2011 FRAXA Investigators Meeting Report

September 18-21, 2011

For three days in September 2011, more than 160 researchers convened in Southbridge, Massachusetts to present their most recent findings from their Fragile X studies.

Top Left: *Baltazar Gomez-Mancilla, MD, PhD; Angel Angelov, MD; Mark Matthisson, MD, PhD; Emma Huzzey, PhD; Fabrizio Gasparini, PhD (all Novartis)*
Top Right: *Petro Chiurazzi, MD, PhD (Catholic Univ., Rome), Scott Soderling, PhD (Duke Univ.)*
Bottom Left: *Karen Usdin, PhD (NIMH), Justin Fallon, PhD (Brown Univ.)*
Bottom Right: *Eriene Wasef, PharmD (Roche), Michael Tranfaglia, MD (FRAXA), Sasa Zorovic, PhD (FRAXA)*

One of the most prominent features of this year's meeting was the presence of large numbers of pharmaceutical company scientists -- dozens of attendees represented 8 different pharmaceutical companies from around the world. Several companies actively engaged in Fragile X clinical trials brought large teams to the meeting to hear about the latest discoveries. Others about to initiate clinical trials sent representatives to learn about the latest experience in conducting clinical trials in Fragile X. Still other companies have potential therapeutics at an earlier stage of development, and they formed collaborations at this meeting with FRAXA's university-based labs to test their compounds.

Among the highlights of this year's meeting:

- **New Treatment Targets: PIKE, PAK, STEP, and more!**

  Several lab groups presented evidence of preclinical efficacy for potential therapeutic targets, including PI3 kinase, PIKE, PAK, STEP, CPEB, and PDE4. Many of these labs have adopted a similar, semi-standardized method for validating these therapeutic targets by showing rescue of basic neuronal parameters such as dendritic spine shape, protein synthesis, and mGluR-LTD. Though these are still rather labor-intensive methods, this is an encouraging step toward a consensus panel of validation steps which suggest that a therapeutic target may be *disease-modifying*. However, as promising as these targets may be, few of them have good drugs which can address them safely. Nonetheless, pharma representatives in the audience have access to many new compounds which can potentially turn an impractical target into an excellent target instantly---making their attendance even more important.

- **Clinical Trial Results**

  Results from several clinical trials were presented, as were results from ongoing studies of improved outcome measures. The trials of mGluR5 antagonists, baclofen, and minocycline have all shown positive results. The key challenge going forward is to refine the way studies are conducted in Fragile X. Since there have never been specific treatments for Fragile X, these early trials have pioneered methods for demonstrating therapeutic effects in human subjects. It is especially challenging to measure therapeutic effects of different treatments in different age groups; trials are currently under way in patients as young as 3 and as old as 50, with pressure from regulatory agencies to study even younger patients in future trials.

- **Neural Circuits**

  Much more work is now being done on the abnormalities in neural circuits seen in Fragile X. In many ways, these effects are potentially far more important than effects on individual cells or synapses, because there are many different types of cells in the brain, and they are affected in different ways by the Fragile X mutation. By focusing too narrowly on abnormal events at, for example, the synapse, we may miss other important problems in larger circuits of neurons. Additionally, some treatments could help with narrowly measured synaptic function in some cells, while hurting in others. These various ways of measuring neural circuit function could serve as important ways of testing new treatments in the mouse model, and could be a more relevant way to determine which drugs help the whole Fragile X brain to function better.

- **Proteomics**

  A number of proteomic studies have now been done in Fragile X, and there has been some convergence of results in these; several studies were presented at this meeting, utilizing various methods. The levels of many different proteins (perhaps thousands) are altered as a result of the Fragile X mutation, leading many researchers to speculate that the problem in Fragile X may be a

general excess of protein synthesis. While some changes are undoubtedly more important than others, it is striking that many of the altered proteins are also implicated in autism. This has become quite apparent to many of the other rare disease foundations funding research in monogenic causes of autism, and forms the basis for new initiatives for the future. FRAXA and other foundations studying genetic causes of autism are attempting to form a collaborative to explore common interests, and we hope to have many more representatives from other groups at our next meeting.

As always, we solicited feedback from attendees at the meeting. Two comments were repeated over and over, dozens of times in the surveys:

1. This was the best Fragile X meeting ever!

2. The pace of discovery in Fragile X research is astonishing---there was an incredible volume of new information presented at this meeting.

One final bit of good news: thanks to paid registrations and generous sponsorships, this meeting paid for itself. We believe we have found a sustainable, effective model for conducting large research meetings, and look forward to many more like it.

2011 FRAXA Investigators Meeting Sponsors

The Zorovic Family (Leadership)
Seaside Therapeutics (Underwriter)
The Eddy Family (Underwriter)
Afraxis (Benefactor)
European Research Foundation for Fragile X Syndrome and Autism (Benefactor)
Roche (Benefactor)
Novartis
Pfizer
Autism Science Foundation
Chris Ford
Bob Ward
The Casey Family

Future Conferences

1. Gordon Conference on Fragile X and Autism

At the meeting Dr. Elizabeth Berry-Kravis announced the start of a new biannual series of Gordon Conferences on Fragile X. These prestigious meetings typically attract up to 200 scientists from around the world, and are a sure way to keep Fragile X research a hot topic moving ahead well into the future.

The 2012 Gordon Conference details:

Fragile X and Autism-related Disorders - From Basic Neuroscience to Improved Clinical Care

June 10-15, 2012
Stonehill College, Easton, MA

Chair: Elizabeth M. Berry-Kravis
Vice Chair: Jennifer C. Darnell

http://www.grc.org/programs.aspx?year=2012&program=fragilex

2. 2013 FRAXA Investigators Meeting

We plan to host FRAXA Investigators Meetings every two years, opposite the Gordon Conferences; the next FRAXA meeting will take place in early fall 2013.

2011 FRAXA Awards

Three scientists were recognized for outstanding work aimed toward the goal that we all share: finding specific treatments and ultimately a cure for Fragile X, and possibly autism as well:

Dr. Mark Bear and Dr. Emily Osterweil each received a 2011 FRAXA Pioneer Award.

Dr. Bear's award is for translational research that he and his colleagues began with a small FRAXA grant in 2000. Two years later, Dr. Bear first presented his groundbreaking **mGluR theory of Fragile X** to a somewhat stunned and skeptical group of prominent scientists at the 2002 FRAXA Banbury Meeting, thereby jump-starting an entire field. Today experimental new drugs based on Dr. Bear's mGluR theory are in late stage trials in children and adults with Fragile X. However, the work of the Bear lab continues, and they have generated and validated other potential treatment targets in Fragile X.

Dr. Osterweil, a postdoctoral fellow in the Bear lab, received her FRAXA Pioneer Award for two lines of Fragile X research. She has conducted elegant studies to substantiate the mGluR theory. In addition, in an entirely new line of work, Dr. Osterweil has shown that the available drug Lovastatin can reverse many Fragile X symptoms in a mouse model of the disease (not yet published).

Bear Lab publications Bear Lab FRAXA grants

Dr. Elizabeth Berry-Kravis received the 2011 FRAXA Champion Award for extraordinary work designing and implementing Fragile X clinical trials. In 2002, FRAXA awarded a $72,000 grant to Dr. Berry-Kravis to conduct the first-ever Phase II trial of a medication specifically designed to reverse core defects in Fragile X: CX516, an ampakine. The results of the CX516 were equivocal, but generated important information about the best ways to conduct clinical trials in Fragile X. Dr. Berry-Kravis next spearheaded trials of fenobam and lithium, and now she is running trials of experimental new medications from Novartis, Seaside, and Roche.

FRAXA grants to Dr. Berry-Kravis

Meeting Agenda

Sunday, September 18th

6:00-7:00pm **Welcome Cocktail Reception - Conference Center Lobby**

7:00pm **Dinner – Ballroom**

8:00pm **Opening Night Program:**

Becky Zorovic - Introductory Remarks

Video - "Faces of Fragile X"

Mark Bear - "Monogenetic Causes of Autism"

Katie Clapp, Mike Tranfaglia - FRAXA Achievement Awards

David Nelson - "The 20th Anniversary of the FRAXA Gene Discovery"

9:30-11pm **Cocktails/Coffee - Lounge Area**

Monday, September 19th

7:00-8:30am **Breakfast - Dining Room**

8:30-10:45am **Morning Plenary 1 - Prism Auditorium, Moderator: Suzanne Zukin**

8:30 Mike Tranfaglia - "The FRAXA Method"

8:45 Emily Osterweil/Mark Bear - "Downregulation of Ras-ERK1/2 by Lovastatin is a Novel Treatment for Fragile X Syndrome"

9:15 Joel Richter - "Correcting Fragile X"

9:45 Susan Goebel-Goody/Paul Lombroso - "STEP as a Novel Therapeutic Target in FXS"

10:15 Richard Jope - "Overview of the Therapeutic Effect of Lithium and other GSK3 Inhibitors in Fragile X"

10:45-11:15am **Break**

11:15-1:15pm **Morning Plenary 2 – Prism Auditorium, Moderator: David Nelson**

11:15 Stephen Haggarty - "Modeling Fragile X Syndrome Pathogenesis and Treatment Using Human iPSC-derived Neurons"

11:45 Riccardo Bianchi - "Persistent mGluR Activation in Fragile X Syndrome**"**

12:15 Iryna Ethell - "Beneficial Effects of Minocycline in Behavioral Performance in Young and Adult Fmr1 KO Mice"

12:45 Kendal Broadie - "Minocycline Effectively Prevents Neural Circuit Architecture Defects in the Drosophila FXS Model"

1:15-2:30pm **Lunch - Dining Room**

2:30-4:30pm **Afternoon Plenary 1 - Prism Auditorium, Moderator: Craig Erickson**

2:30 Elizabeth Berry-Kravis - "New Outcome Measures for Clinical Trials I"

3:00 Stephanie Maltas/David Hessl - "New Outcome Measures for Clinical Trials II"

3:30 Nicole Tartaglia/Tracy Stackhouse - "Neuromotor Outcome Measures in Fragile X Syndrome"

4:00 Giovanni Neri - "Strategies for the Pharmacological Treatment of FXS"

4:30-4:50pm **Break**

4:50-5:40pm **Afternoon Plenary 2 - Prism Auditorium, Moderator: Mike Tranfaglia**

4:50 Baltazar Gomez-Mancilla - "Novartis AFQ056/mavoglurant Early Phase Clinical Trial Results""

5:20 Paul Wang - "Clinical Trials with STX209 (Arbaclofen): New Analyses and New Studies"

5:45-6:45pm **Breakout sessions 1 and 2**

Breakout session 1 - Prism Auditorium, Moderator: Elizabeth Berry-Kravis

5:45 Craig Erickson - "Open Label Acamprosate in Youth with Fragile X Syndrome"

6:05 Randi Hagerman - "A Controlled Trial of Minocycline in FXS"

6:25 Carlo Paribello - "Open-Label Pilot Trial to Assess the Cognitive Effects of Minocycline in Fragile X"

Breakout session 2 - Breakout Room 1, Moderator: Boris Macek

5:45 Dalit Ben-Yosef - "Neuronal Differentiation of Fragile X - Human Embryonic Stem Cells - Implications for Mental Retardation"

6:05 Kristopher Nazor - **"**X chromosome Instability in Human Pluripotent Stem Cells; Implications for X-linked Disease Models"

Breakout session 3 – Breakout Room 2, Moderator: Justin Fallon

5:45 Carolyn Hogan - "Intracellular mGluR5 in the Hippocampus"

6:05 Deepa Venkitaramani -"Restoration of FMRP Function and Contribution of FMRP Isoforms to Fragile X Phenotype"

6:25 Laetitia Davidovic - "A Metabonomic and Systems Biology Perspective on the Brain of the Fragile X Syndrome Mouse Model"

6:45-7:45pm **Poster Session, Cocktails - Conference Center Lobby**

7:30-9:00pm **Dinner - Dining Room**

9:00-11:00pm **Cocktails, Coffee, and Posters continue - Lounge Area**

Tuesday, September 20th

7:00-8:30am **Breakfast - Dining Room**

8:30-10:30am **Morning Plenary 1 - Prism Auditorium, Moderator: Kendal Broadie**

8:30 Christina Gross - "PI3K Dysregulation as a Novel Therapeutic Target in Fragile X Syndrome"

9:00 Suzanne Zukin - "PIKE as a central regulator of synaptic dysfunction in Fragile X Syndrome"

9:30 Eric Klann - "Targeting Downstream Effectors of mTORC1 to Prevent and

Reverse Abnormalities in Fragile X Syndrome"

10:00 Flora Tassone - "Altered mTOR Signaling in Fragile X Syndrome**"**

10:30-11:00am **Break**

11:00-1:10pm **Morning Plenary 2 - Prism Auditorium, Moderator: Len Kaczmarek**

11:00 Gary Bassell - "Dynamic Regulation of FMRP and Target mRNA Translation"

11:30 Henri Tiedge - "Regulatory RNAs in Neurons"

12:00 Jennifer Darnell - "FMRP-dependent Ribosome Stalling on Specific mRNAs and Implications for Therapeutic Development"

12:30 Boris Maček - "SILAC-based Proteomics Reveals Differentially Regulated Proteins in FMR1 KO Mouse and its Genetic Rescue Model"

12:50 David Nelson - "Fmr1 and the Fxr1 and Fxr2 Genes - How Much Compensation?"

1:10-2:30pm **Lunch - Dining Room**

2:30-4:00pm **Afternoon Plenary 1 - Prism Auditorium, Moderator: Mark Bear**

2:30 Kim Huber - "Disrupted mGluR5-Homer Interactions Contributes to mGluR5 Dysfunction in *Fmr1* KO Mice"

3:00 Hans-Jurgen Kreienkamp/Stefan Kindler - "Significance of an Altered Dendritic Synthesis of the Postsynpatic Scaffold Protein Shank1 for the Pathogenesis of the Fragile X Syndrome"

3:30 Yue Feng - "Functional Link Between FMRP and BDNF Signaling"

4:00-4:15pm **mini-Break**

4:15-5:15pm **Afternoon Plenary 2 - Prism Auditorium, Moderator: Mark Bear**

4:15 Frank Kooy - "*in vivo* Quantification of Cerebral $GABA_A$ Receptors in Fragile X Patients"

4:45 Cara Westmark - "The beta-Amyloid Theory of Fragile X Syndrome"

5:15-5:30pm **mini-Break**

5:30-6:30pm **Afternoon Breakout Sessions 5:30-6:30**

Session 1 - Prism Auditorium, Moderator: Julius Zhu

5:30 Laura Smith - "Fragile X Mental Retardation Protein (FMRP) is Required for Cocaine-induced Behavioral Plasticity"

5:50 Rebecca Vislay-Meltzer - "The Development of Defects in Inhibitory Neurotransmission in the Fragile X Amygdala"

6:10 Chae-Seok Lim - "Serotonergic and Dopaminergic Rescue of Synaptic Plasticity In FMR1 Knockout Mice"

Session 2 - Breakout Room 1, Moderator: Carlos Portea-Cailliau

5:30 Cheryl Gatto - "FMRP in Neuronal Survival: A Different Class of Pruning Defect"

5:50 Darrin Brager - "Impaired Dendritic Expression and Plasticity of I_h in the *fmr1-/-* Mouse Model of Fragile X Syndrome"

Session 3 - Breakout Room 2, Moderator: Frank Kooy

5:30 Andreea Simona Pop - "Behavioral and Dendritic Protrusion Phenotypes in Fragile X Mouse Model; Read-outs for Therapeutic Intervention"

5:50 Inge Heulens – "Craniofacial Imaging of Fragile X Mice Using Dense Surface And Signature Graph Analyses"

6:10 Irina Sinakevitch - "Apis Mellifera Fragile X Mental Retardation Gene (AmFMR1) in the Honey Bee Brain"

6:30-7:30pm **Poster Session, Cocktails - Conference Center Lobby**

7:30-9:00pm **Dinner - Dining Room**

9:00-11:00pm **Cocktails, Coffee, and Posters continue - Lounge Area**

Wednesday, September 21st

7:00-8:30am **Breakfast - Dining Room**

8:30-10:30am **Morning Plenary 1 - Prism Auditorium, Moderator, Gary Bassell**

8:30 Leonard Kaczmarek - "Interactions of FMRP with Potassium Channels"

9:00 Justin Fallon - "Presynaptic Fragile X Proteins in the Developing and Adult Brain"

9:30 Tom Jongens -"Mapping the Spatial Requirements of *dfmr1* Activity Identifies a Key Neuron Important for Several Relevant Phenotypes"

10:00 Carlos Portera-Cailliau - "Defects in Glutamate-induced Elongation of Early Dendritic Protrusions in Fmr1 Knockout Mice"

10:30-10:45am **Mini-Break**

10:45-12:30pm **Morning Plenary 2 - Prism Auditorium, Moderator, Eric Klann**

10:45 Patricia Cogram - "From Bedside to Bench and Back: Validation of Biomarkers in Animal Models and Patients Specific to FXS"

11:15 Sean McBride - "The cAMP Signaling Cascade in Fragile X Fly and Mouse Models, a New Avenue for Therapy"

11:45 Group Discussion - Reflection on New Ideas and Themes at this Meeting, Plans For Future Research, Scheduling the Next Meetings, etc.

12:30pm **Farewell Luncheon - Dining Room**

Monday Posters:

Margaret King	Lithium Ameliorates Behavioral and Physiological Phenotypes of Fragile X Syndrome in *Fmr 1* Knockout Mice
Ai-Hui Tang	The Endocannabinoid System in a Model Mouse of Fragile X Syndrome
Christopher Rex	Pharmacological Inhibition of p21-Actived Kinase Reverses Dendritic Spine Abnormalities in the Fmr1 Knock-out Mouse
Aubin Michalon	CTEP, a Novel, Potent, Long-Acting and Orally Bioavailable mGlu5 Inhibitor
Friso Postma	Disease Modifying Properties of STX209 (Arbaclofen) in a Mouse Model of Fragile X Syndrome
Tracy Stackhouse/ Lisa Cordeiro	Neuromotor Outcome Measures in Fragile X Syndrome Neuromotor Outcome Measures for Clinical Trials in FXS: Strategies and Supports for Success
Paulina Rychenkova	Fragile X and Phelan-McDermid Syndrome – Could Interacting Proteins Lead to Common Treatments?
Susan Goebel-Goody	STEP as a Novel Therapeutic Target in FXS
Wangfa Zhao	FMRP Modulation in Glutamate-Induced Epileptogenesis
Wei Feng	Functional Interplay Between FMRP and BDNF-TrkB Signaling
Odelia Y.N. Bongmba	Implications for the Involvement of Small GTP-binding Proteins in Spine Formation and Synaptic Function

Tuesday Posters:

Joshua Suhl	Disruption of a Cis-Acting microRNA Site in FMR1 Results in Reduced Translation of an FMRP Reporter
Celine deEsch	Involvement of the miRNA Pathway on Synaptic Structure in Fragile X Syndrome
Anna Francesconi	Regulation of Group I mGluR Signaling by Membrane Cholesterol
Tong Zang	Developmental Switch of Postsynaptic FMRP Regulation of Synaptic Function: Interactions with MEF2
Kirsty Sawicka	PIKE as a Central Regulator of Synaptic Dysfunction in Fragile X Syndrome
Aditi Bhattacharya	Targeting p70-S6 Kinase 1 to Reverse Phenotypes in Fragile X Syndrome Model Mice
Shih-Chieh Chuang	Role of Protein Tyrosine Phosphatase in the mGluR-Mediated Epileptogenesis
Lori Dansie/Ethell	MMP-9 Dysregulation in Fragile X and its Effects on Dendritic Spine Development in the *Fmr1* KO neurons
Michael Akins	Distinct Composition and Circuit-Selectivity of Four Classes of Fragile X Granules
Scott Soderling	Role of Signaling to the Actin Cytoskeleton in Fragile X Syndrome
Carlos Maureira	*In Vitro* Coherent Network Activity – a New Electrophysiological Model for Drug Testing in the Mouse Model of Fragile X Syndrome (FXS)

Back to FRAXA.org