

The background of the cover is a dynamic, abstract graphic composed of numerous thin, overlapping lines in shades of orange, red, and yellow. These lines flow and curve across the page, creating a sense of movement and depth. The lines are set against a light gray background, which is divided into three horizontal bands: a top gray band, a central white band containing the text, and a bottom gray band.

Surgical Research Report 2011

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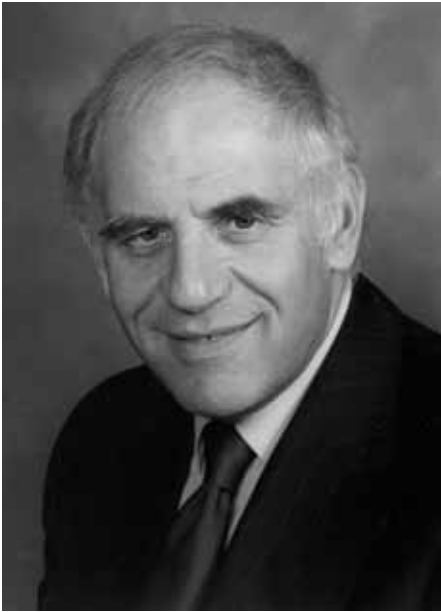
Surgical Research Report 2011

Investing in research
to improve patient welfare



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Chairman's introduction



Professor Norman Williams
Chairman, Academic and Research Board

Research remains one of the cornerstones of the College's activities and, as can be seen from this report, it continues to thrive. Research is vital for the health of the surgical profession and, with this in mind, the College Council has decided to conduct a major fundraising drive over the next few years to boost its research endeavours. This, together with a change in national policy towards translational research, at which surgeons excel, should provide significant opportunities for all who wish to move the barriers forward in advancing surgical standards.

It is quite clear from the numerous applications for our research fellowship scheme that there are many exciting ideas that need to be explored by able trainees with enthusiasm and aptitude. It is always of concern that we can fund only one in five applications. However, through our fundraising drive over the next few years we aim to be able to expand the number of fellowships awarded.

As everyone acknowledges, the fellowship scheme has been a great success. This has only been possible because of the legacies and donations from charitable trusts, individuals and companies who have recognised its importance in improving patient care. The reports in this publication from our research fellows attest to the high quality to which we aspire. However, one must never rest on one's laurels and we are in the process of reviewing the scheme to determine the impact it has made to

healthcare and fellows' careers over the last decade. Any lessons learnt will be acted upon so that the scheme can be strengthened.

Beyond increasing the opportunities for fellowships, it was felt that a research strategy needed to be developed that encompassed other facets of the College's and the profession's research activities. Several workshops were held to hammer out an agreed policy. The individuals taking part included not just leading surgical academics but also trainees and NHS consultants active in research and training, as well as members of the College research board. All the main specialties were represented and we are grateful to all who contributed. As you might imagine, debate was sometimes impassioned and robust but fortunately a consensus was achieved relatively easily. The strategy document was put before College Council in December 2010 and was approved unanimously. The underlying concept is to establish an institute of surgical research, based at the College, with the specific aims of fostering excellence in the subject. The institute will:

- a. develop a module (in collaboration with universities) on research methodology for all trainees, based on a credit system, which can be converted to an MSc
- b. provide external support and advice to those pursuing higher degrees
- c. develop a mentorship/supervisor course for new consultants/senior lecturers

- d. initiate and assist the development of appropriate national research networks in the surgical specialties, in collaboration with the National Institute for Health Research and other bodies
- e. work with the specialty associations, societies and university academic departments to help coordinate their efforts
- f. set a specific remit to enhance the research fellowship scheme and direct it at three groups:
 - i. junior surgical trainees who have the ability to pursue a research theme as part of a multidisciplinary and established research group
 - ii. post-doctoral researchers at the end of their clinical training who wish to pursue a more academic career
 - iii. clinician scientists, provided in partnership with other funding bodies, eg Medical Research Council and Cancer Research UK, for those individuals who have successfully completed an academic clinical fellow post and wish to ascend the academic ladder
- g. develop a strategy for coordinating research across different disciplines both within and outside the College.

This is clearly an ambitious agenda in improving surgical research within the UK and will not be achieved overnight. However, in order to accelerate matters,

the College is recruiting a Director of Research for the new institute who will work with the secretary to implement the policy.

As can be seen, there is a desire to build networks in surgery that can deliver large, meaningful trials and assessments of surgical techniques and management protocols. Such networks are essential if the important questions are to be answered speedily and efficiently. Appropriate organisation and infrastructure are crucial if safe development and dissemination of innovative procedures are to be achieved. Surgical techniques are not drugs and need to be assessed in a different way and be taught appropriately.

We have already begun this network development with the establishment of trainee research networks in the West Midlands, London and Southampton, and thousands of patients are now being entered into trials. At present, relatively simple questions are being asked but as these networks evolve more demanding studies will be performed. The trainees' enthusiasm has been inspiring and I am sure that many of those individuals involved will continue these activities into consultant practice. It is this type of activity that will provide the evidence base for surgical therapy that will be so essential for the development of surgical practice in the future.

I would like to thank members of the College Research Board for their tremendous support over the last twelve

months. They have given their time and expertise most generously and without their hard work the research activities of the College could not continue. Likewise, I pay tribute to Martyn Coomer and his team for the excellence of the administration of the department. They are highly dedicated individuals with tremendous enthusiasm for all they do.

Finally, and most importantly, I would like to thank all the generous supporters who have funded the surgical research fellowship scheme. Donations and legacies have enabled the College to support surgical research projects throughout the country, which have shown real benefits and improvements in patient care. Without these gifts none of the projects in this report could have been funded. We need that support to continue to help improve care and safety for patients.

I hope you enjoy reading this report and will be impressed by the breadth of ideas being pursued and the standard of the science being executed. Surgery never stands still and the activities reported here are a testament to this.

Norman Williams

Gallery

From left to right: Research fellows Amir Malkawi and Eddie Choke at a Society of Academic and Research Surgery meeting in Dublin, January 2011.



Rakesh Heer and procession following his Hunterian Lecture at a Society of Academic and Research Surgery meeting in Dublin, January 2011.

Council members at a student surgical society evening in Belfast, November 2010.



Local surgeon Richard Reyes teaching at a skills workshop in Dubai, May 2010.



Martyn Coomer (second from left) and Bill Thomas (third from left) meeting the Minister of Health for Brunei (third from right), March 2011.



From left to right: Jagdeep Singh (Stefan Galeski research fellow), Becky Street and Dame Sue Street, at the Queen Elizabeth Hospital, Borneo, March 2011.

Devi Shetty hosting a College visit to Health City, Bangalore, May 2010.



Even vice-presidents have operations.... Mr Richard Collins, ably supported by Professor Vishy Mahadevan, at a roadshow, Kings Lynn, February 2011.



Knot tying with pupils from the City of London School, September 2010.



Pupils from the City of London School try their hand at laparoscopic surgery, September 2010.



On set for the research fundraising film, February 2011.



New fellows and members of the College at a Diplomates' Ceremony in Dubai, May 2010.

Norman Williams meeting academics from Imperial College London, February 2011.



Bill Thomas teaching a skills workshop at Bugando Hospital, Mwanza, Tanzania, July 2010.



Presidential roadshow and local hosts at Bradford Royal Infirmary, September 2010.



Su-Anna Boddy talking to medical students at a careers evening in Belfast, November 2010.



Akan Emin teaching surgical skills at Birchwood High School, Bishops Stortford, January 2011.



Course participants and faculty from the Borneo Basic Surgical Skills workshop, March 2011.

Professor Jonathan Shepherd (centre) chairing the Welsh Research Board in Swansea, February 2011.



Council members visiting orthopaedic colleagues at Musgrave Park Hospital, Belfast, November 2010.



Presidential visit to Merthyr Tydfil, where Dr Clive Tovey (centre), the Mayor, is also an A&E consultant, October 2010.



5

the average number
of surgical episodes
we will experience
in our lifetime

Supporting surgical research



The Royal College of Surgeons of England plays a vital role in supporting surgical research in the UK. Every year the College awards competitive research fellowship grants for specific projects that aim to advance surgical standards and improve patient care.

As a registered charity, the College relies on voluntary donations to support its surgical research programme. Donations from legacies, individuals, charitable trusts and companies have enabled over 500 research fellowships to be awarded since 1993 as well as over 90 pump-priming grants to support newly appointed consultant surgeons with their research.

Most of us will have surgery at some point in our lives and, with over four million operations carried out in England alone each year, there are few people who have not benefited in some way, either directly or indirectly, from advances made in surgical research.

Surgical research continues to provide significant advances in a wide range of areas including:

- cancer survival rates
- less invasive surgery and quicker recovery
- hip and knee replacements
- organ transplantation
- prevention of strokes
- reconstructive surgery for trauma and war-wounded victims
- skilled operations to improve hearing and sight.

Future innovations in surgery will continue to be driven by research. However, with less than 2% of national funding for medical research given to surgical projects, we need further funding so that we can support more surgical research, which will help advance surgical care for the current and future generations of patients.

For more information on supporting the College's research programme please:

- see www.rcseng.ac.uk/fundraising
- or contact the Development Office on 020 7869 6086 or email fundraising@rcseng.ac.uk



Less than
20%
of government
funding for health
research is spent on
surgical projects

Research fellows reports

The main focus of the College's surgical research programme is the surgical research fellowship scheme, which was established in 1993 to support research at centres of excellence throughout the country.

These fellowships are awarded to aspiring academic surgeons to fund projects that aim to contribute to the advancement of surgical techniques and treatment for patients. Each fellowship supports a full-time research programme lasting from one to three years, supervised in a UK department of surgery.

Competition for grants is intense and applications are rigorously assessed by an expert panel of surgeons and scientists to ensure that the science, the surgeon and the facilities are of a high standard, and that the proposed work will be a valid,

beneficial and original piece of research. Unfortunately, we are unable to support 80% of those who apply but each year we aim to award between 20–30 research fellowship grants, depending on funding available.

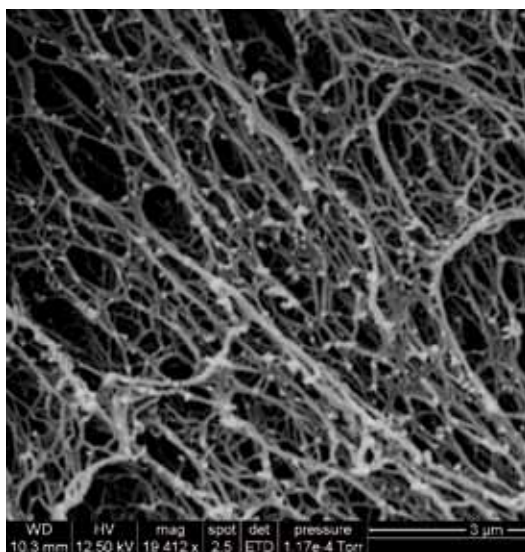
Since 1993 over £20 million has been invested in over 500 fellowships in all surgical specialties with significant results across a range of research areas. The College is very grateful to the many individuals, legacies, charitable trusts and companies who have recognised the importance of surgical research in driving forward patient care, by supporting the fellowship scheme.

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Self-assembling peptides as support for cranial nerve repair

Up to 300,000 peripheral nerve injuries happen in Europe every year and despite surgical repair disability persists for a lifetime.

Nerve injury repair remains a challenge to modern medicine. Despite advances in surgical technique, complete success in making muscles work again is still limited since regenerating nerves do not always grow back with the speed and accuracy necessary for normal function.



High resolution image of synthetic scaffolds showing fibres and pores at nanoscale level.

This study aims to create scaffoldings in the laboratory, which are envisioned to help nerves regenerate in the body and aid them to grow back to enable normal function. These novel biomaterials are made up of two short proteins, which when mixed in physiologic condition, will form long, thin and non-rigid fibres similar to the native scaffoldings in the body called extra-cellular matrix. They are made up of 99% water and 1% proteins; thus they are called hydrogels. While other hydrogels depend on animal sources for their main components, the proteins in our product are made from scratch in the laboratory by tying up the primary building blocks of proteins (the naturally occurring amino acids in humans), which in theory could overcome the problems of rejection and non-biodegradability common in implanted tissue-engineered materials. Furthermore, we decorated the hydrogels with

functional amino acid sequences that are able to direct the growth of the regenerating arms of nerve cells in three-dimensional culture. We tested these gels using human cells grown in the laboratory and have shown that they influence the growth pattern of nerve cells. With the help of neuroscientists at Bristol University, we showed that the regenerating nerve cells grown in our hydrogels were actually behaving like neurons since they were sending electrical signals to each other.

Much is still to be done before these hydrogels reach clinical application. However, we have laid the foundation of a protein-based matrix for three-dimensional cell culture studies not just for nerves but also for other tissue-engineered organs.



Edgardo trying to grow nerve cells on synthetic protein scaffolds he created in the lab similar to native extra cellular matrix.



EDGARDO ABELARDO

Fellowship/sponsor
The Dr Shapurji H Modi Memorial ENT Research Fellowship.

Supervisors
Professor Martin Birchall and Professor Dek Woolfson.

Site of work
Bristol University, Bristol.

Publications
Banwell E, Abelardo E, Adams D *et al.* Rational design and application of responsive alpha-helical peptide hydrogels. *Nat Mater* 2009; 8: 596–600.

Presentations

- *Decorating peptide-based hydrogel scaffolds for nerve-cell culture and tissue engineering.* Symposium on Biologic Scaffolds for Regenerative Medicine; April 2010; Napa Valley, USA.
- *Peptide-based hydrogel scaffolds for nerve cell culture and tissue engineering.* Bionanotechnology II: from biomolecular assembly to applications; January 2009; Cambridge, UK.

Prizes
Biotechnology and Biological Science Research Council grant, 2010.

Tissue engineering with endothelial progenitor cells



**THANASSI
ATHANASSOPOULOS**

Fellowship/sponsor

College Research Fellowship with support from the Rosetrees Trust, Thriplow Charitable Trust and Oakdale Charitable Trust.

Supervisor

Professor Suzanne Watt.

Site of work

Stem Cell Research Laboratory, National Blood Service, Oxford.

Publications

- Watt SM, Athanassopoulos A, Harris AL, Tsaknakis G. Human endothelial stem/progenitor cells, angiogenic factors and vascular repair. *J R Soc Interface* 2010; 7 (Suppl 6): S731–751.
- Zhang Y, Fisher N, Newey SE *et al*. The impact of proliferative potential of umbilical cord-derived endothelial progenitor cells and hypoxia on vascular tubule formation in vitro. *Stem Cells Dev* 2009; 18: 359–375.

Presentations

- *Tissue engineering with endothelial progenitor cells*. Australia and New Zealand Burns Association; September 2008; Melbourne, Australia.
- *Engineering microvascular networks*. International Society for Stem Cell Research; June 2008; Philadelphia, USA.

Prizes

Young Scientist Prize, British Blood Transfusion Society, 2007.

Further funding

Restore Research Trust for 2.8 years.

Burns are a serious, global health problem causing 300,000 fatalities worldwide each year and disabling or disfiguring millions of people.



Thanassi in the operating theatre inspecting a paediatric patient's hand

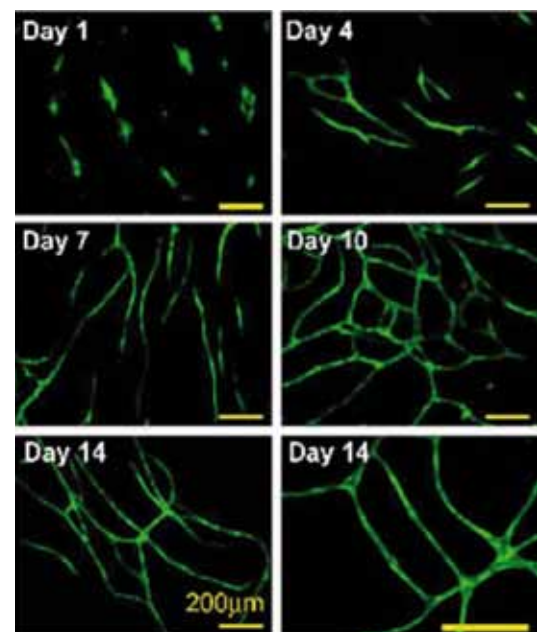
Tissue-engineered skin may provide the solution to many of the limitations associated with the use of skin grafts in patients with major burns. The incorporation of a blood supply into artificial skin substitutes is a critical step that requires a large number of functional endothelial cells. The aim of this project was to investigate various sources of stem cells, including umbilical cord blood and adult blood, for the generation of functional endothelial cells.

Although stem cells are rare in the peripheral blood, there is strong evidence that endothelial progenitors are present in the circulation although little is known about their function. Blood was cultured in the laboratory with a variety of endothelial growth factors. Over a period of eight weeks, colonies of endothelial precursors were grown from the umbilical cord and adult peripheral blood samples. The endothelial nature and stem cell origin of the cells was confirmed by flow cytometry, a technique that allows accurate determination of the expression of cells' surface markers. Vast numbers of endothelial cells suitable in quantity for tissue-engineering applications were cultured and used in subsequent experiments

These progenitor cells were able to integrate into mature capillaries, mimicking the *in vivo* process of vascular repair and furthermore, with

the correct stimulation, the progenitor cells would line up and form capillary-like tubes in artificial skin substitutes.

This research is continuing with the assessment of the safety of these cells for human use and further development of the microcirculation in skin substitutes. Burns injuries are devastating for the victims and living artificial skin offers improved reconstruction and quality of life.



The development of capillaries over two weeks from stem cells (green) derived from blood samples.

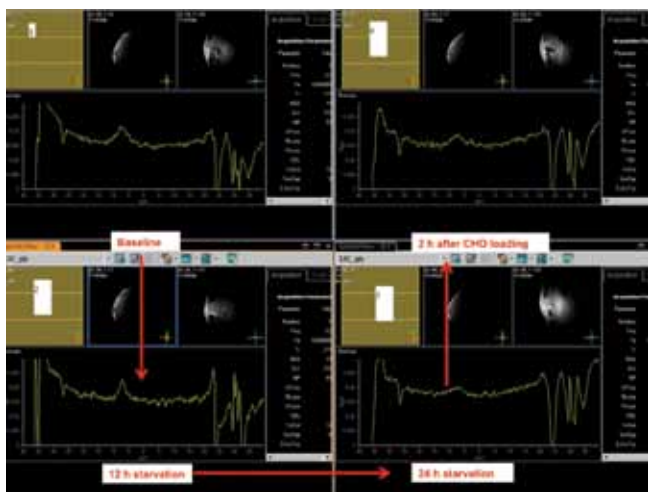
Metabolic and cellular effects of carbohydrate-based preconditioning drinks

Preoperative loading of carbohydrates attenuates the development of postoperative insulin resistance by up to 50% but the cellular mechanisms underlying this effect remained unknown.

The traditional practice of fasting patients before surgery ('nil by mouth') harms the body by inducing metabolic-stress and the development of a diabetic-like state called insulin resistance. This is of importance as insulin resistance increases the risks of developing complications after surgery and prolongs the patient's length of stay. Ingestion of carbohydrate-based drinks before surgery reduces insulin resistance by up to 50% and leads to clinical benefits but the cellular mechanisms underlying these effects remained unknown.

drink that contained glutamine (an essential amino acid in critical illness) and antioxidants was well tolerated by patients; iii) the effects of this drink on mitochondrial function, gene and protein expression; and iv) the metabolic/hormonal responses and effects on the rate of stomach emptying following ingestion of this drink.

We demonstrated that even short-term fasting had adverse effects on energy reserves and mitochondrial function, effects that were partially reversed following ingestion of a preoperative



Dynamic changes in liver glycogen following a 12/24-hour fast, followed by re-feeding using a preoperative carbohydrate drink, as determined by ¹³C magnetic resonance spectroscopy.



Sherif isolating peripheral blood mononuclear cells using density gradient centrifugation.

We undertook a number of healthy volunteer and patient studies that utilised magnetic resonance spectroscopy (a non-invasive technique allowing study of distinct molecules); spectrophotometric mitochondrial (the way cells generate energy) assays; reverse transcription polymerase chain reaction analysis and Western Blotting (to study genes and proteins); and gamma scintigraphy (to study rate of stomach emptying).

Our research aimed to study i) the effects of a 12 and 24-hour fast, followed by carbohydrate loading, on energy reserves and mitochondrial function; ii) whether ingestion of a carbohydrate

drink containing carbohydrate, glutamine and antioxidants. The latter was well tolerated by patients and led to beneficial effects on genes and proteins that controlled energy utilisation in the body. Furthermore, the constituents of these drinks were shown to 'modulate' the ensuing metabolic/hormonal responses. Our new findings will help optimise these drinks and design new interventions to reduce postoperative insulin resistance. This should improve the metabolic preparation of patients before surgery with the aim of reducing complications and speeding recovery.



SHERIF AWAD

Fellowship/sponsor
Doris Mary Sheppard Legacy with support from the Rosetrees Trust.

Supervisor
Mr Dileep N Lobo.

Site of work
Queen's Medical Centre, Nottingham.

Publications

- Awad S, Stephenson MC, Placidi E *et al.* The effects of fasting and refeeding with a 'metabolic preconditioning' drink on substrate reserves and mitochondrial function. *Clin Nutr* 2010; 29: 538–544.
- Awad S, Constantin-Teodosiu D, Constantin D *et al.* Cellular mechanisms underlying the protective effects of preoperative feeding: a randomized study investigating muscle and liver glycogen content, mitochondrial function, gene and protein expression. *Ann Surg* 2010; 252: 247–253.

Presentations

- *Investigating the dynamic metabolic and hormonal responses following ingestion of two 'preoperative' conditioning drinks: a randomized double-blind crossover study.* Association of Surgeons of Great Britain and Ireland (ASGBI); April 2010; Liverpool, UK.
- *Oral ¹³C-bicarbonate tracer technique versus indirect calorimetry for measurement of energy expenditure at rest and during exercise in healthy adults: a prospective randomised validation study.* European Society of Clinical Nutrition and Metabolism; September 2008; Nice, France.

Prizes

- Moynihan Prize, ASGBI, 2010.
- Rosetrees Trust Essay Prize, 2009.

Rapamycin toxicity in islet cell transplantation



ADAM BARLOW

Fellowship/sponsor

College Fellowship with support from Sir Samuel Scott of Yews Charitable Trust, and The Family Rich Charitable Trust.

Supervisor

Professor Michael Nicholson and Dr Terry Herbert.

Site of work

Division of Transplant Surgery, and Department of Cell Physiology and Pharmacology, University of Leicester.

Publications

- Barlow AD, Nicholson ML, Herbert TP. Mechanisms of rapamycin toxicity in pancreatic beta cells. *Transpl Int* 2009; 22 (Suppl 2): 141.
- Barlow AD, Nicholson ML. Immunosuppression in islet transplantation. *Bri J Transpl* 2009; 4: 10–13.

Presentations

- *Rapamycin toxicity in pancreatic beta cells is mediated via PKB*. Society of Academic and Research Surgery; January 2010; London, UK.
- *Mechanisms of rapamycin toxicity in pancreatic beta cells*. European Society of Organ Transplantation; August 2009; Paris, France.

Type-1 diabetes, the inherited form, currently affects over 250,000 people in the UK. These individuals are at risk of serious complications, with type-1 diabetes reducing life expectancy by an average of 20 years.

Type 1 diabetes is caused by the destruction of the islet cells in the pancreas, which produce insulin. One potential cure for people with severe diabetes that is not well-controlled with insulin injections is an islet transplant. This involves removing the islets from the pancreas of a deceased donor and injecting them into the liver of the diabetic patient. The islets then seed in the liver and are able to produce insulin normally. However, the transplanted islets are viewed as foreign material and the patients therefore have to take medication to prevent rejection. The main anti-rejection drug used in islet transplantation is called rapamycin.

The results of islet transplantation are initially very good, with over 90% of patients being able to stop insulin injections altogether. However, the long term results are not as promising, with the vast majority of patients being back on insulin injections within five years of their transplant. This suggests that there is something damaging the transplanted islets over time. One suggestion is that rapamycin, used to prevent rejection, may itself be damaging the islets.

My research project has involved looking at the effects of rapamycin on islets and also investigating the mechanism of any toxic effects.

This study has demonstrated that rapamycin reduces the amount of insulin produced by islets and also causes increased death of the islets. Furthermore, I have shown that this is due to inactivation of a key protein within the islets called PKB.

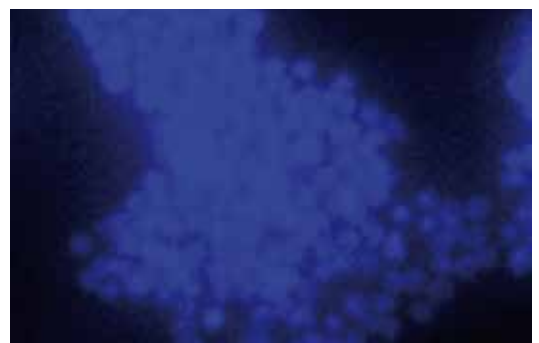
This work provides evidence for stopping the use of rapamycin as an anti-rejection treatment for islet transplantation. It also highlights the key role that PKB plays in both the function and the survival of islets. By developing new treatments specifically aimed at activating PKB in islets we may be able to improve the outcome of islet transplantation for sufferers of diabetes.



Adam preparing cells for experimentation.



Adam viewing treated cells through a microscope.



Beta cells from pancreatic islets viewed through a fluorescent microscope.

Effects of tumour micro-environment on the differentiation and function of human-liver-derived dendritic cells

The incidence of hepatocellular cancer (HCC) in the UK is rising and it is currently the third most common cause of cancer-related death worldwide.

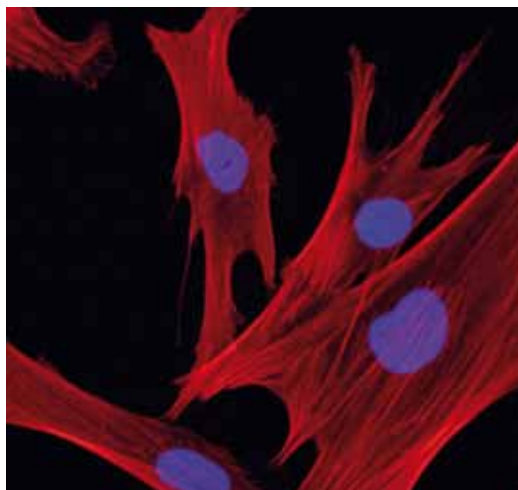
Surgical resection and liver transplantation are the only curative therapies currently available for HCC. 70–80% of HCC patients are inoperable at the time of diagnosis, due to advanced liver cirrhosis, co-morbidity or the tumour severity. There is an urgent need to develop new treatment strategies and this is reflected in the very poor overall survival rates (less than 10% at five years).

We know that the immune system is capable of killing tumour cells if appropriately activated and that tumours manipulate their local environment to suppress the immune system. The aim of this project was to try to identify factors in the tumour that do this. The work has focused on a critical immune cell called a dendritic cell (DC). DCs sample the local environment and stimulate immune cells (T-cells) that will kill unwanted cells. We have isolated DCs from liver tumours and shown they lack the receptors required for inducing effective T-cells and, in fact, are likely to induce immunosuppressive T-cells.

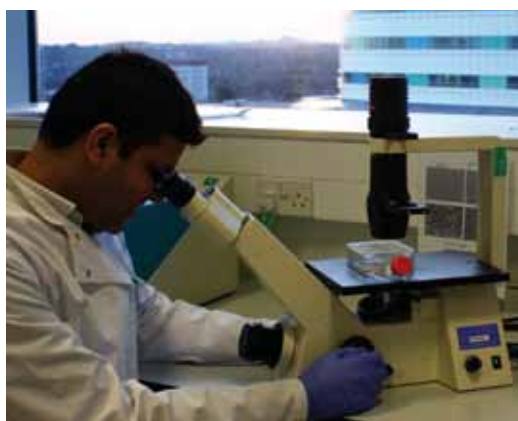


Right lobe of liver with HCC, with cut into cancerous liver tissue.

A significant bulk of the tumour is made up of scar cells (fibroblasts). We have found that tumour fibroblasts suppress the appropriate maturation of DCs, rendering them unable to mount an effective immune response against tumours. A proportion of this suppression of DCs is via a soluble factor and we are trying to block the effect of this factor, with promising preliminary results.



Fluorescent staining of tumour scar cells (fibroblasts).



Anand looking at liver cancer cells through a microscope.

This basic science complements a current clinical trial looking at the effect of injecting DCs into tumours. This work offers promising results with a potential treatment strategy involving the use of DCs and blocking drugs to stunt or shrink liver tumours, making more patients with this condition amenable to resection or transplantation.



ANAND BHATT

Fellowship/sponsor
College Research Fellowship.

Supervisor
Professor David H Adams.

Site of work
Centre for Liver Research,
University of Birmingham.

Publications

- Bhatt A, Curbishley SM, Haughton EL *et al*. The stromal compartment of hepatocellular carcinoma promotes the local differentiation of tolerogenic dendritic cells. *Gut* 2010; 59: 30–31.
- Bhatt AN, Adams DH. Beyond fibrogenesis: Stellate cells take center stage as immune-response modulators. *Hepatology* 2009; 49: 2,115–2,118.

Presentations

- *The stromal compartment of hepatocellular carcinoma promotes the local differentiation of tolerogenic dendritic cells.* American Association for the Study of Liver Disease; October 2010; Boston, USA.
- *The stromal compartment in HCC contributes to the induction of tolerogenic dendritic cells.* EASL Special Conference on Hepatocellular Carcinoma: from Genomics to Treatment; June 2010; Dubrovnik, Croatia.

The role of hypoxia in urological malignancies



CHRISTOPHER BLICK

Fellowship/sponsor

Joan Rosa Cox Research Fellowship with support from the Rosetrees Trust.

Supervisor

Professor Adrian Harris and Mr David Cranston.

Site of work

The Weatherall Institute of Molecular Medicine, University of Oxford.

Publications

- Favaro E, Ramachandran A, McCormick R, Gee H *et al.* MicroRNA-210 regulates mitochondrial free radical response to hypoxia and krebs cycle in cancer cells by targeting iron sulfur cluster protein ISCU. *PLoS One* 2010; 5: e10,345.
- Patel NS, Muneer A, Blick C, Arya M, Harris AL. Targeting vascular endothelial growth factor in renal cell carcinoma. *Tumour Biol* 2009; 30: 292–299.

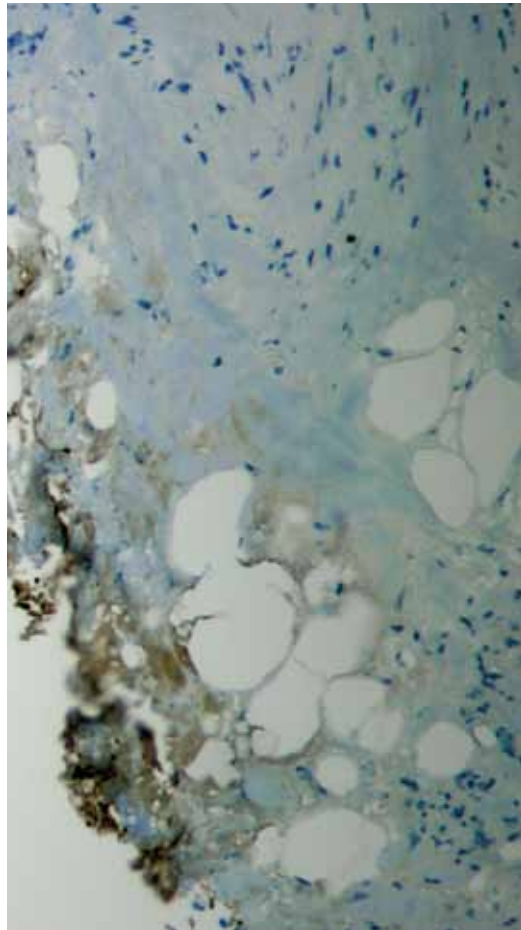
Presentations

- *The hypoxic and miR-100 regulation of FGFR3 in low grade bladder cancer.* Keystone Symposia Conference; February 2011; Fairmont Banff Springs, Canada.
- Hypoxia regulated microRNAs in bladder cancer. *European Association of Urology*; March 2011; Vienna, Austria.

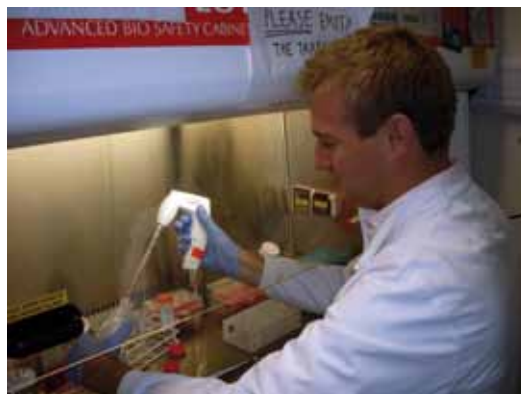
Further funding

The British Urology Foundation for one year.

Bladder cancer has the highest recurrence rate of any malignancy.



Staining of a superficial bladder cancer for CAIX (a marker of low oxygen).



Christopher culturing bladder cancer cells.

Approximately 80% of cancers arising from the bladder are superficial and hence non-muscle invasive (NMI) tumours at diagnosis. NMI disease carries a favourable prognosis with reported five-year survival figures of between 80–90%. Despite the relatively low incidence of disease progression, NMI disease is associated with three-year recurrence rates of 40–80%.

The molecular subtype attributed to NMI is associated with increased FGFR3 expression. FGFR3 is a gene involved in many cellular processes such as cell growth and multiplication and its activation is thought to be key to NMI bladder cancer development. We believe that low oxygen levels (hypoxia) found in superficial bladder cancers are one cause for this increase in FGFR3 expression. This project aims to confirm the hypoxic induction of FGFR3 and demonstrate the effects on tumour growth.

Another potential mechanism leading to increased expression of FGFR3 is related to the function of microRNAs (miRNAS) – short strands of DNA that regulate the function of their target genes. We and others have shown that a number of miRNAs are either up or down-regulated in hypoxia. One of these miRNAs, miR100, targets FGFR3 and we hypothesise that this pathway may also play an important role in the hypoxic induction of FGFR3.

This work forms part of a larger project investigating the role of hypoxia in both bladder and kidney cancers. The results will be compared with patient outcome data in order to identify markers of disease progression and survival. Greater understanding of molecular pathways in cancer will allow the development of diagnostic and prognostic markers, which in turn will aid the early detection and appropriate management of urological cancers.

Decreasing complications in open fractures using a novel bone graft

Patients with severe limb injuries may need multiple operations and can suffer severe pain and stiffness through to limb amputation or even death.



Care of a wounded soldier in Camp Bastion, Helmand Province, Afghanistan.

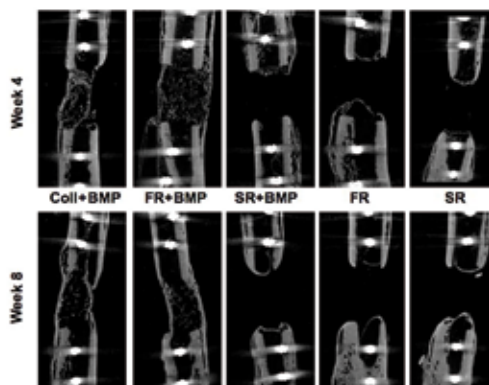
The risk of infection and non-union in patients with severe extremity injuries has been shown to be up to 23% and 32% respectively. There is nothing currently available that can simultaneously help bone formation and deliver antibiotics.

Recently, bone has been successfully grown using factors to stimulate bone growth (recombinant human bone morphogenetic proteins (rhBMPs)). The aim of this project was to develop a substance (scaffold) that could deliver both BMPs and antibiotics into a large infected bone defect.

We used large defects in animal models that would not heal on their own. We characterised the time from infecting the bone defects to treatment. We conducted separate investigations into delivering BMPs and antibiotics from our scaffold to the defect and the subsequent effects on bone healing and on infection respectively. We compared our scaffold to current practice.

We established a decrease in infection with earlier treatment and the addition of antibiotics. We then demonstrated that an initial burst release of BMPs from the scaffold followed by a more sustained release profile and a prolonged release of antibiotic is better than current clinical practice. This scaffold therefore shows potential for clinical use to promote healing in severe open fractures.

Research into bone regeneration and treatment of infection has been in effect for the last 40 years. There have been previous studies showing that this scaffold can deliver BMP and antibiotics but the model used here was more stringent. This project was in small animals – it will now move towards testing in larger animals and ultimately in humans.



Bone regeneration using the new scaffold.



KATE BROWN

Fellowship/sponsor
Surgical Research Fellowship in Military Surgery.

Supervisor
Dr Josh Wenke.

Site of work
Institute of Surgical Research, San Antonio, USA.

Publications

- Brown KV, Walker JA, Cortez DS *et al*. Early debridement and antibiotic administration decreases infection. *J Surg Orthop Adv* 2010; 19: 18–22.
- Li B, Brown KV, Wenke JC, Guelcher SA. Sustained release of vancomycin from polyurethane scaffolds inhibits infection of bone wounds in a rat femoral segmental defect model. *J Control Release* 2010; 145: 221–230.

Presentations

- *Decreasing complications in open fractures with a novel bone graft*. Orthopaedic Trauma Association; October 2010; Baltimore, USA.
- *Local antibiotics do not inhibit bone growth when administered with growth factor*. European Federation of National Associations of Orthopaedics and Traumatology; June 2010; Madrid, Spain. Also presented at: Combined Orthopaedic Associations; September 2010; Glasgow, UK.

Prizes
Shortlisted for AOUC Research Prize, November 2010.

Further funding
Postgraduate Military Surgical Deanery for one year.

Examination of neuronal pathways in patients with faecal incontinence and the effect of sacral neuromodulation



EMMA CARRINGTON

Fellowship/sponsor
DBP Trust Research Fellowship.

Supervisor
Mr Charles Knowles.

Site of work
Academic Surgical Unit, Queen Mary, University of London.

Publications
Carrington EV, Knowles CH. The influence of sacral nerve stimulation on anorectal dysfunction. *Colorectal Disease* 2011; 13: 5-9.

Presentations
Examination of neuronal pathways in patients with faecal incontinence and the effect of sacral neuromodulation.
Royal College of Surgeons/
Association of Surgeons of India;
May 2010; Bangalore, India.

Prizes
Stefan Galeski Fellowship, 2010.

10% of the UK population suffer from faecal incontinence; however, symptoms are often ignored due to social stigma and the perceived lack of treatment options.

Faecal incontinence is a devastating condition that affects people from all walks of life. Sufferers lose the ability to control their bowel function. Many patients become confined to their house and refuse to socialise for fear of an embarrassing accident. Worse still, people feel unable to talk about their condition due to the intense stigma of their symptoms. For this reason faecal incontinence is often termed 'the silent affliction'.

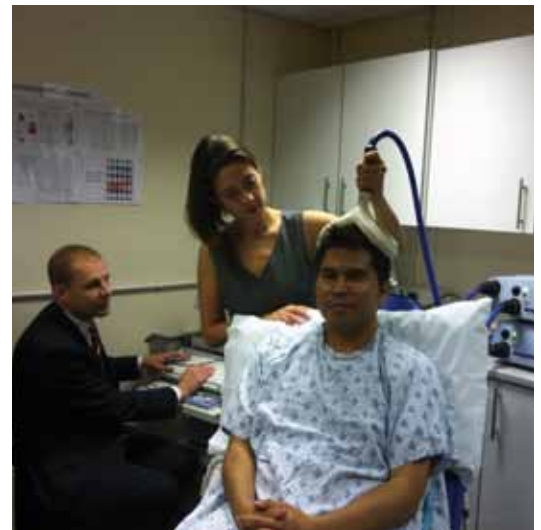
In 2007, a novel treatment called sacral nerve stimulation (SNS) received approval for the treatment of faecal incontinence. SNS involves the insertion of electrodes in the lower back, which are connected to a stimulator implanted in the buttock acting like a pacemaker. Impulses stimulate the nerves supplying the lower bowel. This is important as it is believed that abnormalities in nerve function may contribute to the development of faecal incontinence.



A radiograph showing the position of a sacral nerve stimulator.

Research has shown that SNS can halve the number of incontinence episodes in up to 65% of patients; however, doctors are unable to predict which patients will respond to this type of treatment. Although it is understood that the nerves to the bowel are being stimulated, the next step of understanding why this is important remains elusive.

A technique called 'evoked potentials' involves measuring brain responses to stimulation of nerves in the periphery, giving a measure of how well these nerves are working. This research project involves the use of rectal evoked potentials, ie measuring the response of the brain to stimulation of the lower bowel.



Measurement of the motor nerves involves the use of a powerful magnetic coil held over the motor cortex.

The objective of this research is to evaluate whether evoked potentials demonstrate reduced nerve function among patients with faecal incontinence and if so whether a change in function is seen after treatment. If this is the case, doctors may be able to select patients who are likely to benefit from SNS.

Work on this project began one year ago and it is expected to take a further three years to complete. So far, preliminary data suggest that nerves in patients with constipation and reduced bowel sensation may function more slowly than in normal volunteers. Investigation of patients undergoing sacral nerve stimulation is ongoing.

The pedagogy of the operating theatre

Working time regulations have reduced surgical training time from 30,000 to 8,000 hours. This research maps the operating theatre as a site of teaching and learning with a view to improving educational opportunities for all trainees.



ALEXANDRA COPE

Fellowship/sponsor
Edward Lumley Research Fellowship.

Supervisor
Dr Roger Kneebone and Professor George Hanna.

Site of work
St Mary's Hospital, Imperial College Healthcare NHS Trust.

Publications

- Bezemer J, Murtagh G, Cope A *et al.* Tying knots and cutting threads: shared understanding in surgical activity. *Symbolic Interaction*; in press.
- Bezemer J, Cope A, Kress G, Kneebone R. Do you have another Johan? Negotiating meaning in the operating theatre. *Applied Linguistics Review*; in press.

Presentations

- *Assessing educational activity in the operating theatre.* Ottawa Conference; May 2010; Miami, USA.
- *Researching teaching and learning in the operating theatre.* Association for the Study of Medical Education; November 2009; London, UK.

Further funding
London Deanery – Simulation Technology-enhanced Learning Initiative – for one year.



Public engagement with science in the simulated operating theatre at the Cheltenham Festival.

European Working Time Regulations, patient-safety issues and increased pressure to maximise efficiency and throughput of the surgical service have all diminished the opportunities available to surgical trainees to learn how to operate within a traditional apprenticeship model of training. Improving the quality of training with the restricted opportunities available is a challenge, and it is first necessary to establish what trainees actually learn in theatre and how they learn it.

This study used observational methods to analyse teaching and learning in the operating theatre as well as in simulated settings. Detailed field notes as well as audio and video recordings of operations were analysed to provide a rich picture of how teaching and learning actually happens in this complex workplace.

It is a common perception that teaching involves verbal discourse between the teacher and learner; however, we found that in the operating theatre teaching and instruction occurred through gaze, stance, silences and gesture as well as through spoken word. Because this surgical teaching occurs through different senses it can be considered multi-modal.

Surgical trainees learn far more than just the method of the operation while they are in theatre

– they learn how to identify and dissect anatomy in the living subject as well as teamworking, situational awareness and contingency planning.

It is anticipated that the findings of this research will inform simulation design, so that skills that can be acquired in simulated settings could be practised away from the operating theatre, freeing time to learn skills that can only be learnt in theatre. In addition, illuminating how teaching and learning happens, and what factors into these processes, may be used to shape faculty development programmes so that teaching can be optimised for trainees.

Alexandra explaining how to stop bleeding in the simulated operating theatre.



Chemotherapy resistance in pancreatic cancer



KHALED DAJANI

Fellowship/sponsor

College Research Fellowship.

Supervisor

Miss Paula Ghaneh and Professor John P Neoptolemos.

Site of work

Division of Surgery and Oncology, University of Liverpool.

Publications

- Smith RA, Dajani K, Dodd S *et al.* Preoperative resolution of jaundice following biliary stenting predicts more favourable early survival in resected pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2008; 15: 3,138–3,146.
- Dajani K, Tonack S, Greenhalf W *et al.* Gemcitabine resistance correlates with the expression of key proteins in its uptake and metabolism in pancreatic cancer cell lines. *Pancreatology* 2009; 9: 480.

Presentations

- *Gemcitabine resistance in pancreatic cancer cell lines correlates with the expression of key proteins its uptake and metabolism.* European Pancreatic Club; July 2009; Szeged, Hungary.
- *As above.* National Cancer Research Institute; October 2008; Birmingham, UK.

Prizes

- European Pancreatic Club and International Association of Pancreatology Scholarship, 2009.
- Pancreatic Society of Great Britain and Ireland Travel Bursary, 2008.

With less than 1 in 20 patients surviving 5 years from diagnosis, pancreatic cancer is a devastating disease. The cancer is aggressive and can have inherent and/or acquired resistance to current chemotherapeutic agents.



Khaled with a patient taking part in the pancreatic research, as part of the ongoing tissue collection project.

85% of patients diagnosed with pancreatic cancer have advanced disease at the time of presentation. For this group, chemotherapy is the only treatment modality proven to extend survival. For the 15% with early disease, surgery followed by chemotherapy improves survival to an average of 21 months.

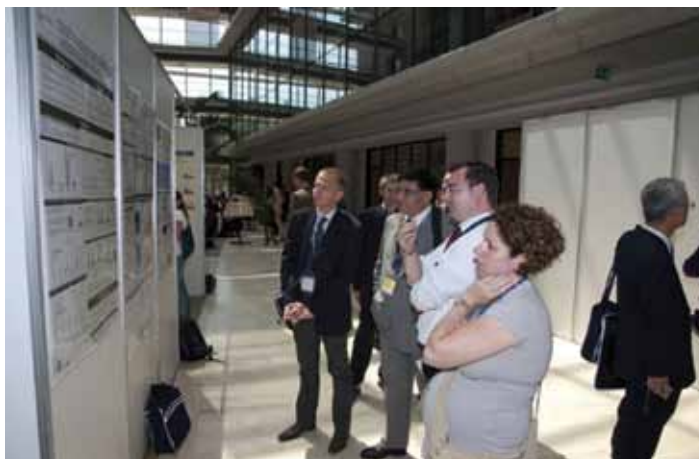
It is clear that chemotherapy plays an important role in the management of such patients. However, response rates vary from 1 in 5 to 1 in 10, making the decision to offer chemotherapy on an individual basis difficult. A simple test is urgently required that would predict patients' likely response to a specific chemotherapeutic agent, allowing treatment to be tailored to the individual.

The aim of this study was to identify potential biomarkers of response to common chemotherapies used in pancreatic cancer.

The Liverpool Cancer Trials Unit has led the world's largest randomised trials of chemotherapy following surgery in pancreatic cancer: the ESPAC-1 and ESPAC-3. Tissue blocks have been collected from participants with the aim of validating potential biomarkers identified in the laboratory for use in clinical practice.

For this project we generated pancreatic cancer cells that were resistant to chemotherapy by growing the cells in increasing concentrations of the drug. We then examined the expression profile of these cells on the genetic level (using whole genome expression arrays) and protein level (using pancreas-specific antibody arrays) and compared them with the cells from which they were generated. We looked more specifically at enzymes and proteins that metabolise chemotherapy in these cells and in tissue samples taken from patients with pancreatic cancer.

This generated a number of potential biomarkers, on which further validation is ongoing. This work may ultimately result in a simple test identifying those who will respond to a particular drug, allowing tailored treatment for patients with the ultimate goal of improving survival for patients with this aggressive disease.



Khaled presenting a poster of his research at a European pancreatic meeting in Szeged, Hungary, 2009.

Functional characterisation of acute traumatic coagulopathy

After serious injury, 1 in 4 people develop deranged clotting before they reach an emergency department and, as a result, are five times more likely to die from uncontrolled blood loss.

The aim of this study was to evaluate bedside technologies for a rapid assessment of the derangements that occur in blood clotting following severe injury, called acute traumatic coagulopathy (ATC). Current laboratory measures of clotting take over an hour for a result and therefore have limited use in the emergency patient with life-threatening haemorrhage. It was hypothesised that these devices would not only permit early identification of ATC but also guide appropriate and effective blood transfusion as well as reduce wastage.

300 trauma patients were recruited on arrival in the emergency department and blood samples were collected during resuscitation. Each sample was analysed by rotational thromboelastometry (ROTEM®) which measures the strength of blood clots and, importantly, is able to provide a result within minutes. In addition, chemical biomarkers of clotting which circulate in the blood were measured to try to unravel the precise mechanisms which give rise to ATC.

ROTEM® has been used for a number of years in other surgical fields but has not been subject to large scale evaluation in trauma care. I have shown that ROTEM® is able to diagnose ATC within five minutes and that it has a greater accuracy than standard laboratory tests in predicting blood transfusion requirements. Building on previous work from our research group and in collaboration with partners in San Francisco, we have identified a novel mechanism that appears responsible for causing ATC. Proteins in the blood appear to be switched from their normal clot-building function to an anti-clotting role that not only prevents clots from forming but also destroys them.

Current recruitment for the study stands at just under 500 patients and based on these important findings we have been granted ethical approval to extend the study to 2,800 patients, which will allow a more detailed investigation into this area.



Trauma call at the Royal London Hospital.



Ross carrying out ROTEM® analysis.



ROSS DAVENPORT

Fellowship/sponsor
Fletcher Legacy Research Fellowship.

Supervisor
Professor Karim Brohi and Dr Rupert Pearse.

Site of work
Royal London Hospital and Queen Mary, University of London.

Publications

- Davenport R, Manson J, De'Ath H *et al.* Functional characterisation and definition of Acute Traumatic Coagulopathy. *Crit Care Med*; (under consideration).
- Davenport R, Curry N, Manson J *et al.* Haemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. *J Trauma* 2011; 70: 90–95.

Presentations

- *Coagulation response to different plasma:red cell ratios in trauma transfusion.* Eastern Association for Trauma; January 2010; Phoenix, USA.
- *Acute traumatic coagulopathy: functional characterisation by rotational thromboelastometry.* International Society of Thrombosis and Haemostasis; July 2009; Boston, USA.

Prizes

Young Investigators Award, British Blood Transfusion Society, 2010.

Further funding

National Institute for Health Research grant for duration of PhD (three years).

Trauma coagulopathy in the military



CATHERINE DORAN

Fellowship/sponsor
Surgical Research Fellowship in Military Surgery.

Supervisor
Surgeon Captain Mark Midwinter and Dr Emrys Kirkman.

Site of work
Academic Department of Military Surgery and Trauma, Birmingham.

Publications

- Doran CM, Woolley T, Midwinter MJ. Feasibility of use of rotational thromboelastography (ROTEM) to assess coagulation status of combat casualties in a deployed setting. *J Trauma* 2010; 69: S40–48.
- Doran C, Midwinter M. Dealing with trauma coagulopathy on deployment. *Medical Corps International Forum* 2009; 4: 34–36.

Presentations

- *Feasibility of use of ROTEM® to manage coagulopathy of military trauma in a deployed setting.* Advanced Technology Applications for Combat Casualty Care; August 2008; St Pete Beach, USA.
- *Use of ROTEM® to manage coagulopathy in military trauma.* NATO Blood Conference; September 2008; Lisbon, Portugal.

Prizes

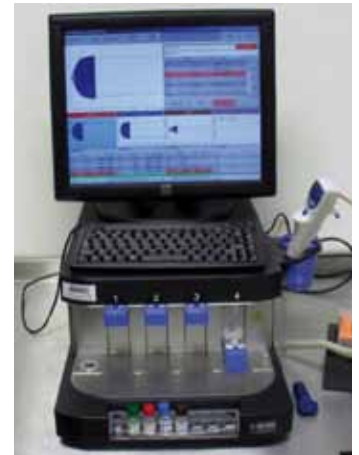
- Stefan Galeski Fellowship, 2010.
- Rosetrees Trust Essay Prize, 2010.

Further funding
Academic Department of Military Surgery and Trauma.

Coagulopathy is common in trauma patients, especially in military casualties, and is associated with a higher risk of mortality.



Arrival of casualties by helicopter into the hospital at Camp Bastion, Afghanistan.



ROTEM® machine used to determine the strength and speed of blood clotting rapidly.

Coagulopathy, where the blood is not clotting properly, occurs in 25% of civilian trauma patients and 38% of military casualties. Coagulopathic patients are four times more likely to die. With over 40% of deaths from military trauma caused by haemorrhage, stopping bleeding remains a priority. Bleeding may not only require surgery but also correction of the patient's innate clotting.

Interest in the coagulopathy of trauma has risen dramatically. It is now known that the rapid replacement of blood and blood products (eg plasma containing clotting factors) and platelets (blood cells involved in coagulation) can improve the survival rates for this group of patients. My research project has two components; one based in the Defence Scientific and Technical Laboratories in the UK and the second in the UK military field hospital in Afghanistan, looking at the feasibility of introducing a new technology to a deployed field hospital to monitor coagulation. This report covers the latter.

The aim of this work was to assess the use of a rotational thromboelastometry (ROTEM®) machine (a rapid, near-patient test of clotting). The machine translates the dynamic development of clot formation into a simple graph, which can

be rapidly and easily interpreted by medical staff in the resuscitation room and operating theatres. This helps determine the patient's requirement for platelets or plasma to ensure optimal correction of any coagulopathy.

I showed that ROTEM® can be used effectively in the austere environment of a field hospital and that it can detect a higher proportion of coagulation abnormalities than standard tests. The Ministry of Defence and a number of NATO allies have now accepted that ROTEM® will be deployed in combat hospitals.

Timing of surgery after radiotherapy in rectal cancer

In the UK, 14,000 people are diagnosed with (and 6,000 people die from) rectal cancer each year. Preoperative radiotherapy and chemotherapy can help make surgery more effective and reduce complications and recurrence.



Jessica and her supervisor, Mr Swift, examining rectal MRI scans of a patient about to undergo surgery following radio/chemotherapy, showing a good response.



JESSICA EVANS

Fellowship/sponsor
Freemasons Grand Lodge 250th Anniversary Fund Fellowship.

Supervisor
Dr Gina Brown, Mr Ian Swift and Mr Paris Tekkis.

Site of work
Mayday University Hospital and Royal Marsden Hospital, London.

Publications
Evans J, Tait D, Swift I *et al*.
Timing of surgery following preoperative therapy in Rectal Cancer – the need for a prospective randomized trial?
Dis Colon Rectum; (in press).

Presentations
Timing of surgery following radiotherapy for rectal cancer.
The European Society of Coloproctology; September 2009; Prague, Czech Republic.

Rectal cancer is a painful and miserable condition with 80–90% of patients succumbing to the disease within five years. Patients often present late due to embarrassment with symptoms. Preoperative chemoradiotherapy shrinks the tumour thereby facilitating complete surgical resection and reducing local recurrence. Shrinking the tumour can also facilitate preservation of the anal sphincter reducing the necessity for stomas. Operations should therefore take place after chemoradiotherapy has had maximum effect.

However, the optimum time to operate following radiotherapy is unknown. The aim of this study is to determine whether a greater delay to surgery following chemoradiotherapy increases tumour shrinkage.

Initial retrospective analysis confirmed that a greater delay to surgery could potentially decrease tumour size. We developed the first prospective, randomised study examining the timing of surgery following chemoradiotherapy, recruiting patients in multiple UK centres. In addition, we have received interest in launching an international study in this area from a renowned Brazilian research team. The study has also been adopted by the National Institute of Health Research,

integrating our work into the UK's main public health research agenda.

This is an ethically approved study comparing surgical patient outcomes at 6–8 weeks and 12–14 weeks following chemoradiotherapy. Potential patients for the study are identified during multi-disciplinary meetings discussing all local rectal cancer cases. They are invited to join the study and consented for treatment. Participants are then randomised to either the 6–8 or 12–14 week group. Magnetic resonance imaging (MRI), positron emission/computed tomography scans, final pathology stage and patient outcomes are compared between the two groups.

The main achievement of our work so far is setting the groundwork for a change in surgical practice. The preliminary evidence of potential improvement in surgical outcomes provides hope for changes in surgical treatment and significant patient benefit. If results are supportive, a major phase 3 trial will be launched, which will have significant implications on all trials involving chemo/radiotherapy nationally and internationally.

A proteomics-based approach for the identification of biliary markers of cholangiocarcinoma



SHAHID FARID

Fellowship/sponsor

College Research Fellowship with support from the Browns Legacy.

Supervisor

Mr KR Prasad, Dr RA Craven and Professor RE Banks.

Site of work

Cancer Research UK Clinical Centre, Leeds Institute of Molecular Medicine, and St James's University Hospital, Leeds.

Publications

- Farid S *et al.* Shotgun proteomics of human bile in hilar cholangiocarcinoma. *Proteomics*; (under consideration).
- Young A, Igami T, Farid S *et al.* Evolution of the surgical management of hilar cholangiocarcinoma in a Western centre. *Bri J Surg*; (under consideration).

Presentations

- *Application of proteomics to bile biomarker discovery in cholangiocarcinoma.* British Society of Proteomic Research/European Bioinformatics Institute; July 2010; Cambridge, UK.
- *Identification of differentially expressed proteins in hilar cholangiocarcinoma using a label free shotgun proteomic approach.* European Hepato-Pancreato-Biliary Association; April 2011; Cape Town, South Africa.

Prizes

Leeds Regional Surgical Gold Medal, 2010.

There are approximately 1,000 people diagnosed with bile duct cancer (also called cholangiocarcinoma) each year in the UK and the incidences of certain forms of this cancer continue to rise.

Bile is a fluid made by the liver and plays an essential role in digestion of our food. It is delivered to the intestine (small bowel) via a series of interconnecting tubes called bile ducts. Cholangiocarcinoma is a cancer affecting these bile ducts leading to blockage (obstruction) and back flow into the liver, blood stream and tissues, leading to the appearance of jaundice. Currently, only surgery offers the hope of cure but more than two-thirds of patients are diagnosed too late for this treatment and will die within 6–12 months. One of the greatest challenges to improving outcomes from this cancer is the development of better tests to enable individuals to be diagnosed earlier in disease and differentiate individuals who have bile duct obstruction from non-cancer (benign) causes.



Clinical encounters during Shahid's research, highlighting clinical consultation and teaching.

Proteins are the building blocks of all cells and tissues. Abnormalities in proteins can result in transformation of cells into cancer and serve as useful diagnostic markers (tests). Proteomics is the study of these proteins and our centre is one of only a few in the world engaged in the analysis of bile in patients with and without cholangiocarcinoma using proteomic technologies. We have chosen bile to study as it is the closest fluid to the tumour environment and potentially contains proteins that are expected to be different to non-cancer bile. Although

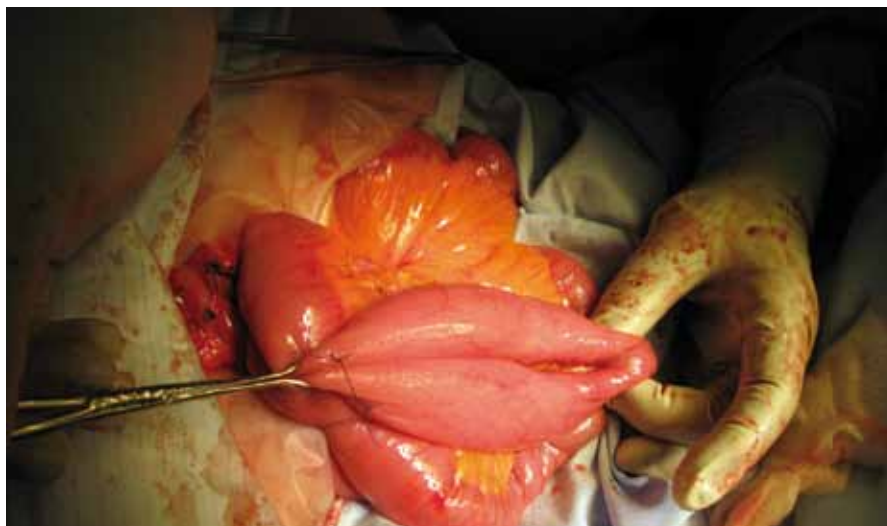
difficult to obtain compared with blood, we have shown that protein profiles between blood and bile and between cancer and non-cancer bile are sufficiently different to focus research on this fluid. Already certain protein molecules have been shown to be differentially expressed and ongoing studies are attempting to validate findings in a larger number of bile samples. Our work will continue to provide valuable information for biomarker discovery for this devastating condition and offer the chance of increased survival.



Organ donor operation in which sample of normal bile is obtained for research.

IL23/Th17 pathway in ileal pouch anal anastomosis

A third of people suffering from ulcerative colitis will require excision of their colon and creation of an ileal pouch to enable restoration of normal bowel continuity.



Left: Initial stage of pouch formation.

Below: Myles recruiting a patient for the study.

In recent years there has been an expansion in knowledge of the aetiology of ulcerative colitis and Crohn's disease. Using animal models, a new class of immune cell (Th17) and new cell signalling molecules (IL23 and IL17) have been shown to play a vital role in colitis. The important role of these cells and molecules has been replicated in humans by genome-wide association studies.

In people with ulcerative colitis a third will require excision of their large bowel either due to a colitis that has become refractory to medical treatment or because of cancerous change. In this group the majority are offered the formation of an ileal pouch anal anastomosis. This acts as a neo-rectum, so enabling them to have restoration of normal bowel continuity.

Although there is a large volume of clinical data on people with pouches, there has been no recent reassessment of the immunological changes that the pouch undergoes from its formation through the various stages of its life. Not only is this interesting from a scientific viewpoint but also it will hopefully help the 50% of people with pouches that suffer from pouchitis, which is a reactivation of their inflammatory bowel disease within their pouch.



I have looked at the immunological changes in ileal pouches from their formation, through steady state and to pouchitis. Initial data show no difference in Th17 cell number between newly formed and established pouches but they do show an increase in the Th17 cell surface marker IL23R and in the expression of the Th17 cell cytokine IL22, which has been shown in animal models to have a protective function in gut mucosa. Work continues to see if disruption of this pathway contributes to pouchitis.



MYLES FLEMING

Fellowship/sponsor
The Professor Norman Williams
IA Research Fellowship.

Supervisor
Mr Baljit Singh.

Site of work
John Radcliffe Hospital, Oxford.

Presentations
Pouchitis: aetiology and diagnosis. International Colorectal Forum; January 2011; Verbier, Switzerland.

The role of haem transporters and iron chelation in oesophageal cancer



SAMUEL FORD

Fellowship/sponsor

College Research Fellowship.

Supervisor

Dr Chris Tselepis and Professor Derek Alderson.

Site of work

Cancer Research UK laboratories, Birmingham.

Publications

Boult J, Roberts K, Brookes MJ *et al*. Overexpression of cellular iron import proteins is associated with malignant progression of oesophageal adenocarcinoma. *Clin Cancer Res* 2008; 14: 379–387.

Presentations

- *Building bridges with bio-iron from bench to bedside*. The European Iron Club; September 2010; Nijmegen, The Netherlands.
- *The expression of haem import proteins LRP1 and HCP1 and export proteins FLVCR and BCRP in the progression of Barrett's metaplasia to oesophageal adenocarcinoma*. Association of Surgeons of Great Britain and Ireland; April 2010; Liverpool, UK.

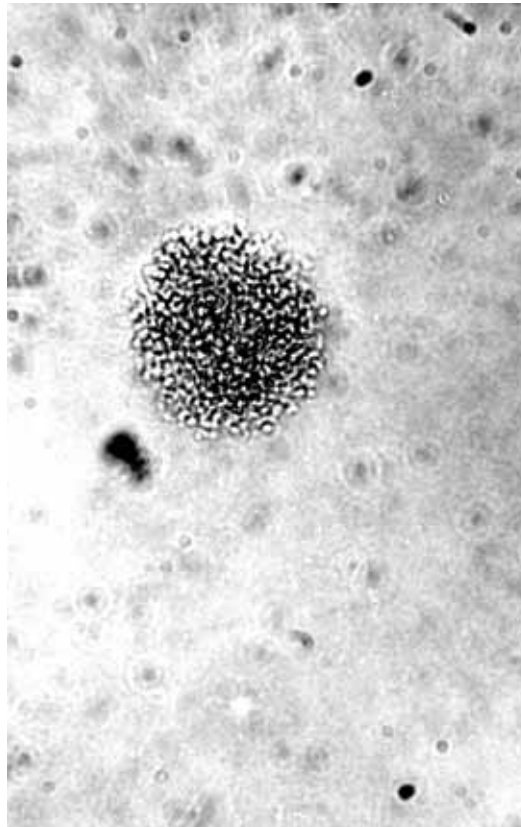
Prizes

Runner-up, Rosetrees Trust Essay Prize, 2010.

Further funding

Cancer Research UK Clinical Research Fellowship for three years.

The incidence of gullet cancer is rising extremely fast yet overall survival remains very poor with less than 1 in 10 patients surviving for 5 years.



An oesophageal cancer metastasis grown in the laboratory – a single cancer cell can form a new tumour in other organs.

The aim of this project was to determine if cancer cells become more aggressive by taking up haem iron and to see if iron binding can be used to treat gullet cancer.

Gullet cancer cells were modified to prevent them taking-up haem and their behaviour observed. Gullet cancer cells were also treated with iron-binding drugs to determine if they can be killed or made less aggressive by depriving them of iron.

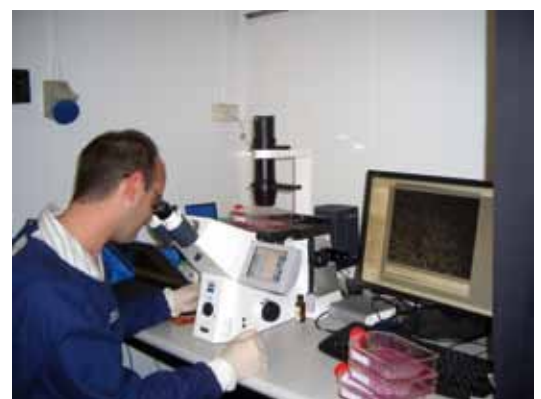
Our results showed that stopping the cells from taking-up haem impeded their ability to divide and spread to other sites. Iron binding caused the majority of cells to die and prevented their ability to divide, invade, migrate and potentially spread. These effects were seen using clinically established iron-binding drugs and more powerful experimental agents.

This research complements previous work that determined how cancer cells capture iron from the blood stream and use it to grow faster.

This project has huge potential for future work. I am continuing to look at the action of iron binding in animal models that have been given gullet cancer to see if it is safe and effective to trial in human patients. Many cancers appear to take-up iron and this needs to be explored.

Patients with gullet cancer often present too late to be cured and succumb very quickly. Palliative chemotherapy is largely ineffective and eating food becomes difficult. Patients who could potentially be cured by surgery undergo a massive operation to remove the gullet but sadly 50% of these patients die from recurrent cancer within a year.

Iron binding may offer an improvement in chemotherapy treatment, potentially extending the life expectancy of those with advanced disease and improving survival rates for those suitable to curative treatment.



Studying the growth of cancer cells with the aid of a video microscope.

The pathological role of thrombomodulin in acute traumatic coagulopathy

Bleeding is the number one cause of preventable death after injury in the UK.

Trauma is a leading cause of death worldwide and kills more young people than any other disease. In the UK, approximately 16,000 people die each year from injuries and half of these occur as a result of excessive bleeding. Trauma surgeons at the Royal London Hospital recently discovered that up to one-third of seriously injured patients arrive in the emergency department with a blood-clotting disorder. This acute traumatic coagulopathy (ATC) develops rapidly after injury, exacerbates blood loss and increases mortality by 400%.

Although the cause of ATC was previously unknown, one human study had suggested that thrombomodulin, a particle bound to the lining of blood vessels, captures proteins released by injured cells and uses them to generate large amounts of anticoagulants that impair clotting. The aim of this project was to develop laboratory models to test this theory and therapeutics capable of blocking it.

We successfully reproduced the conditions occurring after trauma and measured a host of procoagulant and anticoagulant responses. This confirmed that thrombomodulin does indeed activate harmful anticoagulant pathways (eg activated protein C) in the presence of injury and bleeding. By using an antibody to block these pathways we were able to prevent ATC developing in these models. We are now testing various compounds to identify the most effective to take forward to larger trials. If such a substance were given to patients shortly after injury it could improve coagulation function, reduce blood loss and save lives.



Daniel working in the lab.



DANIEL FRITH

Fellowship/sponsor
Enid Linder Foundation
Research Fellowship.

Supervisor
Professor Karim Brohi.

Site of work
William Harvey Research
Institute, Queen Mary,
University of London.

Publications

- Frith D, Goslings JC, Gaarder C *et al*. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. *J Thromb Haemost* 2010; **8**: 1,919–1,925.
- Frith D, Brohi K. The acute coagulopathy of trauma shock: clinical relevance. *Surgeon* 2010; **8**: 159–163.

Presentations

- *Rodent coagulation responses to trauma and haemorrhagic shock*. World Congress on Trauma, Shock, Inflammation and Sepsis; March 2010; Munich, Germany.
- *Acute traumatic coagulopathy is dependent on both injury severity and shock: clinical and experimental validation*. International Society of Thrombosis and Haemostasis (ISTH); July 2009; Boston, USA.

Prizes
ISTH Travel Award for 'Best Junior Researcher'.

Further funding
National Institute for Health
Research for four years.

Identifying molecular targets in osteoarthritis



MATTHEW GARDINER

Fellowship/sponsor

Freemasons Grand Lodge 250th Anniversary Fund Fellowship.

Supervisor

Professor Hideaki Nagase and Professor Jagdeep Nanchahal.

Site of work

Kennedy Institute of Rheumatology, Imperial College London.

Presentations

Proteomic analysis of cartilage protein profiles in a mouse model of osteoarthritis. British Society of Matrix Biology (BSMB); September 2010; Norwich, UK.

Prizes

- Bursary from BSMB, 2010.
- Stefan Galeski Fellowship, 2009.
- Kennedy Institute of Rheumatology Trust Fellowship, 2007.

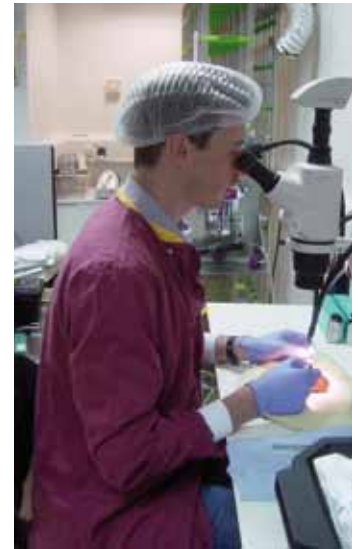
Further funding

Kennedy Institute of Rheumatology Trust for three years.

Osteoarthritis is the most common joint condition in the world. In the UK, approximately 8 million people suffer from the disease with about 1 million needing treatment. There is currently no cure for osteoarthritis.



X-ray showing osteoarthritis at the base of the thumbs and wrists.



Matthew in the laboratory micro-dissecting cartilage.

Osteoarthritis (OA) is a painful and debilitating condition, which has a major impact on the quality of life of patients suffering from this condition. It is caused by degeneration of joint cartilage and associated tissues but the initiating factors remain unknown. It is challenging to study osteoarthritis in humans as the tissue from joint replacement surgery is retrieved at the end stage of disease. The aims of this project were first to investigate the changes in cartilage gene expression and protein profile during the initiation and progression of osteoarthritis in an animal model; and second to apply these techniques to a genetically modified animal model, developed in our laboratory, that is protected from osteoarthritis.

Following a small surgical procedure the animal models develop OA in their knee. At two, four and eight weeks following surgery the knee cartilage is isolated using a new micro-dissection technique. The cartilage was processed for whole-genome expression analysis and proteomic profiling at these time points.

My study provides a detailed analysis of the molecular changes that occur during the

progression of cartilage degeneration. Regulated genes are involved in energy production, chondrocyte structure and cartilage production and function. This builds on previous work in our laboratory, which has developed a transgenic animal model that is protected from osteoarthritis. We are now applying these techniques to this animal model. This will identify key differences in the regulation of cartilage metabolism.

Past trials of drug inhibitors in OA have failed, owing to their broad spectrum and associated side effects. This study is contributing to promising work in our laboratory to develop a selective inhibitor of the key enzymes implicated in the disease.

Diagnostic studies in oral precancer

An equal number of oral cancers develop from lichenoid inflammation and hyperkeratosis as oral dysplasia.



Brush biopsy of the tongue.



Precancerous white patch of the tongue.



VELscope® examination of the oral mucosa.

In 2004, 4,769 people were diagnosed with oral cancer in the UK. Current treatments for oral cancer include surgery and chemoradiotherapy, but these treatments are associated with considerable morbidity, affecting speech, swallowing and appearance. Despite treatment advances, five-year survival rates overall remain around 50%. By identifying high-risk patients with precancerous patches we are able to offer early surgical intervention, preventing development of oral cancer. This study is concerned with development of techniques that can identify patients at high risk of developing oral cancer from precancerous patches. The aims of the study are:

1. To determine whether brush biopsy can effectively detect early cancerous changes
2. To assess the association of human papilloma virus (HPV) with oral precancers.
3. To assess the accuracy of tissue autofluorescence in identifying unstable areas of the mouth.
4. To assess the number of patients in the north east of England who have developed a preventable oral cancer from a white or red patch.

350 patients were recruited into the study. Each completed a questionnaire assessing their smoking status, alcohol consumption and exposure to HPV and received a clinical examination, Velscope autofluorescence examination, brush biopsy, conventional scalpel biopsy and removal of their precancerous patch with laser. The tissue removed was then analysed for HPV and micro RNA (miRNA).

Following the VELscope® examination we have developed a classification system for grading VELscope® appearance. Preliminary studies have shown 90% accuracy compared to conventional scalpel biopsy.

Previously clinicians have suspected 'oral dysplasia' was the most likely group of potentially malignant disorders to transform to oral cancer. However, recent findings have demonstrated that 50% of patients in our cohort ($n=1,248$) treated over the last 10 years have developed oral cancers from a condition known as lichenoid reaction with hyperkeratosis.



MICHAELA GOODSON

Fellowship/sponsor
Shears Northern
Research Fellowship.

Supervisor
Professor P Thomson and
Professor P Sloan.

Site of work
Department of Oral and
Maxillofacial Surgery,
Newcastle University.

Publications

- Goodson ML, Thomson PJ. Management of oral carcinoma: benefits of early precancerous intervention. *Br J Oral Maxillofac Surg* 2010; epub ahead of print.
- Goodson ML, Hamadah O, Thomson PJ. The role of alcohol in oral precancer: observations from a North East population. *Br J Oral Maxillofac Surg* 2010; 48: 507–510.

Presentations

- *Oral cancer: how relevant is oral epithelial dysplasia?* British Association of Oral and Maxillofacial Surgeons (BAOMS); May 2010; Manchester, UK.
- *Brush cytology: preliminary results using the Orcellex® brush.* International Association of Oral Pathology; August 2010; Seoul, South Korea.

Further funding
BAOMS.

Investigating the phenotype and mechanisms of chronic pain in musculoskeletal disease



STEPHEN GWILYM

Fellowship/sponsor

Joint College–Arthritis Research UK Orthopaedic Clinical Research Fellowship.

Supervisor

Professor Andrew Carr and Professor Irene Tracey.

Site of work

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford.

Publications

- Gwilym SE, Filippini N, Douaud G *et al*. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. *Arthritis Rheum* 2010; 62: 2,930–2,940.
- Gwilym SE, Keltner JR, Warnaby CE *et al*. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum* 2009; 61: 1,226–1,234.

Presentations

- *The role of central sensitisation in the presentation of shoulder pain - insights from functional MRI of the brain*. The 11th International Congress on Shoulder and Elbow Surgery; September 2010; Edinburgh, UK.
- *Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients*. The 12th World Congress on Pain; September 2009; Glasgow, UK.

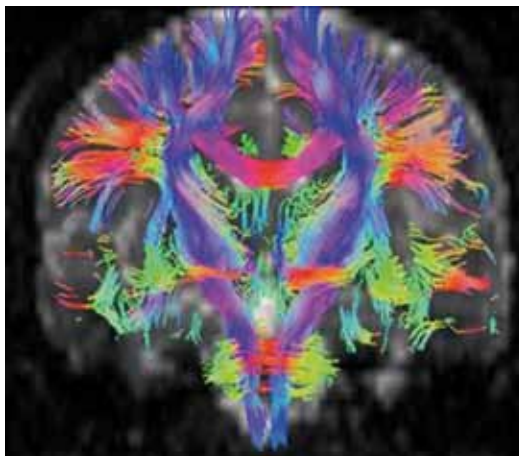
Further funding

National Institute for Health Research, Biomedical Research Unit, for three years.

Only a third of patients with osteoarthritis seen on radiographs have symptoms of pain. The differences between those who do and those who do not feel pain may be due to variations in central pain processing.

Musculoskeletal pain has previously been thought of as being a primarily peripheral disease, with peripheral targets for treatment. However, clinical observations suggest that there is a need to evaluate musculoskeletal pain in a rather more complex model. These include the fact that only a third of osteoarthritis seen on radiographs is symptomatic and evidence that some people continue to have pain after a diseased joint has been taken away (so-called ‘phantom-joint pain’).

Such observations implicate a greater role of central (brain) influences than previously acknowledged. This work hypothesised that pain perception in musculoskeletal disease is associated with altered processing in the brain of painful inputs from the joints and, furthermore, that these alterations in processing induce changes in the physical structure of the brain.



An example of the white matter tracts in the human brain. Differences in these for patients with pain hip arthritis was measured before and after their hip replacement and compared with pain-free controls.

In order to investigate the role of the central nervous system in the perception of musculoskeletal pain this work utilises bedside testing of nerve function (quantitative sensory testing) and magnetic resonance imaging (MRI) of the brain (functional MRI and structural MRI).

Functional MRI allows us to visualise areas of brain that are active during a painful stimulus. By

comparing how the brains of patients with painful musculoskeletal conditions process painful inputs with those of pain-free controls, insights can be gained into altered pain processing induced by chronic pain. Similar comparisons can be made into the structural changes in both the grey and white matter architecture of the brain.



Stephen performing a hip replacement on a subject in the study to see the effect the relief of pain has on brain structure.

By using a model of chronic pain that is potentially reversible (eg hip osteoarthritis and shoulder impingement) this work has also been able to see the reversal of some of these architectural changes in the brain after the painful stimuli have been removed via surgery.

The work performed attempts to advance our understanding of the painful musculoskeletal condition we manage at the bedside. This work has implications for the development of future analgesic targets and raises questions regarding the optimal timing for orthopaedic interventions.

Developing novel modified commensal bacterium for the controlled *in situ* delivery of therapeutic growth factors for the treatment of bowel disorders

Inflammatory bowel disease affects 1 in 400 people. Current therapy is restricted to drugs that suppress the body's immune system; these are not curative, cause severe side effects and are needed for long periods.



Zaed endoscopically examining a patient.



Zaed in the laboratory undertaking a molecular biological experiment.

Inflammatory bowel disease has a significant impact on human health and wellbeing. It affects the digestive system and produces sores in the lining of the gut and, consequently, intolerable pain, diarrhoea and bleeding. Patients with this condition are usually young people and are prevented from achieving their full educational and career potential because of it.

Most patients are treated with drugs to control the gut inflammation. Some people need surgery, which may result in an opening on the 'tummy area' for emptying liquid faeces. There is currently no cure for this disease and patients remain under long-term hospital follow-up.

Recently identified human proteins can be used to induce healing. However, due to their inherent instability and potential toxicity, these proteins cannot be administered to patients by conventional means. The challenge lies in the optimal method of delivering these agents.

At the University of Leeds, I have genetically engineered one of the hundreds of harmless microbes normally present in the human body to make it produce proteins that can heal damaged intestinal tissues. It is vitally important to be able to control when and how much of the protein is produced. We have solved this major problem by using a naturally occurring sugar called xylan to

'switch' the bacterium on and off. By eating the sugar, a patient will set the medicine to work and then can end the treatment simply by stopping consumption of the sugar. The technique has been shown to work in the laboratory, and the new treatment has been successfully tested in animal models. Treatment of other gut diseases is possible by adapting these smart bugs to produce factors specific for each disease.

The effectiveness of these modified probiotics will soon be tested in patients after further optimisation and analysis of their effect. If this regime proves to be successful in humans, this would be considered a leap forward in the treatment of inflammatory bowel diseases, reducing the rate of disability from these disorders.



ZAED HAMADY

Fellowship/sponsor
Joint College/Medical Research Council Fellowship.

Supervisor
Professor Simon Carding and Professor Peter Lodge.

Site of work
Institute of Molecular and Cellular Biology, Leeds University.

Publications

- Hamady ZZ, Scott N, Farrar MD *et al*. Xylan-regulated delivery of human keratinocyte growth factor-2 to the inflamed colon by the human anaerobic commensal bacterium *Bacteroides ovatus*. *Gut* 2010; 59: 461–469.
- Hamady ZZ, Farrar MD, Whitehead T, Lodge *et al*. Identification and use of the putative *Bacteroides ovatus* xylanase promoter for the inducible production of recombinant human proteins. *Microbiology* 2008; 154: 3,165–3,174.

Presentations

- *Sugar-controlled growth factor delivery system for the treatment of experimental murine colitis*. Association of Coloproctology of Great Britain and Ireland (ACPGBI); July 2008; Birmingham, UK.
- *Genetic engineering of a human commensal gut bacterium for controlled delivery of growth factor (KGF-2) to treat inflammatory bowel disease*. INRA/Rowett Research Institute; June 2008; Clermont-Ferrand, France.

Prizes

- The Royal College of Surgeons of England Hunterian Professorship, 2010–2011.
- First prize, Society for Academic and Research Surgery, ACPGBI, 2008.

Further funding

British Journal of Surgery Research Bursary 2004 for three years.

The ophthalmological sequelae of severe traumatic brain injury



ADEL HELMY

Fellowship/sponsor
Joint College/Medical Research Council Fellowship.

Supervisor
Mr Peter Hutchinson.

Site of work
Neurosurgery Department, Addenbrooke's Hospital.

- Publications**
- Helmy A, Kirkpatrick PJ, Seeley HM *et al*. Fixed, Dilated Pupils Following Traumatic Brain Injury: Historical Perspectives, Causes and Ophthalmological Sequelae. *Acta Neurochirurgica Supplementa*; (in press).
 - Helmy A, Carpenter KL, Menon DK *et al*. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. *J Cereb Blood Flow Metab* 2010; 31: 658–670.

- Presentations**
- *Fixed, dilated pupils following traumatic brain injury: What are the implications?* 14th International Conference on Intracranial Pressure and Brain Monitoring; September 2010; Tübingen, Germany.
 - *Causes, consequences and historical perspectives with regards to a fixed, dilated pupil following traumatic brain injury.* Society of British Neurological Surgeons; May 2010; Cambridge, UK.

Prizes
BRC Research Seminar Prize, 2009.

Further funding
Joint Medical Research Council/Royal College of Surgeons Clinical Research Training Fellowship for three years.

Head injury is the commonest cause of death in those aged under 40 years. Pupillary abnormalities are common but long-term consequences are less acknowledged even though they affect patients' quality of life.



Adel (right) running through some laboratory results with his supervisor.

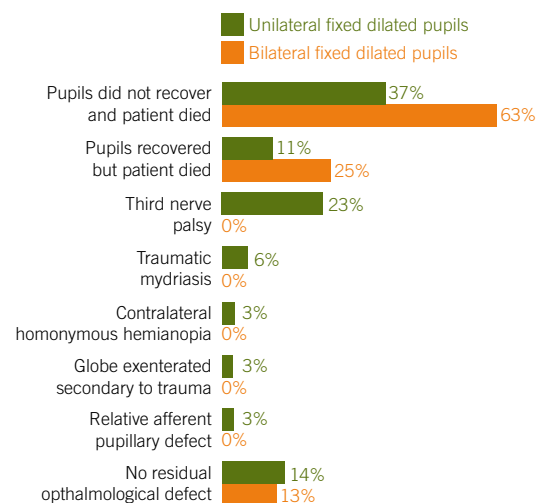
Following a head injury, the pupil size and its reaction to light is an important part of the examination. It usually indicates raised pressure in the skull that is compressing the parts of the brainstem that control the pupils. This research has looked at the consequences of having an abnormally functioning pupil after a head injury. Our study looked at 428 patients admitted to neuro-intensive care following a severe head injury and selected those that also had pupil abnormalities. We then looked back at the patient demographics, mechanisms of injury, computed tomography (CT) scan findings, long-term eye problems and the clinical outcomes of these patients.

Young men involved in road traffic accidents are the most likely group of people to present with a head injury and a pupil abnormality. We have found that the swelling shown on the CT scan is on the same side as the pupil abnormality in only one-third of cases. Almost three-quarters of patients that survive a head injury and a pupil abnormality will have problems with moving the eye and double vision (a third nerve palsy) at six month follow-up. This is much higher than has been previously reported and highlights the

need to recognise this particular consequence of head injury. While most patients with pupil abnormalities and a head injury had a poor outcome, in those whose treatment could be started rapidly, a proportion went on to have good outcomes.

Following on from this project I have started a PhD investigating another aspect of head injury: neuroinflammation.

Consequences of unilateral and bilateral fixed dilated pupils.



Whole genome scanning and identification of biomarkers in Dupuytren's disease

This study has added to the current global genetic work on Dupuytren's disease (DD) and is the first described to look at the role of stem cells in the origin of DD cells.



A patient with bilateral Dupuytren's disease.



SANDIP HINDOCHA

Fellowship/sponsor
Newman Foundation
Research Fellowship.

Supervisor
Mr Ardeshir Bayat.

Site of work
University of Manchester.

Publications

- Hindocho S, Iqbal A, Farhatullah S *et al*. Characterisation of stem cells in Dupuytren's Disease. *Br J Surg* 2011; **98**: 308–315.
- Hindocho S, McGrouther DA, Bayat A. Epidemiological Evaluation of Dupuytren's Disease: Incidence and prevalence rates in relation to etiology. *Hand (N Y)* 2009; **4**: 256–269.

Presentations

- *Dupuytren's disease shows profound hematopoietic and mesenchymal stem cell abnormalities involving palmar fat and skin in addition to fascia: novel implications for pathogenesis and therapy.* International Symposium on Dupuytren's Disease; May 2010; Miami, USA.
- *Familial pattern and inheritance of Dupuytren's disease: a comparison of populations and pedigrees in the UK and Iceland.* International Symposium on Dupuytren's Disease; May 2010; Miami, USA.

Prizes

- Best scientific paper, Association of Surgeons in Training/Society for Academic and Research Surgery, 2009.
- Best clinical paper, Clinical Academic Training Forum 2009.

DD affects the hand due to contraction of the layer of tissue (fascia) deep in the skin of the palm of the hand. DD is a physically and psychologically disabling condition. In its most severe state, permanent bending of the fingers to both hands prevents one from the most simple of daily activities. Although surgery is the mainstay of treatment to correct the contracture, recurrence is inevitable.

The aims of this project are to i) identify susceptible genes in DD; and ii) identify specific proteins that may be used as markers of disease prognosis.

The largest family known to suffer with DD, from Reykjavik, Iceland, was selected to undergo whole genomic scanning. From 45 family members, 22 are affected with DD. Assessment of environmental risks and severity was carried out. The genetic material of each individual was scanned to look for susceptible genetic markers.

Nine DD patients were enrolled and biopsies taken from the diseased tissues. Various laboratory

techniques were used to identify specific stem cell markers and provide clues to the pathological nature of DD. Two areas of genetic interest have been identified on two separate regions of the genome. There is one significant genetic region on chromosome 8 and another on chromosome 11 that are potentially involved in the pathogenesis of Dupuytren's disease (DD). We found three stem cell markers that were significant in the DD tissue (CD13, 34, 44), creating a new hypothesis for the origin of the cellular cause of DD.

There is now a global collaborative network studying the genetics of DD. The stem cell markers identified are currently being studied for their functional role in the pathogenesis of DD.

Towards immunotherapy for recurrent respiratory papillomatosis



OWAIN HUGHES

Fellowship/sponsor

College Research Fellowship.

Supervisor

Dr Siobhan Burns, Professor Martin Birchall and Professor Adrian Thrasher.

Site of work

Molecular Immunology Unit, Institute of Child Health, University College London.

Presentations

- *Detection of human papilloma type-11 E6-specific memory T-cells in healthy subjects.* European Society of Paediatric Otorhinolaryngologists; September 2010; Pamplona, Spain.
- *Joint British Association for Paediatric Otorhinolaryngologists (BAPO) and ENT-UK national survey on the prevalence and burden of recurrent respiratory papillomatosis in the UK.* BAPO; September 2010; London, UK.

Prizes

Medical Research Council Clinical Research Training Fellowship, 2009–2012.

Further funding

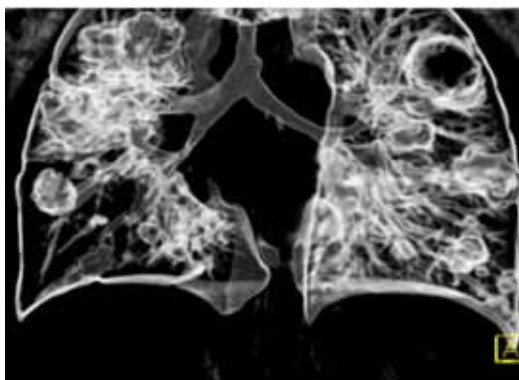
Medical Research Council for three years.

Dendritic cell immunotherapy is able to initiate a specific immune response against the virus that causes recurrent respiratory papillomatosis.

Recurrent respiratory papillomatosis (RRP) is a devastating disease caused by the human papilloma virus (HPV). Those affected suffer from fulminant growth of papilloma tumours within the lining of the airways, which cause life-threatening airway obstruction and changes to the voice. The only effective treatment is surgical tumour debulking, which becomes impossible once disease spreads to the bronchi and lungs. Children with RRP undergo, on average, four surgical procedures each year for recurrent tumours and some ultimately require over 200 operations. Currently available medical therapies are not generally effective and there are no treatments that prevent disease recurrence, making this a critical area for the development of novel treatments.



A growth of the lining of the voice box caused by RRP that is partly obstructing the entrance to this child's wind pipe.



Destruction of the lung tissue caused by RRP, seen here via magnetic resonance imaging.



Owain with Dr. Siobhan Burns, one of his supervisors.

My research is focused on developing new treatments against RRP. I am using specialist immune cells, called dendritic cells (DCs), to prime a patient's own immune system to recognise and clear the virus causing RRP. Using blood and tissue samples from patients, I have developed a method to measure the specific immune response to HPV. Using these measurements, I have been able to demonstrate in the laboratory that DC immunotherapy can initiate a specific immune response against the HPV types that cause RRP.

After being awarded the College Fellowship, I have been successful in securing a prestigious Clinical Research Training Fellowship from the Medical Research Council worth more than £250k. This funding enables me to continue my research both at the Institute of Child Health, University College London, and at Yale University, USA. In addition to gaining high-quality research training in internationally renowned laboratories, my aim is to bring new treatment options to patients afflicted by RRP. In pursuing this aim, I will also gain an understanding of how HPV interacts with the immune system, which is important for developing new treatments for other HPV-induced diseases, including head and neck cancer.

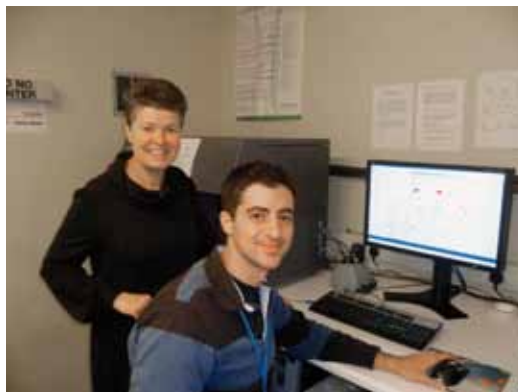
Immunoregulation of rejection in a humanised animal model

In transplantation, short-term organ and patient survival rates are excellent but long-term survival rates are poor, with one-third to half of all transplanted organs being lost by 10 years.

Transplantation is the most effective treatment for irreversible organ failure. However, transplanted organs are recognised as foreign by our immune systems and therefore subjected to a destructive rejection process. Organ acceptance is therefore achieved with immunosuppressive drugs that dampen immune responses as a whole. Despite this, long-term organ and patient survival rates are poor due to this 'blanket' approach of suppressing all immune responses, which can lead to tumour development, serious infections, kidney damage and heart disease. Furthermore, these drugs are unable to control all aspects of the immune response and lead to late, or chronic, rejection.

An ideal solution is therefore specifically to control the response to the transplant but leaving all other arms of the immune response intact. The immune system has a 'built-in safety system' to control unwanted and harmful immune responses, using cells termed regulatory T cells (Treg). These cells suppress specific immune responses, such as those towards the body's own cells. We are therefore exploring methods to harness Treg as a therapy to block the immune response towards a transplanted organ, thereby achieving a state termed 'tolerance'.

We have designed protocols for isolating and expanding human Treg to produce large numbers of cells for therapy. In order to test the functionality of these Treg in an experimental setting, we have developed experimental animal models that have a human immune system, which receive a human skin transplant that is normally rejected. Using this model we have shown that Treg therapy promotes the acceptance of a human skin transplant in the complete absence of any immunosuppression. Skin is particularly susceptible to rejection and therefore controlling rejection in this model by Tregs alone is a significant achievement. We are now further refining Treg therapy in order to establish the groundwork for the first clinical trials in Europe.



Fadi and his supervisor, Professor K Wood, analysing cell phenotype data on a fluorescence-activated cell sorting machine.



Regulatory T cell culture is performed using sterile techniques in a biosafety cabinet.



FADI ISSA

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship.

Supervisor
Professor Kathryn J Wood.

Site of work
Nuffield Department of Surgical Sciences, University of Oxford.

Publications

- Issa F, Hester J, Goto R *et al.* Ex vivo-expanded human regulatory T cells prevent the rejection of skin allografts in a humanised mouse model. *Transplantation* 2010; 90: 1,321–1,327.
- Issa F, Wood KJ. CD4+ Regulatory T cells in solid organ transplantation. *Curr Opin Organ Transplant* 2010; epub ahead of print.

Presentations

- *Regulatory T cells prolong skin allograft survival in a humanized mouse model.* 23rd International Congress of the Transplantation Society; August 2010; Vancouver, Canada.
- *Immunoregulation of skin rejection in a humanised mouse model.* Medical Research Society; February 2010; London, UK.

Prizes

- The Medawar Medal, The British Transplantation Society, 2011.
- Phizackerley Award, Balliol, College, Oxford, 2011.
- Stefan Galeski Fellowship, 2009.

Further funding

- The Wellcome Trust Clinical Research Training Fellowship (three years).
- Oxfordshire Health Services Research Committee Fellowship (one year).

Surgically reversible dementia – a magnetic resonance imaging model of pathophysiological changes



NICOLE KEONG

Fellowship/sponsor

Joint College/Dunhill Medical Trust Research Fellowship.

Supervisor

Professor John D Pickard, Mr Stephen J Price and Professor Jonathan H Gillard.

Site of work

Department of Neurosurgery, University of Cambridge.

Publications

• Keong NC, Czosnyka M, Pickard JD. Clinical Evaluation of Adult Hydrocephalus. In: Winn RH ed. *Youmans Neurological Surgery*. 6th edn. Philadelphia: WB Saunders; (in press).

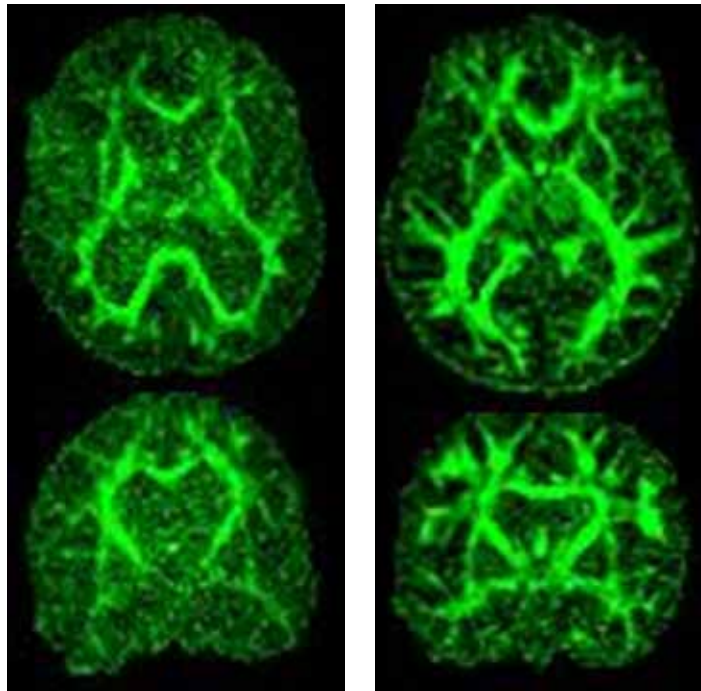
Presentations

• *White matter injury patterns in normal pressure hydrocephalus*. Society of British Neurological Surgeons; April 2010; Cambridge, UK.
• *Modelling normal pressure hydrocephalus using diffusion tensor imaging*. International Society for Hydrocephalus and Cerebrospinal Fluid Disorders; September 2008; Hannover, Germany.

Prizes

Tunku Abdul Rahman Centenary Fund Research Project Grant Holder, 2007–2008.

There is a type of dementia that can be reversed with surgery: normal pressure hydrocephalus. Studying why this type of dementia is reversible may make it possible to refine our surgical techniques to treat it.



Above: Nicole preparing for a patient scan in the 3-Tesla MRI suite.

Left: White matter wiring (coloured green) in a patient with normal pressure hydrocephalus (left) compared with an age-matched healthy volunteer (right). Note how stretched and thin the white matter has become in the patient's scan.

Normal pressure hydrocephalus affects up to 5% of the elderly population, causing memory loss, unsteadiness and urinary incontinence. It poses a clinical conundrum – patients deteriorate from cerebrospinal fluid build-up but the pressure inside the head remains normal. In addition, it is not understood why some patients have a greater degree of improvement or longer-lasting results than others. We hope that developing novel tools to understand the underlying disease mechanisms may allow us to predict which patients are likely to improve with surgery and also lead to at-risk patients being identified at an earlier stage than is currently possible.

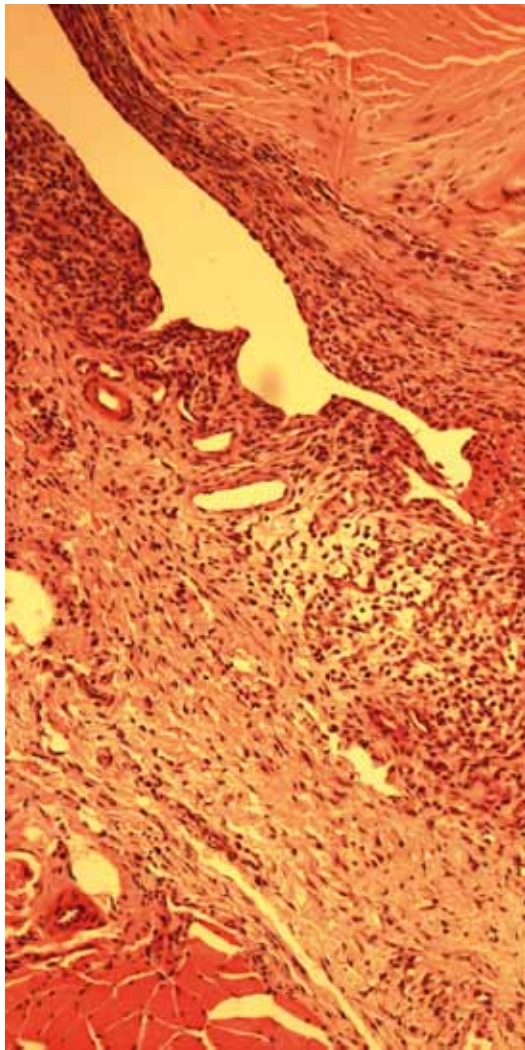
Specialised sequences of magnetic resonance imaging (MRI) brain scans are used before and after surgery. These allow us to measure changes in the white matter wiring, flow characteristics of cerebrospinal fluid and 'leakiness' of blood vessels in the affected brain. These changes are then correlated to clinical findings, such as gait disturbance and neuropsychology tests, as well as outcomes following surgery.

Comparisons of preoperative patients versus age-matched volunteers have demonstrated that patients have a typical profile of white matter changes. We have also found that imaging improvement in the early postoperative stages can be seen before any clinical change is noted. Work is now being carried out to correlate different types of clinical improvement, using imaging changes to look for patterns of reversibility.

Participants have been able to access more extensive testing and information as well as safer, more detailed imaging than clinically possible (MRI versus computed tomography scans). In some cases, subclinical complications were identified early, allowing patients to access treatment before they experienced a decline.

Novel therapeutics in the prevention of flexor tendon adhesion formation

Flexor tendon injuries are common with approximately 300,000 new cases per year in the USA. Adhesion formation (excess scarring) is a frequent problem following surgical repair.



Light microscopy (x40 magnification) showing a typical tendon adhesion lying between the tendon and the tendon sheath.

Flexor tendons are notoriously difficult to repair and the main complications are either tendon rupture or adhesion formation. Adhesions remain a problem despite many previous attempts at prevention. The overall aim of this study was to understand further the biology of tendon adhesion formation and to develop novel treatments targeting this process.

Three different flexor tendon cell types (core, surface and tendon sheath) were cultured and subjected to various assays using a growth factor (TGF- β) with or without the following two

treatments: epigallocatechin-3-gallate (EGCG) (an extract from green tea) and resveratrol (an extract from red wine).

Using an experimental model of flexor tendon adhesion formation, the two treatments (compared with control groups) were infiltrated into the flexor sheath of immobilised tendons. After two weeks the tendons were randomised to either mechanical or microscopic assessment of adhesion formation. Resveratrol showed the most promising results and it would be worthwhile investigating this further.

The 'tendon healing' project has been running at RAFT for over 10 years. My predecessor also investigated tendon adhesions but looked mainly at their structure and movement. This has helped my research in identifying the different types of adhesions that can form. I hope to pass on this research project to another research fellow at the Royal Free Hospital as there is further work that needs to be performed prior to clinical trials.

Finally, patients that develop tendon adhesions find this extremely disabling for them as the affected finger/s become stuck in a flexed position and the overall hand function is impaired. This obstructs most daily activities and normally affects their ability to work. It is hoped that this treatment could act as a suitable adjunct to tendon repair in the future and improve the lives of patients with tendon injuries.



Genetic analysis of tendon cells in the laboratory at the RAFT institute.



BEN KLASS

Fellowship/sponsor
Joint College/BSSH Research Fellowship with support from the Rosetrees Trust.

Supervisor
Mr AO Grobbelaar.

Site of work
The Restoration of Appearance and Function Trust (RAFT), Mount Vernon Hospital, Middlesex, and The Royal Free Hospital, London.

Publications

- Klass BR, Branford OA, Grobbelaar AO, Rolfe KJ. The effect of epigallocatechin-3-gallate, a constituent of green tea, on transforming growth factor-beta1-stimulated wound contraction. *Wound Repair Regen* 2010; 18: 80-88.
- Klass BR, Rolfe KJ, Grobbelaar AO. The in vitro flexor tendon cell response to TGF- β 1: A gene expression study. *J Hand Surg Am* 2009; 34: 495-503.

Presentations

- *A novel treatment to prevent flexor tendon adhesion formation.* The European Association of Plastic Surgeons; May 2009; Barcelona, Spain.
- *Resveratrol and tendon healing: More reasons to drink red wine.* The British Society for Surgery of the Hand; May 2008; Leicester, UK.

Structural remodelling, inflammation and the role of statins in atrial fibrillation following cardiac surgery



ANTONIOS KOURLIOUROS

Fellowship/sponsor

With support from the Rosetrees Trust and Pomfret Legacy.

Supervisor

Professor Marjan Jahangiri.

Site of work

St George's Hospital, London.

Publications

- Kourliouros A, Valencia O, Hosseini MT *et al.* Preoperative high dose atorvastatin for prevention of atrial fibrillation following cardiac surgery: a randomised controlled trial. *J Thorac Cardiovasc Surg* 2011; 141: 244–248.
- Kourliouros A, Karastergiou K, Nowell J *et al.* Protective effect of epicardial adiponectin on atrial fibrillation following cardiac surgery. *Eur J Cardiothorac Surg* 2011; 39: 228–232.

Presentations

- *Randomised controlled trial of intensive atorvastatin pretreatment for the prevention of atrial fibrillation following cardiac surgery.* Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS); March 2010; Liverpool, UK.
- *Protective effect of epicardial adiponectin release on atrial fibrillation following cardiac surgery.* European Association for Cardiothoracic Surgery; October 2009; Vienna, Austria.

Prizes

- John Parker Medal, SCTS, March 2010.
- Runner-up, Rosetrees Trust Essay Prize, 2009.

Further funding

St George's Charitable Foundation for one year.

Atrial fibrillation is the most common heart rhythm abnormality following cardiac surgery (20–40% occurrence), which leads to prolonged hospital stay and may increase early and long-term mortality.



Antonios (centre), his supervisor (far left) and the research team.

Atrial fibrillation (AF) is a common complication following cardiac surgery. The exact mechanism that causes AF is unknown; however, it appears that more than one factor contributes to its development and perpetuation. The objectives of this study were to:

- evaluate the role of statins in the prevention of postoperative AF
- examine the role of inflammation in the development of postoperative AF
- identify the potential susceptible substrate in the heart muscle (left atrium) of patients predilected to postoperative AF.

The preventative effect of statins on postoperative AF was examined through an observational study and randomised controlled trial (RCT). In order to decipher the role of inflammation in AF pathogenesis, circulating and locally produced cytokines were measured. Cardiac proteomics were also used to identify atrial structural changes contributing to AF.

Based on the observational study, patients receiving statins had a significantly lower incidence of postoperative AF compared with patients not receiving statins – this effect was dose-dependent. In the RCT, intensive treatment for seven days with high-dose statin conferred a non-significant reduction in postoperative AF when compared with a routine statin dose. Although systemic levels of pro-inflammatory

cytokines did not correlate with AF, local release of the anti-inflammatory hormone adiponectin from fat tissue surrounding the heart was increased in patients who remained in normal sinus rhythm after surgery. Metabolic dysfunction, oxidative stress and apoptosis preceded the development of AF, based on atrial proteomic analysis.

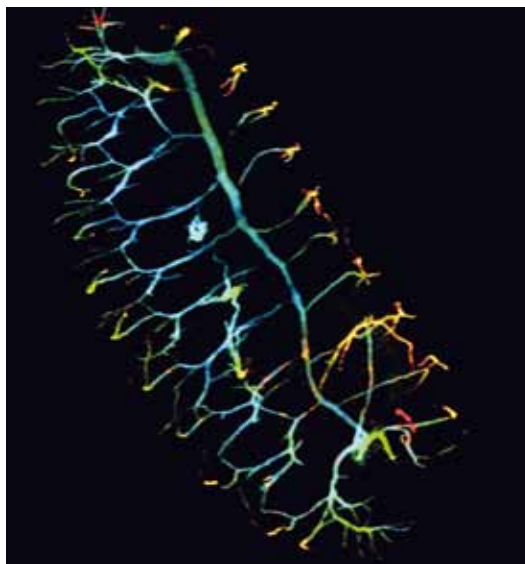
The findings from the statin study bear important clinical implications as they have been used for the development of recommendations for the pharmacological prophylaxis of AF. The lab-based component of this work has highlighted, for the first time, the role of epicardial fat in the development of the arrhythmia, whereas the proteomic study identified novel changes in the heart muscle that pre-exist and are possibly responsible for postoperative AF.



Antonios (centre) with two fellow researchers and registrars in cardiac surgery.

Investigating the role of sarco-endoplasmic reticulum Ca^{2+} -ATPase (SERCA) in prenatal lung development

Congenital diaphragmatic hernia (CDH) is as common as cystic fibrosis: more than one in three babies born with this condition will die, predominantly as a result of inadequate lung development.



Confocal microscopy 3D image of fruit fly (*Drosophila*) embryonic tracheal system – it is genetically homologous to the human lung and can be used as a model to investigate airway development.

Inadequate lung development causes death and disability to a large number of infants born prematurely or with birth defects such as CDH. As common as cystic fibrosis, CDH retains a mortality of around 40%, largely due to pulmonary manifestations of the disease. In an attempt to rescue prenatal lung growth in CDH, surgeons have trialled foetal surgery but the benefits are limited and new therapeutic strategies are required.

Previous work by our laboratory demonstrated that lung development is coupled to airway peristalsis (spontaneous contractility of the prenatal airway). This contractility is underpinned by calcium waves and is abnormal in lung hypoplasia. Calcium waves therefore appear important for normal lung development.

My work builds on this and investigates the role of a specific calcium channel, SERCA, on prenatal airway development. SERCA is a key regulator of cellular calcium levels and its function appears important in airway smooth muscle: SERCA dysfunction has already been demonstrated in asthma sufferers.

Using an animal model of prenatal airway development, we have demonstrated that SERCA inactivation in embryonic lung explants with cyclopiazonic acid halts airway peristalsis, lung growth and cell proliferation. Critically, these effects are both reversible and dose-dependent, indicating that this is not a simple toxic effect and SERCA has a key regulatory role in airway development. In order to explore the genetic pathways involved in this effect, we developed a fruit fly embryo model of airway development. The fruit fly provides unique and powerful genetic tools that allow us to inhibit SERCA in specific tissues and at specific time points in the developing embryo. Preliminary results indicate that there is a critical, threshold level of SERCA expression that is required for airway development.

Future work will explore the mechanisms behind these striking effects and aim to discover novel therapeutic targets that could be exploited prenatally to rescue lung growth. SERCA-modulating drugs are already being tested in the treatment of malaria, prostate cancer and heart disease: our work may ultimately provide further yield for these pharmaceutical initiatives.



Thoracoscopic image of an infant with CDH, demonstrating the defect in the diaphragm and bowel reduced back into the abdomen.



**NICHOLAS
LANSDALE**

Fellowship/sponsor
Clarke Legacy Research
Fellowship.

Supervisor
Mr EC Jesudason.

Site of work
Institute of Child Health,
Alder Hey Children's Hospital,
University of Liverpool.

Publications
Lansdale N, Alam S, Losty
PD, Jesudason EC. Neonatal
endosurgical congenital
diaphragmatic hernia repair:
a systematic review and
meta-analysis. *Ann Surg*
2010; 252: 20–26.

Presentations
Cyclopiazonic acid (CPA)
inhibition of sarco-endoplasmic
reticulum Ca^{2+} -ATPase (SERCA)
reduces, with similar dose-
dependency, prenatal airway
branching, peristalsis and cell
proliferation and modulates
gene expression required for
lung development. American
Thoracic Society; May 2010;
New Orleans, USA.

Further funding
The Wellcome Trust for two years.

Hypoxia-inducible factor pathway in varicose veins



CHUNG SIM LIM

Fellowship/sponsor

College Fellowship with support from the Rosetrees Trust.

Supervisor

Professor Alun H Davies.

Site of work

Charing Cross Hospital, Imperial College London, and Brigham and Women's Hospital, Harvard Medical School.

Publications

- Lim CS, Qiao X, Reslan OM *et al*. Prolonged mechanical stretch is associated with upregulation of hypoxia-inducible factors and reduced contraction in rat inferior vena cava. *J Vasc Surg* 2010; epub ahead of print.
- Lim CS, Davies AH. Pathogenesis of primary varicose veins. *Br J Surg* 2009; 96: 1,231–1,242.

Presentations

- *Activation of hypoxia-inducible factor (HIF) pathway in varicose veins*. The Vascular Society; November 2010; Brighton, UK.
- *Prolonged mechanical stretch is associated with upregulation of hypoxia-inducible factors and reduced contraction in rat inferior vena cava*. American Venous Forum; February 2010; Amelia Island, USA.

Prizes

- Runner-up, Cardiovascular Technology Symposium Poster Prize, 2010.
- Member-in-Training Scholarship, American College of Phlebology, 2008.

Further funding

- European Venous Forum Pump Priming Grant, European Society of Vascular Surgery.
- Graham-Dixon Charitable Trust, Royal Society of Medicine Venous Forum Travelling Fellowship.
- Simpson-Smith Travelling Scholarship.

Varicose veins affect one-third of the adult Western population and the complications consume 2% of the NHS budget in the UK.

Varicose veins are excessively dilated, tortuous and elongated veins. Patients with varicose veins suffer pain, itchiness, heaviness, ankle swelling, skin changes and ulceration. The mechanism of varicose veins formation remains unclear. Various biochemical and structural changes of the vein wall have been identified. These changes are thought to be contributed by stresses including oxygen deprivation (hypoxia) and mechanical stretch. The hypoxia-inducible factor (HIF) pathway is now known to be the 'master regulator' of genes involved in cell adaptation to stresses including hypoxia and mechanical stretch. The study aimed to compare the expression of HIF and target genes in varicose and non-varicose veins, and their regulation by hypoxia and mechanical stretch.

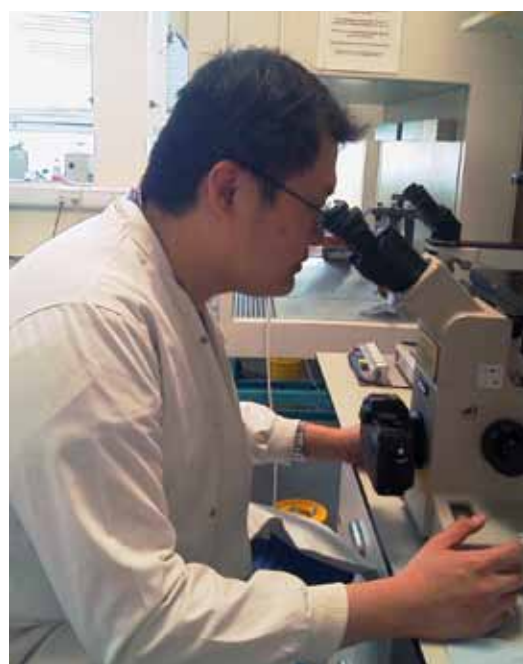


A venous ulcer.

Varicose and non-varicose veins retrieved surgically were processed to measure HIF and target genes expression using polymerase chain reaction, immunoblot and immunohistochemistry. Vein organ cultures were also prepared and subjected to normal oxygen tension or hypoxia. Veins were also subjected to prolonged mechanical stretch with and without HIF inhibiting drugs. The contractility of veins, HIF and target genes were then measured.

This study found that the expression of HIF, and genes regulated by HIF, was increased in

varicose compared with non-varicose veins. Hypoxia significantly increased HIF and target genes expression in vein organ cultures. Prolonged mechanical stretch significantly increased HIF expression in veins which was reversed by HIF inhibiting drugs.



Assessment of the histology of varicose and non-varicose vein specimens using light microscopy.

The study concluded that the HIF pathway is activated and may contribute to various biochemical and structural changes in varicose veins. Therefore, the HIF pathway is an attractive therapeutic target. Drugs targeting HIF are now being developed for the treatment of diseases including anaemia, cancer and rheumatoid arthritis. Developing a cost-effective drug treatment for varicose veins will benefit many patients, especially those not fit for surgery.

Preventing treatment resistance by altering tumour microenvironment in breast cancer

Breast cancer is one of the most common cancers in the UK. Approximately 125 people are diagnosed with the disease every day.

Recent research suggested that cancer cells and non-cancerous stromal cells interact with each other in the tumour microenvironment (stroma). This is known to enable a small population of cancer cells to survive drug treatment, leading to cancer recurrence. During this process, cancer cells activate stromal cells (fibroblasts) and attract immune cells (macrophages), which enhance the cancer-promoting quality of the stroma.

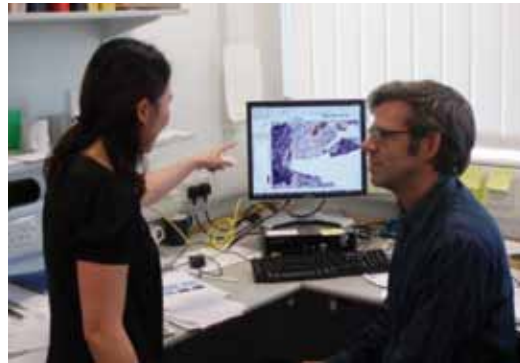


The protein-loading step of Western blotting method.

The aim of my project was to investigate the effect of targeting tumour microenvironment in breast cancer in both laboratory and clinical settings.

I examined the effect of experimental drugs, Src and FAK inhibitors on the tumour microenvironment in breast cancer cell line models. The growth of cancer cells and the level of stromal activation were measured using sulphorhodamine B assay and Western blotting method. In the clinical study, I investigated the effect of two-week treatment with the drugs letrozole and zoledronate in 110 breast cancer patients. Their tissue samples were analysed using tissue microarray (TMA) technique and antibody staining.

The use of Src and FAK inhibitors was effective in reducing overall cancer cell growth



Christina and Professor Landberg analysing the stromal activation level of a TMA sample.

and stromal activation. Most importantly, the growth of a selected population of cancer cells with stem cell-like properties, which is known to be more drug resistant, was also reduced. The next step will be to confirm these findings on cells extracted from patients' cancer samples.

In the clinical study, letrozole was effective in reducing cancer cell growth. Among patients who received zoledronate, lower immune cell number and lower stromal activation after treatment were linked to reduction in cancer cell growth. This suggests a beneficial inhibitory effect of the two drugs on the tumour microenvironment. These findings would support the design of larger clinical trials to investigate the effect of the two drugs in the long term with a view to future clinical use.



CHRISTINA LO

Fellowship/sponsor
Joint College/Association of Breast Surgeons (British Association of Surgical Oncology (BASO)) Research Fellowship with support from the Hong Kong Freemasons Overseas Trust.

Supervisor
Professor Nigel Bundred and Professor Goran Landberg.

Site of work
Paterson Institute for Cancer Research, University of Manchester.

Publications
Lo C, Busch S, Lee A *et al.* Stromal response to aromatase inhibition is associated with improved treatment response in breast cancer patients. *Eur J Surg Oncol* 2010; 11: 1,099–1,100.

Presentations

- *Stromal response to 14-day preoperative therapy in postmenopausal oestrogen receptor positive breast cancer.* San Antonio Breast Cancer Symposium; December 2010; Texas, USA.
- *Stromal response to aromatase inhibition is associated with improved treatment response in breast cancer patients.* BASO/ Association of Cancer Surgery; November 2010; London, UK.

A magic bullet for biliary cancer



SIOBHAN MCKAY

Fellowship/sponsor

Heslop Legacy Research Fellowship.

Supervisor

Mr Robert Hutchins, Mr Duncan Spalding and Professor Gerry Thomas.

Site of work

Hammersmith Hospital, Imperial College London.

Publications

- McKay SC, Unger K, Pericleous S *et al.* Array comparative genomic hybridization identifies novel potential therapeutic targets for cholangiocarcinoma. *HPB* 2010; 12: 1–468.
- McKay SC, Unger K, Sriraksa R *et al.* Differing copy number alteration profiles identified by array CGH in Thai intrahepatic cholangiocarcinoma related to prognosis. *Hepatology* 2010; 52 (Suppl 1): 945A

Presentations

- *Cholangiocarcinoma: opening the door for molecular based prognostic testing?* European Hepato-Pancreato-Biliary Association; April 2011; Cape Town, South Africa.
- *Differing copy number alteration profiles identified by array CGH in Thai intrahepatic cholangiocarcinoma related to prognosis.* American Association for the Study of Liver Diseases: The Liver Meeting®; October 2010; Boston, USA.

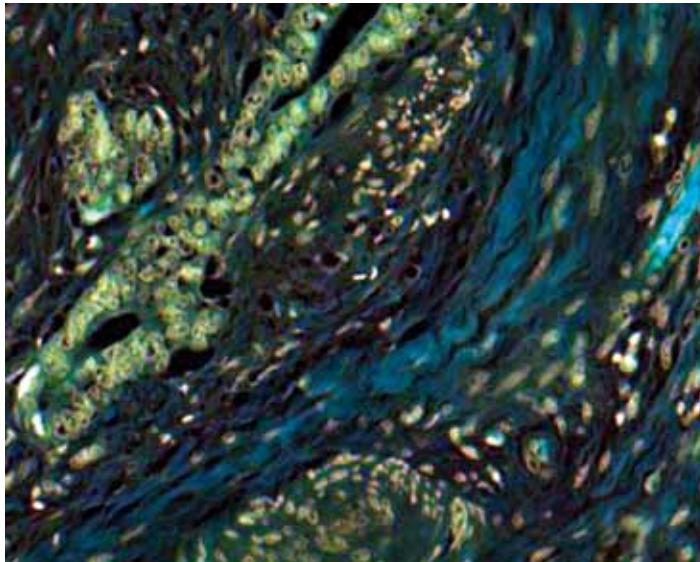
Prizes

- Stephan Galeski Fellowship, 2010.
- Best Scientific Presentation, London Surgical Symposium, 2010.

Further funding

HCA International; LAP Research UK; Barts and The London Charity; Liver and Pancreas Fund for three years.

Biliary cancer is the leading cause of death from primary liver cancer among women in the UK.



Biliary cancer cells.



Siobhan with a patient.

Biliary cancer (cholangiocarcinoma) is cancer of the bile ducts, which carry bile from the liver to the gut. It is a devastating cancer, with the number of cases diagnosed per year almost equalling the number that die per year. The numbers of cases are rising. Surgery provides the only chance of a cure; conventional chemotherapy has little or no effect. Four-fifths of people have too advanced disease at diagnosis to offer surgery. These people will only live for approximately six to nine months.

We have investigated DNA changes in biliary cancer by scanning the whole human genome to identify areas of DNA that have been gained or deleted. We fluorescently labelled the cancer DNA and used microchips containing the whole human genome to see the differences in fluorescence, which are caused by areas of gain or deletion in cancer DNA. We then mapped the cancer DNA changes to the specific region on the human chromosome.

As our understanding of cancer increases, we realise that it is an incredibly complex disease, caused by many abnormal cellular processes. New targeted treatments are in use in malignancies such as breast and stomach cancer

that specifically target these abnormal cellular processes. We have identified DNA changes in biliary cancer related to key cancer genes that can be specifically targeted with these new treatments, with the aim of shrinking the cancer to make more cases surgically operable.

With biliary cancer, surgery offers the only chance of cure. However, even with surgery some people have recurrence of their cancer and poor survival. We have identified specific signatures of DNA changes in biliary cancer that relate to good and bad survival. These DNA signatures can be utilised for a DNA-based test to help predict how long a patient is likely to survive with biliary cancer, helping people decide which treatments to undertake.



Siobhan working in the laboratory.

Information and informed consent for oesophageal cancer surgery

Oesophageal cancer patients want detailed information, for example, over 88% of patients thought it extremely important to know if the cancer could come back.

Gullet cancer is the seventh most common cancer worldwide and represents the sixth most common cause of death from cancer. Surgery forms the mainstay of a potential cure; however, evidence suggests that surgeons are not providing patients with adequate information prior to surgery, potentially reducing their ability to make fully informed choices.

Previous research has focused on patients' information needs in other cancers but little relates to oesophageal cancer and there is lack of qualitative research exploring information provision in practice.

The project aims were to i) investigate information needs of patients with potentially curable oesophageal cancer (gullet cancer); and ii) assess patients' understanding of information about the outcomes of surgery.

A questionnaire survey assessed patients' views of the importance of different types of information to be provided during treatment. A sample group were also interviewed to explore these views in more depth. A further study assessed patients understanding of graphical outcome data, presented in a hypothetical clinical scenario involving two treatments for oesophageal cancer. Interviews were audio-recorded, with a second, blinded assessor judging patient understanding.

The questionnaires were completed by 136 patients (response rate of 61%). Patients' highest reported need for information was related to data about the disease and treatment, and they wanted complex and sensitive information (eg concerning prognosis). Interviews revealed that information was required to aid coping strategies, reduce fear and improve expectations. Patients had a high level of understanding graphical outcome data with 87% correctly interpreting two outcomes and 64% being able to understand all four.

This research builds on work undertaken within the department to measure health-related

Right: Angus performing a gastroscopy.

Below: An oesophageal tumour.



quality of life outcomes in oesophageal cancer, providing methods to communicate these outcomes in clinical practice.

This long-term project will define baseline information that surgeons should tell all patients and a 'core disclosure' set, and develop evidence-based methods to communicate such information.

Gullet cancer is serious and survival is often less than a year from diagnosis. Surgical resection is the main chance of cure but benefits are balanced against the risks of complications and a potentially irreversible deterioration in quality of life.

This study helps inform patients of quality of life following surgery, allowing more patients to make informed treatment choices in keeping with their values.



ANGUS MCNAIR

Fellowship/sponsor
Sir Alan Parks Research Fellowship.

Supervisor
Professor Jane Blazeby.

Site of work
University of Bristol.

Publications

- McNair AG, Brookes ST, Davis CR *et al.* Communicating the results of randomized clinical trials: do patients understand multi-dimensional patient reported outcomes? *J Clin Oncol* 2010; 28: 738–743.
- McNair AG, Blazeby JM. Health-related quality of life assessment in gastrointestinal randomised trials: improving the impact on clinical practice. *Expert Rev Pharmacoecon Outcomes Res* 2009; 9: 559–567.

Presentations

- *The provision of information prior to oesophago-gastric cancer surgery.* Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; September 2010; Oxford, UK.
- *Informed consent in surgical oncology: do patients know what they are signing up for?* National Cancer Research Institute; November 2010; Liverpool, UK.

Further funding
National Institute for Health Research for three years.

Manipulating NF-kappa oscillations and linked pathways to promote cell death in neuroblastoma primary cultures and cell lines



DHANYA MULLASSERY

Fellowship/sponsor
Joint College/Medical Research Council Research Fellowship.

Supervisor
Professor Michael White, Professor Paul Losty and Mr Edwin Jesudason.

Site of work
Centre for Cell Imaging and Academic Paediatric Surgery Unit, University of Liverpool.

Publications

- Mullassery D, Dominici C, Jesudason EC *et al.* Neuroblastoma: contemporary management. *Arch Dis Child Educ Pract Ed* 2009; 94:177–185.
- Mullassery D, Horton CA, Wood CD, White MR. Single live-cell imaging for systems biology. *Essays Biochem* 2008; 45: 121–134.
- Salim A, Mullassery D, Pizer B *et al.* Neuroblastoma: a 20-year experience in a UK regional centre. *Pediatr Blood Cancer*; (in press).

Presentations

- *Role of NF-Kappa B signalling in neuroblastoma.* Society of Academic and Research Surgery; January 2011; Dublin, Ireland.
- *Role of NF-Kappa B in cell fate decisions in neuroblastoma.* National Cancer Research Institute; November 2010; Liverpool, UK.

Neuroblastoma is the most common lethal solid tumour in childhood, accounting for 15% of all paediatric deaths from cancer.



Dhanya assisting Professor Losty in the resection of a thoracic neuroblastoma.

Neuroblastoma is a devastating childhood cancer where survival remains dismally poor (<50%) despite advances in chemotherapy, radiotherapy and heroic efforts to achieve ‘complete’ surgical resection of the offending tumour. Proteins within cells belonging to the ‘NF kappa B’ (NF-κB) family are known to aid several types of cancer develop resistance to chemotherapy. The aims of the project were to i) investigate the pivotal role of the NF-κB pathway in neuroblastoma; and ii) from these investigations seek to manipulate a ‘molecular switch’ that would make the cancer cells more vulnerable to chemotherapy.

Using state-of-the-art ‘live cell’ imaging, we observed persistent ‘cycling’ and expression of the NF-κB proteins in different parts of the cancer cell that resulted in neuroblastoma cells evading the effects of chemotherapy. Crucially, inactivation of NF-κB cycling using chemotherapeutic drugs, or biological agents, resulted in tumour cell death, with combination regimens of an NF-κB inhibitor and chemotherapy agents significantly increasing cell death compared with chemotherapy

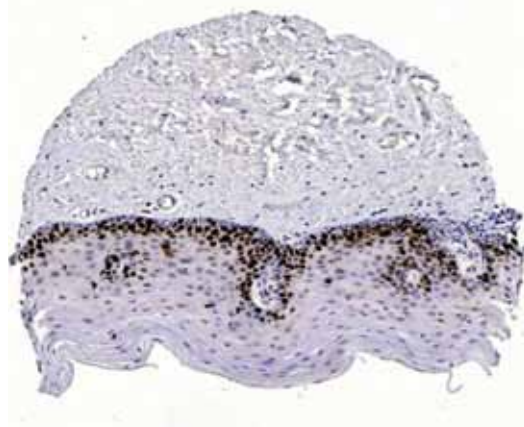
treatment alone. Further work revealed that NF-κB inhibitors blocked another cell death pathway involving the critical regulatory protein p53 – a tumour-suppressor gene.

For the first time primary cell cultures of neuroblastoma derived from tumour resections from patients have also been successfully maintained and studied, validating novel findings from the experiments on commercial cell lines as mentioned above. This vital resource of primary neuroblastoma cultures will form the basis for further screening the efficacy of new pharmacological agents targeted against this aggressive childhood malignancy. Taking the work further, these studies will need to be performed in a neuroblastoma xenograft model to provide ‘proof of principle’ concepts before embarking on phase-one clinical trials in humans.

Improving patient selection and management in oral and laryngeal dysplasia

Accurately predicting which of the 20% of oral or laryngeal dysplasia lesions will progress to cancer is not currently possible. This means 80% of patients may be overtreated, with subsequent unnecessary morbidity.

Head and neck cancer (HNC) is the sixth most prevalent cancer type worldwide. These tumours carry significant morbidity, including problems with speech and voice production, swallowing, pain and disfigurement. Some patients may present with 'dysplasia' – a precancerous condition that may develop into HNC in around 20% of cases. It is not possible to predict which lesions will progress, meaning around 80% of patients may potentially be overtreated. Furthermore, the only treatment for these potentially malignant lesions is surgery, which may have disabling functional consequences.



Oral dysplasia slide showing positively stained cells with Ki67 antibody, (cells stained dark brown).

The first aim of this project is to improve identification of which dysplasia lesions are likely to progress to cancer, thereby allowing more targeted treatment. Archived tissue samples from patients with known clinical outcome, ie progression to cancer or not, have been analysed for the levels of certain biomarkers in them. Biomarkers are proteins that can be differentially expressed in cancer, pre-cancer and normal tissue. Comparison of the biomarker level with the clinical outcome in these tissues may reveal certain biomarkers that can have a predictive ability. Although there are many studies on the level of individual biomarkers in dysplasia tissue, very few have examined how these levels might

predict progression to cancer. Those that have done this have been on much smaller numbers.

The second aim is to study new, non-surgical therapies that may prevent these pre-cancerous lesions from transforming to cancer and have lower morbidity than current surgical therapies. A clinical trial has been set up and is currently still examining the role of an aspirin mouthwash in patients with oral dysplasia.

This project is part of an ongoing research program. The results will help direct a much larger multi-centre trial that has already gained ethical approval and is currently being opened.



Paul preparing dysplasia tissue for sectioning and staining with antibodies.



PAUL NANKIVELL

Fellowship/sponsor
Freemasons Grand Lodge 250th Anniversary Fund Fellowship.

Supervisor
Mr Hisham Mehanna and Professor Janet Dunn.

Site of work
Institute of Head and Neck Studies, University Hospitals Coventry and Warwickshire NHS Trust.

Publications

- Nankivell PC, Weller MD, McConkey C *et al.* Biomarkers in laryngeal dysplasia: a systematic review. *Head Neck*; epub ahead of print.
- Weller MD, Nankivell PC, McConkey C *et al.* The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case series and meta-analysis. *Clin Otolaryngol* 2010; 35: 364–372.

Presentations

- *Comparison of the prognostic ability of the WHO and binary oral dysplasia grading systems.* American Head and Neck Society; October 2010; Arlington, USA.
- *Treatment and follow-up of laryngeal dysplasia – a systematic review and meta-analysis.* European Head and Neck Society; March 2010; Athens, Greece.

Extracorporeal membrane oxygenation (ECMO) to ameliorate hepatocyte ischaemia reperfusion injury after non-heart-beating organ donation



MOHAMED NOORMOHAMED

Fellowship/sponsor
Shears Northern
Research Fellowship.

Supervisor
Mr SA White and Dr MC Wright.

Site of work
Institute of Cellular Medicine,
Newcastle University.

Publications

- Ray C, Kanwar A, Noormohamed MS *et al.* Securing the aorta for organ perfusion in donation after cardiac death donors; novel techniques and a cautionary tale. *Transpl Int* 2009; 22: 856–857.
- White SA, Noormohamed MS, Robinson S, Manas DM. Methods of surgical haemostasis in liver surgery. *Clin Risk* 2009; 15: 151–152.

Presentations

- *Extracorporeal membranous oxygenation in a porcine non-heart beating liver model – a valuable tool for improved hepatocyte viability.* Society of Academic and Research Surgery; January 2010; London, UK.
- *Porcine model of extra-corporeal membrane oxygenation (ECMO) in uncontrolled non-heart beating donor (NHB): the effect on liver viability.* European Society for Organ Transplantation; August; Paris, France.

Further funding
Liver NORTH for one year.

There were 371 patients on the liver transplant list as of 31 March 2010, an 11% increase from 2009. There were 706 deceased liver donors (4% increase from 2009) and 679 transplants (3% increase from 2009).

Extracorporeal membrane oxygenation (ECMO) is an artificial blood circulating process used in heart–lung bypass operations to maintain blood flow, simulating normal heart and lung functions. The aim of this study was to evaluate the use of ECMO to decrease organ preservation injury in the non-heart-beating donor liver. The questions to be answered were as follows:

1. Does ECMO decrease preservation injury and improve the biochemical markers of liver injury?
2. Does ECMO improve the quality of isolated liver cells (hepatocytes) after preservation injury?
3. Does ECMO reduce cell death by minimising preservation injury?

A randomised series of animal models were allocated into three groups and euthanised. Two groups underwent preservation for two hours either by cooling with ice-cold fluid or using ECMO. Following this, the livers were removed and washed with a preservation fluid to clear the organ of any blood. To simulate an actual liver transplant we created another simple circulation circuit, which pumped blood and oxygen into the livers, which were placed in bowls at normal body temperature conditions. This recirculation was carried out for two hours then the liver cells were isolated to compare the viability of the cells.

The findings to date were in support of the ECMO group. The liver functions were significantly better and the isolated liver cells had better viability, seeding efficiency and an increased trend in preserving cell energy status. The research has shown that by using ECMO the liver can be better preserved and even marginal donors can be utilised, which will certainly increase the number of livers available for transplant, leading to decreased waiting times and deaths.

My project has reached a stage where an animal transplant model is being carried out to evaluate the preservation technique to give

us more evidence and insight of this intricate process, before translating into clinical practice.



Insertion of tube into blood vessels and tissue thermometer to measure temperature.



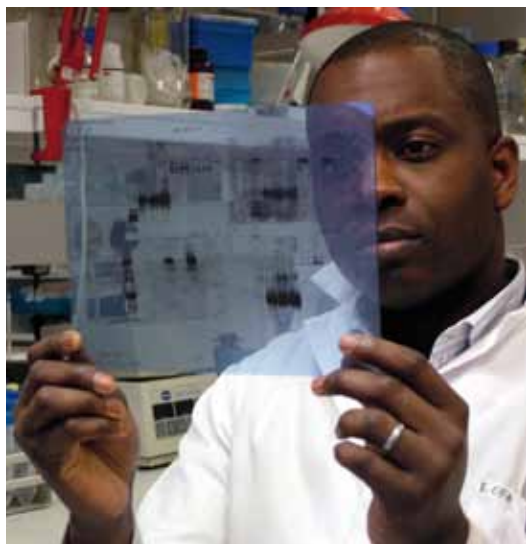
Liver removed and washed with perfusion fluid.



Liver in the circulation circuit pumped with blood and oxygen.

Fluorescent biosensor-based, predictive imaging techniques for understanding epidermal growth factor receptor signalling in head and neck cancer

More than 50% of head and neck cancer patients present with locally advanced (stage III or IV) disease, with a five-year survival rate ranging from 15–60% depending on the anatomical subsite.



Left: Enyinnaya analysing an experiment to detect proteins of interest in head and neck cancer cells (Western blotting method).

Below: Coronal computed tomography scan of patient with advanced left oropharyngeal (tongue base) cancer and cervical lymph node metastasis.



Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world and patients with advanced or recurrent disease currently have a very poor prognosis, usually surviving for no more than 6–12 months. Elevated levels of a cell surface protein known as the epidermal growth factor receptor (EGFR) have long been identified as a possible cause of HNSCC but drugs developed to block this receptor have not been as successful as anticipated, most likely due to the complex interaction of signalling proteins that promote cancer cell survival. One of these proteins is Cdc42. My research focuses on the activity of Cdc42 and how it may prevent anti-EGFR drugs from working.

I used the novel optical imaging techniques of fluorescence resonance energy transfer (FRET) and multiphoton fluorescence lifetime imaging microscopy (FLIM) to analyse the location and strength of protein–protein interactions in head and neck cancer cells. Using the Cdc42 FRET biosensor Raichu-Cdc42, as well as a protein pull-down assay for endogenous Cdc42, cancer cells treated with small molecule EGFR tyrosine kinase inhibitors (TKIs) had significantly elevated Cdc42 activity, compared with untreated cells.

This result suggests that a positive feedback loop between EGFR and Cdc42 may occur in response to EGFR inhibition with TKIs, which would have implications for receptor trafficking and may account for resistance to anti-EGFR therapy currently observed in the clinic.

In addition, using gene-silencing techniques and carrying out experiments with specialist bioinformatics knowledge to identify proteins that interact with Cdc42, I have demonstrated that the protein MAPK8 may be involved in regulating Cdc42 activity. MAPK8, like Cdc42, serves as an integration point for multiple biochemical signals and has a particular role in controlling cell death (apoptosis).

This research contributes to our understanding of the mechanisms of resistance to targeted drug therapy for head and neck cancer. It may allow us to predict patients most likely to respond to treatment and will thus improve patients' quality of life because they are not exposed to unnecessary side effects. Further work is ongoing from my research to decipher the complex interacting proteins involved in EGFR signalling in HNSCC.



ENYINNAYA OFO

Fellowship/sponsor
Enid Linder Foundation
Research Fellowship.

Supervisor
Professor Tony Ng and Mr
Jean-Pierre Jeannon.

Site of work
Kings College and Guy's and St
Thomas' Hospitals, London.

Presentations
*Elevated Cdc42 activity as
a resistance mechanism to
lapatinib and AG1478
treatment in squamous cell
carcinoma of the head and
neck.* American Head and
Neck Society; October 2010;
Arlington, USA.

Further funding
• National Institute of Health
Research/King's College
London/Guy's and St Thomas'
Charity Comprehensive
Biomedical Research Centre.
• Wellcome Trust Clinical
Research Fellowship.
• Dimpleby Cancer Care
Research Fellowship.

Improving outcomes in post cardiopulmonary bypass renal failure: targeting endothelial dysfunction



NISHITH PATEL

Fellowship/sponsor
Freemasons Grand Lodge 250th Anniversary Fund Fellowship.

Supervisor
Mr Gavin Murphy and Professor Gianni Angelini.

Site of work
Bristol Heart Institute, University of Bristol.

Publications

- Patel NN, Rogers CA, Angelini GD, Murphy GJ. Pharmacological therapies for the prevention of acute kidney injury following cardiac surgery: a systematic review. *Heart Failure Rev*; in press).
- Patel NN, Toth T, Jones C *et al.* Prevention of post cardiopulmonary bypass acute kidney injury by endothelin-A receptor blockade. *Crit Care Med* 2011; epub ahead of print.

Presentations

- *Sitaxsentan sodium, an endothelin-1 receptor antagonist, prevents post-cardiopulmonary bypass acute kidney injury in a novel pre-clinical recovery model.* American Heart Association; November 2009; Orlando, USA.
- *Transfusion of stored leucodepleted red blood cells causes cardiac, pulmonary and renal dysfunction and injury.* European Society of Intensive Care Medicine; October 2009; Vienna, Austria.

Prizes

- Margaret Kenwright Young Scientist Award, British Blood Transfusion Society, 2009.
- Eli Lilly Award, Intensive Care Society, 2008.

Further funding
National Institute of Health Research for three years.

Kidney failure affects one in three patients undergoing cardiac surgery and is associated with a devastating four-fold increased risk of death, a doubling of healthcare costs and prolonged hospital stays.



Nishith receiving the Margaret Kenwright Young Scientist Award in 2009.

Our understanding of acute kidney injury (AKI) is currently poor and there is a lack of appropriate animal models. Our aim was therefore to develop an experimental animal model that allows us to characterise the effects of cardiac surgery and red blood cell (RBC) transfusion on kidney function and injury and to assess the protective effect of the drugs sitaxsentan sodium and sildenafil on preventing AKI.

We exposed animal models to the heart–lung machine (cardiopulmonary bypass), similar to that seen in cardiac surgical patients. We then administered various drugs or RBC transfusion to the animal models and examined the kidneys under a microscope to determine the effects of the interventions at a cellular level.

We have made several new findings that have advanced knowledge and understanding in this field and will provide numerous benefits to patients and the NHS. We have developed a new animal model of post cardiac surgery AKI with significant similarities to cardiac surgical patients. It is therefore a platform for the development of novel therapeutic strategies.

Using this model we have discovered that cardiac surgery induces kidney injury by damaging endothelial cells on arterial walls and

increasing levels of hormones such as endothelin. Using drugs such as sitaxsentan sodium (to block endothelin) or sildenafil (to protect endothelial cells) we prevented post cardiac surgery AKI and also demonstrated beneficial effects in other vital organs, such as the lungs and heart.

We also found that RBC units degenerate over their storage period with accumulation of toxic agents within the blood bag. Transfusion of this stored blood causes kidney and lung injury in our animal model and this injury is mediated through activation of platelets. Targeting these mechanisms will help us improve the safety of blood products and thus improve clinical outcomes in patients.



Nishith (right) receiving the award for the best research poster presentation at the Intensive Care Society 'State-of-the-Art' meeting in 2010.

Oncolytic virotherapy in an isolated limb perfusion model of advanced extremity malignancy

Isolated limb perfusion represents a method of avoiding amputation in patients with unresectable melanoma or sarcoma, and the addition of oncolytic virus aims to extend this approach to more patients.



Tim (left) discussing results with a lab colleague.

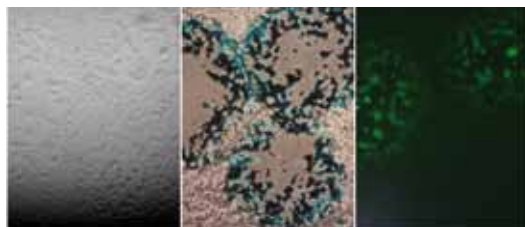


Image of virus killing cancer cells.

Melanoma is the most aggressive form of skin cancer and is increasing in incidence worldwide. Sarcoma is a rare tumour type but, in patients with unresectable tumours, amputation leads to significant functional and cosmetic deficit while having no effect on survival.

Isolated limb perfusion (ILP) involves administering high-dose chemotherapy directly to the affected limb without exposing the rest of the body to its toxic effects. It is an established technique that can be used in patients with advanced (stage 3b or above) melanoma and otherwise unresectable sarcoma to gain control of disease and avoid amputation. Recently, increasing interest has developed in oncolytic

viruses, those that show the ability to infect and destroy tumour cells selectively. In addition, such infection can alert the immune system to the presence of cancer. Therefore, combining ILP with viruses may not only increase treatment response rates in the limb but also provide a mechanism to affect other sites of disease.

So far we have shown that this approach is feasible, without increasing the toxicity of treatment. Combining viruses with existing regimens slows down the growth of tumours and can result in a cure. The next steps are to identify the best possible agent and treatment strategy before progressing into human trials.

This project indicates the potential of this approach for these tumours; should these results be replicated in human patients the capabilities of surgeons treating these devastating diseases will be hugely expanded. Fewer patients will require amputation, with its attendant effects on their quality of life.



TIM PENCAVEL

Fellowship/sponsor

Freemasons Grand Lodge 250th Anniversary Fund Fellowship.

Supervisor

Dr Kevin Harrington and Mr Andrew Hayes.

Site of work

The Institute of Cancer Research/ Sarcoma/Melanoma Unit, The Royal Marsden Hospital.

Publications

- Pencavel T, Seth R, Hayes A *et al*. Locoregional intravascular viral therapy of cancer: precision guidance for Paris's arrow? *Gene Ther* 2010; 17: 949–960.
- Pencavel T, Strauss DC, Thomas G *et al*. Does the two-week rule pathway improve the diagnosis of soft tissue sarcoma? A retrospective review of referral patterns and outcomes over five years in a regional sarcoma centre. *Ann Royal Coll Surg Engl* 2010; 92: 417–421.

Presentations

- *Neoadjuvant therapy for soft-tissue sarcomas – what and when? Isolated limb perfusion.* European MusculoSkeletal Oncology Society; May 2010; Birmingham, UK.
- *Isolated limb perfusion and viral therapy: precision guidance for Paris's arrow?* British Sarcoma Group; February 2010; London, UK.

Prizes

2nd Prize for Oral Presentation, London Surgical Symposium, 2009.

Further funding

The Sarcoma Trust for consumables up to £30,000 over two years.

The role of biofeedback in improving anal continence after anterior resection in the elderly



SOPHIE PILKINGTON

Fellowship/sponsor

Joint College/Dunhill Medical Trust Research Fellowship.

Supervisor

Miss Karen P Nugent.

Site of work

University Surgical Unit, Southampton General Hospital.

Presentations

- *Anal incontinence before anterior resection.* American Society of Colon and Rectal Surgeons; June 2008; Boston, USA.
- *Loss of anal continence after anterior resection.* UK Continence Society; April 2009; Swansea, UK.

Prizes

- First Prize for poster presentation, Southern Pelvic Floor Conference, 2009.
- Royal Society of Medicine Travelling Fellowship (Coloproctology), 2009.

Rectal cancer is the fifth most common cancer in the UK. Approximately 80% of those diagnosed will have major surgery and bowel leakage is a persistent problem for 15% of those operated on.



Sophie with her supervisor investigating patients with bowel leakage in Sweden.



Sophie operating with her supervisor on a patient who has bowel leakage.

Rectal cancer is common; in England and Wales, 10,400 people are diagnosed annually and most require surgery. Although the first priority of surgery is to cure cancer, the overall five-year survival is only 53%. In addition to a cure, patients also expect a good quality of life with normal bowel, bladder and sexual function.

The aim of this project was to assess the impact of major rectal resection on bowel leakage and quality of life, and to determine whether routine biofeedback (exercises to improve bowel function) enhanced the outcome of surgery. A trial was carried out on 121 people undergoing major rectal resection. They were randomly assigned to receive standard treatment or additional biofeedback training. Follow-up to one year was completed by 89 participants.

Before surgery, 17% of participants had severe bowel leakage due to poor anal function or presence of cancer. At three months after surgery, 27% reported leakage, with a negative impact on quality of life. This improved but 15% still complained of severe leakage at one year. The most reliable predictor of long-term bowel leakage was leakage at three months.

Biofeedback is a useful therapy for reducing bowel leakage. Previous studies suggest that it is effective in up to 90% of people with leakage due to other causes. Although I did not

demonstrate an overall improvement after surgery with biofeedback training, there may be a role for targeted biofeedback. In particular, my study found that participants with severe bowel leakage before surgery did better with biofeedback. These findings have led to further research that targets rectal cancer patients with bowel leakage.

Bowel leakage is one of the most feared complications after surgery for rectal cancer. Biofeedback training is a promising therapy for reducing this debilitating condition. However, some patients may have a better quality of life with a permanent stoma.

Investigating the feasibility of randomised clinical trials in breast reconstruction

Breast reconstruction is offered to improve quality of life for 40% of the 45,000 women diagnosed with breast cancer each year in the UK who face the loss of their breast.



Left: Delayed breast reconstruction using skin and muscle from the back (latissimus dorsi flap) with a nipple tattoo.

Right: A patient following mastectomy.

Women are offered breast reconstruction to improve their quality of life but choosing which type of surgery will best suit their needs can be difficult as several procedures exist, from simple implants to complex operations using abdominal fat to recreate the breast.

To help with these decisions, women need impartial information about the advantages and disadvantages of surgery. The best source of such information is a randomised clinical trial (RCT), in which treatments are allocated randomly by a computer, allowing various treatments to be compared fairly.

Currently, RCTs in breast reconstruction have been limited as it has been suggested that neither patients nor surgeons would accept randomisation. This project therefore aimed to establish whether RCTs in breast reconstruction are possible by summarising the published literature and exploring patients' and health professionals' views of randomisation.

Reviews of the cosmetic, clinical and patient-reported outcomes of breast reconstruction demonstrated a lack of high-quality information to inform decisions. 62 in-depth interviews exploring the attitudes of patients and healthcare professionals to randomisation then revealed that 20% of women would participate in trials

comparing different types of reconstruction and a further 40% would participate in trials comparing aspects of their chosen procedure. The majority of healthcare professionals felt that randomisation to different types of reconstruction was inappropriate as women should make their own decisions but approximately half considered that randomisation within procedure types was both acceptable and feasible.

RCTs in breast reconstruction are therefore needed and both women and their healthcare professionals are prepared to participate in appropriately designed trials. Future research will establish whether a multi-centre trial is possible to allow future patients to make fully informed decisions about reconstructive surgery.



SHELLEY POTTER

Fellowship/sponsor
Dr MP Starritt Research Fellowship.

Supervisor
Professor Jane Blazeby.

Site of work
Bristol Royal Infirmary.

Publications

- Potter S, Brigid A, Whiting PF *et al.* Reporting clinical outcomes of breast reconstruction: A systematic review. *J Natl Cancer Inst* 2011; 103: 31–46.
- Potter S, Harcourt D, Cawthorn SJ *et al.* Assessment of cosmesis after breast reconstruction surgery: A systematic review. *Ann Surg Oncol*; (in press).

Presentations

- A systematic review of methods for cosmetic outcome assessment in breast reconstruction. British Association of Plastic Reconstructive and Aesthetic Surgery (BAPRAS); June 2010; Sheffield, UK.
- How do cosmetic outcomes of breast reconstruction influence recommendations for surgery? BAPRAS; June 2010; Sheffield, UK.

The contribution of type 1 insulin-like growth factor receptor signalling to alkylating drug resistance and survival in malignant melanoma



ROGER RAMCHARAN

Fellowship/sponsor
Blond McIndoe Research Fellowship.

Supervisor
Dr Valentine Macaulay and Professor Mark Middleton.

Site of work
Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford.

- Presentations**
- Can we improve on malignant melanoma treatment? Introducing the IGF1R. *British Association of Plastic Reconstructive and Aesthetic Surgery*; June 2010; Sheffield, UK.
 - *The contribution of the IGF1 Receptor to alkylating drug resistance in malignant melanoma*. European Plastic Surgery Research Council; August 2009; Hamburg, Germany.

Further funding
Department of Medical Oncology, University of Oxford, and Oxford Biomedical Research Centre for six months.

The incidence of malignant melanoma is rising faster than any other cancer in the world. Once it spreads, there is no effective treatment.



Roger using cell colony counting equipment to quantify the killing of melanoma cells.

Melanoma is an aggressive type of skin cancer that can develop following excessive sun exposure, especially in fair-skinned individuals. Its incidence is rising faster than any other cancer worldwide, with 10,000 new cases diagnosed annually in the UK. Surgery remains the main hope for cure, though mortality rates continue to rise. Once melanoma spreads, no form of treatment has shown any promise. Of the agents available, temozolomide (TMZ), a DNA-damaging agent, has shown the most promise with response rates of only 15 to 20%. These responses have, however, been short lived and there is urgent need for new therapeutic options.

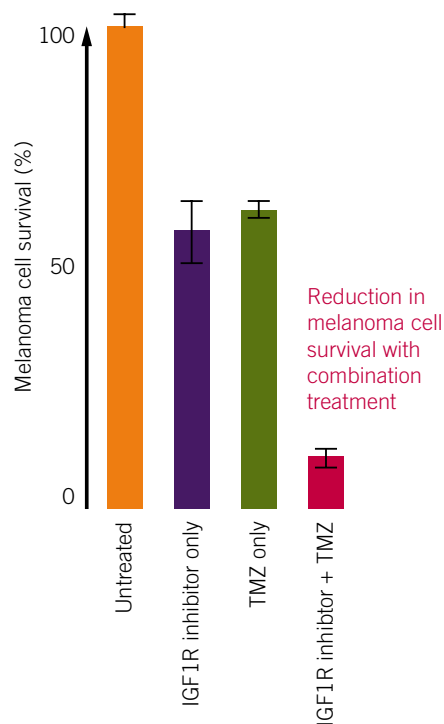
Growth factor receptors have been found to be important in many cancers and have led to the development of now popular drugs such as Herceptin®. Our laboratory explores another of these receptors, the type 1 insulin-like growth factor (IGF1R) in cancer. IGF1R is more abundant in many cancers, including melanoma, and promotes cancer growth and survival making it a potentially attractive therapeutic target.

We are investigating whether blocking the IGF1R can improve the effect of the standard chemotherapy, ie temozolomide, in melanoma.

Our results show that we can improve the destruction of melanoma cells by combining an

IGF1R inhibitor with temozolomide *in vitro*. We are exploring the mechanism behind this beneficial combination treatment in order to understand further the biology of this complex disease. We will explore whether IGF1R is enhancing the DNA-damaging effects of temozolomide, in collaboration with the Paterson Institute of Cancer Research, Manchester.

The results are promising and we are in the process of carrying out pre-clinical testing of this new combination therapy in animal models to determine the safety and efficacy. If the results continue to be favourable, this novel combination therapy should be trialled in human melanoma sufferers in the next couple of years.



We can reduce melanoma cell survival using an IGF1R inhibitor alone (purple) or TMZ (green) but combining these agents significantly improves melanoma cell killing (red).

Regulation of human epidermal stem cells in squamous neoplasia

Head and neck cancer is the sixth most common cancer worldwide, and despite improvement in morbidity, mortality has not changed in the last three decades.



Amit performing high-resolution microscope studies of human skin cancer growth.



Preoperative reconstruction access planning for a patient with a parotid tumour.

Head and neck cancer accounts for over 500,000 new cancer cases each year. While there have been significant improvements in surgical care, resulting in better functional and psychological outcomes, the rate of deaths has not changed significantly. Identification of molecular-targeted therapies will focus on the most treatment-resistant cells, leading to improved survival and identifying future research avenues in other cancers.

My research aims to develop a quantitative model that predicts head and neck cancer growth and identify the mechanisms by which newer targeted drugs can change the balance of this growth.

Currently it is thought that cancers originate from 'stem cells', which are long-lived cells that accumulate the genetic changes required to transform from a normal cell to a cancer-initiating cell. Pilot experiments on human head and neck cancer cultured in the laboratory reveal that there is a mixture of cell types including large-colony-forming cells (likely stem cells) and smaller-colony-forming cells. Studying quantitative growth patterns within this cellular variation, using collaborative techniques from statistical physics,

can show us the cell of origin (and therefore identify specific targets) within this cancer.

This work builds on previous work from our laboratory that defined quantitative growth modelling on animal and human skin. This work has shown stem cells remain dormant while a more committed progenitor cell maintains day-to-day tissue turnover. Stem cells are mobilised in the event of injury and my line of investigation will elucidate their role in cancer. This is a long-term project with cross-disciplinary collaboration between statistical physicists, oncologists and head and neck surgeons.



AMIT ROSHAN

Fellowship/sponsor
College Research Fellowship with support from the Rosetrees Trust.

Supervisor
Dr Phillip H Jones.

Site of work
MRC/Hutchison Research Laboratories, Cambridge.

Presentations
A quantitative predictive model of skin behaviour: homeostasis, wound healing and cancer.
British Association of Plastic and Reconstructive Surgery; December 2010; London, UK.

Prizes
Cambridge Cancer Centre Clinical Research Fellowship, 2010.

Further funding
Cambridge Cancer Centre Research Fellowship for three years.

Multi-factorial risk stratification in atherosclerotic carotid stenosis



JOSEPH SHALHOUB

Fellowship/sponsor
Rosetrees Trust Research Fellowship.

Supervisor
Professor Alun H Davies.

Site of work
Imperial Vascular Unit,
Charing Cross Hospital.

Publications

- Owen DR, Shalhoub J, Miller S *et al.* Inflammation within carotid atherosclerotic plaque: assessment with late-phase contrast-enhanced US. *Radiology* 2010; 255: 638–644.
- Shalhoub J, Owen DRJ, Gauthier T *et al.* The use of contrast enhanced ultrasound in carotid arterial disease. *Eur J Vasc Endovasc Surg* 2010; 39: 381–387.

Presentations

- *Molecular characterisation of inflammation in human carotid atherosclerosis by multi-analyte profiling and non-invasive imaging with late-phase contrast enhanced ultrasound.* Japanese Society for Vascular Surgery; May 2010; Omiya, Japan.
- *Novel late phase contrast enhanced ultrasound to assess inflammation within the carotid atherosclerotic plaque in humans.* The Vascular Society of Great Britain and Ireland; November 2009; Liverpool, UK.

Prizes

- Royal Society of Medicine Glaxo Travelling Fellowship.
- European Society for Vascular Surgery Japan Congress Travel Grant.

Further funding

- Circulation Foundation.
- Stroke Association.
- Graham-Dixon Charitable Trust.
- Peel Medical Research Trust.

60,000 strokes relating to narrowing of the carotid artery occur every year in the UK. A third of these patients die within a year. Of the remainder, some are left significantly disabled and often lose their independence.



Joseph scanning a patient.

People with carotid artery narrowing who have preceding, temporary warning signs are very likely to go on to have a stroke, while those who have no warning signs may or may not suffer a stroke in the future. Our objectives are to assist the prediction of individuals (without warning signs) at high risk of suffering a future stroke.

Microbubbles are bubbles engineered to be the same size as red blood cells, which are injected into a vein and are able to enter the carotid narrowing where they may readily be detected by ultrasound scan.

In addition to imaging carotid narrowing, we have been undertaking laboratory analysis of specimens of diseased carotid arteries, obtained from stroke-prevention operations to remove carotid narrowings.

We have shown that microbubble ultrasound signal is higher in patients who have had a stroke or mini-stroke compared with individuals with narrowing of the carotid artery who have not had warning signs. It is postulated that the greater the number microbubbles entering and being retained within a carotid narrowing, the more inflammation there is in that narrowing and, therefore, the greater the risk of future stroke.

The pattern of molecules produced by carotid artery narrowings that caused stroke was different from the pattern of molecules from the narrowings of patients who had not experienced stroke or mini-stroke warning signs.

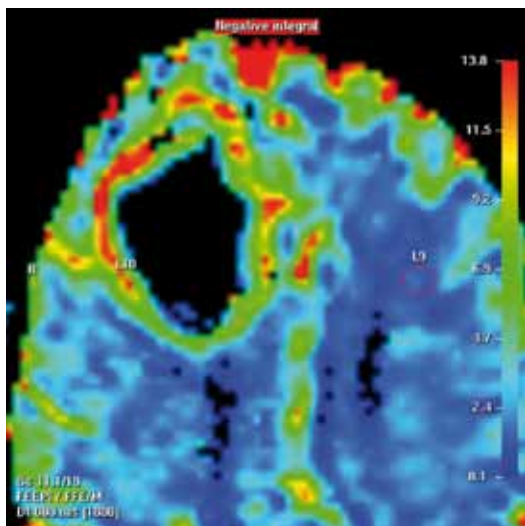
By selecting those patients who are at risk, based on safe and acceptable tests, it may be possible to predict which of these patients is likely to have a stroke in the future, so they may be able to have surgery (or other appropriate therapies) to prevent that stroke. Our understanding of the cells and molecules involved in making a carotid artery narrowing responsible for stroke will help the development of imaging modalities and medicines targeted at these identified cells and molecules.

The molecular genetics of microvasculature in paediatric high grade gliomas

Life expectancy for children with high grade glioma can be predicted by the number of new blood vessels within their tumour.

This project has focused on paediatric high-grade glioma (pHGG), an aggressive, incurable brain tumour of childhood that currently has an extremely poor prognosis with an average survival from diagnosis of less than 18 months. We aimed to identify key molecular pathways controlling the growth and development of pHGG, in particular those involved in new blood vessel development.

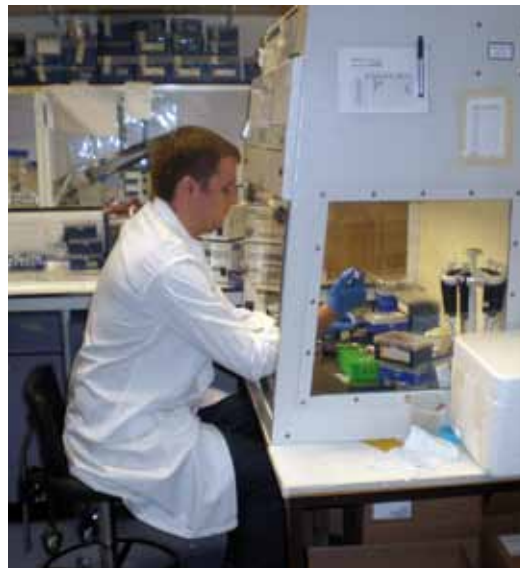
Using antibody-based staining on 150 pHGGs (one of the largest cohorts ever examined) we have identified the amount of new blood vessels present. Computer software was used to analyse the genetic profiles of tumours, grouped according to their characteristics on antibody staining. By comparing tumours with high and low levels of blood vessel formation we have identified which genes and pathways seem to be most associated with blood vessel growth.



Magnetic resonance imaging perfusion scan showing ring of increased blood flow (bright colours) around the dark centre of a brain tumour.

The 15 genes most associated with differing levels of blood vessel formation have been identified. Markers of abnormal, newly grown blood vessels seem to be the most informative for stratifying tumours. The level of the marker CD105 in particular correlates with the length of survival – the more vessels displaying CD105, the

shorter the survival of the patient: a statistically significant finding. All patients surviving greater than seven years had the lowest levels of CD105 in their blood vessels. Little research has been performed in children but, in adults, drugs that inhibit the growth of blood vessels are now in clinical trials.



Stuart in the laboratory.

We hope that this work will guide the introduction of these vitally needed new treatments into the paediatric age group. At present, despite surgery, radiotherapy and chemotherapy, the prognosis for these children is bleak, with risks of neurological damage and very small chances of cure. Novel treatments targeting blood vessels may offer a real chance of extending survival in patients suffering this aggressive form of cancer.



STUART SMITH

Fellowship/sponsor
Dr MP Starritt Research Fellowship with support from the Rosetrees Trust.

Supervisor
Professor Richard Grundy.

Site of work
University of Nottingham.

Publications
Rahman R, Smith S, Rahman C, Grundy R. Anti-angiogenic therapy and mechanisms of tumor resistance in malignant glioma. *J Oncol* 2010; epub ahead of print.

Presentations

- *Does immunohistochemistry correlate with genetic and clinical factors in paediatric high grade glioma?* International Symposium in Paediatric Neuro-Oncology; June 2010; Vienna, Austria.
- *Angiogenesis in paediatric high grade glioma: gene expression signatures.* Society of British Neurological Surgeons; September 2010; London, UK.

Evaluating individual chemotherapy response in head and neck cancer patients



DEBORAH SYLVESTER

Fellowship/sponsor

College Research Fellowship with support from the Donald Forrester Trust.

Supervisor

Professor John Greenman.

Site of work

Postgraduate Medical Institute, Daisy Research Laboratories, University of Hull.

Publications

- Sylvester DC, Hattersley SM, Haswell SJ *et al.* Microfluidic devices for evaluating HNSCC tumor biology. *Otolaryngol Head Neck Surg* 2010; 143 (Suppl 2): 166.
- Sylvester DC, M Hattersley SM, Dyer CE *et al.* An innovative explant tissue model using microfluidics for the study of tumour tissue responses. *Proc Natl Acad Sci*; (under consideration).

Presentations

- *Development of microfluidic based devices for studying tumour biology and evaluating treatment response in head and neck cancer biopsies.* International Conference on Miniaturized Systems for Chemistry and Life Sciences; October 2010; Groningen, The Netherlands.
- *Microfluidic devices for evaluating head and neck tumour biology.* American Academy of Otolaryngology Head and Neck Surgery; September 2010; Boston, USA.

Survival rates for head and neck squamous cell carcinoma (HNSCC) have not improved significantly over the last 30 years. Multiple treatments and chemotherapy regimens exist, to which tumours have a varied response.

The poor survival figures for HNSCC are due in part to the heterogeneity of tumour response, ie some patients respond to chemotherapy or radiotherapy regimens and others require surgery after failing therapy. The aim of this project is to optimise a unique experimental platform that allows different therapies to be tested on individual tumours, meaning that the most appropriate modality is selected.



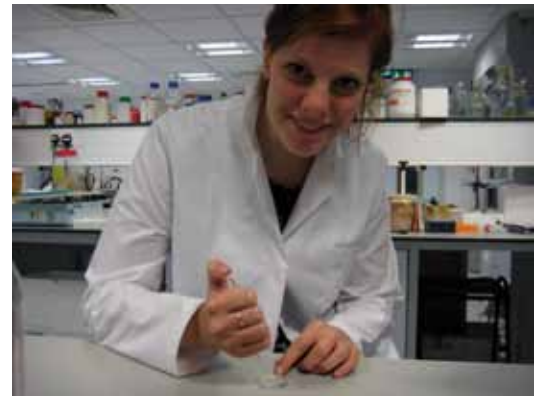
Deborah examining the incubating tumour biopsies in the microfluidic chips with her supervisor.

Our group had previously designed a micro device (incorporating microfluidic technology) capable of keeping whole pieces of tissue in a viable state for a number of days. By using whole pieces of tumour rather than traditional cell-based tumour cultures, the tumour microenvironment is preserved, which better represents how tumours behave within the body. Furthermore, this system allows tumours to be 'interrogated' with chemotherapy agents.

We demonstrated that HNSCC from individual patient biopsies could be kept alive in this system for up to eight days by looking at indicators of cell death and proliferation. By adding chemotherapy drugs in various doses and combinations, preliminary results demonstrated increased cell death for combined regimens as compared with single agents or the control. Ongoing work is being carried out to determine how accurately this reflects the clinical response of the tumour. The

chemotherapy regimen received by the patient is being given to his or her tumour *in vivo* and the patient's clinical response will be monitored for three years for correlation with *in vitro* findings.

If, as predicted, this model mimics the *in vivo* state and can be used to determine clinical outcome, different combinations of chemotherapy would be tested on the tumour biopsy and the most effective single agent or combination would then



Preparing the glass microchips and testing for blockages.

be given to the patient. With further refinement of this technology its immediacy and simplicity will allow for personalised chemotherapy at the bedside in years to come.

DNA methylation in breast cancer stromal fibroblasts – potential epigenetic biomarkers?

One-out-of-nine women will get breast cancer in their lifetime. Differences in the methylation status of breast stroma cells may help identify patients who have more aggressive forms of pre-invasive breast cancer.

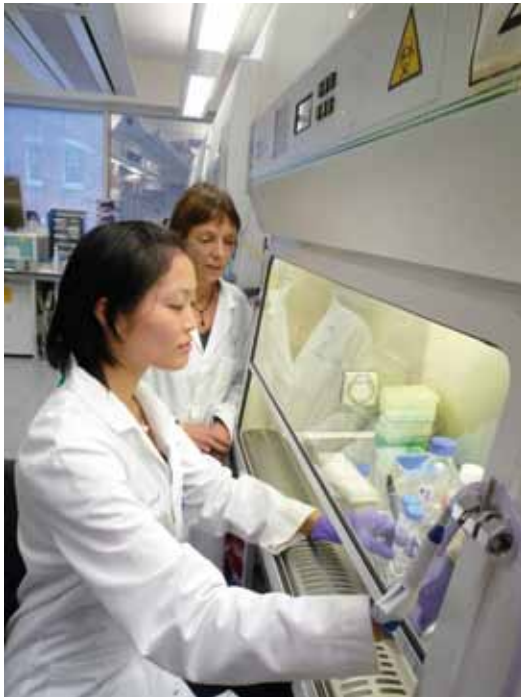


SARAH TANG

Fellowship/sponsor
Joint College/British Association of Surgical Oncology Fellowship.

Supervisor
Mr Gerald Gui and Professor Clare Isacke.

Site of work
Royal Marsden NHS Trust and Breakthrough Breast Unit, Institute of Cancer Research, London.



Sarah being supervised by Professor Isacke in the tissue culture hood, where isolated fibroblasts were fed and divided.

cancer genetics that studies changes in genes that cannot be detected by looking at the gene sequence. These changes can switch off cancer-inhibiting genes and switch on cancer-promoting genes. The changes that we are looking for are whether these genes carry an extra chemical bond (methyl group). As yet, no one has carried out a global methylation screen on stromal fibroblasts in breast cancer; the results from this project will be entirely novel.

Discovering differences in the methylation status of breast stroma cells is just the start. It would then be possible to investigate the relationship between the presence of these changes with disease progression (rate of local recurrence or metastasis) and with response to treatment (radiotherapy or chemotherapy), or possibly to identify patients who have more aggressive forms of pre-invasive breast cancer.

The aim of this project is to identify epigenetic biomarkers in breast cancer connective tissue (stroma). 10 women undergoing breast cancer surgery were recruited. At the time of surgery, breast cancer tissue and normal tissue from the same breast were collected. Fibroblasts (cells in the stroma) were isolated and grown in a cell culture. DNA was then extracted from these cells and analysed for differences between the cancer samples and the normal samples. We used cutting-edge technology that searches every gene within the cell for specific chemical changes (methylation). Data analysis with the aid of bioinformaticians is currently under way.

Cancer cells are surrounded by connective tissue, called the stroma. Previous work has shown that there is a very intimate relationship between cancer cells and the stroma and that specialised cells in the stroma, such as fibroblasts, have a role in cancer progression, spread and even initiation. Epigenetics is an emerging field of



Sarah examining a patient with Mr Gui, prior to breast cancer surgery.

The anatomy, structure and function of the rotator cuff



SIMON THOMPSON

Fellowship/sponsor

Phillip and Lydia Cutner Legacy Research Fellowship with support from the Rosetrees Trust.

Supervisor

Professor Anthony Bull, Professor Roger Emery and Mr Peter Reilly.

Site of work

Department of Bioengineering, Imperial College London.

Publications

An anatomical description of the pennation angles and central tendon angles of the supraspinatus both in its normal configuration and with full thickness tears. *J Shoulder Elbow Surg*; (in press).

Presentations

- *A description of the pennation angles and central tendon angles of the supraspinatus both in its normal configuration and with full thickness tears.* International Congress of Shoulder and Elbow Surgery; September 2010; Edinburgh, UK.
- *A comparison of the degree of retraction of full thickness supraspinatus tears with the Goutallier grading system.* International Congress of Shoulder and Elbow Surgery; September 2010; Edinburgh, UK.

Further funding

The Robert Luff Foundation one-off grant.

It is estimated that rotator cuff disease accounts for a third of the referrals to shoulder clinics.



Cadaveric testing rig with specimen in situ.



Simon performing arthroscopic shoulder surgery.

Rotator cuff disease is a disease of old age and associated trauma. 58% of the population over the age of 60 have asymptomatic rotator cuff tears. The prevalence is 9.5 per 1,000 patient population in primary healthcare. This is one of the most significant problems for both the patient and, on a financial level, for the healthcare industry.

Operating on patients with a known rotator cuff tear can undoubtedly yield good results but there is a significant population group with asymptomatic tears for the shoulders that become symptomatic. Some patients with tears never require surgical intervention or presentation to an orthopaedic surgeon, as shown in cadaveric studies.

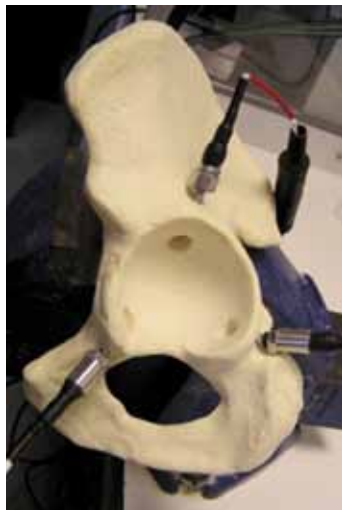
If we can identify why these patients have a problem we may be able to predict rotator cuff failure. Therefore surgical intervention may occur in a timelier manner or be avoided altogether. Avoidance of unnecessary surgery or provision of surgical intervention at the correct stage of the pathology and symptomatology would provide a substantial benefit to patients. It would also offer savings in medical resources and finances.

The aims are to describe the normal anatomy and the anatomy of the pathological rotator cuff with associated tears. This has been achieved with the use of magnetic resonance imaging and study of cadaveric shoulders.

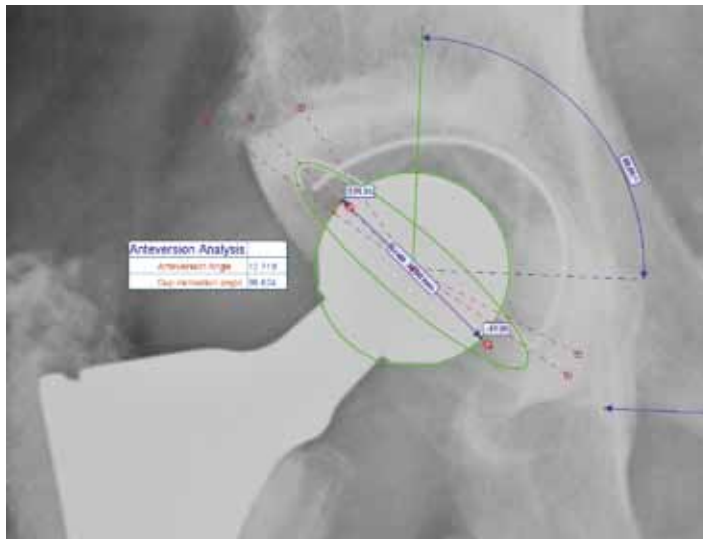
Rotator cuff tears can have a significant impact on patients' quality of life and can become a functionally debilitating disease. Surgical repair of the pathological rotator cuff can yield mixed results and high failure rates have been published. Our study has shown that distinct changes occur in the muscle pennation of the torn supraspinatus and may directly affect surgical repair and hence function.

An investigation of the cemented acetabular component in total hip arthroplasty

Total hip replacement (THR) aims to provide a pain-free, well-functioning joint that will last the rest of the patient's life. 10–16% of THRs fail and need to be revised, commonly due to aseptic loosening of the acetabulum.



Acetabular model for cement pressure study.



Postoperative radiograph of a hip replacement demonstrating analysis of cup angle.

5.5% of people over 60 years old suffer from osteoarthritis (OA) of the hip. THR is a highly effective treatment for OA and the third most common elective procedure performed in England and Wales. The aims of the research were to identify factors relating to patient anatomy that may predict signs of early loosening of total hip replacements and to identify surgical techniques that may reduce this risk or even exacerbate it. The study comprised three arms:

- The analysis of pre/postoperative radiographs to look at the effect of patient anatomy and surgical technique on the incidence of radiolucency (failure to interdigitate the cement into the bone).
- To look at the thickness of bone cement used and whether this caused damage to the bone due to the heat released by cement as it cures.
- To look at the method of preparing the acetabulum (cup) in the laboratory and to see if the pressure in the cement and the penetration of the cement could be improved.

The angle at which the cup is inserted, and the use of keyholes in the acetabular bone significantly reduced the incidence of radiolucency after the operation. Radiolucency

is a strong predictor of subsequent loosening. The cement thickness influences the amount of damage to the bone, which may cause resorption of bone after the operation. Forming a shelf around the acetabulum for the cup rim to sit on significantly improves the pressure in the inserted cement.

This research continues the work that has been done in this field since the popularisation of cemented THR in the 1960s and 1970s. Scientists around the world have used a large number of different strategies to improve the survivorship of THRs but this has not been rewarded with substantial improvements in survivorship, unlike the femoral stem.

Patients recruited to the study will be followed up in the long term to see if the short-term improvements we have obtained are sustained. Patients that require a revision operation do not achieve results as good as those observed in the primary operation. Ultimately, our patients want a hip replacement that gives them good function, relieves their pain and lasts for as long as possible and we hope to improve their chances of achieving this.



MICHAEL WHITEHOUSE

Fellowship/sponsor
College Research Fellowship.

Supervisor
Professor GC Bannister
and Professor AW Blom.

Site of work
Department of Academic
Orthopaedics, University
of Bristol.

Publications
Whitehouse MR, Evans SL. Bone
cement: an overview. *Int J Nano
Biomaterials* 2010; 3: 4–19.

Presentations
• *Predicting the presence of zone 1 radiolucency in the early postoperative period following cemented total hip replacement.* European Federation of National Associations of Orthopaedics and Traumatology (EFORT); June 2010; Madrid, Spain.
• *Thermal osteonecrosis due to curing polymethylmethacrylate bone cement in vivo.* EFORT; June 2010; Madrid, Spain.

Prizes
• Best research paper, Royal College of Surgeons of England and Bangalore Surgeons Forum, 2010.
• Stefan Galeski Fellowship, 2010.
• Second prize for research presentation, Bristol Orthopaedic Registrars' Group, 2009.

The background of the entire page is a detailed electromagnetic micrograph of bone cells. It shows various cellular structures in shades of brown, green, and dark blue. A large, prominent cell in the center has a reddish-purple nucleus. The surrounding tissue is highly textured and complex, showing the intricate architecture of bone cells.

The Royal
College of
Surgeons of
England has
supported over

500

research
fellowships
since 1993

Electromagnetic microscopy
of bone cells.

Cancer Research UK

Pump priming reports

Pump priming grants of up to £10,000 are awarded to newly appointed consultants and senior lecturers in surgery who are working at hospitals and universities in the UK. The purpose of these grants is to give assistance and encouragement to these clinicians in the crucial early stages of their independent research careers when funding is especially scarce. Awards are made competitively and may be used flexibly to support the award holder's research programme. The College Council is very grateful to all those who have donated to the pump priming grants.

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Development of methylation-based prognostic biomarkers to stratify risk of recurrence in early rectal cancer



SIMON BACH

Specialty
Colorectal surgery.

Current position
Senior Lecturer in Colorectal Surgery, University of Birmingham.

Title of fellowship
Pump Priming Award.

Site of work
Queen Elizabeth Hospital, Birmingham.

- Publications**
- Leong KJ, Wei W, Tannahill LA *et al*. Methylation profiling of rectal cancer identifies novel markers of early stage disease. *Br J Surg* 2011; (in press).
 - Bach SP. Developments in early rectal cancer treatment. *Eur J Cancer* 2009; 45: 464–465.

- Presentations**
- *Genome-wide methylation profiling of rectal cancer identifies novel markers of early stage disease*. Society of Academic and Research Surgery; January 2011; Dublin, Ireland.
 - *Methylation profiling of rectal cancer identifies novel markers of early stage disease*. Association of Coloproctology of Great Britain and Ireland; June 2010; Bournemouth, UK.

Further funding
Medical Research Council for three years.

Methylation of two from a panel of five genes was associated with localised rectal cancer suitable for treatment by local excision.

The NHS bowel cancer screening programme leads to earlier diagnosis of rectal cancer. Standard treatment for rectal cancer involves an operation to remove the entire rectum. This approach offers high rates of cure at the risk of significant complications and poor long-term bowel function. Local surgical treatments that remove only the affected rectum are likely to be safer and functionally far better, offering improved quality of life for the patient. Unfortunately, a minority of small, apparently early cancers have already spread to rectal lymph glands and are undertreated by local surgery alone. We investigated whether such 'aggressive' behaviour is associated with distinct genetic features. We wish to construct a laboratory test to identify these cases.

We measured hypermethylation, a process known to switch off gene activity, at 24 key sites containing tumour suppressor genes. Tissue from 51 tumours removed by radical surgery was analysed and compared with normal tissue from the same individuals. Methylation values were compared with standard staging criteria (tumour, node, metastasis system).

5 of the 24 sites (ESR1, CDH13, CHFR, APC and RARB) were more methylated in cancer



Left to right: Mrs M White (colorectal specialist nurse at Queen Elizabeth Hospital, Birmingham), Mr Sheppard (patient), Mrs Sheppard and Simon.



A locally excised tumour before it goes to pathology.



Transanal endoscopic microsurgery equipment.

compared with normal tissue. Increased methylation at two sites (GSTP1 and RARB) was specifically associated with localised disease. We defined a panel of five sites that discriminated localised from advanced tumours (APC, RARB, TIMP3, CASP8 and GSTP1). Tumours highly methylated at two or more of these sites were always localised.

This pilot study has shown that methylation of key tumour

suppressor genes is a feature of localised as opposed to advanced disease. With further refinement and validation this may form the basis of a laboratory test to guide treatment options for early rectal cancer. We shall evaluate these markers as part of the forthcoming Cancer Research UK transanal endoscopic microsurgery and radiotherapy in early rectal cancer study.

K-RAS expression in anal cancer and its alteration by chemoradiotherapy

Can cetuximab work in anal cancer?



Patients in the chemotherapy clinic.



CHARLES BAILEY

Specialty
General and colorectal surgery.

Current position
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Maidstone and Tunbridge
Wells NHS Trust.

Every year, 30 patients are referred to our service for treatment of their anal cancer. If caught early this disease can be cured with chemotherapy, radiotherapy and surgery; however, the treatment is less successful for patients who present late or relapse. The aim of this study was to find out if a new type of chemotherapy called cetuximab could be used to treat patients with anal cancer.

All anal cancer patients who developed recurrent disease over a five-year period (2005–2010) were identified. Samples were retrieved from the original and the recurrent cancer specimens and tested for a gene called K-RAS. The reason for testing for K-RAS is that it has been shown that bowel cancers that express normal K-RAS are sensitive to cetuximab, whereas those that express abnormal, also called mutated, K-RAS

do not. We wanted to see if recurrent anal cancers express normal or mutated K-RAS to find out if, like some bowel cancers, they could be sensitive to cetuximab therapy.

The project is ongoing and provisional results are encouraging as we have found that all the samples from both the original anal cancers and from the recurrent cancers express normal K-RAS. We hope this means that anal cancers will be sensitive to cetuximab therapy, which has been shown to improve the quality of life and prolong life in patients with advanced cancer.

Peripheral bladder function: understanding urine storage and emptying functions



MARCUS DRAKE

Specialty
Urology.

Current position
Senior Lecturer in Urology,
University of Bristol.

Title of fellowship
Pump Priming Award.

Site of work
Bristol Urological Institute.

Publications

- Drake MJ, Fowler CJ, Griffiths D *et al.* Neural control of the lower urinary and gastrointestinal tracts: supraspinal CNS mechanisms. *Neurourol Urodyn* 2010; 29: 119–127.
- Neural control of the lower urinary tract: peripheral and spinal mechanisms. Birder L, de Groat W, Mills I *et al.* *Neurourol Urodyn* 2010; 29: 128–139.

Presentations

- *Investigation of the role of TRPM8 channels in mediating detrusor contraction in pig urinary bladder.* International Continence Society; September 2010; Toronto, Canada.
- *A novel arterially perfused decerebrate preparation for the study of bladder autonomic control.* International Continence Society; September 2010; Toronto, Canada. Also presented at: Physiological Society; June 2010; Glasgow, UK.

Further funding

- Higher Education Funding Council of England Clinical Senior Lectureship award for five years.
- European Union FP7 TRUST Programme whole-organism work package for three years.

Overactive bladder affects one-in-ten of the whole UK population and one-in-four older people in the UK. Given the high prevalence of the problem, particularly in the elderly, new treatment options are extremely desirable.



Marcus delivering a lecture on neurophysiology to the Spanish Functional Urology Association.

The project aspires to a better insight into how the bladder functions as an organ. It is usually regarded as a simple structure but my previous RCS research fellowship demonstrated substantial structural and functional complexity. The previous work looked at small animal bladders; with this project we have started to establish whether similar properties can be seen in large animal bladders.

The objective was to set-up an organ bath in which we could measure physiological aspects from a bladder that has a closer resemblance to that of humans. The method has been to develop an apparatus in which the bladder can be housed in an environment that will keep it healthy, allowing measurement of pressure and

movement, and will allow us to see how drugs can affect the responses. Our results have been very encouraging. We have kept bladders alive for several hours and we have been able to undertake experiments to demonstrate that the organs are viable and functioning effectively. The unique aspect of this model is its potential to stimulate the bladder by different routes of administering drugs. Normally experiments can only be undertaken by a drug given either into the blood stream or into the bladder itself. With this apparatus, we can administer drugs through both routes and this allows us to get a much better insight into the contribution of individual cell types to whole-organ functions. For organs this size the work is unique.

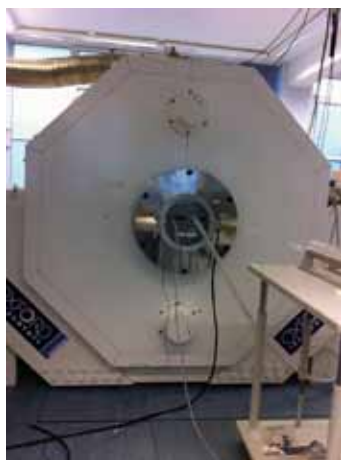
For patients with an overactive bladder, there is a strong need for new drug treatments. Current therapeutic options are effective for many people but can have significant side effects that make therapies hard to tolerate in the longer term. The ability to suppress overactive bladder contractions would profoundly improve quality of life for patients.

MRI of endothelial adhesion molecules in carotid atherosclerosis using targeted ultrasmall superparamagnetic particles of iron oxide

Stroke is the third most common cause of mortality in the UK and providing healthcare for survivors is an enormous financial burden. The project aims to improve the identification of patients who need surgery to prevent stroke.

Recent research has focused on inflammation as a cause for plaque instability, leading to acute symptoms, such as stroke. There is currently no clinical imaging technique available to assess the degree of inflammation associated with plaques.

This study aims at visualising and characterising atherosclerosis using targeted ultrasmall superparamagnetic particles of iron oxide (USPIO) as a magnetic resonance imaging (MRI) probe for detecting inflamed plaque disease. This novel work will allow accurate imaging of the inflammatory process within plaques and increase accuracy in predicting which patients need surgery to prevent stroke and which patients do not.



9.4 Tesla small animal MRI.

The study comprised three stages. The initial *in vitro* feasibility study involved MRI detection of



Richard teaching at a thoracoabdominal workshop in Belgrade.

activated endothelial cells by molecular-targeting the specific inflammatory markers (E-selectin and VCAM-1) using antibody-conjugated USPIOs with confirmatory immunocytochemistry. In the *ex vivo* stage we have detected inflammatory markers on human atherosclerotic plaques (harvested during carotid endarterectomy) by anti-E-selectin antibody and anti-VCAM-1 antibody conjugated USPIO using MRI. In the final *in vivo* stage we have detected plaque lesions in an atherosclerotic animal model using dual-targeted USPIO against VCAM-1 and E-selectin.

We have successfully developed an *in vitro* cellular model to detect and characterise

inflamed endothelial cells by immunocytochemistry and MRI. We are able to image the degree of inflammation associated with human carotid plaques by *ex vivo* MRI and we can detect atherosclerosis in animal models by *in vivo* MRI.

This novel work will increase our ability to discriminate unstable atherosclerotic plaque disease from stable, quiescent lesions; hence identifying the 'at risk' group with carotid plaque disease and aiding decision making for appropriate intervention. The next stage of this work will be to apply this methodology to patients after safety studies have been performed.



RICHARD GIBBS

Specialty
Vascular surgery.

Current position
Consultant Vascular Surgeon,
Honorary Senior Lecturer.

Title of fellowship
Pump Priming Award.

Site of work
St Mary's Hospital, London.

Publications

- Chan J, Monaco C, Bhakoo K, Gibbs RGJ. Imaging of the vulnerable carotid plaque: biological targeting of inflammation using ultrasmall superparamagnetic particles of iron oxide (USPIO) and MRI. *Atherosclerosis* 2010; 213: e14.
- Chan J, Monaco C, Bhakoo K, Gibbs RGJ. Visualising inflamed atherosclerotic plaques: Molecular imaging using MRI and targeted USPIOs. *Heart* 2010; 96: e17-e18.

Presentations

- *Imaging of the vulnerable carotid plaque: biological targeting of inflammation using ultrasmall superparamagnetic particles of iron oxide (USPIO)*. Vascular Society of Great Britain and Ireland (VSGBI); November 2010; Brighton, UK.
- *Visualising inflamed atherosclerotic plaques: molecular imaging using MRI and targeted ultrasmall superparamagnetic particles of iron oxide (USPIO)*. 7th World Stroke Congress; October 2010; Seoul, South Korea.

Prizes

- The British Journal of Surgery Prize for Best Scientific Paper, VSGBI, 2010.
- First Runner-up in Poster Prize competition, 4th Symposium of Cardiovascular Technology Network, 2010.

Proteomic markers of resistance to neoadjuvant chemoradiotherapy in rectal cancers



IAIN HUNTER

Specialty
Coloproctology.

Current position
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Castle Hill Hospital, Hull.

Around 50% of rectal cancer patients receiving pre-operative chemoradiotherapy fail to demonstrate any meaningful response to the treatment, while up to 30% of patients demonstrate a complete response.



Sajid Mehmood (research fellow) preparing cells for analysis after irradiation.



Rachael Lawrence (research fellow) taking biopsies of a rectal cancer using a colonoscope.

Current treatment of rectal cancer commonly employs a course of chemoradiotherapy followed by surgery. While this regime is very effective at curing cancer, it can have a significant impact on quality of life due to bladder, bowel and erectile dysfunction and permanent stoma formation. However, despite the prevalence of this treatment route, many tumours fail to demonstrate any meaningful response to chemoradiation.

The aim of this study is to identify rectal cancer protein markers that can predict the response of individual cancers to chemoradiotherapy. This will potentially benefit patients in two ways: patients who will gain no benefit from chemoradiotherapy can avoid it and reduce radiation-related side effects; and robust markers of radio sensitivity may allow

some patients to be treated with chemoradiotherapy alone, thereby avoiding major surgery.

Protein markers will be detected using mass throughput proteomic techniques that enable the direct comparison of all the proteins present in two different tissue samples. This study will employ two different models of radioresistance. The first is an in vitro model that utilises cell lines derived from rectal cancers. Radioresistant cell line clones have now been generated by repeatedly exposing cells to radiation. The differential expression of proteins between these clones and the original radiosensitive parents will be analysed. The second model will examine rectal cancer tissue taken from patients prior to chemoradiotherapy. Cancer radioresistance will be quantified by examination of

the surgical specimen after completion of treatment. Differential protein expression between complete and non-responders will be assessed

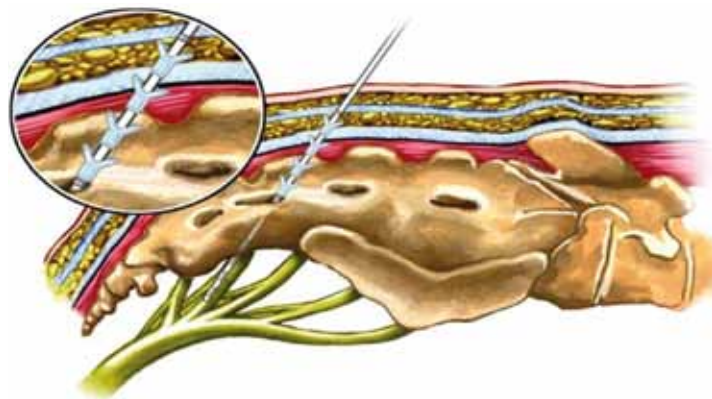


Colon cancer cells being subjected to external beam radiation in the linear accelerator.

Once markers are identified they will be further evaluated in a clinical setting to validate their use in planning therapy on an individual basis. It is also hoped that marker proteins will provide the starting point for functional studies that will reveal new therapeutic targets for standard and molecular therapies.

Prospective controlled study of the effect of sacral nerve stimulation on anorectal neuronal afferent and efferent signalling

Initial studies of brain activity in response to electrical stimulation of the rectal wall confirm differences in rectal sensation between patients and controls. We are starting to assess the effect of sacral nerve stimulation on these responses.



Schematic picture of the permanent lead used for sacral nerve stimulation. The lead is implanted through the tailbone to lie adjacent to the nerves going to the bowel and anal muscles. It is attached to a stimulator unit that is implanted in the buttock and acts like a pacemaker to the bowel nerves and muscles.

Faecal incontinence and constipation are debilitating conditions. Sacral nerve stimulation (SNS) is emerging as the first-line surgical option for patients where conservative measures have failed. However, not all patients respond to this expensive treatment and the mechanism of action (MOA) is unknown. The MOA of SNS has thus far only been studied by tests that require subjective reporting, leading to inconsistent results that will almost certainly be heavily influenced by placebo effects. The broad aim of this study is to utilise special tests of nervous system connections between the brain and bowel before and after treatment with SNS, and correlate these findings with patient reported outcomes.

Following validation studies, changes in the signalling in motor (brain to bowel) and sensory (bowel to brain) pathways will be studied. The former uses 'rectal evoked potentials' – recordings of brain

An X-ray of a patient with the stimulator implanted: the stimulator unit and the lead going to the nerve can be seen on the patient's right side.



activity on the scalp; the latter uses 'single pulse transcranial-translumbar magnetic stimulation evoked responses' – recordings from the lower bowel while magnetically stimulating the brain or spinal cord.

Our group has already determined that patients undergoing SNS ($n=12$) have changes in rectal sensation with treatment, as determined by blowing up a balloon in the lower bowel. Furthermore, we have shown that there are differences between patients with blunted rectal sensation and controls in terms of rectal-evoked brain potentials. These studies are paving the way for

the studies outlined above for which we have just secured full ethics approval and the final pieces of equipment. This project may also help to perform the operation of SNS more accurately due to our acquisition of specialised recording equipment.

SNS is an expensive treatment requiring two operations with potential for complications. Objective proof of physiological effect in relation to clinical effectiveness will allow rationalisation of significantly increasing NHS expenditure on SNS by improved patient selection and lead placement.



CHARLES KNOWLES

Specialty
Coloproctology.

Current position
Clinical Senior lecturer and
Honorary Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Barts and The London School
of Medicine and Dentistry.

Publications

- Carrington EV, Knowles CH. The influence of sacral nerve stimulation on anorectal dysfunction. *Colorectal Dis* 2011; 13: 5–9.
- Boyle DJ, Knowles CH, Lunniss PJ *et al*. Efficacy of sacral nerve stimulation for fecal incontinence in patients with anal sphincter defects. *Dis Colon Rectum* 2009; 52: 1234–1239.

Presentations

- *Prospective randomised double-blind placebo-controlled crossover study of SNS in patients with severe rectal evacuatory dysfunction and rectal hyposensitivity*. Society for Academic and Research Surgery; January 2010; London, UK
- *Prospective randomised double-blind placebo-controlled crossover study of SNS in patients with severe rectal evacuatory dysfunction and rectal hyposensitivity*. International Neurogastroenterology and Motility Meeting; August 2009; Chicago, USA.

The use of an *ex vivo* liver perfusion model in the study of the ablation of liver lesions



MATTHEW METCALFE

Specialty
Hepatopancreatobiliary surgery.

Current position
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Transplant Laboratory,
University of Leicester.

Publications

- Gravante G, Ong SL, Metcalfe MS *et al.* Cytokine response of electrolytic ablation in an *ex vivo* perfused liver model. *ANZ J Surg* 2010; 80: 537–541.
- Gravante G, Ong SL, Metcalfe MS *et al.* The effects of radiofrequency ablation on the hepatic parenchyma: Histological bases for tumour recurrences. *Surg Oncol* 2010; epub ahead of print.

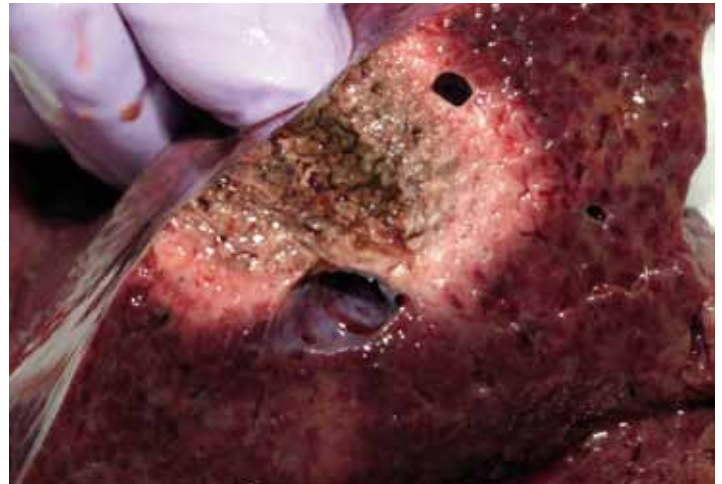
This study has shown that new technologies for treating liver cancers, including microwave ablation, can now be reliably tested for safety and effectiveness without the need for animal models.

Killing liver cancers by burning them with microwave probes (and other ways of heating the liver) can be used for patients who have liver cancer that cannot be removed surgically. These techniques are known as ablation. As they are new types of treatment, they have to be rigorously tested for safety and effectiveness before they can be used in patients.

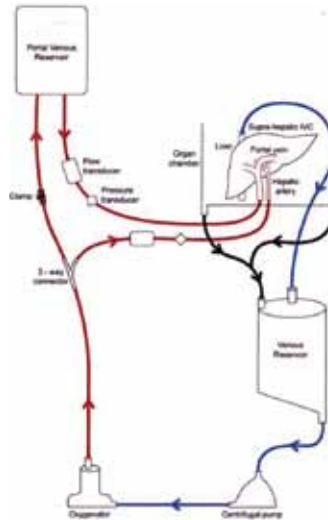
Experimental study of microwave ablation of the liver is limited by the ethical issues surrounding animal model experiments. We investigated whether the use of animal models could be replaced by our liver perfusion model (in which a liver from a slaughterhouse is kept alive outside the body) to perform these studies. If so, this would address ethical concerns while gathering the information needed to make sure that when microwave and other ablation treatment options for liver cancer are used to treat patients they are as safe and effective as possible.

This project had two major aims: i) to validate the liver perfusion model for the experimental study of ablation; and ii) to begin to assess the safety and efficacy of microwave liver ablation in the model.

The preliminary results have validated this liver model for use in the study of liver ablation, as the microwave probes burn



The effect of a microwave ablation in the liver substance.



The *ex vivo* liver perfusion circuit diagram and model in action.

holes in the liver of this model in exactly the same way as occurs to the liver in the body.

We have gone on to show that the same is true for other ways of burning cancers in the liver, including radiofrequency ablation and electrolysis. The pump-priming award has therefore allowed us to establish a model that we can now use to start to address key unanswered questions in ablation such as if

enough liver (and all the cancer) has been ablated and if it is safe or effective to use ablation next to big blood vessels or bile ducts.

The clinical presentation and aetiology of encapsulating peritoneal sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare and lethal complication of long term peritoneal dialysis.



Staff with a patient recovering from surgery.

Peritoneal dialysis (PD) is a successful treatment for kidney failure. Encapsulating peritoneal sclerosis (EPS) is a devastating complication of long term PD. Between 3–17% of patients who are on PD develop this condition. The chance of developing this illness seems to increase as more time is spent on PD. Patients who develop EPS present with symptoms ranging from bloating, abdominal pain, intra-abdominal infection, weight loss and blockage of the bowel. Untreated, EPS leads to nutritional failure and death.

These symptoms occur because the gut becomes encased in a cocoon. The surgical treatment of this condition involves releasing the cocoon and freeing the loops of bowel. This in turn allows

absorption to resume. Since 2001 our unit has treated over 100 patients surgically for this condition. In April 2009 our unit became one of two national specialist referral centres for the surgical treatment of EPS.

We have noted that EPS presents in a variety of ways. Furthermore, some patients who have been on PD for a long time do not develop the condition whereas other patients develop the condition relatively quickly. Although there has been some work in animal models on the molecules that may cause this condition there has been no work done on humans.

In order to study which molecules are involved in the development of this condition we are collecting tissue samples from the abdomen of patients who present to us for surgery.

We are also collecting tissue samples from the abdomen of patients at the time of insertion of a dialysis catheter as a control group. To date we have recruited 75% of the patients we need for the study. We plan to compare the expression of certain molecules involved in fibrosis in each group. This may give us an understanding of how this condition develops.



The 'cocoon' encasing the bowel.



**RAVI
PARARAJASINGAM**

Specialty
Transplant and general surgery.

Current position
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
The Transplant Unit, Manchester
Royal Infirmary, Manchester.

Publications

- Kirkman MA, Heap S, Forgacs B *et al.* Encapsulating peritoneal sclerosis presenting as acute limb ischemia. *Perit Dial Int* 2010; 30: 578–580.
- Forgacs B, Shiell K, Farqharson F *et al.* Pseudoachalasia of the esophagus caused by encapsulating peritoneal sclerosis. *Perit Dial Int* 2010; 30: 246–249.

Presentations

The histological findings in encapsulating peritoneal sclerosis. Association of Surgeons of Great Britain and Ireland; April 2010; Liverpool, UK.

Obesity and colorectal cancer risk: lack of correlation between body mass index and intestinal crypt cell kinetics in humans and animals



ANDREW RENEHAN

Specialty
Colorectal surgery.

Current position
Senior Lecturer in Cancer Studies and Surgery.

Title of fellowship
Pump Priming Award.

Site of work
Paterson Institute for Cancer Research, The Christie NHS Foundation Trust, Manchester.

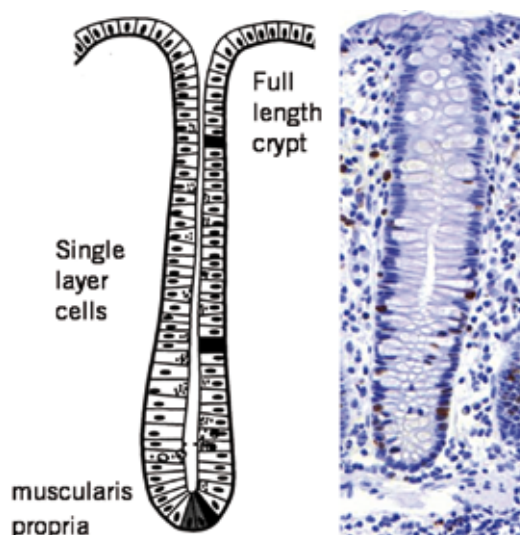
Publications
• Renehan AG, Soerjomataram I, Tyson M *et al.* Incident cancer burden attributable to excess body mass index in 30 European countries. *Int J of Cancer* 2010; 126: 692–702.
• Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* 2010; 61: 301–316.

There are around 37,000 cases of colorectal cancer (CRC) per year in the UK with approximately 50% patient mortality in the first five years. Weight reduction as a treatment may potentially reduce CRC incidence by 10–15%.

The strategy of weight reduction to prevent colorectal cancer is attractive but there is currently no robust tissue biomarker linking body weight and an individual's cancer risk. Body mass index (BMI), as an approximation of obesity, is a risk factor for colorectal cancer (CRC). We tested the hypothesis that intestinal crypt cell proliferation, as a surrogate of CRC risk and potential tissue biomarker in prevention trials, is increased in relation to BMI and markers of insulin resistance.

We performed cell positional cryptal analyses (yielding seven parameters per crypt) in well-orientated mucosal samples from rectum, and left and right colon, in 40 individuals without pathology undergoing screening colonoscopy. Similar analyses (for small and large intestines) were performed in insulin-resistant animal models at 6, 11 and 16 weeks of life, and compared with wild types (6 per group). Correlations were made with BMI, serum measurements of insulin, glucose, adiponectin, IGF-I, and IGFBP-1.

For humans, there was lack of correlations between BMI, serum IGF-I, IGFBP-1 and any of the crypt parameters. There were paradoxical negative correlations with insulin and positive correlations with adiponectin (which is normally reduced in obesity). Lack of



Schematic diagram of an intestinal crypt in the colon and accompanying photomicrograph with Ki67 staining for cell proliferation.



Andrew in the laboratory scoring tissue sections.

correlations of crypt parameters and indices of obesity were observed for the animal model studies at each time point and with increasing weight over time.

Crypt cell proliferation is advocated as a biomarker endpoint in several colon cancer prevention biomarker trials. Our preliminary revisit of this field questions this approach.

There is a wealth of literature on cell proliferation indices in the colon of humans and animals but a limited amount in the context of obesity and

weight reduction trials. Similar projects to this are ongoing in other genetically driven obese animal models.

The presence of angiotensin II in Barrett's disease

Barrett's disease is a major cause of oesophageal cancer. We propose that angiotensin II may exert pro-inflammatory effects in the oesophagus and also play an important role in Barrett's oesophagus.



Amjid going through the effects and risk of Barrett's disease to a patient in the outpatient department.

Barrett's oesophagus affects up to 2% of the UK population and is responsible for around 50% of all oesophageal cancers. The cause in most cases is thought to be long-term reflux of acid into the oesophagus from the stomach. The acid damages the normal lining of the oesophagus which can turn cancerous. The progression of Barrett's oesophagus to cancer progresses through varying degrees of dysplasia from low-grade dysplasia to high-grade (severe) dysplasia. Cells that are high-grade dysplasia have a high risk of turning cancerous. Angiotensin II (Ang II) is an inflammatory modulator. The principal damage occurring during acid reflux (Barrett's disease) into the oesophagus is via activated white blood cells.

The first aim of this study is to characterise the association of Ang II in normal and Barrett's oesophagus. 25 specimens of biopsies of patients with Barrett's disease of varying degrees of severity are taken and, using immunohistochemistry, the distribution of Ang II receptors are recorded.

We have found that there is an association between the level of angiotensin II expression with increased severity of Barrett's disease. However, this is one of a handful of studies looking at the role of angiotensin II as an inflammatory marker in Barrett's disease. This is a really exciting area of research as if we can establish a genuine link between angiotensin II and Barrett's disease, we may be able to

treat it and reduce morbidity and mortality associated with Barrett's disease. This will have a huge effect on the quality of life for patients and possibly lead to reduction in patients with Barrett's disease developing oesophageal cancer.



AMJID RIAZ

Specialty
Upper GI, laparoscopic
and general surgery.

Current position
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Malmö University Hospital and
University of Hertfordshire.

Methylation of the human papilloma virus genome as a predictive biomarker for vaccine trials in head and neck cancer



RICHARD SHAW

Specialty

Oral and maxillofacial surgery/
head and neck oncology.

Current position

Clinical Senior Lecturer in
Head and Neck Surgery, and
Honorary Consultant in Oral
and Maxillofacial Surgery

Title of fellowship

Pump Priming Award.

Site of work

University of Liverpool.

Publications

- Shaw R, Robinson M. The increasing clinical relevance of human papillomavirus type 16 (HPV-16) infection in oropharyngeal cancer. *Br J Oral Maxillofac Surg* 2010; epub ahead of print.
- Robinson M, Sloan P, Shaw R. Refining the diagnosis of oropharyngeal squamous cell carcinoma using human papillomavirus testing. *Oral Oncol* 2010; 46: 492–496.

Presentations

- *Host-viral epigenetic interactions in HPV-16 mediated oropharyngeal cancer.* National Cancer Research Institute; October 2009; Birmingham, UK.
- *Evidence for the role of HPV in oropharyngeal cancer.* Association of Oral and Maxillofacial Surgeons of India/ British Association of Oral and Maxillofacial Surgeons; November 2009; Cochin, India.

Prizes

- CR-UK, Award from Clinical Trials Advisory and Awards Committee, 2010–2012.
- Wellcome Foundation, PhD doctoral fellowship, 2010–2013.

More than 7,000 people are diagnosed with head and neck cancer each year in the UK. These include tumours of the mouth, lips, throat and voice-box, and some have been linked to a human papilloma virus (HPV) epidemic.



HPV-positive tonsil cancer.

It has been recently shown that tonsil cancers are the fastest rising cancer site in the UK and HPV-related cases are likely to be fuelling this rise. We aimed to find out the proportion of tonsil cancers caused by HPV infection in the 1980s, the 1990s and in more recent cases. We also aimed to increase our understanding of exactly how the infection

causes the cancer, specifically how chemical alterations in the virus's DNA trigger the production of proteins that can alter the rate at which cells grow and repair.

We made use of tissue donated by 125 patients who had undergone cancer surgery in recent decades at our centre. The DNA was extracted from these samples and analysed

using cutting-edge molecular techniques to look for evidence of HPV and the chemical forms present.

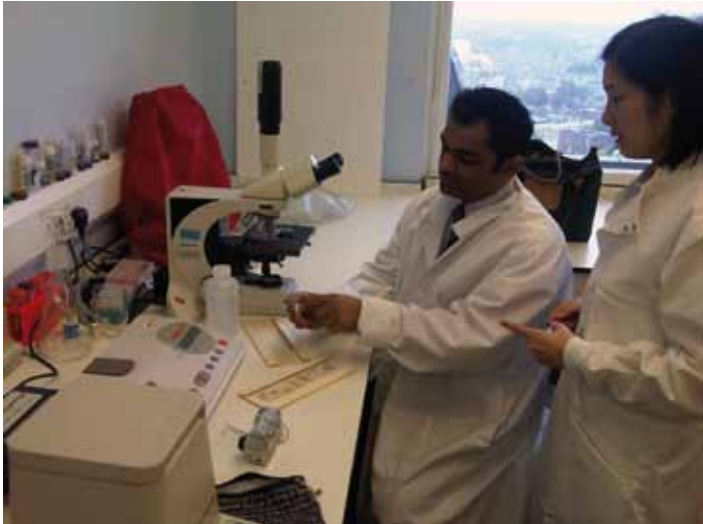
The proportion of tonsil cancers caused by HPV was 20% in the 1980s, rising to 40% in the 1990s and it is now 75%. The patients are younger, have fewer other risk factors (such as smoking) and have better prognosis. Chemical changes in the virus DNA are associated with high cancer risk and might be used as a marker for early diagnosis.

Understanding this rapid change in the cause of these cancers is already allowing us to design new targeted treatments using clinical trials. We are also thinking about whether it is safe to use less intense treatments in cases where we now know the outcome is very good – this is important because it will improve the quality of life for the survivors.

The results have helped us develop head and neck cancer as one of the main interests at the Cancer Research UK (CR-UK) centre in Liverpool. We have recently been awarded a significant grant from CR-UK to run a clinical trial of a therapeutic vaccine in HPV-driven tonsil cancers.

Pathophysiology of lower limb muscle ischaemia in peripheral arterial disease

Peripheral arterial disease affects almost 30 million people in the Western world and over 20% of those with severe disease face major amputation within a year.



Janice working in the laboratory with Hemanshu Patel.

Peripheral arterial disease (PAD) is a major healthcare issue: in the UK, 1 in 2,000 people develops critical limb ischaemia (CLI) each year (where the viability of the limb is threatened) and over 20% of these patients undergo major amputation within a year. Current revascularisation techniques are associated with relatively high failure rates and pharmacological treatment options have limited efficacy.

This research programme aims to investigate key pathways that may be involved in PAD, by analysing muscle biopsies from patients with PAD and by using a laboratory model of muscle ischaemia. Preliminary data have shown:

1. Activation of toll-like receptor (TLR) signalling occurs in CLI and contributes to tissue damage. TLRs are important receptors in the

immune system that are also implicated in ischaemic tissue damage. We have found activation of specific TLRs in ischaemic muscle. Blocking TLR-2 signalling *in vitro* reduced ischaemia-induced cell damage and inflammation.

2. The asymmetric dimethylarginine (ADMA)/nitric oxide (NO) pathway is involved in CLI. Preliminary studies have found that ADMA, an inhibitor of NO production is increased within ischaemic muscle where it may contribute to impaired angiogenesis and tissue damage.
3. Non-haematopoietic erythropoietin (EPO)-derivatives may reduce tissue damage in CLI. We have demonstrated the expression of the specific tissue-protective EPO



Critically ischaemic leg with necrosis.

receptor in ischaemic skeletal muscle and the ability of EPO-derivatives to reduce ischaemia-induced tissue damage *in vitro*.

Further work will investigate the therapeutic potential of agents which modulate the TLR and ADMA pathways in reducing tissue damage in PAD. In addition, the potential of EPO derivatives in the treatment of PAD will be studied in more detail. Better understanding of processes that exacerbate tissue damage in PAD may lead to novel therapeutic strategies to reduce limb loss and improve outcome for patients with PAD.



JANICE TSUI

Specialty
Vascular Surgery.

Current position
Senior Lecturer and
Consultant Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
UCL, Royal Free Campus.

Publications

- Tsui J, Abraham D, Mehdizadeh A *et al*. Raised asymmetric dimethylarginine in ischaemic skeletal muscle. *Bri J Surg*; (in press).
- Joshi D, Ho TK, Tsui J *et al*. Erythropoietin is angiogenic and tissue protective in human critical limb ischaemia. *Bri J Surg*; (in press).

Presentations

- *The potential role of toll-like receptor 2 in critical limb ischaemia*. International Society of Applied Cardiovascular Biology; September 2010; Cambridge, Massachusetts, USA.
- *141 helix-B peptide of erythropoietin could be used as pharmacotherapy in critical limb ischaemia*. The Vascular Society of Great Britain and Ireland; November 2010; Brighton, UK.

Further funding

Royal Society Joint Project Grant for two years.

A study to investigate the mechanisms of chemotherapy-associated liver injury



STEVEN WHITE

Specialty

Hepatobiliary and liver transplantation.

Current position

Professor of HPB and Transplant Surgery.

Title of fellowship

Pump Priming Award.

Site of work

The Institute of Cellular Medicine.

Publications

- Robinson S, Manas DM, Pedley I *et al.* Systemic chemotherapy and its implications for resection of colorectal liver metastasis. *Surg Oncol* 2009; epub ahead of print.
- Robinson S, Mann J, Mann D *et al.* Irinotecan treatment is associated with impaired expression of cytokines required for effective liver regeneration as a result of the NFkB DNA damage response. *HPB (Oxford)* 2010; 12 (Suppl 1): 314.

Presentations

- *Cytokine production by colorectal tumours in response to irinotecan may be linked to the development of chemo associated steatohepatitis.* International Hepato-Pancreato-Biliary Association; April 2010; Buenos Aires, Argentina.
- *Culture of hepatocyte cell line in the presence of irinotecan is associated with the production of pro-inflammatory cytokines.* British Association for the Study of the Liver; September 2009; London, UK.

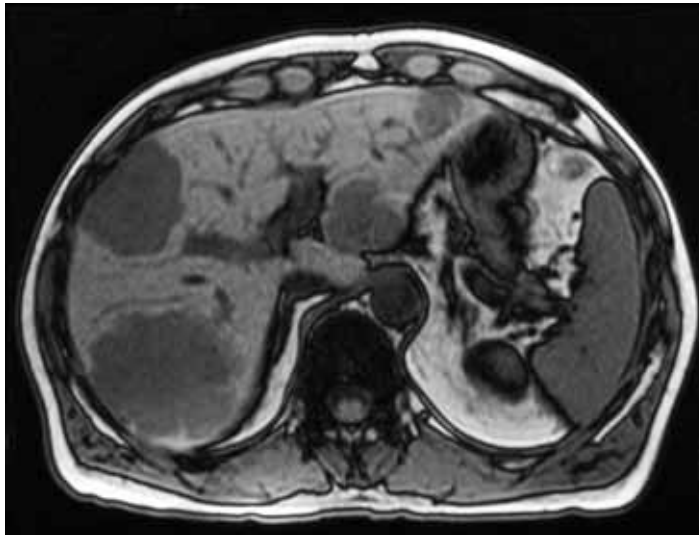
Prizes

Ella Foster Memorial Award, 2011.

Further funding

The Wellcome Trust for 2.5 months.

Colorectal cancer is the second most common cause of cancer-related death in Western Europe and the USA. Up to 50% of patients will develop liver metastasis and 25% will have liver metastasis at presentation.



An MRI from a patient with extensive colorectal liver metastasis.



A normal liver.



A liver damaged by chemotherapy.

Colorectal liver metastasis occurs in 50% of patients during the natural history of the disease. The only hope of long-term cure is by liver resection. However, many patients have chemotherapy (irinotecan) before liver surgery in the hope of improving patient survival but this can damage the liver and makes surgery more risky. The features of this are sinusoidal obstruction syndrome and steatohepatitis.

Tissue samples ($n=40$) from patients having liver resection for metastatic colorectal cancer will be analysed for factors

that may influence hepatocyte growth and proliferation, eg HGF, EGF and IL-6 and TGF- β). The activity of various transcription factors (STAT and NF- κ B) that drive the cell cycle will also be assessed as will the balance between cell death and proliferation. An in vitro model to assess cell death was also developed.

The use of a hepatocyte cell line demonstrated the release of pro-inflammatory cytokines (IL-6 and TNF- α) when exposed to irinotecan at increasing doses, leading to the potential development of steatohepatitis.

Similar findings were found when colorectal cancer tumour cells were exposed to irinotecan at clinically relevant doses. An in vivo model suggested impaired expression of IL-6 occurs despite increasing binding of p65 to its promoter on the IL-6 gene. This suggests that following treatment with irinotecan NF- κ B functions as a transcriptional repressor, impairing expression of cytokines required for effective liver regeneration. As yet, microarray gene analysis of human samples has not been completed and results are still awaited at the time of writing.

This is an important area as there has been little research published on this subject. For those patients with advanced disease the likelihood of curative surgery is poor as their liver is unable to regenerate after receiving chemotherapy. Understanding some of the mechanisms of chemotherapy-induced liver injury will help us understand ways in which we can prevent this, so many more patients could have potentially curative surgery.

The effect of pamidronate treatment on bone health in patients with neuromuscular disease undergoing hip surgery

The incidence of post-operative fractures in patients with cerebral palsy undergoing hip reconstruction has been reported to be up to 30%.

Fractures following hip spica removal in children with cerebral palsy undergoing hip reconstruction is a relatively common and serious complication following hip spica removal.

Prophylactic pamidronate treatment has been shown to improve bone mineral density in non-ambulatory children with cerebral palsy. The effect of pamidronate treatment on bone mineral density in relation to hip surgery has not been studied. If we show that bone mineral density is significantly improved by prophylactic pamidronate treatment then a randomised study is going to follow investigating whether the incidence of fractures (which is more clinically relevant) can be reduced with prophylactic pamidronate treatment.

If the incidence of fractures can be reduced by prophylactic pamidronate treatment it will improve the clinical outcome of surgery, avoid the pain associated with fractures, avoid re-hospitalisation and allow physiotherapy to continue.

The children with cerebral palsy undergoing hip reconstruction who consent for the study will be randomised into treatment and placebo groups. The treatment group will receive intravenous pamidronate for three consecutive days three weeks prior to surgery. The

placebo group will be treated with intravenous saline rather than pamidronate for three consecutive days two weeks prior to surgery. The two groups would otherwise be treated in the same way. Computed tomography scans will be performed prior to surgery and after hip spica removal (the time in which fractures occur), which will allow us to determine whether pamidronate improves bone mineral density at the end of treatment.



Michalis (right) discussing the hip x-rays of a child with cerebral palsy with a trainee.



In theatre performing an open reduction for a dislocated hip.



MICHALIS ZENIOS

Specialty
Orthopaedic surgery.

Current position
Consultant Paediatric
Orthopaedic Surgeon.

Title of fellowship
Pump Priming Award.

Site of work
Royal Manchester
Children's Hospital.

A biliary cancer microchip scan.
Siobhan McKay

In 2009–2010

4,800,000

hospital admissions
resulted in surgical
care in England

Preiskel prize reports

The Preiskel prize is an award of up to £500 for clinical students who wish to pursue a career in surgery and who are planning to undertake an elective in surgery in the developing world.

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Cleft lip and palate surgery in Mexico City

PRIYANKA CHADHA

Medical school
Imperial College London

Site of work
Hospital General,
Mexico City, Mexico

I reflect with great fondness on the time that I spent on my elective in Mexico City. I travelled with the hope of gaining clinical experience in plastic surgery and to observe rare cases from this part of the world. Plastic surgery is a great interest of mine and I was very keen to expand my knowledge and expertise in this field through an elective abroad. I was fortunate enough to acquire a period working in a hospital with a plastic surgery team, who welcomed me very warmly, led by one of the most eminent cleft lip and palate surgeons in the world, Professor Ortiz Monasterio.



Priyanka and Professor Monasterio in Hospital General.



Priyanka and the surgical team prior to a cleft lip and palate repair.

The majority of my time during the elective period was spent with a small but very successful plastic surgery unit in Hospital General Dr Manuel Gea González. The typical day started at 7am and approximately five surgical procedures were completed. There was no shortage of patients waiting to be seen outside the unit but only a few patients were admitted for surgical procedures on a daily basis. The main operating days were Monday and Wednesday. The other weekdays were occupied with ward rounds, conferences, meetings, lectures and smaller surgical procedures that required local anaesthetics. The plastic surgery unit focused on teaching and it was not uncommon for surgeons to leave one surgery in order to come into the adjacent room to observe another interesting case.

I was allowed to observe and assist the surgeries of my choice during my time in the hospital. I spent some days assisting with the surgical procedures that are commonly performed in the UK and others observing remarkable and rarer surgeries. I would highly recommend this elective to others wishing to gain experience in plastic surgery outside the UK.

Challenges in providing surgical care in remote areas of Papua New Guinea

CLARE FRANCIS

Medical school
Newcastle University
Medical School

Site of work
Kiunga Hospital,
Western Province,
Papua New Guinea



Clare using the haemoglobin scale with a patient in traditional grass skirt.

I wanted a challenging elective and was inspired by the story of a surgeon nun called Sister Jo working in the Western Province of Papua New Guinea, who answered my question 'why?' by saying there is a need. I was curious to see how this translated and what it meant in terms of making clinical decisions, allocating scarce resources and living in an isolated and inhospitable wilderness.

Life expectancy in Papua New Guinea is low and health indicators are stagnating. Ranked 137 on the Human Development Index, the country trains only 40 doctors per year and rural areas are painfully neglected. My supervisor, Sister Joseph, Consultant Surgeon, was the only doctor at the government hospital she had been sent to overhaul. In the first week she was the subject of a death threat warranting a restraining order, indicating the difficult conditions in which she works.

I led a project to train community health workers to use haemoglobin kits recommended by the World Health Organization for use in resource-poor settings to screen for and treat anaemia, particularly targeting women of childbearing age. This was achieved in outreach patrols down the Fly River to outlying villages. These villagers are lucky if a doctor visits twice a year. The rest of the year they live without healthcare and must suffer the hazards of their environment: malaria, tuberculosis, hookworm and simple infections, to name a few. A lot of pathology is attributed to traditional beliefs encompassing sorcery.

My time in Kiunga reinforced those elementary principles of attention to detail, perseverance and determination and I have had my eyes opened to making personal sacrifices to try your best to serve patients' needs.

Prognostic measures of outcome for traumatic head injuries in rural Kenya

JASMINE HO

Medical school
Royal Free Hospital,
London

Site of work
Tenwek Hospital,
Bomet, Kenya



Jasmine suturing the wounds of a patient from a bus accident in accident and emergency.

I spent my electives at Tenwek Hospital, a teaching hospital located in the Bomet District of Kenya's Rift Valley Province. Since its founding in 1959, the hospital provides primary and outpatient care and also serves as a tertiary referral centre for inpatient and surgical services to the population of south-western Kenya.

Personally, the elective was an eye-opening experience into how medicine and surgery is practised in a rural setting. The hospital is frequently visited by overseas surgeons of various specialties. As a result, I was able to assist operations in various fields such as neurosurgery, ophthalmology and obstetrics, and observe many interesting cases that are rarely seen in the developed world. I also attended weekly teaching sessions and trauma calls, which allowed me to put into practice my surgical skills, including suturing and triaging of patients in emergency situations.

The elective also gave me an opportunity to carry out the neurosurgery research project on traumatic head injury patients in Tenwek. The research aimed to identify prognostic factors of outcome in head injury patients by means of a retrospective study of patient records. The results will assist medical staff in establishing more appropriate management plans with respect to the patient's prognosis. This research is expected to continue through a prospective study, which will hopefully result in a publication in one of the African surgical journals. This will help shape the management of head injury patients across rural Africa, where there is a lack of guidelines for such cases.

I highly recommend this elective to other medical students as it helped me develop not only my surgical skills but also my appreciation of the challenges of trauma and surgery in the developing world. This has further encouraged me to pursue a career in surgery.

A summer in Soweto assisting the trauma and orthopaedic team

PETER HODGINS

Medical school
Swansea University

Site of work
Chris Hani Baragwanath
Hospital in Soweto,
South Africa

In August 2010 I spent eight weeks with the trauma team at the Chris Hani Baragwanath Hospital. It has a reputation for being a great place to gain practical experience in a challenging environment. I was based in the 'surgical pit', the receiving ward for trauma and surgery. There was no system of triage in the pit and patients would sit in the corridor to await treatment. As a result, the most important skill I learnt was how to assess a patient properly and prioritise his or her treatment.

It was often chaotic and unpredictable. On my first day I examined a man with a wound to the head; my intention was to suture this. On examination I found him to have a flail segment on the right side, with surgical emphysema. His chest x-ray showed a haemothorax. The patient had to be intubated and have a chest drain inserted. The prevalence of guns in the local area was highlighted by the case of a seven-year-old boy brought in by his mother, having 'swallowed a bullet'. He was comfortable at rest but I noted an absence of breath sounds on the left and so sent him for a chest x-ray. The boy and his mother did not understand the difference between swallow and aspirate, and had nearly been sent home by one of the nurses. In the end the bullet was removed by endoscopy.

My aim before undertaking this elective was to gain practical experience in treating and helping to manage critically ill patients. This aim has definitely been met. In a hospital chronically short on staff, I think the presence of medical students who were willing to pitch in and help with anything from suturing to acting as porters was greatly appreciated.

The surgical pit.



Chest x-ray of child that had aspirated a bullet.



An elective in paediatric surgery at the Hospital Nacional De Niños in San José

SHIREEN IBISH

Medical school
University of Liverpool

Site of work
Hospital Nacional de Niños, San José, Costa Rica

During my paediatric placement I worked with Professor Paul Losty from Alder Hey Children's Hospital, who has done previous work with the surgical team in Costa Rica. I was inspired by the tales and wanted to visit the country to experience their hard work for myself. Before departing for Costa Rica I set myself learning objectives, which included the following:

- Learn and experience the main paediatric surgical complaints in Costa Rica and differences in management compared with the UK.
- Assist in an audit on neonatal surgical complications with Dra Salas, Professor of Paediatric Surgery.
- Assist in surgical procedures and be able to practise and improve my clinical skills.
- Experience Costa Rican cultures and traditions and their impact on healthcare.



(Right to left) Anaesthetist; Shireen; Dr Andres Catrillon, Plastic, Reconstructive and Aesthetic Surgeon; Tavo Vargas, Intern in the children's burns unit.



Shireen (left) and Dra Salas in scrubs on a night shift at the paediatric surgical unit.

During my five weeks' elective period at the national paediatric hospital of Costa Rica I was allocated to shadow the surgical team. In a very short amount of time I was given the opportunity to shadow over 100 paediatric surgeries and assist under strict supervision. I worked with the team to develop knowledge of the common conditions faced by the surgical team, including appendicitis, abdominal conditions (gastroschisis and exomphalos), undescended testes and many more. I also worked with anaesthetists to develop knowledge of anaesthesiology and patient preparation for surgery as well as post-operative management, to gain a full experience of a surgical journey.

Gaining an insight into the work of surgeons under different healthcare systems, watching their excellent team work and their determination to do their best for the children was a priceless experience.

Surgical site infections in the Solomon Islands

PIYUSH MAHAPATRA

Medical school
University College London

Site of work
National Referral Hospital, Honiara, Solomon Islands



Piyush closing after plating of an ankle fracture.



A visiting orthopaedic team from Australia training staff in dealing with complex cases.

My time in the Solomon Islands was spent at the National Referral Hospital in the capital Honiara, which as the name suggests, is where patients are referred to from the over 900 islands that make up the country. As such, I got to be involved in interesting and complex surgical cases, for many of which I obtained valuable hands-on surgical experience.

I also took the opportunity to research infection rates after surgery. It is a well-known major surgical complication in the UK; recent guidelines have been published by the National Institute for Health and Clinical Excellence to try to improve surgical practice to reduce the numbers of these infections. I wanted to explore further how surgical practice differs between an under-resourced and underfunded healthcare system and our own and to ascertain whether these differences result in more infections.

My results showed that 13.5% of patients having surgery in the National Referral Hospital would go on to develop an infection. This compares with about 5% of patients in the UK. However, I discovered that surgical practice varied very little between the Solomon Islands and the UK. Therefore, it appears that in the Solomon Islands, increasing funding and resources would be the key method for improving the infection rate as surgical practice appears to be up to date.

The challenge of conducting research in a poorly resourced healthcare system was made considerably easier by the friendly and helpful staff. The entire experience including theatre time and research was thoroughly rewarding and I would highly recommend the country for any medical student hoping to gain further experience by going on a surgical elective.

Exploring enzymatic liquefaction of pancreatic necrosus in New Zealand

PKK ELECTIVE PRIZE WINNER

CHARLOTTE MILLS

Medical school
University of Aberdeen

Site of work
University of Auckland,
Auckland, New Zealand



Auckland City Hospital.

Acute pancreatitis is a relatively common disease, which in its severe form is characterised by pancreatic tissue death, infection and a significant mortality rate. Surgical removal of dead pancreatic tissue can be life-saving but is often delayed to allow for pre-operative liquefaction and clear demarcation of pancreatic necrosis. During this waiting period, the systemic effects of acute pancreatitis can worsen patient outcome. It would thus be a major advance if the liquefaction process could be accelerated.

I travelled to Auckland, New Zealand, to investigate the novel hypothesis that the liquefaction process could be facilitated with the use of enzymes, under the supervision of Professor John Windsor and Dr Benjamin Loveday of the Pancreas Research Group. Enzymes are currently used in the debridement of necrotic skin wounds and thoracic empyema (collection of pus in the pleural space) and have been shown to be effective in targeting protein debris in dead tissue without causing injury to healthy tissue.

I carried out the project in a laboratory and conducted experiments using purpose-designed 'liquefaction chambers' to test the efficacy of a range of enzymes at degrading samples of necrotic pancreatic tissue. The project provided me with first-hand experience of project design, data collection and analysis as well as exposure to fascinating laboratory processes and practical procedures such as protein assays, immunochemistry and the use of a cryostat in frozen section histology. When not in the lab I had the opportunity to observe hepatopancreatic biliary surgery in the new Auckland City Hospital.

My elective provided the rare opportunity to be involved in and contribute to the initial stage of an ongoing research project, which aims to pioneer a new treatment solution for an often devastating disease. I would recommend the experience to anyone interested in frontline laboratory research and cutting-edge surgery in a beautiful country.

Surgical elective in Namibia

MIRAE SHIN

Medical school
University of Oxford

Site of work
Katutura State Hospital,
Windhoek, Namibia



Mirae closing a wound in the emergency department.

I spent five weeks in Katutura State Hospital in Namibia, attached to the general surgery team. My aim for the elective was to experience surgery in the developing world, an interest of mine from an early age. Moving from South Korea to the UK at age 12 gave me a taste of what it is like to immerse

oneself completely in an unfamiliar environment. Spending time in a hospital in Uganda several years ago gave me a taste of what it is like to immerse oneself completely in an unfamiliar environment. Spending time in a hospital in Uganda several years ago gave me a taste of what it is like to immerse oneself completely in an unfamiliar environment. Spending time in a hospital in Uganda several years ago gave me a taste of what it is like to immerse oneself completely in an unfamiliar environment.

My time in the hospital was divided between ward work, assisting in theatre and being on call in the emergency department. Common surgical complaints in the UK were still common in Namibia, with many cases of appendicitis, abscesses, cancers and trauma. However, the details of these common conditions were somewhat unfamiliar, with many gunshot trauma victims and most cancers presenting at extremely late stages. The biggest learning area for me was in managing acutely sick surgical patients. I was encouraged to make management decisions, which was terrifying to begin with but good training for being the on-call doctor in a few months' time. I was given the opportunity to perform minor surgeries under local anaesthetic such as draining abscesses and taking biopsies. I had many opportunities to close wounds both in the emergency department and in theatre.

Katutura State Hospital is a great place to do a surgical elective because it is a referral centre for many complex cases from throughout Namibia. I found that the consultant surgeons were extremely keen to teach and explain anything I did not understand. The five weeks gave me the desire to become very skilled at what I do and return to Africa to make a useful contribution.

Plastic surgery and more in India

VENKATESH SUBRAMANIAN

Medical school
University of Nottingham

Site of work
Right Hospital,
Chennai, India



In theatre after the reconstruction of a young girl's deformed limb.



Dressing the wounds of a teenager who suffered severe burns while attempting to free his dead friend from a live electrical circuit.

Fascinating cases included the reconstruction of flail limbs in children as a result of obstetric trauma and the skin-grafting techniques used to minimise the severe disfigurement of facial burns. I also spent time in a government hospital where, despite funding being even scarcer, the doctor-to-patient ratio is much greater. It was remarkable to see how the surgeons have adapted the available resources; for example, the prepping of skin involves pouring warm saline from a kettle directly on to the patient. I also had the privilege of contributing to the teaching of students and gaining an appreciation of the similarities and differences of training in India. Furthermore, I was able to practise basic surgical skills such as suturing and knot-tying under close supervision and guidance.

I also spent two weeks at Sri VPK Medical Charities, a centre of excellence for pre and post-operative diabetic management. Diabetes is very prevalent in Chennai and the careful, well-planned management of the surgical diabetic patient is essential. At this hospital I was able to get a grasp on how to optimise diabetic management and avoid complications of the disease. I was fully involved in all decisions and received one-to-one training. I would recommend this experience to students with an interest in plastic surgery to witness first hand the highly skilled surgical management that takes place at the Right Hospital.

The creativity and technical ingenuity involved in plastic surgery that I have seen so far in the UK inspired me to undertake an elective in this specialty at the Right Hospital in Chennai. The Right Hospital provides excellent clinical care to insured clients as well as the wider community, while facilitating the life-saving treatment of numerous burns victims from economically deprived areas.

During my seven weeks I was actively involved in theatres, outpatient clinics, teaching and audit.

Surgical education and the WHO checklist in Tanzania

SHAUN SHI YAN TAN

Medical school
University of Glasgow

Site of work
Kilimanjaro Christian
Medical Centre,
Moshi, Tanzania



Shaun examining a child with a mass in his abdomen caused by late presentation of a renal tumour.

My surgical elective was carried out for a period of five weeks in Kilimanjaro Christian Medical Centre (KCMC), Tanzania, in east Africa. Tanzania is populated by 36 million people and is one of the poorest countries in the world. KCMC is a specialist referral hospital serving 11 million people with more than 450 beds in Moshi. My elective was spent in the urological and general surgical departments. The aims of the elective were to experience developing-world medicine and be exposed to conditions not commonly seen in the UK; to hone my existing clinical surgical skills and knowledge; and to fuel my interests in working for an international medical relief organisation on qualifying.

I sought to contribute to and improve surgical safety in the operating theatres of KCMC by undertaking a surgical education project. Currently, the UK has adopted the 19-point World Health Organization (WHO) surgical safety checklist, which involves a series of checks before, during and after surgery. A paper by Gawande *et al* has shown that the use of this checklist significantly reduced the mortality and morbidity of surgical patients worldwide. Hence my project involved educating surgeons, trainees, nurses, anaesthetists and medical students in KCMC on the importance of surgical safety as well as the implementation of this checklist. This took place during department meetings, ward rounds and theatre sessions, where I produced posters to facilitate understanding and summarise the checklist steps.

I believe that at the end of my elective I had gained not only valuable insight into the rarer surgical presentations in the developing world but also a better understanding of surgical practice in Tanzania. While surgical procedures are intended to save lives, unsafe surgical practices can lead to substantial harm. My project has improved awareness of surgical safety as an important public health measure.

General surgery in Tanzania

KALPESH VAGHELA

Medical school
Imperial College London

Site of work
Teule Hospital, Muheza,
Tanga, Tanzania

Teule Hospital, located in the north-eastern corner of Tanzania, is the designated district hospital for the Muheza region, serving a predominantly rural population of 280,000. It was my east African roots that first drew me to Tanzania. It is where I hoped to learn about my cultural heritage and gain an insight into a healthcare system very different to our own. I was not disappointed on either account.

I spent my time at Teule under the supervision of Dr Leonard Mbago, the chief general surgeon. I was quickly assimilated into the busy surgical service and with the aid of my trusty Swahili



Assisting with a mastectomy for fungating breast cancer.

phrase book, I set about clerking and examining patients. I then formulated a management plan and followed up the patients in theatre, where I was able to assist in numerous surgical procedures.

Trauma constituted a large amount of the workload. The patient demographic, interestingly, was mainly young men who presented with broken legs and severe head injuries. As I travelled I quickly realised that they were foolhardy dala-dala drivers (local unofficial buses) who trapeze in and out of the buses as they hurtle along the treacherous Tanzanian roads. They would be cast and strung to a bag of stones and would spend the next six weeks under traction as their fractures healed.

Over a hundred patients would be seen, two at a time, in the weekly surgical clinics. Snake bites, burns, elephantiasis, malignancy and complications of labour would be commonplace. In a place where resources and money were sparse, I was humbled by the surgeon's outstanding experience and clinical acumen, skills which I feel have decayed in Western medicine. I left Teule with not only a renewed and fortified interest in surgery but also an unforgettable experience of a remarkable country. I have no hesitation in recommending Tanzania as an outstanding elective destination.



Jasmine Ho assisting in an emergency caesarean section – closing of the incision.



Shaun Shi Yan Tan in theatre after the reconstruction of a young girl's deformed limb.



Kalpesh Vaghela in surgical clinic with Dr Mbago.



Clare Francis and a patient on the general ward.

A scanning electron micrograph (SEM) of breast cancer cells. The cells are shown in a cluster, with some appearing as smooth, rounded spheres and others as more irregular, fragmented structures. The color palette is primarily blue and purple, with bright yellow highlights indicating areas of programmed cell death (apoptosis). The background is black, making the cells stand out.

Scanning electron micrograph of a cluster of breast cancer cells, showing visual evidence of programmed cell death (apoptosis) in yellow. Each cell is 15 micrometers across.
Annie Cavanagh/Wellcome Images

Approximately

90%

of cancer patients have some type of surgery for diagnosis, initial treatment, or management of complications

Higher degrees for intercalated medical students

Grants of up to £5,000 are competitively awarded to medical students studying at medical schools in the UK who are undertaking an intercalated BSc degree related to surgery. This is helping to encourage and support those who wish to consider a career in surgery to undertake a period of surgical research and broaden their understanding of disease and illnesses.

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USAMA AHMED

Medical School
Division of Surgery and Interventional
Science, University College London.

We conducted a molecular study investigating male urethral cancer, in order to characterise it with immunohistochemical markers previously studied in conventional squamous cell carcinoma of the penis. Staining of urethral and penile cancer samples was performed using immunohistochemistry techniques.

Our results showed that urethral squamous cancer cells both cycle and proliferate faster than penile squamous cell cancer and therefore may contribute to a more aggressive pattern of malignancy.



Usama (centre) with supervisors Dr A Freeman (left) and Mr A Muneer (right).

The findings have been submitted as an abstract to an international urology conference and will be published in a peer-reviewed journal. My immense gratitude goes to the College, whose generous grant enabled me to undertake this intercalated degree and helped fund this novel research.

PRIYANKA CHADHA

Medical School
Imperial College London.



Priyanka with her supervisor
Mr C Bicknell.

The grant that I received from the College has enabled me to carry out my project on endovascular robotic simulation at St Mary's Hospital, London. The grant was divided to purchase consumables, including state-of-the-art robotic catheters, and also to contribute to student subsistence. Having completed my project, I have been fortunate enough to

present at national and international conferences, including at the VEITHsymposium™, New York. I am grateful to the College for the support it has provided, without which I would not have been able to complete my project or have the opportunity to present the work at meetings and conferences across the world.

RADHIKA CHADHA

Medical School
University of Oxford.



Radhika in the lab.

This generous grant enabled me to continue my work in the Transplantation Research Immunology Group in the Nuffield Department of Surgical Sciences, University of Oxford. Using an animal model of skin and cardiac transplantation, I have been examining the immune responses that prevent anti-rejection strategies from working. I have also been focusing on developing cellular therapies that induce tolerance to the transplant with the aim of improving long-term survival outcomes in the clinical arena. I am extremely grateful to the Royal College of Surgeons for their invaluable support

MOHAMMED CHOWDHURY

Medical School
University of Manchester.

I undertook a Masters in Research in Medical Sciences degree at the University of Manchester with the department of Cardiovascular Research and Department of Vascular and Endovascular Surgery at Manchester Royal Infirmary.



Mohammed and Dr Y Alexander, lab supervisor.

My one-year research project looked at carotid plaque stability and carotid disease biomarkers, and I was awarded a distinction

for my research. The research was awarded first prize at the Joint International Society for Vascular Surgery/International Vascular and Endovascular Congress in Milan at the end of 2009. I commenced an academic foundation programme at Manchester Royal Infirmary and plan to continue this research.

ANTHONY GIBSON

Medical School
Imperial College London.



The team
neuromonitoring;
from left to right:
Dr S Burch,
Anthony,
Professor J
Lieberman and
Mr R Lyon.

The College award enabled me to carry out a series of experiments in spinal cord neuromonitoring at The University of California, San Francisco. We were able to better define the nature of intra-operative spinal nerve root damage and produce evidence on which stage of surgery imparts most damage on the roots. I presented my findings at the North American Spine Society and American Academy of Orthopaedic Surgeons conferences in 2010. I also submitted data on intra-operative radiation doses using cone-beam computed tomography scanning, and I am writing up work in quality-of-life outcomes research.

ROBERT GROUNDS

Medical School
Cardiff University.

This generous award from the Royal College of Surgeons enabled me to conduct a pre-clinical *in vitro* gene transfer study into the treatment of pyoderma gangrenosum. The investigations led to the creation of a protocol for lipofection, which will be invaluable



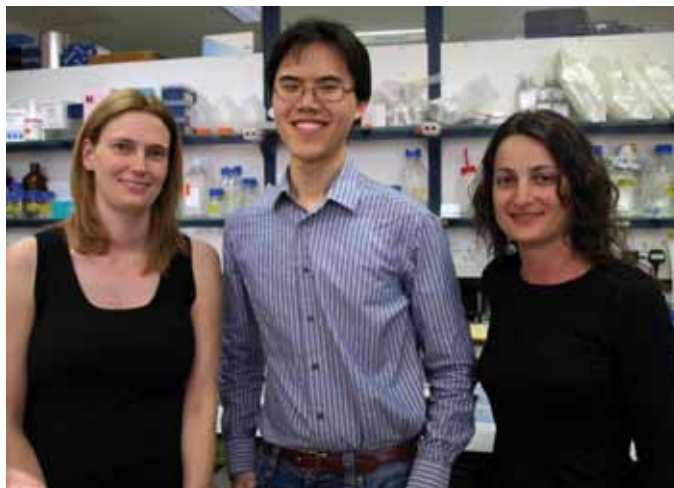
Robert working in the laboratory.

for the insertion of therapeutic genes in future research into treating the disease.

The grant gave me an invaluable opportunity to work alongside experts in the field, improve my communication and organisation skills, acquire laboratory skills and, most importantly, provide an insight into how research and medicine can be integrated to produce new therapeutic techniques that ultimately improve patient care.

CHIU LEE

Medical School
Imperial College Healthcare NHS Trust.



Chiu (centre) with Dr K Midwood (left) and Dr A Piccinini (right).

Thanks to the generous grant from the College, I was able to carry out my BSc project in the Kennedy Institute of Rheumatology with Dr Kim Midwood and Dr Anna Piccinini. We studied the effects of the matrix glycoprotein tenascin-C on apoptosis in animal model cells with the long-term aim of discovering new treatments for scarring and chronic inflammatory diseases. During my time at the lab, I learnt numerous techniques in cell culture and sample analysis. More importantly, I gained an insight into the scientific method and acquired critical thinking skills.

FINDLAY MACASKILL

Medical School
Newcastle and Durham Universities.

The generous College grant enabled me to undertake an MRes degree focusing on stem cell and regenerative medicine. My research project was working with tissue samples from keloid and expanding these into cell lines. The dramatic improvement of these skin tumours by intralesional injection of bleomycin has been noted clinically but a mechanism of action is still not known. We concluded that bleomycin may be acting via cell-cycle arrest and apoptosis. We also discovered a potential role for genotyping an enzyme known to break down bleomycin, as this may be a fruitful predictor of outcome. This research will comprise part of a paper to be published next year.

I went on to obtain a distinction in my degree and won best student research proposal from my institute.



Mr A Owens (left), Dr N Hole (centre) and Findlay (right).

SIMON PARKER

Medical School
Imperial College London.

Based at the Kennedy Institute of Rheumatology, I was able to contribute to ongoing research exploring the involvement of muscle-derived stromal cells in tibial fracture repair – a basic science project in the field of plastic and reconstructive surgery.



Simon with his supervisor Dr N Horwood, a researcher and lecturer from The Kennedy Institute of Rheumatology.

This generous grant meant that I was able to carry out my own research, as the additional funds allowed expansion of the project into the most current and cutting-edge aspects of stem cell biology. I have no doubt that my experience was enhanced by this opportunity, for which I am extremely grateful, and hope that I will be able to carry through the many and varied skills I have acquired into a career involving research.

DAVID RUTKOWSKI

Medical School
University of Manchester.

My project involved investigating a cohort of patients with established keloid scars. The scars are resistant to steroids, often leaving surgery as the only treatment, which is innately problematic. I recruited 20 patients and evaluated their clinical responsiveness to steroids using non-invasive imaging techniques. In addition, biopsies were taken before and after treatment from which I compared the levels of the glucocorticoid receptor in responsive and non-responsive patients by using immunohistochemistry, qRT-PCR and Western blotting.

I would like to thank the Royal College of Surgeons for the funding it has provided for me. This year has encouraged me to pursue a career in surgical academia, which I will be continuing as part of my academic foundation track at Wythenshawe Hospital, Manchester.



David (centre) with his supervisors Mr A Bayat (left) and Professor A McGrouther (right).

ADELINE SALIM

Medical School
University of Liverpool.

I took an intercalated year to pursue an MPhil in Child Health under Professor Paul Losty and Professor Mike White, focusing my research on neuroblastoma and how manipulation of key molecular targets can result in cancer cell death. I am very grateful for the College's support of the project.



From left to right: Dr D Spiller, Adeline, Adeline's supervisors: Professor M White and Professor P Losty, and Dr V See.

During the year, I have presented a poster at the Postgraduate Researchers In Science Medicine conference (Manchester 2009), which won the best poster award, and an oral presentation on the clinical outcomes of neuroblastoma patients treated in Liverpool at an International Paediatric Surgical Oncology conference in Boston, USA. The manuscript has been submitted to the journal *Pediatric Blood and Cancer* and is awaiting publication.

OMAIR SHARIQ

Medical School
Imperial College London.

The College's award helped me undertake a BSc in Surgery and Anaesthesia at Imperial College London and carry out research in the field of regenerative medicine. In view of the ageing population and shortage of donor material, tissue engineering is emerging as a novel approach that overcomes the limitations of current bone repair strategies. My project investigated the differentiation of pluripotent embryonic stem cells into functional osteoblasts for potential use in bone tissue engineering and reconstructive surgery. The award allowed me to present my work at the Association of Surgeons in Training and Future Orthopaedic Surgeons conferences in 2010, where I was awarded prizes for the best oral and poster presentations, respectively.



Omair (left) with his supervisor Professor S Mantalaris.

YIZHOU WAN

Medical School
Imperial College London.

The generous grant from the Royal College of Surgeons has helped me carry out research with experts in the Division of Neurosciences at Charing Cross Hospital. My project involved investigating the vestibular-guided spatial memory using electroencephalography. This is important in determining how deep brain stimulation surgery may be used to alleviate cognitive symptoms in neurodegenerative conditions such as Parkinson's disease.



From left to right: Mr D Buckwell (Honorary Research Officer), Professor MA Gresty, Yizhou and Dr B Seemungal (supervisor).

During the course of my work I acquired many skills in how to design clinical experiments and gained valuable insight into the role of academia in modern medicine. I am currently conducting further experiments with the aim of publishing in a peer-reviewed journal.

Every
minute

9

hospital admissions
in England result
in surgical care



Funding partnerships

The College is very grateful to all those individuals, charitable trusts, companies, College fellows and members who have supported the surgical research programme. We would particularly like to acknowledge the following:

Charitable trusts, foundations, companies and individuals

Andrew Anderson Trust
Ballinger Charitable Trust
C A Redfern Charitable Foundation
Caravan Club (Suffolk Centre)
DBP Trust
Donald Forrester Trust
Dunhill Medical Trust
EF and MG Hall Charitable Trust
Enid Linder Foundation
Eranda Foundation
Ethicon UK Ltd
Family of the late Mr Stefan Galeski
Family Rich Charities Trust
Fellows Fellowship Fund *the College is very grateful to its members and fellows who donate regularly*
Frances & Augustus Newman Foundation
Golden Bottle Trust
Golden Charitable Trust
Grand Lodge of Freemasons 250th Anniversary Fund
Hong Kong Freemasons Overseas Trust
Michael and Anna Wix Charitable Trust
Oakdale Trust
Philip King Charitable Settlement
Roger Vere Foundation
Roger Raymond Charitable Trust
Rosetrees Trust
Shears Foundation
Sir Samuel Scott of Yews Trust
Thriplow Charitable Trust
W E Dunn Charitable Trust
Wyndham Charitable Trust
Women's Institute - West Sussex Federation
Wyseliot Charitable Trust

Freemason Lodges

Bedfordshire Lodge of Installed Masters (no. 7301)
Berkshire Installed Masters Lodge
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Claydon Lodge of Freemasons
Croydon Lodge of Achievement
Clerkenwell Lodge of Installed Masters (no. 9628)
Gloucestershire Installed Masters' Lodge (no. 7900)
Huddersfield & District Installed Master Association
Humber Installed Masters Lodge (no. 2494)
King's Court Lodge (no. 8441)
Lodge of Lu Pan (no. 9387EC)
Masonic Province of Yorkshire, West Riding
Provincial Grand Lodge of Somerset
Shropshire Installed Masters Lodge (no. 6262)
Warwickshire Installed Masters Lodge
South West Surrey Masters Lodge (no. 5965)

Endowments, restricted and legacy funds

Anderson Reid Fund
Bernhard Baron Fund
Blond McIndoe Fund
Buckston Browne Gift
Burghard Bequest
Children with Cancer Research Fund
Dennis F Clark Legacy
Michael M Brown Legacy
Jessie Butt Legacy
Patricia Constance Curry
Lillian May Coleman Legacy
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Geoffrey G T Fletcher Legacy
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The Dr Shapurji H Modi Memorial ENT Research Fund
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Sir Arthur Sims Fund
Sir John Lang Bequest
Richard J Stafford Legacy

The estate of the late Dr MP Starritt
Tudor Edwards Fellowship
Vandervell Research Fund
John L Williams Legacy
Derek P Winks Legacy

Joint fellowships

Association of Breast Surgeons
British Association of Surgical Oncology
British Association of Plastic, Reconstructive and Aesthetic Surgeons
Cancer Research UK
Society of Academic and Research Surgeons
Arthritis Research UK
British Society for Surgery of the Hand
Get Ahead
Medical Research Council

For more information on supporting the College's research programme please:

- see www.rcseng.ac.uk/fundraising
- or contact the Development Office on 020 7869 6086 or email fundraising@rcseng.ac.uk

Prizes and travelling awards

The College is pleased to be able to offer a variety of awards as a result of the generous support of companies and individuals. These awards give surgeons the opportunity to work in an overseas institution to learn more about a particular surgical technique or area. The surgeon can then use the experience and know-how gained during the overseas fellowship to improve the care of patients in this country. The committees that decide the recipients of the travelling awards always include leading surgeons.

Ethicon Foundation Fund

The Ethicon Foundation Fund was established by the generosity of Ethicon Limited. The fund provides financial assistance towards the cost of the travel to and from a research or training fellowship, thereby promoting international goodwill in surgery. Applicants should be sufficiently advanced in their training to benefit from such an experience or be within one year of their appointment as consultant surgeon.

Recipients October 2009

Robert Brightwell
Stephen Broomfield
Thomas Chapman
Marc Gladman
Paul Phillips
Marcus Wagstaff

Recipients April 2010

Seema Biswas
Anna-May Long

Recipients October 2010

Charles Durrant
Steven Lo
Matthew Potter
Shiba Sinha
James Snelling

Colledge Family Memorial Fellowship Fund

The Colledge Memorial Travelling Fellowship was established by Miss Cecilia Colledge in 1979 in memory of her father, the distinguished surgeon Lionel Colledge, and her brother, Maule, who died in active service during the Second World War. The fellowship was founded to promote and advance the study and knowledge of surgery, in particular head and neck surgery, for the benefit of patients. Applicants must be senior trainees or new consultants who plan to a study for a period overseas.

Recipients 2010

James Russell Tysome
Charles Edward Buckland Giddings
Joanne Rimmer

Sir Ratanji Dalal Research Scholarship

This research scholarship was founded under the will of Sir Ratanji Dinshaw Dalal. It is awarded jointly by The Royal College of Surgeons of England and the Royal College of Physicians of London. Applications are invited for this research scholarship, which is intended to support a project in either tropical surgery or tropical medicine. The scholarship is tenable for one year and is open to all medical practitioners registered in any part of the Commonwealth. It may be held in any institution in Britain or overseas that is approved by The Royal College of Surgeons of England and the Royal College of Physicians of London.

Recipients 2010

Andrew John Stevenson
Helen Nabwera
James John Aird



From left to right: Samuel, Catherine and Paul receiving their prizes at the College Diplomates' Ceremony on Tuesday 6 July 2010.

The Rosetrees Trust Prize 2010

The Rosetrees Trust Prize was established in 2009 and applicants are asked to write an essay to: 'Describe how your research project will contribute to improvements in patient care within the next five years?'. The winners of the 2010 Prize were:

1st Prize: Surgeon Lt-Commander Catherine Doran: 'To stop the bleeding in a war zone'.

Runner Up: Mr Samuel Ford: 'Iron chelation and oesophageal cancer'.

Runner Up: Mr Paul Malone: 'The importance of a better understanding of DRUJ anatomy, function and disability'.

Catherine, Samuel and Paul were awarded their prizes at the College Diplomates' Ceremony on Tuesday 6 July 2010.

Norman Capener Travelling Fellowship

This biennial travelling fellowship was founded with funding provided by friends and admirers of the late Norman Capener, a past vice-president and honorary medallist of the College. Applicants should be enrolled for orthopaedic surgical training or have recently completed a course in orthopaedic or hand surgery.

Recipients 2010

Danyal Nawabi
Harvinder Pal Singh

Ronald Raven Barbers Award

The Ronald Raven Barbers award was established by the generosity of The Worshipful Company of Barbers (at Ronald Raven's bequest). The award is aimed at assisting trainee surgeons going abroad to develop their individual skills through special education or training of an innovative nature. Particular weight is given to the excellence of the applicant, the innovative qualities of the work to be done and the relevance of such work to patient care.

Recipients 2010

Seamus Phillips
Anna Pantling
Emma Stormer

Lectures delivered in 2009–2010

2009

Hunterian	Mr Mohammed Ali Akhavan • British Society for Surgery of the Hand • 12 November <i>The interplay between hypoxia, angiogenesis and inflammation in rheumatoid hand disease</i>
Hunterian	Mr John Carmel Watkinson • British Association of Endocrine and Thyroid Surgeons • 20 November <i>Personal perspectives on a career in thyroid surgery</i>

2010

Zachary Cope Memorial Lecture	Professor Andrew Bradley • Society of Academic and Research Surgery • 6 January <i>Challenges and opportunities in renal transplantation</i>
Hunterian	Mr Oliver James Kayes • British Association of Urological Surgeons • 7 January <i>The role of the DNA replication license and conservative surgery in penile cancer</i>
Hunterian	Mr Michael Ka Wah Li • Colorectal Day, Royal Free Hospital • 5 February <i>Laparoscopic resection for rectal cancer – towards a new gold standard</i>
Hunterian	Mr Zain Ismail Khalpey • Society for Cardiothoracic Surgery in Great Britain and Ireland • 7 March <i>Species differences in adenosine metabolism; implications for cardiac transplantation</i>
Hunterian	Professor John Patrick Vincent Collins • Regional Representatives Day • 15 June <i>Educating and training surgeons in a changing world</i>
Hunterian	Mr Andrew Owens • Cardiothoracic Section of the Royal Society of Medicine • 25 June <i>Is the adult mammalian heart capable of self-renewal? The identification of native cardiac stem cells</i>
Hunterian	Professor John Knowles Stanley • British Orthopaedic Association • 13 September <i>The problems of the distal radioulnar joint</i>
Robert Jones	Professor Nicholas Clarke • British Orthopaedic Association • 13 September <i>Paediatric orthopaedics and the Robert Jones birthday volume</i>
Hunterian	Dr Steven John Thomas • British Association Surgical Oncology • 1 November <i>An aetiological model for oral cancer in betel quid chewing populations</i>
Hunterian	Miss Vivien Clare Lees • British Association of Plastic, Reconstructive and Aesthetic Surgeons • 1 December <i>Functional anatomy of the distal radioulnar joint in health and disease</i>
Arris and Gale	Mr Darryl Benjamin Dunn • British Association of Plastic, Reconstructive and Aesthetic Surgeons • 3 December <i>Understanding and preventing metastatic melanoma migration in vitro and in vivo</i>
Hunterian	Mr Brian David Hancock • College of Surgeons of East, Central and Southern Africa • 3 December <i>Obstetric fistula in Africa: a continuing surgical challenge</i>

Clinical Effectiveness Unit

Academic collaboration

The Clinical Effectiveness Unit (CEU) was established in 1998 as an academic collaboration between the College and the Health Services Research Unit of the London School of Hygiene and Tropical Medicine (LSHTM). The CEU has become a national centre of expertise in methods, organisation and logistics of large-scale studies of the quality of surgical care. It has fostered collaborative links with numerous NHS organisations, the Department of Health (DH) and relevant regulatory bodies.

Currently, the CEU has sixteen staff members, eight of whom are academic staff members of the LSHTM. The multidisciplinary character of the CEU is shown in the varying backgrounds of

its staff, eg health services research, epidemiology, medical statistics, clinical medicine, public health and social science. In May 2011, Dr David Cromwell, Senior Lecturer in Health Services Research at the LSHTM, took over the directorship of the CEU from Jan van der Meulen.

Funding

The CEU receives an annual contribution from the College's research funds and the College underwrites four senior academic posts within the LSHTM. However, the CEU aims to be self-funding by obtaining external project grants and contracts. As a result, the financial support from the College is kept to a minimum.

At the heart of NHS policy

Around the same time that the CEU was founded, DH published a policy document, *A First Class Service: Quality in the New NHS*, which emphasised the importance of clinical governance as an approach for NHS organisations to improve the quality of their services. One of its key recommendations was that all healthcare providers should participate in national audits appropriate to their specialty.

More than a decade later, DH re-emphasised the importance of clinical audit in its consultation document, *Liberating the NHS: an Information Revolution*, published in December 2010. Clinical audit is given a critical role 'in comparing the effectiveness of different



David Cromwell leading a research methods course at the Beit CURE Hospital in Blantyre, Malawi.

clinical approaches and in identifying areas for quality improvement'. The participation in clinical audit is seen as a 'professional norm' and clinicians and other healthcare professionals are expected 'to continue to play an active role in developing information solutions that are safe, that work for patients and service users and that help improve outcomes.'

The document recognised the importance of eradicating duplicate information and improving the efficiency of data collection by exploiting data held in existing systems, including the hospital episode statistics database. Although these policy developments were set for England only, many of its intentions regarding the information needs are mirrored in Scotland, Wales and Northern Ireland.

Using information provided by patients is highlighted as an effective way to involve patients in the decisions about their care. Patient reported outcome measures will be used increasingly to look at the outcomes of care for patients with a wide range of health problems

Epidemiological approach

The CEU has adopted an epidemiological approach (the study of the causes, distribution and control of disease in populations) for its involvement in national audit projects.

An essential element of this approach is that epidemiological methods are being used to generate quantitative evidence on the processes and outcomes of surgical care as well as on their determinants.

In simpler words, many projects of the CEU aim to answer two generic questions:

why patients with similar health problems are treated differently and why patients undergoing similar treatments have different outcomes.

Audit and research

Many projects that the CEU carries out straddle clinical audit and research. Clinical audit is a means of quality assessment, focusing on the structure, process and outcome of care. The objective of research is to provide answers to questions that directly or indirectly contribute to defining what is best practice. Research is finding out what you ought to be doing whereas audit is finding out whether you are doing what you ought to be doing. However, most audit projects the CEU is involved in also aim to provide an insight into why variations occur: are you doing what you ought to be doing and if not, why not? This is a very important element of these audit projects because it has the potential to guide activities that aim to address the observed deficiencies in quality of care.

Furthermore, methodological research is required to solve the many challenges that national clinical audits bring about. Minimum datasets need to be developed that are detailed enough to capture all essential clinical information to address the audit questions in a meaningful way but at the same time keep the burden on health service staff involved in data collection as small as possible. Questionnaires and data collection forms need to be designed and validated and their feasibility needs to be determined.

There is a need to refine and further develop the statistical techniques that take the specific clinical context into

account. The development of methods to adjust for case mix is essential to ensure that we compare 'like with like' and that we avoid penalising surgeons and teams who treat more serious cases. For example, regression models that can predict the risk of a poor outcome are often used to produce 'risk adjusted outcomes'. An alternative approach to take case mix into account is based on matching patients on their 'propensity' to receive a certain treatment.

Development of data linkage techniques is needed to allow patient data from different sources to be combined, which will reduce the burden of data collection and improve completeness and coverage. Methods of presentation should reflect the needs of the different target audiences, including surgeons, patients, managers and commissioners.

As a result, most projects carried out by the CEU address audit as well as research questions. The research questions add value to the audits by improving the methods that are being used and by guiding the audits' implications and recommendations for clinical practice.

Patient-reported data

Traditionally, national clinical audits only considered information that was reported by clinicians. However, changes in clinical measures based on clinicians' judgements or derived from laboratory or imaging data do not always translate to improvements in patients' symptoms and quality of life. It has been recognised that patient-reported outcomes add important information to quality improvement initiatives. The CEU has led the way in this area. We carried

out a pilot study demonstrating the feasibility of collecting patient-reported information after elective surgery and then used patient-reported measures to compare outcomes of patients undergoing elective surgery in independent sector treatment centres with outcomes of patients treated in the NHS.

Other CEU projects invited patients to answer questions about their experience of the care they received. These questions can not only address the accessibility and cleanliness of the facilities but also the information that patients were given about their conditions as well as the extent to which they were involved in making decisions about their treatment.

Patients can also provide valuable information about co-existing conditions that may affect their prognosis. These co-morbidities need to be taken into account when outcomes are evaluated. Similarly, questions about complications and adverse events may be included in questionnaires given to patients after their treatment. It is often very difficult to obtain this information accurately through other means.

Since 2009, NHS providers in England are required to support the collection of patient reported outcomes for a number of frequent elective surgical procedures. About 250,000 patients a year are invited to complete a questionnaire before and after their operation. The CEU plays a leading role in improving methods to compare outcomes reported by patients and in designing summary measures that are meaningful to the public, clinicians and other stakeholders (metrics). This project also includes the analysis of patient-reported outcomes of hip and knee replacement, linked to the data that clinicians report to the National Joint Registry.

Hospital episode statistics

During the last decade, the CEU has increasingly used administrative data for its audits and research projects. The hospital episode statistics (HES) database and the equivalent database in Scotland, Wales and Northern Ireland contain records of diagnostic and procedure information for all NHS admissions in the UK. The major advantages of these databases are that they provide a national picture and the treatment pathway of patients can be followed over time.

Although the quality of the available information has been challenged, the CEU has demonstrated the value of HES in a range of clinical areas.

Administrative data need to be used judiciously and in the right circumstances. The CEU has built up considerable experience in the use of diagnosis and procedure codes in the HES database to identify particular groups of patients and their condition, the treatments they receive and their outcomes.

HES data are being used in almost all CEU projects. In some projects, the HES data are being used in isolation. However, HES data are especially valuable in combination with other data sources, especially when linked at the level of the individual patient. This linkage approach may provide the 'best of both worlds': completeness of coverage of follow-up based on HES and clinical detail derived from clinical data.

Revalidation

In 2009, the CEU started a project that aims to assess the value of administrative data (HES in England and patient episode data for Wales) for revalidation. Revalidation refers to new requirements for doctors to renew their licence to practise every five years and to complete a process of recertification if they are on the specialist register. HES has the potential to be an important source of information as it is expected that recertification is based as much as possible on clinical outcomes.

This project aims to develop procedure-specific metrics for individual clinicians and multiprofessional teams. It also explores the feasibility of disease-



specific metrics. The latter is achieved by linking HES records related to a patient's journey to enable the description of outcomes of a disease pathway.

Information governance

The CEU is continuously strengthening the security of its data storage systems. These activities have had an impact on the information governance arrangements within the College as a whole. The College is continuously updating its information systems so that it can complete the Information Governance Statement of Compliance that is prescribed by the NHS for organisations that aim to handle sensitive clinical data. An action plan has been agreed that will further strengthen the College's information governance arrangements.

Teaching

Each year, the CEU runs a number of courses for surgeons and other healthcare professionals on statistics, clinical research methods and evidence-based surgery. The courses use a mixture of teaching methods, ranging from lectures to interactive seminars and hands-on computer practicals. Course faculty often include methodologists recruited from CEU staff as well as senior clinicians with a strong interest in research and audit.

Major projects in 2011

National Audit of Oesophagogastric Cancer

This audit started on October 2006 and is being carried out in partnership with the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology

and the national clinical audit support programme of the NHS Health and Social Care Information Centre (NHS HSCIC). The audit is funded by the Healthcare Quality Improvement Partnership (HQIP).

National Mastectomy and Breast Reconstruction Audit

This audit is being carried out in partnership with the Association of Breast Surgery, the British Association of Surgical Oncology, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, and the NHS HSCIC. The audit, which started in January 2007, was funded by the HQIP until March 2011.

Patient-reported Outcome Measures in Elective Surgery

CEU staff, working closely with academics of the LSHTM, contribute to the further development of the use of patient reported outcome measures after inguinal hernia repair, varicose vein surgery, and hip and knee replacement. The programme is funded by DH. Northgate Information Systems is responsible for data collection and routine analysis and presentation.

Specific areas of interest for CEU staff are the potential bias in observed outcomes introduced by selective recruitment and response, variation in outcomes by subgroups, and variation in the severity of symptoms and treatment thresholds before treatment. Further work is carried out on the development of metrics that can be used to present results to different groups, including clinicians, commissioners and patients. The programme also involves an analysis of the outcomes and cost-effectiveness of

the most frequently used prostheses for hip and knee replacements.

Craniofacial Anomalies Network (CRANE) Database

This is a registry of all children born with cleft lips and palates in England, Wales and Northern Ireland, their treatment and the outcomes. The CEU has been the host organisation for this registry since April 2005. CRANE is funded by the NHS specialist commissioners involved in cleft care.

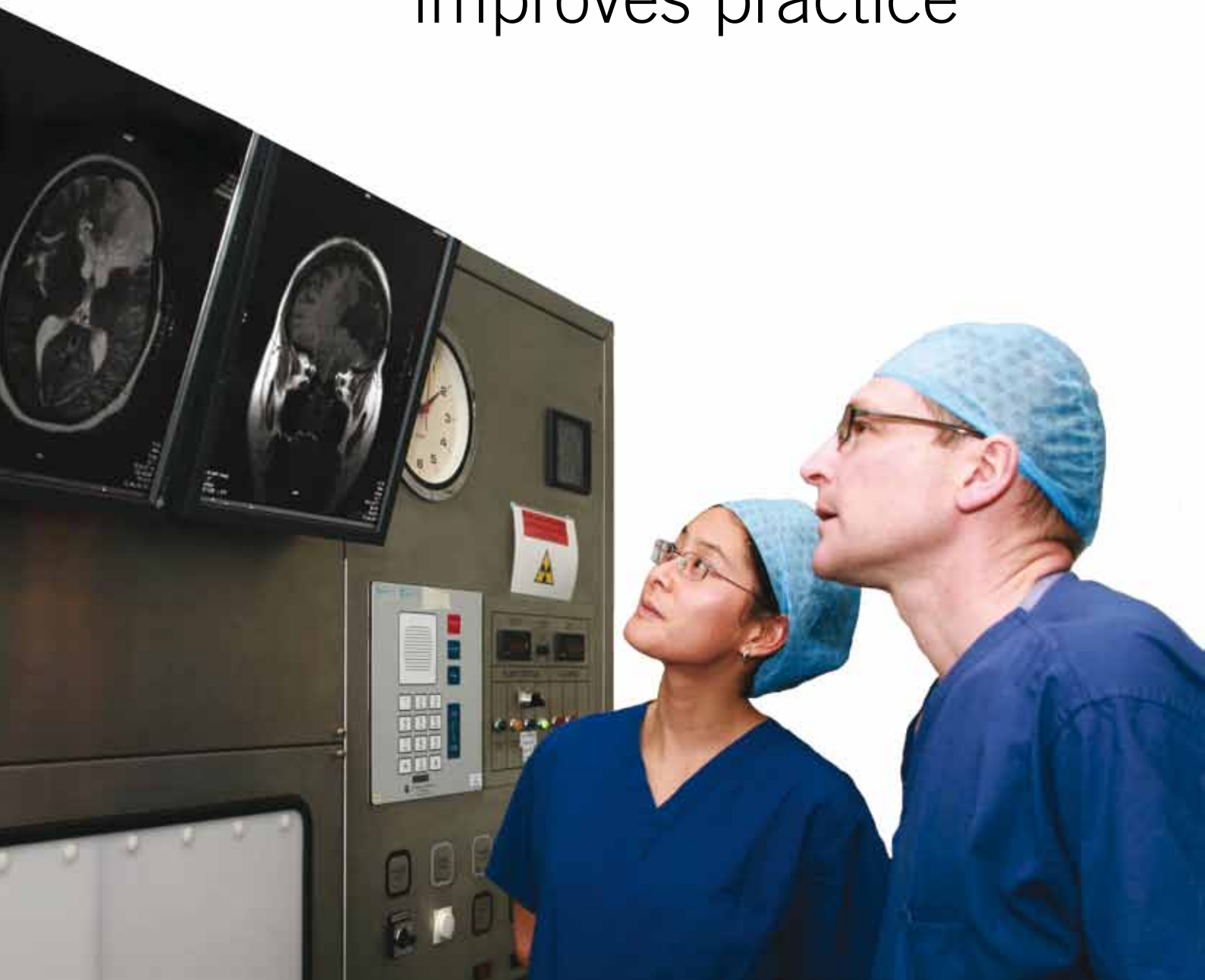
UK and Ireland Liver Transplant Audit and the UK Intrathoracic Transplant Audit.

These audits are carried out in collaboration with UK Transplant. They accrue and validate data from all transplant centres in the UK and Ireland from 1994 and 1995 respectively. The CEU is responsible for the analysis and interpretation of the data on post-transplant outcome for each participating centre, stratified for major risk factors. The audits are funded by the NHS National Specialised Commissioning Group.

Value of administrative data for revalidation

This project aims to develop procedure-specific and disease-specific metrics, derived from administrative data, to assess the performance of individual hospitals and/or consultants in the UK and elsewhere. Case studies are being carried out to evaluate the feasibility and validity of these metrics in the areas of ischaemic heart disease, urological malignancies and peripheral vascular disease. The project is funded by the Academy of Medical Royal Colleges.

High quality
research
improves practice



Centre for Evidence in Transplantation

The Centre for Evidence in Transplantation (CET) is situated in the College's Clinical Effectiveness Unit (CEU). The centre was established in 2005 to evaluate the quality of evidence available in solid organ transplantation (www.transplantevidence.com). Furthermore, the CET has developed an electronic library of all randomised controlled trials (RCTs) and has, more recently, selected good-quality systematic reviews in solid organ transplantation. The transplant library is available to members of the European Society for Organ Transplantation (ESOT) as well as to subscribers to the journal *Transplantation*. Some medical school libraries have purchased it from Ovid, who was responsible for the technical development of the library. We expect its use to spread fairly rapidly over the next few years. In 2010, the Oxford University libraries named the transplant library as 'database of the month'.

It is often asked why we need an electronic library in transplantation but if we remember that RCTs and systematic reviews/meta-analyses of RCTs are level-one evidence in any medical discipline then the aim was to develop a very easily-searched and comprehensive library that could produce the relevant references in minutes rather than hours. Indeed, the great Archie Cochrane, after whom the Cochrane library is named, predicted the need for specialist/sub-specialist libraries of RCTs some 30 years ago: ours is the first!

The CET and the ESOT have begun a collaboration in which it has been agreed that the CET would become the knowledge centre for ESOT with a special emphasis on helping with the design and

reporting of RCTs in Europe. One aim of this collaboration is to improve the methodological quality of European trials in organ transplantation by helping the investigators with the early stages of trial design and planning. This, of course, is not unique to European trials in that the CET has carried out an analysis of all RCTs in organ transplantation published between 2004 and 2006 (around 300), which shows that only one-third of trials reported were of good methodological quality. This does detract from the value of the evidence provided by these trials.

Publications during the past year include:

- Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis and a systematic review. *Transplantation* 2010; **89**: 1–14.
- Currie AC, Knight SR, Morris PJ. Tuberculosis in renal transplant recipients: the evidence for prophylaxis. *Transplantation* 2010; **90**: 697–704.

In addition, a systematic review and meta-analysis of calcineurin inhibitor sparing regimens in solid organ transplantation has been carried out by Neil Russell, a surgical research fellow. This was part of his thesis, successfully submitted for his MChir degree at University of Cambridge.

We are pleased to announce that John O'Callaghan has been appointed as a clinical research fellow jointly between the CET and the Oxford Transplant Centre. He will be leading a systematic review of organ preservation in transplantation.

This review will be a collaborative project between the CET and the Cochrane Renal Group in Sydney, Australia.

Finally, the third *Evidence in Transplantation (EVIT)* course was held at The Royal College of Surgeons of England on 18–19 March 2011, for European transplant clinicians, and was again regarded as a success by the participants.

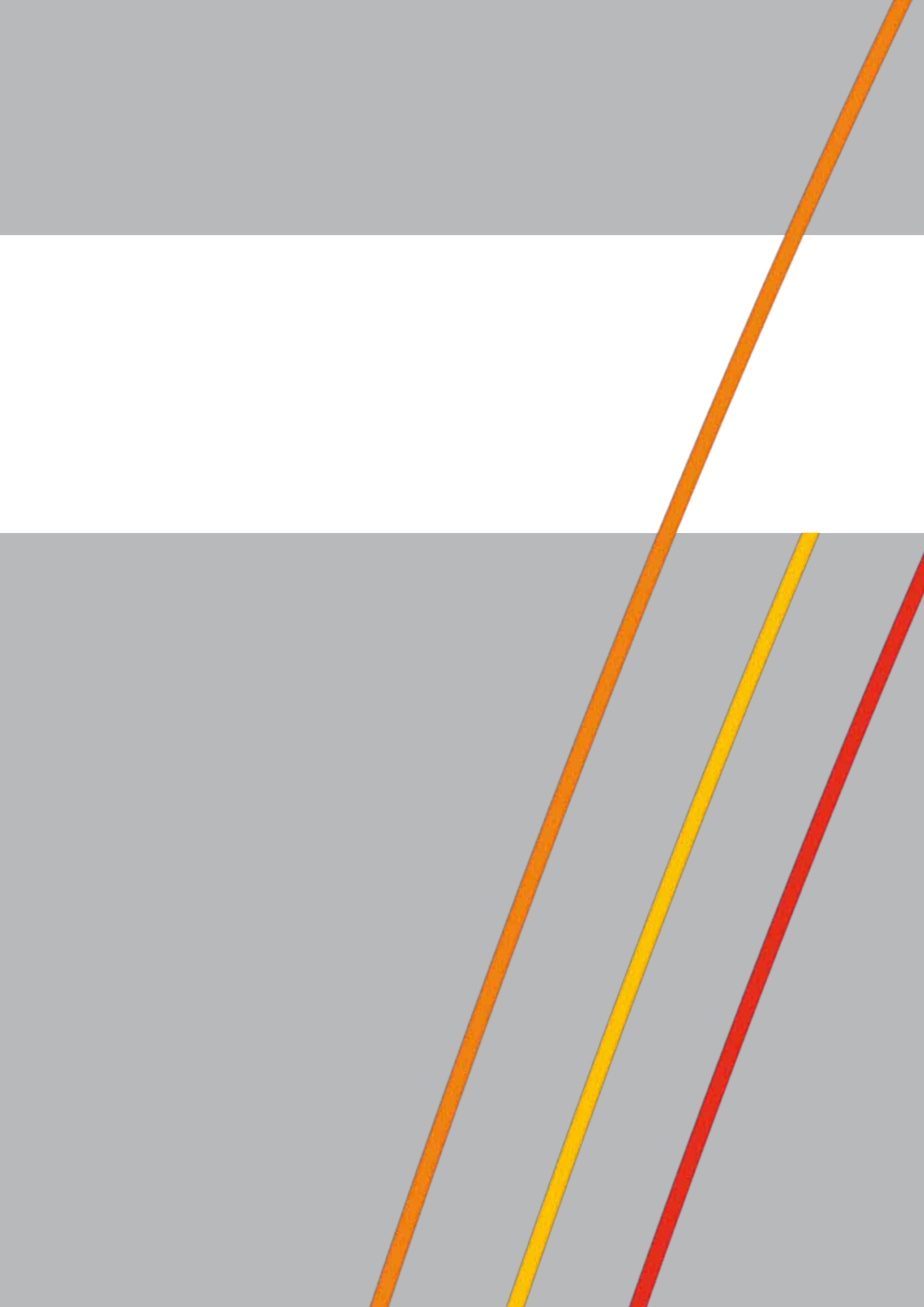
Keep the future in safe hands

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for more information
or for an informal
chat about how your
legacy or donation
can help support the
future of surgery



t: 020 7869 6086
e: fundraising@rcseng.ac.uk
www.rcseng.ac.uk/fundraising







The Royal College of Surgeons of England plays a vital role in supporting surgical research in the UK. Every year the College awards competitive research fellowship grants for specific projects that aim to advance surgical standards and improve patient care.

Most of us will have surgery at some point in our lives and, with over four million operations carried out in England alone each year, there are few people who have not benefited in some way, either directly or indirectly, from advances made in surgical research.

To find out more about supporting the College's research programme please contact the Development Office:

t: 020 7869 6086

e: fundraising@rcseng.ac.uk

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