QUEEN SQUARE BRAIN BANK

UCL

Brain Matters 2022

The newsletter from Queen Square Brain Bank for Neurological Disorders

Welcome

Professor Tom Warner, Head of Queen Square Brain Bank welcomes you to Brain Matters 2022:

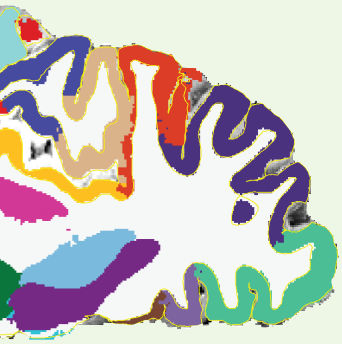
The last few years have been extremely challenging for everyone and the Queen Square Brain Bank has been no exception. As the NHS came close to being overwhelmed, it was almost impossible to organise brain donations and we were regrettably unable to honour our commitment to a number of donors. When circumstances gradually improved, work in the laboratories progressed and tissue retrieval became achievable.

Despite restrictions, research has continued with a good output of significant publications in scientific and medical journals. This edition of Brain Matters highlights some of the important accomplishments in advancing knowledge of neurodegenerative conditions such as Parkinson's disease, multiple system atrophy, fronto-temporal lobar degeneration and Alzheimer's disease.

Also on a positive note, we recently appointed a much-needed neuropathologist after the retirement of **Professor Janice Holton**, the pandemic having hindered recruitment. I am pleased to announce that **Dr Karl Frontzek** will be joining the team from the University of Zurich and will work alongside **Dr Zane Jaunmuktane** who has performed heroically as the lone neuropathologist during this taxing period.

Another piece of good news is the richly deserved promotion of **Dr Rina Bandopadhyay** to Principal Research Fellow. Rina is a scientist of long-standing who has focused her studies chiefly in the field of Parkinson's disease. She also has a commendable record in the training and supervision of students, many of whom have established successful careers in science.

I sincerely hope that 2022 will be a better year for us all and a period of renewed vigour at the Queen Square Brain Bank. As always, we remain deeply indebted to all our donors and families for their generosity and understanding at this difficult time. We are also grateful to our sponsors and those who have made financial contributions to support the brain bank, without which we would be unable to continue as a vital global resource for research into neurodegenerative disease.



"I sincerely hope that 2022 will be a better year for us all and a period of renewed vigour at the Queen Square Brain Bank. As always, we remain deeply indebted to all our donors and families for their generosity and understanding at this difficult time."

Research

Alex Bampton, a Leonard Wolfson and Eisai funded PhD student, is studying neurodegeneration with Professor Tammaryn Lashley, QSBB Director of Research:

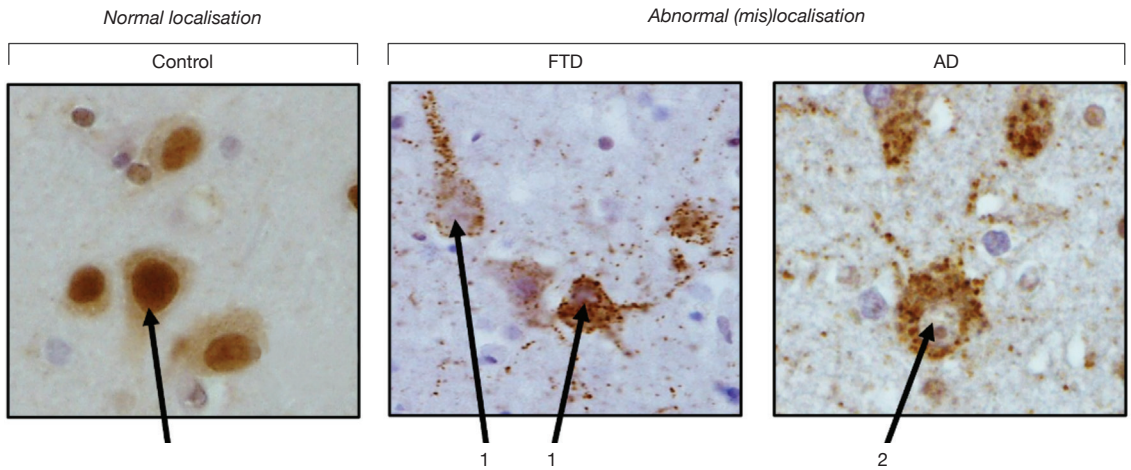
Genes within our DNA contain the instructions to make all the body's proteins that are necessary to sustain life. Machinery within our cells decodes these instructions (transcription) and then makes proteins (translation). A large amount of energy and a sophisticated system of checks and balances are required to finely regulate these functions to ensure they run smoothly. Processes can become corrupted and are commonly associated with many diseases, especially neurodegenerative. Cells in the adult brain called neurons are particularly vulnerable due to their high energy demands and reduced capacity to regenerate.

My PhD centres around a particularly important protein in this network called hnRNP K found predominantly in the nucleus, the part of the cell containing the DNA code. By examining post-mortem brain tissue, we have identified two entirely new pathological findings. Firstly, that in illnesses such as Alzheimer's disease and frontotemporal dementias, hnRNP K is displaced from its normal location in the nucleus and is detected in a depleted form in the cytoplasm, the part of the cell surrounding the nucleus. Secondly, by comparing with 'control' tissue from donors without a neurological condition, we also observed the occurrence in the aged brain, although not to the same extent. This suggests abnormal protein localisation, seen as part of ageing, is accelerated in disease.

Findings indicate that when hnRNP K can no longer perform its usual task because it is depleted and in the wrong place, this may cause the build-up of products that are potentially toxic to the brain. Our work is largely exploratory in aiming to investigate the wider role of the protein, which until now has only been intensively studied in cancer, and understand the underlying mechanisms of neurodegeneration and ageing. Through gaining a fuller appreciation of the consequences of hnRNP K nuclear displacement, we may be able to pinpoint fresh targets for therapeutic development.

Images (below) show location of hnRNP K in control and neurodegenerative disease tissue.

From left-right: Control brain exhibiting normal (nuclear) location of hnRNP K. Frontotemporal dementia (FTD) and Alzheimer's disease (AD) brain, by contrast, exhibit marked nuclear depletion of hnRNP K and accumulation (mislocalisation) of the protein within the cytoplasm.



Dr Zane Jaunmuktane, Clinical Lecturer and Consultant Neuropathologist and Professor John Hardy, Chair of Molecular Biology of Neurological Disease at the UCL Institute of Neurology have received funding from the Aligning Science Across Parkinson's (ASAP) initiative, in partnership with The Michael J. Fox Foundation for Parkinson's Research. The team include Dr Alice Rockliffe, Post-doctoral Researcher and Maria Afentakis, Research Assistant, and the aim is to understand the causes and progression of Parkinson's disease.

Parkinson's disease is a progressive condition of neurodegeneration which can cause a variety of symptoms, typically including tremors, stiffness and slowness of movement. Currently there are no reliable measures to track its advancement in the brain and clinicians therefore rely on monitoring symptoms through observation and examination. Treatments can alleviate the symptoms, but do not slow the course of the illness.

By utilising the extensive resources at Queen Square Brain Bank, which holds over two thousand clinically and pathologically characterised brains with degenerative movement disorders, the group are seeking to establish the reasons for the spread of pathology and which factors influence this.

Dr Jaunmuktane explains "The progression of Parkinson's disease is very variable, with some individuals experiencing a rapid course whilst others have a more gradual one. Our goal is to find and understand the mechanisms and genes involved in this variability. By developing a comprehensive model of the biology of progression we hope to find new approaches to treatment.

We have already found that genetic changes (mutations) in a specific protein involved in the maintenance of cells called GBA, leads to a rapid disease course. Also, mutations in another protein LRRK2, which is linked to familial forms of Parkinson's, negatively affects the course of a parkinsonian-type condition, progressive supranuclear palsy. The team will test whether regulating the levels of the proteins experimentally influences the course of pathology and see if this approach has value for therapies in the future."

Dr Conceição Bettencourt, Senior Research Fellow, continues her investigations into the pathology of multiple system atrophy:

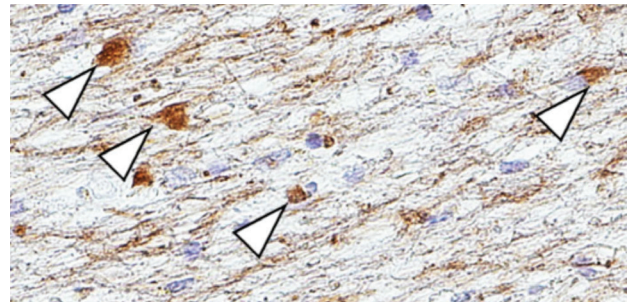
Multiple system atrophy (MSA) is a neurodegenerative illness causing balance difficulties, slow movements and stiffness. At present there are no effective treatments to halt or delay the disorder. Lumps of a sticky protein called alpha-synuclein form in brain cells of affected individuals, leading to nerve cell death in certain parts of the brain. Building on the findings of our recently published work, which highlighted the significance of two other proteins associated with MSA called MOBP and HIP1, we decided to look in more detail.

In multiple system atrophy some brain regions such as the cerebellum, which is responsible for balance, are markedly affected by pathology and show a high number of typical sticky alpha-synuclein lumps whilst other areas are relatively spared. In order to assess the amount and location of MOBP and HIP1 in cells, a comparison was made of tissue samples with advanced disease to samples with mild or no disease.

Microscopic analysis revealed that the quantity of those proteins changed with MSA disease progression and interestingly, there were less in the cerebellum than seen in other neurodegenerative conditions. In MSA, MOBP and HIP1 are often misplaced and trapped in the typical sticky alpha-synuclein lumps, and their ability to function normally is reduced. We believe this is connected to changes that lead to nerve cell death.

Dr Megha Murthy, Research Fellow has recently joined the group and will continue this line of study. Identifying new protein partners of alpha-synuclein in MSA could help to explain disease processes and inform researchers of additional possibilities for therapeutic development.

Image (below): Microscopic view of brain tissue with multiple system atrophy showing white arrowheads pointing to sticky lumps containing MOBP (in brown).



Q&A

Dr Patrick Cullinane, Neurologist and Clinical Research Fellow joined Queen Square Brain Bank in 2019 to commence a PhD in Parkinson's disease:

What inspired you to become a neurologist?
My interest in neurology started in medical school when I was fortunate enough to help with a project investigating patients with tremor. In my early training I was intrigued by the broad spectrum of neurological conditions, ranging from the commonplace to the rare. Reaching a diagnosis often hinges on carefully listening to a person's story and detecting clues from the examination. Observing experienced colleagues skilfully making sense of seemingly complicated issues is always inspiring.

How long did it take to get to this position?
Over 13 years and counting! I still have a couple more until I finish training.

What is the most interesting aspect of your work?
Studying at QSBB has given me the time and opportunity to really consider clinical presentations in a completely different light. Researching the molecular pathways involved in disease has been particularly fascinating and learning the techniques used in the laboratory to explore these for myself is exciting.

Are we nearer to unravelling the mysteries of Parkinson's disease?
There have been numerous important discoveries made since Parkinson's disease was first described in Dr James Parkinson's '*Essay On The Shaking Palsy*' in 1817. The genetic basis of the disorder and factors that influence an individual's risk of developing it are now better understood. While undoubtedly a complex illness, I think if research continues with the same persistence, it is only a matter of time before breakthroughs are converted into new treatments, even before the mysteries are fully unravelled.

When you are not seeing patients and doing your research, what do you enjoy?
An unforeseen benefit of coronavirus restrictions has been discovering the joys of running which I find helpful for relaxation. Since moving to London from Ireland, I have joined a five-a-side football team and play (poorly) every week. Like others, I look forward to travelling again and would like to visit my brother in New Zealand.

Contributors

Top row (left to right):
Dr Zane Jaunmuktane, Dr Alice Rockliffe, Maria Afentakis.

Middle row:
Dr Conceição Bettencourt, Dr Megha Murthy, Alex Bampton.

Lower row:
Professor Tammaryn Lashley, Dr Patrick Cullinane, Karen Shaw, Brain Bank Nurse and editor of *Brain Matters*.

Donations




Coordinators (left to right):
Top row: Lynn Haddon, Cheryl Pearce.
Lower row: Robert Courtney, Natalie Woodman.

Brain donation coordinators

QSBB Administrators, **Lynn Haddon** and **Cheryl Pearce** are often the first point of contact for potential donors. Coordinating the brain donor scheme with help from Laboratory Technicians **Robert Courtney** and **Natalie Woodman**, the team work closely with relatives, hospital staff, funeral directors and couriers, to ensure the careful donation and safe receipt of tissue with the minimum of distress to families.

The importance of controls

We encourage people without a neurological condition, 'controls' to register with our donor scheme. Control tissue is vital for comparison with disease and provides researchers with an understanding of the normal appearance and function of the brain.

If you would like further information please log on to the website: www.ucl.ac.uk/ion/qsbb Or contact Lynn Haddon l.haddon@ucl.ac.uk and Cheryl Pearce cheryl.pearce@ucl.ac.uk on 020 7837 8370.

Brain banking

Brain banking is expensive and we continue to depend almost entirely on charitable benefactions for our survival. The QSBB is primarily funded by donations from the Reta Lila Weston Institute of Neurological Studies. We gratefully acknowledge the generosity of donor families, sponsors and several benefactors.

If you would like to offer a financial donation to help our research, please visit our website: www.ucl.ac.uk/ion/qsbb or contact Lynn Haddon.

Thank you.

Sponsors

UCL Queen Square Institute of Neurology

Reta Lila Weston Institute of Neurological Studies

Multiple System Atrophy Trust

The Multiple System Atrophy Coalition

Alzheimer's Research UK

Alzheimer's Society

Rosetrees Trust

The Michael J. Fox Foundation for Parkinson's Research

The Wolfson Foundation

European Research Council under the European Union's Horizon 2020 Research and Innovation Programme

The International Concussion & Head Injury Research Foundation

Aligning Science Across Parkinson's (ASAP)

QS BB

Front and inside cover images by Dr Eugenio Iglesias Gonzalez and team, depicting high-resolution 3D magnetic resonance images of brain hemisphere with regions overlaid.