Battling viral rheumatism

Professor Andreas Suhrbier explains his work on chikungunya virus, which has recently reemerged in a global epidemic, using newly developed models that have greatly facilitated investigations into inflammatory disease and new interventions.

Over the last 15 years, how has the Immunovirology Group developed and what has been achieved?

The Immunovirology Group started its life working on Epstein Barr virus (EBV) vaccines and Ross River virus disease (a primarily rheumatic disease caused by a mosquito borne alphavirus). Highlights include a successful phase I trial of the first CD8 T cell epitope-based EBV vaccine for infectious mononucleosis and the first human study to accurately describe the natural history of Ross River Virus disease. An association with the Cooperative Research Centre for Vaccine Technology continued the vaccine theme; some highlights are the development of the polytope technology, contributions to the ISCOM technology, and development of a prophylactic retroviral vaccine against bovine leukaemia virus. Collaborative research on the Kunjin replicon vector technology resulted in formation of a company Replikun Ltd, which was a victim of the global financial crisis. Our expertise in mouse models and inflammation biology resulted in a long association with Peplin, a company sold to Leo Pharma in 2009 for US $287 million. The companies developed a new topical drug for actinic keratoses, which was recently approved by the FDA in the US.

How has the recent outbreak of chikungunya (CHIKV) affected the work that you do?

After the 2004-11 global epidemic of the alphavirus, CHIKV, our research has recently returned to alphaviral rheumatic disease and understanding why anti-viral immune responses fail to clear the virus and how the virus persists to cause chronic inflammation. The refocusing on inflammation has spawned other research endeavours, including recent progress in understanding the physiological function of SerpinB2, a protein that is nearly always one of the most up-regulated proteins during most inflammatory reactions. We are also working with CBio Ltd (Australia) to understand how their new immunomodulator, Cpn10, mediates its effects on the immune system.

Which companies and organisations support the group, and how have they actively contributed to research and collaboration efforts?

The basic research in the Immunovirology Group is currently supported by a fellowship and project grants from the Australian National Health and Medical Research Council, and smaller grants from the Queensland Cancer Council, the Australia Centre for Vaccine Development and the Australian Infectious Disease Research Centre. Alongside this we currently also have industry funded collaborative research projects with Leo Pharma and CBio Ltd.

Currently our main focus is in CHIKV disease with some collaborative work on Ross River virus. CHIKV is a mosquito borne alphavirus, which is transmitted to humans through Aedes mosquitoes. CHIKV disease has symptoms similar to dengue fever, with an acute febrile phase lasting several days; however, CHIKV disease is characterised by weeks to months of polyarthritis that generally affects the joints in the extremities. The disease is usually found in tropical Africa and Asia, but the recent epidemic reached Europe and a past epidemic reached the US. In the recent outbreak imported cases were also reported in 40 countries. The attack rate can be very high, for instance, in Reunion Island one-third of the 270,000 population was afflicted, with severe effects on services and the largely tourist-based economy. Current treatments are often inadequate, with patients incapacitated to various degrees for weeks to months. Ross
Alphaviral rheumatic disease

The global impact of chikungunya virus and related alphaviruses is substantial, but a team from the Queensland Institute of Medical Research is developing models and gaining insights into how better to manage the chronic rheumatic diseases caused by these viruses.

River virus is the Australian relative of this arthritogenic alphavirus with a mean 4,000 case per annum. The virus also caused an explosive outbreak in 1979-80 in several South Pacific islands involving tens of thousands of cases.

What would you highlight as the most successful moments during the beginning of the research so far?

The development of a wild-type adult mouse model of CHIKV arthritis, which recapitulates many of the features of human disease, has been very important. Our meticulous attention to removal of endotoxin and mycoplasm contamination from viral preparation was, we think, critical to this development. It is exciting when such leaps forward are made, and I’m proud of my team for leading this innovation in the field.

Have there been any challenges or limitations that have prevented particular areas of exploration?

The regulatory burden is increasingly complex and processes are often slow and cumbersome. Some new rules are often confusing, inappropriate and poorly conceived or interpreted, often resulting in long hold ups for mindless bureaucratic reasons. Access to good bioinformatics support also remains a major issue for our work and work of others, and this is a continual limiting factor.

A group at Australia’s Queensland Institute of Medical Research (QIMR) has been working on improving our understanding of the arthritic disease. Their use of models has provided unprecedented results, making clear that this is an inflammatory disease driven by virus persisting in macrophages, with disease likely caused by innate and cognate immune responses directed at persistent virus or viral products. These findings have also revealed how important monocytes/macrophages and T cells, as well as their products, are to disease pathogenesis. Earlier in vitro work, together with recent clinical, histological and molecular analyses in recently established wild-type animal models, have provided compelling physiological relevant insights into how these viruses cause disease.

The researchers’ development of a simple wild-type adult mouse model of CHIKV disease has led to numerous collaborative and commercial investigations into new treatments and therapeutic approaches for CHIKV disease. A number of vaccine approaches including simple inactivated whole-virus vaccines, recombinant adenovirus vaccines, nanopatch-delivered inactivated whole-virus vaccines and baculovirus vaccines, have all been shown to be highly effective.

However, Professor Andreas Suhrbier who leads the team, argues that CHIKV vaccines may be difficult to develop commercially and deploy effectively given the disease is so unpredictable in its behaviour, reappearing every two to 50 years to produce large epidemics in different parts of the world. Consequently, they are also investing effort in the testing of new biologicals, including neutralizing antibodies, and in identifying anti-inflammatory drugs that could provide more effective treatment.

BUILDING ON SUCCESS

The work has been assisted by new investment in the QIMR, providing new state-of-the-art facilities in a recently completed 15 floor building. Suhrbier is excited about working in this new environment: “The new building is up and we have moved in, and the biosafety level 3 (BSL3) suites are operational and we now have integrated, fully equipped BSL3 laboratory, animal house and insectary facilities”. With 20 new research laboratories housing 400 additional scientists, the new building will raise the number of scientists working at the QIMR to over 1,000, thus offering at QIMR a dynamic, high-quality, multifaceted research environment. With the new building QIMR is looking to increase the Institute’s research capacity in (inter alia) tropical diseases and immunological interventions. The group’s association with the Australian Infectious Disease Research Centre, the Queensland Tropical Health Alliance and the team’s various national biotech and pharma companies

The team has a substantial track record in generating intellectual property – 17 patents so far – and in undertaking industry-funded collaborative research with large and small, local and international

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CHIKUNGUNYA VIRUS INFECTION, DISEASE AND INTERVENTIONS

OBJECTIVES

• To understand how alphaviruses, like chikungunya virus, cause rheumatic disease
• To determine how alphaviruses interact with their hosts (humans, animals and mosquitoes)
• To develop physiological relevant model systems to test new interventions
• Improve alphaviral disease management and to inform rheumatic and inflammatory diseases research generally

KEY COLLABORATORS

Alexander Khromykh and Roy Hall, University of Queensland, Australia • Helder I Nakaya and Bali Pulendran, Emory University, USA • Thibault Larcher, École Nationale Vétérinaire, France • Pierre Roques, Commissariat à l’énergie atomique, France • Philippe Gasque and Marie-Christine Jaffar-Bandjee, Université de la Réunion and Hôpital Félix Guyon, France • Gorben Pijlman, Wageningen University, The Netherlands • Yutaro Kumagai and Shizuo Akira, Osaka University, Japan • Suresh Mahalinham, Griffith University, Australia

FUNDING

National Health and Medical Research Council, Australia
The International Alliance Program of the Government of Queensland (Australian Centre for Vaccine Development)
Various commercial sources

Suhrbier holds a Principal Research Fellowship with the National Health and Medical Research Council, Australia

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PROFESSOR ANDREAS SUHRBIER

is Group Leader of the Immunovirology Lab at the Queensland Institute of Medical Research. He has published over 120 papers in the fields of virology, immunology and oncology and is an inventor on 17 patents, 13 of which are commercialised and eight cover products tested in clinical trials. Suhrbier takes part in biotech/pharma-sponsored collaborative research and consultancies.

and international collaborators, together with the new building and particularly the BSL3 facilities, means substantial new scope and capacity has been generated for new academic and commercial collaborations. The team has a substantial track record in generating intellectual property – 17 patents so far – and in undertaking industry-funded collaborative research with large and small, local and international biotech and pharma companies. The Brisbane group will also continue working in the associated areas of inflammation biology and anti-inflammatory drug development and will utilise the ever-expanding resources at QIMR, which include a large number of knock-out and reporter mice allowing the importance of individual inflammatory and antiviral pathways to be analysed in vivo.

NEW CONNECTIONS

Suhrbier’s recent collaborative research with Dr Helder Nakaya and Dr Bali Pulendran and their systems biology group at the Emory Vaccine Center in the US, has investigated the similarities between CHIKV arthritis and rheumatoid arthritis using microarray technology and bioinformatics analyses. The two conditions, an infectious self-limiting viral arthritis and a progressive autoimmune arthritis, appear to share a significant number of inflammatory pathways. “We were really surprised to see the high levels of overlap between these diseases, which have quite distinct aetiologies, and are extremely pleased with the insights provided,” Suhrbier comments.

The work was recently published in the American College of Rheumatology’s monthly journal Arthritis and Rheumatism. These results highlight the potential for using new drugs being developed for rheumatoid arthritis, also finding utility in the treatment of alphaviral arthritides. In broader terms, the project also adds to the growing body of literature that is promoting the notion that the best way in the future to treat disease is not only to define the disease clinically, but also to define the deregulated molecular pathways involved. Drugs that target a particular pathway can then be used in the treatment of multiple diseases where that pathway is known to be dysregulated, rather than restricting the use of that drug to a defined clinical presentation.

KNOCK-OUT MICE

The researchers have been able to exploit the large number of knock-out mice available at QIMR and from collaborators. These mice, deficient in specific immune factors, have dramatically increased our understanding of the importance of specific anti-viral and inflammatory pathways in protection and disease. “What has surprised me is how often a specific pathway is largely irrelevant or extremely critical, and how removal of certain pathways can completely change disease pathology,” notes Suhrbier.

For example, in the journal of Virology, published by the American Society of Microbiology, the team, together with several international collaborators, published findings that show Interferon Response Factor 7 and 3 (two transcription factors involved in generating anti-viral interferon α/β responses), were critical for survival after infection.

Surprisingly, Interferon Response Factor 7 and 3 deficient mice died of haemorrhagic fever and shock, an entirely unexpected pathology with broader implications for the regulation of cytokine storms such as those seen during dengue haemorrhagic fever and dengue shock syndrome. “We have recently also shown that depleting TNF or CCR2, two major targets of next generation anti-inflammatory drugs, can have major detrimental effects on alphaviral rheumatic disease. Such work in knock-out mice can therefore also reveal the potential dangers associated with targeting of specific pathways with new drugs or biologicals,” adds Suhrbier.