MiSAC matters
MICROBIOLOGY IN SCHOOLS ADVISORY COMMITTEE
50th Anniversary Articles

The African trypanosome and human trypanosomiasis

Keith Gull

Human African Trypanosomiasis (HAT) will be better known to many as “sleeping sickness” – a deadly disease that attacks the central nervous system and can render sufferers unable to walk and talk, affects sleep patterns, and is fatal if not treated. HAT is transmitted *via* the bite of infected Tsetse flies, which ingest the parasite when they feed upon an infected host (*e.g.* a person, or animals such as cattle or antelopes). The ingested parasites then multiply in the insect – first in the gut and then in the salivary glands. It is from this latter location that they can be injected into the skin of new hosts, then spread to the bloodstream (**Figure 1**) and the brain.

HAT is caused by *Trypanosoma brucei* and its distribution in sub-Saharan countries reflects the distribution of its vector (the tsetse fly). There are two sub-species of *T. brucei* and these cause variants of the disease – *T.b. rhodesiense* causes a rapid onset disease in east Africa. The first signs and symptoms are observed a few months or weeks after infection; the disease develops rapidly and invades the central nervous system and can kill within a few months. *T.b. gambiense,* the cause of most current infections (95% of reported cases), occurs in west and central Africa and causes a chronic form of HAT that can take months or even years for symptoms to develop. In *T.b. gambiense* infections the patient often presents in an already advanced disease stage where the central nervous system is affected.

HAT is considered a neglected tropical disease that occurs in tropical and subtropical areas, affects large numbers of people, usually those living in conditions of poor sanitation and poverty, and has a huge economic burden. The World Health Organization (WHO), governments and Non-Governmental Organisations (NGOs) have maintained attention on this neglected disease and, with continuing surveillance, diagnosis and tsetse control efforts, the number of reported cases has dropped below 10,000 for the first time in 50 years. However, underdiagnosis is likely and continued efforts will be needed to ensure that the WHO's ambitious target to eliminate HAT as a public health problem by 2020 is achieved.

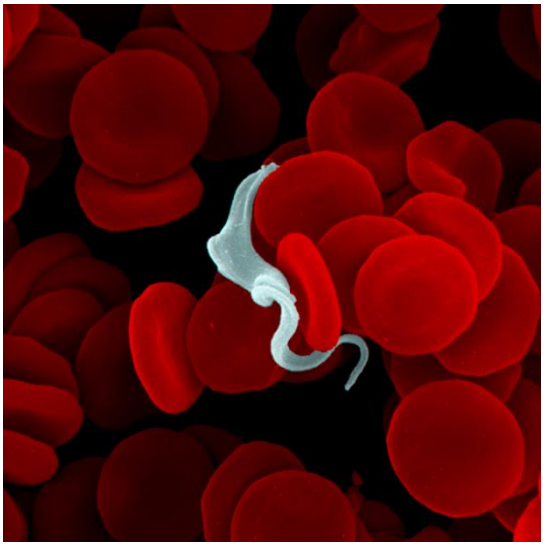

Figure 1. False colour, scanning electron microscope view of a trypanosome in blood.

In addition to HAT other trypanosome species, along with *T. brucei*, cause further development issues in Africa in that they are pathogenic to wild and domesticated animals. In cattle the disease is called Nagana and is a major obstacle to the economic development of affected rural areas.

Trypanosomes are single-celled flagellated protozoa and are members of a group termed the Kinetoplastid parasites. This group is named after a very characteristic aspect of the cell biology – the possession of a large, easily stained spot of DNA in their cells that is separate from the nuclear DNA. This concentration of DNA is a mass of

mitochondrial DNA at one point in their single mitochondrion. This kinetoplast was visualised over a 100 years ago and is recognised as one of the very first examples showing DNA in an organelle apart from the nucleus. Similar kinetoplastid parasites cause a series of other devastating diseases throughout the world. Leishmaniasis is caused by *Leishmania* parasites that are transmitted by phlebotomine sandflies. Visceral leishmaniasis (fatal without treatment) and cutaneous leishmaniasis are the two most common forms of the disease, which is prevalent in 98 countries with 350 million people at risk. Chagas disease is caused by the kinetoplastid parasite *Trypanosoma cruzi*. Nearly 7 million people are infected and the disease is endemic in 21 countries of Latin America.

There are no effective vaccines for these neglected diseases and drug regimens rely on rather old drugs with difficulties of administration and side effects. Since the turn of the century massive efforts harnessing public, private and philanthropic partnerships have aimed to apply modern molecular understanding to the parasite-host relationship and then translate discoveries into targets, screens and ultimately better diagnostics and treatments.

Part of that effort was the work to provide the sequence of the trypanosome parasite's genome and our laboratory played an important part in that programme. One early outturn was that the genome sequence explained some of the intricacies of how the African trypanosome evades the human immune system by changing the nature of its antigenic surface coat. The single celled parasite has nearly a thousand variant gene copies encoding its one surface coat protein. One parasite expresses only one variant gene and so its surface is coated with a thick layer of millions of copies of that one encoded protein. The immune system recognises this protein eventually and antibodies kill the parasites. However, a very few parasites in the blood will have randomly switched to express another gene variant and so these escape the immune system and form another wave of infection.

Trypanosomes are very sophisticated parasites. They perform exquisite antigenic variation; they are able to use their flagellum for motility that is important for infection in the tsetse fly and animals; they have a complicated life cycle whereby the parasite changes its cell form and biochemistry to suit the vector or host environment. Such intricate biology is unfortunately harnessed to devastating effect. The African trypanosome has been a fascinating object of study by microbiologists for over 100 years. The challenge now is to continue to study the exquisite details of its biology so as to understand its pathogenic mechanisms – but also to parallel that, in this century, with translational science that makes a real difference to patients in Africa.

AUTHOR PROFILE

Professor Keith Gull CBE FMedSci FRS, is Professor of Molecular Microbiology at the Sir William Dunn School of Pathology, University of Oxford. The main focus of his research is the protozoan parasites *Trypanosoma brucei* and *Leishmania* spp. - the causative agents of human sleeping sickness and Leishmaniasis. His work addresses several aspects of microbiology from both an evolutionary and health perspective. He also runs annual training courses for scientists in Africa. Professor Gull is a fellow of the Royal Society and the Academy of Medical Sciences, and was awarded a CBE in 2004 for his services to microbiology.

This article is one of a number invited as part of the MiSAC 50th anniversary celebrations. The articles are written by experts and are both up to date and relevant to microbiology in schools. MiSAC is grateful to all contributing authors.