

# FRAXA UPDATE

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FOUNDATION

"NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

ever has."

— Margaret Mead



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.

#### Also in this issue:

- Report from Washington
- FRAXA Night at the Copa
- Fragile X Research Day/Fall Fling

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).

Priorities 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.

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

By Mary Beth and David Busby

# Washington:

## 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.

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.

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

**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.



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

## 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



Jay Brenman and Paul Medina

by Jay Brenman

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.

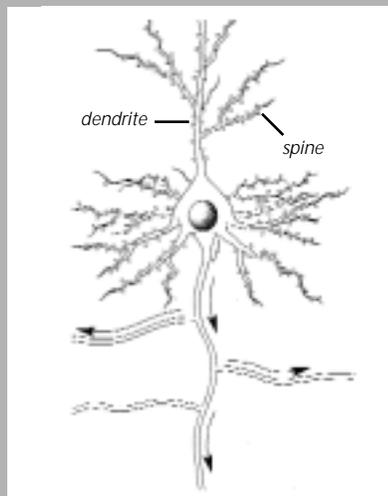
Despite the importance of dendrite and dendritic spine formation for cognitive function, few genetic approaches exist to analyze dendrite development. A better understanding of the genetic basis of dendrite and dendritic spine formation may provide insights into human neurodevelopmental disorders, including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

## 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 feedback 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, PhD

University of Illinois, \$26,600

by Ivan Jeanne Weiler



Ivan Jeanne Weiler  
PHOTO BY DON HAMERMAN

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.

# u p d a t e :

## 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](http://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 researchers 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/](http://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](http://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.

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Patrick with his favorite dog, Sadie

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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.



Debbie Stevenson, FRAXA Vice President, and Eileen Naughton

“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!

# G R O W I N G   T H E   T E A M

## 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](http://www.CharityNavigator.org) on the Web for a nice set of charts rating specific aspects of our organization. Guidestar, [www.Guidestar.org](http://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](http://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](mailto:NICHDInformationResourceCenter@mail.nih.gov), Web: [www.nichd.nih.gov](http://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](http://www.fraxa.org) for details.

# FRAXA UPDATE

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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](mailto: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 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

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

# FRAXA

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RESEARCH  
FOUNDATION

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