

FRAXA UPDATE

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FOUNDATION

"NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

ever has."

— Margaret Mead

New Research on Fragile X

FRAXA Research Foundation has just funded new grants and fellowships for a total of over \$500,000! Over the past several years, FRAXA has funded over one million dollars in research each year, accelerating the pace of progress, scientific publications, and discoveries towards our goal: specific treatments and ultimately a cure for Fragile X, the most common inherited cause of mental impairment and the most common known cause of autism.

We are excited about the direction that the current crop of research grants is taking; it seems that many of these projects were born out of the last two Fragile X Banbury conferences. Many of the senior scientists who participated in these meetings have since gone on to start new projects based on the information presented at Banbury. The speed with which previous findings are being followed up is particularly impressive. The "mGluR Theory" proposed by Mark Bear, Kim Huber, and Steve Warren has now been strengthened by multiple investigators in multiple model systems, and major efforts are underway to build on this discovery. It is our hope that the focus on metabotropic glutamate signaling pathways will lead to human trials of new medications in the very near future.

Lest it seem we are putting all our eggs in the mGluR basket, work on other directions is moving forward quickly as well. Turn to page 4 to read about all fourteen newly funded projects.

Over 700 Gather for FRAXA's 10th Anniversary Gala

by Leslie Eddy

Boston Attorney Harry Manion has a reputation as a fierce advocate and a 22-year record of exceptional results. When asked to chair the 10th Anniversary Gala for FRAXA, Harry upheld his reputation, adding perhaps the most personal win of all.

Proceeds for the first Boston gala topped \$700,000! Over 725 guests filled the Copley



Mary Higgins Clark, Harry Manion, Stacy Lucchino, Mike Dee

Plaza with glamour for a once in a lifetime event. The conglomerate of major media, sports (Red Sox, Patriots, Celtics and Bruins), political and business worlds created a momentum unrivaled in the Boston area. In attendance were Mayor Tom Menino, Congressman William Delahunt, Attorney General Tom Reilly, author Mary Higgins Clark, news anchor Roger Mudd, and over 200 friends and family members from all over the country lending support to Harry and FRAXA. *continued on page 9*

Also in this issue:

- Report from Washington
- NIH/FRAXA sponsored research workshops
- Upcoming events in CA, NY, OH, DC

FRAXA is a nonprofit, tax-exempt charity run by parents of children with Fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 4000 males and 1 in 6000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of Fragile X, by direct funding of promising research projects and by raising awareness of this disease.



Report from **Washington:**

By Mary Beth and David Busby

Fragile X in Congress

Every year the House and Senate Appropriations Committees each issue a Report telling the National Institutes of Health, Centers For Disease Control and Prevention, and all other agencies how to spend the money appropriated to that agency. A mention of Fragile X research in either the House or Senate Report is sufficient to require action by the agency (unless specifically repudiated in a later “Conference Report”).

As a matter of practice, non-controversial language like health provisions stands and governs, so if Fragile X funding is mandated by either the House or Senate Appropriations Reports, it will govern agency expenditures.

The House of Representatives

Even though 81 members of the House signed on to the “Dear Colleague” letter of Congressmen Radanovich and Sandlin to the House Health Subcommittee of Chairman Regula and Ranking Member Obey, only 1 of our 9 suggested provisions made it into the Committee’s Report. It calls for support for “promoting early intervention through developmental screening,” “developing a Fragile X public health program to expand surveillance and epidemiological study of Fragile X,” and providing “patient and provider outreach on Fragile X.” We support this, of course, but we were disappointed that most of our requests were excluded.

All the basic research requests – which were agreed upon and urged by FRAXA, the

National Fragile X Foundation, and Conquer Fragile X – were ignored by the House Subcommittee.

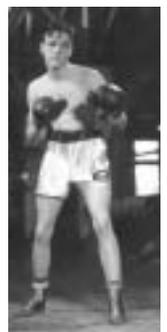
The Senate

But we have another chance! Fortunately, if the “Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education” will adopt the language requested by our champions, Senators Hagel and Edwards, all 9 provisions will effectively be resurrected in full force. The Hagel/Edwards “Dear Colleague” letter has gained the support of 24 senators. They forwarded it to Senate Appropriations Chairman Specter and Ranking Member Harkin on July 8, asking for funds to:

- enhance pediatric training and career development grants to include new Fragile X researchers.
- coordinate Fragile X research throughout the NIH institutes.
- study neurobiological and pharmacological treatments for Fragile X and related disorders such as autism.
- study the effects of Fragile X outside the central nervous system.
- expand research of Fragile X Tremor Ataxia Syndrome and study the effect of Fragile X on fundamental brain circuitry, especially on older carriers.
- enhance the new Fragile X Research Centers and recruit new Fragile X researchers.
- develop a public health and epidemiological research initiative focused on Fragile X.
- screen and provide help for families and individuals affected by Fragile X and other heritable disorders and developmental disabilities.
- expand the newborn screening, counseling, testing, and special services program for newborns and children at risk for heritable disorders, including Fragile X.

Contact your Senators!

Now is the time for you to email, fax, or visit your two senators. If they have already signed on, thank them and ask them to follow up on the “Dear Colleague” letter and to let you know the status of these requests. If they have not signed on, make an appointment with your Senators or their staffers in your state during Congress’ current recess – we have until early September – and ask them to help you and your children in this great cause by writing a letter to the Senate Appropriations Committee supporting the 9 funding requests! Your senators are now campaigning in your state and asking for your help. Ask for theirs!



Who's This?
See p. 11

RESEARCH WORKSHOPS

5th Annual Fragile X Banbury Meeting



In April, the 5th annual Fragile X research meeting was held at the Banbury Center at Cold Spring Harbor Laboratory, New York. The meeting was co-chaired by Will Spooren, a drug development scientist of Hoffman LaRoche, and Bill Greenough, professor at the University of Illinois at Urbana-Champaign.

This year's focus was pharmacological treatments for Fragile X: which existing drugs and experimental new compounds might be effective for treating Fragile X. The participants were equally drawn from the pharmaceutical industry, representing seven different companies including Novartis, Addex, Lilly, Merck, and Hoffman LaRoche, and the university-based basic research community. The meeting had a "cut to the chase" treatment-development orientation.



Randi Hagerman, Fabrizio Gasparini

Much discussion centered on receptor/transmitter systems which research indicates are impaired in Fragile X, particularly those involving glutamate and GABA, and compounds which target

those systems. By the time we finished, it had become clear that more work is needed to design good clinical trials to effectively test drug treatments for Fragile X. Several exciting new collaborations between industry and university scientists were estab-



David Nelson, Ben Oostra, Eric Klann, Fen-Biao Gao, Steve Warren

lished at the meeting, and a new drug trial in Fragile X patients is now being planned.

Fragile X Banbury meetings were established five years ago thanks to Nobel Laureate James D. Watson, who proposed them as an effective means to stimulate new research. Meetings are funded by a grant from NIMH with additional help from NICHD. They last two and a half days and are wonderfully intense because people are together discussing Fragile X from 8am until late in the evening. Planning has begun for the next Banbury meeting in the Spring of 2005.

At the Crossroads: Fragile X and Autism

In July, scientists gathered at Salve Regina University in Newport, RI, to investigate the common neurobiological pathways in Fragile X and autism spectrum disorders. The meeting was sponsored by FRAXA and three of the National Institutes of Health (NIMH, NICHD and NINDS).

Researchers have found a number of similarities in individuals with Fragile X and autism spectrum disorders. In fact, at least 25% of people with Fragile X also have autism, and Fragile X is the most common known genetic cause of autism.

Many people believe that there are shared genetic mechanisms between Fragile X and at least a subgroup of individuals with autism. Further study of the Fragile X gene and genes it regulates could offer important insights into the genetic basis of autism. But very little research has been conducted involving direct comparison between individuals with autism spectrum disorders, Fragile X, and autism with Fragile X.

This workshop brought together leaders in these fields to develop future directions for research that will accelerate progress on each of the disorders. The results were new collaborations among investigators and some specific plans to support research on the overlap between Fragile X and autism spectrum disorders. We thank Steve Moldin of NIMH, Laura Mamounas of NINDS, and Alice Kau of NICHD, the co-chairs, Dr. Dan Geschwind and Dr. Robert Wong, and all the participants for an extraordinary meeting.

FRAXA Grants Awarded in July 2004

If you would like to explore the entire portfolio of FRAXA-funded research, past and present, please visit our website, www.FRAXA.org. Each FRAXA investigator has a page devoted to his or her research.

These descriptions are written by Michael Tranfaglia, MD, FRAXA Medical Director.

The mGluR Theory of Fragile X

MARK BEAR, PhD

Principal Investigator

NAVEEN NAGARAJAN, PhD

Postdoctoral Fellow

Mass. Institute of Technology (MIT)

\$37,476 renewal



Mark Bear

This group hypothesizes that Fragile X syndrome is a consequence of exaggerated responses to synaptic activation of the group 1 mGluRs that are coupled to local protein synthesis (see box).

The goal of this project is to determine if the malfunction in the mGluR pathway causes the delayed development of synapses, using the Fragile X mouse model. If so, they will investigate whether mGluR antagonists, like MPEP, will correct this delayed development. Naveen Nagarajan, a postdoctoral fellow in Dr. Bear's lab, is using live-cell imaging techniques and other assays to investigate precisely how stimulating mGluRs affects AMPA receptors and the shape of dendritic spines in Fragile X mice. The overall goal of this study is to further investigate mGluR antagonists as potential treatments for Fragile X.

Role of the Cerebellum in the Dysfunction of Fragile X Syndrome

BEN OOSTRA, PhD

Principal Investigator

BAS KOEKKOEK, MD, PhD

Postdoctoral Fellow

Erasmus University, The Netherlands;

\$55,000



Ben Oostra

The mGluR Theory of Huber, Bear, and Warren predicts that excessive function of signaling pathways associated with mGluRs causes most of the symptoms of Fragile X. It appears that mGluR5 is responsible for most of the problem in the brain overall. However, mGluR5 is not present at all in the cerebellum, a part of the brain associated with coordination of movement and sensory integration, and the area

research

which is known to express very large quantities of FMRP in the normal brain. Clearly, the cerebellum is important in the pathogenesis of Fragile X (and autism, too!), but here mGluR1 regulates the activity of these hyperactive pathways.

Dr. Oostra's lab has demonstrated altered synaptic plasticity in the cerebellum of FMR1 knockout mice and correlated this with changes in the shape of dendritic spines in the neurons of the cerebellum. This change is also correlated with changes in a specific behavior in mice: eye-blink response. Furthermore, eye-blink response can be tested in humans, and Dr. Oostra's group will attempt this test with Fragile X patients. They will also attempt to treat these abnormalities in mice with mGluR1 and mGluR5 antagonists. Additionally, they will study another critical brain region, the amygdala, which mediates the startle response and is probably very important for causing many of the psychiatric symptoms seen in Fragile X.

Life imitates the movies

DNA Our genes are made up of DNA. Think of this as the master copy of a movie locked away in a Hollywood vault (neuron's nucleus).

mRNA DNA is transcribed into messenger RNA, which can travel outside the cell body along dendrites to the synapses, where cell-to-cell communication takes place. mRNAs are like movie prints that travel to your local movie theatres (i.e., synapses).

protein Each mRNA encodes a protein. Just as a movie can be shown many times a day at a theatre, each mRNA can be translated into its protein many times a minute.

synapse This is where the show goes on ... where neurons exchange signals. A synapse has two parts: the signalling neuron's axon and dendrite of the receiving neuron's dendrite. When Neuron #1 spits out a message, receptors on dendrites of Neuron #2 are poised to receive it.

The mGluR theory Receptors come in many flavors, but we are especially interested in mGluRs, metabotropic glutamate receptors. The mGluR Theory suggests that "Group 1 mGluRs" function excessively in Fragile X and that this explains many of the symptoms of the disorder. For no good reason, "Group 1 mGluRs" include two types: mGluR1 and mGluR5. This concludes our lesson for today.

Glutamate Receptors and Their Associated Postsynaptic Proteins in the FMR1 Knockout Mouse

WALTER KAUFMANN, MD, PhD

RICHARD HUGANIR, PhD

PAUL WORLEY, PhD

Kennedy-Krieger Institute
Johns Hopkins University, \$60,000



Walter Kaufmann

This experienced group of investigators has a long-standing interest in the molecular basis of synaptic plasticity, both during development and in cognitive processes (i.e., learning and memory) in the mature brain. In an effort to test the mGluR Theory of Fragile X, they propose to examine the molecular dynamics of mGluRs in areas involved in cognition in the Fragile X knockout mouse.

Since several dendritic proteins which interact with glutamate receptors show altered levels in the Fragile X knockout mouse, the project will focus on these molecular interactions as the potential for abnormal function of synapses in Fragile X. Among the proteins with elevated levels in the knockout mouse is Arc, a key component of synaptic plasticity in dendrites, originally characterized by Drs. Worley and Kaufmann almost a decade ago.

By further defining the mechanisms through which synaptic plasticity is changed in Fragile X, new targets for drug development may be identified. Because this project will delineate interactions between different types of glutamate receptors, this work should enable more precise testing of compounds which affect function of glutamate receptors for the treatment of Fragile X.

INVESTIGATORS' NOTE:

Fragile X Knockout Mice now available from Jackson Laboratory: <http://jaxmice.jax.org> and Neuromice: www.Neuromice.org

The Effects of Group II mGluR Antagonists on Synaptic Plasticity in FMR1 KO Mice

CATHERINE CHOI Principal Investigator, Drexel University

SEAN MCBRIDE Co-Investigator, Albert Einstein College of Medicine

TOM JONGENS, PHD Co-Investigator, University of Pennsylvania

The lab of Dr. Tom Jongens at the University of Pennsylvania has obtained remarkable results with their studies of drosophila mutants – fruit flies with the equivalent of the Fragile X gene knocked out show significant impairment in cognitive function, as shown by studies of their defective courtship behavior. More importantly, this impairment can be reversed by treatment with MPEP, an experimental compound which dampens mGluR function. Furthermore, lithium treatment was also able to completely rescue this cognitive phenotype. Lithium is a common psychiatric treatment which is readily available and may serve to stabilize the mGluR pathways affected by Fragile X. Of course, humans are not quite the same as fruit flies. Therefore, Catherine Choi and her collaborators, Sean McBride and Tom Jongens, are attempting to replicate these results in the Fragile X knockout mouse. A lithium effect in mice would probably justify immediate trials in humans with Fragile X. This \$7600 grant will allow the team to purchase Fragile X mice to test this theory.

Specific Tests of the mGluR Hypothesis

PETER VANDERKLISH, PhD

Scripps Research Institute, La Jolla, CA, \$45,000



Before he became a Fragile X investigator, Dr. Peter Vanderklish had demonstrated that activation of group I metabotropic glutamate receptors (mGluR1 and mGluR5) could cause rapid changes in dendritic spine shape. In as little as 15 minutes, spines of cultured neurons could become long, thin, and immature-looking. Since this shape is characteristic of the spine shape previously seen in Fragile X brains, this would appear to support the notion that excessive function of these mGluR pathways might be the primary pathology in Fragile X.

Since last year when Dr. Vanderklish attended a Fragile X Banbury meeting, he has been studying neurons from the Fragile X knockout mouse in great depth. Initial studies in his lab have already shown therapeutic effects of MPEP (the prototype mGluR5 antagonist) in his model system. His results have been so promising that FRAXA is adding funding for an additional technician position. One of the most intriguing aspects of this line of inquiry is that it strongly suggests that some structural changes seen in Fragile X brains may not only be treatable, but may reverse surprisingly rapidly with specific treatment.

Is There a Dysregulation of Activity-Induced mRNA Translation in FMR1 Knockout Mice?

OSWALD STEWARD, PHD

Principal Investigator

FEN HUANG Graduate Student
University of California at Irvine; \$50,000



Oswald Steward

Dr. Oswald Steward was the first scientist to demonstrate that protein synthesis could occur in dendrites in response to synaptic activity. Prior to this discovery, dogma in neuroscience held that protein was synthesized only in the body of the cell, and then transported out to the far reaches of the dendritic arbor. We now know that protein is, indeed, synthesized in dendrites – and FMRP is intimately involved in the process. Activity-dependent protein synthesis in dendrites is now thought to be essential for most kinds of learning and memory.

This grant will enable the Steward lab to test Fragile X knockout mice for alterations in protein synthesis in response to various kinds of activity – seizure, fear conditioning, or different kinds of chemical stimulation. They will also look closely at alterations in regulation of protein synthesis in interneurons, an important but often overlooked population of cells in the brain which helps to coordinate activity among groups of neighboring cells. Dysfunction of interneurons may cause the seizures often seen in Fragile X, but could also account for many other observed symptoms. Messenger RNA for FMRP is especially concentrated in the dendrites of interneurons, according to previous work of the Steward group, indicating that these cells may be especially hard hit by this disorder, making further study especially important.

Studies of FMRP Function in the Xenopus Visual System

HOLLY CLINE, PhD Principal Investigator

JENNIFER BESTMAN, PhD

Postdoctoral Fellow

Cold Spring Harbor Laboratory, NY; \$40,000



Holly Cline

Jennifer Bestman is new to the Fragile X field, having started her first Fragile X study with FRAXA funding last year. This research group is examining the normal role of FMRP using tadpoles as a model (when multiple model systems yield similar results, the perceived weight of the evidence produced is much greater). So far, they have shown that FMRP and associated proteins and translation factors are involved in the development of neurons in tadpoles; they now plan to explore the effects of numerous pharmacologic interventions in this model system. These

studies may yield further support for the mGluR Theory of Fragile X by demonstrating the process (excessive mGluR-LTD) in yet another species, and – hopefully – demonstrating potential efficacy of mGluR antagonists.

Drosophila CYFIP, a Molecular Link Between Actin Cytoskeleton Remodeling and Fragile X Mental Retardation

ANGELA GIANGRANDE, PhD

Universite Louis Pasteur, Strasbourg; \$45,000



The normal function of FMRP, the protein missing in Fragile X, involves two primary actions:

1. regulation of protein synthesis in dendrites, and
2. transport of messenger RNA from the nucleus of the cell to the dendrites.

Both these functions require significant interactions with the cytoskeleton, the scaffold which holds the cell together. In the first instance, cytoskeletal changes (dendritic spines become long and thin) occur whenever LTD (Long Term Depression) occurs, and this is known to occur too much in Fragile X. In the second case, transport of mRNA requires that FMRP hook onto the cytoskeleton and propel itself along, like a railroad train, to transport the mRNA to the dendrite, where it will be used as the template for protein synthesis. Clearly, these two functions are closely related, and both appear to be stimulated by activation of metabotropic glutamate receptors.

While much interest has been focused on the signaling pathways connected to mGluR's, these interactions with the cytoskeleton may have important implications for understanding the basic mechanisms of Fragile X. Dr. Giangrande will investigate these interactions in detail in fruit flies, which are a simple yet powerful system in which multiple genes can be manipulated with relative ease.

Clinical Trial – Ampakines

Dr. Elizabeth Berry-Kravis is conducting a clinical trial at Rush University in Chicago to evaluate CX516, a new potential treatment for Fragile X and autism. The study is funded by FRAXA.

Just a few more adult participants with Fragile X are needed to complete this study. Prospective subjects should contact study coordinator Tina Potanos at 312-942-4036.

Identification and Characterization of Novel Targets of FMR1 that Affect Responses to Sensory Stimuli

FEN-BIAO GAO, PhD Principal Investigator

FAY WANG, PhD Postdoctoral Fellow

University of California at San Francisco; \$55,000



Fen-Biao Gao

Since FMRP, the Fragile X protein, is an RNA-binding protein, it is widely assumed that symptoms of Fragile X occur because of an alteration in the handling (transport and translation) of various messenger RNAs. Previous studies have shed much light on which mRNAs are “handled” by FMRP, but these have not been definitive by any means.

Dr. Gao’s group aims to add to our knowledge of the targets of FMRP by adding a functional assay: locomotion (wandering in response to external stimuli). Using drosophila as his model system, he will look for the mRNAs which interact with the fly version of FMRP and which can alter locomotor function when mutated. Since fly genes and mRNAs correspond quite precisely to human genes and mRNAs, this investigation will provide a working model to study the cause of the heightened sensitivity that Fragile X patients display toward touch, light and sound.

Trafficking of FMRP and Associated mRNAs in Response to Activation of Metabotropic Glutamate Receptors

GARY BASSELL, PhD Principal Investigator

LAURA ANTAR Graduate Student

Albert Einstein College of Medicine, NY; \$15,000 bridge renewal



This fellowship renewal will continue a successful series of experiments demonstrating trafficking of FMRP and its associated mRNAs in response to activation of metabotropic glutamate receptors (mGluRs). In other words, when the mGluRs that we have previously discussed are stimulated, the Fragile X protein and associated messenger RNAs are all transported along the dendrites to synapses. The specifics of this process are being delineated by this team.

FRAXA has supported the Bassell lab since 2000, and we are very gratified to report that Gary Bassell has secured funding from NINDS to support and expand the work in his laboratory starting December 1st, so this FRAXA award will help support the lab until then. Laura Antar, an MD-Ph.D. student, is completing the PhD portion of her studies and will soon

move on to clinical work (for the MD degree). Bassell and Antar recently published articles in the journal *Cell* (called “Sunrise at the Synapse”) and in the *Journal of Neuroscience* discussing the Fragile X protein and mGluRs.

Dissection of the Fragile X Protein Binding Domains

STEPHEN WARREN, PhD Principal Investigator

REID ALISCH, PhD Postdoctoral Fellow

Emory University; \$40,000



Stephen Warren

This group will use novel strategies to examine the binding activity of FMR1 protein, to see which target mRNAs it associates with and presumably regulates. They will also investigate the RNA targets of two similar proteins, FXR1 and FXR2, which are thought to work with FMRP in most, if not all, of its functions. They also plan to look at the different binding patterns of different isoforms of FMRP; one important fact which is seldom discussed is that FMRP can exist in cells in at least 12 distinct forms, depending on how it is “spliced” by various cells. It is entirely possible that each of these forms has somewhat different characteristics, which need to be better understood. Furthermore, the investigators hope that by comparing FMRP from different species, such as chicken and frog, they can learn more about which parts of the Fragile X protein perform specific functions (such as binding RNA, engaging transport mechanisms, etc.)

This is an important area of research because greater understanding of FMRP’s targets will enable us to identify other genes and other proteins which may be causing the pathology in Fragile X. These may, in turn, be potential targets for drug development.

Xenopus Model of Fragile X

EDOUARD KHANDJIAN, PhD

Principal Investigator

LAETICIA DAVIDOVICH, PhD

Postdoctoral Fellow

Laval University, Quebec; \$35,000



Edouard Khandjian

This group is studying the functions of FMR1 and the related genes FXR1 and FXR2 in frogs. While frogs have the same number of genes (3) in this family of genes, they have far fewer isoforms of the protein products compared to humans (where FMRP alone can exist in at least 12 distinct forms), making study of the different functions somewhat simpler. Progress has been made in this project identifying genes which are regulated by FMRP, FXR1P, and FXR2P using microarray analysis; funding is being continued in hopes of identifying new targets for potential drug development.

Analyses of Functional Interactions Between dFMR1 and RNAi Genes

RICHARD CARTHREW, PhD

Principal Investigator

YOUNG SIK LEE, PhD

Postdoctoral Fellow

Northwestern University; \$40,000



Young Sik Lee

Almost 2 years ago, several papers were published showing that the Fragile X gene is involved in the RNAi (“interfering RNA”) pathway. RNAi is a widespread biological process that until 1998 remained undiscovered, but plays important roles in combatting viral infection, organizing chromosome DNA, and silencing gene expression during embryo development.

A major question now being asked is how the Fragile X gene normally contributes to the RNAi process. Moreover, does Fragile X syndrome arise because human RNAi is improperly working, due to the absence of FMR1? The Carthew lab studies RNAi in the fruitfly and has done some incisive experiments to understand this conserved process in both flies and humans.

So far, this study has not found definite links between the fruitfly FMR1 gene and RNAi. However, not all potential avenues linking FMR1 and RNAi have been explored. Additional experiments to be conducted over the coming year should give us a clear idea of whether or not there is a general role for the Fragile X gene in RNAi. This is an important mechanism of biological control, so it is important to know whether Fragile X might in any way be related to RNAi.

Reactivating the FMR1 Gene

ANDRE HOOGEVEEN, PhD Principal Investigator

VIOLETTA STOYANOVA, PhD Postdoctoral Fellow

Erasmus University, The Netherlands;
\$35,000 renewal



Several years ago, this group made an interesting finding when they were studying cells from an individual who had an unusual case of Fragile X. This person had a large expansion of the FMR1 gene but it was unmethylated (not shut down), so that the gene continued to function, resulting in normal intelligence. When cells from this unusual individual were fused with typical, fully methylated Fragile X cells in a test tube, the methylated full mutation chromosomes quickly became demethylated and started to function normally. Obviously, there is some “active ingredient” in the unusual cells which is able to restore function to typical Fragile X cells. The goal of this study is to identify this active ingredient and exploit this knowledge for future treatment based on targeted demethylation.

Research Forum

Attendees at the Society for Neuroscience annual meeting in San Diego are cordially invited to attend a Fragile X Research Forum hosted by FRAXA Research Foundation, Conquer Fragile X Foundation, and the Fragile X Research Foundation of Canada.

Scheduled to speak are Society for Neuroscience Treasurer-elect Bill Greenough, Howard Hughes Investigator Mark Bear of MIT, and Oswald Steward of the University of California at Irvine. This event will be an excellent opportunity for investigators, postdoctoral fellows, and students to meet leaders in this field and to learn about the latest advances in understanding the neurobiology of Fragile X. There will be opportunity for informal discussion with the speakers and to talk with officials of the hosting foundations about their research funding programs. Wine, cheese, and light hor d'oeuvres will be provided.

The Society for Neuroscience annual meeting attracts a whopping 25,000 - 30,000 scientists each year. FRAXA hosts a booth to inform investigators about the extraordinary advances happening in Fragile X research.

Attn: Fragile X Families:

Individuals who carry fragile X or who have the full mutation can register as tissue donors with the Brain and Tissue Bank for Developmental Disorders at the University of Maryland. The Brain and Tissue bank is an NIH-funded central resource for researchers around the US who are studying Fragile X.

For more information, contact FRAXA or contact the Brain and Tissue Bank directly at (800)-847-1539 or visit their website: <http://som1.umaryland.edu/BTBank>

FRAXA's 10th Anniversary Gala in Boston



Ruth Pointer of The Pointer Sisters, and Harry Manion

continued from page 1

Despite the large numbers, the evening was filled with intimate moments. Shortly after singer Ruth Pointer had everyone dancing between the tables, Harry took the stage and spoke candidly of the humility that comes with asking people for help. Researchers, caregivers and teachers “who do so much to enrich the lives of all of our Fragile X children” were recognized and saluted.

The “Once in a Lifetime Auction” included the pairing of celebrities who masterfully worked the room, tapping into the competitive and generous spirit of the crowd to drive up the bidding. Eddie Andelman, from Boston Radio’s 1510 The Zone, led off by offering lunch for two in D.C. with Eddie and the legendary Red Auerbach.

Hawaiian Paradise, presented by auctioneers Sara Underwood and Ted Wayman, a private jet to a villa in the Bahamas, and a seaside casita in Cabo San Lucas were among the fantasy packages bringing in the highest bids. The last item, a Season with the Red Sox, secured the evening’s largest bid of \$35,000!

For FRAXA, there were many wins that evening. Abundant news coverage before, during, and after the event brought FRAXA and Fragile X into the public eye. New England Cable News, the Boston

Globe, Herald, Boston Business Journal and many local papers covered the story, and both NESN and Fox 25 broadcast live from the Copley that evening.

Thanks to Harry

Manion for serving as our leader and to everyone who made FRAXA’s 10th anniversary celebration a success. For all those involved, it was a night to remember and a night that brought all of us a few steps closer to helping our children.



Terry O'Reilly and Rick Middleton



Congressman William Delahunt, Katie Clapp



Attorney General Tom Reilly



Kathy Campanella, Harry Manion, Kathy Meyer



Leslie Eddy, Debbie Stevenson, Claire Dunsford and Mike Tranfaglia

Guests who drove to the gala from the North Shore were greeted by FRAXA's highway billboard, donated by ClearChannel thanks to Fred Ford.



FRAXA FUNDRAISERS

Raising Awareness and Funds for Research



Kelley Randels with Mary Higgins Clark

Omaha Hosts 7th Annual Mary Higgins Clark Gala

The Nebraska Fragile X Families Association hosted the Seventh Annual Mary Higgins Clark FRAXA Gala. The Nebraska group was started in January 2003. A dream of theirs was to host a Gala for FRAXA, and they did not waste any time in getting down to business! Their exciting event was held on Thursday, May 6, 2004 at the Holiday Inn Central. There were over 300 guests and they raised over \$100,000 for FRAXA! Special guests included best-selling author, Mary Higgins Clark, and TIME Magazine president and FRAXA Board member, Eileen Naughton. The Nebraska Fragile X Families Association appreciates the attendance of Mary Beth and David Busby, Debbie and Jeffrey Stevenson, Dr. Elizabeth Berry-Kravis, Dr. Brad Schaefer, and Katie Clapp. Megan Massey presented the Research Beacon Award to U.S. Senator Chuck Hagel for his role in helping to raise funding and awareness for Fragile X Research. Due to late votes in Washington, Senator Hagel arrived seconds before he was introduced; he addressed the guests without missing a beat! It was a wonderful evening.



Megan Massey and Senator Chuck Hagel

Fragile X Alliance of Ohio 8th Annual Golf Benefit attracts Record Number of Attendees

On Monday, June 28th, the Fragile X Alliance of Ohio held their 8th Annual Golf Benefit at the famous Firestone Country Club, Home of the NEC Championships.



Leslie and Ara Bagdasarian, Coach Dave Frantz

The field of 252 golfers and over 50 volunteers enjoyed a memorable day. Golfers played on both the North and West courses - with rain unfortunately arriving during the last hole of play. The rain didn't dampen spirits though, and 80 additional guests joined us for the Silent Auction, cocktails and banquet.

Our program this year featured Dr. Mike Tranfaglia, of FRAXA, and Dr. Rob Bauchwitz, a key Fragile X researcher, who brought us up-to-date on the progress with Fragile X and the importance of parents working together with scientists. After the "First Down Towards a Cure" video, a special award was presented to Coach Dave Frantz, the high school football coach who helped Jake Porter, who has Fragile



Robert Bauchwitz, Mike Tranfaglia, Marty Boise

X, score his now-famous touchdown. Coach Frantz was recognized for setting an extraordinary example with his leadership, compassion and humility.

Finally, our special guest, Doug Dieken (former Cleveland Browns player & current radio announcer) entertained us all with his humor during the exciting live auction, which included a Masters Flag signed by Phil Mickelson, Paris and Las Vegas trips and other items.

An estimated \$100,000 from the 2004 benefit proceeds will be donated by the Fragile X Alliance of Ohio to FRAXA. An additional \$50,000 is also being donated by TravelCenters of America and First Data/Western Union Foundation through their matching grant program announced last year. In total, \$150,000 was raised for FRAXA!

Co-chairs Leslie and Ara Bagdasarian wish to thank the event committee and the many Fragile X Alliance of Ohio family members, friends, and the staffs at TravelCenters of America and Conferon who helped make this event bigger and more successful than ever!

If anyone would like a copy of our program or has any questions, please email Leslie Bagdasarian at fraxohio@adelphia.net.

Paul Solotaroff, whose feature article "Me and the X-Man" was published in Men's Journal in November 2003, was one of 5 finalists for a National Magazine Award for best essay of 2003! The article is a candid, emotional piece about life with his son, Luke, who has Fragile X.

You can read "Me and the X-Man" at <http://www.fraxa.org/IX-Man.pdf>



Luke Solotaroff

CALENDAR OF EVENTS

OCTOBER FRAXA FALL FLING

Fall Fling Fundraisers are being planned across America. Contact us to join in!

Gala in Canton, Ohio

At the magnificent McKinley Grand Hotel in Canton on October 22.

NOVEMBER

Gala in Newport Coast, CA

On November 10th, FRAXA's Southern California Chapter and Staubach Retail Services are hosting a dinner fundraiser at the Pelican Hill Golf Club.

MARCH

New York City Gala

On March 10th, Debbie and Jeffrey Stevenson will host their third gala for FRAXA at New York City's Capitale.

APRIL

Mary Beth and David Busby will host the **Eighth Annual Mary Higgins Clark Gala** on April 11 in Washington, DC – just in time for cherry blossoms!

PUBLICITY!

This year, we are happy to report a great 3-day leadup to National Fragile X Awareness Day.

Sunday, July 18th, FRAXA Director Mary Jane Clark was on CBS morning news "Author Profile" talking about her son David who has Fragile X.

Tuesday, July 20th, the *Boston Globe* featured FRAXA on the front page of their Science section. For a copy, email kclapp@fraxa.org.

Wednesday, July 21st, the New York Times front page story on genetic testing featured prominent discussion of Fragile X.

Thursday, July 22nd was National Fragile X Awareness Day!

Thank you everybody who is working so hard to get the word out – and in such a positive and hopeful way! If we keep this up, everyone "out there" will want to help our kids and help us reach for that cure.

FRAXA'S NEW BUSBY T-SHIRT.

Why a Knockout Mouse?

Whenever FRAXA Board member Susan Cohen saw references to the Knockout Mouse -- from whom researchers remove (knock out) the FMR protein missing in Fragile X Syndrome – all she could think of was a mouse in boxing gloves. And the image stuck....

Why's he called Busby?

Anyone who knows FRAXA knows our "power couple" in Washington DC, David and Mary Beth Busby. Tireless advocates, hosts, fundraisers and cheerleaders for the cause of defeating Fragile X. When David later told us he'd been a boxing champion in high school, the choice was clear and FRAXA's mouse was dubbed "Busby."

Who designed it?

An appeal went out to creative friends, and a committee chose an image by graphic designer Jeri Froehlich of Froehlich Bonini Associates in Ossining, NY. Jeri contacted



David Busby, Captain of Boxing Team, Culver Military Academy, 1944



How do I order?

There are cute small ones for your kids and bigger ones for adults. FRAXA makes much-needed money on each sale, and the shirts help publicize our our fight to find a cure! Send your order specifying

Leslie Geist of MRP Lawrence Marketing of Armonk, NY, had the shirts ready in time to debut at the NFXF Conference in Washington DC in June. Thanks to them both!

quantities and sizes along with your check to FRAXA, 45 Pleasant St., Newburyport, MA 01950.

All are 100% pre-shrunk cotton.
Youth Sizes: \$15. Youth-Small (6-8), Medium (10-12), Large (14-16).

Adult Sizes: Adult \$20. S, M, L, XL. (includes shipping within US; add \$5 for Canada, \$10 overseas). Please specify quantity and size(s). Allow 2-3 weeks for delivery.

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

FRAXA offers fellowships and grants to encourage research aimed at finding a specific treatment and ultimate cure for Fragile X syndrome:

- Postdoctoral fellowships of up to \$40,000 each per year
- Investigator-initiated grants for innovative pilot studies aimed at developing and characterizing new therapeutic approaches (no funding limit)

FRAXA is particularly interested in preclinical studies of potential pharmacological and genetic treatments for Fragile X and studies aimed at understanding the function of the FMR1 gene. A special RFA has been issued; see www.fraxa.org for details.

FRAXA UPDATE

EDITOR: Katie Clapp, MS

CONTRIBUTORS: Michael Tranfaglia, MD
Leslie Bagdasarian
Mary Beth and David Busby
Leslie Eddy
Recipients of FRAXA
Research Awards
Kelly Randels

DESIGN: Mary Lou Supple

This newsletter is published regularly and sent to all supporters of FRAXA Research Foundation. Permission is granted to reproduce and distribute this newsletter for noncommercial purposes.

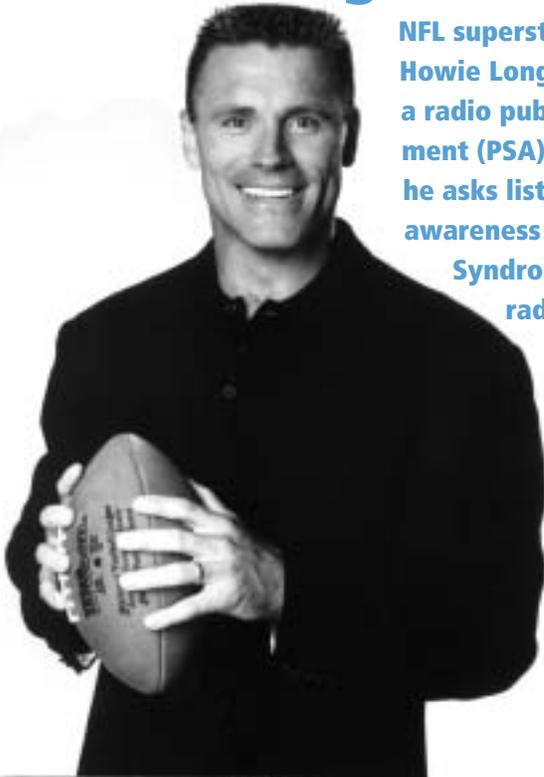
Howie Long PSA Available!

NFL superstar and Hall of Famer Howie Long generously produced a radio public service announcement (PSA) for FRAXA in which he asks listeners to help raise awareness for Fragile X

Syndrome. Call your local radio stations and ask

them to air it. We can edit this clip to fit any time slot that your stations may have available.

Contact FRAXA for the clip by email: kclapp@fraxa.org or by phone 978-462-1866.



PLEASE HELP

FRAXA

in supporting research

FRAXA is a national 501(c)(3) tax-exempt organization run by parents of children with Fragile X. Every penny you donate goes to research: FRAXA has specific grants to cover all overhead. Supporters receive this newsletter and are welcome to participate as active volunteers.

Yes, I would like to help FRAXA

- | | |
|---|---|
| <input type="checkbox"/> Member (\$25+) | <input type="checkbox"/> Benefactor (\$500+) |
| <input type="checkbox"/> Donor (\$50+) | <input type="checkbox"/> Research Underwriter (\$1000+) |
| <input type="checkbox"/> Sponsor (\$100+) | <input type="checkbox"/> Named Research Fund (\$5000+) |
| | <input type="checkbox"/> Named Research Chair (\$25,000+) |

send to: FRAXA, 45 Pleasant St., Newburyport, MA 01950

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