[Nicotinic acetylcholine receptor agonists for the diagnosis of ageing-related cognitive decline]

[Ageing and Digital Technologies]

**Supervisory Team**
- Dr Michael A. Carroll, School of Chemistry, http://www.ncl.ac.uk/chemistry/staff/profile/michael.carroll
- Dr Mohammed Shoaib, Institute of Neuroscience, http://www.ncl.ac.uk/ion/staff/profile/mohammedshoaib.html#research
- Dr Ed Robins, Singapore Bioimaging Consortium, A*STAR
- The Lead Supervisor is Early Career or newly hired Staff ☐

**Key Words**
1. Dementia, Cognition, Medicinal Chemistry, Medical imaging.

**Overview**
Dementia currently affects 850,000 people in the UK, and this is expected to rise to over 1 million by 2025 and 2 million by 2051. That’s 225,000 people who will develop dementia this year – one every three minutes [1]. Dementia typically affects older people and may include memory loss, this age-related cognitive decline involves transient deficits in cholinergic function mainly in cortical regions of the brain [2]. Dementia describes a constellation of cognitive symptoms, with a decline from the previous state, sufficient to impair the ability of a patient to live a normal life. With the secular trend of ageing in the population, dementia is becoming more frequent.

A great deal of attention has focussed upon the protein β-amyloid peptide (βA) in dementia which is believed to be responsible for synaptic dysfunction and memory loss as well as the later stages of the disease [3]. However, the sequence of events prior to the accumulation of βA is much less well understood, as is detecting the early stages of memory loss. The opportunity to detect and diagnose the early onset of cognitive impairment using non-invasive imaging techniques offers great potential in improving the quality of life for the ageing population via more effective therapeutic interventions, at a time when neuronal loss is less catastrophic. Currently, dual modality PET is the most advanced in vivo imaging technique for brain receptors implicated in a range of neurological conditions and as such offers significant potential in understanding the physiological and pathological processes of various diseases in the CNS.

The proposed PhD will develop selective nicotinic acetyl choline receptor (nAChR) agonists, guided by their effect on cognition, with the view to the development of a PET imaging agent suitable for use with patients. The project objectives are:

1. To develop fluorinated derivatives of selected nAChR agonists suitable for fluorine-18 radiolabelling.
2. To evaluate the lead compounds in a pre-clinical behavioural cognitive task.
3. To prepare the necessary PET precursor and associated standards to establish a GMP compliant QC protocol.

**Methodology**
Successful translation of nAChR imaging to routine clinical practice has been impeded by the absence of suitable PET agents. To address this unmet clinical need the main impetus of the project is to develop a PET imaging agent that has optimal characteristics of affinity and selectivity for the α7 nAChR subtype coupled with the necessary pharmacokinetic profile associated with the use of short-lived radioisotopes.

To date, there are no studies that have established how the number of α7 nAChRs varies during the
ageing process or in patients with Alzheimer’s disease or their relationship to other nAChR subtypes such as α4β2. The relationship between this receptor and the neuropathological features such as neurofibrillary tangles and accumulation of βA is also unknown.

Year 3: Training/familiarity in pre-lead compounds.

Year 1: Literature review, preparation and in competitive studies with SBIC and associated publication. Thesis preparation and conference presentations.

Year 4: Completion of pre-clinical studies and evaluation of radiochemistry/pre-clinical imaging options with SBIC. The student will also benefit from the interaction with the pharmaceutical/biotech industry.

Training & Skills
The student will primarily be based in the Radiochemistry Group in the School of Chemistry with sometime spent in the Institute of Neuroscience and SBIC as the project progresses. The student will engage in regular research group meetings, developing research skills and broadening their knowledge of synthetic/ medicinal (radio)chemistry to encompass other methodologies and therapeutic areas, in addition to training in pre-clinical studies. The students Personal Training Programme will ensure that they receive the necessary technical and research skills to support their development as an independent researcher. The student will also benefit from the

Timeline
Year 1: Literature review, preparation of initial nicotinic agonists 1a and 1b (α7).

Year 2: Expand portfolio of nicotinic agonists (2a/2b-α4β2 and SSR180711A-α7). Evaluation/selection of lead compounds.

Year 3: Training/familiarity in pre-clinical behavioural studies to assess cognition. Preparation of PET precursors and QC standards plus a paper on data collected in Y1/Y2.

References & Further Reading

Further Information
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