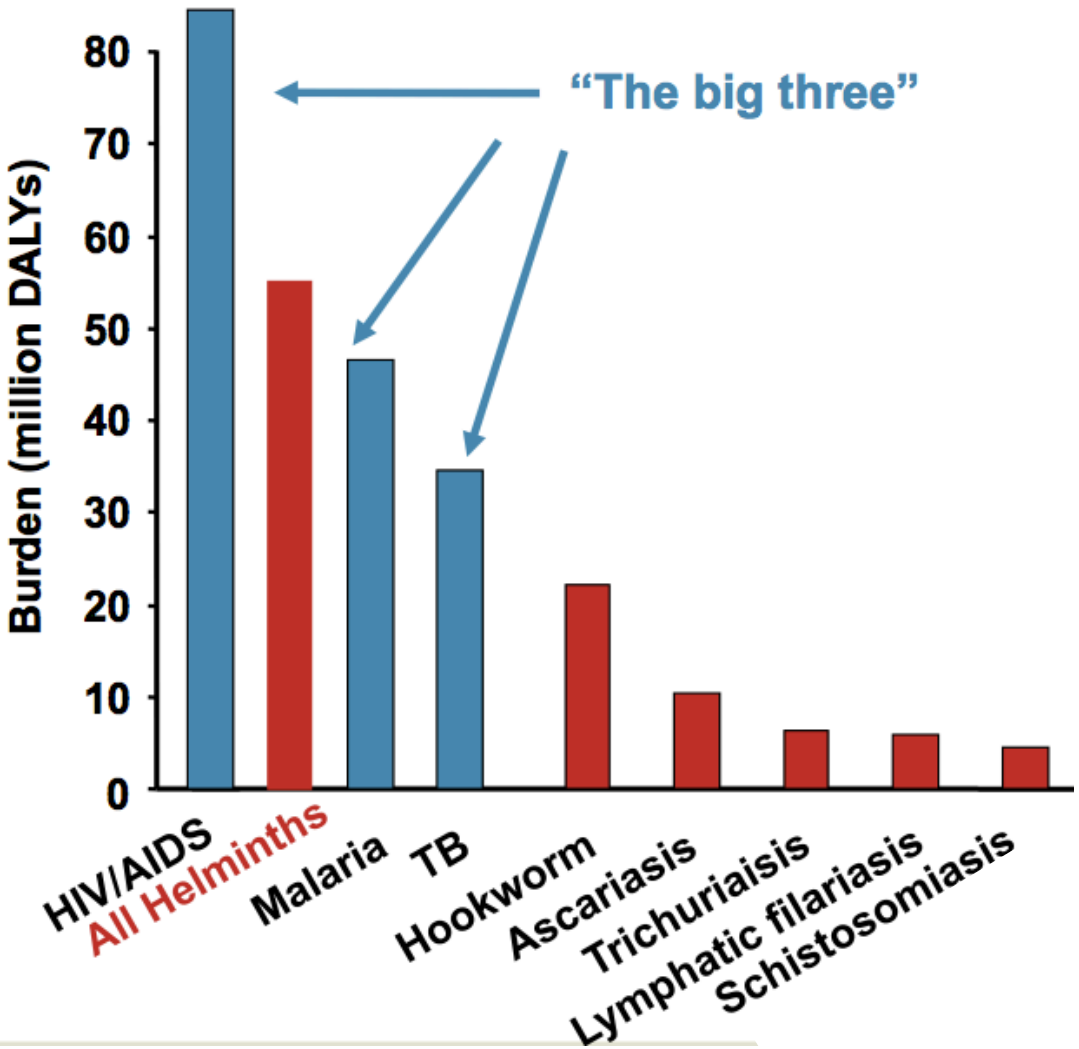
PREVIOUS ENTRY

Dubai Cares Donates 1 million USD to combat NTDs

NEXT ENTRY

Worm tales: One scientist’s inspiration to turn tropical diseases into ‘stories told by a past generation’”

The health burden by helminths is similar to the „big three“



Adapted from Swiss TPH

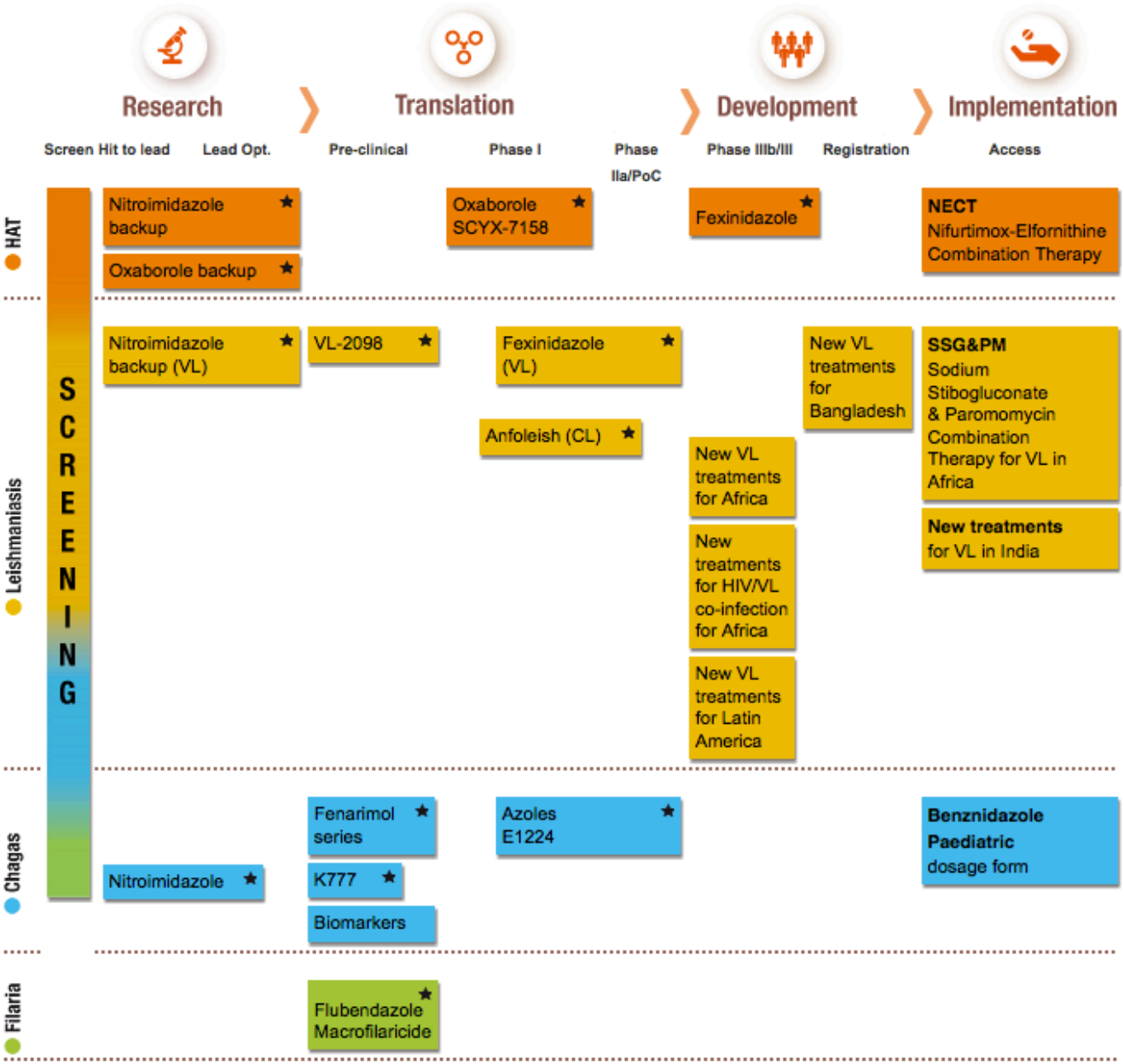
APPENDIX: MAJOR NEGLECTED TROPICAL DISEASES, GROUPED BY TYPE

	DISEASE NAME	CAUSATIVE AGENT	PREVALENCE	POPULATION AT RISK
Helminth infections	Soil transmitted helminthiasis	*Ascaris lumbricoides, Trichuris trichiura,* hookworm	ascariasis: 807 million trichuriasis: 604 million hookworm: 576 million	ascariasis: 4.2 billion trichuriasis: 3.2 billion hookworm: 3.2 billion
	Schistosomiasis (Bilharzia, snail fever)	Some *Schistosoma* spp.	207 million	779 million
	Lymphatic filariasis (elephantiasis)	*Wuchereria bancrofti, Brugia malayi, B. timori*	120 million	1.3 billion
	Cysticercosis	*Taenia solium*	50 million	Unknown
	Onchocerciasis (river blindness, Robles' disease)	*Onchocerca volvulus*	37 million	90 million
	Fascioliasis (Distomatosis)	Fasciola hepatica, F. gigantica	2.4 million	180 million
	Dracunculiasis (Guinea-worm disease)	*Dracunculus medinensis*	0.01 million	Unknown
	Echinococcosis (Hydatid disease)	*Echinococcus granulosus, E. multilocularis, E. vogeli, E. oligarthus*	Unknown	Unknown
Protozoan infections	Leishmaniasis	*Lutzomyia,* sandfly	12 million	350 million
	Chagas disease (American trypanosomiasis)	Trypanosoma cruzi	8-9 million	25 million
	Sleeping sickness (Human African tryp anosomiasis)	*Glossina, Trypanosoma brucei gambiense and T.b.rhodesiense*	0.3 million	60 million
Bacterial infections	Trachoma (granular conjunctivitis, Egyptian ophthalmia)	*Chlamydia trachomatis*	84 million	590 million
	Leprosy (Hansen's disease)	*Mycobacterium leprae*	0.4 million	Unknown
	Buruli ulcer	*Mycobacterium ulcerans*	0.05 million	Unknown
	Yaws (Frambesia tropica)	*Treponema pallidum*	Unknown	Unknown
Viral infections	Dengue	*Aedes aegypti, Aedes spp.*	Unknown; as many as 50 million infected annually	Unknown, but increasing numbers at risk
	Rabies		Unknown; 55,000 deaths annually	Unknown

Source: World Health Organization

- Diseases
- Portfolio
  - R&D Phases
- R&D Organisation
- Building Portfolio
- Clinical Trial Protocols
- Open Innovation

DNDi R&D Projects - 2013 Outlook



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

Clinical Infectious Diseases 2010; 50(9):1205–1213

1058-4838/2010/5009-0001$15.00
DOI: 10.1086/651682

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,[4] Koffi D. Adoubryn,[5] Kigbafori D. Silué,[4,6] Penelope Vounatsou,[2] Christoph Hatz,[3] Jürg Utzinger,[2] and Eliézer K. N'Goran[4,6]

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

	Drug			
Characteristic after treatment	Mefloquine (n = 19)	Artesunate (n = 20)	Mefloquine-artesunate (n = 18)	Praziquantel (n = 26)
Children with cure	4 (21)	5 (25)	11 (61)	23 (88)
GM *Schistosoma haematobium* eggs per 10 mL of urine (range)	7.9 (1–694)	6.2 (1–267)	1.7 (1–73)	1.1 (1–5)

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

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

Keiser et al.

(Reprinted) JAMA, April 23/30, 2008—Vol 299, No. 16 **1939**

Ivermectin co-administration enhances efficacy against Trichuris!

Efficacy and safety of mefloquine, artesunate, mefloquine–artesunate, tribendimidine, and praziquantel in patients with *Opisthorchis viverrini*: a randomised, exploratory, open-label, phase 2 trial

Phonepasong Soukhathammavong, Peter Odermatt, Somphou Sayasone, Youthanavanh Vonghachack, Penelope Vounatsou, Christoph Hatz, Kongsap Akkhavong, Jennifer Keiser

Lancet Infect Dis 2011; 11: 110–18
Published Online November 25, 2010

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.

Food-borne trematodes:
750 million people at risk;
40 million people infected

	Mefloquine	Artesunate	Mefloquine–artesunate	Tribendimidine	Praziquantel
Opisthorchis viverrini					
Patients cured/ patients infected	0/25 (0)	1/24 (4%)	1/24 (4%)	19/27 (70%)	14/25 (56%)
GM egg per g of stool (range)	1052·2 (537·8–2058·4)	1229·4 (625·1–2417·7)	653·9 (323·9–1320·1)	578·5 (47·7–7009·5)	159·9 (38·1– 671·2)
Egg reduction rate	30·2%	31·5%	41·3%	99·3%	98·4%
Co-infection with hookworm					
Patients cured/ patients infected	3/17 (18%)	4/20 (20%)	3/15 (20%)	11/17 (65%)	2/17 (12%)

Data are number (%) of patients, unless otherwise indicated. GM=geometric mean.

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

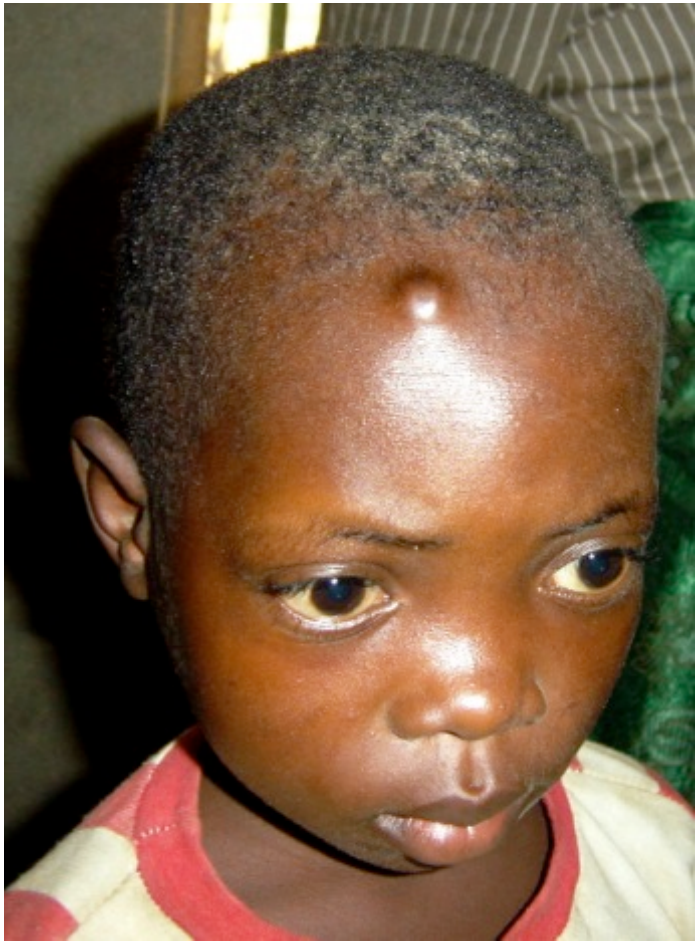
Efficacy also against *Clonorchis*, *Ascaris*, *Trichuris*, *Strongyloides*, *Enterobius*

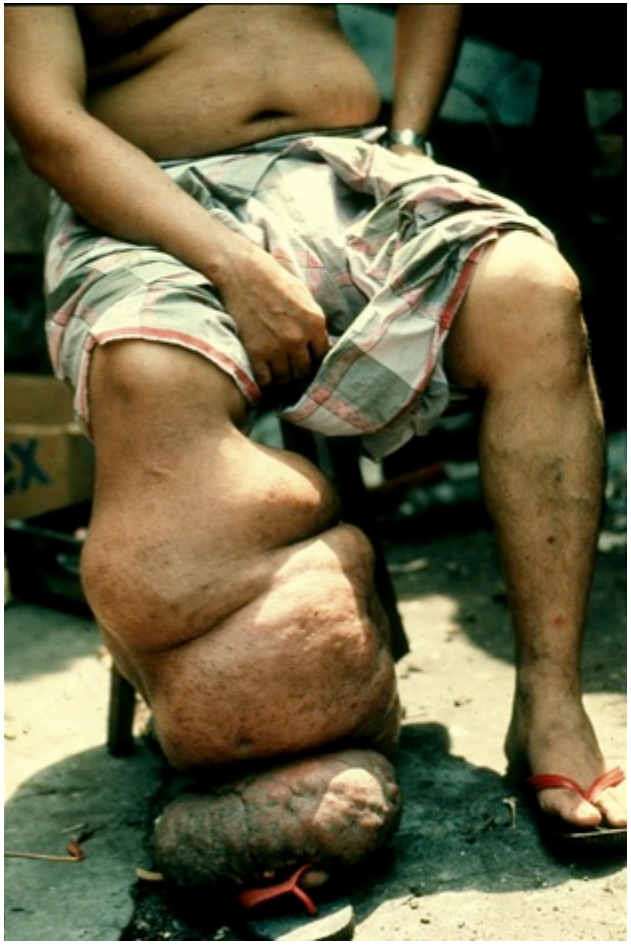
HUMAN FILARIAL NEMATODE DISEASE

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

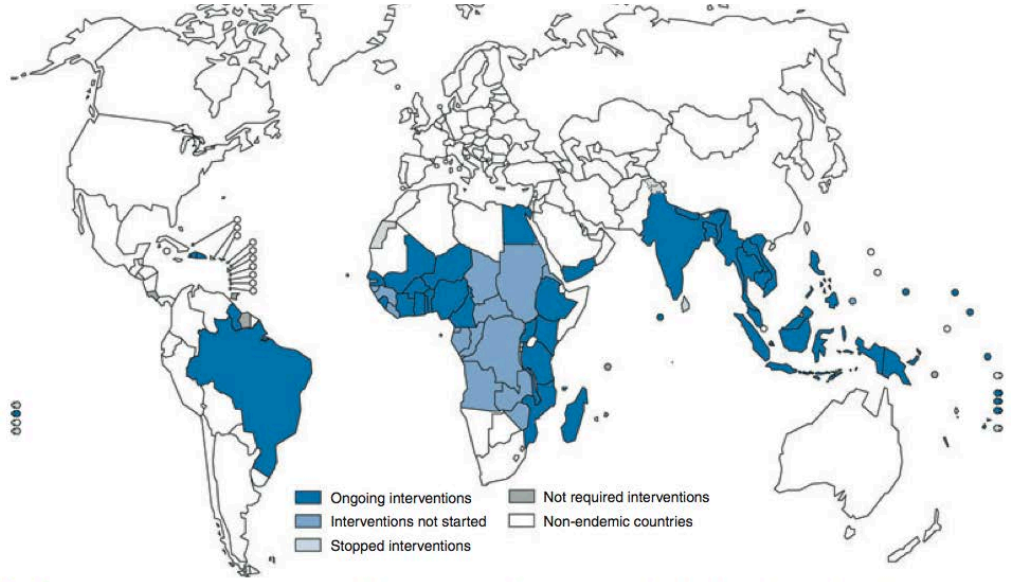


FIG. 4. Distribution and status of preventive chemotherapy for lymphatic filariasis, worldwide, 2009. Note: The distribution of lymphatic filariasis is focal in many countries. For the detailed epidemiological situation in countries, please refer to World Health Organization.

Lymphatic filariasis:
> 120 Mio. infected

Onchocerciasis (River blindness):
> 37 Mio. infected

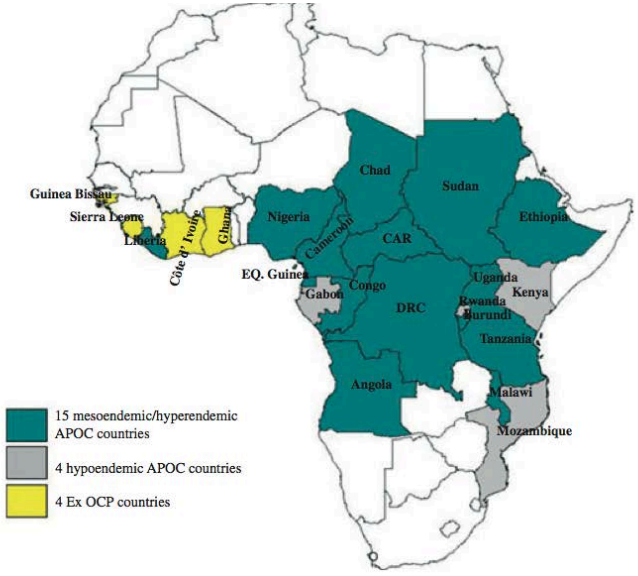
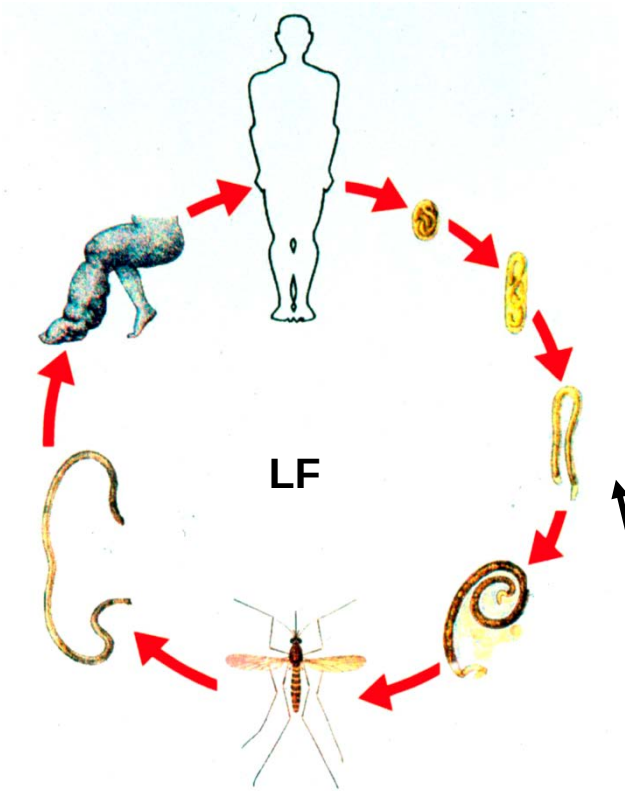
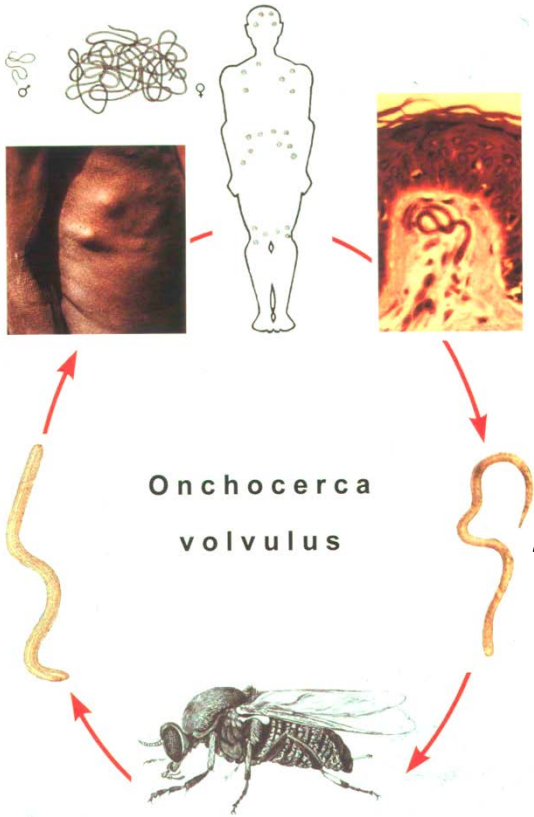


FIG. 3. Distribution and control of onchocerciasis in Africa.

Control by drugs in filariasis
Mass Drug Administration (MDA)





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

- Ivermectin (IVM)

Global Programme to Eliminate Lymphatic Filariasis: 2012

Number of endemic countries	73
Estimated population at risk	1.4 B
Number of countries implementing MDA	53
Number of countries scaling down MDA implementation (Post MDA Surveillance)	12
Total number of people treated (including 153m children)	538.6m
Total number of people targeted for treatment	736.9m
Number of Countries yet to implement MDA	19

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

Western Sahara
Guinea
Eritrea

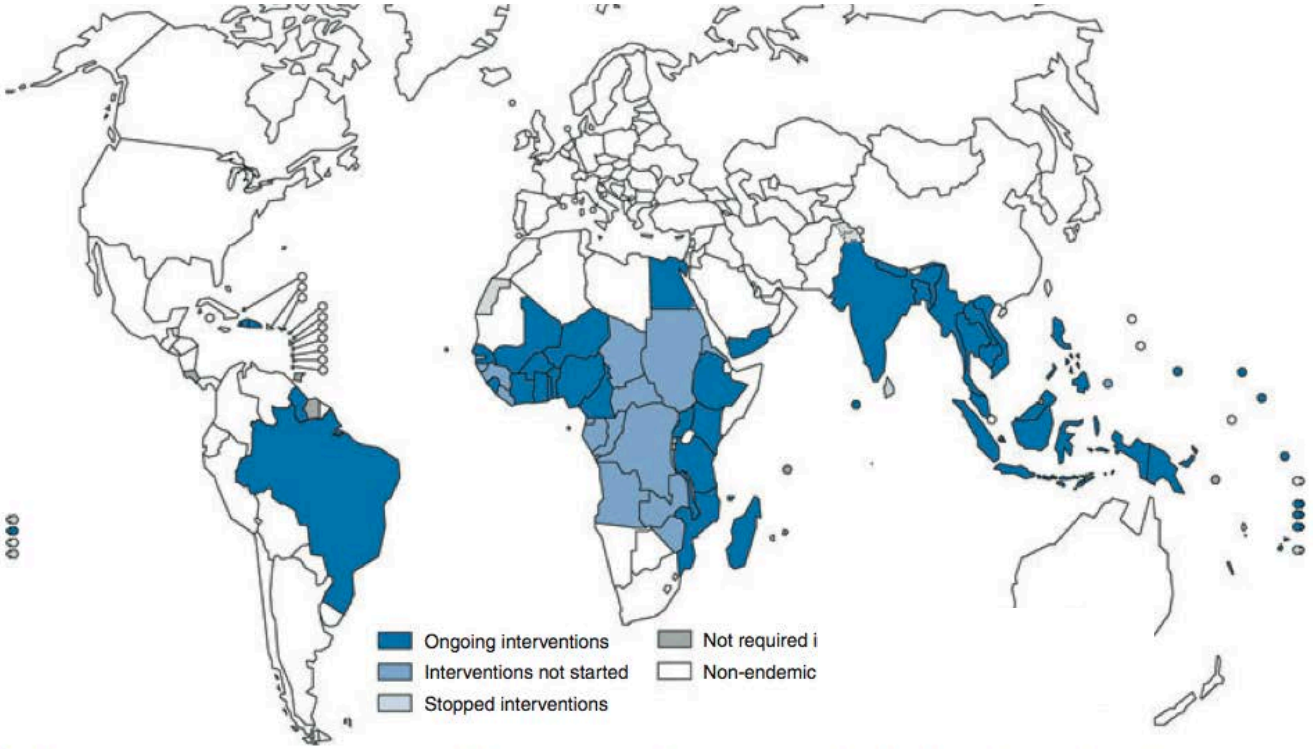
Guinea-Bissau
Zimbabwe
Sudan

AFRICA

Gabon
Gambia
Sao Tome and Principe

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!!

Annals of Tropical Medicine & Parasitology, Vol. 98, No. 3, 231–249 (2004)

An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana

K. AWADZI*, D. A. BOAKYE†, G. EDWARDS‡,§, N. O. OPOKU*, S. K. ATTAH*, M. Y. OSEI-ATWENEBOANA†, J. K. LAZDINS-HELDS¶, A. E. ARDREY‡, E. T. ADDY*, B. T. QUARTEY*, K. AHMED**, B. A. BOATIN†† and E. W. SOUMBEY-ALLEY††

Annals of Tropical Medicine & Parasitology, Vol. 98, No. 4, 359–370 (2004)

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

K. AWADZI*, S. K. ATTAH*, E. T. ADDY*, N. O. OPOKU*, B. T. QUARTEY*, J. K. LAZDINS-HELDS†, K. AHMED‡, B. A. BOATIN§, D. A. BOAKYE¶ and G. EDWARDS**

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

www.lancet.com Vol 369 June 16, 2007

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Phenotypic Evidence of Emerging Ivermectin Resistance in *Onchocerca volvulus*

Mike Y. Osei-Atweneboana[1,5], Kwablah Awadzi[2], Simon K. Attah[2], Daniel A. Boakye[3], John O. Gyapong[4,6], Roger K. Prichard[1]*

March 2011 | Volume 5 | Issue 3 | e998

TOPICAL REVIEW

Evidence for Macrocyclic 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

Flubendazole and Onchocerciasis

Table 2. Effect of flubendazole and diethylcarbamazine on adult *Onchocerca volulus* isolated from human nodules.

Status of parasites	2 months post-Rx		3 months post-Rx	
	DEC[†]	*FLUB*[†]	*DEC*	*FLUB*
Degenerated adults	12	10	12	27
Intact adult worm	44	11	16	0
Females with empty uteri	6	1	5	0
Females with only oocytes	8	6	14	0
Reduction in dermal microfilariae[‡]	Yes	No	Yes	No

[†]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.

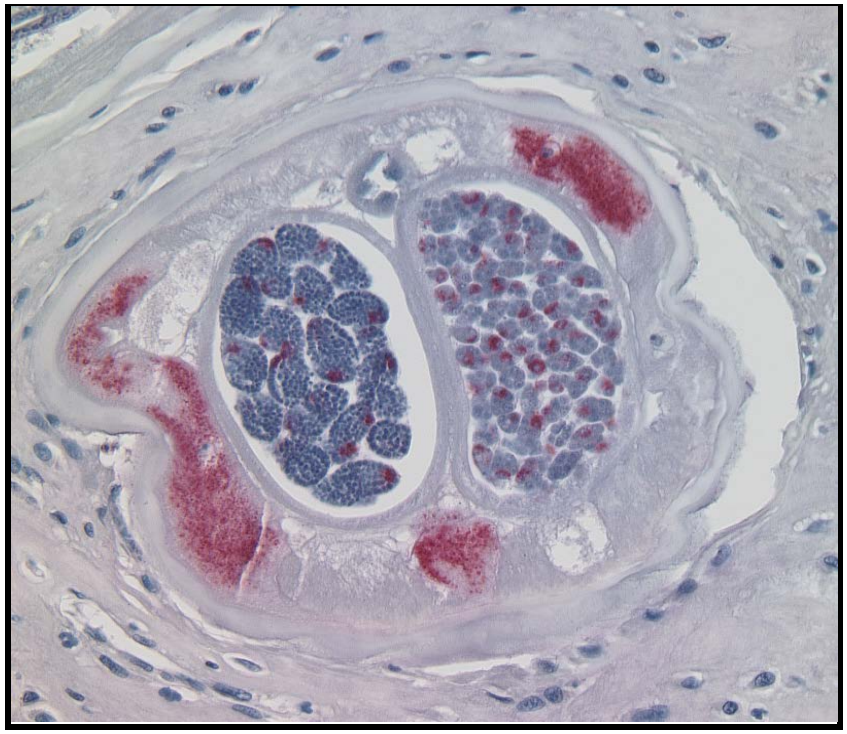
Listen to podcast
Bernard Pécoul speaking about DNDi's portfolio expansion to helminth infections

Read DNDi's Press release
"DNDi expands its activities to tackle urgent unmet needs for neglected patients in the field of helminth infections"

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



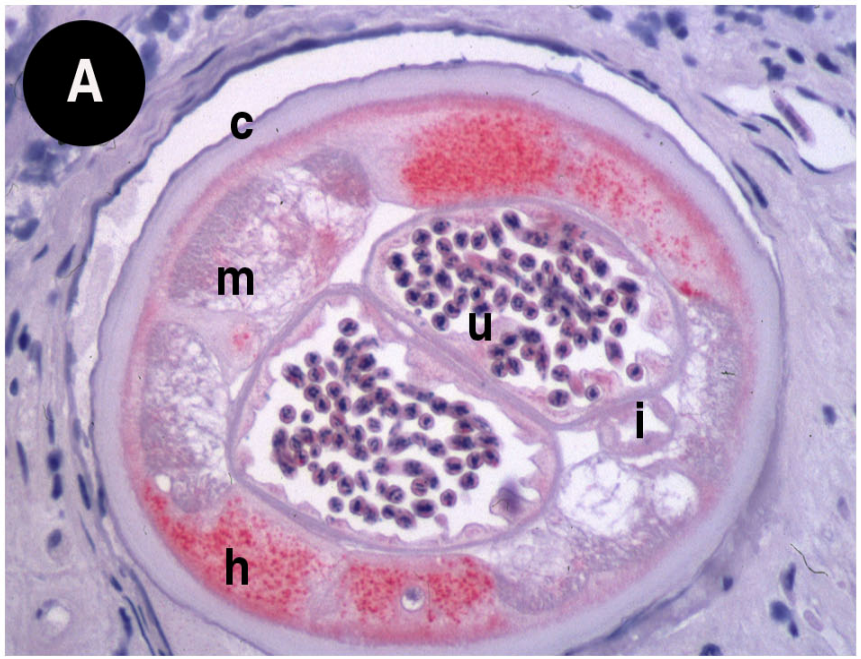
- symbionts in some filarial species:

O. volvulus, *W. bancrofti*, *Brugia* spp., *Mansonella* spp., *Dirofilaria* spp.

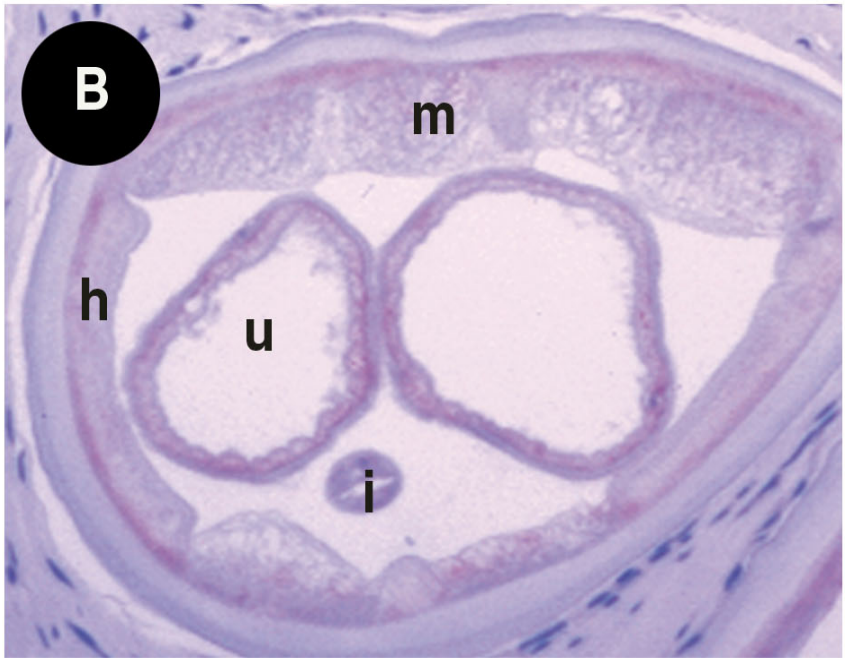
NOT *Loa loa*, *O. flexuosa*, *A. viteae*, *Setaria* spp.

- 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!



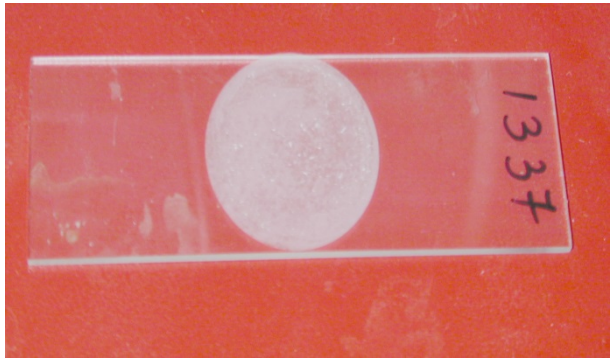
Untreated



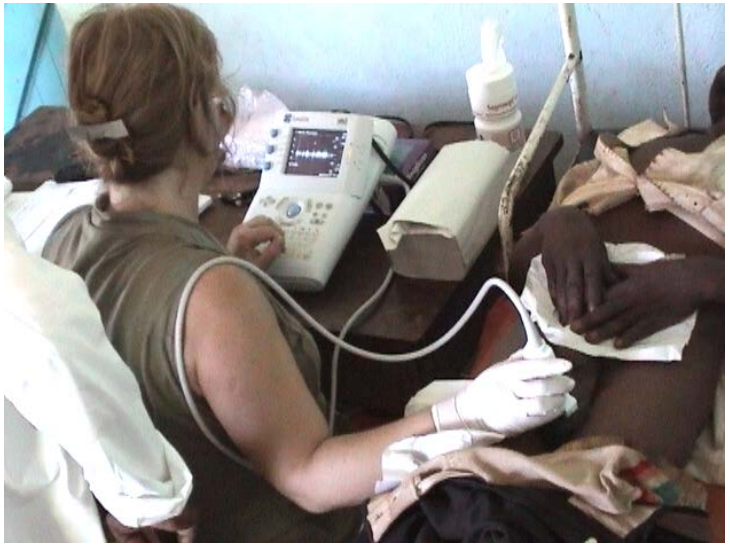
Doxycycline 100 mg/d for 6 weeks

Hoerauf et al., Lancet 2000, 2001

Results: LF



-> PCR of microfilariae



-> scrotal ultrasound

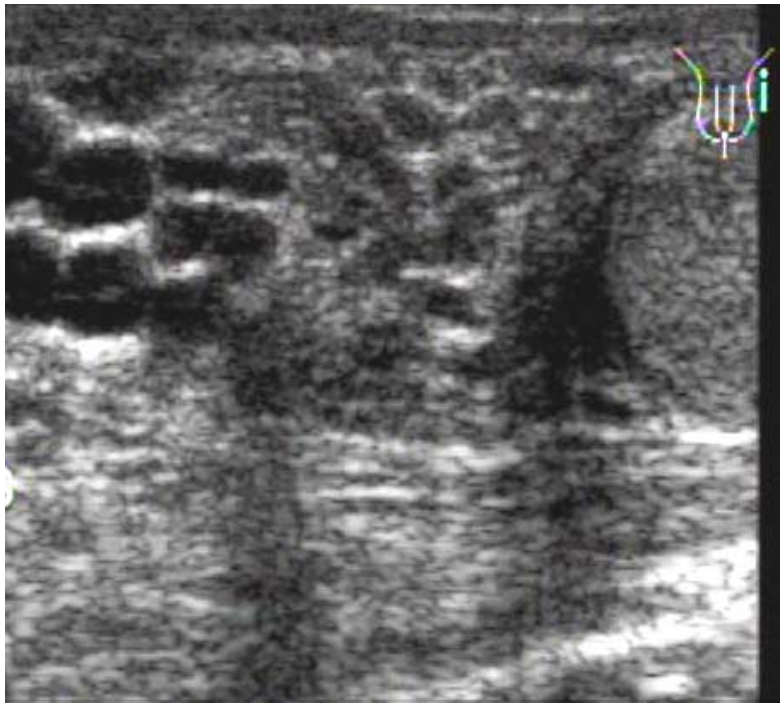
- Microfilariae: significant reduction of *Wolbachia* (>90%) in doxycycline treated groups
- Reduction in *Wolbachia* led to sterility of adult worms
- Ultrasonography: reduction of no of worm nests (FDS)

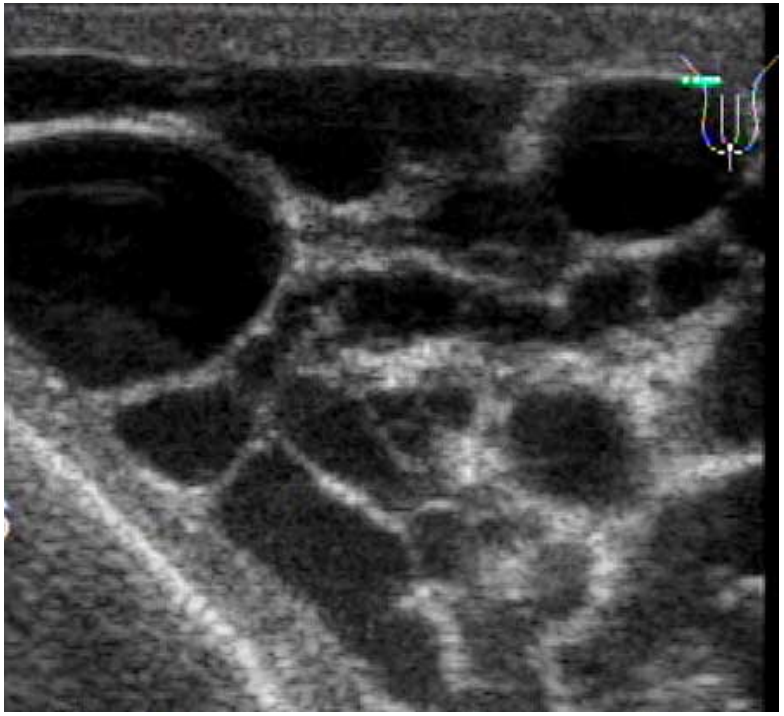
  -> 90% of male patients without scrotal worm nests => macrofilaricidal effect

- 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 macrofilaricial)
- 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

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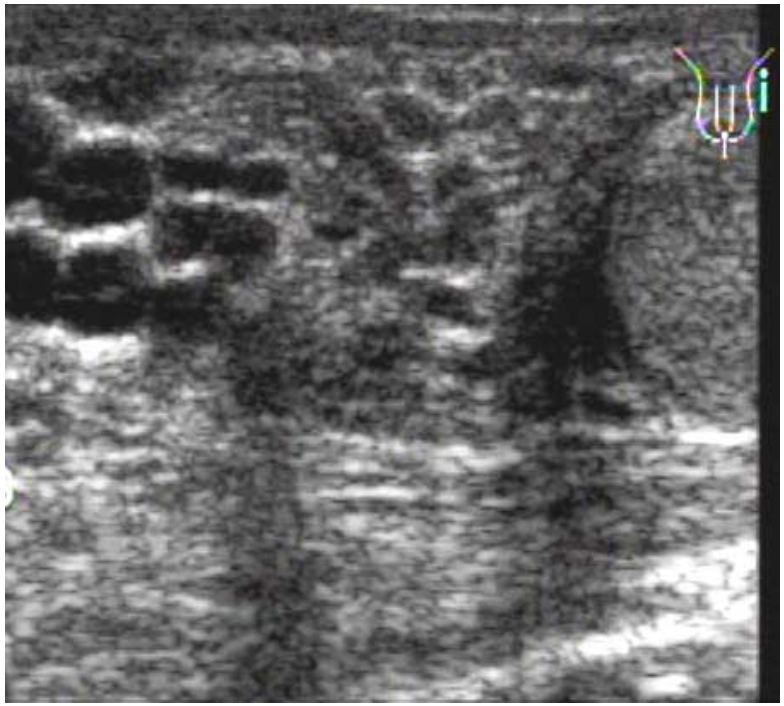
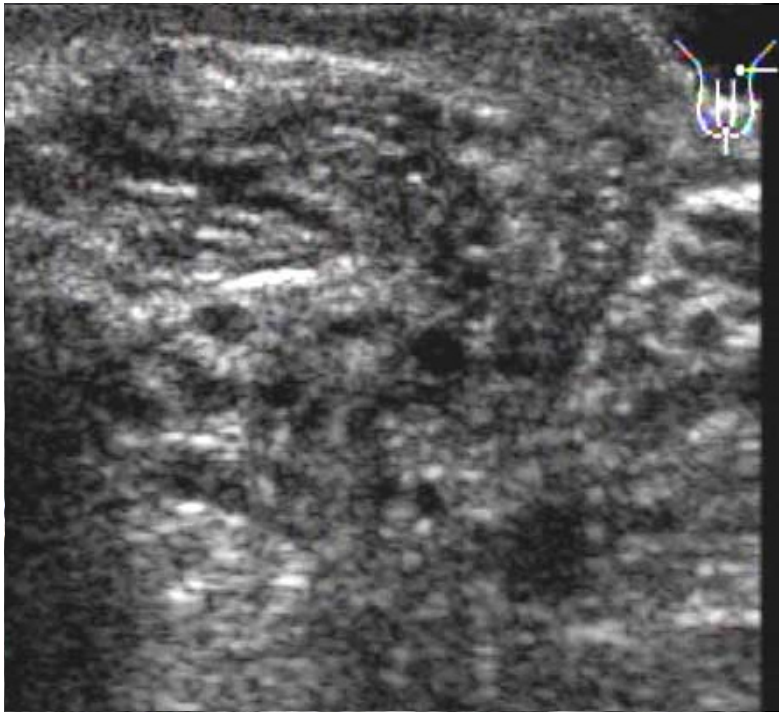




Human lymphatic filariasis - VEGF plasma levels

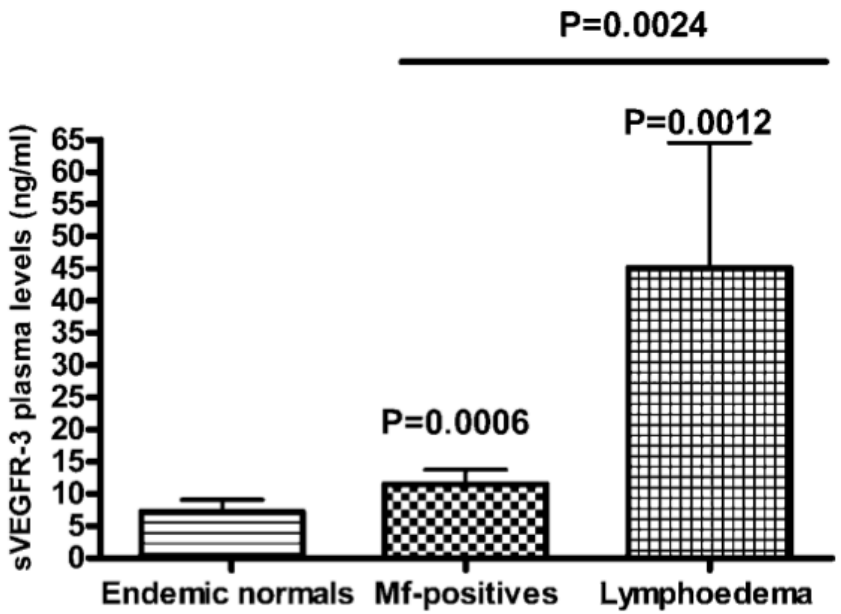
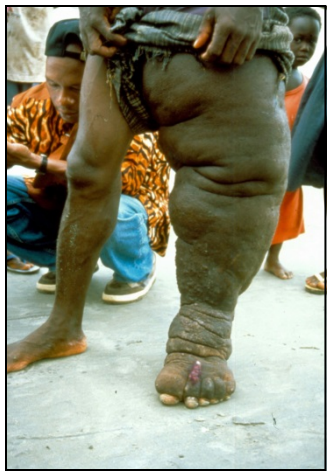


Figure 4. Pretreatment Plasma Levels of sVEGFR-3 in Filaria-Infected Patients and Endemic Controls

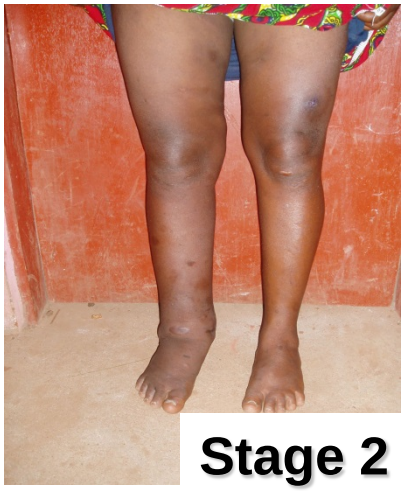
Plasma concentrations (mean ± SD) of sVEGFR-3 were measured using a commercial kit from plasma of lymphedema patients ($n = 26$), microfilaremic patients ($n = 76$), and endemic controls ($n = 23$, who did not have filarial infection). Mean plasma levels of sVEGFR-3 were significantly elevated in the microfilaremic ($p = 0.0006$) 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 microfilaremic patients.



Debrah et al. PloS Pathog, 2006

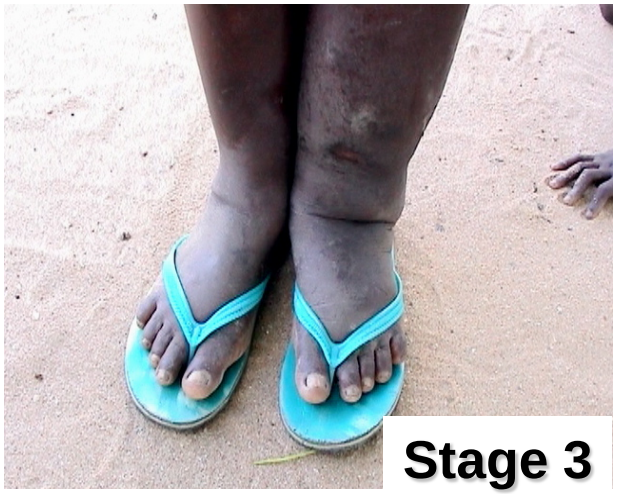
Lymphedema: Characteristics

swelling is not reversible overnight



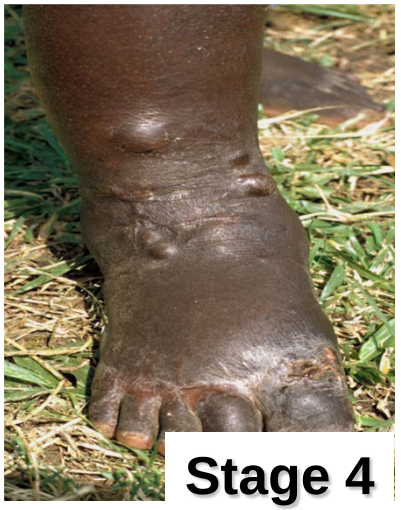
Stage 2

shallow skin folds



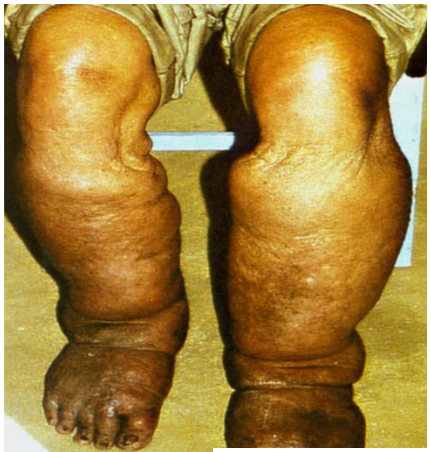
Stage 3

knobs



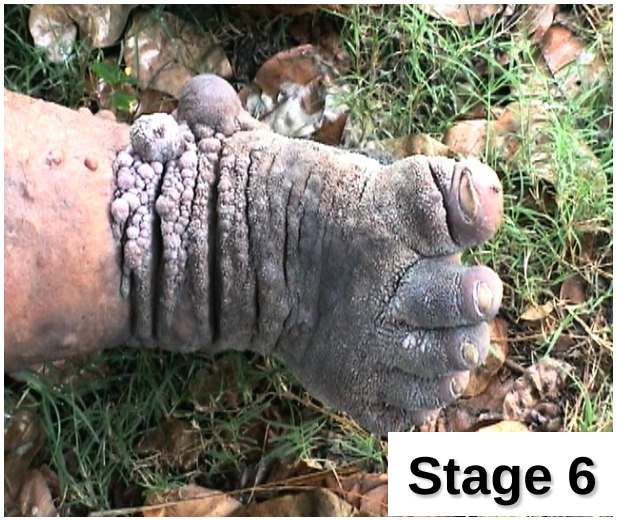
Stage 4

knobs and deep skin folds



Stage 5

knobs, deep skin folds and mossy lesions

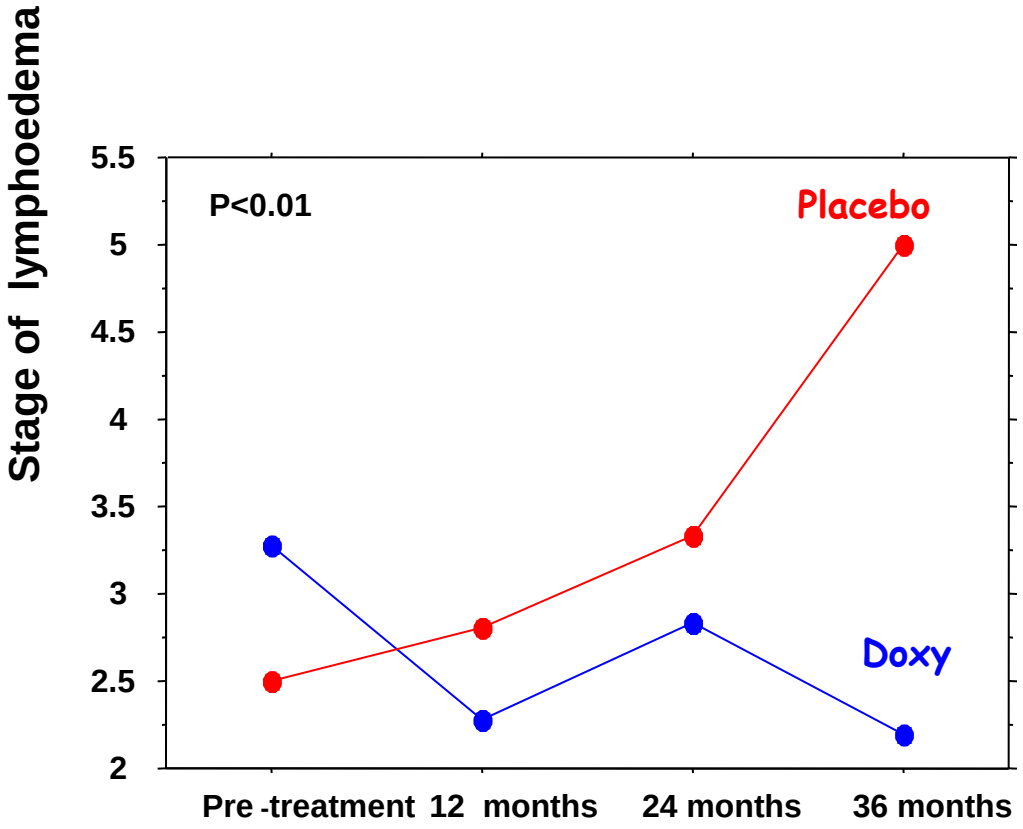


Stage 6

patients are unable to perform daily activities

Stage 7

Doxycycline improves conditions of LE patients

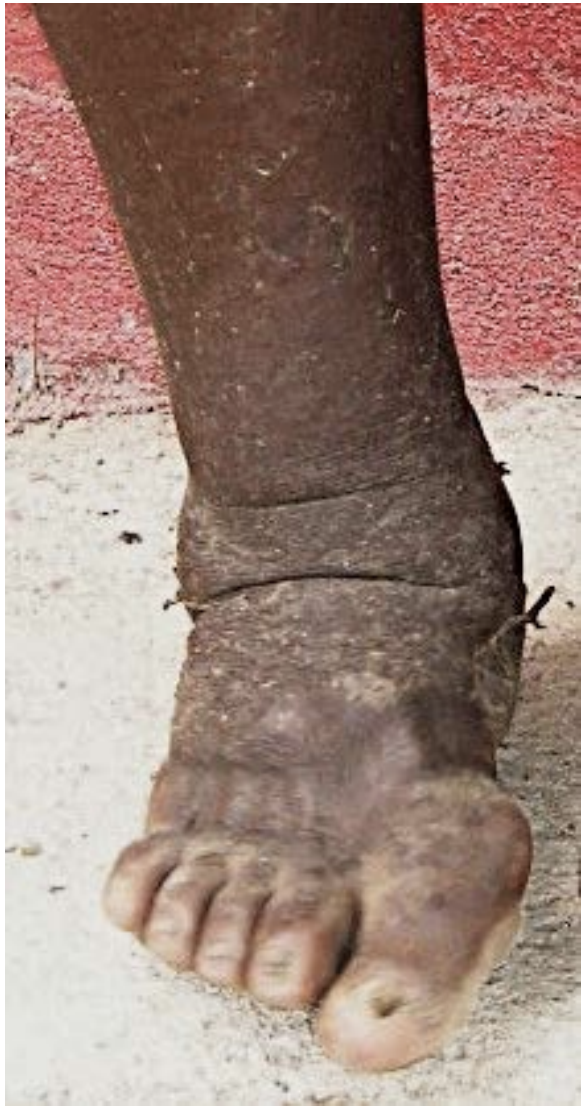


Improvement manifests as

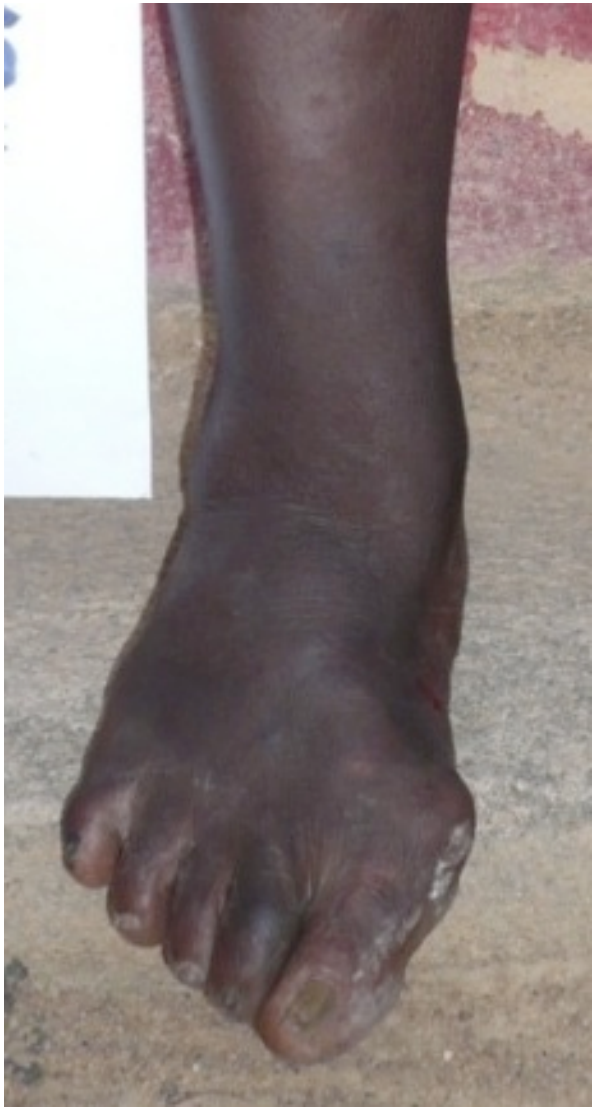
- improvement in skin texture
- reduction of knobs
- fewer entry lesions

Debrah et al., PLoS Pathogens 2006

Before doxycycline



After doxycycline



Mand et al., Clin. Infect. Dis. 2012

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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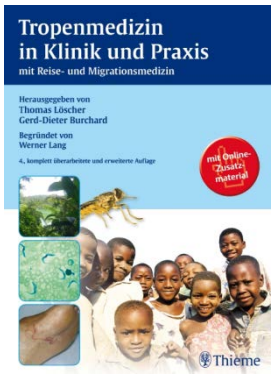
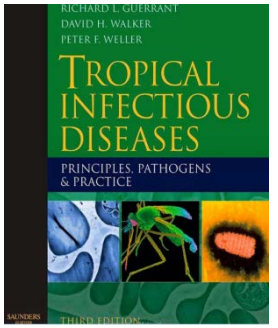
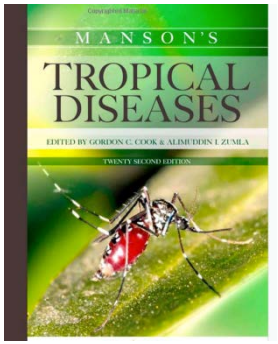
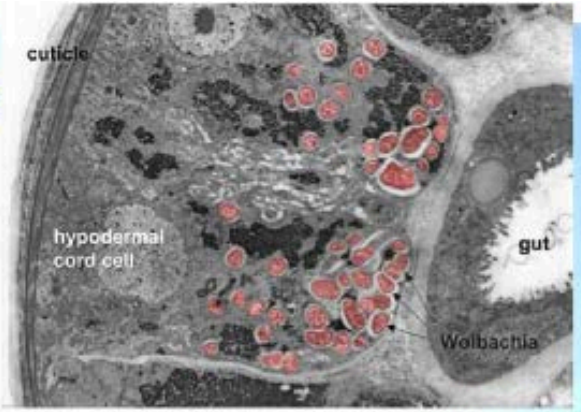


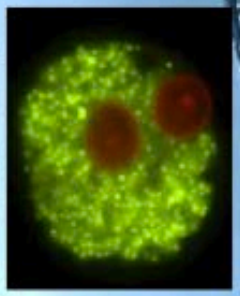




Hoerauf, Curr Opin Infect Dis 2008,
Taylor-Hoerauf-Bockarie Lancet 2010

Wolbachia is essential for:





Development
- Larval development
- Embryogenesis

PROPHYLAXIS
TRANSMISSION BLOCKING

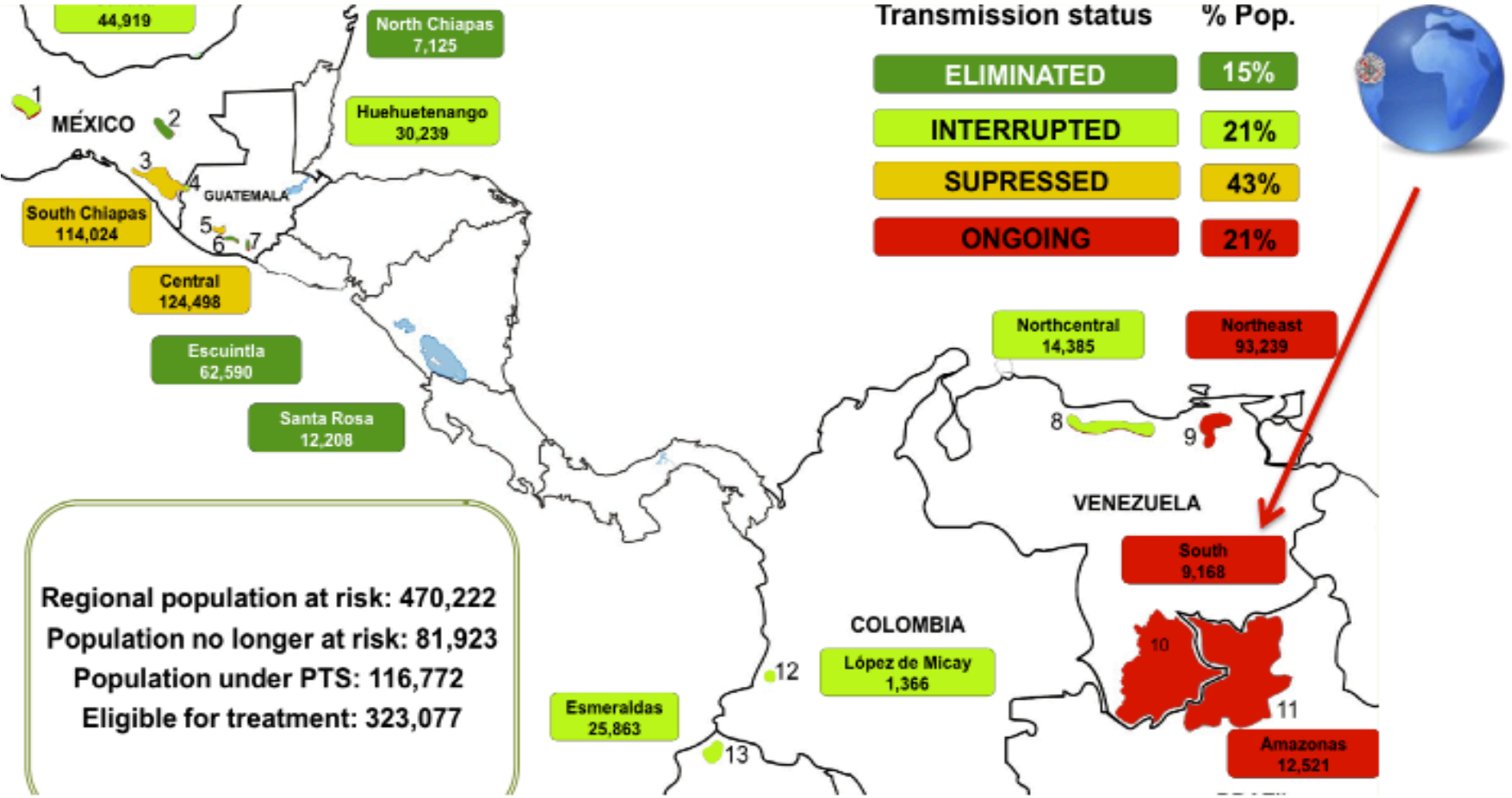
Adult worm longevity (10-14 years)
- Adults depleted of *Wolbachia* die 1-2 years later

MACROFILARICIDAL

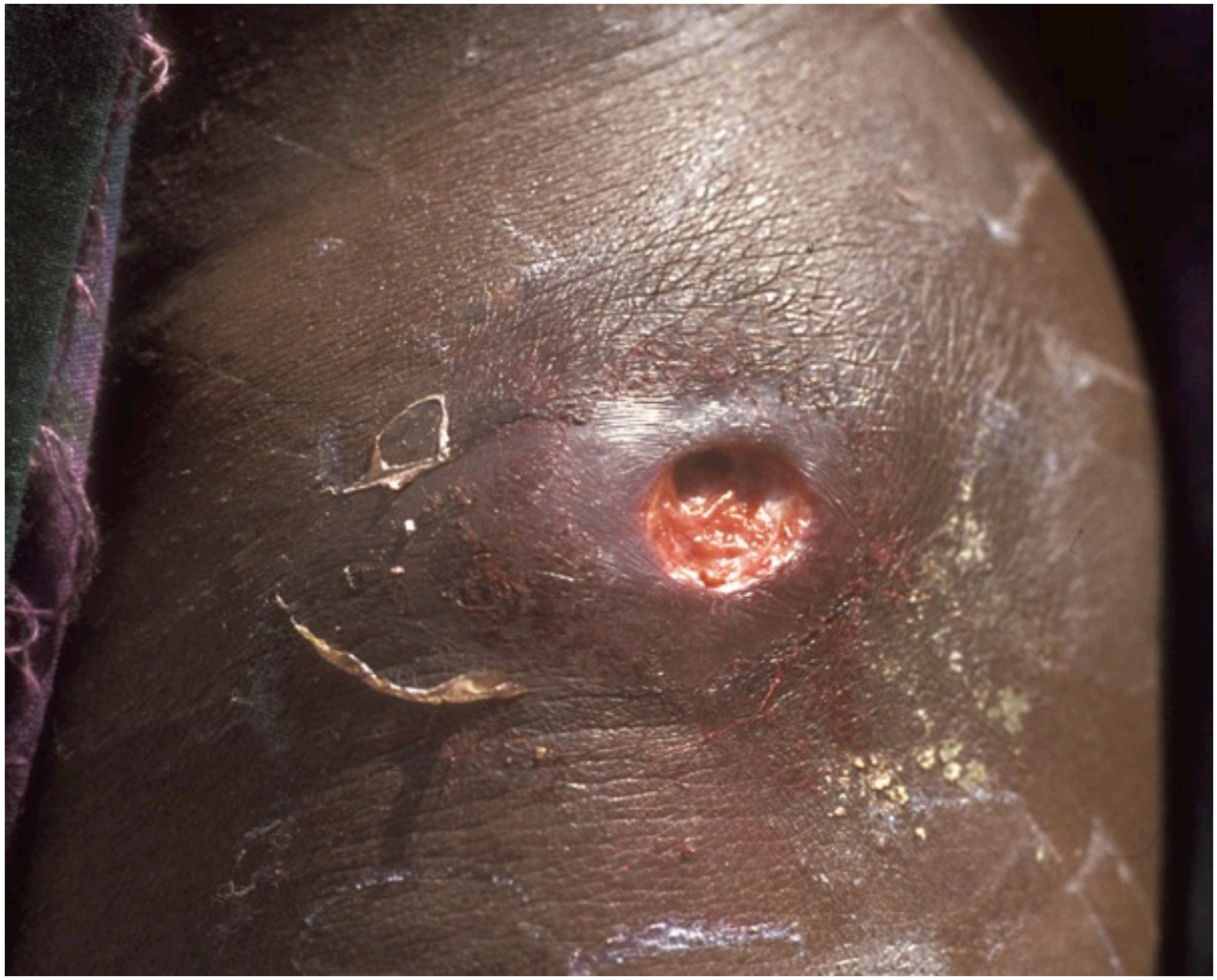
Disease pathogenesis
- Inflammatory SAE
- Clinical disease

CLINICAL CASE MANAGEMENT

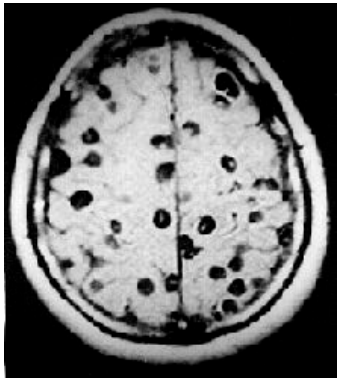
DOXY adopted by OEPA to shorten MDA timeframe



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

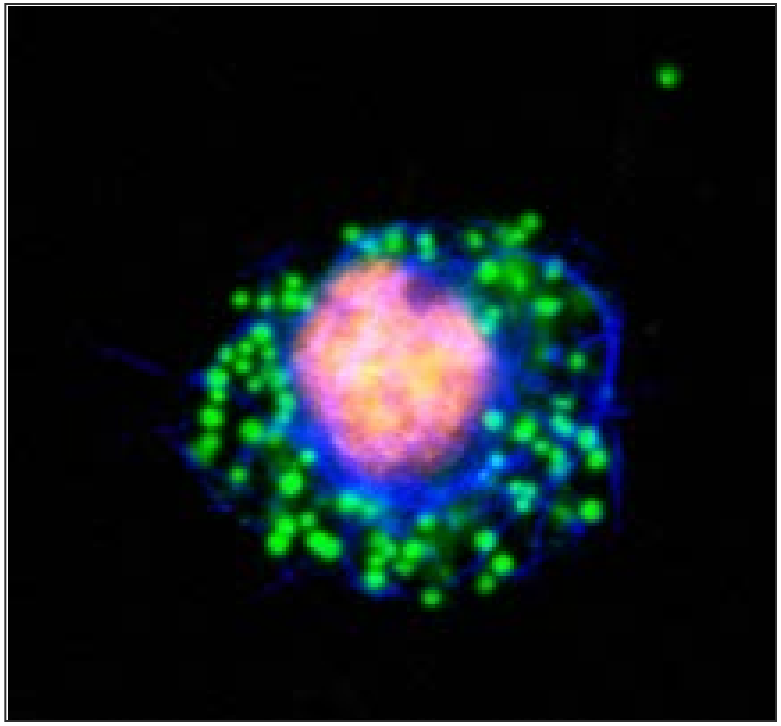
= Scrotal inflammatory lesions

- Cysticercosis – *Taenia solium*

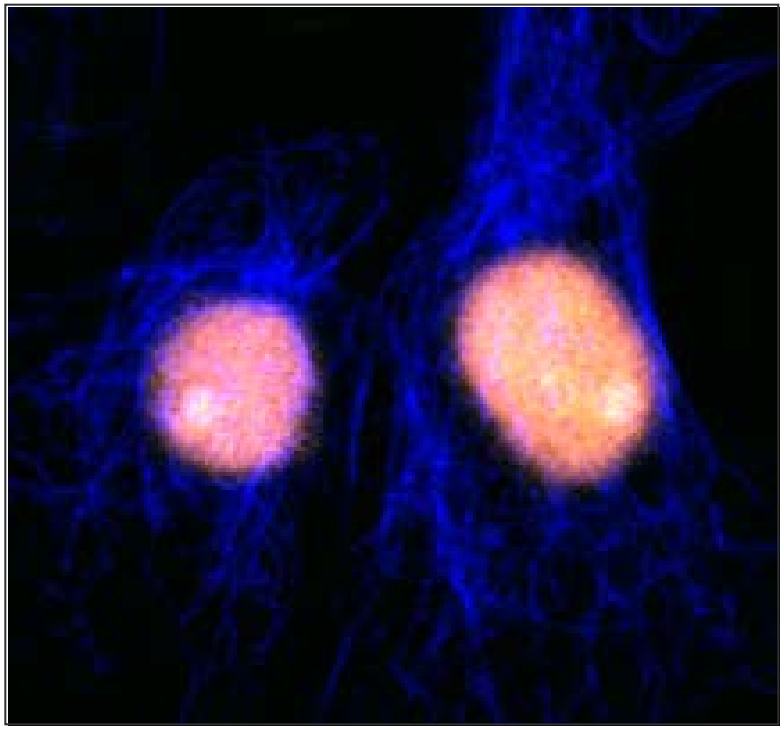
Microfilaricidal SAE (parasite and *Wolbachia* mediated)

- **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 Anti-Wolbachia Consortium ©2007

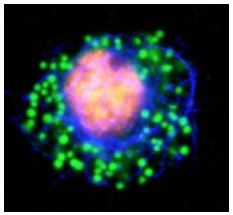
A·WOL ANTI-WOLBACHIA CONSORTIUM

LSTM LIVERPOOL SCHOOL OF TROPICAL MEDICINE

A·WOL Screening Funnel

Wolbachia cell assay in vitro

7 day assay
qPCR readout



Onchocerca/ Brugia Adults in vitro

5 day assay
qPCR, motility

Litomosoides mouse in vivo

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

Brugia Jird in vivo

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

Human

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

Abbott A Promise for Life
Pfizer
ANACOR PHARMACEUTICALS
AstraZeneca
TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
SIMM
BioFocus A Galápagos Company
Medicines for Malaria Venture
BROAD INSTITUTE

A·WOL's GOALS

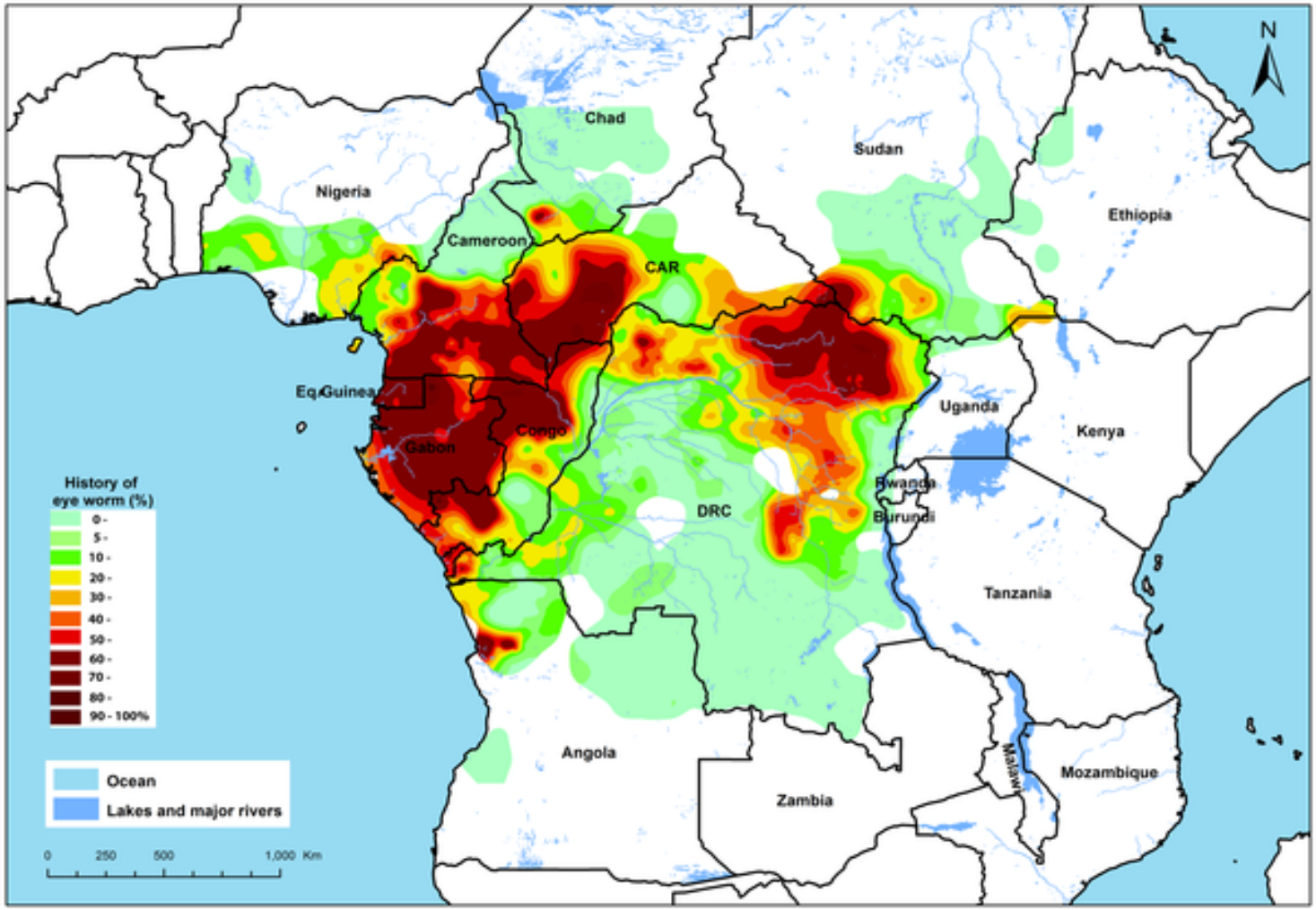
1) To find a new anti-*Wolbachia* treatment compatible with **MDA** programmes for onchocerciasis and lymphatic filariasis.

- 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**

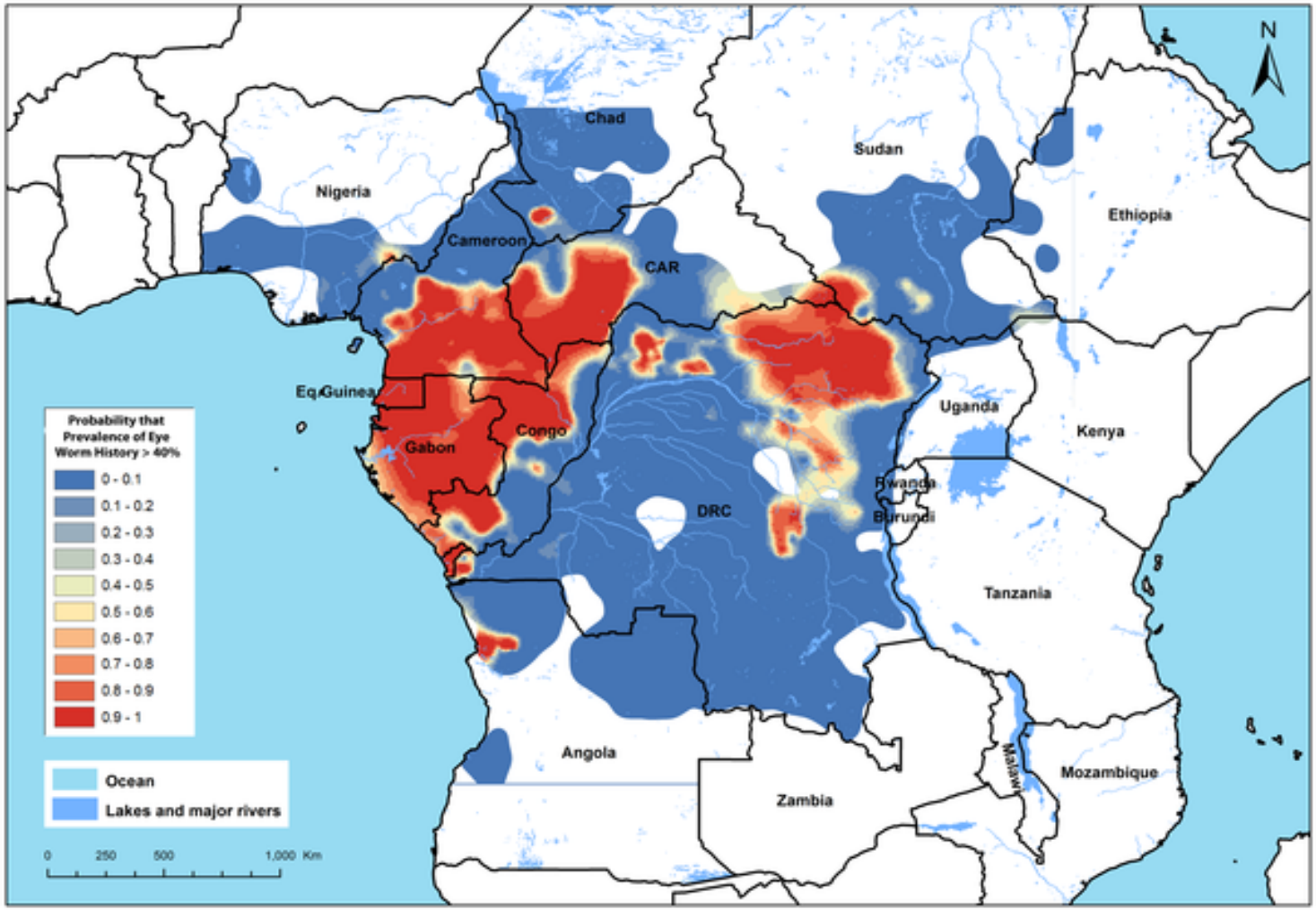


Zouré HGM, Wanji S, Noma M, Amazigo UV, et al. (2011) The Geographic Distribution of Loa loa in Africa: Results of Large-Scale Implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). PLoS Negl Trop Dis 5(6): e1210. doi:10.1371/journal.pntd.0001210
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001210

PLoS NEGLECTED TROPICAL DISEASES

Map of the predictive probability that the local prevalence of eye worm history exceeds 40%.

~15 MILLION AT RISK OF SAE



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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.

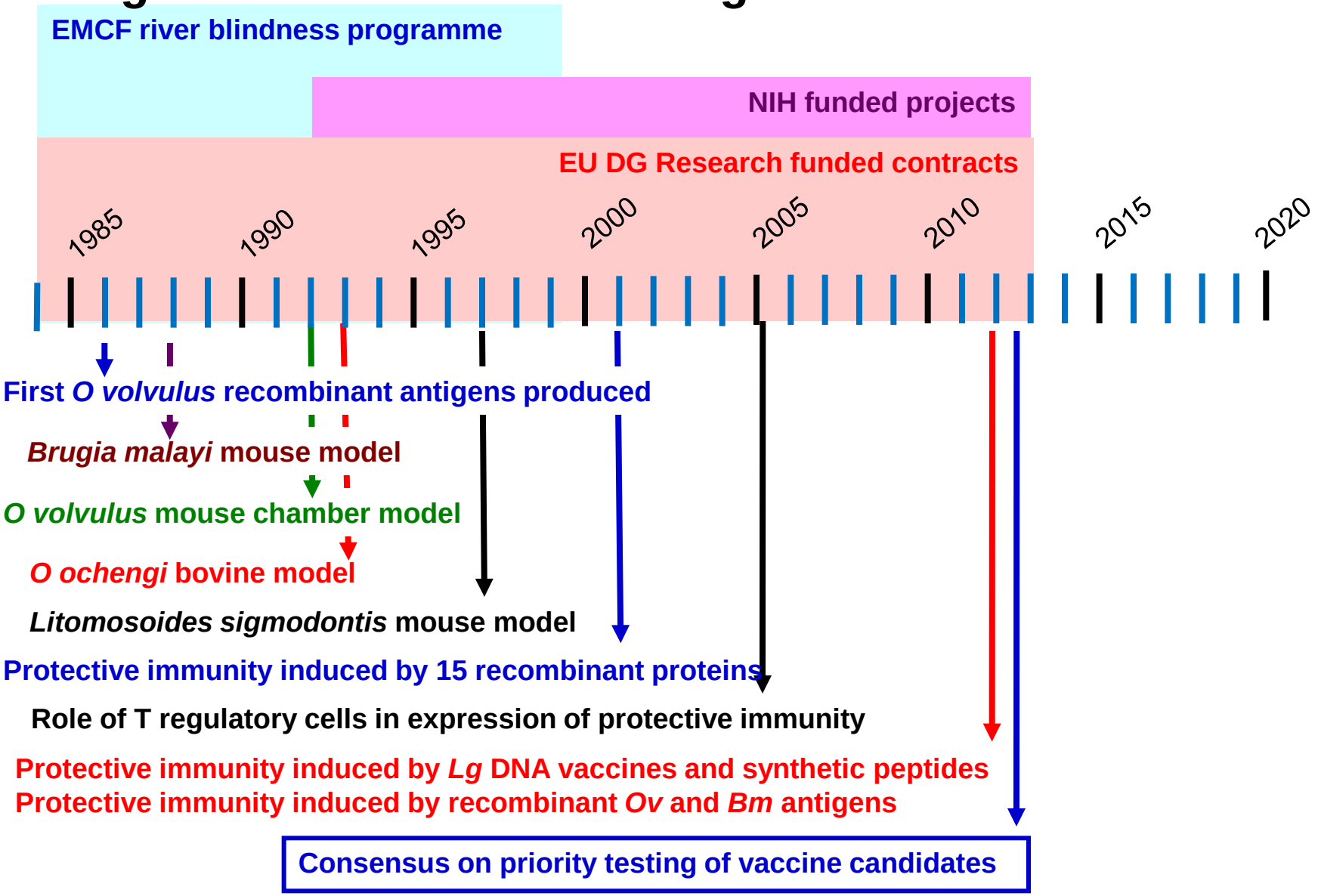
2013: Optimized combination and improved monotherapy with registered **2nd generation A·WOL drugs** with delivery from **weeks to days**

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

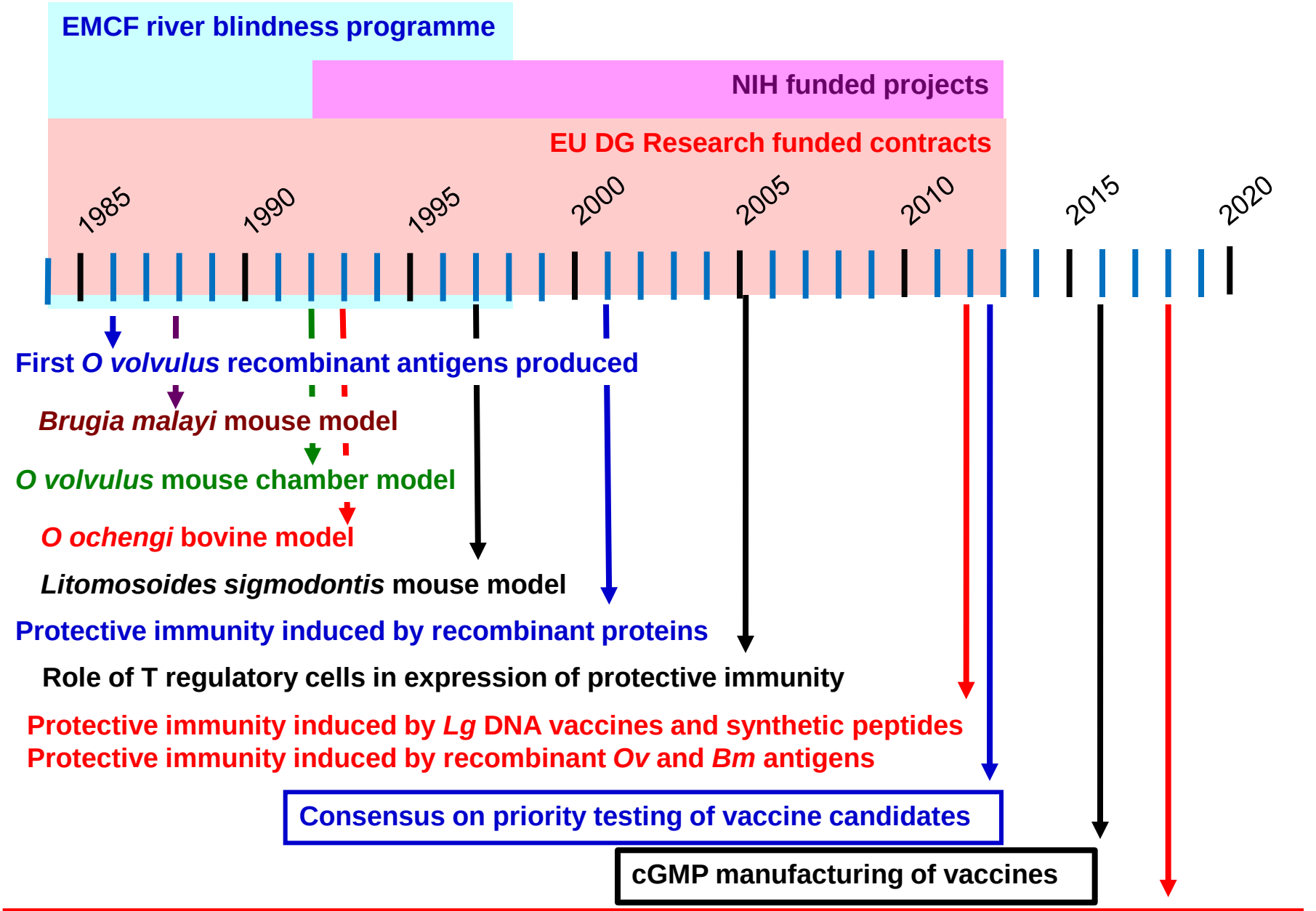
2017: Pre-clinical candidates of **3rd generation A·WOL drugs**

2020: **A·WOL 3rd generation clinical candidate - Phase III trial**

Progress towards a vaccine against river blindness



Progress towards a vaccine against river blindness

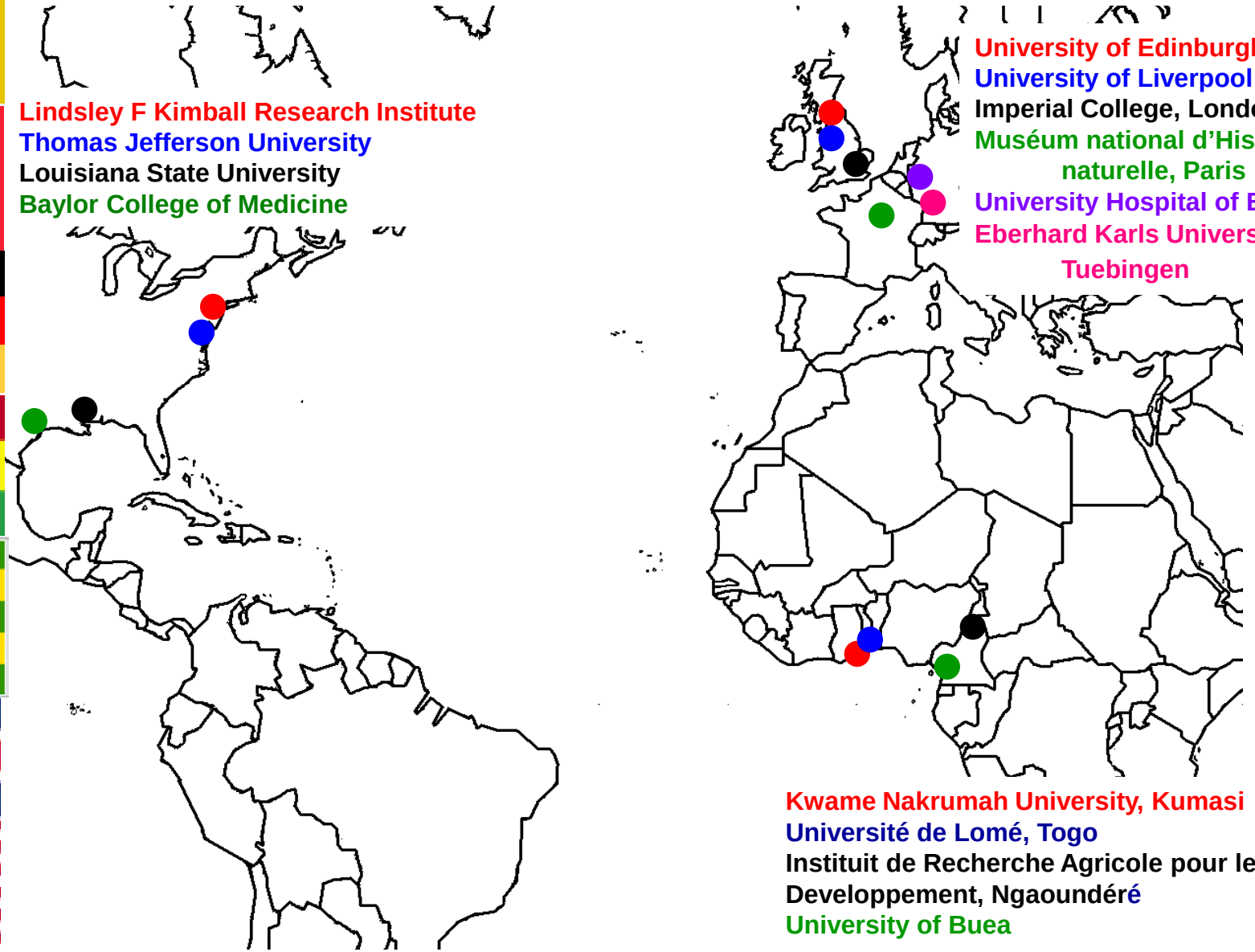


The vaccine candidates

Antigen	Location	In vitro killing	In vivo L3 killing	In vivo Adult killing	In vivo Mf killing
CPI	ES, Surface, all stages	*Ov* L3 94% neutrophils	*Ov* 37% (recom prot)	*Ls* 50% (recom prot) *Ls* 70% (DNA)	*Ls* >85% (DNA) *Ls* >85% (syn pep)
RAL2	ES, surface, all stages	*Ov* L3 100% neutrophils	*Ov* >44% (recom prot)	*Bm* >60% (recom prot)	*Bm* >90% (recom prot) Ls >90% (DNA)
Ov103	Surface, all stages	*Ov* L3 100% neutrophils	*Ov* >40% (recom prot)	*Bm* >40% (recom prot)	*Ov* Mf 93% neutrophils

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
Instituit 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

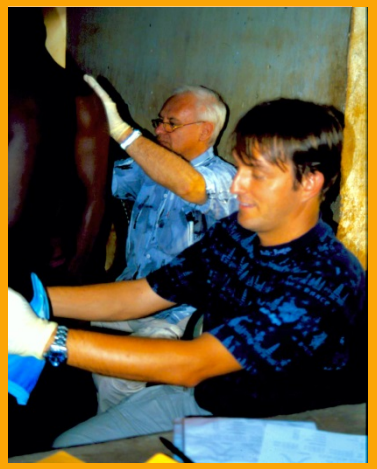
Summary - needs for filariasis

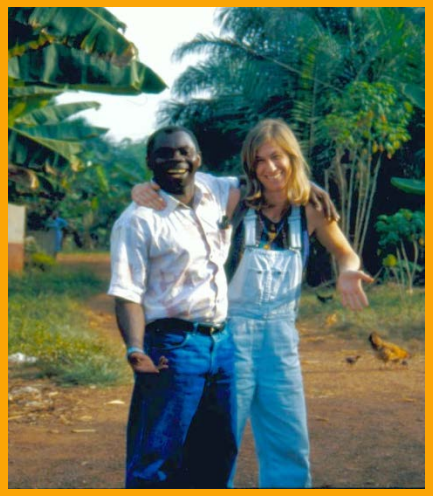
- Develop new macrofilaricidal drugs
  - Surrogate animal models are in place
  - Ideally compatible with MDA (incl. children)
- Implement existing macrofilaricidal drugs, e.g. doxycycline
  - („Mopping-up“ scenarios)
  - Test & treat strategies
  - Lymph edema case management
- Define and validate biomarkers (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

Thank you!

ATO