THE ROYAL COLLEGE OF SURGEONS OF EDINBURGH

RESEARCH REPORT 2020–22

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Foreword from the President

FROM THE PRESIDENT
President, The Royal College of Surgeons of Edinburgh

The last introduction I wrote for this report was when we were at the height of the Covid-19 Pandemic. We are not free of the virus, but I am delighted to be writing about a revitalised and exciting period of work. The speed and relish our researchers have taken in getting back to their respective projects is something I find inspiring in the midst of such a challenging period for us all.

Inevitably not all aspects of our work are back to full strength, particularly in relation to some of our international activity. Yet, the following pages reveal so much more about what we have been able to do. The obstacles we face in healthcare are at times overwhelming but the research and innovation we commit to brings long term benefits and, in some cases, transformations for the patients we endeavour to help.

No introduction to this report would be complete without thanking our formidable panel of volunteer clinicians who have given much of their precious time to allow this work to progress.

First and foremost, I would like to thank Professor Steve Wigmore for his extraordinary leadership and stewardship of our Research Committee. Steve has overseen some of the great innovations in our work from the creation of the Bowel Cancer UK Research Chair to partnerships with organisations like ORUK and the Vascular Society. As a clinician in great demand, we have been very fortunate to have him guide us through the years. Having recently demitted office, I extend my heartfelt thanks for his wisdom and dedication.

Professor Wigmore is not the only great researcher we are losing this year. Professor Hamish Simpson, Professor Michael Steele and Paul Shiels stand down having dedicated many years to our Research Committee. Hamish and Michael embody the best traditions of the College, supporting innovation and the next generation. I am deeply grateful for the years of time and effort they have put into the Committee.

Professor Angus Watson has been appointed Chair of the Research Committee and will lead us into a promising future of new partnerships, global engagement and growing resources for our membership. I would like to thank him and our committee for their dedication and contribution. Without their steadfast support and oversight, our commitment to research grants would not be possible on the scale you see in these pages.

This is my last year as President and as a member of the Research Committee. It has been a privilege to see the growth and ambition our volunteers have nurtured in my four years on the Committee. I am sure our work will go from strength to strength under Professor Parks' and Professor Watson's leadership.

Professor Michael Griffin OBE PRCSEd
November 2022

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Introduction

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

Covid-19 has had a major impact on research with closure of laboratories, disruption of travel and reduction and limitation of clinical surgical services. Coupled with this, the economic consequences for the stock markets have reduced the ability of many charitable organizations to offer grants and support research and innovation. In spite of this I am pleased to report that the activities of the Research Committee have continued largely uninterrupted and the competition for grants and awards remains intense. We are grateful to Sight Scotland (formerly Royal Blind) for their renewed support for the ophthalmology grants programme. We are also grateful to our industry collaborators B Braun who have supported new travel and innovation grants to support young surgeons exploring novel technologies. Our partnerships with the Circulation Foundation and Orthopaedic Research UK (ORUK) have allowed us to create new fellowships in vascular and orthopaedic surgery respectively.

Credit must be given to Michael Stitt who has spearheaded many of these collaborations and to Professor Hamish Simpson who was actively involved in the initiation and delivery of the RCSEd/ORUK fellowship. Perhaps our most exciting collaboration is with Bowel Cancer UK to create a Scottish Chair in Colorectal Surgery. This initiative has taken a lot of work from many people and has just been launched for expressions of interest to Scottish Universities.

In spite of the impact of the pandemic there has been no diminution in the quality or productivity of surgeons involved in research and this is very pleasing to see. Research remains an integral part of surgical training and the role of the College in facilitating research and innovation is extremely important.

From a cultural perspective the biggest benefit that the Research Committee has seen in recent years has been the high level of engagement from the Office Bearers and the high priority that research has been given in the portfolio of activities of the College.

I am extremely grateful to the members of the research committee who give their time and expertise voluntarily to score grants and awards and attend committee meetings. As I hand over the chair of the committee to Professor Angus Watson, I do so in the knowledge that the committee is in very safe hands and that the research and awards activities of the College are in a strong position and offer many fantastic opportunities for members and fellows.

Professor Stephen J Wigmore
November 2022

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Donors

DONORS TO THE 2020-2022 RESEARCH REPORT

Alban Barros D'Sa Family
Cutner Memorial Bequest Fund
Ethicon Foundation
The James Weir Foundation
Lindsay Stewart
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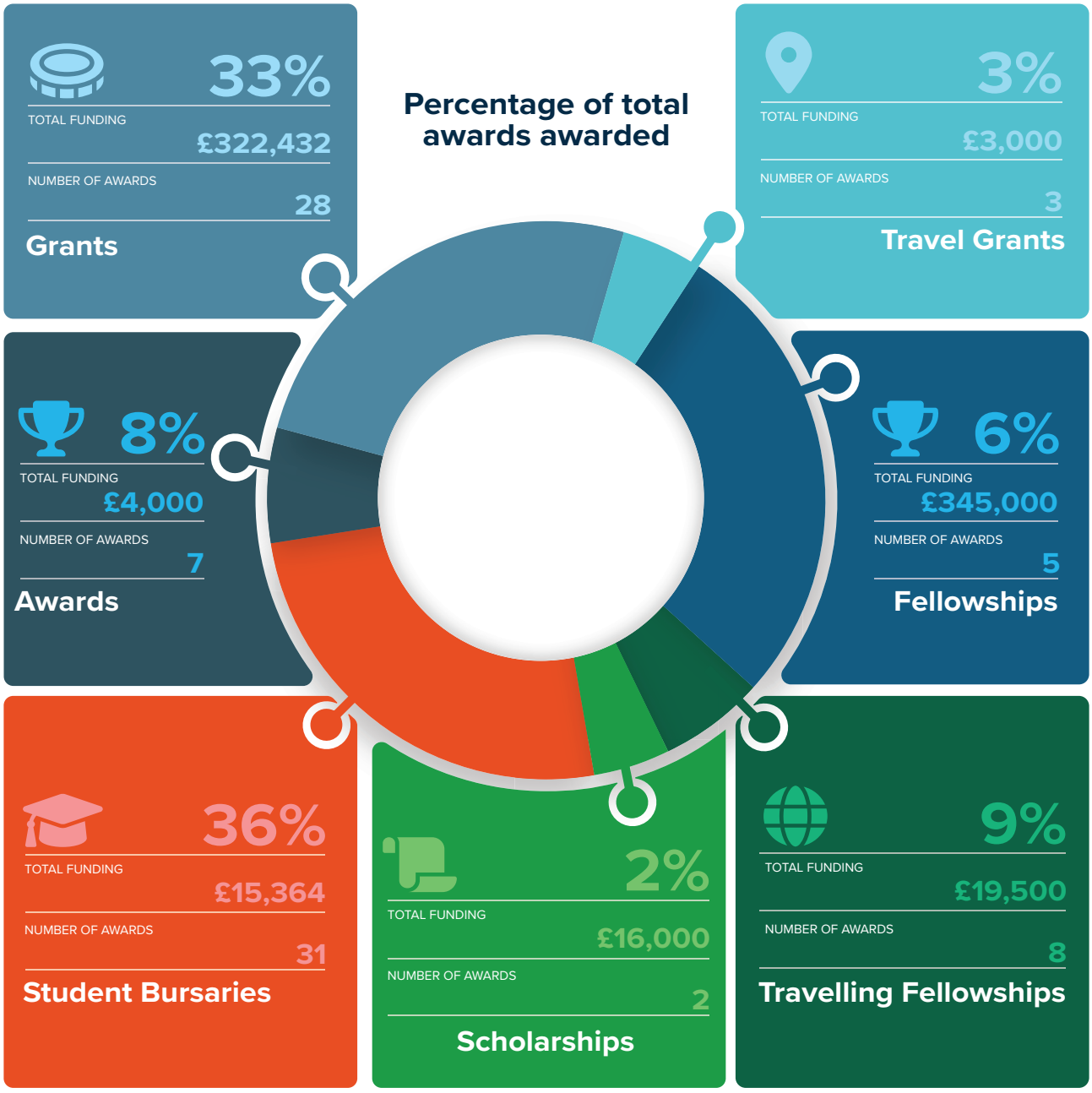
Medical Research Council
B. Braun
Maurice Wohl Foundation
Mr Iain Fraser
Palliation and the Caring Hospital (PATCH)
Robertson Trust
Sight Scotland
Scottish Oral & Maxillofacial Society
Peter Chung, Shanghai Head and Neck Maxillofacial Oncology Centre at the Ninth People's Hospital of Jiaotong University
Peter Chung, National Cancer Hospital, Beijing
Somes Guha
Dato' Hj Mohamed Zainal Abidin Bin Hj Abdul Kadir
Amanda Wong-Powell
Binks Trust
Russell Trust
Jane Goodman Charitable Trust
Orthopaedic Research UK

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

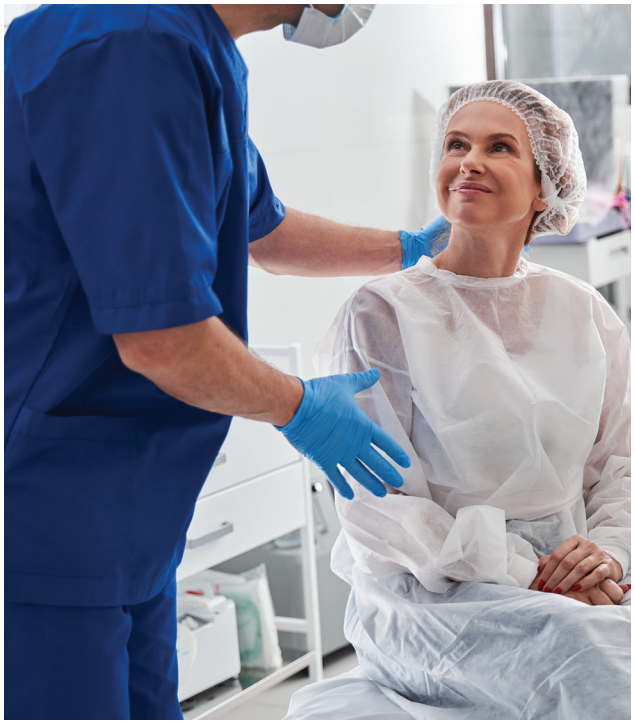
Research Report in Numbers

Total awards awarded: 86



Total amount of Funding

£725,296



EDUCATION

TOTAL FUNDING

£6,344.00

4 NUMBER OF AWARDS

1% PERCENTAGE OF FUNDING

GENERAL SURGERY

TOTAL FUNDING

£44,224.00

13 NUMBER OF AWARDS

6% PERCENTAGE OF FUNDING

DENTAL

TOTAL FUNDING

£48,815.00

10 NUMBER OF AWARDS

7% PERCENTAGE OF FUNDING

ORTHOPAEDICS

TOTAL FUNDING

£196,442.00

12	NUMBER OF AWARDS
27%	PERCENTAGE OF FUNDING

PAEDIATRIC SURGERY

TOTAL FUNDING

£9,700.00

9	NUMBER OF AWARDS
1%	PERCENTAGE OF FUNDING

VASCULAR

TOTAL FUNDING

£170,250.00

3	NUMBER OF AWARDS
23%	PERCENTAGE OF FUNDING

CANCER

TOTAL FUNDING

£55,890.00

7	NUMBER OF AWARDS
8%	PERCENTAGE OF FUNDING

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Research Funding

Research Funding Fellowships

This project is investigating if the cholesterol-lowering drugs statins, can reduce inflammation from wear debris and prevent bone break down to allow patients to mobilize pain free for longer.

£60,000

THE LORNA SMITH CHARITABLE TRUST RESEARCH FELLOWSHIP:

Peter Gallacher, Clinical Research Fellow and GP Trainee, University of Edinburgh

"Burden of comorbidity in ANCA vasculitis: a national data-linkage study"

Current treatments have significantly improved outcomes of ANCA vasculitis patients. These patients are now living longer and are therefore at an increased risk of developing other medical conditions, or 'comorbidities' (e.g. cardiovascular disease). In the general population, comorbidities reduce quality of life, increase resource consumption and risk of death. This study will utilise routine patient data from hospitalisation, prescribing and death records to:
1) characterise temporal trends in the risk of developing various comorbidities in a large population of ANCA vasculitis patients, compared to the general population; and,
2) evaluate the financial burden associated with comorbidities in this at-risk group

£50,000

THE MAURICE WOHL RESEARCH FELLOWSHIP IN SURGERY AND DENTAL SURGERY:

Mr Sami Anjum, NIHR Academic Clinical Fellow in Trauma and Orthopaedic Surgery, Newcastle

University / Northern Deanery – Health Education England

"Improving the longevity of joint replacements for patients - can statins reduce the inflammatory response to orthopaedic biomaterials 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

Travelling Fellowships

ALBAN BARROS D'SA MEMORIAL TRAVELLING FELLOWSHIP IN GENERAL SURGERY:

Chris Johnston, Clinical Lecturer/ ST8 in HPB/Transplant Surgery, Royal Infirmary, Edinburgh
Cambridge Transplant Centre (Addenbrooke's Hospital). Acquiring focussed clinical experience in transplantation and novel perfusing technologies (including NRP and Organox) and to establish new collaborative research projects building on the success of previous clinical trials.

£1,000

Francis Robertson, ST 8 HPB Transplant Surgery, Royal Infirmary of Edinburgh

European Pancreas Centre, Heidelberg, Germany

Attending to visit a high-volume pancreatic centre and gain an understanding of their approach to the management of pancreatic disease and to gain exposure to robotic pancreatic resections.

£1,000

B BRAUN FELLOWSHIP IN GENERAL SURGERY:

Mohan Singh, Senior Clinical Fellow in Oesophago-Gastric Cancer Surgery, University of Oxford Cancer Center, Department of Surgical Oncology, University Medical Center Utrecht and the Cancer Institute Hospital Tokyo, to study robotic and minimally invasive approaches in cancer resections and to learn the Japanese techniques in lymphadenectomy.

My B Braun Fellowship to The Cancer Institute Hospital in Tokyo is to learn the optimal way of performing radical oesophageal (gullet) and stomach cancer surgery using minimally invasive principles. This is a prolifically high volume centre performing traditionally radical life-prolonging cancer surgery utilising key-hole techniques which have demonstrated significantly lower post-operative complications, lower cardiopulmonary complications, less post-operative pain, less blood loss, better quality of life and better short-term functional recovery, all at comparable costs and oncological outcomes to standard open surgery. My learning objective also includes recording their delivery of a highly effective enhanced recovery program for oesophageal surgery.

£5,000

Travelling fellowships Continued...

CUTNER TRAVELLING FELLOWSHIP IN ORTHOPAEDICS:

Paul Stirling, Orthopaedic Surgical Registrar, ST5, Royal Infirmary Hospital for Sick Children, Edinburgh University of Michigan and University of Chicago

I am an Orthopaedic Registrar focusing on a career in Hand Surgery. I plan to visit four centres of excellence in the USA: Ann Arbor, Michigan; Chicago, Illinois; Austin, Texas; and Louisville, Kentucky. This fellowship will provide me with exposure to a large volume of high-energy hand trauma that is not commonly encountered in my geographic region. A further goal is to share ideas for improving the coordination of outcomes-based research. I hope that discussing this with leading experts in the field will enlighten me and may even enable me to improve our system here on my return.

£3,000

Prithee Jettoo, ST8 Trauma and Orthopaedics Registrar, Northern Deanery Training Programme

Institut de Chirurgie Réparatrice Locomoteur & Sports-Institute For Sports and Reconstructive Bone & Joint Surgery, France

My planned fellowship is in upper limb surgery with Professor Boileau for a year. I have completed my trauma and orthopaedic training in the Northern deanery. This has endowed me with a holistic approach to providing patient care and safety. There is more training that is yet to be mastered and I am excited to continue this lifelong learning. I believe this fellowship will allow me the opportunity to learn and develop further skills in shoulder arthroscopy and arthroplasty, which I can translate to my clinical practice. I thank the RCSEd for contributing to this.

£1,500

ETHICON FOUNDATION TRAVEL GRANTS:

Daniel Winson, ST8 Trauma and Orthopaedics Registrar, University Hospital of Wales

Mater Public Hospital Brisbane, Wesley Hospital Brisbane, Brisbane Private Hospital

During my fellowship I will be practicing Foot and Ankle surgery with a particular focus on arthroscopic surgery. Along side my clinical work I have also been given the opportunity to become involved in some ongoing research projects. I will be working with a PhD student to provide guidance on the clinical aspects of their study. The study in question is looking at biomechanical performance of children with Talipes Equinovarus (Club foot) both before and after surgery. It is our hope that this work will improve the future treatment of this condition.

£1,500

Michael Hart, Specialty Registrar, Neurosurgery, Addenbrooke's Hospital, Cambridge.

Vancouver, British Columbia, Canada.

Fellowship in Functional Neurosurgery.

£1,000

Iain Murray, Specialty Trainee Year 8, Trauma and Orthopaedic Surgery, Royal Infirmary Edinburgh.

Stanford University, Department of orthopaedic Sports Medicine, California.

Clinical Fellowship in Orthopaedics Sports Medicine.

£1,000

Richard Stevenson, General & Colorectal Surgery, Glasgow Royal Infirmary.

Peter MacCallum Cancer Centre, Melbourne. Post-CCT Fellowship

£1,000

Travelling fellowships Continued...

JOINT RCSED/SOMS/SHANGHAI HEAD AND NECK FELLOWSHIP:

Pavan Padaki, ST7 Oral and Maxillofacial Surgery, Royal Preston Hospital

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

£4,500

THE SIR JAMES FRASER TRAVELLING FELLOWSHIP IN GENERAL SURGERY:

Kenneth Elder, ST8 General and Breast Surgery, Western General Hospital, Edinburgh

Kameda Medical Centre, Japan, To learn about cryoablation under image-guidance as a nonsurgical treatment for Small Breast Cancer.

The current UK practice involves general anaesthetic and invasive surgery for all breast cancers. Cryoablation is a new technique that can be done with local anaesthetic for small nonaggressive cancers in the outpatient setting which is not only quicker and less painful for patients, but for those deemed unfit for general anaesthetic offers a safe treatment modality outside of endocrine therapy and observation alone. Currently no centre in the UK offers this service.

I plan to visit a centre in Tokyo with extensive experience in this technique with a view to trialling the therapy at the Edinburgh Breast Unit.

£2,000

Awards

KING JAMES IV PROFESSORSHIP:

Michael Beverley, Post-Doctoral Researcher, Nuffield Orthopaedic

Centre, Oxford

"Dry Bones"

£500

Gerry McKenna, Senior Lecturer/ Consultant in Restorative Dentistry, Queens University Belfast

"Rethinking Oral Care for Older Adults

£500

Douglas Peterson, Professor Oral Medicine, UCONN School of Dental wMedicine, USA

"Dental Management of the Oncology Patient: Translating Research into Guidelines for Clinical Practice and Improved Patient Care"

£500

Dr Barry F.A. Quinn, Professor of Restorative Dentistry & Dental Education, University of Liverpool

"Can we simulate dental surgery in virtual worlds and how real does the simulation have to be?"

£500

Professor Prokar Dasgupta, King's Health Partners Professor of Surgery, Chair in Robotic Surgery and Urological Innovation, King's Institute of Robotic Surgery

"The translational implications of the science behind the overactive bladder"

£500

Professor Leela C Biant, Academic Head of Department Trauma & Orthopaedic Surgery, University of Manchester; Honarary Consultant Orthopeadic Surgeon, Manchester University Hospitals; Clinical Reader Cell Matrix Biology & Regenerative Medicine, University of Manchester; Honorary Professor of Trauma and Orthopaedic Surgery, University of Salford

"Regenerating Damaged Joints; from bench to bedside to theatre and round again"

£500

Awards Continued...

SYME MEDAL:

Janice Miller, University of Edinburgh

"Characterisation and mechanisms of altered body composition and tissue wasting in cancer cachexia".

Simon Matthew Graham, Orthopaedic Surgical Trainee, University of Edinburgh

"Fracture Healing in Human Immunodeficiency Virus Positive Patients: HIV in Orthopaedic Skeletal Trauma (HOST) Study".

F**rancis Paul Robertson,** Speciality Training General Surgery, Royal Infirmary of Edinburgh (HPB +Transplant)

"The Effect of Remote Ischaemic Preconditioning on CD4+ T Cells following Hepatic Ischaemia Reperfusion Injury"

Kamran Asim Gaba, ST4 Vascular Surgery, University Hospital Southampton NHS Trust

"Identifying Optimal Pathways of Care in the Delivery of Cardotid Interventions".

Dr Iestyn M Shapey, Specialist Trainee in General and Hepatobiliary Surgery, NHS Education North West and Honorary Clinical Lecturer, University of Manchester

"Insulin Therapy in Pancreas and Islet Transplantation".

Jamie Nicholson, Specialist Trainee and Honorary Clinical Teaching Fellow, Edinburgh Orthopaedic Trauma Unit, Royal Infirmary of Edinburgh

"NONUNION OF THE CLAVICLE: Novel use of clinical recovery and ultrasound to improve our ability to predict fracture healing"

Ishaan Maitra, ST7 General and Colorectal Surgical Registrar, Health Education Northwest.

"Delineating the difficulties in diagnosing oesophageal adenocarcinoma destined to arise from Barrett's oesophagus and exploring the role off vibrational spectroscopy from biofluid and tissue analysis".

LINDSAY STEWART PRICE:

Dr Webster Musonda

“Risk Factors for Surgical Site Infection following Intramedullary Nailing of Closed Diaphyseal fractures of the Femur and Tibia in Adult Patients at the University Teaching Hospitals, Lusaka, Zambia: Cross-sectional study”.

£1,000

Grants

FACULTY OF DENTAL GRANTS FOR EDUCATION:

Alice Kathleen Duke, Duke, University of Kent

MSc Advanced and Specialist Healthcare (Applied Dental Professional Practice)

£2,877

Morag Powell, University of Glasgow

MSc Health Professions Education (Research Year)

£3,000

Laura Timms, University of Sheffield

PG Cert Medical Education

£3,000

Adam Jones, University of Leeds

Post Graduate Certificate in Clinical Education

£3,000

FST/ASME EDUCATIONAL RESEARCH GRANTS:

Karin Baatjes, Stellenbosch University, South Africa

Real-life procedural videos: an additional assessment tool for structured oral examinations of surgical trainees?

The global COVID pandemic provides opportunities for innovation in the postgraduate surgical teaching program. Real-life recordings of procedural surgery cases as an addition to the traditional teaching methods seems fitting.
These videos also have the potential to be utilised during surgical oral assessments. An additional benefit of the recordings is the possibility of remote application, thereby limiting person-to person contact as well as long distance travel to exam venues in wide geographical areas. The COVID pandemic has stimulated the revision of teaching and assessment practices in our surgical curriculum, but thorough evaluation of such actions should be researched.

£2,367

Aimee Marie Charnell, Leeds Institute of Medical Education

How do Surgical Trainees Learn in Outpatient Clinics? A Video Reflexive Ethnography Study.

Outpatient clinics form a significant workload within surgical practice, both for consultants and trainees. In other elements of surgery, training is incremental; however, in clinics, large responsibility is often given early in surgical training. While learning in the outpatient clinic has been studied previously, it is yet to be explored by observing trainees in their natural clinical practice. This study examines how trainees learn within outpatient clinics by filming trainees completing outpatient clinics. Clips chosen by the trainee and consultant will be shown to multi-disciplinary surgical teams who will determine how to best support trainees in clinics.

£977

James Ashcroft, Academic Clinical Fellow, Department of Surgery, University of Cambridge

Exploring the legitimate participation of surgical trainees within the operating room

In the operating room, newcomers to surgery are inducted into a unique world by shadowing a skilled mentor in an entirely new physical environment with a host of new surrounding faces. The goal of this study is to understand how surgical trainees, through their participation in the operating room community of practice, can learn to 'become a surgeon'. A multi-method strategy of observing and interviewing surgical trainees will be undertaken with reference to their experiences in the operating room. The evidence gained from this study will give insights into how to support the trainer-trainee relationship in modern surgical training.

£1400.98

Grants Continued...

GLOBAL SURGERY FOUNDATION:

Matyas Fehervari, General and UGI Surgical Registrar in the NW London Deanery, Association of Surgeons of Training NW London Representative, and Research Fellow, Imperial College

"Validation of online laparoscopic surgical training"

Online surgical skills teaching has the advantages to serve learners simultaneously in different regions, reduce the cost, time and carbon footprint of travel. It offers more equity in access to resources compared to face-to-face tutorials. Our previous experience with online hands on surgical skills teaching suggest that most of skills development originates from the learner own experience with the instruments. Building on this we will set up a trial online key-hole surgical skills course with trainers only virtually present and compare learning outcomes and development of skills to simultaneously held traditional face-to-face teaching.

£1599.02

Prof. Thomas Weiser, Senior Clinical Lecturer in General Surgery

Clean Cut: Reducing Surgical Site Infections in Ethiopia

£12,000

Dr Joseph Epodoi, Senior Consultant Surgeon and Urologist

Urology workshop - A new experience at Soroti Regional Referral Hospital, Uganda

£7,828

Mengistu Gebreyohanes Mengesha, Assistant Professor of Orthopedic Surgery

James Harrison, Consultant Trauma and Orthopaedic surgeon, Countess of Chester NHS Foundation Trust, Honorary Professor of Musculoskeletal Biology and Aging, Africa Regional Director, AO Alliance.

Ethiopian BOne Setter Associated Disability (BOSAD) multicenter national prospective cohort study

£11,922

Kids OR, Fundraiser

Kids OR Scholarship Program for South Sudan

£6,500

OPHTHALMOLOGY MAJOR GRANTS:

FUNDED BY Sight Scotland

Professor Robert MacLaren, University of Oxford

“Developing CRISPR delivery strategies for the treatment of inherited retinal diseases”.

The CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) pathway is a bacterial defence system whereby adapted RNA molecules (known as guide RNAs) bind to invasive viral DNA and target them for cleavage by Cas9 (CRISPR associated protein 9) endonucleases. Adeno-associated viral (AAV) vector-mediated delivery of modified CRISPRCas9 systems into human cells is currently being evaluated for corrective editing of DNA mutations in situ. However, as each CRISPR-Cas9 system can only target a specific DNA mutation, several hundred bespoke CRISPR-Cas9 systems would potentially need to be designed to treat all possible mutations associated with any particular genetic disorder. Our proposal intends to develop a safe and versatile gene editing therapy combining a single universal AAV-Cas9 vector that can be applied to all patients, in combination with guide RNA (gRNA) that has been customised for a single type of mutation.

£59,992

Dr Roly Megaw, University of Edinburgh

“Identifying Therapeutic Targets for Retinitis Pigmentosa by defining Photoreceptor Cell Death”

The inherited retinal dystrophies are a group of untreatable, monogenic eye diseases and the leading cause of visual loss in children and adults of working age. Mutations in over 100 genes cause death of the light sensing photoreceptors, with the mechanism of cell death poorly understood. Determining the final common pathway through which photoreceptors die could identify novel targets for therapy; a form of ‘imprecision medicine’ that could be applicable across several disease-causing alleles. Preliminary work carried out by our lab has identified novel cell types which enter the retina as photoreceptors are degenerating that may contribute to cell death. Further investigating this process, with a long term goal of developing a novel therapeutic for the condition, forms the basis of this grant application.

£59,996

Grants Continued...

SMALL PUMP PRIMING GRANTS:

David Edwards, Academic Clinical/Fellow Honorary StR, Newcastle University

"Evaluating bioaerosol and splatter following dental aerosol generating procedures – preliminary investigation"

The COVID-19 pandemic has severely impacted the provision of dental care and dental education across the UK. This is because of concern that the virus which causes COVID-19 (SARS-CoV-2) may be carried from the mouth of infected patients in the water spray produced by dental equipment such as drills. Our project will develop two methods to look at how much of a problem transfer the of virus is in dental surgeries and open-plan clinics in dental hospitals. This will involve using fluorescent dyes and a 'safe virus' to show how big a risk dental treatment poses for transmission of COVID-19.

£9,562

Cathal Hannan, Neurosurgery Research Registrar, University of Manchester

"Angiopoietin/TIE2 in Vestibular Schwannoma. A tumour microenvironment and biomarker study"

Vestibular Schwannomas (VS) are tumours arising from the hearing and balance nerve at the base of the skull.
Although these tumours do not spread to other areas of the body, as they grow they can cause hearing loss, balance problems and even death due to pressure on adjacent structures. The formation of abnormal blood vessels is a key part of the growth of many tumours, and this is especially the case for VS. Drugs targeting the growth of abnormal blood vessels have been shown to be successful in the treatment of this tumour. Our research will focus on investigating how these abnormal blood vessels that are critical in facilitating VS growth are formed, to help us identify drug targets that may lead to the development of new treatments for VS.

£10,000

Ed Parkin, Consultant Colorectal Surgeon, Royal Preston Hospital

"Diagnosing Colorectal Neoplasia using Infrared and Raman Spectroscopy"

Patients with bowel symptoms may be asked to submit a Faecal Immunochemical Test (FIT) to check for blood in their stool. If this is positive they are referred for a colonoscopy. FIT is also used in the bowel cancer screening programme. However, FIT does not always give an accurate result (some cancers are missed), it may not detect pre-cancerous polyps, and some patients decline as they do not want to submit a sample of their stool. We are hoping to develop a bowel cancer blood test using Raman spectroscopy that is more accurate than FIT and more acceptable for patients.

£10,000

Hussain Abbas, Clinical Research Fellow in Transplantation. University of Oxford

"High-risk steatotic donor livers in the era of normothermic machine perfusion: Modulation of the Hypoxia Inducible Factor pathway to reduce ischaemia-reperfusion injury"

A third of donated livers cannot be transplanted due to non-alcoholic fatty liver disease. We have developed an innovative defatting strategy for treatment of fatty human livers through delivery of intervention during preservation on a machine in very similar conditions to those in the body (normothermic preservation). However, other key pathways may further enhance the success of these interventions, in particular, pathways associated with oxygen sensing (hypoxia inducible factors, HIFs). In the proposed study, we aim to optimise fatty human livers declined for transplantation through selective pharmacological modulation of the HIF pathway during normothermic preservation and similuation of ischaemia-reperfusion injury.

£9,978

Grants Continued...

Sohail Nisar, Academic Clinical Fellow, University of Leeds

Do patients from BAME backgrounds have a worse outcome following neck of femur fracture? A case controlled observational study using a national dataset.

We aim to examine whether variations exist in outcome across ethnic groups following a neck of femur (NOF) fracture. Results from a pilot study demonstrated that traditionally accepted distribution of fracture types, patient demographics, patient mobility and targets for ideal treatment may not be reliable for BAME patients. To investigate this further data will be acquired from the National Hip Fracture Database (NHFD) and linked with Hospital Episode Statistics (HES) and Office of National Statistics (ONS). The primary outcome will be patient mortality at 365-days post fractured neck of femur for BAME patients as compared to White population.

£10,000

Esther Platt. PhD Student, University College London

Identification of Origin of Neutrophil Gelatinase Associated Lipocalin (NGAL) in Acute Kidney Injury (AKI) following Orthotopic Liver Transplantation

50% of patients who undergo liver transplantation (LT) experience Acute Kidney Injury (AKI), with worse outcomes. We identified that Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) accurately predicts AKI following LT. Whether NGAL is released from the kidney or following ischaemia reperfusion (IR) injury to the liver, is unknown. In this study we will use mouse liver and kidney samples from a model of liver IR injury and AKI to identify cell populations displaying NGAL upregulation and protein aggregation.

This will support development of diagnostic clinical trials using NGAL in AKI, and identification of therapeutic targets for amelioration of IR injury.

£10,000

Satnam Virdee, Clinical Lecturer & Speciality Registrar in Restorative Dentistry, University of Birmingham

“Characterisation of lyophilised dentine extracellular matrix components liberated by irrigants during root canal treatment: an ex vivo study”.

Apical periodontitis” is an infection around the root of a tooth affecting ~6% of the UK population. Current therapies focus on removing bacteria inside infected root canals however, 20% of teeth consistently fail to heal. We therefore need strategies that also directly promote tissue healing. Application of bioactive growth-factors found naturally within teeth, called “dentine-extracellular-matrix-components” (dECMs), may present such an opportunity. The proposed project aims to identify the types and quantities of dECMs that can be obtained from within waste cleaning solutions during root canal treatment. This will contribute to the development of more biologically-driven treatment strategies for apical periodontitis.

£9,876

Frances Robertson, ST7 HPB and Transplant Surgery, University of Edinburgh

“Exploration of Micro RNA -122 as an early marker of liver injury and acute kidney injury following hepatic ischaemia-reperfusion injury”

Liver transplant remains the only treatment available to patients with end stage liver failure. This project aims to identify which micro RNAs are released from the injured liver during liver transplant surgery. Micro RNAs are small sections of RNA that can attract and activate immune cells which we know cause liver injury. How immune cells are activated remains unknown and this project will provide value information to help guide future studies into the role of micro RNAs and immune cell activation which we hope will help make liver transplant surgery safer.

£10,000

Grants Continued...

Emma Howie, Speciality Trainee, General Surgery, University of Edinburgh.

- "Development of a surgical sabermetrics simulation model incorporating objective physiological measurements to improve performance and patient safety"
- Surgical sabermetrics uses data to "optimise clinical and safety outcomes" and evaluate surgical performance, similarly to the use of athletic performance data in sport. Non-technical surgical skills (NOTSS) are "the cognitive and social skills that underpin knowledge and expertise in high demand workplaces" and at the heart of RCSEd's drive for improving patient safety. NOTSS directly influence technical skill andperformance. Physiological data provides information on increased mental workload that negatively affects performance. We will investigate the best method for collection and analysis of this data, contributing to developing a surgical sabermetrics programme with benefits for surgeons and patients, enhancing the NOTSS programme run and supported by RCSEd.

£9,974

Adam Gerrard, Clinical Research Fellow, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh

"Does genetic susceptibility for bleeding affect quantitative faecal immunochemical test (qFIT) results? -a feasibility study"

My research investigates how the process of diagnosing colorectal cancer may be improved by using a stool test for microscopic blood, quantitative Faecal Immunochemical Testing (qFIT). Through this, we know around 10% of symptomatic people will have a raised qFIT have a normal colonoscopy. This project aims to investigate if this population have a genetic susceptibility for bleeding which can cause increased physiological 'normal' bleeding in the bowel and effect the qFIT result. Studying 'false-positive' results like this, improves the use of the test and can help reduce the number of invasive unnecessary further investigations.

£9,350

Joe Esland, SPr in Trauma & Orthopaedic Surgery, University of Edinburgh

“Understanding why pathological fractures due to systemic cancer fail to heal”

Half of cancers spread to bone, causing the bone to break in one-in-five of these patients. This is extremely painful and impairs function. Unfortunately, bones that break due to cancer are much less likely to heal than normal bones, even after surgery, and we do not know why this is.

This study aims to identify the reasons why these bones heal so poorly, as well as to understand if giving medication, alongside surgery, can increase the chances of the bone healing. These findings will help patients with cancer get the most effective treatment first time.

£9,940

Aya Musbahi, ST7 General Surgery, Royal Victoria Infirmary

“A Retrospective study of the impact of Microsatellite Instability (MSI) and Programmed Cell Death Ligand 1 (PDL-1) status in resected oesophago-gastric cancers on postoperative and oncological outcomes”

Cancers can express different biomarkers which are naturally occurring molecules that can be used to identify the type of cancer, its aggressiveness and in order to target different treatment options. PDL-1 (programmed death ligand 1) , dMMR/MSI-H (deficient MMR and Microsatellite instability) are examples of such biomarkers and are poorly understood in oesophageal (gullet) and gastric (stomach) cancers. Previous small volume research has suggested that such cancers may not respond to traditional chemotherapy medications and these patients may benefit from targeted medications for these biomarkers (immunotherapy). We do not know how widespread these biomarkers are in oesophageal and gastric cancer patients and the aim of this study is to find this out from previous cancer specimens and find out the outcomes of those patients with traditional treatments we use today.

£10,000

Grants Continued...

Winson Wong, Consultant ENT Surgeon, Department of Otolaryngology Head and Neck Surgery, Hull, University Teaching Hospitals

"Exploiting microfluidic technology to predict chemoradiation responses in HNSCC"

Head and neck cancer is the 6th most common cancer worldwide. There are number of variables dictate treatment outcome as well as treatment related side effects. Because of these variabilities a personalised treatment is an ideal way to provide optimal treatment to patients. Using our bespoke microfluidic devices to maintain patient's tumour tissue we can measure cell deaths whilst running various drugs and radiation. With this result we can identify the most effective regimes in treating head and neck cancer in a personalised manner.

£10,000

Simon Goldie, Rhinology Research Fellow, Southampton General Hospital

"Repurposing simvastatin to treat Intracellular and biofilm associated S. aureus in chronic rhinosinusitis"

Chronic rhinosinusitis affects 15% of the global population and causes debilitating symptoms including facial pains, nasal obstruction, loss of smell and nasal discharge. The bacteria, S. aureus promotes the condition by hiding within cells, producing inflammation and evading the effects of antibiotics. Sufferers are typically managed with multiple surgeries, steroids and extended courses of antibiotics. My lab has shown commonly used, inexpensive drugs such as statins can kill intracellular S. aureus and reduce the inflammation seen in the condition. We hope to develop this exciting therapy to reduce the cost of treatment, patient suffering and our use of antibiotics.

£9,215

Michael Hart, Fellow in Functional Neurosurgery, St George's University Hospital, London

"High Performance Computing and Ultra-high field 7T MRI for Deep Brain Stimulation – Improving Accuracy, Maximising Benefit"

Movement disorders, including tremor and Parkinson's disease, are among the most common neurological conditions. Deep Brain Stimulation involves inserting electrodes into specific target regions deep in the brain to modulate function and relieve symptoms. Performing this effectively relies on sub-millimetric accuracy otherwise there may be a lack of benefit and prohibitive side effects, potentially requiring revision surgery.

We propose to utilise ultra-high resolution 7 Tesla MR, over twice the strength of current scanners, to allow better target identification. We hypothesise that this improved accuracy will allow improved clinical outcomes, fewer treatment limiting side effects, and less need for revision surgery.

£10,000

Susan Moug, Consultant General and Colorectal Surgeon, Royal Alexandra Hospital Paisley

"An investigation into the biology and outcomes of frailty in patients requiring emergency general surgery"

About 30 000 adults undergo emergency surgery every year in the UK. This surgery carries risks and can result in significant life-changing consequences for each individual patient. These risks are even higher for those patients that are frail. We aim to investigate frailty using different measurements (physcial tests, radiological tests, questionnaires and blood analysis) to see what measurement/s is/ are better at measuring frailty and how those/ they relate to death at 30 days after emergency surgery. We also aim to see how frailty changes as a result of emergency surgery. Overall we hope to improve our understanding of frailty that could lead to future 'frailty interventions' to improve outcomes for this large, vulnerable patient population.

£10,000

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Scholarships

JANE GOODMAN MEMORIAL SCHOLARSHIP:

Dr Louise Davidson, University College of **London**

MSc Paediatric Dentistry

£6,000

Sing Ying Lim, Queen Mary University of London DClinDent, Paediatric Dentistry

£10,000

Student Bursary Awards

AFRICA BURSARY:

Caroline Evenden, University of Birmingham

Good Shepherd Hospital, Eswatini, South Africa

£500

Patricia Leitch, St George's University of London

Charlotte Maxeke Johannesburg Academic Hospital, South Africa

£500

CARDIOTHORACIC BURSARY:

Hanad Ahmed, University of Southampton

Cardiovascular Division, The Hospital for Sick Children (SickKids). Toronto, Canada

£500

Arian Arjomandi Rad, Imperial College London

GVM Care & Research, Istituto Clinico Ligure di Alta Specialità (ICLAS) (Ligurian Institute of High Specialty – Italy)

£500

Caleb Johnson, University of Warwick

Hospital for Sick Children, Toronto

£500

Momna Raja, Brighton and Sussex Medical School

Cardiac Surgery department at the Faisalabad Institute of Cardiology, Pakistan

£500

Student Bursary Awards
Continued...

RUSSELL TRUST BURSARIES:

David Li, Cardiff Medical School

Department of Paediatric Trauma at the Red Cross Children's Hospital, South Africa.

£500

Jigishaa Moudgil-Joshi, University of Edinburgh

Red Cross War Memorial Children's Hospital Cape Town

£500

Nadine Paul, Kings College London

King College Hospital and Guy's and St. Thomas Hospital UK.

£500

Jakov Tiefenbach, University of Edinburgh

The Royal Melbourne Hospital Australia

£500

William Cambridge, University of Edinburgh

Department of HPB Surgery, Amsterdam Medical Centre,

Faculty of Medicine, University of Amsterdam

£500

Claire McGregor, Swansea University Medical School

Groote Schuur Hospital, Cape Town, South Africa

£500

Myat Pan, Cardiff University

Tokyo Women's Medical University, Japan

£500

Laura Wilkins, University of Oxford

Kamuzu Central Hospital, Malawi

£500

UNDERGRADUATE BURSARY:

Violet Borkowska, University of Edinburgh

"Neurotisation vs regional muscle transfer vs free muscle transfer in facial reanimation surgery – comparative retrospective cohort study of patient outcomes."

£1,500

Anusha Kumar, University of Birmingham

"A Multicentre Study Evaluating the Effectiveness of Shock Wave Lithotripsy Management for Ureteric Stones at Tertiary Centres in the United Kingdom."

£314

Melina Pelling, University of Warwick

"Salivary Volatile Organic Compound Analysis for Early Detection of Oesophagogastric Cancer"

£1,200

Tengku Saifudin, University of Glasgow

"Evaluation of microbiotal changes in head and neck cancer"

£900

Jaclyn Tan, University College London

"Prevalence and care of children with Auditory Neuropathy Spectrum Disorder (ANSD) in UK; a national multi-method project (PANSpect-UK)"

£1,200

36 Research Reports

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RCSEd & MRC Joint Research Training Fellowship

Grant Holder Name **Department(s) in which the Fellowship was held**	Mr Iestyn Matthew Shapey Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK Department of Renal and Pancreatic Transplantation, Manchester Royal Infirmary, Manchester, UK
Type of Grant/Fellowship;	MRC Clinical Research Training Fellowship
Project Title;	**Insulin Therapy in Pancreas and Islet Transplantation**
Period grant held	
From:	April 2017
To:	March 2020

Lay Summary

Pancreas and islet transplantation are highly-effective life-saving therapies which allow patients with complex diabetes mellitus to produce their own insulin. However, the relationship between insulin use during the peri-transplant period and longer term insulin independence is unknown. My research aimed to determine whether data on insulin use in the pancreas donor and transplant recipient could help surgeons make better decisions regarding which donors to select.

Using data from the entire UK experience of pancreas and islet transplantation to date, I showed that use of insulin during the donation process was associated with poorer outcomes in patients undergoing pancreas and islet transplantation. This was confirmed using “liquid biopsies” from the blood of organ donors and relating the data to transplant function and survival. I also showed that insulin may exert a protective effect against major blood clots that cause transplants to fail.

During the transplantation process, the use of insulin therapy differs based on the type of transplant being performed: pancreas or islet cell. Insulin is not routinely use during the peri-tranpslant process in pancreas transplantation, and I showed that higher blood sugar levels during the first five days will predict survival several years later. However, this was not the case in islet transplantation where insulin is routinely used.

A. Clinical and Scientific Significance of advances made

Establishing the need for research (BMJ Aug 17;358:j3784.)

Pancreas and islet transplantation are highly-effective life-saving therapies in complex type 1 diabetes. Due to the well-documented shortage of organs for transplantation there is an urgent need to: a) optimise methods for assessment and selection of high quality pancreases; and b) identify the ideal conditions for a transplanted pancreas to achieve optimal long-term function.

Insulin therapy in organ donation and transplantation (Diabetes Obes Metab. 2019; Jul 21 (7) 1521-1528.)

Hyperglycaemia is common in hospitalized individuals, and is often caused by physiological stress associated with critical illness or major surgery. Insulin therapy plays an important yet poorly understood role in both organ donation and transplantation. There is evidence to suggest that the use of insulin to manage poor glycaemic control in both pancreas donors and transplant recipients. My research aimed to determine whether data on insulin therapy could be used to improve clinical decision making in pancreas and islet transplantation.

Donor insulin use (DIU) predicts beta-cell function after islet transplantation (Diabetes Obes Metab. 2020 May 25)

Using data from the UK Transplant Registry and the UK Islet Transplant Consortium I showed that DIU was associated with lower islet function, higher 3-month post-transplant HbA1c levels, and lower fasting C-peptide levels. I also demonstrated that glycaemic control and variation did not predict outcomes post-transplantation. Data on DIU predicts beta-cell dysfunction 3 months after islet transplantation and could help improve donor selection and transplant outcomes.

Donor insulin therapy in intensive care predicts graft survival after pancreas transplantation
(data under submission for publication)

Using data from the UK Transplant Registry I showed that DIU was associated with graft failure at both 3-months and 3-years post-transplantation. However, the relationship between DIU and outcomes varied according to the cause of graft failure. DIU was associated with higher rates of graft loss owing to lost islet function and which further supported my data outlined above. However, DIU was associated with lower rates of graft thrombosis. This adds to the evidence base from islet transplantation that peri-transplant insulin therapy boasts anti-thrombotic properties that are beneficial in terms of improving graft survival post-transplantation.

Donor insulin therapy as a marker of beta-cell death (data under submission for publication) It has long been believed that hyperglycaemia following brain death was caused by temporary reversible metabolic stress (insulin resistance).
However, this theory could not account for the clinical findings following islet or pancreas transplantation.

RCSEd & MRC Joint Research Training Fellowship Continued...

I hypothesized that insulin use in organ donors was a marker of beta-cell death. Using circulating cell-free microRNA-375 and circulating cell-free methylated DNA of the INS1 gene as tissue specific markers of beta-cell death, we showed that levels of beta-cell death are higher in donors receiving insulin. This provided a biomolecular validation of the donor insulin hypothesis.

Moreover, these circulating markers were also related to post-transplant islet function and graft survival and could function as highly predictive biomarkers to provide the first objective assessment of donor pancreases in order to guide decision making and donor selection.

Peri-transplant glycaemic control in pancreas and islet transplantation (Diabetes Obes Metab. 2020 Sep 7)

I hypothesized that peri-transplant glucose levels predict outcomes after pancreas and islet transplantation independently of use of insulin therapy in recipients.

In pancreas transplantation, we showed that higher glucose levels assessed over the first five days predict graft failure above, beyond and independently of a requirement for insulin during the hospital stay. However, it remains unclear whether peri-transplant hyperglycaemia is a cause or a consequence, or both, of graft dysfunction in the transplanted pancreas.

Peri-transplant hyperglycaemia is strongly associated with graft loss and could be a valuable tool guiding individualized graft monitoring and treatment. The 5-day peri-transplant glucose AUC provides a robust and responsive framework for comparing graft function.

Peri-transplAnt InsuliN Therapy to improve outcomes after pancrEas tRansplantation (PAINTER): an open label randomised clinical trial.

Using the data above, I designed the PAINTER trial to determine whether it would be safe and feasible to perform a future mutli-centre trial of peri-transplant insulin therapy in patients undergoing pancreas transplantation.

B. Problems encountered and steps taken to overcome them

1. Cell free assays – In the first instance, microRNA assays were performed using RT-PCR technology. This was sufficient to support the original objectives of determining whether insulin therapy was a marker of beta-cell death. However, absolute quantities could not be reliably calculated and could not therefore be used to determine the relationship with post-transplant outcomes. Consequently I changed the technology platform to digital droplet PCR which provided the data required.

2. PAINTER trial – The original objective was to determine whether a trial of peri-transplant insulin therapy would be feasible. Whilst this objective was met, I had originally hope to have completed the randomised controlled trial as part of my research fellowship. Unfortunately, I was unable to do so because the proposed start of the trial did collided with additional department-wide changes to insulin therapy protocols throughout the critical care unit at the study institution. On the basis of patient safety, it was more appropriate for the trial to be delayed until the new protocols had been established.

C. Collaborations established

Several collaborations have been established:

1. Quality in Organ Donation (QUOD) – to provide organ donor plasma samples
2. Dr James O'Sullivan, Manchester Genetics Centre – to support the work on circulating microRNA.
3. Prof Yuval Dor, Hebrew University of Jerusalem/Hadassah Medical centre – to support work on circulating methylated DNA in organ donors.
4. Prof James Shaw, UK Islet Transplant Consortiwum – access to islet transplant data in order demonstrate relevance of the hypotheses in two distinctly different populations of patients receiving beta-cell replacement therapy

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

Publications

1. Shapey IM et al Peri-transplant glycaemic control as a predictor of pancreas transplant survival Diabetes Obes Metab. 2020 Sep 7
2. Shapey IM et al Donor insulin use predicts beta-cell function after islet transplantation. Diabetes Obes Metab. 2020 May 25
3. Shapey IM et al. Insulin therapy in organ donation and transplantation. Diabetes Obes Metab. 2019; Jul 21 (7) 1521-1528.
4. Shapey IM et al Pancreas transplantation: the donor's side of the story. BMJ. 2017 Aug 17;358:j3784.

Presentations

International – Oral

1. I Shapey et al Peri-transplant insulin therapy to improve outcomes after pancreas transplantation (PAINTER): an open label randomised controlled trial, Pitch presentation prize session, International Pancreas and Islet Transplant Association, Lyon, 2019
2. I Shapey et al Peri-transplant glycaemic control does not predict 3-month islet transplant graft function. International Pancreas and Islet Transplant Association, Lyon, 2019
3. I Shapey et al Optimising the donor pancreas selection process using hierarch based decision trees International Pancreas and Islet Transplant Association, Lyon, 2019
4. I Shapey et al Donor insulin therapy predicts better graft survival in pancreas transplantation. American Transplant Congress, Boston 2019
5. I Shapey et al MicroRNA-375 provides an objective measure of pancreas quality in organ do Transplant Congress, Boston 2019

RCSEd & MRC Joint Research Training Fellowship Continued...

6. Shapey I, Summers A, Khambalia H et al Donor insulin therapy in intensive care predicts early graft function/failure in pancreas and islet transplantation. International Pancreas and Islet Transplant Association, Oxford, June 2017
7. Shapey I, Summers A, Yiannoullou P et al Associations of donor vasoactive drugs with pancreas transplant graft survival. International Pancreas and Islet Transplant Association, Oxford, June 2017

International – Poster

1. I Shapey et al Insulin treatment in pancreas donors on the intensive care is a marker of beta cell death as evidenced by microRNA data. Poster of distinction, American Transplant Congress, Boston 2019
2. I Shapey et al Insulin use on intensive care units as a marker of beta-cell death in brain dead pancreas donors. American transplant Congress, Seattle, 2018
3. I Shapey et al Peri-transplant glycaemic control as a predictor of pancreas transplant survival. American transplant Congress, Seattle, 2018
4. I Shapey et al Insulin therapy in pancreas donors as a predictor of subsequent transplant outcome. American Transplant Congress, Chicago, May 2017
5. I Shapey et al The association of donor vasoactive drugs with pancreas transplant graft survival. American Transplant Congress, Chicago, May 2017

National – oral

1. I Shapey et al Donor insulin therapy predicts better graft survival in pancreas transplantation. Medawar medal session. British Transplant Society Congress, Harrogate 2019
2. I Shapey et al MicroRNA-375 provides an objective measure of pancreas quality in organ donors. British Transplant Society Congress, Harrogate 2019
3. I Shapey et al Peri-transplant insulin therapy to improve outcomes after pancreas transplantation (PAINTER): an open label randomised controlled trial. British Transplant Society Congress, Harrogate 2019
4. I Shapey et al Peri-transplant glycaemic control as a predictor of pancreas transplant survival. British Transplant Society Congress, Brighton, 2018
5. Shapey et al Peri-transplant glycaemic control in solid pancreas transplantation, Society of Academic and Research Surgery, Nottingham, 2018

6. I Shapey et al Insulin use on intensive care as a marker of beta-cell death in brain dead pancreas donors, Society of Academic and Research Surgery, Nottingham, 2018
7. Shapey et al Donor insulin therapy in intensive care as a marker of beta-cell death in pancreas donors and a predictor of early graft function/failure in pancreas and islet transplant recipients. Royal Society of Medicine, Section of Surgery, London, October 2017

National – poster

1. I Shapey et al Insulin treatment in pancreas donors on intensive care is a marker of beta cell death as evidenced by microRNA data. British Transplant Society Congress, Harrogate 2019
2. I Shapey et al Insulin therapy in pancreas donors as a predictor of subsequent transplant outcome. British Transplantation Society, Harrogate, March 2017
3. I Shapey et al The association of donor vasoactive drugs with pancreas transplant graft survival. British Transplantation Society, Harrogate, March 2017

Prizes

Norman Tanner prize, Royal Society of Medicine, Section of Surgery (2017)

Higher Degree

PhD awarded by the University of Manchester, December 2019

E. Achnowledgements

I would like to acknowledge:

1. Supervisors – Mr David van Dellen, Dr Martin Rutter, Dr Angela Summers
2. Advisors – Mr Titus Augustine, Prof Neil Hanley
3. Collaborators (internal) – Mr Hussein Khambalia, Mr Ray Tan
4. Collaborators (external) – QUOD, UKITC, NHSBT, IPTR, Manchester Genetics Centre, Hebrew University of Jerusalem
5. Funding organisations – I would like to thank the RCSEd and Medical Resarch Council for supporting my work and providing me with the opportunity and resources to pursue my passion for surgical research

The Joint RCSEd/Cutner Research Fellowship in Orthopaedics

Grant Holder Name	Mr Antony Kameel Sorial
Department(s) in which the Fellowship was held	Institute of Genetic Medicine, Newcastle University
Type of Grant/Fellowship;	RCSEd Cutner Research Fellowship
Project Title;	**Molecular Genetics of Osteoarthritis – Enhancing Cartilage Integrity for Future Patient Benefit**
Period grant held	
From:	01/08/2018
To:	07/08/2019

Lay Summary

Inherited errors in DNA (genes) affect the way our bodies are made and maintained. These genetic changes influence our chances of developing diseases. This study investigated how genetic differences cause osteoarthritis and sought ways of providing better treatment for this and related diseases. These common, painful and disabling conditions will affect an estimated 17 million people in the UK by 2030. In this study we looked at ways of altering (editing) a specific gene called PLEC in stem cells to try and understand how it could cause osteoarthritis.

A. Clinical and Scientific Significance of advances made

OA is a complex, polygenic disease with an extensive socioeconomic burden in the western world. As the average life expectancy continues to rise, OA prevalence will increase, affecting an estimated 17 million in the UK by 2030. OA heritability values are around 50%, a significant proportion of which is accounted for by common genetic variation.

Genome wide association scans (GWAS) in large cohorts have identified and replicated robust single nucleotide polymorphisms (SNPs) with a strong association to OA development[1]. One of the largest OA GWAS performed thus far utilised the unique UK Biobank to assess associations between OA and genotype at 17.5 million SNPs in 30,727 affected patients. One of the most compelling SNPs identified in this cohort was rs11780978, a G>A polymorphism with a minor allele frequency of 0.4, which significantly associated with hip OA ($p = 1.98 \times 10\text{-}9$)[2]. The SNP resides on chromosome 8 in an intron of the PLEC gene, which encodes Plectin, a large, complex cytoskeletal protein.
Plectin is involved in mechanotransduction[3] and the mechanical response of the cell to load[4]. With the increasing awareness of the concept of mechanoinflammation in OA[5], aberrant mechanotransduction is gaining increased interest as a major contributor to OA and Plectin may be central to this.

SNPs can exert functional effects upon disease development through epigenetic mechanisms such as modulation of DNA methylation (DNAm) at CpG dinucleotides, which can serve as a conduit to differential gene expression[6,7]. Our published data reported a functional characterisation of rs11780978 in which we identified an expression quantitative trait locus (eQTL) operating on PLEC in the cartilage of patients with OA, and two distinct methylation quantitative trait loci (mQTLs) correlating with OA genetic risk at this locus[7]. We quantified DNAm at a total of 12 PLEC CpGs across two distinct clusters: cg19405177 and 7 flanking CpGs (cluster 1), and cg14598846 and 3 adjacent CpGs (cluster 2) and demonstrated that DNAm at multiple CpGs within the two clusters were acting as mQTLs.

Of particular note, the direction of the correlation was identified as acting in opposing directions between the two clusters. Analysis of correlations between DNAm and allele- specific PLEC expression revealed 3 methylation-expression QTLs (meQTLs) in cartilage.

Based upon this data, we hypothesised that rs11780978 correlates with reduced expression of PLEC in articular cartilage and that inadequate production of Plectin may increase the risk of OA development.

During my 12-month research fellowship I was able to begin to test this hypothesis. I recapitulated the effect of the risk allele by undertaking a custom designed, CRISPR-Cas9 based knockdown of Plectin in immortalised MSCs (iMSCs) and assessed the phenotype of Plectin deficient iMSCs by RNAseq. The knock-down impacted on a range of cellular pathways. Of particular note, both the innate and acquired immune response showed an upregulation, an effect that has been reported on previously in OA for both cartilage and synovium[8,9]. Downregulation of Wnt signalling was also observed. This pathway is critical to normal cartilage homeostasis[10,11] and there is growing evidence of an interplay between Wnt signalling and joint tissue inflammation[12].

B. Problems encountered and steps taken to overcome them

Consumables funding not available with the Cutner fellowship, this was a challenge as the laboratory work required further funding. This was address by submitting a second grant application to a regional charity (The John George William Patterson Foundation).

The Joint RCSEd/Cutner Research Fellowship in Orthopaedics Continued...

C. Collaborations established

Internationally collaborative PhD Fellowship developed and funded by Wellcome Trust, Royal College of Surgeons of England and UK-US Fulbright Commission

Collaborators include:

Professor Farshid Guilak (Washington University in St Louis, MO, USA)

http://www.orthoresearch.wustl.edu/content/Laboratories/2965/Farshid-Guilak/Guilak-Lab/Overview.aspx

Professor Judith Hoyland (University of Manchester, UK)

https://www.research.manchester.ac.uk/portal/judith.a.hoyland.html

Professor Gerhard Wiche (Universität Wien, Vienna, AT)

https://www.maxperutzlabs.ac.at/research/research-groups/wiche

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

Publications

- **Sorial AK**, Hofer IM, Tselepi M, Cheung K, Parker E, Deehan DJ, et al. Multi-tissue epigenetic analysis of the osteoarthritis susceptibility locus mapping to Plectin gene PLEC. bioRxiv. 2020 doi: https://doi.org/10.1101/2020.01.28.917401 (Being revised for publication in Osteoarthritis and Cartilage)

International Poster Presentations

Sorial AK, Hofer IM, Tselepi M, Cheung K, Parker E, Deehan DJ, et al. Multi-tissue epigenetic analysis of the osteoarthritis susceptibility locus mapping to Plectin gene PLEC. (Accepted as poster to be presented at Osteoarthritis Research Society International 2020, Vienna, AT) – event cancelled due to coronavirus.

Regional Oral Presentations

- **Sorial AK**, Hofer IMJ, Tselepi M, Rice SJ, Deehan DJ, Loughlin J. Employing Genome Editing to Study Osteoarthritis Risk. Kreibich Memorial Annual Event. Durham, UK. 21/06/2019 (Kreibich Prize Winner)
- **Sorial AK**, Hofer IMJ, Tselepi M, Parker E, Rice SJ, Deehan DJ, Loughlin J. Epigenetic Analysis and CRISPR/Cas9 Genome Editing of the Novel Osteoarthritis Susceptibility Locus residing at the PLEC gene. The North East Surgical Training Academy (NESTAC) Annual Meeting. Newcastle Upon Tyne, UK. 03/05/2019 (Feggetter Prize Medal Nominee)

Further Funding Awarded

2019-20

- **~£200,000** – Wellcome Trust 4Ward North Doctoral Training Programme Fellowship
- **£97,300** - RCSEng/UK-US Fulbright Scholar Award

- **£69,382** - Joint RCSEng/Shears Northern Research Fellowship
- **£9,850** - The Centre for Integrated research into Musculoskeletal Ageing (CIMA) ACF Bursary

2018

- **£51,921** - The John George William Patterson Foundation (pump-priming grant)

E. Acknowledgements

My family and partner Helen, without whom the above could not have been achieved.

All supervisors and collaborators who assisted in completion of the current work (Professors Loughlin, Deehan and Wiche) and the formation of the subsequent fellowship applications (Professors Guilak and Hoyland).

Co-authors of the submitted manuscript (Hofer IMJ, Tselepi M, Parker E, Rice SJ) and Dr Colin Shepherd for his expertise.

The Northern Deanery Training Programme for providing flexibility, support and encouragement to undertake out of program research training (particularly Mr Steve Aldridge, training programme director and Professor Richard Bellamy, director of speciality training).

The Royal College of Surgeons of Edinburgh for the opportunity to undertake this work.

F. References

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The Joint RCSEd/Cutner Research Fellowship in Orthopaedics Continued...

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The Joint RCSEd & MRC ORUK/RCSEd Research Fellowship In Orthopaedics

Grant Holder Name Rebecca Stoner
Project Title **Predicting mortality in major trauma using an artificial intelligence risk prediction model**
Submission Date June 2022
Period Grant Held Dec 2021 to 2022

Lay Summary

When patients have multiple injuries, it can be difficult to estimate their risk of dying. This needs to be calculated for several reasons: to prioritise which patients should be treated first, to plan which treatments will have the greatest benefit, and in assessing performance of medical teams.

We have developed a prediction tool that finds the risk of a patient developing several conditions that we know increase the risk of dying, such as problems with blood clotting or kidney failure. These are made of Bayesian networks, which uses AI to calculate the risk of a condition occurring given the chance of other contributing factors being present.

We are developing a tool that will provide doctors with information concerning their patient's risk of death in the hours following severe injury.

The tool will incorporate changes in blood pressure and heart rate over time into its predictions, making the predictions more powerful than using "one-off" measurements and will allow the prediction to update as the patient's condition improves or worsens.

This work is a collaboration between clinicians and computer scientists, to develop precise tools that will help trauma doctors make more evidence-based decisions about which patients will benefit from which treatments.

Research Aims and Objectives

The aim of this work is to develop a Bayesian Network predictive model for mortality in trauma, using patient information gathered in the early phases of assessment.

Objectives:

Objective 1: To undertake a systematic review of existing prognostic models for mortality in trauma and identify their limitations

Objective 2: To develop a causal structure containing multiple Bayesian Networks (organ failure, coagulopathy, traumatic brain injury prognostication)

Objective 3: To incorporate dynamic prediction updating from the use of serial physiological observations

Research Milestones

The data required for the development and training of the mortality model has been acquired and prepared. Several prototype model structures have been designed and work is underway to establish the most appropriate structure. This has involved combining the previously fully developed TIC-MIL (trauma induced coagulopathy) model and the previously partially developed TAKI (trauma induced acute kidney injury) model, along with a new acyclic graph to represent the effect of traumatic brain injuries.

Within the literature, a systematic review has been identified that reviews prognostic models for mortality in trauma up until 2015. This review's search strategy has been adapted to generate an updated search for models published since 2015, as well as to include models excluded by their search, such as predicting mortality in specific injury cohorts, also published since 2015.

Coding work on generating text-based explanations for model outcomes has been completed for the models included within the mortality model (e.g. TIC-MIL), and is easily generalisable to the mortality model.

Design work on the model interface is ongoing.

Impact

The use of Bayesian Networks as prediction models is well founded in other fields such as engineering and finance, but not yet within healthcare.

The development of this mortality model is part of demonstrating the utility of Bayesian Network modelling to provide accurate prognostics in an area that lacks the large datasets that usually characterise machine learning work, and that deals with imprecise or incomplete data.

Being able to accurately predict an individual patient's risk of mortality from early assessment data can ensure the provision of appropriately timed and evidence based treatment plans, and aid prioritisation of patients in multiple casualty scenarios.

Intellectual Property (IP)

Intellectual property (IP) plays a crucial role in the innovation process, where good ideas develop into new products. Please consider if your research will lead to generation of IP in the future. If so, please explain how you are planning to achieve this.

The Queen Mary University of London Intellectual Property policy can be found here: https://arcs.qmul.ac.uk/media/arcs/policyzone/IP_Policy_Final_Senate_March2015.pdf
The model developed in this work is intended to be shared for clinical use, if found to be safe and effective for this purpose. Previous models developed by our research group have been made publicly available, e.g. on www.traumamodels.com, and it is intended that the mortality model would be made similarly available.

Publications and Presentations

Oral presentation at the European Congress of Trauma and Emergency Surgery, April 2022, in Oslo, Norway:

Predicting Trauma-Induced Coagulopathy in combat casualties: updating a civilian AI risk prediction model for use in a military population

RS Stoner, E Kyrimi, E Pisirir, JM Wohlgemut, W Marsh, T Woolley, ZB Perkins, NRM Tai

'Quickshot' presentation accepted at the American Association for the Surgery of Trauma conference, September 2022, in Chicago, USA:

Developing an AI prediction model for Trauma Induced Acute Kidney Injury

RS Stoner, E Kyrimi, E Pisirir, JM Wohlgemut, W Marsh, ZB Perkins, NRM Tai

Paper submitted to the Journal of Biomedical Informatics, May 2022:
Updating and recalibrating causal probabilistic models on a new target population
Evangelia Kyrimi, Rebecca S Stoner; Zane B Perkins; Erhan Pisirir; Jared M Wohlgemut; William Marsh; Nigel RM Tai

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The Lorna Smith Charitable Trust Research Fellowship

Grant Holder Name	Dr Peter James Gallacher
Department(s) in which the Fellowship was held	BHF Centre for Cardiovascular Science, University of Edinburgh
Type of Grant/Fellowship:	Lorna Smith Charitable Trust Fellowship
Project Title:	**Burden of comorbidity in ANCA vasculitis: a nationaldata-linkage study (PROJECT NO. LSRF/20/007)**
Period grant held	
From:	October 2020
To:	October 2021

Lay Summary

New treatments have improved outcomes for patients with vasculitis. Patients are now living longer, but unfortunately are more likely to develop other medical conditions, or 'comorbidities' (e.g. heart disease, diabetes). 'Multimorbidity' describes patients living with ≥2 comorbidities. Multimorbidity is increasingly common and is associated with a greater use of healthcare resources, lower quality of life, and increased risk of death. Previously, no study has investigated how common multimorbidity is, or what kind of burden it is associated with, in patients with vasculitis.

The award of a Lorna Smith Charitable Trust Fellowship has enabled me to perform one of the largest and most comprehensive studies of patients with vasculitis ever published. We used a method called 'data-linkage' to recruit most patients diagnosed with vasculitis in Scotland over 20 years. We used national healthcare data – which is automatically collected and stored by the NHS, and includes data on hospital admissions, prescriptions, and death records – to follow-up all patients included in the study without bringing them back to hospital for more questions/tests.

We compared each patient with vasculitis to five members of the general population, before looking at how common multimorbidity was and what financial costs were associated with it (e.g. due to hospital admissions/clinic appointments).

This Lorna Smith Charitable Trust Fellowship award has been fundamental in bringing this work to fruition, whilst also providing me with a platform to continue my research and improve the lives of vasculitis patients.

A. Clinical and Scientific Significance of advances made

Background

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a set of systemic autoimmune diseases, comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). With modern immunosuppressive therapy, these previously fatal diseases have become chronic, relapsing conditions with mean five-year survival rates of ~70%.

With improved survival, patients with vasculitis are now considered to be at an increased risk of multimorbidity, defined as the presence of two or more concurrent long-term disorders. Multimorbidity is increasingly common in the general population and has also been described in other chronic inflammatory conditions, including rheumatoid arthritis.

It complicates chronic disease management and is associated with reduced functional status, decreased quality of life and increased mortality. Multimorbidity also has important implications for the organisation and delivery of healthcare, which is traditionally structured to optimise the management of individual diseases.

Previous studies have demonstrated an increased risk of several individual comorbidities in patients with vasculitis, including cardiovascular disease, diabetes mellitus and venous thromboembolic disease. These associations are thought to be a consequence of either chronic inflammation or the increasingly potent and toxic medications used to treat vasculitis. However, to our knowledge, no studies have previously investigated the frequency or burden of multimorbidity in patients with vasculitis. In this national, multi-centre, data-linkage study, we compared temporal trends in the incidence of a wide range of individual comorbidities and multimorbidity between patients with vasculitis and matched general population controls, and reported the cost of excess resource consumption attributable to multimorbidity in patients with vasculitis.

Summary & discussion of findings

This is the first study to describe longitudinal trends in the incidence of multimorbidity and report the healthcare expenditure attributable to multimorbidity in a large, national cohort of patients with vasculitis. There were several important observations. First, patients with vasculitis were at a significant risk of developing individual comorbidities throughout their disease course, but especially in the first two years following diagnosis (Figure 1). Second, multimorbidity (the presence of ≥2 comorbidities) was common in patients with vasculitis and increased significantly in frequency over time. Indeed, it affected almost one-quarter of patients with vasculitis in their first year after diagnosis, but over one-third by year ten of follow-up (Figure 2). Third, in patients with vasculitis, multimorbidity was associated with an approximately three-fold increase in excess healthcare expenditure.

The Lorna Smith Charitable Trust Research Fellowship Continued...

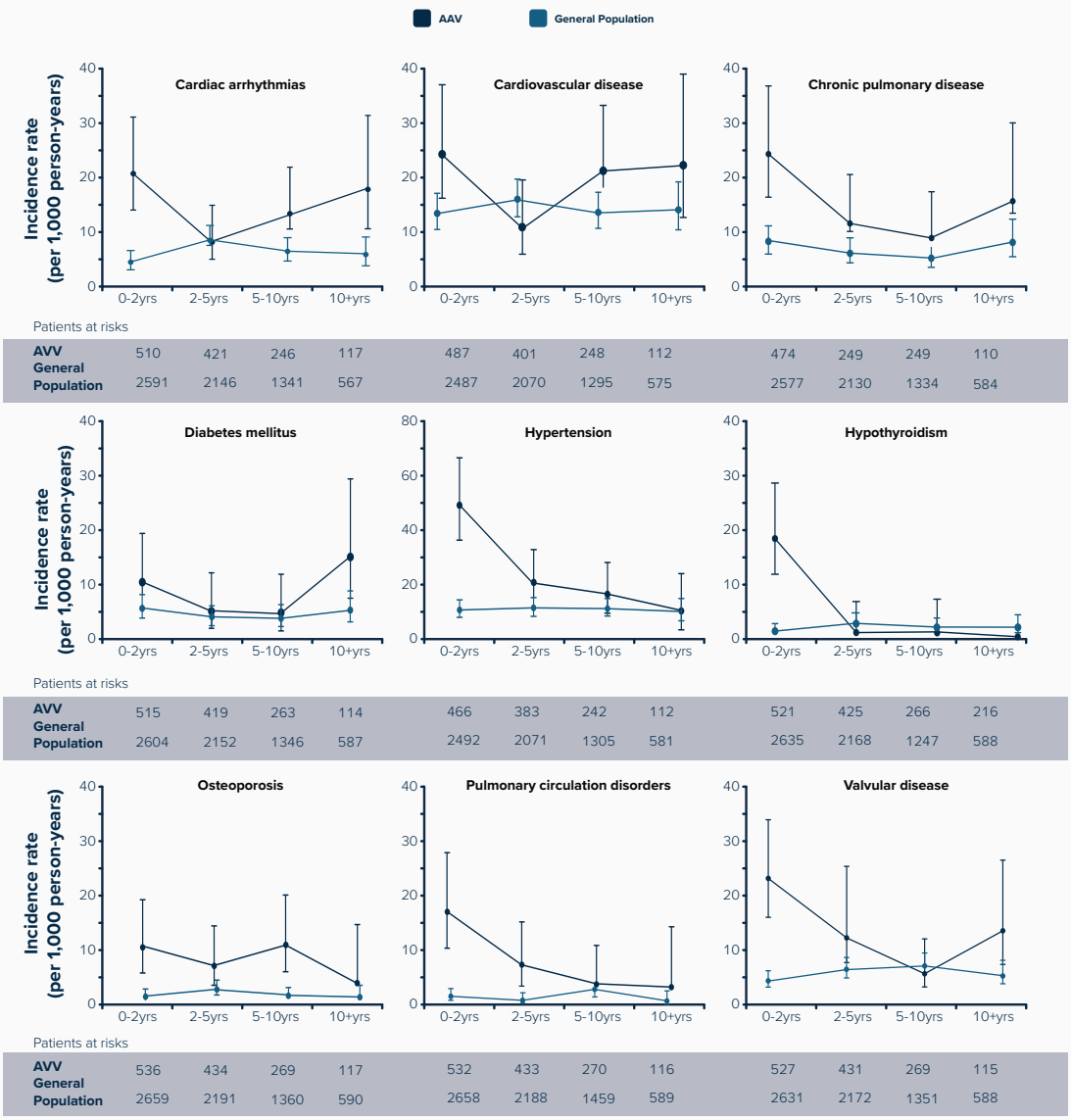
Uniquely, our study demonstrated that patients with vasculitis were at an increased risk of developing multimorbidity compared to general population controls. Whilst the impact of multimorbidity has not been studied previously in patients with vasculitis, we also found that multimorbidity was associated with a disproportionate increase in the cost of overall excess resource consumption. In comparison to patients with vasculitis with no comorbidities, the development of multimorbidity in patients with vasculitis was associated with a two- to four- fold increase in total healthcare expenditure, and a three- to five-fold increase in inpatient healthcare expenditure. Relevant studies in other chronic disease populations, for example in patients with cardiovascular or chronic kidney disease have also demonstrated that multimorbidity is becoming the rule rather than the exception. The implications of this are significant, given the striking association between multimorbidity and polypharmacy, greater resource consumption, reduced quality of life and poorer outcomes.

Our findings have important implications for clinical practice. Specifically, the results of our temporal analysis highlight the importance of early screening for many common conditions in patients with vasculitis, whilst also highlighting the significance of late-onset cardiovascular disease and diabetes mellitus.

Our observation that peptic ulcer disease was no more likely in patients with vasculitis than in general population controls, despite the administration of high-dose corticosteroids to the former group, also appears to reflect the relative success of prophylactic therapies aimed at suppressing gastric acid secretion. Therefore, our data encourage similar preventative strategies for other comorbidities.

In conclusion, this novel study is the most comprehensive and detailed analysis of multimorbidity in patients with vasculitis to date. Patients with vasculitis were at a high risk of individual comorbidities, especially early in their disease course. Multimorbidity was also common in patients with vasculitis and was associated with disproportionate increases in healthcare expenditure. Our findings emphasise the importance of holistic care in patients with vasculitis and the need to consider early screening for other conditions.

Figures



▲ Figure 1. Temporal trends in the incidence of individual comorbidities in patients with vasculitis (red) and general population controls (blue). AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis. Scale of y-axis is different for hypertension.

The Lorna Smith Charitable Trust Research Fellowship Continued...

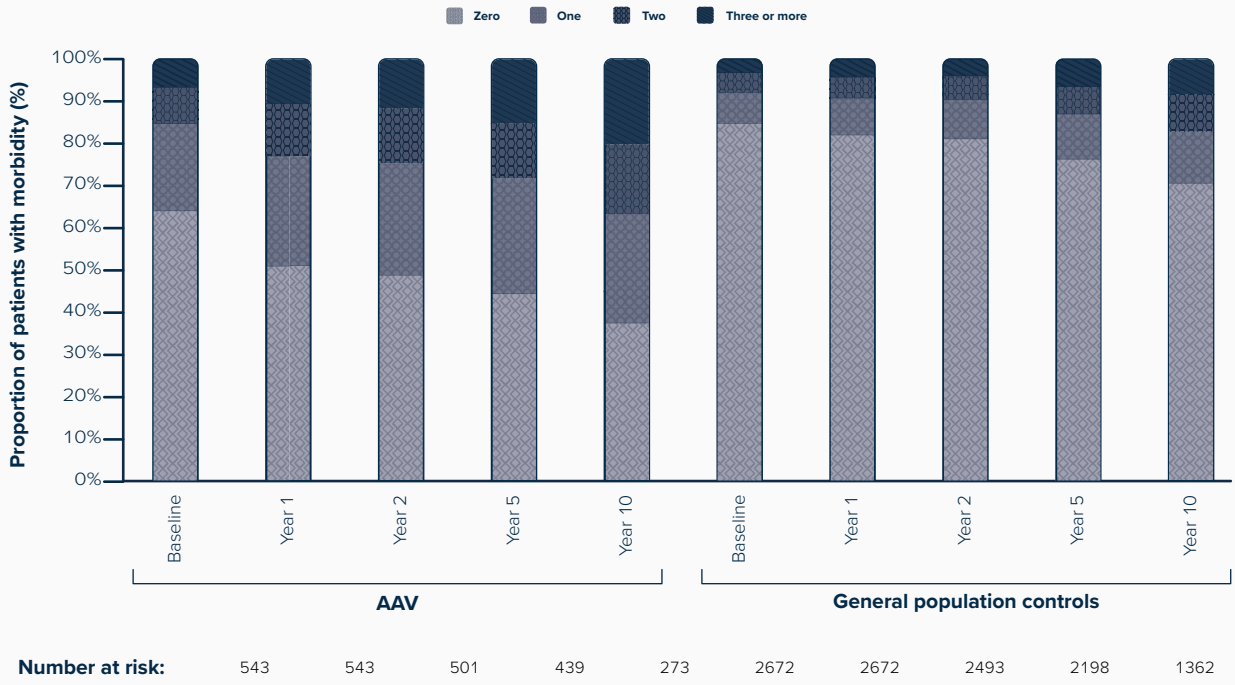


Figure 2. Prevalence of morbidities at baseline and cumulative incidence of morbidities and multimorbidity at 1, 2, 5 and 10 years in AAV patients and general population controls. AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis. P for $\chi 2$ test for trend <0.0001 for all timepoints. AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis.

B. Problems encountered and steps taken to overcome them

One difficult aspect of performing this type of research is obtaining the appropriate ethical and governance approvals for the study in a timely manner.
Fortunately, I have avoided any significant delays to receiving approvals or accessing linked data by forming a strong working relationship with my research coordinators at Public Health Scotland.

This has ensured that my applications for ethical/governance approval have been completed well ahead of deadlines and thoroughly critiqued before going for panel review. My experiences have also made me realistic about planning timescales for obtaining ethical approvals in future studies.

Finally, I think it is incredibly important to discuss my research methodology and findings with patients to ensure my work continues to focus on a subject matter that resonates.

As such, I have had the privilege of presenting the findings of the work described in this report to patients with vasculitis at a meeting organised by the vasculitis charity, Lauren Currie Twilight Foundation.

C. Collaborations established

I collaborated closely with Dr Neil Basu, a leading academic rheumatologist based at the University of Glasgow, to complete the study described in this report.
I am delighted to report that the cohort of >500 vasculitis patients formed for this study is one of the largest of its kind.
It will continue to inform important data-linkage studies in vasculitis patients and will now be managed and updated by a fellow clinical PhD student, Dr Matthew Rutherford (University of Glasgow).

During the first year of my PhD studies funded by a Lorna Smith Charitable Trust Fellowship, I have also had the opportunity to collaborate with Dr Samira Bell, a leading academic nephrologist based at the University of Dundee. In addition, I also chair monthly REA Cardiovascular Health Data Science meetings at the Centre for Cardiovascular Science, University of Edinburgh. This has proved an excellent way for junior researchers such as myself to present work in a friendly and supportive environment, and has also been an important way to meet potential collaborators from other institutions.
Over the past year, we have welcomed several external speakers from institutions including Karolinska Institute, Erasmus University MC and University of Glasgow.

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

The award of a prestigious Lorna Smith Charitable Trust Fellowship enabled me to begin my PhD studies, which broadly aims to evaluate the changing burden of cardiovascular disease in patients with kidney disease, including vasculitis.

In addition, the present award has also facilitated the following:

- **Higher degree progress in relation to this award**: I successfully passed my first year PhD review and was subsequently awarded a prestigious British Heart Foundation Clinical Research Training Fellowship.
- **Prizes in relation to this award**: I presented the results of our study during the Nephrology section President's Prize Day at the Royal Society of Medicine. I was awarded the Rosemarie Baillod prize for the best oral presentation of a clinical research project.
- **Publications in relation to this award:** Sarica SH*, Gallacher PJ*, Dhaun N, Sznajd J, Harvie J, McLaren J, McGeoch L, Kumar V, Amft N, Erwig L, Marks A. Multimorbidity in Antineutrophil Cytoplasmic Antibody– Associated Vasculitis: Results From a Longitudinal, Multicenter Data Linkage Study. Arthritis & Rheumatology. 2021 Apr;73(4):651-9

E. Acknowledgements

I would like to thank my supervisors, Dr Neeraj Dhaun (Bean) and Professor Nick Mills, and my primary collaborator, Dr Neil Basu (University of Glasgow), for their support and guidance in relation to this work. I would also like to thank the Lorna Smith Charitable Trust and the Royal College of Surgeons of Edinburgh for so generously funding me to complete this work. Finally, I would like to thank all patients included in our study, without whom this work would not have been possible.

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Maurice Wohl Research Fellowship

Grant Holder Name	Sami Adam Anjum
Department(s) in which the Fellowship was held	Tyson-Capper Research Group, Translational and Clinical Research Institute, Newcastle University
Type of Grant/Fellowship;	Maurice-Wohl One Year Research Fellowship
Project Title;	**Improving the longevity of joint replacements for patients - can statins reduce the inflammatory responseto orthopaedic biomaterials and inhibit pseudotumour formation?**
Period grant held	
From:	04/08/2021
To:	04/06/2022

Lay Summary

Total joint replacement is an effective treatment for osteoarthritis.
However, survival of the implants used for total hip replacement is 85% at 20 years, with patients potentially requiring a second revision operation. The most common reason for revision surgery is aseptic loosening of the implants in the bone.
This is due to bone breakdown driven by inflammatory reactions to wear debris.
Revision surgery is associated with higher rates of infection, mortality, venous clots and poorer function.

There is evidence that statins can significantly reduce the risk of patients requiring revision surgery, but the explanation for this is unclear.
The Tyson-Capper group were the first to identify how cobalt from metal debris could activate immune cells through toll-like receptor 4 (TLR4), an immune receptor which helps recognize and fight bacteria. Mr Anjum has demonstrated that cobalt can activate TLR4 on immune cells to increase inflammation responsible for aseptic loosening and formation of soft tissue tumours.

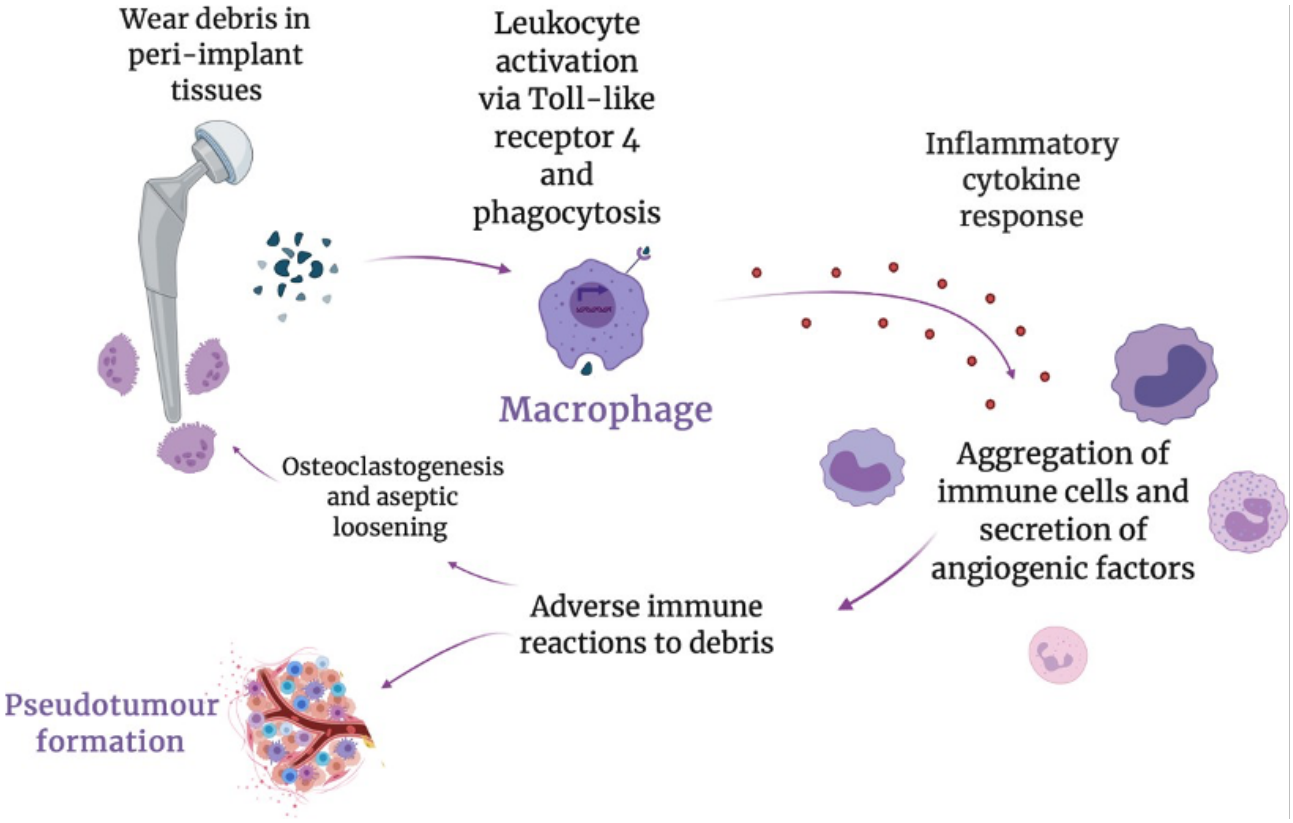
This project will investigate if statins reduce inflammation from wear debris and if TLR4 implicated.

If statins reduce the inflammatory response to wear debris, this will inform further work to use this cheap and safe drug to allow patients to mobilize pain free for longer.

A. Clinical and Scientific Significance of advances made

Hypothesis

I hypothesise that statins reduce host inflammatory immune responses to constituent biomaterials in orthopaedic debris and that this is as a result of modulating TLR4 expression.



Aims

- To investigate the ability of statins to attenuate the immune cytokine response in- vitro in response to a range of relevant orthopaedic biomaterials and to determine if TLR4 is implicated in these responses
- To investigate the ability of statins to attenuate secreted factors responsible for pseudotumour formation and pro-inflammatory adhesion molecule expression in- vitro in response to biomaterials

Maurice Wohl Research Fellowship Continued...

Methods

Cells

TLR4-expressing human monocyte/macrophage THP-1 cells were used as a model for the macrophage response in peri-implant tissues. THP-1 cells require activation using phorbol 12-myristate 13-acetate (PMA), as this differentiates the cells towards an M1 phenotype.

Treatments

THP-1 cells were initially pre-treated with 50µM simvastatin for 2 hours or a vehicle control prior to exposure to a variety of relevant orthopaedic biomaterials and further co-incubated with simvastatin or control for 24 hours. TLR4-specific LPS diluted to a stock concentration of 100ng/ml in complete media was used as a positive control at 10ng/ml. Complete media was added to untreated samples and used as a negative control.

Cobalt chloride hexahydrate was dissolved in complete media to a concentration of 0.75mM, as this concentration has been previously optimised by the Tyson-Capper group to elicit a TLR4-mediated immune response, is non-toxic to these cells, and is clinically relevant. Cells were also treated with 50µm3 per cell aluminium oxide or zirconium oxide (found in ceramic implants) nanopowders diluted in blank medium as these doses have been previously optimised by the Tyson-Capper group.

Changes in relative gene expression of TLR4 in cells treated with statins compared to controls will be assessed by qPCR

Cell Cytotoxicity

THP-1 cells were treated with the range of controls and orthopaedic materials used in vitro prior to being centrifuged, their supernatant extracted and the cell pellet resuspended in trypan blue solution. The cells were then added to a cell counting slide and assessed by percentage live cells in a Luna II Automated Cell Counter.

Assays

Cellular supernatant was collected for use in enzyme-linked immunosorbent assays for protein secretion analysis. Cells were then lysed and used in order to isolate RNA. The quality and yield of RNA was measured by a Nanodrop spectrometer and cDNA synthesised for use in real-time quantitative polymerase chain reaction (RT-qPCR) to assess changes in gene expression.

Changes in relative gene expression of TLR4 in cells treated with statins compared to controls will be assessed by qPCR

Statistical Analysis

GraphPad Prism 10 was used for statistical analysis which included a Student's t-test of treatment versus untreated control and a one-way ANOVA with multiple comparisons.

Genes of Interest	Proteins of Interest
IL-6	IL-6
IL-8	IL-8
TNF-a	TNF-a
ICAM-1	sICAM-1
VCAM-1	CCL2
TLR4	CCL3
CCL2	CCL4
CCL2	
CCL4	

Table 1 - Markers of interest

Rationale for markers of interest:

- IL-6 – a pro-inflammatory cytokine and stimulates osteoclastogenesis, which can result in bone resorption and aseptic loosening
- IL-8 – chemokine produced by macrophages and endothelial cells which induces chemotaxis of neutrophils, can induce osteoclastogenesis and promotes angiogenesis
- TNF-a - cytokine secreted by macrophages inducing inflammation
- CCL2 – cytokine which recruits monocytes (which can undergo osteoclastogenesis), T-cells and dendritic cells
- CCL3 – recruits granulocytes
- CCL4 – recruits natural killer cells and monocytes
- ICAM-1, VCAM-1 – adhesion molecules necessary for leukocyte extravasation
- sICAM-1 – a biomarker for inflammation and an angiogenic factor

Results

Protein Data

IL8

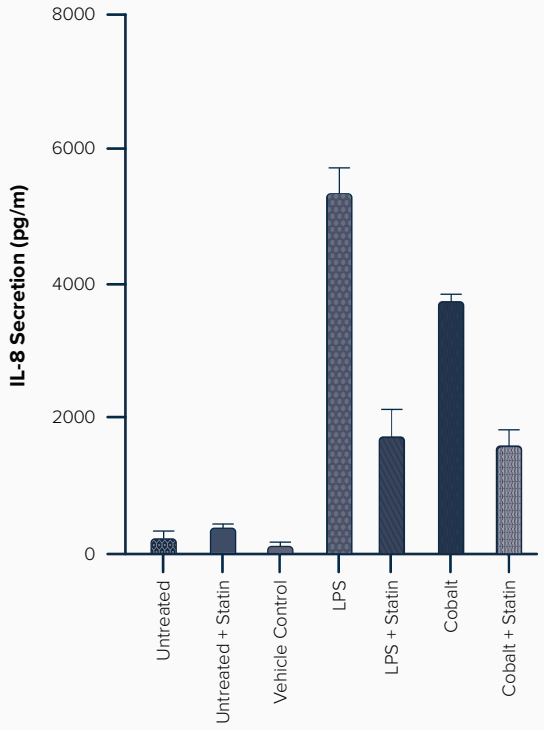


Figure 1 - Effect of 2-hour pre-incubation, followed by 24-hour co-incubation of simvastatin on cobalt mediated- IL-8 secretion. THP-1 cells were pre-incubated with 50µM simvastatin for 2- hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS and cobalt-mediated IL-8 secretion. N=5 (representative of 5 biological repeats).

Figure 1 demonstrates that exposure to 50µM simvastatin, for 2-hours followed by a 24- hour co-incubation with the relevant treatment, significantly reduces LPS and cobalt- mediated IL-8 protein secretion.

Maurice Wohl Research Fellowship Continued...

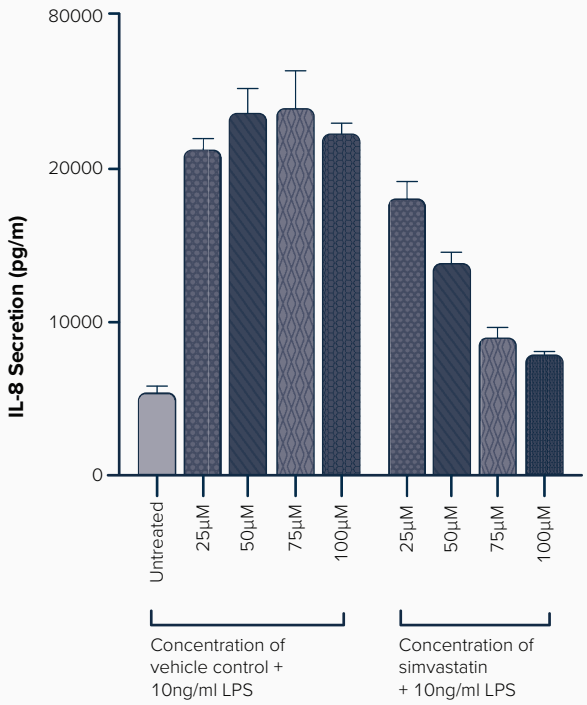


Figure 2 - Preliminary simvastatin dose response curve: IL-8. THP-1 cells were pre-incubated with a range of simvastatin doses for 2-hours or an equivalent dose of vehicle control, before being exposed to exposed to 10ng/mL LPS, in addition to a further 24-hours with the matched dose of simvastatin or VC. N=2 (representative of 2 biological repeats)

Figure 2 demonstrates a dose response curve of 2-hour pre-incubation with simvastatin followed by a further 24-hour co-incubation of simvastatin and LPS 10ng/ml. It is clear that with increasing concentrations of simvastatin there is a reduction in LPS-mediated IL-8 secretion. There was no significant difference between 25µM of simvastatin and 25µM vehicle control, but there was a significant difference for 50µM, 75µM and 100µM simvastatin and equivalent VC dose. The reduction in IL-8 secretion at 75µM and 100µM was such that there was no significant difference from the untreated sample.

No positive control of LPS without VC was included in this experiment, therefore the experiment was repeated to include this.

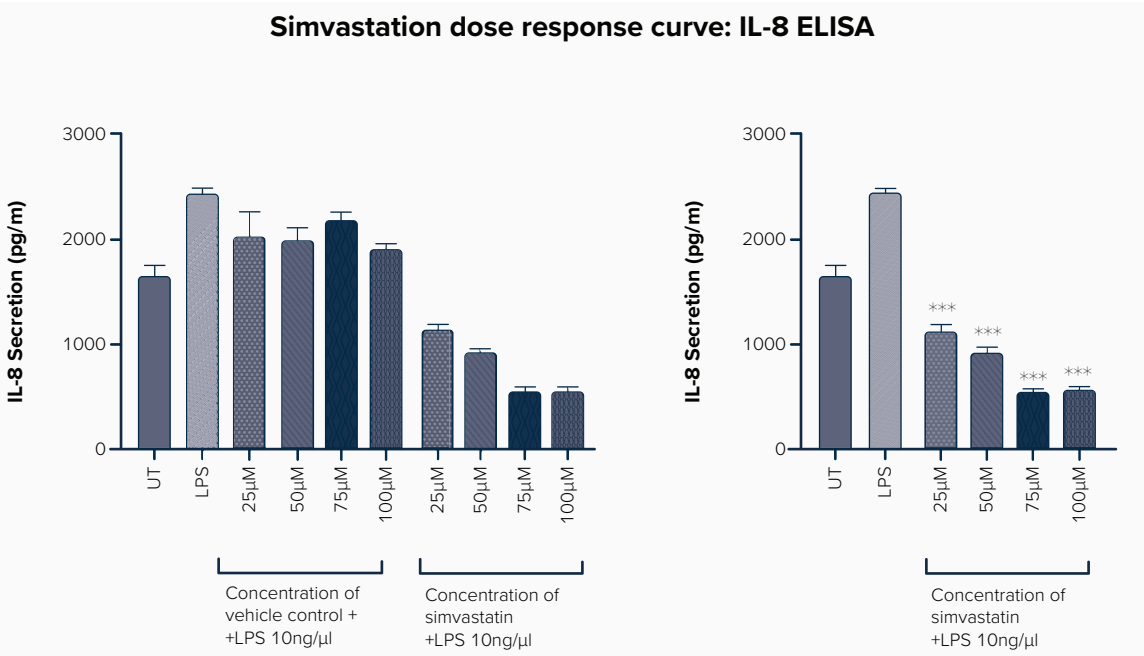


Figure 3 - Simvastatin dose response curve: IL-8. THP-1 cells were pre-incubated with a range of simvastatin doses for 2-hours or an equivalent dose of vehicle control, before being exposed to exposed to 10ng/mL LPS, in addition to a further 24-hours with the matched dose of simvastatin or VC. LPS 10ng/mL was used as a positive control. Graph A demonstrates the complete dataset with VC data, Graph B is the same data highlighting the effect of simvastatin alone. N=2 (representative of 2 biological repeats)

Figure 3 demonstrates a dose response curve of 2-hour pre-incubation with simvastatin followed by a further 24-hour co-incubation of simvastatin and LPS 10ng/ml. It is clear that with increasing concentrations of simvastatin there is a reduction in LPS-mediated IL-8 secretion. Indeed, there is a significant reduction in IL-8 protein secretion between the positive control of LPS and each of the samples treated with LPS and a dose of simvastatin. In addition, there is a significant reduction between the matched concentration of simvastatin and vehicle control at each dose.

The VC treated samples did not affect the LPS-mediated response at any concentration.
The dose of 50µM simvastatin was selected for treatments further experiments, as it was shown to elicit a significant reduction in IL-8 secretion to cobalt, and using higher doses would be wasteful or reagents and could have physiological consequences for the cells.

Maurice Wohl Research Fellowship Continued...

CCL2

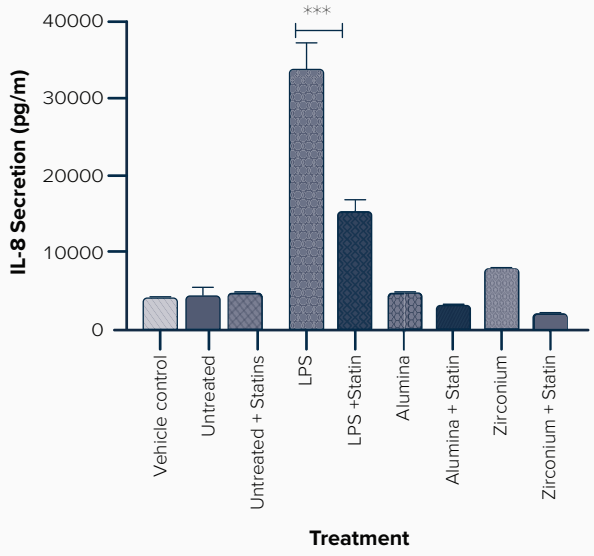


Figure 4 - Effect of simvastatin on ceramic-mediated IL-8 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, prior to the media being replaced and exposed to 50µM simvastatin for 24-hours in addition to either 10ng/mL LPS, 50µm3 per cell zirconium oxide or 50µm3 per cell alumina oxide. N=5 (representative of 5 biological repeats).

Figure 4 demonstrates that the ceramics did not elicit a significant IL-8 protein response in the THP-1 cells and that simvastatin did not impact this.

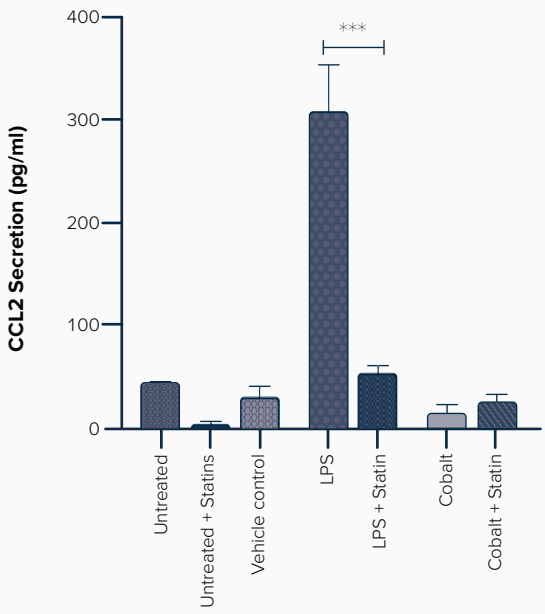


Figure 5 - Effect of simvastatin on cobalt-mediated CCL2 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS mediated CCL2 secretion, but there was no significant cobalt induced CCL2 response. N=2 (representative of 2 biological repeats)

Figure 5 demonstrates that simvastatin was able to significantly reduce LPS-mediated CCL2 protein secretion but a cobalt response was not produced. As this dose of cobalt has produced a significant CCL2 response in this cell line in previous work in the group, this experiment will be repeated.

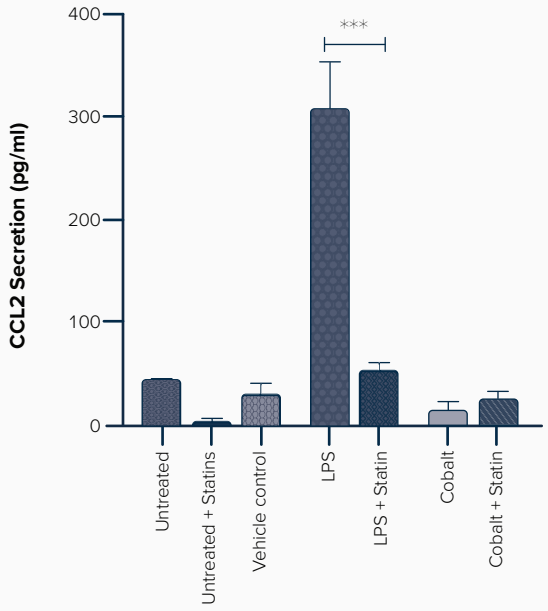


Figure 5 - Effect of simvastatin on cobalt-mediated CCL2 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS mediated CCL2 secretion, but there was no significant cobalt induced CCL2 response. N=2 (representative of 2 biological repeats)

Figure 6 demonstrates that simvastatin significantly reduced LPS-mediated CCL2 secretion and zirconium-mediated CCL2 protein secretion, but there was not a significant aluminium oxide response. Given that aluminium oxide has been shown to generate increased levels of CCL2 in this cell line by previous work in the group, this will be repeated.

CCL3

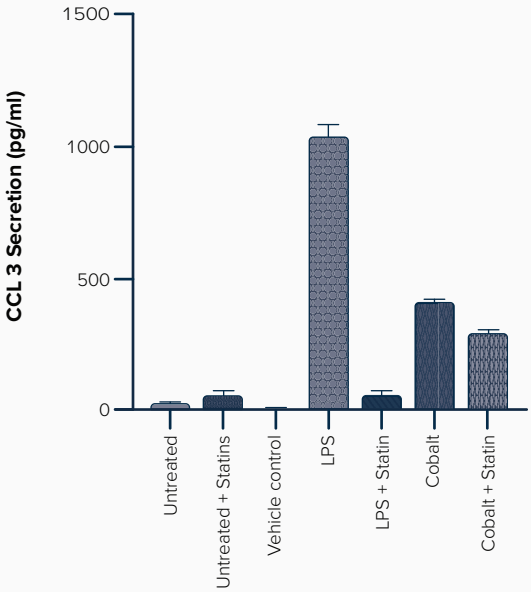


Figure 7 - Effect of simvastatin on cobalt-mediated CCL3 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS and cobalt- mediated CCL3 secretion. N=1.

Figure 7 demonstrates that incubation with statins significantly reduces the LPS mediated and cobalt-mediated CCL3 secretion in the THP-1 cell line.

Maurice Wohl Research Fellowship Continued...

CCL4

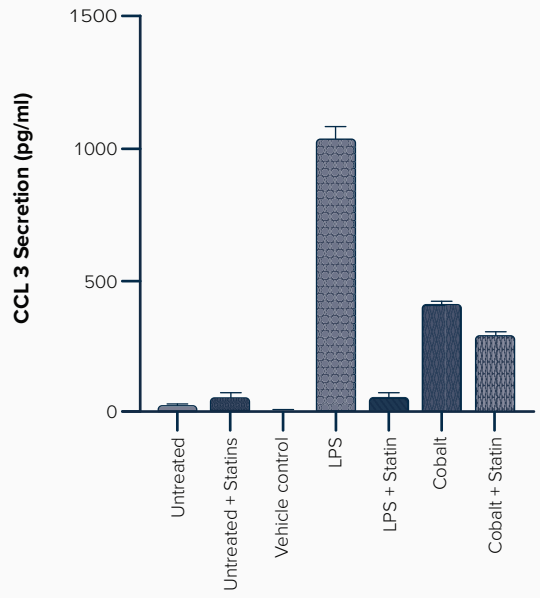


Figure 7 - Effect of simvastatin on cobalt-mediated CCL3 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS and cobalt- mediated CCL3 secretion. N=1.

Figure 8 demonstrates that incubation with statins significantly reduces the zirconium oxide-induced CCL4 secretion in the THP-1 cell line, but there was no effect on the LPS or cobalt chloride response.

sICAM-1

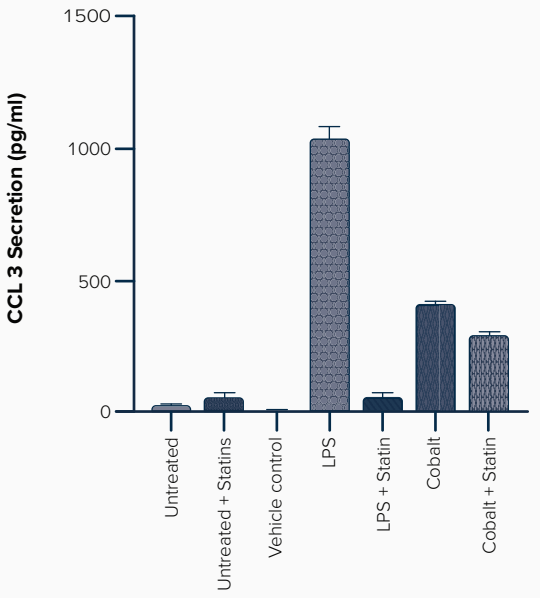


Figure 7 - Effect of simvastatin on cobalt-mediated CCL3 secretion. THP-1 cells were pre- incubated with 50µM simvastatin for 2-hours or a vehicle control, before being exposed to exposed to 10ng/mL LPS or 0.75mM cobalt chloride, in addition to a further 24-hour co-incubation with 50µM simvastatin or vehicle control. Simvastatin significantly reduced LPS and cobalt- mediated CCL3 secretion. N=1.

Figure 9 demonstrates that simvastatin significantly reduces LPS and cobalt-mediated sICAM-1 secretion. In addition, Figure 10 demonstrates that simvastatin can significantly abrogate zirconium oxide-induced sICAM-1 secretion, however there was no aluminium oxide response.

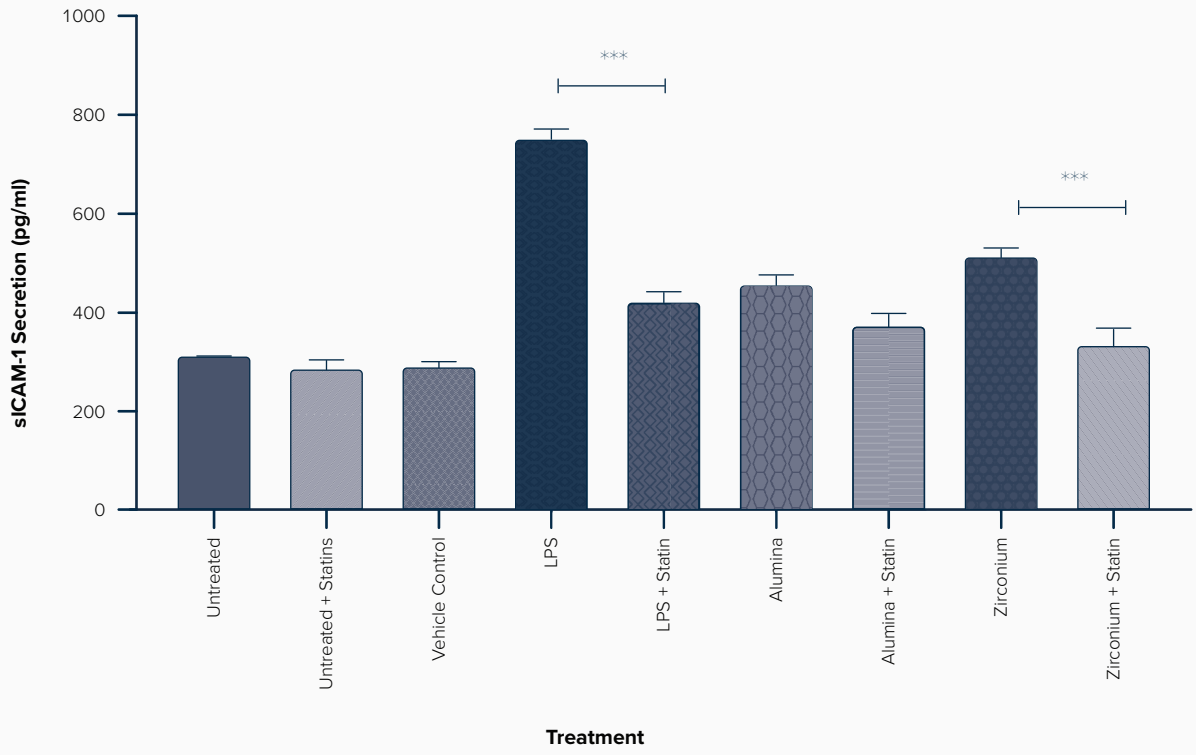
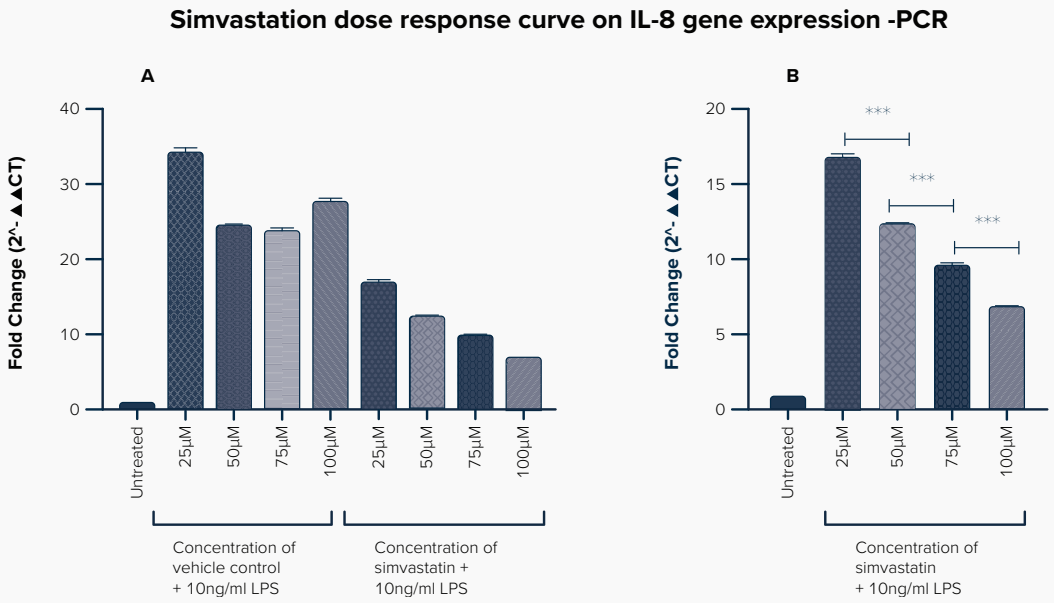


Figure 10 – The effect of simvastatin on ceramic oxide-induced sICAM-1 secretion. THP-1 cells were pre-incubated with 50µM simvastatin for 2-hours or a vehicle control, prior to the media being replaced and exposed to 50µM simvastatin for 24-hours in addition to either 10ng/mL LPS, 50µm3 per cell zirconium oxide or 50µm3 per cell aluminium oxide. N=1

Maurice Wohl Research Fellowship Continued...

Gene expression Data

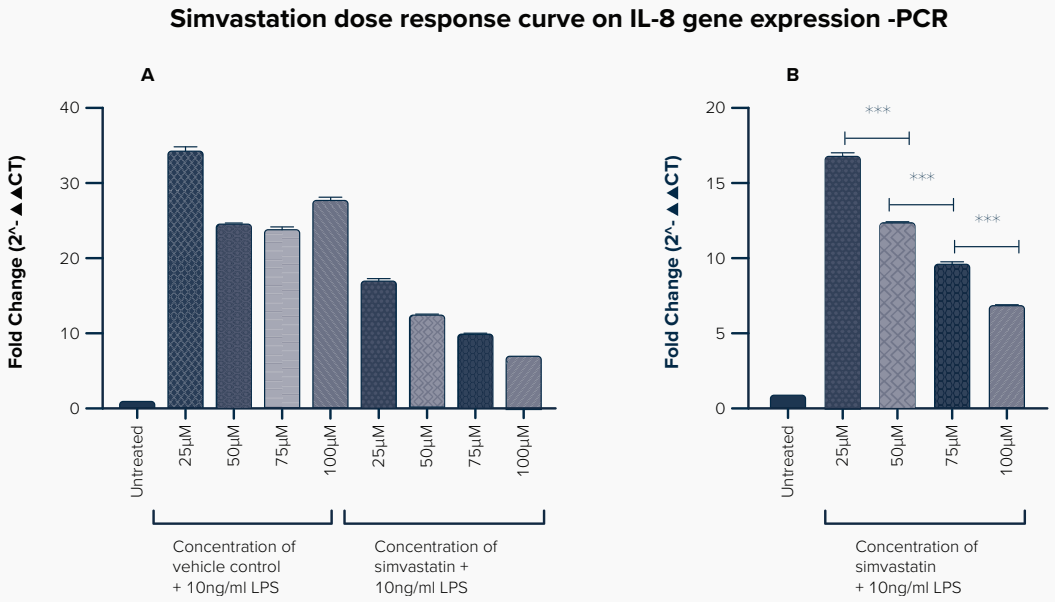
IL8



▲ Figure 11 - Effect of simvastatin dose response curve on LPS-mediated IL-8 gene expression. THP-1 cells were pre-incubated with a range of simvastatin doses for 2-hours or an equivalent dose of vehicle control, before being exposed to exposed to 10ng/mL LPS, in addition to a further 24-hours with the matched dose of simvastatin or VC. Graph A demonstrates the complete dataset with VC data, Graph B is the same data highlighting the effect of simvastatin alone. (N=1)

Figure 11 demonstrates that with increasing concentrations of simvastatin, there is a decrease in LPS-mediated IL-8 gene expression. There is a significant reduction ($p<0.0001$) between each concentration of simvastatin (which has been treated with LPS) and its equivalent dose of VC and LPS.

There was also a significant reduction in IL-8 gene expression when the dose was increased to the next highest dose, i.e. from 25µM to 50µM simvastatin. As a positive control of LPS without VC was not included in this experiment, this will be repeated to reflect this.



▲ Figure 11 - Effect of simvastatin dose response curve on LPS-mediated IL-8 gene expression. THP-1 cells were pre-incubated with a range of simvastatin doses for 2-hours or an equivalent dose of vehicle control, before being exposed to exposed to 10ng/mL LPS, in addition to a further 24-hours with the matched dose of simvastatin or VC. Graph A demonstrates the complete dataset with VC data, Graph B is the same data highlighting the effect of simvastatin alone. (N=1)

Figure 12 demonstrates that simvastatin significantly reduces LPS-mediated IL-8 gene expression but there was no significant ceramic oxide-induced IL-8 gene expression response.

Maurice Wohl Research Fellowship Continued...

CCL2

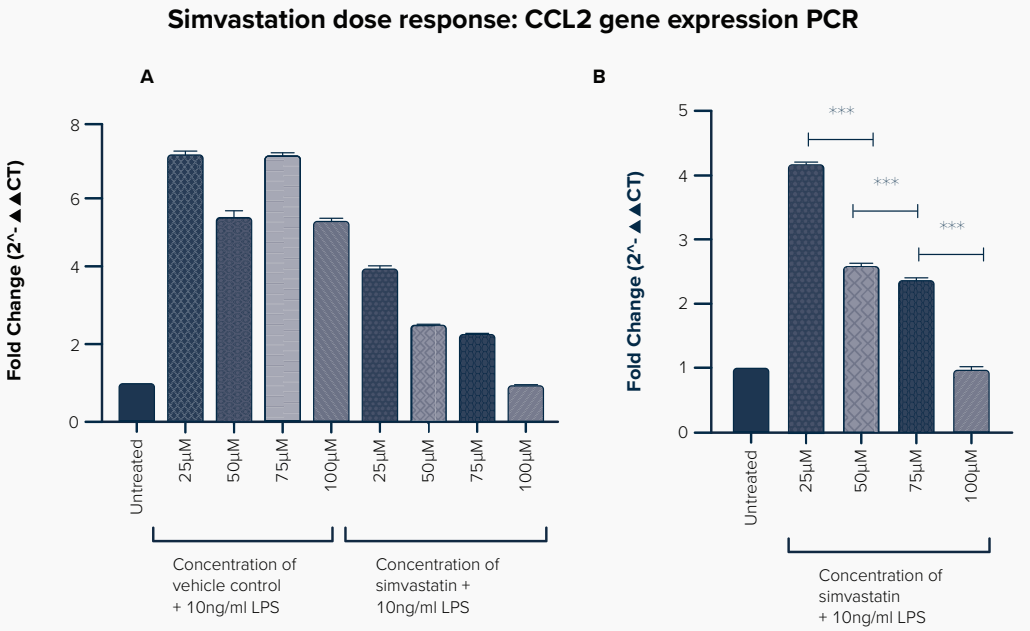
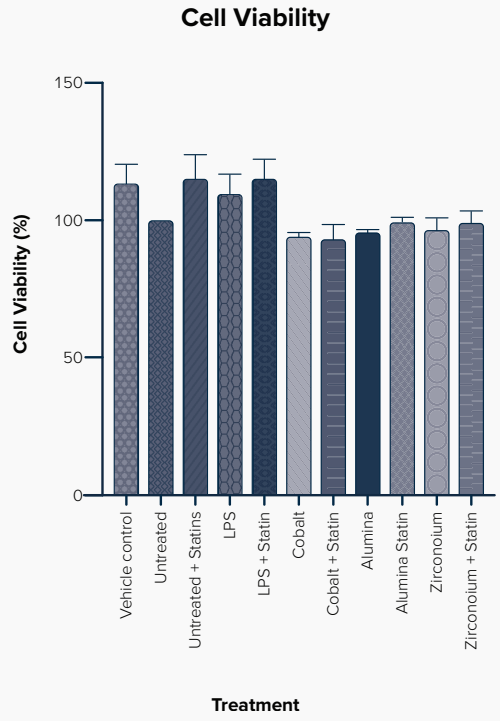


Figure 13 - Simvastatin dose response on LPS-mediated CCL2 gene expression. THP-1 cells were pre-incubated with a range of simvastatin doses for 2-hours or an equivalent dose of vehicle control, before being exposed to exposed to 10ng/mL LPS, in addition to a further 24-hours with the matched dose of simvastatin or VC. Graph A demonstrates the complete dataset with VC data, Graph B is the same data highlighting the effect of simvastatin alone. (N=1).

Figure 13 demonstrates that with increasing concentrations of simvastatin, there is a decrease in LPS-mediated CCL2 gene expression. There is a significant reduction ($p<0.0001$) between each concentration of simvastatin (which has been treated with LPS) and its equivalent dose of VC and LPS.
There was also a significant reduction in CCL2 gene expression when the dose was increased from 25µM to 50µM and from 75µM to 100µM.

As a positive control of LPS without VC was not included in this experiment, this will be repeated to reflect this.

Cell Viability



▲ Figure 14 – Cell viability assay. THP-1 cells were pre-incubated with a range of treatments used in the above methodology prior to their supernatant extracted and the cell pellet resuspended in trypan blue solution. The cells were then added to a cell counting slide and assessed by percentage live cells in a Luna II Automated Cell Counter (N=3).

Figure 14 demonstrates the treatments used in the above experiments did not significantly affect cell viability.

Discussion

Aim 1

The above work demonstrated that when THP-1 cells were pre-treated with 50µM simvastatin for 2-hours followed by a 24-hour co-incubation, it could significantly reduce cobalt mediated IL-8 protein and gene expression, with this effect becoming more prominent with increasing doses of simvastatin.

Simvastatin was also able to significantly reduce cobalt-mediated CCL3 protein secretion, although further biological repeats are necessary (n=1). When investigating the effect of cobalt-mediated CCL2 gene expression changes there appeared to be a dose response effect (although this experiment needs to be repeated with a further positive control), although further biological repeats are necessary (n=1).

This preliminary data also suggested that zirconium oxide mediated CCL2 and CCL4 secretion was abrogated by simvastatin.

These in-vitro findings complement discussion in the literature of the anti-inflammatory properties of statins, however there is no published record of the effect of simvastatin on cobalt and ceramic oxide responses in THP-1 cells.
Given that this is a macrophage cell line and that macrophages are key leukocytes known to drive the host response to orthopaedic debris, and that IL-8, CCL2 and CCL3 are potent cytokines in attracting immune cells and initiating osteoclastogenesis, this could help account for the improved survival rates of implants in pharmacoepidemiological studies.

Aim 2

Simvastatin was demonstrated to significantly reduce cobalt mediated and zirconium mediated sICAM-1 secretion. Given that sICAM-1 is an angiogenic factor known to support pseudotumour formation, this could implicate the role of statins in reducing the incidence of pseudotumours in failed TJA. Further qPCR work is needed to assess any change in ICAM-1 and VCAM-1 expression.

Discussion

Simvastatin significantly reduces cobalt-ion mediated IL-8 and sICAM-1 protein secretion in THP-1 cells.

Maurice Wohl Research Fellowship Continued...

This in-vitro finding demonstrates the potential for simvastatin to reduce recruitment of leukocytes which mediate the deleterious inflammatory processes driving aseptic loosening and pseudotumour formation. However, the process in-vivo of statins affecting joint survival is one that takes place over months to years, with a complex intersection of joint biomechanics, patient soft tissue anatomy and metabolism of statin compounds, which is difficult to replicate in an in-vitro model.

Significance/Clinical Relevance

If it can be demonstrated that statins via-TLR4 reduce the inflammatory response to cobalt ions in-vitro and thereby reduce aseptic loosening, this could be an exciting mechanism for a cheap, relatively safe and widely available drug to improve implant longevity and reduce costly and complicated revision surgery rates for patients. This research could inform clinical trials and further translational research.

B. Problems encountered and steps taken to overcome them

THP-1 cells pre-treated for only 2 hours prior to exposure to treatments with 50µM of simvastatin did not significantly abrogate IL-8 secretion for LPS, cobalt or ceramic oxides at this time point. Therefore, the exposure time was adjusted to include a simvastatin 2- hour preincubation and 24-hour co-incubation with the relevant treatments which resulted in significant results.

C. Collaborations established

Professor Haycock is Head of the Materials Science and Engineering department at Sheffield University. The group are experts in the use of 3D scaffolds for 3D in-vitro models for inflammatory testing.

Professor Haycock has agreed in principle in a future award if funding is available to collaborate. This collaboration would involve:

- Use of optimised pre-clinical in-vitro models to assess the impact of statins on bone growth
- Using 3D porous titanium surfaces on human primary osteoblast cell proliferation, morphology change and mineralisation.

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

- 15/09/21 – Oral and Poster Presentation at the European Orthopaedic Research Society (EORS) Meeting. Rome, Italy.
- 05/02/22 – Poster Presentation Accepted at the Orthopaedic Research Society Meeting. Tampa, Florida.

E. Acknowledgements

Thank you to the generous funding and flexibility from the Maurice Wohl Foundation and the Royal College of Surgeons of Edinburgh, without whom the progression of this project would not be possible. Thank you to Professor Tyson-Capper, Professor David Deehan and Professor John Kirby for their continued guidance, motivation and mentorship throughout this project. Thank you to Mr James Holland for helping to frame this research in a clinical context. Thanks are due to Shannon Jamieson for instruction, help and troubleshooting with the methodology of the project and to Vic Hart and Chelsea Griffiths in the Tyson-Capper and Kirby research groups.

74 Travelling Fellowship Reports

The Cutner Travelling Fellowship in Orthopaedics

Report on the Cutner travelling fellowship (4 Oct 21 to 22 Dec 21)

Prithee Jettoo, Trauma and Orthopaedic surgery

Fellowship with Prof Pascal Boileau at Institut Chirurgie reparatrice in Nice

I thank the Royal College of Surgeons of Edinburgh for awarding me the Cutner travelling fellowship grant for a period of 3 months. I have visited the Institut Chirurgie reparatrice Locomoteur & Sports in Nice with Mr P Boileau to gain experience in both trauma and elective shoulder surgery in October 21. His practice includes shoulder arthroplasty and arthroscopic surgery involving the rotator cuff repair and shoulder instability conditions.

This is a high-volume centre allowing me to gain new insights and learn new techniques in shoulder surgery.

The clinic is highly efficient in both the outpatient department and the operating theatres. Patients in the outpatient clinics have a spectrum of shoulder pathologies, some referrals are after multiple failed surgeries or failure of conservative management. The patients come from all over the world to see Mr Boileau for his expertise.

Mr Boileau has a philosophy of having a strategy, tactic and technique which he inculcates in fellows. We discussed about the training system in France comparing it with that in UK.
Getting the correct diagnosis is the main emphasis in the clinic as well as shared decision-making process with the patient about treatment options. The operative plan is also made in the clinic in a detailed fashion including intra-operative tactic.
The patient consultation is recorded electronically on a software, from which data can be subsequently analysed for scientific research and projects.

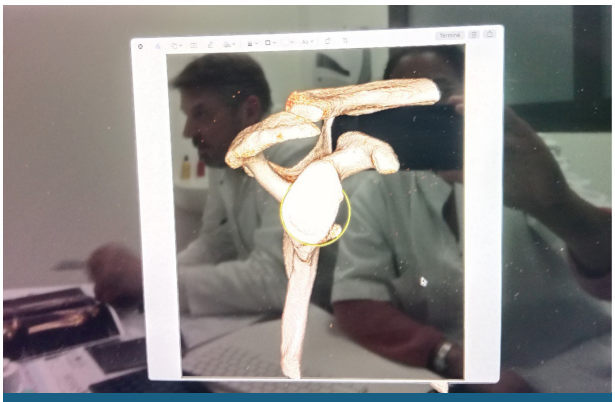
This fellowship has provided me with the opportunity to acquire further knowledge and skills in arthroscopic rotator cuff repair, shoulder arthroscopic stabilisation and instability surgery. For instance, rotator cuff repair surgery is precisely carried out after effective debridement and thorough releases including opening the rotator interval, preparing the footprint and meticulously undertaking the repair.

Mr Boileau developed a double layer repair, instead of using the double row repair. For instability, Mr Boileau does the arthroscopic latarjet using 2 endobutton technique, which he developed. There is also access to a cadaveric lab, which is very useful for practising new skills.

He is extensively published in shoulder surgery having carried out significant clinical research, he has more than 180 articles published in peer-reviewed journals and has edited 15 books. Each clinical encounter is a discussion with reference to the literature. Furthermore, he readily shares his knowledge and encourages discussion and insights about intra-operative techniques, tips and tricks. There is a dedicated scientific day on a weekly basis, where cases are discussed with brainstorming activity and generation of ideas to encourage further research activity.

Mr Boileau developed the bony increased offset reverse shoulder arthroplasty (BioRSA) technique as well as the software for pre-operative planning. I acquired a better understanding in pre-operative planning and decision-making process in complex shoulder cases with associated bone loss and deformity by carrying out pre-operative templating for patients for shoulder arthroplasty. This is an important part of planning as we carry out the surgery (obtaining correct implant orientation, inclination, version and tilt using the software before implantation in the patient including identifying potential impingement points through range of motion that may need further intervention (acromioplasty/ tuberoplasty). For this, we use CT with 3D reconstruction that is entered in the software and the pre-op planning is carried out by fellows.

I believe I would be able to translate this clinical experience from a different health setting and benefit patient in the UK, and I thank the RcSEd for this award.



Anteroinferior glenoid bone loss pre-op planning for arthroscopic latarjet

Mr Daniel MG Winson MBBS, MSc SEM, FRCSEd (Tr&Orth)

Specialty: Foot and Ankle Surgery

Location: Mater Public Hospital, Brisbane/ The Wesley Private Hospital, Brisbane/ St. Andrew's War Memorial Private Hospital, Brisbane

Dates: February 2022 to August 2022

I undertook my 6 month fellowship in Foot and Ankle Surgery in Brisbane Australia. The fellowship is approved by the Australian Orthopedic Association and run by Dr Michael Lutz and Dr Ben Forster. This fellowship has been running for many years and was previously supervised by renowned foot and ankle surgeon Dr Terry Saxby.

It is a combined public and private fellowship, running on a four-weekly timetable split between the three hospital sites.

The Cutner Travelling Fellowship in Orthopaedics Continued...

The Mater Public Hospital is located in South Brisbane and is the public arm of the Mater group. Although not part of Queensland Health it has a reciprocal agreement and has both training and non-training (Principal House Officers) registrars working there. The fellow has 1-2 elective clinics a week at the Mater. These are either solo clinics or alongside a consultant clinic. You are encouraged to treat then as your own clinics and develop your consultant decision making.
However, Dr Lutz and Dr Forster are always happy to discuss or see patients as required. You will have a Principal House Officer allocated to your clinics which is useful for developing your team leading skills required for future consultancy.

The fellow is allocated 3 theatres list a fortnight. These are parallel lists to the consultants. You are encouraged to book and run these lists yourself and select (within reason) which cases you wish to do. There is only one list every month with a consultant in theatre with you.

This is an opportunity to put more complex cases on this list to do with more direct supervision. Both Dr Lutz and Dr Forster are happy for you to amend their parallel lists to complement the fellows list.

This gives you the opportunity to arrange it so that the consultant can be flexible enough to pop into your theatre to lend advice and support.
In truth, if you are wanting to do a lot of supervised trainers scrubbed or un-scrubbed operating on your fellowship, this is not the one for you! What it does do is give you the opportunity to experience what it is like to run lists and clinics as a consultant. You will also be allocated a Principal House Officer to you lists giving you the opportunity to do some teaching in theatre and develop the careers of your junior colleagues.

As in much of Australia, the trauma is managed by the registrars with minimal consultant input. Therefore, it is much appreciated by both the registrars and consultants if the fellow is able to supervise this aspect of the service. This gives you the opportunity to manage complex foot and ankle surgery, which will inevitably be a requirement of your future consultancy. There is no requirement to do fracture clinics, on call or general trauma theatre list. However, should you wish to do this, there is plenty of time in the timetable to facilitate this.

Dr Lutz works in both the Mater Public Hospital and St Andrew's War Memorial Hospital in Brisbane. His practice is elective foot and ankle both publicly and privately, with adult trauma publicly and foot and ankle trauma privately.

The fellow is allocated patients in his private clinics. These are all new patients, and you can consultant and formulate a management plan prior to Dr Lutz seeing the patient.

Although at times this can feel a bit like a return to medical school, in truth its incredibly useful to see the basics done well by an experienced colleague and there are plenty of little tips and tricks that can be picked up. Privately you are required to assist in theatre. You don't get an opportunity to operate yourself privately and are limited to assisting only.
However, once again it is incredibly useful to watch and learn how things are done and then take that experience back to the public hospital where you can perform it yourself.

Dr Forster works in both the Mater Public Hospital and The Wesley Private Hospital. His practice is elective foot and ankle both publicly and privately with foot and ankle trauma privately. He also has a large interest in sports injuries and is involved with the Queensland Reds Rugby Union Team, Brisbane Lions Australian Rules Football League, North Queensland Cowboys National Rugby League Club, Gold Coast Titans NRL and the Gold Coast Suns AFL. A significant proportion of his private practice is professional athletes giving you the opportunity to see how practice might differ in this subset of patient. He is part of a larger private group called Queensland Combined Orthopaedic Specialists, based out of the Wesley.
As the fellow you see new private patients in clinic and assist in theatre.
Once again it is an exceptional opportunity to study how he performs certain procedures and apply those techniques with his public patients.

If like me, your understanding of private practice during your training has been limited it is very interesting to see how both Dr Lutz and Dr Forster have set theirs up. For those considering entering private practice once they attain a consultancy it can be a useful learning opportunity.

The fellowship allows for number of sessions for research and learning.

This time is flexible however and often I have timetabled complex trauma into these slots when I am not otherwise engaged. I have however, managed to conduct 2 research projects with the gait lab and these sessions are useful gaps in the timetable in which to work on these projects. They also provide you time to plan you upcoming lists.

When researching fellowships in Australia, you will find that many are based solely in the private sector. This can affect your hands on surgical experience and also how you are paid. The Mater public hospital is the fellow's principal employer and therefore you are paid via the public system. In Australia, this means that you are eligible for certain financial benefits including salary packaging and overtime (a strange concept for us UK trainees!).

In terms of the city itself, Brisbane is a wonderful place to live. With a population of 2.28 million it is a large city but essentially made of multiple smaller areas each with a distinct style and character. COVID has significantly affected the rental market in the short term as many Australia citizens from other cities such as Melbourne have flocked to Queensland to avoid frequent lock downs. This means that rental properties go quite quickly due to high demand. It is also not common for properties to be rented furnished and frequently unfurnished properties to do not come with a fridge, meaning that has to be factored into your initial costs.
I have moved out here with my wife and three children and the state schools (primary age) in Brisbane are truly exceptional.

The Cutner Travelling Fellowship in Orthopaedics Continued...

The outdoor lifestyle suites the children well and there a multitude of well managed sporting clubs that are easy to join. With the Sunshine Coast north of the city and the Gold Coast to the south there are plenty of opportunities to get away for the weekend. Both the beaches and the hinterland are stunningly beautiful offering different types of trips with fun for all the family.

In summary, this has been a truly incredible fellowship. I feel that I have developed well as a clinician and as a leader during this time. It has defiantly benefited me and will continue to do so in my consultancy. I would recommend it to any trainee considering a career in foot and ankle surgery.

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Ethicon Foundation Travel Grants Reports

Michael Gavin Hart, FRCS (Neuro.Surg)

Clinical Fellow in Functional Neurosurgery, St George's Hospital, London

Clinical Fellow, Division of Neurosurgery, Department of Surgery, Faculty of Medicine, The University of British Coloumbia, Vancouver, B.C. Canada

May 30 2020 to July 1st 2021

Functional neurosurgery involves the modulation of nervous system activity. Historically, this involved injuring ('lesioning') key structures involved in a specific areas of the brain. Subsequently, deep brain stimulation (DBS) has evolved which allows electrical neuromodulation to provide similar effects to these lesions but with the advantage that the effect can be titrated and reversed. Conditions treated by functional neurosurgery typically include movement disorders (Parkinson's disease, dystonia, and tremor), pain, epilepsy, and psychiatric conditions. Currently over 175,000 DBS systems have been implanted worldwide.

The fellowship was led by Professor Chris Honey in Vancouver, British Columbia. The programme is well established having been running for over 20 years with almost 25 alumni. One of the attractions of the fellowship was the variety of operations performed and conditions treated. For instance, Professor Honey's practice encompasses almost the entire range of functional neurosurgery, including lesional surgery, microvascular decompression surgery, as well as neurosurgery for pain and psychiatric conditions. In addition, he also performs procedures that are dropping out of the surgical vocabulary due to their rareness and complex indications, such as trigeminal nucleotractotomy and motor cortex stimulation. Naturally, the fellowship also includes a large and highly efficient DBS practice too, and this clinical exposure was also a priority for me given the paucity of functional neurosurgery experience during my training in Cambridge. Anything broader than this in terms of surgery e.g. epilepsy or non-invasive approaches (such as HiFU or LITT) would have diluted this core experience in DBS too much.

Location wise, the fellowship runs from two main hospitals. Vancouver General Hospital is a large, busy, teaching hospital nestled in the bustling centre of the city that incorporates all main surgical specialties and is a major trauma centre too. This is where our team – a wonderful quartet of exceptionally talented specialist nurses – was based, and where we did our on-calls. The University of British Columbia encompassed a smaller, 6 theatre elective hospital where our operating occurred. This was part of the University campus, idyllically located in the Pacific Spirt National Park overlooking the Pacific Ocean on the western fringes of the city. Working in two locations helped to broaden the experience and provided a contrast both in their ethos as well as the contrasting areas of the city in which they were located.

British Columbia has a population of approximately 5 million, which conveniently is similar to the catchment area of my own neurosurgical alma matter (Cambridge and the east of England deanery), as well as Scotland where I grew up. However, the difference is in the population distribution, with British Columbia essentially concentrating its entire 5 million inhabitants in Vancouver and the surrounding suburbs. Outside of this metropolitan area was a province approximately the size of France and Germany combined. Next to British Columbia the surrounding provinces were equally large and even more sparsely inhabited. This brought about unique challenges related to communication and transport with remote communities, many of whom were First Nations.

Healthcare in Canada is similar to the UK in that it is almost entirely publicly funded. Indeed, in British Columbia the prevailing New Democratic Party (NDP) government has essentially prohibited private practice in neurosurgery.

Overall healthcare was well funded like in the UK, with a healthcare budget of approximately $20 billion CAD (approximately £12 billion GBP) per year. One peculiar detail is that while operations are publicly funded, medications are not: this led to a situation where a patient was implanted with a specific drug delivery device for free, but then had to pay by themselves for the medications used to refill the device. Overall, while it is hard to make specific comparisons as to the level of funding between the UK and Canada, there appeared to be a much higher usage of philanthropy in Canada with many large projects or expensive items of equipment (e.g. the new surgical robot for epilepsy surgery) funded and subsequently named after notable benefactors.

Covid presented a new challenge to pursuing an overseas fellowship. Additional difficulties encountered included those related to travel, relocation, and overall logistics. For instance, while in quarantine I was unable to visit a bank to start a local account, which meant I was unable to be paid and was not able to rent an apartment immediately. Furthermore, the required tests, quarantine accommodation, and general increased travel expenses added significantly to the overall cost of the fellowship. Ultimately, I had to leave before my family who joined me later once restrictions had relaxed in the UK.

Having said that, I feel that there wouldn't have been a better place to do a fellowship during the covid pandemic than in Vancouver, for both personal and professional reasons.

Fortunately, British Columbia was relatively spared from the original first wave of the pandemic, for reasons typically attributed to it closing its borders early and before the spring break of 2020 (which was after its neighbouring provinces and typically would involve a large volume of travel between Vancouver and Asia). Couple this to an outdoor-centric and healthy-living focused population, Vancouver enjoyed relatively low levels of covid throughout.

Healthcare authorities were in the seemingly contradictory position of wishing to control the covid pandemic, but also had significant surgical waiting list numbers that required to be reduced and for which they had heavily invested in reducing over the prior 24 months. Fortunately, during my fellowship we were able to continue operating at record levels throughout and performed over 80 primary DBS insertions.

Possible reasons for this, in addition to those mentioned above, include operating at a geographically distinct and smaller sized elective hospital that specifically did not admit patients with covid (the main emergency department was at VGH). All patients were thoroughly screened prior to admission and were rarely in hospital for more than 24 hours, while the elective nature of surgery meant that we presented no demand on intensive care facilities. It should be mentioned that these advantages held true for the other surgical specialities we shared the facility with, including orthopaedics, general surgery, maxillo-facial surgery, and plastic surgery. Finally, credit should go to our patients who often went into self-imposed isolation prior to surgery to minimise their risk, such was the importance they placed on the operation and their gratitude that we were able to continue with surgery.

This strategy is in contrast with that in other countries where for example elective cases were cancelled and only high priority (and often higher risk) procedures were allowed to proceed.

Professionally, the fellowship offered more than what is required to become a safe and effective practitioner in functional neurosurgery, both in terms of volume and training quality. I was essentially able to routinely lead all operative cases myself and run my own clinic too. One of the striking features of the fellowship was the high number of procedures that were performed. It readily became apparent that to do this one needs a highly efficient set up, with a great team, and a low rate of complications. The Vancouver practice had all those ingredients, and I was able to not only appreciate having an excellent exposure to functional neurosurgery but also in how to perform the surgery well. Prior to leaving for Vancouver, I had experienced the doldrums of the cessation of elective operating during the first wave of covid. This, coupled with the outstanding surgical experience available to me in Vancouver, led to an invigoration of my appreciation for the privilege of being able to actually operate and perform as a surgeon.

From a family perspective, my memories of Vancouver will be of the most wonderful family experiences. It was a joy seeing our children settle into school so well and make so many great friends. The school emphasised the community feel of the Davie village area (home of the LGBTQ2CIS community) and charismatic West End where we lived.

Ethicon Foundation Travel Grants Reports Continued...

Additionally, the school placed a priority on educating about the local environment, which they were well placed to do being juxtaposed between the Pacific-lapping shores of English bay and authentic old-growth rainforest of Stanley Park (the largest urban park in North America). Undoubtedly, a happy family life leads to a more fecund professional life.

Outside of work we quickly became accustomed to the British Columbian ethos of exploring and enjoying the big outdoors. During the winter months a highlight was the whole family learning how to snowboard together on the local mountains every weekend, less than 30 minutes from downtown Vancouver. In between times we enjoyed hiking, mountain biking, and paddle boarding, all of which were essentially new to us. Overall, the impression was that the entire Pacific North West really has got the whole work-life balance worked out. Returning to work on Monday after enjoying a weekend of outdoor pursuits in spectacular scenery was truly refreshing and energising.

In conclusion, this fellowship was undoubtedly the highlight of my training. Not only was it professionally rewarding but it was also uniquely productive at a time when much of the world's elective operating was significantly curtailed. Professionally, I feel thoroughly well prepared to lead a busy functional neurosurgery service.

While the knowledge and skills I have learnt will serve me well for the rest of my consultant career, it will be my memories of the great team I worked with and wonderful patients I helped to treat that will endure. Personally, it was a wonderfully fulfilling family experience, punctuated by a reinvigoration for enjoying the great outdoors and becoming part of a truly unique city. Overall, I would highly recommend not only this fellowship, but spending any time possible in beautiful British Columbia.

Iain Murray, Consultant Orthopaedic Surgeon, Edinburgh Orthopaedics, Royal Infirmary of Edinburgh, UK.
Fellowship: Stanford University Orthopaedic Sports Medicine Fellowship, Stanford University, California, USA.

I recently returned to Edinburgh from California, having completed the Stanford University Orthopaedic Sports Medicine Fellowship in July 2021.

The Leland Stanford Junior University was founded in 1885 by California Senator Leland Stanford and his wife, Jane, in memory of their only child, Leland Jr., who died of typhoid fever at 15. Over the past 125+ years Stanford has become one of the world's leading universities with a particular reputation for innovation and research excellence in the fields of technology, business and Medicine.

In addition, Stanford is the US's most successful sporting university having won more National Championships than any other institution and with a host of famous Sporting Alumni including Tiger Woods and John McEnroe.
If Stanford were a country it would have tied for 7th most gold medals won at the Tokyo Olympics.
Stanford was therefore the perfect destination for an aspiring orthopaedic sports surgeon seeking experience at one of the world's leading centres for sports and orthopaedic surgery.

My first impressions of Stanford was the impressive campus and beautiful surroundings set in the wealthy town of Palo Alto, in the San Francisco Bay Area. Palo Alto is protected from the cold Pacific winds and fog by the Santa Cruz Mountains and set on the west side of the Bay has an extremely pleasant year round climate ranging with average temperatures of 14oC in winter and 26oC in summer and very little rain. Although the weather is extremely pleasant, there are no shortage of natural challenges. It is situated on the San Andreas Fault and, as we experienced, the surrounding area is increasingly plagued by forest fires and the smoke they produce, drought, and seasonal 'sneaker waves' that make some of the coastlines dangerous for paddling.

With 19 current Nobel Laureates on faculty there was a 'buzz' around the campus. The recently opened Stanford Hospital felt extremely futuristic inside with robots delivering supplies around the hospital and state of the art integrated operating rooms. Almost all daycase surgery was delivered within the Stanford Outpatient Surgery Centre which was equally as impressive.

Figure. Stanford is situated in Palo Alto within the San Francisco Bay Area. The campus is set on the grounds of a farm owned by its Founders Leland and Jane Stanford, and is fondly known as 'The Farm'.

The Stanford Campus is incredibly large and impressive with immaculately manicured gardens and lawns, with iconic academic buildings set alongside state of the art sports facilities. Although Stanford has considerably fewer students than some of the larger Scottish Universities, it was clearly a very wealthy institution that had benefited from its huge success in research and innovation.

Ethicon Foundation Travel Grants Reports Continued...

	Edinburgh University	Stanford University
Undergraduate students	23,098	6,366
Post graduate Students	12,160	8,791
Faculty Members	3,071	2,279
Nobel Laureates on staff (2020)	1	19
Athletic Department Revenue	Not known	$139m USD
Academic Expenditure	£449m	$1.9b USD
Endowment	£489m	$28.9b USD

▲ Table. Although it has fewer students and faculty, Stanford has an impressive track record of academic success and funding.

The Orthopaedic Sports Medicine Fellowship is an ACGME (Accreditation Council for Graduate Medical Education) accredited fellowship with entry through the US National Matching Scheme. To be eligible to apply I had to complete the United States Medical Licensing Examinations. The fellowship covered the spectrum of orthopaedic sports medicine, including intensive experiences in arthroscopic knee, hip and shoulder surgery in addition to non-arthroplasty open surgery. The program provides an immersive experience in being a Team physician, and I was attached to the San Francisco 49ers (National Football League) with my co-fellows attached to Oakland Athletics (Major League Baseball) and Stanford (American Football). In addition, the program includes a formal education program and examinations and assessments at both the beginning and end of the fellowship.

Figure: clinical work was split between the Stanford Orthopaedic Day Surgery Centre and the Stanford Hospital (above left).
I was also assigned to the San Francisco 49ers who are based at the Levis Stadium (above right) in nearby Santa Clara

The fellowship follows a mentor model, with four fellows rotating around four attachments to the core Sports Medicine Faculty. Each faculty member was a world-leader in their field, and while all faculty took care of the spectrum of sports injuries and were each allocated to a Stanford or Professional local team, they all had particular areas of expertise and interest with examples including cartilage restoration, hip arthroscopy and injuries in throwing athletes. This meant that the fellows had the opportunity to immerse themselves in the practice of these experts, with this experience complemented by twice weekly formal teaching and regular journal clubs.

Stanford University has its own orthopaedic cadaveric skills laboratory and I found this to be a fantastic resource for consolidating skills learnt in the operating theatre. In addition to a monthly formal fellow skills with faculty, the fellows led weekly labs for Stanford residents and were able to use the facility regularly to consolidate skills we learned in the operating theatres.

In addition to gaining huge experience in the operating room, fellows were also able to make the most of local cadaveric labs (Image 1). Receiving a gift at the 'graduation' celebration from my mentors (and now friends) Prof Marc Safran and Dr Seth Sherman.

I was able to gain huge operative experience in the management of sports injuries and gained unique experience managing athletes from all backgrounds whether that be weekend warriors, college athletes and professional athletes.

Ethicon Foundation Travel Grants Reports Continued...

Although a clinical fellowship, the program was very supportive of research and I was able to establish links in both clinical and translational research and have submitted grant applications for Stanford-Edinburgh Collaborations. Stanford University is particularly strong in regenerative medicine and this was very much aligned with my own interests.

Without doubt the highlight of my experience at Stanford was the people I met and the friendships we made. I could not have hoped for better co-fellows and all our families became extremely close friends by the end of the year. We continue to message daily and I look forward to firendships for years to come. I am also hugely grateful to the inspirational mentors I met. The fellowship Directors Marc Safran and Seth Sherman have a wealth of experience and also became great friends. They pride themselves on continuing to mentor Stanford fellows throughout practice and I have already benefitted from them in this way.

Figure. When not working we were able to enjoy the great outdoors and sights in California. My son Oscar was a particular fan of Baseball and we enjoyed being part of the community to celebrate occasions such as 4th July Independence day.

I travelled to Stanford with my wife and our three children who arrived ages 6, 4 and 2 years. I am incredibly grateful to my wife Katie who put on hold her career as a GP to support this adventure, which began many years before with study for the USMLEs!

The COVID pandemic meant that she was home schooling three children without support with little help from me as I left early and arrived home late almost every night. We did make the most of the experience and were able to enjoy much of what California had to offer at weekends. Highlights included watching humpback whales breaching at Stinson beach, Pacific sunsets in Carmel, Walks in Yosemite, and skiing at Lake Tahoe. I am extremely grateful to the RCSEd and Ethicon for supporting this once in a lifetime opportunity.

Mr Richard Stevenson PhD FRCS(Ed) MFST.

Consultant General & Colorectal Surgeon, Glasgow Royal Infirmary.

I attended the Marques de Valdecilla University Hospital in Santander for a 2 week robotic observership in September 2021.

I am grateful to Ethicon for supporting this observership through part funding of the flights.

The unit is highly regarded as a training centre for robotic colorectal surgery with Professor Marcos Gomez Ruiz acting as my mentor during my stay. Marcos is a proctor for Intuitive and has over 10 years of robotic experience.

The colorectal operating lists are Monday - Friday, bar Wednesday when MDT and clinics take place. The unit has a busy practice and receives referrals from throughout the Cantabria region in the North of Spain. There are 2 Intuitive da Vinci Xi robots which are used by all of the general surgical specialities, however I only attended the colorectal theatres.

Ethicon Foundation Travel Grants Reports Continued...

During this time, all of the major cases observed were robotic.

These included 2 low anterior resections, panproctocolectomy with ileo-anal pouch anastomosis, Hartmann's procedure (for colovesicle fistula), central pelvic exenteration with ileal conduit and a right hemicolectomy for a stricture at the site of a previous ileo-caecal resection for Crohn's disease.
There was also a day case list of proctology.

Ward rounds commenced at 07.50.
The hospital has 900 beds and is single occupancy. They have an established ERAS program and this, in combination with their shift towards minimally invasive procedures over the past 10 years has reduced their mean post-operative length of stay considerably with the majority of resections discharged on day 3 if the CRP is on a downward trend. Their state of the art operating theatres are well equipped with excellent HD displays for trainees.

The hospital has a well-established observer program and multiple other medical professionals were present ranging from medical student to Consultant – some were Spanish residents, others had travelled from Germany and as far afield as Venezuela. The surgeries generally finished around 3-4pm for lunch in the hospital canteen – somewhat different from the UK as it was fully licensed with an a la carte menu.

Satander itself is a beautiful port city, dating back to the 12th century on the North Western coast of Spain with direct flights from Edinburgh. Sadly, the majority of the medieval architecture was burnt down in a great fire in 1941 with the cathedral one of the few remaining historic buildings. It is, of course the headquarters of the multinational Santander banks (albeit the financial centre is now based in Madrid). Out with my time in the hospital I was able to explore the city and coastline (running) along with a couple of swims. I was grateful to the colorectal department for their hospitality, enthusiasm for teaching and patience with my pidgin Spanish.

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The Sir James Fraser Travelling Fellowship in General Surgery

Mr. Robert O'Neill

Consultant Upper GI Surgeon,

Cambridge Oesophagogastric Centre

Addenbrookes, Cambridge

Visit to

Professor's Richard van Hillegersberg, Professor Jelle Ruurda

Utrecht Medical Centre, Netherlands

Both Japan and Korea have traditionally been attractive destinations for UGI surgeons to study techniques of minimally invasive upper GI resection.

Unfortunately, the rarity of adenocarcinoma of the oesophagus, the relatively early stage of disease and significantly different body habitus in these centres countries limits the generalisability of their approach to a UK population. In contrast surgeons in the Netherlands treat patients with a similar spectrum of disease to the UK, with 80% of patients undergoing resection for adenocarcinoma of the oesophagus or OG junction and a similar prevalence of obesity.

Dutch surgeons have a strong tradition in academia and many landmark clinical trials have arisen from the Netherlands.

The 1000 bed Utrecht Medical Centre sits at the centre of a biomedical science park with extensive links to Utrecht university. It has an excellent international reputation having recently been nominated as one of the top 20 hospitals in the world.

Some of the important clinical trials led by the Utrecht group include the ROBOT trial comparing robotic and open oesophagectomy, the LOGICA trial comparing laparoscopic and open gastrectomy, and the forthcoming REVATE trial to compare robotic and minimally invasive oesophagectomy. The impact of this evidence base has been to encourage the uptake of minimally invasive surgery for oesophageal cancer. In 2018 over 90% of all oesophageal cancer operations in the Netherlands were performed minimally invasively, twice that of the UK.

Professor Richard van Hillegersberg is the chair of surgical oncology in Utrecht and is one of the leading exponents of robotic oesophagectomy in the world with a personal experience of over 400 robotic oesophageal resections. Robotic surgery has the proposed benefits over standard thoracolaparoscopy of increased precision of dissection due to a magnified stable 3D view and 7 degrees of freedom of the operating instruments. The UMC were one of the first centres in the world to use a surgical robot in 2003. Since then Prof. Hillegersberg has continued to develop the procedure and together with Intuitive now leads a proctoring programme for robotic resection to encourage safe dissemination of the technique.

It was therefore with some excitement that I took up a travelling fellowship to visit the upper GI unit in Utrecht.

My principle aim was to visit the UMC to gain first-hand experience into their robotic approach to oesophageal cancer to determine the extent of any benefit over standard thoracolaparoscopy and how their technique might change my practise.

A constant team was involved in most operations so that the theatre nurses were well versed in the procedures and everything was performed slickly.

This efficiency meant that a laparoscopic-assisted transhiatal oesophagectomy for example, was performed in 2 ½ hours. Staff morale generally appeared high and in addition to working within a stable team, I wondered to what extent the freely available coffee and food for all staff in the comfortable theatre coffee room contributed.

Around 100 oesophagectomies and 20 gastric resections are performed annually at the UMC, the highest number in the Netherlands in the most recent Dutch Upper GI cancer audit.

Although in the UK a team of 5 -7 surgeons might provide this service, in the UMC the team only consists of Professor van Hillegersberg, Professor Ruurda and their physician assistant Sylvia van der Hors. Although both participate in general surgery on-call, out of hours cover is provided for specialist upper GI emergencies on an ad hoc rather than rota'd basis. This contrasts with many resectional centres in the UK.

I was surprised that despite a very high rate of laparoscopic surgery, patients undergoing oesophagectomy were still managed post-operatively on ITU due to the ongoing use of thoracic epidurals. In typically Dutch fashion, however, they are currently undertaking a randomised trial of paravertebral regional anaesthesia vs. thoracic epidurals so this may change soon.

It impressed me how integrated the many PhD students were into the running of the unit including being present for each morning clinical handover. This had the added benefit of building a strong relationship between supervisors and students. This was clearly a recipe for success as the completed theses of previous students consumed an entire wall of Professor van Hillegersberg's office.

I had the great privilege of observing robotic oesophagectomy through the robotic console. Both Professor Ruurda and Hillegersberg displayed a mastery of robotic surgery such that movement of the additional retracting arm was performed almost continuously with the two operating arms so that dissection progressed smoothly, but with such precision that blood loss of more than 50ml was rare for these cases. I was particularly impressed with the superb access and view within the superior mediastinum, not achievable at open surgery.

This enhanced the ability to undertake a radical and precise dissection in this area, important for middle and proximal oesophageal cancers. Similar benefits to robotic over laparoscopic surgery were evident in performing feeding jejunostomy placement.

During my visit I also had the opportunity to take part in the European Society of Surgical Oncology hands on course in minimally invasive gastrectomy and oesophagectomy. This course blended lectures from an experienced international faculty, anatomical demonstrations and hands-on practise in thoracoscopic and laparoscopic techniques for upper GI cancer resection in the excellent university of Utrecht cadaveric laboratory.

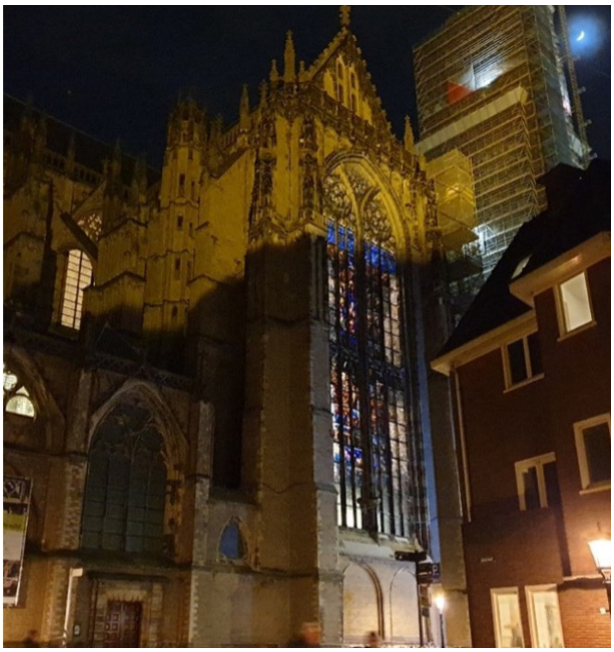
A key attraction of this course is the ability to train in the use of the Da Vinci Xi robot with multiple consoles offering robotic simulations, skills tests and the chance to undertake both abdominal and thoracic robotic cadaveric dissection. This provided a unique insight into the opportunities and challenges presented by robotics over conventional thoracolaparoscopy.

Throughout my visit I was welcomed by students, residents and surgeons alike and made to feel as an extension of their team. This collaborative spirit was evident in the global network of surgeons they have proctored in robotic surgery. Utrecht was beautiful city to visit, even more so in the very rare glimpses of sunshine.

Indeed, I was impressed that I had found a city more prone to rain than anywhere I have seen in the UK. The inclement weather did not seem to dampen anyone's spirits as the hospitality was second to none and will be a high bar should they ever take up my offer of a return visit to the UK. I am very grateful to the RCSEd for the award, without which I would not have been able to undertake this visit.

I have gained a huge amount and look forward to collaborating further with the Utrecht team in the future.

On a ward round with Professor Ruurda (left) and Professor van Hillegersberg (right). White coats are still mandatory on surgical rounds.



- **Top Left:** The Da Vinci Xi four arm robot available for training in the cadaveric lab.
- **Top Left:** A typically Dutch scene with bikes surrounding one of the many picturesque canals.
- **Bottom Right:** Course faculty and participants at the ESSO cadaveric course in minimally invasive gastrectomy and oesophagectomy.
- **Middle Left:** The “Dom” Cathedral. Unfortunately, the famous tower in the distance was covered with scaffolding for refurbishment.

94 Awards Manuscripts

King James IV Professorship

King James IV Professorship

Global prevention of glaucoma blindness and the EAGLE trial

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Introduction

Good vision is vital for full participation in society. Vision loss is among the most common disabilities in low to middle income countries (LMIC), and has been linked with significantly increased risk of poverty and mortality.[1] In the UK and the Western world blindness is also a major burden to individuals and society.[2]

Glaucoma is an age-related and chronic eye disease typically associated with increased eye pressure and progressive optic nerve damage that may lead to blindness if untreated. Glaucoma is the leading cause of irreversible blindness according to the World Health Organisation.[1] Approximately 4 million people are blinded by this condition, and the vast majority are in low-income countries.

Although with timely treatment most people with glaucoma do not become blind, many have substantially impaired quality of life due to restricted peripheral vision and the need for long-term treatment.

There are two major types of glaucoma, depending on the appearance of the drainage channels (trabecular meshwork) in the front part of the eye: open or closed angle glaucoma. Angle-closure glaucoma is less common but more severe, and causes approximately half of worldwide glaucoma blindness. The current prevalence of angle closure glaucoma is just over 20 million, and expected to rise to 34 million by 2040.[3] Angle-closure glaucoma is most prevalent in women and among people of East Asian and Chinese origin.

In the UK approximately 1 out of 6 glaucomas are due to angle closure.[4,5] Acute presentations of angle closure are relatively rare.[6]

The crystalline lens plays a key role in the pathogenesis of angle closure glaucoma. The increased lens volume associated with age generates a chain of events: first, there is an increased contact between the iris of the lens, leading to a bigger resistance to aqueous humour flow from the posterior chamber, causing a forward displacement of the peripheral iris that will block the aqueous humour drainage channels at the angle. Angle closure will lead to an increased eye pressure that will cause optic nerve damage, i.e., glaucoma, and visual loss.

For many years, angle-closure glaucoma has been treated with laser to open a small hole in the peripheral iris, i.e., laser peripheral iridotomy, and open the drainage channels, allowing aqueous humour to drain away.

The EAGLE trial tested an early surgical intervention, removal of the lens or cataract surgery, in people without cataract and compared it with standard laser treatment.[7] The results of the EAGLE trial were first published in 2016,[8,9] followed by a series of additional papers.[10-13]

We found that early lens extraction was safe and more effective than standard laser treatment, and patients had better quality of life. Our concurrent economic evaluation showed that this treatment also represented good value for money.

The superiority of clear-lens extraction in terms of patient, clinical and economic outcomes, along with the absence of any serious safety issues with this technique, as shown in the EAGLE trial, provided compelling evidence to support a change in current practice towards improved health outcomes for people with primary angle-closure glaucoma. The results are of particular relevance to LMICs where access to chronic medical therapy for the management of glaucoma is often not possible, but the skill and facilities to undertake lens extraction is well developed. Of note, at 3 years 126 (60.6%) of participants in the clear-lens extraction group did not require any medication to control their condition and only one participant (0.5%) required glaucoma surgery. In contrast, in the standard care group (laser iridotomy) only 45 (21.3%) participants did not require medications and 24 (11.3%) participants required further glaucoma surgery.

Lens extraction was cost-effective compared to standard laser care. Long-term health economic modelling shows that clear lens extraction is cost saving to the health provider.[11]

Methodological highlights

The design of the EAGLE trial demonstrated a number of innovative methodological aspects and novel features, in particular the use of a patient-reported, general health utility measure (EQ-5D) as primary outcome. The EQ-5D is well known to be a particularly useful measure to directly inform health policy in the UK.[8-10]

The use of a primary patient-reported outcome (PRO) and robust safety monitoring by an independent committee reflected our concerns for study participants.

King James IV Professorship Continued...

Patients and a glaucoma patient organisation (The International Glaucoma Association, IGA) had an active input in the design and conduct of the trial, and dissemination efforts. The selection of a PRO as primary outcome was strongly supported by patients and the International Glaucoma Association.

I would like to quote the author of The Lancet commentary:[9] "This is also the first prospective randomised therapeutic trial in ophthalmology in which one of the primary outcome measures is patient reported, through quality-of-life questionnaires." ..."This pragmatic trial is clinically relevant because it addresses a topic with widespread practical implications."

Management of this large multi-centre international trial faced substantial challenges

1. Swift navigation through multiple ethical, financial and regulatory procedures to try and quickly gain the correct approvals for the study to begin in each site.
2. Working through language and cultural barriers to develop a fully trained and reliable collaborative team, adapting (and where relevant translating and back-translating into 4 different languages) the training, data collection tools and all other trial support documents
3. Finding unbiased ways to access eligible patients in highly variable public and private health care systems.

Attrition was reduced by effective management and support of local investigators, including training and monitoring visits to each of the 30 sites from five different countries. With a budget of approximately £1.5m this was an example of efficiency in delivering a complex and large international trial. I would also highlight the small attrition after three years of follow-up (over 87% of participants completed the 36 months follow-up).

Considerations for implementation

The pragmatic nature of the study design and the inclusion of 30 sites in five different countries, with very different health care models and average income (UK, Singapore, Australia, Malaysia, China) was intended to secure generalisability of findings and facilitate implementation.

This, however, brought challenges for which the trial team had to develop swift and transferable solutions

We are confident that are results are valid as we have minimised the risk of bias and all PROs show clinically significant changes in the same direction (favouring clear lens extraction). Intraocular pressure data, as well as number of medications and need for glaucoma surgery, also showed superiority of the novel intervention (clear lens extraction) over standard care.

Implementation of our findings is facilitated because the lens extraction procedure is already widely used for cataract surgery - it is the commonest surgical procedure performed in the western world, and one of the commonest operations in the LMICs. As such, equipment and skills are immediately available to allow a swift and straightforward change in management policy without additional training or capital expenditure leading to better outcomes at minimal cost.[12]

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Osteomyelitis: New perspectives on an old disease

Martin McNally MD FRCSEd(Orth)
The Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals

"My sins sicken me like pus in my bones Help me Jesus, Lamb of God, for I am sinking in deepest slime" Cantata 179 Johann Sebastian Bach, 1723.

Osteomyelitis is an old disease. It is found in Jurassic dinosaurs and in early hominids from East Africa. It is documented in Greek and Egyptian literature and is often found in pathology collections, such as the remarkable tibia of Charles Anderson in the Surgeons' Hall Museum.
The condition would have been well known to the Barber Surgeons practising in the reign of King James IV.

65 million year old Tyrannosaur "Sue" in the Field Museum of Natural History, Chicago. She has established chronic osteomyelitis of her left fibula.

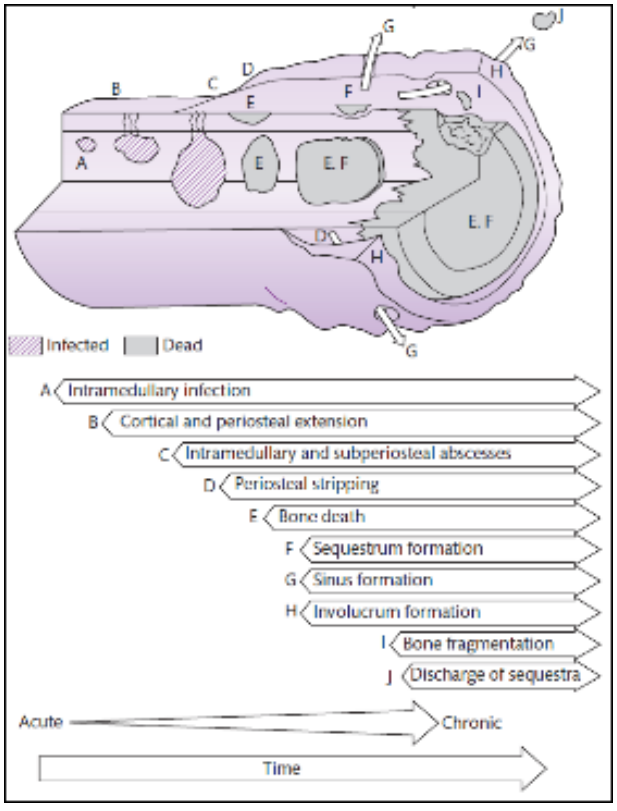
Native skeletal infection remains a potent cause of disability and limb loss worldwide, but the epidemiology is changing.

King James IV Professorship Continued...

Bone infections arising from surgical intervention, injury, peripheral vascular disease and the sequelae of diabetes mellitus and immune compromise are now more frequent than haematogenous osteomyelitis. Antibiotic resistance and bacterial strategies to evade eradication around implants, have presented new challenges for diagnosis and treatment.

This lecture will bring together studies on pathogenesis, diagnostic methods and clinical management which will, in a practical way, allow surgeons to appreciate their role in the care of patients with bone and joint infections.

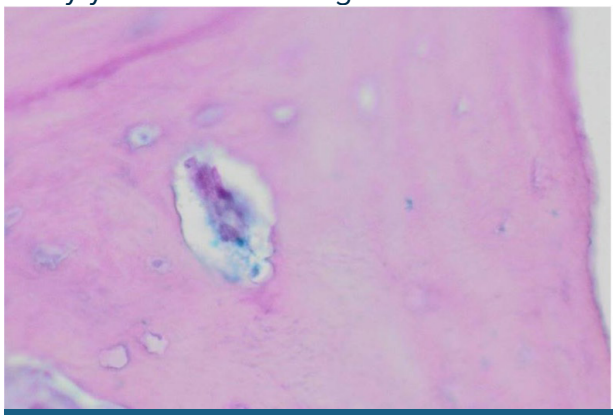
Pathogensis



The classical picture of haematogenous osteomyelitis with central dead bone (sequestrum) and peripheral new bone formation (involucrum) is well known. We can easily visualise this, but it simplifies a much more interesting interaction between bacteria and host bone.

Healthy bone is extremely resistant to invasion by microorganisms. However, small changes due to injury, surgery or disease can allow bacteria to attach to tissues by a series of complex cellular interactions, mediated by bacterial adhesins.
These surface components recognise host proteins which are present on damaged tissue (or covering implants). Once attached, the bacteria enter a biochemical relationship with the host. Both partners produce a polysaccharide extracellular matrix within which, bacterial micro-colonies develop and mature. This combination of ordered colonies in polysaccharide ‘slime’ is known as a biofilm. In this state, there is enhanced cell-to-cell signalling (quorum sensing) which allows maintenance and further production of the biofilm. New data suggests that quorum sensing also occurs between bacteria and human cells, impairing immune response and preventing bacterial eradication (‘frustrated phagocytosis’). Many bacteria induce biofilms, which are found on teeth, implants, poorly vascularised tissues, chronic wounds and even in synovial fluid.

The classical pathology does not describe the complex microdistribution of bacteria in bone. Bacterial invasion can produce small areas of dead bone, remote from the original infection. Within these, organisms can enter a ‘resting state’ (small colony variants) with very little metabolic activity, becoming highly resistant to antibiotics. They can survive inside living human cells (particularly osteocytes) as ‘persister cells’. It may be this mechanism which allows recurrence of quiescent osteomyelitis many years after the original infection.



Staphylococci ‘persisting’ inside living cells in a bony lacuna.Courtesy of Prof. Peter Ochsner

Osteomyelitis has been classified by its aetiology (haematogenous or contiguous focus) or its onset (acute or chronic). The staging system of Cierny and Mader recognised that the extent of pathology in the bone and the health of the host were factors in determining treatment and outcome. We have shown that the soft tissue quality and the infecting organism (especially resistance to antimicrobials) are at least as important. We designed the **BACH** Classification (**B**one involvement, **A**ntimicrobial options, **C**overage by soft tissues, **H**ost status) which has been correlated with clinical outcome and functional recovery at one year with EQ-5D-5L scores.

King James IV Professorship Continued...

The BACH Classification of Osteomyelitis

	***B*one involvement**	***A*ntimicrobial options**	***C*overage by soft tissue**	***H*ost status**
Uncomplicated	B_1 Cavitary infection without joint involvement (including cortical, medullary and non-segmental cortico-medullary)	A_X Unknown / culture negative osteomyelitis A_1 All isolates: ▪ Sensitive to ≥80% of susceptibility tests and resistant to ≤3 susceptibility tests	C_1 Direct closure possible: Plastic surgery expertise not required	H_1 Well-controlled disease *Or* Patient is fit and well
Complex	B_2 Segmental infection without joint involvement B_3 Any bone infection with associated joint involvement	A_2 Any isolate: ▪ Sensitive to <80% of all susceptibility tests performed *Or* ▪ Resistant to ≥4 susceptibility tests *Or* ▪ Resistant to anti-biofilm antibiotics in the presence of an implant	C_2 Direct closure not possible: Plastic surgery expertise required	H_2 Patient with poorly controlled co-morbidity *Or* Severe co-morbidity (with evidence of end organ damage) *Or* Recurrent osteomyelitis after previous debridement
Limited Options		A_3 Any isolate: ▪ Sensitive to 0 or 1 susceptibility test performed		H_3 Unfit for definitive surgery despite specialist intervention *Or* Patient declines surgery

Diagnosis

Culture of the causative organism in fulminant acute osteomyelitis is not often difficult but this scenario is now rare. Chronic presentation after suboptimal treatment with antibiotics, low-grade implant-related infections and delayed or late fracture-related infections are more common and present significant diagnostic dilemmas. In other areas of infection, such as endocarditis, diagnostic criteria have been established based on microbiological and histological tests. These have been applied to prosthetic joint infection (PJI) twenty years ago.

The lack of an agreed definition and diagnostic criteria in osteomyelitis and fracture-related infection (FRI) has hampered research in this area. In 2017, we proposed (with an international expert group) an algorithm for FRI diagnosis, which has been endorsed by the European Bone & Joint Infection Society, the Orthopaedic Trauma Association, The International Consensus on Musculoskeletal Infection and the AO Foundation. We have produced new data to support the criteria with evidence on nuclear imaging, serum biomarkers and histological assessment of tissues from infected fractures.
We have shown how combining nuclear imaging with a localising scan (18FDG-PET with CT or WBC/AGA with SPECT/CT) improves diagnostic accuracy and allows preoperative planning to reduce the need for segmental resections of bone, in chronic osteomyelitis or infected non-unions.

Detection of the infecting organism with antimicrobial sensitivities is central to modern therapy. We developed a systematic approach to surgical sampling and culture (modified from PJI), which has been validated in large cohorts from three countries. This approach reduces contamination in theatre and in the laboratory, and allows rapid identification of pathogens. The combination of automated BACTEC tissue cultures with Maldi-TOF mass spectrometry gives results within 5 days in over 95% of cases.
We also evaluated ultrasonic disruption of biofilm on hard tissue (Sonication) and showed enhanced sensitivity for diagnosis in non-PJI infections when combined with our multiple sampling technique.

An exciting advance has been our early experience of whole genome sequencing for the detection of bacterial DNA in sonication fluid from bone samples and implants.

This novel and rapid technique offers the possibility of in-theatre diagnosis within minutes of tissue sampling. We have shown that difficult-to-culture organisms can be identified.

Clinical Management

Improved understanding of the mechanisms of the disease has allowed more patient-friendly surgery.
However, we still struggle with critical questions concerning completeness of excision, management of dead space after resection, bone reconstruction and antimicrobial stewardship.

During surgery for osteomyelitis, we always face the decision of when to stop resection. This is a complex question. Answering it implies that we can determine if we have excised all the dead bone, removed all biofilm, retained only healthy tissue with a competent immune system and healing potential, and avoided vascular compromise which would prevent penetration of systemic antibiotics.
We have no investigation which can inform our decision. If we fail, we create a biological environment with planktonic bacteria and persister cells in tissues which will receive a low concentration of antibiotic, fostering early antimicrobial resistance and recurrence. We must be careful not to rely on our ego to make these decisions. Albert Einstein stated that ego is inversely proportioned to knowledge. When we are unsure, we fall back on ego. In this situation, we must assume that we are not perfect surgeons and will always leave some persister cells, biofilm and small areas of dead bone.

Once this is accepted, we must consider how effective systemic antibiotics are in eradicating residual bacteria in the dead space.

King James IV Professorship Continued...

The Minimum Biofilm Eradication Concentration (MBEC) may be 100-1000 times greater than the level required to kill planktonic bacteria. Microdialysis studies have shown that it is impossible to deliver such levels by systemic administration of antibiotics without unacceptable toxicity. As surgeons, we cannot rely on systemic antibiotics as a 'get out of jail free card'.

We have extensively studied the use of local antibiotics implanted into the infected cavity in bioabsorbable carriers which facilitate bone growth. We have shown (with co-workers) that above MBEC levels can be reached, without toxicity and maintained for up to 21 days.
In several large prospective, consecutive clinical series, we have reported some of the lowest recurrence rates in the literature. Local antibiotic therapy provides almost perfect antimicrobial stewardship; correct drug at the correct dose, given at the right time, with guaranteed compliance.

We have pioneered single stage surgery, combining local antibiotic delivery with immediate stabilisation (external or internal fixation) and soft tissue cover, including free tissue transfer. This protocol has reduced hospital stay, costs and secondary morbidity for our patients. Our recently published OVIVA trial has extended patient convenience, by allowing safe early transfer to oral antibiotics, avoiding prolonged intravenous therapy. The current SOLARIO study will further investigate the place of postoperative antimicrobial therapy.

Conclusion

For over 25 years, I have been fascinated by bone infection. The interaction between host and pathogen and how we, as surgeons can intervene, continues to captivate. These studies have confirmed that surgery remains central in diagnosis and treatment. We must continue to develop imaging and diagnostic modalities which help us to understand this old disease. Better understanding will allow us to treat our patients in a more targeted way. There is still much to learn. New projects on genomics, antimicrobial implant coatings and methods of bone reconstruction in the presence of infection await.

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Restoring the Matrix; from simple cuts to blast injuries

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June 28th 2021

Introduction

I was most grateful to the BAPRAS secretariat for allowing me to present a plenary lecture at their BAPARS unlocked conference, the first face to face meeting since the covid 19 pandemic began.
The meeting hosted over 100 socially distancing delegates at Nottingham Conference Centre.

Summary of Lecture

Background to Academic Plastic Surgery in Manchester and links to Matrix biology.

The talk focused around my 18 years in academic Plastic Surgery working in the field of matrix & cell biology at the University of Manchester, and clinically in the field of extremity trauma. I am very fortunate to be a Principal Investigator at the Blond McIndoe Laboratories, University of Manchester.
A lab specifically set up to foster surgical fellows in their pursuit of basic science and translational research in a number of tissue types that are frequently damaged, including tendon, blood vessels, cartilage, nerves and muscle.

Much of the credit to the development of the plastic surgery academic pathway can be attributable to Professor Gus McGrouther, who has influenced many a plastic surgeons career and was instrumental in setting up Academic Plastic Surgery in Manchester and the Blonde McIndoe laboratories. In addition, he was key to bringing the Healing Foundation Centre to Manchester with the purpose of understanding the mechanisms of regeneration in amphibians (Love, Chen et al. 2013), in order to one day hopefully translate this knowledge to human regeneration. The scope of the labs has increased since then and look at numerous technologies that may rebuild or replace damaged limbs, including limb transplantation, tissue engineering, tissue regeneration and bionic replacement (Amin, Leonard et al. 2021).

As a plastic surgeon I developed a growing interests in dynamic anatomy and how tissues move (Wong, Geyer et al. 2016) when they were injured and healing.

Over the years I gained a deeper knowledge in the healing of basic injuries like simple lacerations (Wong, Lui et al. 2009), simple sutures (Wong, Alyouha et al. 2010), and how these processes could be manipulated generate grafts (Bosworth, Alam et al. 2013, Alam, McGrouther et al. 2014) or engineer new tissues (Wong, Donno et al. 2019), and also how potentially we could regenerate tissue loss (Buckley, Wong et al. 2012).

These academic interests evolved to complement the clinical challenges I saw in trauma, where tissue is lost through damage and disease, with a particular focus on complex wounds.
As such, with my colleagues Professor Anand Pillai (Orthopaedics) and Mr Adam Reid (Plastics), we developed the Manchester Orthoplastic Service and provided a tertiary referral service for limb salvage and complex wound management (Aljawadi, Islam et al. 2020).

Through both my clinical and research observations, it became apparent that

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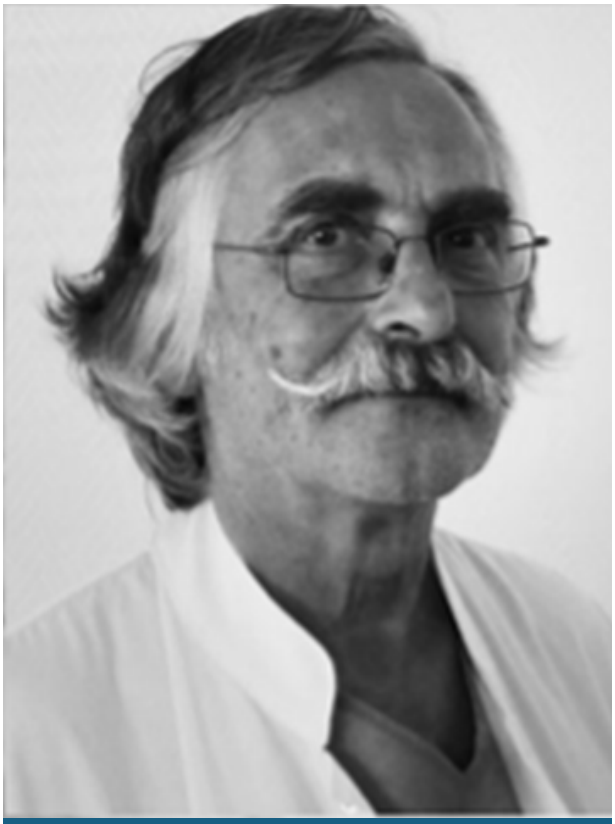
matrix biology was incredibly important to understanding some of the problems encountered with trauma. A brilliant and visionary hand surgeon, Jean Claude Guimberteau, highlighted to me through his endoscopic work, a tissue that had largely been neglected (Guimberteau, Delage et al. 2010) that surrounded all moving body parts below the skin and above the deep fascial boundaries of muscle. Sometimes referred to as the “microvacuolar system”, superficial fascia, areolar tissue, or interstitial tissue, this ill-defined organ, surrounds and protects blood vessels, nerves and lymphatics as they course through the skin (Figure 1). It has gel like, hydrophillic properties and facilitates frictionless gliding and movement to these delicate structures, whilst also acting as a reservoir for fluid (Benias, Wells et al. 2018).

Neglected Matrix



Jean Claude-Guimberteau

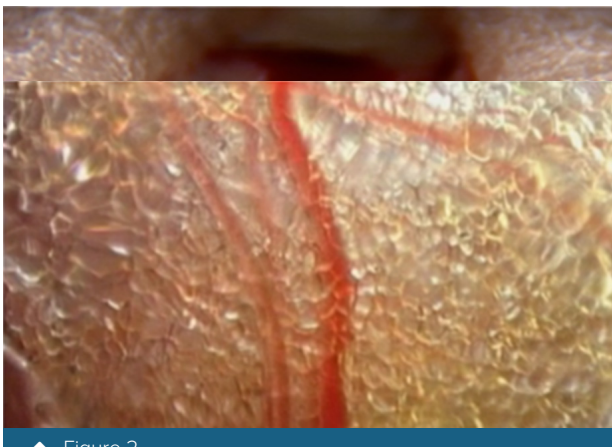


Figure 2

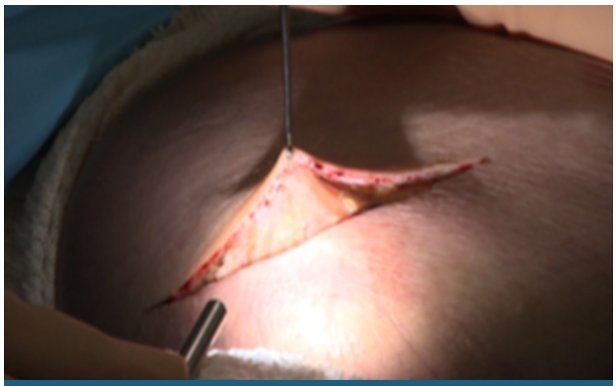


Figure 3

Figure 1-3. The fascial matrix or “microvacuolar system” described by Jean Claude Guimberteau

Our research into simple injuries of deeper structures like tendons in mice, led us to the observation that this surrounding soft tissue rapidly swells, and becomes infiltrated with inflammatory cells and fibroblasts and repairs through fibrotic adhesions (Wong, Lui et al. 2009) (Figure 2). We observed that greater energy transfer from trauma to these tissues results in an elevated inflammatory response and greater fibrosis of this fascial matrix during repair.

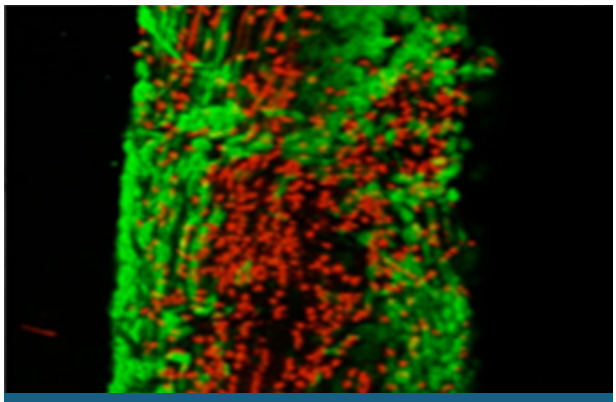


Figure 4. Tissue Injury

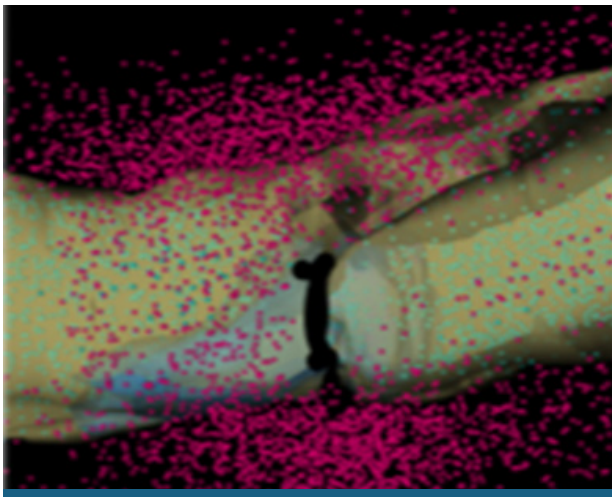


Figure 5. Inflammation

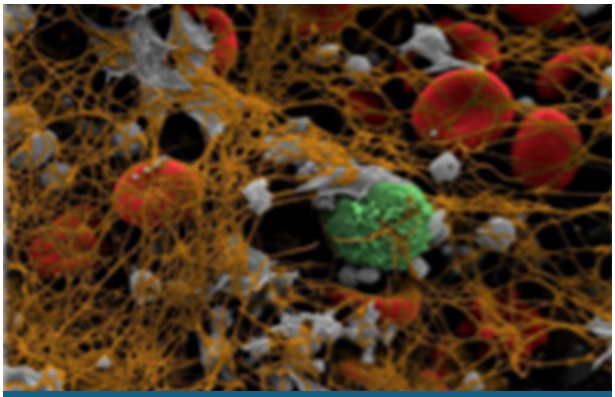


Figure 6. Matrix

Figure 7. Repair

Figure 6-4. My research focuses on the interactions between tissue injury, inflammation, matrix biology and repair.

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We study the fascia from a number of perspectives including living ex vivo perfused models as previously it was difficult to visualise in fixed tissue, or as post mortem tissues (Amin, Stone et al. 2021).

This has allowed us to appreciate how critical it is for normal limb movement (Figure 1). We are also examining the role of fascia in healing of chronic wounds (Correa-Gallegos, Jiang et al. 2019), how the tissue can potentially be engineered from hydrogels and bioprinting vascular channels (Zheng, Derby et al. 2020), and how we can use this platform to engineer transplantable tissue by creating simple vascularised fascia (Wong, Donno et al. 2019).

However, the area of greatest interest is fibrosis of the fascial planes after trauma, as this causes pain, stiffness and restriction of function, which is clearly the biggest burden on healthcare (Figure 3). To date there have been no effective therapies other than aggressive physiotherapy.

Scar and fibrosis and functional loss

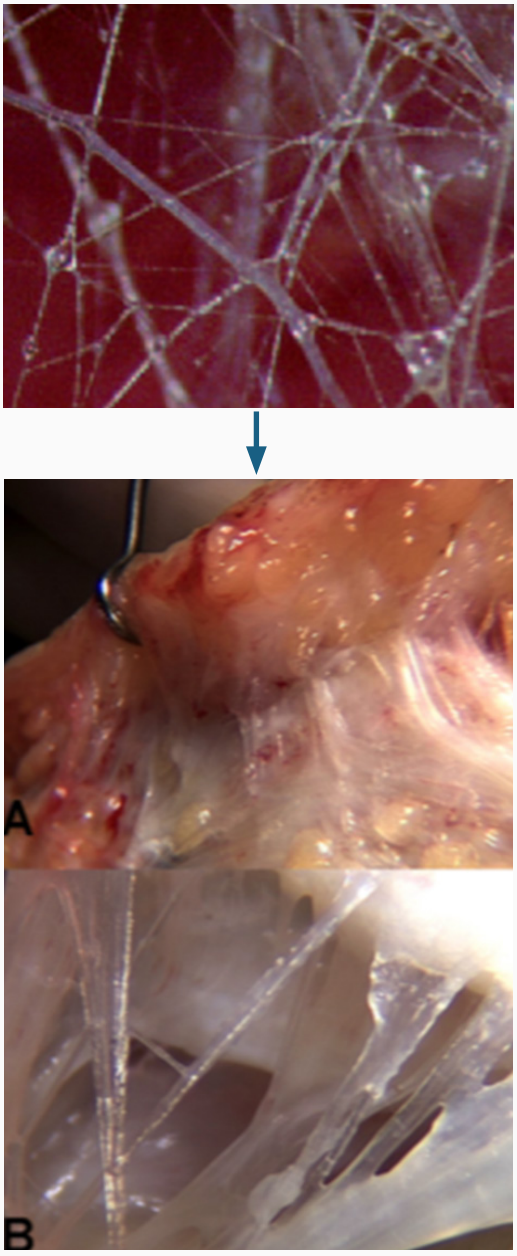

Figure 3. The Microvacuolar system fasica and fibrotic response under the skin seen after injury. It is easy to appreciate how this restricts function.

On the 22nd of May 2017, Manchester came to realise exactly how devastating and challenging this problem would be after the Manchester Arena attack.

I was one the first plastic surgeons at the Major trauma centre attending to patients that were victims of the blast, and it was an incredible coordinated trauma response by all teams across the city on that night and subsequent days for the victims of the attack (Dark, Smith et al. 2021).

We saw diverse pattern of penetrating projectile injuries from “nuts” that were contained within the improvised explosive device. The vast majority of these were seen as injuries to the limbs with 70% of patients sustaining injuries to the limbs, and around 30 % of the patients requiring acute plastic surgery input.

Complex open wounds, burns, bone loss, cartilage loss, nerve gaps, and tendon damage, were just some of the injuries, we had to reconstruct (Figure 4).

Having operated on a number of these patients on the night, many still remain under my care to date and a number are still under my care for future surgical management.

Despite our best efforts to repair and reconstruct the victims, it was apparent that due to the nature of these injuries, many patients would suffer from significant functional loss.

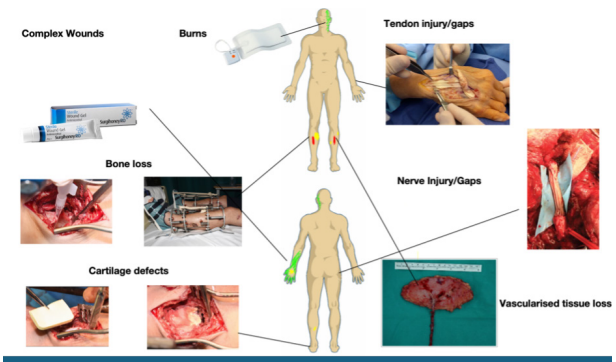

Figure 4. The types of injury seen after the attack and methods used to reconstruct

After the initial acute wound management of these patients, there was a realisation that we would be managing a large volume of complex injured patients with a diverse pattern of injury, with significant physical and psychological needs to return them to society.

I was seeing patients return to follow up with little to no access to musculoskeletal (MSK) rehabilitation in the community and it was clear the physical and psychological needs of the patents were not being served on the return to their local environment. There was no expertise or support for civilian blast injury/ major trauma rehabilitation in the Community. NHS MSK rehab at the time focused on restoring basic function and actions for daily living, but did not have the time or resources to meet the needs of the most badly injured patients. One year on, a significant number of patients were still walking aided or in wheelchairs, so we quantified this through questionaries to victims who were willing to be contacted.

I knew from my research that the greatest impact to functional recovery from scarring to tissues was aggressive physiotherapy. I began to explore ways that we could capitalise on Manchester’s rich sporting heritage and encourage the use of Elite sports recovery programmes to major trauma patients. Could we cross fertilise ideas from my basic research to sports sciences and translate back into the NHS an innovative programme of rehabilitation, and have something really positive arise from the incident.

My enquiries led to discussions with the Manchester Institute of Health and Performance (MIHP), A partnership between Manchester City Council, Sports England, and Manchester City Football Club (MCFC) Group. The remit of the facility was to create a world class environment

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for the diagnosis, education and research of health and performance. The focus of the institute was to ensure elite athletes returned to form after injury, but never before had the facilities or expertise been involved in civilian trauma.

The facilities at the MIHP are state of the art. They hosted the physiological labs for the British Cycling Team, hydrotherapy pools and cryotherapy chambers to modulate tissue inflammation, a state of the art performance gym, and a state of the art gait analysis lab.

With the director of the facility Dr Steve McGregor, biomechanics Professor, Richard Jones, and my colleague Mr Adam Reid, we sought to put together a comprehensive plan to recover these patients. Our proposal was to invite all the adult patients to therapy with a significant limb injury. We would design a bespoke programme of recovery to each patient's needs and keep it entirely patient focused. We would work out all the logistics of travel, stay and intensity of the rehabilitation programme in Manchester. We built around the programme a comprehensive array of assessments, including biomechanics, muscle mass, physiological parameters beyond the scope of the NHS. This was nested in research infrastructure from the University of Manchester and University of Salford.

It was a challenge to set this programme up, we had no funding at the time, some doubted the benefit, especially as so much time had passed from the time of the patients' injuries. We had series of meetings and invited all the trauma interested therapists to discuss how we would deliver such a programme, how would we second people to the project, what we had in our minds that would constitute the ideal rehab programme for severely injured patients, what outcome measures we would use both from a quantitative and patient reported perspective would be of merit.

Eventually we managed to secure funding support from the WeLoveManchester emergency fund, Manchester Health and Care Commissioning and the Greater Manchester Major trauma network.

After assessing the injury patterns of all 141 injured victims we narrowed it down to the 50 most severely injured patients and 48 were successfully contacted by letter in April 2018.
We hosted a series of open evenings at the MIHP for patients who wanted to visit and ask questions.
In total 27 patients signed up for the rehabilitation programme and 25 engaged in at least a 6 month individualised programme of rehabilitation (Figure 5).

Recruitment

- **48 patients** were contacted by letter in April 2018.
- **Four open evenings** ran in May and June at MIHP, 18 patients in total attended.
- To date we have received **27 signed consent forms** from patients wishing to participate.
- **25 engaged** on their individual 6 month rehab programme.

Figure 5. Recrutiment to the enhanced rehabilitation programme at the Manchester Institute of Health and Performance (MIHP).

We assembled a team of NHS and Elite performance therapists in an enhanced MDT. This included 5 physiotherapists, 2 occupational therapists, and a programme manager. This core team was supported by surgeons, senior AHPs and Rehabilitation consultants. In addition we had a technical team and biomechanics team supporting the programme development who had a wide range of experience delivering pro sports rehabilitation. This performance team was led by Dr Steve McGregor and consisted of therapists from MCFC and Academy, the British Tae Kwon Do Team, British Cycling team.

Our team was also sent to the Harrogate Police Treatment centre, and Headley court, Defence Rehabilitation Centre to see how care was delivered to the military or service injured personnel.

We then began to identify the assessments and outcome measures that we would use to chart the patient's recovery. This included routine physiotherapy assessments, PROMS, and also high-performance outcome measures used in recovering athletes, and functional assessment equivalents that could be run back into the NHS.

We were able to measure in 15 minute intervals what the patients received in terms from treatment, from general talking, assessment, to strength and conditioning, manual soft tissue therapy, to specific classes.
We collected very granular data on what it took to recover these badly injured patients, effectively allowing us to measure the "dose" of rehabilitation over a variety of different injuries.

On average it was calculated that around 80 hours of contact time would significantly enhance the performance of a severely injured patient.

We prioritised treatment of scarred limbs with soft tissue manual therapy and active motion to move through strength and conditioning and restore range of motion and power.

After 6 months we saw significant enhancement of performance, in terms of walking speed, gait quality and gait performance scores. We also saw significant improvements in mental health, in terms of anxiety scores and depressions scores related to performance improvements, Qualitative interviews indicated that the programme had made a considerable impact to the wellbeing of the patients.

Overall the programme was a massive success in restoring confidence and function back to the victims of the blast, which many of them have maintained after the programme.

King James IV Professorship Continued...

We had learnt that multi-disciplinary collaboration is still critical for major trauma patients at the rehabilitation stage.

A key factor is providing “time” for the necessary physiotherapy, psychological interventions, and occupational therapy that at present is not facilitated in the NHS.

Along with functional improvements came significant psychological gains and patients really valued the experience and were incredibly resilient to being pushed hard to recover.
Critically rehabilitation benefits were seen even after starting one year on from their index injury and would have significant implications for those who still suffer from chronic disability after trauma.

We have achieved;

1. Enhancement of patients physical and psychological wellbeing.

2. Scientific knowledge of civilian blast injury recovery.

3. A state of the art program to deliver enhanced rehabilitation to major trauma patients.

Based around applied knowledge of manipulating damaged matrix through enhanced rehabilitation.

Conclusion

There is a wealth of interesting biology and lots to learn about the fascial matrix that lies “more than skin deep”, and we are only beginning to appreciate its role in health and trauma. We have novel ways in which we can study its biology, and are exploring its importance in wounds and have developed platform technologies that potentially can engineer it. Clinically we have developed an enhanced rehabilitation programme that can help modulate the scar and restore function of the fascia, and as surgeons we really are well placed to begin to integrate its unique biology into new areas of clinical practice.

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The translational implications of the science behind the overactive bladder and the role of OnabotulinumtoxinA

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Introduction

Urinary incontinence is one of the commonest clinical conditions worldwide affecting patients of all ages. It is thought to affect around 423 million people globally with women 5 times more likely to be affected than men.[1] Urinary incontinence has a significant impact on quality of life and health with majority suffering in silence due to embarrassment and social stigma.

There are 5 types of urinary incontinence including stress, urge, mixed, overflow and functional. The most common cause of urinary incontinence however, is the overactive bladder syndrome.

Overactive bladder syndrome (OAB) involves symptoms of urinary urgency (with or without urge incontinence), frequency and nocturia.[2] It's prevalence, increases with age reaching a peak in both sexes over the age of 75.[3] Diagnosis of OAB is based on clinical symptoms alone in most of the patients and urodynamic studies are needed in some to confirm the diagnosis. The recommended first line treatment includes conservative measures such as fluid intake modification, reduction of caffeinated drinks, pelvic floor exercises and weight reduction followed by pharmacotherapy. This includes anticholinergics and more recently beta-3 agonists either alone or in combination. Although these medications have shown to be effective, more than 60% of patients suspend treatment due to poor symptom control and adverse effects.[4]

Patients who are either unresponsive or discontinue treatment are offered botulinum toxin A as a second line treatment.[5] The management of OAB has evolved over several decades. In this review we present the evolution of various treatments over time in the quest of finding an effective modality with minimal morbidity.

Clam Ileocystoplasty

Although Mikulicz first described augmentation ileocystoplasty in humans in 1889,[6] the procedure gained wider acceptance in the 1950s for the management of contracted bladder secondary to tuberculosis. The technique was subsequently popularised in 1980s by Bramble for the treatment of refractory overactive bladder.[7]

It is a major surgical procedure and since the native bladder and intestinal segmental patch do not contract simultaneously, emptying the augmented bladder is largely dependent upon abdominal straining and simultaneous relaxation of the pelvic floor. However, the majority of these patients have to perform clean intermittent self-catheterisation (CISC) and rates vary from 26% to 100%.[8]

The other potential complications include urinary infections, stone formation and metabolic complications in patients with poor renal function.
A minimally invasive alternative that filled the gap between oral anticholinergics and ileocystoplasty was clearly necessary.

Sacral Neuromodulation

Sacral Neuromodulation (SNM) was introduced by Tanagho and Schmidt for management of lower urinary tract dysfunction including treatment for OAB.[9]

It entails permanent electrical stimulation by an implantable lead at the S3 nerve root which controls the bladder and pelvic floor muscles. The implantation is usually performed in two phases to ensure that patients who receive a permanent implant are the most suitable candidates for this expensive treatment. The benchmark in clinical practice is at least 50 % improvement in urinary symptoms. Currently it is offered to patients who are not willing or agreeable to perform CISC.

Its mechanism of action is still debated. The InSite trial with a 5-year follow-up reported that 38% of the patients were completely continent and 67% were improved after SNM.[10]

The most frequent adverse events reported include pain at the implant site, lead migration, loss of therapeutic efficacy, reduction in libido and problems in achieving an orgasm.[11]

Capsaicin

Over 25 years ago, Dasgupta and Fowler et al studied the presence and role of C fibres in the human bladder which have previously been described by De Groat in the spinalised cats.[12] These studies demonstrated that bladder has afferent and efferent neural pathways connecting to the pontine micturition centre, periaqueductal grey and other parts of the brain through ascending and descending spinal tracts. In a healthy bladder, afferent signalling is facilitated via afferent myelinated A delta fibres. In OAB, neurotransmitters released from the urothelium and sub-urothelium cause an increase in C fibre activation leading to reflex hyperactivity in the bladder. In patients with diseases such as spinal cord injury and multiple sclerosis, the afferent signalling occurs through these C fibres.[13,14]

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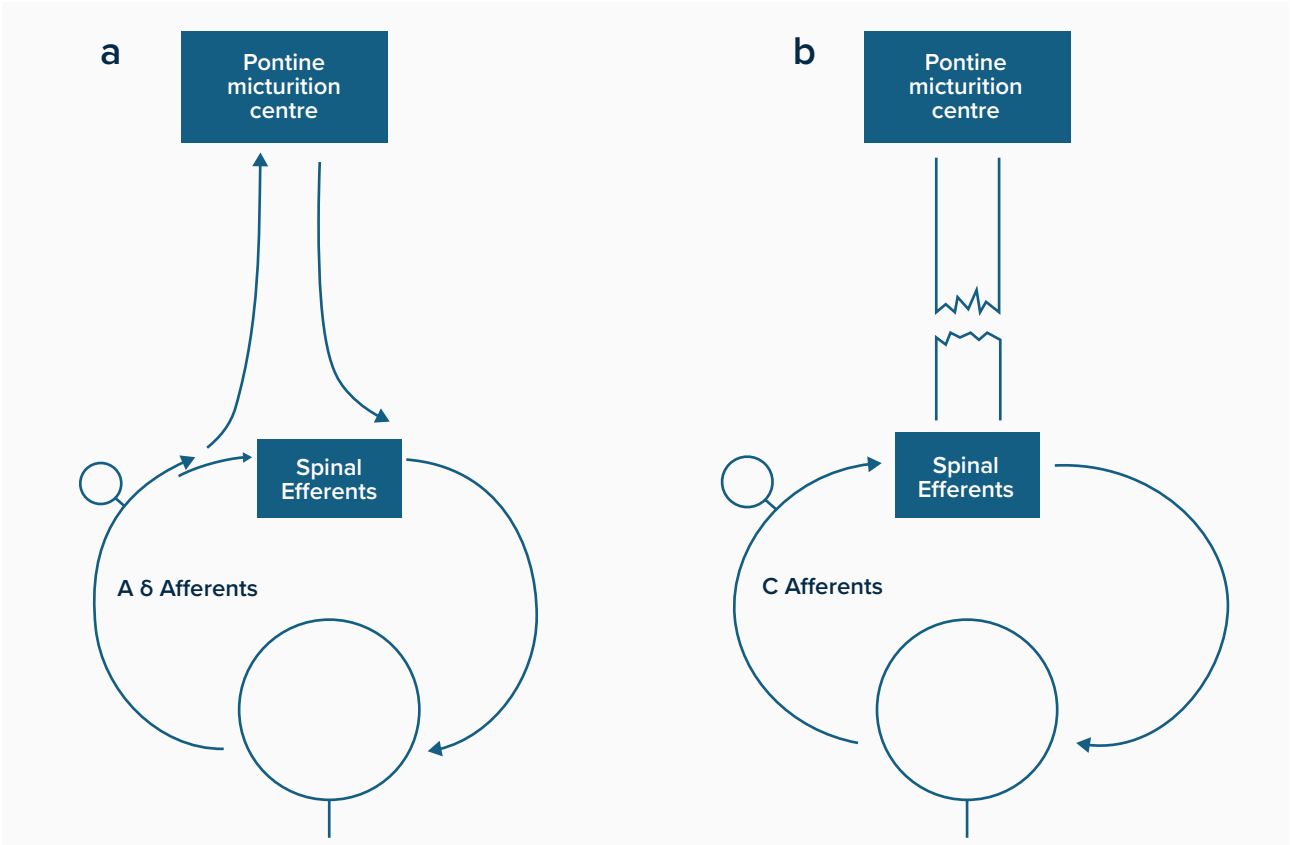

Figure 1. Neural pathways in the bladder15

C-fibres express many receptors including transient receptor potential vanilloid 1 (TRPV1) which is highly sensitive to an active ingredient in chillies called capsaicin.[15] In 1989, Maggi et al reported the first case of capsaicin used to treat hypersensitive bladder.[16]

A study by Fowler et al involving 14 patients with spinal cord and non-spinal related detrusor over activity showed that 9 patients had improvement in the bladder function after instillation of intravesical capsaicin and duration of the effect lasted between 3 weeks to 6 months. [17] Furthermore, Dasgupta et al showed that capsaicin reduced the nerve densities of afferent C-fibres in the lamina propria of the bladders in patients who responded to this treatment.[18]

Capsaicin in its semi-synthetic form was replaced by another vanilloid, Resiniferatoxin (RTX) a naturally occurring chemical found in Euphorbia Resinifera, a cactus like plant found in Morocco.[19] Multiple studies have shown it to be a highly potent analogue considered to be equally effective but with fewer inflammatory and pain related side effects. Doses of 100nM of resiniferatoxin were found to be equally effective as 1mmol/L of capsaicin with the added benefit of causing less irritation to the bladder.[20] RTX however failed to achieve any significant role in in the clinical practice because it stuck to the plastic containers in which it was dispensed, rendering the trials ineffective.

Botulinum Toxin A

Botulinum toxin (BTX) is a neurotoxin, produced by an anaerobic gram-positive bacterium, Clostridium Botulinum. Historically it has been responsible for numerous cases of food poisoning known as botulism. The first reported epidemic of botulism was reported from South of Germany in 1793 when 50% of those who consumed uncooked blood sausages died.[21] Clostridium Botulinum was discovered by the Belgian Scientist, Emile Pierre van Ermengem in 1895 during an outbreak in a small Belgian village.[22] After the discovery of the fact that food poisoning was caused by rancid sausages, this toxin was named as “Botulinum toxin” derived from the Latin term “Botulus” meaning sausage.[23]

The first therapeutic use of botulinum toxin was pioneered by Alan B. Scott and Edward J. Schantz in the early 70s, when they reported using type-A serotype to treat strabismus. Subsequently the toxin has been used for diverse indications but principally muscular hyperactivity, glandular hypersecretions and pain.[24]

The therapeutic use of botulinum toxin-A in the urinary tract was first reported by Dykstra in1988 who injected the toxin into the striated urethral sphincter to treat detrusor sphincter dyssynergia.[25] Schurch et al. subsequently reported the use of OnabotulinumtoxinA (Botox – Allergan) in the treatment of detrusor hyper-reflexia in the neurogenic bladders secondary to spinal cord injury.[26]

Botulinum Toxin has been used in a variety of urological conditions including overactive bladder (OAB), neurogenic detrusor overactivity (NDO), interstitial cystitis (IC)/bladder pain syndrome (BPS), Detrusor Sphincter Dyssynergia (DSD) , benign prostatic hyperplasia (BPH), and chronic pelvic pain. However, the FDA and other licensing bodies have only approved OnabotulinumtoxinA treatment for OAB and NDO.[27]

Botulinum neurotoxin has 7 subtypes A, B, C, D, E, F, and G. The most commonly used subtypes in clinical practice are Type A and Type B. The dose equivalency of Botox and Dysport, the 2 preparations used, is approximately 1 to 3-5.[28,29]

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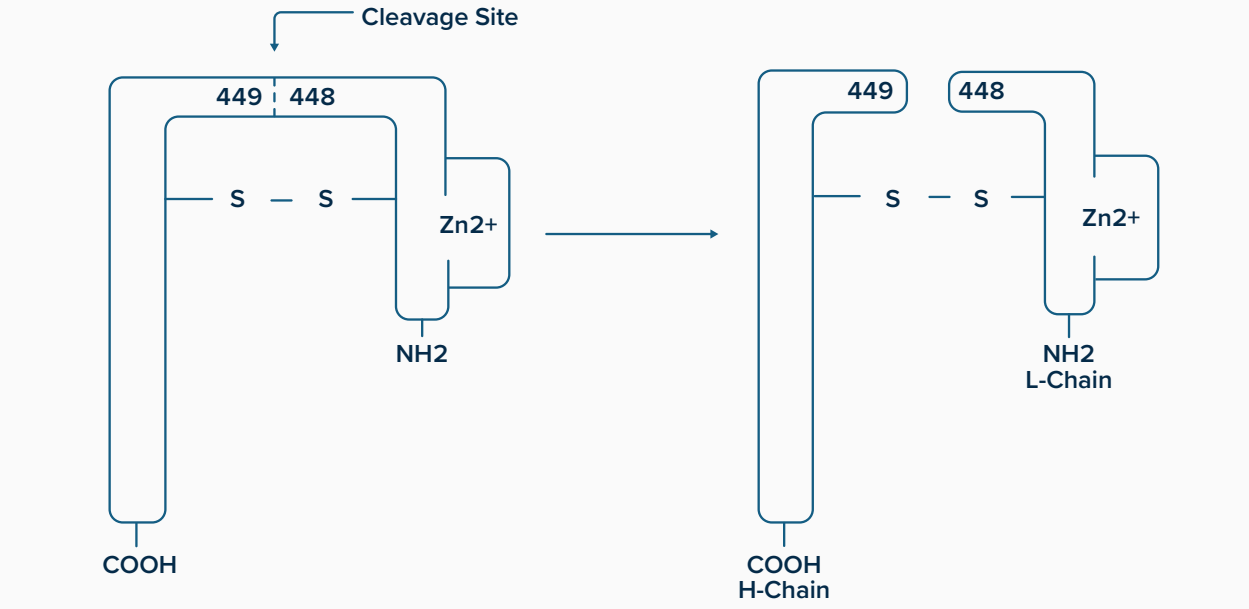
Brand Name	New Drug Name	Old Drug Name
Botox	OnabotulinumtoxinA	Botulinum toxin type A
Dysport	AbobotulinumtoxinA	Botulinum toxin type A
Xeomin	IncobotulinumtoxinA	Botulinum toxin type A
Myobloc	Rimabotulinumtoxin	Botulinum toxin type B

▲ Table 1. Commercial forms of botulinum toxin

It's mechanism of action involves inhibition of acetylcholine (ACh) release at the presynaptic neuromuscular junction resulting in paralysis of detrusor smooth muscle. This is achieved when OnaboptulinumtoxinA binds to the synaptic vesicle 2 (SV2) receptor protein and subsequently enters the presynaptic neuron.[30]



▲ Figure 2. Molecular structure of botulinum toxin31

OnabotulinumtoxinA is a 150kDa molecule with light and heavy chains. The heavy and light chain of are cleaved in the endosomal vesicle after entering the nerve via endocytosis. Following translocation into the cytosol, the light chain divides a protein called Synaptosomal-Associated Protein, 25kDa (SNAP-25). This plays an instrumental role in the fusion of vesicles containing acetylcholine with the neuronal cell membrane. Parasympathetic signals to the bladder are inhibited through blockage of acetylcholine release, thereby reducing involuntary detrusor contractions.[32,33]
It also inhibits release of ACh, Adenosine triphosphate (ATP) and substance P from the urothelium which are all involved in spinal and intrinsic reflexes contributing to OAB. In addition, it is also affects afferent C fibres resulting in a reduced sensation of urgency.[34]

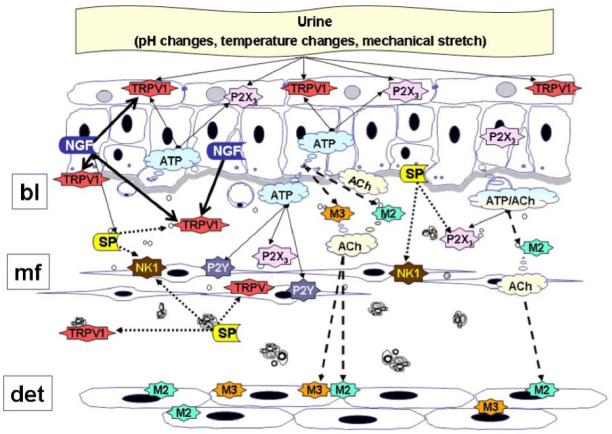


Figure 3. Mechanism of action of botulinum toxin in detrusor overactivity.[31,35]

Administration of OnabotulinumtoxinA posed a significant challenge after it was introduced into urological practice as it was administered through a rigid cystoscope either under general or spinal anaesthesia in high risk patients with NDO.

However, the pioneering work of Dasgupta revolutionised the administration of this agent using a 27G ultrafine needle within a sheath inserted through a flexible cystoscope under local anaesthesia.[36] The technique of Botox injections was named after Dasgupta by Sahai and colleagues[37] and featured in Smith's textbook of Endourology amongst others. OnabotulinumtoxinA is injected at 10-20 sites in the detrusor muscle of the bladder wall, avoiding the trigone, 1 ml per site with each 1 ml containing 10 units (U) of the toxin.

This innovative technique enabled the treating clinicians to inject the toxin under local anaesthesia in an outpatient setting. Procedure time is roughly 15 minutes. Patients are given either 100 units diluted in 10 mls of saline in case of idiopathic bladder overactivity (IDO) or 200 units diluted in 20 mls of saline in case of neurogenic over-activity (NDO).[38]

Schurch et al reported the first pilot study treating 21 spinal cord injury patients with NDO using OnabotulinumtoxinA.

All patients were performing CISC having failed anti-cholingeric treatment.
After 6 weeks of treatment, 10 patients were able to reduce the dose of anti-cholinergic medication and 17 were fully continent with improvement in urodynamic parameters.[39]
This initial work led to further studies including the first randomised control trial (RCT) of 59 patients with spinal cord injury (SCI) and multiple sclerosis (MS) assigned to two groups with 2 different doses of BoNT-A (200U and 300U) and saline injections (placebo). There was no significant difference between outcomes of both treatment groups however there was improvement in continence and quality of life in both treatment groups compared to placebo.[40]

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Two further major phase 3, double blinded, placebo controlled trials were carried out on a total of 691 patients with SCI and MS. These patients had been unsuccessfully treated with anticholinergics for at least a month and had 14 or more episodes of urge incontinence per week. These trials used OnabotulimtoxinA with groups assigned to either 200U, 300U or placebo. They supported the results of previous RCT's with no difference in both dosing groups however significant improvement in episodes of UI and urodynamic results in groups receiving Botox compared to placebo.[41,42]

In 2007, Sahai et al carried out the first double blinded, placebo-controlled RCT involving patients with IDO. Patients who were given 200U of OnabotulinumtoxinA were found to have significant improvement in maximum cystometric capacity as well as frequency and urgency urinary incontinence compared to placebo group. These beneficial effects lasted for up to 24 weeks.[43]
Several other studies supported these findings and led to multiple placebo-controlled dosing trials to determine the optimum dose for patients with IDO. Dmochowski conducted a phase 2 multicentre trial and recruited 313 patients with IDO into groups receiving OnabotulinumtoxinA in doses of 50, 100, 150, 200 or 300 or placebo.

This study found that doses of 100U provided sufficient efficacy and improvement in quality of life whilst limiting the problem of high post void residual urine.[44]
The findings of these studies were further supported by placebo-controlled phase 3 trials reported by Chapple et al and Nitti et al.[45,46]

A larger cohort of 557 patients with overactive bladder with at least 3 episodes of urgency urinary incontinence and a minimum of 8 micturitions per day were randomised into placebo group and those receiving 100U of OnabotulinumtoxinA. After 12 weeks of treatment, 22.9% of patients receiving OnabotulinumtoxinA were found to be completely continent compared to 6.5% of those receiving placebo with remaining having significantly reduced episodes of urinary incontinence vs placebo (-2.65 vs -0.87). There was also an overall improvement in quality of life in those treated with OnabotulinumtoxinA. The most common adverse effect was urinary tract infection.[46]

Ginsberg et al led a multicentre prospective study over the course of 3.5 years on the long term outcomes of OnabotulinumtoxinA for OAB. There was an overall reduction in urinary incontinence with an improvement in quality of life with median duration of effect at 7.6months.[47]
Another single centre study on patients receiving OnabotulinumtoxinA for refractory OAB reported the median term outcomes and discontinuations rates.

There was a statistically significant improvement in urgency, frequency and urge urinary incontinence following first injection of OnabotulinumtoxinA and continued after repeated injections.
A total of 37 patients out of 100 discontinued treatment after 2 injections mostly due to the need for CISC related issues (11%) and poor efficacy (13%).[48]

Malde et al and colleagues focused primarily on patient satisfaction and experience with OnabotulinumtoxinA for refractory overactive bladder.
They contacted the first 100 patients who underwent OnabotulinumtoxinA over the past 20 years and found 49 to be still on treatment. Using the patient-reported experience measure (PREM), they found a significant difference in satisfaction scores between those who continued treatment (mean score 29.8) compared to those who discontinued (mean score 25.1).
Overall satisfaction for those receiving treatment was high at 8.6 (mean SD score).[49]

After extensive trials over many years OnabotulinumtoxinA is now licensed for use in OAB and appears in NICE and international guidelines. Compared to other treatments for overactive bladder, OnabotulinumtoxinA, it is more cost effective and less invasive. A study into cost effectiveness was carried out in the US in 2018 comparing several treatments for OAB.
The authors found that BTX-A provided the greatest gains in QALYs – this is a common metric in health policy that measures the value of health outcomes for a medical intervention. BTX-A injections cost just $32,680 per QALY; the next cheapest treatment (Percutaneous Tibial Nerve Stimulation) costs $71,126 per QALY.
Furthermore, the National Institute for Health and Care Excellence (NICE), the European Association of Urology (EAU) and the American Urological Association (AUA) all updated there guidelines to include BTX-A for lower urinary tract disorders.[50]

Undoubtedly it has changed the quality of life of an estimated 5 million patients worldwide to date. The beneficial effect of injecting 100 units of OnabotulinumtoxinA in idiopathic detrusor overactivity and 200 units in neurogenic detrusor overactivity lasts for 6-12 months. The injections can then be repeated with the increase in bladder capacity and reduction in urinary frequency/urgency maintained in the majority of the patients in the long term.

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King James IV Professorship Continued...

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Grant Reports

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Faculty of Dental Grants for Education

Laura Timms

I was very grateful to be awarded an education grant from the Faculty of Dental Trainers, Royal College of Surgeons of Edinburgh in 2021 to undertake a post graduate certificate in medical education. I completed the qualification through the University of Sheffield. The University of Sheffield course focusses on a reflective approach to teaching and discusses various teaching styles to engage with a range of learners in different clinical settings directly appliable to dentistry. It also focussed on course design and assessment, and how to ensure assessment of quality and the different facets required to make an excellent dental professional. This included development of teamworking, professional and communication skills.

I am a National Institute of Health Research Academic Clinical Fellow in paediatric dentistry at the University of Sheffield/ Sheffield Teaching Hospitals and I am due to start a PhD funded by the National Institute of Health Research in March. As such my job involves research, teaching and clinical practice in paediatric dentistry. I have involvement in teaching and assessment of undergraduate dental students and dental therapists in a variety of clinical settings and at different stages of their curriculum. I also carry out other professional teaching roles with postgraduates and other non-dental clinicians. Through the course I was able to reflect on, adapt and improve several of my current teaching sessions. Completing the post graduate certificate in medical education at this stage, where I have regular teaching opportunities but am still at an early stage in my career, has allowed me to develop and significantly improve my teaching ability. Specifically my clinical teaching and provision of feedback has improved. This means I am able to immediately put what I have learnt into practice to improve the experience of learners. It also means as I progress, I can underpin this with the knowledge I have gained, ensuring as I develop as a teacher I have the necessary foundation knowledge. Having the qualification means that as I develop more responsibility I may be eligible for career opportunities that would not be possible otherwise. For example, the course involved overall curriculum design, which is something I hope to be involved in in the future.

I am also interested in assessments that are both patient and student focussed but also ensure competence, the post graduate certificate has given me the

knowledge required to consider this further through teaching on constructive alignment and assessment. The course also promoted a collaborative style to teaching, ensuring it was student focussed. Thorough-out I had the opportunity to build networks with other teachers through a collegiate approach, which also provided opportunity to learn from my peers. Without the support of the Faculty of Dental Trainers it would not be possible for me to complete this qualification, which will help support me attain the role of a clinical lecturer following my PhD, the next step on my career pathway. I would encourage trainees of all stages who are interested or involved in teaching to join the Faculty of Dental Trainers, which provides a network of more experienced teachers, educational events and support to further develop your skills such as through the education grant.

Morag Powell

In 2020, I applied and was successful in receiving a grant towards my final year of fees towards the MSc in Health Professions Education, University of Glasgow. The grant allowed me to continue my studies at masters level and complete my dissertation, which would have been financially challenging without. My initial research proposal to investigate the benefits of interprofessional dental education between Dental Students and Dental Therapy students was impacted by the COVID pandemic. With this however, came new challenges previously unrecognised and unseen and this gave me opportunity to explore the wellbeing of dental therapy students during the COVID pandemic.

Undertaking a dissertation and working full time during a pandemic was a huge undertaking. Prior to the dissertation year, there had been an 18-month period of working seven days a week to complete the required credits for the post graduate diploma. This was gruelling, however I am grateful that the course at University of Glasgow was designed in a way that work had to be submitted by the end of every weekend as this definitely kept me on track and ensured that the diploma modules were completed on time. After a short break, and with the additional funding sought, I commenced the dissertation year in September 2020.

In contrast to the taught diploma modules, I encountered a lot of freedom within the dissertation year, which in turn meant that I had to be more structured with planning my time. Forward planning and working to a pre-determined agreed timeline was beneficial for me and I was extremely fortunate to have very understanding supervisors.

Overseeing and organising the research focus groups was relatively straight forward. At Peninsula Dental School, we were fortunate that we were able to keep clinics open during the pandemic with multiple changes including the use of clinical pods and speed increasing handpieces. Both dental and dental therapy students returned to an integrated clinic early on in semester one of their final year, which in turn generated the interested in conducting research into the impact of the pandemic on the wellbeing of the students.

Ethical approval was sought and granted, which was a complex process!

However, I have found the experience gained from this hugely beneficial in my current academic role.

Completing the literature review highlighted wellbeing issues within the dental professions, both pre pandemic and during the pandemic. Common themes arising from the literature published during the pandemic focused on factors that contributed to students' stress including the fear of catching COVID; adapting to the change to online learning and the affect the pandemic had on their clinical activity. Once the literature review was completed, the decision was taken to conduct qualitative research in the form of focus groups to capture how the students had been feeling on clinic during the pandemic. Thematic analysis was then undertaken on the focus group transcripts with themes identified and discussed.

The main themes from the research included stress of completing minimum clinical requirements of the programme and exit cases for final year assessments; and pandemic behaviours of students.

Writing the thesis was extremely time consuming and undertaken during a time in a pandemic that was incredibly stressful. However, now that it is completed I feel very fortunate to have been able to complete this small piece of research during a pandemic.

I am extremely grateful to the Faculty of Dental Trainers for awarding me the education grant, which without doubt was instrumental in allowing me to complete the dissertation year of the MSc in Health Professions Education. I addition, I am grateful to Dr Viv Binnie and Dr James Donn of the University of Glasgow for supervising the dissertation and to Dr Sally Hanks of the University of Plymouth for overseeing the process of turning the thesis into a submissible article for potential publication.

FST/ASME Educational Research Grants

Grant Holder Name	Kartik Logishetty
Department(s) in which the Fellowship was held	MSk Lab, Department of Surgery and Cancer, Imperial College London
Type of Grant/Fellowship;	FST/ASME/19/006
Project Title;	**Can team-training in Virtual Reality improve performance of complex open surgery**
Period grant held	
From:	October 2019
To:	September 2021

System errors are the most common cause of adverse events in surgery, so team-based (for the scrub nurse, first assistant and surgeon) training may be more effective for delivering successful surgery than individual members training alone. Virtual Reality (VR) headsets enable healthcare professionals to be fully immersed in a simulated operating room, use virtual instruments to perform surgery, and interact with other participants in the same environment. This study was a randomised controlled trial of a team-based simulation curriculum.
It tested whether the surgical team which trains to perform virtual hip replacement together performed real-world surgery better than these individuals trained independently – as is current practice.
We found that teams who had trained together in VR performed more steps of hip replacement correctly, and demonstrated better collaborative, problem-solving, decision making, and communication skills, and committed fewer mistakes.
This indicates that the future of surgical training should change to incorporate team based training, and that virtual reality can facilitate this.

A. Clinical and Scientific Significance of advances made

Performing planned complex surgery requires role-specific skills executed in sequenced choreography between surgical team members; yet conventionally, surgeons and scrub nurses are trained separately.

This study assessed if collaborative training – using immersive virtual reality (iVR) for anterior approach total hip arthroplasty (AA-THA) – was superior to individual, role-specific training for acquisition of technical and non-technical skills.

40 participants with no prior experience of AA-THA (20 surgeons (PGY1-3 level) and 20 scrub nurses) were randomised to individual or team training.

Individually-trained participants learnt to perform AA-THA with a simulated AI surgeon or nurse counterpart, while teams trained live in pairs (surgeon and nurse). Both groups underwent 5 iVR training sessions over six weeks. Subsequently, they underwent a real-world assessment in which they performed AA-THA on a high-fidelity model with real equipment in a simulated operating room. Team-trained participants were assessed as a pair, and individually-trained participants were randomly paired with a participant in a complimentary role. The primary outcome was team performance as graded by two independent blinded raters using video-based assessments to measure NOTSS, NOTECHS-II and SPLINTS. Secondary outcomes were procedural duration, and number of technical errors.

Teams-based training was superior to training separately for acquiring non-technical skills (NOTECHS-II score 51.7 ± 5.5 vs 42.3 ± 5.6, p=0.001). Teams completed the assessment 28.1% more quickly (27.2 minutes ± 5.5 vs 41.8 ±8.9, p<0.001), and made approximately half the number of technical errors when compared to the individual group (12.9 ± 8.3 vs 25.6 ± 6.1, p=0.001).

Training surgeons and scrub nurses together improved the acquisition of procedural and non-technical skills, and resulted in faster simulated hip replacement surgery. Team training has previously been used in the emergency setting and for some endoscopic procedures. The present study is the first to demonstrate the importance of team-based training for complex open surgery. This method can improve the safety, effectiveness, and efficiency of these procedures. Further, this is the first study which demonstrates that virtual reality facilitates team-based training in a reproducible, safe, accessible, and measurable way.

B. Problems encountered and steps taken to overcome them

Challenges to this study were two-fold:

1. Developing a novel virtual reality platform for team-training for hip replacement surgery – this platform did not exist prior to this study. Challenges involved working with an industrial partner to work remotely and collaboratively to communicate the workings of hip surgery, the operating room environment, and the dynamics of the scrub nurse/surgeon relationship in the choreography of surgery. This required a cognitive task analysis approach to break down the procedure and responsibilities in great detail, and explain the translate this knowledge to software engineers in lay language.

Faculty of Dental Grants for Education Continued...

The platform underwent exhaustive testing to ensure the educational impact and relevance, as well as finding and fixing software bugs to allow a seamless implementation in this study's randomised controlled trial.

2. Recruiting and delivering this study during the COVID-19 pandemic – national restrictions and the diversion of healthcare staff to assist in helping patients with COVID-19 initially limited our ability to recruit nurses and training surgeons. This improved with time, but also meant that we recruited some senior undergraduate medical students to be in the 'scrub nurse' role. We also created 'COVID-safe' protocols for when participants did attend our VR laboratory for training, and ensured that these were vetted by Imperial College London prior to starting.

C. Collaborations established

This project strengthened our collaborations with industry (Pixelmolkerei, Switzerland and Depuy Synthes Johnson & Johnson, Switzerland), as well as began new relationships with scrub nurse training programs in universities around London. This has resulted in ease of recruitment to future studies, and the integration of VR training into King's College London's nursing curriculum – planned for Summer 2022.

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

- First Prize for Oral Presentation at the Liverpool 7th Annual Research Conference, Adaptability in Medicine: Healthcare for the 21st Century and Beyond - First Prize for Oral Presentation at the Liverpool 7th Annual Research Conference, Adaptability in Medicine: Healthcare for the 21st Century and Beyond Issued by Liverpool Research Society - National Student Research Conference - Feb 2022
- Oral Presentation: "A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery" - Oral Presentation: "A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery" Issued by BOMSA - Feb 2022
- First Prize at the High Yield Poster Competition of the Imperial College London Surgical Society International Conference of Trauma Medicine - First Prize at the High Yield Poster Competition of the Imperial College London Surgical Society International Conference of Trauma Medicine Issued by Imperial College London Surgical Society - Nov 2021

- Poster Presentation: “A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery” - Poster Presentation: “A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery” Issued by GIANT Health - Nov 2021
- Poster Presentation: “A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery”Poster Presentation: “A Randomised Controlled Trial Comparing Multiplayer and Single Player Immersive Virtual Reality Training for Anterior Approach Total Hip Arthroplasty Surgery” Issued by British Orthopaedic Research Society - Sep 2021
- Poster Presentation: “Who learns best: The tortoise or the hare? A randomised controlled trial of spaced practice versus intense training in immersive virtual reality” - Poster Presentation: “Who learns best: The tortoise or the hare? A randomised controlled trial of spaced practice versus intense training in immersive virtual reality” Issued by British Orthopaedic Association - Sep 2021
- Surgical teams who train together in virtual reality out-perform those who train individually: A randomised controlled trial for learning anterior approach total hip arthroplasty Thomas C Edwards, J P Cobb, K Logishetty Issued by Royal Society of Medicine, UK - Feb 2022
- This study’s report has been submitted for consideration for publication to JAMA Surgery. During the same period, our group performed a study for scrub nurse training for complex total knee replacements. The publication is: Edwards TC, Patel A, Szyszka B, Coombs AW, Liddle AD, Kucheria R, Cobb JP, Logishetty K. Immersive virtual reality enables technical skill acquisition for scrub nurses in complex revision total knee arthroplasty. Arch Orthop Trauma Surg. 2021 Dec;141(12):2313-2321. doi: 10.1007/s00402-021-04050-4. Epub 2021 Jul 28. PMID: 34319473; PMCID: PMC8317146.

E. Acknowledgements

ASME and FST

Faculty of Dental Grants for Education Continued...

Grant Holder Name **Department(s) in which the Fellowship was held**	KJ Baatjes Surgical Sciences, Stellenbosch University, South Africa
Type of Grant/Fellowship;	FST/ASME EDUCATIONAL RESEARCH GRANTS
Project Title;	**Real-life procedural videos: an additional assessment tool for structured oral examinations of surgical trainees?**
Period grant held	
From:	03.07.2020
To:	8.11.2021

Lay Summary

The COVID pandemic provided opportunities for innovation in the postgraduate surgical teaching program. Expansion of traditional teaching methods by the addition of educational procedural videos as a learning tool seemed fitting. The real-life recordings also have the potential to be utilised during the surgical mock oral assessment. These recordings of real-life surgical procedures have the extra benefit of remote application thereby limiting person-to person contact as well as long distance travel to exam venues in wide geographical areas.

The pandemic further stimulates revision of teaching and assessment programs in the surgical curriculum, but thorough evaluation of such decisions should be researched. This study explored the experiences of surgical trainees and specialists at a South African university and tertiary hospital, of the video assisted structured mock oral assessments, both in a face to face and on-line format.

The preliminary findings showed that the participants were positive about this initiative of utilizing procedural videos as part of the mock oral assessments, but the participants believed there were certain limitations to the use of it. They suggested more attention be given to technical aspects of videos in the assessment with regards to the producing and editing of the videos.

A. Clinical and Scientific Significance of advances made

The study aimed to explore the experiences and perspectives of surgical registrars and consultants in a tertiary academic hospital in South Africa, of structured mock oral assessments utilizing video recordings, both in a face to face and on-line format. In this study, data was produced by means of individual interviews and focus groups.

Findings indicate that this approach was well-received by both the students and the examiners during this mock assessment. Suggestions towards improving the assessment practices in the department are as follows:

- Structured examiner training before every examination
- Suggested questions made available to all the examiners before the examination
- Videos that are used should all be edited
- Feedback should be included as part of the mock examination

The significance of the study will be evident as soon as the suggestions listed above have been implemented. It is however anticipated that better assessment practices will lead to better qualified surgeons and ultimately better patient outcomes

B. Problems encountered and steps taken to overcome them

On the day of data collection, several consultants and registrars were called away to clinical duties just prior to starting and some during the examination. Similarly, it took careful planning to arrange the individual interviews with the clinically busy consultants. This is a stark reflection of the nature of doing research in the clinically active domain. We proceeded with the examinations and could complete the session as well as the focus group and interviews.

Another challenge was structured examiner training. Due to the busy schedules of the examiners some of them did not get proper examiner training and they then did not prepare the questions related to the videos well.

C. Collaborations established

In the process of doing the research the researchers that are part of the Department of Surgery built close relationships with the Centre for Health Professions Education staff. These collaborations will continue in the future.

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

The project was presented at the Annual Academic day of the Faculty of Medicine and Health Sciences, Stellenbosch University.

Format: Poster, Virtual

Abstract:

Real-life procedural videos: an additional assessment tool for structured oral examinations of surgical trainees.

K. Baatjes 1, W. Conradie 1, J. Edge 1, E. Archer 2

Faculty of Dental Grants for Education Continued...

1 Division of Surgery, 2 Simulation and Clinical skills Unit, Centre for Health Professions Education, Faculty of Medicine and Health Sciences, Stellenbosch University.

Background

Surgical registrars are assessed before acceptance to the South African College of Surgeons, with oral examination as a main component. Concerns with regards to the reliability and validity of this method, remains. Structured oral examinations (SOE), based on a clinical case with pre-defined questions and goals, is reproducible. Adding procedural videos to the SOE may allow for greater depth of enquiry of the candidate's knowledge.

This study explored the experiences of a group of surgical registrars and the consultants (examiners), utilizing video assisted structured oral assessments, in a face-to-face and virtual manner.

Method

The descriptive study was undertaken at the Division of Surgery at Stellenbosch University. Institutional ethics approval was obtained (N20/09/090).
All registrars and consultants in the division were invited to a voluntary mock assessment, followed by a discussion of their experience. One group had face-to-face contact and the second group was tested virtually on Microsoft Teams™.
This was followed by a focus group interview with the registrars, and individual interviews with the consultants.

On the day of the mock examination, several members were called to clinical duties leading to a final participant number of 8 consultants and 12 registrars. The interviews were transcribed verbatim and analyzed by means of a thematic analysis process.

Results

The significant findings were: videos can play a role in assessment, standardization is possible, pre-exam preparation for the examiner is critical, the technical aspects need to be addressed and registrars appreciated the feedback given to them during the sessions.

Conclusions

Consultants and registrars found the use of videos during oral assessment valuable, however more planning and preparation is required from the consultants' point of view. While both the face-to-face and virtual oral assessments were experienced positively, it seems as if the registrars preferred to have the examiners with them in the same room.

E. Acknowledgements

Consultants and registrars of the division who freely participated and engaged in the project.

The team also acknowledges receipt of the grant from the Faculty of Surgical Trainers at the Royal College of Surgeon of Edinburgh and the Association for the study of Medical Education.

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Global Surgery Foundation

Report of Training Workshop For Basic Surgical Skills (BSS) Instructors and BSS Course

Simulation and Skills Centre,

University Teaching Hospital of Kigali ('CHUK')

October 23rd - 25th 2018

David Sedgwick, MBChB, FRCS(Ed)

Stuart Fergusson, MBChB, MRCS(Glas)

Christian Urimubabo, MMED

Executive Summary:

The Basic Surgical Skills course (BSSC) was originally designed by the UK and Irish Colleges of Surgeons in 1994, as a response to the Calman report on specialty training, which recommended an increased emphasis on training in a simulated environment.

The BSSC focuses on key technical skills, including knot tying and safe, effective use of instruments. Following review and practice of principles, it rapidly contextualizes these skills into high-fidelity simulated models which largely use animal material.

The BSSC has continued to evolve and has proven popular around the world. In the African sub-continent, the BSSC is now a mandatory component of the curriculum for surgeons training in the COSECSA region (College of Surgeons of East, Central and Southern Africa).

The UK and Irish Colleges continue to badge or credential BSSCs around the world and along with COSECSA, these colleges credential the East African courses. A formal observational study was carried out on the Rwandan BSSC 2 years ago and demonstrated significant improvements in objective technical performance, and an increase in trainee confidence levels[1].

The BSSC is an important component of the Rwandan Surgical Society educational / training programme and the course this year was the fifth consecutive annual course run with the support of the Royal College of Surgeons of Edinburgh (RCSEd). It had run intermittently in previous years. Other funding partners, this year, were Johnson and Johnson / Ethicon, Doctors' Academy, RCSED Access to Surgery and Scotland-Africa Surgical Training.

A training workshop for the instructors was delivered and 2 new trainee instructors were identified and mentored closely in the course. This year's course was delivered to the new cohort of surgical trainees in Rwanda (PGY1s), which amounted to 20 candidates and a further 3 COSECSA candidates from DRC. The delivery partners in Rwanda were the Rwanda Surgical Society and the University of Rwanda. The faculty training workshop which immediately preceded the course was an integral part of preparation.

This year, the BSSC was convened by Dr David Sedgwick with Dr Christian Urimubabo as co-convenor. Dr Urimubabo is a consultant general surgeon at CHUK. Our previous Rwandan convener, Dr Egide Abahuje, is currently in the USA undertaking a scholarship in Surgical Skills teaching and simulation. The course ran well and finished in the set time.

Feedback from candidates was very positive, although access to pre-course materials was universally difficult and will need to be addressed next year.

The feedback from the faculty was generally good and raised some issues that will be discussed in the coming months. Topics include the plans for preparation, delivery and funding of the course.

Planning:

The RCSEd has supported delivery of the BSSC to Rwandan surgical trainees annually since 2014. Until 2017 these courses had been convened by Dr Sedgwick, with a clear strategy to train and mentor a Rwandan convenor to facilitate sustainability of the course using in-country resources. Dr Egide Abahuje acted as convener for the course in October 2017, but subsequently won a 2 year fellowship in Surgical skills teaching and simulation, to Harvard University, Boston, USA.

Therefore he was unavailable to act as convener of the 2018 course. The Rwanda Surgical Society and University of Rwanda again invited RCSEd to support delivery of the BSSC to their trainees, and Dr Christian Urimubabo was invited to be co-convener of this year's course to co-ordinate the local planning.

Rwandan colleagues organized the use of the Simulation Centre in the main University Teaching Hospital of Kigali ('Centre Hospital Universitaire de Kigali', or CHUK). The sutures required for the course were kindly donated by Johnson & Johnson / Ethicon. They were dispatched to the UK from MAP, an American based surgical and medical supplier.

After the surgical staff meeting at CHUK on Friday October 19th the instruments and equipment in the Simulation Centre were checked.

Dr Christian Urimubabo and Dr David Sedgwick made plans for obtaining the porcine animal tissue for the course with an intern, Dr Zeta Mutabazi who agreed, as before, to coordinate the sourcing and retrieval of the appropriate tissues. Arrangements were made to purchase 2 pigs which would provide appropriate models for bowel anastomosis, arterial repair, chest drain insertion and crico-thyroidotomy. A further 16 trotters were needed for the participants and instructor. The chicken legs were purchased at a Kigali supermarket.

The refreshments for the course instructors and candidates were booked with the catering department at CHUK.

The education section at RCSEd provided essential administrative support and local administrative support was given by Mercy Kamukama from RSS.

Funding:

Doctors Academy generously donated £1250, RCSEd Access to Surgery Committee £800, Rotary Club of Lochaber £550, Mr Boyd Tunnock £500 and a donation of £100 was made by Mr and Mrs Ian MacDonald, Fort William.

The Scotland – Africa Surgical Training SCIO provided residual funds.

Setting – The Simulation Centre, CHUK:

The centre is a two-roomed building with one area designated for preparation and storage of equipment, and the other for the delivery of teaching activities.

The two new folding tables provided good work surfaces for 12 candidates; unlike previous years, no candidate had to be seated around a normal office desk with limited leg-room.

The centre laptop and projector were not available on this occasion and so a projector was borrowed from another department in the hospital and a faculty member's laptop had to used. A new webcam with surrounding light was purchased in the UK before this visit.

This created high definition images and allowed magnification of the techniques for the benefit of all candidates. Refreshments were taken in the area just outside the centre and lunch was served in the adjacent marquee.

Train the Trainer Workshop for BSS:

Arrangements were made for revision of some aspects of a COSECSA/RCSEd Train the Trainer course, specifically designed for BSS instructors. Dr Sedgwick delivered short talks on identification of learning goals and the principles of adult learning, teaching a skill was presented by Dr Stephen Bennett and giving feedback by Dr Christian Urimubabo. This course was well received by the 2 new instructors and was a useful revision for the other instructors.

After lunch the instructors then set up the equipment for the Basic Surgical skills course. This involved preparing the animal material, setting up the abdominal wall jigs and preparing the teaching environment. Feedback from those attending the Train the Trainer workshop was positive.

The final programme is included as Appendix 1.

BSS Course Programme:

The course programme was altered once again, to accommodate the problems of potential degradation of the animal material. The full course programme, including details of the faculty who delivered each element, is included as Appendix 2. Faculty meetings were led by Dr Sedgwick at the beginning and end of both days.

Global Surgery Foundation Continued...

Mrs Vivienne Akimana (VA), administrative and technical assistant at the SIM centre, and Mercy Kamukama organised the registration of participants.
This year we also had valuable technical and administrative assistance from Dr Jess Cooper (JC), a GP from Islay who travelled with the team from the UK. VA and JC assisted throughout the course in the preparation of and distribution of materials between sessions.

At the end of both day 1 and day 2, participants were asked to reflect on their training to identify what went well and where improvements were necessary. Course feedback was collected and Paul Rafferty in the Education Section of RCSEd performed the analysis. The results are reported below in Appendix 3.

In addition to the standard RCSEd BSSC feedback form, the candidates completed a skills confidence matrix and gave an estimate of their surgical experience in numbers of particular procedures performed or observed. This data is presented in Appendix 4.

Catering:

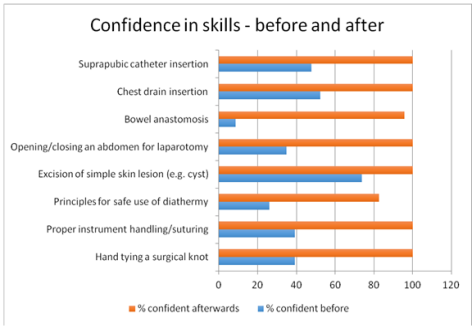
Morning coffee breaks and afternoon refreshments were taken immediately outside the simulation centre. Meals were provided in a small marquee adjacent to the simulation centre, by the catering team at CHUK.

BSS Feedback:

The feedback from the candidates was very positive and has been itemized in Appendix 3.
Among the most popular aspects of the course were, the organisation by the faculty and the quality of the teaching. The majority stated that the quality of the venue, location, audio-visuals and catering were satisfactory to excellent. Amongst the most important things the candidates valued were knot tying, correct instrument handling and techniques, and chest drain insertion.
All the candidates said they would be making changes to their working practices as a result of the course and will also pass on information to their colleagues.

The aspect that the candidates disliked most was the congested schedule with insufficient time for practice. Almost all the candidates had difficulty accessing the on-line pre-course materials. However all the candidates who answered said the course had met their expectations and that they would recommend it to a friend.

Candidate confidence in key skills was assessed on a 5-point Likert scale before and after the course. Confidence levels were then dichotomized into confident/not confident and results are shown graphically below, demonstrating marked increase in confidence in all the skills about which they were questioned. Full results are in Appendix 4.



Topics for further courses were suggested and included Advanced Trauma Life Support, fracture management, hernia repair, laparoscopic surgery, central line insertion, stoma formation, and burns management.

Faculty Feedback:

The feedback from the faculty last year highlighted the following issues which have been acted upon:

- upgrading the webcam and projector
- extra gowns were obtained from the theatre at CHUK
- two large folding tables were brought from UK

The feedback from the faculty obtained at the faculty meetings and from the written submissions was very positive. Six of the faculty stated that it was a well-organised and valuable teaching session. Others stated it was interesting for trainees, with good equipment. Overall the reaction of the faculty members was very positive. Faculty feedback included the following points for improvement:

- Space in the Simulation Centre was limited. We should review the venue or limit the number of candidates to 20.
- Better pre-course planning by local faculty with earlier invitations to join faculty.
- Better access to the videos for preparation for teaching.
- Add videos of Chest Tube Insertion, Cricothyroidotomy and Suprapubic Catheter insertion.
- Consider inviting trainees from other surgical specialties.
- Further development of the Rwandan faculty
- Consider obtaining a diathermy unit for training. (? reconditioned unit from Ebay)
- Purchase more dissecting scissors (?10 pairs) and 5 more self-retaining retractors.

Accounts:

The accounts in Appendix 4 show that financial support for the course came from Doctors Academy, Johnson and Johnson, RCSEd Access to Surgery, Rotary Club of Lochaber, Mr Boyd Tunnock, and Mr and Mrs Iain MacDonald. The expenses are listed and show a small surplus which is held in the account of Scotland–Africa Training SCIO. The faculty and candidates are all extremely grateful for the generous financial support from all the donors above.

Summary and Conclusion:

A Basic Surgical Skills Course was delivered for the 2018 intake of PGY1 Rwandan surgical trainees (20 candidates) and 3 COSECSA trainees from the DRC. All 23 candidates successfully completed the course. The faculty comprised 2 UK instructors working with 1 instructor from DRC and 4 from Rwanda. This year, Rwandan faculty delivered almost the entire course. The Simulation Centre provided a suitable venue in CHUK, the main university hospital in Kigali; although it was slightly cramped for the number of candidates. The course was taught according to the RCSEd template with substitution of laparoscopic skills with four other techniques.

Global Surgery Foundation Continued...

The feedback from the candidates was very positive and improvements in skills confidence were impressive. Comments from the faculty were very positive, with some helpful suggestions to improve the delivery of the course. Plans have been drawn up to provide a BSSC for the 2019 intake of surgical trainees shortly after they have taken up their posts in October.

Further plans:

1. Planning will be started for the next course to take place shortly after the next annual intake of trainees in to the Rwandan Surgical Training Programme, in November 2019, and avoiding Umuganda, to facilitate acquisition of the animal material.
2. In order to reduce expenses, tutors and support staff in Rwanda should plan to obtain some of the animal tissue in advance from a local butcher or abattoir and store in a deep freeze.
3. Decide with the trustees of 'Scotland – Africa Surgical Training Charity' how to take forward future funding of the course.
4. Invite some Consultants and trainees from DRC and Burundi who are not currently able to access Basic Surgical Skills training.
5. Purchase some new instruments particularly dissecting scissors (10 items) and self retaining retractors (5 items). Plans will be made to obtain these from a UK instrument supplier and transport them in hand luggage to Rwanda
6. Consider setting up a bank account in Rwanda so that the Convener and faculty members can pre-purchase and store some of the animal material. For governance purposes this would ideally be administered by the University of Rwanda.

Acknowledgements:

Thanks to Doctors Academy, the RCSEd Access to Surgery Committee, Rotary Club of Lochaber, Mr Boyd Tunnock, Mr and Mrs Ian MacDonald for their generous financial support. We give a special thanks to Johnson & Johnson / Ethicon for the generous donation of suture materials.

We are grateful to RCSEd for making the on-line pre-course materials available to the candidates with no charge.

Thanks also to Catherine Thwaites, International Activities Manager at RCSEd for her administrative support and encouragement.

Mrs Vivienne Akimana and Laurence Mizero were present throughout the course and we thank them for their preparation of instruments, arranging for cleaning and catering provision.

Many thanks also have been given to Mr Archie Paterson and Nevis Bakery for delicious shortbread for the tea and coffee breaks;and to Gordon and John at the Gift Shop in Fort William for Highland Gifts to thank Rwandan colleagues.

Clean Cut Ethiopia: Final project report for the Royal College of Surgeons of Edinburgh February 2021

Prepared by: Thomas Weiser, Bella Lima, Senait Bite

Project Overview

Clean Cut aims to improve compliance with critical standards of perioperative infection prevention, and reduce deaths and complications from surgery in a scalable, sustainable fashion. Since this grant was awarded, we finalized publication of the preliminary work in the BJS that had been ongoing and have extended the work to several new facilities.

Project Progress

The COVID-19 pandemic caused major delays, but we adapted the Clean Cut implementation tools to allow remote delivery. In partnership with the Federal Ministry of Health (FMOH), this autumn we launched programme implementation efforts at four hospitals selected as quality hubs for this work. The four hospitals where Clean Cut is being implemented and/or supported are:

1. Jimma University Hospital - Oromia Region
2. Tebeb Ghion University Hospital - Amhara Region
3. Hawassa University Hospital - Sidama Region
4. Hiwot Fana University Hospital - Harari Region

A fifth hospital, Ayider Comprehensive Specialized hospital, is located in the Tigray region which is currently facing political unrest; work in this facility has not been initiated.

Further funding

Lifebox is adapting the Clean Cut program to improve the safety of caesarean sections as part of the Bill & Melinda Gates Foundation's Grand

Global Surgery Foundation Continued...

Challenges Initiative, funded by UBS Optimus Foundation. The trial is a stepped wedge, cluster randomized interventional study evaluating the impact of this adaptive, multimodal checklist-based intervention to reduce perioperative and postoperative infections following cesarean delivery and other invasive obstetric and gynecological operations.

We have also received funding to implement Clean Cut in hospitals in Liberia, Madagascar and India.

Impact of the work

Across the original five pilot hospitals, there was a 64% increase in compliance across the six infection prevention standards that comprise Clean Cut (from 2.9 to 4.5 out of six). Examples include the maintenance of the sterile field improving by 49% and confirmation of instrument sterility increasing by 50%. As a result, the relative risk of infection dropped by 35% for all surgical patients. When comparing surgical patients with low versus high compliance of infection prevention standards, high compliance reduced the risk of infection by 46%. We are in the process of preparing a manuscript evaluating the longer term sustainability of the program; preliminary results indicate that four of the five original hospitals have maintained the improvements in compliance that we observed at the end of the implementation period.

The FMOH plans to ensure sustainability and longer impact of quality improvement projects in the Quality Hub and beyond through a cascading implementation model. The aim is eventually to roll out the lessons learned on a national level in the coming years.

We have also improved the programme's online materials to train trainers and others in how to implement Clean Cut. These materials now live in what is called the Lifebox Learning Network, an online platform that not only serves as a repository for information but also helps promote communities of learning and supports local programme implementation by walking teams through each phase of the process.

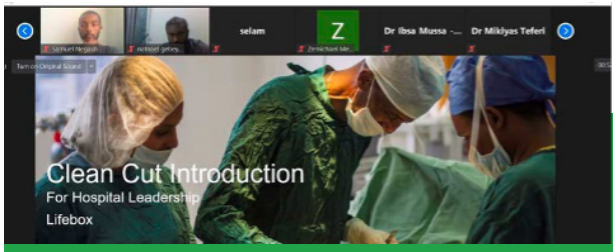
Feedback we have received

"This is welcome news for surgical patients in Ethiopia; like in many low-income countries, Ethiopian patients suffer disproportionately from surgical infections. Clean Cut is a locally-led and affordable way for surgical teams to make every single patient safer. With the backing of the Federal Ministry of Health, we're rolling Clean Cut out across Ethiopia to replicate our successes to date."

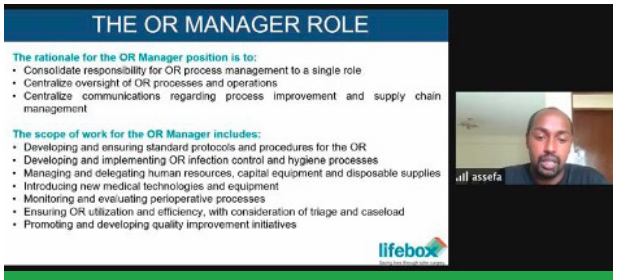
- Dr. Tihitena Negussie of Black Lion Hospital, Addis Ababa, Ethiopia.

Photos and other social media content

We include here photos from some of our training using the Lifebox Learning Network. All of these sessions are now run entirely by local teams that help provide context and testimony to the importance of the work, its scalability, and its attractiveness to providers, surgical teams, and hospital administration alike.



Picture 1. Clean Cut Orientation and Introduction virtually conducted for the four hospitals



Picture 2. OR Management training conducted for the selected QI and OR leads as part of the implementation plan

Picture 3. Safe Instruments training at Zewdito hospital as part of Clean Cut

Picture 4. Safe Instruments training at Zewdito hospital as part of Clean Cut (2)

Picture 5. Lifebox tweet on the publications of the BJS article

RCSEd support

The RCS grant was an important step in helping us build and strengthen our networks in Ethiopia and start to organize teams from other hospitals to replicate and reproduce the results from the five original pilot hospitals. We felt it was critical to demonstrate to the ministry and others that this programme can be rolled out nationally to strengthen surgical health services and improve the safety of surgery and anaesthesia.

References

[1] Fergusson SJ, Sedgwick DM, Ntakiyiruta G, Ntirenganya F. The Basic Surgical Skills course in sub-Saharan Africa: an observational study of effectiveness. World Journal of Surgery. 2017 Oct 20:1-7.

Report on RCSEd Global Surgery Foundation Grant

Improving Access to Safe Surgery at Gahini Hospital, Rwanda – Creation of Surgical High Dependency Area & Surgical Ward improvements October 2020

Location: Gahini District Hospital, Kayonza District, Eastern Rwanda

Date of Submission: 27th August 2019

Grant Received: £4000

Organisation Information

Name of Organisation: Gahini District Hospital

Address: BP75, Rwamagana, Rwanda

Applicant: Mr Stephen Bennett, MBChB, MD, FRCSEd, MFSTEd

Position in Organisation: Consultant General Surgeon

Telephone Number: +250 781 888015

Email address: s.p.bennett@icloud.com

Project Overview - The need for an improved surgical ward environment

In August 2019, Gahini Hospital was a small rural District Hospital in Eastern Rwanda, with one Ex-pat General Surgeon, and one Ex-pat Anaesthesiologist, operating on

80-90 general surgical patients each month, with a 25 bed Surgical Ward to look after patients.

Several barriers to accessing safe surgery were identified including:

1. An old ward building with poor facilities
2. No separation of male and female patients
3. Separation of nurses office from patient areas
4. No beds for higher-dependency patients
5. Poor availability of Oxygen
6. Poor environment with regard to infection control

The aim of the project was to improve the surgical ward environment to provide safe post-operative care, reduce infection risk, facilitate patient dignity, and have the ability to look after slightly sicker patients.

Progress Towards Completion

Building work started very soon after receiving the RCSEd Global Surgery Foundation Grant and was mostly complete by the end of December.

This broadly followed the plan submitted in August 2019:

1. Full height internal walls were removed to create a more open ward environment. This allows for much better staff awareness of patients than was possible previously when patients were often shut away behind closed doors.
2. A new Nurses Station was created in the middle of the Ward. This allows for much better observation of patients and awareness of potential problems.
3. The ward has been separated into Male & Female Sides, with an extra room for Burns patients. The previous mixing of different gendered patients has been mostly stopped, leading to much improved patient dignity.
4. The floor has been covered with Ceramic floor tiles, which has instantly made for a cleaner ward environment, as the daily cleaning regime is now much more effective.
5. Improvements in lighting, window mesh covering, light-coloured wall paint, and new curtains throughout have made further improvements in patient safety.
6. The opportunity was also taken to add hand-washing sinks in the main ward and treatment room areas, to further enhance infection control.

The Nurses Station and Office facilities have worked as planned, with a new desk, two new networked laptop computers, and a great location in the middle of the refurbished ward all contributing to easier nursing care of patients.

The High Dependency Care area was designated, and equipment ordered. Unfortunately at this point travel restrictions with China due to Chinese society lockdown for Sars-CoV-2 infection started to cause problems, and our new oxygen concentrator, patient monitors, and wall mounting accessories took a couple of months to arrive in Rwanda. We managed to process these through customs in the middle of March 2020, but then Covid-19 hit Europe, and Steve & Catriona Bennett were repatriated to the UK for six months, only returning in September 2020.

Since then the High Dependency area has been equipped and started receiving patients almost immediately. The first to benefit from a dedicated bed with oxygen and continuous monitoring was a one-year-old girl who underwent nephrectomy for a large renal tumour. She had signs of a possible respiratory infection, but the risks of delaying surgery were thought to outweigh the possible risks of anaesthesia. It was very reassuring for the nurses to be able to see her oxygen saturations displayed on a monitor in direct view from the Nurses Station, and she made an excellent recovery from surgery, being discharged four days later.

In the same week, a 35 yr old woman underwent laparotomy for a ruptured ectopic pregnancy, and a 29 yr old woman had drainage of a large post-pregnancy pelvic abscess – both were able to be looked after with much more observation and care than would previously have been possible.

Report on RCSEd Global Surgery Foundation Grant Continued...

Over the last six weeks, since returning from the UK, upwards of 120 patients have received General Surgical operations, and only one patient suffered the complication of a surgical wound infection – an infection that was not unexpected given the infective nature of their operation. We hope that this trend will continue, and a clear reduction in post-operative infection rates will result.

Unexpected Developments

Just as the work on this project started, Gahini Hospital found further benefits to its improved Surgical facilities in the form of additional staff. We have been delighted to be joined by two full-time Rwandan Orthopaedic Surgeons, and Gahini Hospital is now the designated Orthopaedic Referral Centre for the Eastern Province of Rwanda. This came about due to the presence of the new Orthopaedic Operating Theatres, and the now-widespread knowledge that General Surgery was well established at the hospital.

We have refurbished an additional old ward to be the Orthopaedic Ward, and in addition to the 80+ General Surgery operations carried out each month, there are now about 100 orthopaedic operations. Additional non-medical anaesthetists have been recruited, and these have had further training from Dr Catriona Bennett which is enabling safe surgery to be carried out on children as young as one year old, and even younger under Dr Catriona's direct care.

At about the same time, the Surgery department received pre-intern doctors for the first time, and in August 2020, in recognition of the medical work being done at the hospital, we have now been allocated intern doctors throughout the hospital. It is exciting that the facilities and medical care carried out are now facilitating the training of the next generation of doctors, who will hopefully be able to disseminate their knowledge around the country when they move on.

Despite Stephen & Catriona Bennett being in the UK for six months, the RCSEd Global Fund Grant was able to continue to benefit Surgical patients as these facilities were overseen by the Rwandan Specialist surgeons, and junior doctors even with the absence of General Surgery. Having safe and hygienic facilities were in fact even more beneficial to patients from the East of Rwanda, as many of these came to Gahini instead of to the tertiary centre in Kigali due to the restrictions on travel associated with Rwanda's response to the global pandemic.

Next Steps

There are a few minor amendments to the buildings that still need to be made, but now at the end of October 2020 we are delighted to have a much improved ward environment and a high-dependency care area in operation. Over the next few months, we expect to run training in critical care for the Surgical nurses and junior doctors to enable them to make the

best use of the facilities and maximise the benefit to patients.

There is a reasonable expectation that over the coming year a Rwandan Anaesthesiologist and a Rwandan General Surgeon will be appointed to join Gahini Hospital, in addition to the Rwandan Orthopaedic Surgeons who are already here. This should improve further the access of patients requiring safe surgical care from the rural areas of the East of Rwanda, and gain further progress towards the goals of the Lancet Commission on Global Surgery.

Conclusions

Despite the disruptions of the last year causing delays to the implementation of our Improving Access to Safe Surgery project, I am delighted to report the progress made, and to indicate how the project is already benefiting patients. Gahini Hospital and the people of the wider region of Eastern Rwanda would like to thank the Royal College of Surgeons Global Fund for supporting the hospital's development of Surgical Facilities, and trust that as a result we can continue to provide increasingly safe surgical services to our local population over the coming years.

Drs Steve & Catriona Bennett at Gahini Hospital, Rwanda

A brighter, cleaner, Surgical ward!

Surgical Ward back in use

Building work to open up the Surgical Ward environment

High Dependency area with Monitored beds and oxygen concentrator. (The second monitor has been temporarily borrowed by Maternity Theatre Recovery while the hospital sources replacement accessories for their own monitor.)

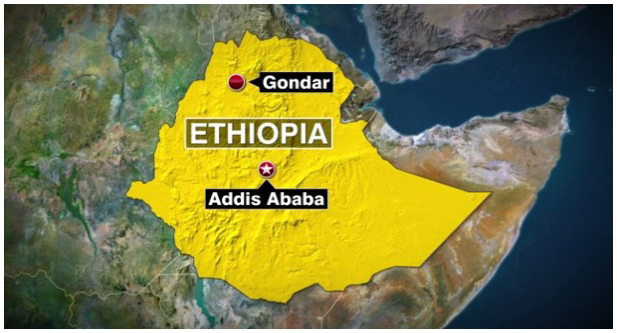
Report on RCSEd Global Surgery Foundation Grant Continued...

Leicester Gondar Orthopaedic Partnership

Final Report

Introduction and Project Aims

In the 1990's Leicester University established a link with Gondar University to promote healthcare delivery and education in Gondar, one of the larger Ethiopian cities situated in the Amhara region in northwest Ethiopia. The city itself has a population c.300,000 but the hospital serves a catchment area of c.5 million i.e. similar to the East Midlands region of England.



In 2014 an Orthopaedic trainee from Leicester, Laurence Wicks, undertook an attachment to the surgical unit in Gondar. It became very apparent that the Orthopaedic facilities and staffing were minimal with an operating theatre built in the 1930's during the Italian occupation of Ethiopia and a single Orthopaedic surgeon with very limited expertise and very basic equipment.

The following year Laurence Wicks returned to Gondar accompanied by two Consultants from Leicester, Alwyn Abraham and Chris Kershaw as well as a plaster technician, Dean Birch. While there they were approached by the senior doctors in the hospital and were asked for help in establishing a modern trauma service in Gondar. The hospital was commited to refurbishing the old operated block and giving one of the Theatres specifically for Orthopaedic Trauma. They had neither the equipment nor clinical expertise to progress the service.

On returning to the UK the group approached Richard Power, a fellow Orthopaedic Consultant but also President Elect of the Rotary Club of Leicester to see whether Rotary could raise the funds to purchase all the equipment necessary to have a fully functioning Trauma facility. (See appendix 1).

Richard Power visited Ethiopia with Laurence Wicks in 2016 to meet the senior doctors from Gondar to discuss the project. This was followed by a further feasibility visit in March 2017 including this time Tim Beacon, CEO of Medical Aid International, a Social Enterprise dedicated to the provision of medical equipment to the developing world, predominantly in Africa. The estimated cost including OR table, anaesthetic machine, power tools, internal and external fixation instrumentation with one years supply of implants, a portable xray machine, a field sterilization unit and sundry items was estimated at c. $200,000. Some of the equipment was new purchase, some donated, some ex-demonstration or pre-owned and refurbished. All shipping and import costs were also included.

It was at this point that the Leicester Gondar Orthopaedic Partnership was formed with the specific aim of establishing a 21st century Orthopaedic Trauma service in Gondar capable of carrying out

up-to-date internal and external fixation of fractures. This would include the creation of a surgical team of Orthoapedically trained Consultants, supporting trainees and dedicated Orthoapedic nursing staff. The overall project was set up in two phases: Phase I to refurbish the Operating Theatre and provide the equipment and Phase II to carry out staff training and assist ongoing service development.

The Rotary Club of Leicester agreed to raise the $200,000 to purchase the equipment through Medical Aid International. This was supported by a Rotary Foundation Global Grant. Gondar University Hospital committed to the building refurbishment and the hospital agreed to work with the Orthopaedic Training scheme at the Black Lion Hospital in Addis Ababa to recruit 3-4 trained surgeons and subsequently trainees.

The Orthopaedic Department at the University Hospitals of Leicester NHS Trust agreed to support the training through bilateral team visits.
Funding to support this needed to be raised separately through the established Leicester Gondar Link charity, Hale Action Leicester for Ethiopia. A major contribution to support this was received from the Global Surgery Foundation at the Royal College of Surgeons of Edinburgh.

Report on RCSEd Global Surgery Foundation Grant Continued...

Phase I

Fund-raising

Personal Donations	£40,000
Club Fundraising Events	£15,000
Individual Fundraising	£25,000
Trust Donations	£5,000
Other Rotary Club Contributions Leicester De Montfort and Guimaraes	£10,625
Rotary District Contributions D1070, D1130, D1970	£10,125
Rotary Foundation World Fund	£52,500

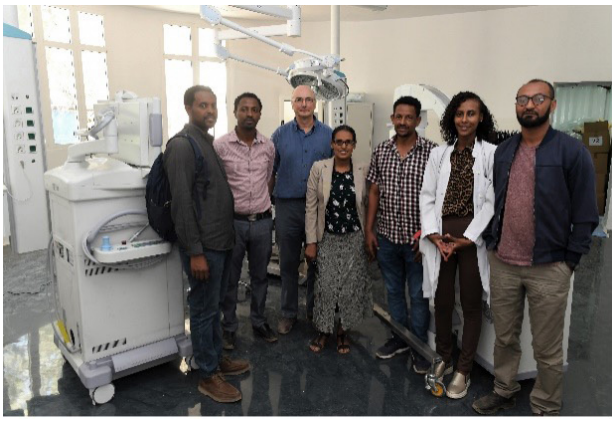
The proposed timeline for this part of the project was for the funding to be raised during the Rotary Year 2017/18 whilst at the same time Gondar University Hospital carried out the refurbishment with a view to setting up the new Operating Theatre in early 2019. The fund-raising was completed on schedule in mid 2018.

Equipment assembly, transport and commissioning

All the equipment was assembled at the Medical Aid International depot in Bedfordshire. Having received assurances that the building works were approaching completion the container containing all the equipment was dispatched and arrived in Gondar in April 2019.

Unfortunately contractual and financial difficulties between the University Hospital and the building contractors resulted in the building refurbishment coming to a halt until early 2020. In the intervening period the container remained undisturbed on a concrete plinth alongside the Operating Theatre building.

In March 2020 Richard Power, Tim Beacon and Theatre Sister Sarah Shawkat travelled to Gondar to unpack and set up the equipment. At this point the building works, although approaching completion, were still subject to significant dust producing activity. It was therefore decided to unpack and assemble all the equipment and replace it in storage pending full completion of the works and a scheduled training visit combined with official opening in July 2020.



At this point two major events intervened. The first was the emergence of the Covid 19 pandemic which prohibited any travel to Ethiopia. The second event was the developing conflict between the Ethiopian Federal Government and Tigrayan Peoples Liberation Front. The Amhara region borders on to the Tigray region and as Gondar is the nearest major referring hospital to the border many casualties were arriving in Gondar.

Report on RCSEd Global Surgery Foundation Grant Continued...

As the building work was by this time complete it was agreed that the local team could start using all the equipment even though the Operating Theatre hadn't been formally opened.

In the three weeks November 7th through to November 28th 2020 126 major orthopaedic procedures were performed.

Phase II

Training and support

The primary objective of the Leicester Gondar Orthopaedic Partnership is to provide a sustainable improvement in Trauma care in Gondar University Hospital. Therefore simply providing the equipment without ongoing training and support would result in no improvement in service and with most of the equipment lying redundant.

A fund was therefore set up within Health Action Leicester for Ethiopia to support bilateral training visits. This was pump-primed by a grant of $10,000 (£7,582) from the Royal College of Surgeons of Edinburgh.

This was augmented by £7,300 from the Rotary Club of Leicester (excess funds raised) and £3,707.66 from the AO Alliance. A further £4,634.22 was raised through individual fund-raising.

Improving Access to Safe Surgery at Gahini Hospital, Rwanda – Creation of Surgical High Dependency Area & Surgical Ward improvements October 2020

Location: Gahini District Hospital, Kayonza District, Eastern Rwanda

Date of Submission: 27th August 2019

Grant Received: £4000

Background

Haiti has a significant burden of traumatic injuries due to the increased use of motorcycles and public transport vehicles. The mortality and morbidity rates associated with these injuries are high and continue to rise. The need for better trauma care delivery across Haiti, is crucial for the survival of trauma patients. Development of trauma systems could reduce trauma- related preventable mortality and minimize morbidity.

Initial Project Design

Initial Aims

The original design of the project focused on two aims:

1. To identify the Preventable Death Rates (PDR) due to Trauma in Northern Haiti
2. To reduce the Preventable Death Rate through implementation of an essential aspects of a trauma system model: clinical trauma education

Initial Objectives

1. To establish the PDR in each of the three main hospitals in Northern Haiti over the last 12 months pre-intervention
2. To implement Primary Trauma Care training for surgical and emergency medicine residents and remote trauma care givers – nurses in rural areas.
3. To measure the effects of Primary Trauma Care training in all three centres – using prospective measure of PDR over 12 months

We conducted the initial epidemiological baselining, a retrospective 12 month analysis of traumatic injury presentations to the emergency department at Hôpital

Global Surgery Foundation Report

Convention Baptiste d'Haïti (HCBH) between March 2018 and February 2019. The in-hospital death rate revealed a much lower rate than anticipated - less than 1%. The decision was therefore made to identify pre-hospital mortality data. The study team collaborated with Stop Accident, the Haitian Civil Society that collects data on prehospital accidents and fatalities based on satellite reporting sites. These satellite points are specific road/highway intersects across Haiti, known for frequent road traffic accidents. Stop Accident receives information from locals at these satellite points, who provide daily reports on accidents and fatalities. Based on the method of reporting/data collection, we anticipated the proportion to be an underrepresentation of the true mortality rate. We retrospectively analyzed nine months of this pre-hospital data, from January to September 2019 and found the pre-hospital mortality rate was 15%. See Figure 1.

15% prehospital mortality
stop Accident Civil Society
Jan - Sept 2019
2990 serious accidents
6350 victims

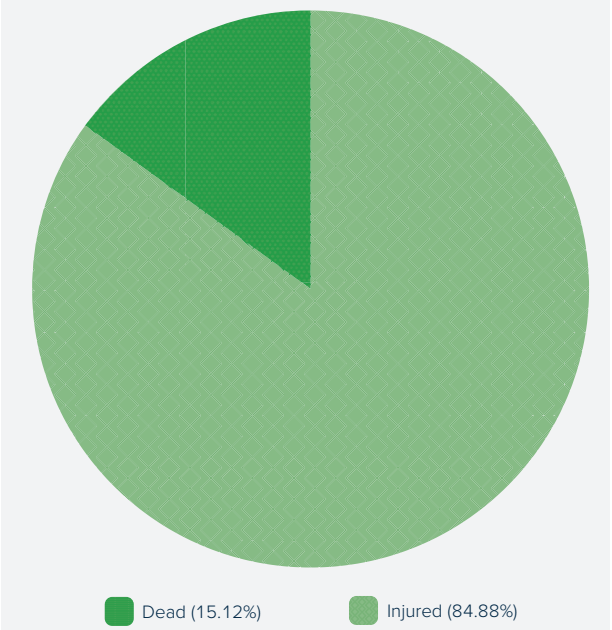


Figure 1: Prehospital Mortality and Injury Rates

Acknowledging the disparity between the pre-hospital mortality and in-hospital mortality rates, we modified the project to focus on improving in-hospital trauma morbidity rather than mortality.

Project Modifications

Over the past 16 months (September 2019 – January 2021), travel to Haiti has been prohibited. For the first six months this was due to political unrest and US travel risk Level 4 enforcement. In the latter 10 months COVID has prevented all travel.

Despite these unanticipated delays, we have utilized the time to conduct:

1. Methodology refinement: following the initial modification of the primary outcome, we formulated a more detailed implementation science/ quality improvement methodology that would lead to sustainable change
2. Epidemiology data analysis
3. Build partnerships

The following 20 pages of this report provide the project study design, epidemiology results and academic outputs.

Modified Research Questions

1. To what extent were the trauma system components adopted in all four facilities and what were the barriers and facilitators?
2. Was the intervention associated with improvements in in-hospital acute trauma care quality indicators in a resource-limited setting and was implementation effectiveness achieved?

Modified Aims

To determine the impact of a trauma care intervention package on trauma care quality indicators and trauma patient outcomes through utilizing quality improvement and implementation science methods.

Modified Objectives

1. To retrospectively assess the pattern of traumatic injuries presenting at four facilities
2. To conduct cross-sectional baseline trauma care capacity assessments
3. To assess pre-intervention trauma care quality improvement indicators
4. To implement a trauma care package intervention
5. To assess the effectiveness of the intervention

To assess the outcomes and sustainability of the intervention

Impact

Despite the politically instability in Haiti and the COVID-19 pandemic both prohibiting travel and thus the implementation of the training component of this project, we have managed to pivot effectively. The time was used to understand and disseminate the epidemiological variation of traumatic injuries (summarized above), to develop the project methodology, to establish new and build on stronger bidirectional equitable partnerships and commenced mechanisms for integration with national level evaluation programs at the Ministry of Health. Here is the impact summary of these four accomplishments:

6. Dissemination:
   a. Epidemiology and Patterns of Trauma at a Secondary Hospital in Northern Haiti: InciSioN Global Surgery Symposium (IGSS), November 2020
   b. Patterns of Trauma at a Secondary Hospital in Northern Haiti: AcademyHealth Annual Research Meeting August 2020
   c. Orthopedic Trauma in Northern Haiti: A Disease of the Young Male: 15th Annual Surgical Congress February 2020
   d. Patterns of Paediatric Traumatic Injuries at a Hospital in Northern Haiti: Global

Initiative for Children's Surgery IV (GICS IV) January 2020

5. Project Methodology:
   a. Implementation Science and Quality Improvement adaptations
   b. Utility of the Consolidation Framework for Implementation Research

Global Surgery Foundation Report Continued...

c. Utility of the RE-AIM Framework for assessment of sustainability and scale-up.

d. Atlas Initiative – Ariadne Labs

e. Quality Improvement Driver Diagrams and PDSA (Plan-Do-Study-Act) Cycle tools - Institute of Healthcare Improvement (IHI)

6. Partnerships:

a. Association Haitienne de Chirurgie (Haitian Surgical Association)

b. Comité de Trauma (Trauma Committee)

c. Faculté de Médecine et de Pharmacie Université d'Etat d'Haïti (Faculty of

d. Medicine and Pharmacy, State University of Haiti

e. Société Haitienne de Médecine d'Urgence et de Catastrophe (Haitian Society for Disaster and Emergency Medicine)

Project Sustainability

A partnership agreement has been developed with the four Haitian professional organisations listed above. The agreement is for the entire length of the project which is now four years. The primary goal during this time, is to ensure adoption of the principles of trauma care quality improvement independent of external or project resources.

The methods chosen for this study incorporate this 'capacity independence' structure, which we hope will enhance the sustainability factor.

In addition, the project sits within the larger vision to scale up trauma care training in Haiti, involving prehospital and post hospital delivery of care. The sustainability of this project is critical for the next phases of trauma systems development.

Benefits of Global Surgery Foundation Grant

The Global Surgery Foundation grant was one of our first grants awarded. This initial funding afforded us the ability to begin this project and purchase equipment required to conduct the Primary Trauma Care courses. The grant will also contribute to the development of the e- learning platform and data administrators. Without this grant we would not have been able to devise and start this study prior to the heightened political unrest and pandemic. Although political instability significantly limited our time 'on the ground', we have been able to leverage the relationships established and therefore build a more robust study; one that is aligned with the country-led trauma agenda and national health priorities.

Project Infographics

Global Surgery Foundation Report Continued...

My Experience as a UNC-Edinbugh Surgery Resident at Kamuzu Central Hospital, Malawi Linda

Kayange, MB, BS, MCS-ECSA

My journey to becoming a woman in surgery started in my third year of medical school. While I had always wanted to take the surgery path in my career, it was during my internship that I began to think about urology seriously. My urology department experience during my internship at Kamuzu Central Hospital (KCH) was very eye-opening. I was exposed to a wide range of complex procedures. With this newfound interest in urology, I started aligning my career towards pursuing the dream of becoming the first female urologist in Malawi. I attended a urology short course training in India under Indian Technical and Economic Cooperation (ITEC). I was awarded a scholarship by UNC/Edinburgh to study urology under the College of Surgeons of Eastern Central Southern Africa (COSECSA) at KCH. And thus, my journey in urology began.

I reported to KCH in September 2018. I was welcomed by the surgery postgraduate training coordinator, Dr. Mulima, who oriented me to the program. I rotated through the Emergency Department, Orthopedics, General Surgery, and Urology and Neurosurgery for my basic surgical training. There I learned the value of time and efficiency as most of the cases seen there are emergencies. While casualty was more acute care of life-threatening illnesses, general surgery is more of learning from seasoned consultants while performing various surgical procedures. I have gained a lot of insight into many procedures during the three months that I have been there.

Under the UNC-Edinburgh scholarship, I registered and sat for Membership of College of Surgeons exams in 2020, the written part in September, which I passed, and the Orals in December, which I passed. I have since registered for Higher surgical training in Urology under COSECSA and will continue my training at KCH.

I am also enrolled in the Edinburgh surgical sciences qualification (ESSQ) programme developed by the University of Edinburgh and the Royal College of Surgeons of Edinburgh. This Master's programme has been going well.

With UNC, I have been involved in research, and I have published two manuscripts:

1. Akinkuotu AC, Purcell LN, Kayange L, Phillips MR, Hayes-Jordan A, Charles AG. Trends and outcomes following intentional injuries in pediatric patients in a resource-limited setting. Pediatr Surg Int. 2021 Jan 18.
2. Purcell LN, Kayange L, Gallaher J, Varela C, Charles A. The Inter-Relationship Between Employment Status and Interpersonal Violence in Malawi: A Trauma Center Experience. World J Surg. 2020 Sep;44(9):2927-2934

And I am currently working on a project on Ileal Perforations. I also had the opportunity to present my research at the Academic Surgical Congress in Orlando, Florida, in February 2020.

The experience at KCH as a COSECSA urology resident has been great so far. The clinical aspect has broadened my surgical skills while at the same time I have networked with fellow a resident as well as a consultant with whom I will be conducting a research.

The journey has not been all rosy. There have been a number of challenges so far, the biggest being limited resources and the current COVID-19 pandemic.

I look forward to the next 2 years of my residency and the knowledge I will acquire and the challenges I will try to help and solve.

Global Surgery Foundation Report Continued...

My Craniofacial fellowship experience in the UK

Jointly Sponsored by the Royal College of Surgeons of Edinburgh and BFIRST

Abdurezak Alil Mohammed MD, FCSECSA Plastic and Reconstructive Surgery

My name is Abdurezak Ali Mohammed and I am a consultant in the ALERT hospital, Addis Ababa, Ethiopia. I was delighted to be awarded the first ever joint RCSEd/ BFIRST Overseas Fellowship award in 2018. For this 6- week fellowship, I was based at the John Radcliffe hospital, Oxford University Hospital NHS Trust which is one of the four craniofacial units in the UK from March 12 to April 20, 2018. My supervising consultants were Mr David Johnson and Mr Steven Wall.

Oxford

My fellowship focused mainly on craniofacial surgery. This is my specialty interest and also a great need in Ethiopia. I was delighted to be able to attach to the Oxford unit because of its wide variety of cases, set-up and complex surgeries.

The unit mainly deals with syndromic and non-syndromic craniosynostosis. In addition, I was able to observe facial palsy cases and other minor craniofacial conditions. In addition to craniofacial surgery, I was also able to learn how the unit manages trauma, breast and hand surgery.

The majority of my fellowship was spent in outpatient clinics, seeing pre and post operative cases and also multi-disciplinary team discussions on craniofacial synostosis cases. I learned the importance of these MDT set ups where experts on craniofacial surgery, neurosurgery, speech and language therapy, psychology, ophthalmology and clinical genetics all come together to provide the best care for the patient. This is something I really hope to see in my country one day.

I also had the privilege to attend surgeries where I observed the entire range of major craniosynostosis cases. The consultants were extremely helpful and patient, and explained each case to me and their modality of treatment including sophisticated surgical methods of total calvarial remodeling.

In addition, they were very kind in hosting me and really looked after me during my stay in Oxford. My accommodation was at the hospital flats at Ivy Lane which was a extremely convenient and allowed me to explore the beautiful city of Oxford.

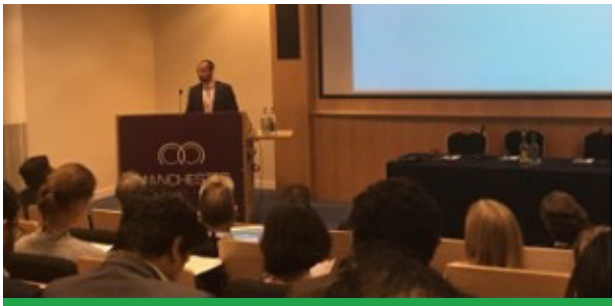
Dinner after a long day surgery with the Oxford craniofacial surgery team members

During my stay, I witnessed two days of heavy snowing at Oxford for the first time, which is never seen in my country. It was a life time experience for me!

A look of outside from my accomodation window on March 18

Other Activities

On 13th April, I was invited to the 2nd Annual BSSH/BFIRST Overseas Conference which was held at Manchester. I had the privilege to give a short presentation about Ethiopia and my fellowship in Oxford. The conference gave me a clearer understanding about works done by BFIRST and BSSH all around the world and I was able to meet different individuals which was excellent for networking.



Oral presentation at BFIRST overseas conference.

Following the event, I travelled to Edinburgh where I had a chance to explore this historic city, and to visit the Royal College of Surgeons, Edinburgh. On Monday, I was privileged to meet the Vice President of the College, Professor Graham Layer and also the Head of Development, Mr Michael Stitt for lunch.

This meeting was special to me because it allowed me to formally thank the College for supporting my fellowship to the UK.

Meeting Professor Graham Layer and Mr Wee Lam in Edinburgh Conclusion

The BFIRST/RCSEd fellowship has been an excellent addition to my training and education. Due to the kindness of my supervisors, the 6-week period has met every expectation I had for the fellowship, which was to strengthen my basic plastic surgical knowledge, learn options of management when treating congenital and acquired craniofacial diseases from the simple to most complex, and different techniques which I can now apply here in Ethiopia.

Upon my return to Ethiopia, I believe my patients will benefit from the skills that I have gained. I will transfer my experience to surgical trainees and colleagues in the hospital that I am working in, and also present my experience to the Plastic Surgical Society of Ethiopia. I will also share my experience to the wider public using available social media tools, mainly on the prevention of plastic surgical diseases, be it congenital or acquired, how to integrate patients into society and avoid stigma. Importantly, I want to create awareness among people in Ethiopia to seek medical attention when they get diseases that were once neglected and at times hidden, due to the perception that their loss of function or disfigurement is a curse and that cannot be treated.

Plastic surgery in Ethiopia is a relatively new specialty, and we currently have a limited number of plastic surgeons of 18, which caters to a population of approximately 104 million. My basic plastic surgical training lacks some of advanced techniques that I have learned in Oxford and that is why I believe this fellowship will help me minimize that gap which will in turn allow me to provide quality care for patients in my country.

I would very much like to thank BFIRST and RCSEd for giving me this fellowship. I hope the support from these two organisations will continue by giving the opportunity to more surgeons from my country for such fellowships and also by visiting our unit in Ethiopia to provide hands-on teaching and training.

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Ophthalmology Major Grants

Grant Holder Name	Roly Megaw
Department(s) in which the Fellowship was held	MRC Human Genetics Unit, University of Edinburgh
Type of Grant (Major or Small);	**Major**
Project Title;	**In vivo genome editing of post-mitotic mammalian photoreceptors as therapeutics for inherited retinal dystrophies.**
Period grant held	
From:	April 2019
To:	April 2020

Lay Summary

'Inherited Retinal Dystrophies (IRDs)' are a leading cause of blindness in children and middle-aged adults. They are caused by 'spelling mistakes' in our genetic DNA. These mistakes are called 'mutations' and result in abnormal function of the gene, causing death of light-sensing cells in our eye. When they die, patients lose vision.

At present, we have no treatment for IRDs.

A recent breakthrough for genetic disease has been the discovery of CRISPR genome editing. This involves 'gene scissors' that can be programmed to cut our DNA with total precision.

By doing this, scientists have shown it is possible to replace misspelt, disease-causing sections of a gene by 'pasting' in the correct, healthy copy in its place. This results in the gene's function being restored.

In theory, 'gene repair' by CRISPR technol

ogy could be performed in the light-sensing cells in the eye, offering a cure for IRDs.

This project sought to determine the potential for CRIPSR technology to edit the light-sensing cells' genome. Using a fluorescent reporter mouse, we were able to show delivery of CRISPR machinery underneath the retina led to gene editing.

It thus demonstrates that CRISPR technology could be a viable treatment strategy for IRDs in the future.

A. Clinical and Scientific Significance of advances made

CRISPR/Cas constructs were successfully packaged into AAV vectors with known tropism for photoreceptors. These AAV2/5 vectors have been successfully used for gene replacement therapy products that are now available on the NHS. The vectors were made for use in the fluorescent, in vivo editing reporter (FIVER) mouse developed by the Mill lab.

The FIVER mouse expresses a tomato protein knocked in at the ubiquitous Rosa26 locus, meaning the membrane of every cell fluoresces red. Three different read outs can be used to measure three different methods of DNA repair following induction of a double stranded break by Cas9 protein at the tomato locus:

- If imperfect non-homologous end joining (NHEJ) is employed due to the absence of an exogenous repair template, expression of a downstream EGFP results instead of tomato, thus shifting the membrane fluorescence from red to green.
- If a repair template is provided that provides homology to the locus, the lesion can be repaired by homology directed repair (HDR), providing a nuclear localisation signal and thus shifting the green fluorescence from the membrane to the nucleus.
- Finally, if a homology independent targeted integration (HITI) cDNA repair template is provided, then NHEJ can be employed to knock in a nuclear-tagged BFP construct to the locus, leading to a shift from membrane red to blue nuclear fluorescence.

Three different AAV2/5 vectors were thus produced:

- One containing the Cas9 nuclease
- One containing the repair construct and guide RNAs
- One containing the HITI cDNA minicircle

The above were mixed at 1x1011 viral genomes at a 1:1:1 ratio and 1.5ul of plasmid mix was injected sub-retinally into P3 mice. Retinas were harvested and petaloid explants were mounted on coverslips and assessed for evidence of gene editing. No editing was identified using spinning disc microscopy.

Following discussions with a fellow academic ophthalmologist, experiments were repeated using a reduced concentration of virus (1x108 vg). Reassessment of petaloid explants using spinning disc microscopy showed evidence of NHEJ in photoreceptors and retinal pigment epithelium, with a shift from membrane red to membrane green (see link for bioRxiv paper below). No evidence of HDR or HITI was observed in the treated retinas.

This work shows that gene editing mammalian photoreceptors is possible. Though progress will need to be made at targeted editing, it is proof-in-principle that this could be achieved.

Further, the work in confirmation that the novel, multispectral fluorescent reporter mouse can be used to track in vivo genome editing for NHEJ, HDR and HITI editing outcomes. In theory, this FIVER reporter system could be rapidly expanded to include novel nucleases to explore efficiencies of editing in vivo, as they are taken forward for preclinical use. One of the major applications for FIVER will be in optimising delivery of genome editing tools.

B. Problems encountered and steps taken to overcome them

Several problems were encountered during this project requiring optimisation. Firstly, initial attempts to assess editing by cryo-embedding and sectioning treated retinas, followed by confocal imaging, identified no editing. Such imaging only manages to capture a limited number of photoreceptors due to the cross-sectional nature of the technique. We therefore switched to a retinal explant technique. Due to the speed that Andor spinning disc microscopes can gather images, it is possible to image z stacks of a large area of retina, with sequential images moving up through the tri laminar retina. As a result, large numbers of photoreceptors could be imaged at once, thus allowing us to identify edited cells.

Secondly, as outlined above, 1 x 1011 viral genomes were initially used to treat the mice. This is the concentration used in several gene therapy clinical trials. This resulted in zero editing. Having discussed this with Stephen Trang at Columbia university, it was discovered this concentration is likely toxic to the retina. As a result, we reduced our viral concentration, to good effect.

C. Collaborations established

Robin Ali / Jim Bainbridge at UCL taught me how to perform murine sub retinal injections. This project helped form what should prove to be a long term collaboration with Dr Pleasnatine Mill at the MRC Human Geentics Unit.

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

Our publication has been deposited on bioRxiv.org (https://www.biorxiv.org/content/10.1101/2020.07.14.200170v1) and is under review at eLife. We have received reviewers' comments back and are carrying out final experiments for resubmission.

I was invited to present this work at a gene therapy symposium organised by the University of Edinburgh in September 2020.

E. Acknowledgements

This work could not have been carried out without the model, help and expertise of Dr Pleasantine Mill, in who's lab this work took place.

Most importantly, this work would not have been possible without the generous support of the Royal Blind and the Royal College of Surgeons (Edinburgh).

Ophthalmology Major Grants Continued...

Grant Holder Name	Prof Parwez Hossain
Department(s) in which the Fellowship was held	Clinical & Experimental Sciences & Ophthalmology, Faculty of Medicine, University of Southampton
Type of Grant (Major or Small);	Major
Project Title;	**Real-Time Pathogen Identification & Antimicrobial Sensitivities in Human Corneal Infection Using Microfluidic Impedance Cytometry**
Period grant held	
From:	01/01/2019
To:	30/05/2020

Lay Summary

Microbial keratitis(MK) is a severe ocular infection of the cornea & presents with rapid loss in vision. Prompt identification of the infective organism helps to reduce ocular damage & preserve vision. In the UK, 40.3 per 100,000 people/year develop MK with 6,000 cases present to hospital per year. The WHO estimates that 2 million individuals/year loose vision.

In clinical practice, delays in identifying the pathogenic organism(s), results in inappropriate antimicrobials therapy or injudicious use of topical steroids.

This approach risks of progression of disease & developing antimicrobial resistance.

'Conventional' microbial testing requires samples taken from the infected site, which then undergo laboratory processing for microbial culture & microscopy.

In this project, with RCSEd funding, we developed a novel technology-Microfluidic Impedance Cytometry (MIC) specifically to test whether this as a viable approach for the real-time detection of ocular bacteria. In our pilot laboratory and clinical studies, our developed technology shows that MIC can provide rapid, instantaneous data.

The developed device uses small amounts of sample, is independent of refrigeration, portable and can work on battery power without the need for microbial culture. When applied to patients with ocular infection, The technology can discriminate patients with the disease. Further grant funding has applied for, to take the technology to a higher level of technology readiness.

A. Clinical and Scientific Significance of advances made

Electronic sensor technologies are a potentially more rapid, highly sensitive, specific, and cost-effective diagnostic method than standard microbial culture techniques. In a partnership between University Hospital Southampton and the University of Southampton, we piloted a new electrical-based technology that can instantly indicate causative agents of non-viral eye infections.

Our proof of concept pilot data shows that with this equipment, we can detect non-viral ocular microbial pathogens immediately. Over the past year, we have performed several experiments to develop and validate a MIC prototype device as a potential diagnostic tool for non-viral MK for use at the point of care. Our machine can do the following:

1. Differentiate between bacterial species such as Staphylococcus and Pseudomonas in cultured samples (Figure 1).
2. In vitro, distinguish between non-bacterial species such as Acanthamoeba and bacteria based on differences in their electrical properties (Figure 2).
3. In patients with bacterial keratitis, we can show the presence of bacterial infection. We can also determine the ‘infective load” and distinguish bacteria from larger particles such as white blood cells. (Figure 4).
4. In patients presenting with non-viral MK, compare their electrical profiles before and after antibiotic treatment (Figures 3 and 4, respectively).

In our pilot studies, tiny sample volumes (~ 50 µl) without the need for pre-labelling were used. The platform does not require microbiology laboratory facilities, is portable, requires no refrigerated reagents and can potentially work on battery power.

The device has also been tested in the setting of an acute frontline emergency service, and we have found that it has the potential in detecting and the treatment response in patients with non-viral microbial keratitis (See attached supplementary figures showing design and data).

With the funding, we have built a new equipment platform which uses a novel application of an electrical technique called Microfluidic Impedance Cytometry (MIC) (Figure1). MIC analyses populations of single cells in a biological fluid specimen(Figures 2&3). The measurement is rapid (<5 minutes) and provides potential diagnostic information immediately. The platform can detect the presence of bacterial infection at the point of care in patients with ocular disease (Figures4). Also, the technology can the ‘infective load”, and with repeat ocular sampling, the data indicate the effect of antibiotic bacterial clearance in the course of the disease (Figures 4&5).

This prototype version was tested in a clinical environment: in our NHS Eye Emergency Department, in patients with microbial keratitis.

Ophthalmology Major Grants Continued...

In our clinical testing, we were also able to show the effectiveness of antibiotic therapy in patients with bacterial keratitis (Figures 4&5).

In laboratory studies, we can show the effectiveness of MIC to differentiate bacterial species, as well as, rarer non-bacterial pathogens such as Acanthamoeba and possibly other pathogens such as fungi, which regularly confound clinical diagnosis and result in unnecessary use of antibiotics.

B. Problems encountered and steps taken to overcome them

In our study, our MIC technology can detect a range of bacterial species like Pseudomonas and the device will aim towards a more targeted treatment and effective use of antimicrobials, minimising the threat of developing antimicrobial resistance.

We can show with our work that MIC has the capability for accurate sensing and rapid detection of ocular infections, allowing more efficient and targeted use of antibiotics at an earlier stage of the clinical pathway, before receiving formal microbiology results. Our clinical and laboratory data suggest that, with further technology development, our platform could be a viable solution at the bedside for ocular infections. However, due to the impact from the COVID-19 pandemic, clinical assessment with the device was limited.
Still, we were able to apply for funding to the NIHR for funding for technology development so that we can have a higher level of technology readiness for this device. We await an outcome.

C. Collaborations established

The study has only been possible via effective collaborations between our Faculties of Medicine and Engineering (University of Southampton), working with an active clinical team involved in providing frontline NHS emergency care (University Hospitals Southampton NHS Trust). Our technology was Our project was approved by the NHS National Research Ethics Committee and Health Research Authority to do a pilot study in such patients.

If our device were developed to such a higher level of technology readiness, then we would have a clinically tested technology for acute infection. This would have profound implications for the application of MIC to other infectious diseases, where similar timely bacterial detection is critical, e.g. septicaemia, meningitis.

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

None at the moment Because of intellectual property (IP) issues, we are unable to publish details of the results so far but plan to do so when the project and the technology are more complete.

Further funding applied to NIHR (antibiotic resistance) and MRC In this project, we plan to develop our device in three years to a much higher level of technology maturity(Technology Readiness Level 7).

Royal Blind and The Royal College of Surgeons of Edinburgh

Figure 1 (see below). Microfluidic Impedance Cytometry (MIC) technology as a novel diagnostic platform for non-viral microbial keratitis (MK). MIC glass chip (upper image) on which infection sample is applied, (detection platform not shown to save space), schematic of system (lower image).

Electronic sensor technologies are a potentially more rapid, highly sensitive, specific, and cost effective diagnostic method than a standard microbial culture techniques[1]. The aim of our proposal is therefore to develop a real-time Microfluidic Impedance Cyctometry (MIC) assay as a high-throughout single-cell analytical method that can instantly distinguish between different non-viral corneal pathogens based on differencea in their size and dielectric properties.

Upper image - This new methodology is non-invasive, only requires a small sample volume (- 50µl) without the need for pre-labelling and it is independent of microbial culture. MIC developing sensor technology consist of two sets of parallel facing electrobes fabricated inside a micofluidic channel. Cells suspended in an electrolyte are driven through the channel by pressure driven flow.

Lower image - An alternating current (AC) field is applied to the top two electrobes. Particles/cells disturb the electric field, which can be detected as a change in electrical impedance - the opposition that a circuit presents to a current in an AC circuit. At low frequencies of AC, the electrical field lines pass around the outside of the cell membrane and so the change in impedance is proportional to the cell size. At higher frequencies, the field lines start to pass through the cell so the impedance gives information on cell membrane capacitance and the cell internal properties.

The platform therefore has the potential to distinguish between populations of microbial pathogens based on differences in their size and dielectric properties[2,3]. Moreoverm MIC technology have the potential to be adapted into a miniaturised, portable device, with a simple user interface which may allow diagnostic assessment at the patient's bedside (point-of-care) without the need for an expert operator and dedicated laboratory space.

References

1. Monzo, J.; Insua, I.; Fernandez-Trillo, F.; Rodriguez, P. Fundamentals, achievements and challenges in the electrochemical sensing of pathogens. Analyst 2015, 140, 7116-7128, doi: 10.1039/c5an01330e.
2. Spencer, D.; Elliot, G.; Morgan H. A sheath-less combined optical and impedance microcytometer. Lab Chip 2014, 14, 3065-3073, doi:10.1039/c4lc00224e.
3. Bernabini, C.; Holmes, D,; Morgan, H. Micro-impedance cytometry for detection and analysis of micron-sized particles and bacteria. Lab Chip 2011, 11, 407-412, doi: 10. 1039/c01c00099j.

Ophthalmology Major Grants Continued...

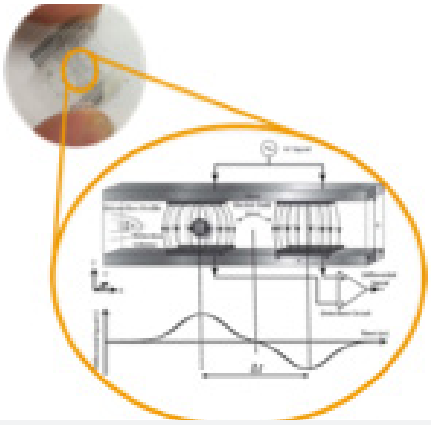


Figure 1

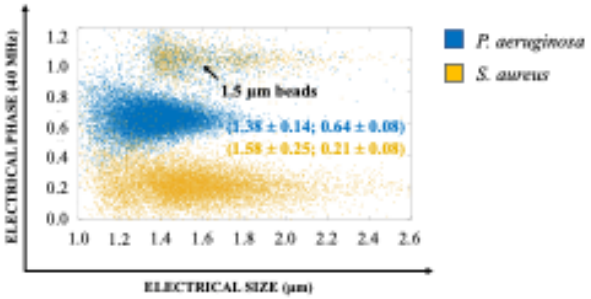


Figure 2. Electrical profile shown by MIC of the common bacterial ocular pathogens.

MIC can identify distinct populations of bacterial ocular pathogens and 1.5µm polystrene microbeads in vitro.

The average electrical phase (40MHz) and average electrical size (µm) for each bacterial population, with their corresponding standard deviation, is detailed for both Pseudomonas aeruginosa (Gram-negative) and Staphylococcus aureus (Gram-positive).

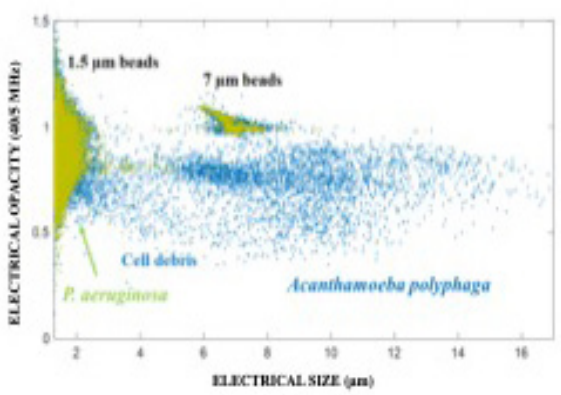


Figure 3. Microfluidic Impedance Cytometry (MIC) can distinguish an amoebic ocular pathogenm Acanthamoeba polyhaga, from Pseudomonas aeruginosa PAO-1 by their electrical profile.

Acanthamoeba polyphaga (blue) and Pseudomonas aeryginosa (green), polystyrene beads of 1.5µm and 7µm were used as regernece of size for normalization.

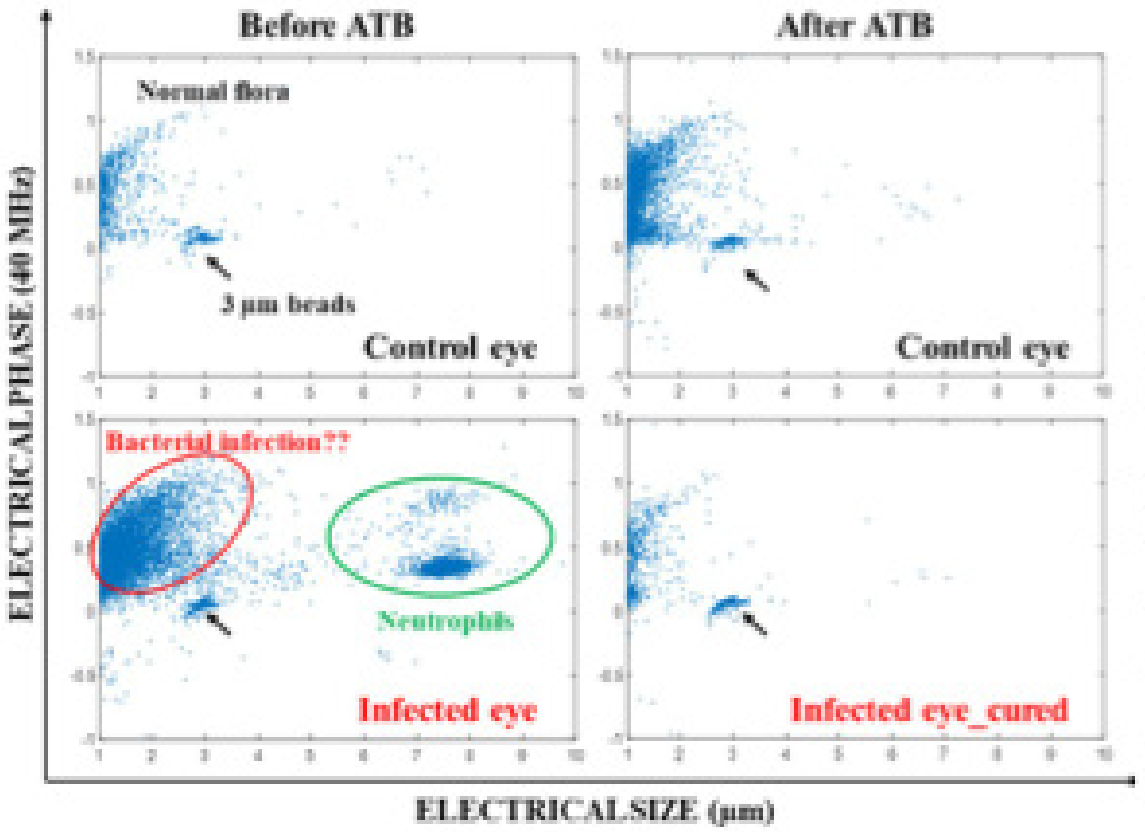


Figure 4. Electrical profile of a clinical sample from a patient diagnosed with Microbial Keratitis (MK) tested on the Microfluidic Impedance Cytometry (MIC) platform.

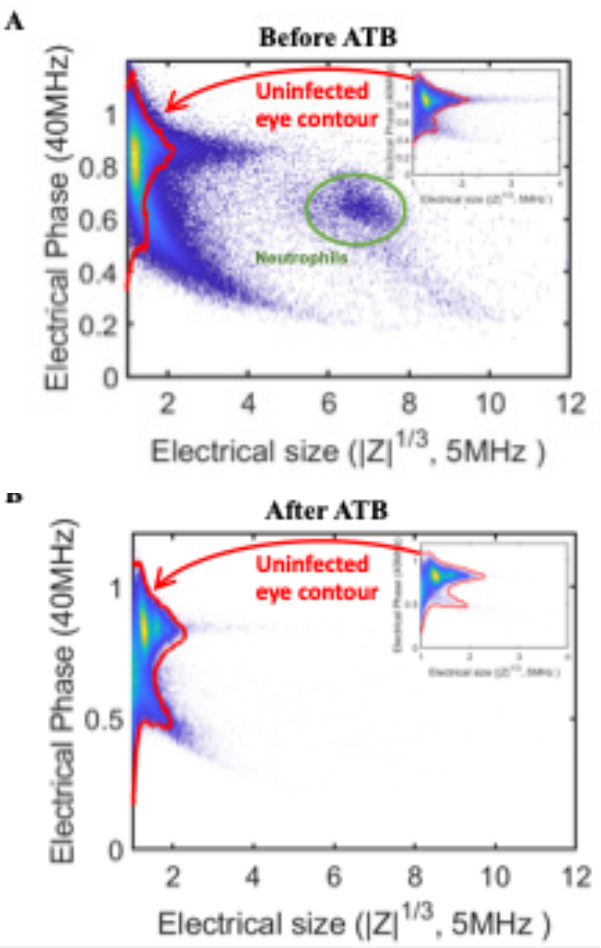
Tear samples were collected from a consenting patient diagnosed with suspected bacterial keratitis (<2mm diameter of corneal infection/infiltration) before and after antibiotic (ATB) treatment.

The contralateral eye (non-infected eye) was used as a control ('healthy').

Polystyrene beads (identified with an arrow) were used as external reference to normalize all scatter plots.

The electrical phase (40 MHz) was measured before and after ATB treatment and compared. Recruitment of neutrophils (inflammation) indicates bacterial infection.

Ophthalmology Major Grants Continued...



▲ Figure 5 (A&B). Test of Microfluidic Impedance cyctometry (MIC) platform showing electrical profile in a clinical sample from a patient diagnosed with severe microbial keratitis (MK) (bacterial).

Tear samples were collected from a consenting patient diagnosed with severe MK (>2mm diameter of corneal infection/ infiltration) before and after antibiotic (ATB) treatment. The non-infected eye was used as a negative control ('healthy').

Polystyrene beads were used as external reference to normalize all scatter plots. The electrical phase (40MHz) was measured before and after ATB treatment and compared.

Figures depict the infected eye scatter plot overlaid with the contour from the non-infected eye scatter plot before (A) and after (B) ATB treatment. All scatter plots are coloured by density. Recruitment of neutrophils (inflammation) is a sign of possible bacterial infection.

E. Acknowledgements

Prof Myron Christoulouides, Professor of Molecular Microbiology, University of Southampton

Prof Hywel Morgan, Professor of Electronic Engineering, University of Southampton

Dr Daniel C Spencer, Lecturer in Electronic Engineering, University of Southampton

Royal Blind and The Royal College of Surgeons of Edinburgh

Grant Holder Name	Prof Shareen Forbes
Department(s) in which the Fellowship was held	Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh
Type of Grant (Major or Small);	Major
Project Title;	**Impact of insulin pump therapy and islet transplantation on progression of diabetic retinopathy in Type 1 diabetes.**
Period grant held	
From:	August 2017
To:	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 (DR).

Treatments for Type 1 diabetes include delivery of insulin via a pump system, or islet transplantation, where islet cells from a donor pancreas are transplanted into a recipient liver. These treatments have been shown to improve diabetes control, which may lead to an improvement in DR in the longer term. However, rapid improvements in glucose control can lead to a short term progression in DR.

This effect has not been fully assessed in those treated with insulin pump therapy or islet transplantation.

We followed subjects who underwent conversion to insulin pump therapy or islet transplantation from conventional treatment with multiple daily injections of insulin. We have serially examined their vision before and after this therapeutic intervention and assessed changes in retinopathy with respect to changes in glucose control.

Ophthalmology Major Grants Continued...

Our study has shown that there is no increase in progression of retinopathy following the introduction of insulin pump therapy or islet transplantation.
In addition, those on insulin pump therapy had reduced retinopathy progression compared to those who continued on multiple daily injections of insulin.

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 were carried out pre and at regular intervals post changes to treatment. Changes in glycaemic control and variability were also assessed using continuous glucose monitoring systems (CGMS) which enable glucose levels to be measured every few minutes over a six day period.

3. Advances made in Retrospective Study

B. Outcomes of Graded Retinopathy Screening

Screening data has been analysed for 324 insulin pump recipients from Edinburgh, and nearly 100 islet transplant recipients from Edinburgh and Edmonton, 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 three year follow up. There was no evidence of early worsening of retinopathy in insulin pump patients in the first year compared with MDI controls. Results show improved retinopathy outcomes over 3 year follow up in pump recipients versus MDI. Glycaemic control, measured by HbA1c, was significantly improved in pump recipients at one year follow up compared to the control group. This finding was not associated with reductions in glycaemic control measured by HbA1c.

High baseline HbA1c was found to be a risk factor for retinopathy progression in MDI participants, though not for pump participants, suggesting the latter may be protective against retinopathy in those with high HbA1c.

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 three year follow 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.

C. 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 tortuosity and fractal dimensions (vessel branching patterns) have been postulated as markers for diabetic retinopathy progression. These parameters were analysed using semi-automated computer software, and images taken prior to changes in diabetes management were compared to those taken one year post commencing insulin pump therapy or islet transplantation, and to the most recent images on record.

Analysis of pump recipients showed reduced vessel width and fractal dimension over time. Increases in vessel width and fractal dimensions have been shown to be associated with increased risk of DR progression, therefore reductions post pump therapy may indicate a reduction in DR risk. 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. These findings support the previous analysis of graded retinopathy outcomes, suggesting that insulin pump therapy and islet transplantation are not associated with an increased risk of early retinopathy progression, and pump therapy may be associated with reduced DR risk.

4. Advances made in Prospective Study

Analysis of 25 participants has been completed: 16 insulin pump recipients, 4 islet transplant recipients and 5 MDI controls. Comparison has been made to previously collected data from non-diabetic healthy controls.

In pump and islet transplant recipients, retinal assessment was 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), ultrawide-field scanning laser ophthalmoscopy (UWF-SLO) and optical coherence tomography angiography (OCT-A). Glycaemic changes were assessed using CGMS and HbA1c. Weight, blood pressure, cholesterol, renal function, liver function, urinary protein and peripheral neuropathy assessment were also carried out.

Ophthalmology Major Grants Continued...

Findings indicate stable retinopathy in the 12 months following change to insulin pump therapy with no significant changes in retinal biomarkers on OCTA, OCT, UWF-SLO and fundus imaging.
When compared to healthy non diabetic controls, those with diabetes were found to have significantly thinner choroid thickness, and higher acircularity index of the foveal avascular zone (FAZ), indicating a more irregular FAZ perimeter. Both choroid thickness and FAZ acircularity index may provide novel retinal markers for monitoring DR progression using non invasive imaging in the future.

D. 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, analysis using propensity score matching was used in addition to and multiple linear regression analyses. 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 was 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. Retrospective retinopathy data from Edmonton was analysed alongside data from Edinburgh which enabled a larger cohort to be assessed.

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.

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 a 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.

E. Collaborations established

Collaborations have been established with the islet transplant team in Edmonton. With the cooperation of the Edmonton islet transplant and ophthalmology teams we have received ethical approval to review existing retinopathy data and obtain further retinopathy data from people who have previously received islet cell transplants.. This will provide one of the largest datasets for retinopathy data in islet transplant recipients to date, with the longest follow up to date.

We have also worked alongside the diabetes research team in NHS Tayside. They have facilitated 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.

Within the University of Edinburgh we have established collaborations with teams from the Centre for Medical Informatics at the Usher Institute, who have facilitated advanced image analysis of OCTA retinal images from our diabetes cohort to identify novel retinal imaging markers.

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

Continuous Subcutaneous Insulin Infusion Therapy Is Associated With Reduced Retinopathy Progression Compared With Multiple Daily Injections of Insulin But Is Not Associated With A Reduction In HbA1c. LJ Reid, F. Gibb, H. Colhoun, S. Wild, M. Strachan, K. Madill, B. Dhillon, S. Forbes. Original article submitted to Diabetololgia 2020

Effects of Islet Transplantation on Long Term Microvascular and Macrovascular Complications in Type 1 Diabetes. LJ Reid, F Baxter, S Forbes. Review submitted to Diabetes Care 2020

Stable retinopathy post islet transplantation compared to continuous subcutaneous insulin infusion and multiple daily injections of insulin. LJ Reid, A Lam, B Dhillon, K Duncan, C Ibbotson, A Sutherland, J Casey, A Koh, C Rudinsky, M Tennant, A Malcolm, AMJ Shapiro, P Senior, S Forbes. Original article in preparation for American Journal of Transplantation 2020

-A framework for revealing retinal biomarkers in Optical Coherence Tomography Angiography (OCTA). Ylenia Giarratano, Alisa Pavel, Jie Lian, Rik Sarkar, Dan Pugh, Tariq Farrah, Neeraj Dhaun, Laura Reid, Shareen Forbes, Tom MacGillivray, Baljean Dhillon, Miguel O. Bernabeu. Oral presentation at SINAPSE 2020 Annual Scientific Meeting

A framework for the discovery of retinal biomarkers in Optical Coherence Tomography Angiography (OCTA).

Ylenia Giarratano, Alisa Pavel, Jie Lian, Rayna Andreeva, Alessandro Fontanella, Rik Sarkar, Laura J Reid, Shareen Forbes, Dan Pugh, Tariq E. Farrah, Neeraj Dhaun, Baljean Dhillon, Tom MacGillivray, and

Miguel O. Bernabeu. Oral presentation at 7th MICCAI Workshop On Ophthalmic Medical Image Analysis 2020

Reduced Progression Of Diabetic Retinopathy In Type 1 Diabetes Over Three Years With Clinical Islet Transplantation Or Continuous Subcutaneous Insulin Infusion Compared With Multiple Daily Insulin Injections. LJ Reid, A Lam, B Dhillon, K Duncan, C Ibbotson, A Sutherland, J Casey, A Koh, C Rudinsky, M Tennant, A Malcolm, AMJ Shapiro, P Senior, S Forbes. Oral Presentation at 17th World Congress of International Pancreas and Islet Transplant Association 2019

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

G. Acknowledgements

Royal College of Surgeons, Edinburgh

Royal Blind

Islet Transplant Unit, NHS Lothian

Diabetes Departments, NHS Lothian and NHS Tayside

Ophthalmology Department, NHS Lothian

Scottish Diabetes Research Network

Islet Transplant Department, University of Alberta, Edmonton

Grant Holder Name	Professor Robert E MacLaren
Department(s) in which the Fellowship was held	Nuffield Laboratory of Ophthalmology, University of Oxford
Type of Grant (Major or Small)	Major
Project Title	Developing CRISPR delivery strategies for the treatment of inherited retinal diseases
Period grant held	
From:	1 October 2020
To:	30 April 2022

Lay Summary

The retina is the light-sensitive area in the eye that allows us to see. Most incurable forms of blindness are caused by faulty genes in retinal cells that eventually lead to their dysfunction and death. Gene therapy is a technique that uses modified viruses called adeno-associated viral (AAV) vectors to carry healthy copies of the affected gene back into cells to help them to function normally again.

Some genes are too large to fit into AAV vectors and so a new approach, gene editing, has been developed in which AAV vectors carry a special molecular tool into the retinal cells to repair the damaged area of the original genes.

However, current gene editing techniques require several hundred bespoke AAV vectors to be designed to treat all possible damaged areas (known as mutations) associated with any particular gene.

In this project, we successfully tested a novel approach that used a single gene editing construct in combination with a guide molecule that was customised to target a single type of mutation.

The success of this project will further the development of universal gene editing therapies for treatment of currently incurable forms of blindness and, in particular, promote their future evaluation in clinical trials.

Ophthalmology Major Grants Continued...

We remain extremely grateful to the Royal College of Surgeons of Edinburgh and Royal Blind for their 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 adeno- associated viral (AAV) vector technology developed in previous College-funded research projects, Nightstar Therapeutics (now owned by Biogen) launched a first-in-human 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.

More recently, in 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. Further evaluation of the gene therapy will be conducted in two forthcoming Phase 2 clinical trials.

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.

A. 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.
- A Cas9 endonuclease that cuts the target DNA sequence at the points directed by the gRNA.
- 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). For S. pyogenes, the standard PAM is NGG.

However, current applications of the CRISPR-Cas9 systems are limited to specific DNA mutations. Whereas gene replacement or supplementation strategies using AAV vectors to deliver the entire coding sequence of a therapeutic gene in target cells can be applied to patients having different mutations in the same gene, gene editing strategies using CRISPR- Cas9 systems are limited to a specific genetic mutation and are therefore considered less broad in application.

For example, >150 mutations have been identified in the RHO gene (where these mutations cause autosomal dominant retinitis pigmentosa) and >600 mutations in the ABCA4 gene (where these mutations cause autosomal recessive macular degeneration). Hence, several hundred bespoke CRISPR-Cas9 systems would potentially need to be designed to treat all possible mutations associated with any particular genetic disorder. Clearly, this is not a viable approach.

Our research project proposed the development of a versatile gene editing therapy, combining delivery of a single universal Cas9 system (to be delivered by AAV) that can be applied to all patients, in conjunction with separate administration of a synthetic gRNA that has been customised for a single type of mutation. Delivery of synthetic gRNA to the retina is likely to be well tolerated given the recent results of a clinical trial (ClinicalTrials.gov NCT03140969) demonstrating the safety and efficacy of intravitreal delivery of RNA anti- sense oligonucleotides to the human eye.

Specific objectives of the current project

The efficacy of our novel approach has been evaluated in this project by assessing the editing/knockdown of green fluorescent protein (GFP) expression in an established HEK293- EGFP cell line. Cas9 constructs (S. pyogenes and S. aureus variants) were co-transfected with validated GFP gene-specific gRNA sequences that were synthetically prepared.
The project comprised the following three primary objectives:

1. Initial assessments to determine the optimal transfection conditions and modification options of synthetic gRNA.

Ophthalmology Major Grants Continued...

2. Degree of GFP gene editing/ knockdown in HEK293-EGFP cells following intracellular delivery of SpCas9/SaCas9 and GFP gene-specific gRNA sequences.
3. Proof-of-principle gRNA delivery to the retina by intravitreal injection.

Results obtained

In vitro assessments

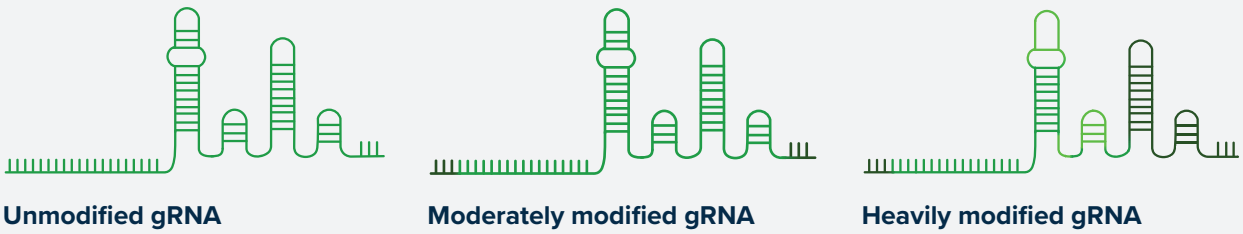
Given the common usage of SpCas9, proof-of-principle experiments were initially conducted with SpCas9-expressing plasmid co-transfected with synthetic gRNA molecules. A previously validated gRNA sequence targeting EGFP was used to generate synthetic gRNAs containing different modifications (**Figure 1A**).

A dose range of unmodified and moderately modified synthetic gRNA molecules were co- transfected with SpCas9 plasmid and knockdown of EGFP fluorescence and on-target editing were assessed.
These outcomes were compared to cells co-transfected with the SpCas9 plasmid and the standard gRNA plasmid (**Figure 1B-D**). Modified gRNA at all doses provided greater knockdown of EGFP fluorescence and associated DNA editing compared to equivalent treatment with unmodified gRNA. Doses of 250ng and above caused a reduction in editing and fluorescence knockdown, likely due to toxicity. 31-125ng of modified gRNA provided equivalent editing/knockdown outcomes to co-transfection with 125ng of gRNA plasmid.

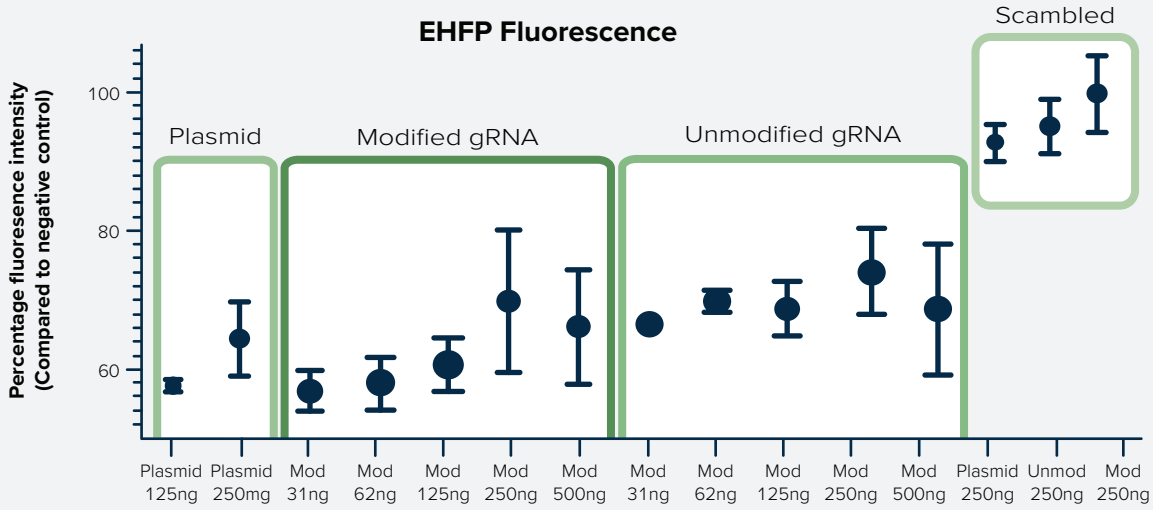
Despite the success with unmodified gRNA, modified gRNA provided significantly better editing outcomes. Transfection of scrambled gRNA forms provided no editing, as expected. Changes in EGFP expression were also evident by western blot assessment (**Figure 1E&F**).
A further synthetic gRNA form, being heavily modified, was also assessed and performed equivalently to the modified EGFP targeting gRNA (**Figure 1G**).

Three SaCas9 gRNAs targeting EGFP were then tested, achieving a range of editing of 6- 15% (**Figure 2A**). EGFP targeting in the reporter HEK cell line is less efficient when assessing SaCas9 editing compared to SpCas9 editing but these data indicated synthetic gRNAs are also viable for interaction with SaCas9, with editing levels similar to those achieved with previous plasmid transfections performed in our lab.

Further gRNAs were assessed that were Cas-targeting. One long-term aim of this project is to provide Cas9 by AAV injection followed by intravitreal injection of targeting gRNA. Once the desired on-target edit is made, a Cas9-targeting gRNA could then be delivered by intravitreal injection to switch off Cas9 activity. For SaCas9, two gRNAs were assessed and both achieved knockdown of SaCas9 protein detected by western blot compared to scrambled gRNA-treated samples (**Figure 2B**).


Unmodified gRNA
Moderately modified gRNA
Heavily modified gRNA

A


EHFP Fluorescence
Percentage fluoresence intensity (Compared to negative control)
100
80
60
Plasmid
Modified gRNA
Unmodified gRNA
Scambled
Plasmid 125ng
Plasmid 250mg
Mod 31ng
Mod 62ng
Mod 125ng
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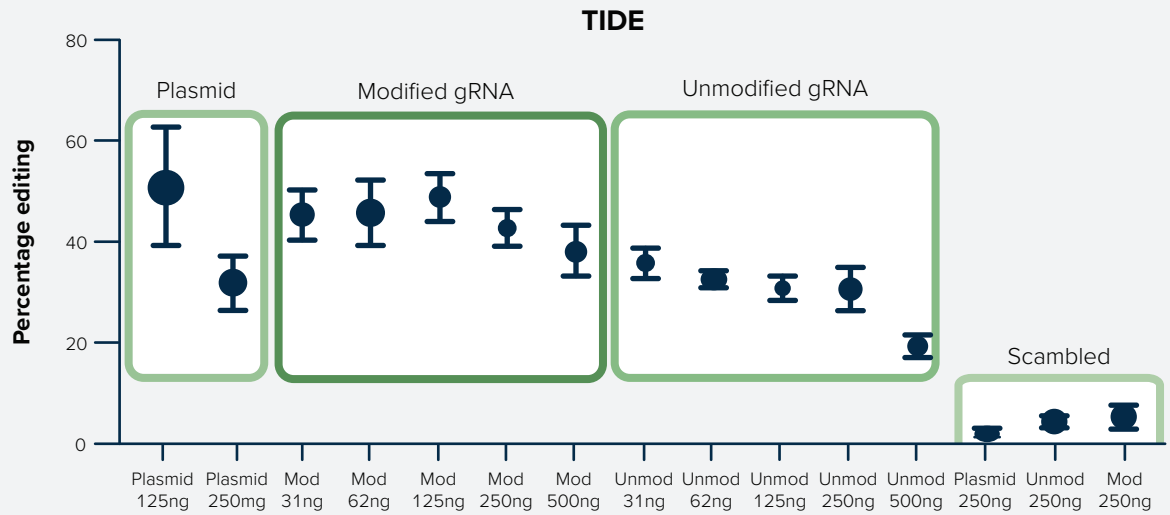
B


TIDE
Percentage editing
80
60
40
20
0
Plasmid
Modified gRNA
Unmodified gRNA
Scambled
Plasmid 125ng
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Mod 62ng
Mod 125ng
Mod 250ng
Mod 500ng
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C

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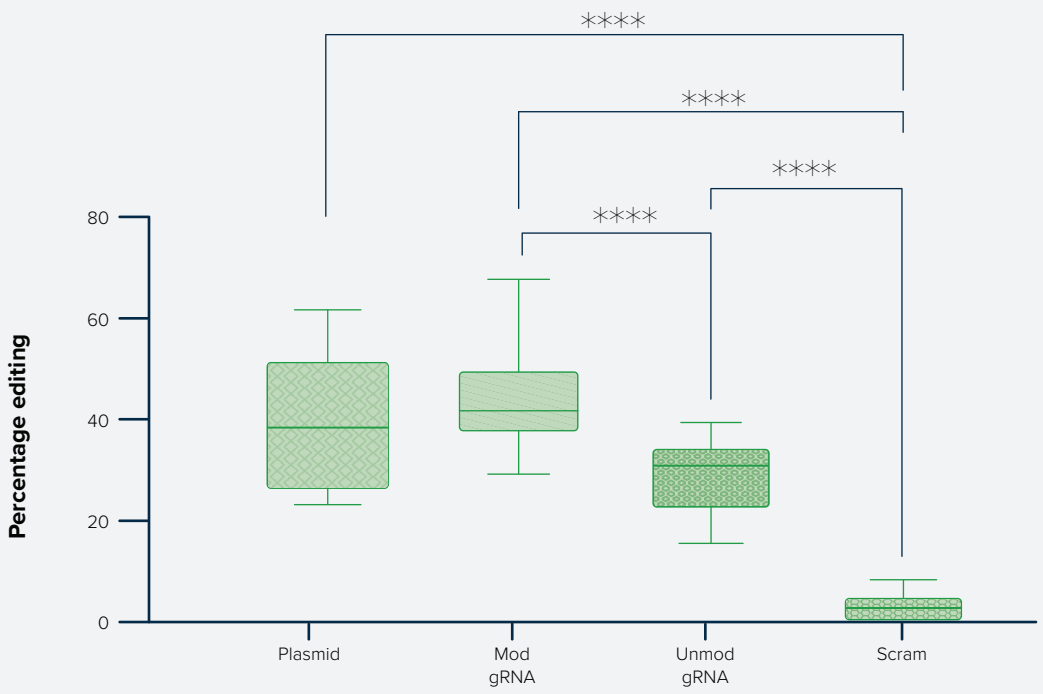
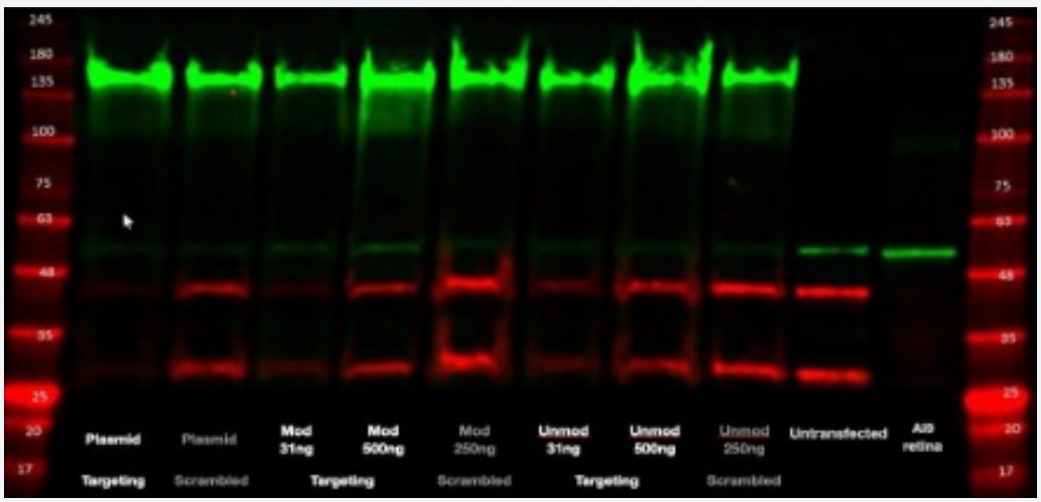


D

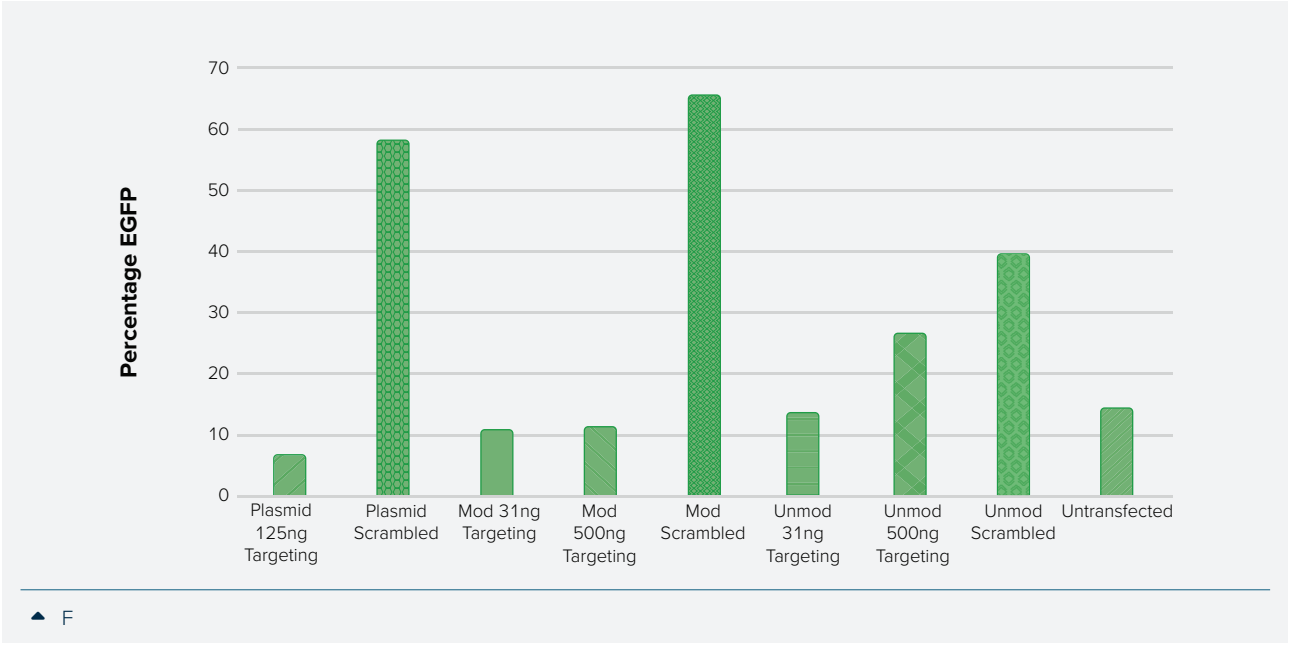


SPACAS9, 168kDa

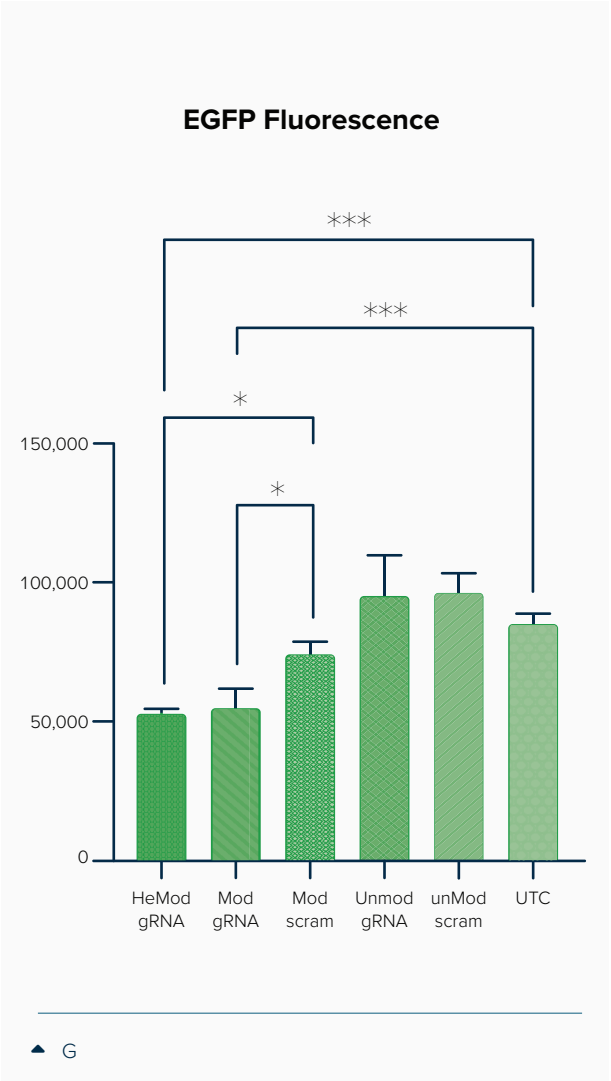
Alpha-tubulin, 50kDa

EGFP, 29kDa

E



F

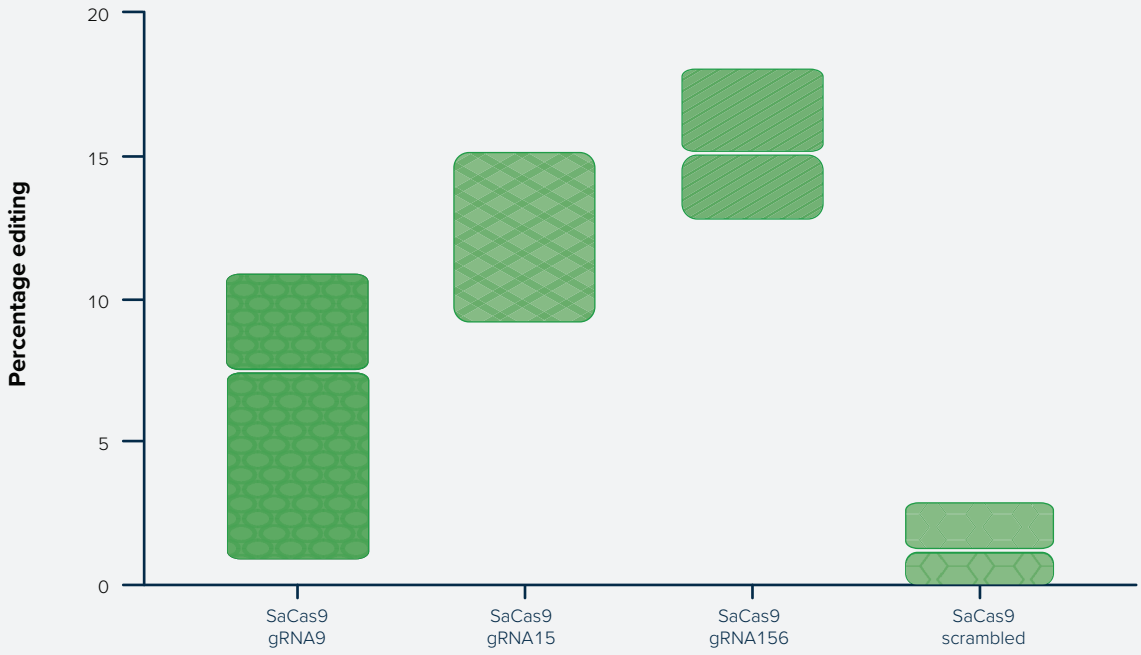


G

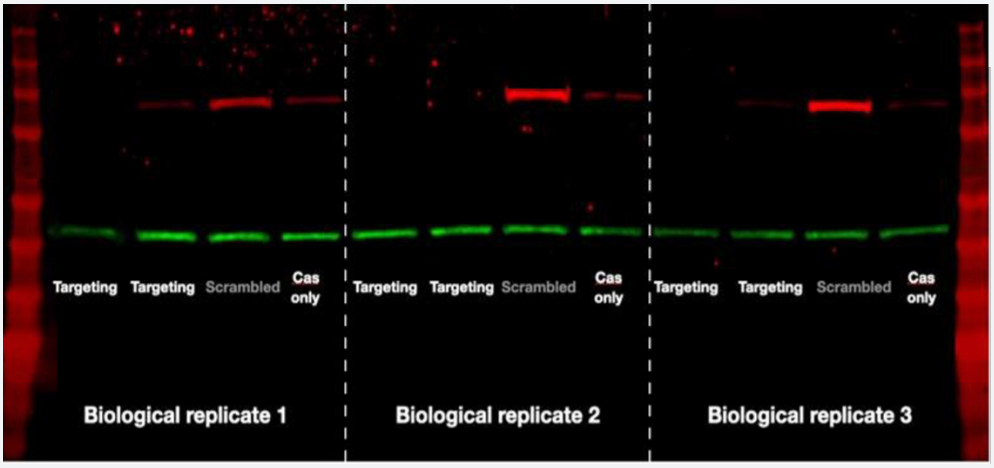
For SpCas9, three Cas-targeting gRNAs were tested and again, reduced levels of SpCas9 protein were detected by western blot compared to scrambled gRNA-treated samples
(**Figure 2C**).

Figure 1. In vitro assessments confirmed synthetic gRNAs can interact with SpCas9 to effect genome editing. **A**) Synthetic gRNAs were assessed with different degrees of modification. **B**) Different doses of unmodified and moderately modified GFP-targeting gRNA produced a 25-40% knockdown in GFP fluorescence 48 hours post- treatment that corresponded to on-target genome editing (TIDE analysis, **C**). **D**) Pooled data indicated modified gRNAs effected more genome editing than equivalent unmodified gRNAs. **E**, **F**) Western blot assessments identified strong levels of SpCas9 expression with reduced detection of EGFP in samples that received GFP- targeting gRNA. **G**) Co-transfection of SpCas9 plasmid with heavily modified gRNAs produced similar knockdown of EGFP fluorescence as achieved from moderately modified gRNA in vitro.

Ophthalmology Major Grants Continued...



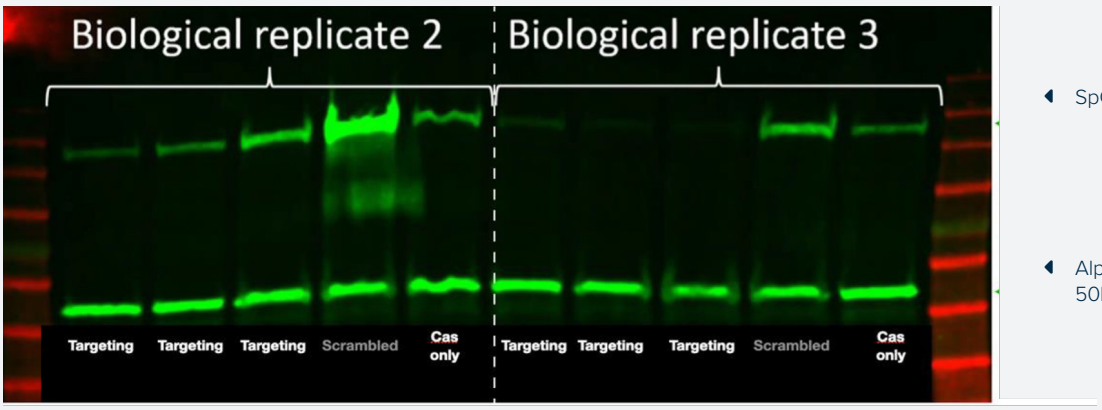
▲ A



◀ SaCas9, 124kDa

◀ Alpha-tubulin, 50kDa

▲ B



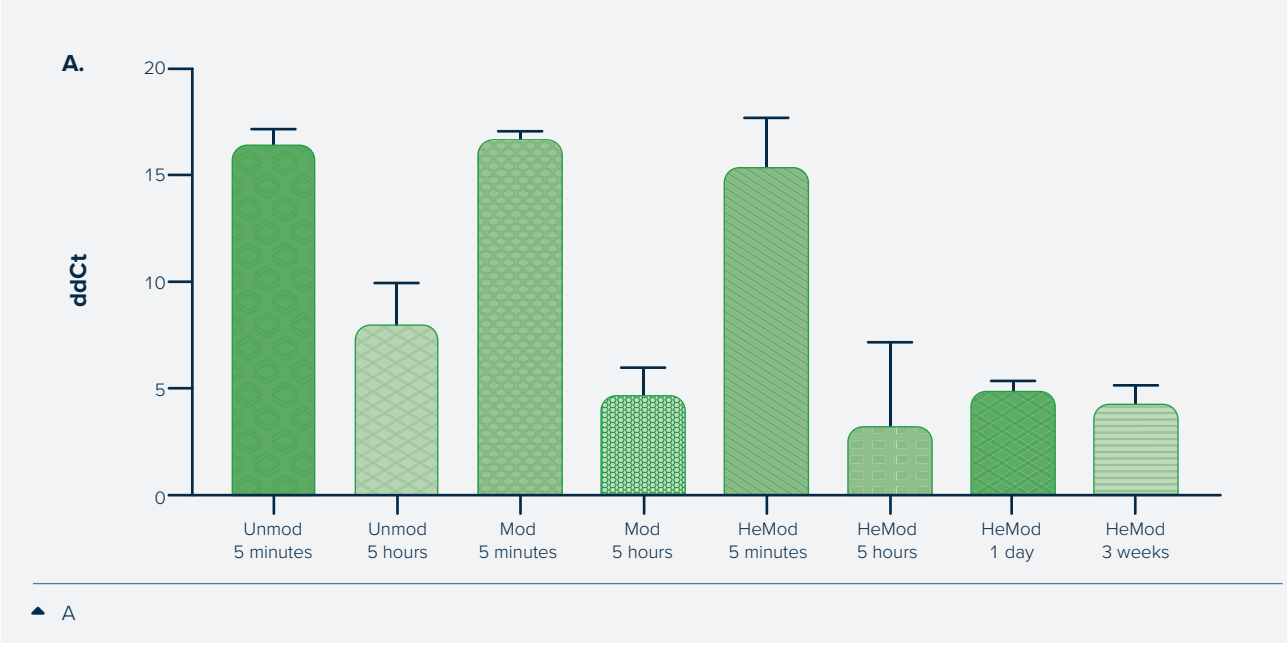
C

In vivo assessments

Before proceeding to AAV production, it was considered critical to confirm the synthetic gRNA forms could be injected in vivo and survive in the retina post-injection. Our research team has a mouse model that endogenously expresses SpCas9, therefore pilot studies of intravitreal gRNA delivery were performed using the SpCas9 synthetic gRNAs validated in vitro. Unmodified, moderately modified and heavily modified versions of the same gRNA were injected at the maximum dose possible. Initially, preparations of gRNA were provided at 10µg per eye. Eyes were harvested at different time points post-injection: at 5 minutes, whole eye RNA extractions indicated similar levels of gRNA for each variant; at 5 hours, surviving gRNA levels had reduced for all eyes but no significant differences were detected between the variants. For the heavily modified gRNA, further time points of 1 day and 3 weeks post- injection indicated that surviving gRNA levels stabilised after 5 hours (**Figure 3A**).

Following further optimisation of the intravitreal injection technique, a maximum dose of 20µg gRNA per eye was achieved. As the ultimate goal is to confirm gRNA presence in the retina, neural retinae were harvested at 1 week post-injection and gRNAs were clearly detected in all samples with no significant differences between the modification types at this time point (**Figure 3B**). Studies are ongoing to determine the survival time of the different modified variants.

Ophthalmology Major Grants Continued...



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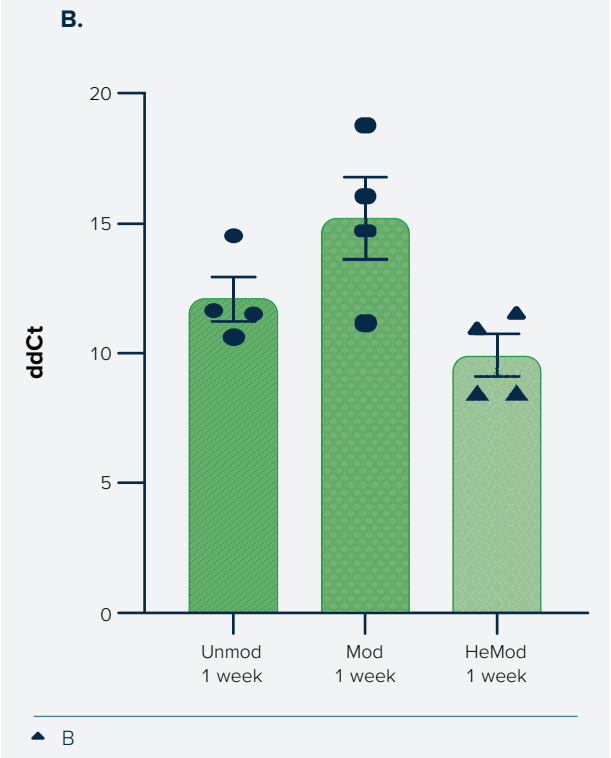


B

Figure 3. Pilot assessments of intravitreal injection of synthetic gRNA in vivo. **A**) Eyes received 10µg of gRNA, qPCR assessment detected surviving gRNA in whole eyes at different time points post-injection. **B**) Eyes received 20µg of gRNA, qPCR assessment detected surviving gRNA in the neural retina one week post-injection.

Summary

This project was designed to understand the feasibility of the proposed gRNA delivery method. Our studies have confirmed that synthetic gRNAs for both SpCas9 and SaCas9 can be delivered to cells and interact with Cas9 protein elements to effect on-target DNA-editing.

In vivo studies have further confirmed that synthetic gRNA can be provided by intravitreal injection and survive in the neural retina post-injection. The project has therefore provided encouraging data confirming that an AAV-Cas subretinal injection followed by intravitreal gRNA delivery is a viable approach worth pursuing further.

B. Problems encountered and steps taken to overcome them

In addition to operational disruptions caused by the COVID-19 lockdowns, the progress of the project was further delayed following an unexpected staff vacancy, which required Dr Michelle McClements's urgent management of several research projects until the staff vacancy could be filled. Fortunately, the College kindly agreed for the end date of this project to be deferred to the end of April 2022, which has enabled the project to reach a successful conclusion.

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 clinical trial led by Professor Robert MacLaren at the Oxford Eye Hospital.
The first patient was treated in January 2019. The significance of this gene therapy trial was underlined by Boris Johnson in his first Prime Minister's speech on 24 July 2019, when he stated: "It is here in Britain that we are using gene therapy, for the first time, to treat the most common form of blindness."

This Phase 1/2 clinical trial (FOCUS: NCT03846193) now includes additional patients who will be treated using the proprietary OrbitTM subretinal delivery system (SDS), which has been designed and optimised with the clinical advice and assistance of Professor Robert MacLaren for precise microinjection into the subretinal space. The Orbit SDS uses a flexible cannula designed to contour the globe and access the back of the eye, targeting a subretinal location in the posterior segment. The procedure enables precise delivery of a specific dosage of infusate to the subretinal space without removing the vitreous body or creating a retinotomy, thus avoiding potential vitrectomy- and retinotomy-related complications.
As the possibility of efflux of vector suspension into the vitreous body is eliminated, the likelihood of inflammation is also greatly reduced. (See surgical video and instructions.)

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.

Ophthalmology Major Grants Continued...

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

Dr Lewis Fry was awarded a DPhil in 2021 by the University of Oxford for his thesis "Development of CRISPR gene therapy for retinal degenerations". Dr Lewis undertook much of the laboratory research in this and previous major ophthalmology grants funded by the Royal College of Surgeons of Edinburgh.

Prizes

Dr Lewis Fry was awarded the 2020 Master's Medal by the Worshipful Company of Spectacle Makers (at a virtual ceremony, due to the current COVID-19 lockdown) for his paper 'Association of Messenger RNA Level With Phenotype in Patients With Choroideremia: Potential Implications for Gene Therapy Dose'.
This paper demonstrates the first genotype-phenotype association in choroideremia and suggests that relatively low expression (less than 1%) of the wild-type levels of mRNA, through treatment with gene therapy, would be sufficient to slow disease progression.

The development of this gene therapy for choroideremia was made possible in preclinical work supported by previous College-funded projects, and the support of the Royal College of Surgeons of Edinburgh was acknowledged in this publication.

Publications

A number of scientific papers acknowledging the support of the Royal College of Surgeons of Edinburgh, including the paper referenced above, have been published during the course of the last year. Their details are as follows:

- McClements ME, Steward H, Atkin W, Goode EA, Gándara C, Chichagova V, **MacLaren RE**. Tropism of AAV Vectors in Photoreceptor-Like Cells of Human iPSC- Derived Retinal Organoids. Transl Vis Sci Technol. 2022;11(4):3. doi: 10.1167/tvst.11.4.3. PMID: 35377942.
- Piotter E, McClements ME, **MacLaren RE**. The Scope of Pathogenic ABCA4 Mutations Targetable by CRISPR DNA Base Editing Systems-A Systematic Review. Front Genet. 2022;12:814131. doi: 10.3389/fgene.2021.814131. PMID: 35154257.
- Fry LE, Patrício MI, Jolly JK, Xue K, **MacLaren RE**. Expression of Rab Prenylation Pathway Genes and Relation to Disease Progression in Choroideremia. Transl Vis Sci Technol. 2021;10(8):12. doi: 10.1167/tvst.10.8.12. PMID: 34254989.

- McClements ME, Butt A, Piotter E, Peddle CF, **MacLaren RE**. An analysis of the Kozak consensus in retinal genes and its relevance to gene therapy. Mol Vis. 2021;27:233-242. PMCID: PMC8116250. PMID: 34012226.
- Fry LE, McClements ME, **MacLaren RE**. Analysis of Pathogenic Variants Correctable With CRISPR Base Editing Among Patients With Recessive Inherited Retinal Degeneration. JAMA Ophthalmol. 2021;139(3):319-328. doi: 10.1001/jamaophthalmol.2020.6418. PMID: 33507217.
- Fry LE, Patrício MI, Williams J, Aylward JW, Hewitt H, Clouston P, Xue K, Barnard AR, **MacLaren RE**. Association of Messenger RNA Level With Phenotype in Patients With Choroideremia: Potential Implications for Gene Therapy Dose. JAMA Ophthalmol. 2020;138(2):128-135. doi: 10.1001/jamaophthalmol.2019.5071. PMID: 31855248.

Further funding

Professor McLaren has been awarded £119,610 by the Macular Society and Retina UK for a jointly-funded research project "Using gene editing to stop progression of Stargardt disease" that builds on earlier work funded by the Royal College of Surgeons of Edinburgh.

E. Acknowledgements

We would like to thank the Royal College of Surgeons of Edinburgh and Royal Blind 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.

Small Pump Priming Grant

Grant Holder Name	Mr Alexander Laird
Department(s) in which the Fellowship was held	Department of Urology, Western General Hospital. Edinburgh. Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, The University of Edinburgh
Type of Grant/Fellowship;	RCSEd Small Pump Priming Grant (SPPG/19/129)
Project Title;	**Detection of circulating cell free DNA in renal cancer patients using renal cancer-specific DNA methylation and mutation changes**
Period grant held	01/04/2019-01/04/2020

Lay Summary

Kidney cancer is the deadliest cancer of the urinary tract, affecting 3.4% of adults in Scotland with a 17% increase in Scotland over the last 10 years. When kidney cancer is diagnosed, it is confined to the kidney in ¾ of cases, where surgery to remove the tumour can offer the patient cure. Unfortunately, 30-40% of patients who undergo apparently curative surgery develop recurrent or metastatic disease, which is often incurable. There are two significant areas of unmet clinical need. These include early detection of kidney cancer to improve outcomes for patients and predicting which patients will develop recurrent disease to tailor follow-up and offer early intervention.

There is emerging evidence that tumour DNA can be detected in the blood of patients with kidney cancer. We propose that studying mutations and methylation changes in the blood of patients with kidney cancer could lead to the development of a minimally invasive test for the early detection of kidney cancer and/or for predicting which patients will develop disease recurrence after surgery.

This project funding has allowed us to extend our sample collection to ensure we have the numbers required to make clinically meaningful conclusions. We have confirmed the samples collected are of appropriate quality for further study and have profiled the DNA changes in the matched kidney tumours to allow correlation of subsequent results. These initial advances will provide useful initial results to allow further larger grant applications.

A. Clinical and Scientific Significance of advances made

1. Development of the Edinburgh RCC biobank

During this project, we have extended the sample collection of matched tissue and blood from patients with renal cell cancer (RCC) to 203 patients. These patients have blood stored pre-operatively and longitudinally during follow-up.
There is linked clinico-pathological and follow-up data. This resource provides the necessary cohorts for discovery of a RCC specific cell free circulating tumour DNA (ctDNA) profile and test the diagnostic and prognostic significance of this. This data provides an excellent resource to develop and translate this project into the clinic as well as to develop further translational research projects.
Patent recruitment is on-going.

2. Assessment of cfDNA quantity and quality in RCC patients

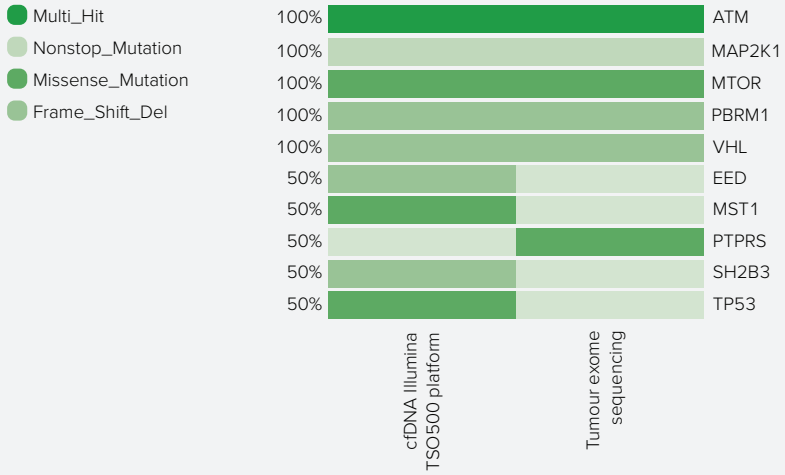
We have collected 20ml of blood from patients at each time point. After enrichment for smaller cfDNA fragment sizes (thus enriching for ctDNA), we have a median extraction yield of 17.95ng (7.89-54.4ng) from 4-5ml of plasma from our first 24 samples tested. This provides sufficient input for down-stream analysis.

3. Mutation and methylation profiling of 20 primary RCC tumour samples and testing of cfDNA Genome wide methylation data using the Illumina EPIC array, and somatic exome mutation data using Agilent SureSelect Human All Exon V7 library preparation kits and sequencing on Illumina HIseqX sequencer, has been generated on paired RCC tumour and buffy coat samples from 20 patients with well annotated clinical diagnostic and follow-up data.

a. Detection of RCC ctDNA using mutation analysis alone

cfDNA isolated from the plasma of three patients was tested using a TS500 assay and compared with tumour exome sequencing. For one patient (patient 42) mutations in VHL, PBRM1, MTOR and MAP2K1 identified within the tumour were also identified within the patient's plasma (figure 1). However, mutations with the highest VAF identified in the tumours of two patients were not detectable in the plasma of these same patients.

Small Pump Priming Grant Continued...



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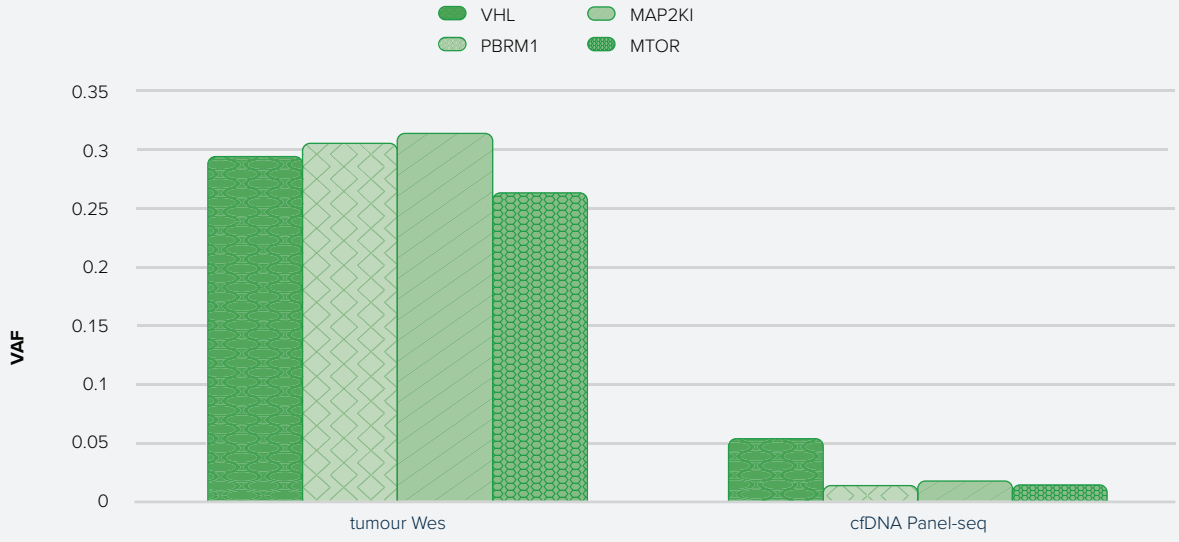


B

Fig 1. Correlation of RCC tumour exome sequencing and cfDNA Illumina TSO 500 analysis for patient 42. A. Oncoplot of mutations detected in cfDNA and matched solid tumour tissue, restricted to targets present on the cfDNA panel. B. Plot of Variable Allele Frequency (VAF) between tumour and cfDNA for four major linked mutations.

The relatively low ctDNA detection using mutation analysis (33%), which is similar to that reported by Bettegowda et al [1] who detected ctDNA in 40% of RCC patients using somatic mutation analysis, confirms the futility of this approach alone to detect ctDNA in RCC patients. The results however do confirm that we are able to isolate good quality cfDNA in patients with RCC and identify ctDNA in the expected proportion of patients.

b. Detection of RCC ctDNA using differentially methylated regions
Recently, the use of renal cancer-specific differentially methylated regions (DMRs) to detect RCC ctDNA in both the plasma and urine of patients with advanced [2] and localised RCC [3] has been reported to have high sensitivity (>95%) and specificity (>85%), which is very encouraging and supports our hypothesis. Our initial plan was to select a panel of informative CpGs and design multiplex barcoded PCR assays for targeted methylation analysis on the Fluidigm Access Array platform followed by Illumina MiSeq sequencing, based on methodology that we developed previously. However, the panel identified and reported by Nuzzo et al [3] consisted of a panel of 300 DMRs and therefore a higher throughput method to allow greater DMR interrogation from the fluidigm assay would be better.
This RCC study was therefore put on hold while alternative methods under separate funding to the Aitman lab were investigated that will achieve the sensitivity required at the low levels of tumour-derived cfDNA that are available in the blood samples collected to date by the grant holder from the RCC patients.
To this end, The Aitman lab, in collaboration with Nonacus, have adapted the Cell3TM Cell-Free DNA Target Enrichment System originally used to detect DNA mutations in cfDNA to detect DNA methylation. The protocol uses 100 bp molecular biotin labelled baits designed to pull down regions of interest containing biomarker CpGs from the extract of patient plasma and urine cfDNA and combines Nonacus library preparation pipeline with New England Biolabs DNA enzymatic conversion protocol followed by illumina MiSeq sequencing. This protocol can allow the detection of up to 10,000 DMRs from each sample and will be used for further study of ctDNA in RCC patients.

3. Dataset identification for in-silico development of cfDNA profile
Publicly available Infinium 450K array methylation data from normal lymphocyte (GSE51057, GSE40699; n=334), normal leucocyte (GSE67393, GSE68456; n=167), whole blood (GSE123914, GSE110554, GSE48472; n=123), normal erythroblast (GSE68456, GSE63409; n=17), normal liver (GSE48472, GSE40699, TCGA-LIHC/CHOL; n=64), normal bladder (TCGA-BLCA; n=37) and RCC profiles (ccRCC: TCGA-KIRK, data from Sato et al; n=560; papillary: TCGA-KIRP; n=291;and chromophobe TCGA-KIRH; n=66) will be used for cfDNA profile development in both blood and urine. This work has now begun with the assistance of a bioinformatician in the Aitman lab and will be the basis for the development of a RCC specific DMR ctDNA profile for early detection or RCC and prognostic assessment.

Small Pump Priming Grant Continued...

References

1. Bettegowda, C. et al. Sci Transl Med. 2014 Feb 19;6(224):224ra24
2. Lasseter et al. Genet Med. 2020 Aug;22(8):1366-1373.
3. Nuzzo et al. Nat Med. 2020 Jul;26(7):1041-1043.

B. Problems encountered and steps taken to overcome them

1. Poor detection of ctDNA using tumour mutation analysis.

The difficulty in detecting ctDNA in the blood of RCC patients may be due to the smaller mutational burden or heterogeneity of mutations within renal tumours. The identification of patient specific VHL mutations within the primary renal tumour using exome sequencing, with the knowledge that VHL is ubiquously mutated throughout the tumour, and testing the matched patient blood was used to overcome these challenges. Despite this the rate of RCC specific ctDNA detection remained at 33% (n=1 of 3), which is similar to that reported by others when non-RCC specific assays are used (Bettegowda et al). As detailed above the focus of future study with be on the detection of RCC specific DMR ctDNA profiles.

2. Development of a robust ctDNA assay.

As detailed above, it became apparent that the proposed fluidigm assay would not be appropriate for large scale interrogation of cfDNA for RCC specific DMRs.

As a result the Aitman Lab have optimised the Nonacus platform for methylated ctDNA detection.

3. COVID pandemic

Like many projects, our research has been affected by the COVID pandemic. During the latter part of this award and over the last 18months patient recruitment was significantly reduced. Both wet lab and bioinformatic capacity has also been significantly reduced.

This did delay our study progression. Our research nurse who was key to sample collection was seconded to clinical practice and has since taken up a new post. Despite this we have now recommenced patient recruitment. The Lab team have made progress on Nonacus assay development and we are in the process of developing our RCC-specific in-silico DMR ctDNA profile to test on samples. We anticipate that this will progress over the next 6 months.

C. Collaborations established

This one year pump-priming award has strengthened the collaboration between the myself and the Aitman laboratory. Together we plan to further investigate the role of plasma and urine methylation changes for the detection of RCC specific ctDNA. This award has provided data for inclusion in a larger scale grant application to the MRC.
As well as the generation of raw data, this award has helped me work more closely with the Aitman Lab with attendance at lab meetings and Journal clubs, furthering my understanding of the study of cfDNA.

More generally, my involvement in the IGMM has helped me network with other researchers and develop other project ideas. This has lead to a RCSEd Pump priming award with Mr James Blackmur and Prof Malcolm Dunlop to study eQTLs in RCC (£9.5K) and an EC Horizon 2020 grant to investigate the role of Artificial Intelligence for the prediction of response to systemic therapies in metastatic RCC (€8.5M).

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

Presentation:

MRC IGMM cfDNA Symposium
January 2020

A., Laird, MJ. Adamowicz, JP. Thomson, TJ. Aitman

Study of cfDNA in Clear cell Renal Cell Carcinoma.

AACR Liquid Biopsy conference 2020.

MJ. Adamowicz, JP. Thomson, SJ. Warlow, U. Patra, H. Thain, S. Marion de Proce, A. Laird and TJ. Aitman. Abstract A02: Detection of circulating cell-free DNA in renal cancer using renal cancer-specific DNA mutations and methylation changes. Clin Cancer Res June 1 2020 26 (11 Supplement) A02-A02; DOI:10.1158/1557-3265.LiqBiop20-A02

Funding application:

MRC Clinical Academic Programme Fellowship.

Application submitted and successful progression to round 3 (final) review.

The detection of methylated cell free tumour DNA in renal cancer patients to aid early detection and determine prognosis. PI: Alexander Laird.

NRS Career Researcher Fellowship. Successful award in March 2021 or 2PA/week to support clinical trial and translational research projects including cfDNA in RCC.

E. Acknowledgements

The work on this project would not have been possible without members of the Aitman Lab including Martyna Adamowicz, John Thomson and Sophie Warlow who have lead sample processing and analysis; Sophie Marion de Proce and Prasun Datta who have provided bioinformatic support; Helen Thain for sample collection and Tim Aitman for academic guidance. My Colleagues, Steve Leung and Edward Main have helped with patient recruitment for sample biobanking. Thanks to RCSEd for funding this project. Assay development has also been supported by funding for the Aitman Lab from CRUK. A special thanks to all the patients for agreeing to be involved in this research project.

Small Pump Priming Grant Continued...

Grant Holder Name	Fungai Dengu
Department(s) in which the Fellowship was held	Nuffield Department of Surgical Sciences, University of Oxford
Type of Grant/Fellowship;	Pump priming grant;
Project Title*;	Immuno-molecular modulation of donor livers during NMP
(*updated with grant extension)	
Period grant held	
From:	April 2019
To:	January 2021

Lay Summary

Increasingly, donor livers can be preserved using a machine that pumps blood with oxygen, medicines and nutrients through it at normal body temperature as opposed to being stored on ice, which can be harmful. Particularly in higher-risk donor organs, which have exaggerated immune responses to the restoration of blood flow to the organ in the recipient after preservation, so called “ischaemia reperfusion injury” or IRI.

Machine perfusion reduces liver damage related to IRI, permits increased preservation times before transplant and allows assessment of the liver before implantation. Crucially, it also provides an opportunity to ‘treat’ the liver with novel therapies or interventions.

Using samples collected from previous clinical trials, we investigated immune responses within the liver during machine perfusion to understand how restoration of blood flow during perfusion affects the liver. We found that similar to what occurs in the recipient, upon restoring blood flow on the device, organs that have

been stored on ice for prolonged periods, develop exaggerated and possibly harmful immune responses during perfusion. These insights allowed us to develop a large animal (pig) model to explore protective interventions for higher risk livers against harmful immune responses that occur after the liver is placed on the device.

A. Clinical and Scientific Significance of advances made

In view of the rapid adoption of novel dynamic organ preservation technologies a deeper understanding of the impact these technologies have on donor organs during preservation is critical if they are to be expanded more broadly. Normothermic machine perfusion (NMP) of the liver has been shown to reduce early graft injury, increase utilisation and prolong preservation, while also providing a platform for assessment of higher risk grafts or extended criteria donor (ECD) organs.

However, when marginal or ECD livers undergo reperfusion during NMP, the associated reperfusion injury can result in poor graft function during NMP, failure to meet functional assessment criteria for transplant and consequent organ discard. Moreover, ECD grafts that do manage to meet functional assessment criteria for proceeding with transplantation during NMP may still develop severe IRI related complications such as early allograft dysfunction, post reperfusion syndrome and acute kidney injury.
The characteristics and mechanistic underpinnings of this “ex situ reperfusion injury”.

(ERI) are poorly understood, both in livers that function poorly during NMP and livers that demonstrate sufficient function to procced to transplantation and go on to develop clinical manifestations of severe IRI.

This project has focused on understanding the molecular and immunological events occurring during NMP and in particular explored the role of cold ischaemia prior to NMP in impacting the events that occur on the device and subsequently in the recipient. We have managed to establish some important molecular features of livers during NMP. Primarily, we have been able to characterise “ex situ reperfusion injury”, which is a similar but distinct entity to in situ (in the recipient) reperfusion injury i.e. traditional allogenic ischaemia reperfusion injury. Ex situ reperfusion with oxygenated blood based perfusate results in a cascade of inflammatory events within the graft involving immune cells, damage associated molecular patterns and inflammatory cytokines that occur during preservation and seem to impact graft function during NMP. This is particularly evident in ECD grafts and following long periods of cold ischaemia prior to NMP. This hold particular significance as the predominant application of this technology is in ECD livers and using a back to base approach, which necessitates a variable period of cold ischaemia, thus potentially exacerbating ex situ reperfusion injury and may explain poor graft function ex situ observed this group of organs that are known to be sensitive to reperfusion insults.

The insights from profiling the molecular and immunological events occurring during NMP have also facilitated the formulation of a number of strategies to intervene on livers during NMP to modulate processes occurring that will affect graft function ex situ and also post-transplant. Furthermore, we have developed a large animal (porcine) model for DCD (ECD) liver NMP, that has allowed us to systematically investigate various interventions during NMP.

Small Pump Priming Grant Continued...

This has led to a proliferation of collaborations and joint projects catalysed by the RCSEd pump priming grant that underpinned the core objectives of the project and ongoing work.

In summary, this project has:

- Characterised immune and molecular events occurring during human NMP (including characterising ex situ reperfusion injury as a distinct entity from traditional (in situ) reperfusion injury,
- Established a large animal model for investigation of DCD NMP,
- Investigated novel approaches to modulating the immune compartment.

B. Problems encountered and steps taken to overcome them

This project has unfortunately encountered a number of problems.

Firstly, the original project plan had to be revised after the sudden (on medical ground) retirement of the key scientific supervisor. This meant that the initial approach to modulation of grafts during NMP using a novel therapeutic developed in his lab had to be abandoned and alternative strategy to modulation of grafts taken. To overcome this issue, we pivoted to gaining a deeper understanding of the system on a molecular level prior to trying to modulate the system.

This allowed us to identify and characterise the features of ex situ reperfusion injury and then focus our efforts on modulating this aspect of liver machine perfusion.

The second major challenge was the COVID 19 pandemic. This resulted in a nine-month lockdown of University research facilities and further 4 months or restricted access to our lab and animal facilities due in large part to staff illness and backlogs. I was also recalled to clinical duties and retuned to full time clinical activity to support the re-deployment efforts within our hospital and the Transplant department. This was more challenging to overcome, but with the support of the RCSEd, my grant was extended and my delayed experiments were able to be performed in 2021.

C. Collaborations established

This project has helped consolidate local collaborations with a number of research groups here in Oxford, strengthened established collaborations and sparked the initiation of new national and international projects.

We have worked closely with Dr Fildes (University of Manchester, Immunology & Perfusion) and now have a strong working collaboration on liver perfusion (previously their group has focused on ex vivo lung and kidney perfusion).

In terms of the modulation of donor livers we have forged a local (Oxford) collaboration with an Extracellular Vesicle (EV) research team and established a project which has received funding. This new project is based on findings from our work and predicated on the model we developed. Similarly, we have formed a new Oxford-Liverpool collaboration for delivery of pharmacological agents to donor livers during NMP, specifically looking at oxidative stress using our extended criteria donor (ECD) donation after circulatory death (DCD) liver model.

Internationally, we have worked with collaborators at the University of Chicago looking at the immune compartment during NMP. This has resulted in a multi-institution NIH grant application with co-PIs Professor John Fung & Professor Peter Friend)

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

This funding has been central to my DPhil(PhD) thesis*, which is due to be submitted in April 2022.

*The work entering my thesis is unpublished and will be written up upon submission of thesis.

Awards

Trinity College Outstanding Academic Performance – Graduate Scholar 2020/21

PUBLICATIONS

2021

Abdominal Multiorgan Procurement from Slaughterhouse Pigs: A Bespoke Model in Organ Donation After Circulatory Death for Ex-Vivo Organ Perfusion compliant with the 3 Rs.

Fungai Dengu, Flavia Neri, Etohan Ogbemudia, Georg Ebeling, Laura Knijff, Kaithlyn Rozenberg, Richard Dumbill, Julien Branchereau, Peter Friend, Rutger Ploeg, James Hunter, - Annals of Translational Medicine Accepted Dec 2021

2020

Dengu F, Abbas SH, Ebeling G, Nasralla D. Normothermic Machine Perfusion (NMP) of the Liver as a Platform for Therapeutic Interventions during Ex-Vivo Liver Preservation: A Review. J Clin Med. 2020;9(4):1046. Published 2020 Apr 7. doi:10.3390/jcm9041046

PMID: 32272760

PRESENTATIONS – NATIONAL & INTERNATIONAL

2021

European Society of Transplantation (ESOT) Biennial Congress 2021, Milan

*Prolonged Static Cold Storage prior to Normothermic Machine Perfusion alters the molecular and proteomic profile of donor livers: insights from 'Back to Base' liver NMP.

F. Dengu, A. Thorne, M. L. Lo Faro, H. Huang, S. Shaheed, M. Kaisar, S. Davis, J. Mulvey, R. Fischer, C. Ceresa, D. Nasralla, A. Santos Delgado, B. Kessler, H. Leuvenink, P. Friend, R. Ploeg [POSTER]

Proteomics profiling of molecular changes during normothermic machine perfusion of the liver.

M. L. Lo Faro, A. Thorne, H. Huang, M. Kaisar, S. Davis, **F. Dengu**, S. Shaheed, J. Mulvey, R. Fischer, D. Nasralla, A. Santos Delgado, B. Kessler, H. Leuvenink, P. Friend, R. Ploeg on behalf of the COPE consortium

Small Pump Priming Grant Continued...

*** Also presented at Nuffield Department of Surgical Sciences Away Day & Abstract published in the JNDS (Journal of Nuffield Department of Surgical Sciences)**

2020

British Society of Transplantation 2020 & American Transplant Congress 2020 (Virtual Abstract)

Abdominal multiorgan retrieval from pigs in a slaughterhouse: a reliable and efficient donation after circulatory death model for ex vivo organ perfusion.

Fungai Dengu, Flavia Neri, George Ebeling, Laura Knijff, Kathlyn Rozemberg, Julien Branchereau, Peter Friend, Rutger Ploeg & James Hunter.

Acknowledgements

I would like to acknowledge all members of the team at the abattoir who wish to remain anonymous. Without their dedicated support and patience, the research work carried out over the course of the project would not have been possible. They allow us to disrupt their busy job for the sake of research and with no direct personal gain for which we are very grateful.

I am extremely grateful for the support I have received from Professor Peter Friend who has been enormously generous with his time. He has been academically stimulating and steadfast in his support for my project and the DPhil more generally. Mr Carlo Ceresa has been a great source of wisdom and support, without which I would not have been able to deliver this project. My co-fellows in the Nuffield Department of Surgical Sciences: Ann Ogbemudia, Hussain Abbas, and Flavia Neri have been fantastic colleagues and I'm eternally grateful for their support.

I also appreciate the efforts of Professor Paul Fairchild and his team (particularly Tim Davies) who have both been valuable contributors, albeit their involvement was curtailed in unfortunate circumstances.

Finally, I'd like to thank Professor Wigmore & the RCSed Team, who have been excellent throughout my interactions.

Grant Holder Name	Miss Esther Platt
Department(s) in which the Fellowship was held	Department of Surgical biotechnology, University College London
Type of Grant/Fellowship;	Small Pump Priming Grant
Project Title*;	Identification of Origin of Neutrophil Gelatinase Associated Lipocalin (NGAL) in Acute Kidney Injury (AKI) following Orthotopic Liver Transplantation
(* updated with grant extension)	
Period grant held	
From:	November 2020
To:	September 2021

Lay Summary

One of the main complications of Orthotopic Liver Transplantation is Acute Kidney Injury. The development and severity of AKI is linked to the severity of liver ischaemia reperfusion (IR) injury. Previous work, performed in a mouse model, identified that liver IR injury and AKI were linked to high circulating serum NGAL. NGAL is a biomarker, that predicts early AKI in a variety of clinical settings. In this study, we sought to identify whether serum NGAL from our mouse model originated from the liver, blood or kidney. We used previously stored liver and kidney specimens.

Quantitative PCR identified no increase in NGAL mRNA expression and immunohistochemical staining (IHC) demonstrated no increase in NGAL staining in either liver or kidney following IR injury and AKI, indicating that neither organ is the primary source of serum NGAL.
IHC did demonstrate that Kupffer Cells and another currently unconfirmed population of hepatic immune cells were positive for NGAL across the experimental groups. Previous work demonstrated early liver infiltration with monocytes following IR injury and we are now investigating whether circulating monocytes might be the primary source of NGAL in response to liver IR injury and AKI.

Small Pump Priming Grant Continued...

A. Clinical and Scientific Significance of advances made

In the literature on liver IR injury, NGAL mRNA is reported to be upregulated in murine liver tissue 4 hours post re-perfusion. Other data suggest that the kidney is the source of NGAL in AKI following systemic injury. NGAL is interesting, both as an early biomarker of AKI and because it has renal effects in both mouse models and in vitro; sometimes reno-protective and in other experimental scenarios, injurious to tubular cells. Little is understood about the mechanism of NGAL in AKI. Additionally, the role of NGAL in the mediation of AKI following liver IR injury is unknown.

Liver IR injury is strongly linked to AKI development in liver transplantation, with clinical studies demonstrating an independent association between severity of liver IR injury and likelihood of AKI development. AKI post liver transplantation increases mortality, contributes to poor graft function, and is associated with development of chronic renal failure, even in patients who initially return to “normal” renal function following the AKI episode.

Given the strong association between liver IR injury and AKI, it is postulated that mediators released by the liver are responsible for renal injury in this setting. However, individual mediators of injury have not been isolated. Because of the close temporal relationship between liver IR injury, AKI and NGAL release, it is thought that NGAL may contribute to the mediation of renal injury in this setting. However, even basic information such as the site of NGAL release in this context is unknown. The purpose of this work was to identify the site of NGAL release.

We used previously collected formalin fixed, paraffin embedded liver and kidney samples from a mouse model of remote ischaemic preconditioning (RIPC), liver IR injury and AKI. 6 biological replicates from 4 experimental groups were used, as detailed in figure 1a. This model demonstrated an association between liver IR injury, AKI and elevated circulating NGAL (figure 1b).

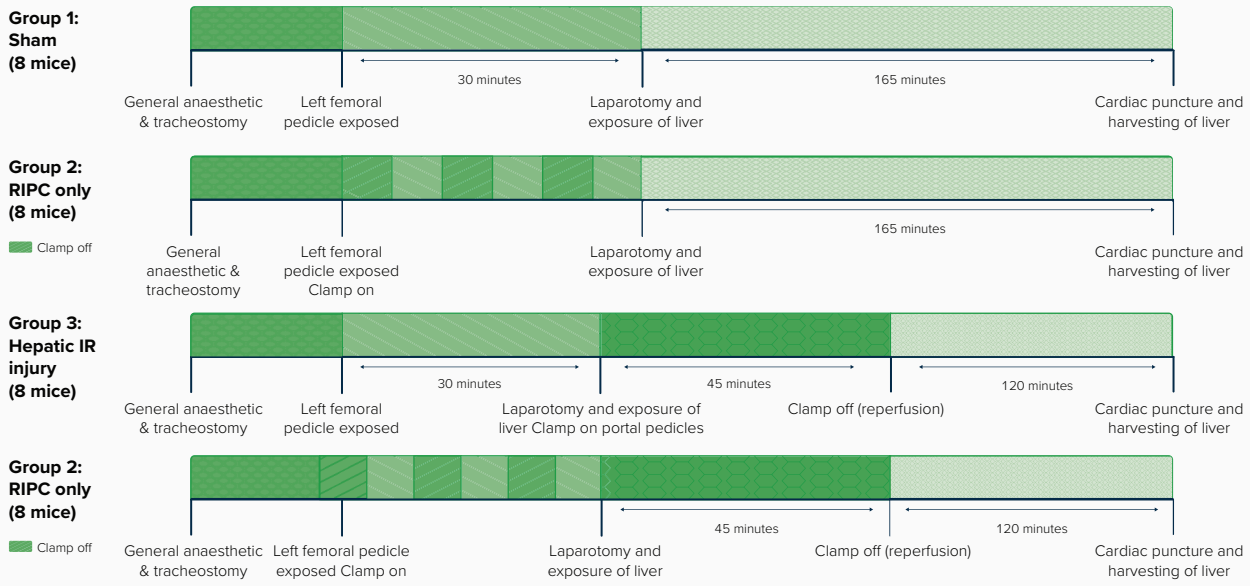


Figure 1a: diagram of the experimental protocol. There were 4 experimental groups. Liver and kidney FFPE samples from 6 biological replicates/group were used in this study. Samples were used for both IHC and qPCR.

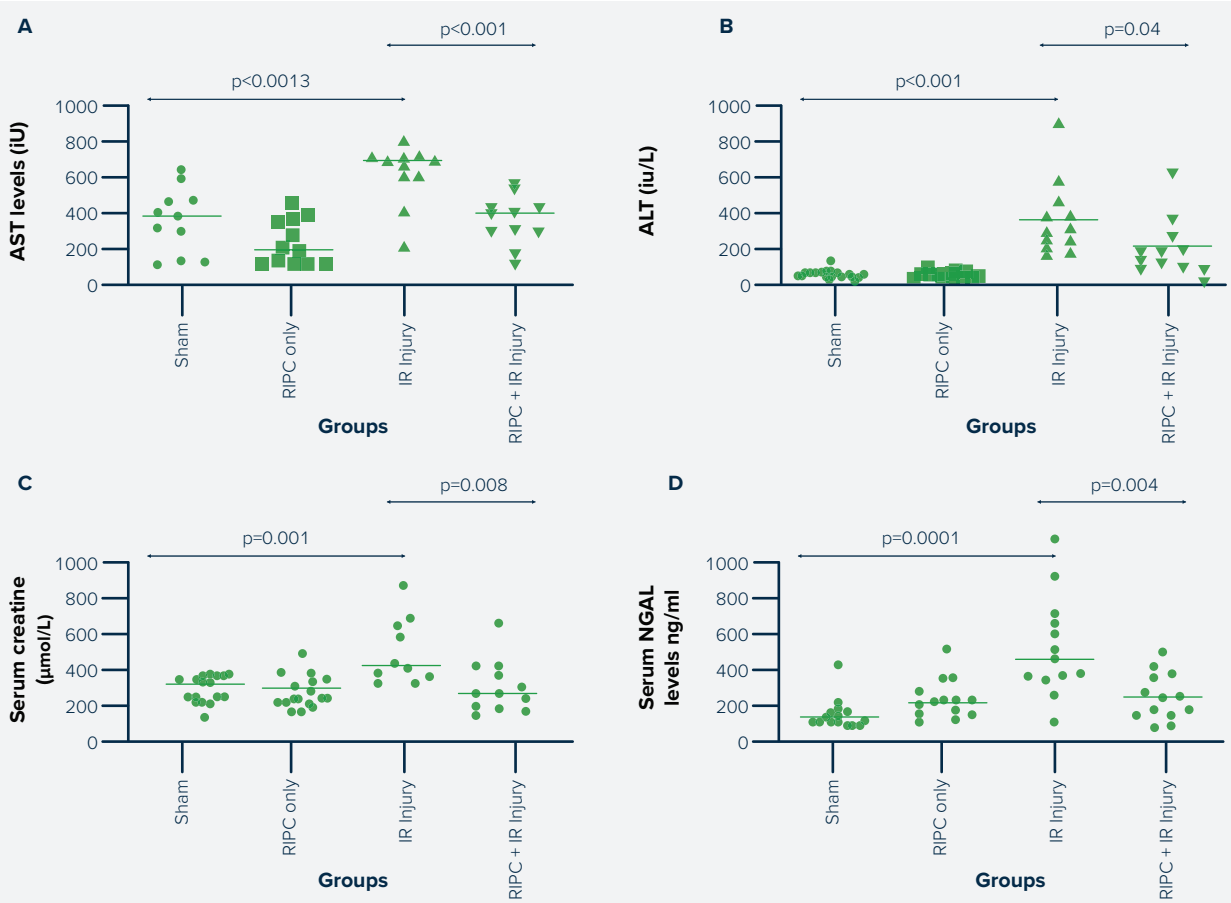


Figure 1b: Previous results from mouse model confirming statistically significant association between liver IR injury (AST/ALT), AKI (creatinine) and serum NGAL seen in liver IR injury group.

Small Pump Priming Grant Continued...

Results

NGAL does not originate from the kidney following early liver IR injury

NGAL staining revealed likely uptake from the tubular filtrate, with granular staining within the apical third of proximal tubular cells as identified in figure 2. There was no difference in either staining intensity or proportion of tubules staining for NGAL between the different murine groups (figure 3). qPCR normalised to GAPDH identified low NGAL expression across the experimental groups, with no increase in NGAL expression in the IR injury group (figure 4).

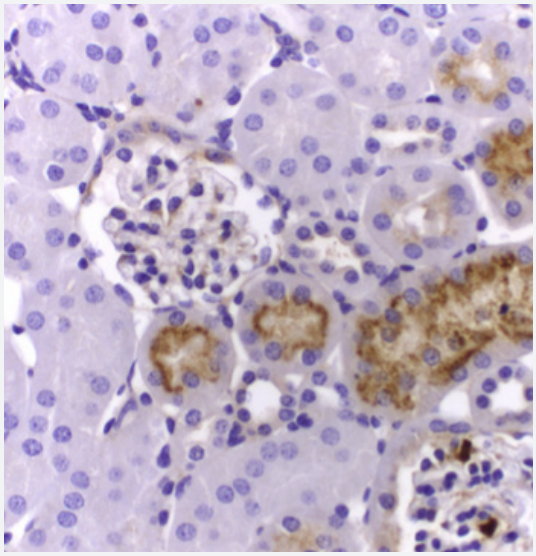


Figure 2: NGAL staining in brown. Staining is granular and concentrated around the apical third of proximal tubular cells, suggestive of uptake from renal filtrate.

Percentage Staining (median)		P Value	Staining Intensity (Scale 0-3)
Sham	10		Hint-1
RIPC	20	P=0.60	Hint-3
IR Injury RIPC +IR	<10	P=0.47	0-3
Injury	20	P=0.94	Week-Moderate

Figure 3: A table to demonstrate quantification of renal staining for NGAL Histological specimens stained variably in both intensity and proportion of tubules staining for NGAL at 2 hours post reperfusion. There was no observed difference between groups.

Small Pump Priming Grant Continued...

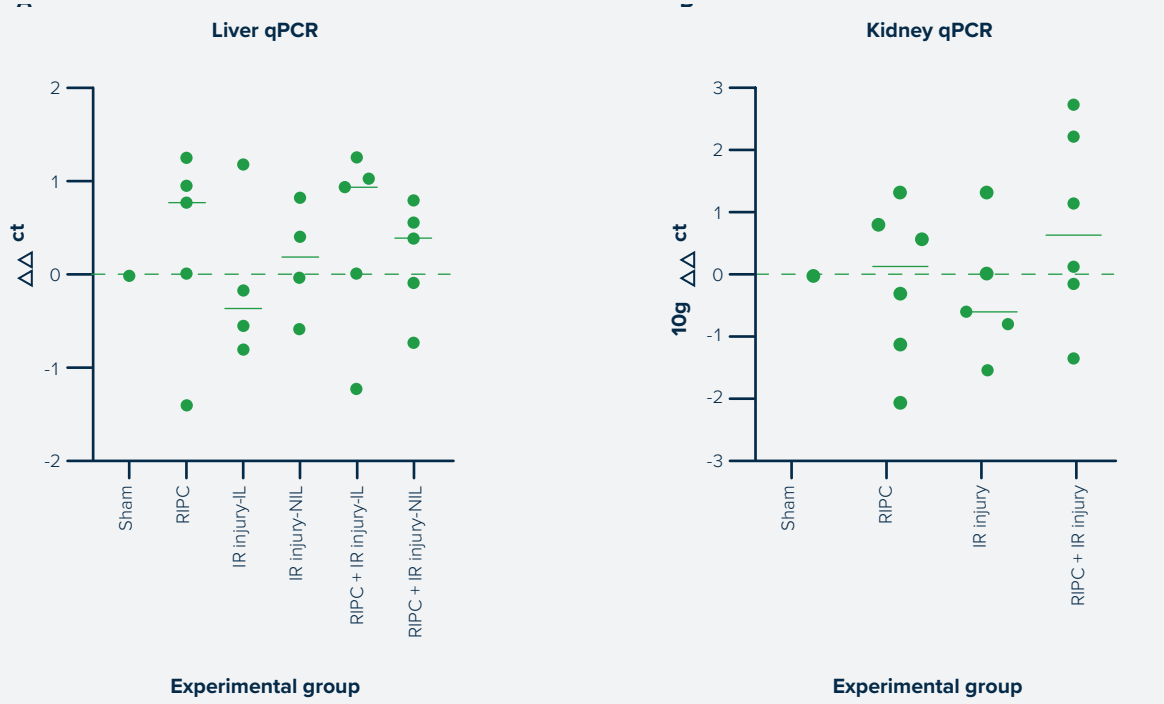
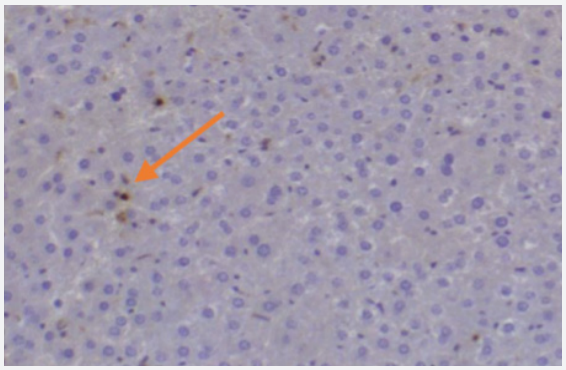


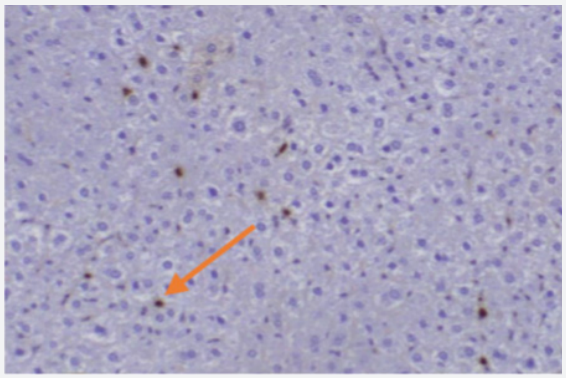
Figure 4: qPCR of Lcn2 RNA expression normalised to GAPDH identified no difference in NGAL expression between the IR experimental group (which demonstrated increased serum NGAL levels) and other experimental groups.

NGAL does not originate from the liver following early IR injury

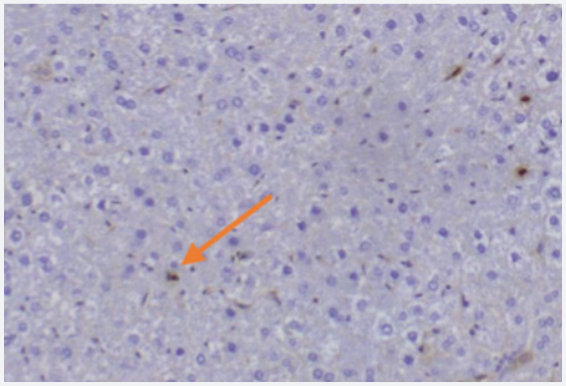
NGAL staining identified selective staining of non-parenchymal cells (i.e. non-hepatocytes) within the liver (figure 5). There was no difference in the number of cells staining for NGAL across the experimental groups (figure 6) and low NGAL RNA expression across the groups with no increase in NGAL expression in the IR injury group (figure 4).



Sham (group A)

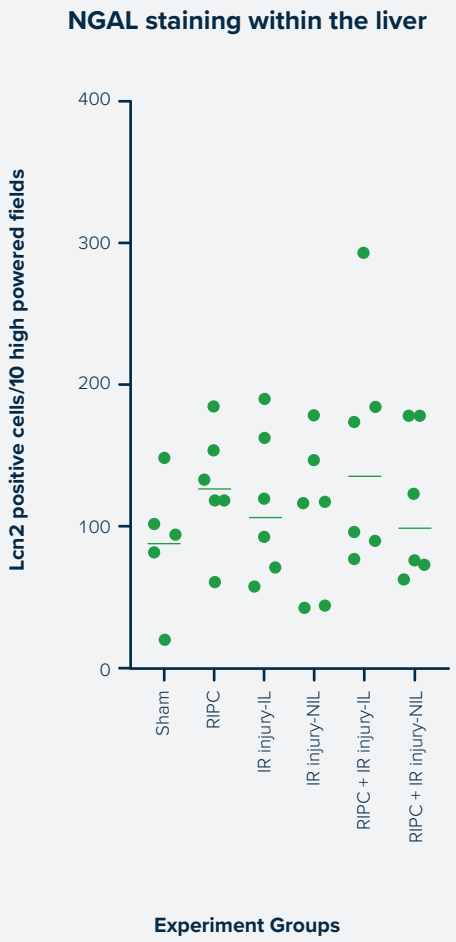


IR injury, ischaemic liver lobe (B1)



IR injury, non-ischaemic liver lobe (B2)

▲ Figure 5: Slides at x10 magnification. All depict intense staining (dark brown) of non parenchymal liver cells, as demonstrated by arrows.



▲ Figure 6: A graph to show the number of Lcn2 positively staining cells within 10 high powered fields (x20 magnification) within the liver. There was no significant difference between the IR group (B) and other experimental groups (all p>0.05).

NGAL staining within the liver is localised to immune cells.

We performed co-localisation of NGAL with F4/80 (marker of Kupffer cells). This identified three populations of cells (figure 7):

1. F4/80 positive, Lcn2(mouse NGAL) positive cells (no change in frequency between experimental groups)
2. F4/80 positive, Lcn2 negative cells
3. F4/80 negative, Lcn2 positive cells

Small Pump Priming Grant Continued...

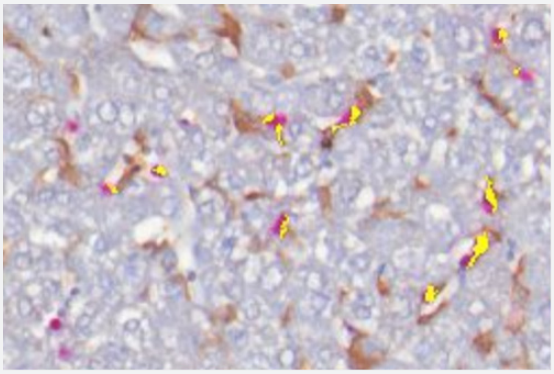


Figure 7: An example of co-localisation of Lcn2 and F4/80. Lcn2 staining shown in pink, F4/80 in brown. Co-localisation demonstrated by yellow. As demonstrated, three populations of cells emerged. Phenotypical features of Lcn2 positive, F4/80 negative cells are suggestive of a population of monocytes with some neutrophils. The ratio of F4/80 positive, Lcn2 positive cells did not change between the different experimental groups.

These data suggests that Kupffer cells are a source of NGAL within the liver, but that Kupffer cells are not recruited to NGAL production at 2 hours post liver IR injury. Other populations of immune cells, that are in the process of recruitment to the liver, may be important for initial NGAL production following IR injury. Further work is required to characterise the F4/80 negative, Lcn2 positive population and to compare this to circulating populations of immune cells post liver IR injury.

Discussion

Our data demonstrate that 2 hours post liver IR injury, neither the liver nor the kidney stains more positively for NGAL protein (compared to other experimental groups including sham laparotomy) and neither liver nor kidney demonstrates increased NGAL mRNA expression.
Instead, we demonstrate that renal tubular cells stain positively for NGAL within the apical third of cells which is suggestive of NGAL uptake from renal filtrate.
This finding was identified across the different experimental groups and is supported by some literature that suggests NGAL is taken up by the kidneys and recycled into the circulation under normal (non-AKI) circumstances.

We also demonstrate that NGAL staining within the liver across the experimental groups is limited to non-parenchymal cells. Neither staining intensity or the number of positively staining cells increased with liver IR injury. Following on from this work we performed dual staining with F4/80 and NGAL (data not shown). This confirmed that a proportion of NGAL positively staining cells within liver tissue are Kupffer cells. Phenotypically the remaining NGAL positive cells resemble monocytes with occasional neutrophils and further work is ongoing to dual stain liver tissue with Lcn2 (mouse NGAL) and CD115 (a marker of circulating monocytes).

Other work previously performed by our group has identified that following liver IR injury, the liver is infiltrated by a population of Ly6C+, CD11b+ monocytes. From the literature there is some suggestion that circulating mononuclear cells may express NGAL and we hypothesis that circulating monocytes which are activated and recruited in response to liver IR Injury may be the main source of initial NGAL production. It may be that recruitment of these cells to the injured liver is important for parenchymal upregulation of NGAL mRNA. Hepatocyte mRNA upregulation of NGAL has been demonstrated at 4 hours post reperfusion by other groups.

These findings are important because they represent a development in our understanding of NGAL upregulation following liver IR Injury and suggest that the systemic immune system is more critical to this process than previously believed. For development of NGAL as a useful clinical biomarker of AKI, an improved understanding of the biomechanics underlying production and release is vital. These data contribute significantly to that improved understanding.

Additionally, these data again hint at a significant role for monocytes in the response to liver IR injury which requires further investigation. From these data, our focus has shifted to the investigation of PBMCs following liver IR injury in liver transplantation and the role they play in the development of AKI post liver IR injury

B. Problems encountered and steps taken to overcome them

4. RNA yields from RNA extraction was initially low, requiring upscaling of the tissue quantity to ensure sufficient yields.
5. Some FFPE liver and kidney samples had both very low yield of RNA and poor staining indicating possible issues with the previous fixation process. This was mitigated by exclusion of these samples and addition of other samples from the unused pool of biological replicates.
6. Quantitative PCR proved problematic. The yield of NGAL was extremely low and the variability between samples was high. Two sets of primers for NGAL were used initially and the best selected for further work. NGAL and GAPDH primer activity and PCR reaction efficiency was checked using serial dilutions of RNA extracted from mouse neutrophils (obtained from mouse blood) as a positive control. Samples with mRNA content of 100ng/microlitre and similar GAPDH (within 1.5 fold Ct values) were used for additional comparative analysis to confirm no difference between the IR and other experimental groups.

C. Collaborations established

This project established a collaboration between the Department of Surgical Biotechnology and the academic Liver Histopathology unit which will be developed with further research looking at Ischaemia Reperfusion Injury following Liver Transplantation.

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

This work has been presented at the British Association for the Study of the Liver and forms part of the manuscript currently being prepared for submission for publication.

Small Pump Priming Grant Continued...

The work also forms the main body of an upgrade from MPhil to PhD for the grant recipient and will be used as evidence to support an application for a substantial fund to investigate the role of monocytes and NGAL in the development of AKI following Orthotopic Liver Transplantation.

E. Acknowledgements

I would like to acknowledge the support of Prof Quaglia, Dr Heppinstall and Andrew Hall in completion and interpretation of immunohistochemical staining of liver and kidney specimens and the support and advice provided by Dr Klootwijk and Dr Chivu in completion and analysis of the quantitative PCR. I would also like to thank my other supervisors Prof Davidson, Prof Salama and Mr Robertson.

Grant Holder Name	Rachael Forsythe, David Newby, Adriana Tavares
Department(s) in which the Fellowship was held	Centre for Cardiovascular Science, University of Edinburgh
Type of Grant/Fellowship;	Pump Priming Grant SPPG/17/110
Project Title;	Edin-Vasc Molecular Imaging Study
Period grant held	
From:	Sept 2017
To:	Sept 2018

Lay Summary

An “aortic aneurysm” occurs when the main artery in the body enlarges and becomes at risk of rupturing, which is usually fatal. An aneurysm is usually repaired when it reaches a size where it becomes more likely to rupture. However, aneurysm surgery carries major risks (including death), so it is important to choose the right patients to undergo this operation; ideally those at high risk of expansion or rupture.

Using specialist scanning techniques (PET-CT) after intravenous injection of a radioactive dye (radiotracer; 18F-NaF) into patients with aneurysms, we have previously identified those at increased risk of expansion and rupture.

During the Edin-Vasc Molecular Imaging Study, we scanned tissue samples of aortic aneurysms from patients undergoing repair, using radiotracers that are known to detect specific biological processes associated with aneurysm expansion. We also scanned aortic tissue samples obtained from patients who did not have an aneurysm.

We demonstrated that 18F-NaF is present in much higher levels in aneurysmal tissue than in normal aortic tissue. This confirms our previous study using this radiotracer in patients. Another radiotracer (called RGD) was present in similar levels in aneurysmal tissue and normal aortic tissue, suggesting that this tracer may not be useful to help predict aneurysm biological activity.

A. Clinical and Scientific Significance of advances made

Introduction

18F-Sodium fluoride is a radiotracer that has been used in clinical studies to detect microcalcification. Microcalcification correlates to microscopic calcium and phosphate-rich hydroxyapatite crystals.[1] Microcalcification can identify culprit lesions in high-risk plaque in coronary and carotid arteries.[2] It has also been used to study patients with abdominal aortic aneurysms: Higher 18F-sodium fluoride (NaF) uptake on Positron Emission Tomography/Computed Tomography (PET/CT) was associated with aneurysms which expanded more rapidly on follow up.[3]

18F-NOTA-RGDfk (RGD) is another PET radiotracer, it is frequently used to quantify angiogenesis. It binds to αvβ3 integrin, a cell surface glycoprotein which is expressed in repair processes including angiogenesis, fibrosis and inflammation. Since it is expressed by both activated endothelial cells and by macrophages, it is not specific in this regard. [4-6]

This study's aims were to:

1. Identify NaF microcalcification in diseased and non-diseased aorta.
2. Compare RGD uptake within diseased and non-diseased aorta and investigate whether this uptake correlates with NaF uptake.

Methods

This was a prospective single centre ex-vivo case control study. Aortic aneurysm tissue specimens were obtained in patients who were undergoing open aortic surgery in the Department of Vascular Surgery at the Royal Infirmary of Edinburgh. Control aortic tissue specimens were obtained from the Edinburgh BioBank, these were patients who had died with sudden cardiac death in the community. Full informed consent was obtained from patient or relatives as appropriate.

PET-CT protocol

Intact tissue then underwent microPET-CT with NaF and RGD. The intact tissue was incubated with the radiotracer for 30 minutes. PET data was then acquired using a nanoPET/CT scanner (Mediso, Hungary). A 30-minute emission scan was first obtained and then a CT scan obtained for attenuation correction. The specimen was left overnight to allow complete radiotracer decay.
The process was then repeated for the second radiotracer. PET data was then reconstructed using a 3D reconstruction algorithm, correcting for random effects, scatter, and attenuation.

Image analysis

Image analysis was then performed using PMOD 4.2 (PMOD Technologies LLC, Zurich). The images obtained in the RGD PET/CT session were first co-registered to the NaF PET/CT session using the two attenuation-correction CTs to obtain the co-registration mathematical algorithm.

Two types of image analysis were performed:

1. Whole Tissue image analysis

This involved drawing a 3D volume of interest around the whole of the tissue specimen.

This gave the 'average' radiotracer uptake across the whole specimen (in kBq/cc). This was performed for both radiotracer scans. Each tissue specimen's density (in Hounsfield Units) was also obtained from the attenuation-correction CT.

2. Hot Spot image analysis

a. NaF

This involved drawing three 3D spherical volume of interest spheres of equal size (1.5mm radius) in the 3 visually highest uptake areas on each individual tissue specimen in the NaF PET session. This was repeated in 3 visually lowest uptake areas on the same specimen in the same PET session to analyse three cold spots. Corresponding radiotracer uptake in those same six volumes of interest uptake could then be obtained for the RGD PET session for that same specimen. Average radiotracer uptake (in kBq/cc) across each volume of interest sphere was obtained. The tissue density (in Hounsfield Units) from the attenuation-correction CT for each of the volumes of interest was also recorded.

b. RGD

The same process (in 2a above) was then similarly performed, but this time using the 3 visually highest uptake and 3 visually lowest uptake regions for each tissue on the RGD PET session.

All the values obtained were normalised for the radiotracer incubation concentration by dividing the value obtained by the corrected radiotracer concentration (kBq/ml) for each study scan.

Statistical analysis

Statistical analysis was performed using statistical software package R (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was taken as a two-sided P<0.05.

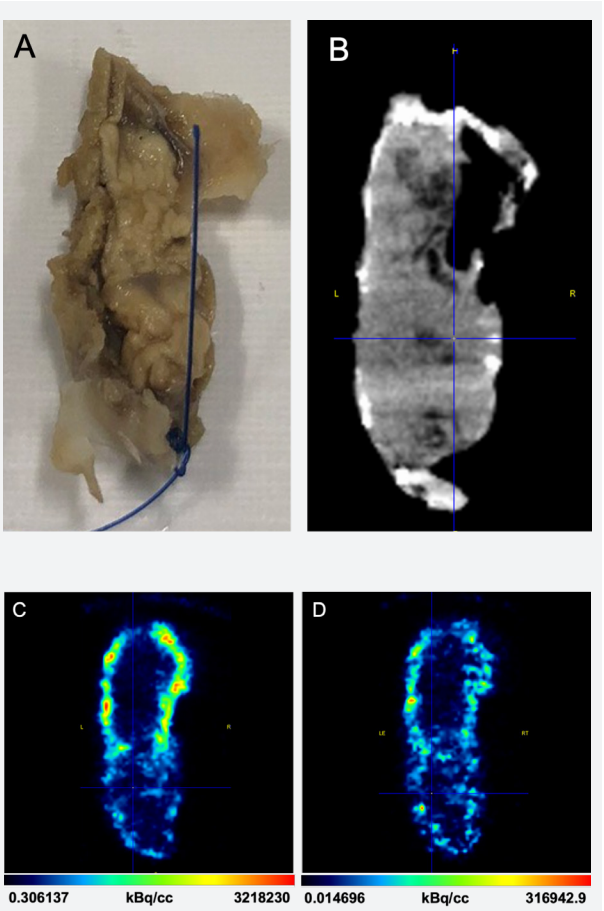


Figure 1 - Aortic aneurysm specimen example. Photograph of tissue (A), Computed tomography (B), 18F-sodium fluoride positron emission tomography (C), 18F-NOTA-RGDfk positron emission tomography (D)

For correlations, Spearmen's correlation was used.

Results

9 aortic aneurysm specimens and 7 control specimens were obtained (Figure 1).

Whole tissue image analysis

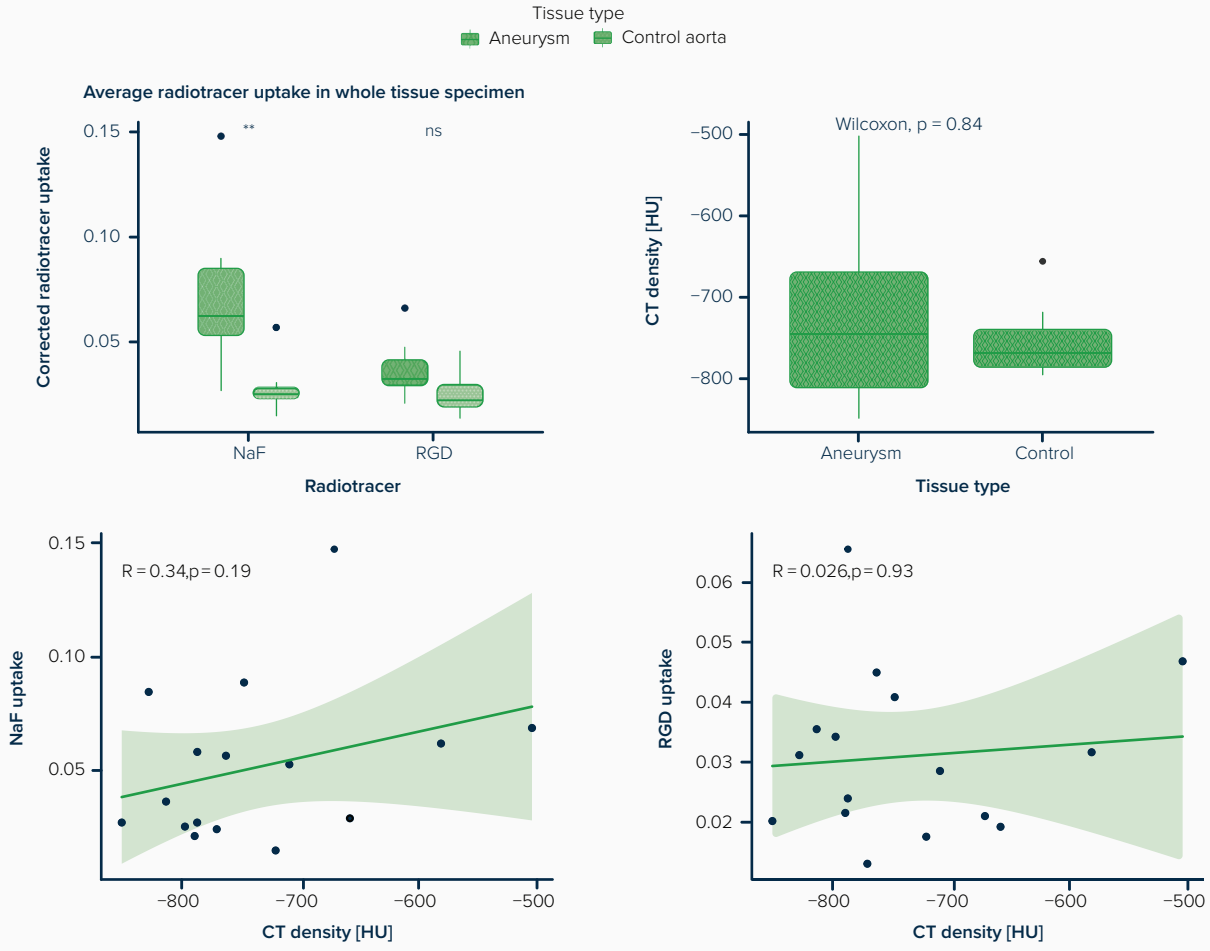
The corrected averaged NaF uptake within the aneurysm specimens was significantly higher than that in the control aortic specimens (p=0.009, 95 CI 0.01-0.07).

The corrected averaged RGD uptake in both types of specimens was lower than the NaF uptake (p=0.04, 95 CI 0.0009-0.04).

Small Pump Priming Grant Continued...

There was however no difference in the mean RGD uptake between the aneurysm specimens and controls (Figure 2).

There was no difference in whole tissue density on CT between aneurysm and control aortic tissue and this was not associated with radiotracer uptake.



▲ Figure 2 - Whole image tissue analysis. Left box plot shows radiotracer uptake in aneurysm and control aortic tissue. Right box plot shows density on computed tomography between aneurysm and control aortic tissue. Tissue density (on computed tomography) scatter plots with 18F-sodium fluoride (left) and 18F-NOTA-RGDfk (right)

NaF Hot Spot Analysis

The corrected averaged NaF uptake within hot spots on aneurysm specimens was significantly higher than that in the control aortic specimen hot spots ($p < 0.001$, 95 CI 0.4-0.8). This was also true for the cold spots ($p < 0.001$, 95 CI 0.06-0.17). There was however no difference in the RGD uptake of the same volumes of interest between the aneurysm specimens and the controls (Figure 3).

The corresponding corrected mean RGD uptake in both types of specimens was significantly lower than the NaF uptake ($p < 0.001$, 95 CI 0.33-0.62).
This was also true for the uptake within the cold spots ($p=0.03$, 95 CI 0.004-0.06).

There was no correlation between NaF hot spot values and corresponding RGD values, however the cold spot values seemed correlate positively ($R=0.71$, $p < 0.001$).

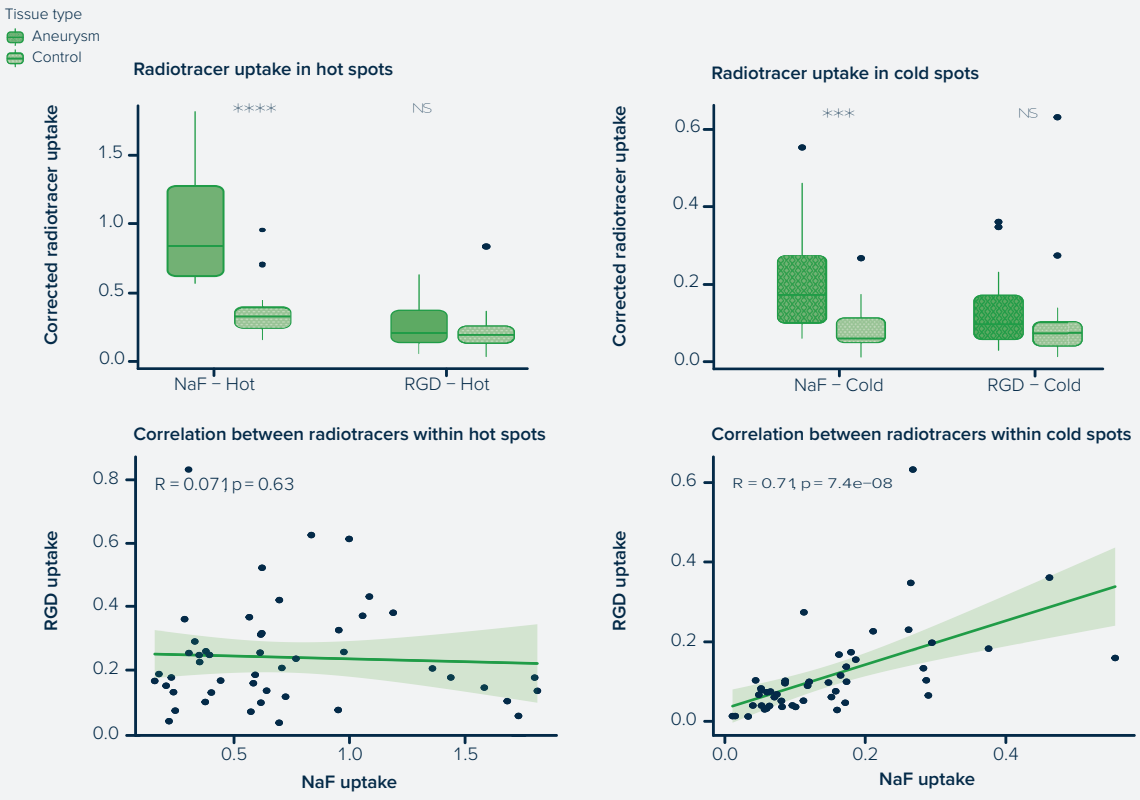


Figure 3 - Hot Spots with 18F-sodium fluoride. Left box plot shows radiotracer uptake in hot spots of aneurysm and control aortic tissue. Right box plot shows radiotracer uptake in cold spots of aneurysm and control aortic tissue. Scatter plots demonstrating 18F-sodium fluoride uptake and 18F-NOTA-RGDfk uptake in hot spots (left) and cold spots (right).

Small Pump Priming Grant Continued...

RGD Hot Spot Analysis

When hot spots of RGD were analysed, there was no difference between tissue types, however this was demonstrated in the values of corresponding volumes of interest on the NaF scans ($p < 0.001$, 95 CI 0.19-0.43).
There was also no difference between tissue types in RGD cold spots and corresponding areas on the NaF scans (Figure 4).

There was also no correlation between corrected RGD values in either hot spot or cold spot values and corresponding volumes of interest in the NaF scans.

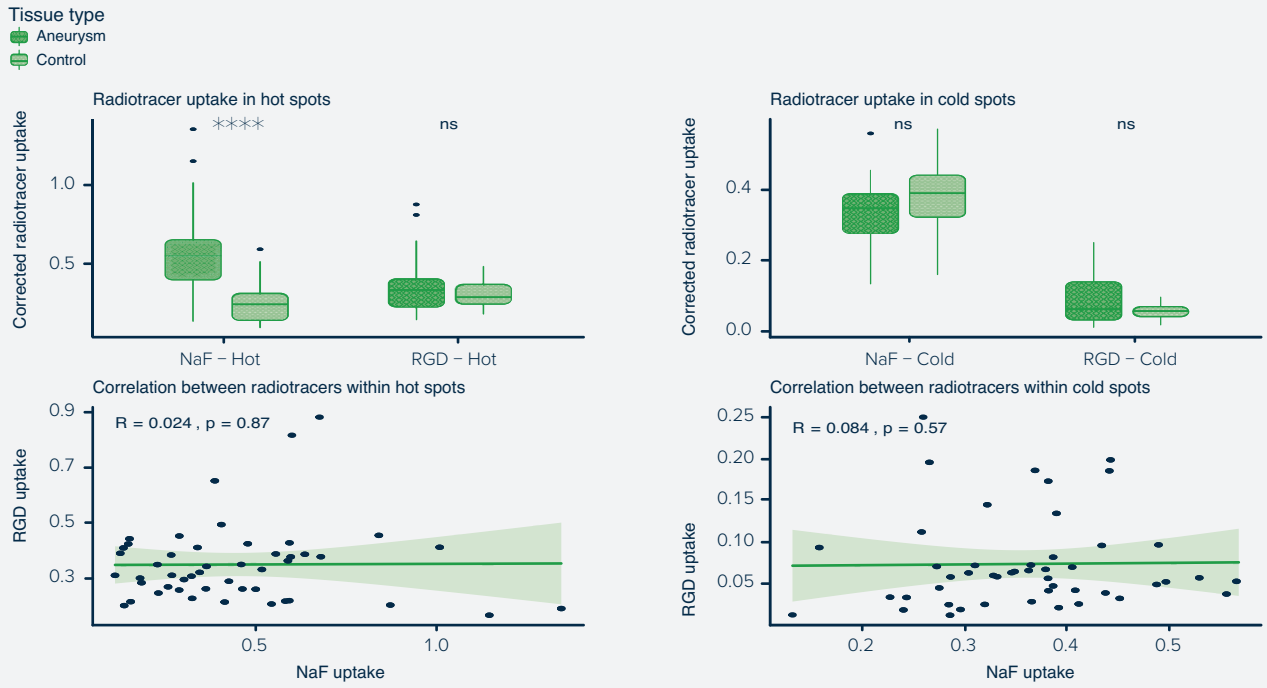
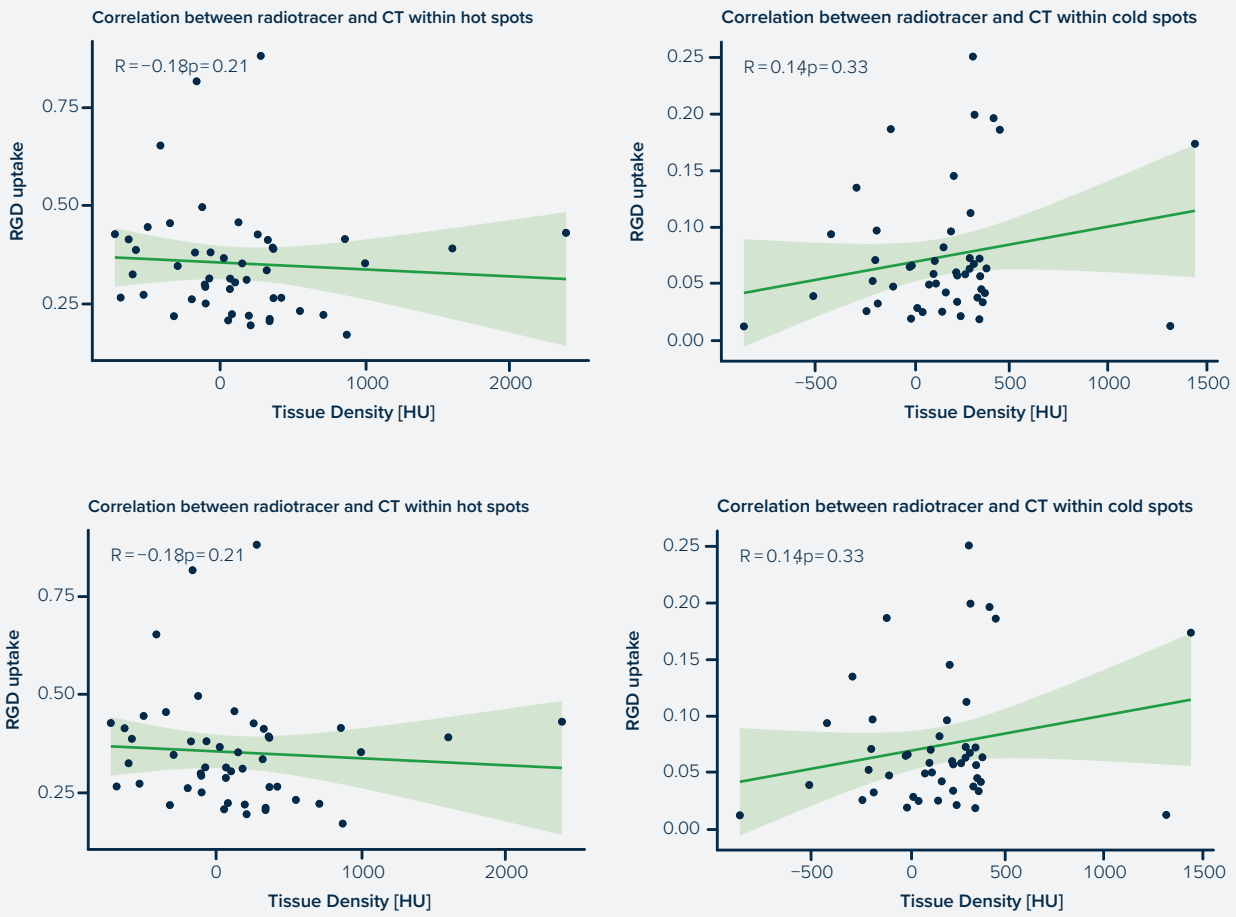


Figure 4 - Hot Spots with 18F-NOTA-RGDfk. Left box plot shows radiotracer uptake in hot spots of aneurysm and control aortic tissue. Right box plot shows radiotracer uptake in cold spots of aneurysm and control aortic tissue. Scatter plots demonstrating 18F-sodium fluoride uptake and 18F-NOTA-RGDfk uptake in hot spots (left) and cold spots (right)

Hot Spot Tissue Density



▲ Figure 5 - Hot Spot Tissue Density. Tissue density (on computed tomography) scatter plots with 18F-sodium fluoride and 18F-NOTA-RGDfk in hot spots of each radiotracer (left) and cold spots of each radiotracer (right)

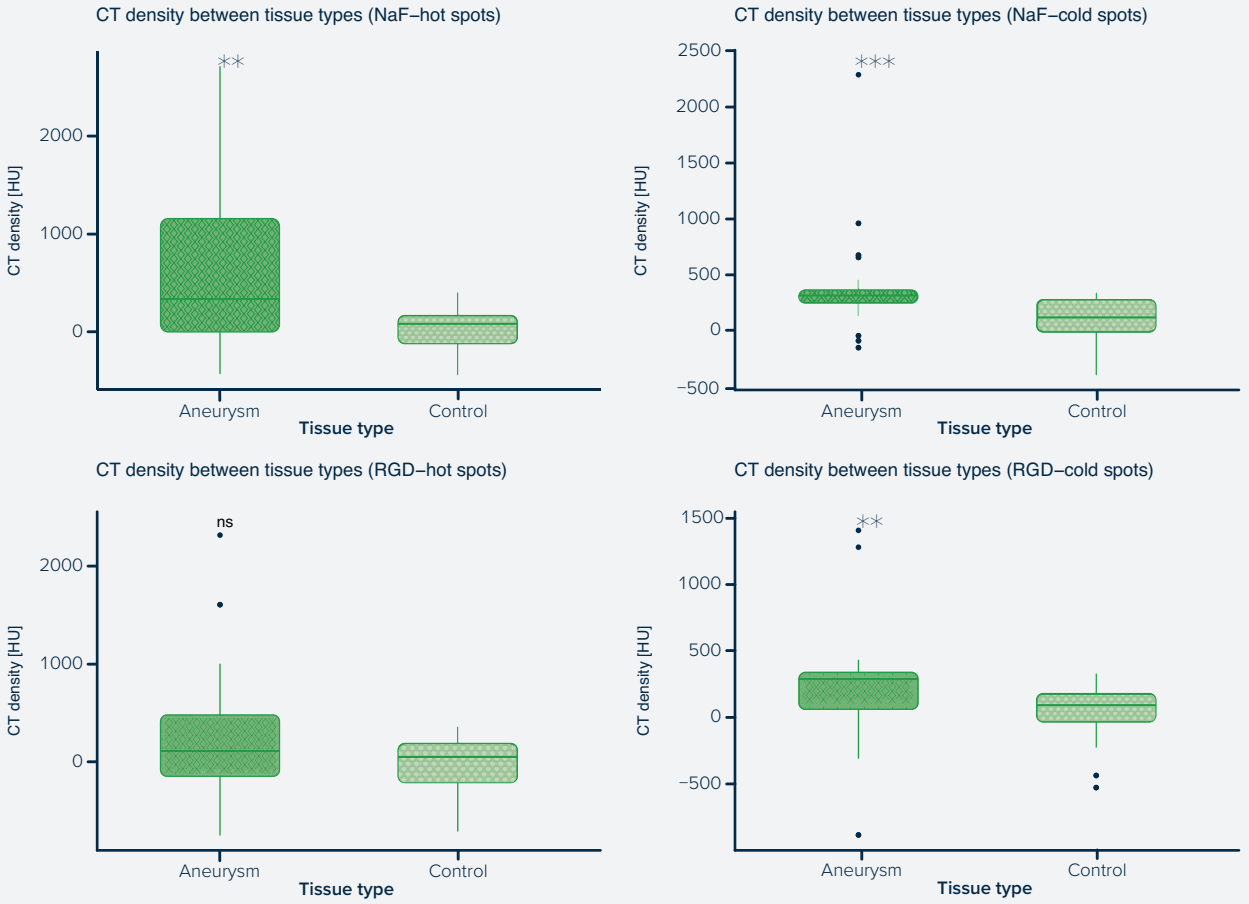
There was a positive correlation between corrected NaF hot spot values and the hot spots' tissue density on CT (in HU) (R=0.4, p=0.005). This correlation was even stronger within cold spots (R=0.53, p < 0.001). This correlation with tissue density was not present in the RGD hot spot and cold spots (Figure 5).

The CT density within NaF hot spots on aneurysm specimens was significantly higher than that in the control aortic specimen hot spots (p < 0.001, 95 CI 283.2-941.4). This was also true for cold spots (p= 0.008, 95 CI 74.3-125.6) (Figure 6).

In contrast, the CT density within RGD hot spots on aneurysm specimens was not significantly higher than that in the control aortic specimen hot spots. This was however significantly different in the cold spots (p= 0.04, 95 CI 8.3-404.3).

Small Pump Priming Grant Continued...

Conclusions



▲ Figure 6 - Tissue density in aneurysm and control aortic tissue. In 18F-sodium fluoride hot spots (top left) and cold spots (top right) and in 18F-NOTA-RGDfk hot spots (bottom left) and cold spots (bottom right)

NaF uptake within ex-vivo tissue (both in whole tissue and hot spot analysis) is significantly increased in aneurysm tissue when compared to control tissue.

This study demonstrates that there is no significant RGD uptake within aneurysm tissue when compared to control tissue. This suggests there may be low αvβ3 integrin expression within aneurysm tissue.

The difference in CT density between aneurysm and control tissue in NaF hot and cold spots and RGD cold spots is interesting. It suggests that there may be some integrin expression in the early aneurysm process and this merits further investigation.

C. Problems encountered and steps taken to overcome them

The radiotracers used in this study are manufactured in a very limited number of centres in the UK. Whilst this makes our study valuable and novel, it also provided a number of key logistical issues during the grant period. The production of some of the radiotracers was delayed by many months and this meant that we were unable to carry out the study during the proposed time period. This had a significant knock-on effect on our timelines, as did the COVID-19 pandemic. Due to the expense involved, it would not have been possible or affordable to carry out the study in other centres.

D. Collaborations established

This study helped foster a closer working relationship with the clinical imaging research fellows and the pre-clinical imaging team.

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

The data obtained from this study will form part of Samuel Debono's PhD thesis. In addition, we plan to submit these data as part of original research papers when we have more data from the planned tissue sectioning to augment the findings.

F. Acknowledgements

Samuel Debono (vascular surgery clinical research fellow working with the Grant Holders) oversaw the project, performed the analysis and wrote the report. The tissue samples were collected by Rachael Forsythe, Jakub Kaczynski and Maaz Syed. The samples were scanned by Carlos Corral Alcaide.

Calum Gray and Mark Macaskill also provided assistance with the analysis. The final report was revised and approved by the Grant Holders.

Small Pump Priming Grant Continued...

Grant Holder Name	David Edwards
Department(s) in which the Fellowship was held	School of Dental Sciences, Newcastle University
Type of Grant/Fellowship;	Small research pump priming grant (SPPG/20/145)
Project Title;	**Evaluating bioaerosol and splatter following dental aerosol generating procedures – preliminary investigations**
Period grant held	
From:	12 Oct 2020
To:	12 Oct 2021

Lay Summary

At the start of the COVID-19 pandemic, most dental care provision was halted due to concerns over virus transmission during aerosol generating procedures (AGPs). Face to face dental education also ceased. To inform a safe return to clinical practice and education, robust evidence was required to identify risks posed by dental AGPs, particularly in the 'open clinic' environment (treatment bays without dividing walls).

This study investigated the risk from various AGPs (e.g. drilling teeth, removing braces, and cleaning teeth) by using a tracer dye in the handpiece coolant and artificial 'saliva' in a mannequin. A number of ways of reducing spread were then investigated, including opening windows, altering air exchanges within the clinic, different types of handpieces, use of high-volume aspiration, and "fallow time".

Various methods including particle measurement, and detection of the tracer "dye" by capturing this on filter papers and also from the air using air-samplers.

We also developed a method to use a “safe virus” (a virus that can’t infect people) to measure how this might be spread.

The project has impacted national policy, and enabled an informed return to clinical care and dental education. Five high impact research papers were produced from this grant.

A. Clinical and Scientific Significance of advances made

To date, this work has produced five peer-reviewed papers (with another manuscript in preparation). Several of these papers were cited in national documents; a review on infection prevention/control from NHS National Services Scotland; a review of aerosol generating procedures from the Scottish Dental Clinical Effectiveness Programme (SDCEP); and a guidance document from the Dental Schools Council/ Association of Dental Hospitals (DSC/ADH) on reopening clinical dental education. These had a direct impact on the resumption of dental services in primary care and secondary care and the resumption of dental education.

The aerosol research group has presented the work to SDCEP, DSC/ADH and the NIHR Clinical Research Network—AGP Research Group. We were also invited to submit evidence to Public Health England and were consulted on the latest revision of the dental IPC guidance from UKHSA. The findings also contributed to recommendations on the minimum “fallow time” in dental settings, thereby helping dental practices and secondary care increase the number of patients that can be seen, as well as clarifying the effectiveness of a number of mitigating factors.

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The work also resulted in a national radio interview, two University press releases and a press release from the International Association for Dental Research which were picked up by several international press outlets. The most impactful paper resulting from this grant (https://www.altmetric.com/details/96796139) was highlighted on the Journal of Dentistry’s webpage, made open access at the request of the editor and currently has a top 5% altimetric score. Another paper (https://www.nature.com/articles/s41415-020-2503-9) was commended as the top 5 cited articles of 2021 in the British Dental Journal.

Small Pump Priming Grant Continued...

Key findings include:

- Maximum contamination using a fluorescein tracer dye was within 1 – 1.5 m but quantitative evaluation using spectrofluorometric analysis identified spread up to 4 m.
- Minimal fluorescein was detected 30-minutes after the procedure, even without any mitigating factors (≤0.1% of initial level).
- Following orthodontic debond procedure, contamination of the experiential rig (8 m diameter) was 3% of positive control, which was localised to the operator, assistant and mannequin. This suggests debonding is unlikely to produce widespread contamination.
- Unmitigated spread of tracer dye in 'open clinic' designs suggests spread is possible up to large distance but at low levels; the majority of contamination from splatter and aerosol was within the bay.
- With mitigation, spread was significantly reduced: High volume suction reduced spread within the bay by 53% and to adjacent bays by 81 – 83%. Cross ventilation reduced contamination of adjacent bays up to 89%.
- In the open clinic environment, very little aerosol settled after 10 minutes of fallow time.
- Using an 'air turbine' handpiece, aerosol was significantly elevated at 0.5 m, and at 1.5 m and 1.7 m where no mitigating factors were used. In contrast, using an electric micromotor handpiece at 200K RPM and 120K RPM resulted in minimal elevation, and no detectable aerosol at 60K RPM. This critical finding means such handpieces are unlikely to produce aerosol and can be used safely.

We developed a model of viral carriage in aerosols from dental procedures using a bacteriophage viral tracer.

This will allow detailed examination of the risk of viral transmission in bioaerosols which can be used in dentistry and other areas of healthcare. A validation of this methodology is due to be submitted for publication imminently.

In summary, the above findings had national and international impact, helping to maximise benefit to patients by increasing availability of care, whilst also ensuring minimal risk to dental teams and patients. Data on the open clinic environment also contributed to the resumption of clinical dental education, resulting in several hundred dentists graduating in 2020.

B. Problems encountered and steps taken to overcome them

The first hurdle was how to conduct this research during national lockdowns. We were able to secure approvals from the University and from the Trust, who were both very supportive, to allow us to conduct the work. We ensured all relevant risk assessments were followed to allow the project to progress.

As clinical work and clinical teaching began to increase, it was often hard to get the research team together to run experiments, which involved using parts of the hospital estate. The committed team were flexible in fitting the work around their commitments, including running experiments out of hours.

From early on in the project, we wanted to make sure that our methodologies were as robust as possible. We spent quite some time making sure we had the methods working well before taking these forward in full-scale experiments. Some specific methodological issues were establishing the initial bacteriophage culture and validating the PCR methods we used. In the end we were able to over come these by working with our collaborators and co-investigators to troubleshoot problems.

C. Collaborations established

Invitation for co-investigators James Allison (JA), Richard Holliday, and Nick Jakubovics to join NIHR CRN AGP Research Group, and contribution to research priority setting exercise which was published by NIHR.

Fellowship supervision for JA for follow-on project from Thushan de Silva (Infectious Diseases/ Virology; University of Sheffield) and Louise Fletcher (Environmental Engineering; University of Leeds).

Invitation for JA to join National Physical Laboratory Postgraduate Institute, and collaboration on Fellowship.

Collaboration on follow-up project:

- Prof. Cath Noakes (Engineering, University of Leeds; Member of SAGE).
- UK Health Security Agency, Porton Down (Allan Bennett, Ginny Moore).

Collaboration and submission of Fellowship application for Charifa Zemouri (Public Health Advisor; Dutch Parliament) with supervision from members of the research team.

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

The following papers were published as a direct output from the grant:

- Allison JR, Dowson C, Pickering K, Cervinskyte G, Durham J, Jakubovics N, Holliday R. Local Exhaust Ventilation to Control Dental Aerosols and Droplets. Journal of Dental Research. DOI: 10.1177/00220345211056287.
- Allison JR, Edwards DC, Bowes C, Pickering K, Dowson C, Stone SJ, Lumb J, Durham J, Jakubovics N, Holliday R. The effect of high-speed dental handpiece coolant delivery and design on aerosol and droplet production. Journal of Dentistry. 2021;112 DOI: 10.1016/j.jdent.2021.103746.
- Holliday R, Allison JR, Currie CC, Edwards DC, Bowes C, Pickering K, Reay S, Durham J, Lumb J, Rostami N, Coulter J, Nile CJ, Jakubovics N. Evaluating contaminated dental aerosol and splatter in an open plan clinic environment: Implications for the COVID-19 pandemic. Journal of Dentistry. 2021;105, DOI: 10.1016/j.jdent.2020.103565.

Small Pump Priming Grant Continued...

- Llandro H, Allison JR, Currie CC, Edwards DC, Bowes C, Durham J, Jakubovics N, Rostami N, Holliday R. Evaluating splatter and settled aerosol during orthodontic debonding: implications for the COVID-19 pandemic. British Dental Journal. 2021; DOI: 10.1038/s41415-020-2503-9.
- Allison JR, Currie CC, Edwards DC, Bowes C, Coulter J, Pickering K, Kozhevnikova E, Durham J, Nile CJ, Jakubovics N, Rostami N, Holliday R. Evaluating aerosol and splatter following dental procedures: addressing new challenges for oral healthcare and rehabilitation. Journal of Oral Rehabilitation. 2021;48(1):61–72.

Grants secured with support of RCS grant:

- Wellcome Trust Clinical Research Training Fellowship; 4Ward North Clinical PhD Academy £186,676 (James Allison); 27th May 2021.
- Faculty of Dental Surgery Research Fellowship; Royal College of Surgeons England £62,426 (James Allison); 5th May 2021.
- In-kind support from National Physical Laboratory; £20,000 (James Allison).

E. Acknowledgements

We would like to thank the Royal College of Surgeons of Edinburgh for supporting this work. The direct impact on a safe return to clinical practice and education has benefited patients, dental professionals and students. The outputs from the work have already received 92 citations and attracted international press attention. The co-applicant has also received two prestigious fellowships and further in-kind support.

Grant Holder Name	Miss Ann Etohan Ogbemudia
Department(s) in which the Fellowship was held	Nuffield Department of Surgical Sciences University of Oxford Oxford Transplant Centre
Type of Grant/Fellowship;	Small Pump priming grant SPPG/19/138
Project Title;	Pancreagenesis: Incorporation of pancreatic islet cells into ex-situ preserved skin flaps to create a transplantable endocrine allograft
Period grant held	
From:	September 2019
To:	October 2021

Lay Summary

Pancreas and islet transplantation are the current procedures used in the management of patients with type 1 diabetes (T1DM) to restore their glucose control.

These procedures are reliant on organs from carefully selected deceased donors to reduce the risk of transplantation complications.

Being selective to an 'ideal organ' limits the capacity to provide transplantation to more patients and utilise more invaluable organ donations.

Ex-situ machine perfusion is technique used to provide 'life support' to an isolated organ so it can be assessed, preserved for longer and be potentially repaired.

This research focused on developing this strategy in two work streams to provide pre- clinical solutions for the treatment of T1DM.

Ex-situ perfusion of skin flaps was developed, and pancreatic islets were injected into the flaps to produce a model of an 'insulin producing' graft. Preliminary results showed that this is a feasible model and that the skin has potential as a site for islet transplantation.

Small Pump Priming Grant Continued...

Ex-situ perfusion of pancreases was also developed. Early results show that machine perfusion of pancreases is not only possible but appears to provide better organ preservation than the current clinical strategy and facilitates organ assessment which to date has not been possible.

A. Clinical and Scientific Significance of advances made

The objective of this research was to develop prolonged ex-situ machine preservation of donor skin flaps to provide a biological scaffold to support engraftment and functioning of incorporated pancreatic islets. Clinical translation of this research was to produce an experimental model of a transplantable 'endocrine' skin allograft for the management of diabetes mellitus. Additionally, this model could be used in studies investigating the subcutaneous space as an attractive, alternative site to the liver for islet transplantation.

Methods: a custom normothermic machine circuit was designed and constructed using similar principles used for extracorporeal life support in cardiothoracic medicine (figure 1).

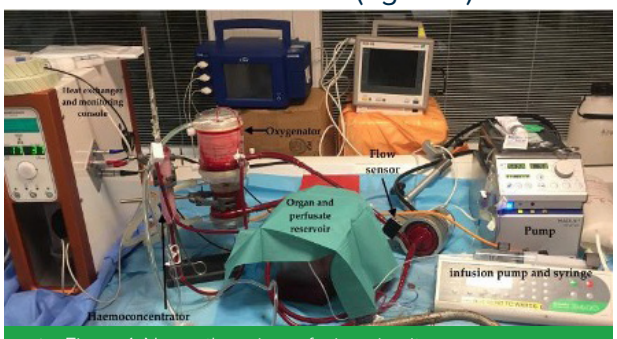

Figure 1: Normothermic perfusion circuit

This circuit was used to support 12 skin flaps donated from either extraneous tissue from surgery or from human deceased donors with the appropriate research consent. 2 of the 12 skin flaps had subsequent injection of allogenic human islets. The skin flaps were evaluated for viability and function by glucose challenge to assess endocrine function, tissue biopsy for histological review and microcirculatory blood flow assessment by Microscan™ (figure 2).

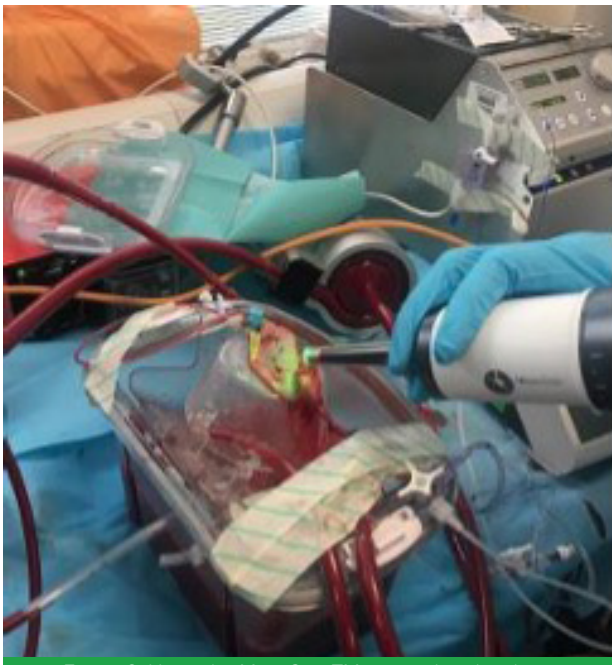

Figure 2: Using the MicroScanTM to visualise the skin microcirculation during normothermic machine perfusion

The MicroscanTM by Microvision medical uses side stream field (SDF) optics to visualise the microcirculation by using illumination by concentric lights emitting from a hand-held scanner.

A functioning microcirculation is a prerequisite for tissue oxygenation, nutrition, and exchange of metabolites; therefore, an intact microcirculation is essential for life and being able to visualise it in ex-situ preserved organs is potentially a marker of viability.

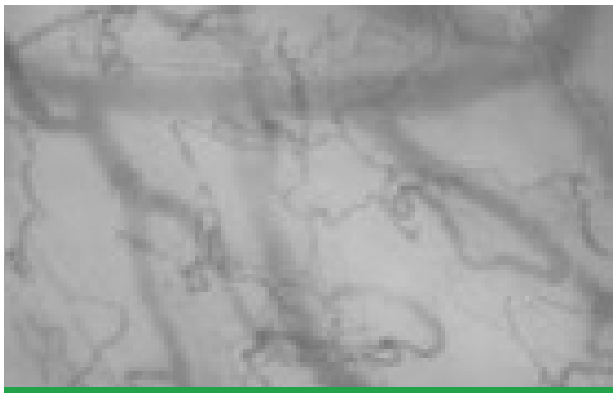

Figure 3: Positive control - sublingual

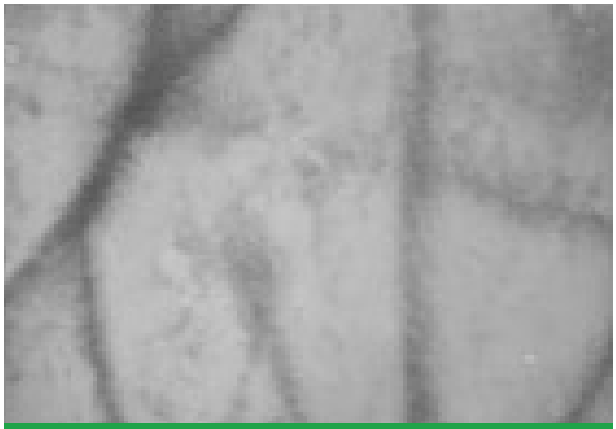

Figure 4: #10 - day 1 perfusion

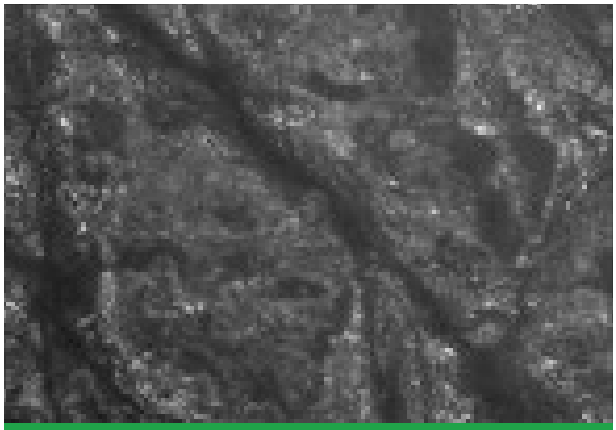

Figure 5: #10 - day 16, end of perfusion

Figure 3-5: Microcirculation images of the control (top image) sublingual region. Day 1 of perfusion of skin flap with islets (middle image) and at the end of the perfusion on day 6 (bottom image).

Findings: using the Microscan™ and its associated software, video images (figure 3) were obtained to show a patent and perfused microcirculation during the during normothermic perfusion of the skin flaps (figure 4) until tissue death (figure 5).

Histological assessment of 1 of the 2 skin flaps with islets showed presence of the injected islets, in single cells but not in characteristic clusters, with surrounding endothelial cells suggestive of vascular 'sprouting' i.e., new blood vessel growth (figure 4).

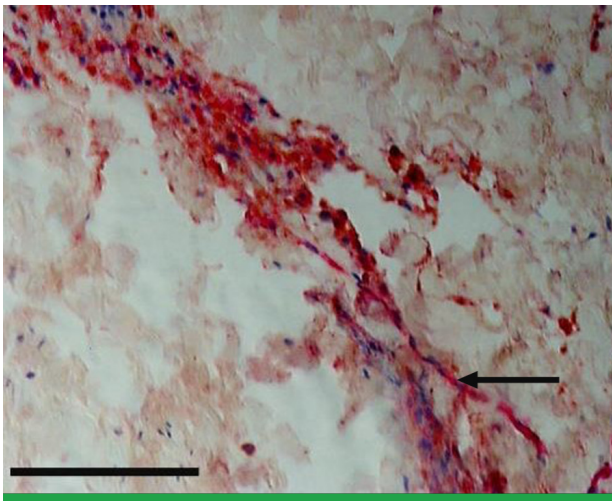

Figure 6

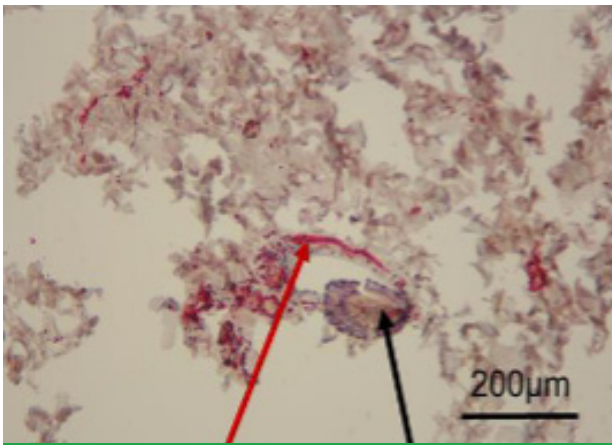

Figure 6-7: Histopathology of a tissue biopsy from a perfused skin flap with islets. The red arrow in the left image points to CD31 positive endothelial cells and the black arrow points to synaptophysin positive islet cells. The image on the right is the magnified image (x20) of the region of interest on the left with the back arrow pointing to sprouting endothelial cells.

Small Pump Priming Grant Continued...

Scientific significance

In this initial work, I established that skin flaps can be preserved by ex-situ normothermic perfusion for an average duration of 3 to 5 days with maintained viability determined by microcirculation patency and histological assessment. Additionally, although the incorporated islets did not maintain their characteristic clustered appearance there were encouraging appearances of sprouting, which suggests islet engraftment into to the skin flap.

B. Problems encountered and steps taken to overcome them

The covid pandemic caused several challenges for this novel research, including closure of the experimental laboratory as well as the clinical pancreas and islet programmes therefore halting my access to necessary tissue to continue the research.

After the limited resumption of activity, a decision was made to change the research proposal to a realistic one that fits in with available resources. During this period the RCSEd permitted an appreciated grant extension.

The new research proposal was chosen to be similar to and build on the experience of the earlier work; that is to investigate how ex-situ machine perfusion could be utilised to enable preservation and assessment of whole pancreas grafts to further advance research in beta cell replacement therapies for diabetes mellitus.

After making minor adaptations to the custom perfusion circuit, new studies were carried out on 13 pig pancreases procured in a donation after circulation death (DCD) transplantation model. The pancreases were divided into 3 groups, differing by type of preservation technique over 6 hours. These preservation techniques were either static cold storage (SCS) or hypothermic machine perfusion with oxygenation (HMPO2).

SCS is the current method for pancreas preservation prior to transplantation, however it does not permit organ assessment. HMPO2 is an alternative preservation strategy established to be beneficial in other transplantable organ groups and therefore a potential new strategy to optimise pancreas preservation.

The established normothermic perfusion protocol was used to simulate reperfusion in organ transplantation; reperfusion being a time when the recipient's blood supply reanimates the donor organ during transplantation.

As normothermic machine reperfusion mimics physiology it enabled evaluation of the pancreas experimental groups over the duration of an hour (figure 5).

Outcome measures were perfusion characteristics (vascular flow rate and resistance), fluid biochemistry and change in tissue water mass as oedema assessment.

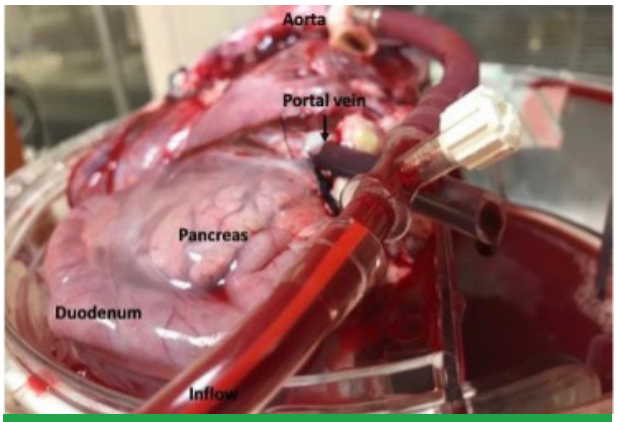

Figure 5: Normothermic reperfusion of a pancreas graft to enable assessment. Pancreas anatomy is labelled in the image.

Findings: during reperfusion, the HMPO2 groups demonstrated significantly better perfusion characteristics, normal macroscopic appearances, decreased oedema and one HMP group demonstrated an appropriate response to glucose stimulation as part of endocrine functional assessment.

Conversely, the SCS group developed early macroscopic appearances of oedema, interstitial haemorrhage, and minimal portal venous outflow.

Scientific and clinical significance

This second stream of research suggests that ex-situ assessment of pancreases by reperfusion is feasible and that HMPO2 may be a better preservation strategy to SCS (graphical abstract figure 6).

In conclusion, ex situ assessment of pancreases by NR is promising and HMPO2 may be beneficial over SCS.

Figure 6: Graphical abstract

Small Pump Priming Grant Continued...

C. Collaborations established

Industry collaborations:

1. Institut Georges Lopez, France.
2. Microvision, Netherland.

University and clinical

1. Centre de Recherche en Transplantation Et Immunologie, Université de Nantes, France.
2. The Oxford Islet isolation Centre, University of Oxford, United Kingdom.

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

The generous RCSEd grant greatly facilitated my research and has led to tremendous research outputs.

A peer reviewed publication on original research.

- Ogbemudia AE, Hakim G, Dengu F, El-Gilani F, Dumbill R, Mulvey J, et al. Development of ex situ normothermic reperfusion as an innovative method to assess pancreases after preservation. Transpl Int. 2021;34(9):1630-42.
- 4 national/international oral presentations.
- Feb 2021 - European pancreas and islet transplantation society (EPITA).
- Feb 2021- British Transplant Society (BTS).
- May 2021 - Societe Francophone de Transplantation (SFT).
- Aug 2021- European Society of Transplantation (ESOT).

2 Awards

- People's Choice for best communicator. Nuffield Department of Surgical Sciences, University of Oxford, Research Away Day. Feb 2020.
- Top 5% abstract accepted for oral presentation at 2021 20th European Society for Organ Transplantataion (ESOT) Sept 2021.

Contribution to a higher degree

- This research will be contributing to the achievement of my DPhil (PhD) at the University of Oxford and this RCSEd grant has being instrumental in allowing this happen. Additionally, this research will be continued by incoming research fellows and could potentially inform the design of a phase 1/early phase clinical trial in pancreas preservation for transplantation and islet isolation.

E. Acknowledgements

I would not have the inspiration or motivation for my research if not for the all the patients living with diabetes mellitus as well as organ donors along with their families and friends who forever hold my highest regard.

My supervisors, Professors Peter Friend and Paul Johnson, whose drive to improve the lives of their patients is infectious.

Grant Holder Name	Mr Daniel Doherty
Department(s) in which the Fellowship was held	Faculty of Biology of Medicine & Health, University of Manchester; Department of Renal & Pancreatic Transplantation, Manchester University Hospital NHS Foundation Trust
Type of Grant/Fellowship;	Small Pump Priming Grant
Project Title;	**Understanding the hepatic microenvironment for islet survival and function following transplant**
Period grant held	
From:	March 2020
To:	March 2021

Lay Summary

Type 1 Diabetes Mellitus (T1DM) effects sugar levels. Islet cells in the pancreas are destroyed by the body's own protective cells, meaning they can't produce insulin which controls sugar levels.
This means patients with T1DM need to inject insulin to stop their blood sugar going dangerously high.

Islet transplantation is a treatment for severe T1DM. It involves removing the islet cells from a donor's pancreas and adding them to the recipient's liver. These donor islet cells can then produce insulin, meaning injections are not required.

However, islet transplants do not always work, and many will carry on needing injections. For some, the islets will never work or only work for a short period and most patients need repeat transplants.

Small Pump Priming Grant Continued...

I have been investigating how the islet cells interact with the foreign liver environment. I have analysed samples from islet transplants in animal models. These studies have shown changes around the islets which look like microscopic scar tissue.

I have planned a PhD project to interrogate how this scar effects the islet cells. I will study ways of improving this interaction so that islet transplants can work better, for longer and be available for more people.

A. Clinical and Scientific Significance of advances made

A patient with Type 1 Diabetes Mellitus (T1DM) administers 65,000 insulin injections and takes 80,000 capillary glucose readings during their lifetime. T1DM results from autoimmune destruction of beta-cells in the pancreatic Islets of Langerhans. This prevents homeostatic glucose control, leading to exogenous insulin requirements. This affects approximately 400,000 people in the UK, 29,000 of whom are children with a predicted rise to 600,000 and 48,000 in 2035. Worldwide this figure is approximately 37 million. This represents a significant financial burden for the healthcare system and in 2010/11 the NHS spent £1 billion on direct patient care for T1DM. Severe T1DM can cause loss of vision, renal failure and cardiovascular disease causing morbidity and mortality at a young age.

Since 2000, islet transplantation has emerged from an experimental technique into a widespread treatment option for severe T1DM. However, islet supply is limited, and commonly multiple transplants are needed due to initial beta-cell loss and functional decline over time.
Sustaining transplanted islets better will allow a limited resource to treat more patients. While ideal donor selection and islet preparation is clearly multifactorial, whether and how islets survive and why they lose function over time in the alien liver environment is not well understood.

I have conducted mouse models of islet transplantation in association with my collaborators. I have analysed the liver tissue produced which has demonstrated an area of fibrotic deposition surrounding transplanted islet allografts. This suggests that islet transplantation might trigger liver injury pathways and create a locally profibrotic environment. This interaction requires further interrogation to assess its implications for islet function and survival.

The data that has been generated through this pump priming grant will be used to secure further funding awards (detailed below) and has allowed me to build strong collaborative links internationally.
I have been able to produce preliminary data in support of a high-quality PhD, with an internationally recognised supervisory team, analysing the post-transplant microenvironment in detail.

I hope that these findings can inform strategies to improve islet survival and function, with the potential to improve glycaemic control for patients and negate the need for multiple transplantation to allow this precious resource to be used for the benefit of more patients suffering with severe T1DM and its devastating sequelae.

B. Problems encountered and steps taken to overcome them

COVID-19 Pandemic

The COVID-19 pandemic has caused significant disruptions to surgical training. The cessation of elective surgical activity in 2020 and subsequent reduction in capacity within the NHS for elective surgery has greatly affected my surgical development at a crucial early phase of training where development is typically achieved in the elective setting (operative cases ST1 – 296; ST3 – 136; ST4 - 159). Consequently, I had to shift my training focus toward developing operative skills in 2021, which has negatively impact on research opportunities.

Fortunately, laboratory work has continued due to the support of the team. However, progress has been limited and not all my planned objectives have been achieved.

Islet Immunohistochemistry

Islet transplantation in the mouse model employed is performed via infusion into the hepatic parenchyma via the hepatic portal vein. Consequently, these islets are spread out throughout the hepatic parenchyma. As a result, detection of these areas of interest for histological analysis is challenging. As part of this a systematic method for identification was established. The antibody product which had been used and optimised as part of an established insulin staining protocol in the lab was discontinued by the manufacturer. Consequently, through collaboration with the Shapiro group new products were utilised and optimised. Finally, immunofluorescent techniques within the hepatic parenchyma have posed challenging due to autofluorescence which has meant a need for the optimisation of staining strategies.

C. Collaborations established

I have been embedded within Prof Karen Piper Hanley's group at the University of Manchester and consolidated the groups existing collaborations and established new links. Through this grant and previous RCSEd funding awards, I have built strong links with Prof James Shapiro's group at the University of Alberta, Edmonton, Canada. Prof Shapiro has 30 years of experience in the field of beta-cell replacement and remains a highly respected world leader and has been the forefront of novel treatment strategies since he published the landmark Edmonton Protocol in the New England Journal of Medicine in 2000. The lab group in Edmonton possess world leading experience in animal models of diabetes and islet biology.
Some of the samples analysed were produced during a Royal College of Surgeons of Edinburgh funded visit to the group. The data we have produced, has strengthened this relationship, and allowed me to develop skills as an islet researcher from the best in the world.

Locally, I have built links with Dr Rachel Jennings' group at the University of Manchester. Her group has interest in single cell analysis of the pancreas in development and adulthood, with particular focus on the surrounding parenchymal impact on the development of Type 2 Diabetes Mellitus. The application of such single cell genomic investigations is crucial to further investigation of the topic in my future work.

Small Pump Priming Grant Continued...

These collaborations have been built into the supervisory team for applications to the funding awards detailed below.

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

Data from the pump priming grant has been used as preliminary data to demonstrate proof of principle for external funding awards.

Applications for Clinical Research Training Fellowships have been submitted to the Wellcome Trust in December 2021 and Medical Research Council in January 2022.

A further submission to Diabetes UK for the Sir George Alberti clinical research training fellowship is planned for Autumn 2022.

E. Acknowledgements

I am grateful for the support, assistance and guidance of Kara Simpson and Rena Pawlick, laboratory technicians at the University of Manchester and University of Alberta, respectively.

Grant Holder Name	David Edwards
Department(s) in which the Fellowship was held	School of Dental Sciences, Newcastle University
Type of Grant/Fellowship;	Small research pump priming grant (SPPG/20/145)
Project Title;	**Evaluating bioaerosol and splatter following dental aerosol generating procedures – preliminary investigations**
Period grant held	
From:	12 Oct 2020
To:	12 Oct 2021

Lay Summary

At the start of the COVID-19 pandemic, most dental care provision was halted due to concerns over virus transmission during aerosol generating procedures (AGPs). Face to face dental education also ceased. To inform a safe return to clinical practice and education, robust evidence was required to identify risks posed by dental AGPs, particularly in the 'open clinic' environment (treatment bays without dividing walls).

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Small Pump Priming Grant Continued...

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We also developed a method to use a "safe virus" (a virus that can't infect people) to measure how this might be spread.

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The aerosol research group has presented the work to SDCEP, DSC/ADH and the NIHR Clinical Research Network—AGP Research Group.

We were also invited to submit evidence to Public Health England and were consulted on the latest revision of the dental IPC guidance from UKHSA. The findings also contributed to recommendations on the minimum "fallow time" in dental settings, thereby helping dental practices and secondary care increase the number of patients that can be seen, as well as clarifying the effectiveness of a number of mitigating factors.

The work also resulted in a national radio interview, two University press releases and a press release from the International Association for Dental Research which were picked up by several international press outlets. The most impactful paper resulting from this grant (https://www.altmetric.com/details/96796139) was highlighted on the Journal of Dentistry's webpage, made open access at the request of the editor and currently has a top 5% altimetric score.
Another paper (https://www.nature.com/articles/s41415-020-2503-9) was commended as the top 5 cited articles of 2021 in the British Dental Journal.

Key findings include:

- Maximum contamination using a fluorescein tracer dye was within 1 – 1.5 m but quantitative evaluation using spectrofluorometric analysis identified spread up to 4 m.

- Minimal fluorescein was detected 30-minutes after the procedure, even without any mitigating factors (≤0.1% of initial level).
- Following orthodontic debond procedure, contamination of the experiential rig (8 m diameter) was 3% of positive control, which was localised to the operator, assistant and mannequin. This suggests debonding is unlikely to produce widespread contamination.
- Unmitigated spread of tracer dye in 'open clinic' designs suggests spread is possible up to large distance but at low levels; the majority of contamination from splatter and aerosol was within the bay.
- With mitigation, spread was significantly reduced: High volume suction reduced spread within the bay by 53% and to adjacent bays by 81 – 83%. Cross ventilation reduced contamination of adjacent bays up to 89%.
- In the open clinic environment, very little aerosol settled after 10 minutes of fallow time.
- Using an 'air turbine' handpiece, aerosol was significantly elevated at 0.5 m, and at 1.5 m and 1.7 m where no mitigating factors were used. In contrast, using an electric micromotor handpiece at 200K RPM and 120K RPM resulted in minimal elevation, and no detectable aerosol at 60K RPM. This critical finding means such handpieces are unlikely to produce aerosol and can be used safely.

We developed a model of viral carriage in aerosols from dental procedures using a bacteriophage viral tracer.
This will allow detailed examination of the risk of viral transmission in bioaerosols which can be used in dentistry and other areas of healthcare.

A validation of this methodology is due to be submitted for publication imminently.

In summary, the above findings had national and international impact, helping to maximise benefit to patients by increasing availability of care, whilst also ensuring minimal risk to dental teams and patients. Data on the open clinic environment also contributed to the resumption of clinical dental education, resulting in several hundred dentists graduating in 2020.

B. Problems encountered and steps taken to overcome them

The first hurdle was how to conduct this research during national lockdowns.
We were able to secure approvals from the University and from the Trust, who were both very supportive, to allow us to conduct the work. We ensured all relevant risk assessments were followed to allow the project to progress.

As clinical work and clinical teaching began to increase, it was often hard to get the research team together to run experiments, which involved using parts of the hospital estate. The committed team were flexible in fitting the work around their commitments, including running experiments out of hours.

From early on in the project, we wanted to make sure that our methodologies were as robust as possible. We spent quite some time making sure we had the methods working well before taking these forward in full-scale experiments. Some specific methodological issues were establishing the initial bacteriophage culture and validating the PCR methods we used.
In the end we were able to over come these by working with our collaborators and co-investigators to troubleshoot problems.

Small Pump Priming Grant Continued...

C. Collaborations established

Invitation for co-investigators James Allison (JA), Richard Holliday, and Nick Jakubovics to join NIHR CRN AGP Research Group, and contribution to research priority setting exercise which was published by NIHR.

Fellowship supervision for JA for follow-on project from Thushan de Silva (Infectious Diseases/ Virology; University of Sheffield) and Louise Fletcher (Environmental Engineering; University of Leeds).

Invitation for JA to join National Physical Laboratory Postgraduate Institute, and collaboration on Fellowship.

Collaboration on follow-up project:

Prof. Cath Noakes (Engineering, University of Leeds; Member of SAGE).

UK Health Security Agency, Porton Down (Allan Bennett, Ginny Moore).

Collaboration and submission of Fellowship application for Charifa Zemouri (Public Health Advisor; Dutch Parliament) with supervision from members of the research team.

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

We would like to thank the Royal College of Surgeons of Edinburgh for supporting this work. The direct impact on a safe return to clinical practice and education has benefited patients, dental professionals and students.

The outputs from the work have already received 92 citations and attracted international press attention.
The co-applicant has also received two prestigious fellowships and further in-kind support.

Grant Holder Name	Mr Sandip Nandhra
Department(s) in which the Fellowship was held	Northern Vascular Centre, Freeman Hospital, Newcastle, NE7 7DN
Type of Grant/Fellowship;	Pump Priming grant
Project Title;	Prima – Pain Relief in Major Amputation: A Randomised control trial comparing pre-incision single-shot blocks to indwelling nerve catheters for patients under going major lower limb amputation.
Period grant held	
From:	2019
To:	2021

Lay Summary

The RCS Edinburgh pump priming grant as pivotal to the PRIMA study. This grant has been used to fund the development of a randomised trial to compare two type of pain control for those patients who have to undergo a major lower limb amputation as a result of blood vessel disease and narrowing. An amputation can be associated with short- and long-term pain. These two already utilised techniques can control these aspects of pain within the short and possibly longer-term.

The pump priming grant (implementation delayed over the last year and a half) lead ot the successful registration of the study and adoption onto the National Institute of Health Research study portfolio. The study is now ready to recruit its first patient, having gain successful ethical approval and registration with the Newcastle hospitals trust. By randomly allocating either of these two methods of pain control to 34 patients, we hope to determine which offers superior pain control and which is preferred by patients in their rehabilitation. We also intend to study this into the longer term.

Small Pump Priming Grant Continued...

We hope to complete recruitment and the initial study objectives over the next 3 months.

A. Clinical and Scientific Significance of advances made

Please accept this is a provisional and early grant report due to unexpected delays with repsecto to set up and ethical approval.

Due to significant delays attributed in the most part to COVID-19 we were unable to register and begin the study until 2021. We have now gained ethical approval. There have been no outputs but our first randomisation and recruitment begin this month. The PRIMA study group intend to update the RCS Edinburgh in a future grant report with the concrete outputs.

B. Problems encountered and steps taken to overcome them

There were delays with respect to COVID – non-covid related research was suspended. Once we were able, we obtained trust and ethical approval by April 2021. Sponsor approval was achieved by the beginning of June 2021.
We have now worked well with a wide team to begin recruitment imminently and expect to compelte recruitment of 34 patients by October 2021.

C. Collaborations established

This is a collaborative study between the surgical and anaesthetic departments within Newcastle. This involves medical and allied healthcare professionals.

The work has led to national collaboration with other units, from the UK to enhance patient care with respect to pain following major lower limb amputation. The CI and grant holder is now co-applying for a NIHR RfPB grant with three other UK centres, the results of PRIMA will support this work in due course. In addition, the PRIMA group have supported a James-Lind Alliance project in conjunction with the Vascular Society of Great Britain and Ireland.

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

The PRIMA project is aiming for VSGBI presentation, with publication by the end of 2021. We would be delighted to update the RCS Edinburgh in due course.
This will contribute towards a Doctorate of Medical Sciences degree.

E. Acknowledgements

RCS Edinburgh.

Newcastle Joint Research Office.

Newcastle Anaesthetic and Vascular Departments.

Grant Holder Name	Dr Jose M Rodriguez
Department(s) in which the Fellowship was held	Prosthodontics. King's College London, Faculty of Dentistry, Oral & Craniofacial Sciences. Tower Wing, Floor 26. Great Maze Pond. London. SE1 9RT.
Type of Grant/Fellowship;	Small Research Pump Priming Grant
Project Title;	**Multi-modal digital intra-oral imaging for patients with trismus as a result of treatment for head and neck cancer.**
Period grant held	
From:	February 2020
To:	August 2022

Lay Summary

Patients who have had treatment for cancer affecting the palate (roof of the mouth) may undergo surgery which leaves a defect (hole) on the palate which communicates with the nasal passages. These patients require a type of denture called an obturator which seals the defect. The obturator helps them to eat, avoiding choking and food inhalation, helps with speech, and improves function and aesthetics.

Cancer treatment can also involve radiotherapy, which can result in reduced mouth opening and this makes it difficult for dentists to take impressions of the mouth to make obturators.

This project used two digital techniques, intra-oral scanners and cone-beam computer tomography, to create digital casts of the patients' mouths by digitally combining the two modalities.

The techniques we created are as good as the established conventional techniques and have potential to be used in patients.

Small Pump Priming Grant Continued...

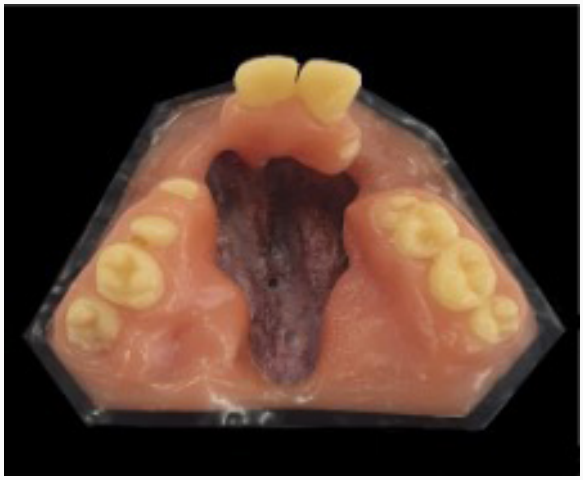
The next phase of this project will be to carry out a research project with patients on how to fabricate the dentures, removing the need for conventional impressions altogether, and reducing the numbers of clinical appointments from 8-10 visits, to 4-5 visits.

A. Clinical and Scientific Significance of advances made

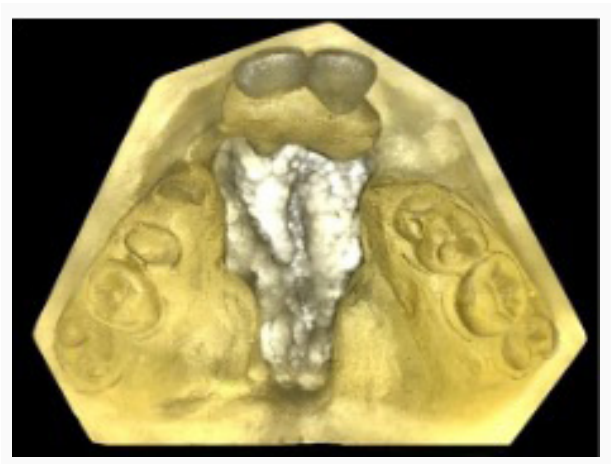
This in-vitro study had two aims:

To assess the suitability of composite 3D-printed models from digital techniques (Cone- Beam Computer Tomography (CBCT), and Intra-Oral Scanning (IOS) applicable for the fabrication of obturator prostheses in patients with palatal defects.

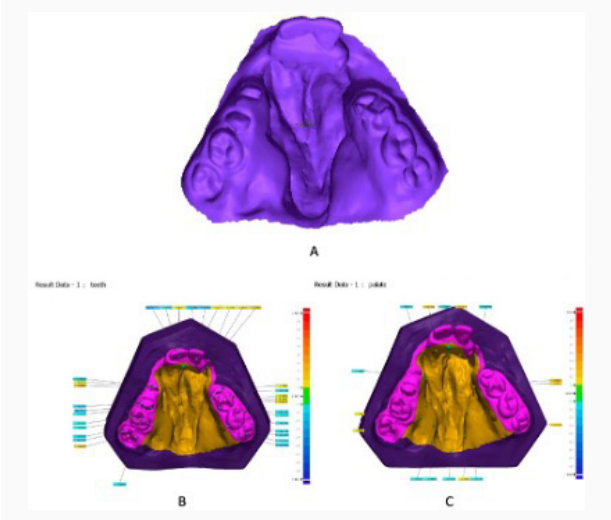
For the first part of the study we took repeated impressions of a master reference model (shown below) with an intra-oral scanner. Data from the scanner was combined with scans of the master reference model taken with two CBCT machines.



The composite cast (made from CBCT and intra-oral scanner data) was 3D printed and scanned digitally (shown below). The soft tissue portion of the composite cast was from the CBCT data, and the tooth portion of the cast was from intra-oral scanning data.



Conventional impressions of master reference model were also taken which served as the control. Comparisons between the techniques were made by digitally superimposing scans of each of the composite casts with scans of the master reference model. Accuracy and repeatability were measured with Geomagic Control™ via 3D heat maps that showed differences between the techniques (in millimetres). An example of a 3D heat map is shown below.



The results revealed that composite 3D-printed digital models were more accurate than gypsum casts and the differences were within clinically acceptable levels.

One of this study's objectives was to assess the repeatability of the composite 3D-printed models and the gypsum models used for obturators fabrication. Repeatability represented how reproducible the models of the palatal defect of each technique can potentially be. The experiment's results showed the digital techniques being more repeatable than the gypsum casts specifically (mean 0.161mm). Gypsum casts are considered the gold standard for obturators fabrication; however, they are labour-intensive, depend on operators' skills for repeatability, and are sensitive to mishandling the materials in the clinic and the dental laboratory.

The second objective of this study was to assess the linear accuracy of 3D-printed models and gypsum casts at the tooth, soft tissue, anterior, and posterior levels. Comparing accuracy at different levels is crucial to ascertain the fit of clasps and rest seats of the obturator framework around abutment teeth, and the peripheral seal of the acrylic around the margins of the defect anteriorly and posteriorly.
Accuracy measurements revealed the superiority of the composite digital models over the gypsum casts on all levels.
We measured a median deviation for the composite casts of 0.172mm compared 0.289mm for the conventional gypsum casts.

Composite 3D-printed models showed higher repeatability and accuracy than gypsum models. They also displayed higher linear accuracy at all levels. Overall, mean deviations scores for the accurate composite digital techniques approached 100µm which could be deemed clinically acceptable for removable prostheses.

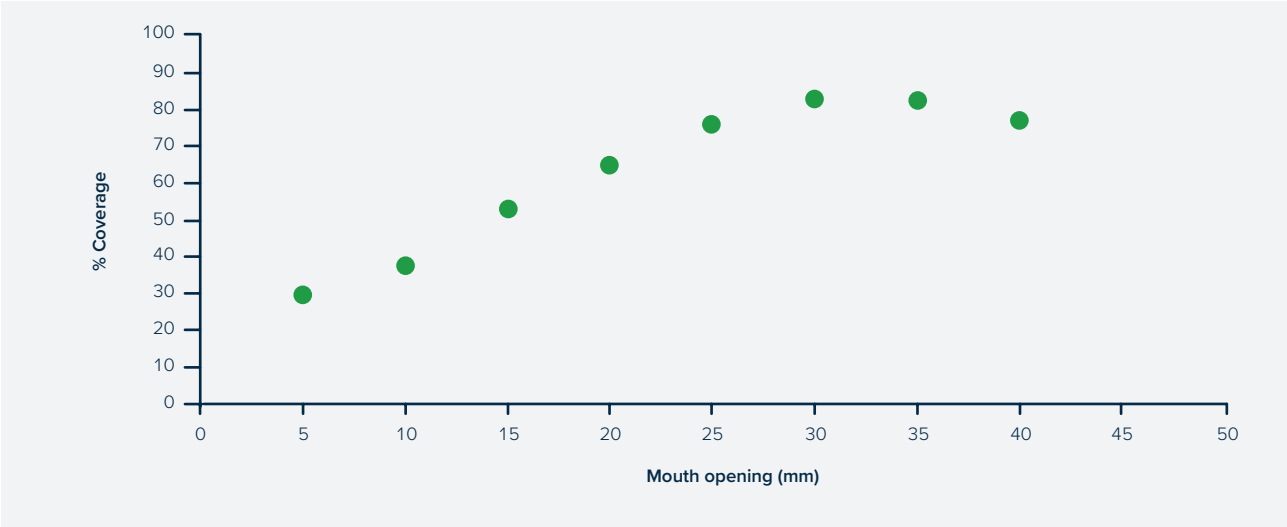
Small Pump Priming Grant Continued...

The second aim was:

To evaluate the accuracy of intra-oral scanning at a range of mouth openings to aid the fabrication of prosthetic obturators in patients presenting with palatal defects and trismus following treatment for HANC.

The master reference model was scanned using an intra-oral scanner (3M True Definition Scanner) at a range of simulated mouth openings (from 5mm to 40mm). The accuracy of the scans were compared to the master reference model using Geomagic Control using similar methods as described above.

The scatter plot below shows the percentage coverage from each composite scan against each mouth opening. The results plateaued at 35mm with only a slight increase in percentage coverage. At 40mm, the percentage coverage of the scan decreased to the level of 25mm mouth opening.



At 5 and 10mm mouth opening, the scans were not adequate at hard and soft tissue levels. At 15mm mouth opening, only the anterior teeth and anterior palatal gingivae was captured. From 20mm mouth opening, the scan adequately captured the hard and soft tissues including the palatal defect. Results are shown on the Table below.

Mouth opening (mm)	Tooth level		Soft tissue level		
	Anterior	Posterior	Palatal Gingivae		Palatal defect
			Anterior	Posterior	
5	×	×	×	×	×
10	×	×	×	×	×
15	✓	×	✓	×	×
20	✓	✓	✓	✓	✓
25	✓	✓	✓	✓	✓
30	✓	✓	✓	✓	✓
35	✓	✓	✓	✓	✓
40	✓	✓	✓	✓	✓

Our results showed that an intra-oral scanner can be used to capture adequate soft and hard tissues at 20mm mouth opening for the construction of an obturator prosthesis. For mouth opening <20mm, there were major deficiencies in the scan which may hinder the construction of an obturator prosthesis.
However, merging limited intra-oral scanning data with CBCT data as described above would address these shortcomings by creating composite digital models.

Future studies will include in vivo assessment of the accuracy and repeatability of the composite models in a fully digital workflow. This will include assessing reduction in clinical time and numbers of appointments and assessing patient related outcome measures.

B. Problems encountered and steps taken to overcome them

In this experiment, the master reference model was made of acrylic, therefore it did not represent the in vivo clinical situation, such as presence of saliva, hard and soft tissues, patient movement, mouth opening and restricting anatomical features such as tongue, cheeks, and lips. Moreover, the use of a CBCT scanner in a clinical situation may yield different results since soft tissues and teeth may scan differently compared to an in vitro experiment. Furthermore, the use of solid models to evaluate deviations on soft tissues, which are movable and compressible in clinical settings, may limit the future applicability of this experiment's results to the clinical situation.

Small Pump Priming Grant Continued...

These issues could not be overcome in this study and will be investigated in the future clinical study.

Gathering accurate data from the intraoral scanners had to be considered carefully as most modern scanners stitch data to there are no gaps in the scan.
Utilising the altered files would have resulted in inaccurate measurements so it was decided to export the raw files from the scanners to overcome this issue.

The accuracy of the 3D printed composite models introduced the stair-step effect which affected models' surface details and smoothness introducing inaccuracies. This was overcome by utilising the highest resolution in the printer which was 16 microns, but this had the effect of increasing printing time (16 hours for 10 models).

The use of an intraoral scanner requires operator experience and in this experiment, it was difficult to scan the palate and the palatal defect using the intraoral scanner. This was overcome by regular training.

C. Collaborations established

This project resulted in close collaboration with the Restorative Dentistry department at Guy's and St Thomas NHS Trust, and the Cancer Centre as Guy's Hospital.
It was carried out in conjunction with The Centre for Oral, Clinical and Translational Sciences and The Academic Centre of Reconstructive Science which is at the forefront of digital technology for maxillofacial prostheses.

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

To be published in due course.

E. Acknowledgements

The Royal College of Surgeons of Edinburgh for their financial support.

Professor David Bartlett and Dr Rupert Austin for providing guidance and assessing the validity of the project.

Miss Sapna Patel, Miss Nour Albuloushi, and Miss Dima Abu Baker for carrying out the research.

Miss Caroline Reed for her help with 3D printing.

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Student Bursary Reports

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Africa Bursary

Trauma, Chris Hani Baragwanath Academic Hospital

Patricia Leitch, final year medical student, St George's University of London

Elective Dates- 02/06/2021 to 27/06/2021

In June 2021 I travelled to South Africa to complete a 4-week trauma elective at the Chris Hani Baragwanath Academic Hospital. The hospital, more affectionately known as "Bara", serves the population of Soweto, which is the largest township in South Africa. Soweto was created during the apartheid era and despite apartheid ending over 30 years ago poverty and gun violence is remains rife. It is therefore unsurprising that Bara is renowned for its expertise in treating trauma victims.

I have had an interest in the more acute side of medicine and so completing an elective in South Africa naturally appealed to me. I certainly may have got more than I bargained for. First year interns are expected to know how to intubate, perform chest drains and basic anaesthetics. I was able to get involved in triaging patients, taking handovers from ambulance technicians, operating the lodox (full body x-ray imaging) performing the primary survey, and initiating initial resuscitation and work-up.

The trauma doctors were keen to teach and I gained experience performing chest drains, FAST scanning and was able to assist in intubation.

I spent the majority of my time in the trauma pit which has 16 resuscitation bays and 11 triage cubicles with 3 dedicated emergency theatres that run around the clock. On my first day I got involved with helping resuscitate victims of gunshots, blunt trauma, road traffic accidents and burns. Without a doubt I seen more trauma in one day at Bara than I had during my entire time at medical school in London. The healthcare needs of Soweto far outstrip the resources of a free public hospital and the medical team gladly welcomed the additional help of elective students. I was taught how to scrub down burns, suture all kinds of wounds from arm lacerations to sucking chest wounds and was able to assist in theatre, including a repair of the common carotid that had been lacerated by a bullet.

I also gained an understanding of the realities of working within a healthcare system that is resource scare. A lack of resources forces clinicians to be creative and look for simple solutions. In this photo, instead of using donated blood products which are scare, blood which was collected from a chest drain was mixed with a saline-heparin solution and transfused back to the patient.

On a personal level I did find the sheer amounts of violent trauma unsettling. It was not uncommon to hear gunshots on my way to Bara and during one of my shifts eight gunshot victims were brought in. “Mob justice” was also common and so severe that victims develop crush syndrome (traumatic rhabdomyolysis). I did spend 3 days away from the trauma pit and was welcomed by the plastics team. The highlight of this experience was assisting with a pediceled pec major flap for reconstruction of an oral defect caused by a gunshot wound.

Overall, the hands-on experience and learning was incredible. This experience has cemented my interest in surgery I hope has made me a better doctor.
This experience has also made me reflect and appreciate how fortunate we are in the UK to have the NHS. I am also very grateful to the Royal College of Surgeons Edinburgh, as without the Bursaries for Affiliate Medical Student Elective Placements in Africa, I would not been able to go on this elective.

Cardiothoracic Bursary

Elective report: Royal College of Surgeons of Edinburgh Cardiothoracic Elective Award

Name: Arian Arjomandi Rad, Imperial College London

Elective placement: ICLAS, Ligurian High Specialty Clinical Institute, Prof. Salvatore Spagnolo

The great complexity, intricacy and potential for innovation which exists around cardiothoracic surgery was one my main motivators in undertaking the following elective.
The elective supported me in my objective of becoming a future highly skilled surgeon and a leader in the field of cardiac surgery. During the elective I worked with the cardiac surgery centre at ICLAS under the supervision of Professor Salvatore Spagnolo. Working with top grade surgeons in a leading centre allowed me to gain an insight into more complex and intricate procedures performed in cardiothoracics. Prof. Spagnolo being the director of the cardiovascular department of the clinic, constitutes one of the highest skilled cardiothoracic and vascular surgeons in Italy, operating on cardiac pathologies (mainly valvular pathologies and coronary pathologies) deemed inoperable and too complex in other Italian Cardiovascular departments.

The elective allowed me to explore both the surgical techniques and the preoperative-postoperative care which these high risk patients receive. During the elective I was able to follow Prof Spagnolo in theatres and on the wards, also being able to build up on my medical knowledge. Additionally, I developed a collaborative clinical project with the surgical team of Professor Spagnolo focussing on their novel microscopic surgical technique for plastic repair of jugular stenosis.
The surgical technique was established by Professor Spagnolo and aimed at treating patients presenting with severe stenosis of the jugular vein using a saphenous or bovine pericardium patch.
The clinical project also focussed on the on the cause of continuous passage of blood from venous system territory to the cerebrospinal venous circulation and possible cohorts for several neurodegenerative diseases.

The research study allowed me to collaborate with the team to assess the role the vasculature in neurodegeneration. The team had already started working on the preliminary findings of the research which give a promising prospect for patients. Through the use of Near-Infrared Spectroscopy (NIRS) and perfusion MRI an assessment of whether stenosis of the jugular vein can determine cerebral hypoperfusion secondary to stagnant hypoxia was also studied. Through this research project I was able further build up on my understanding of cardiovascular pathologies. I am looking forward to set up a collaborative project with centres at Imperial College London to showcase the application of microsurgical techniques in both cardiothoracic and vascular surgery, a unique work carried out only in a few centres in the world, one of them being by Prof Spagnolo at ICLAS.

The Royal College of Surgeons of Edinburgh Cardiothoracic Elective Award broadened my understanding of cardiothoracic surgery and made me determined to pursue this unique specialty in my future. It allowed me to gain a deep insight into the potential for innovations in the field and motivated me into pursuing other opportunities to explores other aspects of this specialty such as Robotic and minimally invasive Cardiothoracic Surgery.

Student details: Momna Sajjad Raja, 5th Year Medical Student, Brighton and Sussex Medical School.

Elective details: Department of Cardiac Surgery, Faisalabad Institute of Cardiology (FIC).

Elective Period: 2/07/2021 till the 27/07/2021.

Elective Supervisor: Professor Shahbaz Ahmad Khilji FCPS Faisalabad Institute of Cardiology (FIC) is a high-volume government-funded tertiary centre located in Faisalabad. It is also known as the 'Manchester of Pakistan' due to its textile production. Built in 2009, FIC covers a catchment area consisting of 7 million people with the next closest cardiac centre being 128 kilometres away in Lahore. Having had most of my exposure to cardiothoracic surgery in the United Kingdom, I was grateful to receive support from RCS Edinburgh to visit FIC for 4 weeks.

Global Cardiac Surgery

At FIC, I was able to see surgical conditions that are at the verge of being eradicated in the high-income countries, such as rheumatic heart disease. Moreover, the burden of cardiac disease is higher as the patients tend to present during later stages of disease progression due to the challenging economic conditions.
This put a lot of pressure on the unit, with the wait list for some surgeons being over 2 years long. Reflecting, this experience taught me the art of being creative and adapting treatment algorithms to provide excellent patient with the resources available. This will be transferable for my future practice in the NHS where I can effectively manage resources to deliver a high-quality sustainable service.

Despite the high-volume load, the quality of care the hospital staff provided was exemplary and comparable to the standard I have seen in the UK. Moreover, patients had their surgeon's personal numbers to contact them if they had any troubles in the post-operative period. This was done in hopes to provide continuity of care and save patients from travelling.

Cardiothoracic Bursary Continued...

Placement

I had an 8am start with most of my time being spent in clinics, theatres, or cardiac intensive care unit (CICU). It was a life-changing experience as I was able to follow patients throughout their journey, from pre-operative clinic to their follow-up appointments. During clinics, I was able to clerk and examine my patients.

It honed my clinical skills as well as understanding the rationale for selecting patients for surgical treatment, and the most appropriate surgical management of cardiovascular diseases.

It was heart-breaking to see that some patients would have travelled hours for their appointment and were staying outside as they were unable to afford accommodation in the vibrant city.

In theatres, I had the privilege of being able to observe various cardiac procedures such as CABG, ablation, mitral valve replacement and repairs. This not only allowed me to solidify my anatomy but also learn more about the complex surgical techniques. I also learnt the importance of teamwork and the crucial role each MDT member plays both, inside and outside, the operative room.

Conclusion

Overall, this elective provided me with undoubtedly an invaluable opportunity to immerse myself in the field of cardiac surgery at a renowned tertiary centre. I was learnt the art of patient care, resource allocation and honed my clinical skills.

Caleb Johnson Personal and Professional Development

I chose this elective project due to my academic interests in the field of congenital heart defects (CHDs). I have done previous secondary research in this area as part of my master's degree dissertation and the student selected component project during my second year of medical school. However, as a medical student, routine exposure and clinical immersion in this area has been minimal - in addition to having dedicated time to focus on this area of interest in a specialist unit due to other concurrent pressures within the curriculum. At the start of block, I felt a mixture of excitement but also nervousness. Managing CHDs is specialised field requiring a high degree of clinical reasoning, understanding of complex anatomy, and manual dexterity in both surgical and interventional facets[1]. Fortunately, at the start of the block I was reminded by one of my co-supervisors of this complexity, and that knowledge and skills come with years of dedication and practice.

When analysing my own abilities as an aspiring surgeon, there are several aspects of improvement I noted throughout the placement in relation to my abilities. One example is the understanding of normal vs abnormal anatomy and its effects on the haemodynamics of the cardiovascular system. Similarly, the ability to conceptualise CHDs due to the heterogeneity between patients requires adequate visual-spatial intelligence to create and manipulate 3D images in one's mind.

Fortunately, this is a skill that can be improved[2] and is aided by advanced imaging e.g. echocardiography and angiography, but nevertheless is a crucial skill particularly for surgeons in intra-operative situations.

This experience also highlighted the importance of communication and from a professional development perspective how it can impact both current and future patient- centred care[3].
A scenario that demonstrated this involved a disruption in communication within the multi-disciplinary team (MDT).
This patient was in the intensive care unit (ICU) awaiting an interventional procedure in the catheter lab. Due to a respiratory illness, it was felt that the procedure should be postponed, but at some point, this was not fully disseminated to ICU staff and subsequently the parents. The result was an unnecessary nil by mouth approach that morning, which understandably led to frustration and confusion that may have otherwise been avoided.

From a clinical skills perspective, I have created a list of skills I aim to improve on in the coming years in my practice as a foundation doctor. An example is pursuing a surgical training course to develop foundational competence in procedures such as suturing, chest, drain insertion etc.

I've found the insight into the importance of communication particularly challenging due to its importance within the structural efficiency of the NHS [4]. This is something I want to carry forward in developing my professionalism as a doctor in the coming years. I look forward to practical application of these skills in workshops at the medical school and within the trusts during the assistantship block.

A Broader Understanding of Health and Healthcare

The field of CHDs and pursuing a deeper understanding in the complexity of their management is crucial within any branch of medicine and surgery. Not only are CHDs the most common birth defect[5], but due to the advancements of management in the previous decades involving surgical and non-surgical interventions, there is an expanding population of adult CHD patients[6]. Even though these patients will require lifelong follow-up with specialists, it is imperative that clinicians and ancillary staff are aware that their unique anatomy and physiology may predispose them to differing complications and treatment regimens for otherwise routine medical or surgical management.

Having been exposed to the criticality of managing these issues, it has certainly enhanced my awareness of the need to take detailed histories and perform thorough examinations in future practice.

Determinants of health and particularly those within CHD patients is something I looked at extensively in my dissertation, particularly with a global perspective[7].

Thinking more locally, I learned from parents that being present with their children (particularly post- operatively) posed great challenges, especially considering Covid-19 restrictions.

Cardiothoracic Bursary Continued...

Additionally, during outpatient clinics I saw the importance of education as caring for CHD patients can be complex with various signs to look out for to know when and how to act[8]. The cardiologists I spent time with were always empathetic to these concerns and took time to ensure that they were addressed fully.
I would be interested to spend time on the other side of CHD management to understand what the transition to adult services entailed. Being able to streamline this transition with confidence may be an area for further research, particularly given the aforementioned demographic shifts of the CHD population.

Priorities for Development

Upon reflection of the elective placement, I have learned several things and been challenged in so many ways.
There are several aspects of managing CHD patients and their accompanying complexities. However, due to the specialisation of this field much of this will invariably require addressing at a further stage in career progression.
However, the importance of teamwork and communication between staff members and with patients and their families is something I can improve on and apply to current practice now as I begin my foundational doctor role. Additionally, I aim to expand my portfolio as I prepare to apply to specialty training in cardiothoracic surgery.
This will entail publishing previously done research projects, completing closed-loop audits, and enhancing basic surgical skills through training courses in addition to daily learning opportunities.

Conclusion

During my time on elective placement in paediatric cardiac surgery I learned so much about strategies in managing these complex CHD patients.
One of the biggest learning points was the way in which various specialties and teams coalesce to form an MDT approach in managing these patients and the importance of good communication and teamwork. I believe I addressed all my aims and objectives for the elective and have been challenged to continue my pursuit in this truly incredible field of medicine and surgery.

References

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3. Mr Nigel Drury (Hunterian Professor and Consultant Paediatric Cardiac Surgeon) for his continued support as my mentor in paediatric cardiac surgery and aiding in facilitating and supervising the elective at Birmingham Children's Hospital.

4. Dr Adrian Crucean (Specialty Doctor in Congenital Heart Surgery and Consultant in Cardiac Morphology) for his aid in facilitating and supervising the elective at Birmingham Children's Hospital.

Russel Trust Bursary Reports

Nadine Paul

I undertook my elective within the urology department at King's College Hospital, between February-March 2021. I thoroughly enjoyed my time within the department, and despite several adaptations being made to the service due to COVID, it was an incredibly valuable learning experience. Seeing how the surgical speciality had been impacted by the pandemic was eye-opening- with surgeries being limited to emergencies or urgent cancer pathways, and staff shortages being even more pressing. Despite these challenges, I found all the surgeons and allied health professionals I worked beside to be incredibly resilient and optimistic, and I appreciated the time they took to teach me more about urology and a career in surgery.

In my first week, I scrubbed into an open nephrectomy to treat an advanced renal cell carcinoma. The patient had delayed seeking medical help for her symptoms of haematuria due to the pandemic and being a nurse herself had not found the time to visit her GP. CT scans revealed a left kidney tumour the size of an orange, and the proximity of the tumour to the great vessels meant that the surgery would be complex. I observed as they carefully dissected the tumour away from these vessels, which proved difficult due to its mucinous consistency. It was incredibly satisfying to watch them remove the kidney and tumour mass in its entirety, and they were hopeful of a complete cure.

Another aspect of my elective that I've thoroughly enjoyed, is my involvement with a urology-based quality improvement project, which looks at whether patients have sufficient knowledge of the potential complications which can arise from a radical prostatectomy when used to treat prostate cancer. The project is still ongoing and aims to assess the patient's understanding of complications such as erectile dysfunction and incontinence and the likelihood of this occurring. This QI has emphasised the importance of clear communication between surgeons and patients, and the importance of adapting language to best suit the patient.

Through this elective, I improved my confidence in my surgical skills and also being within the surgical environment. Before commencing my elective, I had completed a laparoscopic skills course at the learning suite at Guy's hospital, and it was eye-opening to see these skills used so deftly in reality.
One of the highlights for me was the chance to initially observe and later assist with trans-rectal ultrasound-guided trans-perineal prostate biopsies (TP-Bx). This cutting-edge technique is employed in both King's and Guy's hospitals but has yet to be rolled out nationwide.
The ability to perform the biopsies under local anaesthetic enables more patients to utilise the service with a lower risk of general anaesthetic risks.
However, the most impressive feat of this novel technique is the significant reduction in infection rates compared to trans-rectal biopsies (which can have up to a 2% sepsis risk). Each biopsy is preceded by a multi-parametric MRI, which enables the surgeon to map out the prostate and target any suspicious areas- leading to a more accurate rate of detection. This experience enabled me to reflect more on the patient journey, and some of the fears and questions patients have when confronted with a potential prostate cancer diagnosis.

Overall, I found my elective in urology to be an eye-opening experience and it has further cemented my desire to pursue a career in surgery.

William Cambridge, Final Year Medical Student, The University of Edinburgh.

Elective Dates 28th February – 3rd April 2022.

Royal Surrey County Hospital & The University of Surrey.

The Regional HPB unit at the RSCH is a high-volume tertiary HPB centre headed by Professor Nariman Karanjia.
The service includes seven HPB surgeons, including my elective supervisor Mr Adam Frampton, with multiple liver, pancreas and benign operations occurring weekly. The RSCH is also a centre of excellence for minimally invasive surgery, which allowed me to witness complex laparoscopic and robotic HPB surgery for the first time in my career.

From day one at the RSCH I was made to feel welcome by seniors and juniors alike, I attended ward rounds, assisted and observed in theatre, and was allowed into clinic to observe interactions with patients pre- and post-surgery. The fact the unit serves a population of two million meant I was in theatre almost every day, and I was happy to leave the centre having added considerably to my surgical eLogbook. This population size also meant I was able to observe a variety of pathologies both rare and common, improving my surgical and anatomical knowledge, and assisting capability, whilst also demonstrating to me the complexity of HPB surgery and the requirements needed to be a competent HPB surgeon.

Russel Trust Bursary Reports Continued...

The elective solidified my career plans. I had left Edinburgh with a keen desire to pursue a career in HPB surgery, this was developed further in Guildford due to supportive consultants and registrars, who involved me in operations and patient management.
The elective showed me the fast-paced, but meticulous performance HPB surgeons have to achieve, as well as how to manage complications when they do occur.
The elective also allowed me to understand how one balances their research activities and clinical work.

Whilst in Guildford, I was tasked with both working on my own project, a systematic review evaluating different techniques of inducing liver hypertrophy, and supervising two Bachelors of Science students at the University of Surrey with their own projects, following my appointment as a Visiting Research Fellow.
Wanting to pursue a career in academic surgical oncology, this experience of managing clinical and academic work gave me a great insight into the working life of an academic, having to plan one's timetable well, splitting time between theatre and the lab, whilst making sure patient care does not suffer.

Finally, through a generous grant from The University of Surrey, I was able to attend the IHPBA World Congress in New York City with Mr Adam Frampton. This was an amazing experience which allowed me to network, meet, and listen to some of the world's most renowned HPB surgeons, all of whom I have great admiration for.

The trip to New York was also my first time in the United States and I was also able to experience the sights and sounds of one of the greatest cities in the world.

I would like to thank The Russell Trust and Royal College of Surgeons of Edinburgh for their generous support in completing this elective.
It is an experience I will look back on with fond memories for many years.

Images

Image 1, Myself and Mr Adam Frampton in the Operating Theatres of the RSCHImage 1, Myself and Mr Adam Frampton in the Operating Theatres of the RSCH

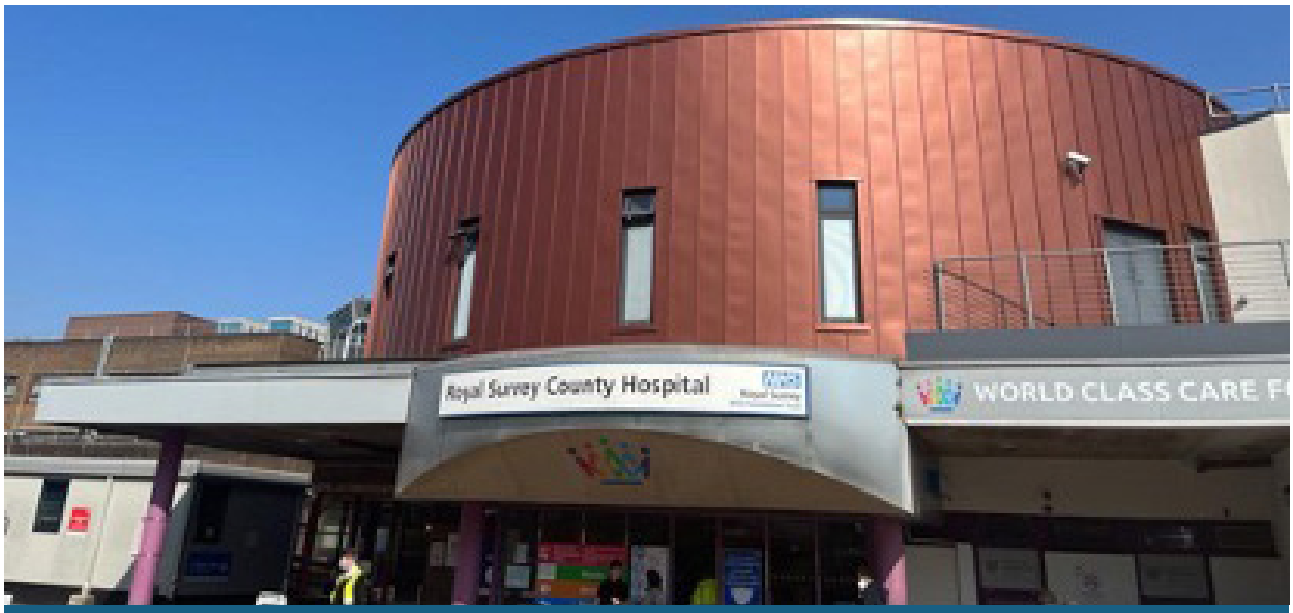

Image 2, The Royal Surrey County Hospital

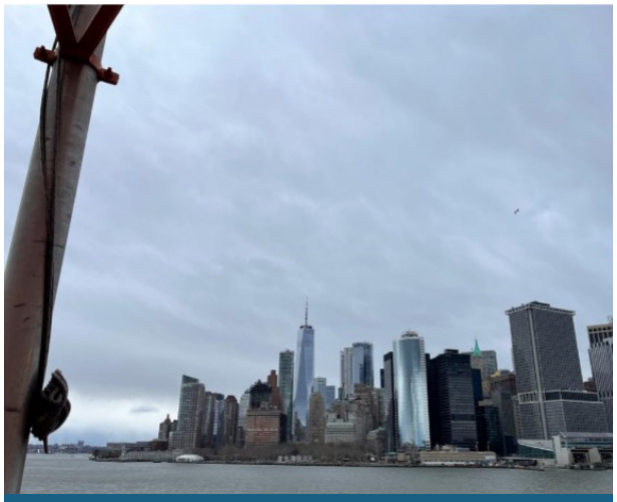

Image 4, Downtown Manhattan as seen from the Staten Island Ferry

Image 6, HPB in the BIG APPLE, IHPBA World Congress

Image 3, Abbot's Hospital in Guildford Town Centre, opened in 1619 as a home for the elderly

Image 5, View of Manhattan from South-North, taken at the top of One World Trade Center

Russel Trust Bursary Reports Continued...

Name: Pan Myat.

Medical School: Cardiff University.

Placement dates:
28/03/2022- 24/03/2022.

Host Institution: Mater Dei Hospital, University of Malta Medical School.

My medical elective took place in the General Surgery department at the Mater Dei Hospital with Mr Gingell Littlejohn and his firm. The placement offered me many learning opportunities within GI surgery as well renal transplantation as this was Mr Gingell's sub-speciality. The elective also proved to be a great experience to get to know Malta's rich culture and heritage through our many excursions across the island.

My placement hours were normally between 7.30 am to 1pm as medical students were expected to have self-study or lectures in the afternoon. In these hours, I attended ward rounds, acute surgical admissions, theatre sessions, endoscopy lists and surgical tutorials with my supervising consultant. I particularly enjoyed scrubbing in for a laparoscopic appendectomy and performing subcutical sutures. I was also able to see laparoscopic and open hernia repairs as well as peritoneal dialysis catheter insertions.

Perhaps the most poignant case I saw was a trauma call for a road traffic accident (RTA). It is well known in Malta that RTAs are becoming more frequent due to lax road rules on the island. Sadly, the patient did not survive resuscitation which required some reflection from me as I had never seen a patient die before.

Another interesting case I observed was a patient with Tufting's enteropathy, a rare genetic disease of malabsorption, who was admitted under Mr Gingell's team for bowel obstruction. He had a complex surgical history due to this disease and his care involved multidisciplinary input from both surgeons and gastroenterologists, as well as specialists from Great Ormond Street Hospital and St Mark's Hospital in the UK. I found it interesting to see the liaison of a patient's care between different countries.

Moreover, I noted some differences within medical training between Malta and the UK despite their close association in the UK Foundation Programme.

The Maltese medical students explained that even in final year, they do not often get time to do skills, help with ward jobs or clerk in patients. We discussed how UK medical students, by clinical school, gain more autonomy and responsibility as we progress through the years whereas in Malta, their main focus of learning is teaching during ward rounds throughout medical school. Another interesting difference was the rota of the junior doctors.

They work Monday to Saturday from 7.30am to 2.30 pm and do on-calls every six days. They spend on average between 60-100 hours in hospital each week. The political nature of junior doctors' contracts in Malta holds many similarities with the discussion around staffing issues within the NHS.

Finally, I discovered on this elective the beauty and richness of Malta as a country. It is a wonderful place to live with friendly people, good food and an abundance of social and cultural activities for everyone. It was a very worthwhile experience, thanks to the funding from RCS Edinburgh.

Claire McGregor

ENT, Cape Town.

Groote Schuur Hospital & Red Cross War Memorial Children's Hospital.

4 weeks 11/4/22-6/5/22.

Worked with Professor Johan Fagan, Professor Darlene Lubbel attended theatre, clinics and ward rounds in both Groote Schuur Hospital and Red Cross War Memorial Children's Hospital. Both were invaluable, as a large number of patients were seen each day. I examined many patients and learnt lots from the team when it came to management. I was able to see acute presentations be taken to emergency theatre as well as many routine ear nose and throat surgeries in both adults and children.

I was privileged to observe endoscopic trans-orbital surgery by Professor Lubbe on multiple occasions.
Although Transorbital neuroendoscopic surgery (TONES) was pioneered in the US, Prof Lubbe was the first to use this to operate on the opposite side of the brain. It was fascinating to be able to witness this surgery from such a renowned Professor and see what such innovation has been able to do for patients with diseases previously thought inoperable. The surgeries I observed were often performed with a view to decompress the optic nerve or repair CSF leaks.
I was also involved in an operating list where the endoscopic surgery was being broadcast live across the world as a tutorial with regards to how to use this specific equipment. This was an excellent learning opportunity, not only in terms of the surgery but particularly how the team communicated to one another and taught viewers across the globe.

Head and neck MDTs were conducted in person and were particularly interesting as once each patient had been discussed, the team would assess the patient who was in attendance in an adjacent room and be able to determine their most current symptoms, concerns and enable consultation directly after discussion of the case. Many of the patients had very advanced oral or neck tumours.

A handful of these patients were in this unfortunate position of their disease being unrescecatable due to being lost to follow up after previous surgery or initial diagnosis. This was upsetting to see, but highlighted the importance of follow-up.

There is a huge wealth disparity in cape town, sometimes evident in the diseases that patients presented to clinic with.
I learnt about conditions that arose due to malnourishment, for example laryngeal disease in a child attributed to malnourishment as this child should have moved on to solid food but was still breastfeeding due to financial difficulty. This was upsetting however doctors were able to escalate patients towards financial support in these situations.

Outside of the hospital, a great wealth disparity was evident. Some of the richest areas of South Africa can be found in Cape Town, however these are starkly contrasted with the neighbouring townships. Townships often have poor infrastructure, limited sanitary facilities, and are liable to flooding. These patients may have to travel much further, or with greater difficulty, to attend clinics, perhaps this is why many patients in the MDT presented with unresectable, advanced tumours as they were unable to attend earlier on in the disease process.

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Elective Report – Paediatric Surgery in The Gambia

Student: Joanna Low, Barts and The London.

Supervisor: Dr Cherno Jallow, Consultant Paediatric Surgeon.

Placement: Paediatric Surgery, Edward Francis Small Teaching Hospital (EFSTH), Banjul, The Gambia.

Special acknowledgements to the Royal College of Surgeons (Edinburgh) for making this elective possible.

I spent a total of 5 weeks in The Gambia doing my elective in Paediatric Surgery at the Edward Francis Small Teaching Hospital, the largest hospital in The Gambia. During my time there, I participated in ward rounds, clinics, theatres and other departmental teaching sessions. I was able to examine patients during clinics, assist in surgery and practise closing up the skin.

The clinical exposure that I received here has been unparalleled. I saw a lot of conditions that I have never seen before in the UK, mostly due to late presentation of disease. Most locals prefer to stick to herbal remedies and traditional healers in the village and wait until they cannot cope with the problem to see a doctor. As such, most patients that I saw had a late stage of disease when they first presented. For example, there was a 15 year old girl who presented for the first time with a rectovestibular fistula – the reason why she only came to see a doctor now was because her parents wanted to marry her off in a few years' time. Other interesting conditions I saw included a tracheooesophageal fistula secondary to battery ingestion, persistent omphalomesenteric duct, bladder exstrophy, disorder of sexual differentiation, large abdominal tumours, caustic ingestion and necrotic penis with unknown aetiology.

This was my first time experiencing healthcare in a low resource setting. Despite having used the phrase "low resource setting" many times previously, it was only until I came to The Gambia that I truly understood what it meant.

There are many differences between the healthcare system in The Gambia and the UK. Despite EFSTH being the biggest hospital in the country, they still lack adequate resources. For example, they have no MRI scanners and the CT scanners that they have were broken during the period of my stay. Manpower is also an issue–there is only one paediatric surgeon and urologist in the entire country, and there usually only one house officer to look after the entire ward (40 patients). The range of medications are much more limited compared to the UK. Power cuts are common and phone torchlights are used during surgery when this happens. Despite this, Gambians are very resourceful and they always find ways to overcome these limitations. They have developed their clinical acumen and surgical skills to such a high standard as a result.

The highlight of the elective has definitely been the new friendships I have formed there. Everyone has been incredibly kind and hospitable, sharing their food with me and looking out for me. I will also miss their lively and energetic culture. Another highlight has been seeing how surgery can make a significant difference in a patient's quality of life – from correcting anorectomalformations to making someone with bladder exstrophy continent, I have seen how these young children and their caregivers have had their lives transformed.

I really enjoyed learning about a new culture and meeting new people, and this elective has definitely strengthened my desire to do more global health work. This elective has also affirmed my interest in paediatric surgery - I like working with this patient group and being able to be a 'true general surgeon' but for children. Seeing that children make up 50% of the population in developing countries, such as The Gambia, there is an urgent need for more paediatric surgeons in these countries.

In the future, I definitely want to come back as a more experienced doctor so that I can contribute more to the health system. In the meantime, I want to maintain these relationships I have formed here and continue working together on joint-research projects and engage in online sharing sessions.

Paediatric surgical ward entrance at EFSTH

Assisting in surgery

With one of our patients on ICU

Me and my supervisor (Dr Cherno Jallow)

Undergraduate Bursary Reports

Name: Violet Borkowska.

University: The University of Edinburgh.

Dates: 31/05/2021 – 27/07/2021.

Location: Department of Plastic, Reconstructive and Hand Surgery, St John's Hospital, Livingston.

Project title: Neurotisation vs regional muscle transfer vs free muscle transfer in facial reanimation surgery – comparative retrospective cohort study of patient outcomes.

Last summer I was very fortunate to receive the RCSEd Bursary for Undergraduate Vacation Studies. The grant allowed me to undertake a retrospective cohort study comparing competing surgical techniques of facial reanimation (neurotisation, regional muscle transfer, and free muscle transfer) in the context of facial paralysis. I conceived the research idea a couple months prior, when I learnt that the choice of facial reanimation surgery is an area of ongoing controversy (Kim & Byrne, 2016). As a result, establishing the best type of surgical treatment was named one of the top 10 research priorities in facial palsy in a Delphi study conducted by Facial Palsy UK and Centre for Appearance Research in 2020.

Since then, I pondered how I could establish superiority of either of these surgical approaches within NHS Lothian and my efforts cumulated in the summer project outlined below.

Having no prior experience of conducting retrospective cohort studies, I began by familiarising myself with the unique advantages and disadvantages of this type of research, as well as the quantitative methods typically used to interrogate datasets. I quickly realised that in order to ensure replicability and external validity of my study, I needed to follow standardised guidelines for cohort studies. I decided to focus on STROBE statements and checklists and used these as a guide throughout my project.

The next step was to identify patients who had undergone a facial reanimation surgery in the NHS Lothian within the past 10 years. To my surprise, obtaining such list proved to be the most challenging part of the project. After numerous discussions with plastic surgeons working at the St John's Hospital in Livingston, I was eventually redirected to the Information Management Team of NHS Lothian.
With the help of the team, I submitted an ORSOS Report Request Form based on which a list of patients' CHI numbers was generated. However, the list included thousands of irrelevant records, and I had to find a way of refining the Request Form. Through trial and error, I settled on using the OPCS Classification of Interventions and Procedures to query the electronic patient records and obtained a more succinct list of highly relevant CHI numbers.

Once I knew which patients to include in my study, I started extracting relevant data from the TrakCare® Electronic Medical Record System. I found navigating the system unintuitive and frustrating, forcing me to seek senior support in optimising my search and query strategies. However, once I gained confidence in finding the information I needed, the data collection process progressed without major complications. I soon obtained an organised dataset full of rich operative and peri-operative data pertaining to each facial reanimation surgery performed in the health board since 2010.

The last step of my project was to interrogate and analyse the dataset I put together. Through my intercalated Bachelor of Surgical Science degree, I have already gained proficiency in data analysis tools such as Microsoft Excel, SPSS and GraphPad PRISM. However, wishing to maximise the learning opportunity of the project, I set out to use the R Studio software for my quantitative analyses.

R Studio is a highly versatile programming platform and is currently the software of choice for most frontline surgical informatics research, hence my interest in it. Having received only rudimentary R Studio teaching in medical school, my knowledge of the R script was far from sufficient to perform complex statistical analyses and thus I needed gain a much better understanding of the R programming language. Thanks to the financial support provided by the College, I was able to access R Studio courses on platforms such as CodeAcademy and DataCamp and apply my newly-found programming skills to my study.

Preliminary results suggest that utilisation of neurotisation approach correlated with the greatest improvement in functional outcomes (such as the House-Brackmann facial paralysis grade), especially in facial palsy caused by trauma. Other factors associated with marked improvements in outcomes were identified, such as younger age, lower ASA physical status grade and nerve insult location distal to geniculate ganglion, highlighting that the success of facial reanimation procedure is highly multi-factorial. As some of the outcomes studied involved a degree of arbitrariness, I decided it will be best for these to be double-scored by a plastic surgery consultant, after which I will assess the inter-rater reliability to corroborate the study's internal validity.

As highlighted by the above summary, every step of my summer research project was an excellent opportunity for me to learn useful knowledge and acquire new skills.

Firstly, I gained an in-depth understanding of the design and conduction of retrospective cohort studies, as well as developing methods of effective data extraction from local databases for the purpose of such research.

Undergraduate Bursary Reports Continued...

As I have discovered a couple of weeks into my Y4 clinical attachments, my ability to effectively navigate TrakCare® records has also allowed me to be more helpful to the healthcare team I work with and become a much better integrated member the team. Additionally, the project gave me a chance to greatly improve my programming skills and confidence in using R Studio, as recognised by a number of DataCamp certificates I obtained. Operating the software is a highly transferrable skill and I am presently already looking into how I could utilise it in my other research initiatives.
On top of all that, and perhaps most importantly, through the project I gained an insight into the patient journey through secondary and tertiary care. Tracking back through the records made me realise how the nature and severity of a condition may affect patient experience of healthcare, and how collective multidisciplinary team effort can make that experience a positive one.

I would like to sincerely thank the College for facilitating this research project and all learning opportunities it provided.
I am also thankful to Mr. Aidan Roche and Mr. Patrick Addison for their patient supervision, and to the NHS Lothian Information Management Team for their input into data collection.
I can wholeheartedly recommend the Bursary for Undergraduate Vacation Studies to any medical student interested in surgical research and academia.

A Multicentre Study Evaluating the Effectiveness of Shock Wave Lithotripsy Management for Ureteric Stones at Tertiary Centres in the United Kingdom Queen Elizabeth Hospital

Birmingham, May-June 2021, KumarOver the last year, I had the pleasure of designing and undertaking a research project in Urology for my Elective.
The project aimed to evaluate the effectiveness of extracorporeal shock wave lithotripsy (ESWL) management for ureteric stones at tertiary centres in the UK and was based at the Urology Department of the Queen Elizabeth Hospital Birmingham (QEHB), a major tertiary healthcare provider. I would like to thank the wonderful team who welcomed me to their busy department, led by Mr Subramonian. I would like to extend my thanks to the Royal College of Surgeons of Edinburgh and Arthur Thomson Trust for their kind financial support.

Prior to commencing the project, I had a brief taster in Urology with my supervisor. The purpose of this was two-fold;

Firstly, I was keen to explore Urology as a clinical specialty and consequently, the opportunity to spend time in theatre observing intricate procedures, ESWL, and on wards practising hands on skills such as catheters was invaluable.

Secondly, this enabled me to brainstorm ideas for meaningful research projects. I discussed these with my supervisor and agreed ESWL effectiveness would be worth exploring. This was confirmed through a literature review, which involved a literature search, title and abstract screen.

Designing the project meant I was solely responsible for conducting these tasks independently and significantly helped develop these academic skills. It also involved seeking ethical approval in a timely manner and ensuring I had familiarised myself with several trust policies regarding data protection, confidentiality and clinical governance. On reflection, ethical approval was the most time-consuming step of the entire project. As I had not submitted a project for approval previously, I wanted to ensure it was as accurate and polished as possible, meaning a slight delay. Fortunately, this had no impact on the project as it was approved well in advance of data collection however, I will make a note to ensure this is completed far in advance of any project I intend to undertake.

Whilst awaiting ethical approval, I expanded upon my academic writing skills through developing the protocol. This was a useful skill as it meant I became familiar with the requirements for applying for funding and meant there was a timeline in place for the project. This is certainly a habit I intend to take forwards to ensure projects are on track.

ESWL is currently recommended as first-line management of acute presentation or readmission for ureteric stones in multiple countries including the UK, in accordance with NICE guidelines. This particular lithotripter model is used at several tertiary centres nationally, providing care to thousands of patients. The aim of the project was to evaluate the effectiveness of the SLX-F2 model, measured by rate of stone recurrence at 3 months follow-up on imaging. Secondary outcomes included complication rates such as pain, renal injury, haematuria and post-operative infection, amongst others. Confounding factors were also measured and analysed during a multivariate analysis.

The bulk of the elective period itself was consumed with data collection for approximately 300 patients. This involved analysing patients' medical records for demographic and operative factors, in addition to reviewing imaging pre- and post-treatment. Data was categorised into four separate areas for analysis, the first being demographics. This included age, gender, WHO status, BMI and eGFR. The purpose of this data was to identify if comparison could be made to other literature and possible confounding factors. Lithotripsy factors measured were numerous; this included, but was not limited to, reason for ESWL, ureter side, number of sessions, stone size, density and skin to stone depth. Outcome variables included stone clearance and date to calculate time to clearance. Additionally, the mode of imaging was noted, whether the procedure was completed and if not, the reason for this, as well as if the patient went on to have surgery and if so, which procedure. Stone composition and analgesia were also noted in the database. The final category was adverse effects. This included whether a patient had an emergency re-admission within 48 hours of lithotripsy and the reason for this, any other complication, and the presence of Steinstrasse.

Statistical analysis demonstrated the overall success rate of ESWL to be 62.64% (n=265; 12 lost to follow-up), with an average time to success of 50.48 days (n=146).

Undergraduate Bursary Reports Continued...

Elective ESWL accounted for 84.48% of procedures, the remainder being emergency procedures. Analysis of factors affecting ESWL success showed that stone size (p=0.004), stone density (p=0.01), and BMI (p=0.033) significantly affected outcome. Success rate was subsequently stratified based on these factors. The highest success rate was found in patients with stones <5mm, density <984 Hounsfield units (HU), and BMI <30kg/m2. Complication rates in the study group were low, with only 7.5% of patients requiring emergency re-admission. Of these, one patient was admitted with urosepsis requiring drainage, the remainder related to pain.

Conclusions from the research include highlighting the importance of counselling patients prior to treatment. Whilst the project in itself was informative and adds to the wealth of knowledge surrounding ESWL, another major outcome from the elective was on the professional development front. I initially aimed to publish the results, however, collaboration with other tertiary centres in the UK as originally planned was not possible due to COVID. I hope this will still be possible in the near future, and if not, aim to publish the data as open access to enable clinicians worldwide to benefit from the data.

Additionally, I successfully submitted to present my work at the University of Birmingham's Annual Clinical Academic Training event.

This involved creating a poster to present the information in a clear and aesthetically pleasing manner.
I subsequently orally presented the project to a panel of judges and was delighted to win first place. More recently, our poster was accepted for oral presentation on an international level at the Association of Surgeons in Training Conference; an incredible additional outcome from my elective.

I am very grateful for my elective experience, which was incredibly useful for both my clinical and professional development. The skills I have developed through this project, including academic, clinical and interprofessional have been invaluable and will no doubt stand me in good stead for future research endeavours throughout my career.

Name: Melina Pelling.

University: University of Warwick.

Dates: 05/07/2021 – 13/07/2021.

Location: Department of Surgery and Cancer, Imperial College London, London.

Last summer I was fortunate enough to be awarded the RCSed Bursary for Undergraduate Electives which enabled me to complete a 6-week research project in London.

The title of my project was Salivary volatile organic compound analysis for early non-invasive detection of Oesophagogastric cancer.

There were several reasons why I wanted to do a project like this.

Firstly, my previous degree was in biochemistry and during this time I found that, although I knew I wanted to pursue a career in medicine, I also enjoyed being in the lab, therefore I decided to undertake a lab-based project at St Mary's Hospital.

I was also in my first year studying medicine and I wanted to put some of the techniques I learned in my previous degree to use. Lastly, I am interested in a career in surgery, and I wanted to explore the academic aspects of a surgical career. When I came across this bursary, I was very excited as I knew this would allow me to spend most of the summer exploring a topic and career that interests me.

Before this project, my only experiences in a lab had been through my previous degree where choices were limited, and you were not always able to do something of your own interest. I was keen to pursue a project which really interests me and has clear application in my future career.

I was also looking forward to working with like-minded people who could guide me in the right direction at this stage of my career.

During my time at St Mary's, I met so many amazing people who were kind and helpful throughout my project and after. I was able to learn more about a career in surgery, academic medicine and how they both intertwine. I was surprised about the variety of projects happening in one department and it showed me that the possibilities are endless. There were many new aspects of research which I wasn't familiar with such as ethics approval, recruiting participants and the use of tissue banks.

Throughout the project I was exposed to these, and I feel that I now have a sound understanding of how medical research projects work.
This project also exposed me to the realities of lab-based research, and how things can go wrong, be delayed and be extremely time consuming.
When doing a lab-based project you rely on having enough resources, equipment functioning properly and the schedules of other researchers in the lab. While these may not directly relate to one's project, they have an impact on how smoothly a project can run. I feel that I now have a realistic view on what a career in academic surgery may be like, and this project has given me the independence to start making plans towards my future career.

As well as learning about the career and how research projects work, I also gained practical lab skills which I can take with me into future projects. I became familiar with mass spectrometry by using machines such as the SYFT-MS and observing other researchers using various types of mass spec techniques. These skills are invaluable, and I believe it will help me when applying for future projects and jobs. Even during this short time, I could see the progress I was making in my own confidence and ability to learn new skills and put them to use immediately.
This made me feel useful and like I was a valued member of the team.

I also learned more about oesophagogastric (OG) cancers, their treatment pathways and why projects like this are so important. Treatment for patients with OG cancer is limited and if not eligible for surgery they are placed on a palliative pathway. Even the patients who are eligible for surgery undergo resection of their oesophagus or stomach, which is lifechanging and not without risk.

Undergraduate Bursary Reports Continued...

It was interesting to see the variety in work 'behind the scenes' for cancer patients, and to see first-hand how important good diagnostic tools can be.
When learning about the tissue banks, I was lucky enough to be able to observe an oesophagectomy; here I was able to see the direct interaction between surgery and research. I found this experience inspiring, and it solidified my interest in a career in surgery.

Overall, I had such a positive experience during my project, and it was because of this bursary that I was able to undertake research during the summer.

The knowledge and skills that I gained will be extremely beneficial in my future, and the confidence I gained throughout the project has changed the way I view opportunities. Before starting the project, I was curious about a career in academic surgery and having learned more about it and experiencing some of it first-hand I know that this is something that I am interested in and want to pursue further.
I understand that if unpaid, opportunities like this can be difficult and only seem possible to those who do not need to work during the summer.
However, with bursaries like this available it gives students the opportunity to pursue an interest without sacrificing potential money earned.
I would strongly recommend applying for this bursary because as well as being able to earn money, the experiences I had during my time in the lab and hospital were invaluable and I learned so much from the people around me, things that I probably would not have learned in medical school. It can be hard to find the time to take part in research during the academic year, and for me, having the opportunity to do this in summer meant that I was able to put a lot more focus into my project and get the most out of this learning experience.

I would like to sincerely thank RCSed and the Department of Surgery and Cancer at Imperial for providing me with such a fantastic opportunity.

Name: Tengku Nur Sabrina binti Tengku Saifudin.

University: University of Glasgow.

Dates: July 2021 - September 2021.

Location: West of Scotland Regional Maxillofacial Unit, Queen Elizabeth University Hospital, Glasgow.

Project Title: Evaluation of Microbiotal Changes in.

Head and Neck Cancer

I undertook my elective at the West of Scotland Regional Maxillofacial Unit based at the Queen Elizabeth University Hospital in Glasgow.

This unit provides a diagnostic and management service for all of the principle subspecialties of oral and maxillofacial surgery (OMFS), including head and neck oncology, craniofacial deformity, temporomandibular joint disorders, trauma and salivary gland diseases; providing the opportunity to gain a wide range of experience in the specialty.

Having previously completed student selected components in Head and Neck Oncology with both the ENT and OMFS departments, I have been involved in several retrospective cohort studies and other smaller scale projects. The Royal College of Surgeons of Edinburgh Bursary for Undergraduate Elective or Vacation Studies allowed me to take part in an exciting project during the summer period when the formal requirement for electives had been suspended by the medical school due to the COVID-19 pandemic.

The West of Scotland Head and Neck Cancer Network manages over 700 cases of head and neck cancer each year. Smoking and excess alcohol consumption are two well known risk factors for developing head and neck cancer, but despite decreasing trends in these lifestyle factors, the incidence of head and neck cancer in Scotland has increased in the last 10 years. Unpublished data from our department and reports from other institutions have identified a distinct cohort of non-smoking and non-drinking patients presenting with dysplasia or invasive carcinoma. This group has a higher proportion of female cases, a different subsite of disease pattern, present later in life and have worse disease free and overall survival outcomes. This suggests an alternative aetiopathogenesis for this disease.

Recent research identifies differences in microbiome, tied to socio-economic, lifestyle and diet factors that may impact the presentation of cancer and precancerous changes.
The prospect of better understanding the microbiota in the head and neck cancer and precancer population leads to intriguing therapeutic possibilities.

This project was an observational study to identify distinct patterns of oral, circulating and gut microbiotal diversity between head and neck squamous epithelial dysplasia and invasive carcinoma, with or without traditional risk factors for the disease, and the established age and sex matched disease-free population. Patients with current or previous oral epithelial dysplasia or cancer were asked to provide a salivary swab, blood and faecal samples. The presence of microbial DNA within these samples were analysed and the data correlated with clinical information including tobacco and alcohol use, dental history, presence of periodontal disease, disease site and treatment modality. Comparison was then made with the established microbiome of the normal population from the same geographical location.

Through my involvement in this project, I have gained a clearer understanding of high level research methodology, from inception, through to the publication process. Prior to this elective period starting, I was a significant contributor to the ethics application process through the Integrated Research Application System (IRAS) and in the protocol development of this study.

Undergraduate Bursary Reports Continued...

This has given me insight into how arduous these administrative processes can be and thus, completing these tasks for future projects ahead of time will allow me to fully immerse myself in the clinical aspects, data, analytics and write up of the project.
I also completed the introduction to Good Clinical Practice (GCP) module from the National Institute for Health and Care Research (NIHR) to gain an understanding of the standards expected to be upheld when conducting clinical research.

I was responsible for the overall logistical running of this study during this elective period. I have gained valuable organisational, time management and team working skills through my involvement in this project.
I had to coordinate patient appointments, equipment, sample collection from patients and data collection from electronic health records with various members of the team, and collection of samples by the university laboratory for analysis.
These are skills that I have carried forward and allowed me to continue working on this project as I returned to my final year of medical school once this elective period had ended.

One of my main roles was to identify eligible patients from clinics and theatre lists, provide verbal and written information about the study, and follow up with a phone call to answer any questions.

I would then organise for these patients to return to the clinic to obtain consent and collect samples. My involvement in patient recruitment, as well as being present during the consent process which was undertaken by a senior clinician, provided an opportunity to learn valuable communication skills beyond that of the medical school curriculum.
It was important to build a good rapport and communicate empathetically, given that many of these patients had just received a cancer diagnosis.

Since a blood sample was required from each patient enrolled in the study, I had ample opportunity to practice my clinical skills in venepuncture which gave me further confidence upon returning to clinical placements on the wards.
I also learned the importance of diligence and attention to detail during the data collection process.

In addition to my involvement in research, I was also able to access many clinical opportunities within the department.
I was able to observe and assist in theatre for many OMFS procedures including head and neck cancer resection and free flap reconstructions, salivary gland surgery, drainage of abscesses, and fracture reduction and fixations. This allowed me to conceptualise and put into practice my knowledge of head and neck anatomy from medical school.

Under appropriate supervision, I had the opportunity to practice my surgical skills in theatre including suturing and harvesting skin grafts, as well as carrying out dental extractions.

I also attended weekly multidisciplinary team meetings which gave me an insight into how diagnostic and management decisions for head and neck cancer patients are made and the various roles each healthcare professional plays. Attending clinics and ward rounds allowed me to gain a better understanding of both inpatient and outpatient management, as well as an appreciation for the importance of post-operative care and rehabilitation. As the pandemic had severely limited clinical opportunities for medical students over the last year, I was grateful to be able to access a large amount of clinical training during my time spent in the department.

This elective provided the opportunity to network and gain valuable career advice from trainees and consultants in the field of OMFS. My involvement in the project remains ongoing and we have plans for our work to be presented in the future, as well as submitting manuscripts for publication once data analysis has been completed. I have a better understanding of what a career in academic surgery entails and look forward to both the clinical and research aspects of my future career.

This elective has been an incredibly rewarding experience. I have gained a wealth of clinical and research skills, as well as developed personally and professionally during this time.
I would like to extend my deepest gratitude to Professor James A McCaul for his supervision, the entire OMFS team for being so welcoming and RCSEd for their generous bursary which made this period of elective study possible.

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