FRAXA UPDATE

WINTER 2002-2003

VOLUME 9, NO. 3

A PUBLICATION OF FRAXA RESEARCH FOUNDATION

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

— Margaret Mead

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)

continued on page 8

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!

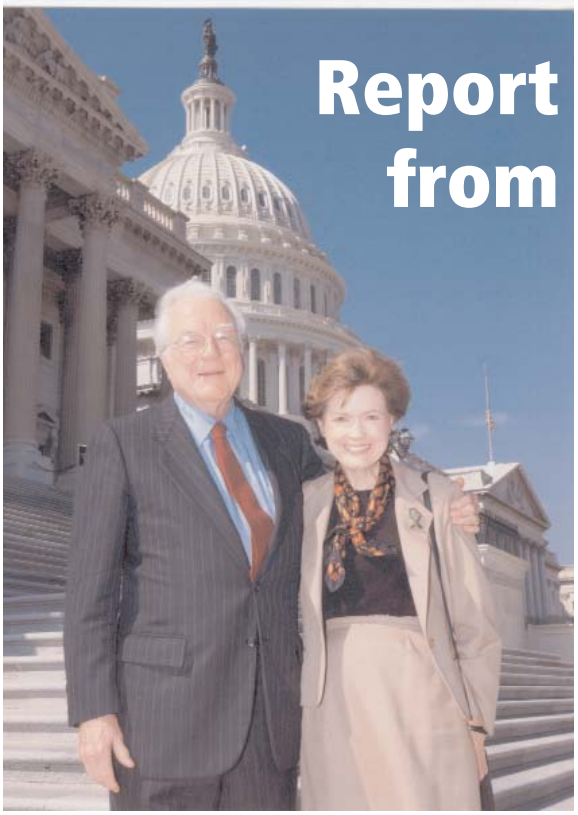
Events were held in Arizona, California, Colorado, Delaware, Florida, Georgia, Illinois, Maine, Maryland, Maryland, Massachusetts, Minnesota, New York, Nebraska, North Carolina, Oklahoma, Ohio, Oregon, Pennsylvania, Virginia, Washington, and Wisconsin. Fall Fling featured a remarkable variety of events, reflecting the imagination and energy of each member of our growing team.

Continued on page 10

Jake Nardo had a ball at FRAXA Fall Fling!

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 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

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 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.

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.

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.

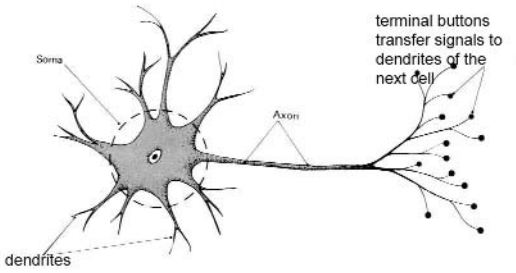
The Defect

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

continued on page 6

Synapse – continued from page 5

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

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 leant 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
Knighted 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

continued from page 1

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 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.

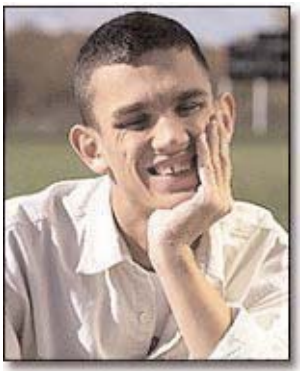
Robby Miller, Executive Director, NATLFX@FragileX.org / 800-688-8765, Po Box 190488 / San Francisco, CA 94119

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 tailback, 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

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.

Continued from page 1

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

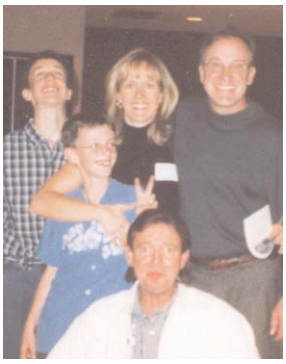
Dr. Pasternak at the wine tasting

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.

CALIFORNIA

OctoberFest, San Jose
Dean and Stefanie Clark

Letter Campaign
Kareen 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

Mike Morton

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

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?"

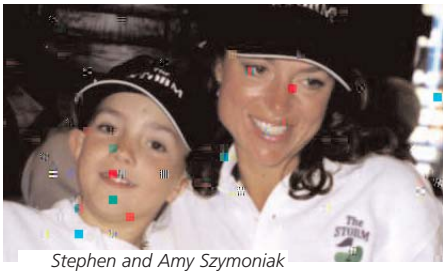
Marie agreed and, true to her promise, when she died, FRAXA was listed as the beneficiary of one quarter of her estate.

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 or by contacting FRAXA.

FRAXA UPDATE

EDITOR: Katherine Clapp, M.S.
CONTRIBUTORS: Leslie Bagdasarian.
David and Mary Beth Busby
Mary Jane Clark
Michael Tranfaglia, MD
and others
DESIGN: Mary Lou Supple

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

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

PLEASE HELP FRAXA

in supporting research aimed at treatment for Fragile X

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

Yes, I would like to help FRAXA

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

FRAXA
45 Pleasant St.
Newburyport, MA 01950

NONPROFIT ORG.
U.S. POSTAGE
PAID
W. NEWBURY, MA
PERMIT NO. 59

ADDRESS CORRECTION REQUESTED

FRAXA UPDATE

SUMMER 2002

VOLUME 9, NO. 2

A PUBLICATION OF FRAXA RESEARCH FOUNDATION

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

— Margaret Mead

Major Advance in Fragile X Research

By Michael Tranfaglia MD
FRAXA Medical Director

FRAXA has funded millions of dollars of research with the intent of developing a treatment for the core symptoms of Fragile X. Much of this research has taken the form of basic scientific efforts to understand the exact nature of the defect caused by the Fragile X mutation. Now, a stunning new finding in the knockout mouse model of Fragile X offers the promise of a drug treatment for the underlying cause of this single-gene disease.

Dr. Kim Huber, working first as a FRAXA Research Foundation postdoctoral fellow in the Brown University lab of Dr. Mark Bear and now a professor at the University of Texas Southwestern, has found a significant increase in a basic neural process called Long Term Depression (LTD) in the Fragile X knockout mouse (Proc Natl Acad Sci U S A. 2002 May 28;99(11):7746-50.) Essentially, LTD causes a weakening of the contacts (synapses) between brain cells when certain kinds of neural activity occur; it is thought to be an important mechanism in learning and memory, and is the subject of intense research interest.

continued on page 4

An Explosion in Scientific Publications

Two years ago Nobel Laureate Dr. James Watson (who co-discovered the structure of DNA in 1953) said:

"I became very excited when the Fragile X gene was discovered in1991. It was the first major human triumph of the Human Genome Project. The impact upon affected families rivals that of Down Syndrome. Unlike Down Syndrome, with Fragile X there is just one functional protein missing. So we must entice key young scientists now working on nerve cells to focus on Fragile X. It has to be a simpler disease to understand and eventually conquer."

In recent months, there has been an extraordinary increase in publications about Fragile X in the most prominent journals. All but one of these teams have been funded by FRAXA.

In May, BioMedNet News reported, "After decades of incremental but slow progress, research on Fragile X is now poised to expand exponentially." It quotes former FRAXA Fellow, assistant professor Jennifer Darnell of Rockefeller University: "Because of recent technologies and recent developments, the number

Continued on page 7

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 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

Once again, Congress has responded enthusiastically to all of the letters, emails, phone calls, and meetings initiated by Fragile X Advocates around the country. Each year, Congress specifies in its Appropriations Committees' Reports how the Federal Budget for the coming year is to be spent. In its 2002 Appropriations Report, the U.S. House of Representatives said,

> "Fragile X is the most common inherited cause of mental retardation. The Committee commends NICHD for its research actions, both intramurally and extramurally, in this area. The Committee encourages NICHD to enhance its research efforts on Fragile X through all available mechanisms, as appropriate, including establishment of research centers."

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 are due July 23, 2002 and a peer review panel of scientists will recommend awards in the fall. The earliest start date for the new Fragile X Research Centers is April of 2003.

Among other things, the Senate Report said,

> "*The Committee is gratified that the NICHD has enhanced its research efforts on Fragile X both internally and by partnering with the FRAXA Research Foundation in the issuance and funding of a Request for Applications [RFA] to research scientists.*"

The establishment of the Fragile X Research Centers and the expanded funding of extramural research, are just examples of the exciting progress being made toward finding treatment and a cure of Fragile X. This momentum continues to snowball. In addition to funding numerous separate grants, the NIH and FRAXA Research Foundation are now partnering in the funding of nine grants, which resulted from the Request For Applications (RFA) of 2000.

We are also pleased to announce that on April 25th, House Resolution 398 was introduced by Congressman Watkins, Delahunt, and 13 others (see below) in support of "National Fragile X Research Day" on October 5th of every year. To celebrate "National Fragile X Research Day" this year, FRAXA is kicking off its first annual "Fall Fling for Research Funds." Please join us if you can! And, please write your member of the House of Representatives and ask him or her to co-sponsor and pass House Resolution 398.

NATIONAL FRAGILE X RESEARCH DAY

107TH Congress, 2D Session
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.

IN THE HOUSE OF REPRESENTATIVES

APRIL 25, 2002

Mr. WATKINS of Oklahoma (for himself, Mr. DELAHUNT, Mr. MURTHA, Mrs. ROUKEMA, Mr. KENNEDY of Rhode Island, Mr. WYNN, Mr. OLVER, Mr. SULLIVAN, Mr. LUCAS of Oklahoma, Mr. OBERSTAR, Mr. WATTS of Oklahoma, Mr. CARSON of Oklahoma, and Mr. BEREUTER) submitted the following resolution; which was referred to the Committee on Energy and Commerce.

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.

Whereas Fragile X is the most common inherited cause of mental retardation, affecting people of every race, income level, and nationality;

Whereas 1 in every 267 women is a carrier of the Fragile X gene;

Whereas children born with Fragile X typically require a lifetime of special care at a cost of over $2,000,000 each;

Whereas Fragile X frequently remains undetected because the defect was relatively recently discovered and there is a lack of awareness about the disease, even within the medical community;

Whereas the gene causing Fragile X has been discovered and is easily identified by testing;

Whereas inquiry into Fragile X is a powerful research model for neuropsychiatric disorders, such as autism, schizophrenia, pervasive developmental disorders, and other forms of X-chromosome-linked mental retardation;

Whereas individuals with Fragile X can provide a homogeneous research population for advancing the understanding of neuropsychiatric disorders;

Whereas with concerted research efforts, a cure for Fragile X may be developed;

Whereas Fragile X research, both basic and applied, has been vastly underfunded despite the prevalence of the disorder, the potential for the development of a cure, the established benefits of available treatments and interventions, and the significance that Fragile X research has for related disorders;

Whereas Members of Congress are in unique positions to help raise public awareness about the need for increased funding for research and early diagnosis and treatment for Fragile X; and

Whereas throughout the United States, families and friends of individuals with Fragile X have designated October 5 as National Fragile X Research Day to promote efforts to find a treatment and cure for Fragile X:

Now, therefore, be it Resolved, That the House of Representatives—

(1) recognizes the devastating impact of Fragile X on thousands of people in the United States and their families;

(2) calls on the National Institutes of Health, the Centers for Disease Control and Prevention, and other sources of Federal and private research funds to enhance and increase their efforts and commitments to Fragile X research;

(3) calls on medical schools and other health educators, medical societies and associations, and Federal, State, and local health care facilities to promote research that will lead to a treatment and cure for Fragile X; and

(4) commends the goals and ideals of a National Fragile X Research Day and supports interested groups in conducting appropriate ceremonies, activities, and programs to demonstrate support for such a day.

Update from the National Fragile X Foundation

By the time most of you are reading this, the 8th International Fragile X Conference will have concluded. Even as I write this, one month prior, the Chicago event is already slated to be our largest ever. Through the financial support of the NFXF, over 140 faculty members, from over 20 nations, representing every possible area of Fragile X research and treatment, will have convened to share, teach, inspire and learn from each other as well as from the hundreds of family members present. If, by some unfortunate chance, you were unable to attend, you can always purchase the "Conference Proceedings" filled with presentation summaries, handouts and scientific abstracts. Contact the NFXF for your copy.

Once again, the National Fragile X Foundation has reworked its website to aid the new user, add to the content and make the overall process of seeking information an easier and more pleasurable experience. With over 100,000 hits to our home page each year, and over 350 pages of content including 60 pages of new treatment information, it is essential that parents and professionals be able to quickly zero-in on the desired information. When you visit www.FragileX.org, I think you will enjoy the clean interface and new menu system, but more importantly, I think you will appreciate the comprehensive selection of articles and materials.

Robby Miller, Executive Director

Major Advance in Fragile X Research – Continued from page 1

This finding comes as something of a surprise, since early speculation theorized a decrease in an opposing force called Long Term Potentiation (LTP) as a basic problem in Fragile X. Initial investigation showed no decrease in LTP, however, leaving neuroscientists stumped. The net effect of increased LTD can be seen as roughly equivalent to a decrease in LTP, though the mechanisms and locations of these 2 processes are quite different.

There are actually several kinds of LTD and only one specific type is increased in Fragile X – it is the protein-synthesis-dependent LTD. Drs. Huber and Bear have also demonstrated that this form of LTD is regulated by one subtype of glutamate receptor, called mGluR5 (glutamate is the major neurotransmitter in the brain). In Fragile X mice, when mGluR5 receives its normal input (in the form of glutamate), it causes excessive LTD. This, in turn, causes weakening of synapses and fewer AMPA receptors.

This is especially important work for several reasons. First of all, when looking for potential avenues of drug treatment for any condition, it is critical to identify areas of excessive function, rather than deficient function. This is simply because small molecules (like drugs) are better at blocking the function of large molecules (like proteins) than they are at duplicating their functions. Most drugs act by blocking the function of proteins such as enzymes or cell surface receptors, and it is highly unlikely that any small molecule could duplicate the function of a complex protein like FMRP, the protein missing in Fragile X. While functional deficits in Fragile X have been identified in previous research, this is the first time that a functional excess has been shown.

Furthermore, the fact that this excess function is controlled by a single, specific receptor means that this pathway can potentially be manipulated by drugs which block (or partially block) that receptor. Amazingly, in the past 3 years, several compounds have been synthesized as research tools which block this receptor potently and specifically; this class of drugs had been investigated as possible anti-anxiety medications, but no one had previously identified a good use for them – until now. The most promising compound of this class is called MPEP, which was developed by Novartis researchers in 1998 and has been in widespread use as a research tool since then.

Another reason why this finding is so important is that it correlates very well with behavioral observations of people with Fragile X. Recent research has suggested that one of the normal functions of LTD is to signal novelty – rats exposed to novel and/or stressful situations exhibit much more LTD. The nearly universal observation that individuals with Fragile X react excessively (often catastrophically) to

research

Dr. Kimberly Huber receives grant to further research into mechanisms involved in mental retardation

This spring, Dr. Huber was awarded a nationally competitive three-year, $300,000 grant from the McKnight Endowment Fund for Neuroscience to support her research on Fragile X.

Huber and her colleagues at UT Southwestern will focus on how synapses – connections between brain cells responsible for transferring information – change during brain development and during adulthood. The researchers will study these changes in a mouse model of Fragile X syndrome.

"There are no gross abnormalities of the nervous system thought to give rise to Fragile X syndrome," said Huber. "Instead, there is evidence that the structure of synaptic connections between neurons is abnormal. The fact that this disorder is caused by the loss of one protein provides an extraordinary opportunity to discover the neural mechanisms of mental retardation and devise therapeutic strategies."

Specifically, Huber and other scientists will study a form of synaptic weakening, known as long-term depression (LTD), in the mice to understand how synaptic function is altered in Fragile X syndrome. The researchers aim to define the function of the missing protein in neuronal communication.

"By understanding the developmental functions of this protein we will be able to determine if FMRP is really essential during early neuronal development or if we can reintroduce the protein into the neuron and re-establish its function after the neuron is developed," Huber said. "Results of our research will provide the framework for future clinical trials and facilitate progress towards a treatment for Fragile X syndrome."

novel or stressful situations supports the theory of a central role for increased LTD in the behavioral phenotype of Fragile X. In addition, excessive stimulation of mGluR5 in normal mice causes seizures – so this pathway could account for much of the Fragile X phenotype. Perhaps even more significantly, these aspects of Fragile X are shared by nearly all other autism spectrum disorders, and may represent a "final common pathway" linking all these different conditions. More important still, this type of treatment that we are developing for Fragile X may turn out to be a specific treatment for many different kinds of autism spectrum disorders.

Naturally, many questions remain unanswered. Will any of these compounds be safe and effective for humans? (We know they show little toxicity in mice and rats, even at very high doses.) Would this kind of treatment be helpful for individuals with Fragile X at any age, or would it be necessary to treat very young children? (We know that LTD is greatest in young animals, but does continue throughout life at lower levels.) Would this type of drug treat all the symptoms of Fragile X, or only some of them?

Fortunately, we do have the knockout mouse on which to test any potential therapy, and we are now increasing our funding of follow-on studies to answer just these questions – we are funding several trials of MPEP at different labs around the country (see FRAXA's new Request for Grant Applications). In addition, we have teamed up with a pharmaceutical company which is planning to develop these agents for human use (something well beyond the scope of a non-profit foundation); FRAXA has provided them with technical assistance to expedite drug testing in the knockout mice. If these initial preclinical studies go well, we may see human trials in 1-2 years!

How does this relate to our recently initiated Ampakine trial?

We originally developed an interest in Ampakines because of their pharmacologic profile and because it was known that the defect in Fragile X involved glutamate synapses. However, it turns out that there is a close connection between these two treatment strategies. LTD results in a decrease in the number of AMPA receptors, and this effect has been demonstrated by Mark Bear's group. Indeed, this appears to be the primary mechanism by which synaptic response is diminished in LTD.

Treatment with Ampakines enhances the response of individual AMPA receptors to stimulation, in a rare exception to the rule that most drugs function as inhibitors of proteins. Thus, the idea behind using Ampakines is to make the most of the smaller number of AMPA receptors at Fragile X synapses. Since blockade of the receptors which cause this form of LTD would (at least partially) prevent this reduction of AMPA receptors, these two treatment strategies could eventually make an ideal combination.

The mGluR Hypothesis: Studies in the Fragile X Knockout Mouse

MARK BEAR, PHD

Brown University, $50,000

by Katie Clapp

The goal of this project is to obtain more preclinical evidence to support the mGluR hypothesis. Previous studies have shown that dendritic spines are elongated in neurons of fragile X knockout mice at specific developmental ages, compared to their wildtype counterparts. Dr. Bear's team will study the effects of chronic MPEP treatment in the fragile X mice during the first two weeks of life, looking to see if MPEP normalizes the length of dendritic spines. A student in Dr. Bear's lab has spent the last few years optimizing a method to measure changes in spines which will be used in this study.

These studies have the potential to reveal the mechanism responsible for one of the most common neuropathological features of mental retardation: altered dendritic morphology. More importantly, they assess the feasibility of targeting mGluRs for the pharmacological treatment of fragile X syndrome.

The FRAXA award will pay for supplies, reagents, and a full-time technician to assist with microscopy and other aspects of these studies.

research

Flies for kids: developing a genetic model for the neuropathology and behavioral deficits in Fragile X

BASSEM HASSAN, PHD

Flanders University, Belgium, $50,000

Any potential future medical treatment of Fragile X requires a comprehensive understanding of the protein that, when absent, causes the disorder. For obvious reasons, these studies cannot be performed on humans, and so we need to search for other, more maleable model organisms. In our lab we use the fruit fly, Drosophila melanogaster, which has proven a powerful tool for unraveling genetic mechanisms. Drosophila has a single copy of the Fragile X related gene, called dFXR, which corresponds with three genes in mice and humans: the Fragile X gene, FMR1, and two related genes, FXR1 and FXR2. Like the human FMR1, the fruit fly dFXR protein is known to interact with other proteins and RNAs (the intermediaries between genes and proteins). We are using techniques at our disposal to help uncover these interactions, thereby providing insights into the neural pathology observed in Fragile X patients.

Bassan Hassan (bottom left) and lab members

Children with Fragile X display two major behavioral impairments (among others): cognitive delay, and sleep/activity disorders probably linked to an abnormal circadian rhythm (the normal 24 hour activity-rest cycle). Underlying these behavioral disorders, in humans, are anatomical defects in how brain cells, called neurons, connect to each other. We have already shown that flies lacking the dFXR gene have anatomical defects in the brain similar to those found in patients. The flies also have circadian rhythm problems. We are now developing Drosophila as a model for the cognitive disorders by specifically removing dFXR from the part of the fly brain involved in learning. We are also continuing to explore the basis of the neuronal connectivity problems and the circadian rhythm problems. In addition, we are investigating how the Fragile X protein affects the function of other proteins and how it interacts with them.

These approaches allow for a detailed analysis of the dFXR gene and will, hopefully, enable significant advances towards a gene and/or drug based approach to therapy for Fragile X syndrome.

Mouse models of Fragile X

ROBERT BAUCHWITZ, MD, PhD

Columbia University, $95,000

by Robert Bauchwitz

Our laboratory specializes in the production and study of mouse models of Fragile X, to identify treatments for the disorder in the short term and a cure in the longer term.

We have created 15 FMR1 transgenic mouse lines. These mice lack the normal mouse FMR1 gene, but have various portions of the human X chromosome spanning the FMR1 gene inserted into their genome. Our goal is to produce a viable FMR1 sequence for use in human gene therapy for Fragile X syndrome. One of the challenges of gene therapy is to introduce a new gene (transgene) into cells in such a way that it functions precisely like the normal gene, producing the right amount of its protein product, FMRP, at the right time and in the right cells. We aim to find the smallest piece of DNA (the FMR1 gene and regulatory sequences) necessary for the gene to function properly. Our transgenic mice have already given us important information on the acceptable and necessary dose of FMRP which can be present in mice in order to restore function without causing toxicity. These studies are now being extended through cognitive testing of the animals.

We have also continued our extensive molecular and cognitive analysis of the original mouse model for Fragile X, the FMR1 tm1Cgr mutant. We are assessing the effects of novel pharmacologic agents on intelligence in these mice. One agent we are testing is MPEP, which blocks mGluR5, a receptor involved in protein synthesis dependent LTD (long term depression). LTD, a response that neurons can make when stimulated, may be important in Fragile X, since Huber and Bear have recently shown that it is elevated in the Fragile X knockout mouse brain (see article, p. 1). We are investigating whether blocking the mGluR5 receptor with MPEP in the Fragile X knockout mice makes their behavior more similar to that of their otherwise identical wild type brothers. This is exciting work because MPEP has the potential to be one of the first drugs to provide an enhancement of intellectual function in Fragile X.

update:

Modeling Fragile X Syndrome: Conditional Expression of FMRP in Cells and Mice

DAVID NELSON, PH.D. Principal Investigator

David Nelson and lab team

RUITING ZONG, PH.D.

Postdoctoral Fellow

Baylor College of Medicine, $35,000

This study is designed to improve methods for defining the function of FMRP. We are developing new mouse models for Fragile X in which we can selectively express the Fragile X protein, FMRP, at different times and in different parts of the brain. These mice will be engineered such that we can regulate the amount of FMRP produced in their cells by feeding the animals a common antibiotic, tetracycline. Tissue-specific expression of FMRP will be provided by the human FMR1 promoter so that the mice will show a similar pattern of expression for FMR1 as that in humans. We will also construct cellular models that conditionally express FMRP. These models will be used to study the developmental role of FMRP and determine the potential for therapeutic approaches to Fragile X syndrome.

Our models will also provide tools to help identify and characterize mRNA targets of FMRP in cells and tissues. Recently, several mRNA targets of FMRP have been identified. However, which of these is altered by changes in FMRP abundance in living animals? How does FMRP regulate the activity of its mRNA targets? To characterize some of these targets, we have created inducible FMRP in neuronal cell lines (N2a) that conditionally express FMRP. Using these cell lines together with YAC FMR1 transgenic mice as a complementary model, we expect to validate candidate target mRNAs and begin to unravel the consequences of absence of FMRP. These models should also provide the ability to measure effects of therapeutic interventions.

Explosion in Scientific Publications – Continued from page 1

of people now working in the field has risen dramatically. It used to be one paper (on Fragile X) every 4 months. Now it's six new papers every month."

The recent flurry of interest began with two reports in the November 16th, 2001 issue of Cell, which identified a set of proteins in the brain which are affected by the absence of the Fragile X protein (Cell 2001;107:477-487,489-499) by Dr. Steven Warren and his associates at Emory University and by Dr.'s Jennifer and Robert B. Darnell and their associates at Rockefeller University. "Fragile X syndrome is interesting to scientists because here's a single gene that, when turned off, leads to behavioral problems and cognitive thinking problems," Dr. Robert Darnell told Reuters Health.

Previous studies showed that the protein FMRP binds RNAs in an unusual manner. (RNAs are the intermediate steps between genes – DNA – and the proteins that genes produce.) "But nobody knew what RNAs it was regulating, and that was key to understanding how it is involved in behavior and thinking," he added. Dr. Darnell and associates identified genes that displayed consistent translational profile shifts between cells derived from Fragile X patients and from control subjects.

Some of these affected proteins are potential targets for treatment, Dr. Robert Darnell told Reuters Health. "The ideal treatment would be to turn the FMRP gene back on, but that's still in the realm of science fiction." However, he said, "some of these targets are receptors, which are the 'bread and butter' of the pharmacology industry" in that small molecules can be identified to alter the activity of the receptors and perhaps restore some of the deficiencies in patients with Fragile X syndrome.

ADVANCES WITH FRUIT FLIES

One of the proteins identified by Darnell, Warren, and colleagues, MAP1B, stands out: its levels are significantly increased in humans with Fragile X. In Cell's next issue, Dr. Kendall Broadie and his team including FRAXA Fellow Yong Zhang, showed that deleting the Fragile X gene in fruit flies causes cognitive problems. Those problems can be reversed by also deleting a second gene, futsch, which is the fruit fly version of MAP1B. Follow-up studies are now needed, to see if a treatment strategy could be designed based on this result (see FRAXA's RFA, below).

Shortly after the Cell articles, additional papers were published which described defects in the fruit fly model of Fragile X.

continued on page 8

Explosion in Scientific Publications – continued from page 7

Dockendorff TC, Su HS, McBride SM, Yang Z, Choi CH, Siwicki KK, Sehgal A, Jongens TA., Drosophila Lacking dfmr1 Activity Show Defects in Circadian Output and Fail to Maintain Courtship Interest., Neuron. 2002 Jun 13;34(6):973-84.

Morales J, Hiesinger PR, Schroeder AJ, Kume K, Verstreken P, Jackson FR, Nelson DL, Hassan BA., Drosophila Fragile X Protein, DFXR, Regulates Neuronal Morphology and Function in the Brain. Neuron. 2002 Jun 13;34(6):961-72.

These new articles in Neuron demonstrated that the Fragile X fruitfly has defects in neuronal connectivity, sleep-wake cycle, and courtship patterns – problems which correspond fairly well with the human syndrome. The fruitfly is emerging as an extremely "fruitful" tool for future study; in fact, FRAXA has funded several fruit fly studies in the past year and is funding more fruit fly work in conjunction with the National Institutes of Health.

PNAS – THE MGLUR5 CONNECTION

The most eagerly awaited article of all was published in the Proceedings of the National Academy of Sciences in May 2002, by Kim Huber, Mark Bear, and colleagues. This article is exciting because it points to another potential target for drug treatments of Fragile X syndrome. (see lead article by Mike Tranfaglia).

In response to the recent discoveries of potential targets for treatment of Fragile X, FRAXA has focused our funding strategy to pursue these leads vigorously. Hence, the RFA below. The challenge for us will be to raise adequate funds to support these new directions and still fund the kind of basic research that uncovered these leads in the first place. Here follows our new RFA:

TREATMENT RESEARCH DIRECTIONS: AN NIMH SPONSORED MEETING

In November 2001, the National Institute of Mental Health convened a workshop to identify the most promising research directions which should be emphasized to develop effective treatments. The meeting was organized by Dr. Benedetto Vitiello and Dr. Edgardo Menvielle of NIMH, and the participants were Don Bailey, Elizabeth Berry-Kravis, Mark Bear, Katie Clapp, Linda Crnic, Bill Greenough, Paul Hagerman, Walter Kaufmann, Richard Paylor, Alan Reiss, and Michael Tranfaglia. The report is now published on the Web at http://www.nimh.nih.gov/research.fragilex.pdf

FRAXA'S NEW RFA

In response to these recent and exciting scientific advances, FRAXA is now issuing a new, directed Request for Research Applications.

Request for Applications
FRAXA Research, July 2002

3 major strategies for drug discovery have emerged from recent research. Applications deadlines are December 1 and May 1.

1. Nootropic agents ("smart drugs")

The clinical features of both Fragile X and autism suggest global deficits in the brain that are likely to involve glutamate systems. In addition, a recent study by Carlen et. al. demonstrated decreased expression of AMPA receptors in FMR1 knockout mice. FRAXA is currently funding a double-blind, placebo controlled trial of Ampakines in adult humans with Fragile X and autism. Further exploration of the mechanisms underlying this therapeutic option, including facilitation of AMPA transmission, would be highly desirable.

2. The MAP1B connection

Convergence of several studies recently published in Cell (Nov. 2001) points to overproduction of MAP1B as a prominent factor in the pathophysiology of Fragile X. FRAXA is interested in pursuing drug discovery projects which may utilize inhibition of MAP1B as a therapeutic strategy. There is some evidence that MAP1A and MAP2 may also be involved, so FRAXA also encourages work in delineating the precise defect resulting from overexpression of this family of proteins.

3. The mGluR hypothesis

It has recently been reported that Fragile X knockout mice have excessive hippocampal long-term synaptic depression (LTD) (PNAS, April 24, 2002). The particular type of LTD involved requires protein synthesis and is mediated by group I metabotropic glutamate receptors (mGluRs). mGluR5 appears to account for most of this mechanism, although the contribution of mGluR1 requires further elaboration. The group 1 metabotropic glutamate receptor antagonists are an exciting near-term therapeutic possibility. Further research to follow up this lead is FRAXA's highest priority at this time.

This RFA is also available at www.fraxa.org. Requests up to $75,000 for one year will be accepted, but smaller requests are encouraged. Awards are renewable for a second year, based on reasonable progress.

FRAXA Needs Your Help to Fund Research

Over the last two years, FRAXA's contributions have decreased significantly and yet our funding of research has increased dramatically. In order to do this, we have dipped into savings and – as always – we have kept overhead expenses to a bare minimum. In seven years of existence, FRAXA's Management and General expenses have never exceeded 6% of income – lower than any other national nonprofit.

In addition to tax-deductible gifts to FRAXA, there are many other ways in which you can help. Here are a few ideas:

FRAXA Fall Fling

This fall, to celebrate National Fragile X Research Day (see Congressional Resolution, p.3), FRAXA is kicking off our First Annual Fall Fling fundraising events run by families and friends around the country. Help us put "stars" in your state. PUT MAP IN HERE WITH STARS. Each star on the map reflects an event planned for FRAXA's Fall Fling. Join us! Call us at 978-462-1866 or email us at kclapp@fraxa.org for details.

Federal Employees' Combined Federal Campaign

FRAXA is CFC #0220

FRAXA is proud to have been accepted as an approved charity for the Combined Federal Campaign, or CFC. The CFC is the workplace charity fund drive for members of the Armed Forces, federal employees, and postal service employees. Fewer than one in ten charities meet the standards to qualify for this fund drive. If you work for "Uncle Sam," don't forget to make a contribution to FRAXA in this fall's campaign. Or, if you know someone in the Armed Forces or the federal government, please make sure they know that we are listed in their fund drive brochure.

Corporate Matching Grants

If your company has an employee charitable fund drive, please consider making a gift to us there. Your company may add a matching gift to accompany yours!

Many companies will add a charity to their "approved charity list" if one or more employees ask to make a gift to that charity. And, of course, being on the approved charity list means that other employees will see FRAXA's name and may decide to choose us too. If your company has a United Way campaign that allows you to direct your contribution to a specific charity, please take advantage of that opportunity to support FRAXA.

FRAXA accepts donated vehicles

Turn your old junker into research!

After three people called in a single day to ask if FRAXA can accept donated cars, trucks, and vans, we filed the necessary paperwork to establish this great new program. Instead of accepting a minimal trade-in credit for your old vehicle, you might consider donating it to FRAXA. You get a tax deduction, and 70% of the car's resale value pays for Fragile X research.

FRAXA is registered with The Car Program, www.donateacar.com, which works with charities across the country to take care of the details of picking up your car and selling it to a dealer or at auction. If you have a car you would consider donating, please call or email us.

Thank you for your help – past, present and future!

FRAXA CALENDAR

SATURDAY, AUGUST 17

Fun Run/Walk
Bradley Palmer State Park, Topsfield, MA
Hosted by Jerri Pratt, (781) 334-6914

THURSDAY, OCTOBER 10

Wine Tasting Extravaganza in Scottsdale, AZ
Hosted by Anne Souder
(480-483-6803) or email JAYSOUDER@msn.com

SATURDAY, SEPTEMBER 17

Norman A. Szymoniak, Jr. Memorial Golf Tournament
Glen Oak Golf Course, NY; Hosted by
Stephen & Amy Szymoniak & Lisa Kowal (716) 912 3177

THURSDAY, MARCH 6

Gala Dinner at the Copa Cabana in NY City
Hosted by Debbie Stevenson (212)828-1883, dstevenson@pop.net

THURSDAY, MAY 14

Gala in Philadelphia
Hosted by Cristy Hollin

SPECIAL

THANKS...

We are grateful to all of the friends and families who contributed to honor ...

- in celebration of the 50th anniversary Arlene and Elliott Harris, of Florida
- in honor of Jay Canel's special birthday
- the Tom and Linda Leonard Foundation, and to the Foundation for a generous matching gift
- in honor of Ryan Robinette, on the occasion of his cousins' birthday
- in memory of Kathleen Staving, of Pennsylvania
- in memory of Elizabeth A. Supple of Newburyport, MA, mother of Mary Lou Supple, who has contributed her talent and time to FRAXA for many years, designing our brochures and newsletters.
- And, kudos to Dian Bolling for donating $1000 of computer equipment, to make the daily work at FRAXA move along faster!

We are greatful to every one of FRAXA's supporters! All the advances of recent months, and all the advances to come, would not happen without you.

5th Annual Mary Higgins Clark Gala, Washington, DC

April brought more than cherry blossoms, masses of tulips, azaleas, and demonstrators against the World Bank to Washington. It also brought the wonderful Mary Higgins Clark, Katie Clapp and Mike Tranfaglia, and a whole group of Fragile X parents to town to demonstrate their support for our research at the Mary Higgins Clark Gala on April 29th. 314 people packed the Corcoran Ballroom at the Four Seasons Hotel to celebrate the work of our researchers, raising $175,000 to back their projects. We were honored with a letter of greeting from Mrs. Laura Bush, followed by an in-person greeting from the Secretary of Education, Dr. Roderick Paige, who was introduced by host, Roger Mudd.

Roger Mudd, emcee, and Rod Paige, U.S. Secretary of Education

The Assistant Secretary of Education for Special Education, Dr. Robert Pasternack, also attended the dinner, along with the Director of the NICHD (National Institute for Child Health and Human Development), Dr. Duane Alexander, Dr. James Hanson, the chief of the Mental Retardation branch at the NICHD, and Mrs. Bettilou Taylor, Minority Clerk of the Senate Appropriations Committee. Mrs. Clark spoke movingly of her commitment to our research, and Dr. Mike Tranfaglia spoke inspiringly about the exciting research FRAXA is currently funding and how it is leading toward a viable treatment.

Roger Mudd, Carol Higgins Clark, Mary Higgins Clark, John Conheeney

Despite having danced the night away, 40 parents packed the Hugh Scott room of the U.S. Capitol the morning after, for the Lobby Breakfast. Lisa Graham Keegan topped the agenda, which included Kyle Kinner, of Senator Edwards' staff, and Kevin Fisher, of Congressman Watkins' staff, both of whom told us the do's and don'ts of lobbying. David Busby dispensed packets of talking points to the participants, who then fanned out over the Hill, visiting the offices of their senators and representatives. They also took copies of Dani Steiger's book, "My Brother has Fragile X," to offer as gifts to congressional staffers. Their special mission for the day was to enlist signatures on House Resolution 398, acknowledging October 5th as the day to focus on and honor Fragile X Research. The offices of both Congressman Watkins and Delahunt report that our star lobbyists were effective: they got numerous calls of support from their colleagues. It was a successful day for furthering awareness of the importance of our research.

E V E N T S

The Winning Teams, co-champions of Patrick's Pals 2002

Hockey Coach Jerry York (Honorary Pal 2002), Jim Vershbow, Pamela Vershbow, and Sportscaster Steve Burton (Honorary Pal 2001)

Boston's First

Over $35,000 was generated in the first New England Gala! Trevor and Leslie Eddy sponsored the benefit for FRAXA Research at the Corinthian Yacht Club in Marblehead, MA on May 16th. The event attracted nearly 200 people, the full capacity of the yacht club. In addition to those from the local area, attendees traveled from Florida, North Carolina, Virginia, New York, New Hampshire, Pennsylvania, Ohio, Illinois, and California!

Boston's own Kim Carrigan from WBZ TV was the Master of Ceremonies, and Mary Higgins Clark was gracious enough to travel to Marblehead for the event. Along with dinner and dancing, the silent auction sparked high drama with its competitive bidding wars.

The event raised awareness to an all-time high in the New England area with news coverage in the Boston Globe, Herald, Marblehead Reporter, and Merrimack Current. Plans are already underway for the second annual gala next spring, so please do let us know if you would like to join the team.

"Thank you to all who helped make this fundraiser such a tremendous success. We appreciate all the people of Marblehead who showed such generosity and those who traveled great distance. Thank you to Joan Stewart for volunteering time and energy to publicize our cause, and to Mary Higgins Clark for coming to Marblehead and telling her wonderful stories … to Katie Clapp and Mike Tranfaglia for devoting their lives to FRAXA ... to everyone on the dinner committee who donated time and to friends and family who consistently show their unwavering support. We are eternally grateful."
- Leslie and Trevor Eddy

Patrick's Pals 6th

This year's "Patrick's Pals 3-ON-3 Basketball Tournament" in Cambridge, MA, resulted in a full 32 team tournament and in another $20,000.00 raised for FRAXA. The event helped to raise much needed awareness of Fragile X with articles in three Boston area newspapers and an evening news feature on a local television station.

The day was marked by heartfelt wishes of good luck for us and for Patrick and sincere enthusiasm for the progress being made by FRAXA and its researchers. And, as we pointed out at the tournament, this progress is extraordinary!

Our first "Honorary Patrick's PAL", local sports newscaster Steve Burton, returned this year as a player, and Boston College Hockey Coach Jerry York joined us as the 2002 "Honorary PAL". Coach York did a fantastic job of getting everybody into the spirit of the day. The wonderful spirit of good sportsmanship, generosity and kindness was no more in evidence than when the final game had to be called off, due to heat related illness, and both teams graciously agreed to become co-champions.

We will continue to carry on with the challenge of helping our son Patrick live life to his fullest abilities, advocating for all families who live with such great challenges on a daily basis, and raising funds to help find effective treatments and a cure for Fragile X. But, we can only do this with the help of all of "Patrick's Pals" and so we are grateful for your continued support of this special cause. To all of Patrick's Pals … THANK YOU!!!!!!

To those of you who are, like us, coping with Fragile X on a daily basis and watching your child/children struggle with the enormous difficulties presented by the disorder … please join us in celebrating the progress being made and the people whose generosity is making it possible.

Sincerely,

- Pamela & Jimmy Vershbow

P.S. As we told all of those at the tournament…you'll be hearing from us again this Fall. Let's join together to make the first "National Fragile X Research Day" on October 5, 2002, a nationwide event of which we can all be proud!

Hamsa Omaha Benefit

On June 6th, a Cocktail Buffet was held at the Omaha Country Club to celebrate FRAXA's extraordinary successes. Katie Clapp, Michael Tranfaglia, and Lisa Keegan, CEO of the Education Leaders Council, were our guest speakers. The Fragile X video was shown as well as quick clips of Jack and Jacob Massey and their own successes.

It was great fun to share in an evening so full of hope and excitement for the promising research explained by Michael Tranfaglia, FRAXA's Medical Director. Anyone who has chaired a fundraiser for Fraxa, knows the feeling of immense gratitude for all those who have joined in our commitment to treatments and cures for children and adults affected by Fragile X.

Proceeds from the event raised over $30,000.

-Megan Massey and Diane Hamsa

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Upcoming Deadlines:
December 1, 2002 and May 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 or by contacting FRAXA.

FRAXA UPDATE

EDITOR: Katherine Clapp, M.S.
CONTRIBUTORS: Robert Bauchwitz, MD, Ph.D.
David and Mary Beth Busby
Leslie Eddy
Bassem Hassan, Ph.D.
David Nelson, Ph.D.
Michael Tranfaglia, MD
Pamela Vershbow
and many others
DESIGN: Mary Lou Supple

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

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

Publicity!

In the past few months, magazines and newspapers have featured FRAXA families, helping to educate millions about Fragile X.

The July 2002 issue of Redbook Magazine features a four-page article written by FRAXA Board member Debbie Stevenson about her son Taylor, who has Fragile X.

Stories also appeared in The Washington Times, which goes on every Congressman's desk, and several newspapers and a TV station in Boston, MA.

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

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

FRAXA RESEARCH FOUNDATION

NONPROFIT ORG.
U.S. POSTAGE
PAID
W. NEWBURY, MA
PERMIT NO. 59

FRAXA UPDATE

SPRING 2002

VOLUME 9, NO. 1

A PUBLICATION OF FRAXA RESEARCH FOUNDATION

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

— Margaret Mead

FRAXA Funds Clinical Trial

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

Over the past decade, several pharmaceutical companies have been developing a new class of promising medications, called "Ampakines", which seem to enhance learning. FRAXA's very first 1994 newsletter featured an article by Dr. Michael Tranfaglia about the potential that Ampakines offered for people with Fragile X. For the past year, FRAXA has been funding a study of one such compound in the Fragile X knockout mice in the laboratory of Dr. William Greenough. Now FRAXA has approved $72,000 to fund a trial of this compound in adults with Fragile X, under the direction of Dr. Elizabeth Berry-Kravis.

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

Treatment strategies in Fragile X syndrome are currently supportive treatments or treatments directed at managing specific behavioral symptoms, in order to maximize functioning. Treatments specifically directed at the underlying brain defect in Fragile X are not presently available.

In the last few years we have learned much about what FMRP does in the brain and specifically at synapses, the connections between brain cells. The relative strength or

continued on page 4

Toward Therapeutic Treatments

An overview of FRAXA Strategy

FRAXA Research Foundation's primary mission is to speed up progress towards effective treatments and a cure for Fragile X. Here we describe the research approaches that FRAXA supports.

The basic problem in Fragile X is that brain cells have a defect in a gene (FMR1) such that this gene cannot produce its normal product, the Fragile X protein (FMRP). Without FMRP, brain cells cannot communicate cleanly with each other, probably at least in part due to FMRP's roles in development. This underlies the learning and behavioral challenges seen in Fragile X syndrome.

Potential therapeutic approaches are:

1. Fix the gene so that it can make its normal protein.
2. Make and deliver the protein by some other means.
3. Substitute for the function of the protein.
4. Treat the symptoms of Fragile X.

continued on page 10

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 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

There is very good news: in the last two years, federal funding for Fragile X research has increased dramatically. The National Institutes of Health is composed of 27 separate institutes and other organizations, and several of them have recently made Fragile X a priority. Here are the numbers:

NATIONAL INSTITUTES OF HEALTH
FUNDING for FRAGILE X

	FISCAL YEAR 2000	FISCAL YEAR 2001
NICHD	$ 4,130,000	$6,247,000
NIMH	$ 1,635,000	$ 2,970,000
NINDS	$ 573,000	$ 1,666,000
NCRR	$ 464,000	$ 507,000
GMS	$ 324,000	$ 306,000
TOTAL	$7,128,000	$11,698,000

NICHD ONLY

1994: $1,860,000	1998: $4,329,000
1995: $1,894,000	1999: $4,617,000
1996: $1,808,000	2000: $4,130,000
1997: $3,628,000	2001: $6,247,000

Source:L. Kaesar, Senior Program Analyst,Office of Public Affairs, National Institute of Child Health & Development, National Institutes of Health

KEY

NICHD: National Institute of Child Health & Human Development

NIMH: National Institute of Mental Health

NINDS: National Institute of Neurological Disorders & Stroke

NCRR: National Center for Research Resources

GMS: General Medical Sciences

We think there are three reasons this funding has grown over the past few years:

1. Increasing interest in medical research in general, among members of Congress
2. Increasing interest in Fragile X among the scientific community
3. Efforts by Fragile X families and friends

In terms of Federal funding, Fragile X would have gotten lost in the crowd BUT FOR YOUR EFFORTS and those of the entire Fragile X community.

Highlights

On January 4, 2002, the NICHD announced the Fragile X research funding required by the **Children's Health Act of 2000**. You will find the announcement on the web at *http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-02-009.html*

Some of the key provisions are:

- $3,375.000 is committed starting in October 2003 to fund at least three Fragile X Research Centers. These Centers are "to form networks that foster communication, innovation, and high-quality research in Fragile X syndrome."
- Annual Meetings of the Research Center Directors will be sponsored and funded by the NICHD staff.
- A Loan Repayment Program for young researchers will be instituted.

The Children's Health Act of 2000 authorized the NIH to establish a program of loan repayments to attract qualified health professionals into research on diseases, disorders, and other conditions in children. Qualified health professionals who contractually agree to conduct pediatric research for a two-year period are eligible to apply for this program. Participants can receive educational loan repayments of up to $35,000 annually. Visit *www.lrp.nih.gov* for details.

This year, we continue our work to ensure that the Fragile X Research Centers authorized last year are fully funded and that research funding by the NIH will continue to grow. On April 30, the day after the Mary Higgins Clark Gala, FRAXA will hold a second Lobby Day on Capitol Hill.

You can help by letting your members of Congress know of your commitment to Fragile X research. If you have not already done so, please call David Busby at (202) 824-8820 or email him at busby.david@dorseylaw.com.

FRAXA CALENDAR

THURSDAY MAY 16

Gala with Mary Higgins Clark and Master of Ceremonies, News Anchor Kim Carrigan Corinthian Yacht Club in Marblehead, MA

SATURDAY, JUNE 1

Patrick's Pals 6th Annual 3-on-3 Basketball Tournament Cambridge, MA

THURSDAY, JUNE 6

Evening Celebration in Omaha Hosted by Diane Hamsa and Megan Massey

MONDAY JULY 15

6th Annual Golf Tournament in Cleveland Ohio Hosted by Fragile X Alliance of Ohio

THURSDAY, OCTOBER 10

Anne Souder is kicking off a new chapter in Arizona, celebrating FRAXA's Fall Fling with a Wine Tasting Extravaganza. You can reach Anne at: 6111 E. Karen Drive, Scottsdale, AZ 85254. (480-483-6803) or by email at JAYSOUDER@msn.com

Debbie Stevenson's son, Taylor

FRAXA'S FALL FLING – First Annual Fling: October 2002

by Debbie Stevenson

What is it? An annual national fundraising day, to raise awareness for Fragile X and to raise much needed funds for FRAXA Research Foundation. The progress FRAXA-funded researchers are making right now is exciting, but research is expensive. In the past, most of the fundraising burden has fallen on just a few people. If everyone around the country pitches in just a little bit, WOW!

Who: We're looking for volunteers all over the country to participate in FRAXA's Fall Fling. Anyone and everyone who would be willing to do a fundraiser, no matter how small or large, is welcome. Every little bit counts.

When: Friday, October 5th (any date within a few days of October 5th is absolutely no problem)

Where: Wherever you live! We're hoping to eventually have an event in every state in the country, and more than one in each state is perfectly fine! Some day we hope FRAXA's Fall Fling will take place worldwide.

Why: First, to raise funds so that when new research proposals arrive on December 1st, FRAXA can fund every worthy project. Second, to get nation-wide publicity for Fragile X. Our goal is to make Fragile X known across the country. Reporters love the idea of families across the nation banding together for a single goal.

How: Here are some ideas–but remember, anything goes: Beef & Beer, Football Party, Golf outing, a brunch, lunch or dinner (large or small, in your home or not in your home), gala event, cocktail party, car wash,bowling, a walk or run, bake sale, collect a jar of coins, garage sale, bake sale, coin collections from local merchants or from fountains of local malls, letter writing campaign, benefit night at a local fast food restaurant, designate a Sunday to have your church or synagogue donate a percentage of the day's collections to FRAXA, having a local merchant donate a percentage of purchases to FRAXA.Some merchants will match funds raised. For example, WalMart stores will match the first $1000 you raise and provide volunteers to help with the event or with mailings. Target stores have a similar program.

We can provide you with a fundraising kit:

- *Invitations* – we will have invitations printed with blank space inside where you can fill in the details of your event – letterhead, brochures, and other materials.
- *FRAXA T-shirts or pins*
- *Ideas* – We know others who have run many kinds of events and we can help you brainstorm if you need ideas
- *Help* – We will help you with mailings, thank you letters, and whatever else you need to make your event a success!

Contact: If everyone pitches in – we'll cure Fragile X sooner than later. If you KNOW you would like to do a fundraiser, please let me know. Even if you're JUST THINKING about it, let me know that also. Just send me an email at dstevenson@pop.net with your phone number or give me a call at 212/828-1883.

continued from page 1

weakness of specific synapses appears to be very important in generating the "wiring" in the brain necessary for learning and higher intellectual and behavioral functions. Recent findings have identified specific neurochemical, structural and electrophysiological mechanisms at the synapse that are altered in the absence of FMRP. This new knowledge, coupled with new drug development in neuropharmacology, has allowed us to think about new medicines that might actually enhance cognitive functioning in individuals with Fragile X by targeting specific brain mechanisms deficient in the disorder.

In Fragile X syndrome, absence of FMRP leads to alteration in synaptic morphology (shape and structure) and strength and thus, deficient ability to maintain mature connections and eliminate unnecessary connections between brain cells. One specific abnormality of synaptic strength in the Fragile X mouse seems to be a decrease in AMPA-receptors in certain brain areas. Also, long-term depression (LTD), a process through which neurons regulate synaptic responsiveness and which is associated with down-regulation of AMPA receptors, is exaggerated in brain cells from the Fragile X mouse, implying that AMPA receptor activity is deficient.

AMPA receptors mediate the level of excitability of brain cells at synapses. Maintaining the proper level of excitability or "strength" of these connections is important for normal learning to occur and for promoting the structural changes in brain connections which represent the "hard wiring" of the brain's network.AMPA receptor activity is increased or decreased when synapses are activated and therefore represents one way brain cells can change the strength of selected connections, based on a specific experience.

Recently, a new class of medications which enhance AMPA receptor activity, called AMPAKINES, or "AMPA-receptor modulators," have been developed. One of these medications, developed at Cortex Pharmaceuticals and called CX516 or Ampalex®, has been found to improve learning and memory in rats and also has produced improvements in rat models of schizophrenia and ADHD. Clinical trials have now been done in patients with early Alzheimer's disease and schizophrenia, in which CX516 was helpful. CX516 has had minimal toxicity and is now in phase II studies in humans, as an investigational new drug. CX516 activates AMPA-receptors only after the synapse has been stimulated and therefore results in experience-dependent synaptic stengthening, in a manner that would parallel learning or memory. Given the early results with CX516 in other models, and the recent data suggesting deficiency of AMPA-receptor activity in Fragile X syndrome, we thought that CX516 might partially correct a defined neurochemical defect in Fragile X, with resultant improvement in cognitive and behavioral functioning.

Our project will investigate the effects of CX516 on memory, cognition and behavior in adults (>18 years) with Fragile X syndrome (FXS). Males and females are eligible but subjects must have an IQ in the subnormal range to participate. The study will involve a 4-week placebo-controlled, double-blind trial of CX516, with behavioral, intellectual, memory, attention and speech testing performed at baseline, at 4 weeks of treatment, and 2 weeks after discontinuance of treatment. The study will involve 50 subjects (25 CX516, 25 placebo) and will be conducted at RUSH-Presbyterian-St. Luke's Medical Center in Chicago. An additional group of 50 individuals with Fragile X and autism will participate in the study at the MIND Institute at the University of California, Davis. Although some of the study monitoring can be done by a local physician and much study screening can be done by phone, participation in the study will require a minimum of three visits to a study site (Chicago or Davis). The tests of thinking and behavioral functioning will be analyzed in the entire group, to see if the individuals who are treated with CX516 show improvements when compared to the control subjects who receive placebo pills, and whether the improvement declines two weeks after stopping CX516. Blood tests, EKGs and any possible side effects will be monitored so as to help show that CX516 is safe for individuals with Fragile X.

This treatment trial with CX516 represents the first ever attempt at treatment directly aimed at reversing the intellectual disability in Fragile X. The study is a first step in an effort to see if CX516 might be useful to enhance long-term thinking and learning skills in individuals with Fragile X syndrome.

At the time of this printing, final FDA approval for this study is still pending, so there is a possibility that it could be delayed.

update:

DFXR and synaptic tagging in drosophila

JERRY YIN, PHD

Cold Spring Harbor Lab.

$50,000

by Jerry Yin

My laboratory is interested in the molecular mechanisms of memory formation. We study the Drosophila (fruit fly) and mouse model systems. All animals can form memories that persist for various lengths of time. Long-term memories, which require new proteins to be made in brain cells, enlist cell-wide processes such as gene transcription and translation. While these processes occur in the cell body, most neuroscientists agree that the specificity of neuronal circuits requires changes in the individual synapses that define the circuit. Since mammalian nerve cells can contain thousands of synapses, how are individual synapses targeted when cell-wide changes such as gene expression occur? This problem is a central issue in the field of memory formation. We are trying to test whether FMRP is involved in the molecular mechanism of synaptic specificity. We will use genetic and biochemical approaches in fruit flies to address this problem.

Analysis of FMRP ribonucleoprotein complex association with the cytoskeleton through molecular motors

GARY BASSELL, PhD, Principal Investigator

JASON DICTENBERG, PhD, FRAXA Fellow

Albert Einstein School of Medicine, $65,000

by Jason Dictenberg

Neurons are highly polarized cells that are specialized to form interneuronal connections, or synapses, that facilitate cell-to-cell communication. During brain development, neurons utilize structural elements within the cell to form extensions, or processes, that specialize in forming these connections. These structural elements are known as the cytoskelton, which supports growth of the processes and is the "superhighway" for transport of proteins, or building blocks, into these developing processes. Process formation requires that many proteins be available in high concentrations at the sites of growth, and recent studies suggest that the cell accomplishes this efficiently by synthesizing the proteins at the very site of growth. This requires that the messages (mRNAs) that encode these proteins be localized to these sites, and it is the job of mRNA binding proteins to direct their transport there.

FMRP is an mRNA-binding protein that may be important for the transport of mRNAs and local synthesis of proteins required for growth of neuronal processes. We are interested in how FMRP is transported into these processes, which cytoskeletal elements are required and which molecular motors are involved in transporting FMRP. We will also study the active transport kinetics of particular mRNAs that FMRP binds to in normal neurons and those lacking FMRP, by tagging mRNA localization sequences with fluorescent reporters in live neurons. These approaches may reveal a greater understanding of the defects that underlie neuronal growth in Fragile X syndrome.

What are mRNAs?

mRNAs are the templates that cells use to transform genetic codes (genes) into proteins. From each gene, mRNA is made, and from mRNA, protein is made. The fragile X gene, FMR1, normally produces the protein, FMRP, but in fragile X syndrome, a mutation in this gene results in a lack of FMRP protein.

Defects in mRNA localization to growth cones, filopodia and spines assessed in hippocampal neurons from fmr1 knockout mice

GARY BASSELL, PhD, Principal Investigator

LAURA ANTAR, FRAXA Fellow

Albert Einstein College of Medicine, $30,000

by Gary Bassell

My laboratory has been interested in the role of mRNA binding proteins, including FMRP, in the regulation of neuronal process outgrowth and the establishment of proper connections (synapses) between axons and dendrites. The ability of these processes to grow is dependent on a specialized structure at the tips of processes, called the growth cone. We have shown that FMRP is localized to a network of actin filaments within growth cones. At a later stage of

continued on page 6

continued from page 5

neuronal development, FMRP is localized to dynamic actin structures, called dendritic filopodia, and spines, which are important for synapse formation and plasticity. Our objective is to investigate the regulation, mechanism and function of FMRP trafficking to these dynamic actin structures.

Recent advances in our laboratory have made it possible to see RNA binding proteins such as FMRP in live neurons by using fluorescent tags. Another new technology to study Fragile X is the use of fluorescent DNA probes for in situ hybridization and multi-color fluorescence microscopy. This will enable us to visualize the spatial association of FMR protein with specific mRNAs; we can then evaluate whether the localization of mRNA to dynamic actin structures is impaired in cultured neurons from FMR1 knockout mice. These innovative approaches to Fragile X should offer new insights into the normal function of FMRP and the biological basis for Fragile X Syndrome.

Axonal Elimination and Synaptic Maturation in Development and Early Adulthood in the FMR1 Knockout Mouse

IMJOO RHYU, PhD & WILLIAM GREENOUGH, PhD

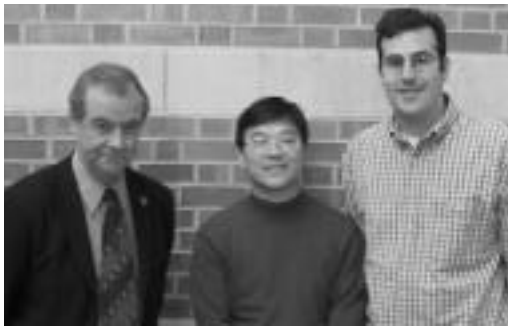
Univ. of Illinois $68,000

by William Greenough

There has been significant progress in understanding how nerve cell structure is changed in Fragile X syndrome (FXS). An important finding in the Fragile X affected human brain is the altered shape of dendritic spines, the projections from a neuron's dendrites that receive input from other neurons. Affected brains have more immature-appearing spines and fewer mature synapses, compared to unaffected brains. It is common during development of the brain and other parts of the body that structures created during development are removed as a part of the maturation process. In FXS, at least in the cerebral cortex, there are excess spines, and in some cases wrongly-directed dendrite branches, which are not removed during development. While one might first assume that "extra" synapses would be good things, the fact that their removal is a normal part of development suggests that they are not. In the case of FXS, extra dendrites and synapses might make the brain function in a more noisy and excitable manner.

Is this failure to mature without FMRP characteristic of all synapses? When do the unaffected and affected brains begin to differ from one another in development? Answers to these questions might provide clues to possible intervention points.

We are focusing on the dendritic branching pattern and spine shape, especially in the hippocampus, which has long been known to be associated with learning and memory.



Bill Greenough, ImJoo Rhyu, and Aaron Grossman

This brain area has received very little attention in Fragile X research, despite its importance in additional cognitive processes such as attention. We will also pursue spine morphology of Purkinje cells in the adult cerebellum, a huge sensory-motor coordination center at the rear of the brain, as impairments in sensory and motor functioning are also common in FXS.

Developmental analyses of Fragile X knockout mice will be run in parallel using three morphological tools: high voltage electron microscopy (HVEM), three-dimensional reconstruction of spines using conventional electron microscopy (EM), and light microscopy (LM) for counting spine numbers. Using the three techniques in parallel will provide precise 3 dimensional spine data, refined detail regarding internal structure and location of "organelles" such as the polyribosomes that synthesize FMRP, and spine numbers and dendritic branching pattern measures.

This project is expected to provide precise information regarding the developmental course of hippocampal maturation in Fragile X syndrome. This information can be used in studies evaluating the effects of potential therapeutic intervention, ranging from behavioral treatment to gene therapy.

Alterations of GABA receptor subunit expression and the absence of FMRP in the Fragile X mouse

CARL DOBKIN, PhD

NY State Inst. for Basic Research, $15,000

by Carl Dobkin

This project will investigate the alteration in the expression of the major inhibitory system in the brain of the Fragile X mouse. Receptors for gamma amino butyric

acid (GABA) normally serve to balance the excitatory input received by neurons; however, we have found that these receptors are reduced in many regions of the brain in at least one strain of Fragile X mouse (FVB/N). This may contribute to the seizure susceptibility and other behavioral features of the Fragile X mouse.

We will examine heterozygous female Fragile X mice (which have some brain cells with FMRP, and some without) to see if neurons with a non-functional Fragile X gene express GABA receptors at a lower level than neurons with a functional gene. By comparing neurons in the same brain, we will be able to tell whether the absence of the Fragile X protein within a neuron influences its GABA receptor expression.

Studies on FMR1 Gene Delivery using Viral Vectors

DAVID C. BLOOM, PhD

Univ. MiamI,$54,000

WILLIAM GREENOUGH, PhD

Univ. of Illinois, $21,000

by David Bloom

Fragile X knockout mice, which lack the ability to produce normal FMRP, show defects in their central nervous systems which may be similar to those present in the disease in humans. The goal of this project has been to develop a gene therapy approach to deliver a functional copy of the FMR1 gene into the brains of the Fragile X knockout mice and determine if this will repair the observed defects in their central nervous system.

Viruses that have been altered to make them safe (vectors) can be used as delivery systems for gene therapy. During the past two years we have been constructing two unique delivery systems to introduce the FMR1 gene into the brain. One system we are using is a vector based on the Herpes Simplex Virus (HSV) and the second is a vector based on Adeno Associated Virus (AAV). Each vector possess different properties, which will increase the likelihood of successfully delivering the FMR1 gene to as many brain cells as possible, as well as ultimately controlling how much FMRP is made. We have now built first versions of both these vectors, and initial tests in cultured cells show that they do produce FMRP. Tests will soon begin in the knockout mice to determine if delivering the FMRP can restore function in live animals.

This study will allow us to determine if delivering the FMR1 gene to the brain is a possible therapeutic approach for the treatment of Fragile X Syndrome. This study will also allow us to learn more about how the FMR protein works, which may lead to the development of other types of therapies.

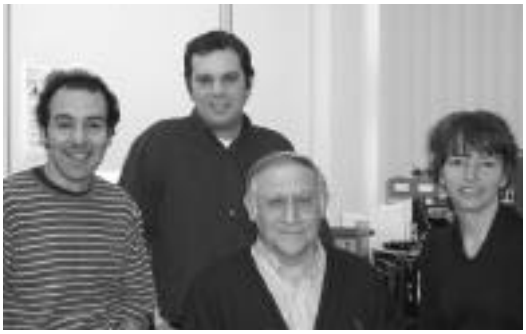
Xenopus (frog) model system for the study of Fragile X and related proteins

EDOUARD KHANDJIAN, PhD

Univ. of Quebec $24,000

by Edouard Khandjian

Animal models have been generated to study the normal functions of the FMRP protein, which is lacking in Fragile X syndrome. These models are either extremely complex---such as mouse, or very primitive---such as fish, worm and fly. Mammals have two other genes, FXR1 and FXR2, which are closely related to the Fragile X gene. Altogether, these three genes code for many different forms of proteins that have a complex pattern of expression in different tissues and organs. It is thought that the two related proteins FXR1P and FXR2P can partially compensate for the absence of FMRP, but this hypothesis needs further testing. In the more primitive fly model, these three different genes are all replaced by a single gene (dFXR), so differential tissue expression studies are not possible.



Edouard Khandjian and lab team members

We began to study an animal model that is genetically closer to man than to flies. This animal, the frog *Xenopus* laevis, contains all three genes, but the number of protein forms coded by these genes is much smaller than in mammals, which allows us to study

continued on page 9

FAMILY CORNER

In Memory of Jess Stringer

1976-2002

Jess, who had fragile X syndrome, was blessed with a warm and loving family. He died recently of a heart attack, at the age of 25. Contributions made in Jess's name are going directly to support research.

His mom, Judy, writes:

Jess, in his short life, touched more people than any of the rest of us. He made everyone smile, from the cashier at the 7-Eleven to the CEOs of huge companies; he loved everyone for themselves. He lived totally in the present. Jess loved trains, trucks, bridges, music, his pets, the waitresses at his favorite restaurant, skiing, hiking, riding his mountain bike, driving his scooter and truck. He had no driver's license, but that didn't stop him. He had over 5 acres in which to drive, run and be happy. He loved every human being and was always eager to say "hi" and "how are you."

All who knew Jess will be changed forever. He had a big smile for all of us, all the time. He would get excited and enjoy the smallest of things and have everyone in convulsive laughter many times a day. He taught us all the true meaning of loving life; we are all better people for knowing Jess.

Lorraine Morley wishes to thank the therapists of the Farmington Group for their donation to FRAXA. Lorraine writes "these are wonderful people who work with my 8 year old son, who has Fragile X."

Carol Collins wrote: Our church, Mary's Catholic Church in Sandusky, Ohio, donated part of their weekly collections to FRAXA. I'm excited that this worked out; if there is anyone out there who belongs to a church that tithes, it might be worth asking if they donate any part of the tithing to organizations.

FRAXA would like to thank the family and friends of Ricky Godorov, who chose to direct donations in her memory to FRAXA. Ricky had boundless energy; she was a loyal friend, trusted confidante, and loving mother of a daughter, Stacy Cohen, and two sons with Fragile X, Brad and Craig Godorov. She would have been thrilled to know that her memory will live on and continue to touch lives through the funds donated to FRAXA. Stacy writes, "Because of all of you, one day we will make a difference in the lives of people affected with Fragile X."

Thank you, FRAXA Volunteers!

Lynne Koltookian, thank you for giving up so many Thursdays to help in the office, and Joanie Stewart, thank you for wonderful public relations work.

Update from the National Fragile X Foundation

A Preliminary Program Agenda is now available for the 8th International Fragile X Conference, to be held this summer, July 17-21 in Chicago. Over 125 faculty members,including many of the scientists funded by FRAXA, will be presenting the latest in scientific,medical and clinical research. Other presenters will discuss the best ways to provide for your child's education, manage behavior, evaluate the efficacy of medications, and numerous other topics of high interest to families. As in prior conferences, each time block will offer a choice of scientific and family-focused sessions. The informative and stimulating presentations, the chance to meet hundreds of families and professionals, and the special events and activities will make this a memorable experience.(And once again, childcare for ages 2-16 will be free to those staying at the conference hotel.) To view the preliminary agenda and the registration form, visit www.FragileX.org and click on the red Chicago logo. Adjustments made to the session topics,days, times or presenters will be updated online on a regular basis and color-coded in such a way that viewers can easily plan their itinerary in advance.

After six months of work, a revised and updated edition of *Fragile X Syndrome,A Handbook For Families and Professionals*, is now available. Numerous Fragile X specialists contributed to the effort to make this an exceptionally useful and very understandable publication. The Handbook is provided at no cost to all who contact the NFXF, with additional copies available for a nominal fee. Please call, email or write us for your own free copy.

See you in Chicago! Robby Miller, Executive Director, The National Fragile X Foundation, PO Box 190488 / San Francisco, California 94119 / 1-800-688-8765 / NATLFX@FragileX.org

continued from page 7

protein expression in a simpler environment. In the frog, it is possible to directly investigate the functions of each protein, either during development or in the adult animal. This can be done by introducing different molecules into the egg through micro-injection, before or after fertilization, in order to induce a phenotype. Once this model has been developed, new avenues to study the functions of the Fragile X and related proteins in the nervous system will hopefully be unveiled.

A Genetic screen for dominant modifiers of drosphila FMR overexpression in the eye

KEVIN MOSES, PhD

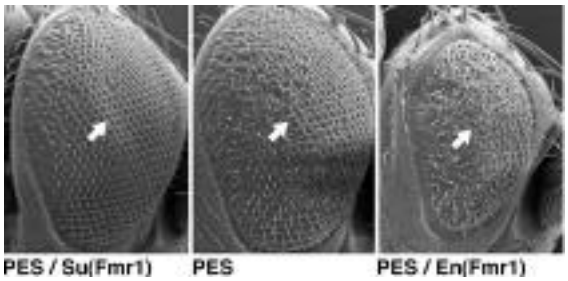
DANIELA ZARNESCU, PhD

Emory Univ., $35,000

by Daniela Zarnescu

We are employing the fruitfly, *Drosophila melanogaster*, as a model for discovery of genes in the Fragile X pathway. The past decade has seen a revolution in our understanding of the genetic homology (similarities) between flies and humans. Drosophila is an excellent system for gene discovery because of the economy of the system, the short generation time, and the available molecular and genetic technology.

The fly eye is comprised of about eight hundred facets arranged in such a precise order that it rivals a crystalline array. This precision in structure requires extreme precision in development: any additional or missing cells can be seen as external disruptions ("rough eye phenotypes"; see figure, middle panel). It is therefore easy to detect any mutation that even slightly disrupts essential cellular processes. The sensitivity to mutations of the Drosophila eye give us the means to conduct a genetic screen and identify genes that function in the Fragile X pathway.



Eye morphology of dominant modifiers of PES compared to the parent phenotype (see text). Note that the regularity of the facets is restored in the suppressor (left) and more disrupted in the enhancer (right).

We have obtained transgenic flies that overexpress the fly Fragile X gene in the eye (from our collaborator Tom Jongens; University of Pennsylvania). In these flies, eye development is disrupted and a rough eye phenotype can be easily observed (see figure, middle panel) – we call this the parent phenotype (PES). Then we generated flies that carry random mutations in addition to high levels of Fragile X protein in the eye. The principle of our quest is quite simple: if any of the random mutations affects a gene that functions in concert with the Fragile X gene, chances are that the parental rough eye phenotype will be either enhanced or suppressed, depending on the relationship between the two genes.

Recently, by generating mutations into virtually every gene in the fly, we were able to identify several genes which alter the expression of the Fragile X gene in the eye (see figure - PES/Su(Fmr1) and PES/En(Fmr1)). We are currently in the process of cloning these genes in the fly. We look forward to uncovering the relationship between these yet unknown genes and the Fragile X syndrome and hope to enhance our understanding of this disease and also of more general issues such as cognition and intelligence.

Additional grants awarded in the past few months will be described in our next newsletter. They include:

Patterns of Protein Expression in Fragile X Syndrome

WALTER KAUFMANN, PhD

Kennedy Krieger Inst.,$10,000 renewal

Towards Gene Therapy of Fragile X syndrome

MARIO RATTAZZI, MD

NY State Inst. For Basic Research, $40,000 renewal

Creation of a Model of Fragile X Syndrome: Condtional Expression of FMRP in Cells and Mice

DAVID NELSON, PhD

Baylor College of Medicine;$35,000

Generating Human Neurons carrying the Fragile X Mutation

CLIVE SVENDSEN, PhD

Waisman Center, University of Wisconsin;$50,000

continued from page 1

Currently, treating symptoms is the only option available, and the available interventions -- special education, drugs, psychological counseling -- often do not help enough. FRAXA's goal is to do more. We fund scientists who are pursuing each of these four approaches. Much of the work we fund is collaborative, as no single research team has the full range of technical skills to address all of the issues involved in developing treatments.

Therapeutic Approach #1: Fix the Gene

In people with Fragile X, the FMR1 gene is present but switched off (methylated) by a mutation in the DNA which controls activation of the gene. The gene itself is functional and could, theoretically, be switched on. One challenge is to target the FMR1 gene selectively, without turning on other genes that are supposed to remain off. It is also possible that too much Fragile X protein or expressing FMRP in the wrong cells may be toxic. So, FRAXA funds research to evaluate these approaches in animal models, including mice and fruit flies, and in tissue culture. Recent grants have been awarded to Andre Hoogeveen, Giovanni Neri, and Paul Hagerman.

Gene therapy aims to deliver a new, working copy of the Fragile X gene to brain cells so that the gene will function, producing its normal protein. Since all the symptoms of Fragile X arise from the lack of FMRP, this in principle could "cure" the syndrome. Gene therapy has received a lot of attention in the press because although it has great potential, there are no reports of clinical success with this technique in the human brain. FRAXA is funding investigators who are working out basic details using tissue cultured nerve cells before attempting anything with intact brains, including Mario Rattazzi, David Bloom, and Robert Bauchwitz.

Therapeutic Approach #2: Make and deliver the protein by some other means

Cells use a signaling pathway (or molecular cascade) to trigger the synthesis of FMRP. If we understood how FMRP is normally made and where it needs to be made, we might find a way to bypass complications in this pathway caused by the Fragile X mutation. Knowledge of this pathway could also provide alternatives to bring about the expression of other proteins regulated by FMRP. Many teams are currently exploring this area; those with some FRAXA support include Claudia Bagni, Gary Bassell, Carl Dobkin, Justin Fallon, Bill Greenough, Kimberly Huber, Walter Kaufmann, and Robert Malinow.

Toward Therap

Therapeutic Approach #3: Substitute for the function of the protein

If we knew precisely what the Fragile X protein does in nerve cells, we might find ways to bypass the need for it. We now know that FMRP aids in the production of certain proteins, some of which appear to be necessary for communication at the synapses – the connections between the brain's nerve cells. Messenger RNA is the intermediate step between a gene and the protein that it makes. An exciting current research direction is identifying the mRNAs that are overexpressed or underexpressed when FMRP is lacking. Since mRNAs code for proteins, this may tell us which proteins depend on FMRP for their normal expression in cells. Robert and Jennifer Darnell, Jean-Louis Mandel, and Kendall Broadie have all been funded first by FRAXA and currently by a joint NIH/FRAXA program for work in this area.

Therapeutic Approach #4: Treat Symptoms

How much can we modify the brain by behavioral therapy? Can the actual shape and size of nerve cell connections be reversed by behavioral intervention? Can behavioral symptoms be reversed by behavioral intervention? Can symptoms be reversed by pharmacological intervention? FRAXA awarded grants to Don Bailey, Elizabeth Dykens, Mina Johnson-Glenberg, John Larson and Kenneth Mack to conduct studies of the human symptoms of Fragile X, and to Linda Crnic, Rich Paylor, and Frank Kooy, to pinpoint symptoms in the Fragile X mouse model. If therapies and educational strategies can be designed with the specific needs of patients in mind, they are more likely to be effective. Likewise, the more we understand specific symptoms and their causes in Fragile X syndrome, the more likely it is that drugs can be selected, or discovered, that can target these symptoms. The new class of drugs called Ampakines, is an example: FRAXA has funded a trial of Ampakines in Fragile X mice and now will fund a trial of this medication in adults with Fragile X, under the direction of Elizabeth Berry-Kravis.

Teamwork and Future Prospects

Naturally, these four areas of research overlap and most

tic Treatments

teams work in several areas (although each investigator has been listed here only once). It is critical to develop models and tools to accelerate progress in all areas. Antibodies enable scientists to detect specific proteins within cells; Alan Tartakoff has engineered a set of Fragile X antibodies that he has made available to other researchers. Fruit fly models have emerged as a fruitful avenue of study for many genetic disorders; FRAXA is funding fly studies by Kendal Broadie, Kevin Moses, David Nelson, Tom Jongens, David Nelson, Lynn Regan, and Jerry Yin. A refined Fragile X mouse model is being developed by Nobel Laureate Eric Kandel; and Edouard Khandjian will study Fragile X in frogs.

Research Meetings

Since no one research facility has the time, funding, or personnel to do all the things necessary to develop effective treatments for Fragile X, coordinating and facilitating collaborative efforts among researchers is critical. Several recent research meetings have brought together small groups of leading scientists from around the world to brainstorm aggressively about the causes and symptoms of Fragile X and possible routes to a cure. While some of these researchers have worked on Fragile X for many years, others are new to this ever-growing field and provide a critical infusion of ideas which will make this field dynamic.

Workshop: Treatment Research Perspectives

In November, the National Institute of Mental Health (NIMH) held a workshop, Mental Health Aspects of Fragile X Syndrome: Treatment Research Perspectives. The inspiration for this meeting was provided by Dr. Steven Hyman, formerly Director of NIMH and now Provost of Harvard University and FRAXA's newest Scientific Advisor. The goal was to determine if there are specific mental health aspects of Fragile X which merit (and even require) targeted research approaches and treatments and, if so, to pinpoint what those are. A group of leading investigators was convened, resulting in creative and productive discussions.

A report on the meeting, including recommendations for future research directions, has been written by Dr. Linda Crnic and Dr. Bill Greenough, with input from other participants. It is available at the NIMH and FRAXA websites and printed copies are available from FRAXA.

We sincerely thank the organizers, Dr. Edgardo Menvielle and Dr. Benedetto Vitiello of NIMH, and the participants, Don Bailey, Mark Bear, Elizabeth Berry-Kravis, Paul Hagerman, Walter Kaufmann, MaryLou Oster-Granite, Jaswinder Ghuman, Richard Paylor, and Allan Reiss. Also participating from FRAXA were Katie Clapp, Michael Tranfaglia, and Debbie and Jeffrey Stevenson.

Fragile X Investigators' Meeting

In 2000, a five year, seven million dollar, research initiative was established by NICHD, FRAXA, and NIMH. Nine teams, currently funded under this program, are investigating topics ranging from math abilities of carrier women to fruit fly models of Fragile X. On

March 25-26th, these investigators and others funded by NICHD were invited to come together to present and discuss their latest findings. The discussions were a testament to the rapid progress being made in this field. After each presentation, other scientists in the room asked questions and shared their own perspectives. It was striking to see how very different lines of research are converging to confirm conclusions. We are grateful to Mary Lou Oster-Granite at NICHD for organizing this productive meeting.

Banbury Meetings

The third annual Banbury meeting on Fragile X is taking place as this newsletter goes to print. The Banbury Center at Cold Spring Harbor Laboratory in New York accommodates about 35 people, far away from city distractions; even phones are hard to find. This year's meeting is being organized by Robert Darnell, Steve Warren, and David Nelson, and will focus on RNA metabolism and Fragile X. Topics vary from year to year, depending on the hottest emerging research trends. Fragile X Banbury meetings are funded by the National Institute of Mental Health (NIMH) with additional funding from NICHD and FRAXA.

The Future

Clearly there is more to do, but we think the Fragile X field is on the right path!

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: May 1, 2002 and December 1, 2002

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 or by contacting FRAXA.

FRAXA UPDATE

EDITOR: Katherine Clapp, M.S.
CONTRIBUTORS: Elizabeth Berry-Kravis, MD, PhD
David and Mary Beth Busby
Jen Nardo
Debbie Stevenson
Michael Tranfaglia, MD
Judy Stringer
and many others
DESIGN: Mary Lou Supple

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

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

Delaware Benefit

Delaware's First Annual Fragile X Benefit was held on Saturday, February 9th in Hockessin. More than 75 people attended, some from as far away as Fairfax, Virgina, and Hamden, Connecticut. A disc jockey, courtesy of The Stone Balloon nightclub in Newark, Delaware, kept everyone dancing all night! Area businesses donated food, beverages, and items for the silent auction.

The auction was a huge success. Bidding wars throughout the night added a lot of excitement. There were original works of art, with the featured painting by Donna Crescenzo-Nardo, "Jake's Flight". This piece centers on a butterfly with bright colors exploding under it as it soars upward. The painting was named after Nardo's nephew, Jake, whose mother, Jennifer, coordinated the event.

After all was counted, the benefit raised over $6,600 as well as a higher level of understanding of Fragile X. Plans are already in the work for next year's event!

PLEASE HELP FRAXA

in supporting research aimed at treatment for fragile X

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

Yes, I would like to help FRAXA

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

FRAXA

NONPROFIT ORG.
U.S. POSTAGE
PAID
W. NEWBURY, MA
PERMIT NO. 59