BREATHROUGH
IN THE FIGHT AGAINST FLU

Welcome: New Lecturers

Our History: Memories of Cambridge

Research Matters: Exposure to micronutrients prior to pregnancy associated with gene modifications in offspring

Featured Academic: Professor David Dunne

To find out more about the Pathology Department visit our website www.path.cam.ac.uk
Scientists have discovered a new gene in the influenza virus that helps the virus control the body’s response to infection. Although this control is exerted by the virus, surprisingly it reduces the impact of the infection. The findings will help researchers better understand how flu can cause severe infections, as well as inform research into new treatments. Researchers found when the virus gene - called PA-X - was active, mice infected with flu subsequently recovered. When the PA-X gene did not work properly, the immune system was found to overreact. This made the infection worse, and did not help destroy the virus any quicker.

The study looked at how the gene affected the behaviour of “Spanish flu”, a virulent strain of influenza that caused a pandemic in 1918. It was carried out by the Universities of Cambridge, Cork, Edinburgh and Utah, the Institute of Systems Biology in Seattle and the United States National Institutes of Health. Scientists discovered the PA-X gene some 30 years after flu genome was first decoded.

The researchers include Dr Andrew Firth of the Department of Pathology, University of Cambridge, Professor Paul Digard of The Roslin Institute at the University of Edinburgh, and formerly of the Department of Pathology Cambridge, and Drs Brett Jagger and Helen Wise, also formerly of the Department of Pathology Cambridge. Dr Andrew Firth said: “The flu virus has a very, very small genome - just 12 genes. Finding a new gene makes a pretty significant change to our understanding of this virus.”

The first indication of the PA-X gene’s existence came from a computational analysis of the evolution of influenza virus sequences which revealed a sequence region where evolution was highly constrained. The researchers recognized this as the signature of a ‘hidden’ gene which could be expressed via an unusual mechanism know as ‘ribosomal frameshifting’. Dr Firth said: “This is not just a discovery in flu, but also a discovery of a new variant of ribosomal frameshifting that we believe may also be used by other viruses, and perhaps also in some human genes”.

The research was funded by the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the U. S. National Institutes of Health, Science Foundation Ireland, and the Wellcome Trust.

Eukaryotic cells contain a dynamic network of actin filaments that are assembled and disassembled to drive fundamental processes such as cell migration, phagocytosis, synapse plasticity and tissue repair, and pathologies like pathogen invasion.

Professor Vassilis Koronakis of the Department of Pathology has recently begun to study how cellular machineries like N-WASP and the WAVE complex assemble actin filaments. By setting up a novel in vitro reconstitution of the mammalian signalling platforms at defined phospholipid membrane bilayers, he discovered that membrane recruitment and activation of the WAVE complex requires the cooperative action of two GTPases, Arf and Rac1. Now, building on this discovery, he and his group - Drs Daniel Humphreys and Peter Hume and PhD student Anthony Davidson - have begun to unravel the ways by which the infamous intestinal pathogen Salmonella usurps the WAVE complex to elicit host cell membrane ruffling and pathogen invasion. How Salmonella manipulates the WAVE complex was unknown. In a new study they show that Rac1 GTPase activation by delivered Salmonella guanine nucleotide exchange factor (GEF) SopE triggered WAVE complex recruitment to the membrane but not activation, which required host Arf GTPase. Salmonella hijacked host Arf GEF ARNO to activate Arf and generate pathogen-containing invasion vacuoles. ARNO recruited and activated the WAVE complex, which was enhanced when SopE and ARNO cooperated. This synergy provides a mechanism by which pathogen and host GEFs regulate the WAVE complex for Salmonella invasion.

This novel cooperation between bacterial and host GEFs introduces a new layer of complexity in the mechanisms used by pathogens to control the host actin cytoskeleton, which has profound implications actin-dependent cellular processes in both health and disease.

For more information contact Professor Vassilis Koronakis (vk103@cam.ac.uk). This work was funded by the Wellcome Trust and the Isaac Newton Trust.


The trypanosomes are an important group of pathogens and are the causative agents of a number of ‘Neglected Tropical Diseases’, neglected because they afflict many of the poorest parts of the world, and also attract a disproportionately low level of investment for the development of new drugs, vaccines and control measures. Prof Field of the Department has been researching the African trypanosome for over two decades, and how it interacts with its host. Recently, in collaboration with scientists at the London School of Hygiene and Tropical Medicine, headed by Dr David Horn, studies have advanced our understanding of the mechanisms by which many existing trypanocidal drugs operate. Using a novel genome wide screen, the teams identified many of the genes required for sensitization of trypanosomes to the five currently used chemotherapeutics, discovering scores of genes that are important in the interactions between trypanosomes and drugs, many of which were completely unexpected. These insights not only provide a huge advance to our understanding of current therapies, but also provide clues to new targets and approaches and the potential mechanisms by which resistance could arise. One such new target appears to be endocytosis, the process by which material is taken into the cell, and an aspect of trypanosome biology that especially interests Field. “This may represent an Achilles’ heel, as we know that endocytosis is essential in these organisms, but also that it provides a near superhighway to deliver toxic compounds into the trypanosome cell,” he suggests. Exploiting that superhighway may take some time, but is one of the most promising possibilities to have emerged recently. See Alsford et al., High-throughput decoding of antitrypanosomal drug efficacy and resistance. Nature. 2012;482:232-6 for additional information.

For more information contact Professor Mark Field mcf34@cam.ac.uk

A new study by Department of Pathology scientists has found that the offspring of women who were given micronutrient supplements (minerals needed in small quantities, such as iron, iodine and vitamin A) before they became pregnant had gene modifications at birth as well as when they were tested at 9 months. The changes to the genes, called methylation, have previously been associated with the development of the immune system, although this study did not provide direct evidence that the activity of these genes has changed. The research, funded by the BBSRC, was published recently in the journal Human Molecular Genetics in advance online publication (DOI number DDS026).

Professor Nabeel Affara, lead author of the study and Head of Cellular and Molecular Pathology at Cambridge, said: “The mechanism by which micronutrients influence methylation changes is still to be worked out, but it is known from other work that the genes of the immune system undergo such changes as immune function develops, particularly in early postnatal stages and early childhood.

“These changes are part of the normal development of the immune system provided adequate nutrition is available. Where this is not the case, different patterns of methylation may occur, altering the activity of key genes and therefore potentially the effectiveness of the immune system. The result is likely to be reduced ability to fight infection and hence susceptibility to infectious diseases.”

The study used DNA samples from a Medical Research Council (MRC) micronutrient supplementation trial where women attempting to get pregnant are given either a cocktail of micronutrients or a placebo until pregnancy is confirmed (approximately an 8 weeks period). The research was conducted in The Gambia where there is seasonal variation in the availability of micronutrients with an alternation between the dry season (when they harvest and food is plentiful) and the wet season (when there is less food available and therefore poorer nutrition). Individuals born in the wet, nutritionally poor season have been found to be more susceptible to infection.

Professor Affara added: “This has huge public health implications for regions of the world where food security is an issue. If we have an improved understanding of what nutrition is important and the mechanisms by which this important environmental factor interacts with gene function, we can target nutritional intervention to improve health in later life.”

For more information contact Professor Nabeel Affara na@mole.bio.cam.ac.uk
Our History: Memories of Professor R.I.N Greaves

By M.J. Kelly MChir FRCS MRCP (UK) Consultant Colorectal Surgeon & National Advisor for Colorectal Cancer

I was a member of the 22 strong Part-II Class of 1966 in the third year of Prof. Greaves’ reign. At the start of the (preceding) long vac. term we were all sent to the wonderfully eccentric coffee room on the 1st floor. It was my first introduction to cross-specialty working, what we would now call MDT working, and I have been a devotee ever since. It was still going strong ten years later when I spent another happy year in the Department doing research for my MChir.

My undergraduate project was the successful experimental demonstration of synergy between aerobic (E coli) + anaerobic (B fragilis) bacteria Annals R C S (Eng) (1980) 62, 52-59

My PhD worked on the labile Corynebacteriophage provided by Prof. Carne from sheep, and my main supervisor was Greaves’ PhD student, Desmond Davies. When we were both stuck we went to Prof. Greaves who was charm personified. He was always available, knew everybody in the university and beyond. When I wanted to do some electron microscopy he told me to cycle up to the Department of Molecular Biology at Addenbrookes and see Max Perutz while he fixed up the appointment. My sister was working there as Francis Crick’s secretary.

Later when we were trying to secure the maximal cooling rates of the small vials in liquid nitrogen we were having difficulty getting the proper coating for the tubes, kieselgur, and Prof. told us to use cigarette ash because it was just as good, and it was. (He and Dr Fry seemed always to have plenty to hand) Desmond and I didn’t dare say this in our published paper, claiming we had used kieselgur, I still have the reprint. It was a golden time long before Health & Safety had been invented. I was given my own key to the laboratory and to the back gate of the Downing Site and my culture sequence meant that I was often there till midnight all alone. Our worst fear was that we might leave a tap running or forget to lock the back door securely. I don’t think that any of us ever did.

1; Kelly MJ & Tracy Cook. The colorectal MDT: how we do it at Leicester. Colorectal Dis (2010) 12, 596-600
2; Kelly MJ Hunterian Lecture: “Wound infection: a controlled clinical and experimental demonstration of synergy between aerobic (E coli) + anaerobic (B fragilis) bacteria” Annals R C S (Eng) (1980) 62, 52-59
3; Davies JD & Kelly, MJ “The preservation of bacteriophage H1 of C. ulcerans by freeze-drying.” J Hyg Cam (1969) 67, 573-584

Pathology in the pub

Hayley Frend believes in the importance of taking science out of the lab and making it palatable to non-scientists. This is exactly what she did when she took part in the new SciBar venture, organised by the British Science Association, taking scientific talks out into pubs.

Hayley is a third year PhD student with Professor Christine Watson in the Department of Pathology on the Wellcome Trust four-year Stem Cell Programme. Her PhD focuses on the problem of mammary gland lineages and she is working to identify both mammary gland stem cells and other populations of cells in the normal breast.

Hayley recently took part in the new SciBar venture which takes science out into pubs, to explain why fundamental knowledge about the mammary gland is still needed and how much research in the field will impact on the treatment of breast cancer in the future.

Nicola Graves went to meet Hayley after the first SciBar session at the Emperor Pub in Cambridge to find out how it went and what she plans to do next.

Q. Why did you get involved in the SciBar sessions?

I was approached by the organisers as they had heard about previous work I’d done to take the science of breast cancer research out into the community. I wanted to see how people would react and wanted to put forward the idea that you need basic research in order to make headway in translational research. I wanted to make the point that it takes a long time to get anywhere.

Q. Did you encounter any misconceptions about breast cancer at the event?

Yes and it was really valuable to hear them and be in a position to tackle them. Firstly, when I mentioned that I work in the Department of Pathology a few people found it strange that I should be looking at breast cancer. They had a view of Pathology along the lines of the TV drama ‘Silent Witness’ and expected me to carry out post mortems. I was able to explain that Pathology is about studying illnesses. A number of people in the audience expected me to work on breast cancer samples in the lab but that’s rarely the case. One of the most interesting misconceptions I encountered was that larger breast are more prone to breast cancer. This has not been found to be the case.

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Featured Academic: 
Professor David Dunne

Interview by Nicola Graves

Professor David Dunne has been studying human parasitic diseases in sub-Saharan Africa for more than twenty-five years. For the last five years, he has also directed Cambridge’s contribution to the Africa-led MUII (Makerere University/UVRI Infection and Immunity Research Training) and THRiVE (Training Health Researchers into Vocational Excellence in East Africa) programmes. These, as well as a new CAPREx (Cambridge-Africa Partnership for Research Excellence) programme funded by the Carnegie Corporation, seek to enable African researchers to become internationally competitive. 

African researchers to become internationally competitive

A study led by Dr James Traherne and Prof John Trowsdale has carried out an in-depth genetic analysis of the human KIR gene complex – one of the most rapidly evolving sites in the human genome (Jiang et al. Genome Research 2012).

Natural killer cells are a first line of defence against tumours or virus-infected cells. They employ a large battery of cell surface receptors to regulate their activity and development. The most diverse of these receptors are the KIR, which interact with HLA molecules.

The expanded KIR complex is unique to the human species and has considerable biomedical importance, its significance to HIV infection probably being the most well-known. The complex has been omitted from genome-wide analyses in the past because of high levels of polymorphism and duplication, which make it refractory to high-throughput methods.

Using a newly developed high-throughput typing system the team analysed over seven hundred families for KIR gene copy number. The unique assay provides, for the first time, a ‘gold standard’ for KIR typing that is accessible, reproducible and cost effective. The study unveiled much more diversity than previously recognised, and provides an important resource to carry out more informative and simplified disease studies. Seventy unique genes configurations (haplotypes) were characterised, carrying expansions and contractions of numbers of loci.

The research creates important new targets for functional and disease studies. It is applicable to the fields of infectious and autoimmune disease, reproduction and cancer as well as other conditions where NK cells play an important role. Exploiting the new method, the team are now approaching KIR variation and disease with a network of local and international collaborators who have collected large patient cohorts, each in excess of 1,000 patients. In the Pathology Department there are strong links with Ashley Moffett’s group, who have pioneered the effects of KIR variation on placentation.

The approach has direct applications in tissue typing where, for example, it is estimated that a 7% reduction of relapse after transplantation for acute myeloid leukaemia (AML) can be achieved by KIR typing donors. Plans are currently in development with the Addenbrooke’s Hospital Tissue Typing laboratory in Cambridge to establish a worldwide KIR typing service.

The research creates important new targets for functional and disease studies.

Congratulations on securing $1.2m from the Carnegie Corporation of New York, $1m from the Alborada Trust and £179,000 from the Isaac Newton Trust to continue your work in Africa. How do you feel about garnering such financial support?

This builds on what our core ‘Africa team’: Profs James Wood (Veterinary Medicine), Megan Vaughan (Centre of African Studies), Dr Pauline Essah (Pathology) and I have done over the last few years. It widens Cambridge’s engagement with Africa, because whereas the Wellcome Trust-funded MUII and THRiVE Programmes focus on health-related research, the latest funding provides a wider ‘Cambridge in Africa’ Programme that incorporates clinical, biological and social sciences plus engineering, mathematics and the humanities. These programmes are bringing diverse parts of Cambridge together, helping African research towards its full potential, and providing exciting opportunities for Cambridge researchers to collaborate with African researchers working on African priorities, in Africa.

What are the greatest successes of the Cambridge in Africa Programme (e.g. MUII and THRiVE) so far?

It is a pleasure to realize that there is fantastic enthusiasm from all parts of the University to help African researchers. A key success is that we now have a multi-disciplinary, cross-faculty approach. Because of these programmes, I’ve met far more people across...
Cambridge in the last five years than I did in the preceding twenty. This integrated approach is tremendous for Cambridge. With respect to the success of MUII and THRiVE, I think we’ll see the real benefits over the next few years. There are on-going post-doctoral and PhD projects that look extremely promising. As an example, an African fellow mentored by Prof Ashley Moffett (Pathology) is focusing on the immunogenetics of pre-eclampsia, and is building an invaluable resource of genetic information from Africa. Another fellow mentored by Dr Mike Stratton (Director of the Wellcome Trust Sanger Institute) is researching breast cancer genomics in Ugandan women. His research could generate exciting results which, for example, could be compared with data for European women. Another fellow mentored by Prof Peter Jones (Head of the Department of Psychiatry) is focusing on mental health of war-affected youth in Uganda, which could provide new insights into the prevention/management of devastating secondary consequences of war anywhere in the world. Therefore, such projects are good for Africa, and global health, generally.

**How much time do you now spend in Africa?**

I make six/seven trips per year, with a significant part of my Africa time spent on capacity building-committees, interview panels and advisory board, rather than in our field research. However, apart from facilitating new collaborations with African universities and research institutes, my research on human parasitic diseases is still the reason I am in science, and it’s still very important to me. Chronic infections such as schistosomiasis still affect hundreds of millions of people, and are designated ‘great neglected diseases’ and ‘diseases of poverty’ by WHO. Our Cambridge research group integrates disciplines including molecular biology, epidemiology, computational modeling, immunology and parasitology. However, even our most laboratory-based researchers have to experience the sharp end of our collaborative work with colleagues in Africa. Therefore, our group spends a significant amount of time in Africa.

**What are your ambitions for the Africa programme now?**

We have just submitted, with Prof Sharon Peacock (Pathology/Medicine), and eight co-applicants from across the University, a proposal to the Wellcome Trust to establish a Cambridge Centre for Global Health Research. If funded, the Centre will focus on Africa, with a supportive and cross-disciplinary philosophy. Although each of these programmes has its own main focus, they complement each other. Our new Carnegie-CAPReX programme is particularly interesting because it’s based on a three-way link between Cambridge, Makerere University, Uganda, and the University of Ghana, Legon. This provides the prospect of collaborative regional hubs in East and West Africa. This is great, because although most of our early links focused on East Africa, South-South collaborations are crucial to the long-term consolidation of African research excellence. I would now like to see Cambridge linked to an institution in Southern Africa, to provide a regional hub for Cambridge to support Universities and researchers there too, combining North-South and South-South collaborations. Our ambition is to efficiently organise and harness the enthusiastic support for African researchers we see across the University, so that Cambridge becomes known as the University that is really engaged in supporting the development of academic research throughout Africa.

**How can readers of Pathology News support the Cambridge in Africa programme?**

- Volunteer for ‘Meet the Expert’ sessions to inspire African researchers
- Make a donation to support African fellows (e.g. for purchasing software). Please make cheques payable to ‘University of Cambridge’, with ‘Cambridge in Africa’ written on the back, and send to Dr Pauline Essah at the address below. Any amount will be gratefully received.

Cambridge in Africa
Department of Pathology
University of Cambridge
Tennis Court Road
Cambridge
CB2 1QP

For more information about the Cambridge in Africa programme, please contact Dr Pauline Essah (pae21@cam.ac.uk), or visit http://www.thrive.cam.ac.uk/.

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**Research Matters:** New study looks at cell fate specification in mammary stem and progenitor cells.

**Cell fate specification in mammary stem and progenitor cells is not well understood.** In a new study by Professor Christine Watson and colleagues, the authors identify a novel transcriptional regulator, Zfp157, as a target of Stat6. The authors have been able to demonstrate that Zfp157 regulates mammary progenitor cells by deleting Zfp157 in luminal cells, which resulted in a dramatic shift in the cellular composition of the mammary gland. In addition, Professor Watson’s group found that Gata-3 is not an essential regulator of mammary gland morphogenesis and luminal cell differentiation as previously suggested, but is required simply to suppress expression of Zfp157. Thus, this study significantly advances our understanding of the regulation of multipotent alveolar progenitor lineage commitment and represents an exciting breakthrough in the understanding of mammary gland behaviour.

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**Recent publications**

Recent publications by Department of Pathology staff can be found at: http://www.path.cam.ac.uk/research/publications2012.html
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