Meeting Report

MRC workshop on neurovascular ageing in health and disease: interplay of the CNS and vascular system

25 March 2015

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Report overview
This document represents a synopsis of the Medical Research Council (MRC) workshop on neurovascular ageing in health and disease: interplay of the CNS and vascular systems, held on 25 March 2015 in London. The aim of this report is to summarise the meeting and highlight the key issues and major discussion points that arose.

1 Executive Summary

Vascular ageing and neurodegenerative diseases are two of the leading health challenges faced by our society. The MRC workshop on neurovascular ageing in health and disease highlighted significant knowledge gaps in current understanding of the biology of ageing as it relates to the CNS, and particularly to the interplay between the vasculature and neuronal systems. The workshop identified a number of specific opportunities to advance the field which fall into three broad categories for which recommendations are outlined below: Biological Factors; Tools and Technology; and Capacity Building.

Biological factors

Knowledge expansion
1. The biological risk factors for neurovascular ageing and cardiovascular disease are very similar. At the same time, there is regional differentiation in the vasculature throughout the body. There are opportunities to build on the existing substantial body of work in cardiovascular disease in order to expand our knowledge, for example:
   - repurposing existing murine models of cardiovascular disease;
   - addition of cognitive assessment of participants (baseline and at relevant time-points) to cardiovascular disease clinical trials;
   - exploring the potential to repurpose cardiovascular disease drugs;
   - providing detailed biological and structural descriptions of the CNS vasculature at an organ, cellular and molecular level;
- comparative functional studies throughout the body to help understand the interplay of vascular function and neuronal systems.

**Key areas for focus**

2. The Blood-Brain Barrier (BBB) and Neurovascular Unit are key areas for further research. Specific recommendations were for:
   - studies to compare normal and age-related changes, including functional assessments;
   - application of novel approaches to assess BBB integrity in humans.

**Tools and technology**

3. Imaging is a key tool to understanding the relationship between the vasculature and neuronal systems in the brain. Opportunities include:
   - the development of new PET ligands and enhanced imaging technology;
   - linking imaging data with molecular pathology
   - comparing data from human post-mortem tissue with ‘in life’ functional assessments and associated clinical data.

4. Human cohort studies play an important role in understanding neurovascular ageing including:
   - the collection of data on comorbidities;
   - the mining of existing population data records to generate new hypotheses.

5. More use can be made of available human tissue to increase our mechanistic and translational understanding of the brain, including:
   - tissues used as brain surrogates, such as the retina, and non-CNS tissues including the kidney small vessels
   - surgically resected tissue.

**Capacity building**

6. A more cohesive UK neurovascular ageing community can be built through encouragement of interdisciplinary working and greater collaboration between the fields of neurological science and cardiovascular biology. Sharing resources, tools and experimental knowledge will add value to the research base.
2 Background to the workshop

The consequences of ageing and neurodegenerative diseases are two of the leading health challenges faced by our society. We have only limited understanding of the underlying neurobiology, but know that vascular factors play a major role.

To help identify research opportunities in the field of neurovascular ageing in the UK the MRC organised a one-day workshop which, for the first time, brought together the vascular and neuronal communities around this topic. Focused on the underlying scientific mechanisms, the purpose was to identify how best to advance the field in terms of gaining a deeper understanding. The workshop structure was developed in collaboration with partners from Alzheimer’s Research UK, the Alzheimer’s Society, the British Heart Foundation, the Physiological Society and the Stoke Association.

The interplay between the vasculature and CNS in ageing and the pathogenesis of disease have also been highlighted as areas of relevance to the MRC’s strategy and initiatives such as the MRC Dementias Platform UK\(^1\) (DPUK), an academic/industry cohort-based resource set up to further the understanding of the early stages of dementia, before and after diagnosis. The DPUK places emphasis on the interplay of comorbidities with the onset of dementia and has three themes for experimental medicine, one of which is vascular disease mechanisms.

The MRC’s funding for research relevant to neurovascular ageing over the last 5 years is at a modest level and has remained relatively constant with a total spend of £25 million, or £5m per year. By comparison the MRC funded £209m of Neurodegenerative Disease research and £144m of Cardiovascular Disease research over the same time period. The vascular ageing research funding portfolio reflects the relatively small number of people working in vascular and endothelial cell biology in the CNS within the UK.

The importance of vascular factors in the progression of neuronal diseases has been highlighted in several recent workshops and initiatives. The Stroke Association held a Research Round-table meeting on Vascular Dementia and Stroke\(^2\) on 29 January 2015. The meeting included leading experts in the field and highlighted the need for basic scientific research to be conducted to understand neuropathology, mechanisms of disease, and pathways involved in vascular dementia. Furthermore, vascular dementia

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\(^1\) http://www.mrc.ac.uk/research/facilities/dementias-platform-uk/

was identified at the meeting as a strategic research priority. Similarly, Alzheimer’s Research UK held a *Dementia Prevention Research Workshop* on 3 February 2015. The meeting focused on dementia risk factors, including neurovascular ageing, and highlighted barriers to and opportunities for prevention research.

### 3 Format of the workshop

Fifty participants attended the *MRC workshop on neurovascular ageing in health and disease*, which included representatives from diverse academic fields, the pharmaceutical industry, together with the above UK charities (Annex 1). The workshop was jointly chaired by Professor Hugh Perry, University of Southampton, MRC Neurosciences and Mental Health Board Chair and Professor David Lomas, University College London, MRC Population and Systems Medicine Board Chair reflecting the research portfolio interests of the two relevant MRC Boards.

The **workshop aims** were:

- To consider the current knowledge of the role that the vasculature plays in systemic disease in ageing and how systemic disease itself affects the vasculature. To include consideration of:
  - vascular diseases;
  - metabolic diseases;
  - stroke;
  - neurodegenerative diseases including vascular dementia;
  - inflammatory conditions.

- To consider the role of the blood brain barrier and if there are important differences between peripheral and CNS vascular responses to ageing.

- To consider the natural changes that occur to the homeostasis of the vasculature with ageing. In the CNS the role of perivascular cells and astrocytes in neurovascular coupling and the regulation of cerebral blood flow should be addressed.

- To identify, where possible, the key inflammatory, metabolic and other risk factors for the development of peripheral and CNS vascular pathology.

- To identify the priority areas for action and what tools are needed to advance neurovascular ageing research in the UK.

- To advise how best to enable cross-disciplinary working and bring research communities together in this area.
Workshop structure (Annex 2 and 3)

The workshop included three keynote presentations from international researchers working within the field of neurovascular health and disease, followed by a discussion structured around key questions.

4 Keynote presentations
4.1 Professor Eli Keshet, The Hebrew University Jerusalem, Israel

Vascular homeostasis and rejuvenation: a VEGF-centered view (Annex 3.1)

Professor Keshet, a vascular biologist, described the elaborate control that Vascular Endothelial Growth Factor (VEGF) elicits over the genesis of new blood vessels and the maintenance of vascular homeostasis. Three studies using murine genetic models to manipulate organ vasculature were described. Firstly, VEGF gain- or loss-of-function murine models have demonstrated that in the heart VEGF is indispensable for maintaining homeostatic microvascular density and that VEGF is needed to replenish the heart microvasculature. Secondly, murine genetic models which allow for inducible and reversible VEGF blockade during brain development have demonstrated that a developmentally programmed wave of cerebral vessel maturation leads to the development of a functional blood-brain barrier (BBB) and exit from a VEGF-dependent phase. Finally, the link between blood vessels and adult neurogenesis was explored through murine models which have indicated that VEGF induces hippocampal angiogenesis and neurogenesis in the adult mouse brain. Future work exploring the potential of rejuvenating the vascular niche and attenuating the age-dependent decline of adult neurogenesis was described.

4.2 Professor Elga de Vries, UV University Medical Center, the Netherlands

The neurovascular unit in health and disease (Annex 3.2)

Professor de Vries, a neuroimmunologist, provided an overview of the role of the neurovascular unit in health and disease. The importance of the brain vasculature and surrounding cell types in the maintenance of the function of the BBB was outlined. Work was described explaining how pathological alterations in the integrity and function of the BBB are observed in a range of neurological diseases such as Multiple Sclerosis, stroke, vascular dementia and Alzheimer’s disease. The ‘BBBNedwork Foundation’ was highlighted as a successful interdisciplinary collaboration which aims to gather knowledge to understand the central role of the BBB in the treatment of brain diseases. Finally, in

the context of the overlap between risk factors for cerebrovascular disorder and Alzheimer’s disease, the two-hit vascular hypothesis for Alzheimer’s disease was outlined\(^4\).

### 4.3 Dr Anton Roks, Erasmus Medical Center, the Netherlands

*Vascular and neurological problems related to genomic instability (Annex 3.3)*

Dr Roks presented his work investigating the pathophysiology of vascular ageing through the hypothesis that delaying vascular ageing will improve healthy ageing. Genomic instability, widely recognised as one of the primary hallmarks of ageing\(^5\), was shown in murine models to contribute to age-related vascular and neurological function, in a manner reminiscent of human ageing\(^6\). Diet restriction studies were described and proposed as an effective intervention with possible genoprotective properties in mutant mice. Furthermore, organ-specific DNA repair-defective mice were proposed to serve as useful tools to study the interactions between ageing organs. Future work included investigating the interaction between systemic and vascular ageing; clinical work to recognise and predict vascular ageing; and intervention studies to delay vascular ageing.

### 5 Summary of views

Key points arising from the discussion are summarised below:

#### 5.1. What are the main biological factors that influence vascular ageing?

- **Cardiovascular disease risk:** there is an assumption that established risk factors for cardiovascular disease are the same biological risk factors as for vascular ageing, including brain ageing, cognitive decline and neurodegenerative disease. This assumption may or may not be true and therefore represents a starting point for further studies to challenge.

- **Timing of studies:** the importance of understanding the biological factors that influence vascular ageing in humans, by using human tissue, was emphasised. In particular, individuals in middle age need to be targeted through longitudinal studies to gain an insight into how vascular ageing begins and progresses through the life course, in addition to late life research when the effects of vascular ageing have developed.

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• **Regional aspects/differences:** to understand biological risk factors it is important to consider the regional differentiation which exists in the vasculature throughout the body at an organ, cellular and molecular level.

• **Elasticity of blood vessels:** ageing impacts on the elasticity of the vasculature. Studies are needed to look at differences in the blood vessel matrix, basement membrane, smooth muscle cells, pericytes, signalling molecules and the effect of ageing. Furthermore, it was suggested that imaging vascular elasticity in the brain may be useful in gaining a deeper understanding of ageing: measures of CNS vascular stiffening would be helpful here.

5.2. **Does vascular ageing differ in the brain from other tissues and if so, why?**

There are structural (BBB/neurovascular unit) and functional (e.g. baroreflex) differences in the brain compared with other peripheral tissues:

• **CNS sensitivity:** The brain is highly perfused and has a complex function. Therefore the impact of vascular dysfunction following relatively small pathological changes is profound.

• **Regional variations:** The brain is comprised of a dense network of vessels, with distinct structural and functional differences in blood vessels occurring in different brain regions. These differences are more evident at the level of small vessels rather than large vessels. Similarly, within the brain, regional differences in the extent of vascular ageing are observed, for example between the basal ganglia and cortical white matter.

• **Metabolic demand:** In the CNS the vessels will undergo autoregeneration to maintain normal blood pressure, much more so than in the periphery. The brain has a higher metabolic demand than the periphery. Endothelial cells play an important role in mediating the effects of metabolites on smooth muscle cells and meeting the need for that demand. This mechanism breaks down with age.

• **Peripheral vessels** are surrounded by adventitia which has an impact on vascular function, whereas in the brain, especially in small vessels, adventitia is very thin/not present.

• **Drainage:** Most peripheral tissues have lymphatic drainage including the meninges, but there is generally thought to be no lymphatic drainage in the brain, drainage is through the perivascular space, which is a constraint for the brain compared with other tissues.

• **Beta amyloid angiopathy** is unique to the brain. Amyloid diseases observed in other tissues involve different amyloid protein species.
5.3. How does the vasculature convey signals from the periphery to the brain in early and late life and how might systemic comorbidities modify this?

- **Types of signal**: the vasculature transduces physiological and pathological signals from the periphery to the brain including: inflammatory signals; blood pressure (fluctuations in pressure versus absolute baseline values); metabolic signals, including lipids; endocrine and paracrine signals; preconditioning signals.

- **Three mechanisms of signal transduction** were identified: direct through the blood-brain barrier; indirect through paracrine and angiocrine signalling (for example VEG-F); and direct contact through endothelial cells, synapses, astrocytes and pericytes. The complexities of each of these mechanisms of contact require further consideration.

- The mechanisms of transduction are modified throughout the life course with inputs affecting the types of signals transduced and comorbidities amplifying the effects and processes. Examples from across the life course were cited including: early life (low birth weight infants); through life comorbidities such as type II diabetes and traumatic brain injury; and late life, where a convergence of common inflammatory endpoints is observed.

- It was recognised that little information exists on how systemic comorbidities affect the signal transduction of the vasculature.

- Research in this area needs to be interdisciplinary and to take a broad systems approach.

5.4. How can we gain further insights on the interplay between the vascular and neuronal systems in the brain? What tools could be used or repurposed to advance the field?

- Further detailed biological and structural descriptions of the vasculature in the brain are needed to understand vascular function and the interplay with the neuronal systems in the brain.

- The comparative assessment of peripheral and CNS smooth muscle cell biology should be encouraged.

- Novel measurements and approaches to assess the BBB integrity in humans are needed.

- Genetic manipulation of brain-specific proteins in transgenic mice models was considered a useful approach, especially if animal studies are conducted in parallel with, and to inform, human clinical studies. This requires the development of preclinical testing strategies that explicitly link animal studies through to human clinical trials.
• Imaging was considered to be key to advancing our understanding of the relationship between the vascular and neuronal systems in the brain. Essential imaging technologies included: PET imaging, retinal imaging, and vascular amyloid imaging approaches, with a need to develop improved ligands.
• A lack of detailed phenotypic data linked to molecular pathology was considered to be a barrier.
• The disciplines of vascular and neuronal biology use different tools and methodologies. By working together to integrate technologies from across disciplines it should be possible to expand experimental design, maximise outputs and gain further insights into the interplay between the vascular and neuronal systems.
• Existing population data such as General Practice records (for example common prescribed medications, medical history, records for cognitive decline) were considered to represent a valuable resource to be mined to generate new hypotheses around vascular comorbidities.
• It was suggested that all large phase II/III trials in cardiovascular or other indicators of relevance should include cognitive assessments (baseline and at relevant time points) to maximise the available information.
• The repurposing of drugs currently used to treat cardiovascular disease should be examined for potential treatments and may benefit the area of neurovascular ageing and dementias.

5.5. Are we taking sufficient advantage of human tissue (surgery and brain banks) for pathology at a molecular level of analysis?
• The use of human tissues was viewed as an area of paramount importance.
• Human post-mortem tissue analysis was regarded as adding significant value to the field: to compare what is observed in life, e.g., imaging studies, to tissue parameters that can only be measured after death.
• Attendees emphasised the importance of linking the collected brain tissue with detailed patient demographic and clinical history information. ‘In life’ clinical imaging data was considered to be particularly desirable.
• Surrogate human tissues such as the retina and the kidney small vessels were suggested as useful sources of alternative information to inform mechanistic and translational understanding of the brain vasculature. Surgically resected tissues in general offered a feasible approach to achieve functional measurements with pathological comparisons. There was scope for novel technology development in this area.
• The recently launched DPUK Vascular Disease Mechanisms Experimental Medicine theme could be used as a vehicle for the coordination of further studies. It was
important to translate back into animal models where exemplars of coupling neurovascular burden with cognitive decline are discovered in human studies.

- To study vascular ageing, human cohort studies should:
  - collect data on comorbidities;
  - factor in a strong organisational capacity to collect and use medical history and risk factors; and
  - obtain a comprehensive data set linked into post-mortem tissue.

### 6 Next steps

The meeting report would be presented to the MRC’s NMHB and PSMB for the Board members to consider whether a highlight notice in neurovascular ageing should be advertised to highlight the issues identified in the workshop.

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Annex 3 Workshop presentations
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  - 3.2 Professor Elga de Vries
  - 3.3 Dr Anton Roks
## Annex 1 Delegate list and biographies

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<td>Professor of Molecular and Cellular Physiology at the University of Leeds. He is a member of the BHF’s Chairs and Programmes Grants Committee and Wellcome-DBT India Alliance Fellowship Committee, and former member of the MRC PSMB. Research interest is in calcium ion entry into cells and particularly cells of the vasculature in physiology and disease.</td>
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| **Professor Tony Day**  
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| **Professor Elga de Vries**  
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| **Dr Paul Edison**  
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| **Professor Michael Frenneaux**  
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m.frenneaux@uea.ac.uk | Clinical Cardiologist, Professor and Head of UEA’s Norwich Medical School. He is a past member of the MRC’s PSMB and present member of the BHF Chairs and programmes grants committee. He is an integrated cardiovascular physiologist and his clinical interests focus on heart failure and cardiomyopathies. |
| **Professor Christopher Garland**  
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Christopher.garland@pharm.ox.ac.uk | Professor of Vascular Pharmacology at the University of Oxford. His research investigates how the very small endothelial cells that line the vasculature of the body control the flow and pressure of the blood. |
| **Professor John Greenwood**  
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j.greenwood@ucl.ac.uk | Hugh Davson Professor of Biomedical Research and Head of the Department of Cell Biology at the UCL Institute of Ophthalmology. Research includes: the role the vascular endothelium in the pathogenesis of brain and retinal disease; identification of novel drivers of vascular pathology and retina; factors that contribute to |
the development of neovascularisation and vessel remodelling.

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interface between Alzheimer’s Disease and vascular dementia, Post-Stroke Dementia and Small Vessels Diseases of the brain.

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<td>Professor of Medicine and Dean of the Faculty of Medical Sciences at UCL. He is the Chair of the Population and Systems Medicine Board at the MRC. His research interests are the pathobiology of a1-antitrypsin deficiency, the serpinopathies and COPD. sessionStorage.set</td>
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health; and molecular pathways that regulate inflammation, angiogenesis and vascular stability are studied.

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<td>Professor of Medicine and Cardiovascular Medicine at Imperial College London. His current research interests include genetic and epigenetic mechanisms and systems biology studies in cardiovascular and metabolic diseases, including Alzheimer’s disease, and preventive medicine.</td>
</tr>
<tr>
<td><strong>Professor Catherine Shanahan</strong></td>
<td>King’s College London</td>
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<td>Professor of Cellular Signalling in the Cardiovascular Division at King’s College London. Research focuses on mechanisms of vascular smooth muscle cell dysfunction in ageing and disease.</td>
</tr>
<tr>
<td><strong>Professor David Sharp</strong></td>
<td>Imperial College London</td>
<td><a href="mailto:david.sharp@imperial.ac.uk">david.sharp@imperial.ac.uk</a></td>
<td>Professor of Neurology at Imperial College London. His clinical research programme aims to improve clinical outcome after traumatic brain injury, focusing on common cognitive impairments in domains such as memory and attention. He uses advanced neuroimaging technologies and focuses on the effect of brain injury on brain network function.</td>
</tr>
<tr>
<td><strong>Professor Rhian Touyz</strong></td>
<td>University of Glasgow</td>
<td><a href="mailto:rhian.touyz@glasgow.ac.uk">rhian.touyz@glasgow.ac.uk</a></td>
<td>Professor and Director of the Institute of Cardiovascular and Medical Sciences and the British Heart Foundation Chair of Cardiovascular Medicine at the University of Glasgow. She is a clinician-scientist with a focus on hypertension research, with a particular interest in translational research.</td>
</tr>
<tr>
<td><strong>Dr Patric Turowski</strong></td>
<td>UCL Institute of Ophthalmology</td>
<td><a href="mailto:p.turowski@ucl.ac.uk">p.turowski@ucl.ac.uk</a></td>
<td>Senior lecturer in Cell Biology at the Institute of Ophthalmology, University College London. His research studies signal transduction in neural vascular endothelial cells, with a focus on vascular permeability during cerebral and retinal inflammation and oedema.</td>
</tr>
<tr>
<td><strong>Professor Joanna Wardlaw</strong></td>
<td>University of Edinburgh</td>
<td><a href="mailto:joanna.wardlaw@ed.ac.uk">joanna.wardlaw@ed.ac.uk</a></td>
<td>Professor of Applied Neuroimaging at the University of Edinburgh. Her research is focused on the pathophysiology and treatment of acute ischaemic stroke, particularly thrombolysis in stroke, the use of imaging in stroke diagnosis and prevention and the effects of ageing on the brain.</td>
</tr>
<tr>
<td><strong>Professor Peter Weissberg</strong></td>
<td>British Heart Foundation</td>
<td><a href="mailto:weissbergp@bhf.org.uk">weissbergp@bhf.org.uk</a></td>
<td>Medical Director of the British Heart Foundation. His predominant research interest has been in the cell biology of atherosclerotic plaques and his group were amongst the first to develop clinical</td>
</tr>
</tbody>
</table>
imaging techniques to characterise the cellular composition of atherosclerotic plaques in patients.

**Professor Roy Weller**  
University of Southampton  
row@soton.ac.uk  
Professor of Neuropathology at the University of Southampton until he retired, he now holds an emeritus position. His main research interests have focused on Alzheimer’s disease and in particular the role of vascular disease in the pathogenesis of Alzheimer’s disease.

**Dr David Werring**  
University College London  
d.werring@ucl.ac.uk  
Reader in Clinical Neurology and Honorary Consultant Neurologist at UCL Institute of Neurology. His research focus is in stroke with a particular interest in neuroimaging and small vessel disease, especially intracerebral haemorrhage and cerebral amyloid angiopathy.

**Professor Matt Whiteman**  
University of Exeter  
m.whiteman@exeter.ac.uk  
Professor of Experimental Therapeutics at the University of Exeter Medical School. His research focus is on the biomedical application of hydrogen sulfide donors in health and disease including acute/chronic inflammation, cardio- and neurovascular, stroke/MI and diabetes.

**Professor William Wisden**  
Imperial College London  
w.wisden@imperial.ac.uk  
Professor of Molecular Neuroscience at Imperial College London. Research interests in neurobiology with a focus on establishing neural circuitry involved in sleep, utilising murine genetic models.

**Dr Paul Wren**  
GlaxoSmithKline  
Paul-bryan.b.wren@gsk.com  
Dr Wren is a Clinical Development Director in GSK Neurosciences with over 20 years Pharma experience. He is a Project Leader and Early Development Leader of therapeutic approaches relating to neurodegeneration. His research interests are in conducting robust experimental approaches for treatment options for patients that suffer from neurological and psychiatric disorders.

**Professor Ian Zachary**  
University College London  
I.Zachary@ucl.ac.uk  
Professor of Vascular Cell Biology at University College London. His current research focuses on the role of the VEGF receptor, Neuropilin, in health and disease.

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**Medical Research Council Staff**

**Dr Kate Adcock**  
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Dr Adcock is the Head of Neurosciences and Mental Health at the Medical Research Council. Her role is to ensure that the MRC’s neurosciences portfolio remains leading-edge, high impact, strategically aligned and excellent value for money.

**Dr Rob Buckle**  
MRC  
Robin.buckle@headoffice.mrc.ac.uk  
Dr Buckle is Director of Science Programmes at the MRC, with responsibility for the four MRC Research Boards that allocate and oversee the majority of the MRC’s research funding. Rob is
<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
<th>Role and Responsibilities</th>
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</thead>
<tbody>
<tr>
<td><strong>Dr Joe McNamara</strong></td>
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<td>Head of Theme for two major scientific areas at MRC, neurodegeneration research and regenerative medicine.</td>
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<td><strong>Dr Stephen Meader</strong></td>
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<td>Senior Programme Manager within the Neurosciences and Mental Health Board team with responsibility for neurodegenerative diseases and stroke. Subtopics have included: imaging, brain banking, the Joint Programming in Neurodegenerative Diseases and CoEN initiatives and the creation of the Dementias Platform UK.</td>
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<td><strong>Dr Rebecca Ward</strong></td>
<td><a href="mailto:Rebecca.ward@headoffice.mrc.ac.uk">Rebecca.ward@headoffice.mrc.ac.uk</a></td>
<td>Programme Manager for Cardiovascular and Respiratory Medicine within the Population and Systems Medicine Board at the MRC. She is the scientific point of contact and manages the review process, the current portfolio of awards and strategic activities in the areas of cardiovascular and respiratory medicine.</td>
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</table>
# Annex 2 Workshop agenda

**Workshop on neurovascular ageing in health and disease: interplay of the CNS and vascular system**

Wednesday 25 March 2015  
BMA House, Tavistock Square, London WC1H 9JP

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker / Chair</th>
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<tbody>
<tr>
<td>10:15</td>
<td>Registration and coffee</td>
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<tr>
<td>10:45</td>
<td>Joint Chair Introduction and welcome</td>
<td>Professor David Lomas</td>
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<td></td>
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<td>Professor Hugh Perry</td>
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<tr>
<td>10:50</td>
<td>Workshop context</td>
<td>Professor Hugh Perry</td>
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<tr>
<td>11:05</td>
<td>Workshop context</td>
<td>Professor Hugh Perry</td>
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<tr>
<td>11:05</td>
<td>Vascular Homeostasis</td>
<td>Professor Eli Keshet</td>
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<tr>
<td>11:35</td>
<td><strong>The Neurovascular Unit in Health and Disease</strong></td>
<td>Professor Elga de Vries</td>
</tr>
<tr>
<td>12:05</td>
<td>Genomic instability and Vascular Ageing</td>
<td>Dr Anton Roks</td>
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<tr>
<td>12:35</td>
<td>Questions and initial discussion</td>
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<tr>
<td>13:10</td>
<td>Explanation of afternoon session</td>
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<tr>
<td>13:15</td>
<td>Networking Lunch</td>
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<tr>
<td>14:00</td>
<td>Breakout group discussions (6 tables, each with chair and rapporteur)</td>
<td>Professor Hugh Perry</td>
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<tr>
<td>15:15</td>
<td><strong>Afternoon Tea (preparation of headline summaries by rapporteurs)</strong></td>
<td>Professor Hugh Perry</td>
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<td>15:30</td>
<td>Breakout group plenary (5 minutes per group) and general discussion</td>
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<tr>
<td>16:20</td>
<td>Summing up, agree conclusions and next steps</td>
<td>Professor Hugh Perry</td>
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<tr>
<td>16:30</td>
<td><strong>Workshop close</strong></td>
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Annex 3 Workshop presentations
Vascular homeostasis and rejuvenation: A VEGF-centered view

Eli Keshet, Ph.D.
The Hebrew University–Hadassah Med Sch, Jerusalem
MRC Workshop on neovascular ageing
London, March 25, 2015

VEGF is indispensable for maintaining homeostatic microvascular density in the heart

Conclusion: VEGF is indispensable for hypoxia-driven angiogenesis

MVD deficit leads to a compromised cardiac function that can be rectified by VEGF-induced re-vascularization

VEGF Dependence / Vessel Regression / Brain Injuries of Prematurity (PVL)

At greatest risk for PVL are premature, very low birth-weight (VLBW) infants. It is estimated that approximately 3–4% of infants who weigh less than 1,500 g have PVL,

Tissue-specific conditional (and reversible) VEGF Gain or loss-of-function

MHCα promoter tTA TET sVEGFR1

VEGF GOF

CamKII–P–tTA / tet-VEGF

Vascular homeostasis: matching supply to demand

Maintenance level

Vascular expansion

Shweiki et al., Nature 1992

Vascular regression

Alon et al., Nat Med, 1995

Tissue-specific conditional & reversible VEGF Gain or loss-of-function

Toolbox for manipulating the organ vasculature

VEGF VEGF-decoy receptor

On

Off

VEGF dependence / vessel regression / brain injuries of prematurity (PVL)

Last to mature” vascular beds in the developing brain determine the brain region vulnerable to certain insults associated with premature birth (e.g. VEGF loss-of-function?)
Periventricular GE vessels are the last cortical vessels to mature and seal their Blood-Brain-Barrier (BBB) functionality.

VEGF suppression during the critical gestational window produces a PVL-like phenotype.

Neuronal out-migration from the SVZ in the developing human brain.

A deficit in late out-migrating GABAergic inhibitory interneurons.

The vascular maturation – vascular regression- neurovascular injuries of prematurity connection:

- A developmentally-programmed maturation wave of cerebral vessels (associated with BBB closure and VEGF refractoriness)
- Peri-ventricular vessels are the last to mature and hence become refractory to VEGF
- VEGF suppression at a critical gestational window (even episodic) results in selective ablation of peri-ventricular vessels
- Obliteration of peri-ventricular vessels produces a PVL-like phenotype both with respect to the primary lesion in deep white matter, as well with respect to a reduction in late out-migration GABAergic inhibitory interneurons
- A first animal model recapitulating both temporal and spatial specificities of PVL
- A hyperoxia – VEGF – vessel obliteration - focal ischemia/hypoxia as an etiologic axis ??
Blood vessels and adult neurogenesis

Conditional VEGF induction at the DG neurogenic niche

Hippocampal Neurogenesis

VEGF induces hippocampal angiogenesis and neurogenesis

Increase in hippocampal neurogenesis is proportional to increased hippocampal MVD

Even a short duration of VEGF induction is sufficient for enhanced neurogenesis to persist months later!
Adult DG neurogenesis decays with age: The stem cell disposal model

ENCINAS ET AL., CELL STEM CELL, 2011

VEGF-enhanced neurogenesis does not cause premature NSCs exhaustion!

Summary

Mere expansion of the DG vasculature is sufficient to increase the basal level of adult neurogenesis! (mediated by augmented NSC/vascular engagements?)

Vascular niche expansion leads to enhanced neurogenesis without premature exhaustion of neuronal stem cells.

Vascular niche expansion attenuates the natural age-dependent decay of adult neurogenesis, at least partly via attenuating age-related NSCs quiescence.

Prospects of rejuvenating the vascular niche?
The neurovascular unit in health and disease

Prof.dr. Elga de Vries, Neuro-immunology research group
VU University medical center Amsterdam, The Netherlands

The brain is highly vascularized

- Brain > 20% of glucose
- Over 600 km of length
- Dense capillary network
- Optimal function CNS

The neurovascular unit: cellular complex

Dynamic regulation

- Essential in maintaining brain homeostasis
- Limits entry of immune cells and hydrophilic molecules (TJ)
- Efflux waste products (ABC transporters)
- Actively transports nutrients
- Regulated through surrounding cell types (Shh, Wnt, RA)


Dutch water management: a royal affair

Alzheimer’s disease (capillary CAA)
Multiple sclerosis
Stroke (as secondary event)
Aging
Brain trauma
Epilepsy
Migraine

BBBNedwork Foundation

Dutch water management: a royal affair

King Willem Alexander

Conditions affecting the barrier

This should open for the bilingual version.
Understanding NVU in neurological disorders

Neuro-inflammation and neurodegeneration
Barrier dysfunction – glial activation – neuronal dysfunction

- Traumatic brain injury
- Epilepsy
- Ageing
- Multiple sclerosis
- Cardiovascular / stroke

Translational approach

1. Immunohistochemistry on post-mortem brain tissue
2. In vitro expression and function analysis on brain endothelial cells
3. In vivo expression analysis on tg mouse

Alzheimer’s Disease

- Neuro-fibrilary tangles
- Amyloid Plaque

Diagnostic Symptoms

- Changes in Personality
- Disorientation and misinterpreting spatial relationships
- Memory Loss

Disease course

- 80-90% of AD patients has CAA
- Genetic mutations
  - Sporadic CAA
  - CAA type 1 (capillary involvement) → capCAA
  - CAA type 2 (no capillary involvement)

Cerebral amyloid angiopathy (CAA)

Pathological features

- Aβ 1-17
- MHC class II (microglia)
- GFAP (reactive astrocytes)

Richard et al., JNEN 2010
Vascular Hypothesis


PET: reduced glucose metabolism

Boxplot for (R)-[11C]verapamil BPND of the global cortical region.


PET: reduced P-gp activity

Controls AD

Boxplot for (R)-[11C]verapamil BPND of the global cortical region.


MRI: microbleeds

Gradient echo -weighted magnetic resonance sequence of a 78-year-old woman suffering from Alzheimer’s disease.

Charlotte Cordonnier, and Wiesje M. van der Flier Brain 2011;134:335-344

A-beta 1-42 and A-beta 1-40 deposits

Carrano et al., Neurodegener Dis 2012
Carrano et al., Antioxid Redox Signal 2011

The BBB in capCAA: tight junctions?

ZO-1

Abeta ZO1 CD31 merge

Carrano et al., 2011 / 2012
Loss of tight junctions in capCAA

Reduced P-gp expression in capCAA

Pgp expression in human brain tissue

FUNCTION
EXPRESSION

Thank you......

Ananya Chakraborty
Claudio Derada Troletti
Bert van het Hof
Jack van Horssen
Alein Kamermans
Wouter Kamphuis
Gijs Kooij
Melissa Lopes-Pinheiro
Mark Mizee
Philip Nijland
Susanne van der Poel
Hripsime Snkhchyan
Laura Wierts
Nienke de Wit

Collaborators
Alzheimer center VUMc
(Roos, van der Flier, Scheltens)

ZonMw

Neuroscience Campus Amsterdam
Vascular & Neurological Problems related to Genomic Instability

Anton JM Roks
Division of Vascular Medicine and Pharmacology
Dept. of Internal Medicine
Erasmus Medical Center, Rotterdam
a.roks@erasmusmc.nl

Cardiovascular events: one of the major causes of death in the elderly

Hidden vascular problems
- Cardiac disease
- Brain dysfunction (motoric, cognitive etc.)
- Renal disease
- Food malabsorption
- Muscle weakness
- …

“A man is as old as his arteries”

Thomas Sydenham (1624–1689)

HYPOTHESIS
DELAYING VASCULAR AGEING WILL IMPROVE HEALTHY AGEING
What is vascular ageing?

- Increased arterial stiffness
- Arterial thickening
- Atherosclerosis
- Endothelial vasodilation
- Increased thrombosis
- Hypertension
- Rarefaction
- Decreased angiogenesis
- Aneurysms
- ...

The Hallmarks of Ageing (biological age)

- Systemic changes
  - Increased blood pressure
  - Increased vascular stiffness
- Cellular changes
  - Endothelial dysfunction
  - VSMC dysfunction (decreased vasodilation)
- Molecular changes
  - Reduced aortic eNOS levels
  - Increased cellular senescence
  - Increased DNA damage response

Human genomic instability syndromes

Striking parallels between TTD patient/mouse

Trichothiodystrophy

More aging symptoms in Ercc1 mutants with ≥3 repair defects: severity of repair defect determines the speed

<table>
<thead>
<tr>
<th>Repair defects</th>
<th>Ercc1&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>Ercc1&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>Ercc1&lt;sup&gt;−/−&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1: GG-NER</td>
<td>Knock-out</td>
<td>Mutant</td>
<td>Knock-out</td>
</tr>
<tr>
<td>2: TC-NER</td>
<td>No Ercc1 protein</td>
<td>Mutant</td>
<td>No Ercc1 protein</td>
</tr>
<tr>
<td>3: X-RCA repair</td>
<td>Lifespan 3.8 wks</td>
<td>Lifespan 4.6 mo</td>
<td>Lifespan 1.5 y</td>
</tr>
<tr>
<td>4: OGG repair</td>
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</tbody>
</table>

Aging phenotype

- Shortened lifespan
- Kyphosis, sarcopenia
- Liver, kidney aging
- Bone marrow aging
- Vascular aging
- Ataxia, dystonia
- Neurodegeneration
- Dementia, loss of vision, etc...

Recapitulation of human aged vascular phenotype

Durik M et al. Circulation 2012
Effect DR on vascular dilatation in Ercc1<sup>Δ<sup>-</sup> aorta

No change of vasodilatation in ad lib.-fed (AL) WT aorta segments, ex vivo.

Age-dependent decline of vasodilatation in AL Ercc1<sup>Δ<sup>-</sup></sup> aorta segments, ex vivo.

Disrupted nitric oxide signaling:
- decreased eNOS
- increased phosphodiesterase (cGMP)

Neurological problems
Aging features of Ercc1Δ/- mice

Laura Niedernhofer (Scripps, Florida)

Progressive neurodegeneration in Ercc1Δ/- mice

GFAP (activated astrocytes)

Brain shrinkage
Neuronal loss, Neuron-dependent microglia activation
Loss of neuronal plasticity, memory, motor performance, hearing, vision, etc

Age 8 wks

NEUROLOGICAL PROBLEMS

VASCULAR PROBLEMS

Vascular-specific strains

• Endothelial cells: Tie2Cre - Ercc1 flox
• Vascular smooth muscle cells: SM22α – Ercc1 flox
  • In vivo hemodynamic and ex vivo vascular function in organ baths
  • 3 - 6 -12 months

Manipulating rapid aging

By generating conditional repair mutants we can selectively target aging to specific organs/tissues or induce rapid aging to occur in desired stages of development:

e.g. brain-, cardiac and vascular-specific Ercc1, Csb/Xpa or Xpg mutants

Ingrid van der Pluijm

TREATMENTS
**Summary effect DR on aging in DNA repair models**

Concomitant with lifespan extension DR delays aging in a wide variety of organs/tissues (in progress):

- Liver (anisokaryosis, polyplody)
- Kidney (tubulonephrosis, anisokaryosis)
- Immune system (T-helper subpopulation, IgA levels)
- Retina (photoreceptor loss)
- Neuronal system (preservation of neurons, behavior: motor coordination, sciatic nerve vacuolization, GFAP/Mac2/Hsp25)
- Vascular system (vascular dilatation)

**Summary**

- Genomic instability, a primary hallmark of ageing, contributes to age-related vascular and neurological function, reminiscent of human ageing.
- Diet restriction is a very effective intervention, and possibly genoprotective.
- Organ-specific DNA repair-defective mice may serve as useful tools to study interactions between ageing organs.

**What is important for the future?**

- Dept. of Internal Medicine: Matej Dunk, Haiyan Wu, Jan Danser
- Dept. of Genetics: Jan Hoeijmakers, Ingrid van der Pluijm, Wilbert Vermeij
- Dept. Of Neurology: Dick Jaarsma, Ype Elgersma
- RIVM: Erwin Reiling, Martijn Dölle, Jan van der Steeg
- Maastricht University: Harald Schmidt
- Odense University: Jo de Mey
- Von Goethe University, Frankfurt: Annemarieke Loot, Ingrid Fleming
- King’s College, London: Catherine Shanahan

**Acknowledgments**