FRAXA UPDATE

WINTER 2004

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A PUBLICATION OF 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

"Everybody's Studying Fragile X!"

As in past years, FRAXA hosted a booth at the annual meeting of the Society for Neuroscience. More than 25,000 scientists – including most of the researchers FRAXA supports – converged on San Diego at the end of October to present and discuss their latest discoveries.

But this year was different: Fragile X was featured front and center, as illustrated when three young scientists walked by the FRAXA booth and one of them commented, "There's Fragile X. Everybody's studying Fragile X!"

One of FRAXA's top goals is to bring Fragile X research to the forefront of neuroscience. To that end, we joined with two other Fragile X research foundations to host a research forum open to all 25,000 conference attendees. It was enthusiastically received. *See page 3 for more on the meeting.*

Cindy de Gruchy, David Lustig, Karen Fay at FRAXA's booth

FRAXA Fall Fling Celebrations Across America

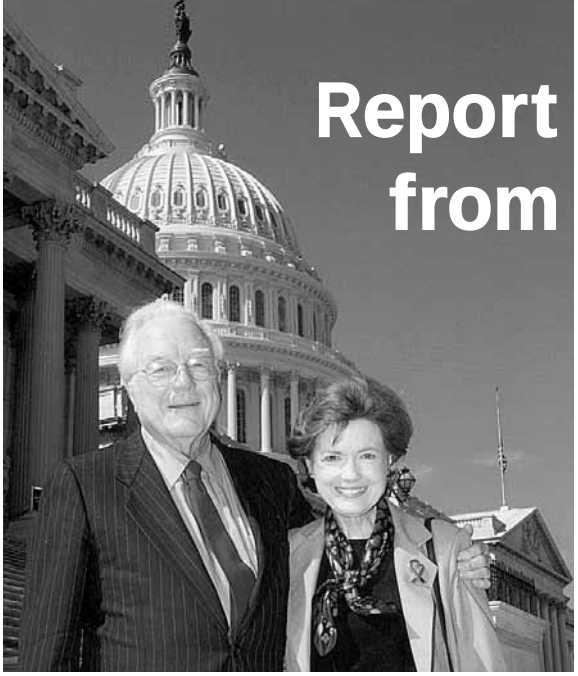
LaGrangeville Middle School students in New York celebrate National Fragile X Research Day

In celebration of National Fragile X Research Day, October 5th, endorsed by Congress two years ago, families around the U.S. hosted events raising over $105,000 for research! These funds have come in just in time to help support the best of the new proposals which arrived on December 1st and are currently under review by FRAXA's Scientific Advisory Board. Awards will be announced in our next newsletter.

See page 8 for Fall Fling reports.

Also in this issue:

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



Report from Washington:

By Mary Beth and David Busby

Saved by the Senate!

As noted in our last newsletter, we were disappointed by this year's Annual Report of the House Appropriations Committee, because it included only 1 of the 9 requests of the Fragile X community: support for "promoting early intervention through developmental screening," "developing a Fragile X public health program to expand surveillance and epidemiological study of Fragile X," and providing "patient and provider outreach on Fragile X." We wanted this, of course, but we were disappointed that our 8 basic research requests – which were agreed upon and urged by FRAXA, the National Fragile X Foundation, and Conquer Fragile X – were ignored by the House Subcommittee.

The good news is that the Senate Appropriations Committee Report included all 9 of our requests directing the Department of Health and Human Services (which includes the Health Resources and Services Administration, the National Institutes of Health, and the Center for Disease Control and Prevention). Unless specifically overruled by the Conference Committee Report (which won't happen), the Senate language will govern next year's allocations.

Fragile X was mentioned in the Senate Report 34 times – a record!

Our champions in the Senate – as has been the case since 1999 – were Senators Chuck Hagel and John Edwards. Their bipartisan "Dear Colleague" letter persuaded 22 of their fellow Senators to sign on and to ask Senate Appropriations Chairman Specter and Ranking Member Harkin to support enhanced funding to:

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

This best ever result was achieved by the combined effort of the entire Fragile X Community. Special recognition is due to our members from Pennsylvania and Indiana who worked with their Senators, Health Subcommittee Chairman Senator Arlen Specter and Ranking Member Senator Tom Harkin and the Subcommittee's superb staff. Thank you – especially – Bill Parker, Michele and Jim Cox, Cristy and Harris Hollin, and Joseph and Tricia Judge!

Next Year

As with football, there is always a next year. Mary Beth and I are confident that your visits and letters to the House and Senate offices raised the level of awareness and that the (another record) 81 members of the House signing the "Dear Colleague" letter each learned the merits of our cause and will welcome us back next year. All of you "Advocates" get a sincere vote of thanks from all Fragile X families and friends!

However, realistically speaking, next year may be tough. It will not be an election year, and indications are that the Congress will feel that government spending – even spending on Children's health – should be curtailed because of record deficits.

While your Senator and House Members are at home this winter, you should thank him, her and/or them for this year's support and keep Fragile X in their thoughts!

Contact David Busby at Busby.David@dorsey.com or 202-442 3512

RESEARCH MEETINGS

Fragile X Research Forum: Forefronts of Research

Fragile X Highlighted at Society for Neuroscience Annual Meeting

The annual meeting of the Society for Neuroscience is one of the largest gatherings of scientists anywhere in the world, with over 25,000 attendees this year. It provides a great opportunity for FRAXA to attract new scientists to one of the new hot topics in neuroscience: Fragile X.

Each year, Fragile X parents staff FRAXA's booth at the meeting for four days, and thanks to a plum location abutting a main aisle, we talked with hundreds of scientists. Most of the researchers FRAXA supports attend this meeting each year, so it is a great opportunity to learn about their current work.

David Bloom, PhD; Robert Bauchwitz, MD, PhD; Zane Zeier

Fragile X Research Forum

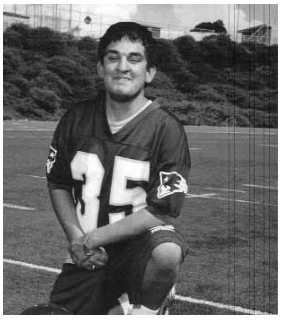
This year, we held a special forum to highlight the extraordinary advances being made in Fragile X research. The event was hosted jointly by FRAXA Research Foundation, Conquer Fragile X Foundation, and the Fragile X Research Foundation of Canada. Brief presentations were given by four leading investigators, all of whom have current FRAXA research grants: Bill Greenough, of the University of Illinois at Urbana-Champaign, Mark Bear of MIT, Holly Cline of Cold Spring Harbor Laboratory, and Oswald Steward of the University of California-Irvine.

Clockwise from top left: Oswald Steward, PhD; Mark Bear, PhD; Holly Cline, PhD; Bill Greenough, PhD

The forum provided an opportunity for investigators, postdoctoral fellows, and students to meet others in the field and to learn about the latest advances in understanding the neurobiology of Fragile X. There was much informal discussion after the talks and several collaborations were forged.

We were also gratified that FRAXA grantees, Fen-Biao Gao of UCSF and Stephen Warren of Emory University, co-chaired a Fragile X minisymposium which was extremely well-attended.

We thank all the parents who helped us staff FRAXA's booth for four days: Cindy de Gruchy, Karen Fay of Conquer Fragile X Foundation, David Lustig, Andrea Shelly, and a very special thank you to Danielle Andreassi, her son AJ Andreassi, and Jacques LaChappelle for for setting up, breaking down, and shipping FRAXA's booth displays.



AJ Andreassi

6th Annual Banbury Meeting

Fragile X Banbury meetings were established six years ago thanks to Nobel Laureate James D. Watson, who proposed them as an effective means to stimulate new research. Hosted initially by FRAXA and now funded by a grant from NIMH with additional support from NICHD and FRAXA, these meetings have been tremendously successful. They are very small meetings (36 participants) held at the Banbury Center at Cold Spring Harbor Laboratory, New York.

This year's meeting entitled "Translational Approaches to Fragile X" is being organized by Elizabeth Berry-Kravis, Rush University and William Greenough, University of Illinois.

At the Banbury meeting last spring, it was clear that important progress is being made in understanding Fragile X at the molecular and synaptic levels, in the mouse and fly models of the disease. Pharmaceuticals which could target some phenotypes are in various stages of development.

However, it was also clear that quantitative measurements to assess treatments for Fragile X are severely lacking. Lack of outcome measures has limited translation of basic science knowledge to clinical trials of existing and new pharmaceuticals in the syndrome.

Therefore, our next Banbury meeting at the end of February will focus on strategies for translating basic science knowledge to clinical treatment trials in patients. The goal will be to identify specific requirements for clinical trials.

Something Old, Something New…

by Michael Tranfaglia, MD, FRAXA Medical Director.

Research is shedding new light on the basic mechanisms of disease in Fragile X, and much of this new information has direct implications for treatment. Since FRAXA's mission is to promote research that can help our children as soon as possible, we've been especially busy lately pursuing a number of promising leads. The following projects are now making the transition from the laboratory to the clinic.

Something Old: Lithium

Lithium is a psychiatric treatment that was first approved in this country in the early 70's to treat manic-depressive illness (Bipolar Disorder). Lithium is still an effective treatment for this disorder but is not now widely used because of competition from newer treatments, as well as potential toxicity which requires frequent blood testing. It has not been used much in the treatment of Fragile X, but we may want to reconsider this based on new evidence from two animal models of Fragile X.

Oddly enough, the drosophila (fruit fly) model of Fragile X exhibits a strong *cognitive phenotype*. It is relatively easy to demonstrate that these flies have impaired learning and memory. While it may be surprising that fruit flies are capable of learning at all, or that scientists can measure it, there are robust ways to measure fly cognitive function, usually in the context of mating rituals and behavior. These "Fly IQ" tests are powerful tools for measuring the effects of drugs or genetic mutations on cognitive function.

Once a cognitive deficit was found in the Fragile X fly, attempts were made to "rescue the phenotype" (i.e. correct the problem) with several drugs. We have previously noted that MPEP (an mGluR5 antagonist) can rescue a learning and memory deficit in the Fragile X fly – even though fly metabotropic glutamate receptors (mGluRs) are not the same as human receptors. Lithium can also rescue this cognitive phenotype in the same experiments. Lithium inhibits the same mGluR signaling pathways which are thought to be excessive in Fragile X. Lithium has not previously been reported to cause cognitive enhancement; in fact, normal control flies treated with lithium showed some cognitive *impairment* from it. This demonstrates a therapeutic effect which is specific to Fragile X.

Of course, flies are not people. It would be difficult to base human trials of lithium on drosophila studies. Fortunately, the Fragile X mouse model can take us a step closer. Mouse studies of lithium are preliminary at this point, but results have been impressive so far. A reliable phenotype in the Fragile X knockout mouse is audiogenic seizure: in all strains studied, mice with the FMR1 gene knocked out have far more seizures when exposed to very loud noise. The mGluR5 antagonist MPEP rescues this phenotype completely. Initial testing shows that lithium can also rescue this phenotype. This is compelling because lithium is generally thought to have some pro-convulsant (seizure inducing) properties in humans, indicating an effect which may be specific to Fragile X. These experiments are ongoing, but if the results hold up to further study, human trials are indicated. FRAXA is currently exploring the possibility of organizing human trials of lithium as a treatment for Fragile X.

Something New: Abilify

Drugs called "atypical antipsychotics" have often been used to treat severe behavioral problems associated with developmental disorders. Medications in this class include Risperdal, Zyprexa, Seroquel, and – the newest addition – Abilify. These medications are vastly superior to older, "typical" antipsychotics; in particular, Risperdal has been well studied in the treatment of autism and related conditions, with favorable results. They are not without problems, though: Risperdal and Zyprexa can cause weight gain in children and young adults, and the entire class carries a small risk of drug-induced movement disorders.

Because Risperdal has been around the longest, it is probably the most widely prescribed treatment for severe behavioral problems in Fragile X. However, Fragile X can be a difficult condition to treat; so the hunt is always on for something new and better. As children and young adults around the country were tried on Abilify, a pattern began to emerge. Many individuals with Fragile X experienced a significant improvement on this drug, often in ways that went beyond the expected effects. In many cases,

update:

Abilify seemed to stabilize mood and improve attention, as well as treat agitation and aggression, more effectively than the older drugs. It also was reported to be easier to take, with fewer side effects for most kids; younger children who had gained weight on Risperdal or Zyprexa actually lost that weight without trying.

It is not unusual for a new drug on the market to make a big splash – lots of patients who have responded poorly or partially to available treatments are switched over to the latest thing, and some of them will inevitably have a very good response. Others don't respond as well, but we often don't hear from them. This kind of anecdotal evidence of drug efficacy doesn't mean much by itself; however, the qualitative differences in response to Abilify treatment were reported frequently enough to arouse interest.

Intriguing results from studies of social behavior in the Fragile X knockout mouse by Lauder *et al* at the University of North Carolina stoked this interest further. They found that some strains of KO mice showed significant alterations in social behavior, preferring to be alone in situations where their normal littermates preferred to interact with others. When the KO mice were treated with Abilify, this behavior normalized.

Several facets of this research are noteworthy. The social behavior model used here appears relevant to the study of autism, with the abnormal mouse social behaviors reminiscent of autistic human behavior. Interestingly, one mouse strain exhibited this abnormal behavior, while the other did not; genetic background influenced the expression of complex social behavior in mice as it certainly does in humans. The investigators are studying the differences in gene expression between the two kinds of FMR1 knockouts, using powerful new microarray techniques which can analyze thousands of different genes simultaneously on one small glass slide.

Most remarkable of all, this abnormal social behavior responded well to low doses of Abilify. While further mouse studies are in order to delineate the extent and specificity of this response, this is further evidence in support of trials of Abilify in humans with Fragile X. FRAXA is now organizing a clinical trial of Abilify.

Something Borrowed?

We have previously mentioned our interest in developing mGluR5 antagonists as potential treatments for Fragile X. MPEP is a chemical compound which is the prototype of this class; it has been used in animal studies of Fragile X and many other disorders of the central nervous system. MPEP is not a patented drug and could potentially be developed as a treatment for Fragile X. However, our testing has revealed some major shortcomings. MPEP is short-acting, with a duration of action of less than 90 minutes in mice. It has also shown evidence of possible toxicity in lab testing at very high doses though no toxicity has been observed in any of the live mice given MPEP.

Fortunately, pharmaceutical companies, both large and small, are developing newer and better mGluR5 antagonists. We have developed close contacts with several companies, with a two-pronged strategy in mind. On one hand, we are collaborating with a small pharmaceutical company in an attempt to license several improved mGluR5 antagonists for development as a treatment for Fragile X; on the other hand, we are working with a large company to incorporate Fragile X into an existing mGluR5 development program.

These compounds, mGluR5 antagonists, are of interest to large pharmaceutical companies because they may be good treatments for anxiety; they may also help with pain management and treatment of substance abuse. These are potential "blockbuster" indications, far more common than Fragile X. But when a drug has progressed in the development process to the point of human trials, it is possible for researchers to petition the FDA, in conjunction with the pharmaceutical company, for permission to test the drug in another indication – like Fragile X.

So, if large pharmaceutical companies bring mGluR5 antagonists into human trials for more common conditions, we hope to piggyback Fragile X trials onto their development programs. This has the advantage of a big company's marketing muscle and development expertise, but this approach can take a long time and drug development programs can be canceled for various business reasons. The direct approach of partnering with a smaller pharmaceutical company to develop a drug offers greater control over the process, with possibly faster approval since relatively uncommon indications like Fragile X get preferential treatment from the FDA. We are pursuing both strategies, while continuing animal testing with MPEP to look at the developmental effects of long-term treatment.

These are exciting times to be working in the Fragile X field. We plan to continue FRAXA's strategy of keeping many irons in the fire, to turn the research breakthroughs of the last few years into routine clinical treatments for everyone with Fragile X.

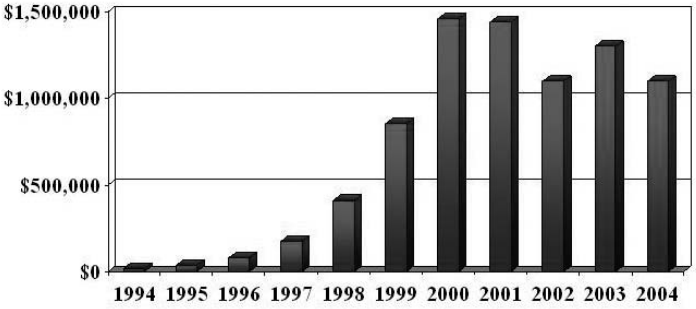
FRAXA Research - New Awards to be announced in February 2005

FRAXA's mission is to accelerate research aimed at finding specific, effective treatments to help all children and adults with Fragile X.

New research proposals just arrived on December 1st and are now being reviewed by members of our Scientific Advisory Board (see box) and other members of the scientific community, all of whom generously volunteer their time to FRAXA. We will announce the new awards in the next issue of this newsletter.

FRAXA accepts grant proposals twice each year, on May 1st and December 1st. The number of proposals we receive has steadily increased thanks to ever-growing interest in Fragile X in the scientific community. This is very good news – new ideas and talent have added up to exciting progress towards finding treatments and a cure for Fragile X. Since 2001, FRAXA has not been able to fund all of the meritorious proposals; hence the increasing importance of raising funds.

FRAXA FUNDS SPENT ON RESEARCH



Donations received by December will support the best of these projects. Please send in your contribution today so that FRAXA can fund more projects and the scientists speed up their work! If you would like a fun way to support FRAXA and inform others about Fragile X at the same time, gift items are available (cookbooks, playing cards, pins, T-shirts, video or DVD, books and booklets). Call for a catalog or visit www.FRAXA.org.

research

FRAXA Scientific Advisory Board

Don Bailey, PhD – University of North Carolina at Chapel Hill

Robert Bauchwitz, MD, PhD – Columbia University

Mark Bear, PhD – Massachusetts Inst. of Technology (MIT), Howard Hughes Medical Institute

Elizabeth Berry-Kravis, MD, PhD – RUSH University, Chicago

W. Ted Brown, MD, PhD – New York State Institute for Basic Research

Robert Darnell, MD, PhD – Rockefeller University

Justin Fallon, PhD – Brown University

William Greenough, PhD – University Illinois Urbana-Champaign

David Gwynne, PhD – Cambridge NeuroScience Inc.

Steven Hyman, MD – Harvard University

Eric Kandel, MD – Nobel Laureate, Columbia University, Howard Hughes Medical Institute

Pamela Mellon, PhD – Univ. of California at San Diego

Kevin Moses, PhD – Emory University

David Nelson, PhD – Baylor College of Medicine

Oswald Steward, PhD – University of California, Irvine

Owen Rennert, MD – Georgetown University; National Institutes of Health

Steven Warren, PhD – Emory University

James D. Watson, PhD – Nobel Laureate, Cold Spring Harbor Laboratory

Robert Wong, PhD – State University of New York (SUNY) Downstate

Jerry Yin, PhD – University of Wisconsin

TRIBUTE TO LINDA CRNIC

Dr. Linda Crnic, Director of the University of Colorado Mental Retardation and Developmental Disabilities Research Center, and world recognized authority on adaptation of behavioral testing into rodent models of both Down syndrome and Fragile X died as a result of a bicycle accident in September. Linda was a member of FRAXA's Scientific Advisory Board and FRAXA grant recipient. On October 7th, she was honored by Senator Jim Jeffords, who said, "She was a researcher to whom parents of children with Fragile X and Down syndrome could always go with their concerns, regardless of whether or not their concerns were related to Dr. Crnic's area of research."

update:

FAMILY CORNER

New Fragile X Clinic at Emory

Stephee Warren, PhD

Emory University in Atlanta, Georgia, has launched a new clinic to serve families with Fragile X. Since the early 1980s, Drs. Stephen T. Warren and Stephanie Sherman have been performing research on Fragile X. In 1991, Dr. Warren led the international team of scientists that discovered the FMR1 gene responsible for Fragile X syndrome.

The clinic team provides current information regarding clinical and basic research in Fragile X. For appointments or more information, call (404) 712-8232.

Clinical Trial of Ampakines

Elizabeth Berry-Kravis, MD, PhD

Dr. Elizabeth Berry-Kravis is conducting a clinical trial at Rush University, Chicago, to evaluate Ampakine CX516, a potential treatment for Fragile X and autism. This experimental new drug is the first specific treatment for learning and memory deficits in Fragile X ever tested in people with Fragile X. The compound, made by Cortex Pharmaceuticals, may help improve cognition in Fragile X by correcting a defect in the strength of brain cell communications. The trial is being funded by FRAXA.

Experimental new drugs must go through three successive stages of trials. This is a Phase II clinical trial, which means that its primary purpose is to determine safety, with a secondary goal of evaluating efficacy. Phase III is typically a large-scale test of a drug's efficacy. If Phase III testing is successful, then the company that makes the compound can apply to the FDA to market the new drug.

The trial was slated to finish this summer, but because of difficulty in finding the last few participants needed, the study will be completed in December. Several more months will then be needed for statisticians to analyze the and publish the data.

For more information on Ampakines and this clinical trial, visit the websites of Cortex Pharmaceuticals (cortexpharm.com) and FRAXA (fraxa.org).

Information About Tissue Donation

Human neural stem cells that carry the Fragile X mutation provide a crucial tool for studying the biology of Fragile X as well as for testing of potential therapeutic drugs. These cells can be grown in the lab for over a year, generating millions of brain cells that carry the Fragile X mutation. Neural stem cells are derived from post-mortem fetal cortex and their derivation is acceptable and legal under federal stem cell guidelines.

Anyone, regardless of age, is invited to register as a tissue donor. Human tissue donated at the time of surgery or death by people of all ages, or after a miscarriage or pregnancy termination, is a precious gift to humanity.

If you have questions about tissue donation, please contact Christine Wade at the NIH-funded University of Maryland Brain and Tissue Bank for Developmental Disorders, 800-847-1539, btbumab@umaryland.edu, www.btbank.org) or Dr. Anita Bhattacharyya at the University of Wisconsin, bhattacharyy@waisman.wisc.edu, or Katie Clapp 978-462-1866, kclapp@fraxa.org.

Families Needed for Research Project

We are recruiting families for a research project designed to investigate the language and communication difficulties of males and females between the ages of 10 and 15 who have Fragile X. Participation would require visiting the Waisman Center at the University of Wisconsin-Madison. Families can be reimbursed for eligible travel expenses, including hotel and airfare, if necessary. We will ask families to return for additional testing at yearly intervals for four years. For more information, contact Dr. Len Abbeduto, abbeduto@waisman.wisc.edu, or 608-263-1737 or Susan Schroeder, M.A., sschroeder@waisman.wisc.edu, mcduffoe@waisman.wisc.edu, or 608-263-5145.

This research is approved by a University of Wisconsin Institutional Review Board for the Protection of Human Participants.

INVESTIGATORS' CORNER

INFORMATION FOR STEM CELL DISTRIBUTION

Human cortical neural stem cells that carry the Fragile X mutation are available for distribution to interested researchers. These cells are grown as neurospheres and are mainly neural progenitor cells. They can be differentiated into neurons and astrocytes that lack FMRP with long-term culturing. For more information about these cells please refer to Svendsen et al., J Neuroscience Methods 85:141-163 (1998), or contact Dr. Anita Bhattacharyya at the University of Wisconsin-Madison, Waisman Center, bhattacharyy@waisman.wisc.edu.

OTHER RESOURCES FOR RESEARCHERS

Resources currently available to researchers include Fragile X Knockout mice, monoclonal antibodies for FMRP and drosophila FXRP, MPEP, and more. Visit www.FRAXA.org and select Research Resources for details.

F R A X A F A L L

National Fragile X Research Day was celebrated on October 5th. In honor of the day, Fall Fling fundraisers were held all around the country with one thing in common – proceeds going to FRAXA to help find a cure for Fragile X.

CALIFORNIA

Festival of Children

Andrea Shelly, David and Stephanie Lustig

Each year in September, the Festival of Children Foundation, founded by Sandra Segerstrom-Daniels to support Orange County children's charities, celebrates the wonders of childhood at Costa Mesa's South Coast Plaza. The month-long event is chock-full of celebrity appearances, activities, performances and fun for children of all ages. The Festival sponsors charities which showcase information about their work and goals.

This year, the Festival of Children supported 54 children's charities, including, for the first time, FRAXA. Andrea Shelly, the Orange County Chapter head of FRAXA, and David and Stephanie Lustig displayed information about Fragile X in a beautiful custom-made booth designed for FRAXA, located in Carousel Court, the busiest section of the mall. Most weekends, FRAXA's booth competed with the carousel ride and on-stage performers. Andrea Shelly reported that the booth was very busy – a large basket of beans with hidden toys satisfied children's sensory need for hours!

Jacob Lustig

FRAXA will be at South Coast Plaza again in September 2005. We are also talking to other participants (Special Olympics, Cure Autism Now, and others) about attending or organizing community events together to help gain public awareness of Fragile X and FRAXA.

Cell Phone Collection

Barbara Bott

Barbara and her colleagues at Northrop Grumman Space Technology collected old cell phones throughout their company. The phones were resold, raising over $1000 for research and informing lots of people about Fragile X, all while keeping hazardous waste out of landfills.

FLORIDA

Yard Sale

Bonnie Lucio

My family and I held a garage and bake sale. It was very well-attended – people were at my door at 6 am! A lot of people asked about Fragile X and were eager to help the cause. Michael, my four-year-old son, participated at the sale the entire time. He then went and played his soccer game and his coach (his proud dad) said it was his best game yet!

Bonnie, Michael and Jessica Lucio

GEORGIA

Casino Night

Elly and Michael Scott

Our Casino Night was a big success. Everyone had a great time and we raised $20,000 for FRAXA! Over 100 people attend and the room was full and festive. People loved the video and many shed a few tears. One of my husband's business contacts who works for BMW donated a free 6-month lease on a convertible BMW there on the spot for our auction ... raising an additional $2,800 that we didn't expect.

Michael and Ellie Scott

INDIANA

Walkathon

Carrie O'Sullivan

Carrie and family and friends organized a walkathon for FRAXA. Over 75 people turned out to show their support on a beautiful day. In addition to thousands of dollars raised, the walkathon familiarized hundreds of people with Fragile X and FRAXA.

ILLINOIS

Chicago Marathon

Michael "Shane" Clift

Fragile X afflicts my 8-year-old nephew, Matthew, and has caused heartache for his entire family. I have watched Matthew struggle with things many of us take for granted, like eating with a spoon and figuring out how and when to use the restroom. Watching him fall farther and farther behind his peers is tearing at my heart. I want what every Uncle, Grandparent, and, of course, parent wants for a child – for him to live a happy, healthy, full life. I see how it hurts my brother to see his son flapping his hands while other boys his age are playing baseball and peewee football. I HAD to do something.

I was struggling with a weight problem so I decided to shape up and help Matthew at the same time by running in the Chicago Marathon. I lost 100 pounds training for this event and then finished the Chicago Marathon with a time of 4:12:33. Flowing with the sea of 40,000 runners was exhilarating. The crowd, over one million strong, kept me going.

When Matthew's teacher learned of of this endeavor, she wanted to do something too – and so did her class. They invited the whole

Shane and Matthew Clift

F L I N G 2 0 0 4

school to help them raise money and awareness of Fragile X. They created "Color Our World" week, asking all students to brighten the lives of those around them by helping with chores, working around the house, or helping a neighbor in need, to show their support for this worthy cause. They also suggested that students wear a particular color each day.

People can see photos and donate to Shane's marathon fundraiser until February at http://www.justgiving.com/PFP/Fragilex

OHIO

Irish Night

The Maloney Family

We had karaoke, live Irish music and Irish dancers at our Third Annual Irish Night. We use our Irish heritage as the theme each year, and it is both fun and educational. My sons, Liam and Nolan, loved every minute. Liam ran around for a week before the event saying "fundraiser, fundraiser, fundraiser!"

We have raised over $8,600, and we're not done yet: an area high school is doing a collection and will be showing FRAXA's video on Fragile X to the whole school.

MASSACHUSETTS

Mystic Places Marathon

Mike Okenquist

When his good friends' son, Matthew Shelley, was diagnosed with Fragile X this summer, Mike decided to run the Mystic Places Marathon in his honor. Mike and Matthew's parents, Bob and Melissa Shelley, sent a letter asking family and friends for pledges. Their results: Mike completed the marathon and they raised $6,114 for FRAXA!

Happy Trails Run

Jerri and Mo Pratt organized the 3rd annual Happy Trails 6 Mile Run in Topsfield, raising $800 and lots of awareness among the runners. Join us next fall for this annual run in a beautiful park during peak foliage viewing season.

Pennies For A Cure

Lisa, Joanne, and Seth Thomas

During the month of October, students at East Fairhaven Elementary School where Seth Thomas' mom, Lisa Thomas, is a second grade teacher, have been saving their spare change and raising awareness of Fragile X at the same time. The students collected cans, sold cakes, saved their ice cream money, and did extra chores all to raise money for research to help Seth and other children with Fragile X. The response from the children and their families was phenomenal. The children raised a over $2700 during the three week long Pennies for a Cure fundraiser!

Seth Thomas

MICHIGAN

Mary Beth Langan of Grosse Pointe and Sally Nantais of Wyandotte, Michigan, affectionately known to each other as "the mom to the north" and "the mom to the south" decided their lives did not have enough chaos. Ted and Jerry, their husbands, may disagree. Mary Beth and Sally decided to organize a FX family cookbook to raise money and awareness and create something the whole FX family could share.

Food eXtraordinaire is their creation. For $15, you will receive a crisp red, white and black

Mary Beth Langan and Sally Nantais

spiral cookbook with 154 recipes from more than 90 contributors from Australia to New Hampshire to New Mexico. Recipes included are favorites of FX families, FX gurus, with added local flavor from politicians including U.S. Senator Debbie Stabenow and State Representative Ed Gaffney. It's a great gift and awareness piece, with "Food for Thought" and "Fragile X Information" sections.

To purchase copies, visit fraxa.org or send a check to FRAXA for $15, or call FRAXA to order by credit card.

NEW MEXICO

Craft Fair Booth

Mary Lee Shelton

I hosted a booth at a Las Cruces craft fair where high school art honor society students painted piggy banks for display and auction, and children painted piggy banks for $5 each. I bought the piggy banks in Tonala, Mexico, near Guadalajara.

Spencer Shelton at the booth of pigs

Getting the pigs through customs was an adventure! After three unsuccessful attempts by three Mexican women, I finally succeeded in importing the swine. Three burly customs officials pulled me into an inspection stall where they examined all 200 pigs. They wanted to know what non-profit activity I was supporting, so I offered a lengthy explanation of Fragile X, raising a bit more awareness on the way home!

M O R E F A L L

NEW YORK

Summer Gala

Ron and Amy Watkins

The Watkins family held their second annual gala in July at The Links at Union Vale. Guest Speakers were Eileen Naughton, President of TIME Magazine and Dr. Mike Tranfaglia, Co-founder of FRAXA. This year's event proved to be a success once again due to the support and generosity of friends, family and local businesses. Next year's gala is scheduled for September 16, 2005, so save the date and plan to attend. The Watkins' are thrilled to support FRAXA through their fundraiser. "This is one day each year we feel we are making a direct impact on Niklas' future. It's a surreal feeling to be a part of such an event and to feel the love and support of everyone in our life."

School Dollar Drive

LaGrange Middle School

Students from LaGrange Middle School participated in the Dollar Homeroom Drive to raise money as part of the Community Service Club fundraiser. This year the club chose to raise money for FRAXA to support families affected by Fragile X. The winning homeroom earned a well-deserved breakfast and FRAXA tote bags as a token of appreciation. The students at LMS raised $940. Thank you to everyone for their generous support.

Letter Campaign

Josh and Bracha Samber

On behalf of their chIdren, Chananya and Yaakov, the Sambers mounted a letter campaign; we thank all the Sambers' friends and family for their generosity!

NORTH CAROLINA

Bar-B-Que

Philip and Heather Lopina

The Lopinas and their friends and family hosted their second annual barbeque in Waxhaw, with live bands, and donated beer and food, so that all the funds raised – over $800 – could go straight to research.

B&B Fundraiser

Stations Inn Bed and Breakfast in North Springs (www.stationsinn.com) has started a fundraiser for FRAXA, with donation cans and brochures at their popular bar. They have informed many people about Fragile X and raised over $2000 and much excitement for the cause; plans are in the works for a major campaign next year.

PENNSYLVANIA

Candy Sales

Matthew Hollin and friend

Cristy Hollin

The Hollin family and their friends held a successful candy sale on Saturday October 2nd, raising more than $1,100. The candy was donated by Frankford Candy and Chocolates and the event was hosted by the Gladwyne Superfresh. Also, two more candy sales were held ... one by Gabrielle and Danielle Bembry and one by Tyler, Lexi and Chase Dennenberg at the Penn Wynne Elementary School.

Dani and Gabi Bembry

Awareness Booth

Judy Armstrong

Matthew Armstrong

I hosted a Fragile X booth at an autism walk-a-thon outside Philadelphia where several thousand people turned out. Most people who stopped by my booth were only vaguely aware of Fragile X, let alone its connection with autism. The popcorn machine I rented was quite an attraction; people gravitated right to it. I feel good about having done this, and am looking for opportunities to do more to raise awareness!

Friends Helping Friends

Angela Ross

We sold passes for a special sale evening at Boscov's, a Boothwyn department store. Our goal was $500 and we raised $1,000! It was a great opportunity to raise awareness of Fragile X, and our friends and family were very supportive.

Brett Ross

RHODE ISLAND

Letter Campaign

Rob and Janice Murphy

My husband and I feel that we need to do everything we can to provide for our son. After five long months of many therapists following his diagnosis, we decided that the next step in dealing with having a child with Fragile X was to raise as much money for research as we can. We want our son, Collin, to reach his full potential. So we took out our wedding list, added a few new names, and wrote to everyone with an update on how we all were doing, especially Collin. We asked people to donate to FRAXA because we felt that FRAXA was making the biggest difference. Mailing letters (there are many examples on the

F L I N G S !

Collin Murphy

FRAXA CD) and putting self addressed, stamped envelopes asking for donations was the next logical step for us to help find a treatment and eventual cure for Fragile X. We plan on raising funds until a cure is found.

TEXAS

Birthday Celebration

Happy Birthday, Ryan Robinette!

Thank you to Ryan's family and friends for donating to FRAXA in celebration of his birthday.

WASHINGTON

Marathon

Rob McCuistion

I completed the Portland marathon on October 5th. This was my first marathon, although I have been running for 20 years. A friend, whose child

also has a disability, ran a marathon last year and raised funds for a charity. She wrote a personal letter about her son and his disability, along with a photo of him. This really motivated me. So I mailed between 150 – 200 letters requesting sponsorships and raised $3000 for FRAXA Research!

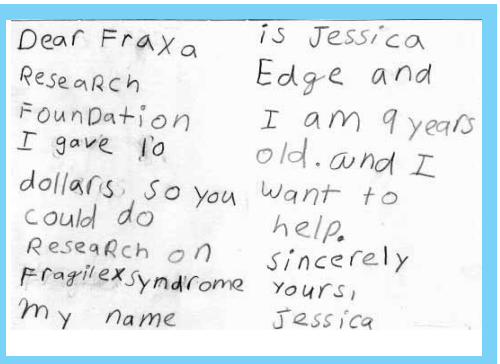
WISCONSIN

Bratfry

Carol Grunwald

Our brat fry was a big success! We were happy to have on hand FRAXA T-shirts, umbrellas and other materials. All of us working at the fry bought FRAXA T-shirts and wore them proudly. Lots of people stopped to ask about Fragile X and to buy brats and hamburgers. We made over $600 and we are already talking about a bigger and better event for the future!

Combined Federal Campaign


Dear Fraxa Research Foundation I gave 10 dollars so you could do Research on Fragilex Syndrome my name is Jessica Edge and I am 9 years old. and I want to help. sincerely yours, Jessica

The CFC is the donation program of the federal government. If you have family and friends who work at the post office, in the military, or at any government office, consider mentioning to them that FRAXA is CFC #0220. In 2004, CFC campaigns raised over $25,000 and introduced many people to Fragile X, including a very special 9-year-old whose dad works for the Forest Service in New Mexico. After listening to Fragile X parent, Frank Roth, speak about Fragile X, he wrote:

When I got home from work, I gave my daughter a big hug and was feeling very fortunate and blessed. My daughter sensed this and asked what was up. I told her that a man had given a talk at work about his son who had an illness, and I felt very glad that we had our health and each other. She asked why you were talking to us and I said it is a time at work when we donate money to people who are doctors, scientists, and care givers for people who are sick, homeless, or in need. She nodded and left the room. In a few minutes she came back with $10 of her allowance (she gets $2 a week) and said she wanted to give it to the scientists that would find a cure for your son. We sat down and wrote a letter to FRAXA and sent a donation.

C A L E N D A R O F E V E N T S

MARCH: NEW YORK CITY GALA

Join us March 10th to celebrate recent signficiant research breakthroughs and help FRAXA continue to stack the deck toward a cure for Fragile X. FRAXA's third gala in New York City will be chaired by Debbie and Jeffrey Stevenson and Eileen Naughton and Craig Chesley at Capitale.

APRIL: WASHINGTON, DC GALA

Let's all plan to have fun next April 11th at the 8th annual Mary Higgins Clark gala at the Four Seasons Hotel in Washington. We hope all our friends around the country will come to your nation's Capital to join Mary Higgins Clark in celebrating the astonishing strides our researchers have made since our last Washington gala in 2002. Thanks to the efforts of all who support their research projects, the pieces of the puzzle are indeed beginning to fit together.

Diane Rehm and Kitty de Chiara have once again agreed to co-chair with me, and Roger Mudd will be our host. Any of you who would like to help insure the success of this celebratory event are welcome to serve on the gala committee. Please contact Mary Beth Busby at (202) 462-2323 or MBBBusby@aol.com. We need and welcome lots of help and participation!

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

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

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

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

FRAXA UPDATE

EDITOR: Katie Clapp, MS
CONTRIBUTORS: Michael Tranfaglia, MD
Mary Beth and David Busby
Leslie Eddy
Susan Cohen
Hosts of Fall Flings
DESIGN: Mary Lou Supple

Students at a Columbus Ohio high school and Liam Maloney (who has Fragile X) donned FRAXA's Knockout Mouse T-shirts to help celebrate National Fragile X Research Day and raise funds for research. Fall Fling events hosted by Fragile X families around the United States raised over $105,000 to support new research at universities around the world.

PLEASE HELP FRAXA in supporting research

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

Yes, I would like to help FRAXA

☐ Member ($25+) ☐ Benefactor ($500+)
☐ Donor ($50+) ☐ Research Underwriter ($1000+)
☐ Sponsor ($100+) ☐ Named Research Fund ($5000+)
☐ Named Research Chair ($25,000+)

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

FRAXA RESEARCH FOUNDATION
45 Pleasant Street
Newburyport
Massachusetts 01950

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FRAXA UPDATE

SUMMER 2004

VOLUME 11, NO.2

A PUBLICATION OF 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 on Fragile X

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

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

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

Over 700 Gather for FRAXA's 10th Anniversary Gala

by Leslie Eddy

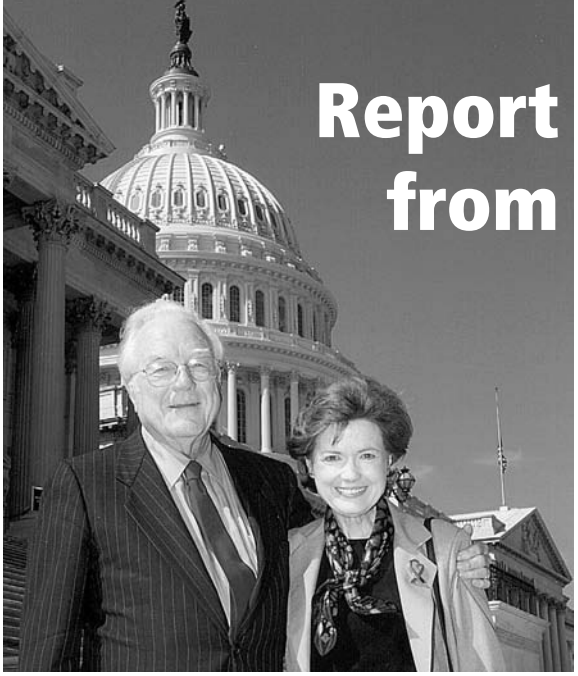
Boston Attorney Harry Manion has a reputation as a fierce advocate and a 22-year record of exceptional results. When asked to chair the 10th Anniversary Gala for FRAXA, Harry upheld his reputation, adding perhaps the most personal win of all.

Proceeds for the first Boston gala topped $700,000! Over 725 guests filled the Copley Plaza with glamour for a once in a lifetime event. The conglomerate of major media, sports (Red Sox, Patriots, Celtics and Bruins), political and business worlds created a momentum unrivaled in the Boston area. In attendance were Mayor Tom Menino, Congressman William Delahunt, Attorney General Tom Reilly, author Mary Higgins Clark, news anchor Roger Mudd, and over 200 friends and family members from all over the country lending support to Harry and FRAXA. *continued on page 9*

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

Also in this issue:

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



Report from Washington:

By Mary Beth and David Busby

Fragile X in Congress

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

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

The House of Representatives

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

All the basic research requests – which were agreed upon and urged by FRAXA, the National Fragile X Foundation, and Conquer Fragile X – were ignored by the House Subcommittee.

The Senate

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

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

Contact your Senators!

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

Who's This? See p. 11

RESEARCH WORKSHOPS

5th Annual Fragile X Banbury Meeting

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

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

Randi Hagerman, Fabrizio Gasparini

Much discussion centered on receptor/transmitter systems which research indicates are impaired in Fragile X, particularly those involving glutamate and GABA, and compounds which target those systems. By the time we finished, it had become clear that more work is needed to design good clinical trials to effectively test drug treatments for Fragile X. Several exciting new collaborations between industry and university scientists were established at the meeting, and a new drug trial in Fragile X patients is now being planned.

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

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

At the Crossroads: Fragile X and Autism

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

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

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

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

FRAXA Grants Awarded in July 2004

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

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

The mGluR Theory of Fragile X

Mark Bear

MARK BEAR, PhD

Principal Investigator

NAVEEN NAGARAJAN, PhD

Postdoctoral Fellow

Mass. Institute of Technology (MIT)

$37,476 renewal

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

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

Role of the Cerebellum in the Dysfunction of Fragile X Syndrome

Ben Oostra

BEN OOSTRA, PhD

Principal Investigator

BAS KOEKKOEK, MD, PhD

Postdoctoral Fellow

Erasmus University, The Netherlands;

$55,000

The mGluR Theory of Huber, Bear, and Warren predicts that excessive function of signaling pathways associated with mGluRs causes most of the symptoms of Fragile X. It appears that mGluR5 is responsible for most of the problem in the brain overall. However, mGluR5 is not present at all in the cerebellum, a part of the brain associated with coordination of movement and sensory integration, and the area which is known to express very large quantities of FMRP in the normal brain. Clearly, the cerebellum is important in the pathogenesis of Fragile X (and autism, too!), but here mGluR1 regulates the activity of these hyperactive pathways.

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

Life imitates the movies

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

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

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

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

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

update:

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

WALTER KAUFMANN, MD, PhD

RICHARD HUGANIR, PhD

PAUL WORLEY, PhD

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

Walter Kaufmann

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

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

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

INVESTIGATORS' NOTE:

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

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

CATHERINE CHOI Principal Investigator, Drexel University

SEAN MCBRIDE Co-Investigator, Albert Einstein College of Medicine

TOM JONGENS, PHD Co-Investigator, University of Pennsylvania

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

Specific Tests of the mGluR Hypothesis

PETER VANDERKLISH, PhD

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

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

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

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

Oswald Steward

OSWALD STEWARD, PHD
Principal Investigator

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

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

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

Studies of FMRP Function in the Xenopus Visual System

Holly Cline

HOLLY CLINE, PhD Principal Investigator

JENNIFER BESTMAN, PhD
Postdoctoral Fellow
Cold Spring Harbor Laboratory, NY; $40,000

Jennifer Bestman is new to the Fragile X field, having started her first Fragile X study with FRAXA funding last year. This research group is examining the normal role of FMRP using tadpoles as a model (when multiple model systems yield similar results, the perceived weight of the evidence produced is much greater). So far, they have shown that FMRP and associated proteins and translation factors are involved in the development of neurons in tadpoles; they now plan to explore the effects of numerous pharmacologic interventions in this model system. These studies may yield further support for the mGluR Theory of Fragile X by demonstrating the process (excessive mGluR-LTD) in yet another species, and – hopefully – demonstrating potential efficacy of mGluR antagonists.

research

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

ANGELA GIANGRANDE, PhD
Universite Louis Pasteur, Strasbourg; $45,000

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

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

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

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

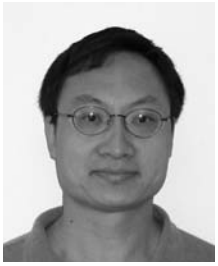
Clinical Trial – Ampakines

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

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

update:

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


Fen-Biao Gao

FEN-BIAO GAO, PhD Principal Investigator
FAY WANG, PhD Postdoctoral Fellow
University of California at San Francisco; $55,000

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

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

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

GARY BASSELL, PhD Principal Investigator
LAURA ANTAR Graduate Student
Albert Einstein College of Medicine, NY; $15,000 bridge renewal

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

FRAXA has supported the Bassell lab since 2000, and we are very gratified to report that Gary Bassell has secured funding from NINDS to support and expand the work in his laboratory starting December 1st, so this FRAXA award will help support the lab until then. Laura Antar, an MD-Ph.D. student, is completing the PhD portion of her studies and will soon move on to clinical work (for the MD degree). Bassell and Antar recently published articles in the journal Cell (called "Sunrise at the Synapse") and in the Journal of Neuroscience discussing the Fragile X protein and mGluRs.

Dissection of the Fragile X Protein Binding Domains

STEPHEN WARREN, PhD Principal Investigator
REID ALISCH, PhD Postdoctoral Fellow
Emory University; $40,000


Stephen Warren

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

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

Xenopus Model of Fragile X


Edouard Khandjian

EDOUARD KHANDJIAN, PhD
Principal Investigator
LAETICIA DAVIDOVICH, PhD
Postdoctoral Fellow
Laval University, Quebec; $35,000

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

Analyses of Functional Interactions Between dFMR1 and RNAi Genes

Young Sik Lee

RICHARD CARTHEW, PhD
Principal Investigator
YOUNG SIK LEE, PhD
Postdoctoral Fellow
Northwestern University; $40,000

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

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

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

Reactivating the FMR1 Gene

ANDRE HOOGEVEEN, PhD Principal Investigator
VIOLETTA STOYANOVA, PhD Postdoctoral Fellow
Erasmus University, The Netherlands;
$35,000 renewal

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

Research Forum

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

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

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

Attn: Fragile X Families:

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

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

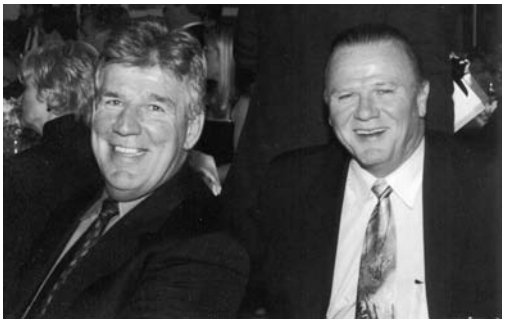
FRAXA's 10th Anniversary Gala in Boston

Ruth Pointer of The Pointer Sisters, and Harry Manion

continued from page 1

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

The "Once in a Lifetime Auction" included the pairing of celebrities who masterfully worked the room, tapping into the competitive and generous spirit of the crowd to drive up the bidding. Eddie Andelman, from Boston Radio's 1510 The Zone, led off by offering lunch for two in D.C. with Eddie and the legendary Red Auerbach. Hawaiian Paradise, presented by auctioneers Sara Underwood and Ted Wayman, a private jet to a villa in the Bahamas, and a seaside casita in Cabo San Lucas were among the fantasy packages bringing in the highest bids. The last item, a Season with the Red Sox, secured the evening's largest bid of $35,000!



Terry O'Reilly and Rick Middleton

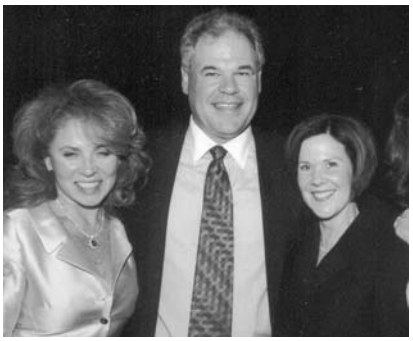
Congressman William Delahunt, Katie Clapp

For FRAXA, there were many wins that evening. Abundant news coverage before, during, and after the event brought FRAXA and Fragile X into the public eye. New England Cable News, the Boston Globe, Herald, Boston Business Journal and many local papers covered the story, and both NESN and Fox 25 broadcast live from the Copley that evening.

Leslie Eddy, Debbie Stevenson, Claire Dunsford and Mike Tranfaglia

Attorney General Tom Reilly

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



Kathy Campanella, Harry Manion, Kathy Meyer

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

FRAXA FUNDRAISERS

Raising Awareness and Funds for Research

Kelley Randels with Mary Higgins Clark

Omaha Hosts 7th Annual Mary Higgins Clark Gala

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

Megan Massey and Senator Chuck Hagel

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

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

Leslie and Ara Bagdasarian, Coach Dave Frantz

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

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

Robert Bauchwitz, Mike Tranfaglia, Marty Boise

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

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

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

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

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

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

Luke Solotaroff

CALENDAR OF EVENTS

OCTOBER FRAXA FALL FLING

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

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

NOVEMBER

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

MARCH

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

APRIL

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

PUBLICITY!

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

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

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

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

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

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

FRAXA'S NEW BUSBY T-SHIRT

Why a Knockout Mouse?

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

Why's he called Busby?

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

Who designed it?

An appeal went out to creative friends, and a committee chose an image by graphic designer Jeri Froehlich of Froehlich Bonini Associates in Ossining, NY. Jeri contacted Leslie Geist of MRP Lawrence Marketing of Armonk, NY, had the shirts ready in time to debut at the NFXF Conference in Washington DC in June. Thanks to them both!

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

How do I order?

There are cute small ones for your kids and bigger ones for adults. FRAXA makes much-needed money on each sale, and the shirts help publicize our our fight to find a cure! Send your order specifying quantities and sizes along with your check to FRAXA, 45 Pleasant St., Newburyport, MA 01950.

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

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

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

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

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

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

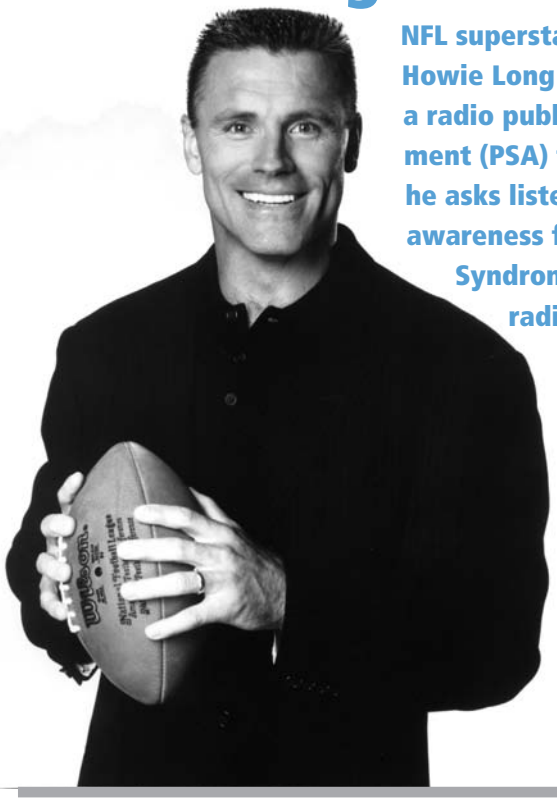
FRAXA UPDATE

EDITOR: Katie Clapp, MS

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

DESIGN: Mary Lou Supple

Howie Long PSA Available!



NFL superstar and Hall of Famer Howie Long generously produced a radio public service announcement (PSA) for FRAXA in which he asks listeners to help raise awareness for Fragile X Syndrome. Call your local radio stations and ask them to air it. We can edit this clip to fit any time slot that your stations may have available.

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

PLEASE HELP FRAXA

in supporting research

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

Yes, I would like to help FRAXA

☐ Member ($25+)
☐ Benefactor ($500+)
☐ Donor ($50+)
☐ Research Underwriter ($1000+)
☐ Sponsor ($100+)
☐ Named Research Fund ($5000+)
☐ Named Research Chair ($25,000+)

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

FRAXA RESEARCH FOUNDATION
45 Pleasant Street
Newburyport
Massachusetts 01950

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FRAXA UPDATE

SPRING 2004

VOLUME 11, NO.1

A PUBLICATION OF 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

FRAXA Funds New Research

by Katie Clapp, president & co-founder

FRAXA Research Foundation FRAXA kicked off 2004 by funding 10 grants and fellowships for a total of $555,000! Over the past several years, FRAXA has funded over one million dollars in research grants each year, accelerating the pace of progress, scientific publications, and discoveries towards our goal: specific treatments and ultimately a cure for Fragile X syndrome.

The new projects pursue two lines of inquiry:

1. Solving the mystery of FMRP, the protein lacking in brain cells of people with Fragile X. Scientists are identifying the molecular targets of this protein in order to guide the design of effective new treatments and to identify existing treatments to help people with Fragile X.
2. Pursuing the mGluR theory of Fragile X and the drug therapies (Ampakines and mGluR antagonists) that it suggests.

FRAXA's next deadline for new research proposals is May 1, 2004. After peer review by our Scientific Advisory Board and other scientists expert in Fragile X research, the additional awards will be announced in July.

"... for the first time in 22 years I can see a rational therapeutic approach."
– Dr. Stephen T. Warren

As you will see from the descriptions starting on page 3, there has been great progress in Fragile X research. In the words of Dr. Stephen T. Warren, a FRAXA Scientific Advisor and co-discoverer of the Fragile X gene in 1992, "although a great deal of work remains to be done before clinical trials [based on the mGluR theory] can be initiated, for the first time in 22 years I can see a rational therapeutic approach."

10th Anniversary FRAXA Galas Set for this Spring

May 6th in Omaha

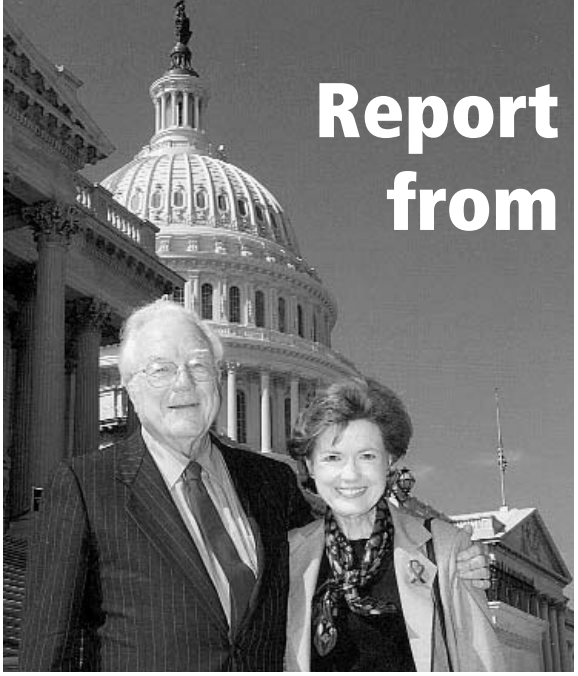
The Nebraska Fragile X Families Association presents the Seventh Annual Mary Higgins Clark Fragile X Gala, with Special Guests **Senator Chuck Hagel, TIME Magazine president Eileen Naughton, and author Mary Higgins Clark.**

May 19th in Boston

Harry Manion agreed to chair FRAXA's 10th Anniversary Gala at the Copley Plaza Hotel in Boston and has assembled a spectacular evening with celebrity guests including **Governor Romney, Boston's Mayor Menino**,author **Mary Higgins Clark, Roger Mudd, Boston sportscasters Bob Lobel and Bob Neumeier, and sport stars Danny Ainge, Howie Long, Sean McDonough, Willie McGinest, Rick Middleton, and Terry O'Reilly**. **Ruth Pointer** of the fabulous Pointer Sisters will perform. This is not an event to miss! Contact Katie Clapp at 978-462-1866, FRAXA.org or kclapp@fraxa.org.

Also in this issue:

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



Report from Washington:

By Mary Beth and David Busby

Congress is hard at work, and the annual Reports of the House and Senate Appropriations Committees are our major focus. These Reports accompany the appropriations bills of the House and Senate and tell the administrative offices of the federal government (the National Institutes of Health (NIH) the Centers For Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA)) how to spend the appropriations. We are asking our FRAGILE X ADVOCATES (that's you!) to urge members of Congress to provide funds for the following ten requests:

1. the National Institute for Child Health and Human Development (NICHD) to issue a Request for Applications to enhance its new Fragile X Research Centers and to recruit new Fragile X researchers.
2. the National Institute of Mental Health (NIMH) for its studies of causes of, and pharmacological treatments for, Fragile X and related disorders such as autism.
3. the Office of the Director of the NIH for coordination of Fragile X research.
4. the program of the Director of the NIH to enhance pediatric training and career development grants to include new Fragile X researchers under the Children's Health Act of 2000.
5. the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) to study the effects of Fragile X outside the brain.
6. the CDC's National Center on Birth Defects and Developmental Disabilities to develop a public health and epidemiological research initiative on Fragile X
7. the CDC to screen and provide help for families and individuals affected by Fragile X and other heritable disorders.
8. HRSA to expand the Title XXVI newborn screening, counseling, testing and special services program for newborns and children at risk for heritable disorders, including Fragile X.
9. the National Institute of Neurological Disorders and Stroke (NINDS) to study the effect of Fragile X on fundamental brain circuitry, especially on older carriers.
10. NINDS to expand research of Fragile X-associated tremor/ataxia syndrome and provide counseling for daughters of FXTAS patients about their carrier status of the Fragile X mutation.

Here is how you can help make these requests become reality:

Write, call or visit your Senators and Congressional representatives. Explain your personal interest in Fragile X. You will be surprised how much impact just a few letters or calls or visits can have!

HOW TO CONTACT CONGRESS

Write to Senators at:
Senate Office Building
Washington, D.C. 20510

Write to Representatives at:
Cannon House Office Building
Washington, D.C. 20515

Or, visit www.congress.org on the web.

HOW TO JOIN OUR FRAGILE X ADVOCATES

David Busby maintains an email list of ADVOCATES who are willing to contact members of Congress at critical moments in our advocacy efforts. You can join this list by calling David at (202) 442-3512 or emailing Busby.David@dorseylaw.com

FRAXA's Law Firm Wins Award

DORSEY & WHITNEY LLP, which has served pro bono publico as FRAXA's counsel for the last 10 years, was honored to receive the coveted National Law Journal's 2003 Pro Bono Award to large firms for its long-time commitment to pro bono service. By agreement with the American Bar Association, the Dorsey firm donates at least 3% of its billable hours to charitable organizations. FRAXA is a major recipient of this program. The firm is headquartered in Minneapolis and has 21 offices worldwide. David Busby, a father of two Fragile X sons, is "of counsel" to the Washington, D.C. office and serves as, among other things, FRAXA's liaison with the Federal Government.

Megan Massey Appointed to Federal Post

FRAXA Board member, Megan Massey, has been appointed by the Secretary of Education to the Federal Interagency Coordinating Council, which was formed as part of the Individuals with Disabilities Education Act (IDEA) in 1991. Megan's two sons, Jack and Jacob, both have Fragile X.

The FICC advises cabinet secretaries from the Departments of Education, Health and Human Services, Agriculture, Defense, and the Interior, as well as the commissioner of the Social Security Administration. The council's goal is to improve opportunities for children with disabilities. The FICC meets quarterly to identify gaps in programs and services, ensure the provision and support to children and their families, coordinate technical assistance activities across agencies, and identify barriers to this coordination of services.

These meetings take place in Washington, so Megan will be making the trip from Scottsbluff, Nebraska, on a regular basis. Congratulations to Megan for taking on this important work.

Kathy May is Public Citizen #1

FRAXA co-founder Kathy May of Fairfax, VA, was recently selected as the 2004 Public Citizen of the Year by the Virginia Chapter of the National Association of Social Workers. Kathy will now compete with winners in all 50 states for the overall national title.

Kathy May helped to start FRAXA in 1994; without her unflagging enthusiasm, there would not be a FRAXA. Kathy's son Sam, now 14, has Fragile X. Kathy has worked for the ARC of Northern Virginia for 10 years.

In her current position as Lead Advocate she focuses on influencing outcomes that directly affect the lives of individuals with developmental disabilities.

FRAXA Financial Report for 2003

Our audit for 2003 is done, and again FRAXA excels at efficiency.

2003

Income	
Donations, fundraising, investments, book sales	$1,841,000
Expenses	
Research (FRAXA Grants)	$1,103,000
Research (jointly funded with NICHD)	$200,000
Education	$28,000
Management	$36,000
Fundraising	$180,000

FRAXA dollars spent on research grants and fellowships

In 2003, FRAXA raised more than twice the amount we raised in 2002, which means that we can now fund significantly more research. The 2003 increase was thanks to a growing number of individual donors – more than 3000 in all! Our task for 2004 is to spread the word and broaden our base of support so that we can, in turn, accelerate the pace of Fragile X research.

Four Stars for FRAXA!

FRAXA has again received a 4-star rating from Charity Navigator, the largest independent evaluator of charities in the United States. Receiving four out of a possible four stars indicates that FRAXA excels, as compared to other charities in America, in the area of strong fiscal management. Visit www.CharityNavigator.org on the Web for a nice set of charts rating specific aspects of our organization. Guidestar, www.Guidestar.org, is another site featuring further details on FRAXA and other national charities.

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

FRAXA Grants and Fellowships Awarded in January 2004

research

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

These descriptions are written by the investigators and edited for a general audience by Katie Clapp.

Specific Tests of the mGluR Hypothesis

PETER VANDERKLISH, PhD

Scripps Research Institute, San Diego, CA; $50,000

Dr. Vanderklish became fascinated by Fragile X after attending last year's Banbury meeting. Banbury conferences are sponsored each spring by FRAXA through a grant from the National Institute of Mental Health (NIMH).

Funded thanks to Andrea and Damon Shelly, who hosted a Christmas luncheon to benefit FRAXA in December, 2003.

Our Previous Work

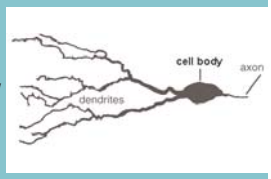
Consistent with the mGluR theory (see box at right), we observed that stimulation of mGluRs leads to elongation of dendritic spines. These changes in dendritic spine shape are dependent on protein synthesis and resemble those that occur in the Fragile X brain. Interestingly, multiple lines of evidence indicate that LTD and spine elongation are mechanistically linked; that is, that longer, thinner spines express the depressed synaptic state. Thus, altered synaptic plasticity and morphology (shape) may result from the same translation-dependent process that, once induced, is not properly limited in the Fragile X brain. As the saying goes, form follows function.

Our Current Project

Currently, we are testing three predictions of the mGluR theory:

1. Mark Bear and Kim Huber have already shown that LTD is enhanced in mice lacking FMRP. We predict that mGluR-induced spine elongation should be exaggerated in these mice. We are using live-cell imaging techniques to test this possibility and the ability of candidate pharmacological therapies for Fragile X, such as Ampakines and MPEP, to correct any imbalances.
2. We have evidence that two modes of translation initiation operate in dendrites (CAP-dependent and IRES-dependent), and that stimulation of mGluRs primarily activates just one of these (CAP-dependent). The mGluR hypothesis predicts that lack of FMRP increases CAP-dependent translation; we are testing to see if this is true.

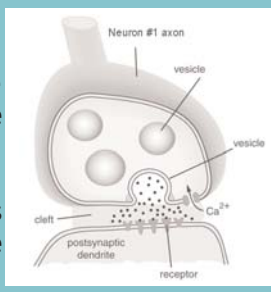
Life imitates the movies



DNA Our genes are made up of DNA. Think of this as the master copy of a movie locked away in a Hollywood vault (neuron's nucleus). DNA is too valuable to be allowed to travel outside the nucleus.

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

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



synapse This is where the show goes on … the site where neurons exchange signals. A synapse has two parts: the signalling neuron's axon and the receiving neuron's dendrite.
When Neuron #1 spits out a message, receptors on dendrites of Neuron #2 are poised to receive it. Many kinds of receptors coat dendrites, but we are especially interested in mGluRs, metabotropic glutamate receptors, because growing evidence indicates that group 1 mGluRs function improperly in Fragile X.

Life Beyond the Movies

Imagine that watching a movie causes the theatre to change its size and shape. In neurons, when proteins are synthesized from mRNAs, one result is synaptic plasticity: a synapse changes its size and shape, depending on how much activity it is getting. One form of synaptic plasticity is LTP (*long term potentiation*), in which a synapse grows stronger and larger in response to high-frequency activity; another is LTD (*long term depression*), in which it shrinks and weakens in response to low-frequency activity. These changes underlie learning and memory.

The mGluR Theory of Fragile X

Several years ago, Drs. Kim Huber, Steve Warren, and Mark Bear found in Fragile X mice an excess of one kind of LTD. Lack of a single protein, FMRP, causes Fragile X syndrome. In the normal brain, stimulation of mGluRs leads to translation of many mRNAs into proteins at dendrites, including FMRP. Recent work suggests that FMRP normally suppresses translation of some of these mRNAs. In the Fragile X brain, however, FMRP is not present to put the brakes on protein production and as a result, too much mGluR-LTD occurs. Scientists believe that LTD is one of the primary mechanisms of learning and memory. The "mGluR theory" of Huber and Bear proposes this as the cellular basis for cognitive impairment and other symptoms of Fragile X.

3. Finally, we are testing whether preponderance of long, thin, and presumably lower efficacy, synapses in the Fragile X brain leads to compensatory changes in neurons. Recent research has shown that neurons adapt to deficits in net input by lowering firing thresholds and altering a number of intrinsic properties. If long, thin spines reduce net synaptic input, we would expect to see such changes, and they could underlie a number of symptoms of Fragile X. We are characterizing the intrinsic properties of neurons in the cortex and hippocampus of mice lacking FMRP. If differences are found with respect to control animals, this system could provide a testbed to see if potential therapeutic drugs (such as Ampakines and MPEP) can restore basic neuronal properties to their normal state.

Audiogenic Seizures and Effects of mGluR5 Agonist MPEP in the Fragile X Mouse

ROBERT BAUCHWITZ, PhD
Principal Investigator
QI JIANG YAN, PhD Postdoctoral Fellow
Columbia University, $107,000 renewal


Robert Bauchwitz

Dr. Bauchwitz's work on seizures in Fragile X mice suggests that mGluR5 antagonists may effectively treat a range of symptoms of Fragile X.

As described above, mGluR receptors have been implicated in the abnormal neuronal responses observed in Fragile X syndrome. To address whether reversing mGluR signaling alterations might ameliorate the effects of Fragile X, we have tested a drug, MPEP, which specifically blocks one type of group 1 mGluR receptor (mGluR5).

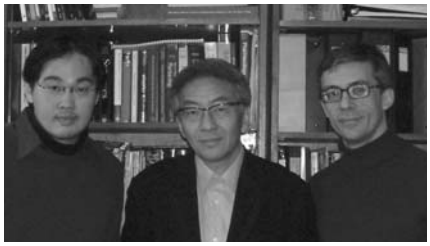
Using MPEP, we have been able to reverse the susceptibility that Fragile X mice have to audiogenic seizures, which are triggered by very loud sound.

We have also shown that the degree of rescue is equivalent to that found by placing a copy of the human FMR1 gene into the genome of Fragile X mice, suggesting that MPEP can compensate for lack of FMRP in protecting against audiogenic seizures. We are also testing the effects of mGluR5 antagonists in other learning and behavioral assays.

Finally, we are producing new mouse models of Fragile X which might give more robust learning deficits comparable to those observed in humans. If that is the case, we will use such animals to further assess the effectiveness of mGluR antagonists and other compounds on Fragile X cognition.

Metabotropic Glutamate Receptor Function in Fragile X Syndrome

ROBERT WONG, PhD
SUNY Downstate, NY
$46,000


Abraham Chuang, Ph.D., Robert Wong, Ph.D., and Riccardo Bianchi, Ph.D.

Like Dr. Vanderklish, Dr. Wong began his Fragile X studies after last year's Banbury meeting. He is investigating how seizures are generated in Fragile X neurons. More generally, he is looking at how synapses are modified to enable learning and memory and how this process is impaired in Fragile X.

We are studying the processes that cause the normal brain to become epileptic. There may be multiple mechanisms involved. We study seizures triggered by the activation of one kind of neuronal receptor, metabotropic glutamate receptors (mGluRs), in hippocampal neurons of mice.

When hippocampal neurons are exposed to chemicals which stimulate only group 1 mGluRs, the neurons fire epileptiform discharges (which trigger seizures). We and others have shown that this occurs only if new proteins are being synthesized.

Our results show that intense stimulation of the glutamate synapses cannot elicit the group 1 mGluR-mediated epileptogenesis in normal mice. Apparently, neurons of normal mice have a mechanism to protect them from seizures. In contrast, using tissue from Fragile X knockout mice, this same stimulation easily and consistently elicited robust seizure activity.

We are testing the theory that in normal mice, the protein FMRP suppresses group 1 mGluR-dependent epileptogenesis by suppressing the translation of one or more proteins which are involved in triggering seizures. Our experiments will evaluate whether the function of group 1 mGluRs is exaggerated in neurons in the cortex of Fragile X knockout mouse. We plan to extend our studies to evaluate whether abnormalities in mGluR function can also affect other basic brain functions involved in learning and memory.

INVESTIGATORS' NOTE:

Fragile X Knockout Mice now available from Jackson Laboratory

The new strain is FVB.129P2-Fmr1<tm1Cgr>/J.
Visit http://jaxmice.jax.org for details.

Pharmacological Rescue of Behavioral Abnormalities in FMRP Deficient Mice by a GABA (B) Receptor Agonist

MIKLOS TOTH, PhD

Cornell University; $50,000

An exciting aspect of this project is that it evaluates an already-approved drug as a treatment for seizures – and perhaps additional symptoms – in Fragile X.

Fragile X syndrome causes a broad range of symptoms, from cognitive deficiency to anxiety and sensory (tactile, visual and auditory) abnormalities. Some of these symptoms are well reproduced in Fragile X mice; in particular, their response to sound is significantly altered. This includes increased neuronal excitability in the auditory neuronal pathway, audiogenic seizure susceptibility, and increased filtering of sensory input, indicating a functional abnormality in the flow and processing of auditory information. Central auditory processing abnormalities in humans are manifested as inattention, poor listening skill, and difficulty in speech-understanding, which are also typical characteristics of autism, attention deficit disorder and Fragile X syndrome.

The aim of our research is to use drugs to correct neural abnormalities in Fragile X mice. We have found that chronic administration of the GABA(B) receptor agonist baclofen normalizes the defect in sensory information filtering in Fragile X mice, presumably because it suppresses excitability and/or compensates for mGluR activation. We will then test whether other behavioral defects in Fragile X mice can also be corrected by baclofen. By targeting the GABA(B) receptors rather than the glutamate system, these studies may provide an alternative strategy for the treatment of Fragile X syndrome.

CLINICAL TRIAL OF AMPAKINES

Dr. Elizabeth Berry-Kravis is conducting a clinical trial of Ampakines, a new class of experimental drugs. The study is funded by FRAXA at RUSH University in Chicago.

One consequence of mGluR-LTD, which is thought to be excessive in Fragile X syndrome, is fewer than normal functional AMPA receptor proteins. Ampakines work by increasing the activity of AMPA receptors.

Adults with Fragile X are still welcome to participate. See p. 9 or www.fraxa.org for details.

research

Pharmacological Rescue of the Drosophila Fragile X Model

TOM JONGENS, PhD

University of Pennsylvania; $70,000

Dr. Jongens first received a FRAXA award in 2002 and this new project builds on the previous work. Dr. Jongens was recently awarded tenure at the University of Pennsylvania.

The Drosophila (fruit fly) genome contains a single gene, called dfmr1, that is similar to the human FMR1 gene. In flies, loss of dfmr1 function leads to behavioral and neuronal defects similar to symptoms observed in Fragile X patients. One behavioral defect displayed by Fragile X flies is the loss of normal circadian rhythms. A normal fly is active for 12-14 hours during daylight and relatively inactive for 10-12 hours at night. If entrained to a light:dark cycle of 12 hours of light followed by 12 hours of dark for several days, a normal fly can maintain a normal pattern of activity in total darkness for up to 3 weeks. But dfmr1 mutant flies lack this capacity and display an erratic pattern of activity. Similarly, some children with Fragile X have great difficulty sleeping through the night.

Another behavioral change in Fragile X flies is a failure to display immediate recall in a courtship-based learning and memory assay. When placed in a small chamber with an unreceptive female (a previously mated female), normal males learn that their courtship attempts will not be successful and they drastically reduce their attempts. This learning occurs within one hour. These "trained" males remember this negative experience over the next several hours and so they do not court when placed in a new chamber with a receptive (unmated) female. Interestingly, we have observed that the dfmr1 mutant males learn during the one-hour "training" session with the unreceptive female, but fail to display any memory of this experience, even if they are immediately placed in a new chamber with a receptive female.

In collaboration with Sean McBride and Tom McDonald at Albert Einstein College of Medicine, we are attempting to identify drugs that ameliorate the two defects described above. Since these studies and others suggest that there is a defect in synaptic plasticity in all Fragile X models, we will test the effect of drugs that are known to alter the activity of neuronal receptors that modulate synaptic plasticity.

update:

Already we have tested mGluR antagonists (MPEP and other compounds) and have seen some very promising rescue of the defects observed in the courtship based learning and memory assay, including rescue of short-term memory.

The Role of MicroRNAs in the Pathogenesis of Fragile X

THOMAS TUSCHL, PhD Principal Investigator

ALEXEI ARAVIN, PhD Postdoctoral Fellow

Rockefeller University; $35,000

Thomas Tuschl

More than ten years have passed since it was discovered that Fragile X syndrome is caused by the absence of a single protein, FMRP. Studies have demonstrated that FMRP regulates the translation of mRNAs into proteins by recognizing and binding to numerous mRNAs. This process is crucial for the function of neurons. However, it is not well understood how FMRP recognizes a particular mRNA and how it regulates the mRNA's translation into a protein. Understanding this will help facilitate the development of therapeutic treatments.

Alexei Aravin

Recent discoveries in the new field of RNA interference (RNAi) have lent insight into how FRMP recognizes its target mRNAs. Like FMRP, the RNAi machinery regulates the translation of numerous mRNAs. The RNAi machinery recognizes its target mRNAs through tiny non coding RNAs termed microRNAs (miRNAs). miRNAs are found in all animals, so 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 the RNAi machinery to regulate gene expression. FMRP and miRNAs most likely recognize and regulate a common set of mRNA targets in the human brain. The misregulation of these target mRNAs in Fragile X patients probably causes the disease.

Our laboratory pioneered the biochemical investigation of RNA interference. To understand miRNA function, we have developed tools that interfere with miRNAs in human cells. We will use "bioinformatics predictions" in combination with the tools and assays we have developed to identify miRNA targets, and hence possibly new targets of FMRP.

Flies for Kids: Developing a Genetic Model for the Neuropathology and Behavioral Deficits in Fragile X

BASSEM HASSAN, PhD

Flanders University, Belgium; $25,000

Bassem Hassan (left) and lab members

Dr. Hassan's decision to go into this field is not only a matter of pure scientific interest, but also personal since Fragile X has touched his family.

In our lab we use the fruit fly, which has proven a powerful tool for unravelling genetic mechanisms. Fruit flies have a single copy of the Fragile X gene, called dFMR1. The fly dFMR1 protein, as with the human protein, is known to interact with other proteins and mRNAs (the intermediate between DNA and protein).

Children with Fragile X display behavioral impairments and anatomical defects in how neurons (brain cells) connect to each other. We have already shown that flies lacking the dfmr1 gene show behavioral and anatomical defects in their brains. How do these defects occur? The Fragile X protein appears to play a major role in controlling the expression of other genes – many other genes! How, then, can we tell which of these genes are most important in causing the brain defects?

To tackle this question, we checked all genes in flies for the sequences to which the dFMR1 protein binds. We found around 260 such genes. Next we asked which of these genes are not correctly regulated in mutant flies. We found that genes which regulate the shape of cells, *cytoskeleton* genes, were most consistently affected. Next, we asked if playing with the amounts of these cytoskeletal proteins and the amount of dFMR1 could prove a functional relationship between the two. This was the case. It appears that the major problem in the brains of Fragile X flies, and perhaps in the brains of patients as well, is that genes which give neurons their shape and control their connectivity are not present in the right amounts.

The key now is to understand the relationship between the misregulated genes, the defects we see in brain cells, and the behavioral problems of the Fragile X flies. To do that, we have to be able to switch the dFMR1 gene off and back on whenever and wherever we want and ask which brain cells need this protein and when do they need it for normal development and behavior. Using a new trick called "transgenic RNAi," we are testing the requirements for dFMR1 in different neurons at different times and should be able to correlate the genetics with the anatomy and the behavior to paint a detailed picture of how this one gene can have such dramatic effects on brain development.

MGluR-Dependent Protein Translation in Wildtype, FMR1 Knockout, and FMR1 YAC Transgenic Mice

ERIC KLANN, PhD Principal Investigator

LINGFEI HOU, PhD Postdoctoral Fellow

Baylor University; $57,000

Dr. Klann, who first received a FRAXA grant last year, collaborates with several other Fragile X investigators at Baylor University, the site of one of the federally-funded Fragile X Research Centers created under the Children's Health Act of 2000.

Previous studies indicate that FMRP binds to certain mRNAs and may regulate the translation of these mRNAs into proteins. As explained above, other studies show that mGluR-LTD is enhanced in mice that lack FMRP. Taken together, these two findings suggest the intriguing possibility that mGluR-LTD may be enhanced in Fragile X mice *because of* an increase in the translation of specific mRNAs. We are investigating this possibility.

We have found that several signaling pathways couple mGluRs to the protein translation machinery during mGluR-LTD. These pathways point to candidate mRNAs that may be rapidly translated after the induction of LTD. We have observed that rapid translation of several mRNAs occurs during LTD in normal mice, and that, in contrast, translation of these mRNAs is altered in Fragile X mice. In complementary studies, we have begun to study mGluR-LTD in mice that overexpress human FMRP (YAC FMR1 transgenic mice) to determine whether there are differences in LTD-induced mRNA translation between wild-type mice and YAC FMR1 transgenic mice.

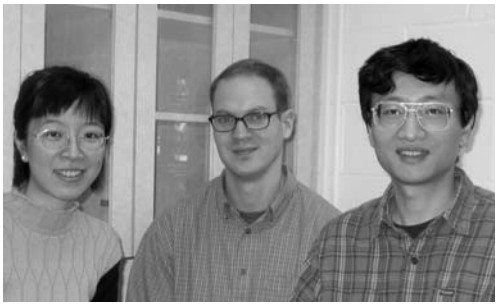
We believe that identifying mRNAs translated in response to mGluR activation, and finding out whether their translation is altered during LTD in FMR1 knockout mice and/or YAC FMR1 transgenic mice, will be helpful in designing therapeutic agents for the treatment of patients with Fragile X.

FMRP Regulates Small GTPase Ras Signaling and Glutamate Receptor Trafficking

JULIUS ZHU, PhD

University of Virginia $65,000

Dr. Zhu's team is investigating synaptic plasticity in the Fragile X knockout mouse. They have found that two particular signaling pathways – small GTPase Ras pathways – are impaired in the knockout mouse. In these mice, they find very few of the AMPA receptors which are normally at synapses. Lack of AMPA receptors results in reduced synaptic plasticity in the Fragile X mice. This research complements Dr. Elizabeth Berry-Kravis's ongoing clinical trial of AMPAkines, compounds specifically designed to enhance the activity of AMPA receptors, so that each existing receptor is more effective. Dr. Zhu and his team are using physiological and molecular biological techniques to investigate the defects in Ras signaling and AMPA receptor trafficking in Fragile X mice. They will test whether Ras-GEF (a protein which activates Ras and is regulated by FMRP) can restore normal delivery of AMPA receptors to synapses. Their findings may point to promising targets for the design of new drugs to treat Fragile X.



Hailan Hu, Joel Baumgart, and Julius Zhu

Generating Human Neurons Carrying the Fragile X Mutation

CLIVE SVENDSEN, PhD Principal Investigator

ANNA BHATTACHARYYA, PhD Postdoctoral Fellow

University of Wisconsin, Madison; $50,000

Neural stem cells have exciting implications for the potential treatment of many nervous system disorders. Dr. Svendsen, a world-reknown expert in stem cell technology, is growing human neurons that express the Fragile X mutation. These stem cells are generating infinite quantities of neurons in cell culture, in the form of neurospheres, balls of neurons which increase in size. These neurons will be characterized in detail to understand the effects of lack of FMRP. The neurons will be made available to the scientific community.

There are essential differences in biology between mice and humans (not to mention the even greater differences between fruit flies and humans) which make these human neurons invaluable tools to advance studies of Fragile X and evaluate potential treatments. Unlike the mouse and fly neurons, in which the Fragile X gene is deleted (knocked out of the genome), these human neurons contain the actual Fragile X genetic mutation, so that therapeutic strategies aimed at reactivating the gene can be explored.

STUDIES IN SEARCH OF PARTICIPANTS

Please note that there are no direct medical benefits to individuals participating in these studies; rather, they will help advance the Fragile X field.

Clinical Trial – Ampakines

Dr. Elizabeth Berry-Kravis is conducting a clinical trial at RUSH University in Chicago to evaluate a new potential treatment for Fragile X and autism. The compound, Ampakine CX516, may help improve learning and memory in Fragile X. The study is funded by FRAXA.

Adults with Fragile X are welcome to enroll in this study. Prospective subjects should contact study coordinator, Tina Potanos, at 312-942-4036. Tina will explain the details, answer any questions, and set up the schedule for visits to Chicago for those who decide to participate. Dr. Berry- Kravis is also available at the same phone number to answer questions.

Study of Carriers

Maureen Leehey, MD, a movement disorders neurologist and professor of neurology at the University Of Colorado School Of Medicine in Denver, is conducting a study in collaboration with Randi and Paul Hagerman's group in California, Elizabeth Berry-Kravitz's group in Chicago, and Ann Reynolds, at the Child Development Unit/Fragile X Clinic in Denver.

We have recently found that some Fragile X carriers (particularly men) develop progressive neurological problems after about age 50. These include tremor, balance difficulty, Parkinsonism, and memory problems. We intend to determine why this happens, what these neurological problems are specifically, and how often they occur.

We will evaluate Fragile X premutation carriers over 50 years of age. We will also evaluate persons over 50 that do not have a change in their FMR1 gene (often a spouse) for comparison. We can travel to your home if you live in Colorado or an adjoining state.

Please call Cathlin Rice, Study Coordinator, at 303-315-2389 if you are interested.

Medical Issues in Children

Ann Reynolds, MD, at the Child Development Unit/Fragile X Clinic in Denver, is leading a study comparing medical issues in children with autism, Fragile X, developmental delay and typical development.

WHO: Children 4 to 7 years with autism, Fragile X, developmental delay or typical development

WHAT: Involves sleep and family history questionnaires, and diet and stool diaries

If you are interested, please call: Dr. Ann Reynolds at 303-861-6619.

Improving Parents' Experiences with Diagnosis of Their Children

Elizabeth Taylor is a graduate student in the Genetic Counseling Program at Brandeis University in Waltham, Massachusetts. Elizabeth is conducting a study on parents' experiences with the diagnosis of their child with a genetic condition. Participation in the study involves completing an anonymous online survey and an optional interview.

Please contact Elizabeth Taylor at etaylor@brandeis.edu if you are interested in participating.

Genes and Behavior in Fragile X

Dr. Walter E. Kaufmann, at the Kennedy Krieger Institute in Baltimore is investigating how certain proteins controlled by the Fragile X gene contribute to intellectual and behavioral problems in children with Fragile X. With new laboratory techniques, scientists can now measure proteins in blood samples and determine whether the amount of these proteins relate to certain intellectual and behavioral problems in boys with Fragile X.

Boys aged 3 to 10 who are diagnosed with Fragile X and boys without known learning problems are invited to join this study. Participants will be reimbursed for expenses. For more information, please contact Pia Stanard at 443-923-7617 or Stanard@kennedykrieger.org.

Update from the National Fragile X Foundation

A preliminary agenda for the 9th International Fragile X Conference is now available at www.FragileX.org. While this agenda will be enhanced and updated numerous times in the months to come, the preliminary version gives you a good sense of the comprehensiveness of this event which will range from the latest in molecular research to detailed "How to" sessions dealing with the day-to-day learning and behavior of children with Fragile X. Sessions will also address the very latest information on Fragile X-associated Tremor Ataxia Syndrome (FXTAS).
The registration form and related information about the 9th International Fragile X Conference can be found at www.FragileX.org under the "Conferences & Events" button on our home page. Please mark your calendars now for June 23-27, 2004 in Washington, DC. Deadline for early registration is April 23rd.
The National Fragile X Foundation was pleased to recently cosponsor, along with the NICHD, a recent three-day "Early Intervention Working Conference" in Palm Springs, California. Under the leadership of Dr. Don Bailey from FPG at the University of North Carolina, and Dr. Steve Warren from the University of Kansas, twenty-three of the country's leading early intervention professionals gathered to discuss the state-of-the-art in their field, and to discuss how this knowledge can be applied to infants and toddlers with Fragile X. The NFXF was pleased to play a role in this important enhancement of the body of knowledge regarding Fragile X.
Robby Miller, Executive Director, 1-800-688-8765 or NATLFX@FragileX.org, The National Fragile X Foundation, PO Box 190488, San Francisco, CA 94119

FRAXA FUNDRAISERS

Raising Awareness and Funds for Research

Where does FRAXA get the funds to support the pivotal projects described in this newsletter? FRAXA has no government funding and no endowment. Every dollar is donated by dedicated families and their friends. Over 3000 people donated to FRAXA in 2003 through fundraisers such as those featured here.

As you know, FRAXA is one of the most efficient charities in the world, with only one paid staff and hundreds of volunteers, so your dollars are hard at work advancing research towards our goal: effective treatment and ultimately a cure for Fragile X.

Los Angeles Luncheon

With less than one month of planning, Andrea Shelly, of Newport Coast, California, organized the first fundraiser in Orange County, California, for FRAXA. The Shelly's seven year-old, Elisabeth, was diagnosed three years ago with Fragile X, and has been in intense therapy since then, including behavioral modification, speech therapy, occuptional therapy, equestrian therapy, swimming and gymastics. Elisabeth is currently enrolled at UCI CDC, a day treatment program which specializes in teaching children with ADD/ADHD by combining educational intervention with behavior modification strategies.

The Christmas-themed luncheon event, held on December 18th, attracted close to 100 guests and featured Christmas hand-bell carollers, a silent auction chock-full of goodies, including a Louis Vuitton limited edition Dalmation pochette handbag, two Baby Phat pastel-pink limited edition cell phones, and an adorable tea-cup Chihuahua, and casual French food catered by Pascal's. Despite the winter date, the event was held outside in Shelly's front tented courtyard with the winter sun warming the guests and the purpose of the event. It raised over $45,000 for FRAXA research. Shelly plans on holding another event this year.

Dallas/Plano, Texas

David and June Sturgell raised over $5000 for FRAXA by hosting a party in December in their Plano home. In attendance were Dr. Kim Huber, Professor at the University of Texas at Southwestern and past FRAXA grant recipient, and many friends and parents of Fragile X children. The Sturgells thank all who attended and those who couldn't but generously contributed donations to the party.

In addition, Alexander Sturgell's school, Hughston Elementary hosted a "STOP" fundraiser for FRAXA. STOP -- "Students Thinking about Peers" -- is a Plano school system program which promotes developing leadership skills. Over a two-week period students donated change, raising over $500. Each day over those weeks, a Fragile X fact was communicated during morning announcements. This was public education at its best!!! Thanks go to all the students, Principal, Mrs. Louann Collins, and Counselor, Mrs. Pam Hart. "Hughston, best in the West, every day, every way."

San Diego Badminton Bash

Cindy and Brendan de Gruchy and their family and friends hosted a Badminton Bash in San Diego. The event not only raised awareness of Fragile X and $4000 for FRAXA but also promoted the sport of Badminton. With no experience necessary to play, over 50 players of all ages showed up to give it their best shot. Trophies were awarded to all levels of play with first place ribbons going to all kids with Fragile X.

A New York Holiday Gift

We thank Writers House Literary Agency for their year-end donation to FRAXA in lieu of the usual holiday gift book to their clients. FRAXA Board member Susan Cohen is an agent there, and her colleagues decided to make the contribution in honor of her son, Julian-whose father, Barry Berg, is also a Writers House author.

In addition to the value of the agency's monetary contribution, the holiday card sent to several hundred clients included a FRAXA brochure which helped spread awareness of Fragile X – and spurred a few authors to make their own contributions as well!

Will you host a Fall Fling event in Fall 2004? If we can organize more than 30 events around the US, the collective impact of that many events, small or large, will help us entice the media to feature stories about Fragile X.

All events are welcome ... yard sales, bake sales, letter campaigns, runs, walks, bike rides, dinner parties in your home, children's events, pizza parties, bowling tournaments. Need help? We have "To Do" recipes for each type of fundraiser and a list of other parents who have run similar events. We can supply brochures, ideas, and even a FRAXA Files CD with a large collection of resources for volunteers.

Hosting an event can be a lot of work but it is fun, rewarding, and worthwhile! Call or email Katie Clapp, (978) 462-1866 or kclapp@fraxa.org

CALENDAR OF EVENTS

MARCH

For those of you who have always wanted to pull a 100,000+lb. Boeing 727 your opportunity awaits on March 27, 2004 at the **2004 Tug of War!** FRAXA's Michigan chapter and Goodwill Industries of SW Michigan are teaming up for a Jet Pull at the Kalamazoo International Airport. Teams will compete to pull the Boeing 727 the fastest for 12 feet. Visit www.goodwillswmi.org/events.htm or contact Denise King at (269) 382-0490.

APRIL

Join the festivities Saturday, April 3, at St. Mary Church in Hockessin, DE, with drinks and hors d'oeuvres, **live band and silent auction**. For tickets, call Jen Nardo at (302) 234-7854 or email Jen9612@aol.com

MAY

The Nebraska Fragile X Families Association presents the **7th Annual Mary Higgins Clark Gala.** Special guest include Mary Higgins Clark, Eileen Naughton, and Senator Chuch Hagel. Founded last year, the Nebraska Fragile X Families Association consists of 26 familes with 36 members affected by Fragile X, ranging from 1 year old to 52 years old. They are very excited to be hosting such a major event. For invitations, please call Kelly Randels at (402) 778-5802 or visit www.fragilexnebraska . We hope to see you!

On Wednesday, May 19th, Harry Manion will host **FRAXA's 10th Anniversary Celebrity Gala** in Boston. See p. 1 or FRAXA.org.

JUNE

The **8th Annual Patrick's Pals** 3-on-3 Basketball Tournament happens Sunday June 6, at BB&N in Cambridge, MA. Rolling Stone and Men's Journal feature writer Paul Solataroff is 2004 Patrick's Pal of the Year. This tournament is hosted every year in honor of Patrick Vershbow by his lifelong friends.

The Fragile X Alliance of Ohio will host their **8th Annual Golf Tournament** on June 28th in Cleveland. Register online at www.fragilexohio.org

JULY

Ron and Amy Watkins will host their **Second Annual FRAXA Dinner** on July 31, 2004 at The Links at Union Vale, New York.

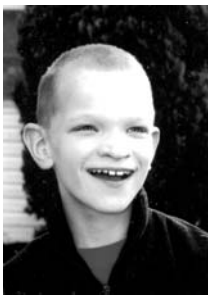
Help FRAXA Through the Combined Federal Campaign

Imagine that FRAXA added a million dollars to its annual budget. Does that sound like wishful thinking? It's not really, because $1 million is less than one percent of the more than $100 million raised annually during the Combined Federal Campaign (CFC). The CFC is the sole fundraiser for federal agencies and the military. It is an annual autumn event during which federal and military employees are encouraged to donate funds to the charity of their choice.

Last year, the first time FRAXA was involved, CFC donors designated over $13,000 dollars for FRAXA with little fundraising on our part. To boost this figure, FRAXA was represented by Frank and Susan Roth and Mary Beth Busby in the Fall of 2003, with keynote speeches or appearances at three fundraising kickoffs and 15 charity fairs. It is too soon to know how much FRAXA's donations will increase in 2004 because of their efforts, but we do know that hundreds of federal employees learned about Fragile X for the first time.

At one event, Frank talked with more than 50 people who had never before heard of Fragile X. Ninety percent of them asked questions because they knew someone who had children with problems or were going to have children or grandchildren. People want to know about Fragile X. Benjamin Roth, who has Fragile X, was the star attraction at the Bethesda National Medical Center CFC Kick-off, where he shook hands with an Admiral!

More than 3000 charities meet CFC criteria, but many of the other charities do not have the message that we have of "We are just one gene away from a cure," nor are they helping children with a medical condition. Frank, a USDA Forest Service employee, had many friends tell him that they wanted to give to someone they knew or to something that would make a real difference. Others, who knew that the Roths' son Benjamin has Fragile X, did not know that FRAXA is a CFC charity. FRAXA's CFC number is 0220.



Benjamin Roth

There are CFC events in almost every U.S. city and wherever there is a military or federal installation worldwide, and the event sponsors are always looking for new charities to come speak about their work.

Frank and Susan have agreed to help interested families and supporters get started. They will contact the CFC organizers in your area and get you the information you need. The 2004 campaign will start in the early fall, and planning events and getting our name in front of the CFC organizers will begin in late summer. If you have some time and want to hand out information, give presentations, or just talk with others, please let the Roths know. You can contact the Roths at writeroth@xecu.net. Just think what we can do with a small piece of $100 million!

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

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

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

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

FRAXA UPDATE

EDITOR: Katie Clapp, MS
CONTRIBUTORS: Michael Tranfaglia, MD
Mary Beth and David Busby
Recipients of FRAXA Research Awards
Frank and Susan Roth
Andrea Shelly
DESIGN: Mary Lou Supple

Fragile X in the News

Cody Randels is the son of Kelly and Ryan Randels. Kelly is chairing FRAXA's May 6th gala in Omaha. Cody, who has Fragile X, will be three years old in March. He walks, runs, and is beginning to talk.

Seth Thomas of Swansea, MA, was in the news! Seth's mom Joanne has almost succeeded in informing everyone in the Swansea area about Fragile X! She has contacted newspapers, the local cable TV station, and area businesses to raise both awareness and funds for research.

PLEASE HELP FRAXA

in supporting research aimed at treatment for Fragile X

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

- ☐ Member ($25+)
- ☐ Benefactor ($500+)
- ☐ Donor ($50+)
- ☐ Research Underwriter ($1000+)
- ☐ Sponsor ($100+)
- ☐ Named Research Fund ($5000+)
- ☐ Named Research Chair ($25,000+)

FRAXA RESEARCH FOUNDATION
45 Pleasant Street
Newburyport
Massachusetts 01950

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