MRC Human Brain and Nervous Tissue Resource Workshop

Report of a scientific workshop on 26th November 2020, Chaired by Professor Paul Matthews, Chair MRC Neurosciences and Mental Health Board

Introduction

Research involving human brain and nervous tissue remains essential to support cutting edge discovery and translational science, to validate findings from model systems and ultimately advance understanding of human brain disorders. Aligning closely with this, the MRC Neurosciences and Mental Health Board identified research providing 'Insight into the Living Human Brain' as a priority area. To better understand the human brain in detail, there is a need to gain comprehensive knowledge of human neural and glia cell biology, circuitry and function spanning different levels of spatial and temporal resolution.

The research landscape and approaches to using human tissue have evolved considerably over the last decade. These changes have largely been driven by the development of new experimental methods and technologies, the emergence of data-rich platforms and a greater emphasis on interdisciplinary science to accelerate innovation. In addition, the scale and depth of health-related data has expanded exponentially in recent years. This includes the wealth of nationally collated NHS healthcare datasets and large-scale national investments to establish population-based collections such as UK Biobank and the Our Future Health project.

On the 26th November 2020, the MRC held a virtual workshop to explore current and emerging needs that could be addressed through a human brain and nervous tissue resource. The meeting brought together 40 experts in the neurosciences and wider research community across a range of sectors, including academia, industry and neurosurgery together with representation from research charities. The meeting included a series of talks covering international tissue resources to inform participant consideration on approaches to the provision and use of human tissue. During breakout groups, participants identified needs and opportunities where tissue resourcing could help to deliver a step change in understanding the human nervous system and that would enable the UK to maintain a leading international position in this area.

This report summaries the key themes highlighted at the meeting around a human brain and nervous tissue resource that would facilitate innovative research across the breadth of the neurosciences and mental health community.

International human tissue resources and initiatives: Summaries of presentations

The Human Developmental Biology Resource

Professor Andrew Copp, HDBR Co-Director, UCL Institute of Child Health

Key points:

- HDBR is a unique fetal tissue resource for human developmental research that supports tissue users through an ethical, legal and clinical framework
- The resource adopts a flexible approach to sample provision based on researcher needs
- Specialist lab and data services are provided to users such as an in-house gene expression service and 'hotel' facilities to promote collaborations.

The MRC/Wellcome Trust Human Developmental Biology Resource (HDBR) is a centralised fetal tissue bank providing samples from staged embryos and fetuses (4-22 weeks). The bank, operated from two sites (UCL and Newcastle University), facilitates fundamental studies of human development by providing access to ~7000 samples across a variety of developmental stages and tissue types. HDBR has been a valuable source of tissues and sample metadata for researchers globally and for the Human Developmental Cell Atlas, which aims to generate a complete profile of the cell types and states present during development. The resource offers users a range of lab and data services including 'hotel' facilities for collaboration on customised dissections, collection 'to order' and in-house gene expression facilities. HDBR has recently started to offer users access to newer technologies such as spatial transcriptomics.

Lieber Institute Brain and Cell Culture Repository Summary

Dr Thomas Hyde, Chief Medical Officer, Lieber Institute for Brain Development

Key points:

- LIBD was established as an independent institute with a hybrid academic-biotech model
- The LIBD brain repository represents one of the largest collections of human brains for the study of neuropsychiatric disorders
- The institute's cell bank contains living fibroblast lines from clinical samples and post-mortem brains for the generation of patient specific induced pluripotent stem cell lines
- Data resources are made publicly available by LIBD, including genomic datasets from post mortem brain samples analysed as part of the BrainSEQ Consortium.

Founded in 2010, the Lieber Institute for Brain Development (LIBD) is an independent, non-profit research institute that studies basic genetic and molecular mechanisms of schizophrenia and related developmental disorders. Its brain repository holds ~3900 samples with confirmed diagnoses across a spectrum of developmental neuropsychiatric disorders (schizophrenia, bipolar disorder, autism, depression and anxiety disorders). Control brains (~300) represent the most numerous sample type. Tissue collection sites are located across the US, which helps to ensure sample diversity. Tissues are obtained with informed consent and LIBD supports donations with dedicated staff at several autopsy sites. The resource has established living fibroblasts (>1000 cases) for the generation of patient specific iPS cell lines, valuably enabling access to living cells and post-mortem tissues from the same subjects. LIBD participates in BrainSEQ, an early-stage research consortium with pharma to characterise the genetic and epigenetic regulation of transcription across lifespan in neuropsychiatric and control tissues samples. Data from BrainSEQ are publicly available, typically within one year of completion of the data analysis.

The NIH NeuroBioBank: creating opportunities for human brain research
Dr Roger Little, Deputy Director NIDA/NIH, Dr Abigail Soyombo, NIMH/NIH

Key points:

- The NIH Neurobiobank is a federated network of brain/tissue repositories integrated by a centralised IT system, with the goal of increasing access to tissue and data
- The NIH-funded GTEx Project provides an atlas of human gene expression including open access to gene expression data, QTLs and histology images
- Big data science, use of AI/machine learning and better linking data derived from samples were highlighted as some of the key challenges facing tissue resources.

NeuroBioBank is a central resource coordinating brain donation and the distribution of tissue samples to researchers. It brings together six banks with an inventory of ~14k cases, covering neurodegenerative, neurodevelopmental, neuropsychiatric disorders and unaffected controls. The resource adopts shared standards for patient data collection, consent processes, MTAs and aspects relating to tissue processing, storage and distribution. The average request for samples takes 4-8 weeks from initiation to fulfilment. Recently, the resource has been working on revised tissue collection protocols for single cell preparations, which are increasingly in demand. NIH partners with the Brain Donor Project to raise awareness of brain donation and engage with patient advocacy groups. The Genotype-Tissue Expression (GTEx) Project of the NIH Common Fund is an ongoing initiative to establish a data resource and associated tissue bank to study tissue-specific gene expression and regulation. It consists of samples from ~1000 post-mortem donors that undergo various molecular assays including WGS, WES, and RNA-Seq.

Patient Contributions and The Neuro's C-BIG Repository
Dr Jason Karamchandani, Montreal Neurological Institute and Hospital

Key points:

- The Neuro's C-BIG Repository is an open science clinical biological imaging and genetic resource with a longitudinal data collection platform
- It adopts an 'open science' philosophy where all results and data are made freely available at the time of publication
- Research groups that use tissue samples, return data to further enrich the repository
- External collaborations, including those with industry, are conducted in an open capacity.

The Neuro's (Montreal Neurological Institute-Hospital) C-BIG repository (launched 2016) is an open science collection of biological samples, clinical information, imaging and genetic data from patients with neurological disease. The resource has access to more than 30k samples (e.g. DNA, blood, iPSCs, plasma, skeletal muscle) from ~2700 patients and healthy controls, including ~1000 patients with Parkinson's disease. Uniquely, C-BIG has adopted an open transfer agreement with McGill University that has reduced transfer time for participant samples from months to weeks. The resource has access to patient derived cells implicated in disease through the generation of iPSCs that can be used to create organoids in combination with CRISPR gene editing. C-BIG has established a longitudinal data collection platform and has invested substantially in the area of computer science to manage the large data needs of the resource.

ROSMAP: An approach to Cohort-Based Biospecimen Collection
Professor David Bennett, Dep. of Neurological Sciences, Rush Medical College

Key points:

- ROSMAP are longitudinal cohorts of aging and Alzheimer's disease that incorporate brain and tissue donation as a condition of study entry
- Ante- and post-mortem biological samples are collected and used to generate multi-layered omics data to support a novel drug and biomarker discovery pipeline
- Functional validation is carried out via targeted proteomics on brain tissue and using a range of high throughput ex vivo models (e.g. iPSCs RNAi expression, drosophila, CRISPR).

The Religious Orders Study and the Memory and Aging Project (ROSMAP) are longitudinal clinical-pathologic cohorts for the study of aging and Alzheimer's disease. ROS started enrolment in 1994 and MAP began in 1997. Participants (>3,700) are older adults without known dementia that agree to detailed longitudinal clinical evaluations and annual blood sampling. Of these participants, ~20% have developed dementia and ~30% MCI with 1750 brain autopsies performed to date. Brain donation at time of death is a condition of study entry, with spinal cord, muscle and nerve tissue also collected. The resource stores a wide range of samples and data such as post-mortem neuroimaging, serum, plasma, DNA, together with fibroblast and iPSC lines. Assays have been developed for disease phenotyping of AD relevant cell types derived from cohort participants. These include cellular assays (e.g. beta-amyloid uptake), molecular assays (e.g. RNAseq, single cell multiomics) and electrophysiology using multielectrode arrays. The resource promotes the sharing of data and biospecimens through a dedicated resource hub.

Emerging Needs and Opportunities for a Human Brain and Nervous Tissue Resource

Participants were divided into breakout groups to consider emerging needs and opportunities that could be addressed through a human brain and nervous tissue resource. Groups also discussed innovative approaches and technologies that could be employed in the study of human tissue to facilitate a step-change in understanding the nervous system in health and disease.

➢ Deep phenotyping

Cutting-edge approaches need to be exploited to phenotype human tissue at a higher resolution and in a finer grained way. This would include application of single cell approaches and multiomic analytics (e.g. genome, transcriptome, proteome, metabolome analysis) that can integrate across multiple scales and bridge the gap from genotype to phenotype. For example, spatial transcriptomics can be employed to map gene expression directly in tissue sections which can then be correlated with cell morphology and pathology. Importantly, a tissue resource needs to be sufficiently flexible in providing a range of sample preparations (e.g. nuclei suspensions) and tissue collection/storage protocols that are compatible with newer technologies.

The availability of a centralised resource to establish standardised human tissue datasets would be beneficial. Donated samples that had undergone a limited number of analyses (e.g. basic genetic and biomarker analysis) would enrich the information held on tissues. For DNA sequencing data, it would be advantageous to link to pre-sequenced samples from large scale genomic projects. Further insight into the early detection of disease could be harnessed by collecting premorbid samples such as blood plasma or fibroblasts derived from patient biopsies. It was noted that pairing premorbid and post-mortem sample analysis had already been adopted by some centres and groups, however it currently lacked coordination at a UK national level.

- **Promoting access to live/resected tissue**

Widening access to living brain and nervous tissue could lead to a step change in translational neuroscience research. Living human tissue can be obtained from neurosurgeries (e.g., for focal epilepsies, tumour excision, shunt or stimulation electrode placement) and can be applied to a range of techniques including slice cultures, electrophysiology, spatial transcriptomics and live cell imaging. The lack of research detailing the neurological gold standard of fresh surgical samples was noted by participants and represented a key knowledge gap. Additionally, further work on improved understanding of what is considered 'normal healthy' tissue was needed.

Increasing access to living nervous tissue would require greater engagement between neurosurgeons and academic researchers to coordinate aspects such as consent and tissue processing. These collaborations could be facilitated by the creation of training programmes for early career neurosurgeons or related specialities (e.g., neuropathology, neurology) in academic labs. An efficient distribution system would be needed to connect neurosurgical units collecting tissues either directly with research labs or with a central resource enabling multiple technologies to be co-located on a single site. A critical mass of trained tissue processors would need to be formed, who could also collate associated tissue data (e.g. patient MRI data, clinical history etc.) across a network of surgical sites. In addition, consideration would need to be given to addressing ethical and regulatory issues associated with creating an open resource for patient material.

- **Live tissue from organ transplant donors**

Tissues from organ transplant donors were highlighted as a potential route for collection of live samples which could be explored. For a limited number of centres and cases, through collaborations with transplant surgeons, access could be provided to tissues maintained in a physiological state. This could be a resource for obtaining well preserved tissue from regions of the nervous system not easily accessed in traditional brain banks, yet potentially intact in many organ donors, (e.g., spinal cord and peripheral nerves, as well as brain regions that might be preserved). Additionally, these tissues would have extensive historical lifestyle and clinical data recorded as part of the organ donation system. Sampling of different brain regions from donors could be used to perform studies such as the physiological characterisation of neurons across multiple biological scales. Regulations, consent and ethical issues relating to accessing tissue from organ donors for research purposes would need to be carefully considered as part of any future activity in this area.

- **Access to neonatal and adolescence tissue samples**

A key gap identified in the UK was the lack of availability of high quality neonatal/postnatal samples and tissues from children and adolescences, which would be of important for neurodevelopmental research. A 2019 report from the Academy of Medical Sciences[1] had highlighted this issue and noted that the formation of baby and juvenile biobanks could help to promote further understanding of normal development and variation. It was acknowledged that obtaining tissue from these early stages of life was extremely difficult and complicated, given the sensitivities around parents providing consent for the use of tissues for research.

- **Emerging experimental models using human tissue**

Emerging *in vitro* experimental models including recent advances in organoid technology were noted as important approaches for modelling human brain development and diseases. For example, there was significant interest in using organoids as models for pharmacological screening. Employing *in vitro* tissue models for the study of disease pathogenesis would be valuable, as the majority of banked samples are characteristic of end-stage pathology. For a more complete understanding of disease development, data from premorbid samples, cell-derived *in*

[1] The developing brain in health and disease (The Academy of Medical Sciences, 2019) - https://acmedsci.ac.uk/file-download/9487768

vitro models and post-mortem tissue from the same subjects need to be better integrated. For increasing access to iPSC lines, it may be beneficial to partner with established resources such as HipSci that have a range of lines from healthy individuals and patients with genetic disorders.

It was noted that it will be crucial to determine which models can provide key insights over the next decade and to what extent developments in this area can be anticipated. It was agreed that research will be needed to determine how these models can be best utilised and to establish how closely they replicate human tissue, including their suitability to study ageing neurons characteristic of neurodegeneration. Importantly, future approaches to tissue collection and storage will need to be sufficiently agile to enable tissue use across a wide range of models.

- **Development of a platform for sharing data derived from human nervous tissues**

Greater access to data relating to human CNS tissue would have significant impact across the landscape. A nationally accessible data platform could support the integration of large volumes of data generated from deep phenotyping of tissues through 'omics' approaches and linkage to more granular clinical and health-related data. New frameworks would need to be developed to extract key information from the datasets by applying emerging 'big data' approaches (e.g. machine learning and AI). This would require creation of an integrated data management system adopting FAIR data principles, to ensure that research outputs are findable, accessible, interoperable, and reusable. It would be valuable to provide researchers access to health data at scale. It was noted that HDR UK lead an initiative, to develop secure environments for the use of health data for research, which importantly would negate the need to manually transfer clinical data to secure data sites. To enrich data held on tissues an open science approach would be essential, including strict regulations requiring researchers to return raw and processed data derived from samples, ensuring that this information is accessible to the wider scientific community.

- **Linking tissue donation to cohorts**

A key opportunity would be the integration of brain and tissue donation in large population cohorts such as UK Biobank and the 100,000 genomes project. Establishing a separate tissue bank for samples with linked longitudinal data would be valuable and it would prevent highly characterised tissues been used as controls or in method development studies. It was noted that it would be important to ensure that tissue collection was fully representative of the UK population. Additionally, more research integrating a life course perspective was needed to account for positive and adverse exposures (e.g. lifestyle, medications, education), including studies focused on resilience and protection. These studies would require the selection of disease-free cases or older individuals based on genetics. Case control studies of normative brain development combined with increased longitudinal research involving human tissue would also be beneficial.

- **Partnerships with industry**

A future resource would need to consider partnerships to form precompetitive consortia where pharmaceutical and related companies could contribute funding to key resource elements. Collaboration with industry would help to progress objectives with greater scale and speed, while supporting the longer-term sustainability of the resource.

Operational Considerations

- **Consent**

Consent was viewed as a key bottleneck, particularly for the availability of developmental, and some types of adult, tissues, (e.g., brains from people with psychiatric disorders). It was noted that several international tissue resources had streamlined consent process, which had increased tissue donation recruitment rates. Furthermore, resources for a dedicated consent team would help to facilitate consent for post-mortem brain/tissue donation and resected tissues from

surgeries. Greater consideration should be given to understanding tissue donor perspectives and motivations, which could be affected by factors such as disease status and geography. It was noted that the scientific scope and focus of a future resource would likely be limited by the extent of the agreements with donors. Consideration would also need to be given to strategies to promote wider public engagement to ensure that tissue collection was reflective of the national population in terms of gender, age, ethnic, racial, and socio-economic diversity.

- **Tissue quality**

Quality was viewed as a parameter that would need to be maintained from the selection of samples right through to the processing and storage of tissue. Key criteria will be needed to determine sample quality consistent with the intended use. Tissue quality can be maximised by the adoption of standardised protocols for tissue collection, processing and provenance across resources. Promoting the rapid collection of samples to reduce post-mortem delay would be optimal, particularly for studies involving RNA analysis, although taking into account the constraints of the current ecosystem. It was discussed that reducing the post-mortem delay would require engagement with coroners. Differences in systems across the devolved nations (e.g in England coroners operate independently) could result in disparity across the UK, due to varying levels of engagement with individual coroners.

- **Approaches to tissue collection and access**

It will likely remain necessary to prioritise tissue collection, particularly as the range of associated analyses expands. Tissue collection should ideally focus on a limited number of samples that could be maximally utilised and accompanied by good clinical or longitudinal data. Exceptions should be made for tissue from donors with rare diseases (e.g. mutation carriers), even in the absence of associated data. In general, participants agreed that the process for obtaining tissues needs to be streamlined and importantly, dissection protocols need to be tailored to requirements of the science and technologies employed currently and in the future.

Tissue collection and analysis should be seen in a ‘whole person’ context and extend beyond investigating the brain in isolation. The collection of peripheral tissues in parallel needed to be considered (e.g. gut in Parkinson’s disease, skin for stem cell derivation). Normal/healthy ‘control’ brain samples were noted as difficult to obtain, however represented one of the most important sample types. A future resource should provide tissue samples that are representative of the UK population, particularly in terms of ethnicity, age and gender, however also across disorders and different life stages. It would be important to consider what criteria would be used to determine acceptable inclusiveness and representation, given that a strategy to sample tissues from a population cohort at scale would be expensive to implement.

Summary

The following core themes and opportunities were identified at the workshop.

Data availability

Increasing access to data related to human tissues at a UK national level was identified as an important priority. This could be achieved by establishing a common data platform for human brain and nervous tissue to integrate large volumes of data generated from samples and linked to tissues indexed by genetics, clinical history and related data. A common cloud analysis environment and access to data tools would enable bioinformatics to be conducted at scale and across interlinked studies. Critical to enabling this would be a common national approach to the ethics of consent, tissue collection and data sharing and approaches to information governance.

Research on living human tissue

Promoting access to neurosurgically resected tissue was acknowledged as important. Closer engagement between neurosurgery and academic research would increase capacity in this area and enable new avenues of scientific investigation to be pursued. Further research on the neurological gold standard of living tissue was needed in comparison to post-mortem samples.

Emerging experimental models

Opportunities exist for employing new and evolving models of human brain development and disease to accompany the study of human post-mortem tissues. These include cerebral organoids and iPSC lines derived from post-mortem or premorbid tissues. Additional research will be required to determine the best approach for utilising these models and in which areas they can add the greatest value.

Deep phenotyping

Newer technologies such as single cell approaches and multiomic analytics need to be employed more widely to increase the resolution of data available on human tissues and to integrate across multiple biological scales. For a more complete understanding of disease initiation, data from premorbid samples, cell-derived models (patient specific) and post-mortem tissues need to be better linked.

Incorporating tissue collection within deeply phenotyped population cohorts would be an important opportunity and would enable new data linkages to be formed. It would build on existing UK strengths, including the availability of large population cohorts with extensive longitudinal datasets and the potential to link with clinical data.

Centralised resource model

A federated tissue resource model would allow specialist capabilities to contribute maximally at a national level. It would enable shared standards to be adopted in areas such as tissue quality and sample and data access (e.g. material transfer agreements), together with the harmonisation of consent and the collection of common data elements relating to tissues.

Annex 1 - Workshop Participants

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