TrypanoGEN: An integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis

www.trypanogen.net

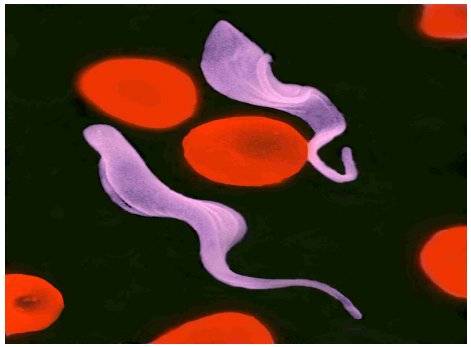
African Trypanosomiasis Associates with Tsetsefly Distribution

Animal African Trypanosomiasis (AAT)

- *T. Vivax*
- *T. Congolense*
- *T. brucei brucei*

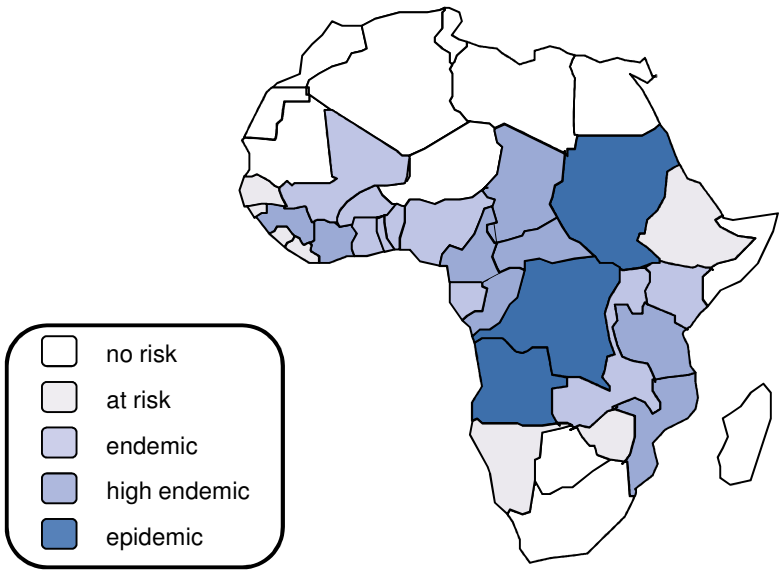
Human African Trypanosomiasis (HAT)

- *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



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

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PLoS NEGLECTED TROPICAL DISEASES

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

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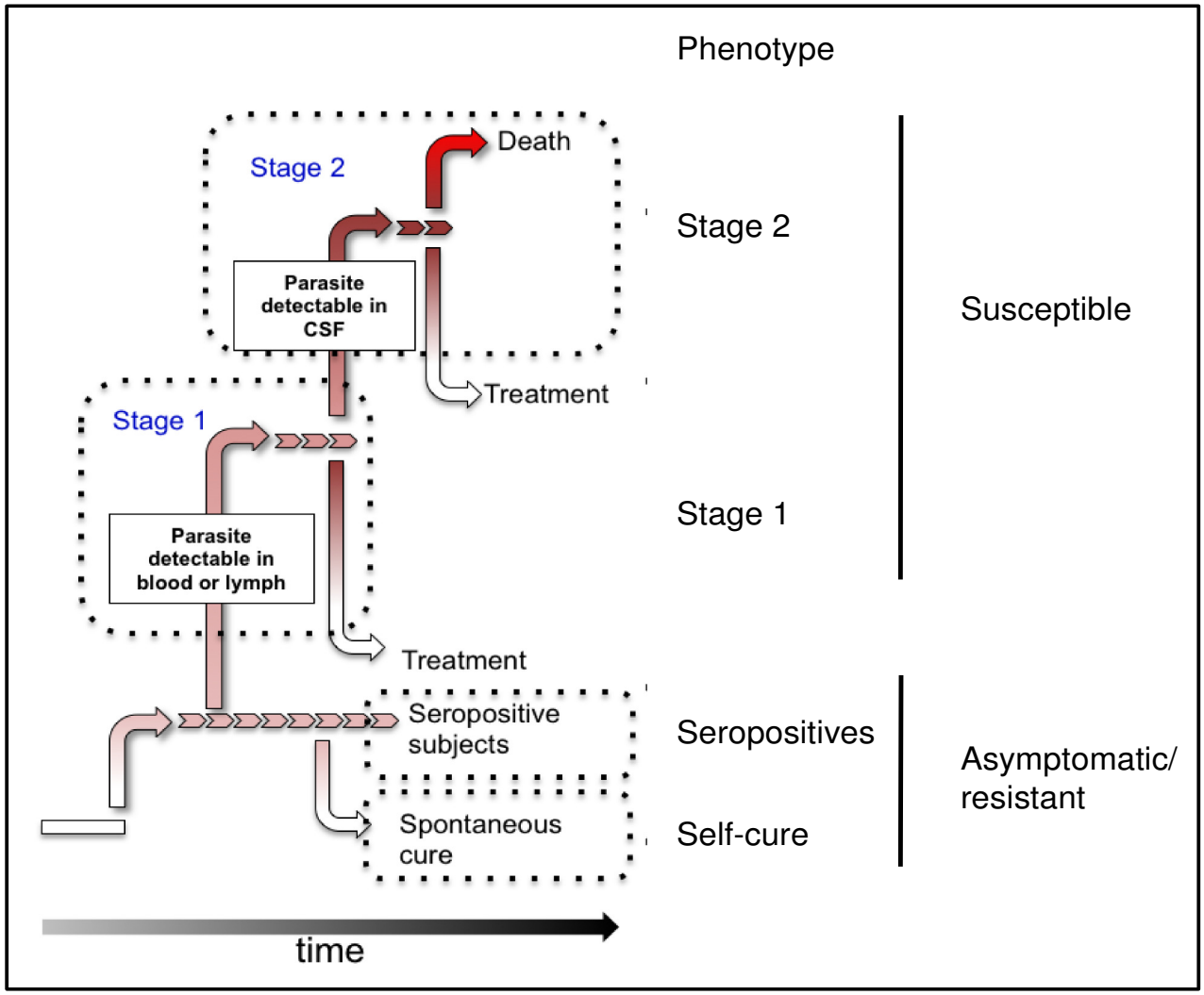
Abstract

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 progressing to an apparently

The diversity of infection outcomes



Research Question/Aim

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

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

Objectives

- Create a network that systematically investigates genetic diversity in relation to HAT in endemic areas across Africa
- 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

Hypothesis

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.

Project overview

The TrypanoGEN Biobank

Existing samples

Controls	SERO	HAT
390	165	1060

Minimum required for GWAS

Controls	SERO	HAT
600	400	1200

Year 1 **Year 2** **Year 3** **Year 4** **Year 5**

Activities

Biobanking existing samples
Ethical agreement

WGS of 130 controls → Candidate gene testing

Design custom Omni2.5 Illumina

Genotyping 2800 individuals

GWAS → Candidate gene testing

Training

Ethics
Sampling/biobanking
Sequence bioinfo

Ethics
NGS bioinfo
SNPs arrays

Imputation meth.
GWAS statistics

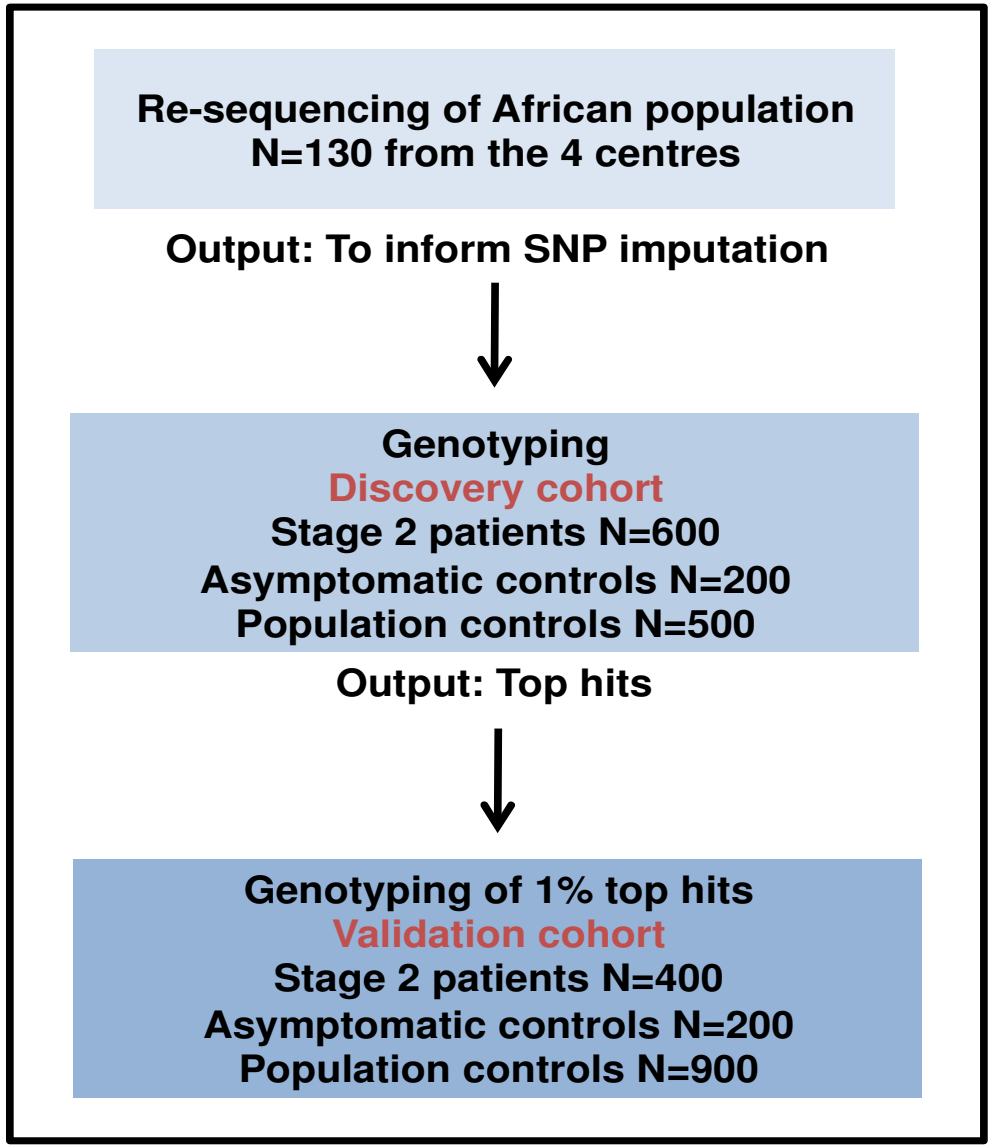
3rd Generation Seq
Grantmanship

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)

Details of GWAS



Case and Control definitions

Cases

- Individuals confirmed as HAT infected by demonstration of Trypanosomes in, blood, Lymph or cerebralspinal fluid

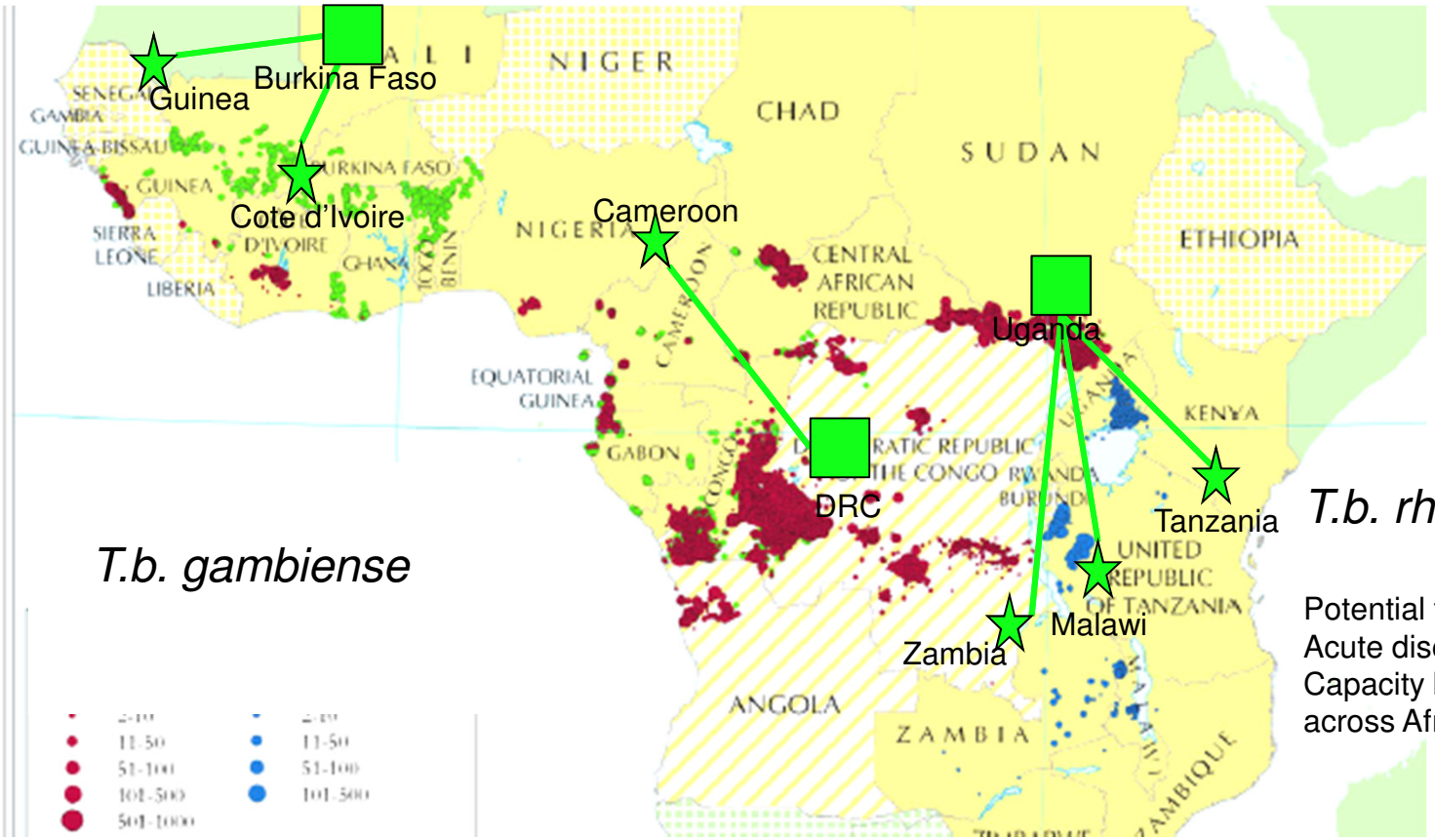
Controls

- Living in same villages as cases
- No Trypanosomed demonstrated in any body fluids
- Serologically negative
- Species specific PCRs to confirm negativity

Who/where we are

9 African + 3 European countries

UK France Belgium

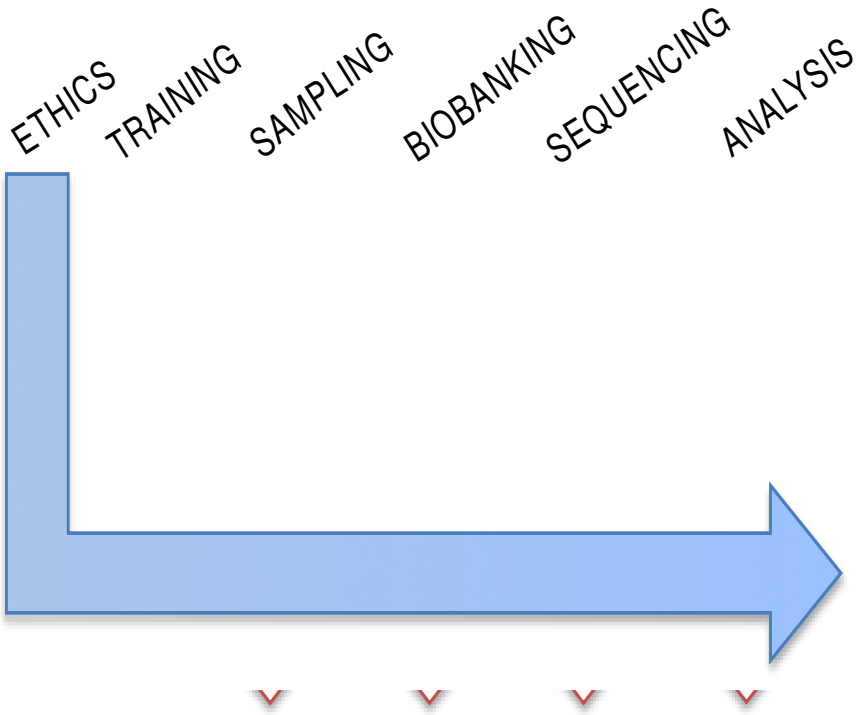


T.b. gambiense

T.b. rhodesiense

Potential for epidemics
Acute disease
Capacity building
across Africa

Ensuring delivery



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

TRAINING
Lead: I. Sidibe
Deputy: D. Mumba

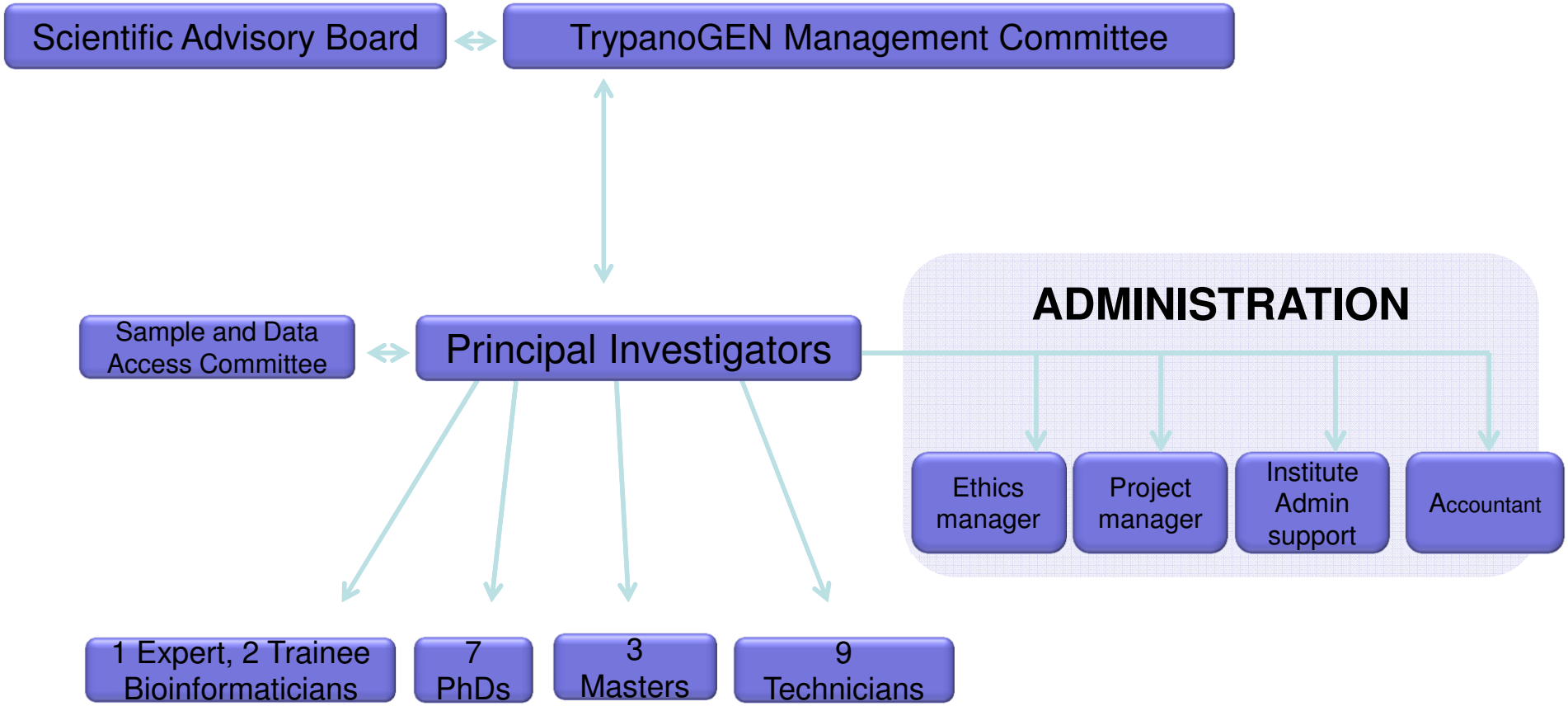
SAMPLING
Lead: M. Simuunza
Deputy: D. Mumba

BIOBANK
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



Areas of potential synergy with other H3 Africa networks

- Ethics
- Training -grantsmanship
  -bioinformatics and GWAS (H3ABionet)
  -ethics workshops
- Sharing data policies
- Shared samples (Kidney Disease)
  SNP database

- 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

Developments since the Award

- Sub-Awards Issued
- Funds transfer just began
- SOPs for sample collection/storage in place
- Sample collection in DRC started (78 cases so-far)
  - Uganda, Cameroon, CIRDES to start October-December
- Piloted with DNA preparation kits
  - Blood
  - Saliva

Streamlining consent documents

- 4 examples on data/sample sharing

	Approved?	**Data**	**Sample**	**Remarks**
Uganda	Yes	X		Protocol amendment to specify sample sharing underway
DRC	Yes	X	X	
Zambia	Under Review	X	X	
Malawi	Under Review	X	X	

On-going activities

- Recruit key personnel
  - Study coordinator application under review
  - Expert bioinformatician
- Finalise sub-awards and funds transfer
- Formally recruit identified PhD students
- Workshop on sample processing,storage and DNA extraction

We are challenged by poor intra-network communication!