FXRFC Participates in Research Meeting

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

In March, 2003, FRAXA (our U.S. counterpart), sponsored an intensive Fragile X research meeting through a grant from the U.S. National Institute of Mental Health.

For three days, 37 top scientists converged upon Cold Spring Harbor’s famous Banbury Center on Long Island, New York, to explore the newest findings on synaptic function in Fragile X. (See Focus on the Synapse, page 2). Canadian participants included Dr. Carlo Paribello, President of the Fragile X Research Foundation of Canada, and two FXRFC grant recipients, Dr. Edouard Khandjian from Laval University and Dr. Peter Carlen from the Toronto Western Hospital. The Banbury Center is an extraordinary setting for a meeting. Far from city distractions, the scientists participated in full day discussion sessions, ate meals together, and talked late into the night. It was a great mix of people who have worked in the field for some time and those who were new to it.

The agenda and list of participants at the meeting, which was entitled “Synaptic Function in Fragile X”, are available from the Banbury Center, e-mail: Banbury@cshl.org, or from FRAXA or the FXRFC. It was an excellent forum for intense learning about synaptic function in Fragile X, as well as for the exchange of ideas and the initiation of collaborative research efforts.

The Banbury meeting has now been made an annual event with the hope that it will encourage collaborations between investigators, sharing of data and reagents, and the exploration of new and creative approaches to treatment.

We would like to thank the conference organizers, Dr. Mark Bear of the Howard Hughes Medical Institute, Brown University and Dr. Mike Tranfaglia of the FRAXA, for inviting the Fragile X Research Foundation of Canada to participate in this meeting.
Focus on the Synapse in Fragile X

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

For the first time in over 50 years, since the symptoms of Fragile X were first described, researchers are getting to the point where they can say what is actually wrong in people who have this disorder. There have been several major breakthroughs in Fragile X research in the past year, which we believe will lead to exciting new treatments for Fragile X and other autism spectrum disorders. In order for the non-scientist to make sense out of all of the technical and scientific jargon, it is helpful to briefly review some of the basic terminology first.

The Basics

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, which 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 spindly 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 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, while those that are not used wither away. This is what neuroscientists mean when they speak of the plasticity of synapses and is generally thought to be the basis for most of our learning and memory.

What goes wrong in Fragile X?

In 1991, researchers determined that the FMR1 gene is “shut off” in individuals with Fragile X, and that this renders their neurons unable to manufacture the FMR protein. It is the absence of the FMR protein in the neurons of the brain that causes the symptoms of Fragile X.

Two breakthrough discoveries were published in 2002. With funding
from the Fragile X Research Foundation of Canada, Dr. Peter Carlen’s lab discovered that the Fragile X Knockout mouse had a deficiency of a particular subunit of a receptor that mediates Long Term Potentiation in its brain cells. Dr. Huber at the University of Texas at Southwestern, and Dr. Bear at Brown University, made the second breakthrough when they discovered that the Fragile X knock-out mouse exhibits excessive Long Term Depression in its neural circuits. Suddenly, a clearer picture of the synaptic dysfunction seen in Fragile X began to emerge. Too little, or inefficient, LTP and too much LTD, impair synaptic plasticity, which is necessary for efficient learning and memory.

Prior to the finding of increased LTD in the knockout mouse, Huber and Bear had established that this form of LTD was controlled by one specific type of glutamate receptor, called mGluR5 (for “metabotropic glutamate receptor, subtype 5”). Metabotropic receptors do not cause immediate electrical changes in target cells, but instead cause longer lasting changes, such as protein synthesis. One of the proteins synthesized in response to normal activation of mGluR5 is FMRP. It is thought that FMRP normally serves to regulate this process by negative feedback, keeping it from running out of control. However, since FMRP is absent in individuals with Fragile X, there is too much LTD, which causes big problems.

We can get some sense of exactly what problems are caused by excessive LTD by intentionally over stimulating the mGluR5 receptor using specialized chemical probes. When this is done in normal mice, we see seizures and stereotypic behaviors which are reminiscent of human Fragile X. Conversely, when chemicals which block mGluR5 are administered to normal mice, the results strongly suggest potential therapeutic effects for Fragile X. Chemical agents, with the acronyms, MPEP and MTEP, show pronounced anxiolytic (anti-anxiety) and anticonvulsant (anti-seizure) effects. These agents are especially effective at reducing anxiety induced by new situations or experiences, the kind most likely related to LTD. They also do this without causing the sedation or cognitive impairment that typical anxiolytic drugs (like Valium) usually cause. The obvious next step is to try treating knockout mice with these compounds.

Canadian researchers, funded by the FXRFC, are collaborating with American scientists as several labs are conducting studies to assess this “mGluR Hypothesis”. Initial results have already shown strong positive effects in preventing seizures in the knockout mice, and ongoing work will be done to examine potential beneficial effects on cognition, socialization, anxiety, and response to new situations or experiences.

What does all this mean?

The good news is that synapses, receptors, and synaptic functions have the potential to be manipulated with drugs more easily than DNA and genes can. Modern psychopharmacology has correlated behavioral symptoms with changes in specific neurotransmitter levels, forming the basis for drug treatment of many psychiatric disorders. For example, decreased dopamine levels in frontal areas of the brain are associated with attention deficit, while increased dopamine in the midbrain is associated with psychosis and agitation. Decreased norepinephrine can cause depression, while too much can cause anxiety and hyperactivity. Too little serotonin can cause irritability, aggression, and obsessive-compulsive behaviors.

What if we could design medications that could facilitate Long Term Potentiation, and what if we could engineer other medications that could block excessive Long Term Depression? Theoretically, this would restore synaptic plasticity in individuals with Fragile X and allow the synapses to change in response to the neural activity that occurs when we learn and process information. Studies to evaluate the first approach have already been initiated. In June of 2002, a landmark clinical trial began to evaluate a new potential treatment for Fragile X and autism in adults. The compound being tested is an investigational new drug called Ampakine CX516, which may be able to help improve learning and memory in Fragile X, by enhancing LTP. Participants are adults with Fragile X between 18 and 50 years old. Each person takes either the drug or a placebo (sugar pill) for four weeks. During the study, neither the patient, family, nor the investigators know whether placebo or drug has been taken, to guard against bias in interpreting the outcome. A variety of cognitive and behavioural tests are done to evaluate any changes in functioning and a
medical assessment is also done to ensure that no ill effects are seen. The study will take two years to complete and is designed to give a preliminary idea of effectiveness and to extend safety data.

The second approach for a potential treatment of Fragile X, namely decreasing LTD, is also an exciting possibility. Excessive LTD is present in the brains of the Fragile X knockout mouse because of the absence of the FMR protein. This is presumably also true in people with Fragile X and leads to behavioural and learning problems.

The pharmacology of the mGluR5 receptor suggests that this excess of mGluR-LTD could account for most of the central nervous system symptoms of Fragile X, but we won’t really know for sure until drugs that are mGluR5 antagonists can be tried in human subjects. This will be one of the Fragile X Research Foundation of Canada’s highest priorities over the next year. So far, this class of drugs has not been tested in humans, but several pharmaceutical companies are actively developing these compounds for a number of uses. Initial testing of one of these compounds, MPEP, in the FMR1 knockout mouse has yielded a therapeutic effect, and further testing is under way. In fact, the therapeutic effects of mGluR5 antagonists may extend well beyond Fragile X. It is also likely that there are other neuropsychiatric disorders which result from increased LTD. Unraveling the details of this basic neural mechanism offers hope for the development of a drug treatment for the core symptoms of Fragile X and possibly the first effective treatment for autism.

Stanford University Looking for Research Participants

By Ellen Van Stone, Research Coordinator, Behavioral Neurogenetics Research Center
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

At the Behavioral Neurogenetics Research Center (BNRC) at Stanford University, we are interested in how genetic, environmental, neurobiological and hormonal factors interact to influence the development of children with Fragile X. We are commencing a longitudinal study of children with Fragile X and their unaffected siblings, which to our knowledge, will be the first investigation to track the development of affected and unaffected siblings over time. We travel to families’ homes to perform the evaluations.

We are seeking families who meet the following criteria:
• Have a child who is affected with fragile X syndrome
• Have a second child of the same gender who is not affected with the mutation
• Both children must be between 6-13 years and be full siblings

We are particularly interested in locating families with girl-girl pairs. We believe that studies such as this will contribute to our shared goal of improving the lives of persons with Fragile X and their families.

Those interested in participating in this research study or in obtaining more information are encouraged to call Stanford’s Behavioral Neurogenetics Research Center, toll-free at 1-888-411-2672.

Fundraising CD

If you would like to help raise money for Fragile X research and you’re looking for a fun and educational Children’s CD that the whole family can enjoy, please consider Squirmy Wormy by Peacock Studios. “Squirmy” has been used successfully in speech therapy sessions for children and is part of the B.C. Teacher’s Federation Lesson Aids Catalogue.

Through the generosity of Keith Peacock, $5.00 from each CD and $3.00 from each cassette sold, through the Peacock Studios Canadian mail order program, will go to the Fragile X Research Foundation of Canada.

You can visit http://www.peacock-studios.com to hear samples and see reviews of Squirmy Wormy. Mail order forms are also available at this web address.

Keith Peacock, Peacock Studios, Box 56519, Burnaby, B.C. V3J 7W2
Tel: (604) 420-9880 • Fax: (604) 420-9830 • Email: music@Peacock-Studios.com • Website: www.Peacock-Studios.com
We found out that several attractions in Ontario offer special services to people with disabilities, and their escorts. We have listed some of these below. Please make sure you either call ahead or check out their websites to get the most up to date information.

**CANADA’S WONDERLAND**
Located off Hwy. 400, north of Hwy 401. Exit Rutherford Rd. if heading north or south on Hwy. 400. Their website indicates that specific ride boarding times at certain attractions apply to disabled guests and their escorts - limited to three escorts per guest.

[www.canadaswonderland.com](http://www.canadaswonderland.com) - click on Guest Services, then Services, then Guests with Disabilities to find out more.

**ONTARIO SCIENCE CENTRE**
The Ontario Science Centre is located at 770 Don Mills Road in Toronto. (416) 696-3127. Escorts of visitors with a disability get free admission.

[www.ontariosciencecentre.ca](http://www.ontariosciencecentre.ca)

**VIA RAIL CANADA**
Riders with Special Needs children get a special rate with Via Rail. With a doctor’s letter stating the diagnosis and need for supervision, the child pays, but the accompanying adult doesn’t. Inquire at time of booking.

[www.viarail.ca](http://www.viarail.ca) - type in “Special Services” in their Ask Via section, then Escorts, to get more information.

We have been told that both DisneyLand and DisneyWorld offer special privileges to families when someone in the party has a disability.

**VARIETY VILLAGE** - check out pages 6 & 7 for more info. and website.

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**Activity List for Children with Fragile X**

In the last newsletter, we included a list of organizations and programs for leisure and therapeutic activities for children with Fragile X. Members of the board of the FXRFC compiled the list, based on their own or their friends’ experiences with their children. The list was not official or exhaustive. Below you will find additional information which was sent in since our last newsletter. We know there are other excellent programs across the country, and we invite our readers to send us their tips, which we will publish in subsequent newsletters and add to the website. We have not included the cost of these activities, to avoid inaccuracies.

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**Events Calendar**

*Here are just a few of the exciting Fragile X fundraising and public awareness events coming up this year! If you are planning an event in your area, please let us know and we will post it on the FXRFC website and publish it in the Quarterly Newsletter.*

**Ballard Family Golf Tournament**

**Chris and Dagmar Ballard** of Pickering, Ontario have a son with Fragile X syndrome and they have been contributing to the Foundation by organizing an annual Fundraising Golf Tournament for the past 3 years. Last year they had 66 participants and raised **over $2,700.00**; this year’s tournament promises to be even bigger! If you would like to help out or participate, please contact Chris Ballard. He can reached at: cballard@pathcom.com or phone (416) 561-3805.

**5th Canadian Fragile X and ASD Conference**

**July 4-6, 2003 - Kingston, Ontario**

Ongwanada will once again be hosting a conference in Kingston, Ontario, from July 4-6, 2003 and it promises to be an exceptional one. The conference opens with separate Workshops for Moms, Dads and Professionals, a great opportunity to get together, share ideas and meet other participants. Also new this year will be a morning long session for siblings, where they can have some fun and discuss issues that are important to them (2 sessions - ages 8 to 12 and 13+). Limited to 20 participants per group.

This year’s conference will be held at the beautiful Royal Military College grounds near downtown Kingston, where facilities and dining are superb. The Saturday session will culminate with the popular 1000 Islands Dinner cruise. The guest speakers this year include many returning experts and some fascinating new ones! This promises to be another great weekend, full of up-to-date information and fun.

E-mail: fragilex@post.queensu.ca or visit their website at: [www.autismresearch.ca](http://www.autismresearch.ca) to register on-line.
It's the 2\textsuperscript{nd} Annual FX Foundation Family Fun Day!

Saturday June 21\textsuperscript{st}, 11am-2pm
This year our Fun Day will be held at Variety Village!
Mark your calendar NOW!

That's right, you'll enjoy an all expenses paid, action packed day of amazing games & fantastic gourmet food (hotdogs, hamburgers, drinks) along with other incredible FX families, just like yours! This is your chance to meet other families, connect, relax and let the kids play together at a great facility. There is a fenced-in green space, party room, and patio as well as a reserved indoor space in the fieldhouse in case the weather does not co-operate.

Please make sure you let us know if you plan on attending no later than June 3\textsuperscript{rd}, so we can bring along enough food for everyone.
Call Lori Beesley at (416)261-2666 and tell her how many people you're bringing.

So bring along your smiles - but not your pets (sorry Rover, you are not allowed) and get ready to have a great time, with lots of fun and laughter! There will be organized games, but feel free to bring your kites, balls, frisbees etc.

See you there - rain or shine!
For directions and more details, please see next page.
Variety Village is located at 3701 Danforth Avenue
Toronto, Ontario M1N 2G2
Tel. # (416) 699-7167
http://www.varietyontario.com/village/

Please note you can only exit south off the 401 at Warden Ave. or Brimley Rd. Also be aware that Danforth Rd. & Danforth Ave. are both in this area. Variety Village is on Danforth Ave. It sits next to a high school & you can park in their parking lot, and follow the walkway to Variety Village. There is a set of lights at Variety Village, so just turn in where you see the big dinosaur out front!

Remember to let us know by June 3rd - hope to see you there!

Call Lori Beesley (416) 261-2666 - specify how many adults & children when you call, and please leave a number where you can be reached, just in case. Thank you.
FXRFC Chapters - We are Growing!

We are very interested in starting chapters 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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167 Queen St. W.
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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