How did your academic career guide you to your current research endeavours on Chagas disease?

I obtained my Master's degree in Enzymology in 1991 and PhD in Microbiology in 1994, both from Aix-Marseille II University, France. I took up a postdoctoral position in Dr Roy Riblet’s laboratory working on the physical map of the C57BL mouse Igh locus. Then, I joined Professor Alain Dessein’s laboratory to identify and characterise susceptibility genes for parasitic diseases. Between 1997 and 2010, I focused my research on the identification and characterisation of genetic factors that control human susceptibility to infection and severe disease in schistosomiasis while still in Dessein’s group.

Since 2010, in the same laboratory and in collaboration with several groups, I have been developing programmes to identify human susceptibility genes for chronic Chagas cardiomyopathy (CCC). Mechanisms underlying differential progression to severe cardiomyopathy are still incompletely understood. Familial aggregation of CCC has been described, suggesting that there might be a genetic component to disease susceptibility. The outcome of infection in a particular individual is the result of a set of complex interactions between environmental and social factors, the genetics of the parasite strains, and the host genetic background. Our main aim is to identify the host genetic factors that predispose individuals to chronic disease.

What challenges have you encountered during your research?

The main obstacle was obtaining access to a significant bank of heart tissues and enrolling the largest cohorts of patients ever seen and asymptomatic controls. The development of a systems-based approach is a significant hurdle to overcome.

Are there any key international partners and organisations that you would like to mention specifically?

Our scientific project was set up by our Inserm laboratory in Marseilles, France, in collaboration with the Heart Institute of São Paulo, Brazil. The principal investigators were Professor Edecio Cunha-Neto and myself. Since the beginning of this project, several additional Brazilian partners have been added to this international consortium including the Hospital das Clínicas and Institute of Cardiology Dante Pazzanese in São Paulo; the School of Medicine in Ribeirão Preto and the School of Medicine in Triangle Mineiro in Uberaba. Furthermore, an additional Inserm laboratory (UMR_U980) has joined in Paris, France.

Your project involves setting up a systems biology approach to identify functional polymorphisms that are differentially expressed in the CCC myocardium. What methods are you using?

Development of effective drugs for CCC is hampered by the limited knowledge of its pathogenesis. The best way to analyse this pathogenic process is to develop several approaches at the same time and analyse all the results together. Systems biology is a method that aims to model and discover interactions and emergent properties in complex biological systems, which are addressed using quantitative measures and by rigorous integration of ‘-omics’ data. Omics methods are a great help when using this approach; global non-targeted strategies such as genomics, proteomics and metabolomics are useful for identifying multiple biomarkers in tissue from healthy and diseased individuals. Bioinformatic tools and databases have also been created to facilitate such analyses.

The enemy within

Experienced parasitologist Dr Christophe Chevillard shares the inside story of his career and the details of his unique and ongoing work into the possible genetic markers of susceptibility to Chagas disease
A systematic approach

Health researchers at Aix-Marseille II University in France have been collaborating in recent years with institutes in South America to conduct a unique investigation into inter-individual susceptibility to a prevalent parasitic disease.

CHAGAS DISEASE IS a condition that is chronic in the truest sense of the word. Characterised by renowned Brazilian physician Carlos Chagas more than a century ago, this parasitic disease is caused by protozoans of the Trypanosoma genus, members of which are also responsible for sleeping sickness in Africa. In Latin America, Chagas disease is a highly prevalent killer, partly because it is transmitted by blood-sucking bugs that thrive in low-quality housing, but also as many patients simply do not realise they are infected until it is too late to treat the condition. The acute stage of the disease has ambiguous and innocuous symptoms, and lasts for around 10 weeks after inoculation. The chronic stage, however, is much longer – with symptoms often only becoming noticeable after a period of more than 10 years.

Identifying genetic variations could lead to clinically useful indicators of vulnerability to disease

In around 70 per cent of cases, Chagas disease produces no symptoms even in the chronic stage of infection, and patients in this majority are unlikely to ever realise they are carrying the parasites. For the other 30 per cent, however, the situation is grim; parasites collect in heart tissue causing chronic inflammation, leading to the development of dilated cardiomyopathy. This same process can also take place within the digestive tract and the neurons of the autonomic nervous system.

THE GOOD HOST

There are a few important pieces of evidence that suggest genetic factors influence the pathology of chronic Chagas cardiomyopathy (CCC). The existence of such a significant variance in patient outcomes; the fact that disease progression is largely dictated by the host response, both in the migration of T-cells to the affected areas and the reaction of cells to infection; and the observation that CCC is often aggregated in families all point towards this conclusion. Based on this, one team of health researchers at Aix-Marseille II University has been investigating the hypothesis that genetic polymorphism determines the pathology of Chagas disease to some extent, with the hope that identifying such variations could lead to clinically useful indicators of vulnerability to the disease.

The laboratory at Aix-Marseille has partnered with the Heart Institute of São Paulo, Brazil, and together the scientists have access to both the largest study population of Chagas disease patients described to date and an extensive fresh heart tissue collection that has been under assembly for over 15 years. This allows them to bring a unique, systems biology approach to the study of the infection. “Systems biology is an approach to life science that focuses on a system-level understanding of biological processes, where we are presented with a bunch of parts that are connected to one another and work together,” explains Dr Christophe Chevillard, the leader of the French group involved in the research.

CURRENT PROGRESS

This comprehensive method will serve to accomplish two aims, the first of which is to identify the genes and proteins that are differentially expressed in CCC hearts as compared with asymptomatic organs, while also identifying epigenetic controls. It is here that ‘-omics’ approaches will be at their most effective, as Chevillard and his colleagues will be able to simultaneously subject the tissue samples to transcriptomic, proteomic, methylocmic, chromatinomic, miRnomic and RNA sequencing analyses for a comprehensive insight into the disease pathology. The French scientists have set their standards very high, however, by searching specifically for genes and proteins that not only have a significant association with CCC, but also produce biological effects important to disease pathology.

Towards this end, the group has already confirmed the involvement of six genes (CCR5, CCL2, MAL/TIRAP, TNF, IL12 and IL10) in the pathogenic process, and identified three – CXCL9, CXCL10 and the alpha cardiac muscle actin 1 gene – which exercise significant control over human susceptibility to severe, chronic disease. Discoveries like these will be used to accomplish the second aim: to identify genetic variants around disease-associated genes. With this information in hand, Chevillard and his collaborators will be well positioned to fundamentally alter the way patients are diagnosed and treated for Chagas disease.

INTELLIGENCE

IDENTIFICATION OF A PREDICTIVE/PROGNOSTIC GENETIC SIGNATURE IN CHAGAS CARDIOMYOPATHY

OBJECTIVES

• To use a multidisciplinary approach to identify differentially expressed genes and proteins in chronic Chagas disease cardiomyopathy
• To identify genetic variants in or around the disease-associated candidate genes identified in the first aim

KEY COLLABORATOR

Professor Edecio Cunha-Neto, University of São Paulo, Instituto do Coração São Paulo, Brazil

PARTNERS

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School of Medicine, Ribeirão Preto
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FRANCE:
Inserm (UMR_U980), Paris

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DR CHRISTOPHE CHEVILLARD

gained both his Master’s degree and PhD from Aix-Marseille University, France, where he is currently an associate professor.

In addition to his research on understanding the genetic basis of Chagas disease cardiomyopathy, he is a member of the editorial board of the World Journal of Clinical Infectious Diseases and the World Journal of Medical Genetics. He has authored more than 50 peer-reviewed publications and several book chapters.

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