



FOR IMMEDIATE RELEASE
Sept. 21, 2011

Driving and dementia: Could the theatre act as a resource for caregivers?

Researcher: Alexandra Jouk, University of Victoria, British Columbia

UVic researcher Alexandra Jouk is looking to the arts as a new way to support dementia caregivers. Her upcoming study will use a research-based applied theatre production, entitled "No Particular Place to Go", as a creative, new, and interactive medium for facilitating the conversation about driving safety among older adults with dementia. This work will move beyond information gathering and incorporate the expressed needs of caregivers to improve the lives of older drivers with dementia.

Research Background

Driving safety is becoming an increasingly important topic in our rapidly aging society. Research has shown that older drivers who suffer from Alzheimer's disease and related dementias are more at risk for unsafe driving practices compared to healthy, cognitively-intact older drivers. For caregivers, however, discussing driving and driving cessation with an older adult with Alzheimer's disease can be very challenging due to the emotionally charged nature of the topic.

Although several driving resources are currently available to dementia caregivers, these information guides are predominately print-based (e.g., pamphlets, brochures, informative websites).

"No Particular Place to Go" tells the story of three fictitious family members (grandson, mother, and grandfather) who all face diverse dilemmas or challenges relevant to older driver safety, including the family's prior struggle to discuss driving cessation with the late grandmother who may have had Alzheimer's disease. A caregiver viewer guidebook will be developed to accompany the "No Particular Place to Go" DVD to form a comprehensive driving "toolkit" available to aid informal and formal dementia caregivers approach the topic of driving safety with individuals suffering from Alzheimer's disease and other dementias.

Both informal and formal caregivers will work closely with the researchers throughout the toolkit development process in order to ensure relevant themes and concerns about driving safety among individuals with dementia are incorporated into an effective and innovative resource accessible to all caregivers. The toolkit will also be available to other researchers as an example of a creative, yet effective, alternative to print-based resource materials for individuals with Alzheimer's disease and their caregivers.

This project is jointly funded by the Alzheimer Society Research Program and the Canadian Dementia Knowledge Translation Network through the Research Training Awards Program on Knowledge Translation and Dementia.

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Dementia treatment: when to stop? New study shines a spotlight on previously under-viewed experiences of caregivers

Researcher: Andre Phillippe Smith, University of Victoria (UVic)

Cholinesterase inhibitors are first-line drugs in the treatment of mild to moderate Alzheimer's disease and are commonly used due to their coverage under public drug plans. However, there is a lack of evidence about the long-term benefits of the treatment and inconsistent guidelines to evaluate these benefits, making the issue of when to discontinue the drug therapy one that is much debated. However, the experiences of caregivers have been largely ignored in the debate creating a knowledge gap on an issue that has implications on medical decisions and funding policies.

Andre Smith of UVic wants to address this knowledge gap by including the experiences caregivers who have gone through the difficult process of choosing to discontinue the treatment for their loved one from appraising effectiveness/improvement to decision-making with the physician and the impact of discontinuing treatment on the relationship between the caregiver and person with Alzheimer's disease.

Research Background

Cholinesterase inhibitors (ChEIs) are first-line drugs in the treatment of mild to moderate Alzheimer's disease (AD) and their use has become widespread with the expansion of coverage under public drug plans. The benefits of ChEIs are most notable in the early phase of treatment, although these drugs are also used in the treatment of late stage AD symptoms. The issue of when to discontinue ChEI therapy remains debated due to a lack of clear evidence about the long term benefits of ChEIs and because the guidelines for evaluating these benefits remain inconsistent. Discontinuing ChEI treatment is a difficult decision for caregivers who must confront the reality that the only treatment available to their relatives no longer works. Unfortunately, the experiences of caregivers in regard to ChEI discontinuation have been largely ignored in the research literature.

The proposed study seeks to address this gap in knowledge by exploring the ways in which the process of ChEI discontinuation unfolds in the context of the everyday lives of caregivers of relatives with AD who either have been withdrawn from therapy or are in the process of being withdrawn. The study's intent is to understand how caregivers appraise the lack of ChEI improvement, how such appraisal is taken into account in the physician's decision to discontinue treatment, how caregivers interact with them on this matter, and how discontinuing treatment affects the way(s) in which caregivers understand and relate to affected relatives. The study draws on qualitative methodology, an approach where the researcher pays attention to the interpretive activities of individuals and their lived experiences. We will recruit 30 primary caregivers of relatives who have received ChEIs but are being, or have been, discontinued from treatment. They will participate in a 1.5 hour semi-structured interview. We will also conduct two

focus groups, each with four to five ChEI prescribing physicians, to explore their experiences with discontinuation and the challenges that might arise from interacting with caregivers in these circumstances.

This methodology will help determine how physicians interact with caregivers in the process of making decisions about discontinuing ChEIs, and will allow us to assess the extent to which caregiver appraisal of treatment effects is taken into account in these decisions.

We anticipate finding that the decision to discontinue ChEIs involves a complex interplay between caregiver appraisal, physician prescribing practices, and the pharmaceutical discourse on ChEI therapy. Findings from this study could contribute to the development of "best practice" guidelines to assist physicians and other health professionals in supporting caregivers and care recipients with the process of discontinuing ChEI therapy. These guidelines should also facilitate timely clinical decisions in discontinuing treatment and potentially reduce the costs of funding these drugs.

Finally, we intend to utilize the results of this study to develop a new line of inquiry on the process of discontinuing of ChEI therapy, one that will involve the collection of information via surveys, allowing us to produce generalizable findings on this phenomenon.

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Can the Pill help treat Alzheimer's disease?

Researcher: Cheryl Wellington, University of British Columbia (UBC)

A UBC researcher, Cheryl Wellington, is exploring progesterone-related molecules already used in birth control methods as a way to increase fat distribution in the brain and possibly improve memory and reduce biochemical changes that occur in brains affected by Alzheimer's disease. The results may allow for a hormone based compound specifically designed to benefit the brain as a new type of drug for Alzheimer's disease.

Research Background

Alzheimer's Disease (AD) currently affects nearly half of our population over the age of 85 years, causing gradual memory loss and eventually leading inability to function independently. One of the most important risk factors for AD is inheritance of a protein called apoE4. ApoE is a protein that functions to distribute fats including cholesterol within the brain. These fats are critically important function for the brain cells that must last a lifetime. Our previous studies have shown that the amount of fats carried by apoE affects AD in mouse models, and suggests that methods to increase fat-laden apoE will improve memory and reduce the biochemical changes that occur in the AD brain.

We recently identified molecules related to the female hormone progesterone that increase apoE production in a cell-based model system. Interestingly, progesterone is a promising treatment for traumatic brain injury in humans and has shown beneficial effects in AD mice. Our preliminary results suggest that progesterone-like a molecules may be better than progesterone for AD because they increases the cell's ability to put fats onto apoE as well as increases overall apoE production more effectively than progesterone.

Many progesterone-like molecules are already used in birth control medications and are therefore approved by the Food and Drug Administration for use in humans. In this project we will first test the ability of a progesterone-like molecule to improve memory and slow biochemical changes in a mouse model of AD. These results will determine if this molecule is effective and will establish the necessary preclinical data to begin to evaluate it as an AD therapy in human studies.

We will also perform chemical analysis of progesterone-like hormones to learn about which parts of the molecule are important for their functions in the brain rather than in the reproductive system. These results may allow the design of a hormone-based compound that is specifically designed to benefit the brain as a new type of drug for AD.

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“Cognitive Complainers” may help enhance screening procedures and non-medical interventions for treating Alzheimer’s disease

Researcher: Colette M. Smart, University of Victoria (UVic)

Colette M. Smart from UVic wants to help improve early detection of those at risk for Alzheimer’s disease and determine whether attention training would be an effective non-medical intervention to delay the progression of the disease. She aims to do this by studying “cognitive complainers” – certain older adults who complain about their thinking abilities due to a sensitivity to changes in the structure and function of their brain that are not yet detected by paper-and-pencil testing – and by providing them and healthy controls with training in either mindfulness-based stress reduction or psychoeducation about the effects of aging on cognitive abilities. Mindfulness-based stress reduction has been shown to improve mood, enhance attentional function, and even slow the rate of shrinkage of the brain that can happen with aging.

Research Background

With the aging of the "baby-boom" generation and increased numbers at risk for developing Alzheimer's disease, it is imperative for researchers to increase their efforts toward early detection of those at risk for Alzheimer's, and to find interventions that can decrease their risk for later progression.

Very recent research has suggested that, when certain older adults complain about their thinking abilities, this may be an early sign that they are at risk for developing Alzheimer's. We believe that these individuals are sensitive to changes in the structure and function of their brain that are not yet detected on paper-and-pencil testing. These "cognitive complainers" present a unique opportunity to study individuals who may be at risk for Alzheimer's disease. This would help us not only to better understand the disease process but, more importantly, to determine whether any intervention can be provided to improve these problems and delay any future progression to Alzheimer's.

We believe that one of the early changes experienced in this group is impairment in complex attention (or “cognitive control”), and that this difficulty could be remediated with attention training. In particular, mindfulness-based stress reduction holds great promise as an intervention: research shows that it can improve mood, decrease stress, enhance attentional function, and even slow the rate of shrinkage of the brain that can happen with aging. In this pilot study, we intend to (1) use standardized cognitive testing and brain imaging procedures to better understand the role of complex attention in cognitive complainers as compared to healthy older adults, (2) to provide both cognitive complainers and healthy controls with training in either mindfulness-based stress reduction or psychoeducation about cognitive aging, (3) to conduct structural brain imaging and electroencephalography (EEG) to determine whether these interventions improve attentional function in the cognitive complainers, and (4) to

follow these individuals over a three-month period to determine if these interventions prevent further decline in their cognition.

In addition, we predict that mindfulness-based stress reduction training will confer skills that will impact real-world function in areas such as decision-making and prospective memory. The outcomes of the current study could influence other researchers in this field in several ways. First, they will be provided with important information about changes in cognition and brain structure and function that may manifest at the very earliest stages of Alzheimer's disease, leading to better clinical screening procedures. Second, while there has been a great deal of attention paid to the role of medications in slowing the course of Alzheimer's disease and reducing its symptoms, comparatively less work has been done on cognitive and behavioural interventions for individuals at risk for or experiencing dementia.

This study will provide the field with important information on (1) whether such non-medical interventions are readily implemented and tolerated by a cognitively at-risk population, and (2) whether such interventions can cause a meaningful improvement not only in cognitive function but also in real-world skills relevant to older adults, something that medication cannot offer.

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Charting neuronal gene regulation throughout life

Researcher: Douglas Allan, University of British Columbia (UBC)

Douglas Allan, researcher at UBC, is attempting to be the first person to detail the regulatory networks that govern how gene expression is maintained in aging neurons. Since the loss of normal gene expression is recognized as a hallmark of many neurodegenerative diseases, his research can help us better understand how neurons are (or are not) able to maintain their gene profiles into adulthood. Dr. Allan's study, that takes advantage of advanced genetic technologies available in the common fruitfly, *Drosophila melanogaster*, will be conducted through a series of experiments to directly manipulate the regulatory mechanisms of gene expression in mature and aging neurons.

Research Background:

The nervous system contains an enormous number of neurons with very diverse functions. Ultimately, the differences in neuronal function reflect the differences in the gene expression profiles of those neurons. There has been great effort over many years to determine the gene regulatory mechanisms that generate differences in gene expression between different types of neurons.

We now understand many of those core mechanisms. However, once neurons have been generated and their gene expression profile determined, they must then maintain that gene expression profile for the rest of life of the organism. In humans, this can be for up to 100 years. Loss of normal gene expression is recognized as a hallmark of many neurodegenerative disorders. Yet, we do not understand how neurons maintain their gene expression profiles into adulthood. This proposal outlines a series of experiments designed to specifically address this gap in our knowledge.

We will use the genetically-amenable organism, *Drosophila melanogaster*, in which we can directly disrupt the regulatory mechanisms of gene expression in specific neurons, and at any time of our choice. Strong mechanistic conservation has long made *Drosophila* an ideal model for uncovering fundamental mechanisms of neuronal differentiation. These studies will be the first to detail the regulatory networks that govern the specific gene expression profiles of neurons from initiation to maintenance in aging neurons. As such, these studies will provide fundamental insight into unknown core mechanisms underlying the normal function of neurons throughout life.

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New study seeks to improve understanding of dementia care practices

Researcher: Heather Cooke, University of Victoria

With almost two-thirds of long-term care beds in Canada occupied by individuals with dementia, Heather Cooke's study on physical and organizational environments in dementia care settings, and their influence on care practice, seeks to identify key factors that could ultimately help care facilities move towards a more person-centred, social model of care. The results of the UVic graduate student's study may inform facility administrators and health care planners in their decision-making and resource planning for a more therapeutic and responsive dementia care milieu for residents.

Research Background

Almost two-thirds of long-term care beds in Canada are occupied by individuals with dementia. While care for these individuals has traditionally been provided within an institutional, medical model, in recent years, there has been a shift towards a more person-centered, social model.

Person-centred care emphasizes the uniqueness of the person with dementia, flexible care routines respectful of residents' values, preferences and needs, the development of consistent and caring relationships, and an enriched social environment. However, we currently have only a minimal understanding of the factors that support or inhibit person-centred care for persons with dementia.

Although both the physical and organizational environments of dementia care settings are believed important in the provision of quality care and resident quality of life, research in this area tends to take a fragmented approach, focusing on either the physical (e.g., architectural features, sensory attributes) or organizational environment (e.g., staffing ratios) to the exclusion of the other.

To date, little attention has been paid to how features in both of these environments influence person-centred care practice. Consequently, the overall objective of this two-phase, mixed method study is to explore the relationship between the physical and organizational care environments and the staff provision of person-centred care.

The first phase of the proposed study draws on data collected as part of a larger study of 18 nursing homes in three B.C. cities, for which the applicant was project coordinator. Data on the physical environment were collected through the use of a dementia-focused environmental assessment tool, while information regarding the organizational environment was collected via interviews with facility administrators. Care aide perceptions of person-centred care provision were measured using multi-item, pen and paper scales. These data will be used to determine which features in the physical (e.g., privacy, visual/tactile stimulation, personalization,

homelikeness) and organizational (e.g., staff ratios, staff mix, staff assignment, staff training) care environment are most closely linked to staff perceptions of person-centred care provision. In the second phase of the study, observations, in-depth interviews and focus groups will be conducted with care staff at several of the 18 facilities to develop a more in-depth understanding of the nuances and subtleties of person-centred care practices. For example, data will help identify the ways in which staff incorporate person-centred care into their everyday care work, and how the organizational and physical care environments inhibit or support the provision of person-centred care.

Findings from the proposed study will: a) highlight the person-centred care approaches successfully employed by staff, in addition to those for which further training or environmental modification is required; b) identify environmental features with the potential to enhance the provision of person-centred care within dementia care settings; and c) inform facility administrators and health care planners of the environmental features towards which resources could be directed to create a more therapeutic and responsive dementia care milieu for residents. Other researchers could use these findings to develop and evaluate promising environmental interventions with the goal of generating evidence-based protocols for the provision of person-centred dementia care.

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Determining protein activity may lead to new treatments for Alzheimer's disease

Researcher: Michael Hayden, Centre for Molecular Medicine & Therapeutics (CMMT), Child & Family Research Institute (CFRI), University of British Columbia (UBC)

In 1999, Michael Hayden, director and senior scientists of medical genetics at UBC and his team had identified the ABCA1 gene as a cholesterol transporter in the brain. His team will now examine whether the same gene can influence the development of Alzheimer's disease by regulating brain cholesterol metabolism and inflammation. By analyzing the specific roles of ABCA1 in brain inflammation, cell death, senile plaque, and tangle formation, which are the cardinal features of Alzheimer's disease, the study will also explore new ways to increase brain ABCA1 activity. The findings could lead to new treatments for Alzheimer's disease.

Research Background

35 million people worldwide are currently suffering from dementia, including half a million Canadians, and the number is expected to grow to 115 million by 2050. Alzheimer's disease (AD) is the most common form of dementia after the age of 60. Apart from familial AD linked to mutations in specific genes and the established connection between apolipoprotein E4 and increased risk for developing the disease, the majority of AD cases are sporadic. Factors triggering sporadic AD represent a major challenge for research and are under intense investigation. Cholesterol and inflammation are linked to AD. Changes in cellular cholesterol balance affect the accumulation of brain amyloid plaques, the hallmark feature of AD.

In 1999, our laboratory identified ABCA1 as a cholesterol transporter critical for regulating cellular cholesterol homeostasis. ABCA1 plays a crucial role in brain cholesterol regulation and facilitates amyloid degradation. Increasing ABCA1 activity reduces plaque deposits and improves memory function in AD mouse models. Inflammation in the brain is another key feature of AD. Synthetic compounds that increase ABCA1 levels reduce inflammation. ABCA1 may therefore impact the development of AD by regulating brain cholesterol metabolism and inflammation. The discrete contributions of ABCA1 in specific cell types of the brain to AD are currently unknown. This is particularly important as different cell types of the brain, called neurons and glia, exert unique and vital functions. In the context of AD, these unique cells differently affect cholesterol homeostasis, amyloid secretion and degradation as well as inflammation.

The objectives of our research focus on studying how the activity of ABCA1 in discrete cell types of the brain influences AD. We propose to analyze the specific roles of ABCA1 in neurons and glia in brain inflammation, cell death, senile plaque and tangle formation which are the cardinal features of AD. By using genetically engineered mouse models deficient in ABCA1 in specific brain cell types and crossing them to a mouse model of AD, we will also study how deficits in ABCA1 function in particular cells impact the severity and course of the disease.

The use of currently available compounds that increase ABCA1 is hindered by the fact that they lead to serious side effects including fatty liver. We will investigate a new way to increase brain ABCA1 activity. The effects of this novel pathway on neuropathological features of AD in mice will be studied.

The outcome of our research will provide a better understanding of how ABCA1 and its cell-type specific regulation of cholesterol transport and inflammation contributes to AD. In addition we will explore a new way to increase brain ABCA1 activity which may lead to a reduced manifestation of common AD features. Our studies may further establish brain ABCA1 as a potential therapeutic target in dementia. The findings will influence future AD research specifically those investigators focused on studying cholesterol metabolism and neuroinflammation in AD and other dementias.

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Distinguishing between Alzheimer's disease and other dementias can lead to better clinical outcomes

Researcher: Mirza Faisal Beg, Simon Fraser University (SFU)

Different types of dementia are caused by different physical changes to the brain, however there are several types, such as frontotemporal dementia, whose early signatures look exactly like Alzheimer's disease increasing the risk of misclassification thereby impacting research studies, findings, and clinical treatment.

Mizra Faisal Beg is about to tackle the important problem of distinguishing between patients with Alzheimer's disease and those with Frontotemporal dementias by using the structural analysis of brain MR scans. By characterizing the tissue atrophy over time, his research will then allow for better recruitment of patients whose diagnosis of Alzheimer's disease has stronger footing, and will enhance the study of biomarkers in early Alzheimer's disease.

Research Background

Progress in neuroscience research in the last few decades has begun to show conclusively that many, if not all, of the underpinnings of behaviour are biological. This is most clearly manifested in neurodegenerative diseases such as dementias where a specific pathology progressively damages specific regions of the brain and eventually compromises the integrity of the neuronal systems and circuits recruited in cognitive processing.

This leads to decline in cognitive performance, but in the earliest stages of the disease, this decline is not so noticeable due to the substantial cognitive reserve and redundancy present in the brain. Over time, the damage due to pathology becomes significant and overwhelms the brain's systems leading to observable degradation in cognitive function. This is when a clinical diagnosis of the dementia occurs.

However, the pathology that causes this change in behaviour has already been at work for several years, if not decades, and the destruction of brain tissue, at this stage, is not easily reversible. Hence, there is a strong need to develop biomarkers that can be used to signal the onset of pathology such as Alzheimer's in a non-invasive and accurate manner. There are several approaches being tested for the development of these biomarkers, including analysis of specific proteins in spinal fluid, metabolism of energy in the brain, and structural and functional changes in the brain in patients who have Alzheimer's vis-à-vis those who do not.

However, there are several other dementias such as the frontotemporal dementias whose early signatures resemble Alzheimer's and they are often misclassified as Alzheimer's in their early stages. Hence, the inclusion of patients from these distinct other dementias, makes the study of Alzheimer's pathology related changes in the brain difficult.

In this proposal, we tackle the important problem of distinguishing between patients with Alzheimer's and those with frontotemporal dementias using structural analysis of brain MR scans. We propose to characterize the tissue atrophy over time in these two distinct dementia populations using features such as cortical thickness, folding pattern, segmentation and shape of sub-cortical regions and integrity of white matter pathways.

Based on this, we propose to develop a method that will increase the ability to discriminate between Alzheimer's and frontotemporal dementias. This will allow the recruitment of patients whose diagnosis of Alzheimer's has higher confidence and hence enhance the study of biomarkers of early Alzheimer's.

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Early detection of probable Alzheimer's dementia with new approach

Researcher: Pradeep Reddy Ramana, Simon Fraser University

Pradeep Kumar Ramana, a SFU researcher, is hoping to find a way to detect Alzheimer's disease earlier. Using MRI scans, he is going to measure different biomarkers from different locations to capture different types of neurodegenerative changes caused by Alzheimer's disease. A method will be developed to then fuse the different biomarkers, weighing them in a specific way to enable the early detection of Alzheimer's disease. This is comparable in certain respects to the way an expert radiologist would assess the different aspects of an MRI scan while making the diagnosis.

Research Background

This disorder manifests as a progressive decline in many cognitive functions including memory loss, reading, route finding, attention, perception and speed processing.

In individuals with pathologically confirmed AD, substantial cognitive impairment may not be readily apparent during their lifetime. This suggests that the disease process associated with AD may be ongoing in the brain long before clinical symptoms become detectable. Both the aging population and the promise of disease modifying therapeutics have made the characterization of early stages of AD a critical need.

The disease modifying therapeutics are likely to be most effective at the earliest stages of the disease, before extensive and probably irreversible neuronal degeneration, thus success in treating Alzheimer's disease depends critically on our ability to accurately predict AD in at-risk individuals at a preclinical stage.

Magnetic resonance imaging (MRI) is a safe and non-invasive way of obtaining images of the brain, which gives us a very detailed insight into structure of the brain and the different tissues in the brain. Computer-assisted MR imaging techniques enable scientists and clinicians to monitor and investigate the progression of the deleterious effects of the disease.

Our current research project goal is to measure biomarkers using MRI scans that characterize the signs of AD at its preclinical stage. At the early stages of AD, neurodegenerative changes caused by AD are subtle and spatially distributed. Different types of biomarkers will be measured from different locations to capture different types of neurodegenerative changes caused by AD. We have already developed tools to automatically measure various biomarkers such as hippocampal atrophy, structure deformations of subcortical structures, texture variations, cortical thickness and cortical folding. A method would be developed to fuse different biomarkers, weighing different biomarkers in a specific way, which enables the early detection of AD. This is analogous to the way an expert radiologist would assess the different aspects of

an MRI scan while making the diagnosis. We are in the process of further improving this method by including different biomarkers mentioned earlier, which would enable us to develop methods to detect AD at its preclinical stage.

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Understanding the mechanics of Alzheimer's disease, one protein at a time

Researcher: Shernaz Bamji, University of British Columbia

Frontotemporal dementia (FTD) affects the areas of the brain – frontal and temporal – that are generally associated with personality and behaviour. It tends to occur at a younger age than Alzheimer's disease and makes up 2% – 5% of dementia cases.

While it is clear that the dysfunction of the proteins progranulin and TDP-43 plays a role in FTD, how they normally function in the central nervous system and therefore its connection with FTD has not yet been determined. Shernaz Bamji, a UBC research, hopes her study will help to address that research gap to advance understanding about the causes and risk factors associated with FTD.

Research Background

One of the most exciting breakthroughs in the study of frontotemporal dementia (FTD) was the discovery that the majority of patients with this disease have mutations in the gene that encodes for the protein, progranulin. These mutations cause a decrease in the amount of progranulin circulating in the blood, the cerebrospinal fluid, and the brain.

FTD patients who have PGRN mutations typically exhibit "neuronal inclusions" in the brain. Neuronal inclusions are packets of abnormally accumulated proteins within nerve cells. TDP-43 is a protein that is consistently mislocalized and associated with these inclusions in patients with FTD. It is clear that dysfunction of both progranulin and TDP-43 plays a central role in the development of FTD. Despite this, an understanding of how these proteins normally function in the central nervous system is still in its infancy.

Preliminary data from our lab demonstrates that decreasing PGRN levels in cultured brain cells can profoundly impact how these nerve cells communicate with one another. We have also demonstrated a connection between PGRN and the subcellular localization of TDP-43 within nerve cells.

In this study we will further elucidate the role of progranulin and TDP-43 in regulating neuronal connectivity by disrupting their function in cultured nerve cells. We propose to: 1) examine the function of TDP-43 in the regulation of neuronal connectivity; 2) determine the functional interplay between TDP-43 and progranulin; and 3) determine the regulation of progranulin expression and secretion in nerve cells. Examining the normal function of these two proteins in the brain will be an important step towards elucidating the cellular mechanisms underlying this debilitating disease, and will be highly informative for the development of novel therapeutics.

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FOR IMMEDIATE RELEASE
Sept. 21, 2011

Understanding underlying causes in order to develop solutions for better treatment
Researcher: Zhe Wang, University of British Columbia (UBC)

Zhe Wang, a researcher at UBC, is planning to conduct the first in-depth study on how the UCH-L gene is regulated and its impact on the development of Alzheimer's disease. Reduced ubiquitin carboxy-terminal hydrolase (UCH-L) has been implicated in the development of several human diseases including Alzheimer's disease. Scientists believe UCH-L has a role in the normal functioning of the ubiquitin proteasome system (UPS), which in turn affects the synaptic function of the nervous system. However, little else is known about this gene and thus far no other research of this kind has been conducted. The findings will be fundamentally important not only for understanding the causes of Alzheimer's disease but for developing drug treatments as well.

Research Background: Regulation of UCHL1 in neurodegeneration

The ubiquitin proteasome system (UPS) plays critical roles in many cellular processes including mediating protein degradation and regulating protein trafficking via endocytosis and exocytosis. A balanced process of ubiquitination and deubiquitination is well maintained for normal function of UPS. The ubiquitin carboxy-terminal hydrolase 1 (UCH-L1) belongs to a large family of deubiquitinating enzymes and is highly expressed in the brain, particularly in neuronal cells.

Abnormal UCH-L1 activity has been implicated in the pathogenesis of several human diseases. Reduced UCH-L1 expression was also found in Alzheimer's disease (AD). However the underlying mechanism of reduced UCH-L1 expression in AD and its role in AD pathogenesis is unknown. Thus far no studies have examined how UCH-L1 gene expression is regulated and whether abnormal UCH-L1 expression plays a role in neurodegeneration and contribute to AD pathogenesis.

Our working hypothesis is that abnormal UCH-L1 expression and function are involved in the pathogenesis of AD. This proposal seeks to elucidate the molecular mechanism of UCH-L1 gene transcription and the role of UCH-L1 in neuronal apoptosis in AD pathogenesis. Specifically we propose: 1. to determine whether NF- κ B signalling regulates UCH-L1 expression; 2. to examine if dysregulation of UCH-L1 expression facilitates neurodegeneration.

The underlying mechanism of AD pathogenesis remains elusive and the role of UCH-L1 in neurodegeneration is not well defined. Precious studies showed abnormal UCH-L1 level in neurodegenerative disorders. Understanding its gene expression regulation and the role of UCH-L1 in neuronal apoptosis will be fundamentally important for defining the AD pathogenesis in some sporadic cases and AD drug development.

This pilot project will allow us to embark on an in-depth study of signalling pathways affecting UCH-L1 expression and to test the novel hypothesis that UCH-L1 plays an important role in neuronal apoptosis in AD pathogenesis.

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