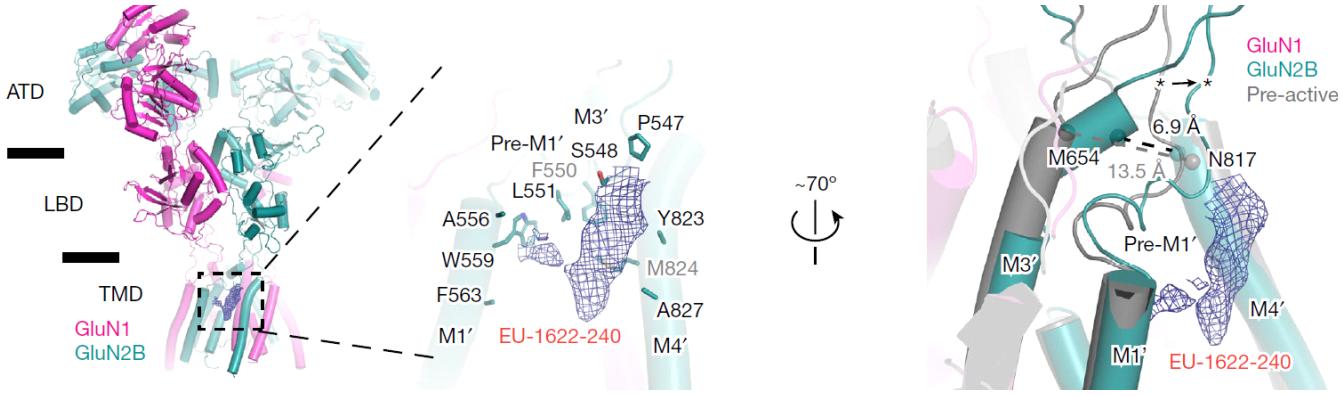
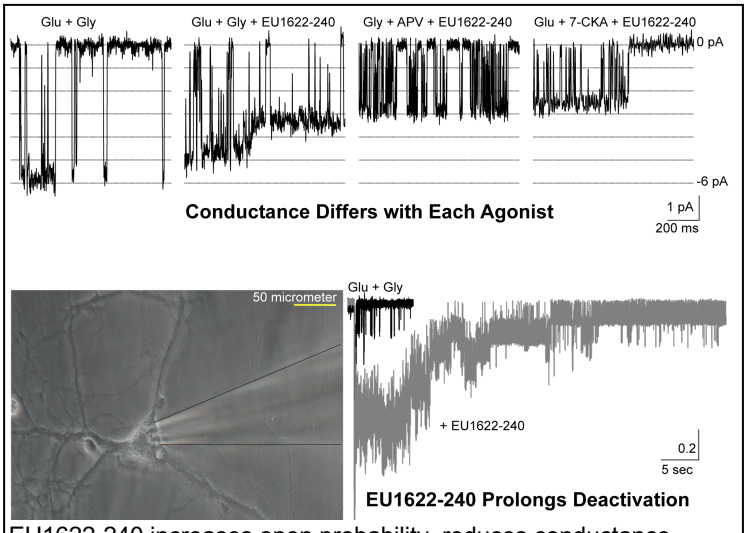
Novel Subunit-Selective Allosteric Modulators of NMDA Receptors



Cryo-EM structure of GluN1/2B NMDA receptor bound to the positive allosteric modulator 1622-240 (Chou et al. *Nature* 2024)

Glutamate receptors are ligand-gated channels that catalyze the transmembrane flux of cations in response to binding of the neurotransmitters glutamate and glycine. These receptors mediate synaptic currents at almost all excitatory central synapses and, thus, are critical for normal brain function and also implicated in a number of neurological diseases. The receptors can be divided into three classes (AMPA, kainate, NMDA), each of which has multiple subunits. At most synapses, it remains unclear which glutamate receptor subunits mediate synaptic transmission. Given the lack of information about post-synaptic receptor composition, there is a critical need to develop subunit-selective tools that can be used to ascertain synaptic receptor identity.

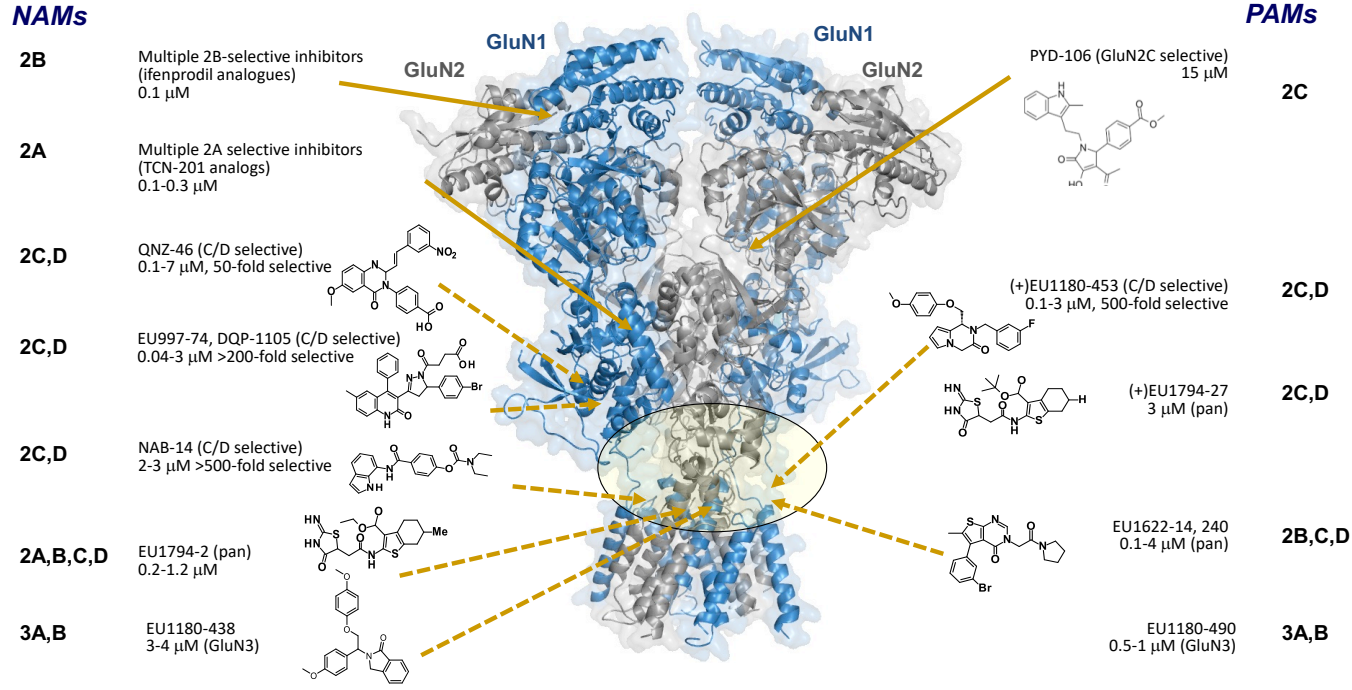
Among the glutamate receptors, NMDA receptors are tetrameric assemblies of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits, of which four types exist (GluN2A,B,C,D). NMDA receptors mediate a slow Ca^{2+} permeable synaptic current when voltage-dependent block by extracellular Mg^{2+} is relieved by neuronal depolarization. The various GluN2 subunits show differential temporal and spatial distribution in the CNS and thus provide an opportunity for region-specific modulation of NMDA receptor function by compounds that are selective for one or another subunit. Despite the potential to modulate NMDA receptors in specific brain structures, few advances in the development of subunit-selective antagonists occurred between 1980-2010. To break this impasse, we developed and implemented a high-throughput screen that identified non-competitive inhibitors and potentiators of NMDA receptors that contained the GluN2C and GluN2D subunits. This screen was highly successful, and we have studied over a dozen new classes of inhibitors or potentiators that prefer GluN2C and/or GluN2D subunits. We currently focus on understanding the site and mechanism underlying the regulation of NMDA receptors by both positive and negative allosteric modulators that we identified.



EU1622-240 increases open probability, reduces conductance, prolongs deactivation, and enables activation by glutamate or glycine alone (Ullmann et al., *Mol Pharmacol* 2024

We collaborate with Dr. Dennis Liotta in the Dept. Chemistry at Emory, a world-renowned chemist with extensive experience (and success) with drug development. This medicinal chemistry campaign is advancing our understanding of multiple new classes of compounds. We also collaborate with Dr. Hiro Furukawa, an

expert in crystallography and cryo-EM, to determine the site of action for these new probes. We explore the effects of allosteric modulators on the channel, synapse, circuit, and whole animal. The information gained with these tools can provide insight into new therapeutic strategies to treat epilepsy, ischemia, Parkinson's disease, Alzheimer's disease, schizophrenia, depression, and clinical symptoms in patients with genetic variation in the genes encoding NMDA receptor subunits.



Our chemistry colleagues have synthesized over 2500 compounds in >12 structurally distinct series with the goal of developing multiple subunit-selective NMDA receptor modulators. Above are some of the classes that we have published on.