SITraN
Sheffield Institute for Translational Neuroscience

2017-8

Equipment Proposal for Funding
Sheffield Institute for Translational Neuroscience
University of Sheffield

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University of Sheffield | 385A Glossop Road | Sheffield | S10 2HQ |

1.0 The Sheffield Institute for Translational Neuroscience (SITraN):

SITraN brings together under one roof, state-of-the-art laboratories and equipment with a collaborative, multi-disciplinary environment including expertise in basic neuroscience, experimental neuroscience, clinical neurology, neuropathology, computational biology, and clinical trials methodology. This multidisciplinary approach enables our team of basic scientists and clinical academics to work together to drive the translation agenda and to harness basic science to drug discovery and clinical trials based on rational targets of proven preclinical effectiveness. The major driver behind the vision for SITraN is to overcome the burden of motor neuron disease (also known as amyotrophic lateral sclerosis –ALS) on patients and their families.

SITraN research teams have key skills in cellular and molecular biology, animal modelling, human neuropathology, viral vector technology, genetics, pharmacology, gene therapy, RNA processing, glial and mitochondrial biology, computational biology/bioinformatics and electrophysiology, together with neurology and clinical trials methodology. Other key areas under development within the institute are stem cell biology and preclinical screening for new therapeutics in ALS/MND; these areas will complete the configuration of scientific staff and skills needed to focus successfully on our goal of developing therapies for MND.

The work of the SITraN research teams is based around the new genetic understanding of ALS/MND underpinned by the development of robust models of neurodegeneration (including transgenic mouse and zebrafish models), biosamples from human patients including the Sheffield Brain Tissue Bank, DNA, RNA, fibroblast, CSF banks, and a repository of lymphoblastoid cell lines for several of the core diseases. Our key scientific strategy for discovery of promising drug targets is to genetically model disease in parallel with detailed investigation of human biosamples. An iterative approach allows us to assess the likely relevance of new findings in the models by comparing them with the human disease state.

ALS/MND shares multiple commonalities with other common neurodegenerative diseases. To enable optimal scientific cross-talk, and cross fertilisation of research ideas, SITraN hosts smaller teams working on aspects of spinal muscular atrophy (SMA) (led by Professor Mimoun Azzouz), Parkinson's disease (led by Professor Oliver Bandmann), and cognitive decline and dementia in the ageing population (led by Professor Paul Ince and Professor Stephen Wharton).

The dedicated research accommodation encompasses tissue culture suites, facilities for image analysis, live cellular imaging, confocal microscopy, laser capture microdissection, gene expression profiling by RNA microarray techniques, genetics, proteomics, histology, gene therapy, and small molecule drug screening and new generation gene sequencing technology. Within SITraN there is also modern office accommodation for our scientists, trainees and students as well as a library, meeting rooms and a conference suite.

Our scientists make use of adjacent core facilities within the University campus: gene sequencing; FACS, the biorepository, animal house capacity for 40,000 mice (including operating theatres and procedure rooms), crystallography, NMR, mass spectrometry, proteomics, small animal 7T MRI. Several SITraN investigators are also members of the Bateson Centre for Developmental and Biomedical Genetics with access to non-mammalian model organisms (zebrafish and fruit fly (drosophila)) used to model molecular and cellular processes in disease. These systems exploit the ease of genetic manipulation, live imaging of fluorescent reporters, and drug screening opportunities

in fish and flies. Capacity includes 3 zebrafish aquaria, a Drosophila vivarium, confocal and intravital imaging, tissue culture, robotics platforms and siRNA screening.

SITraN provides a stimulating, vibrant education and training environment for both medical and neuroscience students from the UK and overseas. The institute leads four taught MSc programmes and has a strong track record of training PhD and BMedSci students and clinical research fellows. At any one time the institute hosts approximately 60 - 70 research students/trainees.

SITraN is closely affiliated with the Academic Directorate of Neuroscience in the Sheffield Teaching Hospitals NHS Foundation Trust (Academic Director Professor Christopher McDermott), a leading national centre for research and clinical training in neurological disease, with strengths in the fields of neurodegeneration, cerebrovascular disease (stroke), neuro-inflammation, epilepsy and functional neurology. Sheffield neuroscience investigators have a strong track record of recruiting patients into clinical research studies and delivering studies to target and on time. Together investigators in the University and the Hospital Trust play key roles within the NIHR clinical research arena and the Yorkshire and Humber Clinical Research Network.

2. Our Core Objectives:

1. To understand the function of motor neurons in health and disease and to translate basic science findings into health benefits for patients with degenerative motor system disorders.

2. To compare key findings in model systems with disease-related changes in the human nervous system through the use of human biosample collections and data.

3. To provide excellent clinical care for patients with motor system disorders, at all disease stages, incorporating multidisciplinary team working, evidence-based standards of care for symptomatic management, and the evaluation of new neuroprotective therapies.

4. To foster excellent training for clinical and scientific junior staff with the aims of ensuring high standards of future care; the linking of new developments in medical science firmly to the needs of patients with neurological disorders; and supporting the career development of the next generation of clinical and basic neuroscientists.

3.0 Quanterix SIMOA HD1 Analyzer for Biomarker Analysis:

Total Cost: £160,375

Biomarkers commonly are naturally occurring molecules found in body fluids that alter during the pathological process of disease. Levels of biomarkers can correlate with the progression, halting or reversion of the disease process. Biomarkers are an essential component of clinical research and a key readout for drug discovery experiments and the testing of potential therapies in clinical trials. Finding a cure for MND has been significantly hampered because as yet no clinical trials have incorporated biomarkers as part of their analysis. A significant block to finding biomarkers especially in neurodegenerative disorders is the fact that molecules in the cerebrospinal fluid (CSF) - the fluid surrounding the brain and spinal cord and the ideal place to find biomarkers, has very low levels of molecules (about 1000 times lower than those found in blood).

We have spent a lot of time and effort interrogating proposed biomarkers highlighted in the scientific literature using standard laboratory techniques; primarily Enzyme Linked ImmunoSorbent Assay (ELISA) which is compatible with clinical trials. To date we have unfortunately not been able to progress potential biomarker candidates. This is not because they are not viable biomarkers, but because the levels of the molecules present are at the lower limits of our current capability of detection with our present system and therefore we cannot at present validate them. However, the latest technology used in the **SIMOA HD1** machine is unique in that it measures individual molecules, digitally, and so it has a greater dynamic range, as it combines this count with the standard ELISA measurement of integrated fluorescence intensity. This means that it is 1000 more sensitive than our currently used ELISA technique, adding a superior power to our ability to detect MND –related changes in these molecules.

The **SIMOA HD1** system is an integrated platform, containing microfluidics and an array disc reader in a fully automated system. Following work up of possible targets, there is the possibility of multiplexing, running multiple assays in the same sample at once, which will give rise to significant cost savings. The system can run 68 tests per hour with a maximum load of 288, meaning it can run non-stop for nearly 4.5 hours. There are several “off the shelf” kits already available, but we will primarily be taking advantage of its recent advancement in “home development” technology to allow us to develop our SITraN identified targets. This machine will allow us to robustly interrogate our large bank of patient CSF samples to find novel biomarkers to advance the possibility of rapidly assessing the potential effectiveness of new treatment trials for MND in the future.