TrypanoGEN: An integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis
African Trypanosomiasis Associates with Tsetsefly Distribution

- Animal African Trypanosomiasis (AAT)
  - *T. Vivax*
  - *T. Congolense*
  - *T. brucei brucei*

- Human African Trypanosomiasis (HAT)
  - *T. brucei rhodesiense*
  - *T. b. gambiense*
The problem

- HAT is a fatal neglected disease
- Estimated 70,000 human cases/year
- No vaccine
- Drugs are toxic
- Zoonotic - livestock cases estimated cost $1.3bn/year
- Major impact on human and animal health
Reported incidence of disease

Estimated that 7-10 x more people are affected than reported
New tools are needed

• Wide-spread consensus of the need for novel approaches to achieve elimination or sustainable control
  • New control strategies
  • New therapies
The diversity of infection outcomes

- No infection
- Infection

Targeted by control measures

Parasite genetic diversity – virulence / pathogenicity
Human genetic diversity – resistance / susceptibility
The diversity of infection outcomes

Untreated Human Infections by *Trypanosoma brucei gambiense* Are Not 100% Fatal

Vincent Jamonneau¹,²*, Hamidou Illboudo³, Jacques Kaboré², Dramane Kaba³, Mathurin Koffi⁴, Philippe Solano¹,², André Garcia⁵, David Courtin⁵, Claude Laveissière¹, Kouakou Lingue⁶, Philippe Büscher⁷, Bruno Bucheton¹

¹ Institut de Recherche pour le Développement, Unité Mixte de Recherche IRD-CIRAD 177, Campus International de Baillarguet, Montpellier, France, ² Centre International de Recherche-Développement sur l'Élevage en zones Subhumides (CIRDES), Unité de Recherches sur les Bases Biologiques de la Lutte Intégrée, Bobo-Dioulasso, Burkina Faso, ³ Institut Pierre Richet, Unité de Recherche «Trypanosomoses», Abidjan, Côte d'Ivoire, ⁴ Université d'Abobo-Adjame, URES de Doloa, Laboratoire de Génétique Moléculaire et Evolution des Maladies Infectieuses Tropicales, Doloa, Côte d'Ivoire, ⁵ Institut de Recherche pour le Développement, Unité de Recherche O10, Faculté de Pharmacie, Paris, France, ⁶ Programme National d'Élimination de la Trypanosomose Humaine Africaine, Abidjan, Côte d'Ivoire, ⁷ Institute of Tropical Medicine, Department of Biomedical Sciences, Antwerp, Belgium

Abstract

The final outcome of infection by *Trypanosoma brucei gambiense*, the main agent of sleeping sickness, has always been considered as invariably fatal. While scarce and old reports have mentioned cases of self-cure in untreated patients, these studies suffered from the lack of accurate diagnostic tools available at that time. Here, using the most specific and sensitive tools available to date, we report on a long-term follow-up (15 years) of a cohort of 50 human African trypanosomiasis (HAT) patients from the Ivory Coast among whom 11 refused treatment after their initial diagnosis. In 10 out of 11 subjects who continued to refuse treatment despite repeated visits, parasite clearance was observed using both microscopy and polymerase chain reaction (PCR). Most of these subjects (7/10) also displayed decreasing serological responses, becoming progressively negative to trypanosome variable antigens (LITat 1.3, 1.5 and 1.6). Hence, in addition to the “classic” lethal outcome of HAT, we show that alternative natural progressions of HAT may occur progression to an apparently
The diversity of infection outcomes

Figure 2: Diversity of T. b. gambiense infection outcomes in endemic areas
Exploit human genetic diversity to find the key to combating the disease:

In developing new control strategies
In developing new therapies
Research Question and Objectives

What are the host genetic determinants of disease susceptibility/resistance?

Objectives

• To create an extensive biobank of both retrospective and prospective samples with standardised parasitological and clinical metadata

• To generate a database of human genetic variation from different African countries
  ➢ In order to identify loci associated with HAT susceptibility
HAT per se is controlled by susceptibility/resistance loci and the GWAS that will be carried out in this project will reveal candidate loci for this phenotype.
The current situation for genetic association studies

- Current research is small-scale
- Asymptomatics are not taken into account
- Samples not logged properly and not available to others, often different sampling strategies
- Lack of provision of infrastructure, training and long-term legacy
Our project

- To create for the first time a network that systematically investigates genetic diversity in relation to HAT in endemic areas across the whole of Africa

- Enhance capacity for African-led research into an African disease
The TrypanoGEN Biobank

### Existing samples

<table>
<thead>
<tr>
<th>Controls</th>
<th>SERO</th>
<th>HAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>390</td>
<td>165</td>
<td>1060</td>
</tr>
</tbody>
</table>

### Minimum required for GWAS

<table>
<thead>
<tr>
<th>Controls</th>
<th>SERO</th>
<th>HAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>400</td>
<td>1200</td>
</tr>
</tbody>
</table>

### Activities

#### Year 1
- Biobanking existing samples
- Ethical agreement
  - WGS of 130 controls

#### Year 2
- Design custom Omni2.5 Illumina
  - Candidate gene testing

#### Year 3
- Genotyping 2800 individuals
  - Candidate gene testing

#### Year 4
- GWAS

#### Year 5
- Candidate gene testing

### Training

#### Ethics
- Sampling/biobanking
- Sequence bioinfo
- NGS bioinfo
- SNPs arrays
- Imputation meth.
- GWAS statistics
- 3rd Generation Seq Grantmanship
Our GWAS plan

• To collect biological samples and clinical data from patients and controls.
  • At least 1000 cases
  • At least 1400 controls

• To conduct a GWAS
  • Sequence 130 individuals to obtain local SNPs
    • Focus on four regions:
      Uganda, DRC, Cote d’Ivoire, Guinea
  • Genotype ~half the samples- discovery cohort
  • Genotype the rest for top 1% hits- validation cohort
Re-sequencing of African population N=130 from the 4 centres

Output: To inform SNP imputation

Genotyping

**Discovery cohort**
Stage 2 patients N=600
Asymptomatic controls N=200
Population controls N=500

Output: Top hits

Genotyping of 1% top hits

**Validation cohort**
Stage 2 patients N=400
Asymptomatic controls N=200
Population controls N=900
What we will deliver - science

Short-term
- New African genomes
- Biobank
- Epidemiological data

Medium-term
- HAT susceptibility loci/pathways
- Intervention strategies - policy change?
- Biomarkers for disease severity
- Relevance of asymptomatics in GWAS

Long-term
- New therapies
- New diagnostic tools
What we will deliver – capacity development

**Short-term**
- Biobanking facilities/samples
- Computer infrastructure for storage and analysis of genomic data

**Medium-term**
- Panel of skilled African scientists in genomic analysis
- Bioinformaticians
- PhDs
- Masters
- Technicians

**Long-term**
- Self-sustaining research projects
Team - Who we are

Leading experts in different aspects of HAT
Where we are

9 African + 3 European countries

- UK
- France
- Belgium

Potential for epidemics
- Acute disease
- Capacity building across Africa

TrypanoGEN

T. b. gambiense

T. b. rhodesiense
• Workshops sample collection, GWAS, Bioethics
• Harmonised SOPs across the network
• On-job training by hub-embedded bioinformatician
• Secured and anonymised data and samples
• Sample and data access committee
• Ethics manager and expert ethicists in field of human genetics
• Research into ethical sensitivities in different countries (PhD)
Ensuring delivery

**ETHICS**
Lead: S. MacLean
Deputy: P. Alibu, M. Parker

**TRAINING**
Lead: I. Sidibe
Deputy: D. Mumba

**SAMPLING**
Lead: M. Simuunza
Deputy: D. Mumba

**BIOBANKING**
Lead: D. Mumba
Deputy: E. Matovu, I. Sidibe

**SEQUENCING**
Lead: G. Simo
Deputy: C. Hertz-Fowler

**ANALYSIS**
Lead: K. Mathurin
Deputy: E. Matovu
Ensuring delivery

Scientific Advisory Board

TrypanoGEN Management Committee

Sample and Data Access Committee

Principal Investigators

ADMINISTRATION

- Ethics manager
- Project manager
- Institute Admin support
- Accountant

3 expert Bioinformaticians

7 PhDs

3 Masters

9 Technicians
Areas of potential synergy with other H3 Africa networks

- Ethics
- Training  - grantsmanship
  - bioinformatics and GWAS
  - ethics workshops
- Sharing data policies
- Shared samples
  SNP database
  potential problems – rural Africa
- Logistics
- Infrastructure building
- Communication across Africa
Developments since the Award

• Visit by WT finance team to Makerere University February 2013

• Ethical review (MoH) and recommendation to UNCST

• Ethical approval Granted

• Kick off meeting in Kampala 28-31 May 2013

• Training finance team from participating institutes
Visit our website

- www.trypanogen.net