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REVIEW

Proceedings from the Albert Charitable Trust Inaugural Workshop on white matter and cognition in aging

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Abstract This third in a series of vascular cognitive impairment (VCI) workshops, supported by "The Leo and Anne Albert Charitable Trust," was held from February 8 to 12 at the Omni Resort in Carlsbad, CA. This workshop followed the information gathered from the earlier two workshops suggesting that we focus more specifically on brain white matter in age-related cognitive impairment. The Scientific Program Committee (Frank Barone, Shawn Whitehead, Eric Smith, and Rod Corriveau) assembled translational, clinical, and basic scientists with unique expertise in acute and chronic white matter injury at the intersection of cerebrovascular and neurodegenerative etiologies. As in previous Albert Trust workshops, invited participants addressed key topics related to mechanisms of white matter injury, biomarkers of white matter injury, and interventions to prevent white matter injury and age-related cognitive decline. This report provides a synopsis of the presentations and discussions by the participants, including the existing knowledge gaps and the delineation of the next steps towards advancing our understanding of white matter injury and age-related cognitive decline. Workshop discussions and consensus resulted in action by The Albert Trust to (1) increase support from biannual to annual "White Matter and Cognition" workshops; (2) provide funding for two collaborative, novel research grants annually submitted by meeting participants; and (3) coordinate the formation of the "Albert Research Institute for White Matter and Cognition." This institute will fill a gap in white matter science, providing white matter and cognition communications, including annual updates from workshops and the literature and interconnecting with other Albert Trust scientific endeavors in cognition and dementia, and providing support for newly established collaborations between seasoned investigators and to the development of talented young investigators in the VCI-dementia (VCID) and white matter cognition arena.

Keywords Brain white matter · Aging · Cognition · Vascular cognitive impairment (VCID) · Myelin · Neurovascular · Oligovascular · Blood-brain barrier

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Introduction

Unlike heart attacks, the slow and long process of cognitive deterioration does not hurt. Instead, clear thinking slips away in silence and only when enough is lost do

we take notice, not knowing when it even happened; and by then, it is too late. Some people seem inexplicably afflicted with cognitive decline or worse, dementia, while others are strikingly resilient and have remarkable brain health through late life. Why is that? What drives that resilience? What drives that ability to bounce back? Invited attendees for this workshop seek answers to these fundamental questions as vital to our mission to preserve brain health and prevent cognitive impairment. Their research is focused on a feature particularly unique to the human brain: our high myelin content, the fatty sheath that coats our nerve axons and constitutes *brain white matter* (Schoenemann et al. 2005; Semendeferi et al. 2002; Smaers et al. 2010).

Brain white matter is a critically important, yet entirely unexploited and poorly understood, area in age-related cognitive decline (Robinson et al. 2018). Transmission of nerve impulses and the fast processing speeds essential to the integration and performance of our complex cognitive abilities hinge on myelin development, maturation, degeneration, and repair—all mechanisms that continue into adulthood (Dubois et al. 2014; Mosser et al. 2017; Mount and Monje 2017; Nickel and Gu 2018; Stiles and Jernigan 2010; H. Zhang et al. 2019; Shobin et al. 2017). This enduring process of myelination in the human brain renders white matter a potentially modifiable lifelong target for enhancing resilience and preserving, promoting, and restoring brain health.

White matter injury is the hallmark of an aging brain and cerebrovascular (e.g., small vessel) disease. White matter hyperintensities (WMH) on brain MRI are the most common finding in the aging brain (Black et al. 2009; de Leeuw et al. 2001; Yoshita et al. 2006). These WMH, which are strongly associated with vascular risk factors, are also associated with cognitive decline, a 3-fold increase in risk of stroke, a 2-fold increase in risk of dementia or death, and a more rapid decline in global cognitive performance, executive function, and processing speed (Debette and Markus 2010; Tamura and Araki 2015; van Dalen et al. 2016; C. R. Zhang et al. 2015; Csipo et al. 2019; de Montgolfier et al. 2019a, b). Brain connectivity, which relies on the functional interplay between neurons, vessels, and glial cells (i.e., the neurovascular unit) and the integrity of the myelinated axons that shape the brain white matter, is disrupted by WMH (Csiszar et al. 2017; Ungvari et al. 2017). The lack of success for clinical intervention in Alzheimer's disease and other "cognitive decline syndromes" may be due in part to our incomplete knowledge and understanding of their natural history and the largely neglected role of ongoing white matter injury and the repair mechanisms involved (Ricciarelli and Fedele 2017).

In order to probe in detail, the roles of brain white matter in cognitive functioning and to facilitate collaborative research towards closing our knowledge gap in this domain "The Leo and Anne Albert Charitable Trust Inaugural Workshop: White Matter and Cognition" were convened. Expert scientists specifically focused on mechanisms, imaging, and preclinical models of white matter injury. Over a 3-day program, specific sessions explored vascular and inflammatory contributions to white matter injury, neuroimaging approaches to study white matter pathology and blood-brain barrier disruption, role of microglia and oligodendrocytes in white matter injury, and repair, as well as biomarkers and pre-clinical models in white matter disease. The obvious success of the progression of the first two workshops into white matter and cognition focus of the third was translated into the establishment of "The Albert Research Institute for White Matter and Cognition," trust support for annual (versus the previous bi-annual) workshops, the inaugural request for applications for pilot funds to foster novel collaborative research among the workshop attendees and to support the development of young investigators. The missions of the institute and the novel collaborative research and young investigator support are to help close the existing knowledge gap in white matter injury and repair in cognitive functioning and to help discover disease mechanisms, biological targets, and interventions that can be harnessed toward healthy brain aging and reduce VCI. We believe that these discoveries will change today's silent, inexorable narrative of age-related cognitive impairment for one that will allow us to improve the lives of our patients, earlier than we previously considered.

White matter and cognition workshop synopsis

The workshop scientific program was organized into six major topics of scientific interest based on the scientific expertise of participants. A brief summary of each participants' presentation (i.e., identified by title, presenter, and institution) under these 6 topics is provided below.

Workshop topic 1: endothelium, pericytes, inflammation, and small vessel disease

White Matter Abnormalities in Cerebral Amyloid Angiopathy. **Eric E. Smith** (Department of Clinical Neurosciences and Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada). Cerebral amyloid angiopathy (CAA) caused by beta-amyloid deposition is the second most common small vessel disease of aging and is usually accompanied by a large burden of white matter lesions visible on T2-weighted MRI as white matter hyperintensities (WMH) (Smith 2018). White matter disconnection underlies the vascular cognitive impairment experienced by most CAA patients (Reijmer et al. 2016). However, the pathophysiology of the severe white matter lesions seen in CAA is incompletely understood, particularly as vascular CAA pathology affects the vessels of the cortex and leptomeninges much more than the vessels of the white matter. Analyses of the topography of CAA-related white matter changes show large degrees of overlap with non-CAA-related small vessel disease (Smith et al. 2010), but with an over representation of posterior WMH in CAA (Charidimou et al. 2016). In CAA, WMH is strongly associated with impaired vascular reactivity (Peca et al. 2013), suggesting that the WMH could be a distal ischemic consequence of dysfunctional CAA-laden arteries supplying the white matter. Another possibility, still speculative at this point, is that protein elimination failure associated with CAA might lead to high white matter concentrations of soluble abeta that is toxic to the small vessels, oligodendrocytes, or myelin.

Disclosures: Dr. Smith reports consulting fees from Portola Pharmaceuticals and Almylam Pharmaceuticals.

Clarifying the Brain Capillary Pericyte with In Vitro Imaging and Optical Manipulation. Andy Y. Shih (Center for Developmental Biology and Regenerative Medicine, Seattle Children's Research Institute, Seattle, WA). Communication between pericytes and endothelial cells is essential for brain capillary health. Recent studies indicate that Alzheimer's disease and Alzheimer's disease-related dementias involve the heightened death or degeneration of brain pericytes. This is thought to contribute to the impairment of both blood-brain barrier integrity and cerebral blood flow, which subsequently exacerbates neurodegeneration (Winkler et al. 2014). Strategies to mitigate or compensate for pericyte loss may therefore lead to preserved vascular function in these neurological diseases and prevent small vessel-mediated white matter injury. Using in vivo multi-photon imaging, we recently discovered that brain pericytes retain the ability to structurally remodel in adulthood. Under basal conditions, pericyte processes extend or retract over days to ensure even tiling of pericytes along the entire capillary endothelium. Following optical ablation of single pericytes, the processes of neighboring pericytes will extend over large distances to regain contact with exposed capillary regions. However, this growth takes days to occur leaving the endothelium transiently uncovered. The consequence of transient pericyte loss on capillary blood flow dynamics and the importance of maintaining pericyte coverage for normal capillary flow resistance were discussed, and ongoing studies to examine whether pericyte remodeling differs across zones of the brain microvasculature and in the context of small vessel disease were addressed.

A Key Role for Neurovascular Inflammation in VCID: Lessons from Mouse and Human. Donna Wilcock (Sauders-Brown Center on Aging, University of Kentucky, Lexington). In Alzheimer's disease, neuroinflammation has been linked to positive and negative outcomes of pathologic processes for several years. However, the role of neuroinflammation in VCID remains unclear. Our laboratory has been studying the hyperhomocysteinemia model of small vessel disease and the underlying pathologic mechanisms driving the development of small vessel pathology, in particular microhemorrhage. In this model, we have found a key role for neuroinflammation, likely initiated through Hsp27, a small heat-shock protein, driving an inflammatory response through p38 MAPK. Ultimately, this inflammatory response increases expression and activity of MMPs leading to blood-brain barrier breakdown. In addition, we have been exploring inflammatory biomarkers in the plasma and CSF of patients selected for the presence of cerebral small vessel disease and MCI. We found a significant association between the levels of white matter pathology and MMPs, proinflammatory cytokines such as TNFα and IL6, as well as association with angiogenic proteins that could play an additional role in inflammation. Collectively, our data support a key role for inflammation in the pathological progression of VCID and this could represent an attractive therapeutic target for clinical development.

Molecular Determinants of Cerebral Small Vessel Disease. Myriam Fornage (Institute of Molecular Medicine, University of Texas-Houston). WMH are part

of the spectrum of vascular injury associated with advancing age and cerebral small vessel disease. Their pathophysiology remains poorly understood and no effective therapies to reduce their burden currently exist. Traditional vascular risk factors, such as hypertension and diabetes mellitus, explain only up to 2% of the WMH variance, suggesting ample opportunities for the identification of additional risk factors that will help unravel WMH pathogenesis and facilitate drug target discovery. The high estimates of heritability consistently reported for WMH suggest a strong genetic component in their etiology. The application of genomic technologies in human populations to the discovery of genetic and epigenetic determinants of cerebral WMH as the primary expression of small vessel disease was reviewed. Specifically, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium has facilitated genome-wide association study meta-analyses and replication opportunities among multiple large and well-phenotyped longitudinal cohort studies. The preliminary signals indicate contributions from molecules such as claudin 5 and indole-3-propionate in the expression of WMH. However, more collaborative initiatives with additional large and well-phenotyped longitudinal cohorts are needed to further delineate the role of such molecular determinants.

Biomechanical Hypothesis of Vascular Related White Matter Injury. Charles DeCarli (Alzheimer's disease Center, University of California Davis). Recent work by our group has found strongly significant associations between pulse wave velocity and the presence of increased "free water" (FW) measured by DTI in the white matter of cognitively normal individuals 51 years of age on average. One hypothesis for this finding is that stiffening of the aorta increases transmission of pulsatile energy into small vessels that are not accustomed to high levels of pulsatility. High levels of pulsatility could lead to changes in pre-capillary pressure gradients thereby resulting in greater flow of solute into the interstitium until interstitial pressure equilibrates with intravascular pressure and a new equilibrium is achieved, albeit with an expanded extravascular FW content. A second hypothesis is that arterial stiffening and elevated blood pressure may result in subtle blood-brain barrier dysfunction, shifting the equilibrium point between arterial and osmotic pressure, which in turn may allow extra water, toxins, proteases, or other substances in the blood to enter the brain interstitial space and disturb the composition of the interstitial fluid within the WM milieu. The formulation of the "Biomechanical Hypothesis of Vascular Related White Matter Injury" including recent data showing evidence of endothelial injury in relation to the FW further supporting our hypothesis was discussed. Ongoing work using exosome cargos will further advance our understanding of the specific biomechanical changes and facilitate protective strategies towards preventing white matter injury.

Workshop topic 2: imaging brain changes in VCID

MRI Measurements of Myelin and BBB Integrity In Vivo: Lessons from Multiple Sclerosis. Doug Arnold (Neurology and Neurosurgery, McGill University, Montreal). Another well-established disease of the brain white matter is multiple sclerosis (MS). In MS research and clinical trials, white matter hyperintense and hypointense lesions have been quantified with respect to their volume, numbers, and changes over time for more than 20 years. Extensive experience has demonstrated the advantages of doing this using automated methods, and also the challenges of developing and validating such methods. T2 signal hyperintensity is sensitive, but pathologically non-specific. T1 hypointensity is less sensitive, but more specific for severe tissue injury, including neuroaxonal loss. Our imaging work in MS has demonstrated that the increased specificity for myelin loss can be achieved using a variety of non-conventional acquisition sequences. Magnetization transfer ratio (MTR) or, better, magnetization transfer saturation (MTsat) imaging and DTI for assessing radial diffusivity are easily implemented on most scanners and in clinical trials to assess remyelination responses to therapy. More quantitative sequences to determine the short T2 component associated with myelin water (so-called myelin water imaging) or to model the macromolecular pool size generally require local implementation and expertise that makes them unsuitable for clinical trial use. Gadolinium-enhanced MRI can provide quantitative assessment of BBB permeability, either using dynamic contrast enhancement or, more practically in clinical trials, by calculating the gadolinium uptake ratio, defined as the natural logarithm of the ratio of the post-Gd to pre-injection image (Cao et al. 2005). Extension of these quantitative imaging approaches to ischemic white matter injury will significantly advance our understanding of gradients of injury, extent of remyelination, and the time course of injury.

In Vivo Imaging of Neuro-Inflammation and Fiber Tract Degeneration after Stroke. Alex Thiel (Department of Neurology and Neurosurgery, McGill University and Jewish General Hospital, Montreal). Compared with controls with no stroke, incident stroke is associated with acute changes in cognition and a changed rate of cognitive decline over time. Mechanisms underpinning post-stroke cognitive impairment are unknown and why, in some patients, ischemic strokes can spark a brain-wide neurodegenerative process that will ultimately lead to progressive cognitive impairment remains a central question. Several lines of evidence suggest that an excessive inflammatory environment in the brain could aggravate post ischemic damage. In vivo imaging evidence for persisting inflammation in patients with ischemic stroke and its link to delayed direct and indirect fiber tract degeneration and how these processes can affect structural networks beyond the primary affected tracts were reviewed. The role of modulating factors such as diabetes, hypertension, or amyloid deposition and how they may contribute to this process either directly or by exacerbating or maintaining the inflammatory reaction were also addressed. If neuroinflammation is a final common pathway leading to post-stroke cognitive impairment, then anti-inflammatory drugs should be considered as a therapeutic strategy.

Understanding Small Vessel Disease Through Neuroimaging: Advanced Modeling and Novel Study Designs. Marco Duering (Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Germany). Diffusion imaging is a sensitive MRI method to detect tissue alterations in white matter injury and VCI. Markers derived from diffusion tensor imaging typically outperform other neuroimaging markers of small vessel disease and enable high-grade automation. However, little is known about the tissue changes driving diffusion signal alterations. Advanced diffusion modeling allows to gain more insight. Using a diffusion bitensor method, we were able to show that diffusion alterations and clinical status in small vessel disease are largely determined by extracellular fluid increase rather than alterations of white matter fiber organization (Duering et al. 2018). Even more advanced diffusion modeling on multishell data (leveraging multiple diffusion weights) is now available. We are therefore currently analyzing the most established multishell models, diffusion kurtosis imaging, and neurite orientation dispersion and density imaging, in two independent samples with small vessel disease. To investigate progression of small vessel disease and white matter injury, we recently established a new study design with monthly MRI examinations (Ter Telgte et al. 2018). The RUN DMC intense provides a better understanding of the role of acute infarcts in the pathophysiology of vascular white matter injury (Ter Telgte et al. 2019). It will further unravel the structural and functional consequences and clinical importance of acute infarcts, with an unprecedented temporal resolution.

Neuroimaging Endpoints in VCID: Defining White Matter Mechanisms and Interventions. Hugh S. Markus (Professor of Stroke Medicine, University of Cambridge, UK). Two main factors impede development of new therapies to improve, or slow progression, of cognitive impairment or dementia associated with small vessel disease. The first is a lack of potential new treatments. The second is difficulties of evaluating new therapies. Here, major challenges are the insensitivity of clinical endpoints, particularly over the 2–3 year time scale of a clinical trial, over which cognitive measures have a poor sensitivity to change. The potential use of MRI as surrogate markers to help evaluate new treatments was reviewed and summarized below. Much of our work has been lacunar stroke and confluent T2-white matter hyperintensities. Cognitive decline could not be detected over 2 or 3 years follow-up period, (Benjamin et al. 2016) but by 5 years was detectable. Power calculations suggested that a clinical trial would require sample sizes of 18,000 and 76,000 for endpoints of executive function and processing speed, respectively (Benjamin et al. 2016), clearly not realistic for a phase 2 trial. The lack of sensitivity of cognitive endpoints appears to be due to a heterogenous pattern of decline, insensitivity of the cognitive scales used, and practice or learning effects. MRI has promising uses in this context as follows: (a) Pre-screening a group who will progress to enrich a clinical trial (e.g., small vessel disease severity score can be simply calculated by visual inspection of a clinical MRI (Staals et al. 2014), as this could predict future dementia risk using lacunar infarcts, microbleed, and white matter hyperintensity severity; submitted for publication); (b) As a surrogate endpoint in clinical trials (e.g., a number of MRI markers are sensitive to change over periods as short as 1 year; diffusion tensor imaging (DTI) correlates strongly with cognition, and is very sensitive to change and can predict future dementia risk (Zeestraten et al. 2017). Its use would reduce sample sizes to about 350 (Benjamin et al.

2016), much lower than cognitive measures above; lacunar infarcts and brain volume correlate with cognition but are less powerful (c) to assess therapeutic efficacy on specific disease processes (e.g., MRI and other neuroimaging modalities can also be used to assess the underlying pathophysiology and in mechanistic studies used to see if treatment approaches can alter these processes. We used PET-MR, combining [11C] (R)-PK-111-95 PET imaging of glial activation and gadolinium contrast-enhanced dynamic MR to image blood-brain barrier (BBB) permeability, to explore the role of BBB leakage and neuroinflammation in sporadic small vessel disease, CADASIL, and controls, and demonstrated evidence of both increased "neuroinflammation" and BBB permeability, and are now translating a hypothesis developed in rodent models Rosenberg and colleagues (Jalal et al. 2015) to determine if these increases can be "switched off" using minocycline in a double-blind randomized controlled trial.

White Matter Hyperintensities in a Population-Based Study. Jonathan Graff-Radford (Mayo Clinic Alzheimer's Disease Research Center and the Mayo Clinic Study of Aging, Rochester). Studying WMH in a population-based sample is important as large registries such as ADNI exclude individuals with a significant vascular burden WMH have traditionally been viewed as a marker of cerebrovascular disease. Recent pathology studies have found an association of WMH with Alzheimer's disease (AD) pathologies. Using a population-based study, we examined the prevalence of WMH in the population, and investigated the topographic patterns of WMH associated with AD biomarkers. Our findings, summarized below, were presented at this workshop. As part of the population-based Mayo Clinic Study of Aging, we analyzed 1462 participants aged 50 years and older for prevalence of WMH. In order to determine the prevalence of WMH, we used WMH scaled by total intracranial volume. We performed Gaussian mixture distribution fit for age versus WMH into three clusters. We picked the highest value of the first two clusters which corresponded to 1.7% WMH/TIV. A total of 434 participants underwent FLAIR MRI and also had amyloid and tau PET scans. We used SPM12-based voxel-wise multiple regression analyses to detect WMH regions associated with AD biomarkers (amyloid-PET and tau-PET) after adjusting for age, sex, and hypertension. We show that the prevalence of WMH increased with age from 4.8% between ages 60 and 69 to 37.4% between ages 80 and 89. Topographic patterns of WMH associated with amyloid included periventricular WMH (frontal and parietal lobes). There were no WMH regions associated with tau. In summary, WMH prevalence increases with age. Amyloid but not tau load is associated with a specific topographic pattern of WMH.

Workshop topic 3: cerebrovascular regulation and blood brain barrier

Blood Pressure Exposure, Cerebrovascular Hemodynamics and White Matter Structure in Midlife. Farzaneh A. Sorond (Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL). Vascular risk factors, particularly hypertension, are strongly linked to white matter injury attributed to cerebral small vessel disease and measured by magnetic resonance imaging (MRI). However, most of the available data come from end-stage disease in aged populations where mechanistic studies are limited and duration and level of vascular risk factor exposure are not available. To address this knowledge gap, we have started to examine the relationship between blood pressure exposure, cerebrovascular hemodynamics, and white matter changes in midlife. Our preliminary data, presented at this workshop, showed that change in blood pressure, extent of blood pressure exposure, and blood pressure variability, rather than absolute levels of blood pressure at any one time point or diagnosis of hypertension, had a more significant impact on cerebrovascular hemodynamics and white matter structural integrity in midlife. Specifically, we showed that (1) neurovascular coupling and trails B performance in midlife were most sensitive to the magnitude of SBP increase over the prior 30 years; (2) cardiovascular health, as measured by AHA's Life's Simple 7 (Lloyd-Jones et al. 2010), during young adulthood was most predictive of cerebral autoregulation in midlife than cardiovascular health at midlife; and (3) white matter microstructural integrity and complexity in midlife, and prior to development of a significant burden of WMH, were significantly influenced by race and gender as well as blood pressure exposure. These findings were discussed in the context of a life course approach to vascular risk factor modification, early markers for risk stratification, and hypotheses for future mechanistic investigations and targeted interventions towards preserving white matter health across life span.

Blood-Brain Barrier Structure, Function, and Pathology: Implications for White Matter Health and Disease. Axel Montagne (Zilkha Neurogenic Institute, UCLA, Los Angeles). Blood vessels in the brain are organized with surprising precision, patterned in parallel with the major brain circuits tasked with sensation, memory and motion. This tight interrelationship may reflect key functional roles of vasculature in normal function of neural circuits in the healthy brain, during aging, and in diseases such as brain small vessel disease and Alzheimer's-type dementia. System level regulation of brain circulation, cellular, and molecular mechanisms underlying self-autonomous and non-autonomous regulations of the BBB, the link between BBB breakdown, and neurodegeneration in human monogenic neurological disorders, genes underlying inheritance or increased susceptibility of familial forms of Alzheimer's disease leading to cerebrovascular damage, and our recent data showing that BBB breakdown is an independent early biomarker of human cognitive dysfunction was reviewed. Next, we focused on our on-going studies on white matter injury and protection showing the following: (a) BBB breakdown in a new model of small vessels disease—a pericyte-deficient mouse, causing early damage to white matter preceding neuron loss; (b) protection of white matter from ischemic injury in models with motor dysfunction and/or "silent stroke" by 3K3A-APC (activated protein C), a BBB stabilizing, anti-inflammatory protein that has completed phase 2 trial for ischemic stroke; and (c) leaky BBB in watershed territories in normal-appearing white matter in individuals with hypertension compared with normotensive age-matched controls, but not in individuals with diabetes and/or hyperlipidemia.

Mixed Dementia Increases Inflammation with Disruption of the BBB. Gary Rosenberg (Department of Neurology and Center for Memory and Aging, University of New Mexico Health Sciences Center, Albuquerque).Vascular cognitive impairment and dementia (VCID) is a heterogeneous group of vascular-related diseases, and biomarkers can be used to stratify patients with dementia into more homogeneous groups. Clinical evaluations are inadequate for patient stratification because of the large overlap in symptomatology of the various causes of dementia. Multimodal biomarkers can be obtained from neuropsychological testing, imaging, and biochemical testing of CSF/blood. Inflammation is an important component of VCID as well as Alzheimer's disease (AD), which results in opening of the blood-brain barrier (BBB). We have recruited patients into a study based on evidence of memory loss suspected to be due to dementia and/or an abnormal FLAIR MRI with white matter changes suspected to be due to vascular disease. We used the research criteria for diagnosis of AD with measurement of amyloid and phosphoTau in CSF, and we used mean diffusion on DTI to show white matter injury as a biomarker of vascular disease. Patients with both CSF AD proteins and abnormal white matter diffusion were called mixed dementia (MX). Patients were separated into homogeneous groups based on the biomarkers: (1) small vessel disease or subcortical ischemic vascular disease (SIVD), (2) large vessel disease or multiple infarcts (MI), (3) AD, (4) MX, and (5) white matter lesions on FLAIR MRI with other evidence of dementia or leukoaraiosis (LA). The UNM Cohort had 149 patients. They were classified as AD ($N = 24$), MX ($N = 22$), SIVD (53), MI (18), and LA ($N = 29$). MX patients identified by a reduced level of the ratio of $A\beta_{1–42}/A\beta_{1–40}$ and elevated levels of phosphoTau (Ptau) in the CSF increased mean diffusivity in the white matter, and poor performance on memory testing. We used the CSF results of levels of MMPs, cytokines, and growth factors to indicate that an inflammatory response was occurring. Neuroinflammation was mainly found in patients with SIVD and MX. The BBB permeability was measured with dynamic contrast-enhanced MRI (DCEMRI). Disruption of the BBB is an indicator of inflammation. DCEMRI indicated that the BBB was open in the white matter in patients with SIVD and MX. We found that patients in these two groups had in addition to increased BBB permeability, higher levels of the inflammatory biomarkers, matrix metalloproteinases (MMPs), and cytokines in the CSF. Our results showed that with the use of multimodal biomarkers, patients can be stratified into precise disease categories prior to autopsy, and, when stratified, MX represents a significant number of patients, corresponding to recent results of large autopsy series of dementia patients. In summary, there is clinical evidence from neuropsychological testing that those patients with dual pathologies have worse cognitive behavior (Snowdon et al. 1997). The reason for the acceleration of the dementia with CVD is possibly the interaction of inflammation due to cell death in AD and vascular damage in SIVD. Our results suggest that the combination of AD and CVD triggers an exaggerated inflammatory response with the release of MMPs and cytokines and disruption of the BBB.

Workshop topic 4: roles of microglia and oligodendrocytes

Repair in Ischemic White Matter Lesions. S. Thomas Carmichael (Brain Research Institute, Neurology, UCLA). A major clinical problem in white matter disease in the brain is progression. By MRI measures, initial white matter lesions progress into the border regions around the lesion. This expansion adjacent to the lesion is seen whether the lesions are deep in the white matter, such as periventricular lesions, or whether the lesions are punctate and more subcortical in location. In both animal models and human pathological material, white matter lesions are characterized by oligodendrocyte and oligodendrocyte precursor cell (OPC) loss. There is secondary myelin "pallor." In animal models of white matter lesions, loss of myelin around axons predisposes these hypo-myelinated axons toward degeneration. These findings thus establish three targets for cerebral small vessel disease in white matter: (1) lesion progression adjacent to the original site of the lesion, (2) oligodendrocyte/OPC loss, and (3) restoration of myelination around injured axons. Using mice, we have determined that, just as in the human condition, focal ischemia in the subcortical white matter of the mouse primarily causes loss of oligodendrocytes and OPCs, with a relative preservation of axons. However, there is loss of myelin ensheathment of axons, and disorganization of the nodes of Ranvier in these axons that is responsible for fast axonal conduction. The initial lesion expands into this partially damaged axonal zone adjacent to the lesion. OPCs respond to this injury, proliferate, and migrate to the lesion border, but are blocked in their differentiation into mature, myelinating oligodendrocytes. Using viral labeling and laser capture microdissection, to isolate the OPCs in the at-risk tissue adjacent to the infarct and perform RNAseq to identify their transcriptome, we identified the unique transcriptional profile of OPC proliferation and of very limited differentiation. The 5-day white matter ischemia OPC transcriptome has molecular pathways associated with nuclear receptor signaling (retinoic acid, PPARalpha, LDR), and the 15-day white matter ischemia OPC transcriptome has inflammatory and growth factor pathways that are significantly activated (e.g., IL-17, TEM1, and NF-kb signaling pathways). Finally, through molecular pathways that are activated at day 5 versus day 15, we have identified two specific targets that might promote repair and recovery. These are Nogo receptor 1 signaling system and the extracellular matrix adapter, matrilin-2. Nogo 1 and Nogo receptor 1 have a role in OPC differentiation in development, and in multiple sclerosis and promote OPC differentiation and remyelination and behavioral (motor) recovery even with systemic delivery. Matrilin-2 is significantly downregulated in day 15 OPCs via inhibin alpha (a TGFb family member) and blocks OPC differentiation. Delivery of matrilin-2 promotes OPC differentiation, remyelination, and recovery in white matter lesions. Our work identifies the biology of expanding white matter lesions, the unique genes involved in this expansion, and identifies two targets for possible therapies. Future work will be to identify other molecular targets and small molecule agents.

Cell Base Models of Phenotypic Changes with Neurovascular Inflammation in Cerebrovascular Ischemic Disease. Rafael E. Flores-Obando (Neurology, Cerebrovascular Research Lab, SUNY Downstate Medical Center, Brooklyn). Oligodendrocytes, the myelinating cells of the central nervous system, are among the most vulnerable to hypoxia-ischemia compared with other brain cell types such as neurons depending on the developmental stage and brain region. We have implemented in vitro cell culture models of hypoxia-ischemia and innate immune stimulation to study the cell and molecular interactions related to our in vivo data of chronic hypoperfusion, white matter inflammation-demyelination in rodent VCID, and to detail oligodendrocyte changes due to hypoxia-ischemia. Preliminary data, shared during this workshop, show a deregulated proliferative capacity of immature oligodendrocytes (O4+) exposed to oxygen glucose deprivation (OGD) compared with controls. The interaction of oligodendrocytes with activated M1 microglia during normoxia or hypoxia-ischemia is being further investigated. We will also use model cell systems to investigate therapeutic strategies that improve oligodendrocyte viability during hypoxia-ischemia and/or reduce M1 microglia activation.

Myelinated Axons Begin and End in Gray Matter (And that's Where the Action is in Alzheimer's Disease). Kai-Hei Tse (Department of Health Technology and Informatics, The Hong Kong Polytechnic University). In the aging brain, myelin is lost in both white matter and gray matter, and this atrophy tracks closely with aging and cognitive decline (Bartzokis et al. 2001; Braak and Braak 1996). These clinical observations have relied on macroscopic neuroimaging methods based on MRI, but cellular mechanisms underlying

myelin fibers loss remain unknown. Recently, we reported that the myelin-producing oligodendrocytes (OL) in the frontal cortex are highly vulnerable to cell death in persons with dementia, and such cell deaths are closely linked with an increase in the burden of DNA double-strand breaks (DSBs) in OL (Tse et al. 2018). As DSBs accumulate with aging (Lodato et al. 2018), DNA repair in OL is critical to maintain myelination (Tse and Herrup 2017). However, both bulk RNA-seq datasets of OLs (Y. Zhang et al. 2014, 2016) and a single cell RNA-seq dataset of the mouse brain (Saunders et al. 2018) showed a robust negative correlation between the expression levels of myelin genes and DSBs repair pathway genes, strongly indicating that DNA repair capacity of OL is compromised as it differentiate. An important question is whether myelin loss is associated with, or even leads to, the neuronal pathology of Alzheimer's and other neurodegenerative diseases. To address, we turned to demyelinating disease of multiple sclerosis, where the loss of intracortical myelination is associated with cognitive impairment (Calabrese et al. 2015) that may mimic Alzheimer's disease (Tobin et al. 2016; Trapp et al. 2018). With kind support from the Multiple Sclerosis Research Australia Brain Bank at Sydney, we examined postmortem frontal cortices of multiple sclerosis patients. In demyelinated gray matter, the widespread loss of $Olig2^{+}$ OL is strongly associated with 53BP1-labeled DSB foci and the ectopic re-expression of cell cycle proteins in surrounding cortical neurons, as ectopic cell cycle progression in neurons precedes neurodegeneration (Halliday et al. 2002; Yang and Herrup 2005). Together, our results suggested that myelin and OLs degeneration can jeopardize genomic integrity and survival of neurons, and therefore are valuable targets for age-related dementia.

Workshop topic 5: VCID mechanisms and models

Non-cell autonomous mechanisms of Oligodendrocyte regeneration in VCID. Ken Arai (Neuroprotection Research Laboratory. Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, USA) OPCs serve as a progenitor cell of terminally differentiated oligodendrocytes. Mature oligodendrocytes form myelin sheaths around axons in the central nervous system, and the myelin sheath is essential in the fast impulse propagation along the myelinated fiber. Because oligodendrocytes do not proliferate, OPCs play a critical role in increasing the number of oligodendrocytes during development or after oligodendrocyte/myelin damage. Although mechanisms of OPC differentiation have been examined and some extrinsic signaling molecules were identified as regulators of OPC differentiation into oligodendrocytes, precise mechanisms of OPC proliferation and differentiation still need to be elucidated, especially under the conditions of VCID. As highlighted by the concept of neurovascular unit, cell-cell interactions should be critical in supporting/maintaining OPC function, including oligodendrocyte generation. In fact, in mouse models of white matter injury, we have shown that astrocytes produce soluble factors to support compensative OPC differentiation. During this workshop, key data from my lab regarding the roles of endothelial cells, astrocytes, and pericytes in OPC proliferation and differentiation were presented, and preliminary data indicating an anchoring protein AKAP12 in pericytes that could support OPC differentiation via a non-cell autonomous mechanism was discussed. Mechanisms of cell-cell interaction in the neurovascular unit that regulate white matter remodeling after prolonged cerebral hypoperfusion were also discussed. Because OPC is one of the major cell types in adult white matter, understanding and dissecting OPC-related non-cell autonomous mechanisms of oligodendrocyte regeneration may lead to novel opportunities for white matter recovery in VCID.

White Matter Inflammation and VCID. Edith Hamel (Laboratory of Cerebrovascular Research, Montreal Neurological Institute, McGill University, Montréal, QC, Canada). Chronic cerebral hypoperfusion is a risk factor for VCID. Mechanisms underpinning this process and therapeutic targets are poorly defined. In this workshop, data from our transgenic mice overexpressing astroglial transforming growth factor-β1 (TGF mice) and fed a high cholesterol diet (HCD) were presented. The cognitive decline observed in these mice occurred together with white matter (WM) alterations related to increased microglial cell activation, functional deficits characterized by lower compound action potential amplitude, increased string vessel pathology, and reduced number of immature oligodendrocytes. Treatment with simvastatin or exercise (spinning wheel, unlimited or limited exercise, 5 days/week for 3 months) resulted in normalized cerebrovascular (endothelial and smooth muscle cell-dependent dilation) and cognitive deficits (spatial, working, and recognition memory depending on the cohort). Concurrently, markers of WM dysfunction, including astrogliosis, microgliosis, string

vessel pathology, and reduced WM conductivity, were also restored. The most striking finding in the TGF HCD-fed groups was the increase in a specific population of microglial cells expressing galectin-3 (Gal-3) selectively in WM, which was present when mice were cognitively impaired and normalized following therapy. Interestingly, while both simvastatin and exercise were effective at counteracting WM changes, only unlimited exercise reduced gray matter inflammation, indicating that WM integrity may be a key to cognitive recovery. Our results were discussed in the context of chronic cerebral hypoperfusion at levels seen in Alzheimer's disease or VCID patients and suggest that similar to our observations in the TGF mice, while cerebral hypoperfusion may not directly cause cognitive failure, it may lower the threshold for developing cognitive decline when combined with other risk factors (i.e., hypercholesterolemia). These findings further demonstrate the high susceptibility of WM inflammatory processes and the high value of aerobic exercise in preventing cerebrovascular, cognitive, and WM dysfunction with even more efficacy than pharmacotherapy with simvastatin.

Targeting Rheo-Erythocrine Dysfunction in VCID. David C Hess (Neurology, Medical College of Georgia, Augusta University). Reduction of cerebral blood flow (CBF) is a key precipitating event in WM damage in cerebral small vessel disease. While much attention has been focused on structural lesions in small vessels and endothelial dysfunction, less attention has been paid to abnormalities in the circulating blood and the red blood cell (RBC). RBCs are 6–8 μm in diameter and must pass through the microvasculature (2–3 um) under a very high shear stress to deliver oxygen. To aid in passage through the microvasculature, healthy RBCs are highly deformable. Abnormalities in the "rheo-erythrocrine" properties, i.e., the ultra-morphology (*rheological*) and endocrine signaling (*erythrocrine*) of RBCs, impair CBF. While endothelial nitric oxide synthase (NOS3) was previously thought to be restricted to endothelial cells, it is now known that functional NOS3 is present in circulating blood cells including RBCs (eryNOS3). Here, we show that chronic hypoperfusion in mice (bilateral carotid stenosis model (BCAS)) causes WM damage, impaired cognition, and RBC rheological alterations with a loss in erythrocytic deformability, as determined by a reduced elongation index (EI). These rheological changes occur in parallel with erythrocrine dysfunction with decreased activities of eryNOS3/eryAMPKα1 (AMP-activated kinase α1, a NOS3 regulator). Also, in chronic remote ischemic conditioning (C-RIC), the repeated inflation and deflation of a blood presue cuff on the limb, is an exercise mimetic. C-RIC increases CBF, induces vascular remodeling and angiogenesis, reduces WM damage, improves cognitive performance, reduces accumulation of amyloid-beta 42 protein ($A\beta_{42}$) in the brain, and ameliorates the rheo-erythocrine abnormalities. We have found that physcal exercise similarly improves CBF and ameliorates rheo-erythrocrine dysfunction in the BCAS model. Thus, targeting rheo-erythrocrine dysfunction may be one of the mechanisms by which physical exercise reduces cognitive dysfunction in SV. C-RIC is a potential safe and effective therapy in small vessel disease, and pilot clinical trials have already been conducted which demonstrate safety and a hint of activity.

Plasma Biomarkers and VCID in Observational Data. Maiken K. Jensen (Department of Nutrition and Epidemiology, Harvard University, T.H. Chan School of Public Health, Boston, MA). In our molecular epidemiology working group, we try to bridge between basic sciences and observational data. We are looking to learn something about non-invasive markers of "risk of" dementia (not presence of, but prediction of future risk) based on blood biomarkers. We are looking for blood-based biomarkers that would indicate a high risk, similar to what high LDL cholesterol blood test if for heart disease. The use of observational data means that we cannot make any claims of causality nor get very close to understanding biological mechanisms. But we might be able to identify early risk factors for the development of the disease. This can have a huge potential for public health and preventive efforts, whether or not it is actually causal. An example of one of the most important pitfalls to watch for in observational epidemiology was that reverse causation was shared at the meeting. The example was that of high BMI being associated with a lower risk of dementia in late life (closer to diagnosis), and to higher risk if we had data from mid-life. BMI is not a biomarker, but just an example. We can see that if we have good data, with more than 10 years of follow-up, then the association of BMI with risk of dementia flips about 10 years prior to diagnosis of dementia. This phenomena are likely caused by a mix of weight-loss caused by underlying, developing pathology (i.e., the disease is causing the change in BMI, not the other way around), and the problems with diagnosing dementia. So if we do not have data with long follow-up, to ensure

that we look at the biological markers in individuals truly free of dementia, we might see spurious associations that would not be meaningful. One can also argue that should we find a biomarker or trait that strongly predicts risk of dementia, then it could be important even if not causal. For instance, risk prediction and hypothesis-free–omics studies might provide clues as to mechanisms that warrant further study. But, there is a need for longitudinal observational studies with rich phenotype collection and stored plasma for investigations of plasma biomarkers as predictors of VCID risk. Preliminary work that extends findings for cardiometabolic biomarkers to risk of dementia was presented at the workshop. Our studies of the link between high-density lipoprotein (HDL) and measures of white matter volume, risk of clinical Alzheimer's disease, and stroke suggest that it is important to consider the presence (or absence) of specific apolipoproteins (apoJ, apoE, or apoC-III) when examining plasma HDL as a risk marker.

Workshop topic 6: preclinical models, neurovascular inflammation, and cognition

Ischemia-Induced Neurovascular Inflammation: Essential Component of VCID Models. Frank Barone (Neurology, Cerebrovascular Research Laboratory, SUNY Downstate Medical Center, Brooklyn). Cerebrovascular disease (e.g., strokes, atherosclerosis, and small vessel disease) produces hypoperfusion/ischemia that results in vascular and parenchymal inflammation and a progressive deep white matter injury/demyelination. Following bilateral carotid artery stenosis in rodents, prolonged white matter hypoperfusion, astrogliosis, activation of inflammatory (M1) microglia, and demyelination occur in white matter (corpus callosum). Thus, chronic forebrain hypoperfusion results in prolonged VCID. Changes in brain white matter DTI-MRI microstructure (fractional anisotropy; radial and axial diffusivity), decreased white matter fat (luxol fast blue histology) and myelin (myelin basic protein Ab immunohistochemistry), occur with long-term deficits in spatial navigation and executive function (active place avoidance, Morris water maze, and decision making T-maze performance). Although white matter hypoperfusion and demyelination are very clear, cortical and hippocampus neuronal numbers are not affected. Available information suggest that oligodendrocyte sensitivity to ischemia and inflammatory (M1) and anti-inflammatory (M2) microglia is involved in white matter and cognitive changes. Continued in vivo, profiling of white matter microglia and oligodendrocyte phenotypic changes is required. In addition, the in vitro study of cultured microglial and oligodendrocytes, including their sensitivity to ischemic and innate immune stress, will help better understand cell and molecular mechanisms of hypoperfusion-induced white matter demyelination.

A Bench to Bedside Approach for VCI and Stroke. Masafumi Ihara (Department of Neurology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan). VCI, the second most common type of dementia, is frequently characterized by white matter changes and responsible for the cognitive decline of the elderly. We use a mouse model of chronic cerebral hypoperfusion, which involves the narrowing of the bilateral common carotid arteries with microcoils (Ihara and Tomimoto 2011; Hattori et al. 2015) to study ischemic white matter injury and VCI in mice. These hypoperfusion models show good reproducibility of the white matter changes characterized by blood-brain barrier disruption, glial activation, oxidative stress, and oligodendrocyte loss following chronic cerebral hypoperfusion with or without ischemic stroke (Hattori et al. 2015). Similarly, we also used a baboon (*Papio anubis*) model to evaluate whether partial cerebral ischemia or oligaemia resulting from reduced blood flow to the brain induces white matter pathology (Chen et al. 2016). Adult, male baboons were subjected to three-vessel occlusion by complete ligation of the internal carotid arteries bilaterally, and occlusion of the left vertebral artery. Subcortical and white matter changes were reported in animals to 28 days after three-vessel occlusion. This model is useful to evaluate interventions at various stages and specifically examine the effects of aging, hypertension, and neuroinflammation. During this workshop, data on adrenomedullin, a peptide hormone, which facilitates recovery of cerebral blood flow through arteriogenesis and angiogenesis, suppress glial activation and maintain white matter integrity after BCAS (Maki et al. 2011) was shared. Adrenomedullin promotes differentiation of oligodendrocyte precursor cells into myelin-basic-protein expressing oligodendrocytes under pathological (chemical hypoxic) conditions in vitro (Maki et al. 2015). In addition, adrenomedullin has been shown to be effective against ischemic stroke in the middle cerebral occlusion/reperfusion model (Miyashita et al. 2006). Through its strong anti-

inflammatory properties, adrenomedullin is currently used in clinical trials for ulcerative colitis and Crohn's disease (Ashizuka et al. 2016). A clinical trial for ischemic stroke, including lacunar stroke involving internal capsule and corona radiata, will be started in 2020 in Japan.

White Matter Inflammation and Cognitive Impairment in Aging and Disease. Shawn Whitehead (Vulnerable Brain Laboratory, Department of Anatomy and Cell Biology, Western University, N6A 5C1). Converging literature implicates a co-existent, and potentially co-dependent, relationship between AD and cerebrovascular disease. Diminished cognitive function may be attributed to metabolic stress and inflammation with studies demonstrating white matter inflammation potentially mediating the critical relationship between vascular risk factors and cognitive impairment. Changes to brain volume and white matter integrity can be measured by MRI but may only be visible upon irreversible damage to neurons and axons. Through the application of positron emission tomography (PET) and radiolabelled ligands targeting specific proteins, it may be possible to quantify physiological events, such as inflammation and synaptic degeneration, prior to manifestation of the aforementioned damage. Our recent preclinical findings that highlight changes to the white matter in aging and following cerebrovascular stress, stroke, and prodromal AD, along with its relationship to cognitive impairment, were shared with the group. Using a combination of behavioral testing, focused on executive dysfunction, live animal imaging with PET/MRI, and brain histopathology, we make the case that white matter is a target for therapeutic intervention to preserve cognition during normal aging and early stages of disease progression. Our results using a transgenic APP21 rat, with human Swedish/Indiana mutations of the amyloid precursor protein (APP) (Agca et al. 2008), have revealed age-dependent increases in activated microglia, diffusely distributed within the white matter tracts (Weishaupt et al. 2018) that correlate with executive dysfunction (Levit et al. 2019), both of which are exacerbated following a subcortical endothelin-1-induced stroke (Levit et al. 2017). Using a PET tracer for activated microglia, we also observed persistent expression of activated microglia in the co-morbid AD/stroke transgenic rats. Overall, our preclinical findings demonstrate that interactions between pathogenic APP, stroke, and neuro-inflammation, predominantly within the white matter tracts, could be occurring within the brains of some patients following a stroke that may explain why they go on to develop dementia.

Summary and next steps

This was the third of biannual VCI and dementia translational workshops provided by the generosity of the Leo and Anne Albert Charitable Trust. It is very special in that it has been built from the first two workshops to fill a knowledge gap and focus into workshops on "White Matter and Cognition" to advance knowledge of white matter pathology and mechanisms of cognitive loss that occurs in cerebrovascular and neurodegenerative diseases. Initiatives set forth from this workshop include the following:

1. "White Matter and Cognition" workshops will be now held annually instead of biannually.
2. The "Albert Trust Research Institute for White Matter and Cognition" was incorporated to facilitate white matter science and communication and to translate white matter disease biology into treatments that can reduce the horrific future projects for dementia in the aging world population.
3. Two annual collaborative research grants submitted by participants that had not previously worked together will be funded by the Albert Trust.
4. The next (forth) annual workshop is planned for April 2020 in San Antonio, TX, and the Scientific Program Committee Members have started working on the scientific program.

Discussion and final thoughts

White matter and gray matter are terms to describe nervous tissue structures segregated by dichotomy of appearances. The whitish appearance of white matter is the primary reflection of the dense lipid-rich myelin tracts, and the dull coloration of gray matter reflects many cell bodies with the lack of myelination. Nevertheless, fine myelin fibers exist in the gray matter and these intra-cortical myelin fibers are important for cognitive performance. While the focus of this workshop was on the brain white matter and cognition, any and all progress in the field of myelin injury and repair will also be applicable to the myelinated fibers in the gray matter

and cognitive function as a whole (Kohama et al. 2012; Farias Quipildor et al. 2019). Moreover, our ability to prevent myelin injury, promote myelin repair or regeneration, and meet the scientific challenges ahead is contingent on an unprecedented cross collaboration of complementary expertise spanning vascular neurologist, neuroimmunologists, cognitive scientists, imaging physicists, epidemiologists, basic scientists, and clinical trials that were represented at this workshop.

A main challenge will be how to best integrate all contributions until the detailed picture of brain white matter health and cognitive function becomes adequately apparent. Clearly, a static approach (hypothesis, experiment, model, intervention) to mechanisms underpinning brain health ignores the time-varying and multidimensional construct of the multitude of mechanisms contributing to white matter health across the life span. Instead, we propose a hybrid, iterative Bench-to-Bedside-to-Bench (B2B2B) model that is mutually reinforcing and in concert with "big data to models to hypothesis to experiment to more data and models" approach for discovery and plotting the life course of brain white matter and cognitive health. This multidisciplinary hybrid approach can be simultaneously predictive and mechanistic. Conventional experimental techniques are ill-suited to the critical knowledge gap that we have to close.

We expect that this strategy, facilitated through the newly incorporated "Albert Trust Research Institute for White Matter and Cognition," will prevent spurious hypotheses and predictions and will facilitate new knowledge and mechanistic insights from the aggregate predictions of systems biology. More importantly, the Albert Trust strategy to facilitate white matter and cognition research communications through annual workshops is complemented by providing two novel collaborative research grants per year that will support novel and collaborative approaches for invited workshop participants, and also includes robust training initiatives with pilot funds to support the development of young investigators with a purpose to develop the next generation of vascular cognitive clinicians and scientists with multidisciplinary skills necessary to integrate biological, clinical, mathematical, and computational sciences necessary for patient care and scientific discoveries. We expect that these future leaders will be better prepared to drive change and alter the course of age-related white matter disease and cognitive decline. We will continue the momentum within the newly established "Albert Trust Research Institute for White Matter and Cognition" and our annual Albert Trust "White Matter and Cognition" workshops in order to help and support cross disciplinary collaboration and new ways of doing science. Clearly, the Leo and Anne Albert Charitable Trust has extended its influences to positively and significantly improve the communication, quality, training, and advancement in VCID research and interventions, and is meeting its primary mission: "To Help People" (Fig. 1).

Fig. 1 The primary mission of Leo and Anne Albert Charitable Trust

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