### General Information

<table>
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<tr>
<th><strong>Project Code</strong></th>
<th>UCAB07</th>
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<tbody>
<tr>
<td><strong>Partner University</strong></td>
<td>University of Central Lancashire</td>
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<tr>
<td><strong>Faculty/School/Department/Research Centres</strong></td>
<td>PABS</td>
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<tr>
<td><strong>First supervisor</strong> &lt;br&gt; Please provide name and weblink</td>
<td>Dr Vicky Jones &lt;br&gt; <a href="https://www.uclan.ac.uk/staff_profiles/dr_vicky_jones.php">https://www.uclan.ac.uk/staff_profiles/dr_vicky_jones.php</a></td>
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<tr>
<td><strong>Second supervisor</strong> &lt;br&gt; Please provide name, email address (for UA use) and weblink</td>
<td>Dr Donna Daly &lt;br&gt; <a href="https://www.uclan.ac.uk/staff_profiles/dr-donna-m-daly.php">https://www.uclan.ac.uk/staff_profiles/dr-donna-m-daly.php</a></td>
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<td><strong>Third supervisor</strong> &lt;br&gt; Please provide name, email address (for UA use) and weblink</td>
<td>Prof StJohn Crean &lt;br&gt; <a href="https://www.uclan.ac.uk/staff_profiles/st_john_cream.php">https://www.uclan.ac.uk/staff_profiles/st_john_cream.php</a></td>
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<td><strong>Fourth (external) supervisor</strong></td>
<td>Prof Alex Verkhratsky &lt;br&gt; <a href="http://www.ikerbasque.net/en/alexei-verkhratsky">http://www.ikerbasque.net/en/alexei-verkhratsky</a></td>
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<tr>
<td><strong>External/industrial supervisor</strong></td>
<td>Dr Salman Karim &lt;br&gt; Consultant Psychiatrist &lt;br&gt; Lancashire Care NHS Foundation trust</td>
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<tr>
<td><strong>Which of the supervisors listed above is an early-career-researcher</strong></td>
<td>Dr Donna Daly</td>
</tr>
<tr>
<td><strong>Contact details for project for informal applicant queries</strong> &lt;br&gt; <strong>Email address</strong></td>
<td>Dr Vicky Jones &lt;br&gt; <a href="mailto:VCJones@uclan.ac.uk">VCJones@uclan.ac.uk</a></td>
</tr>
<tr>
<td><strong>DTA Programme: Please delete as necessary which DTA programme this project relates to:</strong></td>
<td>DTA Applied Biosciences for Health</td>
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<tr>
<td><strong>Project title</strong></td>
<td>Enteric Nervous System dysfunction in Alzheimer’s disease</td>
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**Project Description**

### Scientific Excellence (500 words)

Improving global healthcare has resulted in people living longer but has unfortunately led to an increased number of people with age-related diseases, such as Alzheimer’s disease (AD). AD affects 50-million people worldwide, placing significant socio-economic burdens on developed and, increasingly, developing countries.

AD manifests as a progressive decline in function of aspects of the central nervous system (CNS) associated with learning and memory. Decades of research effort has centred around the study of CNS neurones, yet these have translated to no effective treatments for AD. Increasingly, therefore, the role of non-neuronal cells (such as glia and the cells of the blood-brain-barrier) in disease pathology has been explored. For example, we recently provided the first evidence that a type of glial cell known as astrocytes are chronically atrophic and dysfunctional in a human cell models of AD.

The enteric nervous system (ENS), often referred to as the ‘second brain’ of the body, is an independent nervous system lying within the wall of the GI tract. The ENS is the largest collection of neurones and glial cells outside the brain. It functions autonomously and independently regulates local intestinal function. ENS architecture and function broadly resembles that of CNS, the two are inextricably link via a bidirectional communication known as the ‘gut-brain axis’. Over recent years, it has become apparent that disruption of the gut–brain axis may underlie the pathogenesis of a diverse range of neurological conditions, including many associated with ageing populations such as AD, Parkinsons and motor neurone disease. Moreover, disorders that affect the CNS also tend to alter gut function.

Sadly, however, studies of the ENS in AD are scarce (<10 published studies), and are limited to only to gross changes enteric neurones, in isolation. No studies to-date explore the enteric cousins of the astrocytes, the enteric glial cells (EGC); the function of the ENS as a whole; or gut barrier permeability,
in AD. Notwithstanding, it has been reported that patients with AD have higher incidence of serious upper and lower GI events and that beta amyloid can be deposited in enteric neurones in AD mouse models, enhancing their vulnerability to inflammation.

For the first time, the proposed study will provide a comprehensive view of ENS structure and function in AD, together with important insights into AD influences on gut permeability and neuronal signalling.

To deliver this project we have assembled a globally-recognised team consisting of academics from the distinct research disciplines of cell biology, glial biology, gastrointestinal physiology and neurophysiology, with clinical partners and a NIHR clinical research facility. The roles of each member of the team is outlined below.

**Aim (400 words)**

**HYPOTHESIS AND AIMS**

Hypothesis: Alzheimer's disease will alter the function of the enteric nervous system, echoing those changes seen in the brain.

Our aim is to comprehensively study the impact of AD on the morphology and function of the gut. We will identify how EGCs and neuronal signalling in the ENS are altered as a result of AD and determine the impact AD has on gut permeability and barrier function. In the latter stages of the project we will translate our scientific discoveries from animal models to humans.

**METHODOLOGY AND INNOVATIONS**

**OBJECTIVE 1: Study the effect of AD on EGCs**

a. Morphological investigations will include immunohistochemical staining of EGCs of the GI tract in situ, dual fluorescence labelling and state-of-the-art 3D glial morphometric quantification, pioneered by VJ.
### OBJECTIVE 1: Identify emerging effects of AD on ENS function

- **b.** Isolation and culture of EGCs using immunopanning – the first time such a technique will be applied to the ENS field (VJ) – **INNOVATION**
- **c.** Functional analyses including secretome profiling to establish reactivity and inflammatory marker release (VJ, SC), and Ca²⁺ imaging studies (at ACN; AV)

### OBJECTIVE 2: Measure neuronal signalling from the gut

- **a.** Co-culture of ENS neurones and ECGs to establish non-cell autonomous effects of AD EGCs on neurone growth (axon chambers), survival and synaptic function (staining for synaptic punctae, baseline release of neurotransmitters) (VJ, DD)
- **b.** The effect of AD on afferent transmission from the gut will be explored by extracellular afferent nerve recordings from the small and large intestine and motility studies to investigate enteric neural circuits (DD)

### OBJECTIVE 3: Identify alterations in gut barrier permeability

- **a.** Intact gut epithelial barrier will be modelled using a Caco-2 epithelial monolayer in vitro. Permeability will be measured in the presence of AD or control EGCs or conditioned media by way of a fluorescence permeability assay and trans-epithelial electrical resistance (VJ, DD)

### OBJECTIVE 4: Translate to man

- **b.** Translate our findings from animal models to human AD using donor tissues from cancer resection (healthy margins, SK, VJ, DD).

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### Strategic Relevance (300 words)

**DTA3**

This project will increase our knowledge of AD pathogenesis and healthy ageing of the gastrointestinal tract and is therefore relevant to the applied biosciences theme of the DTA programme.

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This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 801604.
The project adheres to strategic aims of the University – providing inspirational experiences which will allow the student to develop as a global citizen as part of an innovative and socially relevant programme of work.

We will contribute to UCLan’s Research Strategy through the collaborative delivery of research excellence with social impact which will increase the external profile of the University. The project will generate world-leading (4*) outputs which adhere to the principles of open research. We will generate a solid research base in a clinically- and industrially-relevant area from which to secure significant external funding. In this way we will make contributions to research environment, outputs and impact towards future REFs.

This bid aligns to the aims of the LIFE Institute by supporting the development of a doctoral candidate, an ECR and MCR in a globally-relevant and sustainable project. Partnership with LCRF will ensure engagement with AD patients and their carers. The translational elements of the project and links with LCRF/RPH will also permit us to make contributions to UCLan’s ONE Health strategy.

UKRI priority areas
To secure future funding we have mapped this work to the priority areas of the UKRI research councils:
- BBSRC key challenge area of Lifelong Health (understanding/enhancement of health in later life)
- MRC strategic aims of strengthening mechanistic knowledge of neuropathologies and health inequalities in developing countries.
- Governmental Industrial Strategy ‘Grand Challenge’ of Ageing Society

Global perspectives
Our focus on a key non-communicable neurological disease with increasing incidence in developing countries means that the project aligns to a number of the UN Sustainable development goals (3.4, 3.B). Moreover, this ambitious
<table>
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<tr>
<th>Interdisciplinarity and fit with DTA3</th>
<th>An internationally relevant interdisciplinary team</th>
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<td>This project brings together academics from the distinct research disciplines of cell biology, glial biology, gastrointestinal physiology and neurophysiology, with clinical partners and a NIHR clinical research facility; all of the partners are committed to the development of ECRs. The team consists of:</td>
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<td>- Dr Vicky Jones is a member of the ARUK research network and an expert in glial biology with particular emphasis on morpho-functional alterations in neurodegenerative disorders. Dr Jones has significant experience of working with transgenic mouse models, primary cell culture and high-resolution 3D imaging of neural tissues. Dr Jones’ lab recently provided the first evidence (4*) of astrocyte atrophy in a human model of AD using morphological and functional testing techniques which will be utilised extensively in this project.</td>
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<tr>
<td>- Dr Donna Daly is an ECR with &gt;12 years experience working in gastrointestinal and lower urinary tract research. Her current work studies the impact of ageing and age-related diseases on neuronal signalling in the periphery. She has a number of publications in this area (3* - 4*) and in the past 5 years has been awarded 2 prestigious awards in recognition of her work (Water-Ferring prize for new investigators and John Blandy prize for urology). Her expertise in electrophysiology will be utilised for studying neuronal signalling in AD.</td>
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<td>- Prof StJohn Crean is a clinician with experience of leading successful research projects aligned to the role of systemic inflammation in neurodegeneration. Prof Crean is currently involved in the investigation of inflammatory</td>
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influences on the integrity of the blood-brain-barrier in neurodegeneration. This project which has many parallels with the investigation of gut permeability proposed herein and Prof Crean’s expertise in this area will be central to the delivery of this phase of the project. As Pro Vice-Chancellor for Clinical, Health and Research, Prof Crean is uniquely placed to provide an interdisciplinary overview of the project to translate findings to potential clinical interventions.

- **Prof Alex Verkhratsky** is a global leader in glial physiology; holding a Research Chair in the Department of Neuroscience, University of the Basque Country; Adjunct Directorship of the Achucarro Center for Neuroscience (ACN), Bilbao; and Professorship in neurophysiology at the University of Manchester. Prof Verkhratsky adds an unparalleled global angle to this project. An elected member of the academia Europaea, Prof Verkhratsky holds or has held numerous visiting or honorary positions in Universities and research institutions world-wide, including the USA, Germany, Ukraine, China and Israel, and has organised almost 50 international scientific meetings and delivered over 100 invited talks across the world.

- **Dr Salman Karim** is a consultant psychiatrist with Lancashire Care NHS Trust and over 10 years’ experience working in a specialist memory assessment service providing diagnosis and management of dementias, including AD. Dr Karim is and Associate Medical Director of the NIHR Lancashire Clinical Research Facility (LCRF) and has been chief investigator for a number of clinical drug trials. Dr Karim provides a vital link to AD patients and other stakeholders, and for the translation of findings in mouse models to human tissue specimens.
### Provision of outstanding world-class doctoral training

The proposed project has been carefully designed to align to the strategic objectives of DTA3 at every level. The highly experienced supervisory team have designed an engaging, cutting-edge project which will provide outstanding technical skills, against a backdrop of a disease with immense socio-economic impact.

The student will gain a broad spectrum of advanced technical and subject-specific skills with a human translational focus. We have also embedded international mobility into the project, affording opportunities for networking, development of further technical abilities and exposure to inter-sectorial perspectives.

The student will do a series of secondments:

- **In year 1**: the student will do a 1-week shadowing placement to observe ongoing clinical trials for AD and other neurodegenerative conditions at the LCRF and a 2-3 week placement at ACN to perform Ca2+ imaging experiments (objective 1c).

- **In year 2**: the student will spend 2 weeks at the LCRF with SK and the ethics team to secure HRA ethical approval for the use of human gut tissues (objective 4a).

- **In year three**: the student will return to ACN for a 2-month placement completing experiments on EGC morphology (objective 1a).

The student will be introduced to the social responsibilities of a researcher through secondments to the LCRF and interactions with our clinical partners; this will also help them to appreciate the socioeconomic impact of their work. In the secondment, the student will gain an insight into the ethical governance of work with human tissues.

The student will develop communication and networking skills through a range of activities. We will have annual full supervisory team meetings to discuss research progress from an interdisciplinary perspective. The student will be encouraged to give seminar presentations as part of the Neurodegeneration...
Research Group at UCLan and poster and oral presentations at the ARUK network PG/ECR meetings in addition to attendance at national and international conferences. The student will also be encouraged to disseminate their findings by delivering outreach activities for the general public, people living with AD and their carers (e.g. Lancashire Science Festival, Brain Awareness Week).

**Industrial Relevance (300 words)**

Detail external placement opportunities or collaborations available as part of the project

Unfortunately, interest and investment in AD research from the large pharmaceutical companies is currently limited due to the failure of a number of prominent antibody-based therapy trials in recent years. Hence, it is not possible at this time to place the student in AD-focused industrial R&D labs, since these no longer exist.

Notwithstanding, clinical non-commercial AD trials is still underway in a number of research facilities, including the NIHR LCRF, Preston. We will exploit our collaboration with the associate medical director of the facility, SK, to afford the student the opportunity to be involved with a broad range of randomised controlled trials, such as the validation of cognition scoring software to develop clearer clinical diagnostic tools for AD and quality-of-life effectiveness of voice software on Parkinson’s patients.

**Economic and Societal Impact (300 words)**

Globally, dementia is among the primary causes of disability and dependency in older people, incurring significant economic burden both in direct medical and social care costs, and the costs of informal care. In the UK for example, the economic cost of dementia is estimated at £26bn, with almost half of this attributed to informal care. Often thought of as a disease of the West, the majority of the 50-million people living with dementias worldwide reside in middle-income countries, and the biggest increase in numbers over the next few decades is predicted to be in low-income (developing) countries. Given that the worldwide incidence is set to triple by 2050, the socio-economic impact of dementias, especially in the developing world cannot be overstated.
By targeting the gut, this project aims to investigate novel causal elements in AD. Much recent research has uncovered links between the gut microbiome and the onset of other neurodegenerative diseases such as Parkinson's; the implication being that normalising the commensal bacterial community of the gut, by a simple oral probiotic, might provide an inexpensive means to treat, or even prevent, such diseases. A solid foundational understanding of ENS function and gut barrier integrity in AD will be key to such therapeutic developments; this project will provide this vital insight.
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<tr>
<th>Specific Admission Requirements</th>
<th>2:1 or 1st Class BSc in a bioscience related degree</th>
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<tr>
<td>Detail any subject specific degree qualifications or disciplines, relevant skills, experience</td>
<td>Experience in conducting a research project is essential (this can be either a final year wet lab project, summer studentship or masters research project)</td>
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<td>Experience of histology, cell culture and/or electrophysiology would be advantageous, though not essential</td>
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<tr>
<td>Minimum IELTS score</td>
<td>6.5 (no sub-score below 6.0) or equivalent qualification.</td>
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