Medical Research Council Confidence in Concept
Sheffield Consortium Funded Projects
Non-Confidential Abstracts

Rounds
Round 4 1
Round 5 7
Round 6 8
Round 7 13

Round 4
1: Dr James Alix, University of Sheffield
In vivo Raman Spectroscopy: shining light on neuromuscular disease
Disorders of nerve and muscle, collectively known as “neuromuscular disorders” pose considerable diagnostic challenges, leading to delays in diagnosis and treatment. To improve the diagnostic pathway this study will investigate the utility of a novel Raman Spectroscopy probe, constructed within a standard hypodermic needle, to study different models of neuromuscular disease and human biopsy tissue. This project will investigate whether the biochemical “fingerprint” recorded from muscle can discriminate between normal and diseased tissue using in vivo recording from murine models of disease and human muscle biopsy specimens. The aim is to develop a new bedside test that can make the diagnosis of nerve and muscle disorders easier and quicker. The technique also has the potential to be used to monitor disease progression in clinical trials, as well as in preclinical models, providing a translational research tool.

2: Prof Fiona Boissonade, University of Sheffield
Microstereolithography printed nerve guides for long-gap injury repair
There are 300,000 peripheral nerve injuries per year in Europe (Macromol Biosci 6:13–26) (1 in 1000 children and adults), arising predominantly via work, domestic and traffic accidents. Microsurgical repair is the mainstay of treatment, with direct end-to-end suturing of the two nerve ends. However, this approach is not appropriate for longer gap injuries (usually >1–2 cm), as tension in the nerve inhibits regeneration. Longer injury gaps are usually bridged with a nerve autograft, where reinnervation may be achieved, although functional recuperation of muscle movement and skin sensitivity is often poor. Further morbidity may also occur related to loss of neuronal function at the donor site. The use of nerve guide conduits (NGCs) has the potential to avoid this donor site morbidity; however existing conduits produce inadequate regeneration, due to suboptimal materials and fabrication techniques. Current NGCs are produced via simple extrusion methods, giving poor control of the structure. We have recently published a study that demonstrates the ability to manufacture an NGC by photolithography with micrometre resolution (microstereolithography), that is biocompatible and can support regeneration across a 3-mm gap injury in the mouse common fibular nerve over 21 days – equivalent to that achieved with an autologous nerve graft. The main aim of this project is to therefore to manufacture and test a nerve conduit made from a FDA-approved material to establish its ability to promote nerve regeneration over a larger 6-mm gap injury in the mouse sciatic nerve. This will provide proof of concept that PCL nerve conduits fabricated using our microstereolithography methodology are suitable for long-injury gaps such as those occurring in patients.
3: Prof Neil Bricklebank, Sheffield Hallam University
IN-CROWD Cytotoxicity Screening and Efficacy
Testing infected chronic wounds are one of the biggest challenges to healthcare because they are difficult and, consequently, expensive to treat. In the UK there are approximately 200,000 individuals suffering from a chronic wound (predominantly leg ulcers, pressure ulcers, and diabetic foot ulcers) at any one time. The majority of these patients are elderly and/or diabetic and are mostly cared for by nurses in the patient's home or in community-based settings. The annual direct cost to the NHS of caring for patients with chronic wounds is estimated to be to near £4 billion. Failure to treat the infection effectively can have a major impact on patient quality of life requiring hospitalisation and leading to life-threatening sepsis; UK government statistics for 2011 clearly identified bed sores to be a contributory factor in almost 800 patient deaths. The most common treatment for chronic wounds is the topical application of an antibiotic or antimicrobial agent called a biocide, or dressing containing a biocide, which exerts a broad spectrum of non-selective antibacterial action. The biocides act at multiple sites within microbial cells, reducing the likelihood of bacteria multiplying. The most commonly encountered biocides include silver, iodine, chlorhexidene and polyhexanide (PHMB), as well as raw honey, a natural product. The effectiveness of these agents against different bacteria varies considerably. Recent years have seen significant advances in the development of new materials for wound dressings, often based on nano-silver. Studies have suggested, that nano-silver, which has a cost premium, may have limited clinical benefit and may actually be cytotoxic. Many of the antimicrobial gels and solutions do not offer prolonged activity against a broad range of pathogens and therefore need to be changed frequently which is a logistical and capital drain on healthcare providers and is often stressful and technically demanding for the patient. A particularly relevant issue is that many of the controlled release dressings deposit a high initial dose of antimicrobial agent followed by a rapid falling-off; sustained release of the active agents over the lifetime of the dressing (ideally 7 days), would be preferable since this would minimise the number of treatments required, speeding-up the healing process and reducing inconvenience to the patient. We have developed a new dressing that delivers the biocide for up to 7 days and which is extremely effective against a range of bacteria frequently encountered in infected wounds (Fig 1). The aim of this project is to complete additional cytotoxicity testing on the dressing and evaluate its efficacy in a tissue model that replicates the real-world environment of a patient's skin. The data obtained will enable us to attract clinical and commercial partners and move the project forward along the translational pathway so that the socioeconomic benefits of the dressing can be promptly realised.

4: Prof Charmaine Childs, Sheffield Hallam University
Prognosis of Surgical Site Infection using Infra-Red Thermal Imaging (IRTI)
Women who have a high body mass index (BMI) are most at risk of developing a wound infection after giving birth by caesarean section (CS). Our research team has new evidence, across all BMI categories, that thermal images taken from the area of the caesarean section scar could detect signs of potential infection within just 48 hours after surgery. Looking at wounds in the visual spectrum is our traditional approach to wound assessment but we could "see" more. Our research is taking wound assessment to the infrared. From our preliminary observations, we have discovered that infected and non-infected wounds have a distinct thermal signature. We now aim to test this wound thermography concept in identifying patients at risk of infection before it becomes visually apparent. As women leave hospital within just a day or so after the birth of their baby, the majority of wound infections develop at home, typically in the second or third week. However caesarean section is just one of many types of surgical procedures where our technique could be useful. Therefore there is the potential for wider impact for all surgical patients once our thermal imaging technique has been shown to perform well in stratifying patients to low or high risk of postoperative wound infection. Wound infections are a significant personal and healthcare problem. Hospital re-admissions are disruptive and distressing for patients and the associated NHS costs are doubled if a patient has to return to hospital when their wound breaks down and becomes infected. As there is no other independent, non-invasive technique for early surgical site infection diagnosis or wound tracking, our research has potential to bring tangible benefit to patients, new wound assessment "prognosis" as well as NHS cost savings.

5: Prof Frederik Claeyssens, University of Sheffield
Developing a manufacturing strategy for the tissue engineering of pre-shaped small diameter blood vessels
Globally, cardiovascular disease is the number one cause of death. Treatment by surgical intervention is commonplace and there is a great need for suitable blood vessels for use in bypass surgery and the creation of vascular access conduits. Currently, utilising autologous veins or arteries represents the gold standard for
vascular grafting. However, these vessels are of limited availability, may be of poor quality and their extraction causes donor site morbidity. Synthetic vascular grafts are also available, constructed from materials such as polytetrafluoroethylene (PTFE). Although these grafts have shown satisfactory performance as large and medium diameter vessels, they remain inferior to autografts for small diameter applications (<6 mm) and their use is only recommended in such cases if a suitable autologous vessel is unavailable. Tissue engineering offers a potential alternative to autologous vessels or synthetic vascular grafts. Tissue engineered blood vessels (TEBVs) may be grown in vitro for implantation as bypass grafts, vessel replacements or vascular access conduits. These vessels could offer superior performance to synthetic grafts, due to the biological nature of their construction, and be obtained without the need for invasive autograft harvest. Important properties for these vessels are the burst pressure (should be ~2100 mmHg), suture retention strength (should be ~1.9N) and compliance (should be ~25%/100mmHg)[1]. Prominent research groups have made great strides towards producing TEBVs with some products currently undergoing clinical trials [1]. However, the technologies demonstrated by these researchers only offer the ability to generate uniform tubular blood vessels and they would be very difficult to adapt to producing more complex shapes. This is due to their use of sheet-based manufacturing methods which greatly limits the potential to build complex 3D structures. Natural vasculature is composed of complex geometries (tapers and bifurcations) and it has been suggested in a number of studies that the geometry of the vascular constructs created during surgery has a strong influence on their performance. The ability to generate TEBVs with varied geometries would therefore be of great potential benefit. Additionally, the mechanical properties of the leading TEBVs produced to date fall short of those defined above, particularly in relation to vessel compliance. This may limit their clinical success, as graft mechanical properties are strongly linked with performance. Inferior compliance has been linked to the amount of elastin generated in the TEBVs in vitro. Leaders in the field have produced TEBVs by culturing cells on degradable, but stiff, scaffold materials. This limits elastin production, as it has been shown that this is enhanced by the use of elastomeric scaffold materials.[1] Building on previous work, this project aims to further develop a method of manufacturing TEBVs with varied geometries and high elastin contents. In this project these implants will then be explored in vivo for the first time in a relevant animal model. Using a proven approach [2], TEBVs are produced in vitro in a bioreactor by seeding stem cells onto a degradable polymer scaffold and then culturing under physiologically relevant flow. These vessels are then decellularised, using enzymes and detergents, to remove the cellular components leaving behind a non-antigenic construct, composed of only extracellular matrix (ECM) proteins, suitable for implantation. The unique selling point of our approach is the ability to produce porous scaffolds with user-defined geometries from an elastomeric and rapidly degradable material on which TEBVs can be cultured. This allows for the production of TEBVs with improved elastin contents and shapes more complex than those produced currently (simple tubes). This places our approach at the forefront of the state-of-the-art for TEBVs.

6: Dr Charlotte Elder, University of Sheffield / Sheffield Children’s NHS Foundation Trust
The pharmacokinetic evaluation of a novel non-invasive Short Synacthen Test

The adrenal glands sit above the kidneys and are part of the body’s endocrine system. They produce a number of different hormones; those involved in metabolism (cortisol), salt and water balance (aldosterone) and sex steroids (oestrogen and testosterone). Adrenal insufficiency describes the inability of the body to produce adequate levels of the vital stress hormone, cortisol. It is associated with considerable mortality and morbidity. There are numerous causes, both in adults and children. The most common cause in adults from the developed world HIC is autoimmune destruction of the adrenal gland but worldwide it is TB. The commonest paediatric cause is the prescription of steroid medication. Adrenal insufficiency is usually permanent but may be transient, especially in babies and children, and therefore periodic diagnostic testing is required in some patients (3 monthly). The Short Synacthen Test (SST) is the first line and most popular diagnostic test for adrenal insufficiency worldwide. In recent years requests for SSTs have risen in line with increased paediatric steroid usage and heightened awareness of the adrenal insufficiency steroids can cause. The SST requires intravenous cannulation and blood sampling. It is thus invasive, resource-intensive (requiring a daycare admission and trained personnel) and unpleasant for the patient; leading to a rise in both the cost and threshold for investigation. We have developed a non-invasive alternative to the SST, with Synacthen given nasally via a spray and the resultant cortisol and cortisone responses measured on saliva samples. In earlier studies we devised novel formulations of nasal Synacthen (Nasacthin), combining a higher dose of Synacthen with a nasal drug enhancer (chitosan) to improve absorption, and performed pharmacokinetic studies in both adults and children validating our chosen formulation (Nasacthin003). The five studies to date have shown Nasacthin to be reliably absorbed and well tolerated. Our non-invasive test would negate the need for needles and reduce (indeed in some cases avoid entirely) lengthy hospital visits, thus dramatically reducing costs for the healthcare provider and importantly improving the overall patient experience. The novel test has utility in the inpatient, outpatient
and community settings, in adults and children, and will provide a vital research tool for future studies on the adrenal response to steroids in many diverse patient cohorts, including children. Having validated the non-invasive test, in both adults and children, and produced data to support regulatory approval for commercialisation, the next stage of our workstream is to gather normative data in the healthy paediatric population. Currently diagnostic cut-offs for the SST are derived from adult data and this next study will allow us to establish the first normal ranges for the SST in children before going on to study children at risk of adrenal insufficiency.

7: Dr Munitta Muthana, University of Sheffield

**Magnetic Device for targeting therapies to the brain**

We have developed magnetic targeting strategies in Sheffield that can be used to steer therapies from circulation to inaccessible tissues and organs located deep in the body whilst reducing unwanted delivery to healthy tissues (http://www.bbc.co.uk/news/health-33957105). We now wish to extend these studies to provide highly personalized and an economical form of therapy, using Neodymium permanent magnet arrays specifically designed to guide therapy for each individual patient. To achieve this, we will use 3D printing and other rapid prototyping techniques to build an accurate physical flow test model, based on the fully segmented 3D MR scan data, so that we can accurately measure the personalised gradient fields and magnetic particle trapping capability for a range of tumour locations within the representative model of the head. 3D printing and other rapid prototyping techniques will be used to manufacture the magnetic array, tailored to the precise surface geometry of the head, to enable a patient to wear the magnetic device while the therapeutic agent, attached to small ferromagnetic particles, is infused. Our ultimate aim is a full clinical trial of the device in humans. Although this is not feasible in this proposal, we do intend to miniaturise the device for pre-clinical evaluation in mice of the complete procedure to generate confidence in the concept.

8: Prof Amaka Offiah, University of Sheffield / Sheffield Children's NHS Foundation Trust

**Vibrascan: Vibration as a Tool for Bone Density Assessment in Children**

Reduced bone density (osteoporosis) causes weak bones predisposed to fractures. It is a global health issue associated with negative health and economic consequences. In the United Kingdom (UK) for example, in 2010, the National Health Service (NHS) spent 3.5% of its total budget to treat people with osteoporosis. Peak bone mass (PBM) refers to the maximum amount of bone accumulated by an individual (usually by early adulthood). It is well known that a high PBM is protective against fracture and osteoporosis in later life. Causes of osteoporosis may be primary (e.g. osteogenesis imperfecta) or secondary to a large number of conditions and drugs (e.g. age-related, cystic fibrosis, Duchenne muscular dystrophy, leukaemia, steroids). Osteoporosis can be prevented and treated, therefore it is important to make a positive diagnosis, ideally before any fractures have been sustained. Conversely, it is also important to exclude osteoporosis (e.g. in an infant with multiple fractures who may have been abused). The current gold standard for diagnosing osteoporosis is by using dual energy x-ray absorptiometry (DXA) to measure bone mineral density (BMD). However, DXA uses ionising radiation and is unreliable in children below 5 years old (some would argue that it is unreliable for all age groups, children and adults). Vibration analysis is a well-established technique for analysing the physical properties of various materials and so has the potential for assessing BMD. Our overall goal is to further develop and investigate low frequency vibration analysis as a tool to assess BMD, particularly in children. As part of a PhD study, we initially tested the concept on a set of wooden blocks of known variable densities, then moved on to turkey legs, results of which encouraged the development of a small clinical study in which vibration was compared to DXA in 41 children aged between 7 and 15 years old. The correlation coefficient values between vibration outputs and DXA-derived BMD values were 0.79 and 0.86 for impulse and continuous vibration methods respectively. Through the development of a number of novel approaches, it was demonstrated that vibration analysis may be effective in assessing fracture risk, but further work is needed to make it clinically deployable. We now wish to progress the development of the tool by liaising with a design company (257 Ltd) to produce a hand-held device, which process will require patient & public involvement (PPI) to ensure a child-friendly design. Further hardware and signal-processing development is required as is validation of the technique on a larger number of patients, including of a younger age group.

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9: Dr Cecile Perrault, University of Sheffield  
**High-throughput shear stress assay device**

High shear stress has been shown to play a critical role in cardiovascular diseases, and more specifically, cells exposed to it appear to be protected from the complications associated with atherosclerosis. Yet the mechanism behind this protective phenomenon is unclear and research to identify the protective mechanisms involved is restricted by a lack of appropriate testing systems for large-scale studies. Currently, the only technology that allows culture of cells under high shear stress – microfluidic systems - is technically complex, requires extensive training, does not allow high-throughput and challenging for long-term culture. It also requires significant initial capital investments. We have developed a new device aimed specifically at overcoming those challenges and enabling increased throughput of cellular screening for target molecules and genes. Our device is an easy-to-use, hands-off system that employs magnetic force to drive flow in 96 well-plates. The system has been specifically devised to fit in incubators and to enable researchers to perform high-throughput long-term culture of cells in a high-shear stress environment with a hassle-free system. This project will enable us to build on our preliminary work with this device and carry out feasibility studies for manufacturing.

10: Dr Ivan Phelan, Sheffield Hallam University  
**VR Pain Control**

Patients with chronic wounds experience acute pain during dressing changes. This is currently addressed by using strong analgesia, including opiates, which can have unwanted side effects and dependence. This project seeks to investigate how pain and anxiety can be reduced by using immersive distraction techniques in a Virtual Reality (VR) ‘game’, controlled through eye and head movements.

11: Dr Roslyn Simms, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust  
**Automated Determination of total kidney volume to Personalise Prognosis in Polycystic Kidney Disease**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common lethal inherited kidney disease and the fourth leading cause of end stage renal failure (ESRF) in adults worldwide. The condition involves the gradual progressive development and growth of cysts throughout the kidneys which compress and destroy normal kidney tissue resulting in an increased kidney volume. Total kidney volume (TKV) is an approved marker of disease progression, however measuring it is laborious and its use is restricted to research studies. There is a clinical need to resolve this, highlighted by the recent availability of the first treatment to slow disease progression, there is a need to promptly identify patients at highest risk to enable initiation of treatment. The gold standard method of measuring TKV is manual segmentation (tracing the kidney outline) of the kidney on magnetic resonance images (MRI). This is time consuming and dependent on the skills of an experienced operator. Using an INSIGNEO (Institute for in silico medicine) bursary, we have developed a fast semi-automated technique of measuring TKV, Sheffield TKV Tool, which outperforms existing methods of estimating TKV. In the majority of the 120 polycystic kidneys evaluated, the Sheffield TKV Tool measurements were closely comparable to manual TKV results. However, further development of the technique is required to optimise it for translation into clinical use. This project will address the limitations in our existing Sheffield TKV Tool to deliver a fast, reliable, accurate product fit for clinical use in patients with ADPKD and fulfill the current healthcare demand. We envisage that this would ultimately have application internationally, addressing a clearly identified need, and would have considerable commercial potential.

**Round 5**

12: Dr Ian Wilkinson, University of Sheffield  
**Hypoparathyroidism**

Hypoparathyroidism, characterised by low PTH levels, is a rare condition either congenital or more often acquired following surgery to the neck. Patients die from low calcium levels unless they receive treatment and even on current treatment patients, especially those with congenital disease, suffer considerable morbidity including seizures, impaired neurological development and renal failure. Current treatment regimens are inadequate as vitamin D doesn’t correct the renal defect, calcium levels fluctuate and treated patients have a lower quality of life, an increased incidence of depression, infections and renal kidney failure. This project will deliver preclinical proof of concept for a long-acting PTH molecule to provide a weekly physiological PTH replacement therapy for hypoparathyroid patients.
13: Dr Tim Nichol, Sheffield Hallam University
Urinary tract infection (UTI) is one of the most common types of infection, affecting an estimated 150 million people worldwide. Of these approximately 80% are associated with catheterization. UTI is the second most common healthcare associated infection in the UK, and a significant cause of morbidity and cost. The cost of UTIs exceeds $2 billion per annum in the US alone and catheter-related bloodstream infections have been estimated to cost the NHS £19.1 - £36.2 million per year. UTIs are caused by a range of Gram positive, Gram negative and fungal pathogens with Escherichia coli accounting for 70-80% of all cases. Infection progresses via adhesion to the catheter surface and formation of a biofilm. Effective treatment involves the use of antibiotics, however there is increasing multidrug resistance, notably ESBL and carbapenemase producing enterobacteriaceae including E. coli, which are among the top three ‘critical’ antibiotic resistant pathogens identified by the WHO. This has resulted in a need for alternative non-antibiotic based antimicrobial therapies to be developed. We have previously developed a single layer, silica-based, sol-gel coating displaying controlled release of antimicrobial agents. We have data which show the feasibility of putting non-antibiotic based agents individually and in combination, into sol-gel coatings to prevent biofilm development. The technology has demonstrated antimicrobial and antibiofilm activity against planktonic cells and established biofilms of a panel of clinically relevant microorganisms. This project will support further development of the technology to take this technology toward market.

14: Dr Ivan Phelan, Sheffield Hallam University
Children who have injuries to their upper limb and hands often have to undergo complex repetitive therapy exercises that may also be painful to regain optimum function of the hands. It can be very difficult to motivate children to perform these exercises. This project aims to develop interactive Virtual Reality (VR) play scenarios which will require the children to perform the required movements such that they become so engrossed in the VR interaction they become unaware or much less aware of the pain associated with the exercises. Patients would perform the exercises recommended by their pace (over time, by movement or both). The system would monitor adherence to the exercises and progress made. Repeated sessions would enhance the prospect of good and/or complete recovery with optimal restoration of function. The developed system could be made available for patients to use at home, by them using existing computers or games consoles and VR headsets. Different scenarios would be made that would appeal to children’s different motivations to engage.

15: Prof Bazbek Davletov, University of Sheffield
This project aims to demonstrate enhanced therapeutic efficacy of double-binding non-paralytic botulinum molecules in animal models of neuropathic pain and migraine. Currently paralytic botulinum neurotoxins are used for treatment of non-motor neurological disorders with a tight therapeutic window due to the ensuing muscle paralysis. We created non-paralysing neuronal blockers and demonstrated their efficacy in pain treatment. We had to use 100 times higher amounts of the bacterial proteins compared to current botulinum injections. Recently we demonstrated an increased efficacy of botulinum molecules when we duplicate botulinum binding domains, however the quantitative measurement of enhanced neuronal blocking activity in animal models is still missing. We now propose to test improved botulinum molecules in preclinical models of neuropathic pain and migraine paving the way for the development of novel therapeutics for chronic neurological disorders.

16: Dr Andrew Chantry, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust
Osteolytica, developed as a research tool, is a powerful method of detecting and quantifying cancer induced bone destruction using micro CT data. When applied to larger human patient data sets obtained via routine imaging procedures such as CT and MRI, Osteolytica has the potential to provide a diagnostic tool to detect bone disease earlier to allow more immediate and effective treatment. Cancer induced bone destruction ruins patients’ lives and costs the NHS millions of pounds every year. Much of this patient suffering and cost to the NHS could be prevented by effective deployment of Osteolytica. This project will support the translation of Osteolytica into a powerful diagnostic medical device. This project will develop the Osteolytica software to support the robust handling of large human patient data sets and apply Osteolytica to a sample of patients with newly diagnosed myeloma requiring assessment of the presence of bone. We anticipate that Osteolytica could easily be deployed and adopted by the NHS for use throughout the UK and also has the potential to be rolled out worldwide leading to substantial improvements in outcomes for patients with cancer induced bone destruction.

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17: Dr Cheryl Miller, University of Sheffield

Bone repair, especially among the elderly or otherwise compromised patients, is a major challenge facing the United Kingdom and indeed the world. While a number of man-made bone fillers are available, the clinical results are inconsistent and failures such as fracture non-union are a risk. Researchers at Sheffield, working closely with local companies in the orthopaedic device sector, have discovered a new technology that has the potential to substantially improve the rate and consistency of bone healing. The aim of this project is to optimise the formulation and carry out additional tests in order to produce the first commercial prototype. On completion, the intention is to manufacture the improved bone filler in Sheffield, creating jobs and economic growth while improving patient care.

18: Dr James Alix, University of Sheffield

Nerve and muscle disorders cause considerable morbidity and are a source of significant cost for the health service. Diagnosing and monitoring these conditions can be difficult, invasive and expensive. Having a simple method suitable for tracking muscle health across specialist and non-specialist settings, including a patient’s home, would reduce the need for expensive tests, personalise treatments and facilitate clinical trials of new interventions. Electrical impedance spectroscopy (EIS) uses tiny, imperceptible electrical currents to examine the cellular integrity of tissue. When applied to muscle this has great potential as a simple to use, non-invasive marker of disease. We have developed a novel EIS recording approach in order to interrogate tissue health in far greater detail than previously possible. We have demonstrated the potential of our approach by examining the tongue of patients with motor neurone disease. This project will add further confidence to our novel EIS concept through the development of technology for recording from limb muscles. This broadens the use of our approach to age related changes and other neuromuscular diseases. We will develop software and analysis strategies and test our technology in patients with motor neurone disease and sarcopenia resulting in a number of novel devices with which to conduct a multi-centre study of their use across different disorders.

19: Prof Robert Storey, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust

Primary Percutaneous Coronary Intervention (PPCI) is the standard and most effective management for STEMI in developed countries. 25,000 PPCI procedures are performed annually in the UK for the management of STEMI and approximately 95% of procedures involve implantation of a stent (National Audit of PCI, 2015). Acute stent thrombosis is an uncommon but serious complication of PPCI with stenting, occurring within 24 hours of the stent placement in 1-3% of patients (Lancet 2014; 384: 1849–58). Most patients present within an acute coronary syndrome, usually with recurrent STEMI, or die suddenly (Circulation. 2009; 119; 657-659). Its cause is total or subtotal thrombotic occlusion of a coronary artery by thrombus that originates in or close to an intracoronary stent. While survivors of stent thrombosis can be managed by repeat PPCI, we are seeking to conduct a study with the aim to collect pilot data on effectiveness and safety of a novel anticoagulant regimen in PPCI to reduce acute stent thrombosis.

20: Dr Andrew Swift, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust

Pulmonary hypertension (PH) is a condition of varied aetiology defined by mean pulmonary artery pressure (mPAP) 25mmHg measured at right heart catheterisation (RHC). RHC, an invasive test, is the current gold standard for diagnosis of PH by measuring the pulmonary arterial pressure. Doppler echocardiography (DE) is the current non-invasive method of choice when screening patients with suspected PH; however echocardiography is limited by user dependency and ineffectiveness in certain subgroups of PH patients. Early diagnosis and early initiation of treatment improves outcome. Patients present late in their disease course due to the non-specific nature of presenting symptoms and insensitivity of basic imaging and cardiological tests such as the chest radiograph and electrocardiograph. We propose a non-invasive image based tool using standard magnetic resonance imaging (MRI), to infer the status of the pulmonary circulation and estimate pulmonary arterial pressure with the major advantage that MRI is reproducible, non-invasive and non-ionising. Our pilot work has demonstrated that pulmonary hypertension can be diagnosed using this computational MRI tool with high accuracy in a cohort of 72 patients with suspected PH. This project will validate the tool and a develop prototype software tool that can automatically compute the diagnosis of pulmonary hypertension.

21: Dr Lynne Barker, Sheffield Hallam University

Brain injury and stroke are critical global public health problems and acquired brain injury (ABI) is the primary cause of death of youth. 2013-14 figures showed 350,000 hospital admissions for acquired brain injury, 1 every 90 seconds, a 10% increase since 2005 in the UK (1.7 million in the USA). Around 850,000 people in UK have some form of mild or early cognitive impairment or dementia. Market analysts have established that there is a...
global and growing need for reliable cognitive assessment tools that are speedy and cost-effective. Brain injury and disease processes impair cognition: deficits to executive functions (EF’s = planning, dual-tasking, time estimation, prospective memory) are common and associated with poor outcome. Intractable cognitive deficits equal lasting disability, poor quality of life and lifelong care. Current assessment tests are expensive and evaluation is clinically and patient time-costly. We have drawn on our clinical experience, comprehensive knowledge of conventional tests, years of patient testing, to devise a single computerized task measuring memory and EF’s by simulating real world activity. In real life, complex tasks such as cooking are often significantly affected when a person sustains a brain injury or early on in the course of a neurodegenerative disorder because they require the coordination of multiple cognitive functions. We chose cooking simulation as the context for our task because in real life it requires several cognitive functions including multitasking, planning, sequencing, prospective memory, maintaining and completing sub-goals and overall goals within a defined timeframe, and we were able to create simulations that also require these functions for successful completion. Our proof of concept data showed that our task is reliably capturing these target functions commonly worsened by brain trauma. Our task is unique in that it measures multiple cognitive functions in one task at one assessment point. This project will develop our original pre-prototype through commercial collaboration and public and patient involvement in product design, usability, and appearance to progress the task to commercial product level. We will collect pilot data with a neurological cohort to test the psychometric properties of the new rebranded Cog:LAB prototype before clinical trials with our task compared to treatment as usual.

Round 6

22: Dr Alex Rothman, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust
Feasibility of Novel Clinical Trial Infrastructure, Design and Technology for Early Phase Studies in Patients with Pulmonary Arterial Hypertension
The assessment of disease progression and the testing of new drugs, for patients with pulmonary arterial hypertension requires repeated invasive measurement of pressure/flow in the heart and repeated measurement of exercise capacity; this project will determine the feasibility of using percutaneously implanted pulmonary artery pressure monitors and wrist-worn activity monitors in patients with pulmonary arterial hypertension reducing the requirement for repeated invasive investigation and providing a tele-medicine approach to management.

23: Mr Stephen Radley, Sheffield Teaching Hospitals NHS Foundation Trust
BlaST: Bladder Shape Test: Evaluation of trans-abdominal ultrasound assessment of bladder shape in women with lower urinary tract symptoms
World Health Organisation figures suggest that bladder problems affect more than 200 million people worldwide; The syndrome of overactive bladder (OAB) accounts for the majority of cases and is characterised by urinary urgency. OAB affects 1 in 6 women in the UK and USA, creating a huge burden to sufferers, society and health care providers; the condition is associated with abnormal, involuntary contractions of the bladder during filling; investigation often involves invasive urodynamic testing; termed ‘filling cystometry’, a test that uses urethral and rectal pressure-measuring catheters. We have now completed feasibility studies in healthy volunteers and symptomatic patients, which have identified measurable changes in bladder shape with contractions, showing that ultrasound can be used to detect these changes associated with bladder contractions in a non-invasive manner. The modality of ‘Bladder Shape Testing’ (BlaST) therefore has potential to provide a more acceptable, accessible, affordable and less invasive approach to the assessment of lower urinary tract function.

24: Dr Heidi Christensen
COCOA (COmputerised Cognit...
Corneal blindness affects the quality of life of millions of people worldwide. The frontline treatment for this remains corneal transplantation using cadaveric corneas from tissue banks. When this works (as it does for 70% of patients), results can be excellent; however, for the remaining 30%, where the patient lacks residual corneal stem cells to grow over the front of the donor cornea then contactual tissue grows over the cornea causing loss of vision. For the past 20 years a small number of centres (no more than 15 worldwide) have cultured autologous limbal epithelial stem cells and transplanted these back to the eye on a sacrificial human membrane (amniotic membrane, AM). While results with this technique are generally good, many ophthalmic surgeons lack access to specialist assessment and treatment for those found to be at high risk and more rapid reassurance for those at low risk of developing dementia. An ideal tool would allow re-testing for those at intermediate risk or whose performance fluctuates, and would be usable without requiring assessor expertise for example in people’s own homes. Our project will provide proof-of-concept for a diagnostic assessment tool that we have developed to meet this need. COCOA (Computerised Cognitive Assessment) works by detecting signs of early dementia in a person’s speech as they answer specially designed questions -- something which is known to be a cognitively highly demanding task involving multiple domains such as memory, language and attention. We aim to demonstrate that COCOA is accurate when used in multiple settings, on patients with confounding memory symptoms and during repeated testing. Our team comprises expertise in AI, computer science, neurology, neuropsychology and clinical linguistics from the University of Sheffield and Sheffield Teaching Hospitals Trust, and, through our industrial partner MABLE Care, knowledge of commercialisation of products in this area. At the end of this project, COCOA will be ready for validation in a larger-scale study to demonstrate sensitivity and specificity as well as cost effectiveness in those clinical settings where it will be implemented for routine use.

25: Prof Frederik Claeyssens, University of Sheffield

Tissue Engineered Vein Valves

Chronic deep venous insufficiency (CDVI), caused by vein valve incompetence and reflux, affects 2-5% of the global population. In the legs, venous insufficiency causes pain, edema, hyperpigmentation, lipodermatosclerosis and ulcers. Surgical interventions (thermal ablation, sclerotherapy, stripping) are routine in disorders associated with the superficial veins (varicose veins) but not in deep veins, where treatments remain largely palliative (external compression). Surgical valve reconstruction in the deep veins is complex and not suitable for many patients due to poor systemic vein health. Prosthetic vein valves have been explored, either allogeneic, synthetic (polymer/metal), or made from chemically crosslinked animal tissue. However, these valves have performed inadequately due to thrombosis and intimal hyperplasia caused by inappropriate mechanical properties and poor endothelialisation. A great need exists for replacement vein valves. We propose to produce a tissue-engineered vein valve (TEVV) using a degradable polymer scaffold seeded with vascular smooth muscle cells (SMCs) and cultured in vitro under biomimetic conditions. Following culture, the TEVV is decellularised, removing the antigenic components leaving only vascular extracellular matrix (ECM) proteins (collagen/elastin). The decellularised TEVV is suitable for use in any patient without rejection (off-the-shelf), following autologous endothelial cell (EC) seeding. This approach has proven successful in producing off-the-shelf tissue-engineered blood vessels. The TEVV is integrated within a collapsible stent to permit endovascular insertion.

The advantages of the TEVV:

- Made from ECM (collagen/elastin) matching native tissue mechanical properties thus avoiding intimal hyperplasia, as seen in current prosthetic vein valves.
- Decellularised TEVV is suitable for off-the-shelf use in any patient without rejection.
- Decellularised TEVV retains biological cues to promote endothelialisation. This prevents thrombosis, the major cause of failure in current prosthetic vein valves.

26: Dr Ilida Ortega Asencio, University of Sheffield

Simplifying corneal regeneration via the use of pliable tissue delivery membranes containing microfeatures

Corneal blindness affects the quality of life of millions of people worldwide. The frontline treatment for this remains corneal transplantation using cadaveric corneas from tissue banks. When this works (as it does for 70% of patients), results can be excellent; however, for the remaining 30%, where the patient lacks residual corneal stem cells to grow over the front of the donor cornea then contactual tissue grows over the cornea causing loss of vision. For the past 20 years a small number of centres (no more than 15 worldwide) have cultured autologous limbal epithelial stem cells and transplanted these back to the eye on a sacrificial human membrane (amniotic membrane, AM). While results with this technique are generally good, many ophthalmic surgeons lack...
access to tissue banked AM and specialist facilities and staff for the culture of cells. There is a need to develop new approaches that can provide surgeons with more easy-to-deliver and cost-effective strategies for the treatment of corneal disease. At the University of Sheffield we have been now working for 6 years in the development of synthetic membranes for corneal regeneration (as amniotic membrane substitutes) with the aim of gaining understanding of both the biological mechanisms involved in corneal healing and the pathways and challenges to enable future clinical translation. This long-standing collaboration between the University of Sheffield and LV Prasad Institute (LVPEI, India) has sought to widen access to the surgical approach to corneal regeneration by essentially doing two things: (i) using tissue explants as the source of epithelial cells rather than laboratory expansion of cells (this has been a great success and many centres in India and worldwide are now achieving corneal regeneration from tissue explants rather than laboratory cultured cells); and (ii) by developing a synthetic electrospun alternative membrane to AM using electrospun polylactic glycolic acid (PLGA) which has led to a first in-man clinical trial. In this project we aim to respond to clinical feedback to design an improved electrospun PLGA membrane with better membrane pliability for clinicians and with partially enclosed microfeatures to assist surgeons in placing explants within these, avoiding the need to use fibrin glue which is currently used to glue explants to the AM but clinicians report problems in both accessing and using fibrin.

27: Prof Heather Ephick, Sheffield Children’s NHS Foundation Trust
Thermal imaging tool for measuring respiratory airflow to assist with diagnosing apnoea in children with suspected sleep-related breathing disorder.

The work will build on the teams’ well-established and complementary expertise to develop thermal imaging as a practical, noncontact, child-friendly tool for measuring and monitoring respiration airflow for diagnosing apnoea in children suspected of sleep-related disorders. The current approach for diagnosing apnoea requires multiple sensors to be attached to the child’s face and body during an overnight sleep study known as polysomnography (PSG). The current gold standard for measuring nasal airflow is nasal cannula, which are prongs placed in the nares of the nose to directly measure respiration. However nasal cannula are poorly tolerated by children. Nasal cannula are prone to becoming dislodged (requiring regular adjustments), are single use (incurring cost) and can become blocked by mucus and respiratory moisture. Our previous audit on 100 children showed approximately 50% of children refused to accept nasal cannula and of the rest; a significant proportion removed it during their overnight sleep recording. With unavailability of information from nasal cannula, clinicians rely on a thermistor (temperature sensor placed close to the nose and mouth) to monitor airflow which is also poorly tolerated. The thermistor is prone to skin and environmental temperature disturbances and does not give accurate airflow information. Chest and abdominal bands that detect breathing movements are used in conjunction with the nasal sensors to measure and classify apnoeas. This is currently the only combination of sensors that can reliably inform clinicians about respiratory patterns leading to apnoea classification and diagnosis. The proposed thermal imaging approach has the potential to measure respiratory airflow and assist clinicians to diagnose apnoea more accurately. The research team consists of Sheffield Hallam University (SHU), Sheffield University, Sheffield Children’s Hospital (SCH) and an industrial partner (S-Med Ltd) with relevant experience in respiration and sleep monitoring. The collaborators bring together the necessary skills and resources to successfully develop the required innovative tool to help with diagnosing a serious medical condition that affects 1-6% of children. We have recently carried out two sleep-related breathing disorders pilot projects in preparation for this funding. One study involved overnight recordings at Sheffield Children’s Hospital on 30 children suspected of sleep-related breathing disorders and the other on 11 adult healthy volunteers. In these studies thermal imaging was performed in parallel with the current contact sensors including nasal prongs. The study indicated that thermal imaging may have the potential to be a child friendly, noncontact and practical tool for diagnosis sleep related disorders and highlighted the technical developments needed for thermal imaging to be a viable commercial and clinically deployable tool for diagnosing apnoea. The data from these studies will be supplemented with further recordings to develop the required technologies. This MRC CinC will assist us to gather sufficient evidence to demonstrate that the work merits further, more substantial funding, and in collaboration with the industrial partner put forward a path to the approach’s integration to medical diagnostic devices.

28: Prof. Mimoun Azzouz
IMPACT-MS: IMmunotolerant Programmed Autologous stem Cell Therapy for Multiple Sclerosis

Multiple sclerosis (MS) is a chronic immune mediated inflammatory disease of the central nervous system (CNS) and is the most common cause of non-traumatic disability in young / middle-aged adults. It affects 1.1000 individuals accounting for 100,000 cases in the UK, and 2.5 million cases worldwide. In the majority of patients, the illness runs an initial relapsing-remitting course, which culminates in a progressive phase with gradual
accumulation of fixed disabilities. Pathologically, T-cell or T-cell-plus-antibody-mediated autoimmune responses in the CNS result in foci of severe demyelination, decreased axonal and oligodendrocyte numbers, gliotic scarring and atrophy. The disease has marked socioeconomic burden with less than 20% of patients of working age in employment once they reach higher disability levels. MS is also associated with increased mortality. Current treatment regimens are effective in reducing the frequency of relapses but are largely ineffective at stopping disease progression. This project aims to develop a treatment strategy to enhance the potential efficacy observed following autologous haematopoietic stem cell transplantation (AHSC) in patients with MS by an ex-vivo genetic modification of these stem cells to promote the patient’s immune tolerance of their myelin related self-antigens. Preclinical studies have confirmed the potential efficacy of the gene-modified cell therapy approach using the antigen induced experimental allergic encephalomyelitis (EAE) model of MS. Additional preclinical studies are required to refine the ex-vivo approach. If efficacy is confirmed, this treatment strategy could transform the prognosis of this severely disabling common disease. This project brings in all the necessary expertise required for completing its preclinical development (Azzouz, Sharrack, Snowden, Woodroofe and Thrasher).

29: Prof Simona Francese, Sheffield Hallam University
Non-invasive breast cancer test using fingertip smears
In 2014 approximately 55,200 new cases of breast cancer were reported within the UK, making breast cancer the most common neoplasm in British women. However, breast cancer is also a global health issue. Mammography is the gold standard for diagnostic imaging and screening, whereas biopsies confirm diagnosis. Advanced disease is typically monitored with serial CT scans and core biopsy at metastatic diagnosis is used to confirm and characterise disease biology. Whilst effective, current tests expose individuals to radiation, have limitations to their sensitivity and specificity and may cause pain, anxiety and risk of bleeding. Some women find exposure of their breasts for mammography culturally unacceptable and decline screening or delay symptomatic occurrence as a result. Therefore, there is the need for further technological developments for non-invasive and quick tests for screening, diagnostic and monitoring purposes. The project intends to bridge the gap between screening, diagnosis and monitoring of breast cancer by employing fingertip exocrine secretion smears and use oncological molecular markers contained within to enable the discrimination of healthy versus breast cancer patients. Matrix Assisted Laser Desorption Ionisation Mass Spectrometry (MALDI MS) will be employed to recover cancer signatures, assisted by statistical modelling to discriminate oncological versus healthy patients and thus determining the specificity and sensitivity of this technique. The method is not initially intended to replace breast biopsies, rather to offer a preliminary specific and sensitive, non-invasive and pain-free molecular screening opportunity in order to: 1. Reduce the occurrences of patient discomfort and embarrassment (and so enhance screening uptake rates); 2. Reduce false positives/negatives. 3. Indicate appropriateness of further and more in depth tests which will reduce costs to the public health sector, by decreasing the number of requests for advanced diagnostic tests, for first contact and follow up patients. These significant advantages hold the promise to break new ground in screening, diagnosis and monitoring of breast cancer.

30: Prof Marcos Rodrigues, Sheffield Hallam University
AFRICCA – Automatic Facial Action Units Recognition in Critical Care
The emotional expressions of humans and animals has been investigated ever since Charles Darwin, and it is generally accepted that facial movements convey what we’re feeling, although interpretations may vary among cultural groups. Previous collaboration between North Middlesex University Hospital and the GMPR Research Group at Sheffield Hallam University has demonstrated for the first time that patterns of facial action units identified in deteriorating general ward patients can predict admission to intensive care (Madrigal et al., “What faces reveal: a novel method to identify patients at risk of deterioration using facial expressions”, Critical Care Medicine Journal, 2018). This proposed project aims at validating the findings in a critical care environment by extending current data set and comparing with standard methods. The project will collect and analyse facial data from patients in critical care and investigate methods of automatic recognition of facial action units to be used as predictors of patient deterioration. The concept we want to validate is whether or not more accurate predictions can be made than traditional early warning scores currently in use in NHS hospital wards.

31: Dr Paul Morris, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust
GuideGlide: Safer and more successful radial access in coronary intervention
Coronary artery disease is the leading cause of death in the world. Patients with coronary disease undergo cardiac catheterisation to assess their disease and to deliver treatment with stents. More than 250,000 of these
Design and Development of an Innovative Neck Stabilising Aid for Children with Narcolepsy

Narcolepsy is a disabling neurological sleep disorder characterised by excessive daytime sleepiness and attacks of muscle weakness precipitated by strong emotions, known as cataplexy. The symptoms of this debilitating condition have a huge impact on a child’s life in terms of emotional wellbeing and ability to reach academic potential. Supportive aids ranging from a hand-held fan to help the child stay awake to a wheelchair to aid transport when the child falls asleep unexpectedly can help the child and family to function more easily day to day. The concept for development within this project was derived from a workshop held with the families of children attending Sheffield Children’s Hospital’s (SCH) narcolepsy clinic. The project team has already run two workshops to explore some of the everyday problems children with narcolepsy have and potential solutions using technology. The main problem identified was the need for a neck support in the car while their children are asleep. Children with narcolepsy inevitably fall asleep on car journeys and the loss of head control causes immense stress to parents who may be driving the car and unable to support their child, as well as pain and discomfort for the child. There is currently no suitable car-seat or effective neck support for these children. We aim to design and develop a neck stabilising aid for children with narcolepsy to use in the car. The project team comprises a collaboration between design engineering at Sheffield Hallam University (SHU), Sheffield University Neurosciences (SiTraN), Sheffield Children’s Hospital (SCH) narcolepsy clinical team, a young person with

Dr Charlotte Elder, University of Sheffield / Sheffield Children’s NHS Foundation Trust

Non-invasive Short Synacthen Test (NeSST) paediatric normative data study

The adrenal glands sit above the kidneys and are part of the body’s endocrine system. They produce a number of different hormones; those involved in metabolism (cortisol), salt and water balance (aldosterone) and sex steroids (oestrogen and testosterone). Adrenal insufficiency describes the inability of the body to produce adequate levels of the vital stress hormone, cortisol. It is associated with considerable mortality and morbidity. There are numerous causes, both in adults and children. The most common cause in adults from the developed world is autoimmune destruction of the adrenal gland but worldwide it is TB. The commonest paediatric cause is the prescription of steroid medication. Adrenal insufficiency is usually permanent but may be transient, especially in babies and children, and therefore periodic diagnostic testing is required in some patients (3 monthly). The Short Synacthen Test (SST) is the first line and most popular diagnostic test for adrenal insufficiency worldwide. In recent years requests for SSTs have risen in line with increased paediatric steroid usage and heightened awareness of the adrenal insufficiency steroids can cause. The SST requires intravenous cannulation and blood sampling. It is thus invasive, resource-intensive (requiring a daycare admission and trained personnel) and unpleasant for the patient; leading to a rise in both the cost and threshold for investigation. We have developed a non-invasive alternative to the SST, with Synacthen given nasally via a spray and the resultant cortisol response measured on saliva samples. In earlier studies we devised novel formulations of nasal Synacthen, combining a higher dose of Synacthen with a nasal drug enhancer (chitosan) to improve absorption, and performed pharmacokinetic studies in both adults and children validating our chosen formulation (Nasacthin003). The five studies to date have shown nasal Synacthen to be reliably absorbed and well tolerated. Our non-invasive test would negate the need for needles and reduce (indeed in some cases avoid entirely) lengthy hospital visits, thus dramatically reducing costs for the healthcare provider and importantly improving the overall patient experience. The novel test has utility in the inpatient, outpatient and community settings, in adults and children, and will provide a vital research tool for future studies on the adrenal response to steroids in many diverse patient cohorts, including children. Having validated the non-invasive test, in both adults and children, and produced data to support regulatory approval for commercialisation, the next stage of our workstream is to gather normative data in the healthy paediatric population. Currently diagnostic cut-offs for the SST are derived from adult data and this next study will allow us to establish the first normal ranges for the SST in children before going on to study children at risk of adrenal insufficiency.
narcolepsy and the NIHR Children and Young People’s Med-tech Co-operative (CYP-medtech). Children and their families have already been and will continue to be involved in the co-design of the support throughout the process.

Prof Robert Storey, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust

34: WILL IOWer dose Aspirin And Apixaban be better than aspirin alone? (WILLOW AAA)

Aspirin remains the standard treatment for the prevention of cardiovascular events in patients with stable coronary artery disease. Adding a low dose of an anticoagulant drug to aspirin improves the protection against ischaemic events but also increases risk of bleeding, which causes harm, distress and discontinuation of therapy. We will test the effects, feasibility and tolerance of a novel regimen of ultralow-dose aspirin and ultra-low-dose apixaban, an anticoagulant, in patients with ischaemic heart disease. We hope to show that the novel regimen provides superior anti-ischaemic protection to standard aspirin treatment without significantly increasing bleeding tendency.

Round 7

35: Prof Jim Thomas, University of Sheffield

In-vitro antibacterial activity profile, genotoxicity and pharmacokinetic analysis of a novel broad-spectrum antibiotic active against therapeutically resistant pathogens.

Two lead kinetically inert coordination compounds have been developed with a higher activity - sub µM concentrations – than standard clinical antibiotics such as ampicillin across several bacteria strains. The high activity of the compounds is retained in pathogenic, multi-drug resistant strains identified by WHO as priority 1 critical for discovering new antibiotics. The lead compound exhibits more than one mechanism of action, damaging the cell membrane and localising internally within the cell. Both compounds are non-toxic to eukaryotic cells and the wax moth larvae insect model. In addition, the compounds completely cleared pathogenic Acinetobacter baumannii infections from larvae over the course of 4-days. This project will progress these initial infection studies onto the next logical steps in the development pathway. An antibacterial profile, using a library of strains, will be developed to determine an initial patient population. Mammalian genotoxic studies will be conducted to determine if DNA damage is present and an in-vitro pharmacokinetic profile will be developed. This data will provide key information needed to plan subsequent in-vivo studies to investigate toxicology and bacterial clearance. An initial report on this study has been recently published and has attracted huge world-wide media attention, including national US TV (CBS) coverage.

36: Dr Alex Rothman, University of Sheffield / Sheffield Teaching Hospitals NHS Foundation Trust

Optimal target medication up-titration strategy in patients with heart failure with reduced ejection fraction (OptiMUS-HF)

Approved drug therapies for heart failure reduce symptoms and improve clinical outcomes. Achieving the target dose or maximum tolerated dose of these drugs provides greater benefit, however most patients are not on the target dose and do not get maximal benefit from the drugs prescribed, leading to reduced quality of life, worse healthcare outcomes and increased healthcare use. Endotronix have developed a system that allows daily remote monitoring of blood pressure, heart rate, and oxygen saturations through a patient interaction and communication hub that relays data to an online accessible portal. We will use this system in a clinical study to test if it is possible to increase the dose of heart failure medications taken and reduce the time taken to achieve maximal tolerated dose in patients with heart failure.

37: Dr Ivan Phelan

The development of Immersive Virtual Reality environments for children’s lower limb rehabilitation

Children who have injuries or conditions (such as Cerebral Palsy) affecting their lower limb often have to undergo surgery. Many children need to wear an external fixator holding bones in place. Immediately after surgery the clinical team encourage patients to stand, which often children are afraid to do because of the anticipated and actual pain. However, this weight bearing is essential for healing and recovery. This project aims to develop bespoke Immersive Virtual Reality (IVR) play scenarios for in-patients in the immediate post-surgery period to encourage them to perform the required physiotherapy exercises, leading on to weight bearing such that they become so engrossed in the VR interaction they become unaware or much less aware of any pain while they are playing the rehab ‘game’. Intense physiotherapy is required, typically 3 sessions per day for 6 days to enable them to become independently mobile. It is anticipated that by encouraging children to do this at an earlier
38: Miss Swati Jha, Sheffield Teaching Hospitals NHS Foundation Trust
Development of a Vaginal Drain to reduce Morbidity after Hysterectomy
A hysterectomy is the most commonly performed gynaecological procedure with 55,000 performed annually in the UK (approximately 1.2 million globally). It can be performed through the abdomen (open surgery or keyhole) or through the vagina. Irrespective of the route, after a hysterectomy, internal bleeding can result in a collection of blood called a Vault Haematoma. The percentage of patients who develop vault haematomas after a hysterectomy is 10-40% (5,000-20,000 women every year); with the cost of such a procedural complication per case ranging from £1,021 (just for diagnosis) to £9,125 (for multiple interventions alongside an inpatient stay) (https://improvement.nhs.uk/resources/reference-costs/). Therefore, there are potential cost-savings per year ranging from £5m (i.e. £1021 * 5000 women) up to £183m (i.e. £9,125 * 20,000 women) from avoiding such complications, among other avoided morbidity and mortality factors. Haematomas greater than 5 cm can be associated with significant morbidity. It can become infected resulting in a prolonged hospital stay, need for reoperation, antibiotics and need for imaging as well as the need for further surgery. The aim of this study is to develop a vaginal drain that prevents the formation of a vault haematoma following a hysterectomy hence reducing the morbidity arising from this common complication. Haematomas greater than 5 cm can be associated with significant morbidity. It can become infected resulting in a prolonged hospital stay, need for reoperation, antibiotics and need for imaging as well as the need for further surgery.

39: Professor Reza Saatchi, Sheffield Hallam University
PaediResp: Paediatric Acoustic Wireless Device to Assist with Monitoring and Diagnosis of Breathing Disorders
A new prototype child friendly device, PaediResp, is being developed to assist with the diagnosis of breathing disorders in children. The focus is Inducible Laryngeal Obstruction (ILO) due to an increasing clinical need however PaediResp will be adaptable to diagnosing other dysfunctional breathing problems. ILO is an umbrella term to describe a number of conditions that impede respiratory airflow due to problems associated with vocal cord motion. The ‘gold standard’ for ILO diagnosis is visualisation of the upper airway using a camera through the nose during symptoms. However, this is invasive, subjective to the consultant’s expertise and experience, and requires a large amount of NHS resources and time. PaediResp is fulfilling an important unmet clinical need to improve diagnosis of ILO by providing an effective, child-friendly, non-invasive, easy to apply, cost effective tool that can be deployed within and outside clinical environments. Its novelty relates to innovations that allow vocal sounds to be optimally recorded while excluding the obscuring background and heart sounds. Sheffield Children’s NHS Foundation Trust, Sheffield Hallam University and the University of Sheffield will collaborate to develop the device’s proof of concept, carry out a clinical trial, perform PPIE and market research, and integrate regulatory issues.

40: Prof Amaka Offiah, University of Sheffield / Sheffield Children’s NHS Foundation Trust
Clever-dREAMS: Using artificial intelligence to enhance the diagnosis of rare skeletal dysplasias in children
Skeletal dysplasias (SD) are a group of genetically determined disorders in which there is abnormality of bone and cartilage growth and development. Individually rare, together they are more common than many cancers (birth rate = 240-320/million). Diagnosis is dependent on accurate x-ray interpretation. There are only a small number of doctors with the necessary experience. This delays diagnosis and complicates prediction of outcome for the child and for future pregnancies. It also delays the development of novel therapies. The development of machine learning techniques, combined with the expertise of medical professionals, means it is possible to automatically extract knowledge from high quality x-ray images. “dREAMS” – dynamic Radiological Electronic Atlas of Malformation Syndromes – is our bank of over 15,500 x-rays (500 patients, 400 SD) that we are in the process of annotating. This provides a unique opportunity to harness the potential of machine learning towards more rapid and accurate diagnosis of SD. This project aims to design, develop and test the feasibility of a novel artificial intelligence framework based on automatic image analysis. The software will assess an image and provide a grade of confidence for the likelihood of any given SD by comparing the image to all images within dREAMS.
41: Prof Bazbek Davletov
Bonded Botulinum medicine for long-lasting pain relief
This pre-clinical research project aims to demonstrate efficacy of new therapeutic molecules for the treatment of neuropathic pain, a pathological condition arising from nerve damage and causing long-term suffering. In the UK, prevalence of neuropathic pain is estimated at 8.3%, meaning that around 7 to 8 million people may be living with chronic pain in the UK. Opioid drugs that are currently used to alleviate pain are short-lasting, of moderate efficacy, and produce serious side effects. We aim to address this problem by introducing a new protein drug for selective and localized silencing of sensory neurons involved in chronic pain conditions. We will accomplish this by genetic re-engineering of botulinum neurotoxin, a bacterial protease that potently blocks release of neurotransmitters and neuropeptides for several months. Currently, injections of small doses of botulinum neurotoxin are used in clinical and cosmetic medicine to achieve local muscle relaxation. We previously demonstrated the potential of botulinum-based approach in achieving long-lasting relief from chronic pain without causing any muscle effects. We have now invented a process to make pain-specific botulinum therapeutics which we propose to evaluate in pre-clinical studies with the ultimate aim of regulatory approval of this investigational new drug to address the worldwide chronic pain problem.

42: Prof Carl Smythe, University of Sheffield
Earlier diagnosis of pancreatic cancer in liquid biopsy using a switchable magnetic cell isolation and enumeration device.
While earlier diagnosis has improved outcomes for many cancers, survival rates of pancreatic cancer remain extremely poor, with 5-year survival being only 3.7%. Because pancreatic cancer is biologically aggressive and relatively resistant to chemotherapy and radiotherapy, surgical resection remains the only treatment with potential for long-term survival. However, once a pancreatic tumour has exceeded 1cm in diameter, there is a high probability that resection will be impossible and that metastasis will result in incurable spread of the disease. At early disease stages, symptoms are often absent or vague, not clearly indicative of pancreatic cancer. If a sensitive, specific and relatively cheap test were available, this could be applied to patients with ‘suggestive’ symptoms who could then be referred for confirmatory high-resolution diagnostic imaging and biopsy. The present project seeks to develop such a test. It is based on our understanding and applied knowledge of the protein interactions required for proliferative spread of the majority of pancreatic cancer cells and will use our insights into building magnetic cell traps, and low-cost cell imaging systems, to capture and measure numbers of rare circulating tumour cells present in blood.