Novel Compounds for the Treatment of Alcohol Addiction and Anxiety

OTT ID # 1147

APPLICATIONS

Pharmaceuticals, Chemical Addiction (Alcohol, Nicotine and Opioids), Medicinal Chemistry, Drug Discovery, Substance Abuse Treatments etc.

TARGET PROBLEMS

- Drug and alcohol dependence remain a significant public health concern
- Classically used benzodiazepine α1 agonists are addictive, sedating, ataxic, and amnesic with abuse liabilities
- Alcohol dependent individuals represent a heterogeneous group, and often suffer from anxiety and depression during withdrawal making compliance a problem.

KEY BENEFITS

- **More Specific** - Compounds targeted to the α1 subunit of the GABA receptor
- **Less Sedation** - Lead compounds show fewer sedative effects with alcohol
- **Reduced Anxiety -** Animal studies demonstrate anxiolysis
- **Unmet Medical Need** - Current medications for chemical abuse are limited in effect
- **Animal Models for Addiction** - Available on request

TECHNOLOGY

Inventors at University of Wisconsin-Milwaukee have developed novel aza-beta carboline compounds that are useful for the treatment of several diseases and conditions including chemical addiction (alcohol, nicotine, and opioids), anhedonia, anxiety, and other conditions associated with withdrawal. These compounds are designed to bind selectively to the α1 subtype GABAA receptor. Evidence has shown that the α1 GABAA receptor subtype in the striato-pallidal and extended amygdala system regions of the brain regulates alcohol seeking behaviors. GABA systems have been implicated in both the physical/somatic and the motivational symptoms of ethanol withdrawal. Alcohol dependence and anxiety frequently co-occur in psychiatric patients and can significantly complicate treatment outcomes. It has been found that those with anxiety disorders are more likely to be diagnosed with alcohol dependence. The inventors have shown that α1-preferring ligands reduce ethanol intake and produce anxiolysis in alcoholic rats. The lead compounds also show a reduced capacity to potentiate GABA in *Xenopus* oocytes and HEK cells assays, demonstrate fewer sedative effects with alcohol, and can antagonize the reinforcing actions of alcohol in both nondependent and dependent rats. The results of the present study demonstrate that βCCt, 3-PBC, and 3-ISOPBC are highly effective anti-anxiety agents in P and HAD rats but not normal rats. The lead compounds represent prototypes of novel pharmacotherapeutic agents that can be

used to treat alcohol abuse and alcoholism and can be easily scaled up to produce multigram quantities.

INTELLECTUAL PROPERTY

U.S. Utility Patent 8,268,854; Aza-Beta Carbolines and Methods of Using Same

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

INVENTOR(S)

Lead Inventor: James Cook, Ph.D.

Others: Michael Van Linn, Ph.D., Wenyuan Yin, Ph.D.

PUBLICATIONS

- Kaminski, B., et al. Effects of the benzodiazepine GABAA α1 selective ligand, 3-propoxy- β-carboline hydrochloride (3- PBC), on alcohol seeking and self-administration in baboons. Psychopharmacology, *manuscript submitted*.

- Yin, W., et al. Design, synthesis, and subtype selectivity of 3,6-disubstituted β-carbolines at Bz/GABA(A)ergic receptors. SAR and studies directed toward agents for treatment of alcohol abuse. (2010). Bioorg. Med. Chem. 18(21): 7548-64.

- Clayton, T., et al. An updated unified pharmacophore model of the benzodiazepine binding site on gamma-aminobutyric acid(a) receptors: correlation with comparative models. (2007). Curr. Med. Chem. 14(26): 2755-75.

- June, H.L., et al. Dopamine and benzodiazepine-dependent mechanisms regulate the EtOH-enhanced locomotor
- stimulation in the GABA(A) alpha1 subunit null mutant mice. (2006). Neuropsychopharmacology. 32(1): 137-52.

- Harvey, S.C. et al. The GABA(A) receptor α1 subtype in the ventral pallidum regulates alcohol-seeking behaviors. (2002). J. Neurosci. 22(9): 3765-75.

For further information please contact:

Smruti Patil, Ph.D., IPMM
Licensing Associate
UWM Research Foundation
1440 East North Avenue
Milwaukee, WI 53202
Email: smruti@uwmrf.org
Tel: 414-906-4657

Please reference: OTT ID. 1147