EM 3 – Complete

EM 3 – Multi-Modal Imaging **Start date:** Nov 15.	**Completion date:** 2Q 2018
Team members Paul Matthews Paul Edison, Ashwin Vankataraman	
Objectives This proof-of-concept study will characterise the brain uptake of the novel astroglial activation imaging marker, [11C] BU99008, in AD subjects compared to non-AD control subjects. Relationships between [11C]BU99008 brain uptake, Abeta deposition and brain glucose metabolism will also explore how multi-modal imaging indices may inform. 1. To test whether the uptake of a PET astroglial activation tracer ([11C] BU99008) is increased in the brains of people with mild to moderate AD relative to age-matched healthy volunteers 2. To assess the correlation of PET-detected astroglial activation with regional reduction in FDG uptake 3. To assess whether PET-detected astroglial activation co-localises with Abeta deposition.	**Dependencies to and from other work packages, networks and themes** Work catalysed by DPUK leadership for the MRC MRI-PET infrastructure development and the DPUK PET Imaging Network

Lessons Learnt (what went well, what did you have to change)

- The radiotracer needs further biological target data and development of a stronger capacity for cellular resolution post mortem tissue autoradiography would add confidence to new tracer/new target work
- Recruiting people with Alzheimer's disease for complex PET studies remains challenging because of the need for large populations to select those meeting study criteria and willing to consent
- Costs for advanced PET with novel radioligands are high and remain limiting; a fundamental advance in methods is needed to lower cost by ~5 fold

Where all Milestones completed Y/N

(please elaborate on any issues and the mitigation put in place)

Additional analyses were performed for assessment of pathologically increased radioligand uptake preceding amyloid deposition and for understanding its relationship with structural and functional measures of brain connectivity. This initial work was performed. Follow up with cellular resolution methods would be ideal.

Additional analyses were requested as part of the review process for publication. This was recently completed and now is being confirmed. With acceptance of the report of the study the annotated data and modelled images will be made available through the DPUK Imaging Portal.

Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective1:				
D1.1 Assessment of increase in radioligand volume of distribution in brains of people with AD and in healthy Volunteers age matched	M1.1.1 Completion of sufficient scans in patients to test hypothesis of difference	M1.1.1 Complete	None	Paul Matthews (Paul Edison)
Objective2:				
D2.1 Assessment of correlation between regional FDG and [11C] BU99008 update	M2.1.1 Complete set of scans for both FDG and 11C BU99008 for people with AD	M2.1.1 Complete	None	Paul Matthews (Paul Edison)
Objective3:				
D3.1 Assessment of correlation between regional amyloid and [11C] BU99008 uptake	M3.1.1 Complete set of scans for both amyloid and [11C] BU99008 for people with AD	M3.1.1 Complete	None	Paul Matthews (Paul Edison,

				Ashwin Vankataraman))

Outcomes

This project was completed in 2Q18. Preliminary reports were presented at the AAIC Meeting, Chicago, July 2018, both of which cited the DPUK support. These represented first reports of the use of this novel radioligand, developed at Imperial College and with Invicro, in people with Alzheimer's disease:

1. *Relationship between astrocyte activation using [11C]BU99008 PET, glucose metabolism and amyloid in Alzheimer's disease: A Dementia Platform UK experimental medicine study*
   Fan Z, Calsolaro V, Myers J, Tyacke RJ, Venkataraman A, Femminella GD, Perneczky R, Gunn R, Rabiner I, Matthews PM, Nutt D, Edison P

This study demonstrated a voxel-level correlation between [11C]BU99008 PET measuring astroglial metabolism consistent with astroglial activation and glucose metabolism in patients with AD/MCI subjects. The demonstration of positive and negative correlation between astroglial activation and cerebral glucose metabolism suggested that astroglial activation is heterogenous across the AD brain.

2. *Evaluation of novel astrocyte marker [11C]BU99008 PET in Alzheimer's disease: A Dementia Platform UK experimental medicine study*
   Calsolaro V, Myers J, Zhen Fan, Tyacke RJ, Venkataraman A, Femminella GD, Perneczky R, Gunn R, Rabiner I, Wren P, Parker C, Murphy P, Matthews PM, Nutt D, Edison P

This study confirmed the potential of the [11C]BU99008 PET tracer to detect differences in astroglial metabolism consistent with activation between healthy volunteers and people with AD. The higher uptake in the amyloid positive population compared to the amyloid negative and the HCs is consistent with recognised roles for astrocyte activation in AD, e.g., for clearing Aβ deposition.

A first full report from the study is being prepared for submission in late Nov 2018:

3. *Relationship between astroglial activation detected by novel [11C]BU99008 PET and amyloid deposition in subjects with cognitive impairment*
   Calsolaro V, Matthews PM[,,] Myers JFM[,] Fan Z, Tyacke RJ, Venkataraman A, Femminella GD, Perneczky RN, Gunn R, Rabiner EAI[4] Gentleman S, Parker CA[,] Murphy PS, Wren PB, Hinz R, Nutt D, Edison P

The aim of this study was to assess the [11C]BU99008 uptake in subjects with cognitive impairment, and to assess the relationship between [11C]BU99008 uptake and amyloid load, evaluated using [18F]florbetaben. Twenty-one subjects (11 patients with cognitive impairment (AD or mild cognitive impairment (MCI)) and 10 age-matched healthy controls) were studied. The [11C]BU99008 analysis showed significantly higher tracer uptake in the disease group compared the healthy controls in frontal, parietal, temporal and occipital cortices. Individually, seven patients also demonstrated clusters of significantly higher [11C]BU99008 uptake compared to controls at voxel-level. Of these seven, six also were amyloid positive. The sub- group of amyloid-positive subjects demonstrated significant increase in [11C]BU99008 uptake compared to the controls; there was a positive correlation between [11C]BU99008 binding and amyloid load at voxel-level. Together, this work comprehensively describes the first use of this novel tracer in people with dementia, drawn from a DPUK-associated cohort. The study demonstrated that [11C]BU99008 PET tracer uptake is able to define an increase in brain astroglial activation especially in amyloid positive cognitively impaired subjects. The significant voxel-level correlation between amyloid load and astrocyte activation suggests the inter-relationship between these two processes.

The initial peer review of the report suggested further analyses which now are completed and being checked.

Executive Summary of Project

The imidazoline I_2 binding sites (I_2-BSs) are widely distributed in the brain, but found principally on glial cells, where they appear to have a functional role in astrocytes. [^{11}C]BU99008 is a novel PET tracer selective for I_2-BSs. The aim of this study was to evaluate [^{11}C]BU99008 uptake, a novel marker of glial activation, in subjects cognitively impaired (AD, Mild Cognitive Impairment –(MCI)-) and age-matched controls. With the novel [^{11}C]BU99008 PET tracer, we provided new *in vivo* evidence for an increased I_2 uptake in people with AD/MCI, potentially predominantly reflecting astroglial activation. The increased uptake was widely distributed in grey matter, where it was associated with amyloid deposition.

EM3 End Report.pdf