FRAXA UPDATE

FALL 2003

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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

1994-2004: Ten Years of FRAXA Research

Andy Tranfaglia with Cookie, pet hamster, and Mike Tranfaglia

by Michael R. Tranfaglia, MD
FRAXA Medical Director & co-founder

FRAXA Research Foundation will be celebrating its 10th anniversary in January, so it's natural at this time that we look back at how far we've come. 10 years ago, most people in the Fragile X community thought of Fragile X as an irreversible condition, not a treatable disease. Even though the gene that causes Fragile X (FMR1) was discovered in 1991, its function remained mysterious. Now we know much about the normal function of the protein produced by this gene and how its absence causes Fragile X. Indeed, FRAXA researchers have identified a key pathway in the synaptic connections between neurons of the brain that functions excessively in Fragile X. We think this pathway accounts for most of the symptoms of Fragile X. Most importantly, compounds exist which can block this pathway. Some of these are currently being developed as human drugs, so we are testing them in the Fragile X mouse model –

continued on page 3

Latest Fragile X Research Advances Presented

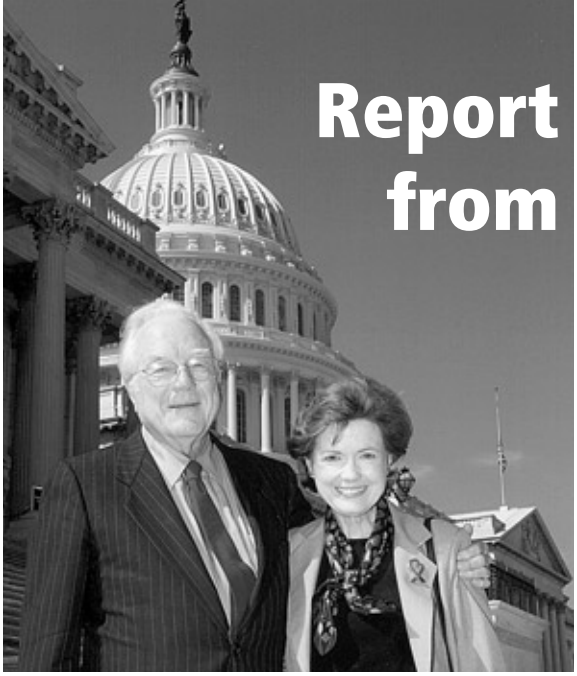
by Katie Clapp, president and co-founder

This year, at the annual meeting of the Society for Neuroscience in New Orleans, November 8-12, we saw 24 Fragile X studies presented, rather than the dozen or so Fragile X studies of the past few years (and less than five the first year we attended). We are proud to note that 15 of these 24 projects are FRAXA-funded and most of the other teams have also received FRAXA support for related studies. No other source supported nearly as many studies … not even the U.S. government! This meeting is the premier showcase for neuroscience research, with over 29,000 people in attendance.

Each year, FRAXA hosts a booth at this meeting to recruit new Fragile X researchers and see the work of current FRAXA grantees. This year, Michael Tranfaglia, Katie Clapp, Debbie Stevenson, and Leslie Eddy staffed our booth with help from New Orleans-area parents, Mary Ann Haase and Theresa Wilson. Hundreds of researchers visited us. (See page 4 for descriptions of the most interesting work.) On December 1st, grant prosposals will arrive from researchers around the world. After peer review by FRAXA's Scientific Advisory Committee, our Board of Directors will look at FRAXA's available funds and determine which projects can be supported. Donations over the next two months are critical – they will determine how many more scientists can help us solve the mystery of Fragile X!

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 8000 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

Fiscal year 2003 is ***not*** a promising year in Congress for Fragile X research. Each year since 1995, we have asked the Congress and the Congress, in turn, has asked the National Institutes of Health (NIH) and/or the National Centers for Disease Control and Prevention (CDC) to institute or enhance specific Fragile X research projects. In large part as a result of these requests and the letters of our Fragile X Advocates to their Members of Congress, NIH funding for Fragile X research has gone up each year. This year our requests fell on (mostly) deaf ears.

In the Spring we asked the Appropriations Committees of the Senate and House to include in this year's annual Report the following:

1. A state-of-the-science conference on Fragile X research to be sponsored by the NIH.
2. Increased funds for the 3 new Fragile X Research Centers of the National Institute of Child Health and Human Development, NIH.
3. Increased funds for Fragile X research at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDKD).
4. A study by the National Institute of Mental Health (NIMH) of new Fragile X pharmacological treatments and identification of key molecular targets for drug treatment.
5. Expansion of Fragile X research at the National Institute of Neurological Disorders and Stroke (NINDS), especially to explore the tremor/ataxia syndrome among older male carriers.
6. Expansion of Fragile X – and autism – screening by the CDC's new National Center on Birth Defects and Developmental Disorders (NCBDDD), to maximize prevention potential, minimize impact on families, and promote early intervention.

The Senate Appropriations Committee (but not the House Committee) endorsed our request only to the extent of asking the NIH and the CDC to effectuate our requests #1 and #6.

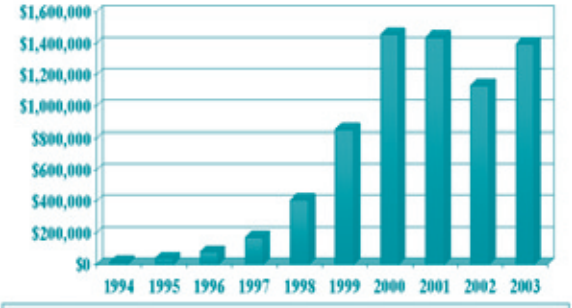
The causes of this lack of responsiveness by the Appropriations Committees are probably:

1. The doubling of the overall NIH budget in 5 years had been accomplished, and the Members of the Committees were not in the mood to push discretionary projects, especially in view of the Iraq war.
2. Failure of your Washington Representatives (us!) to realize the need for special efforts this year. One of our main champions in the House, Congressman Watkins, retired, and several knowledgeable staffers moved.
3. We did not push our FRAGILE X ADVOCATES (you!) to contact their Members as we have in the past.

Lest we become discouraged, let's not forget that since 1995, the Congress has increased NIH spending for Fragile X research from less than $2 million to $19.5 million in FY 2003. Also, the CDC's new National Center on Birth Defects and Developmental Disabilities and Disorders is finally getting under way with a very significant budget.

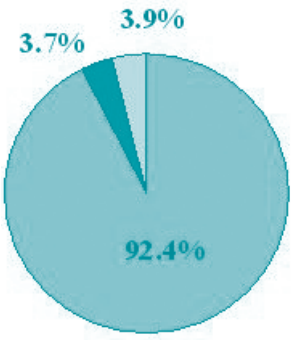
Finally, best of all, FRAXA's own privately-funded research – over $ 7 million since it was founded in 1994 – is producing the most encouraging and meaningful results of all!

FRAXA Funds Research



FRAXA dollars spent on research grants and fellowships

FRAXA Finances



source: www.CharityNavigator.org

OVERALL RATING: 4 Stars (out of 4)

ORGANIZATIONAL EFFICIENCY
- Fundraising Expenses 3.7%
- Program Expenses 92.4%
- Administration Expenses 3.9%

David's Fragile X Advocates

by Diane Hamsa

As Congress gets to work on appropriations, we will have emails again from Busby.David@dorsey.com. David is our "tour director" on a journey that began in the summer of 1999. We are his advocate journeymen from the north, south, east, and west. Webster's Dictionairy defines journeyman as "any sound, experienced, but not brilliant performer." We know who the brilliant performer is – our leader, David Busby. His wisdom and expertise have been responsible for the legislative accomplishments aiding Fragile X research. As advocates, our job was to become acquainted with our own representatives in the House and Senate in order to ask their help toward our final destination – effective treatment and a cure. That is where the rubber meets the road.

Robert and Jack Busby

There were a few road blocks, but that didn't slow us down. The Fragile X Act of 1999 evolved into the Children's Health Act of 2000. Now, near the end of 2003, we are filled with hope and expectation as research shifts into high gear. Three new research centers are being funded by NICHD. FRAXA does "in house" fundraising with Fall Flings, parties, and the Mary Higgins Clark Galas.

David has been mapping out the best way to go and how we'll get there. Another adventure with Congress is on its way. We'll stay the course for increased funding for research and a cure for Fragile X.

Busby.David@dorsey.com, we are with you to help fulfill a dream.

FRAXA: 10 years later continued from page 1

and getting very promising results. *In 10 years we have gone from thinking of Fragile X as untreatable to having a very real, near-term possibility of treatment.*

10 years ago, few scientists were studying Fragile X. A small group of dedicated researchers made significant progress by identifying the FMR1 gene and developing advanced diagnostic tests for Fragile X. However, it was clear from the start that this was a neurological problem and that more neuroscientists would need to be brought into the field. FRAXA has made the recruitment of top neuroscientists its highest priority. We have had great success by reaching outside the small Fragile X research community to bring in new people and new talent. Many leading neuroscientists are currently funded by FRAXA, and most of the major advances in the field have come from their labs. ***In just 10 years, Fragile X has gone from an obscure specialty to one of the hottest topics in all of neuroscience!***

10 years ago, government agencies funded relatively little Fragile X research. Total NIH funding of all Fragile X research was just over $1 million per year, and less than $40,000 of that could have been considered "treatment-oriented." In 2004, total NIH funding of Fragile X research will exceed $20 million, thanks in large part to the lobbying efforts of FRAXA families. In addition, FRAXA has partnered with NIH to co-fund $1.4 million of treatment-oriented research each year through a special grant program outside the regular funding system. While we think Fragile X research is still extremely under-funded, in the past 10 years we have seen remarkable progress.

Andy and Laura Tranfaglia

10 years ago, FRAXA Research Foundation started by funding a single research grant. We are currently funding more than 30 major projects in labs around the world. Not only has the quantity of the research increased dramatically, but also the quality of the research has increased by leaps and bounds. Ten years ago, Fragile X families were a fragmented group without a common purpose; today, the Internet has brought us together to form an effective advocacy group which lobbies government agencies and raises funds for direct sponsorship of biomedical research.

In the past 10 years, we have seen a remarkable convergence: the scientific community, Fragile X families, and government agencies like NIH have all come to see a cure for Fragile X as not only possible, but just a matter of time. Thanks to your support, we can make this happen as soon as possible. With a lot of help and a little more good luck, we're sure it won't take another 10 years.

Research Frontier:

New Fragile X Studies Presented at Neuroscience 2003 Meeting

by Katie Clapp

Current neuroscience research on Fragile X spans a great variety of studies. Much of the work focuses on how the Fragile X protein functions and what goes wrong when it is absent. Researchers are now finding that Fragile X mice show a range of problems similar to problems seen in people with Fragile X. The mice show difficulty coping with stress and are slow to learn to distinguish smells (which are central to a mouse's world). They are prone to seizures and there are changes in the fine structure of the neurons in their brains.

Fragile X mice are critical to progress for two main reasons: we can learn more about Fragile X in humans by studying the mice and we can test new treatments on the mice to see how effective they are before considering human testing.

Rather than summarize all 24 studies here, we've included a sampling. For complete abstracts, contact FRAXA or visit www.sfn.org.

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

Robert Bauchwitz

QI JIANG YAN, MICHAEL TRANFAGLIA, AND ROBERT BAUCHWITZ

Columbia University

This study provides the most dramatic evidence to date that mGluR5 antagnonists may effectively treat a range of symptoms seen in Fragile X.

Audiogenic seizures can be triggered by very loud sound. The Fragile X knockout mouse is quite susceptible to this kind of seizure. The researchers evaluated an experimental drug, MPEP (a selective mGluR5 receptor antagonist), and found that it was able to abolish these seizures in all strains of Fragile X mice. This indicates that the mGluR5 pathway plays an important role in audiogenic seizures. It also offers a well defined model to investigate the neurobiological and genetic cause of seizures and related deficits in Fragile X Syndrome, as well as potentially serving as a model for testing novel anticonvulsant drugs. This and other studies suggest that mGluR5 antagonists will be useful for treatment of more than just seizures.

Supported by FRAXA

A FEW TERMS

FMR1 is the gene that normally produces **FMRP** but is mutated and shut down in people with Fragile X syndrome.

FMR1 Knockout mice have been bred to mimic Fragile X syndrome. They lack the FMR1 gene and therefore also lack the protein, FMRP.

mRNA is code produced by a gene. mRNAs can travel between a cell's nucleus, where all the genes stay, and the cell's dendrites, the extensions which reach out to other cells. Each mRNA contains the code to produce a protein.

synapses are the connections where cells communicate with other cells.

synaptic plasticity refers to changes in shape and structure of dendrites and synapses ... the biological basis for learning and memory.

The Fragile X Mouse: Seizure Susceptibility and Electrophysiological Alterations May be Due to GABA System Changes

CARL DOBKIN ET. AL.

Institute for Basic Research, NY

Childhood seizures are common in Fragile X syndrome, and Fragile X mice also show increased seizure susceptibility. This study suggests that seizure susceptibility in Fragile X is increased because absence of FMRP leads to alterations of the GABA system. The team observed electrophysiological changes in the Fragile X mouse consistent with GABAergic system changes. They also found that these changes are reversed in a mouse model, developed by Dr. Robert Bauchwitz, in which a human FMR1 gene has been added into the genome of the knockout mouse. These studies tell us more about how the Fragile X gene works and give some hope that, one day, gene therapy will be a potential treatment for Fragile X.

Supported by FRAXA

Olfactory Learning and Memory in a Mouse Model for Fragile X

John Larson

JOHN LARSON & COLLEAGUES

Univ. of Illinois, Chicago

In mice, the sense of smell is critical for navigating their world. The investigators tested Fragile X mice to see if they have defects in distinguishing and remembering smells. They found that Fragile X mice take longer than control mice to learn to distinguish between two smells. This knowledge provides a useful new tool for testing candidate treatments for Fragile X in the mice.

Supported by NIDA (part of NIH), FRAXA Research Foundation, and UIC Campus Research Board

update:

Social Behaviors in the FMR1 Knockout Mouse Model of Fragile X

RICH PAYLOR & COLLEAGUES

Baylor College of Medicine

Rich Paylor

Behavioral features of Fragile X include cognitive impairment, hyperactivity, attention deficits, social isolation and anxiety, and autistic behaviors such as gaze avoidance. FMR1 knockout mice exhibit several of the physical and behavioral characteristics of the human syndrome.

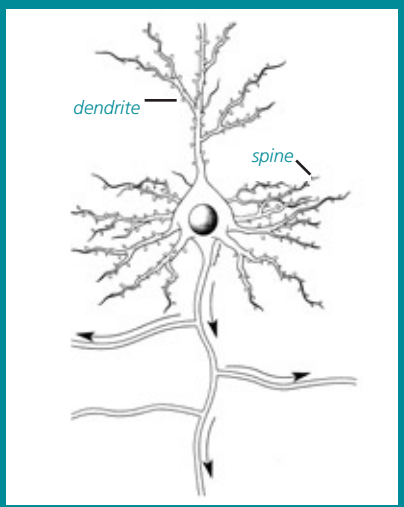
In this study, Dr. Paylor and colleagues analyzed social behaviors in male Fragile X mice. Although many tests did not reveal differences between Fragile X and control mice, they did see a difference using a tube test of social dominance. In this test, a Fragile X mouse is placed at one end of a tube and a control mouse is placed at the other end. Both mice enter the tube and meet somewhere in the middle; the one who backs out "loses" the match, having ceded territory to the other mouse. Fragile X mice won significantly fewer matches than wildtype littermates, suggesting an impairment in social interaction.

This test offers a simple, easy way to try out potential drug or genetic therapies in mice before considering testing them on people.

Supported by FRAXA

Anatomy of a Neuron

Neurons (brain cells) have branches – dendrites – which have spines where synapses form to make connections with other neurons.



Prolonged Elevation of Serum Glucocorticoid Levels in Fragile X Knockout Mice after Acute Stress

A.C.BECKEL-MITCHENER, J.D.CHURCHILL, S.KIM, C.M.ESTRADA, W.T.GREENOUGH

Univ. Illinois, Urbana

Andrea Mitchener

This group has examined the mechanism underlying the heightened anxiety that affects most people with Fragile X syndrome. Recent studies have reported that cortisol levels are increased in patients with Fragile X following a stressful event and that this elevated cortisol level fails to return to baseline as quickly as in unaffected individuals.

Dr. Greenough and colleagues have been studying the Fragile X mice and have discovered that, like people with Fragile X, cortisol levels are higher following a stressful event (physical restraint) and take longer to return to baseline. They were looking especially at the hippocampus, an area of the brain that is important in regulating the stress response.

These data suggest that the hypothalamic-pituitary-adrenal (HPA) axis is improperly regulated in Fragile X patients and in the Fragile X knockout mouse. The reason may be that FMRP is required for the proper expression of the glucocorticoid receptor and, perhaps, other proteins involved in the stress response pathway.

Supported by FRAXA Research Foundation and Kiwanis International

Stress-Induced Changes in BDNF and C-FOS Cortical Expression are Altered in Fragile X Mutant Mice

E.RAMIREZ; G.FOWLER; C.M.GALL; J.C.LAUTERBORN

Univ. of Calif., Irvine

Julie Lauterborn

Dr. Julie Lauterborn received a FRAXA grant this year to study the effects of a new Ampakine compound in Fragile X mice. In this presentation, her group demonstrates that Fragile X mice have an exaggerated hormonal response to stress, as do children with Fragile X. They have quantified the stress response difference. This provides more evidence that the HPA hypothalamic-pituitary-adrenal axis is dysregulated in Fragile X syndrome. The HPA axis is an area of intense interest among psychiatrists and endocrinologists, so this may attract new researchers into the Fragile X fold.

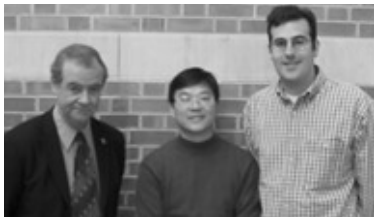
Supported by UC Davis MIND Institute

research

Cerebral Cortical in Vivo Expression of FMRP, but not of FXR1P, is Elevated Following Housing in a Complex Environment

A.W.GROSSMAN, S.H.KIM, K.EDGAR, B.J.DEGRUSH, S.A.IRWIN, I.J.WEILER, W.T.GREENOUGH

Univ of Illinois, Urbana



Bill Greenough, Im Joo Rhyu, Aaron Grossman

Previous studies have suggested that FMRP expression is increased in visual cortex and the motor cortex of rats following experiences that induce structural plasticity (i.e. learning).

Twelve young-adult male rats were housed in a cage of toys whose arrangement became increasingly complex across 20 days of housing. Tissue from these rats was compared with that from littermates housed individually in standard laboratory cages. Rats exposed to the complex environment showed significantly greater FMRP expression in the cortex compared with individually caged rats. Thus FMRP appears to increase its expression in neurons as a result of exploring and learning, tasks which are associated with the development of new synapses. This highlights the key role of the Fragile X protein in the learning process.

Supported by FRAXA Research Foundation, NIMH, NICHD, Kiwanis International

Regulated RNA Binding of the Fragile X Mental Retardation Protein

R.B.DENMAN, N.DOLZHANSKAYA, Y.SUNG

New York State Inst. for Basic Res. Dev Disabilities and Columbia Univ

Dr. Robert Denman previously received a grant from FRAXA to study the molecular targets of FMRP. Recently, Dr. Denman has been examining how FMRP's messenger RNA (mRNA) targets are altered in Fragile X syndrome, in turn leading to the clinical and behavioral features of the disorder. In this presentation, the team defines ways in which FMRP is regulated in brain cells. There are several mechanisms by which proteins are turned on and off within cells; these so-called post-translational modifications work in concert with each other to regulate when and how proteins bind to target mRNAs (which contain the codes to produce other proteins). Dr. Denman's team presents a model signaling mechanism by which FMRP normally regulates its interaction with its target mRNAs; this model can explain how some symptoms of Fragile X arise.

Supported By The Research Foundation for Mental Hygiene, NY

Speaking of mice...

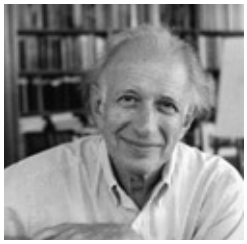
One of the most popular stops at the Neuroscience Annual meeting (aside from FRAXA's booth) was the Neuromice booth because they gave away fuzzy little toy mice. The Neuromice.org folks generously provided us with mice, causing an extraordinary increase in traffic at our booth.

We are currently designing FRAXA Knockout Mice for our booth at next year's meeting, so if you have an idea for a great mouse, let us know!

Characterization of Fragile X and Other Classes of RNA Binding Proteins in Somata and Neuronal Processes of Aplysia

ERIC KANDEL AND COLLEAGUES

Columbia University



Eric Kandel

Dr. Eric Kandel, who won his Nobel prize just after starting Fragile X research with a FRAXA grant, has been studying proteins that enable learning and memory in the lowly sea slug, aplysia. Dr. Kandel's team has identified dozens of RNA-binding proteins that facilitate synaptic plasticity (the basis for learning and memory) in these slugs. One of these proteins is apFXRP, the slug's equivalent to the human Fragile X protein. The researchers have cloned six alternatively spliced forms of apFXRP, all of which are found in the slug's neurons, and they find that the apFXRP mRNAs can be transported to neurites (developing extensions of neurons which reach out to communicate with neighboring neurons). This is strikingly similar to FMRP in mice, suggesting that further studies will shed light on the function of the Fragile X protein in humans.

Supported by FRAXA, Howard Hughes Medical Institute, NINDS, NIMH, McKnight Foundation

In Vivo Rates of Cerebral Protein Synthesis are Increased in Fragile X Knockout Mice

M.QIN, J.KANG, C.B.SMITH

Lab. of Cerebral Metabolism, NIMH, Bethesda, MD

Much recent basic research has focused on how the Fragile X protein regulates mRNAs and proteins, because some of these are likely to be involved in related disorders like autism and because some might prove to be useful targets for treatments. An unresolved question is whether FMRP suppresses the translation of other proteins. The aim of this study was to find out whether FMRP suppresses protein translation in the brain in live animals. They measured rates of cerebral protein synthesis in male

update:

Fragile X knockout mice and control mice. In all 53 brain regions examined, rates were increased by 5-30% in the Fragile X mice (which lack FMRP). This finding is consistent with the hypothesis that FMRP's role is to suppress of mRNA and protein translation in the brain in live animals.

Funded by NIMH

Ultra High Voltage Electron Tomographic Examination of Selectively Stained Dendrites in Fragile X Mice

J.D.CHURCHILL, I.J.RHYU, M.E.MARTONE, H.MORI, N.YAMADA, M.TERADA, M.H.ELLISMAN, W.T.GREENOUGH

Univ of IL, Urbana, and Osaka Univ, Japan

Human autopsy studies have reported increased density and length of dendritic spines in Fragile X individuals. Recent work has shown similar pathology in Fragile X mice. The present study used ultra high voltage electron microscopy of cortical and hippocampal neurons to confirm and extend previous work. This study confirms that the average length and density of spines are greater in Fragile X mice than in control mice.

Pruning dendrites is a normal part of human development which occurs throughout life. This and other studies suggest that pruning doesn't happen as efficiently as it should in people with Fragile X. This contrasts with many brain disorders in which cells actually die.

Supported by NIH/AG, NIH/NCRR and FRAXA

STEM CELL TRANSPLANTS GENERATE FMRP IN THE MOUSE MODEL OF FRAGILE X

L.K.K.PACEY, M.M.AXFORD, L.C.DOERING

McMaster Univ., Canada

Neural stem cells have exciting implications for the potential treatment of many nervous system disorders. This team is studying the cellular characteristics and the behavioral effects of FMRP replacement via stem cell transplants in the mouse model of Fragile X Syndrome. Stem cells were isolated from normal mice and cultured to generate large numbers of neurons which produce FMRP. These neurons were then injected into the hippocampus of FMR1 knockout mice. The researchers are currently using a maze to test learning and memory in the mice at various time points after transplantation. These experiments represent the first attempts to replace FMRP by stem cell therapy and test the corresponding functional effects.

Supported by The Fragile X Research Foundation of Canada

RESEARCHERS' CORNER

Last issue, we reported that several antibodies are now available at the University of Iowa Developmental Studies Hybridoma Bank (www.uiowa.edu/~dshbwww/), and that FMR1 knockout mice were being distributed. There has been continued progress:

Mice

Neuromice.org is a consortium of three sites, Jackson Laboratory, Northwestern University, and the Tennessee Mouse Genome Consortium, established by NIH to enhance genomic and genetic tools for neuroscience research by creating new mutant mouse models for neurological/behavioral disorders. The primary goal of Neuromice.org is to be a research resource center that maintains, characterizes, and, most especially, distributes these mouse lines to interested scientists. Neuromice.org is an initiative funded by six NIH institutes, led by NIMH. FRAXA thanks Dr. Steven Moldin, … at NIMH, Dr. Joseph S. Takahashi, Director of the Neuromice consortium, and Dr. Martha Hotz Vitaterna at Northwestern University for agreeing to distribute a different strain of FMR1 knockout mouse (C57). These mice should be available to inte rested scientists within six months.

In addition, Jackson Laboratory will begin distributing the FMR1 knockout mice (on a sighted FVB background) available in the next few months. To check the status of this model, visit http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi and enter Stock #4624.

MPEP for Pre-Clinical Studies

FRAXA has available a supply of the selective mGluR5 antagonist, MPEP, for donation to investigators who wish to test its effects in the FMR1 mouse or other models of Fragile X. The MPEP was synthesized by "Technically, Inc." of Woburn, MA, and has been validated by several labs.

Family Visits

Investigators, fellows, and students researching Fragile X in the lab have gained tremendous insights by meeting children who have the disorder. Descriptions of the fragile X phenotype in the scientific literature can't convey how these children think, behave, and interact. Many FRAXA families across U.S. would enjoy visiting with scientists.

Call Katie Clapp at FRAXA, (978) 462-1866 or kclapp@fraxa.org

FRAXA Fall Fling 2003 Highlights

Raising Awareness and Funds for Research

October 5th, 2003, marked the second annual National Fragile X Research Day, established by FRAXA and endorsed by Congress in 2002. To celebrate, families hosted events around the country and raised a total of more than $470,000! These funds will enable FRAXA to support more of the new research proposals that will arrive on December 1st.

The key goal of FRAXA Fall Fling is to increase participation: the more events we can hold across the country, in as many states as possible,the better chance we have of getting national media attention for Fragile X.

In addition to the people featured here, we want to thank Cathy Reid and the Piecemakers, who made and auctioned quilts at their Clewiston, Florida church, and Heather and Philip Lopina, whose July barbecue raised both awareness and funds for research.

We are also grateful to Mary B. Porterfield and her family. Mrs. Porterfield passed away this year, and part of her estate was donated to FRAXA in order to support research to help improve the lives of adults affected by Fragile X.

New York: Cocktails in Soho

Elaine Stillerman and Paul Solotaroff hosted a wonderful party and auction at the Soho art gallery loft of their friend, Leeor Sabbah, raising over $12,000. The day after the party, *Men's Journal* published Paul's article about life with his son, Luke, who has Fragile X. Since the story came out, Paul and Elaine have been featured in the media, including MSNBC and the New York Times. The article has been nominated for an award, and Fragile X support groups across the country have been requesting reprints. You can read it at FRAXA's website, www.fraxa.org .

New York: Oldies Dance

Fran Gibb and friends and family recruited a chef from the CIA (that's the Culinary Institute of America) for a dinner and oldies dance in the Bronx. The turnout was terrific, the party raised over $4,000 and plans are already in the works for next year!

Massachusetts: Evening at the Harvard Club

Boston's Fall Fling was a festive evening hosted by Randy and Chuck Welch. The star of the show was Harvard alum and auctioneer Mo Pratt, whose jokes had everyone in stitches as the bidding prices for basketballs and other sports memorabilia topped $1000. The evening raised almost $15,000 and warmed us all up for Boston's upcoming 10th Anniversary FRAXA Gala. In addition, Randy Welch's sister, Jerri Pratt, organized the second annual FRAXA Fun Run at the Bradley-Palmer State Park, raising another $2800 for research.

Maryland: Fragile X Golf Classic

The Maryland Fragile X Resource Group hosted a September 15th tournament at Bretton Wood golf club in Potomac, Maryland. It included a golf clinic by pro golfer, Fred Funk, a luncheon, the tournament itself, a silent auction, and a dinner and live auction. Thanks to the hard work, careful planning and creativity of chairs Mark and Marla Gruzin and the energetic assistance of Michael and Lisa Kelley, as well as a great crew of volunteers, the event netted $40,000 for research and an additional $40,000 for the upcoming International Fragile X Conference in Washington, DC. Many thanks to the Gruzins and the Kelleys and all of the members of the Maryland group who made this event successful and fun.

Maine: Barn Sale

FRAXA thanks Julie and Eric Gosselin, Julie Wilson, Tim and Cheryl Peterson, Julie Follett, and their friends for organizing a tremendous barn sale and bake sale which raised $1000! Maine's Fall Fling was featured in the Portland newspaper as well as local papers, educating thousands about Fragile X.

Ohio: 2nd Annual Irish Night

Judith Maloney and friends raised over $6,500 at an evening of Irish beer, good food, and dancing ... all of this while Judith was in the midst of moving to a new house!

Ohio – Fragile X Alliance's 7th Annual Golf Benefit

Ara Bagdasarian Herb & Nancy Score, Honorary Chairpersons, Leslie Bagdasarian

On Monday, July 14th, 2003, the Fragile X Alliance of Ohio held their 7th Annual Golf Benefit at Shaker Heights Country Club. It was a landmark day for the Alliance and FRAXA. After a day of golf, dinner guests joined the golfers for cocktails, appetizers and a Silent Auction that was a sports fan's delight. For the dinner program, the "First Down Toward a Cure" video was shown highlighting FRAXA and researchers working on Fragile X. The segment about Jake Porter brought tears to the eyes of everyone in the audience.

The live auction was conducted in humorous broadcast style by special guest, Doug Dieken (former Cleveland Browns player & current radio

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. This year, we did not have enough events to attract their notice.

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.

Fall Flings

announcer). Returning Honorary Chairpersons Herb & Nancy Score were on hand to meet guests as well.

The highlight of the evening came when Ara Bagdasarian invited the Chairman & CEO of his company, TravelCenters of America (TA), up to the podium. Mr. Ed Kuhn announced that TravelCenters would donate $25,000 each year for 4 years to FRAXA. It was also announced that the First Data/Western Union Foundation would match TA's contribution, totaling $200,000 to FRAXA over the 4 years!

In summary, $100,000 from the 2003 benefit proceeds was donated by the Fragile X Alliance of Ohio to FRAXA and an additional $50,000 was donated by TravelCenters of America and First Data/Western Union Foundation.

Ed Kuhn, Chairman and CEO of TravelCenters of America announces surprise donation to FRAXA to Ara and Leslie Bagdasarian

The event committee thanks the many Fragile X Alliance of Ohio family members, friends, and the staff at Conferon, Inc. who helped make this event possible and a huge success. If anyone would like a copy of our program or has any questions, please email Leslie Bagdasarian at fraxohio@adelphia.net.

New York: First Annual Fragile X Summer Gala

Ron and Amy Watkins and their family and friends held their first annual dinner gala with silent and live auctions. Best-selling author Mary Jane Clark attended and shared with the guests her experiences as a mother faced with this disorder. Mary Jane's publisher, St. Martin's Press, donated copies of two of her books ("Do You Want To Know A Secret" and "Close To You") for all guests to take home with them. Actor Dan Grimaldi, best known for his role as Patsy Parisi on the HBO series, "The Sopranos" was a rousing speaker, challenging each person to spread awareness to speed the process of finding a cure. The gala was at a country club nestled in the pristine hills of the Mid-Hudson Valley of New York. At the end of the evening, $32,000 was raised for FRAXA! For the Watkins, the evening meant much more than the funds. The love and support of their family, friends and other families affected by Fragile X made the evening one of the best of their lives. "For the first time since Niklas' diagnosis, I felt like I was making a difference," said Amy Watkins. "No one could have prepared me for the high I felt that night. Both Ron and I felt we had finally been given the opportunity to share with those around us the importance of finding a cure and how they too could help, just by raising awareness."

Niklas Watkins

The Watkins have already reserved The Links at Union Vale for the second annual gala on July 31, 2004. They have committed to holding this fundraiser until a cure for Fragile X is found. When *that* happens, they plan to host a party celebrating the hard work and dedication of all families affected by Fragile X.

Philadelphia Reaches for the Stars

On October 8, Cristy Hollin and friends and family held their fourth Philadelphia Fragile X Fundraiser, themed Reach for the Stars. The evening was a huge success, thanks to the tireless efforts of our wonderful Chairs, Robin and Jerry Batoff. Over 250 people turned out to show their support. Upon arrival, each guest was handed a magnetic twinkling star and greeted by two beautiful fairies sprinkling stardust. The song, *When you Wish upon a Star* played over a loud speaker as guests milled about the silent auction, which featured over 270 items.

Guests were treated to a touching video presentation and a live auction. The live auction included a cruise, trips, visits with Oprah and the Good Morning America Show, a chance to play basketball with Aaron McKie of the 76ers and more! We sold beautiful *Reach for the Stars* jewelry and baseball caps throughout the night, and raffled a trip to Bermuda.

In the end, our hard work paid off and we raised over $170,000 for Fragile X Research! We gratefully thank Saks Fifth Avenue for sponsoring a pre-event patrons' fashion show and The Children s Boutique of Philadelphia for hosting Fragile X Day, where a portion of the day's proceeds went to Fragile X Research. Finally, we owe our success to our wonderful committee and to all the children who sold raffle tickets at the Gladwyne Super Fresh before the event.

Can you imagine playing 136 holes of golf in one day? Now imagine accomplishing this feat on a rain soaked August day. That is exactly what Mike Behan did. Mike is the head golf professional at The Woodstock Golf Club in Woodstock, New York. Behan became aware of Fragile X syndrome when Niklas Watkins was diagnosed nearly four years ago. Niklas is the five year old son of Ron and Amy Watkins.

"Mike called me in the spring to let me know he wanted to play as many holes of golf in one day as he possibly could and attract individuals and businesses to sponsor him on a per hole basis," says Ron. The Watkins never dreamed he could play 136 holes in about eleven hours. When the day concluded, Behan had raised $5,000. A great deal of awareness was also raised as Behan talked about FRAXA to anyone who would listen.

"Words cannot express how much we value the friendship of Mike and his wife Stacy. This event was their idea and they made it happen," says Ron. The Watkins would also like to thank Elizabeth Spinelli at The Woodstock Golf Club for their donation as well as making the golf course available for the day.

Roger Mudd, Mary Higgins Clark, Michele and Jim Cox

Pittsburgh Gala

This year Pittsburgh was the host city for FRAXA's 6th Annual Mary Higgins Clark Gala. Several hundred old and new FRAXA friends enjoyed an evening of hors'doevres, dinner, dancing and a silent auction at the elegant Omni William Penn ballroom. All were there to support Fragile X research. Honorary chair Mary Higgins Clark added style and grace to the event. We very much appreciate her lending her time to FRAXA. Master of Ceremonies Roger Mudd entertained the audience with his humor and kept the program running quickly and smoothly.

McKayla and Christopher Cox

After dinner, many saw the video, Fragile X, First Down for a Cure for the first time, and there was not a dry eye in the house! We applaud Debbie Stevenson for producing this incredibly powerful and touching video. Katie Clapp and Dr. Michael Tranfaglia gave exciting updates on the tremendous strides researchers are making towards a potential treatment for Fragile X. Senator Arlen Specter received the Beacon of Light Award for his support of Fragile X Research. We were also thrilled to give Pittsburgh Steeler Tommy Maddox the first ever Children's Champion Award for his commitment to the advancement of children and his support of FRAXA. Tommy was a true champion, offering insightful comments and staying at the party throughout the night. Pittsburgh's two major newspapers made the gala their cover stories for their society sections, and Pittsburgh's Whirl Magazine also covered the evening. We all felt like celebrities as flash bulbs flickered across the ballroom.

Best of all, we could feel the extraordinary warmth and kindness that filled the room. It was one of those rare evenings when everyone seemed to temporarily put aside their personal lives and join together for the good of all affected by Fragile X. It was a night we will always remember, and we would like to thank all who were there in body and spirit.

-Michele and Jim Cox

Nebraska Fall Fling

The community of Scottsbluff gathered together to raise funds for FRAXA at the Scottsbluff Country Club on October 2nd. It was incredible evening. Special guests included Mary Jane Clark, Dr. Mike Tranfaglia, and Dr. Robert Pasternack, Assistant Secretary, Office of Special Education and Rehabilitative Services. Kelley and Ryan Randels also attended from Omaha, NE. along with their son Cody, who has Fragile X. Kelley is the facilitator of the Omaha Fragile X Support Group. Our two sons, Jack and Jacob were in attendance as well. Excellent coverage was provided from the local newspaper, the Star-Herald. KSTF and KDUH, the two local TV stations, provided television coverage. The evening featured a last-minute silent auction, which was organized after the paper (to our surprise) announced we were having one. What a blessing that was in the end! People who read about it on the front page news came forward and offered items to auction. Sandy Gutwein and her daughter Ashley pulled it all together in less then 48 hours. Items included Denver Bronco tickets, Husker football tickets, Papa Murphy's pizza (one a week for a year), an original painting and a homemade quilt which was donated the day of the event. There were over a dozen items and the auction raised $2700!

Jacob and Jack Massey and Mary Jane Clark
photo credit : Roger Holsinger/Scottsbluff Star-Herald

Fifteen event sponsors contributed a large amount of the money raised and more than 150 people attended. The evening can be summed up by an ancient proverb: "A mirror reflects a man's face, but his heart is revealed by the friends he keeps."

Our small Western Nebraska community of Scottsbluff demonstrated its love for others by raising $70,000 for FRAXA Research Foundation. We are humbled and grateful for this overwhelming support and thankful that we live in such a caring community.

– John, Megan, Jack and Jacob Massey

Update from the National Fragile X Foundation

Members of the NFXF will soon be receiving their Fall 2003 Foundation Quarterly newsletter with a special 9th International Fragile X Conference section – including information on our Advocacy Day on Capitol Hill. If, by chance, you're not a subscriber, the conference registration form and related information can be found at www.FragileX.org under the "Conferences & Events" button on our home page. If you didn't heed the call in the last update, please mark your calendars now for June 23-27, 2004 in Washington, DC. We are glad to answer any of your questions about the event, so call us at the number below. The new newsletter also announces our latest project called, "Beyond the I.D.E.A: Adolescents and Adults with Fragile X". Thanks to private seed money, the NFXF will bring together parents, and experts on developmental disabilities and Fragile X who have developed an expertise regarding adolescents and adults and the problems associated with those age groups. One of our objectives is to produce free and user-friendly materials that parents can share with teachers, therapists, employers, group home staff, doctors, etc. These materials will encompass the areas of behavior, communication, medication, counseling, sexuality and other issues that have been identified as problematic for those with Fragile X. We welcome your input.

Robby Miller, Executive Director 1-800-688-8765 or NATLFX@FragileX.org

The National Fragile X Foundation, PO Box 190488, San Francisco, CA 94119

What is is like to Parent a child with Fragile X?

Editor's note: Julie Adams of Wisconsin wrote this note on the FRAXA listserv to help a student who needed information for a school project. You can join the listserv at www.fraxa.org

I applaud the person who came up with the idea of a report on Fragile X Syndrome!!! I'll try to sum up for you, in a few short sentences, what Fragile X Syndrome means to me.

Anything a parent might know about child rearing goes right out the window. Raising a child with FX begins with relearning everything we think we know or did raising our other children. As a parent or sibling of a person with FX, you must work daily on becoming more tolerant, develop the patience of a saint and pretty much become selfless or at least greatly control your own emotions.

You face an entire community of health professionals, educators, neighbors, friends and family, who do not understand why you do what you do for your child with FX. The general belief is that the child's problems have much to do with your parenting skills, or lack there of. I have spent 11 years, fighting 3 different school districts to assure my daughters basic safety issues while at school.

My daughter with FX has very limited access or understanding of what life is like compared to her peers. She can't stand loud or unusual noise levels, so she doesn't go to dances, malls, roller rinks, etc., Just being in school is stressful for her. She's not aware of clothing styles, hair/makeup issues. Her best friends are her stuffed animals.

It is very difficult for her to learn. She needs much repetition (months, years) to learn any academics. She will probably never drive a car, although she thinks she will when she turns 16, she will not go to college or have a career (she wants to be a fire fighter), she will probably not marry or have children (she has a 50% chance of passing on the gene that causes FX, nor could she care for a baby or husband)!

She is the most loving, compassionate person I've ever known. Her sense of humor frequently has me in stitches. While I may feel she is far too sensitive or naive, her desire and will to fit in with the rest of the world, inspires me and gives me meaning and purpose. Parenting a child with Fragile X Syndrome must certainly be one of the hardest tasks on the face of the earth.

Thank you for coming here to get the information you need for this most importat topic. Do us all a favor by writing and excellent report!

GROWING THE TEAM

How you can Help

There are many ways you can help accelerate progress towards effective treatments and a cure for Fragile X. We are now raising money to fund grant applications that will arrive on December 1st. Grant decisions are made in just two months with the help of our scientific advisors, so your money will go to work right away.

Four Stars for FRAXA!

FRAXA has 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 with further details.

Donate a Car

The nonprofit Cars4Charities (www.cars4charities.org or 866-GIVE-4-US (448-3487)) is more efficient than the other groups we have worked with. They will pick up your car, give you a receipt for tax purposes, sell the car, and give over 75% of the sale price to FRAXA.

Combined Federal Campaign

Only 1 in 10 charities qualifies for the Combined Federal Campaign, the nationwide workplace giving campaign for federal employees, and FRAXA is one of them! If you or someone you know works for the government, the post office, or the military, FRAXA's CFC number is 0220.

FRAXA Video

"First Down Towards a Cure"
You can get the new FRAXA movie on video or DVD for $10. This 11 minute movie features the Bolling family, researchers, Mary Higgins Clark, and Jake Porter, the Ohio high school student with Fragile X whose touchdown inspired stories on TV and in magazines and papers across the country.

FRAXA Gift Memberships

Do you have friends and family members who would like to receive our newsletters? A gift membership to FRAXA is only $25. Simply call, email or send a note in the mail with the names and addresses of your guest members. The more members we have, the more power we have when we meet with government officials in Washington. Each member is a voice in support of Fragile X research.

FRAXA Holiday Gifts:

Great gifts that promote awareness of Fragile X!

FRAXA T-Shirt

Heavyweight 100% white cotton shirt with the teal FRAXA logo on left chest. Available in sizes M,L,XL,XX, XXL **$15**

FRAXA Lapel Pin

Gold-plated "X" **$10**

FRAXA Umbrella

Pop-up umbrella with white FRAXA logo. Choose from gray, navy blue, or burgundy **$10**

You can send your order along with a check, or call us at (978) 462-1866 with a credit card number, or order these gifts online at www.fraxa.org

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 $35,000 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
FRAXA Fall Flingers!
DESIGN: Mary Lou Supple

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

FRAXA would like to thank Networx of Newburyport, MA for hosting, at no charge, the FRAXA website and email.

FRAXA 10th Anniversary Spring Galas

Boston, Thursday, May 20th, The Four Seasons Hotel
with Mary Higgins Clark and Boston Area Celebrities
Chaired by Harry and Jaime Manion

Omaha, Thursday, May 6th
Mary Higgins Clark FRAXA Gala
Special Guests Elieen Naughton and Senator Chuck Hagel

Chaired by Kelly Randels, Diane Hamsa, Carol Parsow, Bob and Sheila Gerhman, and Cindy McGowan.

Fragile X in the Media

*Luke Solotaroff, 6, has Fragile X. Read Luke's story in the November issue of **Men's Journal** ("Me and the X-Man" by his father, Paul Solotaroff). If you missed the magazine issue, you can still read this article online at www.FRAXA.org or call us for a copy.*

PLEASE HELP FRAXA

in supporting research aimed at treatment for Fragile X

FRAXA is a national 501(c)(3) tax-exempt organization. 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

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

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FRAXA UPDATE

SUMMER 2003

VOLUME 10, NO.2

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"NEVER DOUBT that a small group of thoughtful, committed citizens can change the world. INDEED, it's the only thing that ever has."

— Margaret Mead

Craig Chesley and Eileen Naughton, holding Leah, Patrick, and Emma

TIME Magazine President Joins FRAXA Board

We are delighted to welcome Eileen Naughton as the newest member of FRAXA's Board of Directors. Eileen is president of *TIME*, the world's largest news magazine with 29 million readers. She manages TIME's global publishing operations, including finance, strategy, business development, circulation and ad sales, and also oversees the *LIFE* franchise, best known for its extensive photo journalism archive, and *TIME For Kids*. Eileen began her career at Time Inc. in 1989, and was general manager of Fortune magazine from 1993 to 1997.

Most important of all, Eileen is the mother of three children, including Patrick, who has Fragile X. "He's a fun-loving boy who's obsessed with dogs, horses and the NYC subway system," says Eileen.

"Patrick was diagnosed with Fragile X at 18 months and he is now 10 years old. He has the full range of global deficits – limited expressive language, high anxiety, obsessive/compulsive tendencies,

continued on p.11

12 Research Projects Funded

New Awards at Universities Around the World

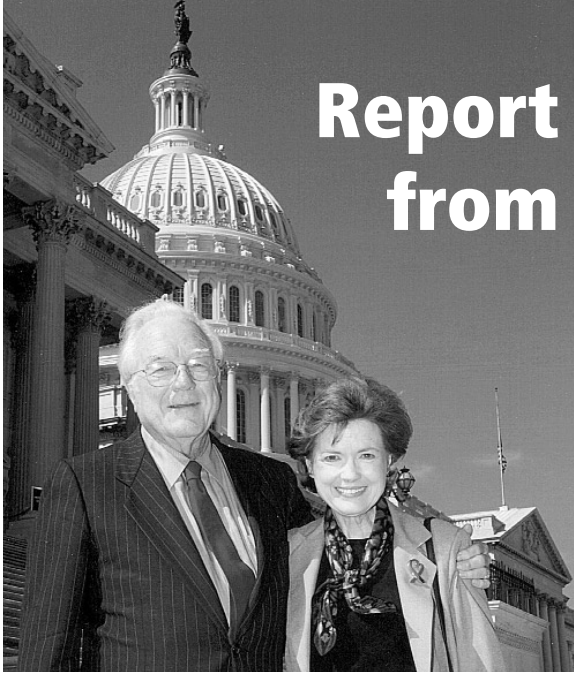
FRAXA is committed to finding treatments and a cure for Fragile X to help the current generation of affected children and adults. We spend 85 – 90% of funds raised on grants and only 6% on management expenses, with the rest going to fundraising, education, and awareness.

This year, FRAXA has already awarded 22 research grants for a total of $1,059,000. In June we renewed support for the ongoing clinical trial of Ampakines and a host of basic research projects (See page 4 for reports). Several of the investigators are new to the Fragile X field and they will help accelerate the pace of progress. We hosted a very productive Banbury meeting this spring (See page 9 for an account of this important meeting).

Plans for the upcoming months include hosting a booth at the Annual Society for Neuroscience meeting, where FRAXA meets with current grantees and recruits additional researchers, and raising funds for the new proposals which will arrive at the end of this year.

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 8000 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

In Washington, May has been Pennsylvania month! Climaxed by the spectacular Pittsburgh gala on May 29, Pennsylvania was in the FRAXA spotlight all month long.

First, on May 8, Bill Parker, Mayor of Paxtang, PA, and David were treated to lunch by Senator Arlen Specter, PA, Chairman of the Senate Appropriations Subcommittee on Health. Senator Specter has always been very supportive of Fragile X research funding. At the Copacabana gala, host Roger Mudd presented him with FRAXA'S ***Beacon of Light*** Award, recognizing his help in increasing NIH's funding of Fragile X research from less than $1 million to more than $19 million in just 8 years!

Then, on May 14, Mayor Parker testified before the House Appropriations Subcommittee on Health, which has two (!) Pennsylvania members, Congressmen John Peterson and Don Sherwood – and the Chairman, Ralph Regula, is from just-over-the-border Canton, Ohio. See Mayor Parker's testimony, at right.

Bill Parker and David Busby

Finally, we are pleased to report that the University of Pittsburgh has received a grant of $1 million dollars from the Department of Defense for basic and clinical research on Fragile X.

Excerpts from the FRAXA Research Foundation Statement presented to the the Senate Appropriations Committee by Bill Parker, Mayor of Paxtang, PA

Chairman Regula and members of the Committee, my name is Bill Parker. I particularly want to thank two members of your Subcommittee, Mr. Peterson and Mr. Sherwood, for making it possible for me to appear today.

Two of my four children are affected by Fragile X, the most common inherited cause of mental retardation. After months of agonizing search, we finally were able to receive a proper diagnosis and were told that our little girl, Sophia, would always be mentally retarded. We sought the advice of the top experts on this disease. One was Dr. James Watson, the discoverer of the DNA double helix. I asked him what was needed to cure Fragile X. He said, "100 million dollars." I am here to ask you for that.

Fragile X research is vastly under funded. Present funding levels by the National Institutes of Health (NIH) are inadequate in light of this disease's prevalence, its cost to the public, the potential for the development of a cure, and the significance that Fragile X research has for related disorders such as autism. (30% of those affected with Fragile X are autistic. Fragile X research is the "portal" for autism research.) Congress should move quickly to correct this deficit. A modest investment made now will pay off handsomely, in terms of dollars saved and reduced human suffering.

I am here to make three suggestions about what the Congress can and should do to help over 90,000 Americans affected with Fragile X and their families, and the more than half-million women who are carriers:

1. Implement fully Title II of the Children's Health Act of 2000

The Coalition for Children's Health has supplied for the Record of this Subcommittee its support for Fragile X research funding, in the amount of $41 million, in Fiscal Year 2004. That would permit a badly needed increase in the funding for the three "Centers without Walls" which were finally approved (but even as yet not funded) by the National Institute for Child Health and Human Development (NICHD) and for critically important research projects underway at universities around the United States.

We also propose the establishment of a new Collaborative Center at the University of Pennsylvania and the University of Pittsburgh for

the testing of promising new treatments. The FRAXA Research Foundation and the MIND Institute are currently funding human drug trials on ampakines. These trials are supervised by Dr. Elizabeth Berry-Kravis at Rush Presbyterian Hospital in Chicago and by Dr. Randi Hagerman at the MIND Institute at the University of California at Davis. In addition, FRAXA Research Foundation and the NICHD are funding the work of Drs. Bear at MIT and Huber at The Southwestern Medical Research Center in Dallas. Their collaboration is close to a breakthrough on the understanding of the neurobiology of Fragile X. This can well lead to a treatment for Fragile X and, perhaps, autism.

2. Support an Expanded Newborn Screening Program

Congress should provide funding to the CDC, and the Health Resources and Services Administration (HRSA) to develop and implement an expanded pilot newborn testing program.

3. Adopt the Report Language proposed by the Coalition for Children's Health.

I respectfully submit, attached, Report language we request that this Subcommittee include in its Annual Report to the Congress concerning Fragile X research funding by the NIH and by the CDC.

Bill Parker with Chairman Ralph Regula

Conclusion

Given its prevalence, I am sure you agree that research on Fragile X is under funded. No one ever dies of Fragile X; life span is normal. But the hopes and dreams of Fragile X parents do die. These children lose the chance to lead normal, productive lives, and their basic needs and sustenance often become the responsibility of American taxpayers. Children born with Fragile X lack only one vital protein. We need your help to support the research that will show us how to replace or compensate for this protein and enable people with Fragile X to live normal, productive lives. Only major research can make this happen. My children, and thousands of other precious children, deserve the chance this research will provide, and I hope you will make it happen as a priority by funding Fragile X research.

Mr. Chairman and Members of the Committee, I want to dance with my daughter, Sophia, at her wedding.

FRAGILE X IN THE MEDIA

Whenever Fragile X is featured on TV, radio, or in print, more people learn about the most common inherited cause of mental impairment. This in turn helps us gather support to accelerate research. Here are some recent stories about Fragile X in the news:

April – The April issue of **Exceptional Parent Magazine** included a section, "Research Reflections" which featured Fragile X. FRAXA Board Member David Clark has been appointed Vice President at **Exceptional Parent**. Congratulations, David!

April 16th – Dr. Francis Collins, Director of the National Human Genome Research Institute, and Dr. Elias Zerhouni, the Director of The National Institutes of Health were interviewed on The Diane Rehm Show, reaching over 1.4 million public radio listeners around the country. Fragile X was a major topic of discussion: the symptoms, the cause, and current research were all discussed in detail.

May 30th – FRAXA's 6th Annual Fragile X Gala was featured prominently in two Pittsburgh newspapers. A report with photos from the gala will appear in our next newsletter. You can read the newspaper stories at

http://www.pittsburghlive.com/x/tribune-review/entertainment/s_137574.html and
http://www.post-gazette.com/seen/20030602event0602fnp1.asp

McKayla and Christopher Cox, children of Jim and Michele Cox, Gala Chairs

June 12th – CNN aired a human-interest segment about sibling relationships and Fragile X featuring Jared, Scott, and Carly Heyman of Marietta, Georgia. Carly has written a book, **My eXtra Special Brother**, about her experiences as a sister of a boy who has Fragile X. The story aired several times to a multi-million person audience!

September 2003 – A feature article on Fragile X is scheduled to appear in the October issue of **Men's Journal**, which will appear on newsstands during the first week of September. This article is written by Paul Solotaroff, twice nominated for a Pulitzer Prize for his writing and also nominated for many other national awards. Paul's four-year-old son, Luke, has Fragile X.

research

Effects of Ampakine CX516 on Cognition and Functioning in Fragile X Syndrome and Autism

ELIZABETH BERRY-KRAVIS, MD, PhD

Rush University, $72,358 renewal

This is a two year clinical trial of the first specific treatment for learning and memory deficits in Fragile X. The trial will be completed in June 2004.

by Elizabeth Berry-Kravis

We have enrolled 26 subjects in our study of this new drug. One subject was autistic and all other 25 have Fragile X. No one has dropped out for any reason, which is quite good for a phase II study of a new drug. We have seen no serious side effects – the most significant thing being a slight increase in headache frequency in one patient. CX516, in fact, appears to be remarkably side effect-free in that we are monitoring patients with excruciating scrutiny for side effects and are not seeing much of anything. We have presumably treated about 12 or 13 patients with actual CX516 and I have not used any currently approved drug with which I could treat 12 consecutive individuals with Fragile X without side effects. So the safety profile of this medication appears to be excellent thus far.

We of course do not yet know who is on treatment and who is on placebo, but we have seen some patients do some new things during the study such as holding a conversation on the phone, putting shoes on the appropriate feet, learning to use the popcorn popper, increased complexity of comments about situations, and better school performance. We are grateful to all the wonderful families and adult Fragile X subjects who have made the considerable effort required to participate in this study. They are helping lay the groundwork for future treatment of cognition in Fragile X syndrome.

A FEW TERMS

Fragile X Syndrome
is caused by a mutation in the FMR1 gene, which shuts the gene down so that it cannot produce its normal protein, FMRP.

FMRP
plays an important role at synapses, the junctions between brain cells where signals are passed from one cell to the next. Understanding FMRP's role in the brain is vital to finding treatments and a cure.

Fragile X Knockout mice
are genetically engineered so that they do not produce the protein, FMRP. They show some symptoms of Fragile X. Models of Fragile X have also been developed in fruit flies, tadpoles, and worms.

Effects of Positive AMPA Receptor Modulation in the FMR1 Knockout Mouse

JULIE LAUTERBORN, PhD

University of CA at Irvine, $40,000

This study complements Dr. Berry-Kravis's clinical trial of the Ampakine drug CX516. Dr. Lauterborn aims to understand the actions of newer Ampakine compounds which are not yet tested for human use but which are more potent than CX516.

by Julie Lauterborn

Studies in Fragile X mice reveal abnormalities in the shape and number of dendritic spines (where neurons receive input from other neurons), similar to the abnormalities seen in brain cells of humans with Fragile X. In addition, in the Fragile X mouse there is less glutamate receptor protein in the forebrain, suggesting that cognitive deficits in this syndrome may arise from impaired maturation of glutamate spine synapses.

Stimulation of AMPA-class glutamate receptors leads to a normalization of spine shape and stimulates brain neurons to synthesize increased levels of Brain-Derived Neurotrophic Factor (BDNF). BDNF is known to reduce spine number and length, as well as to increase AMPA receptor protein levels. These findings suggest that in Fragile X (and in the mouse model), increases in both AMPA receptor and BDNF signaling may effect changes in synapses that should ameliorate deficits in neurotransmission.

Recently we demonstrated that Ampakines, which increase AMPA receptor function, also increase BDNF expression in normal rodents. The data suggest that Ampakines could be useful therapeutics for dendritic spine abnormalities and cognitive deficits associated with Fragile X. We will test the hypotheses that (1) the regulation of AMPA receptor expression within the cell membrane is similar in Fragile X knockout and wildtype mice and (2) Ampakine facilitation of AMPA receptor function can be used to sustain increases in neuronal BDNF protein content in Fragile X knockout neurons.

update:

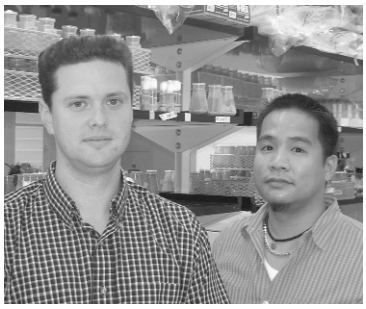
A Genetic Model for Understanding Dendritic Spine Formation and Fragile X

JAY BRENMAN, PhD
Principal Investigator

PAUL MEDINA, PhD
Postdoctoral Fellow

University of North Carolina at Chapel Hill, $35,000

by Jay Brenman



Jay Brenman and Paul Medina

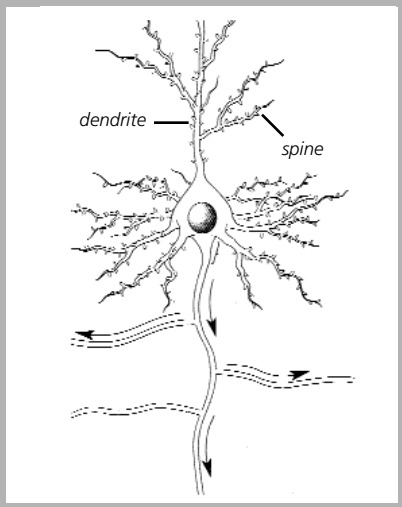
Dendrites are extensions of neurons where information is received, processed and stored in the brain. Dendritic spines are found along dendrites, and on these spines, most synapses form. It is at these synapses that signals are passed from one neuron to the next.

Despite the importance of dendrite and dendritic spine formation for cognitive function, few genetic approaches exist to analyze dendrite development. A better understanding of the genetic basis of dendrite and dendritic spine formation may provide insights into human neurodevelopmental disorders, including Fragile X.

We are developing a genetic model for analyzing dendrite and dendritic spine development utilizing Drosophila, or fruit flies. Surprisingly, 72% of known human neurological disease genes exist in Drosophila, including the Fragile X gene, so Drosophila has often been used to identify and understand genes that can cause human disease. Absence of the Fragile X gene function in both humans and Drosophila results in abnormal behavior and neuroanatomical defects. We hope to identify other genes that function together with the Fragile X gene to properly form dendrites. Hopefully some of these genes will be therapeutic targets for Fragile X and other neurodevelopmental disorders.

Anatomy of a Neuron

Neurons (brain cells) have branches – dendrites – which have spines where synapses form to make connections with other neurons.



Investigating the Role of the Fragile X Protein in Metabotropic Glutamate Receptor Mediated Long Term Depression (mGluR-LTD) and Protein Synthesis

MARK BEAR, PhD

NAVEEN NAGARAJAN, PhD

Massachusetts Institute of Technology (MIT), $37,000

While at Brown University, Dr. Bear and Dr. Kimberly Huber developed the first evidence that the function of one kind of neural receptor (mGluR) is excessive in fragile X mice. The current study is aimed at demonstrating that mGluR antagonists may be potential treatments for Fragile X syndrome.

by Mark Bear

The mGluR Hypothesis

We hypothesize 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. One consequence of this defect is that some AMPA receptors are pulled away from the surface of the neuron, leaving fewer AMPA receptors at the cell surface to perform their normal function. This hypothesis fits neatly with the studies of Dr. Berry-Kravis and Dr. Lauterborn, because Ampakine drugs work by enhancing the function of the fewer AMPA receptors still left. Another consequence of excessive mGluR function is initiation of epileptiform activity, which may explain why many children with Fragile X have seizures.

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, we will investigate whether mGluR antagonists, like MPEP, will correct this delayed development. Thus the overall goal of this study is to further investigate mGluR antagonists as potential treatments for Fragile X.

FMRP-mediated Dendritic Protein Synthesis required for Correct Morphological Development in Neurons

HOLLY CLINE, PhD Principal Investigator

JENNIFER BESTMAN, PhD Postdoctoral Fellow

Cold Spring Harbor Laboratory, $35,000

Stay tuned to the next newsletter for a description of this project.

research

Continued Investigation of FMRP Function and Expression

WILLIAM GREENOUGH, PhD

ANDREA MITCHENER, PhD

University of Illinois at Urbana-Champaign, $40,000, with $5000 for costs of distributing Fragile X mice to the research community.

by Andrea Mitchener

I am studying several aspects of Fragile X. First, I have been involved in the identification and characterization of messenger RNAs that bind to the Fragile X Protein (FMRP). Due to the absence of FMRP in Fragile X Syndrome, normal expression of other proteins is very likely disrupted. We predict that altered expression of these proteins may contribute to the symptoms seen in Fragile X. Using a new technique, Antibody Positioned RNA Amplification (APRA), developed with Dr. Jim Eberwine at the University of Pennsylvania, we have characterized some mRNAs which are bound to FMRP in cultured neurons.

One mRNA target identified by APRA is the glucocorticoid receptor (GR). We have found that GR protein expression is reduced in the hippocampus of FMR1 knockout mice. GR is part of the Hypothalamic-Pituitary-Adrenal (HPA) axis and is necessary for proper functioning of the feed-back loop that regulates the physiologic response to stress. Work by Allan Reiss and colleagues suggests that the stress response in Fragile X patients is perturbed: cortisol levels (the glucocorticoid hormone released in response to stress) are higher in patients and show a protracted return to baseline compared to controls. I am examining the response of Fragile X mice to stress. Since the ability to cope with stress can play a critical role in quality of life and affect learning, these studies may suggest a pathway that can be targeted with drug or behavioral interventions.

A second project involves the construction and testing of non-replicating recombinant viral vectors carrying the FMR1 gene. In collaboration with Dr. David Bloom at the University of Florida, we are testing two viral vector systems, Herpes Simplex Virus (HSV) and Adeno-associated Virus (AAV), for their ability to deliver the FMR1 gene into neurons from knockout mice. Our initial tests revealed that the specificity of FMRP expression needed to be improved. We have now redesigned the vector to ensure exclusive neuronal expression and we expect improved results using a new promoter arrangement. These vectors will be useful tools for Fragile X researchers and they will provide valuable information as to the requirements for (and potential pitfalls of) FMR1 gene therapy.

Design and Commercial Production of Mouse Hybridomas to Produce Antibody to FMRP

Ivan Jeanne Weiler
PHOTO BY DON HAMERMAN

IVAN JEANNE WEILER, PhD

University of Illinois, $26,600

by Ivan Jeanne Weiler

Antibodies to specific proteins, such as FMRP, are currently the most important tools we have to study where the protein goes and what things it interacts with in brain cells. The best antibodies are "monoclonal", because these cells reproduce indefinitely and will continue to produce this specific antibody. (Antibodies form the basis of the body's immune system – they recognize and grab onto foreign proteins, viruses, etc. that may pose a threat.)

Most Fragile X researchers still use a monoclonal antibody (1C3) which robustly recognizes FMRP. However, there are problems with it. First, it reacts slightly with another protein, FXR1p, as well as FMRP, so that if we use it to stain tissue, we cannot be sure we are staining only FMRP. This would be important, for example, when determining whether gene therapy had succeeded in helping cells to produce FMRP.

Much of the current research depends on the ability to purify protein clusters which contain FMRP with associated RNA and other proteins, using a technique called immunoprecipitation. For reasons we do not understand, 1C3 fails to precipitate FMRP under normal conditions. Other laboratories have made antibodies to FMRP which will immunoprecipitate, but cannot be used in staining. Our aim is to produce an antibody which will do both.

Because commercial labs have concentrated on developing tricks to elicit monoclonal antibodies with more success than the average university lab, we are contracting with Strategic Biosolutions to produce new monoclonals. We have identified three promising sequences in the FMRP molecule which have not been used before. The company will produce candidate clones based on these sequences and send the clones to us for selection of the best candidates.

If we succeed in obtaining our "dream antibody" we will donate the cells to the Iowa antibody resource which will make the line available to the entire research community.

update:

Reactivating the FMR1 Gene

ANDRE HOOGEVEEN, PhD
Principal Investigator

VIOLETA STOYANOVA, MD,PhD
Postdoctoral Fellow
Erasmus University, $35,000

by Violeta Stoyanova

In Fragile X syndrome, the FMR1 gene does not function because it is switched off by a chemical modification, called *methylation*, of a commanding part of the DNA (the promoter).

Our studies were performed by growing cells from Fragile X patients in test tubes. In these cells, we can specifically reverse the methylation of the FMR1 gene – an important step toward restoring its normal function.

Rare individuals exist who have long repeats in their FMR1 gene, but for some unknown reason the gene is not methylated and functions normally, so these people do not have Fragile X. We plan to investigate the pattern of gene expression in these healthy people and compare it to that of Fragile X patients. We hope to identify genes important for switching on (demethylating) the silenced FMR1 gene. We are studying cells from members of a family in which some individuals have a methylated FMR1 gene, and are affected by the syndrome, and others whose FMR1 gene is not silenced, in spite of long repeats. Using this strategy, we hope to identify important players in the process which prevents methylation or is even able to reverse the methylated state of the FMR1 gene in Fragile X patients.

FRAXA also funded the following additional grants in June 2003. Stay tuned for our next newsletter for detailed descriptions of these projects:

Regulation of dFMR1 Activity

JERRY YIN, PhD
Principal Investigator
Cold Spring Harbor Laboratory
$50,000

Connection Between Fragile X Syndrome and RNAi

RICHARD CARTHEW, PhD Principal Investigator

YOUNG SILK LEE, PhD Postdoctoral Fellow

Northwestern University
$35,000

Dendritic Trafficking and Determining the Transport Function of FMRP

GARY BASSELL, PhD
Principal Investigator

LAURA ANTAR Fellow

Albert Einstein School of Medicine
$35,000

Understanding the Function of Fragile X Protein in Drosophila

HARUHIKO SIOMI, PhD
Principal Investigator

MIKIKO SIOMI, PhD
Principal Investigator

Tokushima University, Japan
$35,000

Publication

Professor Jean-Louis Mandel and colleagues have published a paper in the June issue of Neuron, entitled CYFIP/Sra-1 Controls Neuronal Connectivity in Drosophila and Links the Rac1 GTPase Pathway to the Fragile X Protein (Neuron, Vol 38). This work establishes a molecular and functional link between Fragile X Syndrome and a pathway within neurons which has been implicated in other forms of mental retardation: the Rac1 small GTPase pathway. Using Drosophila, the team has provided evidence of a Rac1-CYFIP-FMRP cascade, and they have demonstrated that this pathway is crucial for proper establishment of the connections between neurons.

For more details, visit www.fraxa.org/html/research_Mandel.htm The project was funded first by a FRAXA grant and currently by the NIH/FRAXA joint research initiative.

FRAXA's Night at the Copacabana

On a snowy, cold night in New York City, nearly 500 people came out to dance to a hot and steamy Latin beat at the Copacabana. The March 6th dinner was a benefit for FRAXA Research Foundation, and the event raised over $500,000 for Fragile X research.

Chaired by **Debbie and Jeffrey Stevenson**, and co-chaired by **Eileen Naughton and Craig Chesley**, guests were treated to an amazing time at the brand new Copacabana. Guest speakers included Jeffrey Stevenson, who is a Partner at Veronis Suhler Stevenson; *Time Magazine* President and FRAXA's newest board member, Eileen Naughton; AOL Time Warner's CEO and Chairman-Elect, **Richard D. Parsons**. Mr. Parsons was kind enough to introduce another very distinguished guest, **Dr. James D. Watson**, co-discoverer of the DNA Double Helix and a FRAXA scientific advisor. Everyone enjoyed the enlightening and entertaining speech by Dr. Watson, and we were particularly glad he could join us during the busy celebration period of the 50th Anniversary of the DNA Double Helix discovery. CNBC's business news anchor **Sue Herera** was the host for the evening. Dinner and dancing followed, and a hot time in the city was had by all!

A very heartfelt thank you to everyone who braved the weather to be there, and to absolutely everyone who helped make the event such a success. A special thank you also to the Alex Donner Orchestra for providing the fabulous music.

– Debbie Stevenson, Dinner Chair

Photos taken at the Fraxa Copacabana Gala. Clockwise from top:

Eileen Naughton, James D. Watson, Debbie Stevenson, Craig Chesley, & Jeffrey Stevenson

Robert Bauchwitz & James D. Watson

Katie Clapp, Sue Herera, & Mary Higgins Clark

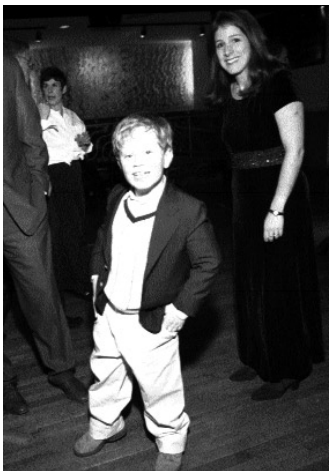
James D. Watson, Richard D. Parsons and Sue Herera

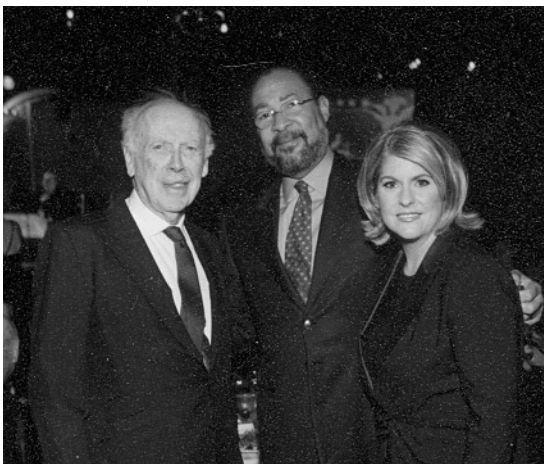
Taylor Stevenson & Leslie Bagdasarian

The Secret of Life

Marking the 50th Anniversary of the discovery of the DNA double helix, Dr. James D. Watson wrote a widely anticipated and wonderful new book, *DNA, The Secret of Life*. Here is what Dr. Watson says on page 333:

"Like ongoing research into Huntington, DMD, and many other genetic afflictions, studies of fragile X have been galvanized by those most directly affected: the families and loved ones of sufferers. FRAXA, the Fragile X Association, has been hugely effective in raising money and in inducing Congress to support fragile X research. Though some scientists may cynically view such groups merely as agencies that offer individuals in dire straits the comforting illusion that they are not entirely powerless, experience shows that dedicated, resourceful, and, above all, motivated organizations like FRAXA sometimes do hold the key to cracking these diseases against the long odds. To those who take the biggest gambles – financial and scientific – sometimes, with luck, go the biggest rewards."





Banbury 2003

The fourth annual Fragile X Banbury meeting was held in Cold Spring Harbor, New York, on March 30-April 2nd, 2003. This year the conference was organized by Dr. Mark Bear, now at MIT, and Dr. Michael Tranfaglia, FRAXA Medical Director and co-founder. These meetings are funded through a grant from the National Institute of Mental Health (NIMH).

Banbury is in a secluded spot on Long Island (NY), so we have a captive audience of leading scientists for three days. A strict limit on the number of participants (37) means that these meetings cannot represent the entire Fragile X field, so each meeting focuses on a hot new treatment-oriented topic. This year we were fortunate to have two scientists from pharmaceutical companies who provided perspectives on how to translate research into treatments.

The topic was the function of the Fragile X protein at synapses, where nerve cells signal each other. Recent

MaryLou Oster-Granite, Jennifer Hill-Karrar

research suggests that the Fragile X protein (FMRP) regulates the synthesis of many proteins at synapses, and that when FMRP is lacking (as in Fragile X syndrome), disruptive changes occur at those sites.

Much discussion focused on mGluRs, a class of receptors which triggers protein synthesis at synapses, and which we are particularly interested in as a potential target for treatment of Fragile X (see article by Mike Tranfaglia in FRAXA's Annual Report 2002 or Newsletter, Volume 3, 2002). Many symptoms of Fragile X syndrome could reflect exaggerated mGluR function occurring in the absence of FMRP. At this meeting, data was presented to support this idea

David Nelson, Steven Warren

and some scientists left at the end of the meeting with plans to test the "mGluR hypothesis."

Banbury meetings are remarkable because there is a free exchange of new scientific data and ideas, including

David Linden, Fabrizio Gasparini, Bob Wong, & Kim Huber

not-yet-published findings. Discussions begin over the breakfast table and end late in the evening, which lends a wonderful intensity to these conferences. Plans are already in the works for next year.

Researchers' Corner: Tools of the Trade

As we reported in the last issue of this newsletter, many scientists investigating Fragile X have been hampered by lack of necessary research tools; in particular, Fragile X knockout mice and antibodies to the Fragile X protein. Over the past three months, progress has been made on both fronts:

Knockout Mice

Since our last newsletter, Jackson Laboratory, which supplies mice bred to model human diseases but currently stocks only frozen embryos of Fragile X mice, is currently importing the FMR1 knockout mice on a sighted FVB background. The mice will be available to researchers in six to twelve months. But, unless JAX receives notice that enough reearchers are interested in purchasing the model, they will cryopreserve the embryos and it will cost each researcher $1500 to thaw them out, on top of per-mouse charges. Scientists with an interest in working with these mice: please take a moment to visit the JAX website and request that these mice be maintained live and available to the research community.

Go to http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi and enter Stock Number 4624. Click on "Search Database". Next, click the square to the left of the stock number and then click "continue". Fill in the Interest Form, click on "Register Interest" and you're done!

To provide stock in the interim before the JAX mice are available, FRAXA has awarded a grant to Dr. Bill Greenough to defray costs of providing mice to the scientific community. The strains available are C57 knockout and matched wildtype or sighted, pigmented FVB, both backcrossed 12 generations and genetically matched except for the KO locus.

Antibodies

Several researchers have generously contributed antibodies to the University of Iowa Developmental Studies Hybridoma Bank (www.uiowa.edu/~dshbwww/), which will distribute them to the scientific community at a nominal cost. Available antibodies include 7G1-1, donated by Dr. Steve Warren, anti dFMR1 5A11, donated by Dr. Haruhiko Siomi, and 7B8 and 2F5, both donated by Dr. Alan Tartakoff. The DSHB website includes details on each of these antibodies or you can call Karen Jensen, (319) 335-3826, at the DSHB for more information.

Patrick's Pals

It was another GREAT year of basketball and a successful one with over $20,000.00 raised! Following are excerpts of a letter we received from one of the participants.

Dear Patrick's Pals 3-on-3 Organizers:

I want to thank you for another great tournament. This was my second year participating and once again I had a fantastic time. Just like last year, it was a day of competition, sportsmanship, philanthropy, camaraderie, and of teamwork - before, clear from the level of planning, and after the first basketball was shot.

I have played in a fair amount of basketball tournaments, camps and events…and, I wanted you to know a few things that I find special about the tournament you have all created.

It is extremely competitive, and physical, the way I like to play. Yet no one would ever think to cross the line of good sportsmanship. Hard fouls, tough losses, even an occasional argument, but never an altercation I haven't seen end with a handshake or a pat on the back. Rare for such a large group of competitors - many of whom are complete strangers.

I love the age range. I only hope to still be playing when I'm 50, 60, and older - and as athletic as some of the gray, white, or even bald tops I see each year!

Of course, the cause. Which, in all honesty, was not my first interest in the tournament when I heard about it - it was the idea of playing the game. But I feel I've grown a bit more attached - in my own mind anyway. My best friend growing up had an older sister with Prader Willi Syndrome, a genetic developmental disorder that to me, as a kid, represented mental retardation. It is easily my closest exposure, as I've known Kerry nearly all my life. Even though it is only a small contribution, and Patrick and Kerry are different people with different syndromes, I walk out of that gym feeling pretty good nonetheless.

And that is perhaps the most special element of the tournament to me. Not so much what you, I, or anyone else gives to Fragile X or to Patrick, but what Patrick has essentially given to me, and to everyone who participates. Patrick, along with his family and friends - his Pal's, has created this wonderful event, and given me a great day. A day I looked forward to this year for quite a while . . . A day I would not have otherwise had . . .

So, again, thank you all. Thank you Patrick, for a wonderful day...It seems like such a community, family, grass roots type charity event - much closer to the cause I feel than others I've participated in. I guess it's a bit infectious…

Sincerely,

Brian Lieber

THANK YOU Patrick's Pals! Every single one of you! -Pamela & James Vershbow

IN MEMORIUM

Daniel Vershbow

The Fragile X community has suffered a great loss: Dan Vershbow passed away this Father's Day at age 79. Dan was a longtime member of FRAXA's board of directors and a benefactor of fragile X research. As an MIT-educated engineer, he brought a unique perspective to our organization; Dan said "This is basically an engineering problem. We need to engineer a solution for Fragile X, based on the research that FRAXA is funding." He leaves behind a remarkable family which has long been a major source of support for FRAXA; there is little doubt that they will continue to pursue Dan's vision.

Update from the National Fragile X Foundation

Recently, the NFXF released its Handbook for Families and Professionals in a new Spanish version. We have begun to distribute them to Spanish speaking individuals and parent support groups including to our fellow member of the International Alliance of Fragile X Parent Support Groups, the Spanish Federation for FXS. If you know of a Spanish speaking family, we'd like to know so that we may send them a free copy. The NFXF is currently working to translate the Handbook into other prominent languages.

We are also excited about our new website Message Boards which feature discussion topics important to those who have a child with Fragile X. This internet-based "bulletin board" allows users to join in ongoing discussions, begin a new discussion or simply follow others' discussions. Topic areas include: Behavior; Occupational and Physical Therapy; Speech and Language Therapy; Medication; Education; Toileting; Adult Issues; Mothers Only; Fathers Only; Siblings Only; Miscellaneous & Other.

The first few of the Education Project lesson plans are now posted on our website at www.FragileX.org under the "Education – Lesson Planning Guide" menu item, and our new Special Topic pamphlets on Behavior and Aggression are now available for free.

As always, we're interested in knowing what resources and information are important to you and your family.

Robby Miller, Executive Director, National Fragile X Foundation, PO Box 190488, San Francisco, CA 94119-0488

Tel: 800-688-8765, E-Mail: NATLFX@FragileX.org, Internet: http://www.FragileX.org

Patrick with his favorite dog, Sadie

continued from page 1

Debbie Stevenson, FRAXA Vice President, and Eileen Naughton

autistic behaviors, cognitive impairment. We began intensive early intervention at 18 months – P/T, O/T, sensory integration, speech therapy, music therapy...even aromatherapy, which did seem to wake up his sensory system! He responded most markedly to O/T and we see real value in the sensory integration approach. His school, The Boston Higashi School, is an enriching, hopeful environment for him: physical exercise, academics, art and music enrichment, daily living skills. Since he began there in April 2002, his gains have been steady and marked. He now rollerblades, eats properly with a fork and knife, is becoming more independent with self-care. He is an emerging musician, now learning to play the recorder, and he's just weeks away from riding a 2-wheel bicycle without assistance.

"I am so very pleased to be involved with FRAXA. The focus that its leaders have brought to this organization from the very beginning – and the determination that a treatment or cure for Fragile X will be found in our kids' lifetime – is truly inspiring. It gives my family hope, and it gives hope to so many thousands of affected families, that a cure is within our reach."

Welcome A-Board, Eileen!

GROWING THE TEAM

Ways you can Help

There are many ways you can help accelerate progress towards effective treatments and a cure for Fragile X. We are now raising money to fund grant applications that will arrive on December 1st. Grant decisions are made in just two months with the help of our scientific advisors. so your money will go to work right away.

Four Stars for FRAXA!

FRAXA has 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 with further details.

FRAXA 10th Anniversary Gala – May 20, 2004 – Boston

Mark your calendar and let us know if you would like to join the gala committee.

Donate a Car

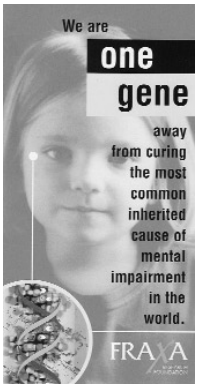
The nonprofit Cars4Charities (www.cars4charities.org or 866-GIVE-4-US (448-3487)) is more efficient than the other groups we have worked with. They will pick up your car, give you a receipt for tax purposes, sell the car, and give over 75% of the sale price to FRAXA.

Combined Federal Campaign

Only 1 in 10 charities qualifies for the Combined Federal Campaign, the nationwide workplace giving campaign for federal employees, and FRAXA is one of them! If you or someone you know works for the government, the post office, or the military, FRAXA's CFC number is 0220.

New Fund-Raising Tool

Fraxa has a new brochure developed to help those interested in sending mailings to friends, family and neighbors. We have plenty and will be happy to send you a supply! This is a great way to help FRAXA fund more research.



New Guide: Families & Fragile X Syndrome

The National Institute of Child Health and Human Development (NICHD) has published a booklet on Fragile X designed for families. It features pictures of children from the Maryland Fragile X Group and an especially charming photo of Mary Beth Busby and her son, Jack. For free copies (Publication No. 96-3402):
NICHD Information Resource Center
P.O. Box 3006, Rockville, MD 20847
Phone: 800-370-2943 Fax: 301-984-1473
E-mail: NICHDInformationResourceCenter@mail.nih.gov, Web: www.nichd.nih.gov

Hertzig Dinner Auction

The Hertzig Family of New York held a wonderful dinner/auction to benefit FRAXA in May. Thank you, Nancy and Jim, and all of the people who made this a very special evening and raised money to fund a full postdoctoral fellowship!

FRAXA Fall Fling

Events will coincide with National Fragile X Research Day, October 5th, endorsed last year by Congress. If at least 30 people host events, we will contact the national media and urge them to cover Fall Fling.

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 $35,000 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: Katherine Clapp, MS

CONTRIBUTORS: Mark Bear, PhD, Elizabeth Berry-Kravis, MD, PhD, Jay Brenman, PhD, David and Mary Beth Busby, Julie Lauterborn, PhD, Brian Lieber, Andrea Mitchener, PhD, Violeta Stoyanova, MD, PhD, Michael Tranfaglia, MD, Ivan Jeanne Weiler, PhD, and others

DESIGN: Mary Lou Supple

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Fragile X Research Day – FRAXA Fall Fling

October 5, 2003

On and around National Fragile X Research Day, FRAXA will hold its Second Annual FRAXA Fall Fling – events everywhere to celebrate research progress and to raise funds for research and awareness of Fragile X. Last year, our members hosted over 30 events: cocktail parties, bowling tournaments, letter-writing campaigns, sporting events, concerts, small dinners at home, and more. Funds raised will enable FRAXA to fund more of the research proposals that arrive on December 1, 2003.

Call us and let us know if you can run an event. We will be glad to help!

A SAMPLING OF UPCOMING EVENTS

Illinois: 5K run in Champaign

Massachusetts: Run - Rowley MA, Bradley Palmer State Park
Dinner at the Harvard Club of Boston, hosted by Randy Welch

Nebraska: Cocktail party/buffet, Thursday October 2nd, at the Scottsbluff Country Club, with special guest Mary Jane Clark

New York: Oldies dance, October 11th, Hyde Park. Hosted by Fran Gibb

Maryland: Golf tournament, Monday, September 15th, in Potomac, with professional golfer, Fred Funk. Contact Mark Gruzin at mgruzin@comcast.net

Ohio: Golf tournament and banquet, July 14, Cleveland, hosted by the Fragile X Alliance of Ohio

Pennsylvania: Dinner/auction hosted by Cristy Hollin in Philadelphia

PLEASE HELP FRAXA

in supporting research aimed at treatment for Fragile X

FRAXA RESEARCH FOUNDATION

FRAXA is a national 501(c)(3) tax-exempt organization. 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

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☐ Donor ($50+) ☐ Research Underwriter ($1000+)
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FRAXA UPDATE

SPRING 2003

VOLUME 10, 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

Research is Accelerating!

Latest Results Published

FRAXA is committed to finding treatments and a cure for Fragile X. The first step toward this goal has been to find the precise cause of Fragile X, at the level of individual brain cells.

Recent studies have come a long way toward attaining this first step. Recent issues of the FRAXA newsletter and this issue describe what is now known about the function of the protein, FMRP, which is lacking in people with Fragile X syndrome. Happily, what we've learned suggests that the defect that causes Fragile X might be corrected – at least partially – to help the current generation of children and adults with Fragile X.

While we certainly don't know everything about Fragile X and we know far from everything about the brain, we now know enough to pursue approaches to treatment.

11 New Grants Awarded

In December 2002, FRAXA received more applications than ever before, and we funded 11 projects. Already, inquiries are coming in from scientists who intend to apply for our May 1 application deadline. A quick search for "Fragile X" in the scientific literature brings up dozens of new research articles published just since the new year! See page 6 for highlights of some of these publications and page 4 for FRAXA grants awarded in February, 2003.

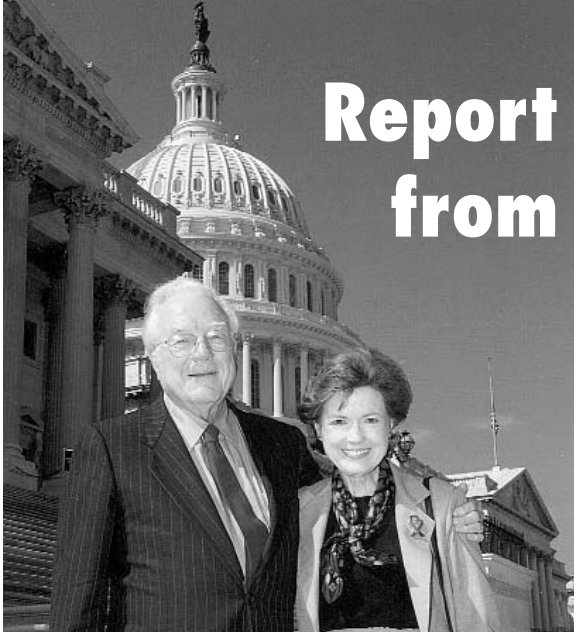
Meeting: Identifying Research Priorities

Left to right:: Oswald Steward, Bruce Hamilton, Ben Oostra, Harry Orr, Marcy MacDonald, Steve Warren, Alexandra Joyner, Lynne Regan, Bill Greenough, Liz Berry-Kravis, Mike Tranfaglia, Kendal Broadie, Linda Crnic, Rob Bauchwitz, Katie Clapp, Mark Mayford, MaryLou Oster-Granite (NICHD). Not pictured: Hemin Chin (NIMH), Paul Nichols (NINDS), Robert Darnell, Jennifer Darnell, John Macauley, Thomas Sudhof

In January, 22 researchers met for two days at the Jackson Laboratory in Bar Harbor, Maine, to discuss the current state of knowledge about Fragile X syndrome and to make recommendations regarding priorities for future research directions. The meeting was organized by the National Institute of Mental Health (NIMH) and FRAXA, and sponsored by NIMH with additional support from the National Institute of Neurological Disorders and Strokes (NINDS) and the National Institute of Child Health and Human Development (NICHD). *Continued on page 3*

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 8000 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 Centers Funded

We are delighted to announce that nearly two and a half years after the passage of the Children's Health Act of 2000, three Fragile X Research Centers have been funded by the National Institute of Child Health and Human Development (NICHD). They will be funded at $3,248,780 for fiscal year 2003 ($126,220 short of the $3,750,000 set-aside) and at slightly higher amounts for each following year, for five years.

The Fragile X Research Centers are:

- **University of North Carolina**
  Dr. Don Bailey, Fragile X Center Director; $1,125,000 for the first year
- **University of Washington**
  Dr. Charles Laird, FX Center Director $874,000 for the first year
- **Baylor College of Medicine**
  Dr. David Nelson, FX Center Director $801,000 for the first year

Each center consists of several related research projects, each led by a different principal investigator. Some are "centers without walls" which include projects at more than one university.

In addition, individual five-year research grants were made to:

- *Dr. Mark Bear, who is now at Brown University but will shortly be moving to MIT; $250,000 for the first year*
- *Dr. Linda Crnic, University of Colorado $198,000 for the first year*

We are proud that FRAXA has, over the years, funded grants for all these researchers. The new centers will be cornerstones in our quest for treatmenta and a cure for Fragile X, and we are also pleased with the additional individual grants.

These centers and grants are in addition to other grants provided by the National Institutes of Health (NIH), the "umbrella" over more than twenty national research institutes. The NIH website – http://crisp.cit.nih.gov – indicates that for fiscal year 2002, there were 83 research grants related to Fragile X funded by 10 institutes. The acceleration and expansion of Fragile X research in the last ten years has been dramatic: in 1994, NIH grants amounted to less than $1 million, while in fiscal year 2002, NIH-wide spending is now conservatively estimated to have reached $16.1 million.

The down side is that with this increase in research projects, there has been no commensurate mechanism for the exchange or coordination of information produced by the various researchers. We hope to remedy that during 2003.

Finally, we hope that this Congress, through its appropriations committees, will once again urge the National Institutes of Health and the Centers for Disease Control to enhance and increase their efforts to find treatments and a cure for Fragile X. Although Congress has not yet settled on the composition of its appropriations subcommittees, we will let you know as soon as it does so that you may establish a relationship with key members.

Simply because we're here in Washington, we get undue credit for the strides made by *you*, the constituents of all of those representatives who have acted on your calls and letters. Another major asset has been the ability of Katie Clapp and Mike Tranfaglia, aided by members of FRAXA's extraordinary Scientific Advisory Committee, to understand and explain our increasingly strong – and increasingly complicated – case for funding research. This ability to "translate" for us, for the Congress, for the scientific community, and for the government's decision makers is unique and vital. We look forward to a productive 2003!

David Busby maintains an email list of "Advocates" who get updates on our legislative accomplishments and who are willing to contact members of Congress at critical moments in our advocacy efforts for Fragile X. You can join this list by contacting him by telephone at (202) 442-3512 or email at Busby.David@dorseylaw.com

Meeting – continued from page1

A meeting report, currently in preparation, will be distributed by NIMH and FRAXA. Among the research priorities identified, one stands out: the critical need for brain tissue from people with the Fragile X mutation. Although this is a painful topic for families to consider, it is important for us to realize that becoming a tissue donor is an invaluable contribution to advancing research. FRAXA has worked with the NICHD-funded Brain and Tissue Banks for Developmental Disorders, at the University of Maryland and the University of Miami; they have papers you can sign to become a tissue donor yourself or on behalf of your children. Contact FRAXA for more information and brochures, or call the Maryland Brain Bank at 800-847-1539 or visit their website at www.btbank-family.org.

We especially thank Dr. Stephen Moldin of NIMH, who provided the initiative to make the meeting happen, Dr. John Macauley of Jackson Laboratories, and the co-chairs, Dr. Oswald Steward and Dr. Mark Mayford.

This is the second research meeting organized recently by NIMH and FRAXA. In November 2001, NIMH held a workshop entitled *Mental Health Aspects of Fragile X Syndrome: Treatment Research Perspectives.* The panel issued recommendations which are published on the NIMH website at *www.nimh.nih.gov/research/fragilex.cfm*

Armed with results from both of these meetings, FRAXA representatives will soon meet with leaders at NIMH to discuss next steps.

Christopher Cox, son of Jim and Michele Cox

Tools of the Trade

As more and more scientists conduct Fragile X research, demand for stocks of Fragile X mice grows. Currently Jackson Laboratory, the foremost source of mice bred to model human diseases, supplies only frozen embryos of Fragile X mice, which then take six months to grow into live study animals. So, in practice, scientists often ask other scientists to give them mice, which becomes a financial and logistical burden, as well as increasing the likelihood that some animals with shady backgrounds (genetically speaking) may muddy the mix.

FRAXA has made it a priority to ensure that Fragile X mice are readily available to qualified researchers. In the short term, we have awarded $5000 to Dr. Bill Greenough's lab in order to defray costs of providing Fragile X knockout mice to the scientific community. To address the long-term growing need for a distribution source, we are discussing with scientists at Jackson Laboratory the possibility of contracting with them to breed and distribute mice.

A similar situation exists with Fragile X protein antibodies – experimental tools used to detect a protein in cells. Availability of good antibodies is critical to progress, but they can be difficult to make and a surprising amount of unscientific luck is involved in building the best ones. There can be many different antibodies to a single protein, each with its own uses.

When FRAXA funds a project, we contract with the researchers that antibodies and other reagents will be shared with the scientific community as soon as the study results are published (see *www.fraxa.org/html/research.htm*). To facilitate sharing, the University of Iowa Developmental Studies Hybridoma Bank (*www.uiowa.edu/~dshbwww/*) maintains and distributes antibodies. A hybridoma is an antibody-producing cell fused to a cancer cell, which can then be grown indefinitely (cancer cells are good at that), providing an immortal supply of a single antibody.

At the Jackson Laboratory meeting, Dr. Steve Warren offered to donate an antibody developed by his lab to the Bank, and this month Dr. Haruhiko Siomi, a FRAXA grantee at Japan's Tokushima University, has also donated a drosophila (fruit fly) hybridoma. Both of these have arrived at the Iowa Bank and are being grown up in quantity for distribution. FRAXA has also awarded grants to Dr. Alan Tartakoff, for development of additional antibodies to mouse FMRP, and to Dr. Kendal Broadie, for fly FMRP antibodies. Since research is only as good as the tools in hand, FRAXA will continue to facilitate sharing, using all the tools in our hands.

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Upcoming Deadlines: May 1, 2003 and December 1, 2003

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 $35,000 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. Information is available at www.fraxa.org or by contacting FRAXA.

research

Role of Fragile X Mental Retardation Protein in Metabotropic Glutamate Receptor-Dependent Synaptic Plasticity

KIMBERLY HUBER, PhD

University of Texas at Southwestern, $72,000

Major support from The Meadows Foundation, a private philanthropic institution established in 1948, has enabled FRAXA to renew funding for this important project. Dr. Huber reports:

Our research focuses on how connections between brain cells (synapses) change in a long term way (synaptic plasticity). It is thought that long-term changes at synapses underlie the refinement of neuronal circuitry during development and mediate processes such as learning and memory in the adult. In the past few years we have been studying synaptic plasticity, in a mouse model of Fragile X syndrome. The 'Fragile X' mouse model was generated by a knockout or removal of the Fragile X mental retardation gene (Fmr1) gene.

To understand how synaptic function and plasticity is changed in Fragile X syndrome, we studied a form of synaptic weakening, termed long-term depression or LTD, in the Fragile X mouse. We have found that LTD is larger in Fragile X mice when compared to their normal littermates.

The fact that LTD is larger in Fragile X syndrome may provide an avenue with which to test therapeutic strategies for treatment of Fragile X syndrome. We have done considerable work determining the cellular mechanisms which underlie LTD in rats and know that it requires activation of a subclass of neurotransmitter receptors called metabotropic glutamate receptors or mGluRs. We are currently testing mGluR antagonists to find a compound which can reduce LTD in Fragile X mice to normal levels. We have had success reducing LTD in rats with one mGluR1 antagonist, termed LY367385. We plan to continue testing mGluR1 antagonists in Fragile X mice and test them in combination with other mGluR antagonists.

We have also planned experiments to reveal the cellular mechanisms by which the Fragile X protein enhances LTD. This research is expected to lead to therapeutic strategies for the treatment of Fragile X syndrome with mGluR antagonists.

A FEW TERMS

Fragile X Syndrome
is caused by a mutation in the gene FMR1, which shuts the gene down, resulting in the lack of a protein, FMRP.

Fragile X Knockout mice
are genetically engineered so that they do not produce the protein, FMRP. They show some symptoms of Fragile X.

mRNAs
are molecules that transport genetic information from the nucleus to other parts of the cell, where this information is translated into specific proteins. Proteins do the work of the cells.

FMRP
performs important functions in brain cells. Understanding FMRP's role in the brain is vital to finding

Treatment of a Mouse Model of Fragile X Syndrome with MPEP

LINDA CRNIC, PhD

University of Colorado, $49,000

As Dr. Huber explains above, we are very interested in mGluR antagonists. MPEP is an mGluR antagonist which specifically reduces activity of mGluR subtype 5 (known as mGluR5). Low doses of MPEP increase social exploration, decrease seizures, decrease anxiety, and decrease responses to stress in normal mice and rats. We injected Fragile X knockout mice with MPEP and measured their startle response to sound. We chose this test because many investigators have shown that Fragile X mice have an altered startle response to sound when compared to wildtype (normal) mice: they are more sensitive to low intensity sounds, normal in their response to intermediate sounds, and less sensitive to intense sounds. This may correspond to the altered sensory reactivity seen in individuals with Fragile X syndrome. Our studies show that effect of MPEP is confined to the intermediate loudnesses of the startle sound. Wildtype mice increased their response to the sound, while the knockouts decreased their response.

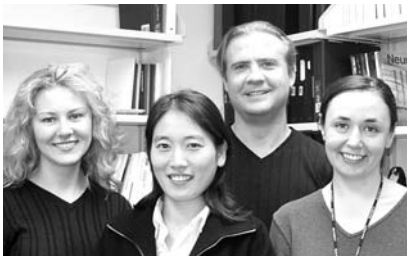
We have just received funding from FRAXA to continue studies of MPEP. We will first explore other behaviors that might be affected by the drug and then determine the minimally effective dose. This dose will then be given on a regular basis, as this would be the likely clinical use of this or similar drugs. Finally, we will determine whether chronic use ameliorates symptoms of Fragile X syndrome without impairing cognitive function.

update:

mGluR-Dependent Protein Translation in the Hippocampus of Wildtype, FMR1 Knockout, and FMR1 YAC Transgenic Mice

ERIC KLANN, PhD

Baylor College of Medicine, $40,000



Lingfei Hou (center left), Postdoctoral Fellow, Eric Klann (center right), Principal Investigator

Previous studies indicate that a neuronal response known as mGluR-LTD is enhanced in Fragile X knockout mice (see Huber, above). Studies also show that the Fragile X protein, FMRP, binds to certain mRNAs and is thought to negatively regulate the translation of these mRNAs into protein.

Other studies suggest that FMRP may limit protein synthesis in general. We aim to explore whether in FMR1 knockout mice, mGluR-dependent LTD is enhanced due to either an increase in the translation of specific mRNAs or an increase in translation in general.

We have been investigating the signaling pathways that couple mGluRs to the protein translation machinery during mGluR-dependent LTD. Identification of these pathways has pointed to candidate mRNAs that may be rapidly translated in response to LTD. We are investigating whether the rapid translation of these mRNAs occurs during LTD in wildtype mice, and if so, whether the LTD-induced translation of these mRNAs is altered in Fragile X knockout mice. In complementary studies, we are determining whether there are differences in LTD-induced mRNA translation between wildtype mice and YAC FMR1 transgenic mice that overexpress human FMRP.

These studies should permit the identification of mRNAs that are translated after the induction of mGluR-dependent LTD and allow us to determine whether the translation of these mRNAs is altered during LTD in FMR1 knockout mice and/or YAC FMR1 transgenic mice. These mRNAs might prove to be targets for designing therapeutic agents for the treatment of Fragile X.

FMRP Regulates Small GTPase Ras Signaling and Glutamate Receptor Trafficking

JULIUS ZHU, PhD

University of Virginia, $44,000

Hailan Hu, Postdoctoral Fellow, Joel Baumgart, student, Julius Zhu, Principal Investigator

Dr. Zhu's team is also 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 gluR1-containing 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 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.

Refined Search for Genes Contributing to Fragile X

WILLIAM GREENOUGH, PhD

ANDREA MITCHENER, PhD, University of Illinois, $11,000

It is well known that certain messenger RNAs (mRNAs) representing different genes are present in the dendrites of neurons. Since FMRP binds to a number of mRNAs, it may be that in the absence of FMRP, the expression characteristics of these genes is altered. We are testing this hypothesis by determining whether certain genes are differentially expressed in dendrites of knockout mice vs. control mice. Using microdissection and gene analysis, we will analyze the mRNA content of dendritic material, which will provide information that is relevant for potential therapeutic interventions for Fragile X Syndrome. In a related project that also uses microdissection and gene analysis, we are looking at gene expression in young neurons from the brains of Fragile X mice. We believe genetic analysis of these neurons will provide important insights into the developmental nature of the syndrome.

Analysis of FMRP RNP Complex Association with the Cytoskeleton through Molecular Motors

GARY BASSELL, PhD
Principal Investigator

JASON DICTENBERG, PhD
Postdoctoral Fellow
Albert Einstein School of Medicine,
$35,000

Jason Dictenberg

How do neurons build synapses during brain development? Neurons use structural elements to form processes – extensions which specialize in building synapses. These structural elements – the cytoskeleton – form a "superhighway" for transport of proteins into developing processes. Recent studies suggest that when neurons are stimulated, they can respond by modifying the activity of specific synapses. This requires local synthesis of some proteins, which means that the mRNAs that encode these proteins must get to these sites. How do the mRNAs get from the nucleus, where all mRNAs are made, to the synapses? mRNA binding proteins, including FMRP, direct their transport to the dendrites and subsequently regulate translation of mRNAs into proteins.

We think FMRP is important for transporting mRNAs to synapses and for local synthesis of proteins required for growth of neuronal processes. We are investigating how FMRP is transported into processes, which cytoskeletal elements are required, and which molecular motors are involved. We are also studying the active transport kinetics of particular mRNAs that FMRP binds to in both normal neurons and those lacking FMRP, by tagging mRNA localization sequences with fluorescent reporters in live neurons. Our data suggest that FMRP can associate with microtubules in a molecular motor-dependent manner, and that functional impairment of these motors can lead to diminished FMRP in developing processes and subsequent changes in the abundance of mRNA targets of FMRP. In Fragile X syndrome, the loss of transport of FMRP and related mRNAs may influence their translation and stability, which ultimately may alter the activity of the synapse itself. This work may help explain the defects that underlie neuronal growth in Fragile X syndrome.

DID YOU KNOW ?

Evolutionarily speaking, humans are much more closely related to mice, rats, and hamsters than they are to dogs and cats!

research

The Molecular Basis of Increased Seizure Severity in the Fragile X Knockout Mouse

CARL DOBKIN, PhD, Principal Investigator

ABDESLEM EL IDRISSI, PhD, Postdoctoral Fellow

NYS Institute for Basic Research, $35,000

This grant could be jeopardized by the possible closing of IBR.

Like many people with Fragile X, the Fragile X knockout mouse is prone to seizures. The mouse is very susceptible to seizures induced by sound (Musumeci et al., 2000). We have found that the Fragile X mouse is also susceptible to seizures induced by the drug kainic acid. However, introduction of a normal human Fragile X gene (FMR1) into this mouse (engineered by Dr. Robert Bauchwitz during a 1998 FRAXA-supported collaboration) eliminates this increased seizure susceptibility.

The heightened seizure susceptibility of the Fragile X mouse implies that there is either an increased function of the excitatory system or decreased function of the inhibitory system in its brain. We aim to find out which one is true. The brain's major inhibitory system is the GABAergic system, named for its dependence on the neurotransmitter GABA, which signals brain neurons to reduce their excitability. We have found a decrease in GABA receptors in the Fragile X mouse brain. We also see an increase in the enzyme that synthesizes GABA, which may be a response to compensate for the reduction in receptors. Preliminary electrophysiological analysis of the Fragile X mouse brain shows functional changes in the GABAergic system. We aim to identify the changes in this system and see which changes are reversed by introducing the human FMR1 gene. Once we determine the critical changes and the cells in which they occur, we will examine how the Fragile X protein influences gene expression in those cells.

Since GABA receptors in one brain region, the cerebellum, appear to be unaffected, we will also determine how the GABA system in the cerebellum differs from other brain regions. These strategies should allow us to begin to understand how absence of the Fragile X protein leads to seizures in the Fragile X mouse as well as changes in overall brain function.

update:

Synaptic Plasticity and Olfactory Learning in the Fragile X Knockout Mouse

JOHN LARSON, PhD

Univ. of Illinois at Chicago, $40,000

We are studying the neurobiology of olfactory (smell) learning in mouse models for Fragile X. The olfactory system is particularly useful for neurobiological studies of learning in mice for two reasons:

1. Because it is their dominant sensory system for exploring the environment, mice show human-like learning abilities for olfactory cues.
2. The olfactory system has more direct connections with brain structures important for cognition and memory than do other sensory systems. This makes it easier to trace the flow of activity through the brain in response to experience.

We are studying normal mice and Fragile X knockout mice. Our specific aims are to determine (1) how olfactory learning is affected in Fragile X mice, (2) whether synaptic plasticity in olfactory structures is altered in Fragile X mice, and (3) if olfactory experience changes the expression of the Fragile X protein in normal mice. Understanding the role of this protein in synaptic plasticity and learning should help in evaluating treatments for learning disabilities in individuals affected by Fragile X.

Hippocampal Synaptic Structure in Development and Early Adulthood in the FMR1 Knockout Mouse

WILLIAM GREENOUGH, PhD; IM JOO RHYU, PhD

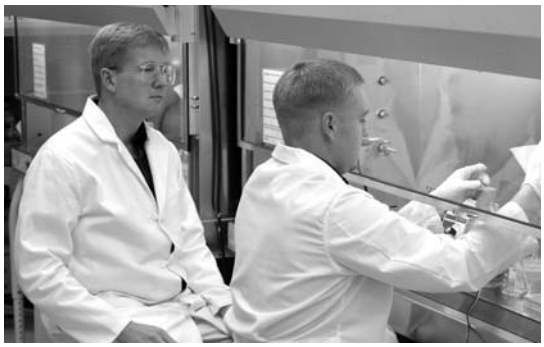
University of Illinois, $73,000

This project will examine detailed shape and structure of dendritic spines (where synapses are found) using high voltage electron microscopy. This technique allows us to examine dendritic spines with very high resolution, and the images obtained can then be used to analyze synapse structure in three dimensions. Using electron microscopy, we will also analyze the distribution of the protein production machinery (polyribosomes) near dendritic spines, which will provide information about whether protein synthesis is altered near synapses in Fragile X Syndrome, as predicted by our other work. A separate project involves whether new neurons are generated to the same degree in Fragile X knockout mice as they are in control mice. Relatively new findings in the field suggest that neurogenesis in specific brain regions is a fundamental process that takes place throughout the life of an animal. We are interested in determining whether the generation of new neurons is altered in Fragile X Syndrome.

Studies on FMR1 Gene Delivery Using Viral Vectors

DAVID C. BLOOM, PhD

University of Florida, $39,000



David Bloom (left) and Zane Zeier, graduate student

Our goal is to develop a gene therapy approach to deliver a functional copy of the FMR1 gene into the brains of FMR1 knockout mice and determine if this will repair the observed defects in their central nervous system.

Viruses that have been altered to make them safe (vectors) can be used as efficient delivery systems for gene therapy. We have been constructing two unique delivery systems to introduce the FMR1 gene into the brain. One system is a vector based on the Herpes Simplex Virus (HSV) and the second is based on Adeno Associated Virus (AAV), a harmless virus which often accompanies the common cold virus. Each of these two vectors possess different properties which will increase the likelihood of successfully delivering the FMR1 gene to as many brain cells as possible, as well as ultimately controlling how much FMRP is made. We have demonstrated that these vectors are capable of expressing FMR1. In collaboration with Dr. Bill Greenough's laboratory at the University of Illinois, tests are underway to determine if vectored expression of FMRP can restore biochemical and behavioral functions that are lacking in the FMR1 knockout mice.

These experiments will allow us to determine if gene therapy is a possible therapeutic approach for treating Fragile X Syndrome. This study will also enable us to learn more about how the Fragile X protein works, which may lead to the development of other types of therapies.

continued on page 9

RESEARCH REPORT: The Fragile X Protein as Traffic Controller

The process of turning genes into protein makes the insides of cells terribly crowded and complicated places. RNA binding proteins, including the Fragile X protein, FMRP, marshal this process in an orderly fashion, organizing and transporting mRNAs until – at the right time and the right place in the cells – the information encoded in these mRNAs is transformed into proteins. In people with Fragile X, lack of FMRP disrupts this process, leading to too much or too little of some proteins. Identifying these proteins, and the mRNAs which encode them, is a top priority for FRAXA because they are potential targets for the development of new drugs to help people with Fragile X Syndrome.

The February 6th issue of the journal *Neuron* reported an exciting advance in understanding FMRP. The research teams of Jim Eberwine (at the Univ. of Pennsylvania) and Bill Greenough (at the Univ. of Illinois at Urbana-Champaign; funded by FRAXA) have invented a new technique called Antibody Positioned RNA Amplification (APRA) to identify mRNA molecules associated with FMRP. APRA works a bit like a homing beacon attached to a photocopier: the researchers connect an antibody that binds to FMRP with a DNA molecule that binds to the RNAs around FMRP in the synapses of neurons. They then create a large number of copies of these mRNAs and run the copies through a microarray chip to identify each one. The result was a list of about 100 mRNAs which may interact with FMRP. This list is then pared down (by testing the binding of each mRNA to FMRP using an ultraviolet light cross link assay and a filter binding assay) to home in on mRNAs (and the proteins they encode) most likely to be disrupted in people who have Fragile X. These may be useful targets for finding or developing drugs to treat the syndrome.

This and other recent studies suggest that the Fragile X protein serves as something like a cell traffic controller of mRNAs inside the brain's neurons. One caveat in interpreting this study is that more mRNAs exist in neurons than can fit on a single microarray chip, so each chip currently on the market is designed to identify many, but not all, mRNAs. Additional work will be needed to identify more mRNA targets of FMRP and to zero in on the best candidates for designing treatments. Many of the new FRAXA-funded projects described below address these questions.

For more information on APRA:
www.nimh.nih.gov/events/prdispatcher.cfm

RESEARCH REPORT: Family Experiences upon Discovering Fragile X

The February 2003 issue of *Pediatrics* included an article by Don Bailey *et. al.* reporting results of their survey of 274 families with one or more children diagnosed with Fragile X. The study emphasized the critical importance of early identification of Fragile X so that families can begin early intervention as soon as possible.

Update from the National Fragile X Foundation

Recently, the NFXF released its Handbook for Families and Professionals in a new Spanish version. We have begun to distribute them to Spanish speaking individuals and parent support groups including to our fellow member of the International Alliance of Fragile X Parent Support Groups, the Spanish Federation for FXS. If you know of a Spanish speaking family, we'd like to know so that we may send them a free copy. The NFXF is currently working to translate the Handbook into other prominent languages.

We are also excited about our new website Message Boards which feature discussion topics important to those who have a child with Fragile X. This internet-based "bulletin board" allows users to join in ongoing discussions, begin a new discussion or simply follow others' discussions. Topic areas include: Behavior; Occupational and Physical Therapy; Speech and Language Therapy; Medication; Education; Toileting; Adult Issues; Mothers Only; Fathers Only; Siblings Only; Miscellaneous & Other.

The first few of the Education Project lesson plans are now posted on our website at www.FragileX.org under the "Education – Lesson Planning Guide" menu item, and our new Special Topic pamphlets on Behavior and Aggression are now available for free.

As always, we're interested in knowing what resources and information are important to you and your family.

Robby Miller, Executive Director, National Fragile X Foundation, PO Box 190488, San Francisco, CA 94119-0488

Tel: 800-688-8765, E-Mail: NATLFX@FragileX.org, Internet: http://www.FragileX.org

continued from p. 7

RESEARCH REPORT: Fragile X Protein's Role at Synapses


Claudia Bagni and lab members

Also on February 7, 2003, Claudia Bagni and colleagues at the University of Rome published an important paper in the journal, *Cell*, entitled "The Fragile X Syndrome protein FMRP associates with BC1 RNA and regulates the translation of specific mRNAs at synapses". Dr. Bagni reports:

We show that the normal function of FMRP, the protein lacking in Fragile X patients, is to limit the translation of some mRNAs into proteins at synapses. Our study shows that lack of FMRP leads to changes at synapses that could impair their function, thereby affecting the transmission of signals responsible for learning and memory. The mechanism by which FMRP works is completely new: we have discovered that, thanks to a small RNA molecule (BC1) that works like an adaptor, FMRP binds specifically only to a subset of the neuronal mRNAs, thereby inhibiting their entry into the ribosomes, the machines that synthesize the proteins. In this way, FMRP "holds back" these mRNAs – at least temporarily – so that they cannot be translated into proteins.

Since we now know that FMRP has an important function at the synapses, we will focus on this region of neurons, with the aim of identifying proteins whose synthesis at the synapses is limited by FMRP ... proteins which would be potential targets for a drug screening approach to finding treatments for Fragile X.

Using a Drosophila Model to Study Fragile X Syndrome

TOM JONGENS, PhD, YAN WANG, PhD

Univ. of PA, $35,000

The Drosophila genome contains a gene, called *dfmr1*, that is similar to the human FMR1 gene. Loss of dfmr1 gene function in flies leads to behavioral and neuronal defects that provide a model to study the cause of Fragile X syndrome in humans. One behavioral defect displayed by the fly model is the loss of normal circadian rhythms. A normal fly is active for 12-14 hours during daylight hours and relatively inactive for 10-12 hours during the corresponding night-time. 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. dfmr1 mutant flies lack this capacity.

The reason dfmr1 mutant flies lack circadian rhythms is being studied by Dr. Yan Wang, a postdoc in our lab. We know that the ability to maintain circadian rhythms depends on a molecular clock that operates in specific neurons of the fly brain. Our previous work has demonstrated that this clock functions normally in the dfmr1 mutants, except that one "output" of the clock is improperly regulated: the CREB protein. This protein has been shown to be required for normal learning and memory, as well as circadian rhythms. CREB activity oscillates throughout the day and is regulated by the circadian clock. In the brains of dfmr1 mutant flies, the oscillation of CREB activity is severely dampened. Yan is trying to understand how CREB activity is affected, given that the clock appears to be functioning normally in the dfmr1 mutant flies. This is especially interesting because there is a human version of the fly CREB protein, which has been shown to be involved in learning and memory.

FRAXA Financial Report

2002 Income	
Contributions	552,675
Fundraising	407,539
Investment Income	(68,105)
Miscellaneous Income	3,779
Total Income	**895,888**

2002 Expenses	
Program – Research	956,129
Program – Education	23,197
Management/General	41,196
Fundraising	126,975
Total Expense	**1,147,497**
Net Income	**(251,609)**

2001 Income	
Contributions	725,816
Fundraising	392,610
Investment Income	27,990
Miscellaneous Income	4,059
Total Income	**1,150.475**

2001 Expenses	
Program – Research	2,241,489
Program – Education	25,501
Management/General	30,103
Fundraising	116,287
Total Expense	**2,413,380**
Net Income	**(1,262,905)**

Note: FRAXA's accounts are audited by Anstiss & Co., an independent CPA firm, on an accrual basis, as opposed to a cash basis. (Accrual accounting is generally preferred and is required in order to be accepted into the Combined Federal Campaign) Multi-year research commitments are counted in the year that the commitment is made. In 2001, FRAXA negotiated a five-year research initiative with NIH which brought $7 million new dollars to Fragile X research. NIH's share is $6 million and FRAXA's is $1 million, or $200,000 per year from 2001 through 2005.

A Marathon for FRAXA

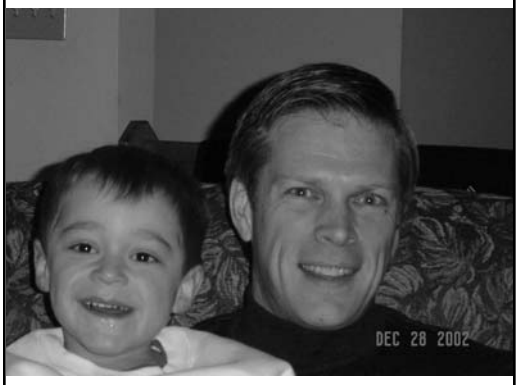
by David Frey

The Frey and Christoff families of Fort Wayne, Indiana had never heard of Fragile X Syndrome prior to the summer of 2000, when Mitchell David Christoff, the then 2-year old son of Joey Christoff and Catherine Frey, was diagnosed with the condition. Since that time, Mitchell has visited the Fragile X centers at Children's Hospital in Denver and the M.I.N.D. Institute in Sacramento. Mitchell's weekly routine includes speech, occupational, and physical therapy. He will turn 5 in April 2003, and attends the Learning & Development Center in Fort Wayne. Mitchell has learned sign language, and uses it on a regular basis to communicate with his parents, teachers, and grandparents.

This past March, one of Mitchell's uncles, David Frey of Cary, North Carolina, decided to take on a challenge in conjunction with his upcoming 40th birthday in September. It had to be something a bit crazy…to prove to himself that he was still somewhat "young." David decided to run a marathon…26.2 miles…which was pretty crazy considering the longest race he had ever run before was a 10K (6.2miles).

David and three friends from North Carolina decided to run the Sun Trust Richmond Marathon in Richmond, Virginia on November 9. The group embarked upon a rigorous 18-week training schedule that would include running nearly 450 training miles prior to the race. Uncle Dave realized he would need some additional motivation and inspiration to get himself ready for the race. He had an idea…

While visiting his family in Indiana in early July, just prior to beginning his training regimen, Dave had lunch with Mitchell's mom, Catherine, and discussed his idea for "motivation." Dave decided to dedicate his training and run to Mitchell and solicit friends and business colleagues to make contributions in Mitchell's honor to the FRAXA



David Frey with his nephew, Mitchell Christoff

Research Foundation. David worked closely with Foundation President Katie Clapp to make sure that checks were forwarded to FRAXA in a timely manner, and to enable the Foundation to take advantage of corporate matching gift programs. Katie and David also made sure that each contributor received a personalized "thank you" letter from FRAXA along with information about Fragile X and the Foundation.

The Frey and Christoff families also began informing friends and colleagues by mail and e-mail of the marathon/fundraising events, and the response was overwhelming. David even set up a regular e-mail communication that included updates on his training and pictures of Mitchell, so everyone knew about the wonderful children they would be helping with their contributions.

Training began the week of July 9, and the first checks for FRAXA started arriving in David's mail from donors within 2 weeks…and more checks kept coming… and coming… and coming, until the week after Christmas!

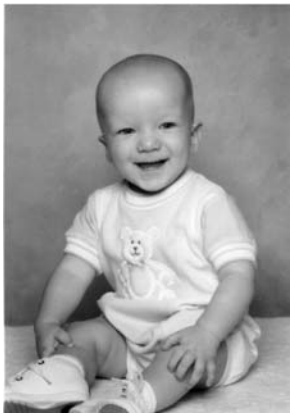
November 9th finally arrived and the weather in Richmond was perfect. The farthest the four guys had run during their 18 weeks of training had been 20 miles. Around mile 21 of the race is when fatigue really started to set in for the runners, and the headwind that started to hit Dave in the face around mile 23 was not much fun. When Catherine and Jim Frey (David & Catherine's father) gave David a t-shirt to put on at the 25 mile marker that had a picture of him and Mitchell on it, he knew he would make it to the finish line! All four men finished the race, with times ranging from 3 hours, 18 minutes, to David's 4 hours, 5 minutes.

The real winner in this story is the FRAXA Research Foundation, because 167 donors from 20 different states contributed $22,800 to FRAXA in recognition of Mitchell Christoff and in support of David Frey's marathon training and run. Uncle Dave will have a great story to tell Mitchell for years to come, and there are many people who helped make the story so wonderful. Thanks to everyone whose contributions and words of support helped keep David motivated over those five months.

Help Grow the FRAXA Team!

With research roaring ahead and the economy sagging, it is more important than ever to expand our fundraising efforts. The number of individual donors has expanded steadily, and we'd like to ensure that that continues. So, if you have lists of family and friends who would be interested in receiving our newsletters, let us know. Also, although Spring has not quite emerged, it is time to begin gearing up for FRAXA's Second Annual Fall Fling. We were gratified by the results of last year's Fall Fling. Our goal this year: events in every state across the country.

Ohio Family Benefit



Christopher Courtney

Four families hosted a FRAXA fundraiser at the Letter Carriers Union Hall in Cincinnati, Ohio, on Sunday, March 9. They are Jeff and Dawn Clark, Darren and Melissa Courtney, Joe Carolin and Amy Heisel, and Jeff and Nikki Wolffram. Melissa Courtney writes: "When I received the invitations from the Mom who did the printing, I could not help crying. If you had told me a year ago that I would learn that Christopher has Fragile X, that I would be helping raise funds for a cure, and that I would meet and become friends with people who had this in common with me, I would not have believed it. It was overwhelming to look at that invitation and see that it is real. It made me feel strong to know three other families joined with ours for a common cause."

New Chapter: Omaha

I am Kelly Randels and my son Cody has been diagnosed with Fragile X. At the time of his diagnosis, my family and I looked for a support group in Omaha, Nebraska. I was given the name of Megan Massey, FRAXA's Nebraska contact parent. I found it comforting talking with Megan and others who had experience with Fragile X. While talking with others in the community it became apparent that there is a need for a support group, so my husband and I have started one. For more information, please contact us: Kelly and Ryan Randels 17668 K Street, Omaha, NE 68135 420-778-5802, fragilexomahagroup@cox.net

FRAXA Speakers Bureau

In recent weeks, two members have given brief talks about Fragile X at meetings of local Lions and Kiwanis clubs. We thank David Sturgell, who spoke at a Kiwanis meeting and liked it so much that he has two more talks booked, and Ken Pitcher, whose 11-minute talk inspired a Lions club to donate $500 to FRAXA! We can provide speeches, brochures, newsletters, and a video. Talk to those who've done this and see how satisfying it can be!

Ways you can Help

On May 1st, scientists from around the world will send in proposals for new research on Fragile X. Help enable FRAXA to fund the best of them! Donate, hold an event, or:

Donate a Car The Car Program (www.donateacar.com, 800-513-6560) will pick up your car, give you a receipt for tax purposes, sell the car, and give 70% of the proceeds to FRAXA.

Combined Federal Campaign

Only 1 in 10 charities qualifies for the Combined Federal Campaign, and FRAXA is one of them! If you or someone you know works for the federal government, FRAXA's CFC number is 0220

United Way Each United Way campaign is different, but most will allow you to write in a charity of your choice. All you need is FRAXA's name & Tax ID: 04-3222167.

Family and Friends

Are there people you know who would appreciate receiving our newsletter? We will we happily send it to them at no charge to raise awareness of Fragile X.

FRAGILE X IN THE MEDIA

Whenever Fragile X is featured in the news, more people learn about this most common inherited cause of mental impairment, which in turn helps us gather support to accelerate research. In the last few months, millions of people have learned about Fragile X:

January 21st – For the first time ever (as far as we know), the New York Times mentioned Fragile X. It appeared in an article about RNAi on the lead page of the Weekly Science Times section – "above the fold."

Late January – FOX News Chicago aired a story on Dr. Elizabeth Berry-Kravis's AMPAkines clinical trial, funded by FRAXA.

Feb 2nd – Harry Manion, parent of JP, a wonderful boy with Fragile X, commented on the Jake Porter touchdown story on the Boston area CBS affiliate, "SportsFinal" show with Bob Lobel. Harry was FRAXA's first major contributor back in our first year, 1994!

Late February – NBC-TV stations across the U.S. broadcast a news piece on Dr. William Greenough's recent Fragile X research. Also featured were the three cute little sons of Dian and Robert Bolling, thanks to Debbie Stevenson who had just filmed the Bollings for FRAXA's latest video. The story was also posted on the ScienCentral website.

Alex, Austen, and Connor Bolling have Fragile X Syndrome

FRAXA'S NIGHT AT THE

An amazing time was had by all at Fraxa's Night at the Copa! On March 6 in New York City, over 500 people had signed up to attend the dinner at the Copacabana, helping to raise over $500,000 for Fragile X research! Thanks to all the attendees who trudged through a snow storm to be there, we had a tremendous turnout as well in spite of the weather. Chaired by Debbie and Jeffrey Stevenson and Co-chaired by Eileen Naughton and Craig Chesley, we enjoyed the company and insightful remarks made by our special guests Time Warner CEO and Chairman-elect, Richard D. Parsons, and Co-discoverer of the DNA Double Helix and Nobel Laureate, Dr. James D. Watson. Watch for our next newsletter for top-to-bottom coverage of the event including photos.

Thanks to all who helped make this such a tremendous success!

FRAXA UPDATE

EDITOR: Katherine Clapp, M.S.

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and others

DESIGN: Mary Lou Supple

RAXA would like to thank Networx of Newburyport, MA for hosting, at no charge, the FRAXA website and email.

6TH ANNUAL MARY HIGGINS CLARK GALA

We hope you can join us May 29 at the Omni Hotel in Pittsburgh, PA
Chaired by Michele and Jim Cox, with Honored Guest, Mary Higgins Clark
and Roger Mudd, Master of Ceremonies
Please let us know if you would like an invitation.

PLEASE HELP FRAXA

in supporting research aimed at treatment for Fragile X

FRAXA is a national 501(c)(3) tax-exempt organization. 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

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