

FRAXA UPDATE

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FOUNDATION

"NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

ever has."

— Margaret Mead

Senators Edwards and Hagel Introduce National Fragile X Awareness Week

March 1, 2000 – FRAXA announced today that U.S. Senators Edwards and Hagel have introduced a resolution which will spotlight fragile X for the public.

RESOLUTION Designating July 17 through July 23 as "National Fragile X Awareness Week"

- Whereas Fragile X is the most common inherited cause of mental retardation, affecting people of every race, income level and nationality;
- Whereas one in every 260 women is a carrier of the Fragile X defect;
- Whereas one in every 4,000 children born is affected, and most require a lifetime of special care at a cost of \$2,000,000 per child;
- Whereas Fragile X remains frequently undetected due to its recent discovery and the lack of awareness about the disease even in the medical community;



Senator Hagel



Senator Edwards

- Whereas the genetic defect causing Fragile X has been discovered and is easily tested for;
- 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-linked mental retardation;
- Whereas individuals with Fragile X are a homogeneous study population for advancing understanding of these disorders;

continued on page 2

Million Dollar Evening!

When Debbie Stevenson started planning a dinner to benefit FRAXA at New York City's famous Russian Tea Room, she took risks. The restaurant was a gaping demolition site soon to be renovated. She negotiated a favorable deal, expecting about 250 people, and hoping that the renovations would be complete on time. Some eight months later, on

Continued on page 11

Also in this issue:

- New Research Projects
- 1999 Finance Report
- Fragile X on the Web

FRAXA Funds New Research

Now in its sixth year, FRAXA is funding cutting-edge research at an annual rate of \$1.5 million. New grants and fellowships awarded in January are detailed here, and another round of applications will be accepted on May 1st. Most exciting of all, the National Institutes of Health (NIH) and FRAXA are sponsoring a joint fragile X research initiative for at least 1.2 million dollars per year. This initiative is currently in the clearance process within NIH; we anticipate that the formal Request for Applications (RFA) will be announced

Continued on page 4

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 David and Mary Beth Busby

We are pleased that so much space in this Update is about Research (as it should be). We must keep this report short. Last April, FRAXA established goals:

- **Acquaint the Congress with Fragile X, its prevalence (although relatively recently-discovered) and the single protein deficiency that gives us hope for a cure,**
- **Persuade both Appropriations Committees to include Report language again this year asking the NIH to accelerate and enhance research for a cure in its Fiscal Year appropriation, and**
- **Secure early passage of The Fragile X Breakthrough Act of 1999, by the Authorizing Committees and the Congress. This bill would authorize \$10,000,000 for the NICHD to “make grants to, or enter into contracts with, public or nonprofit private entities for the development and operation of [at least three] centers to conduct research for . . . improving the diagnosis and treatment of, and finding the cure for, fragile X”. It would authorize \$2,000,000 for the repayment of educational loans to researchers, “including graduate students.”**

HERE'S WHAT'S HAPPENED:

Your hundreds of letters, e-mails, faxes and calls and meetings have made Capitol Hill aware that Fragile X is the most common cause of inherited mental retardation. Fragile X is not yet a household word, but it's becoming that in Washington.

The House and Senate Appropriations Committees each instructed the National Institute of Health (NIH) to increase its expenditures on Fragile X research. More important, the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) have made Fragile X research a high priority, and NICHD is sponsoring a jointly-funded research program with FRAXA, putting up \$5 to FRAXA's \$1.

The Fragile X Breakthrough Act of 1999 secured 17 cosponsors in the in the Senate (S. 1131) and 42 in the House. This popularity led to its provisions being incorporated with other children's health measures in a comprehensive House bill, H.R. 3301, **which we expect to pass this year!** Hopefully, by the time this reaches you, Senator Frist (TN) will have introduced a similar bill in the Senate.

We owe a lot to those 169 families with Key FRAXA Advocates who have served in the front lines of our crusade – in contact with us and with each other by e-mail – mapping out strategies about how to approach their Congresspersons. If you want to join this pro-active lobby group, please e-mail me at:



busby .david@dorseylaw.com. Your letters to Congress made the difference last year and will make a bigger difference this year. For the sake of your children and ours, let's demand that our representatives co-sponsor and pass H.R. 3301, the Children's Health Research and Prevention Amendments of 1999!

Join us at FRAXA Lobby Day 2000, on Sunday afternoon, 2 - 4 PM in Chicago at the Windy City room of the Best Western Hotel, 162 E. Ohio St., Chicago. We will have coffee, meet the key FRAXA advocates, and talk research politics! We need a head count, so e-mail or call David Busby: busby.david@dorseylaw.com • 202-824-8820.

Senate resolution continued from page 1

- *Whereas with concerted research, a cure 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 intervention, and the significance that Fragile X research has for related disorders;*
- *Whereas the United States Senate as an institution and Members of Congress as individuals are in unique positions to help raise public awareness about the need for increased funding for research and for early diagnosis and treatment for the disorder known as Fragile X: Now therefore be it*

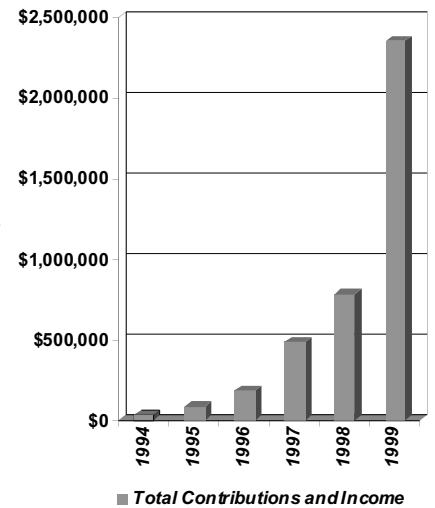
Resolved, That the Senate —

- (1) designates July 17 through July 23 as National Fragile X Awareness Week; and**
- (2) requests that the President issue a proclamation calling upon the people of the United States to observe “National Fragile X Awareness Week with appropriate recognition”**

Financial Report:

Wrapping Up 1999 and Looking Ahead

1999 was a tremendously successful year for FRAXA, thanks largely to the generosity of Lester and Frances Johnson, who made a large donation in order allow us to expand our research funding. As we become able to fund more ambitious research projects, so it becomes increasingly important to be in a financial position to commit to multi-year funding. One example is the joint NIH/FRAXA funding initiative, which will run at least 4-5 years. And so, let us celebrate and thank everyone who has contributed in 1999 – and redouble our efforts to match or surpass this amount in 2000. As the graph shows, FRAXA has grown exponentially since its founding in 1994. Yet, expenses have remained low: 1999 audited financial statements prepared by certified independent accountants Anstiss & Co. show that FRAXA spent \$58,501 on Fundraising and \$80,821 on Management and General expenses. Together, these costs come to less than 6% of total income for the year, which is much better than the average nonprofit.



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within weeks and that full applications will be due from investigators at NICHD by mid-July. Any researcher who would like to be informed when this initiative is announced can email Katie Clapp at kclapp@fraxa.org. A complete listing of all FRAXA-funded projects can be read at www.fraxa.org.

APPROACHES TO THERAPY

The newly-funded projects can be placed into three categories: 1) Approaches to therapy, 2) Enhancing Tools and Models, and 3) Studies of the Fragile X Protein. The projects in the first category explore ways that the fragile X protein might be restored in brain cells, where it is lacking. Possible ways of accomplishing this include: gene therapy (introducing new, working copies of the fragile X gene into cells), protein replacement (finding ways to deliver the protein into cells), reactivating the fragile X gene, and using medications that might compensate for the missing protein.

1. Studies on FMR1 gene delivery using herpes simplex virus vectors

DAVID BLOOM, PH.D. Principal Investigator
University of Florida College of Medicine (\$45,000)

WILLIAM GREENOUGH, PH.D. Principal Investigator
Beckman Institute, University of Illinois, (\$42,000)

By David Bloom

The primary cause of Fragile X Syndrome is a genetic defect that results in the lack of a protein, FMRP. FMR1 knockout mice, which lack the ability to produce normal FMRP, show a number of defects in their central nervous systems which may be similar to those present in the disease in humans.

In this study we will use a gene therapy approach to deliver a functional copy of the FMR1 gene into the brains of the FMR1 knockout mice and determine if this will repair the observed defects in their central nervous system. One tool we plan to use to deliver the FMR1 gene is a vector based on the Herpes Simplex Virus, which causes cold sores or fever blisters. This virus is a common inhabitant of our nervous systems and can be modified to act as a safe vector system for gene delivery.

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.

r e s e a r c h

2. Reactivation of the FMR1 Gene in Fragile X Patients' Cells in Culture



GIOVANNI NERI, MD

Catholic University, Rome, Italy
(\$32,000 renewal, first funded January 1999, \$30,000)

By Giovanni Neri

In individuals with fragile X a chemical switch called methylation “turns off” the FMR1 gene. Simple molecules known as methyl groups attach to the DNA sequence constituting the “promoter”. The result is gene inactivation and lack of its specific protein product FMRP. In addition, proteins known as histones make up a spool around which the DNA thread is wound. If the histones are loaded with acetyl groups (again, simple modifying molecules like methyl groups), the DNA is loosely packed and the FMR1 gene can be freely transcribed. On the other hand, loss of acetyl groups (deacetylation) results in tight packing of the DNA, which becomes inaccessible to the molecular machinery responsible for the production of FMRP. Thus, DNA hypermethylation and histone deacetylation need to be reversed to enable the FMR1 gene to express FMRP.

After showing that demethylating drugs such as 5-azadeoxycytidine (5-azadC) can reverse hypermethylation and reactivate the FMR1 gene (up to 5-15% of its normal expression levels), Dr. Neri and his team have run two sets of experiments in this project aimed at:

1. reversing the silencing of the FMR1 gene by treating fragile X lymphoblastoid cell lines with histone-acetylating drugs such as 4-phenylbutyrate (4-PBA), butyrate (BA) and trichostatin A (TSA).
2. Verifying the possible synergistic action of the histone-acetylating drugs with the DNA- demethylating drug 5-azadC, when used in a combined treatment.

The team has found that 4-PBA and BA can reactivate expression of the FMR1 gene, although at low level (only 1-2% of its normal activity). When 4-PBA or BA were employed together with 5-azadC, a marked synergistic effect was observed. The FMR1 reactivation obtained with 5-azadC alone was enhanced two- to threefold when 4-PBA or BA were added, confirming the hypothesis that DNA hypermethylation and histone deacetylation are sequential steps in a single pathway that leads to the silencing of the fully mutated FMR1 gene. The extent of the FMR1 reactivation seems to correlate with the size of the full mutation: cells with 600-700 CGG repeats responded less to the treatments than cells with 270-350 repeats.

update

3. A novel therapeutic approach for fragile X syndrome: FMRP conjugated with the PTD segment of the HIV-1 TAT protein.



BEN A OOSTRA, PH.D.

Principal Investigator, Erasmus University, Rotterdam, The Netherlands, (\$35,000)

by Ben Oostra

It is generally agreed that mental impairment in fragile X patients is

caused by lack of the Fragile X Protein (FMRP) in the neurons of the central nervous system. Our project is aimed at restoring FMRP to neurons, by using a new tool, the HIV-1 TAT protein. Our work will have three phases:

1. We will produce large amounts of FMRP in insect cells. We will modify this FMRP so that it contains a short sequence taken from the HIV-1 TAT protein, which has been shown to help facilitate the uptake of proteins in cells.
2. We will test whether this modified protein can be taken up by cells cultured in vitro. These can be fragile X patients' cell lines which are completely devoid of FMR1 protein. We will monitor the uptake, hoping that the cells will take in large amounts of protein.
3. Finally, these studies will be followed in vivo by injecting the modified protein into FMR1 knockout mice. The uptake of protein will be tested biochemically and by testing the behavior of the mice, to see if their fragile X symptoms are ameliorated by the introduced protein.

Glossary of Terms

FRAXA *The genetic mutation which causes almost all cases of fragile X syndrome*

FMRP *The Fragile X protein (which is lacking in those who have fragile X syndrome)*

mRNA *Each gene in our bodies produces a protein, via an intermediate step: the gene produces mRNAs in the nucleus of a cell and then these mRNAs migrate out to the various parts of the cell where they, in turn, produce their protein*

Synapse *The part of a neuron (nerve cell) which communicates with neighboring neurons. Communication between neurons is critical: it underlies thinking and learning.*

Plastic *Capable of change in response to activity. Plasticity of synapses is thought to be involved in memory as well as in the development of seizure phenomena.*

FMRP Knockout (KO) Mice *These mice have been genetically engineered to have a defect in the fragile X gene and, therefore, they do not produce the normal fragile X protein. The term Knockout is used because a gene has been knocked out of the normal mouse genome. But, like so much of science, this is an oversimplification: actually, only a small section of the fragile X gene has been damaged, but this appears to be critical to its normal function.*

in vitro *in preparations of cells, not living creatures*

in vivo *in live animals or humans*

ENHANCING TOOLS AND MODELS

Science depends on a vast array of elegant and expensive tools. Antibodies, for example, are needed for any in-depth investigation of the protein's function. As another example, most of the current research depends on having good animal models of fragile X. A variety of animal models are needed, from fruitflies to mice. Generations of fruit flies can be bred in weeks, whereas it would take years to breed many generations of mice. But often, when looking at complex behaviors, a more sophisticated animal like a mouse is needed. FRAXA is funding research on models and tools, hoping that investigators will freely share the results with other teams.

4. Neurological function of fragile X gene in the genetic model system of Drosophila

KENDAL BROADIE, PH.D., Principal Investigator

YONG ZHANG, PH.D., Postdoctoral Fellow, University of Utah, (\$35,000)

by Yong Zhang

One of the most compelling challenges in fragile X research is to understand, on a cellular level, how lack of FMRP gives rise to the clinical mental retardation and associated behavioral abnormalities. A potentially fruitful approach is to assay FMR1 function within a simpler, well-characterized model organism, *Drosophila melanogaster*, the fruitfly.

A FMR1 gene *homologue* (i.e. similar gene) in *Drosophila* has been identified and named *dFMR1*. We are investigating the neurological role of the fragile X protein by generating and analyzing of a series of different *dFMR1* mutations in the fruitfly, taking full advantage of sophisticated genetics and experimental tools available for this organism. These mutations will include a classical "lack of FMRP" null mutation characterized in humans, an "antimorph" point mutation in *dFMR1*, which will have a more severe phenotype (symptoms) than the lack of FMRP, and a "gain of FMRP" mutation by tissue specific mis- or over-expression of FMRP. Mutants will then be assayed by a combination of cell biological and physiological techniques to understand the cellular neurological defects associated with fragile X syndrome.

Our hypothesis is that the function of *FMR1* is conserved across species and that the genetic approach, combined with an array of powerful experimental tools available for the simple fruitfly, is likely to uncover novel aspects of *FMR1* and its role in neurological mechanisms. The results from this study will complement and extend the work in mammalian systems.

Continued on page 6

5. Generation of monoclonal antibodies to FMRP, FXR1 and FXR2



ALAN TARTAKOFF, PH.D.

Principal Investigator, Case Western Reserve University, (\$33,000) Special thanks to our Research Funding Partner The Fragile X Alliance of Ohio

The FXR1 and FXR2 proteins are structurally similar to FMRP, but they cannot take its place. Unfortunately, the only commercially available antibodies for FMRP also recognize the FXR proteins. This is a problem because many experiments depend on the ability to detect and quantify FMRP – and only FMRP – in given cells. To facilitate investigation of each of the three proteins, separately, we will generate a panel of monoclonal antibodies which distinguish between them. These antibodies will be made available to all scientists who need them in order to study fragile X.

6. Studies of the Fragile X Knockout Mouse: characterization of behavioral profile and mnesic abilities



WILLIAM GREENOUGH, PH.D.

Principal Investigator

VALERIE BERTAINA-ANGLADE, PH.D.

Postdoctoral Fellow, Beckman Institute, University of Illinois, (\$38,000)

by Valerie Bertaina-Anglade

Fragile X knockout mice are considered to be a good animal model of the syn-

drome because they lack the ability to express the normal Fragile X protein. But are they really a good model? To be useful, they should express behavioral and cognitive deficits similar to those observed in patients. So far, only a few studies have been published which address their cognitive abilities and no clear picture of the behavioral phenotype has yet emerged. We will submit the fragile X mice to various cognitive tests in order to evaluate their:

1. Behavioral and cognitive profile: Do they exhibit normal locomotion, anxiety, sense of smell, visuo-motor coordination, aggression, social behavior, attention, etc.? Some of these functions are weak in fragile X patients and therefore need to be tested in the mouse.

2. Learning and mnesic (memory) abilities: Are they able to learn as well as the control mice? If not, what aspects of memory are deficient? We will use multiple paradigms to cover the different aspects of memory and multiple levels of difficulty and motivation for the mice.

We hope to improve our understanding of the cognitive effects of the absence of the fragile X gene in mice, in order to determine the validity of this animal model for the study of fragile X syndrome.

7. Behavioral Characterization and Therapeutic Interventions in Fmr1 Knockout and Transgenic Mice



RICHARD PAYLOR, PH.D.

Principal Investigator

KELLIE MCILWAIN, PH.D.

Postdoctoral Fellow, Baylor College of Medicine, (\$109,000)

by Katie Clapp

Preliminary studies by this team indicate that, in mice

as in humans, the level of fragile X protein in brain cells helps determine levels of activity and anxiety. Dr. Paylor's group is comparing knockout mice, which lack FMRP, with YAC mice, which express excessive levels of FMRP. Interestingly, knockout mice show hyperactivity and low anxiety, whereas YAC mice demonstrate high anxiety and low activity. The team aims to better understand these anxiety-related responses in knockout and YAC mice by evaluating them on several types of anxiety tests. Then, they will apply pharmacological interventions in these mice, to begin to evaluate the role of different neurotransmitter systems in regulating the abnormal anxiety-related responses. By testing the effects of particular drugs on anxiety and activity in the knockout and YAC mice, they will determine whether the mice will be a useful tool for screening new drugs for potential use in treating patients with fragile X syndrome.

8. An Expanded Repeat Mouse Model of Fragile X Syndrome and

9. Restoration of Natural FMR1 Expression in FMR1 Deficient Mice by P1 Artificial Chromosome (PAC) Transgenesis

ROBERT BAUCHWITZ, MD, PH.D.

Principal Investigator, Columbia University (\$90,000 renewal)



Special thanks to our Research Funding Partner, The Preiser Fund of Long Island, in honor of Jonathan Preiser and in memory of Marilyn Garrett by Robert Bauchwitz

The existing Fragile X "Knockout Mouse" has limitations as a model for fragile X syndrome in humans. In order to produce a mouse model which much more closely resembles the mutation

seen in the majority of humans with Fragile X Syndrome, we propose to produce a "Knock-in Mouse." This animal will have an FMR1 gene with an expanded CGG-repeat sequence, as do most fragile X patients. It will be particularly useful for tests of drugs to reduce methylation or otherwise repair the FMR1 gene.

If this mouse model can be successfully constructed and is viable, we will first assess whether the expanded repeats are methylated and how stable these repeats are after transmission through the germline and in somatic tissues. Second, we will do cognitive tests to compare the knock-in animal to the current knockout and to humans with comparable repeats. Third, we will begin tests to demethylate the repeats in neurons and/or contract them, as may be relevant, depending on methylation and stability. In addition, if we find that there is no expression of FMR1 mRNA in the Knock-in mouse, we will mate the new mouse to the PAC transgenic mouse, which we are developing in our current FRAXA-funded study.

cells communicate might be smaller and hence weaker both in fragile X patients and in the knockout mouse.

THE FRAGILE X PROTEIN: WHAT DOES IT DO?

Much of the current FRAXA-supported research aims to understand, in great detail, the function of the fragile X protein. Since lack of this protein causes fragile X syndrome, the first step toward a treatment or cure is to know what the protein does and how it does it.

Proteins do not operate in isolation. The brain, our most complicated organ, learns, thinks, feels, and operates by cascades of proteins which regulate each other. Like an involved game of "telephone", every protein in a pathway is critical to function. As we identify and understand the other proteins that interact with our fragile X protein FMRP, we will gain greater insight into how the brain works. Hopefully, we will also uncover ways to use other proteins to compensate for the lack of FMRP in fragile X. We might also discover other proteins that turn out to be the cause of other kinds of mental retardation and developmental disabilities.

Ampakine drugs modulate receptors for glutamate at synapses and should selectively increase responsiveness of the *informational* (AMPA) receptors at the synapse, while having limited effects on the *plastic* (NMDA) receptors that may be involved in the development of seizure phenomena. The study will examine the effect of prolonged treatment with the drug on brain development of FMR1 knockout and normal mice reared either in standard laboratory cages or in an enriched laboratory environment (toy-filled cages), to see if the drug enhances development of the brain or enhances the effects of experience on the brain. Control groups necessary to this study will also examine the effects of behavioral intervention on the neural circuitry of the FMR1 knockout mouse.

10. Studies of Synaptic Regulation of Protein Synthesis and of Possible Therapeutic Approaches to Fragile X Syndrome

WILLIAM T GREENOUGH, PH.D.

University of Illinois at Urbana-Champaign (\$85,000 renewal)
by William Greenough

This award covers two related but separate projects. The first, which will be headed by FRAXA-supported postdoctoral fellow Frank Angenstein, is based on this team's previous finding that FMRP is synthesized at synapses in response to activation by the neurotransmitter glutamate. Dr. Angenstein is working out details of the signalling pathway whereby glutamate activates protein synthesis. There is some evidence that FMRP is involved in or required for the synthesis of other proteins also regulated by this pathway. Thus its mechanisms are of interest in determining whether there may be ways to bypass the inactivity of the FMR1 gene in fragile X syndrome.

The second project, which Dr. Greenough will head, examines effects of *ampakine* drugs on brain development in the FMR1 knockout mouse. Evidence from this and other laboratories suggests that the synapses through which nerve

11. Search for FMRP (Fragile X Mental Retardation Protein) cellular function through the characterization of two novel FMRP interacting proteins



The Mandel Team

JEAN-LOUIS MANDEL, PH.D.
Principal Investigator

BARBARA BARDONI, PH.D.
Postdoctoral fellow, Faculty of
Medicine, Strasbourg, France,
(\$30,000)

by Barbara Bardoni

We have searched for new proteins that interact with the fragile X protein FMRP using a technique called the *two-hybrid assay* in yeast. After screening a mouse embryonic (E9.5-E12.5) library, we found two novel proteins that we are currently characterizing: NUFIP1 (Nuclear FMRP Interacting Protein) and CYFIP (Cytoplasmic FMRP Interacting Protein). Understanding the functions of these new proteins is an essential step in the definition of the molecular and developmental mechanisms by which the absence of *FMR1* expression causes fragile X syndrome.

Continued on page 8

12. Identification of Specific RNA Targets of FMRP

ROBERT DARNELL, MD, PHD

Yale University, (\$35,000 renewal, first funded Jan. 1999, \$35,000)

by Katie Clapp

The fragile X protein normally binds to (interacts with) a number of other RNAs in cells. When FMRP is missing, as in fragile X syndrome, these RNAs, which code for other proteins, are impacted. Identifying these RNAs will yield new insight into the function of FMRP as an RNA-binding protein in the brain and may suggest potential points of therapeutic intervention. To this end, the Darnell team is employing several lines of research concurrently, including Selex with an RNA library from brain, in vivo-crosslinking, tailing and sequencing of bound RNAs, and reporter studies to look at the role of FMRP in dendritic targeting.

13. Regulation of FMR1 Gene Expression

PAUL HAGERMAN, MD, PHD

Univ. of Colorado, (\$35,000 renewal; funded Jan. 1999, \$30,000)

by Paul Hagerman

In individuals affected by fragile X syndrome, expansion of the CGG repeats into the full mutation range is normally thought to be due to a shutting down ("silencing") of the *FMR1* gene, resulting in reduced levels (or absence) of the *FMR1* protein (FMRP). However, the precise relationship between the size of the CGG expansion and activity of the *FMR1* gene has not been quantified. During the course of our FRAXA-supported studies of *FMR1* reactivation, we made the surprising observation that for fragile X males whose *FMR1* gene remains unmethylated, the mRNA levels are much *higher than normal*, despite reduced FMRP levels. This observation has important implications for the treatment of fragile X syndrome: it suggests that there may be a second block to the production of FMRP, with the higher mRNA levels possibly a compensatory response to the lowered FMRP levels. Our intent during the coming year is to test various aspects of this hypothesis. During the course of these studies, we hope to better define the relationship between *FMR1* mRNA levels, CGG repeat size, and FMRP production. This work should improve our prospects for successful treatment of fragile X syndrome.

14. The role of fragile X protein in the functional maturation of dendritic spines in vitro



MENAHEM SEGAL, PH.D. ISRAEL
KATHARINA BRAUN, PH.D. GERMANY
WILLIAM T. GREENOUGH, PH.D. USA

80,000 renewal, first funded Jan. 1999 (\$40,000 each for Segal and Braun labs)

Special thanks to our Research Funding Partner, Conquer Fragile X for their support.

by Katharina Braun



Our work is aimed at understanding how the protein FMRP impacts the structure and function of nerve cell synapses. We use a controlled *in-vitro* test system involving the tissue-cultured neuron. Mice which lack the fragile X protein (knockout mice) have altered dendritic spines on the neurons in their cortex, compared to wild-type (WT) controls. We have used tissue-cultured neurons to examine differences in morphology (shape) and synaptic connectivity between wild-type and knockout mice.

We have already found that hippocampal neurons taken from knockout mice and grown in culture for three weeks have shorter dendrites and fewer dendritic spines compared to controls. Also, knockout cells tend to develop fewer active synaptic connections, which produce smaller excitatory synaptic currents than controls. These preliminary observations may have important functional implications for the ability of the cells taken from the knockout mice to express long term plasticity, which may underlie the mental retardation seen in patients who lack FMRP.

15. Transport of the Fragile X Protein

ALAN TARTAKOFF, PH.D.

Case Western Reserve University, (\$63,000). Postdoctoral Fellowship funded January 1998 (\$30,000); Renewed January 1999 (\$30,000)

by Alan Tartakoff

FMRP is primarily found in the cytoplasm of cells, but its structure suggests that it can enter the nucleus. Our first goal is therefore to identify the circumstances which allow FMRP to enter and leave the nucleus. Since FMRP is not expressed in cells of most Fragile X patients, our second goal is to evaluate a novel strategy which is purported to cause extracellular proteins to enter into the cytoplasm of living cells.

Seventh International Fragile X Conference: July 19-23 in Los Angeles

For more information, contact Robby Miller at the National Fragile X Foundation, 800-688-8765 or www.FragileX.org.

FRAXA is proud to support this conference, helping to bring researchers together to share their latest results.

Fragile X Online

www.fraxa.org



Thanks to web designer Kevin Moffitt, FRAXA's web site has information for everyone. visit www.fraxa.org and read about research projects, the fragile X funding bills, progress through Congress, and upcoming events to celebrate and raise funds for fragile X research.

Fragile X Listserve:

Now in its fifth year, the listserv is a support group for families everywhere to share stories and tips. Joining is free and open to all.

How to Join:

Send email to: listserv@listserv.cc.emory.edu

with the following command in the body of your message:

subscribe fragilex-l (that's "L" for List")

How to send messages to the list:

Send your messages to **fragilex**

How to Leave:

Send email to:

listserv@listserv.cc.emory.edu

with the following command in the body of your message: **signoff fragilex-l** ("L" for List" again)

An extremely useful option: the digest. If your life and inbox are full enough without a dozen or so email messages each day, this option bundles all your listserv messages and delivers them in one daily email: **set fragilex-l digest**

Listserv En Español

Jose Guzman from Madrid announces that the Spanish Federation for Fragile X Syndrome has established a listserv in Spanish for families, professionals, and anyone who would like to discuss fragile X. This listserv is modeled after the Fragile X listserv created by FRAXA.

How to join:

Send email to: xfragil-subscribe@onelist.com

Leave both the subject and the body of the message blank.

How to send messages to the list:

Send email to: xfragil@onelist.com

How to leave (unsubscribe):

Send email to: xfragil-unsubscribe@onelist.com

We hope that this initiative will provide help and the opportunity for information exchange to the entire Hispanic fragile X community. For more details, contact **Jose Guzman** at jgab@ctv.es

Available from FRAXA

NEW VIDEO!

Unlocking Fragile X

An emotional and inspiring look at fragile X, FRAXA and current research featuring author and grandmother Mary Higgins Clark, Nobel-Prize Winner James D. Watson, MD, and many others. This 10-minute video was produced by Debbie Stevenson, a mother and formerly an Associate Producer at MSNBC and a member of Barbara Walters' 20/20 production team. The video is a great fundraising aid and is available from FRAXA at cost (\$6).

Fragile X Articles

The Advocate 1995 – 1997, edited by Pamela Brode and published by Avanta Media Corp., 173 pages, \$25 postpaid within the U.S. This book is jam-packed with useful information.

Fragile X Information Cards

Many families have asked for a card that they can give to people who have no knowledge of fragile X. Business-size cards: \$10 per 100.

Booklet available:

Fragile X: A to Z

Wendy Dillworth, FRAXA Michigan Chapter leader, has created a wonderful guide for families.

Fragile X - A to Z is chock full of stories from daily life with fragile X children. Browse through helpful suggestions on topics such as adolescence, bike riding, computer software, and dental work. Wendy has collected these tips from the Fragile X Listserv with permission from each author. This 73-page soft cover guide is available from FRAXA for \$15 postpaid within the US; elsewhere please add \$5.

A Medication Guide for Fragile X

by Michael R. Tranfaglia MD, Psychiatrist,
Medical Director of FRAXA

This guide is intended to help parents and others understand behavioral symptoms of fragile X and the medications commonly prescribed to help manage these symptoms. Available from FRAXA for \$25.

Free: Updated FRAXA Brochures and gift envelopes are now available.

HAVE YOU HEARD OF FRAGILE X?
Our loved one has Fragile X Syndrome
Fragile X is an inherited genetic disorder which affects 1 in 2000 boys and 1 in 4000 girls. It can cause:

- mental impairment ranging to mental retardation
- behavioral challenges, like
- autistic-like behaviors, such

YOU CAN HELP
Please understand that new situations will cause our loved one to become anxious and afraid. Often, neither we nor (s)he can control this behavior. So please be encouraging and just *Smile!*
For More Information
FRAXA Research Foundation
45 Pleasant Street, Newburyport, MA 01950
web: <http://www.fraxa.org>

FRAXA EVENTS

Upcoming Fundraisers

APRIL

X-TRAORDINARY X-TRAVAGANZA DINNER AND ART AUCTION

NCAA X-HIBITION VOLLEYBALL GAME SCOTTSBLUFF, NEBRASKA

DINNER, FRIDAY, MARCH 31ST AND GAME, SATURDAY, APRIL FOOLS DAY

CHAIRS: SANDY MASSEY AND SHIRLEY SCHAUB

This promises to be a truly Xtravagant celebration. Great auction items have been donated by the Scottsbluff community, including a bronze sculpture by Cowboy Artist of America Herb Mignery! Scottsbluff radio station KNEB will feature parents Megan Massey and Katie Clapp live at 8am.

Contact Megan Massey (phone: (308) 635-7109,
email: mmassey@scottsbluff.net)

THIRD ANNUAL MARY HIGGINS CLARK GALA SUNDAY, APRIL 30, AT THE FOUR SEASONS HOTEL IN CHICAGO

CHAIRS: JAY AND JOAN CANEL

HONORARY CHAIR AND SPECIAL GUEST: MARY HIGGINS CLARK

HOST: ROGER MUDD

FRAXA's third annual gala will feature jazz Grammy-winner Ramsey Lewis, a video appearance by Tipper Gore, and delicious food and wine. Tickets are available for \$350 each; black tie preferred.

Please contact Lynda Canel, phone: (847) 433-9093
email: Inscanel@aol.com
or Katie Clapp at FRAXA for invitations and details.

MAY

BASKETBALL TOURNAMENT

SUNDAY, MAY 21, CAMBRIDGE, MA BUCKINGHAM BROWNE & NICHOLS SCHOOL

ORGANIZING TEAM: PRESSMAN, ROME, SAVARESE, MARKS, AND VERSHBOW

Get your friends together for a spirited 3-on-3 basketball tournament and Buckingham Browne & Nichols School's magnificent new gym near Harvard Square in Cambridge. Come play or watch or volunteer, and bring the kids. Call Pamela Vershbow, at (617) 924-7560, for tickets.

JUNE

CHAMPIONS FOR CHILDREN CELEBRITY GOLF TOURNAMENT 2000 TUESDAY EVENING JUNE 13 - COCKTAIL PARTY WEDNESDAY, JUNE 14 - GOLF, CELEBRITY DINNER, AND LIVE AUCTION, HARRISBURG, PA

CHAIRS: BILL AND DEBORAH PARKER

Come join current and retired players from the Philadelphia Flyers and Eagles, Pittsburgh Penguins and Steelers, Chicago Blackhawks and Detroit Redwings. Golf sponsorships available ranging from \$500.00 to \$4000.00 or \$250.00 for individual golf package. Celebrity dinner and auction only is \$125.00.

Call Bill or Deborah Parker at 717-564-0110 for brochure and information or contact us at Champs4Children@aol.com



2000 NEW ENGLAND MOUNTAIN BIKE ASSOCIATION'S BENEFIT RIDE SATURDAY, JUNE 24

LEOMINSTER STATE FOREST, MASSACHUSETTS

This will be a map guided, non-competitive, fun ride through Leominster State Forest, which is considered the true "holy grail" of the local mountain bike scene. There will be a party after the rides. Application forms can be downloaded from NEMBA's web site, www.nemba.org. For more details, call Shorta Yuasa at (978) 582-3362 or email him at syuasa@massmed.org

JULY

FOURTH ANNUAL FRAGILE X GOLF BENEFIT HOSTED BY THE FRAGILE X ALLIANCE OF OHIO MONDAY, JULY 17TH ACACIA COUNTRY CLUB, LYNDBURST, OHIO

Please join us for our highly successful golf outing and silent and live auctions. Golf sponsorships range from \$500 to \$10,000 with individual golf packages at \$175. Dinner/auction tickets are \$60. For more information contact Mike Sydenstriker at (440) 349-7448 or Leslie Bagdasarian at (440) 519-1517 or email lbadgas@oh.verio.com

Russian Tea Room Gala

March 2nd, 500 people attended FRAXA's dinner, which occupied all four floors of magnificently refurbished Tea Room! Every detail of the evening was exquisite, including nesting Russian dolls given to every guest.

FRAGILE X VIDEO DEBUT

By the end of the evening, every guest had gained an understanding of fragile X. CNBC's business news anchor **Sue Herera** welcomed everyone and introduced our new fundraising video, produced by Debbie Stevenson. Until the birth of her sons, Debbie was a news



MSNBC News Anchor Sue Herera

producer at CNBC and, before that, a member of Barbara Walter's 20/20 production team. Her video (copies are available from FRAXA, see page 9) features author **Mary Higgins Clark**, Nobel Prize winner **James D. Watson, MD**, Lasker Prize winner **Eric Kandel, MD**, and others, with emotional and inspiring looks at fragile X and current efforts to work toward a cure. After the video, Debbie's husband **Jeffrey Stevenson**, Co-Chair, spoke of their son Taylor, who was diagnosed just one year ago, and how he and Debbie had moved forward from the diagnosis to feeling like they can really make a difference in the world. Finally, Katie Clapp described FRAXA's current efforts to jump-start promising research.



Eric Kandel, Mary Higgins Clark, John Veronis, John Suhler

WORDS FROM A FRAGILE X RESEARCHER:

I want to thank you for inviting my lab to your FRAXA benefit. It was an important experience for me: meeting parents and grandparents of children with Fragile X. While I have, of course, read a great deal about Fragile X Syndrome both medically and in basic science journals, and while it is a part of my daily life, I have not, until your benefit, gotten the opportunity to put real faces on family members of children and adults with the disorder. I hope one day you can sponsor a less formal event where we can meet some children with Fragile X.

One of the reasons I chose to study Fragile X Syndrome was that, as an MD/PhD student, I wanted to work on a project that would allow me to bridge the gap between the clinic and basic science. When I graduate I will do a joint residency/post-doc in neuropsychology and neuroscience. The video that you showed was the first opportunity I had to see the kind of direction I can take in my career. The hope and anxiety that the families had for their children and their futures, and the pain that they obviously suffer moved me enormously, and refreshed my stamina. I actually went back to lab after the dinner and began a transfection I'm working on. I didn't intend to write such a long letter. But, I do appreciate the opportunity and perspective you gave me. You obviously had a very successful evening on many levels.

Laura Antar, Ph.D.
Department of Neuroscience
Albert Einstein College of Medicine



Co-host Jeffrey Stevenson thanks assembled guests

A FUND-RAISING SUCCESS

The most dramatic moment of the evening was Jeffrey Stevenson's surprise announcement that the dinner raised over one million dollars! On behalf of FRAXA and all families affected by fragile X, I convey our sincere appreci-

ation to everyone who helped make this possible and especially to Jeffrey's partners at Veronis, Suhler & Associates, **John Veronis**, **John Suhler**, and to Jeffrey and Debbie Stevenson for their generous donations. Because of this event, FRAXA will support critical research that would not otherwise be done. We are poised to make a very significant difference to our children's future. And 500 people had a wonderful evening along the way!

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: May 1, 2000 and
December 1, 2000

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

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*The
Third
Annual*

Fragile X Gala

Honorary Chairman & Special Guest
Mary Higgins Clark

Tickets available
- call FRAXA for an invitation

Sunday, April 30, 2000
The Four Seasons Hotel, Chicago, IL

Please join us!

PLEASE JOIN
FRAXA
in supporting research aimed
at treatment for fragile X RESEARCH
FOUNDATION

FRAXA is a national 501(c)(3) tax-exempt organization. You can join for a tax-deductible donation of \$25 or more per year. Every penny you donate goes to research: FRAXA has specific grants to cover all overhead. Members receive this quarterly newsletter and are welcome to participate as active volunteers.

Yes, I would like to join FRAXA

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

FRAXA

45 Pleasant Street
Newburyport
Massachusetts 01950

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FOUNDATION

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FRAXA UPDATE

SUMMER 2001

VOLUME 8, 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

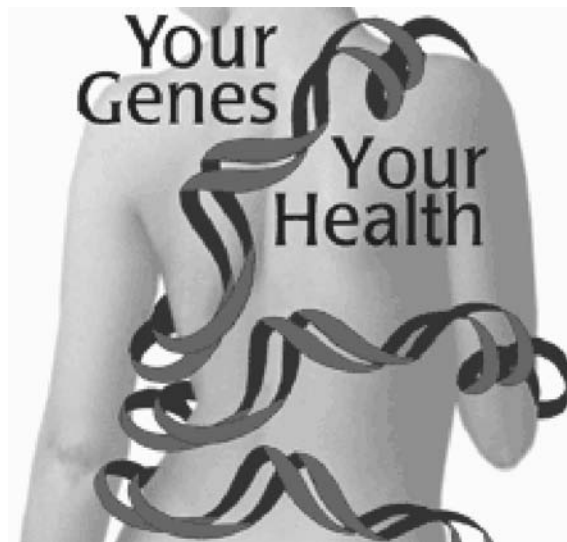
ever has."

— Margaret Mead

NEW RESEARCH FUNDED

In June, FRAXA's Board of Directors voted to award 10 grants and fellowships for cutting edge projects that will bring us closer to finding effective treatments and a cure for fragile X. Much of the research focuses on the fragile X protein, which is lacking in people with fragile X syndrome. Why is this protein so important to learning and memory? Are there ways to compensate for it, or bypass it? These are key questions that investigators are working to answer.

continued on page 4



New Fragile X Website

The DNA Learning Center at Cold Spring Harbor Laboratory has created a new web-based guide to fragile X. Called *Your Genes, Your Health* (vector.cshl.org/ygyh), this interactive site uses a wonderful variety of animations and videos. Cartoons demonstrate how the FRAXA genetic mutation shuts down the fragile X gene so that it cannot produce its normal protein. Dr. W. Ted Brown explains how fragile X is diagnosed and how it can be inherited through

families. Dr. Vicki Sudhalter describes educational strategies and medications that can help reduce anxiety and other common symptoms of fragile X. Dr. Esther Nimchinsky discusses her research aimed at understanding the fragile X protein. FRAXA parents Debbie Stevenson, Mary Lou Supple, Katie Clapp, and Mike Tranfaglia share coping strategies and 9-year-old Laura Tranfaglia talks about what it's like to have a brother with fragile X.

Because this multimedia site requires a fast Internet connection, FRAXA and the DNA Learning Center have also created a CD-ROM version, which is available from FRAXA free upon request with any new donation. (To get the CD, just call or send in a note with your next donation.)

Also in this issue:

- Report from Washington
- Fragile X Awareness Day
- Fundraising Events

The CD-ROM includes the entire DNA Learning Center fragile X site and current FRAXA publications: *Medication Guide for Fragile X*, *Fragile X - A to Z*, *Unlocking Fragile X* video, brochures, and a set of *FRAXA Update* Newsletters. The CD works on PC and Macintosh computers.

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.

FRAGILE X AWARENESS DAY:

Last year, the Senate declared July 22nd to be National Fragile X Awareness Day. This year, we set a goal: to persuade newspapers, radio and TV stations, and municipalities around the world to feature fragile X. Here are a few highlights. If fragile X received publicity in your area, please send it in so we can share the good news in our next newsletter.

... ON VOICE OF AMERICA

On July 23rd, *Voice of America* featured a 1-hour segment on fragile X. Voice of America's daily call-in talk show *Talk to America* is broadcast on radio, TV, and the Internet at www.voa.gov/talk and reaches an international audience of 80 million people! Thanks to Executive Producer Irina Burgener and her husband Robert Burgener for facilitating this broadcast.

... IN CLEARFIELD, UTAH

Martha Mathews writes:

I am thrilled to report that July 3 is Fragile X Day in Clearfield, Utah! A City Councilman asked me why more people were not aware of fragile X. I was asked to give a brief presentation. I presented as much as I could about FRAXA and why its mission is so important to all Americans.

You should receive the original copy of the Proclamation soon. I know that the research will pay off. But the road is a hard one. I am so thankful that many scientists have teamed up with FRAXA. That alone tells the story!

... IN BUFFALO, NEW YORK

Lisa Kowal writes:

I decided that I wanted to try to make a long term difference for my son by raising money for FRAXA. I sent a request to my County office for an "Erie County Fragile X Awareness Day," which was approved! Friday, July 20, 2001 will be the day. I also requested that we be permitted to

hold a fundraiser in the building where I work. It is a large building with thousands of employees and lots of traffic! The Erie County Fragile X Day will give us both the benefit of media coverage and hopefully, an incentive to businesses to participate in a "local" cause.

I then gathered a team of friends together and we mapped out our plan. We will hold raffles at each end of the building, pass out literature on Fragile X and wear FRAXA t-shirts. We have already sent out 80 letters to businesses requesting theme basket donations for our raffle or, if they prefer, a check payable to FRAXA. We will meet our two



Lisa's son Alex Kowal

main goals: awareness and fundraising!

I've decided to establish a FRAXA Chapter here in Western New York. I am grateful for all that the FRAXA team has done to raise funds for Fragile X Research, but think of all that they (we) could raise with each one of us doing a part? Even a small fundraiser when multiplied by many families running one can make a huge difference!

I admit to being a little nervous about this first one since I am new to this, but I am also having a great time doing it. We are already talking about ideas for next year's event!

– Lisa M. Kowal
FRAXA, Western New York Chapter
192 Greenfield Dr., Tonawanda, NY 14150
(716) 694-3030, lisak@buffnet.net

The County of Erie, New York, has issued a proclamation declaring July 20th to be Fragile X Awareness Day. The Erie Proclamation urges "all fellow citizens to support efforts to promote knowledge of the disorder and research projects aimed at treatment. Thank you, Lisa!

Please Consider: Human tissue from people of all ages, donated at the time of surgery or death by people of all ages, or after a miscarriage or pregnancy termination, is a precious resource on which researchers depend. This is not an easy topic to think about, but, for many, there is satisfaction in helping to fight this scourge of our children. You can call Doreen DiMeglio, (800) 847-1539, at the Brain and Tissue Bank for Developmental Disorders in Maryland, or Katie Clapp, (978) 462-1866 at FRAXA to learn more or to register. The MIND Institute in California has a brain bank as well; you can call Dr. Randi Hagerman directly at (916) 734-6348. We will all be working together on this important cause. We would also like to thank Lynne Wolfe for choosing to donate her father's brain to science when, sadly, he died in the spring.

Report from Washington:

by Mary Beth and David Busby

Last year, with your help, the help of other Fragile X advocates, and that of Representatives Delahunt and Watkins, Senators Hagel and Edwards, and other sponsors of the Fragile X Breakthrough Act of 1999, we achieved a landmark victory: passage of the Children's Health Act of 2000.

As you know, among its other provisions, this new law authorized the establishment of at least 3 Fragile X research centers and a loan repayment program to encourage young scientists who conduct pediatric research. The next step is for the Congress to provide funding for these centers and the loan program.

You, your family and friends can help a lot by writing to your Members of Congress (both Senators and your Representative) today asking him or her to support funding for Fragile X research. The sample letter below offers some ideas, but feel free to express your own thoughts.

If you have questions call David Busby at (202 824-8820) or email him at (busby.david@dorseylaw.com).

SAMPLE LETTER:

Date

For Representatives:

The Honorable John Doe
The United States House of Representatives
Washington, D.C. 20515

Dear Honorable John Doe,

For Senators:

The Honorable John Doe
United States Senate
Washington, DC 20510

Dear Senator Doe,

My child (or grandchild, etc.) (name) has Fragile X, the most common cause of inherited mental retardation. Federal financial support for research on Fragile X is authorized in the Children's Health Act of 2000. I am writing now to request your support for an appropriation of at least \$10 million in the fiscal year 2002 Labor - HHS - Education Appropriations Bill.

The Children's Health Act directs the National Institute of Child Health and Human Development to expand, intensify, and coordinate research on Fragile X. It also authorizes the establish-

ment of at least three Fragile X research centers through grants and contracts with public or private nonprofit institutions. To make it possible for health professionals to enter this research field, it authorizes repayment of a portion of their educational loans.

Fragile X is still not well understood, even in the medical profession. Yet it affects one in 2000 boys and one in 4000 girls. One in every 260 women is a carrier. Most children with Fragile X requires a lifetime of special care at a cost of over \$2 million.

Dr. James Watson, Nobel Laureate and discoverer of the DNA Double Helix stated recently: "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."

Current research efforts hold great promise for the development of safe and effective treatments, but additional support for these efforts is urgently needed. I therefore urge you to do all that you can to provide \$10 million to NICHD for the establishment of Fragile X research centers, and \$2 million to implement the loan repayment program.

I appreciate your attention to this request, and hope I can count on your support.

Sincerely,

Name

Address



THREE NEW FRAXA FELLOWSHIPS AWARDED

r e s e a r c h

Effects of FMRP on Glutamate Receptor Trafficking

ROBERTO MALINOW, PH.D., PRINCIPAL INVESTIGATOR

JULIUS ZHU, PH.D., POSTDOCTORAL FELLOW



Cold Spring Harbor Laboratory; \$35,000

By Julius Zhu and Katie Clapp

When a nerve cell receives a signal from another nerve cell, two things happen:

1. The receiving cell passes the signal on to other cells. The brain is composed of a vast number of cells arranged in a network to receive and process input signals.
2. The receiving cell changes as a result of this experience. In particular, the cell's synapses, where inputs are received, undergo changes. It is now generally believed that the brain learns and remembers things by changing the strength of synapses. People with Fragile X often have difficulty in learning and remembering new knowledge, probably because this mechanism is impaired.

Recent studies suggest that synaptic changes result from the movement in and out of synapses of some proteins known as glutamate receptor proteins. But how is the fragile X protein involved?

Recent research suggests that the Fragile X protein (which is lacking in people who have Fragile X syndrome) regulates the expression of a few important intracellular signaling molecules. Preliminary evidence collected by Dr. Zhu and his colleagues indicates that some of these molecules and their related signaling pathways are involved in controlling glutamate receptor trafficking. Dr. Zhu and his colleagues decided to investigate how these pathways signal the delivery and removal of glutamate receptors in normal mice and then to find out if these signaling pathways are altered in Fragile X knockout mice. (One kind of glutamate receptor is the AMPA receptor, the target of a new class of drugs called AMPAkinases, which are currently being tested in fragile X animals by the Greenough lab, with FRAXA funding.)

Dr. Zhu previously trained in the lab of Nobel prize winner

Dr. Bert Sakmann at the Max Planck Institute in Heidelberg, where the state-of-art multiple whole-cell recording technique was first developed. He is now a postdoctoral fellow in the lab of Dr. Roberto Malinow at Cold Spring Harbor Laboratory. He will combine the multiple whole-cell recording technique with other cutting-edge techniques, including recombinant DNA delivery, and electron and two-photon laser scanning microscopy, to address these questions. The findings of their research may suggest many more molecular targets useful for genetic or pharmacological therapies for fragile X syndrome.

Dr. Zhu's FRAXA fellowship is funded with major support by Tyler Gruzin's friends and family, who believe in his future and are committed to helping find a cure.

Translational Regulation of Fragile X Syndrome Proteins

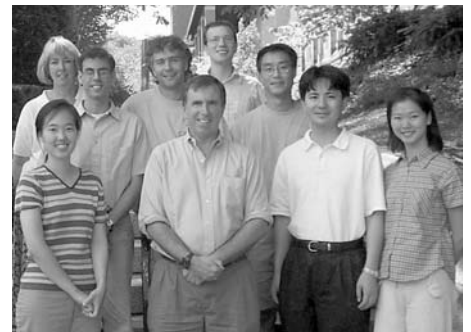
JUSTIN FALLON, PH.D., PRINCIPAL INVESTIGATOR

SANDRA WON, PH.D., POSTDOCTORAL FELLOW

Brown University; \$35,000

By Justin Fallon

Fragile X syndrome is caused by the absence of the FMR1 gene's protein product, FMRP. However, little is known about the normal function and regulation of FMRP or how its loss leads to cognitive impairment. We do know that the translation of RNAs into proteins at synapses (the junctions between nerve cells) is essential for learning and memory. A growing body of evidence suggests a role for FMRP in RNA binding, transport, and/or translation. Intriguingly, FMR1 messenger RNA is present at the synapses and its translation can be stimulated by neurotransmitters. The close relationship between FMRP protein and message and RNA metabolism at synapses provides a pathway to link FMRP function at the molecular level to its role in



update

higher functions in the brain. Therefore, an understanding of the translational regulation of FMRP is necessary for understanding the molecular mechanisms leading to Fragile X mental retardation.

We are investigating the molecular mechanisms of activity-induced Fragile X protein synthesis using a combined molecular, cellular and biochemical approach in cultured neurons and in mice. Of special interest is the potential role of a particular process, recently identified in our laboratory, by which synaptic mRNAs are translated into proteins. The mRNAs encoding FMRP and a related protein, FXR2P, contain unique tags indicating that they may be regulated by this process. The overall goal of our studies is to understand the role FMRP plays in translating other proteins and thereby strengthening and/or weakening synapses and, ultimately, enabling learning and memory. Such information could contribute to designing strategies and treatments for overcoming the loss of FMRP in Fragile X syndrome.

Molecular Basis of Fragile X Syndrome

LYNNE REGAN, PH.D., PRINCIPAL INVESTIGATOR

LILI ARAMLI, PH.D., POSTDOCTORAL FELLOW

Yale University; \$35,000

By Katie Clapp

A normal role of the Fragile X Protein, FMRP (which is lacking in fragile X syndrome) is to bind and interact with a number of RNAs (RNAs are direct products of genes) within nerve cells. Presumably these RNAs have important roles, which may be disrupted when FMRP is not present, leading to symptoms of fragile X syndrome. The Regan lab team has been working to identify these RNAs and their functions in the brain. Dr. Aramli will use a combination of approaches to identify the RNA targets of FMRP, to establish their significance in living animals, and to investigate the role of the interaction between FMRP and the RNAs. She will also use a variety of biophysical techniques to understand the mechanisms of these interactions. Understanding these effects may lead to possible therapeutic interventions, even providing information for the design of drugs to rescue some of the normal interactions between FMRP and the RNAs it binds.

GRANTS AND FELLOWSHIPS RENEWED

The following updates were written by Michael Tranfaglia, MD, FRAXA Medical Director

Study of the Synaptic Function of the Fragile X Mental Retardation Protein

CLAUDIA BAGNI, PH.D.

Univ. of Rome; \$28,000; (2000: \$37,000)

Dr. Bagni has developed a promising new method for understanding the translation of the fragile X protein and related proteins in the body and at the synapses of nerve cells. Dr. Bagni is collaborating with several other teams, including Dr. Ben Oostra and Dr.'s Barbara Bardoni and Jean-Louis Mandel, all of whom have received some support from FRAXA.

Restoration of Natural FMR1 Expression in FMR1 Deficient Mice by P1 Artificial Chromosome (PAC) Transgenesis

ROBERT BAUCHWITZ MD, PH.D.

Columbia Univ., \$155,000; (2000: \$90,000); (1999: \$90,000), (1998: \$17,000)

Dr. Bauchwitz's research team is now laying the groundwork for an eventual cure for fragile X by determining exactly which DNA sequences must be present for normal functioning of the fragile X gene FMR1. Most genes (including FMR1) contain far more material than is actually translated into protein, making them very large and hard to work with in their natural state. Dr. Bauchwitz is working to find the minimum functional length of DNA which will replace the defective fragile X gene. This is a first step in developing practical gene therapy for fragile X.

Special thanks to our Research Funding Partner, The Preiser Fund of Long Island, in honor of Jonathan Preiser and in memory of Marilyn Garret. We also gratefully acknowledge Eric Rosen for all he has done working alongside Dr. Bauchwitz. This past year he has been a tremendous help in our quest to reach our goals.

Studies of Synaptic Regulation of Protein Synthesis and Possible Therapeutic Approaches to Fragile X

WILLIAM GREENOUGH, PH.D.

Univ. of Illinois; \$194,000; (2000: \$238,000); (1999: \$136,000); (1998: \$150,000); (1997: \$55,000)

We now know that one of FMR protein's primary functions is to regulate protein synthesis in dendrites (the receiving end of synapses) in response to neural activity; however,

this involves many other proteins in a complex biochemical pathway. Some of these other proteins could be valuable “targets” for development of potential therapies involving small molecules (i.e. simple drugs). The Greenough group has been the world leader in precisely delineating this pathway, and their highly productive work continues.

Behavioral Characterization and Therapeutic Interventions in FMR1 Knockout and Transgenic Mice

RICHARD PAYLOR, PH.D.

Baylor College of Medicine; \$110,000; (2000: \$109,000)

Although the fragile X mouse model has been available for several years, it has proven to be surprisingly difficult to pinpoint specific measurable and reproducible cognitive and behavioral differences, compared to normal mice. Dr. Paylor is a leading expert on cognitive and behavioral paradigms in mice, and he has designed an extensive battery of tests to measure the actual differences in fragile X knockout mice.

Unfortunately, the city of Houston, Texas was hit by a terrible flood this spring, and Baylor College of Medicine sustained significant damage to equipment and labs. Dr. Paylor and others at Baylor have done a wonderful job recovering from the storm.

Reactivation of the FMR1 Gene in Fragile X Patients Cells in Culture

GIOVANNI NERI, PH.D.

Catholic Univ., Rome, Italy, \$18,000; (2000: \$32,000); (1999: \$30,000)

Dr. Neri’s group has previously shown that it is theoretically possible to reactivate the FMR1 gene by demethylation and to produce some normal protein, even from fragile X cells with a full mutation. However, the chemical demethylation used for this effect is far too toxic for use in humans, and methylation is a widespread mechanism for regulation of gene expression in all cells, so the potential for harm from non-specific demethylation is too great to allow consideration as a therapeutic option. Dr. Neri and colleagues are continuing their work to identify more specific ways to reactivate the gene, which could be of use in potential therapies.

Transgenic Mouse Model of Fragile X Syndrome: Temporal and Spatial Restriction of FMR1 Expression in Mouse Forebrain

ERIC KANDEL, MD.

Columbia Univ., \$110,000; (2000: \$150,000); (1999: \$150,000)

The fragile X knockout mouse, developed by Dr. Ben Oostra in the Netherlands, has been available for some time; it entirely lacks the fragile X protein throughout its life and displays some symptoms which closely resemble the human fragile X syndrome. While this is a useful model for telling us what the gene does, it cannot tell us some very important things, such as when during development the fragile X gene is used most, or where in the brain it performs any of its several known functions. However, the new technology of conditional knockout mutation allows the gene to be selectively deleted in various brain regions, or turned on and off at will during different stages of development — powerful tools for answering the when and where questions. Nobel Laureate Dr. Eric Kandel is leading this ongoing project; he reports that the conditional knockout mouse has been bred and is now ready for testing.

Transport of the Fragile X Protein and Generation of Monoclonal Antibodies to FMRP, FXR1 and FXR2

ALAN TARTAKOFF, PH.D.,

Case Western Reserve Univ.; \$80,000; (2000: \$93,000); (1999: \$30,000); (1998: \$30,000)

One of the less well-studied functions of the fragile X protein is its role in transporting other proteins and/or mRNAs from the nucleus to the dendrites of nerve cells. Dr. Tartakoff is an expert in studying the nuclear transport mechanisms and is working to define how this process works in the case of fragile X.

Dr. Tartakoff has also received a grant from FRAXA to develop and distribute antibodies to the fragile X protein, FMRP, and related proteins, FXR1p and FXR2p. In the first year of this grant, Dr. Tartakoff has developed three monoclonal antibodies which are now available to other investigators (see article in the **RESEARCHERS’ CORNER**). We are extremely grateful to Dr. Tartakoff for tackling this particular project, because the lack of good, widely-available antibodies has been a bottleneck which has slowed progress in the fragile X field.

Researchers' Corner

This new section of the FRAXA Update is intended especially for researchers. Along with providing direct research grants and fellowships, FRAXA aims to increase the pace of progress by providing opportunities for scientists to interact to benefit from the expertise of others. As Fragile X becomes an ever more highly specialized and complex field, no one person or lab can realistically solve the mystery of fragile X alone. The field will progress ever faster if collaborations flourish and more investigators apply their particular talents and expertise to the challenge. Please email kclapp@fraxa.org to submit an item for the next FRAXA Update.

NEW! Researchers' Fragile X Listserv

Recently, several scientists have suggested that we establish an email exchange for researchers. Accordingly, all investigators, postdocs, and graduate students who are active in fragile X research are cordially invited to join the new FRAX-L listserv, kindly sponsored by Dr. Stuart Brown, Assistant Dean of Students at University of Connecticut, and member of the FRAXA "family."

The goal of the Researchers' listserv is to advance biomedical research by facilitating information exchange, collaborative inquiries, requests for reagents, and so forth. Although fragile X research is a competitive field, recent meetings and many other exchanges have demonstrated that it is also a very collaborative field. We hope that FRAX-L will be a useful tool and that the participants will help to make it successful. All of the families affected by fragile X have so much to gain.

How can this listserv be most useful to the fragile X research community? Discussions might address behavioral/animal models, the roles of FMRP, reagents, protocols, troubleshooting, etc. If it becomes active, it can be divided into topics as time goes on. Whenever possible, we will post announcements of new grants and Requests for Applications that might be of interest.

This Researchers' listserv is a counterpart to the very active general fragile X listserv that FRAXA established in 1995. If there is ever a need for family input or a call for subjects for an experiment, we will be happy to post it to the general listserv, collect responses, and report them back to investigators.

Researchers can join FRAX-L by sending an email to kclapp@fraxa.org Everyone can join the general fragile X listserv at www.fraxa.org/html/listserv.htm

Available: Continuous Performance Task Software

We have designed a computerized Continuous Performance Task (CPT) that I think is quite appropriate for assessing attention and impulsivity in both mental-age-matched typically developing individuals and individuals with fragile X syndrome. I would like to offer it to other researchers who might be interested in measuring such variables. It is based on the classic attention paradigm of two parts: 1) hit the space bar when you see a red square; 2) hit the space bar when you see a red square that follows a blue triangle. The program automatically tallies hits and false alarms and takes about 12 minutes to complete. The use of a D prime statistic will be helpful when covarying out participant's attention on other higher level cognitive tasks. The CPT was written with E-prime software (formerly called MEL), so you may have to buy E-prime.

I want to send this offer out to the community because we spend so much time (and money) designing nifty measures and then a lab in the next town over designs a VERY similar tool, and the next thing you know, we have failure to replicate results. I would love to have more of an exchange of experimenter-designed measures in the community.

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continued on page 8

Researcher's Corner

continued from page 7

Available: Monoclonal Antibodies Which Detect Human FMRP

Last year, FRAXA provided a grant to Dr. Alan Tartakoff at Case Western Reserve University to produce monoclonal antibodies to human FMRP. Over the past several years, it had become clear that one major roadblock in the field has been the relative lack of specific FMRP antibodies. The first antibodies are now available. Dr. Tartakoff reports:

We have used recombinant fragments of human FMRP carrying a (his)₆-tag at the N-terminus (RNA, 5, 1248 (1999)) to immunize FMR1 knock-out mice (Jackson Lab). 35 hybridoma supernatants react with distinct recombinant fragments of FMRP (judging from ELISA assays and Western blots) and three detect intact FMRP upon Western blotting of HeLa cell lysates.

These three IgG monoclonal antibodies (7B8, 2F5, 6B5) react with the fragment of FMRP extending from the N-terminus to residue 204, as judged by ELISA and Western blotting. They detect a single protein band in lysates of HeLa cells and normal human fibroblasts and this band is coincident with the signal which is detected by the commercial (Chemicon) antibody number 2160. It is obviously distinct from bands in HeLa extracts which react with polyclonal anti-FXR1 and anti-FXR2 antibodies. This is surprising since the recombinant fragment of FMRP with which this antibody reacts is nearly identical to N-terminal sequences of FXR1 and FXR2. The new antibodies give no specific signal in Western blotting using lysates of fibroblasts from a Fragile X patient.

Small samples of culture supernatants are available and we have recently initiated production of corresponding ascites. Investigators wishing to obtain samples should contact Dr. A. M. Tartakoff, Pathology Institute, Case Western Reserve University School of Medicine, 2085 Adelbert Road, Cleveland, Ohio 44106 (amt10@po.cwru.edu). Since supplies are limited at present, investigators should request samples only if they intend to use them for specific experiments in the near future. Investigators interested in any of the MAb's which do not react with intact FMRP in Western blots should describe the experiments they envisage. Ongoing immunizations have begun with fragments of FMRP, FXR1 and FXR2 which are altogether distinct.

Neuroscience Faculty Search

In September 2000, the Eunice Kennedy Shriver Center for Mental Retardation, Inc. merged operations with the University of Massachusetts Medical School. In partnership with the Medical School, the Shriver Center announces a major effort to expand its programs in translational and basic neuroscience. The Center's mission is to understand neurological and behavioral development, with special emphasis on mental retardation and developmental disabilities, and there is a particular interest in conducting research on fragile X.

Positions open include Associate Director of Research, Translational Neuroscience and several Neuroscience Faculty positions at the rank of Assistant or Associate Professor within the Neurobiology of Developmental Disorders Division (formerly Biomedical Sciences). For more information, consult the website: www.shriver.org. Potential applicants may contact: William J. McIlvane, Ph.D., Chairman, Faculty Search Committee, E. K. Shriver Center, 200 Trapelo Road, Waltham, MA 02452, phone 781-642-0153
William.McIlvane@umassmed.edu.

Update from the National Fragile X Foundation

We hear you! The results of our extensive Fragile X Needs Assessment can be found in the Summer 2001 issue of the Foundation Quarterly. Based on the 463 surveys returned, we have begun work on a series of specialized pamphlets that will address the topics you told us were important.

Many of you have already begun to contact the NFXF in regards to the 8th International Fragile X Conference to be held in Chicago, July 17-21, 2002. Let me reassure you that we are already hard at work preparing for that important event. We hope you are planning on attending! The registration form will be available on October 1, 2001. Look for it in our Fall 2001 Foundation Quarterly,

or online at FragileX.org. Of course, we're always happy to mail or fax you a copy.

The NFXF now has its entire, 200 + page website on CD. To purchase the FragileX.org Website CD — a low-cost alternative to going online — be sure to contact us at 1-800-688-8765.

I hope you were able to spend National Fragile X Awareness Day in a way that was meaningful to you and your family.

Robby Miller, Executive Director
PO Box 190488 / San Francisco, CA 94119
NATLFX@sprintmail.com

Fragile X Research Meeting Held at Banbury



Paul and Randi Hagerman, Sally Till, Steven Warren and Ted Brown

clear that a growing number of scientists are becoming interested in fragile X, and that progress is accelerating, especially the area of identifying proteins and RNAs which work with the fragile X protein in the brain. Planning is under way for next year's meeting, which will focus on proteins and RNAs.

The second annual Fragile X Banbury meeting was held at Cold Spring Harbor, New York, in March. Funded by the National Institute of Mental Health (NIMH), with additional support from the National Institute of Child Health and Human Development (NICHD) and FRAXA, these small, intense meetings enable scientists to present and discuss new findings. This year's meeting made it



Jennifer Darnell and Robert Bauchwitz

Advocating for Research

FRAXA members have been involved in many events aimed at shining the spotlight on fragile X research. Here are a few examples.

Working with the National Institutes of Health (NIH)

FRAXA Medical Director Mike Tranfaglia, Vice President Mary Beth Busby and President Katie Clapp have all helped to evaluate research funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). Katie served on an advisory group which recommended guidelines for the NICHD's priorities over the next 5 years. She has served on NIMH study sections to evaluate research proposals. Mike Tranfaglia and Mary Beth Busby have both served on teams evaluating NICHD-funded Mental Retardation Research Centers. FRAXA members are also working with NICHD on their new fragile X brochure.

A Congressional Luncheon FRAXA and two dozen advocacy organizations, including the National Fragile X Foundation and Conquer Fragile X Foundation, have formed the Coalition for Children's Health to advocate full funding for the Children's Health Act. In June, the Coalition sponsored a Congressional luncheon, entitled **Expanding Federal Research Efforts at NIH for Childhood Diseases and Disorders**. Mary Beth Busby, FRAXA Vice President and mother of Robert and Jack, who both have fragile X, addressed more than 50 key congressional staffers, on behalf of the all of the groups.



"Brain Breakthroughs" with Mohammed Ali

In June, the Society for Neuroscience held a luncheon on Capitol Hill called **Brain Breakthroughs: Delivering Results**. The Society brought together NIH leaders, neuroscience researchers, and a few representatives of advocacy organizations, including FRAXA's Katie Clapp. The goal: to educate Members of Congress who sit on health-related committees and other key players about neuroscience and the real impact research has on the lives of their constituents. The stars of the luncheon were Mohammed Ali, who has Parkinson's disease, and his wife Lonnie, who spoke eloquently about what neuroscience research could mean for her family.

FRAXA Booth at Society for Neuroscience Annual Meeting

The Society for Neuroscience is a professional society of researchers who study brain disorders. Every year, FRAXA staffs a booth at the Annual Meeting, where over 20,000 neuroscientists gather, including most of the researchers FRAXA currently supports. We see presentations of current research, talk with "our" researchers, and recruit new investigators to the fragile X field. This year's meeting is November 10-15 in San Diego.

FRAXA EVENTS

Help FRAXA Accelerate Research

FRAXA has been fortunate to have grown exponentially, from a simple idea in 1994 to a million+ dollar research foundation today, thanks to many generous supporters who are committed to improving the lives of everyone with fragile X. This year, the economy has slowed, and this has hurt FRAXA's fundraising. At the same time, our efforts to accelerate fragile X research have succeeded dramatically. A few examples:

- FRAXA's efforts have resulted in a special five-year research initiative funded jointly by the National Institute of Child Health and Human Services (\$5 million over 5 years), National Institute of Mental Health (\$1 million over 5 years) and FRAXA (\$1 million over 5 years).
- The Children's Health Act became law, authorizing at least 3 fragile X research centers
- Two Nobel Laureates, James D. Watson and Eric Kandel, joined FRAXA's Scientific Advisory Board
- In 1994, FRAXA funded one grant for \$17,800. In the year 2000, FRAXA supported 27 research teams around the world, for a total of \$1,458,531. This year, additional top researchers have joined the fragile X field, and more grant applications are waiting to be funded, **if** we can raise the funds.

There are many, many ways families and friends can help accelerate research. Foremost is helping to find the funds to support the projects described here and the other projects now waiting for funding. You might consider gathering a group of family and friends to raise funds for a specific project, like the Fragile X Alliance of Ohio, the family and friends of Tyler Gruzin in Maryland, and the Preiser family and friends in New York. You may wish to participate in studies or to become a tissue donor. You might choose to devote your efforts to political advocacy (see the Report from Washington by David and Mary Beth Busby) or to help raise awareness of fragile X. All of this is important and all these efforts will build upon each other to enable us to reach our goals: effective treatments and ultimately a cure for fragile X.

The following articles and announcements are included to suggest ways in which each and every person can help to make an enormous difference. Now that so much exciting research is underway, it is more important than ever to grow our team and move forward even faster than before.



Above: Megan Massey, parent and FRAXA Director, **Sopranos** star Vince Curatola, (a.k.a. gangster Johnnie Sack), Katie Clapp, and **Sopranos** star Dan Grimaldi, who plays henchman Patsy Parisi. Below: Parent Marilyn Therrel and Mary Higgins Clark



by Mary Beth Busby

Those of you who were fortunate enough to attend the glorious event that Mary Jane Clark and her sister, Margaret Ann Behrends, chaired in May still likely have visions of flowers, twinkling lights and romantic Japanese lanterns dancing in your heads. Actually, what

dances in my head most of all was a little pre-dinner talk by Dr. Eric Kandel, our Nobel Laureate researcher. His message was one of inspiration and can-do optimism. In fact, he pointed out that only ten months after he first became involved with FRAXA and fragile X research, he won his Nobel Prize! Dr. Kandel, along with Mary Higgins Clark, sent us all out into the night with renewed enthusiasm for our work.

It may not seem so, but it's time to get out your calendar and mark the date for next year's gala. It will be back in Washington next April 29th, 2002, at the Four Seasons Hotel in Georgetown. That will be a Monday night, so plan to make a long weekend of it. For you political types, we plan to have another Lobby Day on Tuesday, April 30th, starting with a breakfast at a downtown hotel and then fanning out over the Hill for appointments with Congressional staffers and — who knows? — maybe even some Members and Senators. So do please mark your calendars, Gala: Monday, April 29, 2002 and Lobby Day: Tuesday, April 30, 2002.

AUSTIN GALA



Sam's Club in Austin, TX presents a check for FRAXA to Claudia Burnett, Katie Clapp, and Mary Higgins Clark, in honor of Mrs. Clark

May was gala month for FRAXA this year! On May 18th, hundreds of people gathered at The Four Seasons Hotel in Austin Texas for a wonderful evening of dinner and dancing. Guest of honor Mary Higgins Clark thrilled our Texas troups when she spoke of her determination to solve the mystery of fragile X. Mrs. Clark's grandson David is affected with fragile X.

Claudia and Michael Burnett and their friends Jill and Bryan Stevenson organized the event, including a very successful silent auction. The following evening, Mary Higgins Clark joined the Burnett family and their friends at their home to celebrate the event's success. We hope this will be the first of many FRAXA events in Texas.

Stone Pony Party in Asbury Park

Denise Sabo will hold a benefit for FRAXA on Sunday, October 14th at the Stone Pony in Asbury Park, New Jersey. Bring all your friends to enjoy music by the Soul Engines, two comedians, and an Elvis impersonator! Bruce Springstein first became famous at the Stone Pony (www.stoneponyonline.com); he still shows up often, and we have high hopes that he will join us! 3pm until whenever; cash bar and food available, entertainment not suitable for children. Tickets are \$20 and will be available through Ticketmaster, at the door, or from Denise Sabo (phone: 201-804-6110; email: dolphi4752@aol.com)

Patrick's Pals Win Again!

We wish that each and every one of you could be present at one of our annual Patrick's Pals fundraisers because it is impossible to adequately describe to you the immense feelings of success, hope, gratitude and love that is generated by the participants of these events. In June, in Cambridge, MA, our fifth annual Patrick's Pals 3-on-3 Basketball Tournament raised more than \$25,000 for FRAXA!

The wonderful thing is that over 100 people played in the basketball tournament and more than 200 others who could not be there made generous cash donations. Additional individuals and companies demonstrated their support with donations of prizes, auction items (we had our first ever silent auction of sports memorabilia at the tournament), t-shirts, lunches, arts & crafts materials for the children, printing services and more.

The tournament grew this year in more ways than one. The silent auction was a lot of fun and instigated some



Patrick's Pals Organizers: Jim Marks, Bill Rome, Scott Katz, Honorary Pal Steve Burton, Steve Savarese, Jon Pressman, Jimmy Vershbow Not pictured: Pamela Vershbow

serious competition of its own! Everyone enjoyed the addition of local sports newscaster Steve Burton as our "Honorary Patrick's Pal" to kick off the day's events. And, the basketball played rose to new levels, and we now have a new first place 'team to beat' for next year: Kevin Maloney, Chuck Trapani, Chris Feeney, and Andrew Solitro.

We want all of the fragile X families reading this to know that we have found a world of good people out there ready and willing to help our children and that we are sure you can too! To all of Patrick's Pals, thank you for another great year!

— Pamela & Jimmy Vershbow

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: December 1, 2001 and May 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.



Mary Higgins Clark Gala
in New York City

FRAXA
RESEARCH
FOUNDATION
45 Pleasant Street
Newburyport
Massachusetts 01950

FRAXA UPDATE

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FRAXA would like to thank Network of Newburyport, MA for hosting the FRAXA website and email. Network has donated this important resource for the past 6 years

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

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"NEVER

DOUBT

that a small

group of

thoughtful,

committed

citizens can

change the

world.

INDEED,

it's the only

thing that

ever has."

— Margaret Mead

MAJOR RESEARCH ADVANCE

For the first time, scientists have identified specific genes in the brain that are affected by the lack of the fragile X protein. The new research demonstrates that the fragile X protein controls the fate of a number of other proteins in brain cells. This may explain how the absence of this single protein causes the range of physical, cognitive and behavioral symptoms seen in people with fragile X.

Basic research breakthroughs like this one have led us to the knowledge we have today, that will ultimately lead to a cure for fragile X.

Every major discovery so far has increased our understanding of what goes wrong in fragile X and shed light on ways to treat it. This finding is exciting because it links the fragile X protein to thirteen other proteins; these proteins are responsible for normal brain function and for some of the symptoms of fragile X. If we can someday learn how to manipulate these other proteins, this could be another avenue leading us to specific, effective treatments for fragile X.

"Our findings suggest entirely new ways of thinking about treating the problems these patients have," says Robert B. Darnell, M.D., Ph.D., a principal investigator of the current research. The work is reported in two papers appearing in the Nov. 16 issue of the journal *Cell*. One study, led by Dr. Robert Darnell and Dr. Jennifer Darnell, professors at Rockefeller University, was funded by FRAXA and the National Institutes of Health. The other study was conducted by Steven T. Warren, Ph.D., an investigator at Emory University School of Medicine and Howard Hughes Medical Institute.



Jennifer Darnell, Robert Darnell and Kirk Jensen discover molecular targets of the protein missing from people with fragile X syndrome.

Continued on page 4

Does Fragile X Protect Against Cancer?

People with fragile X have a lower risk of cancer than individuals without the disorder, according to Danish researchers. Determining the source of this decreased risk could shed light on how genetic mechanisms prevent cancer from developing.

Also in this issue:

- Report from Washington
- Fragile X Research Centers
- Calendar of Events

The encouraging new findings were reported in the October 2001 issue of the *American Journal of Medical Genetics* (103:226-230). The news was distributed by Reuters News Services to newspapers, television, internet and other news outlets around the world. The fragile X genetic

continued on page 6

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

The Congress

As some of you know, both the Senate and House Appropriations Committees issued their annual Reports to accompany their appropriations to the National Institutes of Health, the Centers for Disease Prevention and Control, and other parts of the Department of Health and Human Services. We are delighted that these Reports, in effect, implemented the fragile X provisions of the Children's Health Act of 2000. This is a real victory for all you FRAGILE X ADVOCATES who wrote and called your Members of Congress! Please write them again now to thank them!

Both Reports encourage the National Institute of Child Health and Human Development (NICHD) to enhance its research efforts on fragile X. The Senate goes a step further by urging the NICHD to provide sufficient funds for "at least three fragile X research centers," and it specifically commends NICHD for teaming up with FRAXA to jointly fund new research.

The House Report also urges the National Institute of Neurological Disorders and Stroke (NINDS) to enhance its research activities on fragile X.

Both Reports encourage the National Institute of Mental Health to support fragile X research in concert with the NICHD and NINDS.

The Senate Report urges the Director of the National Institutes of Health (NIH) to use the Act's new "Pediatric Research Loan Repayment Program to . . . encourage promising investigators to enter various areas of pediatric research, particularly in the areas of Duchenne muscular dystrophy and fragile X."

And, finally, the Senate Report supports the Center for Disease Control in "further research and demonstration projects to facilitate the translation of new scientific knowledge into applied newborn public health screening programs, particularly in the areas of fragile X Syndrome and Cystic Fibrosis."



The National Institutes of Health

On September 7, Katie Clapp and Mary Beth and David Busby met with the Acting Director of the NIH, Dr. Kirschstein, her Deputy, Dr. Maddox, and the Director of the National Institute of Child Health and Human Development, Dr. Alexander. We summarize a pleasant, productive and constructive meeting, as follows:

Dr. Alexander and Dr. Maddox feel that the fragile X research centers can be established most expeditiously and economically as affiliates of presently existing NICHD Mental Retardation and Developmental Disability Centers. Dr. Alexander said that three or more centers would each be funded at up to \$750,000 "direct costs". He announced the following timetable:

- November: NICHD issues Requests for Applications for grants for fragile X Centers.
- March/April: Grant applications are received for review.
- September/October: Successful grant applications are funded.

Dr. Maddox suggested, and it was agreed, that the NIH will host a meeting of fragile X researchers on the NIH campus.

Dr. Kirschstein discussed the implementation of the "Pediatric Research Loan Repayment Program" in the Children's Health Act of 2000. She announced that the Office of Management and Budget has approved program guidelines and that the President's FY 2002 Budget requests money to fund loan repayments for 250 researchers, for the combined Pediatric and Clinical Research Loan Repayment Programs. She expects the funding to increase in fiscal year 2003.

Katie Clapp discussed the state of fragile X research and its relationship with autism research. She reviewed exciting new work being funded by FRAXA and expressed FRAXA's appreciation for the projects being jointly funded by FRAXA with the NIH.

Washington Gala and Lobby Day

Mark your calendars for the fifth annual Mary Higgins Clark Gala, to be held Monday evening, April 29, 2002, at the Four Seasons Hotel in Washington. Co-Chairs: Kitty deChiara, Diane Rehm, and Mary Beth Busby. Host: Roger Mudd. Honoree: Mary Higgins Clark. Dancing to the music of Sydney. Y'all come!

On Tuesday, April 30, FRAGILE X ADVOCATES (that means you!) will have breakfast at the Capitol and then branch out over the Hill to talk to their Members of Congress about fragile X. As those of you who attended the Lobby Day in April of 1999 will remember, that was where our lobby effort got started. We've come a long way!

Here are your Members of Congress who serve on the Health Subcommittees of the Senate and House Committees on Appropriations. They are the key players in funding the fragile X Centers and Researcher Loan program.

Subcommittee on Labor, Health and Human Services and Education Members:

Senate:

Tom Harkin, Chairman,
Iowa
Ernest Hollings, South
Carolina
Daniel Inouye, Hawaii
Harry Reid, Nevada
Herb Kohl, Wisconsin
Patty Murray, Washington
Mary Landrieu, Louisiana
Robert C. Byrd, West
Virginia
Arlen Specter, Ranking
Member, Pennsylvania
Thad Cochran, Mississippi
Judd Gregg, New
Hampshire
Larry Craig, Idaho
Kay Bailey Hutchison, Texas
Ted Stevens, Alaska
Mike DeWine, Ohio.

House:

Ralph Regula, Chairman,
Ohio
David R. Obey, Wisconsin
C.W. Bill Young, Florida
Steny H. Hoyer, Maryland
Ernest J. Istook, Jr.,
Oklahoma
Nancy Pelosi, California
Dan Miller, Florida
Nita M. Lowey, New York
Roger F. Wicker, Mississippi
Rosa DeLauro, Connecticut
Anne Northup, Kentucky
Jesse L. Jackson, Jr., Illinois
Randy "Duke" Cunningham,
California
Patrick J. Kennedy, RI
Kay Granger, Texas
John E. Peterson, PA
Don Sherwood, Pennsylvania

If you live in the state or congressional district of any of the above Members of Congress, please write and thank them for funding fragile X research! Your letters made all the difference in the past and will in the future! Also, make an appointment to visit with them when they are home this Fall. They want to see you (and your vote)!

Fragile X Heroes



Our four staunch champions who sponsored the fragile X Breakthrough Act of 1999, carried its provisions into the Children's Health Act of 2000, and went to bat for us this year before the Senate and House Appropriations Committees were: (clockwise from top left) Senators John Edwards of North Carolina and Chuck Hagel of Nebraska, and Representatives William Delahunt of Massachusetts and Wes Watkins of Oklahoma.

Update on Fragile X Research Centers

On November 9th, Dr. Duane Alexander, Director of NICHD, called to report the following adjustments in the plans for implementing the fragile X Research Centers:

The timetable has changed: Request for applications for Centers will be published by NICHD in December.

The eligibility requirements for submitting an application for Center funding have been clarified: Dr. Alexander reports that only the Principal Investigators of the fourteen Mental Retardation Research Centers (MRRC) currently funded by NICHD will be eligible to apply as Principal Investigators of the new fragile X Research Centers. However, by establishing a collaboration with one of the existing MRRC centers, any investigator at any qualified institution can apply to found and direct a fragile X research center.

r e s e a r c h

“The problem of fragile X is intriguing, because the loss of a single protein causes a variety of behavioral and physical changes,” says Jennifer Darnell, Ph.D. Previously, it was known that the fragile X protein, FMRP, binds to messenger RNA (mRNA) molecules — which carry genetic information (DNA) from a cell’s nucleus to its protein-making machinery — yet the specific mRNAs involved as well as the overall purpose of this protein remained elusive. Now, the researchers present evidence that FMRP may turn up or down the production of certain brain proteins by binding to their mRNA molecules. This type of protein regulation is a crucial aspect of every cell’s life, and in the case of brain cells, is essential for learning and memory formation. The Darnells have identified thirteen mRNAs that FMRP binds, and show that these mRNAs are misregulated in the cells of fragile X patients.

“We found FMRP binding sites in a population of mRNAs shown to be abnormally regulated in fragile X patients,” says Jennifer Darnell. “The proteins coded for by these mRNAs are likely to underlie the problems these patients have.”

Jennifer Darnell identified the mRNA targets by first discovering that FMRP recognizes and tightly binds loop-like structures in RNA, called G-quartets, which represent novel human RNA-binding sites. This finding is intriguing because these structures, which resemble in appearance loose knots along a string, are typically found in DNA and not RNA. After searching a computer database of known mRNAs for the G-quartets, she hit upon a significant finding: many of the mRNAs targeted by FMRP, and their corresponding proteins, play a role in learning and memory, the development of the bones of the face and in the formation of the nervous system — all brain activities involved in fragile X syndrome. In fact, almost all of the thirteen mRNAs identified have biologic functions which fit well with symptoms of fragile X syndrome:

- Six of the mRNAs are associated with the functioning of synapses – the points of contact between brain cells, where information is exchanged between the axon of one neuron to the dendrite of a second neuron. These mRNAs are thought to play roles in maturing and maintaining synapses; at least one is directly linked with learning and memory and another is implicated in the regulation of social behaviors and aggression.

- Three of the mRNAs encode proteins that are involved in growth of neurons: MAP1B is highly expressed in developing neurons, and appears to play an important role in the extension of axons and dendrites. Semaphorin 3F has effects on growth cones and is essential for axon pathfinding. ID3 is expressed in the proliferative zone of the hippocampus that gives rise to granule cells and dentate precursor cells.

- Two mRNAs encode proteins found particularly in brain and testes tissues. One of these, MINT, affects craniofacial development, which may explain why many people with fragile X have a long face and prominent brow. An additional target RNA may be linked with epilepsy; seizures affect some children who have fragile X.

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, FMRI, normally produces the protein, FMRP, but in fragile X syndrome, a mutation in this gene results in a lack of FMRP protein.

“It is possible that FMRP is responsible for shuttling certain proteins out to the individual

dendritic spines of neurons, and/or subsequently activating them at the appropriate time during development, as well as during adult memory formation,” says Jennifer Darnell. “This would explain how specific neuronal connections are strengthened to form memories.”

Meanwhile, Steven Warren’s group at Emory also had independently identified mRNA targets of FMRP, using a different technique called microarray, or “DNA chip,” analysis. Robert and Jennifer Darnell met Dr. Warren at the 2001 fragile X Banbury Meeting, the second of a series of annual fragile X research meetings established by FRAXA and funded by the National Institutes of Health and FRAXA. The Darnells and Dr. Warren began collaborating and discovered that nearly 70 percent of Warren’s targets contained the G-quartets.

Using DNA microarray “chip” technology, Warren’s group identified 432 mRNAs from cells in the mouse brain that normally are associated with FMRP. When they compared these to cells derived from people with fragile X syndrome, they identified 251 of those same

update :

mRNAs that were not correctly regulated in the absence of FMRP.

Finally, the researchers demonstrated that the thirteen newly characterized FMRP targets — identified in a test tube in Jennifer Darnell's case — are in fact misregulated in patients' cells, thereby linking their

molecular findings to what's really happening in people's bodies.

Because FMRP plays a role in both the developing and the adult brain, it may eventually be possible to treat some of the symptoms of fragile X syndrome. In addition, the discovery of specific mRNAs involved in the disease has opened the door to new drug targets; it one day may be possible to manipulate the individual

mRNAs or proteins responsible for the symptoms of fragile X, as a means to treat the disease.

For more information, see Rockefeller University press release at www.rockefeller.edu/pubinfo/ment11160/nr.html; original articles in the November 16th issue of Cell (Vol. 107, No. 4).

Research Report: Parent Preferences about Fragile X Screening

*By Don Bailey, Debra Skinner, and Karen Sparkman
Frank Porter Graham Child Development Center
University of North Carolina at Chapel Hill*

Identifying children with fragile X syndrome is a challenging experience for both parents and professionals. As a result, there has been recent discussion about whether systematic screening for fragile X syndrome would be a good policy decision.

Screening for FXS could occur at several points in time. Preconception carrier screening could be offered to women before pregnancy to determine if a woman is a carrier of FXS. [Carrier testing could also be offered to fathers.] Pregnancy carrier screening could be offered to women during pregnancy to determine carrier status. Prenatal screening could determine before birth if a baby has FXS. Newborn screening could identify FXS shortly after birth. And development-based screening could be offered to determine whether a child who is experiencing any developmental or behavioral problems has FXS.

Each of these procedures comes with costs and benefits. Deciding whether to offer screening will be a complicated decision that will include discussions of cost, treatment possibilities, and ethics.

Important to these discussions is how families feel about these options. To determine parent perceptions, we recently conducted a survey of parents of children with FXS to get reactions to different screening options. In collaboration with FRAXA, we mailed written surveys to more than 500 families of children with FXS. The survey asked questions about how



families found out about FXS, the impact of the diagnosis on the family, and opinions about various forms of genetic testing. Questions were developed with input from parents, professionals, and representatives from the Centers for Disease Control. The study was sponsored by a grant from the Office of Special Education Programs, U.S. Department of Education.

We received a great response, with 460 surveys returned that represented 287 mothers and 172 fathers from 299 different families. We are still analyzing the data. Once this process is complete, findings will be submitted for journal publication and posted on the FRAXA web site as well as the Carolina fragile X Project web site. Completed analyses show the following noteworthy findings:

- Only 2% of respondents knew that they or their spouse was a carrier of FXS before getting pregnant
- For all families, the average age of diagnosis of FXS was

57 months. This figure declines significantly for families of children born after 1992, but still remains over 36 months

- More than half of the families had another child before they found out about FXS in their first child
- When asked when is the best time to do genetic screening, 76% said that preconception carrier screening would be their first choice
- Most parents felt that a prenatal or newborn FXS diagnosis would not have a negative effect on parent-child bonding
- More than 90% of families said that if genetic testing showed that their baby was a carrier but not affected, they would still want to be informed.
- More than half said that the diagnosis of FXS affected their decision to have more children

A few parents (4%) felt that screening should never be offered and some concerns were expressed about the consequences of screening. However, most families felt that screening programs would result in a range of positive outcomes for families. We are currently reading and coding the many written comments provided by parents and will summarize this information in forthcoming reports.

This is the first survey of parents to determine their opinions about various forms of genetic screening for FXS. Parents strongly endorsed carrier screening, arguing that this information is needed in order to make informed reproductive decisions. Hopefully this information will be useful as policymakers consider screening options. Because the issue is so complicated, it is unlikely that any form of routine screening will be universally offered in the near future. Thus we will need to keep working with physicians and other professionals to teach them about FXS and encourage testing of children as early as possible.

We appreciate very much the support of FRAXA in conducting this study. The high rate of survey return is rare in survey research. Obviously this means that parents feel strongly about the issues and want their opinions to be heard. Thanks so very much to all parents who participated. We appreciate the time you took to provide information about your lives and your feelings, and we will do our best to make sure that this information is widely circulated to researchers, practitioners, and policy makers.

continued from page 1

defect may somehow protect against cancer, Dr. Soren Schultz-Pedersen of Viborg Hospital, Denmark, and a multicenter team report.

The investigators examined the incidence of cancer in 223 people with fragile X syndrome using the Danish Cytogenetic Registry and the Danish Cancer Registry. Overall, they identified four cases of cancer among the people studied, while almost 11 cases would have been expected based on cancer rates in the general population. The researchers calculated that people with fragile X had only 28% of the cancer risk seen in the general population. Schultz-Pedersen and colleagues point out that in an earlier study of mortality in people with fragile X, only 13 of 83 patients died of cancer, a significantly lower rate than in the general population. "The identification of persons with a decreased risk of cancer opens up possibilities to investigate genetic mechanisms that protect against malignant transformation," the researchers conclude. "Further studies are needed to understand the mechanisms of the ability of the cells to protect themselves against cancer."

This study opens the possibility that some cancer researchers will focus their attention on fragile X, bringing greater attention to our cause. In the meantime, this is good news for families of individuals with fragile X!

FRAXA Booth at Society for Neuroscience Annual Meeting

For the third year in a row, FRAXA sponsored an informational booth at the annual meeting of the Society for Neuroscience. For five days in November, 25,000 neuroscientists converged on San Diego's convention center, including many of the scientists currently supported by FRAXA. This meeting allows us to connect with researchers we know and currently support, and also to introduce fragile X to experts in related fields. Scientists snapped up over 200 FRAXA CDs, a comprehensive multimedia guide to fragile X, including a complete set of FRAXA newsletters, a movie, and texts on education and medication.

This year, Mary Beth and David Busby traveled from Washington, DC to staff FRAXA's booth, and local hero Cindy de Gruchy organized a terrific group of San Diego parents and friends who helped. Thank you to Katie Harris, Hope Busby Burleigh, Shelly Wilson, Carrie Murtagh, Vicky Mulvey, Denise and Jonathan Alvinito, and David Gibson!

Your donation will move research forward

New research project proposals arrived on FRAXA's doorstep on December 1st, and we need your help to fund the best of these! Although the research is heating up, it has been a disappointing year for fundraising; since September 11th, all charities have found it difficult to raise funds for causes unrelated to the tragedy. Contributions to FRAXA over the next two months will determine how many of these exciting new fragile X research proposals can be funded.

Washington Urged to Support Child Health Research

We were pleased that Reuter's News Service reported the following update to news outlets everywhere:

WASHINGTON, Jul 26 (Reuters Health) - Congress needs to immediately renew the law encouraging drug companies to test their products on children, and the Bush administration should fully implement a law passed last year aimed at increasing research on diseases affecting children, a coalition urged at a Capitol Hill news conference Thursday. The Coalition for Children's Health 2001 includes 14 organizations, including United Cerebral Palsy, the Arthritis Foundation and the FRAXA Research Foundation.

"Pediatric research has traditionally been an underfunded medical field," said David Busby of the FRAXA Research Foundation, which supports studies of the genetic disorder fragile X Syndrome. "It is critical that the federal government become more proactive supporting research and encouraging the private sector to take a greater interest in this area of medical research."

The coalition's top priority is passage of the "Best Pharmaceuticals for Children Act," which would reauthorize the law that provides drugmakers with an additional 6 months of market exclusivity for a drug if they conduct clinical trials on children. Without further action, the law expires at the end of this year.

The coalition's other priority is implementation of the Pediatric Research Initiative included in the 2000 Children's Health Act.



Jack and Jacob Massey of Scottsbluff, Nebraska, both have fragile X, but that hasn't slowed them down! This summer, Jack learned to waterski and Jacob won a prize for horsemanship!



Did you know . . .

- You can view detailed financial information about all charities at the website www.guidestar.org. Take a look and you will see that FRAXA's overhead expenses are a mere 6%. We know of no other charity that can top that! If you don't have web access, give us a call.
- This coming year, FRAXA will be part of the Combined Federal Campaign and a number of state workplace campaigns.
- If you have friends and family who might be interested in FRAXA's activities, let us know and we will happily send them our newsletter.

Study Participants Needed in Wisconsin

We are looking for individuals in the 11 to 35 year-old age range with fragile X syndrome to participate in a study researching learning and literacy. Your child should use spoken language as the primary means of communication and know basic shapes and colors. If you are willing to travel to Madison, Wisconsin, you will receive prizes for your child and free hotel accommodations. Contact Mina C. Johnson-Glenberg, Research Scientist at the University of Wisconsin - Madison, email johnsonglen@waisman.wisc.edu., phone: 608/ 262-6768, fax: 608/ 265-4103.

Mina Johnson received FRAXA startup funds for this project last year and has recently received federal funding to continue her work. Congratulations, Mina!

Moms and Kids Needed for Kansas Study

We are researchers at the University of Kansas in Lawrence, KS, studying how young children with fragile X communicate their needs. We are looking for children with fragile X who are 2-6 years old and their mothers to participate in the pilot study for a research project for which we want to write a proposal. We really really need them before the end of the year 2001 as the proposal will be due in February. A family's participation takes about 2-3 hours and can be divided into two sessions. We are offering incentives to families because we know this is a busy time. We reimburse the families for mileage up to \$35 and will give them \$100 in cash at the completion of their participation. Families can come to our site in Lawrence or the Kansas University Medical Center in Kansas City, KS.

If you have children who would qualify or know a family, please contact us or them. We would be glad to answer any questions you may have.

Nancy Brady and Tammy Steeples, Schiefelbusch Institute for Life Span Studies, Wakarusa Research Facility, 1315 Wakarusa Drive, Lawrence, KS 66049, 785-312-5364 or toll free 866-591-3084

Female Carriers of Fragile X Wanted for a Research Study on the Menstrual Cycle.

The Reproductive Endocrine Unit at the Massachusetts General Hospital seeks female carriers of the fragile X premutation for a research study to examine the menstrual cycle. Mothers of children affected with fragile X and any other women who are fragile X carriers are invited to participate. The study will help determine whether there are changes in the menstrual cycle hormones in women who carry the fragile X premutation. The study also involves the option of participating in neurological and psychological testing to examine thinking and personality traits. Women should be age 18-50 yrs. Up to \$50 stipend. Call Patty at 617-726-5387.

About Tissue Donation

Human tissue donated at the time of surgery or death by people of all ages, or in the case of miscarriage or pregnancy termination, is a precious resource on which researchers depend. FRAXA and the Brain and Tissue Bank for Developmental Disorders in Maryland have produced a joint brochure about fragile X tissue donation. If you would like a supply of these brochures for your support group meeting or family members, please call Doreen DiMeglio, (800) 847-1539, at the bank, or Katie Clapp, (978) 462-1866 at FRAXA.

Fragile X Listserv, in Spanish and Portuguese

This forum is for sharing personal and professional experiences and opinions about fragile X Syndrome. Over 140 professionals and family members from all the Spanish and Portuguese-speaking countries are currently subscribed. All spanish/portuguese-speaking persons from any country in the world are welcome to join.

To subscribe, send mail to: xfragil-subscribe@onelist.com

To unsubscribe, send mail to:
xfragil-unsubscribe@onelist.com

To send messages, send mail to: xfragil@onelist.com

To reach list owner, send mail to:
xfragil-owner@onelist.com

URL of this page:
<http://www.onelist.com/community/xfragil>

FRAXA Gets a New Volunteer

Hi! My name is Dawn Ward and I am the parent of two boys, ages 5 and 7, who have fragile X. Now that they are in school full-time this year, I have begun working as a volunteer for FRAXA.

When my children were at home during the day, I didn't have enough energy or time to really even think about volunteering; I was just coping with our family's very stressful day-to-day life. But now that my days are "free", it is with great satisfaction that I sit down to my desk and computer in my newly created home office (I moved my boys into the same bedroom). There's nothing else I'd rather be doing. I have every hope and belief that a cure will be found for fragile X and I intend to speed up progress toward that day!

You can help FRAXA by letting me know of any ideas that you have, but just don't have the time or energy to pursue alone. My email address is CureFragileX@aol.com and my phone number is 703-631-1845. I am presently working on:

- organizing an annual Walk for Fragile X at various sites around the globe;
- putting together a fundraising guide to help those who want to fundraise but need some help on how to;
- and anything that Katie Clapp sends my way.

I look forward to hearing from you!



Robert and Dawn Ward with their two sons, Atticus and William, both of whom have fragile X

Would you like to start a support group or organize an event?

As FRAXA's mailing list has grown, chances are that we might know of families who live nearby but don't know each other. If you would like us to help you connect with others in your area, send an email, call, or drop us a line. Let us know whether you are a parent (grandparent, friend, etc.) and if we have permission to share your name with others in your area.

Update from the National Fragile X Foundation

I'm pleased to announce the first titles in our "special topics pamphlet series," Females and Fragile X and Fragile X and Sexuality, are now available. Both are the result of collaboration between NFXF staff and advisors. A third pamphlet, Behavior Management and Fragile X, will be available in the near future. All three deal with subjects that are related to common questions that the NFXF receives. Like all NFXF pamphlets, these are designed to be an introduction to a specific topic. They are intended to help parents and professionals formulate questions relevant to their specific concerns, and as a starting point for further learning. Each includes references to resources that address the topics in greater detail. Additional titles will be released in the months to come.

I'm also pleased to announce an exciting new endeavor called the Education Project. This project is designed to help teachers better include children with fragile X within the regular classroom. The project is a collaborative effort

of the NFXF, parents from the NY and NJ support groups, Dr. Vicki Sudhalter, Dr. Marcia Braden and others.

The final product will be produced in a loose-leaf binder and will address preschool through young adulthood. It will include sections on:

What is Fragile X?

General information about fragile X, characteristics, and learning styles.

Adapting Curriculum

Recommendations, suggestions and guidelines regarding adapting curriculum and lesson plans.

Examples of Lesson Plans

Gathered from parents and teachers across the country, and at the July, 2001 Chicago Conference.

Please contact me with any questions or comments.

Robert Miller, Executive Director 800-688-8765

NATLFX@FragileX.org www.FragileX.org

FRAXA EVENTS

5th Annual Fragile X Golf Benefit

The 5th Annual fragile X Golf Benefit was held on Monday, July 30, 2001 at the Shaker Heights Country Club in Shaker Heights, Ohio. The event, with AT&T as the Title Sponsor, was a major success raising over \$100,000 again!

The 156 golfers enjoyed the challenging golf course and were then joined by an additional 150 guests after the tournament. The three hundred attendees enjoyed appetizers, drinks and the large variety of exciting Silent Auction items.

During the dinner program, Dr. Michael Tranfaglia of FRAXA Research Foundation spoke of the rapid progress being made in fragile X research. He also recognized the importance of Dr. Alan Tartakoff's research at Case Western Reserve University here in Cleveland. This grant is funded primarily from the proceeds of this benefit. We showed a video entitled "Hope for the Future" which told the audience about fragile X and the promising research projects underway.

Special guest, Doug Dieken (former Cleveland Browns player & current radio announcer) and Honorary Chairpersons, Herb & Nancy Score conducted a fun and entertaining Live Auction.



Ara Bagdasarian, Jay Bagdasarian, and Larry Karobiwian man the golf leader board

Our core committee of Leslie and Ara Bagdasarian, Jeanne & Mike Sydenstricker, Rod Tyler and Jim Vitalie were joined this year by more volunteers from the fragile X Alliance of Ohio, friends and family members. Special thanks go to Kristie Braley and Conferon, a local meeting planning company, who provided support and volunteers to help with this event.

A fun day was had by all, but we cannot lose sight of the reason behind this benefit – to raise awareness and research funds for fragile X Syndrome – the most common inherited form of mental impairment and learning disabilities worldwide. If you would like a copy of our program or have any questions, please email Leslie at lbagdas@oh.verio.com.

Nascar Racing and the Civitans support FRAXA

Dear FRAXA,

I am a member of the local Civitan Club and have a 4-year-old son with fragile X. I recently gave a talk to the club about fragile X and they generously gave me a check for your foundation. Developmental delays and mental retardation are the primary interests of the Civitan Clubs nationwide, so it is very appropriate that the money be given to this cause. This photo is of me accepting the check from the President of the Richmond Civitans, Inell Allen.

This money was raised by selling concessions twice a year at the North Carolina Motor Speedway in Rockingham, NC. These popular Nascar races usually attract 30,000 people per day, so it is hard work, but a lot of fun!

Thank you from me, the Richmond Civitans, and from my son, David, for all of your hard work. Hopefully we can continue our support in the future.

– Sarah Tamura
Rockingham, NC



A few of the many volunteers



Stone Pony Party in Asbury Park

In October, New Jersey couple Denise and John Sabo hosted a benefit

for FRAXA Research Foundation at The Stone Pony. The Sabos have a 3-year old son Kyle, who has fragile X. There was music by "The Soul Engines," stand-up comedy by "Dr. Sensitivity" Joe Picolli and Otto and George, and a performance by Elvis impersonator Angel Pastrana. FRAXA friends came from as far away as Virginia (thank you, Carol and Brian!) and Massachusetts to celebrate the event.

Pennies from Heaven!

Jen Nardo of Hockessin, Delaware, persuaded officials at a local mall to donate coins dropped in their fountain to FRAXA. Jen reports:

I just received the coins from my area mall. I was able to get one of the five crates of coins counted and I am going to try to wrap the rest with some help. This could add up to almost \$1000 for FRAXA! I just wanted to let everyone know that there indeed are "pennies from heaven!"

Jen is organizing a fundraiser for February 9th at a local church. There will be entertainment, hors d'oeuvres, cash bar, and a silent auction; anyone who would like to join in can call Jen at (302) 234-7854 or email jen9612@aol.com.

Upcoming Gala in New England

Springtime is celebration time for FRAXA! Join us for an evening at the Corinthian Yacht Club, on the seashore in Marblehead, Massachusetts, on Thursday, May 16th. Plan a long weekend and explore the history and beauty of Marblehead in the spring. This event takes place two weeks after our Washington, DC, Mary Higgins Clark Annual Gala, which is on Monday, April 29th – come join us for both!

If you can help recruit sponsors, both corporate and individual, or if you would like to reserve a table for the evening, please contact Leslie Eddy at (781) 631-9196 or Katie Clapp at FRAXA.

Available from FRAXA:

All prices include shipping within the U.S. Please call or e-mail for international orders.

FRAXA CD

One CD-Rom holds FRAXA's video Unlocking Fragile X, publications on educational strategies and medications, newsletter issues, fragile X articles and FRAXA's brochure (Acrobat format). Works with PC or Macintosh computers. Upon request with any donation.

FRAXA "X" Lapel Pin

Gold-plated FRAXA logo pin is a wonderful gift! \$10

FRAXA Umbrellas

Pop-up umbrellas in an assortment of colors, with FRAXA's logo in white. This is a terrific gift for teachers and friends. \$12

Unlocking Fragile X

An emotional, inspiring look at fragile X, FRAXA and current research, with author and grandmother Mary Higgins Clark, Nobel Prize Winners James D. Watson, Ph.D, and Eric Kandel, MD, and many others. This 10-minute video is a great fundraising aid. \$8

FRAXA Tribute and Memorial Cards

Both are available in packages of 10 cards for \$30.

FRAXA T-Shirts

White, all-cotton T-shirts feature FRAXA's logo on left chest. Adult sizes: M, L, XL, XXL. \$12

Fragile X: A to Z

Edited by Wendy Dillworth, this is chock full of stories from daily life with fragile X children. Browse through helpful suggestions on topics such as adolescence, bike riding, and dental work. 73 pages, \$15.

A Medication Guide for Fragile X

By Michael Tranfaglia, MD, Psychiatrist and Parent. This guide helps parents and others understand behavioral symptoms of fragile X and the medications commonly prescribed to help manage these symptoms. \$20.

Educating Boys with Fragile X

By Gail Spiridigliozzi, Ph.D., this guide has specific helpful suggestions aimed particularly at teachers and therapists. 20 pages, \$10.

Free: FRAXA Brochures and Gift Envelopes

Fragile X Information Cards

Many families have asked for a card that they can give to people who have no knowledge of fragile X. Business-size cards: \$10 per 100.

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.

Calendar of Events

MONDAY APRIL 29

5th Annual Mary Higgins Clark Fragile X Gala, at The Four Seasons Hotel, Washington, DC. Chaired by Diane Rehm, Kitty de Chiara, and Mary Beth Busby. Call Mary Beth at 202-462-2323 to reserve tables or for sponsorship information.

TUESDAY APRIL 30

Fragile X Lobby Day in Washington, DC. The morning after the gala, we will fan out across Capitol Hill to meet with Members of Congress. Please contact Mary Beth Busby at 202-462-2323

THURSDAY MAY 16TH

Black Tie Gala, at the Corinthian Yacht Club, Marblehead, Massachusetts, with celebrity guests. Help us fill the club! Chaired by Leslie Eddy; call her at 781-631-9196 to join in.

Additional events are planned in New York, OHIO, Massachusetts, and Maryland – stay tuned!

FRAXA
RESEARCH
FOUNDATION
45 Pleasant Street
Newburyport
Massachusetts 01950

FRAXA UPDATE

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FRAXA would like to thank Networx of Newburyport, MA for hosting the FRAXA website and email. Networx has donated this important resource for the past 6 years

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+) |
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