Final Project Report - Vascular

- **Introduction**

The VEM group was established in spring 2015, led by Joanna Wardlaw (academic) and Paul Wren (industry) with 14 individuals including representatives of four industry partners and 11 academic members, all of whom were very active in a range of aspects of clinical and preclinical research into vascular disease and neurodegeneration. At the outset, the group was organised by Paul Wren at GSK who utilised GSK resource for teleconferencing and secretarial support. Joanna Wardlaw provided the secretarial assistance when Paul Wren moved to San Diego in 2017 and DPUK provided the support for teleconferences. The group expanded in 2017 with five additional members to widen the specialty representation; Atticus Hainsworth took over as lead of the group in January 2018.

The group has functioned successfully since spring 2015, holding monthly teleconferences until mid-2017 and alternate monthly thereafter. There has been some turnover particularly amongst industry several of whom moved to other companies with different interests or to other world regions with one academic moving to Australia but remaining in contact. It now has 16 members forming a functional multi-disciplinary team. It comprises (some individuals represent several areas of expertise): stroke physicians (Bath, Quinn) old age psychiatrists (O'Brien), neurologists (Markus, Werring, O'Sullivan), a neuroradiologist (Wardlaw), a cardiologist (Touyz), neuropathologists (Love, Carare, Kalaria), a medical physicist (Williams), stem cell expert (Cader), neuroscientists and vascular biologists (Hainsworth, Horsburgh, Allan), clinical trialists and representatives from industry collaborators. It benefits from engagement with other UK and global networks (DRI, Cochrane Dementia Group, ISTAART, VasCog, the COEN and JPND funded global SVDs Network, large clinical trials networks, Brain Bank Networks).

The VEM group has won major external funding, with support from the DPUK Network. This includes the £1.2m Stroke Association Priority Programme award given in May 2017 by Stroke Association, British Heart Foundation, Alzheimer's Society. This award is to establish the "Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)" project, which will track the changes in memory and thinking skills of over 2000 stroke survivors across the UK and started in 2018. The group were also successful in securing from the same funding call, two other grants for lab studies: a multicentre group led by Prof Karen Horsburgh will study the cerebrovascular matrisome as a central component of cerebral microvascular disease focused on experimental model work (£799,806); Dr Roxana Carare and colleagues will study the brain's interstitial fluid drainage pathways (£245,198). Several members are involved in EPAD, a €50million IMI on dementia prevention, in PREVENT and DFPT both multi-funder UK studies examining biomarkers for dementia prediction, the DPUK MRI-PET infrastructure grant and the MRC MRI-PET Partnership to establish the scanners, and Cader contributed to an 18million Euro FP7 grant under the Innovative Medicine Initiative awarded in collaboration with Roche. In the same time period, and relevant to DPUK, the members secured several other large UK and international grants for work on clinical trials (PRESERVE, PASTIS, LACI-1, LACI-2, PROHIBICH), or mechanisms of vascular neurodegeneration (EU Horizon 2020; Fondation Leducq), the UK Dementia Research Institute, to enhance neuropathology studies (ARUK; MRC/TSA) and several were involved in recent bids to BHF Research Excellence Awards with vascular dementia now included in the BHF's five-year strategy. In all of these, the group have increased awareness of vascular disease and ensured that relevant medical information (eg vascular risk factors, blood pressure), and image acquisition and analysis protocols that were sensitive to vascular disease were in place (eg EPAD has

explicit vascular markers included in the protocol with over 1000 subjects now having been recruited across Europe).

The group ran several workshops. A joint workshop with UK wide brain banks including those in the Brain Bank Network in 2015 led to collaborative projects between Bristol and Edinburgh and greater awareness of tissue sampling protocols that are sensitive to vascular disease. A joint workshop on methodologies with the Drug Discovery Centre in Oxford in Jan 2016 helped contribute to the Cader IMI bid and the Horsburgh Stroke Association Priority Programme Award on the matrisome. The largest workshop was a highly successful international workshop on improving use of animal models in studies of small vessel diseases and vascular dementia held at the BHF Cardiovascular Centre in Glasgow in Jan 2017 supported by the BHF, RSE, ARUK and DPUK. Internationally high profile speakers included Maiken Nedergaard (now widely known for her work on glymphatics) and Anne Joutel (widely known for her work on monogenic forms of small vessel diseases like CADASIL). The workshop was run as part of a special edition of the journal *Clinical Science* (IF 5.38) on Small Vessels and Chronic Diseases was guest edited by Wardlaw, Horsburgh and Touyz and included several reviews and original papers including papers from the workshop debating the potential mechanisms and long term effects of brain microvascular disease. The Special Edition opened with an editorial on the importance of brain microvascular disease and ended with a report from the workshop on improving models for vascular dementia.

A focussed meeting was held in June 2018 on **Outcome Measures in Preclinical Models of VCI**, at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow. This was organised by Vascular EM member Dr Terry Quinn and Dr Lorraine Work, and supported by Alzheimer's Research UK and DPUK. Several other Vascular EM members attended (Carare, Hainsworth, Horsburgh). The meeting addressed outcome assessment in pre-clinical models of vascular cognitive impairment. Information was collated from a pre-circulated questionnaire. At the meeting round-table discussions addressed common outcome assessment tools, their application and whether there is scope for standardisation.

Three pilot DPUK Experimental Medicine projects have originated from discussions within the group. This includes EM1, a pilot project on lipidomics with Paul Wren, Simon Lovestone and Ian Deary, which used the National Phenome Centre to perform the lipidomic bioassays, the data for which is currently been written up. Project EM4 from Steve Williams focuses on cardiac and brain disease utilising imaging data from UK Biobank, and EM8 supported the large UK wide R4VaD project which is led by Joanna Wardlaw involving many members of the VEM group, and primarily funded by The Stroke Association, British Heart Foundation, Alzheimer's Society under The Stroke Association's Priority Programme in Vascular Dementia (see above).

The VEM group has generated a series of thought-leading multi-author publications. In 2018 when the USA Alzheimer's Association and National Institute of Aging published a proposal to refine the diagnosis of Alzheimer's Disease to one based on biomarkers, the VEM group were able to respond rapidly with international colleagues to rebut the proposals (in press)– a debate which is currently ongoing.

Members of the group have been leading the JPND HARNESS (HARmoNising Brain Imaging MEthodS for VaScular Contributions to Neurodegeneration) initiative to provide recommendations for image acquisition and analyses that are sensitive and specific to vascular contributions to dementia, including a website (www.harness-neuroimaging.org) with protocols, examples, links to downloadable analysis software and templates, which builds on the highly cited Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) published in 2013 now with >950 citations. Like STRIVE, it is anticipated that HARNESS will encourage standardised and replicable approaches to facilitate comparisons between studies and meta-analyses, disseminate analysis software and thus improve consistency of measurement of typical vascular lesions, and thus accelerate research into identifying causes and treatment to prevent vascular damage to the brain.

- **Conclusion**

DPUK's investment in a workpackage to facilitate the setting up of a network of active researchers interested in vascular health in dementia has been a huge success. The VEM network has identified tractable experimental medicine questions and secured significant funding to conduct the research. Of particular note is the Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD) study, funded as a DPUK Experimental Medicine Study (EM8) in partnership with the Stroke Association, British Heart Foundation and Alzheimer's Society. This study is challenging, and will require additional time to complete but as outlined above, the work is progressing well and has stimulated significant interest. A variety of research outputs from this projects are anticipated in future.

At the time of submitting this report (December 2018), publications are being drafted by group members and a workshop to encourage continued participation in the VEM network was held in November 2018. The focus of this workshop was to get the group's input into projects that could be suitable for inclusion as part of the experimental medicine component of the DPUK renewal application. Ideas from the workshop are now being developed further by Atticus Hainsworth who is working DPUK Experimental Medicine lead/Associate Director, James Rowe.

- **Recommendations**

Vascular Health in dementia remains an area that does not currently attract large research funding investment but we believe will be shown to have an increasingly important role in the progression of dementia. The VEM network has been encouraged to utilise its multi-disciplinary expertise to formulate exciting projects for inclusion in the experimental medicine component of the DPUK renewal application to be submitted to MRC. We remain in active discussions with both academics and industry to take advantage of the opportunities afforded through the DPUK platform. We have shown by our significant productivity to date that we will continue to make a very important contribution to DPUK.