Great Neglected Diseases Network

- Started by the Rockefeller Foundation in 1977
- First and only director Kenneth Warren
- Networks of 14 research units across the world (US, UK, Egypt, Australia, Israel, Sweden, Mexico, Brazil, Thailand)
  - Multidisciplinary
  - Emphasis on research - immunology, biochemistry, molecular biology, genetics
  - Disease focus – parasitic infections including malaria

- Lasted only 8 years
  - But spawned the careers of a generation of parasite-oriented scientists
The Millenium Development Goals

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

2000-2015 MDGs
From GNDs to Neglected Tropical Diseases (NTDs)

• Attributed to and popularized by
  – Peter Hotez
  – David Molyneux
  – Alan Fenwick

• Grew out of frustration from the use of the term “Other Diseases” in MDG #6 as it
  – created a two-tier system (HIV, malaria vs everything else)
  – made public advocacy for these “other diseases” impossible
  – left out these “other diseases” in most discussions on global health

• NTD “marketing” has driven funding worldwide
The Neglected Tropical Diseases (NTDs)

- The most prevalent infections of poor people
  - Up to half of the 2.7 billion people who live on less than $2 per day

- Non-emerging ancient conditions

- Indigenous populations

- Chronic disabling conditions
  - Growth delays
  - Blindness
  - Disfigurement
  - Stigma

- Poverty promoting conditions
  - Child development and education
  - Pregnancy outcome
  - Productive capacity
The 10 Leading Causes of Life-Years Lost to Disability and Premature Death

<table>
<thead>
<tr>
<th>Condition</th>
<th>Disability-Adjusted Life-Years (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory tract infections</td>
<td>91.4</td>
</tr>
<tr>
<td>HIV-AIDS</td>
<td>84.5</td>
</tr>
<tr>
<td>Unipolar depression</td>
<td>67.3</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>62.0</td>
</tr>
<tr>
<td>Ischemic heart diseases</td>
<td>58.6</td>
</tr>
<tr>
<td>Neglected tropical diseases</td>
<td>56.6</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>49.2</td>
</tr>
<tr>
<td>Malaria</td>
<td>46.5</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>38.7</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>34.7</td>
</tr>
</tbody>
</table>
The Neglected Tropical Diseases

- Scabies
- Snakebites
- Mycetoma and other deep mycoses
Common Human Helminth Infections

- **Trematodes**
  - *Schistosoma mansoni*: >200 million infected
  - *Brugia malayi*, *Onchocerca volvulus*, *Wuchereria bancrofti*: 157 million infected
  - *Ancylostoma duodenale*, *Nector americanus*: 576 million infected

- **Cestodes**
  - *Echinococcus, Taenia spp*: >100 million infected

- **Nematodes**
  - *Ascaris lumbricoides*: >1 billion infected
  - *Strongyloides stercoralis*: 50-100 million infected
  - *Trichinella spiralis*, *Trichuris trichiura*: 600 million infected

References: Babu and Nutman, Clin Immunol, 2017
## Filarial Infections of Humans

<table>
<thead>
<tr>
<th>Infection</th>
<th>Disease</th>
<th>Number infected</th>
<th>Wolbachia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Lymphatic Filariasis</td>
<td>120 million</td>
<td>Yes</td>
</tr>
<tr>
<td>Brugia spp.</td>
<td>Lymphatic Filariasis</td>
<td>10 million</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Onchocerciasis</td>
<td>29 million</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Loiasis</td>
<td>13 million</td>
<td>No</td>
</tr>
<tr>
<td><em>Mansonella ozzardi</em></td>
<td>Mansonellosis</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Mansonella perstans</em></td>
<td>Perstans Filariasis</td>
<td>~90 million</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Mansonella streptocerca</em></td>
<td>Streptocerciasis</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Collectively 2\textsuperscript{nd} leading cause of disability worldwide (>1.2 million DALYs lost)
Loiiasis

- **Organism:** *Loa loa*
- **Vector:** Chrysops spp. (deerfly)
- **Microfilariae:** Blood-borne
- **Adult worms:** Subcutaneous
- **Prevalence:** 13 million
- **Geographic Distribution:** West and Central Africa
- **Host range:** Human
Geographic distribution of *Loa loa* infection
Lifecycle of Loa loa
Loiasis - Clinical Manifestations

- Asymptomatic (subclinical)
- Non-specific
  - urticaria, pruritus, myalgias
- Calabar swellings
- Eyeworm
- Complications
  - Endomyocardial fibrosis, renal disease, encephalopathy, entrapment neuropathy
Loiasis – Calabar Swellings

- Episodic angioedema
- Most common on extremities
- Duration 1-4 days
Loiasis - Eyeworm
Clinical differences between endemic and non-endemic patients with loiasis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Expatriate N=42</th>
<th>Endemic (Benin) N=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabar swelling</td>
<td>80%</td>
<td>16%</td>
</tr>
<tr>
<td>Eyeworm</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>16%</td>
<td>74%</td>
</tr>
<tr>
<td>Nonspecific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria/myalgia/arthritis</td>
<td>54%</td>
<td>???</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria/proteinuria</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>2%</td>
<td>???</td>
</tr>
</tbody>
</table>

Clinical differences between endemic and non-endemic patients with loiasis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Expatriate N=144</th>
<th>Endemic N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabar swelling*</td>
<td>80%</td>
<td>15%</td>
</tr>
<tr>
<td>Eyeworm*</td>
<td>14%</td>
<td>62%</td>
</tr>
<tr>
<td>Asymptomatic (MF+)*</td>
<td>22%</td>
<td>74%</td>
</tr>
<tr>
<td>Nonspecific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria*</td>
<td>19%</td>
<td>2%</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Lymphadenopathy*</td>
<td>11%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Complications associated with *Loa loa* infection

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Expatriate N=144</th>
<th>Endemic N=37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria/proteinuria</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Eosinophilic endomyocardial fibrosis in a patient with loiasis
Modulation of Immune Response to Filarial Infection as a Function of Time

**Antibody and Eosinophil Responses**

- Eosinophils
- IgE
- IgG4

**CD4+ T Cell Responses**

- Response to Parasite Antigens
- Response to Bystander Antigens/Allergens/Vaccines

**Chemotherapy**

- Anti-filarial Chemotherapy
- Anti-IL-10 *in vitro*

**Life Cycle of Lymphatic Filariae**

- EGG
- L1
- L2
- AD
- U
- LT
- L3
- L4

**Early Infection**

- 0 to 6 months

**Chronic Infection**

- 6 months to Decades
Immune Responses as a Function of Time in Human Helminth Infection

Initiation and establishment of infection

Development of adult worms

Patency

Response to parasite antigen

Response to bystander antigen/vaccines/allergens

Response to parasite antigen

0 - 2 weeks - Up to 6 months - Decades

Response to parasite antigen
Immune-mediated pathology

Parasite → Host

Uncontrolled response
Pro-inflammatory

Immune-mediated pathology

Modulated response
Tolerant/suppressed

Patent subclinical infection

IL-10

Lympahtic Filariasis
Onchocerciasis
Loiiasis
Loiasis: treatment

- **Diethylcarbamazine (DEC)**
  - treatment of choice
  - mechanism of action unknown
  - macro- and microfilaricidal
  - associated with severe side effects in patients with high levels of circulating microfilariae

- **Ivermectin**
  - microfilaricidal
  - also associated with severe side effects in patients with high microfilarial levels
Loiasis: adjunct therapy

- **Corticosteroids**
  - decrease rate of microfilarial clearance
  - reduce severity of post-treatment reactions
  - DO NOT prevent severe CNS complications of treatment in patients with high microfilarial loads

- **Apheresis**
  - transient reduction of microfilarial load
  - ?decreased incidence of severe side effects
Filarapheresis

From 1990 - present

• Numbers
  – 46 heavily microfilaremic patients
  – 68 procedures
  • Often on successive days

• Issues
  – Must be done at midday

Efficiency of filarapheresis

Average reduction 67%
Periodicity of various microfilariae in blood
The *Loa loa* Genome

Extraordinary degree of synteny among the filariae

Desjardins et al *Nature Genetics* 2013
## Worm kinases that are targets of FDA-approved drugs

<table>
<thead>
<tr>
<th>Classification</th>
<th>FPKM</th>
<th>L. loa</th>
<th>W. bancrofti</th>
<th>B. malayi</th>
<th>A. suum</th>
<th>P. pacifica</th>
<th>C. elegans</th>
<th>C. briggsae</th>
<th>M. hapla</th>
<th>T. spiralis</th>
<th>Approved drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGC/DMPK/ROCK</td>
<td>58.18</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Fasudil</td>
</tr>
<tr>
<td>ATYPICAL/PIKK/FRAP</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>TK/ABL</td>
<td>18.87</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Imatinib, Nilotinib, Dasatinib</td>
</tr>
<tr>
<td>TK/EGFR</td>
<td>0.18</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Gefitinib, Erlotinib, Lapatinib</td>
</tr>
<tr>
<td>TK/SRC</td>
<td>40.86</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>TKL/RAF/RAF</td>
<td>27.55</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Sonafenib</td>
</tr>
</tbody>
</table>
Structural similarity between the filarial abl-like kinase and the human Bcr-abl oncogene.
Repurposing imatinib for antifilarial chemotherapy

O’Connell EM et al, JID 2015
Filarial c-abl Localizes Most Strongly to the Female Reproductive Tract of the Filariae

Clinical Protocol to Establish Efficacy and Safety of Single Dose Imatinib in *Loa loa* Microfilaremia

Randomized-controlled dose escalation trial of imatinib, evaluating the kinetics of *Loa loa* microfilarial (MF) response over 1 year in Cameroon

Severe adverse reactions (encephalopathy, death) to ivermectin is related to the *Loa loa* MF count and the rapidity with which it works.

Proposed use:
Give drug for routine mass drug administration (MDA) during MF nadir to avoid severe reactions.
It Takes a Village Large Community