Schistosomiasis Transmission Control

Reality or just a dream?

Chronic Health Impacts of Schistosomiasis

Less obvious symptoms: growth stunting, anemia, abdominal pain, exercise intolerance, poor school performance, lowered work capacity

Total impact of Schistosomiasis

Our former 'objective' morbidity standards (e.g., hepatosplenomegaly, hematuria) are only the tip of the disease/disability iceberg

Pain, diarrhea, undernutrition and anemia are clearly associated with infection, worse with heavier infection, and reversible, at least in part, by elimination of infection

Significant chronic inflammatory disease

DALY: disability-adjusted life year

Chronic infection/transmission has been overlooked

Praziquantel

DALYs lost: 6-13.5 million

TREND in transmission
Idea of the “poverty trap”

Schistosomiasis Control Initiative

http://www.sci-ntds.org

1. To encourage development of a sustainable schistosomiasis control programme in sub Saharan Africa.
2. In the selected countries:
   - To reach at least 75% of school-age children and other high-risk groups with chemotherapy - praziquantel and albendazole.
   - Reduce schistosomiasis-related morbidity in high risk groups.
   - Reduce prevalence and intensity of schistosomiasis infections.
   - Reduce burdens due to intestinal helminths in the targeted populations.
3. Create a demand for sustained schistosomiasis control.
4. To promote access to anthelmintic drugs and good case management in the regular health system.

Disease Control

Chemotherapy

Single drug use praziquantel
Artemisinin for schistosomiasis and beyond

Good News
Decrease in price
Decrease in morbidity (as defined)

Bad News

Vector Control

Transmission
Prevention

Vaccines

Disease Symptoms
Constant use

Disease Control
**Disease Control**

Treatment would reduce the number of eggs, thereby reducing transmission and re-infection.

**Who was treated?**
School-age children in attendance

**Bad News**
did not stop transmission
Super-spreaders
Zoonotic reservoirs

**Next comprehensive phase - prevent re-infection**

**Vector Control**

**Disease**

**Symptoms**
Constant use of drug

**Prevention**

**Transmission**

**Vaccines**

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**Poyang Lake**

**Largest freshwater lake**

The lake helps regulate water in the Yangtze River by providing water to the river during low water periods and receiving water from the river during the high water period.

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**Schistosoma Genomics**

- Schistosoma Genome Network (SGN): international collaboration of labs
- Finally! Genome of *Schistosoma mansoni* is sequenced 2009
  [http://www.sanger.ac.uk/Projects/S_mansoni](http://www.sanger.ac.uk/Projects/S_mansoni)
- Genome structure: ~ 363 Mbp (~1/9 human genome; C. elegans ~ 100 Mbp; Drosophila melanogaster ~ 182; Anopheles gambiae ~ 278; Plasmodium falciparum ~ 23 Mbp; E. coli ~ 5 Mbp)
  - ~ 20% repetitive sequences, much of which is retrotransposable elements (or other mobile genetic elements)
  - Diploid, with 8 pairs of chromosomes (1 sex determination pair)
- Estimated to be 11,809 genes – 13,197 transcripts - (can you explain this?)
- Mitochondrial genome – analysis says *Schistosoma* genus has an Asian origin (but *Biomphalaria* Africa SM yrs)
- Additionally, Transcriptome (microarrays) and proteome projects
What about the biology?

- What life cycle stage should be studied?
- Material?
- Genetics?
- Biochemistry?
- Huge technical hurdles
- Most of the work has been on the host immune response - not the parasite itself
- Now - Genome Project!

RNAi in flatworms

- Planaria - turbellarian
- Feed worms bacteria expressing dsRNA + food coloring
- Know which animals ingested the dsRNA

Ingestion of bacterially expressed double-stranded RNA inhibits gene expression in planarians
PNAS 2003 vol 100, Suppl. 1, 11861

Methods to Introduce dsRNA

- Soaking
- Electroporation
- Microinjection
- Biolistic
Optimization

Life cycle stage: Schistosomula

Initial RNAi studies: cathepsin B (most abundant cysteine protease)

Study the function of genes

- RNA - early studies
- Schistosomula form
- CB1 - cysteine protease
  - Major proteinase
  - Hemoglobin digestion
  - Electroporation
  - Transient transfection
  - Lasting effect of dsRNA
  - 7 days, 26 days
  - In vitro culture
  - In vivo mouse model
  - Essential for growth!

Logic: If the major protease is depleted, the parasite will suffer from malnutrition and growth retardation.

Schistosomula 25 days post dsRNA transfection
- Gut development normal
- Growth was stunted

Impaired Development

- Interesting kinetics
  - 3 vs 7 d. post transfection
- In vivo studies
  - Transform cercaria
  - 3 hr: transfected w/ dsRNA
  - Injected i.m. into mice
  - Development for 3 wks
  - Perfuse to recover parasites

Cathepsin B is important for normal growth (in vitro and in vivo)

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Figure 1: SmInAct is a member of the TGF-β/Activin subfamily

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Figure 2: SmInAct expression is linked to reproductive capability
Figure 3: SmInAct is essential for egg development