



PATRICK'S PALS WITH NFL STAR BEN WATSON. SEE PAGE XXXXXX

“NEVER doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it’s the only thing that ever

— Margaret Mead

Fragile X Treatments: From Labs to Trials

FRAGILE X CLINICAL TRIALS OF NEW TREATMENT NOW IN PROGRESS

THE NATION’S TOP scientists recently stated that “genetics and neuroscience finally have the tools to transform the diagnosis and treatment of mental illness” (Tom Insel, article). Fragile X is leading the way for *rational drug discovery*, the deliberate and thoughtful process from discovering cause, mechanism, treatment targets, and finally, developing drugs to reverse disease.

A small group of parents formed FRAXA Research Foundation to accelerate progress along this long road. This approach, which looks so promising for Fragile X, will work for other diseases as well.

We had no idea how long a road it would be, and yet - built on this idea 16 years ago, As Dr. Insel writes, “But first, it is time to re-think mental disorders, recognizing that these are disorders of brain circuits.”

Imagine that you are a parent and it suddenly becomes clear to you that your mentally disabled and autistic son has a simple protein deficiency? This is both liberating (there’s no reason to be ashamed of disability if it’s merely a missing protein!) and frustrating (why has no one provided that protein?). In Fragile X, there is simply a protein missing. It is a simple problem with, hopefully, a straightforward fix.

This annual report summarizes FRAXA’s research grant and fellowship programs during 2010, research meetings, education and outreach activities, and fundraising. It has been a challenging year because of the economy but also a very exciting year with scientific advances and new treatment trials moving forward. It has been a year of great progress toward effective treatments and ultimately a cure for Fragile X!



2010 FINANCIAL REPORT



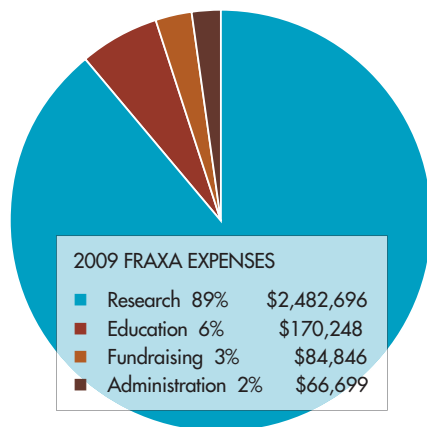
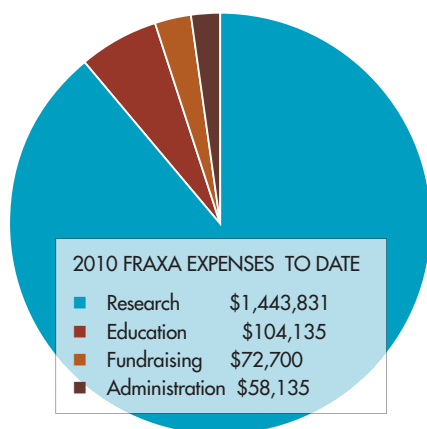
Imagine a cure for autism and intellectual disabilities. In 1994, a group of parents of children with Fragile X — the most common inherited cause of intellectual disabilities and autism – dared to dream that big. *This is the mission of FRAXA Research Foundation.*

IN JUST 17 YEARS, FRAXA-FUNDED teams have moved from understanding the cause of Fragile X to reversing signs of Fragile X in animal models. Thanks to magnificent work by 110+ research teams around the world, we are poised to bring newly-discovered drugs into human clinical trials. To help those already afflicted with Fragile X, time is of the essence.

FRAXA leverages every dollar spent in a number of ways. First, we fund research that government agencies might consider too risky, but which often leads to bigger government grants. These grants can be ten times the size of FRAXA grants, and that's a lot of leverage!

Second, FRAXA cannot afford to fund drug development. Developing a single drug costs many millions of dollars. Instead, we fund critical "proof of principle" studies in Fragile X models (like knockout mice and mutant fruit flies.) These studies are powerful inducements to pharmaceutical companies to consider developing their compounds for Fragile X — an indication that they might otherwise consider too rare and risky. FRAXA will continue to seek opportunities to "de-risk" drug development through philanthropic-pharmaceutical partnerships.

Third, when time is critical, what better approach is there than to quickly test thousands of compounds to see if they might reverse signs of Fragile X? FRAXA is now funding several high-throughput drug screens to identify available compounds which demonstrate therapeutic effects in Fragile X model systems. We are leveraging our past research



(which enabled development of these systems) against the vast resources of the pharmaceutical industry, which has already developed many thousands of drugs, some still seeking a purpose.

In the current worldwide financial crisis, charities are being hit hard. FRAXA's overhead costs are low, so we are well positioned to weather the storm.

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CURRENT DEVELOPMENTS

From Basic Research to Treatment Trials

NEW YORK TIMES FRONT PAGE NEWS

FRAGILE X RESEARCH HIT THE FRONT page of the NY Times this spring thanks to a surprising and exciting announcement by pharmaceutical company Novartis.

They reported positive results in a small clinical trial of a new experimental treatment for Fragile X.

There has been a race between pharmaceutical companies to be the first to develop a treatment for Fragile X based on mGluR5 antagonists. Giants Novartis and Roche are currently in the lead, with smaller companies like Seaside Therapeutics close behind.

The race began when scientists Mark Bear, Steve Warren, and Kim Huber discovered that signs of Fragile X could be reversed in mice using compounds that block mGluR5.

Read the New York Times article at www.nytimes.com/2010/04/30/health/research/30fragile.html or go to fraxa.org and find the link under “What’s New?”



KATIE CLAPP AND SON ANDY
TRANFAGLIA (21)

❖ Afraxis

Founded: 2007

When Jay Lichter read in the July 2007 journal of the National Academy of Science about a Nobel laureate’s theory for reversing an inherited form of mental impairment, the local venture capitalist had an “aha moment.” That “aha” resulted in Afraxis, a tiny San Diego biotech that is developing a drug for treating Fragile X syndrome. Nobel Prize winner Susumu Tonegawa, a professor of neuroscience at MIT, first proposed the idea of developing drugs for the syndrome after his lab reversed symptoms of the disorder in mice. Tonegawa found that by inhibiting an enzyme called PAK, the symptoms of Fragile X reversed dramatically, both at the cellular and behavioral levels.

Lichter, managing director at San Diego’s Avalon Ventures, contacted Tonegawa and put together a licensing deal that involved MIT and another firm that could screen potential drug compounds against the gene target. Now Afraxis has an experimental drug that appears to have a “profound effect” in reversing the damage caused by Fragile X and schizophrenia — at least in mice, said Lichter. And while it’s a long way from mice to men — the company hopes to begin testing the drug in humans in 2012 — the early-stage work shows tremendous potential, said Lichter, who also serves as CEO for Afraxis.

CLINICAL TRIALS IN PROGRESS

Trials of new treatments and interventions are currently underway in individuals with Fragile X, at sites across the U.S. and beyond:

ARBACLOFEN — MULTI-CENTER TRIAL

This study aims to evaluate if an investigational medication, Arbaclofen, can manage the irritability associated with Fragile X. Sponsored by Seaside Therapeutics, this Phase II trial was completed in 2010 and showed encouraging results which have now been published.

BRAIN IMAGING STUDY — NIH, BETHESDA, MARYLAND

The National Institutes of Health is seeking men (18-24 years) with fragile X syndrome for a study to determine how well they can accept lying down in a scanner. This study has minimal risk, requires one outpatient visit lasting about 4 hours, and participants will be compensated.

ARIPIRAZOLE (ABILIFY) — INDIANA UNIVERSITY

This trial is testing aripiprazole (Abilify) in the treatment of Fragile X. The investigators, Dr. Christopher McDougale and Dr. Craig Erickson, believe that aripiprazole will decrease aggression, self-injurious behavior, agitation, and repetitive behavior commonly observed in individuals with Fragile X. Ages 6 to 35 are eligible.

FRAXA RESEARCH GRANTS 2010

Working toward a cure

This year, more than 50 university teams have applied to FRAXA seeking a total of \$7 million — an impressive measure of the growing level of interest in Fragile X research. Despite the economic downturn, FRAXA was able to fund a fair number of high-quality projects, thus bringing more outstanding researchers into the field. We expect to fund nearly \$2 million in direct research grants in 2009, and the work being done now is more impressive than ever.



LEFT: TED PRICE
(UNIV. OF ARIZONA)
BELOW: BECKY ZOROVIC
(FRAXA), RANDI HAGER-
MAN (MIND INSTITUTE)



FRAXA 2010 Investigators Banbury Meeting

Novartis Roche - how they got hooked
NY Times, Bloomberg, NPR
Doris Buffett
Afraxis, Seaside
Repurposing Existing Drugs
FRAXA 2010 Grants and 2009 Results
This year's theme was *New D tics*. 128
registered participants

86% of labs receiving a new grant are coming (13 out of 15 labs)

79% of individuals on a '09 grant (66 yes, 18 no) are coming

Pharma Representatives from Pfizer, Roche, Novartis, Lundbeck, Afraxis, Seaside Therapeutics, and Glaxo Smith Kline

Sponsorships:

Leslie and Michael Cheverie \$20,000

Becky and Sasa Zorovic \$20,000

Afraxis \$5000

Seaside \$5000

Roche \$5000

Awards to Roche, Seaside, Novartis
• two days after the NYT article which set the stage for focus on bringing medicines to our medicine cabinets.

The signaling pathways through which brain cells communicate are now better understood. Each step in pathways involving FMRP may be a therapeutic target.

- Randi and Liz discussed arbaclofen results.
- Carlo Paribello discussed minocycline results.

Most gratifying of all were the informal discussions between researchers who were trading advice, brainstorming new ideas, and designing their next experiments. discussions may have saved scientists months (or even years) of wasted time using the wrong mouse strain or a sub-optimal technique. Fragile X scientists, while extremely competitive, share information and collaborate with a spirit of common purpose.



FROM LEFT TO RIGHT:
KIMBERLY HUBER,
PETER VANDERKLUSH,
JOEL RICHTER, MARK
BEAR, PETER KIND

FRAXA 2010 PIONEER AWARDS

FRAXA is run by parents, but we do not operate alone. Our Scientific Advisory Board, which includes 3 Nobel laureates, has evolved with our research portfolio and we have been fortunate to gain the expertise of key members of the pharmaceutical and biotechnology industries. Please join us in congratulating the winners of FRAXA 2010 Pioneer Awards:

Will Spooren, PhD
ROCHE

Mike Snape, PhD
CHIEF SCIENTIFIC OFFICER

Neuropharm Group, PLC
London, UK
Dr. Snape is a founder of Neuropharm and, with his wife Rose, is a parent of a young person with autism. He has over twenty years of experience in pharmaceutical development and is named as an inventor on five pharmaceutical patents.

Dr. Snape began working with FRAXA in 2006, after discovering FRAXA's studies on the internet and concluding, on the basis of those studies, that developing a Fragile X treatment would fit well into Neuropharm's programs. The result is the recently completed trial of fenobam in adults with Fragile X.

Fabrizio Gasparini, PhD
NOVARTIS

Graeme Bilbe, PhD
**GLOBAL HEAD FOR THE
NEUROSCIENCE DISEASE AREA**

Novartis Institutes
for BioMedical Research
Basel, Switzerland.
Dr. Bilbe began his career at Ciba-Geigy in 1989 and now directs research into neurodegenerative and psychiatric diseases at Novartis.

When asked why he chose to work in industry, Dr. Bilbe said, "The idea of converting pure science in a directed way, bringing scientific results to the patients, caught my interest."

After attending FRAXA's 2004 Banbury meeting, Dr. Bilbe launched Novartis' Fragile X research program – an effort so successful that an investigational new drug (the mGluR5 antagonist AFQ056), is now being tested in Fragile X patients in France, Italy, and Switzerland. Dr. Bilbe was back at Banbury this year.

BELOW: DR. MIKE SNAPE
BOTTOM: DR. GRAEME BILBE





FUNDRAISING

DORIS BUFFETT'S CHALLENGE MET!

Patrick's Pals Basketball Tournament

*Cambridge, MA
Saturday, May 30*

On Saturday, May 30, the Buckingham, Brown & Nichols gym will be the scene of Patrick's Pals XIII. Started by 5 loyal childhood friends of James Vershbow, whose son Patrick has Fragile X, the event brings pros and Joes together in a double elimination tournament. Recent Patrick's Pals participants include Bob Lobe, Steve Burton, and Ben Watson. Join us to see who appears this year! Contact James Vershbow at pjversh@comcast.net or 617-599-2641.



Mt. Rainier's Strongest Man & Woman 4

*Sumner, WA
Saturday, August 1*

Laurie Bowler of Rainier Crossfit reports that this year's Mt. Rainier's Strongest Man and Woman 4 will be back at The Old Cannery in Sumner. Last year we had 31 competitors from 4 states and we raised \$13,000, bringing our grand total donation to FRAXA to just over \$25,000. The contest now has its own website where people can go for information and updates: www.mtrainersstrongest.com.

2nd Annual Robert Langell Golf Tournament

*Turner Hill, Ipswich, MA
Monday, September 28*

Golf and dinner at the gorgeous Turner Hill mansion. Contact Didi Langell at langelldidi@hotmail.com.

Boston Gala

*Seaport Hotel,
Thursday October 8*

Join families, friends, researchers and supporters at Boston's Seaport Hotel as we honor Doris Buffett, whose 2007 challenge grant to

FRAXA energized volunteers across the country. Celebrate with Ms. Buffett and other distinguished guests Dr. Mark Bear, authors Mary Higgins Clark and Mary Jane Clark, The Sopranos actor Dan Grimaldi, The Weather Channel storm tracker Jim Cantore, Boston trial attorney Harry Manion, and Boston news reporter Kelley Tuthill on October 8th in Boston. Sponsorships and tables now available. Hosted by Liz and Jason Mazzola, and Leslie and Michael Cheverie. Contact Katie Clapp at kclapp@fraxa.org.



7th Annual Fall X Ball

*Poughkeepsie, NY
Friday, October 9*

The annual gala will be held at the Dutchess Golf and Country Club. For info, please email Ron and Amy Watkins at rwatkins@fraxa.org or call Ron at 845-797-0846. Last year's gala raised over \$70,000.



Walk for Fragile X

*Bernville, PA
Saturday, June 20*

Held at the Tulpehocken Jr/Sr High School Track, 428 New Schaefferstown Rd, Bernville, PA. Contact Jennifer Mathias at 610-488-1612, 717-813-1289 or LukeJen97@aol.com.

2nd Motorcycle Run to Cure Fragile X

*New Castle, Delaware
Sunday, July 26*

A bike run starting at Mike's Harley-Davidson in New Castle, followed by BBQ, live band and silent auction. Activities for kids, childcare, and fun and prizes for grownups too! Live band and silent auction. Organized by Jen Nardo, contact her at jlcardo1@verizon.net.

FRAXA HOLIDAY CARDS



Calendar at fraxa.org
— check often!



How can you help most? Please consider an automatic monthly donation online at fraxa.org. It is easy for you, incurs no fees, and can be ended anytime. For FRAXA, knowing that funds will come in every month means we can commit to supporting new research grants, from start to finish (typically 2 years). You can also help by attending an event (see page 10) or hosting your own.

Please donate now at fraxa.org or using the enclosed envelope. Thank you!



invaluable.

Golf Tournament *Litchfield, NH*

Dawn, Pete, and Dave Hall and their friends outdid themselves at the 3rd Annual FRAXA Charity Golf Tournament at the Passaconaway Country Club. Over \$18,000 was raised **XBall**

Poughkeepsie, NY

In addition to Cocktails and Dinner, Music by The Michael Dell Orchestra, Silent and Live Auctions, the annual ball included honored guest, Mary Higgins Clark, guest speaker, Dan Grimaldi – Actor (Patsy Parisi from the Sopranos), and a research update by Dr. Eric Klann - NYU over \$70,000 was raised



Night at the Jackals & Elks Benefit *Rutherford, NJ*

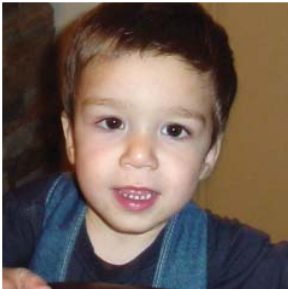
Denise Sabo and her friends stepped up to the plate again with their annual events: Fragile X Benefit at the Elks Lodge (Denise Sabo also sponsored Night at the Jackals Game in 2009)



ANNUAL REPORT 2010

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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 volun-



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