THE NEWSLETTER FOR ALUMNI & FRIENDS OF CAMBRIDGE UNIVERSITY DEPARTMENT OF PATHOLOGY

pathology news

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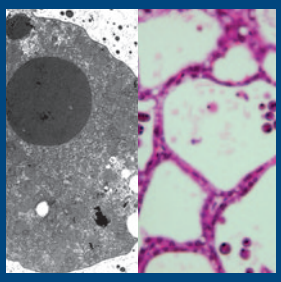
INSIDE:



THE MOTHER AND HER BABY:
A BALANCING ACT WITH RISKS AND BENEFITS

To find out more about the Pathology Department visit our website www.path.cam.ac.uk

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Welcome to the 2012 edition of Pathology News. In this edition we bring you up-to-date with a number of exciting projects taking place within the Department and one member of our Alumni community fondly recalls his time in Cambridge. Thank you to everyone who provided their memories of the Department. I hope to be able to print them all over the next few editions.

All the best
Nicola Graves
Development Officer

Note: If you would prefer not to be contacted by us in the future, please let us know and we will remove you from our mailing list.

The mother and her baby:
A balancing act with risks and benefits

Professor Ashley Moffett is a Professor of Reproductive Immunology based in the Department of Pathology, and Director of Medical Sciences at King's College, Cambridge.

Her work on the immunology of pregnancy, in collaboration with Professor Charlie Loke and the Wellcome Trust, has led to a greater understanding of the mechanism underlying recurrent miscarriage, fetal growth restriction and pre-eclampsia.

The work has far reaching consequences, not just in the UK but particularly for low income areas such as the South Sahara and Africa where pre-eclampsia is responsible for 25% of maternal deaths.

Key facts: Pre-eclampsia

- Pre-eclampsia is one of the 5 major causes of maternal death worldwide and occurs mainly in first pregnancies
- A first pregnancy is protective but subsequent pregnancies may be at risk of pre-eclampsia when with a different father or when there is a long gap in between pregnancies
- There has been found to be a high incidence of pre-eclampsia after oocyte donation
- Certain fathers are known to carry 'pre-eclampsia risk'
- Pre-eclampsia only affects humans

Placentation holds the key

Professor Moffett explains 'I felt it important to approach this topic as a clinician rather than an immunologist. In doing so, it quickly became clear that the key area of interest is the point at which the placenta implants into the uterus. Defining this boundary between two individuals requires a delicate balancing act. Invasion of placental cell needs to go far enough but not too far'.

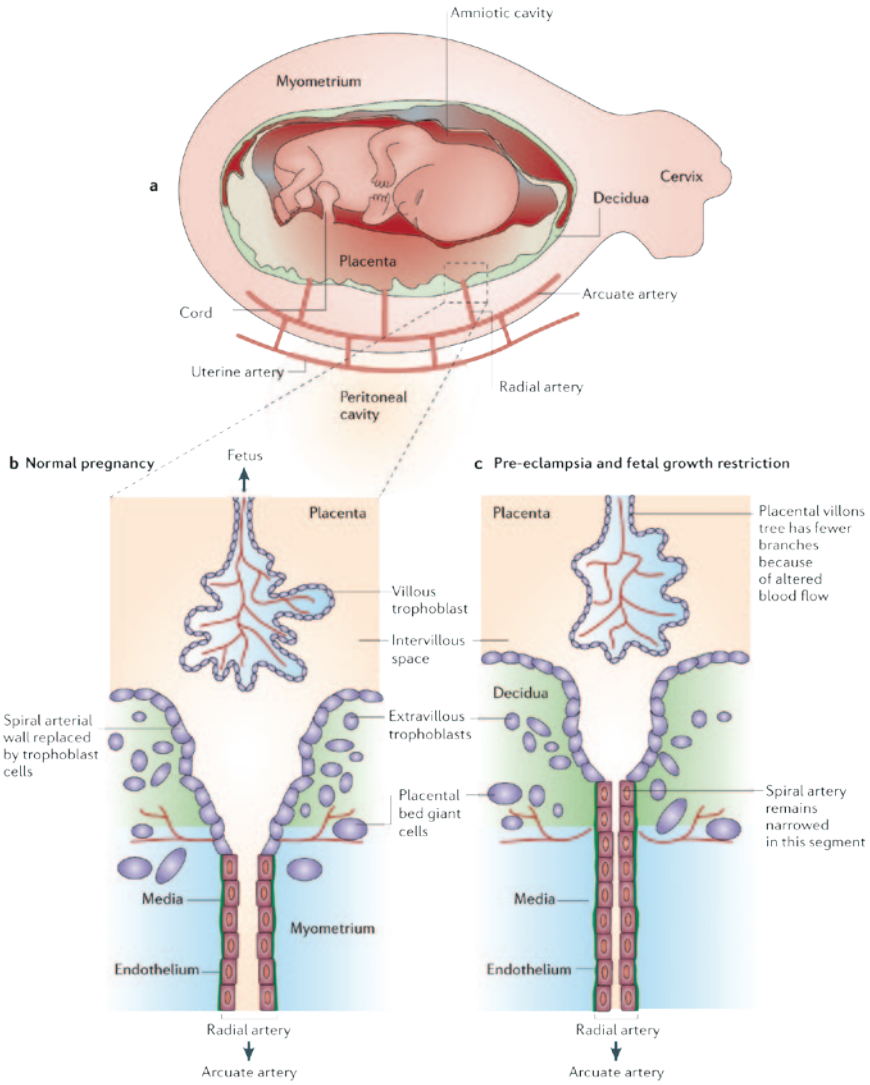
Cover photo: A 14-year old mother and her 30-minute old baby in the Mulago Hospital, Uganda. Photograph taken by Professor Ashley Moffett during her research trip in 2010

Professor Moffett goes on to say 'We are interested in the fact that the maternal uterine immune system is crucial in regulating the process of placentation. Specifically, we need to know how the dominant population of uterine leukocytes, Natural Killer cells, recognise MHC Class I ligands on fetal trophoblast cells and how this might result in altered trophoblast function'.

More recently, Professor Moffett's research has focused on two trophoblast MHC Class I ligands, HLA-G and HLA-C. There is increasing evidence that a major function of the NK receptors that bind HLA-C (known as KIR) are pivotal in determining how far trophoblast penetrates into the uterus.

This trophoblast invasion is essential to tap into the maternal supply line. Professor Moffett's laboratory has been able to show that one particular maternal KIR and fetal HLA-C are associated with recurrent miscarriage, fetal growth restriction and pre-eclampsia. The impact of the immunological maternal-fetal interaction on low birth weight has far reaching consequences including on adult health.

For more information on Professor Moffett's work, please see www.path.cam.ac.uk/research/investigators/



Deregulation of SGK1 in the endometrium causes reproductive failure

A collaboration between Dr Andrew Sharkey of the Department of Pathology at Cambridge University and Professor Jan Brosens at Imperial College has resulted in a breakthrough in the understanding of human infertility.

After fertilization, the embryo develops to the blastocyst stage and hatches from the protective zona. It must then attach to the endometrium, which lines the womb, to access the maternal blood supply, and begin development of the placenta. Even in fertile women up to 70% of embryos fail to attach and in many women with infertility, it is this stage which fails. Part of the problem appears to be in the endometrium itself. This is normally refractory to embryo attachment. Following ovulation, rising levels of the hormone progesterone render the endometrium transiently receptive to embryo implantation. This 'window of implantation' lasts for only 5 days and allows the blastocyst to adhere to the luminal epithelium lining the endometrium.

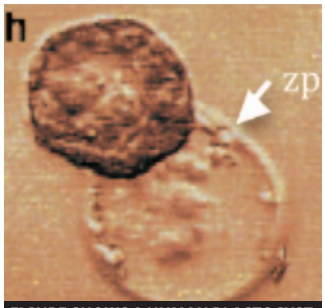


FIGURE SHOWS A HUMAN BLASTOCYST (H) NOW READY TO ATTACH TO THE LUMINAL EPITHELIUM, AFTER HATCHING FROM THE EGGSHELL-LIKE ZONA (ZP). (COURTESY OF PETER BRAUDE AND MARTIN JOHNSON, PUBLISHED IN ESSENTIAL REPRODUCTION).

The project looked at whether in some infertile women, the endometrium never becomes receptive. The collaboration compared gene expression in endometrium taken during the 'receptive phase' from women with unexplained infertility with fertile controls. They have shown that expression of a gene called SGK1 was increased in the luminal epithelium of infertile women (Feroze-Zaidi et al 2007). This suggested that increased SGK1 in these cells somehow prevents embryo attachment. In the new study in Nature Medicine, the team artificially increased SGK1 expression in the luminal epithelium of the endometrium in the mouse, by transfection with an SGK1 expression vector. This resulted in failed implantation by altering expression of genes, which permit embryo attachment.

The study also identified a second role for SGK1 during implantation. After embryo attachment, endometrial stromal cells differentiate in a process known as decidualization, which is essential for successful placental development. In mice lacking SGK1, initial attachment was unhindered, but stromal decidualization was grossly impaired, with subsequent loss of the pregnancy. SGK1 deficiency was also found in decidualizing stromal cells from human subjects with recurrent pregnancy loss. Thus, increased SGK1 activity in the luminal epithelium of endometrium interferes with embryo attachment, leading to infertility, whereas decreased levels in decidualizing stromal cells predispose a woman to miscarriage by rendering the feto-maternal interface vulnerable to oxidative damage.

This research has exciting translational potential because inhibition of SGK1 levels in the endometrium, prior to embryo transfer may benefit those infertile women in whom SGK1 remains too high during the implantation period. Conversely, increasing SGK1 levels transiently in the endometrium might be used as a new method of contraception. Work is underway to identify which patients with infertility might benefit from this approach because they show altered SGK1 expression.

For more information, please see: http://www.path.cam.ac.uk/news/2011110901.html

Welcome Professor Geoffrey L Smith, FRS

Following the retirement of Professor Andrew H Wyllie in September 2011, the Department of Pathology has a new Head of Department. Professor Geoffrey L Smith has returned to this department, where he worked in 1985-9. Professor Smith joins us from Imperial College London where he was Professor of Virology and a Wellcome Trust Principal Research Fellow. Professsor Smith will remain a Wellcome Trust Principal Research Fellow while also being Head of Department here.

Professor Smith graduated in Biochemistry and Microbiology from the University of Leeds in 1977 and obtained his PhD in 1981 at the National Institute for Medical Research, Mill Hill, London. As a postdoctoral fellow at the National Institutes of Health, USA (1981-84) he developed vaccinia virus as an expression vector and pioneered the use of genetically engineered viruses as live vaccines.

On his return to the UK he continued working with poxviruses, first in the Department of Pathology in Cambridge (1985-89), then in the Sir William Dunn School of Pathology, Oxford (1989-2000) and more recently at Imperial College London (2000-2011). His research group studies the interactions of poxviruses (particularly vaccinia virus) with the host cell and immune system.

Professor Smith is a Fellow of the Royal Society, the Academy of Medical Sciences, and the Institute of Biology. He is President of the International Union of Microbiological Societies, Chairman of the WHO Advisory Committee for Variola Virus (smallpox) Research, Chairman of the Royal Society Committee for Scientific Aspects of International Security, a Governor of the Lister Institute of Preventive Medicine and a member of the Royal Society Science Policy Advisory Group.

In 2005 he was awarded the Feldberg Foundation Prize in Medical and Biological Science. In 2009 he was elected a Founding Member of the European Academy of Microbiology and this year was elected a member of the German National Academy of Sciences, Leopoldina.

We are delighted to have Professor Smith on board.

RECENT AWARDS

MRC BACK MAMMARY GLAND CELL DEATH RESEARCH

An MRC programme grant has been awarded to Professor Christine Watson to investigate lysosome-mediated programmed cell death in mammary glands.

MRC FUND VITAL HERPES PROJECT

Dr Stacey Efstathiou has been awarded an MRC research grant to perform analyses of the herpes simplex virus latency and reactivation at the single cell level.

LEUKAEMIA & LYMPHOMA RESEARCH BOOST

Leukaemia and Lymphoma Research has awarded Dr Suzanne Turner a research grant to explore the characterisation of the existence and origins of lymphoma stem cells using a murine transplant model.

INDUSTRIAL BACKING FOR CANCER RESEARCH

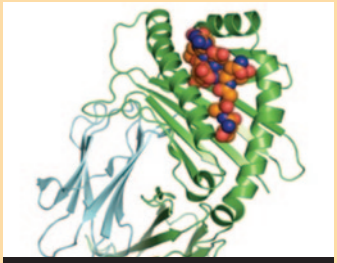
Dr Peter Goon has been awarded a research grant by Leo Pharma for investigation of the small molecule on HPV+ cancer cell lines and primary keratinocytes in vitro.

Perfect partnership

The Department of Pathology is delighted to be part of the Amazon Associates Program. Every time you make a purchase at Amazon.co.uk by accessing the site from the Campod website (www.campod.path.cam.ac.uk), Amazon will donate up to 10% of your total purchase to Campod, at no extra cost to you. This applies to all items, not just books.

NEWS IN BRIEF

10,000th STRUCTURE CURATED BY THE PROTEIN DATA BANK IN EUROPE



2YF6 MHC IS IN GREEN, MICROGLOBULIN IN BLUE, PEPTIDE BOUND TO MHC IN SPACEFILL, COLOURED BY ATOM

The Protein Data Bank in Europe (PDBe) has annotated its 10,000th structure for inclusion in the Protein Data Bank (PDB), a freely available resource for life science researchers.

The 10,000th entry, 2yf6, is of a Major Histocompatibility Complex (MHC)-peptide complex and was determined in the lab of Professor Susan Lea at the University of Oxford. The protein was generated in a collaboration with Professor Jim Kaufman's group at the University of Cambridge. This structure is helping to clarify how the immune system recognises an infected cell. The structure is of a chicken MHC from the B21 haplotype, which confers resistance to Marek's disease, a contagious disease that can wipe out entire flocks. MHC proteins are present in all cells. Their job is to continually sample the internal protein environment and display short fragments of these proteins - peptides - on the cell's surface. Passing T-cells determine whether these peptides are 'self' or foreign, and hopefully destroy the right ones.

Acknowledgment: Gerard Kleywegt, Head of PDBe

CAMBRIDGESHIRE BOOST FOR PIONEERING PROJECT TO IMPROVE GENETIC TESTING FOR CANCER PATIENTS

Professor Peter Collins, Department of Pathology and a lead researcher at the Cambridge Experimental Cancer Medicine Centre Network (ECMC) based at the University of Cambridge, is involved in an exciting initiative to establish a world-class NHS genetic testing service for cancer patients in the UK. Cancer Research UK's Stratified Medicine Programme means that as and when new targeted treatments become available, doctors will have access to the tests they need to help them decide which drugs are best for their patients.

Medical staff from Cancer Research UK's Cambridge Experimental Cancer Medicine Centre (ECMC), and six of the charity's other ECMCs, will ask up to 9,000 patients to participate in the first phase of the programme.

Patients suffering from breast, bowel, lung, prostate, ovary and melanoma skin cancer will be asked to give consent for a small sample of their tumour. This will be sent to one of three leading NHS genetic testing labs where DNA will be extracted and analysed.

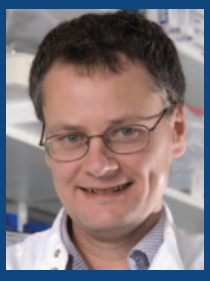
Find out more about the ECMC at www.ecmcnetwork.org.uk

MICHAEL REIDY OUTSIDE TENNIS COURT ROAD, MAY 1976

Michael Reidy, now Professor of Pathology at the University of Washington, recounts his memories of his time at Cambridge from 1972-1976.

"I arrived in Cambridge in 1972 as a potential research student with a B.Sc from a London University but an M.Sc from a Canadian University that was not really recognized, therefore I was employed as a "research person" for my first year in the Department. After a year my mentor, Dr David Bowyer proposed I become a research student and work for my Ph.D in the Department. This was a major event in my life. I was allowed to

Research Matters: Common gene fault triggers a ripple of molecular signals leading to more aggressive cervical cancer



Scientists have discovered that a common gene fault in cervical cancer cells triggers a ripple of molecular signals - which makes the disease more aggressive, according to research published in The Journal of Pathology.

The scientists at Cambridge University increased and decreased the activity levels of a gene called Drosha in cervical cancer cells. Drosha is located on chromosome five which is overabundant in the majority of advanced cervical cancer tumours. Scientists believe the genes on chromosome five are linked to the development of the disease, but they do not yet understand how.

Cells require Drosha to make tiny cell signalling molecules called micro-RNAs, which control the activity of hundreds of genes vital to life.

The team discovered that when Drosha is present in greater quantities in cervical cancer cells there is a change in the production levels of micro-RNAs. These changes can have the knock-on effect of triggering unusual behaviour in hundreds of important cell signalling genes. The end result of having too much Drosha is that the cancer cells become more aggressive.

This suggests that Drosha and related genes could be important targets for the development of future drugs to treat cervical cancer.

Professor Nicholas Coleman of the Department of Pathology, Cambridge, said: "This important research shows that one gene can create a ripple effect to send behaviour-changing messages to hundreds of additional genes - leading to more aggressive cervical cancer.

"We're now going to research whether new treatments for cervical cancer should target this gene, Drosha, itself, or some of the key micro-RNA signalling molecules it affects.

"It'll also be important to discover whether Drosha, or genes that co-operate with it, change levels of microRNAs in additional cancer types - not just cervical cancer."

Dr Lesley Walker, director of cancer information at Cancer Research UK, said: "Back in the 1970s, fewer than half of the women with cervical cancer survived for more than 10 years. Today, around two thirds survive - but there is more to be done.

"We're investing in new ways to prevent and treat the disease - for example we funded pioneering studies behind the development of the cervical cancer vaccine that is now available for girls and young women in the UK.

"And this latest study, which reveals how gene faults can make the disease progress, opens up new avenues of research to find ways to treat cervical cancer which may one day increase survival from the disease."

For more information on Professor Coleman's work, please see: http://www.path.cam.ac.uk/research/investigators/coleman/research.html

Our History: Memories of Cambridge

formulate a thesis proposal and with a great deal of support from Dr Bowyer I eventually achieved a Ph.D. I have a great deal to thank Dr Bowyer for. I thought of Professor Greaves, the Head of Department, as a demi-God. He was generous to me and significantly instrumental in allowing me to become a research student and earn a Ph.D.

One of my fondest memories is of the Department library. There was the main room with an adjacent room with large tables. This room was hardly visited by medical students or anyone else for that matter. So I subverted a large table as my personal office to write my thesis. I am sure current students will laugh but I wrote my thesis on the back of used computer mainframe printouts. I spent over 3 months in the library writing day and night and by the end I had a large stack of hand written sheets which I left totally unprotected in the library. It never crossed my mind that anything could happen to my work but in June 1976 I received a major shock when I heard of a major fire at the Downing site and rode to the Department with great apprehension to check on my thesis. To my relief it was Chemistry that was burning but I did hear of a research student who had lost all 3 years of data.

The rumour by research students was that the longer the external examiner had spent on the train to Cambridge then the more difficult one's exam could be. The belief was that the examiner only read the thesis while travelling to Cambridge. Indeed one of my fellow students had an external examiner from Aberdeen and it took him at least another 12 months before his thesis was accepted. To my relief my external was from Oxford and after about 60 minutes the exam was ended. I then had to wait in the library while they deliberated my fate. After about 20 minutes I was called back, offered a glass of sherry, and told I had passed with a few corrections. To correct the text, however, was not simple. This meant the bound thesis had to be broken open and the corrections inserted. This involved retyping many pages, having it rebound and then re-submitting to the examiners. I hope that current research students have an easier time. Another financial concern was that the thesis included multiple electron micrographs and figures. This meant many hours in the Department dark room printing up to 40 prints for each of my 5 thesis copies. If I knew that in the future images could be so easily managed by modern software, I might have waited 30 years before completing my thesis.

I thoroughly enjoyed my time in the Department and express my best wishes to the current research students.

If any past members of the Department remember me, I would be delighted to have you contact me."

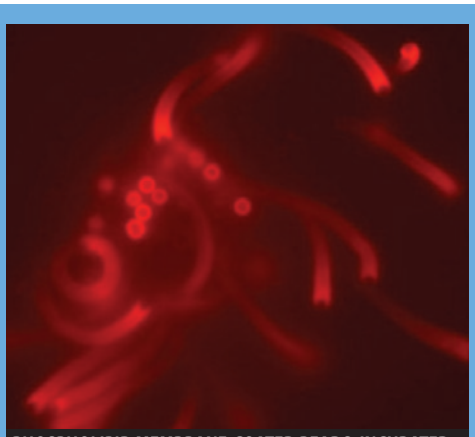
Please contact Nicola Graves on 01223 330291 or email campod@path.cam.ac.uk

Key to combating bacterial disease

Animal and plant cells contain a dynamic network of actin filaments, which are assembled and disassembled to drive fundamental processes such as cell migration, phagocytosis, synapse plasticity and tissue repair, and also pathologies like tumour and pathogen invasion. Prof Vassilis Koronakis and colleagues study how pathogenic bacteria exploit this actin cytoskeleton to establish infection. The newest findings from the Koronakis lab emphasise how such research is not only key to understanding and countering bacterial disease, but also in uncovering new aspects of mammalian cell biology.

Recently Prof Koronakis successfully developed a new technique for studying the actin cytoskeleton. He introduced silica beads coated with phospholipid membrane bilayers into a mammalian brain cell extract, such that the beads recruit the cellular machinery that triggers assembly of actin filaments, and generates actin 'comet tails' that propel the beads energetically through the extract (see Figure). Prof Koronakis and his colleagues Drs Peter Hume and Daniel Humphreys have used this innovative assay to study the pathways controlling actin assembly, focusing in particular on the cellular WAVE complex, a critical regulator of actin filament production. They have discovered that membrane recruitment and activation of the WAVE complex requires the cooperative action of two mammalian GTPases, Arf and Rac. Arf directly recruits WAVE to membranes and is required to activate WAVE, while Rac is dispensable for recruitment, but necessary for Arf-dependent actin assembly. This previously unknown dual control and synergy represents a new level of complexity in the mechanisms the cell uses to control the actin cytoskeleton. It also has profound implications for understanding normal and pathogenic actin-dependent cellular processes.

Current work by the group, together with its graduate students Anthony Davidson and Qi Hui Sam, is delving further into this key mammalian phenomenon, and is showing that Salmonella, the infamous intestinal pathogen that infects humans and animals, exploits this newly discovered mechanism in taking control of the cytoskeleton to invade host cells.



PHOSPHOLIPID MEMBRANE-COATED BEADS, INCUBATED IN A BRAIN CELL EXTRACT, ASSEMBLE ACTIN 'COMET TAILS' (RED) WHICH PROPEL THE BEADS THROUGH THE EXTRACT

● *For more information on Professor Koronakis' work, please see www.path.cam.ac.uk/research/investigators/*

WAVE regulatory complex activation by cooperating GTPases Arf and Rac1.
Koronakis V, Hume PJ, Humphreys D, Liu T, Hørning O, Jensen ON, McGhie EJ.
Proc Natl Acad Sci U S A. 2011 Aug 30;108(35):14449-54.

The *Salmonella effector* SptP dephosphorylates host AAA+ ATPase VCP to promote development of its intracellular replicative niche.
Humphreys D, Hume, PJ and Koronakis, V
Cell Host Microbe, 2009; 5:225-33.

Featured Academic: Golden Moments in

Interview by Nicola Graves

Professor Andrew H Wyllie, FRS, FMedSci, FRCPath, led the Department of Pathology at Cambridge University for 13 years. Nicola Graves caught up with him just before his retirement in September 2011 to find out more about the man who changed the face of cancer research and his eminent career.

Did you always know that you wanted to be a professor of Pathology?

Manifestly, no. I did know that I wanted to do something in Biology. Around the time that I needed to start making choices at school, I remember visiting the Physiology Department of the local university and getting very switched on by the fact that you could analyse living things in a quantitative way. Subsequently I met some very charismatic people, one in particular became a role model for me. He happened to be a Professor of Pathology. So pathology was the subject, the professorship was not in the vision at the time.

You have had an incredibly successful and illustrious career. What has been your proudest moment?

Proud means different things to different people. To me, it's a few golden moments in research. Some have many, I have only a few. One was when I first saw cells that should have been dying because they had been exposed to x-rays, looking completely normal, because they lacked the tumour suppressor called P53. Absence of just that one gene meant these cells had lost the ability to switch on their death programme following serious DNA damage. I could identify for you the place and the time. It was in the lab in Edinburgh and around 2am.

How does it feel to have personally made such an enormous impact on cancer research throughout the world?

People were looking at cell death before it got called Apoptosis so it's a bit difficult to know what one is taking credit for, new discovery is very exciting. Very few people, I think, have the privilege of seeing a subject emerge from almost total darkness into a tremendous vogue subject. It's tailing off a bit now. Science moves on and things that seem very simple become more complex and then become modified and the story that one thought was very simple and captivating turns out to be not quite as straightforward but that's always the case. You expect that. It's lovely to have been involved in a subject over its early history. There's no question, it's a delightful feeling. It's exciting to see also a whole tranche of very bright scientists moving into a field to take it further.

You have been Head of the Department of Pathology at Cambridge University for 13 years. What changes have you seen over this time?

I think that the requirements to run a research career are more stringent and more difficult now than they used to be. I think the Department has risen to that challenge. When I came (and I had an illustrious predecessor), the research income to the Department was about £5m a year and now it's between £9-£10m a year and that's not all just inflation! I think the managerial aspects of the post have also changed. The amount of administration has increased along with administration in almost every other academic subject. Again, I think we have higher expectations of the people who underpin that administration, whether it's at School level or in the Department.

NEWS IN BRIEF

Dr Barry Kingston has been awarded a Pilkington Teaching Prize for consistently achieving the highest student appreciation scores. Dr Kingston and the other 11 prizewinners received their awards from the Vice-Chancellor during a reception at Homerton College.

The Pilkington Teaching Prizes were established in 1994 by businessman and alumnus of Trinity College, Sir Alastair Pilkington. The aim was to ensure that excellence in teaching at the University was given proper recognition.

In memory of Elizabeth Mann

An article appeared in the 2011 edition of Pathology News in recognition of a Cambridge lady whom we knew very little about but whose generous bequest in 1993 enabled Campod, the Department of Pathology's charity, to support researchers to an extent it had not been able to previously. The Department would like to extend its thanks to the friends and former colleagues of Elizabeth Mann who got in touch to tell us more about the lady who has helped the Department support ground-breaking research into chronic diseases since 1993…

Elizabeth Mann was Cambridge born and bred. Her father, Frederick George Mann, FRS, was a fellow of Trinity College and was appointed to a university lectureship there in the natural sciences in 1930. Elizabeth was born on 29th July 1954.

She attended Girton College and worked throughout her life at Trinity College Library as a Library Assistant, shelving books and periodicals and was in charge of the Law Library. Elizabeth has been acknowledged in a number of books for the support she gave to researching authors. She enjoyed watching sport at the University, particularly rowing, and scored at women's cricket matches. Elizabeth died of lupus at the age of 38 on 28th February 1993 after a long and painful illness and left her legacy in memory of the love she had for Cambridge University.

If you would like to leave a legacy to Campod in your will, please contact Nicola Graves on 01223 330291 or email campod@path.cam.ac.uk

Research

You have made a number of changes to the Department yourself. Which one do you think has had the greatest impact?

The first thing to note about this Department is that it's full of highly motivated people and I think the role of the Head of Department is to represent the Department in places where that's important and have a care for the individuals in the Department as far as one can. In terms of initiating something, everyone wants to feel they've made a mark and hopefully benefited something that they've touched. I think the issue that has certainly been most interesting and is most likely to have long-term repercussions are the appointments that we've made during that time. I have made around 13 senior academic appointments in 13 years. 6 were to personal chair posts or won chairs shortly afterwards. They were people coming in with new ideas – clout. If you were to ask me which has been the most influential of these appointments, it's almost impossible to say because all of us are doing things that affect people. One of the things that was not in place at all before any of these came, and is now part of our strength on the Addenbrookes site, was the development of Molecular Pathology with a diagnostic, cutting edge to it. But several very interesting people have all brought something distinctive to the Department. In answer to the question 'what has made the greatest impact?' I would have to say people. The Department is, by its very nature, its people.

Do you have a message for your successor, Professor Geoffrey Smith?

Well, I don't think he needs it but there is a message. The Department of Pathology in Cambridge is, I think, unique in the country even if you include in comparison the Dunn School of Pathology at Oxford. It is a high powered, intellectually rich academic environment with a diagnostic commitment, a lot of undergraduate teaching and a huge breadth of subjects, from diseases of Sub-Saharan Africa to molecular studies in fine detail in cancer, immunology and infection. So its great strength is its breadth and to hold all of that together would have to be a priority. I think Geoffrey knows well what he is coming to and is well able for it. I am thrilled with the appointment. He's a very enthusiastic and talented individual and I wish him the very best.

Research Matters: Exciting breakthrough in cancer treatment

A project within the Department of Pathology, Cambridge, has led to a breakthrough in the understanding of cancer cells in the breast.

The work was carried out primarily by two PhD students in Christine Watson's lab; the first author Peter Kreuzaler was previously funded by a Department of Pathology PhD studentship and is now funded by a Trinity College Fellowship and Anna D. Staniszewska, a current graduate student funded by the Breast Cancer Campaign.

As Prof Watson explains, billions of cells in our body die every day. Damaged, infected or superfluous cells are thus disposed of to keep our bodies healthy. It is thought that most of these cells die by a process called apoptosis. We have shown that cells in the breast, following lactation, do not die by apoptosis but by a novel mechanism that requires organelles called lysosomes. These tend to be thought of as cellular waste bins since they digest cellular components and recycle them. However, we have discovered that during regression of the breast, enzymes called cathepsins leak out of the lysosomes into the cell and induce a process that we call lysosomal-mediated programmed cell death (LM-PCD). This is the first time that this type of cell death has been shown to occur in a normal mammalian organism. Furthermore, we have shown that a transcription factor, Stat3, that is often associated with breast cancer, is responsible for executing LM-PCD as it induces high levels of cathepsins while suppressing expression of a naturally occurring cathepsin inhibitor, a protein called Spi2a. Since a common feature of all cancers is their ability to evade cell death, our work will be of major importance in the design of treatments for cancers by targeting this new death mechanism.

Our findings have led us to establish a multi-step model for the execution of LM-PCD during involution. We hypothesise that in late lactation cells become sensitized to cell death insults. When breast feeding is stopped, leakiness is induced. This however is not enough to induce cell death and the action of Stat3, which upregulates the cathepsins while downregulating a potent cathepsin inhibitor (Spi2a), is needed to execute cell death.

For more information, please see: www.path.cam.ac.uk/research/investigators/

Recent publications by Department of Pathology staff

Affara NA, Ellis PJ, Bacon J
Association of Sly with sex-linked gene amplification during mouse evolution: A side effect of genomic conflict in spermatids?
Human Molecular Genetics 20(15): 3010-3021

Arends MJ and others
Disruption of mouse Slx4, a regulator of structure-specific nucleases, phoncopies Fanconi anemia.
Nature Genetics 43(2): 147-152

Cooke A, Zaccone P
Infectious triggers protect from autoimmunity.
Seminars in Immunology 23(2): 122-129

Du Ming-Qing, Appert A, Hamoudi RA and others
Cleavage of NIK by the AP12-MALT1 fusion oncoprotein leads to noncanonical NF-κB activation.
Science 331(6016): 468-472

Edwards PAW, Howarth K and others
Large duplications at reciprocal translocation breakpoints that might be the counterpoint of large deletions and could arise from stalled replication bubbles.
Genome Research 21(4): 525-534

Field Mark C and others
Evolution: On a bender-BARs, ESCRTs, COPs and finally getting your coat.
Journal of Cell Biology 193(6): 963-972

Field Mark C and other
Evolutionary reconstruction of the retromer complex and its functions in Trypanosome brucei.
Journal of Cell Science 724(9): 1496-1509

Koronakis, V, Hume P and others
WAVE regulatory complex activation by co-operating GTpases Arf and Rac1.
Proceedings of the National Academy of Sciences USA 108(35): 14449-14454

Kouzarides T, Bannister AJ
Regulation of chromatin by histone modifications.
Cell Research 21(3): 381-395

Watson, Christine J and others
Stat3 controls lysosomal-mediated cell death in vivo.
Nature Cell Biology 13(3): 303-309

A full list of publications is available on the Pathology Department's website: www.path.cam.ac.uk

Our apologies…

In the 2011 edition of Pathology News it was stated that Professor R.I.N Greaves passed away on 29th August 1975. Pathology News would like to apologise for this error. Professor Greaves taught in the Department until 1975 but died on 29th August 1990. Our thanks to all who got in touch regarding this inaccuracy.

Help us fight chronic diseases

Current Fundraising Goals

At the Department of Pathology work is underway to find cures and treatments for a spectrum of life-limiting diseases. Research grants usually only cover modest researcher salaries and rarely extend to the vital equipment that is needed. Please consider making a contribution, however small, to one of the items we currently need.

WE ARE CURRENTLY WORKING HARD TO RAISE FUNDS FOR:

- **Next Generation Sequencing Equipment (Cost £80,000)**
  Help our researchers to identify important genes and sequences leading to disease, particularly cancer, diseases of the immune system and infectious and reproductive diseases.
- **A FlowCytometer (Cost £400,000)**
  Help the Department continue its ground-breaking work to identify and understand cell behaviour, enabling us to combat diseases such as cancer and malaria.
- **A Mass-Spec Set-up (Cost £150,000)**
  Support our researchers by helping purchase a Mass-Spec set-up. This will allow them to identify protein complexes and unveil how bacteria invade our cells and cause disease, and to develop new antibiotics to conquer multi-drug resistant bacterial diseases.
- **A Centrifuge System (£50,000)**
  Support our researchers by helping purchase a high-speed centrifuge essential in the purification of viruses and their complexes, enabling us to conquer diseases caused by influenza, herpesviruses, noroviruses and HIV.

All contributions, whatever the size, are greatly appreciated and will help us reach our targets.

Campod

CAMBRIDGE FUND FOR THE PREVENTION OF DISEASE

A charity directly supporting research in the Department of Pathology

HOW YOU CAN HELP:

- **Make a donation** by completing and returning the slip below with a cheque made out to 'University of Cambridge', or by visiting www.path.cam.ac.uk/campod
  We are grateful for gifts of all sizes
- Remember us in your will.
  Contact Nicola Graves on 01223 330291 to discuss leaving a legacy to Campod
- Join our Alumni list by emailing campod@path.cam.ac.uk
- Contribute to one of our current fundraising goals

For more information about Campod visit www.campod.path.cam.ac.uk

We are currently tackling…

- Cancer of the breast, brain, bowel, cervix, oesophagus
- Lymphoma
- Auto-immune diseases
- Diabetes
- HPV
- Multiple Sclerosis
- Herpes
- Neurodegenerative diseases
- Pre-eclampsia
- Influenza
- Miscarriage

I WOULD LIKE TO SUPPORT CAMPOD

I would like to donate ☐ £25 ☐ other £ _____ *We are grateful for gifts of all sizes.*
to Campod (Cambridge Fund for the Prevention of Disease) *Please make cheques payable to 'University of Cambridge'.*

☐ I would like further information about supporting the Department of Pathology

☐ I am a UK tax payer and would like Gift Aid to be collected on this and any future gifts to Campod.

Return to: Campod, Department of Pathology, Tennis Court Road, Cambridge CB2 1QP, UK

Title: Forename: Surname:

Address:

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