BRAIN
Repair & Intracranial Neurotherapeutics

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan **Lywodraeth Cymru**
Funded by **Welsh Government**

2019-20 Annual Report


BRAIN
Repair & Intracranial Neurotherapeutics
Neuroscience Research Unit
www.brain.wales
BRAIN
Repair & Intracranial Neurotherapeutics
Developing innovative therapies for neurological and neurodegenerative diseases through collaboration
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BRAIN

Foreword

I am pleased to present our 2019- 2020 annual report, showcasing another busy year for the BRAIN unit. This year marks the completion of our initial 5 year funding and is a time to reflect on our many achievements as well as an opportunity to look forward to our exciting plans with our funding renewal over the next three years. It's also a time for reflection amidst the current COVID-19 pandemic and an opportunity to re-focus our aims and ambitions.

Over the past 5 years, our Neuroscience Research Unit (NRU) under the directorship of Prof Khalid Hamandi has gone from inception to a highly successful Clinical Research Facility which has delivered local, national and International trials including the now landmark trial of anti-sense oligonucleotide (ASO) trial for treating Huntington's Disease (HD) by Professor Rosser's group. Over the last year, the HD team, led by BRAIN Unit deputy director Professor Anne Rosser, have gone on to recruit into the follow-on Generation HD1 trial and negotiations are at an advanced stage for two more interventional trials in HD. Over the past year we have expanded our trials portfolio to include on-going trials of a novel potassium channel inhibitor in epilepsy and novel immunomodulatory therapies in multiple sclerosis and have completed key trials of cannabis oil to treat epilepsy and the RESCUE-ASDH and Dex CSDH studies in traumatic brain injury. Through these studies, we have developed close collaborations with the Research & Development Department and Clinical Neurosciences Division at University Hospital Wales, resulting in the NRU becoming financially self-sustaining and generating commercial profit which we are reinvesting back into the NRU supporting clinical and nursing research staff appointments going forward.

Thanks to the hard work and dedication of our BRAIN Unit members and support staff, for every £1 invested into the BRAIN unit we attract a further £30.92 to Wales. We continue to push the boundaries of clinical and translational neurological research and treatment and in March 2020 were poised to perform the first neural transplantation for patients with Huntington's Disease in Europe over the last 20 years. Unfortunately this was paused due to the outbreak of COVID-19 in the UK, but we are looking forward to restarting the trial as soon as conditions permit. This and follow-on trials delivering Advanced Therapeutic Medicinal Products (ATMPs) will be a major focus of our work over the next three years. We continue to actively involve patients and the public in both the strategic planning and the practical execution of our research in collaboration with the Wales Neurological Alliance (WNA) with whom we have built a valuable relationship. Our industrial collaborations with Takeda® using human tissue to identify new approaches for the drug treatment of schizophrenia have gotten off to a great start and our exciting collaborations with Renishaw® for therapy delivery to human brain continue to progress, emphasising the importance of good industry collaboration to Wales.

Central to our goal of delivering novel cell, drug and other complex therapies to the human brain, we have received international recognition for our efforts, with the appointment of Professor Rosser and myself to lead international working groups on ATMPs and surgical delivery of cell therapies in HD funded by the European Huntington's Disease Network in collaboration with the Stem Cell for HD (SC4HD) global network. Over the last year we have completed NC3Rs funded work on developing novel culture technology for human brain tumours with the goal of developing lab based cultures for drug discovery and personalised therapy and are planning to work collaboratively with the Wales Cancer Research Centre to expand our portfolio of research into this area going forwards. Over the past five years we have built a strong foundation for translational research and clinical trials in brain repair in HD and other neurological diseases and we look forward to making further progress to help our patients and advance knowledge in this important area.

Finally, I would like to thank all of the BRAIN Unit members, staff and administrative team for their commitment to the work of our BRAIN Unit, and hope that you enjoy reading this report.

BRAIN Unit Director, Professor William Gray

Key achievements 2019-20

Financial

Total Grant Income to Wales

Commercial Profit (19/20)
£106,924

Return on Investment to Wales:
For every £1 invested attract in £33

Research

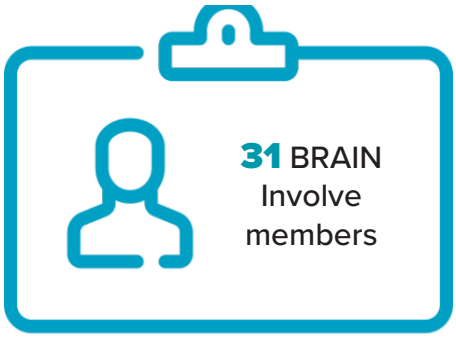
23 Research Submissions

5.9 Average Impact Factor of Publications

Research Awards

80 Peer Reviewed Papers Published

Public Engagement and Involvement



31 BRAIN Involve members

502 Twitter Followers

30 Public Engagement and Involvement Events and Activities

Who we are

The Team

Director
Professor William Gray - Cardiff University Professor of Functional Neurosurgery and Consultant Neurosurgeon at UHW

Deputy Director
Professor Anne Rosser - Professor of Clinical Neurosciences & Consultant Neurologist at UHW

Administration
Dr Cassy Ashman leaving and Jo-Ann Baker coming on board as BRAIN Unit Manager
Victoria Saunders- Finance Officer
Clare Anderson- Administrative Assistant
Camila Araya-Larrain- Communications Officer

Neuroscience Research Unit
Professor Khalid Hamandi- NRU Lead and NIHR Speciality lead.
Belinda Gunning - Research Nurse Manager
Cynthia Butcher, Dympna Mcaleer, Rajimol Sibichen, Alison Johnson and Andy Davison - Research Nurses

Research Associates & Fellows
Dr Erini Messaritaki - Imaging Research Associate
Dr Feras Sharouf - Clinical Research Fellow
Dr Cheney Drew- Senior Clinical Trials Manager
Dr Ying Zhu- Post Doctoral Researcher-Human neural tissue-Takeda Project
Dr Dmitri Sastin- WCAT (Wales Clinical Academic Trainee) and also a GW4CAT (Clinical Academic Trainee funded by the Wellcome Trust)

Research Technicians
Dr Samantha Loveless - Biobank Officer (Cardiff)
Beata Fonferko-Shadrach - Biobank Officer (Swansea)
Dr Chloe Ormonde - Stem Cell Technician
Dr Anne-Marie McGorrian- Research Technician

Introduction

Funded by Welsh Government through Health and Care Research Wales, the Brain Repair and Intracranial Neurotherapeutics (BRAIN) is a Research Unit within the Infrastructure, developing novel therapeutics and treatment delivery systems for neurological conditions.

The Unit operates under the directorship of Professor Gray with 24 principle investigators (PIs) and collaborators, with a total grant income of over £46 million since the Unit's inception in 2015.

Principle Collaborators & Partners

BRAIN is a multi-disciplinary research unit with strong academic and NHS clinical leadership. Based in Cardiff, the Unit's all-Wales brief also involves groups of research excellence in Swansea University and Health Boards across South Wales.

The Wales Neurological Alliance (WNA) is a forum of not-for-profit organisations representing people affected by neurological conditions in Wales. The WNA sit on both the BRAIN and BRAIN Involve executive boards, and continues to support BRAIN Unit activities with its far-reaching membership and input.

Cardiff University
Prifysgol Caerdydd

Swansea University
Prifysgol Abertawe

MRC Medical Research Council

GIG CYMRU NHS WALES

Cynghrair Niwrolegol Cymru
Wales Neurological Alliance

Our Mission

It is our vision to make the BRAIN Unit top-5 worldwide as a pre-eminent centre for international leadership and a Wales and UK national centre for excellence in:

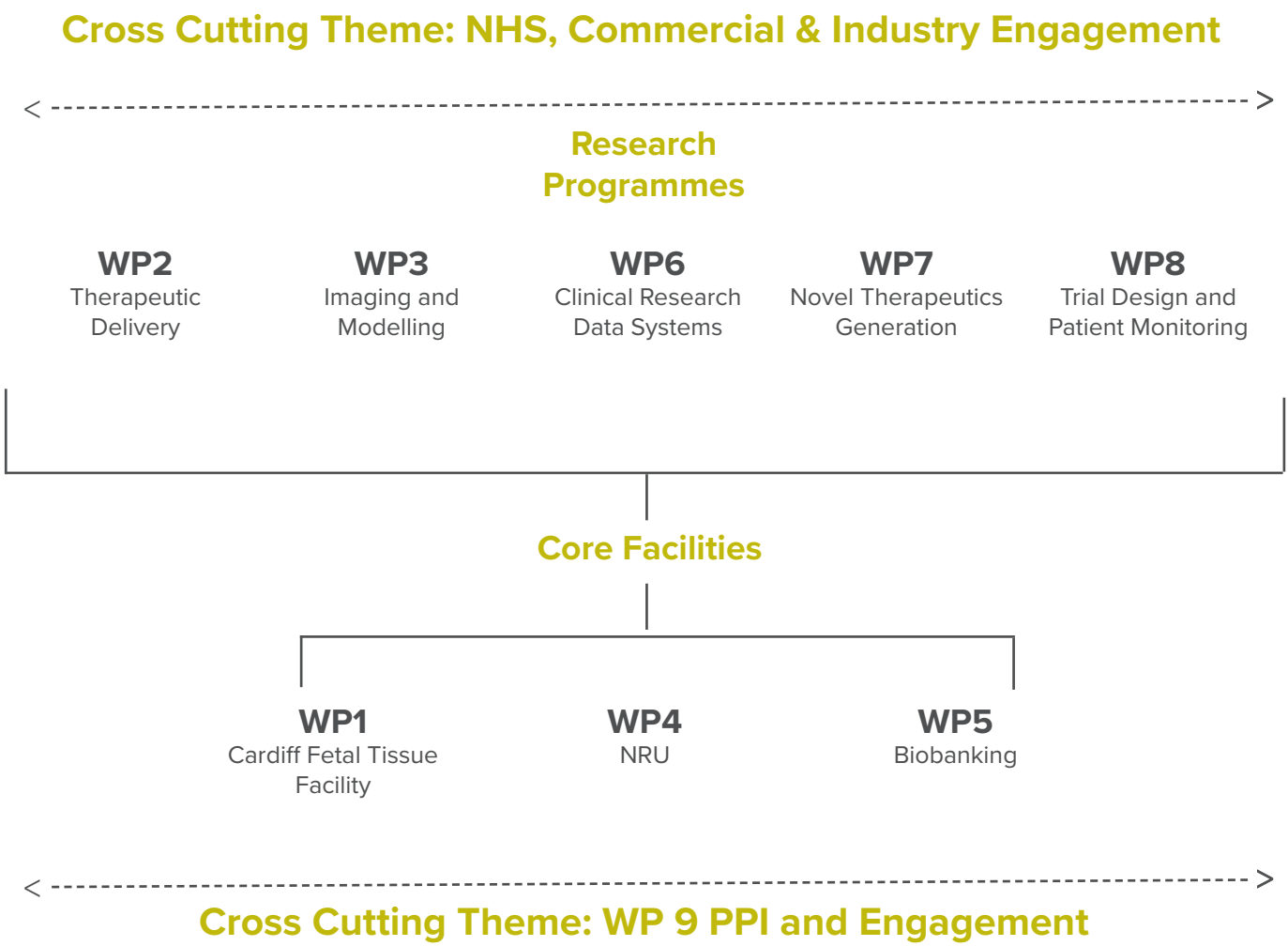
- Delivering novel cell, drug, growth factor and other complex therapies to the human brain.
- Supporting translational research underpinning disease modification and brain repair in people with neurological conditions.

Our Aims

Through innovation and collaboration, the BRAIN Unit aims to:

- Develop new and refine existing systems for delivery of therapeutics into the human brain.
- Develop the appropriate infrastructure for capturing relevant, high quality patient data to measure real clinical and social impact, as well as continuing to support ongoing mechanistic translational research.
- Build a clinical and health economic outcome, social care and service delivery research portfolio.

Work Packages and Cross Cutting Themes



Glossary

- **Intracranial-** Within the skull.
- **Neurotherapeutics**- The treatment of disorders that affect the nervous system.
- **In-vitro**- (Latin for "in the glass") studies performed with micro-organisms, cells, or biological molecules outside their normal biological context.
- **Stem Cell-** Cells of the body (somatic cells) which can divide and become differentiated. When an organism grows, stem cells specialize, and take specific functions. For instance, mature tissues like skin, muscle, blood, bone, liver, nerves, all have different types of cells.
- **Striatum**- The striatum, or corpus striatum (also called the neostriatum and the striate nucleus) is a nucleus (a cluster of neurons) in the subcortical basal ganglia of the forebrain. The striatum is a critical component of the motor (movement) and reward (pleasure) systems.
- **Hippocampus-** The hippocampus (Greek for "seahorse") is a major component of the brain of humans and other vertebrates. Humans and other mammals have two hippocampi, one in each side of the brain. The hippocampus is part of the limbic system, and plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation.
- **Cerebrospinal fluid (CSF)-** is a clear, colourless body fluid found in the brain and spinal cord.
- **Peripheral blood mononuclear cell (PBMC)-** is any peripheral blood cell having a round nucleus. These cells consist of lymphocytes (T cells, B cells, NK cells) and monocytes.
- **Neurogenesis-** is the process by which nervous system cells, the neurons, are produced by neural stem cells (NSC).
- **AMPAKine molecules**- A subgroup of AMPA receptor modulators currently being investigated as potential treatments for a range of conditions involving neurological and psychiatric disorders.

Cardiff Fetal Tissue Facility

Work package aim: Provide a Human Tissue Authority (HTA) licensed facility to prepare and deliver cell therapies for human use in clinical trials for neurodegenerative diseases.

Processing

The first surgery was scheduled for March 17th, 2020. Suitable maternal donors were consented, tested and tissue was procured and was due to be processed. However, on March 13th 2020, shortly before the scheduled surgery date, all non-emergency surgery at the University of Wales was cancelled due to Covid-19.

Since this time, fetal tissue activities related to human use have been paused, but we plan to restart activities as soon as we are permitted to do so. We have 4 fully trained staff who will undertake all relevant activities for both the facility and the tissue processing. We have continued to train in the lead up to the first surgery (hopefully to take place in the autumn following the receipt of HTA approval) by using replica tissue. This involves following Standard Operating Procedures (SOPs), completing documentation, undertaking the multi-stage tissue processing steps in the cleanroom, and transporting the tissue under exact 'live' conditions to the surgical site, as well as performing quality checks at each stage. This allows us to collect ongoing validation data and ensures all the staff can seamlessly transition to tissue processing for actual surgery.

Processing of tissue requires ongoing validation, and this will continue with every surgery as quality checks are performed by taking microbiological samples of tissue washes before and after processing using blood culture bottles, which when cultured, detect the growth of organisms.

HTA License

The Human Tissue Authority (HTA) completed their review of the Process Preparation Dossier (PPD) submitted by the Cardiff Fetal Tissue Bank (CFTB) between July - October 2019. This comprehensive document details the critical tissue processes (procurement of tissue, transport, storage, processing and distribution to the surgical team); safety and quality control measures; reagents and materials used at every stage of processing and final proof of validation of all the above. The HTA provided approval for our cell production processes on October 29th, 2019, which allowed us to collect and process tissue in preparation for the first planned surgery on 17th March 2020.

The HTA license is renewed annually in April, but the April 2020 renewal has been delayed by the HTA who have imposed a 5-month delay to all renewals due to Covid-19.

Facility

The facility grading is maintained through multiple streams:

- It is inspected and validated by Clean Air Technology every 3 months, where room pressure cascades, air change rates, High Efficiency Particulate Air (HEPA) filter integrity and particle counts are checked. The Cardiff Fetal Tissue Bank (CFTB) suite continues to perform as required for GMP standards.
- Monthly cleans with specific biocide cleaning agents are undertaken, followed by microbiological monitoring using agar settle plates, contact plates, and air sampling. All samples are incubated at the appropriate temperature, and any plates with colony growth are sent to Public Health Wales for analysis.
- Room pressures in the suite as well as temperatures of critical equipment such as fridges, incubators and storage areas are continually monitored by Contronics which provides 24-hour monitoring and alarm raising deviations.

Any equipment used throughout the entire process which is deemed as critical to the safety and quality of the final product is calibrated and serviced by certified providers.

Work package aim: Refine existing systems for effective delivery of cell therapy and other therapies into the human brain.

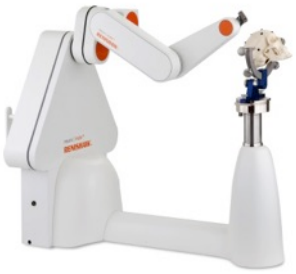
Therapeutic Delivery into Patients

Highlights

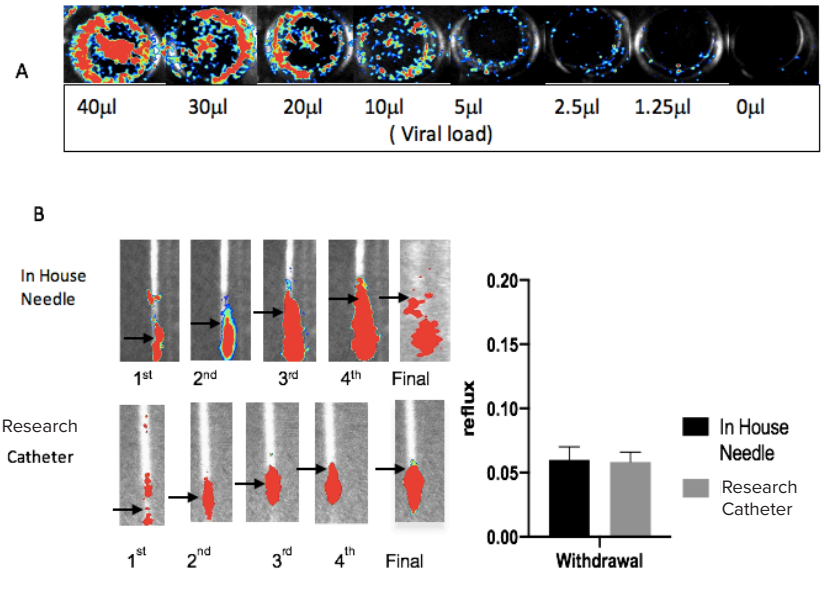
- Dr Sharouf has developed a novel in-vitro system for evaluating the ability of neurosurgical devices to deliver live cells into human brain, for the first time allowing the simultaneous monitoring of both the viability of the delivered cells as well as the pattern of their delivery. This is an important advance as the reflux of cells back along the outside of the needle delivery device reduces the quantity of cells delivered to target and also results in dispersion of cells back along the delivery needle track resulting in cells being deposited in areas where they should not, potentially compromising efficient and safe cell delivery.
- Testing of the device we have developed for the TRIDENT trial showed it to be effective for delivering viable cells without significant reflux along the needle track.
- Applications for further development of this in-vitro model have been submitted.
- Prof Rosser appointed to lead an international Working Group on Advanced Therapeutic Medicinal Products and Prof Gray to lead an international Surgical Taskforce of cell delivery to human brain.
- Further agreements have been signed with industrial collaborators Arrotek and other academic collaborators to develop further optimised devices for cell delivery to the human brain, including the TRIDENT study and other studies going forward.
- Stem Cells for HD International group constituted with active leadership and involvement by members of the BRAIN Unit (Profs Rosser, Gray, Busse).

TRIDENT Trial

- We have recruited **4 additional participants** into TRIDENT observational cohort this financial year, taking the total to **19 overall**
- 5 participants have been screened for inclusion in the surgical cohort.
- Ethics amendments submitted to support parallel acquisition of biological samples to study graft rejection in HD patients after transplantation in collaboration with Prof Cozzi, University of Padua.
- Initial surgical transplantation scheduled for March 17th - postponed due to cessation of all non-emergency neurosurgery on 13th March due to the COVID-19 pandemic.



Stereotactic Robot for guiding cell transplantation into human brain



A. Human cells emitting light (bioluminescence model) introduced with the help a virus (lentiviral transduction). 40ml of viral products produced maximum bioluminescence in 100,000 Whole Ganglionic Eminence cells (WGE) cells.

B. Cells emitting light as they are delivered into brain phantom through a needle showing reflux of cells. Comparing in house-manufactured needles with research catheter. 4 deposits of 5ml of transduced Human Embryonic Kidney (HEK) cells were delivered into 0.6% agarose phantom. The arrow indicate the point of distal tip of the inner needle/catheter, cells proximal to this point are considered to be due to reflux. Reflux in the needle is comparable to that of the research catheter (no significant difference).

MRI and Tissue Modelling of Cell and Drug Delivery

Work Package aim: To utilize high resolution and microstructural Magnetic Resonance Imaging (MRI) scanner and Positron Emission Tomography (PET) scans to support accurate modelling of cell and drug delivery to the brain.

Highlights

- Dr Eirini Messaritaki, our BRAIN Unit imaging researcher, was awarded a prestigious Wellcome Trust Research Fellowship.
- As part of gaining greater understanding of structural and functional brain networks and how they are affected by disease as well as treatments and interventions such as cell delivery and repair, Eirini has worked on how brain network nodes cluster and communicate to form functional communities and this work has been submitted for publication. You can find it here: https://bit.ly/Eirinipaper.

Achievements

- We have been continuing to assess the effect of therapeutic interventions on brain structure and function including how to correctly measure white matter tracts in the brain.
- Dr Sastin has been working on delineating cortico-cortical white matter tracts developing novel methods with lower registration errors and greater spatial accuracy. He has had three abstracts accepted for two international conferences (ISMRM 2020, OHBM 2020)
- Collaborations have begun with colleagues in Cambridge modelling cell and drug delivery from delivery devices at the device/brain interface, building on our previously published work modelling the distribution of therapies into the surrounding brain (10.3389/fneur.2018.01092) which has had 1939 views and 266 downloads since 2018.
- We continue to work towards identifying the optimal metrics that will allow us to assess the effect of brain surgery on epilepsy patients that undergo hippocampus resection, who are scanned on the high-resolution Connectom scanner before and after the resection.

Work Package aim: To establish a fully functional clinical research facility at the University Hospital Wales, Cardiff. To support commercial and academic clinical trials.

Neuroscience Research Unit (NRU)

The NRU supports patient facing clinical research studies and trials in neurological disorders.

The unit is now firmly embedded in the Cardiff and Vale University Health Board (CVUHB) neurosciences directorate infrastructure, with quarterly management and finance meetings and line management of staff through the UHB clinical board.

The unit now has 2 clinical research fellows, one band 7 nurse manager and 5 band 6 nurses, funded through a combination of Activity Based Funding and commercial trials income to CVUHB and Cardiff University.

The NRU currently hosts 18 clinical trials focussing on epilepsy, Huntington's disease (HD) and multiple sclerosis, and supports research studies and recruitment across the neurosciences directorate. Clinical trials include phase II and phase III trials, in Huntington's disease the novel antisense oligonucleotide therapy, in epilepsy a novel potassium channel inhibitor, and in multiple sclerosis novel immunomodulatory therapies.

Completed trials include the phase 1, IONIS (now Roche) trial of intrathecal RNA transcriptase inhibitor in HD, the phase 3 trial of cannabis oil (Epidiolex (GW Pharma)) to treat epilepsy in Tuberose Sclerosis Complex, and in neurosurgery, the rescue ASDH and Dex CSDH studies (now closing out).

61 patients recruited to studies and there have been 200 patient visits from August 19 until COVID-19 'lockdown' - visits vary from half hour to 6hrs in duration according to trial protocols.

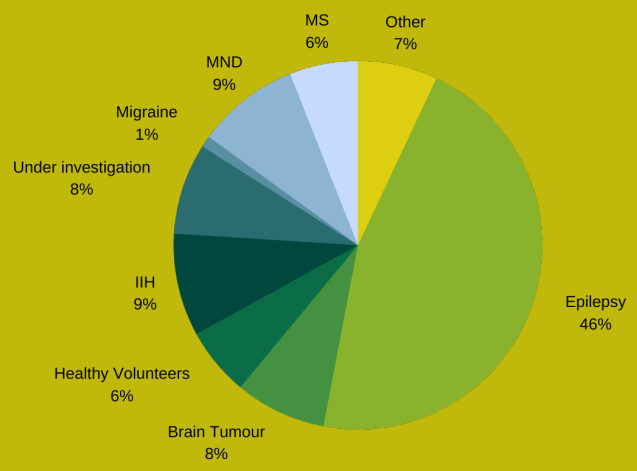
No new participants are currently being recruited to patient facing studies (March 2020 – ongoing as of May 2020), though necessary study visits (by telephone where possible) continue for existing research participants.

Increase in commercial trial activity has brought a substantial increase in income profit, increasing from £60,433 in 18/19 to £106,924 income profit in 19/20. These monies are 100% reinvested into the NRU and its non-commercial projects.

Biobanking

Work Package aim: Expansion of sample collection across neurological and neurodegenerative conditions in the Welsh Neurosciences Research Tissue Bank (WNRTB) Cardiff and Swansea Neurology Bank (SNB).

Cardiff Neuroscience Research Tissue Bank data from August 2019.

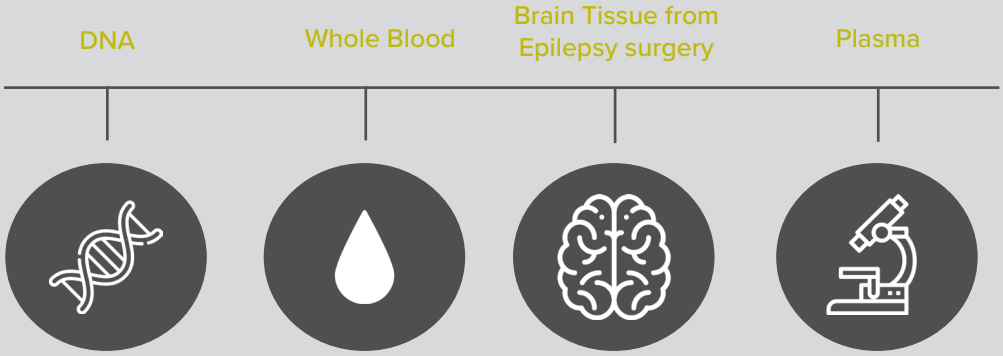


4,849 samples issued for research from WNRTB

750 Total consents collected from WNRTB end March 2020

Examples of sample types collected

106,395 Total number of samples acquired from WNRTB at end April 2020. These included whole blood, serum, plasma, DNA, brain tumour tissue, cerebrospinal fluid, cerebrospinal fluid cells and Peripheral Blood Mononuclear Cells (PBMCs).



Cardiff Neuroscience Tissue Bank Highlights

- Ethics extension approved March 2019 until March 2024.

- The BRAIN unit was successfully awarded a further 3 years funding 2020-2023 from HCRW, securing funding towards neurology biobanking consumables and part time salary for the biobank co-ordinator.

- The WNRTB and research lab were successfully awarded funds from C&V UHB R&D to purchase:

1. A brain slice keeper – enabling safe transport of fresh brain tissue slices between sites for analysis i.e. from the bank to the research teams.

2. A Sceptor Automated Cell counter – allowing more efficient and accurate cell counting.

- A new part time technician appointed using external funds has provided some extra support to sample collection, processing, storage and retrieval, specifically for Multiple sclerosis research and trial sample collections.

- New collections of brain tissue from patients undergoing neurosurgery are allowing expansion of the biobank with regards to both sample type (brain tissue) and diagnoses (glioblastoma, tumour and epilepsy). Tissue is used both acutely for cell culture and stored at -80 degrees for future research use.

- By mid-March 2020 the bank has received; 53 requisitions from 34 research collaborations (locally, nationally, internationally)

Swansea Neuroscience Tissue Bank

The Swansea Neurology Biobank (SNB) collects samples from patients to understand the genetic and biochemical basis of a range of devastating neurological diseases, including epilepsy, Parkinson's and multiple sclerosis. Dr Owen Pickrell has been elected as the new principle investigator for the SNB.

The SNB collected **416 individual patient samples**, including from those with a diagnosis of epilepsy, multiple sclerosis and Parkinson's disease.

The SNB hosted a very successful patient information day on Tuesday Nov 19th. Over 40 donors and health care workers came to hear about the bank and to contribute to the sessions. The Biobank also hosted a stall at the 4th Swansea Science Festival in October 2019, where we met with kids and grown-ups to about the work we do.

The Biobank patient group was launched with 10 members and will meet bi-annually to discuss our activities and future. As an example of the close working relationships being fostered between the public and researchers at SNB a biobank donor and member of the Advisory group undertook a research placement with the SNB team. SNB and the MS Lab at Swansea University hosted two patient information and fund raiser days for the UK MS Society.

Mark Baker, who has been so instrumental to the recent activities and successes of the SNB, has moved on to pastures new.

Clinical Research Data Systems

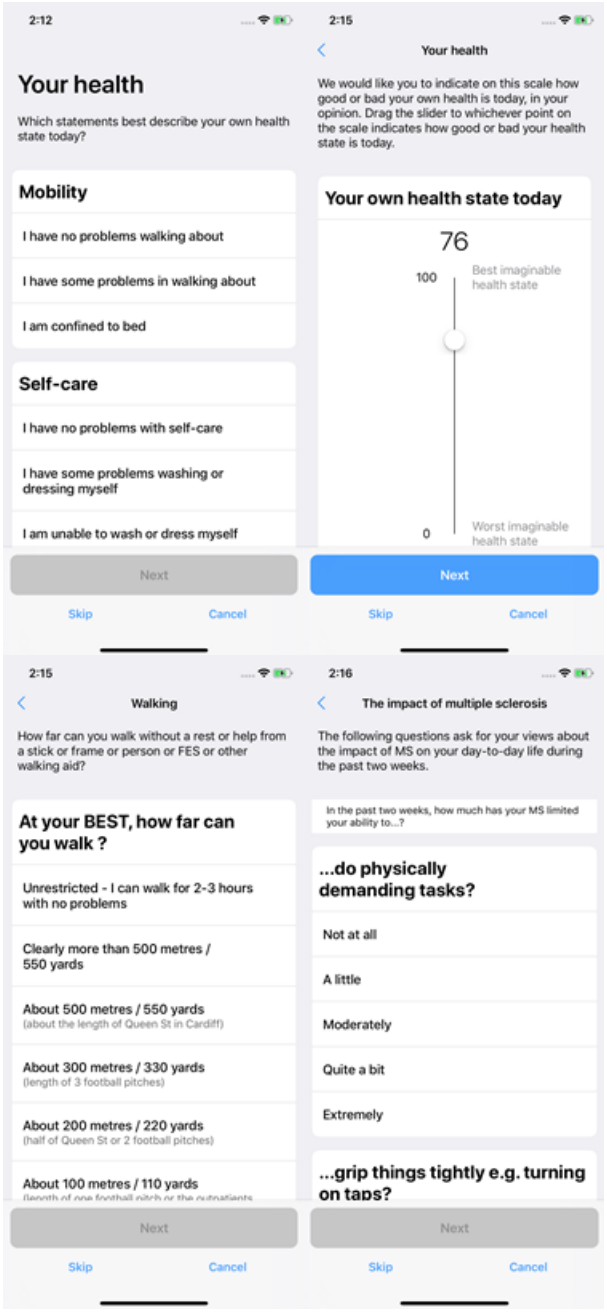
Work Package aim: Develop and implement a clinical research database system that supports clinical care and is integrated within BRAIN Biobanks and the NRU. Providing real time data capture that will also benefit NHS service delivery.

Highlights

The continued roll-out of the PatientCare clinical research application has gone well, with 34587 registered patients from across Wales, with 36% Cardiff and Vale University Health Board, 15.9% Aneurin Bevan University Health Board, 11.3% Swansea Bay Health Board, 7.5% Cwm Taf University Health Board and the remaining distributed across Hywel Dda, Betsi Cadwaladr and Powys University Health Boards.

There are 111 defined patient cohorts, with 78 NHS cohorts and 32 research cohorts and 577 health professionals registered to use the system including 81 specialist nurses, 78 administrators, 75 consultants, 63 physiotherapists, 52 doctors-in-training, 34 speech and language therapists, 30 occupational therapists, 25 dieticians and 10 psychologists, with the remaining comprising research associates, administrators and students.

There have been 436,145 clinical encounters recorded using the software with usage increasing during the COVID-19 crisis to record patient clinical and research contacts. Of these, there have been 175,144 telephone calls, 116,977 outpatient clinic assessments, 91,854 virtual encounters, 17,504 home visits, 11,234 inpatient encounters, 7639 multi-disciplinary team assessments and 5891 therapy group encounters. There are 4843 electronic consent forms recorded. On average, 6000 clinical or research encounters are recorded each month.



iPad/iPhone mobile application measuring disease-specific outcomes

This highlights the widespread integrated and cross-disciplinary use of the clinical research database system in the care of patients and its value in supporting ongoing research across the complete spectrum of clinical care to generate real-world multidisciplinary data for meaningful research and improving patient care.

Work Package aim: To support the generation of pre-clinical grade cell therapies, drug development and evaluation of biologically active molecules for potential therapeutic use.

Novel Therapeutic and Devices Generation

Highlights

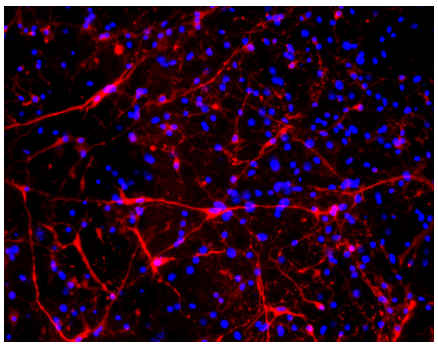
The joint drug discovery project with Takeda and the NMHRI to explore new approaches for treating schizophrenia and other psychiatric disorders, has progressed very well.

Dr Ying Zhu was appointed as the post-doctoral researcher for this work package within the TAKEDA collaboration.

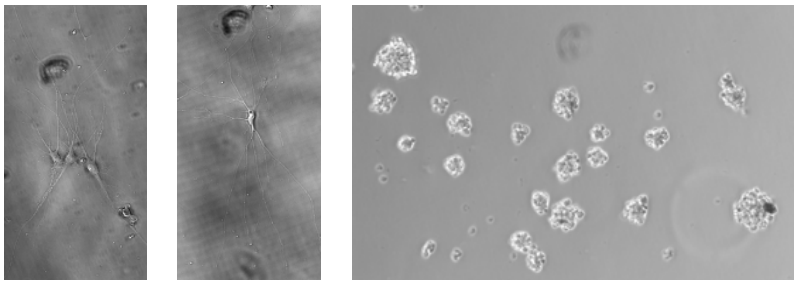
Over the past year we have been actively evaluating pathway discovery using excess primary human brain tissue removed at neurosurgery operations, in collaboration with our Biobank and neurosurgical colleagues at University Hospital Wales via the BRAIN Unit infrastructure.

Collaborative work with Prof John Atack the Medicines Discovery Institute has been completed and yielded important results on the effects of novel compounds on neurogenesis within the hippocampus and this is being taken forwards.

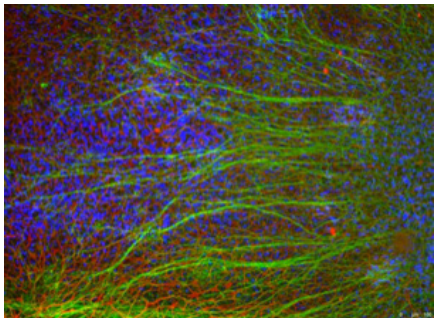
A collaboration with Prof Matthias Eberl Division of Infection and Immunity at Cardiff University has revealed biomarkers in cerebrospinal fluid that allow differentiation of infection from sterile inflammation. This is a potentially important advance allowing point of care diagnosis of infection in patients undergoing neurosurgical procedures and operations where the diagnosis of infection and its differentiation from the neuroinflammation accompanying neurological disease, is notoriously difficult.



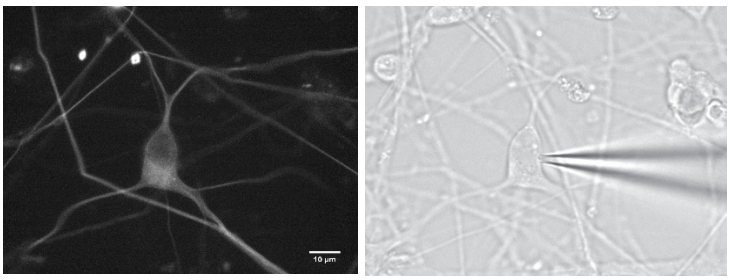
Tuj1+ neurons cultured from primary human cortex.



Live image of Astrocytes (left), neurons (middle) and neurospheres (right), containing neuron stem cells cultured from primary human cortex.



Human nerve cells (green) growing on a layer of glia (red).



Recording from human brain cells in culture.

Trial Design, Evaluation and Patient Monitoring

Work Package aim: To develop more accurate and reliable testing of mobility and cognitive dysfunction across trials, through developing novel clinic based and remote monitoring.

- Over the past year we have continued our focusing on improving complex small-cohort clinical trial capabilities and efficiencies. A major focus of activities over the last year alongside being part of a cutting-edge network delivering Antisenseoligotide Therapies in HD (Roche) in our now established Clinical Research Facility has been on the delivering of the RfPPB funded TRIDENT trial.

- Trident provides a unique example of the multiple methodological and operational challenges faced in trials of a highly specialised, emergent area of direct brain delivery. Our design involves the use of a trial within cohort that has been developed to address many of the constraints inherent in such early phase activities. Over the past year we have progressed to achieving all the regulatory approvals for opening all phases of the TRIDENT trial. The first surgery was scheduled for 17th March 2020. We also completed 5 of the 12-month assessments with those recruited to the observational cohort. Unfortunately, this was not able to be completed due to COVID-19 however all aspects are in place for the team to complete the surgery as soon as possible.

- Our team was selected to present our TRIDENT research at the UK clinical trials network showcase at International Clinical Trials Methodology Conference in October. The team were also instrumental in leading a clinical trial design workshop at the inaugural meeting of the European Huntington's Disease Network (EHDN) advanced therapies working group which met in Barcelona in September. This is a working group that brings together a diverse group of contributors, including neurologists, neurosurgeons, healthcare workers and providers, scientists, and other interested parties from academia and industry to address the complex, wide-ranging and multi-component challenges in delivery of substances and cells to the brain for therapeutic purposes.

- Monica Busse, Anne Rosser and William Gray are also on the executive committee of SC4HD which is a global initiative whose mission is to define and publish guidelines for preclinical testing and clinical development of cell therapies to be transplanted in the brain for treatment of Huntington's Disease (HD). They also were invited to present a focussed symposium at the IDEAL collaboration annual conference (now postponed to 2021). This symposium has emerged from our ongoing collaboration with IDEAL and the EHDN advanced therapies working group with the global stem cells for HD consortium and will focus on the complexities associated with advanced therapies using the TRIDENT trial as an exemplar.

- From a patient monitoring perspective, we have continued to expand our dataset of C3t scores and accompanying sensor data through collaboration with multiple different national and international sites using modern data collection technology built and maintained in-house in the Centre for Trials Research, Cardiff University. Analysis of the dataset to date has suggested C3t sensor data may be highly correlated with clinical scoring of the C3t and potentially predictive of multiple other clinical outcome measures, including the Unified huntington's Disease Rating Scale (UHDRS) Total Motor Score and the UHDRS Ocular Motor scores. This is important from a research perspective given the known subjectivity inherent in the clinical assessment of Huntington's disease phenotype.

- We are nearing the completion of follow-up in the PACE-HD study which is being conducted across six sites globally. Here we are exploring the feasibility and utility of both data from in-home monitoring and how data routinely collected via Enroll-HD (global platform observational study of people with HD) can be used to supplement trial assessment data to improve trial efficiencies. We are also making significant progress in our DOMINO-HD consortium (funded through JPND) which is aiming to demonstrate feasibility of a digital sensing platform capable of providing meaningful and user acceptable objective monitoring of physical activity, sleep and nutrition in HD.

Key Investigators: Dr Emma Lane and Mr Peter Roberts.

Public Engagement and Involvement

BRAIN Involve

BRAIN Involve is the Public and Patient Involvement group that helps to inform and shape research activities within the Brain Unit. It is made up of people who are, or have been affected by neurological diseases such as (but not limited to) epilepsy, Huntington's disease, multiple sclerosis or Parkinson's disease.

Our BRAIN Involve members have supported several studies, across the whole breadth of our remit, from how to better support public engagement in multiple sclerosis and the wider neurology area, to digital tools in Parkinson's disease. We are very grateful to all our BRAIN Involve members for their contributions.

We continue to grow our BRAIN Involve community which will enable us to continue this vital support research activities within BRAIN and the wider neuroscience community. Influenced by our community day consultation last year, we are excited to be launching a new BRAIN Unit website which will support both our academic work and public engagement and involvement activities creating a broader reach and opening up our community to a wider group of people.

This is in its final stage before we look to launch later this year after consultation with our BRAIN Involve members and will be one of the tools we use to implement the National Standards for Public Engagement more effectively. We are engaging with other Pubic Involvement communities within Cardiff University to work towards improved understanding of public involvement at all levels of research and to ensure that best practise is shared our community valued for the guiding hand it can provide to achieve the highest standards of research for the community around us.

Public Engagement

Key investigators: Dr Emma Lane and Mr Peter Roberts

Public engagement activities continue to be a major focus for the BRAIN Unit and we have had several successful events largely through collaborations with CUBRIC, Cardiff University, NCMH, and the NMHRI, with fantastic support from the BRAIN Unit Communications Officer Camilla Araya Larrain. Our events are predominantly aimed at informing and supporting both the medical and social care community and patient communities locally and further afield. We have developed new activities to support our growing portfolio of hands-on tools to engage all ages including our VR Headsets simulating what it is like to have an MRI at CUBRIC and showcasing our collaboration with the imaging centre.

Our engagement with local patients, carers and family members included a Huntington's Disease Engagement Event at the Haydn Ellis Building, Cardiff University which was attended by 70 patients, family members and carers. The event started with a welcome from Prof Anne Rosser updating on the latest in Huntington's Disease research. This was followed by an exciting Speed Science session, with delegates moving around stands to talk to researchers. We are also weaving public involvement into our information events, with a DOMINO-HD focus group held to discuss attitudes and opinions on using wearable technology.

Meet the Researcher: Mr Dmitri Sastin

Mr Dmitri Sastin is a trainee neurosurgeon and scientist in Cardiff funded by the Wellcome Trust under their UK wide Clinical Academic Training scheme. He is supported by the BRAIN Unit working with University Hospital Wales in conducting his research into novel imaging techniques at Cardiff University's Brain Research Imaging Centre (CUBRIC) to identify abnormal brain white matter networks in patients with drug resistant epilepsy - helping to guide surgical interventions to stop seizure activity and better understand altered brain function in epilepsy.

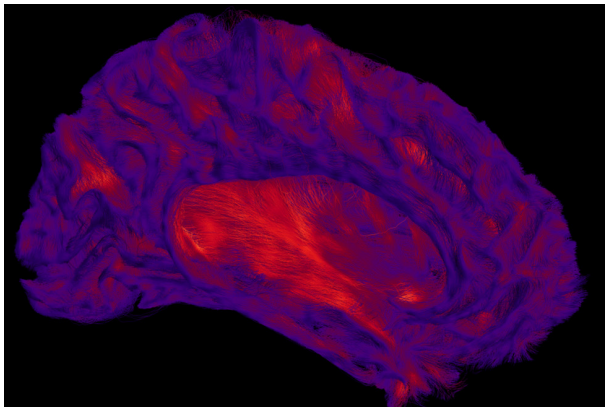
Mr Dmitri Sastin's research aims to explore the changes in brain activity and architecture that are key drivers of seizures in patients with epilepsy. Dmitri hopes that his work will assist clinicians with formulating better treatment plans and predicting outcomes, ultimately making epilepsy surgery safer, more effective, and more widely available.

Having spent a few years during medical school investigating the effects of seizures on abnormal neuronal pathways in a mouse model of epilepsy, Dmitri then shifted focus to clinical studies. Interacting with patients from neurological and neurosurgical backgrounds he discovered that there was a significant willingness in this group to engage with researchers.

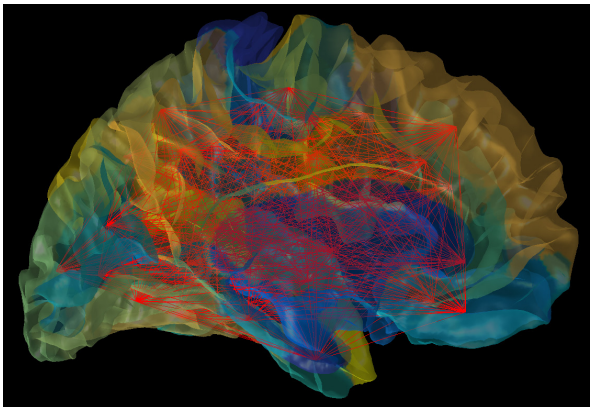
Following on from this discovery, Dmitri began inviting patients with certain types of epilepsy to undergo brain scanning and record brain activity using cutting-edge equipment. He combines mathematics, physics, and computer science in his analysis of the data to extract markers unique to each patient to help better understand the mechanisms behind seizure development.

Being actively involved in the delivery of the epilepsy surgery programme in Cardiff has allowed Dmitri to take a pragmatic approach to scientific work, allowing him to identify research targets based on the clinical need while also viewing his methods in the context of what is practically feasible and always having clinical application in mind as the end product of his research.

Amongst the most promising venues for advancing epilepsy surgery are identification of novel therapeutic targets, development of minimally invasive surgical techniques and implantable "closed loop" systems as well as outcome prediction tools for clinical decision making. Dmitri strongly believes that using patient-specific data from a variety of sources and having a strong multidisciplinary approach is integral for the success of this work.



Connecting white matter tracts within the brain



Network analysis of the short white matter fibre connections

Outcomes & Impact

Objective: To develop new and refine existing systems for therapeutics delivery into the human brain.

1

We have made substantial progress in understanding the requirements of devices optimised for delivering cells to human brain.

2

We are on the cusp of performing a world-leading neural cell transplantation trial in Huntington's Disease patients.

3

We have set up an International Task Surgical Force to identify the key challenges in cell delivery and take these issues forwards.

Objective: To build appropriate infrastructure including a dedicated NRU.

1

We have succeeded in building an excellent Clinical research facility delivering world-leading clinical trials in therapy delivery to brain as well as leadings trials in epileptic drug development and MS immunotherapy clinical trials

2

We have succeeded in making our NRU financially self-sustaining, based on collaborations between R&D, the NHS Neurosciences Directorate and our BRAIN Unit, generating a model for R&D development at University Hospital Wales.

3

We have grown and further developed our Biobank facility into a nationally leading Biobank in Neurosciences in the UK.

Objective: To continue supporting patient data and tissue bio-banking.

1

We have increased sample access supporting more national and international research projects.

2

We have further diversified our biobank biologicals to include human tissue, supporting national and international collaborative research.

Objective: To embed into all relevant work-packages cross-cutting excellence in the relation to public involvement and engagement and commercial and industry engagement and collaboration.

1

More members continue to be involved and engaged with our research.

2

Building on and growing established relationships with industrial partners Takeda, Arrotek, Renishaw and Roche.

Conclusion

Since establishment of the BRAIN Unit in 2015 we have made substantial progress in establishing Cardiff and Wales as a major UK centre for research into brain repair and translation into clinical practice. This last year has seen many of our work packages come to fruition, with the most important being the successes in establishing the Neurosciences Research Unit, our dedicated clinical research facility at University Hospital Wales, its delivery of the international ASO trials in Huntington's Disease and the establishment and full recruitments to the TRIDENT trial, poised to deliver the first neural transplants to patients with Huntington's Disease in nearly 20 years in Europe.

Our bio-banking expertise and translational use of human biologicals including tissue is UK leading and is a resource which we are keen to promote going forward both nationally and internationally. We have long recognised the importance of forming genuine collaborative links with partners in academia, the NHS and industry. It is a testament to the hard work and dedication of all members of the BRAIN Unit that we have achieved what we have over a short number of years from a standing start in 2015.

Public Involvement and Engagement

BRAIN has been very innovative in engaging and informing the public about our research, which led us to win a top prize at the Health and Care Research Wales Conference for three consecutive years. We have attended and ran over 30 events and activities over the past year. The complexity and ethical challenges in some of our research has made that achievement even more challenging as well as rewarding and we have had amazingly useful input from our BRAIN Involve members in both delivering these achievements and in guiding us though their dissemination. A key tool for dissemination will be the new website we are launching this year which will function as one of the tools we will use to implement the National Standards for Public Engagement more effectively.

The Future

With our funding renewal to 2023, we intend to build on our infrastructural successes focussing on all aspects of therapy delivery to the human brain for a wide variety of neurological diseases. There will be much commonality across different diseases with respect to the technical, regulatory and clinical trial methodologies to support the clinical evidence base for brain repair and other regenerative strategies.

The expertise we are building in Cardiff and Swansea is unique and we will continue to collaborate with leading groups in Wales such as the Dementia Research Institute, the Neuroscience and Mental Health URI and the world class imaging capacity in CUBRIC, as well as across the UK and internationally. We are also embarking on a collaboration with the Wales Cancer Research Centre to apply our tissue and imaging expertise to translational research in brain tumours as part of our wider collaborative strategy for translational research. We will as ever continue to develop our Public Involvement and Public Engagement activities working towards more effectively meeting the National Standards for Public Involvement, aligning them seamlessly with the needs of BRAIN.

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