Expression of Interest – Canadian Consortium for Neurodegeneration and Aging (CCNA)
13-05-21 Dr. Howard Chertkow NPA

Dear Dr. Joanette,

It is with great pleasure that I submit this Expression of Interest in forming the CCNA.

Background and Objectives

a. General Introduction. My colleagues and I have been preparing for this effort for more than a decade, since applying (and coming within a hair's breadth of being funded) to develop a Canadian Cognitive Impairment National Centre of Excellence. That galvanized the Canadian dementia research community, making clear to us the potential for major breakthroughs in treatment and prevention of dementia if we worked together.

Our EOI includes 37 principal applicants (9 are junior researchers), and 285 other members of the dementia research community grouped into 20 Teams. Virtually every dementia researcher in Canada with an "H-Index" over 25 is part of this submission. The 37 PIs include 4 from B.C., 5 from Alberta, 1 from Saskatchewan, 13 from Ontario, 11 from Québec, and 3 from Nova Scotia.

Our mission can be summarized as follows: to create teams that will do transformative research, advancing our understanding of the biology, natural history, clinical presentation, and management of Alzheimer's disease (AD) and other neurodegenerative diseases (NDD). We will catalyse development of new molecules and therapies, which can be tested in appropriate clinical cohorts within the CCNA, using innovative designs and evaluative measures, to lead to new treatments and approaches to prevent the disease through delaying its onset. Such efforts will be complemented by Teams seeking to advance care of individuals affected or at risk and their families by using novel gerontechnologies and new approaches that can address co-morbidities, accompanying sensory losses, and specific functional challenges such as driving. The approach of this consortium will also focus on the unique needs of rural and indigenous communities. Our Teams will be national, rather than local or regional, and will promote the active engagement of junior researchers, building the next generation of dementia researchers.

b. Objectives of the CCNA

1. To transform the Canadian NDD community into a synergistic clinical and research network that regularly meets, exchanges ideas, and cross-fertilizes in order to increase research productivity and new knowledge, but also its translation and implementation.

2. To create a novel Canadian dementia research infrastructure that will transform Canada into a single (using an NIH analogy) Alzheimer's Disease Research Centre (ADRC). This approach will ensure that collaborations are optimized and progress is accelerated as clinical assessments, imaging protocols, biobanking protocols for blood /CSF samples, brain banking, and biomarkers are coordinated, shared, and made available for the broadest use.

3. To address issues that are of particular importance within the Canadian landscape, including service delivery challenges, care for indigenous individuals, and addressing challenges of care within different provincial systems.

4. To include Teams focussing on neurodegenerative diseases beyond Alzheimer's disease to allow that common mechanisms can be addressed and comorbidities, as well as distinctive and shared pathologies, can be better understood and treated.

5. To position this Canadian network to partner with global efforts and other national plans. As a single national network, there will be benefits of being able to move quickly and nimbly to advance promising collaborations.

6. To provide a critical link between basic science research programs in NDD and clinical populations. Example: the CCNA will connect basic research on inflammation and nerve growth factors in AD with research on biomarkers in early dementia, and a national brain imaging platform.

Research Program Themes

Theme 1 - Prevention of Cognitive Impairment and Dementia.

Theme leaders - Jane Rylett, David Hogan (associate leader)

Five teams will pursue novel complementary basic research into mechanisms underlying the development and progression of AD and NDD, and identify targets for therapeutic intervention. A sixth team will investigate potentially modifiable lifestyle factors in clinical studies of prevention of AD. With the establishment of the CCNA, access to large patient populations (particularly mildly impaired individuals) and biological specimens from well-ascertained individuals will become feasible for our basic scientists. The availability of essential biological samples including brain tissue, cells, CSF, and DNA will accelerate work on the early pathophysiological changes of cognitive impairment while access to brain imaging and genetic analysis will facilitate translational work to complement the basic studies. The potential of partnering with the Canadian Longitudinal Study on Aging (CLSA) (1) and other community normative aging cohorts will allow validation of preliminary results in a community-based population and assess the generalizability of diagnostic algorithms. Since genetic profiling has major ethical and legal implications, our ELSI committee will interact actively with CCNA research teams. It is evident that potentially modifiable lifestyle factors like leisure pursuits, physical activity, and diet can decrease the magnitude of age-associated cognitive decline and the occurrence of dementia. We are well positioned to design and carry out studies of combined biological, lifestyles, and psychosocial interventions. We will be able to use the genetic, clinical, laboratory, and imaging information available on our subjects to "enrich" the sample of subjects studied, enabling researchers to rapidly test these intervention strategies.

Team 1: Clinical Genetics and Gene Discovery. Leader - Peter St. George-Hyslop

This Team will assemble Canadian experts in clinical genetics, clinic-pathological correlations, molecular genetics and gene discovery, and molecular/cellular functional genomic approaches to study a range of age-related neurodegenerative diseases. They will use a shared platform of genomics and informatics tools, with analysis of biological samples collected from the CCNA clinical cohorts being set up to ensure adequate sample sizes for each disease phenotype. New samples will be pooled with existing cohorts, and Canadian work included in international consortia focused on discovery of new disease susceptibility loci, gene: gene modifier interactions, genotype-clinicopathological correlations, and detection of recurrent, highly-penetrant mutations with large effect sizes causing rare forms of neurodegeneration. The Team will leverage existing core facilities including genotyping for known disease-associated SNPs; copy number variants and regions of homozygosity; epigenetic studies with DNA methylation; next-generation sequencing methods; and informatics tools (2). This work will inform many other CCNA translational Teams and allow construction of genetically-stratified cohorts for therapeutic trials. The Team will also underpin pre-clinical studies directed towards target discovery for novel therapeutics and diagnostics by identifying individuals with genotypes of interest for creation of human neuronal cell models that will complement animal and cellular models. Pooled data will be focused on discovery of gene: gene interactions and genotype: phenotype correlations that define candidate biochemical pathways that can be mined for new diagnostic and therapeutic targets that are more tractable than primary disease-associated genes themselves.

Team 2: Inflammation and Nerve Growth Factors. Leader - Claudio Cuello

This Team brings together Canadian researchers working on inflammation and trophic factor deregulation in AD (3, 4). The focus is to identify targets for AD prevention or treatment by unraveling "early" and "late" inflammatory processes, and alteration in trophic factor mechanisms in disease progression. These events likely occur prior to clinical diagnosis and may yield new diagnostic biomarkers defining onset and staging of AD pathology, and reveal therapeutic targets that could arrest or delay disease progression related to inflammatory-immune responses and/or trophic factor deregulation. Studies include: 1) interventions to reduce AD incidence in non-

demented elderly and monitor inflammatory markers, 2) biomarkers for early AD diagnosis and prediction of memory deterioration in mild cognitive impairment, 3) deregulation of NGF and BDNF metabolic pathway and "pre-plaque" inflammatory process, 4) biophotonic signals imaged in live animals as biomarkers to screen biocompatible molecules and visualize AD inflammatory events, 5) anti-inflammatory therapeutics for early AD and applications of agents modulating complement activity in CNS, 6) molecular motifs of APP and Aβ causing AD pathology and intervention with anti-inflammatory agents to arrest Aβ formation, and 7) protein mimicry application in AD therapeutics.

Team 3: Protein Misfolding. Leader - Neil Cashman

Protein misfolding and aggregation is a universal feature of neurodegenerative disease, with distinct but overlapping protein families implicated in the dementing illnesses with aging (5,6). Thus, AD is accompanied by extracellular aggregation of the peptide Aβ into plaques, intracellular accumulation of phosphorylated tau in neurofibrillary tangles, and cytosolically mislocalized TDP43; Parkinson's Disease Dementia and Lewy Body Dementia are accompanied by aggregation of α-synuclein in the substantia nigra and cortex, respectively; ALS can be caused by mutations in SOD1 and RNA binding proteins TDP43 and FUS, and wild-type mislocalized TDP43 is a constant feature of sporadic ALS and frontotemporal dementia caused by expansion mutations in C9ORF72. Protein misfolding in these diseases can corrupt biological functions of normal conformers or create gain-of-function toxic components, both of which are tractable to develop novel therapies. Our objectives are to identify new immunologic and small molecule targets to block the seeded propagation of misfolded proteins implicated in AD, PD, and ALS; our milestones are to validate targets up to preclinical studies for translation and commercialization for the diagnosis and treatment of neurodegeneration.

Team 4: Synapses and Metabolomics. Leader - Robert Bartha

This Team will focus on early changes in synaptic neurochemical function and plasticity by leading Canadian researchers in rodent and primate models of neurodegenerative disorders, with expertise ranging from cellular, molecular and pathological analysis, behavioural phenotyping, and advanced imaging of animal models and human subjects. While many studies document changes that occur in brain during the course of various neurodegenerative diseases (7, 8), few have addressed alterations that occur in the period preceding clinical symptoms of cognitive change. These likely involve oxidative-nitrosative stress-related modification of cellular constitutents, accumulating Aβ oligomers and modified signal transduction events, development of altered metabolic states including neuronal insulin resistance, and altered neurochemical transmission. Goals are to provide systematic analysis of synaptic metabolic changes and behavioural alterations occurring in brain of genetically-modified AD model mice, and in primates with Aβ oligomer administration. Metabolomic data will be analysed in context with findings from brain imaging by MR and MR-spectroscopy, and pathology. This will lead to identification of new therapeutic targets, some associated with modifiable risk factors.

Team 5: Lipid and Lipoprotein Metabolism. Leader - Cheryl Wellington

This team brings together clinical and basic science experts in brain and peripheral lipid and lipoprotein metabolism, lipidomics, and cardiovascular disease with a strong foundation in genetics of metabolic disorders to address how these factors contribute to dementia. Most dementia subjects have mixed pathology, with Aβ and tau deposits, extensive small vessel disease, capillary loss, and microlesions on MRI. The collective expertise of this team will be harnessed to address the question of how metabolism impacts cerebrovascular disease and thereby affects dementia (9). This will enable rapid progress in identifying novel therapeutic approaches for dementia based on cerebrovascular and metabolic interventions. Critical areas for study are 1)Aβ clearance by perivascular fluid drainage pathways and transport across the BBB to plasma as failure of these mechanisms increases Aβ accumulation, 2) modifiable risk factors for AD that affect endothelial

function and contribute to BBB compromise including hypertension, type II diabetes and dyslipidemia, and 3) how apoE affects cerebrovascular function, particularly with comorbid metabolic conditions, as this is the most important genetic risk factor for AD.

Team 6: Nutrition, Exercise, and Lifestyle in AD prevention. Leader – Carol Greenwood

Robust evidence from human epidemiologic and animal studies (10, 11) pointing to the benefits of diet and exercise in preventing or delaying the onset of cognitive decline and dementia has not been supported by human intervention trials. Multiple experimental factors likely contribute to this discrepancy. The Team's primary objective is to develop, optimize, and pilot a multi-center platform for nutrition and exercise clinical trials using sensitive outcome measures, drawing on state-of-the-art psychosocial, electronic, and web supports to enhance intervention uptake and retention. To facilitate platform and data sharing, outcome measures will be chosen in collaboration with other CCNA teams and longitudinal initiatives (e.g., CLSA). The diet and exercise intervention will be informed by current literature and evidence emerging from the CLSA. Through protocol development, we will test the hypothesis that a combined nutrition and exercise intervention improves cerebral blood perfusion, enhances cerebral energy metabolism and indicators of neural plasticity, lowers oxidative stress and inflammation, and that these benefits are reflected in improved cognitive function across multiple domains.

Theme 2 - Treatments.

Theme leaders - Sandra Black, Mario Masellis (associate leader)

Members of CCNA have participated in the implementation of industry-driven multi-centre AD drug trials in Canada (12, 13), and participate in ADNI. CCNA will allow us to initiate hypothesis-driven studies of novel therapies or the use of existing therapies in novel ways. Seven teams will address particular forms of dementia (vascular, Parkinson's disease and LBD, Frontotemporal dementia), the need for developing better biomarkers for earlier diagnosis, non-pharmacological (cognitive) therapies, treatment of behavioural problems, and the gait/cognition interface for therapy.

Team 7:- Vascular Illness and its Impact on NDD. Leader - Eric Smith

Cerebrovascular disease is a common and potentially the most treatable and preventable contributor to dementia risk, yet it remains difficult to recognize clinically, and it is not yet known whether improving vascular health prevents or delays dementia (14,15). The objectives of the Vascular Team are to: 1) discover personalized early markers of cerebrovascular disease that identify patients at risk for vascular cognitive impairment, and 2) discover mechanisms that produce cognitive impairment in persons with cerebrovascular diseases, using both animal and human studies, to identify promising avenues for prevention and treatment. Studies of risk stratification and early diagnosis will leverage existing large Canadian cohorts of presymptomatic individuals from the community (CVCD Cohort Alliance study, and PURE) (16), cohorts with MCI, and cohorts with established cerebrovascular disease (SPS3 trial and CATCH studies) (17), using imaging (of brain, carotid, and heart), genomics, and neuropsychological assessments as candidate markers. Studies of mechanisms of impairment will utilize the results from animal models with analogous biomarkers in pilot human studies, identifying therapeutic approaches that will be translated to early phase intervention trials.

Team 8: Lewy Bodies (PDD and LBD), Aging, and Dementia. Leader - Richard Camicioli

After Alzheimer disease, Lewy body (LB) dementias (18) represent the *second most common cause of degenerative dementia* (19). Its features put patients at high risk of falls and other untoward medical events. Our goal is to define the contribution of vascular damage and non-motor features in predicting progression of cognitive decline in LBD and PDD. The CCNA will establish a registry for the full spectrum of LB disorders ranging from mild cognitive impairment to those with PD. This registry will identify non-motor features as well as vascular risk factors and determine their relationship to adverse health outcomes, including falls/hospitalization/nursing home

placement/dementia/death. We will bank and store plasma and serum for examination of metabolomic, genetic and epigenetic contributions to transitions. We hypothesize that for LB patients at all levels of severity (MCI, PD, PDD, LBD), a) non-motor features and b) evidence of concomitant vascular disease will each be independently associated with more rapid progression of disease: more falls/hospitalizations/nursing home placements/progressions to dementia/deaths.

Team 9: Developing New Biomarkers. Leaders - Roger Dixon, Pierre Bellec (associate leader)

If accurate diagnosis of AD using biomarkers could be made when no or only mild cognitive impairment symptoms were present, it might be possible to initiate therapies that prevent or delay the onset of clinical manifestations (20)**.** Often working independently, Canadian researchers have discovered promising biological and neural markers (i.e., *biomarkers*) of MCI and AD (21-25). This Team has recruited experts from especially promising domains to consolidate and coordinate the development of a set of valid biomarkers for early detection of MCI. Specifically, we will a) interact with the platform of clinical cohorts and neuroimaging platform being established across the country in CCNA, as well as other patient cohorts, b) implement common protocols for assessing and testing key biomarker domains (e.g., genetic, imaging, protein, metabolomics), and c) quantitatively examine novel and effective biomarkers both independently and interactively.

Team 10: Cognitive Intervention and Brain Plasticity. Leader - Sylvie Belleville

Non-pharmacological interventions can have a positive impact in AD, and intermediate mechanisms of neural plasticity and functional compensation likely modulate the detrimental effect of the disease on symptoms (26-28). The Team will carry out cognitive therapy studies for individuals with different levels of disease severity. This includes: 1) assessing cognitive therapy in persons with MCI where we will identify the temporal dynamics allowing for naturally-occurring and training-induced brain plasticity using multi-modal brain imaging to investigate their effects on brain structure and function in treated subjects; 2) increasing cognitive reserve in older adults with a familial risk of AD and subjective cognitive impairment (SCI) with a novel a multi-faceted intervention program meant to provide cognitive and psychosocial stimulation and reduce physical inactivity through participation in engaging leisure activities; and 3) measuring cognitive stimulation based on art, reminiscence, and communication between carer and patients to improve cognition and well-being in persons affected by early-to-moderate dementia and their care-givers.

Team 11: Prevention and Treatment of Neuropsychiatric Symptoms. Leader - Nathan Herrmann

Older adults with dementia in long-term care (LTC) represent some of the most vulnerable and exposed consumers of health care services (29). Neuropsychiatric symptoms (NPS) like agitation, aggression, apathy, anxiety, depression, and psychosis affect 80% of LTC residents with dementia and are a major risk factor for LTC admission (30). We propose to establish a Canadian alliance of LTC facilities for the performance of randomized controlled trials (RCTs) of innovative pharmacological, non-pharmacological, and education interventions aimed primarily at preventing the onset of NPS, and where they do occur minimizing their severity, duration, and impact. We will recruit subjects at 30 LTC facilities across Canada and carry out a detailed analysis of the incidence and prevalence of NPS. Beginning in year 3, we will initiate at least 3 RCTs covering pharmacological, non-pharmacological, and education/training interventions. Examples of possible hypothesis-driven trials include: duloxetine for depressive symptoms, aggression, and pain; transcranial direct current stimulation (tDCS) for depressive symptoms and anxiety; and individualized therapeutic recreation for depressive symptoms, wandering, and verbal agitation.

Team 12: Mobility, Exercise, and Cognition. Leader - Manuel Montero-Odasso

Over five years we plan to: identify and validate a standard "language" for assessing Cognition and Motor relationships in MCI and AD; develop standardized outcome measures to assess the relationship between mobility and cognition (31); establish ecological motor assessments (i.e., mobility measures applicable in the real world); establish ecological measures of cognitive

function (e.g., executive function); link clinical signs and symptoms with measures of disease involvement and severity (e.g., magnetic resonance imaging); and, establish a multicentre intervention protocol based on novel and alternatives approaches to improve cognition via exercise and to improve motor function via cognitive treatment. If successful, our research program will determine whether there is a "motor signature" that precedes cognitive decline or vice versa and the effect of motor and cognitive exercises on cognitive domains.

Team 13: Frontotemporal Dementia. Leader - Robin Hsiung

Recent advances in the genetics and neuropathology of FTD, many by Canadian researchers (32-35), have now identified enticing targets for therapeutic interventions, soon to be available for clinical evaluation. However, unlike AD, the clinical presentation of FTD is highly heterogeneous, with behavioural and personality changes, executive dysfunction, language disorders, and abnormalities of motor function that may or may not be present in each individual, and are not captured in scales designed for AD, which are generally focused on memory dysfunction. With the establishment of a national FTD team, we will: 1) establish a longitudinal cohort of FTD; 2) organize a national repository of blood and fluid samples on patients with FTD to expedite novel genetic and biomarker discovery and validation; 3) collect standardized neuroimaging data to study anatomico-cognitive correlation; and 4) translate the knowledge garnered in 1, 2, and 3 above to develop FTD centres of excellence with expertise in management and conduction of clinical trials for FTD. Our findings will also provide important insights into related neurodegenerative disorders such as AD, corticobasal degeneration, progressive supranuclear palsy, and amyotrophic lateral sclerosis.

Theme 3 - Quality of Life

Theme leader - Ken Rockwood

Within CCNA, we intend to bring together researchers examining psychosocial issues (such as caregiver burden and quality of life of older adults with cognitive impairment, as well as their caregivers) (36-40) with clinical and basic scientists to address questions of common interest. For example, what are the biological concomitants of caregiver burden (e.g. biological measures of stress) and what is the relationship between these measures and caregiver illness? By encouraging these linkages, innovative and important questions can be posed and quickly answered using our combined national resources. Practical gerontechnological aids (41) to help dementia caregivers (e.g., innovative artificial intelligence, electronic monitoring, and telemedicine support) will be assessed to determine if they can help maintain dementia individuals at home. The unique problems of dementia individuals in rural and indigenous communities (42-44) will also be investigated. CCNA researchers will assess the validity and cultural acceptability of tools for the diagnosis of dementia in First Nations populations. The teams will also assess the impact of gender on driving, caregiver burden, use of technology, and frailty as a risk factor for late life dementia.

Team 14: How Multi-Morbidity Modifies the Risk of Dementia and the Patterns of Disease Expression. Leader - Melissa Andrew

Vascular risk factors are non-controversially known to increase the risk of all causes of late life cognitive impairment. They may also be amenable to well-studied interventions that are widely available (45-48). In addition to vascular risk factors, a wide variety of other health deficits, including some not traditionally associated with dementia, also appear to increase the risk of late life cognitive decline, especially when seen in combination (49-50). The challenge of multiple health problems is especially important because they usually occur in late life, when the risk of dementia is highest. This team will explore how health problems combine to increase the risk of late life cognitive impairment, how they affect disease expression in dementia, how they affect mortality, and how they affect management/therapy and heath service use. In addition, we will aim to consider the influence of reserve/resilience. A particular focus will be on what readily available interventions (especially exercise) might now be employed to lessen the burden of late-life cognitive impairment.

We will also seek to explore how other interventions (e.g. reduction in polypharmacy, patient-centred information systems) might likewise make care better, and commonly at lower cost.

Team 15: Gerontechnology and Dementia. Leader - Alex Mihailidis

The focus of this team will be harnessing the potential of emerging and innovative technologies to maintain older adults with dementia in the community through the development and commercialization of a suite of differing but complementary technological solutions (51-53). Our research questions are: what needs do older adults with dementia and their caregivers prioritize that technology-based systems could meet; are there national or gender-based differences in these needs; and how can technology-based systems and services be used to enhance the well-being of older adults with dementia and enable them to live more independently? Specifically, this Team will focus on a range of different technological platforms, including smart homes and ambient-based systems, robotics, on-person systems, information and communication technologies (ICT), and cloud-based technologies. The development of these different systems will focus on the following application areas: completion of activities of daily living; manage of disease through support in therapy; health monitoring and evaluation; and, mitigating caregiver burden.

Team 16: Driving and Dementia. Leader - Gary Naglie

Within five years, four regional teams in Canada will test the hypothesis that in older people with MCI (due to prodromal AD or PD), mild AD, or mild PD dementia, an intervention that prepares them and their family members for driving cessation can shorten the time to driving cessation and significantly reduce the negative consequences of driving cessation (54-56). Specifically, we will see if the intervention improves out-of-home activity level and quality of life of older people with NDD who stop driving while positively impacting on the quality of life of family members, increasing physician comfort with reporting unsafe cognitively impaired older drivers, reducing healthcare utilization, and improving public safety.

Team 17: Interventions at the Sensory and Cognitive Interface. Leader - Natalie Philips

There is a high prevalence of cognitive impairment and sensory impairment in old age (57-58). The fact that the two frequently co-occur is poorly recognized in research and in the care and management of patients with dementia. Difficulties in one domain may mask or potentiate problems in the other (59). Inadequately treated sensory loss can amplify cognitive deficits, which will impact both diagnosis and functional abilities. Appropriate sensory rehabilitation may help to optimize communication with family, friends, and caregivers, which in turn should improve an individual's well-being by allowing them to engage more fully in activities of daily living. Our over-arching goal will be to better understand how dual sensory and cognitive loss combine and interact to affect individuals' everyday functioning, communication, social participation, and quality of life. Within this framework, the impact of patient gender on sensory loss will be a particular focus.

Team 18: Program to Improve the Effectiveness of Dementia Caregivers. Leader - Joel Sadavoy

At the Cyril & Dorothy, Joel & Jill Reitman Center for Alzheimers Support and Training of the Mount Sinai Hospital in Toronto, an innovative manualized, 10-week therapeutic skills training program for dementia caregivers known as the CARERS program has been developed and tested (60). It has been empirically evaluated and shown both clinically and statistically to improve carer's caregiving competence, coping ability, and mental well-being. With recent funding, the program will be rolled out at a national level. Through partnership with CCNA, this roll-out will be carried out as a true clinical trial with appropriate outcomes, methodology and follow-up, using natural history controls. Our hypothesis is that this intense intervention program for working carers will be effective in enhancing productivity and retention in the workforce, ameliorating caregiver stress, decreasing in-patient time for AD patients, and improving quality of life for both carers and individuals with dementia. Mediating caregiver factors such as gender and education will also be studied.

Team 19: Integrating Dementia Patient Care into the Health Care System. Leader - Howard Bergman

This team's research program focuses on the evaluation of two alternative innovative health care system interventions in Quebec (Qc) and in Ontario (ON) geared towards dementia patients (61-63). The objectives are to: identify key components and contextual factors that are linked with an optimal impact; and facilitate the adaptation, dissemination, scaling up, and sustainability of the interventions in two provinces (Qc-ON) as well as in the rest of Canada. The team will conduct two interrelated studies. A qualitative study consisting of semi-structured interviews with clinicians (family physicians and specialist physicians, nurses), decision makers-managers, family caregivers, and patient representative groups will be undertaken. The second study will be a longitudinal quasi-experimental study to assess the impact of these interventions on accessibility, quality of care, continuity of care, coordination of care, patients' health outcomes, caregivers' outcomes, and utilization of healthcare services. The team will compare 10 Qc and 10 ON family practice groups where the innovative system is implemented, with 10 Qc and 10 ON control sites. The findings will inform government policy and design of health care systems for dementia across Canada.

Team 20: Issues in dementia care for rural and indigenous populations. Leaders - Debra Morgan, Kristen Jacklin (associate leader)

We will be developing and evaluating Primary Health Care (PHC) interventions tailored to the rural context (64, 65). This research will produce evidence on: 1) the design, implementation, and effectiveness of team-based, collaborative, rural dementia PHC programs and models based on chronic disease management principles, 2) the effectiveness of regional Dementia Advisors and Working Groups in stimulating and sustaining innovation in rural dementia PHC, and 3) design of integrated care pathways and decision support toolkit for rural PHC professionals. Aboriginal people face a unique set of determinants of health driven by their constitutional and historical relationship with the federal government. In keeping with values of two-eyed seeing (66), the Indigenous research team collaboration brings together Aboriginal and Non-Aboriginal health researchers to provide a Western/biomedical and Indigenous lens on our work (67). We will assess the impacts of participation in ceremony, Indigenous language use, and elders' roles as knowledge keepers on quality of life and care outcomes for Indigenous peoples diagnosed with dementia and their family care-givers. We will investigate the complexity of dementia care in indigenous communities – especially geographic isolation, high rates of co-morbid illness, and jurisdictional barriers to care.

Shared Resources and Platforms

We will establish a set of national resources to support these Teams. These resources will be described in detail in the full application.

Establishment and Coordination of Clinical Cohorts. Coordinator - Michael Borrie

A set of national NDD patient cohorts (i.e. patients with MCI, AD, mixed dementia, FTD, LBD, PDD) will be established using subjects seen at academic (largely C5R) Memory and Movement Disorder Clinics across the country (68). These centres typically carry out rigorous standardized subject ascertainment and longitudinal follow-up (69). Until now, they have lacked the necessary infrastructure support to carry out collaborative clinical research. CCNA will fund creation of a national clinical registry to support the research agenda of all teams and supply well-ascertained volunteers for clinical trials. A web-based computerized intake will allow participating centres to directly upload information into the anonymized database stored on the LORIS system (see next section). To acquire a normative comparison group, we will explore the possibility of developing a matching (by age and sex) population-based cohort of normal older subjects recruited within the CLSA and other Canadian longitudinal studies such as NuAge (70).

Imaging Platform. Coordinators - Alan Evans, Louis Collins, Simon Duchesne

Each cohort subject's clinical MRI image will be acquired using a standardized ADNI-compatible protocol, supported by a quality control and assurance program. The processing of images after

acquisition will be performed in a controlled environment to ensure proper extraction of salient information, e.g. hippocampal volume (71) or cortical thickness (72). We propose to establish a national data analysis platform specifically for research into NDD, leveraging the existing CBRAIN (www.cbrain.mcgill.ca) network. CBRAIN is a mature IT platform for the integration of the Canadian high-performance computing network (www.computecanada.ca) with brain researchers. Anonymized data will be consolidated within the web-based LORIS database system (73) and pre-processed in preparation for deeper analyses by researchers across Canada. Interoperability between LORIS and other databasing systems, e.g. Brain-CODE, will be established to ensure pan-Canadian database compatibility and transparent data access. We will maintain demographic, psychological, biomarker, imaging, and genetic information in a user-accessible framework. All images will be processed using fully-automated data analysis "pipelines" developed by team members (74-77). Partnerships will be established to rapidly provide referring radiologists with hippocampal volumes and medial temporal lobe atrophy estimates using automated segmentation and grading algorithms (78-80) Finally, the platforms will be available for all CCNA researchers.

Biosamples, CSF/Genetic samples/Biomarker resources/ DNA Sequencing and Genotyping. Coordinator - Judes Poirier

All subjects will have samples collected and sent for centralized genotyping of relevant polymorphisms as well as having blood and tissues collected for future research (81, 82). There will be ongoing communication between CCNA research teams and this platform to ensure that samples taken, processed, and analyzed are those needed by the various research teams. A CSF facility, already established at Douglas Hospital at McGill University in Montreal, will be upgraded as an academic resource for CSF determination at minimal cost of tau, phospho tau, and Aβ peptide levels on research samples collected across the country.

Normative Controls and Biobanking. Coordinator-David Hogan

Exploratory meetings have been held to explore ways to take advantage of the extensive infrastructure developed by the CLSA as well as other national normal aging cohorts (83, 84). Ensuring collaboration and compatibility with CLSA will allow us to maximize the benefits from these two large investments by the CIHR.

Brain Banking. Coordinator-Sultan Darvesh

Currently, there are a number of poorly resourced and uncoordinated brain banks in Canada. A national consortium of brain banks is desperately needed to establish national standards for acquisition, handling and distribution of these vital tissues. CCNA (with support from provincial agencies and other funders) will catalyze a set of adequately financed, nationally coordinated brain banks for NDD across the country. These will be located at five potential NDD brain bank sites currently in operation. These will be funded for the assessment of the NDD clinical cohorts. A national brain donation program will be established for those enrolled in our clinical cohorts. Standardized protocols for brain autopsy will be established. An accessible database with a central sample gateway will allow researchers to quickly obtain access to necessary tissue for pathological and basic studies of the different NDDs.

Support for Transgenic Colonies. Coordinator-David Westaway

Many Canadian laboratories create or purchase transgenic mouse colonies that are vital for basic research on causation of dementia only to find that their grants are insufficient to support the maintenance of such colonies. CCNA will adjudicate requests for support of transgenic mouse colonies involved in NDD research in laboratories across the country. With a simple one-page request explaining the importance of the colony to the researcher, a grant of $15,000 per colony per year will be forwarded to laboratories supporting TG colonies being used for research on NDD.

Academic Clinical Trials and Drug Development. Coordinator-Howard Feldman

We will adopt a multifaceted approach to developing novel AD and neurodegenerative disease therapies. This will include novel target identification and drug screening through

collaborations between CCNA investigators carrying out research in Theme 1 and 2 teams, and labs with significant compound screening capabilities. The CCNA will take an active role in advancing promising candidates emerging from preclinical work, and enable collaborations between academic and commercial partners to ensure that the steps in development run optimally (85, 86). The consortium will be charged with not only seeking novel discovery targets and drugs but also seeking repurposed drugs of interest to neurodegeneration. Through an inventory of resources and units across the consortium, it will be possible to rapidly move molecules through phased development, across the specialized academic and commercial facilities in Canada.

Cross –Cutting Aspects of CCNA

a) Training and Capacity Building

Building capacity in the growing area of basic and clinical aging research is an urgent priority for Canada, as is the development of front line health care professionals with expertise in cognitive impairment and dementia. Training available directly and indirectly through CCNA will be critical to building capacity in these areas and retaining our current cutting edge research capacity in the face of highly competitive international initiatives in dementia research. In terms of direct support, we will be seeking partnering commitments from provincial funding agencies and pharmaceutical firms and other partners for a "**CCNA training partnership program"** that will fund at least 22 research fellowships across Canada on an annual basis in the area of dementia and cognitive impairment. These "**CCNA Fellows**" will carry out research projects in labs and clinics across the country as part of a CCNA team. Novel aspects of their training will include menu-driven access to selected areas of interdisciplinary training (e.g. business training, use of new technologies, ethics), internships and training in industry settings, and web-based learning and virtual classroom opportunities. All Fellows along with postdoctoral fellows involved in CCNA research will be tracked to follow their future career paths, and catalyse their transition to independent researcher.

b) Knowledge Transfer (KT)

CCNA will sponsor and organize a set of KT activities. Much of this will involve continuing the momentum achieved by the Canadian Dementia Knowledge Transfer Network (CDKTN), whose funding is ending this year. Dr. Ken Rockwood, the director of CDKTN, will sit as Theme 3 leader on the CCNA and will oversee the transition of CDKTN into the KT arm of CCNA (see: http://lifeandminds.ca). CDKTN will become the vehicle for on-line contact between members of the Canadian dementia research community within CCNA. Relevant basic and clinical research developments within CCNA, new initiatives, and collaboration opportunities will all be shared online and via monthly newsletters to our research community. The KT group will promote synergy within and between themes by use of the websites, organizing an annual CCNA meeting, and hosting smaller workshops to bring key members of multiple teams together. Contact with stakeholders and partners such as the various levels of government and the community at large will be regularly maintained. A dementia educational initiative targeted at physicians and care providers will be developed. The KT group will actively seek out potential new researchers in dementia annually as they emerge in Canada, and (through discussions with the team and theme leaders) seek a means of linking them with existing teams and projects.

c) ELSI – Ethical, Legal, and Social Issues Committee

Each of the teams and platforms described will encounter issues of an ethical, legal, and social issue nature (87, 88). These will range from best approaches to anonymization and biobanking, obtaining consent from cognitively-impaired persons, dealing with unexpected findings during brain imaging, the relationship between research and clinical assessments, and the organization of brain donation programs. Among the teams these include appropriate inclusion of gender in studies, prevention of misuse of novel biomarkers potentially indicative of future dementia, and legal aspects of our proposed work on driving and cognitive impairment. In the context of randomized clinical trials, there is the need to ensure safety when testing potentially harmful agents in asymptomatic

individuals. To address the ethical, legal and social issues (ELSI) pertaining to dementia, Dr. Serge Gauthier has been asked to put together a wide-ranging committee of national experts to advise the Research Executive Committee (REC), Management Committee, Theme leaders, and Team leaders regarding the ELSI implications of the projects being planned. The coordinator of the ELSI committee will sit on the REC. Proposed initial committee members are listed in Table#2.

Nine value-added aspects of CCNA and positioning within the international landscape.

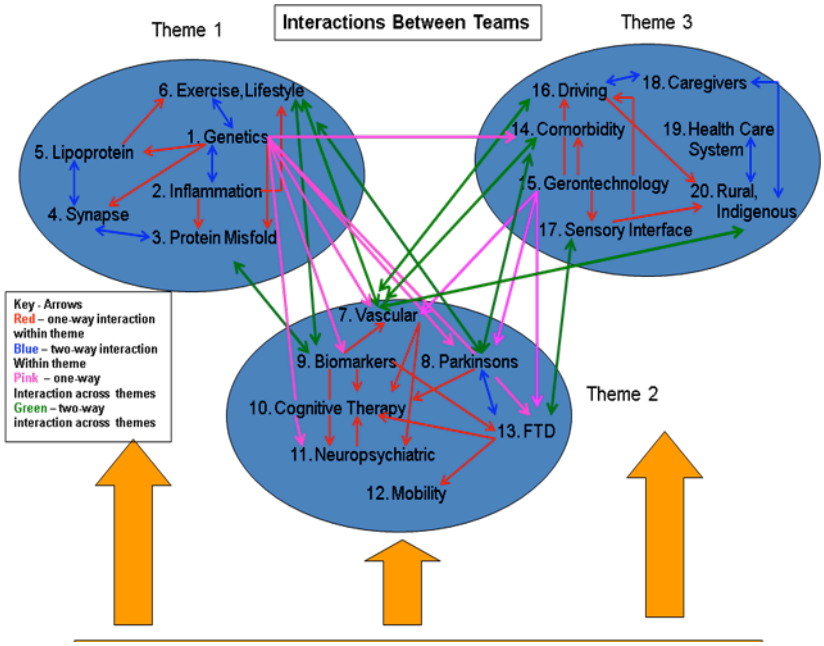
We recognize the existence of national AD research groups in various countries such as France, USA, and the U.K., as well as strong clinical/imaging cohorts such as AIBL in Australia and ADNI in USA. Our goal is in no way to duplicate any of these. There are elements in our CCNA plan which will make it unique internationally and will position the Canadian research community to make significant and high impact contributions to NDD research internationally:

•Canada has the ability to function as a **single cohesive "Alzheimer's Disease Research Centre (ADRC)"**, with shared clinical assessment tools, pathology protocols, imaging protocols, database, and clinical trials designs across the country. We will thus be building national imaging standards and imaging platforms. We will become the first country where imaging algorithms (e.g., brain hippocampal volumes, cortical thicknesses,etc.) can be made available to clinical research centres across the country in real time, in order to select similar patients for research studies.

• We will be constructing **national platforms which are hypothesis driven** and constructed to support cutting edge research teams. We are in the unique position of constructing our platforms and database resources simultaneously with setting up the research teams that will utilize the data they produce. The data that we collect will be directly designed to catalyse team projects and advance their scientific hypotheses. For example, genetic research in AD and NDD has moved beyond the "GWAS era" when mere description of individuals as AD+ or AD- was sufficient. Future advances will rely on "deep phenotyping", where detailed clinical and imaging data as well as multiple biomarkers and post-mortem brain tissue are tied to genetic research. Our structure will robustly link these elements, allowing transformative genetic research developed from "deep phenotyping" of or clinical cohorts.

•There will be construction and collection of unique cohorts, which depart from the "pure AD" model hitherto favoured by the pharmaceuticals industry. We will entertain **cohorts of mixed dementias,** where multiple pathologies are at play and multiple therapies may be necessary. Canadian expertise in the "Vascular illness and its impact on neurodegenerative diseases" team [Team #7] will drive inclusion of vascular elements usually excluded.

• This application represents a unique unified effort of **researchers from all four CIHR research "pillars"** and will establish a potentially transformative group. Basic scientists, clinical researchers, epidemiologists, social scientists, and health service research scientists will all be united in efforts to make progress against AD and other NDD. Some of the team synergies and interactions already emerging are shown in the diagram on the left.



•We will address **uniquely Canadian concerns** such as optimal health care delivery systems to benefit dementia patients, and dementia issues in rural and aboriginal populations. These groups have lagged in terms of research efforts, and may benefit

greatly from cross talk with other teams such as the one focussed on caregiver stress [Team #18].

• This application has established nascent **collaboration with the already existing Canadian Longitudinal Study of Aging (CLSA)**, a population-based study that will follow 50,000 Canadians (30,000 in the comprehensive cohort) aged 45-85 for up to 20 years, and is a potential source of valuable normative partner for the cognitive impairment studies of CCNA. We hope that CCNA and CLSA will be able to share resources (e.g., data storage, genetic and epigenetic testing, biobanking), and a series of talks between our research executive and leaders of CLSA are taking place. At minimum, we hope to explore potentially utilizing the exceptional biobanking facilities in Hamilton that the CLSA has developed.

•This CCNA proposal emphasizes close collaboration between basic science teams and clinical researchers, and includes a proposal to set up a unit for **Academic Clinical Trials and Drug Development.** This will allow us to rapidly take molecules from pre-clinical work on dementia therapy, to Phase 1 and small Phase 2A human trials in Canada. Furthermore, we will be able to stratify well-ascertained and imaged subjects according to their genetic/imaging risk factors profile, and we will be able to assess the degree to which the presence of genetic polymorphisms affects therapeutic response to various drug therapies.

• As already noted, the clinical research teams are closely tied in to clinical care in a set of academic Memory Clinics in Canada under the auspices of C5R. This means that we can use the imaging and biomarkers platforms to examine the utility and impact of access to standardized brain imaging (e.g., hippocampal volumes on MRI) or other biomarkers (e.g., CSF tau and Aβ peptide levels) in order **to better manage care of patients in direct clinical settings.** We will be able to assess, for instance, whether diagnosing "prodromal AD" changes clinical decision-making.

• The timing of our setting up CCNA cohorts and databases is advantageous. For instance, we have already had discussions with the UK Prime Minister's Office Dementia group regarding the sharing of DNA samples for genetic research on FTD, AD, and other NDD. We can ensure that our cohorts and databases are compatible and complementary, in order to **effectively partner** in order to share samples and techniques in order to catalyse genetic research in Canada as well as the U.K.

Plans for Management of the Infrastructure

The Nominated Principal applicant (NPA) Dr. Howard Chertkow will become Scientific Director of the CCNA. A **Research Executive Committee (REC)** will include the Scientific Director (chair), the Theme PA's and associate leaders, along with key "Shared Resources" PAs, and the **ELSI committee** chairman. The REC will meet via videoconferencing monthly and face-to-face, bi-yearly. The REC will set research priorities, coordinate activities among the general research themes and the shared resources, decide on the specific allocation of resources, and review Team budgets annually. It will implement a framework of early and late milestones for CCNA projects, including redirection of funds in response to the achievement of milestones. A **Community Advisory Group (CAG)** will be appointed by the REC to provide advice, guidance, and support. It will include representatives from the Alzheimer's Society and CIHR, and representation from the non-governmental organizations who advocate for older Canadians and care-givers. A full time Network Manager (NM) will be a key person who will drive the agenda and coordinate team management. A **Management Committee** will handle the day to day operations of CCNA. Staff may potentially include the NM, a Business and Finance Officer , and a Communications and Education officer. The Management Committee will also include selected partners involved in the enterprise, along with business consultants. A **Data and Sample Access Committee** will be appointed. And finally, an **International Scientific Advisory board** will be established, reporting to the REC.