



## Novel GABAAR- $\alpha$ 6 Subtype Selective Ligands for Pain and CNS Disorders

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### TECHNOLOGY

Through a joint collaboration, the inventors have synthesized and tested novel non-benzodiazepine GABA<sub>A</sub> receptor ligands functionally selective to the alpha 6 subtype ( $\alpha$ 6GABA<sub>A</sub>R). Recent studies have implicated the  $\alpha$ 6GABA<sub>A</sub>Rs as the valid target in trigeminal orofacial pain, neuropsychiatric disorders with sensori-motor gating deficits, depression, and migraine. The group has observed promising results in animal models for several of these indications, and the lead compounds show a lack of cytotoxicity, improved metabolic stability, an excellent bioavailability after oral administration, and appropriate brain concentrations, rendering them potential candidates for treatment of CNS disorders.



Many GABAergic drugs on the market today offer little subtype selectivity and thus exhibit undesired side effects (sedation, ataxia, amnesia, tolerance, and addiction). There has been a lack of new drugs developed for CNS disorders, while the social, clinical, and economic need remains. We believe our team has discovered the first  $\alpha$ 6GABA<sub>A</sub>R selective ligands. The team continues to explore indications including epilepsy, tic disorders, schizophrenia, obsessive compulsive disorders, attention deficit disorders, depression, migraine, and pain.

### FEATURES/BENEFITS

- **Functionally selective** – The novel compounds are functionally selective for the  $\alpha$ 6GABA<sub>A</sub>R subtypes
- **Non-Sedating** – Avoidance of the  $\alpha$ 1-subtype aids in preventing sedative and other psychomotor-impairing effects
- **Metabolically stable** – Deuteration of the methoxy group of aryl-pyrazoloquinolinones improves metabolic stability and optimizes bioavailability
- **Safer/Less addictive** – Compounds which are silent or nearly silent at the  $\alpha$ 1-and  $\alpha$ 5- receptor subtypes should demonstrate limited tolerance and less addictive effects

### INTELLECTUAL PROPERTY

US and EP Nationalized Applications PCT/US2016/035761.

This technology is part of an active and ongoing research program and is seeking partners for development of the final product. It is available for developmental research support/licensing under either exclusive or non-exclusive terms.



## Technology Overview



### MARKETS

At some point 45% of people will be affected by some type of neuropsychiatric disorder, and unmet needs are increasing. Global migraine sales are expected to grow to \$8.7 billion by 2026, however current treatments leave a large number of patients undertreated; many of the drugs, for both acute and preventative treatment, have poor efficacy profiles which are ineffective in a large number of patients. Epidemiologists forecast the diagnosed prevalent cases of ADHD to grow by 2.86% per year over the next 10 years, to 34M cases in 2024.



People with Tourette's disorder or chronic tic disorder are over four times more likely to die by suicide than the general population, according to a new study in Biological Psychiatry. The results highlight an under-recognized need in patients with chronic tic disorders.

### INVENTORS

James Cook, Margot Ernst, Miroslav Savic, Werner Sieghart, Lih-Chu Chiou, Pi-Chuan Fan

Dr. James Cook is a University Distinguished Professor in the Department of Chemistry & Biochemistry at the University of Wisconsin-Milwaukee. His laboratory is currently seeking drugs to treat schizophrenia, addiction, neuropathic pain, and asthma. His goal is to create drugs that are better and safer than those currently on the market for CNS disorders.

Dr. Margot Ernst is an Assistant Professor in the Department of Molecular Neurosciences at the Medical University of Vienna. Her laboratory focuses on identification and pharmacology of subtype selective compounds and the molecular mechanisms behind so-called functional selectivity for the GABAR.

Dr. Miroslav Savic is a Professor in the Department of Pharmacology at the University of Belgrade. His laboratory interests include tests and models used in behavioral pharmacology and psychopharmacology, especially of GABAR-active ligands, conventional and novel drug delivery systems, and pharmacokinetics.

Dr. Werner Sieghart is a Professor in the Department of Molecular Neurosciences at the Medical University of Vienna, whose group studies the pharmacological properties of the GABAAR.

Dr. Lih-Chu Chiou is a Professor in the Department of Pharmacology of the College of Medicine at National Taiwan University. Her laboratory focuses on neuropharmacological studies using electrophysiological and behavioral approaches, investigating the roles of various neurotransmitter receptors in neurological and psychiatric disorders, including pain, addiction, migraine, schizophrenia, Tourette syndrome, depression, ADHD, and Alzheimer's disease.

Dr. Pi-Chuan Fan is an assistant professor in the Department of Pediatrics of the College of Medicine at National Taiwan University, and an attending pediatric neurologist at National Taiwan University Hospital. She is an expert in migraine studies in both clinical and basic aspects.

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