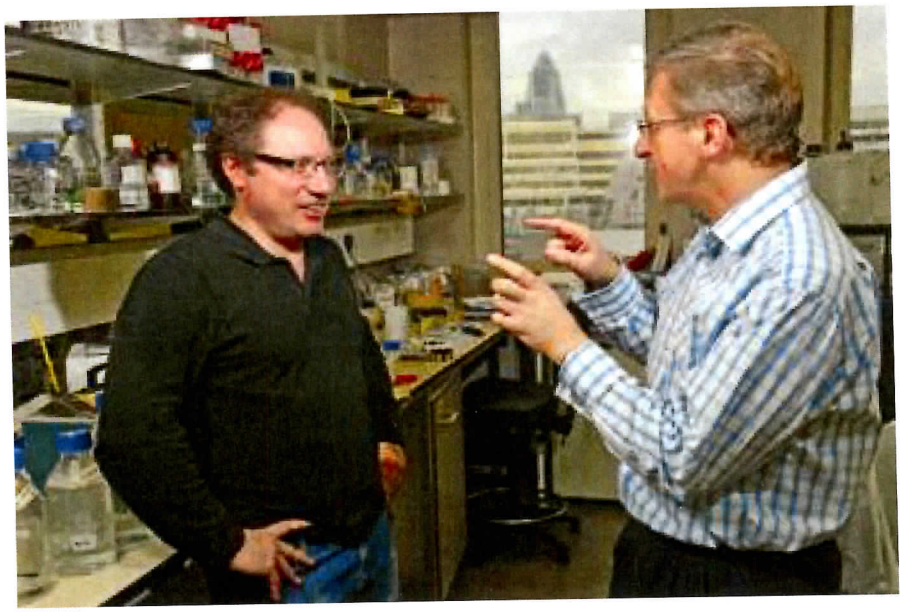


Professor Frederic Geissmann and Professor Andrew Cope

Top Guys at King's

The two new **arc** professors at King's College, London, talk to *Arthritis Today* about their new roles – and their exciting plans for future research.

There's nothing modest about Andy Cope and Frederic Geissmann's ambitions.

The pair, both newly appointed as Arthritis Research Campaign professors at King's College London (KCL), have big plans for the future of research into inflammatory forms of arthritis. In a nutshell, by combining their clinical and scientific expertise, they are planning new ways of tackling inflammation that could lead to improved treatment – and even prevent inflammatory disease from happening in the first place.

With a £4.1m endowment from **arc** and input of £2.6m from KCL and Guy's and St Thomas' charity, a new research centre is being constructed at the heart of the Guy's campus where a large group of scientists and clinicians will collaborate in a multidisciplinary programme of research on inflammation and inflammatory diseases.

The new Centre for Molecular and Cellular Biology of Inflammation is opening in a phased way through the year, and should be fully up and running towards the end of 2009.

Frederic Geissmann, a world authority on immune cells called phagocytes, was lured to KCL with the promise of funding and freedom to pursue his research interests. With his impressive CV and research track record, new colleague Andy Cope describes him as a "superstar".

A stimulating environment

Professor Cope in his turn could hardly resist the offer of being a part of this new centre from its inception, leaving his long-time base of the **arc** Kennedy Institute of Rheumatology for the promise of new opportunities for making important contributions to arthritis research. Showing visitors around the fledgling unit, both men are openly excited about the opportunities that the centre offers them and their team of up to 70 researchers. It will provide a stimulating environment for the next generation of trainee scientists and clinicians, including the PhD students soon to be recruited as part of the Oliver Bird Rheumatism Programme.

They are also keen to stress that the two of them are very much a package. It's the first time that two **arc** professors have been appointed at a single institution; Frederic Geissmann as professor of inflammation biology, Andy Cope as professor of rheumatology. They fill a post left vacant since the retirement of previous incumbent Professor Gabriel Panayi a few years ago.

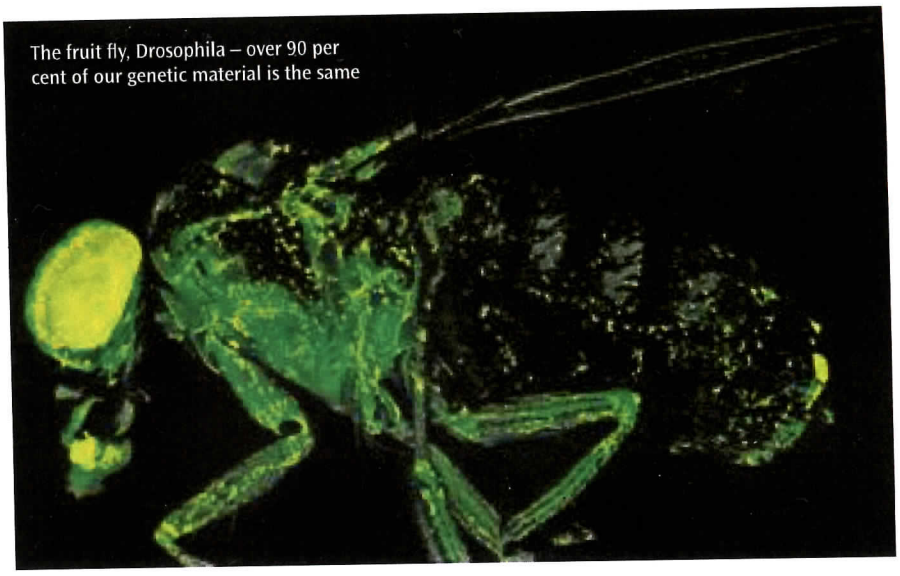
Andy Cope explains the reasoning behind this: "If you were to go back 20–30 years, senior academics served multiple roles, being responsible for the clinical service and at the same time running a laboratory dedicated to clinical or basic research. This would involve significant administrative duties in the hospital and university setting, and a big commitment to teaching and training. It was a challenging job, even back then. The landscape has changed in recent years with growing pressures on clinical service delivery and a highly competitive research environment. This has made it very difficult for a clinician to make major contributions in clinical medicine and in the laboratory. In fact, clinical and laboratory-based career paths in medicine have diverged, and so in recent years it has become increasingly difficult for universities to recruit individuals who can deliver excellence in all three domains – clinical service, research and teaching."

A great opportunity

Frederic Geissmann adds: "This is not only about spreading responsibilities or workload. Over the past 30 years, science has become a major force that has driven progress in clinical medicine, and there is a real opportunity today to build a better clinical medicine based on an in depth knowledge of the precise, molecular, mechanisms of diseases. However, only relatively few universities in the world have the will and means to lead this process. So when Adrian Hayday, chairman of the Division of Immunology, Infection and Inflammatory Disease (which includes the academic department of rheumatology) at KCL, told me that that Professor Alan Silman, the medical director of **arc**, and KCL were keen to give financial support to create a basic science centre working on the mechanisms of inflammation – that would work together with the rheumatology department to improve our understanding of chronic inflammatory diseases, and to develop new diagnostic

markers and better treatments – I decided it was a great opportunity for me, and I accepted to be the head of this centre."

There are obvious synergies between the new professors. Professor Cope has been interested for many years in understanding how the immune system, in particular the T lymphocyte, becomes activated in inflammatory disease, and why the joint becomes the focus of this activity in patients with arthritis. Monocytes and macrophages, the cells whose function is the focus of Professor Geissmann's research, play a central role in immune activation and are likely to drive the inflammatory process that attracts T-cells and other cell types to joint tissues during the very early stages of disease.



The fruit fly, Drosophila – over 90 per cent of our genetic material is the same

Working towards the 'Holy Grail'

Another of Professor Cope's clinical research interests focuses on what he believes is the 'Holy Grail' for researchers and clinicians working in rheumatoid arthritis research – identifying healthy people in the community who are most at risk of developing the condition – and actually then being able to carry out studies that might even prevent RA in the first place.

"The research groups that have made the biggest impact on patient care have been those who have invested in building up large cohorts of patients," explains Andy Cope. "A cohort is a large collection of patients with the same or closely related disease. By capturing detailed information from patients and comparing this with data from healthy control subjects you can learn a lot about the disease at the population level."

"The question we now want to ask how is: can we establish a cohort of apparently healthy individuals who are at high risk of developing RA? This would be a great opportunity to study the interactions between genes, environmental factors, and the immune system, and how they interact to cause disease."

Treating the high risk group with cheaper, safer drugs

With collaborators at the **arc** epidemiology unit in Manchester and at Imperial College, Professor Cope is setting up the first stage, looking to recruit a substantial cohort of subjects at high risk of developing RA – for example women smokers, who may be overweight, and also carry the genes associated with susceptibility for RA. The team will then watch these individuals very closely to see if they go on to develop the disease, and compare the results from a low risk cohort of the same gender and age but who don't carry the susceptibility genes. Cope believes that the population in south east London is an ideal setting for such studies. The ultimate goal would be to treat the high risk group with cheaper and safer drugs before showing signs and symptoms of the disease and so prevent it from occurring.

Andrew Cope with
Tharsana Tharmalingam (research technician) *centre* and
Dr Joanna Clark (senior postdoctoral research fellow) *right*

Professor Geissmann has already gained valuable new insights into the vital role that phagocytes play in the inflammatory response to disease. These cells patrol our body in the bloodstream and move into infected tissues when required, engulfing invading microbes and secreting chemicals that stimulate other immune cells and cause inflammation. How do they do this and why don't they stop doing this in arthritis?

To answer these questions, Professor Geissmann has developed a novel technique that reveals cell behaviour in a totally new way. The cells are made to fluoresce so that they glow when viewed under a powerful microscope, and are viewed in real time, in living tissue. The images are fascinating – the cells can be seen as blobs of colour moving around the tissues and interacting with other cells.

Cutting edge imaging

"The methods we use to investigate the cells are technically very demanding," says Professor Geissmann, "and that's why it's so important to have good collaboration with our imaging department specialists. We're using cutting edge imaging and cell targeting techniques that allow us not only to view the cells but to investigate how their development and actions are controlled."

Advanced imaging is also generating new knowledge at the molecular level as well. Within immune cells, genetic material is responsible for programming the manufacture of inflammation chemicals, such as tumour necrosis factor (TNF) and other cytokines. Understanding this control is crucial to inflammation research.

Professor Geissmann explains: "We want to find out which genes are responsible and how they affect the metabolic pathways that start and stop cytokine manufacture after infection. In arthritis, cytokine production is excessive and sustained. We may be able to design therapies that interrupt or stimulate the relevant pathways to prevent this. The goal is to correct the imbalance without compromising the body's ability to fight infection."

The role of the humble fruit fly, Drosophila

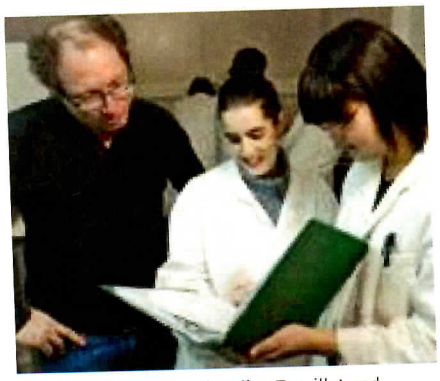
The research model for these studies is the humble fruit fly, Drosophila. This may seem a surprising model but in fact the genes responsible for cytokine production in the fly are similar to those in the human – over 90 per cent of our genetic material is the same – and the research will eventually translate into human studies. The fly is a very convenient experimental model – easy to reproduce quickly in large numbers and without the ethical constraints of rodent models.

The relevant Drosophila genes are tagged with fluorescent proteins so that once they are activated, the fluorescence can be tracked using advanced imaging techniques able to monitor living systems, and the images are simply stunning.

Christine Wong and Celine Trouillet, PhD student and laboratory manager respectively, have been establishing this novel technique and preparing the genetic material in preparation for the studies: "We can't wait to move into the new research centre facilities. The new laboratory facilities have been purpose-built to our particular research specifications and will make a huge difference to our operational ability and throughput."

Mapping the outcomes of the immune response

The flies will be infected with microbes to stimulate an immune response and the resulting gene activity tracked in real time. "We already know," says Christine Wong, "that the genes responsible are active in the joints in humans and interestingly, this has been found to be the case in Drosophila too. We are going to study each gene in turn and map the outcomes of the immune response for each one."



Frederic Geissmann with Celine Trouillet and Christine Wong

Professor Geissmann agrees: "During infection the body fights to restore health, and the cytokine system relies on a finely-tuned control mechanism. We'll investigate how this control is achieved, why the joint is a focus of activity, and potential avenues for manipulating the system to block excessive inflammation in arthritis. The analysis will be challenging, but we should achieve the first detailed genetic blueprint of inflammation control in Drosophila – a world first."