PET imaging: changes in cerebral protein synthesis rates in AD
Start date: 1 Nov 2016. **Completion date: Mar 2020**

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, TFI B, 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, new clinical fellow, JO'B, TF, FA, BU
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, new clinical fellow, JO'B, TF, FA, BU

Updates on delivery against milestones since last report:

M3.1.1 Pilot study of 20 participants.

13 participants (6 AD and 7 healthy controls) for the initial scans have been recruited and further recruitment is ongoing. Scans of the first 3 participants have been undertaken. The first scan was unsuccessful due to 'tissueing' of the radioligand but the second and third were successful with excellent images for quantitation of rCPS rates.

Since then, all scans have been on hold due to equipment breakage for radiosynthesis. This is a major issue that requires installation of new equipment.

The upgrade is due to be completed by early February 2020 with production of the radiochemical due to start soon afterwards.

This is out of our control but we will finish this study as possible.

Summary of plan to deliver on outstanding work (with dates)

- To continue scanning on AD patients and aged match healthy controls
- To scan all participants by 31st March 2020
- To analyse all data by end of May 2020

Risks	Mitigation
1) Equipment breakages and delays in radiotracer production	1) A new system is being installed
2) Not all 20 participants will be scanned in time	

	2) Discussion are on-going to allow additional scan time for this study once production of the radiotracer has recommenced in order to get all participants scanned by the end of March 2020.

Team members <u>funded</u> (full or part-time) by DPUK None

Team members involved with the project but <u>not</u> funded by DPUK

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Outcomes

The project is not at the stage of producing publication outputs but should be by Spring/Summer 2020.

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, 13 participants (6 AD and 7 healthy controls) for the initial scans have been recruited and further recruitment is ongoing. Scans of the first participants have been undertaken in spite of delays due to the upgrade of the Cyclotron in January/February and unavailability of the radiotracer during June-August 2019. Scanning has now been further delayed by equipment breakages and is due to recommenced in February 2020. We anticipate the majority of participants to be scanned by the end of March 2020. Data analysis will be undertaken by June 2020.

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:

1. £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.
2. £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.