RESEARCH WITHOUT BORDERS

PARTNERS IN SCIENCE

YOUR GIFT IN ACTION

PROGRESS REPORT – YEAR ONE

on partnered projects between
St. Boniface Hospital Research,
in Winnipeg, Canada
and Ben Gurion University of the Negev,
in Beersheba, Israel

CANADIAN ASSOCIATES OF Ben-Gurion University of the Negev

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Research Without Borders

A JOINT RESEARCH INITIATIVE BETWEEN ST. BONIFACE HOSPITAL RESEARCH IN CANADA AND BEN-GURION UNIVERSITY OF THE NEGEV IN ISRAEL

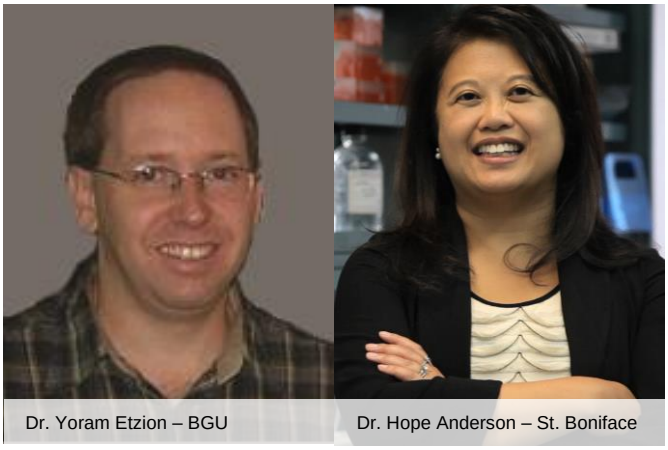
In 2017, two leading research institutions, St. Boniface Hospital and Ben-Gurion University of the Negev established a collaborative partnership to look at the prevention and treatment of chronic health issues with a focus on cardiac disease, neurodegenerative disorders, and food sciences.

Leveraging complementary expertise and shared resources, these partnerships will accelerate discovery, scientific advancement and opening doors to novel medical treatments.

Generous support from our donors made this unique international collaboration possible and we are pleased to provide this progress report on the results of the first year of funding for six innovative research projects.

Discovering new treatments for an abnormal heartbeat

Dr. Yoram Etzion & Dr. Hope Anderson



Dr. Yoram Etzion – BGU

Dr. Hope Anderson – St. Boniface

Dr. Etzion's and Dr. Anderson's project explores a new class of drugs that may effectively treat abnormal heart rhythm.

The electrical system in the heart tells the heart how and when to beat. Your brain talks to this system and can change or modulate how your heart beats (for example, when you are exercising, anxious or excited). When the brain sends the wrong signals to the heart, it can contribute to Atrial Fibrillation (AF), which is the most common form of irregular heartbeat.

Drs. Anderson and Etzion have found that drugs that activate cannabinoid (CB) receptors can also block signals in the heart that contribute to AF. Using innovative technology, they will then assess the effects of CB-activating drugs on relevant signalling pathways. By learning how CB receptors might control the heart abnormalities that give rise to AF while avoiding adverse side effects, we may discover molecular targets that can be manipulated for therapeutic gain to treat heart disease.

Why it's important

Irregular heartbeat is a condition that affects more people each year, often leading to serious complications like heart attacks and strokes which require interventions and corrective procedures. One such procedure, called an ablation, was performed 400 times in 2018 at

St. Boniface Hospital's cardiac treatment centre, a number that is expected to continue to rise significantly in the future.

The economic impact of continuing to treat the growing prevalence of irregular heartbeats with inadequate treatments cannot be understated, making AF an important research priority.

What was accomplished in Year One
Ms. Danielle Lee, a PhD student in Dr. Anderson's lab, spent the winter at Ben Gurion University working in Dr. Etzion's lab with a colleague to assess the efficacy of a candidate drug on AF markers in the intact heart.

Ms. Lee is now working at St. Boniface Hospital's Albrechtsen Research Centre to analyze the archived heart tissue samples from Dr. Etzion's lab. She presented her initial findings at the Canadian Student Health Research Forum in June 2019 in Winnipeg.

Moving forward, the research team will continue to analyze the heart tissue samples to determine the effects of the candidate drug on AF. They plan to share their findings in an original article in a peer-reviewed scientific journal and then present at a relevant biomedical scientific conference. Dr. Anderson recently visited Ben Gurion University. She and Dr. Etzion discussed strategies to secure future collaborative grant funding to continue this important work.

Finding markers of autism in blood from children with autism

Dr. Idan Menashe & Dr. Harold Aukema

Dr. Idan Menashe – BGU

Dr. Harold Aukema – St. Boniface

Dr. Menashe and Dr. Aukema are studying a large sample of metabolites in children with Autism spectrum disorder from the Negev Hospital-University-Based (HUB) database, which was designed specifically for such studies and already contains comprehensive behavioural and clinical data on these children.

The data will be used as follows:

1. Identify clusters of children with autism that share similar profiles of blood compounds;
2. Examine whether these autism subtypes are associated with specific dietary patterns and behavioural and clinical characteristics in these children; and
3. Determine whether there are sex differences between these autism subtypes.

Why it's important
Autism spectrum disorder (ASD) is a collection of complicated and diverse conditions of brain development that are currently referred to as a single disorder due to the lack of an efficient subgrouping approach. Currently, the diagnosis of ASD is based on behavioural assessments that cannot distinguish between different subtypes of the disorder.

Metabolites are excellent biomarkers for different human traits as they can be easily measured in blood samples and vary according to diverse biological conditions. Dr. Aukema and Dr. Menashe hypothesize that ASD subtypes can be identified based on their unique profiles of blood metabolites. By developing classifications of ASD subtypes based on metabolites, researchers would facilitate further research, diagnosis and treatment of these disorders.

Having a better understanding of the specific subtypes of ASD will help patients lead more fulfilling lives and support families and caregivers in better understanding the nuances of their loved one's condition. This research is considered a first-of-its-kind globally.

What was accomplished in Year One

An overview of the project was shared by Dr. Menashe and Dr. Aukema at a public event held at the St. Boniface Hospital's Albrechtsen Research Centre in the spring of 2019, sponsored by Canadian Associates of Ben-Gurion University of the Negev. Dr. Menashe has been collecting blood samples from ASD children over the past year, and those samples are expected to arrive in Winnipeg in the first half of 2020, at which time both labs will begin their analysis. The resulting dataset will be analyzed using several clustering approaches aimed at identifying subgroups of ASD children with distinct metabolic profiles. These profiles will be contrasted among defined groups of children with specific ASD characteristics, for example, "Savants", to determine metabolic profiles of specific ASD subtypes.

Using new drugs to correct nerve damage in diabetics

Dr. Daniel Gitler & Dr. Paul Fernyhough

Dr. Daniel Gitler – BGU

Dr. Paul Fernyhough – St. Boniface

Dr. Daniel Gitler's and Dr. Paul Fernyhough's collaboration will use new drugs to correct nerve damage in people who have diabetes.

Dr. Fernyhough has been studying the cause of peripheral nerve damage (neuropathy) in diabetics for several years and has developed a topical cream to help treat this painful condition, which also revives and heals the damaged nerves.

The basic science behind the treatment is not completely understood, so Dr. Gitler's work is focused on investigating the mechanism of nerve loss and how Dr. Fernyhough's product might help stop the nerve damage from happening altogether.

The cornea is often where signs of diabetic neuropathy first begin to appear, so the researchers will use corneal imaging to help determine changes in the nerve endings and the ability of anti-muscarinic drugs in the topical cream to repair nerve damage. For the first time, these new optical techniques will enable the researchers to see real-time imaging of nerve fibres in the cornea. The results of the project are hoped to accelerate the availability of this cream to diabetic patients around the world.

Why it's important
About 40 million people in North America have some form of peripheral neuropathy. Sixty per cent of these people have diabetic neuropathy. In 2001, the annual cost of treating diabetic neuropathy and its consequences was between $4.6 and $13.7 billion, accounting for up to 27 per cent of the direct medical costs of diabetes. In Israel, pain in diabetic patients is ruled as neuropathic in almost half of the cases.

People with diabetic neuropathy experience incapacitating pain, sensory loss, foot ulceration, infection, gangrene and poor wound healing. These alarming figures are predicted to increase five-fold over the next ten years, making it more important than ever to develop effective treatments.

What was accomplished in Year One
This past year Dr. Fernyhough's team generated novel data which was presented at the Peripheral Nerve Society meeting in Genoa, Italy and the annual meeting for the International Society for Neurochemistry in Montreal. Data was presented showing energy deficits in cultured adult sensory neurons in diabetes. Using an innovative imaging approach, we used ATP sensors to detect this key intermediate in various parts of the sensory neuron axis (for example, we were able to focus on ATP levels in the axon).

Dr. Gitler's team learned to perform corneal imaging in mice with induced diabetes to observe the nerve endings in their eyes. The team's successful imaging confirmed the feasibility of the next step of the experiments, which will move forward in year two.

In the second year of the project, Dr. Fernyhough's lab will purchase the equipment needed to image the cornea in live mice, a critical step in advancing the potential application to humans. They will then compare the results of imaging in normal and diabetic mice when treating them with the drugs.

Controlling cellular energy production by calcium

Dr. Israel Sekler & Dr. Larry Hryshko

Dr. Israel Sekler – BGU

Dr. Larry Hryshko – St. Boniface

Every cell in the body needs energy to live. A loss of energy results in the death of the cell. Essentially, every disease condition involves cell death which, if it is significant enough, can affect the performance of an organ like the heart. If a very large number of cells die, it can result in heart failure.

Dr. Sekler's and Dr. Hryshko's project studies the mechanism of cell life and death through the production of energy within the cell. The mitochondria within all cells in the body are the engines that produce energy for the cell. Therefore, the function of the mitochondria becomes key for the life and death of all cells. Their project examines how one specific protein (called NCLX) within mitochondria influences mitochondrial function. The researchers have learned how to generate more of this protein and place it in mitochondria. The goal of the

project is to see how this influences mitochondrial function and, ultimately, the function of the tissue in disease models.

Why it's important
If we can understand how NCLX influences mitochondrial function, we can learn how to influence energy production in cells. If NCLX is important in improving or inhibiting mitochondrial function (and, therefore, energy production), we would have an avenue to improve energy production and preserve cell life by creating drugs that would either inhibit or stimulate the function of NCLX.

What was accomplished in Year One
Dr. Sekler's lab has produced a method to increase the amount of NCLX in mitochondria. Over the last year, he has been helping Dr. Hryshko's lab learn how to do this technique. Dr. Hryshko's lab has then been checking its effects on cell function.

Dr. Sekler's lab is examining how neural cells specifically react to this intervention. This has direct relevance to diseases like Alzheimer's and Parkinson's where energy production in neural cells is thought to be at the root of the problem.

Dr. Sekler's and Dr. Hryshko's efforts will continue over the coming year towards obtaining an electrophysiological profile for the NCLX protein. In conjunction with these studies, the two labs will be collaborating on investigating novel pharmacological agents that affect sodium-calcium exchange function.

Understanding novel factors involved in cardiac fibrosis and heart failure

Dr. Ramon Birnbaum & Dr. Jeffrey Wigle

Dr. Ramon Birnbaum – BGU

Dr. Jeffrey Wigle – St. Boniface

Dr. Birnbaum's and Dr. Wigle's project investigates the novel factors that are involved in the development of heart failure after a heart attack.

After a heart attack, patients often experience cardiac fibrosis. Fibrosis is commonly observed as a thickening of the heart valves and excess deposits of collagen in the heart. This excess collagen stiffens the heart and hinders its pumping performance. Cardiac fibrosis is a critical indicator of heart failure with no known treatments.

When fibrosis is first triggered, fibroblast cells become myofibroblasts which leads to thickening of the heart and fibrosis. Certain proteins such as Zeb2 are thought to regulate the molecular mechanism that controls this process. Understanding the role of Zeb2 in fibroblast to myofibroblast transition will pave the way for developing effective treatments for cardiac fibrosis and heart failure.

Why it's important
Cardiovascular disease is the number one cause of death worldwide, with almost 23.6 million people predicted to die from heart disease by 2030. After a heart attack, cardiac fibrosis can affect areas of the heart that weren't harmed by the heart attack causing the heart muscles to stiffen and become less efficient. By improving our understanding of cardiac fibrosis, Drs. Wigle and Birnbaum will bring us closer to developing an effective treatment for this condition.

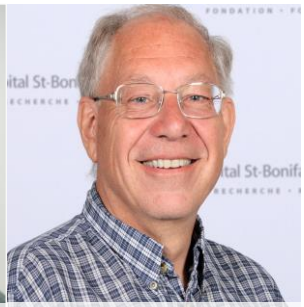
What was accomplished in Year One
Dr. Wigle's team worked closely with Dr. Birnbaum over the past year to design their experiments in the most efficient manner. They have isolated different cells from the heart: cardiac fibroblasts, myofibroblasts and cardiomyocytes in their lab at St. Boniface Hospital Albrechtsen Research Centre to be analyzed in Dr. Birnbaum's lab at BGU. Dr. Birnbaum's lab will identify genomic regions that control the expression of the gene Zeb2, which is a key switch in controlling the process of fibrosis.

Dr. Wigle presented on this work at the 5th European Section meeting of the International Academy of Cardiovascular Sciences (IACS-ES) Advances in Cardiovascular Research: from basic mechanisms to therapeutic strategies (Bratislava, Slovakia) and at the Cardiology 2018 meeting (Havana, Cuba).

Over the next year, the researchers will further study how the proteins Zeb1 and Zeb2 act as genetic switches in the activation of fibrosis. One of Dr. Wigle's students, Mr. Zachary Meikle will visit Israel to observe and participate in the cutting-edge genomic analyses of the cells isolated at St. Boniface Hospital. The cells will also be analyzed here at the Institute of Cardiovascular Sciences in the Albrechtsen Research Centre.

Preventing coronary disease using fish oil supplements
Dr. Dan Levy & Dr. Peter Zahradka


Dr. Dan Levy – BGU


Dr. Peter Zahradka – St. Boniface

Researchers at St. Boniface Hospital have confirmed that DHA, the omega-3 fat in fish oil, can prevent harmful changes in endothelial cells in blood vessels that are typically detected in coronary artery disease.

Dr. Zahradka's research shows that taking fish oil supplements will slow or prevent the development of coronary heart disease and decrease the probability of a heart attack.

Dr. Levy has expertise in a technique that will help determine if DHA can alter cells without changing their genetic structure. If this is the case, researchers will be able to develop a DHA drug therapy that would prevent plaque build-up in arteries that can lead to coronary heart disease.

Why it's important
The endothelial cells being studied by Dr. Zahradka and Dr. Levy line the inside of our blood vessels and are responsible for keeping them healthy. When the properties of these cells change, it can result in problems such as high blood pressure and the thickening of the vessel wall – hallmarks of coronary artery disease. Heart disease causes irreparable damage to human

heart cells. If researchers can develop a therapy that prevents coronary artery disease, they will save lives.

What was accomplished in Year One

Dr. Zahradka and Dr. Levy's labs had two important achievements over the last year, facilitated by regular interaction and collaboration between the teams as their experiments were designed and the results analyzed. First, they confirmed that DHA does affect SETD6, a key enzyme involved in regulating the health of the endothelial cells that line the surface of our blood vessels. Endothelial cells are important in ensuring our blood pressure remains constant, so losing this ability can lead to hypertension and other forms of cardiovascular disease. Second, the two labs successfully exchanged materials relevant to the study, expanding the abilities of both partners to perform experiments.

The two teams hold monthly Skype meetings, which helped them to collaborate and develop improved ways to determine how DHA and SETD6 interact, which will be valuable as they continue their work in the coming year. Dr. Zahradka's lab has obtained fat samples from surgical patients through St. Boniface Hospital, for use in the research project. This will allow the lab to examine the properties of the blood vessels present in the fat samples. Dr. Zahradka and Dr. Levy's teams are keen to complete this experiment since the fat cells can influence the health of blood vessels, with fat cells from persons who are obese causing blood vessels to function less efficiently, which is why obesity is closely associated with cardiovascular disease.

In the coming year, the researchers will also examine how DHA and SETD6 affect blood vessel function in an animal model. It is anticipated that comparable results will be obtained relative to the human fat samples, thus providing evidence that all blood vessels respond to DHA similarly. In this way, they will have shown that SETD6 is a common factor in the processes that keep our blood vessels healthy and for this reason may represent a potential therapeutic target for the development of treatments that prevent heart disease.

Thank you!

By supporting ***Research Without Borders*** you enable St. Boniface Hospital and Ben Gurion University to share ideas, resources, and knowledge that will help us advance health care for generations to come.

Your generosity empowers our researchers to work together towards the same end goal – to change the face of health care as we know it. Thank you for offering us a chance to overcome today's most debilitating diseases and conditions.