WEBINAR ON CLINICAL TRIALS FOR FRAGILE X

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AGENDA

Welcome and introductions

- Katie Clapp, FRAXA president/co-founder, Fragile X parent

Our family's experience in one of the trials

– Jim Cantore, Storm Tracker, FRAXA Honorary Board, Fragile X parent

The investigational new drugs being tested and what they do

- Mike Tranfaglia MD, FRAXA medical director & co-founder, Fragile X parent

What is involved in participating in these trials

- Elizabeth Berry-Kravis MD PhD, FRAXA Scientific Advisory Board
  Professor and Fragile X Clinic Director, Rush University Medical Center, Chicago

Our family's experience in one of the trials

– Becky Zorovic MD, FRAXA director of scientific affairs, Fragile X parent

Questions

Jim Cantore

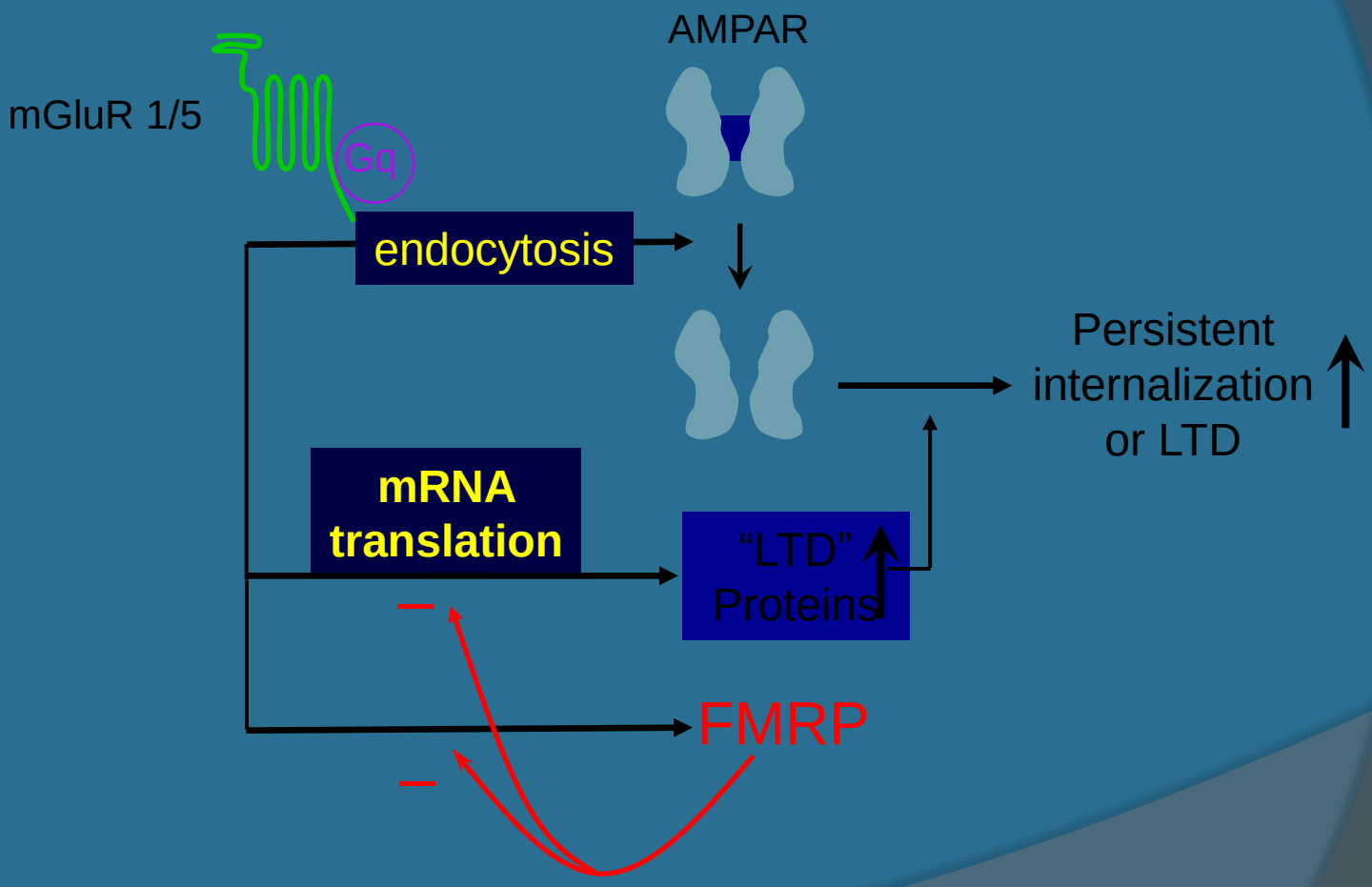
Parent of two children with Fragile X

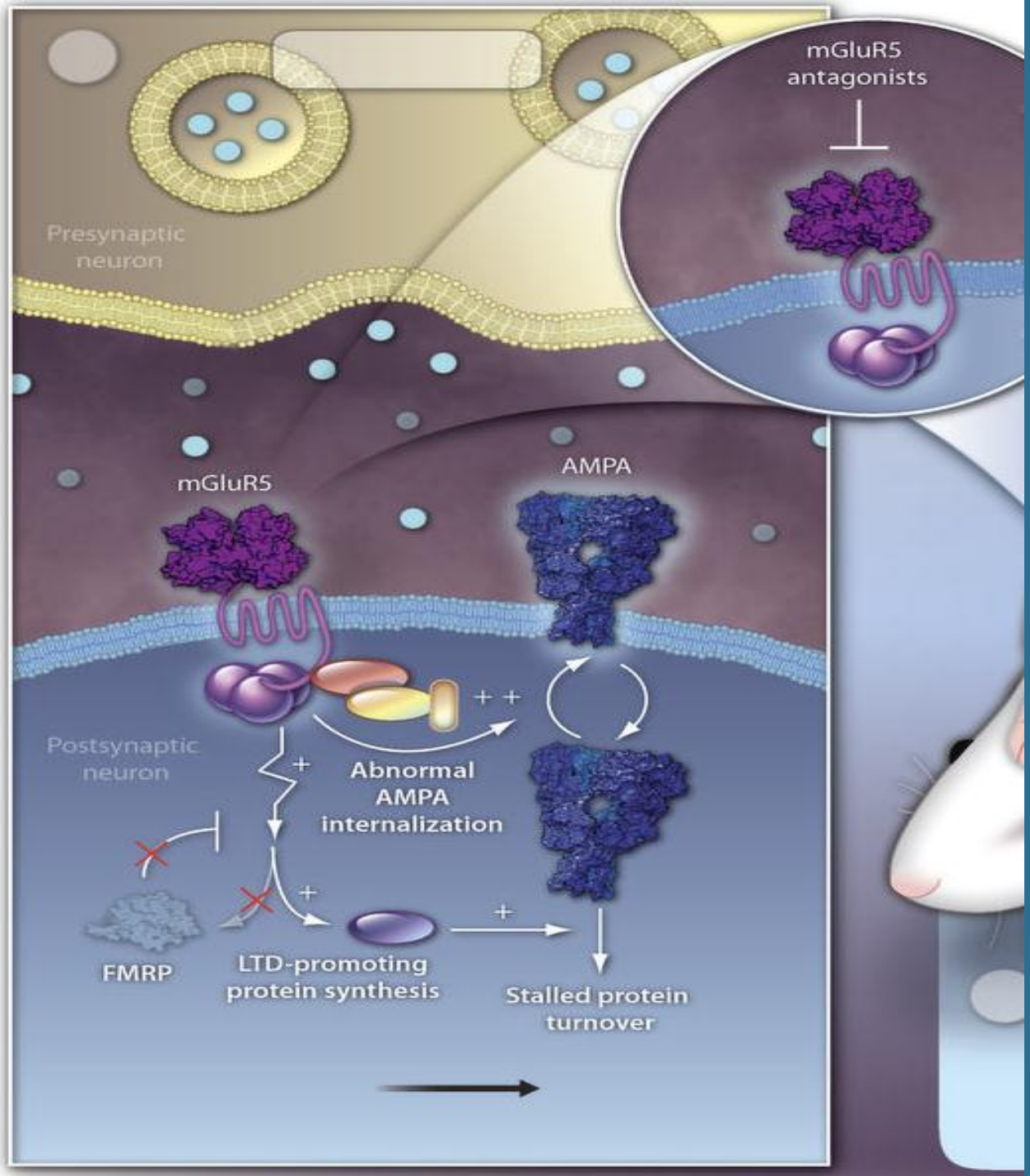
Participating in trial of AFQ056

Mike Tranfaglia, MD

FRAXA medical director & co-founder, Fragile X parent

Model of FMRP function in mGluR-dependent LTD





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AFQ vs RO

AFQ056

- Novartis lead mGluR5 antagonist
- Medium potency (150 mg dose)
- Medium-length duration of action (taken twice a day)
- Also being developed for Parkinson's Disease (LID) and Huntington's Disease

RO4917523

- Roche lead mGluR5 antagonist
- High potency (1 mg dose)
- Ultra long-acting (taken once a day, or even every other day
- Also being developed for Major Depression

STX209 (arbaclofen, R-baclofen)

- GABA-B agonist
- Inhibits the release of glutamate
- May work with mGluR5 antagonists in a useful combination
- Moderate potency
- Short-acting, requires multiple daily doses
- R isomer appears to have fewer side effects and greater potency

Validated Targets for Fragile X Therapeutics

- AMPA receptor
- GSK3 beta
- MAP1b
- mGluR5
- mGluR1
- mGluR2/3
- GABA (a & b)
- PDE4
- PAK
- MEK/ERK
- MMP-9
- M1
- STEP
- PI3K
- S6K
- BK (Maxi-K) Channel

Elizabeth Berry-Kravis, MD, PhD

FRAXA Scientific
Advisory Board Member

Professor
Fragile X Clinic Director
Rush University
Medical Center Chicago

STX 209 Arbaclofen (Seaside) GABA-B

- Targets social withdrawal/anxiety – measure with scale to qualify for entry
- "301" Placebo-controlled trial for adolescents and adults ages 12-50
  - 50% chance placebo, 50% chance arbaclofen
  - flexible dose titrated to best dose for 4 weeks then 4 weeks on "best dose" then wean off (total treatment period 8 weeks + wean)
  - 5-6 visits over 12-15 weeks, 5 blood draws, 3 EKGs, questionnaires
  - Up to 3 other meds allowed but NO SSRIs (Prosac, Zoloft, Celexa...)
- "302" Placebo-controlled trial for kids ages 5-11
  - 25% placebo, 25% each low, med, high dose arbaclofen
  - fixed dose – titrate up to set dose, 4 or more weeks on assigned dose, then wean off (total treatment period 8 weeks + wean)
  - 5-6 visits over 12-15 weeks, 5 blood draws, 3 EKGs, questionnaires
  - Up to 3 other meds allowed but NO SSRIs
- "303" Extension that everyone can join after the placebo-controlled trial to go on treatment with arbaclofen; medication titrated like in clinic to best effect; visits after 1 month, 2 months, every 3 months; 2 blood tests/yr

AFQ056 (Novartis) mGluR5 “Blocker”

- Targets global behavior – measure on scales to qualify for entry – need significant behavioral issues

- “2212” Placebo-controlled trial adults age 18-45
  - 25% chance placebo, 25% each low, med, high dose AFQ
  - fixed dose – titrate to set dose, 2 mo on assigned dose (total treatment 4 mo)
  - 8 visits over 4-5 mo, 4 blood draws, 6 EKGs, thinking tests, questionnaires
  - Up to 2 other meds allowed, have to meet methylation criteria, subnormal IQ

- “2214” Placebo-controlled trial adolescents age 12-17
  - 25% chance placebo, 25% each low, med, high dose AFQ
  - fixed dose – titrate to set dose, 2 mo on assigned dose (total treatment 4 mo)
  - 8 visits over 4-5 mo, 4 blood draws, 6 EKGs, thinking tests, questionnaires
  - Up to 2 other meds allowed, have to meet methylation criteria, subnormal IQ

AFQ056 (Novartis) mGluR5 “Blocker”

- “2279” Extension
  adults can join at last visit of placebo-controlled trial to go on treatment with AFQ;
  AFQ titrated to best effect;
  visits 2, 4 wk, 2, 3 mo, every 3 mo to 2+ yrs, 4 blood draws

- “2278” Extension
  adolescents can join at last visit of placebo-controlled trial to go on treatment with AFQ;
  AFQ titrated to best effect;
  visits 2, 4 wk, 2, 3 mo, every 3 mo to 2+ yrs, 4 blood draws

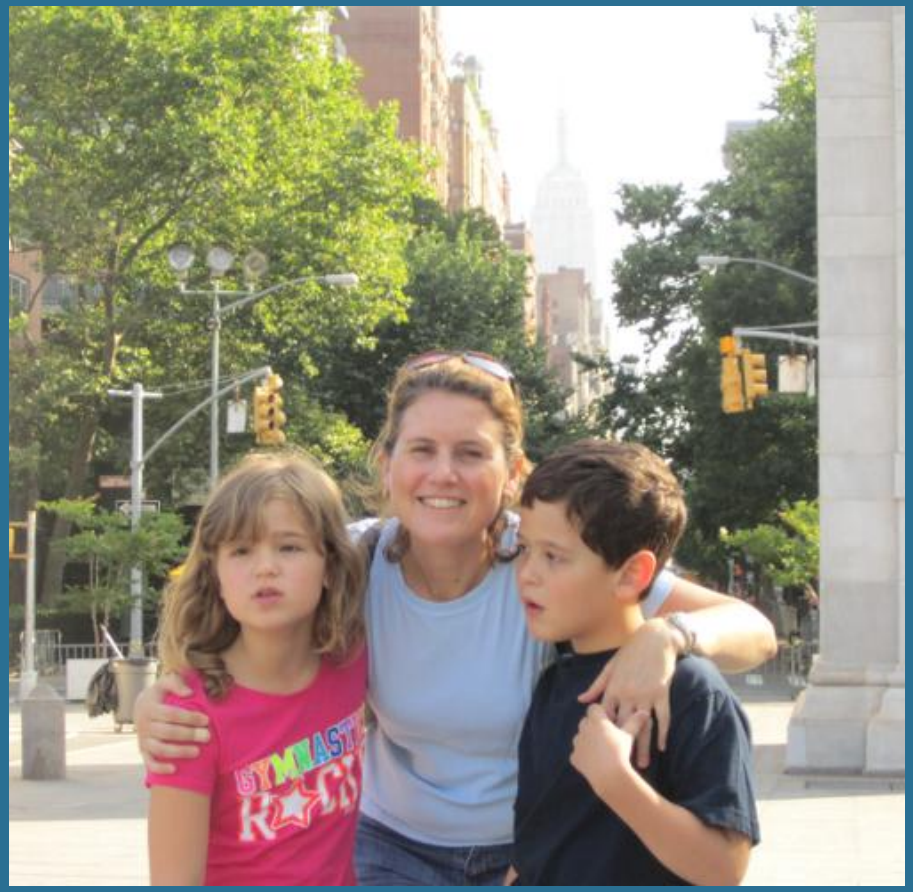
AFQ056 (Novartis) mGluR5 "Blocker"

- "2154" Child PK Study, kids age 5-11
  - To evaluate safety and blood levels
  - No IQ, behavior, methylation criteria for entry
  - Period 1 single dose followed by all day PK (blood draws), then Period 2 a week of treatment with all day PK at end
  - 4 visits: screen, 3-day visit (2 overnights), two 2-day visits (1 overnight each although can stay all week)
  - 6-7 days of blood tests – IV when multiple, several EKGs, thinking tests, questionaires
  - PK participants have option to go into extension directly without doing placebo-controlled study if/when child study opened
  - May be 3-4 year old study when 5-11 done

RO4917523 (Roche) mGluR5 “Blocker”

- Target is anxiety-related behavior - measure on scales to qualify for entry – can have mild behavioral issues
- NP27936 – Placebo-controlled trial age 16-50
  - 1/3 chance each placebo, medium dose, high dose
  - Fixed dose, 3 mo on assigned dose (total treatment period 3 mo)
  - 7 visits over about 4 months, 7 blood draws, 4 EKGs, thinking tests, questionnaires
  - No medication restrictions, no IQ or methylation restrictions
- No extension with treatment on drug – but hope is that will occur in future and participants from NP27836 will be able to enroll

Becky Zorovic, MD



Parent of two children with Fragile X

Participating in trial of arbaclofen

For more information

- Fraxa.org – click brown clinical trials button
- Clinicaltrials.gov – search “fragile X”
- Fragilex.org podcast – “Latest News”
- Individual clinic coordinators
  (listed on fraxa.org and clinicaltrials.gov)