2018 Seed Funding Competition Awardees

Title: Neuroanatomical Focus, Drug Enrichment and Discovery from Depression Genome Wide Association Results. PI: **Leon French**

Abstract: In Canada, almost one in 20 people over 15 years old reported symptoms that met criteria for major depressive disorder (MDD) in the preceding year. Globally, the World Health Organization found that depression is the largest contributor to years lived with disability. Recently, the Psychiatric Genomics Consortium published the largest genetic study of MDD, which involved over 450,000 participants and revealed 44 locations in the genome that increase risk for MDD. The problem is that these locations do not provide clear pointers to biological mechanisms or treatment.

Few of these 44 locations are near genes that have been studied in the context of MDD. Further, it's not clear which nearby genes are linked to these locations or where these genes are used in the brain. Thankfully, transcriptomic studies have measured gene expression of all genes. This allows us to study the potential MDD genes near these 44 markers across disease, anatomy, and response to drugs. This supports our objectives to determine if these genes have different expression levels in MDD cases versus controls; are specifically expressed in certain brain areas; and can be used to find drugs that correct expression of these genes. These objectives align with our central hypothesis, which is that our analyses will translate the 44 risk variants into valuable neurobiological targets and thereby identify potential new ways to treat MDD. Our approach is supported by the increased chances of approval for drugs supported by genetic findings.

Furthermore, knowing where in the brain the disease processes occur can help target therapies. For example, the observed degeneration of dopaminergic neurons in Parkinson's disease demonstrates how an identified brain region and cell-type can guide treatment (levodopa to increase dopamine).

We will use existing datasets and methods that have performed well on the similar tasks. The novel application of these methods to the new MDD results will drive discovery in our project. Use of this existing data means this project will skip the slow recruitment and sample collection stages of other projects. Unlike findings in pre-clinical models that may not translate to the clinic, all the transcriptomic data will be from human samples. Furthermore, the drugs with transcriptomic data are already approved for other uses, providing a faster path to potential new MDD therapies. This repurposing approach is supported by massive catalogs of drug-induced changes in gene expression. This project will spur new collaborative projects with the many scientists at CAMH studying depression. For example, regionally specific expression information can help guide and personalize treatments that stimulate specific parts of the brain. We will also help focus CAMH studies by providing gene and protein shortlists. The analysis pipeline created for this project will be used as a seed for a general tool that will be open and easily applied to other complex brain disorders such as anorexia nervosa and schizophrenia. Most importantly, we will point to candidate drugs that can be tested for response in CAMH labs and with success, in future clinical trials.

camh
mental health is health