Docket #: S17-467

Highly selective Beta-2 adrenergic receptor agonists for treating asthma, COPD and other bronchoconstrictive disorders

Disease indication -Acute asthma, COPD, other bronchoconstrictive disorders (bronchial asthma, allergic asthma, intrinsic asthma, airway hyper-responsiveness, chronic bronchitis) with potential for treating heart failure. In particular, these molecules could be used in a rescue inhaler.

Drug format - Small molecule (analogs of catecholamine type compounds such as isoprenaline, adrenaline and noradrenaline).

Drug class - Improvement of existing class of bronchodilators.

Research stage and Preliminary data - The inventors have validated the compounds in vitro, demonstrating 100-fold selectivity for the β_2-AR over the β_1-AR in a radioligand binding assay, and 1000-fold selectively for the β_2-AR over the β_1-AR in an arrestin recruitment assay.

Target - Beta-2 adrenergic receptor (β_2-AR).

Background - The adrenergic family of receptors are the primary points of action for the hormones adrenaline and noradrenaline. The receptors are divided into two subfamilies (α and β) which differ in ligand specificity, expression in tissues, and downstream signaling. In particular, activating β_2-AR induces relaxation of airway smooth muscle. Thus, compounds that target β_2-AR have been used as bronchodilators to treat various respiratory diseases including asthma and chronic obstructive pulmonary disorder (COPD). In contrast, β_1-AR is highly expressed in the heart and activating this AR can lead to elevated blood pressure, exacerbate coronary artery disease and cause arrhythmias. Therefore, if βAR drugs are not

selective, they activate β_1-AR along with β_2-AR, causing severe and unwanted side effects in asthma or COPD therapy.

Mode of action - These compounds are analogs of adrenaline and noradrenaline which activate β_2-AR with high selectivity over β_1-AR. They are short-acting β_2-AR agonists that can dilate airways in the lungs. In addition, the β_2 selectivity, makes them potential candidates for treating heart failure.

Competitive edge - These compounds could greatly **reduce the risk of cardiovascular side effects** (e.g., arrhythmia, elevated blood pressure) compared to traditional bronchodilators that target the β_2-AR. The molecules are 100 to 1000-fold selective for β_2-AR over β_1-AR whereas current therapies (e.g., salbutamol) are only 20-fold selective. In addition, the selective agonists are **likely to be more effective** than current therapies because they are full rather than partial agonists.

Potential competitor - Current bronchodilator agents such as albuterol (Ventolin, Proventil etc.).

Patents

- Published Application: WO2019112913
- Published Application: 20200360304
- Issued: 11,590,089 (USA)

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