

**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 (analog 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  $\beta_2$ -AR over the  $\beta_1$ -AR in a radioligand binding assay, and 1000-fold selectivity for the  $\beta_2$ -AR over the  $\beta_1$ -AR in an arrestin recruitment assay.

**Target** - Beta-2 adrenergic receptor ( $\beta_2$ -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 ( $\alpha$  and  $\beta$ ) which differ in ligand specificity, expression in tissues, and downstream signaling. In particular, activating  $\beta_2$ -AR induces relaxation of airway smooth muscle. Thus, compounds that target  $\beta_2$ -AR have been used as bronchodilators to treat various respiratory diseases including asthma and chronic obstructive pulmonary disorder (COPD). In contrast,  $\beta_1$ -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  $\beta$ AR drugs are not

selective, they activate  $\beta_1$ -AR along with  $\beta_2$ -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  $\beta_2$ -AR with high selectivity over  $\beta_1$ -AR. They are short-acting  $\beta_2$ -AR agonists that can dilate airways in the lungs. In addition, the  $\beta_2$  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  $\beta_2$ -AR. The molecules are 100 to 1000-fold selective for  $\beta_2$ -AR over  $\beta_1$ -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 \(USA\)](#)

## Innovators

- Roger Sunahara
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