Optimization of chemotherapy for control and elimination of onchocerciasis and lymphatic filariasis

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Death to Oncho and LF, the “DOLF” project
DOLPH LUNDGREN
Welcome and introductions

Meeting participants

Overview of the DOLF project

Outline and Agenda for the Meeting

**Administrative issues:** Travel reports/reimbursement, US Govt forms, Social functions
Filariasis Research at Washington University 1982-2010

Diagnostic tests for LF and Oncho: Antigen, antibody, DNA detection
- Pioneered use of school children as sentinels to assess infection prevalence and interruption of transmission of LF and Oncho (Egypt, Burkina Faso)
- Detailed studies of effects of MDA on filariasis parameters (Egypt, PNG, Sri Lanka)

Protective immunity:
- Antigens recognized by animals vaccinated with irradiated L3
- First protective immunity with a recombinant filarial antigen (paromyosin)
- First to show humoral and cellular immune responses after DNA vaccination
- Effects of radiation on gene expression in filarial L3
- Population-based field studies of protective immunity to filariasis (Egypt)

Gene expression in filarial parasites
- First high density microarray for a nematode parasite (WashU GSC, FGP)
- Studies of gender and stage regulated gene expression
- In situ localization of gender-regulated genes associated with reproduction

Wolbachia research:
- Effects of antibiotics on Wolbachia and filarial worms
- Filarial species without Wolbachia contain Wolbachia-like sequences in chromosomal DNA (virtual Wolbachia).
New Golden Age for Global Health

- Global Fund (HIV, Malaria, TB)
- PEPFAR: USA Intl HIV/AIDS (2010, $6.8 Bn)
- USAID Integrated Control of NTD (2011, $155M)
- Presidents Malaria Fund (2010, $0.5 Bn)
- PHARMA Donation Programs
- Bill and Melinda Gates Foundation (2008, $1.8Bn) – (Malaria, LF, HIV, NTDs, etc)
- Clinton Global Initiative

These initiatives represent new opportunities for “making a difference” and for funding!
Bill and Melinda Gates Foundation

- Global Development Program
  - Overcome hunger and poverty in developing countries

- Global Health Program
  - Discovery, delivery, advocacy
  - Diarrheal diseases, AIDS, malaria, pneumonia, tuberculosis, *neglected tropical diseases*
  - Grand Challenges Explorations
    - $100 million to foster innovation in global health research

- United States Program
  - Libraries
  - Secondary and postsecondary education
  - Pacific Northwest
**Box 1. The Thirteen Neglected Tropical Diseases in Africa and Their Major Etiologic Agents**

**Protozoan Infections**
- African trypanosomiasis: *Trypanosoma gambiense, T. rhodesiense*
- Kala-azar (visceral leishmaniasis): *Leishmania donovani*

**Helminth Infections**
- STH Infections
  - Ascariasis: *Ascaris lumbricoides*
  - Trichuriasis: *Trichuris trichiura*
  - Hookworm infection: *Necator americanus*
- Schistosomiasis
  - Urinary schistosomiasis: *Schistosoma haematobium*
  - Hepatobiliary schistosomiasis: *Schistosoma mansoni*
- Lymphatic filariasis: *Wuchereria bancrofti*
- Onchocerciasis: *Onchocerca volvulus*
- Dracunculiasis: *Dracunculus medinensis*

**Bacterial Infections**
- Trachoma: *Chlamydia trachomatis*
- Leprosy: *Mycobacterium leprae*
- Buruli ulcer: *Mycobacterium ulcerans*
Lymphatic filariasis endemic countries and territories by mass drug administration (MDA), 2007

3 Billion treatments 2000-08; now approx 400 million/year
Challenges to the MDA Strategy

• Inadequate financing / political will, especially in Africa

• Endpoints: When to stop MDA

• Compliance

• Loa co-endemicity (risk of SAE’s)

• We need new and better treatments
  – Better activity vs. adult worms
  – Over-reliance on a few drugs makes programs vulnerable (drug resistance, availability, etc.)
River blindness (Onchocerciasis)

- ~37 million people infected (Africa)
- Blindness in 300,000
- Also severe dermatitis
- No good treatment for adult worms
- APOC limited to areas with >20%
- Now being considered for global elimination
Loa / Oncho overlap areas. LF also overlaps with loiasis, but more information needed

Burnham, Lancet 1997

Chrysops sp., copyright, Univ. FL
Death to Onchocerciasis & Lymphatic Filariasis (DOLF)

• **Objective 1**: Accelerated MDA: Large scale annual vs twice/year MDA with modeling and cost analysis (P. Fischer)

• **Objective 2**: Randomized clinical trials of new combinations/schedules (J. Kazura, C. King)

• **Objective 3**: Preclinical development of *Flubendazole* as a macrofilaricide: “Teaching an old *drug* new tricks” (C. Mackenzie, T. Geary)
Major questions and goals of DOLF

Lymphatic Filariasis
• Cost / efficacy impact of accelerated MDA for LF in 6 countries
• Can single drug MDA with Albendazole solve the problem of controlling or eliminating LF in Loa-coendemic areas?

Onchocerciasis
• Is repeated combination treatment with Alb/Ivermectin more effective than Iver alone for onchocerciasis?
• Impact of Iver/Alb provided for LF on coendemic Oncho
• These studies will improve the evidence base to support plans to go for Oncho elimination in Africa
Soil-Transmitted Helminth Infections

- DOLF is an *integrated NTD research program* (LF, Oncho, STH)
- We will compare the impact of annual and semiannual LF MDA regimens on STH prevalence rates and intensities in 6 countries
- *The scale and breadth of these STH studies are unprecedented*
- This work will use the new FLOTAC method for detecting worm eggs

Flubendazole project: *high risk / high reward*

A safe and effective macrofilaricide would answer many prayers. This would change everything for LF, Oncho, and Loiasis
Outline for the First DOLF Meeting

Part 1: Monday-Tuesday
Plenary sessions for TAT and Project Researchers
A. Technical Advisory Team meeting 08:30-10:30
B. Combined meeting of participants and advisors
• Review DOLF Goals, Objectives
• Review progress
• Scientific presentations
• Country presentations
• Draft protocols for MDA and Clinical Trials

Part 2: Wednesday-Thursday
Practical sessions for project researchers
• SOPs for laboratory, data collection, cost data
• GCP, IRB issues
• Country-specific protocols
• Development of country-specific budgets
Administrative Issues
Jennifer Klenke, Gina Haida, and Andrew Majewski

Travel expense reimbursement
• Some travel self pay or covered by CWRU, MSU

For Wash U-sponsored travel
• US Govt forms for international visitors
• WashU Travel Reports
• Receipts

Social Events
• Dinner Monday evening
• City tour Tuesday evening