Disclosures: EBK has received funding from Seaside Therapeutics, Novartis and Roche Pharmaceuticals to consult on trial design and conduct clinical trials in FXS, and from Asuragen, Inc to develop testing standards for diagnosis of FXS
Fragile X-Associated Disorders (FXD)

- CGG expansion mutations in *FMR1*
- Full mutation (>200 repeats)
  - fragile X syndrome (FXS)
  - 1:4000 males and females
- Premutation carriers (55-200 repeats)
  - fragile X-associated tremor/ataxia syndrome (FXTAS)
  - fragile X-associated primary ovarian insufficiency (FXPOI)
  - USA 1:151-1:209 females, ~25% risk FXPOI, ~10% risk FXTAS
  - USA 1:430-1:468 males, ~50% risk FXTAS
- All ethnic groups worldwide
- Affect families in multiple generations
- FXS is
  - MOST COMMON KNOWN GENETIC CAUSE OF AUTISM
  - MOST COMMON KNOWN INHERITED FORM OF COGNITIVE DISABILITY

*Tassone et al. 2012, Seltzer et al. 2012*
FXPOI
Fragile X-Associated Primary Ovarian Insufficiency

• 15-22% of female premutation carriers have early menopause
• 0.8-7.5% women with POF have premutation, 13% if FHx POF
• Now called POI because many have ovarian dysfunction early but don’t fully stop menses by 40 years
• Premutation carriers have increased FSH
• Carrier females enter menopause average of 5 years earlier than non-carrier family members
• Early menopause highest at 80-100 repeats (8X), lower with less or more (2-4X)
FXTAS
Fragile X-Associated Tremor/Ataxia Syndrome

- Multidimensional tremor
- Ataxia
- Parkinsonian symptoms
- Neuropathy
- Executive function problems and cognitive deterioration (frontal subcortical dementia)
- Characteristic MRI with white matter changes and MCP sign
- Neuronal inclusions

MCP sign
Abnormal white matter signal
Gray and white matter atrophy
FXTAS, FXS and FXPOI Affect Multiple Generations in a Family

**FXTAS**
- Progressive ataxia
- Dementia
- Full time care

**Premutation Carrier**
- Full time caregiver
- Stress/Anxiety
- Risk of FXPOI, FXTAS

**FXS**
- Anxiety, Hyperactivity
- Autistic behavior
- Poor verbal skills
- Full time care
Stability and rate of expansion in alleles depends on AGG interspersions in CGG sequence

Most commonly 2 AGGs roughly every 10 triplets (can be 0-4) and spacing varies

Common FMR1 alleles include an AGG at repeat 9 or 10 (1\textsuperscript{st} interruption) and 19 or 20 (2\textsuperscript{nd} interruption when present)

Alleles with expansions tend to have less AGGs (mostly 0-1)
New Technology Shows AGGs Mediate Risk of Expansion

Grey Zone and Small Premutation – chance of changing size based on CGG length and AGGs
57 repeat allele – 0 AGG 96%, 1 AGG 50%, 2 AGGs 5%

Mid-Size Premutation – chance of going to full mutation based on CGG length and AGGs
75 repeat allele – 0 AGG 75%, 1 AGG 50%, 2 AGG 12%

Nolin et al. 2013

Yrigollen et al. 2012
Features of Fragile X Syndrome

- **Physical**: large prominent ears, long face, large head, prominent jaw & forehead, midfacial hypoplasia; hyperflexible joints, large testis
- **Intellectual Disability or LD**
- **Motor Coordination/Praxis Problems**
- **Behavior problems**: hyperactivity, distractibility, anxiety, perseveration
- **Autism**: 18-36% AD, 43-67% ASD
- **Seizures** – 15%
- **Strabismus** – 30%
- **Medical**: otitis; sinus; MVP; reflux; sleep apnea, loose stools, allergies
Seizures in Fragile X Syndrome: Rush/RTI Study of Co-Occurring Conditions/Symptoms

Seizure cohort vs. matched no seizure cohort: autism co-occurs with seizures, likely shared neurobiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Seizures (%)</th>
<th>No Seizures (%)</th>
<th>N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention Problems</td>
<td>88.1</td>
<td>82.1</td>
<td>134</td>
<td>0.18</td>
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<tr>
<td>Hyperactivity</td>
<td>62.9</td>
<td>68.2</td>
<td>132</td>
<td>0.39</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>48.9</td>
<td>34.6</td>
<td>133</td>
<td>0.015</td>
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<tr>
<td>Self-Injury</td>
<td>52.2</td>
<td>43.3</td>
<td>134</td>
<td>0.16</td>
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<tr>
<td>Autism</td>
<td>63.6</td>
<td>41.1</td>
<td>129</td>
<td>0.0002</td>
</tr>
<tr>
<td>Anxiety</td>
<td>75.2</td>
<td>57.9</td>
<td>133</td>
<td>0.0038</td>
</tr>
<tr>
<td>Depression</td>
<td>12.6</td>
<td>8.7</td>
<td>127</td>
<td>0.30</td>
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<tr>
<td>Developmental Delay</td>
<td>98.5</td>
<td>95.6</td>
<td>135</td>
<td>0.16</td>
</tr>
<tr>
<td>Poor Verbal Ability</td>
<td>30.6</td>
<td>18.2</td>
<td>121</td>
<td>0.019</td>
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<tr>
<td>Poor Reading Ability</td>
<td>64.5</td>
<td>66.9</td>
<td>124</td>
<td>0.70</td>
</tr>
<tr>
<td>Fair-Poor Thinking</td>
<td>89.5</td>
<td>87.3</td>
<td>134</td>
<td>0.59</td>
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<tr>
<td>Fair-Poor Quality of Life</td>
<td>13.2</td>
<td>13.9</td>
<td>136</td>
<td>0.85</td>
</tr>
<tr>
<td>Fair-Poor Overall Health</td>
<td>14.1</td>
<td>6.7</td>
<td>135</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Children with Fragile X Syndrome Present Most Often with Developmental Problems

- Motor delays in some
  - Hypotonia – truncal and orofacial when young
  - Fine motor problems - poor writing ability
  - Gross motor clumsiness

- Speech/language delays is most common reason to present for evaluation and diagnosis

- Also can present with
  - Delayed play skills/autistic features
  - Behavioral issues
  - Learning problems after starting school

Symptoms should prompt FMR1 DNA testing on blood
FXS Developmental Problems

• Most FXS patients can be identified with delay on developmental screens by 9-18 months
• Average age of diagnosis still between 3-4 years – no change in past 10 years (Bailey)
• Miss early intervention
• New NFXF/FXCRC goal: diagnosis before age 2 – working on Pediatricians
Testing Guidelines for FXS

Clinician should test for *FMR1* mutation if the patient has any of the following:

- ID/DD of unknown etiology
- Autism or Autism Spectrum Disorder of unknown etiology (including PDD-NOS or Aspergers)

Clinician should test for FMR1 mutation if the patient has any of the following AND additional cognitive or physical features of FXS OR family history of FXS or FXTAS:

- Learning Disability, especially Nonverbal Learning Disabilities or math disability
- Behavioral issues, including poor eye contact, anxiety, attention problems, hyperactivity
- Seizures

from Berry-Kravis et al. 2007
Intellectual Disability in FXS

- Males - average adult IQ about 40 and mental age 5-6y, range severe ID to normal (mosaics)
- IQ scores higher when young, decline with age
- Specific cognitive profile
- Achievement and Adaptive skills higher
Fragile X Syndrome
Characteristic cognitive pattern with prominent executive function deficits

• Strengths
  – Receptive vocabulary
  – Syntax
  – Imitation
  – Grammatical structure
  – Visual memory
  – Simultaneous processing
  – Experiential learning

• Weaknesses
  – Auditory processing
  – Sequencing
  – Abstraction
  – Short-term memory
  – Topic maintenance/
    "connectedness"
  – Mathematics
  – Working memory
  – Coordination/praxis
FXS - Pattern of Speech/Language Deficits

- **Most abnormal**
  - Jargon/tangential language
  - “Jocular litanic phraseology”
  - Perseverative speech
  - Lack of gesture use
  - Talking to self
  - Cluttering

- **Less abnormal**
  - Fluency
  - Prosody

- **Strengths**
  - Grammar
  - Vocabulary

Receptive > expressive, different from autism
Language Characteristics in FXS Relative to Normal Mental-Age Matched Controls and Developmentally Delayed Subjects

• Decreased intelligibility
  – Vowels sounds more variable than normal developmentally matched controls
  – Poor oromotor control
  – Faster rate of speech
• Decreased length of utterances
• Increased self-repetitious and perseverative language
• Single word vocabulary a strength
FXS Social Deficits and Autistic Behaviors

- Good understanding of facial expression – different from typical autism – high level of empathy
- Deficits in peer entry, interpreting social cues, using non-verbal and body language cues – correlate with anxiety and attention problems
- Distinct but overlapping language patterns/social style
- FXS with autism more similar to IA than FXS without autism – maybe second hit/modifier
- Subgroups of autism ?similar to FXS – ?molecular overlap/treatment relevance

Friendly but social anxiety
Eye Gaze in FXS and Autism

- Decreased eye gaze to face, decreased activation of fusiform gyrus with face gaze in ASD (less in FXS but correlates with ASD in FXS)

- Activation of multiple brain regions on fMRI when looking at faces in FXS not ASD (suggest overstimulation rather than avoidance)

*Dalton et al. 2008*

*Farzin et al. JADD 2011*
FXS and Autism Comparisons – about 2/3 FXS males, ¼ females meet ASD criteria, 2-3% of ASD has FXS

**Similarities**
- Seizures (different peak age of onset)
- Macrocephaly
- Increased sympathetic responses, decreased vagal tone
- Sensorimotor gating problems – heightened sensitivity to sensory input
- Social and emotion processing problems
- Difficult/maladaptive behaviors similar

**Differences**
- Coordination worse in FXS
- Expressive language worse, receptive language better in FXS (*Roberts*)
- More perseverative language in FXS, more echolalia in autism
- Social anxiety in FXS, social indifference in autism
- Caudate bigger, amygdala smaller in FXS (*Reiss*)
- Medial prefrontal and anterior cingulate smaller in autism (*Meguid et al. 2010*)
Behavior Problems in FXS

- Hyperactivity/fidgety (90%)
- Short attention span (~100%)
- Anxiety (~100%)
- Tactile defensiveness (80%)
- Eye (gaze) aversion (>90%)
- Perseverative speech/thinking (>80%)
- Hand flapping (60%)
- Hand biting (50%)-self regulatory
- Mood swings
- Outbursts/aggression

Behavior in FXS out-of-proportion to cognitive level

THE BIGGEST PROBLEM FOR MANY FAMILIES

Psychologist after testing FXS child
Family members may sustain frequent injury from child
Behavior Variation with Age

• Hypoactive before 2 years of age – under-responsive – babies that are “too good” – may seem normal
• Big increase in hyperactivity and clear attention deficits in preschoolers between age 2 and 6
• Elementary years of childhood ADHD symptoms predominate although anxiety and irritability are also common
• Anxiety/social avoidance and aggression/irritability/oppositional behavior increase during adolescence and are more problematic than ADHD symptoms
• Hyperactivity decreases and aggression/irritability gets somewhat better but anxiety/social avoidance tend to worsen throughout adulthood
• Perseverative and fixated behaviors are present throughout and may worsen in adulthood
FXS – Affected Females

- More mildly involved
- Average IQ 80
- NVLD, VIQ > PIQ, poor math, very impaired executive function, distractibility
- Same cognitive pattern as males
- Physical features/medical problems variably present
- Social/psychiatric disability common – anxiety/shyness, oddness
- Decreased education, job stability, socioeconomic status
Mosiacs - Mildly Affected FXS Males

- IQ > 70
- Mosaic = Partially or fully unmethylated mutation
- Methylation mosaic - Grey zone (170-250 repeats, may have partial methylation) or unmethylated full mutation
- Size mosaic – premutation and full mutation
- Long repeats - decreased translation even if unmethylated
- Cognitive abilities similar to females
- Variable physical features

Patient with learning disability, Brother has MR

Unmethylated full mutation
FXS Treatment in Clinic - Supportive

- Early intervention
- Intensive speech therapy
- OT with sensory integration
- Inclusion in school as much as possible
- Educational curriculum, environment, teaching style matched to FXS cognitive profile
- Socialization program
- Behavior plan
- Behavior medications for ADD/anxiety

- Aggressive tx of otitis – tubes/audiology
- Manage sleep apnea and other sleep problems
- Yearly eye exams
- Control seizures
- Orthopedics if needed
- Monitor for MVP/heart
- Genetic counseling
- Discuss reproductive options (CVS, amnioscentesis, egg donation, PGD, adoption)

Rush FXS Clinic since 1992 > 550 patients
Supportive Treatment is Helpful in FXS...

Rush Fragile X Clinic

- **Attention Hyperactivity**
  - Stimulants: 208
  - SSRIs: 231
  - Antipsychotics: 100
  - α-agonists: 52

- **Anxiety Mood**
  - Stimulants: 136
  - SSRIs: 123
  - Antipsychotics: 58

- **Aggression Irritability**
  - Stimulants: 123
  - SSRIs: 58

- **Hyperarousal Oversensitivity**
  - Stimulants: 52

---

Berry-Kravis et al, 2012, Int J Peds

...clearly unmet need for better behavioral treatments and for cognitive treatments

SO treating the underlying disorder would be better...

Family perceived efficacy of medication in FXS based on National Survey

Bailey et al. 2012, JDBP
FMRP Expression is Related to Disability

FMRP is important: what does it do?

- Social anxiety/shyness
- Distractibility/hyperactivity
- Executive deficits
- Spatial perceptual deficits
- NVLD
- Intellectual Disability
The Fragile X Mouse (Knockout; K/O)

- *Fmr1* gene inactivated
- No active FMRP
- Subtle cognitive problems
- Audiogenic seizures
- Good neurobiological model to answer question: WHAT DOES FMRP DO?
FMRP Regulates Synaptic Plasticity and Morphological Maturation of Dendritic Spines

FMRP is an RNA binding protein that regulates dendritic protein translation in response to synaptic activation—needs to be regulated precisely for synaptic maturation.

FMRP in protein complex at ribosome

Both FXS Mouse and Human Brain: Dendritic spines abnormal in FXS: immature long spines

McKinney et al, AJMG, 2005
FMRP Regulates Synaptic Plasticity and Strength of Dendritic Connections (Fmr1 K/O mouse)

- Exaggerated mGluR-dependent LTD
- AMPA receptors internalized
- Reduced LTP
- Weaker more immature synapses
- Findings vary from one brain region/neuron to another depending on forms of plasticity and receptors expressed
Regulation of protein synthesis needed to strengthen connection, mature spine shape.
Abnormal mGluR-activated dendritic protein synthesis and synaptic plasticity in FXS

mGluR Theory of Fragile X

Huber et al. PNAS 2002
NIH Study Shows Increased Rates of Cerebral Protein Synthesis in Fragile X Knockout Mice

Protein synthesis dysregulated, connections can’t maintain mature state

FXS Learning

2 + 3 = 5
mGluR Translational Signaling Mechanism Provides Many Targets for FXS Treatment

Treatments aimed at many of these targets reverse phenotypes in the \textit{fmr1} K/O mouse
Potential Mechanisms for New Treatments for FXS

Fragile X Immature connection (too weak)

Dendrite

1A
STX 107
RO4917523
AFQ056
Fenobam
MPEP

1B
PI3K blockers, PAK inhibitors
Lithium
ERK inhibitors/statins

2
Minocycline
cAMP activators
STEP inhibitors
APP inhibitors

3
CX516

4
Other systems
STX209/
Arbaclofen (GABA-B)
Ganaxolone (GABA-A)
Acamprosate (GABA)
mGluR2/3 agonists
Donepezil

5
miRNA
Mechanism 1B: Block Excessive mGluR-Activated Pathway Signaling (Inside Cell)

- **Lithium** – blocks PI and GSK3β in signaling pathway
  - Mouse/fly – behavior/spine phenotypes reversed
  - open label proof-of-concept 2 month trial, 15 patients
  - behavior, CGI, adaptive, ERK biomarker, cognitive task better

Average Scores on ABC-C Subtests for Subjects with FXS During treatment with Lithium, n=11

ABC – behavior, p=0.005

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Baseline</th>
<th>2 Month</th>
<th>1 Year</th>
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<tbody>
<tr>
<td>Irritability</td>
<td>8.4</td>
<td>8.6</td>
<td>8.4</td>
</tr>
<tr>
<td>SD Lethargy</td>
<td>6.6</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>SD Stereotypy</td>
<td>4.5</td>
<td>7.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>6.7</td>
<td>6.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Inappropriate Speech</td>
<td>2.7</td>
<td>4.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Total SD</td>
<td>21.6</td>
<td>34.7</td>
<td>38.4</td>
</tr>
</tbody>
</table>

Average ABC-C score

**ERK activation, p=0.007**

**RBANS – verbal memory, p=0.03**

Berry-Kravis et al, JDBP 2008
Mechanism 1A: mGluR5 Blockers (Outside Cell)
MPEP, fenobam, AFQ056, RO4917523, CTEP

Mouse Phenotypes Reversed
- Audiogenic seizures
- Epileptiform bursts
- Dendritic spine shape
- AMPA receptor internalization
- Excessive LTD
- Excess protein synthesis
- Behavioral phenotypes

Chuang et al. J Neurosci 2005
MPEP

Yan et al. Neuropharmacology 2005
MPEP

Michalon et al Neuron 2012

Fig 2. Effects of MPEP on total dendritic spines in FNMRP-/- mice (Chuang et al. unpublished).
(1) mGluR5 antagonists MPEP did not alter the properties of dendritic spines recorded in wild type preparations (Fig A).
(2) Total dendritic spines in FNMRP-/- preparations after 48 hours of spine loss were suppressed by MPEP.
(3) One out of 15 preparations (not shown).

11/26/2013
Trials of mGluR5 Blockers in FXS: Fenobam

RUSH and UC Davis (Neuropharm and FRAXA)
Phase I safety trial of 1 dose (50-150 mg)
12 adult FXS (6M, 6F), age 18-38, IQ 36-85

- PPI improved 20% in 6/12 subjects (control test-retest group 2/13, p=0.03)
- Positive behavioral changes in 9/12 subjects
- No fenobam-related AEs
- Erratic PK

Berny-Kravis et al. JMG 2009
Trials of mGluR5 Blockers in FXS: AFQ056 - First Phase II Multiple-Dose Trial (Novartis)

AFQ056 significantly improved ABC-C, CGI-I, CGI efficacy index, RBS-R, SRS, VAS scores for patients with complete methylation at FMR1 promoter.

These results prompted larger, ongoing trials

AFQ056
- Phase IIb placebo-controlled (age 12–45)\(^3,4\)
- PK age 3-11
- Ongoing extension study looking at long-term effects

RO4917523
- Phase IIb placebo-controlled (age 14–50)\(^5\)
- Phase IIa trial (age 5–13)
Mechanism 2: Decrease Activity of Overactive Protein - Minocycline and MMP9

- Minocycline is Matrix Metalloprotein-9 (MMP9) blocker, MMP9 key synaptic protein regulated by FMRP
- Rescue spine shape, open field hyperactivity, ultrasonic vocalizations in FXS mouse, neuronal morphology in mushroom body of FXS fly
- Placebo-controlled crossover trial at MIND: 3 months treatment each arm – 66 subjects, 48 completed

Safety – ANA elevations, some GI effects, monitored for pseudotumor – no issues

CGI shows benefit for minocycline: Minocycline = 2.49 ±0.13, Placebo = 2.97 ±0.13, p= 0.0173

MMP9 biomarker lowered post-treatment with drug but not placebo

11/26/2013
Mechanism 4: GABA Receptor Activating Agents

- GABA systems abnormal in FXS models
- GABA agonists rescue glutamate-induced lethality in FXS fly
- GABA-B activator arbaclofen reverses protein synthesis, AMPA internalization, spine density, audiogenic seizures, behavior phenotypes in mouse
- GABA-A activator ganaxolone reverses audiogenic seizures in mouse
- Prompts trials of ganaxolone (phase 2 in progress), acamprosate, and arbaclofen
Acamprosate

- Activates GABA-A and GABA-B receptors, maybe NMDA
- Open label trial in 6 adults: improved ABC – Social Withdrawal, CGI
- Open label trial in 12 children age 5-17: improved ABC – Social Withdrawal, ABC – Hyperactivity, SRS, ADHD-RS
- Abnormal elevated sAPP levels in FXS blood improved (APP regulated by FMRP) – potential biomarker

*\( p=0.01 \), **\( p=0.003 \)

Phase 2 placebo-controlled trial underway
Erickson and Berry-Kravis

Erickson et al. 2011
Arbaclofen (STX209): Decrease Excessive Glutamate Transmission

GABA-B agonist
More potent isoform of racemic baclofen
# STX209 (Arbaclofen)

- Phase 2 placebo-controlled crossover trial: 4 weeks of treatment each arm – 63 subjects (Seaside – 12 sites)
- Good safety/side effect profile

<table>
<thead>
<tr>
<th>Per Protocol Population (N=52)</th>
<th>STX209 (mean ± SD)</th>
<th>Placebo (mean ± SD)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>ABC-Irritability</td>
<td>-4.2 ± 6.47</td>
<td>-4.5 ± 6.58</td>
<td>ns</td>
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<tr>
<td>CGI-I</td>
<td>3.3 ± 0.93</td>
<td>3.5 ± 0.94</td>
<td>0.181</td>
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<tr>
<td>CGI-S</td>
<td>-0.6 ± 0.86</td>
<td>-0.3 ± 0.87</td>
<td>&lt; 0.10</td>
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<tr>
<td>Treatment preference (clinician)</td>
<td>57%</td>
<td>28%</td>
<td>&lt; 0.10</td>
</tr>
<tr>
<td>Treatment preference (parent)</td>
<td>59%</td>
<td>33%</td>
<td>&lt; 0.10</td>
</tr>
<tr>
<td>Visual analog scales</td>
<td>-2.2 ± 2.24</td>
<td>-1.2 ± 2.36</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ABC-FXS Factored Social Avoidance</td>
<td>-1.2 ± 2.37</td>
<td>-0.1 ± 2.53</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Arbaclofen (STX209) Trials

“Responders”, 35% vs. 18%  
$p = 0.11$

44% vs. 6%, (p < 0.05)

58% vs. 19%, < 0.01

Per Protocol, N=52  
Autism, N=18  
Low Social, N=27

• Phase 2 ad hoc: In low sociability group (N=27) significantly better CGI, treatment preference, ABC social withdrawal, Vineland socialization  
  * Berry-Kravis et al. Sci Trans Med 2012

• Phase 3 placebo-controlled trial (N=120 FXS, age 12-50) flexible dose, arbaclofen not better than placebo for social withdrawal, Phase 3 age 5-11 trial pending

• Some patients seem to be responders, did extremely well during open-label extension, much worse when open-label extension stopped: hard to show in trial due to: variability in type of response, placebo effects, length of time to establish full response, not measuring the most prominent effects of drug
Arbaclofen – Preliminary One Year Data (N=33)

Vineland – Communication (standard scores)

Baseline  Week52

Vineland – Composite (standard scores)

Test-retest average 2.3 + 0.9 years

Avg +1

Avg -10

Scoring artifact

Fisch et al, 1996

11/26/2013
Challenges in Trial Design to Show New Drugs Work

Basic Science Targets Mismatch

To Speed this up.... Building the Bridge While Crossing It
Clinical Trial Issues in FXS

- **Dosing** – same mosaics/females (some FMRP), careful balance – too much & too little mGluR signaling both give autism
- **Safety** – reporting in ID patients, agents with activity inside cell may have off-target effects (brain specific isoforms, blocker not enter brain)
- **Timing** – reverse mouse phenotypes any age, but human brain more wiring time, probable developmental and acute functions of FMRP, younger likely better
- **Length of Treatment** – behavior changes for FDA approval, may take a long time to see cognitive effects, especially if older, speed up with intensive training protocols
- **Outcome Measures** – phenotype/biomarker (more scientific, translate from animal models) vs rating scales (functional link for FDA approval, need FXS validation (ABC)) vs cognitive (re-norm to avoid floor effects), expressive language measures (objective data, patient observation)

We are working on all these issues
FXCRC Objectives:

- FXS clinical research on natural history to understand disease (FORWARD Registry and Database)
- mechanism for research access to do studies with sufficient patients
- clinical trial consortium to run trials to translate targeted treatments to patients
- Optimize/standardize care delivery in FXS across USA with best practices
State of Development of FXS Targeted Treatments

13 years, 5 years in trials
9 drugs to get 1, $$$$$$$

Basic Research

Translational Research

Clinical Develop

Exploratory

Target Identification Validation

Assay Development

HT Screening

Lead Optimization

Pre-clinical Efficacy

Safety Tox/ADME

Clin Research

Phase I

Phase II/III

Rolipram
STEP Inhibitors
ERK Inhibitors
PI3K Inhibitors
SLACK K Channel blockers

AMPA Activators
PAK Inhibitors
BK Ca channel blockers
Other GABA-A

CX516
Fenobam
AFQ056 (Novartis)
RO4917523 (Roche)
STX209 (Seaside)

NNZ-2591
Ganaxolone (Marinus)
Lithium
Acamprosate
Lovastatin
Donepezil
Minocycline

Investigational Drugs

Approved Drugs – New Indication

11/26/2013
How Will Clinical Practice Change With Successful Targeted Treatment for FXS

• All FXS individuals would be treated including adults – need clinic resources to accommodate management, patient education and monitoring - FXCRC

• Dosing may be tricky, combinations with different pathway targets may work best – need practitioners with FXS experience to assess response

• Early diagnosis and treatment imperative – newborn screening

• Likely stepwise improvement in treatments – need ongoing clinical trials network (FXCRC) to keep building best treatment protocols (like cancer tx model)
Potential Pathway Overlap with Autism – Likely Have Treatment Overlap

A. Proteins involved in other forms of autism are in signaling cascade for translational regulation.

B. FMRP likely binds and regulates half of proteins identified in autism in exome screens.

C. May be convergence of glutamate/GABA pathways involved in both disorders.

Wang, Berry-Kravis, Hagerman; Neurotherapeutics 2010

ID
FXS
LD
Autism
Acknowledgements/Disclosures

- FRAXA Research Foundation
- NIH – NINDS, NICHD, NIMH
- Kiwanis Spastic Paralysis Foundation
- National Fragile X Foundation

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- Cortex Pharmaceuticals
- Asuragen

Clinical Trial Funding
- Seaside Therapeutics
- Neuropharm
- Roche
- Novartis