



FXRFC Newsletter

News for Friends of the Fragile X Research Foundation of Canada

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FXRFC Awards Three New Research Grants for 2006

One of the goals of The Fragile X Research Foundation is to encourage more scientists to work towards finding a treatment for Fragile X. **The Fragile X Research Foundation of Canada started off 2006 by funding 3 new research projects, awarding over \$120,000.00 for research aimed at finding a treatment or cure for Fragile X.** The new work, at universities in Quebec, Ontario, and British Columbia, will not only yield valuable information on the pathology of Fragile X, but will hopefully stimulate further research and encourage other researchers at these institutions to divert some of their scientific resources towards Fragile X research.

On the next few pages are brief descriptions of these new projects. The updates have been submitted by the researchers themselves and may be rather technical at times so I have included a “translation” of some of the technical and scientific phrases within the text of the articles. I have also included a glossary of terms. If you would like to explore the entire portfolio of FXRFC funded research, past and present, please visit our website, www.fragile-x.ca and click on “Fellowships and Grants awarded”.

Scientists are making significant progress in understanding Fragile X syndrome and it is a direct result of the work that we have funded with your generous donations – please keep them coming!

Dr. C. Paribello M.D.

President, Medical Director

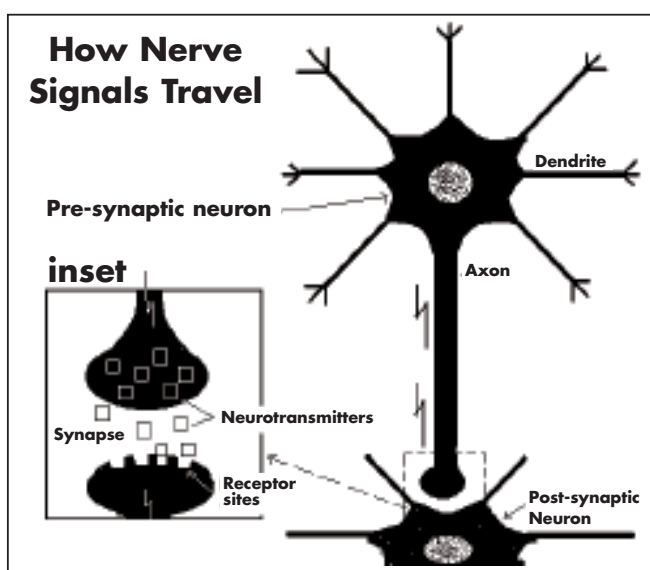
FXRFC is a nonprofit, tax-exempt charity run by parents and volunteer professionals. Fragile X syndrome is the most common form of inherited mental impairment and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FXRFC’s goal is to accelerate research aimed at the treatment of Fragile X, by direct funding of promising research projects and by raising awareness of this disorder.

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Fundamentals and Glossary of Terms for Non-Scientists

The human brain is made up of 10 billion nerve cells called “**neurons**” which form a complex interconnected network of neural circuits. The neurons carry all the signals through the brain, and are the basis of our thoughts and actions, our learning and memory, our consciousness and our personality. Each individual neuron looks like an uprooted tree, with long spidery roots on one end (called **dendrites**) and a main trunk on the other (called an **axon**). Signals pass from the axons of one cell and are received by the dendrites of the next cell across a gap called a **synapse** (see inset). There can be thousands of synapses scattered over the dendrites and the **dendritic spines** that project from each dendrite on a single neuron.



When an electrical impulse is transmitted from the dendrites of a neuron, it travels one way, along the axon, until it reaches any of the axon terminals. This triggers the release of a chemical called a “**neurotransmitter**” from this **pre-synaptic neuron**. The neurotransmitter then floats across this microscopic gap, or synapse, until it lodges in specific **receptor sites** of the **post-synaptic neuron**. The interaction of neurotransmitters with their corresponding receptors causes electrical and chemical changes in the receiving neurons as well as altered gene activity.

There are many different types of neurotransmitters in various parts of the brain, but **Glutamate** is the major **excitatory** neurotransmitter, accounting for the vast majority of brain activity. **GABA**, the major **inhibitory** neurotransmitter, keeps this process in check so that runaway electrical activity does not lead to seizures.

As a result of all of this neural activity, the synapses and their connections can change constantly in response to their experience. Certain patterns of synaptic activity cause the synaptic connection to strengthen; this is called **Long Term Potentiation (LTP)**. Other patterns of activity cause the synapse to weaken; this is called **Long Term Depression (LTD)**. Some people refer to it as a “use it or lose it” effect. Synapses that are heavily used get built up, or stronger, while those that are not used wither away. This is what neuroscientists mean when they speak of the **synaptic plasticity** of synapses and it is generally thought to be the basis for most of our learning and memory.

FMR1 is the Fragile X gene which produces a protein called **FMRP**, that is necessary for normal development and functioning of the brain. In individuals with Fragile X syndrome, the FMR 1 gene is mutated so it cannot produce FMRP.



DNA is the master template for genetic information in cells. Your genetic code determines who you are. Each of the 40,000 or so genes in each cell consists of a sequence of DNA.

Messenger RNA (mRNA) is a working copy of the genetic code transcribed from DNA. It is carried from the nucleus of a cell (where the DNA resides) to the rest of the cell, where it is translated into the actual proteins that perform most of the functions of the cell. The purpose of each gene is to produce a protein.

Phenotype refers to the total characteristics displayed by an organism as the result to the expression of its genes.

Knockout mice are Fragile X mice that lack the protein FMRP because they have been bred to delete the FMR1 gene.

Research Update

A novel method to discover therapy for Fragile X syndrome

Mathew Lorincz Ph. D. Principal Investigator

Margaret Rush, Ph. D. Postdoctoral Fellow

Department of Medical Genetics, The University of British Columbia, \$40,000.00

Fragile X syndrome is a very common genetically inherited form of mental disability, affecting 1 in 4000 births, ranging from mild learning disabilities to severe mental retardation. The Fragile X mental retardation protein (FMRP), the loss of which causes Fragile X syndrome, is important for neuronal cells to develop correctly and for normal learning ability. Prior to birth, changes in the structure of the gene required to produce FMRP occurs in Fragile X patients. This change, known as DNA methylation, prevents FMRP from being made in Fragile X individuals, and is initiated due to the presence of an altered form of the DNA sequence encoding the FMRP. The extent of DNA methylation has been linked to both the level of FMRP produced and the severity of Fragile X syndrome. Currently, no therapy exists that prevents Fragile X syndrome.

Using a novel molecular approach, researchers at the University of British Columbia aim to develop an efficient system to facilitate the process of identifying potential new drugs for the treatment of Fragile X syndrome. In collaboration with the Ordway Research Institute in Albany, NY, a library of over 100,000 medicinal compounds will be tested for their potential to reactivate production of the important FMRP protein, despite DNA methylation of the gene encoding the FMRP. Successful compounds will be further investigated and may eventually be used to treat Fragile X patients. Simultaneously, using molecular tools to study DNA structure, the researchers at UBC will investigate what physical characteristics in the inheritable, mutated DNA sequence are associated with DNA methylation of the Fragile X mutation. Understanding how the mutated sequence is packaged prior to DNA methylation, which subsequently inhibits FMRP protein production, may open new avenues for treatment.



Phasic and Tonic Components of the GABAA Current in a Mouse Model of Fragile X syndrome

Massimo Avoli, Ph. D. Principal Investigator (pictured)

Giulia Curia, Ph. D. Postdoctoral Fellow

*Montreal Neurological Institute, McGill University,
Montreal, Quebec, \$40,000.00*

Fragile X is the most common form of inherited mental impairment and it is caused by the absence of the Fragile X mental retardation protein (FMRP). About 20% of the patients affected by this syndrome experience epileptic seizures. A similar incidence has been observed in the *fmr1* knockout (KO) mice (Fragile X mice). Moreover, after several inbred crossing of mice experiencing seizures, we have created a KO seizure-prone colony. The goal of my project is to understand the mechanisms underlying epilepsy in Fragile X patients.

Neurons receive electrical impulses via synapses from many other neurons. Some of these neurons inhibit neighbouring cells while other excite them. Therefore it is the balance between excitatory and inhibitory impulses that determines the overall level of electrical activity in the nerve cells of the brain. γ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Alteration of this system in the brain has been linked to other forms of epilepsy. The study proposed here will elucidate whether an altered expression of the GABA system causes the neurons to be persistently hyperexcitable and therefore lead to epilepsy in fragile X patients.

Because GABAA receptor impairment could produce neuronal hyperexcitability, the lower expression of the inhibitory GABAA receptor-mediated current in fragile X animals could explain the hyperexcitable EEG profile and the epileptic seizures of the fragile X patients. I am confident that the findings of this project will have great potential to be beneficial for improving the quality of life of Fragile X patients.

Inhibitory Synaptic Transmission and Plasticity in the Anterior Cingulate Cortex of FMR1 Knockout Mice

Min Zhuo, Ph. D. Principal Investigator (pictured left)

Long-Jun Wu, Ph. D. Postdoctoral Fellow (pictured right)

*Department of Physiology, Faculty of Medicine,
University of Toronto \$40,000.00*



Fragile X syndrome is an inherited cause of mental impairment. The disease is a result of a loss of function of the Fragile X mental retardation gene, FMR1, and its encoded protein, FMRP. This results in impaired communication at the synapses



(the connections between neurons). Synapses that are heavily used get built up, while those that are not used wither away. This is what neuroscientists mean when they speak of the synaptic plasticity and it is generally thought to be the basis for most of our learning and memory. *(continued next page)*

Previous studies showed that there is a change in excitatory synaptic plasticity in the cortex of the brain in FMR1 knockout mice. However, little is known about inhibitory synaptic transmission and plasticity in these knockout mice. GABA is a major inhibitory neurotransmitter and the fast synaptic inhibition is largely mediated by GABAA receptors in the adult brain. The level of activity of GABA mediated neurotransmission modulates the excitability of target neurons, thereby shaping the activity of neuronal networks in relation to the behavior. Here, we will examine the potential changes in GABA mediated synaptic transmission and plasticity, as well as the cellular mechanisms underlying these changes in the anterior cingulate cortex (ACC), a cortical region of the brain related to memory and emotion, of FMR1 knockout mice. This study will reveal the potential role of FMRP in GABA mediated transmission and plasticity and the subsequent balance of inhibition and excitation. Therefore, we will characterize the inhibitory synaptic mechanisms of FMRP on the symptoms of Fragile X syndrome-like seizure, anxiety, or autism, which are believed to be related to the GABA system in the central nervous system. These studies will lead to a better understanding of Fragile X neuropathophysiology, and provide new molecular targets for treating patients who suffer from Fragile X syndrome.

Fundraising and Public Awareness Events

We would like to share with you several events organized by families impacted by Fragile X across Canada. The articles below describe just three examples of the kinds of creative events organized by dedicated, committed "Friends" of the FXRFC across the country!

From The Ridsill family, Etobicoke, Ontario

Dear Fragile X Research Foundation of Canada,

Our family purchased the awareness bracelets for our friends and family. Our son Calvin was proud to send them to his teachers at school as a gift.

As a result, they have donated this money, a \$20 bill, as a gift back to you.

Thank-you, keep up the great work!



From Raymond Jessome, Montreal, Quebec



Keeping in mind all the families affected by Fragile X Syndrome, the employees at Jesswood Packaging in Montreal decided to lend a helping hand by raising money to support research into finding a cure for Fragile X.

This year, our employees again agreed to lunch together once a month at the office. The meals were prepared by volunteer employees, with everyone paying \$7.00. All monies collected go directly into funding Fragile X Research. We also have our own little general store where we keep goodies for urgent cravings of employees. The extra money goes into a jar kept for spare change at the reception desk.

Today, we are all very proud to present the Fragile X Research Foundation of Canada with a cheque for \$2,000.00. Along with this, we send our hopes and prayers that a cure will soon be found.

From Mary-Lynn Riddell, Nova Scotia

Moving to Nova Scotia just over a year ago was a great adventure for our family. My husband Irwin, myself, Hunter, 11, and Troon 9, left behind many friends and family in Ontario. Hunter was diagnosed with Fragile X Syndrome in Toronto when he was 4. Our support system, family, and doctors had been in place for many years, so this move was a huge step for us. Of course, moving is always a challenge, even more so when you have a child with special needs. Once here, we discovered that there are very few diagnosed cases of Fragile X Syndrome in the province (approx. four). October 5, also known as “National Fragile X Research Day” became my opportunity to spread the word in my community!

Our school, Astral Drive Elementary, was more than happy to accommodate my requests. The youngest child of each family took home a Fragile X flyer with a cover letter noting the event. Approx. 370 were handed out. The October school calendar was marked on October 5 as being, “National Fragile X Research Day”. I read “Andy and his little yellow Frisbee”, about a boy with Autism, to 3 classes. It was an excellent resource and developed great discussions amongst the classes. One of the classes was my son, Troon’s grade 4 class. He had been approached several times by children asking why his brother Hunter did this or that, and he was finding it difficult answering the questions. This gave me an excellent opportunity to handle the questions in a group setting. The teachers were more than happy to devour the carrot cake which I had made and set up in the staff room with a donation box close by. As always, the staff were extremely supportive, and donated \$57.00 towards the FXRFC.

I was also lucky enough to tag team with the Autism Support Group which was recognizing Autism Awareness Month at the local malls’ community booth. This enabled me to hand out flyers and speak to many people that stopped by. All in all, it was a great day raising awareness for Fragile X Syndrome!

The FXRFC would like to thank all the wonderful people who make raising awareness and funds for Fragile X Research a part of their lives.

FXRFC Bulletin Board

If you have an announcement or request to make that is related to Fragile X, and would like other families to know about it, please e-mail the Foundation at fxrfc@on.aibn.com, or fax us at: (905) 453-0095.

Hi,

I am the Mother of 3 FX adult children. I am also the carrier and have FXTAS. I am looking for other women with the same disease, or a caregiver of a male with this condition or the male involved.

It is a lonely thing when there is no one with your condition around - not even on CORD.

Thank you,

Patty e-mail: pmpbof@sasktel.net

Hammersmith Gritt Concert

On Saturday November 5, 2005, a crowd of caring supporters assembled in happy anticipation of a great evening's entertainment at the Irish Centre in Brampton, Ont. They were assembling, not so much in support of Fragile X research, something that most of them didn't know much about, but in support of a family and their little boy who, they were told, suffered from Fragile X Syndrome. Little Connor McGlade has a wonderful uncle, Joe McGlade, who decided to help his nephew (his brother's son), by holding a fundraising evening to raise money for Fragile X research.



*Wendy McGlade, Dr. Carlo Paribello,
Campbell McGlade, Joe McGlade.*

The evening headlined Joe's rock band Hammersmith Gritt, along with opening act Sometimes Arty. Wendy and Campbell, Connor's parents, assembled silent auction prizes and prepared a delicious buffet. And as the crowd grew and the music started, you could feel the warmth and good fellowship spreading through the room. After the first set, Dr. Paribello spoke briefly about FX to a very receptive audience. The results of the evening were a tremendous opportunity for outreach by the FXRFC and the successful raising of \$4,600.00 for FX research! The FXRFC is most grateful to the McGlades and everyone who volunteered their time and talents to make this such a fabulous event!

SALUTE TO SURREY PLACE CENTRE, TORONTO

We all know how grateful we are to the “behind-the-scenes” heroes that make our lives easier! They give us what we need, without conditions, in a way that allows us to tackle other issues with all our might! Such is the service and assistance afforded the FXRFC by Surrey Place Centre in Toronto. Even before we were a Foundation, the tireless help of Marika Korossy, librarian at Surrey Place, helped Dr. Paribello research years and years of studies on the “inherited mental impairment” that we now know to be Fragile X Syndrome. With every scientific journal that Marika forwarded, Dr. Paribello's vision of a treatment and cure began to gel. The Foundation was formed, tremendous strides have been made and we are now at the stage of potential clinical trials. When it came time to find a central meeting place, where we could access teleconferencing and audio visual equipment, Surrey Place graciously opened it's doors for our evening Board Meetings. The staff has made us feel particularly welcome, as we assemble in meeting rooms that have become think tanks and planning rooms for the Foundation's work. It has been nearly 8 years that we have maintained our relationship with Surrey Place and we extend a heartfelt thank you to them for being so supportive to the FXRFC!

FXRFC Participates in Colloquium for the Medical Care of Adults with Developmental Disabilities

By Carlo Paribello, M.S.M., M.D., President, FXRFC

In November 2005, Surrey Place Centre in Toronto, honoured me with an invitation to participate in a Colloquium on the Primary Care of Adults with Developmental Disabilities. The Colloquium was attended by a group of 60 health care professionals, drawn mainly from Ontario's six University-based Health Sciences Centres, with experience and expertise in providing primary care to adults with developmental disabilities (DD). Consultants from other parts of Canada, England, and Australia also attended.

The Colloquium's main goal was to develop a consensus statement on health care guidelines for the primary health care of adults with developmental disabilities. These guidelines covered a range of topics under three main themes: 1) physical health, 2) behaviour and mental health, and 3) health care systems. As the representative of the FXRFC, I was able to provide input concerning the unique problems of Fragile X patients and made recommendations regarding medical treatment and health promotion for these patients.

We know that people with Fragile X syndrome and other developmental disabilities experience more physical health problems and more psychiatric disorders than the general population. Unfortunately, these problems are often undiagnosed, under diagnosed, and untreated. Furthermore, mortality is higher in people with DD because there are also fewer health promotion and disease prevention interventions conducted for these patients compared to people without a developmental disability.

By March 2009, approximately 1000 adults with DD will be moved from three residential facilities in Ontario to community settings. Their average age is 49 years and their mean length of stay overall has been 38 years. There is already a critical shortage of Family Physicians across Ontario and they will be unable to cope with this extra workload. The problem is further compounded by the fact that most physicians are unfamiliar with the unique medical needs of these patients. That means that roughly 1000 people with DD, who have been living in institutions since childhood, will be discharged into the community with no Family Physician to provide them with medical care! Furthermore, a significant number of these residents likely have Fragile X syndrome and have never been tested.

A major goal of this Colloquium is to facilitate the work for physicians, nurses, and other allied health professionals by creating a set of guidelines that would educate them as to the unique medical needs of adults with developmental disabilities. Another goal is to establish ongoing clinical support networks for health care professionals who work with persons with DD. We hope that these networks will foster a sense of community, offer opportunities for continuing medical education, and help enlist a sufficient number of health care professionals with expertise in this area.

This event was a tremendous success and will result in improved health care and quality of life for adults with Fragile X syndrome and other developmental disabilities across Ontario.

I would like to acknowledge and thank the Surrey Place Centre Charitable Foundation for its generous sponsorship of this Colloquium. I would also like to gratefully acknowledge the support of Ontario's Ministry of Community and Social Services and Ministry of Health and Long Term Care.

Update on Orphan Drug Policy

In the Fall of 2005, the Fragile X Research Foundation of Canada conducted a mailing campaign to support The Canadian Organization for Rare Disorders (CORD) in advocating for the creation of a Canadian Orphan Drug Policy (ODP). An orphan disease, such as Fragile X, is one that affects people at a frequency of one in two thousand, (1/2000) or less.

The Fragile X Research Foundation of Canada supports CORD's efforts to help create a Canadian Orphan Drug Policy (ODP) that has guidelines and opportunities to provide/develop/offer treatments for rare disorders in Canada. The Orphan Drug Policy (ODP) would develop a social program that will provide funding to enable individuals affected by rare disorders to obtain access to those treatments. It would also provide incentives for Pharmaceutical companies to research and develop drugs for rare disorders.

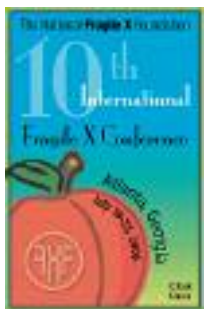
Health Canada is currently working on draft legislation for a Canadian Orphan Drug Policy. The Federal, Provincial and Territorial Health Ministers, along with the deputy ministers met in October, 2005 and a Canadian Orphan Drug Policy was on the agenda. The FXRFC took this opportunity to mount a letter writing campaign to all Federal, Provincial and Territorial ministers to support CORD's efforts to influence the development of a Canadian Orphan Drug Policy.

The ministers agreed to provide treatment to patients with Fabry Disease and MPS1-Hurlers Schie through a time-limited research program, on a risk-shared basis, as quickly as possible. While this does not directly benefit patients with Fragile X, it does represent significant progress towards developing a comprehensive Orphan Drug Policy that will ultimately benefit patients with Fragile X.

Work is also progressing on a larger Catastrophic Drug Coverage (CDC) and an Expensive Drugs for Rare Diseases (EDRD) policy framework under the auspices of the National Pharmaceutical Strategy. Ministers reaffirmed their commitment to report on the development and implementation of all elements of the Strategy to First Ministers in June 2006 and are hopeful that progress can be achieved in all areas, including Fragile X.

The National Fragile X Foundation's 10th International Conference

Hosted by The Fragile X Association of Georgia, Atlanta - July 19 - 23, 2006



The National Fragile X Foundation's biannual international conference is highly regarded and well known for bringing together families, researchers, medical personnel, therapists and educators in a setting that is specifically designed to optimize interaction among families and professionals. Increased collaboration between researchers, improved treatment skills of professionals, optimized development of individuals affected by Fragile X and increased understanding and well being of those impacted by the syndrome are the most significant outcomes often cited by previous conference attendees.

Online registration forms for the 10th International Fragile X Conference are available at www.FragileX.org > 10th International Fragile X Conference. Registration forms will also be published in NFXF Quarterly Journals beginning January 2006. Registration fees for NFXF Members are \$350 US for individuals and \$575 US for couples (2 parents). Nonmember registration fees are an additional \$60 US per registration.

The conference will be held at the Omni Hotel at CNN Center, Atlanta, Georgia. Rooms are available for attendees of the conference for a special rate of \$134 US per night, plus taxes. Be sure to let them know that you are with the 10th International Fragile X Conference to get the special room rate! For more information, please visit the National Fragile X Foundation's website at www.FragileX.org or call them at: 1 800 688-8765

FXRFC Support Groups - We are Growing!

We are very interested in starting support groups in the other provinces and territories and will provide assistance to anyone able to help out. If you would like to network with other parents of children with Fragile X, or if you would like to volunteer for fundraising events in your area, please contact any of the people below.

National Headquarters

167 Queen St. W.
Brampton, Ontario, Canada
L6Y 1M5
Phone: (905) 453-9366
E-mail: fxrfc@attglobal.net

Quebec Support Group

Evelyn Lockett
32 Lakeview
Baie d'Urfe, Quebec
H9X 3B1
Phone: (514) 457-3284
E-mail:
evelyn_lockett@hotmail.com

Ontario

Kitchener-Waterloo Fragile X Support Group

Teresa Burch, Co-ordinator
62 Corfield Drive, Kitchener,
Ontario N2A 3W9
Phone: (519) 894-3689
Fax: (519) 894-6333

British Columbia Support Group

Pam Winthrope
7968-112A Street
Delta, BC V4C 4Y6
Phone: (604) 590-6822
E-mail: pwinthrope@hotmail.com
Web:
<http://fragilexbc.tripod.com/fragilexbc/>



*Please become a Friend of The FXRFC
in supporting research aimed at treatment
for Fragile X. Friends of the FXRFC
receive this quarterly newsletter and are
welcome to participate as active volunteers.*

FXRFC Newsletter

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The Fragile X Research Foundation of Canada (FXRFC) is a national, nonprofit, tax-exempt organization; charitable # 88643 3762 RR0001. You can become a friend of the FXRFC for a tax-deductible donation of \$35 or more per year. The FXRFC is a 100% volunteer organization run by parents and professionals - which means more of your donation goes directly towards research. We now accept VISA and Mastercard payments; simply phone (905) 453-9366 and pass on the details. You may send your cheque or money order to:

The Fragile X Research Foundation of Canada
167 Queen St. W., Brampton, Ontario, Canada L6Y 1M5
Come visit our site on the web at: <http://www.fragile-x.ca>