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

Closer Than Ever To FX Treatment!

This is FRAXA's thirteenth year working towards the development of effective Fragile X treatments – from initial ideas hatched in university labs to actual medications on the horizon, to help people with Fragile X. FRAXA's many supporters and their unwavering efforts, as parents, advocates and researchers have brought us all to this point.

Current FRAXA-funded research (see page 4) is now headed toward development of effective medication for Fragile X. FRAXA Research Foundation wants to speed these studies through clinical trials as quickly as possible to get them into people's medicine cabinets. To accomplish this, we've collaborated with top physicians to start two new clinics, where, ultimately, some of these treatments will be tested. FRAXA has a critical role in developing treatments for Fragile X because no one else has taken the lead on this challenge – not the U.S. government, which has funded basic research but no Fragile X clinical trials, and not big pharmaceutical companies, which don't see a profit in this small market.

In these pages, you will read about university-based research, new clinics, and corporate and government partnerships. All these endeavors have the same ultimate goal: to bring treatments to children and adults with Fragile X as soon as possible. All this is possible because we have all worked so hard, so long together.

Fragile X and Autism: Testing the Ties

Those who have been following recent exciting developments in Fragile X research will have heard about the mGluR theory of Mark Bear and others, which may explain Fragile X and lead to possible treatments. What you may not know is that multiple studies at several universities have converged to suggest that this may also be a common pathway shared by Fragile X syndrome and many autism spectrum disorders.

One way to prove the existence of a common pathway is to use full-length DNA sequencing to test specific genes in children who have

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Also in this issue:

Fundraising Successes

Just a few months ago, doctors told Kevin and Chrissy Blackmon, of Georgia, that their two young sons have Fragile X syndrome. Since then, the United All Stars kart racers and their friends have raised thousands of dollars for FRAXA.

This was one of many events organized by friends and families to support FRAXA's mission. See page 10.

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 4000 males and 1 in 6000 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 Fragile X Clinics

Children's Hospital Boston

Fragile X Featured in Boston Autism Consortium

Boston has long had an abundance of outstanding scientists and clinicians, but little coordination among them. As one researcher from the Southeastern U.S. recently remarked, *"We in the rest of the country have always said that we'd be in big trouble if those folks in Boston could ever get their act together. Well, I think we're in trouble now!"*

Many Boston-area clinicians and researchers who work in the developmental disorders field are coming together in a new Autism Consortium. This consortium aims to facilitate the advancement, understanding and treatment of autism and related developmental disorders. Scientists from Massachusetts Institute of Technology (MIT) will collaborate with researchers from Tufts, Boston University, Harvard Medical School, and other Boston medical institutions.

Fragile X research will play a central role in the consortium with significant resources devoted to its study. One of the consortium leaders is Dr. Christopher Walsh, a Harvard Medical School Professor, Howard Hughes Investigator and Chief of the Division of Genetics at Children's Hospital Boston. Dr. Walsh became convinced of the potential Fragile X research holds as a model for autism after hearing a talk by FRAXA researcher Dr. Tom Jongens. Dr. Walsh and colleagues at Children's Hospital have now established a Fragile X Clinic, directed by Dr. Jonathan Picker. The clinic is currently scheduling patients. Interested families can call Sharyn Lincoln at 617-355-4688. Visit visit www.childrenshospital.org/clinicalservices.cfm for general information.

The new clinic would not have been possible without the generous support of Harry Manion. Harry is a partner at the Boston law firm of Cooley Manion Jones, LLP, and a father of four children; his oldest son, J.P., has Fragile X. In 2004, Harry chaired FRAXA's Boston gala, raising over $700,000. Harry's dedication to helping Fragile X families is inspiring to all.

Harry Manion

One of FRAXA's goals is to help establish Fragile X clinics, like this one, where multi-center trials of new Fragile X treatments can be conducted. With two first rate Fragile X clinics now in Boston – as far as Fragile X is concerned – Boston really is getting its act together!

Indiana University

Clinical Trial of Abilify starting at Indiana Clinic

Years ago, FRAXA's Medical Director Mike Tranfaglia met Dr. Christopher McDougle at an NIH autism conference and tried hard (and unsuccessfully) to interest him in studying Fragile X. Dr. McDougle leads an internationally renowned group in the Section of Child & Adolescent Psychiatry at Indiana University School of Medicine. They specialize in the psychopharmacology of autism and other developmental disorders. We are pleased to introduce their new Fragile X clinic and site for clinical trials.

Craig Erickson and Christopher McDougle

This clinic, run by Dr. Craig Erickson under the direction of Dr. McDougle, may be a good option for people with Fragile X in need of behavioral and psychopharmacological services.

Contact info:

Riley Child and Adolescent Psychiatry Fragile X Syndrome Treatment Center, Indianapolis, phone: 317-274-8162.

Appointments are scheduled for Thursday afternoons, typically within 2-6 weeks of your initial phone call. All patients with Fragile X are welcome regardless of age.

Trial of Abilify

The Section of Child & Adolescent Psychiatry at Indiana University School of Medicine will be conducting a 12-week study funded by the FRAXA Research Foundation designed to study the effects of aripiprazole in individuals with Fragile X syndrome. Participants must be between the ages of 6 and 35 with Fragile X Syndrome and have behavioral difficulties such as irritability, tantrums, aggression or self-injurious behavior. Participants will receive study medication at no charge. For additional information about study procedures, please call Marianna at 317-278-6253.

RESEARCH MEETINGS

FRAXA Research Forum: Atlanta, Georgia

The largest annual gathering of scientists studying brain disorders is the Society for Neuroscience annual meeting. Each year FRAXA staffs a booth to reach out to students and researchers. We thank Atlanta parents Elly and Michael Scott, and FRAXA Board Member Leslie Eddy for their help. Elly and Leslie spent two days at the FRAXA booth, "talking the talk" of flies, genes, and mice.

Leslie Eddy, Elly Scott

During this event, FRAXA hosts a Fragile X Research Forum to present new discoveries and to encourage collaborative research. This year's forum, organized by Drs. Yue Feng and Gary Bassell, and funded by Novartis, addressed progress in understanding the neurobiology of FMRP and possible directions for treatments.

Examples:

Dr. Mark Bear, Professor at MIT, has bred two kinds of mice together (Fragile X mice and mice that have less mGluR5). Those baby mice which have both Fragile X and reduced mGluR5, are "cured" in terms of three of four tests that were used. This result confirms the mGluR Theory of Fragile X, which says that drugs which decrease mGluR5 signaling in brain cells could treat Fragile X.

Dr. Steve Warren and his team at Emory accidentally discovered that a fruit fly food with excess glutamate kills Fragile X flies, although it is harmless to normal flies. (This is no accident: the Glu in mGluR5 is glutamate, so the mGluR theory of Fragile X is consistent with this result.) Dr. Warren's group tested 2000 existing and experimental drugs to see if any of them can save the flies. A subset of drugs which protect the flies – many of which act on the GABA system – are now being evaluated as potential treatments.


Eric Klann, PhD, Baylor, "Translational and proteosomal regulation of FMRP during mGluR dependent LTD"


Stephen Warren, PhD, Emory, "A 2000 compound drug screen using the Drosophila Fragile X model"


Story Landis, PhD, NINDS, "Neuroscience insights offer therapeutic promise: FRAXA as a case


Robert Wong, PhD, Suny-Brooklyn, "Epileptogenesis in Fragile X model mice: Role of synaptic metabotropic glutamate receptors"


Mark Bear, PhD, MIT, "The mGluR Theory of Fragile X"


Gary Bassell, PhD, Emory, "The stimulating Travels and functions of FMRP"

Our keynote speaker, Dr. Story Landis, Director of the National Institute of Neurological Disorders and Stroke (NINDS), remarked on the fast pace of recent progress and emphasized the importance of Fragile X research as a model for other more complex neuropsychiatric disorders.

Michael Tranfaglia at FRAXA booth at the Society for Neuroscience annual Meeting

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unexplained symptoms of Fragile X and autism, but test negative on current Fragile X tests. These children may, for instance, have other mutations on the FMR gene, or mutations on related genes, that mimic symptoms of Fragile X.

Advances in robotic genetic testing now make it possible to do full-length sequencing of genes at a reasonable cost. If this testing succeeds in finding new mutations, it could result in powerful new tests for autism spectrum disorders, providing specific genetic diagnoses for many undiagnosed children. This could open the door to developing targeted treatments for hundreds of thousands of children and adults who suffer not only from Fragile X, but from a far larger number of autism spectrum disorders.

FRAXA is currently trying to raise funds for this project, which we believe has the potential to alter the landscape of autism research. If successful, it could result in precise diagnosis and treatment for a major subset of autism spectrum disorders.

EDITOR'S SUMMARIES

Dr. Christopher McDougle and **Dr. Craig Erickson** are conducting a trial of Abilify, a drug currently prescribed for many people with Fragile X.

FRAXA has now funded three treatment trials. A trial of ampakine CX516 by Elizabeth Berry-Kravis has been completed. It showed no therapeutic effects, but demonstrated the ability to conduct large scale trials in Fragile X subjects.

In retrospect, this study was hampered by an inadequate dose of the medication being evaluated. More potent Ampakines are now in development.

Another of Dr. Berry-Kravis studies is an ongoing trial of lithium. Initial feedback is promising.

Dr. Mark Bear, Dr. Emily Osterweil and colleagues are pursuing the **mGluR Theory of Fragile X** which states that a pathway between brain cells, called mGluR-LTD, is overactive in Fragile X and that a class of compounds which block this pathway (called mGluR antagonists) have promise as specific treatments for Fragile X syndrome.

Aripiprazole in Fragile X Syndrome (Open Clinical Trial)

CHRISTOPHER MCDOUGLE, MD
Principal Investigator

CRAIG ERICKSON, MD
Postdoctoral Fellow
Indiana University, $30,000

Many children and adults with FX currently take the drug aripiprazole (a.k.a. Abilify) to treat symptoms like aggression and self-injurious behavior, but there has never been a clinical trial of this drug in Fragile X patients. This will be an open trial, in which all participants take the drug and none are given a placebo. A similar trial is being conducted by this research group in autistic patients, so the results from the two patient groups can be compared. *(KNC)*
Also see article, page 2.

Investigating mGluR-Mediated Protein Synthesis in Fragile X Syndrome

MARK BEAR, PhD

EMILY OSTERWEIL, PhD

Massachusetts Institute of Technology, $40,000

by Emily Osterweil

The mGluR theory of Fragile X is based on the assumptions:

1. that many lasting consequences of group I metabotropic glutamate receptor (mGluR) activation require protein synthesis, and
2. that these are exaggerated in the absence of the Fragile X protein (FMRP).

This theory suggests a scientific rationale for the treatment of Fragile X syndrome (FXS). While much attention has recently been devoted to use of mGluR antagonists for treatment of FXS, there has been little attention paid to other potential downstream targets. Targets in the biochemical pathways that link mGluRs and FMRP-dependent protein synthesis may offer new, more specific therapeutics.

My long-term goal is to understand the biochemical pathway that links mGluR activation to protein synthesis and LTD, and to understand the consequence of the loss of FMRP. I am studying the molecular mechanisms of protein synthesis in hippocampal slices and T-lymphocytes (a kind of white blood cell) isolated from FMR1 knockout mice.

Emily Osterweil

Specifically, I will measure protein synthesis in hippocampal slices and T-lymphocytes, in the presence and absence of mGluR5 agonists and antagonists, and utilize proteomic screening to identify proteins made in excess in tissues lacking FMRP.

My hope is that such understanding will suggest new drug targets for the treatment of Fragile X.

Decreased Excitatory Drive onto Neocortical Inhibitory Neurons in a Mouse Model of Fragile X Syndrome

JAY GIBSON, PhD

KIMBERLY HUBER, PhD

Co-Principal Investigators
University of Texas at Southwestern, $40,000

Jay Gibson

by Jay Gibson

Cortical neurons in Fragile X patients and from mouse models of Fragile X have abnormally long dendritic spines and more spines than normal. Synaptic plasticity alterations have also been found. However, altered behavior and epilepsy in Fragile X Syndrome are not directly mediated by such properties, but rather by the strength and timing of synaptic connections between neuron types. The basic synaptic connectivity of neuronal circuits must differ in Fragile X patients, but no data exist addressing this issue. Furthermore, once a synaptic connectivity difference is found, how does this impact brain function in patients?

We have found a decrease in the excitatory synaptic strength onto a specific subclass of inhibitory neurons in Fragile X mice. This decreased excitation would be expected to result in less activation of these neurons, which could lead to sensory hypersensitivity and perhaps epilepsy in Fragile X patients. If this deficit occurs in other areas of the brain, it could also underlie cognitive deficits in patients.


Kimberly Huber

We are examining this deficit. Because mGluR signaling regulates somatosensory cortical development and is enhanced in Fragile X mice, we will test whether enhanced mGluR5 activity contributes to this phenomenon. If it does, this adds evidence that mGluR5 blockers could effectively treat Fragile X.

Assessing the Role of Development in Fragile X Syndrome Using Inducible Mouse Models of FMR1

DAVID NELSON, PhD Principal Investigator

RUITING ZONG, PhD Postdoctoral Fellow
Baylor College of Medicine, $40,000

by David Nelson

We are generating additional mouse models of Fragile X which have had the FMR protein removed or replaced at various time points during their lives. Our aim is to study neuronal and behavioral aspects of these mice.

Deletion of FMR1 in mice during early development will be achieved by in vivo application of an inducible enzyme that can delete the FMR1 gene. A similar approach will allow restoration of full FMR1 expression in mice. We will determine whether the differences between normal mice and mice lacking FMR1 result from an ongoing lack of FMRP or are due to the absence of FMRP during early development.

We will investigate whether restoring FMRP in Fragile X mice after birth can rescue the abnormal neuronal and behavioral phenotypes and whether loss of FMRP in later stages can cause those phenotypes. We will study their sleep/wake cycles and other behaviors, electrophysiology in the brain, and misregulation of specific genes such as MAP1B.

These new mouse models will provide additional tools for testing potential therapies.

Glucocorticoid Regulation and the Phenotype of the Fragile X Knockout Mouse

WILLIAM GREENOUGH, PhD
Principal Investigator

JULIE MARKHAM, PhD
Postdoctoral Fellow
University of Illinois at Urbana-Champaign, $12,800


Julie Markham

Studies in the Greenough lab have demonstrated that one "target" regulated by the Fragile X protein (FMRP) is the messenger RNA for the glucocorticoid receptor. Glucocorticoids like cortisol are the body's primary "stress hormones," so this research suggests that absence of FMRP may result in an abnormal response to stress. This dovetails with the findings by Dr. Alan Reiss of abnormal salivary cortisol response to social stressors in a small group of boys with Fragile X.

Julie Markham has shown that corticosterone response to stress in Fragile X mice is abnormal. There are several possible explanations for this: stress could be perceived abnormally by the mice, the response to stress could be exaggerated, or the secretion of stress hormones could be misregulated. This study will use behavioral and pharmacologic techniques to determine the reason for this stress response. – *MRT*

EDITOR'S SUMMARIES

Dr. Jay Gibson and **Dr. Kimberly Huber** have found a striking deficit in some brain circuits in Fragile X mice – which may explain the epilepsy and hypersensitivity observed in many Fragile X patients. It may also be involved in learning. They will determine whether the mGluR Theory of Fragile X can explain it.

Drs. Gibson and Huber also collaborate on the home front: they are married and the parents of two young children.

This award is funded with support from The Meadows Foundation. **Dr. David Nelson's** project addresses a key question: if we find a way to restore the missing protein to people with Fragile X, to what extent could it reverse their symptoms? What if they are already well into adulthood? Dr. Nelson will develop new mouse models to answer this question.

As every parent knows, high stress levels are a huge problem for children with Fragile X. **Dr. Greenough** and Dr. Markham are looking at the stress response in Fragile X mice to see why it might be abnormal.

EDITOR'S SUMMARIES

Dr. Warren and Dr. Narayan are looking at the link between the Fragile X protein and RNAi – a recently discovered mechanism which cells use to turn genes on and off.

Dr. Tonegawa and Dr. Hayashi have discovered another possible treatment target: a protein called PAK which seems to be overactive in Fragile X mice.

Compounds exist which decrease PAK's activity in cells, so the researchers will try to use one of these compounds to reverse symptoms in the mice.

About 1/4 of boys with Fragile X suffer from seizures, and **Dr. Wong** studies the mechanisms which explain this. He has found abnormal activity patterns in neurons of Fragile X mice, and he has also shown that MPEP (a compound that blocks mGluR5) can stop this abnormal pattern,thus avoiding seizures.

Characterizing Phosphorylation as a Regulator of FMRP Translational Suppression in Response to mGluR Activity

STEPHEN WARREN, PhD Principal Investigator

USHA NARAYAN, PhD Postdoctoral Fellow

Emory University, $40,000 RENEWAL

This group is studying how the Fragile X protein is modified in response to mGluR activation in a biochemical process called phosphorylation. This common control mechanism in cells is one way that protein translation is regulated. Dr. Warren's team has identified the enzyme activity driven by mGluRs as the main mechanism for dephosphorylating FMRP and allowing dendritic protein synthesis. This change in phosphorylation status is associated with disengagement of FMRP from the miRNA machinery, which is thought to enhance sequence-specific translational suppression.

Previous FRAXA grants have funded investigation of the "RNA interference" mechanism, and now we are beginning to develop a coherent picture of how this process relates to mGluR signaling. This research has yielded several potential therapeutic targets for Fragile X and has generated candidate genes for autism. – *MRT*

Interaction Between FMRP and PAK on Synaptic Morphology, Function and Animal Behavior

SUSUMU TONEGAWA, PhD
Principal Investigator

MANSUO HAYASHI, PhD
Postdoctoral Fellow

Massachusetts Institute of Technology
$40,000 RENEWAL

The goal of this project is to identify new signaling pathways that regulate or interact with FMRP. The investigators have found that a protein called PAK, a regulator of cytoskeletal and synaptic structure, has an opposite effect from FMRP on synaptic shape and function.

Many biological processes exist in a yin/yang constant state of tension, and so it may be that absence of FMRP allows too much PAK activity. This opposing pathway may offer a convenient therapeutic option, since blocking PAK is easier than replacing FMRP.

These researchers previously found that mice with reduced PAK have neurons with fewer dendritic spines and a lower proportion of long, thin spines, compared to normal mice. In contrast, neurons in FMR1 knockout mice and FXS patients show opposite features: more spines, especially the longer and thinner ones.

These two knockouts have now been crossbred, and the offspring (which lack FMRP and have reduced PAK) have dendritic spines of normal shape, size, and distribution. Current studies are investigating whether other phenotypes (like behavior) are also rescued.

This evidence suggests that PAK inhibitors may be therapeutic for Fragile X. A biotech company in Cambridge, MA is developing PAK inhibitors to treat Parkinson's disease; these compounds may find another use in the treatment of Fragile X. – *MRT, KNC*

NEW FRAXA

Metabotropic Glutamate Receptor and Epilepsy in Fragile X

ROBERT WONG, PhD
Principal Investigator

State University of New York
$45,000 RENEWAL

This lab studies the signaling pathways involved in the induction and maintenance of epileptic activity (seizures) in the brain's hippocampus. In their model system, Dr. Wong and col-

leagues trigger epileptic activity in normal mouse brain slices by administering drugs which stimulate mGluR1 and mGluR5. However, when they looked at hippocampal slices from Fragile X mice, they saw spontaneous epileptic activity – without any need for drug stimulation.

In keeping with the mGluR theory of Fragile X, they hypothesized that blocking mGluR5 might restore normal function to this brain tissue. Indeed, application of MPEP (an mGluR5 antagonist) eliminated this abnormal spontaneous seizure activity.

The team has now shown that this seizure activity can also be inhibited by other treatments which suppress mGluR signaling pathways. These results suggest that FMRP plays a key role in the control of signaling at the recurrent glutamatergic synapses in the hippocampus. Absence of this control causes synaptically activated group I mGluRs to elicit epileptogenic activity. This may be the basis for seizures in Fragile X, and it may also disrupt neural circuits important for normal learning, memory, and behavior. – *MRT*

Analysis of Expression of FMR1 Transcript Isoforms in Mouse Brain

DAVID R. MORRIS, PhD
Principal Investigator

DAVID R. BRACKETT, PhD
Postdoctoral Fellow
University of Washington, $40,000 RENEWAL

While we commonly discuss the Fragile X protein FMRP as if it were a single protein, actually 12 different versions of FMRP (called isoforms) have been found in mouse brain cells. Alternative splicing of the FMR1 gene results in proteins with different sizes and physical properties.

This team aims to understand the variation in distribution and function of FMRP isoforms. They seek to identify isoforms of FMRP in mouse brain, and define their expression patterns. This information, along with the reagents generated by this project, will be valuable to the Fragile X field. – *MRT*

Role of FMRP Interacting Protein CYFIP1 in the Pathogenesis of Prader-Willi and Fragile X Syndromes

YONG-HUI JIANG, PhD
Principal Investigator
Baylor College of Medicine, $45,000 RENEWAL

The protein CYFIP1 was discovered by FRAXA-funded researchers in France several years ago. It works with the Fragile X protein, apparently to shuttle messenger RNAs around the cell. Recently, lack of this protein has been implicated as a possible cause of Prader-Willi Syndrome, a disorder with clinical features similar to those seen in a subset of people with Fragile X (the so-called "Prader-Willi phenotype").

This group is studying the connection between Fragile X and Prader-Willi. They are investigating whether CYFIP1 knockout mice share some of the features of Fragile X knockout mice, like enhanced LTD. This will shed light on the common mechanisms involved in these two syndromes and may suggest treatments for both disorders. – *MRT*

dRac1-CYFIP-dFMR1 Pathway: Actin Cytoskeleton Remodeling and the Regulation of Local Protein Translation at the Synapses

ANGELA GIANGRANDE, PhD
Principal Investigator
CNRS Strasbourg, France
$45,000 RENEWAL

This group has been studying the link between FMRP and the cytoskeleton of neurons, a process which regulates transport of mRNAs in neurons. They were the first to demonstrate interactions of FMRP with CYFIP, the protein implicated in Prader-Willi Syndrome. They will now

EDITOR'S SUMMARIES

Dr. Morris and **Dr. Bracket** are conducting an important basic study of the alternate forms of Fragile X protein found in brain cells. There are 12 different known versions of the protein, and it is important to know whether they have unique roles in the brain.

Dr. Jiang's study explores a gene called CYFIP1 which links Fragile X and Prader-Willi syndrome. Prader-Willi is a developmental disorder which causes mental impairment and obesity.

The next project, conducted by **Dr. Giangrande**, also involves the overlap between Fragile X and Prader-Willi Syndrome. The more we learn about the underlying cause of Fragile X, the clearer it becomes that developmental disorders and autism share common pathways. The world of Fragile X research is quickly producing advances will help not just those with Fragile X, but also people with other brain disorders.

EDITOR'S SUMMARIES

Dr. Contractor and **Dr. Harlow** plan to find out whether Fragile X symptoms in mice can be reversed by enhancing AMPA activity in their brain cells. This is important because we do not yet know whether AMPAkine drugs (which enhance AMPA activity) could effectively treat Fragile X. If this approach works, it offers hope that the potent AMPAkines now being developed by pharmaceutical companies might be effective in Fragile X patients.

Dr. Cox is investigating cell-to-cell communication in Fragile X mice. He finds a change in LTP, which (along with LTD) is a key building block of learning and memory.

Dr. Fallon's basic research project explores how experience – in this case, exposing Fragile X mice to different odors – can directly modify protein levels in brain cells.

Dr. Gao's project shows how extraordinarily productive fly research can be. He has found 42 potential treatment targets in Fragile X flies, and he is in the process of further investigating the potential of these targets.

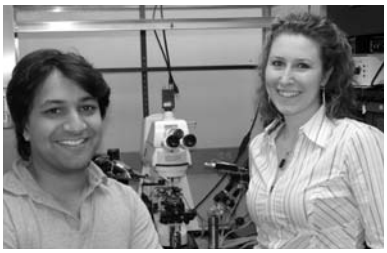
delineate the molecular interactions of FMRP which enable proper transport and translation of dendritic mRNAs. They may generate additional targets for drug discovery. – *MRT*

Rescuing Synaptic Function in Fragile X with Mutant AMPA Receptors

ANIS CONTRACTOR, PhD Principal Investigator

EMILY HARLOW, PhD Postdoctoral Fellow

Northwestern University, $55,000



Anis Contractor, Emily Harlow

This project investigates AMPA receptor signaling in Fragile X. Excitatory synaptic connections in the cortex of Fragile X patients are disrupted and display an immature morphology, suggesting that deficits in glutamate signaling may underlie some learning impairment seen in Fragile X. This team aims to define the alterations in synaptic transmission and rescue deficits in AMPA receptor signaling in Fragile X mice.

Engineered AMPA receptor subunits will be targeted to synapses in the cortex using viral mediated gene transfer and genetic manipulation in a newly created mouse strain, in an attempt to rescue deficits in the Fragile X mice. If successful, this would support the pursuit of AMPA receptor modulators, like Ampakines, as a potential treatment.

This team has already found a striking deficit in AMPA receptor function in the Fragile X mouse model. – *MRT*

Alterations in Neocortical Neuron Excitability Associated with Fragile X

CHARLES COX, PhD

Univ. of Illinois, $50,000 RENEWAL

Dr. Cox is studying electrophysiology and synaptic plasticity in Fragile X mice. They have confirmed the findings of Peter Vanderklish, that intrinsic electrical properties of neurons are normal in Fragile X.

They have also found significant changes in

FRAXA RESEARCH

cortical LTP, in Fragile X mice, which appear to be caused by loss of the "priming" function of mGluR5. They have demonstrated that normal mice treated with MPEP are indistinguishable from both treated and untreated knockout mice, in terms of this form of LTP. This implies that mGluR5 antagonists may cause a small degree of cognitive impairment in normal subjects via this pathway, while mGluR5 antagonists are unlikely to cause this impairment in Fragile X subjects. –*MRT*

Transcriptional Regulation of the Fragile X Gene in the Olfactory Bulb

JUSTIN FALLON, PhD Principal Investigator

ANNE BOOKER Graduate Student

Brown University, $20,000 RENEWAL

by Justin Fallon

We are interested in how FMR1 expression is regulated.. Recently we developed a new model to study FMR1 transcription in the brain. We have shown that olfactory (smell) experience bi-directionally regulates FMR1 gene expression. This regulation depends on developmental stage. We have observed that DNA methylation patterns in the FMR1 promoter correlate with developmental changes in gene expression. We will now investigate the mechanisms of activity-induced FMR1 mRNA expression.

Analyses of the dFMR1 Pathway in Drosophila PNS

FEN-BIAO GAO, PhD Principal Investigator

Univ. of California at SF, $50,000 RENEWAL

This lab has been exploring the alterations in gene expression in the fly peripheral nervous system caused by absence of drosophila FMRP. During their first year of FRAXA funding, they found 42 genes significantly dysregulated in mutant flies – all up-regulated. In other words, all these genes are producing too much protein in the Fragile X flies; however, it is still not clear which ones are most important in causing the symptoms of Fragile X. They are now validating these findings using the power of

MPEP Scores Again – This Time, in Zebrafish

In addition to directly funding research, FRAXA finds creative ways to accelerate progress towards a cure. For example, FRAXA frequently donates important research reagents to researchers – saving scientists thousands of dollars and sometimes spurring on research that would not otherwise be done.

One such reagent is MPEP, a compound (not for human use) which blocks mGluR5. It has been shown to reverse symptoms of Fragile X in both mouse and fly models.

MPEP comes as a white powder, and sending white powder through the mail, while perfectly legal, can be problematic these days. Aussie researcher Ben Tucker discovered this when he had to drive down to the docks to assure postal workers of the safely of his vial of FRAXA-donated MPEP. But it was worth it: just eight months later, Dr. Tucker has published a study in which he demonstrates that MPEP can reverse features of Fragile X in a zebrafish model of the disorder. *Human Molecular Genetics, 2006 Oct 25, Contribution of mGluR and FMR1 Functional Pathways to Neurite Morphogenesis, Craniofacial Development and Fragile X Syndrome, by Ben Tucker et. al. at the University of Adelaide in Australia.*

The case is growing stronger that mGluR5 antagonists will be effective treatments for Fragile X syndrome in humans. – *KNC*

DEVELOPING TREATMENTS – FROM RESEARCH TO MARKET

FRAXA has funded outstanding basic research since 1994. We now know of several potential drug treatments for Fragile X – compounds which have been shown effective in animal models of Fragile X but which are not yet available for humans. The challenge is that millions of dollars and several years of testing are required before the Food and Drug Administration (FDA) allows a new drug on the market.

FRAXA has raised and spent over $10 million on Fragile X research over the past 13 years. But this is a drop in the bucket compared to the resources needed to turn research successes into available treatments. We will need to raise much more money to realize the promise of research. FRAXA will also need to work with drug companies which have the expertise to develop new drugs.

One such company is Seaside Therapeutics, of Cambridge, MA. Seaside's Scientific Founder, MIT Professor Mark Bear, discovered the "mGluR Theory of Fragile X" and other researchers have confirmed that compounds which reduce mGluR activity are effective in animal models of Fragile X.

Seaside plans to translate this research into effective treatments for patients with Fragile X, autism, and related disorders. Seaside has licensed mGluR antagonists from Merck & Co., Inc. Their lead compound is in preclinical development and has demonstrated efficacy in animal models of Fragile X. Seaside aims to submit this compound to the FDA under the Orphan Drug Act.

The Chairman of Seaside's Board of Directors is Harvard University Provost, Steven Hyman, MD. Dr. Hyman was formerly Director of the National Institute of Mental Health and is a member of FRAXA's Board of Scientific Advisors. Seaside's senior management includes CEO Randall Carpenter, MD and Sr. VP of R&D Timothy Ocain, Ph.D. Through their combined 40+ years of experience in the pharmaceutical and biotechnology industry, Drs. Carpenter and Ocain have introduced a large number of new chemical entities into clinical development, and have successfully advanced drugs through all phases of clinical development. Please visit www.seasidetherapeutics.com for more information.

RAISING FUNDS

FRAXA is a grass roots organization, founded in 1994 by parents and run by parents. FRAXA depends on families and friends for the funds that drive progress towards a cure for Fragile X. Check www.FRAXA.org often for a listing of upcoming events.

Unfortunately, FRAXA is currently having to postpone funding new research because of lack of funds. Until donations increase, FRAXA will accept research applications once rather than twice each year. The next deadline is February 1, 2007.

Please take a moment to make a donation to FRAXA, by phone (978-462-1866), fax (978-463-9986) or online at FRAXA.org. All major credit cards accepted! Now more than ever before, your donation matters!

Kevin Blackmon and son

Race for a Cure: S. Carolina

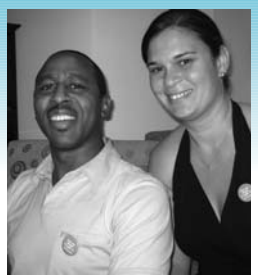
The United All Stars, who race professional Go-Karts, first learned about Fragile X this past summer. On August 12, the United All Stars 1st Annual Cure Fragile X Mid-Summer Nationals was held at Danny's Southern Raceway in Loris, South Carolina. A percentage of the gate and entry fees were designated for FRAXA. Danny Prince, the track owner, and his daughter Fran, the track manager, were so moved by the cause, that they contributed the entire net gate receipts, around $1,000.

The idea of making the race a Fragile X benefit came about when racers learned that Kevin Blackmon, a regular with the United All Stars, had quit racing because his two beautiful boys, aged 2 and 4, had Fragile X. Taking care of them would become his lifetime role.

Since then, the United All Stars and their friends and supporters have contributed over $3,000 to FRAXA. We are very grateful for their support.

New York, New York . . .

Chinatown Fundraiser a Smash Hit!



Paul and Renee Cann

On July 13, nearly 60 friends and family celebrated at the beautiful Chnatown home of Renee and Paul Cann. The event was hosted by Elaine Stillerman, Luke Solotaroff's mom. The Sopranos' Dan Grimaldi and FRAXA's Dr. Mike Tranfaglia spoke. The event raised over $15,000 for FRAXA and a terrific time was had by all.

Simon Feather and Luke Solataroff

Elaine Stillerman also wrote a segment on Fragile X for the PBS-TV show "Real Moms, Real Stories, Real Savvy." It featured FRAXA co-founder Katie Clapp and FRAXA-funded researcher and Nobel Laureate, Dr. Susumu Tonegawa. Check your local PBS television listings for times.

Elaine Stillerman and friend

Elaine and Luke were featured in an article about special needs children in the AMTA Journal, a national massage magazine.

Hudson River Valley . . .

What's full of laughs, good friends and makes the difference in the lives of everyone who attends? The 4th Annual Fragile X Ball! Amy and Ron Watkins welcomed over 130 family, friends and colleagues to Dutchess Golf & Country Club in Poughkeepsie, New York. Actor Dan Grimaldi, from the HBO series Sopranos, attended the event for the fourth year. The evening was captured through the artistic eye of Dan Stockfield who donated his time. A gallery of photographs can be viewed at www.danstockfield.com/fraxa06. This year's event raised nearly $40,000! The continued generous support of Mary Jane Clark, the Ryan McElroy Foundation, Darlind Construction, St. Francis Hospital, D'Arcangelo, John P. Cunningham and the Gibb family is truly appreciated.

Florence and Dan

Don't let another event pass you by! Next year's X Ball will be September 28, 2007.

The Gibbs Family

Artists' Night

What can one family do to make a difference for Fragile X Syndrome? Anne Squeglia and Shirley Murray, planned, choreographed and recruited performers for an exceptional evening in Poughkeepsie to support our cause. Niklas Watkins, who is now 8 years old and has Fragile X, sang songs from the 1920's on stage with his singing partners, the Outreach Performers.

The Murray Family

AND AWARENESS

Anthony Ryan, playing patty cake

Wedding: Michigan

Jim and Elaine Patterson of Rochester Hills, Michigan, wrote that their son Jim was married to Jennifer Holtz on June 16. Jim and Jen elected to make a donation to FRAXA in lieu of presenting their guests with wedding favors. They honored their 3-year-old nephew Anthony, the son of Albert and Amy Ryan, of New Castle, PA.

Waxhaw Bash: North Carolina

Heather, Philip, Emmett and Roma Lopina hosted the Fourth Annual Waxhaw Bash at their home. There were two bands, lots of food and fun for all ages. They raised over $2,000 and created lots of awareness of Fragile X. Emmett and Roma have Fragile X.

Supermarkets: Texas

If you live in Texas, perhaps you shop at Randalls or Tom Thumb supermarkets. If so, please apply for their Remarkable Card or link your existing card to FRAXA. Just give the cashier FRAXA's number, 3715. Each time you shop and present the card at checkout, 1% of your purchase will go to FRAXA. Thanks to Roger Hoh for setting up this program. Please tell your Texas friends! If you'd like to pass this along to others, contact FRAXA for business cards which promote this program.

Bliss and Shaun Glover

Wedding: New Jersey

Bud Glover of Brick, NJ, wrote: "I attended my nephew's wedding this fall and, to my surprise, saw that the reception favors at all the tables were FRAXA's "Cure Fragile X" wristbands, along with a request for donations to FRAXA. This touched my heart and my wife's heart more than I can say! Our son Bryan has Fragile X. My wife and I will always remember that Shaun and Bliss Glover chose to honor their cousin on the most important day so far in their life together!"

Bryan Glover on the dance floor

"Dear Megan"

FRAXA Board members Mary Beth Busby and Megan Massey each have two sons with Fragile X. They have written a book about their experiences. U.S. Senator Chuck Hagel (Nebraska) writes: "Megan and Mary Beth are brave to share their deeply personal story of adversity, love, and triumph during their journey to discover the answers to Fragile X. This is a wonderful book." Megan and Mary Beth were featured on National Public Radio's Diane Rehm Show. You can purchase their book on FRAXA.org; the sale price benefits FRAXA.

Dr. Mike's eBay Store

Dr. Mike Tranfaglia wears many hats at FRAXA, including Medical Director, Treasurer, repairer of electronics, and most recently, auction manager. Mike runs an eBay store where all funds go to FRAXA. We've sold computer parts and donated clothing. If you have items to donate, please contact Mike at fraxa@comcast.net. You'll find a link to the store at FRAXA.org's SHOPPING page.

Golf Tournament: London

FRAXA thanks our loyal friend across the Atlantic, Andrew Neill, who organized a benefit golf tournament for the second year, raising approximately $4,000.

Patrick's Pals: Bill Rome, Jim Marks, Scott Katz, honored guest New England Patriots tight end Ben Watson, James Vershbow, Steve Savarese, Jon

Patrick's PALS X: Boston

Patrick Nolan Vershbow was diagnosed with Fragile X in 1993, before he turned one year old. When he was three, an idea was hatched to support the efforts of FRAXA by raising awareness and money through a special event. This past February, Patrick became a teenager (*Yikes!*) and on June 3, 2006, our special event, Patrick's PALS 3-on-3 Basketball Tournament turned ten years old.

Donations hit a new high, $30,000, bringing the 10-year total to well over $200,000. Every year, a crowded gym and all the noise of the day makes it impossible for Patrick to attend. Yet, despite never meeting Patrick, his PALS continue to provide overwhelming support. The money raised seems truly amazing! This event does not happen without the enormous efforts of the "PALS Board of Trustees," all whom are close friends. With gratitude that can't be measured, thanks to Scott Katz, Jimmy Marks, Jon Pressman, Billy Rome and Steve Savarese.

As we plan for Patrick's PALS XI, we hope for the same thing that we hope for every year: that the day will come soon that this event is no longer needed. In the meantime, THANK YOU to each of you who has lent your support to Patrick's PALS over the past 10 years!

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

• New Deadline is February 1 each year

FRAXA offers fellowships and grants to encourage research aimed at finding effective specific treatments and an ultimate cure for Fragile X syndrome:

- Postdoctoral fellowships of up to $40,000 each per year
- Investigator-initiated grants for innovative pilot studies aimed at developing and characterizing new therapeutic approaches (no funding limit)

See www.fraxa.org for details.

FRAXA FRAGILE X RESEARCH FOUNDATION

EDITOR: Katie Clapp, MS
CONTRIBUTING EDITORS: Susan Cohen, Sally Nantais, Mary Beth Langan
CONTRIBUTORS: FRAXA Event Hosts, Research Grantees, Michael Tranfaglia, MD
DESIGN: Mary Lou Supple

SAVE THE DATE

FRAXA GALA
MARCH 1, 2007
GOTHAM HALL
NEW YORK CITY

See complete event listing at FRAXA.org

PLEASE HELP FRAXA

FRAGILE X RESEARCH FOUNDATION

FRAXA is a national 501(c)(3) tax-exempt organization run by parents of children with Fragile X. FRAXA's overhead is 5%, one of the lowest of all charitable organizations. 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+)

send to: FRAXA, 45 Pleasant St., Newburyport, MA 01950

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FRAXA UPDATE

SPRING 2006

VOLUME 13, NO.1

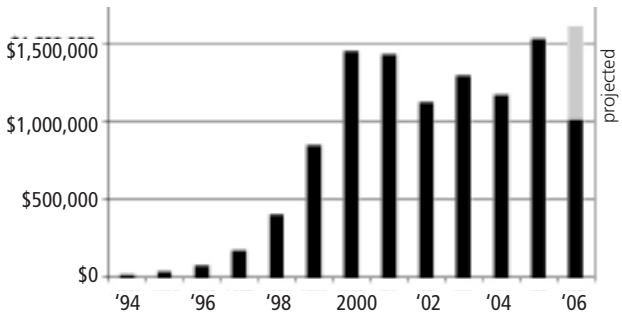
A PUBLICATION OF FRAXA RESEARCH FOUNDATION

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

— Margaret Mead

New FRAXA Grants Top $1,000,000

As FRAXA becomes able to support more research and bring more scientists to the Fragile X field, prospects for finding effective treatments and a cure for Fragile X are brightening. FRAXA-funded research now spans basic science, pre-clinical studies, and clinical trials – all coordinated to make the most of each dollar.



The first step towards a cure is to understand the cause of Fragile X. In the words of Nobel Prize Winner and FRAXA Scientific Advisor, James D. Watson, the discovery of the Fragile X gene in 1991 "was the first major human triumph of the Human Genome Project." Researchers now know that this gene shuts down in affected people, failing to produce its normal protein product, FMRP. Now that we understand what is wrong, we can attempt to fix it. In the words of FRAXA Scientific Advisor, Dr. Justin Fallon, "*Fragile X is poised to become a triumph for translational research and the design of rational therapeutics for brain disease.*"

What is the Most Promising Research?

While no one can foresee the future, we are optimistic that the mGluR Theory will lead to treatments for Fragile X, and possibly for other autism spectrum disorders, in the near future.

Recent research suggests that many of the symptoms of Fragile X – including cognitive impairment, anxiety, hyperactivity, and sometimes seizures – can be traced to a single pathway by which brain cells

continued on page 3

Also in this issue:

MILESTONES

1. FRAXA spearheaded a joint research initiative for Fragile X and autism with three other disease foundations and six government agencies from three countries.
2. Total FRAXA research funded since 1994 topped $10 million. Leveraging this research, annual U.S. government Fragile X research funding rose from 1 million (1994) to over 20 million (2006).
3. Nobel Laureate Susumu Tonegawa became the newest member of FRAXA's Scientific Advisory Board, joining 20 other top scientists including two other Nobel Laureates: Eric Kandel and James Watson.
4. FRAXA grantees demonstrated that a new class of drugs (mGluR5 antagonists) reverses Fragile X symptoms in mouse and fly models of the disorder. Follow-up research is proceeding rapidly.
5. FRAXA funded its second clinical trial of a specific treatment for Fragile X. Lithium, an available drug, is being tested by Dr. Elizabeth Berry-Kravis in Chicago.

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 4000 males and 1 in 6000 females. FRAXA's goal is to accelerate research aimed at the treatment and cure of Fragile X, by direct funding of promising research projects and by raising awareness of this disease.

Report from Washington:

By David and Mary Beth Busby

Things look pretty grim for any increase in federal funding of Fragile X research. Congressional folks say that the National Institutes of Health (NIH) budget will be flat this year – and that actually means less spending on research, especially on new projects, since those already funded may extend out for three or five years.

NIH Fragile X funding (in millions)
1999 - $5.8
2000 - $7.4
2001 - $10.4
2002 - $16.1
2003 - $19.5
2004 - $19.8
2005 - $22.3
2006 Estimated $22.4
2007 Estimated $22.4

In the past, our strategy has worked well: cutting-edge research funded by FRAXA has jump-started many researchers who go on to gain NIH funding. Over the last twelve years, while FRAXA's annual research budget has increased from $30 thousand to $1.5 million; the NIH's budget has increased from about $1 million to $22 million!

Actually, last year saw a substantial increase in the number of FX research projects being conducted by the NIH: from 75 to 87. These are being financed by 12 different NIH "Institutes," but most by The National Institute of Child Health and Human Development, The National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.

In addition, FRAXA urged the Congress to support funding of states' newborn screening through the Health Resources and Services Administration and the Centers For Disease Control and Prevention (CDC). This year the CDC funded a Cooperative Agreement with FRAXA and others to provide public information on Duchenne and Becker Muscular Dystrophy and Fragile X.

Harris Hollin appointed to President's Committee

FRAXA congratulates Harris Hollin on his appointment by President George Bush to the President's Committee for People with Intellectual Disabilities. Harris is the founder of Conquer Fragile X, with which FRAXA has collaborated over the years to increase federal research appropriations. His appointment will enhance the presence of our cause at a high level. Harris is the father of FRAXA Advisory Board member, Cristy Hollin, and grandfather of Matthew Hollin, who has Fragile X.

FRAXA FINANCES 2005

2005 was a year of progress for FRAXA. As always, we aim to keep overhead expenses as low as humanly possible. FRAXA now has a staff of three: 1 full time (Katie Clapp), and 2 part time (Michael Tranfaglia and Melissa Budek).

We thank all the people who have donated goods and services: Dave Fullam at Icovia.com, for web design and hosting; Kris at Networx for email hosting; Altaf Shaikh at ListEngage.com for email hosting; Mary Lou Supple for newsletter and other print design. We also thank the local moms near Newburyport, MA, and Andy Tranfaglia's school peers for mail preparation.

2005

Income

Contributions	$615,000
Fundraising Events	$1,333,000
In-Kind Contributions	$252,000
Product Sales & Investment Income	$84,000

Expenses

Research	$1,233,000
Education and Awareness	$305,000
Fundraising	$278,000
Management and General	$47,000

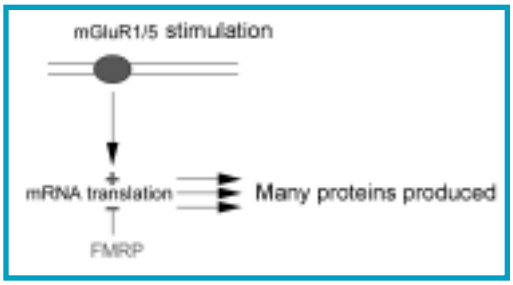
Figures are rounded to the nearest $1000 from financial statements audited by Anstiss & Co, P.C., CPA.

continued from page 1

communicate. Specifically, evidence suggests that Fragile X syndrome is caused by exaggerated signaling through group 1 metabotropic glutamate receptors (mGluR1 and mGluR5). This "mGluR Theory of Fragile X" was formulated by Dr.s Mark Bear, Kimberly Huber and Stephen Warren.

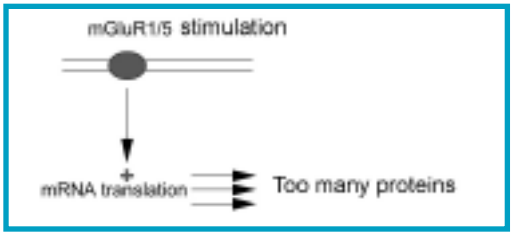
A basic mechanism underlying learning and memory is the ability of neurons to respond to signals by creating new proteins at the connections between neurons (synapses), thus fine-tuning these connections. In a normal brain, increases in the rate of protein synthesis caused by synaptic activation of mGluR5 are balanced by the FMR protein, similar to the way the accelerator and brake balance the speed of a car. But people with Fragile X lack the FMR protein, leading to excessive protein synthesis.

Normal Neuron



When a signal comes from neighboring neurons to stimulate mGluRs, it triggers protein production. FMRP acts as a brake to limit protein production to achieve a normal balance.

Fragile X Neuron



Without FMRP to put the brakes on, there is runaway protein production. These extra proteins cause symptoms of Fragile X.

The logic behind mGluR5 antagonists for treating Fragile X is to restore the normal balance of protein synthesis. (mGluR1 antagonists are not likely treatments due to side effects.)

Experiments with compounds which decrease mGluR5 signaling (mGluR5 antagonists) in Fragile X mouse and fly models have demonstrated positive effects in both species, suggesting that mGluR antagonists could benefit people with Fragile X.

The New Projects

FRAXA funded a record number of research projects in March 2006. The number and quality of proposals was the highest ever received – an indication of how exciting this field is becoming to scientists.

Many of the new projects (see next page) explore the potential of mGluR antagonists to treat Fragile X and autism. Studies in flies and mice are in progress, human trials of new compounds are being planned, and a clinical trial of one drug which acts on mGluR pathways - lithium – is underway.

FRAXA is working with pharmaceutical companies to bring mGluR antagonists into clinical trials as soon as possible. Several companies are attempting to develop compounds specifically for Fragile X, and others are developing drugs for related indications, like anxiety disorders.

Other treatment strategies are also emerging. FRAXA has funded basic research and a clinical trial of compounds which target another step along the mGluR pathway: ampakines. Cortex Pharmaceuticals, the company which developed ampakines, recently announced that a newer, more potent ampakine, CX717, reduced symptoms in a trial of adults with ADHD. FRAXA researcher Julie Lauterborn is now testing CX717 and other new ampakines in Fragile X mice.

How long will it take until a treatment reaches patients? Not surprisingly, the rate-limiting factor is lack of funds. Along with the projects FRAXA has supported were additional projects that were approved by our Scientific Advisors – but could not be funded. This is a time of extraordinary opportunity to improve the lives of people everywhere who live with Fragile X – and a time for fundraising with renewed vigor!

2006 FRAGILE X RESEARCH FORUM

The 2006 Fragile X Research Forum at the Society for Neuroscience Annual Meeting will be held Sunday October 15th, 6 - 8:30pm, in Atlanta, Georgia. This event will offer investigators, postdoctoral fellows, and students a chance to learn about the latest advances in understanding Fragile X and meet leaders in the field. The meeting is chaired by Drs. Gary Bassell and Yue Feng, both of Emory University, and funded by a grant from Novartis Pharmaceuticals.

This session will summarize recent progress in understanding the neurobiology of FMRP and possible directions for treatments. Gary Bassell (Emory) will discuss the role of FMRP during axon growth and synapse formation. Eric Klann (Baylor) will discuss translational and proteosomal regulation of FMRP during mGluR dependent LTD. Bob Wong (SUNY) will discuss epileptogenesis in Fragile X model mice and the role of synaptic mGluRs. Mark Bear (MIT) will discuss recent tests of the mGluR theory. Steve Warren (Emory) will discuss progress using high throughput screens of dFMRP deficient flies to identify drugs that may be useful in treating Fragile X.

EDITOR'S SUMMARIES

When the Fragile X fruit flies in **Dr. Stephen Warren**'s lab mysteriously began dying, team members discovered the cause: a new fly food called JAZMIX was killing them. They found the offending ingredient – glutamate – and an antidote.

The treatment is an mGluR antagonist. It dampens the activity of a type of glutamate receptor (mGluR5) in neurons.

Dr. Warren's team then tested 2000 drugs and supplements to see if any of those, like MPEP, could save the flies. They found 20, and are now evaluating the best drugs to see if they can treat Fragile X in mice. The next step is to evaluate the most effective drugs as potential treatments.

Last summer, MD-PhD student **Catherine Choi**, working with colleagues Sean McBride and Dr. Tom Jongens, showed that Fragile X fruit flies have learning disabilities. Male flies have difficulty completing the normal courtship ritual ... they tend to stop in the middle of their mating dance to clean their wings. The scientists also found compounds that can correct this behavior: MPEP and lithium (an available drug).

Catherine Choi is now testing Fragile X mice, to see if MPEP and lithium will effectively treat them as well.

RESEARCH

Identification of novel compounds for the treatment of Fragile X

STEPHEN WARREN, PhD
Principal Investigator

SHUANG CHANG, PhD
Postdoctoral Fellow
Emory University

$40,000

by Stephen Warren

Shuang Chang and Stephen Warren

We have discovered that Drosophila embryos deficient in dfmr1, the fly model of fragile X syndrome, die when placed on a commercial food source but survive on a standard laboratory food preparation. The commercial food source was found to contain excess glutamate when compared to the lab food and adding glutamate to the lab food resulted in lethality. The mGluR antagonist MPEP rescued the lethality on commercial food, consistent with the mGluR theory of fragile X syndrome.

Using this lethal phenotype on commercial food as a drug screen, we evaluated a panel of 2,000 drugs and natural products, identifying compounds that could rescue the phenotype. This screen identified 20 drugs that could rescue the phenotype and further replication showed four lead drugs to be superior to MPEP in reversing the lethality. Those flies that survived with drug treatment also showed significant correction of the morphological brain abnormality (mushroom body defects) seen in dfmr1-deficient flies growing on lab food.

Three of these four drugs appear to modulate the GABAergic inhibitory pathway. Since this inhibitory pathway could temper the excess signaling from the mGluR excitatory pathway in fragile X, we have identified the GABAergic pathway as a druggable target for fragile X syndrome. We plan to expand the drug-screening panel and test these four lead drugs in mice deficient in FMR1.

Pharmacologic Interventions in the FMR1 Knockout Mouse

ROBERT NICHOLS, PhD Principal Investigator

CATHERINE CHOI MD-PhD Candidate
Drexel University, $55,000

Sean McBride, Tom Jongens, Catherine Choi

by Catherine Choi

Recently, we demonstrated in our fruit fly (Drosophila melanogaster) model of Fragile X, which is lacking the single gene dFMR1, a robust impairment in cognitive function. Using this behavioral readout as a tool, we used the fruit flies to investigate the effect of enhanced mGluR signaling on their cognitive phenotype.

We chronically treated the flies with either antagonists of mGluRs or with lithium, a drug that inhibits a component of mGluR signaling. Much to our excitement, we found that all of these agents returned cognition to the level of control flies, thus supporting the hypothesis that absence of dFMR1 expression contributes to a learning deficit involving exaggerated mGluR signaling. Our work in flies indicates that decreasing mGluR signaling may be a potential treatment strategy.

Our next goal is to investigate this treatment approach in FMR1 knockout mice. We will study the effects of an mGluR antagonist and lithium on the excessive mGluR-dependent long-term depression (mGluR-LTD) seen in Fragile X knockout mice. We will also perform biochemical studies to investigate the effects of these treatments on levels of relevant proteins, to further elucidate and validate the mechanisms by which these drugs act.

UPDATE

Characterization of transgenic mouse models to investigate the molecular mechanisms underlying FMRP function at the synapse and therapeutic intervention in Fragile X

ROB WILLEMSEN, PhD

Principal Investigator

FEMKE DE VRIJ, PhD

Postdoctoral Fellow

Erasmus University, The Netherlands, $50,000

Femke de Vrij, Rob Willemsen

by Rob Willemsen

In Fragile X patients and in FMR1 knockout mice, lack of FMRP may lead to excessive protein synthesis at synapses when mGluRs are stimulated. Reducing mGluR activation may (partly) reverse effects due to lack of FMRP. MPEP, a compound which blocks mGluR5, has been shown to rescue some symptoms in FMR1 knockout mice.

As a step toward treatment of Fragile X patients, drugs like MPEP need further behavioral and functional testing in mice. Also needed are studies to understand the molecular mechanisms underlying these therapeutic approaches.

We will generate and characterize new mouse models to study the role of FMRP in mRNA transport and translation, and the molecular mechanisms underlying therapeutic intervention with mGluR antagonists. The role of FMRP in transport/translation of dendritic mRNAs will be studied in cell cultures from neurons in which the FMR1 gene can be switched on/off by adding drugs to the cell culture medium. The FMR1 gene will be fused to a fluorescent dye so we can see it during transport from the cell nucleus to a synapse. Spine abnormalities will be studied in a mouse strain that expresses a fluorescent plasma membrane marker. These mice can also be used to visualize changes in abnormal spines in rescue studies such as MPEP treatment. Finally, a mouse strain with fluorescent AMPA receptors will be used to study AMPA receptor surface expression after mGluR stimulation in the absence/presence of mGluR antagonists.

The Drosophila Model of Fragile X: Testing the mGluR Hypothesis

KENDAL BROADIE, PhD

Principal Investigator

CHARLES TESSIER, PhD

Postdoctoral Fellow

Vanderbilt University, $40,000

Charles Tessier

by Kendal Broadie

Over the past four years, we have developed an exciting new model of Fragile X in that genetic "workhorse," the fruitfly Drosophila melanogaster. We previously generated mutant flies lacking or over-expressing the Drosophila Fragile X protein, dFMRP, and showed that these flies have the hallmarks of the disease, including neuronal and behavioral defects.

We have also generated mutant flies lacking or over-expressing the sole mGluR present in Drosophila (dmGluRA). These efforts now enable us to genetically test the mGluR hypothesis, which is the focus of this project.

We will compare characteristics of mutant neurons with altered levels of dmGluRA and dFMRP. We will use various levels of microscopy, electrophysiology and study output behavior to determine the degree to which dmGluRA and dFMRP operate in the same neurological pathways.

We will then assay any changes to these convergent phenotypes in response to drug treatments that enhance or inhibit mGluR signaling. We will determine whether drug treatments are ineffective in animals that lack both dmGluR and dFMRP, thus testing the specificity of the drug targets. We will more specifically test the nature of the dmGluRA-dFMRP signaling interaction using a combination of genetic studies and microarray technologies.

EDITOR'S SUMMARIES

Much Fragile X research depends on two key animal models which mimic the disorder: mice and flies. The FMR1 Knockout

Mouse, developed in 1994, lacks a key part of the FMR1 gene and, like humans, cannot produce the protein FMRP.

Dr. Rob Willemsen is developing new improved mouse models of Fragile X. In one mouse strain, the FMR1 gene can be turned on or off, simply by feeding the mice different substances. Another will feature a flourescent green FMR protein, so researchers can watch how, when, and where it travels within brain cells. Dr. Willemsen plans to treat these new mice with drugs which dampen mGluRs.

Dr. Kendal Broadie's group was the first to engineer a fruit fly model for Fragile X. He has recently developed another model: flies which lack the fly version of mGluRs. Together these two models enable

the team to test the mGluR Theory of Fragile X and a variety of potential drug treatments.

RESEARCH

EDITOR'S SUMMARIES

Many parents agree that the emotional toll of Fragile X is greater than its cognitive effects. Children with Fragile X are easily overwhelmed, upset, and "meltdowns" in public places are all too frequent. **Dr. Joseph LeDoux** and his team aim to understand this anxiety by looking at the part of the brain that controls anxiety, the amygdala, in Fragile X mice. Dr. LeDoux is a well-known authority on the biological basis of anxiety; we are pleased to welcome him to our field.

Many people with Fragile X have rapid, repetitive speech which can be hard to understand. **Dr. Stephanie Ceman** is studying songbirds to better understand the speech problems often seen in this disorder.

All animals studied have a gene which corresponds to the human Fragile X gene, including birds. But unlike most other non-human animals, birds are quite vocal. Dr. Ceman will use a new technology (RNAi) to turn off the protein FMRP in bird brains and see how this affects song learning. This study may help pinpoint the causes of speech problems in people with Fragile X.

Examining the Amygdala in Mouse Models of Fragile X

JOSEPH LEDOUX, PhD Principal Investigator

LINNAEA OSTROFF, PhD Postdoctoral Fellow

HIROKI HAMANAKA, PhD Postdoctoral Fellow

New York University, $63,000

by Joseph Ledoux

Linnaea Ostroff, Joseph LeDoux, Hiroki Hamanaka

Fragile X in humans is accompanied by alterations in brain regions that are thought to control anxiety-related behaviors. In particular, the amygdala, a small structure near the back of the brain, has structural abnormalities which are accompanied by behavioral changes associated with amygdala activation, including increased fear, anxiety, and elevated secretion of the stress hormone, cortisol.

To understand the neurobiological basis for these changes, we are conducting studies in genetically modified mice which mimic Fragile X syndrome (FMR1 knockout mice).

Existing data regarding fear and anxiety in the FMR1 knockout mouse are inconclusive and even contradictory, especially in studies using fear conditioning. Because detailed information about the neural system and cellular and molecular mechanisms is available, fear conditioning would be an important tool for attempting to relate behavioral symptoms of Fragile X to brain mechanisms.

Our studies in mice have four aims:

1. to clarify the behavioral effects of fear conditioning.
2. to examine the expression and localization of key proteins in the amygdala which have been implicated in the Fragile X disease process in other brain regions and may have a similar impact on amygdala function.
3. to explore the role of receptors which control learning and anxiety in the amygdala. We will focus on receptors whose function has been shown to be modified by mutations of FMR1.
4. We will assess the therapeutic value of compounds which alter receptor signaling by examining Fragile X symptoms in mice which have been fed these compounds.

FMR Expression in Zebra Finch

STEPHANIE CEMAN PhD Principal Investigator

CLAUDIA WINOGRAD MD-PhD Student

University of Illinois at Urbana Champaign, $18,000

by Stephanie Ceman

Claudia Winograd,Stephanie Ceman

Individuals with Fragile X syndrome (FXS) often have delayed and affected speech. FXS speech can be arrhythmic, repetitious, or run together, making it difficult to comprehend. We will study the underlying mechanism for this altered speech, and how it relates to the absence of the fragile X protein, FMRP, by developing a new animal model: the songbird.

Birdsong can be used to study human speech because songbirds, like humans, are vocal learners – that is, both young songbirds and children must learn proper vocalization from a 'tutor' and must have normal hearing in order to do so. For a songbird, the tutor is typically the father, as only male birds sing.

The first part of our study is to characterize FMRP in the areas of the songbird brain termed the 'song control circuit'. This circuit, which has been studied extensively, includes brain regions shown to be involved in human speech as well as FXS. Next we will eliminate FMRP expression in specific brain regions and examine the effect on song learning. This study will give us insight into the speech pathology of Fragile X.

UPDATE

The Neurobiology of Fragile X: A Unifying Neuro-Endocrine Hypothesis

ABDESLEM EL IDRISSI, PhD
City University of New York, $40,000

by Abdeslem El Idrissi

Abdeslem El Idrissi

Fragile X syndrome includes hyperarousal, hypersensitivity to sensory stimuli, and an increased prevalence of seizures. The Fragile X mice also have increased seizure susceptibility, a feature dependent on hyperexcitability of neurons. Alterations in GABA (the major inhibitory neurotransmitter in the brain) have been associated with hyperexcitability. We have found a reduction in GABA(A) receptors in Fragile X mice. Since these receptors help to inhibit seizures, their reduction helps explain the increased seizure susceptibility of Fragile X mice and suggest that the GABA system is affected in Fragile X patients. We also found other biochemical changes in the brains of Fragile X mice that seem to be compensatory mechanisms to increased excitability.

Our preliminary data show another potentially important change: somatostatin levels are decreased in the brains of Fragile X mice as compared to control mice. Somatostatin is a small protein released by neurons, which can function either as a hormone or a neurotransmitter. One of its many functions is to inhibit growth hormone secretion. Understanding the distribution of this protein and its receptors would allow us to target specific brain regions with the hope of normalizing their function, especially since somatostatin can be administered intravenously to humans.

Characterization of Kv3.1 in Auditory Brainstem Nuclei in the Fragile X Knockout Mouse

LEONARD KACZMAREK, PhD
Principal Investigator

JACK KRONENGOLD, PhD
Postdoctoral Fellow
Yale University, $40,000

by Leonard Kaczmarek and Jack Kronengold

Leonard Kaczmarek

Many individuals with Fragile X have extreme sensitivity to sounds. The debilitating behaviors associated with "sensory overload" are likely due to changes in synaptic connections in the brain's auditory circuitry.

Fragile X knockout mice also exhibit abnormal sensitivity to sounds, including hyper reactivity and the triggering of audiogenic seizures by loud sounds. While audiogenic seizures have not been reported in Fragile X patients, the onset and manifestation of autistic behaviors in these individuals have been directly correlated with auditory hypersensitivity. The source of the audiogenic seizures in mice is believed to be increased excitation in auditory nuclei and not an overall increase in brain excitability.

FRAXA-funded researchers Robert and Jennifer Darnell have identified the mRNA for the potassium channel, Kv3.1, as a candidate binding target of the Fragile X Protein (FMRP). The absence of FMRP in Fragile X knockout mice would be expected to result in altered regulation of Kv3.1 which is itself critical for normal synaptic function.

Our goal is to determine the changes in Kv3.1 expression in auditory neurons of Fragile X knockout mice. The response to all sound frequencies is dependent on a precise expression of Kv3.1 in neurons of the auditory nuclei. Disruption of the brain's auditory space code, or map, by altered regulation of Kv3.1, would be expected to interfere with auditory processing. It is our belief that these studies will define abnormal sensory processing at the cellular and molecular level and will likely lead to strategies for therapeutic intervention.

EDITOR'S SUMMARIES

Dr. **Abdeslem El Idrissi** began his Fragile X work with a FRAXA Fellowship in the lab of Dr. Carl Dobkin. His work dealt with seizures.

He is now studying the interactions of mGluRs, GABA systems, and a hormone, somatostatin. He suspects that decreased somatostatin levels could explain many symptoms of Fragile X, and that this may be linked to excessive mGluR signaling. He has found low levels of somatostatin in Fragile X mice.

Somatostatin can be given to humans intravenously, so this line of inquiry might, if confirmed, lead to a new treatment strategy.

Dr. Kaczmarek and **Dr. Kronengold** will study Fragile X mice to see if the auditory circuits of their brains are properly wired.

Many people with Fragile X experience sensory overload. Sirens, loudspeakers, and other sounds can be extremely disturbing.

Fragile X mice are also sensitive to sound; in fact, they are prone to seizures triggered by alarm sirens. In another FRAXA project, investigator Robert Bauchwitz has shown that MPEP completely protects the mice from sound-induced seizures.

EDITOR'S SUMMARIES

Dr. Suzanne Zukin is new to the Fragile X field. She has studied the role of AMPA receptors in in stroke, epilepsy, ALS and Alzheimer's disease. In this project, Dr. Zukin will study AMPA receptors in the Fragile X mice. It is thought that AMPA receptors are underactive in Fragile X, probably because of the excessive activity of mGluRs. A treatment strategy which combines an mGluR antagonist with an ampakine might be especially effective.

Dr. Anita Battacharyya has developed a line of human neural stem cells with Fragile X. These stem cells are extremely valuable for research

studies. Cells from mice, flies, and other animals are useful, but they cannot replace human cells. These cells can divide indefinitely, providing a critical resource for many researchers. Dr. Battacharyya is making the cells available to other scientists (see box).

In this project, Dr. Battacharyya will compare signalling in human neural cells that have the Fragile X mutation with the signalling of normal

Activity Bidirectionally Regulates AMPA Receptor mRNA Abundance in Dendrites of Hippocampal Neurons

R. SUZANNE ZUKIN, PhD

Albert Einstein College of Medicine, $40,000

Suzanne Zukin

by Suzanne Zukin

Regulated mRNA trafficking and local protein synthesis play central roles in synaptic remodeling and plasticity. By restricting gene expression to specific synapses, local protein synthesis endows neurons with the capacity to regulate their own structure and function.

We recently found that AMPA receptor mRNAs are targeted to synapses and that mGluR activation promotes targeting of AMPA receptor mRNAs to synaptic sites. The goal of this project is to determine if dysregulation of mRNA localization and local protein synthesis impairs synaptic transmission, using the Fragile X mouse model. We will use molecular, biological, and live-cell imaging techniques to examine precisely how stimulating mGluRs affects AMPA receptor mRNA targeting to synaptic sites and local synthesis of AMPA receptor protein in dendrites.

Understanding the mechanisms underlying dysregulation of mGluR-dependent synaptic plasticity could help in developing novel therapeutic strategies for Fragile X.

Cyclic AMP signaling in human Fragile X Neural Cells

ANITA BHATTACHARYYA, PhD

Principal Investigator

University of Wisconsin at Madison, $30,000

Anita Bhattacharyya

by Anita Bhattacharyya

Fragile X syndrome is defined by the loss of the protein FMRP. Cells respond to signals (both electrical and chemical) by signal transduction cascades that relay information from the outside of a cell to the nucleus where changes in gene expression occur. We want to test how loss of FMRP affects a neural cell's signal transduction cascades. One signal transduction relay molecule that has been implicated in Fragile X is cyclic AMP (cAMP). Previous work by Fragile X researcher Elizabeth Berry-Kravis and colleagues showed that cAMP is lower in platelets and lymphoblastoid cells in blood from Fragile X individuals.

Our project will test the hypothesis that the cAMP signaling cascade is lower than normal in human Fragile X neural cells as well as blood cells. Human neural cells that do not express FMRP are generated from human neural stem cells that express the Fragile X mutation (through previous FRAXA funding for Bhattacharyya and Svendsen; see below). Results of these basic experiments will shed further light on the biology of the disorder.

Available to Investigators: Human Fragile X Neural Precursor Cells

Human neural precursor cells are used as tools to study how the brain develops and as potential therapeutics for neurodegenerative diseases. Human cortical neural precursor cells that carry the Fragile X mutation are available for distribution to interested researchers. These neural precursor cells were isolated from developing Fragile X brain and are destined to become neurons and glial cells. Neural precursor cells can be grown in culture for extended periods of time, generating almost limitless numbers of neurons and astrocytes that do not express FMRP.

Unlike animal models, these cells possess the trinuceotide repeat mutation in the FMR1 gene, rather than a knockout of the gene. Two different Fragile X mutations were detected in the DNA of these cells: methylated full mutation (>200 CGG repeats) and an unmethylated premutation (55-220 repeats). These cells are valuable for testing reactivation of the FMR1 gene, because the gene itself is functional and could, theoretically, be switched on.

For more information, contact Dr. Anita Bhattacharyya at the Waisman Center at the University of Wisconsin-Madison (bhattacharyy@waisman.wisc.edu; www.waisman.wisc.edu/faculty/bhattacharyya.html)

RENEWALS

FRAXA renewed funding for these projects in March 2006 for the coming year. Typically, grants and fellowships are awarded for one year and investigators are welcome to apply for a second year if continued support is needed and the work is progressing well.

Several investigators have secured other support for projects funded last year by FRAXA, including Rita Mihaelescu (Duquesne University, Pittsburgh, PA) who received a grant from the National Institutes of Health (NIH), and Karel Svoboda, who has gained ongoing support from the Howard Hughes Medical Institute. This has been a difficult year to gain NIH support because the proportion of applications funded is only about 10% of the applicant pool -- a significant belt-tightening from previous years.

A range of exciting research is being conducted by the investigators listed below. Some aim to identify new treatment strategies for fragile X, and others focus on testing known treatment targets. One promising target is a protein, MAP1b, which is produced by neurons and normally interacts with the fragile X protein, FMRP. MAP1b levels are extremely high in fragile X mice -- and presumably also in people with fragile X. Dr. Eric Klann has preliminary data showing that treating fragile X mice with MPEP restores normal levels of MAP1b. Dr. Yue Feng is investigating how FMRP and MAP1b together regulate development of neurons. These studies suggest that a drug which dampens MAP1B might be an effective treatment strategy for fragile X.

Dr. Bauchwitz's work on seizures in Fragile X mice suggests that mGluR5 antagonists may effectively treat a range of symptoms of Fragile X. Much of his current effort is devoted to pre-clinical testing of potential therapeutic agents in the knockout mouse model. These experiments are the essential "proof-of-principle" which will enable pharmaceutical development and human trials of several important new classes of therapeutic compounds for fragile X.

FRAXA is pleased to be able to support these projects and we look forward to the resulting discoveries.

Audiogenic Seizures and Effects of mGluR5 Agonist MPEP in the Fragile X Mouse

Robert Bauchwitz, MD, PhD, Columbia University $85,000

Function of FMRP-Mediated MAP1b Regulation in Neuronal Development

Yue Feng, PhD, Principal Investigator, Emory University $50,000

Evaluation of Protein Synthesis Insensitive MGluR-LTD in Fragile X Mice

Kimberly Huber, PhD, Principal Investigator
Elena Nosyreva, PhD, Postdoctoral Fellow
University of Texas at Southwestern $50,000

Molecular Mechanisms of Cytoskeletal Regulation by FMRP

Samie Jaffrey, MD, PhD, Cornell University $60,000

Glutamate Receptors and Their Associated Postsynaptic Proteins in the FMR1 Knockout Mouse

Walter Kaufmann, MD, PhD, Johns Hopkins University $40,000

mGluR5-dependent Translational Regulation of MAP1b in Fragile X Mental Retardation Model Mice

Eric Klann, PhD Principal Investigator
Lingfei Hou, PhD Postdoctoral Fellow
Baylor College of Medicine $60,000

Pharmacologic Treatment of Social Deficits in a Mouse Model for Fragile X Syndrome

Jean M. Lauder, PhD, Principal Investigator
Sheryl Moy, PhD, Co-Investigator
University of North Carolina School of Medicine $50,000

Biochemical Markers and Treatment for Impaired Avoidance Learning in FMR1 KO Mice

Richard Paylor, PhD, Principal Investigator
Baylor College of Medicine $25,000
David Albeck, PhD, Co-investigator
University of Colorado at Denver $15,000
Francis Brennan, PhD, Co-investigator
Philadelphia VA Medical Center & University of Pennsylvania $20,000

Is There a Dysregulation of Activity-Induced mRNA Translation in FMR1 Knockout Mice?

Oswald Steward, PhD, Principal Investigator
Fen Huang, Graduate Student
University of California at Irvine $50,000

GABA(B) Receptor Supersensitivity and Normalization of Behavioral Abnormalities by Various GABA(B) Agonists in FMRP Knockout Mice

Miklos Toth, MD, PhD, Cornell University, $60,000

Specific Tests of the mGluR Hypothesis

Peter Vanderklish, PhD, Scripps Research Institute, $80,000

Defining Functional Domains of FMRP and Uncovering its Partners via Large Scale Mutagenesis in Drosophila

Yong Zhang, PhD, Principal Investigator
Xinda Lin, PhD, Postdoctoral Fellow
Chinese Academy of Sciences $40,000

RAISING FUNDS AND AWARENESS

FRAXA is a grass roots organization, founded in 1994 by parents and still run by parents. FRAXA depends on families and friends for the funds that drive progress towards a cure for Fragile X.

We need your help to continue this important work. Please consider fundraising for FRAXA. Take a moment to make a donation to FRAXA, by phone with a credit card, or donate online at FRAXA.org. It's easy – and it will make a difference!

"Studies of Fragile X have been galvanized by those most directly affected: the families and loved ones of sufferers. FRAXA, the Fragile X Foundation, has been hugely effective in raising money and in inducing Congress to support Fragile X research. ... experience shows that dedicated, resourceful, and, above all, motivated organizations like FRAXA sometimes do hold the key to cracking these diseases against the long odds. To those who take the biggest gambles – financial and scientific – sometimes, with luck go the biggest rewards."

– James D. Watson, PhD
Nobel Laureate
DNA – The Secret of Life

A New Look

before...

Alan Cohen cares deeply about his nephew with Fragile X and is excited about the research FRAXA is funding. So did he simply convey this concern and enthusiasm to his colleagues and encourage them to give money? No. Instead, he issued a challenge to the folks in his hedge fund office: If they kicked in "enough" money to his favorite charity (no amount specified), he'd shave his head. Well, they did – and he did.

After the initial success and his trip to the barber, Alan extended the challenge to a few folks outside the firm. The many people who begged to see the photos were charged per view! Alan feels great about the dare's success. It shook him out of his mid-winter doldrums, and his hair is already growing back. Most importantly, it netted FRAXA nearly $12,000. So maybe we should all consider new and creative fundraising techniques! As Alan says, "Never underestimate what people will pay to see someone embarrass himself!"

after!

Randy's RoadHouse

On February 19th, friends and family of Matthew Clift raised funds by enjoying an evening of food, drinks, and Karaoke at Randy's Roadhouse in Batesville, Indiana. Randy and Cindy Stoneburner generously donated a portion of purchases to benefit FRAXA.

Restaurant celebrations are a fun, effective way to raise funds and awareness. Talk to the proprietor at your favorite local bar or restaurant and see if they are interested.

Craft Sales

Rita Wolfson (right) and friend Sara

Rita Wolfson sold her handcrafted jewelry and frames at the Newton Center Fall Fair, the UMASS Boston campus, the Microsoft lobby in Waltham, and other venues across Massachusetts, raising $1500 for FRAXA research! She used the opportunity to raise awareness by prominently displaying FRAXA literature in her selling display. She made and sold her crafts throughout the fall.

Rita's grandson Billy

We are very grateful to Rita for the many hours she devoted to this process with the hope that the money she raised will benefit the research of organizations that mean the most to her (and us!). Rita's grandson Billy Mitchel has Fragile X.

California Fragile X Awareness Day

Earlier this year, Senator Hollingsworth authored a law making April 18 of each year **California Fragile X Awareness Day**. To celebrate the day, a rally and news conference were held on the steps of the state Capitol in Sacramento. Speakers included Cindy de Gruchy, President of the Fragile X Center of San Diego, and Andrea Shelly, President of FRAXA's Orange County Chapter and member of FRAXA's Board of DIrectors.

Senator Hollingsworth said he hopes Fragile X Awareness Day brings about more public education leading to quicker diagnoses for families dealing with the disease.

Later the same day, a ceremony was held in San Diego to honor three scientists who have made extraordinary contributions to the Fragile X field. Honored were Dr. Pamela Mellon, Professor at the University of California at San Diego, and the founding member of FRAXA's Scientific Advisory Board; Dr. Peter Vanderklish, a FRAXA Investigator at Scripps Research Institute, and Dr. Nicholas Cosford, the lead inventor of a series of compounds which hold promise as potential treatments for Fragile X.

Congratulations California! We hope that other states will follow California's lead and designate their own Fragile X Awareness Day.

CALENDAR OF EVENTS

The X Ball Gala, Pittsburgh, PA, Thursday, May 11

Michele and Jim Cox will host FRAXA's black tie "X" Ball 2006 in Pittsburgh. Dance to the tunes of Nova Era, a band direct from Disney. Special guests include Mary Jane Clark, best-selling mystery author, and Dan Grimaldi, who plays Patsy Parisi on HBO's hit series, The Sopranos. Contact Michele Cox at 303-770-2914 or mmcox@zoominternet.net

Gala - Omaha, NE – Thursday, May 11

The Nebraska Families Association will host a gala with special guest meteorologist Jim Cantore of The Weather Channel. Jim has two children with Fragile X. Contact Kelly Randels at 402-778-5802 or Fragilexomahagroup@cox.net

Basketball Tournament – Cambridge, MA – Sunday, June 3

The Tenth Annual Patrick's Pals Three-on-Three Basketball Tournament will be held at The Buckingham Browne and Nichols Gymnasium in Cambridge, Massachusetts. The double elimination tournament pits old and young together in a grueling test of basketball stamina in a half-court series of games. Contact James Vershbow at 617-924-7560 or PJVersh@comcast.net

Fragile X Golf Tournament – Leicester, MA – July 8

The tournament starts at 1:30 pm at Leicester Country Club, a few miles west of Worcester. The cost is $100.00 per player which includes 18 holes of golf with a cart and a steak dinner to follow at the country club. Contact Gordon Cole at 508-347-5283 or sccrdog@charter.net

Cocktail Party - Manhattan (Chinatown), NY – Thursday, July 13

Cocktail party and auction hosted by Elaine Stillerman in New York City's trendy Chinatown. Auction items include trip to Bermuda and other exciting items. Contact Elaine Stillerman at 718-832-6575 or estillerman@cs.com

Hoop-It-Up Basketball Tournament – Washington, DC – June 24-5

Be a sponsor of the largest participatory basketball tournament in the world. Contact Lindee Norton at 410 353 0326 or fragilexVA@comcast.net

Motorcycle – Hockessin, DE – late summer 2006

FRAXA's Delaware Chapter is hosting a motorcycle run, details forthcoming. If you'd like to help out, contact Jen Nardo at 302-234-7854 or jen9612@aol.com

Gala, Poughkeepsie, NY – Friday, September 29

Amy and Ron Watkins will host their 4th annual Fragile X Gala at Dutchess Golf and Country Club. For more information and tickets please contact Ron and Amy Watkins at 845-797-0846 or roname@frontiernet.net)

Gala and Live Auction, Newport Beach, CA, November 15

Join us at the beautiful Balboa Bay Club overlooking the Pacific Ocean. Contact Andrea Shelly at 949-466-4521 or aashelly@aol.com

National Fragile X Research Day October 5

Now is the time to plan your National Fragile X Research Day event. Call FRAXA for brochures, awareness wristbands, and other items at 978-462-1866 or kclappFRAXA@comcast.net

FRAXA RESEARCH GRANTS AND FELLOWSHIPS

Deadlines: May 1 and December 1 each Year

FRAXA offers fellowships and grants to encourage research aimed at finding effective specific treatments and an ultimate cure for Fragile X syndrome:

- Postdoctoral fellowships of up to $40,000 each per year
- Investigator-initiated grants for innovative pilot studies aimed at developing and characterizing new therapeutic approaches (no funding limit)

See www.fraxa.org for details.

FRAXA UPDATE

EDITOR: Katie Clapp, MS
CONTRIBUTING EDITOR: Susan Cohen
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DESIGN: Mary Lou Supple

This newsletter is published regularly and sent to all supporters of FRAXA Research Foundation.

FACES of Fragile X

PLEASE HELP

FRAXA
FRAGILE X RESEARCH FOUNDATION

FRAXA is a national 501(c)(3) tax-exempt organization run by parents of children with Fragile X. 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+)
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- ☐ Donor ($50+)
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- ☐ Named Research Fund ($5000+)
- ☐ Named Research Chair ($25,000+)

send to: FRAXA, 45 Pleasant St., Newburyport, MA 01950

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