Title: Preclinical Assessment of Novel Targets for Rapid-Acting Antidepressants

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Abstract: Globally, clinical depression is the leading cause of disability. In light of the health and economic burden of depression, research into the causes of, and treatments for, depression must be considered a global health priority. Although progress in the treatment of depression has been made since the discovery of first generation antidepressants in the 1950's, modern therapies remain limited in their effectiveness, have unfavourable side-effects, and the onset of therapeutic benefits often take weeks-to-months, which increases the risk of suicide in this vulnerable population. Recently, new drug targets in the brain have shown promise. Drugs such as ketamine and scopolamine can achieve an antidepressant effect within hours of treatment. Additionally, they are effective in patients that are resistant to standard therapies. However, these drugs remain clinically limited by addiction liability and unfavourable side- effects. The proposed project aims to advance research into novel fast-acting antidepressants with favourable side-effects profiles. The project will focus on specific channels on the surface of brain cells that seem to be a converging point for the antidepressant action of ketamine and scopolamine. Several compounds will first be screened for their ability to block these downstream channels, and assess their specificity. Using animal models, promising compounds will be characterized in terms of their behavioural effects, as well as their structural and functional effects on brain regions known to be involved in depression. With preliminary results already showing promise, this project has a strong potential for propelling our understanding of clinical depression and how to effectively and safely treat this debilitating disorder.