Depression is a chronic and debilitating psychiatric illness affecting roughly 16% of the US population. Current pharmacologic therapies targeting the monoamine neurotransmission exhibit limited effectiveness. However, emerging evidence suggests ketamine could lead the way to a breakthrough in developing a new generation of highly effective and rapid-acting antidepressants. Ketamine has long been used as general anesthetic acting primarily through blockade of NMDA receptors in the brain. At sub-anesthetic doses, ketamine has shown promising results as a potent and fast-acting antidepressant. These effects are particularly evident in patients with treatment-resistant depression and with high risk of suicide. However, dissociative/psychotogenic effects of ketamine and risk for abuse limit its potential use as an antidepressant. Our research goals have been to 1) reduce side effects associated with Ketamine’s antidepressant actions; 2) uncover antidepressant mechanisms of ketamine for previously unknown molecular drug targets. I will present recent progress from my lab that represents our effort to reach those goals.