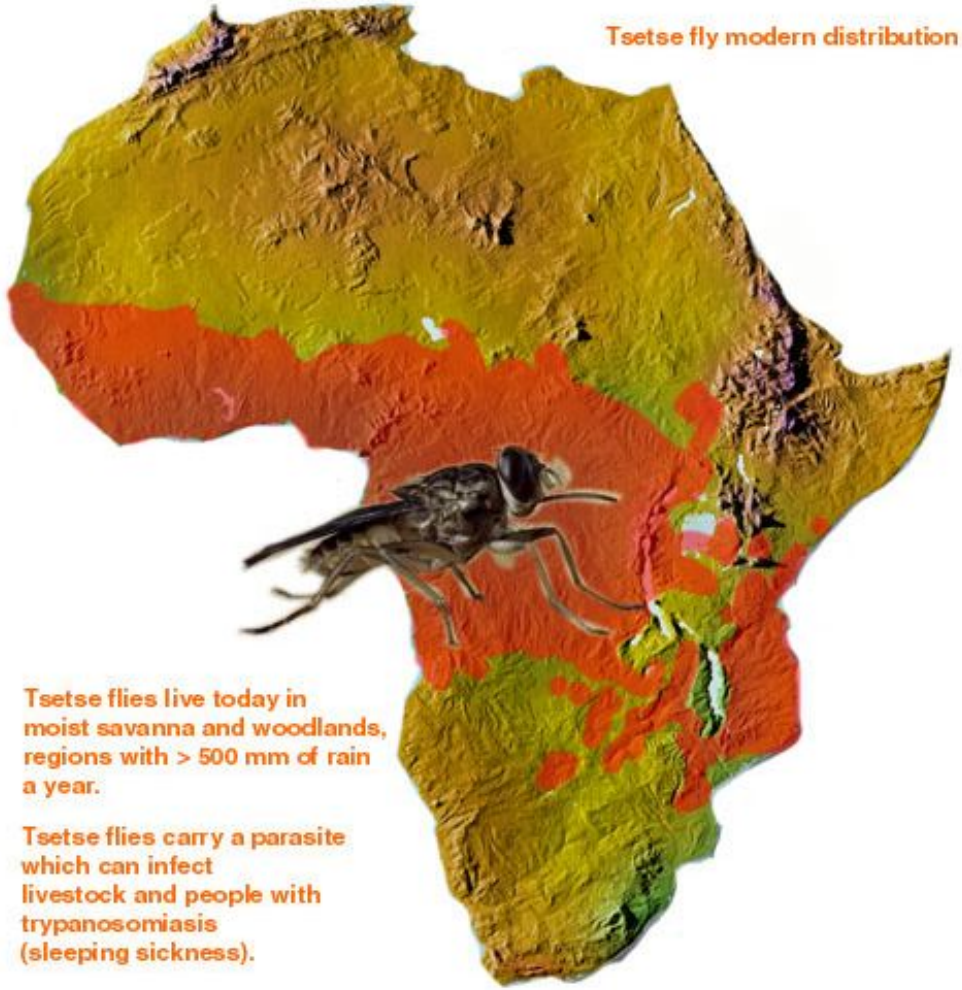
TrypanoGEN: An integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis

African Trypanosomiasis Associates with Tsetsefly Distribution

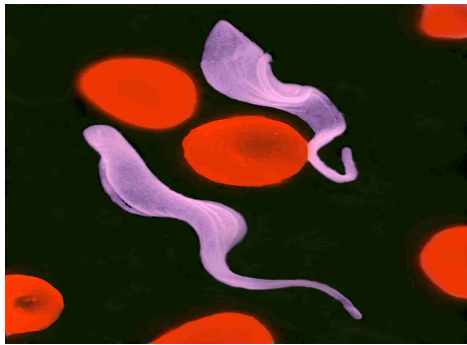


Animal African Trypanosomiasis (AAT)

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

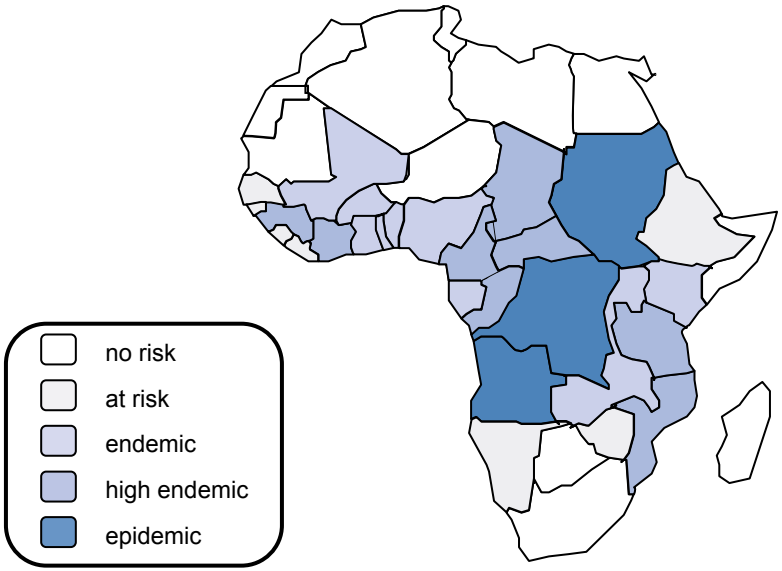
Human African Trypanosomiasis (HAT)

- *T. brucei rhodesiense*
- *T. b. gambiense*

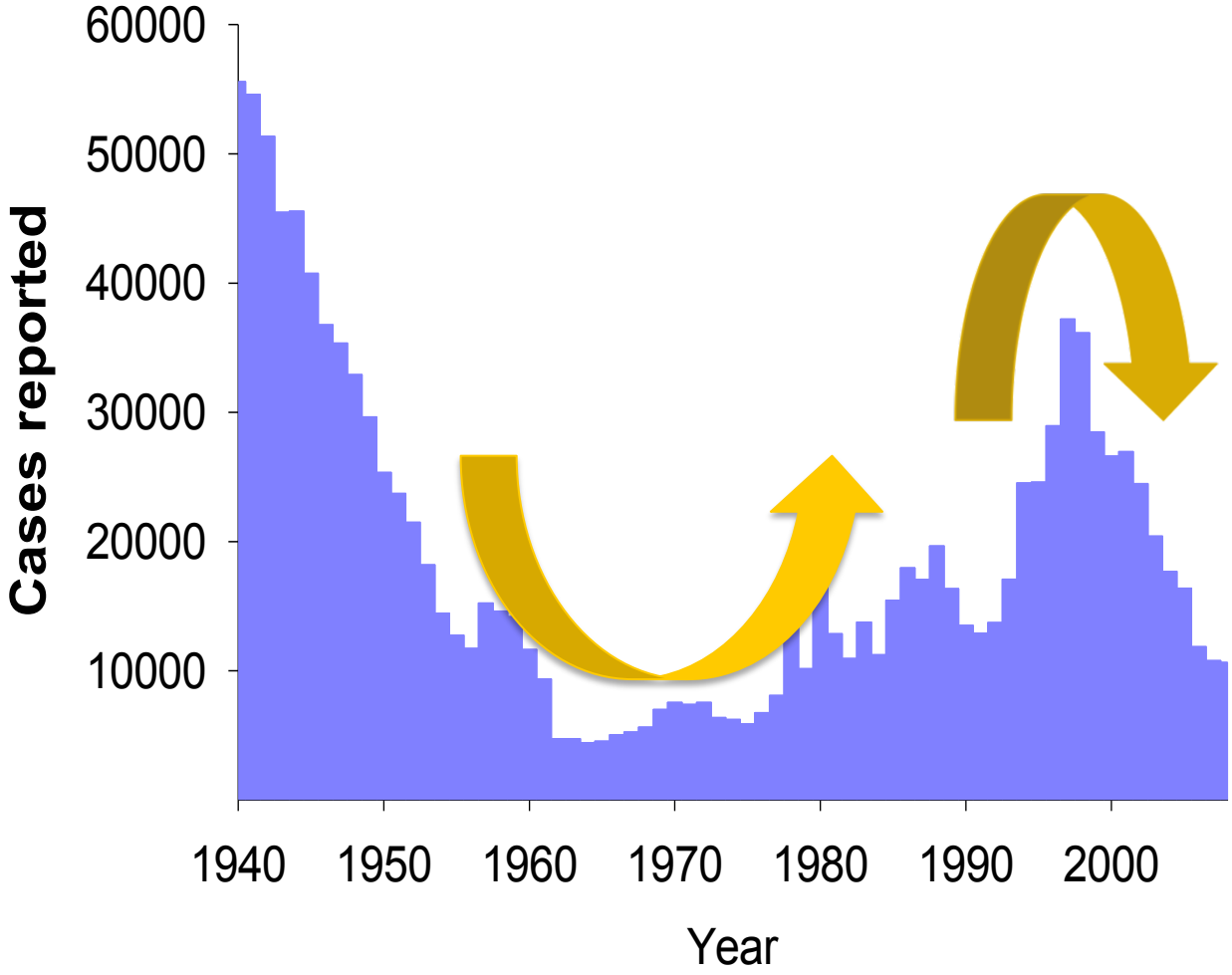


The problem

- 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



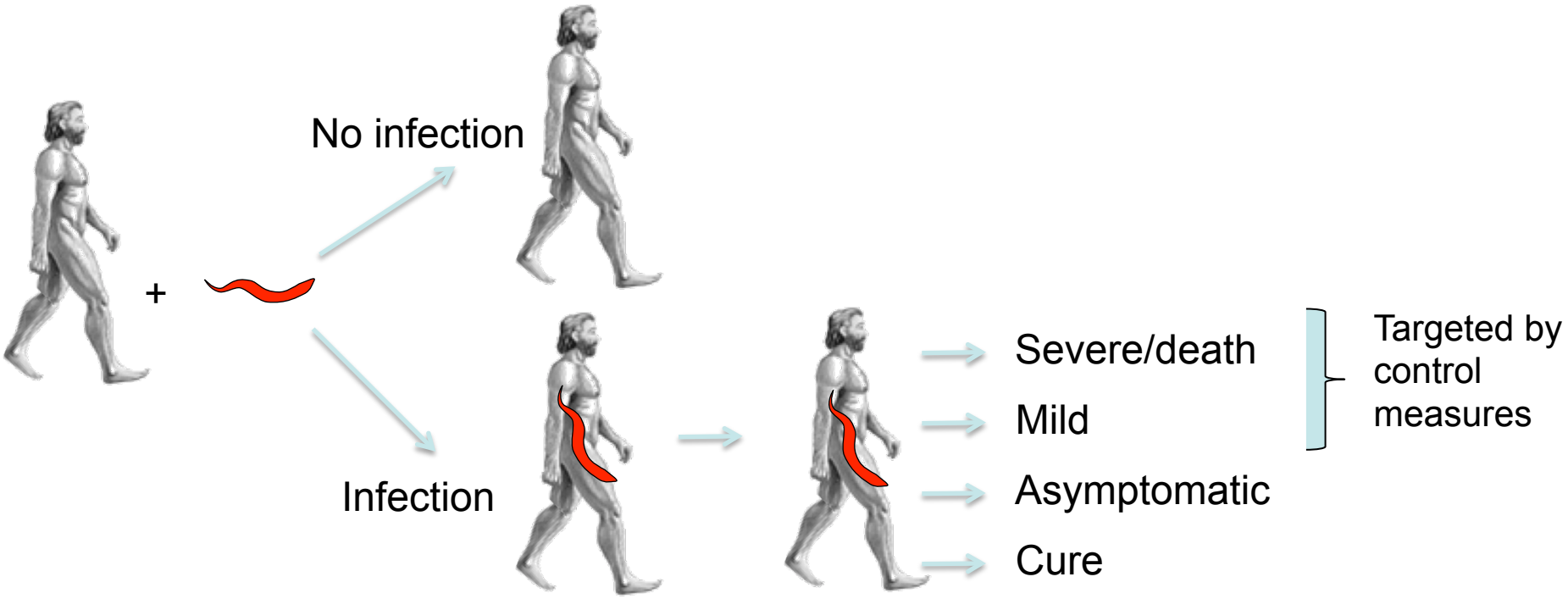
Estimated that 7-10 x more people are affected than reported

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



Parasite genetic diversity – virulence / pathogenicity

Human genetic diversity – resistance / susceptibility

The diversity of infection outcomes

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

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

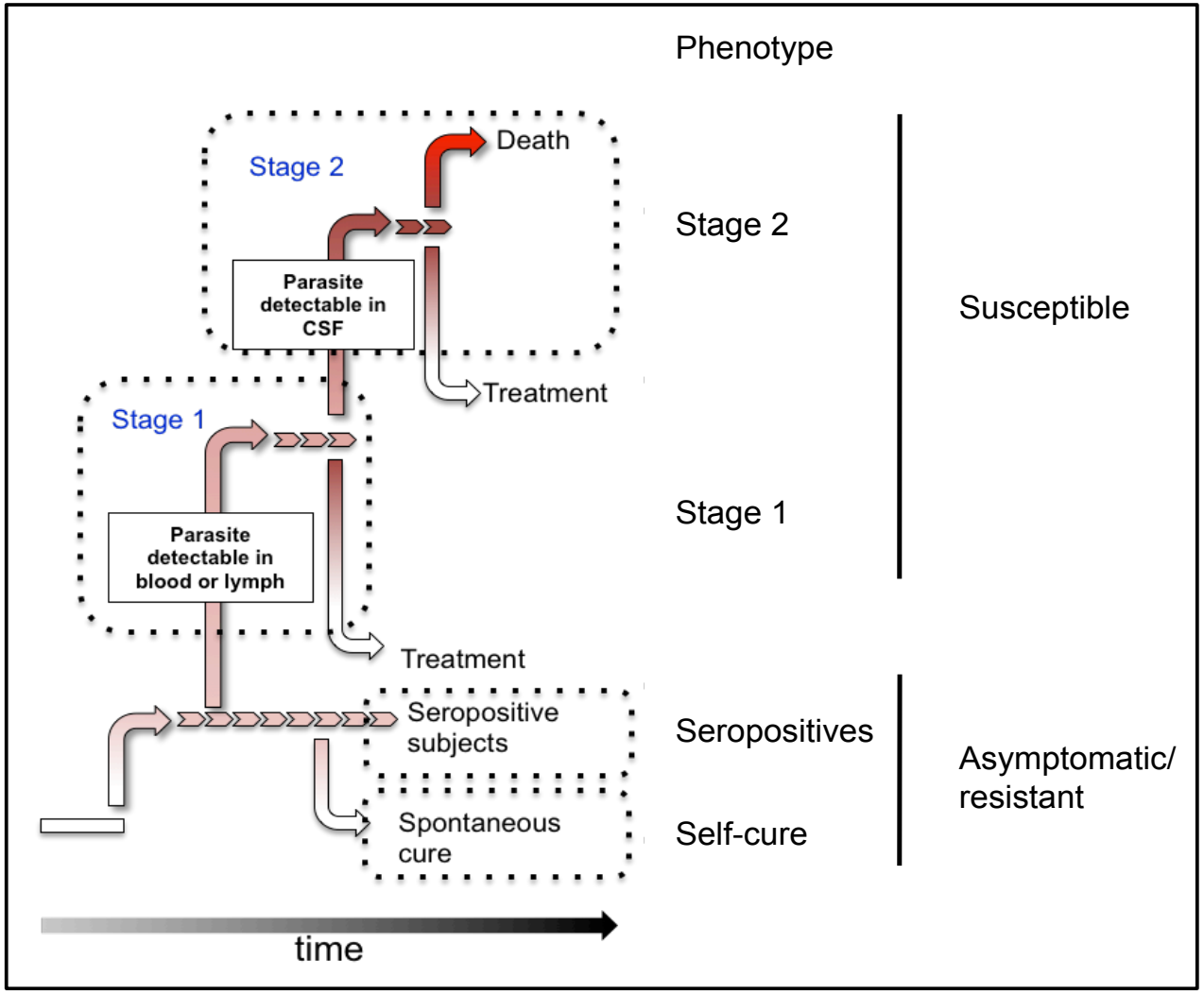
Vincent Jamonneau[1,2]*, Hamidou Ilboudo[2], Jacques Kaboré[2], Dramane Kaba[3], Mathurin Koffi[4], Philippe Solano[1,2], André Garcia[5], David Courtin[5], Claude Laveissière[1], Kouakou Lingue[6], Philippe Büscher[7], Bruno Bucheton[1]

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'Elevage 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-Adjamé, URES de Daloa, Laboratoire de Génétique Moléculaire et Evolution des Maladies Infectieuses Tropicales, Daloa, Côte d'Ivoire, **5** Institut de Recherche pour le Développement, Unité de Recherche 010, Faculté de Pharmacie, Paris, France, **6** Programme National d'Elimination 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

The diversity of infection outcomes



The aim

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

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.

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

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

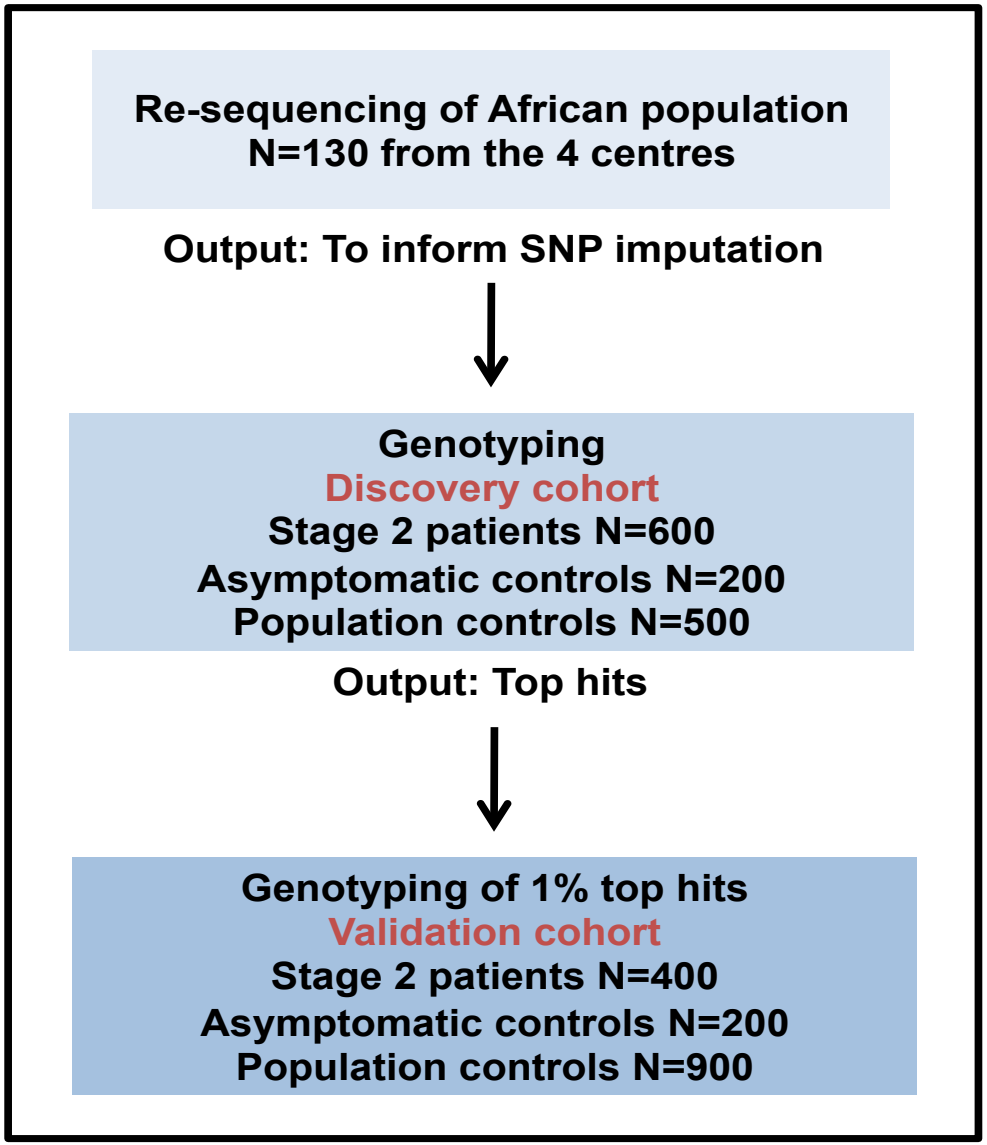
Imputation meth.
GWAS statistics

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



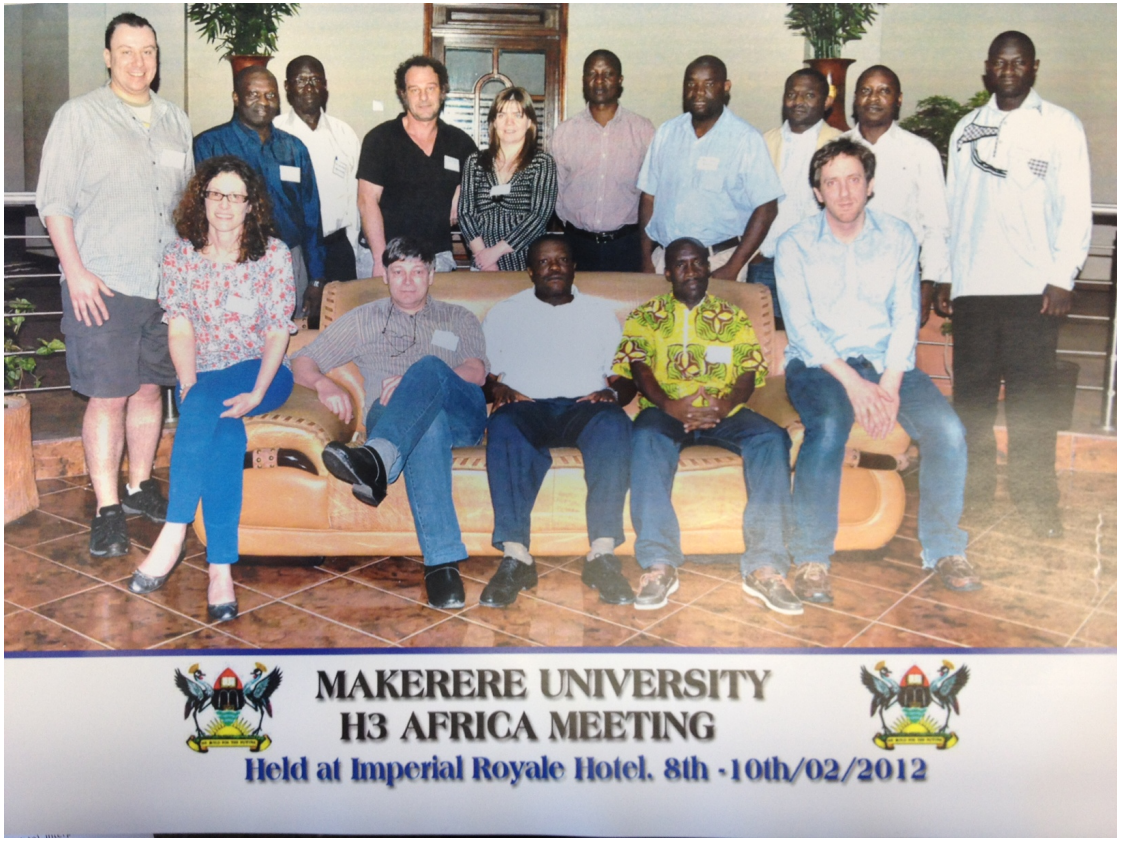
What we will deliver - science

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

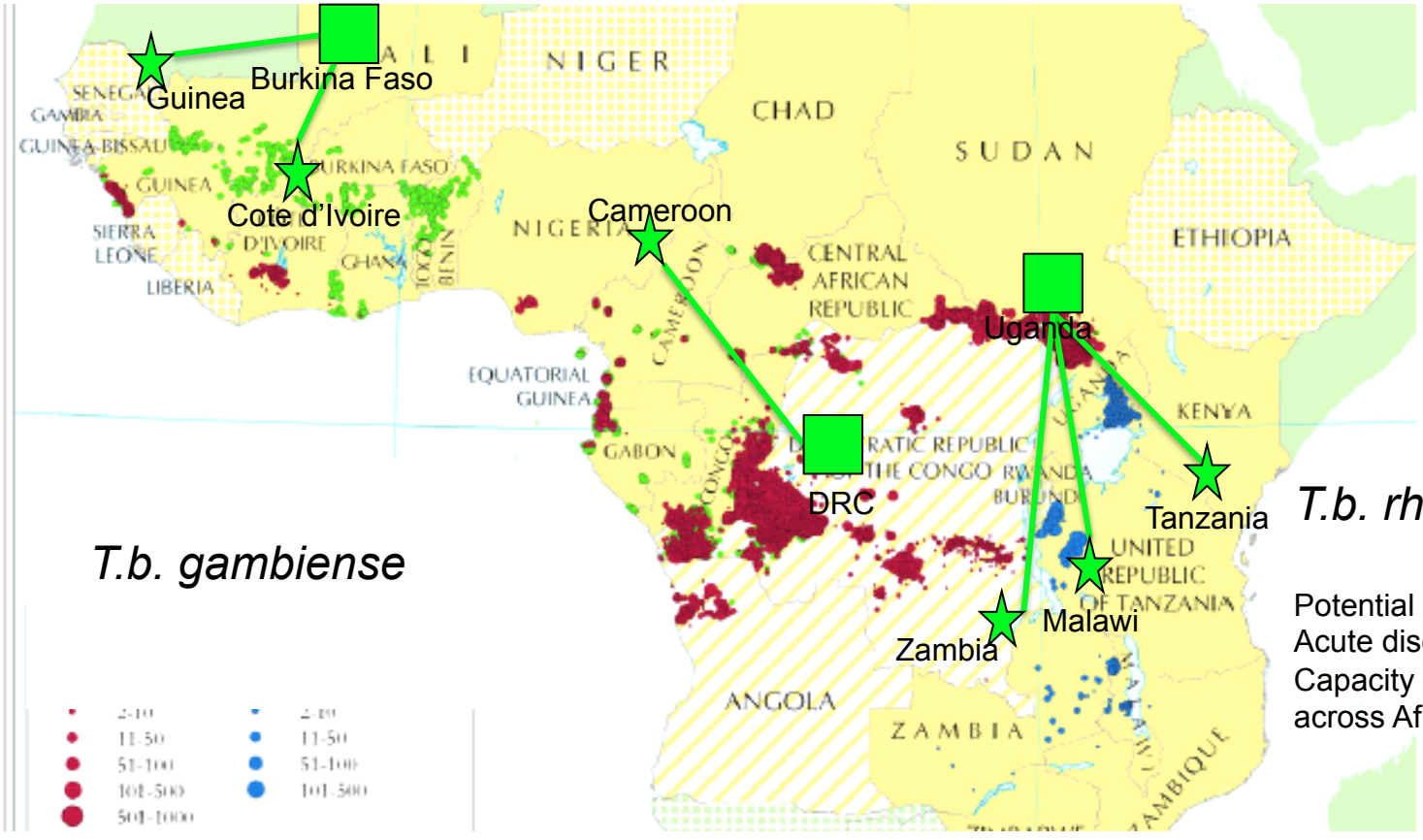


Leading experts in different aspects of HAT

Where we are

9 African + 3 European countries

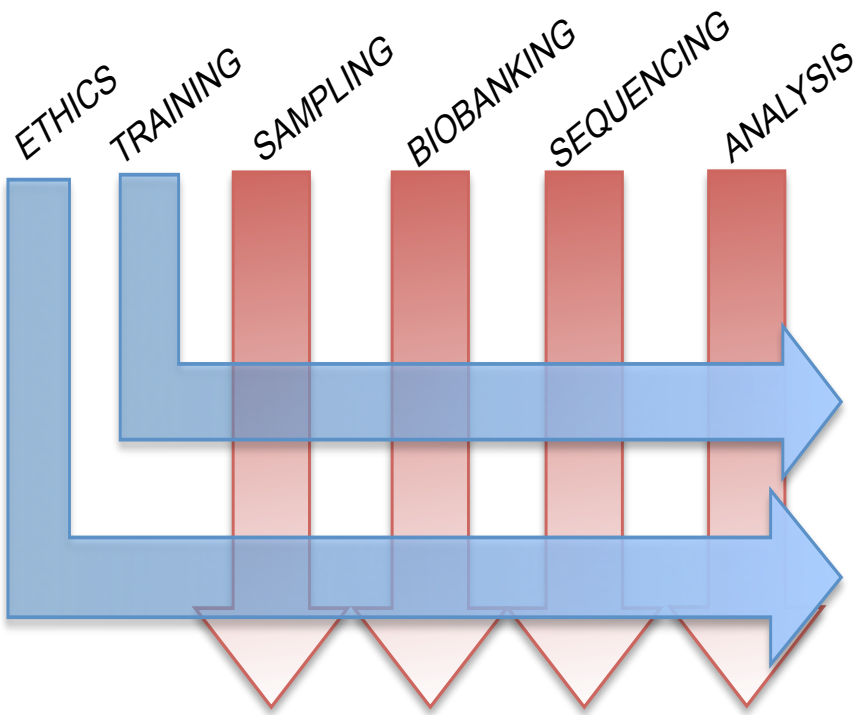
UK France Belgium



Training/capacity building/Ethics

- 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

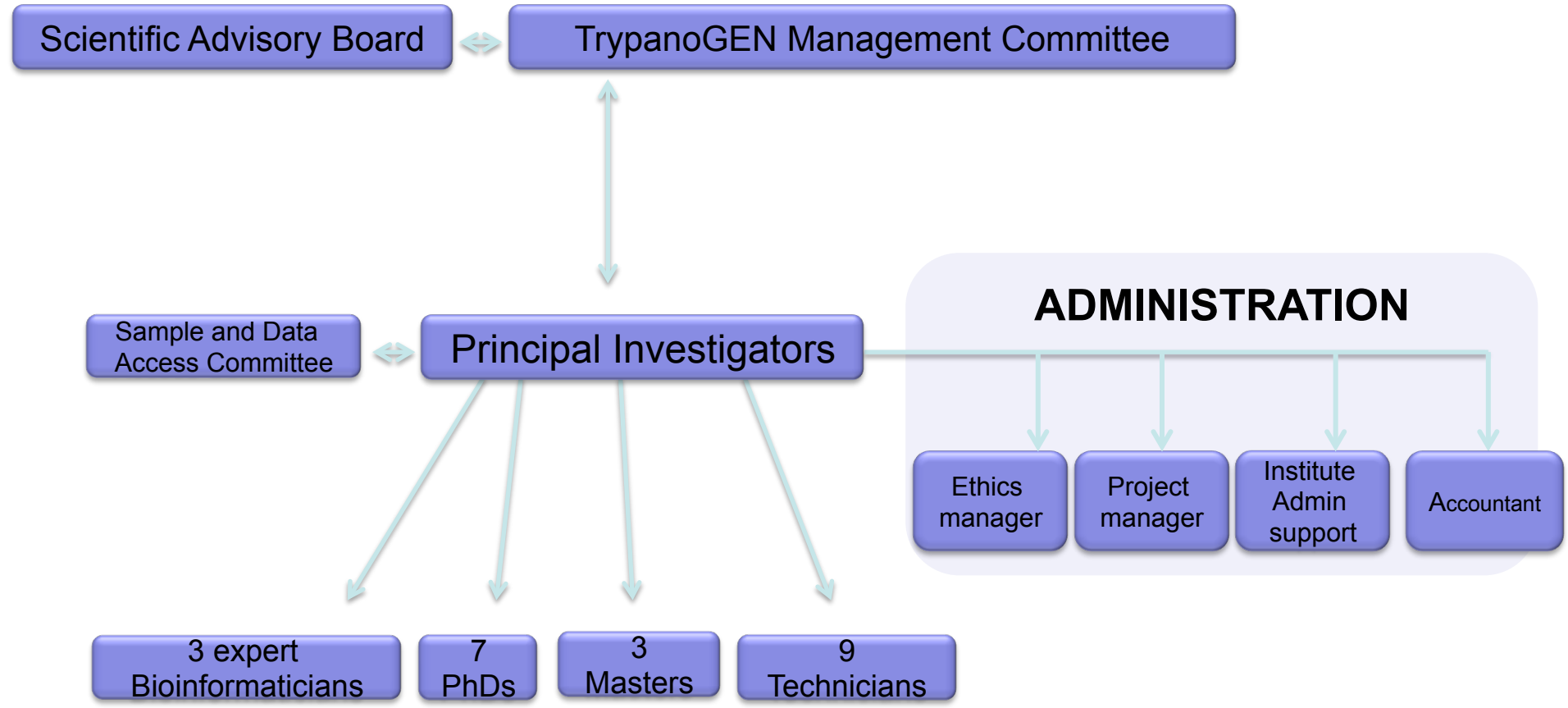
SAMPLING
Lead: M. Simuunza
Deputy: D. Mumba

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
  -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