

# FRAXA UPDATE

WINTER 2002-2003

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FRAXA RESEARCH  
FOUNDATION

“NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

ever has.”

— Margaret Mead

## Clinical Trial Update

Since June of this year, a landmark clinical trial has been underway to evaluate a new potential treatment for Fragile X and autism. The compound being tested is an investigational new drug, Ampakine CX516, which may be able to help improve learning and memory in Fragile X, by correcting a defect in the strength of brain cell communications. This trial is being conducted by Dr. Elizabeth Berry-Kravis at RUSH University in Chicago and funded by FRAXA.

Participants are adults with Fragile X between 18 and 50 years old. Each person takes either the drug or a placebo (sugar pill) for four weeks. During the study, no one – patient, family, or the investigators – knows whether

placebo or drug has been taken, to guard against bias in interpreting the outcome. Before, during, and after the period of taking drug or placebo, patients are assessed with a variety of cognitive and behavioral tests to evaluate any changes in functioning. Medical assessment is also done to ensure that no ill effects are seen.

This is a Phase Two clinical trial. Potential new drugs go through three phases of study:

I: testing for safety in normal adults (already completed for Ampakine CX516)

II: a small-scale trial in the target population, mainly to extend safety data but which may also give a preliminary idea of effectiveness (this study)

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## FRAXA's First Fall Fling a Tremendous Success

This year, for the first time, FRAXA coordinated a nationwide grassroots effort to raise funds for research and awareness of Fragile X. To celebrate National Fragile X Research Day, October 5th, families held 34 events in 22 states, raising more than \$100,000!

Events were held in Arizona, California, Colorado, Delaware, Florida, Georgia, Illinois, Maine, Maryland, Maryland, Massachusetts, Minnesota, New York, Nebraska, North Carolina, Oklahoma, Ohio, Oregon, Pennsylvania, Virginia, Washington,

and Wisconsin. Fall Fling featured a remarkable variety of events, reflecting the imagination and energy of each member of our growing team.

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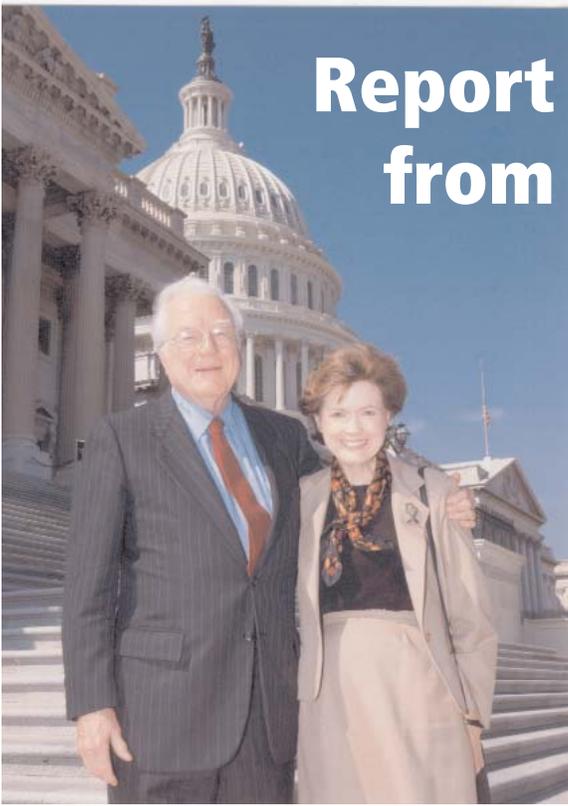


*Jake Nardo had a ball at FRAXA Fall Fling!*

### Also in this issue:

- Report from Washington
- Research Update
- Football Player Jake Porter's glorious day

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 2000 males and 1 in 4000 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

Congressmen Wes Watkins of Oklahoma and William Delahunt of Massachusetts, aided by those 46 Members whom you persuaded to sign on as Cosponsors (See Box.) In addition, Representative Watkins was able to secure the support of Chairman “Billy” Tauzin (LA) of the Committee on Energy and Commerce and Chairman Michael Bilirakis (FL) of its Subcommittee on health. The continued support of John Dingell (MI) and Sherrod Brown (OH) was also of great help.

Representatives Watkins, Delahunt, Bilirakis and Doug Bereuter (Megan Massey’s Congressman from Nebraska !), John Shimkus (IL) and Gene Green (TX) were eloquent in their remarks on the floor of the House concerning Fragile X and its effects.

Congressman Watkins stated in part:

“Mr. Speaker, my cousin was afflicted with this condition, a fact which has profoundly affected our families. I have worked both to provide funding for its research and to raise public awareness of this particular problem.”

This Resolution would not have passed without your letters and contacts with your congressmen, especially those who served as Cosponsors. All Fragile X parents and their children owe you a debt of gratitude.

Now, please do one more thing: write a letter to your member of Congress to thank him/her for his/her support. (Address: United States House of Representatives, Washington, DC 20515.) Your letters will make all the difference in the world when you ask them for help next year with appropriations for the Fragile X research at the National Institutes of Health.

## NICHD Fragile X Research Center Grants

*Earlier this year, in response to our Fragile X provision in The Children’s Health Act of 2000, the National Institute of Child Health and Human Development (NICHD) announced that it will fund three Fragile X research centers. Each center must propose at least three separate research projects integrated around a central theme; collaborative proposals involving multiple universities are encouraged.*

*The overall amount of money allocated for each center grant is \$1.125 million. Of that total, up to \$750,000 will directly support the research and the remainder will cover university overhead.*

*Center applications were reviewed in November by a panel of scientists; awards should be announced in the next few months. The earliest start date for the new Fragile X Research Centers is April of 2003.*

## We have three bits of good news:

**First, the U. S. House of Representatives passed House Resolution 398** “recognizing the devastating impact of Fragile X, urging increased funding for research on Fragile X, and commending the goals of National Fragile X Research Day, and for other purposes.” The Resolution breezed through unanimously when it reached the floor of the House. Since any one member could have prevented its passage, you can thank your Member of Congress for his/her support. The “heavy lifting” was done behind the scenes by

**Second, Mary Beth and I attended a meeting of the Centers for Disease Control (CDC) in Atlanta** September 17 – 20. Jeff Cohen and Robby Miller of National Fragile X Foundation and Karen Faye of Conquer Fragile X also attended. The focus of the conference was the formation of the Center for Birth Defects and Developmental Disabilities (CBDDD) authorized in the Children’s Health Act of 2000. \$90,000,000 was appropriated for these centers in the Children’s Health Act of 2000, and the CDC wants the advice and support of the some 200 nongovernmental organizations which will benefit from the activities of this center. We will do our best to keep the CDC focused on Fragile X and Fragile X research, especially in the areas of early diagnosis and early intervention.

### **Third, and perhaps the most exciting development of all**

— The National Institute of Child Health and Human Development (NICHD) implemented Title II of the Children's Health Act of 2000! This requires the NICHD to provide at least three Fragile X Research Centers. We hear that several excellent applications were submitted in July and are being evaluated now with the expectation that the winners will be announced in January. The NICHD has promised first year funding for the centers of \$3,375,000 from the discretionary budget of the director, Dr. Duane Alexander

Again, those of you who helped bring this about with your letters and other contacts with Congress get stars in your crowns! We will look back on the Children's Health Act of 2000 as a cornerstone of the search for the treatment and cure of Fragile X!

*Be a pro! To read the text of the Resolution and the Remarks in the Congressional Record on the Internet, go to <http://thomas.loc.gov> and follow the directions. Under CONGRESSIONAL RECORD, click TEXT SEARCH, then enter fragile x in the WORD/PHRASE box.*

## **House Resolution 398**

**Sponsor: Rep Watkins, Wes (OK)  
introduced 4/25/2002**

**Passed/agreed to in House 10/1/2002**

**Title: Recognizing the devastating impact of fragile X, urging increased funding for research on fragile X, and commending the goals of National Fragile X Research Day, and for other purposes.**

#### **COSPONSORS(46)**

Rep Bereuter, Doug (NE)	Rep Bishop, Sanford D. Jr. (GA)
Rep Bonilla, Henry (TX)	Rep Capito, Shelley Moore (WV)
Rep Cardin, Benjamin L. (MD)	Rep Carson, Brad (OK)
Rep Collins, Mac (GA)	Rep Delahunt, William D. (MA)
Rep Deutsch, Peter (FL)	Rep Ford, Harold, Jr. (TN)
Rep Frelinghuysen, Rodney (NJ)	Rep Hart, Melissa A. (PA)
Rep Hastings, Alcee L. (FL)	Rep Hayworth, J. D. (AZ)
Rep Hyde, Henry J. (IL)	Rep Inslee, Jay (WA)
Rep Isakson, Johnny (GA)	Rep Kennedy, Patrick J. (RI)
Rep Lee, Barbara (CA)	Rep Lewis, Jerry (CA)
Rep Lucas, Frank D. (OK)	Rep Maloney, Carolyn B. (NY)
Rep Markey, Edward J. (MA)	Rep McDermott, Jim (WA)
Rep Morella, Constance A. (MD)	Rep Murtha, John P. (PA)
Rep Norwood, Charlie (GA)	Rep Oberstar, James L. (MN)
Rep Olver, John W. (MA)	Rep Osborne, Tom (NE)
Rep Ros-Lehtinen, Ileana (FL)	Rep Roukema, Marge (NJ)
Rep Sanders, Bernard (VT)	Rep Shaw, E. Clay, Jr. (FL)

Rep Shimkus, John (IL)	Rep Smith, Christopher H. (NJ)
Rep Sullivan, John (OK)	Rep Tauzin, W. J. (Billy) (LA)
Rep Terry, Lee (NE)	Rep Tierney, John F. (MA)
Rep Upton, Fred (MI)	Rep Watts, J. C., Jr. (OK)
Rep Waxman, Henry A. (CA)	Rep Wexler, Robert (FL)
Rep Wilson, Joe (SC)	Rep Wynn, Albert Russell (MD)

The Daily Oklahoman praised the Fragile X Resolution, Representative Watkins, and our own David and Mary Beth Busby. Mary Beth has been our Vice President, and David has been our lawyer in Washington almost since the beginning of FRAXA. Many thanks to his firm, Dorsey and Whitney, for representing FRAXA pro bono for all these years! Based in Minneapolis, Dorsey and Whitney has 24 offices in the United States and abroad, and has a wonderful (for us) agreement with the American Bar Association to do lots of pro bono work.

### **A Day Worth Noting: Resolution Marks Fragile X Research 10/05/2002**

*FOR GOOD or bad, resolutions and proclamations approved by government at all levels are a dime a dozen. Most of them are laudatory in nature, toward an individual or institution. Nearly all are approved unanimously or by acclamation.*

*And they seldom make news.*

*But we want to make an exception today, to a group that has a decidedly Oklahoma flavor but doesn't get a lot of national attention.*

*Thanks to Rep. Wes Watkins of Oklahoma and a few other lawmakers, the House approved a resolution designating today as National Fragile X Research Day.*

*Haven't heard of Fragile X? It is the most commonly inherited cause of mental impairment, affecting nearly one in 2,000 newborn boys and one in 4,000 girls in this country. One in every 260 women is a carrier. Most of the children afflicted will require a life of special care.*

*As Watkins, R-Stillwater, noted, Fragile X families have worked hard to raise public awareness about the disease and to increase research funding. Scientists in 1991 discovered the gene that causes Fragile X. Watkins' resolution was designed to show bipartisan support for improving treatment and finding a cure for the disease.*

*One of the places where Fragile X patients are welcomed is McCall's Chapel in Ada. The facility, Watkins said, is willing to help Fragile X families with their adult children when other institutions across the country will not.*

*Actively involved with the Fragile X community are Mary Beth and David Busby, former Oklahomans who live in Washington. The Busbys are parents of adult sons with Fragile X and have worked tirelessly for years, as Watkins said, "educating and inspiring" people like him who are in a position to help. Mary Beth Busby serves as vice president of a national group interested in Fragile X research and funding.*

*On the cosmic scale of things, the resolution approved by Watkins and his counterparts has limited reach. But it does serve to focus attention, if only for a day, on a stubborn and tragic problem. Let's hope it does some good.*

# A Funny Thing Happened on the Way to the Synapse



## A Brief History of Our Understanding of Fragile X

By Michael R. Tranfaglia MD,  
Medical Director, FRAXA

(Editor's note: Reading this article may cause significant synaptic activity.)

At last we are getting to the point where we can say what is actually wrong in people who have Fragile X. Of course, we have known for more than 50 years that a specific constellation of symptoms is seen in males with this disorder, known in the early days as Martin-Bell Syndrome. We have known since 1991 that this was a single gene disease that resulted from a malfunction of the FMR1 gene; we have even had a mouse model of Fragile X since 1994. However, until recently, we really had no idea how the lack of the Fragile X protein (FMRP) actually caused the specific symptoms of Fragile X syndrome. That has changed dramatically in the past year.

This newsletter has previously noted the accomplishments of Drs. Kim Huber and Mark Bear, working at Brown University with the support of a FRAXA Fellowship, who demonstrated that the Fragile X knockout mouse consistently shows an excess of a particular neural process called mGluR-LTD. This is shorthand for “Long Term Depression mediated by the metabotropic glutamate receptor”—which probably doesn't help anyone to understand this unless that person is already a neuroscientist. The purpose of this article is help the non-scientist understand this major breakthrough, which we believe is one of the great scientific advances of our time, and one which will lead to exciting new treatments for Fragile X and other autism spectrum disorders.

### The Basics

To understand the importance of this research, one must know a few basic details about how the brain works. The brain is composed of billions of individual cells; for the most part, these can be divided into two broad categories, neurons and glia. Glial cells, once thought to be little more than inert packing and insulation, actually perform a wide variety of supporting functions in the brain; however, there is no *known* problem with glial cell function in Fragile X, so these cells will not be discussed further. We are here primarily interested in neurons, because these cells carry all the signals through the brain which are the basis of our thoughts and actions, our learning and memory, our consciousness and our personality.

# research

Neurons conduct electrical impulses along their length, then transmit the signals to neighboring cells across gaps called synapses via sudden pulses of chemicals called *neurotransmitters*. There are many known neurotransmitters (and probably many more that have yet to be discovered), and there can be many different receptors for each neurotransmitter, resulting in immense complexity. But the basic principal is the same for all of these neurons; each cell is a tiny input/output device which processes a number of inputs and produces an output signal. Chemical signals are received on a web of branch-like *dendrites*, causing a number of changes by their interactions with various receptors. Some of these changes are electrical, some are chemical, and others result in altered gene expression. The cumulative effect of these changes over the entire cell determines what the output signal of that cell will be, but the form of that signal is still electrical impulses carried down the *axon* of the cell until converted into more chemical pulses at the axon terminals. The brain is often compared to a computer, but even the individual neuron has some properties of a computer!

The really interesting part about all this communication between the neurons of the brain is that each of these synapses (and there can be thousands on each cell) seems to have a life of its own—each one changes constantly in response to its experience. Certain patterns of synaptic activity cause the synaptic connection to strengthen; this is called Long Term Potentiation (LTP). Other patterns of activity cause the synapse to weaken; this is called Long Term Depression (LTD). Think of this as a “use it or lose it” effect: synapses which are heavily used get built up, while those which are not used wither away. This *plasticity* of synapses is generally thought to be the basis for most of our learning and memory, so one might expect to find abnormalities in these processes when studying a developmental disorder like Fragile X. Surprisingly, when the Fragile X knockout mouse was first developed, investigators found no detectable changes in synaptic plasticity.

### The Defect

In retrospect, it appears that scientists were only beginning to understand synaptic plasticity back then (and

# update :

recall that we are only talking about 1994 – the year FRAXA was founded!). More recent studies have shown that there are definite abnormalities of both LTD and LTP in the knockout mouse. This illustrates both the complexity of the brain and of these processes, since there are now known to be several forms of both LTD and LTP, each utilizing distinct cellular mechanisms.

At this point, we might consider how alterations in these basic synaptic processes could account for the symptoms of Fragile X in humans. Modern psychopharmacology has correlated behavioral symptoms with changes in specific neurotransmitter levels, forming the basis for drug treatment of many psychiatric disorders. Decreased dopamine levels in frontal areas of the brain are associated with attention deficit, while increased dopamine in the midbrain is associated with psychosis and agitation. Decreased norepinephrine can cause depression, while too much can cause anxiety and hyperactivity. Too little serotonin can cause irritability, aggression, and obsessive-compulsive behaviors. Too much glutamate or too little GABA will likely result in seizures. The problem is that we often see all of these at the same time in Fragile X, so the defect is clearly global, and it certainly seems to involve more than one neurotransmitter system.

Or does it? The widespread disturbances throughout differing areas of the brain could easily be accounted for by a defect in just one neurotransmitter system: glutamate. Glutamate is the major *excitatory* neurotransmitter in the brain, accounting for the vast majority of brain activity (GABA, the major *inhibitory* neurotransmitter, keeps this process in check so that runaway electrical activity does not lead to seizures.) All the other neurotransmitter systems previously mentioned modulate and control aspects of glutamate function, but glutamate does most of the real work in the brain. So, if we are looking for one simplifying mechanism which could cause the myriad effects seen in Fragile X brains, the glutamate system is really the only possibility. But, it would not be reasonable

to expect a major disturbance — glutamate is so widely used in the brain that any major dysfunction would probably be incompatible with life. Therefore, a subtle change in one aspect of glutamate function would be an intriguing possibility for explaining Fragile X.

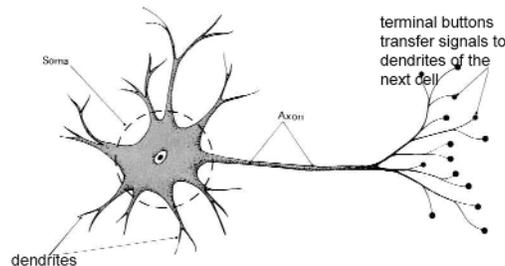
We have had hints for some time that Fragile X is primarily a defect of neural connectivity, and many Fragile X researchers have commented on this; in fact, this was the topic of an article in one of FRAXA's very first newsletters. The pattern of deficits seen in Fragile X is simply much more consistent with a synaptic defect than anything else. To oversimplify, basic cellular defects tend to cause cell death and degeneration—which is not seen in Fragile X. Errors of embryogenesis and early brain development tend to cause immediate problems and decreased survival in infancy, which is very much unlike Fragile X, where children appear normal at first but fail to develop at the

expected post-natal rate. Individuals with Fragile X show an “irregularly irregular” pattern of behavioral disturbances, a pattern that does not fit neatly into previously described categories. However, there is a common thread in this pattern, and it is one that is well known to parents of children with Fragile X: the response to experience is far different for these individuals.

People with Fragile X respond very aversively to novelty; situations which are different, sometimes only in trivial ways, tend to evoke dramatically negative responses. This has usually been interpreted as a form of obsessive-compulsive behavior (and may, indeed share some basic mechanisms), but may actually be the clearest direct manifestation of excessive LTD.

When neuroscientists want to elicit LTD in experimental animals, they often expose the animal to a novel and/or stressful situation. The type of LTD which is increased in these novel situations is the same type of LTD that is excessive in the Fragile X knockout mouse. Thus, it appears that the normal, adaptive purpose of this type of LTD is to signal novelty (and perhaps to enhance retention of novel events.) But since this system is not properly regulated when FMRP is absent, the signal is much too great in the FMR1 knockout mouse (and presumably in people with Fragile X) leading to behavioral and learning problems.

Prior to the finding of increased LTD in the knockout mouse by Huber and Bear, the same team had established that this form of LTD was controlled by one specific type of glutamate receptor, called mGluR5 (for “metabotropic



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glutamate receptor, subtype 5”). *Metabotropic* receptors do not cause immediate electrical changes in target cells, but instead result in longer lasting changes such as protein synthesis. In this case, one of the proteins synthesized in response to normal activation of mGluR5 is FMRP; but of course, this is absent in Fragile X. It is thought that FMRP normally serves to regulate this process by negative feedback, keeping it from running out of control. Without FMRP, too much LTD causes big problems.

We can get some sense of exactly what problems are caused by excessive LTD by intentionally overstimulating the mGluR5 receptor using specialized chemical probes. When this is done in normal mice, we see obvious effects — seizures and stereotypic behaviors — which are reminiscent of human Fragile X. Conversely — and this is the good news — if chemicals which block mGluR5 are administered to normal mice, the results strongly suggest potential therapeutic effects for Fragile X. Agents such as MPEP and MTEP show pronounced anxiolytic (anti-anxiety) and anticonvulsant (anti-seizure) effects; these agents are especially effective at reducing novelty-induced anxiety, the kind most likely related to LTD. They also do this without causing the sedation or cognitive impairment that typical anxiolytic drugs (like Valium) usually cause.

The obvious next step is to try treating knockout mice with these compounds; these studies are now under way at numerous labs across the country as part of FRAXA’s recent Request for Applications for research on the “mGluR Hypothesis”. Initial results have already shown strong positive effects in preventing seizures in the knockout mice, and ongoing work will be examining potential beneficial effects on cognition, socialization, anxiety, and response to novelty. When we meet at the end of March 2003 for FRAXA’s next annual Banbury Conference, the synaptic physiology of Fragile X will be the main topic; this will provide a valuable opportunity for some of the world’s top neuroscientists to share information and form collaborations in this rapidly evolving area.

The pharmacology of mGluR5 suggests that this excess of mGluR-LTD could account for most of the central nervous system symptoms of Fragile X, but we won’t really know for sure until mGluR5 antagonists can be tried in human subjects. Making that happen will be one of FRAXA’s highest priorities over the next year; so far, this class of drugs has not been tested in humans, but several large pharmaceutical companies and many smaller ones are actively developing these compounds for a number of uses. Indeed, the therapeutic effects of

# research

mGluR5 antagonists may extend well beyond Fragile X; it is likely that there are other neuropsychiatric disorders which result from increased LTD. The regulatory pathway which controls this process involves approximately 25-30 other genes, so there are many other ways that excessive LTD could occur, other than lack of FMRP.

What would these other neuropsychiatric disorders look like clinically? One would expect that they would all share a common feature: over-reaction to novelty, which would be expected to cause obsessiveness, rigidity, and an inflexible focus on minor details. Think of this as an exquisite sense of pattern recognition run amok. Clinically, most people like this are called autistic, and this raises the very real possibility that mGluR5 antagonists may be effective treatments not only for Fragile X, but also for other autism spectrum disorders. Further support is lent to this theory by the observation that people with autism have the same overall prevalence of seizure disorders (approx. 25%) as people with Fragile X. It is possible that we have found the final common pathway (mGluR-LTD) which links all autism spectrum disorders. Future studies will examine mouse models of conditions like Rett Syndrome and Angelman Syndrome, which are also associated with autism, to see if they also exhibit increases in this type of LTD.

## Summary

The new work of Kim Huber and Mark Bear has given us a detailed look at how neurons in the Fragile X brain actually function. The increase they have found in Long Term Depression, mediated by metabotropic glutamate receptors, could account for most of the major neuropsychiatric symptoms of Fragile X. This type of excessive function, which is receptor mediated, is especially amenable to drug treatment— and promising new compounds that could serve as small-molecule therapies for Fragile X are already in development. Initial testing of one of these compounds, MPEP, in the FMR1 knockout mouse has yielded a therapeutic effect, and further testing is well under way in a number of labs. Understanding this basic neural mechanism offers hope of near term drug treatment for the core symptoms of Fragile X, as well as the exciting possibility of the first effective treatment for autism.

# update:

## FRAXA's Scientific Advisors

Selecting the most promising research to support may be even more challenging than rocket science. To help with this task, FRAXA is extremely fortunate to have a remarkable Board of Scientific Advisors.

Each year in May and December, FRAXA receives 15-30 applications from scientists around the world. Like the National Institutes of Health, FRAXA relies on a peer-review system to determine which proposals merit funding. Members of our volunteer Scientific Advisory Board review the proposals, evaluating their technical and scientific quality, and make recommendations to FRAXA's Board of Directors. Sometimes they are aided by additional researchers in the Fragile X field who volunteer their specialized expertise. The Directors then vote on which projects can be supported, based on these recommendations and funds available. Scientific Advisors also help set strategy, organize scientific meetings, and provide invaluable advice and instruction along the way. Finally, they help us to identify specific scientific challenges that are slowing down progress and to find ways to bypass these bottlenecks.

Our Scientific Advisory Committee includes four Howard Hughes Investigators (Eric Kandel, Steve Warren, Mark Bear, Robert Darnell), three member of the National Academy of Sciences (Bill Greenough, Eric Kandel, James Watson), two Nobel Laureates (James D. Watson, Eric Kandel), one Harvard Provost (Stephen Hyman) ... and one Knight! Members volunteer their time because they know that they are making a significant contribution to the advancement of scientific inquiry and ultimately to all families affected by Fragile X.

These are some of the people who ensure that FRAXA funds the best possible research:

### **Don Bailey, Ph.D.**

Professor, University of North Carolina at Chapel Hill  
Robert Bauchwitz, MD, Ph.D.  
Research Scientist, Department of Neuroscience, Columbia University

### **Mark Bear, Ph.D.**

Howard Hughes Investigator and Professor, Brown University

### **W. Ted Brown, MD, Ph.D.**

Professor and Chairman, Human Genetics, New York State Institute for Basic Research in Developmental Disabilities

### **Linda Crnic, Ph.D.**

Professor, University of Colorado

### **Robert Darnell, MD, Ph.D.**

Head, Lab. of Molecular Neuro-Oncology, Rockefeller University Dr. Darnell was selected as a Howard Hughes Investigator this summer. This award provides ongoing funding to support research.

### **John Donoghue, Ph.D.**

Professor and Chairman, Dept. of Neuroscience, Brown University

### **William Greenough, Ph.D.**

Professor of Psychology and Neuroscience, University of Illinois at Urbana-Champaign

### **David Gwynne, Ph.D.**

Senior Director of Biotechnology, Cambridge NeuroScience Inc.

### **Randi Hagerman, MD**

Professor of Pediatrics and Director, The MIND Institute  
University of California at Davis

### **Steven Hyman, Ph.D.**

Provost, Harvard University. Previously, Dr. Hyman was Chief of the National Institute of Mental Health, and under his tenure, NIMH funding for fragile X research nearly tripled.

### **Eric Kandel, MD**

Nobel Laureate, Howard Hughes Investigator,  
University Professor, Columbia University

### **Herbert Lubs, MD**

Professor, University of Miami School of Medicine

### **Pamela Mellon, Ph.D.**

Professor, Department of Reproductive Medicine and Neurosciences,  
Univ. of California at San Diego

### **David Nelson, Ph.D.**

Professor of Molecular and Human Genetics  
Baylor College of Medicine

### **Owen Rennert, MD**

Professor Emeritus, Georgetown University

### **Oswald Steward, Ph.D.**

Professor, University of CA at Irvine

### **Steven Warren, Ph.D.**

Howard Hughes Investigator, William Paterson Timmie Professor of Human Genetics and Professor of Biochemistry, Genetics, and Pediatrics, Emory University

### **Sir James D. Watson, Ph.D.**

Nobel Laureate  
President, Cold Spring Harbor Laboratory  
Knighthood by the Queen of England this summer for his contributions to medicine, Dr. Watson has just written a new book on DNA, which includes a discussion of the Fragile X gene and FRAXA. Look for a copy when it reaches bookstores in April.

### **Jerry Yin, Ph.D.**

Professor, Cold Spring Harbor Laboratory

III: a larger-scale, longer-term study in the target population, mainly to determine effectiveness.

The current two-year study will include 50 people who have Fragile X and (pending additional funding sources) 50 people with autism. The trial is being run on a “rolling” basis; currently seven people have finished the full treatment phase of the protocol and four more are in the middle of the protocol. The study requires a lot of time from a limited number of specialized staff, so it was not feasible to conduct the entire trial in less than two years because of budget limitations. This trial at RUSH University costs over \$144,000 over two years; FRAXA has funded the first year and is currently raising funds for the second year, and Cortex Pharmaceuticals is donating supplies of the drug, Ampkine CX516.

No one has experienced any ill effects, even mild, that can be attributed to the drug — which is extremely encouraging. At this point it is impossible to speculate about any pattern of improvement, and the investigators truly do not know because they are conducting the trial “blind”, which means that they do not know which people have taken the Ampakine and which have taken sugar pills.

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

## PUBLICITY

Recent months have been fantastic for raising public awareness of Fragile X. It all began with Fragile X Research Day on October 5th and has culminated in the story of football player, Jake Porter ...

### ABC Nightline with Ted Koppel

In late September, Nightline featured an hour-long segment about Michael and Lisa Kelley and their children. The Kelleys have a Bed ‘n Breakfast in Maryland, where they’ve gotten to know Ted Koppel over the years. One of their sons has Fragile X. This family has been incredible - their willingness to share their story has introduced Fragile X to millions of people. The story aired in time to kick off FRAXA Fall Fling and to celebrate National Fragile X Research Day.

### Fragile X News printed around the World

When the Centers for Disease Control released a study on the potential benefits of newborn screening, the Associated Press covered the news in a story printed by newspapers around the world, including (to name a few) the Dallas Morning News, Cleveland Plain Dealer, Arizona Republic, Vancouver Province, Philadelphia Inquirer, Baltimore Sun, MSNBC News, Las Vegas Sun, London Free Press, various online news sites, Malaysia newspaper, Sun-Sentinal South Florida, Herald-Sun, Times-Picayune (Louisiana), the Canadian Press, and the Fort Worth Star-Telegram., St. Louis Post-Dispatch, Arizona Daily Star, and the Schafer Autism Report. Millions more were educated.

## Update from the National Fragile X Foundation

If you were not one of the over 900 family members and professionals who were able to attend our 8th International Fragile X Conference last July, the Conference Proceedings are now available. This document contains all of the scientific abstracts, the majority of session handouts, along with post-conference summaries for many of the presentations. The NFXF has made this available, at no cost, on [www.FragileX.org](http://www.FragileX.org) by clicking on the menu item “Conferences - Previous conferences.” A CD-PDF version can also be purchased for \$8.00 and a hardcopy version, in a binder, for \$25.00. At the same menu item, you will also find information about “Upcoming conferences” including our 9th International Conference to be held June 23-27, 2004 in Washington, DC.

With the big event behind us, more of our time and energy is focused on our other initiatives such as the Education Project. For those of you with school-age children, be sure to take a look at the first tangible results on our website, under the “Education – Lesson Planning Guide” menu item. (Available late-November) Other projects include additions to our “Special Topics” pamphlet series, including pamphlets on behavior and aggression. Adult issues, such as independent living and employment opportunities, will also be increasingly discussed within our published materials and website.

As always, we welcome your suggestions and feedback.

Robby Miller, Executive Director, [NATLFX@FragileX.org](mailto:NATLFX@FragileX.org) / 800-688-8765, Po Box 190488 / San Francisco, CA 94119

## Act of Kindness Speaks Volumes About Football's Spirit

*In Ohio, a highschool football player named Jake Porter has changed history! Since October 18th when this wonderful incident occurred, the national media has embraced this story. It has been featured on NBC Nightly News, ESPN Sportscenter, Rush Limbaugh's radio show, the Today Show, CBS Morning News, and in Sports Illustrated magazine. James Walker, author of the original story, has given us permission to reprint it here ...*

By JAMES WALKER — Thursday quarterback

In an age when arrogance and "Sharpie" pens steal the national spotlight, it is often the smallest, most unnoticed acts of kindness that remind us that football is merely a game. The story, which is destined to become legendary in Southern Ohio circles, starts in Waverly.

Northwest football coach Dave Frantz and Tigers' coach Derek DeWitt shared a conversation the week leading up to the game. But the two coaches weren't discussing strategy, instead they were talking about a mentally-handicapped Northwest player by the name of Jake Porter. Porter, a senior, has a disorder called "Chromosomal Fragile-X," which is the most common cause of inherited mental retardation. Porter still shows up on time for practice every day and dresses in full gear during games, but he has yet to take an official snap in a football game. Frantz wanted that streak to end last Friday. "I told them (Waverly) ahead of time that he can't take a hit or anything," Frantz said. "If the game's not at stake on the last play, I wanted him to come in and take a knee." Yet a week after their conversation, with Waverly leading 42-0 with five seconds remaining, coach DeWitt offered Frantz one better. "During the timeout, he met me in the middle of the field and said 'We'll let him score,'" Frantz explained. "(Initially) I said 'Nah.' Then we talked about it with the referees, and they said 'Hey coach, we understand.'" What soon followed will forever go down in Southern Ohio football lore.

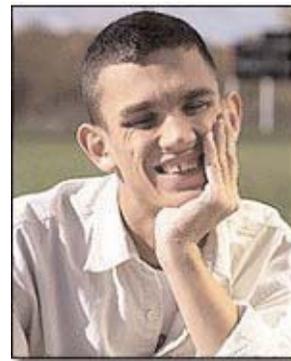
At Waverly's 49-yard line, Porter entered the game at tail-back, had his play, "84-iso," called in the huddle, and when the ball was snapped all 21 players parted ways.

Porter was somewhat surprised when he slowly walked through the huge hole. He initially turned back around to the original line of scrimmage, but everyone on the field — including defensive players from Waverly — pointed and guided Porter toward the Tigers' end zone.

"When we practiced it, he was supposed to down it, so I think he was a little confused at first," Northwest tailback Zach Smith said. "But once he figured it out, he took off." The 49-yard trek to glory took about 10-12 seconds in all, and was culminated by players from both sidelines cheering

and running step-for-step with Porter to the end zone. Tears flowed from the bleachers well into the night, and the life of one young man was changed forever. "At Waverly, we didn't do anything special. We were just happy to be a part of that," a humbled DeWitt said. "That young man was just excited to get the ball. Our guys didn't care about the shutout, those stats went out the window.

"When you're involved in a moment like that, you want to make sure you end the game with class, decency and respect." Those who play football on the highest levels should take notice. No pen that Terrell Owens ever pulls out of his sock could write a scene more touching than this.



## Fragile X Alliance of Ohio Golf Benefit

The Fragile X Alliance of Ohio held their 6th Annual Golf Benefit at Shaker Heights Country Club. With AT&T returning as the Title Sponsor, the event raised over \$100,000 for the third year in a row!

After a great round at Shaker, 152 golfers joined our dinner guests for cocktails, appetizers, and a Silent Auction. Cleveland Indians radio announcer Tom Hamilton made a special appearance. Our speaker was Gil Van Bokkelen, PhD, President and CEO of Athersys Inc., a leading biotech company here in Cleveland. Also attending was Dr. Huntington Willard, internationally known researcher and Director & President of The Research Institute of University Hospitals of Cleveland.

The auction was conducted with a generous dose of humor by special guest Doug Dieken, former Cleveland Browns player & current radio announcer, and returning Honorary Chairpersons, Herb & Nancy Score.

We thank family members and friends who helped make this event possible! Special thanks to Kristie Braley, Kelly Moir and the staff at Conferon, a national meeting planning company.

— Leslie Bagdasarian, [fraxohio@adelphia.net](mailto:fraxohio@adelphia.net)

## Donations to FRAXA will be Matched!

Thanks to a generous donor, contributions made to FRAXA in December and January up to \$50,000 will be matched! So please send in your donation now. These funds will be used to fund the best of the new research proposals just received on December 1st.

Many families persuaded newspapers, TV stations, and radio shows to feature their stories, so the Fling raised awareness as well as dollars to support new research.

Congress's House of Representatives endorsed the goals of Fall Fling by passing the National Fragile X Research Day Resolution (see Report from Washington).

All funds raised by Fall Fling will go to FRAXA's 2003 contribution for the NIH/FRAXA Joint Research Initiative, where each dollar will be matched six to one by federal dollars. As you may know, FRAXA negotiated a special program with the National Institutes of Health (NIH) which runs from 2001-2005. This public/private funding program leverages donations to fund the most (and best!) possible research. For each of five years, FRAXA contributes \$200,000 and the NIH contributes \$1.2 million to this program. Each spring, the funded investigators come together with other NIH-funded researchers at a meeting to discuss their results. Last year it was very exciting to hear about the work being done, and we eagerly anticipate this year's meeting.

Thank you to everyone who helped to make FRAXA's First Fall Fling a fantastic success. We are already making plans for next year, so if you missed this first event, please join us for the next one!

## Fall Fling Events

### ARIZONA

#### Wine Tasting

Ann and Jay Souder chaired an evening of wine, dining, and entertainment in Scottsdale, with special guests from Washington, DC : Dr. Robert Pasternak, Assistant Secretary for Special Education, and Lisa Graham Keegan, CEO of the Education Leadership Council, and many guests from as far away as Boston and Nebraska.



Dr. Pasternak at the wine tasting

### CALIFORNIA

#### OctoberFest, San Jose

Dean and Stefanie Clark

#### Letter Campaign

Karen Weidenfeller



Powell family with entertainer

### COLORADO

#### Denver Concert

Marie Powell, Kelly Lambert, Kelly Wilson

Hundreds of people attended this wonderful event, raising \$11,000 for research!

### DELAWARE

**Yard Sale** – Jen Nardo



Billy Mitchel

### FLORIDA

#### Table at hospital & Burger King benefit

Lauren & Kevin Springsteen

#### Crockfest

Martha Mathews

#### Yard Sale

How good it made me feel to write this check out to the foundation! I was afraid at first, but it all came together and we did it! My son, Marcus, made an appearance at the sale but stayed at a distance watching. – Cathy Reid



Mike Morton

### GEORGIA

**Flea Market Sale** – Misty Riggins

### ILLINOIS

**Letter Campaign** – Deb and Vern Gillan

### MAINE

#### Halloween Cocktail Party

Julie and Eric Gosselin, and Julie Wilson

### MARYLAND

**Yard sale** Maryland Fragile X Resource Group

### MASSACHUSETTS

#### Dinner/Dance/Auction

Pamela Vershbow – \$23,000!

#### Birthday Party and letter campaign in honor of Billy Mitchel

Cambridge – Jane Wolfson, Betsy Cohen

**Yard Sale** – Denise Devine

### MINNESOTA

**Yard Sale** – Peg Perry

### NEBRASKA

#### Donations Only Yard Sale

Norfolk – Jo and Steve Morton (newspaper article about the family and the event!)

### NEW JERSEY

#### One good turn . . .

by Mary Jane Clark

Marie Alexander was a quiet, reserved woman who made her living as the manager of a dress shop and lived alone for the last years of her life. Unable to drive, Marie reached out to a local church community concerns group for help with going to the grocery store and getting to doctors appointments.

It happened that the woman who volunteered to drive Marie had a grandson with Fragile X. Over the seven years that this volunteer spent time with Marie, the older woman enjoyed hearing stories about the volunteer's young grandson, following his progress, and joining the volunteer in her hopes for a cure.

At lunch one day, Marie said she would like to do something nice for the volunteer. The volunteer considered the offer and responded. "When you do your will, Marie, would you mention FRAXA?"

Marie agreed and, true to her promise, when she died, FRAXA was listed as the beneficiary of one quarter of her estate.

The kindness of Marie Alexander is remembered here. Marie's generosity brings us ever closer to a treatment or a cure.

## NEW YORK

### Golf tournament at the Glen Oak Golf Course, Amherst

Lisa Kowal and Amy Szymoniak chaired the



Stephen and Amy Szymoniak

first and flagship event in FRAXA's Fall Fling. The Tournament was held in memory of Norman A. Szymoniak, Jr. It raised over \$10,000!

### Current Catalog sales

Nancy Pitcher reports that anyone can join in from anywhere. Please call us if you'd like to participate.

### Cocktail party, LaGrangeville

— Ron and Amy Watkins

### Candy Bar Sales, Buffalo

Nicole Zimpfer

## NORTH CAROLINA

### Marathon

Run with style by David Frey in honor of Mitchell Christoff, this fundraiser is still raising funds!

**Pampered Chef Party** — Sarah Tamura

## OKLAHOMA

### Beef Jerky Sales

Thanks to Tim Kingsbury and friends, five schools are now selling boxes of beef jerky to benefit FRAXA. Anyone can join in this fundraiser ... just contact us at FRAXA!

### Irish Pub Night

Our pub night was packed with over 200 people, including six families with Fragile X. Kids were welcome and they had a great time. We raised over \$7500 and articles about



Fragile X and our event appeared in area papers. We're already

planning for next fall!

— Judith Maloney

## OREGON

**Garage Sale, Donation Can** — Carole Hellman

## PENNSYLVANIA

### Lollypop sales

Our candy sale was a huge success. The kids of our community did all the work and raised over \$1000. Thanks to Matthew and Noah Hollin and friends, including Ben and Caroline Batoff, for making our day wonderfu. Miss Cook's Fourth Grade class at the Penn Wynne School sold pencils, raising over \$60. Finally, Josh and



Mitchell Hollin and the kids who sold the candy

Stephen Silverman gave presentations to students about Fragile X and our quest for a cure. — Cristy Hollin

## PENNSYLVANIA

### Birthday party for Christopher Cox

We were thrilled when Pittsburgh's Fox 53 TV chose to do a story about our son Christopher and to make Fragile X their lead story for the 10 o'clock news. They included a great interview with the pediatrician who diagnosed Christopher's condition, Dr. Dena Hofkosh, Director of Child Development at Pittsburgh's Children's Hospital. Even more exciting is that Sinclair Broadcasting is planning to air the story on their 60 Fox affiliate stations across the country! — Michele and Jim Cox

## VIRGINIA

### Cookbook sales and Luncheon

The cookbook *All American Recipes from Hanover AARP Favorite Family Foods* is available for sale to benefit FRAXA. Contact FRAXA if you'd like to buy a copy. Erlyne Mangum writes: "They couldn't say enough good things about our son who spoke at our AARP meeting. One



Erlyne Magnum accepting check from the AARP

fellow broke down crying when he tried to tell me how much that meant to him. Our son (Jon) has been asked to speak at a church in our county on Oct. 6. So I guess he going to start up a speaking tour!"

### Harley Run October 5, Rustburg

Dian Bolling and 15 volunteers to served food and beer for the festivities, raising over \$2100. A new weekly national magazine, In Touch for Women, featured a two-page spread on the Bolling family, who have three little boys with Fragile X and the Roanoke Times also had a front page story!

## WISCONSIN

### Bratfry

Wisconsin is the home of Bratwurst sausages, so a brat fry is a favorite event here. Our group cooked bratwursts and hamburgers and sold them to hundreds of people who came by. We raised over \$1,200 for research and spread the word about Fragile X. The local paper had article about our family and I put posters of our kids all over town. Many, many people have asked me about Fragile X since I started this project.

- Carol Grunwald

# 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. Applications are accepted twice each year. Information is available at [www.fraxa.org](http://www.fraxa.org) or by contacting FRAXA.

## SPRING FLING GALAS

### FRAXA GALA NEW YORK CITY

*As the world celebrates the 50th Anniversary of the Watson and Crick discovery of the DNA Double Helix, Sir James D. Watson will pause from the festivities to celebrate with us as our honored guest*



*March 6th, 2003, at the Copacabana*

*With Special Guest, Richard D. Parsons, CEO of AOL Time Warner*

*Hosted by Debbie and Jeffrey Stevenson*

*Co-Hosted by Eileen Naughton and Craig Chessley*

### SIXTH ANNUAL MARY HIGGINS CLARK GALA

*May 29, at the Omni Hotel, Pittsburgh, PA*

*Hosted by Michele and Jim Cox, Master of Ceremonies: Roger Mudd*

# FRAXA UPDATE

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

# 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

- |   |   |
|---|---|
| <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+) |   |

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