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

FRAXA Research Leads to Orphan Drug Designation

For the first time, a compound being developed to treat Fragile X has received an Orphan Drug Designation from the Food and Drug Administration (FDA).

In collaboration with FRAXA, Neuropharm Group intends to develop fenobam to treat Fragile X syndrome. Neuropharm Group PLC is a United Kingdom based pharmaceutical company focused on developing treatments for central nervous system disorders. The FDA has granted Neuropharm an Orphan Drug Designation for the use of fenobam in Fragile X.

The U.S. Congress passed the Orphan Drug Act in 1983 to accelerate development of treatments for rare diseases, defined as affecting 200,000 or fewer people in the U.S. Fragile X affects almost 100,000 US residents.

Fragile X – A Disease of Excess

Fragile X results from the lack of one protein, the Fragile X Mental Retardation Protein (FMRP). Without FMRP, brain cells do not communicate normally. The most exciting recent research advance has been the discovery of a hyperactive brain pathway (mGluR5) in Fragile X animal models. Dr. Mark Bear, Director of MIT's Picower Institute, has called Fragile X "a disease of excess." Studies have found excessive mGluR5 signaling in the brains of Fragile X animal models. The good news is that compounds which block mGluR5 (mGluR5 antagonists) can tone down this excess, potentially reversing Fragile X symptoms such as learning problems, anxiety, and autistic behaviors. Further studies suggest this excess may also occur in other Autism Spectrum Disorders.

Also in this issue:

DORIS BUFFETT'S CHALLENGE

Doris Buffett, president and founder of the Sunshine Lady Foundation, has donated $500,000 to FRAXA.

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Jim Cantore Joins FRAXA

The Weather Channel's Storm Tracker Jim Cantore is on the front line of hurricanes and severe weather everywhere. Jim has his own storm story too: his son Ben and daughter Christina have Fragile X.

Watch Jim's 30-second video at fraxa.org, and Jim help FRAXA.

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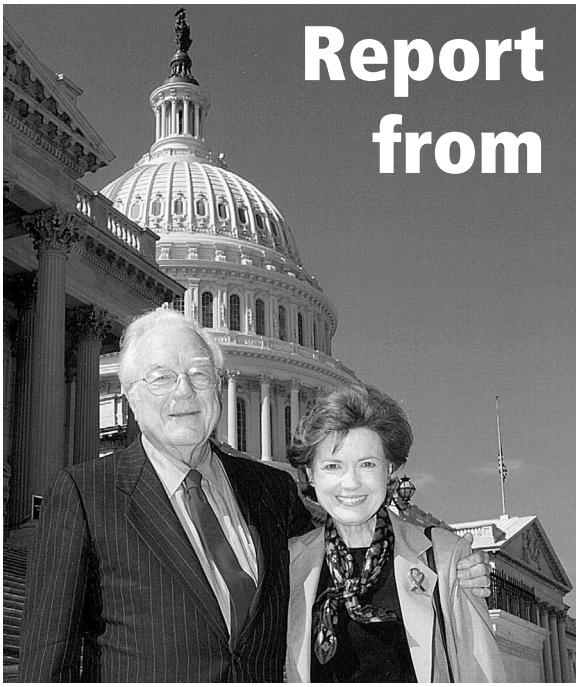
FRAXA is a nonprofit, tax-exempt charity run by parents of children with Fragile X syndrome. Fragile X syndrome is the most common inherited cause of mental retardation and developmental disabilities, affecting approximately 1 in 4000 males and 1 in 6000 females. FRAXA's goal is to accelerate research 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

The National Institutes of Health (NIH) has 27 Institutes and other major units. Eight of them currently fund a diverse array of Fragile X research projects. The Fragile X community has petitioned the Congress, and Congress has asked NIH, to improve coordination of this research. We are pleased that the first inter-Institute meeting was recently held.

Here's a report by guest editor, Dr. Tiina Urv of the MRDD Branch of the NICHD. Dr. Urv is coordinator of the new NIH Fragile X Research Coordinating Group.

In recent years, a growing number of National Institutes and Centers (ICs) within the National Institutes of Health (NIH) have been involved with the expanding NIH research portfolio that has contributed to our knowledge of Fragile X syndrome and associated disorders. This growth of Fragile X research supported and conducted by NIH has created a need to coordinate the communication of these research efforts both within NIH and with outside advocacy groups.

In response to Congressional Appropriations Committee report language, Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development (NICHD), convened the first meeting of the NIH Fragile X Research Coordinating Group on March 28, 2007.

Participants included representatives from NICHD, the National Institute of Mental Health, the National Institute on Aging, the National Institute of General Medical Sciences, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, and the National Cancer Institute.

Information regarding Fragile X research being supported by NIH was presented and discussed at the meeting. Other topics discussed by the group included:

- the development and dissemination of resources both across NIH and to advocacy groups;
- opportunities for collaboration and communication between the NIH institutes and with outside groups; and
- future meetings of the group, including an annual meeting with Fragile X organizations.

Doris Buffett Challenge continued from page 1

Doris Buffett has also challenged FRAXA to raise an additional $500,000 in new money before November 1, 2007. If we succeed, she will match it 100%! All Buffett Funds are designated exclusively for Fragile X research, so this would enable FRAXA to support many new projects aimed at treatment.

Doris Buffett has been a close friend of Mary Beth Busby, a founding member of FRAXA's Board of Advisors, for many years. When she read the book, ***Dear Megan***, by Mary Beth and FRAXA Vice President Megan Massey, Ms. Buffett decided to learn more about FRAXA and its mission.

An article in Worth magazine called the Sunshine Lady Foundation "uniquely hands-on, folksy, a person-to-person enterprise – the un foundation" because of Doris' hands on, personal involvement with every aspect of the foundation's grant-making process. Since its inception in 1996, the Sunshine Lady Foundation has awarded more than $30 million in grants.

Raising $500,000 in NEW money means that we need to reach out beyond FRAXA's loyal supporters to new people who may not have direct experience with Fragile X.

By now, you should have received our special Sunshine Edition Newsletter about the Doris Buffett Challenge to FRAXA. Please help us meet the Challenge! We will be happy to provide you with brochures, flyers and other materials to spread the word.

RESEARCH OVERVIEW

FRAXA has spent almost $12 million on Fragile X research, and one third of that total has been spent building the case for using mGluR5 antagonists to treat Fragile X, starting with an award in 2000 to Dr. Mark Bear and Dr. Kimberly Huber. Several mGluR5 antagonists have been tested in Fragile X animal models (mice, flies, and zebrafish), and the compounds reverse most Fragile X symptoms that have been identified in those animals.

Fenobam – Mystery Solved

Fenobam was developed in the 1970s at McNeil Laboratories for anxiety disorders. In trials in hundreds of patients, fenobam showed a good safety profile and some effectiveness, but how it worked was a mystery (as with many – even most – psychiatric drugs). Fenobam was never marketed for human use and is now off-patent.

Two decades later, scientists at Roche revealed that fenobam is an mGluR5 antagonist, making it a promising candidate for treatment of Fragile X.

Fenobam is one of many potential treatments for Fragile X which we hope will emerge from the translational research FRAXA has sponsored since 1994; others are in the pipeline. Since researchers identified basic brain pathways which are disrupted in Fragile X, they have found many possible points of intervention (treatment). Other promising drugs do not affect mGluR5 directly, but help to tone down the excessive activity of the brain's mGluR pathway in other ways. This is how lithium seems to help.

The key question remains: how well will these medications work for people with Fragile X? Evidence in animal models is encouraging, but we won't know how well these drugs work until clinical trials can begin.

Could these drugs treat Autism?

It is likely that lithium, mGluR5 antagonists, and several other drug classes currently under investigation will effectively treat Fragile X. But they may do more. Since many people with genetically unrelated Autism Spectrum Disorders appear to have defects in the same cellular pathways, they may respond to the same treatments. FRAXA is funding studies to develop "biomarkers" – blood tests to identify those non-Fragile X individuals who have abnormalities in the same pathways. These tests may be able to identify autism cases which are biochemically similar to Fragile X and thus likely to respond to the same treatments. Thus, Fragile X is an important area for expanded funding of translational research, not only because it is a tractable problem, but also because it is an important testbed for the development of new autism treatments.

Clinical Trial Update – Lithium

FRAXA is funding a trial of lithium in Fragile X patients conducted by Elizabeth Berry-Kravis, MD, PhD, at Rush University Medical Center in Chicago. Lithium is a mood stabilizing drug which has been in use for decades to treat bipolar disorder. Lithium has many effects on the brain, not all of which are understood, but one of its known actions is to dampen mGluR5 activity. FRAXA-funded studies in Fragile X mice and flies have shown that lithium can reverse some symptoms of Fragile X.

by Dr. Elizabeth Berry-Kravis

All participants have completed two months of treatment in our lithium trial, allowing initial data analysis. An early look at the results is encouraging.

Sixteen individuals with Fragile X were enrolled, ranging from age 6 to young adulthood. Of the 15 who completed two months of lithium treatment, some improvement in language was noted by 12 families. Twelve families chose to continue treatment for a year. Of those, 11 improved in some area and one was unchanged. Side effects have been mild for most participants, with increased thirst and urination and mild changes in thyroid function being the most common problems. No kidney problems or tremor have been seen.

Although full analysis has not yet been done, it appears that there was overall improvement in at least three behavioral measures and at least one cognitive test. For all participants continuing treatment past five months, behavioral improvements have persisted.

This small open trial suggests that lithium may be a useful Fragile X treatment. We hope that this trial will provide support for a larger placebo-controlled trial to further evaluate the potential and safety of lithium.

A Case Study

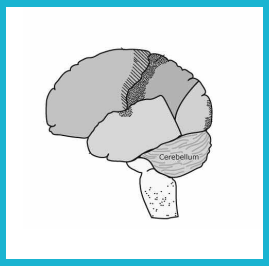
Eric (22 yrs old) began the study in September 2006. We have noticed subtle changes. He is better able to communicate the events of his day and upcoming events. At our Christmas office party, three people who don't see him regularly were impressed with how he joined the group and held a conversation. My sister-in-law called the house one day and Eric answered. She later said how surprised she was when she realized she was speaking with Eric!

EDITOR'S NOTES

What causes Fragile X?

A gene on the X chromosome, called FMR1, shuts down and cannot produce its normal protein product, FMRP. Loss of FMRP affects brain development, leading to symptoms including learning problems, anxiety, autistic behaviors, and sometimes seizures.

The brain is a network of cells (neurons) which send electrical and chemical signals from one to the next. Cell-to-cell communication occurs at synapses.



The good news about Fragile X is that it appears to effect communication between cells, but the cells themselves may not be permanently damaged. Brain **plasticity** refers to the brain's ability to adapt and remodel its connections. The brain is by far the most plastic, adaptable organ of the body.

Development of mGluR5 Antagonists to Treat Fragile X Syndrome and Autism

RANDALL CARPENTER, MD
Principal Investigator

MARK BEAR, PhD Co-Investigator
Seaside Therapeutics, $10,000

Seaside Therapeutics was founded by Dr. Mark Bear, Director of the Picower Institute at MIT, and Dr. Randall Carpenter, a physician with many years of drug development experience. Seaside has received a major grant from the NIH, with additional funding from FRAXA and Cure Autism Now (CAN).

Seaside has licensed from Merck several selective, potent mGluR5 antagonists. They intend to develop the lead compound, STX107, to treat Fragile X and, potentially, autism. They will advance the compound through the preclinical studies necessary to fulfill FDA requirements to open an Investigational New Drug application and perform initial testing in humans.

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

ABDESLEM EL IDRISSI, PhD

Principal Investigator
College of Staten Island/CUNY
$34,000 RENEWAL

Our early data shows that the expression of a protein called somatostatin is significantly decreased in the brains of Fragile X mice. Reduced somatostatin could account for many features of the syndrome.

We have found that adding taurine to drinking water increased somatostatin expression in the brains of both Fragile X and normal mice. The increase in somatostatin reversed some of the Fragile X symptoms seen in these mice.

This raises the possibility that either somatostatin or taurine could treat Fragile X. While somatostatin must be infused intravenously, taurine is an over-the-counter nutritional supplement (and a major ingredient in Red Bull, along with a lot of caffeine). This project will confirm and extend the preliminary results with further trials of agents which enhance somatostatin function.

FRAXA

Targeting MMPs to Treat Dendritic Spine Malformation & Behavioral Defects in Fragile X Mice

IRYNA M. ETHELL, PhD Principal Investigator
University of California Riverside, $60,000

Douglas Ethell, Iryna Ethell, Tina Bilousova

We are investigating how the brain's neuronal network develops and how problems with this process can cause cognitive impairment, with a focus on dendritic spines. This project will investigate the role of matrix metalloproteinases (MMPs) in the development of abnormal dendritic spines in Fragile X. We will use an MMP inhibitor, minocycline, to accelerate spine development in the brains of Fragile X mice. Minocycline is an antibiotic sometimes used to treat acne.

We hypothesize that excessive levels of MMP activity in FMR1 knockout mice contribute to dendritic spine abnormalities and cognitive dysfunction. We propose that inhibiting this excess MMP activity with minocycline will prevent abnormal dendritic spine development and related behavioral defects, effectively treating Fragile X.

Cellular Processes Regulated by FMRP During Development

PETER KIND, PhD Principal Investigator

SALLY TILL, PhD Postdoctoral Fellow

University of Edinburgh, $60,000

Many of the cognitive and behavioral features of Fragile X emerge during childhood

RESEARCH

and are associated with abnormal organization of connections in the cortex. Lack of the protein FMRP causes the syndrome. While recent work has begun to reveal roles for FMRP in the plasticity of adult brain cells, the mechanisms by which it influences development of the cortex remain unclear. We are testing the hypothesis that lack of FMRP during development leads to abnormal cortical organization. We are focusing on the primary somatosensory cortex in a Fragile X mouse model. This brain region is an excellent system to study cortical development because it contains easily identifiable and highly organized structures called "barrels" which emerge and are refined through a stereotypical sequence of developmental events.

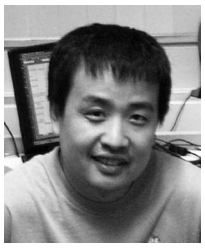
If we find that loss of FMRP results in abnormal cortical development in mice, we will go on to investigate whether these abnormalities can be reversed by reducing signaling of group 1 metabotropic glutamate receptors (mGluRs).

In Vivo Imaging Of Synaptic Abnormalities In A Mouse Model Of Fragile X

WEN-BIAO GAN, PhD Principal Investigator

FENG PAN, PhD Postdoctoral Fellow

New York University, $40,000



Wen-Biao Gan

Studies have revealed an overabundance of long, thin dendritic spines in the brains of Fragile X patients and knockout mice, suggesting that abnormal formation and plasticity of neuronal connections play important roles in causing behavioral and learning deficits.

Using a new transcranial two-photon imaging technique, we will examine the development and dynamics of synapses by following individual postsynaptic dendritic spines and presynaptic axonal boutons over extended periods of time in the brains of living Fragile X mouse. We do this by marking single neurons with Yellow Fluorescent Protein.

We will determine if and when abnormal structural plasticity occurs in Fragile X mice. We will also test whether abnormal structural plasticity of synapses can be reversed with drugs (including mGluR5 antagonists) that have been shown to correct behavior problems in fly and mouse models of Fragile X.

Imaging Aberrant Synaptic Structure and Function in an Animal Model of Fragile X

CARLOS PORTERA-CAILLIAU, MD, PhD

Principal Investigator

UCLA, $50,000 RENEWAL

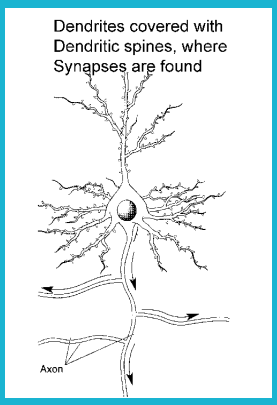
We are testing the hypothesis that a defect in dendritic filopodia occurs in Fragile X syndrome and impairs the ability of these tiny protrusions to form synapses and mature into spines.

Using two-photon microscopy, we are imaging dendritic filopodia (emerging spines) in the brains of anesthetized Fragile X knockout mice and looking for defects in their density, length, or dynamics. We are also investigating the role of group I mGluRs in glutamate-induced filopodia growth. We intend to find a link between abnormal signaling through mGluRs and the increased density and length of spines in Fragile X mice.

Ultimately, the new knowledge derived from this research may identify new treatment targets, including but not limited to the use of drugs that modify mGluR neurotransmission.

EDITOR'S NOTES

A synapse is a junction between two neurons. A neuron receives signals via **receptors** at synapses on its **dendritic spines**: small protrusions on the surface of its **dendrites**.



Defects in dendritic spines have been found in the brains of patients with Autism Spectrum Disorders including Fragile X and Rett Syndrome.

Brain Development

Neuroscientists believe that learning occurs when the synapses are strengthened (Long Term Potentiation or LTP) or weakened (Long Term Depression or LTD) in response to activity. Unneeded synapses are eventually pruned away.

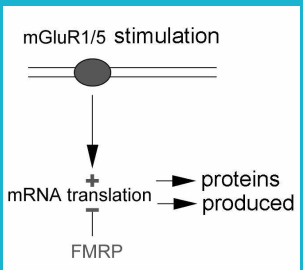
EDITOR'S NOTES

This process is tightly regulated and depends on the creation of new proteins at synapses in response to activity. Normally, the Fragile X protein FMRP plays an important role in fine-tuning the process.

The mGluR Theory

In Fragile X syndrome, with FMRP absent from brain cells, growing evidence suggestions that there is excessive signaling through one set of receptors at synapses: group 1 metabotropic glutamate receptors (mGluRs). (To confuse matters, group 1 mGluRs are also known as mGluR1 and mGluR5).

The mGluR theory of Fragile X proposes that this excessive mGluR activity causes too many new proteins to be made.



In a normal brain, FMRP acts to check the synthesis of new proteins.

Effect of MPEP on Neuronal and Glial Cell Specific Glutamate Metabolism in Fragile X Mouse Brain

MARY MCKENNA, PhD
Principal Investigator

University of Maryland, $42,000

According to the mGluR theory of Fragile X, excessive mGluR activation underlies symptoms of the syndrome. Although mGluR activation involves glutamate neurotransmission, it is not known how the increased mGluR activation affects glutamate metabolism in brain. Since ongoing neurotransmission requires coordinated interactions between synapses and surrounding astrocytes that remove glutamate from the extracellular space, and since mGluRs are found on both postsynaptic dendrites and astrocytes, increased activation of mGluR could alter both neuronal- and astrocyte-specific aspects of glutamate metabolism.

Our preliminary data suggests that synthesis of glutamate, GABA and glutamine is increased in Fragile X mice and that these alterations are normalized in mice treated with the mGluR5 antagonist, MPEP. We will determine the effects of MPEP on cell specific alterations in glutamate, GABA and glutamine metabolism in brains of Fragile X mice using the powerful, state of the art technique of nuclear magnetic resonance (NMR) spectroscopy. Any alterations found in metabolism may help identify new targets for therapeutic interventions.

Homer and Hippocampal mGluR-LTD in Fragile X

Jennifer Ronesi

KIMBERLY HUBER, PhD
Principal Investigator

JENNIFER RONESI, PhD
Postdoctoral Fellow

UT Southwestern, $49,000

Absence of FMRP results in altered function of metabotropic glutamate receptor (mGluR) pathways. Recent studies have shown abnormalities in a protein called Homer in Fragile X animal models. Homer links mGluRs, which sit in the cell membrane, to the interior of the neuron. Alterations in Homer cause changes in mGluR location and function and may be responsible for the observed increase in mGluR-LTD in Fragile X.

This team will investigate these interactions with an eye toward discovering additional treatment targets.

FRAXA

Treatment of Fragile X Syndrome via the GABA-A Receptor

FRANK KOOY, PhD Principal Investigator
University of Antwerp, $50,000

While most studies have focused on excessive activity of glutamate pathways, notably the mGluR5 pathway, there is also evidence of decreased function of the brain's inhibitory pathways in Fragile X. For example, 20-30% of boys with Fragile X experience seizures, probably due to a failure of inhibitory pathways.

The brain's inhibitory circuitry is primarily controlled by the neurotransmitter GABA. Naturally-occurring substances called neurosteroids enhance GABA function and are important for normal brain function. This project will test whether recently developed synthetic neurosteroids can reverse symptoms of Fragile X in mice.

Sleep and Circadian Rhythms in Fragile X Mutant Drosophila

RAVI ALLADA, MD Principal Investigator

ELAINE MERRILL SMITH, PhD
Postdoctoral Fellow

Northwestern University, $40,000

Elaine Smith

Many people with Fragile X have problems with sleep. The fruit fly has a gene, dfmr, that is similar to the human FMR1 gene. Flies lacking dfmr exhibit altered behaviors consistent with the human syndrome,

including disrupted circadian rhythms. Circadian rhythms control the daily timing of physiology and behavior in organisms from bacteria to humans. I have demonstrated that flies mutant for dfmr also have decreased sleep and poor sleep quality, just as is observed in humans with Fragile X.

I will test whether the altered behaviors in mutant flies can be restored with a normal copy of the dfmr gene introduced during adulthood, or whether this gene is also required during development. I will also investigate the link between dfmr and other known genes to shed light on the normal activity of dfmr with regard to sleep and circadian rhythms. These findings may yield novel treatment targets.

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

LEONARD K. KACZMAREK, PhD
Principal Investigator

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

Individuals with Fragile X syndrome and autism spectrum disorders exhibit extreme sensitivity to sounds which interferes with attention, learning, and social interactions. This sensitivity is likely due to changes in electrical properties in neurons of the auditory brainstem. Our studies will define abnormal sensory processing at the cellular and molecular level and will likely lead to strategies for therapeutic intervention.

We have identified a new FMRP-interacting protein which is widely expressed in neurons in many parts of the brain. We are currently examining its function in the auditory brainstem and how this is likely to be misregulated in Fragile X and Autism Spectrum Disorder individuals.

Our project now includes not only studies of the Kv3.1 channel but of the newly discovered protein as well. Because of the exciting discoveries centered around the *mGluR theory of Fragile X*, we have added studies involving the *inferior colliculus*, a brain region which expresses high levels of mGluR5. Fortuitously, we can study all these components simultaneously in neurons of the auditory brainstem.

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
Erasmus University, The Netherlands, $50,000 RENEWAL

Dr. Willemsen is generating sophisticated new mouse models for Fragile X which will facilitate many studies. One mouse strain has an inducible fluorescent FMR1 fusion gene. In this mouse, the FMR1 gene can be switched on by adding doxycycline to the animal's feed. The mouse will then produce FMRP which can be seen easily, since green fluorescent protein will be produced wherever FMRP is present.

They will generate other mouse models to study the role of FMRP in AMPA receptor expression in neurons. This will allow further study of the mGluR theory of Fragile X, since excessive mGluR signaling is thought to cause a significant decrease in AMPA receptor expression in Fragile X.

Activity-Dependent Trafficking of AMPA Receptor mRNAs in Dendrites

R. SUZANNE ZUKIN, PhD
Principal Investigator

SHO FUJISAWA, PhD
Postdoctoral Fellow
Albert Einstein College of Medicine, $65,000

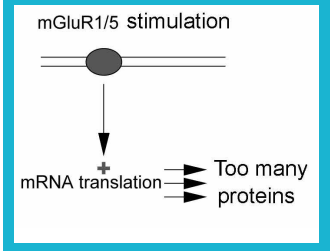
Sho Fujisawa

Suzanne Zukin

Cognitive impairments in Fragile X may result from dysregulation of messenger RNA localization and local protein synthesis. This project aims to understand how AMPA receptor mRNA

EDITOR'S NOTES

But in people with Fragile X, FMRP is not present and the result is thought to be runaway protein synthesis.



mGluR antagonists

mGluR antagonists are compounds that block or dampen mGluR activity. The logic behind using mGluR antagonists to treat Fragile X is to restore the normal balance of protein synthesis. Drugs which block mGluR1 are not likely treatments due to side effects. However, mGluR5 antagonists like MPEP have been effective in mice and other animal models of Fragile X.

Several pharmaceutical companies are currently developing mGluR5 antagonists to treat Fragile X. Neuropharm (neuropharm.co.uk) and Seaside Therapeutics seasidetherapeutics.com, are discussed in this newsletter.

EDITOR'S NOTES

Fragile X Knockout Mouse

FMR1 knockout mice have been genetically engineered so that the FMR1 gene is "knocked out" of their genome. Fragile X knockout (KO) mice produce no FMRP.

Because they show social behaviors and brain development abnormalities similar to those of patients with Fragile X and some other forms of autism, these mice are excellent animal models to study the underlying mechanisms of the disorder and to test potential treatments.

It is even possible to develop mice in which the Fragile X gene can be turned on or off at any point during development.

localization in dendrites is altered in Fragile X. We will use molecular, biochemical and imaging techniques to look for possible alterations in AMPAR mRNA trafficking in the Fragile X mouse.

We will also identify signaling pathways involved in regulation of dendritic targeting of AMPAR mRNAs and local protein synthesis and examine their possible dysregulation in KO mice. A focus will be on signaling cascades known to be downstream of group I mGluR activation and important to local protein synthesis.

Defective Cyclic AMP Signaling in Fragile X

ANITA BHATTACHARYYA, PhD
Principal Investigator
University of Wisconsin, $60,000

Cells respond to signals (e.g. electrical or chemical signals) by signaling pathways that relay information from the cell's surface (membrane) to the nucleus where changes in gene expression occur. We want to test how the loss of FMRP affects these pathways. One relay molecule that has been implicated in Fragile X is cyclic AMP (cAMP). Fragile X researcher Elizabeth Berry-Kravis has shown that cAMP is lower in blood cells from Fragile X patients. We have found that cells of the brain are also not able to produce cAMP as well in Fragile X. Lowered cAMP affects how FX neurons function during development and during plasticity.

We want to understand why cAMP production is lower in Fragile X. How does the lack of FMRP cause lower cAMP signaling? Is there a link between defective cAMP production and the mGluR pathway? Using a drug assay on human FX cells, we hope to find compounds that can rescue the cAMP defect in FX cells.

Regulation of Group I Metabotropic Glutamate Receptor Trafficking in a Fragile X Animal Model

ANNA FRANCESCONI, PhD, Principal Investigator
Albert Einstein College of Medicine, $43,500

Abnormalities in the Fragile X brain's mGluR pathways have been demonstrated by many

studies. This group is the first to study how mGluRs move around in Fragile X neurons. These receptors are not fixed but move around in the cell membrane, from one part of a synapse to another, in ways that are tightly controlled. There is reason to suspect that absence of FMRP damages these processes.

Understanding these movements may lead to new targets for drug discovery and may help optimize Fragile X treatments with mGluR antagonists.

The Drosophila Model of Fragile X Syndrome: Testing the Metabotropic Glutamate Receptor Hypothesis

KENDAL BROADIE, PhD
Principal Investigator
CHARLES TESSIER PhD
Postdoctoral Fellow
Vanderbilt University $40,000
RENEWAL

Charles Tessier

We are using the powerful genetic system of the fruit fly, Drosophila melanogaster, to investigate the molecular basis of Fragile X Syndrome (FXS). Mutant animals lacking the Drosophila Fragile X protein, dFMRP, develop characteristic FXS neuronal and behavioral defects. An exciting hypothesis in the field suggests that FMRP may be regulated via metabotropic glutamate receptors (mGluRs). The mGluR theory suggests that FMRP functions to limit neuronal activity in response to these receptors.

We are testing this hypothesis by using animals that lack both dmGluRA and dFMRP. We are employing physiology and molecular tools to understand the roles of each protein in FXS. We are also using drugs that specifically block mGluR signaling to identify the convergence of these two important biological pathways. This research may lead to developing new drugs that specifically target molecules involved in the disease and avoid those which may lead to unwanted side-effects.

RESEARCH

Specific Tests of the mGluR Theory of Fragile X: High-throughput Determination of Synaptic Protein Changes in the FMR1 KO Mouse

PETER VANDERKLISH, PhD
Principal Investigator

Neurosciences Institute, San Diego
$50,000 RENEWAL

The most critical gap in our understanding of Fragile X is the identification of proteins that are dysregulated in the absence of FMRP.

We use high throughput proteomic techniques to understand how the absence of FMRP affects levels of other proteins in neurons. We have identified several proteins that may contribute to the abnormalities in synaptic shape seen in Fragile X and a few proteins that have been implicated in autism. One protein presents a potential opportunity for therapeutic intervention with drugs that are currently in clinical trials for unrelated indications.

Effects of Alternative Splicing at FMR1 Exon 15 on Understanding Fragile X Syndrome

ROBERT DENMAN, PhD Principal Investigator
New York State Institute for Basic Research, $57,500

While we often speak of FMRP as a single protein, it is actually a set of related isoforms (proteins) made by alternate splicing of its mRNA. These proteins can also be modified in a number of ways, such as phosphorylation and methylation. The activity of FMRP is the sum of all of the isoforms in their various modified states.

We seek to understand the role these processes play during brain development and in different brain regions. We will also determine whether stimulating GABA receptors alters FMRP methylation, or other locally synthesized proteins in dendrites. We hope to further our understanding of the role FMRP plays in normal cellular metabolism.

FMRP-MAP1B RNA interactions in Fragile X

MIHAELA RITA MIHAILESCU, PhD
Principal Investigator
Duquesne University, $45,000 RENEWAL

The Fragile X Protein, FMRP, is thought to repress translation of specific messenger RNAs (mRNAs) within cells. FMRP stops mRNA from being translated into protein until the appropriate signal occurs, indicating the right time to make a protein.

This team is investigating the effects of modifications of FMRP on its interactions with RNA targets, particularly MAP1B which is important because several studies have shown that it is misregulated in Fragile X.

FMRP as a Modulator of Dendritic mRNA Translation in Response to Metabotropic Glutamate

GARY BASSELL, PhD Principal Investigator
RAVI MUDDASHETTY, PhD
Postdoctoral Fellow, Emory University, $40,000

FMRP modulates dendritic mRNA translation in response to mGluR activation. An understanding of how the process may be dysregulated in FXS is essential to understand the function of FMRP.

I will study mRNA targets of FMRP using synaptoneurosomal preparations and cultured hippocampal neurons in the FMR1 KO mouse. Agonists to mGluR and NMDA receptors will be used to determine a role for FMRP in either or both pathways. We will also assess the ability of the mGluR5 antagonist, MPEP, to correct alterations in dendritic mRNA translation in cultured neurons from mice.

We believe that our work will help in screening potential therapeutic compounds to target Fragile X.

EDITOR'S NOTES

Fragile X Fruit Flies

Remarkably, scientists have have made great

discoveries about complex disorder like Fragile X by studying the lowly fruit fly. The fly's simplicity is its power. The fly genome is easily manipulated, and a wide range of Fragile X fruit fly models have been genetically engineered. Fragile X flies exhibit symptoms, such as sleep disorders and learning problems. Flies breed quickly and adapt well to laboratory life.

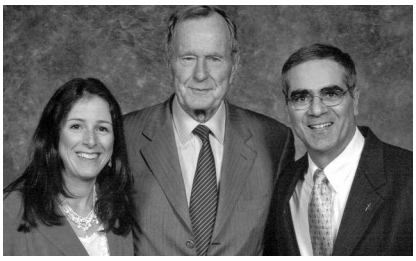
Researchers and Parents

Since 1994, FRAXA has funded over $11 million in Fragile X research conducted by scientists around the world. Perhaps the most remarkable discovery we have made is that many scientists are also parents – or brothers or sisters – of children with Fragile X or related disorders. For these scientists, the potential of this important work is especially clear!

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 fraxa.org often for a listing of upcoming events.

Please take a moment to give to FRAXA by phone: 978-462-1866, fax: 978-463-9986 or online at fraxa.org. All major credit cards accepted. Your donation matters!



Fragile X Shares the Stage with Former President George H. W. Bush

Since 2003, the First Data Western Union Foundation and TravelCenters of America have supported FRAXA with a joint annual $50,000 donation. Ara Bagdasarian, trustee of the Fragile X Alliance of Ohio, is a marketing executive for TravelCenters of America. Ara's wife Leslie is a FRAXA board member, and 14-year-old Julie and 12-year-old Alex both have Fragile X.

Last Fall, Ara and Leslie Bagdasarian were asked to share their own Fragile X story at the Outlook Leadership Conference in Phoenix, Arizona, an event attended by over 700 executives from the convenience store industry. FRAXA was chosen as the conference-featured charity by The Children's Leadership Foundation.

Ara described their family's experiences of diagnosis and living with Fragile X and their hope for a future cure or treatment. He discussed FRAXA's mission and progress and showed the video "First Down Towards a Cure." The audience gave Ara a standing ovation and generously gave to our cause.

President George H. W. Bush viewed FRAXA's video and heard the Bagdasarians' story. Mr. Bush, who spoke immediately following Ara, remarked on Fragile X and stressed the importance of supporting this worthy cause! Ara and Leslie then attended a private reception with the President where they spoke further with him about Fragile X and FRAXA.

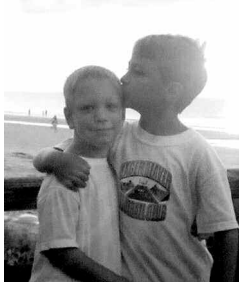
A raffle was held to benefit FRAXA. The audience was overjoyed when none other than Ara Bagdasarian won the $10,000 grand prize! Ara and Leslie donated their prize back to FRAXA, and in combination with the other contributions, the total raised for FRAXA was $45,000!

Front row, left to right: 2Lt. Dorian Sherman, Capt. Giuseppe Scaglione, Capt Teodoro Apolisok. 2nd row: 2Lt. Patricia Lowry, Capt. Kwibisa Muyunda (Zambia), Mr. David Sturgell, Capt. Todd Dye, 2Lt. Hamad Rejairan (Bahrain) , 2Lt. Brian Krusemark, 2Lt. Josephine Beacham, 2Lt. Andy Glindmeyer, 1Lt. Abdullah Isa Almaeeli (Bahrain), 1Lt. Abdulrahman Aloun (Bahrain). Back row: 2Lt. Ben Lowry, 2Lt. Aaron Pauli, 2Lt. Trevor Johnson, Capt Andrew Holko.

Air Force Officers Fundraiser

Renee Butler's son Brian Krusemark attended a 14-week aircraft maintenance course at the Sheppard Air Force Base in Texas. The officers learned how to manage various aircraft, including fighters, bombers, cargo planes, and refueling platforms. They also learned about avionics, hydraulics, electrical systems, and more.

In their free time, the officers delivered Meals on Wheels, built homes for Habitat for Humanity, and sold breakfast burritos for charity. Two thirds of the burrito funds were donated to the Air Force Aid Society. Students made presentations to the class to determine to whom they would donate the remaining $400. Second Lt. Brian Krusemark advocated for FRAXA. Brian's younger brother Adam has Fragile X Syndrome.



Adam and Chris Krusemark

Over 100 people attended the graduation and presentation ceremony, where David Sturgell of Plano accepted the check on behalf of FRAXA.

Marathon for Fragile X

Alexa Jaccarino, a member of the class of 2008 at Stonington High School in Pawcatuck, CT, ran a half marathon in New York City. She decided to run the race in honor of her friend Dave Clark, Jr.

Alexa writes "I proudly crossed the finish line in two hours and forty six minutes with the knowledge that I was helping millions of children through your extremely valuable organization." Congratulations, Alexa!

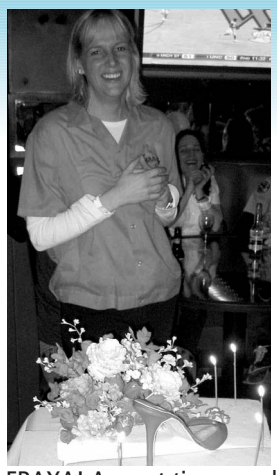
Pittsburgh Zone Team

In November, the Pittsburgh Zone Sales Team from Kellogg's Snacks held a Chinese Auction to benefit FRAXA at their annual Holiday Party. With over 140 employees and spouses in attendance, over $1200 was raised. Many thanks to Zone Manager, Tom Beal, for all his support. Kellogg's Snacks had previously donated four tickets to their Pittsburgh Steelers' suite for FRAXA's X Ball gala, raising an additional $2500.

A Bowling Birthday

On March 17, Franziska Klebe and her husband Chuck Samuelson hosted a FRAXA bowling fundraiser in New York City in honor of Franziska's 40th birthday. In lieu of gifts, guests were asked to

AND AWARENESS



donate $2 per strike and $1 per spare thrown. Notwithstanding the complete lack of bowling talent, everyone's generosity resulted in raising over $16,000 for FRAXA! A great time was had by all and Franziska loved her favorite shoes-inspired cake!

Texas Bash

To celebrate FRAXA Fall Fling 2006, FRAXA Advisory Board member Susan Cohen and her friends Lainie Gordon and David Mincberg hosted a festive evening in Bellaire, Texas. Susan's friend Elaine Scott captured the magic of the evening:

"Parker and I both agreed it was the best charity event we have ever attended. I loved the intimacy of the setting; we were able to mix and mingle and learn much about Fragile X. I loved the sense of hope that was present Saturday night – and also the joy the parents expressed as they celebrated their children's strengths. These kids who have Fragile X are special in the best, most positive sense of that word!"

FRAXA Investigator Dr. Richard Paylor gave an entertaining summary of research underway at Baylor College of Medicine, and Dr. Jay Gibson represented the Fragile X research team at the University of Texas at Southwestern. Singer Nancy Fauber-Hoh gave a delightful performance.The evening raised over $18,000 for FRAXA.

Dr. Richard Paylor, Dr. Jay Gibson, Debbie Stevenson, David Busby, Tanya and Warren Robinson, Katie Clapp, Susan Cohen, Mary Beth Busby

Texas Residents:

If you shop at any Randalls or Tom Thumb supermarket, you can raise money for FRAXA by using your Remarkable Card. The first time you use it, give the cashier FRAXA's number: 3715. Present the card each time you shop, and 1% of your purchase will automatically be donated to FRAXA. Please share this news with your friends in Texas!

Contribution in honor of the Eddys

For many years, FRAXA Board member Leslie Eddy and her husband Trevor, of Marblehead, MA, have shared their experiences with Fragile X and FRAXA with their close friends and neighbors, Kathy Sidford and Ted Truscott. After Kathy and Ted learned about the mGluR Theory of Fragile X and met the author of the theory, Dr. Mark Bear, they decided to pledge $150,000 in contributions to FRAXA, in honor of the Eddy Family.

As if that were not generous enough, when Ted learned of Doris Buffett's Challenge to FRAXA, he decided to contribute an additional $20,000 toward FRAXA's Buffett Cup Challenge in Marblehead, on October 4th.

Alison Eddy

Jeans Day

We are grateful to the employees of Levi, Ray & Shoup, in Springfield, Illinois, who raised $806 for FRAXA through a casual dress-down day at the company.

Calendar

Check often at fraxa.org EVENTS section

Patrick's Pals XI
Cambridge, MA
Sunday, June 2

Play or watch the three-on-three Basketball Tournament at 9am at the Buckingham Browne & Nichols School in Cambridge, MA. Contact Jimmy Vershbow at pjversh@comcast.net or 617-924-7560.

Bike Run
New Castle, Delaware
Sunday, July 22

Celebrate National Fragile X Awareness Day at our Bike Run and BBQ with live band and silent auction. Contact Jen Nardo at jlnardo1@verizon.net or 302-234-7854.

Gala – Marblehead, MA
Thursday, October 4

The Buffett Cup Challenge will be held at the Corinthian Yacht Club on the coast in Marblehead, MA. This is the height of foliage season in New England and space is limited, so reserve your table now. Contact Katie Clapp at kclapp@fraxa.org or

Storm Tracker Jim Cantore Speaks out for FRAXA

The Weather Channel's Storm Tracker Jim Cantore is on the front line of hurricanes and severe weather everywhere. Jim has his own storm story too: his son Ben and daughter Christina have Fragile X.

Ben

We are very pleased to welcome Jim Cantore as the newest member of FRAXA's Board of Directors. All FRAXA Directors are parents of children affected by Fragile X.

Jim reflects on the years when Christina and Ben were diagnosed with Fragile X:

"I love my life as a Storm Tracker. It's something I wanted to do from the time I was a kid, but there's a downside. I've watched hurricanes devastate whole parts of the country, and it's tough to have to watch as the lives of families are torn to pieces. I can empathize with the emotional toll it takes on people. Talk about a change in forecast. In a few short years, our lives had gone from full of sunshine to dark and ominous, as if two storm systems had collided overhead.

Christina

My family lives in a category five state of crisis – the invisible storm felt by other families with children who have Fragile X."

Jim decided to become active in FRAXA to increase awareness of Fragile X and raise funds for research aimed at finding a cure. Jim's Public Service Announcement is now airing on Comcast Cable stations on the eastern seaboard. Watch Jim's 30-second video at fraxa.org, and help FRAXA spread the word about Fragile X by sending the video to your friends and family. Contact your local cable and radio stations and ask them to air this Public Service Announcement.

FRAXA UPDATE

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

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 checks to: FRAXA, 45 Pleasant St., Newburyport, MA 01950 or donate online at fraxa.org

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