Could you explain the primary research objectives of your laboratory?

Our laboratory is focused on understanding the basic biology of the group of pathogens known as the Kinetoplastida. These organisms include the sleeping sickness (African trypanosomiasis) parasite Trypanosoma brucei. Trypanosome cell shape is maintained and modulated by a highly organised sub-pellicular matrix of proteins that form the cytoskeleton. The cytoskeleton of T. brucei is primarily microtubule-based, but there are numerous minor proteins that are yet to be characterised. Our primary objectives are to focus on the biogenesis of the trypanosome cytoskeleton and to identify and characterise the role of these minor, but essential, proteins in detail. We also wish to test these proteins as potential targets for therapeutic intervention.

How is the parasite transmitted, and what is its effect on human health?

African trypanosomes are mainly transmitted by a group of biting flies called tsetse flies that belong to the genus Glossina, where a differentiation-based life cycle is initiated. Transmission can also be caused by other biting flies such as Stomoxys species where the flies act as hypodermic needle-like transmitters of parasites. Sleeping sickness is fatal if not treated, because it places a tremendous burden on human health. Treatment is also costly, difficult and dangerous. However, it should not be forgotten that animal trypanosomiasis also has a significant impact on food production and agriculture as most infections occur in rural areas, and there is a clear link between human-vector contact and agricultural expansion.

How did your interest in trypanosome research develop?

As an undergraduate student, I was interested in the fascinating way certain organisms can be (commensal or mutualistic) symbionts, whilst others take advantage of a host organism (parasitic). My parasitology lecturers were also passionate about the diversity and complexity of parasite systems and were able to communicate this energy to me. My real interest in parasitology as a career was initiated whilst backpacking through South East Asia in 1988 where I saw tropical diseases first hand.

The flagellar pocket collar (FPC) is likely made of a complex of proteins in addition to BILBO1. Do you have any plans to characterise these?

Yes, we have used yeast two-hybrid analysis and other techniques to identify FPC components and BILBO1 binding proteins. We have identified seven FPC proteins and are currently working to characterise them in detail. However, we are always looking to recruit enthusiastic and innovative scientists to help with our research and to take up the challenge of understanding and characterising the basic biology of protozoan pathogens. We are of course biased towards trypanosomes, but are open-minded because there is much to discover!

How could your findings be used to develop therapeutics, and in what way would they overcome the limitations of existing trypanosomiasis treatments?

We consider our findings important because we highlight the flagellar pocket as essential for the parasite. Therapeutics could therefore be focused on interfering with pocket function and/or biogenesis. In the case of African trypanosomes, we could focus on restricting variant surface glycoprotein (VSG) trafficking through the pocket, or we could focus on preventing FPC division and/or biogenesis. Neither BILBO1 nor the FPC are present in mammals, which make this protein and structure potentially very interesting targets. Additionally, as FPC is complex and BILBO1 has many protein partners, it is possible that the pocket may have many targets.

What are the challenges for the future of your research, and how do you hope to surmount them?

Challenges are often based on obtaining funding and recruiting. We need more good scientists and better means to overcome infrastructural and technical limitations. Essentially, more funding would help in employing PhD students and young scientists to undertake the work we need for identifying protein-protein interacting domains, carrying out high-content screening, high-throughput screening, crystallography and mass spectrometry analysis. We also need to identify more pharmaceutical companies that are interested in focusing on tropical diseases and developing tools and diagnostics in the area of parasitology.
Putting sleeping sickness to bed

Scientists at the University of Bordeaux have furthered our understanding of the parasite responsible for sleeping sickness – a condition that threatens millions of people. Their work has elucidated a novel and unique protein, which may be a suitable target for future therapeutic development.

**SLEEPING SICKNESS IS** an insect-vectored disease that has devastating effects in sub-Saharan Africa. The disease itself is caused by the parasite *Trypanosoma brucei*, a member of the Kinetoplastida order of pathogens. The parasite is spread primarily by the tsetse fly and presents a major public health and economic challenge to countries in affected areas. In total, around 60 million people are at risk from sleeping sickness and 50,000-70,000 are estimated to be infected. The parasite is aggressive and as such the disease is fatal if not treated. Considering the impact of this condition and its difficulty to treat, research is required in order to identify new therapeutics and methods of reducing the rate of infection.

It is this need that has been recognised by Drs Derrick Robinson and Mélanie Bonhivers from the Laboratory of Fundamental Microbiology and Pathogenicity at the University of Bordeaux, France. The two are working to elucidate novel proteins within *T. brucei* that could be targeted in therapeutic development.

*T. brucei* is able to access its mammalian host via the bite of the tsetse fly. Once given access, the parasite migrates to the blood and cerebrospinal fluid where it continues to replicate. The parasite has different morphological forms within its life cycle, which progress as it migrates from insect to mammalian hosts. Similar to this morphological plasticity is the antigenic plasticity of the cell surface molecules found on the parasite membrane. Antigenic variation and the diversity of antigens expressed allow the parasite to stay ahead of the host immune response. It is due to this antigenic plasticity and repertoire that *T. brucei* infections are so difficult to fight and why Robinson, Bonhivers and colleagues chose to focus their work on processes more fundamental to the parasites cellular biology.

**THE FLAGELLAR POCKET**

Two of the most important processes in any living organism are endocytosis and exocytosis – the ability to incorporate and expel molecules in and out of the cell, respectively. In *T. brucei*, as in almost all members of the kinetoplastida class, this process happens in one specific region of the surface membrane: "In the African trypanosome both processes take place uniquely via a structure called the flagellar pocket," explain Robinson and Bonhivers. It is this morphological uniqueness that attracted the attention of the British/French team. The flagellar pocket is so named due to its location at the base of the flagellum. It is a multifunctional structure essential for the localisation and recycling of cell-surface proteins as well as the removal of host antibodies. In the context of parasite and host interactions, the flagellar pocket is important for trafficking surface proteins called variant surface glycoproteins (VSGs). VSGs hold the key to *T. brucei*’s evasion of the mammalian host immune system. Separate populations of *T. brucei* express different VSGs. The immune system is capable of both recognising the most dominant of these and destroying the organisms bearing them. However, due to the diversity of VSGs within the infection, a smaller sub-population rapidly grows to fill this gap: "A minor population of parasites exist that will be expressing different VSGs; one of these will become dominant," highlight Robinson and Bonhivers. The combination of these important functions makes the flagellar pocket essential to the health and pathogenicity of the parasite.

**BILBO1**

The group from the University of Bordeaux has made a substantial breakthrough regarding the structure of the flagellar pocket, identifying for the first time an essential flagellar pocket cytoskeleton protein, which they have labelled BILBO1. This protein is important for the formation and persistence of *T. brucei* morphology, as Robinson...
INTELLIGENCE

BIOGENESIS OF THE TRYPANOSOME ENDO-EXOCYTOTIC ORGANELLE IS CYTOSKELETON MEDIATED

OBJECTIVES

Trypanosomes are pathogens. BILBO1 is a trypanosome protein within a structure called the flagellar pocket collar (FPC). BILBO1 is essential for pathogenicity. The objectives are to: identify BILBO1 partner proteins, characterise BILBO1 orthologue, obtain a better understanding of how the flagellum cytoskeleton and the FPC are constructed, and identify new FPC-based potential drug targets.

KEY COLLABORATORS

Drs Mélanie Bonhivers and Nicolas Landrein, University Bordeaux 2

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DR DERRICK ROBINSON is British. He earned his PhD at the University of Manchester, UK, with Professor Keith Gull. He obtained two Wellcome Trust Fellowships, which took him to Johns Hopkins University, USA, and Kenya.

DR MÉLANIE BONHIVERS is French. She earned her PhD in Paris, France, in Biophysics, and she conducted her postdoctoral work with Nobel laureate Professor Peter Agre at Johns Hopkins University.

The observation that ablating BILBO1 led to parasite death within hours creates hope that targeting this protein in a clinical context may represent a powerful tool in the battle against sleeping sickness. Furthermore, this breakthrough may not be limited to a single condition: “We would like to raise the question of whether the flagellar pocket could be considered a drug target not just for T. brucei, but for all pathogenic kinetoplastids,” Robinson and Bonhivers suggest. This may be an exciting prospect, as all pathogenic kinetoplastids possess flagellar pockets. As such, generic treatments capable of targeting similar flagellar pocket characteristics across the family could provide solutions to other kinetoplastid diseases, such as Chagas (A fatal South American disease caused by T. cruzi).

The researchers have also been able to establish that the FPC and BILBO1 are both absent in mammals. This is important as the specificity of the drug target to the parasite may reduce the chances of any new drugs having unpredicted and adverse reactions in the host. While BILBO1 itself is a good initial candidate for drug development, the team is keen to identify other proteins within the flagellar pocket and, as such, diversify their range of potential targets.

Sleeping sickness is a familiar and widely feared condition threatening millions of people in sub-Saharan Africa. This work provides hope that in the future, drugs and other management tools may become available to help treat and prevent infection by this insect vectored parasite. The identification of a protein essential to the health and pathogenicity of T. brucei is an impressive step towards achieving these goals. Future work to further explain the structure of the flagellar pocket may have positive implications for both sleeping sickness and other conditions caused by this parasitic family.

The group has made a substantial breakthrough regarding the structure of the flagellar pocket, identifying the first time an essential flagellar pocket cytoskeleton protein, which they have labelled BILBO1.