Dear Friends and Supporters,

This year brings us a high water mark in SITraN’s six year history. In September we had the wonderful news that an NIHR-Biomedical Research Centre for Chronic Neurological Disorders will be established in Sheffield. This will really help to bridge the translation of findings from SITraN into early phase clinical trials.

Exciting studies poised to seek funding will now receive a necessary seeding boost of support to get them underway in Sheffield. These include a drug repurposing trial for Parkinson’s Disease and a first-in-man gene therapy study using a viral vector for SOD1-linked Motor Neuron Disease.

We bring you news also of exciting new collaborations and investments which are afoot and expanding our research horizons.

We hope you enjoy reading our 2016 newsletter.

With kindest regards,

Professor Dame Pamela Shaw
BRC status for Sheffield: Government boost to Neurological Research

This September, Sheffield joined the ranks of Oxford, Cambridge, University College London and Imperial College London, when the Department of Health announced that our bid to be designated as 1 of 20 UK Biomedical Research Centres (BRCs) had been successful. In July Prof Pam Shaw and a team of partners from the University of Sheffield and Sheffield Teaching Hospitals interviewed in front of a multinational panel of experts from around the world for the opportunity to become a BRC of Translational Neuroscience for Chronic Neurological Disorders.

This is a tremendous development in the evolution of SITraN and comes with a £4m injection of funding for experimental medicine and early phase clinical trials. Read more about the Sheffield BRC on page 7.

Igniting the interests of Big Pharma

SITraN is firmly on the drug industry’s radar with visits from AstraZeneca, Sanofi and Pfizer among those from large multinational corporations and smaller contract research organisations alike. The expressions of interest are for their libraries of drug compounds to be tested in our drug screening assays. This represents new interest in rare diseases from the big pharma giants. Dr Richard Mead (shown left embarking on a fund raising cycle to the European Net-

SITraN is getting bigger

SITraN is set to expand with a site identified by the University estates team for SITraN 2, to accommodate our growing team of scientists and clinicians. New appointments are being sought for experts up to Professorial level in Stem Cell Neurobiology, Neurogenetics and Neuropharmacology/Drug Discovery to help us hone in on major developments in neurodegeneration.

For our latest news visit our website:

www.sheffield.ac.uk/sitran
You can now also connect with us on
@neuroshef #SITraN
SITraN.uk
SITraN on youtube
SITraNsmissions
Biomarkers are a more prominent research focus than ever in MND

This year’s newsletter features no less than 3 clinical studies that are either underway or in the pipeline at SITraN which focus on biomarker discovery in MND. A biomarker is a chemical or process in the body which is tied to the progression of disease and can be measured in the body fluids or by a scan or biopsy. The amyloid protein for example, can be considered a biomarker for Alzheimer’s disease with levels of a particular amyloid informing clinicians about the physical status of the disease and possibly providing a target for therapeutic intervention as well. Disease specific, objective read-outs of how effective a response to treatment is, are highly valued for therapy development. A signature biomarker for MND may come in the form of a specific protein or a panel of indicators in body fluids. Electrical signals from nerve fibres measured in an neurophysiology exam and images provided by MRI scans also provide read-outs. For more information on neurophysiology and MRI biomarkers in MND, see pages 8 and 9.

Enter the age of gene therapy

Several gene therapy trials for diverse diseases have been in progress around the world since the field entered a renaissance in 2010. In Sheffield we are poised to enter the age of gene therapy for MND. More on pages 5 &10.

Professor Shaw talks: This year in SITraN

Professor Shaw’s hour presentation at the MNDA annual general meeting in September (left) was well received by those in attendance and who watched the stream online. Her round up of current research on MND in SITraN is very accessible to the lay person and can be free viewed here: http://livestream.com/eventstreamingcompany/mnda

State of the art medical imaging upgrade for the Royal Hallamshire Hospital

Currently, patients in need of both MRI and PET repeat scans are faced with multiple appointments and trips to hospital. These can be halved by combining MRI and PET into one scanner. The scan information obtained through MRI-PET is of a higher visual quality than what is possible through the current PET-CT equipment too. This is a joint initiative between Sheffield Teaching hospitals and several Faculties at the University of Sheffield, and will be 1 of only 80 combined MRI-PET installations worldwide. The scarcity of MRI-PET machines means that Sheffield researchers can play a leading role in the development of techniques to use MRI-PET for our own medical specialities.
Research News

New genetic cause of MND discovered

A gene called NEK1 has been newly discovered to underlie susceptibility to MND in 3% of cases, both inherited and sporadic. NEK1 was identified from the complete DNA sequences of 4 MND patients from a small community in the Netherlands and validated using the data of Project MinE – an international collaboration between 80 researchers including those at SITrAaN. Project MinE aims to sequence the complete DNA of more than 15,000 MND patients with the UK arm of the project providing 1700 of those, and has in part been funded by the $100 million raised worldwide by 2014’s ice bucket challenge. It is also supported by the MNDA.

Equipment boost for our Drug Screening laboratory: 2 new pieces

In December last year, the ‘Opera Phenix Laser Based Confocal High Throughput Cell Imaging System’ made by Perkin Elmer was our number 1 priority item on the SITrAaN wish list for laboratory equipment. This automated microscope delivers 10x more light than normal and comes with multi cameras for optimum speed and sensitivity. As a confocal microscope, the OperaPhenix can focus the light hitting our sample into a single plane, this removes all the blur that is obtained in a normal microscope due to the confounding signal from out of focus objects. But unlike a manual confocal microscope, the automated OperaPhenix can take over 23,000 images overnight of the cells we are studying. This amount of images would take about 100 days to acquire on a manual instrument! Our drug screening assays will now be vastly speeded up thanks to the amazing level of funding patrons donated towards this £400k piece of equipment within the space of 6 months. The machine is installed and scientists have been undergoing training to use it and the associated analysis software. This set up is more commonly used to screen for cancer drugs and now that expertise can be transferred to the field of neurodegeneration.

A second addition to the drug screening laboratory came in the form of another automated system; The Biolog OmniLog® machine. Funding for which was awarded from Neurocare to Dr Scott Allen for the continuation of his work looking at the role of energy metabolism in motor neuron disease. Tray space for up to 50 microplates is provided in the machine, in total allowing for up to 1920 assessments of cells subjected to different nutrient availability. Dr Allen uses this in conjunction with the Seahorse Bioanalyser, also funded by Neurocare in experiments described further on page 13.
**Clinical Update**

### New MND drug trial

A new therapy based on enhancing the body’s immune response called ‘MIROCALS’ (Modified Immune Response And Outcomes in ALS) is gearing up to be launched in the next few months. This new proof-of-concept project will be taking place at the Clinical Research Facility at the Royal Hallamshire Hospital and aims to test whether stimulating the body’s immune system can decrease nerve damage in Motor Neuron Disease.

### LEVALS drug trial nears completion

The multicentre Levosimendan in ALS (LEVALS) trial is finishing the last appointments from the 6 month open label follow up extension looking at the effects of a muscle activator on disease progression. This trial involved drug repurposing as Levosimendan has been in use for over 10 years to treat heart failure as an intravenous drug. Sponsor Orion Pharmaceuticals will assess its oral efficacy for motor neuron disease.

### Telehealth in MND pilot study concludes

Dr Esther Hobson has completed the study this year having recruited 40 patients and carers in total to give their feedback on using the Telehealth app to remotely enter data about the patient’s condition every week. The results have been prepared into a paper for publication and Dr Hobson presented her findings to the MND Association symposium in December.

### Sheffield hosts two new Biogen sponsored clinical trials for MND

Sheffield is the sole UK site for two worldwide studies by Biogen. One; a new ground-breaking methodology study commenced this year to investigate over time how well new outcome measures in electrophysiology, physical assessment and blood serum markers can assess progression in MND. See page 9 for more on the neurophysiology for this trial. The first four patients have been recruited onto this study and screening for more to take part is ongoing. Two: Sheffield has begun hosting the second phase of an investigation into the knock-down of the SOD1 protein which is mutated in a specific, usually heritable form of MND. This trial will use lumbar puncture to administer initially a single, then repeated doses of an antisense oligonucleotide which is one form of gene therapy. For other gene therapy plans using a different approach, see page 10.

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**Introducing:**

Lee Tuddenham pictured below is our new research nurse, so will become a familiar face to patients taking part in clinical trials at the Royal Hallamshire hospital. For information on trials conducted at the Clinical Research Facility, see here: http://smndrug.group.shef.ac.uk/

https://www.ukctg.nihr.ac.uk
Awards & Grants

AMBRoSIA: A Multicentre Biomarker Resource Strategy In ALS

Prof Shaw and Dr Janine Kirby have been awarded a major grant by the MNDA to fund a 5-year collaboration between SI-TraN, the Sheffield Diagnostic Genetics Service, the University College London, the University of Oxford and Barts & the London School of Medicine & Dentistry. The project aims to build a large resource of biological samples from MND patients to look for biomarkers that could speed up diagnosis before a person develops major disability and help to monitor response to treatment. Biomarkers are chemicals that can be detected in the blood, urine and cerebrospinal fluid but this project also plans to use SI-TraN’s expertise in cell reprogramming technology to grow personalised motor nerve cells from skin samples taken from patients to test new drug treatments.

SITraN has attracted over £20 m research funding since 2010

Some other examples of recent grant funding and research awards

- **Prof Chris McDermott** is a partner and UK PI in the ALS-Care joint programme awarded £2,011,860 for a multinational European study into ALS care packages.
- **Professor Dame Pamela Shaw** is a co-applicant of the ALS MicroNeurotrophin Research Consortium funded by ALS Worldwide for £166,150.
- **Dr Scott Allen** was awarded £247,954 by the MNDA for Bioenergetic profiling of cellular ALS models.
- **Professor Dame Pamela Shaw** is the PI for the multicentre AMBRoSIA study funded by the MNDA for £660,033.
- **Dr Scott Allen** received an equipment grant to fund the Omniolog™ from Neurocare for £73,755.
- **Prof Oliver Bandmann** and co-applicants for ‘RNA-seq based pathway analysis to characterise the mode of action of UDCA in Parkin deficiency’ were granted £71,890 by the Michael J Fox foundation.
- **Prof Stephen Wharton** and co-applicants were awarded £69,998 from Alzheimer’s Research UK and is the PI on ‘The Model—AD Study’ modelling synaptic connections in sporadic AD using astrocytes and neuronal cells derived from the fibroblasts of patients and controls.
- **Prof Chris McDermott** was awarded an extension for the MND Care Centre Programme from the MNDA for £37,830.
- **Dr Guillaume Hautbergue** and co-applicants were awarded £169,558 by the MNDA to develop Novel therapeutic strategies to prevent toxic nuclear export and RNA translation of repeat transcripts in C9orf72-related MND.
- **Dr Paul Heath** is a co-applicant on a £94,631 project sponsored by Weston Park Hospital Cancer Charity to Predict disease relapse and treatment failure in Gestational Trophoblastic Neoplasia.
- **Prof Neil Lawrence** is a co-applicant on a Horizon 2020 project funded by the European Commission for £454,600 for the Open DreamKit: Digital Research Environments project.
- **Drs Richard Mead and Laura Ferraiuolo** were awarded £154,840 by collaborators Stratified Medical Ltd.
- **Prof Winston Hide** was awarded $225,308 by the Cure Alzheimer’s Fund for his part in a functional mapping project ‘CureALZ CIRCUITS’ in collaboration with Harvard, MIT and Max Planck Institute.
Translational Neuroscience for Chronic Neurological Disorders BRC

In September the NIHR announced that Sheffield will be awarded £4,049,681 over 5 years from April 2017 to establish as a Biomedical Research Centre with the theme of ‘Translational Neuroscience for Chronic Neurological Disorders’. This designation has been achieved in part on the basis of SiTraN’s standing as a world leading centre for MND research and the potential of the BRC to positively impact on the lives of patients with diverse neurological illnesses. This will kick-start early phase clinical trials in the areas of Neurodegeneration, Neuroinflammation and Cerebrovascular disease. Ongoing research in these areas will be supported by underlying and expanding research infrastructures in Advanced Medical Imaging, Genomic Medicine and Bioinformatics, and in silico medicine. Thus in conjunction with SiTraN and the Institute for in silico medicine (INSIGNEO), the BRC formally brings together outstanding researchers from both the Departments of Engineering, and Neuroscience, the recently formed Centre for Genome Translation, with hospital based Academic Units of Neurology, Radiology and NIHR-Clinical Research Facilities. Professor Dame Pamela Shaw speaking as the Director of the new Sheffield BRC said that, “The philosophy of having clinicians and multidisciplinary teams of different scientists working collaboratively has been very deliberate since the inception of SiTraN.” This major strategic investment in embedding partnerships across scientific disciplines with clinical practice, for the common goal of improving patient’s lives and reaching towards therapies which slow disease progression is a huge boost to clinical neuroscience research.
Feature: Muscle Energy MRI

MRI can measure muscle energy

Last year Dr Tom Jenkins won the prestigious Vera Down Award to investigate the use of whole body MRI scans to measure signals from the muscles as a marker to track progression and response to treatment in MND. He is now extending his study in a highly distinctive direction by applying whole body MRI to identify targets that could be used to measure metabolism in muscles using a phosphorus isotope. So far 29 patients with MND and 22 volunteers serving as control subjects have been recruited on to the longitudinal muscle energy project. In total 20 patients and 20 controls have been scanned at an initial time-point and 4 months later, while some have been scanned at both 4 months and 12 months, to investigate changes in the muscles over time. A muscle compartment in the leg has been identified as a common site of disease burden. Further work is now being done to find the best sites in the body to apply the technically challenging 31-phosphorus spectroscopy technique. Dr Jenkins and colleagues presented some preliminary findings at the international MNDA and NiSALS meetings in Orlando, Florida in December 2015.

“Patients with MND have problems with energy metabolism and we can explore this using a cutting edge tool which is 31-Phosphorus MR spectroscopy”

Dr Tom Jenkins

“I felt more relaxed in the scanner than I thought I would. I was able to choose my own lighting scheme in the room and watch ‘Blue Planet’ on a television by looking at a mirror angled inside”

Dr Jenkins in the image analysis suite
Volunteer in the scanner
Watching nerve fibres fire motor signals

Neurophysiology is the study of nervous system function and a key method in this specialism is electromyography (EMG). EMG records the electrical activity in muscle. Dr James Alix analyses the EMG read out generated as a patient contracts their muscles. These signals can be used to find out what is causing symptoms like muscle weakness which can be due to problems with the muscles themselves, or the nerves and motor neurons that control them. In conditions like MND this means examining lots of muscles to build up a picture of what is happening to the whole patient.

Ongoing research to improve EMG monitoring

Promising new therapies for MND have often become stymied at the Phase 3 Clinical Trial stage, in part due to insufficient ways of measuring response to treatment. As part of a wider European study for Sampling and biomarker Optimization and Harmonization In ALS (SOPHIA), Dr Alix is assessing a method called Motor Unit Number index (‘MUNIX’) as a longitudinal biomarker in MND. A motor unit is a motor neuron plus all the individual muscle fibres supplied by that motor neuron. By recording the electrical signals generated by muscle Dr Alix gets a summation of all the functional motor units within that muscle.

Neurophysiology in practice:

During the test, electrodes deliver a small electrical pulse through the skin to a nerve supplying all the muscle fibres within a muscle. This makes the muscle twitch and that response is captured on a computer. The patient then contracts the muscle against gentle resistance provided by Dr Alix. The signals are then analysed to produce a count of the motor units that are working.

A volunteer kindly lends a hand to Dr Alix

The new MUNIX method can be applied to several muscles in the arms and legs and is quick to perform. This means that clinicians tracking disease change over time in a clinical trial can get a better idea of what is happening to the patient.
Feature: Gene Therapy

What is Gene Therapy?

Genetic mutations that cause disease can be corrected in some cases by using gene therapy. A gene therapy product that is delivered to the body’s cells can either provide a healthy copy of a mutated gene that is not working properly, or silence the effects of a gene that is having a toxic effect. A mutated gene leads to the SOD1 protein functioning in a toxic way in 20% of inherited MND cases and it has been found that the disease gene can be safely silenced by RNA interference (see below) to extend survival and function in mouse models of MND. Prof Mimoun Azzouz’s group at SITraN are getting ready to start a first-in-man experimental medicine trial using SOD1 silencing gene therapy, but this will require regulatory body approved pharmaceutical grade (GMP) manufacture of the gene therapy product.

How does it work? For SOD1-linked MND, gene therapy shoots the messenger!

Faulty genes that create toxic proteins cannot safely be simply cut out from the tightly coiled DNA with current technology. Instead they can be prevented from exerting their effect through small molecules called messenger RNA, which carry the instructions from the blueprint of DNA to special enzymes that build the proteins. Therapeutic bioengineered messenger RNA molecules bind with those from the faulty gene and stop the protein from being made.

Turning viruses into tools for medicine

Getting inside the cell membrane is a challenge for the large nucleic acid molecules that can target messenger RNA in gene therapy. One way to overcome this that is utilised by scientists is to harness viruses that have evolved methods that trick cells into letting them in.

Adenovirus model

Certain viruses have the necessary tricks to get into the body’s most difficult to access cells—the nerve cells which sit behind an often impenetrable blood-brain-barrier in the central nervous system (CNS). Adeno-Associated Virus 9 (AAV9) is a stand out viral vector that can deliver gene therapy products to the CNS, is non-immunogenic and non-pathogenic and has a track record of therapeutic delivery of gene therapy products to the nerve cell bodies in vivo.

However, there aren’t currently enough facilities that can produce clinical grade AAV9 quickly enough to meet demand worldwide.
What challenges does the GMP manufacture of gene therapy medi-
AAV9 and other viral vectors are in limited supply for administration to patients. Pharmaceutical (GMP) grade material requires special fa-
cilities and the refinement of scaling up processes to generate sufficient quantities of virus to be as effective in humans as in mice. GMP grade viruses can be produced in commercially available bioreactor units but these need to be housed inside special clean room environments built to eliminate the risk of contamination of the product. Prof Azzouz is campaigning for a GMP facility to be built in Sheffield as the current bottleneck in GMP production for gene therapy in the UK and Europe is slowing down clinical translation.

Gene Therapy holds far reaching potential
Several studies are now showing that gene therapy can safely and effectively treat an array of diseases that result from a single defective gene. The childhood form of MND called Spinal Muscular Atrophy, is caused by the loss of function of a gene called SMN. Gene Therapy using the AAV9 vector to deliver a healthy copy of the gene to the affected nerve cells is already in use in children and infants in the USA, confirming the safety and tolerability of this medicinal virus. It is particularly attractive that a single treatment has the potential to cure lethal diseases but a decade ago the gene therapy revolution faltered when carcinogenic effects and a severe immunogenic reaction to a viral vector surfaced during trials. Regulatory bodies such as the MHRA in the UK now provide more robust requirements before candidate gene therapies can enter human trials and safe new sub-strains of vectors such as AAV9 are available. Gene transfer can also be achieved by non-viral methods. An alternative strategy for delivering RNA interference to SOD1 mRNA in MND has entered phase 2 trials with an antisense oligonucleotide (ASO). ASOs are not contained within self-replicating carrier viruses and currently require repeated lumbar puncture administrations to keep knocking down the SOD1 protein.

Different types of viral vectors
The choice of virus for clinical gene therapy depends on the efficiency of transgene expression, whether transient or permanent expression is required, and the safety and stability of the vector. In addition to AAV, Adenoviruses, lentiviruses, pox viruses, baculoviruses and herpes simplex viruses are being investigated to deliver genes to cells. They each have a number of advantages and disadvantages that make them suited to particular applications. The AAV vector can infect non-dividing cells like neurons as well as dividing cells, which are more common targets for viral infections. Reproducing the virus genome in a non-dividing cell means that AAV is independent of the host cell’s DNA. The lentivirus reproduces its genome by integrating into the hosts DNA which then divides into two daughter cells during mitosis. Integrating viruses like this can pose a risk if they integrate in an area of DNA that causes uncontrolled mitosis leading to cancer.
New Insight Into the Most Common Genetic Cause of MND and Frontotemporal Dementia

SiTraN Senior Lecturer Dr Kurt de Vos (right) and his team (below) have resolved for the first time, the intrinsic function of the protein product of the gene, C9orf72. A mutation in this gene is the most common known cause of both MND and FTD, occurring in 40% of familial and 6% of sporadic MND cases. The mutation is a repeated expansion in an area of the gene that does not normally code for protein. Three possible mechanisms for how the mutation causes neurodegeneration have been proposed: 1. The RNA produced from the mutation is toxic. 2. The mutation produces an unusual protein which is toxic. Or 3. The mutation causes the protein to lose its normal function and this is detrimental to the cell. It is likely that all 3 mechanisms may contribute.

This pioneering study identified that C9orf72 functions in the cellular autophagy system—the process by which a cell consumes unwanted proteins and other debris to recycle the re-usable parts. Dysfunctions in this ‘self-eating’ system have long been suspected to play a role in the disease processes of MND and FTD. This research has been published in the prestigious EMBO journal—see page 20 for a list of our selected publications this year. This paper comes out just as the Nobel Prize in Physiology has been awarded to Yoshinori Ohsumi for elucidating the process of autophagy, indicating the importance of the process to the cell and the timeliness of Dr de Vos’s report on its relevance in MND.

First transgenic zebrafish model of C9orf72

The C9orf72 mutation has been incorporated into the DNA of a zebrafish line by SiTraN’s Dr Tennore Ramesh. His student is now studying the transgenic fish to characterise the model, which may later be used to screen new therapeutic compounds. Previously transient zebrafish models have been created by injecting genetic material into the embryo but this material is degraded within days. In this model the mutant DNA is retained through to adulthood, thus more closely modelling MND in humans. A fluorescent red marker to denote cellular stress in the fish was inserted along with the C9orf72 mutation.
Investigating C9orf72 toxicity

Dr Ke Ning and Dr Guillaume Hautbergue are researching the mechanisms through which the C9orf72 mutation causes neurodegeneration in MND. To do this they have grown cells taken from patient skin biopsies and chemically induced these to become motor neurons and their support cells, astrocytes. Post-doctoral researcher Marga Segovia Rolan is investigating the electrical properties of the motor neurons and astrocytes which have the exact genetic make-up of the patients sampled.

C9orf72 investigation at SITraN demonstrates a spiral shaped research strategy. Observations are made in patient samples, testable theories are teased out and verified in animal models. Zebrafish and patient-derived cell models can then be used to test therapies in our high throughput drug screening laboratory and hits can then be translated into early phase clinical trials.

New projects

Evidence has been accumulating that a toxic protein is made from the C9orf72 repeat expansion. This initially puzzled researchers as the mutation is in an area of the gene that is usually cut out before the messenger RNA exits the nucleus. mRNA then usually requires a specific sequence to initiate protein production from the mRNA code in the cellular machinery. In the case of the C9orf72 mutation, the region of the machine is somehow being exported from the nucleus and made into protein without any of the normal mandatory requirements to do so. A new research project led by Dr Hautbergue was funded by the MNDA this July to investigate ways to stop the pathological protein production.

Studying cell metabolism in patient skin cells.

How does the C9orf72 expansion affect cell metabolism? This is a question that Dr Scott Allen, MND Association Senior Research Fellow, is lining up to address as he performs thousands of assays subjecting cells to different nutritional substrates. Dr Allen’s theory is that healthy cells are resilient to certain forms of nutritional stress because they have a flexible metabolism that can generate energy from what is available when starved of a more preferred substrate, but in MND cells lose that flexibility and become vulnerable to an energy crisis.

‘Seahorse’ bioanalyser

Neurocare have funded both machines in Dr Allen’s energy research.

Dr Scott Allen with OmniLog and Seahorse
Repurposing an epilepsy treatment for stroke

Vagus nerve stimulation (VNS) has the potential to boost neuroplasticity (the way the brain “learns” tasks). The Stroke Research team are conducting a feasibility study, led by Dr J Redgrave combining physiotherapy exercises with a new form of VNS delivered through the external ear (transcutaneous vagus nerve stimulation, tVNS). The stimulation is perceived as a mild tingling sensation and so far 8 stroke survivors with arm weakness have successfully undergone an intensive 6 week programme of physiotherapy combined with tVNS. All participants achieved a meaningful improvement in arm function and tolerated the treatment well. A pilot randomised controlled trial is planned to further investigate this new technique which could in future be delivered by patients in their own homes.

Dr Redgrave’s fourth year PhD student, Harvey Leung has been exploring the physiological and psychological effects of VNS in patients recovering from stroke. In particular he is looking to see whether anti-inflammatory mechanisms mediate the effect of VNS. He has been sampling patient’s blood before and after VNS and assaying for a panel of inflammation biomarkers as well as examining changes in mood and heart rate variation. VNS therapy has been in use in epilepsy for many years and has helped many patients to achieve long-term seizure control. However the exact mechanisms underpinning this observed effect are not well understood. Part of the ethos behind working an institute like SITraN is to advance cross-talk between the scientific study of different diseases and share therapies and theories to advance medicine.

Investigating carnosine and stroke vaccination

Prof Arshad Majid worked together with Prof Shaw and colleagues on the BRC bid this year as the leader of the cerebrovascular research sub-theme, encompassing preclinical stroke therapy development, acute stroke trials, biomarker studies and rehabilitation trials. His focus is on understanding the pathogenesis of cerebrovascular diseases with the overall aim of developing new treatment and brain repair strategies. Two exciting early phase trials that are planned for the BRC are the use of carnosine as a neuroprotective agent during ischemia and developing a stroke vaccine for patients predisposed to cerebrovascular disease that would reduce death and disability should a stroke occur. Further investigation into non-invasive vagus nerve stimulation in motor stroke rehabilitation is also in line to be taken forward through the BRC.
New Appointments

Dr James Alix (left) joined SITraN in 2015 as an NIHR-sponsored Clinical Lecturer in neurophysiology. He has a research focus on developing new techniques to diagnose and monitor neuromuscular disorders and conducts clinical research at the Royal Hallamshire hospital—featured on page 9.

Dr Denis Wang (right) recently joined from Cambridge University as a lecturer in Bioinformatics and Genomic Medicine. His research interest in the emerging field of Translational Bioinformatics is geared towards the development of personalized medicine and involves integrating genomic data to predict clinical outcome and identify genetic biomarkers.

Dr Alisdair McNeill (left) joined from UCL to become an INSIGNEO Senior Clinical Fellow & Honorary Consultant in Clinical Genetics, Sheffield Children’s Hospital, is in part based at SITraN. His research focuses on the genetic cause of neurological disorders, in children and adults. He uses patient wearable movement sensors and 3-dimensional facial image analysis to identify new ways of phenotyping patients with a focus on chromosome microdeletion diseases.

Dr Scott Allen (above) won a Fellowship from the MND Association and began as a non-clinical senior research fellow in January 2016. Scott has been with SITraN since its inception in 2010. He was previously Prof Pam Shaw’s post-doctoral researcher. This Fellowship is a wonderful continuation of Scott’s research into the cellular metabolism of MND.

Business cases for high profile recruitments put forward SITraN is set to expand and is seeking to make new appointments in the areas of Dementia, Stem Cell Neurobiology, Neurogenetics and Neuropharmacology / Drug Discovery from Senior Lecturer to Professorial level. For the latter three positions, a suitable candidate with enough experience will have the potential to join Prof Shaw as a Scientific Co-Director for SITraN or Head of Department for Neuroscience.

Recruiting in the areas of Stem Cell Neurobiology, Neurogenetics, Neuropharmacology / Drug Discovery, NeuroInflammation / Glial Biology

An excerpt from the splash advert in planning
Collaborations

ALS-CarE: A programme for ALS Care in Europe

A large multinational collaboration for evaluating health care policies for MND is underway with SiTraN based Neurologist, Prof Chris McDermott as the Principal Investigator for the UK arm of the study. The Programme for ALS Care in Europe (ALS-CarE) will use a patient questionnaire to compare how care for MND is carried out in different countries across Europe in order to determine the best care package for the future. The countries included in the study are the Netherlands, UK, Italy, Germany and Belgium. The observational research will track the patient’s experience using quality of life measure and assessing their needs and the needs of carers and interactions with healthcare providers. A sub-study comprising an extra questionnaire on end of life care is being run alongside the main study. The Health Economics Analysis on the results of the study will be conducted by the School of Health and Related Research (SchARR) within the University of Sheffield. SchARR has experience of working with NICE to implement guidelines for care and advise them on the cost effectiveness of technological and medical interventions.

The School of Health and Related Research
EU Joint Programme
Prof Chris McDermott

Scientific collaboration helps to accelerate our research

Continuing working relationships from Ohio

In 2014 Dr Laura Ferraiuolo returned from 2 years working in Prof Brian Kaspar’s lab in Columbus, Ohio. She completed her Marie Curie Fellowship back in SiTraN where she continues now as a lecturer in Translational Neurobiology. She continues collaboration with Prof Brian Kaspar and his team, bridging our gene therapy research group with theirs. The SiTraN team led by Prof Mimoun Azzouz has been using a therapeutic construct made by the Kaspar group, virally delivered to knock-down SOD1 in a mouse model of MND. The collaboration is working together to publish this work and procure material for a clinical trial.

Dr Laura Ferraiuolo

Prof Brian Kaspar
of Ohio State University

16
Collaborations

Postgraduate student exchange with Tongji University, Shanghai

In April, delegates led by the Dean of the Medical School at Tongji University visited the Faculty of Medicine at the University of Sheffield. This September, SITraN PhD candidate Yuri Ciervo started a 12 month placement with SI-TraN’s collaborators from Tongji University in Shanghai. Yuri is studying how stem cells derived from adult fat tissue can be reprogrammed into motor neurons for their application to MND therapies. This area of regenerative medicine is a specialism of Yuri’s supervisor at Tongji University, Prof Jun Xu. Future visits and exchanges are planned between SI TraN and Tongji researchers in order to learn specialist techniques from each other, share our ideas and work together to advance our science.

Our Partners and Collaborators

USA & China
- Ohio State University
- Pennsylvania State University
- NIH, Bethesda
- Harvard University, Boston
- Mt Sinai Hospital, NY
- ALS Worldwide
- Tongji University, Shanghai

Pan-European Research
- EUROMOTOR-SOPHIA
- ENCALS
- MIROCALS
- JPND

UK Clinical Research
- NIHR DeNDRoN Network of 19 MND Care & Research Centres

Industry Partners
- AstraZeneca
- Biogen
- Vertex Pharma
- ReNeuron
- Heptares
- Benevolent Bio

SITraN PhD Student, Yuri Ciervo in Shanghai
Events

Wine tasting and activity auction for Neurocare go down well

Always up for a challenge; when SiTraN heard of the ‘Neurocare November’ annual fundraising event where they ask 100 corporate and community supporters to raise £100 they rose to the challenge. Getting their creative hats on, food and drink seemed to be at the common theme and following a short discussion a ‘Wine tasting night’ was quickly agreed upon.

SiTraN has benefitted from the Neurocare charity on a number of occasions over the years, with purchasing specialist pieces of equipment to assist our research programmes into neurodegenerative diseases. The generosity of staff in the department quickly became apparent with donations of wine meaning that the vast majority of funds raised would go to the charity. Staff were also encouraged to offer their skills in a charity auction on the night with volunteers offering a range of experiences from cookery master classes, to archery and canoeing lesson.

Neurocare is a charity which raises money for the neurosciences and neurology departments at Royal Hallamshire, Northern General, Children’s Hospitals as well as SiTraN. They have an extremely exciting project at the moment which is a robot that assists with brain surgery called ROSA. They are striving to raise £250,000 towards the ROSA robot to be the first NHS hospital right here in Sheffield to help transform the lives of thousands of patients needing complex brain surgery in areas such as epilepsy and deep seated tumours.

A fun night was had by all with lots of staff and students looking forward to taking up new hobbies or learning new skills. The evening was an amazing success, raising over £1900 towards the excellent work supported by Neurocare.

Over 40 attendees from SiTraN enjoyed the wine tasting evening with even more people participating by donating, bidding and offering activities for auction for the event.
Charity golf matches drive ace event days

Charity golf day organisers Peter Taylor of leading local health insurers, Westfield Health and Kim Jordan of the Kier group presented a cheque to SITraN in November of monies raised by their teams this year in support of MND research at the institute. Peter Taylor has been involved in annual charity golf days supporting various causes since first organizing one for the South Yorkshire MNDA in 2012. Charity golf matches are some of the most successful regular charity events in the region and contribute very import support and awareness to MND. Thanks to everyone involved for their generosity in time and donations towards the event.

This has been a great year for local MND charity golf matches. The third annual MNDA golf day teed off on Friday 17th June at Halilowes golf club in Dronfield. Amongst the festivities this year were an auction of touching memorabilia including signed commemorative items from golfing champions, vouchers for play from various clubs and souvenirs from historic competitions. The day raised a grand total of £9500 which was split equally between SITraN and the South Yorkshire MNDA. Many thanks to Matthew Rowland for organising this excellent event. Proving always to be very popular fundraisers, further charity golf matches were held for the MNDA in August at the Dore and Totley Golf club, and for SITraN in September at Phoenix golf club in Rotherham. Many thanks to our kind patron, Stuart Keane for organising the latter event and the sponsors and supporters who raised £2650 towards MND research at SITraN. These fun events held in beautiful settings are a big draw for golfers and non-golfers alike. For information and advice from the MNDA on organising your own charity golf match, please type the web link below into your browser.

Scientists soaked, once again!

In August, researchers from SITraN together with members of the South Yorkshire branch of the Motor Neurone Disease Association (MND Association) held the annual soak a scientist event in Endcliffe park, raising money and awareness under the banner: #EveryAugustUntilACurecause. The sun came out for the day which also saw a treasure hunt, bake sale, tombola and the opportunity for children to engage in questions about SITraN, MND and neuroscience. The event attracted journalists from The Star and Sheffield Live, conferring a fantastic awareness raising opportunity on our very scientist representatives. £650 was raised and this money will be used to buy new equipment for the SITraN laboratories and to fund further public outreach activities. A great outcome after a day packed with water splashes, cake and generous people who wanted to help find a cure for MND.

PhD Candidates
Jodie Stephenson (right) and Alejandro Lorente Pons (left) were among the many SITraN personalities who took a refreshing splash on the day. A bargain at £1 per soak! Look out for next year’s event.

SITraN Open Days

Our yearly public Open Day gives all our friends and supporters the opportunity to get a behind-the-scenes look at our research. The day usually offers a few short talks with research updates, as well as guided tours and lab demonstrations. Our guests will have plenty of opportunity to talk to our researchers and sample some cakes home baked by SITraN staff and students.

Look out for information on the next SITraN Open Day

July 2017

Entry is free, however registration is required. Please email sitran@sheffield.ac.uk or phone 0114 222 2230.
SI TraN welcomes Spanish Researchers in the UK  http://www.sruk.org.uk

Dr Margarita Segovia Roldan (second from right) with the SRUK Yorkshire board of directors, from left to right, Secretary Dr. Jacobo Elies-Gómez, Vice Director Dr. Maria Huete-Ortega and Director Dr. Javier Iglesias-Gonzalez

The Society of Spanish Researchers in the UK (SRUK) is a social and professional network for Spanish researchers in the UK. The Spanish scientific diaspora numbers over 10,000 world-wide and 3500 of those are in the UK. This September SRUK held a networking workshop in SI TraN with the help of Dr Margarita Segovia Roldan, a post-doctoral researcher in Dr Ke Ning’s laboratory at SI TraN, who is also the treasurer of SRUK. As well as offering advise and support to Spanish researchers, SRUK aims to engage the public and act as Ambassadors for science between Spain and the UK. In November they hosted a Christmas lecture on epigenetics in Sheffield with guest speakers Dr. Manuel Esteller and Dr. Ron Chen. Upcoming events in the new year include a cinema night planned to be held at SI TraN, all are welcome.

SI TraN joins in the Third Annual Festival of the Mind

This September SI TraN representatives took part in the 3rd annual Festival of the Mind to engage the public with the exciting research that we do. People of all ages had the opportunity to examine slices of brains under the microscope and test their reactions and reflexes by catching a falling ruler as quickly as possible and trying not to blink whilst wearing lab goggles and having cotton wool balls thrown at their faces. The Moor Market pitch also included a ‘mitochondria station’ which was a hit, using electronic circuits to demonstrate how the complex processes that take place in mitochondria can become faulty in neurodegenerative diseases and explaining research into potential treatments for these illnesses that aim to identify and fix these faults.

Look out for next year’s Festival flyers
### Selected Publications

**PNAS** 113, October (2016)

**Oligodendrocytes contribute to motor neuron death in ALS via SOD1 dependent mechanism.**

**EMBO J** 35(15):1656-76 (2016)

**The C9ORF72 protein interacts with Rab1a and the ULK1 complex to regulate initiation of autophagy.**

**Nature Genetics** 48, 1043-1048 (2016)

**Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis.**

**JAMA Neurology** 73 (7): 812-820 (2016)

**Association of a Locus in the CAMTA1 Gene With Survival in Patients With Sporadic Amyotrophic Lateral Sclerosis.**

**Stem Cell Reports** 7(1):110-125 Jul 2016

**Integrated Genomic Analysis of Diverse Induced Pluripotent Stem Cells from the Progenitor Cell Biology Consortium.**

**Molecular Therapy** 24(4):746-758 Apr (2016)

**Development of Nonviral Vectors Targeting the Brain as a Therapeutic Approach For Parkinson’s Disease and Other Brain Disorders.**

**Molecular Therapy — Methods & Clinical Development** 3, 15055 Feb 17 (2016)

**AAV9-mediated central nervous system–targeted gene delivery via cisterna magna route in mice.**
Lukashuchuk V, Lewis KE, Coldicott I, Grierson AJ, Azzouz M


**Neuronal DNA damage response-associated dysregulation of signalling pathways and cholesterol metabolism at the earliest stages of Alzheimer-type pathology.**

**Biomarkers in Medicine** 10(1):5-8 (2016)

**Paradigm shift: semantic memory decline as a biomarker of preclinical Alzheimer’s disease.**
Venneri A, Mitolo M, De Marco M


**UDCA exerts beneficial effect on mitochondrial dysfunction in LRRK2 carriers and in vivo.**


**C9ORF72 GGGGCC Expanded Repeats Produce Splicing Dysregulation which Correlates with Disease Severity in Amyotrophic Lateral Sclerosis.**
A special “Thank You”

“Thank You”
to everyone who has supported us through their fundraising and donations over the last year!

We are immensely grateful to all our supporters who so generously give their time and money to support our research at SITraN.

A special thank you also to the following groups and organisations

Academy of Medical Sciences
ALS Association
ALS Worldwide
Alzheimer’s Research UK
Alzheimer’s Society UK
Barlow Small Well
Basil Samuel Charitable Trust
Bet365 Foundation
Bridlington Lions Club
British Academy
British Medical Association
Brookfield Aviation Foundation
Castleford Christadelphian Ecclesia
Charles Wolfson Charitable Trust
Chesterfield & Scarsdale Rotary Club
Deafness Support Network (DSN)
DLA Piper UK LLP
Department of Health - DeNDRoN
Dransfield Novelty Company Ltd
European Commission Framework 7
European Commission Horizon 2020
European Research Council (ERC)
EU-JPND Programme
Ex-Parkside RL Players
Flow Foundation
Frick Foundation for ALS research
Gordon Bramah Charitable Settlement
GS & Gl Brown Fund
Hemlington Bowls Club
Hereditary Neuropathy Foundation
Hunslet Hawks Rugby League Club
Hutton Collins Foundation
Inner Wheel Club of Sheffield
John Greenwood Trust
Kings Heath Christadelphian Church
Ladies Eastwood Probus Group
Lions Intl. District Charity Trust
Longley Community College
L6ve Life Charity
Marie Curie Fellowships
Maris Street Motors Ltd.
Medical Research Foundation
Mills & Reeve Charitable
MND Association (MNDA)
National Institute for Health Research
Neurocare
Parkinson’s UK
Retail Computer Solutions Ltd.
Resource New Jersey
Richard Nagy Ltd.
Rotherham United Football Club
Royal Society
ReNeuron
Ryder Briggs Trust
SIF Foundation for MND
Sigma (Leeds) Ltd.
Sound Leisure Ltd.
Skelton Ltd.
Spastic Paraplegia Foundation
Sterling Hydrotech Ltd
Stockbridge Medical Group
The Streaking Meerkats
Stroke Association
Target ALS
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York and District against MND
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