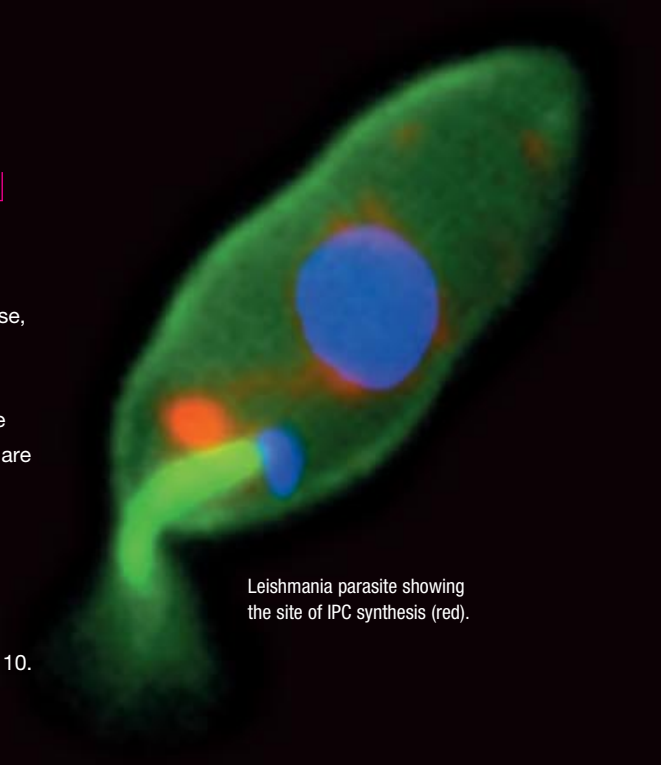
Turning up the heat on **tropical disease**

Scientists at Durham University have developed a screening system, which promises to help in the fight against tropical diseases such as Leishmaniasis and African Sleeping Sickness. Already they have identified and characterised a protozoan enzyme, with no mammalian equivalent, raising the possibility of new drugs with reduced side effects.



Leishmania parasite showing the site of IPC synthesis (red).

Leishmaniasis is a neglected disease, and yet, since the early 1990s, the disease has spread significantly, both in endemic tropical regions and also in more temperate climates. An estimated 350 million people are at risk from infection around the world, and 12 million are believed to be infected[1]. In Europe, cases of the more deadly, 'visceral' form of the disease are being reported among intravenous drug users with HIV, where infection occurs in the absence of an insect vector.

Many available drugs against these types of parasite have toxic side effects, resulting in deaths of up to one in 10. Until recently, the search for safe and effective treatments has been hampered by the conservation of biochemical processes between parasitic protozoa and their human hosts. Now, Dr Paul Denny and colleagues at the Centres for Infectious Diseases and Bioactive Chemistry at Durham University have identified and characterised a protozoan enzyme that catalyses the production of an essential cell membrane component – a 'complex sphingolipid'.

Sphingolipids are ubiquitous components of all eukaryotic membranes: protozoa, fungi, plants and animals. The biosynthetic pathway is conserved up to the formation of a substance called sphinganine, but then the pathway splits. Unlike mammalian cells, which go on to produce sphingomyelin, the primary membrane sphingolipid in plants and fungal species is inositol phosphorylinositol (IPC). IPC synthesis also occurs in protozoa, although its precise role in pathogenesis is unclear.

The gene encoding the IPC synthase enzyme in fungi, *AUR1*, was first identified in the model organism *Saccharomyces cerevisiae*. "Using this yeast model, we have developed a screening assay to identify related genes in *Leishmania* and other parasites," explains Dr Denny. "Not only have we identified a protozoan IPC synthase gene, we have also identified an inhibitor with specific activity against this enzyme"

Their system, for which the team recently filed a patent, has many benefits in the search for non-toxic anti-protozoan drugs. "Potentially we can rapidly screen thousands of compounds for inhibitory effects against the IPC enzyme using our multi-well plate assay; and because it is a yeast-based system, it avoids the expense and time involved in growing these pathogenic protozoa in contained laboratory facilities," says Dr Denny.

Working with Dr Patrick Steel, a synthetic chemist, and Dr Ehmke Pohl, a structural biologist, the next step is to understand the structure and mechanism of the enzyme. This work will inform rational drug design.

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[1] World Health Organization