Market Need: A drug development standstill in the midst of a paradigm shift in neuropsychiatry.

According to the World Health Organization, neuropsychiatric disorders are the leading causes of years lost due to disability worldwide. Major depressive disorder (MDD) leads these statistics, affecting ~1.8 million Canadians and 350 million people worldwide. Adding to this, neurological disorders, such as Alzheimer’s disease represent a leading cause of disability with approximately 10-30% of the population between 65 and 85 years afflicted with the early stages of AD. The global cost of Alzheimer’s and dementia is estimated at $605 billion. Adding to this challenge, pharmaceutical companies have mostly withdrawn from developing new antidepressant drugs and there are few Alzheimer’s medications on the market.

Coinciding with this standstill in drug development, an explosion of data in brain science is now fueling a paradigm shift in neuropsychiatry. In brief, the historical symptom-based approach to defining mental illnesses does not reflect the emerging knowledge about the biological bases and complexity of brain-based illnesses. Potentially hundreds of genetic, epigenetic and environmental factors are implicated in diseases like depression and Alzheimer’s. It is also becoming increasingly clear that these factors are present across categorical disorders in patterns not yet fully understood, and that the classical categorical disorders may represent the common outcome of multiple underlying pathologies. Accordingly, neuropsychiatry is moving (slowly) away from a strictly categorical diagnostic system (DSM-5), towards a more sophisticated perspective that integrates symptoms, biological, genomic, brain and clinical data.

Technology Description: Moving towards rational drug development in MDD and Alzheimer’s

The paradigm shift in neuropsychiatry dictates that a new model should be applied to mental health drug research, as exemplified by the NIMH adoption of “experimental medicine” clinical trials. This approach relies on key features that ensure trials will have a greater probability of success and will contribute knowledge on the causes of success or failures. Such features include a deeper understanding of the pathology of these diseases, the pre-selection of subjects harboring the pathological endophenotype of interest (disease stratification), and the monitoring of biological markers tracking those pathologies during the trial (i.e. target engagement).

Over the past 15 years, the main goals of Dr. Sibille’s research program have been (1) to identify cellular and molecular mechanisms in depression, aging, and their interaction, using human post-mortem brain samples, (2) to characterize their putative contribution to symptom dimensions (rodent causal studies; Rule IN/OUT), and (3) to use this knowledge to develop strategies for new therapeutic approaches in psychiatry. Candidate pathway leads from these studies represent novel targets in the proposed novel drug development pipeline. An overview on these candidate targets will be discussed at the meeting.

Innovative antidepressant drug development – Approach and structure.

To accelerate the translation of basic science findings into clinically-useful drugs, we propose an accelerated drug development model that will allow for Fast-Try/Fast-Fail of lead targets and compounds. This concept relies on
identifying key components at the intersection of academia, biotech and pharma. Necessary steps can be summarized as such: (1) Target identification, (2) lead compound identification, (3) pre-clinical validation, (4) target engagement assay development in humans, (5) intellectual property portfolio development, (6) toxicology studies (animals and humans), and finally (7) proof of concept clinical trial in a stratified population (based on genetics and target engagement) (i.e. Phase 2a). This adapted structure is based on the stage of development of available compounds. For instance, selected pharmas and biotechs may be currently developing similar compounds although for different purposes.

The disruptive concept is to perform a target-specific thorough analysis of the market and of available reagents, assays and tools and to then implement and complete the key stages described above in parallel rather than in a traditional sequential process. This will lead to a proof-of-concept clinical trial that is informed by the primary pathology and monitored by novel target engagement tools. The goals are (1) the rapid development of the most promising treatments for mental illness, (2) to jumpstart the neuropsychiatry drug development process and landscape, and (3) provide an informed plan to de-risk the next clinical phase (i.e. 2B and 3). To implement this strategy we propose to establish a holding company with expertise in this “innovative antidepressant drug development”. This entity would assess/vet all key elements for each new lead, manage the parallel processing of the key steps, and maintain constant contact with all stakeholders. Resources for the holding company will be provided by venture capitalist investment, CAMH Foundation, private donors and grants.

**Stage of Development:** Several human pathology-informed targets have been identified. The most advanced target and compound leads focus on augmenting signaling at Alpha5-containing GABAA receptors with alpha5-PAMs for mood and cognitive symptom dimensions in rodent models of stress/depression. These studies provide a proof-of-concept that the drug platform identifies lead drug targets - patent application filed.

**Advantages:**

- More **efficient process and pipeline** to translate basic science on brain disorders into drug development
- Intrinsic **target engagement** and patient stratification tool development for personalized medicine
- Target discovery informed by the primary pathology in human subjects
- Moving from a categorical definition of disease towards a continuous modular perspective
- Accelerated drug development model that will allow for Fast-Try/Fast-Fail of lead targets and compounds
- **Multidisciplinary team** - CAMH is the largest psychiatry hospital and research center specialized in neuropsychiatry in Canada, and as such it houses a considerable level of expertise in basic science, genetics, imaging, preclinical and clinical research. Collaborations with experts at multiple other sites (US and EU) are also established on a project basis.


**Patent Application:** Patent application filed in US

**Business Opportunity:** We are seeking partnerships with pharma who may be interested in partnering to utilize this platform as a screening tool for early stage drug discovery.
A Conceptual Shift in Brain Disorders:
Moving from categorical definitions...
...towards a continuous modular perspective

Compare to Cardiovascular Disorders:
Moving from categorical definitions...
...towards a continuous modular perspective

Identified phenotype: Altered SST-expressing inhibitory GABA neuron function

A pipeline of new targets (Sibille lab, CAMH)

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TEAM

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- **Zafiris Jeff Daskalakis, M.D./Ph.D.** CAMH senior scientist; Professor, Department of Psychiatry, University of Toronto; Director of the Temerty Centre for Therapeutic Brain Intervention. Expert in TMS-EEG/EMG and inhibitory protocols in human subjects.
- **Beverly Orser, M.D./Ph.D.**, Professor of Physiology, University of Toronto, Canada. Expert in anaesthetics and on electrophysiological properties on GABAA receptors, anesthesia, behavior and pain.
- **Miroslav Savic, Ph.D.**, Assistant professor, Faculty of Pharmacie, University of Belgrade, Serbia. Expert in PK/PD, and drug brain penetration, metabolism and therapeutic levels.
- **Margot Ernst, Ph.D.**, Assistant Professor, Department of Molecular Neurosciences, Center for Brain Research, Medical University of Vienna, Austria. Expertise in oocyte electrophysiology.
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- **Margot Ernst, Ph.D.**, Assistant Professor, Department of Molecular Neurosciences, Center for Brain Research, Medical University of Vienna, Austria. Expertise in oocyte electrophysiology.
- **Catherine Belzung, Ph.D.**, Professor, Université de Tours, France. Expert in preclinical rodent models of neuropsychiatric disorders, specifically depression.
- **David A. Lewis, M.D.**, Professor and Chair, Department of Psychiatry, Director of Brain Bank Donation program, University of Pittsburgh, PA, USA. Expert in postmortem studies in neuropsychiatry.
- **Benoit Mulsant**, and **Tarek Raji**, PaCT-MD

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