PROJECT SUMMARY (See instructions):

Severe mental illness affects 1 in 17 people in the US, and costs a staggering $300 billion dollars per year. However, *the medications used to treat these disorders are often confounded by poor efficacy, side effect profiles and/or toxicity, emphasizing the urgency to develop better therapeutics*. Recently, proteins that impact the excitation-inhibition (E/I) balance in neural circuits have been strongly implicated in many neuropsychiatric diseases. For example, the synaptic organizing proteins, neurexins, neuroligins, and MDGAs, which interact with each other in the synaptic cleft, tilt the E/I balance through their ability to regulate excitatory versus inhibitory synapse development and maintenance in immature and mature neurons. The *key knowledge gap* is whether the protein interaction network coordinated by neurexins, neuroligins and MDGAs can be leveraged pharmacologically to regulate the E/I balance in a therapeutically beneficial way. We are developing chemical tools to probe the neurexin-neuroligin-MDGA interaction network. Our long term goal is to regulate this 'interactome' to restore the E/I balance as a treatment strategy for neuropsychiatric disorders. We are particularly interested in disrupting protein interactions that would boost inhibitory tone in a neuron- and circuit-specific way. The *objective* of this proposal is to establish methodology, proof-of-principle and first generation probes targeting protein complexes between specific neurexins, neuroligins and MDGAs. The overarching hypothesis is that proteins like neurexins, neuroligins, and MDGAs, that mediate and regulate the balance between excitatory and inhibitory synapses, are completely novel strategic targets to combat neuropsychiatric disease. We will 1) synthesize an initial panel of disrupting peptides that target specific protein complexes between neurexins, neuroligins and MDGAs; 2) develop a biophysical platform in order to screen small molecule libraries; and 3) evaluate novel probes *ex vivo* in validated animal models relevant to neuropsychiatric disease. *Benefit:* This new collaborative team will generate neuroprobes targeting neurexins, neuroligins, and MDGAs in order to test the effect of disrupting the protein:protein interactions that they form. These results will enable us to assess if the neurexin-neuroligin-MDGA interactome can be leveraged to control the E/I balance in a therapeutically beneficial way. Our approach is both novel and innovative because efforts to control excessive synaptic excitation or inhibition have traditionally focused on targeting the neurotransmitter receptors and channels producing excitatory and inhibitory currents, rather than the development and maintenance of the excitatory or inhibitory synapses themselves. The positive impact of this proposal is to nucleate a multi-disciplinary chemical probe discovery team in a therapeutically unexplored area, and to produce preliminary data and joint publications that will drive the submission of an NIH BRAIN initiative proposal. Outstanding training opportunities will also be generated in an integrated, multi-disciplinary team focused on neurotherapeutics.

RELEVANCE (See instructions):

Recently, huge strides in the synapse biology field have revealed that specific 'synapse organizing molecules' exist that not only regulate synapse development and maintenance at excitatory and inhibitory synapses, respectively, but that many of these same proteins are also implicated in serious mental disorders (e.g., autism spectrum disorder, schizophrenia). Capitalizing on these fundamental discoveries, we are pursuing the synaptic organizers neurexins, neuroligins and MDGAs as potential therapeutic targets for brain disorders.

While many pharmaceutical compounds target excitatory and inhibitory tone by regulating neurotransmitter receptors and channels, these approaches are relatively non-selective because they target receptors and channels that are largely ubiquitously expressed in the brain. Our strategy is **novel and innovative** because it targets the formation and maintenance of excitatory and inhibitory synapses themselves, leading to potentially more long-term and stable alterations. In addition, by exploiting specific synapse organizing proteins, this strategy has the potential to be neural- and circuit-specific. The proposed research is therefore novel and a dramatic departure from traditional neurotherapeutic strategies.

Our proposal is relevant to the UTBrain Initiative because the proposed research will not only help us better understand the link between synapse development, brain function and behavior, but also identify potential novel drug targets. This proposal is thus both fundamental as well as translational in nature. This proposal will nucleate a new probe discovery team at UTMB consisting of a medicinal chemist (Zhou), a structural biologist/biophysicist (Rudenko) and a neuropsychopharmacologist (Cunningham). Together, we will be able to establish the methodology, proof-of-principle, and multi-disciplinary team needed to pursue long term external funding to develop innovative neurotherapeutics. With the results obtained through this proposal, we will also be able to attract one of the outstanding electrophysiologists within the UT System to further characterize the effects of our bioactive probes on a cellular and mechanistic level, thereby expanding our team to other institutions within the UT System.