Seaside Therapeutics

Convergence of Scientific Discoveries Enables Targeted Therapeutics for Individuals with Autism Spectrum Disorders

IACC Full Committee Meeting

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Best Pharmaceuticals for Children Act
FRAXA & Autism Speaks

Autism is an Urgent Unmet Medical Need

- 1:38 Prevalence (Kim 2011)
- 1:110 Diagnosed (CDC 2009)
- $3.2 M Lifetime Cost (Ganz 2007)

Daunting Phenotypic and Etiologic Complexity Has Hindered Progress in Developing New Therapies

- A ***spectrum*** disorder with widely varied
  - behavioral manifestations
  - severity
  - comorbid conditions
- For the majority of cases, cause(s) are unknown
- Strong genetic basis, but
  - risk architecture is highly heterogeneous
  - large number of genes implicated
- Contribution of environmental influences further complicates scientific analyses

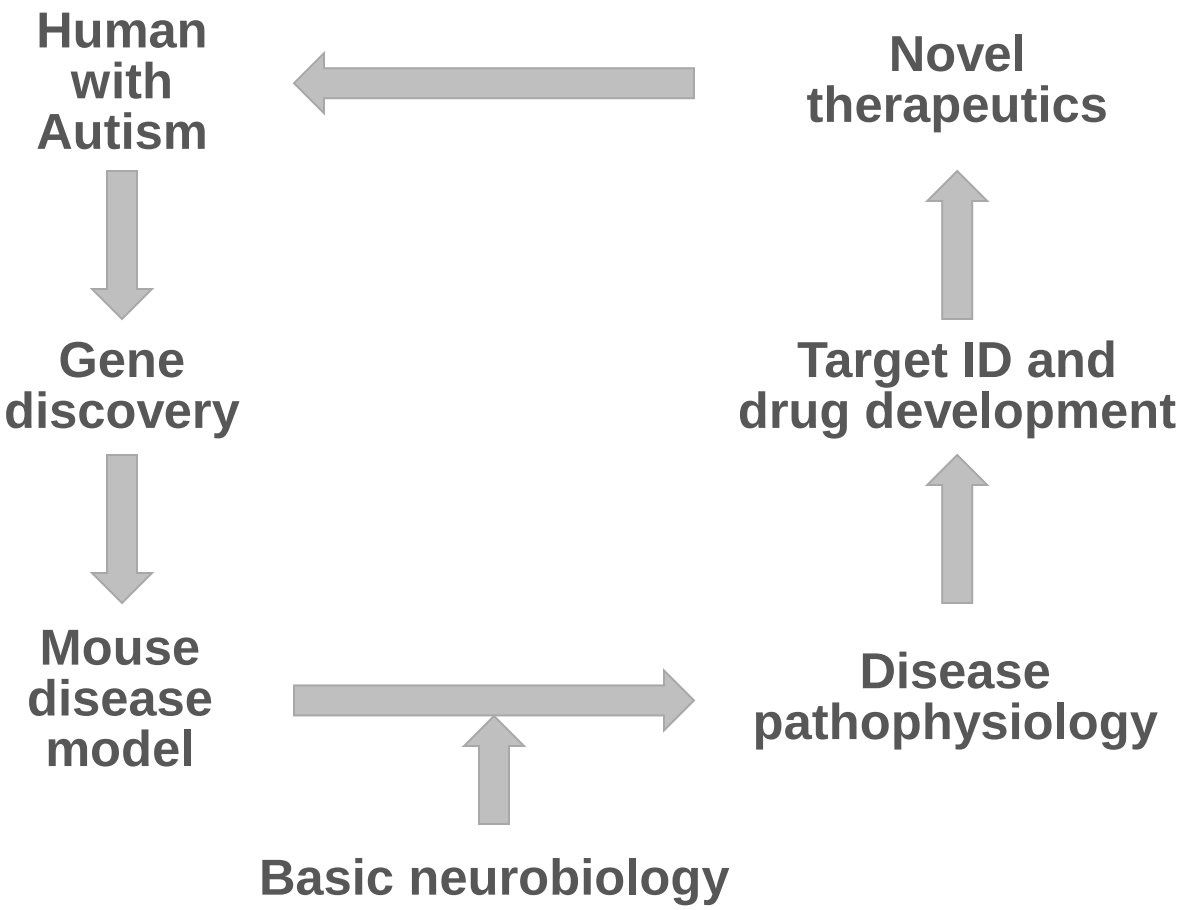
Reasons for Optimism That Substantial Progress Will Soon Be Realized

- Genes have been identified for a number of syndromic disorders that have ASD as a prominent feature
- These gene mutations have been reproduced in animal models that allow detailed examination of the underlying brain pathophysiology
- Animal research has converged on altered synaptic function as one likely basis for intellectual disability and ASD
- Insights gained on how synapses function differently in the face of these mutations have suggested novel therapeutic interventions that have been validated in preclinical models and have shown promise in preliminary human clinical trials

Reasons for Optimism That Substantial Progress Will Soon Be Realized (2)

- The fact that ASD and ID can be diagnosed in early childhood maximizes the potential benefit of therapy because it can be started at a time when the brain is most plastic
- **Finally, animal studies using gene reactivation or pharmacological interventions have suggested that substantial improvements can be seen even when treatments are begun in adulthood**

A Molecular Medicine Approach to Discover and Develop Novel Treatments for Autism



Single-Gene Disorders With High Rates of Autism

Leading Edge
Essay

Cell

The Autistic Neuron: Troubled Translation?

Raymond J. Kelleher III[1,*] and Mark F. Bear[2,*]

Table 1. Single-Gene Disorders with High Rates of Autism

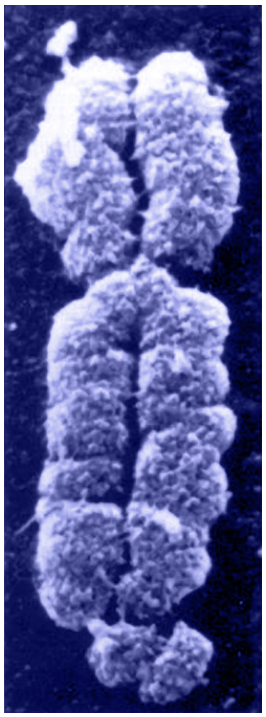
Gene	Disorder	Rate of Autism	Rate in Autism	MR	Gene Function
FMR1	Fragile X syndrome	15%–30%	2%–5%	+	Translational repressor
TSC1/2	Tuberous sclerosis complex	25%–60%	1%–4%	+	Inhibitor of mTOR
PTEN	PTEN hamartoma syndrome (ASD with macrocephaly)	ND	1%	+	Inhibitor of PI3K/mTOR signaling
NF1	Neurofibromatosis type I	4%	0%–4%	+	Ras GAP
MECP2	Rett's syndrome	100%	2%	+	Global transcriptional repressor
UBE3A	Angelman's syndrome	40%	1%	+	E3 ubiquitin ligase
CACNA1C	Timothy's syndrome	60%	<1%	+	L-type voltage-gated calcium channel ($Ca_v1.2$)
NLGN3/4	Familial ASD	ND	<1%	+	Synaptic adhesion
NRXN1	Familial ASD	ND	<1%	+	Synaptic adhesion
SHANK3	Familial ASD (22q13 microdeletion syndrome)	ND	<1%	+	PSD scaffolding

Several monogenic human disorders are characterized by cognitive impairment and autism. The estimated rate of autism spectrum disorders (ASDs) in each disease and the estimated rate of each disease in children with ASDs are indicated (rate of autism and rate in autism, respectively). MR refers to the association of mental retardation with each disorder. ND indicates that the prevalence of ASDs among individuals carrying mutations in the specified gene has not been determined.

2008, *Cell* 135, 401-406

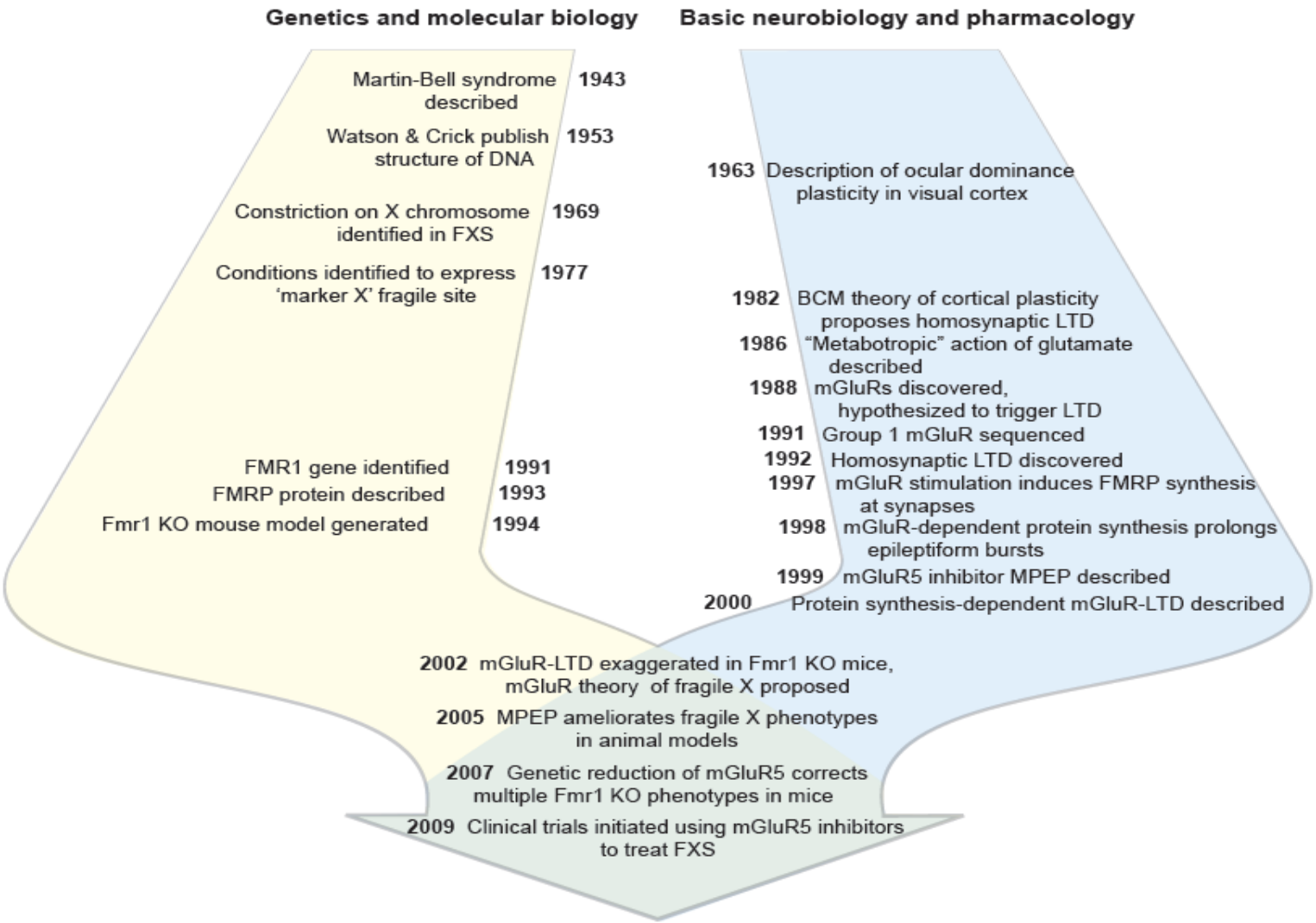
Fragile X Syndrome (FXS)

- Most common known genetic cause of autism
- Most common inherited cause of intellectual disability
- Results from mutation in a single gene
- Genetically defined, orphan patient population



Seaside is validating the single-gene approach to autism drug discovery in FXS

Scientific Discoveries in Diverse Disciplines Converge to Enable Identification of Targeted Therapeutics for FXS



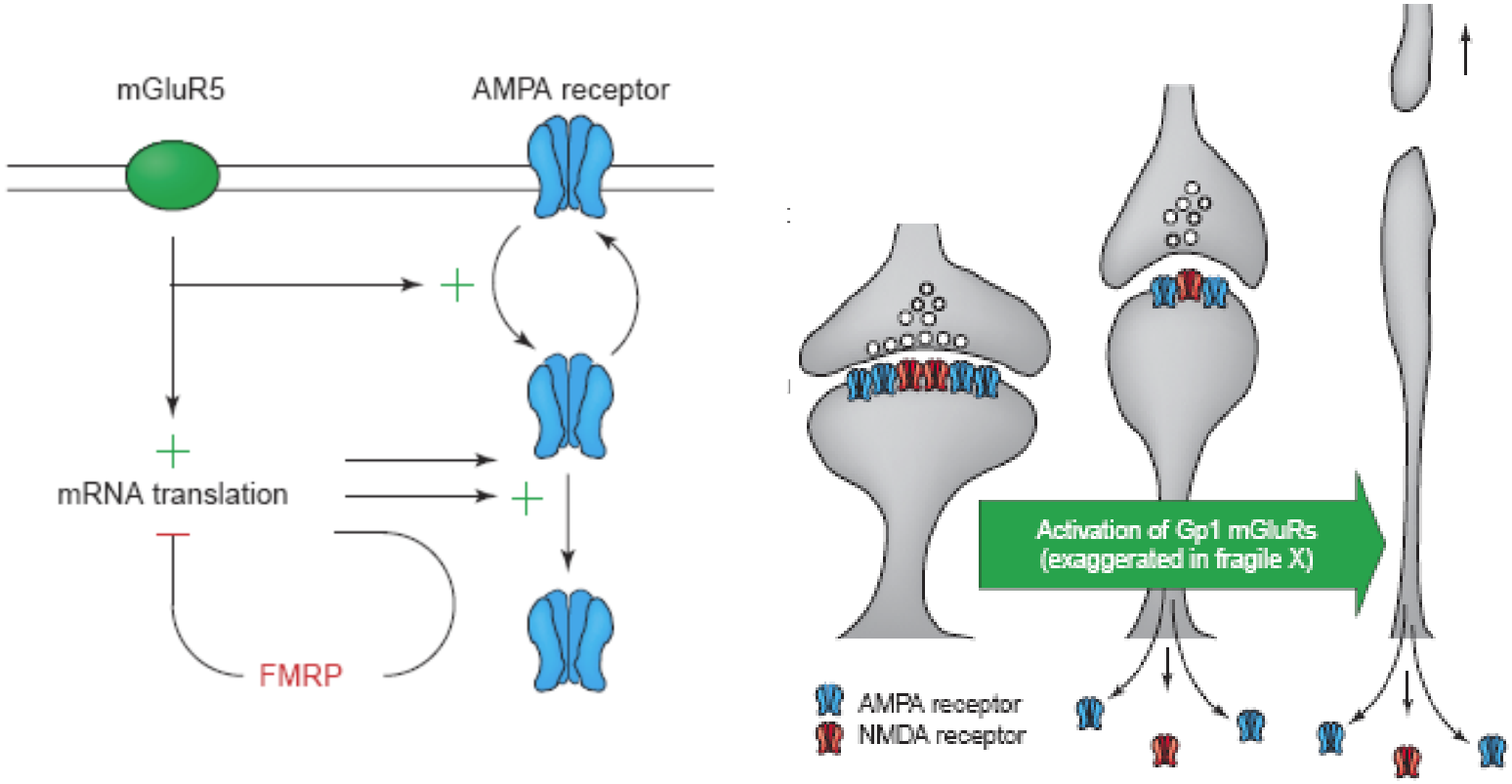
Krueger and Bear, *Annu Rev Med*, 2011

Breakthrough Scientific Discovery

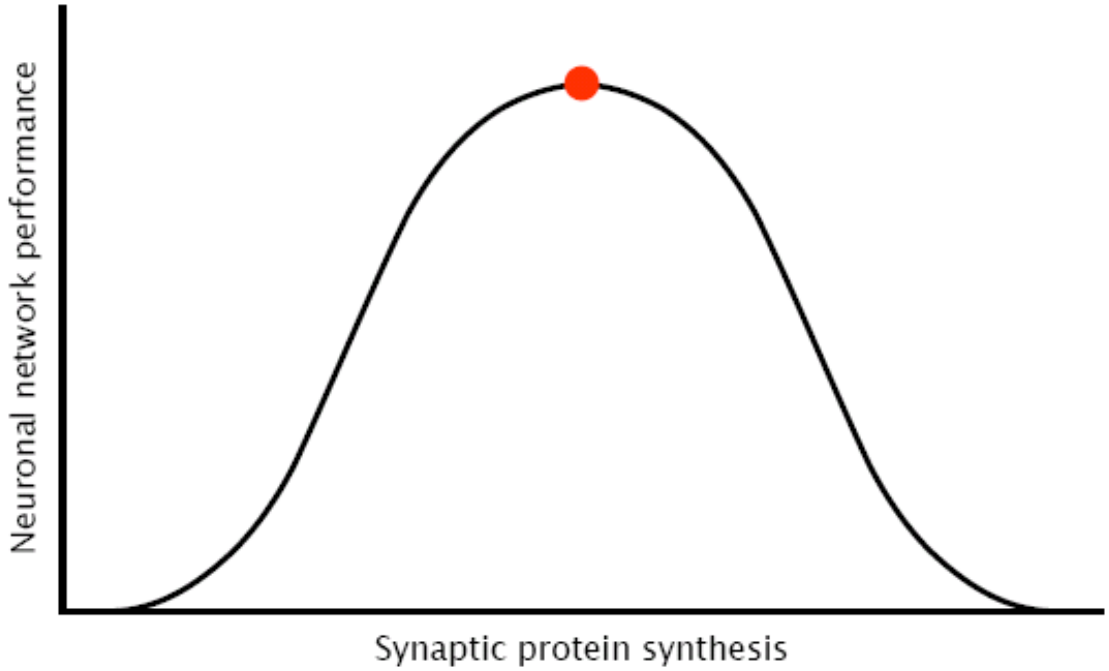
Opinion TRENDS in Neurosciences Vol.27 No.7 July 2004

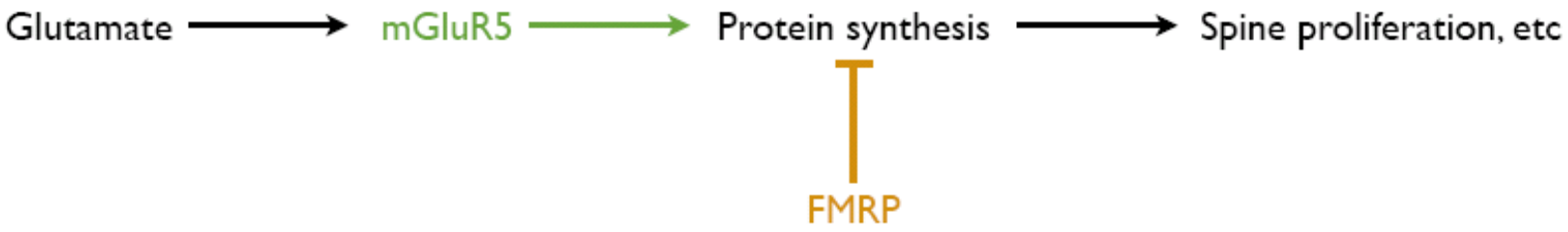
The mGluR theory of fragile X mental retardation

Mark F. Bear[1], Kimberly M. Huber[2] and Stephen T. Warren[3]

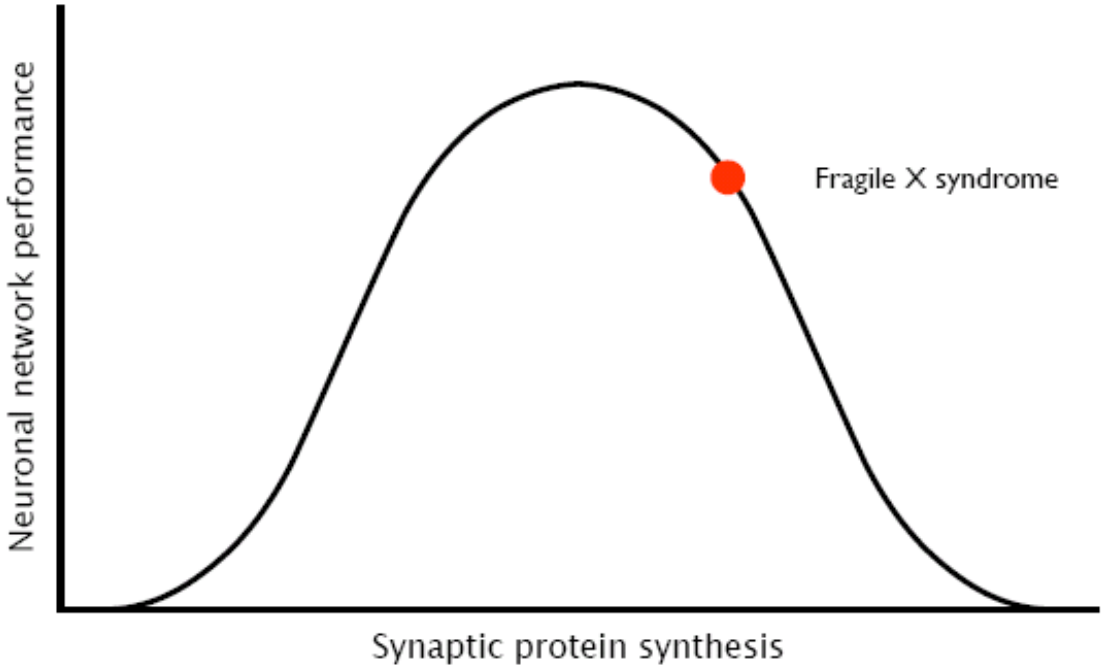


Optimal Synaptic Function Requires Optimal Protein Synthesis

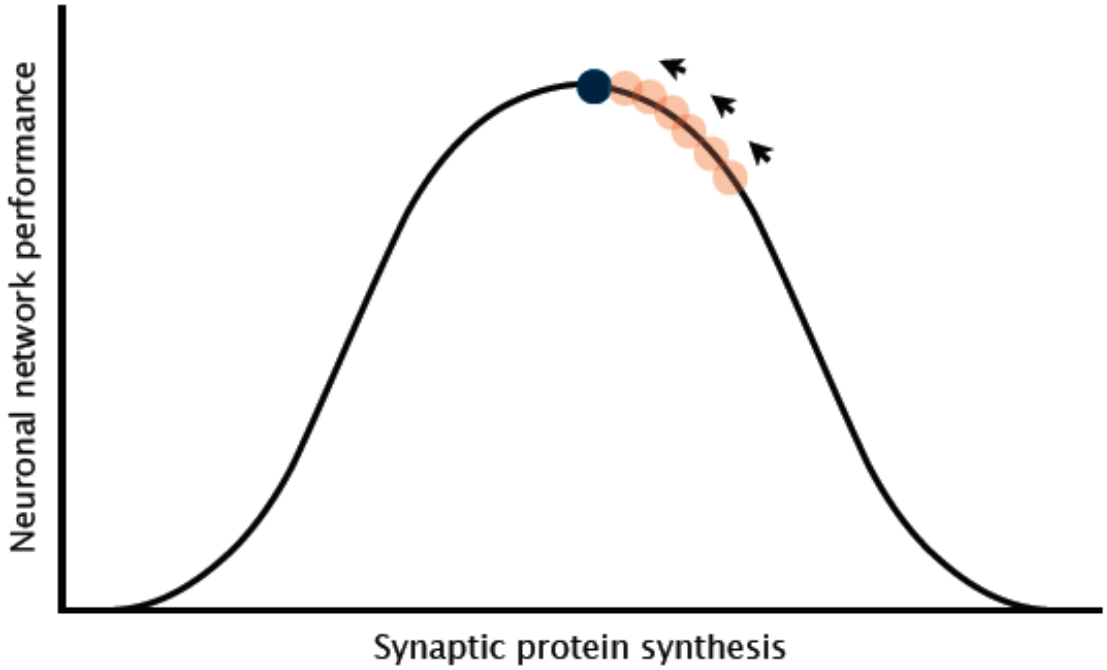


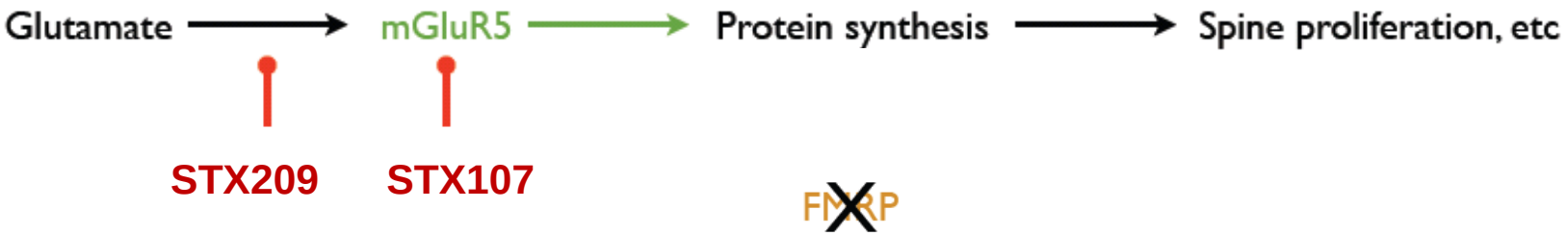


Excessive Protein Synthesis in FXS Disrupts Synaptic Function



Synaptic Protein Synthesis and Function Can Be Corrected in Mouse Models of FXS



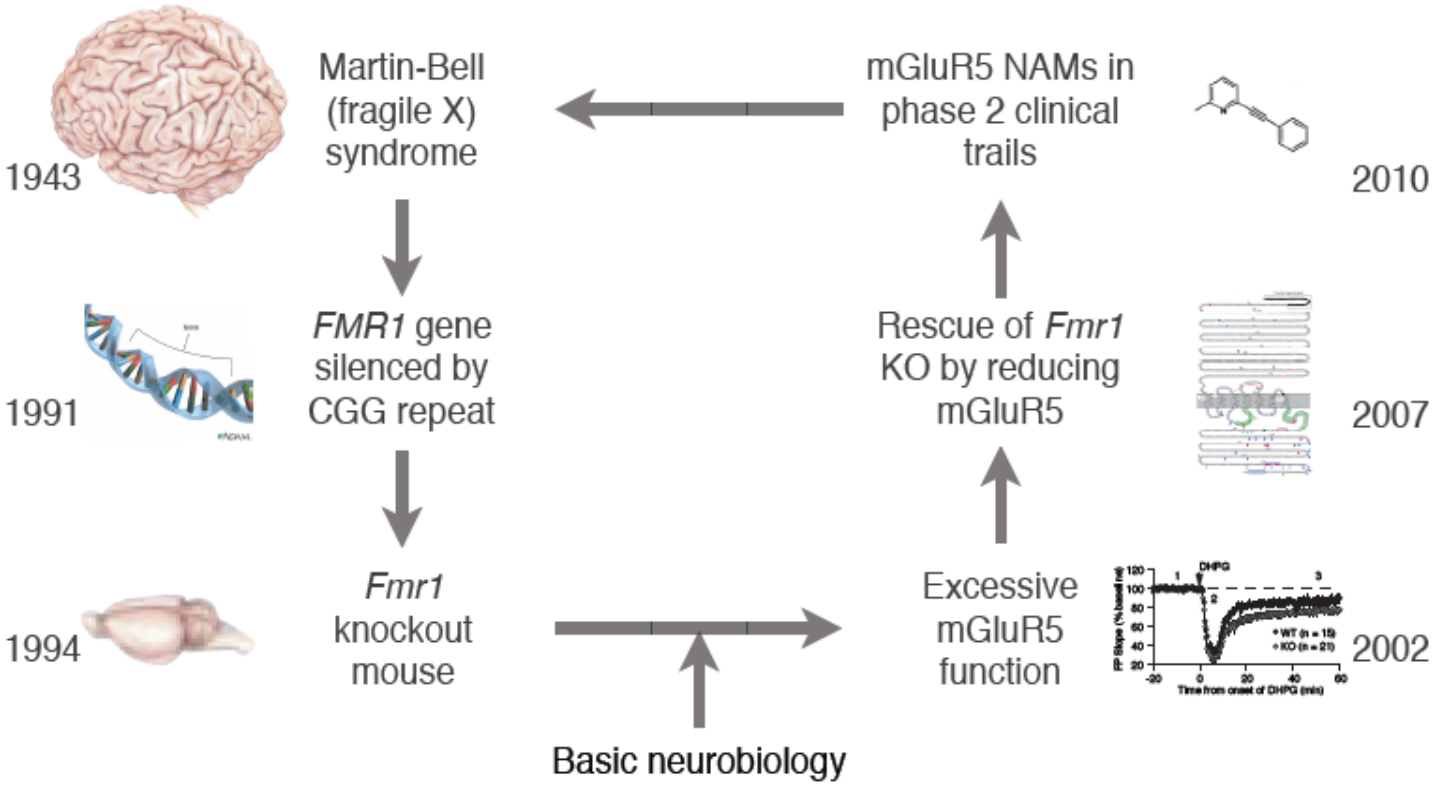


Inhibiting mGluR5 Treats Underlying Brain Pathophysiology in Mouse Models of FXS

Affected circuit:		Phenotypes **rescued**:
hippocampus	✓	Long-term depression
visual cortex	✓	Ocular dominance plasticity
visual cortex	✓	Increased spine density
amygdala?	✓	Fear memory extinction
hippocampus	✓	Basal rate of protein synthesis
hypothalamus?	✓	Weight gain
brain stem	✓	Audiogenic seizure

Gül Dölen, *et al., Annu Rev Med*, 2007

Seaside's Approach to Translational Medicine in FXS



Paradigm shift in drug development

Single-Gene Disorders With High Rates of Autism Converge on Common Disease-Causing Pathways

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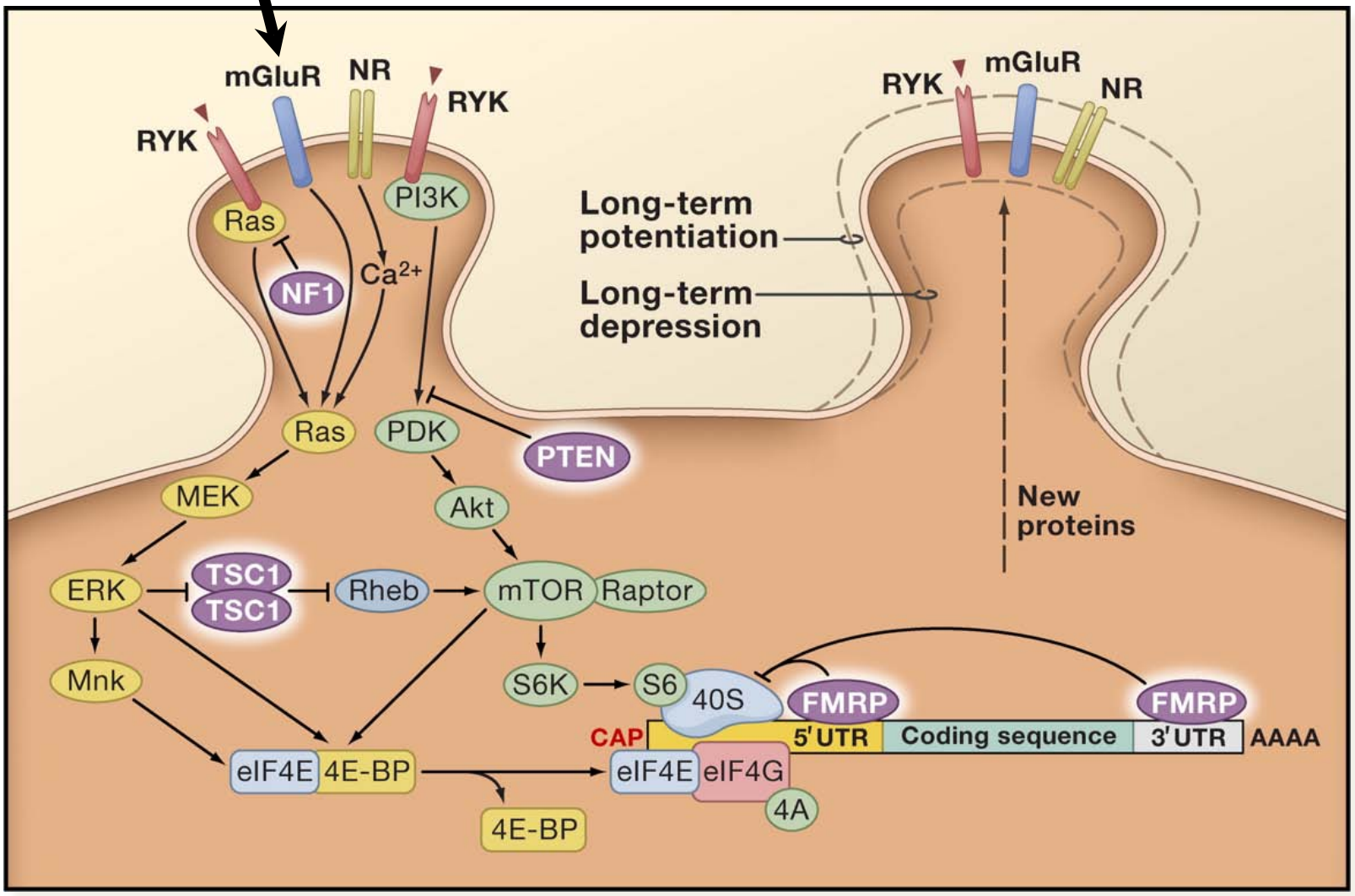
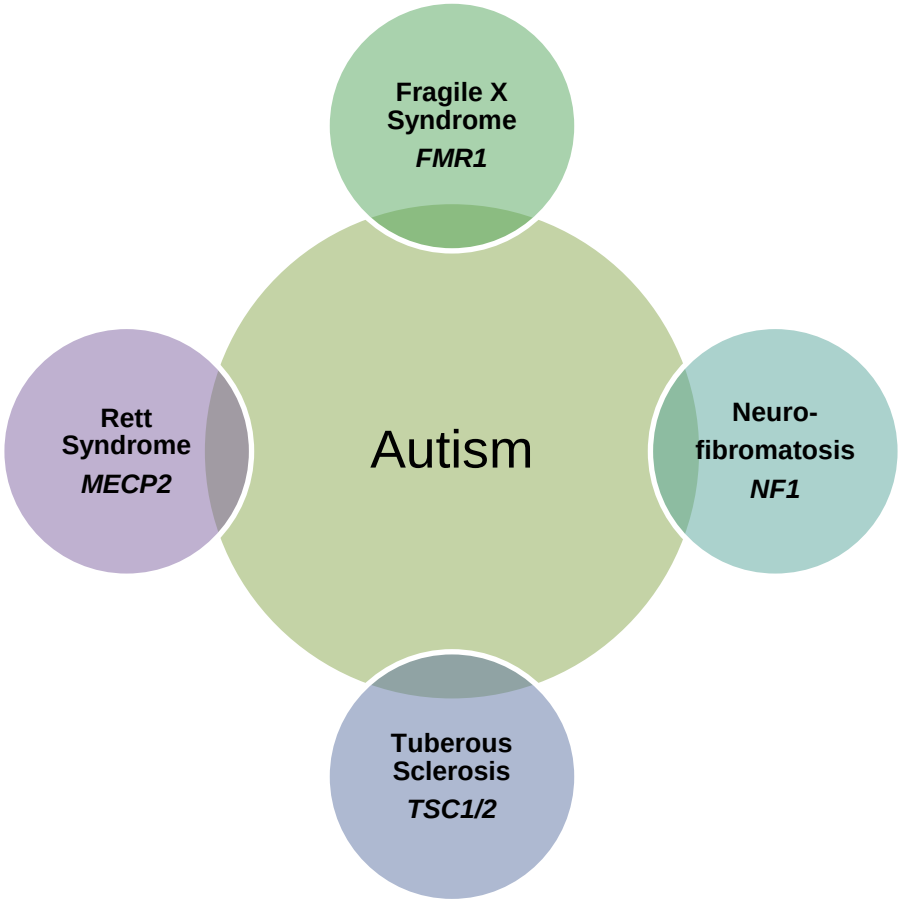
2008, *Cell* 135, 401-406

A Molecular Machine to Ensure That Protein Supply Keeps Up With Demand



Kelleher and Bear, *The Autistic Neuron, Cell*, 2008

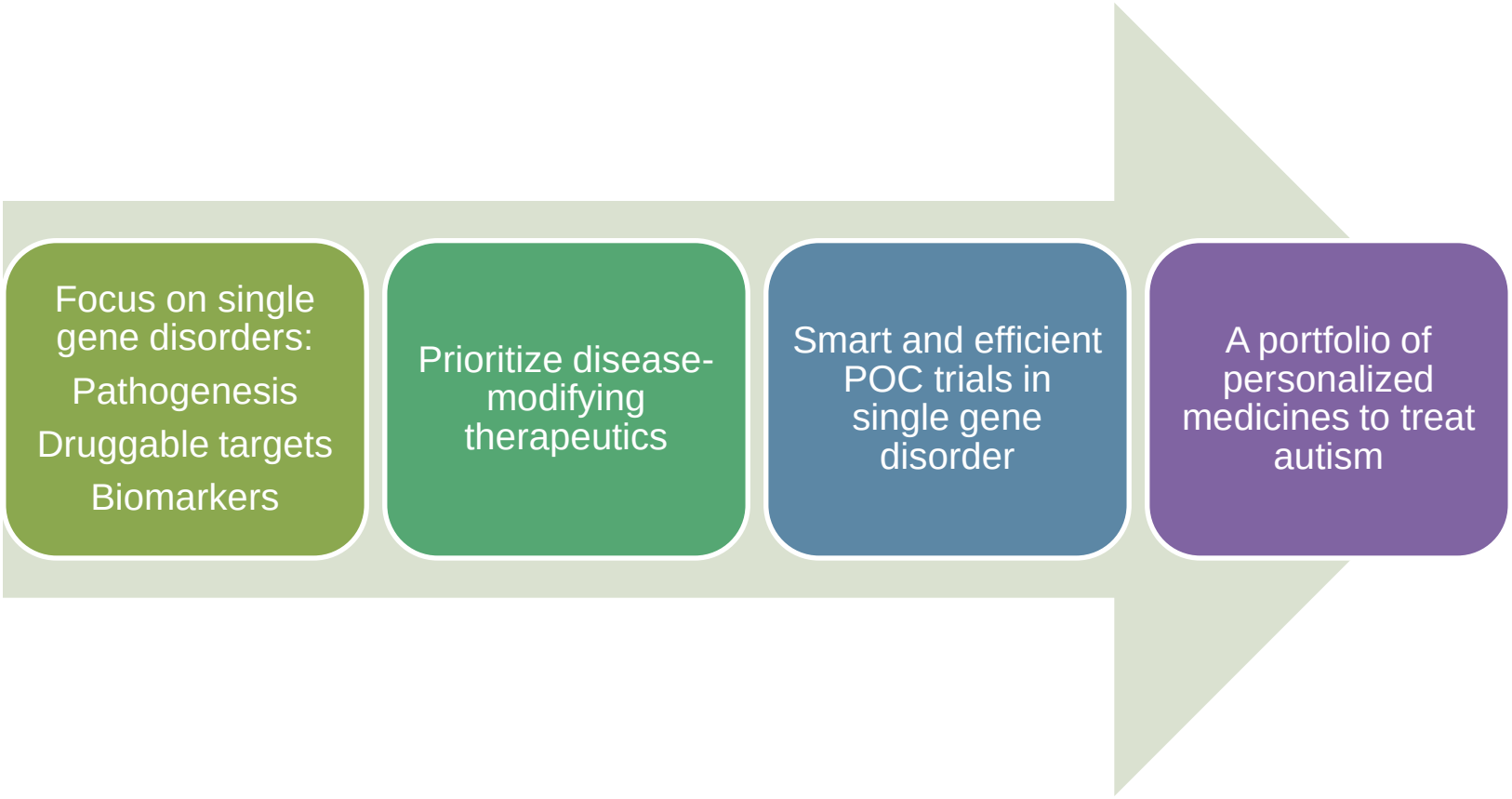
Discovering New Treatments for Autism



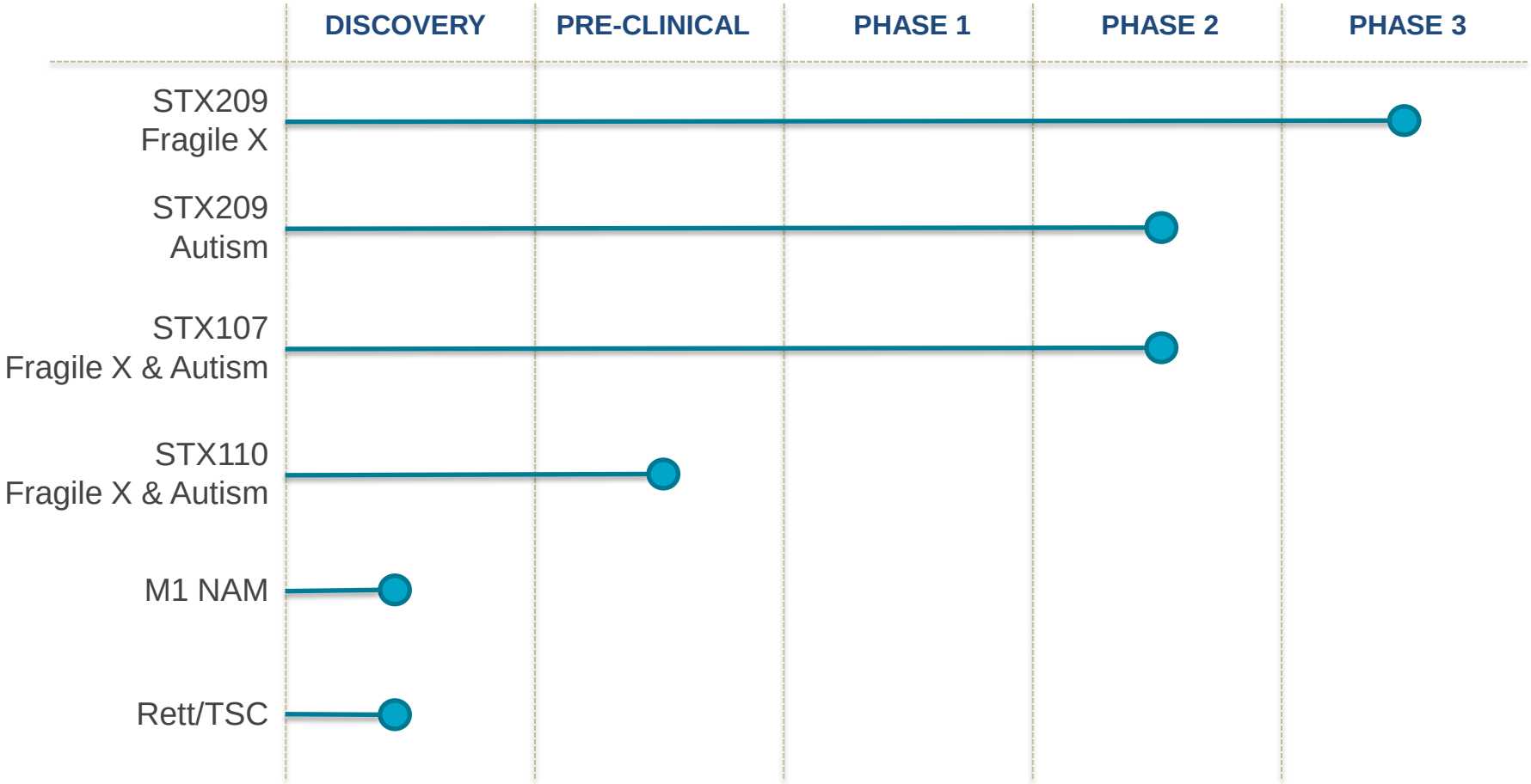
Leveraging therapeutic insights from single gene mutations to develop personalized treatments for autism

Vision and Strategic Focus

Discover and Develop a Portfolio of Personalized Medicines to Treat Autism



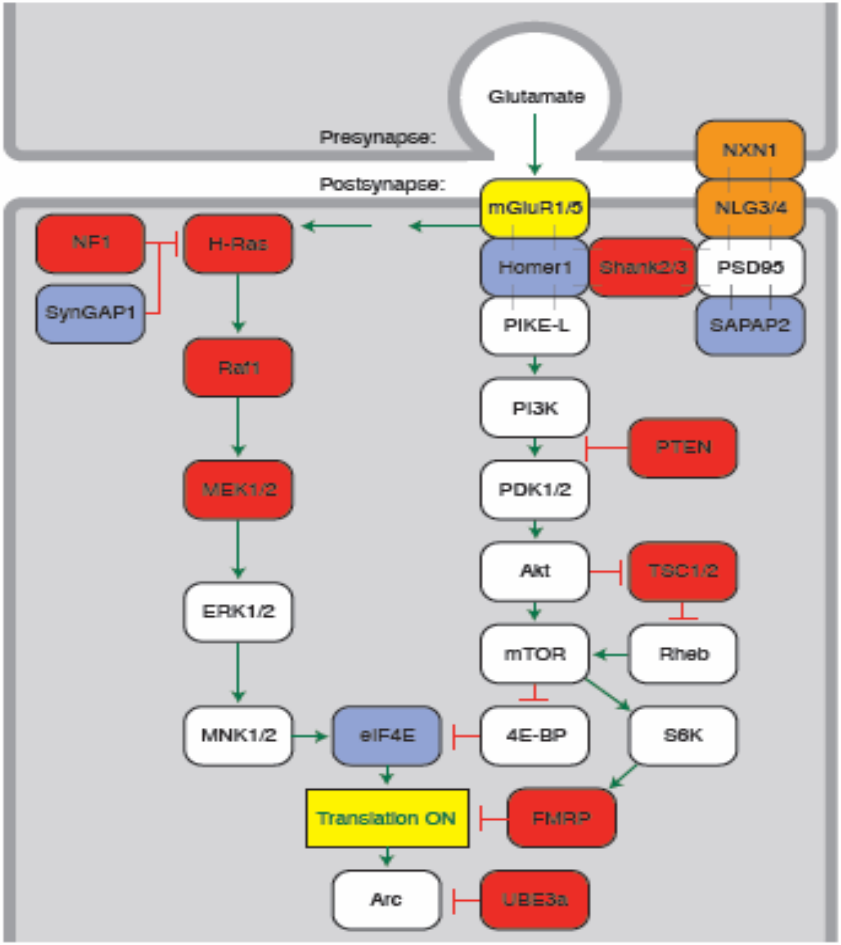
Pipeline of Personalized Therapeutics



Opportunity for Targeted Treatments for Idiopathic ASD

- Recent evidence suggests that genetic and environmental risk factors converge to perturb a common set of molecular signaling pathways in the brain
  - Preponderance of penetrant mutations in genes associated with synaptic structure and function
  - Therapeutic developed for one mutation may benefit individuals with other mutations in the same pathway
- Efficacy of mGluR5 antagonists demonstrated in animal models of
  - Idiopathic autism (Silverman 2010)
  - Environmental toxin induced autism (Gandal 2010)

Diverse Genetic Mutations Converge on Brain Signaling Pathways That Regulate Synaptic Function



Syndromic disorders with increased prevalence of ASD

- Phelan-McDermid Syndrome (Shank2/3)
- Noonan syndrome (Raf1, MEK1)
- Neurofibromatosis type 1 (NF1)
- Costello syndrome (H-Ras, MEK1)
- Cardio-facio-cutaneous (CFC) syndrome (MEK1/2)
- Cowden syndrome (PTEN)
- Tuberous sclerosis complex (TSC1/2)
- Fragile X syndrome (FMRP)
- Angelman syndrome (Ube3a)

Rare mutations causing non-syndromic ASD:

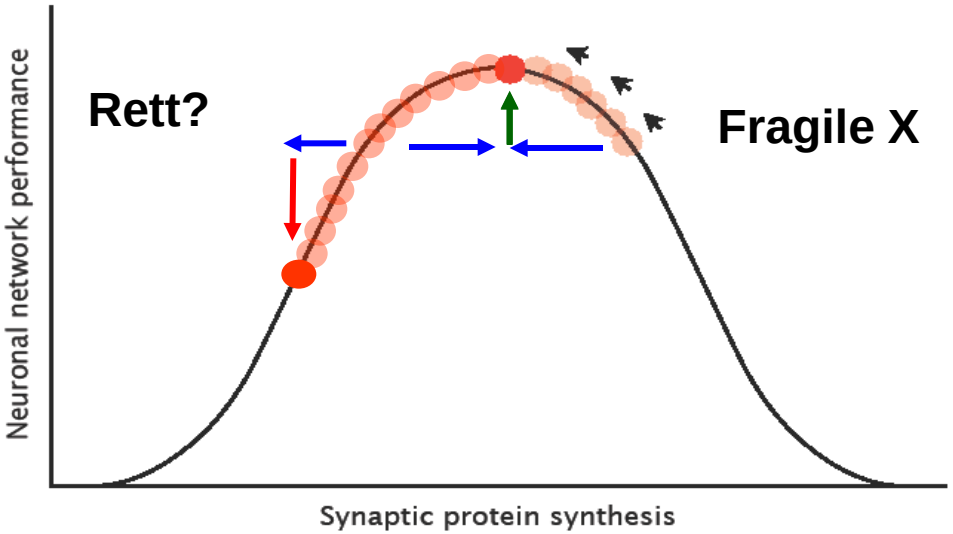
- NLG3/4
- NXN1

Rare structural variants associated with ASD:

- Homer 1
- SAPAP2
- SynGAP1
- TSC1/2
- Shank3
- eIF4E

Krueger and Bear, *Annu Rev Med*, 2011

Heterogeneity in Autism



Personalized Medicine Will Require Development of Autism Biomarkers

Predictive biomarkers

- For patient selection, by identifying patients more likely to show a favorable response to treatment

Pharmacodynamic markers

- Molecular marker of drug response, to facilitate selecting the optimal drug dose

Seaside Therapeutics

Translating breakthrough discoveries in neurobiology into innovative drug treatments that improve the lives of patients and families with fragile X syndrome, autism and other neurodevelopmental disorders