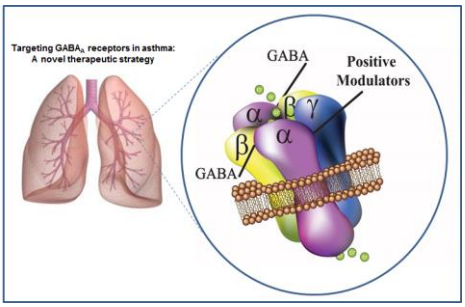
Technology Overview

A New Oral Drug for Asthma Treatment

OTT ID #1319, 1516, 1519

TECHNOLOGY



Inventors at the University of Wisconsin-Milwaukee and Columbia University have developed lead drug compounds for asthma based on a **fundamentally novel mechanism of action**. These small molecule drugs are orally active, improving compliance over inhaled medications. The drugs target functional gamma-amino butyric acid type A receptors ($GABA_AR$) expressed on airway smooth muscle (ASM) and immune/inflammatory cells, avoiding the use of corticosteroids and adrenergic agonists. The lead drugs are positive allosteric modulators of $GABA_AR$ that relax pre-contracted human and rodent ASM. In rodent allergic asthma models, the drugs reduce airway hyper-responsiveness (AHR), inflammatory cells, and inflammatory cytokines. Pharmacokinetic and ADME studies show good plasma half-life and lung distribution, without CNS exposure. Repeat-dose toxicity studies show no systemic adverse effects or immune alterations. Taken together, studies show that these new molecular entities, orally delivered, effectively alleviate the cardinal signs of asthma (AHR and inflammation) without systemic toxicities or immune suppressive effects. Despite the growing appreciation of $GABA_AR$ signaling in asthma cell types, a strategy that unifies and targets $GABA_AR$ responses in the lung has not heretofore been developed or exploited therapeutically.

Families of chemical compositions are claimed in the patent applications, along with formulations and methods of treatment for various constrictive lung disorders. The invention sets forth an innovative strategy for a first-line asthma drug based on a fundamentally novel mode of action, novel drug compositions, improved dosing, and reduced potential for adverse effects compared to current corticosteroids or adrenergic agonists. Current first-line asthma treatments have known safety, efficacy, compliance, and immunosuppression liabilities. Asthma remains the most prevalent chronic disease in children, with an overall prevalence estimated at 8% of the U.S. population. Over one-half of pediatric patients and three-fourths of adults are reported to be non-compliant with current medications. Taken together, an unmet need exists for a safe, effective, oral drug for the majority of asthma sufferers.

FEATURES/BENEFITS

- **Known Drug Target -** $GABA_AR$ structure and function are well characterized and have been drugged for 50 years for other indications; safety profile well established.
- **Target Selectivity –** A restricted set of $GABA_AR$ are found on target tissues in the lung, allowing for ligands (drugs) with narrowly tailored activity (lead compounds interact selectively with α4 and/or α5 containing $GABA_AR$). Lead drugs are designed to act in the lung tissue to suppress inflammation and AHR, but are designed to avoid off-target effects and CNS distribution.
- **Efficacy Demonstrated –** Lead compounds reduce AHR in isolated human and rodent ASM. Compounds reduce AHR and inflammation in established asthma models.
- **Reduced Side Effects** – Avoiding corticosteroid use will improve safety and avoid potential resistance and immunosuppression.
- **Improved dosing –** Compounds are orally available; can avoid inhaler delivery, improve dosing, and promote better compliance.

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INTELLECTUAL PROPERTY
US2015-0232473 pending; separate PCT filed August 2017 for new lead compounds

MARKETS

According to the Global Initiative for Asthma (GINA), in the year 2013, approximately 300 million persons globally were estimated to be afflicted with asthma and this number is expected to grow in the coming years. The global COPD and asthma therapeutic market is predicted to reach $34.3 billion by 2020.

SELECTED PUBLICATIONS

- Forkuo, G., et al. 2017. Alleviation of Multiple Asthmatic Pathologic Features with Orally Available and Subtype Selective GABAA Receptor Modulators. Mol Pharm. 14(6):2088-2098.
- Yocum, G., et al. 2017. GABAA Receptor α4 Subunit Knockout Enhances Lung Inflammation and Airway Reactivity in a Murine Asthma Model. Am J Physiol Lung Cell Mol Physiol. 313(2):L406-L415.
- Jahan, R, et al. 2017. Optimization of substituted imidazobenzodiazepines as novel asthma treatments. Eur J Med Chem. 126:550-560.
- Forkuo, G., et al. 2016. Development of GABAA Receptor Subtype-Selective Imidazobenzodiazepines as Novel Asthma Treatments. Mol Pharm. 13(6):2026-38.
- Yocum, G., et al. 2016. Targeting the γ-Aminobutyric Acid A Receptor α4 Subunit in Airway Smooth Muscle to Alleviate Bronchoconstriction. Am J Respir Cell Mol Biol. 54(4):546-553.

INVENTORS

Douglas Stafford, James Cook, Charles Emala, Alexander Arnold, George Gallos, Michael R. Stephen

Dr. Douglas Stafford is the Director for the Milwaukee Institute for Drug Discovery at the University of Wisconsin-Milwaukee. He has over 25 years of experience in biomedical product companies with senior management responsibilities in research and development, manufacturing operations, regulatory and clinical affairs, organizational development, patent licensing, and finance. Dr. Stafford is inventor on over a dozen biomedical patents, has formed numerous public and private research collaborations, and participated in the development of several entrepreneurial businesses. Dr. James Cook is a University Distinguished Professor in the Department of Chemistry & Biochemistry at the UW-Milwaukee. A large focus of the Cook laboratory is designing compounds that selectively target $GABA_AR$ and their development as drugs for diseases such as asthma, anxiety, schizophrenia, Alzheimer's disease, and neuropathic pain. Dr. Charles Emala is the Henrik H. Bendixen Endowed Professor of Anesthesiology and Vice Chair for Research in the Department of Anesthesiology at Columbia University College of Physicians and Surgeons. His laboratory was the first to describe the expression of $GABA_A$ channels on airway smooth muscle and their ability to mediate relaxation. Dr. Alexander Arnold is an Associate Professor in the Department of Chemistry and Biochemistry at the UW-Milwaukee. The Arnold Group applies high-throughput screening, rational design, and virtual screening for the discovery process as well as medicinal chemistry and molecular biology to determine small molecule modes of action. Dr. George Gallos is an Assistant Professor of Anesthesiology at Columbia University Medical Center. His research interests include mechanisms of smooth muscle relaxation, in particular the role $GABA_A$ channels may play in modulating airway smooth muscle and uterine smooth muscle relaxation.

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