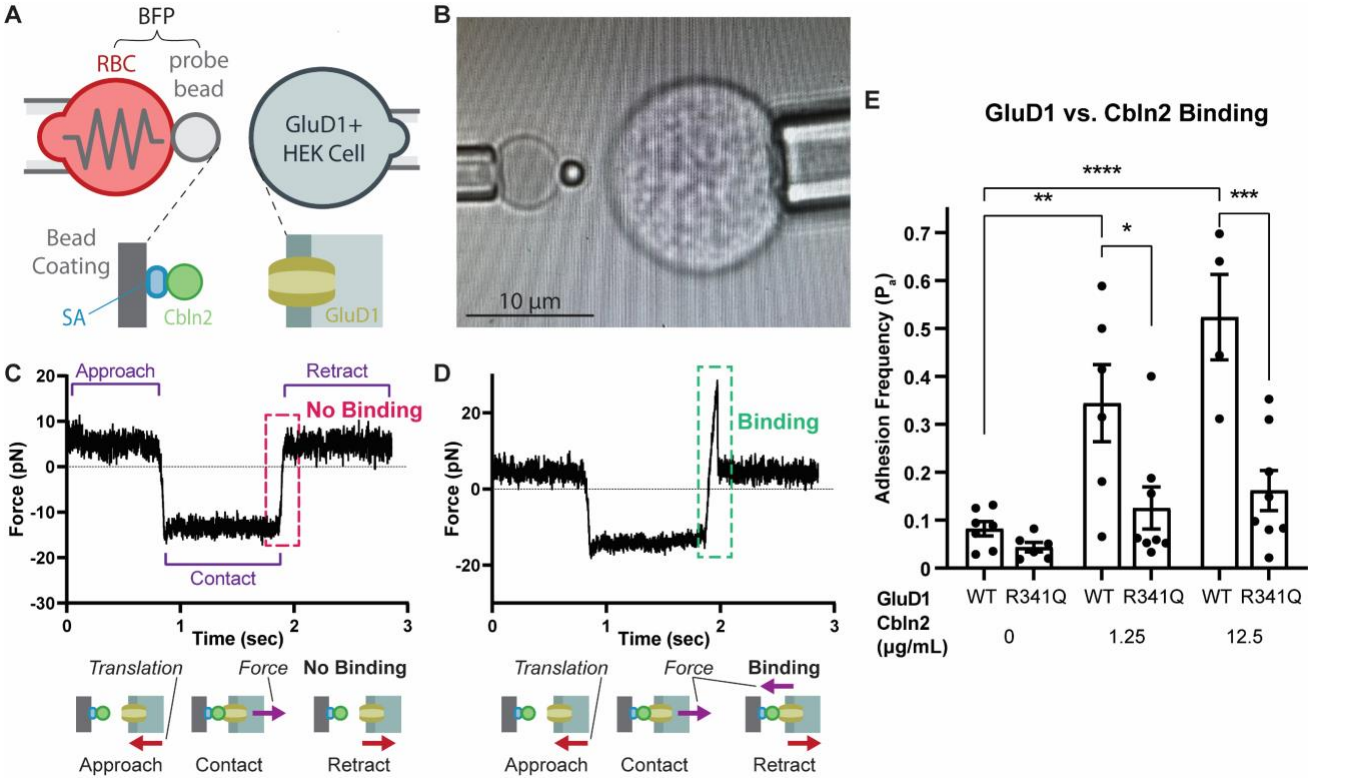
Unique pharmacology of GluN1/GluN3 as a probe for functional roles

The glutamate receptor family contains 18 subunits that can form 5 classes of receptors. Three of these receptors comprise the glutamate-gated ion channels known as AMPA, kainate, and NMDA receptors. A subset of NMDA receptor subunits (GluN1 and GluN3) that bind glycine can form a fourth, poorly understood, class of receptors. Under certain circumstances, inward cationic current can be activated by glycine. However, under normal circumstances, glycine binding to GluN1 induces desensitization at concentrations lower than those required to activate the receptor via binding to the GluN3 subunit. We have developed a new series of both positive and negative allosteric modulators that are highly selective for GluN1/GluN3 receptors over other glutamate receptors (including NMDA, AMPA, and kainate). We are using these tools to explore the functional consequences of GluN3 activation in neurons expressing these subunits. Our newer series appear selective for GluN3A or GluN3B.

Potential mechano-sensitive roles of GluD1 in presynaptic-postsynaptic coupling

A fifth class of receptors are formed by two delta subunits, which do not appear to act as ligand-activated ion channels, although human mutations that occur in gating regions can lead to constitutively active ion channels that pass large inward currents. Our recent studies show that these receptors, which form transsynaptic protein complexes with cerebellin and neurexin family members, can respond to and sense force. Thus, these receptors could be a developmental switch to help synapses form and strengthen. Not only can GluD1 influence the type of “bond” formed by the two proteins, but it also alters force transduction across the protein complex when a neurotransmitter binds. This binding rigidifies a bilobed domain that otherwise allows the protein to flex. This work opens an entirely new aspect of glutamate receptor biology.



Analysis of force profile for protein-protein interactions between GluD1 and cerebellin. From Allen et al. 2023.