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NON-CONFIDENTIAL SUMMARY

INVENTOR(S): **ETIENNE SIBILLE, JAMES COOK ET AL**

CAMH TECHNOLOGY ID: 005-2016

BUSINESS OPPORTUNITY

The Centre for Addiction and Mental Health is seeking partners to either license or co-develop this technology. CAMH is open to various forms of collaboration.

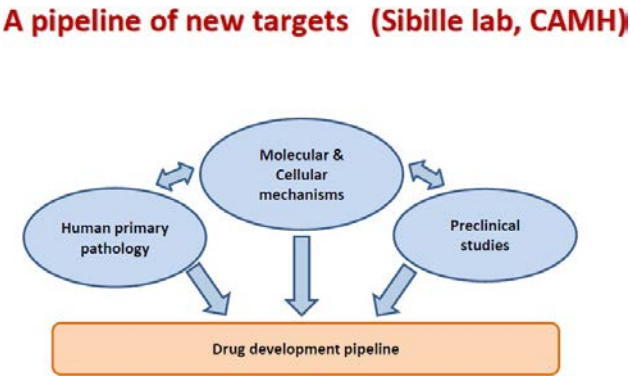
Treatment of Cognitive and Mood Symptoms with $GABA_A$-Receptor Alpha5 Subunit Agonists

Market Need

According to the World Health Organization, major depressive disorder (MDD) is a leading cause of disability, affecting 350 million people worldwide. It is a complex disorder with symptoms that include low affect, anhedonia, anxiety, rumination, appetite changes, sleep disturbances, and cognitive impairments. Its early onset and chronic nature have serious consequences for lost education and unemployment. Cognitive impairments are part of the comorbid symptoms that develop alongside anxiety, anhedonia, sleep disturbance and other deficits. Cognitive dysfunction refers to deficits in attention, visual and auditory processing, short term and working memory, motor function, learning and memory processes. Despite overwhelming consensus on the importance of cognitive impairment in depression, there is no conclusion regarding the full profile of cognitive impairment in depression. Cognitive impairments may be a primary dysfunction in MDD and several other core symptoms may act as mediators of cognitive dysfunction. Current antidepressant medications are all derived from approaches and modes of action that were discovered by chance over 50 years ago. These drugs act predominantly on the monoamine (serotonin and norepinephrine) systems. They often take weeks to achieve therapeutic effects, and subjects experience poor response, low remission rate (~50%) and considerable side-effects. Moreover, available antidepressants are not designed to treat cognitive impairment, and in some cases (like some benzodiazepines), their positive effects on some dimensions of the illness (anxiety, anhedonia) are counterbalanced by negative side effects affecting cognition. Furthermore, clinical studies have demonstrated that cognitive deficits are still detected even in periods of remission from mood symptoms. Hence, developing antidepressants that can potentially rescue the cognitive dysfunction as well as the emotional and motivational symptoms seem critical for future treatment of MDD.

Technology Description

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 basis and complexity of brain-based illnesses. Recent landmark studies show that genetic, molecular and cellular pathologies are partly shared across brain disorders.



This suggests novel strategies for drug development with therapeutic potential across psychiatric (e.g. depression and schizophrenia), cognitive and extending to neurodegenerative (e.g. Alzheimer's disease) disorders.

Over the past 15 years we have identified several such targets for major depression, cognition and other brain disorders through direct molecular investigations of the brain of affected and control individuals. These targets have been further validated in pre-clinical rodent studies and include neurotrophic factors, proteostasis, astroglia and others. This has led to the GABA system and to the alpha5 subunit containing $GABA_A$ receptor as a novel target for cognitive remediation and antidepressant/anxiolytic treatment.

Genetic and pharmacological studies from our group suggest that deficits in SST-positive GABA neurons play a causal role in depression and loss of cognition. Preliminary results also suggest rapid and sustained antidepressant effects and pro-cognitive effects (without any overt side-effects) for compounds that target α5-containing $GABA_A$ receptors (α5$GABA_A$R). We have a series of small molecules which primarily target inhibitory $GABA_A$ receptor Alpha5 subunit, the pharmacological effect is positive allosteric modulation (Alpha5-PAM), and the therapeutic indication is for depression and other disorders that share mood and cognitive deficits, potentially focusing on the cognitive and rumination core symptoms. Our most advanced compounds have moved to the medicinal chemistry hit to lead compound optimization stage. Recent development: one of our more advanced compounds has demonstrated the ability to not only treat symptoms but to also halt and reverse an underlying pathology associated with dementia and Alzheimer's disease. In detail, this compound reversed the shrinkage of neurons normally observed during aging.

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 $GABA_A$ receptor with alpha5-PAMs for mood and cognitive symptom dimensions in rodent models of stress/depression. Our most advanced compounds have moved to the medicinal chemistry hit to lead compound optimization stage. We are currently testing our most promising compound in a large animal cognitive deficiency model to determine safety and efficacy.

Advantages

- Target discovery informed by the **primary pathology in human subjects**
- Intrinsic **target engagement** and **patient stratification** tool development for **personalized medicine**
- *In vitro* and *in vivo* behavioural mouse models and compound efficacy data package available
- Large animal studies in progress
- Proprietary compounds that show either or both pro-cognitive and antidepressant effects, treating both symptoms and pathology
- **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.

Notable Publication(s)

Sibille, E. Molecular Neuropsy (2019); DOI10.1159/000496086

Sibille, E., Molecular Psychiatry (2014); 19: 966–977

Sibille, E., Biological Psychiatry (2017); 81: 467–469

Sibille, E. et al, Frontiers in Pharmacology (2016); Vol 7, Article 446

Intellectual Property

This invention is protected by several patent applications in various stages of prosecution.

FOR MORE INFORMATION CONTACT

Dr. Klara Vichnevetski
Director, Industry Partnerships & Technology Transfer
klara.vichnevetski@camh.ca
416 595-6056

Centre for Addiction and Mental Health
33 Russell Street, Suite 4039
Toronto, Ontario, Canada M5A 2S1
www.camh.ca