

FRAXA UPDATE

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"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

Nobel Prize Winner joins FRAXA

We are very pleased to welcome Dr. Susumu Tonegawa, Director of the Picower Institute at Massachusetts Institute of Technology (MIT) to FRAXA's Scientific Advisory Board.

Dr. Tonegawa's research centers on mechanisms underlying learning and memory. Recently, Dr. Tonegawa extended his work to address the Fragile X protein's role in brain cells, and Dr. Mansuo Hayashi, a researcher in his lab, has won a FRAXA Fellowship. Dr. Tonegawa also works closely with FRAXA grantees Dr. Mark Bear, at MIT, and Dr. Sumantra Chattarji, of NCBS in Bangalore, India. Dr. Tonegawa remarked:

"Research on the neural mechanisms underlying Fragile X is helping to resolve some of the most fundamental problems in neuroscience, namely regulation of synaptic function and neuronal structure as well as their relationships with cognitive abilities. In the coming decades, an array of important discoveries will emerge from this research and these discoveries will, in return, help develop new therapeutic and diagnostic methods for not only Fragile X but also other developmental brain disorders such as autism."



Dr. Susumu Tonegawa

Dr. Tonegawa joins 20 prominent scientists on FRAXA's Scientific Advisory Board, including Nobel Laureates Eric Kandel and James Watson. FRAXA is privileged to have the guidance of this extraordinary team to ensure that we make the most positive possible impact on the Fragile X community and on research to find a cure.

FRAXA and Partners Receive Education Grant

The Centers For Disease Control (CDC) has awarded a major grant to five leading health organizations for a new resource for everyone affected by genetic disease: the "Access to Credible Genetics Resources Network."

This award provides \$850,000 per year for five years to the Genetic Alliance, the University of Maryland School of Medicine, the National Coalition of Health Professional Education in Genetics (NCHPEG), Parent Project Muscular Dystrophy, and FRAXA.

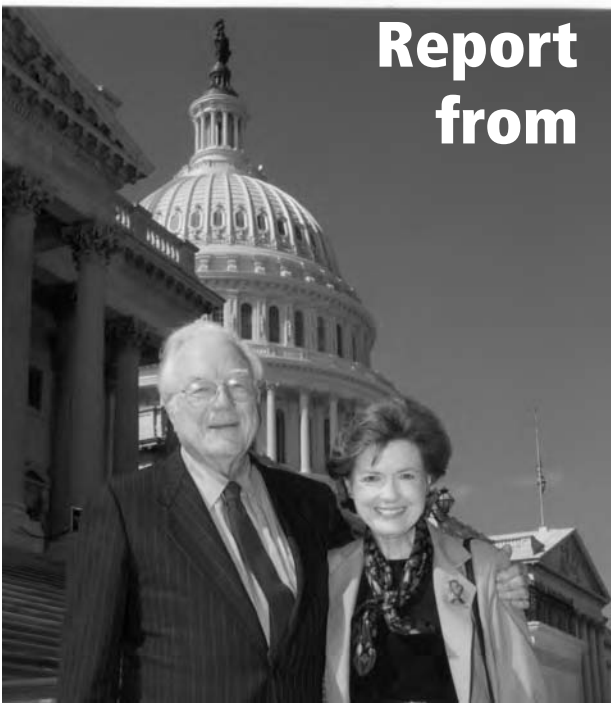
The partners will develop and distribute scientifically based information on two of the most prevalent and – as determined by Congress – important single gene disorders: Fragile X and muscular dystrophy. The project goal is to provide increased access for consumers and health professionals to information on the causes, diagnosis, treatment and management of these disorders. The team will develop open-source models for creating the best possible educational materials for all genetic disorders.

Also in this issue:

- FRAXA Hosts Research Meetings
- New Research Awards Top \$800,000
- Fall Fling Fundraisers

We look forward to this unique opportunity to serve the entire Fragile X community and, ultimately, people affected by many genetic disorders.

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

by Mary Beth and David Busby

Washington

In 1994, FRAXA was a “voice in the wilderness” in Washington. That year, FRAXA began to lobby Congress for federal medical research dollars, and the NIH spent about \$1 million for Fragile X research. This year NIH will provide more than \$20 million, and the CDC and even the Defense Department will kick in substantial additional amounts for Fragile X research. NIH is now funding 81 separate Fragile X research grants and the CDC is launching an extensive newborn testing program – as well as FRAXA’s information program mentioned above.

How did this happen? Mothers and fathers and friends of people with Fragile X went to their Members of Congress and asked for research help. FRAXA began funding cutting edge research projects, many of which became catalysts for NIH projects. Also, in 2002, FRAXA, together with others in the Fragile X community, sponsored Congressional receptions and a House Resolution proclaiming October 5 to be “National Fragile X Research Day” – so this single-gene disorder became known to the Congress.

Our congressional champions include Senators Chuck Hagel of Nebraska, Debbie Stabenow of Michigan and ex-Senator Edwards of North Carolina; and House Members George Radanovich of California, William Delahunt of Massachusetts and ex-Member Wes Watkins of Oklahoma. They were our leaders, but every Member of the House and Senate should be thanked.

This is a good time for you to thank your members – during their holiday recess and before the next session begins in January. Call FRAXA or visit www.congress.org on the web for contact details. They want to hear from you and they will respond. After all, you pay their salaries. Let’s keep up the momentum!

Not all news from Washington is depressing! There’s good news about Fragile X Research. This year’s Congressional support was the strongest yet, and we can already see the first results: FRAXA was named to share an \$850,000 CDC award (see page 1).

24 Senators and 55 House Members signed letters to their respective Appropriations Committees asking that they direct the Department of Health and Human Services, its National Institutes of Health (NIH), and The Centers For Disease Control and Prevention (CDC) to enhance their Fragile X research. As a result of all this support, Fragile X was mentioned 32 times in the House Report and 38 times in the Senate Report – a Fragile X record!

Dr. Holly Cline Receives 2005 NIH Director’s Pioneer Award

National Institutes of Health Director Elias A. Zerhouni, MD named 13 new recipients of the NIH Director’s Pioneer Award, including Cold Spring Harbor Laboratory’s Director of Research, Holly Cline.

The Pioneer Award supports exceptionally creative scientists who take innovative approaches to major challenges in biomedical research. The award gives recipients the intellectual freedom to pursue groundbreaking research directions that could have significant impact if successful but that, due to their novelty or other factors, also have inherently high risks of failure. The 2005 awardees, who were selected from 840 scientists, will receive up to \$500,000 per year for five years.

Dr. Cline has been investigating Fragile X for the past two years with a FRAXA grant. She has shown that the Fragile X protein affects the development of neurons in tadpoles. Since tadpoles are transparent, she can use time-lapse 2-photon microscopy to capture changes in the structure of individual neurons in living tadpoles, over a period of minutes to days.

Dr. Cline will use her Pioneer Award to launch a large-scale project to understand the architecture, development, and plasticity of brain circuits. She recently commented, “Our understanding of the cellular and molecular mechanisms governing brain development have now progressed to the point where our basic science investigations can have a significant impact on our understanding of complex diseases like Fragile X. Amazingly, our investigations of diseases such as Fragile X have also revealed important mechanisms of normal brain development.”



RESEARCH MEETINGS

FRAXA Hosts New Conference



Andy Tranfaglia, Mike Tranfaglia

by Michael Tranfaglia, MD,
FRAXA Medical Director and Fragile X Parent

FRAXA held a major conference this summer at Arden House, the former estate of Governor Averell Harriman, 45 miles north of New York City. “The Neurobiology of Fragile X” was designed to bring together seasoned Fragile X researchers and younger neuroscientists just entering the field. Nearly 100 investigators gathered in the palatial surroundings to share information about the basic mechanisms that lead to Fragile X.

Many of FRAXA’s previous grant recipients presented their latest results, giving some of our newest grantees a chance to get up to speed in the fast-moving field of Fragile X. Most of the new laboratories funded by FRAXA this summer (see page 4) sent scientists to the meeting.

The field as a whole showed significant progress, with further elaboration and refinement of the “mGluR Theory” of Fragile X. Results from several labs

demonstrated potential therapeutic effects of new drugs based on the mGluR Theory, and follow-up studies are now under way.

This meeting was intended to be the first in a series of regional scientific conferences hosted by FRAXA. Our goal is to augment the highly successful series of Banbury Conferences. Annual Fragile X conferences at the Banbury Center of Cold Spring Harbor Laboratory have proven so popular with researchers from around the world that we have run out of room—there simply isn’t enough space to accommodate all the scientists who would like to attend. FRAXA’s new series of meetings will attempt to capture the energy and intimacy of Banbury, while offering greater capacity and flexibility of location. Midwest and West Coast venues are now being considered for future meetings.



Some of the attendees of FRAXA’s Neurobiology of Fragile X Conference

NIMH FUNDS BANBURY MEETINGS

Over the past six years, FRAXA staff and Scientific Advisors have organized Fragile X conferences at Cold Spring Harbor’s Banbury Center on Long Island, New York. These small, focused meetings have brought new researchers to the Fragile X field and jump-started many fruitful collaborations.

Nobel Laureate Dr. James D. Watson, co-discoverer of the DNA double helix, first proposed these meetings and has been attending them ever since. The initial conference, in 2000, was hosted and funded by FRAXA, NIMH and NICHD; the next five meetings were fully funded by an NIMH grant with NICHD support.

Based on the extraordinary success of Banbury meetings, NIMH has renewed funding for annual meetings through 2010! The investigators on the grant, Bill Greenough of the University of Illinois, Elizabeth Berry-Kravis of RUSH University, and Katie Clapp of FRAXA, anticipate an extremely successful five years!

FRAXA RESEARCH FORUM

About 200 Fragile X investigators and FRAXA volunteers attended a Fragile X Symposium at the Society for Neuroscience annual meeting on the evening of November 15th, in Washington, DC.

This event was an excellent opportunity for investigators, post-doctoral fellows, and students to meet leaders in this field and learn about the latest advances in understanding Fragile X. It was sponsored by FRAXA and organized by Dr. Justin Fallon of Brown University. The speakers were:

Justin Fallon, Brown University
Kendal Broadie, Vanderbilt University
David Nelson, Baylor College of Medicine
Kimberly Huber, University of Texas at Southwestern.

FRAXA also host as booth at the meeting. For additional details visit the RESEARCH section of FRAXA.org.

Summer 2005 FRAXA Research Grants

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

Interaction between FMRP & PAK on Synaptic Morphology, Function & Animal Behavior

SUSUMU TONEGAWA, PhD

Principal Investigator

MANSUO HAYASHI, PhD

Postdoctoral Fellow

Picower Institute, Massachusetts Institute of Technology, \$40,000



Susumu Tonegawa and Mansuo Hayashi

Dr. Tonegawa, a Nobel laureate, is studying how the Fragile X protein normally regulates the shape and function of neurons; this will likely generate more targets for potential therapy.

by Mansuo Hayashi

Fragile X syndrome results from lack of a single protein, FMRP. Studies in mice and Fragile X patients have shown that FMRP regulates the shape and function of synapses – sites of cell-to-cell communication in the brain. Though little is known about how FMRP exerts these effects, we do know that it binds certain RNAs and can block translation of their encoded proteins, some of which are critical for the formation and maintenance of synapses.

To gain further insights into FMRP's function, we will identify new signaling pathways in the brain that regulate or interact with FMRP. Our hypothesis is that a protein known as PAK, a regulator of cytoskeleton and synaptic structure, may antagonize FMRP (e.g. by relieving FMRP-mediated translational repression) to regulate synaptic shape and function. We previously found that neurons in transgenic mice with reduced PAK activity have fewer dendritic spines and a lower proportion of long, thin spines, as compared to normal mice. In contrast, neurons in Fragile X knockout mice and Fragile X patients show more spines and a higher proportion of longer, thinner spines.

Our preliminary data indicate genetic and physical interactions between FMRP and PAK. We are investigating how FMRP and PAK affect each other's subcellular localization and activity. Since FMRP and PAK regulate protein synthesis and the cytoskeleton, respectively, this research may explain how FMRP and PAK coordinate these two cellular events in order to modulate synaptic shape and function. This will advance our understanding of the molecular mechanisms underlying Fragile X and may lead to identification of new drug targets and treatments for this disorder.

RESEARCH

Effect of Chronic mGluR Blockade on Surface Expression and Plasticity of AMPA Receptors in Fragile X KO Mice

MARK BEAR, PhD

Principal Investigator

NAVEEN NAGARAJAN, PhD

Postdoctoral Fellow

Picower Institute, Massachusetts Institute of Technology, \$41,000

The mGluR Theory of Fragile X was first proposed by Dr. Bear, Dr. Kimberly Huber, and colleagues in the year 2000. The theory states that symptoms of Fragile X arise from overactivity of one pathway that is critical for brain function:

the mGluR pathway. Drugs which dampen this pathway (mGluR5 antagonists) might treat many symptoms of Fragile X.

FRAXA has provided funding for Dr. Bear's work for the past five years, first at Brown University and now at MIT. Dr. Bear's group is now testing the long term effects of treating Fragile X cells with mGluR5 antagonists to see if this can normalize many of their properties.

"There is no greater thrill than the realization that one's basic research might, in the foreseeable future, provide new therapies, and possibly a cure, for Fragile X."

– Mark Bear



Imaging Aberrant Synaptic Structure & Function in an Animal Model of Fragile X

CARLOS PORTERA-CAILLIAU, MD, PhD

UCLA, \$60,000

Using cutting-edge microscopy, Dr. Portera-Cailliau will photograph live Fragile X neurons to see how they differ from normal brain cells.

by Carlos Porter-Cailliau



Carlos Portera-Cailliau

Brains of children with Fragile X and of mice that lack the FMR1 gene have abnormally long and densely packed dendritic spines. Spines are tiny protrusions on the surface of neurons. They receive most of the excitatory synaptic inputs in the brain and are therefore crucial for learning and memory.

During brain development, dendrites are covered by thinner, longer appendages known as filopodia which are

UPDATE

thought to develop into spines. Because spines in individuals with Fragile X appear immature, a failure in the transition from dendritic filopodia to spines has been invoked in this disorder. Yet, the development of dendritic filopodia in Fragile X mice during the first week of life has never been explored.

Recently, we showed that filopodia lengthen in response to glutamate (the most important chemical for transmitting signals between brain cells). This observation fits nicely with the notion that filopodia initiate synapse formation, because it implies that glutamate released by nearby axons may attract dendritic filopodia to form early synapses. These contacts can presumably stabilize filopodia and allow them to mature into spines.

We believe that the mechanism whereby filopodia make synapses is defective in Fragile X, and that an excess of protrusions is generated as a compensatory mechanism.

Interestingly, abnormal glutamate signaling, particularly through mGluRs, has been linked to Fragile X. The 'mGluR Theory' postulates that lack of FMRP leads to exaggerated mGluR-mediated silencing of brain synapses, which in turn leads to increased synapse turnover and abnormal spine morphology. But exactly how this takes place is not known. Keys to this puzzle might come from investigating glutamate-induced filopodial growth and synapse formation in Fragile X mice.

We want to test the hypothesis that a defect in filopodia, linked to abnormal glutamate transmission or actin dynamics, impairs their ability to form synapses and mature into spines in Fragile X.

We will use two-photon and electron microscopy to image filopodia in brain slices of Fragile X mice. We will test the effects of specific agonists and antagonists of mGluRs on filopodia of wild type and Fragile X mice. These experiments could provide new ideas about how the abnormalities in dendritic development in Fragile X come about and also identify novel molecular targets that can be exploited for developing treatments for Fragile X.

Add-On Pilot Trial of Lithium in Fragile X

ELIZABETH BERRY-KRAVIS, MD, PhD

RUSH University, \$35,000

STEVEN PORGES, PhD

Univ of Illinois at Chicago, \$30,000

by Elizabeth Berry-Kravis



Elizabeth Berry-Kravis

We are conducting a small clinical trial to look at the effects of lithium on behavior and thinking in Fragile X. Lithium partially blocks the mGluR pathway which is overactive in the Fragile X brain. Tom Jongens' group, partially funded by FRAXA, has shown that lithium can reverse learning problems in the Fragile X fruit fly, and there is data to suggest that it also reduces sound-induced seizures in the Fragile X knockout mouse (by Robert Bauchwitz, funded by FRAXA).

Fifteen subjects with Fragile X will be treated with lithium to get pilot data to justify a large placebo-controlled trial of the drug. Treatment will last for at least two months and up to a year if the lithium is helpful. Tests will be given at the beginning of the study, after two months, and after a year of treatment for those who are treated a full year. Side effects will be monitored closely to make sure that lithium is safe in the Fragile X population and that benefits of treatment are greater than risks.

For this trial, we will use a battery of behavioral and thinking tests which we are validating specifically for use in future medication trials in Fragile X. We will also pilot new physiological tests to measure overstimulation and eye aversion, new tests of associative learning, and a blood test that may serve as a biomarker for improvement in the cellular defect in Fragile X.

These new tests, in combination with some of the tests that worked best in our previous ampakine CX516 study funded by FRAXA, should measure whether lithium is improving some of the behaviors and learning deficits seen in Fragile X syndrome. If the new tests are successful, we can then use them for future studies.

Positive results with lithium treatment in this study will support the mGluR theory of Fragile X and will provide support for ongoing development and eventual clinical trials of other mGluR antagonists.

FRAXA RESEARCHERS AT JANELIA FARM

Howard Hughes Medical Institute, a nonprofit organization which funds medical research, will soon open a \$500 million research campus in Ashburn, Virginia. At Janelia Farm Research Campus, small research groups will explore fundamental biomedical questions in a collaborative, interdisciplinary culture.

Dr. Kevin Moses, FRAXA Scientific Advisor and grant recipient, will serve as Janelia Farm's Associate Director. Dr. Moses previously conducted *Drosophila* Fragile X research at Emory University. Dr. Moses and his wife, Carol, have a son affected with the syndrome. Also moving to Janelia Farm is Dr. Karel Svoboda, who currently holds a FRAXA grant to study brain circuitry in Fragile X mice at Cold Spring Harbor Laboratory. Dr. Svoboda will continue his fragile X investigations at Janelia Farm.

RESEARCH

Rescuing Synaptic Function in Fragile X with Mutant AMPA Receptors

ANIS CONTRACTOR, PhD, Principal Investigator

DIYA ZHANG, PhD, Postdoctoral Fellow

Northwestern University, \$55,000

In Fragile X mice (and presumably also in humans with Fragile X), there are fewer AMPA receptors at the surface of neurons, which means that those neurons cannot receive some signals from neighboring cells as efficiently as normal cells. AMPA receptors are the targets of the new generation of Ampakine drugs now being tested by another FRAXA grantee, Dr. Julie Lauterborn, at UC Irvine. Dr. Contractor aims to restore normal function to Fragile X mice by using specially engineered AMPA receptors which function at a higher-than-normal rate.

Analysis of Expression of Fmr1 Transcript Isoforms in Mouse Brain

DAVID R. MORRIS, PhD

Principal Investigator

DAVID BRACKETT, PhD

Postdoctoral Fellow

University of Washington, \$40,000



David Morris, David Brackett

The Fragile X protein (FMRP) contains functional domains that govern its movement within cells and its association with target mRNA molecules thought to be important for proper brain maturation.

Full-length FMRP is translated from only 1 of at least 12 related mRNA forms generated from the FMR1 gene. The additional 11 alternatively spliced *isoforms* all have the potential to synthesize additional protein products possessing altered, or missing, functional domains. Each one may have a unique role in neurons, yet little is known about them.

As a first step towards understanding the functions of all 12 products of the FMR1 gene, we will determine which of them actually produce functional proteins. We will then focus on those FMRP isoforms, quantifying where and when they occur in the brain. Finally, we will incorporate this information into existing models for the biology of the FMR1 gene and Fragile X syndrome.

Characterizing Phosphorylation as a Regulator of FMRP Translational Suppression in Response to mGluR Activity

STEPHEN WARREN, PhD, Principal Investigator

USHA NARAYAN, PhD, Postdoctoral Fellow

Emory University, \$40,000

Dr. Warren's lab is studying the mechanism by which the Fragile X protein regulates the production of other proteins in neurons.

The Role of the Cerebellum in the Dysfunction of Fragile X

BEN OOSTRA, PhD

CHRIS DE ZEEUW, MD, PhD

Principal Investigators

BAS KOEKKOEK, MD, PhD

Postdoctoral Fellow

Erasmus University, Rotterdam \$64,000



Ben Oostra

FRAXA has renewed funding for this project for a second year.

In the August 4, 2005 issue of *Neuron*, Ben Oostra, Chris De Zeeuw and colleagues reported that they have pinpointed a cause of motor learning problems in Fragile X patients.

They found that mice lacking the Fragile X gene (FMR1) have deficits in a motor learning task largely controlled by the cerebellum. In this "eyeblink conditioning" task, mice were taught to associate a tone with a puff of air on the eye. The speed of their blink response measures how well the animals learn the task.

The researchers found that mice completely lacking the FMR1 gene showed deficits in this task. Most importantly, mice lacking the FMR1 gene only in specific neurons, called Purkinje cells, in the cerebellum also showed the deficit. These cells showed abnormally enhanced LTD (weakening of the signaling connections between cells), which fits with the mGluR Theory of Fragile X.

When the researchers conducted similar eyeblink tests in Fragile X patients, they found the same severe deficits.

The team will now test Fragile X mice to see whether this learning deficit can be reversed by compounds that dampen mGluRs. They aim to identify a robust phenotype in Fragile X patients and develop a test that can be used in clinical trials of treatments for Fragile X.

Regulation of Group I Metabotropic Glutamate Receptor Trafficking in a Fragile X Animal Model

ANNA FRANCESCONI, PhD

Albert Einstein College of Medicine, \$40,000

Abnormalities in glutamate neurotransmission account for most symptoms of Fragile X. Dr. Francesconi and her colleagues are studying problems in how glutamate receptors get to the surface of nerve cells, where they need to be in order to transmit and receive signals to/from neighboring cells. The team will then attempt to control this process with therapeutic compounds using Fragile X mice.

UPDATE

Glutamate Receptors and Their Associated Postsynaptic Proteins in the *fmr1* Knockout Mouse

WALTER KAUFMANN, MD, PhD, Principal Investigator

DAVID LIEBERMAN, MD, PhD, Postdoctoral Fellow
Kennedy Krieger Institute, University of Maryland, \$60,000

Dr. Kaufmann and Dr. Lieberman are conducting experiments to better understand mGluR signaling in Fragile X mice. They are finding possible therapeutic drug targets downstream of mGluR which may be helpful in designing treatments for Fragile X. Some of these cell signaling pathways are being studied in other fields, such as oncology, and new drugs which target them are under development. We thank Wanda Wisner and the Jack Kent Cooke Foundation for supporting this work.

Composition and Dynamics of FMRP-Containing RNP Complexes

BARBARA BARDONI, PhD

CNRS, Nice (France), \$30,000

Many proteins in cells interact with the Fragile X protein. Dr. Bardoni is studying these proteins and may uncover new targets for drug discovery.

by Barbara Bardoni



Members of the Bardoni lab

FMRP is a RNA-binding protein containing at least three domains mediating its binding to RNA, and it appears to be involved in several steps of mRNA metabolism. It is probably a component of different complexes whose identification will help us to better understand FMRP function.

We will analyze FMRP-containing complexes in cultured cell lines and mouse brain, taking into consideration the composition and the dynamics of FMRP-containing complexes, the expression of FMRP-interacting proteins and, as a long term project, the expression level of mRNAs that are targets of FMRP.

We aim to elucidate the molecular structure of the FMRP/mRNA complex. In the last four years, many putative RNA targets for FMRP have been identified. However, so far, it has been reported that FMRP binds only two structures (G-quartet and kissing complex RNA) and one sequence. We will use a novel approach to identify sequence and/or structures that are recognized and bound by FMRP.

Transport, Anchoring, and Translation of FMRP-Associated mRNAs

VLADIMIR GELFAND, PhD, Principal Investigator

SHUO-CHIEN LING, PhD, Postdoctoral Fellow
Northwestern University, \$40,000

Protein synthesis at dendrites of neurons is one of the mechanisms contributing to learning and memory. For this to occur, mRNA has to be delivered from the nucleus to dendrites and anchored at the proper location. FMRP binds to some mRNAs and regulates their expression. How FMRP does this is not known.

We study transport mechanisms of FMRP and associated mRNAs. FMRP and mRNAs form granules that are transported into dendrites. We are investigating how this movement is regulated.

Once mRNA is delivered to dendrites, transport stops and the mRNAs can be translated into proteins. We are investigating how this transition occurs and how metabotropic glutamate receptor (mGluR) signaling influences and regulates this process.

Our goal is to understand the mechanisms of localization and translation of FMRP and related proteins, and how mGluR regulates this process. We believe that this will help to identify therapeutically useful targets.

Alterations in Neocortical Neuron Excitability Associated with Fragile X

CHARLES COX, PhD

University of Illinois, \$57,075

by Charles Cox



Brian Wilson, Govindaiah, Charles Cox

The single gene defect which cause Fragile X can produce many changes in the brain. The circuit activity of neuronal networks is ultimately influenced by the intrinsic excitability of individual neurons and their synaptic connectivity. We will use modern intracellular recording techniques to look for alterations in intrinsic properties or synaptic transmission in neurons in the neocortex -- a region of the brain not much studied in Fragile X. We will also investigate alterations in long-term potentiation (LTP), with an emphasis on mGluR (metabotropic glutamate receptor) mediated plasticity.

Differences in these properties of neurons could affect their ability to communicate with surrounding neurons, potentially providing explanations for some of the deficits associated with Fragile X.

RAISING FUNDS

Since our last newsletter, people everywhere have supported FRAXA. Many events celebrated National Fragile X Research Day, which was endorsed by Congress several years ago in response to FRAXA families.

Here are just a sampling of the fundraising events hosted by our families and friends. We are truly grateful to each and every person who has supported FRAXA. Together, we have raised enough money to support the projects described in this newsletter AND begin to stock the coffers for the upcoming round of projects. New proposals arrive on December 1st and we will need every dollar we can raise to support the best of them!

As this holiday season approaches, please consider fundraising for FRAXA. We can provide brochures, donation envelopes, articles, a video, a presentation, and sample letters to family, friends, or business contacts to help you raise funds for Fragile X.

Not Your Typical Lemonade Stand!

What did your eleven-year-old do this summer? While some may have been playing sports, reading books or just enjoying the break from school, Alex Mellor decided to make a difference for those affected by



Alex Mellor



Shirley Murray

Fragile X.

While visiting her father in Pennsylvania, Alex designed and posted flyers explaining Fragile X, collected donations from neighbors and shared her enthusiasm for finding a cure. Alex, granddaughter of Shirley Murray, has known Niklas Watkins since her grandmother began babysitting for him five years ago. Alex's passion is fueled by her grandmother and their entire family. Each year, the family plans a Fragile X fundraiser. They have organized a Pampered Chef fundraiser, a music festival, and have sold FRAXA "Cure Fragile X" wristbands at a family picnic. "It must be in their genes to make a difference in ours! Niklas is a lucky boy to have so many people who love him and work every day to make a difference for those affected by Fragile X," offers Niklas' mother.

Poker Run – North Carolina

The owner, staff and friends of Station's Inn Motorcycle Resort on North Carolina's Blue Ridge Parkway were proud to support FRAXA with their first annual Poker Run. They played 5 card stud: contestants rode their bikes from Station's Inn to bars in 3 other states and then back to Stations Inn, picking up a single card at each stop. The person with the best poker hand won! They raised over \$9000 for research and are already planning next year's run.



Poker Run – New York

Bob and Elaine Rogers of Adams, NY held a poker run, chicken barbeque and raised over \$5,000 for FRAXA! Over 100 motorcycle riders attended and enjoyed a barbeque and an auction. Bob and Elaine organized the event to honor their eight-year-old son, Dalton, who has Fragile X.

3rd Annual Gala a Knockout!



Dan Grimaldi, Ron & Amy Watkins and Gerry Cooney

Amy and Ron Watkins' 3rd annual Fragile X Gala drew 130 guests to The Links at Union Vale in New York. Guests enjoyed cocktails accompanied by the melodic sounds of the Dukes and Dutchess, followed by the extraordinary Michael Dell Orchestra. Dan Grimaldi, known as Patsy Parisi on the HBO hit series, The Sopranos, joined the event for the third year and the Watkins also welcomed former heavyweight boxer Gerry Cooney. It was a knockout combination, as shown by the excellent photography generously donated by Daniel Stockfield. A gallery of photographs can be seen at www.danstockfield.com/fraxa/. Dutchess County Sheriff, Adrian Anderson, presented the Watkins with a

\$3000 donation from The Ryan McElroy Foundation. At the silent auction, guests were seen out-bidding one another for fantastic items such as two front-row tickets to the Boston Red Sox donated by Harry Manion. The event raised \$40,000! The Watkins and everyone at FRAXA are grateful for the generosity and support of new and familiar friends. Without all of you, this would not be possible. Thank you! For an invitation to next year's event (tentatively scheduled for Friday, September 29th), please email Ron and Amy at fragilex@frontiernet.net.



Detective Kirk Imperati, Detective Chip McElroy, Gerry Cooney and Sheriff Adrian Anderson

FOR FRAGILE X

Fragile X Alliance of Ohio – 9th Annual Golf Benefit

New Fragile X Patient Program Announced at Successful Event!

On Monday, June 27th, the Fragile X Alliance of Ohio held their 9th Annual Golf Benefit at the famous Firestone Country Club, Home of the NEC Championships. Over 40 volunteers and 280 golfers enjoyed a spectacular sunny day. Golfers and dinner guests were in awe of the 200-item



Hadden & Shannon Atwood with Doug Dieken

Silent Auction with something for everyone, and former Cleveland Browns player and current broadcaster Doug Dieken entertained the crowd with his comedic Live Auction.

This year's program featured the announcement of a new Fragile X clinic at Akron Children's Hospital. Dr. Keith Powell, Chairman of Pediatrics, welcomed Fragile X Program Clinical Director, Dr. Carol Delahunty, and Dr. John DUBY, Director of Developmental and Behavioral Pediatrics, who thanked the Fragile X Alliance of Ohio for supporting and helping to create this new program. The clinic includes a developmental

pediatrician, behavioral psychologist, occupational therapist, speech therapist and other team members to assist Fragile X families with their specific needs.

Our marvelously energetic and resourceful 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!



Dr. John DUBY, Dr. Keith Powell, Dr. Carol Delahunty, Leslie and Ara Bagdasarian

With \$100,000 in proceeds from the golf benefit and a \$50,000 grant from First Data and Travelcenters of America, a total of \$150,000 was raised for FRAXA to support Fragile X research.

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



Pete and Jacob Boise help their mom, Julianne

Waxhaw Bash

During each of the past three summers, Heather and Philip Lopina of Waxhaw, North Carolina, have hosted a bash for FRAXA.



This year they raised \$2021 –

Patrick Rafferty, Phil Lopina (Fx Parent), Thomas Smith and Ryan Marcum

more than double last year's contribution. Kids enjoyed a moonbounce, dunk tank, and other fun games. Over 20 volunteers, all wearing Waxhaw Bash Staff shirts, made sure everyone had a great time. They are already planning for next year.

Marathon

Kari Espinosa and her 16-year-old son Josh successfully completed the Chicago Marathon on October 9. The Espinosa family raised over \$10,000 for FRAXA from their marathon sponsors. It was the eighth marathon for Kari and the first marathon for Josh.



Josh and Kari Espinosa

Bat Mitzvah

FRAXA thanks Michaella Gabrielle Katz of Blue Bell, Pennsylvania, who chose to raise awareness and funds for Fragile X for her Bat Mitzvah project. Michaella is a longtime friend of Matthew Hollin, son of FRAXA Board member Cristy Hollin and her husband, Mitchell.

Silverton/Allergan Benefit – Michigan

Nearly 80 patients signed up for the 3rd Annual Botox Benefit at the Silverton Skin Insitute in Grand Blanc, Michigan. Board certified dermatologist, Dr. Kimball Silverton joined forces with Allergan, the company that manufactures Botox, to provide Botox injections for a significantly reduced price, with all proceeds – more than \$12,000 – going toward Fragile X research. Dr. Silverton and his wife, Jennifer, have a 7-year-old son, Aidan, affected with Fragile X. Aidan has a younger sister, 5-year-old Camryn, who is unaffected. The fourth annual Botox Benefit will be held next Spring.



Aidan Silverton

FUNDS FOR FRAGILE X



Some of the members of the Greenough and Ceman labs who staffed the FRAXA Fall Fling table.

Krispy Kremes for FRAXA

At the University of Illinois at Urbana-Champaign, researchers in the laboratories of Dr. William Greenough and Dr. Stephanie Ceman took time out from their Fragile X studies to sell donuts and "Cure Fragile X" wristbands for FRAXA. Aaron Grossman, an MD-PhD student in Dr. Greenough's lab, organized this special event.



Sally Nantais, Trina Lengyel, Mary Beth Langan with their sons, Austin, Tyler and Andrew Langan

Fast Food Funds – Michigan

Sally Nantais in Michigan organized a benefit night at her local Burger King to raise funds for FRAXA and celebrate National Fragile X Research Day. The store manager did not have an "X" letter in stock for their lighted sign, so they improvised, using FRAXA's X magnet instead.



Evening for FRAXA – Kansas

Jodi Bjerke and her friends and family hosted an evening of dinner, deserts, silent auction, and lots of fun, raising almost \$3000. Jodi served goodies from her newly established family business, Heart 2 Heart Bakery.



Nolan Maloney

Irish Night – Ohio

The Maloney family hosted their 4th annual Irish Pub Night in Columbus with live Irish music, step dancers and karaoke. They raised over \$10,000 through donations and raffles and had a grand time doing it. Several other Fragile X families attended and hun-

dreds of people learned about Fragile X. Says Judith Maloney, "We can't wait to see if we can top \$10,000 next year!"

Denver Concert

Marie Powell and Laura Ayres organized their second benefit concert featuring a wonderful performance by John Adams and Friends. More than 200 guests enjoyed the concert in Denver's historic Trinity United Methodist Church. Thanks to the Powell and Grant families, the Ayres family, Kelly Wilson and all the other people who helped and contributed, the concert raised over \$15,000!



John Adams. Photo by Ceci Grant

Voices for Fragile X – Virginia

The Fragile X Resource Group of Virginia hosted a "Voices for Fragile X" concert on September 23rd in Charlottesville, VA. Six a cappella groups performed for an audience of 300 people, raising over \$4,000 for Fragile X.

Unlock the Mystery – California

FRAXA's Orange County Chapter held its second annual gala, "Fragile X: Unlock the Mystery," at the Balboa Bay Club in Newport Beach. The event drew local Newport residents, real estate professionals, UC Irvine doctors, researchers and loyal supporters.



Mary Higgins Clark with Juliet and Elisabeth Shelly

FRAXA was happy to see last year's key sponsors return again this year: Volvo Motorcars of North America, Shelly Group, Staubach Retail and Majestic Realty. Table favors were generously provided by David Yurman, who also sponsored a kick-off party for FRAXA. THANK YOU to our supporters!

Guests were warmly welcomed by children handing out teal awareness ribbons. They enjoyed mystery martinis, the smooth piano chords of Vince Torbey, and a



Dr. Oswald Steward, FRAXA Scientific Advisor

dozen select live auction items artfully presented by Tailored Baskets. Items included: fabulous get-away trips, unique sports experiences, beautiful jewelry, bags and clothes, and the highlight - a sleek turbo-charged Volvo S60 sedan, with bow atop.

Once seated, guests were treated to a surprise performance by aerialist Dreyja Weber, followed by an introduction by Andrea Shelly, Head of the Orange County Chapter of FRAXA, and an update on FRAXA research by Dr. Oswald Steward of UC/Irvine. The live auction alone raised \$140,000! Mary Higgins Clark, famous mystery novelist and longtime FRAXA supporter, wrapped up the evening with a heart-felt talk about her grandson, David, who has Fragile X.



Around the Volvo from back left: Teri Koosed, Lici Denning, Andrea Shelly, Katie Clapp, Mary Higgins Clark

FRAXA was excited to net close to \$200,000, of which 95% will be channeled directly into exciting new and existing research. FRAXA looks forward to the Orange County Chapter's third annual fundraiser in 2006!

how you can help us find a cure

Online Donations

Visit www.FRAXA.org and click on Donate to give using your credit card or PayPal. You can make a one-time contribution or give the amount of your choice automatically each month.

Holiday Campaigns

This holiday season, write a letter to family and friends requesting donations to FRAXA in lieu of gifts. We will be happy to send you brochures and sample letters.

Events

Hosting an event is a lot of work but it is extremely satisfying work! We will provide step-by-step directions, support, and materials to help you along the way.

Phone, Fax or Snail Mail

Send your check payable to FRAXA or your credit card information using the enclosed donation envelope, or give us a call or fax. We accept Visa, Mastercard, AMEX and Discover cards.

Gifts of Stock

Support FRAXA and realize tax benefits by donating stock that has increased in value. Call or email FRAXA for stock transfer details.

United Way and CFC

FRAXA is charity #0220 in the Combined Federal Campaign (CFC), the giving campaign of the federal government. United Way donors can ask for a Donor Designation form and write in "FRAXA Research Foundation, Newburyport, MA."

Gift Shopping

FRAXA has a selection of fun gifts to spread awareness of Fragile X. Give something meaningful this holiday season. Support research and raise awareness at the same time.

You can shop by phone, fax, mail, or online. Shop online at www.FRAXA.org (click "Shopping"). Email info@fraxa.org or call us at (978) 462-1866. Order by December 1st to guarantee delivery by Christmas. (but we will do our best to help you if it is after that). Here are a few FRAXA gift ideas. For a complete list, call us or visit FRAXA.org.

Charm bracelet



FRAXA's signature bracelet has gold-plated "X" charm flanked by two teal stones in squarecut gold settings. The stainless steel links can be swapped out with additional charms which are available in stores. \$29



Fragile X Awareness Magnets

These magnets are shaped like FRAXA's "X" and say "Cure Fragile X" and "www.FRAXA.org." They look great on vehicles and are very effective for raising awareness of Fragile X. 6x8 inches. \$3 each



Fragile X Awareness Bands

These silicone rubber wristbands say "Cure Fragile X" and "www.FRAXA.org." A favorite with teens and kids! \$2 each



DVD - First Down Towards a Cure

This 11-minute video is an emotional look at Fragile X, FRAXA, and current efforts to find a cure starring writer Mary Higgins Clark, Nobel Laureates James D. Watson and Eric Kandel, football star Jake Porter, and others. Produced by Debbie Stevenson. \$8

Call for Participants

This project is designed to help understand what symptoms are present in young girls to prompt medical personnel to suspect a diagnosis of Fragile X syndrome. I am currently recruiting parents of girls with diagnosed Fragile X syndrome to participate in a survey.

This survey will take 15-20 minutes to complete. The survey will ask questions about your daughter's physical, behavioral and cognitive symptoms that were apparent to you before the diagnosis of Fragile X was made. Complete confidentiality will be maintained.

For additional information or to participate, please contact Terri Greenfield, Principal Investigator of this project, at tagpt@aol.com or 516-922-1519. There are no significant risks involved with participation, nor any direct medical benefits. Minor risks include finding some of the questions too personal or upsetting.

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

FRAXA offers fellowships and grants to encourage research aimed at finding effective specific treatments and an 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)

See www.fraxa.org for details.

FRAXA UPDATE

EDITOR: Katie Clapp, MS

CONTRIBUTING EDITOR: Susan Cohen

CONTRIBUTORS: Mary Beth and David Busby
FRAXA Fall Flingers
Research Grantees
Michael Tranfaglia, MD

DESIGN: Mary Lou Supple

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This newsletter is published regularly and sent to all supporters of FRAXA Research Foundation.

SAVE THE DATE!

May 11, 2006

Celebrate May 11th, 2006 with FRAXA by attending one of our two spectacular spring galas:

East of the Mississippi, Michele and Jim Cox will host FRAXA's black-tie "X" Ball 2006 in Pittsburgh, Pennsylvania. Dance to the tunes of Nova Era, a band direct from Disney which performs classical with groove.



West of the Mississippi, the Nebraska Families Association will host a gala with special guest, meteorologist Jim Cantore of The Weather Channel. Jim has two children affected with Fragile X; we are very happy to welcome him on board!

PLEASE HELP

FRAXA

FRAGILE X RESEARCH FOUNDATION

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

FRAXA

FRAGILE X RESEARCH FOUNDATION

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FRAXA UPDATE

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"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

Major Research Initiative Announced

On May 12th, four foundations and the governments of three countries entered into a public/private partnership to sponsor a unique research program. This program, "The Shared Neurobiology of Fragile X and Autism," will advance studies aimed at understanding and identifying treatments for Fragile X and autism, including autism spectrum disorders such as Rett Syndrome.

This public/private partnership may be the first of its kind. The sponsors are:

1. National Institute of Mental Health (NIMH)
2. National Institute for Neurological Disorders and Stroke (NINDS)
3. National Institute of Child Health & Human Development (NICHD)
4. Canadian Institutes of Health Research (CIHR)
5. Health Research Board, Ireland (HRB)
6. FRAXA Research Foundation (FRAXA)
7. Cure Autism Now (CAN)
8. National Alliance for Autism Research (NAAR)
9. Autism Speaks



Dr. Thomas Insel

Researchers around the world are invited to submit proposals for funding to NIH; all 9 partners intend to fund projects.

The idea for this program first emerged at a 2003 meeting of FRAXA representatives and Fragile X researchers with NIMH Director, Dr. Tom Insel, and members of his staff.

"I see you've brought the Dream Team of Fragile X," said Dr. Insel, referring to the scientists present: Mark Bear of MIT, Bill Greenough of the University of Illinois, and Steve Warren of Emory. The team decided to convene a workshop in Newport, Rhode Island, sponsored by NIMH, NINDS, NICHD, and FRAXA, to bring Fragile X and autism

continued on p.2

Raising Funds for Fragile X

More than 1000 people welcomed spring by hosting or attending a FRAXA event to raise funds for research and raise awareness of Fragile X. We are thrilled with the results on both counts. Stories and pictures begin on page 7.

Also in this issue:

- Banbury Meeting Report
- Clinical Trial Report on CX516
- Fruit Fly Research Suggests Fragile X Treatment



Nobel Laureate Dr. James Watson and CNBC's Sue Herera at FRAXA's New York City Gala

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.

Program Announcement

continued from p.1

experts together to identify the most promising avenues of research, which then formed the basis of this program announcement.

Applicants will apply to NIH on three deadlines each year between now and July 2008; NIH will fund what they can and distribute “near-misses” to the partners. With all 9 partners funding projects, this initiative will have a major impact!

We thank Dr. Story Landis, Director of NINDS, Dr. Duane Alexander, Director of NICHD, and Dr. Tom Insel, Director of NIMH, for supporting this initiative along with their staff at NIH who helped develop it, particularly Drs. Laura Mamounas and Alice Kau. We applaud Dr. Andy



Dr. Steven Moldin

Shih of NAAR, Dr. Sophia Colamarino of Cure Autism Now, Alison Singer of Autism Speaks, Astrid Eberhart, Dr. Roderick R. McInnes, and Dr. Remi Quirion of the Canadian Institutes of Health Research, and Drs. Mairead O’Driscoll and Ruth Barrington of the Health Research Board of Ireland for joining.

Credit for this initiative is due most of all to Dr. Steven Moldin, Director of Human Genetics and Genomic Resources at NIMH, who first suggested this initiative and led this effort from start to finish. Thank you, Steve!

SHARED NEUROBIOLOGY OF FRAGILE X SYNDROME AND AUTISM

(Adapted from the official Program Announcement, available on the web at <http://grants.nih.gov/grants/guide/pa-files/PA-05-108.html>)

This Program Announcement is aimed at characterizing, understanding and treating etiological and pathophysiological mechanisms common to both Fragile X syndrome and autism, including autism spectrum disorders such as Rett syndrome.

Between 2.5% and 6% of individuals with autistic features have Fragile X, and 15% to 25% of children with Fragile X have autism. An additional 50% to 90% of children with Fragile X exhibit some autistic features, including poor eye contact, hand flapping, hand biting, speech perseveration and other language problems, as well as tactile defensiveness, mental retardation, developmental delay, sensory hyperarousal, and social anxiety.

Researchers have argued that autistic features in Fragile X reflect a common pathway underlying the two conditions. Ongoing neuroscience research on Fragile X in model systems like mice and flies are providing a wealth of information at multiple levels – subcellular, cellular, and intercellular networks or circuits – to define the neurobiology of this disorder. These studies should help to identify novel targets for new drugs to treat both disorders.

Applications submitted in response to this Announcement should focus on understanding neural pathways, circuits, systems and molecules that play a role in Fragile X and may be implicated in autism and autism spectrum disorders such as Rett syndrome. Studies aimed at identifying targets for new therapeutic drugs to treat Fragile X and autism are encouraged.

Special Issue Targets Fragile X

This summer, a special issue of the scientific journal *Genes, Brain, and Behavior* will focus exclusively on Fragile X. Edited by Steven Moldin, the issue contains five articles which highlight critical discoveries that have made Fragile X one of the hottest topics in all of neuroscience. Abstracts for a general audience are available at www.FRAXA.org.

Authors of the articles are: Jennifer and Robert Darnell and colleagues at Rockefeller University, Gary Bassell and colleagues at Albert Einstein, Mark Bear and Gul Dolen at MIT, Peter Vanderklish and Nobel Laureate Gerald Edelman at Scripps Research Institute, and Daniela Zarnescu and colleagues at Emory. All of these research groups have received major funding from FRAXA.

“We are truly at a watershed in FXS research,” notes Steve Moldin in his editorial. “Symptomatic commonalities among FXS and other pervasive developmental disorders like autism and Rett syndrome may reflect an overlap in underlying neural circuits and pathways, and hence shared pathophysiologic mechanisms. This raises the intriguing possibility that new therapeutics developed to treat FXS also may have efficacy in treating aspects of autism and Rett syndrome. And herein lies the promise of a truly successful roadmap for translational research, in which converging basic research in molecular, cellular and genomic neuroscience across multiple model systems leads us in the direction of new therapeutics for complex human diseases.”

Banbury: 2005

Initiated by FRAXA six years ago, the annual Fragile X research meeting was held in February at the Banbury Center, Cold Spring Harbor Laboratory, New York. This year's topic, "Translational approaches to Fragile X: turning basic research findings into therapeutic targets," was perhaps the most stimulating yet.



Stephen Porges, Fabrizio Gasparini

The 36 participants presented their work on topics ranging from fruit flies to mice to human trials. Dr. Tom Jongens described success using lithium and MPEP (an mGluR5 antagonist) to treat Fragile X symptoms

in fruit flies two days before his paper was published (see story on p. 4). Dr. Elizabeth Berry-Kravis reported preliminary results of her Ampakine CX516 clinical trial which, unfortunately did not indicate significant therapeutic effects in the cognitive domains that have been analyzed to date (see p. 5). Dr. Julie Lauterborn presented promising results in Fragile X mice using an advanced Ampakine which is still in development. Several investigators presented data supporting the mGluR theory of Fragile X, first presented by Mark Bear at the 2003 Banbury meeting. By the close of the meeting, it was clear that tremendous progress had been made since the previous year.

The small size and marvelous remote location of these meetings stimulates intense discussion of the latest unpublished research from early morning until late at night. We are grateful to the National Institute of Mental Health (NIMH) which, with additional support from NICHD and FRAXA, funded the last six annual meetings.

Over the past six years, FRAXA's Banbury meetings have attracted 39 newcomers to Fragile X research. Each year, five to ten scientists in related fields were invited to Banbury and, in the months following the meeting, became at least part-time Fragile X researchers.

During this time at least 9 major discoveries were first presented at a Banbury meeting before being published, allowing scientists to bounce ideas off their colleagues and establish collaborations to jumpstart further research.

Here's a sampling of the feedback from this year's meeting: "This was the best, most informative, and most collaborative meeting I have been to in the past year." "The



Breaktime at Banbury: Eric Klann (standing), Elizabeth Berry-Kravis (at laptop), Stephen Warren, David Nelson, Miklos Toth (sipping coffee), Katie Clapp



Ivan Jeanne Weiler, Julie Lauterborn



Jennifer Darnell and Kim Huber

Banbury Conference has been the most important meeting for my research on Fragile X ... it is truly a unique venue that brings together a very diverse group of scientists focused on a common goal of curing Fragile X." "For me, that meeting is simply great. Being new to the field, the mix of human and model is perfect for me to learn about the problem."

The combined expertise and discussion of the participants helps us identify priorities for the coming year, shaping the field and guiding FRAXA's research funding decisions.



Richard Paylor and Eric Klann

New Discoveries Come to Light

As this newsletter goes to print, dozens of research proposals are being reviewed by FRAXA scientific advisors and additional peer reviewers who have generously volunteered their time and expertise. The next issue of this newsletter will feature newly funded projects.

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.

In the last few months, more than 50 new Fragile X studies have been published in the scientific press. The pace of research discoveries continues to accelerate. Here is a very exciting example.

Potential Treatment for Fragile X Demonstrated in Fruit Flies

TOM JONGENS, University of Pennsylvania

SEAN MCBRIDE, Albert Einstein University

CATHERINE CHOI, Drexel University



Tom Jongens

When FRAXA funds basic research, it is always with the hope that discoveries made will ultimately translate into effective treatments to help people with Fragile X. Now, work that FRAXA began supporting in 2002 is bearing fruit.



Sean McBride

In a fruit fly model of Fragile X syndrome, Dr. Tom Jongens, from the University of Pennsylvania School of Medicine, and colleagues have shown that it is possible to reverse some of the core features of the disorder using drugs that reduce the overactivity of specific

neuronal receptors known as mGluR5. The findings appeared in the March 3, 2005 issue of *Neuron* and were also featured in the April 11th issue of *Newsweek Magazine*.

Characteristics of Fragile X include deficits in certain types of short-term memory, autistic behaviors, sleep problems, hyperactivity, attention deficits, and susceptibility to seizures. In humans, Fragile X is caused by a defect in the FMR1 gene which renders it unable to make its protein product, FMRP, which is involved in neuron-to-neuron communication.

Dr. Jongens and his colleagues, Sean McBride from Albert Einstein College of Medicine and Catherine Choi from Drexel University College of Medicine, study the fruit fly model for Fragile X. This fly has been genetically engineered



Catherine Choi

so that it lacks a gene, dFMR1, which is the fly version of the human Fragile X gene and two other closely related human genes. The mutant flies show many physical and behavioral characteristics similar to symptoms displayed by Fragile X patients, including structural defects in certain neurons, enlarged testes, failure to maintain proper day/night activity patterns; attention deficits and hyperactivity, and defects in behavior-dependent memory.

A mouse model of Fragile X also shows symptoms like those of Fragile X patients. Both mouse and human studies suggest that Fragile X patients have abnormally increased activity in the metabotropic glutamate receptor (mGluR), which is located on the surface of neurons, including in the hippocampus – the memory and learning center in the brain. This increased activity compromises cell-to-cell communication for memory-associated functions.

Jongens and colleagues designed studies to test whether mGluR overactivity is at the root of Fragile X characteristics in flies. The team tested drugs that block mGluR's activity to see if the drugs could rescue any of the observed behavioral and memory defects observed in the fly model.

“What we found was very striking,” says Jongens. The drug treatments restored memory-dependent courtship behavior in mutant flies and reversed some of the neuronal structural defects. The group used lithium because it is known to have activities analogous to blocking mGluR activity, and it is already an FDA-approved drug used to treat other ailments in humans such as bipolar disorder. They also used MPEP, a compound which specifically dampens mGluR5 activity.

“The big take-home message from our work is that maintaining proper regulation of mGluR signaling is a conserved function of the dFMR1 and FMR proteins and that loss of dFMR1 function in flies leads to at least a subset of the cognitive and behavioral defects observed in the fly model,” says Jongens. “These results provide a potential route by which symptoms of Fragile X patients may be ameliorated.”

This work was funded by FRAXA and is currently being supported by the National Institutes of Health (NINDS).



Clinical Trial Report

ELIZABETH BERRY-KRAVIS, MD, PHD, Rush University

A total of 57 adults with Fragile X completed a clinical trial of a new compound, Ampakine CX516. Dr. Elizabeth Berry-Kravis enrolled 50 adults at Rush University in Chicago, and all but one completed the study; in addition, 8 adults with Fragile X completed the same protocol at the UC Davis M.I.N.D. Institute under the direction of Dr. Randi Hagerman. All participants took either the drug or placebo (sugar pills) for four weeks. The study was “double blind” which means that neither the participants nor the doctors knew which people were on drug and which were not. The RUSH study was funded by FRAXA and the drug was contributed by Cortex Pharmaceuticals.

Dr. Berry-Kravis and her team are currently analyzing the massive amount of data collected during the course of the study. It does not appear that the drug had a significant effect on thinking skills in Fragile X participants. Behavioral information is still being analyzed.

What does this mean for the future of ampakines as treatments for Fragile X? The compound used in this trial, CX516, has been demonstrated to be remarkably safe but not potent. In fact, the dose of CX516 might have to be as much as four times higher to see good effects on cognitive skills. Because the drug was safe and did not cause side effects like seizures, future trials with more potent ampakines more likely to provide cognitive benefit can be considered. Potent new ampakines are currently being tested in the mouse model of Fragile X by Dr. Julie Lauterborn, with FRAXA funding (for details, visit FRAXA.org). The outcome of this and other studies will help determine whether stronger ampakines may be effective in treating Fragile X.

We thank everyone who participated in this study. Although the drug did not show therapeutic effects on participants with Fragile X, the team has obtained valuable information regarding how best to test individuals with Fragile X in a medication study. This new knowledge has already helped immensely in designing an upcoming medication study using a different drug.

Report from Washington: Conference

by Mary Beth Busby, FRAXA

A fascinating diversion from fundraising and the Washington gala this spring was the NICHD conference on “Reproduction and the Fragile X Premutation.” Dr. Larry Nelson, an NICHD researcher who studies reproduction, has become interested in the fact that many women with the premutation for Fragile X have experienced Premature Ovarian Failure (POF). This two-day meeting was attended by an impressive group of medical professionals and researchers. I was delighted to see Drs. Duane Alexander, Owen Rennert, James Hanson, and Mary Lou Oster-Granite, all from NICHD, Dr. Steve Moldin from NIMH, Dr. Karen Usdin from NIDDK, and long-time FRAXA friends, Drs. Steve Warren, Randi and Paul Hagerman, Stephanie Sherman, and Charles Schwartz – all of whom were there wearing their POF hats.

I came away from the conference realizing how important it is for carriers of the premutation, both men and women, to know about their carrier status, as it affects many reproductive decisions and can play a major role in later life when symptoms of FXTAS (Fragile X-Associated Tremor/Ataxia Syndrome) can appear.

Several recommendations for the NICHD came out of the conference: 1) to sponsor a consensus development conference to establish clinical definitions and make recommendations for testing for the premutation; 2) to coordinate all research in this area, and 3) to stimulate research into the molecular mechanisms by which the FMR1 premutation impairs ovarian function.

The conference agenda and report including recommendations and future plans for additional research are available at FRAXA.org (Research Meetings section) or call FRAXA for a copy.

RESEARCHERS' CORNER

Now Available: Knockout Mice

FMR1 knockout mice on a C57 background are available from Neuromice; see www.Neuromice.org for details.

Fragile X Research Forum

FRAXA will host a symposium at the Society for Neuroscience annual meeting on the evening of November 15th, in Washington, DC. Justin Fallon of Brown University is organizing this meeting; speakers include Drs. Justin Fallon, Kimberly Huber of the University of Texas Southwestern, and David Nelson of Baylor College of Medicine. All participants attending the annual meeting are invited, and there may be room for additional guests. Please contact Katie Clapp at FRAXA if you are interested in attending.

For additional Research Resources please visit www.FRAXA.org.

FAMILIES HELPING RESEARCHERS

FRAXA Listserv Serves Families and Researchers

Hundreds of families know the FRAXA Listserv as their virtual community devoted to supporting one another in all aspects of caring for children and adults affected by Fragile X. For 10 years, the listserv has provided a free forum for people from all over the world to gather, support, and educate each other. On occasion, families who participate in listserv discussions also help advance research by sharing their considerable experience with “real life” Fragile X. Recently a scientist posted this update:

Hello to all the members of the listserv,

My name is Ted Price, and I am a NIH NRSA (National Research Service Award) postdoctoral fellow at McGill



Ted and Rubria Price. Rubria, a nurse, is also interested in Fragile X.

University in Montreal, Canada. My work thus far has been centered on how pain is felt and how the proteins underlying pain sensation are expressed and transported within sensory neurons. I have worked primarily with a

protein, Staufen, which interacts with the Fragile X mental retardation protein (FMRP) in central nervous system neurons. FMRP is the protein that is lost in Fragile X.

FMRP acts as an RNA binding and shuttling protein, and it represses translation of mRNAs into proteins at synapses. To my knowledge, Fragile X is the only genetic disease that involves the loss of a protein involved in RNA transport and synaptic translation. For this reason, Fragile X and FMRP knockout mice (the animal model of the disease) offer me the unique opportunity to test some of my theories of RNA transport in sensory neurons and how this influences pain.

My work with the transport process and pain led me to wonder about how individuals with Fragile X experience pain. Though I had read through the Fragile X literature, I had never seen anything directly related to pain. It seemed to me there should be some connection, so I contacted Katie Clapp at FRAXA to see what she knew about pain in people with Fragile X. Katie offered to post the question to FRAXA's listserv to ask the “real” experts ... parents and caregivers!

I received over 60 response from listserv participants and am now thoroughly convinced that there is something going on with Fragile X and pain. Of the responders, 82% said their child had a high pain tolerance. Many noted that cuts and bruises, ear or throat infections, high or low noxious temperatures and even burns did not seem to phase their children/brothers/sisters. Many also noted that individuals with Fragile X did not seem to react to infections with pain and that they seemed to be insensitive to the hyperalgesic type response most of us have after an injury.

I cannot begin to tell you how valuable those responses have been. Based on the information shared, it is now my plan to test some of my theories in animal models of inflammatory pain (using FMRP knockout mice) and in normal pain responses. It will be interesting to see if these mice have different behavioral responses and/or if their protein levels are altered. Fragile X and the FMRP knockout mice offer a unique opportunity to test some of our ideas.

How can this work help advance Fragile X research? It may not seem, on the surface, that anything I hope to do will directly impact potential treatments for Fragile X. This may be true but I am a firm believer that seemingly disconnected pieces of information are often sources of breakthroughs.

There are many similarities between learning and memory in the central nervous system and pain in the spinal cord. What people who study the brain call “long-term potentiation” we call “central sensitization,” and they are very similar processes. Both rely heavily on mGluR5 receptors, which appear to be pivotal in Fragile X, so it is likely that research in one area can inform the other.

Moreover, several respondents mentioned that infections can become serious in individuals with Fragile X before treatment is given because the individuals frequently don't report pain. If this is true in animal models of the disease, it would be possible to come up with pharmacological approaches to increase pain awareness and/or improve awareness of this issue in clinicians who treat patients with Fragile X.

I am new to Fragile X, but am very excited about becoming involved and about the possibilities that the future holds. I regularly attend Society for Neuroscience conferences (where I understand FRAXA hosts a booth and a Research Forum) and I look forward to meeting some of you there!

Theodore J. Price, Ph.D.

Department of Anesthesia, McGill University

Since writing this, Dr. Price has persuaded the other members of his laboratory to initiate a Fragile X research project; they are currently hard at work and making good progress.

To join the listserv, visit www.FRAXA.org and choose the Get Involved section. Everyone is welcome; the listserv is free of charge. You can join or leave at any time.

RAISING FUNDS & AWARENESS

Over the past several months, people supported FRAXA on many special occasions. Together, everyone who participated has raised enough funds to enable FRAXA to support between 10 and 15 research teams at universities around the world next month!

Here are few of the creative ways in which people have raised funds. If you would like to make your next special occasion REALLY special, consider fundraising for FRAXA. We can provide brochures, donation envelopes, articles, a short video, or a presentation to help you spread the word about Fragile X.

An Xtra Special Day in Ohio

Cincinnati area families organized a day of festivities for all ages, with face painting, puppet shows, music, dancing, and silent auction. Over 250 children and adults enjoyed a wonderful afternoon while raising \$25,000 for FRAXA research. This is the second event organized by a hard-working, motivated team of families: Jeff and Dawn Clark, Joe Carolin and Amy Heisel, Jeff and Nikki Wolfram, Barry and Wendy Rollinger, Jim and Kelly Broxterman, and Darren and Melissa Courtney.



Christopher Courtney



Back row: Melissa Courtney, Amy Heisel, Dawn Clark, Kelly Broxterman. Front row: Wendy Rollinger and Nikki Wolfram



The kids danced all afternoon

Elizabeth's Birthday

Kerry Huffman of Minneapolis/St. Paul, MN wrote:

My cousin Elizabeth turned 6 years old on May 5 and had a birthday party with 27 little boys and girls. In lieu of presents, she asked



Elizabeth on her 6th Birthday

her guests for donations for FRAXA. You see, my son Zachary (4), my niece Alyssa (4) and nephew Tyler (7) have Fragile X. Elizabeth never knew this until her mom, Cassie, explained it to her and asked her if she would be willing to forego presents and to receive money instead so researchers can try and help her three cousins.

Elizabeth turned to her mom and said: "If I had known about this before, I would have done this for all of my birthdays." Such a strong statement from such a little girl! Elizabeth raised over \$250!

Oldies Dinner Dance

Fran and Neil Gibb hosted their second Oldies Dance in Fishkill, NY, raising over \$5000. Fran reported that after the fundraiser, her local WalMart store called to ask her to submit a matching grant request. A week later, WalMart sent a check for \$1000. If you are planning a fundraiser, consider contacting your local WalMart store for a grant and, if needed, volunteers to help you with your event.

Wedding Gifts

Congratulations to Amy and James Kahn of Colorado on the occasion of their wedding. Mr. and Mrs. Kahn requested contributions to FRAXA in lieu of wedding gifts to honor their nephew, Avery Louis Smith Kahn.

Art Show in Brooklyn

Susan Cohen and Anita Inz hosted an art exhibit and sale called *Spectrum*, which featured the work of 37 artists-including two young men with Fragile X. There was local press coverage and a proclamation sent by the Borough

President's office. Proceeds will go to FRAXA, NFXF and the Fragile X Clinic at IBR on Staten Island.

Bar Mitzvah

Ben Stillerman of Palo Alto, CA, chose to make an impact while celebrating his Bar Mitzvah. Ben donated almost \$1000 to FRAXA in honor of his 6-year-old cousin,



Ben Stillerman

Luke Solotaroff, who has Fragile X. At his Bar Mitzvah, Ben gave a speech about Luke and Fragile X that brought half the invitees to tears – especially his aunt Elaine, Luke's mom!

Walk for Fragile X

Holly Roos of Canton, IL, wrote:

Over 200 walkers joined in our Walk for Fragile X, and we raised over \$8,000! The money will be

donated to FRAXA, NFXF, and UC Davis M.I.N.D. Institute, all for Fragile X research. We had beautiful, sunny weather and families came from all over the state of Illinois. When asked if we will do it again next year, my husband Scott replied, "only if there's not a cure yet." Next year our goal is to top \$10,000!



London Golf Tournament

Not all fundraisers are limited to the United States. Andrew Neill organized a tournament at his West London golf club to benefit FRAXA research. The event was a resounding success and Andrew has been invited to make it an annual event.

CALLING ALL HELPERS:

Spreading the Word . . .

Even though Fragile X was discovered more than two decades ago, few people are aware that Fragile X is:

- the most common inherited cause of mental impairment in the world
- the most common known cause of autism

We need your help to spread the word about Fragile X. FRAXA can provide you with help and materials. Not only is it much easier than it seems, it is very exciting and will make a big difference.

We are grateful to Deb Gillan and her son, Aaron, who gave a presentation at a Kiwanis Club meeting of over 600 teenagers in Central Illinois, in conjunction with a research grant Kiwanis awarded to Dr. Stephanie Ceman at the University of Illinois.

Nancy Pitcher of Yorktown Heights, NY, wrote:

Last month, my husband, Jeff, and I and gave a presentation on Fragile X for a group of local college students studying to be teachers. I can hardly put into words how successful it



Jeff, Nancy, Ryan (11, Fragile X) and Bradley (9, no FX) Pitcher

was! We spoke for over an hour, we showed FRAXA's video, "First Down Towards a Cure," and passed out brochures and newsletters. One woman cried during our talk when she realized what our children go through each day. Another stood up and offered to be a mother's helper for our boys. A man asked to come visit our son's special education class, and a woman asked if she could attend an upcoming Fragile X conference.

We plan to spread the word further and further ... The students took information home to show others because we left such an impression on them. The professor, a doctor, invited us to speak every semester and at her summer school classes.

If you can, check out colleges in your area and educate these future teachers. **Not one** of them had ever heard of Fragile X. They know now, and they want to learn even more. Feel free to contact me at npitch@bestweb.net or 914 962-5565 if I can help get you started.

Designer Clothing to Benefit FRAXA

Support Fragile X Research by donating your used, high-end clothing! Leslie Eddy, who opened a luxury designer consignment shop for women last year in Marblehead, MA, will donate a portion of sales to FRAXA. The clothing, handbags and accessories she is seeking must be less than two years old; brands include Chanel, Armani, BCBG, Theory, and Laundry. If anyone has these clothing items that they no longer wear, this is a great way to help raise money for research to help our kids. Clean up your wardrobe and bring funds to FRAXA. For additional information, please contact Leslie Eddy at lesliemartini@comcast.net or call 617-957-3099.

CALENDAR OF EVENTS

9th Annual Fragile X Golf Benefit, Firestone Country Club, Cleveland, OH, June 27
Contact Fragile X Alliance of Ohio, 440 519-1517, fraxohio@adelphia.net

Jet Pull – Tug of War, Sat., July 16th. Organized by Goodwill Industries of Southwestern Michigan to benefit Goodwill and FRAXA. Visit www.goodwillswmi.org

Dinner Dance, LaGrangeville, NY, Sept. 16. with Gerry Cooney, Dan Grimaldi of The Sopranos, and writer Mary Jane Clark.
Contact Ron and Amy Watkins, 845 226-6770 or fragilex@frontiernet.net

Concert, Denver, CO, October 7th, featuring John Adams and Friends (Celebrating the music of John Denver), with emcee, Denver TV newscaster Anna Alejo.
Call Laura Ayres at 720 841-5489.

Gala and Live Auction, Newport Beach, CA, October 12, with Mary Higgins Clark.
Contact Andrea Shelly, 949 466-4521, aashelly@aol.com

Celebrate National Fragile X Research Day, October 5th.
Host a FRAXA FALL FLING event anytime in the Fall. Contact Katie Clapp at FRAXA.

Call for Manuscripts – Fragile X Anthology

Flying Trout Press, a 501(c)(3) nonprofit literary organization, is seeking literary non-fiction (memoirs, creative essays, autobiographies, noteworthy personal experiences, interviews, biographies), poetry, art, and short fiction.

Submissions are welcome from anyone with experience on Fragile X from any angle. Deadline is August 30, 2005

Please contact Chuck Luckmann at

Flying Trout Press

P.O. Box 1256

Bellingham, WA 98227-1256

flyingtroutpress@comcast.net

Support Fragile X research and raise awareness at the same time!

You can shop online or by phone, fax, or mail. Checks and credit cards accepted. Order by phone at 978-462-1866, shop online at www.FRAXA.org, or circle the items you want on this page and fax to 978-463-9985 or send with check or credit card information to FRAXA. Please add 10% of total order to cover shipping.

Fragile X Awareness Wristbands

These teal wristbands say "Cure Fragile X" and "www.FRAXA.org." A favorite with teens and kids! 100% silicone rubber.

1-49 : \$2.50 each, 50 or more: \$2 each



Magnets

These teal magnets are shaped like FRAXA's "X" and say "Cure Fragile X" and "www.FRAXA.org." They look great on vehicles or your fridge and are very effective at raising awareness of Fragile X. 6x8 inches \$3



DVD – First Down Towards a Cure

This 11-minute video is an emotional look at Fragile X, FRAXA, and current efforts to find a cure, starring author Mary Higgins Clark, Nobel Laureates James D. Watson and Eric Kandel, football star Jake Porter, and others. \$8



FRAXA CD

One CD contains our video, First Down Towards a Cure (in MPEG format), a multimedia website about Fragile X, articles, FRAXA's newsletters and brochure. Also, the Medication Guide, Fragile X – A to Z, and other useful materials. All for only ... \$5



Fragile X Family Cookbook

This red, white and black spiral cookbook includes 154 recipes from families, researchers, politicians, and other extraordinary people from Australia to New Hampshire to New Mexico. Includes "Food for Thought" and "Fragile X Information" sections. \$13



Medication Guide for Fragile X

by Michael Tranfaglia, MD, Psychiatrist and Parent. Updated 2004, this is a detailed, thorough, and user-friendly guide to medications commonly prescribed to help manage symptoms of Fragile X. It will help parents understand the behavioral symptoms of Fragile X and how medications act on these symptoms. Reference pages rate each drug's effectiveness, safety, convenience, and cost. \$20

Fragile X – A to Z: A Guide for Families

This guide offers advice on daily challenges of living with a child or adult who has Fragile X. Anecdotes were provided by parents, grandparents, friends, and professionals who participate in FRAXA's Listserv, a free email support group for discussion of Fragile X. \$15

My Brother has Fragile X

Written by 8-year-old Charles Stieger about his brother who has Fragile X, this 23-page book with color photos is suitable for young children and for reading in an elementary school classroom to educate children about what it's like to have Fragile X. \$20



Educating Boys with Fragile X Syndrome

By Gail Spiridigliozzi, Ph.D., Duke University. This 20-page guide offers parents, teachers and therapists specific, helpful educational strategies. \$10

Fragile X Information Cards

These business size cards are perfect for handing to people who know nothing about Fragile X, in the grocery store or wherever else a quick explanation is needed. \$5 per 75 cards

FRAXA Knockout Mouse Tshirts

White 100% cotton with "Busby the Fragile X Knockout Mouse on the front and "FRAXA" on the back. Please select size: M, L, XL, and kids size 10-12 \$20



FRAXA Logo Tshirts

White heavyweight 100% cotton, FRAXA teal and black logo on left chest. Please select size: S, M, L, XL, XXL \$15



FRAXA "X" Lapel Pin

Sport FRAXA's gold-plated pin on jackets and sweaters. Push-pin, just under 1 inch square \$10



Charm Bracelet

from Zedora. FRAXA's signature bracelet has gold-plated "X" charm flanked by two blue topaz charms. Additional charms for this stainless steel bracelet are available in stores. \$50



"X" charm and blue topaz charms also sold separately. \$15

Playing Cards

Poker-size bright orange decks include a "Fragile X information" card. \$3



RAISING FUNDS

New York Gala

March 10 was a night to remember in New York City for nearly 500 guests who found their way to lower Manhattan for a dinner to benefit FRAXA.



Eileen Naughton

Debbie and Jeffrey Stevenson along with Eileen Naughton and Craig Chesley co-chaired the event at Capitale. The evening started with cocktails and a silent

auction, followed by dinner and dancing to Alex Donner's "New York Minute" band. CNBC's Business News Anchor, Sue Herera, was the eloquent and radiant host for the evening. The list of distinguished speakers included author Mary Higgins Clark, Jeffrey Stevenson, dinner co-chair and partner at Veronis Suhler Stevenson, Suzanne Wright, founder of Autism Speaks, Eileen Naughton, dinner co-chair and President of Time Magazine, and Nobel Prize Winner, Dr. James D. Watson, co-discoverer of the DNA double helix and a FRAXA Scientific Advisor. Thank you to all of the speakers for providing a vibrant and informative program.

Thanks to everyone who contributed, the event raised over \$600,000 for FRAXA research. This money is appreciated now more than ever as FRAXA moves into an extremely exciting, yet very expensive, world of drug development. Compounds now being tested in laboratory experiments are looking promising, and every single dollar moves us closer to having safe and effective drugs to treat Fragile X and possibly other related neurological disorders, such as autism. We are most grateful and thank you for your support!

*Debbie Stevenson
Chairman, FRAXA Research Foundation
Dinner Co-chair*



Wendy Belzburg, Jeffrey Stevenson



Ralph Ford and Heavyweight boxing great, Gerry Cooney



Jeffrey Stevenson, Larry Leighton



Suzanne Wright, Sue Herera, Debbie Stevenson



Sopranos star Dan Grimaldi, Sue Wilson



Mary Higgins Clark



Debbie Stevenson, Craig Chesley



Frank Anton viewing auction items



David F. Clark, dancing up a storm



Dr. Mike Tranfaglia, Katie Clapp, Shobha Swaminathan, Jay Rambhaskar

F O R F R A G I L E X

April Showers in Washington

At the peak of April showers which bring May flowers to Washington, FRAXA's supporters showered our researchers with more than \$175,000 for their search for a treatment and cure for Fragile X. Host Roger Mudd introduced Dr. Mark Bear, who gave the crowd of over 300 an exciting update on his mGluR5 research. Senator Chuck Hagel, FRAXA's Republican champion in the Senate every year since 1999 and the 2004 recipient of our "Beacon of Light Toward Research" award, presented this year's award to former Senator John Edwards, in recognition of his work as our Democratic champion. The Wall Street Journal mentioned Senator Edwards' attendance and participation.

Mary Higgins Clark gave us, as only she can, a sense of what it's like to be the grandmother of a wonderful young man with Fragile X. Her words touched the hearts of our guests from the research community, the NIH, HRSA, Congress, and the world of journalism, and inspired our families and friends to redouble our efforts to find a treatment and cure.

Our sincere thanks go to gala co-chairs Kitty de Chiara, Diane Rehm, and Mary Beth Busby. Kitty de Chiara and her husband, Enzo, had five tables of FRAXA supporters, all there in support of their son, Michael!



Dr. James Hanson, Dr. Elizabeth Thomson, Dr. Michele Puryear, Mark Puryear, Jill Shuger, Dr. Rodney Howell



Standing: Dr. Tom Insel, Al Sapienza, Carol Higgins Clark, David Clark, Marianne and Dr. Duane Alexander. Sitting: Katie Clapp, Mark Vershbow, Mary Higgins Clark, Patty Clark, Dr. Mark Bear



Kate and Jim Lehrer



*Standing: Ted Rebarber, Lisa Losty, James Rees
Sitting: Tim Losty, Maria Miller, Lisa Keegan, Kathy Madigan*



Standing: Donna Kaufmann, Dr. Walter Kaufmann, Judith Randall-Hines, Nick Kotz, Mary Lynn Kotz. Sitting: Wanda Wisner, George Wisner, William Ward, Dr. Karl Pribram, Katherine Neville



Standing: Jim McGlinchy, Dr. Don Bailey, Pam Bailey, Kathy May, John May, Joyce Margie, Dr. Robert Margie, Sitting: Joanne McGlinchy, Mary Jane Clark, Regina Hopper, Diane Hamsa



Senator John Edwards and Katie Clapp



Diane Jones, wife of General James L. Jones, and her son, Kevin Jones

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)

See www.fraxa.org for details.

FRAXA UPDATE

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Debbie Stevenson

and many others

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Raising Funds for Fragile X Research



Guest of Honor, Senator Chuck Hagel of Nebraska, former Senator John Edwards of North Carolina, and Master of Ceremonies, Roger Mudd at FRAXA's Mary Higgins Clark gala in Washington, DC.

PLEASE HELP

FRAXA

FRAGILE X RESEARCH FOUNDATION

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

FRAXA

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FRAXA UPDATE

SPRING 2005

VOLUME 12, NO. 1

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FRAXA RESEARCH
FOUNDATION

"NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

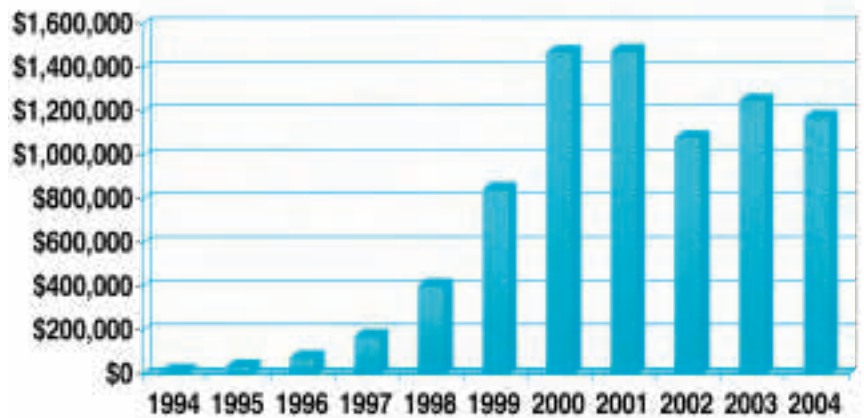
ever has."

— Margaret Mead

New Research Funded

FRAXA kicked off 2005 by funding 14 research teams, spending \$607,000 on research to cure and/or treat Fragile X. The new work, at universities in India, China, and across the US, addresses pivotal questions: Will mGluR antagonists prove to be effective treatments for Fragile X? Does Fragile X share a common molecular pathway with disorders like autism and Prader-Willi syndrome? If so, can Fragile X research lead to treatments for these other disorders?

FRAXA RESEARCH GRANTS Research Funded at Universities Around the World



See page 4 for new research reports.

Sention Teams up with Merck on Fragile X Drug

January 19, 2005 – Sention Inc. announced that it has entered into an exclusive licensing and research collaboration agreement with Merck & Co. to develop a family of Merck compounds known as mGluR5 antagonists as potential treatments for Fragile X.



Mark Bear

The use of metabotropic glutamate receptor (mGluR) antagonists for the treatment of mental retardation was first suggested by Mark Bear, Ph.D., one of Sention's founders. The agreement provides Sention with access to preclinical drug candidates discovered by Merck, the develop-

ment of which Sention is pursuing at its own expense with the intention of moving a candidate into clinical trials. The agreement also allows Sention to develop the drug for Down Syndrome and includes an option to develop the drug for Huntington's Disease.

"Abnormal mGluR signaling offers a clear molecular logic behind a diverse constellation of symptoms associated with Fragile X syndrome," said Dr. Bear, Professor of Neuroscience at MIT's Picower Center. "An exciting prospect is that some

continued on page 2

Also in this issue:

- Report from Washington
- 2004 Financial Report
- Meet FRAXA's Directors and Advisors

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 David and Mary Beth Busby

APRIL 11th GALA IN WASHINGTON

Join us at the 8th annual Mary Higgins Clark gala at the Four Seasons Hotel in Washington, DC. Diane Rehm, Kitty de Chiara have once again agreed to co-chair with Mary Beth, and Roger Mudd will be our host. Please contact Mary Beth Busby at 202-462-2323 or MBBBusby@aol.com.

Democrat counterpart, Tom Harkin, have been great bipartisan champions of Fragile X research.

The bad news is that we are told by all our friends on the Hill – and at the NIH and CDC – that their

budgets this year will be cut to the bone. That’s all the more reason to come to the April 11th Mary Higgins Clark Gala* at Washington’s Four Seasons Hotel. We need to provide as much private and public support as possible to increase FRAXA’s funding of “translational research”. That’s a new term we’ve learned. Oversimplified, it means converting “research” into “pills” for our children.

In any event, that’s the exciting next step for FRAXA. We’re working with Washington representatives of the entire Fragile X community to enlist Members of Congress in our march toward a cure!

But FRAXA’s privately funded research projects will continue to lead the way. So, “Y’all come!” to the Gala and the next morning’s breakfast at the Russell Senate Office Building.

*We’re delighted that Senator and Mrs. Lamar Alexander of Tennessee and Senator Chuck Hagel of Nebraska (FRAXA’s 2004 Research Beacon Award recipient) have accepted our invitation to the gala. We also expect other “notables”!

Good News and Bad News

The good news is that Senator Specter of Pennsylvania has decided to “stay put” as Chair of the Senate Appropriations Subcommittee on Labor, Health and Human Services and Education. This subcommittee decides on the programs and funding of the National Institutes of Health, the Centers For Disease Control, and other federal organizations dealing with medical research. Senator Specter was awarded FRAXA’s “Research Beacon Award” at the Pittsburgh Gala in 2003. He and his

continued from page 1

or all of these symptoms could be improved by drug therapies that specifically target signaling by mGluRs.”

Since licensing the use of mGluR antagonists for Fragile X from Dr. Bear’s laboratory, Sention has worked closely with FRAXA, which funds some of Bear’s work. “We are thrilled that these companies are collaborating to work toward providing a therapeutic option for our children,” said Michael Tranfaglia, M.D., Medical Director and Co-Founder of FRAXA. “We’re excited to see Dr. Bear’s work move closer to the clinic and look forward to working with Sention and Merck in hope of seeing this happen.”

“Merck is pleased to enter into this collaboration,” said Dennis W. Choi, M.D., Ph.D., Executive Vice President, Neuroscience at Merck. “Dr. Bear’s work represents a potential scientific breakthrough, and this agreement with Sention offers the opportunity to work toward translating this science into clinical practice.”

Randall Carpenter, M.D., President and CEO of Sention, added: “The agreement exemplifies an ideal synthesis of academic research, non-profit foundation support, small biotech innovation and large pharmaceutical company resources and know-how. Most importantly, we hope to advance an mGluR5 antagonist into clinical development for Fragile X, a syndrome that currently has no therapeutic options.”

Please note that the drug development process is always risky and sometimes excellent drugs don’t make it to the market for any number of reasons including rare toxicity, the nature of the treatment proposed, or simple market forces.



Michael Tranfaglia with son, Andy, who has Fragile X

2004–Year in Review

FRAXA 2004 Financial Report

Our audit for 2004 is done, and again FRAXA excels at efficiency.

2004

Income

Donations, fundraising, investments	\$2,133,000
-------------------------------------	-------------

Expenses

Research grants, meetings, support	\$1,176,000
------------------------------------	-------------

Education and raising awareness	\$220,000
---------------------------------	-----------

Management and General	\$37,000
------------------------	----------

Fundraising	\$237,000
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Figures are rounded to the nearest \$1000 from financial statements audited by Anstiss & Co, P.C., CPA.

2005–A Look Ahead

Highlights of 2004

As the economic recovery continues, donations to FRAXA have climbed steadily. Most encouraging of all, recent increases have come as a result of growing numbers of individual donors – more than 3100 last year. Increased revenues have allowed us to add to our strategic reserve for use in the very near future in several evolving drug development projects.

Goals for 2005

Our task for 2005 is to spread the word and broaden our base of support so that we can, in turn, accelerate the pace of Fragile X research. Thank you to everyone who has contributed to this team effort.

PROGRESS NOTES

New Fragile X Clinics Established

Boston – A multidisciplinary Fragile X clinic has started at Massachusetts General Hospital in Boston. This fills a longstanding unmet need for specialty services in the area. For information, call Sandy Massalski at 617-726-1561.

Pittsburgh – A Fragile X clinic has started at the Children’s Hospital of Pittsburgh, PA. To find out more about the Fragile X Center, please call Children’s Hospital at 412-692-7027.

Baltimore – A multidisciplinary Fragile X clinic has started at the Kennedy Krieger Institute, an institution affiliated with Johns Hopkins Medicine.

For appointments, call toll-free 888-554-2080 or locally 443-923-9400. For information visit the website of the Center for Genetic Disorders of Cognition & Behavior, www.gbccenter.kennedykrieger.org.

Research Discoveries Published

So many papers on Fragile X have appeared in top scientific journals recently that we cannot list them all for fear of omitting someone.

To see all the recent papers, visit www.pubmed.org on the Internet. Type “Fragile X” in the Search field and click “go.” Some articles are available free, others offer free abstracts. In the past month, papers have been published by FRAXA grantees, **Assam El-Osta, Peter Vanderklish, Lynn Regan, Kevin Moses, Tom Jongens, Steve Warren, Ben Oostra, Kendal Broadie, and Yong Zhang.**

Fragile X Newborn Testing Evaluated

Drs. Roger E. Stevenson of the Greenwood Genetics Center and **Don Bailey** of the University of North Carolina at Chapel Hill are leading a pilot program to evaluate the potential of universal newborn testing for Fragile X. Testing of newborn males has begun at Greenville Hospital System in South Carolina, and several hospitals in North Carolina are scheduled to begin testing this spring.

The program is funded by National Institute of Child Health and Human Development (NICHD) and the Centers for Disease Control (CDC). FRAXA’s **Mary Beth Busby** and **Katie Clapp** are members of the program’s advisory committee.

Book on Fragile X Forthcoming

FRAXA grant recipients **Barbara Bardoni, Justin Fallon, Angela Giangrande, Andre Hooegeven, Edouard Khandjian, Ben Oostra, Haruhiko Siomi, Miklos Toth and Ivan Jeanne Weiler**, along with colleagues in the greater Fragile X scientific community **Annalisa Pastore, Stephanie Ceman, Gary Bassell, Herve Moine, Henri Tiedge, Rob Willemsen and Robert Denman**, will be making a serious scholarly effort to summarize our current understanding of the disease. Each has co-authored a chapter for *The Molecular Basis of Fragile X Syndrome*, which will be edited by Robert Denman and Ying Ju Sung and published by Research Signposts (www.researchsignpost.com). The book is scheduled for publication later this year. Inquiries concerning this endeavor should be directed to Robert Denman at: rbdenman@yahoo.com.

FRAXA Grants Awarded: January 2005

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.

The mGluR Theory and Stress-Induced Plasticity in the Amygdala: Implications for Affective Symptoms in Fragile X

SUMANTRA CHATTARJI, PhD

National Centre for Biological Sciences (NCBS), Bangalore, India, \$30,000



Sumantra ("Shona")
Chattarji

Dr. Chattarji spends part of each year at MIT where he collaborates with Mark Bear and Nobel Laureate Susumu Tonegawa. This project will be done in India, where the modest budget will fund 1 postdoctoral fellow and 2 research assistants who will work full time on this project.

by Sumantra Chattarji

A growing body of evidence supports the "mGluR theory" which proposes that aspects of fragile X syndrome are a consequence of exaggerated metabotropic glutamate receptor (mGluR) function. This theory accounts for many symptoms of fragile X and integrates molecular and cellular correlates of the disease with basic research findings on synaptic plasticity mechanisms. Most studies to date have focused on the hippocampus, cerebellum, and cortex. However, emotional or mood-related symptoms of Fragile X, including anxiety and aggression, are likely to involve changes in the amygdala (the brain's central emotion processor). No comprehensive studies have examined amygdalar plasticity in the context of the mGluR theory.

This project will extend the mGluR theory into the domain of amygdalar plasticity. We will build upon our recent findings on amygdalar function that relate to three key elements of the disease – (i) spine morphology, (ii) mGluR-mediated synaptic plasticity, and (iii) anxiety-like behavior.

Inside a Neuron ... Definitions

DNA Genes are made up of DNA, which is like the master copy of a movie locked in a Hollywood vault (nucleus).

mRNA DNA is transcribed into mRNAs which can travel from the nucleus along dendrites to the synapses, where communication with neighboring cells happens. These mRNAs are like movie prints at your local movie theatre.

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

synapses are where the show goes on ... where neurons exchange signals. When Neuron 1 spits out a message, receptors on dendrites of Neuron 2 are poised to receive it.

mGluR theory Receptors come in many flavors, including mGluRs, metabotropic glutamate receptors. The mGluR Theory suggests that "Group 1 mGluRs" function excessively in Fragile X, causing symptoms of the disorder.

mGluR antagonists Compounds which dampen mGluR function, including MPEP and MTEP.

r e s e a r c h

Biochemical Markers and Treatment for Impaired Avoidance Learning in Fmr1 KO Mice

RICHARD PAYLOR, PhD

Baylor College of Medicine, \$25,000

DAVID ALBECK, PhD

University of Colorado at Denver, \$15,000

FRANCIS BRENNAN, PhD

Philadelphia VA Medical Center & University of Pennsylvania School of Medicine, \$20,000

by Richard Paylor

To understand the role of the FMR1 gene and its product FMRP in central nervous system function, researchers have engineered a mouse that lacks FMRP (FMR1 KO mouse). Although several laboratories have found that these mice are hyperactive, have abnormal startle responses, and are prone to seizures, there appears to be no consistent learning and memory impairment in the mice. This has hampered efforts to identify and test therapeutic interventions for the cognitive impairments associated with Fragile X.



Richard Paylor, David Albeck, Francis Brennan

We have recently discovered that FMR1 KO mice have a profound impairment on a specific test of learning: the lever press escape/avoidance test. Performance in this test can be associated with changes in two neuropeptides, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in various brain regions.

Our project has three goals: 1. To better understand this learning impairment; 2. To determine whether there is a relationship between BDNF and NGF levels and the avoidance learning of FMR1 KO mice; 3. To rescue the leverpress avoidance learning impairment with MPEP and/or ampakines, while monitoring changes in BDNF and NGF levels.

With this robust learning impairment in mice, we believe we are in a unique position to better understand the role of FMRP in learning and memory and to evaluate potential treatments.

update :

Pharmacologic Treatment of Social Deficits in a Mouse Model for Fragile X Syndrome: Do Gene-Gene Interactions Play a Role?

JEAN LAUDER, PhD

SHERYL MOY, PhD

Univ. North Carolina at Chapel Hill, \$50,000

by Jean Lauder



Jean Lauder

The goal of this project is to investigate drug therapies for treating autistic behaviors in Fragile X and to see if different genetic backgrounds affect the success of these drug therapies.

We will test the effectiveness of drug treatments on social behavior in FMR1 KO mice on two different genetic backgrounds (FVB/129 and C57Bl/6) compared to their wildtype (normal) counterparts. Drugs targeting different neurotransmitter systems (brain chemicals) will be tested: Abilify and Risperidal, which block both dopamine and serotonin receptors; MPEP, which blocks glutamate (mGluR5) receptors, and lithium, which affects multiple neurotransmitter systems. Young adult male mutant and wildtype mice will be treated with different doses of each drug. Effects on social behavior will be tested using an automated system that measures the length of time a mouse spends visiting strange mice in adjacent chambers. We will determine which drugs make the mutant mice more interested in social contact. Mechanisms contributing to effective drug therapies will be investigated using cellular and molecular methods to profile drug effects on brain gene expression.

Exploring the Role of FMRP Interacting Protein CYFIP1 in the Pathogenesis of Prader-Willi and Fragile X Syndromes

YONG-HUI JIANG, PHD

Baylor College of Medicine, \$55,000

We became interested in Fragile X after identification of CYFIP1 (by J.L. Mandel's group), an FMRP interacting protein. The CYFIP1 gene is implicated in Prader-Willi syndrome (PWS), a genetic disorder with symptoms including moderate mental retardation, behavioral problems, childhood obesity, and short stature. Interestingly, there are well documented



Yong-hui Jiang

clinical observations of a PWS-like phenotype in some Fragile X patients.

Although the role of CYFIP1 in the pathogenesis of PWS remains unclear, it has been suggested that CYFIP1 deficiency may contribute to the abnormal social and communication behaviors seen in PWS patients. We will test whether Fragile X and PWS share a common molecular pathway. We have generated CYFIP1 mutant mice and will analyze them by 1) neuropathological studies, 2) electrophysiology studies with a focus on hippocampal long term potentiation (LTP) and long term depression (LTD), and 3) behavioral studies with a focus on hippocampal mediated learning and memory and social behaviors. We believe that the results from studying the CYFIP1 mutant mice will help to understand the pathogenesis of Fragile X and PWS and may shed light on developing a therapeutic strategy for Fragile X.

Study of Intracortical Circuitry in the Barrel Cortex of FMR1-KO Mice

KAREL SVOBODA, PhD

Principal Investigator

INGRID BUREAU, PhD

Postdoctoral Fellow

Cold Spring Harbor Laboratory, \$40,000

by Ingrid Bureau



Ingrid Bureau

In humans with Fragile X and in Fragile X knockout mice, dendritic spines are abundant and tend to have immature forms. Dendritic spines stud the surface of most neurons in the cerebral cortex. They are the receiving end of most synapses and play a pivotal role in the communication between neurons.

We do not know, however, whether these abnormalities are related to changes in the structure and function of synaptic circuits in the cerebral cortex. Ultimately, mental retardation syndromes must have a basis in neural circuits. We propose to unravel changes in neocortical circuits in FMR1 knock-out mice. We will study the barrel cortex, an area in the brain that responds to whisker stimulation. FMRP expression is regulated by whisker stimulation. The barrel cortex is widely used to study the development and plasticity of cortical connectivity.

We use laser scanning photo-stimulation to map the pattern of neuronal connectivity in brain slices. This method provides an 'image' of functional connectivity impinging onto individual neurons. We will map synaptic pathways onto neurons from different layers in the barrel cortex of FMR1 knock-out mice and compare them to wild-type littermates.

If we discover significant circuit differences in FMR1 knock-out mice, we propose to reintroduce the missing gene in mice in utero and determine whether this corrects the defect. Our study may provide new tools to study FMR1 biology.

Evaluation of Protein Synthesis Insensitive mGluR-LTD in FMR1 KO Mice

KIMBERLY HUBER, PhD

Principal Investigator

ELENA NOSYREVA, PhD

Postdoctoral Fellow

University of Texas at Southwestern, \$50,000

by Kim Huber



Elena Nosyreva

It is thought that long-term changes at connections between brain cells (synaptic plasticity) underlie the refinement of neuronal circuitry during development and mediate processes such as learning and memory in the adult. In the past few years we have been studying a form of synaptic weakening, called long-term depression (LTD), in FMR1 knockout mice. We previously demonstrated, with Mark Bear, that LTD induced by metabotropic glutamate receptors (mGluRs) is enhanced in FMR1 knockout mice.

Elena Nosyreva has recently demonstrated in normal animals that there is a developmental switch in the cellular and synaptic mechanisms of mGluR-dependent LTD. In other words, different genes and proteins are involved in youth vs. adulthood. We have preliminary data that the mGluR-LTD in adult FMR1 knockout mice is similar to the immature form of mGluR-LTD. With her funding from FRAXA, she will further characterize the properties of mGluR-LTD in FMR1 knockout mice to determine if it is indeed the “immature” form of mGluR-LTD or a mature form of LTD with distinct properties. Our work will further the understanding of synaptic plasticity and functional maturation in Fragile X and may aid in the development of therapeutic strategies for the disease.

Molecular Mechanisms of Cytoskeletal Regulation by FMRP

SAMIE JAFFREY, MD, PhD

Cornell University, \$60,000

by Samie Jaffrey



Samie Jaffrey

One feature of neurons in Fragile X humans and animal models is that dendritic spines have abnormal shapes. This suggests that FMR1 has a role in controlling spine shape. Since spines are key structures involved in learning, memory and behavior, the abnormal structure of these spines may explain some of the features seen in patients with Fragile X.

What is unclear is how FMR1, which is known to regulate mRNA translation, controls the underlying cytoskeleton of dendritic spines. We are investigating how FMR1 regulates an mRNA that encodes a critical regulator of the neuronal

cytoskeleton, called RhoA. RhoA has been shown to affect dendritic structure and its mRNA has been shown to interact with FMR1, suggesting an appealing connection between FMR1, RhoA, and spine abnormalities. If spine abnormalities are due to the inability of FMR1 to regulate RhoA, then pharmacotherapy directed against RhoA or the RhoA molecular pathway may be suitable for reversing the symptoms of Fragile X.

Function of FMRP-Mediated MAP1b Regulation in Neuronal Development

YUE FENG, PhD

Emory University, \$32,000 from FRAXA and an additional \$18,000 thanks to the Wiser family and the Jack Kent Cooke Foundation.

by Yue Feng



Yue Feng

We have a long-standing interest in understanding how FMRP controls translation of its mRNA targets, and how FMRP deficiency leads to misregulated protein production in Fragile X. Our recent studies focus on brain development of newborn FMR1 KO mice. We found that lack of FMRP causes overproduction of MAP1b and aberrantly increased microtubule stability in brain neurons, which may be a factor underlying abnormal synapse development in the Fragile X brain.

The goal of this project is to understand the consequences of misregulated MAP1b in neuronal development and in epilepsy. We will attempt to correct such abnormalities by manipulating MAP1b expression and microtubule dynamics in the Fragile X neurons with drugs that target microtubules or neurotransmitter receptors. These studies could provide important insights for identifying potential drug targets for the treatment of Fragile X.

mGluR5-dependent Translational Regulation of MAP1b in Fragile X Mental Retardation Model Mice

ERIC KLANN, PhD

Principal Investigator

LINGFEI HOU, PhD

Postdoctoral Fellow

Baylor College of Medicine, \$60,000

by Eric Klann



Eric Klann, Lingfei Hou

Studies have shown that FMRP is an mRNA binding protein, and that one of its “targets” is

the mRNA for a protein called MAP1b. The FMR1 knockout mouse, which lacks FMRP, has much more MAP1b in neurons than control animals. The KO mouse also shows much more long-term depression (LTD) in response to stimulation of metabotropic glutamate receptors (mGluRs). This suggests that mGluR-LTD may be enhanced in Fmr1 knockout mice because of an increase in the translation of specific mRNAs, such as MAP1b. Our studies are designed to investigate this possibility.

Our current experiments build upon our previous studies funded by FRAXA. We have identified several proteins with levels that increase rapidly during mGluR-LTD in wildtype mice. Baseline levels of these proteins are increased in the brain of FMR1 knockout mice, as compared to their wild-type littermates. Furthermore, we found that mGluR-LTD in Fmr1 knockout mice did not result in an increase in the levels of these proteins.

One of these proteins is MAP1b. Our current studies focus on mGluR5-dependent regulation of MAP1b during mGluR-LTD in FMR1 knockout mice. We will use mGluR5 and MAP1b knockout mice to determine whether the enhanced mGluR-LTD in knockout mice can be reversed. We believe these studies will provide important information concerning the defective synaptic plasticity observed in mouse models of Fragile X—information that could be relevant for treatment of patients with Fragile X.

Defining Functional Domains of FMRP and Uncovering its Partners via Large Scale Mutagenesis in *Drosophila*

YONG ZHANG, PhD

Principal Investigator

XINDA LIN, PhD

Chinese Academy of Sciences, \$40,000

by Xinda Lin

FMRP is a widely expressed RNA-binding protein involved in RNA transport and translation. Intensive studies in the last decade have demonstrated that FMRP contains four RNA binding domains, but their actual functions are mostly untested.

Meanwhile, a dozen or so protein partners and hundreds of mRNA targets interacting with FMRP have been identified, but again their functions are poorly understood. It is important that the functional domains of FMRP and its interacting



Yong Zhang, Xinda Lin

partners be identified and characterized in order to understand the pathogenesis of Fragile X.

In the last five years, a *Drosophila* Fragile X model has provided a number of novel insights into FMRP function. Previous work was primarily focused on making null mutations of the gene and then analyzing the phenotypes of mutants to infer the normal functions of FMRP. We have recently developed a simple, efficient scheme to screen for genes that suppress FMRP. Overexpression of FMRP is fatal to flies, but a suppressor generated through mutagenesis can produce viable progeny. We plan to exploit the mutagenesis approach to 1) define essential sections of the FMRP molecule, and 2) to uncover physiologically important partners of FMRP, taking full advantage of sophisticated *Drosophila* genetics, molecular tools and cellular assays. The results of this project will advance our understanding of FMRP's role, elucidating the pathways in which FMRP is involved and the molecular pathogenesis when FMRP is absent in Fragile X. This understanding will ultimately be used for the development of a drug treatment for the disease.

Transcriptional Regulation of the Fragile X Mental Retardation Gene (FMR1) in the Olfactory Bulb

JUSTIN FALLON, PhD

Principal Investigator

ANNE BOOKER

Graduate Student

Brown University, \$40,000

by Anne Booker



Justin Fallon, Anne Booker

We are interested in mechanisms that regulate FMR1 gene expression. We have developed a model to study them in the central nervous system and shown that olfactory experience (smelling) regulates FMR1 gene expression in mice and that this is dependent on developmental stage.

The main goal of this study is to discover the processes responsible for the regulation of the FMR1 gene. One aim is to identify transcription factors – proteins that bind to specific regions of DNA and promote the synthesis of messenger RNA. Second, recent studies have shown that modifications like gene methylation and histone acetylation are influenced by both development and activity. Our preliminary data suggest that the FMR1 gene is regulated throughout development and following activity by these modifications.

We hypothesize that some regulatory mechanisms are particularly important in early development, while others play a prominent role later in life. Results from these studies will help us understand the normal function and regulation of FMR1 in early childhood and in the adult. These insights could aid in the design of therapeutic strategies to treat FXS that are tailored to particular developmental stages. *cont. on p. 11*

F R A X A D I R E C T O R

FRAXA was founded by parents of children affected by Fragile X and is run by parents to this day. These are the members of FRAXA's Board of Directors and Board of Advisors. Directors and Advisors meet and talk regularly, making all major decisions together. Research funding decisions are based on input from FRAXA's Board of Scientific Advisors, to be profiled in a future newsletter.

Megan Massey of Scottsbluff, Nebraska, has two children, Jack, 15, and Jacob, 14, who have Fragile X. Megan and her husband John have been involved with FRAXA for over five years. "The experience of being surrounded by caring and motivated individuals who truly are making a difference in finding a treatment and cure for FX has been heartwarming," says Megan. Megan and her family and friends have enlisted all Nebraska's Congressmen and Senators to support Fragile X research.



Jack, John (in front), Megan, and Jacob Massey

Eileen Naughton is president of TIME, the world's largest news magazine. She is a graduate of the University of Pennsylvania, where she received an M.B.A. degree from The Wharton School and an M.A. degree from the Lauder Institute of International Studies. Eileen lives in New York City with her husband Craig Chesley, two daughters, and one son affected by Fragile X.



Craig Chesley, Eileen Naughton, and their three children

Andrea Shelly, born in Wellington, New Zealand, has been affiliated with FRAXA since 2004, shortly after the diagnosis of her daughter Elisabeth.

Andrea and her husband Damon Shelly have four children. Andrea practiced law and worked in commercial real estate until the birth of her first child.

Cristy Hollin became an attorney after graduating from Boston University and Delaware Law School. Cristy and her husband Mitchell have three children: Matthew, 12, who has Fragile X, and two other boys, Noah, 9, and Reid, 1. Cristy and Mitchell have been involved with FRAXA for the last eight years.

Debbie Stevenson, FRAXA board of directors chairman, is a former associate producer at CNBC Business News and a former production assistant for ABC News' "20/20." She now devotes her considerable talents to helping FRAXA. Debbie was born and raised in Dallas, and graduated from Texas A&M University.



Samantha, Debbie, James, Jeffrey and Taylor, Stevenson

Jeffrey Stevenson, head of FRAXA's Finance Committee, is a partner at Veronis Suhler Stevenson, an investment bank and private equity firm, where he has worked since graduating from Rutgers College in 1982. Jeffrey is a member of the Young President's Organization (YPO). Debbie and



Andrea Shelly and her four children

Jeffrey live in New York City and Rye, NY. They have three children: Taylor, 8, who has Fragile X, James, 6, and Samantha, 3, neither of whom have Fragile X. Samantha was born by using preimplantation genetic diagnosis.

Leslie Eddy has two daughters: Allison, 8, who has Fragile X, and Olivia, 5, who is unaffected. Leslie has been involved with FRAXA for the last 7 years. She is a graduate of the University of Florida and does freelance writing in Marblehead, MA, where she lives with her husband Trevor and their children.

Leslie Bagdasarian is the mother of Julie, 13, and Alex, 11, both diagnosed with Fragile X in 1995. Leslie and her husband, Ara, founded the Fragile X Alliance of Ohio, a parent support group and FRAXA chapter. She is developing a Fragile X clinic at Akron Children's Hospital. Leslie earned a BS in Medical Communication from Ohio State University and co-chairs the annual Fragile X Golf Benefit.



Leslie and Ara Bagdasarian

Ara Bagdasarian is vice president for retail marketing of TravelCenters of America, a nationwide chain of travel plazas headquartered in Cleveland. Ara earned a BS in Business from John Carroll University in Cleveland and an MBA from University of Dayton. Ara says "I am inspired by Mike, Katie and the organization's leadership and the extraordinary effectiveness of FRAXA in navigating the way for cutting-edge Fragile X research in such a short period of time.

Mary Beth Busby joined FRAXA's Board in 1994 and became vice president of FRAXA in 1999. She and her husband David live in Washington, DC, where they lead the effort on Capital Hill. Mary Beth's leadership roles

S A N D A D V I S O R S

include: the Steering committee for NICHD's upcoming conference on Premature Ovarian Failure and the Fragile X Premutation; the D.C. Mayor's Advisory Committee on Newborn Screening for Metabolic Disorders; the Advisory Panel of the Human Genome Educational Model Project on Ethical, Legal, and Social Issues; National Capital Area Chapter of the March of Dimes-1988-1994; Coalition for Children's Health, 2000-present. Mary Beth and her husband David have two sons, Robert and Jack, with Fragile X.



Mary Beth and David Busby at The White House

David Busby, counsel for FRAXA, is a graduate of Yale '48; University of Oklahoma School of Law '51 and a retired partner, Dorsey & Whitney, LLP, Washington, DC. He is listed in Who's Who In America and Who's Who in American Law.

Michele Cox and her husband, Jim, have two children: McKayla, 6, and Christopher, 4, who has Fragile X. Michele earned her degree in Communication and Political Science from the University of Arizona and Walsh University. Michele has recently started an event planning business. Michele says of her commitment to FRAXA, "It's because of the FRAXA pioneers that parents like us were able to replace the initial feeling of despair with great hope. Being involved with FRAXA is the greatest gift that I can give to my son."



Michele, Jim, McKayla, and Christopher Cox

Jim Cox earned his BA from Georgetown University and co-founded BrabenderCox, a leading political media firm. Jim also authored the Quiet Confidence golf program. Jim says, "The parents involved with FRAXA are some of the most extraordinary people I have ever met. Regardless of the number and scope of roadblocks facing them, they never lose sight of their ultimate goal of finding a treatment and a cure for Fragile X. It is this type of determination that has given our family tremendous hope."

Ron Watkins and his wife Amy live in LaGrangeville, New York where he is employed as a CPA. Their 7-year-old son, Niklas, has Fragile X. Ron and Amy have been involved with FRAXA for four years;



Ron, Niklas, and Amy Watkins

their goal is to help FRAXA continue to fund the best researchers in the world.

Susan Cohen joined FRAXA when her son, Julian, was diagnosed at age 2. Susan has taken bold steps to raise funds and awareness for FRAXA via mail campaigns and projects including the "Knockout Mouse T-shirt." Susan, a literary agent in New York City, frequently lends her editorial experience to FRAXA.



Susan Cohen and son Julian Berg

Mary Jane Clark is the best-selling author of seven mystery novels and a producer and writer at CBS News in New York City. She has two children, Elizabeth, a college student, and David, a highschooler with Fragile X. Mary Jane has lent her time and energy to many fundraisers, galas and public events for FRAXA. She has a degree in



Mary Jane Clark

journalism and political science from the University of Rhode Island. Visit her website at www.maryjaneclark.com.

Kelly Randels of Omaha started the Nebraska Fragile X Families Association in 2002, two months after her son, Cody, was diagnosed with Fragile X. Last year, the group raised over \$105,000 for FRAXA. They look forward to another fundraiser for the year 2006.



Cody, Kelly, and Ryan Randels

David Clark of Hillsdale, NJ, father of David and Elizabeth, is former Vice President of *Exceptional Parent Magazine*, where he worked to raise public awareness of Fragile X and helped parents dealing with disabilities of many kinds.



David Lustig and his wife Stephanie have a young son, Jacob (left) who was diagnosed with Fragile X just last year. As David said, "One small

gene; one life-altering decision" is all it took for him to decide to devote his efforts to help FRAXA work towards a cure.

Katie Clapp and **Mike Tranfaglia** co-founded FRAXA along with their friend, Kathy May, in 1994. Katie and Mike met as undergraduates at Harvard. They have two children, Andy and Laura, who have the Fragile X gene (only Andy is affected).



Mike, Andy, Katie and Laura and friends

NEWS AND NOTES

Newport Coast Gala

Andrea Shelly, head of the Orange County Chapter of FRAXA, together with David Lustig, recently elected member of the FRAXA Board of Advisors, were thrilled when the first Newport Coast dinner benefitting FRAXA netted close to \$300,000. The dinner was held on November 10, 2004, at the magnificent Pelican Hill Golf Club.



Roger Staubach and Harry Manion

Keynote speakers were NFL Hall of Famer and Dallas Cowboys great Roger Staubach, and Fragile X researcher Dr. Oswald Steward. Staubach's local office of The Staubach Co, supported the event. Steward is working on Fragile X at the University of CA, Irvine, with a FRAXA grant. Also joining FRAXA as corporate sponsors were Volvo Motorcars of North America, LLC., and Majestic Realty Co., a real estate investor/developer in Southern California.

The Spanish-themed event with flamenco dancers and musicians was great fun, as was the live auction with Gloria Lieberman officiating. Out-of-town FRAXA supporters and FX parents Harry and Jaime Manion and Debbie Stevenson won a \$10,000 trip for four to Dallas to spend an evening with Roger Staubach in his private suite at a Cowboys game. Dr. Marc Lerner, pediatrician with UCI, outbid Steward to win a sleek Volvo S40, netting FRAXA \$33,000. The live auction made over \$90,000, and, inspired and touched by Debbie Stevenson's video, 'First Down Towards a Cure,' Shelly's neighbors and supporters, Kent and Karen

Jordan, matched every dollar made in the auction.

Although still recovering from the event, Shelly is planning another gala on October 12, 2005, to fuel the momentum begun last November.



Andrea Shelly and her daughter, Juliet



Mary Higgins Clark signing her latest thriller

Canton Gala

The First Bi-Annual Fragile X Gala was held on October 22nd in Canton, Ohio, at the McKinley Grand Hotel. In attendance were best-selling mystery author, Mary Higgins Clark, Congressman Ralph Regula's wife, Mary, Akron radio host, Doug Lane, Dr. Carol Delahunty and her colleagues from Akron Children's Hospital, and 250 guests. Thanks to everyone involved in organizing this event, especially Michele Cox and her mother, Annie Hochwarth.

Tribute to Alice and Alex Bagdasarian

A special way to honor the memory of a loved one is to suggest that donations (in lieu of flowers) be made in their name to FRAXA. This is a wonderful way for others to support a cause that was important to their family member.



Alice & Alex Bagdasarian whose grandchildren, Julie & Alex Bagdasarian, have Fragile X

Our sincere thanks to the family of the late Alice and Alex Bagdasarian who requested that donations in their parent's names be sent to FRAXA. More than \$12,000 was donated and awareness of Fragile X was heightened.

For FRAXA gift envelopes and/or brochures explaining Fragile X, please contact Katie Clapp at 978-462-1866 or kclapp@fraxa.org.

CALENDAR OF EVENTS

Mary Higgins Clark Gala - Washington, DC, April 11

Contact Mary Beth Busby, 202-462-2323, mabbusby@aol.com

Oldie Dinner Dance/Raffle, Knights of Columbus in Fishkill, NY, April 16

Contact Fran Gibb, ag1010@frontiernet.net

Patrick's Pals IX Annual 3-on-3 Basketball Tournament, Cambridge, MA, June 4

Contact Katie Clapp at FRAXA

9th Annual Fragile X Golf Benefit, Firestone Country Club, Cleveland, OH, June 27

Contact Fragile X Alliance of Ohio, 440 519-1517, fraxohio@adelphia.net

Gala, LaGrangeville, NY, Sept.16. Contact Ron and Amy Watkins, fragilex@frontiernet.net

Gala and Live Auction, Newport Coast, CA, October 12

Contact Andrea Shelly, 949 466-4521, aashelly@aol.com

Role of miRNAs in the Pathogenesis of Fragile X

THOMAS TUSCHL, PhD

Principal Investigator

ALEXEI ARAVIN, PhD

Postdoctoral Fellow

Rockefeller University, \$40,000

by Alexei Aravin



Alexei Aravin

More than ten years have passed since scientists discovered that Fragile X syndrome is caused by the absence of a single protein, FMRP. Studies have shown that FMRP regulates the translation of mRNAs into proteins by recognizing and binding to numerous mRNAs. However, it is unknown how FMRP recognizes a particular mRNA and how it regulates the mRNA's translation into a protein. Understanding this will help facilitate development of therapeutic treatments.

Recent discoveries in the new field of RNA interference (RNAi) have provided insight into how FMRP recognizes its target mRNAs. Like FMRP, the RNAi machinery regulates the translation of numerous mRNAs. It recognizes target mRNAs through tiny non-coding RNAs termed microRNAs (miRNAs). Since miRNAs are found in all animals, they must have a fundamental role in regulating gene expression.

The recent finding that FMRP interacts with the RNAi machinery suggests that FMRP functions with this machinery to regulate gene expression. FMRP and miRNAs most likely recognize and regulate a common set of mRNA targets in the brain. Misregulation of these mRNAs in Fragile X patients probably causes the disease. We are investigating the mechanism of translational regulation of mRNAs that are believed to be targeted by miRNAs as well as FMRP.

FMRP-MAP1b RNA Interactions in Fragile X Syndrome

MIHAELA MIHAILESCU, PhD, Principal Investigator

SAMANTHA MADER

Graduate Student

LAKSHMI MENON

Graduate Student

Duquesne University, Pittsburgh, \$50,000

by Mihaela Mihailescu

Our group will study the interactions of FMRP with RNA targets that form G-quartets, complex 3-dimension-

al structures that appear to function as binding recognition sequences. Previous studies have shown that G-quartets are important in Fragile X syndrome, and MAP1b mRNA has been identified as a target of FMRP with a G-quartet sequence.

We will study the interactions of FMRP with MAP1b mRNA and address questions such as:

- What is the molecular basis of FMRP-MAP1b mRNA recognition? Does FMRP regulate translation of its RNA targets by altering their 3-D structure?
- To what extent do post-translational modifications such as phosphorylation and methylation, affect the FMRP binding activity for specific RNA targets, such as MAP1b mRNA?

We also plan to perform a comparative study of the interactions of different FMRP isoforms with MAP1b RNA, to determine to what extent sequence modifications near its RGG box affect FMRP's interactions with specific RNA targets.

The normal function of FMRP depends upon its ability to interact with and act upon its RNA targets. A detailed study of the FMRP-RNA interactions will contribute to our understanding of the mechanisms by which FMRP achieves its function.

Metabotropic Glutamate Receptor Function in Fragile X Knockout Mice as a Possible Etiologic Factor in Autism

WALTER KAUFMANN, MD, PhD

Kennedy Krieger Institute, \$43,000

DAVID LIEBERMAN, MD, PhD

Postdoctoral Fellow

RICHARD HUGANIR, PhD

Co-Investigator

PAUL WORLEY, PhD

Co-Investigator



Walter Kaufmann

This project is funded thanks to the Wisner Family and the Jack Kent Cooke Foundation.

Fragile X is becoming more and more widely accepted as a powerful model for investigating autism. This project focuses on proteins that are misregulated in Fragile X and may also underlie cases of autism. This grant extends Dr. Kaufmann's current FRAXA-funded study of the mGluR theory to areas of the brain that have not been extensively studied: the hippocampus and the cerebellum.

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)

See www.fraxa.org for details.

FRAXA UPDATE

EDITOR: Katie Clapp, MS

CONTRIBUTING EDITOR: Leslie Eddy

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CONTRIBUTORS: Mary Beth and David Busby
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and many others

DESIGN: Mary Lou Supple

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This newsletter is published regularly and sent to all supporters of FRAXA Research Foundation.

Magnets are Here!

Car magnets are available for \$4 each. Visit www.fraxa.org or call us with a credit card or send a check to FRAXA.

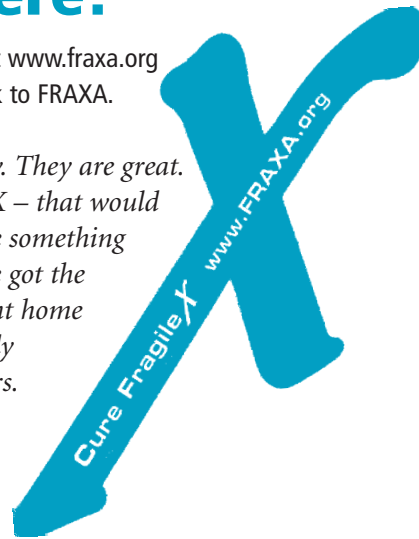
"I got the FRAXA X-magnets yesterday. They are great. I hope they raise awareness of Fragile X – that would be wonderful. But they've already done something very important for our family. After we got the package at the post office, we came right home and opened it eagerly. Our whole family went out to put the magnets on our cars. We debated best placement and best positioning, and we raved about how we much we liked them. I know this



Spencer

made Spencer feel good ... that we thought enough of him to splash his genetic uniqueness all over our cars. Even his teenage sister and brother were involved! Spencer felt important and included and special ... things he already is, but I like tangible evidence."

– Mary Lee Shelton in NM



PLEASE HELP

FRAXA

FRAGILE X RESEARCH FOUNDATION

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.

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