**TITLE PAGE**

**Title:**

**Do we really need to keep redesigning β2-agonists for the management of asthma?**

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**Abstract:**

There is an enormous drive to refine therapeutic designs and delivery systems, but in this review we ask if this is always the right direction? We choose to play devil's advocate, and argue that refining drug design is not always needed, and what is actually needed is a greater understanding of the biology of the disease. Here we focus on asthma and the β2-agonist group of bronchodilators as an example of how a class of therapeutic has been developed and continues to be developmentally refined. In this review we define viral-induced exacerbations as the greatest cause of lung attacks and the most crucial time β2-agonist therapy is needed. We explore the reasons why β2-agonist therapy fails in patients with rhinovirus-induced exacerbations, and explain why further “engineered” β2-agonist therapies is likely to continue to fail in this subset of asthmatic population. We justify our perspective by returning to the biology that underlies the cause of disease and highlight the need for “more research” into alternative therapies for this population of asthmatic patients.

**Keywords:**

Rhinovirus

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β2-agonists

## The search for better therapeutics?

To improve treatment of chronic diseases, researchers and the pharmaceutical industry strive to develop better therapeutics. Usually this includes better delivery systems, greater selectivity, increased potency and a longer duration of action. The medicines we use today are a result of ongoing research and development by both parties. But at times one needs to ask how beneficial it is to over engineer an already effective drug? Is the pharmaceutical industry truly driven by need or by antiquated IP laws that only allow exclusivity for a relatively short period of time? In this review, we choose to play devil's advocate by arguing that refining drug design is not always needed and what is actually needed is a greater understanding of the biology of the disease. In this review we use asthma and the β2-agonist group of bronchodilators as an example of how a class of therapeutics have developed to treat and control asthma symptoms; explain when more can be ineffective and how we can address therapeutic failure by returning to the biology of the disease.

## Asthma

Asthma is a chronic inflammatory disease of the airways characterized by reversible airflow obstruction and if not controlled can cause morbidity and mortality amongst sufferers. A recent report inAsthma in Australia 2011 by the Australian Centre for Asthma Monitoring (ACAM) and the Australian Institute of Health and Welfare (AIHW) reported that over the last 10 years in Australia, asthma amongst people aged 5-34 years is decreasing, while there was no improvement amongst people over the age of 35 years [[1](#_ENREF_1)]. Despite this positive improvement in health, asthma remains problematic both in Australia and globally, affecting 2 million Australians [[2](#_ENREF_2)], 25 million in the USA [[3](#_ENREF_3)] and 300 million people worldwide [[4](#_ENREF_4)]. This disease is now also beginning to increase in developing countries [[5](#_ENREF_5)].

In a longitudinal study of an asthmatic population of 245 patients over a period of one year, it was found that hospital admission was the primary contributor to the total cost for health services, costing A$23,766 out of a total of A$28,938 for the health care sector in New South Wales [[6](#_ENREF_6)]. As such, asthma creates an economic burden by impacting directly on medical costs mostly through hospital visits but also indirectly through loss of productivity from work and premature death.

People with asthma react to a variety of allergic and non-allergic stimuli including house dust mites, pollen and mould, exercise, air pollution and agents in the workplace [[7](#_ENREF_7)]. These can result in reversible airflow obstruction, inflammation and hyper-responsiveness of the airways which clinically manifest with symptoms of episodic breathlessness, wheezing, coughing and chest tightness ranging from mild to life threatening if not controlled.

There are 2 classes of therapeutics that are used in the management of asthma and they include symptom reliever medications and symptom controller medications. According to the Global Initiative of Asthma (GINA) report, inhaled short acting β2-agonists are highly recommended as the first line therapeutic for relief from exacerbations [[8](#_ENREF_8)]. Long acting β2-agonists on the other hand have an increased duration of action, however for undetermined reasons its use as a mono-therapy has been reported to be detrimental on asthma health and carries the US Food and Drug Administration black box warning against mono-therapeutic use [[9](#_ENREF_9)]. As such the GINA report recommends long acting β2-agonists use only in combination with a corticosteroid as a low dose controller medication for the prophylactic or prevention of asthma symptoms [[8](#_ENREF_8)]. Nevertheless, many people with asthma remain under treated or non-compliant with their therapeutic regimens and are over reliant of short acting β2-agonists and this continues to affect successful asthma therapy [[8](#_ENREF_8), [10](#_ENREF_10)].

***History of bronchodilators in asthma***

The long history of research and development from the pharmaceutical industry has resulted in the evolution and discovery of selective β2-agonists which are amongst the best treatments for asthma management today [[11](#_ENREF_11)]. But prior to modern medicine, alternative bronchodilators were used in the treatment of asthma and their use dates back to ancient history.

Ma Huang (Ephedra Seneca) is an example of one of the first uses of bronchodilators for the treatment of respiratory symptoms. The active ingredient in this plant extract is ephedrine and its use in tea dates back to 2700 B.C. in Ancient China by Chinese Emperor Shen Nung and is documented in the Chinese pharmacopoeia "Shen-nung pen tsao ching" (Divine Husbandman's Materia Medica) as a natural medicine that was a heart stimulant and a reliever of breathing disorders. Ephedrine functions by indirectly releasing adrenergic derivatives (sympathetic amines) from the sympathetic nerve endings and results in an effect similar but more sustained to those of adrenaline.

In Western medicine, uses of adrenaline for the treatment of asthma originated from attempts to ingest adrenal glands [[12](#_ENREF_12)] and the biggest drive towards the use of adrenaline as a treatment of asthma came in 1906 when it was synthesized and made readily available by the chemist Friedrich Stolz. Initially, multiple modes of parenteral injection of synthesized adrenaline were explored because it was ineffective when administered orally, but by 1929 it was reported that inhalation was by far most effective and was soon combined with other bronchodilators such as stramonium in nebulizers but with quite severe adverse effects [[13](#_ENREF_13)].

Details of the adrenergic derivative isoprenaline, were first published in 1940 [[14](#_ENREF_14)]. Uses of isoprenaline were effective in all modes of delivery, however were also associated with adverse effects, albeit much less compared to adrenaline [[13](#_ENREF_13), [15](#_ENREF_15), [16](#_ENREF_16)]. In some cases high doses led to increased mortality rates as shown by global asthma epidemiological data. Soon after, researchers found that these adrenergic compounds had variable effects on different tissues. By 1948, adrenoceptors (AR) were characterised into α and β subtypes based on different functions [[17](#_ENREF_17)] and by 1967 the β AR receptors were further sub-divided to β1 and β2 isotypes and it was identified that the β2 isotype was responsible for bronchodilatation [[18](#_ENREF_18), [19](#_ENREF_19)].

Structure-activity pharmacology led to the development of salbutamol the first selective β2-agonist in 1960 [[20](#_ENREF_20)] which via an inhaled route was far superior to isoprenaline in terms of reduced adverse effects [[21](#_ENREF_21)]. Salbutamol became clinically one of the most effective drugs in asthma and paved the way for long acting forms of β2-agonists such as salmeterol. The discovery of long acting β2-agonists is without a doubt a very important step in the therapy of asthma. Whilst short acting therapeutics aided in the acute relief of symptoms, long acting β2-agonists in the presence of anti-inflammatory corticosteroids functioned to prophylactically treat bronchoconstriction in asthma. This provided asthma control and protection from symptoms over longer periods which short acting therapeutics could not. When combined with corticosteroids, long acting β2-agonists significantly improved patient outcomes, compliance, reduced exacerbations and acted as the most recommended and used therapy in the control of asthma symptoms [[7](#_ENREF_7)]. Today an enormous amount of resources are invested into the further development of more potent, long acting and ultra long acting forms of β2-agonist such as the long acting (12h) formoterol and more recently the ultra long acting (24h) indacaterol to name a few [[11](#_ENREF_11)]. Despite this pharmaceutical investment, current asthma guidelines still recommend the conventional salbutamol or salmeterol and corticosteroid combinations for the respective first line relief or management of asthma [[7](#_ENREF_7)].

Adrenergic derivatives were not alone in the history of bronchodilators. Xanthines are purine bases from which caffeine and theophylline are derived from, act as competitive non-selective phosphodiesterase inhibitors and adenosine receptor antagonists and were also used as bronchodilating therapies of asthma. The first documented use of xanthines and its effects on asthma were by Henry Hyde Salter in 1859 where he described an exciting relief as an asthmatic with strong black coffee [[22](#_ENREF_22)]. Following on, in 1922 the first clinical investigation of theophylline on bronchospasmolytic action in man was reported by S. R. Hirsch [[23](#_ENREF_23)]. Despite carrying a narrow therapeutic index and potential adverse effects on the cardiovascular system, xanthines have been proven to be very effective in the treatment of asthma [[11](#_ENREF_11), [24](#_ENREF_24)]. Today their variant formulations are still available as treatment for asthma and COPD, and have also paved the way for the development of more specific drugs such as selective PDE4 inhibitors and selective A1 adenosine receptor antagonists [[25](#_ENREF_25), [26](#_ENREF_26)].

### *Diagnosis of asthma and bronchodilators*

Airway hyperresponsiveness and the ability of bronchodilators to reverse airway obstruction are for many, the key clinical criteria by which asthma is diagnosed, and as mentioned above many different types of bronchodilators have been developed for this. Even today, many different types of bronchodilators are used in the management of asthma, but the most commonly used worldwide are β2-agonists.

***β2-agonists and the route of administration.***

It is interesting to note that inhalation of various drugs, for example through smoking, has been used for centuries. It therefore would seem logical that the administration of a drug to treat respiratory diseases should be given via this route. In the first half of the 20th century nebulisation of bronchodilators generally required large cumbersome apparatuses, however this was transformed by the development of the first pressurised metered-dose inhaler (MDI) by Riker laboratories in 1956 [[27](#_ENREF_27)]. This revolution in drug delivery technology spearheaded numerous advances in MDI design. Today's MDIs are vastly superior to those used in 1956, but even with such advances in technology most of the drug delivered from an MDI fails to reach the lungs as it is swallowed following deposition into the oropharynx.

Direct delivery to the lung does however have many advantages over oral delivery. Even in the initial studies using poor inhaler design, the most important advantage of this delivery was that the dose of bronchodilator needed to achieve bronchodilatation was considerably lower than when given via any other routes - thus reducing unwanted side effects [[15](#_ENREF_15)]. However inhalation of bronchodilators is not without its own limitations. Considerable skill is needed to co-ordinate actuation of the MDI with procedures involving deep inhalation and breath holding. As a result alternate routes of administration remain available for the very young, the infirm, and the incapacitated.

***β2-agonists mechanism of action***

Following administration of β2-agonists, bronchodilatation occurs as a direct result of the activation of β2 AR on airway smooth muscle cells. Classical β2 AR signalling involves stimulation of the G proteins coupled to the β2 AR, which in turn activates adenylyl cyclase which catalyses the conversion of ATP to cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA) which phosphorylates host proteins leading to its effector functions, including smooth muscle relaxation (Figure 1). The amount of cAMP induced following receptor activation depends upon the presence of functional receptors and the amount/activity of degradative enzymes. In airway smooth muscle cells, phosphodiesterase 4 (PDE4) is primarily responsible for the degradation of cAMP.

**Figure 1: Mechanism of β2-agonist induced airway smooth muscle relaxation.** Activation of the β2 AR results in the activation of adenylyl cyclase and increase in cAMP. Increased cAMP activates PKA and phosphorylates (P+) a number of proteins which subsequently alter the actin/myosin interaction and results in airway smooth muscle relaxation.

***Lung attacks: acute exacerbations of asthma***

Acute exacerbations of asthma are the major cause of morbidity, mortality and health costs related to the disease. Respiratory viral infections trigger approximately 85% of asthma exacerbation in adults and children and the mechanisms by which this occurs remain unclear [[28](#_ENREF_28)]. There are multiple respiratory viruses which can induce asthma exacerbations such as respiratory syncytial virus (RSV) which causes 11% and influenza 5% of all viral-induced asthma exacerbations. Of the respiratory viruses that result in asthma exacerbations, rhinovirus accounts for the majority causing about 62% of all viral-induced asthma exacerbations [[28](#_ENREF_28)]. Asthma medications such as corticosteroids and β2-agonists are the most common therapies for asthma management. During acute exacerbations including those caused by respiratory viruses, β2-agonists remain the primary rescue medication [[8](#_ENREF_8)]. In most cases lung attacks are immediately resolved in response to inhaled β2-agonists, however this is not the case in some people, especially during virally induced asthma exacerbations [[29](#_ENREF_29), [30](#_ENREF_30)]. Currently there is no absolute answer as to why β2-agonists fail in this small subset of exacerbating asthmatics. However 3 schools of thought exists that attempt to explain this clinical phenomenon.

***β2-agonist over use and tachyphylaxis***

The β2 AR is a G-coupled protein receptor (GPCR), and in fact is one of the prototypic GPCRs from which most of our knowledge of GPCR function is derived [[31](#_ENREF_31)]. In general GPCRs act to regulate homeostasis. As such, in circumstances when an abundant amount of ligand is present this would have the effect of continually activating the GPCR and producing deleterious biological effect. However, over stimulation of the receptor is prevented through a protective biological process called desensitization [[31](#_ENREF_31)]. In the treatment of asthma, tachyphylaxis to β2-agonists is extremely controversial [[32](#_ENREF_32)]. β2-agonists have two different effects on airway physiology; bronchodilatation - direct induction of smooth muscle relaxation, and bronchoprotection - the ability of previously administered β2-agonists to protect against bronchospasm. In experimental conditions it is easy to demonstrate that tachyphylaxis to β2-agonist occurs, both to bronchoprotection and bronchodilatation [[33](#_ENREF_33), [34](#_ENREF_34), [35](#_ENREF_35), [36](#_ENREF_36), [37](#_ENREF_37)]. Tolerance to β2-agonists has also been observed in clinical situations when β2-agonists are misused or overused [[38](#_ENREF_38)]. Interestingly, this phenomenon also occurs when they are used appropriately, for example it has been reported that the protection against exercise wains with regular use of β2-agonists [[39](#_ENREF_39)]. “Overuse” of β2-agonists can reflect a patient’s lack of response or tachyphylaxis to β2-agonists, indicate poor asthma control or identify the need for alternative therapies such as steroids. As such, this behaviour can diagnose the severity of a patient’s asthma, reflect the quality of their asthma management and be used to predict lung attacks [[40](#_ENREF_40)].

If we now take the time to think about what happens during a lung attack, as patients begin to experience difficulty breathing they will begin to use β2-agonists. As such when they present themselves at emergency departments, they have already used large amounts of β2-agonists and have marked bronchoconstriction [[41](#_ENREF_41)]. We know experimentally that tachyphylaxis to β2-agonist induced bronchodilatation occurs proportionally to the degree of bronchoconstriction (the more muscle contraction the greater the lack of response to β2-agonists) so overuse-induced tachyphylaxis might explain why some people fail to respond to β2-agonists [[35](#_ENREF_35)]. In some people however, inadequate use of bronchodilators is a contributing factor leading to their lung attacks. As these people haven’t taken large doses of β2-agonists in the lead up to their lung attack, it is difficult to imagine how β2-agonist induced tachyphylaxis could be occurring. Therefore we need to look into greater detail at what is actually occurring in the lungs.

***Airway Physiology, mucous and virus-induced lung attacks.***

The lungs are composed of a series of branching airways that are essentially asymmetrical. As the airways branch they become continually smaller until they end in the acinous – the smallest functional unit consisting of a respiratory bronchiole and alveoli. This heterogeneity in lung structure is also mirrored by heterogeneity of ventilation, especially when constriction occurs, first demonstrated by imaging techniques in 2005 [[42](#_ENREF_42)]. The patchiness of ventilation and airway collapse has obvious implications for the delivery of inhaled β2-agonists. If the drug never reaches the site of obstruction could this be the reason why there is a lack of response during a lung attack? The answer is we currently do not know. Due to the difficulty of administering inhaled β2-agonists in young children, many countries administer β2-agonists in syrups, however this means the drug is distributed through the systemic circulation. Similarly, during hospital emergency room visits for lung attacks, β2-agonists can be administered intra-venously. In both situations, patients respond to β2-agonists albeit at much larger doses that would be required to provide bronchodilatation during periods of poor asthma control and/or in lung challenge tests in a laboratory setting. Therefore, altered ventilation is likely to be important, but may not be the only reason why an impaired response to β2-agonists occurs during lung attacks.

The increased mucous production that occurs during viral infections and the mucous plugging of airways which is observed in fatal cases of asthma are often proposed as a mechanism by which the airways become occluded, and as a consequence may impair inhaled drug delivery. This in our opinion is highly unlikely to be the cause of impaired responses to bronchodilators during virus induced lung attacks. In people with asthma, mucolytics have little effect [[43](#_ENREF_43)], and this was emphasised in a recent study which specifically treated asthmatic patients who were admitted to emergency for a lung attack and were refractory to β2-agonists with rhDNAse, a mucolytic with proven clinical efficacy in cystic fibrosis. In addition to rhDNAse, patients also received usual asthmatic treatment (β2-agonists and corticosteroids) but this did not improve lung function [[44](#_ENREF_44)]. Furthermore β2-agonists also have clinical benefits in respiratory diseases with abnormally high mucus production such as cystic fibrosis [[45](#_ENREF_45), [46](#_ENREF_46)] and COPD [[47](#_ENREF_47)].

***Do viruses cause desensitization of the β2 AR?***

Given the observation that insensitivity to β2-agonists is one of the reasons why virus-induced lung attacks occur and are problematic to treat, it is worth reviewing what we know in this area. Under normal circumstances, airway obstruction in asthma improves in response to inhaled β2-agonists. However, this is not the case during virally induced asthma exacerbations [[29](#_ENREF_29), [30](#_ENREF_30)]. Reddel and colleagues reported that in asthmatic adults, during a respiratory viral infection, exacerbations was characterized by a reduced response to β2-agonists despite having good asthma control and a good response to β2-agonists prior to infection [[29](#_ENREF_29)]. Similarly, Rueter et al. reported that asthmatic children responded less effectively to β2-agonist therapy in response to a viral-induced exacerbation in which rhinovirus was the most frequently identified virus [[30](#_ENREF_30)]. These reports indicate that the underlying cause of this reduced response to β2-agonists during these asthma exacerbations may be unique to a viral infection and affecting their response to β2-agonists.

*In vivo*, bronchial epithelial cells form a physiological barrier in the airways and are the principal cell type infected by rhinovirus in the lower airways [[48](#_ENREF_48)] even though there is evidence that underlying submucosal cells can be infected by rhinovirus [[49](#_ENREF_49)]. Since rhinovirus-induced inflammation is thought to contribute to asthma exacerbations, it is likely that the viral-epithelial infection is critical in mediating viral-induced exacerbations. In human bronchi, β-agonists induce the relaxation of airway smooth muscle via activation of a homogenous population of β2 ARs, while in mice β1 ARs are responsible for the mediation of relaxant responses whilst accounting for 69% of the total βAR population on the airway smooth muscle [[50](#_ENREF_50)]. Although using an *in vivo* mouse model to investigate the role of rhinovirus infections in airway disease could produce physiologically relevant data [[51](#_ENREF_51)], the difference in β1 and β2 AR distribution and function between human and mouse species significantly limits its use in studies relating to β2-agonist activity.

**Figure 2: Modelling the route of respiratory rhinovirus infections *in vitro*.** *Left*: Cross section of an airway showing the direction of viral infection from the lumen to epithelial cells and smooth muscle. *Right*: The *in vitro* model of respiratory rhinovirus infection in the airway.

In order to investigate this matter we developed an *in vitro* model that mimicked this physiological infective route of respiratory viruses. To do this we infected primary human epithelial cells with rhinovirus to generate conditioned medium. This conditioned medium was UV irradiated to inactivate residual rhinovirus and then treated on airway smooth muscle cells. β2 AR function on airway smooth muscle either exposed to control or rhinovirus induced conditioned medium was then assessed by measuring the production of cAMP in response to a β-agonist (Figure 2). Using this model we were able to propose that impairment to β2-agonist therapy may be due to desensitization of the β2 AR on airway smooth muscle cells [[52](#_ENREF_52)]. *In vitro*, we found that rhinovirus infection of epithelial cells produced a unique conditioned medium, that when applied to airway smooth muscle cells, caused internalisation of the β2 AR, and resulted in reduced generation of cAMP in response to a β2-agonist [[52](#_ENREF_52)]. Furthermore, the effect observed was not due to the impaired ability to generate cAMP as the adenylate cyclase activator forskolin induced cAMP response was not reduced. Together this suggested that mediator/s present in virus induced conditioned medium were responsible for desensitization of the β2 AR. Using an array of proteomics, chemistry and molecular research techniques to compare between control and virus induced conditioned medium, we identified the responsible mediator as viral RNA induced prostaglandins [[53](#_ENREF_53)]. Results from this investigatory study proposed that rhinovirus infection of epithelial cells resulted in an increase in viral RNA concentration in the conditioned medium, which when treated on airway smooth muscle, subsequently activated the pattern recognition toll-like receptors. This resulted in the activation of the cyclooxygenase-2 (COX-2) enzyme and the generation of COX-2 induced prostaglandins from airway smooth muscle cells. These prostaglandins then activate prostaglandin receptors on airway smooth muscle, which are also GPCRs and consequently cause β2 AR desensitization via non specific GPCR heterologous desensitization [[53](#_ENREF_53)]. Although we were unable to detect the other forms of eicosanoids such as the leukotrienes from our model, leukotrienes are very capable of being produced in a multicellular environment particularly in the presence of leukocytes and have also been shown to cause desensitization of the β2 AR [[54](#_ENREF_54)]. Since rhinovirus infection of airway structural cells produce prostaglandins [[53](#_ENREF_53)] and potentially leukotrienes in an *in vivo* setting*,* it is likely this eicosanoid combination could further contribute to β2 AR desensitization and translate to the possible reason why asthmatic patients with rhinovirus-induced asthma exacerbations do not respond to β2-agonists clinically.

***Perspective***

Bronchodilators used in the treatment of respiratory symptoms have been in constant development since Ancient China and today are the mainstay inhalant therapy for respiratory diseases including asthma. Presently, multiple classes of bronchodilators are available for the treatment of respiratory disease. They include xanthines and muscarinic acetylcholine receptor antagonists but by far the most effective bronchodilators are the β2-agonists. Two of the most effective inhaled β2-agonists in the management of asthma has evolved from the long history of pharmaceutical research and development, and are still used today. They include the short acting β2-agonists such as salbutamol to treat asthma exacerbations and the formulated combination of a corticosteroid and a long acting β2-agonist such as salmeterol to control asthma symptoms. The pharmaceutical industry today now spends millions of dollars attempting to further engineer structural derivatives of these compounds to make even more potent and sustained β2-agonists. But β2-agonist therapy is not perfect and both short and long acting β2-agonists can result in tachyphylaxis and β2 AR desensitization [[55](#_ENREF_55), [56](#_ENREF_56)] and can still be ineffective in a specific subset population of asthmatics with virus-induced exacerbations, which means there is a need for research into alternative therapies for these people instead of designing agonists that may not be useful.

According to our research, rhinovirus infections which are the main cause of asthma exacerbations are also responsible for interfering with the effectiveness of β2-agonist therapy by desensitizing the β2 AR [[53](#_ENREF_53)], therefore drugs that activate the β2 AR in these patients will simply not work [[52](#_ENREF_52)]. Ideally, treatments of viral infection should be addressed with the use of anti-virals, however to date there are no anti-rhinovirus agents available for the treatment of rhinovirus infection. As our research proposes, the problem relates to COX-2 induced prostaglandins and future research could investigate potential combinational therapy of β2-agonists with already available selective COX-2 inhibitors to restore their effects [[57](#_ENREF_57)]. PDE 4 inhibitors are currently being used in the treatment of COPD for their inflammatory effects [[58](#_ENREF_58)], but in this context they could also be used in combination with β2-agonists to delay the degradation of cAMP and prolong or promote airway smooth muscle relaxation.

Research can also reveal potential new therapeutic targets, such as the discovery of bitter taste receptors in the lungs which when activated leads to smooth muscle relaxation through a calcium-dependent mechanism [[59](#_ENREF_59)]. Agonists to these receptors potentially form a new class of bronchodilators for the treatment of respiratory disease but because they are also members of the GPCR super family, they may also undergo desensitization [[60](#_ENREF_60)]. Whether bitter receptor agonists may potentially be useful during rhinovirus induced asthma exacerbations remains to be investigated.

But the question remains, is it necessary to redesign or further engineer the β2-agonist? Based on our perspective, most likely not. Although novel designs of β2-agonists may be pharmacologically better, it is outweighed significantly by the cost involved in its research and development. Understanding the disease deeper is crucial in drug development and can potentially unlock novel therapeutic targets that can lead to medical break-throughs especially in this context. Furthermore, a greater understanding of the disease can also lead to the development of new combinational therapeutics with already available drugs to make them more effective. In both cases, there are potentially better places where money can be spent than redesigning the β2-agonist.

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