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Sheffield Healthcare Gateway.

Non-confidential summaries of MRC Confidence in Concept funded projects at the University of Sheffield.

This list is intended to provide some background on the types of projects that have been funded under the MRC Confidence in Concept schemes. All summaries here are non-confidential and comprise all the projects funded to date under this scheme at The University of Sheffield.

Round 1 - FUNDED

Albert Ong- Developing small molecule channel modulators to treat polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease affecting the kidney. It has an incidence of 1 in 1000 and affects up to 12 million people worldwide. Up to 50% of individuals with ADPKD will develop end-stage renal disease by age 60 years and there are currently no approved treatments for patients. This project seeks to develop a specific treatment for ADPKD by reducing cyst number and therefore preventing disease progression.

Allan Lawrie- Developing Anti-OPG and TRAIL therapies for Pulmonary hypertension

Pulmonary hypertension (PH) describes a group of rapidly progressive conditions, each with a different origin but sharing a common haemodynamic diagnosis that results in right heart failure. Current treatments carry an annual cost per patient of between £5,000 - £300,000 and target the sustained vasoconstriction via the prostacyclin, endothelin or nitric oxide pathway in isolation or combination. My group has generated data describing a critical role for OPG and TRAIL in the pathogenesis of PAH. Loss of OPG or TRAIL signalling, either by genetic deletion or treatment with a polyclonal antibody can protect against disease. Furthermore treatment of established disease with anti-OPG or anti-TRAIL antibodies can reverse the disease. I now wish to generate new monoclonal antibodies that can be readily humanised and developed for clinical testing.

Prof Carl Smythe- A novel approach for the treatment of cystic fibrosis

There is a huge unmet need for novel approaches to treat genetic or inherited disorders such as cystic fibrosis. The scale of disease arising as a consequence of mutations is staggering. By 2007, there were 43,000 disease associated genetic mutations described in the human gene mutation database (www.hgmd.org). Nonsense mutations arise when a genetic change results in the introduction of an inappropriate stop signal in the coding region of a gene. In principle, such mutations might be expected to give rise to a truncated protein which may have reduced or altered functional properties. Nonsense mutations account for up to a third of all described gene lesions causing human inherited disease. In almost all cases, the resulting clinical pathology associated with nonsense mutations arises because relevant cells fail to produce functional protein. However, this is not simply because a non-functional truncated protein is generated, but most often, almost no protein derived from the mutant gene is produced at all.

The reason forth is the existence of a cellular process termed nonsense-mediated decay (NMD). This is a quality control mechanism that monitors the nature of newly synthesized message and subsequently programmes the protein synthesis machinery (ribosome) to make copies of the relevant protein. It ensures that only full-length messages are allowed to be used as the template for new protein synthesis. Messages that contain a nonsense mutation are destroyed. It is this destruction that leads to the vastly reduced amounts of relevant protein in these genetic diseases. This proposal seeks to establish proof of concept of a novel approach to restore functional CFTR protein in cells derived from cystic fibrosis patients.

Helen Bryant- Development of a novel light activated anticancer therapy

Cancer claims millions of lives a year world-wide. Existing treatment methods are either surgical or chemotherapeutic, and whilst much advance is being made every day, less invasive, less harmful and more specific methods are urgently needed. This project uses the method of photodynamic therapy – light therapy where the drug is not active or harmful unless activated by light. It provides an excellent minimally invasive alternative to surgical methods. It also provides an excellent alternative to chemotherapy, which is frequently non-specific, and, as a consequence, highly toxic. We combine specifically binding drugs with focussed light delivery to achieve specificity and selectivity. We have already shown that our novel drugs work under high energy light. But this light is absorbed by tissues – with the major drawbacks that the penetration depth is small, and the toxicity is high because the light harms the tissue even without a drug. An alternative route of activation is low energy light. We have shown our novel drugs are activated with this form of light in vitro. Here we will prove the concept that low energy light can activate our pro-drugs in live cancer cells and lead to efficient cell death. This will pave the way for a new generation of efficient, specific, non-invasive anti-cancer treatment with reduced side effects for patients.

Ian Douglas- Development of a novel system to detect early onset of urinary tract infection in patients ('Pam's Pants)

Patients suffering from physical handicap, dementia or other cognitive impairment can often suffer from incontinence and the remedies available can make them susceptible to increased risk of urinary tract infection. The early detection of urinary tract infection is crucial in improving their quality of life and reducing the spread of infection. It is also important to develop methods for monitoring patient's urine using a dignified and non-invasive technique without the need for active co-operation by the patient, who may struggle to provide conventional midstream urine samples. The purpose of this project is to combine these elements together to develop a method of detecting early signs of a urinary tract infection which can be incorporated into an existing continence pad design.

Ian Sabroe- The Development of a novel treatment for viral-induced exacerbations of airways disease

The World Health Organization (WHO) estimated in 2008 that 64 million people and 235 million people worldwide suffer from chronic obstructive pulmonary disease (COPD) and asthma, respectively (1). In the UK alone, over 3 million people have COPD and more than five million people currently receive treatment for Asthma. COPD alone costs the NHS £1bn/year (2). Lung infections with viruses are the biggest single cause of bad attacks of breathlessness for people with asthma or COPD increasing visits to hospital and mortality. We are developing a new way to prevent inflammation in the lungs caused by respiratory viruses. We think that we will be able to use our proposed therapy to stop people with asthma or COPD suffering from bad attacks of breathlessness when they get colds. We plan to generate an emergency

treatment that can be given to people becoming wheezy and ill with a cold, and reducing the necessity of going into hospital.

(1) [The global burden of disease: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html].
(2) http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_127974

Julian Gunn- Radiofrequency ablation of pulmonary hypertension

Pulmonary hypertension (PH) describes a group of rapidly progressive conditions, each with a different pathology, but sharing a common haemodynamic diagnosis that results in right heart failure. Current treatments carry an annual cost per patient of between £5,000 - £300,000 and target the sustained vasoconstriction via the prostacyclin, endothelin or nitric oxide pathway in isolation or combination. We will study the effect of catheter-delivered energy to ablate the sympathetic nerves in the pulmonary arteries of animals with experimentally induced pulmonary hypertension, with the aim of reversing or reducing, the high blood pressure in the lungs.

Simon Atkins- Studies on Nerve Regeneration and Neuropathic Pain

Peripheral nerve injuries are very common. They occur as a result of accidents and sometimes as an inevitable consequence of surgical operations. These injuries are very distressing as they can prevent the normal function of muscles, cause loss of sensation and sometimes lead to the development of chronic pain. Although surgeons can repair damaged nerves, the level of recovery is highly variable and the pain often persists. Treating the pain is difficult and often unsatisfactory. This project aims to conclusively demonstrate the potential of a therapeutic agent to deliver significantly improved recovery after peripheral nerve repair.

Stephen Renshaw- Novel kinase inhibitors for the treatment of inflammatory disease

Using phenotype based compound screening in zebrafish, we have identified novel kinase inhibitors which drive inflammation resolution in vivo. There is a huge unmet need for pro-resolution anti-inflammatory compounds, and these compounds have high activity in these assays. To move these compounds towards a drug discovery programme, we need to identify the targets and to validate these compounds in human cells and mouse inflammation models

Round 2 - FUNDED

Dilly Anumba-The development and validation of a novel Sensor for assessing cervical remodelling prior to birth- proof of concept for predicting and preventing premature birth. Premature birth is the principal cause of perinatal death of structurally normal babies. Its prediction and prevention remain limited and the need to develop tools that make these goals possible remains unmet. Over a billion pounds is spent annually in the UK to care for the additional needs of children born prematurely, excluding lifetime costs. Many parents often have to give up work to provide round-the clock care for severely handicapped children. This work aims to develop a device that sensitively detects changes in the cervix long before premature labour starts, in order to provide timely MRC Confidence in interventions to prevent it or to plan for mitigating its consequences more appropriately.

Sheila MacNeil- Prevention of premature birth Women at risk of premature delivery due to cervical insufficiency or premature rupture of the amniotic membrane have few options. The current practice involves putting a stitch in the cervix or prolonged bed rest to reduce the risk of premature labour. Once membranes rupture there are no treatment options currently available and this leads to delivery of babies too early to survive. This proposal is to develop an approach to prolong gestation.

Richard Eastell- VERTEBRAL FRACTURE: Vertebral analysis and fracture risk assessment from 2D DXA scans
Researchers at the Mellanby Centre for Bone Research (MCBR), The University of Sheffield have developed a more accurate way of identifying vertebral fractures from spine images using an algorithm-based qualitative approach. This collaborative project, between the MCBR and the Faculty of Engineering, aims to develop a computer-assisted method that automates this identification process. This will result in a more objective and quantitative approach to vertebral fracture assessment which has considerable potential for dissemination worldwide.

Vincent Cunliffe- Zebrafish genetic models of epilepsy for in vivo antiepileptic drug discovery Epilepsy is a common neurological disorder affecting 50 million people worldwide, and whilst some patients respond positively to the existing drugs, up to a third of all people with epilepsy do not gain any therapeutic benefit from these treatments. The scope for developing new treatments has recently begun to widen as some of the genetic causes of epilepsy have been identified and new drug targets have been defined. This project will validate some of these drug targets and identify compounds that suppress seizures in zebrafish genetic models of human epilepsy.

Eva Qwarnstrom-Developing TILRR as a therapeutic target in cardiovascular disease
Interleukin-1 is a potent regulator of inflammatory responses, and activation of the IL-1 receptor is central to development of cardiovascular disease. The current project will test recently developed monoclonal antibodies, which block aberrant IL-1 receptor activation, using models of vascular disease. We will select monoclonal antibodies demonstrated to bind the cell surface of inflammatory cells and to reduce IL-1 induced activation by 50-90%, and determine their impact on disease development and test for potential adverse effects. The data will be used to inform future translational studies focusing on developing novel therapeutics.

Illaria Bellantuono- Preventing radiation induced mucositis in a preclinical model
We have identified a new use for a drug already given extensively in patients with bone disease and cancer. We have discovered that it enhances DNA repair in stem cells and protects them from damage. It also protects normal stem cells but not cancer cells from the damaging effects of radiotherapy. This means that it may be possible to increase the radiotherapy dose given to cancer patients or reduce the time of administration thereby increasing both the effectiveness of the treatment while also reducing its side effects. Extensive data are available on the safety of this molecule in cancer patients to prevent bone disease. This study will give us data to demonstrate the efficacy of the marketed drug at ameliorating mucositis at doses already used in patients and considered safe. These data will be the basis for obtaining a more substantive translational award to test the efficacy in patients.

Jon Sayers-New drugs for parasitic diseases
Flap endonuclease (FEN) enzyme activity is essential in all cells. These FEN enzymes are required for processing branched DNA structures that occur during DNA replication and repair processes. The gene encoding FEN proteins has been knocked out in organisms as diverse as bacteria and mice. For example, in Streptococcus pneumoniae deletion of the gene proves lethal and similarly so in mice. Thus, inhibitors of FEN enzymes are expected to prove lethal to cells with a susceptible FEN enzyme. We have determined the crystal structure of the FEN protein from a parasite and developed efficient enzyme activity assays that can be used to screen for inhibitors to identify compounds for drug development.

Pat Lawford and Paul Morris- Improving the assessment of coronary artery disease.
Coronary artery disease (CAD) is the leading cause of death worldwide. Patients with CAD undergo imaging with coronary angiography which identifies disease inside the coronary arteries and guides treatment. Traditionally, angiograms are assessed visually. It is now known that this subjective approach can be unreliable. Newer techniques involve invasive physiological assessment during angiography. Physiologically guided treatment improves outcomes and reduces cost. This project will investigate an objective, and more accurate, physiological means to assess CAD using computational modelling methods.

John Newell-Price-Developing novel parathyroid imaging agents
We are seeking to develop a novel and improved means to image abnormal parathyroid glands. Over-activity of the parathyroid glands leads to osteoporosis, high blood pressure and kidney failure. Selective removal by surgery of the causative gland results in cure, but the tiny glands need identifying first. Our approach seeks to solve this problem by a novel imaging approach, as current methods are not satisfactory. Ultimately we aim to improve outcomes for patients and improve services in hospital by better and quicker scans.

Stathes Paganis - Cryogenic Detector development
Positron emission tomography (PET), single photon emission computed tomography (SPECT) and combined computed tomography (CT) provide a mainstay for patient diagnosis in hospitals worldwide with a global market forecast of $10.3bn by 2015. Current X-ray and electron tracking detectors used in these complex machines are based on pixilated inorganic scintillator technology that is expensive and has limitations in position and energy resolution. Better image quality would improve diagnosis, while also reducing the X-ray dose and increasing the throughput of patients, allowing reduction in referral-to-diagnosis times. We propose to build a new multipurpose prototype detector to address this medical need.

Round 3 – FUNDED

Bazbek Davletov – Development of a sensitive cell-based assay for the detection of neurotoxins

This project aims to develop a highly sensitive cell-based assay for measuring activities of neurotoxins. Neurotoxins are used in the development of vaccines and also therapeutics for neuromuscular disorders. Currently there are no simple sensitive quantitative assays to measure neurotoxin activity forcing manufacturers, regulatory agencies and academic researchers to use laboratory mice for biological testing often with a lethal endpoint. Recently we developed a cell line, which is responsive to commercially relevant neurotoxins; however the quantitative measurement of neurotoxin activity is still missing. We now propose to engineer a highly sensitive reporter molecule which will allow quantitative non-animal based assay thereby aiding development of new therapeutics and vaccines.

Julian Gunn – Development of a novel, small calibre stent

Atherosclerosis, an inflammatory disease of the arterial vessel walls, is frequently treated with percutaneous coronary intervention (PCI), usually involving stent implantation. Some vessels are too small to stent with current technology; the future of cerebral vessel intervention, for instance, depends upon miniature stent technology. Arterial damage caused by PCI triggers two processes that still trouble the practice of PCI. First, endothelial cell loss triggers an inflammatory reaction and a number of signalling cascades that converge on medial smooth muscle cells to stimulate their proliferation, leading to repair and the development of neointimal hyperplasia or restenosis. Drug eluting stents (DES) are a partial answer but the drugs and polymers can interfere with healing, leading to the second problem, stent thrombosis. Biodegradable vascular scaffolds hold some promise, but are in the early stages of evolution (ABSORB study). Therefore, further stent research needs robust animal models that accurately represent the clinical situation. Our group has successfully developed a model of stenting that allows investigation of PCI in the 1mm diameter mouse aorta, in either un-diseased or genetically modified (atherosclerotic) animals. In this proposal, we will manufacture and test a miniature stent, which will have utility in clinical coronary, cerebral or paediatric use, and in mouse-based stent research.

Dr Ivana Barbaric - Derivation of enteric neurons for cell – based therapy of Hirschsprung's disease

Hirschsprung's disease is a life-threatening intestinal disorder caused by the absence of enteric neurons in the most distal bowel. Given that enteric neurons mediate propulsive gut motility necessary for normal secretion, the absence of enteric neurons in Hirschsprung' s patients causes severe constipation or intestinal obstruction. With an incidence of around 1 in 5000 live births, Hirschsprung's disease is one of the most common congenital diseases affecting the gut. The only existing treatment is the surgical resection of the affected part of the colon combined with a 'pull through' procedure, which entails connecting the healthy part of the gut to the anus. Recent advances in the understanding of development of the enteric nervous system and pathogenesis of Hirschsprung's disease have highlighted potential for alternative treatments, such as cell replacement therapy. In this project, we aim to develop functional enteric neurons from human pluripotent stem cells that could be used to transplant to affected patients to re-innervate the affected part of the gut. The availability of enteric neurons would form a basis for developing a cell based therapy for Hirschsprung's disease.

Harry Moore - Stem Cell Manipulation
The Centre for Stem Cell Biology (CSCB) has devised a novel method of manipulating stem cells in the laboratory. Working with the Medical Advanced Manufacturing Research Centre (MAMRC), we will design and manufacture a near market prototype to demonstrate the method in an automated process. Details of the method are currently confidential.

Aileen Crawford – Novel medical implants to promote in situ repair of traumatic and early osteoarthritic cartilage defects
Osteoarthritis is the most common joint disease and leading cause of physical disability in the UK and worldwide. It affects mainly the knee, hip and hand joints and causes painful stiff joints, joint deformity and loss of joint mobility which can have a substantial impact on quality of life. Osteoarthritis also had a large economic impact on health and social care systems of 1-2% GDP. In the UK 8.5 million people have symptomatic osteoarthritis with 25% of people over 50 years having symptomatic disease in one of both knees. Currently, there is no cure for osteoarthritis; available treatments give valuable symptomatic relief, but do not prevent disease progression. Replacement of the osteoarthritic joint with a prosthetic joint maybe required to restore joint mobility, particularly in the knee and hip. While successful, replacement joints do not have the full range of natural movement and currently have an accepted working life of 20 years. Device loosening requiring revision surgery is a longer-term problem, in approximately 5% of patients. Due to increases in life expectancies and aging populations, there is a greater need to prolong the functional, pain-free life of the natural joint to maintain or restore patient mobility and delay the need for joint replacement. Also, efficient repair of the joint surface after traumatic injury could prevent the later development of osteoarthritis due to the injury. We have designed a novel multifunctional medical device (implant) to repair lesions in the joint surface caused by trauma and early osteoarthritis. The implant is used with a common orthopaedic procedure to release stem cells into the joint. The implants will actively attract and retain these stem cells and promote their maturation to cartilage cells which make new tissue to repair the defect.

Martin Zeidler – Repurposing methotrexate as a JAK/STAT inhibitor
This proposal builds on our previous finding that methotrexate reduces the activity of the JAK/STAT signalling pathway. We are now undertaking in vitro, in vivo and patient sampling-based research to gain a better understanding of how this interaction occurs. These experiments will generate preliminary data required to obtain funding for clinician-led Phase Ib clinical trials. Our longer-term goal is to repurpose methotrexate for the treatment of myeloproliferative neoplasms and other JAK/STAT-associated diseases.

Marco Rivolta – A delivery platform of otic neuroprogenitors for the treatment of hearing loss
Hearing loss is a condition that affects millions worldwide, with a huge toll in quality of life and social integration. The vast majority of this sensory deficit is produced by the irreversible loss of the sensory hair cells and their associated neurons. Regenerative medicine and the use of sensory cell progenitors produced in vitro offers hope for the treatment of a condition that until now remains without a cure. Using human embryonic stem cells (hESCs), we have previously created otic progenitors and, in a seminal paper published in Nature, we have shown that these progenitors can be used to elicit functional restoration on deaf animals. However, the way to deliver these cells into the ear needs to be optimised for a clinical application in humans. In this project we are aiming to explore, in vitro, how a particular delivery mechanism modulates cellular behaviour. We will test the effect of these materials on the otic vehicle as they could be used to transfer the cells from the production facility to the point of surgical intervention in a safe, effective and economical manner. This will help us to develop cell-based therapy for the treatment of hearing loss.

Eran Elhaik - A Match-Maker tool to optimise case-control matching in clinical trials and genetic studies

Currently, clinical trials designed to test new drugs match patient cases with controls based solely on simplistic demographic criteria (age, sex etc.) making them highly vulnerable to 'stratification bias'. This bias is a direct result of differences in genetic ancestry between cases and controls, which is not factored in when trial participants are separated based on demographics. This undetected bias can contribute to incorrect interpretation of trial results due to lack of information, leading to false negative or positive results for a drug, with subsequent financial and patient health impacts. To overcome stratification bias, we propose to develop Match-Maker, a unique genetics-based software tool that matches cases with controls based on demographics and genetic similarity, allowing pharmaceutical companies to make more informed decisions about the results of their clinical trials. This increased resolution will allow clinical trials to become more accurate (important because they are the most costly part of the drug development process) and will ultimately translate into benefits for patients with increased drug availability and more information being available on specific drug effectiveness.

Heidi Christensen - Cloud-based speech recognition for people with paralysis using ventilators (CloudVent)

People with a high-level spinal cord injury (SCI) are hugely dependent on carers, families and friends. They cannot use traditional interfaces to digital devices such as keyboards, touchscreens and buttons. This compounds their dependence and can have a devastating effect on rehabilitation and the ability to regain an independent professional and social life -- the majority of people sustaining SCIs are under 40. An attractive alternative is to use a speech recognition system to provide a means of communication. In this project, we will provide a proof-of-concept that we can adapt our technology to cope with the particular characteristics of the speech of people using ventilators.

If your organisation would like to find out how to collaborate with academics in the healthcare sector please contact one of the Business Manager's in the Sheffield Healthcare team, who would be happy to discuss your requirements.