FXRFC Awards Three Research Grants for Summer 2006

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

The strategy of The Fragile X Research Foundation of Canada is twofold. One is to provide financial support for scientists who have chosen to work in the Fragile X field, and the other is to encourage more scientists to start working towards finding a treatment for Fragile X. In the summer of 2006 the FXRFC renewed two grants and awarded one new one, bringing the Foundation’s overall research commitment to $218,000.00 in 2006.

The new work at the Toronto Western Hospital and the Brain Research Centre at the University of 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.

Included in this Fall’s newsletter 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!
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 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 presynaptic neuron. The neurotransmitter then floats across this microscopic gap, or synapse, until it lodges in specific receptor sites of the postsynaptic 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. A synapse’s strength depends on the number of receptors it has. Neurons change the density of receptors on their postsynaptic membranes as a mechanism for changing their own excitability in response to stimuli. In a dynamic process that is maintained in equilibrium, two particular receptors called NMDA and AMPA receptors are added or removed to the membrane by specific processes. These processes, and the number of receptors on the membrane, can be altered by synaptic activity. Experiments have shown that AMPA receptors are delivered to the membrane due to repetitive NMDA receptor activation. 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. Many researchers are now referring to Fragile X as a disorder of synaptic plasticity and there is much excitement surrounding this mechanism since it has the potential to be corrected.

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**FXRFC Newsletter**

**• News for Friends of the Fragile X Research Foundation of Canada**

The Role of FMRP (Fragile X Mental Retardation Protein) in Central Nervous System Synaptogenesis and Development

Principal Investigator: Dr. Peter L. Carlen MD, FRCP(C)
Postdoctoral Fellow: Dr. Chris Feeney, Postdoctoral Fellow
Toronto Western Hospital

**2006 Update**

The genetic abnormality causing Fragile X syndrome has been identified. The mutation of the FMR1 gene shuts down the production of the Fragile X Mental Retardation Protein – FMRP, and mice deficient in this protein have been created. We are studying the cellular electrophysiological factors underlying the cause of seizure activity in the brain tissue of FMRP gene knock-out mice, with the aim of targeting potential therapies for the seizure disorder associated with the fragile X syndrome. We are particularly interested in the interaction(s) between excitatory (glutaminergic) and inhibitory (GABA) networks of the Fmr1 knock-out hippocampus (a key part of the brain used in learning). In addition we are interested in understanding how alterations in rhythmicity of electrical activity in the brain may contribute to the cognitive impairments occurring in the FX condition. We hope that a better understanding of the pathophysiology of FX syndrome will aid in the development of novel treatments for those who suffer with this syndrome.

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**Research Grant Awards**

**The Role of FMRP (Fragile X Mental Retardation Protein) in Central Nervous System Synaptogenesis and Development**

Principal Investigator: Dr. Peter L. Carlen MD, FRCP(C)
Postdoctoral Fellow: Dr. Chris Feeney, Postdoctoral Fellow
Toronto Western Hospital

Dr. Peter L. Carlen & Dr. Chris Feeney

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.
Cellular and molecular mechanisms mediating the alteration of GABAA receptor expression in Fragile X Syndrome

Principal Investigator: Dr. Qi Wan
Postdoctoral Fellow: Dr. Lijun Li
Toronto Western Hospital

Fragile X Syndrome, the most prevalently inherited form of mental impairment, results from the silencing of Fmr1 gene that codes for a protein called FMRP (fragile X mental retardation protein). This syndrome is characterized by many symptoms, including cognitive impairment, autistic behavior, anxiety and compulsive disorders, seizures, and physical manifestations such as macroorchidism. Recently, excessive excitatory neurotransmission triggered by certain glutamate receptors was found to occur in Fragile X Syndrome. Because the balance between excitatory and inhibitory activity determines the overall outcome of neurotransmission, probing the role of the GABA\textsubscript{A} receptor (inhibitory neurotransmission) in FMR1 knockout mice may be critical for the understanding of the pathogenesis of Fragile X Syndrome. Interestingly, recent studies provide evidence suggesting that alterations of the inhibitory GABA transmission in neurons and the expression of GABA\textsubscript{A} receptor gene and protein may occur in FMR1 knockout mice. Together with the well-established evidence that disturbed GABA\textsubscript{A} Receptor function in certain parts of the brain (hippocampus and neocortex) can evoke hyperactivity and epileptic seizures, these results indicate that the absence of FMRP may lead to alterations in this GABA system alterations that could account for the increased seizure susceptibility of the fragile X mouse. These alterations may also be relevant to the seizures and the abnormal behaviors in the human Fragile X Syndrome. Accordingly, we propose to investigate the cellular and molecular mechanisms underlying the observed alterations of GABA\textsubscript{A} receptor function and expression in FMR1 knockout mice. We will employ biochemical, molecular biological and electrophysiological approaches to examine whether altered GABA\textsubscript{A} receptor expression contributes to the functional change of GABA\textsubscript{A} receptors in the knockout animals. We will also examine intracellular signaling that may be responsible for the altered GABA\textsubscript{A} receptor expression in the FMR1 knockout mice.

Synaptic Changes in Fragile X Syndrome

Principal Investigator: Dr. Brian Christie Ph.D.
Postdoctoral Fellow: Dr. Wei-Ning Zhang, Postdoctoral Fellow
Brain Research Centre, University of British Columbia

We will examine the morphology of neurons and study synaptic plasticity using electrophysiological techniques. We will also evaluate the functional capacity of the hippocampus (a part of the brain involved in learning) in Fmr1 knockout animals. One would expect that the two forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), would be dramatically altered by the changes in neuronal
morphology that have been described for Fragile X syndrome. However the deficits that have been documented to date appear to be very discrete and area specific. The mGluR story is fascinating and will undoubtedly contribute greatly to our understanding of Fragile X Syndrome, however we believe that there are additional deficits in LTP and LTD that are induced by other receptors (called NMDA receptors) that remain undisclosed. We will investigate the possibility that a substance called BDNF (Brain Derived Neurotrophic Factor) can modulate NMDA mediated synaptic transmission and plasticity in the Fragile X knockout mouse.

The Fragile X Clinic

The Fragile X Clinic at Surrey Place Centre opened in June of 2006, and is now serving as a centre to assess and treat patients of all ages who have Fragile X Syndrome.

It is located in the heart of downtown Toronto, and is the first dedicated Fragile X Clinic in Canada. It provides affected patients and their families with access to physicians with the expertise and knowledge to treat this neuropsychiatric disorder.

Once the Fragile X Clinic is established, it will also conduct clinical trials with new drugs that enhance learning, memory and cognitive functioning and will therefore put Surrey Place Centre in a position to make a global impact in the field of neuroscience and autism.

These services are offered free of charge to their clients because Surrey Place Centre receives core funding through the Ministry of Community, Family and Children’s Services. The Surrey Place Centre Foundation also raises funds from individuals, corporations, and foundations for additional support. It is affiliated with the University of Toronto, York University, the University of Guelph and many other teaching institutions. It is accredited with the Canadian Council on Health Services Accreditation.

All patients will be assessed Dr. Carlo Paribello M.S.M, M.D., Family Physician, President, Medical Director, Fragile X Research Foundation of Canada and Leeping Tao, RN, MN-ACNP, Nurse Practitioner, Surrey Place Centre. If required, patients can be referred to allied health professionals at Surrey Place Centre and Toronto General Hospital. Health professionals include a geneticist, an occupational therapist, an audiologist, a speech pathologist, and a psychologist.

The recommendations that arise from these assessments will then be given to the patient’s family members, caregivers or workers for implementation by their local healthcare providers.

For further information about the clinic and for patient booking, please contact the office of Dr. Carlo Paribello at (905) 453-9366 or e-mail your request to fxrfc@on.aibn.com.
Navigational Abilities in Individuals Affected by Fragile X Syndrome

By Isabelle Boutet, Ph.D., University of Ottawa, School of Psychology

We are looking for volunteers to participate in a study being conducted by Drs. Cary Kogan and Isabelle Boutet from the School of Psychology at the University of Ottawa.

Using fun and engaging tasks, our laboratory is exploring whether novel non-verbal tests can be used to evaluate thinking abilities in individuals affected by Fragile X. The task we are currently evaluating is a learning and memory test that relies on an individual’s visual-spatial navigational abilities. The task was originally designed to evaluate spatial learning in mice and has only recently been adapted for humans.

Participants will be presented with computerized virtual 3-dimensional mazes. They will learn to navigate through increasingly more complex configurations to arrive at a goal destination where they will be rewarded. Participants will be asked to sit comfortably in front of a computer monitor and use a joystick to navigate through computerized mazes. The time required to reach the end of each maze will be recorded. Upon reaching the end of the maze, participants receive a reward (sticker or candy). The procedure will last approximately two hours.

There are no known side effects associated with participating in the present study. Due to the nature of the 3-dimensional mazes there is a small chance of dizziness, headaches or mild nausea but no more than what one might experience playing a video game. Participants will be encouraged to discontinue if any of these problems are experienced. A compensation of $50 will be given for participation and traveling expenses will be reimbursed.

We will examine the performance of individuals with FXS on the navigation task in order to evaluate the utility and feasibility of these measures for tracking change in thinking abilities that might result from medical, behavioural, or educational interventions.

We are seeking participants living in the regions of Ottawa, Montréal or Toronto. If you or someone you know is affected by Fragile X Syndrome and is interested in participating please contact Dr. Isabelle Boutet at 613-562-5800 x2612 or iboutet@uottawa.ca.

The Board Needs Your Help!
Activity List for Children with Fragile X

I am a Fragile X parent and member of the board of the FXRFC. I am in the process of compiling an updated resource list of organizations and programs that provide leisure and therapeutic activities for children with special needs, including Fragile X Syndrome. The current list is based on my own experiences and those of other board members and friends; it is neither official nor exhaustive. Many of the programs of which I am aware are situated in the Toronto area, where I live, but I am sure that there are other excellent programs across the country.

I am asking you, the readers of the newsletter, to let me know about programs that have helped you and your family, wherever you live. Please send your tips to the FXRFC at 167 Queen St. W., Brampton ON L6Y 1M5 or fxrfc@on.aibn.com.

The list will appear in a subsequent newsletter and eventually will be posted on our website.

Dr. Myra Sourkes M.D.
**XXX-tra Special Person!**

The FXRFC Newsletter often publishes stories about the people that have sparked the formation and inspired the growth of the FXRFC. If you have a story about a child or adult with Fragile X, please send it to us and we will share it and a picture of the X-tra Special Person with our readers.

Tell us a funny or heart-warming story, or share a success.

This newsletter’s X-tra Special person is Adam, aged 4 1/2.

By Kirsten J. Madsen, Mother of Adam, Vancouver, B.C.

My husband, John, and I first heard of Fragile X Syndrome when our four year old son, Adam, was diagnosed with the full mutation at 22 months. Since then, we have struggled to cope with the condition, and tried to thrive, rather than just survive, as a family.

We live in Vancouver, British Columbia, and we like to vacation in the great outdoors. John has been going to Denman Island for summer vacation since 1964 (when he was in diapers). Adam’s grandparents have a rustic cabin there on a beautiful beach. When I was pregnant, we talked of taking our child there in hopes of reviving all the fun John fondly remembered as a child.

To reach Denman Island from our Vancouver home requires two ferry voyages, the first lasting about two hrs. to Nanaimo. After driving an hour from Nanaimo, the second voyage takes only 15 minutes to Denman Island. Six months after his diagnosis, we took Adam on the trip to Denman Island, hoping for a relaxing and enjoyable holiday for our little family. But the first ferry was completely overwhelming for Adam, who refused to leave our vehicle, forcing us to remain on the sweltering vehicle deck for the whole voyage. The second ferry voyage was the same, but thankfully much shorter. We arrived at the cabin still hoping for the best. But it was all too much, and too new, for Adam. He refused to step on the beach, play with water toys, look at fish or crabs, touch a pebble, or wear a lifejacket much less go near the canoe. He constantly complained and cried for rides in the truck (his comfort zone). By the time we arrived home (more horrible ferry rides) John and I were more stressed than before our “vacation”. I thought Adam would never enjoy Denman Island and I felt quite dejected.

But things have changed. Since that disaster two years ago, we have taken Adam to the Denman Island cabin several more times; each time better than the last. We now always make ferry reservations to minimize waiting in lines. We learned to let Adam stay on the vehicle deck as long as he wants (sooner or later he asks to go on the passenger decks). We have learned, as at home, he likes routine on vacation, and familiarity brings him comfort over time. We now bring enough apples for the whole vacation since he eats crunchy foods to calm himself.

This past August, Adam (now age four and a half) surprised us at Denman Island and taught his parents a thing or two in the process. He walked on the beach and threw rocks with his Daddy every morning (he called this “kerplunks”). He walked barefoot at low tide, turning over rocks looking for small crabs (we then replaced the rocks for ecological purposes.) He let the crabs nip his fingers and happily handled some larger ones that frightened me. He learned from his Daddy that red jellyfish are “dangerous”. He climbed large boulders, and arranged small stones on top. He rode in the canoe, and asked to wear his life jacket, demanding “lifejackets… so we can be safe!” (Mommy nearly forgot). He loved a wobbly inflatable boat, and squealed with delight while his Daddy pulled and bounced him over the water.

*Continued next page...*
When his young cousins enjoyed other water toys, balls, and games, Adam happily joined in. He raced, skipped, and danced. In the evening, there are deer to be seen near the cabin, and Adam led the daily hunt, telling us to “be very, very quiet” in a reasonably loud voice. Since returning to Vancouver, he still searches for deer on our city streets, and in local parks. He greeted starfish, otters, seagulls, and herons by name.

This past August, Adam finally learned to enjoy much of what his Daddy had enjoyed as a child at Denman Island. With planning and patience, John and I learned more about Adam’s limitations, and his surprising abilities. Within a day of returning from vacation (the ferries are still difficult, but not completely overwhelming) John and I checked our calendars to plan our next Denman Island vacation with anticipation, rather then dread. One more part of our life with Fragile X seems to be getting easier.

**FXRFC Support Groups**

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.

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**FXRFC Newsletter**

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The Fragile X Research Foundation of Canada • 167 Queen St. W., Brampton, ON, Canada L6Y 1M5

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