

FRAXA UPDATE

SUMMER 2002

VOLUME 9, NO. 2

A PUBLICATION OF
FRAXA RESEARCH
FOUNDATION

“N
EVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

I N D E E D ,

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 in 1991. 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

Also in this issue:

- Report from Washington
- New Grants Funded
- Calendar of Events

Continued on page 7

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

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.”

update :

The mGluR Hypothesis: Studies in the Fragile X Knockout Mouse

MARK BEAR, PHD

Brown University, \$50,000

by Katie Clapp

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 pre-clinical studies go well, we may see human trials in 1-2 years!

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.

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.

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 malleable 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



Bassam Hassan (bottom left) and lab members

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.

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.

research

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.

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

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 I 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 JAYSOUDE@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

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

FRAXA

Gala,

5th Annual Mary Higgins Clark 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



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

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.

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.

EVENING



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.

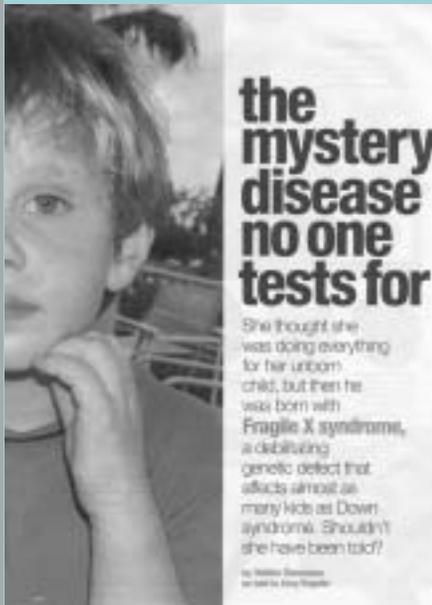
FRAXA UPDATE

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 Network 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

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

FRAXA

RESEARCH
FOUNDATION

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