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Genome Analysis

A case for a *Glossina* genome project

Serap Aksoy[1], Matt Berriman[2], Neil Hall[3], Masahira Hattori[4], Winston Hide[5] and Michael J. Lehane[6]

[1]Yale University School of Medicine, 60 College Street, 606 LEPH, New Haven, CT 06520, USA
[2]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, CB10 1SA, UK
[3]The Institute for Genomics Research, Rockville, MD 20850, USA
[4]RIKEN Genomic Sciences Center, Kitasato University, Kanagawa 222-8555, Japan
[5]South African National Bioinformatics Institute, Belville, South Africa
[6]Liverpool School of Tropical Medicine, Liverpool, L3 5QA, UK

Given the medical and agricultural significance of *Glossina*, knowledge of the genomic aspects of the vector and vector–pathogen interactions are a high priority. In preparation for a full genome sequence initiative, an extensive set of expressed sequence tags (ESTs) has been generated from tissue-specific normalized libraries. In addition, bacterial artificial chromosome (BAC) libraries are being constructed, and information on the genome structure and size from different species has been obtained. An international consortium is now in place to further efforts to lead to a full genome project.

Outlining the problem

Male and female tsetse flies (Diptera: Glossinidae) are the cyclical vectors of the trypanosomes that cause African sleeping sickness in humans (HAT) and nagana in animals (AAT). It is conservatively estimated by the World Health Organization (WHO) that there are currently 300 000–500 000 cases of HAT, with 60 million people at risk in 37 countries covering ~40% of Africa (11 million square kilometers) [1]. After a devastating epidemic in the early 20th century, when a million people died of HAT, the disease almost disappeared from Africa by the 1960s. However, we are now in the midst of another epidemic, with increasing numbers of new infections and mortality (55 000 deaths in 1993; 66 000 in 1999), and a disease burden of 2.05 million disability adjusted life years (DALY) [1–4]. The breakdown of surveillance, allied to displacement of populations by war and natural disaster, are contributory factors to this new epidemic. Given that HAT affects hard-to-reach rural populations, and that these war-torn areas lack active surveillance, the disease prevalence numbers are undoubtedly a gross underestimation. The considered view is that the situation might worsen [5,6].

In addition to the public health impact of HAT, it has been estimated that AAT limits the availability of meat and milk products in large regions of Africa. It also excludes effective cattle rearing from ten-million square kilometers of Africa [7], with wide implications for land use (i.e. constraints on mixed agriculture and lack of animal labor for ploughing) [8]. The Programme Against African Trypanosomiasis (PAAT; http://www.fao.org/ag/againfo/programmes/en/paat/home.html) estimates that AAT causes ~3 million cattle deaths per year and farmers are required to administer ~35 million doses of costly trypanocidal drugs, many of which fail because of the development of resistance in parasites [9–11]. Economic losses in cattle production are estimated at US$ 1–1.2 billion per year and total agricultural losses are estimated at US$ 4.75 billion per year.

Transmission of trypanosomiasis requires four interacting organisms: the human host, the insect vector, the pathogenic parasite and the domestic and wild animal reservoirs. HAT is caused by the protozoan *Trypanosoma brucei rhodesiense* in East Africa and by *Trypanosoma brucei gambiense* in West and Central Africa. The related trypanosomatids *Trypanosoma vivax* and *Trypanosoma congolense* are regarded as major pathogens of cattle and other ruminants, whereas *Trypanosoma simiae* causes high mortality in domestic pigs. All livestock are affected by *T. brucei*, with particularly severe effects in equines and dogs. Members of both the *morsitans* and *palpalis* subgroups of *Glossina* are efficient vectors for HAT and AAT. The recent epidemics caused by *T. b. gambiense* in Central Africa are transmitted by the *palpalis* group tsetse species *Glossina fuscipes*, which is also an important vector for *T. b. rhodesiense* in East Africa. The

Corresponding author: Aksoy, S. (serap.aksoy@yale.edu).
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Box I. Trypanosomiasis control

Much research on African trypanosomes has focused on efforts to develop a vaccine for immunization of humans and cattle. Unfortunately, the antigenic variation of trypanosomes while in the mammalian host has hampered efforts for vaccine development, with no effective products forthcoming for disease control in the foreseeable future. Current disease management primarily depends on active surveillance and treatment of patients and some vector control initiatives. The drug treatment of HAT is in a parlous state [29–31]. It relies on old and often dangerous drugs, and high levels of parasite resistance are emerging as a major problem. Recently, the synthesis of suramin and eflornithine used for treatment in the early stages of disease was about to be terminated by their manufacturers and was only saved at the last minute by an international outcry [32]. The successful experimental results obtained with DB333 derivates for *Trypanosoma brucei gambiense* stage 2 disease is very welcome news. By contrast, no new drugs are in the pipeline for the end-stage disease. Melarsoprol, an arsenical drug, has been used as first-line treatment for late-stage HAT for several decades. The drug is dangerous in its own right, producing a commonly fatal reactive encephalopathy in ~5% of patients. Furthermore, the reported parasite resistance to melarsoprol is alarming, with at least 20% of patients not responding to melarsoprol in this epidemic [11,33]. It is hoped that the parasite genome sequence information now available will provide the impetus and opportunities for the identification of unique targets for which effective drugs can be developed.

In the absence of vaccines and effective and affordable drugs, control of the insect vector has been found to be a highly effective disease control. It is likely that tsetse control will remain one of the most effective overall approaches to the control of African trypanosomiasis. Current vector control efforts center largely either on trapping or on killing the tsetse with insecticides [34,35]. Although these efforts are effective, they have been difficult to sustain at the local community level [36]. The reduction of populations by sterile insect technique (SIT), which has an area-wide impact, has been found to be highly effective [37]. Findings from genomic studies have the potential to improve significantly upon the existing control strategies. Knowledge of genes related to host–parasite interactions are vital for the development of genetically engineered lines that are unable to transmit trypanosomes, which can be immediately used in the ongoing SIT release programs. This application of refractory strains in SIT would reduce the cost of the projects and would also increase the efficacy of their application in HAT-endemic areas [15]. Undoubtedly, genes related to olfaction can result in enhancement of trapping technologies, especially in the case of the human-disease-transmitting *palpalis* group flies for which efficient trapping systems do not exist.

savannah species of tsetse in the *morsitans* complex, such as *Glossina morsitans morsitans*, are also involved in the transmission of *T. b. rhodesiense*, as well as being potent vectors for animal diseases.

The African trypanosome has been most studied in efforts to develop a mammalian vaccine for disease control (Box 1). Recently, through a collaborative international effort, the two largest chromosomes of *T. b. brucei* have been sequenced and others are in the final stages of assembly (http://www.genedb.org) [12]. Realizing the importance and previous neglect of African trypanosome species other than *T. brucei*, whole-genome shotgun sequencing projects for *T. congolense* and *T. vivax* have been recently initiated at the Wellcome Trust Sanger Institute (WTSI). To date, *T. vivax* and *T. congolense* have been sequenced to sixfold and threefold coverage, respectively, with the coverage of *T. congolense* expected to rise to fivefold shortly. Although both the genomics and functional genomics of trypanosomes are being extensively explored, and the human host has been fully sequenced, information on the genomic aspects of tsetse biology has been sparse.

The availability of genomic information can lead to the development of new control strategies aimed directly at the fly or at its parasite transmission ability (vector competence). The data from ongoing studies indicate that knowledge on tsetse–trypanosome interactions during the establishment of infections in the fly is central for the development of such strategies [13,14]. Through a symbiont-based transformation system (paratransgenesis), it has been possible to express foreign gene products in the tsetse midgut [15–17]. To harness this system, it is now important to characterize trypanosome-inhibitory products to express by paratransgenesis in the midgut milieu. Among such products are the tsetse immune system components, which will be elucidated through the genomics project [18,19]. The interactions of parasites with tsetse salivary gland tissue/saliva still remain a 'black box' and the recently completed project on salivary gland expressed sequence tags (ESTs) should provide a major resource for this important research area. The recently developed tool of gene silencing by double-stranded (ds)RNA interference has been found to function successfully in tsetse (S. Aksoy and M.J. Lehane, unpublished). Hence, results beginning to be obtained from genomic studies could lead to functional analysis to better understand the biology of tsetse and parasite transmission in order to interfere with disease [20]. Another near-term benefit of genomics will be its impact on our knowledge of vector population biology. This information has the immediate potential of improving the efficacy and implementation of the current control programmes on the ground [21]. Any approach relying on paratransgenesis and population replacement will also require a good understanding of vector populations and dynamics. Genomic information would also enable the development of new vector control initiatives, including potential targeted insecticide development and host-seeking studies leading to improved trap and target design.

Finally, despite advances in the field of vector genomics, the small size of the tsetse research community remains a key obstacle to advancing research. Unfortunately, given the lack of funds, especially in African laboratories, many centers have disengaged their tsetse research programs and there are few laboratories in the developed world that currently maintain colonies and engage in research on tsetse. During the past decade, the WHO has invested heavily in bioinformatics training courses in Africa, Latin America and Asia. In a recently announced initiative, the South African government has pledged funds over ten years to create a national bioinformatics network to support novel genome annotations related to health in South Africa [22]. The involvement of African scientists and governments in the *Glossina* genome project would facilitate the application of various disease control tools anticipated to be developed from this new knowledge. A larger scientific community will help generate a research resource development and access facility in addition to promoting training and capacity building in disease-endemic countries. Finally, comparative analysis

Table 1. EST collections either currently available, in progress, or in planning stages

Tissue source of library	No. ESTs	Known genes	Investigator (status)
Normalized midgut from naive and trypanosome-infected *Glossina morsitans morsitans*	21 427	4035	http://www.sanger.ac.uk/Projects/G_morsitans
Normalized salivary gland from *G. m. morsitans*	27 426	5895	http://www.sanger.ac.uk/Projects/G_morsitans
Normalized fat body from naive and immune-challenged *G. m. morsitans*	20 257	6372	http://www.tigr.org/
Developmental stages of *G. m. morsitans*	5000		S. Aksoy (in progress)
Antenna of *G. m. morsitans*; *Glossina palpalis palpalis*	3000		M.J. Lehane (in progress)
Adult, naive, full-length *G. m. morsitans*	10 000		S. Aksoy/RIKEN GSC (planned)
Fat body and gut of *G. p. palpalis*	10 000		Genoscope (in progress)

of *Glossina* genes with their homologs in other diptera, *Drosophila*, *Anopheles gambiae* and *Aedes aegypti* would be welcomed by the vector biology community because they will shed light on the evolutionary processes that are conserved and play a role in invertebrate biology in general [23].

Outline of proposed activities on tsetse genomics

The genomics of tsetse can be planned in three phases. Phase I consists of: obtaining information on the genome size of *Glossina* species; cloning and sequencing of an extensive set of ESTs as part of a gene discovery project; construction of bacterial artificial chromosome (BAC) libraries and the preliminary sequencing of BAC-ends; and sequencing of the tsetse symbiotic bacteria. Phase II would build on the preliminary information obtained above and aim to achieve partial threefold shotgun coverage of the genome sequence, scaffolded together using BAC-end sequences. Furthermore, sequencing a small number of BAC clones would also allow us to understand better the complexity of this genome with respect to the organization of coding and noncoding regions, and the distribution of the repetitive elements. In addition, functional analysis of the tsetse transcriptome and its relationship with trypanosomes and its symbiotic flora will mediate a better understanding of the parasite transmission mechanism(s). Finally, Phase III would be full genome sequencing. The status of the ongoing work is presented below.

Analysis of EST libraries

Considerable progress has been made in generating ESTs and full-length gene sequences from *G. m. morsitans* (Table 1). Three tissue-specific libraries – midgut, fat body and salivary gland – prepared following normalization of mRNA to reduce redundancies, have produced over 67 000 tags. Generation of large-scale EST data is important because they represent an opportunity to identify genes expressed collectively among various developmental stages and in adults, and thus are generally reflective of the entire transcriptome. In addition, analysis of transcripts from specific tissues in response to trypanosome challenge and infections will provide the opportunity to identify important genes that are expressed in response to infection, hence can help understand the basis of vector competence. These libraries now represent a valuable immediate community resource and will permit subsequent full-length sequencing, and can also be used for furthering the study of functional genomics by microarray analysis. They will also be useful from a comparative perspective to understand the functional genomics of different vectors. Lastly, they will be important for training gene-finding software and the subsequent annotation of the full genome.

Genome size of Glossina *species*

Members of both the *palpalis* and *morsitans* species complexes are important vectors of trypanosomes and there are good justifications for investigating the genome sequence from both species complexes. The laboratories of Spencer Johnson and Biemont Christian have independently investigated the genome size of several *Glossina* species using a FaxCalibur flow cytometer (Table 2). Their results indicate that the genome of different species varies from 500–600 Mb in size, and is ~1.5 times the size of the *Drosophila virilus* genome. Interestingly, William Black (University Fort Collins, CO) has used reassociation kinetics analysis to determine the genome size of *Glossina palpalis palpalis*, which predicted a much larger size estimate of over ~7000 Mb. This analysis showed that 35% of the *G. p. palpalis* genome corresponds to foldback DNA, indicating the presence of a large heterochromatic region. It is possible that the large load of the bacterial symbionts associated with tsetse might have been a confounding factor in the size variation observed between the two techniques used.

Genomic DNA libraries

BAC libraries for *G. m. morsitans* are currently being constructed, funded through National Institutes of Health (NIH)/National Human Genome Research Institute (NHGRI) (http://www.genome.gov/10001852) and the

Table 2. Genome size estimates of different *Glossina* species

Glossina species analysed	Haploid genome size (pg or Gb)	Ratio *Glossina*/*D. virilis*[a]
Glossina morsitans morsitans		
Male	0.579 (0.590[b])	1.546
Female	0.613 (0.596[b])	1.634
Glossina pallidipes		
Male	0.509	1.356
Female	0.533	1.422
Glossina palpalis palpalis		
Male	0.482	1.285
Female	0.479	1.278
Glossina fuscipes		
Male	0.534	1.523
Female	0.524	1.398

[a]The haploid genome size of *Drosophila virilus* has been estimated as 0.34–0.38 pg.
[b]Values independently determined by S. Johnston (Texas A&M, TX, USA). All values determined using FaxCalibur flow cytometer by B. Christian, C. Nardon and M. Weiss (Université Lyon 1, France).

WTSI. The desired average insert size of the libraries will be around 120–140 kb, with an overall genome coverage of approximately tenfold. Funds have also been made available for the sequence analysis of 60 000 BAC-ends and for the complete sequencing of several BAC clones through RIKEN Genomic Sciences Center (RIKEN GSC) and WTSI. These paired BAC-end sequence data are important as sequence-tagged connectors to assist in linking contiguous sequences together, into longer chains or scaffolds. These data will also provide valuable preliminary information on genome structure including, for example, repetitive element type, frequency and variability, and putative coding sequence frequency.

Genomics of tsetse symbiotic bacteria

Three microbial organisms closely interact and influence tsetse physiology. These symbiont genomes are of interest since, in the absence of their gut flora, tsetse flies are severely impaired in important physiological functions such as longevity and reproduction [24]. The bacteria are also of interest because they have been implicated in modifying the vector competence of their host [25]. Two of the symbionts are enteric – genus *Sodalis glossinidius* and *Wigglesworthia glossinidia* [16]. The *Wigglesworthia* [26] and *Sodalis* genomes (near completion) have been sequenced at RIKEN GSC. Work with microarrays is in progress to investigate the functional genomics of the tsetse–symbiont interactions (Serap Aksoy, Yale University, CT). The third symbiont, *Wolbachia*, can confer mating incompatibilities to the various insects it infects, which results in the spread of the infected insect phenotypes in the field. *Wolbachia* has also invaded many natural tsetse populations and such mating incompatibilities it might confer have the potential to drive engineered parasite-refractory tsetse into natural populations as an alternative strategy for disease control [16,27,28].

Phase II resources needed

Additional resources will enable the genomic initiative, and allow for full exploitation of the existing genomic information. These include the construction of a full-length cDNA library to expand the gene discovery studies. With an extensive set of BAC clones now being partially sequenced, a physical map of tsetse chromosomes is needed to facilitate the scaffolding. Physical mapping in tsetse can be based on *in situ* hybridization to metaphase chromosomes, because its genome organization (probably due to the repetitive nature) is not conducive to suitable polytene chromosome preparations. Alternatively, a BAC restriction-mapping approach might allow for additional genomic information. These resources would facilitate the development of studies of functional genomics to ensure that genomic data can result in applications that lead to disease reduction. In particular, the construction of microarrays and their application for gene expression analysis would immediately benefit the host–pathogen studies aimed at interfering with trypanosome transmission in tsetse.

Phase III studies

Finally, the community would be ready to undertake the genome sequence project using the whole-genome shotgun approach with an eightfold to tenfold coverage that will lead to a complete annotated genome of *Glossina*. We would hope that random paired-end sequences providing eightfold redundant coverage would produce an assembly of over 90% of the euchromatin of the tsetse genome. The preliminary information gathered from Phase II will ultimately influence the final strategy used to obtain a full sequence. For instance, the balance of benefits between clone-by-clone and whole-genome shotgun sequencing are influenced by clone library representation and genome polymorphisms, respectively. Physical and fluorescence *in situ* hybridization (FISH) mapping of BACs and their fingerprints will allow large scaffolds to be mapped to chromosomes and will provide a framework for any future gap closure efforts. All information can then be deposited to a general vector database to benefit the larger vector biology groups. One such database, VectorBase, has recently been initiated and the inclusion of *Glossina* information on this network would be desirable (F.H. Collins, University of Notre Dame, IN, pers. commun.).

Community interest in a *Glossina* genome project

In an effort to review the status of genomic resources in *Glossina* and further its development, a small meeting was held in January 2004 in Geneva, under the auspices of the WHO Special Programme for Research and Training in Tropical Diseases (TDR), and the International *Glossina* Genomics Initiative (IGGI) was formed. This meeting brought together scientists with molecular interests from about a dozen laboratories studying sleeping sickness and genome centers, in an effort to promote the genomic-related activities [22]. A mail server has been established at the South African National Bioinformatics Institute (SANBI) to ensure efficient communication and distribution of information to interested scientists (mailman-owner@sanbi.ac.za). The IGGI will hold its second meeting in February 2005 to review progress and to assess the prospect of attaining the full genome sequence.

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