GABAA RECEPTOR AGONISTS FOR TREATMENT OF BRONCHOCONSTRICTIVE DISORDERS

OTT#1319

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 (GABAAR) 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 GABAAR 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 GABAAR signaling in asthma cell types, a strategy that unifies and targets GABAAR 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.

Key Features

- **Known Drug Target** – GABAAR 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 GABAAR 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 GABAAR). 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.

Intellectual Property

US9879020B2 "GABAA agonists and methods of using to control airway hyperresponsiveness and inflammation in asthma" (expiration 2033)

US11447495B2 "Substituted benzo[f]imidazo[1,5-a][1,4]diazepines as GABA(a) receptor modulators" (expiration 2039)

AU2017313753A1 "GABA(A) receptor modulators and methods to control airway hyperresponsiveness and inflammation in asthma" (expiration 2037)

EP3500573B1 "Gaba(a) receptor modulators and methods to control airway hyperresponsiveness and inflammation in asthma" (expiration 2037)

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.

Publications

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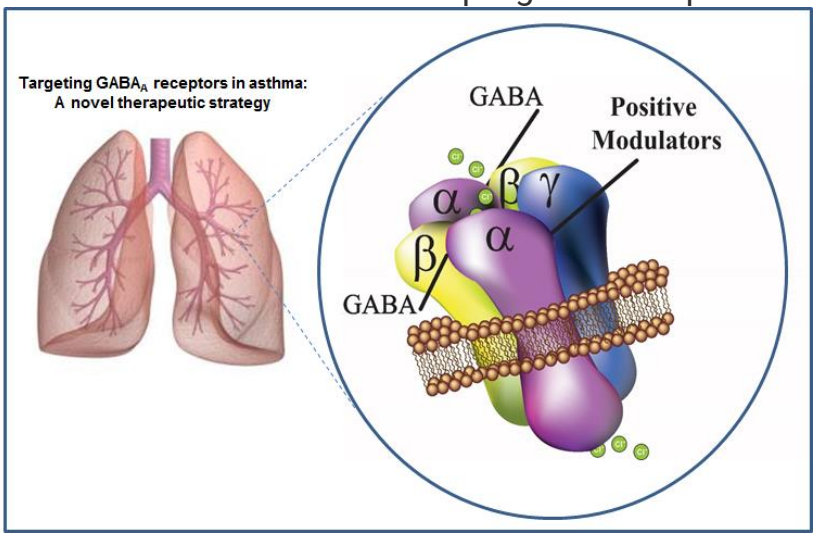
Inventor(s)

Alexander Arnold is an Professor in the Department of Chemistry and Biochemistry at the UW Milwaukee and is directing the Milwaukee Institute for Drug Discovery. The Arnold Group supports all part of drug discovery and development from high-throughput screening and rational drug design to in vivo pharmacodynamics and pharmacokinetics. **Dr. Douglas Stafford** has been the former director for the Milwaukee Institute for Drug Discovery at the University of Wisconsin-Milwaukee and is current the CEO of Pantherics Inc. 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. James Cook** is a retired 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 GABAAR 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 GABAA channels on airway smooth muscle and their ability to mediate relaxation.

UWM scientists developing asthma pill



Dr. Alexander (Leggy) Arnold is a Professor in the Department of Chemistry and Biochemistry at the University of Wisconsin-Milwaukee and is directing the Milwaukee Institute for Drug Discovery. During the last decade, the Arnold Group has developed GABA(A) receptor ligands that do not cross the blood brain barrier and elicit airway smooth muscle relaxation and antiinflammation.

Dr. James Cook is a retired University Distinguished Professor in the Department of Chemistry & Biochemistry at the University of Wisconsin-Milwaukee. A large focus of the Cook laboratory revolves

around compounds targeting GABAAR and their development as drugs for diseases such as anxiety, schizophrenia, neuropathic pain and asthma.

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