FRAXA UPDATE

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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

Katie Clapp, Mary Beth Busby, and (former) President Bill Clinton

FRAXA Invited to The White House

CELEBRATING THE CHILDREN'S HEALTH ACT

On short notice, Katie Clapp and Mary Beth and David Busby hurried to attend the January 4 White House ceremony celebrating the bipartisan enactment of the Children's Health Act of 2000, which boosts federal funding of research on children's diseases, including fragile X. This was a rare, unforgettable opportunity to meet both (now, former) President and Senator Clinton in "The Blue Room," along with several members of Congress and 30 or so other advocates for children's and women's health issues. We were thrilled that Senator Clinton mentioned fragile X in her short speech. Former President Clinton ended his remarks with this memorable statement: "And to all of you who are focusing on genetic research, let me just say that the best stuff is still out there. So, go get it!" Hearing those encouraging words, surrounded by White House holiday decorations, and stirred by music by a Marine Corps orchestra, we felt optimistic that fragile X research will, one day soon, get the attention that it deserves. We all need to renew our efforts to raise fragile X in the consciousness of the Congress and the new administration. Perhaps, while The White House is occupied with replacing "W" keys on computer keyboards, we should offer to send them our golden "X" keys as well!

NEW RESEARCH FUNDED

This issue of our newsletter is double-dipped in research news. Every six months and as funds become available, FRAXA awards grants and fellowships for innovative research that will move us along the path toward finding effective treatments and a cure for fragile X. We place a premium on jump-starting new investigators in the fragile X field, so that they will be able to develop their ideas and preliminary data and compete successfully for other sources of funding. The first set of projects described on page 2 is fully funded by FRAXA.

In addition, nine grants have just been awarded under the special initiative **Neurobiology and Genetics of Fragile X Syndrome.** As we have previously reported, this initiative was funded by the National Institute of Child Health and

New Research Continued on page 2

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

New Research – continued from page 1

research

Human Development (NICHD), National Institute of Mental Health (NIMH), and FRAXA. NICHD has committed $5 million dollars to this project over five years, and NIMH and FRAXA have each committed $1 million dollars. This is an enormous amount of money for a grass-roots foundation like FRAXA to raise, and yet it will fund only a fraction of the deserving proposals received from researchers around the world. See more on page 6. For information on all current FRAXA-funded research and our overall strategy, visit www.fraxa.org or call Katie Clapp at (978) 462-1866.

FRAXA Grants and Fellowships

Funded January 2001

Altered mRNA localization to growth cones, filopodia and spines assessed in hippocampal cultures from FMR1 knockout mice

GARY BASSELL, PH.D. AND LAURA ANTAR, PH.D.

Albert Einstein College of Medicine, The Bronx, NY
Renewal/Extension, $30,000

by Katie Clapp

Nerve cells have two types of long processes called axons and dendrites. During brain development, these processes extend for long distances and interact with other nerve cells and form connections (synapses). The ability of neuronal processes to grow correctly and form appropriate connections depends on the presence of specialized structures, called filopodia, which project from the surface of neuronal processes and growth cones.

Dr. Bassell's team has developed powerful molecular genetic techniques to visualize the movements of RNAs and proteins along these tiny structures. They can track FMR1 mRNAs and FMRP particles as they move through the growth cones, dendritic filopodia, and spines of hippocampal neurons in FMR1 knockout mice and normal controls. This work further indicates an important role for FMRP in normal development of neurons. Comparing fragile X mice with normal mice will enable them to explain which proteins and mRNAs are affected when FMRP is lacking, and how these differences affect the normal structure and development of nerve cells.

Studies on FMR1 gene therapy delivery using viral vectors

DAVID C. BLOOM, PH.D.

University of Miami
Renewal, $52,000

WILLIAM GREENOUGH, PH.D.

University of Illinois at Urbana-Champaign, Renewal $32,000

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 central nervous system defects which may be similar to those present in the disease in humans.

We have been using a gene therapy approach to deliver a functional copy of the FMR1 gene into the brains of the FMR1 knockout mice and to determine if this will repair the observed defects in their central nervous system. One tool we have been developing 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 deliver a gene to brain cells. During the past year, we have also been preparing a second vector based on adeno associated virus, a harmless virus associated with the common cold, which has great promise for use in gene therapy. The use of these two vectors together will increase the likelihood of successfully delivering the FMR1 gene to as many brain cells as possible. The construction of the first of these vectors is nearing completion, and initial tests in mice will soon begin.

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.

FRAXA first funded this collaborative project in January 2000. Construction of the viral vectors is underway at David Bloom's lab, and, once gene therapy tests have been performed on the fragile X knockout mice, testing of molecular and synaptic functioning of rescued knockout mouse neurons will be done at Bill Greenough's lab.

update:

Startle and Startle modification by prepulses in males with Fragile X Syndrome

ELISABETH DYKENS, PH.D.

EDWARD ORNITZ, PH.D.

UCLA, $37,720

by Katie Clapp and Elisabeth Dykens

Startle is a quick motor response to a loud noise; this is a normal response to a jarring, unexpected noise. If the loud noise is preceded by a much quieter sound, or prepulse, then the startle response is normally inhibited; this is called prepulse inhibition. It is thought that disturbances of prepulse inhibition reflect disruptions of pre-attentional mechanisms which underlie information and sensory processing. Prepulse inhibition is reduced in a number of mental disorders including schizophrenia, obsessive compulsive disorder, nocturnal enuresis (bed-wetting), and Tourette's syndrome, and attention deficit hyperactivity disorder when it occurs with enuresis or Tourette's syndrome.

In general, prepulse inhibition of startle measures sensory gating, that is, how the nervous system "gates" or modulates motor responses to strong stimuli so as not to interfere with the processing of preceding stimuli.

Interestingly, preliminary studies suggest that the fragile X knockout mice have a marked increase in prepulse inhibition. Dr. Dykens and Dr. Ornitz plan to test these responses in children who have fragile X, to see if they show similar responses. If so, then prepulse inhibition will be a target symptom in the knockout mice which can be used to evaluate potential genetic or pharmacological treatments. If fragile X boys show excessive prepulse inhibition, this might be related to the working memory deficit reported in these subjects. Attentional resources, locked to the stimuli such as the prepulse, would not be available for normal storage and retrieval of information.

FMR1 repression and the signals to chromatin

ASSAM EL-OSTA, PH.D.
PETER JONES, PH.D.

Peter MacCallum Cancer Inst., Melbourne, Australia, $35,000

by Michael Tranfaglia

This group is studying mechanisms of methylation-dependent silencing of FMR1, as well as regulation by histone acetylation/deacetylation. They have previously worked with MeCP2, the gene that causes Rett Syndrome, and present interesting pilot studies of the regulatory interactions of the Rett Syndrome gene with FMR1. They plan to extend these findings by studying other members of the methyl-CpG binding family with FMR1. This study is important because understanding the mechanism of transcriptional repression of FMR1 may point to ways to reactivate the gene so that it can function normally.

Restoring FMRP expression in cells from Fragile X patients

ANDRE HOOGEVEEN, PH.D.

Erasmus University, Netherlands, Renewal, $30,000

by Katie Clapp

In people with fragile X Syndrome, a mutation in the FMR1 gene shuts down the gene, so that no gene product, FMRP, is produced. Methylation is the chemical switch which shuts down the gene: several different sites on the promoter region of the gene are methylated. One possible strategy for the treatment of fragile X is to reverse the methylation of the gene, in order to restore FMRP production.

These studies are aimed at removing or preventing methylation in cells from fragile X patients by using antisense strategies. One promising antisense strategy is to use PNAs, artificial molecules that can be constructed to bind to a specific stretch of DNA. The result of this binding can be to alter the function of a gene. PNAs are particularly useful because they are relatively stable and not easily neutralized

GLOSSARY

Neuron brain cell

Synapse junction where a neuron communicates with another neuron or with a muscle cell; correct synaptic development (growth, strengthening, pruning, etc) is key to proper brain development, especially learning and memory.

Axon long arm that serves as a neuron's input from other neurons

Dendrite long branching arms through which a neuron sends output signals to other neurons or muscle cells

In vitro in a test tube or lab dish; not using live tissue

by a cell's natural housekeeping mechanisms which defend against viruses and other foreign bodies. PNAs have been shown to have the ability to pry apart the strands of inactivated, methylated DNA and actually cause demethylation, which in turn, in the case of the fragile X gene, could restore its normal function.

Work is well underway on this project. Dr. Hoogeveen and his team have produced a panel of PNAs, each directed at a specific site in the FMR1 gene. They have demonstrated that these PNAs can cross the blood brain barrier to reach brain cells. Now they are testing the various PNAs to see which ones can effectively reverse methylation of the gene. The timing of expression and the targeting to the brain will be major challenges. This is a time-consuming process because multiple sites of the FMR1 gene are methylated and no one knows which one(s) must be reversed in order to reactivate the gene so that it can produce protein. Over the coming year, they will produce new PNAs and test the effectiveness of each one.

Monoclonal Antibodies to Distinguish Between and Investigate FMRP, FXR1 and FXR2

ALAN TARTAKOFF, PH.D.

Case Western Reserve University; $30,000 renewal

by Alan Tartakoff

The fragile X research field has been plagued by an absence of antibodies which cleanly discriminate between FMRP and two closely related proteins, FXR1 and FXR2. For example, only a single, non-discriminatory antibody is commercially available. We have therefore undertaken the production of a panel of discriminatory antibodies which will be made public. They should be valuable both for diagnosis and for investigation of the fundamental biology of the fragile X Syndrome.

In the first year of work on this project, we have used fragments of FMRP to raise antibodies. The approach is promising and some antibodies are already available. We are now concentrating on the production of antibodies which cleanly discriminate between FMRP and the two related proteins. This involves further rounds of immunization using segments of all three of the proteins.

Cell Growth and the Fragile X Syndrome

DEVIN ZARKOWSKY

Middlebury College, Vermont; $1000 materials grant

by Devin Zarkowsky

Observing dermal fibroblast (immature skin cells) growth is an unusual, yet promising, tack in fragile X research. Transgenic mouse cell lines exhibit diminished growth rates in comparison to their wild-type counterparts. We hypothesize that the fragile X gene may indirectly regulate a cell's life cycle. We will introduce a working fragile X gene into affected cells to, hopefully, induce growth similar to wild-type cells. If so, we will investigate whether an additional copy of the gene might spur increased proliferation.

Devin is an undergraduate at Middlebury College, who received funding from Howard Hughes Medical Institute last summer to conduct his research on fragile X. FRAXA is pleased to provide supplemental funds to allow Devin to complete this extraordinary project.

Patterns of Protein Expression in Fragile X Syndrome

WALTER KAUFMANN, PH.D.

Johns Hopkins University School of Medicine; $41,000

by Katie Clapp

Dr. Kaufmann will identify proteins which have abnormal levels and/or patterns of expression in males with fragile X syndrome. He will use a powerful technology, 2D PAGE, which will enable him to distinguish proteins from each other. He will correlate specific changes in protein levels with behavioral indicators, such as degree of autism or anxiety or cognitive impairment, in order to better understand what causes these symptoms and how they might be treatable.

Several studies investigate an important new model of fragile X Syndrome, the common fruit fly, scientifically known as drosophila. Although it may seem remarkable that fruit flies can shed light on a complex human disorder, fruit flies have a gene, known as dFMR1, which is quite similar to the human FMR1, FXR1 and FXR2 genes. Early studies show that "fragile X fruit flies" - which have been developed to lack the gene dFMR1 - have some behavioral, learning, and motor deficits, suggesting that this is a promising new line of research.

Neurological Function of Fragile X Gene in Drosophila

KENDAL BROADIE, PH.D. AND

YONG ZHANG, PH.D.

University of Utah; renewal, small bridge grant

By Yong Zhang and Kendal Broadie

One of the most compelling challenges in fragile X research is to understand how lack of the affected protein (FMRP) gives rise to mental impairment and associated behavioral abnormalities. A potentially fruitful approach is to assay FRAXA gene (FMR1) function within a simple, well-characterized genetic model organism such as the fruitfly, Drosophila melanogaster. Drosophila has a long and distinguished history as a genetic system to assay underlying causes of inherited human genetic diseases. In the last few years, Drosophila has contributed enormously to our understanding of a number of common neurodegenerative diseases including Alzheimer's and Parkinson's disease. We anticipate a similar revolution in our understanding of fragile X through developing a Drosophila model.

Last year, we identified and characterized a Drosophila FMR1 gene homologue (i.e. highly similar gene) which is now named dFMR1. Like its human counterpart, the dFMR1 protein product is highly expressed in most, if not all, nerve cells of the central nervous system, from embryogenesis to adulthood. Like human patients, when dFMR1 is completely removed from the fly genome (i.e. null mutants), the mutant fly is fully viable and morphologically normal, but exhibits uncoordinated movement behaviors. Microscopic assays of these mutants show that neuronal synapses (where a neuron communicates with another neuron or with a muscle cell) develop abnormally, resulting in clear structural defects. When dFMR1 is over-expressed in transgenic flies, making excess protein, an opposite structural change is observed. These results show that the level of dFMR1 protein directly dictates the level of synaptic structural development. Similarly, electrophysiological assays of synaptic function in both mutants and transgenic flies show that neurotransmission is abnormal, in agreement with the severity of the structural defects. These phenotypes, together with complementary human and mouse studies, strongly suggest that fragile X Syndrome may result from synaptic defects.

This year, we will focus on looking for dFMR1 interacting partners by employing powerful genetic interaction screens available only in Drosophila. We will mutate the entire fruit fly genome while screening for genes which can ameliorate fragile X symptoms in flies. Identifying and characterizing genes which interact with dFMR1 will help us understand the mechanism by which the fragile X gene and its protein product perform their normal function — and what goes wrong in the absence of the protein. We intend to use this information to develop treatments for fragile X.

This grant was approved by FRAXA's Directors for a second year of funding, but, happily, it will be funded at a higher level by the NIH/FRAXA initiative described below. A small bridge grant was awarded until the NIH funding takes over.

Using flies to Study FMR1 in Learning and Memory

JERRY YIN, PH.D., CARLA MARGULIES, PH.D.

Cold Spring Harbor Laboratory, $38,000

By Carla Margulies

We know that fragile X syndrome results from mutations in the gene encoding the FMR1 protein, but we do not understand the role of FMR1 protein in the central nervous system or how it is regulated. In addition, we do not know when, during a life-time, a person requires FMR1 protein. These questions are relevant in designing a therapy for fragile X syndrome and determining when therapy can be administered.

To answer these questions, we will take advantage of the sophisticated genetic tools developed in Drosophila, commonly known as fruit flies. Because flies have a very short generation time compared to mice, flies are an ideal system to investigate how FMR1 is regulated and to identify proteins that FMR1 protein regulates. Identifying these proteins will provide drug targets and gene therapies. Recently, the FMR1 gene and its protein were identified in Drosophila. This fly protein has the same biochemical properties as the mouse and human fragile X proteins. Mutations in the fly gene cause abnormal morphology (shape and structure) of neurons similar to the neuronal morphology seen in fragile X patients and FMR1 mutant mice.

Our first experiment will be to determine whether FMR1 mutant flies have learning and memory defects similar to FMR1 mutant mice. We will use a paradigm that involves exposing flies to one odor in the presence of an electrical shock. Then the flies are exposed to a second odor without shock. Later, the flies are given a choice between the first and second odor. If the flies remember, they will go to the second odor.

Then, we will use genetically modified flies to test whether the FMR1 protein plays a role in memory. We will construct a genetically modified fly with an extra copy of a FMR1 gene that will "turn off" FMR1 protein production in an adult fly brain. We will test this fly for memory. Later, we will determine whether "turning on" FMR1 protein expression will ameliorate the symptoms of FMR1 mutations in adults.

Proteins/mRNA Interactors of FMRP

JEAN-LOUIS MANDEL, PH.D.

CNRS, INSERM, IGBMC, Strasbourg, France

by Michael Tranfaglia

This project is aimed at pinpointing the function of the fragile X protein, FMRP. The team headed by Dr. Mandel, one of the seminal researchers working on fragile X, has recently discovered four novel proteins that interact with FMRP. This team of investigators will analyze the functions of these new proteins, and how they modulate FMRP functions. They have joined forces with another group in Strasbourg that is expert in analyzing RNA-protein interactions, and together, they will identify the mRNAs binding specifically to FMRP and the target RNA sequences/structures that are responsible for that binding. They will construct mutations affecting the binding site on the mRNA or the KH2 domain of FMRP and study the effect of their interaction on FMR1 mRNA export, stability, and translatability in cell culture. Further, they will analyze the role of these protein and mRNA interactions in model systems, such as cells in culture, Drosophila mutants, and transgenic mice, using a unique in vivo approach.

Over the past year, FRAXA awarded a postdoctoral fellowship to Dr. Barbara Bardoni, an investigator in Dr. Mandel's lab. This project will be funded through the NIH/FRAXA initiative, and FRAXA is providing a small bridge grant until the NIH funding takes effect.

Drosophila as a model to study FMRP function

THOMAS A. JONGENS, PH.D., AND THOMAS DOCKENDORFF, PH.D.

Univ. of PA School of Medicine, $35,000

by Katie Clapp

This group is developing mutant fruit flies which lack FMRP. They have begun to assess this loss of function, with particular emphasis on embryological and electrophysiological studies. They will look for other genes that are involved in the same pathway as dFMR1, in order to identify potential targets of dFMR1 activity. They will also investigate aspects of learning and memory through behavioral paradigms based on the courtship behavior of fruit flies. Fruit fly flirtation is a relatively complex behavior which depends on the ability to learn and remember. This team will compare the courtship of normal flies with that of fragile X fruit flies. Together these studies will help to define the role of the FMR1 protein in flies, which will also shed light on the function of the human FMR1 protein.

Two more grants were approved by FRAXA's Board for a second year of funding, for the laboratories of Dr. Kendal Broadie and Dr. Jean-Louis Mandel. Happily, these two teams have been generously funded under the NICHD/NIMH/FRAXA RFA, and so FRAXA is providing small bridge grants to fund the projects until the RFA funding takes over.

Back row: Dr. Felix de la Cruz, George Gaines, and Dr. Mary-Lou Oster-Granite, all of NICHD Front row: David Busby and Katie Clapp, FRAXA, and Dr. Duane Alexander, Chief, NICHD

Research funded jointly by NICHD, NIMH and FRAXA

Nine grants have been funded under the special initiative "Neurobiology and Genetics of fragile X Syndrome" by the National Institute of Child Health and Human Development (NICHD), with help from the National Institute of Mental Health (NIMH), and FRAXA.

The top five laboratories funded under this initiative have, over the past year, received direct funding from FRAXA for their fragile X work. One of our strategies in funding research is to select and support promising projects in their early stages, to enable the investigators to develop their ideas and gather preliminary data in order to

successfully compete for NIH funding. We think that this strategy works! Some risk-taking is required, but thanks to excellent guidance from FRAXA's Scientific Advisory Committee, we've made good choices.

FRAXA would not be able to function without our Scientific Advisors, who give their time and expertise in order to guide us and, most importantly, to evaluate grant proposals. This is no small task, as we now receive dozens of applications every six months. Thank you, Dr.s W. Ted Brown, Robert Bauchwitz, Seymour Cohen, Linda Crnic, Robert Darnell, John Donoghue, William Greenough, David Gwynne, Randi Hagerman, Eric Kandel, Herbert Lubs, Pamela Mellon, David Nelson, Owen Rennert, Stephen Warren, and James D. Watson.

This new initiative will fund two types of grants: Project Grants, with a direct cost budget up to $200,000 per year for up to five years, and Small Grants, with a direct cost budget of up to $50,000 per year for two years. Indirect costs for university expenses are paid as well, but only the direct annual costs are listed here.

Neurological Function of Fragile X Gene in Drosophila

KENDAL BROADIE, PH.D.

University of Utah, $200,000

This grant will be funded by funds from FRAXA to NICHD, by NICHD, and by NIMH

Fragile X Protein and Synaptic Receptor Deficiencies

IVAN JEANNE WEILER, PH.D.

University of Illinois at Champaign-Urbana $50,000

This grant is funded solely by NIMH. FRAXA has provided continuous funding since 1995 for fragile X research at the University of Illinois under Dr.s IJ Weiler and Bill Greenough.

The remaining grants will be funded jointly by funds from FRAXA to NICHD and NICHD. Dollar amounts are direct yearly costs.

Identification of FMRP Target RNAs

JENNIFER DARNELL, PH.D.

Rockefeller University, $175,000

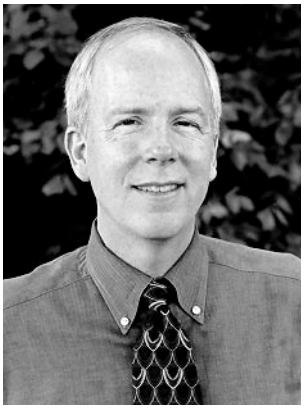
Dr. Jennifer Darnell received a FRAXA postdoctoral fellowship in 1999.

Proteins/mRNA Interactors of FMRP

JEAN-LOUIS MANDEL, PH.D.

CNRS, INSERM, IGBMC, Strasbourg, France; $125,000

Over the past year, FRAXA awarded a postdoctoral fellowship to Dr. Barbara Bardoni, an investigator in Dr. Mandel's lab.



Attention, Memory, and Executive Function in Fragile X

DONALD B. BAILEY, PH.D.

University of North Carolina at Chapel Hill; $200,000

FRAXA provided $30,000 in interim funding for this team over the past year and previously funded a two-year fellowship for Dr. Jane Roberts, a fellow in Dr. Bailey's lab.

Phenotype Consequence of High Repeat FMR1 Alleles

STEPHANIE SHERMAN, PH.D.

Emory University; $50,000

Phenotypic Markers in Females with Fragile X Premutation

AVE M. LACHIEWICZ, PH.D.

Duke University School of Medicine; $50,000

Gene Repression in Fragile X Syndrome

HOWARD CEDAR, PH.D.

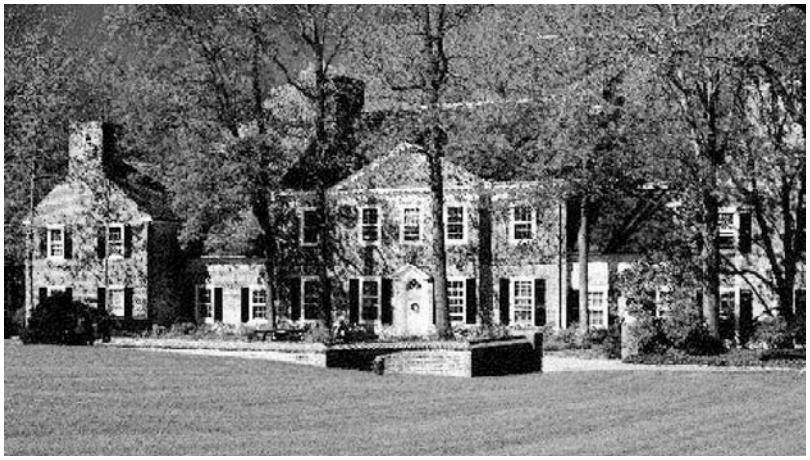
Hebrew University Medical School, Jerusalem, Israel; $100,000

Hearing and Speech in Young Males with Fragile X Syndrome

JOANNE E. ROBERTS, PH.D.

University of North Carolina at Chapel Hill; $50,000

Banbury Meetings



Last April, 39 scientists converged upon Cold Spring Harbor Laboratory's famous Banbury Center to discuss new findings and explore research strategies aimed at understanding and treating fragile X. The Banbury Center is known for small, focused, intense research meetings, where scientists share ideas openly and forge new collaborations. Last year's meeting, funded by the National Institutes of Health and FRAXA, was so fruitful that we decided to hold annual research meetings. We are very, very pleased to report that the National Institute of Mental Health (NIMH) will fund the next five years of Banbury meetings on fragile X, with a generous contribution from the National Institute for Child Health and Human Development (NICHD) and supplemental funding by FRAXA. We thank Dr. Bill Greenough for writing a successful grant proposal to secure NIH funding and Dr.s Bill Greenough, David Nelson, and Don Bailey for organizing the 2001 meeting. In addition, we thank Dr. James D. Watson, Dr. Bruce Stillman, and Dr. Jan Witkowski at Cold Spring Harbor Laboratory for offering to waive conference registration fees for the coming five years.

The program for this year's meeting, Understanding the Neural Basis of fragile X, held March 4-7th, is available from the Banbury Center (www.cshl.org/banbury) or FRAXA.

An impossible challenge in organizing research meetings is to include everyone who should be included and yet keep the meetings small enough to facilitate productive, open communication. Banbury imposes severe discipline because accommodations are limited. As new investigators join the fragile X field, the need for additional targeted research meetings grows. Banbury is a wonderful beginning, and we will continue to work to expand opportunities for collaborative research to blossom.

Fragile X Researchers are in need . . .

Human tissue donated at the time of surgery or death by people of all ages, especially those who have a developmental disorder like Fragile X, is a precious resource on which researchers depend.

The Brain and Tissue Bank for Developmental Disorders at the University of Maryland in Baltimore is one of two tissue repositories that is funded by the National Institute of Child Health and Human Development for the study of childhood disorders. The second bank is located at the University of Miami. The purpose of the Banks is to make human tissue available for research. Tissue donations are needed both from people with developmental disorders and their relatives, people of all ages and either sex.

The Banks provide information to anyone having questions about tissue donations and maintain a registry of individuals who wish to donate tissue either at time of surgery or at time of death. There is no cost to families who donate tissues. Currently a number of families with Fragile X are registered as potential tissue donors with the Bank at the University of Maryland. However, since this is not a fatal disorder, it is necessary to have a large pool of registrants to assure that the few isolated deaths may benefit the vast number of affected individuals both living now and those that will be born in the future. It is especially important that families with older members diagnosed with Fragile X consider registration for tissue donation. Also, families that have established an in utero diagnosis of Fragile X, and have made the decision to terminate the pregnancy, can make an important contribution by donating aborted tissue for research. Contact with the Bank several days before the procedure will enhance our chance of obtaining tissue that is of maximum value for research.

For more information or to receive a registration form, please call or write: Brain and Tissue Bank for Developmental Disorders, University of Maryland, 655 W. Baltimore St., 10-035 BRB, Baltimore, MD 21201-1559 1-800-847-1539 Attn: Patricia L.W. Nash, PA-C, Project Coordinator.

National Fragile X Foundation Update

By Robert Miller

By the time you read this, or shortly thereafter, our new website will have premiered. The site has been completely reworked and you can be sure that the site has been designed with you, the parent or professional, in mind. The site not only features a great deal of new content, but also a layout designed to make the search for and comprehension of material much easier. Information about specific topics within Fragile X is now more self-contained, while the extensive use of hyperlinks allow you to easily jump to related topics.

Also of note is our new database containing all of our resources, including the excellent FRAXA materials carried by the NFXF. By contacting us you will be able to learn the location of any Fragile X related topic within the almost 20 titles we carry. That includes all of our books, newsletters, videos, audiotapes, CD's, and our website. If, for example, you're seeking to learn more about preparing students with Fragile X for the work-world, we'll do a database search for "employment," "pre-vocational," "vocational," and similar keywords. The results of that search will allow us to direct you to each title that contains information about those subjects.

These are just some of the ways the National Fragile X Foundation is committed to assisting families and professionals in the Fragile X community. As quickly as new information about Fragile X intervention, treatment and therapy becomes available we will add it to our resource list and database. As always, I can be reached at 1-800-688-8765, or at NATLFX@sprintmail.com. You can find us on the web at www.FragileX.org and, of course, you can always write us at PO Box 190488 / San Francisco, CA 94119.

Best Buddies

Best Buddies International, a nonprofit organization, aims to enhance the lives of people with mental impairment by providing opportunities for one-to-one friendships and integrated employment. Best Buddies works with high schools and middle schools to set up friendships between students with and without mental impairment. They currently have offices in about one dozen states. To find out more, visit www.bestbuddies.org or call 1-800-89-BUDDY.

Best Buddies' newest program, e-Buddies, builds e-mail friendships between people with and without mental retardation. People twelve years or older are eligible. All e-Buddies participants complete the same online application found at www.ebuddies.org. After the application is submitted, all prospective e-Buddies are screened before matching. e-Buddies agree to e-mail each other once a week for one year, or more often if they wish.

Some people with mental retardation may need assistance in typing or reading their e-mail messages, according to Lisa Derx, e-Buddies Director. "e-Buddies creates friendships," Derx said. "Friendship can occur even if one party needs help reading an e-mail or has to dictate a response to someone else for typing."

Derx said that special education teachers have found that e-Buddies helps motivate students to want to improve their keyboard skills, as well as reading and writing. "Getting a regular message from a friend is a powerful motivator," Derx said. You can reach Lisa Derx, e-Buddies Director at 202-266-2295 or EbestBuddies@aol.com.

Bridge Over Troubled Waters

by John May

The years since our child was diagnosed with Fragile X and the subsequent founding of FRAXA have slipped by with ever increasing speed. Some of the years have been hard and hurtful while others have filled us with joy and hope.

The development of FRAXA, much like the development of our child, has been wondrous to behold, far exceeding our expectations. FRAXA has grown into an ever more powerful and influential force in its drive to increase awareness, funding and research for a cure to the common disease that unites us.

Reading about the research being done in the many grants being financed by FRAXA, gives us hope for a future where our child may not be limited in his options, dreams and experiences because of a genetic fluke. Plank by plank, FRAXA is building a bridge to the future that can do much to still the troubled waters of our past.

John May's wife Kathy was one of the original founders of FRAXA in 1994 and has served on its Board of Directors ever since. For all of the energy, the brainstorms, and most of all, for all of the hundreds of phone calls, Kathy, thank you! May there be many more phone calls over the coming years.

FRAXA EVENTS

Fundraising for FRAXA

Have you ever read the newsletter and wondered where all the grant money our researchers receive comes from? It comes from YOU! None of this would be possible without the people who are dedicated to helping raise funds for FRAXA. So if you have any idea for a fundraiser in your community - big or small — FRAXA would be grateful for the help. Even a few hundred dollars is meaningful! Anything is possible — from a garage sale to a dressy dinner party to a letter to family and friends, asking that they donate to FRAXA instead of giving you that new tie or scarf at holiday time. Anything goes!

With so many research projects now underway and dependent on our support, FRAXA needs to build consistent, longterm funding sources. Most serious research projects are multi-year endeavors which require commitments of funds over several years. FRAXA depends entirely on donations and fundraising. In 1999, a single, million dollar donation raised our income dramatically. If we knew we could raise this kind of money every year, we could commit more funds to research NOW, thus speeding up progress towards a cure.

You can help. One possibility is to call or write us to pledge a monthly credit card donation. This is easy to start and just as easy to stop or change with a phone call or a letter. If you would like to talk about your ideas, or if you would like to see brochures, invitations, and other materials that others have used successfully, call Debbie Stevenson at 212-828-1883, email dstevenson@pop.net, or Katie Clapp at 978-462-1866, email kclapp@fraxa.org .

Texas Fragile X Gala

With Honored Guest Mary Higgins Clark
May 18, 2001
7:00 – Cocktails & Silent Auction
8:00 –Dinner
At The Four Seasons Hotel, Austin, Texas
Music by The Beamers

The tickets are $125. The sponsorship levels are as follows:

Friends of FRAXA - $1000	Patron - $2500
Bronze Sponsor - $5000	Silver Sponsor - $10000
Gold Sponsor - $15000	Platinum Sponsor - $20000

Contact: Claudia & Michael Burnett: (512) 453-4210 or 453-4806, wilburne@aol.com

Patrick's Pals V

by Jon Pressman, Steve Savarese, Bill Rome, Scott Katz, and Jimmy Marks

We proudly and enthusiastically announce our annual Patrick's Pal's Three on Three Basketball Tournament to be held on June 2, 2001 in Cambridge, MA. Patrick's Pals V represents our fifth year of organizing the event to raise awareness and funds for the research of Fragile X.

We emphasize the word proud for a number of reasons. When you set out to try and make a difference in the world of medicine and someone's life, there are numerous hurdles. The relatively modest hurdles that we have overcome in organizing this tournament for five years have shown each of us how difficult the hurdles must be for those with Fragile X or any serious condition. Accordingly, we once again honor Patrick, his parents Pamela and James, our boyhood friend, with Patrick Pal's V. 100% of the funds that we raise will go to FRAXA to further scientific research, so that each of you who plays, makes a donation, or lends your time to the tournament will contribute to the cause.

This year there will, of course, be the traditional three-on-three double elimination tournament, shooting contests and games (including prizes) for the younger hoopsters, an art table, lunch for all attendees, and, for the first time, a silent auction of sports memorabilia. As day turns to night, join us for more fun and friendship at our Patrick's' Pals annual barbeque and softball game. No one will leave hungry! For an invitation or more information, call Katie Clapp at FRAXA.

Thursday, May 3, 2001
The 4th Annual
"Solve the Mystery of Fragile X"
Gala
Hosted by Mary Higgins Clark
at New York City's
Tavern on the Green

Co-chairs, Mary Jane Clark and Margaret Ann Behrends

The flowers will be bursting into bloom again, signaling another rebirth of our efforts to find treatments and a cure for Fragile X Syndrome. The site of the 2001 Gala is truly an appropriate place to renew our fundraising quest. The Tavern on the Green in May is arguably the prettiest spot in New York. Distinguished journalist Roger Mudd has graciously agreed to guide us through the evening as we unite in our cause. Mark your calendars now for a beautiful evening of cocktails, dinner and entertainment along with, most importantly, an update on the state of our progress in solving the mystery of Fragile X.

Individual ticket: $350
Individual table sponsor: $3500
Individual table benefactor: $5000
Corporate sponsor: $5,000
Corporate Patron: $10,000
Corporate Benefactor: $25,000

YOU CAN HELP: In order for the Gala to be the biggest success possible, ***We must have corporate sponsorships***. Please let us know if you have any suggestions, connections, or ability to help with this. ***It's crucial!*** For more information contact Katie Clapp at 978-462-1866 or email Mary Jane Clark at maryjane.b.clark@worldnet.att.net.

EVERY SINGLE BIT HELPS

If you'd like to do something to help with FRAXA fundraising, how about running a raffle? The prize: Two tickets to the Mary Higgins Clark Gala on May 3, 2001 at NYC's Tavern on the Green? One sister of a Fragile X boy is doing just that, selling tickets at her high school for a dollar a piece. Think about doing it in your neighborhood, at your club or community center. Sell the raffle tickets for whatever seems best to you . . . one, five or ten dollars...you need to raise at least $700 to cover the cost of the tickets. We want to broaden our FRAXA base and get the word out to more people. This is a great way of doing it.

Philadelphia Fundraiser

by Cristy and Mitchell Hollin

On October 19th, 2000 over three hundred people gathered at Green Valley Country Club, just outside Philadelphia, to support our Third Fragile X Fundraiser. The event was chaired by our dear friends, Nicole and Todd Kendall, Jamie and Warren Klein, and Marla and Robert Friedman, who worked tirelessly to help us raise over $120,000 for fragile X research. The theme of the evening was "team spirit…being part of a winning team."

After being greeted by an energetic and beautiful squad of cheerleaders, guests were free to roam around our boutiques, which were set up by local stores donating 20% of the proceeds to our charity. Guests could also bid on an impressive and lavish display of auction items including jewelry, trips, and sports memorabilia generously donated by wonderful retailers . One of our most popular items was an autographed picture of Britney Spears. We also had a cruise and a trip to Aspen Colorado with a stay at the Aspen Club Lodge.

Our evening then kicked off with a team spirit cheer led by local entertainer, Reggie Williams. Reggie's cheer was followed by a moving speech from Jonathan Doring, a twenty year old who is affected by fragile X. Jonathan flew in from Florida to tell us what it's like to live with fragile X. He shared his failures, hopes and dreams with us leading us into the world of fragile X. After Jonathan's speech, we all cried for the person he'll never be due to fragile X, while rejoicing in the remarkable person he is. Jonathan's speech was followed by a video featuring our eight year old son, Matthew Hollin, who is also affected by fragile X. Following that, Bill Parker, father of two children with fragile X, spoke of his experience with fragile X and then live auctioned tickets to a Flyer's hockey game and introduce some of the past and present professional players.

Finally, after a full course, sit down dinner, we were all treated to a fabulous fashion show by Saks Fifth Avenue. To say that we were awed and overwhelmed by the tremendous show of support we received from our family and friends would be an understatement. What a night! We chose to divide the proceeds of the evening between Fraxa Research Foundation and Conquer Fragile X Foundation with the hopes that a cure or treatment will be found for fragile X.

FRAXA POSTDOCTORAL FELLOWSHIPS REQUEST FOR GRANT APPLICATIONS

Upcoming Deadlines: May 1, 2001 and December 1, 2001

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's Katie Clapp, Mary Beth and David Busby and Senator Hillary Clinton at The White House

FRAXA UPDATE

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PLEASE HELP FRAXA

in supporting research aimed at treatment for fragile X

RESEARCH FOUNDATION

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

Yes, I would like to help FRAXA

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

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FRAXA UPDATE

SUMMER 2001

VOLUME 8, NO. 2

A PUBLICATION OF FRAXA RESEARCH FOUNDATION

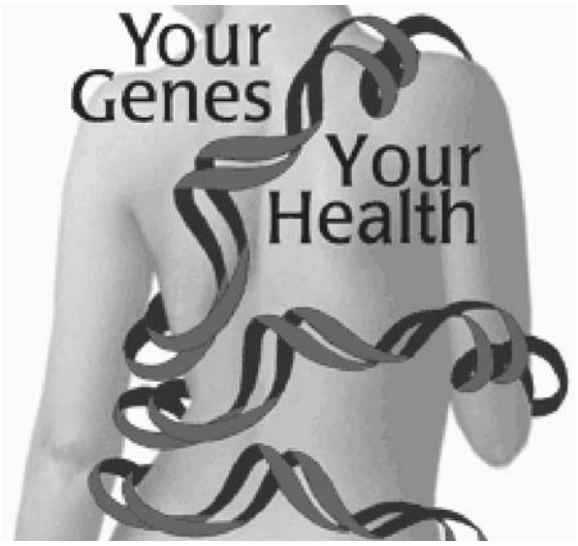
"NEVER DOUBT that a small group of thoughtful, committed citizens can change the world. INDEED, it's the only thing that ever has."

— 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 Nimchimsky 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.) 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.

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

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 main goals: awareness and fundraising!

Lisa's son Alex Kowal

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 establishment 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

continued from page 1

research

THREE NEW FRAXA FELLOWSHIPS AWARDED

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 AMPAkines, which are currently being tested in fragile X animals by the Greenough lab, with FRAXA funding.)

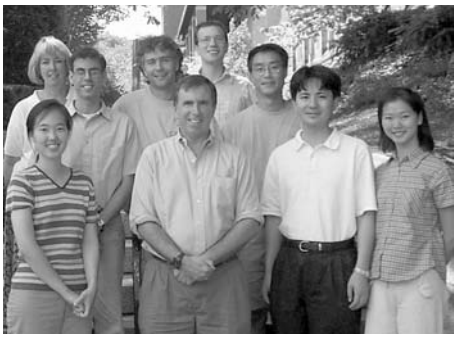
Dr. Zhu previously trained in the lab of Nobel prize winner Dr. Bert Sakmann at the Max Planck Institute in Heidelberg, where the state-of-art multiple whole-cell recording technique was first developed. He is now a postdoctoral fellow in the lab of Dr. Roberto Malinow at Cold Spring Harbor Laboratory. 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:

GRANTS AND FELLOWSHIPS RENEWED

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

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.

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 MAbs 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

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 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.

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 word, 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.

The Mary Higgins Clark Gala

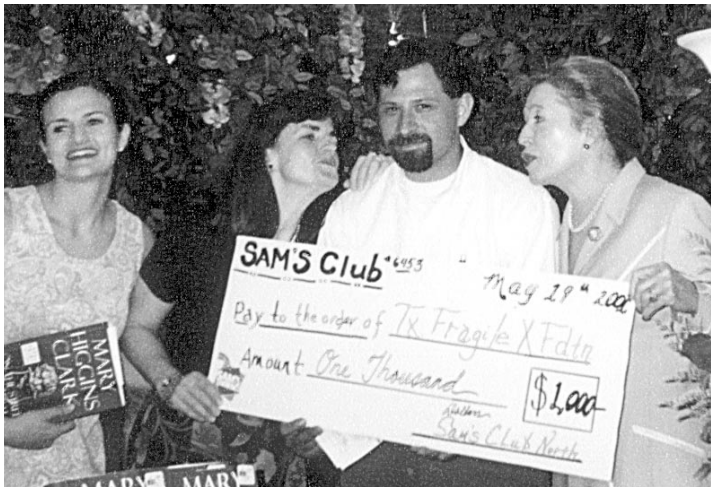
Above: Megan Massey, parent and FRAXA Director, **Sopranos** *star Vince Curatola, (a.k.a. gangster Johnnie Sack), Katie Clapp, and* **Sopranos** *star Dan Grimaldi, who plays henchman Patsy Parisi. Below: Parent Marilyn Therrel and Mary Higgins Clark*

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 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.

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

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 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

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

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FRAXA UPDATE

WINTER 2001-2

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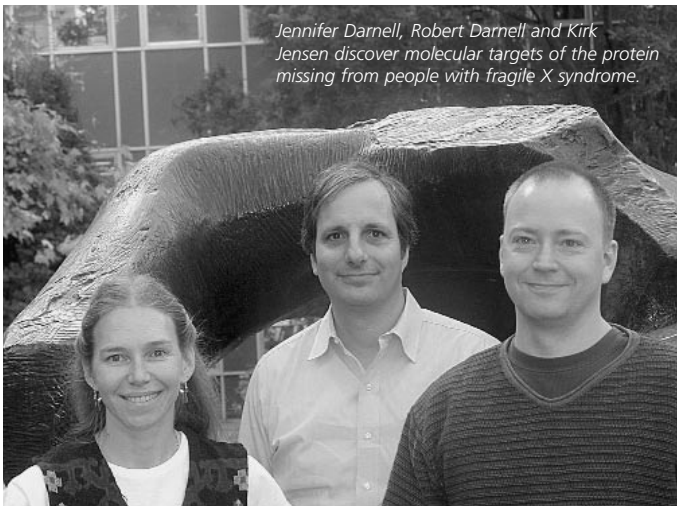
"NEVER DOUBT that a small group of thoughtful, committed citizens can change the world. INDEED, it's the only thing that ever has."

— 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.



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

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.

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.

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

Also in this issue:

FRAXA is a nonprofit, tax-exempt charity run by parents of children with fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 2000 males and 1 in 4000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of fragile X, by direct funding of promising research projects and by raising awareness of this disease.

Report from Washington:

by Mary Beth and David Busby

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.

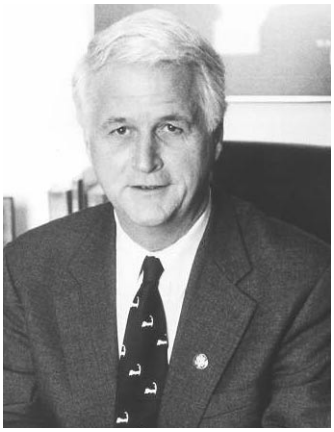
House:

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.

Continued from page 1

"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."

WHAT ARE mRNAs?

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

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.

"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

Debra Skinner, Don Bailey, and Karen Sparkman

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.**

PARENTS' CORNER

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

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

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.


A few of the many volunteers

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

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.

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

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!

PLEASE HELP FRAXA RESEARCH FOUNDATION

in supporting research aimed at treatment for fragile X

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

Yes, I would like to help FRAXA

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

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