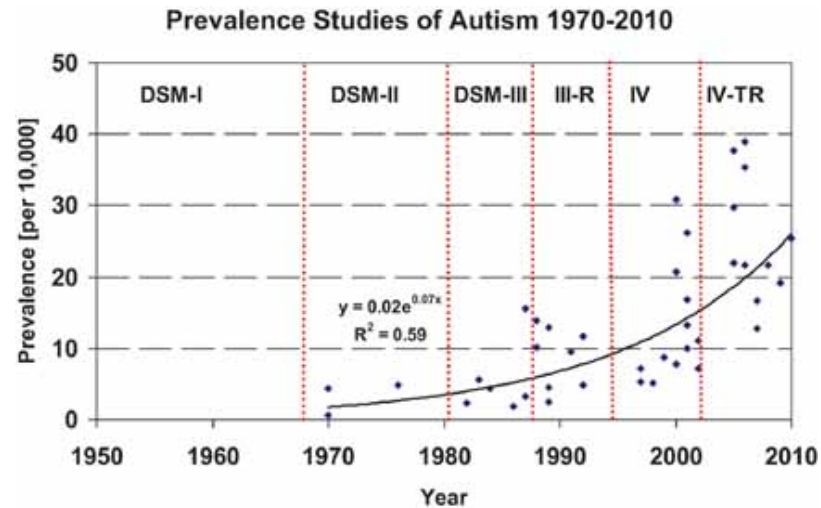


Current therapeutic strategy on childhood neurological diseases: a reflection from multicenter

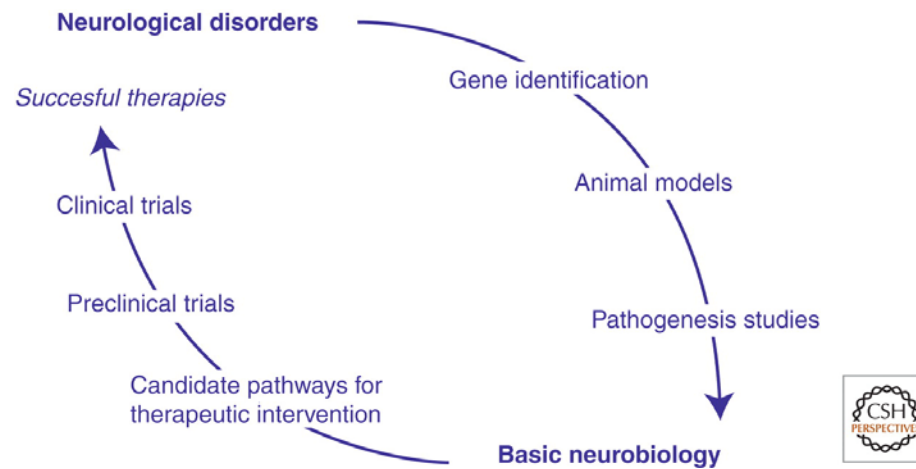
Ming Tong MD, MBE

Biomedical Advances of Autism 2012
Harvard Medical affiliated Mclean Hospital

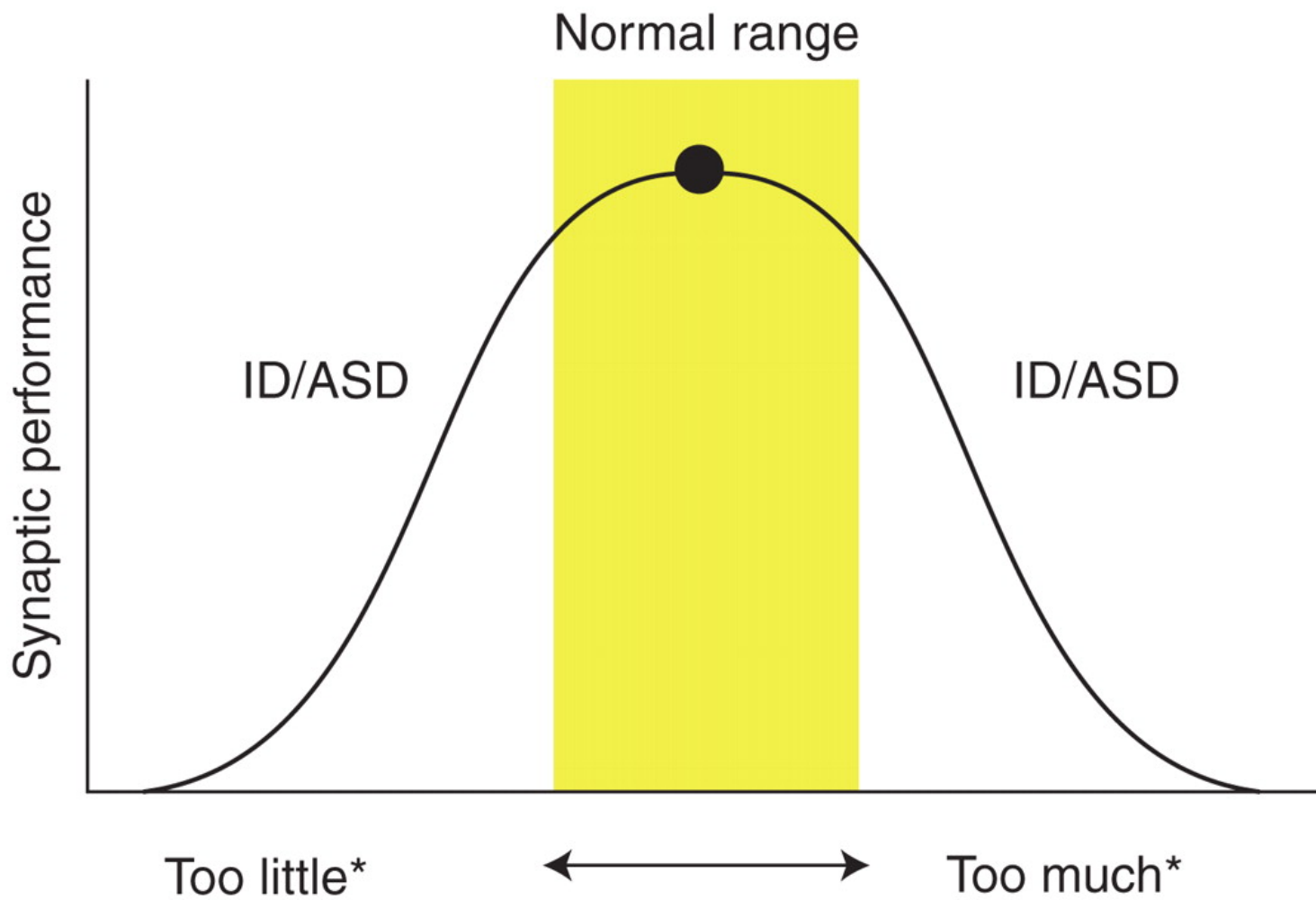
Nosology and epidemiology in autism: Classification counts



The promise of molecular medicine in genetically defined disorders of brain development.



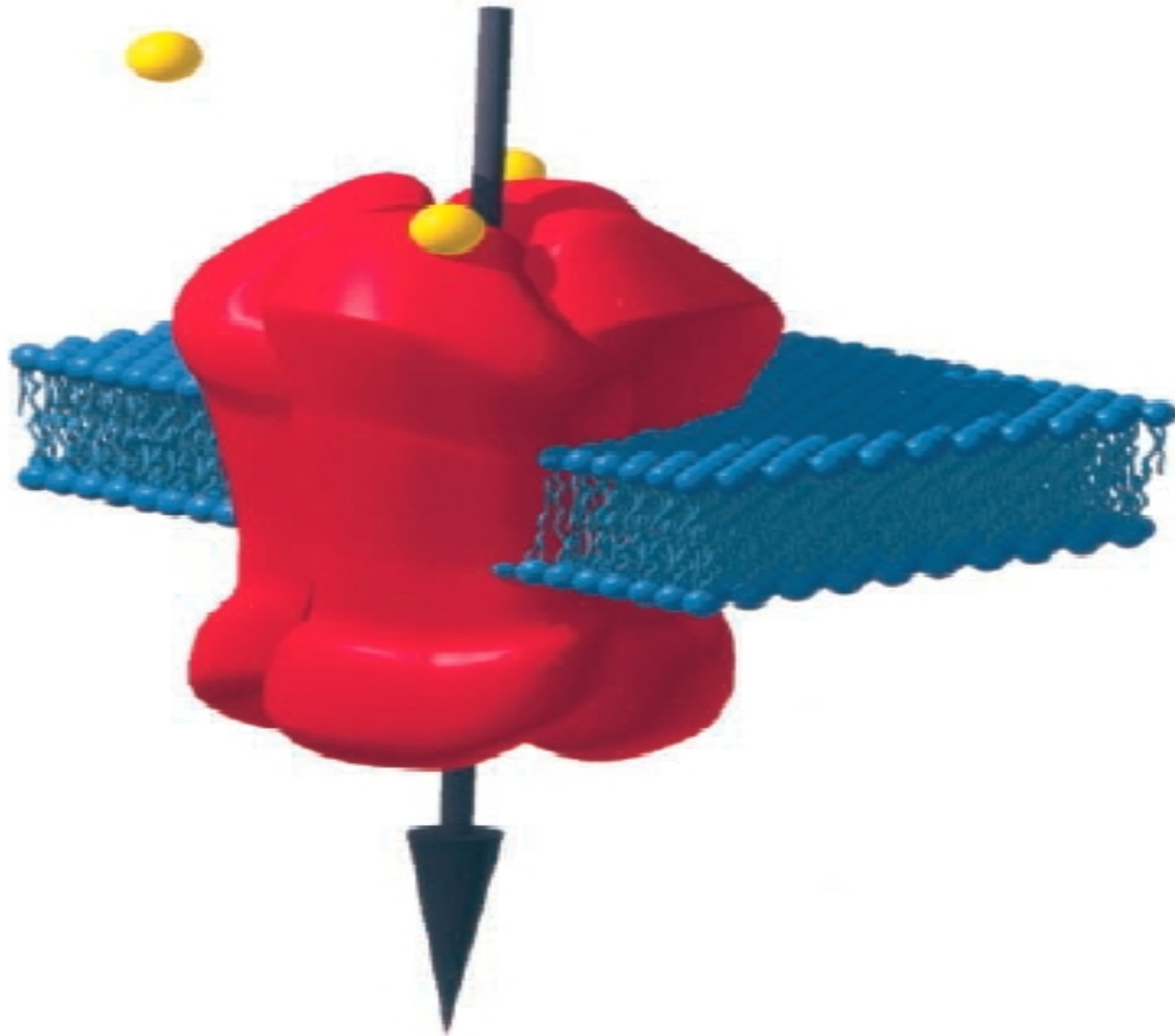
Zoghbi H Y , Bear M F Cold Spring Harb Perspect Biol
2012;4:a009886



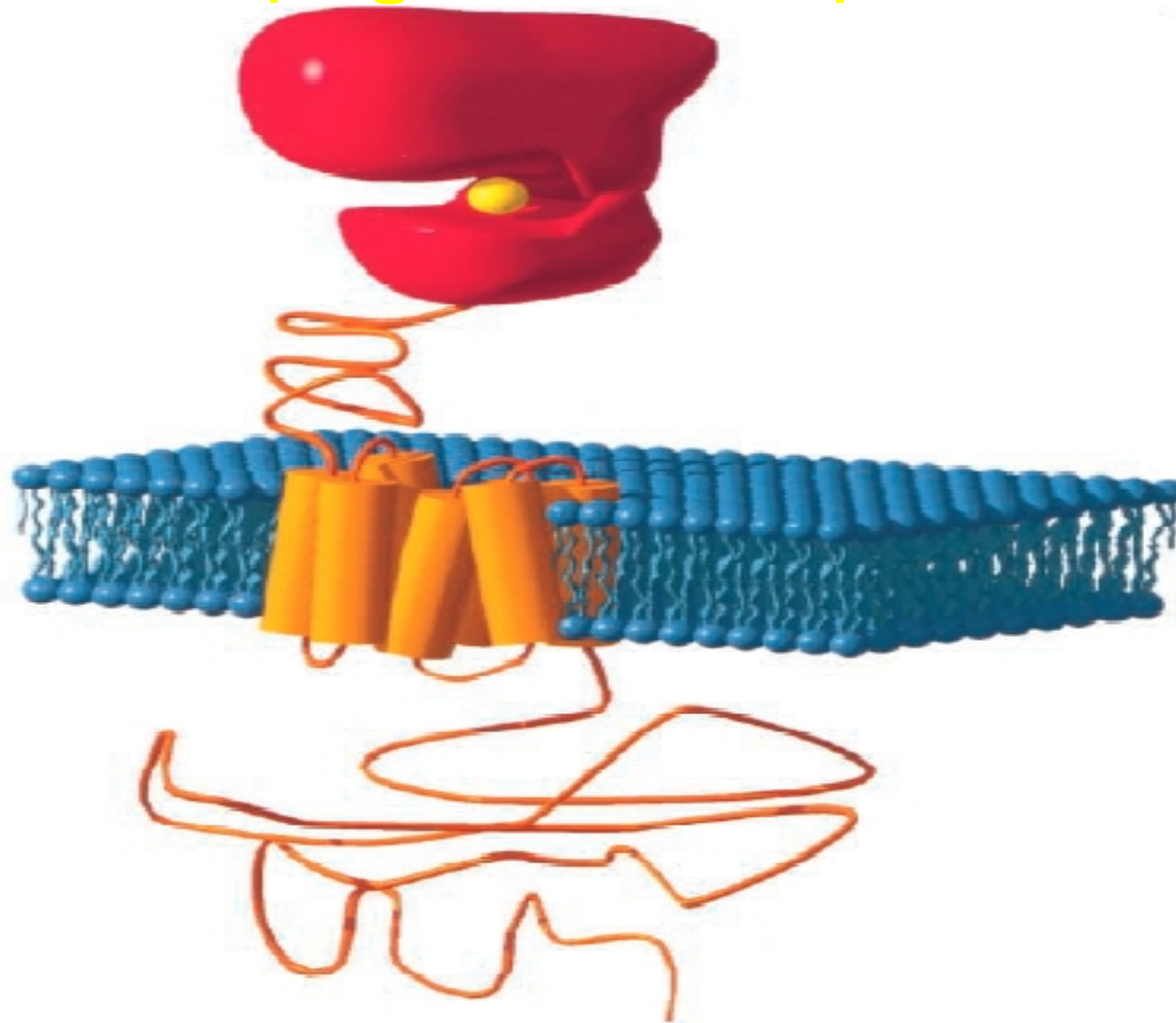
*SHANK3, NRXN1, MeCP2, synaptic protein abundance, etc.

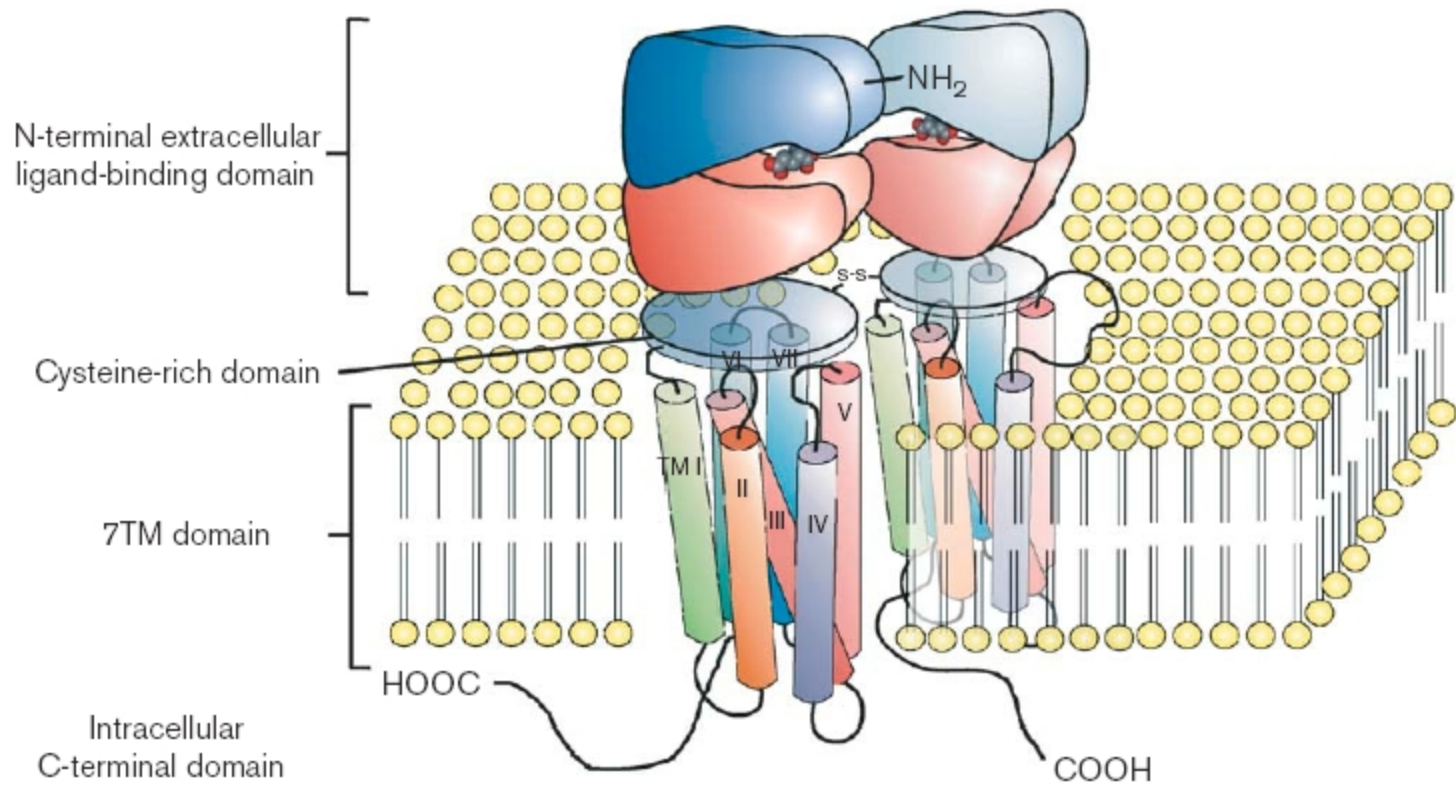
Moving from genes to receptors

Schematic Structure of ionotropic glutamate receptors



Schematic Structure of metabotropic glutamate receptors

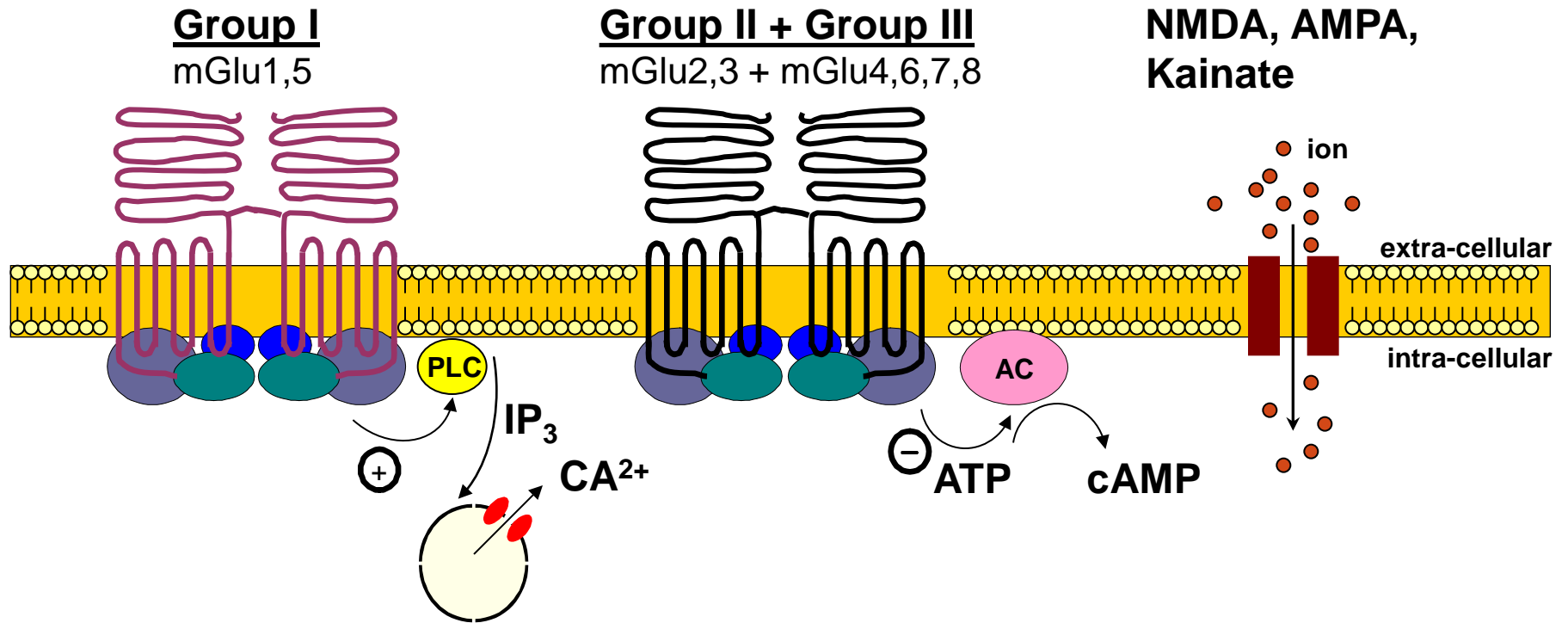




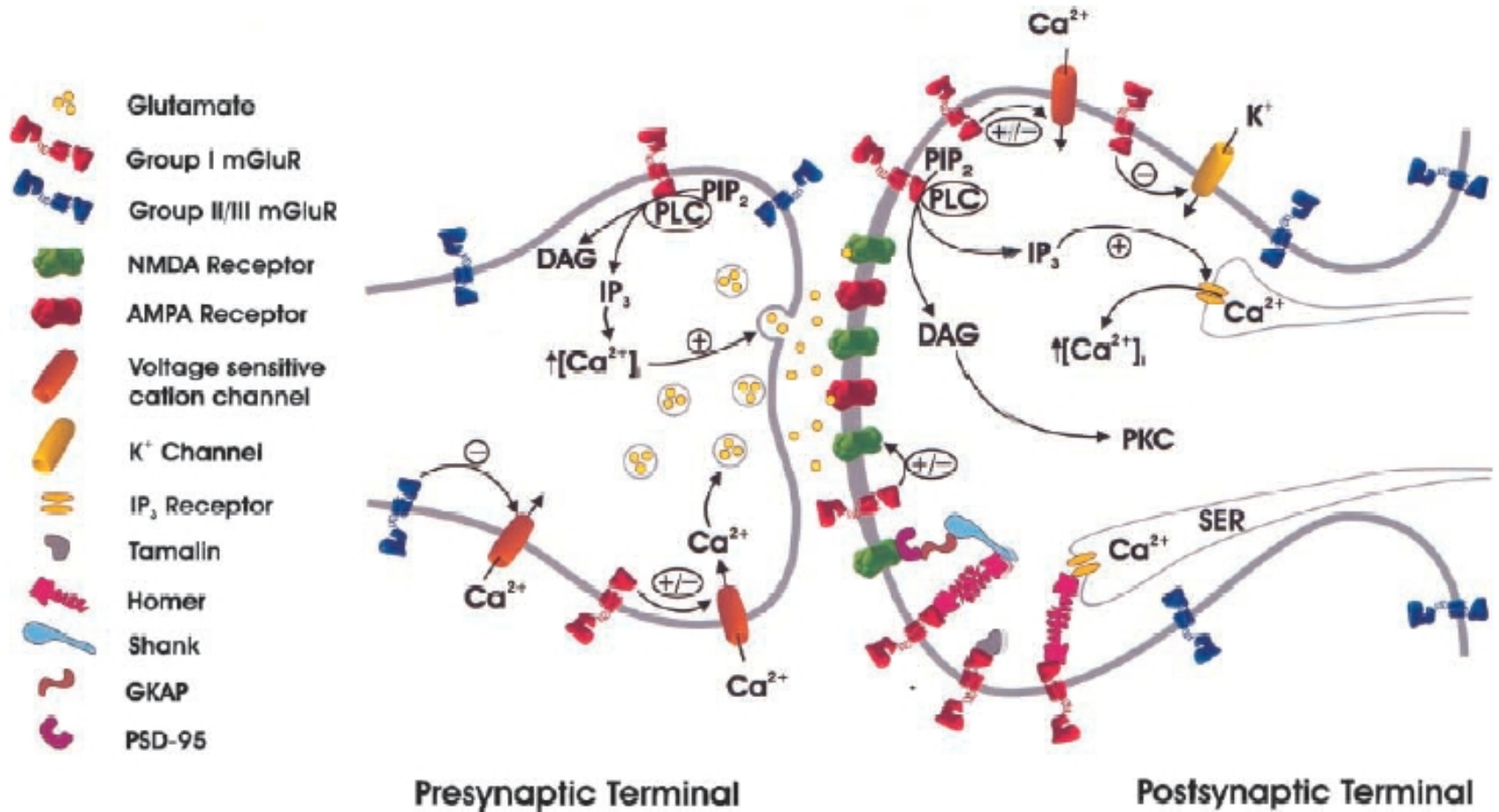
Spooen W. et. al., 2003

Metabotropic receptors

Ionotropic receptors



Schematic representation of the chemical and molecular signaling pathways mediated by mGluRs at glutamatergic synapses



Moving from receptors to systems

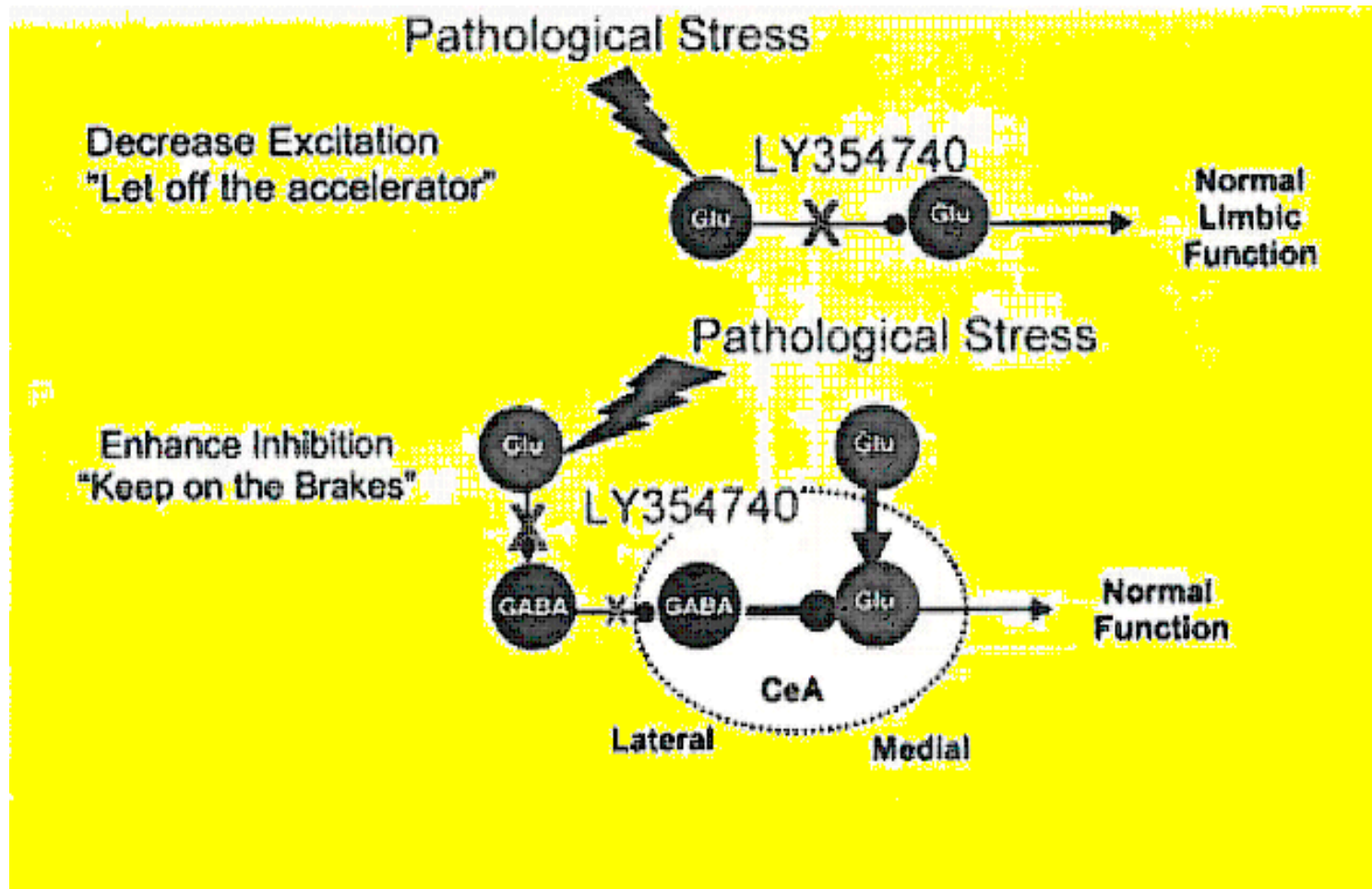
Prospects & Concerns

- **Synapse Configuration & Circuitry-dependent**
(Schoepp's model in limbic systems, APA, 2003)
- **Complex neuron-neuron/neuron-glia**
interaction
(Aronica's new findings, 2003)

Mills CD et al, 2002 Jan, Fundytus ME, 2001 Jan,

Sung B, Lim G & Mao J, 2003 April

Schoepp's Model

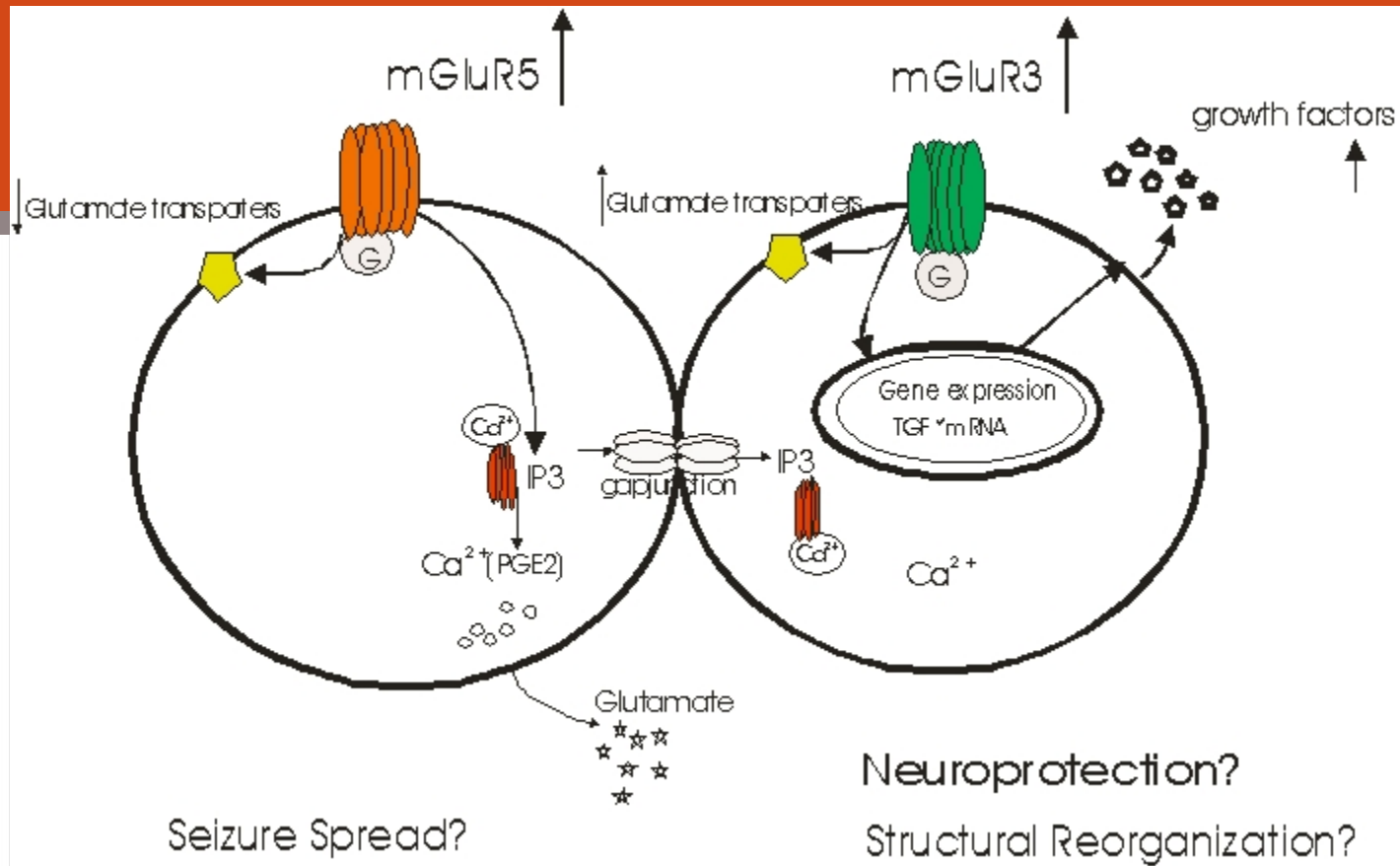


Schoepp's model in limbic systems,

APA, 2003

Functional role of mGluR5 and mGluR3 in reactive astrocytes

It might depend on the neuron-glia signalling at a particular moment which effect might be promoted (Professor Aronica, MD-PhD)



Excitotoxicity ?

Cytokines



Insights from Comparative CNS drugs development

- **Novel mGluR & iGluR drugs as comparative modulators**
- **Side effect profile comparable to risperidone (2006) ?**
- **Comparative studies from CB1R**

Moving to clinical studies/database



U.S. Food and Drug Administration
Protecting and Promoting Public Health

Safety results:

Commonly observed adverse reactions in short-term, placebo-controlled trials of pediatric patients (6-17 years) with Autistic Disorder treated with oral Abilify®

Percentage of Patients Reporting Reaction

Aripiprazole

Placebo

Preferred Term

(n=212)

(n=101)

Sedation

21

4

Fatigue

17

2

Vomiting

14

7

Somnolence

10

4

Tremor

10

0

Pyrexia

9

1

Drooling

9

0

Decreased Appetite

7

2

Salivary Hypersecretion

6

1

Extrapyramidal Disorder

6

0

Lethargy

5

0

Rank	Status	Study
1	Recruiting	Interoception and Learning in Autism
		Condition: Autism Spectrum Disorder
		Intervention: Drug: Intranasal Oxytocin (Trade name: Syntocinon)
2	Recruiting	Interoception for the Treatment of Autism Spectrum Disorder
		Condition: Autism Spectrum Disorder
		Intervention: Drug: Intranasal Oxytocin; Drug: Placebo
3	Completed	Interoception for the Treatment of Autism
		Condition: Autism
		Intervention: Drug: Oxytocin; Drug: Placebo; Comparator
4	Recruiting	Interoception for the Treatment of Autism Spectrum Disorder
		Condition: Autism Spectrum Disorder
		Intervention: Drug: oxytocin
5	Recruiting	Interoception Treatment for Social Difficulties in Children With Autism
		Condition: Autism
		Intervention: Drug: Oxytocin nasal spray; Drug: Placebo
6	Active, not recruiting	A Study of Oxytocin in Children and Adolescents With Autism Disorder
		Condition: Autism
		Intervention: Drug: Oxytocin nasal spray; Drug: Placebo; Unknown
7		The Effects of Oxytocin on Complex Social Cognition in Autism Spectrum Disorder
		Condition: Autism; ASD
		Intervention: Drug: Syntocinon
8	Unknown	The Effect of Intranasal Oxytocin, Placebo on Response Inhibition and Face Processing in Autism
		Condition: Autism
		Intervention: Drug: Oxytocin
9	Recruiting	Brain Response to Social Adults With Autism Spectrum Disorder
		Condition: Autism Spectrum Disorder
		Intervention: Drug: Oxytocin; Drug: Vasopressin
10	Completed	Interoception Study: Beta-oxo-Pancre-Willy Patients With Late-Onset Prader-Willi Syndrome
		Condition: Prader-Willi Syndrome
		Intervention: Drug: Synthroid; Spray: Drug: Physiologic Saline (Sodium Chloride)
11	Active, not recruiting	Interoception Treatment for Children With Autism and Their Parents
		Condition: Autism Spectrum Disorder
		Intervention:

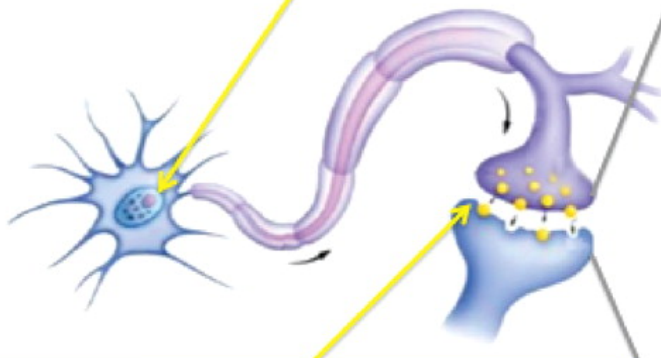
Found 11 studies with search of: **autism** oxytocin

Moving to validated pathways

A

Disorders of transcriptional dysregulation

- RTT – *MECP2*
- *MECP2* duplication disorders – *MECP2*
- ASD/ID – *MEF2C*
- RTS – *CBP* and *EP 300*



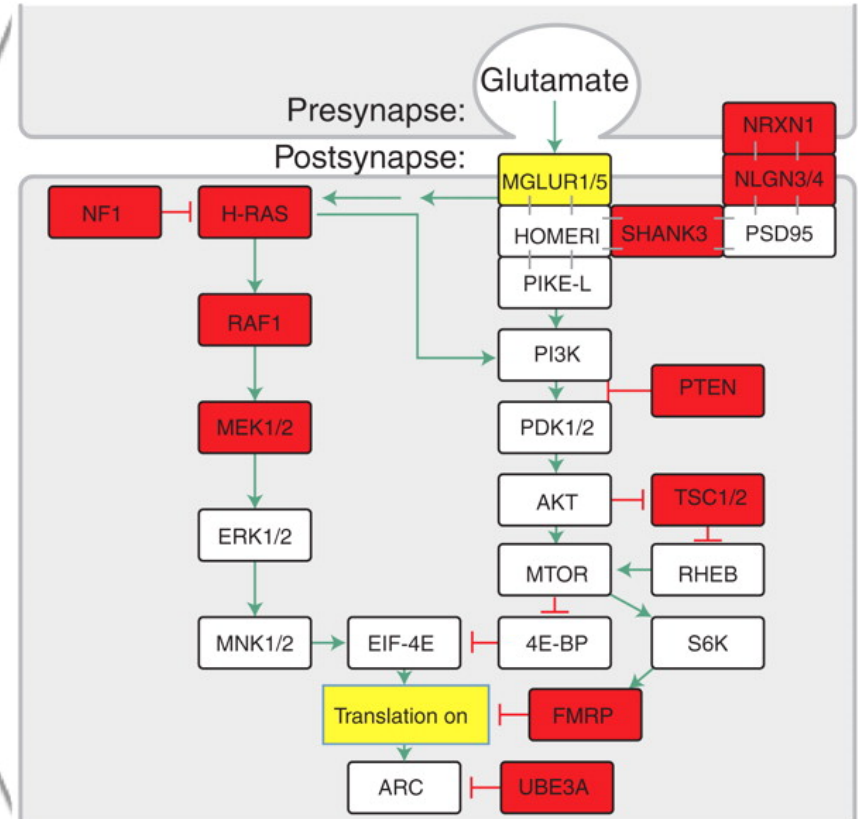
Disorders of synaptic scaffolding and structures

- PMS – *SHANK3*
- AS/ID – *NRXNs*; *NLGNs*; and *SHANK2*

Disorders of synaptic signaling

- FXS – *FMR1*
- AS – *UBE3A*
- TSC – *TSC1/TSC2*
- NF – *NF1*

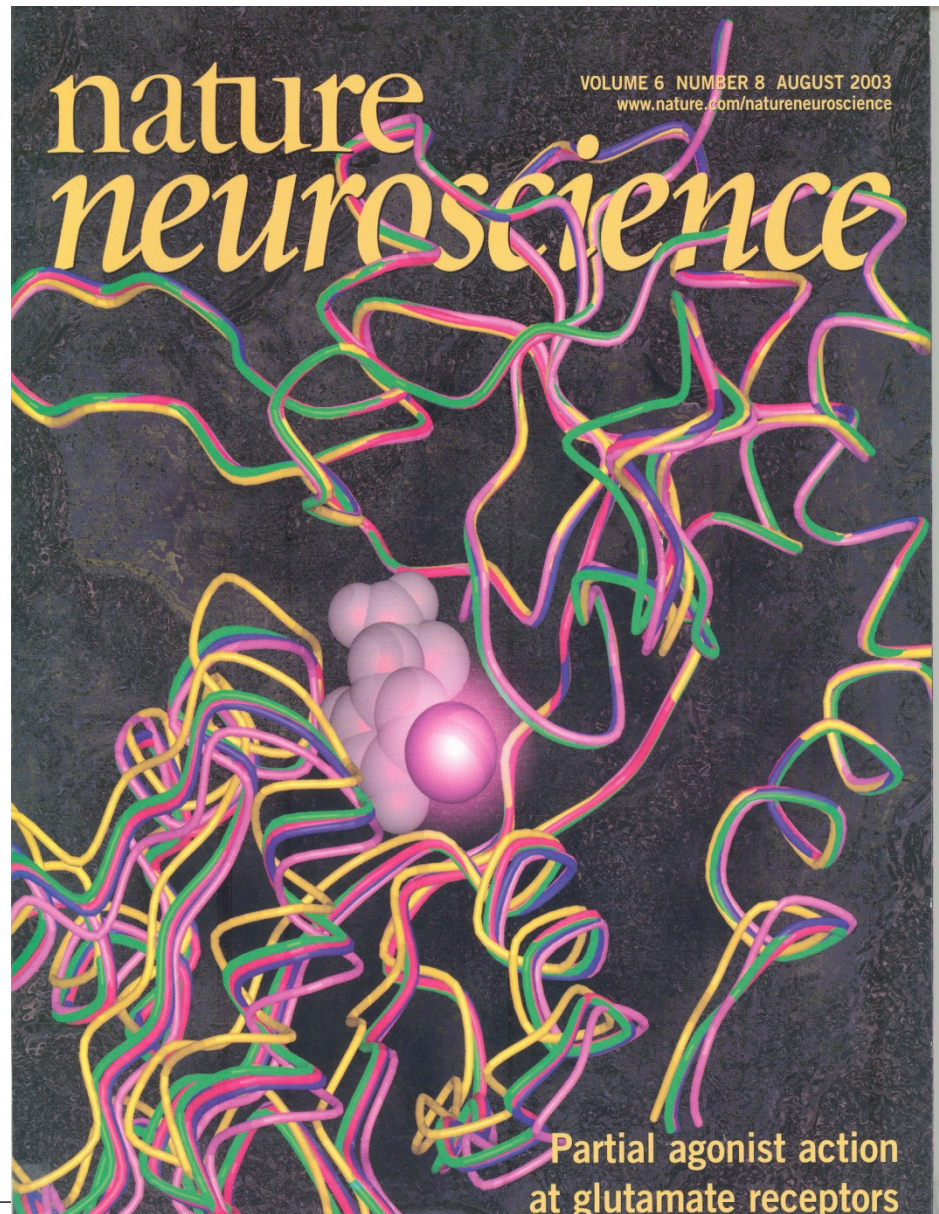
B



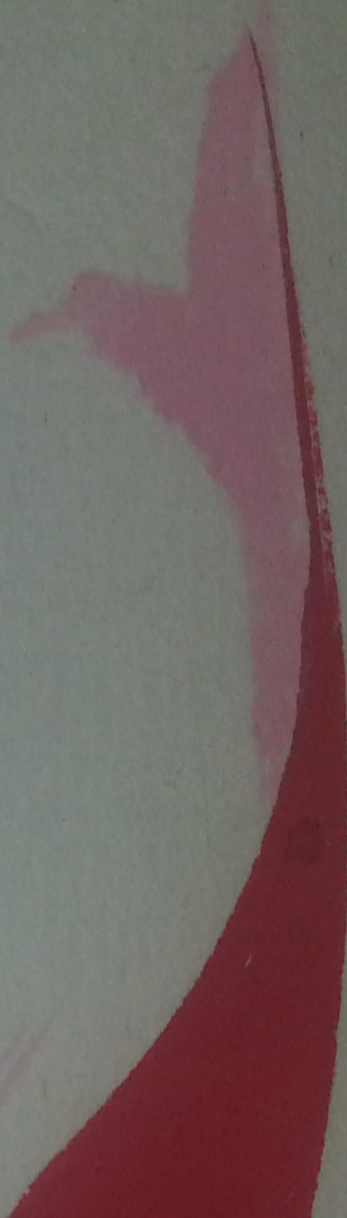
Current Trending

- Partial agonists ?
- Antisense oligonucleotides?

success story of other
glutamate receptor
ligands?







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