GABAA Receptor Agonists for Oral Treatment of Asthma

OTT1319

Applications

Asthma pill avoids inhaler delivery and corticosteroid side effects

Target Problems

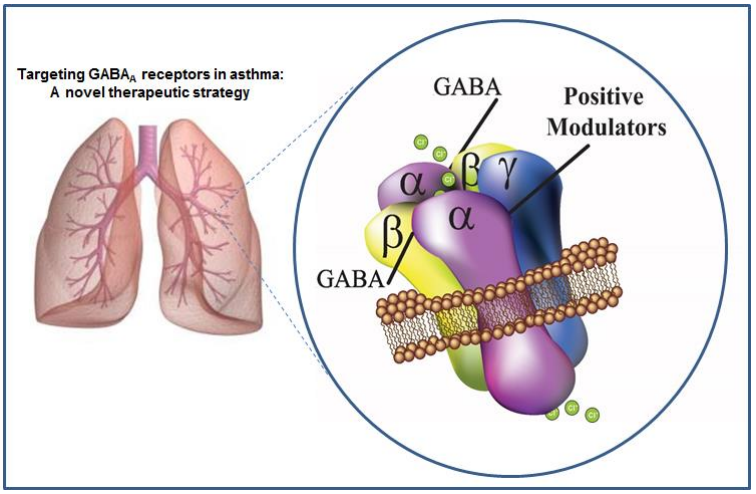
Over one-half of pediatric patients and three-fourths of adults are reported to be non-compliant with current asthma medications. This technology improves compliance over inhaled medications with small molecule drugs that are orally active.

Key Features

- **Improved Dosing** – Compounds are orally available; can avoid inhaler delivery, improve dosing, and promote better compliance.
- **Reduced Side Effects** – Avoiding corticosteroid use will improve safety and avoid potential resistance and immunosuppression.
- **Efficacy Demonstrated** – Lead compounds reduce airway hyper-responsiveness in isolated human and rodent airway smooth muscle.
- **Target Selectivity** –Lead drugs are designed to act in the lung tissue to suppress inflammation and airway hyper-responsiveness but are designed to avoid off-target effects and central nervous system distribution.
- **Known Drug Target** – GABAAR structure and function are well characterized and have been drugged for 50 years for other indications; safety profile well established.

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 and immune/inflammatory cells, avoiding the use of corticosteroids and adrenergic agonists.



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)

About the Inventor(s)

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Publications

Perez-Zoghbi JF et al. Imidazobenzodiazepine PI320 Relaxes Mouse Peripheral Airways by Inhibiting Calcium Mobilization. Am J Respir Cell Mol Biol. 2022 Oct;67(4):482-490

Rashid Roni MS et al. Comparative pharmacodynamic and pharmacokinetic study of MIDD0301 and its (S) enantiomer. Drug Dev Res. 2022 Jun;83(4):979-992

Zahn NM at al. Development of Inhaled GABAA Receptor Modulators to Improve Airway Function in Bronchoconstrictive Disorders. ACS Pharmacol Transl Sci. 2022 Feb 1;5(2):80-88

Roni MSR et al. Identification and Quantification of MIDD0301 Metabolites. Curr Drug Metab. 2021;22(14):1114-1123

Zahn NM et al. Nebulized MIDD0301 Reduces Airway Hyperresponsiveness in Moderate and Severe Murine Asthma Models. ACS Pharmacol Transl Sci. 2020 Dec 2;3(6):1381-1390.

Knutson DE et al. Improved scale-up synthesis and purification of clinical asthma candidate MIDD0301. Org Process Res Dev. 2020 Aug 21;24(8):1467-1476

Roni MSR et al. The Effects of pH on the Structure and Bioavailability of Imidazobenzodiazepine-3-Carboxylate MIDD0301. Mol Pharm. 2020 Apr 6;17(4):1182-1192

Zahn NM et al. MIDD0301 - A first-in-class anti-inflammatory asthma drug targets GABAA receptors without causing systemic immune suppression. Basic Clin Pharmacol Toxicol. 2019 Jul;125(1):75-84

Yocum GT et al. A novel GABAA receptor ligand MIDD0301 with limited blood-brain barrier penetration relaxes airway smooth muscle ex vivo and in vivo. Am J Physiol Lung Cell Mol Physiol. 2019 Feb 1;316(2):L385-L390

Forkuo GS et al. A Novel Orally Available Asthma Drug Candidate That Reduces Smooth Muscle Constriction and Inflammation by Targeting GABAA Receptors in the Lung. Mol Pharm. 2018 May 7;15(5):1766-1777

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

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