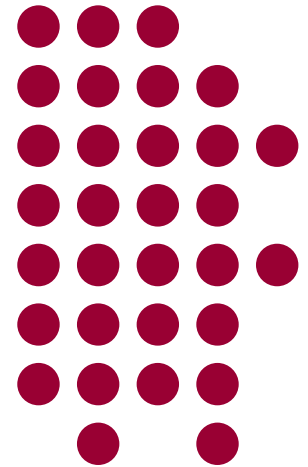


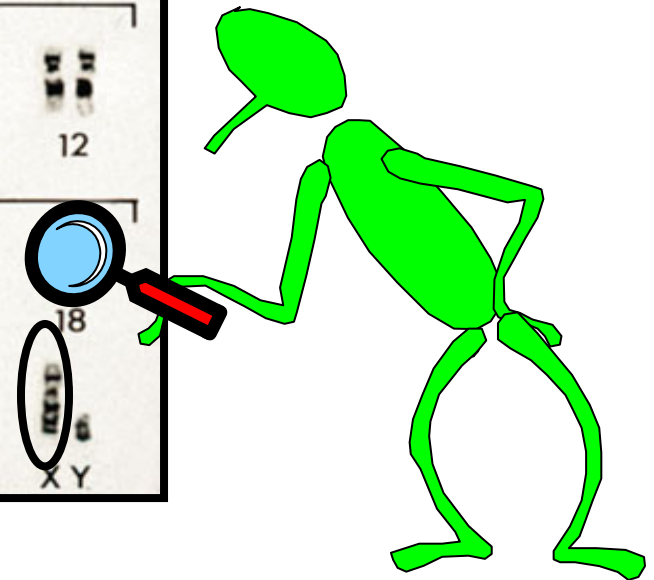
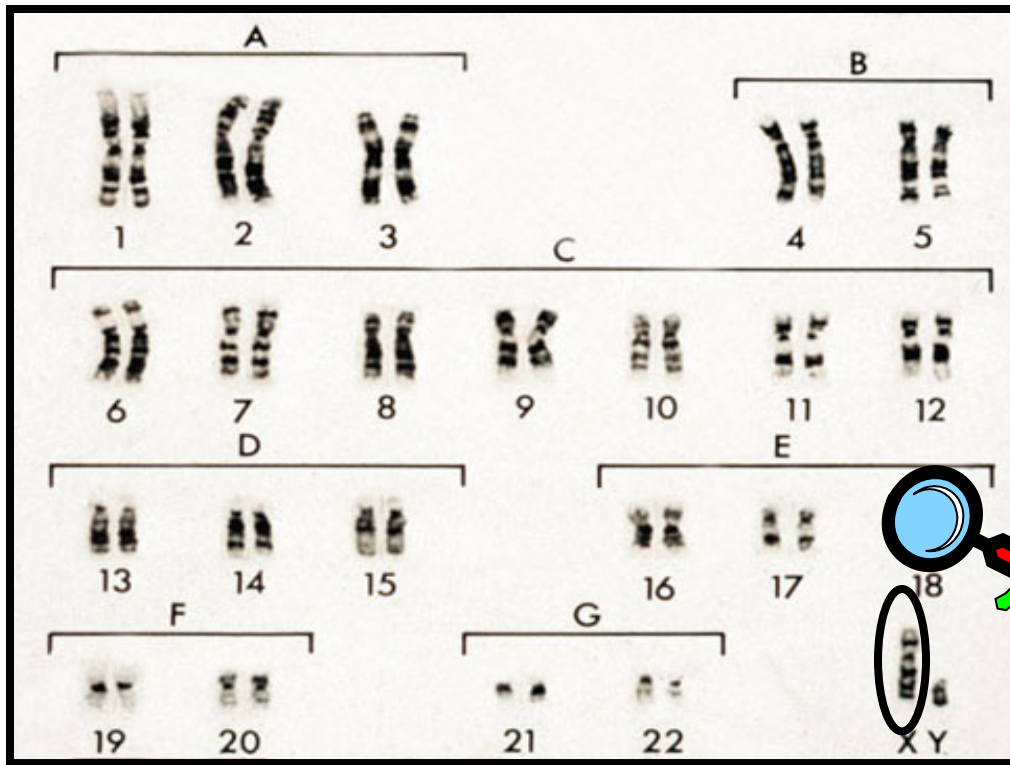
The Promise of Targeted Pharmaceutical Treatments for Fragile X Syndrome

Brenda Finucane, MS, CGC
Executive Director, Genetic Services
brenda_finucane@elwyn.org

Funding for this symposium
generously donated in honor
of Joshua A. Gammon



Fragile X Syndrome



Fragile X Syndrome

- Most common hereditary cause of developmental disabilities in all populations
- Occurs in both males and females, although males are more commonly affected
- Diagnosed through DNA blood testing
- Physical features often subtle
- Majority of those affected are undiagnosed

Physical Findings

- Macrocephaly (large head)
- Large ears
- Hyperextensible joints
- Long, narrow face
- Macroorchidism (enlarged testicles)
- Low muscle tone
- Mitral valve prolapse

Intellectual Functioning

- Majority of males function in the moderate range of intellectual disability
- <5% of males have IQs above 70
- Much more variability among females, ranging from severe intellectual disability to above average IQ

Behavioral Characteristics

- Hyperactivity
- Hand-flapping
- Hand-biting
- Tactile defensiveness
- Perseverative speech
- Sensory hyperarousal
- Gaze aversion

Fragile X and Autism

- Up to 21% of young boys with fragile X syndrome meet diagnostic criteria for Autistic Disorder
- A majority of males and many females with fragile X syndrome have symptoms consistent with an autism spectrum disorder

Autism and Fragile X

- Autism: recognizable pattern of behavioral symptoms
- Numerous known and unknown causes
- Fragile X: most common known single gene cause of autism
- Prevalence of fragile X among children with autism estimated to be around 1 in 20

Just One Gene

- 1991: scientists discover the cause of fragile X syndrome
- A single gene called FMR1 shuts down and fails to produce its normal protein (called FMRP)
- FMRP is expressed in the brain and essential for normal brain functioning
- Fragile X inheritance is complicated; gene changes cause a wide range of effects from one generation to the next

Targeted Pharmaceuticals

- Traditional approaches to pharmaceutical intervention for people with ID and behavioral challenges: symptom-based
- Targeted pharmaceutical treatments for genetic disorders: target underlying biochemical pathways

A New Age of Targeted Intervention

Advances over past decade:

- completion of Human Genome Project: wealth of information about DNA code
- new laboratory technologies allow faster pace of genetic research
- development of animal models for human genetic conditions

Next phase of intervention research:

- targeted pharmaceuticals to address the underlying pathology in genetic disorders

A New Age of Targeted Intervention

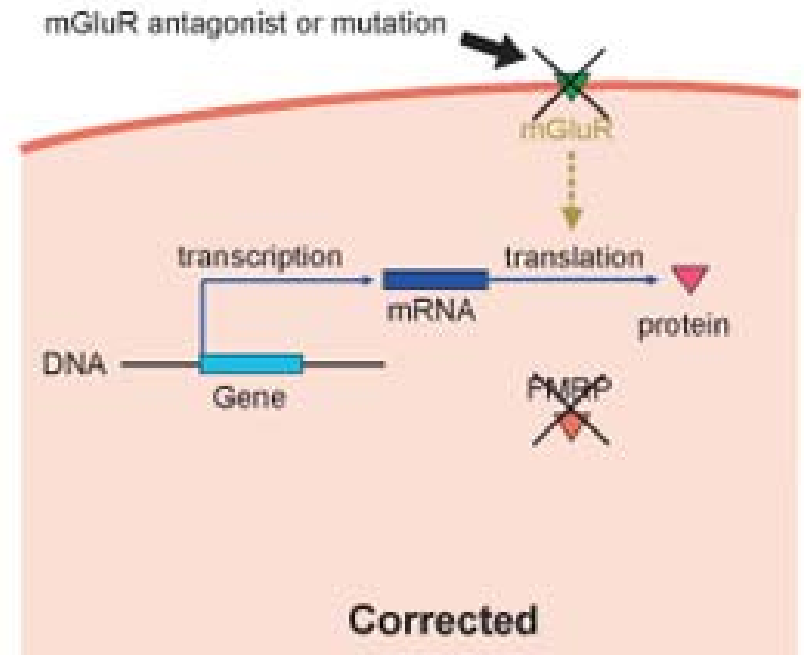
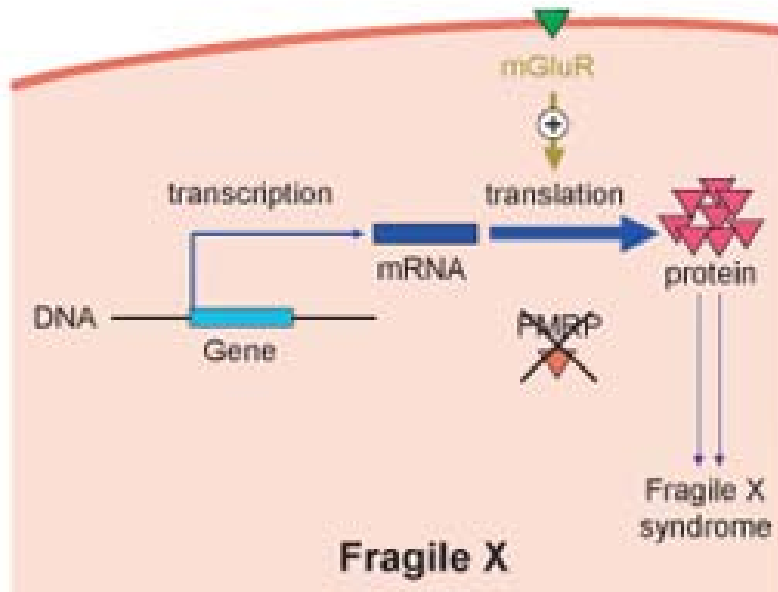
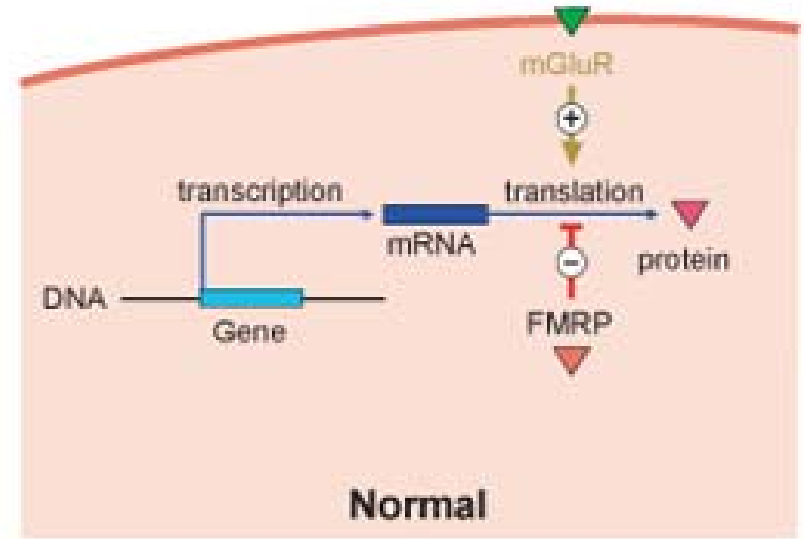
Current Research on Potential Single Gene Targets

- Fragile X syndrome (FMR1):
www.fragilex.org
- Rett syndrome (MeCP2):
www.rettsyndrome.org
- Angelman syndrome (UBE3A):
www.cureangelman.org

mGluR Theory of Fragile X

- Group I metabotropic glutamate receptors (mGluR) stimulate synthesis of proteins at neuronal synapses
- FMRP normally acts to inhibit this protein synthesis
- Two systems act in tandem to regulate synaptic connections
- Without FMRP, mGluR activity is unchecked
- Synapses are weak, abnormal structure – impaired synaptic signaling, learning / behavioral abnormalities

Model for Pathogenesis and Treatment of Fragile X Syndrome



Of Mice and Flies



Drosophila (fruit flies):

Well-characterized genetically, behaviorally

FraX fruit fly shows structural abnormalities, measurable differences in behavior (courtship)

Mice:

Well-characterized genetically, behaviorally

FraX mouse shows physical differences, audiogenic seizures, hyperactivity, anxiety issues



Drosophila Love

A. Innate Courtship:



WT males court
receptive females

KO males court
less vigorously

B. Courtship Suppression: Learning



When placed with an unreceptive trainer female
the male initially courts vigorously, but over time
courtship activity declines (training suppression).
KO males show normal suppression (learning)

Drosophila Love

C. Courtship Suppression: Memory



WT males will not court
receptive tester female

KO males court tester
female at naive levels

D. Courtship Suppression: Memory Recovery



Drug treatment has no
effect on WT courtship
memory.

Drug treated KO males
now exhibit courtship
memory after training

Transgenic mice

- Fragile X mice: structural neuronal abnormalities (long, thin dendritic spines with weak signaling, excessive spine formation)
- p21-activated kinase (PAK): one of many enzymes activated by mGluR, involved in dendritic spine formation, synaptic signaling; PAK mice show reduced spine formation, excessive signaling
- Genetically-crossed mice strain “rescues” fragile X phenotype

Lithium

- Well-studied in treatment of mood disorders
- mGluR antagonist: reduces unregulated mGluR-mediated protein synthesis
- Reverses memory problems in fraX fruit fly
- Reduces audiogenic seizures, hyperactivity in fraX mouse
- Clinical trials in humans (2008): improved verbal memory, problem behaviors, blood markers related to abnormal protein production

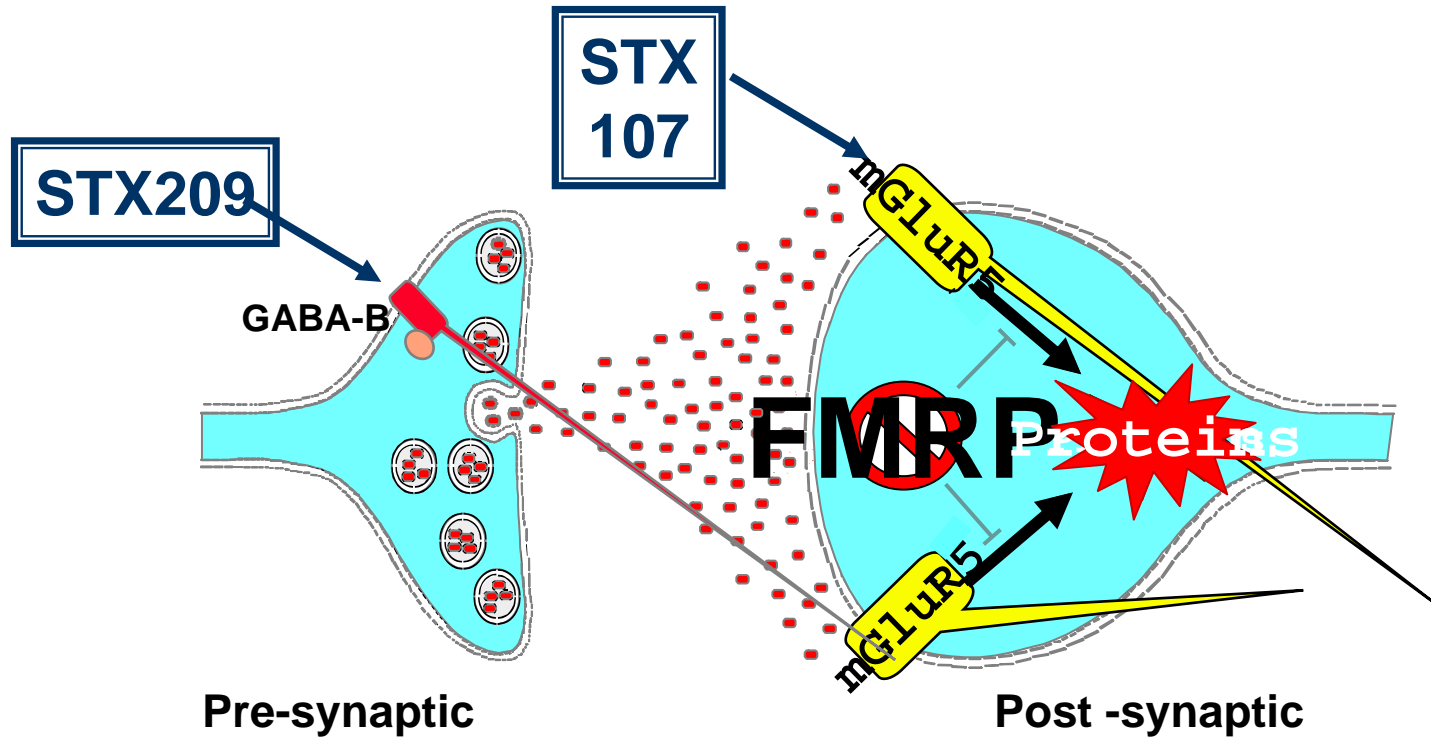
MPEP

- Older drug, not for use in humans
- mGluR antagonist: reduces unregulated mGluR-mediated protein synthesis
- In fraX fruit fly, corrects memory problems and structural abnormalities
- In fraX mouse, corrects audiogenic seizures, hyperactivity, structural abnormalities and multiple behavioral issues

Fenobam

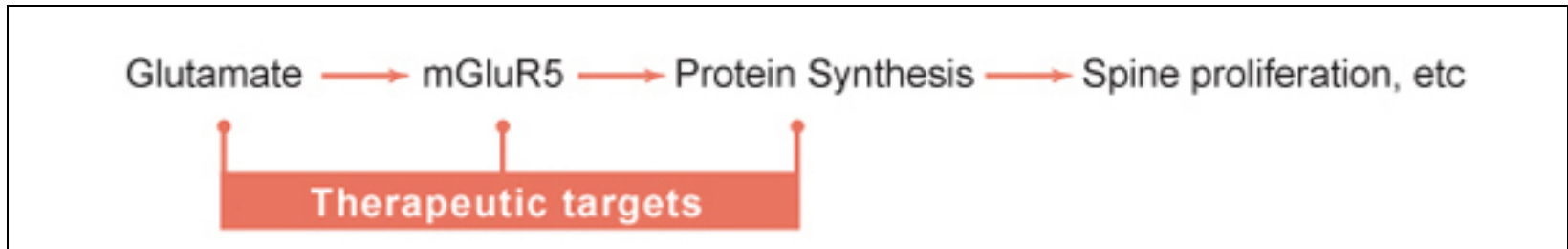
- In clinical trials as an anti-anxiety drug in 1970s; recently found to be an mGluR5 antagonist
- Granted orphan drug status for fragile X syndrome by FDA – fast track for approval
- Preliminary human trials in adults with fragile X underway
- Several other similar drugs in pipeline

Clinical Trials of Targeted Pharmaceutical in FXS



STX209 (arbaclofen)

- indirectly inhibits excessive mGluR-mediated protein synthesis
- related to baclofen, commonly prescribed drug with excellent safety profile and decades of clinical use in people with CP
- Elwyn Genetics one of 12 sites in Phase 2 clinical trial for fragile X



STX209 (arbaclofen): inhibits glutamate signaling in the brain and should thereby indirectly inhibit excessive mGluR mediated protein synthesis in fragile X syndrome

STX209 (arbaclofen)

Phase 2 Study Results (July 2010)

- Double blind, placebo-controlled phase 2 study
- 54 people with FXS (6 to 40 years)
- Clinically well-tolerated, few side effects
- Clinical Global Impressions of Improvement (CGI-I) scale:
 - positive trend for all global measures
 - one third of treatment population: “much improved” or “very much improved” vs placebo scores

For more information, visit www.seasidetherapeutics.com

STX209 (arbaclofen)

Phase 2 Study Results (July 2010)

- Subgroup of 15 children with most severe impairments in sociability at baseline:
 - statistically significant improvements on all global measures, including CGI-I, Aberrant Behavior Checklist - Social Withdrawal subscale, and the Vineland Play and Leisure subscale
 - Responders: score of “Very much” or “Much improved” on the CGI-I scale plus 25%+ improvement on the ABC-SW.
 - > 50% showed positive response on STX209 versus 13% on placebo

For more information, visit www.seasidetherapeutics.com

STX209 (arbaclofen)

- Majority of families opted to continue treatment under open label extension
- Phase 3 clinical trial now underway

For more information, visit www.seasidetherapeutics.com

Resources

National Fragile X Foundation
www.fragileX.org

FRAXA Research Foundation
www.fraxa.org

Research Review

Fragile X Research: A Status Report

Elizabeth Berry-Kravis, MD, PhD

July 2008 issue of Fragile X Quarterly

Nat'l Fragile X Foundation, www.fragileX.org

Wang LW, Berry-Kravis E, Hagerman RJ.(2010). **Fragile X: leading the way for targeted treatments in autism.** *Neurotherapeutics* 7(3):264-74.

Berry-Kravis et al., (2011). **Targeted treatments for fragile X syndrome.** *J Neurodev Disord.* Feb 19. [Epub ahead of print]