A cure for Chagas disease?

Professor Claudio Vieira da Silva has discovered a novel mechanism by which a widespread parasitic infection overcomes the immune response. Having identified a promising peptide-based strategy, he is now actively seeking funding for testing what he thinks could be an effective treatment for this deadly disease.

How did you come to research parasitic diseases?

It is impossible to talk about my professional background without going back to my childhood. I was raised in Barraçao, a small rural community in Araguari, Brazil. Even then I dreamt of being a scientist. However, life took me on another path, and I graduated in dentistry. After some years in the clinic, I decided to go back to my original dream, and now I am doing what I have always wanted to do with my life. My doctorate explored host/Trypanosoma cruzi parasite interactions, and I fell in love with the field – my hope is to contribute important findings to society.

What are the causes of Chagas disease – how is it transmitted and what are its effects?

It is caused by T. cruzi, a protozoan parasite which is transmitted to humans by blood-sucking triatomine bugs, or else via blood transfusion, pregnancy, organ transplants, laboratory accidents and oral means. The acute phase lasts six to eight weeks, followed by a prolonged chronic phase. Several years into the chronic phase, 20-35 per cent of infected individuals develop life-threatening lesions in the heart, oesophagus and colon.

Can you explain your team’s findings concerning different strains of T. cruzi?

We aimed to understand why amastigotes from the T. cruzi G strain, while highly infective in vitro, do not contribute to parasitaemia in vivo. Our results showed that they were highly susceptible to interferon-gamma (IFN-γ) treatment in vitro and secretion by immune cells in vivo. It appears that IFN-γ secretion is sufficient to control infection by this strain without the onset of acute parasitaemia, but the parasites remain dormant in host tissues. Our study highlighted the need to consider strain biases when investigating immune response against T. cruzi. Also, these findings were important for the hypothesis that we have developed involving T. cruzi protein P21.

What is the significance of the P21 protein?

During my doctorate studies, when pursuing the intriguing question of why extracellular amastigotes from the G strain were highly infective in vitro but not in vivo, we studied the carbohydrate epitope expressed on T. cruzi SSP-4.

A neglected epidemic

Despite financial obstacles, research from the Federal University of Uberlândia in Brazil has unearthed exciting findings about the mechanisms of host-parasite interactions that lead to life-threatening infection with Chagas disease.

First characterised in 1909, Chagas disease infects about 9 million people worldwide, mainly in rural parts of South America. Carried by insect vectors, the parasite responsible for the disease, Trypanosoma cruzi, cannot be cleared from its human host unless treated with one of the only two drugs currently available is administered in the initial acute stage. However, both drugs are highly toxic and because they are more than 40 years old, T. cruzi has begun to develop resistance to them.

Chagas disease is highly debilitating. The symptoms of the acute stage include fever, fatigue, diarrhoea, vomiting and an enlarged liver or spleen; in its chronic stage, the disease can cause an enlarged heart, colon or oesophagus, and culminate in congestive heart failure, meningitis or sudden cardiac arrest. There is currently no vaccine or cure for chronic infection.

A worldwide threat

The parasite has now begun to spread beyond its initial range due to increasing migration, poverty and environmental change. This has led the US Centers for Disease Control and Prevention to declare Chagas disease a neglected parasitic infection’, marking it out as one to target in order to protect public health. “Chagas disease has become a worldwide threat,” explains Professor Claudio Vieira da Silva, a specialist in immunology, parasitology and microbiology, who lectures at the Federal University of Uberlândia and is Head of the Laboratory of Trypanosomiasis there. “But whatever the disease, whenever it occurs, whomever it affects, it deserves scientific attention.”

Over the last decade, da Silva has closely studied the molecular-level interactions of T. cruzi with mammalian host systems, in search of more effective means of preventing or treating infection. His research has been incredibly successful, but has also been beset by difficulties with funding and resources.

Debts and difficulties

In Brazil, young scientists at state universities seldom receive grants or any other funding for research, so are unable to afford laboratory space, equipment or even reagents: “In many cases, we have nothing more than a table and chair,” da Silva observes. Competition for funding is fierce and established laboratories are much more likely to succeed in a call. To da Silva, this means that research in Brazil is being held back, despite the current trends of great scientific and technological advances. Unchecked, this state of affairs will result in young Brazilian scientists’ creative energies going to waste, and lead them to seek opportunities elsewhere.

In the course of his research, da Silva has had very little financial support from government or any other bodies, and has had to resort to funding the expenses of his laboratory largely by himself. “I have extensive bank debts to pay,” he reflects. “However, I have always endeavoured to provide my students with the best in 21st Century science”.

Making breakthroughs

Despite the financial obstacles, da Silva has made significant breakthroughs in understanding the mechanisms of Chagas disease. He discovered that a protein, P21, is expressed during all the stages of parasite development and that in recombinant form the protein encourages the parasitic invasion of cells and induces phagocytosis, which serves to advance the infection to the chronic stage. “We now hypothesise a triangulation involving parasite P21, host interferon-gamma (IFN-γ) and the actin
and concluded that it may help G strain amastigotes to better adhere to the host cell membrane – the first step towards cell invasion. These were the glorious days of microarrays and my supervisor, Professor Renato Mortara, subsequently established collaborations with Professors Samuel Goldenberg and Marco Krieger in order to utilise this technology. This is what led to our discovery of P21.

Over the next few years, our experimental results with T. cruzi led us to predict that P21 plays an important role in parasite evasion of the immune response, by inducing parasite entry into cells where they can replicate and propagate. Our recent – currently unpublished – work attempts to better understand this protein’s role; and we have verified that P21 is a potent chemoattractor of murine immune cells. Also, long-term infected mammalian cells treated with the recombinant form of P21 in vitro showed a decrease in parasite multiplication and an increase in host cell actin polymerisation. The same results were found in IFN-γ treated infected cells. Quantitative polymerase chain reaction revealed that amastigotes from low virulence strains express higher levels of P21 transcripts than those of virulent strains.

Might your research be translated into novel treatments for Chagas disease?

We strongly believe that, by interfering with P21 activity, we can expose the parasite to the host immune response, and so achieve a cure for both the acute and chronic phases of this disease. Our group has found four peptides that strongly inhibit P21 pro-phagocytic activity. Now we plan to test these peptides in further experiments – there are already indications that anti-P21 peptide-based therapy could be effective against Chagas disease.

How do you see your work progressing?

My dream is to have a productive, independent laboratory to investigate the use of anti-P21 peptides to treat infection. I would like to manage a lab to advance our ideas without barriers to creativity. However, it is very difficult for young researchers to obtain funding in Brazil and specific calls for neglected diseases are rare and strongly competitive. I believe that private initiatives would help the future of research in my country greatly, and although private investment in research is uncommon, I have tried to get celebrities and companies interested – so far without success.

In addition, da Silva believes that there is great potential for further research. The parasite has potential for use in treating cancer – some of its components kill cancer cells – and low virulence strains are used as vaccine vectors in research animal models. In addition to its chemoattraction of host immune cells, da Silva has observed that the recombinant form of T. cruzi P21 also inhibits angiogenesis, and believes that it could hold promise for treating solid tumours. This pioneering Brazilian team is full of ideas, and, if given the right tools, could make a real difference to worldwide healthcare.

MURINE MACROPHAGES

MURINE MACROPHAGES infected with Trypanosoma cruzi. One is treated with recombinant P21 and as such shows intense actin polymerisation (red) and low parasite multiplication (green).