BRAIN

Repair & Intracranial Neurotherapeutics

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

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

2020 - 2021
Annual report

Contents

Foreword

I am pleased to present our 2020-21 annual report, reflecting on what has been a challenging first year to our new Welsh Government funding through Health and Care Research Wales.

Whilst none of us could have predicted the events of the past year, with challenges come opportunities and we have strived to take advantage of them where we can.

The onset of the COVID-19 pandemic resulted in the cancellation of all elective surgeries in Wales and indeed across the UK as a whole. The reinstatement of elective clinical services has been a heroic effort but with a much-reduced capacity, which has had a knock-on effect on clinical research in neuroscience, against the prioritised COVID-centric approach to the pandemic itself.

We welcomed Jo Baker, our new BRAIN Unit Manager, who took up her post in August 2020. She has been a huge asset in effortlessly taking up the reins from Cassy Ashman and effectively progressing our aims and objectives, throughout the pandemic and beyond.

Delivering Advanced Therapeutic Medicinal Products (ATMPs) continues to be a major focus of our work and we have successfully attracted a number of commercial partners to Cardiff to bring these innovative therapy trials to patients in Wales.

Our industry collaborations with Takeda continue to progress and our collaborations with the UK Dementia Research Institute are beginning to examine the promise of new and exciting approaches to many neurodegenerative conditions.

We continue to push the boundaries of clinical and translational neurological research and treatment and highlight a few of our achievements here.

Thanks to the hard work and dedication of our BRAIN Unit members and support staff, for every £1 invested into the BRAIN Unit, we have attracted a further £23 to Wales.

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.

Professor William Gray
BRAIN Unit Director

- Please note, stock images and event photos used were taken prior to the COVID-19 pandemic.

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
Jo Baker - BRAIN Unit Manager
Victoria Saunders - Finance Officer
Clare Anderson - Administrative Assistant
Catrin Hopkins and Becs Parker - Communications Team

Neuroscience Research Unit
Professor Khalid Hamandi - NRU Lead and NIHR Speciality lead
Belinda Gunning - Research Nurse Manager
Dr. Abuzeer Hanif- NRU Clinical Fellow
Dr. Zin Min Htet- NRU Clinical Fellow
Cynthia Butcher, Alison Johnson, Rajimol Sibichen, Megan Voisey, Dympna McAleer, and Ffion Davies- Research Nurses

Research Associates & Fellows
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 and Laboratory Manager (Cardiff)
Dr. Chloe Ormonde - Stem Cell Technician
Dr. Anne-Marie McGorrian - Research Technician
Russell Khan – SAIL Analyst (Swansea)

Introduction

Funded by Welsh Government via the Health and Care Research Wales infrastructure, the Brain Repair and Intracranial Neurotherapeutics (BRAIN) is a research unit developing novel therapeutics and treatment delivery systems for neurological conditions.

BRAIN operates under the directorship of Professor William Gray with 24 principle investigators and collaborators, with a total grant income of over £44 million since its inception in 2015.

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.

Our Mission

It is our vision that the Brain Repair and Intracranial Neurotherapeutics (BRAIN) unit will be a Welsh and UK national centre of excellence, and on a path towards international leadership for:

- Delivering novel cell/gene/small molecules and other pioneering complex therapies to the human brain.
- Supporting translational research underpinning disease modification and brain repair in patients with neurological conditions.

Our Aims

- To develop new and refine existing systems for therapeutics delivery into the human brain.
- Develop appropriate infrastructure for:
  - Advance adult and fetal brain tissue resources, supporting translational research and therapy validation across neurological diseases.
  - Bio-banking and bio-resource management using linked and deeply phenotyped clinical data,
- Consolidate and extend appropriate clinical trials and expertise, including refinement of appropriate methodologies for evaluating novel complex interventions.
- Embed into all BRAIN work, cross-cutting excellence in the relation to:
  - Public and Patient Involvement & Engagement
  - Industry and NHS Engagement and Collaboration.

Work Packages and Cross Cutting Themes

Cross Cutting Theme: NHS, Commercial & Industry Engagement

Research Programmes

WP1
Intracranial Delivery

WP2
Providing human adult neural tissue to model disease + validate novel therapies

WP3
Welsh Neuroscience Research Tissue Bank **(WNRTB)** + Swansea Neurology Biobank **(SNB)**

WP4
Neurosciences Research Unit **(NRU)**

WP5
Patient and Public Involvement + Engagement

Cross Cutting Theme: WP5 PPI and Engagement

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) that 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.
- **Advanced therapy medicinal products (ATMPs)**- are medicines for human use that are based on genes, tissues, or cells. They offer ground-breaking new opportunities for the treatment of disease and injury.
- **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 on 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.

Core Metrics
Reporting period: 2020/2021

BRAIN
Repair & Intracranial Neurotherapeutics

Health and Care Research Wales infrastructure award to the group

Direct funding awarded
£257.4k

Jobs created through direct funding
CV
4

Grants won during reporting period

Grants won	Led by group	Group collaborating
Number	4	6
Value	£663k	£3.2m
Funding to Wales	£663k	£2.9m
Funding to group	£10k	£0.00
Additional jobs created for Wales	3	3
Additional jobs created for group	1	1

25
Number of publications

4
Number of public engagement events

5
Number of public involvement opportunities

Intracranial Delivery

Work package aim: We are on the cusp of a new era of potential disease-modifying therapies for neurodegeneration, with many of the most promising requiring direct delivery into the central nervous system. Despite this, there are no optimised devices or protocols for delivering therapies directly to the human brain.

Our objectives are to:

1. Address this unmet need relating to delivery devices and expertise.
2. Establish Cardiff as a major international centre for delivering advanced therapies to the human brain.

Work package leads: Professor William Gray and Professor Anne Rosser

Huntington's Disease is a genetically inherited neurodegenerative disease which is fatal.

We are delighted to be selected as a site for the delivery of the UniQure Phase I/II gene therapy trial focussed on knocking down the production of huntingtin protein (which causes the disease) within the brain of patients with Huntington's Disease.

As well as being a cutting-edge Gene Therapy, its delivery is minimally invasive, with the complete operative procedure taking place within an MRI scanner. This will allow us to monitor the delivery of the therapy in real-time, thus ensuring adequate coverage of the target structures within the brain.

There are only a few global centres with the specific expertise to deliver a trial of this kind, of which we are one. Recruitment is due to start in the third quarter of 2021.

Further information on this trial can be found here.

This trial will allow people in Wales access to innovative Advanced Therapeutic Medicinal Products (ATMPs), a key objective of our BRAIN Unit and for the Welsh Government (Advanced Therapies Statement of Intent, 190409 - VG - Advanced Therapies Statement of Intent - English.pdf (gov.wales)).

Given the advanced nature of the neurosurgical techniques involved, this trial will be delivered via our Neurosciences Research Unit (NRU) at University Hospital Wales but will be open to participants across Wales.

We also published the world's first detailed clinical trial protocol for cell therapy directed at brain repair in patients with Huntington's Disease, which also received an editorial highlight for its importance to the field.

Providing human adult neural tissue to model disease and validate novel therapies

Work package aim: To support and expand a previously funded unique human adult (hA) tissue facility to perform 2D & 3D culturing of primary brain tissue (Gray, Zaben), for disease modelling and extend this to developing 3D cultures to support brain tumour research.

Work package lead: Professor William Gray

Work in our human tissue research lab was stopped for over four months due to the cessation of elective surgery and the protocols put in place by Cardiff University to protect students and staff during the first and second waves of the COVID-19 pandemic. The commitment of our staff to getting our research restarted ensured a rapid reopening of the labs allowing us to continue our delivery of significant outputs and translational support.

Key examples

- **Collaborations with the pharmaceutical company Takeda (Dr. Ying Zhu and Prof. William Gray)**
  - We are using excess adult neural tissue normally removed during neurosurgical operations and destroyed, to grow human brain cells in culture. Our collaborations with Takeda are being used to explore the biology around key signalling pathways in schizophrenia identified by our MRC Centre in Psychiatric Genetics and Genomics, with a view to gaining more scientific knowledge of the mechanisms involved, while simultaneously helping to promote drug discovery for patient benefit.

- **Cerebrospinal fluid (CSF) work at University Hospital Wales (Prof. William Gray, Dr. Joe Merola, Dr. Simone Cuff, and Prof. Matthias Eberl)**
  - Diagnosing infection early in severely ill patients undergoing neurosurgical operations is extremely difficult. Many groups have been trying to identify biomarkers of infection that are distinct from the inflammation that is caused by neurological diseases and neurosurgical operations. We made an important breakthrough in this area using cerebrospinal fluid obtained from patients undergoing neurosurgery in University Hospital Wales. Applying advanced data analysis to a large battery of inflammatory markers led to a unique biologically coherent pattern that reliably identified inflammation caused by brain disease from the superimposed inflammation caused by bacterial infection. If confirmed in larger studies, this offers the possibility of a rapid bedside test that would allow doctors to instigate a much earlier treatment of infection in these seriously ill patients.

We have extended our scientific collaborations with the UK Dementia Research Institute (UK DRI), gaining a funded collaboration (Professors Dion & Gray) to utilise human brain tissue cultures to examine the feasibility of novel genetic treatments for Huntington's Disease and potentially other CAG repeat disorders. This collaboration would not have been possible without the ongoing infrastructural funding of the human tissue labs by Health and Care Research Wales.

We have successfully appointed to the Neuro-Oncology Clinical Research Fellowship post which will commence in August 2021 and will support the full-time Research Assistant position (jointly funded by the BRAIN Unit and the Wales Cancer Research Centre - currently out to advert) for generating 3D cultures of human brain tumours in collaboration with our partners the Wales Cancer Research Centre.

Biobanking

Work package aim: To develop and expand our comprehensive bio-resources of clinical and biological data to facilitate translational, and clinical research across a wide range of neurological diseases, allowing efficient participant engagement and recruitment to study-ready cohorts.

Work package lead: Professor Neil Robertson (Welsh Neuroscience Research Tissue Bank - WNRTB) & Professor Owain Howell (Swansea Neurology Biobank - SNB)

Cardiff

Following a four-month complete closure of the WNRTB labs (March-July 2020), major changes to the biobanking service have been implemented, including postal recruitment of patients (most of SNOWDONIA's 235 consents were obtained via postal recruitment).

The first post-COVID lockdown neurosurgery tissue collection was received in July and seven project extensions/applications have been approved by the Governance Panel. Requests for samples are increasing again; to date, we have received 59 applications from 35 collaborations.

Some of the other changes to resume to the biobanking service following the closure includes:

- Revisions to Material Transfer Agreements (MTA).
- The biobank is overseeing the remote dry blood spot (DBS) sample collection for the COVID-19 DREAM study. The local study team will carry out serology testing of the DBS for COVID immune responses following vaccination. The remaining samples will be available to the biobank for other studies (providing relevant consent has been obtained).
- ·Biobanking arms of the MS Clinical Trials (DELIVER and DECISIVE) continued to recruit with Cardiff as the central repository, but with disruption at external sites.
- Working practices (SOPs/RAs) were reviewed, and an internal audit carried out.

Examples of sample types collected

3,339 total number of samples were acquired from WNRTB at end of March 2021. These included whole blood, serum, plasma, DNA, brain tumour tissue, cerebrospinal fluid, cerebrospinal fluid cells, and Peripheral Blood Mononuclear Cells (PBMCs). Ethics amendments are in progress to allow for remote dry blood spot (DBS) sample collections.

DNA | Whole blood | Brain tissue from Epilepsy surgery | Plasma

Swansea

The appointment of a part-time data analyst to support our SAIL work has been a great success. The post is match-funded through collaborative funds from charity and industry.

SAIL data analysis is proving a rich vein of new and important publications in support of healthcare decision making in Wales (e.g. Latif et al., were widely cited in the media for their SAIL databank-based research into idiopathic intracranial hypertension (IIH). ICH causes increased pressure in the fluid surrounding the brain. This can lead to severely disabling headaches as well as vision loss, which can be permanent).

The team used anonymised health records of Welsh patients held in the SAIL Databank, a national healthcare database managed by the University.

They analysed 35 million patient years of data from 2003 to 2017. They identified 1,765 people with Idiopathic intracranial hypertension (IIH) during that time, 85% of whom were women. Cases diagnosed rose from 12 in 100,000 people in 2003, to 76 in 100,000 in 2017, scientists found.

There were strong links between high body mass index and the risk of developing IIH, and women in more deprived areas were 1.5 times more likely to develop the condition (even after adjusting for body mass index).

BRAIN funding and samples from the Swansea Neurology Biobank (SNB) continue to support important papers published in the last 12 months.

Publications in which BRAIN/ Health and Care Research Wales sponsored biobank samples have been used include those of the impactful Epi25K international consortium. This is a collaboration of over 200 research groups addressing fundamental questions concerning rare and common variants on epilepsy phenomes.

Sample collection

Sample collection has been hugely impacted by the pandemic.

Cardiff

- Between July and March 2021, the biobank has issued **721 samples for research** and **consented 12 more research participants**.

Swansea

- A near-complete **absence of face-to-face clinical appointments** has meant there have been **no new samples captured to the SNB**.
- It is hoped these **processes can begin again soon**, in line with **COVID-19 restrictions and safety guidelines**.

Neurosciences Research Unit (NRU)

Work package aim: To achieve and consolidate financial sustainability through a combination of Activity Based Funding, commercial trials, and research income.

Work package lead: Professor Khalid Hamandi

The Neurosciences Research Unit (NRU), based in Cardiff and Vale UHB, led by Professor Khalid Hamandi (consultant neurologist) and Belinda Gunning (Nurse manager) successfully reopened all existing studies, and maintained recruitment and study visits in clinical interventional studies during 2020-21. Most studies have now met, are on schedule, or have exceeded recruitment targets.

The following examples highlight the high-quality research hosted by and enabled through the BRAIN Unit:

12

studies and trials are ongoing within the Unit

Epilepsy studies

Principal Investigator: Professor Khalid Hamandi
Sponsors: Xenon Pharma & Kings College London
Titles:
- Novel potassium channel modulator, XEN1011 for drug-resistant epilepsy.
- BioJume (Biology of Juvenile Myoclonic Epilepsy), genotype/phenotype analysis in JME.

53

participants recruited so far across two studies

Huntington's Disease studies

Principal Investigators: Professor Anne Rosser & Professor William Gray
Sponsors: Health and Care Research Wales Research for Patient and Public Benefit (RfPPB) Wales, Cardiff University
Title:
- Trial designs for delivery of novel therapies for neurodegeneration (TRIDENT)

Principal Investigator: Professor Anne Rosser
Sponsors: University College London and Roche
Titles:
- HD Clarity: A cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's Disease.
1. A study to evaluate the efficacy and safety of intrathecally administered RO7234292 (RG6042) in patients with manifest Huntington's Disease.
2. Evaluating the long-term safety and tolerability of intrathecally administered RO7234292 (RG6042) in patients with Huntington's Disease.

19

total number of recruits to the TRIDENT study

Principal Investigator: Dr. Duncan McLauchlan
Sponsor: Prilenia Theraupatics
Title:
- Evaluating the efficacy and safety of Pridopidine in patients with Early Stage Huntington's Disease.

Multiple sclerosis studies

Principal Investigator: Professor Neil Robertson
Sponsors: University College London & Roche
Titles:
- Investigating the effectiveness of repurposed Simvastatin /placebo in Secondary progressive Multiple Sclerosis in slowing progression of disability.
- Evaluation of the efficacy and safety of Ocrelizumab in adults with Primary Progressive Multiple Sclerosis.

62
participants recruited so far across three studies

Principal Investigator: Dr. Emma Tallantyre
Sponsor: Nottingham University Hospital
Title:
- Determining the Effectiveness of early Intensive Versus Escalation approaches for the treatment of Relapsing-Remitting Multiple Sclerosis (DELIVER-MS).

Neurology and neurosurgery studies

There are currently **10 new neuroscience - neurology and neurosurgery studies** in set up. Two examples are given below:

Principal Investigator: Dr. Malik Zaben
Sponsor: Cambridge University Hospital
Title:
- Pharmacological management of seizures post traumatic brain injury (MAST).

55
participants recruited so far across two studies

Principal Investigator: Mr George Eralil
Sponsor: Oxford University
Title:
- Functional and Ultrasound-guided Resection of Glioblastoma. A two-stage trial:
  Stage 1 – Non-randomised collaborative learning and evaluation phase of participating centres (IDEAL Stage 2b study), followed by Stage 2 – A Multicentre Phase III trial with two mechanistic sub-studies.

Patient and Public Involvement and Engagement (PPI)

Work package aim: To continue our work on PPI and engagement with patients, the public, the third sector, NHS and Industry.
Work package lead: Dr. Emma Lane and Mr. Peter Roberts

Due to the pandemic, we have been unable to host any face-to-face activities to engage the public as we have done in previous years.

This year, we needed to find new ways of working with our public contributors and transitioned our face-to-face meetings to an online platform. In doing so, we established a series of well-attended monthly meetings, providing updates on current projects across the BRAIN Unit.

This is allowing us to build a more integrated cohort of public contributors in the BRAIN Involve community. Whilst COVID-19 halted the majority of research projects, we have also facilitated a couple of public contributor activities onto projects.

Led by Drs. Emma Lane, Cheney Drew, and Mr. Peter Roberts, supported by the BRAIN Unit administration team, the transition to online has been well received and will be integrated into our future programme of activities, enabling us to have more inclusive opportunities in terms of accessibility and flexibility of our activities/events.

Within this format, we listened to the views of the public contributors and have built-in some protected networking time to support the group.

We used this time to give our public-facing website a refresh, ensuring the navigation and content are up to date and using social media to engage and promote national awareness days, most recently being Wear Purple for Epilepsy Day.

Examples

- We held an MS patient virtual focus group on the 29th of June 2020 to discuss the SNOWDONIA project and the implementation of online annual patient questionnaires versus paper versions. Discussions focused on the new digital platform; accessibility and user-ability. Feedback enabled us to improve the system which is due to be rolled out imminently.

- Dr. Emma Yhnell and Dr. Emma Lane presented activities in the GlobalScienceShow on Twitter, a 24-hour science show with many contributors across the globe reaching many hundreds of views. These pre-recordings aimed at children and adults covered a range of topic areas but our contributions focused on the brain.

- Emma Lane and Emma Yhnell also presented two live broadcasts on Facebook live Cardiff Science Shows, focused on Huntington's disease and Stem cell transplantation for Parkinson's disease.

Meet the Researcher

Dr. Malik Zaben

Clinical Lecturer in Neurosurgery,
Traumatic Brain Injury (TBI) Research Group

Dr. Zaben is a lecturer in neurosurgery with a special interest in understanding neurogenesis and neuroplasticity after traumatic brain injury (TBI).

His research explores potential therapeutic approaches targeting neuroinflammatory pathways to limit brain damage after injury, and enhance repair.

This year has been another successful one for our Traumatic Brain Injury research team at Cardiff University, despite the challenges that the COVID-19 pandemic has caused.
We have been able to address some new facets of our research area covering the broad spectrum of basic science and clinical research.

The research

The COVID-19 pandemic meant that we had to leave the laboratory in mid-March of 2020 and were not able to return until mid-July.

Despite this major disruption, we are now able to continue our research in-house. Building on our previous findings, we have generated novel and relevant data on the inflammatory pathways triggered by seizures and Traumatic Brain Injury (TBI), which are heavily implicated in long-term neurocognitive deficits in patients from both categories.

Our key target of interest is HMGB1, a protein that is released by immune cells significantly after epilepsy and TBI and increasingly recognised as the 'master switch' of neuroinflammation in the acute phase after injury.

Elevated levels of HMGB1 in the blood of patients with TBI are associated with worse outcome in patients with epilepsy as well as TBI. Blocking this protein in a time-specific manner may hold the answer to ameliorating the neuro-toxic milieu created after injury and improving brain repair.

Whilst we previously observed a significant release of HMGB1 after injury, we have now discovered that HMGB1 has a detrimental effect on neural stem cells' ability to generate new neurons or repair nerve cell fibres after injury.

This year we have also identified the receptors and pathways involved in the above-mentioned effect and, more importantly, managed to reverse HMGB1 effects using some novel drug strategies.

These findings pave the way for identifying potential drugs that can be used to enhance nerve cell repair after injury.

We have now published some of our key findings in two peer-reviewed papers in the Journal of Brain Science and Nature Scientific Reports.

We have submitted our work on pathways involving HMGB1 and other inflammatory cytokines involved in epilepsy for publication at the Journal of Neuroinflammation (under revision).

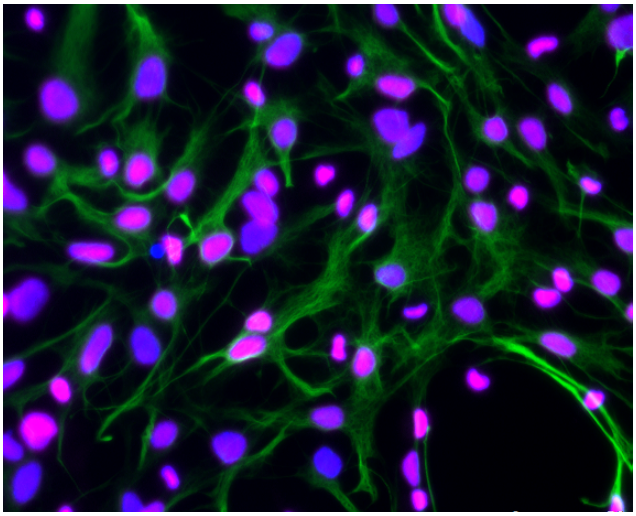
What next?

Moving forward, we will be validating our findings in human brain tissue. With the consent of patients undergoing neurosurgery, we will obtain small samples of normal brain tissue that would otherwise have been discarded as a routine part of the surgery.

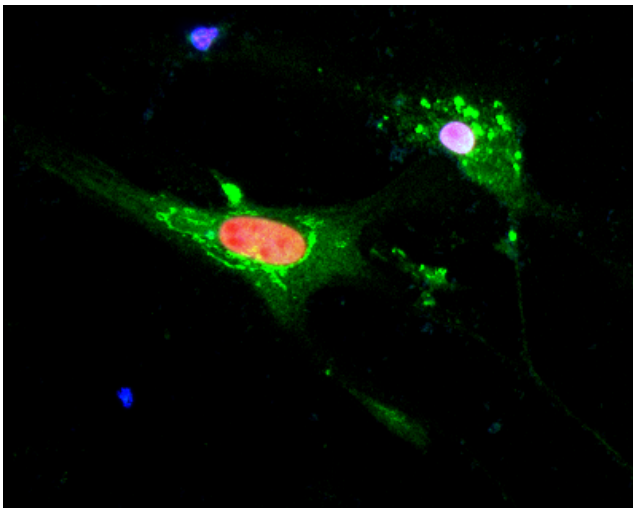
We can then grow these cells in a specialised 3D in vitro culture system that closely mimics their natural parent environment in vivo. With judiciously calculated weight drop injury models; we are studying the effects of blocking HMGB1 on improving brain repair after injury.

With evidence from both rodent and human tissue, we hope to elucidate the potential detrimental role of HMGB1 in TBI and provide promising therapeutic targets for improving outcomes in TBI patients.

We continue to make exciting progress and we are incredibly grateful for our funders ongoing support. Thanks to Health and Care Research Wales and the Rhiannon Jade Smith Memorial Trust.



Astrocyte, HMGB1



Human, Microglia, HMGB1

Spotlight on Huntington's Disease

Professor Anne Rosser

Professor of Clinical Neuroscience at Cardiff University

Huntington's Disease is an **inherited neurodegenerative condition** in which there is a **progressive deterioration of movement, cognition, and mental health**, usually from **mid-life onwards**.
Currently, **no disease-modifying treatments are available**.

Cardiff has a long tradition of Huntington's Disease (HD) research and is now one of the largest HD research centres in the UK, with studies ranging from the genetics and cellular pathology of HD right through to interventional clinical trials.

Various potential disease-modifiers are in development and most of these will require direct delivery of the active agent into the brain or CSF. These two factors (rich HD research environment locally and the requirement for delivery of therapeutics to the brain) have put HD research at the heart of the BRAIN Unit.

Cell therapy

HD is caused by a single gene mutation, which leads to degeneration and death of nerve cells in a brain structure called the striatum. The striatum is part of a widespread network of brain connections and is essential for normal movement, cognition, and mental health.

The concept behind cell therapy is to replace striatal cells that have been lost to the disease process, with the aim that they will connect up with downstream areas of the brain, thus "repairing" brain circuits and restoring function.

TRIDENT study

Cell therapy for HD is a key interest of the BRAIN Unit and through collaborations with the Cardiff Brain Repair Group (Rosser, Lelos), has worked on the preclinical development of cell therapies for many years and the work has now moved into the clinical arena, supported by various grants, most recently from Health and Care Research Wales (RFPPB TRIDENT study, Rosser, Gray, Drew, Pallman, Busse). The neurosurgery within this trial will be conducted by Prof. William Gray.

TRIDENT is a study of foetal cell transplantation in HD. Foetal cells are interesting as a donor cell source because they develop "naturally" through normal development and are thus properly primed to become exactly the sort of cell that is needed to replace function in the adult brain.

What will the TRIDENT study aim to do?

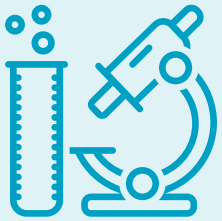
As well as the preclinical evidence that transplanted cells can improve function in HD, there is also proof-of-concept from small human pilot studies. But there is a pressing need for further clinical studies to verify that these cells can indeed improve function in human participants with HD.

TRIDENT will seek to test the safety and effectiveness of various doses of foetal cells, and will also address the various issues of trial design which will be important for future studies of other complex therapies. The first TRIDENT participant was scheduled for surgery on 17th March 2020, but this was cancelled due to the COVID-19 crisis. The first patient is now rebooked for July 2021 and there are a total of 19 participants recruited to the study (Jun 2021).

The long-term aim is to derive donor cells from stem cells, which would be more sustainable than foetal cells, as stem cells can be expanded in numbers in the laboratory and can be encouraged to develop into almost any cell of the body.

We are working on developing these cells for use in HD along with Prof Meng Li, and the TRIDENT trial will be essential for laying the groundwork for the use of stem cells in people with HD. It is also important to emphasise that HD is an excellent model of neurodegenerative disease, so we anticipate that everything we learn about how to transplant cells in HD will eventually be useful for developing cell therapies for other new degenerative disorders.

Ongoing work



- Cardiff scientists, including Professors Lesley Jones, Vincent Dion, and Dr. Tom Massey, are developing new ways of attempting to interfere directly with the pathogenic process in the brain in HD. It is highly likely that these sorts of interventions will require the delivery of therapeutic agents directly into the brain. The current work of the BRAIN Unit will not only develop the capacity to perform transplantation therapies but will be critically important in allowing the eventual delivery of these additional potential disease-modifying treatments in HD and in other diseases.

- We have been active in Cardiff in delivering new and emerging commercial therapies for HD. Cardiff investigators were part of the first study to deliver huntingtin (the toxic protein produced by the mutant HD gene) lowering antisense oligonucleotides (ASOs), sponsored by Ionis and Roche, and have recently been accepted as a site for another ASO therapy developed by Wave Therapeutics. The Wave project is interesting because it will allow the lowering of the mutant huntingtin protein whilst protecting the levels of the normal huntingtin protein in HD participants.

- uniQure has generated a micro-RNA which is delivered directly into the brain substance through a neurosurgical procedure using a modified virus. The idea of this is that the micro-RNA will be permanently expressed, thus providing a "one-off" huntingtin lowering treatment. UniQure has selected only three sites in Europe to pilot this approach, Cardiff being one of them. This is an extremely important study for Cardiff because it will be the first gene therapy procedure for any brain disease in Wales and will help to establish the infrastructure and experience to subsequently deliver a range of gene therapies to the brain for other neurodegenerative conditions.

Conclusion

Whilst the pandemic has had an impact on all our work over the past 18 months, we are actively embracing the opportunity to shape our future activities.

I am extremely proud of all our staff, collaborators and public contributors for their resilience and attitude to working in an ever-changing landscape.

The next year will see us getting our paused activities back up and running to maximum capacity.

We are thrilled to be able to resume the surgical element of the TRIDENT trial in the summer, the outcomes of which will impact the future of intracranial delivery devices. A particular highlight is the uniQure gene therapy trial in Huntington's Disease which is targeted to reduce the production of the protein thought to be a major factor in killing vulnerable nerve cells, causing symptoms and disease progression. The trial has so far successfully delivered the gene therapy into patients in two centres in the USA (USCF and OSU) and we are very pleased that Cardiff will be one of the European centres delivering the trial in the next phase going forwards. This is just one example of the way we continue to push the boundaries of clinical and translational neurological research.

We will continue to work with our clinicians and patients to explore the best ways of sample collection and follow up appointments, particularly looking at how this can be done remotely. Thanks to the dedication, commitment and hard work of our NRU staff, led by Professor Hamandi, we have now successfully re-opened all studies put on hold because of COVID-19.

Moreover, exciting collaborations are ongoing including work with the Medicines Discovery Unit at Cardiff University and the Wales Cancer Research Centre (WCRC). Our collaboration with WCRC will grow as we appoint dedicated research staff to support the development of 3D brain tumour cultures for drug discovery and for personalising medical therapies.

The COVID-19 pandemic generated particular difficulties for our Public involvement and Engagement activities, a challenge which our PPI team more than met by using online platforms for involvement and public engagement. This transition has been well received and will be integrated into our future programme of activities, enabling us to be more inclusive, accessible and flexible going forward.

We also continue to grow our BRAIN Unit website which is the best place to keep up to date on our activities as they happen.

After a challenging past 18 months, we are looking forward to another productive and exciting year ahead at the BRAIN Unit.

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