SURGICAL RESEARCH REPORT

2012

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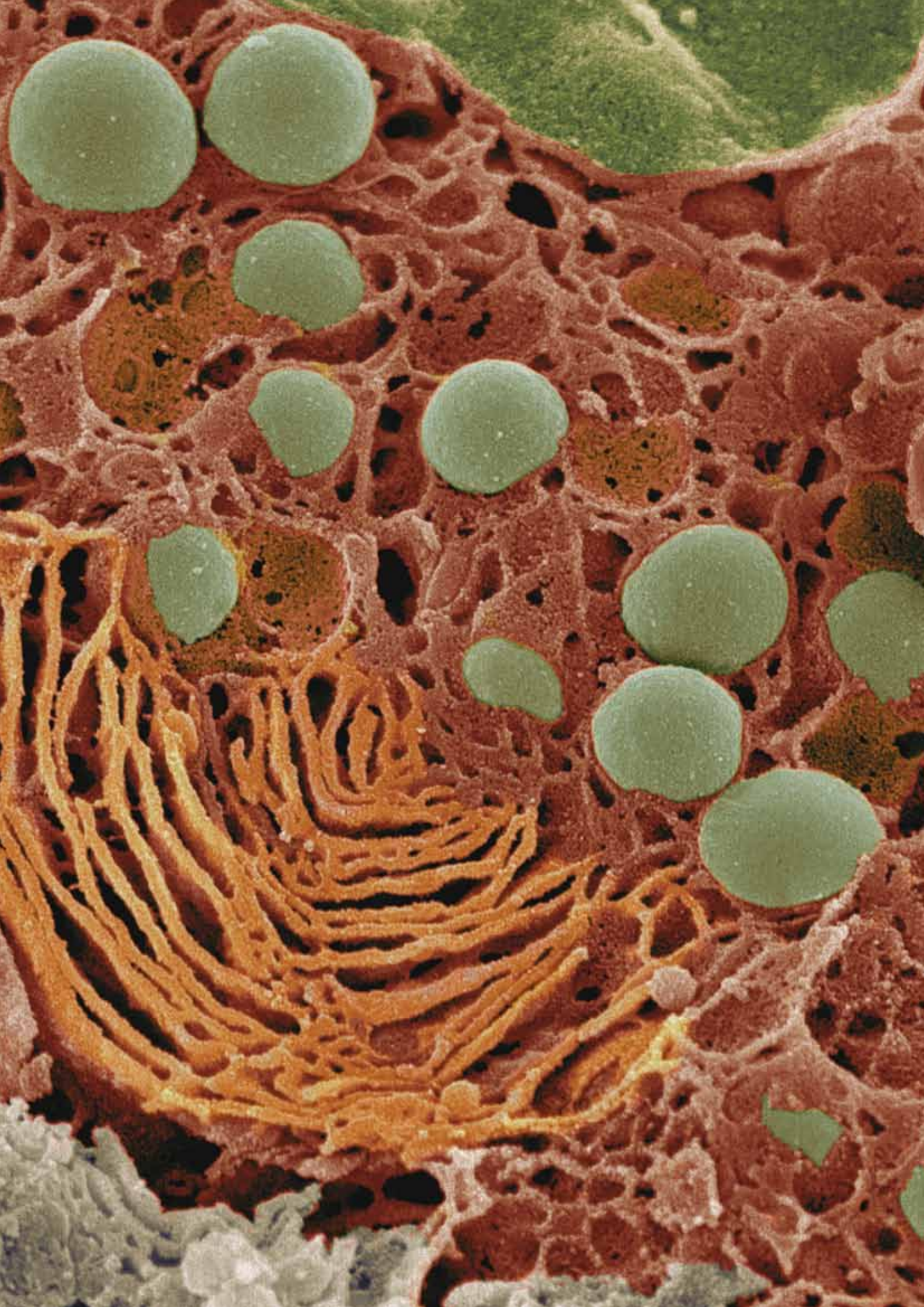
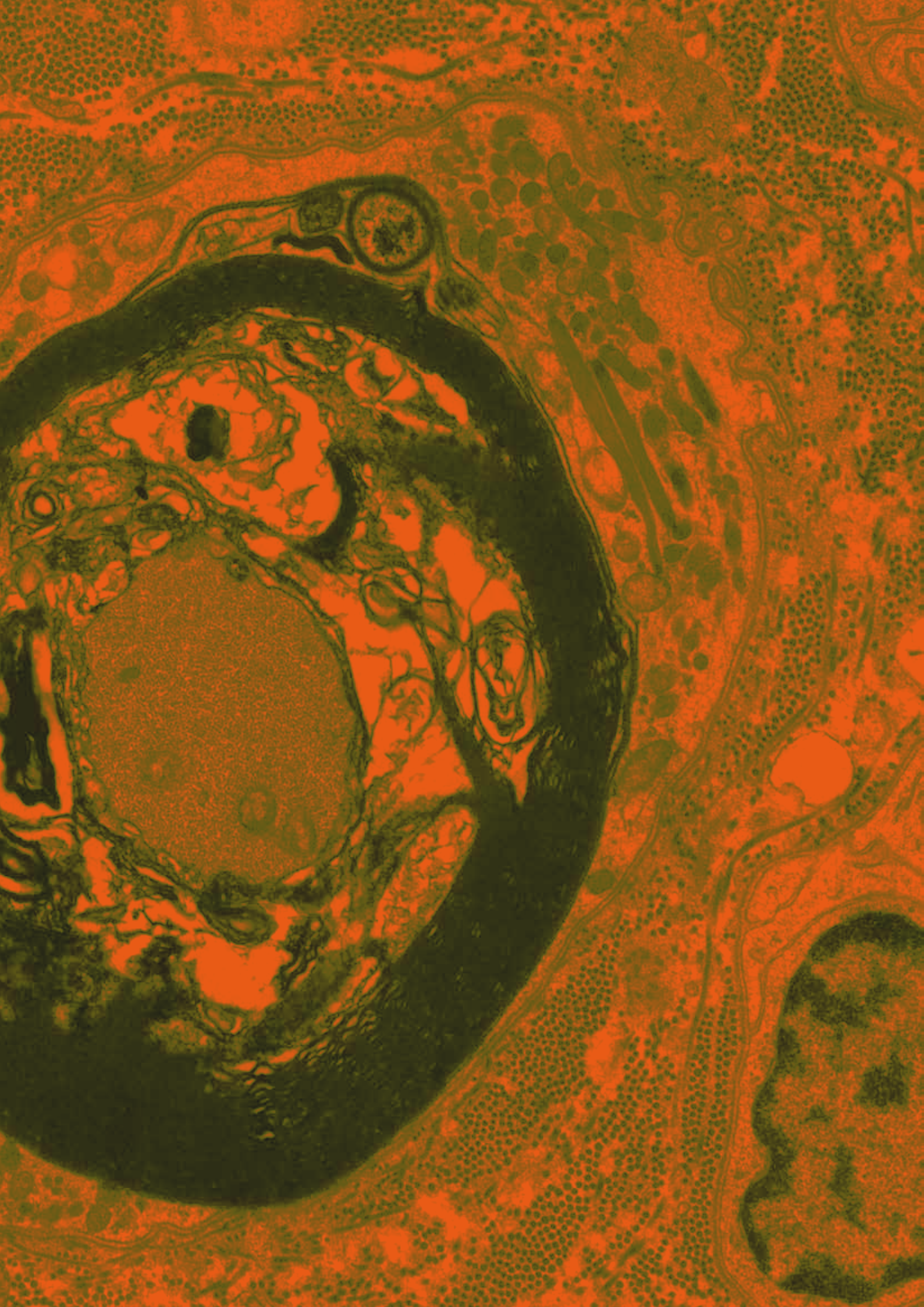
ADVANCING SURGICAL STANDARDS





surgical research report 2012

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Chairman's introduction

Professor Derek Alderson
Chairman, Academic and Research Board

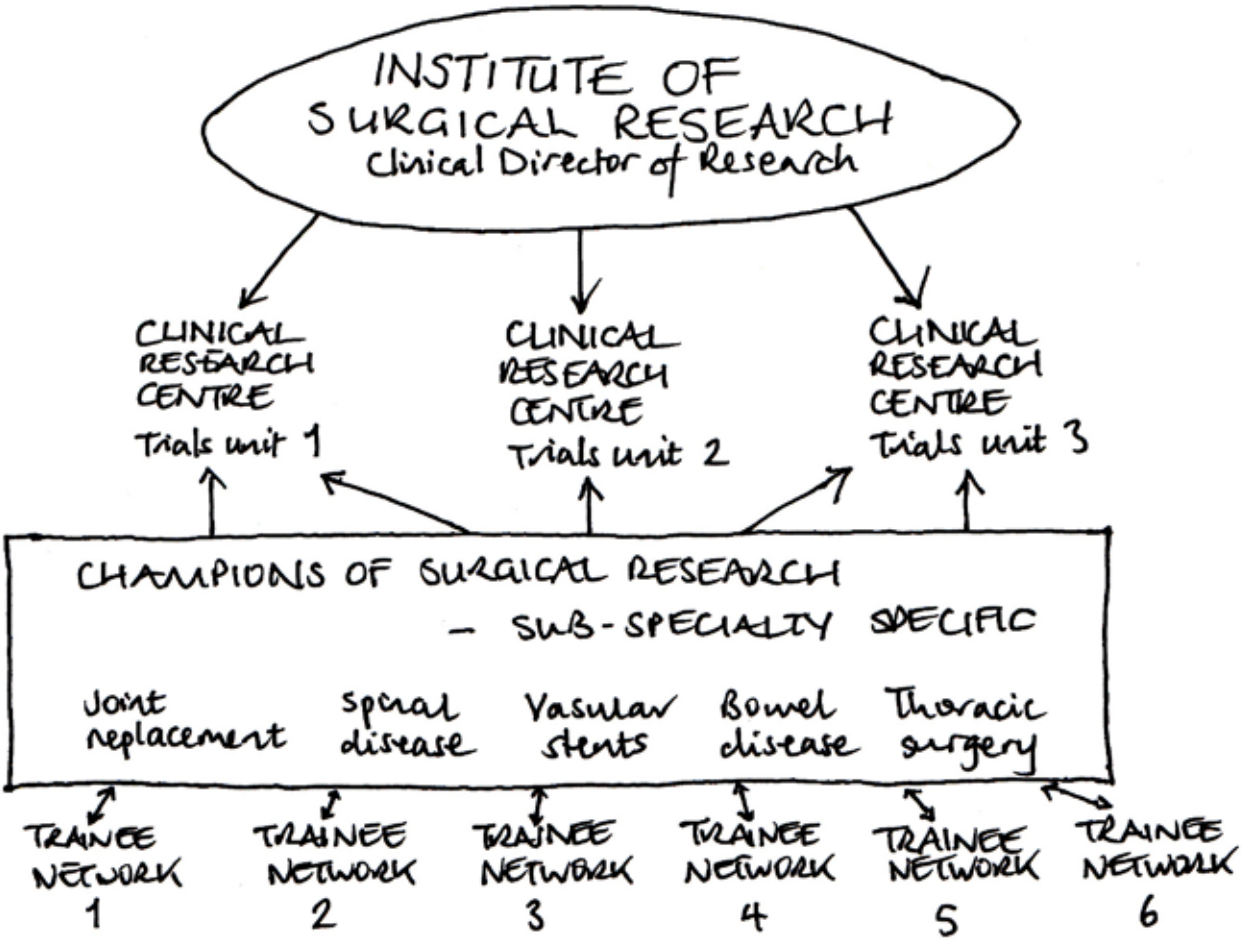
2011 has been another busy and productive year for the Academic and Research Board of the College. The publication of *From theory to theatre: overcoming barriers to innovation in surgery* seemed to strike a chord with most surgeons and certainly raised our profile as a 'research active' organisation in the minds of major funders. Most of the credit for highlighting the various issues must go to our new President, Professor Norman Williams, who during his time as chairman of this board raised the profile of research within the College and initiated the strategy to turn aspirations and recommendations into action.

We felt that a dedicated individual should lead this process and Council was minded to approve the appointment of a Director of Research. Shortlisting took place over the summer and we were delighted to announce that the first holder of this post would be Professor Dion Morton from Birmingham. Dion took up this post in October. The most important element of this role has been to lay out a strategy that will deliver high quality surgical research in a sustainable fashion. The cornerstone of the strategy is the development of clinical research centres that will focus on the development of surgical clinical trials. We realise that successful centres will need investment to ensure that they can provide local training for new surgical researchers and, in due course, offer training in research methods to every surgical trainee within the context of each specialist curriculum. We also realise that surgeons with interests in specific areas of research will need to be identified as 'champions' to promote and initiate surgically relevant studies. These also need to be financed. An outline of this overall scheme is shown in the figure, opposite.

It became apparent that the cost to set up and run such a centre over a five-year period is around £750,000, so an ambitious initial target was set to raise £2.5 million in order to create three centres with national coverage. I am pleased to report that thanks to an enormous amount of hard work by our Development Office we have already secured the funding to advertise and hopefully open the first centre in 2012. The College gratefully acknowledges the support of the Rosetrees Trust in sharing this vision for the future of surgical research and generously making the necessary investment to establish this project. At the same time we must also acknowledge our ongoing support from Freemasonry and their commitment to this College through choosing us as the principal beneficiary of their Royal Arch bicentennial appeal in 2013.

While it remains a strong belief of the board that well-conducted, large, multi-centre trials are the most effective means to actually change surgical practice, creating a trials infrastructure has other benefits. Many clinical trials involve tissue collection that can stimulate new avenues of research or provide the impetus for translational studies. A successful trials culture, led by the UK, should be extended into the rest of Europe to make results more generalisable and enable important answers to be found more rapidly. In this way, the College hopes to provide research opportunities for all and diverse programmes of research designed to meet the needs of each trainee. Perhaps most importantly, we would wish to see research that genuinely meets the needs of the surgical patient.

Despite the serious downturn in the economy and the inevitable consequence that investments that underpin the research fellowship scheme are worth less than they were 12 months ago, the College has managed to maintain the number of awards, due to our longstanding good relations with our major benefactors who have been persuaded to dig that little deeper on our behalf. The Dunhill Medical Trust have provided funding for five new two-year joint fellowships related to surgery for the elderly, a grant from DBP Trust in Jersey has sponsored two breast and two colorectal fellows and we have continued to make joint awards with



the British Association of Paediatric surgeons, the British Society for Surgery of the Hand, Arthritis Research UK and Cancer Research UK. Seven awards have been made to military personnel. An exciting new development was an invitation to participate in the Fulbright award scheme. It is a pleasure to report that two surgical research fellows have been successful. We are the only royal college to have such fellows – so much for the notion that surgical research is not competitive!

With that said, it is not surprising that competition for research fellowships remains intense. Just over 120 applicants meant that there was only about a one-in-seven chance of success. All of the assessors agreed that there were substantially more projects that deserved funding than we were able to award. This only serves to highlight the enthusiasm for research among trainees and the need for this College to do everything possible to foster a research culture and provide the resources to support it.

This sense of greater College involvement has resulted in a series of meetings with important national bodies and allowed us to form much stronger connections. Representatives of the National Institute for Health Research, the Academy of Medical Sciences and the Association of Medical Research Charities have all been invited to discuss and comment on our plans and it seems likely that partnership arrangements will emerge where mutual benefit seems certain.

The Clinical Effectiveness Unit (CEU) has also seen a change in 2011. Jan van der Meulen has stepped down as

Director and David Cromwell has taken up the baton. Many important projects have been completed under Jan's leadership and his contributions have been appreciated both by the research fellows and by the wider surgical community. The unit continues to have a broad portfolio of activity involving a number of national audits. New national audits under an expanded National Clinical Audit and Patient Outcomes Programme have been announced recently and the CEU will be a major partner in the breast and the prostate cancer audits.

All of this activity is not possible without considerable activity behind the scenes. The teams led by Martyn Coomer on behalf of the Research Board and Johnny Fountain in the Development Office deserve a special mention. Individuals give up their own time to attend events on our behalf, raising our profile as well as raising money. We should also remember that many of our research fellows make presentations to lay audiences in order to raise funds for more research. I would personally like to take this opportunity to thank all of the individuals involved for their efforts, hard work and willingness to go the extra mile on behalf of research and the College.

2012 promises to be a busy year. We hope to establish funding arrangements with national bodies, create our first cohort of principal investigators, identify the surgical research units that will participate in our earliest trials networks and launch our first randomised trials.

This report showcases our achievements over the last year. The breadth and quality of these research endeavours indicate that surgical research can flourish. We must now do all that we can to continue this momentum and nurture a thriving research culture. I do hope you enjoy reading this report and share our vision for the future of surgical research.

supporting surgical research

Johnny Fountain
Development Director

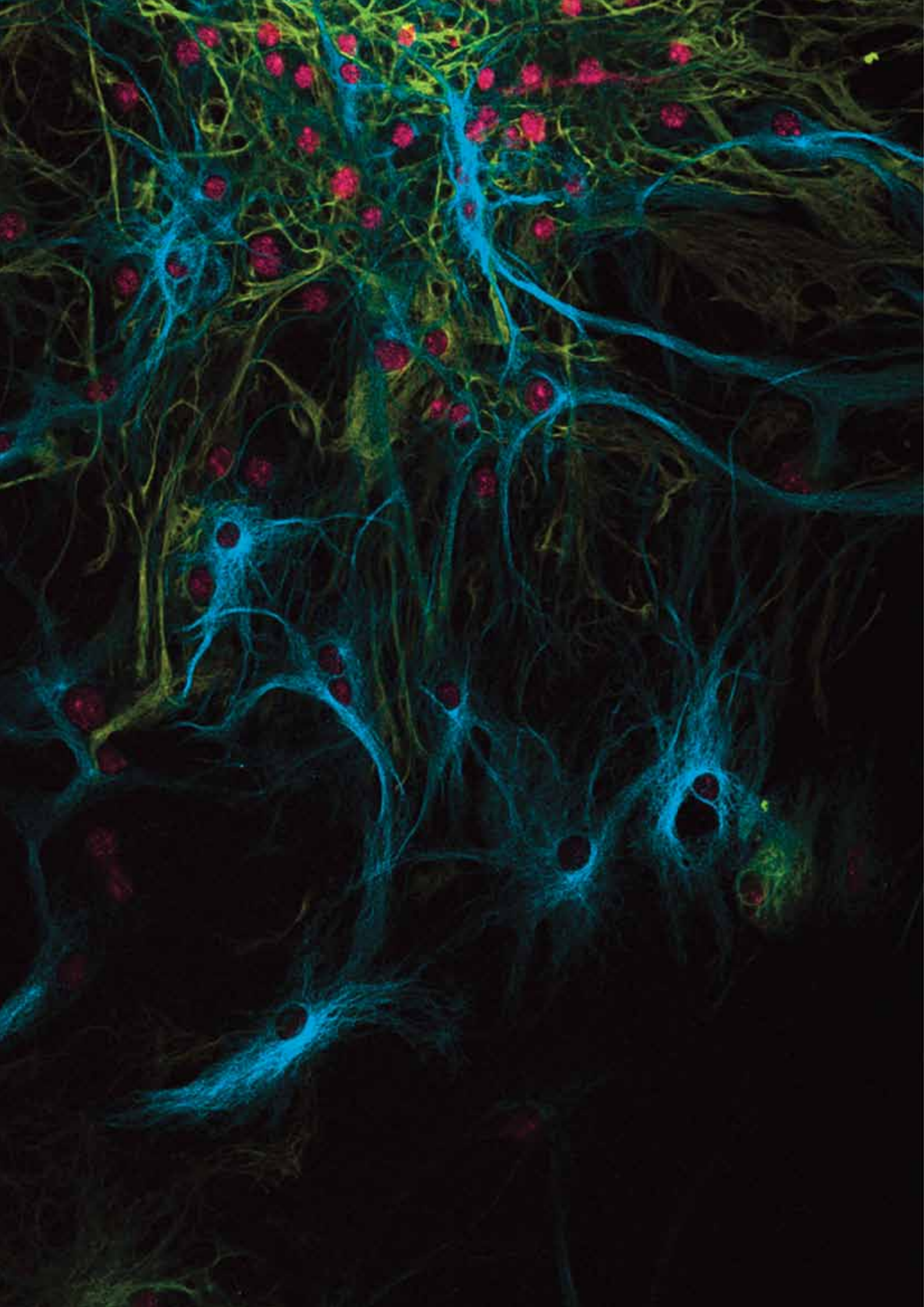
Meeting the costs of surgical research at the College has always relied on the generosity of donors. It may come as a surprise that the College's Research Department and the activities that it supports are funded wholly from voluntary income; no part of the fellows and members annual subscriptions, or other College activity, is used to subsidise it.

When the research fellowship scheme was established in 1993 over half of the fellowship grants awarded were funded from the College's endowed and restricted research trust funds. They had been accumulated from voluntary gifts and legacies over the years and ranged in value from a few millions to a few hundreds of pounds; some were tied to specific professorial chairs and transferred to other research departments while others were restricted to a specific disease or specialty area such as cancer, pharmacology, physics or dentistry. These trusts provided the core funding for the new, post-1992 Research Department and the research fellowship scheme. However, these charitable funds are dwindling with the consequence that an additional and growing number of fellowships are funded through annual contributions by individuals, charitable trusts and companies who recognise the value of surgical research. In addition, legacies have played, and continue to play, a substantial role in funding the research fellowship scheme. The reasons that prompt a legacy are varied but the two most common groups of College legators are surgeons and their families, and grateful patients. We must continue to encourage and promote all these forms of giving to all our audiences if College-sponsored research is to continue to flourish.

Each year, the College aims to award in the region of 20–30 fellowships, depending on the funds available. The number of applications we receive and the cost of supporting the fellowships have, however, doubled since the scheme was introduced. We are currently able to support only 20% of those applying due to lack of funds and our ability to make awards to the most deserving of cases is now largely dependent on external funding. Each research fellowship costs in the region of £50,000–70,000. This includes the cost of maintaining the research fellow's salary, including National Insurance and other contributions, consumables and the presentation of their research work at international meetings. Research grants are not restricted to fellowships: the Research Department also awards pump-priming grants to newly appointed consultants in order to develop their research interests as well as awarding intercalated BSc and travel grants designed to encourage and develop young surgeons. More recently, funding is being sought and secured to support the development of a suitable infrastructure for a national clinical trials initiative, led by Professor Dion Morton.

If these programmes are to continue there is a need to increase the funding available for research at the College. To achieve this we need to both raise the profile and demonstrate the benefit of surgical research to patients and the general public. A first step has been to produce a patient focused promotional film, available on our website, to support our external events programme. The film can be seen at **www.rcseng.ac.uk/fundraising** and is available to fellows and members on request.

There is no doubt that the best ambassadors and advocates for surgical research are the College's own fellows and members. We need to secure more donations and legacies if we are to continue to develop our research programmes for the benefit of patients and the profession as a whole. If you would like any advice on making a donation or leaving a legacy, or would like to become involved in our work, please contact the Development Office at **development@rcseng.ac.uk** or call **020 7869 6086**.



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Endogenous stem cells in the injured brain

The World Health Organization estimates that, by 2020, 10 million people worldwide will be disabled by traumatic brain injury.

Aminul I Ahmed

FELLOWSHIP/SPONSOR
College Research Fellowship.

SUPERVISOR
Professor William P Gray.

SITE OF WORK
University of Southampton.

PUBLICATIONS
1. Ahmed AI, Shtaya AB, Zaben MJ *et al.* Endogenous GFAP positive neural stem/progenitor cells in the postnatal mouse cortex are activated following Traumatic Brain Injury. *Neurotrauma* 2011; epub ahead of print.
2. Ahmed AI, Zaben M, Gray WP. Stem cells in the adult human brain. *Br J Neurosurg* 2011; **25:** 28–37.

PRESENTATIONS
1. *Endogenous Stem Cell Activation.* Physiological Society; April 2011; London, UK.
2. *Endogenous stem cell activation following Traumatic Brain Injury in mice.* British Neurosurgical Research Group; March 2010; Winchester, UK.

FURTHER FUNDING
Wessex Medical Research for two years.

Aminul creating a burr hole with a hand drill prior to inserting an intracranial pressure monitor in a manikin.

Aminul reviewing the imaging of a head injury patient.

Despite its devastating consequences, little progress has been made in generating therapies that protect from, or reverse, traumatic brain injury (TBI), and currently there is no evidence of effective repair in humans. Stem cell transplantation has generated headlines in the popular press but the studies remain preliminary. However, endogenous stem cells, those that reside in the patient's brain, provide a potential source of cells for repair.

We are characterising stem cells already present in the brain (and which are activated only after injury) and we are starting to understand their control mechanisms following injury, with the ultimate aim of manipulating these cells to effect repair. Our recently published research proposed a key concept that could possibly be translated to a clinical neurosurgical setting. In an animal model replicating TBI we found that in the outer cortex, a region traditionally thought to contain no stem cells, endogenous stem cells are activated after a severe injury (equivalent to a 40mph car accident) but generate neurons only when cultured outside of the brain, in a culture dish. We have shown that cells that express a stem cell marker account for the majority of these activated cells following injury. Moreover, we provided evidence for a correlation between upregulation of a pathway known to regulate stem cell proliferation, Sonic hedgehog (Shh) signalling, and the restoration of regenerative potential following TBI. This raises the possibility of harnessing endogenous proliferating cells for brain repair following a model of TBI.

Our current work will further characterise the cues involved in driving these cells out of quiescence following injury in both animal models and human TBI patients. By understanding this, we can begin to develop a strategy to target appropriate pathways that increase the potential for neural repair and improve quality of life for these patients.

The use of skeletal muscle to amplify action potentials in transected peripheral nerves

Loss of an upper limb affects 1 in 6,000 people and is accompanied by enormous physical and psychological morbidity.

Yazan Al Ajam

FELLOWSHIP/SPONSOR
Blond McIndoe Research Fellowship.

SUPERVISORS
Professor Gordon Blunn and Mr Norbert Kang.

SITE OF WORK
Centre for Biomedical Engineering, UCL Stanmore Campus. Royal Veterinary College, Potters Bar Campus.

PRIZES
1. The Sovereign Healthcare Charitable Trust Award.
2. Garfield Weston Foundation Award.

FURTHER FUNDING
RAFT (Restoration of Appearance and Function Trust) for two years.

There are two major drawbacks with standard prosthetic design: attachment and control. Socket-fitted prostheses need a tight fit, resulting in skin irritation, blistering and pain.

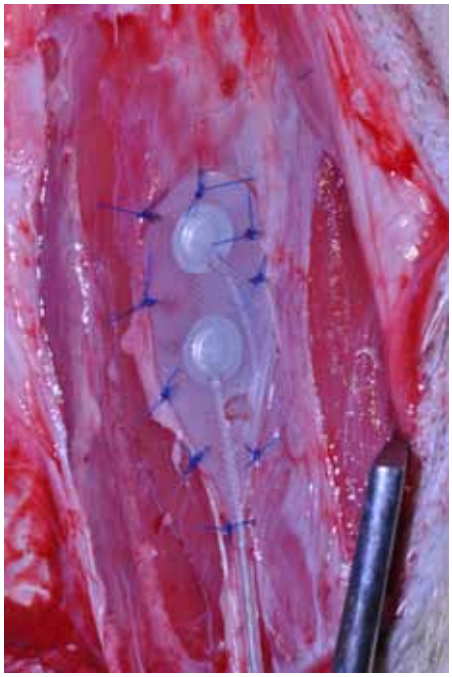
The development of a permanently implanted bone anchored device (intra-osseous transcutaneous amputation prosthesis, ITAP) at UCL has revolutionised the attachment of a prosthesis to the stump by resolving issues with skin irritation at the socket/implant interface. The prosthesis simply 'clips on' to the ITAP. The problem now remains with control. Currently, a prosthesis is controlled by electrical signals generated by contractions of muscles in the amputation stump. These signals are detected by surface electrodes, which trigger the prosthesis to move. At best, for a transhumeral (above-elbow) amputee, all prosthetic actions are controlled by signals generated from the contraction of just two muscle groups resulting in poor and non-intuitive control. For comparison, movements of the human hand are controlled by 38 muscles.

We aim to increase the number of signals by placing the control electrodes inside the stump onto the residual muscles that were used to control upper limb movements, rather than on the skin surface. ITAP will be used as a conduit to take the signals out of the stump and into the prosthesis.

ITAP in the left arm of a patient (left). Prosthetic limb attached to ITAP (right).

Yazan with a prosthetic limb in the laboratory.

Already, we have been successful in capturing signals using implanted muscle electrodes. We have also designed an ITAP/electrode device which we will test in vivo. This approach represents a fundamental shift in how prostheses are attached and controlled. The increase in control channels will massively increase the function of upper limb prostheses. The device will create a man–machine interface that will 'read' the patient's intentions and translate this into the desired action in the prosthesis, paving the way for a new generation of multi-channel, highly functional 'bionic' limbs.



Implanted muscular electrode sutured in place prior to testing.

An investigation into the military applications of near infrared spectroscopy in trauma

In developed nations, major trauma is the leading cause of death of individuals below the age of 35 years.

Tom Barker

FELLOWSHIP/SPONSOR
Surgical Research Fellowship in Military Surgery.

SUPERVISOR
Surgeon Captain Mark Midwinter.

SITE OF WORK
Royal Centre for Defence Medicine.

PUBLICATIONS
Barker T, Midwinter M, Porter, K. The diagnosis of acute lower limb compartment syndrome: Applications of near infrared spectroscopy. *Trauma* 2011; **13**: 125–136.

PRESENTATIONS
Clinical Applications of Near Infrared Spectroscopy (NIRS) in Trauma Resuscitation. International Trauma Care Conference; May 2010; Telford, UK.

Current parameters used to assess blood loss in trauma patients either provide only a crude indicator of patient physiology or require invasive techniques and sophisticated calibrated equipment.

Near infrared spectroscopy (NIRS) is an emerging technique that allows continuous, real-time, non-invasive assessment of local tissue oxygenation (StO_2) using infrared light, which can be used quickly and easily to assess trauma patients.

We began our investigation by examining the normal range of StO_2 values in healthy military subjects at rest and following a controlled exercise program. Establishing the effects of exercise on StO_2 is important as many patients in both military and civilian environments are injured following sustained physical exertion. We found a wide range of normal StO_2 values, which differed significantly between anatomical sites, although the lower limit of normality was the same, 40%, at all sites. StO_2 was significantly raised following exercise but only by 3–9%, which is unlikely to be important in real patients.

Col MacMillan and Tom operating on a trauma patient undergoing NIRS monitoring, Camp Bastion, Afghanistan.

We then compared NIRS measurements from the hand, forearm and deltoid (upper arm) in volunteers undergoing simulated blood loss induced by applying negative pressure to the lower body which redistributes blood from the upper to the lower body. This showed that the deltoid (the most practical location for NIRS recordings in military trauma subjects) is a sensitive site for detecting StO_2 changes associated with blood loss and a suitable site for further investigation in clinical trials.

NIRS is currently undergoing field trial evaluation assessing major trauma patients presenting to Camp Bastion Field Hospital, Afghanistan. The completed pilot study has already demonstrated the feasibility of the technique in an austere environment and we are now working towards establishing its role in the resuscitation of trauma patients.

Unravelling the genetics of 'glue ear' in children

Persistent 'glue ear' is the most common cause of childhood hearing loss and the most common reason for operating on children in the UK.

Mahmood Bhutta

FELLOWSHIP/SPONSOR
College Research Fellowship.

SUPERVISORS
Mr Martin Burton and Professor Steve Brown.

SITE OF WORK
Medical Research Council, Harwell, Oxfordshire.

PUBLICATIONS
1. Rye MS, Bhutta MF, Cheeseman MT *et al.* Unraveling the genetics of otitis media: from mouse to human and back again. *Mamm Genome* 2011; **22:** 66–82.
2. Bhutta MF, Hedge EA, Parker A *et al.* Oto-endoscopy: a reliable and validated technique for phenotyping otitis media in the mouse. *Hear Res* 2011; **272:** 5–12.

PRESENTATIONS
1. *Genetics of Otitis Media.* 1st Congress of the Confederation of the European ORL-HNS; July 2011; Barcelona, Spain.
2. *Oto-endoscopy: A new tool for phenotyping otitis media in the mouse.* 10th International Symposium on Recent Advances in Otitis Media; June 2011; New Orleans, USA.

PRIZES
1. Phizackerley Senior Scholarship, Balliol College, Oxford, 2009–2011.
2. British Association for Paediatric Otorhinolaryngology Susanna Leighton Prize, 2011.

FURTHER FUNDING
The Wellcome Trust, National Institute for Health Research, Action on Hearing Loss, Deafness Research UK, Medical Research Council Technology.

Persistent inflammation of the ear, often called 'glue ear', leads to hearing loss in infancy and can therefore affect language acquisition at a critical period of development. One treatment is the insertion of tubes (grommets) to clear the fluid: this is the most common reason for operations in children in the UK.

We know that glue ear runs in families and if we understand which genes and which alterations within them cause disease, then we may be able to better predict disease outcomes and target new therapies.

Animal models can give clues to genes that may cause disease. At the Medical Research Council's centre in Harwell, we have discovered two animal models (Jeff and Junbo) that develop chronic inflammation of the ear due to variation in only a single gene. The Jeff model has variation in a gene called Fbx011 and the Junbo model has variation in a gene called Evi1.

My research, co-funded by the Royal College of Surgeons, aims to look at whether variations in the genes Fbx011 or Evi1, or genes related to them, could be responsible for disease in families affected by glue ear. By October 2011 we had recruited nearly 600 families (over 2,000 individuals) from 23 NHS hospitals in the UK, making this the largest study in the world in the genetics of glue ear.

Our early findings suggest that the gene Fbx011 does convey risk of glue ear in children. Other work in our lab suggests this gene regulates the levels of oxygen in the ear; we are working on ways to target this gene to hopefully provide new treatments.

Chronic glue ear leads to fluid deep in the ear drum.

Jane Lambie (lead research nurse) recruiting a family to the study.

Developing novel ballistic cervical protection for the dismounted soldier

79% of combat neck wounds currently sustained by UK servicemen in Afghanistan are due to explosive fragments, the majority of which are therefore potentially preventable through the use of cervical body armour.

John Breeze

FELLOWSHIP/SPONSOR
Surgical Research Fellowship in Military Surgery.

SUPERVISOR
Surgeon Captain Mark Midwinter.

SITE OF WORK
Defence Science and Technology Laboratory, Porton Down.

PUBLICATIONS
1. Breeze J, Gibbons A, Shief C *et al.* Combat-related craniofacial and cervical injuries: Five- year review from the British Military. *J Trauma* 2011; **71:** 108–113.
2. Breeze J, Horsfall I, Hepper A, Clasper J. Face, neck, and eye protection: adapting body armour to counter the changing patterns of battlefield injury. *Br J Oral Maxillofac Surg* 2010; **49:** 602–606.

PRESENTATIONS
1. *Mortality and morbidity from UK combat neck injury.* British Association of Oral and Maxillofacial Surgeons; June 2011; Nice France.
2. *Head Face and Neck injuries sustained by British Service Personnel.* American Association of Oral and Maxillofacial Surgeons; September 2010; Chicago, USA.

The incidence of combat neck injury has increased from previous conflicts and has become a significant source of mortality and long-term morbidity for UK servicemen. US forces experience half the incidence of neck injury of their UK counterparts, which has been ascribed to their greater acceptance of ballistic neck collars on body armour. The aim of this research was to develop a validated computer model to simulate explosive neck injury in order to evaluate novel and more acceptable designs of neck protection.

Clinical and post mortem analysis of all UK neck injuries sustained between 1 January 2006 and 31 December 2010 demonstrated that 79% of neck wounds were due to explosions, with an associated mortality of 41%. 85% of deaths were due to damage to either the carotid and vertebral arteries or the internal jugular veins, with the remainder from spinal cord trauma. This analysis also allowed accurate surface wound mapping of the entry points of each wounding explosive fragment and thereby determination of the shot line. Determination of the wounding effects of fragments currently involves attempting to predict the size of the resultant wound tract and the potential effects of temporary cavity formation on cervical neurovascular structures. Future research will involve characterisation of the fragments recovered from injured servicemen to select representative projectiles that can be used to test potential protective materials.

A UK soldier in current body armour. Note there is no ballistic protection of the neck.

John (right) adjusting a prototype neck collar.

John adjusting the gas gun used to fire fragments at novel body armour materials and designs.

Our human factors trial has demonstrated that neck collars currently issued to UK servicemen are unacceptable to soldiers. Future research will evaluate novel designs of collar as well as other methods of neck protection. The computer model of the neck is currently undergoing validation and we intend to publish the model's ability to predict the effectiveness of potential types of ballistic neck protection in the near future.

Towards tissue-engineering airways: a proteomic analysis of de-celullarised laryngeal–tracheal constructs

Using tissue engineering to create airways is increasingly viable, as demonstrated by the successful transplantation of these stem-cell-based organs into adults and children.

Colin Butler

FELLOWSHIP/SPONSOR
Enid Linder Foundation Fellowship.

SUPERVISORS
Professor Justin Hsuan and Professor Martin Birchall.

SITE OF WORK
Great Ormond Street Hospital.

PUBLICATIONS
Butler CR, Hsuan J, Beaumont N *et al.* Proteomic analysis of decellularized tissue engineered laryngeal-tracheal scaffold. *Otolaryngol Head Neck Surg* 2011; **145**: 82.

PRESENTATIONS
1. *Complication rates for RIG in head and neck cancer inpatients.* American Academy of Otolaryngology-Head and Neck Surgery; September 2011; San Francisco, USA.
2. *Towards tissue-engineered laryngeal transplantation: Proteome expression in laryngeal scaffold constructs.* Otorhinolaryngological Research Society; March 2010; Oxford, UK.

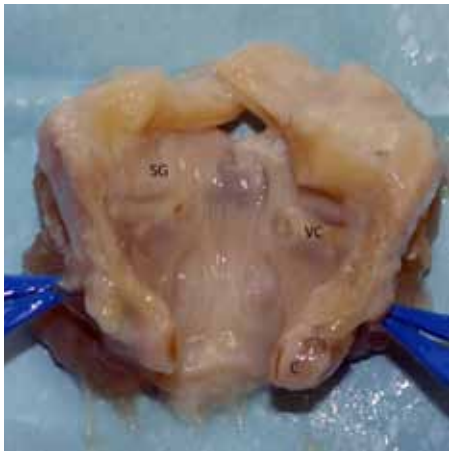
FURTHER FUNDING
Great Ormond Street Hospital Charities for two years.

Patients with severe injury to the windpipe and voice box, be it due to cancer, infection or chronic inflammation, face very limited reconstruction options. Consequently, these patients suffer from swallowing difficulties, are unable to voice adequately and endure long-term breathing problems. Stem-cell-based tissue engineering is emerging as a new and potentially viable solution; however, numerous obstacles need to be overcome before this becomes mainstream clinical therapy.

Fabricating a tissue-engineered organ often requires a scaffold on which cells from the intended recipient (including stem cells) are seeded, and expanded, to create a fully bespoke organ. Current scaffolds include de-cellularised tissues or organs and synthetic materials such as ceramics, metals and plastics. While synthetic scaffolds offer the advantage of being custom made to size and shape, the material does not mimic native tissue effectively. Conversely, decellularised tissue, created from donor organs stripped of their cells and immunogenic properties, appear to retain the complex anatomy of native tissue, including functional proteins. It is these proteins that are of significant interest as they guide cell behaviour, including turning stem-like cells into the appropriate type for the organ into which they are seeded.

This research sought to identify the complex mixture of proteins in airway scaffolds. Advances in protein recognition technology with mass spectrometry have allowed us to investigate these scaffolds in far greater depth than has been previously possible. We have now identified over 300 proteins, far in excess of those found in previous studies. Furthermore, many of these proteins have diverse functions related to cell behaviour, not just limited to structural integrity. It is hoped that with this increased understanding in protein composition, future interrogations can be targeted towards determining which 'mix' of proteins are optimum for regeneration, and may lead to the creation of a next generation of 'off-the-shelf' synthetic scaffolds.

Members of the tracheal team at Great Ormond Street Hospital, a national referral team for the management of complex airways in children.



A de-cellularised larynx (voicebox).

Neural stem cells as therapeutic targets in germinal matrix haemorrhage

Around 2,000 premature babies per year suffer brain haemorrhages.

William John Dawes

FELLOWSHIP/SPONSOR
Freemasons Grand Lodge 250th Anniversary Fund Research Fellowship with support from the Rosetrees Trust.

SUPERVISOR
Professor Silvia Marino.

SITE OF WORK
Blizard Institute, Barts and the London School of Medicine and Dentistry.

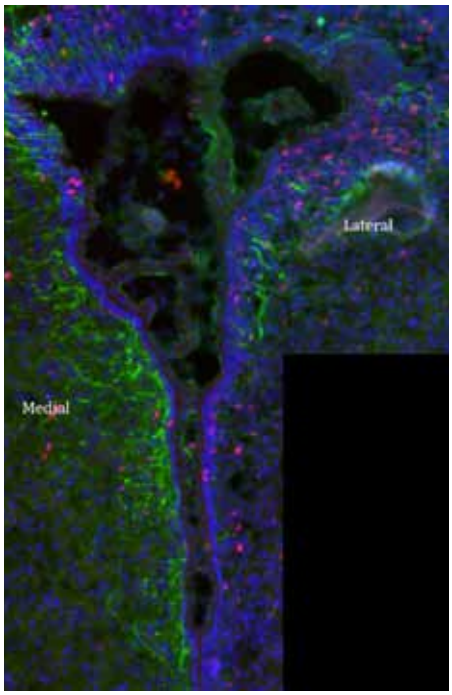
PRESENTATIONS
A mouse model of germinal matrix haemorrhage and its application to stem cell research. British Neurosurgical Research Group; March 2011; Dundee, UK.

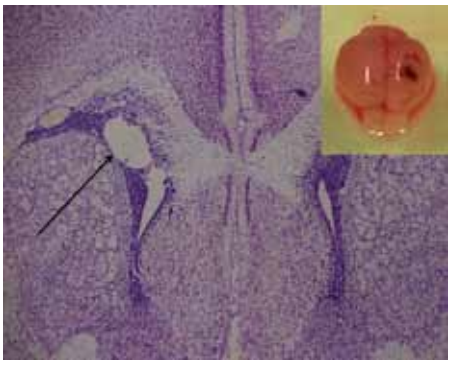
PRIZES
British Neuropathological Society Small Grant Award.

FURTHER FUNDING
Sparks, The Children's Medical Research Charity, for two years.

The aim of this research project is to improve the outcome for extremely premature babies who suffer brain haemorrhages. Sadly, because their blood vessels are underdeveloped and they are unable to control the blood pressure within their heads, around 20–30% of very premature babies (<1,500g) suffer brain haemorrhage.

The site of haemorrhage is within an area of the brain known as the germinal matrix; this is a vitally important region that contains the stem cells of the developing brain. Damage to these stem cells results in abnormal development of the brain and is one of the leading causes of disability in childhood.





(Above) A coronal sample taken through the anterior subventricular zone (stained with H&E) which shows the accuracy of injection into the SVZ. Inset: the macroscopic appearance of animal model brain on removal, showing a heamatoma at the injection site. Images as at day four.

(Left) Immunohistochemistry of animal model showing the left ventricle and subventricular zone of a non-injected pup. Red: EdU labelled cells (those proliferating postnatally). Blue: Hoescht (pan nuclear stain). Green: GFAP (gives an indication of the position of the neural stem cells in the wall of the lateral ventricle). Image as at day four.

At present, there is no treatment for this brain injury once the damage has occurred. To improve this situation we are looking into the possibility of stimulating and optimising the potential of the stem cells that survive the bleed in the hope that this will improve outcomes. This is an entirely novel and unique approach and the bulk of my fellowship has been spent establishing an animal model that closely mimics the human condition. By stereotactically (frame-guided) injecting blood into the germinal matrix of a new-born animal model we are now gaining an insight into the effect of bleeding on the developing brain. Furthermore, by applying this technique to genetically engineered animal models we are able to specifically determine the role of the stem cells in recovery following the bleed.

The preliminary results have been encouraging and, through the support of the Royal College of Surgeons fellowship scheme, I have been fortunate enough to secure a clinical research training fellowship from Sparks, The Children's Medical Research Charity. This will allow me to continue this research and complete a PhD.

Paul Moxey performing a hallux amputation.

The molecular determinants of extracapsular spread in metastatic head and neck cancer

Oral cancer is the most common type of head and neck cancer and is growing in incidence in the UK. Despite treatment advances, overall survival remains relatively unchanged with less than one quarter of patients with extracapsular spread surviving over five years.

Jagtar Dhanda

FELLOWSHIP/SPONSOR
Clarke Legacy and Nuffield Dental Science Research Fellowship.

SUPERVISORS
Professor Ross Sibson,
Mr Richard Shaw and Dr Janet Risk.

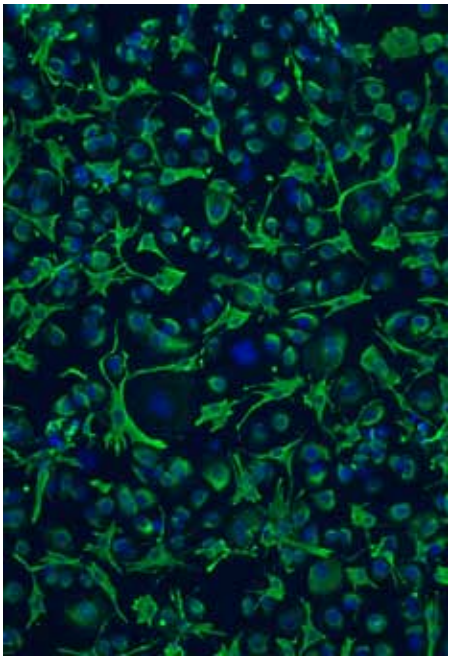
SITE OF WORK
Department of Molecular and Clinical Cancer Medicine, University of Liverpool.

PUBLICATIONS
1. Dhanda J, Shaw R. The Genetics and Epigenetics of Head and Neck Cancer. In: Bernier J ed. *Head and Neck Cancer: Multimodality Management.* 1st edn. New York: Springer-Verlag; 2011.
2. Dhanda J, Cooper C, Ellis D, Speculand B. Technique of temporomandibular joint replacement using a patient-specific reconstruction system in the edentulous patient. *Br J Oral Maxillofac Surg* 2011; **49**: 618–622.

PRESENTATIONS
1. *The molecular determinants of extracapsular spread in metastatic head and neck cancer.* British Association of Oral and Maxillofacial Surgeons (BAOMS); June 2011; Nice France.
2. *Pathways contributing to oral squamous cell carcinoma with respect to nodal status and extracapsular spread as identified by analysis of copy number changes detected by array comparative genomic hybridisation.* American Head and Neck Society; October 2010; Arlington, USA.

PRIZES
1. BAOMS/Saving Faces-Facial Surgery Research Foundation Research Fellowship.
2. BAOMS Endowments Grant.

FURTHER FUNDING
BAOMS. Saving Faces: Facial Surgery Research Foundation.



Antibody staining of primary cell culture using immunofluorescent staining.

Jagtar in the operating theatre obtaining biopsy samples.

Oral cancer remains a debilitating disease and can profoundly affect speech and swallowing. Despite the many advances in managing this condition, the overall survival remains unchanged. The most adverse factor for survival in oral cancer is extracapsular spread (ECS), where the disease spreads from the mouth to lymph nodes in the neck and subsequently spills out from them.

Our research group previously demonstrated a genetic expression pattern in oral tumours that could be used as a molecular signature to predict the likelihood of individuals having ECS. One of the main aims of my research was to validate this expression profile in biopsy tissue collected from 110 patients with oral cancer, and to provide clinical data to determine how good this molecular signature is at predicting ECS.

The clinical data from patient follow-up after surgery confirmed the devastating consequences of ECS and were consistent with a larger previous study in which only 23% of patients with ECS survived five years. Current methods for detecting ECS prior to surgery using MRI scans were shown to be accurate in detecting the disease in only 6.8% of patients.

The second aim of the project was to establish cell lines for head and neck cancer from patients with and without ECS. These will be used in future work looking at factors influencing cell migration and invasion. Three cell lines from patients with ECS and two cell lines from patients without ECS have been created in the laboratory by growing cells from tumour tissue. We will examine their behaviour to see if there is any difference between the cells and to try to explain these differences, at the molecular level, and how this may lead to ECS. By identifying the molecular processes that cause ECS we hope to identify potential targets for future therapies.

Enhancement of systemic delivery of oncolytic vaccinia virus for cancer treatment

The five-year survival rate for laryngeal cancer has remained unchanged at around 60% since 1971 and the two-year survival rate for hypopharyngeal cancer is 46%.

Mark Simon Ferguson

FELLOWSHIP/SPONSOR
Joint RCS/British Association of Surgical Oncology Research Fellowship with support from the Rosetrees Trust.

SUPERVISORS
Dr Yaohe Wang and Mr Ghassan Alusi.

SITE OF WORK
Centre for Molecular Oncology, Barts Cancer Institute.

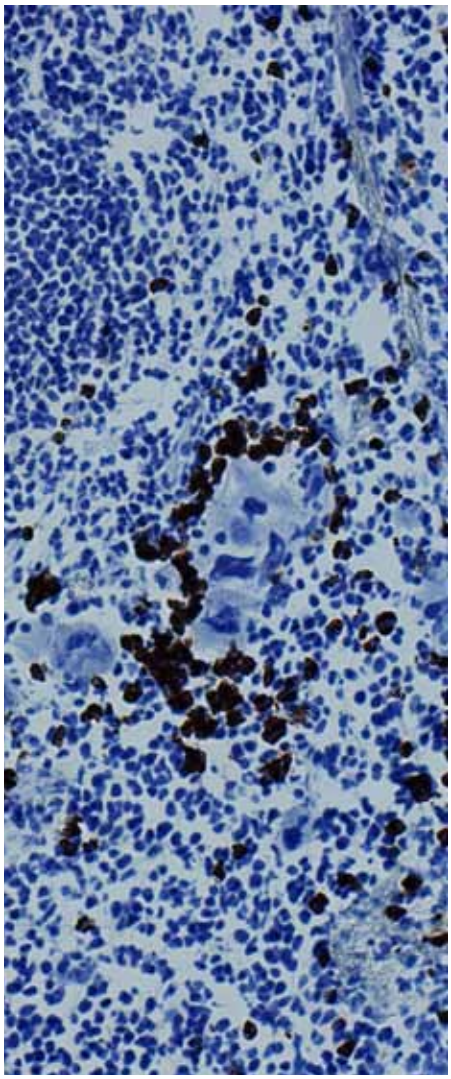
PUBLICATIONS
Ferguson MS, Lemoine NR, Wang Y. Systemic delivery of oncolytic viruses: hopes and hurdles. *Advances in Virology* 2012; Article ID 805629. http://www.hindawi.com/journals/av/2012/805629/

PRIZES
Cancer Research UK Clinical Research Fellowship.

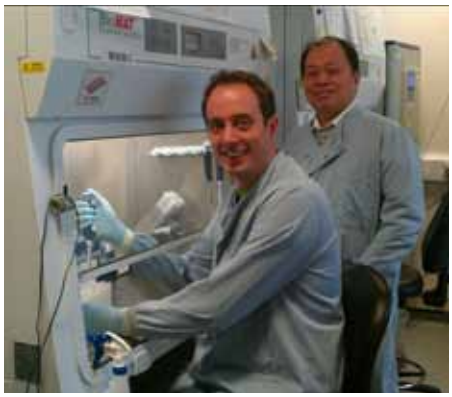
The long-term prognosis for advanced head and neck cancer has remained dismal over the last three decades. Clearly, there is a need for the development of new treatments. Oncolytic viral therapy is one of the most promising novel strategies to have been developed over the last decade, and vaccinia virus has been a particularly promising member of this cohort with a proven safety profile as it was used in the worldwide eradication of smallpox.

Vaccinia naturally infects and kills cancer cells. The strain used in our laboratory has been modified so that it cannot survive in normal cells. Another advantage of vaccinia is that it can be delivered directly into a vein. Such delivery is an attractive method as it can simultaneously treat both the known cancer and any metastatic deposits. However, when vaccinia is injected intravenously much of what is injected is cleared by the immune system. The aim of my work was to develop a novel therapeutic strategy to improve the intravenous delivery of vaccinia to treat cancer.

Our group had already shown that vaccinia delivery can be improved by destroying immune cells called macrophages but my work was the first to demonstrate that vaccinia delivery could be enhanced without causing any lasting damage to the immune system. This was achieved by using a short-lasting inhibitor of a specific function of the macrophage. By using a special imaging system I was able to demonstrate that the addition of the inhibitor resulted in many more viruses reaching and consequently killing the tumour cells. This translated into a greatly improved anti-tumour response with some tumours shrinking dramatically. It is hoped that clinical trials employing this novel strategy could commence within a few years, potentially improving the survival of patients.



A section of spleen at an early timepoint after systemic delivery of vaccinia showing the virus associating with macrophages.



Mark with his primary supervisor Dr Yaohe Wang.

A tissue-engineered approach to cranial neuromuscular regeneration

Of the 2,000 patients diagnosed with laryngeal cancer in the UK each year, almost half undergo local resection (leaving permanent defects in the vocal cords and hoarseness) and 25% have their larynx removed completely.

Jonathan Fishman

FELLOWSHIP/SPONSOR
Starritt Legacy Research Fellowship.

SUPERVISORS
Professor Martin Birchall and Dr Paolo De Coppi.

SITE OF WORK
UCL Institute of Child Health, London.

PUBLICATIONS
1. Fishman JM, Ansari T, Sibbons P *et al.* Decellularized rabbit cricoarytenoid dorsalis muscle for laryngeal regeneration. *Ann Otol Rhinol Laryngol* 2012; **121:** 129–138.
2. Fishman JM, De Coppi P, Elliott MJ *et al.* Airway tissue engineering. *Expert Opin Biol Ther* 2011; **11:** 1,623–1,635.

PRESENTATIONS
1. *Rabbit cricoarytenoid dorsalis (CAD) model for cranial regeneration.* American Broncho-Esophagological Association, Combined Otolaryngology Spring Meeting; April 2011; Chicago, USA.
2. *Corticosteroids for the treatment of idiopathic acute vestibular dysfunction (vestibular neuritis) – a meta-analysis and systematic review.* Otorhinolaryngological Research Society; March 2011; London, UK.

PRIZES
1. UCL–Berkeley Award, 2011.
2. British Foreign and Commonwealth Office UK–USA Stem Cell Collaboration Award, 2010.

FURTHER FUNDING
Two-year Medical Research Council and Sparks, The Children's Medical Research Charity, clinical research training fellowships.

Jonathan (centre) with his two supervisors Professor Martin Birchall (left) and Dr Paolo De Coppi (right) at the UCL Institute of Child Health.

Jonathan culturing T-lymphocytes in the laboratory in order to study the host immunological response towards de-cellularised scaffolds for tissue-engineering.

There is a range of clinical disorders affecting the head and neck for which there are no good conventional therapeutic solutions. Although we have now successfully replaced the airways of patients using stem-cell based techniques, many more patients' needs would be answered by providing the muscles required for moving cranial tissues and organs such as the vocal cords, oesophagus, tongue and face. The loss of a functioning larynx in particular removes normal speech and swallowing, the ability to taste, lift, smell, strain and cough, and results in an impaired quality of life.

The aim of this project was to characterise and determine the immunogenicity of an acellular skeletal muscle extracellular matrix for tissue engineering purposes. Using a combination of histological, immunohistochemical and molecular techniques, we have shown that such scaffolds exhibit preserved structural and biomechanical properties upon the removal of cells. In addition, such scaffolds fail to elicit an immune response when transplanted (they are non-immunogenic) which we have confirmed through cell culture techniques in the laboratory.

The emphasis on non-immunogenicity is critical in order to prevent such tissues rejecting when they are transplanted from one individual to another (or even crossing species barriers) and to avoid the side-effects and complications associated with life-long immunosuppressants. In addition, a scaffold that is non-immunogenic has the potential of overcoming some of the existing shortages in organ donors by removing the requirement for tissue-typing between individuals, thereby increasing the pool of existing donor organs and tissues that are available for transplantation.

This research is on-going in order to gain further insight into the effect of acellular scaffolds on the host immune response and to determine the effect of the addition of stem cells to the scaffolds with regards to structural and functional outcomes.

Gamma knife radiosurgery for the treatment of non-surgical cystic cerebral metastases

Brain metastases affect 25,000 patients a year in the UK.

Pablo Goetz

FELLOWSHIP/SPONSOR
Harry Morton Research Fellowship.

SUPERVISOR
Dr Gelareh Zadeh.

SITE OF WORK
Division of Neurosurgery, Toronto Western Hospital, Canada.

PUBLICATIONS

Pablo Goetz P, Ebinu JO, Roberge D, Zadeh G. Current standards in the management of cerebral metastases, International *Journal of Surgical Oncology* 2012; Article ID 493426. http://www.hindawi.com/journals/ijso/2012/493426/.

PRESENTATIONS

1. *Gamma Knife Radiosurgery for the treatment of non-surgical cystic cerebral metastases.* The Society of British Neurological Surgeons (SBNS); March 2011; Bristol, UK; and Canadian Neurological Sciences Federation (CNSF); June 2011; Vancouver Canada.

2. *Financial, medical and social benefits in day-case craniotomy: Perspectives from two socialized medical systems.* SBNS; March 2011; Bristol, UK; and CNSF; June 2011; Vancouver Canada.

A dedicated frame is fitted onto the patients head to allow precise targeting in 3D of the lesion to be treated (in this case a brain tumour). Local anaesthetic (similar to that used at the dentist) is used to freeze the pin site prior to inserting the pins.

Cerebral metastases (CM), when cancer spreads to the brain, affect up to 25,000 people a year in the UK. This will become even more common as our population is ageing and improved treatment for cancer prolongs survival. However, the diagnosis of CM is catastrophic for patients and caregivers as it results in changes in mental function and personality, seizures, loss of independence, paralysis and ultimately death. Untreated, CM patients will typically live less than two months.

In the past, patients with CM underwent surgery or radiation to the whole brain. Recently, new treatment options have been developed including gamma knife (GK) stereotactic radiosurgery (SRS), where multiple gamma ray beams converge onto a single target to neutralise the tumour cells without damaging the surrounding normal brain tissue. This is done as an outpatient procedure, is well tolerated and allows treatment of tumours deep in the brain that would not be accessible to surgery.

These tumours are often 'cystic' or develop fluid inside them. Traditionally, these were thought to be resistant to radiation and to date no one had formally proved otherwise. In order to test this assumption, all 110 cases of cystic CM (of a total of 350) treated with GK at the University Health Network in Toronto were analysed. At 6 and 12 months, 91% and 63% of the tumours remained controlled respectively, which is similar to published figures for non-cystic tumours. In addition we found that the tumours shrunk an average of 27%.

It is hoped that this research will encourage physicians to use GK or other SRS options to treat cystic CM where previously there may have been reluctance. Although they eventually succumb to the cancer in the rest of their body, by controlling the 'brain part' of their cancer, patients are spared from deterioration in brain function.

The role of similar expression to FGF (Sef) in growth factor signalling in prostate cancer

Prostate cancer is very common, with a diagnosis every 18 minutes and a death from this condition every 43 minutes in the UK.

Satoshi Hori

FELLOWSHIP/SPONSOR
Freemasons Grand Lodge 250th Anniversary Fund Research Fellowship.

SUPERVISORS
Dr Vincent Gnanapragasam and Professor David Neal.

SITE OF WORK
Department of Oncology, University of Cambridge.

PUBLICATIONS
Murphy T, Hori S, Sewell J, Gnanapragasam VJ. Expression and functional role of negative signalling regulators in tumour development and progression. *Int J Cancer* 2010; **127:** 2,491–2,499.

PRESENTATIONS
Expression of the endogenous signalling regulator Sef is predictive of prostate cancer behaviour and alters the cell response to targeted inhibitors of FGF receptors. European Association of Urology; March 2009; Stockholm, Sweden.

PRIZES
1. MRC Clinical Research Training Fellowship.
2. University of Cambridge Raymond and Beverly Sackler Studentship.

FURTHER FUNDING
Medical Research Council / The Prostate Cancer Charity Clinical Research Training Fellowship for two years.

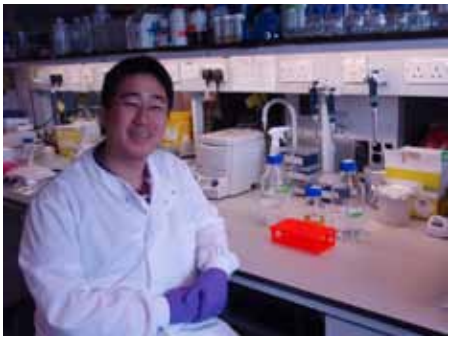
Prostate cancer is the most common male malignancy in the UK, with 35,000 new cases per year. Although most patients are diagnosed early, a proportion of them will develop an aggressive form of prostate cancer known as castration resistant prostate cancer (CRPC). Growth factors (GFs) are thought to facilitate this process by allowing cells to grow and progress independently of testosterone. Despite this, GF inhibitor-based therapies have failed to improve patient survival. This may, in part, be due to proteins within the cells that can attenuate the signalling generated by different GFs. Similar expression to FGF (Sef) is one such example of a naturally occurring signalling regulatory molecule in the body that is lost with the emergence of aggressive prostate cancer. It appears therefore that Sef protein plays a protective role in normal prostate cells.

In this study, I have been testing the hypothesis that Sef protein is able to negatively regulate the prostate cancer cell's response to different GFs. I have been able to demonstrate that increasing Sef can effectively decrease the growth as well as migration of a number of different aggressive prostate cancer cell lines in response to a range of GFs, and that this effect is mediated by disruption of the main intra-cellular signalling pathway known as the Ras/MAPK pathway. In addition, preliminary results suggest that Sef is able to enhance the cytotoxic effect of radiation therapy on prostate cancer cells.

Further work is being carried out to evaluate the potential of Sef as a therapeutic target as well as a biomarker to identify those patients who will develop the more aggressive form of prostate cancer. It is anticipated that my work will provide a proof of principle of a novel way to treat and identify patients with otherwise fatal, aggressive prostate cancer.

Satoshi in theatre with his supervisor Dr Vincent Gnanapragasam before operating.

Satoshi practicing on the operating console of the Da Vinci robot system (used for robotic prostatectomies).



Satoshi at work in his laboratory.

Evaluation of the antitumour potency and biodistribution of vaccinia virus mutants in solid tumour models

The survival of patients with head and neck cancer has not improved over the last 30 years, despite advances in existing treatments. New therapeutics are urgently needed.

Jonathan Hughes

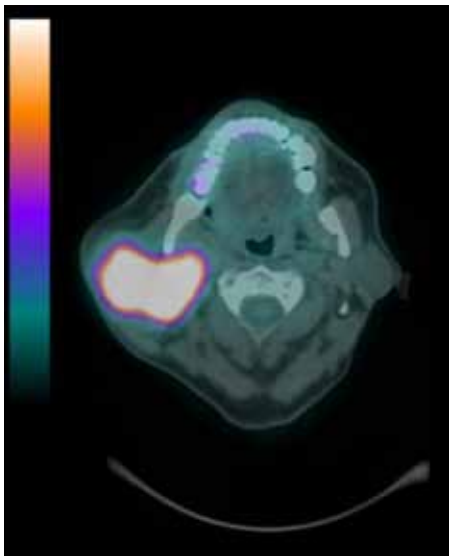
FELLOWSHIP/SPONSOR
Winks Legacy Research Fellowship.

SUPERVISORS
Dr Yaohe Wang, Mr Ghassan Alusi and Professor Nick Lemoine.

SITE OF WORK
Centre for Molecular Oncology and Imaging, Barts Cancer Institute, London.

PRIZES
1. Journal of Laryngology and Otology Research Scholarship.
2. Hartopp Dixon Prize.

FURTHER FUNDING
Barts and The London Charity Clinical Training Fellowship, Barts and The London Charity Cancer Research Fund Award for one year.

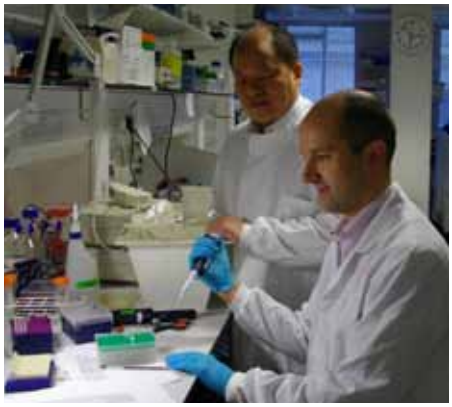


PET/CT scan of a patient with head and neck cancer.

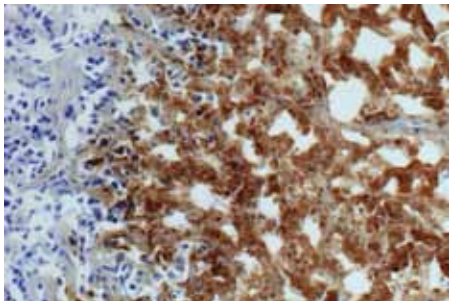
Viral gene therapy is a promising new treatment that uses modified viruses to destroy cancer cells. The first cancer-killing virus treatment received a government licence in 2005. Initial optimism has been confounded by poor efficacy in clinical trials. This has led researchers to consider other viruses and different genetic modifications to elicit more powerful anti-tumour responses.

There are a number of vaccinia virus strains; some of which have a proven safety profile following their use in smallpox immunisation. However, there is uncertainty regarding which of the vaccinia strains would make a better cancer treatment. Current evidence would favour the Western Reserve (WR) strain, which has shown superior anti-tumour potency in some cancer cell lines in vitro. However, this is a non-vaccine strain and therefore untested in humans. In contrast, the Lister strain is the northern European vaccine strain and has recently been demonstrated to have significant cancer-killing properties. My research has evaluated the anti-tumour potency and tumour selectivity of mutants of these two viruses, to determine which would make a better viral gene therapy agent.

I have demonstrated superior Lister strain cancer-killing potency and tumour selectivity in vitro. In vivo experimentation has established the Lister strain has greater anti-tumour effects in animal models. Furthermore, the Lister strain is able to target tumours better than the WR strain when administered to the systemic circulation. This data suggests that the Lister strain represents a more promising virus strain for cancer gene therapy application. I am continuing research on the Lister strain vaccinia virus by investigating the effect of an anti-inflammatory gene on its cancer-killing properties. It is our hope to establish modified Lister strain vaccinia viruses as an effective cancer treatment and challenge the current standstill in survival for head and neck cancer.



Jonathan and Dr Wang preparing samples for qRT-PCR analysis.



Immunohistochemistry of animal model tumour tissue following systemic injection with vaccinia virus (brown).

New tests and treatments for bowel cancer: using curcumin to prevent chemo-resistance in colorectal liver metastases

Half of the 37,000 patients diagnosed with bowel cancer in the UK each year will present with, or go on to develop, advanced cancer that has spread to the liver (metastases).

Glen Irving

FELLOWSHIP/SPONSOR
Newman Foundation Research Fellowship with support from the Rosetrees Trust.

SUPERVISORS
Dr Lynne Howells, Dr Karen Brown, Professor William P Steward and Mr DP Berry.

SITE OF WORK
University of Leicester.

PUBLICATIONS

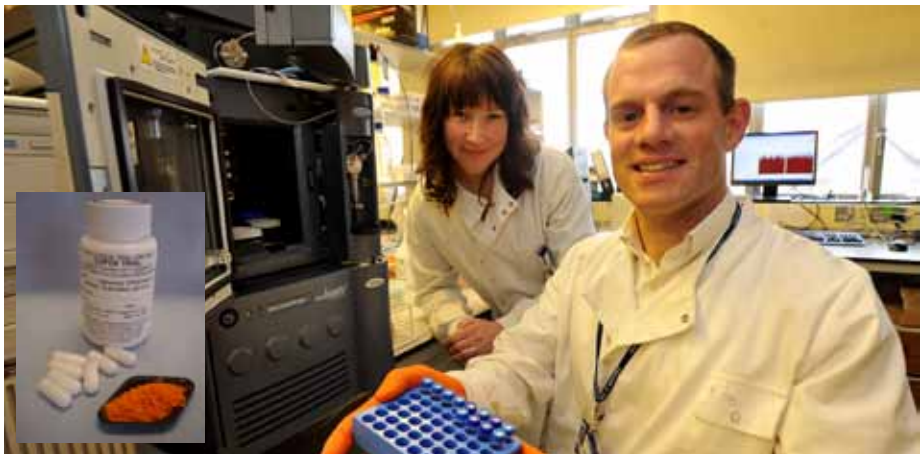
1. Howells LM, Sale S, Sriramareddy SN *et al.* Curcumin ameliorates oxaliplatin-induced chemoresistance in HCT116 colorectal cancer cells in vitro and in vivo. *Int J Cancer* 2011; **129:** 476–486.
2. Irving GR, Karmokar A, Berry DP *et al.* Curcumin: the potential for efficacy in gastrointestinal diseases. *Best Pract Res Clin Gastroenterol* 2011; **25:** 519–534.

PRESENTATIONS

1. *Assessing oral curcumin for clinical adenoma recurrence prevention.* National Cancer Research Institute (NCRI); November 2010; Liverpool, UK.
2. *Chemoprevention and cancer stem cells – expediting translation to clinical paradigms.* NCRI; November 2010; Liverpool, UK.

PRIZES
South Yorkshire Higher Surgical Trainees Annual Research Review: Best Oral Presentation.

FURTHER FUNDING
Bowel Disease Research Foundation, Clinical Trials Awards and Advisory Committee and Experimental Cancer Medicine Centre Network and Cancer Research UK.



Glen and Dr Karen Brown using modern and ultra-sensitive analytical equipment to detect curcuminoids. Inset: Curcumin in its raw powder form and the capsules used for clinical trials.

This study is looking at how bowel cancer cells develop resistance to chemotherapy and how we can improve the efficacy of chemotherapy with the naturally occurring dietary agent, curcumin. Last year, BBC Leicester reported on this work.

Patients with advanced bowel cancer are impeded by side-effects of chemotherapy or the disease itself. Curcumin may permit side-effect reduction without diminishing the efficacy of chemotherapy. Curcumin may prolong the effective period of chemotherapy and ameliorate dose-related side-effects thus preventing early cessation of treatment.

In the laboratory, bowel cancer cells resistant to chemotherapy have been treated with either curcumin or chemotherapy, or both. We have also conducted two clinical trials: one to assess the safety and feasibility of giving curcumin to patients attending cancer surgery or surveillance endoscopy; and another to collect blood and urine to detect and monitor disease in patients with bowel cancer. The information from these components has been used to set up a final clinical trial administering chemotherapy with curcumin to patients with advanced bowel cancer. We aim to test the safety of the combination, further investigate markers of disease, and take X-ray measurements (CT scans) of the response to the new treatment.

We have shown curcumin enhances chemotherapy and overcomes resistance in the laboratory. We have suggested how this may happen. We have added to the clinical safety profile of curcumin, and presented the patients' thoughts about taking curcumin and its long-term clinical use. As an aside, we have found that after consumption curcumin persists in the bowel lining, which is important for studies treating bowel growths.

We have collected and processed blood and urine from patients (by mass spectrometry and nuclear magnetic resonance) and the raw data is being looked at for potential markers of cancer.

Our exciting latest trial has been granted ethical and Medicines and Healthcare products Regulatory Agency approval and recruitment is about to start. This project will continue for five years but early findings (after approximately one year) will contribute towards this PhD.

The use of bone graft in re-do hip replacement with large bone defects

Failed hip replacement with large bone defects are debilitating and difficult to treat. 80% of bone grafts used in re-do hip replacements with large bone defects survive 20 years after surgery and 60% of sockets implanted survived.

Paul Tee Hui Lee

FELLOWSHIP/SPONSOR
Harry Morton Research Fellowship.

SUPERVISOR
Professor Allan E Gross.

SITE OF WORK
Mount Sinai Hospital, Toronto, Canada.

PUBLICATIONS
1. Lee PTH, Safir O, Clayton R *et al.* Structural allograft as a feasible option for treating infected hip arthroplasty with massive bone loss. *Clin Orthop Relat Res* 2011; **469:** 1,016–1,023.
2. Lee PTH, Raz G, Backstein D *et al.* Long term follow-up results for minor column acetabular allograft in revision hip arthroplasty. *Clin Orthop Relat Res* 2010; **468:** 3,295–3,303.

PRESENTATIONS
1. *Long term follow-up results for minor column acetabular allograft in revision hip arthroplasty.* British Hip Society; February 2010; Sheffield, UK.
2. *Long term follow-up results for major column acetabular allograft in revision total hip replacement.* American Academy of Orthopaedic Surgeons; February 2010, New Orleans, USA.

Professor Allan Gross (left) with Paul.

Paul (left) performing a revision hip replacement with Dr Safir (right foreground) and Prof Gross (right background) assisting.

Hip replacement may loosen and fail after many years due to bone resorption around the implant. Occasionally, large bone defects may develop around the implant, making re-do hip replacement difficult because of insufficient bone for implant fixation. The use of bone grafts can address large bone defects and provide adequate stability for implant fixation, with the potential to restore bone to the patient and facilitate future re-do hip replacement. The two major causes for severe bone resorption around hip replacement are the biological response to wear and particle debris over time, and infection.

Concerns remain about if the bone graft will collapse and fail in the long run and if it is safe for treating infected hip replacement. Reports in these areas are scarce although results have been encouraging for bone grafting smaller defects in hip replacement. I reviewed 74 consecutive patients who underwent 85 re-do hip replacements using bone graft for large defects. 80% of bone grafts originally used survived 20 years after surgery and 60% of sockets implanted survived.

In another study, I reviewed 27 patients who were treated for infected hip replacement with large bone defects. The infected implants were removed, the wounds thoroughly cleaned and the patient treated with antibiotics. When the infection was eradicated, bone graft was used to treat large defects to support a re-do hip replacement. One infection recurred when the patient developed a urine infection, giving a comparable rate of infection to re-do hip replacements that do not require bone graft. More than 90% of bone grafts and implants survived after 10 years. Most patients have significant pain relief and functional improvement postoperatively.

Wall stress dependent gene expression in abdominal aortic aneurysms

Abdominal aortic aneurysm (AAA) is a significant problem with an increasing incidence. An age-related condition, AAA affects about 4% of the population over 65 years of age. The overall mortality rate for ruptured AAA is 65–85% and it causes more than 10,000 deaths per year in the UK

Amir Malkawi

FELLOWSHIP/SPONSOR
Joint RCS/Dunhill Medical Trust Research Fellowship.

SUPERVISOR
Professor Matt Thompson.

SITE OF WORK
St George's Hospital, University of London.

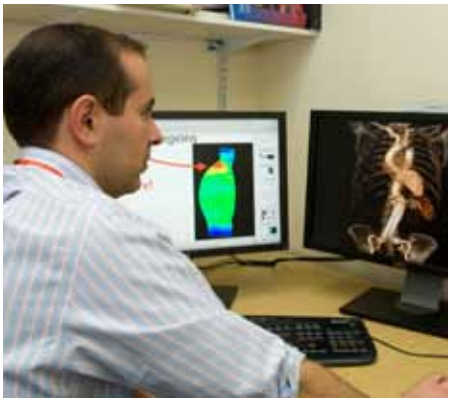
PUBLICATIONS
Malkawi AH, Hinchliffe RJ, Xu Y *et al.* Patient-specific biomechanical profiling in abdominal aortic aneurysm development and rupture. *J Vasc Surg* 2010; **52**: 480–488.

PRESENTATIONS
1. *Lamin A/C over-expression at regions exposed to high wall stress; A novel, mechano-sensitive pathway in abdominal aortic aneurysm (AAA) pathogenesis.* The Society of Academic and Research Surgery; January 2011; Dublin, Ireland.
2. *Abdominal aortic aneurysm (AAA) wall thickness at regions of high and low wall stress: implications for aortic wall stress computation and rupture prediction.* The Vascular Society; November 2009; Liverpool, UK.

The majority of AAAs remain asymptomatic until rupture occurs. For the minority of patients reaching hospital alive, emergency repair carries a high morbidity and mortality. Currently, diameter is used to predict rupture and plan treatment but this can be unreliable. There is a need to be able to predict rupture more reliably and offer timely intervention.

Amir talking to a patient participating in the project.

AAA development and rupture is a result of the interaction of complex biological and biomechanical alterations at the rupture site. Finite element analysis (FEA) is an engineering method used to simulate stress distribution in complex structures. Unlike diameter, it takes into account patient and AAA-specific characteristics, including computed tomography images to estimate mechanical stress distribution. It demonstrated that stress was higher in symptomatic and ruptured AAAs compared to asymptomatic AAAs. FEA was found to predict rupture more accurately than diameter with good correlation between areas of highest wall stress and rupture sites.



Generation of patient specific wall stress maps.

Vascular biology and biomechanics have been traditionally considered separately. This research linked the two disciplines with the aim of investigating differential gene expression between areas of low and high wall stress. FEA was performed on patients with AAAs scheduled for open repair. Regions of high and low wall stress were identified from the obtained patient-specific wall stress maps and paired aortic wall samples were obtained during open AAA repair. RNA and proteins were extracted from biopsied AAA walls. Whole genome profiling demonstrated over-expression of LMNA (lamin A/C) gene in high wall-stress regions compared to low stress regions. Over-expression of lamin A/C protein in high stress regions was also demonstrated on Western blotting.

Our results identify novel pre-rupture changes in AAAs in regions exposed to high stress. Over expression of lamin A/C in high wall stress regions highlights the role of cytoskeletal and nuclear mechanics, mechanotransduction and apoptotic transcriptional pathways in AAA development and rupture.

Informing the surgical management of the distal radioulnar joint: a functional, anatomical, biomechanical and histological approach

20% of patients with distal radioulnar joint (DRUJ) wrist instability suffer a curable, intermittent numbness to the hand. Virtual operative procedures to predict and improve treatment outcomes are on the way...

Paul Malone

FELLOWSHIP/SPONSOR
Joint RCS/British Society for Surgery of the Hand and Cutner Legacy Research Fellowship.

SUPERVISORS
Miss Vivien C Lees and Professor Giorgio Terenghi.

SITE OF WORK
University of Manchester.

PUBLICATIONS
1. Malone PS, Hutchinson CE, Kalson NS *et al.* Subluxation-related ulnar neuropathy (SUN) syndrome related to distal radioulnar joint instability. *J Hand Surg Eur Vol* 2011; epub ahead of print.
2. Kalson NS, Malone PS, Bradley RS *et al.* Fibre bundles in the human ECU tendon are arranged in a spiral. *J Hand Surg Eur Vol* 2011; epub ahead of print.

PRESENTATIONS
Subluxation-related Ulnar Neuropathy 'SUN Syndrome': Anatomical Relationships of the Ulna Nerve in Instability of the Distal Radioulnar Joint. The British Society for Surgery of the Hand; April 2010; Manchester, UK.

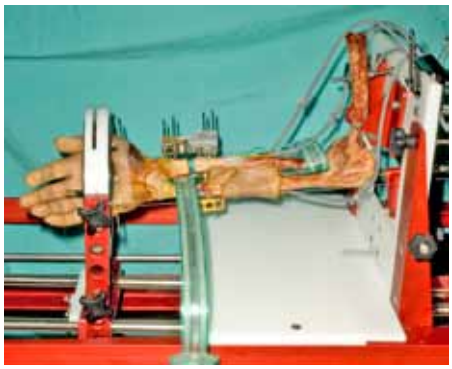
PRIZES
1. RCS Rosetrees Essay Prize.
2. Nominated for 'Healthcare Project of the Year' Bionow Biomedical Award, 2011.

High-resolution research MRI scanning of a patient's wrist joint using a custom-built assessment jig for accuracy and reproducibility.

The College fellowship allowed me to undertake a third year of research on forearm biomechanics in preparation for a PhD, specifically related to the DRUJ of the wrist. The third year also enabled me to complete a clinical project on a patient cohort investigating wrist instability. This involved high resolution MRI scanning and 3D reconstructions in symptomatic patients. We described a new syndrome ('SUN syndrome' – subluxation-related ulnar neuropathy) and delineated the causative mechanisms. 100% of our treated patients have had their symptoms surgically cured with stabilisation of their unstable DRUJ.

Another 'arm' of my PhD was cadaveric biomechanical research on the upper limb, assessing in particular the effect of distal radius fractures on wrist and forearm functioning. A series of five papers is nearing publication, which will equip the upper limb surgeon with better capabilities to diagnose and treat ligamentous DRUJ injuries of the wrist following trauma.

A final pan-UK multicentre project I directed has combined large-scale histological microtomy with nano-CT scanning. This has generated a small paper on tendon spiralling but more importantly allowed me to foster significant collaborations to develop a project on finite element analysis (FEA) mapping. FEA is the future of surgical procedures: we equip individual molecules of a 'virtual upper limb' with my biomechanical data so that it behaves as a real upper limb would. We then simulate injuries and see their effects on normal functioning. Most importantly, we can reproduce a patient's actual injury in the virtual setting and then undertake a virtual operative procedure in order to predict best treatment outcomes. This final project is a large, multicentre follow-on project currently in development.



A cadaveric specimen under investigation using a custom-built biomechanical jig. Green joint pressure sensors can be seen mounted within the joints. External fixators can also be seen affixed about a simulated distal radius fracture. Note that the clamp holding the hand is pneumatic and can be easily rotated through the arc of forearm rotation to replicate normal forearm movements. A 5kg weight loads the forearm across the wrist via a series of cables and pulleys.

Trauma: damage recognition and response

Traumatic injury is the leading cause of death worldwide in people under the age of 45 years.

Joanna Manson

FELLOWSHIP/SPONSOR
Philip King Charitable Settlement Research Fellowship.

SUPERVISOR
Professor Karim Brohi.

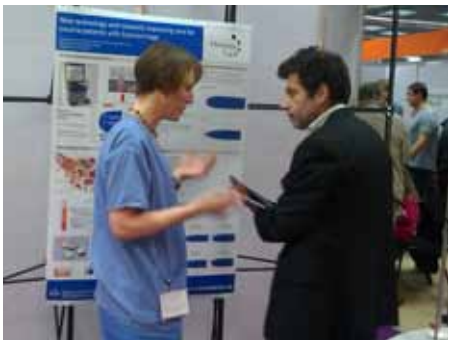
SITE OF WORK
The Royal London Hospital.

PUBLICATIONS
Manson, J, Thiemermann C, Brohi K. Trauma alarmins as activators of damage-induced inflammation. *Bri J Surg* 2012; **99**: 12–20.

PRESENTATIONS
1. *Traumatic tissue damage: the search for trauma alarmins.* 10th World congress of inflammation; June 2011; Paris, France.
2. *Demonstrating the human cytokine response to tissue damage after traumatic injury.* European Shock Society; August 2011; Taormina, Italy.

PRIZES
Inaugural RCS Fulbright Scholars and Fellows Award.

FURTHER FUNDING
RCS/Fulbright scholarship award to go to the University of Pittsburgh, USA, to conduct a post-doctoral year of research.



Public engagement at The Moscow Science Festival. Joanna discusses the work of the Trauma Sciences Unit with a Russian doctor.

The Blizard Building for cell and molecular research houses the laboratory for trauma Sciences.

Trauma is the disease of physical injury. Annually, it leads to 6 million deaths worldwide and 16,000 of these are in the UK. For every death, two patients are seriously injured, thus trauma has huge socio-economic consequences. Good surgical care is essential to optimise patient outcome and function.

Advances in trauma surgery and critical care have made substantial improvements to patient survival. Many patients, however, still experience serious complications during their recovery phase as a result of multiple organ failure. The precise events which lead to the development of organ failure are not fully understood but are attributed to a 'dysfunctional' immune response.

An immune response is activated within 30 minutes of injury, leading to a state of inflammation. Although essential for healing and repair, trauma patients with high levels of inflammation have worse outcomes. The inflammatory response to trauma resembles that seen during severe infections (sepsis). During sepsis, white blood cells become activated when they recognise molecules on the surface of bacteria. A similar process is thought to occur after traumatic injury. In this case, the activating molecules are not foreign particles but danger-signalling proteins that are released by injured cells. These molecules are collectively known as alarmins but their precise identity is unknown.

The aim of my PhD is to identify trauma alarmins and the early activation of white blood cells. The research is conducted at one of London's major trauma centres. Using blood samples from trauma patients (within three hours of injury) I have identified and quantified potential alarmin molecules and also examined white blood cell activity. Few centres in the world conduct research on this subject and my work forms the base for future inflammation research in our unit. Understanding how the immune response is activated by trauma may lead to novel treatment strategies which improve outcome.

Aminul Ahmed using the stretch injury device to cause an injury on cultures brain slices replicating a moderate road traffic accident.

Local factors in the progression of pancreatic cancer

Pancreatic cancer results in over 7,000 deaths in the UK every year.

Quentin Mark Nunes

FELLOWSHIP/SPONSOR
Ethicon Research Fellowship.

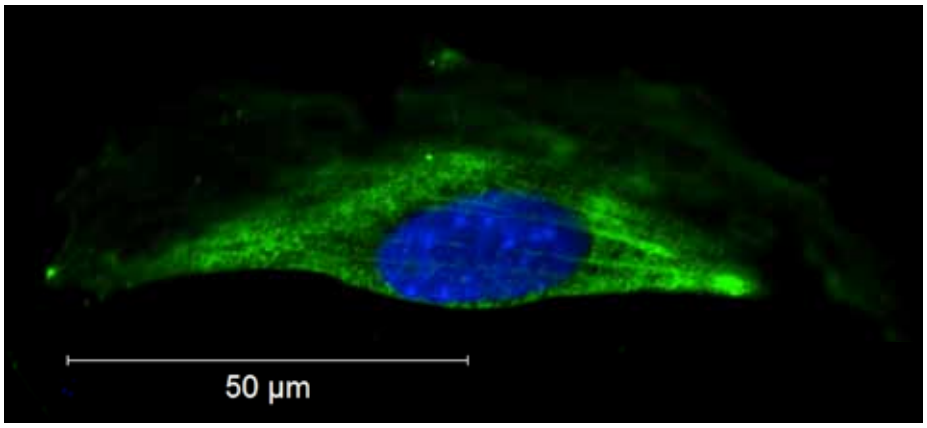
SUPERVISORS
Professors R Sutton, D Fernig and J Neoptolemos.

SITE OF WORK
Liverpool NIHR Pancreas Biomedical Research Unit.

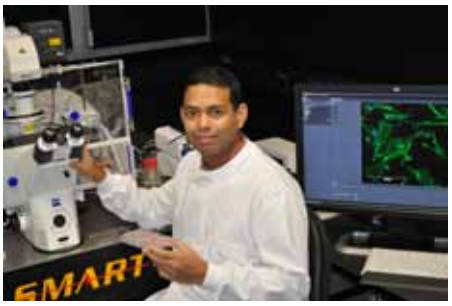
PRESENTATIONS
1. *An in-silico study of the heparin interactome in pancreatic disease.* American Pancreatic Association; November 2011; Chicago, USA.
2. *Isolation and characterisation of activated pancreatic stellate cells.* American Pancreatic Association; November 2011; Chicago, USA.

FURTHER FUNDING
National Institute for Health Research for two years.

Pancreatic cancer is a major cause of cancer death and remains one of the most difficult cancers to treat. Surgical resection forms the mainstay of treatment. The five-year survival rate after resection is around 10% and improves to about 20–30% with adjuvant chemotherapy. There is an urgent need to identify reliable biomarkers and drug targets to improve survival. Recent evidence has demonstrated that various cellular and non-cellular factors in the tumour microenvironment play an important role in tumour proliferation, tumour aggression and resistance to therapy. A key player in the microenvironment is the pancreatic stellate cell (PSC). Among the non-cellular factors, proteins and signalling molecules that bind to heparin and heparan sulphate (HBPs) influence fundamental biological processes in cancer and inflammation. My research investigates the role of HBPs and PSCs in pancreatic cancer using a dry bioinformatics approach and a wet laboratory approach.



Fluorescent staining of a pancreatic stellate cell.


Quentin studying cells in the confocal imaging suite.

Using computer programs and public data sources, I have constructed a network of HBPs in pancreatic cancer and analysed this to generate potential biomarkers and drug targets. I am now identifying therapeutic agents against these targets to be taken forward in clinical trials at the Liverpool National Institute for Health Research (NIHR) Pancreas Biomedical Research Unit.

I have also developed a novel technique to isolate PSCs for further investigations. The cells are being characterised using a variety of techniques, including electron microscopy. I am also in the process of identifying HBPs from pancreatic tissue using gold standard techniques. These techniques complement my dry work and will form the heart of my research over the next two years. My project has fostered collaborations at local, national and international levels, which we hope to continue in future.

Effects of prehospital blood transfusion in severely injured military patients

More than 200 of the most severely injured patients treated in Helmand province, Afghanistan, have received pre-hospital blood transfusions and, of those, more than 70% have survived.

David O'Reilly

FELLOWSHIP/SPONSOR
Surgical Research Fellowship in Military Surgery.

SUPERVISOR
Dr Emrys Kirkman.

SITE OF WORK
Defence Science and Technology Laboratory (DSTL), Porton Down.

FURTHER FUNDING
DSTL Porton Down throughout the project.

RAF Medical Emergency Response Team (MERT) in action.

MERT at dusk.

Bleeding is the leading cause of death in battlefield casualties. The outcome from injuries is worsened by blood loss starving the tissues of oxygen and consuming coagulation factors that allow blood to clot. Shock interferes with clotting, creating a vicious cycle leading to further bleeding. UK Defence Medical Services (DMS) have deployed doctors forward on retrieval helicopters in order to reduce the time from injury to advanced resuscitation interventions, including pre-hospital transfusion of blood products. This has become a routine part of military medical practice for the first time in recent conflicts. Red blood cells and plasma, which contains coagulation factors, can be given to extend the 'damage control resuscitation' philosophy that guides patient care in the field hospital towards the point of injury. This is an extremely resource-intensive model of care and the degree of benefit it gives is unknown. Indeed, there are possible mechanisms whereby the transfusions could potentially have adverse effects in some cases.

My research seeks to clarify these issues using two strategies. Firstly, using operational data to study outcomes among those who receive pre-hospital transfusion of blood products. This involves combining data from multiple sources and requires a unique collaboration with the US military. Secondly, developing a model of complex injury that will allow the assessment of the currently uncertain physiological effects of pre-hospital blood product transfusion.

The outcome of these studies will determine whether the strategy of pre-hospital blood product transfusion confers benefit and will give an evidence base to guide UK DMS practice and that of other armed forces and civilian trauma services. At the same time, the model will allow examination of the fundamental mechanisms that disrupt blood clotting after injury, leading to future development of more focused treatments.

Novel treatments for reducing infection in open fractures

If a serviceman sustains an open fracture on the battlefield, there is a 70% chance it will get infected.

Jowan Penn-Barwell

FELLOWSHIP/SPONSOR
Surgical Research Fellowship in Military Surgery.

SUPERVISOR
Dr Josh Wenke.

SITE OF WORK
US Army Institute of Surgical Research, Ft Sam Huston, San Antonio, Texas.

PUBLICATIONS
Penn-Barwell JG, Murray CK, Wenke JC. Early initial antibiotics and debridement independently reduce infection in an open fracture model. *J Bone Joint Surg (Br)* 2012; **94-B:** 107–111.

PRESENTATIONS
1. British Orthopaedic Association Conference; September 2011; Dublin, Ireland.
2. Orthopaedic Trauma Association Conference; October 2011; San Antonio, USA.

FURTHER FUNDING
US Army Institute of Surgical Research for one year

Jowan flanked by Royal Marines while treating a patient who had just sustained an open fracture to his femur following a gun-shot wound.

Open fractures (where the broken bone ends are exposed through a wound) are a significant challenge to orthopaedic surgeons. Combat wounds especially are heavily contaminated and infection occurs in up to 70% of these injuries and may cause re-hospitalisation, re-operation, amputation and poor recovery. The Royal Centre for Defence Medicine and the US Army Institute for Surgical Research (USAISR) have collaborated to investigate novel methods to improve treatments to reduce infection.

I worked in the USAISR labs in Texas using animal models of open fractures contaminated with S. aureus bacteria. This model allows the testing and comparison of treatments and measurement of the presence and amount of bacteria 14 days after injury and treatment.

Four main studies were performed looking at key areas for improvement: the timing of treatments, disinfectant wound irrigation solutions, local antibiotics and anti-biofilms:

i) Timing of treatment. This study confirmed that urgent antibiotics are critical but early surgical treatment is still essential in making the difference between 100% and 0% infection.

ii) Chlorhexidine for irrigating open fractures. Our results proved that chlorhexidine solutions are not superior to saline for irrigating wounds.

iii) Local antibiotic gel. This study tested a new bio-absorbable antibiotic gel and demonstrated that it is superior to the current technique of using antibiotic in beads made from arthoplasty cement, dropping the infection rate in this model from 100% to 50%.

iv) Bismuth thiols and bacterial biofilms. Bacteria in wounds can form biofilms and resist antibiotic treatment. Our group is the first to show that bismuth thiols can make biofilm bacteria vulnerable again to antibiotics.

It is hoped that these results can be rapidly translated into improved strategies for preventing and treating infection in open fractures. This should lead to fewer repeated operations, fewer amputated limbs and earlier discharge and rehabilitation following these life-changing injuries.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official, or as reflecting the views of the United Kingdom Ministry of Defence or United States Department of Defense.

Lower limb blast fractures: a clinical and engineering perspective

50% of soldiers who fracture their heel in an explosion will require an amputation.

Arul Ramasamy

FELLOWSHIP/SPONSOR
Surgical Research Fellowship in Military Surgery.

SUPERVISORS
Professor Anthony Bull and Colonel Jon Clasper.

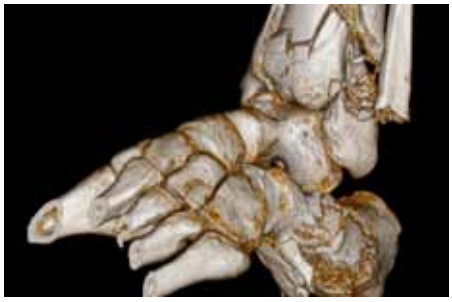
SITE OF WORK
Imperial College London.

PUBLICATIONS
1. Ramasamy A, Hill AM, Masouros SD *et al.* Environmental influence on blast related fracture patterns: a forensic biomechanical approach. *J R Soc Interface* 2011; **8:** 689–698.
2. Ramasamy A, Masouros SD, Newell N *et al.* Extremity injuries from improvised explosive devices: current research and future focus. *Philos Trans R Soc Lond B Biol Sci* 2011; **366:** 160–170.

PRESENTATIONS
1. *Explosion mediated blast fractures.* British Trauma Society; May 2010; Manchester, UK.
2. *Outcomes from calcaneal blast fractures.* Combined Services Orthopaedic Society; May 2011; London, UK.

PRIZES
Best presentation, Combined Services Orthopaedic Society, London, May 2011.

FURTHER FUNDING
Royal Centre for Defence Medicine, Drummond Foundation, Defence Science and Technology Laboratory, Soldiers, Sailors, Airmen and Families Association, Army Benevolent Fund, The Royal British Legion, The FH Muirhead Charitable Trust for three years.



A 3D CT reconstruction of a blast injury to the foot from an explosion, demonstrating fractures to multiple segments of the foot. This injury necessitated an amputation.

The synthetic foot model sits on the 45kg plate, which is capable of accelerating to 45mph within 10cm.

Modern conflict has seen great improvements in medical care and personal protection. This has resulted in service personnel surviving with more complex musculo-skeletal injuries. These injuries are often so severe that amputation remains the only medical option. Even when limb salvage is successful, these young casualties are often faced with a lifetime of disability. There exists an urgent requirement to both characterise and model the effects of explosion on the lower limb, in order to develop novel mitigation strategies.

One of the significant deficits in defence research has been the dearth of clinical data to underpin basic science research. Therefore one element of my research was to investigate the functional outcomes of lower leg injuries from improvised explosive device (IED) blasts. From the analysis of 63 UK casualties with lower leg injuries, the amputation rate was 33%, with only 14% of casualties able to return to full military duty. Statistical analysis of the data allowed the creation of probability curves for amputation and poor clinical outcome as a function of lower leg injury severity. Thus, for the first time, contemporary battlefield data has been utilised to predict clinical outcome. This analysis was used to quantify the injuries produced in traumatic injury simulations, as well as quantitatively evaluate the effect of mitigation on injury prevention.

Due to the difficulties in recreating the blast environment within a laboratory setting, researchers have relied on automative impact simulators as a surrogate for the blast. It was apparent that the injuries caused by explosions are very different from those caused by vehicle collisions and there was a requirement to develop an injury simulator capable of recreating the short duration, high amplitude axial loading witnessed in IED attacks.

My research involved the development and characterisation of a unique injury simulator (AnUBIS, anti-vehicle mine underbelly blast injury simulator) capable of accelerating and decelerating a 45kg metal plate to a velocity of $20ms^{-1}$ within 30cm of travel. Utilising AnUBIS, instrumented cadaveric limbs were impacted in different orientations to investigate the effect of seating position on injury pattern. Based on the experimental data, it was demonstrated that for a given impulse, limb position had a significant effect on injury formation and the injuries produced were of similar severity to that witnessed in battlefield casualties. It is anticipated that this research will enable us to develop new mitigation to prevent such injuries and ultimately reduce the significant injury burden to service personnel who have been wounded in an explosion.

Determining the benefit of post-retrieval organ oxygenation techniques in Maastricht category II donation-after-cardiac-death kidneys

Patients with end-stage kidney failure are reliant on dialysis to sustain life. Kidney transplantation can transform the lives of such patients, freeing them from dialysis and significantly increasing their life-expectancy.

Christopher Ray

FELLOWSHIP/SPONSOR
Shears Northern Research Fellowship.

SUPERVISORS
Professor David Talbot and Dr Noel Carter.

SITE OF WORK
Department of Liver and Renal Transplant, Freeman Hospital, Newcastle-Upon-Tyne. The University of Sunderland and University of Newcastle.

PUBLICATIONS
1. Ray C, Sohrabi S, Talbot D. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; **360:** 1,460–1,461.
2. 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.

PRESENTATIONS
1. *Porcine Model of Extra-Corporeal Membrane Oxygenation (ECMO) in the uncontrolled Non-Heart-Beating Donor; Assessing Tissue Injury.* The European Liver and Intestine Transplant Association/European Liver Transplant Registry; May 2010; London, UK.
2. *Porcine model of extra corporeal membrane oxygenation (ECMO) in the uncontrolled non-heart-beating donor; the effect on renal viability.* European Society of Organ Transplantation; September 2011; Glasgow, UK.

PRIZES
Best Oral Presentation. West of Scotland Surgical Association, 2011.

Chris performing a transplant operation with research colleagues.

Donor nephrectomy operation.

Transplant kidney being implanted into a recipient.

Transplant kidney after reperfusion (re-connected to blood supply).

There are over 7,000 patients on the UK kidney transplant waiting list with the number increasing every year. Due to a shortage of available organs, less than 2,000 transplants are performed each year in the UK. Thus there is a significant deficit in the number of organs available to transplant compared with the number of patients requiring one.

Our research unit aims to make more organs available for transplantation. One way of achieving this is to allow patients suffering from unexpected deaths in the community to become organ donors (donation after cardiac death). These organs are exposed to significant damage because of the mode of death and the effect of prolonged blood and oxygen starvation.

My body of research investigates the use of oxygenation techniques to resuscitate donor organs and correct the damage incurred before they can be used for transplantation.

Thanks to a grant from the Royal College of Surgeons and the Shears Foundation, I investigated whether it would be beneficial to re-connect donor kidneys to an artificial blood supply. Initially, this was trialled in an organ model using the technology of heart-lung bypass to supply oxygen to the organs directly (extra corporeal membrane oxygenation). The benefit to kidney function was dramatic. We extended this line of investigation using a simplified and briefer period of oxygenation in an animal model of kidney transplantation.

Based on the results of this work, applications are now underway to pilot these techniques, in clinical use, in Newcastle. While it is anticipated this will improve the number and quality of kidneys available for transplantation, there is potential to apply this technique to additional transplant organs such as the liver and pancreas – organs that as yet are not used in this donor setting.

Genotoxic effects of orthopaedic nanoparticle wear debris on human cells across cellular barriers

Over 50,000 joint replacements with metal-on-metal bearing surfaces have been implanted into patients in the UK. These implants wear with use and there are concerns about the effects of these wear particles within the body but there is little research to inform us.

Saif Salih

FELLOWSHIP/SPONSOR
College Research Fellowship.

SUPERVISORS
Dr Patrick Case and Professor Ashley Blom.

SITE OF WORK
Bristol Implant Research Centre, Avon Orthopaedic Centre.

PUBLICATIONS
Sood A, Salih S, Roh D. Signalling of DNA damage and cytokines across nanoparticle exposed cell barriers depends on barrier thickness. *Nature Nanotech* 2011; **6:** 824–833.

PRIZES
WG Hampson Memorial Award.

FURTHER FUNDING
North Bristol NHS Trust a one off payment towards consumables and fees.

There have been over 50,000 metal-on-metal bearing joint replacements implanted in the UK. These bearing surfaces have been aimed at younger patients because they are hard wearing and wear slower than traditional metal-on-plastic bearings. However, they still generate particles of metal as they wear. There has been concern recently about the effects of these wear particles and this has led to a medical device alert from the Medical and Healthcare products Regulatory Authority. These wear particles can be found in other parts of the body and the levels of metal in some patients with metal-on-metal implants have been shown to be higher than normal levels.

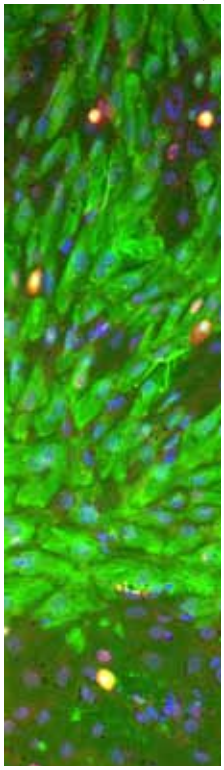
Previous research has shown that the metal particles produced by the wear of these implants can damage the DNA of cells when the cells are directly exposed to them; however, there are many cellular barriers in the body and it is not known if these wear particles can damage tissues across these. Especially as these implants are used in younger patients who potentially want children, there is a need to know if these particles cross cellular barriers (such as the blood-brain barrier, blood-testis barrier or even the placenta) and cause damage to cells on the other side.

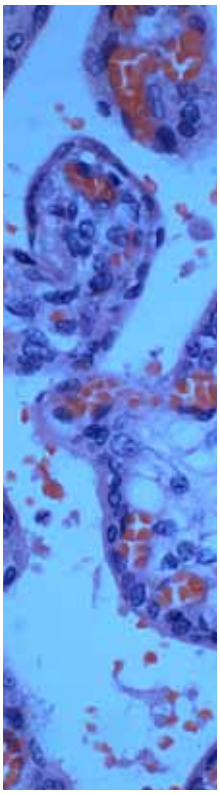
Using cells in culture models of barriers in the body, generally one-cell-layer barriers (like those in the brain, testis, lung, gut and retina) or two-cell-layer barriers were made and particles added to these. Another cell type underneath this barrier was then assessed to determine if they had any DNA damage after this. Using human embryonic stem cells we then tested whether this type of 'indirect' particle exposure could change the way they differentiated.

The work showed that the particles themselves did not cross the barriers (regardless of how thick they were) but when there was a thin, single-layer barrier the cells underneath were not damaged. Conversely when the barriers were thicker there was significantly more DNA damage and the way in which human embryonic stem cells grew also changed.

Although much more work needs to be done in this area, it not only has implications for the safety of metal-on-metal implants but also for other areas of medicine where particles of a similar size (nanoparticles) are being used therapeutically.

Below: Photograph through a microscope of human stem cells stained to show the way they differentiate. This particular group shows a colony that is fated to become neuroextoderm (primitive brain and nerve cells).





Above: Photograph through a microscope of human placenta at term showing the predominantly single layered barrier between the mother's blood and the foetus'.

The epigenetics of HPV16-mediated oral and oropharyngeal squamous cell carcinoma

This research has shown that the proportion of tonsil cancers that are positive for human papillomavirus 16 (HPV16) has increased four-fold in the UK in just two decades (14% in 1988/9 to 57% in 2008/9).

Andrew Schache

FELLOWSHIP/SPONSOR
FDS–Wellcome Trust Research Training Fellowship.

SUPERVISORS
Mr Richard Shaw, Dr Lakis Liloglou and Dr Janet Risk.

SITE OF WORK
University of Liverpool.

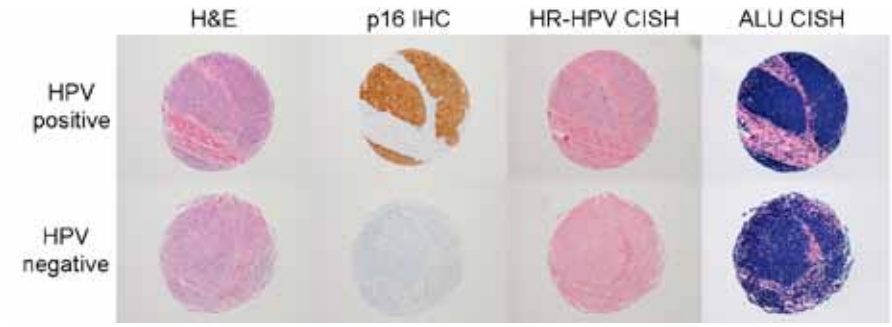
PUBLICATIONS
1. Schache AG, Liloglou T, Risk JM *et al.* Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. *Clin Cancer Res October* 2011; **17**: 6,262–6,271.
2. Schache AG, Simcock R, Gilbert DC, Shaw RJ. The changing face of human papillomavirus related malignancy in the UK. *BMJ* 2011; **343**: 6,675.

PRESENTATIONS
1. *Does human papillomavirus have a role to play in oral cavity squamous cell carcinoma?* National Cancer Research Institute (NCRI); November 2011; Liverpool, UK.
2. *Quantitative promoter methylation differentiates carcinoma ex pleomorphic adenoma from pleomorphic adenoma of the salivary glands.* American Head and Neck Society; October 2010; Arlington, USA.

PRIZES
1. Paul Toller Research Prize, British Association of Oral and Maxillofacial Surgeons, 2011.
2. NCRI Prize Award, 2011.

This project has two primary aims. Firstly, to determine the best test for HPV16-mediated head and neck cancer and, in doing so, establish the role that HPV16 is playing in cancer incidence. Secondly, the project aimed to demonstrate the way in which the virus interacts with the host at a molecular level and explore how this might influence outcomes for individuals with HPV16-mediated cancer.

Andrew (centre left) with fellow head and neck cancer researchers from the Mersey Head and Neck Oncology Research Group.



Defining the best test for HPV-positive head and neck cancer .Tissue microarray tumour cores analysed using a combination of stains to demonstrate tumour and detect viral presence.

The first component of this research is now complete, having demonstrated a dramatic change in the proportions of HPV-positive oropharyngeal (tonsil and base of tongue) cancer in the last two decades (rising from 14% to 57% between 1988–2009). Furthermore, the analysis of several of the available tests (or combinations of tests) for HPV status in tumours has shown significant disparities in accuracy and prognostic ability of the previously published tests. This research is likely to influence important forthcoming clinical trials and, additionally, is likely to hold substantial interest with policymakers charged with deciding whether to vaccinate young males against HPV in addition to young females.

When considering interactions between the virus and the host genome (a patient's own DNA) this research has reinforced previously demonstrated similarities and, more importantly, highlighted profound differences from prior understanding. My results indicate that the virus may be able to influence the expression of key human genes involved in cancer cell regulation. I am presently investigating whether this apparent change in gene expression is directly implicated in the development of virally induced cancer.

Novel binding partners of PBF in thyroid cancer

Thyroid cancer is the most common endocrine malignancy and has the fastest rising incidence of all cancers in women.

Neil Sharma

FELLOWSHIP/SPONSOR
Joint RCS/Get Ahead Charitable Trust Research Fellowship.

SUPERVISORS
Professor Chris McCabe and Professor John Watkinson.

SITE OF WORK
University of Birmingham.

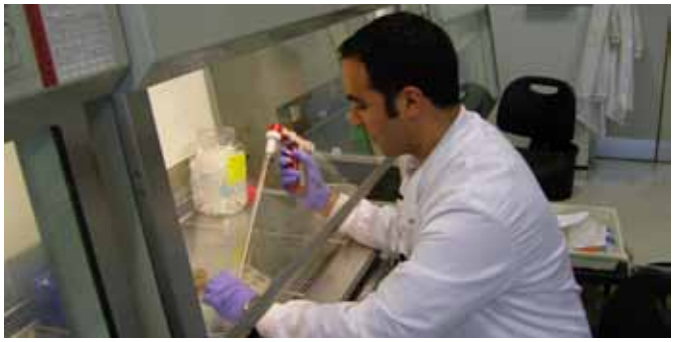
PUBLICATIONS
1. Read ML, Lewy GD, Fong JC *et al.* Proto-oncogene PBF/PTTG1IP Regulates Thyroid Cell Growth and Represses Radioiodide Treatment. *Cancer Res* 2011; **71:** 6,153–6,164.
2. Sharma N, Boelaert K, Watkinson JC. Who should treat thyroid cancer: A UK surgical perspective. *Clin Oncol R Coll Radiol.* 2010; **6:** 413–418.

PRESENTATIONS
1. *The use of tandem mass spectrometry to identify novel binding partners of PBF in thyroid cancer.* Otorhinolaryngological Research Society; March 2011; London, UK.
2. *Novel binding partners of PBF in thyroid cancer.* British Association of Endocrine and Thyroid Surgeons; October 2011; Poitiers, France.

PRIZES
1. Otorhinolaryngological Research Society Philip Stell Prize, 2011.
2. Medical Research Council Clinical Research Training Fellowship, 2010.

FURTHER FUNDING
Medical Research Council for three years.

Neil and Professor John Watkinson, consultant ENT surgeon, discussing patients in the thyroid clinic.



Neil culturing thyroid cancer cells in vitro.

Differentiated thyroid cancer is a disease that affects all ages but has a peak incidence in young women. For most patients treatment involves removal of the thyroid gland followed by administration of radioactive iodine to kill any remaining thyroid cells. Unfortunately, up to 30% of thyroid cancers recur, possibly due to their reduced ability to take up the iodine. These recurrences can occur many years after surgery and for these patients the prognosis is worse.

Cancer is a disease of genes and, while numerous genes have well-characterised roles in thyroid cancer, new therapeutic targets are vital to improved treatment success. Our group has identified a new gene called PBF which is highly expressed in thyroid tumours and which can cause cells to become cancerous. We know that PBF stops thyroid cells from taking up the radioiodine needed to kill them after surgery but the exact mechanisms by which it does this are unclear. Most proteins work co-operatively, binding to other proteins within cells and influencing their functions. I am therefore mapping out the interactions of PBF with other proteins in thyroid cancer cells using tandem mass spectrometry, a state-of-the-art technique that identifies proteins at much lower concentrations than has been possible previously.

My work augments other work that is under way in our laboratory and has produced some very promising preliminary results. These were used to secure a Medical Research Council research fellowship, giving me the opportunity to validate the interactions I have identified. The endpoint of this research will be to examine how altering the expression of these newly identified interacting proteins (with chemotherapy, for example) affects thyroid cancer. If these cancer cells can be made to absorb radioiodine, we may be able to reduce the recurrent rates for the disease.

James Chan creating an animal fracture model using microsurgical techniques.

Preventing the growth of breast cancer stem cells by targeting the HER-2 and CXCR1/2 signalling pathways

Breast cancer is now the most common cancer affecting women in the UK; one-in-eight women will develop the disease during their life-time.

Jagdeep Singh

FELLOWSHIP/SPONSOR
Cecile Pearman and DBP Trust Research Fellowship.

SUPERVISORS
Dr Robert B Clarke and Professor Nigel J Bundred.

SITE OF WORK
Paterson Institute for Cancer Research, Christie Hospital, Manchester.

PRESENTATIONS
1. Gordon Research Conference: Mammary Gland Biology; June 2011; Newport, USA.
2. National Cancer Research Institute Cancer Conference; November 2011; Liverpool, UK.

PRIZES
Stefan Galeski Travelling Fellowship – Royal College of Surgeons of England

FURTHER FUNDING
Manchester Surgical Research Trust for one year.

Breast cancer is a significant clinical problem affecting an estimated 1.38 million women worldwide. It is now the most common cancer in the UK; one-in-eight women will develop breast cancer during their lifetime. Growing evidence supports the concept that breast cancers are sustained by a sub-population of cells known as cancer stem cells (CSCs). These cells are inherently resistant to current therapies and are thought to be responsible for driving tumour formation and disease recurrence. In order to improve survival it is therefore necessary to develop novel therapies aimed at targeting CSCs.

Approximately 25% of patients over-express (make too much) HER-2, a growth receptor, which correlates with a higher rate of recurrence and mortality. Recent studies suggest that over-expression of HER-2 promotes tumour formation and metastasis by promoting CSC activity. Furthermore, HER-2 over-expression is associated with increased production of interleukin-8 (IL-8), an inflammatory cytokine. IL-8 functions via two receptors, CXCR1 and CXCR2 and studies have shown that inhibiting CXCR1/2 can reduce CSC activity and tumour growth.

Jagdeep culturing breast cancer cells in the laboratory and loading a Western blot module to assess protein expression.

Jagdeep with her supervisor, Professor Nigel Bundred, reviewing a patient's mammogram images.

Using breast cancer cell lines and cancer cells extracted directly from breast cancer patients, I have shown that IL-8 promotes CSC activity in vitro. In HER-2 over-expressing breast cancer cells, targeting CXCR1/2 adds to the efficacy of targeting HER-2. Furthermore, I have demonstrated that IL-8 signalling is dependent on HER-2 as targeting HER-2 using drug inhibitors, or reducing the protein expression of HER-2, inhibits the effect of IL-8 on CSC activity. The next stage is to validate these findings through in vivo studies using a combination of drugs to target CXCR1/2 and HER-2 in animal models of HER-2 over-expressing breast cancers. If targeting HER-2 in combination with CXCR1/2 proves to be effective, this could form a novel therapeutic strategy aimed at reducing disease recurrence and improving the survival of HER-2 positive breast cancer patients.

Battlefield vascular injury

Battlefield vascular traumas encapsulate the most lethal and debilitating of injuries, with mortality of 80% in non-compressible haemorrhage and 91% of patients with limb-threatening vascular wounds reporting abnormal function.

Adam Stannard

FELLOWSHIP/SPONSOR
Surgical Research fellowship in Military Surgery.

SUPERVISORS
Professor Gerard Stansby and Colonel Todd E Rasmussen.

SITE OF WORK
Wilford Hall Medical Center and the United States Institute of Surgical Research, San Antonio, Texas.

PUBLICATIONS
1. Stannard A, Brown K, Benson C *et al.* Outcome after vascular trauma in a deployed military trauma system. *Br J Surg* 2011; **98:** 228–234.
2. Hancock HM, Stannard A, Burkhardt GE *et al.* Hemorrhagic shock worsens neuromuscular recovery in a porcine model of hind limb vascular injury and ischemia-reperfusion. *J Vasc Surg.* 2011; **53:** 1,052–1,062.

PRESENTATIONS
1. *Morphometric analysis of torso arterial anatomy in a male trauma population.* Military Surgery Conference, Association of Surgeons of Great Britain and Ireland; May 2011; Bournemouth, UK.
2. *Intra-aterial Lovastatin to preserve neuromuscular function in a large animal model of vascular injury and ischemia reperfusion.* Society of Military Vascular Surgeons; December 2010; Washington DC, USA.

My research aim has been to better understand injuries to blood vessels on the battlefield. It encompasses defining the injuries, describing how they are currently managed and developing new ways to improve outcomes.

The physical and mental health effects on young people who have had such severe limb injuries is significant; the majority having long-term poor quality of life, both physically and mentally. In those with limb injury, not only should this work reduce the need for amputation in a young, at-risk population but also improve the quality of the saved limb, meaning a more normal life.

Using UK and US casualty data, the number and types of injury, including their management, has been recorded. A system of patient contact, follow-up and assessment has been developed, demonstrating 66% of those with limb injury endure daily pain, requiring strong painkillers four years after injury and that 25% would have preferred an amputation rather than having their leg 'saved'. Laboratory studies look at the timing of re-establishing blood flow to injured limbs, to minimise poor outcomes. This demonstrated blood flow should be restored within 90 minutes to preserve function; previously this was thought to be 4–6 hours. Research also suggests giving statin medication at the time of injury improves the quality of walking.

These studies apply research performed from other areas (stroke, heart attack and transplantation) and addresses applicability to trauma.

This is the first comprehensive research into outcomes from vascular injury since the Vietnam war and the first to look at the use of medicine to improve limb outcome following injury.

These projects are all continuing, with further iterations in progress and an ongoing programme to record injuries and outcomes of injured personnel in the US.

Operating on an injured serviceman in Afghanistan.

Characterising enteric nervous system stem cell behaviour in mature muscle models

Despite advances in the surgical management of Hirschsprung's disease, up to 20% of patients suffer from significant long-term morbidities and up to 50% of these patients may require a long-term colostomy.

David John Wilkinson

FELLOWSHIP/SPONSOR
Joint RCS/British Association of Paediatric Surgeons Research Fellowship.

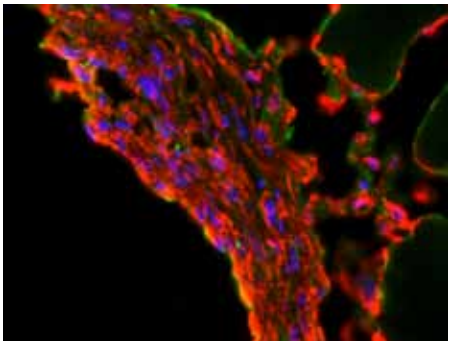
SUPERVISORS
Mr Simon Kenny and Professor David Edgar.

SITE OF WORK
Alder Hey Children's Hospital NHS Foundation Trust and Institute of Translational Medicine, University of Liverpool.

PRESENTATIONS
1. *Enteric nervous system stem cell engraftment into a 3D ex-vivo mature smooth muscle construct.* British Association of Paediatric Surgeons (BAPS); July 2011; Belfast, UK.
2. *Properties of the enteric nervous system stem cells.* BAPS; July 2011; Belfast, UK.

FURTHER FUNDING
Action Medical Research for a two year research training fellowship.

David undertaking laparoscopic assessment of the bowel in theatre.



Tissue section of the human muscle model co-stained for markers of smooth muscle.

David consenting the parents of a new born baby at Alder Hey Children's Hospital.

Hirschsprung's disease results from a failure of the nervous system to fully develop in the bowel (aganglionosis). Affected babies usually present with life-threatening bowel obstruction in the first few days of life and, even when treated appropriately, may suffer from life-long debilitating complications.

Current surgical treatments all leave behind a small amount of the aganglionic bowel around the anal sphincters that may cause ongoing symptoms. Our research group has been investigating the potential of transplanting stem cells from the normal bowel of babies with Hirschsprung's disease back into this residual aganglionic bowel. Our hope is that this will reduce some of the long-term problems caused by this disease.

This study builds on previous work from our group, demonstrating the ability to isolate stem cells from babies with Hirschsprung's disease and proof-of-concept studies that have shown the ability of these stem cells to restore a normal pattern of contractility to an aganglionic embryonic animal model. Our aim was to develop a model that is closer to that of the human bowel, allowing us to investigate safely the behaviour of these stem cells prior to contemplating clinical trials.

Utilising a method first described for potential anal sphincter transplantation, we developed a 3D human smooth-muscle model from Hirschsprung's patients, which is reproducible and stable in long-term culture. We were able to demonstrate the ability to transplant enteric nervous system stem cells into this model and track their migration. As we progress towards clinical trials, this model will enable the investigation of the behaviour of transplanted stem cells in an environment closer to that of our eventual target. I am focusing both on optimising the efficacy of integration with the host muscle and on safety for the remaining two years of my PhD.

Focal adhesion kinase in the malignant transformation of ductal carcinoma in situ of the breast

Ductal carcinoma in situ (DCIS) is an early, non-invasive breast cancer that accounts for 20% of all screening-detected breast cancers in the UK. Despite treatment, 15–20% of patients with DCIS will suffer a disease recurrence within 10 years, 50% of which will have progressed to invasive disease.

Kathryn Williams

FELLOWSHIP/SPONSOR
Ethicon Research Fellowship.

SUPERVISORS
Professor Nigel Bundred and Dr Gillian Farnie.

SITE OF WORK
The Paterson Institute for Cancer Research.

PRESENTATIONS
1. *Focal Adhesion Kinase plays a major role in the regulation of human DCIS stem cell activity.* San Antonio Breast Cancer Symposium; December 2011; San Antonio, USA.
2. *Focal Adhesion Kinase regulates human DCIS stem cell activity.* Society of Academic and Research Surgery; January 2012; Nottingham, UK.

Evidence suggests that breast cancers contain a sub-population of cells called cancer stem cells (CSCs). These are responsible for the initiation of tumour growth through their unique ability to self-renew. Unlike other tumour cells, CSCs survive current treatments (such as radiotherapy) and re-initiate tumour growth at a later date. Targeting CSCs in DCIS may reduce disease recurrence.

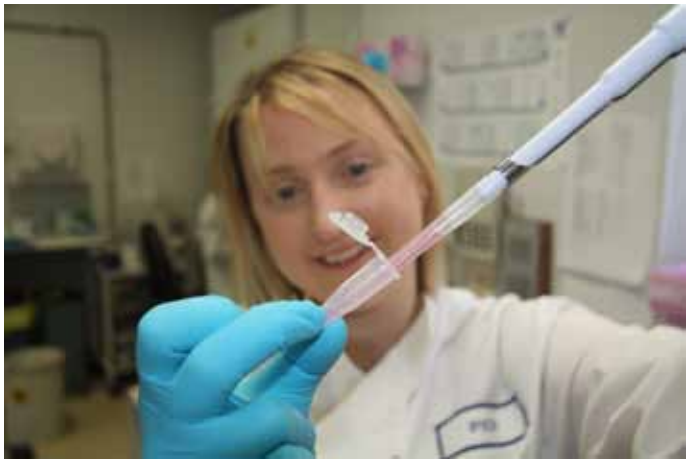
Focal adhesion kinase (FAK) is a protein that is over-expressed in breast cancer. Previous research has shown that genetic FAK knockout in an animal model of breast cancer leads to the development of fewer breast tumours. The number of breast CSCs found within these tumours was reduced, as was their ability to initiate further tumour growth. This suggests that FAK has a role in animal breast CSC activity.

My research aimed to determine the effect of a pharmacological FAK inhibitor on CSC activity in human DCIS cells. I also sought to establish whether FAK inhibition sensitises DCIS CSCs to radiotherapy.

The mammosphere assay was utilised to assess CSC activity in the presence and absence of the FAK inhibitor, with or without a dose of ionising radiation. I have demonstrated that FAK inhibition reduces CSC activity in two human DCIS cell lines and in primary DCIS tissue, taken from patients at the time of surgery. Specifically, FAK inhibition reduced the ability of DCIS CSCs to self-renew and sensitised CSCs to radiation kill.

Next I intend to stain archived clinical DCIS tissue for the presence of FAK and correlate expression to patient follow-up data. Patients expressing more FAK are expected to have a poorer prognosis. Ultimately it is hoped that breast CSCs can be targeted clinically with a FAK inhibitor to reduce DCIS recurrence rates.

Kathryn counting mammospheres, a measure of breast cancer stem cell activity.



Kathryn preparing a novel pharmacological FAK inhibitor for use on cells taken directly from patients at time of surgery.

Understanding colorectal cancer stem cells to provide better treatment options

Colorectal cancer is the third most common cause of cancer in the UK and the second leading cause of cancer death, with over 36,500 people diagnosed annually.

Trevor Yeung

FELLOWSHIP/SPONSOR
Sir Alan Parks Research Fellowship.

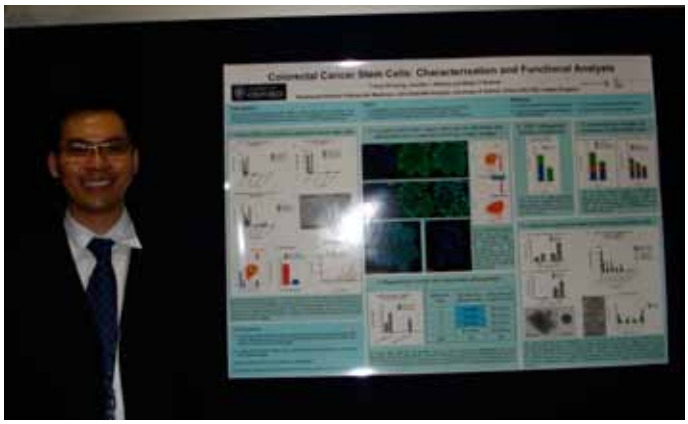
SUPERVISORS
Professor Sir Walter Bodmer and Dr Calvin Kuo.

SITE OF WORK
University of Oxford and Stanford University, California, USA.

PUBLICATIONS
1. Yeung TM, Gandhi SC, Bodmer WF. Hypoxia and lineage specification of cell line derived colorectal cancer stem cells. *Proc Natl Acad Sci USA* 2011; **108:** 4,382–4.387.
2. Yeung TM, Chia LA, Kosinski CM, Kuo CJ. Regulation of self-renewal and differentiation by the intestinal stem cell niche. *Cell Mol Life Sci.* 2011; **68:** 2,513–2,523.
3. Yeung TM, Gandhi SC, Wilding JL *et al.* Cancer stem cells from colorectal cancer derived cell lines. *Proc Natl Acad Sci USA* 2010; **107:** 3,722–3,727.
4. Yeung TM, Mortensen NJ. Colorectal cancer stem cells. *Dis Colon Rectum* 2009; **52:** 1,788–1,796.

PRESENTATIONS
1. American Society of Clinical Oncology; May 2009; Orlando, USA.
2. Association of Coloproctology of Great Britain and Ireland; June 2009; Harrogate, UK.

PRIZES
1. Royal Society of Medicine Travelling Fellowship, Coloproctology Section Overseas Meeting; Berlin, Germany, 2009.
2. Simon Wolff Charitable Foundation Travel Grant for American Society of Clinical Oncology meeting; Oralndo, USA, 2009.
3. Invited speaker, European Society for Medical Oncology, Cancer Biology for Clinicians Symposium; Nice, France, 2010.



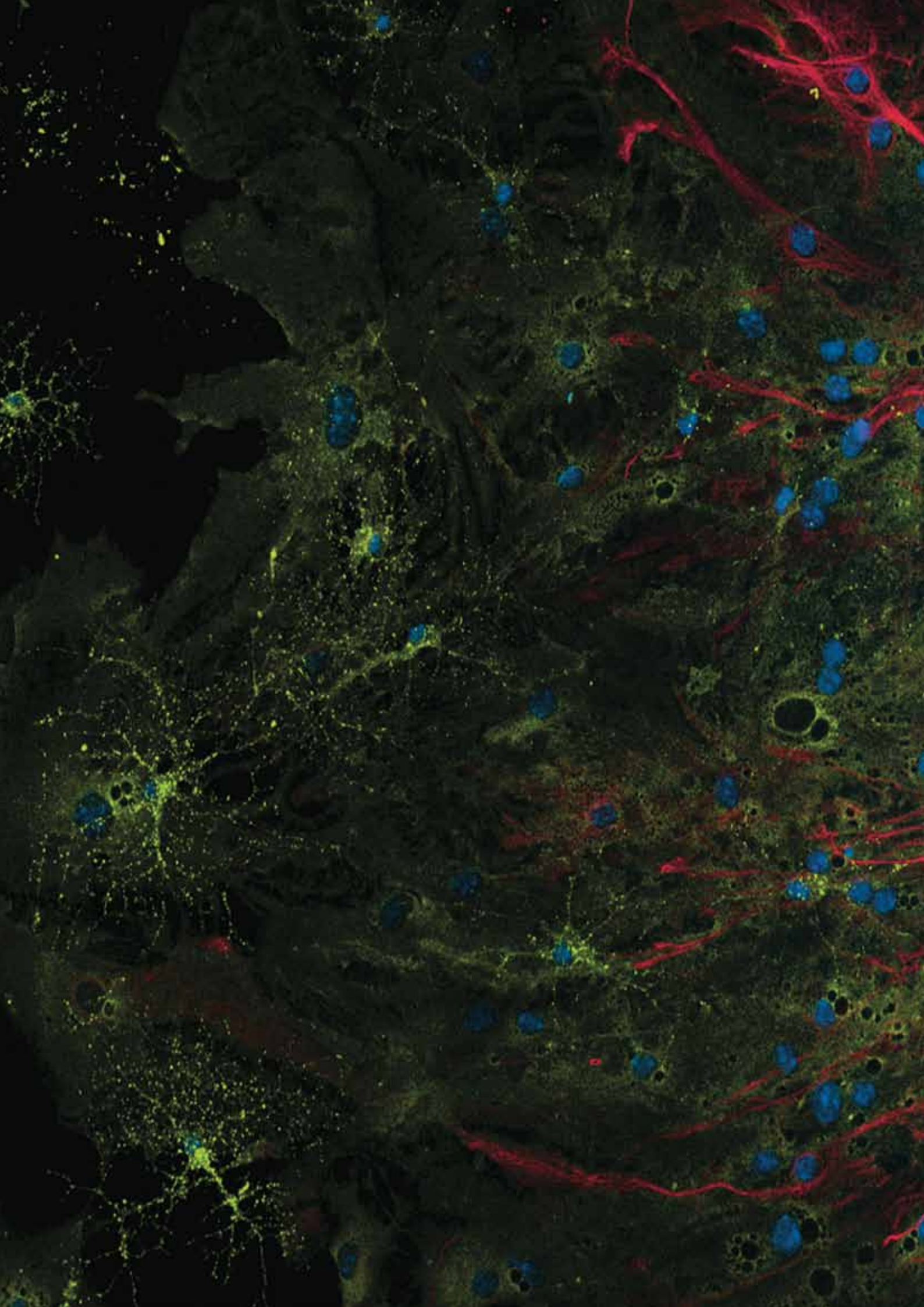
Trevor presenting work at the annual American Society of Clinical Oncology meeting in Orlando, USA, 2009.

Trevor with Miss Carol Makin, President of Section of Coloproctology, Royal Society of Medicine in Berlin, Germany, 2009.

There is increasing evidence that cancer growth is driven by a sub-population of cells within the tumour, called cancer stem cells (CSCs), which are more resistant to current forms of chemotherapy and radiotherapy. Our project involves the search for more specific markers of colorectal CSCs. We identified two markers, CD44 and CD24, which could be used to isolate CSCs. We demonstrate that a single $CD44^+/CD24^+$ colorectal CSC can self-renew, differentiate to form all the lineages found within the original cancer, and induce tumours in animal models. CD44 and CD24 can be used to screen patients with circulating CSCs in their blood, who would be at high risk of developing metastatic disease. In conjunction with colonoscopy, the use of these CSCs markers could also identify early cancer changes in patients.

Previous studies have relied on isolating CSCs from primary human tissue, which is labour intensive and not easily repeatable. We have developed a new method of enriching CSCs from established colorectal cancer cell lines using relatively simple laboratory techniques. This will allow high throughput testing of drugs, identifying those that are more specific against CSCs.

We also investigated the relationship between normal intestinal stem cells and cancer stem cells. By introducing specific genetic mutations, such as adenomatous polyposis coli, in normal intestinal stem cells, we are able to generate CSC-like cells in the animal intestine and observe their behaviour. We found that both normal and cancer stem cells share similar molecular pathways that control self-renewal and differentiation. A better understanding of these pathways could lead to the development of more specific treatments against CSCs. In the long term, targeted therapy against these cancer stem cells could prevent progression of colorectal cancer and improve patient survival.



PUMP PRIMING

David Bowrey 44
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Emma King 48
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Early glycaemic changes after weight loss surgery

Patients with type 2 diabetes have the most to gain from weight-loss surgery as more than 80% are cured of their diabetes in the short to medium term as a result.

David Bowrey

SPECIALTY
Oesophagogastric surgery.

CURRENT POSITION
Consultant Surgeon and Honorary Senior Lecturer.

TITLE OF FELLOWSHIP
Pump Priming award.

SITE OF WORK
University Hospitals of Leicester NHS Trust.

FURTHER FUNDING
Collaborative funding with Department of Diabetes Medicine, University Hospitals of Leicester and School of Sport, Exercise and Health Sciences, University of Loughborough as part of National Institute for Health Research Biomedical Research Unit for five years.

There is currently a global epidemic of type 2 diabetes mellitus (T2DM) with the worldwide prevalence expected to reach 334 million by 2025, a 60% rise from 2003. Obesity is the cause of T2DM in at least half of patients.

To date, lifestyle and drug therapies have achieved only modest benefits in obese patients with T2DM. Weight loss surgery is enjoying renewed interest as it offers a durable, cost-effective alternative to drug treatments. Patients with T2DM have the most to gain from surgery as more than 80% are cured of their diabetes in the short to medium term.

The mechanisms by which blood sugar control improves and the exact timings of the changes are poorly understood. This study will examine in detail the timing of improvements in blood sugar changes after weight loss surgery. Study participants will be those with abnormal blood sugar control (T2DM or impaired glucose tolerance) undergoing two commonly performed weight loss operations: gastric bypass and sleeve gastrectomy. The study will determine if the two operations work to improve blood sugar control in the same manner and how blood sugar improvements change over the first year after surgery. Recruitment to the study started in February 2012. Funding has now been secured to develop the work further and characterise how follow up, exercise and education regimes affect long-term control of weight after surgery.

David performing laparoscopic surgery.

David performing laparoscopic stomach surgery.

A weight-loss surgery planning meeting.

Biomarkers of abdominal aortic aneurysm: A proteomic discovery study

Abdominal aortic aneurysm (AAA) is a significant, serious disease in western populations and over 4,000 people die from ruptured (burst) AAA in England and Wales each year.

Matt Bown

SPECIALTY
Vascular surgery.

SPONSOR
Rosetrees Trust.

CURRENT POSITION
Senior Lecturer in Vascular Surgery.

TITLE OF FELLOWSHIP
Pump Priming award.

SITE OF WORK
University of Leicester.

PRESENTATIONS
1. *Plasma protein profile of patients with Abdominal Aortic Aneurysms (AAA) is significantly different to that of controls: A discovery study.* Human Proteome Organisation 10th World Congress; September 2011; Geneva, Switzerland.
2. *Application of Mass spectrometric (MS) based proteomics coupled with Artificial Neural Networks analysis for biomarker discovery of AAA.* Society of Academic and Research Surgery; January 2012; Nottingham, UK.

AAAs are often diagnosed when they are small and at low risk of rupture but these small AAAs usually grow to a size where they are at risk of rupture. Surgery can prevent rupture but this is associated with a significant risk of mortality in the region of 5%. Little is known about why AAAs grow. It is likely that AAAs cause changes in the proteins that circulate in patients' blood streams. If the precise nature of these changes can be determined it may be that these changes can be used to be able to diagnose AAAs and/or that these changes can tell us what is causing AAAs to grow.

In this study we have examined the blood of patients with AAA and blood from patients without AAA. We have used a technique called mass spectrometry, which allows us to measure the quantity of all the many thousands of proteins present in each blood sample in a single experiment. By comparing the blood samples we can tell what proteins are present in different quantities in patients with AAA.

Our first experiment determined that mass spectrometry could be used to detect differences between patients with and without AAA. In this experiment we found a group of four ions (representing proteins) that could differentiate patients with AAAs from those without with a certainty of 98%. We followed up this study by using a more complex laboratory technique (tandem mass spectrometry) that has been able to tell us which proteins are represented by three out of the four ions. These results will now be taken forward for verification in a larger group of patients to determine whether they can be used clinically to diagnose and monitor patients with AAA.

Matt supervising a trainee performing a vascular anastomosis.

Operation to repair an aortic aneurysm. Image courtesy of Mr Young, St Thomas' Hospital, London.

James Chan investigating the regulation of stem cell behaviour in fracture healing.

Detecting and treating early hip osteoarthritis; by identifying bio-markers of disease progression

Advances in joint-preserving treatments mean that doctors can now treat osteoarthritis at a much earlier stage. However, the use and development of these new therapies is limited because we cannot identify osteoarthritis early enough.

Sion Glyn-Jones

SPECIALTY
Trauma and orthopaedic surgery.

CURRENT POSITION
Senior Lecturer and Consultant Orthopaedic Surgeon.

TITLE OF FELLOWSHIP
Pump Priming award.

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

FURTHER FUNDING
National Institute for Health Research Biomedical Research Unit for five years.

Musculoskeletal disease affects one in four people and the cost associated with its treatment amounts to 4% of the UK's gross domestic product. Most of this treatment is directed at end-stage osteoarthritis in the form of joint replacement.

3D CT of a hip joint of one of Sion's patients.

Osteoarthritis of the hip is a common condition. It results in pain and disability, which has significant social and economic consequences. Patients often spend many years in pain, with reduced mobility, as early osteoarthritis can be very difficult to diagnose on conventional imaging, such as X-rays. It has recently become evident that mild, previously unrecognised deformities of the hip joint can give rise to osteoarthritis.

Inside of the hip joint (during hip arthroscopy) of the same patient showing early arthritis and cartilage detachment

Historically, osteoarthritis of the hip has been treated at a late stage, using surgery or drugs. Recently, surgeons have begun to develop treatments that target osteoarthritis at an early stage, by correcting these deformities. They hope that these treatments may preserve the joint, thereby reducing the need for costly treatments for end-stage disease, such as hip replacement. However, these new treatments rely on being able to detect damage early in the disease process.

The ultimate aim of our work is to develop new imaging markers for early osteoarthritis of the hip. This work has primarily focused on describing early osteoarthritis of the hip in terms of its patterns and the biological changes observed within the cartilage.

This is a new area of research, arising from a desire by doctors and patients to treat osteoarthritis at an earlier stage. We are the first group to investigate this area and our department has dedicated significant resources to identifying the causes and features of early arthritis. To date, our results have demonstrated distinct patterns of early osteoarthritis of the hip. Our biological studies have also enabled us to describe very early pre-arthritic changes in the chemical composition of cartilage. In turn, this has allowed us to develop new scanning methods that enhance the detection of early osteoarthritis.

HPV-induced oropharyngeal carcinoma: the role of the adaptive immune response

Patients with HPV-induced oropharyngeal carcinoma have significantly better overall survival than those patients that develop oropharyngeal carcinoma unrelated to HPV infection.

Emma King

SPECIALTY
Head and neck surgical oncology.

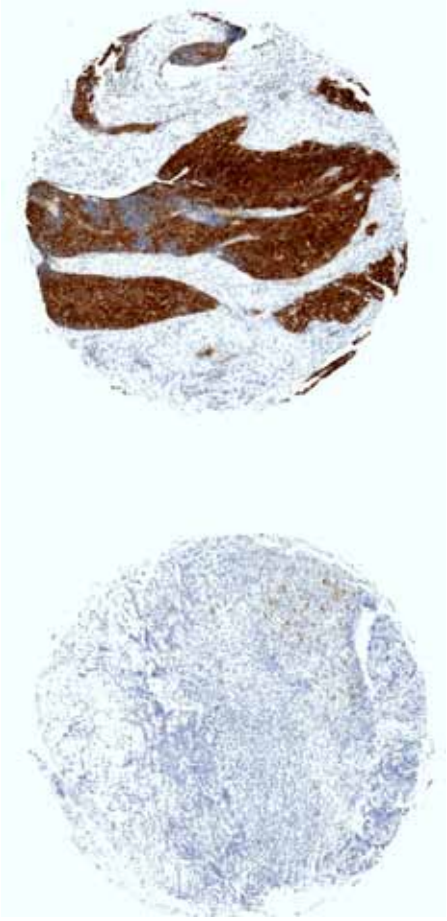
CURRENT POSITION
Senior Lecturer and Consultant Head and Neck Surgeon.

TITLE OF FELLOWSHIP
Pump Priming award.

SITE OF WORK
Cancer Sciences Division, University of Southampton.

The major cause in the development of head and neck cancer (including oropharyngeal squamous cell carcinoma, OPSCC) is cigarette smoking (particularly when combined with heavy alcohol intake). However, over the last decade there has been a significant increase in the number of OPSCC cases, particularly in young non-smokers and non-drinkers. The cause of the increased incidence in this patient cohort appears to be human papillomavirus-16 (HPV-16), which accounts for approximately 25–50% of OPSCC. Interestingly, patients with HPV-driven OPSCC have significantly better overall survival than those that have HPV-negative disease (82.4% verses 57.1% at 3 years). The reason for this improved survival is not known but we have preliminary data to suggest that it is related to the adaptive immune system and that the patient's own immune system 'fights' the cancer in the same way that it 'fights' bacteria and viruses.

We have developed a database with over 500 head and neck patients from the south coast. We have recorded demographics, tumour characteristics, treatment and survival. Corresponding paraffin-embedded tissue micro-arrays have been stained for HPV and quantified for immune-infiltrate.



Oropharyngeal squamous cell carcinoma: 1mm tissue micro-array. (Top) p16 negative tumour and (below) p16 positive tumour.

Somers Building, Cancer Sciences Division, University of Southampton.

Preliminary results suggest that there is a significant correlation between immune-infiltrate and survival. These results are being validated in a larger patient cohort and, in addition, prospective patient data is also being collected. If validated, these results will help unravel the complex relationship between HPV-positive cancers and the patient's immune system. This will ultimately help us determine how patients with this disease should best be treated, and may also help us understand how we can use the immune system to fight other types of cancer.

Using circulating miRNAs for early detection of dysplasia and carcinoma in ulcerative colitis

5% of patients with ulcerative colitis are likely to develop bowel cancer.

Baljit Singh

SPECIALTY
Colorectal surgery.

CURRENT POSITION
Consultant Colorectal Surgeon And Honorary Senior Lecturer.

TITLE OF FELLOWSHIP
Pump Priming award.

SITE OF WORK
Department of Cancer Studies and Molecular Medicine, University of Leicester.

PRESENTATIONS
Midlands Gastroenterological Society; June 2011; Worcester, UK.

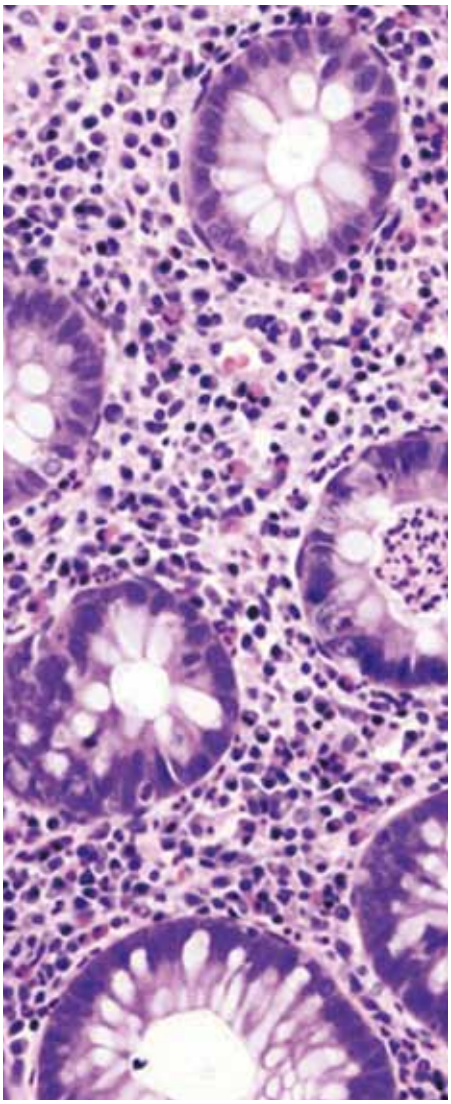
PRIZES
East Midands NHS Innovation Award, 2011.

FURTHER FUNDING
Small grant from Midland Gastroenterology Society for one year.

Ulcerative colitis (UC) is a condition that causes inflammation of the colon and is associated with an increased risk of developing bowel cancer. However, the latter can be prevented by the detection of the initial precancerous changes (dysplasia) in the bowel. Currently the only method of detecting dysplasia is by a camera test (colonoscopy) and taking several biopsies of the bowel. This test requires sedation and is associated with a risk of bleeding and bowel injury. In addition, these random biopsies may miss areas of dysplasia because less than 1% of the bowel is sampled.

The aim of the study was to develop a reliable and non-invasive method for the early diagnosis of dysplasia, which can also distinguish dysplasia from cancer.

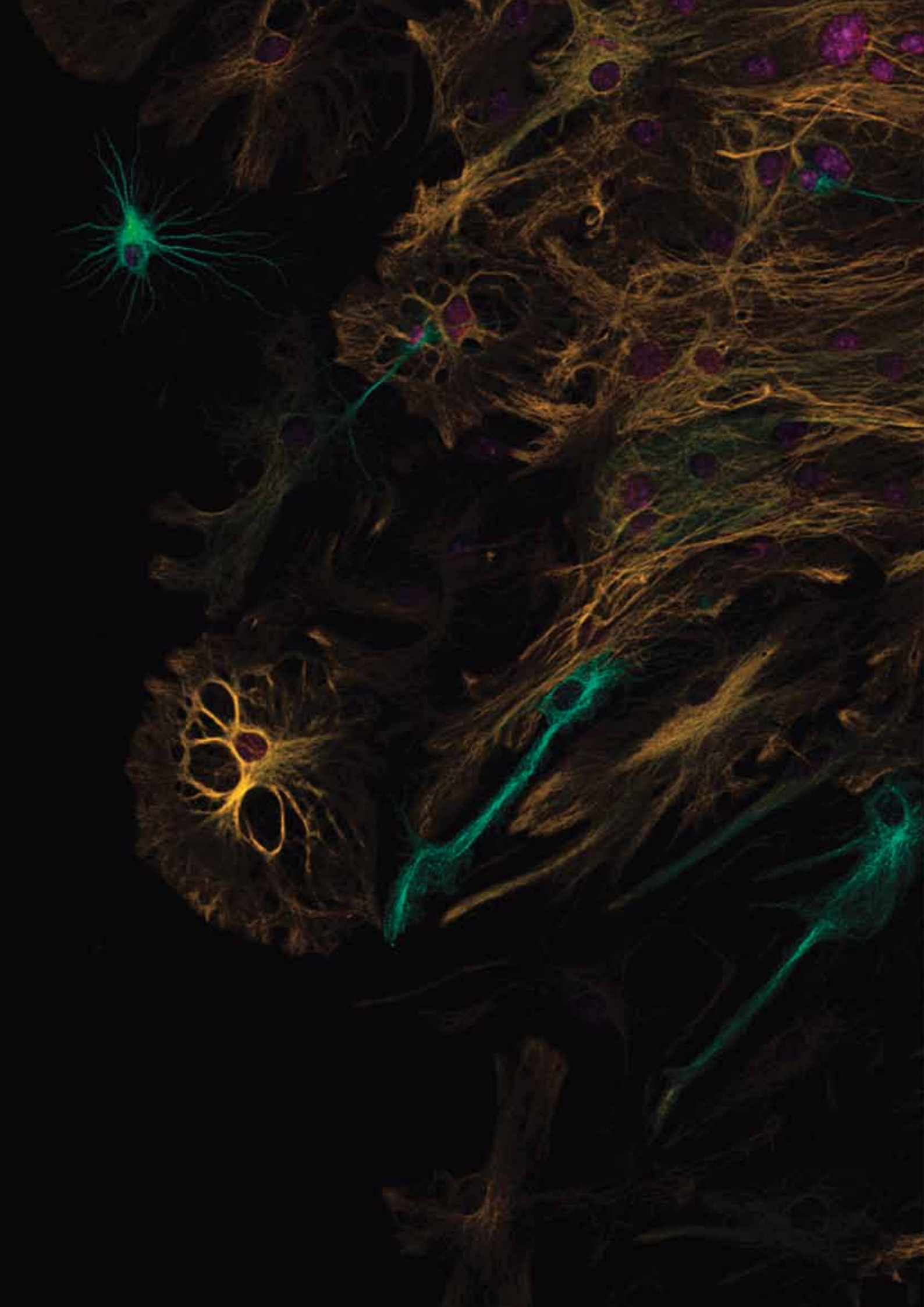
It has recently been demonstrated that different diseases, including cancers, are associated with a unique fingerprint of genetic material (miRNAs) in the blood. These miRNAs affect the development of bowel cancer. The aim of the study was to determine if there were specific miRNAs in the blood that were associated with dysplasia and cancer.



Histopathological image of the active stage of ulcerative colitis. Endoscopic biopsy. Hematoxylin and eosin stain.

Our initial results have shown that a group of miRNAs can be detected in bowel tissue taken at the time of surgery from patients who have had UC and bowel cancer. We are now in the process of using this panel of miRNAs to test whether they are also present in the blood of UC patients with dysplasia and/or cancer.

A blood test that can detect dysplasia or cancer would reduce the requirement for regular colonoscopies and provide a cost-effective, accurate and non-invasive surveillance modality. It would also offer an enormous financial saving for the NHS. The results from this study will also help identify miRNAs that are associated with bowel cancer in the general population.



PREISKEL PRIZE

Deepak Chandrasekharan	52
Matthew Fell	52
Anuja T Mitra	53
Ralph Murphy	53
Tom Paterson	54
James Robinson	54
Chin Lik Tan	55

General surgery in South Africa

Deepak Chandrasekharan

MEDICAL SCHOOL
University of Oxford.

SITE OF WORK
Ngwelezana General Hospital, Empangeni, South Africa.

Deepak assisting with an abdominal washout for severe late appendicitis.

Deepak performing a minor lump removal operation under supervision.

I worked in general surgery at Ngwelezana Hospital under Mr Iain Thirsk. My aim was to gain experience in providing surgical care in the developing world.

I was able to play an active role within the team. I assisted in theatre, helped run clinics and clerked in emergency admissions. Poor transport networks and poverty meant patients came to hospital only when their condition was severe. Even appendicitis was frequently life threatening, requiring major surgery and intensive care.

My placement confirmed my desire to return to work in such settings and I would highly recommend Ngwelezana for electives.

Cleft lip and palate surgery in Ethiopia

Matthew Fell

MEDICAL SCHOOL
University of Manchester.

SITE OF WORK
Yekatit 12 Hospital, Addis Ababa, Ethiopia.

In theatre in Addis Ababa watching the cleft surgeons repair a cleft palate on an eight-year-old boy.

A typical day in the follow-up project where patients would be gathered in village health centres.

I spent my elective placement with a British charity that provides surgical treatment for patients with cleft lip and/or palate who live in rural areas of eastern Ethiopia. The aim of my project was to visit a proportion of the patients that had already received surgery to see if the operation had been a success.

We visited 400 patients and asked each one a set of questions in their local language. I learnt about the effect that surgery can have on the lives of people in rural Africa and, while the majority were extremely satisfied, some needed to be referred for further treatment.

Matthew was the PKK Prize winner in 2010.

Plastic surgery in South Africa

Anuja T Mitra

MEDICAL SCHOOL
Imperial College London.

SITE OF WORK
Groote Schuur Hospital, Cape Town, South Africa.

I organised my elective in the department of plastic, reconstructive and maxillofacial surgery at Groote Schuur Hospital. The unit is the largest in South Africa and the national tertiary referral centre. The division combines an academic hospital service with teaching and high output of research.

The majority of my time was spent in theatre. The great variety of cases in the unit significantly improved my exposure to routine cases in addition to complex, rare presentations. I performed practical procedures in theatre and outpatient clinics. Reflecting on my positive experiences, I absolutely recommend this elective to enthusiasts of plastic surgery.

Operation to reconstruct genital anatomy on a gender reassignment patient.

Anuja with the local children in the township of Gugulethu.

Anuja assessing the post-operative status of a patient diagnosed with metastatic melanoma.

Trauma surgery in South Africa

Ralph Murphy

MEDICAL SCHOOL
Imperial College, London.

SITE OF WORK
Groote Schuur Hospital, Cape Town, South Africa.

Ralph revising the tendon anatomy of the back of the hand, with other students.

Ralph's first experience of assisting with a tendon repair, assisting the registrar in repairing one of the tendons that runs into the thumb and moves the thumb upwards.

I applied to Groote Schuur Hospital having read student reports of the skills development resulting from South African electives, and speaking to consultants who have worked in Cape Town.

During the Christmas period, there was only the registrar and I to perform the trauma operations. I sewed-up surgical incisions, giving me extensive practice in suturing. In the final weeks I completed my first tendon repair, part of a multi-tendon repair of the hand.

Having considerably more clinical responsibilities than I would be allowed in the UK has provided invaluable insights of a surgeon's role, inspiring me to further my clinical and academic interests in surgery.

Plastic and reconstructive surgery in Uganda

Tom Paterson

MEDICAL SCHOOL
University of Glasgow.

SITE OF WORK
Comprehensive Rehabilitation Services in Uganda (CoRSU), Kampala, Uganda.

Tom pictured with a five-month-old cleft lip and palate patient prior to surgery.

At the end of a full day of operating: Tom and Mr Hodges (centre) with the CoRSU anaesthetic and theatre staff.

During summer 2011, I embarked on a humbling elective to discover the role of reconstructive surgery in East Africa. At CoRSU I was fascinated and concerned to meet newborns with disfiguring and disabling facial clefts, young children with horrifying post-burn contractures and adults suffering from rare conditions such as massive peripheral lymphadenopathy and facial cutaneous tuberculosis. As an active team member I gained invaluable theatre experience in suturing and skin-grafting. Above all I was extremely privileged to be able to assist Mr Hodges and his team in transforming the lives of patients in desperate need of plastic and reconstructive surgery.

Neurosurgery and neurotrauma in South India

James Robinson

MEDICAL SCHOOL
Newcastle University.

SITE OF WORK
Calicut Medical College Hospital, Calicut, Kerala, South India.

Although in the developing world and struggling under crushing patient numbers and extremely restricted funding, the standard of care at Calicut Hospital was impressive. I assisted in neurosurgical operations of a quality seen in the UK, with only a few differences. For example, a nurse stood by with a fly-swatter to protect the surgical field from insects, patients provided their own sutures, and two operating tables worked simultaneously in a theatre to reduce the number of anaesthetists required. This was an invaluable experience for a budding surgeon, and eye-opening evidence that the UK is extremely lucky to have the NHS.

James with the Head of Neurosurgery at Calicut Medical College.

James giving a rabies vaccine before suturing a dog-bite.

Piles of drug and saline bottles, and the dilapidated hospital structure.

Neurosurgery in Argentina

Chin Lik Tan

MEDICAL SCHOOL
University of Cambridge.

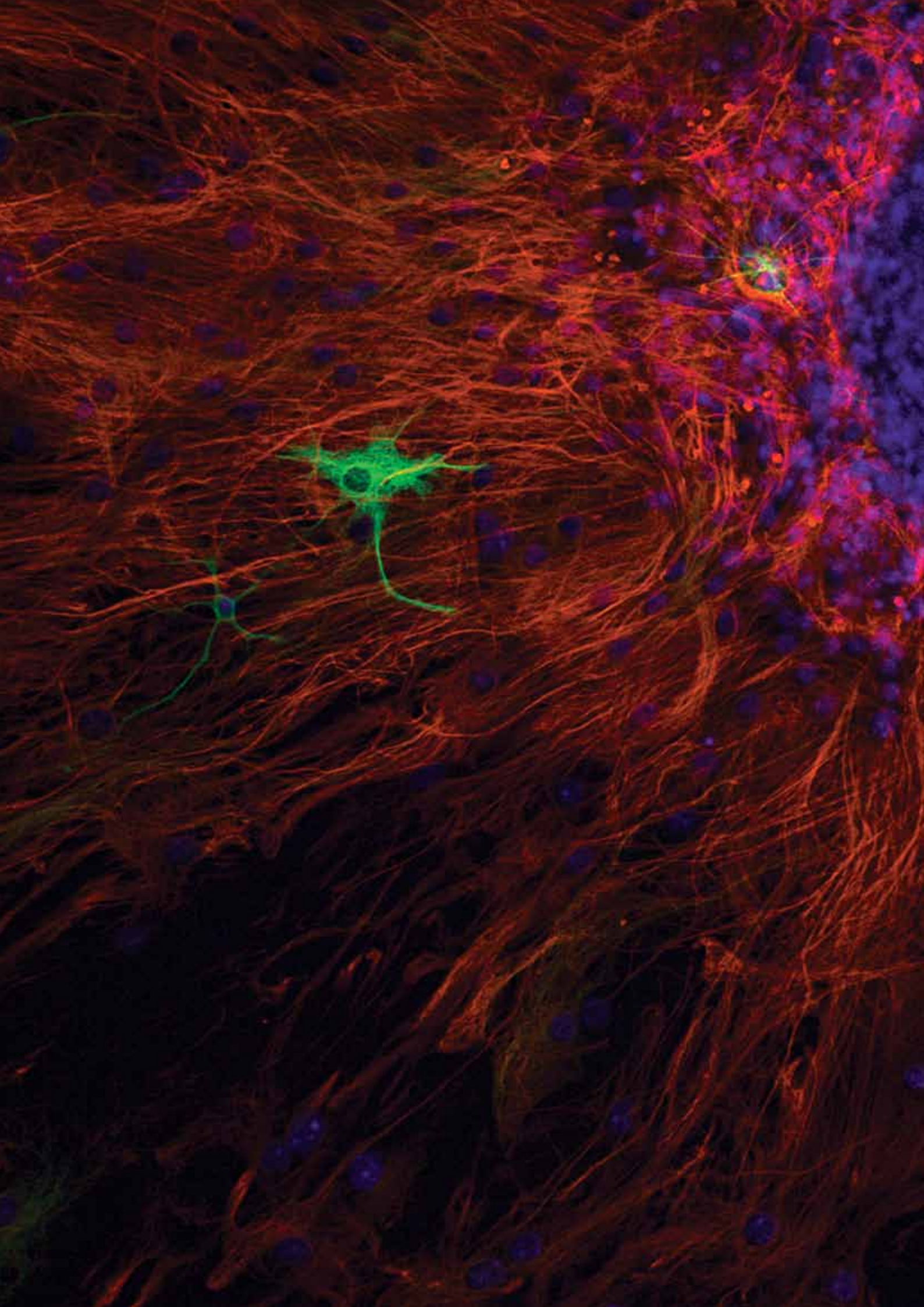
SITE OF WORK
Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, Argentina.

Chin Lik (middle) with neurosurgeons Dr Andrés Cervio (left) and Dr Jorge Salvat (right) outside the theatre.

I intended to learn more about my area of interest, neurosurgery, during my elective, and chose the Department of Neurosurgery at FLENI, Argentina, as my destination. I spent five weeks there observing and taking part in various neurosurgical operations, including tumour resection, discectomy, laminoplasty and clipping of intracranial aneurysms. Outside the theatres I shadowed the residents on ward rounds and attended medical grand rounds. It was an eye-opener, learning about the healthcare system in a developing country, in particular one with a distinct language and culture. Most importantly, this experience re-affirmed my aspiration to pursue a surgical career.

Chin Lik assisting in an operation (brain tumour resection).

Chin Lik with the neurosurgical residents at FLENI.



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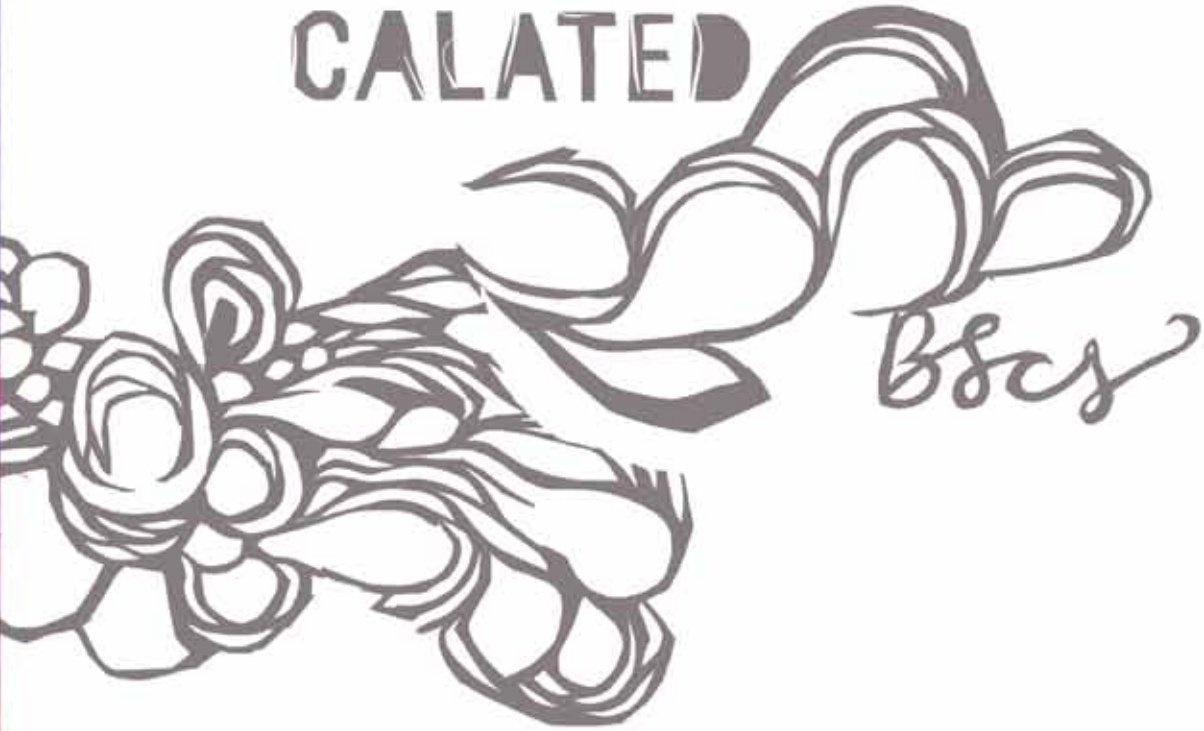

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Exploring the morphology and function of smooth muscle cells derived from abdominal aortic aneurysms

Timothy Guido Angelini

MEDICAL SCHOOL University of Leeds

The RCS award enabled me to investigate inherent differences in characteristics between vascular smooth muscle cells (VSMC) cultured from the wall of abdominal aortic aneurysms (AAA) and from non-aneurysmal blood vessels. We hypothesised that there would be functional and morphological aberrancies in VSMC from AAA, which may contribute to and/or explain the development and progression of the disease. We cultured cells from AAA tissue of multiple patients undergoing surgical repair of AAA. Using a variety of laboratory techniques we determined that the cell populations were large, flat and irregular in AAA tissue in comparison to the 'classical' smaller spindle shaped cells in non-aneurysmal tissue. VSMC from AAA tissue had impaired replication capacity of approximately 50% of non-aneurysmal SMC. Understanding the mechanisms involved in these changes may explain the role of VSMC in AAA disease and provide clues for new treatment targets.

(Left to right) Timothy in the lab with his supervisors Phil Warburton, Dr Karen Porter and Dr Kirsten Riches.

Will heme arginate induce HO-1 and ameliorate ischaemia-reperfusion injury following kidney transplantation?

David James Clark

MEDICAL SCHOOL University of St Andrews/University of Edinburgh

An introduction to suturing in the clinical skills facility.

The award supported my intercalated year in medical sciences and the research project I undertook in transplant surgery with Dr Lorna Marson, consultant transplant surgeon, and former RCS research fellow. Kidney transplantation is often a life-saving treatment; unfortunately, donated kidneys can become damaged by a condition known as 'ischaemia-reperfusion injury' (IRI) during transfer to the patient and this can ultimately cause the transplant to fail. My project, through experiments in animal models, examined whether the drug heme arginate was able to prevent IRI by increasing the levels of the chemical heme oxygenase 1 (HO-1) in the body.

I feel fortunate to have been given the opportunity to explore my interest in academic surgery at such an early stage, as I am now motivated to continue to combine clinical practice and research activities throughout my training and beyond. I am very grateful to the College for its support.

Comparison of body-worn sensor systems for measuring balance and activities of daily living

Selina Rose Graham

MEDICAL SCHOOL Imperial College School of Medicine

The grant enabled me to carry out my project, as part of a BSc in Surgery and Anaesthesia, in the biodynamics laboratory at Charing Cross Hospital. The project compared a new low-cost wearable measurement tool for balance with frequently used and expensive laboratory techniques.

Selina setting up the optical tracking system with supervisor Jeroen Bergmann.

The initial analysis shows promising results during static tasks and has provided some invaluable pilot data on which further studies and clinical work is now based. Thanks to the generous funding I am able to extend this project with an aim towards a future conference abstract submission and publication.

The isolation and characterisation of pancreatic stellate cells

Mehdi Jalali

MEDICAL SCHOOL University of Liverpool

The generous College award enabled me to pursue an MPhil degree at the Liverpool Cancer Research UK (CRUK) centre. Under the guidance of Dr Eithne Costello, I initiated a project investigating pancreatic stellate cells. These cells are responsible for the production of the extensive extracellular matrix and associated dense stromal reaction observed in pancreatic cancer. The 'cross-talk' between pancreatic stellate cells and pancreatic cancer cells is believed to significantly enhance tumour progression. Primary cell culture and immunohistochemistry techniques were employed on pancreas samples from ten patients. Preliminary investigations of microRNA expression were also conducted. The establishment of stellate cell culture in this laboratory is an important step which has opened up new avenues of research with relation to the tumour microenvironment in pancreatic cancer. I plan to continue research at the Liverpool CRUK centre during my academic foundation post.

Mehdi at the Royal Liverpool University Hospital.

The relationship between the physical and functional presentation of patients with knee osteoarthritis

Stevan Jordan

MEDICAL SCHOOL Imperial College London

The generous award from the Royal College of Surgeons allowed me to contribute to the ongoing research on knee osteoarthritis (OA) being conducted by the Department of Surgery and Cancer at Charing Cross Hospital. My project investigated the relationship between the physical and functional presentation of patients with knee OA. We compared patterns of wear from 3D computed tomography scans with the loads being transferred through the knee joint during walking. The research should help contribute to the identification of those patients predisposed to developing knee OA.

I am extremely grateful to the College for its invaluable support with my research project and for providing me with the opportunity to develop a range of new skills working alongside experts in the field.

Stevan with his supervisors Professor Alison McGregor (left) and Lynsey Duffel (right).

Interactions between the corticospinal and vestibular systems in the control of the neck musculature

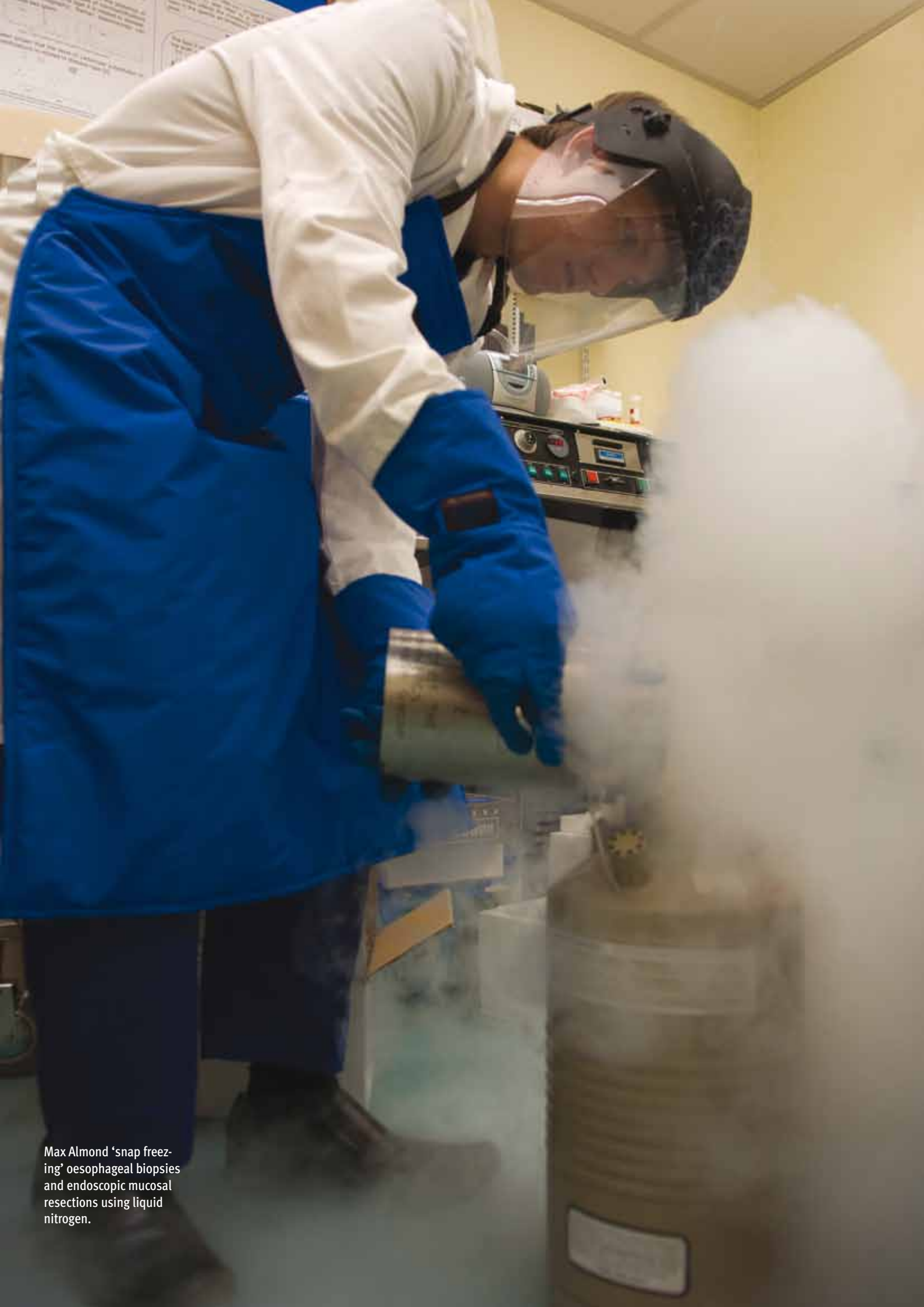
Varsha Rajkumar Kadaba

MEDICAL SCHOOL Imperial College London

Thanks to the generous grant that I was awarded through the College, I was able to carry out research in the field of movement and balance with relation to surgery for acoustic neuroma patients at Charing Cross Hospital, London. Using techniques to stimulate the motor and balance areas of the brain simultaneously, I was able to study normal subjects and an acoustic neuroma patient before surgery. This research may have implications on the rehabilitation of patients after resection of the balance nerve and may explain why some people have difficulty with dizziness after surgery.

The experiment setup.

Importantly, I was able to appreciate the field of medical research and have the opportunity to interact with experts in the field as well as developing critical thinking skills. The experience has been invaluable and I hope to present the findings at conferences this year.



Max Almond 'snap freezing' oesophageal biopsies and endoscopic mucosal resections using liquid nitrogen.

A retrospective analysis of the Leeds Aneurysm Database

Iain Ruairidh Kennedy

MEDICAL SCHOOL University of Leeds School of Medicine

Iain in the exercise lab at Leeds General Infirmary.

I am very grateful to the Royal College of Surgeons for funding my research during my intercalated BSc(Hons) in Clinical Sciences in relation to medicine.

I conducted a retrospective cohort study comparing preoperative exercise-testing data with postoperative morbidity data, for patients who underwent fully open and minimally invasive surgery for abdominal aortic aneurysms.

I was able to spend time in the exercise lab working with patients as well as learning about exercise physiology and vascular risk factors. I am now considering applying for an academic foundation post in vascular surgery.

The role of RhoA/Rac1 in the regulation of cells: cell communication on anisotropic Ti6Al4V surfaces

Robert Pearson

MEDICAL SCHOOL Newcastle University

Receiving the College's generous award supported me in financing my year of intercalated study, where I completed an MRes degree. I did a six-month placement in the Musculoskeletal Research Group at Newcastle University's Institute of Cellular Medicine, where I undertook a research project exploring the affects of different titanium surface topographies on osteoblast intracellular communication.

Robert (left) and his supervisor Dr Mark Birch (right).

The placement was particularly rewarding as it enabled me to pursue further interests and learn new research skills that will undoubtedly be useful in my future career. The intercalated year also refreshed my enthusiasm for my final year of medicine and confirmed my desire to pursue surgical academia.

Engineering biomaterial architecture at the microscale to influence mesenchymal stem cell differentiation

Martyn Charles Stott

MEDICAL SCHOOL The Medical School, Newcastle University

The generous College award allowed me to undertake an MRes degree where my research looked at the use of micro-engineered biomaterial topography to control mesenchymal stem cell differentiation. I was specifically interested in investigating how such topography led to changes in gene expression by altering cytoskeletal and nuclear architecture. My research will now be carried forward in a newly established tissue engineering centre, which aims to translate basic science research into minimally invasive treatments for osteoarthritis.

The funding allowed me to gain knowledge and skills on a multidisciplinary level, incorporating micro and nanoscale mechanical engineering and advanced material science with molecular biology, which I believe is a rather unique skill set for a medical student to possess. Such an approach, however, is undoubtedly essential for future progress. I am indebted to the College for its support, and eager to make research central to my career.

Martyn using immunofluorescence to observe changes in nuclear architecture with his lab supervisor Dr Mark Birch.

Measurement of tumour vascularity in pancreatic cancer

Amarpreet Kaur Thind

MEDICAL SCHOOL Newcastle University

Pancreatic cancer demonstrates a poor response to available chemotherapy agents. The RCS award supported me in undertaking an MRes degree at Newcastle University, where I carried out a research project into the potential of clinical investigations to specifically assess pancreatic tumour vascularity. Through the project we established a methodology for using routine clinical imaging to measure tumour blood flow and have therefore created a platform to help further determine the relationship between tumour architecture and treatment responses.

(Left to right) Mr R Charnley, project supervisor; Dr K Oppong, co-supervisor; Amarpreet; and Dr M Nayar, co-supervisor, at the Freeman Hospital Endoscopy Department, Newcastle-upon-Tyne.

The award provided invaluable assistance to my living and research costs, while the opportunity enabled me to further my interest and experience in hepato-pancreato-billary surgery, develop new clinical, professional and research skills, and further my appreciation for the importance of research in improving patient care. Ultimately, I was awarded a distinction for the degree and will present the findings to the Pancreatic Society of Great Britain and Ireland.

Funding partnerships

The College is very grateful to all those individuals, charitable trusts, companies, 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
CA Redfern Charitable Foundation
Cancer Research UK
DBP Trust
Dunhill Medical Trust
Ethyl and Gywnne Morgan Trust
Enid Linder Foundation
Ethicon UK Ltd
Family of the late Mr Stefan Galeski
Frances and Augustus Newman Foundation
Fulbright Commission
Golden Bottle Trust
Golden Charitable Trust
Grand Lodge of Freemasons 250th Anniversary Fund
Hong Kong Freemasons Overseas Trust
IA - The Ileostomy & Internal Pouch Support Group
Inman Charity
Michael & Anna Wix Charitable Trust
Philip King Charitable Settlement
Roger Vere Foundation
Roger Raymond Charitable Trust
Rosetrees Trust
Royal Arch Masonry
Shears Foundation
United Grand Lodge of England
W D Macpherson Charitable Trust
Worshipful Company of Cutlers
Wyndham Charitable Trust
Women's Institute
Wyseliot Charitable Trust

Endowments, restricted and legacy funds

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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 Legacy
Lillian May Coleman Legacy
Joan Rosa Cox Legacy
Philip and Lydia Cutner Legacies
Darlow Research Fellowship
Jeanette Denker Legacy
N M Linley Legacy
Edward Lumley Fund
Geoffrey G T Fletcher Legacy
Arthur J Gerrish Legacy
Amy E Green Legacy
Guyatt Legacy - Sir Alan Parks Research Fellowship
Harold Bridges Bequest
Harry S Morton Fund
Eleanor M Heslop Legacy
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Shirley M Kanaar Legacy
Doris K King Legacy
Laming Evans Research Fund
Lea Thomas Fund
Osman Hill Collection and Research
Parks Visitorship
May G Pearce Legacy
Elizabeth Rashleigh Legacy
Joan Robb Legacy
Carol Rummey Legacy
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Doris Mary Sheppard Legacy
Gwendoline Shrimpton Legacy
Cicely Fay Simpson Legacy
Sir Arthur Sims Fund
Sir John Lang Legacy
Richard J Stafford Legacy
Dr M P Starritt Legacy
Tudor Edwards Fellowship
Vandervell Research Fund
John L Williams Legacy
Derek P Winks Legacy

Joint fellowships

British Association of Paediatric Surgeons
British Association of Surgical Oncology
British Society for Surgery of the Hand
Get A-Head Charitable Trust
Royal College of Surgeons of Ireland

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 **development@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 specialty. The main benefit of the travelling awards is that the surgeon who benefits can translate the experience and know-how gained during the overseas fellowship to his or her own knowledge base, to benefit future patients in this country. The committees that decide the recipients of the travelling awards always include leading surgeons.

The following travel awards are available:

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 May 2011

Mr Peter Holt
Mr Kyle James
Mr Thomas Martin
Mr Iain McNamara
Mr Thomas Santarius

Recipients October 2011

Mr Anthony George Barabas
Mr James Horwood
Mr Sinclair McLean Gore

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 2011

Mr Dipan Natwarlal Mistry
Mr Scott Edward Henney
Mr Thomas Peter Cultack Martin

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 2011

Professor Jonathan Golledge

HJ Windsor Prize

The HJ Windsor Prize was established in 1975 with a gift of £2,500 from the late Dr HJ Windsor KSG CBE FRCS of Brisbane, Australia. The prize is intended to 'assist in the advancement of surgery by an annual prize or by such other means as the Council shall from time to time determine'.

Recipients 2011

Mr Matthew Potter

Rosetrees Trust Prize 2011

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 2011 Prize were:

1st Prize: Miss Emma Carrington

Sacral root evoked potentials – a new tool to revolutionise treatment with sacral nerve stimulation (SNS)?

Runner Up: Mr Rizwan Attia

The role of functional imaging in aortic aneurysms

Runner Up: Mr Glen Irving

Improving chemotherapy for bowel cancer using low toxicity diet-derived agents

Glen, Emma and Rizwan (pictured right) were awarded their prizes at the College Diplomates Ceremony on 17 January 2012.

lectures delivered in 2011

Hunterian	**Mr Zaed Zoher Raouf Hamady** Society of Academic and Research Surgery, 5 January 2011 *Xylan-regulated delivery of human Immunomodulatory factors to the inflamed colon by the human anaerobic commensal bacterium Bacteroides ovatus*
Hunterian	**Mr Rakesh Heer** British Association of Urological Surgeons, Society of Academic and Research Surgery, 6 January 2011 *Characterisation of prostate stem cell regulation*
Hunterian	**Mr Mazyar Kanani** Society of Cardiothoracic Surgery, 22 March 2011 *Congenital cardiac surgery in the modern era: integrating form and function in the repair of the atrioventricular septal defect.*
Lionel Colledge Memorial Lecture	**Mr David Grant** British Association of Otorhinolaryngologists, 9 September 2011 *From transoral laser microsurgery to robotic thyroidectomy: the evolution of minimally invasive head and neck surgery.*
Robert Jones	**Mr Martyn Porter** British Orthopaedic Association and Irish Orthopaedic Association, 15 September 2011 *What would Sir Robert Jones do?*
Hunterian	**Professor Shanmuganathan Rajasekaran** British Orthopaedic Association and Irish Orthopaedic Association, 15 September 2011 *Biomechanical analysis of the evolution of buckling collapse of paediatric spine and its clinical implications.*
Hunterian	**Professor Timothy Davis** British Society for Surgery of the Hand, 21 October 2011 *Acute Scaphoid Waist Fractures –prediction of outcome with non-operative treatment.*
Joseph Toynbee	**Mr Gerry O'Donoghue** Royal Society of Medicine, 4 November 2011 *Acoustic neuroma in 2011: is the patient the problem?*
Kinmonth	**Professor Bruce Campbell** Vascular Society, 25 November 2011 *The evolution of evidence.*
Hunterian	**Mr Mark Schaverien** British Association of Plastic Reconstructive Aesthetic Surgery, 30 November 2011 *The use of three-dimensional imaging for the investigation of the microvascular arterial and venous anatomies and perfusion of surgical flaps and the integument.*

Paul Moxey palpating the peripheral pulse of a patient.

clinical effectiveness unit

The Clinical Effectiveness Unit (CEU) was established in 1998 as an academic collaboration between the College and the Department of Health Services Research and Policy within the London School of Hygiene and Tropical Medicine. The CEU is largely self-funded through external project grants and contracts, although it receives an annual contribution from the College's research funds and the College underwrites four senior academic posts within the school.

Since 1998, the CEU has become a national centre of expertise in methods, organisation and logistics of large-scale studies of the quality of surgical care. In undertaking these studies, it aims to provide timely comparative information to surgeons and hospitals about the care process and patients outcomes. It is also involved in the RCS initiative to develop and implement a quality and outcomes strategy across the College and specialty associations. The unit has sixteen staff members, eight of whom are academic staff members of the school. They have a variety of backgrounds (eg health services research, epidemiology, medical statistics, clinical medicine, public health and social science) which encourages a multi-disciplinary outlook and approach. In May 2011, Dr David Cromwell, Senior Lecturer in Health Services Research at the school, took over the directorship of the CEU.

Audit and research

The core activity of the CEU is to conduct national clinical audits and research projects. In each clinical audit the aim is to assess specific standards of clinical practice, focusing on the structure, process and outcome of care. Many of these national audits are funded as part of the government's National Clinical Audit and Patient Outcomes Programme (NCAPOP).

The Mastectomy and Breast Reconstruction (MBR) audit was funded as part of the national clinical audit programme. Its fourth and final annual report was published in March 2011 and represented the culmination of the four-year collaboration with the Association of Breast Surgery, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, the Royal College of Nursing, and the NHS Information Centre for Health and Social Care.

The MBR audit investigated the provision of mastectomy and breast reconstruction services across England. In 2002, the National Institute for Health and Clinical Excellence (NICE) published guidance on improving breast cancer outcomes and recommended that 'reconstruction should be available [to all women with breast cancer] at the initial surgical operation'. All 150 English NHS trusts that provide breast cancer surgery participated in the MBR audit, along with 106 independent hospitals and six non-English NHS trusts. The audit found that one in five women treated between 2008–2009 had their breast reconstructed at the time of their mastectomy, compared to one in nine women in 2006. The improved access to immediate reconstruction was a real achievement for breast cancer services. However, the proportion of women who undergo immediate reconstruction varied from 9–43% in different regions of England. The audit also surveyed over 7,000 women about the quality of their care. 88% of women felt that they had always been treated with respect and dignity while in hospital and 90% of women rated the care they received as excellent or very good.

The MBR audit was one of the first national clinical audits to use patient-reported outcome measures (PROMs) alongside clinical data collected by health care professionals. The CEU has led the way in developing this new area. Another national project that used PROMs, the Patient Outcomes in Surgery (POiS) audit, also delivered its final report this year.

The POiS audit was established to compare surgical outcomes for hip and knee replacement, inguinal hernia repair and varicose vein surgery undertaken in independent sector treatment centres (ISTC) with those in the NHS. It was established after an inquiry of the House of Commons Select Committee for Health concluded that the quality of care provided by ISTCs could not be properly evaluated because of the limited data available. The ISTC programme was created in 2002 to increase capacity and give patients a greater

Kailin, before and after surgery to correct a cleft abnormality. The CEU is the host of the CRANE database, which records children born with cleft abnormalities in England, Wales and Northern Ireland

choice of providers but it was feared that ISTCs could have significantly worse patient outcomes and increased complication rates.

The POiS audit captured information about the patients' conditions and their surgical outcomes from the patients themselves. Among patients undergoing surgery in 2008 and 2009, it found that patients treated in ISTCs were slightly healthier on average and had less severe symptoms than patients treated by NHS providers. Patients who underwent a hip or knee replacement in an ISTC reported fewer post-operative symptoms and better health-related quality of life than patients treated by NHS providers but the differences between providers were modest and they are unlikely to be clinically significant. Differences in outcomes of patients undergoing inguinal hernia repair or varicose vein surgery were also minimal. A paper on the POiS audit findings was published in the *BMJ* to coincide with the publication of the final report in October 2011.

The work for the national clinical audits often requires CEU staff to undertake methodological research. An example of this was considering how to compare surgical outcomes across a number of hospitals using PROMs. The problem was directly relevant to a Department of Health-funded initiative to improve the reporting of national health outcomes. Since 2009, NHS providers in England are required to support the collection of patient reported outcomes about a number of frequent elective surgical procedures. About 250,000 patients a year are invited to complete a questionnaire before and after their operation.

A common way to compare the performance of different hospitals is to use a graph called a funnel plot. This contains a set of funnel-shaped limits that lie either side of some expected outcome value (for example, a hospital might be expected to have a postoperative complication rate of 10%). The funnels define the area within which the hospitals would be expected to fall if they only differed from the expected value because of random variations.

Other major CEU projects undertaken in 2011

National Audit of Oesophago-Gastric Cancer

This audit restarted in June 2011 and is being carried out in partnership with the Association of Upper Gastrointestinal Surgeons, the British Society of Gastroenterology, The Royal College of Radiology, and the National Clinical Audit Support Programme of the NHS Health and Social Care Information Centre. The audit is funded by the Healthcare Quality Improvement Partnership (HQIP).

National Bowel Cancer Audit

The National Bowel Cancer Audit is funded by HQIP and was developed by the Association of Coloproctology of Great Britain and Ireland. The analyses for the 2011 annual report were carried out by the CEU with support from the NHS Information Centre. It is managed by the Clinical Audit Support Unit within the NHS Information Centre.

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 & 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 since 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 Commissioning Group for Highly Specialised Services.

While methods for calculating the funnel limits are well understood for many outcomes, they were not defined for some PROMs. This is because PROMs often produce a skewed distribution of values when collected after surgery; patients will typically returned to good health with few of the symptoms they suffered before treatment and so outcome values will typically be bunched at the top of the outcome scale. Staff therefore undertook some research to compare how well standard methods for producing the limits compared to 'exact' funnel limits. We found that, in some situations, the standard approach did not approximate the 'exact' limits very well and this could result in a small proportion of hospitals being mislabelled as 'outliers'. Consequently, if comparisons of provider performance are based on highly skewed data, using 'exact' limits should be considered.

Use of routine data sources

During the last decade, the CEU has increasingly used routine data in its audits and for research projects. The hospital episode statistics (HES) database, and the equivalent databases in Scotland, Wales and Northern Ireland, contain records with diagnostic and procedure information for all NHS admissions in the UK. The major advantage of these administrative databases is that they can provide a timely, national picture of clinical practice.

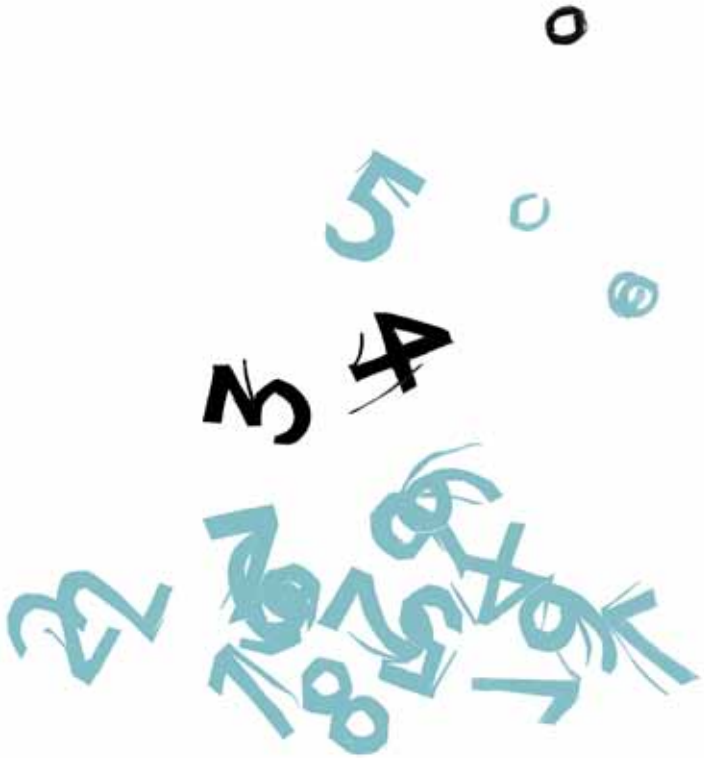
Routine data need to be used judiciously and in the right circumstances. For example, in 2010, the *Guardian* asked English NHS hospitals how many abdominal aortic aneurysm (AAA) repair procedures they had carried out between 2006 and 2008, and how many patients had died after the surgery. The newspaper's comparison of the figures reported by the hospitals with corresponding figures derived from HES led to the conclusion that 'there were flaws in hospital episode statistics'. There are various reasons why the figures may not have been equal, including the possibility of hospitals defining patients with AAAs and the types of procedure using different methods. We found 13 studies on the treatment of patients with AAAs that had used HES data and there was considerable variation in how the diagnosis and procedure codes were used to define the patient

populations. Consequently, we undertook a study into the quality of coding in HES and developed an explicit and transparent coding framework for AAA repair. Our results showed that the coding consistency in HES was high, with 95% of patients undergoing AAA repair procedure having a consistent diagnosis.

This piece of work was undertaken as part of a project that aims to assess the value of routine data for medical revalidation. Revalidation refers to new requirements for doctors to renew their licence to practice 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 for revalidation as recertification is expected to be based on clinical outcomes.

HES data are being used in almost all CEU projects. In some projects, the data are being used in isolation. For instance, for the 2011 CRANE report on the care of children born with cleft lips and palates in England, Wales and Northern Ireland, HES was used to examine annual hospital and surgeon volumes and to- estimate the burden of surgical care associated with cleft abnormalities. In relation to hospital volumes, 69% of units performed primary repairs on at least 70 new patients per year, which confirms the continuing centralisation of services. In relation to the burden of care, we found that around 75% of admissions in the first six years of life occurred before the age of two, and that cleft patients with syndromes and other complicating medical conditions (syndromic) had approximately twice as many hospital admissions and spent almost four times as long in hospital as non-syndromic cleft patients. On average, non-syndromic children had three admissions and spent a total of 10.6 days in hospital before the age of two.

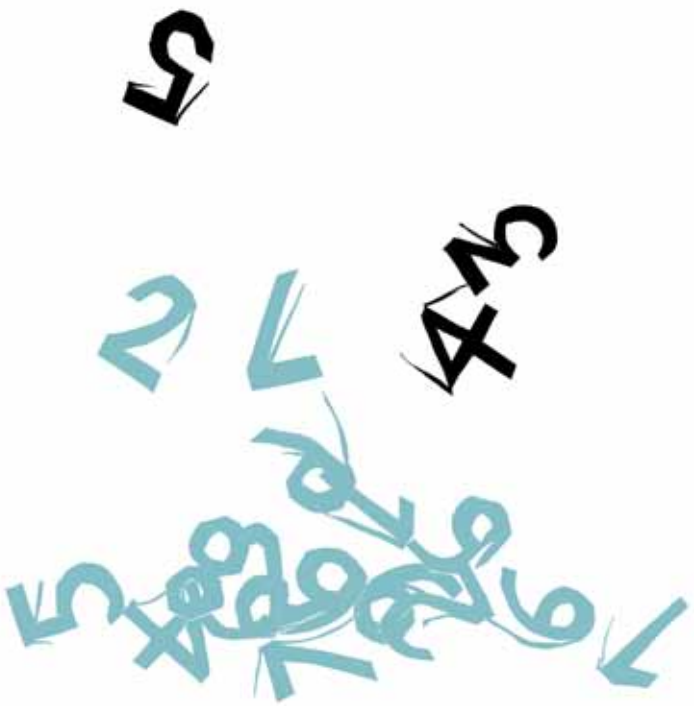
HES data are especially valuable when combined with other data sources. This is another area in which the CEU is among leading methodological exponents. An example of our work using linked datasets was an evaluation of outcomes after total hip replacement in patients receiving either aspirin or low-molecular-weight heparin (LMWH). This evaluation used data from the National Joint Registry for



England and Wales linked to the HES database, and examined 108,584 patients operated on between April 2003 and September 2008. With appropriate risk-adjustment for differences between patients receiving each drug, the mortality rates were 0.65% for patients given aspirin and 0.51% for patients given LMWH (odds-ratio 0.77; 95% CI 0.61 to 0.98).

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. They use a mixture of teaching methods ranging from lectures to interactive seminars and hands-on computer sessions. Course faculty often includes methodologists recruited from CEU staff as well as senior clinicians with a strong interest in research and audit.



Selected CEU publications in 2011

- Chard J, Kuczawski M, Black N et al. Outcomes of elective surgery undertaken in independent sector treatment centres and NHS providers in England: audit of patient outcomes in surgery.
  BMJ 2011; **343:** d6404.

- Neuburger J, Cromwell DA, Hutchings A et al. Funnel plots for comparing provider performance based on patient-reported outcome measures.
  BMJ Qual Saf 2011; **20:** 1,020–1,026.

- Johal A, Mitchell D, Lees T et al. Use of Hospital Episode Statistics to investigate abdominal aortic aneurysm surgery.
  Br J Surg 2011; **99:** 66–72.

- Jameson SS, Charman SC, Gregg PJ et al. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip replacement: A non-randomised comparison from information in the National Joint Registry.
  J Bone Joint Surg Br 2011; **93:** 1,465–1,470.

- Emin A, Rogers CA, Thekkudan J et al. Antithymocyte globulin induction therapy for adult heart transplantation: a UK national study.
  J Heart Lung Transplant 2011; **30:** 770–777.

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).

The CET and the European Society of Organ Transplantation (ESOT) have an active collaboration such that 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 randomised controlled trials (RCTs) in Europe. One aim of this collaboration is to improve the methodological quality of European trials in organ transplantation by helping the investigators in the early stages of trial design and planning. This has arisen as a result of 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. As RCTs represent the highest level of available evidence this does detract from the value of the evidence available.

In addition, the CET has developed an electronic library of all RCTs and selected good quality systematic reviews in solid organ transplantation. The Transplant Library is available to members of the ESOT as well as to subscribers to the journal, *Transplantation*. Some medical school libraries and the Scottish NHS have purchased it from Ovid, which was responsible for the technical development of the library. We expect its use to spread fairly rapidly over the next few years.

It is often asked why we need an electronic library in transplantation. As RCTs and systematic reviews/meta-analyses of RCTs are level-one evidence in any medical discipline, it is very important to develop a searchable and comprehensive library that can 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/subspecialist libraries of RCTs some 30 years ago: this is the first!

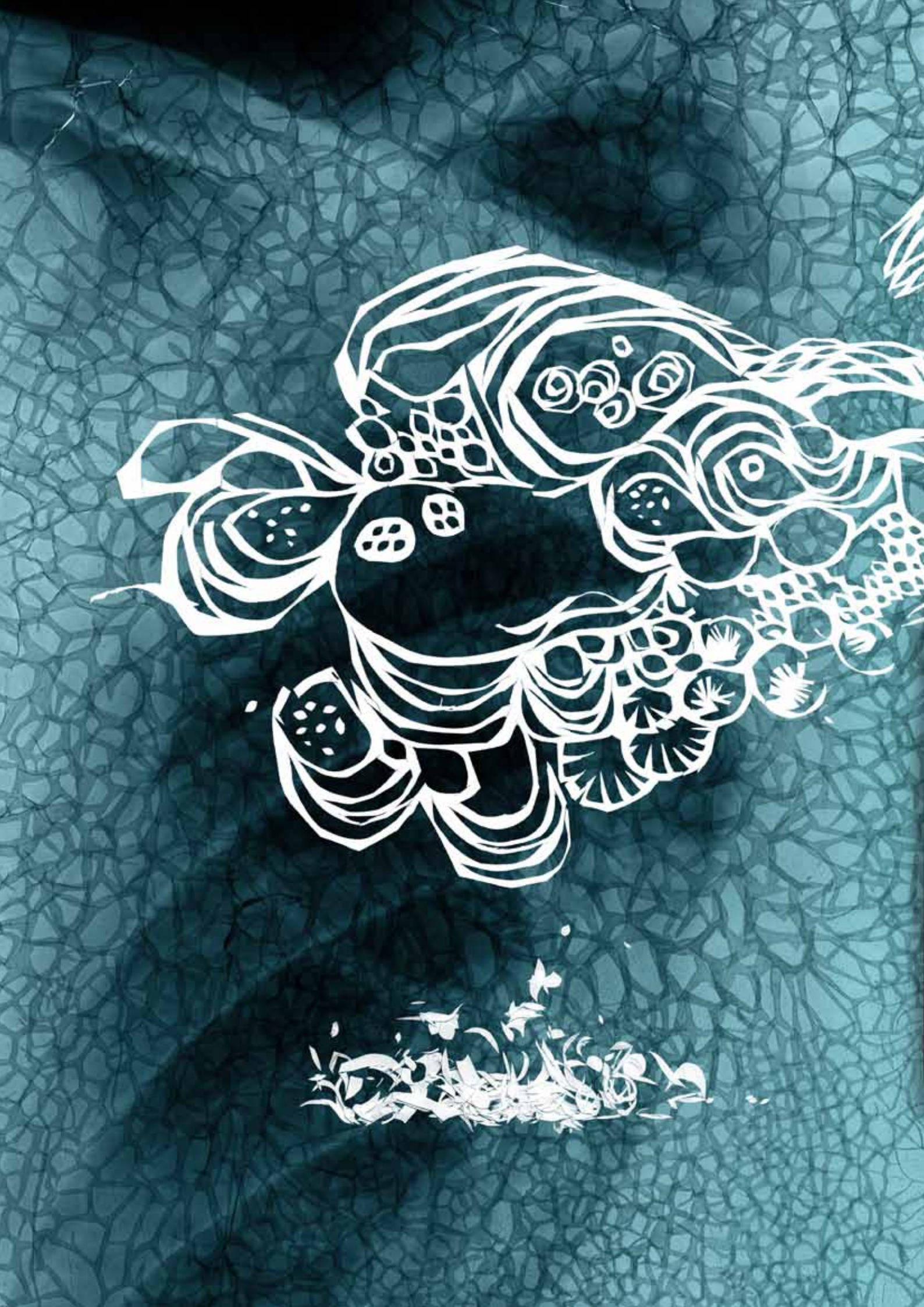
Publications during the past year include:

- Knight SR, Morris PJ. Steroid sparing protocols following nonrenal transplants; the evidence is not there. A systematic review and meta analysis.
  Transpl Int 2011; **24:** 1,198–1,207.

- O'Callaghan JM, Knight SR, Morgan RD, Morris PJ. Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis.
  Am J Transplant 2012; epub ahead of print.

- Pengel LH, Liu LQ, Morris PJ. Do wound complications or lymphoceles occur more often in solid organ transplant recipients on mTOR inhibitors? A systematic review of randomized controlled trials.
  Transpl Int 2011; **24:** 1,216–1,230.

The third Evidence in Transplantation course, sponsored by ESOT, was held at The Royal College of Surgeons of England on 18–19 March 2011, and was again regarded as a success by the participants.

Aminul Ahmed inserting an intracranial pressure monitor in a patient with a head injury.

Surgical research is key to advancing patient care, improving the quality of surgical procedures and developing new surgical interventions, which will benefit patients in the future.
Association of Medical Research Charities