2018 Talent Development Competition Awardees

Title: Somatostatin cell deficits as a contributing pathology in depression: bridging consequences from molecules to symptoms.

Corey Fee

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Abstract: Major depressive disorder (MDD) is a severe mental illness affecting 1.8M Canadians annually. Despite this high prevalence, current antidepressant drugs are ineffective in 50% of patients. This is largely due to the fact that these drugs (discovered by serendipity >60 years ago) target an imbalance of brain chemicals that is secondary to the disorder, instead of the underlying cellular deficits that lead to symptom emergence. Postmortem studies of MDD subjects consistently demonstrate reduced level and function of inhibitory GABA neurons that co-express the peptide somatostatin (SST cells) across brain regions associated with mood and cognitive functions that are disrupted in depression. In preclinical studies, low SST has been linked to general behavioral phenotypes reflecting MDD symptoms. However, diverse human symptomatology and a poor understanding of how SST cell deficits contribute to the emergence of specific symptoms have limited progress in antidepressant development.

Here, I propose to develop a preclinical model that recapitulates SST cell changes as they occur in humans. With this tool, I will determine which behavioral deficits arise solely from chronic low SST cell function, focusing on dimensions that reflect human symptomatology, including anhedonia, helplessness, anxiety, and cognitive impairment. I will then isolate major neuron classes to determine the molecular consequences of low SST cell function, and assess how these changes drive the emergence of dimensional behaviors. This study will be the first to achieve accurate modeling of human SST cell deficits in order to bridge a knowledge gap between primary cellular pathology and clinical symptom emergence. Identifying the molecular mediators linking low SST cell function to depressive-like behavior will facilitate target discovery to improve the treatment of depression and other illnesses with SST cell dysfunction, including bipolar disorder, schizophrenia, Alzheimer's disease, and Parkinson's disease.