



FXRFC Newsletter

News for Friends of the Fragile X Research Foundation of Canada

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FXRFC Awards Five New Research Grants for 2008!

The Fragile X Research Foundation of Canada continues its drive to increase the number of scientists working towards finding a treatment for Fragile X. The FXRFC has started off 2008 by awarding 5 new research grants, committing almost \$150,000.00 for research aimed at finding a treatment or cure for Fragile X. The new projects, at The University of British Columbia, University of Toronto and McGill University, will yield valuable information on the pathology of Fragile X, and should stimulate further research at these institutions.

On the following pages are brief descriptions of these new projects, as presented for you by the researchers. 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!

1. Role of PTEN in Fragile X Syndrome

Principal Investigator: Qi Wan M.D., Ph.D., Postdoctoral Fellow: Baosong Liu, Ph.D.

Location: Toronto Western Hospital, Start date: April 1, 2008, Amount: \$40,000.00 for 1 year

Fragile X syndrome (FXS), a leading cause of mental impairment, results from a CGG expansion in the 5' untranslated region of the FMR 1 gene and the resulting decreased production of its associated protein (fragile X mental retardation protein, FMRP). This causes the structural abnormalities and immature shapes in the dendritic spines of the neurons of people with Fragile X. It is now believed that these changes underly the cognitive, behavioural and autistic features seen in this disorder.

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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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Normal brain cells contain a phosphatase (an enzyme) called PTEN. Interestingly, PTEN mutations have been reported in individuals with autism spectrum disorders. Recent evidence also indicates that PTEN inactivation causes increased growth of the main branch (the axon) of each neuron, and an increase in the number of dendritic spines on each neuron. Given that the deficiency of both PTEN and FMRP is associated with autism and leads to similar abnormalities of dendritic spines, we have examined the effect of FMRP on the production of protein PTEN in cultured neurons of mouse brain (cortex and hippocampus). We found that the production of PTEN was significantly increased in neurons transfected (injected) with wild-type FMRP. This result provides novel evidence suggesting that FMRP may regulate PTEN production in neuronal cells and that dysfunction of this regulation may contribute to the molecular abnormalities of FXS. Accordingly, in this project we propose to test our working hypothesis that the phosphatase PTEN and its interacting signals may be involved in FMRP deficiency-induced abnormality of dendritic spines. The evidence obtained from this study would provide an important basis for the development of a therapeutic strategy to treat Fragile X patients.

2. The role of FMRP in dopaminergic modulation of synaptic plasticity in the prefrontal cortex

Principal Investigator: Min Zhuo Ph.D., *Postdoctoral Fellow:* Hansen Wang, Ph.D.

Location: Department of Physiology, Faculty of Medicine, University of Toronto

Grant Renewal Date: January 1, 2008, *Amount:* \$40,000 for a year



Hansen Wang and Min Zhou

Fragile X syndrome is one of the most common inherited causes of mental impairment. It originates from the loss of FMRP due to the mutation of the FMR1 gene. The neurotransmitter Dopamine, in the prefrontal cortex (PFC) of the brain plays an important role in its cognitive functions, including working memory, reward response, and attention. Previous studies suggest that the dysfunction of dopamine might be involved in cognitive impairments in Fragile X syndrome. We hypothesized that FMRP might be involved in dopamine regulation of synaptic plasticity in the PFC.

In this project, we will systematically study the role of FMRP in dopamine regulation of excitatory transmission and synaptic plasticity (including LTP and LTD) in the PFC of wild-type and Fmr1 KO Fragile X mice. We will use electrophysiological and biochemical methods to determine the effect of dopamine receptor activation on synaptic glutamate receptors and the role of FMRP in dopamine regulation of synaptic plasticity in the PFC. We will further carry out all the necessary molecular biological experiments to investigate how FMRP is involved in the dopamine receptor signaling pathway. To demonstrate the interaction between FMRP and the dopamine neurotransmitter system, we will investigate the role of dopamine-FMRP in different forms of fear memory, including trace fear memory, which is related to the function of the PFC.

This project will provide the direct evidence that FMRP might be involved in the dopamine regulation of synaptic plasticity in the PFC. The proposed studies will help us to further elucidate the cellular mechanisms for impaired learning and memory in Fragile X syndrome. We hope that new insights into potential therapeutic targets for Fragile X syndrome will be obtained in the project.



3. Targeting glutamate receptors to stop the onset of Fragile-X syndrome



Principal Investigator: Derek Bowie, Ph.D., *Location:* McGill Pharmacology & Therapeutics, *Start date:* January 1, 2008, *Amount:* \$15,000.00

Fragile X Syndrome (FXS) is the most common form of inherited mental retardation with impairments ranging from learning problems to severe intellectual disabilities. Although it is established that the *Fmr1* gene is silenced in FXS, it is still unclear how this accounts for the onset of symptoms. It has been proposed that FXS in children and adults occurs because their brains exhibit an exaggerated form of signaling between nerve cells. This signaling involves the removal of ionotropic glutamate receptors (iGluRs) from the surface of nerve cells in a process called long-term depression (LTD). LTD is thought to be important for many brain functions including our ability to learn. The effects of an exaggerated LTD on the structure of the neurons could therefore explain many of the clinical features of FXS. While this finding is helping the development of new types of therapy, it is possible that other iGluR signaling pathways are also disrupted.

The Bowie lab has recently identified a novel type of iGluR signaling that is distinct from LTD. Importantly, it is found in the newborn brain exactly at a time point when FXS symptoms first appear. The Bowie lab will test to see if sufferers of FXS lack this important signaling pathway. Their ongoing studies have already worked out some of the key molecules that contribute to this pathway. Consequently, the aim of the Bowie lab is to use this information to develop novel medications to counteract the onset of FXS in young children.

4. The role of interactive protein relations and synaptic balance in Fragile X Syndrome

Principal Investigator: Alaa El-Husseini Ph.D., *Postdoctoral Fellow:* Regina Dahlhaus Ph.D.

Location: University of British Columbia, Dept. of Psychiatry

Grant Renewal Date: January 1, 2008, *Amount:* \$40,000 for a year

The Fragile X Syndrome (FXS) is the most common inherited form of mental impairment in all races and ethnic groups. Affected individuals display a variety of intellectual deficits from learning problems to autism. FXS is caused by a loss of the FX protein (FMRP), that functions in local protein synthesis. A key advance in FXS research was the generation of a mouse model and an exciting discovery is that synaptic contacts of adult FMRP knockout (KO) mice display characteristics of an early development, indicating a deficit in synaptic maturation. Accordingly, the activity induced increase in PSD95 –a locally synthesized scaffolding protein important for synapse maturation - is found to require FMRP, suggesting that deficits in local synthesis of PSD95 may lead to abnormal synapse development.

Our work indicates the relationship of scaffolding and adhesion proteins (e.g.NLGs) to regulate synapse development and specificity. Hence we hypothesize that altered PSD95 production leads to an altered balance of excitatory and inhibitory synapses (E/I ratio) and that re-establishment of this relationship will be important to rescue synaptic balance. Thus, a comprehensive analysis will be performed on KO mice to determine alterations in the production or distribution of synaptic proteins. We will also quantify the E/I ratio and test if production of PSD95 or other synaptic proteins in cultured neurons will rescue the E/I balance.

The proposed studies will test a novel mechanism by which appropriate amounts of molecules are critical for synapse development and control of the E/I ratio. Important insights into synapse development and the relevance of the E/I ratio in FXS will be obtained. Furthermore, fundamental models of synapse development will be tested in Fragile X mice to find novel strategies in the therapeutic treatment of FXS patients.



5. Testing Metabotropic Glutamate Receptor and GABA Ligands in Fragile X Syndrome Mice

Principal Investigator: David R. Hampson, Ph.D., Postdoctoral Fellow: Laura Pacey Ph.D.

Location: Leslie Dan Faculty of Pharmacy, University of Toronto,

Start date: January 1, 2008, Amount: \$13,310.00

Fragile X syndrome (FXS) is a genetic disorder caused, in most cases, by an inherited mutation of the FMR1 gene, which in turn prevents the production of its corresponding protein. The FMR protein encoded by this gene is normally operative in neuronal branches (dendrites) where it controls local protein synthesis. The FMRP is involved in binding and transporting genetic messages to the synapse where they are held in an inactive state until needed. The loss of this protein in FXS causes many defects including seizures in about 20% of FXS patients, abnormal dendritic spine formation, the inhibition of synaptic growth, and interference with learning and memory. It is believed that the defects in neuronal shape and structure may underlie many of the symptoms seen in the animal models and in patients with Fragile X.

This lab will test the hypothesis that drugs that stimulate the mGluR receptors of neurons (called group I mGluR agonists) will worsen the pathological features and seizure susceptibility of the disorder while drugs that suppress mGluR receptors of neurons (called Group I mGluRs antagonists) will make them better. It will also test compounds that bind to another type of neuronal receptor believed to be affected in Fragile X Syndrome, known as the GABA receptor. The primary emphasis will be on testing various drugs and compounds for use as potential therapeutic treatments for Fragile X.

Addendum to Stem Cell Article

In the Fall issue of the FXRFC Newsletter, we printed an article entitled "Stem cell research generates an important discovery for Fragile X Syndrome". We apologize for neglecting to inform you that **Laurie Doering**, is an associate professor in the Department of Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario. We would like to thank one of our attentive readers for bringing this to our attention.



Dashing Through the Snow!

By Chris Beesley

Five years ago, when our son Mitchell was 8, we signed up to participate in the Ontario Track 3 ski program for disabled kids; he as a student and I as an instructor. What an amazing experience it has been! Once a week, for 8 weeks, we hit the slopes. Mitchell goes off with his two instructors and I go with my student. We hook up again at lunch time and usually get an hour or two to ski together in the afternoon, sharing a sport we both love.

Mitchell loves every minute. He's always the first one on the hills in the morning and the last one off in the afternoon. His balance and coordination have improved as well as his general fitness. At first, he had tethers attached to his skis as well as a "ski bra" which is a

device that holds the ski tips together in a snow plow position. These days, he's a "free skier", meaning he doesn't require any special equipment. Ontario Track 3 is a wonderful organization that provides kids of all ages and abilities with the opportunity to ski and snow board. If you would like more information or would like to volunteer, go to www.track3.org.

Mitchell may never make the World Cup circuit, but coming home at the end of a day of Track 3 skiing, I'd swear he thinks he's just won a gold medal!

Human Trial of a Possible Fragile X Treatment is Underway

The FRAXA Research Foundation in the United States, and Neuropharm, are working together to explore the potential of the mGluR5 antagonist Fenobam to treat Fragile X Syndrome. A phase 1 clinical trial using Fenobam is now underway in normal volunteers in the United States.

In 2007, the Food and Drug Administration (FDA) in the U.S. had granted an Orphan Drug Designation to Neuropharm for the use of fenobam to treat Fragile X. The Orphan Drug Act aims to speed up development of treatments for rare diseases, like Fragile X, defined as affecting fewer than 1 in a 1,000 people .

Neuropharm submitted an Investigational New Drug (IND) application to the FDA in November 2007. An IND is required before human trials can be conducted in the US. Last week, the FDA gave Neuropharm the green light for trials to begin.

Fenobam is a drug that acts as an mGluR5 antagonist (or blocker). Researchers have found a specific excess of metabotropic glutamate receptor (mGluR) signaling in Fragile X brains, and studies indicate this may be a common mechanism underlying many autism spectrum disorders. Research on animal models has shown that it is possible to regulate this hyperactive brain mechanism with compounds such as Fenobam, which partially block mGluRs and may reverse the major deficits of Fragile X such as cognitive impairment, anxiety, and autistic behaviours.

Scientists at the labs of a Johnson & Johnson subsidiary developed Fenobam in the 1970s. It was studied in clinical trials in patients with anxiety disorders and demonstrated some effectiveness and a good safety profile, but exactly how it worked was unknown. It was not until twenty years later that researchers at Hoffmann LaRoche discovered that it is an mGluR5 antagonist, making it a promising potential treatment for Fragile X.

In December, researchers reported that reducing mGluR5 in Fragile X mice can reverse many Fragile X symptoms, such as impaired learning, anxiety, and autistic behaviors. The study, published in the December 20 issue of the journal *Neuron* by Mark Bear and colleagues, has received attention around the world.

A Phase I trial is now underway in normal volunteers. If Phase 1 goes well Phase II trials in Fragile X patients will begin at Rush University, directed by Dr. Elizabeth Berry-Kravis, and at the MIND Institute, directed by Dr. Randi Hagerman. Each of the institutions has an Institutional Review Board (IRB) which must approve the trial before human studies can begin. It is hoped that these Phase II trials will begin in 2008.

What does this mean to Canadian families affected by Fragile X? The Fragile X clinic at Surrey Place Centre (SPC) in Toronto is a member of the Fragile X Clinic Consortium and will therefore be in a position to be the first site in Canada to conduct clinical trials with new treatments or experimental drugs to treat Fragile X. The FXRFC established the FX clinic in partnership with SPC and we will keep families informed about new Canadian trials through our regular Newsletter updates and through separate mailings.

My cousin Eric, The Poet

by Deborah Sheppard

I began to teach my cousin Eric about writing poetry several years ago, after he showed interest at school. Whenever we would see each other at family gatherings, he tended to be too excited to pay much attention to anyone, so I was looking for a way for the two of us to connect and share something special. And as a poet, I had done work with other kids, and I thought that Eric, with his love of language and his great sense of playfulness, might really take to poetry and realize some benefits. Poetry has provided us with just that magical connection.

I had a lot of learning to do, to figure out the best method for us to work together. These are some things that have been successful with him, and might help other kids with Fragile X:

- We try to meet at a regular time, once a week after school.
- A half hour or less seems long enough.
- I may come prepared with some ideas, or a short poem that has strong imagery.
- I've brought sculptures and crafts items, to explore shape and texture as elements that can go into a poem.
- Sometimes he chooses a topic, something that has happened during his school day, or a painting he finds in an art book that strikes his fancy. Then we explore not only the image itself, but whether there might be a story behind the painting. He never lacks for things to say!

- I have expectations for him. He has to try to stay focussed and has to put some thought into his writing.

- I have set up rules for him. If he starts to become repetitive or gets into a loop, eg, naming one colour after another, the rule would be "only one colour today". He has his favourite words, and I try to honour them, but I also want him to find other descriptive language.

- Eric loves to spell words out loud, so we pay attention to that element of writing. For other kids, I usually tell them not to worry about their spelling until they have completed the first draft.

- More than anything, I encourage Eric to be playful with language, to put together words that we might not combine in usual everyday conversation, to think about images and flow of language, and not necessarily meaning. When he creates one of those magical, unexpected images, it's a cause of great celebration and high fives.

Usually, as soon as I arrive, Eric is in his room, getting out his poetry notebook, and writing down the date before I've even taken my coat off. He can't wait, and neither can I!

Eric Lewin, aged 18 years, has Fragile X Syndrome, and enjoys writing poems.

He has been reading Charlotte's Web at school this year, and his teacher asked everyone to write a poem about it.

Here are Eric's poems:

BEST FRIENDS

by Eric Lewin

Wilbur is outstanding

Charlotte is amazing

Charlotte is marvelous

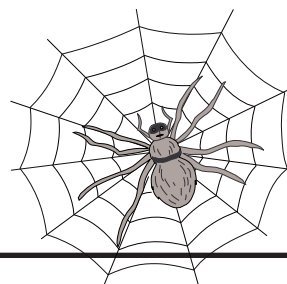
Charlotte is kind

Charlotte is wise

Charlotte is grand

Charlotte is elegant

Charlotte is gone



*ROSE, WHERE DID YOU GET THAT RED? by Eric Lewin
magic spells could say make it work
paint it yellow orange green pink red
we need paint brushes with long brown handles
we need brushes and paint cans
we need to open the cans
mix the paint
swimming oceans of red
we need long brushes
we need paint to make it pink
we need 60 paint brushes and long strokes of red on the rose
the rose is marvelous
the rose is exquisite
the rose is perfect*

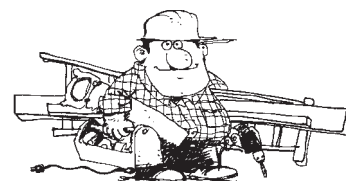


The FX Tool Box

by Lori Beesley

What is The FX Tool Box? A new feature in our newsletter! The Tool Box will be filled with suggestions, helpful hints and coping strategies – tools to make living with Fragile X easier. We invite you to send in your favourite tools to: fxrfc@on.aibn.com for printing in future newsletters. Here are some that have helped in my family over the years:

1. Get a bean bag chair for them to relax in or simply watch TV.
2. Small but silent vibrating toys are great help during school assemblies or whenever they are expected to sit quietly for a long period of time.
3. Inexpensive tape player with music cassettes that they can play with/rewind to their hearts content.
4. Freezies - seem to help with the oral self-stim. Make your own out of watered down juice so they are healthier.
5. Put a dot of the inside, insole of their boots or shoes with bright red nail polish (make sure you let it dry completely) and tell them that the red dots have to be together (side by side) before they put on their boots/shoes so that they go on the correct feet. This has been very helpful and gives a sense of independence!



**Electronic
Mail.**



Send in your Letters or Articles

The FXRFC Newsletter often publishes stories about the people that have sparked the formation and inspired the growth of the Fragile X Research Foundation of Canada. If you have a story about, and a picture of, a child or adult with Fragile X, please send it to us we will share it in our “X-tra Special Person” feature. Tell us a funny story or share a success.

If you are planning or have organized a Fragile X fundraising activity or event in your area – big or small – we’d like to hear about it. Anything goes!

Please e-mail your article for the newsletter to fxrfc@on.aibn.com.

The deadline for submissions to the next newsletter is April 11, 2008.

If you have any questions, please feel free to call us at (905) 453-9366.

FXRFC Support Groups

We would like to welcome *Jaimie Fast* in Saskatoon, Saskatchewan as the newest addition to the Fragile X “family” of support groups. She has a nephew with Fragile X and has chosen to focus her efforts on something that will benefit others and serve a cause that is close to her heart. We are also very interested in starting support groups in the other provinces and territories and will provide assistance to anyone able to help out. We currently have a need for support groups in Manitoba and Nova Scotia. 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.

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FXRFC Newsletter

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