

Vascular Health Network

(Vascular Experimental Medicine Group)

Work Package 15



Dementias
Platform^{UK}
Medical Research Council

Objective(s):

This Work Package 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.

More specifically, the objectives of the Vascular Experimental Medicine (VEM) Group were to:

1. Increase understanding of vascular disease in dementia
2. Enhance protocols to ensure vascular relevance
3. Integrate with other DPUK WPs & other UK and international initiatives
4. Enable vascular basic & human sciences to be integrated into dementia research.

A formal monetary award was not provided to the VEM group. The group benefitted latterly from DPUK resources in supporting workshops and in providing operational support for the regular teleconferences held by the group. Members of the group successfully applied for DPUK funding for three Experimental Medicine projects (EM1, EM4, EM8).

Overview Summary:

Vascular Health is likely to have an increasingly important role in the development and progression of dementia. The Vascular Experimental Medicine (VEM) Group was established in Spring 2015 with members from both academia and industry. It aimed to develop an active network to study clinical and preclinical research in vascular disease and neurodegeneration. With 16 current members from multi-disciplines it has been very successful contributing both to UK and International Initiatives ((DRI, Cochrane Dementia Group, ISTAART, VasCog, the COEN and

JPND funded global SVDs Network, large clinical trials networks, Brain Bank Networks). Additionally, it has successfully applied for major external funding (the R4VaD study).

Executive Summary:

This work package 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 group has generated a series of thought-leading multi-author publications. It also proposed a new work package included in the DPUK renewal application submitted at the end of 2019.

Summary of Outputs: (as per Researchfish categories)

Publications

DPUK-1 Published Outcomes from funding

VEM group members are in **bold**. DPUK support has been beneficial to these outputs, though not always specifically mentioned in the text.

A major output was 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). 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 (Lon)* 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**¹, **Scutt P**¹, **Sprigg N**¹, **Bath PM**². [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. [Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem studies reveal a complex relationship, still poorly understood](#). *Clin Sci (Lond)*. 2017 Jun 30;131(14):1579-1589. doi: 10.1042/CS20170148. Print 2017 Jul 15. Review. PMID: 28667060. *Acknowledging that the contribution of vascular disease to cognitive impairment is under-recognized, this review highlights the value of detailed neuropathology (the use of standard evidence-based –post mortem assessment protocols, and the inclusion of biochemical as well as neuropathological studies) to help address this.*
- 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 1st description of an automated method to detect perivascular spaces, a key part of the lymphatic 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, Harrington 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.*
- Alber J, Alladi S, Bae HJ, Barton DA, Beckett LA, Bell JM, Berman SE, Biessels GJ, Black SE, Bos I, Bowman GL, Brai E, Brickman AM, Callahan BL, Corriveau RA, Fossati S, Gottesman RF, Gustafson DR, Hachinski V, Hayden KM, Helman AM, Hughes TM, Isaacs JD, Jefferson AL,

Johnson SC, Kapasi A, Kern S, Kwon JC, Kukolja J, Lee A, Lockhart SN, Murray A, Osborn KE, Power MC, Price BR, Rhodius-Meester HFM, Rondeau JA, Rosen AC, Rosene DL, Schneider JA, Scholtzova H, Shaaban CE, Silva NCBS, Snyder HM, Swardfager W, Troen AM, van Veluw SJ, Vemuri P, Wallin A, Wellington C, Wilcock DM, Xie SX, **Hainsworth AH**. [White matter hyperintensities in vascular contributions to cognitive impairment and dementia \(VCID\): Knowledge gaps and opportunities](#). *Alzheimers Dement (N Y)*. 2019;5:107-117. *This is an opinion statement from an international multi-expertise group, led by the current VEM group lead.*

- Berry C, Sidik N, Pereira AC, Ford TJ, **Touyz RM**, Kaski JC, **Hainsworth AH**. [Small-Vessel Disease in the Heart and Brain: Current Knowledge, Unmet Therapeutic Need, and Future Directions](#). *J Am Heart Assoc*. 2019;8(3):e011104. doi: 10.1161/JAHA.118.011104. *This is an expert review by neuroscientists and cardiologists specialised in microvascular disease.*
- McFall A, Hietamies TM, Bernard A, Aimable M, **Allan SM**, **Bath PM**, Brezzo G, **Carare RO**, Carswell HV, Clarkson AN, Currie G, Farr TD, Fowler JH, Good M, **Hainsworth AH**, Hall C, **Horsburgh K**, **Kalaria R**, Kehoe P, Lawrence C, Macleod M, McColl BW, McNeilly A, Miller AA, Miners S, Mok V, O'Sullivan M, Platt B, Sena ES, Sharp M, Strangeward P, Szymkowiak S, **Touyz RM**, Trueman RC, White C, McCabe C, Work LM, **Quinn TJ**. [UK consensus on pre-clinical vascular cognitive impairment functional outcomes assessment: questionnaire and workshop proceedings](#). *J Cereb Blood Flow Metab*. 2020 Mar 9:271678X20910552. [Epub ahead of print] *This is a multi-author consensus statement from a DPUK-sponsored workshop.*

Collaborations & Partnerships

The objectives of the VEM Group were all based around collaboration and the establishment of an active researcher network

Further Funding

The VEM group has won major external funding, with support from the DPUK. This includes a £1.2m Stroke Association Priority Programme award in May 2017 by the Stroke Association, British Heart Foundation and 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 also secured two other grants for lab studies in the same funding call. 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, PROHIB-ICH), 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.

Three pilot DPUK EM 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. 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 also submitted a work package for inclusion in the DPUK renewal application submitted at the end of 2019.

Next Destinations

Not applicable

Engagement Activities

The group ran several important workshops.

- 1) 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. This helped establish

brain sampling for vascular disease and further funding for work on PM brain tissue from ARUK (Love, Smith, Wardlaw et al) and MRC (Smith, Salman, Wardlaw).

- 2) 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.
- 3) 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. 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.
- 4) 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. 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.

Influence of policy, practice, patients & the public

Members of the group have been leading the JPND HARNES (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 HARNES 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
Research Tools & Methods
See above under Influence of policy, practice, patients & the public, including the special edition of Clinical Science and the HARNESS website.
Research Databases & Models
Databases of imaging in vascular disease and dementia are available through the HARNESS website and Edinburgh University; The MRC Brain Tissue Bank, Edinburgh, is now enriched for samples from patients with small vessel disease who agreed to prospective brain donation post mortem.
Intellectual property & licencing
All software developed to analyse brain images, or refined cognitive tests, etc are available open access.
Medical products, interventions & clinical trials
The LACI-1 and LACI-2 trials benefitted from the intellectual exchange and expertise in the Vascular EM group. The R4VaD study participants are prospectively consented for recontact for future clinical trials.
Artistic & creative products
None
Software & technical products
See above under Influence of policy, practice, patients & the public
Spin outs
None
Awards & recognition
Professor Joanna Wardlaw was awarded the European Stroke Organisation President's Medal for Lifetime Contribution to stroke research (2016), the American Heart Association Feinberg Award for excellence in clinical stroke research (1 st ever female, one of only 6 non USA awardees, 2018), and a CBE for services to neuroscience and medicine, 2016.
Other outputs & knowledge/future steps
See above for multiple scientific papers, an entire special edition of Clinical Science, workshops and reports.

<p>Members of the group are continuing to work on their respective Vascular Dementia Priority Programme research which will report in 2022-23.</p> <p>Members of the group are planning trials of nutritional agents, repurposed drugs and lifestyle interventions; they are working on analyses of UK Biobank and other datasets.</p> <p>Kalaria in Newcastle will host the 2020 VasCog International Conference (Sept 2020)</p>
<p>Use of facilities & resources</p>
<p>None</p>
<p>Most successful outcome and what it means for future dementia research:</p>
<p>Under the lead of Joanna Wardlaw the vascular group won multi-funder support (Stroke Assoc., BHF, MRC) for a large clinical study, Rates, Risks & Routes to Reduce Vascular Dementia (R4VaD). This multi-site study has achieved excellent recruitment (1270 participants across 53 active centres in all four UK nations) although the study paused from mid -March 2020 due to the Covid-19 outbreak. The study will provide a well-phenotyped cohort of UK stroke survivors, for global dementia research. This is especially valuable as most other large cohorts lack cardiovascular focus.</p>
<p>Lessons learned:</p>
<p>The number of researchers involved in the Vascular Experimental Medicine Group increased significantly between 2015 and 2020 demonstrating the success of the initiative and its appeal to researchers from multi-disciplines, academia and industry. The Group successfully applied for significant grant funding and has continued to make important contributions to initiatives in the UK and internationally.</p> <p>Success was achieved through very little financial investment from DPUK which supported workshops and the regular teleconferences of members but did not provide a monetary award. The Vascular Health Network has been a success story for DPUK.</p>
<p>Other:</p>
<p>None</p>
<p>Date of Report:</p>
<p>6 April 2020</p>