Research Report

THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH

CHARITY NO. SC005317

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Foreword from the President

President, The Royal College of Surgeons of Edinburgh

I write this introduction in difficult and extraordinary times. The global pandemic is now in a third wave and the challenges facing our front-line healthcare staff are growing by the day. The suffering this pandemic has brought globally is depressing and disturbing. It has never been more important to look to things that bring us hope and look to the future.

“Reading the following report has reminded me of the extraordinary work that Fellows and Members of the College do, often on top of their growing clinical demands.”

The pandemic has brought considerable damage on medical research. Funds are depleted in the charity sector and the focus nationally is naturally on a vaccine. Yet I am pleased to report that the ambition and appetite for innovation remains undimmed amongst our Members and Fellows. Since March 2020, we have been inundated with applications from those eager to expand the boundaries of surgery and patient care.

International work is exceptionally challenging at present, yet many of the recipients have found ways to adapt, in some cases travel or simply postpone their work. We have been supportive of this approach. It is our view the projects we support are ultimately of value to patients. Postponement not cancellation is the course we must take. Surgical research is a chronically underfunded area and it is bad enough in the best of times. In the worst of times, it is incumbent on the College to support those undertaking critical projects. Treatments and cures cannot be allowed to be forgotten because of this crisis. It is up to us to deliver what we can as soon as we can.

The pandemic has not dimmed our appetite to expand our research portfolio. In September, we launched our first Research Fellowship into Human Factors and Digital Surgical Education. Our research collaboration in ophthalmology has begun under lockdown and our new Research Chair with Bowel Cancer UK has reached a significant halfway point in fundraising. These are just some of the activities that have been underway at this challenging time.

The success and effectiveness of our Research Committee is largely down to the Chair and its members. Professor Steve Wigmore and members of the Research Committee work on a voluntary basis. They take time out of their busy working days to help score and award the diverse array of funds. I do not underestimate this commitment and extend my heartfelt thanks for their efforts. Supporting this Committee through lockdown has been challenging. All of us have been kept on the right track thanks to Cathy McCartney and Anna Mikelsone. Thanks to their organisational skills, the Committee has moved effortlessly to online working. I would like to take
this opportunity to pay tribute to Cathy McCartney who retires this year. For over 16 years, Cathy has worked tirelessly with students, surgeons and staff to ensure the smooth running of our research and grants programme. I am grateful for her service to the College and wish her a long and happy retirement.

I hope this report is more than interesting reading. I hope it will provide reassurance that pandemic or not, research and treatments continue to be developed. Patients depend on us to innovate and we will continue to work tirelessly on their behalf by supporting the best and most impactful research.

Professor Michael Griffin OBE, PRCSEd

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Introduction

The College has a key role in supporting research and innovation in surgery. The grants and awards made by the College remain one of the key benefits provided to its members and fellows. The Research Committee is a voluntary group made up of a broad range of scientific and surgical backgrounds and this committee assesses and awards grants in several key areas, including cancer and non-cancer research, dental surgery, orthopaedic surgery, urology and vasculitis. We are grateful for the continued support and partnership of Sight Scotland, which generously funds ophthalmology grants administered through the Ophthalmology Sub-Committee of the College.

In addition to the core Research Committee members of College Council including the President, other Office bearers and the Director of Development and Partnerships join the research committee to discuss the strategic direction of the College in terms of its research portfolio. This activity is important and has been very well supported under the current presidency of Professor Griffin.

Development and diversification of the research portfolio will be important for the continued activities of the College in research and the provision of an annual budget to the Research Committee has enabled the Research Committee to become agile in its responsiveness in partnering other charities in research activities. A recent example of this is a partnership between the College and the Circulation Foundation, which has provided a Research Fellowship in Human Factors. We hope to announce further similar partnerships and the potential creation of a number of clinical research Chairs in the next few years.

I am immensely grateful to the Research Committee for their voluntary work in reading and assessing grant applications and awards, research reports and advising the college on the direction of research strategy. I would like to take this opportunity to specifically mention Professor Michael Steele who has served longer on the Research Committee than anyone and who still continues to offer superb insight into research applications and who also curates the research reports on behalf of the committee. We are very grateful to him for his continued service long beyond normal retirement age.

The work of the committee has continued through the COVID-19 pandemic in spite of some disruption to our administration and I am grateful to our long term Research and Grants Co-ordinator Cathy McCartney and her temporary replacement Anna Mikelsone for keeping the committee afloat. We have managed to award the majority of grants that would normally be awarded this year and have offered no cost extensions to a number of individuals whose research work has been disrupted by COVID-19 or who have been pulled back into clinical service during the worst phases of the pandemic.

There has inevitably been some disruption around student vacation scholarships and travel fellowships but we hope that these will return to a more normal pattern with the roll out of a vaccination programme.

Professor Stephen J Wigmore Chairman, the Royal College of Surgeons of Edinburgh, Research Committee

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Donors

Donors to the 2018-2020 Research Report

Alban Barros D'Sa Family

Cutner Memorial Bequest Fund

Ethicon Foundation

Lindsay Stewart

Lorna Smith Charitable Trust

Medical Reserch Council

Maurice Wohl Charitable Foundation

Mr Iain Fraser

Mr John Steyn and Family

Palliation and the Caring Hospital (PATCH)

Robertson Trust

Sight Scotland (formerly Royal Blind) Scottish

Oral & Maxillofacial Society Shanghai Head and Neck Maxillofacial Oncology Centre at the Ninth People's Hospital of Jiaotong University

Professor Somes Guha

Dato' Hj Mohamed Zainal Abidin Bin Hj Abdul Kadir

Amanda Wong- Powell

Binks Trust

The Russell Trust

The College and the Research Committee gratefully acknowledges the donations from numerous Fellows of the College both in the UK and Overseas.

Donate Today and Help Us to Continue Crucial Work

Over the centuries, the Royal College of Surgeons of Edinburgh has received generous support from its donors. We now need to keep pace with the ever-changing demands of a twenty-first century College, renowned globally for its excellence in every area of its teaching, research, and heritage. We are in an economic climate where neither the fees paid by students, nor membership can fully realise our ambition to be at the cutting edge of international surgical education and research.

The support of donors plays a critical role in allowing us to deliver world class education and increasing research capacity worldwide.

Although we have an excellent asset base, in financial terms we are progressively falling behind international competitors who have received a far greater measure of donor support. If we are to compete with other world class medical institutions, we need substantial funds to do so. It is vital to continue with fundraising, to bridge the funding gap on an annual basis and secure the College's future.

If you are considering making a donation, would like to discuss support for projects, scholarships, academic posts or medical research, please contact us at:

The Development and Partnerships Office
The Royal College of Surgeons of Edinburgh
Nicolson Street
Edinburgh
EH8 9DW

Tel: 0131 527 1591

Email: development@rcsed.ac.uk

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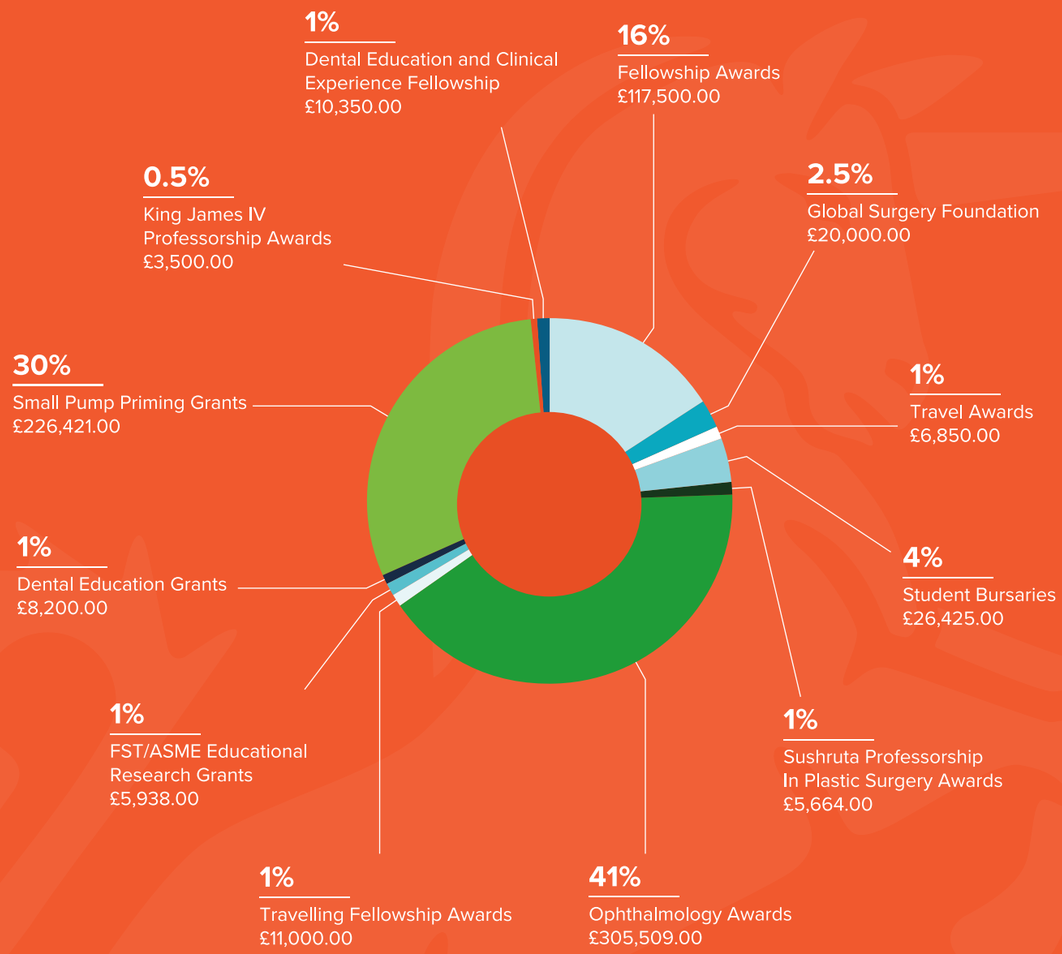
2018 - 2020 Research Report in Numbers



Total amount of funding in the Research Report:

£747,357

Breakdown of Total Funding

Fellowship Awards
£117,500

Sushruta Professorship In Plastic Surgery Awards
£5,664

FST/ASME Educational Research Grants
£5,938

Small Pump Priming Grants
£226,421

Student Bursaries
£26,425

Dental Education Grants
£8,200

Travel Awards
£6,850

Dental Education & Clinical Experience Fellowship
£10,350

Global Surgery Foundation
£20,000

King James IV Professorship Awards
£3,500

Travelling Fellowship Awards
£11,000

Ophthalmology Awards
£305,509

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Research Funding

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Fellowship Awards

THE ROBERTSON TRUST RESEARCH FELLOWSHIP AWARDED TO:

Mrs Samantha Downie - PhD Student, University of Edinburgh, Specialty Registrar Trauma & Orthopaedics, East of Scotland Deanery

“Predicting lesion progression, fracture risk, healing potential and surgical outcomes in patients with bony metastases due to systemic cancer”

When cancer spreads from its primary location to the bone (bony metastasis), a pathological fracture (break from minimal force) can occur. Metastatic fractures are less likely to heal than traumatic fractures, but we cannot predict those who will unite from those who will not.

This fellowship will enable the applicant to enter full-time research in a combined clinical and basic science PhD, exploring the following aims:

- Assess barriers to healing in a mouse model of metastatic fracture healing
- Identify factors associated with risk of fracture and outcomes after surgery in a Scotland-wide clinical study
- Create a computer model which can predict fracture risk based on patient variables.

At the end of the fellowship, we will create generic guidelines (i.e. flowcharts) to guide referral of patients with bony metastases to orthopaedics. We will create novel computer and animal models, which can predict the risk of fracture and investigate potential drug targets for improving metastatic fracture healing. Finally, we will create a national database of patients with bony metastases (Bony Metastasis Audit, BoMA) to standardise care and facilitate future research.

This study will help surgeons give patients enough information for them to make better, informed decisions about their care.

£55,000

THE MAURICE WOHL RESEARCH FELLOWSHIP SURGERY AND DENTAL SURGERY AWARDED TO:

Mr Sami Anjum - NIHR Academic Clinical Fellow in Trauma and orthopaedic Surgery, Newcastle University

“Improving the longevity of joint replacements for patients - can statins reduce the inflammatory response to orthopaedic biomarkers and inhibit pseudotumour formation?”

Osteoarthritis (OA) is the most common form of arthritis and there are no currently licenced medications to limit OA progression. Total joint replacement is indicated where conservative treatment has failed and in the UK the number of patients requiring hip and knee replacements is set to increase with an ageing population. Survival of total hip replacements is around 85% at 20 years with the most common reason for revision being aseptic loosening of the implant secondary to osteolysis, which is caused by immune mediated reactions to implant debris. These debris can also cause pseudotumour formation. As revision surgery is associated with higher morbidity, mortality, infection rates, venous thromboembolism, resource demand and poorer subsequent function it is important to understand the mechanisms underlying the disease process to improve implant longevity. Toll-like receptor 4 (TLR4), an innate immune receptor, has been demonstrated to mediate the deleterious immune response to orthopaedic debris by Mr Anjum. Statin use in epidemiological studies have been associated with reduced overall risk of revision surgery after hip replacement. In-vitro studies have demonstrated the potential for statins to reduce orthopaedic debris induced immune responses which can lead to osteolysis and pseudotumour formation. As literature from cardiological investigations demonstrate that statins can reduce the expression and responsiveness of TLR4, this could be an exciting mechanism to exploit to reduce the host immune response to orthopaedic wear debris, thereby improving implant survival by reducing immune mediated osteolysis. Mr Anjum proposes to investigate the potential for statins to reduce inflammatory cytokine expression and other immune factors in response to cobalt and ceramic oxides found within orthopaedic biomaterials using in-vitro models. Mr Anjum will use this opportunity to identify novel mechanisms for translation for patient benefit and forge collaborations both within Newcastle University and other institutes which excel in immunotribological research of the host interaction to biomaterials, to generate pilot data for an external funded MD/PhD fellowship.

£55,000

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Travelling Fellowship Awards

CUTNER TRAVELLING FELLOWSHIP IN ORTHOPAEDICS AWARDED TO:

Sara Dorman – ST7 Trauma and Orthopaedics, Countess of Chester Hospital, Cheshire

“To visit the Children’s Surgical centre, Cambodia, Phomn Penh to gain experience in the investigation and management of rare and severe pathologies that a UK training program would be unlikely to provide exposure to.”

£3,000

ALBAN BARROS D’SA MEMORIAL TRAVELLING FELLOWSHIP IN GENERAL SURGERY AWARDED TO:

Alexander Leeper – ST6 Upper GI Surgery, Royal Infirmary, Edinburgh

“To Practice General Surgery in an austere environment and participate in development of a sustainable surgical service at Gahini Hospital, Rwanda.”

I intend to spend six months outwith the General Surgery training programme as a volunteer general surgeon in Rwanda. The placement in Gahini hospital under the supervision of Mr Stephen Bennett (Previously Consultant General Surgeon NHS Fife) will provide me with an opportunity to develop a broad spectrum of surgical practice in an austere environment whilst providing the local community with a valuable service. During this placement, I will not only broaden my clinical and operative skills, but also gain insight into the requirements of delivering a sustainable and safe service despite limited resources.

£1,000

ALBAN BARROS D’SA MEMORIAL TRAVELLING FELLOWSHIP IN GENERAL SURGERY AWARDED TO:

Neena Randhawa – Post-CCT Fellow in Intestinal Failure, Nottingham University Hospital NHS Trust

“Visiting the Cleveland Clinic, Ohio to observce a world-renowned intestinal failure unit and improve knowledge and techniques for establishing a state of the art intestinal failure within NHS financial constraints”.

£1,000

THE SIR JAMES FRASER TRAVELLING FELLOWSHIP IN GENERAL SURGERY AWARDED TO:

Mr Christopher Johnston – Clinical Lecturer in General Surgery, University of Edinburgh

To observe the technical aspects of combined advanced endoscopy at the department of Hepatobiliary Surgery, Monash Medical Centre, Australia.

£2,000

Robert O’Neill – Senior Clinical Fellow, Oesophagogastic Surgery, Cambridge University

“Visiting the Amsterdam Medical Centre and the University Medical Centre Utrecht to study both laparoscopic and robotic approaches to totally minimally invasive oesophagogastic resection for cancer”

£1,000

Peter Vaughan-Shaw – ECAT SCREDS Clinical Lecturer & Honorary St7 in Colorectal Surgery, Western General Hospital, Edinburgh

“Visiting Shizuoka Cancer Centre, Japan and Severance Hospital to observe first hand some of the world’s most acclaimed robotic colorectal surgeons”

£1,000

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Travelling Fellowship Awards

JOINT RCSED/SOMS/SHANGHAI HEAD AND NECK FELLOWSHIP AWARDED TO:

Mr Richard Taylor – Honorary Consultant, Oral and Maxillofacial Surgery, University of Dundee

Fellowship in Head and Neck Oncology in Shanghai at the Department of Cranio-Maxillofacial Science, School of Stomatology, 9th Peoples Hospital, Shanghai Jiaotong University.

£3,000

Christopher McDonald – Specialty Trainee OMFS Mersey, Aintree University Hospitals, Liverpool

Fellowship in Head and Neck Oncology in Shanghai at the department of Cranio-Maxillofacial Science, School of Stomatology, 9th Peoples Hospital, Shanghai Jiaotong University, and the Cranial Base Unit 9th Peoples Hospital, Shanghai.

£4,500

TUANKU MUHRIZ FELLOWSHIP IN RURAL SURGERY AWARDED TO:

Angus J M Watson - Consultant Surgeon, Raigmore Hospital, Inverness

To visit the Ministry of Health, Malaysia. Knowledge exchange with Malaysian Surgical Colleagues.

£2,000

Andrew Kent - Consultant Trauma & Orthopaedic Surgeons, Raigmore Hospital Inverness

Malaysian Government MoH and rural health clinics

To foster international relationships and advance College projects.

£2,000

LINDSAY STEWART PRIZE AWARDED TO:

Palesa Mamohaw-Pilo Chisala

Prevalence of Peripheral Arterial Disease among High Risk Patients in Southern Malawi”

£500

Ebenezer Gezahegan Fanta

“Functional Outcome of Patients following Emergency Neurosurgical Intervention for Traumatic Brain Injury

£500

Alik Bwanga

The role of Helicobacter Pylori infection in adults presenting with sponstaneous gastroduodental perforation at the University Teaching Hopsitas, Lusaka, Zambia

£750

Kabongo Kizito

Thirty-day outcome of perforation peritonitis in relation to POSSUM score at the University Teaching Hospital, Lusaka, Zambia

£750

ETHICON TRAVEL GRANTS AWARDED TO:

John Collin – ST7, OMFS, Bristol Royal Infirmary

Head and Neck Oncologic Surgery and Reconstructive Fellowship University of Florida, Jacksonville

£1,000

Htar Hyein – Urology, Mandalay General Hospital, Myanmar

Scottish Lithotriptor Centre, Western General Hospital, to learn latest endourology techniques and stone management, WPBA and audit processes

£1,000

Mark Hughes – ST7 trainee/Clinical Lecturer, Western General Hospital

Fellowship Training in Skull Base Microneurosurgery, Department of Neurological Surgery of New York Presbyterian Hospital/Weill Cornell Medical College of Cornell University

£1,000

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Travelling Fellowship Awards

ETHICON TRAVEL GRANTS AWARDED TO:

Daniel Doherty – ST2 NIHR Academic Clinical Fellow, Transplant & General Surgery, University of Manchester

University of Alberta, Edmonton, Alberta, Canada

To gain clinical experience of islet transplantation in a pioneering and world leading centre and to gain experience of animal models of islet isolation and intra-portal transplantation

£700

Samantha Downie – Specialty Trainee Registrar ST5, Trauma & Orthopaedics, Ninewells Hospital and Medical School, Dundee

The International Bone Metastasis Registry, University of Karolinska, Stockholm, Sweden.

Learn about the experience of the Scandinavian Sarcoma Group (SSG) setting up their national database of bony metastases as a precursor to setting up a new UK national database (Bony Metastasis Audit BoMA UK network)

Conduct retrospective study using data from the International Bone Metastasis registry to provide comparison data for UK retrospective cohort study to be undertaken as part of my PhD

Create new research collaboration with a view to promoting UK as a centre of excellence in research on bony metastases

£400

Adarsh Kudva – Reader, Oral and Maxillofacial Surgery, KMC, Manipal, India. Chung Gung Memorial Hospital, Chayi, Thiwan

Training in Head and Neck Microvascular Reconstruction

£1,000

Arunima Verma – Consultant Surgeon, General Surgery, Tata Main Hospital, Jamshedpur, India

Training in Hepatobiliary Surgery, Edinburgh Royal Infirmary

£750

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Ophthalmology Awards

Funded by Sight Scotland (formerly Royal Blind)

OPHTHALMOLOGY MAJOR GRANTS AWARDED TO:

Robert MacLaren - Professor of Ophthalmology, Nuffield Laboratory of Ophthalmology (NLO) University of Oxford

“Development of CRISPR gene therapy for dominantly inherited retinal diseases”

£59,988

Parwaz Hossain - Associate Professor in Ophthalmology, Clinical Experimental Sciences, Faculty of Medicine, University of Southampton

“Real time Pathogen identification & Antimicrobial Sensitivities in Human Corneal Infection using Microfluidic Impedance Cytometry”

£59,628

Dr Shareen Forbes - Endocrinology Unit, University of Edinburgh

“Impact of insulin pump therapy and islet transplantation on progression of diabetic retinopathy in Type 1 diabetes”

£30,000

Robert MacLaren - Professor of Ophthalmology, Nuffield Laboratory of Ophthalmology (NLO) University of Oxford

“In vivo testing of CRISPR gene therapy vectors for dominantly inherited retinal diseases”

£59,957

Dr Rory Magaw - Clinical Lecturer, University of Edinburgh and Honorary Consultant, NHS Lothian, MRC Human Genetics Unit, University of Edinburgh, Western General Hospital

"In vivo genome editing of post-mitotic mammalian photoreceptors as therapeutics for inherited retinal dystrophies”

£54,308

Dr Shareen Forbes - Reader Islet Transplant Programme, Endocrinology Unit, Centre for Cardiovascular Science, University of Edinburgh

“Impact of insulin pump therapy and islet transplantation on progression of diabetic retinopathy in Type 1 diabetes”

£31,000

OPHTHALMOLOGY SMALL GRANTS AWARDED TO:

David Huggan - Former Consultant, NHS Forth Valley Stirling

“Smartphone Stereophotography of the Ocular Fundus”

£800

Dr Lona Jawaheer - Specialist Registrar in Ophthalmology, Tennent institute of Ophthalmology, Gartnavel General Hospital

“Does pre-operative D-chart score predict improvement in VFQ-25 score following surgery for epiretinal membrane?”

£9,828

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King James IV Professorship Awards

Professor Parwez Hossain - Consultant Ophthalmologist, University of Southampton

“Preventing blindness by application of real-time Healthcare technology”

£500

Professor Christopher Oliver - Senior Retired Fellow, Honorary Professor Physical Activity for Health Research Centre (PAHRC) University of Edinburgh

“Improving data visualisation, information and knowledge transfer for surgeons”

£500

Professor Adnan Saithna - Consultant orthopaedic Surgeon, Southport & Ormskirk NHS Hospital Trust

“ACL reconstruction in contemporary practice – how to achieve better outcomes”

£500

Martin McNally - Consultant in Limb Reconstruction, Nuffield Orthopaedic Centre, University of Oxford

“My sins sicken me like pus in my bones. Help me Jesus. Lamb of God, for I am sinking in deepest slim”

£500

Professor Augusto Azuara-Blanco - Professor of Ophthalmology, Centre for Public Health, Queens University Belfast

“Global prevention of glaucoma blindness and the EAGLE trial”

£500

Jason Wong - Academic Consultant in Plastic Surgery and Senior Lecturer in Plastic Surgery, Manchester University Foundation Trust

“From simple cuts to blast injuries – Understanding soft tissue injury, repair reconstruction, rehabilitation and the hope for regenerative medicine”

£500

Professor Elizabeth Davenport - Dental Education, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London

“The pursuance of excellence and the advancement of Dental Education”

£500

Sushruta Professorship in Plastic Surgery Award

Professor Stefan Hofer – Professor of Surgery, University of Toronto

“Transforming lives. Breast Cancer reconstruction: how we changed a procedure into an academic practice and then changed the world around us”

US$3,500

Professor V B Narayanamurthy - Senior Consultant Plastic Surgeon, Sundaram Medical Foundation, India

“Diabetic foot and training of plastic surgeons and other surgeons in the field of microsurgery”

US$3,500

24

Syme Medals

Mr Paul Monk – Orthopaedic Surgeon, Honorary Senior Lecturer, University of Oxford

“The Patellofemoral Joint: Form and Function”

Mr Jay Nath – ST7 General Surgery, West Midlands Deanery

“The clinical benefits and metabolic mechanisms of Hypothermic machine perfusion of Kidneys prior to Transplantation”

Mr Michael Hart – Specialty Registrar, Neurosurgery, Cambridge

“Network based Neurosurgery”

Mohan Singh – Specialist Registrar in Colorectal & Upper GI Surgery, Queens Hospital Burton, University of Derby & Burton

“Enhancing Upper GI Cancer Diagnostic and Therapy using Gold Nanoparticles”

Carlo Ceresa – ST4 in General Surgery, University of Oxford

“Novel approaches in optimising steatotic livers for transplantation”.

David Metcalfe – DPhil in Musculoskeletal Sciences

“Improving hip fracture outcomes using routinely collected health data”

Dundas Medal Award

PATCH

Awarded in partnership with PATCH Scotland (Palliation and the Caring Hospital), the first charity to specifically support 24/7 specialist palliative care for patients in hospital.

Dr Maria McKenna – Consultant in Palliative Medicine
Professor Stephen Clark – Consultant Cardiac & Transplant Surgeon

Freeman Hospital, University of Newcastle upon Tyne

End of Life Care Team

The Shrewsbury and Telford Hospital NHS Trust (SaTH)

26

Small Pump Priming Grants

Mr Jason Wong - Consultant Plastic Surgeon/Senior Lecturer, University of Manchester

“In Vivo integration of 3D printed capillary networks”

£9,936

Mr Alexander Aarvold - Consultant & Honorary Associate Professor, Paediatric Orthopaedic Surgery, University Hospitals Southampton

“Sulfur biology in skeletal development: An explorative study in development Dysplasia of the hip”

£8,500

Mr Dan Lin - NIHR Academic Clinical Fellow (ST2) in Otolaryngology, Newcastle University

“A preliminary investigation of IDO immune status in head and neck cancer”

£3,837

Dr Richard Holliday - Specialist Registrar (StR) in Restorative Dentistry

“Effects of vapourised nicotine products on oral health: In vitro studies on oral cells, biofilms and staining”

£9,900

Miss Janice Miller - Clinical Research Fellow, University of Edinburgh

“The role of the neuromuscular junction in cancer cachexia”

£8,500

Mr Rory Piper - NIHR Academic Clinical Fellow & Neurosurgical Trainee, University of Oxford

“Detecting meningioma invasion of the optic canal: a novel tractography pilot study”

£6,600

Miss Anne Ewing - ST4 Surgical Registrar, University of Edinburgh, Western General Hospital

“Human intervention study of aspirin and metformin to modify lipogenic-driven colonic epithelium targets and identify relationship to crypt stem cell signalling”

£10,000

Dr Thomas Drake - Clinical Research Fellow, Cancer Research UK Beatson Institute, Glasgow

“Characterising mechanisms of immune evasion in Hepatocellular Carcinoma (HCC)”

£9,977

Mr Gary Dobson - Higher Surgical Trainee/ Clinical Research Fellow, Centre for Cancer Research & Cell Biology, Queens University Belfast

“Characterisation of the Molecular & Genetic relationships between Synchronous Breast Cancers – opportunities for personalised surgery”

£9,545

Mr Alexander Laird - Consultant Urological Surgeon, Centre for Genomic and Experimental Medicine, University of Edinburgh

“Detection of circulating cell free DNA in renal cancer patients using renal cancer-specific DNA methylation and mutation changes”

£10,000

Dr Nick Kalson - NIHR Academic Clinical Lecturer, Fibrosis Research Group, University of Newcastle upon Tyne

“Investigating inflammation in patients with unexplained knee pain following total knee replacement”

£9649

Mr Sandip Nandhra - NIHR Academic Clinical Lecturer, Northern Vascular Centre, Freeman Hospital, Newcastle

“Pain relief in major amputation (PRIMA): A randomised control trial comparing single shot nerve block to continuous nerve catheter for post-major lower limb amputation pain control”

£9,489

Mrs Samantha Downie - PhD Student, University of Edinburgh, Specialty Registrar Orthopaedics, College of Medicine & Veterinary Medicine, The University of Edinburgh

“Bony metastasis audit Scotland (BoMAS): proposal for a national database on fracture risk and outcomes in patients with metastatic bony lesions”

£8,640

James Blackmuir - Clinical Research Fellow, MRC Human Genetics, Institute of Genetics and Molecular Medicine, University of Edinburgh

“Defining genetic variation influencing gene expression in normal renal cortex tissue to identify genetic risk factors for clear cell cancer of the kidney”

£9,160

28

Small Pump Priming Grants

Austin Acheson - Associate Professor, Department of Academic Surgery, University of Nottingham

“The effect of route of administration of iron therapy on immunity and inflammatory responses in established human colorectal carcinoma”

£9,700

Jun Lim - StR Trauma and Orthopaedic, University of Aberdeen

“Progressive muscle ischaemia: what pH level equates to impending cell death and are some muscle fibre types more susceptible than others to ischaemia”

£9,933

Fungai Dengu - Clinical Research Fellow in Transplant Surgery, Nuffield Department of Surgical Sciences, University of Oxford

“Immunomodulation of donor livers during normothermic machine perfusion utilising novel cellular therapies”

£9,925

Katherine Hurst - Surgical Research Fellow, Nuffield Department of Surgical Sciences, University of Oxford

“Stratification of carotid and femoral disease using combined MR and tissue analysis”

£10,000

Etohan Ogbemudia - Clinical Research Fellow in Transplant Surgery, Nuffield Department of Surgical Sciences, University of Oxford

“Pancreagenesis: Incorporation of Human Islet Cells into Ex-vivo preserved skin flaps to develop transplantable endocrine allograft model”

£9,930

Richard McGregor - Clinical Lecturer in General Surgery at the University of Edinburgh

“Laparoscopic Para-oesophageal Hiatal Hernia Repair leads to improvement in cardiorespiratory function and quality of life in addition to improved gastrointestinal symptoms”

£5,240

Daniel Doherty - ST3 NIHR Academic Clinical Fellow General Surgery, University of Manchester

“Understanding the hepatic microenvironment for islet survival and function following transplant”

£10,000

James Richards - NIHR Academic Clinical Lecturer & Honorary Specialty Registrar (HPB & Transplantation Surgery), University of Cambridge

“A preliminary study to assess decellularised cadaveric rectus sheath fascia as a potential biological implant to bridge abdominal wall defects”

£9,850

Christine Causey - Oral Surgery Specialty Trainee, Queen’s University Belfast

“A single centre pilot prospective study to determine the association between oral health and development of ventilator associated pneumonia (VAP)”

£10,000

Rachel Falconer - Clinical Research Fellow, NHS Highland/University of Aberdeen

“Augmenting early years vascular surgical skill acquisition through simulation – the feasibility, functionality and fidelity of delivering a home-based programme of practice.”

£9,130

Jose Rodriquez Lewsey - Consultant in Restorative Dentistry – Honorary Senior Clinical Lecturer, King’s College London

“Multi-modal digital intra-oral imaging for patients with trismus as a result of treatment for head and neck cancer.”

£9,000

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Dental Educational Grants

Katy Martin – Charles Clifford Dental Hospital, Sheffield

Diploma in Dental Education, University of Bedfordshire

£3,000

Hannah Walsh – Charles Clifford Dental Hospital, Sheffield

University of Sheffield – PGCert, Postgraduate Certificate in Medical Education

£2,600

Hannah Desai – Oral Surgery Department, Newcastle Dental Hospital

Newcastle University – Postgraduate in Clinical Research

£2,600

Jonathan Bowman - Aberdeen Royal Infirmary

Postgraduate Certificate in Medical Education, Faculty of Medical Sciences, Newcastle University

£2,775

Ben Steel - Cumberland Infirmary, Cumbria

Postgraduate Certificate in Medical Education (PGCME), University of Newcastle

£2,775

Jonathan Wareing - Oral and Maxillofacial Unit, St Luke's Hospital, Bradford

PG Certificate Medical Education, University of Dundee

£3,000

Dental Education and Clinical Experience Fellowship

Surien Raman – Faculty of Medicine, University of Malaya, Kuala Lumpur

University Hospitals Birmingham NHS Foundation Trust to enhance postgraduate experience by receiving exposure to a range of clinical work suitable for career, develop transferable skills not available in-home country, which can contribute to new perspectives in healthcare management in home country.

£1,800

32

Global Surgery Foundation

Michelle Joseph – ST8 NIHR Clinical Lecturer in Trauma and Orthopaedics, University of Warwick

To focus on the implementation of trauma training and the effects of this training on patient outcomes in terms of preventable death rates in Haiti.

£8,000

Stephen Bennett – Consultant General Surgeon, Gahini Hospital, Rwanda

Improving Access to Safe Surgery at Gahini Hospital, Rwanda – Creation of Surgical High Dependency Area & Surgical Ward improvements.

£4,000

Thomas Weiser – Visiting Professor, University of Edinburgh

Clean Cut: Reducing Surgical Site Infections in Ethopia

£12,000

FST/ASME Educational Research Grants

Arpan Tahim – Doctoral student (Institute of Education Oral and Maxillofacial Surgery ST5 (London Deanery)

“Understanding workplace-based assessment – How surgeons learn through the use of workplace-based assessment during specialist training”

£2,938

Kartik Logishetty - Specialty Trainee in T&O, North West London Training Programme

“Can team-training in Virtual Reality improve performance of complex open surgery”

£3,000

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Student Bursary Awards

BURSARIES FOR ELECTIVE PLACEMENTS IN AFRICA:

Ali Ansaripour – King's College London Medical School

Queen Elizabeth Central Hospital, Blantyre, Malawi

£500

Mariea Brady – University of Oxford

Beit CURE International Hospital, Chipatala, Blantyre, Malawi

£500

Francesca Leone – University of Leicester

Livingstone Central Hospital, Zambia

£500

Francesca Loro – University of Edinburgh

Akim Oda Government Hospital, Ghana

£500

Shareef Mahdi – Barts and The London School of Medicine and Dentistry, Queen Mary University of London

Charlotte Maxeke Johannesburg Academic Hospital, South Africa

£500

Paul O'Connor – Warwick Medical School

Department of Neurosurgery, Centre Hospitaluer Universitaire de Kigali, Rwanda

£500

Matthew Williams – University of Oxford

Kenyatta National Hospital, Kenya

£500

Etienne Chew – University of Edinburgh

Department of Plastic Surgery, Groote Schuur Hospital, South Africa

£500

Dominic Gardner – University of Edinburgh

Tygerberg Hospital, South Africa

£500

Charlotte Greene – King's College London The University Teaching Hospital

Levy Mwanawasa Hopsital (Lusaka), Ndola Teaching Hospital (Ndola)

£500

Laura Tregidgo – University of Oxford

Tygerberg Hospital, South Africa

£500

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Student Bursary Awards

THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH & BINKS TRUST BURSARY:

Tom Handley – Imperial College London

Mayo Clinic & Massachusetts General Hospital, USA

£250

Jamie Mawhinney – University of Oxford

Jigme Dorji Wagchuck National Referral Hospital, Bhutan & Beit CURE Hospital, Zambia

£250

James Russell – King College London

Padhar Hospital, India

£250

Youri Tan – University of Manchester

Department of Plastic Surgery, UT Southwestern Medical Center, USA

£250

Eilidh Bruce – University of Edinburgh

Paediatric Surgery Subinternship, Columbia University College of Physicians and Surgeons, New York Presbyterian Morgan Stanley Children's Hospital

£250

Sujit Gnanakumar – University of Cambridge

The Surgical Neurology Branch of the National Institute of Neurological Disorders and Strike (NINDS) Intramural Research Program at the NIH in Bethesda, USA & Neurosurgery Unit at the University Teaching Hospital in Lusaka, Zambia

£250

Prachi Mann – Brighton & Sussex Medical School

Department of Cardiothoracic Surgery, St, Vincent Hospital, University of New South Wales, Australia

£250

David Stewart – University of Newcastle

St Francis Xavier Health Center, Uganda

£250

Chu Tang – Barts & London School of Medicine and Dentistry

Narayana Institute of Cardiac Sciences, India & Hospital Serdang, Malaysia

£250

Hannah Cornwall – University of Oxford

Perth ENT Centre, Australia

£250

Saad Khan – University of Birmingham

The Royal Children's Hospital, Melbourne, Australia

£250

Matthew Lyons – University of Edinburgh

Columbia University Irving Medical Centre, New York

£250

Hemant Kumar – University of Birmingham

The Amrita Institute of Medical Sciences in Kochi, Kerala, South Asia

£250

Maithili Mehta – University of Edinburgh

Weill Cornell Medical College, New York

£250

Elizabeth Cahya – University of Glasgow

Royal Prince Albert Hospital, University of Sydney, Australia

£250

Adil Rashid – University of Nottingham

Korle Bu Teaching Hospital, Ghana

£250

Ahmed Nur – Imperial College London

Kenyatta National Hospital, University of Nairobi Medical School, Kenya

£250

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Student Bursary Awards

BURSARIES FOR UNDERGRADUATE ELECTIVE OR VACATION AWARDS:

Waheed-Ul-Rahman Ahmed – University of Exeter

Genotype-Phenotype Correlation in a Carpal Tunnel Syndrome Cohort

Nuffield Orthopaedic Centre, University of Oxford

£1,500

Maurice Samake – Newcastle University Medical School

Evaluating shoulder dysfuntion following latissmus dorsi flap reconstruction with perioperative regional block in breast cancer surgery

Newcastle Breast Centre, Newcastle upon Tyne NHS Trust

£1,200

Etienne Chew – University of Edinburgh

Assessment of the post-operative use of intravesical mitomycin C in the prevention of bladder cancer following nephroureterectomy for upper tract urothelial carcinoma and its associated oncological outcomes

Department of Urology, Western General Hospital, Edinburgh

£1,425

Shivank Keni – University of Edinburgh

Assessment of learning curves in simulated laparoscopic surgery and development of benchmarks

University of Edinburgh

£1,200

Quek Roy – National University of Ireland, Galway

Investigation of novel biomarkers in HPV Negative Head and Neck Squamous Cell Carcinoma

Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool

£1,200

William Cambridge – University of Edinburgh

How do different Cancer mutations change inflammation in cholangiocarcinoma

MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh

£1,500

Shivam Kolhe - University of Newcastle

Fluorescent imaging of sarcoma cell surface targets

Northern Institute for Cancer Research, University of Newcastle

£1,050

Joseph Salem – University of Bristol

Assessing the use of computerised tomography for head trauma in a teaching hospital in Sri-Lanka. What is the impact on neurosurgical admissions

University of Bristol

£600

Benjamin Fox – University of Edinburgh

What is the long-term outcome following non-union of the clavicle

Orthopaedic Trauma Service, Royal Infirmary Edinburgh

£600

Richard Mak – University of Edinburgh

Exploration of repurposing Eugenol to treat Fissue in ano

Department of Colorectal Surgery, Western General Hospital, Edinburgh

£900

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Student Bursary Awards

WONG CHOON HEE BURSARIES

Julian Camilleri-Brennan – University of Edinburgh

Auckland City Hospital, New Zealand

£500

Tanya Gupta – King's College London

The Li Ka Shing Faculty of Medicine, University of Hong Kong and Jan Swasthya Sahyog (People's Health Support Group) an NGO hospital in the tribal areas of rural Chhattisgarh, India

£250

Eleanor Lumley – University of Aberdeen Department of Plastic Surgery, Asan

Medical Center, University of Ulsan, Korea and Department of Plastic Surgery, Ganga Hospital, India

£250

Timothy Chu – University of Newcastle

Prince of Wales Hospital, Hong Kong

£500

George Higginbothan – University of Leeds

Department of Neurosurgery and ENT, Sarawak General Hospital, Jalan Hospital Malaysia

£250

Constance Osborne – Kings College London

Groote Schuur Trauma Department, South Africa

£250

Emma Norton – St George's University of London

Department of Neurological Surgery, New York-Presbyterian Hospital/Weill Cornell Medical Center

£250

RUSSELL TRUST BURSARIES

Jean-Luc Duval – Kings College London

Caribbean Heart Care Medcorp Ltd in Trinidad and Tobago

£500

Henry Searle – University of Edinburgh

Sports Medicine and shoulder services, Orthopaedic Research Institute, St George Hospital Campus, University of New South Wales, Australia

£500

Uddhav Vaghela – Imperial College London

Hospital for Special Surgery & New York Presbyterian Hospital and Verb Surgical (in collaboration with Imperical College Kondon department of Surgery and Cancer) USA

£500

Bethany Seale – Keele University

Mercy James Institute of Paediatric Surgery and Intensive Care, Queen Elizabeth Central Hospital, Malawi

£500

Joanne Wolska – University of Edinburgh

Weill Cornell University Medical School, New York

£500

Silvia Allikments – Kings College London

Department of Emergency Medicine, Trauma Center, Groote Schuur Hospital, University of Cape Town

£500

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Fellowship Reports

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Robertson Trust Research Fellowship and Small Pump Priming Grant

The development of a human 3D osteoporotic model for the assessment of microRNA manipulation

Mr Robert K Silverwood

University of Glasgow's Centre for the Cellular Microenvironment

August 2017 - 2018

Lay Summary

Due to ageing populations, osteoporosis (OP) represents a burden of ever increasing proportions to healthcare systems throughout the world. Worldwide a fragility fracture secondary to OP occurs every 3 seconds, and the incidence of these fractures is expected to double by 2050.

The current and commonly used treatments have proven ineffective in stemming the tide of OP related fractures. Developing new, targeted therapies is becoming increasingly important.

MicroRNAs are known to control gene expression in organ development and diseases such as OP. As such they represent a potential target for new therapies. We have identified multiple, promising miRNAs, which are abnormally expressed in OP.

To maximise the relevance of in vitro work it is imperative to reproduce the in vivo environment as closely as possible. We have identified an optimal 3D model of OP bone cells. This model will be used in future studies investigating the manipulation of key microRNAs.

We have furthered the scientific knowledge of microRNAs in patients suffering fragility fractures and developed a model to assess new targeted therapies. The outcomes of this research project will play a role in improving patients' health and quality of life by reducing hospital admissions and surgery for fragility fractures.

Clinical and Scientific Significance of advances made

Due to ageing populations, osteoporosis (OP) represents a burden of ever increasing proportions to healthcare systems. Worldwide a fragility fracture secondary to OP occurs every 3 seconds, with 300 000 occurring per year in the UK alone.[1] The current and commonly used treatments, such as bisphosphonates and strontium ranelate, have proven ineffective in stemming the tide of OP related fractures. They are also associated with serious side effects.[2]

Significant research activity is focussing on microRNAs (miRNAs) potential role as biomarkers or therapeutic targets in OP. miRNAs have been shown to play a key role in bone homeostasis and musculoskeletal diseases such as OP.[3]

Bone marrow aspirates and femoral head samples were taken from 3 osteoarthritic (OA) and 3 low energy neck of femur patients (NOF) undergoing hip arthroplasty. The adherent fraction of the bone marrow was assessed by Next Generation sequencing to determine the miRNA expression profiles. Micro-CT scanning was performed of the excised femoral heads, allowing observation of the bone phenotype in each group, and correlation to miRNA expression.

Expression levels of 4695 miRNAs were evaluated in the OA and NOF groups. There were 105 miRNAs that were significantly differentially expressed, see Figure 1.

Multiple miRNAs known from the literature to be abnormally expressed in OP were identified. Significant upregulation of miRNA-29a, involved in the Wnt signalling pathway and differentiation of mesenchymal stem cells (MSC) to mature osteoblasts was observed, in the NOF group. Furthermore, miRNA-133, a RUNX2 regulator, and miR-21, involved in osteoclast differentiation, were observed to be significantly downregulated in the NOF group.[4-6]
Of these abnormally expressed miRNAs, miR-31 and miR-143 were selected for

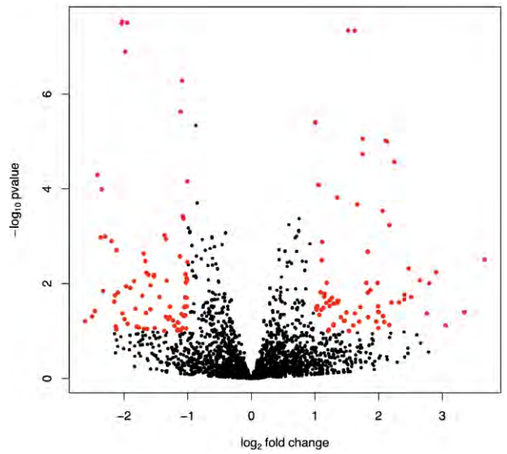

Figure 1 Volcano plot of miRNA expression of OA vs NOF OPGs. Red dots identify up or down regulated miRNAs with log2 fold change expression ≥ 1 or ≤ -1.

further analysis. miR-31 was observed to be significantly increased in the NOF group, which has been observed previously in patients with OP. Inhibiting miR-31 has been shown to be osteogenic, as it negatively regulates osterix, but it has yet to be assessed in 3D OP conditions. MiR-143 was observed to be significantly downregulated in the NOF group, and its role in OP has yet to be understood, it is reported to be a regulator of both adipogenic and osteogenic differentiation.[6]

Gold nanoparticles have been functionalised with miRNA mimics and inhibitors of miR-31 and miR-143. Experimentation in 2D and 3D cultures are being performed to further elucidate the role of these two miRNAs in osteogenesis and adipogenesis.

In keeping with the discrepancies between the two groups observed in the microRNA expression profiles, the initial micro-CT data has shown important differences in bone micro architectural indices such as bone volume/total volume and trabecular characteristics.

Furthermore, we have characterised features of MSCs from patients who have sustained low energy osteoporotic-type fractures. The differentiation capacity and stem cell expression profile of the adherent fraction of bone marrow cells was compared to patients undergoing total hip arthroplasty for OA.

For developing new therapies, it is imperative to utilise a, consistent, reliable and reproducible in vitro model. 3D cellular aggregates, as spheroids, are becoming increasingly utilised in musculoskeletal research. These systems are more reflective of the in vivo environment in comparison to monolayer culture.

Spheroid culturing systems have been used extensively in other fields of research, notably in cancer research, as oxygen, cytokine and nutrient gradients are created which mimic the tumours environment. This is of great significance when trialing new therapies.[7] Furthermore, an optimised 3D in vitro model reduces the reliance on animal models, in keeping with the 3Rs principles of animal experimentation; Reduction, Refinement, Replacement by reducing the gap from simplistic 2D in vitro culture to in vivo animal models.[8]

Many different techniques can be utilised to develop spheroids, such as spinner flasks, hanging drops, low adherence culture vessels and magnetic levitation. The optimal technique for differing cell types has been shown to vary. However, there remains a paucity of information regarding the best technique for culturing osteoprogenitor cells (OPG) in 3D. OPGs cells are derived from MSCs, and they differentiate to mature osteoblasts. OPGs are important for research in quantitative and qualitative diseases of the musculoskeletal system.

Three spheroid-forming techniques have been assessed for osteoprogenitor cells. The efficacy of the magnetic nanoparticle (MNP), hanging drop (HD) and ultra-low attachment (ULA) techniques were assessed by light microscopy, viability staining, scanning and transmission electron microscopy.

The MNP method, involves loading cells with magnetic nanoparticles, then utilising a magnetic field generated from a magnet placed above the well to encourage the cells to aggregate.[9] The HD technique has long been used and for multiple different cell types.[10] Cells sediment in a droplet of cell suspension, which is suspended within a plate. They are unable to form adhesions to the air-liquid interface, and the formation of spheroids occurs within the droplet. The ULA technique utilises round bottom wells with a non-adherent coating to encourage cells to form intercellular connections.

The MNP technique resulted in significant necrosis on viability staining, and spheroid size was observed to not increase with increasing cell number. Cell viability was much improved in both the HD and ULA techniques. Spheroids were produced by the ULA technique within 24 hours, whereas the HD technique required 72 hours. Spheroid size was seen to increase proportional to cell number in both the HD and ULA technique, with the best morphology produced by the ULA technique when assessed by electron microscopy, see Figure 2.

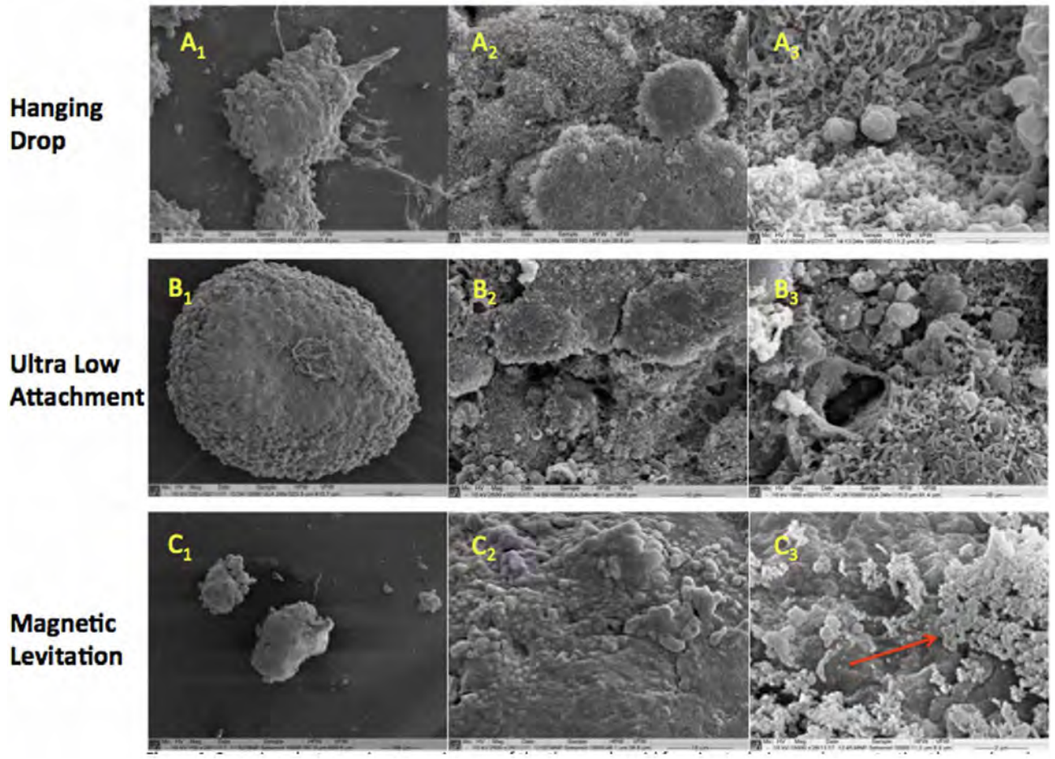

Figure 2: Scanning electron microscopy images of the three spheroid forming techniques, demonstrating the produced morphology after 24 hours. Red arrow indicates nanoparticles on the exterior surface of the MNP spheroid. Cell number 10,000. Magnification of images: 1- 250x, 2- 2,500x, 3- 10,000x.

The MNP method has had previous success within our group, when applied with MSCs.[9,11] However, the MNP method does not produce a favourable environment for OPGs, with a high cell death rate and varying morphology produced.

Conclusion

miR-31 and miR-143 have been chosen to be further assessed in 2D and 3D experiments, by In Cell Western, metabolomics and quantitative PCR analyses, to further elucidate their role in osteogenesis and their contribution to OP. The ULA technique will be applied for the 3D experiments.

This fellowship and grant has provided the opportunity to investigate and characterise an increasingly important disease, in OP. I have identified an optimal 3D culture technique for OPG cells, which will be applied to miRNA mimics and inhibitor experimentation, which will contribute to the development of targeted therapies.

References

1. The National Osteoporosis Society, Fracture Liaison Service. [Internet] 2015 [cited 9/11/2016]. Available from https://nos.org.uk/media/1833/flsit-service-specification-v1-12.docx
2. Bolland MJ, Grey A. Ten years too long: strontium ranelate, cardiac events, and the European Medicines Agency. BMJ. 2016 Sep 30;i5109.
3. Tang P, Xiong Q, Ge W, Zhang L. The role of MicroRNAs in Osteoclasts and Osteoporosis. RNA Biol. 2014 Nov 2;11(11):1355–63.
4. Seeliger C, Karpinski K, Haug AT, Vester H, Schmitt A, Bauer JS, et al. Five freely circulating miRNAs and bone tissue miRNAs are associated with osteoporotic fractures. J Bone Miner Res. 2014;
5. Weilner S, Skalicky S, Salzer B, Keider V, Wagner M, Hildner F, et al. Differentially circulating miRNAs after recent osteoporotic fractures can influence osteogenic differentiation. Bone. 2015;79:43–51.
6. Marini F, Cianferotti L, Brandi ML. Epigenetic mechanisms in bone biology and osteoporosis: Can they drive therapeutic choices? International Journal of Molecular Sciences. 2016.
7. Friedrich J, Seidel C, Ebner R, Kunz-Schughart LA. Spheroid-based drug screen: considerations and practical approach. Nat Protoc [Internet]. 2009;4(3):309–24. Available from: http://www.nature.com/doifinder/10.1038/nprot.2008.226
8. Saleh FA, Genever PG. Turning round: Multipotent stromal cells, a three-dimensional revolution? Cytotherapy [Internet]. 2011;13(8):903–12. Available from: http://dx.doi.org/10.3109/14653249.2011.586998
9. Lewis NS, Lewis EEL, Mullin M, Dalby MJ, Berry CC. Magnetically levitated mesenchymal stem cell spheroids cultured with a collagen gel maintain phenotype and quiescence.
10. Timmins NE, Nielsen LK. Generation of Multicellular Tumor Spheroids by the Hanging-Drop Method. 2007;141–51. Available from: http://link.springer.com/10.1007/978-1-59745-443-8_8
11. Lewis EEL, Child HW, Hursthouse A, Stirling D, McCully M, Paterson D, et al. The influence of particle size and static magnetic fields on the uptake of magnetic nanoparticles into three dimensional cell-seeded collagen gel cultures. J Biomed Mater Res - Part B Appl Biomater. 2015;

Problems encountered and steps taken to overcome them

Obtaining regular bone marrow and femoral head samples from patients who had suffered neck of femur fractures was difficult. The Orthopaedic surgeons at the Queen Elizabeth University Hospital have become engaged with this project, I have presented to them at audit meetings and met many of the team individually to discuss my research. I am very grateful for their contributions. The initial spheroid model trialled with the osteoprogenitor cell type produced unexpectedly poor results. This method has been extensively used in our laboratory. This led to the investigation of other techniques and an improved 3D model.

Collaborations established

I have worked with the University of Edinburgh's Department of Trauma & Orthopaedic research group to perform micro-CT scanning. Their expertise in this area has been a great benefit to my research. Our groups hope to work on future projects together.

Further collaboration was made with the Glasgow Polyomics Facility, where we undertook advanced next-generation sequencing and microRNA analysis. I received a Wellcome Trust pump priming Grant for this.

Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

I have enrolled in a PhD degree with the University of Glasgow, my submission date is February 2019. I have published one article with regards to conducting a higher degree as an orthopaedic trainee, and I aim to publish scientific papers based on my research. I have presented my initial results nationally and internationally.

Publications

Silverwood RK, Shields DW, Young PS. "Swapping a drill for a microscope". Published in The Journal of Trauma & Orthopaedics March 2018

Presentations

Silverwood RK, M Mullin, Meek RMD, Dalby MJ, Berry CC. "The development of a three-dimensional osteoprogenitor culture model for investigating future osteoporosis therapies" European Society for Biomaterials Maastricht 09/09/2018- Poster presentation 09/09/2018

Silverwood RK, M Mullin, Meek RMD, Dalby MJ, Berry CC. "The development of a 3D Osteoprogenitor culture model for investigating future osteoporosis therapies" Podium Presentation Glasgow Orthopaedic Research Initiative, 23/02/2018

Silverwood RK, Berry CC, Ahmed F, Meek RMD, Dalby MJ. "Development of 3D Osteoporotic Model for MicroRNA Assessment and Manipulation." Poster Presentation European Orthopaedic Research Society Annual Meeting 2016, Bologna (14-16/09/2016)

Silverwood RK, Berry CC, Ahmed F, Meek RMD, Dalby MJ. "Development of 3D Osteoporotic Model for MicroRNA Assessment and Manipulation." Podium Presentation British Orthopaedic Research Society Annual Meeting 2016, Glasgow (06/09/2016)

Acknowledgements

Supervisors
Professor Matthew Dalby, Dr Catherine Berry and Professor Dominic Meek
The University of Glasgow's Centre for the Cellular Microenvironment

Micro-CT
Dr Rob Wallace University of Edinburgh's Trauma & Orthopaedic Research department

Queen Elizabeth University Hospital Trauma & Orthopaedic Department

Funding
The Robertson Trust Research Fellowship/ Royal College of Surgeons of Edinburgh
Small pump priming grant from the Royal College of Surgeons of Edinburgh
Wellcome Trust Institutional Strategic Support Fund- Consolidator Funding Application

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Maurice Wohl Research Fellowship

Muscle wasting in cancer: Molecular mechanisms and potential therapeutic targets

Miss Janice Miller

Clinical Surgery, Royal Infirmary of Edinburgh

August 2018 - 2019

Lay Summary

Cancer cachexia (involuntary wasting syndrome) is an under-researched cause of major patient morbidity and mortality, which has no efficacious treatment or generally accepted strategy for management. Skeletal muscle and fat loss are the two markers in the diagnosis and classification of cachexia. We aimed to assess molecular mediators involved in muscle and fat wasting through a variety of ways, including taking samples of muscle, fat and blood from patients with and without cancer cachexia.

Firstly, we undertook a review of tools used to diagnose unintentional weight loss and found that no single tool was currently able to synchronously diagnose Cachexia, age-related muscle loss, and simple malnutrition. We therefore suggested components to make up a new tool which have since been used as the subject of an editorial to inform a consensus on the definition and management of malnutrition. Secondly, CT scans were used to investigate the effect of chemotherapy on muscle and fat wasting. We found that all patients lost muscle mass during chemotherapy, but those who were older lost more fat, and that the type of fat that was lost was different between men and women. Thirdly, we analysed fat samples from patients, and we found that there were large differences in expression of genes between fat from under the skin and inside the abdomen, suggesting that fat from inside the abdomen may play a role in the cachexia process. We identified “Intelectin-1” as a possible marker of this wasting. Fourthly, breakdown products (metabolites) of fat wasting were also able to be identified from the blood of patients with weight loss, suggesting this may be of use as a test to monitor the effects of future anti-cachexia treatments. Finally, the main investigation of muscle in this study was looking at the interface between muscle and nerves. This was found to be the same between healthy individuals and patients with cancer who did and did not have Cachexia, suggesting that cachexia is primarily a muscular disorder.

It is hoped that results from this study will identify potential therapeutic targets and help plan future studies.

(A) Clinical and Scientific Significance of advances made

Cancer cachexia has been defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia affects most patients with advanced cancer and is associated with reductions in treatment tolerance, response to therapy, quality of life, and survival. Thus, amelioration of cachexia would improve both quality of life and survival. However, the aetiology of cachexia is poorly understood, and there are no agreed diagnostic biomarkers or therapeutic interventions. Recent advances in the field of cachexia research include the development of diagnostic criteria for cachexia as well as computed tomography (CT) body composition analysis software making the ability to detect clinically significant muscle wasting in obese patients, in particular, more feasible. Although muscle loss appears to be the most important and physiologically relevant event in cachexia, the importance of fat wasting is less understood. During cachexia, different adipose depots around the body demonstrate differential rates of wasting. Furthermore, recent studies from animal models have suggested that adipose tissue may be a key driver of muscle wasting through fat-muscle crosstalk. However, human studies in this area are lacking. The molecular mechanisms driving muscle loss in humans are also poorly understood, and the relationships between muscle and fat wasting, functional impairment and reduced survival are largely unknown. The main aim of this project was to investigate specific mediators, mechanisms and biomarkers of cachexia in robustly phenotyped patients with upper gastrointestinal cancer (UGI) in whom cachexia is known to be prevalent.

The project was comprised of various studies designed to investigate cachexia diagnosis, staging and management. In order to recruit patients to clinical trials, drive cachexia research, and identify those who would benefit from early intervention, it is important to understand how to screen and diagnose patients with cachexia. Many patients present to clinicians with unintentional weight loss (UWL). This can occur in patients with cachexia, sarcopenia and malnutrition. With increasing rates of obesity worldwide, as well as an ageing population, the assessment of UWL is difficult. Firstly, therefore, in order to investigate the feasibility of screening for UWL, a systematic review was undertaken to determine which screening tools were able to assess cachexia, sarcopenia and malnutrition according to the consensus definitions for each. Each tool was judged against a reference method and psychometric evaluation carried out. The study shows that no current tools are capable of achieving the simultaneous diagnosis of all 3 conditions, but describes a stepwise framework for the development of a novel, future tool. The study was performed in collaboration with palliative care experts from Hull and Sydney and was the subject of an editorial by Tommy Cederholm, the lead for GLIM (Global

Leadership in Malnutrition) initiative, a project designed by the 4 big nutrition societies (ESPEN/ASPEN/FELANPE/PENSA) to achieve consensus on definition and management of nutrition.

Secondly, building upon screening and methods for diagnosing low muscularity, CT body composition analysis was undertaken to determine any age and sex-related variations in patients with upper gastrointestinal (UGI) cancer. CT based cut-offs for determining low skeletal muscle mass are sex and body mass index (BMI)-specific, and have been developed through their ability to predict mortality in these patients. As discussed above, obesity and ageing are becoming more prevalent therefore many patients maybe sarcopenic at diagnosis thus making the assessment of clinically significant muscle wasting difficult. A retrospective, observational study was carried out on patients who had undergone potentially curative oncological and surgical treatment for oesophageal cancer. Analysis of staging CT scans was performed, along with assessment of changes in body composition in those patients who had undergone neoadjuvant chemotherapy (NAC). Males had higher baseline muscle and visceral fat mass whereas females had higher subcutaneous fat mass. Older patients and females lost significantly more fat following chemotherapy. Patients of all ages and both sexes lost muscle mass though there was no difference in rates of wasting between groups. This study is the first to investigate changes in body composition by age. It therefore highlights the need for further investigation to define differences in adipose depots during cancer progression and their prognostic value.

The main biological assessment of cancer-associated muscle wasting in this study therefore investigated the role of the neuromuscular junction (NMJ). The NMJ provides the link between myelinated motor nerves and skeletal muscle. Very little is known about the structure of the human NMJ in health or in disease. Experimental denervation is a recognised model for studying muscle wasting in vivo, and as a result experimental evidence for the role of NMJ degeneration as a mechanism of cachexia is dependent upon animal models. Recent data, however, has shown that rodent and human NMJs are markedly different under healthy conditions. NMJ morph; an imageJ based package was used for morphometric analysis of the neuromuscular junction in UGI cancer patients with or without cachexia and non-cancer controls. No significant differences were found between groups in any of the 21 major pre or post synaptic variables measured. This was the first morphological assessment of the NMJ in disease, and suggests that the NMJ remains structurally intact in cancer cachexia and that, contrary to animal models and age-realted sarcopenia, denervation of skeletal muscle is not a major driver of disease.

Whilst it is recognised that muscle mass plays a significant role in the syndrome of cancer Cachexia, the importance of fat wasting and the effect of metabolic mediators on fat volume requires attention (as has been shown above through body composition analysis). In murine tumour models, loss of fat volume may predate the loss of muscle volume. Fatty acids, leptins, cytokines and other adipokines may cause lipotoxic effects in skeletal muscle. Adipokines have been reported to induce insulin resistance, impair muscle development, alter muscle lipid amino acid metabolism, and modify signalling, thus affecting skeletal muscle mass. Clinical studies have shown that adipokines from murine models are also measurable in patients with cancer cachexia. Through the use of transcriptomics, subcutaneous (SAT) and intra-abdominal visceral adipose tissue (VAT) depots were analysed from healthy controls and UGI cancer patients with and without cachexia to elucidate the biochemistry of fat wasting in cancer cachexia. Over 2000 genes differed between cachexia VAT and SAT. The gene which showed the largest difference in expression between cancer VAT and control was Intelectin-1 (ITLN1), a novel adipocytokine. Genes involving inflammation were upregulated in cancer whereas genes involved in energy metabolism and fat browning were downregulated. VAT may therefore be a target for therapeutic manipulation in cancer. Further investigation is required in to the role of Intelectin-1 as a biomarker in cachexia.

Finally, in the search for biomarkers of cancer, likely responsiveness to treatment, and the presence of cachexia, plasma has previously been used as a readily available biofluid for investigation. No real cachexia biomarker has been found, although as work continues, it seems that individual biomarker targets should be replaced by an array of markers. Plasma samples were taken at the time of anaesthesia from patients under-going UGI resectional surgery. Liquid chromatography mass spectrometry (LC/MS)-based metabolomics was undertaken. This showed two distinct profiles based on percentage weight loss in accordance with the consensus definition. There were 40 metabolites associated with cachexia, with six of those being highly discriminative of weight loss. In particular, many of the metabolites discovered fell in the lipid pathways, lending credence again to the importance of understanding adipose wasting in cachexia.

In summary, the role of adipose wasting as investigated through imaging and biochemical results has been shown to be important in the aetiology of cancer cachexia. Specific CT-derived cut points for differing age groups and sex would define stricter inclusion criteria for clinical trials and possibly lead to improved endpoints. Potential novel biomarkers including ITLN1 and plasma biomarkers of lipid wasting may be useful as inclusion criteria or outcome measures in clinical trials. The discoveries of the lack of fat browning and the stability of the NMJ in cachectic patients also importantly highlights the need for patient rather than animal-based research.

(B) Problems encountered and steps taken to overcome them

Analysis of the patients involved in the NMJ study was very labour intensive. Not all samples collected successfully had NMJs within, meaning that a large number of patients (approx. n=60) had to be recruited to get a final study n of 30. The cachectic patients recruited into this study represented the more extreme end of the diagnostic definition criteria, having both weight loss and low CT muscularity. They were found to have a significantly reduced mean muscle fibre diameter consistent with previous studies. However, our study only enrolled patients who were eligible for surgery with potential curative intent. It is not possible, therefore, to draw conclusions concerning a possible late disruption of the NMJ in palliative cancer patients with refractory cachexia and severe functional impairment. Longitudinal characterisation studies with serial muscle biopsies would be required to answer this question. Moreover, whilst rectus abdominis proved to be an excellent muscle for the current study, it remains possible that skeletal muscles with different functional and/or biochemical properties may respond differently in cachexia.

The adipose study confers similar limitations to other microarray studies, most notably in the small sample size (n=24). However, exploratory work of this nature is valuable as it provides testable hypotheses to be taken forward. Another problem incurred in this study was the availability of omental and perinephric adipose tissue in the cancer and control groups, respectively. There was difficulty in accessing omental fat from the control patients so instead we had to sample perinephric fat. Differences in these two depots are not well defined. In rodents, there are possible depot specific differences in innervation but this has not been documented in humans. A very small study in humans has suggested blood flow in omental fat may be higher than in perinephric fat though the difference was not significant. This may potentially the affect removal of lipolytic products and the rates of lipolysis.

The main problem in the metabolomics study was the numerous potential methods of data analysis that were required making the interpretation of results and drawing of

initial conclusions difficult. The study originally began using urine for analysis which did not yield any meaningful results due to difficulty interpreting the data. We then decided to investigate plasma samples which yielded more meaningful information. It is hoped that the data from this will aid with the analysis from the urine samples.

(C) Collaborations established

Throughout this project we have made new links with Hull York Medical school and the University of Sydney (screening tools work) and strengthened links with our collaborators in the anatomy department at the University of Edinburgh (NMJ study), and with the Universities of Strathclyde (metabolomics) and Stirling (fat transcriptomics). This work will inform future grant applications with the University of Stirling for basic biological studies on active signalling processes in adipocytes in response to a pro-cachectic environment. These future applications will examine the response of adipocytes and myocytes to co-culture with tumour, or culture in tumour-conditioned medium. Information from the proposed study and our previous studies of cachectic muscle will inform on specific signalling pathways to examine. Work will also be continued with the anatomy department investigating proteomics in muscle biopsies of patients with cancer cachexia.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

This project has formed part of an MD which will be submitted towards the end of the year. Further funding was obtained for the MD from Cancer Research UK and small pump priming grants from the college.

Publications:

Boehm I, Miller J, Wishart TM, Wigmore SJ, Jones RA, Skipworth RJE Gillingwater TH. Neuromuscular junctions are stable in rectus abdominis in patients with cancer cachexia. JCI 2019: IN PRESS

Miller J, Skipworth RJE. Novel molecular targets of muscle wasting in cancer patients. Curr Opin Clin Nutr Metab Care 2019; 22(3):196-204

Miller J, Laird BJA, Skipworth RJE. The immunological regulation of cancer cachexia and its therapeutic implications. JCMT 2019;5:68

Miller J, Alshehri A, Ramage MI, Stephens NA, Mullen AB, Boyd M, Ross JA, Wigmore SJ, Skipworth RJE. Plasma Metabolomics identifies lipid and amino acid markers of weight loss in patients with upper gastrointestinal cancer. Cancers 2019;11:1594

MacDonald AJ, Miller J, Ramage MI, Greig C, Stephens NA, Jacobi C, Preston T, Fearon KCH, Skipworth RJE. Cross sectional imaging of truncal and quadriceps muscles relates to different functional outcomes in cancer. Clinical Nutrition 2019;38:2875-2880

Husi H, Fernandes M, Skipworth RJE, Miller J, Cronshaw AD, Fearon KCH, Ross JAR Identification of urinary diagnostic upper gastrointestinal cancer tissue-type specific biological markers. Biomedical Reports 2019;10:165-174

Miller J, Wells L, Nwurulu U, Currow DC, Johnson MJ, Skipworth RJE. Validated screening tools for the assessment of Cachexia, Sarcopenia and Malnutrition: A systematic review. American Journal of Clinical Nutrition 2018;108:1196–1208

Husi H, MacDonald A, Skipworth RJE, Miller J, Cronshaw A, Greig C, Fearon KCH, Ross JAR. Proteomic identification of potential markers of myosteatosis in human urine. Biomedical reports. 2018;8:547-566

Husi H, MacDonald A, Skipworth RJE, Miller J, Cronshaw A, Greig C, Fearon KCH, Ross JAR. Urinary diagnostic proteomic markers for dynapenia in cancer patients. Biomedical reports. 2018;8:557-564

Published abstracts:

Boehm I, Miller J, Wishart TM, Wigmore SJ, Jones RA, Skipworth RJE, Gillingwater TH. Stability of the neuromuscular junction in cancer cachexia. Clin Nutr 2019; 38(1):s306

Miller J, Ramage MI, Wigmore SJ, Skipworth RJE. Age and Sex related variations in body composition during neoadjuvant chemotherapy for oesophageal cancer. Clin Nutr 2019; 38(1):s303

Miller J, Ramage MI, Wigmore SJ, Ross JA, Gallagher IJ, Skipworth RJE. Adipose depot specific mRNA transcriptomics in cancer cachexia. Journal of Cachexia, Sarcopenia and Muscle. 2018; 9(6):1151

Miller J, Alsheri A, Stephens NA, Ramage MI, Wigmore SJ, Ross JA, Watson DG, Skipworth RJE. Plasma metabolomics in oesophago-gastric cancer: A pilot study. Journal of Cachexia, Sarcopenia and Muscle. 2018; 9(6):1161

Miller J, Ramage MI, Wigmore SJ, Ross JA, Gallagher IJ, Skipworth RJE. Adipose depot gene expression in oesophago-gastric cancer. British Journal of Surgery 2018; 105(s6):37

Miller J, Ramage MI, Schuepbach E, Roubenof R, Deans DAC, Wigmore SJ, Ross JA, Jacobi C, Skipworth RJE. CT derived measures of muscle mass in upper gastrointestinal cancer patients: Prevalence and relationship with quality of life and muscle function. British Journal of Surgery 2018; 105(s6):26

Miller J, Alsheri A, Stephens NA, Ramage MI, Wigmore SJ, Ross JA, Watson DG, Skipworth RJE. Plasma metabolomic analysis of weight loss in upper gastrointestinal cancer patients undergoing surgical resection. British Journal of Surgery 2018; 105(s6):37

Presentations:

Miller J, Ramage MI, Wigmore SJ, Ross JA, Gallagher IJ, Skipworth RJE Adipose depot specific mRNA transcriptomics in cancer cachexia: 11th International conference on cachexia, sarcopenia and muscle wasting. Maastricht, December 7th-9th 2018

Miller J, Ramage MI, Wigmore SJ, Ross JA, Gallagher IJ, Skipworth RJE. Adipose depot gene expression in oesophago-gastric cancer. 4th Cancer Cachexia Conference. Philadelphia, September 14th-16th 2018

Prizes:

Professor Fearon Memorial Medal. Edinburgh School of Surgery 2019

MacLeod Medal. Edinburgh School of Surgery 2019

(E) Acknowledgements

I would like to acknowledge the general, vascular and transplant departments at the Royal Infirmary of Edinburgh for their assistance in tissue collection, James Black and Gillian Dreczkowski for their assistance with plasma ELISA's, Dr Iain Gallagher for his assistance with bioinformatics analysis and Professor Gillingwater, Dr Jones and Miss Boehm for their collaboration with the NMJ study.

Particular thanks also has to go to my supervisors: Mr Richard Skipworth and Professor Stephen Wigmore, without their expert help and guidance this work would not have been possible.

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Ethicon Travel Grant Report

John Collin FRCSEd (OMFS)

Specialist Trainee in Oral and Maxillofacial Surgery, Severn Deanery

Head and Neck Oncologic and Microvascular Reconstructive Fellowship, University of Florida, Jacksonville

July 2019 - June 2020

Early in my specialist training I knew that I wished to sub-specialise in head and neck oncology and reconstruction. I therefore researched which centres might offer the best fellowships world-wide. Whilst there are excellent Head and Neck fellowships in the UK, I was keen to experience healthcare and surgery in another country. I was fortunate to be awarded the University of Florida Fellowship via the US Maxillofacial Oncology and Reconstructive Surgery matching scheme, after having visited the department to meet with the Fellowship Director, Dr. Rui Fernandes and the Head of Department, Dr. Tirbod Fattahi. The process of obtaining visas, a medical licence, accommodation and transport was difficult and expensive, so the award of an Ethicon Foundation Travel Grant was very gratefully received.

On arrival in Jacksonville, I was immediately made to feel most welcome by the entire department. I was very impressed by the common sense of purpose, organisation and work ethic that made the team highly regarded within the hospital. The academic ambition of the Faculty and the teaching program for Residents across the full remit of OMFS was excellent, with frequent visits from highly regarded international speakers. The range of head and neck surgery that I performed with Dr. Fernandes and Assistant Professor, Dr. Anthony Bunnell was far broader than that seen in most OMFS units.

The majority of patients presented for resection and reconstruction of oral cavity, pharyngeal and laryngeal tumors (Figures 3&4). Thyroid, parathyroid, salivary gland and skin malignancy surgery made up a large proportion of the remainder. In addition, the OMFS service provided surgical airway and cranial/cervical spine access for the hospital as well as soft tissue reconstruction for limb trauma. In terms of volume, typically 3-3.5 days per week were spent in the operating room, and it was not uncommon for there to be 3 or 4 ORs running simultaneously on these days.

I received excellent technical training in head and neck reconstruction using a variety of local, regional and free flaps. Attention to detail, ensuring minimal blood loss and efficiency of operating was emphasised. Experience with procedures at the periphery of the traditional OMFS remit, such as laryngectomy, facial reanimation, skull base and occuloplastic surgery afforded a more holistic approach to the management of head and neck patients. Most major reconstructive surgery was planned virtually to produce custom guides and implants. Where possible, minimal access and transoral approaches were employed and immediate placement of endosseous dental implants undertaken.

Due to the reputation of Dr. Fernandes and the Head and Neck Oncology team at the UF Proton Institute, patients would often travel from out of state and occasionally internationally for treatment. This meant exposure to unusual pathology. Many patients presented late with advanced disease due to lack of insurance coverage and some because they had received inappropriate treatment elsewhere or had spent time ‘shopping around’ various institutions. High levels of gun ownership also meant that facial gunshot wounds were commonplace. Around one third of American adults are obese and this is associated with a number of health risks particularly in the peri-operative setting. Morbidly obese patients presented a challenge for surgical procedures that would otherwise be straightforward (Figure 5). The culture of US healthcare is even more disparate than I had anticipated, and a lot of time was spent on defensive practice and billing activities. Having to see patients develop inoperable tumors due to lack of insurance and even those with insurance having significant delays and queries over funding has given me a renewed appreciation of the National Health Service.

This fellowship has given me invaluable experience in the management of head and neck oncology patients. I now feel competent in a wide range of reconstructive procedures, and my surgical technique has improved greatly both in terms of precision and expediency. I am sure my future patients in the UK will benefit from this.

I am very grateful to Dr. Fernandes and his colleagues for allowing me to care for and operate on their patients and for providing excellent training in both surgical and non-surgical skills. The Faculty’s support of international fellows at UF Health is to be commended in the face of increasing difficulties in securing visas and medical licensure. I also wish to thank my trainers in the UK, Dr. Ceri Hughes and Prof. Steven Thomas for their mentorship and encouragement with pursuing an international fellowship. Most importantly, I would not have been able to undertake this fellowship without the support of my wife who agreed to take time out from her career, travel with me and give birth to an American baby (Figure 7); fortunately our employee health insurance covered the $26 000 bill for a routine delivery.

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Travelling Fellowship Reports

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Shriners Hospitals for Children™

The Cutner Travelling Fellowship in Orthopaedics

Mr Z Choudhury BA(Hons) FRCS(Ed)(Tr&Orth) DipSEM

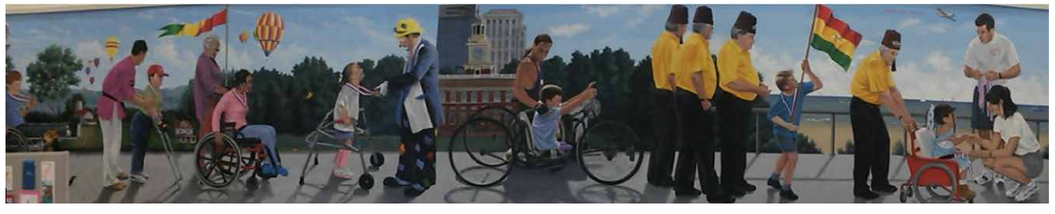
It is my privilege to write this report to reflect on my journey to Philadelphia. I shall forever remain indebted for the opportunity to visit Shriners Philadelphia to learn about the technique of anterior vertebral body tethering (AVBT) of the spine in scoliosis from true experts in the field.

Philadelphia is one of America's most historic cities, yet combines its history with a forward looking medical community, involved in innovation and state of the art technologies. The University of Pennsylvania, Childrens Hospital of Philadelphia (CHOP) and Shriners are all within a short distance of each other and mean that Philadelphia is a hub of spinal knowledge, advancement of techniques, and expertise.

The Shriners are a Masonic body based in the USA. Shriners hospital network extends across the USA, Canada and Mexico. Twenty two non-profit centres provide care for children in Orthopaedics, Burns and Plastics and Facial conditions. For almost 100 years care has been provided on a purely philanthropic basis, irrespective of the financial situation of their patients. Funds are raised from the charitable efforts of members and personal donations, both financial and of time. Examples include driving children hundreds of miles so they can attend appointments.

The Philadelphia Shriners was officially dedicated in June 1926. The centre has a strong history in spine care, establishing the United States' first paediatric spinal cord injury rehabilitation program in 1980. Philadelphia Shriners Hospital is now a 49-bed paediatric specialty hospital and teaching centre, with a joint Research centre with Temple Medical School. The ethos underlying treatment of children is family-centred care, providing resources and programmes designed to assist the whole family during a child's treatment.

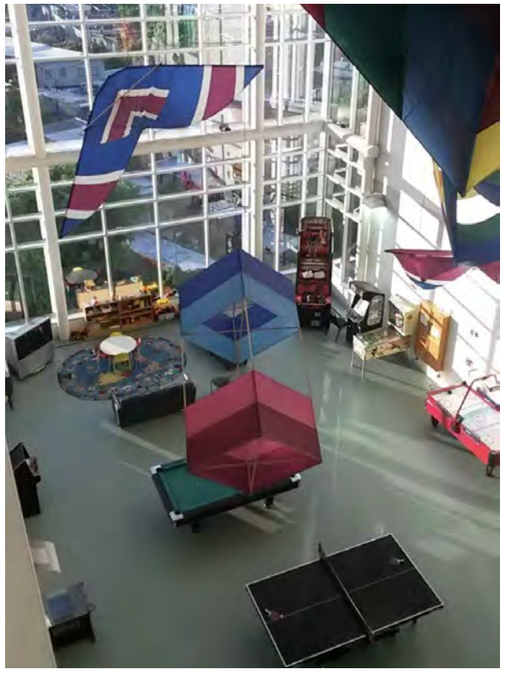
An enormous mural in the entrance lobby shows the community, fundraising, entertaining, support and rehabilitation work undertaken by the Shriners themselves to support the clinical work in the hospital.



The Surgical Team at Shriners (image from Shriners Website)

Planning and arrangements were made very easy by Dr Josh Pahys and very ably assisted by Sharon Mobley. I made contact a few months ahead and we discussed what I wanted to get out of the visit, with the hope that surgical schedules could be adjusted so I could see as many cases as possible.

On my first day I was struck by the size of the hospital and facilities available, including a rooftop outside play area, a "play town" with shops sized for children and state of the art facilities (more later on this).



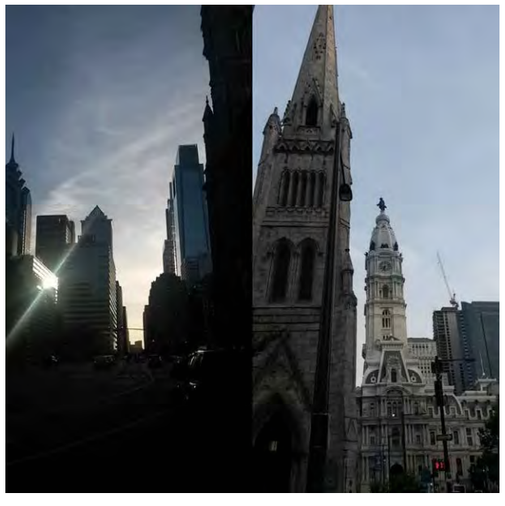
The vast atrium play area, with games machines, televisions and the freedom of space to allow children being treated for chronic conditions to "be normal"

We went to theatre where I was surprised to learn I was already registered; unlike some places I have been formally employed!

Dr Pahys and Hwang had cases on, and I was able to switch between their theatres. They had a broad range of cases, and most interesting for me was that Drs Hwang and Samdani are neurosurgically qualified. From a UK perspective Scoliosis has remained the preserve of Orthopaedic surgeons based historically on associated conditions and the centres where they are based. I observed a definitive fusion of a growing system and a cord de-tethering.

An added bonus was the opportunity to observe the use of intraoperative navigation using the O-arm (Medtronic). In the early evening we discussed cases, and the indications of AVBT. We discussed the concept and development of AVBT from the early work at Shriners undertaken by Dr Randal Betz.

Josh Pahys very kindly went out of his way to drop me back into town, which gave me enough time to have a quick walk about town.



Early evening Philadelphia- Old Colonial history and the foundation of America intertwine with towering skyscrapers.

The next two weeks went very quickly with a mix of theatre and clinics, allowing me an insight into almost every aspect of the practice. I was able to observe freely and ask questions in a totally open manner. It is probably easiest for the reader if I divide the activity into clinic and theatre rather than a day-by-day diary.

Clinic

Given the basic philosophy of treatment being supported even if families are unable to afford it, the clinics are busy. Given the expertise of the spinal team at Shriners they have a wide range of patients, both in terms of complexity, and geographical distribution. There were patients from nearly every corner of the US, and an international reach as far as Australia.

One thing I was not accustomed to was the ability of US patients to freely "opinion shop"- taking different opinions from services across the States. Whilst we have secondary or tertiary opinions these are usually at the request of the hospital, rather than the patient seeing "what the guy down the road has to say". It was evident that some parents would travel almost literally to the ends of the earth to get what they perceived as the best for their child, thinking nothing of flying several hours just for a clinic visit.
In keeping with the concept of treating the family as a whole I was able to see the social work team in action, dealing with some extraordinarily complex social cases.

As a result there were patients who already had opinions from some very well respected figures in the spine world. Furthermore, there was a concentration of incredibly complex cases, such as a patient with upper limb phocomelia and lower limb length inequality.

We extensively discussed the tether concept and indications, and it was very interesting to see follow up patients. There is a heavy social media awareness of AVBT, with UK patients also self-funding to attend centres in the US, Germany and Turkey.

The complexities of the regulatory process mean that AVBT practice at Shriners and across the US is limited. At the current time the technique and application of instrumentation does not have formal FDA approval and hence is carried out in specific centres with very specific restrictions, and out of respect for this I will not discuss too much in depth regarding the technical aspects.

I found the team to be down to earth, open and honest with their patients about the expectations of AVBT and their experience. The indications of the technique are very well thought out and based on follow up of the 500+ cases undertaken so far. Interestingly in cases where short fusion would be more appropriate this was recommended in preference. Social media opinion would have some children believe that fusion is anathema. The mismatch of patient perception and the team's experience was well handled in a very thoughtful manner.

We also discussed the mission activities of the team, Dr Hwang in particular, as he planned his next mission. The Shriners concept of philanthropy allows surgeons the latitude to provide voluntary aid in overseas territories, doing mission work in deprived areas in the Caribbean without ready access to complex spine services otherwise. Whilst this is not always funded by the hospital per se it is very much supported in terms of facilitating time off.

The mission concept also allows for patients from other countries to be brought in, assisting with travel, documentation and immigration issues- as long as children are able to get to Shriners they can be treated.

Theatre

The theatre complex was well staffed and mirrored UK practice to a large degree. The exceptions came in terms of technical expertise of staff - for example the Physician's Assistant and upskilled anaesthetic nursing staff meant there was less demand for medically qualified personnel in roles which we would traditionally see occupied by junior doctors. This meant that many members of the team had been in post for a long period of time, adding to efficiency.

My overall impression was that staff at all levels were generally more appreciated, with practices as simple as providing lunch for the entire team, right up to a range of very comprehensive personal development courses.

The theatres were well equipped, with the intra-operative "O-arm" CT system (Medtronic, USA) and advanced imaging. As a well drilled team the theatre ran well, with much more anticipation of various steps in the procedure.

I observed a broad range of cases, but the main purpose of my visit was to see the AVBT technique. This was a more taxing than usual case carried out by Dr Samdani in conjunction with Professor Grewal, a paediatric surgeon from St. Christopher's Hospital who has particular expertise in minimally invasive surgery. Like the rest of the team Professor Grewal was welcoming, knowledgeable and more than happy for me to pick his brains. For reasons already outlined I will omit specific technical details. We covered the operative aspects of AVBT, and it was impressive to watch Drs Samdani and Grewal in action.

Between cases we continued wide ranging chats. One of the features particular to US practice as opposed to ours is the underlying financial backdrop. The passing of the Sunshine Act now mandates open financial disclosure of payments, company holdings and other interests between companies and medical practitioners and has led to tightening of industry compliance, with websites such as "dollars for docs" outlining all physician payments, with some quite frankly staggering results.

I learned about numerous other aspects of scoliosis treatment, including a futuristic gait lab, with motion capture and green screen technology to make the experience fun for children. I was also able to see the use of freestanding halo traction mounted to frames and wheelchairs custom made and modified to allow children to be free of the dreaded traction bed.

Often when one visits a unit it is easy to feel like just an observer, but I always felt as though we were having our discussions as colleagues.

One feature underlining the dedication of the team was the 6am teaching and research meeting and case conference which was surprisingly well attended and, even more surprisingly, highly interactive!

6am Meeting

Philadelphia

During down times I visited the historic centre of the City, with the iconic liberty bell and the Independence hall, seat of the American constitution.

Reading Terminal market and the Liberty Bell

With a natural lull one morning I was able take a quick tour of the town, which is compact enough to walk much of relatively easily. Benjamin Franklin Parkway houses many of the City's cultural treasures. I visited the Rodin museum, The Barnes Foundation, with its 25 billion dollar art collection, and the Art Museum. Somewhat ironically the art museum is best known for the "Rocky steps", famous for the scene in which Stallone finishes his training run in the eponymous film.

The Philadelphia Museum of Art. Luckily I was able to fight the temptation to run up the stairs.

My final evening in Philadelphia I was treated to dinner- where we discussed terrible allergies, travel plans and international meetings and the utility of having a Physicians Assistant in the American system. Several surgeons had the same PA for decades and they had become well versed with techniques, working up to the level of junior resident.

L to R Drs Hwang, myself, Akshota and Pahys

I should like to thank the team at Shriners for their warm welcome and impeccable hospitality, in particular Drs Samdani, Pahys and Hwang for their generosity in hosting me and affording me so much of their time to pick their brains about almost every aspect of their practice.

I would also like to thank the Spinal team at RHSC, Edinburgh for their inspiration in planning this visit and support in the application for the award and organising the visit.

Finally, I would like to thank my wife and family without whose support and patience I would not be allowed to disappear for weeks at a time to learn about new techniques.

Epilogue

I have now started my Consultant post at James Cook University Hospital, Middlesbrough and am in the process of setting out a business plan for the AVBT technique, along with liaising with thoracic surgery colleagues. In time it is my hope that pending NICE approval we will be well placed to start offering the procedure.

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The Cutner Travelling Fellowship in Orthopaedics

Simon Matthew Graham – Orthopaedic and Trauma Research Fellowship

Groote Schuur and Tygerberg Hospital, Cape Town, South Africa

August 2017 – March 2019

Royal College of Surgeons Fellowship Grant

Supervisors – Professor S Maqungo and M Laubscher

Introduction

I spent 21 months working in Cape Town, South Africa as an Orthopaedic Trauma Fellow and the Principal Investigator for the HOST Study – HIV in Orthopaedic Skeletal Trauma Study.

Clinical work

My clinical duties are summarised in table 1. I spent the majority of my time split between theatre, clinic and leading my research study. For my clinic duties I focused on limb reconstruction and major trauma. I led trauma meeting, ward rounds and daily supervision of more junior surgeons and staff. I also had excellent supervision from Prof Maqungo and Dr Laubscher.
Surgery: The majority of my workload was limb reconstruction and trauma-based, commonly after road traffic accidents or interpersonal violence. Interpersonal violence is a huge burden in South Africa, and it was common to get one gunshot injury per day, if not more. For a variety of reasons, such as logistics, infrastructure, attitudes towards western medicine, these injuries were commonly delayed in presentation and fractures were commonly nonunions or malunions. I also managed a large number of osteomyletis and infections. Another large proportion of my operating consisted of deformity correction and amputations.

A challenge and anxiety shared for all surgeons who have worked or are thinking of working in a developing country is the risk of transmitting HIV. I undertook the standard precautions such as double gloving, eye protection, care when handling sharps and wore an apron under the theatre gowns since they were made of cloth. The hospital also had a strict post-exposure prophylaxis protocol for all health care professionals.

Teaching and education

As an honorary visiting lecturer at the University of Cape Town I had regular scheduled teaching session with the medical students from the local university. Also, I was also actively involved with the teaching and training of junior healthcare professionals within the hospital.

Research summary

- Principal investigator for the HIV in Orthopaedic Skeletal Trauma Study: Funded by the Wellcome Trust
- Co-investigator – Gun Related Injuries in Trauma Study - University of Cape Town, South Africa
- Co-investigator - World Hip Trauma Evaluation Cape Town, University of Oxford and Cape Town

Publications

- Davies P, Graham SM, Maqungo S, Harrison WJ. Total joint replacement in sub-Saharan Africa: a systematic review. Tropical Doctor. January 2019. DOI: 10.1177/0049475518822239
- Graham SM, Wijesekera MP, Laubscher M, Maqungo S, Held M, Ferreira N, Harrison WJ. Implant-related Sepsis in Lower Limb Fractures following Gunshot Injuries in the Civilian Population: A systematic review. December 2018. Injury. DOI: 10.1016/j.injury.2018.12.008
- Graham SM, Simpson AH, Lalloo D, Harrision WJ. HIV in Orthopaedic Skeletal Trauma (HOST) Study: protocol for a multicentre case-cohort study. South African Orthopaedic Journal. August 2018. DOI 10.17159/2309-8309/2018/v17n3a7
- Graham SM, Lubega N, Harrison WJ. Total knee replacement in a low-income country. Journal of Bone and Joint Surgery American. 2018:e0029. http://dx.doi.org/10.2106/JBJS.OA.17.00029
- Yeomans D, Graham SM, Perry D. None operative management of supracondylar fractures in children. A systematic review. Tropical Doctor. Accepted and in press March 2018

Photo 1. Research team

Photo 2. Theatre team

Photo 3. Family in Cape Town

Presentation

- Total Knee Arthroplasty in a Low-Income Country. Graham SM, Lubega N, Mkandawire N, Harrison WJ. South African Orthopaedic Association Annual Congress/ Pretoria, South Africa, September 2018
- Orthopaedic research in low-income countries: a bibliometric analysis of the current literature. Brennan C, Graham SM, Laubscher M, Maqungo S, Ferreira N, Harrison W.J. South African Orthopaedic Association Annual Congress. Pretoria, South Africa, September 2018
- Intramedullary nailing of tibial non-unions not previously treated with a nail using the suprapatellar approach. Botma N, Held M, Graham SM, Laubscher M. South African Orthopaedic Association Annual Congress. Pretoria, South Africa, September 2018
- The reuse of circular external fixator components: an assessment of safety and potential savings. Swanepoel S, Graham SM, Held M, Laubscher M. South African Orthopaedic Association Annual Congress. Pretoria, South Africa, September 2018
- The Malawi National Joint Registry: 10-year outcome. Graham SM, Lubega N, Mkandawire N, Harrison WJ. SICOT International Conference. Cape Town, South Africa, Nov 2017

Summary

This fellowship has given me experience in an enormous variety of pathology and clinical conditions that I will not encounter during my UK training. I gained significant exposure to adult and paediatric trauma, reconstruction and infection management, enabling me to further develop my surgical skills and competencies, benefiting both the local population in South Africa and NHS patients on my return. I have also developed the foundations in research that will allow me to endeavor to push toward my long-term goals of becoming a Professor of Orthopaedic Trauma Surgery. Living and working with people from different cultures and background also enabled my to develop non-surgical skills such as leaderships, communication and problem solving. I would like to sincerely thank the RCSEd for their support and I am eternally grateful.

Table 1. Clinical duties

Working Week	AM	PM
Monday	Theatre – Limb recon	Theatre – Limb recon
Tuesday	Ward round/ research	Research clinic – CURE Hospital
Wednesday	Fracture clinic	Fracture clinic
Thursday	Research clinic	Research clinic
Friday	Theatre - Trauma list	Postgraduate teaching

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The Cutner Travelling Fellowship in Orthopaedics

Sara Dorman

Paediatric Orthopaedic Fellowship at Children's Surgical Centre, Cambodia

My name is Sara Dorman and I am currently an ST7 in Trauma and Orthopaedics from Mersey Deanery. I have recently returned from a 6-month out of programme fellowship in Phnom Penh Cambodia. My role at CSC constituted clinical, teaching and research roles.

Clinical Work & Teaching

During my time at CSC I had the opportunity to learn valuable skills and treat complex pathologies rarely seen in the UK. The local surgeons have a vast experience in management of chronic infection, post-traumatic neglected and iatrogenic injuries. Despite being a low-income country what is unique about the CSC is the capability to perform complex and highly technical surgery, the skilled surgeons, scrub staff and the diligence of the ward nurses. Foreign teams from all over the world visit every couple of weeks to teach and perform a wide range of complex procedures including free flaps, free fibula grafts, huge facial tumours and reconstructions and femoral osseointegration to name only a few.

Within the field of paediatric orthopaedics however there is very little local experience. Common problems in childhood such as DDH, Perthes, bone or joint infections and complex congenital syndromes are often diagnosed late and treatment is often limited. In many of these cases only conservative management is offered leading to high rates of long term morbidity. Over the 6 months I focused my teaching efforts on building a sustainable "orthopaedic curriculum" focusing on basic science, clinical skills and paediatric orthopaedics.

Lecture and practical sessions were arranged to teach local staff in clinical screening for DDH, baby hip ultrasound, radiograph interpretation, principles of practical management for late presenting DDH and training in more advanced surgical procedures for paediatric surgeons including femoral and pelvic osteotomies. Digital resources were provided to the hospital to allow a rolling educational programme around the resident's rotations.

Other common paediatric problems such as limb length discrepancy, angular deformities, congenital foot problems such as clubfoot and congenital vertical talus, congenital pseudoarthrosis of the tibia (CPT) and cerebral palsy were also covered. In addition to pelvic and femoral osteotomies I was able to introduce a number of other new procedures to CSC including reverse Ponseti and open reduction for CVT, Paley X type procedure with periosteal grafting for CPT and alongside the plastic surgeons we built confidence in performing selective denervation's for the management of upper limb spasticity with excellent results!

Finally I was able to liaise with the paediatric department in Bristol and over the 6 months we ran a number of remote case conferences for discussion and collaboration on difficult cases – a resource that hopefully will be ongoing for the future.

Research

Despite having an abundance of trauma and high volumes of what is often considered in western training as "rare pathologies" with valuable clinical experience of interest, research and publications are not seen as a high priority in Cambodia. Many of the residents have never been taught any basic research skills and have no experience of how to conduct, analyse, present a high quality project or appreciate the impact of such projects on daily practice and quality improvement.

During my 6months at CSC as part of the " orthopaedic curriculum" I ran a research module which involved regular presentations in the morning meetings covering the basic principles of types of research, common methodology, practical tips and how to write a paper. This formed the groundwork for a research competition that ran over the 6 months encouraging local staff of any grade or subspecialty to submit a piece of original research or quality improvement project. The research was presented to the CSC staff and a winner was chosen (anaesthetic nurse Phektra) who was awarded $100 as first prize.

This competition promoted the merits of research and led to engagement of local trainees and permanent staff members. As a result a number of good quality research projects were completed and presented at a national conference including (1) a randomised trial of music during spinal anaesthesia on patient anxiety levels (2) The use of selective neurectomy for long term management of spasticity (3) Experience of the first 256 total hip arthroplasty's implanted in Cambodia (4) Opportunistic screening of DDH in infants presenting with skeletal abnormalities, cleft lip or palate (5) A 10 year experience of outcomes in congenital pseudoarthrosis of the tibia. The prize was ultimately won by

a dedicated nurse anaesthetist for her work on perioperative care and clinical airway and spinal screening to reduced perioperative complications.

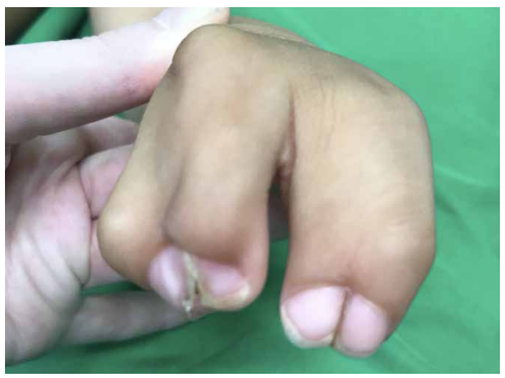
This experience has been both life and career changing, and I am extremely grateful to the RCSEd for their assistance without which it would have been extremely challenging. I would thoroughly encourage anyone considering overseas work to jump at the chance – its easy to find reasons why it is not the right time but I guarantee it will be the best decision you make. If I didn't have to return for CCT I might have stayed forever!

Morning Tuktuk ride to work

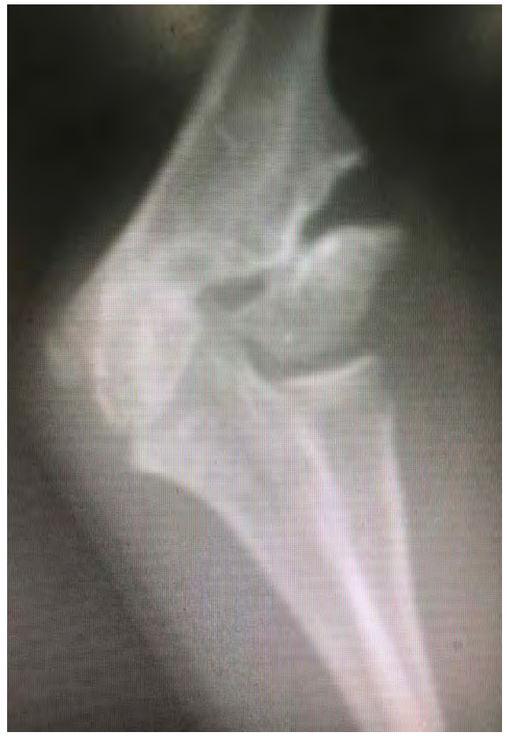
Outpatient clinic area

Table 1 in a three table barn style theatre

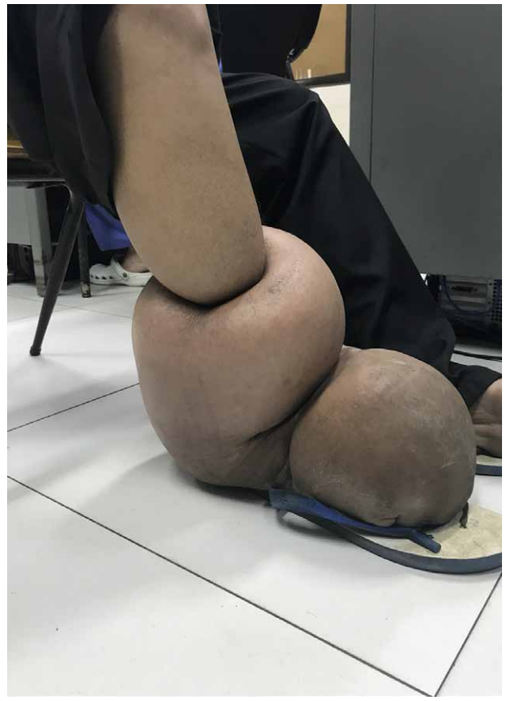
Hospital staff outside front entrance CSC



Complex congenital syndactyl



Neglected Trauma: Lateral condyle non union in a child



Untreated amniotic band in a teenager

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The John Steyn Travelling Fellowship In Urology

James F. Donaldson

International Fellowship in Complex Upper Tract Surgery, 2018.

Department of Urology, Princess Alexandra Hospital, Brisbane

Primary Supervisors: Dr Simon Wood & Dr Malcolm Lawson

I chose the International Fellow role at the Princess Alexandra Hospital, Brisbane to further my knowledge, skills and experience in complex upper tract surgery. The unit has an international reputation of delivering high standard fellowship training for the past 20 years. The unit is Queensland's quaternary referral centre for complex renal surgery including IVC thrombus and retroperitoneal lymph node dissection. The unit is also Queensland's renal transplant centre, including laparosopic donor nephrectomy and bench partial nephrectomy with auto-transplantation. Finally, Queensland has a tropical climate and so the unit treats a high volume of urinary stone disease.

My primary objective was to further my complex open surgical skills and my confidence in laparoscopic dissection and control of larger vessels. In addition, I also wished to build on my experience of obtaining access for percutaneous endo-urological surgery. Lastly, I wanted to improve my general urology experience in preparation for becoming the on-call Consultant.

I was exposed to a wide range of surgical techniques and approaches which were new to me; from access (placement of open incision or laparoscopic ports) to dissection and haemostasis techniques (including the great vessels and vascular suturing). I also gained valuable experience in renal transplantation including retrievals (bilateral open nephrectomy) and implant surgery (including uretero-neocystostomy and vascular suturing).

With a tropical climate and therefore a high incidence of urinary stones, I also undertook percutaneous stone surgery and learnt a new approach for obtaining access. I gained experience in a broad range of emergency urology including renal trauma and primary ureteroscopy. I also had access to simulation during my fellowship including for percutaneous access, laparoscopy and open partial nephrectomy; which helped me to consolidate new techniques quickly.

I participated in complex case discussions at uro-oncology multi-disciplinary team (MDT) meetings and learnt how stereotactic radiotherapy can be utilised for renal cancer; which shows promising results for primary and metastatic lesions not suitable for surgical excision. I also greatly increased my experience of treating urological conditions in patients with a renal transplant or renal failure, including regular Urology-Nephrology-Transplant MDT meetings.

I experienced working in a different health-care system and its systems for organising and treating patients: from triaging referrals, seeing outpatient and emergency referrals to treating conditions. For example, I gained experience of the effective use of oral dissolution therapy (chemolitholysis), avoiding the need for surgery in many patients with uric acid stones. Finally, I experienced living and working in a different culture and climate and was able to see some beautiful parts of Australia.

This fellowship experience has greatly increased my confidence and has taught me different approaches with which to tackle complex operations and management decisions. It has also aided the important transition between being a trainee to becoming a consultant.

My fellowship will benefit my patients in the UK throughout my consultant career as I now have a deeper and broader experience of surgical techniques, patient management approaches and healthcare organisation. For example, during laparoscopic nephrectomy, a transverse abdominis plane (TAP) local anaesthetic block combined with a Pfannanstiel extraction incision gives patients less pain, a shorter hospital-stay and faster recovery as well as lower hernia rates.

I also have the benefit of a more mature and broader view of how to deliver a Urology service which will help me to introduce service improvements throughout my career as a consultant urological surgeon in the NHS. This will be critical as the pace of change in healthcare and technology continues to increase. I am extremely grateful to the support I received to undertake this Fellowship from the Royal College of Surgeons of Edinburgh thanks to the generosity of the John Steyn family.

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Alban Barros D'sa Memorial Travelling Fellowship In General Surgery

Alexander D. M. Leeper MBChB MD MRCS ST7 General Surgery, Western General Hospital, Edinburgh

Practicing General Surgery in an austere environment and participating in development of a sustainable surgical service at Gahini Hospital, Rwanda

Volunteering as a General Surgeon in Rural Rwanda

In August 2018, with the help of the Barros D'Sa travel grant, I travelled to the Eastern Province of Rwanda to work in a voluntary capacity as a general surgeon for six months.

Years previously, a four-month student elective in the Solomon Islands had provided me with some insight into healthcare in developing countries. At the same time, I had felt frustration at my lack of practical skills to deliver meaningful interventions to the local population. I resolved to return to a rudimentary environment at a time in my career when I could be more helpful.

Whilst working in Fife, I had the good fortune to be trained by Stephen Bennett, who had experience working in a voluntary capacity in Africa. As a Registrar and latterly as a Consultant he had dedicated considerable time and resources to working in and developing a missionary hospital in Kiwoko, Uganda. Whilst working for him, Steve told me about his next project: a five-year commitment to Rwanda where he would develop the surgical unit of a rural hospital, alongside his wife Catriona (a consultant anaesthetist) and young daughter.

In 2017, Mr Bennett relocated from NHS Fife to Gahini Hospital. This government-run 200 bed hospital has functional medical, paediatric, maternity and rehabilitation wards and covers a population of roughly 300,000. It is staffed by 10 doctors, trained in Rwanda or neighbouring countries. However, retirement and loss of their surgeons two years previously had meant that the hospital no longer had a surgical service. Within 6 months of arrival, Mr Bennett had developed a staffed, clean and safe operating complex with a functional anaesthetic machine, autoclave and recovery area. His wife Catriona took the role as the department's lead anaesthetist and set to work training local anaesthetic technicians to provide safe and effective regional and general anaesthesia for children and adults. The Outpatient department now provided a regular surgical clinic and the 25-bed surgical ward was staffed by nurses competent in managing surgical cases. As part of the strategy for development of the surgical unit, Steve was keen for able trainees to visit him.

The brief was both exciting and daunting. The workload would consist of a diverse and unselected cohort of emergency and elective surgical patients. Operating would provide the bulk of the work commitment, alongside ward management of surgical patients and providing a weekly Outpatient clinic. Furthermore, in order to encourage sustainability of a surgical service, we would provide motivated resident generalist doctors an opportunity to learn surgical and clinical skills to set them on the path towards surgical specialism.

There were plenty of good reasons not to commit. Moving our young family out of school to a remote part of central Africa without the security of a monthly pay-cheque and the subsequent delay to obtaining my CCT were all considerations. However, the more we talked it over, the greater the enthusiasm for an adventure built and the anxiety diminished. The Deanery, kids' school and Programme Director took a supportive view and within a few months the flights were booked, jabs administered, and bags packed. We were committed.

I arrived a few weeks before Olivia and the three children joined. The capital city Kigali is extraordinary in its infrastructure and cleanliness, it is quite different from any African city I have previously visited. Driving East to Gahini, the neatly maintained urban sprawl soon gave way to terraced paddy fields and startlingly green banana plantations studding the ubiquitous rolling hillside. The recently constructed arterial roads that cross the country are quiet: the government has restricted car buying for the general population with punitive import taxes. The majority travel by bicycle, often carrying their family perched precariously on the frame or outsized goods strapped to the rear wheel. Nearing Gahini, we left the tarmac and joined the hot, red dirt road that climbed the hill to the hospital.

Gahini village, perched on a hillside overlooking the snake-thin Lake Muhazi, is small but provides a representative example of day-to-day living for the 85% of the population living in non-urban Rwanda. The equatorial climate provides sunshine and rain in equal measures most days. Life is effectively pre-industrial, with the family and village units focussed on working the land to provide subsistence living. Earning a wage is essential for purchasing health insurance, school fees and mobile phone data, but beyond this the basic ingredients for survival are obtained from the effective management of the surrounding countryside. This is important as the majority of the population are of school age and therefore not wage earners. Furthermore the population has almost tripled since the unimaginable horrors of the Genocide against the Tutsis 25 years ago. So, whilst disposable income is very limited, destitution is only encountered rarely. The village elder has the power to redistribute land and livestock to ensure that all families have enough to live on. The gulf between rich and poor - so common in developed countries, was less in evidence and I believe enhanced the sense of community and happiness.

The hospital and diocese were kind enough to provide accommodation, which after some ingenious alterations by a talented plumber and electrician provided lodgings approaching western standards. Lake water was delivered by lorry to our water butt on a fortnightly basis and a relentlessly enthusiastic local lady helped keep the house in order with cooking and cleaning, minimising the sporadic infestations of ants and mosquitoes. Daily life was simple,

with household chores of making bread, hand washing clothes and sterilising water taking up a fair proportion of our family's time. A plant based diet provided most of our nourishment. By the end I genuinely enjoyed eating rice and beans every day, the children less so.

The opportunity to practise as a general surgeon was second to none. On average we were performing 60-80 operations per month (with a visiting paediatric orthopod performing an additional 20). Thanks to Catriona's training, the expertise of the anaesthetic technicians increased allowing us to operate on children over the age of one. With Catriona present, emergency laparotomies on infants that would usually have been transported across the country were performed safely at Gahini.

The surgical remit was broad. This is best illustrated through a snapshot from my logbook:

For instance, in November we operated on 76 cases, a third of which were for patients under the age of 12. We performed 50 general surgery operations, the most common being excision of miscellaneous lesions (40%), inguinal hernia repair in adults (20%), paediatric herniotomy (10%), incision/drainage (10%), EUA rectum +/- sphincter repair (6%), thyroidectomy (6%) and laparotomy (4%). 7 urology cases were performed, most commonly for adult hydrocoele, but also urethroplasty and undescended testes. There were 16 orthopaedic cases: most commonly closed reduction of fractures, ORIF and amputation of accessory digits. The 3 gynaecology cases were for a ruptured ectopic, vaginal prolapse and a Bartholin's abscess.

The broad spectrum of our operative remit was quite different from the caseload I have experienced in the UK. However, the patients were usually fit with minimal co-morbidities, have a BMI in the low to normal range and motivated to mobilise at a very early stage. The majority of our general anaesthetic cases would be discharged within 24 hours. There was no local option for receiving care from specialist urologists or gynaecologists and therefore the responsibility for returning these patients back to their families lay with us. Passing the buck was not an option. These factors helped develop in me a sense of surgical competence, lateral thinking and a can-do approach. Being called for the first time to an ectopic ruptured at 13/40 weeks on a Friday evening as the only surgeon on site certainly elevated my heart rate. However, this was more than offset when I discharged her home to her beaming family the following Tuesday. In many respects the sense of having done something good in an effective manner is why I have always wanted to become a surgeon and was realised whilst in Rwanda.

I had had reservations regarding how Olivia, my wife and three children (aged 4, 6 and 8) would manage. However, with retrospect, I don't believe we could have found ourselves in a better destination. As a country, Rwanda feels extremely safe. Tourism remains a fledgling industry and our experience was to be seen as a source of curiosity as opposed to financial income. The initial reserve and proud expressions quickly melted away to huge grins and warm handshakes from all and sundry. Walking around the surrounding hills would invariably result in a few children hanging off arms and legs limpet-like or taking us by the hand and navigating us the correct way through a dense forest.

For the children, the days were spent in a fairly relaxed fashion, with a couple of hours spent reading, writing, doing sums or painting. We ended up with some brightly coloured frescos on our wall, depicting the myriad birdlife we saw, the solar system and a giant map of Africa. By the end, the 4-year-old was better at identifying the location of Benin and Mauritania than I was.

Afternoons were spent by Olivia and the children at the local local primary school helping with teaching or heading to the rehab ward and playing games and reading books with the children in long term beds. We also played a lot of Lego.

The Royal College of Physicians and Surgeons Glasgow has recently delivered a paper on Global Citizenship in the Scottish Health Service, which feeds into the Scottish Government's drive on the concept of Global Citizenship. One could argue we have a moral commitment to help developing countries, but it is important to recognise that there are also mutual learning opportunities available through volunteering. Working in developing countries can provide training benefits for the individual volunteering, but also for the developing healthcare system and indeed on return to work with the NHS, through the development of transferable skills.

A six-month period volunteering in Rwanda was personally extremely rewarding and I hope of some benefit to the individuals I treated. It certainly provided an opportunity for skill acquisition and self-belief which I have continued to draw on since my return. It was a very bonding experience to spend so much quality time and have so many memorable experiences with my family. Like most challenges, it was not easy but I wouldn't change it for the world.

I would not hesitate encouraging trainees and consultants with a sense of adventure embarking on such a worthwhile experience.

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Alban Barros D'sa Memorial Travelling Fellowship In General Surgery

Neena Randhawa

Travelling fellowship to the Intestinal Failure and Intestinal Transplant Unit, Colorectal Department and Abdominal wall reconstruction department at Cleveland Clinic, Ohio

6Th November – 21st November 2019

Introduction

I had planned my Cleveland Clinic visit after finishing my post-CCT fellowship in Inflammatory Bowel Disease and Intestinal Failure at Nottingham University Hospital and before starting my Consultant post at Royal Victoria Hospital, Newcastle upon Tyne. The Alban Barros D'Sa Memorial Travelling Fellowship has kindly awarded £1000 towards my fellowship at the Cleveland Clinic, Ohio.

Background

My interest in inflammatory bowel disease and intestinal failure started very early in my registrar training and I had the opportunity to get more exposure to this field during my final year in the training and then returned as a post-CCT fellow. Cleveland clinic has the world renounced intestinal failure and IBD services and with the grant offered, I had the opportunity to expand my knowledge in my chosen field. My aim was to learn new or novel ways of managing these complex patients and learn about how these services are run, which I could bring back to my own consultant practice. I am grateful to the Royal College of Surgeons of Edinburgh for this opportunity.

Visit

I flew from Heathrow to New York and from New York to Cleveland. A short taxi ride and I was at the airbnb place, which was less than 10 min walk to the Cleveland Clinic.

First day started with a welcome video from the international observership programme administrator followed by a walk around the hospital to get ID badge and white coats. Everyone wears a white coat but there is no concept of hair tied up, no jewellery and definitely no concept of bare below the elbows.

First week

Attached to Dr Michael Rosen's Hernia and complex abdominal wall reconstruction Team. Dr Rosen is internationally renowned for Tranversus abdominis muscle release (TAR) repair for incisional hernias. As part of my intestinal failure practice, I have had seen a few cases of TAR repair but it was a privilege to observe the expert in the field.

First list had two cases of TAR repair for large incisional hernias. It was an opportunity to observe the techniques and learn tips only learnt after performing a few hundred of these cases. Dr Rosen performs approximately 200 TAR repairs a month. He has a systematic approach to each case and takes great pleasure in training his residents and fellow colleagues. At any given time, there were two incisional or primary hernia lists and I had the flexibility to rotate to other theatres to observe. Dr Rosen uses a 50x50 synthetic mesh for most of his TAR cases and is not a great fan of biological meshes. Each patient gets a TAP block for analgesia followed by simple oral analgesia. He does not use drains and most patients are discharged day 2-3 post-operatively. One of the interesting cases was of a young man with a feeding jejunostomy, ileostomy and a large incisional hernia. It was interesting to observe the technique for TAR and mesh placement without compromising the stoma or the jejunostomy tube.

One whole day is dedicated to outpatients only and I had the opportunity to observe the referral pathways and assessment pathway for these complex cases. Most patients have travelled from far-flung areas of USA to come see Dr Rosen. Each patient presents with full complements of blood tests and up to date CT scan. Dr Rosen's secretary ensures all these investigations are performed before they are seen. This definitely appears to streamline the assessment in the clinic. He has very strict criteria for listing these patients for operating and as these patients have travelled so far they are often motivated to comply. The treatment available to these patients is limited by what is covered by the insurance company.

Second week

My consultant practice will predominantly be dedicated to inflammatory bowel disease and Cleveland Clinic has a large IBD practice covered by some renowned figures in the field. The current international fellow in the post happened to be a UK post-CCT trainee, which helped me to get a perspective on the differences in the practice.

Most days there will be at least 2 or 3 IBD theatre lists and it was good opportunity to rotate between theatres and pick interesting cases to observe. Each theatre list begins with a team huddle at 7:15 sharp with first patient ready by 7:30. Most IBD lists were laparoscopic or SILS and only one open case were for J-pouch formation because of difficult pelvis.

I spent two days in theatre with Colorectal lead at the Cleveland Clinic, Dr Scott Steele. Case mix involved subtotal colectomies for failed medical therapy in ulcerative colitis and ileo-colic resection for crohn's mass. I noticed that quite a lot of emphasis is placed on cosmesis and most laparoscopic cases are performed using 5mm ports. A very interesting practice I observed in theatres was the emphasis on training. Each trainee around the table has a dedicated task. Resident will usually take the medical student through catheterisation, who will then be the camera operator for the resident under the supervision of the junior attendee. This is all performed under the supervision of a senior consultant who at one time may be cross-covering two theatres.

The next day was a full day clinic with Dr Amy Lightner. She has won various prizes for her research in IBD and currently running a randomised controlled trial for stem cell therapy for Crohn's peri-anal fistulas and pouch vaginal fistulas. Each colorectal clinic room has a full endoscopy stack so if required patients are given an enema in the

clinic and will have a flexible sigmoidoscopy. There is no room for a rigid sigmoidoscopy. It was a very efficient system for a assessing new patients. There is an attached cleaning room to the clinic where the clinic nurses can access the washed scopes.

Most patients have come from other parts of USA to see Dr Lightner specifically for stem cell treatment. It was very refreshing to see most patients were very well informed about their conditions and consultations were carried out using medical terms unlike UK practice where emphasis is placed on using layman terms.

Every morning begins with a fellow or the residents conducting a ward round at 5:30 am with a medical student. I attended these rounds on two mornings. Residents will review each patient for their assigned team and review the charts and results and report to the consultant for deciding on a management plan. Everything is electronic but ward round notes are written later by the physicians assistants who are trained into using the terminology which correlates with the coding department. This initially felt like a very inefficient system where notes are not written after reviewing each patient but it is definitely a more financially feasible system. Most UK hospitals struggle with matching what is written in the medical notes to the coding terms to get the required tariffs.

Every Wednesday morning is the teaching morning for all departments. The morning begins with a grand round and followed by a teaching on a chosen topic by a fellow. All the residents, fellows and consultants, attend this teaching and I found it very useful. Every other Wednesday, this is followed by IBD MDT, which follows the same pattern to the ones in the UK.

Third week

As well as establishing my consultant practice in IBD, one area I have always found very intriguing is intestinal failure and aim to add that to my practice. This was the highlight of my observership to spend time with the intestinal failure and intestinal transplant team.

First day was on the ward round which started on the paediatric ward. Unlike other departments, transplant team ward rounds start at 8am after a board meeting in the office with the entire medical team.

Each ward round is led by a senior transplant fellow or a junior attendee along with an army of junior residents, physician's assistants, dieticians, pharmacists, occupational therapists, physiotherapists, nurses and paediatricians on the paediatric wards as well as the observers. It is truly a multi-disciplinary ward round and each member has an equal say in the management of patients. It was an excellent opportunity to discuss with a dietician about the challenges I have experienced in UK practice for managing in-patient and outpatient total parenteral nutrition patients.

An interesting case seen on the paediatric ward was a 9-year-old young boy who is currently on treatment for symptoms of rejection of his third multi-visceral transplant. This exceptionally bright boy has a very in depth understanding of his condition and would often be seen informing visitors to gown up and wash hands as he is

Dr Kareem Abu-Elmagd is the clinical lead and one the most humble human beings and a gifted surgeon.

immunosuppressed. He had designed a t-shirt, which were on sale to raise funds for the intestinal transplant charity.

The following day was in the theatre with Dr Osman, a senior fellow and Dr Kareem operating on an obese diabetic patient for restoration of intestinal continuity. This was a truly an exceptional experience to observe Dr Kareem perform small bowel lengthening procedure. Dr Kareem had recently published the outcome of last 500 cases of intestinal transplant and bowel lengthening procedure. It was an opportunity to watch the technique in person and discuss the merits.

The last day was a patient listed for enetrocutaneous fistula repair with short gut who has previously undergone 67 laparotomies as a complication of chronic pancreatitis. His most recent surgery was for abdominal wall flaps because with complication from each surgery, he had lost most of his abdominal wall. Unfortunately, the flap had also failed so currently he was awaiting enetrocutaenous fistula repair with bowel lengthening. After a thorough review it was decided not to perform bowel lengthening because patient had a severely cirrhotic liver and evidence of venous congestion in the bowel. The fistula was isolated and abdomen was closed with a view for adding the patient to the list for multi-visceral transplant.

Summary

This was an invaluable experience for someone transitioning from a fellow to a consultant post to observe international experts in my area of specialist interest. Dr Kareem and his team were the highlight of my visit. The entire department is very welcoming and work well as a team with no room for egos. Watching Dr Kareem interact with his team, secretary and patients gave me a role model for my consultant practice. I learnt a lot about managing complex intestinal failure patients. The time spent with colorectal team was invaluable for my practice in IBD. As part of intestinal failure, I have repaired complex incisional hernias so it was useful to observe Dr Rosen and discus management of the cases I have encountered.

Differences in two health systems

- Working day starts very early in the USA.
- Residents have very little autonomy for decision-making
- Theatre lists start very efficiently with no worry about bed crisis
- From large incisional hernia repairs to SILS colectomies, there is no concept of epidural for pain relief. Most patients get TAP blocks or a long acting local anaesthetic.
- Each scrub kit comes prepared with the named consultant's and his or her juniors' gowns and their required kit.
- Swabs have a QR code, which is used for the electronic swab count.
- All surgical teams use snap off needles.
- Clinics are covered by a dedicated nurse attached to that particular consultant who ensures all the investigations are requested and performed and prepares the pre-op checklist and maintains operative list diary.
- Colorectal clinics have an endoscopy stack in each room.
- Intestinal transplant team uses silk for bowel anastomoses.
- Intestinal transplant ward rounds are truly multi-disciplinary.
- One morning each week is kept for educational purposes with an emphasis on juniors teaching each other.

Once again, I am thankful to the Royal College of Surgeons of Edinburgh and the Alban Barros D'Sa Family for their generosity.

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Joint RCSEd / SOMS Shanghai Head & Neck Fellowship

Richard Taylor
Consultant Oral and Maxillofacial Surgeon, York Hospital, York
December 2018 - January 2019

Introduction

The Joint Royal College of Surgeons of Edinburgh and Scottish Oral and Maxillofacial Society Shanghai Head & Neck Traveling Fellowship offers an exciting opportunity to visit and learn at one of the busiest centres for head and neck oncological surgery in one of the largest cities in the world.

The 9th Peoples Hospital Shanghai, affiliated to the Jiao Tong University School of Medicine, is situated in Shanghai near the east bank of the Huangpu river, a few kilometres south and east from the popular bustling central Nanjing shopping area and from the traditional financial Bung area with its inspiring views of the iconic Lujiazui skyline.

Surgical Experience

On the day of arrival, upon attending the Oral and Maxillofacial Head and Neck Oncology Department, following introductions and completion of various documentation an outline of the Fellowship structure was given. The Fellowship quickly moved on with assignment to one of the main surgical teams, spending the majority of time in theatre.

The day to day activities undertaken progress during the Fellowship from observation, to assistance to undertaking surgeries.

As Head of the department, Prof. Chen Ping Zhang oversees the Fellowship programmes and leads the Oral and Maxillofacial Head and Neck Oncology Department in the 9th Peoples Hospital, Shanghai.

The head and neck oncology department is divided into numerous teams with each, in general, led by a professor, with an associate professor, numerous junior surgeons and trainees as well as research students and fellow in each team. While primarily assigned to one of the surgical teams during the Fellowship, there is opportunity to move between the teams to experience procedures of interest as best suited to maximise the experience and meet any educational objectives.

Major surgery is performed by all teams on most days including some Saturdays. The day usually starts at 7:30am with a group meeting of the surgeons and lead ward staff to discuss the days work and any other significant issues.

The overview of the days cases were presented in English and staff were able to help translate any detailed discussion with took place in Chinese. This meeting would be followed by a ward round before heading to the operating theatres.

Departmental multidisciplinary meetings would take place on Thursday afternoons focusing on difficult cases and those requiring interface with different specialties. There would also be various presentations on the Thursday afternoons and as part of the Fellowship, the visiting Fellow is expected to give a presentation on a subject of their choice. My chosen presentation was relating to some of my recent research works.

The research output and research opportunity in the Head and Neck Oncology department is impressive with a good level of clinical and pre-clinical scientific research activity. Most staff members are well published and continue to be academically active.

With numerous theatres active over several floors, operating was usually continued into the night on most days.

Where usually in the UK only a single major resection/reconstruction case is undertaken on any theatre list on any one day, there were often theatre lists where one or more “simple” cases would be undertaken in addition to a major resection with free tissue transfer reconstruction case. On occasion a list would comprise two different major resection cases back to back, both requiring free tissue transfer reconstruction. It would not be unusual for 3, 4 or even 5 free-flap cases to be running on the same day across multiple teams.

The Head and Neck Oncology Department undertakes the treatment of patients both locally and those referred from other units which may represent more challenging cases.

Most cases were planned directly by the responsible team without the input of any MDT. The general surgical technique for tumour resection, neck dissection and free tissue transfer reconstruction was of a high standard with strategies and approaches broadly like those used in the UK with some subtle differences. The efficient and effective use of hand tied silk for even the smallest vessels was standard practice

as was the use of hand threaded sutures. These techniques required a delicate touch and surgical precision that the Shanghai surgeons were clearly very effective in performing.

Radial, lateral thigh perforator and fibula designs were the commonest free-flaps, with pectoralis major flaps also in frequent use. Custom 3D-planned osseous free-flaps were undertaken and the occasional trans-oral anastomosis for fibula free-flap reconstruction of defects associated with benign disease were also performed. Mandibular cancer resections were at times reconstructed with soft-tissue only flaps on a case-by-case basis. In this situation any subsequent bony reconstruction was considered following initial patient outcomes and patient preferences.

The complication rate that I witnessed while in Shanghai was impressively low, and the return to theatre rate seemed considerably lower than I would have expected for such a high-volume unit. This was combined with impressive success rates for microvascular free tissue transfer. Although I was not aware of any major failures during my visit, I was advised the success rate was an impressive >98% over a total of 700+ cases per year.

Interestingly vein coupler devices were used most frequently (although not always) for venous anastomosis. Witnessing the routine use of vein couplers in high volume with such a low complication rate, I could see just how quick and effective these were in the hands of surgeons familiar with them. The hours of work for the surgeons (including trainees and Fellows) is considerably longer than would be allowed in Europe and the Fellowship demands a high number of hours most days. With trainees in Shanghai effectively sub-specialising to head and neck oncology at an early stage post-graduation, the technical surgical skills and experience in head and neck cancer surgery are developed early.

There is no doubt of the high level of skill and efficiency of the head and neck oncology resection and reconstruction surgery undertaken at Oral and Maxillofacial Head and Neck Oncology Department in the 9th Peoples Hospital. It is a testament to the hard work and long hours undertaken by the staff.

While any surgeon at any stage of their career from the UK (trainee to consultant) would be able to benefit from the Fellowship, it is clearly most suited to surgeons with some considerable experience of major head and neck oncology resection and reconstructive surgeries. The considerable volume and duration of surgeries results in an intense Fellowship most appropriate for surgeons who have already completed their FRCS exams and beyond.

Travel, accommodation

Arrangements for an academic visa via the Chinese Visa Centre were very efficient with the support and sponsorship of Prof. Chen Ping Zhang and the 9th Peoples Hospital. With direct flights and pre-booked transfers travel was very straight forward. Staying in a hotel 5 minutes walk from the hospital was within the Fellowship budget and due to the vigour of the Fellowship, is highly recommended.

Once in Shanghai, travel within the city is not a problem. Taxis are affordable, and the city metro network is intuitive. The national rail network is excellent, and the high-speed trains give access to most of Chinas various cities and sites of interest with only a few hours travel from Shanghai.

The faculty make you feel very welcome during the Fellowship and clearly go out of their way to ensure you feel welcome with their generous hospitality.

Summary

The Joint Royal College of Surgeons of Edinburgh and Scottish Oral and Maxillofacial Society Shanghai Head & Neck Traveling Fellowship is clearly a prestigious Fellowship and of significant importance to the 9th Peoples Hospital, the Royal College of Surgeon of Edinburgh and the Fellows themselves.

Best suited to surgeons who have completed their FRCS, visiting China and undertaking the Fellowship was a valuable and rewarding privilege and the continuation and extension of the Fellowship can only benefit all those involved, surgeons and patients alike. It was a very memorable experience, providing an excellent opportunity to develop both my knowledge and understanding of major head and neck oncological surgical skill.

Acknowledgments

I would like to thank and acknowledge the staff at the 9th Peoples Hospital Oral and Maxillofacial Head and Neck Oncology Department for inviting me to their unit for this amazing opportunity as well as the Royal College of Surgeons of Edinburgh and the Scottish Oral and Maxillofacial Society for supporting the Fellowship. Particular thanks are extended to Professor Zhang, Professor Chung, Professor Wang, Assoc. Professor Zhou, Assoc. Professor Wang and Dr Ong for their welcome, support, time and hospitality during my Fellowship.

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Ophthalmology Grant Reports

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Ophthalmology Grant Report

Development of a CRISPR gene therapy system for treating inherited retinal degenerations

Professor Robert E MacLaren

Nuffield Laboratory of Ophthalmology, University of Oxford

Major Opthalmology Grant

October 2017 - September 2018

Lay Summary

The retina is the light-sensitive layer that lines the back of the eye, and which allows us to see. Most incurable forms of blindness are due to genetic diseases which are caused by faulty genes in the DNA of the retinal cells. These faulty genes eventually lead to the dysfunction and death of the affected cells. Gene therapy is a technique which involves putting normal copies of the faulty gene back into the retinal cells to help them to function normally. Gene therapy uses special modified viruses called adeno-associated viral (AAV) vectors to carry normal genes into the retinal cells.

Another approach, known as gene editing, uses AAV vectors to carry special molecular tools into the retinal cells that can turn off or correct faulty genes. In this project, we are designing a modified AAV vector to switch off a faulty gene in mice that causes them to develop a type of retinitis pigmentosa and eventually go blind. Before proceeding to animal testing in the second half of this project, we have first carefully assessed and optimised this new technology in the laboratory, using a fluorescent protein as a way of measuring gene deactivation.

Grant Report

We remain extremely grateful to the Royal College of Surgeons of Edinburgh for its long-standing support, which has enabled us to pursue a highly successful translational research programme developing novel gene therapies for the treatment of previously incurable forms of blindness. This success led in 2014, through the support of the Wellcome Trust, to the establishment of Nightstar Therapeutics, a retinal gene therapy company spun out of our research programme at the University of Oxford. Utilising the AAV vector technology developed in previous College-funded research projects, Nightstar Therapeutics launched a first-in-man clinical trial of our gene therapy for X-linked retinitis pigmentosa at the Oxford Eye Hospital in 2017, followed by an international Phase 3 clinical trial of our gene therapy for choroideremia in 2018.

Most recently, in January 2019, the world's first clinical trial of a gene therapy for dry macular degeneration was launched at the Oxford Eye Hospital by Gyroscope Therapeutics, using an AAV vector that was developed in our laboratory. We have therefore demonstrated consistent success, not only in developing innovative treatments for hereditary retinal disorders, but also in building the long-term commercial partnerships needed to advance these exciting scientific breakthroughs into real treatments for patients.

Background to the current project

AAV-mediated gene therapy, in which AAV vectors are used to introduce normal copies of a defective gene into the affected cells, has great potential to treat many hereditary forms of blindness. However, one limitation of AAV-mediated gene therapy is the modest packaging capacity of the AAV capsid, which restricts the length of the encapsulated DNA fragment to 4.5 kilobases (kb). Hence, many hereditary retinal disorders cannot presently be treated with AAV-mediated gene therapy, as the coding sequences of the therapeutic genes of interest are too long to be accommodated within an AAV capsid.

A promising alternative approach to whole gene replacement is gene editing, in which therapeutic rescue is effected by repairing or silencing the defective genes in situ. The CRISPR (clustered regularly interspaced short palindromic repeats) pathway, a bacterial defence system that targets and cleaves specific viral DNA sequences using a Cas9 endonuclease, has recently been shown to have great potential as a gene editing tool in eukaryotic cells. The CRISPR system involves three key components:

- A guide RNA (gRNA) component, which is a specific RNA sequence that recognises the target DNA region of interest and directs the Cas9 endonuclease there for editing. The gRNA is made up of two parts: CRISPR RNA (crRNA), a 17-20 nucleotide sequence complementary to the target DNA, and trans-activating crRNA (tracrRNA) that serves as a binding scaffold for the Cas9 endonuclease.
- A Cas9 endonuclease that cuts the target DNA sequence at the points directed by the gRNA. Cas9 from Staphylococcus aureus is preferred, as its coding sequence is only 3.2 kb in length and is therefore small enough to be incorporated in an AAV vector.
- A PAM (Protospacer Adjacent Motif) sequence which is a series of nucleotides on the target DNA to which the Cas9 enzyme binds. The PAM sequences are specific for the different Cas9 enzymes that bacteria express. In the S. aureus variant of Cas9, the PAM sequence is NNGRRT, where 'NN' represent two nucleotides upstream of where the target DNA sequence begins and 'R' represents an adenine (A) or a guanine (G).

In theory a CRISPR system, delivered intracellularly via an AAV vector, could correct defective genes in situ by cutting the target DNA sequence at the mutation point and inserting the correct nucleotide sequence using the RNA template. However, restoration of the wild type sequences in the targeted genes would require the intracellular DNA repair mechanisms of the treated cells to operate at very high efficiencies, and so this outcome is not guaranteed. In addition, the presence of more than one PAM sequence in the DNA of the treated cells could potentially cause new mutations to arise through off-target nucleotide sequence modifications.

Hence, for clinical applications, a safer use of the CRISPR system would be to use a deactivated form of Cas9 (dCas9) that cannot cut the DNA but which can still bind to the target sequence, thereby inhibiting gene expression through obstruction of the transcription pathway. Such an approach should provide a therapeutic benefit in autosomal dominant diseases, in which one copy of an altered gene in each cell is sufficient to cause the disorder. By employing a gRNA sequence specific for the mutant allele (inherited from the affected parent) and not the healthy allele, a CRISPR system could be designed to block intracellular transcription of the mutated gene in patients suffering from an autosomal dominant disease. The use of CRISPR for gene inhibition (rather than for gene editing) has the added advantage that any PAM sequence in a given gene could be selected as the dCas9 binding site, thereby permitting the choice of PAM sequences of higher specificity that would greatly reduce the possibility of off-target binding of dCas9. Moreover, even if off-target binding of dCas9 were to occur, the result of such binding would be unlikely to cause the same problems as an active Cas9 endonuclease, since the binding would not cleave and introduce permanent mutations into the DNA of the treated cells.

Specific objectives of the current project

The overall aim of the proposed project is to develop a method for gene silencing, using an AAV vector for intracellular delivery of a CRISPR system employing dCas9. In the first year of this project, our goal has been to generate preliminary data to show proof of concept of gene silencing with S. aureus dCas9, using in vitro expression of green fluorescent protein (GFP) as a way of measuring gene deactivation.

In the second year of the project, we plan in vivo testing of the optimised AAV vector in transgenic mice expressing GFP. This will be followed by development of an AAV vector for intracellular delivery of a CRISPR system for silencing mutated rhodopsin genes. Ultimately this gene silencing therapy will be tested in vivo in a mouse model of autosomal dominant retinitis pigmentosa.

Specifically, our objectives in the first year of this project were to:

1. Identify the relevant PAM sequences in the GFP gene, design an appropriate gRNA sequence, and clone the gRNA sequence into plasmids encoding the S. aureus dCas9.
2. Transfect dissociated photoreceptor cells from Nrl.GFP mice with the plasmids prepared in Step 1, in order to evaluate the efficiency of CRISPR silencing of GFP expression in vitro.
3. Prepare an AAV vector encoding the S. aureus dCas9 and gRNA for in vivo testing in Nrl.GFP mice of the CRISPR system tested in Step 2, using fluorescence imaging to assess any silencing of GFP expression.

Results obtained

In relation to our initial objective, PAM site locations appropriate for binding of S. aureus Cas9 (SaCas9) in the GFP gene needed to be identified. To achieve this, the GFP gene contained in the HEK293-GFP cell line and the Nrl.GFP mouse model were amplified and fully sequenced (Figure 1) with variations identified in the Nrl promoter and GFP sequences of the mouse model compared to the published sequence (Table 1). The sequence variations identified included loss of a PAM site, highlighting the importance of this step. The confirmed sequences were screened for PAM sites and gRNAs with specificity scores of over 60% were designed to the GFP coding sequence and the Nrl promoter (Table 2).

SaCas9 coding sequence was obtained from Addgene (px601) and site-directed mutagenesis was performed to introduce mutations that would create the deactivated form, dSaCas9 (Figure 2A). The gRNA variants for targeting GFP were cloned into SaCas9 and dSaCas9 constructs. Successful deactivation of SaCas9 was assessed by comparing the knockdown of GFP expression, measured by mean grey value, lysate fluorescence and the extent of DNA editing of GFP in HEK293-GFP cells (Figure 2). Significant knockdown of GFP expression was observed with both SaCas9 and dSaCas9 variants (Figure 2B&C) but DNA editing was only observed with the SaCas9 constructs (Figure 2D). These data indicated the gRNA variants designed were successfully directing both SaCas9 and dSaCas9 to bind the GFP coding sequence and that the dSaCas9 was blocking GFP expression without cutting the genomic DNA target.

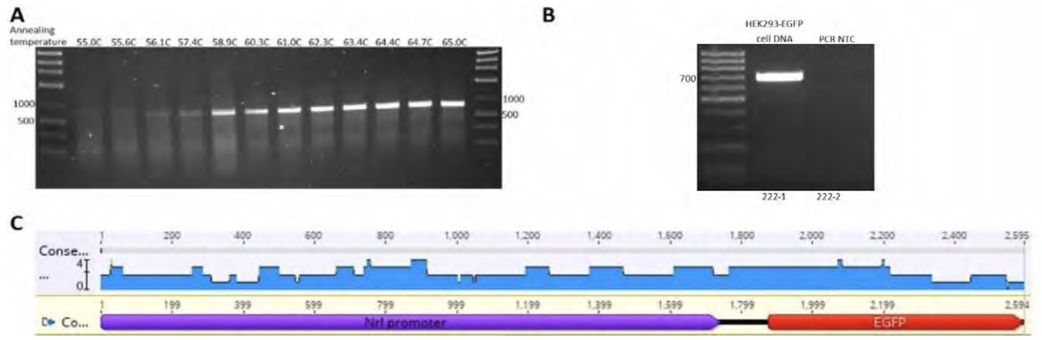

Figure 1. Amplification of the GFP coding sequence in the Nrl.GFP mouse model (A) was optimised by gradient PCR with the GFP sequence also amplified from HEK293-GFP cells (B) with amplicons subsequently purified and sequenced (C).

Nucleotide Position	Mutation Type	Nucleic Acid Change
Nrl promoter		
-1232	Substitution	TATCGTCACGGAACC > GGAACCATAGCAGTG
-1196	Insertion	G
-1139	Substitution	C > G
-825	Insertion	G
-254	Insertion	CT
-175	Substitution	AA > CC
-1	Insertion	TGTTCTGAATACAGGGACGACACCAGCCCCTGCTCTATGGAGTATTTAGCCTCCAGGGAAGCTGTG-CCTTTCTGGTTCTGACAGTGACTACGTCATCTCTGCCATTACATCGGATCCACCGGTCGCCACC
GFP		
193	Substitution	C > T
195	Substitution	G > C
217-218	Substitution	AG > GC (removing PAM site)
450	Substitution	C > G
461-462	Substitution	TG > CC
503	Substitution	T > C

Table 1. Variations in the Nrl promoter and GFP coding sequence identified in the Nrl.GFP mouse model compared to the published sequence.

Name	Position	Strand	Sequence 5' to 3'	PAM	Specificity Score	Efficiency Score
Nrl-EGFP-gRNA-F1R1	204	1	CTTCAGTTTCAGCTGATGGTT	GTGGGT	68.5	1.0
Nrl-EGFP-gRNA-F2R2	536	1	AGCAGTGATAGAAAACTAATG	TAGGGT	68.6	62.1
Nrl-EGFP-gRNA-F3R3	614	1	AAGGTAGGCATCTGTGGAC-CA	GTGGGT	72.2	28.2
Nrl-EGFP-gRNA-F4R4	651	1	AGTGTGTTTCAGAGCTGTTGG	AAGGGT	66.9	30.4
Nrl-EGFP-gRNA-F5R5	689	1	CAGCTGTCTATAACCTACTTA	CTGAGT	84.5	22.3
Nrl-EGFP-gRNA-F6R6	725	1	TGTGAGTTTGAGGTAAAG-CAA	AAGAAT	68.2	55.6
Nrl-EGFP-gRNA-F7R7	1849	1	TACGTCATCTCTGCCATTACA	TCGGAT	83.2	28.8
Nrl-EGFP-gRNA-F8R8	1865	-1	TGCTCACCATGGTGGCGAC-CG	GTGGAT	92.8	29.3
Nrl-EGFP-gRNA-F9R9	1899	1	CAAGGGCGAGGAGCT-GTTCAC	CGGGGT	86.5	15.3
Nrl-EGFP-gRNA-F10R10	2011	-1	GCCGGTGGTGCAGAT-GAACTT	CAGGGT	82	19.3
Nrl-EGFP-gRNA-F11R11	2071	-1	GAAGCACTGCACGCCG-TAGGT	CAGGGT	97.2	21.2
Nrl-EGFP-gRNA-F12R12	2290	-1	GTTGTACTCCAGCTTGTGCCC	CAGGAT	79.4	15.9
Nrl-EGFP-gRNA-F13R13	2383	-1	GCTGCCGTCCTCGAT-GTTGTG	GCGGAT	92.5	18.1
Nrl-EGFP-gRNA-F14R14	2553	1	GCTGGAGTTCGTGACCGC-CGC	CGGGAT	98.8	5.9
Nrl-EGFP-gRNA-F15R15	2572	-1	CTTGTACAGCTCGTCCATGCC	GAGAGT	91.8	9.8

Table 2. PAM sites were identified and gRNAs with specificity scores of over 60% were designed to both GFP

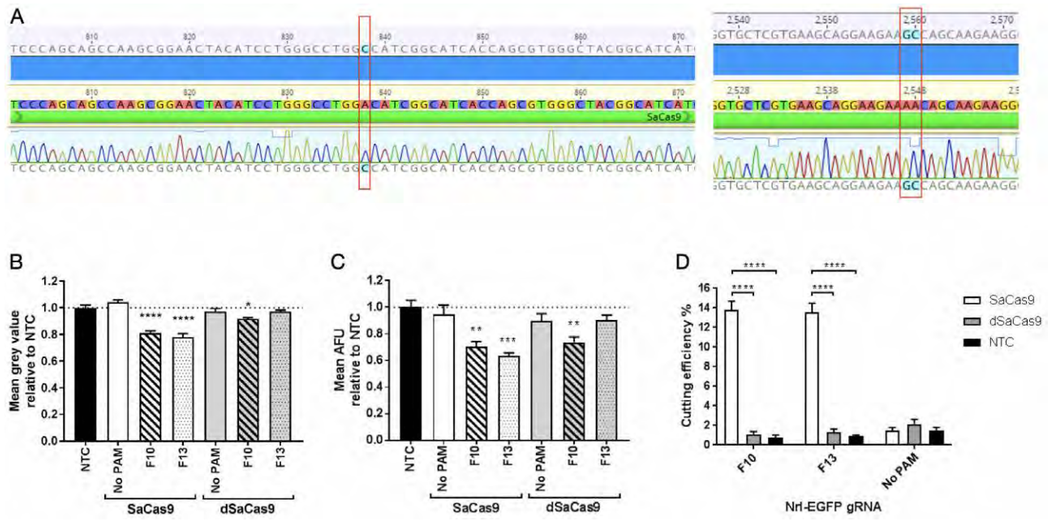

Figure 2. Creation of dSaCas9 and knockdown of GFP expression by SaCas9 and dSaCas9 with multiple gRNAs. A. Deactivated SaCas9 (dSaCas9) was created by introducing D10A and N580A mutations to the original SaCas9 coding sequence. Significant knockdown (N=3) of GFP expression was observed in the HEK293-GFP cell line using gRNA variants F10 and F13 for SaCas9 and F10 for dSaCas9 as assessed by mean grey value (B) and lysate fluorescence (C). TIDE analysis of treated HEK293-GFP cells revealed significant DNA editing of the targeted genomic GFP coding sequence when treated with SaCas9 compared to no DNA editing in cells treated with dSaCas9. NTC = no transfection control; No PAM = construct containing gRNA with a mutated PAM site; F10 = gRNA variant 10; F13 = gRNA variant 13. One-way ANOVA performed for data sets B (p<0.0001) and C (p=0.0005). Two-way ANVOA for data set D (Cas9 p<0.0001, gRNA p<0.0001, interaction p<0.0001). *p≤0.04, **p≤0.007, ***p≤0.0004, ****p≤0.0001.

As evident in Figure 2, the knockdown of GFP expression in vitro was observed to be less efficient with dSaCas9 than SaCas9. Given that future applications of CRISPR intend to use the dSaCas9 variant, we attempted to improve the silencing activity of dSaCas9 by addition of a Krüppel associated box (KRAB) repressor. Addition of the KRAB enabled a significant improvement in the knockdown of GFP expression observed in vitro (two-way ANOVA, N=5, p=0.0009, Figure 3).

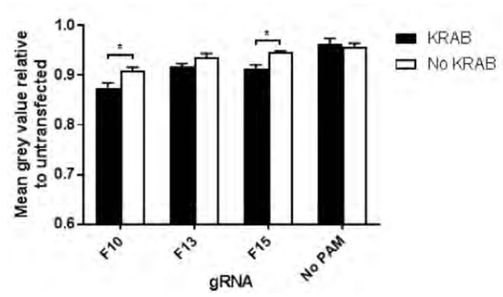

Figure 3. Knockdown of GFP expression in HEK293-GFP cells was significantly improved by fusing a KRAB repressor to dSaCas9. Two-way ANOVA, N=5, KRAB p=0.0009, gRNA p<0.0001, interaction p=0.0455, *p≤0.02.

Regarding objective two of our original research proposal, numerous attempts were made to transfect isolated retinal cells from Nrl.GFP mice post-natal day 3 (PD3) but, despite following established protocols, the data could not be replicated (Figure 4). It was considered that the project would benefit from further optimisation of the transgene in anticipation of testing the CRISPR constructs in vivo.

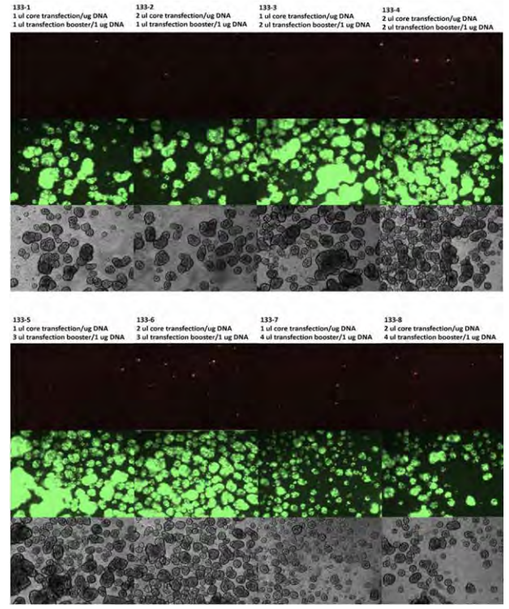

Figure 4. Retinal cells from Nrl.GFP PD3 pups were dissociated and transfected with CAG.dsRED plasmid in attempt to optimise the transfection protocol but the data could not be successfully replicated in subsequent experiments.

Whilst the final objective of this particular project was to achieve proof-of-principle knockdown of GFP in vivo in the Nrl.GFP mouse following sub-retinal AAV delivery of the constructs tested in vitro (Figures 2 and 3), the ultimate long-term goal of the project pipeline is to achieve a clinically relevant gene therapy vector that uses CRISPR to silence disease-causing genes in the retina. This long-term goal encouraged us to consider important elements of the Cas9 transgene that could be implemented and tested at this stage of development. Given the future requirement of rod

photoreceptor-specific expression of a therapeutic CRISPR-Cas9 system, we endeavoured to generate a short rod-specific promoter. With the packaging constraints of AAV vectors and the large size of the Cas9 coding sequence, developing a short promoter would be critical to future applications of CRISPR in the retina. To this end, a 154bp section of the PDE6B promoter was isolated (Figure 5A) and cloned into a reporter construct (PDE6B.dsRED.WPRE), which was then packaged into AAV8 Y733F (Figure 5B).

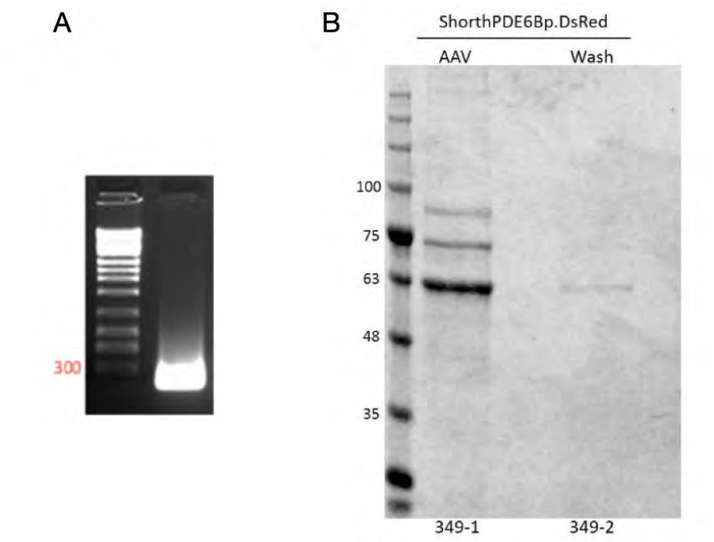

Figure 5. A short fragment of the PDE6B promoter was isolated (A) and cloned into a reporter cassette, PDE6B.dsRED.WPRE, which was subsequently packaged into AAV8 Y733F (B).

Testing of the PDE6B.dsRED.WPRe construct in vitro revealed expression of dsRED in Y79 (human cells derived from retinoblastoma) cells but not HEK293 cells (Figure 6A&B). The vector was delivered sub-retinally into Nrl.GFP mice and 4 weeks post-injection photoreceptor-specific expression of dsRED was observed (Figure 6C).

With confirmation of this unique rod photoreceptor-specific promoter activity in vivo, transgenes have now been cloned containing the PDE6B promoter with SaCas9 or dSaCas9. KRAB in combination with the GFP gRNA variants F10 and F15 (as tested in vitro). These will be packaged imminently into AAV8 Y733F vectors and injected into Nrl.GFP mice for subsequent observation of GFP knockdown and completion of the final project objective.

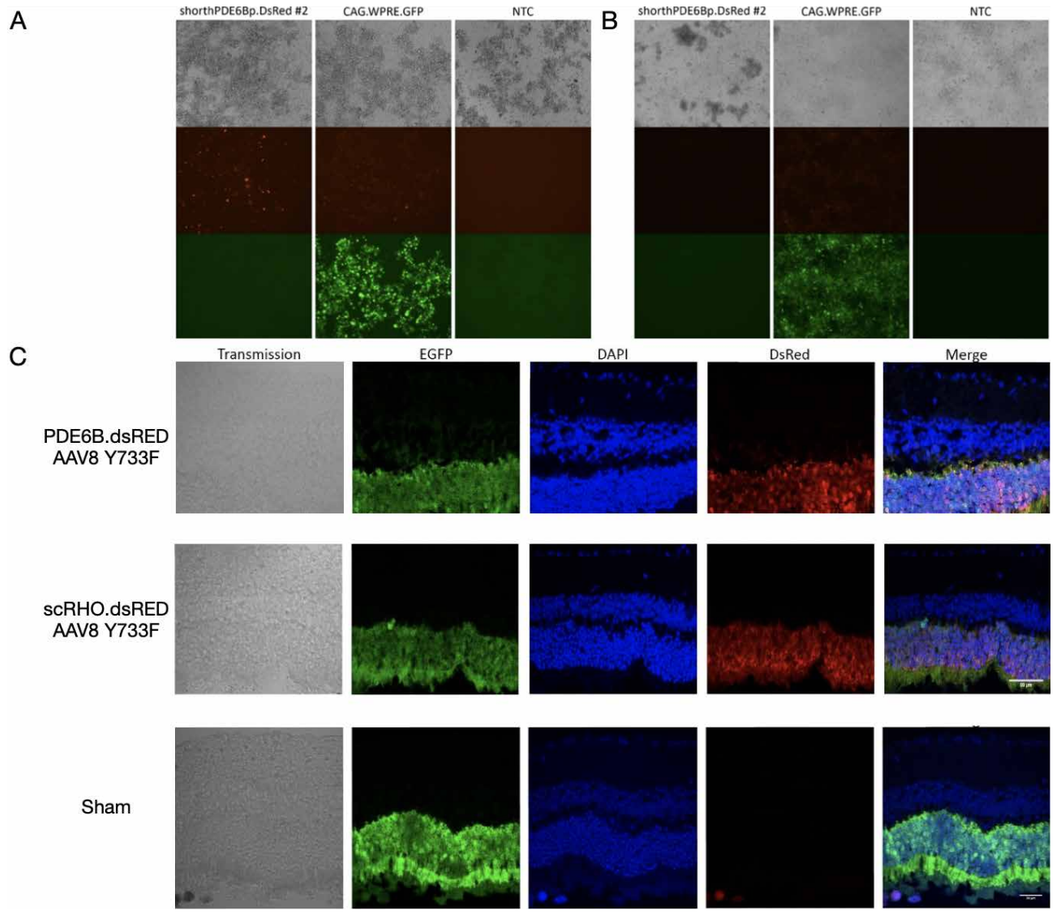

Figure 6. Confirmation of dsRED expression driven by the rod photoreceptor-specific promoter PDE6B in Y79 retinoblastoma cells (A) with absence of expression in HEK293 cells (B) in vitro with CAG.GFP used as a positive control. C. Sub-retinal injections in Nrl.GFP mice revealed rod-specific dsRED expression 4 weeks post-injection in eyes that received PDE6B.dsRED AAV8 Y733F, which showed an equivalent expression pattern to eyes injected with scRHO.dsRED AAV8 Y733F (containing the long rhodopsin promoter). Sham injected eyes revealed no dsRED expression.

(B) Problems encountered and steps taken to overcome them

Initial problems were encountered when attempting to clone dSaCas9 with the KRAB repressor. Cloning of small plasmid preparations was readily achievable but larger bacterial preparations failed to generate the desired plasmid concentrations. Following troubleshooting, this was resolved by growing the bacteria at 30°C instead of 37°C.

Other problems were encountered when attempting to optimise the transfection of dissociated retinal cells isolated from Nrl.GFP mouse eyes. Despite following established protocols and conducting multiple troubleshooting conditions, successful transfection with a reporter construct could not be replicated. Rather than continue to use time on this experimental procedure, it was considered more worthwhile to move forward with generating an appropriate construct to use for in vivo knockdown of GFP.

(C) Collaborations established

In a prior research collaboration between the MacLaren laboratory and Gyroscope Therapeutics, a gene therapy was developed for treatment of dry Age-related Macular Degeneration (AMD) caused by over-activation of the complement system. The gene therapy, which comprises an AAV vector carrying a proprietary therapeutic polypeptide known as Gt005, is now being tested in a first-in-human Phase 1/2 clinical trial led by Professor Robert MacLaren at the Oxford Eye Hospital. The first patient was treated on 17 January 2019.

Dry AMD, which develops when the cells of the macula become damaged by a build-up of deposits called drusen, is the most common type of AMD, accounting for around 9 out of 10 cases. It presents as a progressive and debilitating loss of vision in the centre of the visual field (macula). As the disease progresses to the atrophic form (also called geographic atrophy), characterised by the loss of the retinal pigment epithelium leading to degeneration of the nearby photoreceptors, the corresponding loss of central vision prevents affected patients from being able to recognise faces, drive, read, or perform other activities of daily life.

AMD currently affects more than 600,000 people in the UK and is the leading cause of vision loss. The frequency of the disease increases significantly with age, with more than 10% of the population over 70 years old showing signs of AMD. By 2020, it is predicted almost 700,000 people in the UK will have late-stage AMD.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

Higher degrees

The following PhD students, whose doctoral theses developed and expanded previous research projects funded by the Royal College of Surgeons of Edinburgh, have successfully graduated with DPhil degrees from the University of Oxford:

- Dr Mark Hassall, a medical graduate from the University of Adelaide (Australia), was awarded a prestigious Rhodes Scholarship to undertake a doctoral research project under Professor MacLaren's supervision. His PhD project investigating gene therapy for cone rescue in retinal dystrophies built upon the experimental results of the College-funded projects 'Developing gene therapy for cone neuroprotection in rod cone dystrophies' and 'Testing clinical treatments that might preserve cones in retinitis pigmentosa' undertaken from October 2009 to September 2011. Dr Hassall has been appointed as a Senior Research Fellow at the Centre for Ophthalmology, Eye and Vision Research at Flinders University (Adelaide, Australia).
- Dr Harry Orlans, a medical graduate from the University of Oxford, was awarded a MRC/Fight for Sight Clinical Training Research Fellowship to undertake a doctoral research project under Professor MacLaren's supervision. His PhD project developing a gene therapy for treatment of dominant retinitis pigmentosa extended research undertaken in the College-funded project 'Optimising gene therapy treatments for dominant retinitis pigmentosa' undertaken from October 2015 to September 2016. In addition to completing his DPhil, Dr Orlans has been awarded Fellowship of the Royal College of Ophthalmologists, and is now working as a Specialist Registrar (Ophthalmology) at Moorfields Eye Hospital in London.

Prizes

- Dr Harry Orlans was awarded the Founder's Cup at the 2018 Oxford Ophthalmological Congress for his research investigating innovative treatments for treatment of dominant retinitis pigmentosa.
- Dr Samantha de Silva received the 2018 Royal College of Ophthalmologists Fight for Sight Award for her paper 'Long-term restoration of visual function in end-stage retinal degeneration using subretinal human melanopsin gene therapy' that summarised the experimental data presented in her doctoral thesis. Dr de Silva's PhD research work built upon previous College-funded projects, and the support of the Royal College of Surgeons of Edinburgh was acknowledged in this publication.

Publications

A number of other scientific papers, generated from ongoing research projects based on preliminary work supported by the College, have been published during the course of the last year. These publications, which all acknowledge the support of the Royal College of Surgeons of Edinburgh, are listed below:

- Xue K, Jolly JK, Barnard AR, Rudenko A, Salvetti AP, Patrício MI, Edwards TL, Groppe M, Orlans HO, Tolmachova T, Black GC, Webster AR, Lotery AJ, Holder GE, Downes SM, Seabra MC, MacLaren RE. Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia. Nat Med. 2018;24(10):1507-1512.
- De Silva SR, Barnard AR, Hughes S, Tam SKE, Martin C, Singh MS, Barnea-Cramer AO, McClements ME, During MJ, Peirson SN, Hankins MW, MacLaren RE. Long-term restoration of visual function in end-stage retinal degeneration using subretinal human melanopsin gene therapy. Proc Natl Acad Sci U S A. 2017;114(42):11211-11216.
- Martinez-Fernandez De La Camara C, Nanda A, Salvetti AP, Fischer MD, MacLaren RE. Gene therapy for the treatment of X-linked retinitis pigmentosa. Expert Opin Orphan Drugs. 2018;6(3):167-177.
- Patrício MI, Barnard AR, Xue K, MacLaren RE. Choroideremia: molecular mechanisms and development of AAV gene therapy. Expert Opin Biol Ther. 2018;18(7):807-820.
- Patrício MI, Barnard AR, Cox CI, Blue C, MacLaren RE. The Biological Activity of AAV Vectors for Choroideremia Gene Therapy Can Be Measured by In Vitro Prenylation of RAB6A. Mol Ther Methods Clin Dev. 2018;9:288-295.
- Aylward JW, Xue K, Patrício MI, Jolly JK, Wood JC, Brett J, Jasani KM, MacLaren RE. Retinal Degeneration in Choroideremia follows an Exponential Decay Function. Ophthalmology. 2018;125(7):1122-1124.
- Patrício MI, Barnard AR, Green AL, During MJ, Sen A, MacLaren RE. A clinical-grade gene therapy vector for pharmacoresistant epilepsy successfully overexpresses NPY in a human neuronal cell line. Seizure. 2018;55:25-29.

(E) Acknowledgements

We would like to thank the Royal College of Surgeons of Edinburgh and Sight Scotland for their generous sponsorship of this and preceding Major Project Grants in Ophthalmology, which have underpinned the successful translational research programme in Oxford. We are pleased to report that our early laboratory work has progressed into international clinical trials, and it remains our commitment to research new treatments for currently incurable forms of blindness. To date we have made considerable progress in that regard.

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Ophthalmology Grant Report

A randomised controlled trial to evaluate the effect of face-down posturing on retinal displacement and distortion following retinal detachment repair

Professor David G Charteris

Moorfields Eye Hospital , London, Tennent Institute, Glasgow

March 2017 - March 2018

Lay Summary

Distorted vision is common following surgery for retinal detachment, but there is no good evidence as to how it is best prevented. In this study we compared two commonly used approaches to head positioning following surgery to determine if either has a particular advantage over the other principally in terms of reducing symptoms of distortion following surgery. Patients in the trial were followed-up for one year following surgery to determine if early symptoms of distortion, and associated structural changes in the healing retina, persist over time and are of functional significance to the patient.

We found that there was a slight advantage of posturing face down for the first 24 hours after retinal detachment repair. This will help vitreoretinal surgeons advise their patient of the best post-operative head position following retinal detachment surgery.

Grant Report

(A) Clinical and Scientific Significance of advances made

This randomised controlled trial of head positioning after retinal detachment surgery was completed on time and was fully recruited. We were able to use a combination of objective outcome measures to assess the effect of two posturing regimes. We found an advantage of post-operative posturing in anatomical outcomes – outer retinal folds and retinal translocation (gradable images) but no advantage in visual outcomes or distortion overall. The results suggest a reduction in the risk of severe retinal folds post-operative with face down posturing and vitreoretinal surgeons may elect to use this regime based on the results of the study. This is the first RCT of post-operative posturing and demonstrates a study design using objective outcome measures which can be utilised by other investigators.

(B) Problems encountered and steps taken to overcome them

The imaging requirement for demonstrating retinal translocation required optimisation in both centres (London and Glasgow).

Training of objective grading technicians was required.

(C) Collaborations established

Between Moorfields Eye Hospital and the Tennent Institute of Ophthalmology, Glasgow – outcome measures shared and developed together . researchers in Glasgow were able to develop their objective measure of visual dictation – D Chart.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

Presented at -
BEAVRS (Britain and Eire Vitreoretinal Surgeons) Liverpool November 2018 – Casswell et al
Greek Vitreoretinal society – Athens Jan 2019 Charteris et al

Accepted for ARVO Vancouver 2019
Casswell et al

Publications in preparation

(E) Acknowledgements

The grant has allowed a trainee ophthalmologist Edward Casswell to undertake a research period with a view to submitting a higher degree (MD)
The grant also allowed us to raise the additional funding for infrastructural support to complete the study. Thanks to the Royal College of Surgeons of Edinburgh and Royal Blind (Sight Scotland)

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Ophthalmology Grant Report

Impact of insulin pump therapy and islet transplantation on progression of diabetic retinopathy in Type 1 diabetes.

Dr Shareen Forbes

Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh

Major Opthalmology Grant

August 2017 - August 2019

Lay Summary

Diabetes is a major cause of blindness. High blood glucose readings are associated with progressive complications from diabetes including those affecting the retina termed diabetic retinopathy.

Treatments for Type 1 diabetes include delivery of insulin via a pump system, or islet transplantation, where islets from a donor pancreas are transplanted into the recipient's liver. These treatments have been shown to improve diabetes control, which may lead to an improvement in diabetic retinopathy in the longer term. However, rapid improvements in glucose control can lead to a short term progression in diabetic retinopathy. This effect has not been fully assessed in those treated with insulin pump therapy or islet transplantation.

We will follow subjects who have undergone conversion to insulin pump therapy or islet transplantation and serially examine their vision prior to and after these interventions relating changes in retinopathy to changes in glucose control. This will allow us to examine whether progression of retinopathy occurs and how it is related to improvement of blood glucose control and changes in blood glucose variability.

The study will help inform screening strategies for insulin pump and islet transplant subjects, leading to improved medical outcomes.

Grant Report

(A) Clinical and Scientific Significance of advances made

This study has been undertaken in two parts:

1. A retrospective analysis of diabetic retinopathy screening data, assessing those who have already received islet transplants or insulin pump therapy, and comparing changes in retinal outcomes to control subjects who continue on standard therapy with multiple daily injections of insulin (MDI).
2. A prospective study recruiting patients starting on insulin pump therapy or receiving islet transplantation. Detailed retinal assessments are carried out pre and at regular intervals post changes to treatment. Changes in glycaemic control and variability are also being assessed using continuous glucose monitoring systems (CGMS) which enable glucose levels to be measured every few minutes over a six day period.

1. Advances made in Retrospective Study

A. Outcomes of Graded Retinopathy Screening

Screening data has been analysed for 324 insulin pump recipients and 45 islet transplant recipients, and compared with over 400 control subjects who continued on treatment with multiple daily injections. Screening was carried out using fovea centred fundus photography and graded using the Scottish Diabetic Grading Scheme. Time to a minimum one grade worsening in retinopathy was compared for pump and MDI groups using Kaplan Meier survival curves.

Results were analysed over a three year follow up period. There was no evidence of early worsening of retinopathy in insulin pump patients in the first year compared with MDI controls. Results suggest a trend towards improved retinopathy outcomes over 3 year follow up in pump recipients. Glycaemic control, measured by HbA1c, was significantly improved in pump recipients at one year follow up compared to the control group.

Further analysis has also been carried out using propensity score matching of groups, as the pump group was significantly younger than the MDI group, with lower baseline HbA1c. When matched for age at diabetes diagnosis, age at time of study analysis, HbA1c baseline, gender and social deprivation score, the outcomes were the same.

Similar analyses were done comparing islet transplant recipients with MDI controls. Participant numbers for the islet transplantation group were smaller, but results for matched and unmatched groups indicated there was no increased retinopathy progression over the three year follow up period when compared to MDI controls.

This suggests that reductions in glycaemic control following insulin pump therapy and islet transplantation may not carry a risk of early progression of retinopathy and, in insulin pump recipients, may help reduce progression in the longer term. Further analysis is being done to assess the impact of HbA1c changes on retinopathy progression.

B. Outcomes of Fundus Photograph Analysis

Fundus photographs were obtained from the Scottish Diabetic Screening Programme for Insulin Pump and Islet Transplant recipients. Changes in parameters including vessel width, vessel density, vessel tortuosity and fractal dimensions (vessel branching patterns) have been postulated as markers for diabetic retinopathy progression. These parameters are being analysed using semi-automated computer software. Pre treatment images are being compared to those taken one year post insulin pump therapy or islet transplantation, and to the most recent images on record.

Analysis of pump recipients is ongoing. Data from islet transplant recipients suggests no significant change at either time point in vessel width, density, tortuosity or branching pattern at one year or on most recent retinal follow up. This supports the previous analysis of graded retinopathy outcomes, suggesting that islet transplantation is not associated with an increased risk of early retinopathy progression.

2. Advances made in Prospective Study

To date 25 participants have been recruited: 16 insulin pump recipients, 4 islet transplant recipients and 5 MDI controls. A group of healthy non diabetic controls will also be recruited for a one off visit.

In pump and islet transplant recipients, retinal assessment has been carried out prior to treatment and at 1, 2, 3, 6, 9 and 12 months post treatment. In MDI controls assessment has been carried out at 0, 3, 6, 9 and 12 months. Retinal assessment involves four imaging modalities: fundus photograph, optical coherence tomography (OCT), ultrawise-field scanning laser ophthalmoscopy and optical coherence tomography angiography (OCT-A). Glycaemic changes are assessed using CGMS and HbA1c. Weight, blood pressure, cholesterol, renal function, liver function, urinary protein and peripheral neuropathy assessment are also being carried out.

Data collection for the full twelve month follow up has been completed for seven participants. Initial analysis of data at the three month time-point (20 participants) for vessel density and vessel thickness has identified no significant changes from baseline. Further data collection and analysis is ongoing.

(B) Problems encountered and steps taken to overcome them

1. Allocation bias

Comparison of groups for the retrospective study identified differences in patient demographics. This may be due to bias as to who is allocated an insulin pump. To minimise any potential effect of these differences on retinopathy analysis, propensity score matching was used. This incorporated multiple demographic variables to assign participants from both pump and MDI groups with a probablilty score relating to how likely they would be to be allocated to the pump group. Those with similar probability scores were matched for reanalysis. The trend in outcomes were the same for matched and unmatched groups.

2. Small patient numbers

Patient numbers were small, particularly for the islet transplant group. This was partly expected, as only a small number of islet transplants are carried out each year. Edinburgh is the largest islet transplant centre in the UK and therefore has one of the largest cohorts of islet recipients for retrospective analysis available.

To further improve patient numbers for retrospective analysis of islet transplant recipients, collaboration has been established with the Edmonton islet transplant centre in Canada. The Edmonton centre is where the procedure was established and is the largest islet transplant centre in the world. We have received ethical approval to analyse retrospective retinopathy data for 100 islet transplant recipients from Edmonton, who have up to ten years follow up data. Data collection for this is ongoing.

Recruitment numbers for the prospective study have been lower than anticipated. This has mainly been due to fewer islet transplants being carried out as the waiting list has been reduced, and fewer insulin pump starts due to temporary NHS funding issues. We have set up multiple education sessions with diabetes departments around Scotland and Northern Ireland to improve awareness of the referral pathway for islet transplantation with an aim to increase patient numbers. The temporary funding issues for pump starts has been resolved and recruitment for this group is ongoing.

3. Problems with retinal imaging scanners

On two occasions during the study, one of the retinal imaging machines has been out of action. The OCT machine had to move to a new location to accommodate the new retinal machine, and was unable to be used during this time. The OCT-A machine developed a faulty switch which made it unusable until a new part had been ordered to replace it. Where possible appointments were rearranged to try and ensure all imaging modalities could still be performed. Where this was not possible only the other three imaging modalities could be carried out.

(C) Collaborations established

As discussed, collaborations have been established with the islet transplant team in Edmonton. This involved a visit to the islet transplant centre in Edmonton to collect existing retinopathy data and propose further data collection with the co-operation of the islet transplant team and ophthalmology team. During this visit, an ethical proposal was written and submitted to the local ethics committee for further retinal data to be collected. This has since been approved and further data will be collected over the next 6 months. This will provide one of the largest datasets for retinopathy data in islet transplant recipients to date, with the longest follow up to date.

Collaborations have also been established with the diabetes research team in NHS Tayside. They are facilitating CGMS data collection for healthy non diabetic controls. This will be useful in establishing the normal variability in glucose levels for comparison to study subjects.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

Islet Transplantation in Type 1 diabetes– Moving Forward. Forbes S, Senior P, Shapiro AMJ. Lancet Diabetes and Endocrinology; 6; 516-7; 2018

Insulin Pump Therapy Is Associated With Reduced Retinopathy Progression Compared With Multiple Daily Injections of Insulin.

L. Reid, F. Gibb, H. Colhoun, S. Wild, M. Strachan, A. Ochs, K. Madill, B. Dhillon, S. Forbes. Accepted abstract at Diabetes UK March 2019.

CGM Shows Islet Transplantation Prevents Hypoglycemia, Correcting Time in Range and Reducing Glycemic Variability, Despite Subnormal Beta-Cell Function. Shareen Forbes, Tolu Olutoyin Olateju, Anna Lam, John Casey, John Campbell, Laura Reid, Richard A. Oram, Andrew J. Malcolm, A.M. James Shapiro, Peter A. Senior. Diabetes. 2018; 67 (suppl 1): 143-OR

Donor HbA1c is inversely related to islet yield but does not impact on islet function at one year following islet transplantation in subjects with Type 1 diabetes. LJ Reid, L Irvine, N McGowan, D Mitchell, G Walker, K Duncan, C Ibbotson, A Sutherland, J Casey, S Forbes. Diabetic Medicine, Volume 35, Issue S1, P25, March 2018
Impact of islet transplantation on progression of microvascular disease – invited review Transplantation Medicine March 2019

Funding obtained from Edinburgh Lothian Health Foundation for CGMS funding. Examination of glycemic variability in normal glucose tolerant controls. Forbes S and McCrimmon R.

(E) Acknowledgements

Royal College of Surgeons, Edinburgh Royal Blind (Sight Scotland)
Islet Transplant Unit, NHS Lothian
Diabetes Departments, NHS Lothian and NHS Tayside
Ophthalmology Department, NHS Lothian
Clinical Research Imaging Centre/Eye Lab
Scottish Diabetes Research Network
University of Dundee
Islet Transplant Department, University of Alberta, Edmonton

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Ophthalmology Grant Report

Importance of Stereopsis in Cataract Surgery Simulation

Dr Stewart Gillan
Department of Ophthalmology, Ninewells Hospital, Dundee
Small Opthalmology Grant
February 2014 - February 2019

Lay Summary

Stereopsis is the ability to see in 3D and perceive depth. This has always been perceived as a requirement to successfully being able to carry out microsurgery through a microscope, such a cataract surgery. With the invention of a virtual-reality cataract surgery simulator, it has become possible to ethically investigate factors which contribute to safe and effective surgery. We therefore applied for a grant to investigate the exact importance of having good stereopsis in carrying out cataract surgery, using such a simulator. The ignificance of this, is that at present candidates with poor stereopsis are counselled away from careers involving microsurgery, yet there is little evidence to support this.

Initial barriers obtaining local consent were overcome, and recruitment was slow, given the relatively low incidence of poor stereopsis in the general population. However, this week we achieved our target of 50 subjects with varying degrees of stereopsis, ranging from nil to excellent. We have started to analyse the data, but given the vast quantity of data gained from the simulator, this will take some time. Initial observation is that there is no difference in overall scores between groups, however, those with poor stereopsis may perform less well in some areas.

A full manuscript will be drafted for publication and a copy sent to RCSEd to complete the report.

Grant Report

(A) Clinical and Scientific Significance of advances made

When data has been fully analysed, it will hopefully provide further evidence as to the importance of good stereopsis in carrying out microsurgical procedures, as this evidence is lacking.

Should it agree with current convention that stereopsis is required, then existing standards set by the Royal College of Ophthalmologists can be considered to be appropriate. If it is found that stereopsis is not a requirement, then is it possible such standards should be reconsidered, and further, larger studies may be required to strengthen the results.

(B) Problems encountered and steps taken to overcome them

1. Staff / personal changes have delayed the project from the outset. The primary Grant Holder (SG) undertook a Clinical Fellowship in Manchester shortly after obtaining the grant so little progress was made in the first 2 years. This project was taken up on his return to Dundee, and he is grateful to the committee for extending the duration of the grant. Over the past 2 years a stable team have been working on the project, with good success.
2. Ethical Approval – completing the necessary application to the satisfaction of the local ethics committee was lengthy, but eventually successful with further guidance from the local research administrative team.
3. Incidence of poor stereopsis is thought to be low within the general population (amblyopia / lazy eye is thought to be 5%), therefore it took time to recruit a suitable number of subjects. We were very keen to keep our source group strictly to the medical student population, as they accurately represent the demographic who would go on to seek careers in microsurgery, and this was achieved.

(C) Collaborations established

Nil

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

It is anticipated that a manuscript will worked up for publication in the near future. This will be forwarded to RCSEd on completion.

(E) Acknowledgements

The team are grateful to the RCSEd and Sight Scotland for their support in carrying out this project.

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Ophthalmology Grant Report

New mechanisms and treatment targets in retinoblastoma

Professor Mandeep S. Sagoo & Professor Shin-Ichi Ohnuma
UCL Institute of Ophthalmology
Major Opthalmology Grant
June 2017 - June 2018

Lay Summary

Retinoblastoma, the most common eye cancer of childhood, frequently results in the removal of one or more eyes, which results in lifelong practical and psychological impacts. There is therefore a need to better understand the molecular mechanisms of retinoblastoma to inform the development of novel diagnostic and treatment strategies. Most cases of retinoblastoma are associated with mutations in the retinoblastoma 1 gene (RB1), two RB1 mutations are thought to be required and these can be inherited or occur during development. We sequenced the genome of 25 retinoblastoma tumours, which included 10 rare tumours where no or only one RB1 mutation had been previously identified. Our aims were 1) to fully characterise RB1 mutations and 2) to identify any novel mutations in other genes that might contribute to retinoblastoma development. We demonstrated that at least one RB1 mutation was present in all 25 samples examined, these additional mutations were complex re-arrangements and translocations which were undetectable using the technology previously employed. We have also discovered additional mutations in the N-MYC, BCOR and Ext-2 genes. Our work suggests that employing whole genome sequencing of retinoblastoma provides additional mutational information which may inform the development of novel approaches to diagnosis and treatment.

Grant Report

(A) Clinical and Scientific Significance of advances made

We have made a number of significant advances with the partial support of this grant.

1. We have performed whole genome sequencing and mutational signature analysis on 25 retinoblastoma tumour samples - this is the largest and most comprehensive analysis of the mutational landscape of retinoblastoma to date. It is also the first to attempt to comprehensively analyse the mutational signature in retinoblastoma.
2. The prevailing view of retinoblastoma development is that it requires 2 mutations in the retinoblastoma 1 gene (RB1), one on each allele. We have analysed the mutational landscape of a subset of 10 rare and enigmatic retinoblastoma cases, 4 of these were initially thought to harbour only 1 RB1 mutation and in a further 6 detectable RB1 mutations were elusive. We identified RB1 mutations in all 6 cases that were previously thought to lack any detectable RB1 mutations. These were complex rearrangements and translocations of the RB1 gene to other chromosomes, these mutations were invisible to the previous technology used to locate mutations. This demonstrates that an RB1 mutation is associated with every case of retinoblastoma we analysed (20 patients in total). It does however demonstrate that using this technology that 4 of these cases only harbour 1 detectable RB1 mutation and in 4 the presence of a second mutation is unclear due to a questionable loss of heterozygosity. This suggests that there may be extra RB1 routes to the initiation of retinoblastoma in some cases.
3. We have identified mutations in a number, of other genes thought to be associated with retinoblastoma development these include N-MYC, BCL6 corepressor (BCOR), Creb binding protein (CREBP) and Exostosin-2 (Ext-2). These are sparse, their relationship to retinoblastoma uncertain, fail to show a consistent pattern, but have been recorded before in other studies.
4. There are hypotheses of retinoblastoma development that suggest mutations in the RB1 gene alone are insufficient to initiate retinoblastoma; in this hypothesis other mutations are required to allow its progression. Our data demonstrating that every single tumour has an RB1 mutation, coupled with the lack of a consistent mutational pattern in other genes suggests that this is not the case and any tumour promoting mechanisms exogenous to RB1 are non-mutational in nature. This suggests that further investigation of these putative tumour promoting mechanisms should concentrate on the investigation of non-mutational processes, including epigenetic regulation and DNA repair mechanisms.
5. We have sequenced two separate tumours from the same patient, this demonstrated that they share a common germline c.607+1G>T exonic splicing silencer (ESS) mutation of RB1, the consequences of which are thought to be a skipping of exon 6. In the right eye an additional somatic mutation of RB1, a deletion of exons 8 to 10 was identified. In the left eye the additional somatic mutation was a large scale, deletion of 13q (33026220-115108598) and hence a loss of heterozygosity of RB1. This shows that both tumours are derived from independent mutational processes. In addition, this case provided an ideal to understand the interaction between platinum chemotherapy and the changes in mutational signatures. The right eye was removed prior to chemotherapy and had an undefined mutational signature but the left eye was exposed to four cycles of JOE chemotherapy (containing platinum) before removal, this eye demonstrated a mutational signature characteristic of platinum exposure.
6. Normally retinoblastoma cases where there are profound copy number increases in N-MYC do not harbour detectable RB1 mutations, we have isolated two unusual “hybrid” cases, where there are profound increases in N-MYC copy number and two distinct RB1 mutations.
7. We investigated the possibility that large retinoblastoma tumours demonstrated genetic heterogeneity, we examined two

tumours one with four samples and one with two. We did not find any evidence of tumour heterogeneity in these samples.

8. We have also compared gene expression in five retinoblastoma tumours with three “normal” retinal tissue we have demonstrated that expression of 3228 gene transcripts is increased and expression of 4153 genes decreased (greater than ±1.5-fold, $p<0.05$). Interestingly expression of N-MYC is profoundly increased in all, of the retinoblastoma cases examined.
9. In clinical practice mutations in the RB1 gene are normally detected using a high-resolution melt followed by Sanger sequencing; this approach cannot detect very low level, mutations and translocations. We propose that whole genome sequencing of retinoblastoma tumours provides more comprehensive insights into their mutational landscape. This proposal is timely in the context of the fact that the cost of whole genome sequencing is expected to fall to well under £1,000 in the near, future.
10. We have employed a single cell approach to analyse the gene expression in around 400 single cells derived from a retinoblastoma tumour, these results are still being analysed.

(B) Problems encountered and steps taken to overcome them

We have only encountered two problems

1. There are only 20-25 retinoblastoma new cases per year processed by the Royal London Hospital and these attend in a random pattern. This did slow down our progress but is a factor outside of our control.
2. Single cell work is fiddly, time consuming and difficult, we have gained considerable expertise in this technique and many of these problems have been resolved.

(C) Collaborations established

We have established and consolidated the following collaborations;

Prof Serena Nik-Zainal and Dr Helen Davies at the Academic Dept of Medical Genetics, University of Cambridge, Cambridge, UK, this collaboration extended our abilities to perform and analyse whole genome sequencing data.

Drs Zerrin Onadim and Elizabeth Price at the Retinoblastoma Genetic Screening Unit, The Royal London Hospital, Bart’s Health NHS Trust, London, Dr’s Onadim and Price are experts in retinoblastoma and approximately 50% of the retinoblastoma samples obtained in the UK pass through there laboratory.

Mr Ashwin Reddy and Retinoblastoma team at Royal London Hospital, London, UK for tumour tissue.

Dr Nick Owen at the University College London, Institute of Ophthalmology, London, UK has a range of expertise in the analysis of gene expression data.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

We have enough data to prepare two papers based on this work;

KD Broad, H Davies, Z Onadim, EA Price, K Kolkiewicz, E Karaa, I Scheimberg, M Sagoo, S Nik-Zainal, SI Ohnuma. (2019). Provisional title Whole genome sequencing of 25 retinoblastoma tumours.
(In preparation for submission to Genome Medicine)

KD Broad, H Davies, Z Onadim, EA Price, K Kolkiewicz, E Karaa, I Scheimberg, M Sagoo, S Nik-Zainal, SI Ohnuma. (2019). Provisional title Whole genome sequencing of two retinoblastoma tumours from the same patient demonstrates a conserved germline mutation but separate somatic mutations.
(In preparation for submission to Cancer Research)

(E) Acknowledgements

We are grateful to Sight Scotland and the Royal College of Surgeons of Edinburgh for generously supporting this work.

We would like to acknowledge the expertise of;

Prof Serena Nik-Zainal and Dr Helen Davies at the Academic Dept of Medical Genetics, University of Cambridge for the analysis of whole genome sequencing data.

Dr’s Zerrin Onadim, Elizabeth Price, Kelly Kolkiewicz, Esin Karaa and Irene Scheimberg at the Retinoblastoma Genetic Screening Unit, The Royal London Hospital, London, for expertise in retinoblastoma and the provision of retinoblastoma samples.
Dr Ibrahim Sherriff at the Royal London Hospital, London for the analysis of patient data.

Dr Nick Owen at the University College London, Institute of Ophthalmology, London, UK for help with the analysis of gene expression data.

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Ophthalmology Grant Report

The Scottish Glaucoma Biobank

Dr Andrew Tatham

Princess Alexandra Eye Pavilion, NHS Lothian

Major Opthalmology Grant

March 2016 - Present

Lay Summary

Glaucoma is the world's foremost cause of irreversible blindness. At present the only treatment is to lower pressure within the eye, however, some patients continue to lose vision despite low pressure and a large proportion of patients develop glaucoma having never had high pressure, a condition known as normal tension glaucoma. There is a need for new treatments that do not rely on lowering eye pressure, but a major obstacle is that we do not fully understand why glaucoma occurs.

The aim of this study is to identify factors associated with increased risk of glaucoma. To date we have recruited 49 patients with glaucoma and examined them using an array of new tests so that we can determine which factors are related to loss of vision. Tests include patients measuring their own eye pressure at home over 48 hours, home blood pressure monitoring, measurements of blood flow in the eye and genetic testing. Identification of new risk factors for glaucoma is likely to help determine which patients need more aggressive treatments such as surgery and may identify new targets for treatments that go beyond lowering eye pressure.

Grant Report

(A) Clinical and Scientific Significance of advances made

The overall purpose of the project was to explore novel clinical and genetic risk factors for glaucoma and glaucoma progression. Thus far we have enrolled and completed baseline assessment for 49 patients. The baseline assessment involves a large number of tests including – optical coherence tomography (OCTA), visual field assessment, full ocular examination, phasing (measurement of intraocular pressure in hospital over the course of a day), measurement of corneal thickness and corneal hysteresis (a marker of elasticity of the cornea) using a device known as an ocular response analyser, 48-hour home blood pressure monitoring, 48 hour home intraocular pressure monitoring, and a blood test for mitochondrial DNA analysis.

The study has several important objectives. First, we wanted to determine whether there might be a role for home intraocular pressure monitoring in glaucoma. Home monitoring would enable greater number of pressure measurements and we hypothesised that greater fluctuation would be associated with higher risk of glaucoma. Using the ocular response analyser (funded by the grant) and 5 home intraocular pressure measurement devices (donated by the manufacturers due to the grant), we found 75% of people are able to measure their own pressures showing the method is feasible. We also compared measurements from the home testing device to ocular response analyser measurements showing good agreement. The results of these analyses have been published in JAMA Ophthalmology and Journal of Glaucoma (see below). We are now using the home measurement devices in clinic practice to inform treatment decisions.

Having proven that the measurements are reliable we are in the process of analysing results from the 49 patients who have thus far conducted 48-hour home eye pressure measurements. We expect the study will also identify other risk factors for glaucoma e.g. low corneal hysteresis, high fluctuation in intraocular pressure or nocturnal dipping in blood pressure. Identification of new risk factors will enable better prediction of those at risk of glaucoma blindness. The study is generating a wealth of data and we are in discussion with Tom MacGillivary at the University of Edinburgh regrading advertising for a PhD student to help with this work.

The blood samples we have collected have been sent to Professor Colin Willoughby's laboratory at the University of Liverpool where mitochondrial DNA will be analysed to determine whether there are genetic risk factors.

Our aim is that in coming years patients diagnosed with glaucoma will be able to have a battery of tests to better determine their risk of visual loss and that new treatment targets will be identified.

(B) Problems encountered and steps taken to overcome them

The start of the study faced considerable delay due to the difficulty of recruiting a suitable research fellow. The original person earmarked for the role relocated but we were fortunate to employ Lyndsay Brown (0.4 WTE), an Edinburgh optometrist. Lyndsay has recently completed her MSc in Primary Care Ophthalmology at the University of Edinburgh.

Recruitment has also been slower than expected, largely due to the demands placed on participants due to the large number of tests conducted. We aim to recruit a further 50 patients with glaucoma and 25 controls. We are currently testing approximately 3 patients per week so estimate another 6 months will be required to complete testing. Lyndsay Brown's salary is funded by the Grant until October 2019. We have applied to Edinburgh and Lothians

Health Foundation (ELHF) for funding to extend Lyndsay's position for a further 12 months to October 2020 and there is funding within the Eye Pavilion's ELHF research fund to enable this.

(C) Collaborations established

Collaboration with Eleonora Blanca, an academic foundation year doctor to work fulltime on the project for 4 months between September 2018 and January 2019. Dr Blanca was able to help with recruitment and testing patients.

Providing research projects to 2 University of Edinburgh medical students who are working on analysing data collected from the project. The first is examining the relationship between 48-hour fluctuations in intraocular pressure and fluctuations in blood pressure, and the relationship between these and glaucoma severity. It is suspected that those with higher fluctuations (and lower ocular perfusion) are likely to be at increased risk of glaucoma. If this is proven, it may lead to new treatments aiming to improve ocular blood flow.

The second student is examining results from the OCTA device, along with another collaborator, Dr Tom MacGillivray, senior research fellow at the clinical research imaging centre. Tom's team are developing innovative methods to analyse blood vessels in OCTA images, which are likely to provide further insight the role of compromised ocular blood flow in glaucoma.

Collaboration with Professor Colin Willoughby's group at the University of Liverpool.

(D) Publications and presentations (include any prizes awarded), higher degree and further funding obtained as a result of present award

Publications:

1. Pronin S, Brown L, Megaw R, Tatham A. Measurement of intraocular pressure by patients with glaucoma. JAMA Ophthalmology 2017; 135:1030-36.
2. Brown L, Foulsham W, Pronin S, Tatham A. The influence of corneal biomechanical properties on intraocular pressure measurements using a rebound tonometer. J Glaucoma 2018; 27:511-518.

Lyndsay Brown was awarded the prize for the best University of Edinburgh Primary Care Ophthalmology Masters project for this work. The work was also presented at The Scottish Ophthalmological Club (Sep 2018), American Glaucoma Society Congress (New York, March 2018) and Association for Research in Vision and Ophthalmology (Baltimore, 2018)

Donation of equipment:

Donation of 5 iCare HOME devices by the manufacturers (Icare Finland) for use on the project. These devices, which are not used by any other Health Boards in Scotland, are used to allow patients to measure their own intraocular pressure at home.

Additional funding:

£64,278 additional funding from Edinburgh and Lothian's Health Foundation to purchase an optical coherence tomography angiography (OCTA) device to allow imaging of blood flow in the eye, an important potential risk factor for glaucoma. £20,000 applied for from ELHF to fund Lyndsay Brown's salary for a further year.

(E) Acknowledgements

We are very grateful to Sight Scotland and the College for funding this work.

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Sushruta Professorship in Plastic Surgery

Transforming Lives. Breast Cancer Reconstruction: How we changed a procedure into an academic practice and then changed the world around us.

Professor Stefan O.P. Hofer, MD, PhD, FRCSC

Head Division of Plastic Surgery & Wharton Chair in Reconstructive Surgery, Departments of Surgery and Surgical Oncology, University Health Network, University of Toronto, Canada.

Sushruta-Guha Professorship Lecture 2018

I was grateful to be allowed to present the 2018 Sushruta-Guha Professorship lecture during the International Confederation of Plastic Surgery Societies (ICOPLAST) meeting at the Korean Society of Plastic and Reconstructive Surgery (KSPRS) meeting in Seoul, Korea on November 11, 2018. The lecture is intended to give an overview of the awardee's career contribution towards a specific plastic and reconstructive surgery area of interest.

Summary of lecture

Throughout my career I have had a strong interest for microsurgery, not mainly for the purely technical aspect of it but for the almost unlimited possibilities to solve big and previously virtually insurmountable clinical problems. Through microsurgical techniques we can make a real difference for patients with significant problems. In order to develop microsurgical skills and become confident continuous training and repetition in all aspects and areas of microsurgery are invaluable. The benefits of strong skills and a large experience makes significant impact on individual patients. Examples of a broad range of difficult problems that can be solved following surgical oncology resections in e.g. sarcoma, head & neck cancer, breast, neurosurgery, following trauma and select congenital deformity are shown. In order to make a bigger difference for a subset of patients and their care I present our experience of improving the practice of breast cancer reconstruction patients.

1. Breast reconstruction. The demand for breast reconstruction in women with or following breast cancer and women opting for prophylactic mastectomies due to high risk for developing breast cancer is very large. This can be attributed to good outcomes in patients who have long survival, which has led to a great interest from learners to be trained in breast reconstruction as well as from society in general to improve access and support breast reconstruction. The high volumes of women opting for breast reconstruction makes this population still what we would consider an underserved population.
2. Developing a breast reconstruction practice. The basic requirement to build an evidence based practice is to structure data collection through database development with dedicated staff. Next it is important to be unbiased and able to offer the most appropriate technique for the patient, which requires the surgeon to have the skills to perform all the different types of breast reconstruction or work in a team that has this complete skill set. Continuous audit of results and complications short and long-term is required to improve clinical practice from the surgeon's perspective. At the same time it is very important to be equally diligent with collection of prospective patient reported outcomes over time to be able to provide the best possible service to patients. These data then empower us to improve service delivery,

create guidelines and influence health care policy for our patients.

3. Integrating breast reconstruction into the institution. Several barriers exist when trying to build a breast reconstruction program. These barriers vary between different health care delivery systems. In our system we have engaged our breast surgeons and improved logistics by innovative models to share operating room and clinic resources. We have engaged our anesthesiologists with improved models of intra- and post-operative fluid and pain management. We have engaged our nursing staff and administrators by developing specific models for enhanced recovery after surgery thus improving patient experience and reducing length of stay.

4. Influencing health care policy for breast reconstruction. We studied patterns of care for postmastectomy breast reconstruction in Ontario as this is a quality indicator of breast cancer care. We studied patterns of care, looked at the relationship between breast reconstruction and patient-, surgeon-, and resource-factors, as well as mapped out the geographic distribution of breast reconstruction utilization and manpower of reconstructive surgeons. The main findings were that rates of immediate breast reconstruction in Ontario were lagging about 10 years behind the US rates. Immediate breast reconstruction is a privileged surgical service in Ontario that is only available to a small group of patients, who are younger, without invasive cancer, of higher socio-economic status, not a recent immigrant and come to a higher volume breast centre. From these findings the Provincial Cancer Care authority asked us to be part of developing breast reconstruction guidelines for the Province. This has resulted in a best-evidence document with guidelines on patient indications and appropriate surgical options for immediate and delayed breast reconstruction.

5. Patient education and community engagement. From all our research which has provided us with a wealth of data on patient reported and surgical outcomes we have developed several educational programs to improve decision making and patient advocacy and empowerment where it comes to make the correct individual choice for each patient. Also, it has enabled to develop and partner in a permanent presence of community events with local, regional, national and international impact. These events have different purposes, some purely educational and others more focused on fund raising, and are geared towards raising awareness.

Publications to all these topics are available through Pubmed (search Hofer SO)

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King James IV Professorship Lecture

The Pursuance of excellence and the advancement of dental education

Emerita Professor Elizabeth Shira Davenport BDS, PhD, MSc, FDS RCS(Ed), FHEA

Institute of Dentistry

Barts and The London School of Medicine and Dentistry

Queen Mary University of London

Delivered at the Annual meeting of the Faculty of Dental Surgery, October 3rd 2019

Introduction

I was honoured and pleased to present the 2019 King James IV lecture at the Annual Meeting of the Faculty of Dental Surgery held in the Symposium Hall, Royal College of Surgeons of Edinburgh in October 2019.

Many higher education institutions across the world include the pursuit of excellence as a key element of their mission statement[1,2]. In current education, clinical and research delivery, there are many conflicting factors such as change that contribute to or prevent achieving excellence. Any such change may be connected to world demographics and disease epidemiology, cause and effect, biological, pharmaceutical and dental material advancements, population expectations; their desires and wants on all aspects of health including oral health.

For the dental profession, it is also very clear that evidence-based decision making[3], professional and ethical behaviour and remaining competent safe practitioners is paramount in the delivery of appropriate and safe oral health care for all[4].

The underlying ethos that informs my views as a passionate Paediatric Dentist continues to be the need to recognize the importance of oral health care for children within the holistic picture of child health. This translates into pedagogic practice by adopting strategies for teaching that will foster students to develop as individual learners. A key element has been to embed professionalism, through maintenance of high standards of clinical practice and by setting examples that inspire dental students, trainees and colleagues to appreciate all aspects of oral healthcare, develop competencies and confidence in everyday clinical practice. High quality feedback is crucial for all learning, in that the profession and especially those aspiring to become dental professionals must learn from and reflect on ‘critical incidents’ and accept that each clinical encounter should be recognized as such and treated in the same way. The realization that effective professional practice entails lifelong learning is key to success, remaining current and being ‘safe to practice’. The constant that underpins professional practice is those principles outlined in the General Dental Council’s (GDC) Professional Standards[4,5,6].

To this end, this paper will illustrate how excellence can be achieved in an ever-changing environment of work and learning by research undertaken under my leadership.

Population and disease

Demography and epidemiology are essential elements to recognise exactly what is required of and by the dental

profession to pursue excellence, progress and accommodate change. As previously mentioned, many interrelated challenges create uncertainty of knowing how to respond and provide safe professional oral health care. Indeed, the essentials of recognising population change in terms of size, gender and age. Aging brings with it the notion that different disease patterns and individual needs prevail, often than not uppermost in a clinician's mind.

Excellence is achieved by knowing and recognising the impact that knowledge will have on the delivery of excellent, professional and safe daily practice supported by dental education. Hence, the need for the profession to reflect and ask why, think so what and draw what one observes and hears together in making decisions in a safe and professional manner. Research practice requires the same vigilance as researchers strive to support the profession by identifying the best approach to disease management, clinical technique, dental materials and pharmaceutical developments and dissemination of outcomes to the profession.

Clinical research excellence

Striving to achieve excellence, good ethical research practice is essential[7]. By knowing the question, research should be based on and employing the best suited protocol to achieve an outcome and reported accordingly. Negative results are as valuable as positive as demonstrated by a case control study undertaken in East London to investigate the relationship between maternal periodontal disease and preterm low birthweight (PTLBW)[8]. PTLBW delivery is associated with a complex series of events that are exacerbated by the cascade of events including a build-up of inflammatory mediators linked to inflammation such as periodontal disease, resulting in the maternal environment becoming hostile and the foetus being expelled[9]. But, using different populations, measurement parameters account for known risk factors and poorly calculated studies creates tension in knowing whether a risk of delivering PTLBW infant actually exists. There is support that child bearing women across the world are not at risk at delivering a PTLBW infant if they have periodontal disease[8,9]. In order to follow up the original research question, a small cohort of women from the same population of East London did provide some limited evidence that periodontal pathogens can be translocated to the foetal placental unit[10]. A further such study explored 100 preschool children born pre-term low birthweight of their oral health and associated risk factors, and demonstrated that a relationship between poor diet, pre-term and low birth weight existed but not sufficient other than to provide support to parents to access dental care and oral health advice[11].

Excellence in Dental Education

Considering all of the above principles, promoting excellence in dental education and its advancement is dependent on pedagogy. Again, there are many complexities and decisions to consider and make that are relevant to every day practice. Nevertheless, approaches vary but should reflect the different social, political, and cultural contexts from which they emerge.

The first example here is recognising the importance of good curriculum design, that is innovative, fit for purpose and forward looking underpinned by the best available education principles[12]. Even in 2019 as in 1997, availability of suitable patients continues to create challenges to ensure that undergraduate dental students and trainees gain the necessary experience to become safe practitioners.

The second example encompasses the General Dental Council's need for all dental registrants to undertake continuous professional behaviour to promote life-long learning and that a 'Progress File' for Higher Education should be embedded throughout HE in the United Kingdom. To this end, we designed a Progress Files for Dentistry (PF) for use throughout working life to monitor, build and reflect on one's own personal development that supports the General Dental Council's expectations of the registrants[13].

The benefits of and barriers to PF were explored amongst dental undergraduates and trainees. Reflection, a key element of the PF was found to help to 'know who you are now' and prompt communication. However, completing professional development plans was thought to be a necessary evil but often completed hurriedly before meeting with a supervisor. The culmination of this work was a Progress File Learning System that relied on an honest and full approach[14], and a willingness to reflect in a safe environment but not be required to disclose intensely personal reflections[15,16].

Our research has provided many pointers for best practice, most of which are relevant today. The same barriers persist in that there must be an ability and willingness to undertake whatever is required for reflection and monitoring progress. Many principles continue to be challenged not least personal reflection for example in the recent Abbe Gawa case whereby trainees are now reluctant to be honest in their recorded reflection as discussed on numerous occasions in the British Medical Journal during 2018-19[17].

Monitoring undergraduate and postgraduate students and trainees is essential. What has become more of a challenge is the need to act in the occurrence of an untoward event or where patterns of poor behaviour or practice are exhibited. Certainly, with my student Fitness to Practise hat on believe this is of the utmost importance for both the students, staff and institutions well-being and reputation.

The third aspect of this work was to consider just how do dental students learn in the dental environment? Our work in the United Kingdom and Saudi Arabia confirmed the importance of effective learning environments, in that positive learning embraced reflection and self-directed learning from clinical experience. Importantly dental undergraduates' learning styles were predominantly visual and sensing. If such characteristics are recognised the notion for 'fit for purpose' curricula can be more easily obtained and delivered[18,19].

Pursuance of excellence: Professionalism

The final aspect of this lecture drew together the aforementioned research, developments, expectations that all healthcare professionals should behave and act in a professional manner, this remains a major challenge of every day clinical practice. A clear message is the importance of reflection as part of safe daily practice. Most dental schools now use the LiftUpp system as a means to monitor and respond to deviations of student progression[20]. An illustration of one of the original aims of the PF project being achieved through working developed in partnership with six dental schools, whereby educators remain cognizant of the GDC Standards for the Dental Team[4] and therefore mindful of the need to explore and react to those external and internal factors that might warrant change in process to underpin professional attitude.

Professionalism has many variations, one might be the notion that 'Dentistry is a

vocation in which a dentist's knowledge, clinical skills, and judgment are put in the service of protecting and restoring human well-being. This purpose is realized through a partnership between patient and dentist, one based on mutual respect, individual responsibility, and appropriate accountability' [21]. Another might be 'professionalism may not be sufficient to drive profound and far reaching changes needed in the US health care system, but without it, health care enterprise is lost. Professionalism needs to evolve from being conceptualised as an innate character trait or virtue to sophisticated competencies that can and must be taught over a lifetime of practice' [22].
I believe, professional behaviours are profoundly influenced by the organisational and environmental context of contemporary medical/dental practice, and that these external forces need to be harnessed to support not inhibit professionalism in practice. Our research found professionalism to be multidimensional and multifactorial, as the student practitioner transformed into a professional safe beginner. By using patient centred models learning can support a useful direction for which mechanisms advance the development within the dental curriculum. The research we undertook utilised interpretivist qualitative methodology to explore undergraduates' responses to questions about experiences or interactions that had influenced their professional development. Thematic findings provided a base to compare theoretical perspectives of learning including characteristics, communication skills, patient relationships, knowledge & technical skills[23]. We found that progression of first to final year students demonstrated changes in focus from self to wider and through the students' narratives both positive and negative interactions within and the experience and response to the environment resulted in the recognising the impact of the patients, teachers, other staff and fellow students had also influence and defined moments of development. A key aspect associated with the observation of their teachers as role models both inspired and confused the students. A conceptual patient centred model of learning and the development of empathy has provided a useful direction for mechanisms to support advancement of the development of professionalism within the dental curriculum[24].

My final comments concerned the achievement of establishing the Faculty of Dental Surgery Strategy 2020. Whereby knowing the risk of success and reputation, priorities as evidenced from membership and examination data, funding limitations, communication across the directorates, advisory boards and Dental Council, the capability and capacity of the organisation and partners across the world is dependent on good governance before excellence in dental education can be achieved within the context of the Royal College of Surgeons of Edinburgh worldwide.

Conclusion

Dental Education is in a better state then when I first entered the arena of dental education, it is aligned with best educational practice 5,12 and the Regulator's expectation 4, 5, 6.

Graduates have learnt to reflect, are 'safe to practice' and prepared for clinical practice on graduation 15,16, 20, 24. Professionalism requires constant vigilance by all healthcare professionals.

Finally, I have demonstrated using best professional and research principles that excellence in research has informed and influenced excellence in the delivery of dental education across the world to the benefit of those in training and the patients we provide care for.

References

London School of Hygiene and Tropical Medicine. Mission and Strategy https://www.lshtm.ac.uk/aboutus/introducing/mission (accessed 04.032020)

Royal College of Surgeons, Faculty of Dental Surgery, Advancing the Practice of Dentistry. Strategy 2020

Evidence Based Dentistry: An Introduction. Allan Hackshaw, Elizabeth Paul, Elizabeth Davenport. Blackwell Munksgaard 2006

General Dental Council. 1993. Standards for the Dental Team. www.gdc-uk.org (accessed 04.03.2020)

General Dental Council Standards for Education. Standards and requirements for providers Nov 2012. (v2 revised 2015) www.gdc-uk.org (Accessed 04.03.2020).

General Dental Council Standards for specialty education. Standards and requirements for programme and examination providers . January 2019 www.gdc-uk.org (accessed 03.04.2020).

IADR Code of Ethics May 2009. https://www.iadr.org/IADR/About-Us/Who-We-Are/Code-of-Ethics (accessed 23.05.2019)

Davenport ES, Williams CES, Sterne JAC, Murad S, Sivapathasundaram V, Curtis MA. Maternal Periodontal Disease and Pre term Low Birth weight: Case-control study. Journal of Dental Research 2002; 81: 313-318.

Davenport ES. Pre Term Low Birth Weight and the Role of Oral Bacteria. Journal of Oral Microbiology 2010, 2: 5779 - DOI: 10.3402/jom.v2i0.5779 >2000 hits by Dec 2011

Bearfield C, Davenport ES, Ayisa G, Sivapathasandaram V, Allaker RP. Possible association between amniotic fluid micro-organisms infection and microflora in the mouth. British Journal of Obstetrics and Gynecology 2002:109:527-533.

Davenport ES, Litenas C, Barbayiannis P, Wiiliams CES. The effects of diet, breast-feeding and weaning on caries risk for pre-term and low birthweight children. Int J Paed Dentistry 2004; 14:251-259.

Fry 1997 Fry H, Jones A, Davenport E. and Brook A. Changing Curricula: an evaluation from dentistry. Medical Teacher. 1997:19:108-113

Fry H, Davenport ES, Woodman T, Pee B. Developing Progress Files: a case study. Teaching in Higher Education 2002, 7:1:97-111.

Pee B, Woodman T, Fry H, and Davenport ES. Practice-based learning: views on the development of a reflective learning tool.

Medical Education 2000: 34 : 754-761

Pee B, Woodman TM, Davenport ES. Developing teaching and learning innovations in dental training: the example of the Progress File learning System. (British Dental Journal 2003: 195; 463-465)

Woodman T, Pee B, Fry H, Davenport ES. Practice -based learning: emerging professional characteristics, self-concepts and patterns of knowing in dental training. European Journal of Dental Education. 2002; 6: 9-15.

Dyer C and Cohen D. What Bawa-Garba means for your e-portfolio. British Medical Journal 2018;360:k572

Sindi AM, Davenport E. The Learning Profile of Saudi Undergraduate Dental Students. J Dent Res 90 (Spec Iss A). 1718. 2011.

Sindi AM, Davenport ES, Farsi JM. Learning Styles, Learning Approaches and the Perception of the Dental Learning Environment at KAUFD. J Dent Res 88 (Spec Iss A). 664. 2009.

LiftUpp. https://www.liftupp.com/about (accessed 23.05.2019)

Trathen A and Gallagher JE. Dental Professionalism: definitions and debates. British Dental Journal 2009, 206, 249-53

Lesser CS, Lucey CR, Egener B, Braddock CH, Linas SL, Levinson W. 2010 A behavioural and systems review of professionalism. JAMA 2010. 304, 2732-7.

Illeris K . 2004 The three dimensions of learning: contemporary learning theory in the tension field between the cognitive, the emotional and the social. Translated into English by Dorothy Reader and Margaret Malone, Frederiksberg, Roskilde University Press; Leicester: Niace

Ranauta A, Freeth D, Davenport E. Developing understanding and enactment of professionalism: undergraduate dental students' perceptions of influential experiences in this process. Brit Dent J. 2018: 225, 662-666.

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