

A multidisciplinary mission

Professor Balachandran Ravindran knows the importance of multidisciplinary collaboration, both through his work investigating infectious disease biology and his administrative duties as Director of an important life sciences research institute in India



Could you provide an insight into the history of the Institute of Life Sciences (ILS)? What are its aims and research strengths?

ILS is an Indian Federal Government-funded institution in the eastern region of the country, dedicated to undertaking research in different branches of modern biology. The Institute trains a large number of doctoral students each year and has a state-of-the-art infrastructure that is used by approximately 16-17 research groups.

The Institute maintains a highly competitive and yet hierarchy-free ecosystem. Every investigator functions as a vertical section of the institution, contributing their specialisation, and each Principal Investigator runs a group consisting of graduate students and research associates. The investigators are clustered into three domain areas: infectious disease biology; gene function and regulation; and translation research and technology development. I also function as one of the Principal Investigators, working on the immunobiology of infectious diseases.

The Institute hires faculty members with diverse technical skills from molecular biology and immunology to X-ray crystallography and computational biology. This model allows fruitful collaboration between faculty members, enabling a multidisciplinary approach to specific scientific problems.

In what ways does ILS ensure its findings have real-world translational impact?

The Institute takes a proactive but cautious approach to translating basic research. While we want to translate findings, we ensure that stringency of laboratory research is not compromised.

ILS has links with biotechnology and pharmaceutical companies to enable research findings to be taken to their logical end. One example is our recent work on the development of antibody-coated magnetic nanobeads for use as a cell separation reagent. This kit is being developed in association with Imgenex Corporation, which will be marketing the product.

How did you come to develop a research interest in infectious disease biology?

My own interest in infectious disease biology goes back to the mid-1970s when I started my doctoral thesis on the immunology of primate malaria. Over the years, my focus has shifted to other parasitic diseases such as lymphatic filariasis, other helminth infections and emerging issues such as the hygiene hypothesis. This has allowed me to diversify my activity into disciplines beyond infectious disease biology; for example, my lab has a large programme studying the relationship between helminth infections and susceptibility to a variety of autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. Interestingly, this emerging area of research (under the broad umbrella of the hygiene hypothesis) is bringing together medical researchers in developing and developed countries.

In what ways are filariasis, sepsis and cerebral malaria linked?

My interest in malaria research preceded my research activities on filariasis by a decade, and my group's interest in sepsis is a more recent phenomenon. This evolution from malaria to sepsis was not a conscious effort to switch from one area to the other, but was the outcome of our investigations in one discipline opening up opportunities to study the other.

For example, our interest in filariasis led us to study its co-infection with malaria both in animal models and humans; while one is a protozoan pathogen, the other is a nematode, but both parasites are transmitted by mosquito vectors. However, the immunobiology of host responses to these diseases is very diverse. We found that vector biology and prevalence contribute more significantly to the differential prevalence of these two diseases in human communities. In recent years, while studying immune-modulatory molecules in filarial nematodes, we discovered that filariasis-infected hosts can be less prone to sepsis, a severe pathological consequence of systematic bacterial infections. Incidentally, sepsis is a one of the major killers in intensive care units in developed countries.

What would you pinpoint as your group's most exciting or significant finding to date?

One example in recent years has been our identification of an immuno-modulatory filarial glycoprotein that blocks sepsis in mice models. The active moiety was found to be a carbohydrate residue which was binding directly to Toll-like receptor 4 (TLR-4), an innate immune receptor present on macrophages/phagocytes and the receptor through which bacterial endotoxin induces septicaemia. These serendipitous findings led us to identify a carbohydrate residue – Chitohehexose – a hexosaccharide present in nematode glycoprotein. By virtue of its binding to TLR-4, Chitohehexose effectively inhibited endotoxin-mediated sepsis in mice. Using monocyte cultures, we demonstrated the possibility of extrapolating this observation for management of human sepsis. Since then, we have initiated a study on reprogramming human monocytes of sepsis patients by Chitohehexose. The results of these investigations have also led us to address interesting questions on plasticity of macrophage function in mammals and their pharmacological manipulation for management of acute and chronic inflammatory disorders.

Commitment to collaboration

Using cutting-edge technology to explore cellular and molecular processes, the **Institute of Life Sciences** in Bhubaneswar, India, is a hub of innovation in the fields of pathogen and cancer biology, immune regulation and inflammatory processes

ALTHOUGH THE RISE of noncommunicable diseases as a public health threat is seen as one of the most pressing challenges of the 21st Century, infectious diseases remain a significant concern, particularly in the developing world. Numerous public health initiatives have tackled major infections, but challenges facing national and international organisations in prevention and treatment remain.

The Institute of Life Sciences (ILS) in Bhubaneswar, India, is an organisation committed to finding solutions to these challenges through the provision of useful information on the biology of infectious diseases. As part of the Department of Biotechnology of the Indian Government, ILS is a renowned National Centre for Excellence with a mandate to investigate both basic and translational areas at the forefront of life sciences research. Led by Director Professor Balachandran Ravindran, the Institute probes the biology of pathogens, pathogenesis of disease progression and evolution of pathogens in the context of their relationship to human genetics.

EXPANSIVE APPROACH

ILS subdivides its broad activities into three major areas: infectious disease biology; gene function and regulation; and translation research and technology development. The former is the primary focus of the Institute, with an emphasis on viruses, bacteria, fungi and metazoan parasites.

Such a wide range of research topics requires an equally wide range of approaches: "Infectious disease biology covers a very broad spectrum of specialities, including pathogenesis, immunobiology, immunopathology, host response, computational biology, X-ray crystallography and mathematics," explains Ravindran.

FILARIASIS FINDINGS

In conjunction with his role as ILS Director, Ravindran also leads a group at the Institute dedicated to elucidating the biology of various infectious diseases. This work has led him in numerous directions, most notably studying the pathogens that cause malaria and helminthic diseases in human and experimental models, as well as their interactions with other infectious pathogens.

Several recent investigations by Ravindran and his collaborators have focused on the parasitic infectious disease filariasis. Endemic in many tropical and subtropical regions, the disease is spread by thread-like roundworms and manifests as elephantiasis or the accumulation of fluid in different parts of the body. One study addressed mechanisms behind the development of chronic filariasis. It was already thought that endothelin-1 (ET-1) and the plasma levels of certain tumour necrosis factor receptors (TNFRs) were associated with the development of the condition, but the genetic basis for this link remained a mystery. Using state-of-the-art techniques, the group uncovered that specific polymorphisms of ET-1 and TNFR-II (Ala288Ser and Met196Arg respectively) had strong associations with different manifestations of the disease. Specifically, they found that high prevalence of Ala288Ser mutation is strongly linked to chronic filariasis in patients who suffer elephantiasis, whereas Met196Arg is more closely associated with hydrocele patients.

THE INSTITUTE OF LIFE SCIENCES

Situated in the ancient city of Bhubaneswar, ILS was originally established in 1989 under the administrative and financial control of the Government of Orissa's Department of Science and Technology. In 2002, it was brought under the umbrella of the Indian Government's Department of Biotechnology as an independent and autonomous entity. The Prime Minister of India dedicated the Institute to the nation on 15 July 2003, with a declaration to develop it as a National Centre for Excellence.

INTELLIGENCE

INSTITUTE OF LIFE SCIENCES

OBJECTIVES

To use cutting-edge technology in modern biology to acquire insights into pathogen biology, immune regulation, development of protective immunity and inflammatory processes at cellular and molecular levels.

KEY COLLABORATORS

Dr Satyajit Rath; Dr Vineeta Bal and Dr Anna George, National Institute of Immunology, India

Professor Shobona Sharma, Tata Institute of Fundamental Research, India

Professor Rick Maizels, University of Edinburgh, UK

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FUNDING

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Another line of inquiry found Ravindran's team examining the important issue of whether successful control of filariasis could increase incidence of sepsis and severe malaria in communities. The cellular basis for the development of sepsis and severe malaria is attributed to enhanced inflammatory host responses, whereas filarial infections are associated with a diminished degree of responsiveness. Therefore, Ravindran and colleagues examined 89 patients with sepsis and 196 patients with severe malaria for circulating filarial antigens (a biomarker of filariasis). Interestingly, the team found that pre-existing filariasis indeed has an influence on the development of sepsis, whereas levels of circulating filarial antigens were comparable to healthy controls in severe malaria, indicating that filariasis and severe malaria are not linked. These observations have vital public health consequences for filariasis-endemic regions, as successful control of the disease could have negative ramifications through increasing incidence of sepsis.

DEWORMING CONUNDRUM

Beyond these filariasis studies, Ravindran's group is also exploring a number of other exciting research directions. For instance, basic research by the team on regulation of roundworm embryogenesis uncovered an interesting approach to targeting and eliminating pathogenic nematodes through induction of programmed cell death. "This resulted in us taking an outsiders' viewpoint of the logic of deworming," Ravindran explains. "As a consequence, a paper was published recently – 'Deworming conundrum: Are we missing an undesirable dimension?' – highlighting some of the contentious issues surrounding the currently favoured regimen of deworming human communities".

The World Health Organization advocates deworming at-risk populations, namely school-age children. However, since deworming is a very costly enterprise, particularly for developing nations, and deworming one segment of a community potentially predisposes the untreated population to enhanced worm infections, Ravindran has concluded that an alternative method of treatment or prevention is required: "ILS is keen to be involved

in addressing this issue if international funding is made available".

Meanwhile, the group continues to refine their highly promising lab technique for inducing nematode embryonic programmed cell death, as Ravindran elaborates: "Having developed high-throughput assay systems for screening novel compounds which induce programmed cell death, this line of research remains one of our major interests". Using this technique, the group will be able to translate it into a real-world therapy - that could have the potential to make deworming redundant.

A COLLABORATIVE EFFORT

Translation is only possible through multidisciplinary collaboration and, with an atmosphere conducive to fostering interdisciplinary projects, Ravindran and his colleagues at ILS are thinking ahead to new ways of conducting research: "Systems biology is one emerging area that the Institute is planning to diversify into," he reveals. "We wish to develop mathematical models of disease prevalence in human populations, as well as modelling subcellular events in mammalian cells."

With the addition of extra facilities such as a new laboratory block and a dedicated state-of-the-art animal house facility, ILS will continue its upward trend as a National Centre of Excellence.

Research by the team on the regulation of roundworm embryogenesis uncovered an interesting approach to targeting and eliminating pathogenic nematodes through induced programmed cell death

FURTHER READING

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