PET imaging: changes in cerebral protein synthesis rates in AD

Team members involved with the project but not funded by DPUK
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Location(s):
Cambridge University

Objectives
This study will test our hypothesis that reduction in CPS rates occurs in AD, similar to findings in animal models.
We will use PET-derived CPS rates as an indicator of UPR-mediated translational failure - or lack of it - in AD. This will provide evidence needed to inform whether to pursue clinical trials with repurposed drugs targeting the UPR for the treatment of AD.

Dependencies to and from other work packages, networks and themes
N/A

Overall objective(s):
1) To test the hypothesis that reduction in cerebral protein synthesis (CPS) rates occurs in Alzheimer's Disease (AD)
2) To validate findings in animal models that UPR over-activation causes reduced CPS leading to synaptic failure and neurodegeneration.
3) Specifically, to use PET-derived CPS as an indicator of the unfolded protein response (UPR)-mediated translational failure- or lack if it- in AD.
4) This work will provide evidence on the feasibility of clinical trials with repurposed drugs targeting the UPR for the treatment of AD.

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective 1:				
D1.1 11C-Leucine at GMP grade available for routine use at the WBIC.		M1.1.1 Complete		FA, TF, IB, GB, SS
Objective 2:				
D2.1 Applications submitted in September 2016 to REC, HRA, ARSAC approved		M2.1.1 Complete		GM, JO'B, BU
Objective 3:				
D3.1 To have undertaken a pilot PET imaging study in 10 males, 10 females with early AD, together with and age and sex matched controls	M3.1.1 Maps of CPS rate (rCPS) from dynamic PET and blood data	M3.1.1 Dec 2019		GM, FA, TF, JO'B, BU, ES
Objective 4:				
D4.1 Decision regarding whether larger study should be undertaken or whether a clinical trial would be feasible		M4.1.1 Mar 2020		GM, JO'B, TF, FA, BU

Updates on delivery against milestones since last report:
Objective 3:
We have successfully measured CPS rates using 11C-leucine PET imagining in 3 (control) participants, however, due to critical faults in radiolabel synthesis equipment, we have not been able to complete this milestone. New parts for this aging equipment had been installed in January 2020 and a complete new system was due in March/April 2020 which would have allowed for larger scale and more reliable radiotracer synthesis. Unfortunately, due to Covid-19, we are unable to complete this study at present. The current situation means all systems upgrades have been postponed; all radiotracer production and PET scanning has been haltered; and we are unable to consent new participants.
Objective 4:

The initial scans from the control are very promising and show that CPS rates can be successfully measured in participants using 11C-leuicne PET. Although we don't currently have enough data currently to determine if a larger study is needed, we are already planning further experimental studies which will involve investigating if trazodone can alter protein synthesis rate in patients (''SuperD2''), and a clinical trial for trazodone (''SuperD3'').

Summary of plan to deliver on outstanding work

Complete objective 3:

- scan all AD patients and aged match healthy controls (within 2-3 months post upgrade of radiosynthesis equipment)
- analyse all data (within 1 month of finishing scans)

Due to the on-going covid-19 situation we are unable at present to give an accurate timescale for when the radiosynthesis equipment will be upgraded, however, we hope that this will take place in the summer (2020) and we will able to complete the study 3-4months after this point

Risks	**Mitigation**
1) On-going Covid-19 situation results in current participants no longer able to be included in the study	1) Clinical fellow will continue to identify potential participants that can be consented rapidly once the study resumes
2) Delays installing new equipment and delays in radiotracer production	2) A new system will be installed as soon as possible, extra staff may be recruited in order to ensure tracer production is not delayed
3) Backlog of studies delaying prompt scanning of remaining participants after study resumes	3) Additional scan time for this study has been agreed once production of the radiotracer has recommenced in order to get all participants scanned.

Please tell us the most successful outcome and what it means to dementia research

We have successfully produced GMP grade ^{11}C-Leucine and scanned the first elderly participants, with excellent results. This is crucial validation of the methodology of this study. Once completed, the study will provide the evidence on protein synthesis rates in brains of patients compared to controls which will 1) support pursuing clinical trials with repurposed drugs targeting this pathway for the treatment of AD, and 2) provide the first mechanistic biochemical pathway biomarker of treatment efficacy

Further, we have received two major philanthropic donations based on this work which are contributing to the 1) experimental medicines studies deriving from this and 2) provide salaries for clinical team to deliver this study and related ones (see further funding below).

Lessons Learnt

We have learnt a number of lessons throughout the project including:

- the difficulty of ^{11}C-leucine production. The unexpected difficulty of producing the key radiochemical precursor needed to produce GMP grade ^{11}C-leucine meant protocols had to be optimised before scanning could commence resulting in delays to the study
- the need for a dedicated clinical research team. Having a dedicated clinical team has benefited the study by ensuring that all regulatory approval was obtained, and participants were found and recruited efficiently.
- the importance of frequent meetings. Regular meetings of the entire team from clinicians and research nurses to scientists and radiochemists has helped maintain momentum and enthusiasm despite challenges.

Outcomes

ENGAGEMENT ACTIVITIES

by Giovanna Mallucci:

May 2020 Hay Science Festival, Hay-on-Wye

Feb 2020 Old Age Psychiatry Meeting, Newmarket
May 2019 Alzheimer's Research UK, Anglia Ruskin University, Cambridge
Apr 2019 Cambridge Festival of Science, Cambridge
Feb 2019 Dementias Conference 2019, London
Jan 2019 Guest Speaker, VIII Futures Congress, Santiago, Chile

FURTHER FUNDING

DPUK pilot funding has been successful in leveraging an addition £3.7m to support the group's work in this area. We have received two major philanthropic donations contributing to the experimental medicines studies we are performing in this area:

- £2.5M of £15M (anonymous donation) to fund the Cambridge Centre for Parkinson's Plus – (£2.5M for my programme, which includes an experimental medicines study that will follow on from this DPUK-funded study). This donation was inspired by the discovery of trazodone in UPR manipulation (Halliday et al., *Brain,* 2017). The Centre includes clinical and basic research programmes, including experimental medicine studies: PET imagining of cerebral protein synthesis rates in Parkinson's Plus disorders and early clinical trials with trazodone.
- £1.2M from Kara Gnodde/Goldman Sachs Gives UK to fund a new *Translational Neuroscience Unit* – linked to the Cambridge UK-Dementia Research Institute. The Translational Neuroscience Unit will bridge the gap between bench and bedside and accelerate the translation of scientific discoveries into new treatments for dementia. The Unit consists of a full time Senior Clinical Trials expert, a Clinical Research Fellow and Trials Nurse, and is already involved in this DPUK funded experimental medicines study.

Project narrative

This pilot study of 10 AD patients and 10 aged-matched controls will use established, validated ^{11}C-leucine Positron Emission Tomography (PET) to measure cerebral protein synthesis (CPS) rates in patients with early but established AD and age-matched controls. It will address whether in AD, as in mouse-models, protein synthesis rates are reduced. The results will potentially provide the evidence as to whether it might be fruitful to pursue clinical trials with repurposed drugs targeting CPS [and more specifically the unfolded protein response (UPR)] for the treatment of AD.

To date, we have successfully developed and validated the radiosynthesis methods for GMP grade ^{11}C-Leucine. 13 participants (6 AD and 7 healthy controls) for the initial scans have been recruited and further recruitment is ongoing. Importantly, scans of the first control participants have been undertaken and have shown good penetrance of the radiotracer (see Figure 1),in spite of delays due to the upgrade of the Cyclotron in January/February 2019 and unavailability of the radiotracer during June-August 2019.

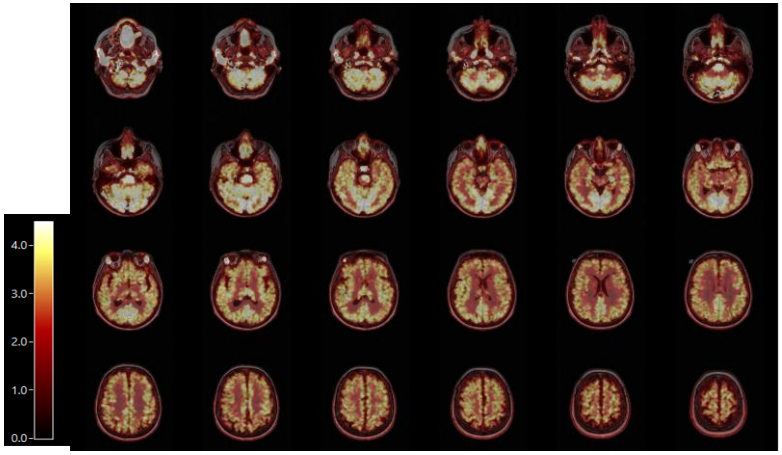

Figure 1: 11C-Leucine PET images of 73-year-old age-matched non-demented control
Signal depicts rates of cerebral protein synthesis (rCPS). Pattern of protein synthesis, including high rates in cerebellum are consistent with published data in young patients. (Aigbirhio, Fryer et al; unpublished).

The study has been further delayed by equipment breakages and scanning was due to recommence in March 2020. However, due to the Covid-19 situation, installation of critical equipment has not been possible and we are unable currently to scan participants. We are planning for this vital equipment to be upgraded and the study resumed as soon as the current 'lockdown' has lifted (see above, 'Summary of plan to deliver on outstanding work').

The DPUK pilot funding has been successful in leveraging an addition £3.7m to support the group's work in this area (see 'further funding' above). We have established the Kara Gnodde Goldman Sachs Translational Neuroscience Unit at the University of Cambridge to accelerate and facilitate translational studies in humans. This is being led by newly recruited senior clinical triallist Dr Ben Underwood who is a consultant old age psychiatrist. We have also recruited a Clinical Fellow, Dr Emad Sidhom, and a Trials Nurse, Vince Mlilo. With Dr Underwood's expertise, we are recruiting participants for our 2nd experimental medicines studies to measure CPS rates using ^{11}C-leucine PET in patients' study with trazodone ("SuperD2"). Further, initial ethical and study protocol approval is currently under review for "SuperD3" (clinical trial for trazodone).