

## WP 15 - Complete

<b>Vascular Health</b> <b>Start date:</b> Jun 15. <b>Completion date:</b> Jan 2017 <span style="float: right;"><b>Date of form completion:</b> Dec 2018</span>				
<b>Lead Team members: Paul Wren, Joanna Wardlaw and Atticus Hainsworth</b> The group comprises stroke physicians, old age psychiatrists, neurologists, neuroradiologists, cardiologists, neuropathologists, medical physicists, neuroscientists and vascular biologists, clinical trialists and representatives from industry collaborators.				
<b>Objectives</b> The overall objectives of the Vascular Experimental Medicine (VEM) Group are to: <ol style="list-style-type: none"> <li>1. Increase understanding of vascular disease in dementia</li> <li>2. Enhance protocols to ensure vascular relevance</li> <li>3. Integrate with other DPUK WPs &amp; other UK and international initiatives</li> <li>4. Enable vascular basic &amp; human sciences to be integrated into dementia research.</li> </ol> The workpackage did not propose to undertake specific research projects but the aim was to establish a network of researchers with interest in the broad area of vascular health to contribute to the design, and implementation of experimental medicine studies in dementia. A formal monetary award was not provided to the VEM group but it has benefitted from DPUK resources in supporting workshops and in providing operational support for the regular teleconference meetings held by the group. Members of the group were also able to apply for DPUK pilot funding and through this gained support for three Experimental Medicine projects.	<b>Dependencies to and from other work packages, networks and themes</b> WP1 and WP2			
<b>Lessons Learnt (what went well, what did you have to change)</b> <ul style="list-style-type: none"> <li>• This DPUK workpackage has been successful as seen by the increased number of group members since its inception. The multi-disciplinary skills of members ensure that there is significant expertise to draw on within the group.</li> <li>• The aim to raise the visibility of vascular disease within the dementia field has been successful and benefits arise from engagement with other UK and global networks (DRI, Cochrane Dementia Group, ISTAART, VasCog).</li> <li>• Three pilot DPUK Experimental Medicine projects have originated from discussions within the group (details below)</li> <li>• VEM members have won other major external funding, strengthened by the DPUK Network. Major successes are the three ACT-VaD projects (collaborative funding from UK Stroke Association, Alzheimer’s Society and BHF) and an €18 million FP7 grant under the Innovative Medicines Initiative, in collaboration with Roche.</li> </ul>				
<b>Where all Milestones completed -Yes</b> As described below all milestones have been successfully completed.				
Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
<b>Objective1:</b>				
D1.1 Core group with wider connections established	M1.1.1 Strategic Lead identified and regular meetings taking place	M1.1.1 Complete	None	Paul Wren
<b>Objective2:</b>				
D2.1 Establish a core set of research questions for future investigation	M2.1.1 Questions presented for discussion	M2.1.1 Complete	To and from WP1 and WP2	Joanna Wardlaw
<b>Objective3:</b>				

D3.1 Plan and implement a coordinated programme of research	M3.1.1 Applications prepared for Internal / External grants	M3.1.1 Complete	None	Joanna Wardlaw
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### Outcomes

#### DPUK-1 Published Outcomes from funding (Nov 2018)

Vascular EM group members are in **bold**. DPUK support has been beneficial to these outputs, though not always mentioned in the text. 50-word statements follow in *italic* text.

A major output is an entire special edition of *Clinical Science* (IF >5) published by the Biochemical Society and organised by Vascular EM members (co-ordinated by Joanna Wardlaw and edited by Joanna Wardlaw, Karen Horsburgh and Rhian Touyz). Selected references below. DPUK contributed funding to host the workshop at the end of the special edition (reported in Horsburgh et al. 2018).

- **Wardlaw JM, Horsburgh K.** Small vessels, dementia and chronic diseases - molecular mechanisms and pathophysiology - Introductory Editorial to the Special Themed Issue. *Clin Sci (Lond)* 2016;130: 1875-1879.

*This editorial highlighted the neglected topic of vascular disease and neurodegeneration and introduced the special edition, supported by the Biochemical Society; it attracted a superb collection of papers from international authors and ended with the workshop described in Horsburgh below.*

- Parkes I, Chintawar S, **Cader MZ.** [Neurovascular dysfunction in dementia - human cellular models and molecular mechanisms.](#) *Clin Sci (Lond)*. 2018 Feb 14;132(3):399-418. doi: 10.1042/CS20160720. Print 2018 Feb 14. Review. PMID:29444850.

*This paper reviewed the use of stem cell technologies to model the neurovascular unit.*

- [Appleton JP<sup>1</sup>](#), [Scutt P<sup>1</sup>](#), [Sprigg N<sup>1</sup>](#), [Bath PM<sup>2</sup>](#). *Clin Sci (Lond)*. 2017 Jun 30;131(14):1561-1578. doi: 10.1042/CS20160382. Print 2017 Jul 15. Hypercholesterolaemia and vascular dementia.

*Summarized all available clinical data on cholesterol and dementia.*

- **Love S,** Miners JS. *Clin Sci (Lond)*. [Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem studies reveal a complex relationship, still poorly understood.](#) 2017 Jun 30;131(14):1579-1589. doi: 10.1042/CS20170148. Print 2017 Jul 15. Review. PMID: 28667060.
- González-Castro V, Valdés Hernández MdelC, Chappell FM, Armitage PA, Makin S, **Wardlaw JM.** Reliability of an automatic classifier for brain enlarged perivascular spaces burden and comparison with human performance. *Clin Sci (Lond)* 2017;131:1465-1481.

*This was a 1<sup>st</sup> description of an automated method to detect perivascular spaces, a key part of the glymphatic system, on brain MRI.*

- Bailey EL, McBride MW, McClure JD, Beattie W, Graham D, Dominiczak AF, Smith C, **Wardlaw JM.** Effects of dietary salt on gene and protein expression in brain tissue of a model sporadic small vessel disease. *Clin Sci (Lond)* 2018;132: 1315-132; DOI: 10.1042/CS20171572.

*This described the effect of modest amounts of dietary salt on worsening of brain microvessel and white matter health in SVD and control rats.*

- Shi Y, Thrippleton MJ, Marshall I, **Wardlaw JM.** Intracranial pulsatility in patients with cerebral small vessel disease: a systematic review. *Clin Sci (Lond)* 2018;132:157-171.

*This systematic review summarised all available data on intracranial vascular pulsatility, a marker of stiffness and emerging component of vascular dysfunction that influences fluid drainage, and SVD.*

- **Horsburgh K, Wardlaw JM,** van Agtmael T, **Allan SM,** Ashford MLJ, **Bath PM,** Brown R, Berwick J, **Cader MZ,** **Carare RO,** Davis JB, Duncombe J, Farr TD, Fowler JH, Goense J, Granata A, Hall CN, **Hainsworth AH,** Harvey A, Hawkes CA, Joutel A, **Kalaria RN,** Kehoe PG, Lawrence CB, Lockhart A, **Love S,** Macleod MR, Macrae IM, **Markus HS,** McCabe C, McColl BW, Meakin PJ, Miller A, Nedergaard M, **O'Sullivan M,** **Quinn TJ,** Rajani R, Saksida LM, Smith C, Smith KJ, **Touyz RM,** Trueman RC, Wang T, Williams A, **Williams SCR,** Work LM. *Clin Sci (Lond)*. 2018;132:851-868. Small vessels, dementia and chronic diseases - molecular mechanisms and pathophysiology.

*This paper formed the final part of the Clinical Science (IF >5) special edition This paper follows a workshop that took place in Jan 2017, supported by MRC DPUK, that brought together researchers in cerebral vascular/cardiovascular disease and dementia to foster interactions and collaborations.*

- Makin SD, Doubal FN, **Quinn TJ, Bath PM**, Dennis MS, **Wardlaw JM**. Eur Stroke J. 2018;3:66-73. The effect of different combinations of vascular, dependency and cognitive endpoints on the sample size required to detect a treatment effect in trials of treatments to improve outcome after lacunar and non-lacunar ischaemic stroke.

*This work analysed the use of different individual and combined endpoints on power and sample size in clinical trials of small vessel disease, a common cause of dementia.*

- Skrobot OA, Attems J, Esiri M, Hortobágyi T, Ironside JW, **Kalaria RN**, King A, Lammie GA, Mann D, Neal J, Ben-Shlomo Y, Kehoe PG, **Love S**. Brain. 2016;139:2957-2969. Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment.

*Disease processes usually cause dementia in combination, and determination of the various contributors requires post-mortem examination. We produced the first validated pathological guidelines for assessing the likelihood that vascular disease contributed to cognitive impairment. The guidelines are now used in all UK brain banks and in cohort studies in other parts of the world.*

- Skrobot OA, Black S, Chen C, DeCarli C, Erkinjuntti T, Ford GA, **Kalaria RN, O'Brien J**, Pantoni L, Pasquier F, Roman GC, Wallin A, Sachdev P, Skoog I, VICCCS group, Ben-Shlomo Y, Passmore AP, **Love S**, Kehoe PG. Progress towards standardised diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study (VICCCS). *Alzheimers Dement* 2018; 14: 280-92.

*This paper was the result of a UK-led international Delphi study of key experts. It describes the first operationalised international consensus on clinical diagnostic criteria for vascular cognitive impairment (VCI) and vascular dementia (VaD), and now forms the international diagnostic standard for all studies of VCI and VaD.*

- **Wardlaw JM, Bath, O'Brien, Werring** et al. *Alzheimers Dement*. 2016; 12:1235-1249. METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the Joint Programme for Neurodegenerative Disease Research.

*This JPND-funded international working group identified as many cohort studies as possible relevant to cognitive decline and dementia, worldwide, and produced a summary of the available variables, and highlighted that there are many studies with relevant information on vascular contributions to cognitive decline outside the typical AD studies.*

- Doubal FN, Ali M, Batty GD, Charidimou A, Eriksdotter M, Hofmann-Apitius M, Kim YH, Levine DA, Mead G, Mucke HAM, Ritchie CW, Roberts CJ, Russ TC, Stewart R, Whiteley W, **Quinn TJ**. *BMC Neurol*. 2017;17:72. Big data and data repurposing - using existing data to answer new questions in vascular dementia research.

*This paper, a product of the International Congress on Vascular Dementia, represents a review and scientific consensus on data-driven research in vascular dementia. The paper has been important in raising visibility of DPUK with international vascular dementia researchers; creating new collaborations and suggesting avenues for future research activity.*

- **Hainsworth AH, Allan SM**, Boltze J, Cunningham C, Farris C, Head E, Ihara M, Isaacs JD, **Kalaria RN**, Lesnik Oberstein SA, Moss MB, Nitzsche B, Rosenberg GA, Rutten JW, Salkovic-Petrisic M, Troen AM. *BMC Medicine*. 2017;15:16. Translational models for vascular cognitive impairment: a review including larger species.

*An international team appraised current pre-clinical models relevant to vascular cognitive impairment. The utility of larger experimental species (primates, sheep, dogs) for dementia research is a core theme of this review.*

- Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, Harrinton MG, Pa J, Law M, Wang DJJ, Jacobs RE, Doubal FN, Ramirez J, Balck SE, Nedergaard M, Benveniste H, Dichgans M, Iadecola C, **Love S, Bath PM, Markus HS**, Salman RA, Allan SM, **Quinn TJ, Kalaria RN, Werring DJ, Carare RO, Touyz RM, Williams SCR**, Moskowitz MA, Katusic ZS, Lutz SE, Lazaroy O, Minshall RD, Rehman J, Davis TP, Wellington CL, González HM, Yuan C, Lockhart SN, Hughes TM, Chen CLH, Sachdev P, **O'Brien JT**, Skoog I, Pantoni L, Gustafson DR, Biessels GJ, Wallin A, Smith EE, Mok V, Wong A, Passmore P, Barkof F, Muller M, Breteler MMB, Román GC, Hamel E, Seshadri S, Gottesman RF, van Buchem MA, Arvanitakis Z, Schneider JA, Drewes LR, Hachinski V, Finch CE, Toga AW, **Wardlaw JM**, Zlokovic BV. Vascular dysfunction – the disregarded partner of Alzheimer’s disease. *Alzheimers Dement* 2018; **In press**.

*Multiple members of the VEM group contributed to this international paper responding to the 2018 USA AA-NIA statement on biomarkers in AD, which failed to mention vascular disease.*

## Executive Summary of Project

The Vascular Experimental Medicine workpackage aimed to raise the visibility of vascular disease within the dementia field. Specific experiments were not proposed but instead the aim was to develop a network of researchers from academia and industry, with multi-disciplinary skills, who could contribute to the identification, and conduct, of experimental studies focused on vascular disease within dementia. This has been very successful and genuine synergy of the group has been achieved through themed scientific meetings, including a DPUK-sponsored workshop in Glasgow (Jan 2017) and a VasCog conference in London (July 2017). This research synergy is already producing useful methodological outputs that will inform future clinical studies. The VEM group has generated a series of thought-leading multi-author publications (see outputs listing). It has also been invited to submit an outline bid for inclusion in the DPUK renewal application.



WP15 Final  
Report.pdf