Could you provide an insight into your background and what drew you to study the immune system; specifically how it responds to infections and sterile injury?

During my PhD I observed dramatic inflammation develop in response to surgery or trauma and during my postdoctorate I saw the amazing amount of inflammation that occurs during myocardial infarcts and strokes. I realised that these events were very similar to infections and that the immune system was doing something very important in these conditions.

The immune system is by far the most dynamic system, racing around the body trying to protect against infections and trauma. I developed simple microscopy that allowed us to visualise immunity in action and it became a passion of mine to be able to see white cells race into sites of infection and trauma and observe what they do there.

In 2011, you were named Canada’s Health Researcher of the Year by the Canadian Institutes of Health Research (CIHR). What is the importance of this accolade on a personal level?

This award was chosen by a committee of exceptional scientists so it was very rewarding to receive this accolade. It has fuelled me to perform more research and to try to help people with devastating diseases. More importantly, it recognised the people I work with and the University of Calgary, which has supported our research, provided infrastructure and made this work a priority.

As an internationally recognised scientist specialising in visualising the mammalian immune system, what is your proudest achievement to date?

I am most proud of the people I have trained, who are now making major contributions to science. They are our legacy; each time one of my trainees succeeds, it makes me very proud. My first postdoctoral student, Mike Hickey recently published a major kidney imaging paper in *Nature: Medicine*, became a professor and had his grants renewed. A new professor, Bryan Heit, University of Western Ontario was funded by our most prestigious funding agency, CIHR. I have also had two of my past trainees, Drs Bryan Yipp and Brent Johnston, obtain Canada Research Chairs, and become faculty at Canadian Universities.

You have a great number of additional time commitments. How do you manage your time effectively?

I surround myself with talented people including great administrative staff, trainees and faculty and trust them to take the ball and run with it. I do not micromanage and trust that the people who work with me will do a great job. We work as a team.

Do you think there is enough research conducted into infectious disease?

Absolutely not! I cannot emphasise this point sufficiently. I was recently asked by a senior administrator why we need a microbiology and immunology department. My answer – you are as likely to die of an infection as of cancer or cardiovascular disease in today’s society. Despite this, we have bikeathons and telethons and all kinds of fundraisers for cancer and heart and stroke, and none for antibiotic resistant bacteria – the emerging big killer. We must make society more aware of infectious diseases. Unfortunately, researchers go where the money is for research and so they are often forced to focus on diseases where funding is available.

Finally, what is the role of government in supporting this type of research?

Fundamental research, which has the biggest impact on the healthcare landscape, takes the longest to show benefit, and so some governments try to change the focus of investigators to problems with quick results and immediate bang for their buck. However, if fundamental research stops our society will stagnate. Governments must be globally responsible for the wellbeing of all citizens, and as such, there is no unimportant fundamental research. Governments also need to stop directing research to what they deem most important. The most important discovery in immunology in the last 20 years was made in a laboratory studying a protein that helps flies develop wings. This evolved into the ability to detect bacteria. Which politician could have predicted that? Fundamental discoveries in one area may provide insight into many diseases and I am convinced noone can possibly predict when and where the next big discovery will appear. Governments need to continue to make fundamental research a priority and invest appropriately.
DESPITE RECENT ADVANCES in immunology, researchers remain some distance from fully understanding exactly how the immune system protects an organism from infection. Historically, the limited tools for visualising and dissecting the mechanisms involved, as well as a relative dearth of funding, have no doubt contributed to this. Antibiotics have proven to be a double-edged sword, saving millions of lives from infection, while simultaneously reducing the economic and social motivators for novel drug research in the fight against infection. Bacterial resistance to antibiotics is becoming a serious problem. The continual emergence of drug resistant strains may lead to a situation not dissimilar to the 1900s, before antibiotics were discovered and death from infection after relatively minor injuries was a frequent occurrence. All the while, infection-related death is on the rise and antibiotic drug development is down by 98 per cent. There is an overwhelming need for new developments in understanding the immune system and how it functions, in order to find alternative forms of treating infection that do not rely on antibiotics.

A NEW HOPE

Canada Health’s Researcher of the Year, Dr. Paul Kubes, is a professor at the University of Calgary’s Faculty of Medicine. He is also the founding Director of the Calvin, Phoebe and Joan Snyder Institute for Chronic Diseases, which comprises over 100 basic and clinical scientists working on chronic diseases, where he leads research projects and develops the institute’s infrastructure to ensure national and international research excellence. He has published over 200 peer reviewed papers to date and his research focuses on the interface between infection, inflammation and injury.

Kubes’ group is currently investigating inflammatory diseases and how a host organism’s immune system responds to bacterial infection or sterile injury. Naturally, this research also seeks to facilitate the host immune system (also called immunotherapy) and provide novel therapeutic strategies to tackle the problems of infection and injury: “The Kubes Laboratory is involved in trying to understand some of the common pathways that lead to inappropriate inflammation. We then relate that understanding back to the physicians and end-users who can develop new therapies for patients,” he explains.

The Laboratory specialises in the visualisation of the cellular and molecular underpinnings of the immune system and looks at several disease models to better understand the mechanisms that ensure an effective immune response. Through unparalleled methods of immune system visualisation in live animals, Kubes hopes to unravel many of the unanswered questions in his field.

VISUALISATION: A NOVEL APPROACH

The Kubes Laboratory has developed and implemented cutting-edge imaging techniques that have facilitated the microscopic visualisation of functional processes occurring in live animals in a range of disease models: “Imagine if you could see the whole inflammatory process happening. That is what we are trying to do. We need to be able to visualise the events as they happen, so we have developed ways of looking inside the body without disturbing anything,” Kubes explains. In order to do this, his team employs a combination of sophisticated cameras and microscopes that create three-dimensional images in real-time, allowing the visualisation of cellular events occurring in a given location. The type of cellular events that can be visualised include motility, adhesion and cell-cell interactions and this has been used to track the movement of immune cells inside of blood vessels.

This visualisation relies on a technique known as spinning disc microscopy, and has been used together with fluorescent markers. Genes that encode for specific types of fluorescent proteins...
Kubes has been able to glean fruitful insights into the mechanisms that underpin a healthy immune response, opening up a variety of therapeutic avenues for future research that will help fight infection.

are expressed in each cell type and allow them to be identified in the image, allowing important players in the immune response to be differentially coloured, and their functions more easily followed: “Then we can see who is coming to the site of injury and what they are doing there,” Kubes reveals.

REAPING THE REWARD
This line of investigation has been particularly fruitful in several areas, and is transforming collective understanding of the immune system’s many functions and mechanisms of action.

One of the Kubes Laboratory’s key recent findings shows platelets to be extremely important in the immune response – a finding that contradicts previous opinion supposing them to be irrelevant in immunity. While imaging a macrophage as it captured and engulfed a bacterial cell, Kubes’ group observed platelets cooperating with the macrophage by surrounding the bacteria and preventing its escape, thus facilitating the macrophage’s function. Platelets have also been shown to serve a highly dynamic function in the detection and rapid sequestering of harmful bacteria in the liver, thus facilitating specialised macrophages called Kupffer cells that trap and destroy bacteria over the course of several hours. This has clinical consequences where drugs that help to reduce pain could also reduce platelet function, leading to an increased susceptibility to infection. It is likely, therefore, that this finding will influence the drugs prescribed to treat a wide range of ailments.

The group has also discovered that death following stroke is more likely due to infection than the direct effects of the stroke itself. This surprising finding is explained by a consequence of immune system and inflammation suppression by the brain after insult. The researchers demonstrated this downregulation of the immune system by tracking natural killer T cells, finding that neural messages signal to these white blood cells to reduce their function and cease production of important inflammatory molecules: “Using imaging we were able to see the immune system go to sleep and stop finding bacteria; if we stopped the brain from sending messages to the immune system then infection did not occur,” explains Kubes. This suppression protects the brain from inflammation, but by default increases susceptibility to infection. Through elucidation of these and other such mechanisms, it may be possible to modify the response of natural killer T cells such that they fight infection with minimal damage caused by inflammation.

FUTURE WORK AND IMPACT
This work demonstrates the power of basic science and its influence in drug development. Through observation of the immune system in action, Kubes has been able to glean fruitful insights into the mechanisms that underpin a healthy immune response, opening up a variety of therapeutic avenues for future research that will help fight infection.

In the future, Kubes hopes to continue searching for new ways to fight emerging pathogens. Among other lines of investigation he aims to determine the role of different cell types in immunity: which cells facilitate the immune system and fight infection? Which ones are dysfunctional and fail to protect the immune system and fight infection? Which host organisms from infection? He also wishes to adapt the immunotherapy approach cancer biologists have used to harness immunity and adapt it to fighting infections. “I will try to identify ways to help the immune system conquer or at least live in harmony with the microbial world. For this we will push the boundaries of imaging, hopefully taking some of this into humans and into patients where we do not know what is hurting them,” Kubes enthuses. “We have it in us to kill invading pathogens, we simply need to harness the power of our immune system.”