BRAIN

Repair & Intracranial Neurotherapeutics

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

2023 - 2024 Annual report

Contents

Foreword

I am pleased to present our 2023-24 annual report reflecting on the achievements of the BRAIN Unit over the past year.

We continue to make significant progress with our advanced therapies work and are delighted to be at an advanced stage of negotiations with a further two companies to deliver their gene therapy trials in Cardiff, for Parkinson's disease and frontotemporal dementia.

Delivering cutting edge trials requires significant work behind the scenes, with patient safety at the forefront of all discussions. I would like to thank all of the teams involved throughout the entire process and, of course, the participants who are paving the way for future treatments.

We are taking the next steps towards understanding the delivery science behind the clinical trials too, via a data sharing agreement set up with UniQure to analyse a globally unique dataset of MRI scans during advanced therapy medicinal product (ATMP) infusion from over 30 participants.

Throughout this report, we offer an insight into the imaging and its importance to understanding how we can improve the delivery of gene therapies for neurological and neurodegenerative diseases.

In September 2023, we bid a fond farewell to one of our long-standing co-investigators, Dr Emma Lane. Emma has led the Public and Patient Involvement (PPI) work package since the BRAIN Unit's inception and has now moved on to her new role as the Global Patient Engagement Lead at UCB Pharma. We wish Emma all the best in her new role, and look forward to continuing to collaborate with PPI work package lead, Dr. Cheney Drew.

I hope you enjoy reading this report.

Professor William Gray
BRAIN Unit Director

2023-24

The team

Director
Professor William Gray

Deputy Director
Professor Anne Rosser

Work Package Leads
Professor Neil Robertson
Professor Owain Howell
Dr Cheney Drew
Peter Roberts

Neuroscience Research Unit*
Professor Khalid Hamandi
Belinda Gunning
Dr Saiful Bari
Dr Aung Saw
Dr Sai Ambati
Dr Magdalene Randa
Dr Karim Kreft
Cynthia Butcher
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Mr Dmitri Sastin*
Mr Susruta Manivannan*
Mr Harsh Bhatt*
Mr Ronak Ved*
Mr Richard Moon*

Laboratory Team
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Dr Anne-Marie McGorrian*
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*These posts receive funding from other sources including the Medical Research Council, Brain Research UK, Guarantors of Brain, Cardiff University and NHS Research and Development.

Introduction

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

BRAIN is a multi-disciplinary research unit with strong academic and NHS clinical leadership, operating under the directorship of Professor William Gray along with 24 principal investigators and collaborators. Since 2015, the unit has received a total grant income of over £50m.

The BRAIN Unit is primarily based in Cardiff but involves research groups from Swansea University and health boards across South Wales. Our work is informed by individuals who are affected by neurological conditions in Wales and we continue to work with third sector partners to support activities with far reaching membership and input.

Our mission

Our mission is to be a UK national centre of excellence, and on a path towards international leadership for:

1. Delivering advanced therapy medicinal products (ATMPs) to the human brain in early phase clinical trials.

2. Supporting ATMP development for neurological disease.

Our aims

We have the following aims:

- 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 cross-cutting excellence in the relation to:
  - Public and Patient Involvement and Engagement
  - Industry and NHS Engagement and Collaboration

Work packages and cross cutting themes

Cross cutting theme: NHS, Commercial and 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)**

Cross cutting theme: WP4 PPI and Engagement

Glossary

- **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 specialise, 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.
- **Neurotherapeutics** - The treatment of disorders that affect the nervous system.
- **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.
- **Intracranial** - Within the skull.
- **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** - 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: 2023/2024

BRAIN
Repair & Intracranial Neurotherapeutics

Health and Care Research Wales infrastructure award to the group

Direct funding awarded

£250k

Jobs created through direct funding

CV

8

Grants won during reporting period

Grants won	Led by group
Number	12
Value	£2.7M
Funding to Wales	£2.7M
Funding to group	£2.7M
Additional jobs created for Wales	10
Additional jobs created for group	0

20

Number of publications

10

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*

As we continue our mission to become a Centre for Excellence for the delivery of advanced therapies to the brain, it is important to consider all the elements required to successfully deliver experimental trials.

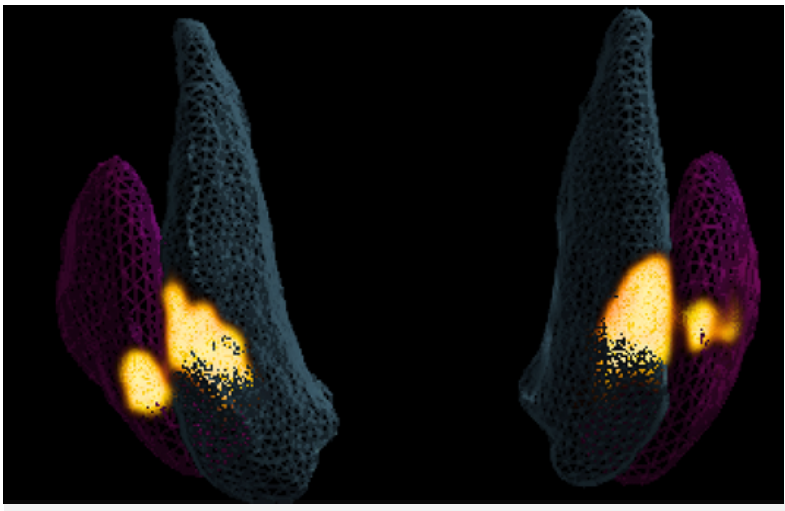
In addition to continuing the UniQure trial, whose latest clinical data has awarded them with a major step forward in regulatory approval planning, we are at an advanced stage of negotiation with a further two companies to deliver their gene therapy trials in Parkinson's disease and frontotemporal dementia respectively, and at an earlier stage of negotiations with a number of other biotech companies whose therapies are on their way to clinical trial stage. Read more at: **bit.ly/uniQure.**

As we increase our advanced therapy clinical trial portfolio, we are also training an increasing number of dedicated staff required to safely deliver these novel trials.

Staff span a number of different departments, which includes the clinical care teams (surgery, radiology, anaesthesia), pharmacists who prepare the therapy and the research teams who to coordinate patients, collect data, and report to sponsors.

All of the current advanced therapy clinical trials we are conducting take place in an MRI scanner. The real-time MRI guidance is especially crucial for ensuring accurate delivery of the gene therapies to the intended brain targets. Analysing that imaging data has the added benefit of generating valuable insights to further refine and enhance the therapies over time.

Our unique expertise in first-in-human (FIH) trials, delivery technology, and bespoke clinic trial design ensures that Cardiff remains a competitive site to deliver these complex studies.



This image shows the distribution of gene therapy (yellow) during delivery into the Anterior Putamen (purple) and Caudate nuclei (blue) on the right and left sides of the brain during surgery.

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 for disease modelling, and extend this to developing 3D cultures to support brain tumour research.

Work package lead: *Professor William Gray*

During this year there has been considerable progress in optimising human tissue processing output, including:

1. Hi-spot models

In collaboration with Dr Rebecca Hodge at the Allen Institute for Brain Science, we have improved cell dissociation protocols, resulting in higher yields of viable cells from surgical patient samples.

This should increase the quantity and quality of cultures set up, allowing for broader collaboration opportunities within Cardiff University. We are currently investigating the cellular constituents of these cultures with the new protocol for further characterisation.

2. Organotypic slice cultures

This year we have formed a collaboration with Professor Erik (Aachen University) who is an expert in producing human organotypic slices from neurosurgical explants.

Our lab technician Olivia Squire was trained at Aachen to establish this approach at Cardiff, which maintains brain microstructure. She is currently setting up slice cultures with cortical and tumour tissue, which has promising preliminary results. This method enables additional collaborations where preserved brain microstructure is critical.

3. Traumatic brain injury (TBI) research

Advanced gene expression analysis of a novel traumatic brain injury model using hi-spots yielded encouraging results, demonstrating model validity and potential therapeutic targets.

This is currently being written up for publication to increase scientific community awareness of using this paradigm to study traumatic brain injury disease mechanisms.

Additionally, the protocol changes allow longer-term tissue culture to enable studying long-term effects and conditions.

The optimised protocols, collaborations, and new organotypic slice and hi-spot models have enhanced tissue processing capabilities, enabling broader research opportunities, preserved brain microstructure studies, traumatic brain injury insights, and potential for increased collaborations within and outside Cardiff University.

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) and Professor Owain Howell (Swansea Neurology Biobank - SNB)*

Cardiff

In the 2023-24 period, the WNRTB consented 362 new participants:

- WNRTB: 50 participants
- SNOWDONIA: 277 participants
- Epilepsy-Bio study: 35 participants.

Additionally, recruitment is ongoing for three external cohort studies (DREAMs, DELIVER, DECISIVE) that will transfer collected samples to the WNRTB biobank upon study completion.

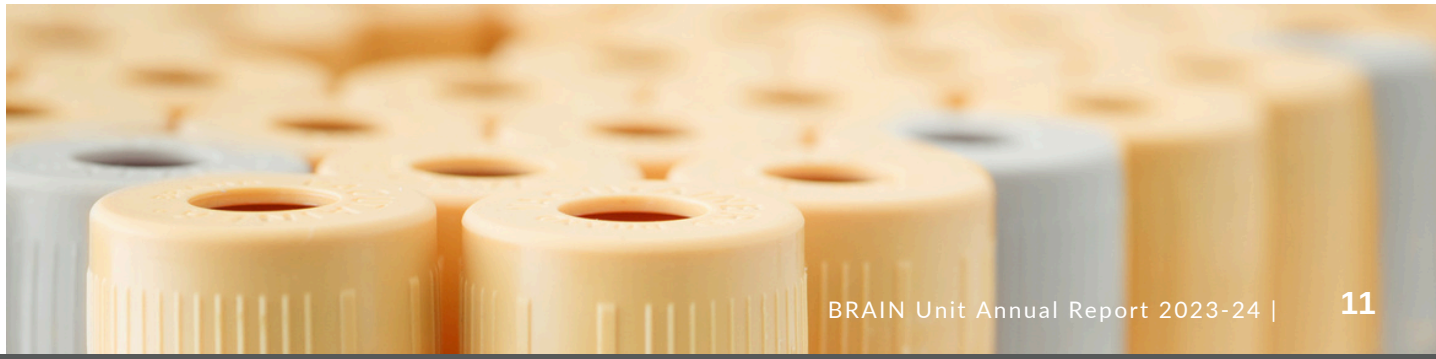
Sample distribution

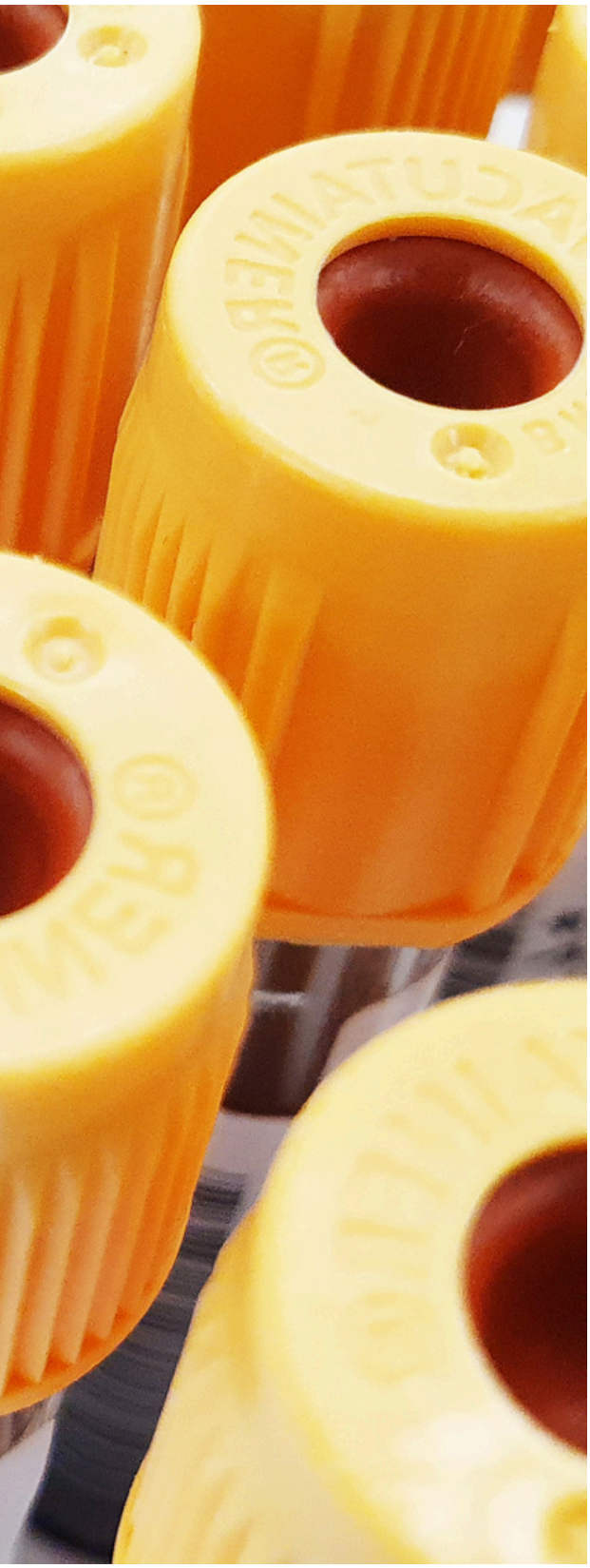
- Seventeen research projects across Wales and the UK were supplied with a total of 688 aliquots of biosamples from the WNRTB collections
- Thirteen new research tissue sample applications were received and approved
- Multiple peer-reviewed publications were enabled by WNRTB biosamples this year.

Since its inception in 2014, the WNRTB has received 93 applications for biosamples from 55 unique research collaborations. Of those, 92 applications (99%) have been approved.
A total of 14,068 aliquots have been requested, with 7,879 aliquots (56%) supplied to researchers as of 31 March 2024.

The WNRTB has successfully renewed its ethical approval to at least 2029 following a rigorous panel review. This five-year renewal allows the biobank to continue its core missions of participant recruitment, biosample collection, processing, storage, and distribution to support neuroscience research in Wales and beyond.

**SNOWDONIA is an epidemiology for Multiple Sclerosis study, and Epilepsy-Bio is an epidemiological study of epilepsy. Participants are consented to these projects with the option of depositing half of their samples to the WNRTB.*





Swansea

Swansea Neurology Biobank (SNB)

- Fifty new samples were captured and processed.
- Fifty samples were released for research studies.
- Two new research projects utilising SNB samples were approved.

Studies using SNB samples have recently resulted in high-impact publications in prestigious journals such as Nature Genetics and Nature Communications.

Neuroscience laboratory

In collaboration with the MRC Rare Diseases platform, the Swansea Lipidomics Team led by Professors Griffiths and Wang secured an MRC MND Accelerator grant titled "Sterol biomarkers for amyotrophic lateral sclerosis," amounting to £385,618.

New collaborations facilitated by BRAIN Unit funding have led to publications in prominent journals like Nature Communications (Nutma et al.) and Annals of Neurology (Knowles et al.).

In 2024, new working partnerships were established to investigate:

1. "Mapping the molecular pathways of white matter pathology" with researchers from Naples, Imperial, UCL, and Vienna.
2. "Sulcal-enriched inflammation as an imaging biomarker of disease severity" with collaborators from Sorbonne and Verona.
3. "MTHFR variants in predicting MS severity" with teams from Imperial College London, Genoa, and Naples.

These studies leverage the digital pathology expertise developed at Swansea University (Howell), supported by BRAIN Unit infrastructure funding.

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 Cheney Drew and Mr Peter Roberts*

A guest experiences a virtual reality MRI scan using a headset at a PPI event hosted by the BRAIN Unit and the National Centre for Mental Health.

BRAIN Involve (the public and patient involvement group for the BRAIN Unit) has continued to support the research happening within BRAIN over the past year.

The group is a highly recognised and valued group of individuals with lived experience of neurodegenerative and neurological disorders, who provide incredibly useful input into the development and design of pre-clinical and clinical research.

The work that BRAIN Involve does has been recognised both nationally and internationally with our academic PPI lead, Dr Cheney Drew, being asked to present about the group's work at various international events including EuroGCTs 'Sharing Best Practice' workshop in Copenhagen, the Institute of Clinical Research Ethics Good Clinical practice forum and at an ATMP Engage webinar.

The group has supported the development of PPI strategies and patient facing documents for new research projects across the BRAIN portfolio, including fellowships focussed on the career progression of early career researchers.

More importantly, the group have received requests to provide input into some of the commercial trials supported and delivered by the BRAIN Unit and its investigators. These include cutting edge, early phase trials of gene therapy for neurodegenerative disease- where BRAIN Involve are making an impact by ensuring the voice of patients is appropriately included at the beginning and throughout this exciting research.

Professor Liam Gray was interviewed by public contributor Jacqui Campbell about the importance of PPI in clinical trials during our Working together for better brain health engagement event.

Recently we were pleased to co-deliver a public facing event called *Working together for better brain health* with the National Centre for Mental Health. The engaging and interactive programme saw 45 members of the public enjoy talks from some of our research partners and learn more about how those leading research value the dedicated contributions from the public. Attendees were also treated to a range of interactive stalls and games, explaining some of the scientific principles behind the work we do.

At the event, one attendee remarked:

“My father had Parkinson's and there wasn't much out there in the way of support or involvement, it felt like a lonely experience for us as a family. I can see from this event that things have changed since 1990.”

The BRAIN Unit has been delighted to support other engagement and network activities to highlight Huntington’s disease (HD) research. The annual Patient and Family Day was held in October 2023 where people with HD and their family members were invited to hear the latest developments in HD clinical care and research, including work led by BRAIN researchers.

The depth and breadth of HD research in Wales has recently been recognised by the launch of the new Huntington’s disease Centre in Wales network, which aims to bring together multidisciplinary researchers across the translational pipeline and provide a platform for developing and supporting world leading HD research, including that into advanced therapies for HD.

Meet the researcher

Mr Richard Moon

Clinical Research Fellow

As a Clinical Research Fellow in Neurosurgery, Richard is working on developing new MRI imaging sequences to make currently 'invisible' pathology visible in patients with epilepsy. Richard's work will support more successful epilepsy surgery, under the supervision of Professors Liam Gray, Derek Jones and Khalid Hamandi.

About me

I am a neurosurgery registrar, currently taking time out of my clinical training to learn advanced imaging research skills.

Cardiff University Brain Research Imaging Centre (CUBRIC) hosts one of Europe's most powerful MRI scanners and the National Microstructure Imaging Facility, which, together with the BRAIN Unit, provides a unique setting to carry out translational research.

The research

This study aims to prove that MRI can identify abnormalities within the brain based on specific changes in the tissue microstructure (e.g. cell density, size or shape). We believe recent advances in MRI physics will enable us to detect abnormalities in more patients than ever before and to obtain the same kind of information about cell structure that would otherwise require a biopsy.

We will perform advanced MRI imaging on an abnormal region of brain tissue (FCD) in patients with epilepsy. Following removal of this region as part of routine epilepsy neurosurgery, we will then perform prolonged imaging of the same abnormal brain tissue with both experimental MRI scanners (that are even more powerful than human MRI scanners) and electron microscopes. This will enable us to learn how the MRI signals reflect changes in the tissue microstructure.

We want to be able to automatically detect microstructural features that are invisible with conventional MRI.

To do so, we will scan healthy individuals to learn how much variation we see normally in each feature. We predict that the abnormal regions of brain tissue will fall outside this range. We will use AI to combine data from MRI scanners with high spatial resolution and with sensitivity to tissue microstructure to create new hybrid images.

Finally, we will test our approach with epilepsy patients who have no disease visible with conventional MRI to see if we can identify abnormal regions that were otherwise invisible.

Research implications

If we can detect abnormalities invisible to standard clinical MRI, we will be able to increase the number of epilepsy patients able to undergo, and receive a good outcome from neurosurgery to reduce their seizures.

We expect to use these MRI techniques providing information on tissue microstructure with a wide range of neurological diseases in the future. They will enable us to generate a more complete picture of diseases that affect the brain's cortex.

We will be able to make earlier diagnoses and track diseases over time, helping improve patient care and outcomes.

Richard is funded by the MRC grant, "Making the invisible, visible."

Spotlight on
Imaging in advanced therapy delivery

Dr Dmitri Sastin
Clinical Research Fellow

As advanced therapy medicinal products (ATMPs) rapidly enter clinical trials, our experience in their delivery, and the appreciation of the challenges that come with it grows. Neurodegenerative conditions such as Huntington's disease, Parkinson's disease, and frontotemporal dementia are typically accompanied by progressive reduction in brain volume that begins even before the patient notices anything unusual. This makes finding a safe approach to the deep regions of the brain that are the target of ATMPs particularly challenging. Some of the surgical corridors, while safe, may only allow a limited amount of ATMP to reach its target, reducing efficacy of treatment.

In Cardiff, we are designing algorithms that enable the computer to analyse brain scans of individual patients, suggesting safe delivery trajectories and predicting delivery efficacy. This is now being applied in a larger group of patients with Huntington's disease, and we hope to gain new insights that not only will help us plan individual administrations in the future, but also tell us something about when it is best to intervene on the whole.

Combined with data coming out of current trials (Fig.1), we can also begin to ask some interesting questions such as how the sequence of trajectories influences the spread of ATMPs and ultimately, how this will improve patients' outcomes. We can consider different options using computer simulations informed by the data we see (Fig.2), and choose the best ones for our patients.

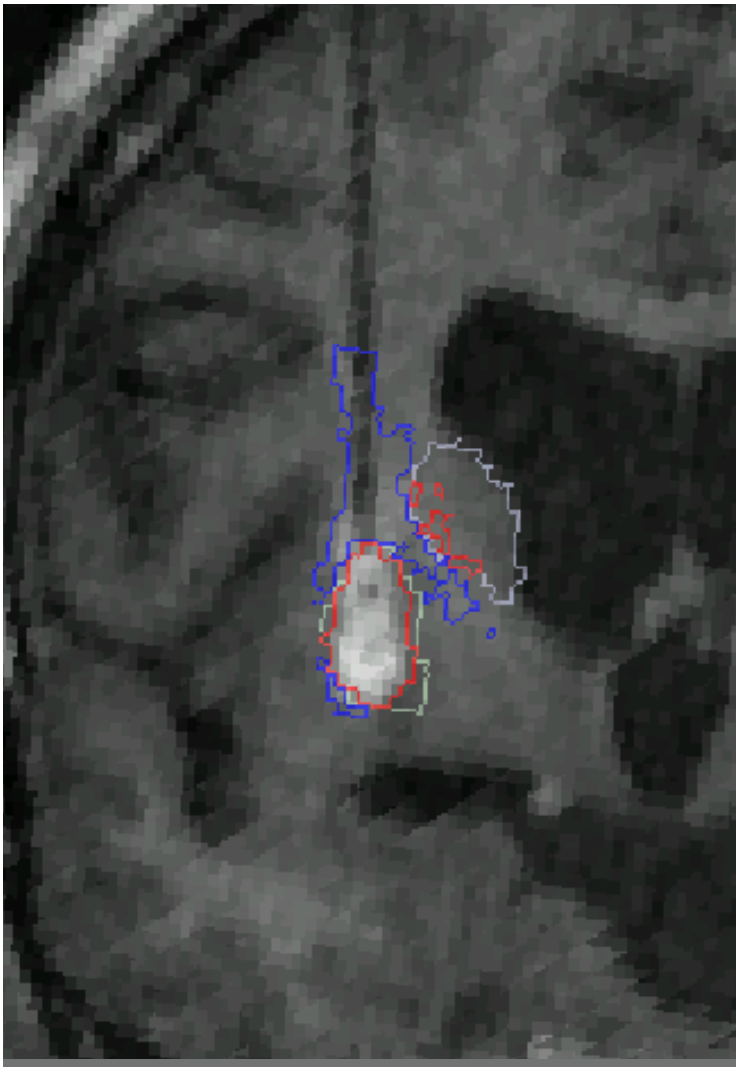


Fig.1. A section through the brain showing the delivery catheter (black vertical structure). Two deep structures, the anterior putamen (green outline) and the anterior caudate (pale violet outline), used for ATMP delivery are also shown. The white dye used to demonstrate ATMP delivery is divided between that inside the putamen (red outline) and outside of it (blue outline). Note that the delivery catheter aims to avoid the sulci, or crevasses, on the brain surface (black curves) as well as the ventricles, or fluid-filled spaces of the brain (large black areas), both of which increase in size due to brain atrophy thus making the placement more challenging.

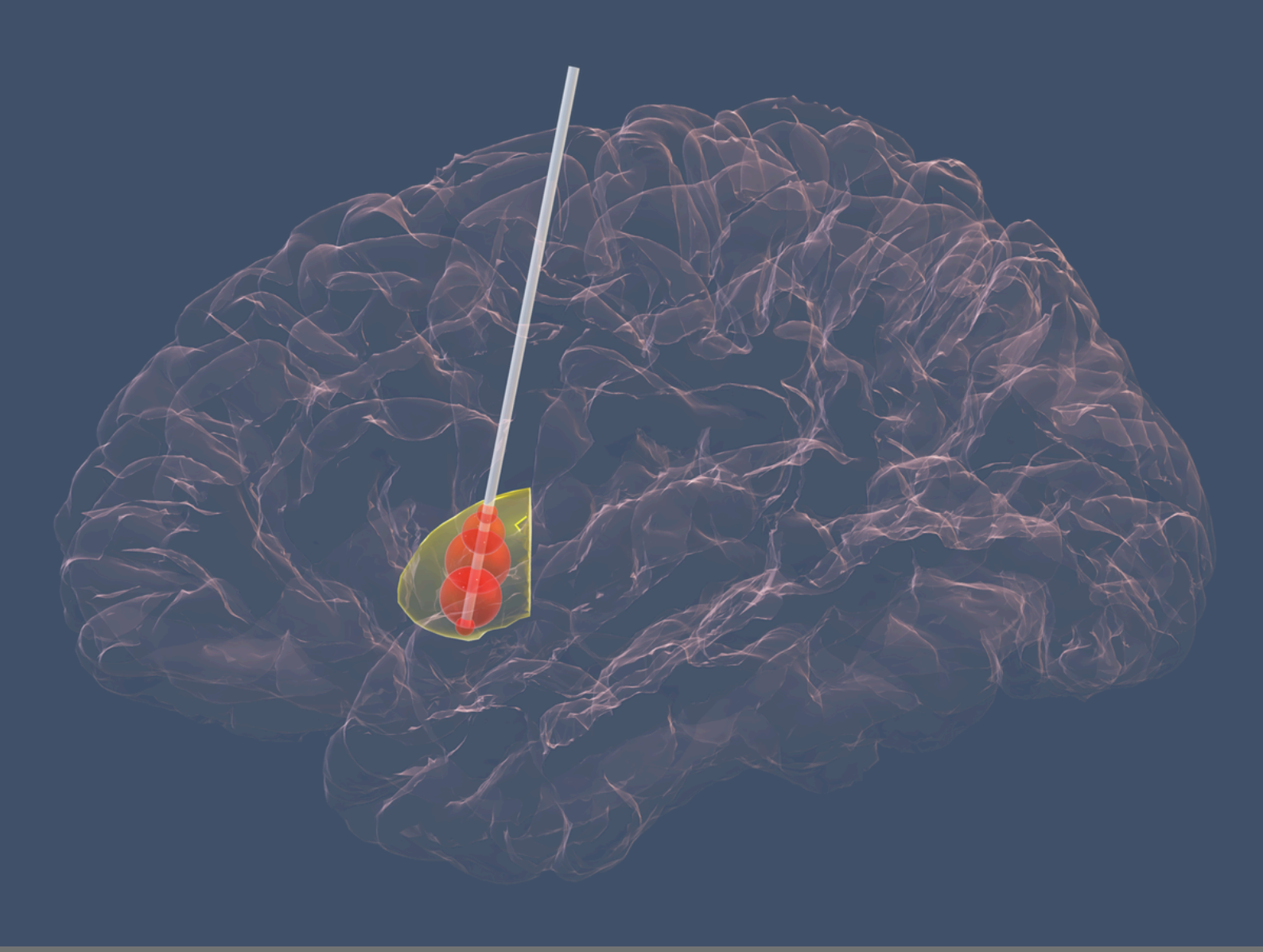


Fig.2. A three-dimensional model of the right brain hemisphere derived from a scan. Yellow volume shows the anterior putamen. The silver tube represents the delivery catheter aligned with the proposed trajectory that is estimated to provide the greatest ATMP distribution. Red spheres simulate ATMP within the anterior putamen, and are used to compute the volume of distribution. More sophisticated models are currently being worked on.

Going the other way, we can also try and explain why ATMPs spread in certain ways through the brain by running tests on the computer, and leverage that knowledge to stir the delivery.

Finally, our in-depth analysis will provide measures that cannot be manually determined (such as interactions between regions with ATMPs), and that might influence outcomes in ways we have not previously appreciated.

Our greater vision is to consistently deliver ATMPs in the best possible way that is tailored to each patient, being able to predict this process precisely.

This will form a cornerstone of the BRAIN Unit's future translational work, and help to advance the field globally.

Conclusion

It has been another busy year for the BRAIN Unit, and I remain as proud as always of what we continue to achieve together.

A large focus of the past year has been developing our next five-year strategy to apply for continued funding from Health and Care Research Wales.

Following a successful performance review in October 2023, we were invited to submit a proposal, which we have now completed. If successful, we plan to rebrand in April 2025 to become the **Advanced Neurotherapies Centre**.

Our objective of becoming an internationally recognised Centre of Excellence for the development and delivery of advanced therapeutics to the brain is coming ever closer, particularly with funders starting to recognise the need to improve the 'delivery science' or how we physically deliver the therapies to achieve optimum success.

We are working with Welsh Government and Advanced Therapies Wales to access funding ringfenced to support work in pioneering clinical trials and bolstering the NHS's capacity to deliver commercial clinical research. We continue to expand our national and international research collaborations to improve delivery by innovative research.

We very much look forward to starting the new clinical trials in Parkinson's disease and frontotemporal dementia over the coming months, as well as continuing our observational and interventional clinical trials in Huntington's disease and epilepsy.

Professor William Gray
BRAIN Unit Director

Stay in touch

Connecting with us on social media is the best way to keep up-to-date with the latest activity from the BRAIN Unit.

@brainunitwales

brainunitcardiff

The BRAIN Unit

Interested in taking part?

Help influence research by joining our public and patient involvement group, BRAIN Involve.

Please contact us for more information:

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