Pacific
Alzheimer Research
Foundation

Dear Friends and Donors,

The Pacific Alzheimer Research Foundation (PARF) funds research into the cause and cure for Alzheimer disease and related dementias. In 2017, PARF revised its strategy to focus on increasing the research funding needed to impact these diseases and I am excited to share our research investments and commitments since that time. We hope you are inspired by our results and that you will join us in this fight, as we need to do much more to end these diseases.

PARF's goal is to increase longer term private funding of basic science (cause and cure) research by having:

- Top notch research that is collaborative, effective and, where possible, levered through partnerships;
- A diverse and experienced board of directors to oversee and guide our research initiatives;
- A low cost funding model (currently run by volunteers and one staff);
- Leadership in encouraging private donors to support dementia research;
- A commitment to have 100% of new donations directly funding research; and,
- Administration & Fundraising met by investment income and Board donations.

Our renewed efforts have raised over $460,000 over the last two years and our goal for 2020 is to raise an additional $400,000. In the 2018-2021 period, PARF is supporting 11 dementia research projects valued in excess of $960,000. Our collaborative efforts have resulted in $640,000 of additional partnership funds, increasing our research impact to over $1.5 Million. And there is more coming.

Our work is only possible thanks to the dedication of caring individuals like you.

If you have any questions or suggestions please contact Scott MacDonald at (604) 678-8138 or scott@parf.ca, or myself at lbeattie70@gmail.com.

We look forward to hearing from you.

Sincerely

B. Lynn Beattie, MD, FRCPC
President

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Research Investment Summary 2018 – 2021

Studying the manipulation of cell membrane channels to protect brain cells.

Highlights

- Strong annual funding in 2018 and 2019
- Research grants planned for this fall could add >$500,000 of multi-year grants, depending on donations

Lead Researcher	Started	2018	2019	2020	2021	Commitments 2018-2021
Dr. Yun Zhang*	2015	$8,645				$8,645
Dr. Sieun Lee*	2015	$8,645				$8,645
Dr. Haakon Nygaard*	2016	$45,000	$45,000	$45,000	$11,250	$146,250
Dr. Arya Mehran*	2017	$20,750				$20,750
Vedrana Cvetkovska*	2017	$19,315				$19,315
Dr. Holly Tuokko*	2017	$60,000				$60,000
Dr. Debra Sheets*	2018	$59,565	$59,565			$119,130
Dr. Dustin King*	2018	$2,042	$19,313	$20,750	$8,646	$50,751
Dr. Gordon A. Francis*	2019		$17,329	$34,658	$17,329	$69,316
Dr. Brian MacVicar	2019		$37,500	$75,000	$37,500	$150,000
Dr. Cheryl Wellington	2019		$75,000	$75,000		$150,000
Process Underway	2020			$70,000	$70,000	$140,000
Upcoming Research Call	2020			TBD	TBD	TBD
PARF Funding		***$223,962***	***$253,707***	***$320,408***	***$144,725***	**$942,802**
Partner Matching		$223,962	$141,207	$170,408	$107,225	$642,802
Funding Impact		***$447,924***	***$394,914***	***$490,816***	***$251,950***	***$1,585,604***

*(*Part of PARF's Partner Matching Projects)*

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1. Human islet amyloid polypeptide aggregation, the missing link between type 2 diabetes and Alzheimer disease?

Dr. Yun Zhang, University of British Columbia*

Type 2 diabetes (T2D) patients have an increased risk of developing Alzheimer disease (AD). However, the underlying mechanism is poorly understood. Human islet amyloid polypeptide (hIAPP) aggregates, occurring in ~95% of T2D patients, induce a variety of pathological processes that are contributing factors to AD neuropathology. We will investigate the effect of hIAPP aggregation on the Alzheimer's development in T2D and the potential mechanism by conducting cell and animal experiments. Additionally, novel transgenic mouse models of diabetic AD will be generated to mimic the natural process of AD development in diabetics.

Grant	Started	Term	2018
$62,250.00	2015	4 Years (15-18)	$8,645.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

2. Are there indicators of Alzheimer's disease in the eye?

Dr. Sieun Lee, Simon Fraser University*

Finding the connection between the eye and Alzheimer disease (AD), by investigating it for potential biomarkers of the disease. The eye is an extension of the brain, with the optic nerve forming a direct physical connection between the retina and the brain's visual cortex. Recent advances in ophthalmic imaging techniques, such as optical coherence tomography (OCT), provides high-resolution 3D visualization of the inner structures of the eye, including the retina, nerve fibres, and blood vessels, in a non-invasive manner.

We will develop image processing and analysis tools to examine chemical biomarkers, structural degradation, and functional loss in the eye that may be associated with AD. The project will potentially lead to discovery of novel AD biomarkers in the eye, and a cost-effective and accessible diagnostic tool for early detection of AD

Grant	Started	Term	2018
$62,250.00	2015	4 Years (15-18)	$8,645.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

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3. Chemical suppression of nonsense mutations for the treatment of Frontotemporal Dementia

Dr. Haakon Nygaard, University of British Columbia*

Frontotemporal dementia is a progressive neurodegenerative syndrome, and the second most common cause of young-onset dementia after Alzheimer disease. Members of our team recently reported that loss-of-function mutations in the gene for a protein called progranulin causes 25 percent of frontotemporal dementia cases. Of these mutations, 30-40 percent are "nonsense mutations" that act as stop signs to prematurely end a process required to produce normal progranulin. When progranulin production ends too early, it leads to a shortened protein that cannot carry out the normal brain functions, eventually leading to dementia in the sixth decade.

The goal of this project is to investigate small molecule combinations that can bypass the abnormal "stop sign" in the progranulin gene, increasing the normal production of this important protein. The small molecule combinations will be refined and optimized to find the most effective combination. This approach, also referred to as "suppression of nonsense mutations", offers the possibility of developing a new drug for patients with frontotemporal dementia caused by a progranulin mutation. The team also plans to develop a mouse model of frontotemporal dementia to test the small molecule combinations in a living organism.

Grant	Started	Term	2018	2019	2020	2021
$225,000.00	2016	6 years (16-21)	$45,000.00	$45,000.00	$45,000.00	$11,250.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

4. Neurally-produced estradiol enhances the neuroprotective actions of insulin*

Dr. Arya Mehran, BC Children's Hospital

Estradiol enhances insulin production and response in the pancreas. However, these effects of estradiol in the brain have never been confirmed. Yet when expressed together in the hippocampus (a brain structure critically involved in memory), estradiol and insulin promote neuron growth and survival as well as synapse formation and maintenance.

Dr. Mehran's hypothesis is that estradiol produced by neurons enhances the production and action of insulin in the brain, and that this has beneficial effects in a rat model of Alzheimer's disease.

Grant	Started	Term	2018
$41,500.00	2017	2 Years (17-18)	$20,750.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

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5. The Mechanism and Significance of the Synaptogenic Activity of Amyloid Precursor Protein

Dr. Vedrana Cvetkovska, University of British Columbia*

Amyloid Precursor Protein (APP) is a cell surface protein that has been mostly studied in the context of Alzheimer's disease. Much about its normal function remains unknown. APP can cause connections to form between brain cells by an unknown mechanism. We believe this happens through an interaction with synaptic organizing proteins (organizers).

This project will investigate the possibility that APP forms synapses by interacting with major organizers in the brain, namely neurexins and receptor protein tyrosine phosphatases (RPTPs).

To test this, we will use a combination of cell cultures and mouse models. We will test whether APP binds to neurexins and RPTPs and whether binding to these organizers is required for the connection-forming activity of APP. We will also compare brain cell connections in normal mice to those in mice that express an altered form of APP that cannot bind to organizers.

This study may shed light on the function of APP through detailing how it can help form connections between brain cells. If defects in connections between brain cells contribute to neurodegeneration in Alzheimer's disease, these results could shed light on the mechanisms behind that as well.

Grant	Started	Term	2018
$24,854.00	2017	2 Years (17-18)	$19,315.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

6. The development of comparison standards for the cognitive measures employed in Canadian Longitudinal Study on Aging

Dr. Holly Tuokko, University of Victoria

Change in cognitive functioning is characteristic of normal aging and is evident beginning in mid-life. However, some people exhibit well-maintained cognitive skills into late life and others exhibit early and precipitous decline. Knowing how Canadians of differing characteristics (e.g., men, women) typically perform on measures of cognitive functioning is of great importance for identifying changes associated with medical conditions such as Alzheimer Disease. The Canadian Longitudinal Study on Aging (CLSA) is collecting detailed information about the performance of people aged 45-85 years on measures of cognitive functioning for English- and French-speaking Canadians.

Grant	Started	Term	2018
$119,500.00	2017	2 years (17-18)	$60,000.00

**Grant doubled through partner matching agreement with The* Alzheimer *Society Research Program*

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7. Does participation in a community choir by people with Alzheimer disease improve cognitive function and quality of life?

Dr. Debra Sheets, University of Victoria
Dr. Stuart MacDonald, University of Victoria
Dr. Andre Smith, University of Victoria

Voices in Motion is an intergenerational choir for seniors living with memory loss and their family caregivers here in Victoria. This two-year study, is a partnership between Pacific Alzheimer Research Foundation, a team of researchers at the University of Victoria, students at St. Andrews High School and Pacific Christian School, Alzheimer Society of Canada and Island Health (community partner).

This study will determine if community choirs are an inexpensive intervention that integrates social, cognitive, and physical activity with potential benefits. These benefits include enhanced memory, reduced depression, and increased social engagement as well as improving caregiver well-being.

Grant	Started	Term	2018	2019
$119,130.00	2018	2 Years (18-19)	$59,565.00	$59,565.00

**Grant doubled through partner matching agreement with The* Alzheimer *Society Research Program*

8. Understanding the Role O-GlcNAc in Protein Stability

Dr. Dustin King, Simon Fraser University

The break down of O-GlcNAcylation is implicated in several human diseases including type II diabetes, Alzheimer's disease, and cancer. However, the basic biochemical roles of O-GlcNAcylation remain largely unanswered. It is likely that a basic function of the O-GlcNAc prevents the unfolding or aggregation of target proteins. The unfolding of proteins can make them toxic and Dr. King is investigating its role in keeping the proteins stable. The results of this research will provide important insights into the basic molecular mechanisms governing O-GlcNAc deregulation in human disease.

Grant	Started	Term	2018	2019	2020	2021
$50,751.00	2018	4 Years (18-21)	$2,042.00	$19,313.00	$20,750.00	$8,646.00

**Grant doubled through partner matching agreement with Michael Smith Foundation for Health Research*

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9. The role of smooth muscle cell metabolism of amyloid beta in cerebral amyloid angiopathy

Dr. Gordon A. Francis, Department of Medicine at St. Paul's Hospital, UBC.

The research goal is to understand how the harmful protein, amyloid beta, deposits in blood vessels of the brain, leading to dementia. A key change in the brains of individuals with Alzheimer's and other forms of dementia is the accumulation of amyloid beta in arteries, in regions normally occupied by smooth muscle cells, the main cell type in arteries.

We will examine why smooth muscle cells have difficulty breaking down this protein compared to other brain cells, microglial cells. We will do these studies using smooth muscle and microglial cells in dishes and using sections of brain tissue donated from autopsies of patients who did or did not have dementia. By understanding why smooth muscle cells fail to degrade this harmful protein it is hoped that this can be prevented to reduce the incidence of Alzheimer's and other dementias.

Grant	Started	Term	2019	2020	2021
$69,316.00	2019	3 Years (19-21)	$17,329.00	$34,658.00	$17,329.00

**Grant doubled through partner matching agreement with The* Alzheimer *Society Research Program*

10. Contribution of microglia activation and neuronal oxidative stress to Alzheimer's disease

Dr. Brian MacVicar, University of British Columbia
Dr. Haakon Nygaard, University of British Columbia

Recent studies have indicated that microglia, our protective immune cell in the brain, might be important in causing the loss of nerve cells in Alzheimer disease (AD). To further understand these processes, we will study how microglia cause oxidative stress, a phenomenon that causes an over production of reactive oxygen radicals. We recently found that oxidised nerve cells around amyloid plaques are surrounded by microglia. This finding raises the following questions which we want to answer using state-of-the-art models of AD: Do microglia generate the oxygen radicals? How do these oxygen radicals damage nerve cells, and can it be prevented?

Grant	Started	Term	2019	2020	2021
$150,000.00	2019	3 years (19-21)	$37,500.00	$75,000.00	$37,500.00

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11. Precision Genetic Model of Neurovascular Unit to Study Alzheimer Disease

Dr. Cheryl Wellington, University of British Columbia
Dr. Haakon Nygaard, University of British Columbia

Although scientists realize that understanding how to keep blood vessels in the brain healthy may offer new ways to treat Alzheimer's Disease (AD), a big challenge is that there are not many methods to study brain's blood vessels that translate to human physiology. We have developed a method to grow functional three dimensional human blood vessels in the test tube using "tissue engineering" technology and aim now to use this technology to make brain blood vessels using AD patient cells. These disease-like vessels will be used to rapidly test questions about AD pathophysiology and assist in the development of therapeutics.

Grant	Started	Term	2019	2020
$150,000.00	2019	2 years (19-20)	$75,000.00	$75,000.00

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