



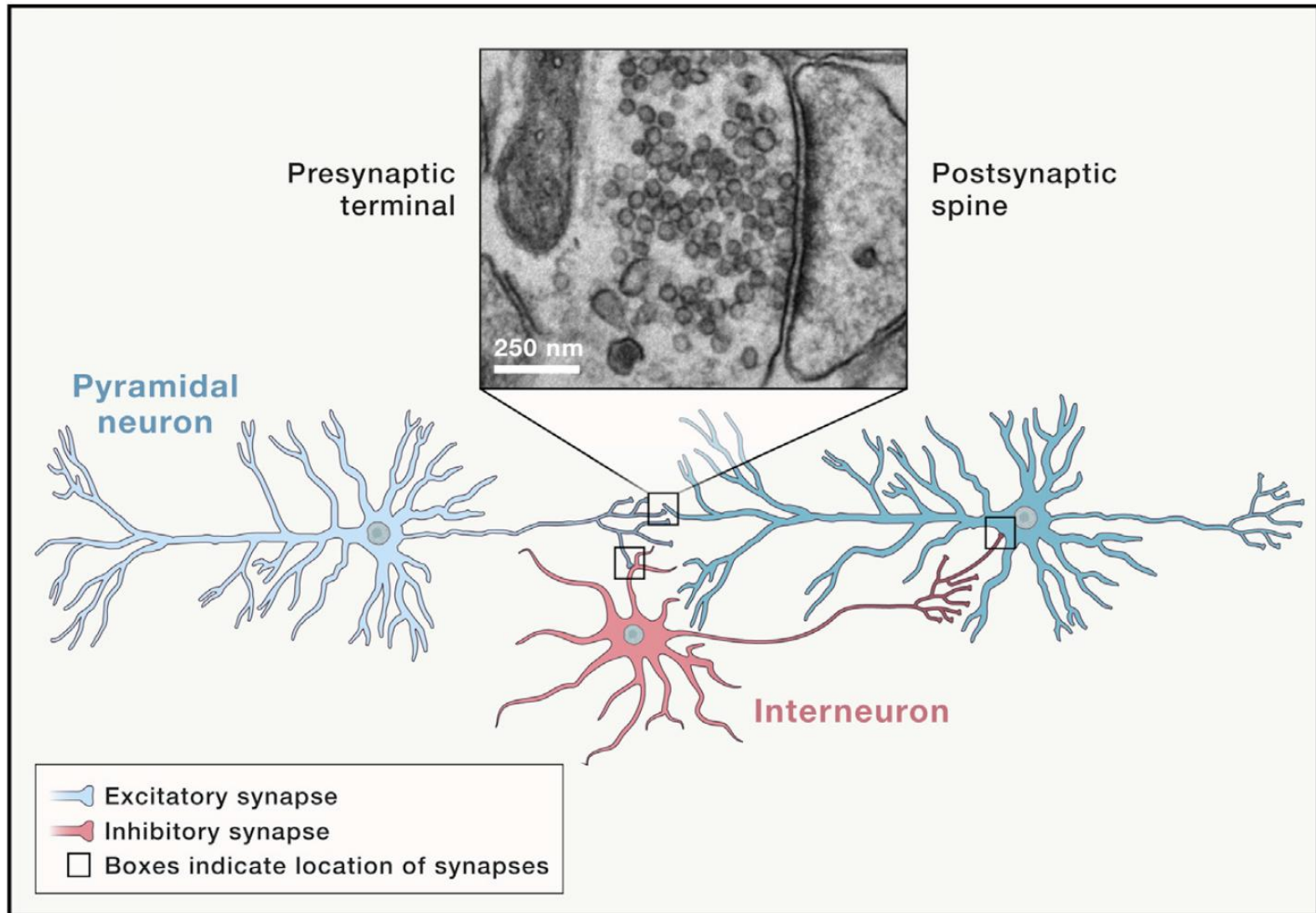
Center for
Synapse
Diversity &
Specificity

Synaptic cell-adhesion molecules in shaping neural circuit organization

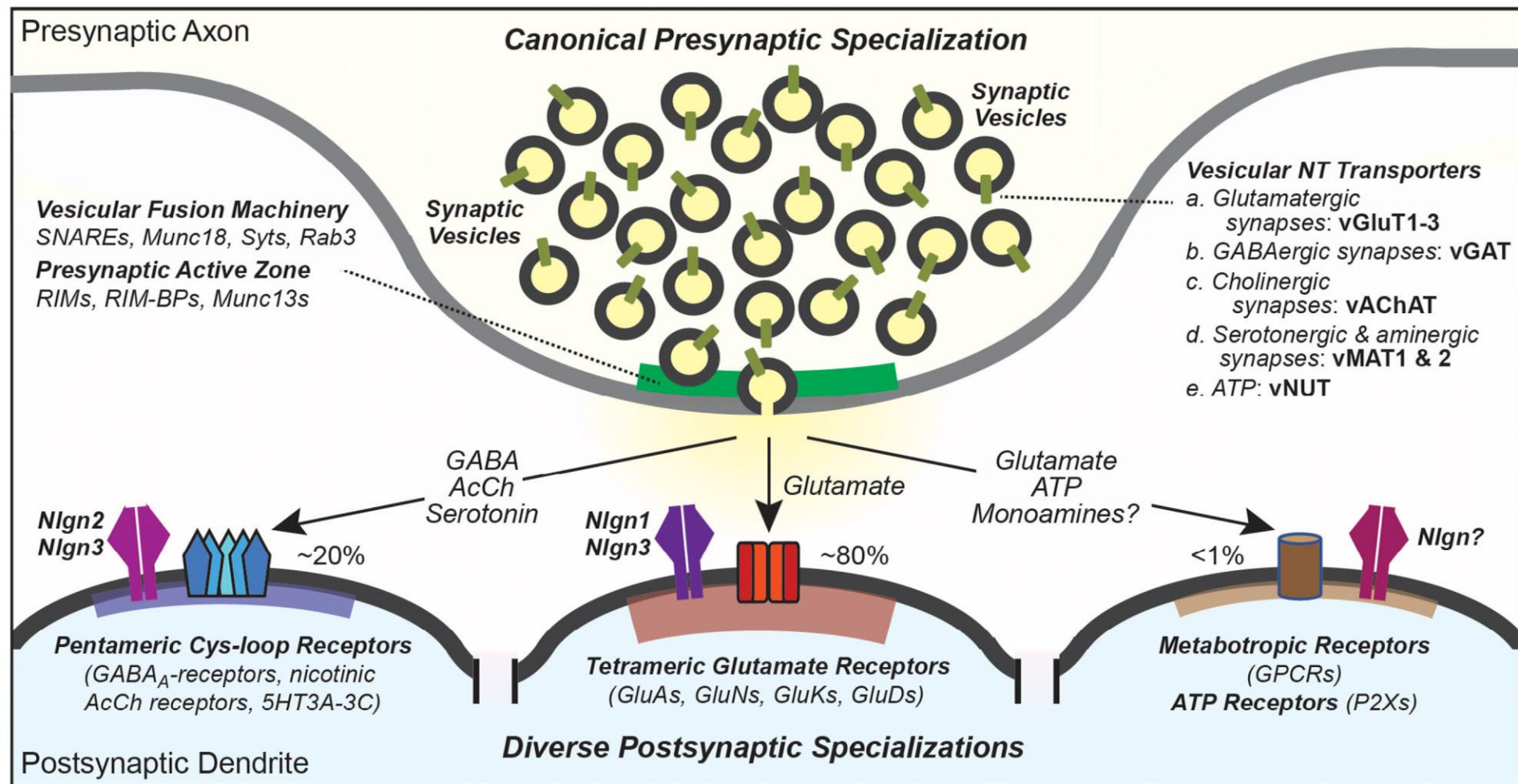


Jaewon Ko | Department of Brain Sciences, DGIST

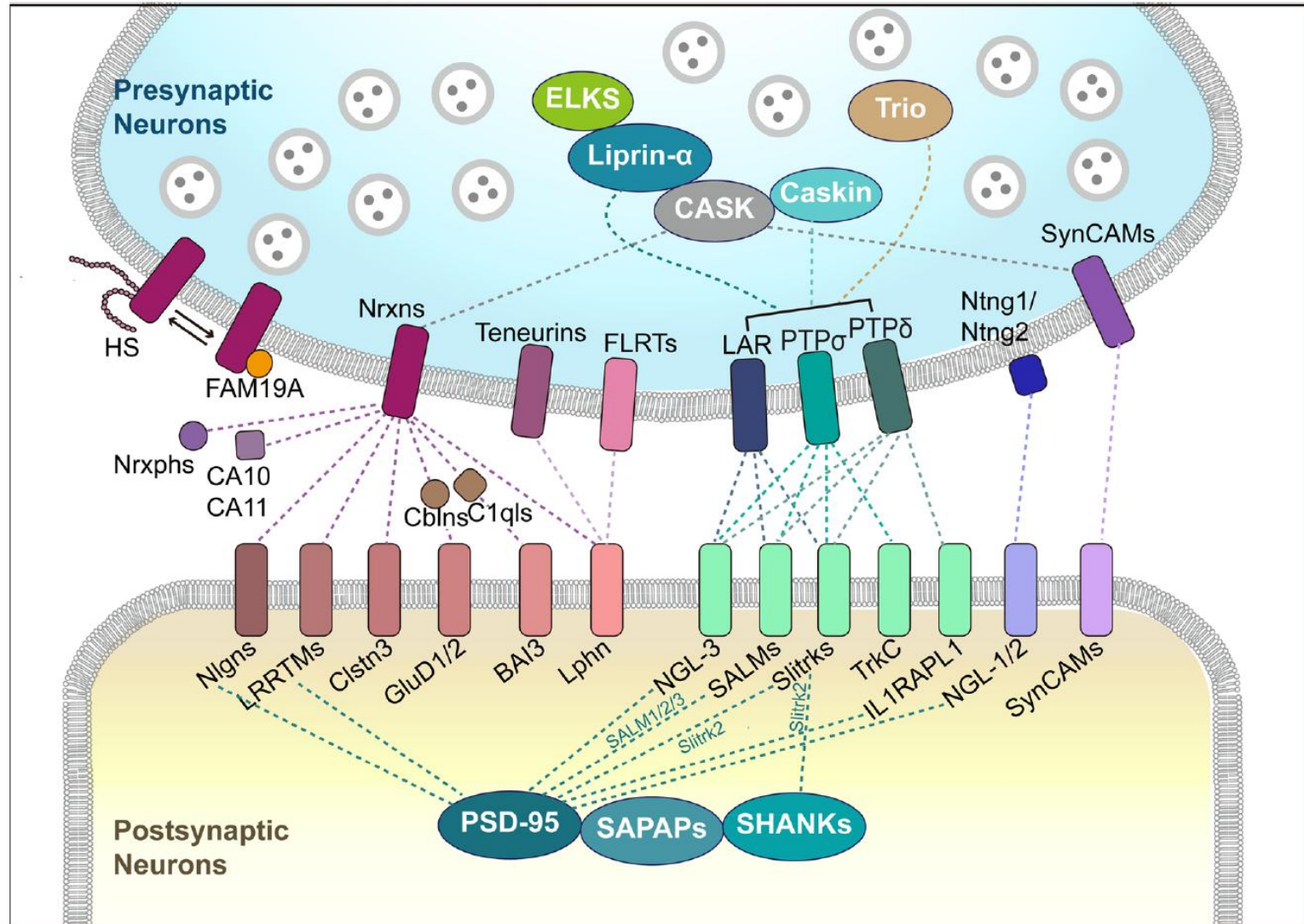
Neural circuits are directed by synapses



Design of pre- and postsynaptic specializations for synapse diversity

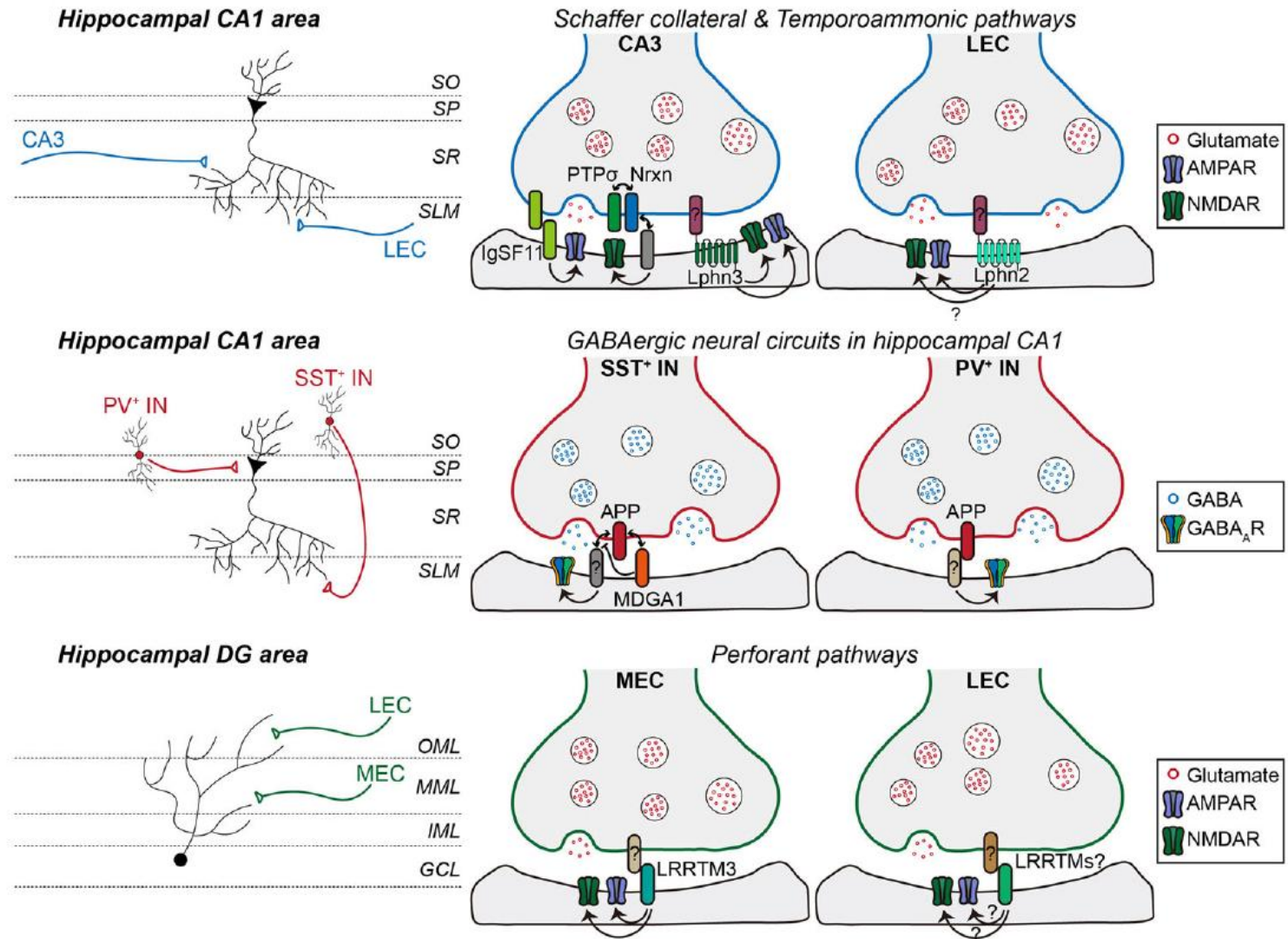


Many synaptic CAMs are described

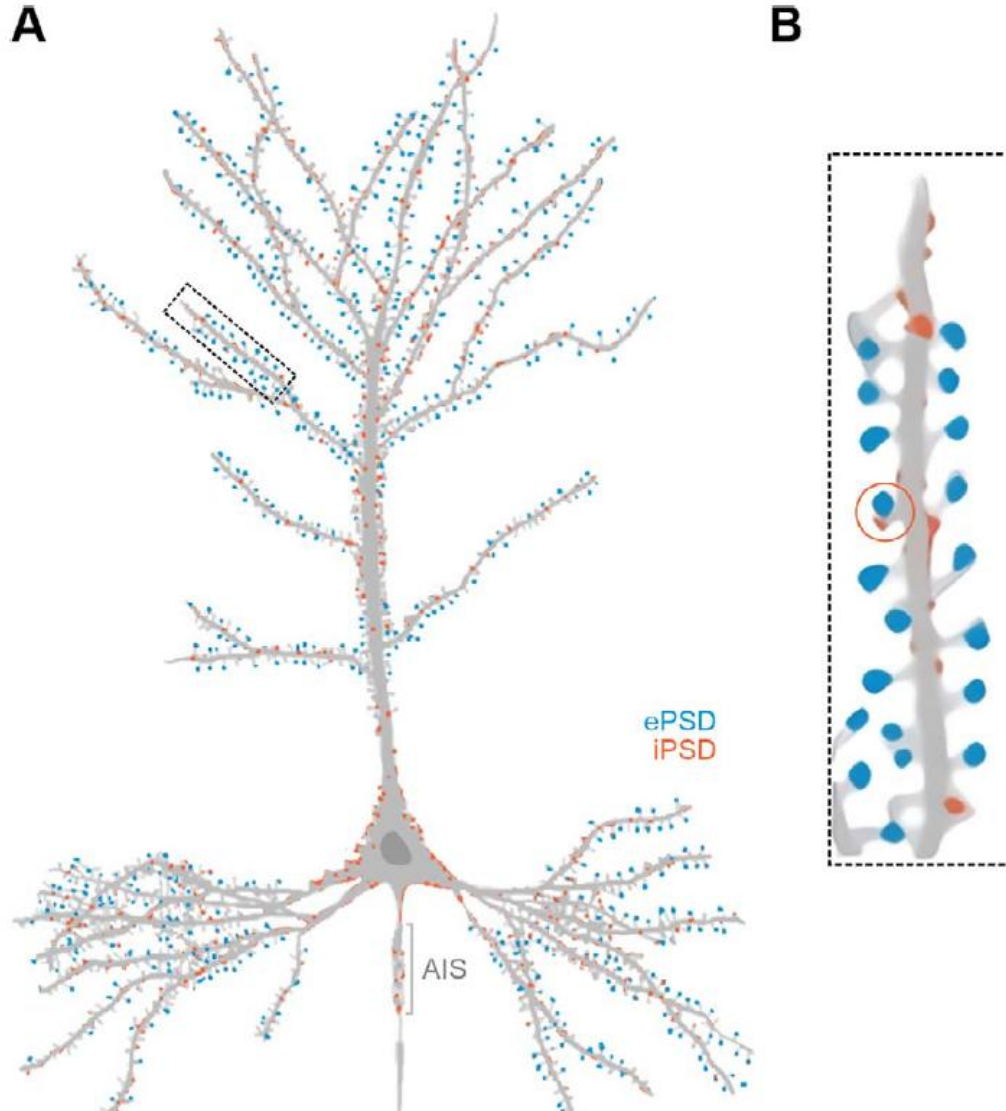


Postsynaptic CAMs

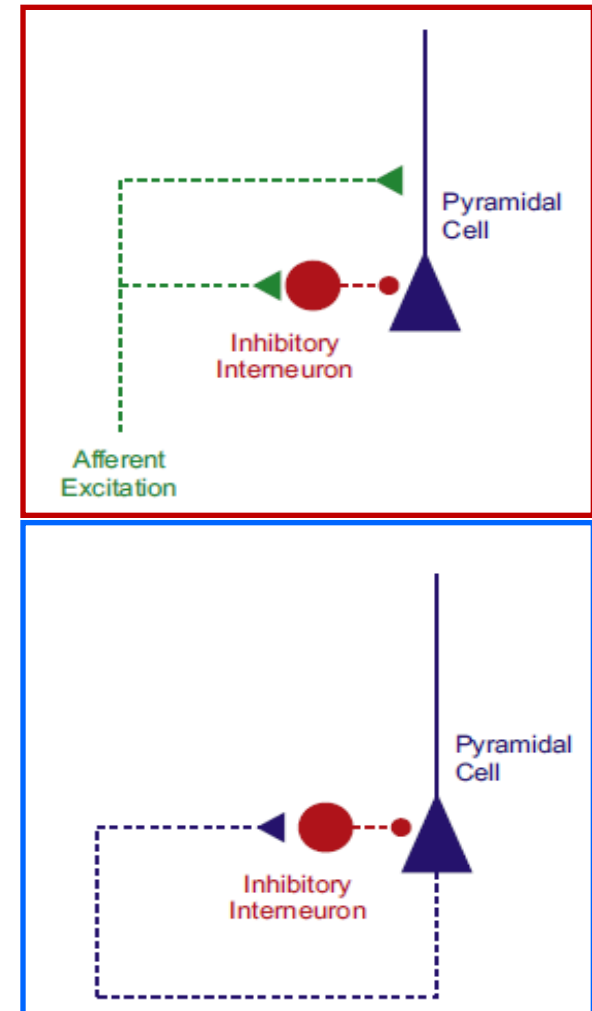
Engines for Synaptic Diversity



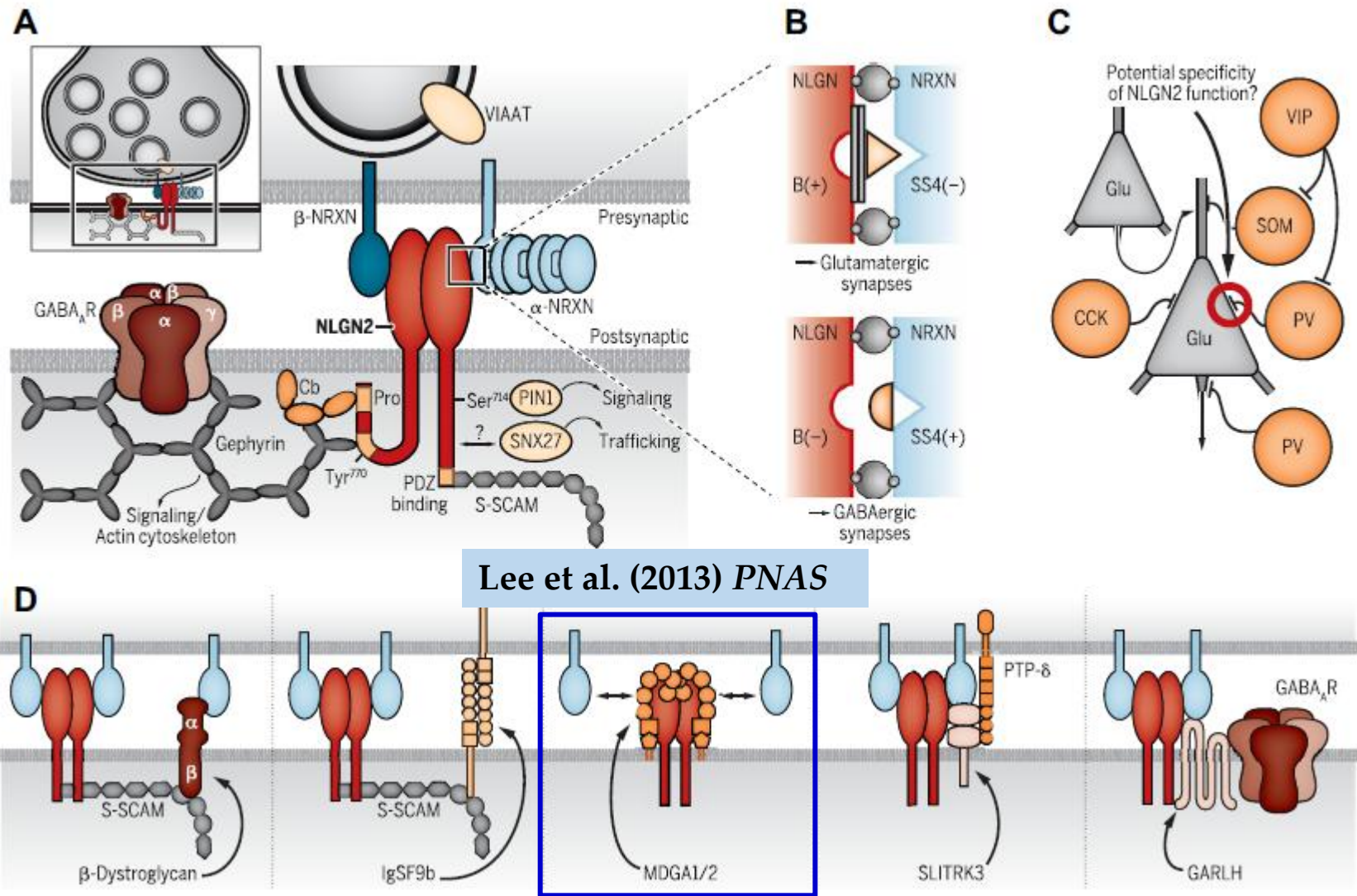
Synaptic properties: *inhibition motifs*



Feedforward & feedback inhibition

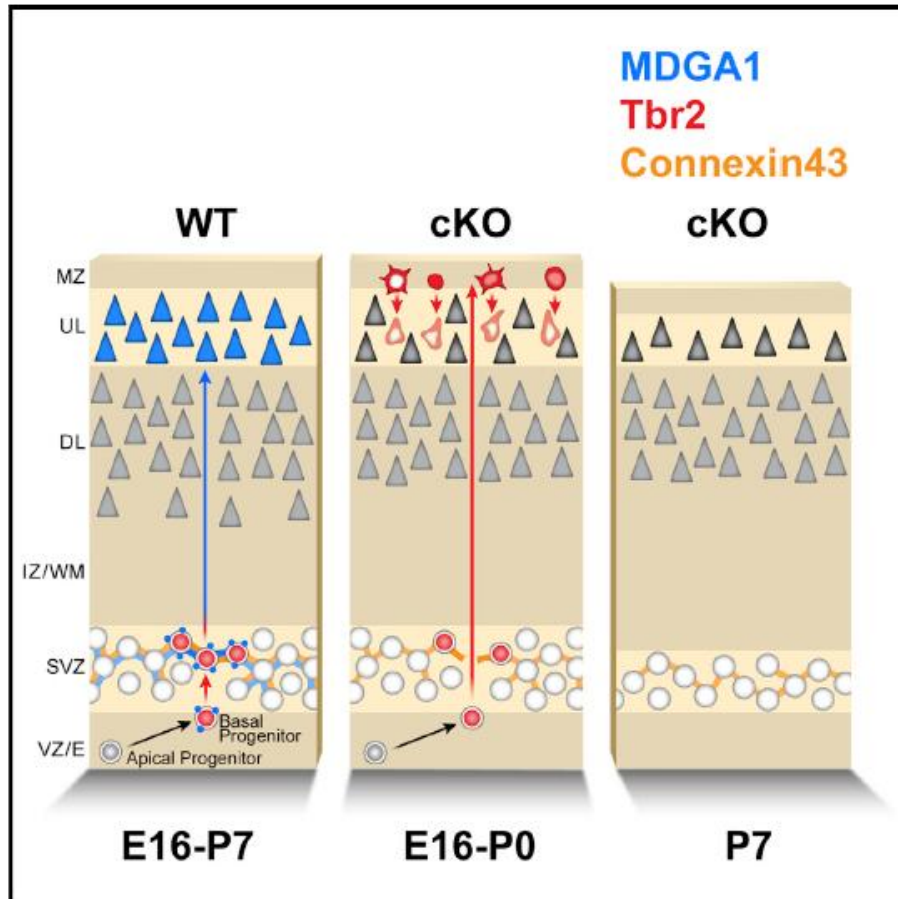


Structure & function of NLGN2: *a central organizer in shaping synaptic inhibition*



MDGA1: *a key factor in neuronal migration*

Dennis O'Leary & colleagues (Salk Institute)

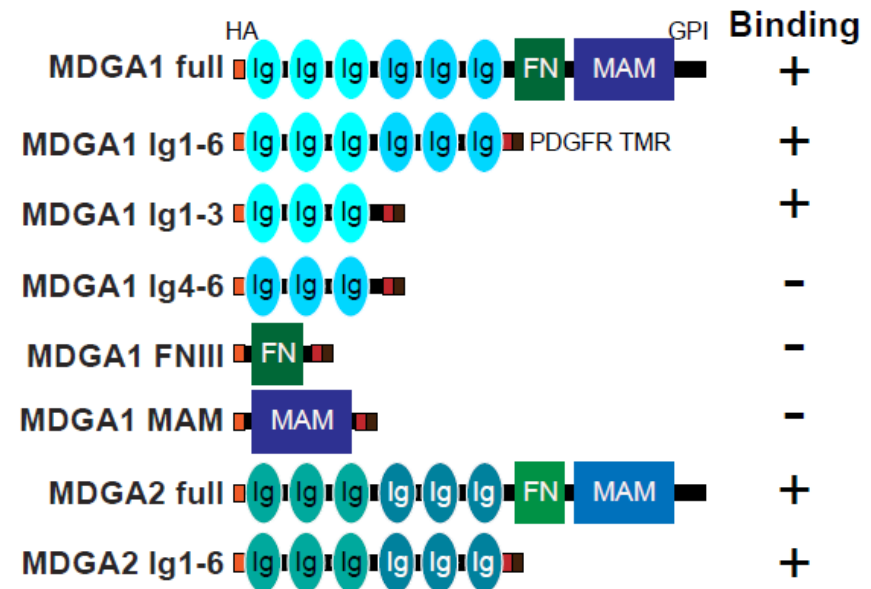
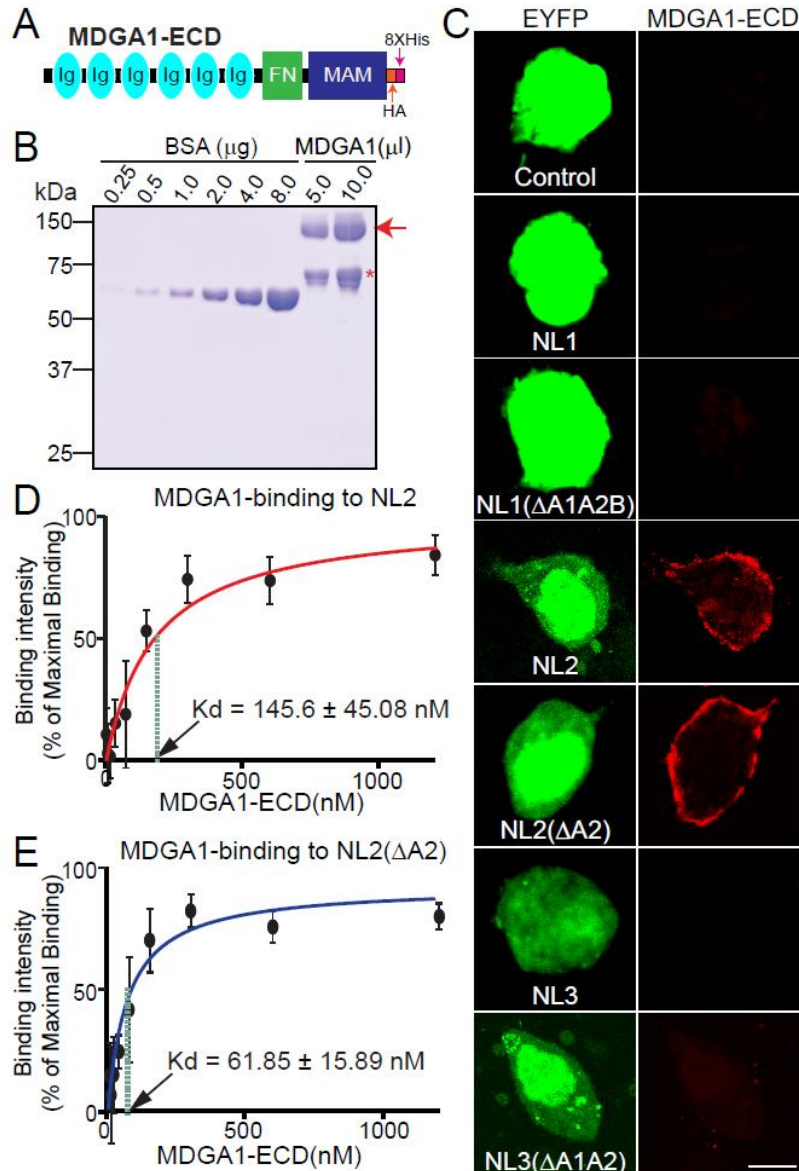


What we knew about MDGA1:

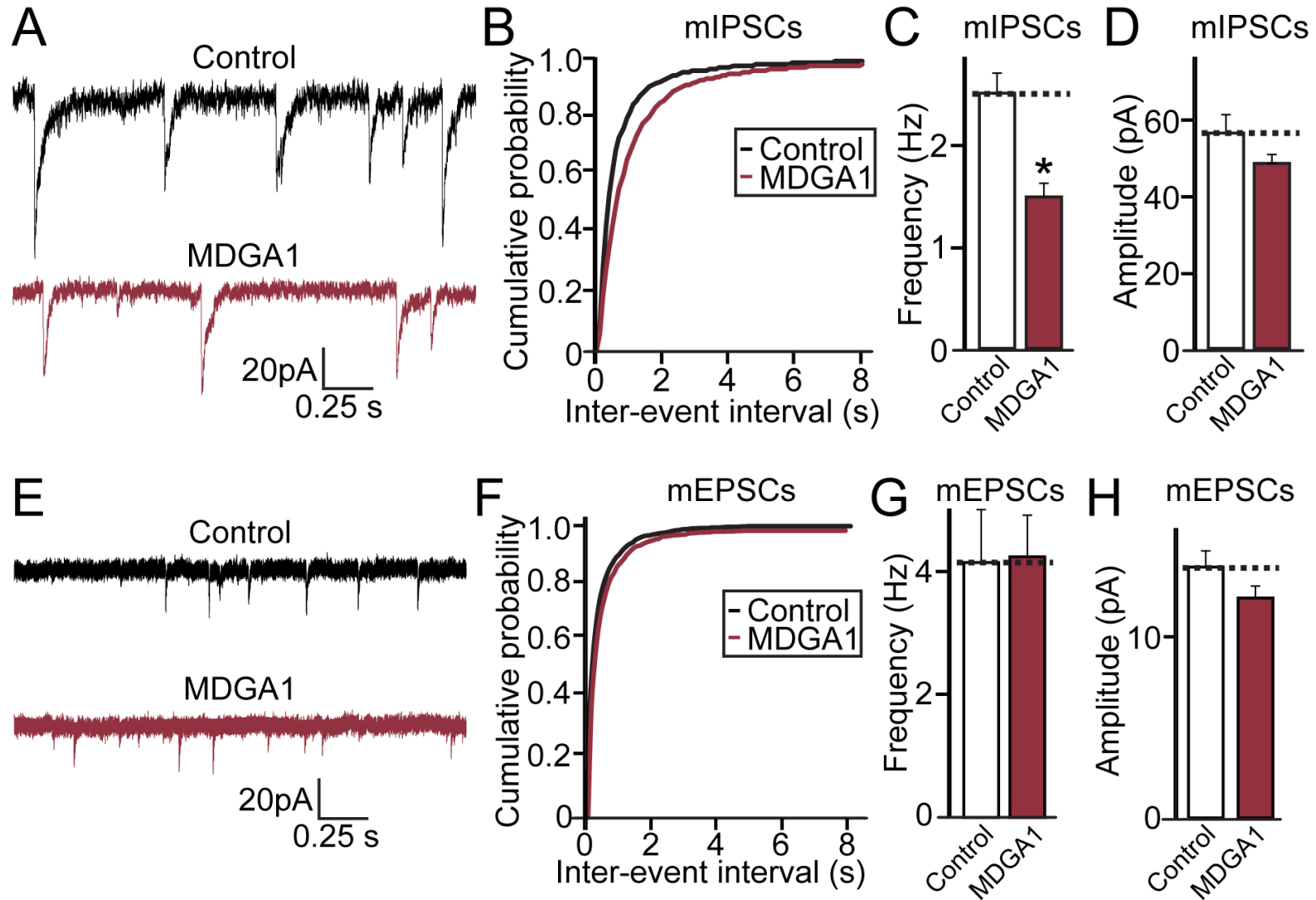
- Restrictive expression in the nervous system
- Critical for cortical neuron migration
- Not compensated by MDGA2
- High expression in embryos but lower expression in adults

Nothing was known about
'synaptic' roles of MDGAs when
we started to work on

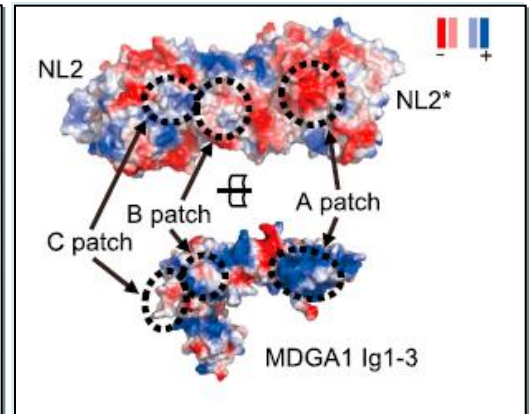
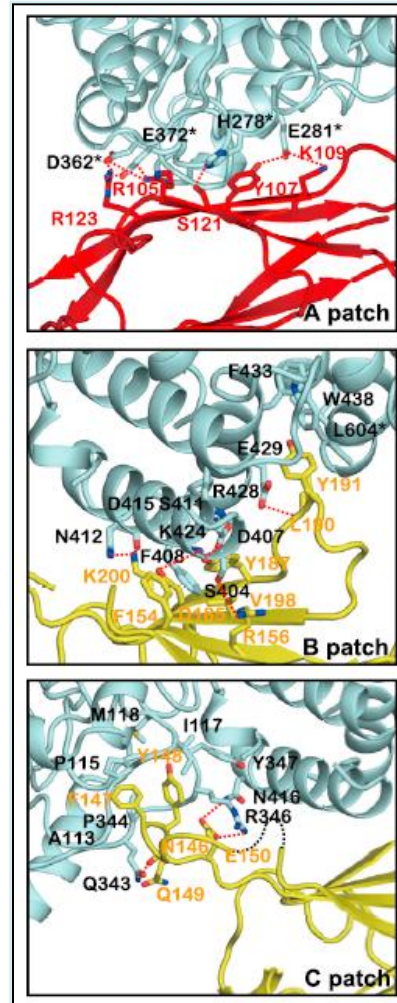
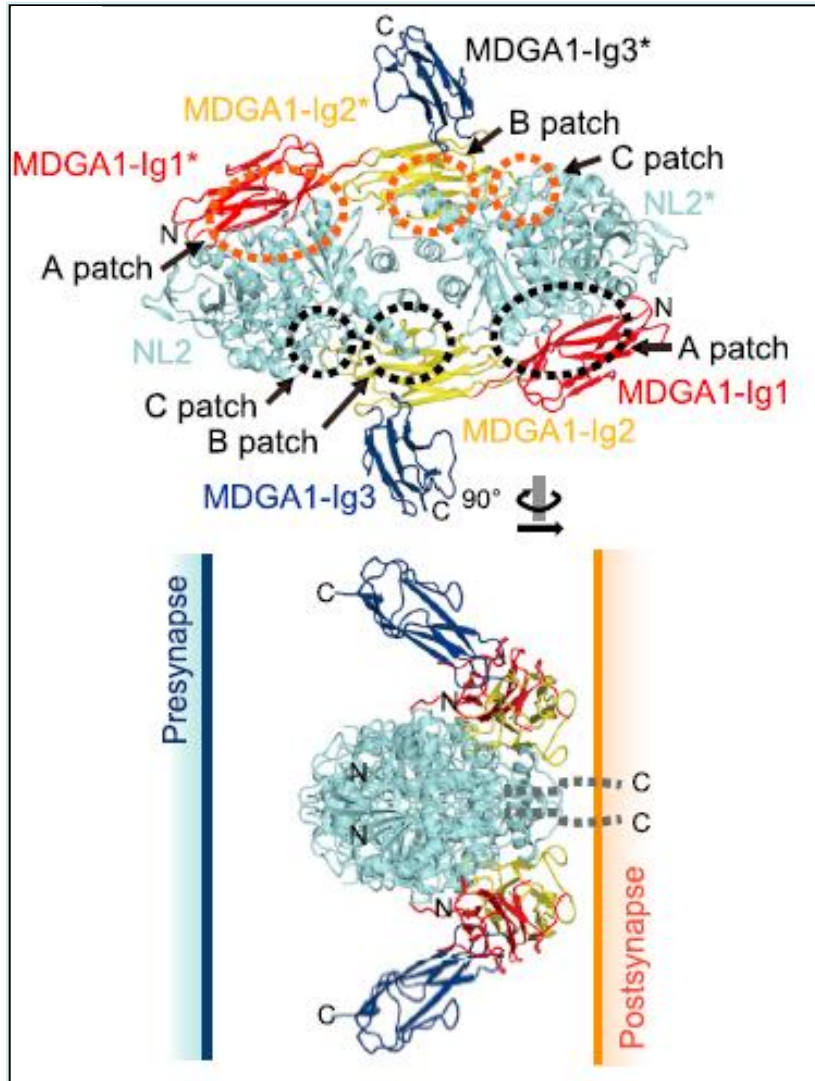
Selective binding of MDGA1 to Nlgn2



MDGA1 as a brake at inhibitory synapses

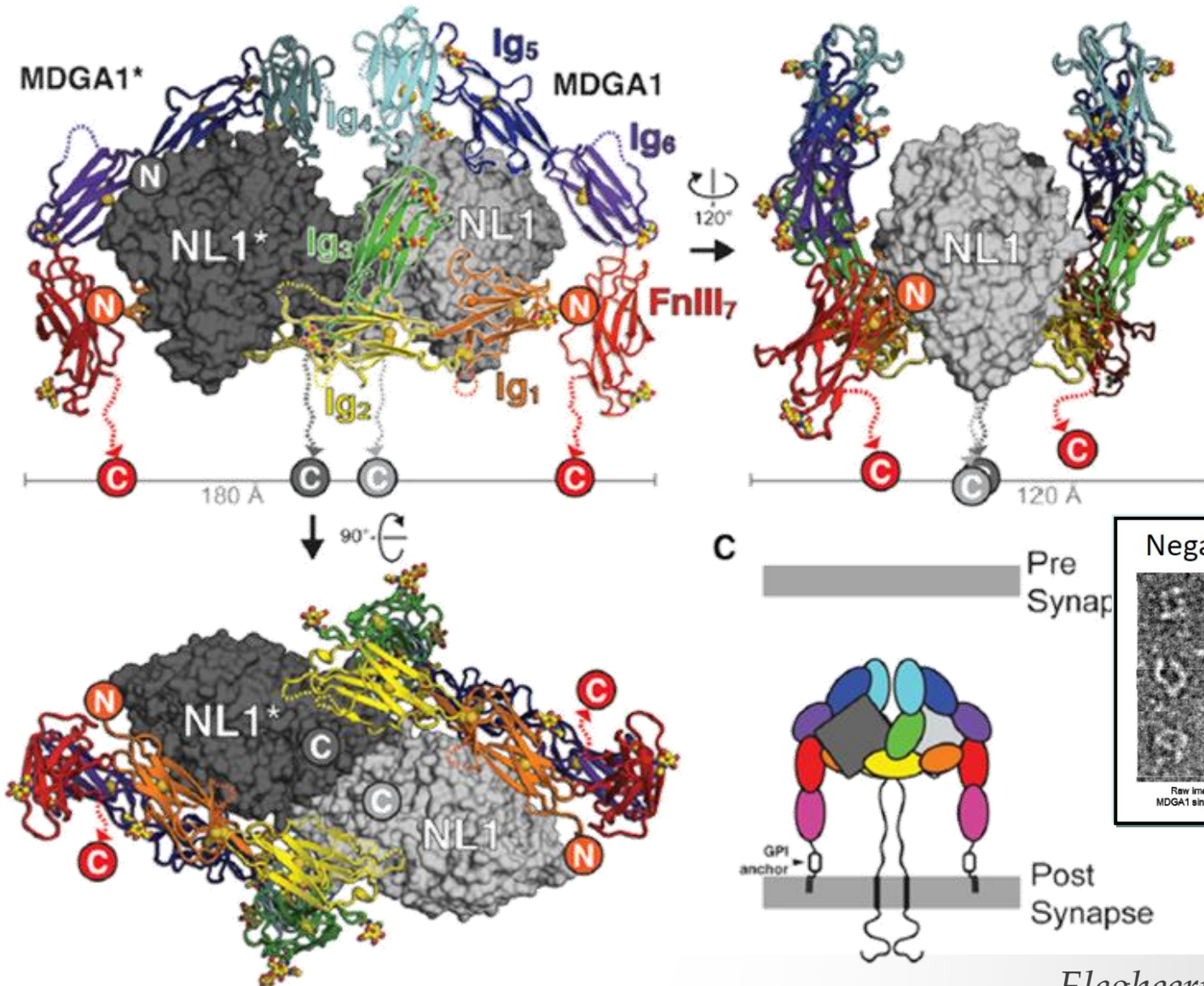


Structure of MDGA1/Ngn2 complex

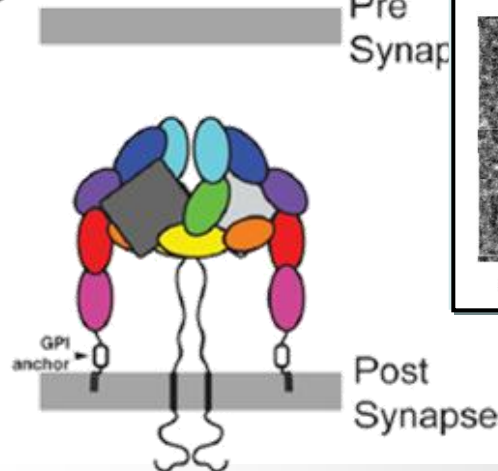


3.1 Å resolution
: minimal binding complex
(Nlgn2 esterase homology domain/MDGA1 Ig1-3)

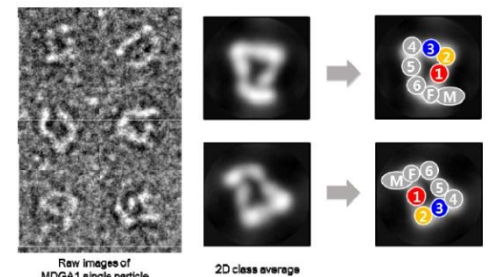
Structure of MDGA1/Nlgn1 complex



C



Negative stain EM of MDGA1



MDGA Interference on Neuroligation

A Triad of Crystals Sheds Light on MDGA Interference with Neuroligation

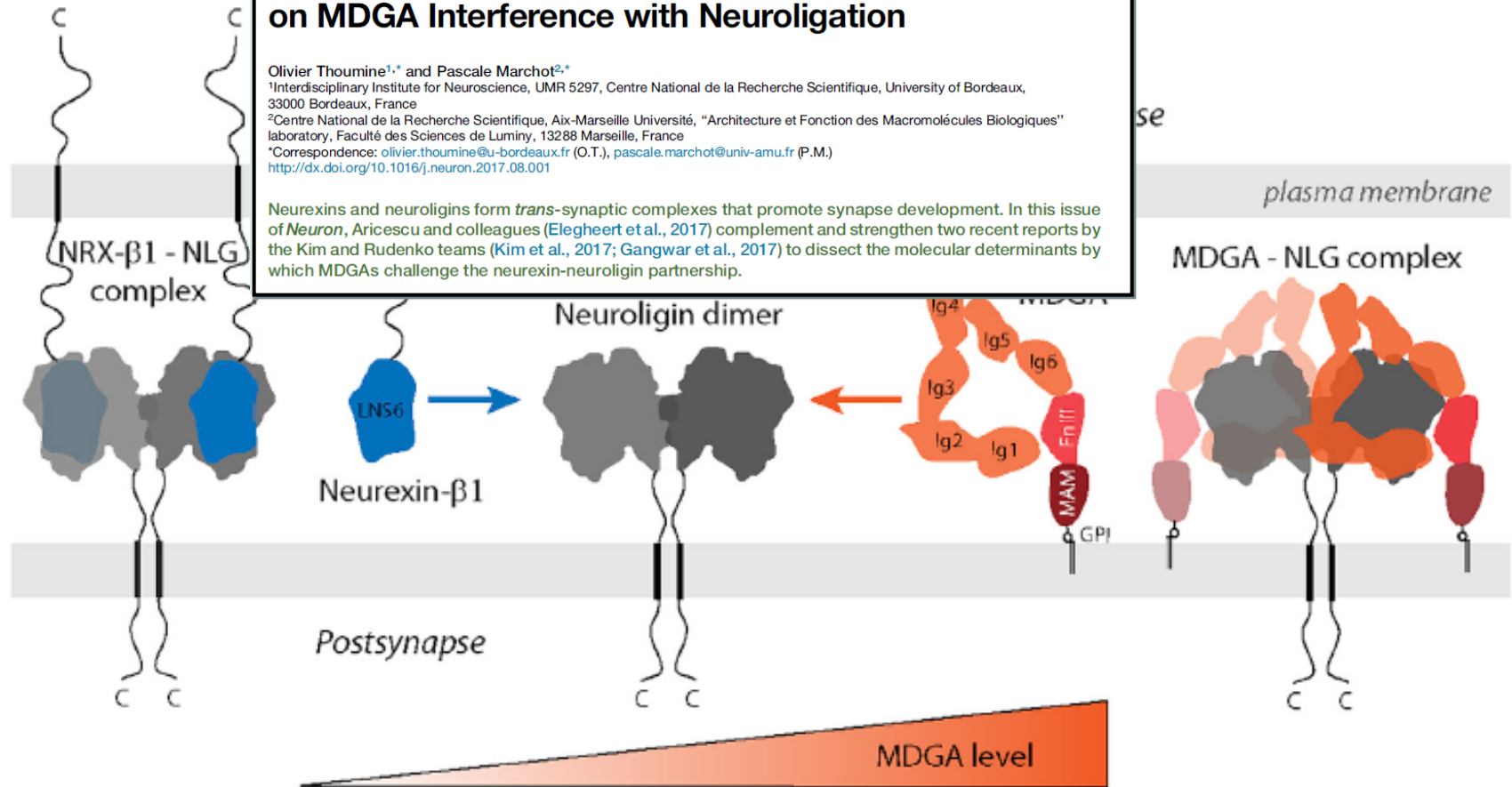
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¹Interdisciplinary Institute for Neuroscience, UMR 5297, Centre National de la Recherche Scientifique, University of Bordeaux, 33000 Bordeaux, France

²Centre National de la Recherche Scientifique, Aix-Marseille Université, "Architecture et Fonction des Macromolécules Biologiques" laboratory, Faculté des Sciences de Luminy, 13288 Marseille, France

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<http://dx.doi.org/10.1016/j.neuron.2017.08.001>

Neurexins and neuroligins form *trans*-synaptic complexes that promote synapse development. In this issue of *Neuron*, Aricescu and colleagues (Elegheert et al., 2017) complement and strengthen two recent reports by the Kim and Rudenko teams (Kim et al., 2017; Gangwar et al., 2017) to dissect the molecular determinants by which MDGAs challenge the neurexin-neuroligin partnership.

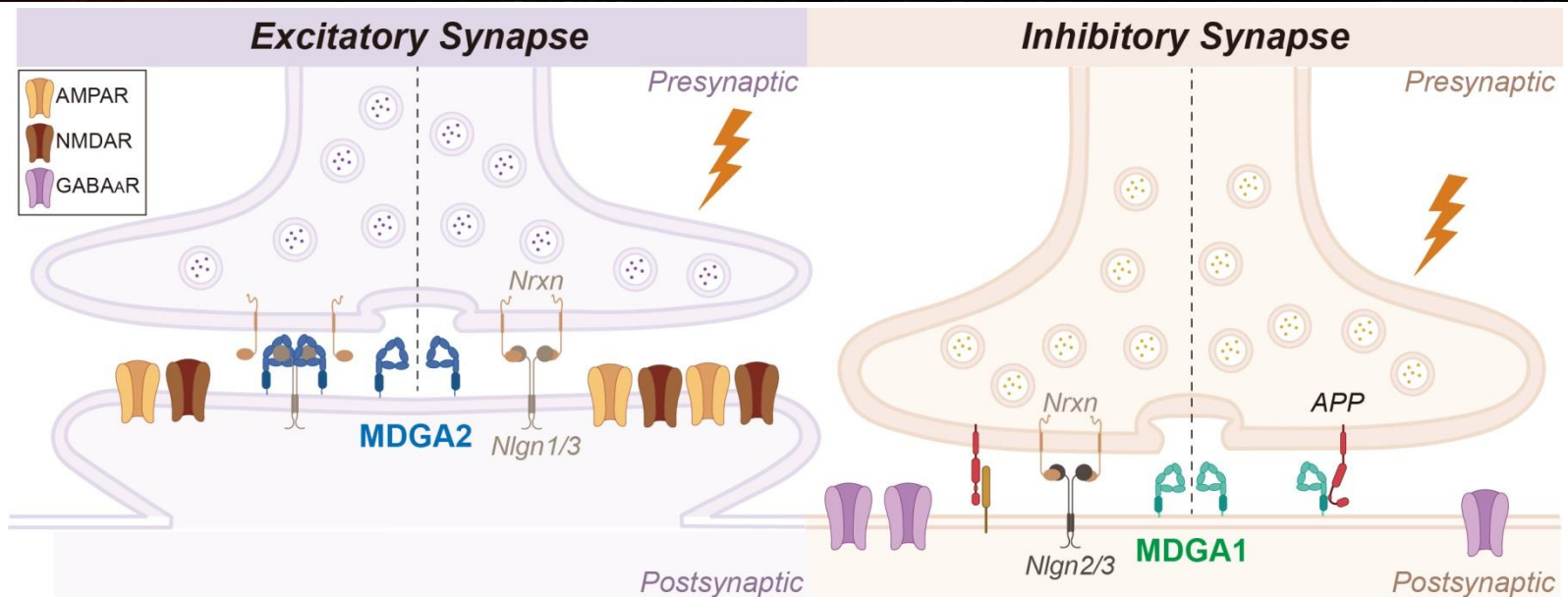


Kim et al., *Neuron* (2017)

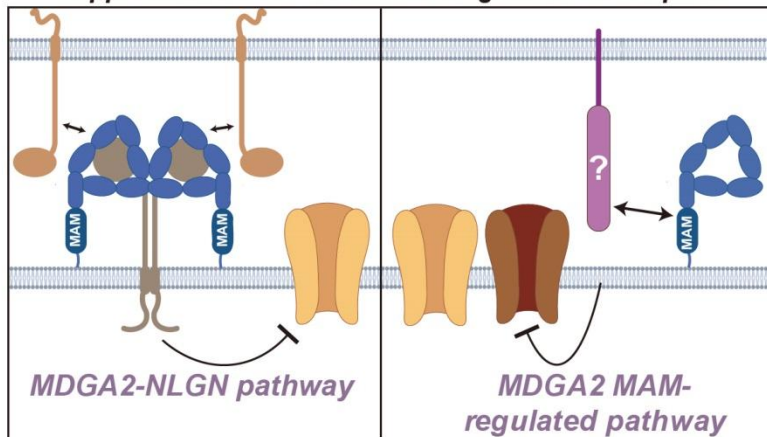
Gangwar et al., *Neuron* (2017)

Elegheert et al., *Neuron* (2017)

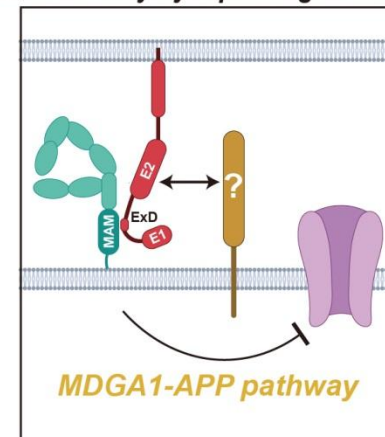
Model of MDGA-mediated synaptic suppression



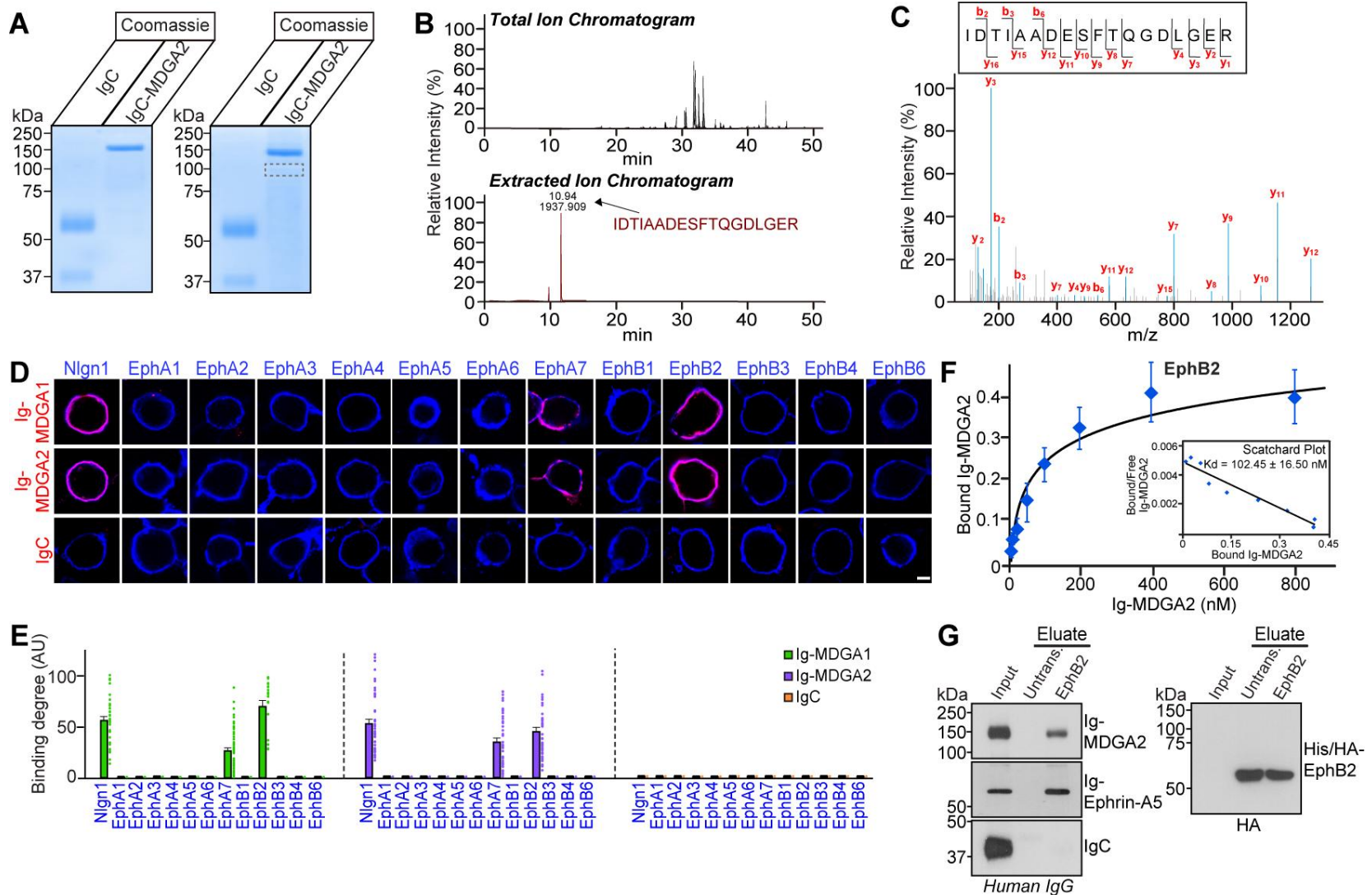
Suppressive action of MDGA2 on glutamate receptors



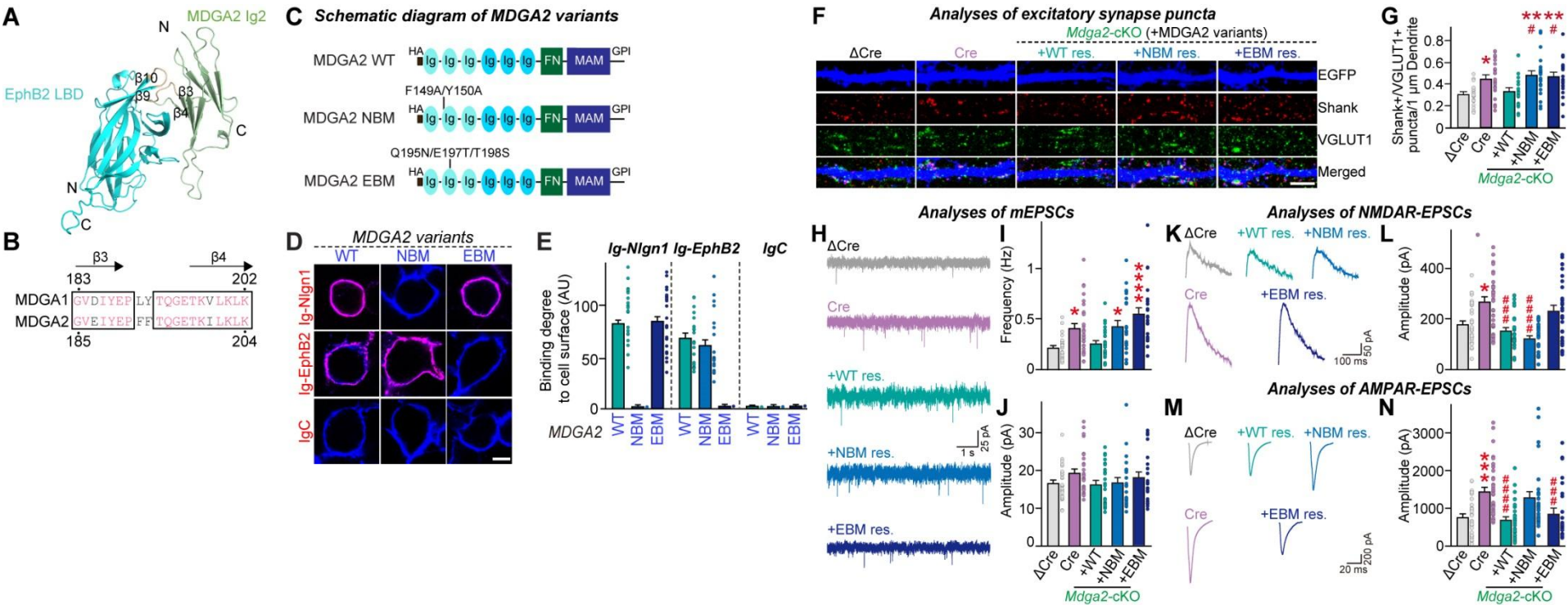
Suppressive action of MDGA1 on inhibitory synapse organization



A new ligand for MDGA2: EphB2

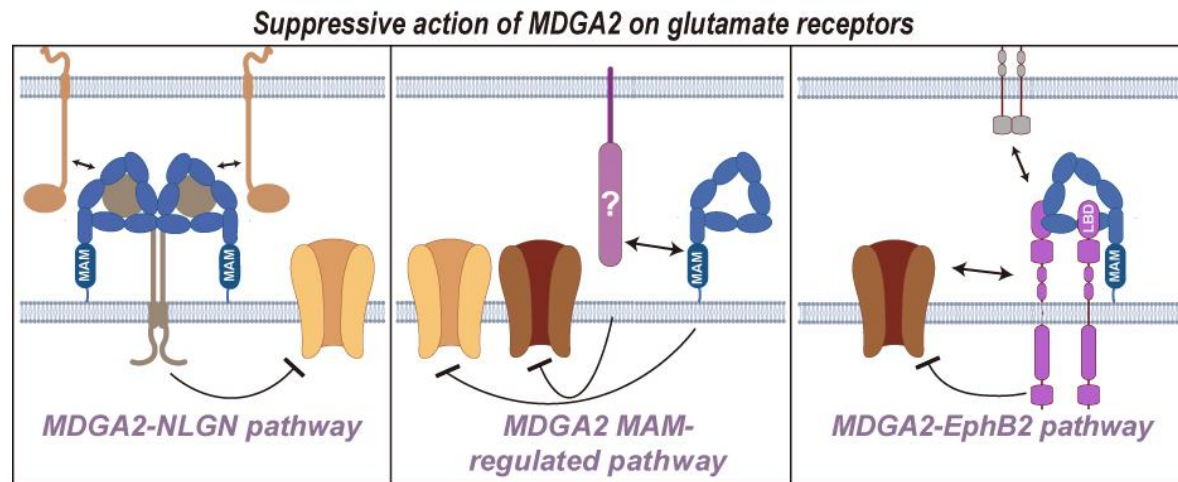
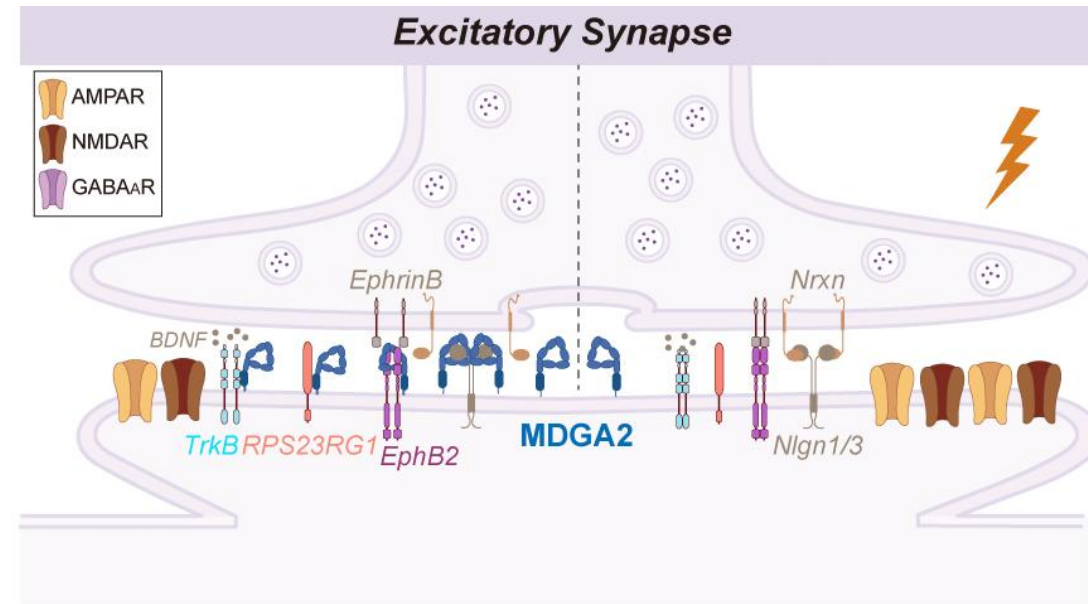


MDGA2 targets EphB2-ephrin pathway to constrain NMDAR functions



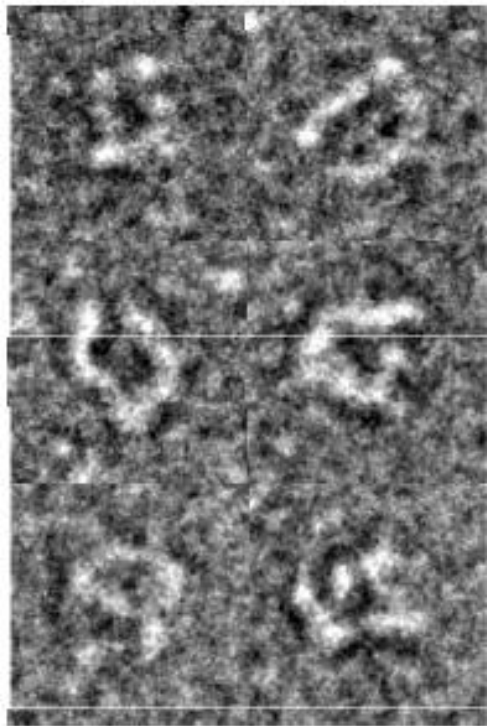
- ColabFold-based design of **MDGA2 EBM** (an EphB2-binding MDGA2 variant) was generated
- Expression of **MDGA2 EBM** in the *Mdga2*-cKO neurons failed to rescue altered NMDAR responses

Revised model of MDGA-mediated synaptic suppression

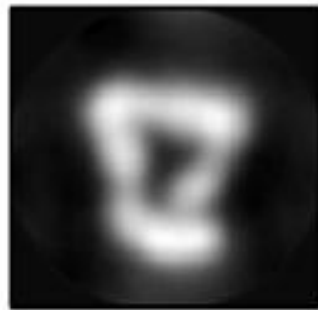


Triangular **MDGA1** ecto structure

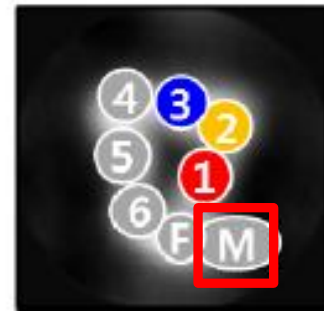
Negative stain EM of MDGA1



Raw images of
MDGA1 single particle

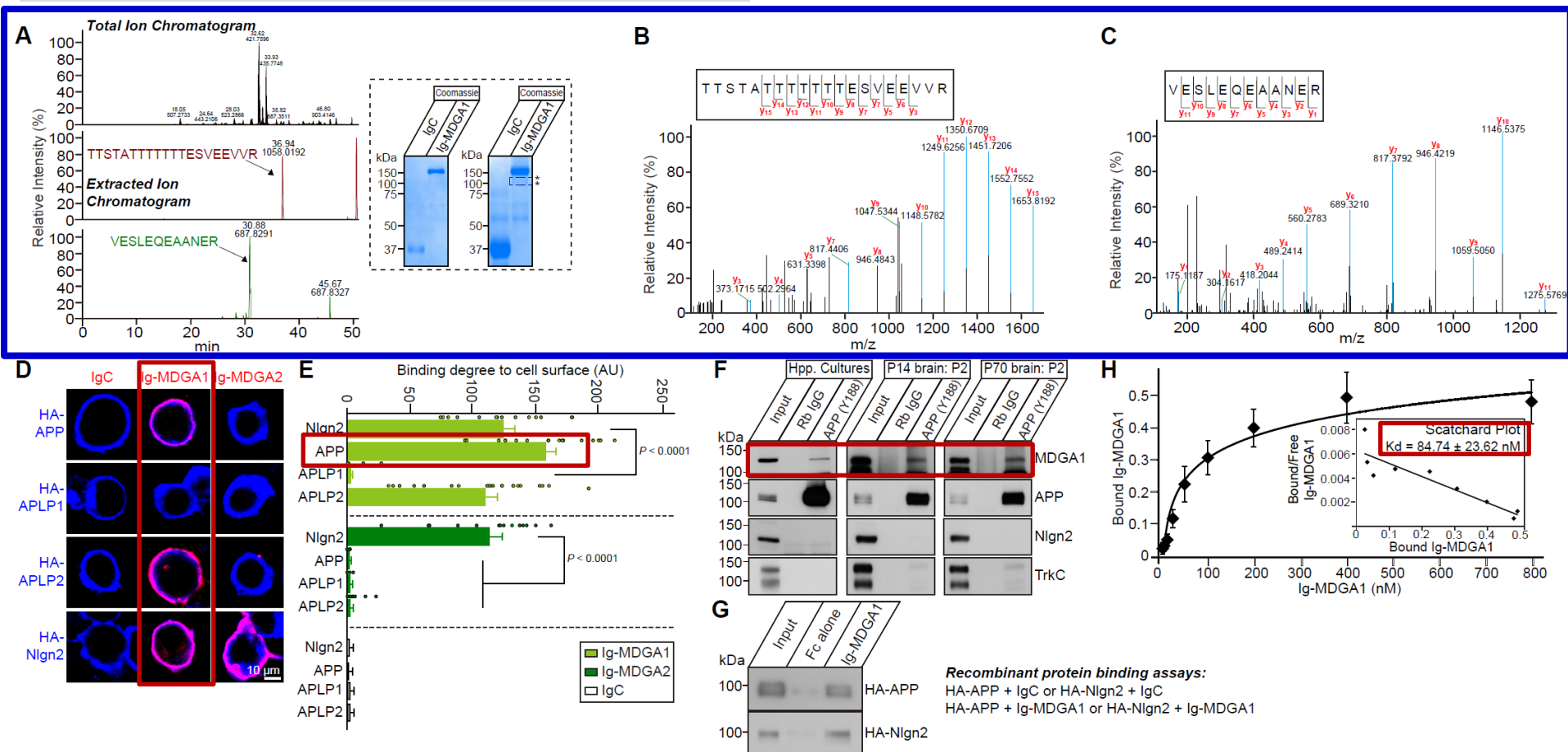


2D class average



Identification of **MDGA1** ligand: *APP*

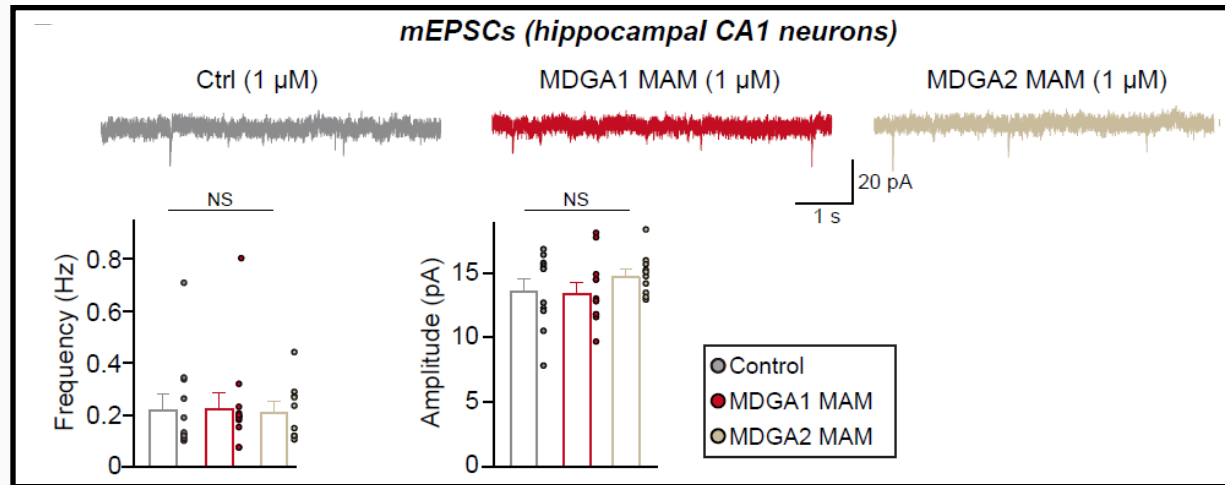
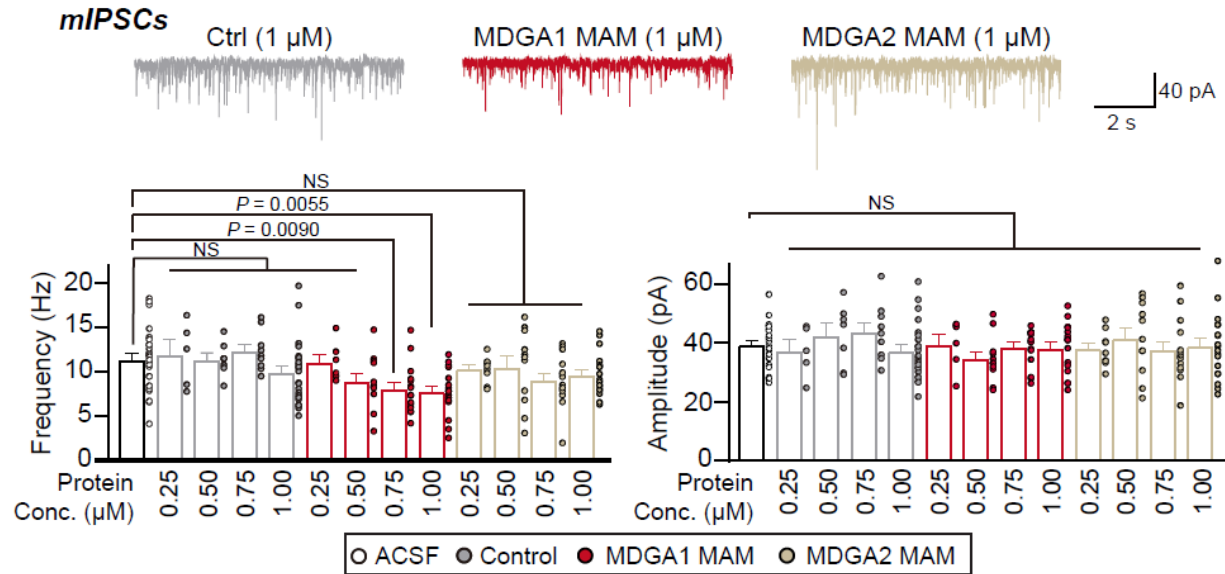
Chromatography + mass spectroscopy



MDGA1 MAM impairs inhibitory synaptic transmission

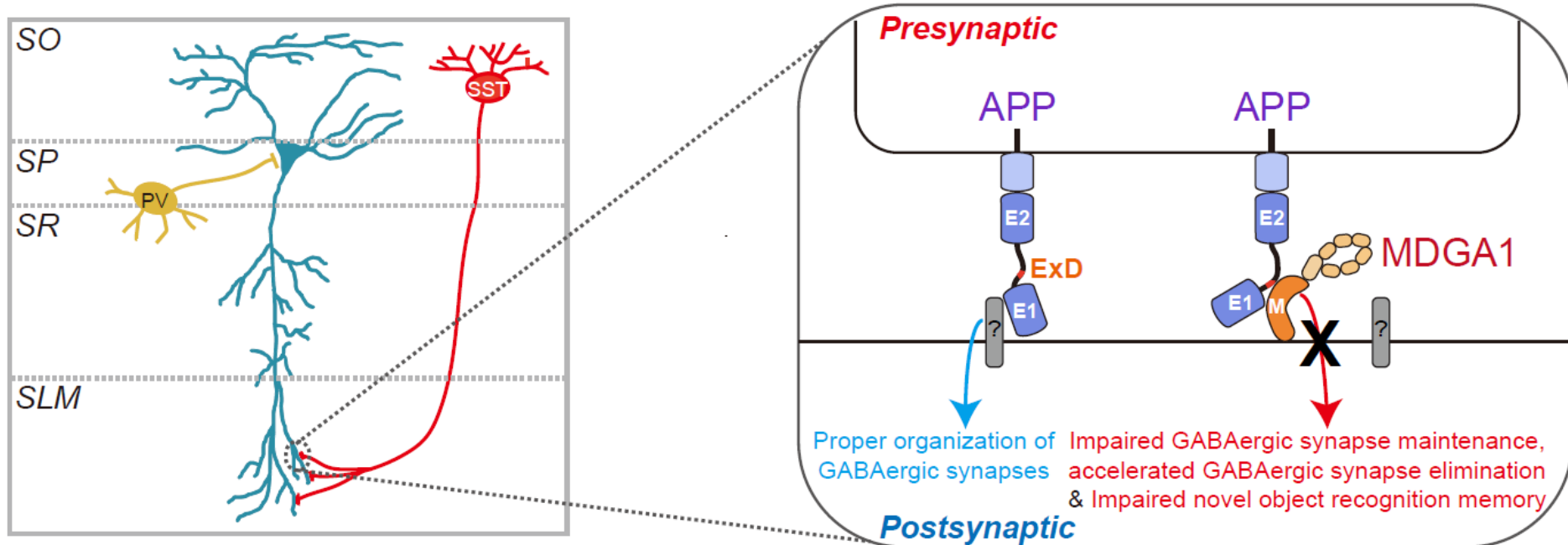
Purification
of
MDGA1
MAM

Treatment
of purified
MDGA1
MAM into
acute CA1
slice for
1 h and
recording
in the CA1
pyramidal
neurons



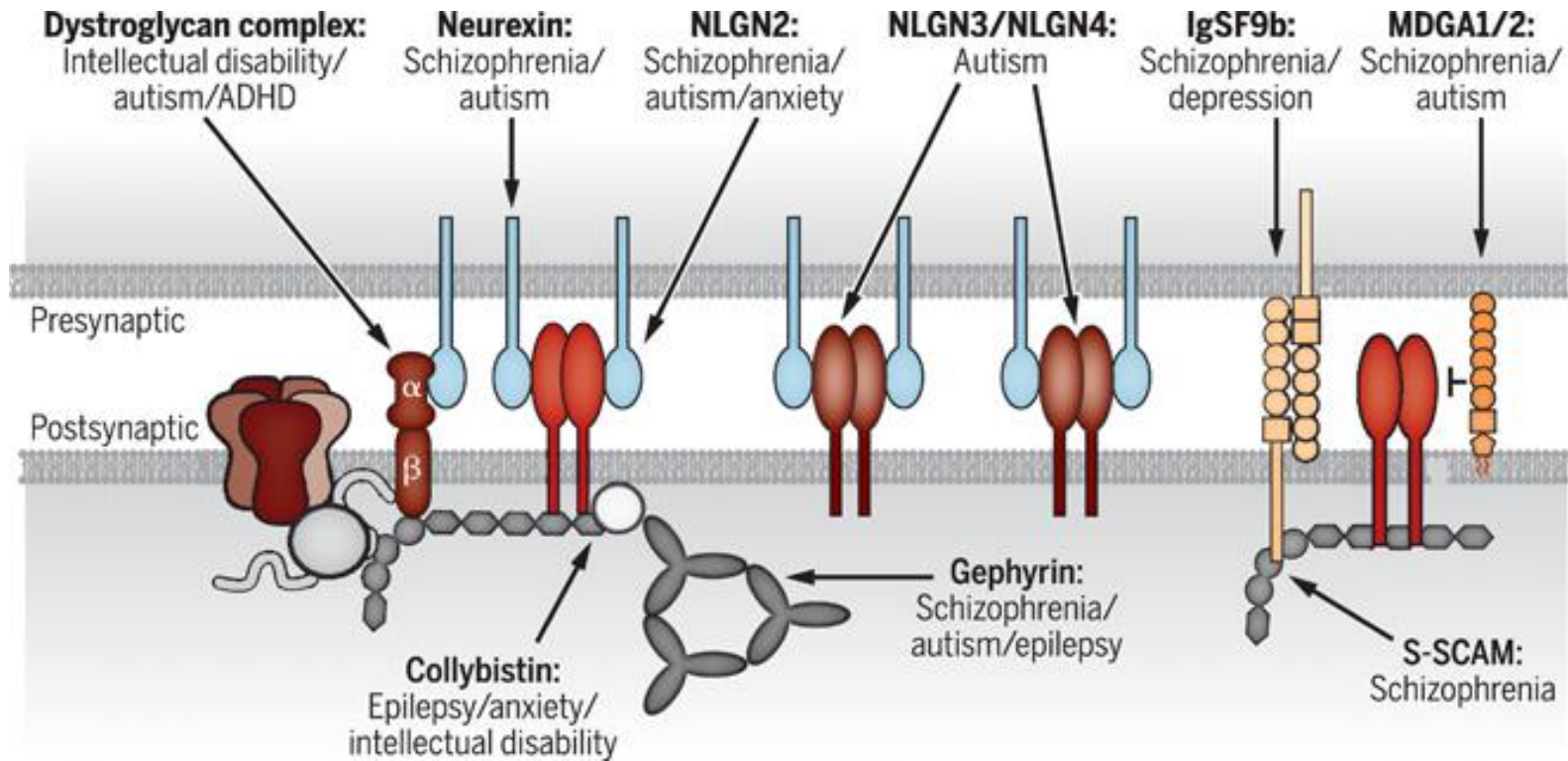
Tentative molecular model: MDGA1-APP complex

Trans-synaptic tuning of MDGA1 on presynaptic APP in hippocampal CA1 circuits



1. Presynaptic APP organizes *trans*-synaptic signaling in regulation of GABAergic synapse properties (i.e., GABA_A receptor functions, Pr)
2. MDGA1 antagonizes the action of APP in distal dendrites via binding to the extension domain (IDRs)
3. MDGA1 does not require NL2 for synaptic disinhibition in the hippocampal CA1

Implication of MDGAs with brain disorders



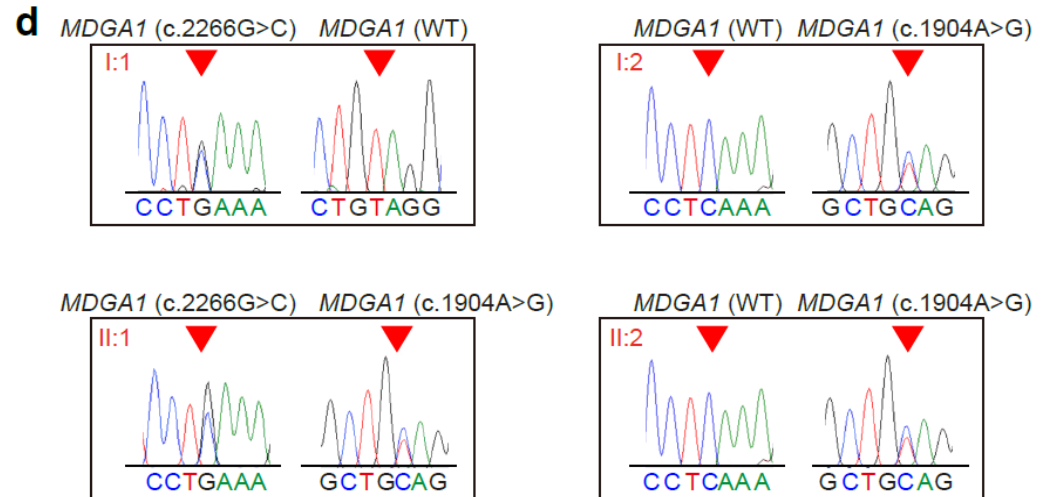
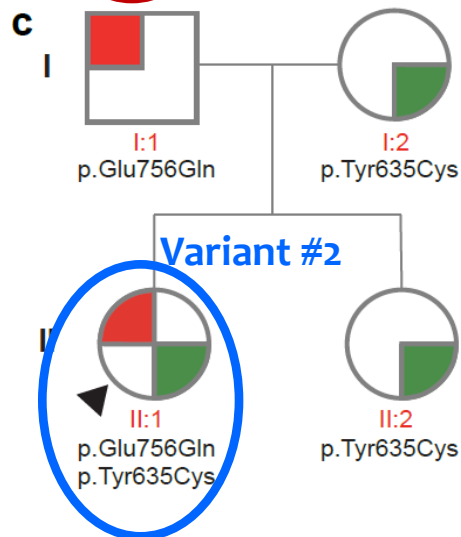
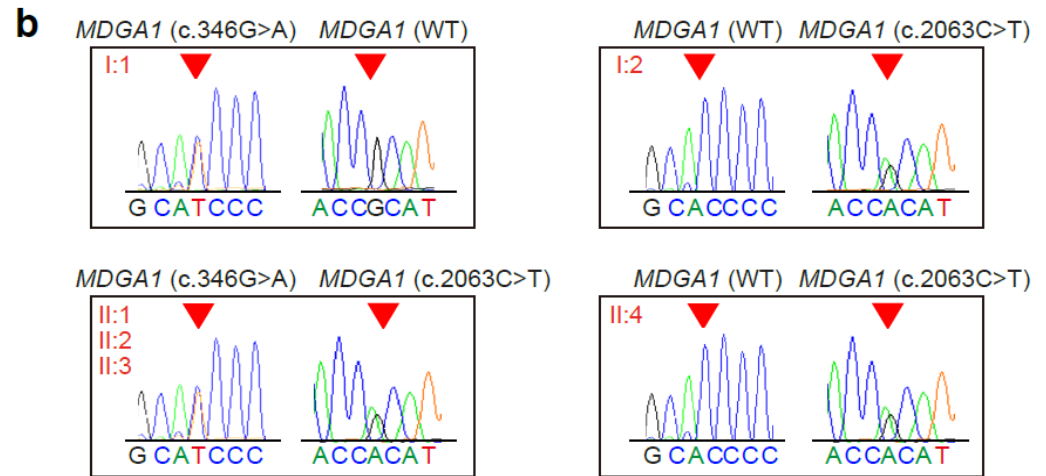
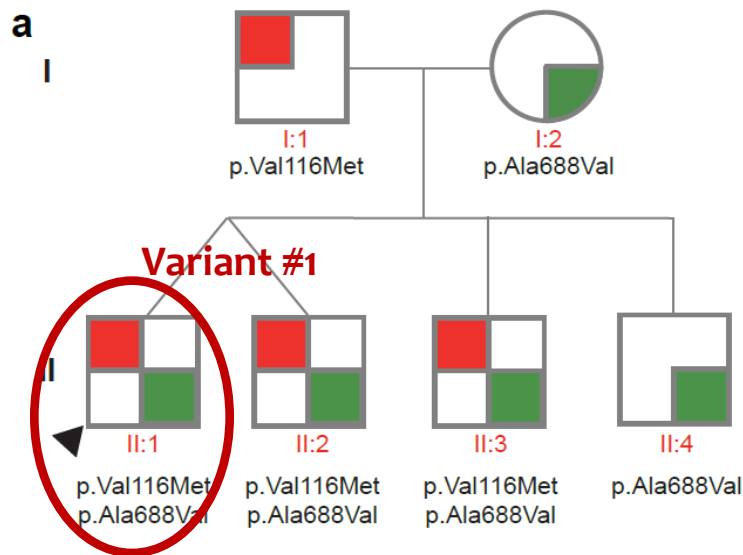
❓ **Schizophrenia:** *Am J Med Genet B Neuropsychiatr Genet.* 2008; *Schizophr Res.* 2011 (**MDGA1**)

❓ **Bipolar disorder:** *Schizophr Res.* 2011 (**MDGA1**)

❓ **Depression:** *Brain Behav Immun Health* 2022 (**MDGA1**)

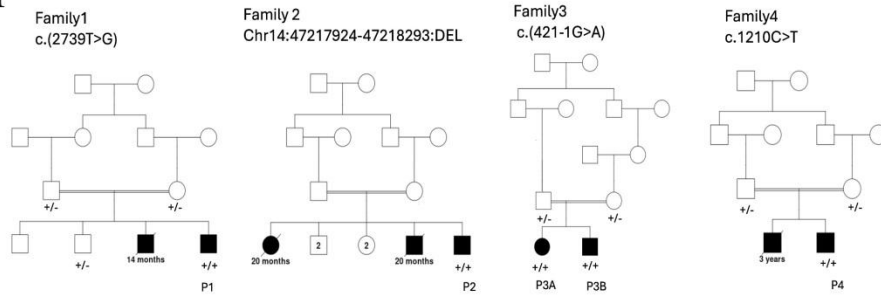
❓ **Autism:** *PLoS Genet* 2009; *Genes Brain Behav* 2021 (**MDGA2**)

Identification of ASD patients with *MDGA1* missense mutations

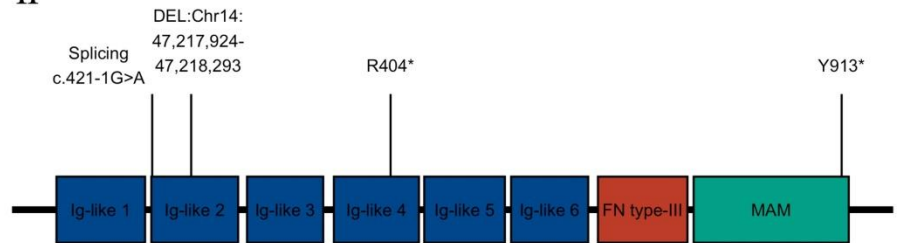


Identification of DEE patients with *MDGA2* missense and nonsense mutations

I



II



III



IV

