RESEARCH GROUP: NICHE

Project Title: Can a berry rich diets reverse the microvascular pathological changes observed in the APP/PS-1 transgenic model of Alzheimer's disease?

Supervisor(s): Professor Christopher A. Mitchell (Chair and supervisor: Core) and Dr Chris Gill (supervisor: Core)
External Supervisor Gordon Mc Dougall (James Hutton Institute; Dundee)

Contact Details: ca.mitchell@ulster.ac.uk Telephone 028 701-24089
c.gill@ulster.ac.uk Telephone 028 701-23181

Level: PhD

Background to the project:
Disruption and deregulation of the microvascular architecture appears to be a common pathogenic mechanism for progression in numerous chronic diseases including cardiovascular disease cancer and Alzheimer's disease. A direct relationship between microvascular pathology and cognitive decline exists [1]. In human AD brain tissues, analyses of cortical microvessels shows a reduced capillary density and ultrastructural changes which include microvascular narrowing and truncation; especially in vessels adjacent to senile plaques [2,3]. Morphometric analyses of human brain tissues demonstrated a significant relationship between reduced mean capillary diameters and a poorer antemortem cognitive score on the CDR scale [1,4].

Of significant interest in this regard, are recent studies in a murine model of Alzheimer's which have demonstrated that treatment with a compound most commonly used in type-2 diabetes patients can restore microvascular pathology to a wild type state [5] and in patients with mild cognitive impairment (mild AD) is currently being evaluated at clinical trial (NCT01843075). These types of studies highlight the potential for a range of compounds to potentially restore microvasculature function systemically (as the compounds are bioavailable throughout the systemic vasculature), ameliorating the effects on AD progression. This concept has led to research investigating the effects of naturally occurring compounds with the potential to modify microvascular architecture and function; an area of untapped interest with respect to raspberry polyphenols. Polyphenol rich fruits including blueberries, strawberries and acai fruit have positive effects on aspects of cognition, that can neither be fully explained by effects on neurogenesis nor on inflammation [6,7]. Given that raspberry polyphenols have been reported to be neuroprotective [8], exerting both anti-angiogenic properties and anti-inflammatory properties [9, 10]. These properties when examined along with the critical role of cerebral microvasculature on cognition, warrants exploration of a role for raspberry polyphenols in a widely accepted murine model of AD. Furthermore, potent inhibition of VEGF signalling by (poly)phenolics (and their metabolites) at sub-micromolar concentrations, has been reported to be mediated by direct binding of the flavanols (found in high concentrations in berries) to VEGF. It is therefore our hypothesis that raspberry polyphenols can ameliorate systemic & cerebral microvascular pathology in the APP/PS-1 mouse model resulting in improved cognition.

Objectives of the research project:
Studies will be conducted on wild type C57BR & APP PS1 transgenic mice (AD model) to establish the impact of diets rich in raspberry polyphenols on both systemic and cerebral vasculature. APP/PS1 mice express a transgene that carries mutations in both the APPswe and Presenilin-1 (which contains a deletion in exon-9 of PS-1; PS-1dE9) under the control of the mouse prion protein promoter giving CNS-directed expression. In addition to examining the effects directly on the vasculature using a range of established techniques, the
student will examine the potential for berry rich diets to reduce leucocyte rolling and adhesion within the vasculature, a process which leads to inappropriate extravasation of these cells and exacerbation of damage within both the CNS and systemic organs.

**Methods to be used:**  
The mouse window chamber assay (Cranial and dorsal skin-fold). In vivo longitudinal measurement of leukocyte rolling and adhesion. DNA isolation and genotyping. Small animal surgery. Vascular casting and scanning electron microscopy. Histological processing, staining and analysis/stereology. Immunohistochemistry. Techniques are established within the laboratories of Dr Gill and Professor Mitchell.

**Skills required of applicant:**  
The candidate should be highly motivated and demonstrate the ability to work independently as well as part of a dynamic research group. During the course of this PhD the candidate will have the opportunity to be trained in advanced imaging techniques by collaborators at the Research Complex at Harwell, so a willingness to travel is necessary. As this PhD project involves the use of animals in Biomedical Research, training for Home Office Personal Licence modules 1-4 (including surgery) is implicit. Experience of small animal surgery is desirable, although not essential as training will be provided. Excellent written and oral communication skills are required as the results of this PhD will be presented at local, national and International meetings.

**References:**