

**Project title: Defining interactions between PDE5 and endothelin-1 inhibition underlying cerebrovascular dysfunction in small vessel disease (VIDA DTC).**

An opportunity has arisen for a 4-year PhD studentship within the Department of Brain Sciences at Imperial College London funded by the VIDA DTC. VIDA (Vascular and Immune contributors to DementiA) is a new multi-institutional partnership between Alzheimer’s Society and four world-leading research sites: the University of Manchester, University of Edinburgh, Imperial, and City St George’s University of London. With projects focussing on the importance of vascular and immune mechanisms in dementia, VIDA PhD students will become the next generation of much-needed dementia researchers, contributing to breakthroughs in dementia diagnosis and treatment.

VIDA students will embark upon a 4 year fully-funded PhD project at one of the four institutions above, with access to the state-of-the-art research facilities and interdisciplinary training available at all sites. Students at each site will come together as a cohort at several points during the programme, most importantly for an induction week at the beginning of the programme, followed by annual conferences and residential workshop retreats which will link in with other Alzheimer’s Society Doctoral Training Centres across the UK. Students will also participate in engagement schemes with the Alzheimer’s Society and beyond, sharing the impact of their research in the community. The programme also benefits from built in opportunities for placements with leading industrial partners, and bespoke training plans including schemes to develop teaching, mentoring, and grant writing skills.

Successful applicants will receive a generous stipend £22,500 rising by £1,000 each year, and home fees will covered\*. Funding is also provided for research expenses, career development and student travel/conference attendance.

*\*international student fees will not be covered.*

**Project Description:**

Cerebral small vessel disease (cSVD) causes 30% of ischaemic stroke, 80% of haemorrhagic stroke and 40% of dementia but has no effective treatment. It is associated with abnormal endothelial function in the brain, manifest as reduced blood flow to the brain and reduced reactivity of blood vessels to stimulation, such as by inhalation of carbon dioxide. Our recent OxHARP clinical trial demonstrated that treatment with the vasodilator sildenafil (a PDE5 inhibitor) improved both cerebral blood flow and cerebrovascular reactivity in patients with small vessel disease, but that this effect was significantly reduced in patients with higher levels of endothelin-1. Endothelin-1 is the most potent cerebral vasoconstrictor, is elevated in acute stroke, and its antagonism reduces progression of small vessel diseases in other organs such as the kidney. Its potential as a treatment for cerebral small vessel disease is currently under investigation. However, understanding which interventions are applicable in which patients, which biomarkers predict response to treatment and whether combination treatment may be beneficial is essential for translation to clinical practice.

This 4-year PhD training program will test the differential role of these antagonistic pathways in the cerebrovascular dysfunction evident in small vessel disease. The successful candidate will use data and samples from previous studies (OxHARP; pig model of inducible endothelin-1, Hainsworth BHF PG/20/10397); carry out cerebrovascular function testing with MRI and transcranial ultrasound within ongoing physiological prospective cohorts in cSVD (the ACCESS@ICL cohort) and planned phase-2, randomised, crossover design clinical studies of the effect on cerebrovascular haemodynamics of PDE5 inhibition and endothelin-1 inhibition in patients with cerebral small vessel disease. They will compare whether fluid biomarkers in each target pathway interact with baseline cerebrovascular function (cerebral blood flow, cerebrovascular reactivity, blood-brain barrier permeability); tissue injury due to excess ET-1 activity (pig model); prediction of the physiological response to treatment in interventional studies; and whether these markers reflect response to treatment.

This PhD will test the core hypothesis that PDE5 and ET-1 have antagonistic effects on cerebrovascular function in cSVD, that overactivity of either pathway impairs monotherapy targeting the antagonistic pathway and therefore that combined treatment has the potential for synergistic effects. The successful candidate will acquire global research skills through the Doctoral Training Centre, and specific skills in data handling, epidemiology and statistical analysis, and highly-focused expertise in testing cerebrovascular physiology with both ultrasound and MRI imaging analysis.

The candidate will be based at Imperial Small Vessel Disease Research Group, but that it is a close collaboration with co-supervisory team at St George's.

**Application process:**

Applicants must hold (or obtain by October 2025) a first or upper-second-class honours degree or equivalent in a neuroscience, cardiovascular science or related discipline. A Master’s degree in a related and related research is desirable but not essential. Applicants must also meet Imperial College’s English language requirements – further details can be found at   <https://www.imperial.ac.uk/study/pg/apply/requirements/english/>. All Imperial College London PhD [entry requirements](https://www.imperial.ac.uk/study/help-centre/postgraduate-admissions/-what-are-the-entry-requirements-and-what-qualifications-do-you-accept.php) must be met.

Applicants should submit their CV and a cover letter, including full contact details of two referees, to Dr Alastair Webb Alastair.webb@imperial.ac.uk . Once shortlisted, the applicant will undergo an interview by the VIDA management board. The successful applicant will subsequently need to [apply online](https://www.imperial.ac.uk/study/apply/postgraduate-doctoral/). We regret that due to the large volume of applications received, we are only able to notify those shortlisted for interview.

The deadline for applications is 20 December 2024

**Links:**

<https://www.dementiaresearcher.nihr.ac.uk/vascular-and-immune-contributors-to-dementia/>

<https://www.alzheimers.org.uk/research/our-research/alzheimers-society-doctoral-training-centres/vascular-and-immune-contributors-dementia>

<https://profiles.imperial.ac.uk/alastair.webb>