Professor Kevin Kain, Canada Research Chair in Molecular Parasitology, sheds some light on his work towards combating severe malaria and its associated complications using a novel approach which focuses on the response of the host to parasite infection.

Affecting 300 million people every year, malaria remains amongst the most prevalent infectious diseases in the world. Why is it such a challenging disease to prevent and treat?

The parasites responsible for malaria display many unique attributes that make them exceptionally successful as pathogens and render them resilient to human efforts to contain and control them. During each stage in its life cycle malaria presents novel antigenic challenges requiring stage-specific immunity for effective control and, consequently, vaccine development has been particularly problematic. Malaria control efforts are further complicated by the ability of malaria to result in long-term asymptomatic infections. In the case of infection with *Plasmodium vivax* and *P. ovale* the disease can also frequently relapse. Finally, malaria parasites have demonstrated their capacity to rapidly develop resistance to all classes of antimalarial drugs currently approved for prevention and treatment – including artemisinin-derivatives. If resistance spreads, it could seriously hamper current malaria elimination programmes.

Could you provide an overview of your research activities as Canada Research Chair in Molecular Parasitology?

Our research programme addresses critical knowledge gaps in our understanding and treatment of life-threatening infections, including severe and cerebral malaria. In particular, we are interested in how the host response to infection may play a critical role in mediating severe and fatal outcomes. If we can identify important host response pathways, it may be possible to therapeutically manipulate them in order to improve clinical outcomes.

To what extent does your research contribute to the development of therapeutic interventions for malaria?

The field of infectious disease therapeutics has, over the last half century, concentrated largely on the development of antimicrobial agents. Unfortunately, almost as fast as they are approved for human use, resistance develops. Moreover, the fatality rates of serious infections like cerebral malaria and sepsis remain high, despite the use of potent anti-infectives. While it is clear that we do have a need for new antimicrobial agents, my group’s research supports a different paradigm: that clinical outcomes for life-threatening infections may be further improved – beyond that possible with antimicrobial agents alone – by modulating deleterious host responses to infection and, in particular, by stabilising vascular integrity in the face of critical illness.

In 2012 you received an award from the Preventing Preterm Birth initiative for research towards the discovery of new biological biomarkers and interventions to prevent preterm birth and stillbirth associated with placental malaria. How are you approaching this project?

Preterm birth and stillbirth are the leading causes of infant mortality worldwide, and are increasing in both high and low resource settings. Despite its impact on global health, little is known about the mechanisms underlying these events. Malaria induces preterm and stillbirth at a high rate, and in this project we are using malaria as a model to understand the underlying mechanisms that arise due to multiple causes.

Highly invested in the study of paediatric malaria, you have examined inhaled nitric oxide as an adjunctive therapy for cerebral malaria in children. Could you provide a brief outline of your project?

The use of inhaled nitric oxide is an example of re-purposing an approved intervention in an attempt to accelerate clinical impact. We know that children and adults with severe malaria have low bioavailable nitric oxide, and the lowest levels are associated with fatal outcomes. Nitric oxide is an important regulator of endothelial activation and integrity through its ability to control the release of endothelial proteins such as angioptotin-2 (Ang-2). Our lab, as well as others, has shown that in humans with malaria, increased Ang-2 levels are independent and quantitative predictors of malarial disease severity and death. In pre-clinical models of fatal experimental malaria, inhaled nitric oxide (at the FDA-approved dose) preserves endothelial and blood-brain barrier integrity, and improves survival over artesunate therapy alone. We are currently conducting randomised trials to determine if inhaled nitric oxide, with additional interventions to preserve endothelial integrity, will improve survival rates and prevent neurocognitive injury in children with severe and cerebral malaria.

Helping hosts

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THE EXTENT TO which some symbiotic organisms have mutually adapted towards one another is testament to the remarkable transformative power of the evolutionary process. Over millions of years, many mutualistic partnerships have been cemented into the very genetic makeup of their constituents, in some cases producing pairings or groups of organisms so interdependent that they appear to live together as one. Unfortunately, however, the same level of refinement applies to non-mutualistic examples of symbiosis. Parasitic relationships, such as those between protozoans of the genus *Plasmodium* and humans, result in genetic changes that are just as radical – but towards a far more deadly outcome.

The effective adaptation of parasite to host is what has allowed malaria to become the grave medical problem that it is today. *Plasmodium* protozoa first attuned themselves to be the perfect parasite for the human system, and then, on a more temporal scale, began to develop a resistance to antimicrobial agents that scientists designed to eradicate them. However, the adaptation is not all one way. Over the years, the human immune system has also adjusted to better respond to malaria parasites – and although this adaptation has not yet resulted in a decisive victory, it has produced the strong innate resistance to the disease demonstrated by those living in historically infected areas.

PROBLEMATIC POPULATIONS

The response of the host system to parasitic invasion is rarely simple, and in the case of malaria, many thousands of years of reflexive adaptation has made it very complex indeed. Understanding this response more fully, and subsequently altering it to the advantage of the patient, is therefore a potential route towards saving lives in the most vulnerable populations: children under five, pregnant women and other immunocompromised individuals. Furthermore, a greater attention to this aspect of parasitic disease may provide therapeutic treatments for some of the complications that can arise from malaria.

This approach is currently being employed by a team based at the University of Toronto in Canada. The group, which is led by Laboratory Director and Principal Investigator Professor Kevin Kain, is investigating a number of issues surrounding malaria, particularly its impact on young and even unborn children. As well as a novel approach to research questions, the team’s work is also grounded in practical considerations that might make their findings more conducive to clinical application in the context of the poverty stricken areas within which malaria operates. Consequently, the advances they have made through their research stand a better chance of rapidly and effectively being translated for use in affected populations.

SIGNIFICANCE OF BLOOD GROUP

One of the most striking of these advances was the revelation that the extent of a patient’s response to malarial infection may be influenced by their blood group. The evolutionary force that malarial infection has exerted on the human genome is extremely strong, and it is therefore possible that traits predominant in the populations of malaria endemic regions are the result of natural selection. The blood group O is especially prevalent in these regions, suggesting that possessing this erythrocyte polymorphism may give an individual enhanced protection against malaria.

Since this hypothesis seemed to be supported by several lines of epidemiological evidence, Kain’s team decided to further investigate the relationship between blood type and malaria vulnerability. Not only did they find that macrophage white blood cells could more easily clear malaria-infected O-type erythrocytes than their A- and B-type counterparts, they also demonstrated that the amount of A-antigen on the surface of red blood cells was inversely proportional to the capacity of macrophages to clear them. Finally, Kain’s researchers found that enzymatic conversion of B-erythrocytes to O-type before infection endowed them with the same protective powers. These conclusions go some way towards explaining the special properties of...
OBJECTIVES
To investigate how the host response to life-threatening infections such as malaria, mediates severe and fatal outcomes. To bridge existing critical knowledge gaps and better understand the underlying pathological mechanisms resulting in critical illness and to therapeutically manipulate these pathways in order to improve clinical outcomes.

KEY COLLABORATORS

USA: Dr Conrad Liles, University of Washington • Dr Chandy John, University of Minnesota • Dr Terrie Taylor, Michigan State University • Dr Diane Taylor, University of Hawaii • Dr Grant Dorsev, Dr Phil Rosenthal, University of California San Francisco

Canada: Dr Philippe Gros, McGill University • Dr Sergio Grinstein, Hospital for Sick Children • Dr Christine Cserti, Dr Howard Mount, Dr John Sied, University of Toronto

UK: Dr Feiko ter Kulf, Dr Melissa Gladstone, University of Liverpool

Worldwide: Dr Stephen Rogerson, University of Melbourne, Australia • Dr Bob Opoka, Mulago Hospital, Uganda • Dr Valérie D’Acremont, Swiss Tropical and Public Health Institute, Switzerland • Dr Victor Mwapasa, University of Malawi, Malawi • Dr Malcolm Molyneux, Malawi-Liverpool Wellcome Trust Clinical Research Programme, Malawi

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O-type blood in the context of malaria, as well as having possible implications for future treatment.

IMMEDIATE ACTION
A major pitfall in the current management of malaria is the difficulty in rapidly identifying the small proportion of patients who will progress to critical and even life-threatening stages of illness. Despite the provision of optimal supportive care and the use of antimicrobial therapies, severe forms of infection, such as cerebral malaria, are still associated with high mortality rates. In order to address this situation, Kain’s team is attempting to provide a method for immediately identifying these high-risk patients at a cost acceptable to the low-resource clinical environments typical of sub-Saharan Africa.

The researchers have chosen to investigate the role of the blood vessel lining, the endothelium, in the progression of severe infection. As the largest interconnected organ in the human body, and a pathway between all vital organs, injuries of the endothelium are a crucial indicator of disease progression. Consequently, the regulators of endothelial cell activation could contain early indicators of severe infection.

“The discovery of endothelial-based biomarkers could help identify individuals at risk of life-threatening infections, including severe malaria, and resulting endothelial interventions would have the potential to improve survival in these individuals,” hypothesises Kain.

INNOCENT VICTIMS
Although these projects reflect the diversity of host-based studies taking place at the University of Toronto lab, they do not feature one issue central to the group’s research programme: placental malaria and its role in preterm and stillbirths. Around a quarter of all pregnancies in sub-Saharan Africa are complicated by placental malaria, which is associated with high rates of preterm and stillbirth. Kain’s team was recently awarded $1.25 million in funding by Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) and the Bill and Melinda Gates Foundation to pursue research in this area, and the group has a variety of projects aimed at mitigating the burden of this pressing problem.

The first step towards accomplishing this goal is to establish the mechanisms by which placental malaria causes adverse birth outcomes. Using field studies of African women, the team has identified a number of candidate genes and pathways in the pathobiology of the disease. One of the most promising involves the excessive activation of the complement system – tasked with amplifying immune responses by producing a cascade of protein fragments. “One of these fragments, known as C5a, has elevated levels in African women with placental malaria, which is associated with an increased risk of experiencing a stillbirth or delivering a low birth weight infant,” states Kain. C5a is also associated with alterations in angiogenic factors required for placental vascular development – disruption to which can leave the placenta unable to adequately support foetal growth.

Building on this discovery, the team has gone on to investigate the impact of placental malaria on the neurodevelopment of children in utero. The efficacy of neurodevelopment in the womb has a great and lasting impact on subsequent learning and behaviour – and this process may be disrupted through the action of placental malaria on the complement system. The disruption of neurovascular angiogenesis and normal synaptic pruning may be having a profound effect on children exposed to malaria in utero, and this is a possibility that Kain’s group is exploring in concert with colleagues at the Malawian College of Medicine and the University of Liverpool.