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# Somatostatin Receptor Agonists and Non-Cancer Respiratory Hypersecretion - A Critical Assessment

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## ABSTRACT

Based on a review of the literature regarding the pathophysiology of hypersecretion across various conditions involving respiratory dysfunction, it would appear there are three main underlying causes for excessive sputum production: hypersecretion of mucus glycoprotein and other glandular products from mucus-producing cells, increased transepithelial chloride secretion, mediated via $PGE_2$, $PGF_{2\alpha}$, $TxB_2$, excessive transudation of plasma proteins into the respiratory tract. These factors may operate independently or in combination. Asthma is characterised by inflammation, increased luminal mucus, with an increased ratio of MUC5B/MUC5AC and MUC2 present in the mucus, epithelial fragility with loss of ciliated cells, goblet cell hyperplasia, submucosal gland hypertrophy, 'tethering' of mucus to goblet cells and plasma exudation. COPD and CF have a similar presentation but with a higher MUC5B/MUC5AC ratio and susceptibility to infection. In contrast with the copious sputum production commonly seen in bronchioalveolar carcinoma, bronchorrhoea is not a common feature of CF, asthma, COPD or other conditions with bronchiectasis, where sputum volumes are lower, and the clinical issue may be related more to the viscosity of mucus than to its quantity. Although dramatic positive effects on the BAC-related bronchorrhoea were seen with octreotide and gefitinib treatment, it is therefore doubtful whether agonist of the SST receptor is of clinical usefulness in these other conditions. The reduction in sputum production in BAC seen with both octreotide and gefitinib is likely a result of modulation of the EGF receptor, which is known to be involved in goblet cell metaplasia, even if other mechanisms of action cannot be ruled out. As such, the mechanism of action is potentially relevant also for other pathologies, although currently available EGF-R inhibitors (gefitinib, erlotinib) and somatostatin are perhaps less well adapted for chronic therapy. In conclusion, bronchorrhoea appears to be a sporadic rather than characterising manifestation of asthma, COPD, cystic fibrosis and non-CF bronchiectasis. As a therapeutic target, therefore, bronchorrhoea is not perceived as a high value proposition in these indications, considering existing treatment options and the clinical and regulatory complexities inherent in demonstrating a favourable risk/benefit ratio in a medically plausible subset of patients.

**Keywords:** Somatostatin Receptor Agonists, Hypersecretion, Bronchorrhoea, COPD, Octreotide

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## INTRODUCTION

Respiratory tract hypersecretion is a pathophysiological feature of acute asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), lung cancer and several other conditions including organophosphorus intoxication, stroke, myasthenia gravis and oculopharyngeal muscular dystrophy. When sputum production exceeds 100 mL/day, the condition is termed bronchorrhoea and sputum volumes can reach litres per day, especially in bronchioalveolar carcinoma (BAC), where bronchorrhoea is a hallmark symptom. The somatostatin analogue octreotide (Sandostatin®) has been successfully used to control bronchorrhoea in BAC, potentially suggesting a role also in non-cancer hypersecretion conditions. The following summary reviews the known pathophysiology of respiratory hypersecretion, the physiology of somatostatin and analyses the regulatory and clinical aspects of a possible role for somatostatin agonism in hypersecretion.

### Respiratory Hypersecretion: Pathophysiology

The underlying reasons for excessive production of sputum can divided into three categories: hypersecretion of mucus glycoprotein and other glandular products from mucus-producing cells; increased transepithelial chloride secretion and/or excessive transudation of plasma proteins into the respiratory tract [1].

Mucus and mucociliary clearance are key components of the lung innate immune function. Airway mucus maintains hydration and acts as a physical barrier to particulates and infectious agents; mucus also has antioxidant, antiprotease and antimicrobial properties. Mucus secretion is derived from airway submucosal glands and from goblet cells lining the airway epithelium. Submucosal glands are located in large conducting airways, where their ducts empty onto the luminal surface, especially at bifurcations adjacent to cough receptor endings[2]. Cholinergic nerves are the dominant neural stimulant to mucin secretion in the air ways [3]. Mucin secretion is mediated via muscarinic M3 receptors on the secretory cells, with water secretion mediated via M1 receptors [4,5] and stimulation with cholinergic agonists can increase mucociliary clearance [6-8].

The gel-forming mucins are the principal components of normal mucus, although other polymeric components may dominate in chronic respiratory disease. In chronic inflammation, the ciliated epithelium is damaged and the increased volume of secretions often requires clearance by cough. In the healthy individual, normal submucosal gland mucus secretion is regulated primarily via the vagal nerve. However, in patients with respiratory tract disease, mucus hypersecretion from metaplastic and hyperplastic goblet cells can be stimulated by several

inflammatory stimuli, such as chemical irritants, oxidants, proteases from bacterial sources and cytokines (e.g. TNF $_{\alpha}$ and platelet activating factor).

Under normal conditions, mucus is cleared by ciliary motion, but requires a balance between the volume and composition of the mucus, adequate periciliary liquid volume, and normal ciliary function [9]. This balance may be upset by inflammatory insult leading to mucin overproduction and hypersecretion or secretion of other components such as the DNA, filamentous actin, proteoglycans and biofilms seen in CF. The MUC genes encoding for the mucins fall into three major families: secreted, gel-forming mucins (predominantly MUC5AC and MUC5B); membrane-associated mucins that may have receptor functions (exemplified by MUC1, MUC4 and MUC11) and a the non-gel-forming secreted mucin MUC7. The major secreted mucin glycoproteins in humans, MUC5AC and MUC5B, are expressed in goblet cells, while the membrane-associated mucins MUC1 and MUC4 are present at the apical surface of ciliated cells and MUC5B is the predominant mucin expressed in the mucous cells of the submucosal gland [10-12]. In chronic inflammatory respiratory disease, MUC2 expression is seen in goblet cells [13] along with increased MUC5AC and MUC5B expression [11].

In the normal situation, the peripheral airways contain few goblet cells [14] but goblet cell metaplasia occurs in COPD [15], CF [16] and acute asthma [17.] Goblet cell hypersecretion can be divided into two steps; initially, epithelial cells are converted to mucus-containing goblet cells, followed by degranulation via stimulation, suggesting that the aetiology of the hypersecretion could be due to increased goblet cell expression or degranulation or both. Epidermal growth factor EGF and its receptor (EGF-R) have been proposed to be involved in the goblet cell metaplasia. While the EGF-R is highly expressed in foetal airways, healthy adult humans show little expression; conversely its expression is up regulated in malignancies and in asthma [18] as well as by stimulus by TNF $_{\alpha}$ in hypersecretory disease [19]. Selective EGF-R inhibitors prevent mucus production in these systems while stimulation with EGF-R ligands (EGF, TGF $_{\alpha}$) resulted in production of MUC5AC, further implicating EGF-R signalling in MUC5AC production and goblet cell metaplasia [20].

**Respiratory Hypersecretion: Current Treatment**

Conventional therapies, including anticholinergics, β2-adrenoceptor agonists, corticosteroids, mucolytics and macrolide antibiotics, have variable efficacy in inhibiting airway mucus hypersecretion, and are less effective in COPD than in asthma. Anticholinergics are bronchodilators, and also have a direct effect on secretions, reducing hypersecretion without changing the viscosity of secretions [21]. Aerosol oxitropium bromide has been shown to

significantly decrease the volume of airway secretions in patients with chronic bronchitis [22]. Atropine and other anticholinergics can decrease mucus hypersecretion in animal models of airway inflammation[23]. The 14- and 15-member macrolide antibiotics have been shown to attenuate mucus secretion, in part by inhibition of ERK1/2 [24,25.] These drugs are mucoregulatory as they do not decrease the protective baseline level of mucus secretion but will decrease hypersecretion driven by inflammation. Although corticosteroids are effective anti-inflammatory medications, they are less effective mucoregulators in neutrophil-driven airway inflammation and have no effect on IL-13-induced goblet cell metaplasia and mucin hypersecretion [26]. Conversely, the macrolide antibiotics have been shown to effectively reduce both IL-13 and LPS-stimulated mucus hypersecretion [27].

**NSAIDs**

Both PGE2 and PGF2α stimulate chloride secretion, thereby promoting water accumulation [28]; blockade of the cyclooxygenase pathway with indomethacin has been shown to provide benefit in treatment of bronchorrhoea in patients with chronic bronchitis, diffuse panbronchiolitis, and bronchiectasis without causing hypotension or bronchoconstriction. The reduction of sputum was accompanied by a significant decrease in the concentrations of prostaglandin PGE2, PGF2 alpha, thromboxane B2, and 6-oxo-PGF1 alpha in the sputum[29]. There are also reports of successful treatment of the copious bronchorrhoea associated with BAC using inhaled Indomethacin.[30]

**EGF-R Inhibitors**

Based on the notion that hypersecretion could be targeted also by preventing the goblet cell metaplasia, the use of the EGF-R inhibitor gefitinib (Iressa®) has been attempted and appears to show benefit in patients with advanced bronchioalveolar carcinoma, where prompt resolution of bronchorrhoea, dyspnoea, and supplemental oxygen requirements were observed [31-33.] As the onset of improvement occurred within 24h, it is likely that its inhibitory action on mucin production is independent of its anti-proliferative effects.

**Other Approaches**

Common signalling intermediates for many insulting stimuli include GPCR activation, protein kinase C activation, tyrosine phosphorylation, and phospholipase activation [34,35] Areas of research include the p38 mitogen-activated protein (MAP) kinase pathway, the MEK/ERK pathway, and the phosphatidylinositol 3-kinase pathway as approaches to modulate mucin synthesis and goblet cell hyperplasia [36-39]. Similarly, modulation of calcium-activated chloride channels is being investigated using talniflumate for asthma and COPD [40-42]. The retinoic acid receptor may also be involved in the development and maintenance of a hypersecretory

phenotype [44] and RAR-a antagonists such as RO-41-5253 have been described. Finally, antisense technology has been explored to inhibit goblet cell hyperplasia; hyperplastic goblet cells in COPD models express the antiapoptotic factor Bcl-2 [45] and reduction of Bcl-2 expression by antisense oligonucleotides induces a dose-dependent reduction of hyperplasia.

**Somatostatin Physiology**

Somatostatin (SST; aka growth hormone-inhibiting hormone, GHIH, somatotropin release-inhibiting factor, SRIF or somatotropin release-inhibiting hormone, SRIH) is an amino acid peptide produced by neurons in the anterior periventricular region of the hypothalamus, in the GI tract and in the delta cells of the pancreas. The peptide was named somatostatin on account of its hypophysiotropic actions, and eventually turned out to be a cyclic peptide with two biologically active isoforms: the tetradecapeptide SRIF-14 and the aminoterminally extended octacosapeptide SRIF-28. The heterogeneity of the regulatory peptide derives from differential posttranslational processing of a prepro-SRIF precursor of 116 amino acids [46,47].

SST is a master regulator of hormone secretion via interaction with G protein-coupled somatostatin receptors in the effector tissues, inhibiting the release of secondary hormones. In the anterior pituitary, SST inhibits the release of growth hormone, thyroid-stimulating hormone, prolactin and suppresses luteinising hormone response to GnRH, while effects in the GI tract include suppression of the release of gastrin, cholecystokinin, secretin, pepsinogen, motilin, vasoactive intestinal peptide, and gastric inhibitory polypeptide. In the pancreas, SST importantly inhibits the release of both insulin and glucagon aside from its effects at the exocrine level. In addition to the pancreas, inhibition extends to the exocrine activity of salivary glands (amylase) and the liver (bile). In terms of GI tract function therefore, SST has an inhibitory effect on absorption of dietary glucose, fat and amino acids. SST delays the late phase of gastric emptying, weakens gallbladder contractions and prolongs the orocecal transit time [48-51]. Mesenteric haemodynamics are also responsive to SST, with reductions in portal and variceal pressure [52-56].

Humans express five SST receptors (SST1-SST5), all of which are GPCRs of the rhodopsin-like class[57]. As can be expected from the multitude of SST actions, the receptors show heterogeneous but overlapping tissue distribution:

| Subtype | Tissue |
|---|---|
| SST1 | Jejunum, stomach, hypothalamus, pituitary, lung, kidney, liver, pancreas |
| SST2 | Brain, cerebellum, pituitary, kidney, pancreas, stomach |

| | |
|---|---|
| SST3 | Brain, cerebellum, pituitary, endocrine pancreas |
| SST4 | Brain, cerebellum, pituitary, lung, pancreas, |
| SST5 | Cerebellum, liver, heart, skeletal muscle, adrenal |

Analogously with other GPCRs, SST receptors have been shown to form both homo- and heterodimers, adding complexity to deconvolution of the downstream actions following stimulation with the endogenous ligand [58-60].

Like most other peptide hormones, SST is rapidly cleared from the systemic circulation by non-specific peptidase activity, and much of the knowledge and therapeutic experience derives not from SST itself but from one of the synthetic analogues such as octreotide (Sandostatin®) or lanreotide (Somatulin®), both of which exhibit a higher binding affinity to the various SST receptors than the native peptide. Upon its introduction in 1988, octreotide was approved for use in acromegaly to suppress levels of GH and IGF-1 and for the symptomatic treatment of severe diarrhoea and flushing in patients with metastatic carcinoid syndrome and VIP-secreting tumours. Off-label uses include glucagonoma, hepatorenal syndrome, Cushing's syndrome and other hypersecretory disorders.

**Octreotide in Bronchorrhoea Associated with Lung Cancer**

Octreotide has found widespread use in palliative management of respiratory hypersecretion in adenocarcinomas of the lung, especially in the bronchio alveolar carcinomas, where sputum volumes can be copious. Prior to octreotide, management of the bronchorrhoea in this patient groups relied on radiotherapy, anticholinergic agents, macrolide antibiotics, pulsed high-dose methylprednisolone and inhaled indomethacin, with variable success [30]. Numerous case reports [61-64] indicate dramatic improvements (from sputum volumes of >1000 mL/day to less than 100 mL/day) within hours or days of initiating treatment with octreotide, which has been considered safe and well tolerated in this setting of fragile patients. It is also noted that therapy with e.g. gefitinib (see above under Current Treatment) or erlotinib [65] is typically not available to this category of patients.

**Octreotide Safety Profile**

Octreotide may cause both hypoglycaemia and hyperglycaemia, depending on underlying pathology; while these effects are usually mild, overt diabetes mellitus may present and may require dose changes in insulin or other hypoglycaemic agents. Severe hyperglycaemia, subsequent pneumonia and death following octreotide therapy has been reported in patients with no history of hyperglycaemia. In patients with concomitant Type I diabetes mellitus, octreotide may reduce insulin requirements. Symptomatic hypoglycaemia, which may be severe, has been

reported in these patients. In non-diabetics and Type II diabetics with partially intact insulin reserves, octreotide may result in decreases in plasma insulin levels and hyperglycaemia, and glucose tolerance should be monitored during treatment with octreotide.

Even a single dose of octreotide may inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials, the incidence of biliary tract abnormalities was 63% (gallstones, sludge without stones, biliary duct dilatation). The incidence of stones or sludge in patients who received octreotide for 12 months or longer was 52%. Incidence of gallstones did not appear related to age, sex or dose. Acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis have been reported, some with fatal outcome [66].

**A Role for Somatostatin Receptor Agonists in Respiratory Hypersecretion ?**

**Bronchioalveolar Carcinoma – A Special Case?**

The anecdotal data collected regarding treatment of bronchorrhoea in BAC with octreotide is compelling, although no larger-scale controlled trials have been conducted: the rapid onset, marked effect size and acceptable safety profile makes the octreotide approach attractive in the palliative setting. Although the precise mechanism of action in this case is not known, it is likely that octreotide – at least in part – acts by antagonising EGF, similar to the effects described for gefitinib and erlotinib [67-70]. Other possible factors include modulation of ACTH release and downstream effects on fluid balance, since BAC are known to produce ACTH ectopically [71].

**Cystic Fibrosis**

Abnormal secretion in CF is not limited to the respiratory tract, but also involves the pancreas and large portions of the GI tract, and is likely secondary to the CFTR-related dysfunction. The airway hypersecretion in CF is characterized by submucosal gland and goblet cell hyper- and metaplasia, leading to mucus over-production and distortion of the mucociliary clearance. While frank bronchorrhoea (defined as sputum volumes exceeding 100 mL/24h), is uncommon in CF, the hypersecretion can be important, although the main clinical issue is perhaps the difficulty in expectoration, rather than the volume of sputum since the surface tension of secretions in CF sputum is higher than normal mucus. Dornase alfa (specific to the DNA polymers in sputum and pus in CF) and hypertonic saline are used to reduce viscosity of mucus secretions to help dislodge secretions and aid in expectoration.

Given the pathophysiology of CF, it is doubtful whether an approach based on reduction of EGF-R-mediated goblet cell metaplasia is beneficial. Indeed, such an approach may be harmful, as it would tend to remove the normal mucosa, potentially exacerbating respiratory issues by reducing volume of the expectorate. Outside the respiratory theatre, agonising the somatostatin receptor

may have other unwanted effects on pancreatic function; CF patients have reduced bicarbonate secretion, altering the efficiency of both endogenous and exogenous pancreatic enzymes. The educed water content of secretions leads to plugging of ductules and acini, which prevents the pancreatic enzymes from reaching the GI tract, causing mal absorption of carbohydrates, fat and amino acids. Autodigestion of the pancreas can leads to pancreatitis [72]. In addition, older patients with CF often present with cystic fibrosis-related diabetes, deriving from progressive pancreatic dysfunction [73]. As noted above, agonising the SST receptor in this situation is likely to have negative rather than positive effects.

Finally, CF is associated with hepatic dysfunction, caused by the absence of functional CFTR in the epithelial cells lining the biliary ductules and leads to reduced secretion of chloride and reduction in passive transport of water and chloride, resulting in increased viscosity of bile, which may cause obstructive cirrhosis [74,75]. Cholelithiasis is more prevalent in patients with CF than in age-matched controls, which is thought to be related to abnormal mucin in the gallbladder. Again, agonising the somatostatin receptor has been shown to cause reduced gallbladder contractility and promote formation of gallstones, suggesting that octreotide should be avoided in this condition.

**COPD**

As per the American Thoracic Society guidelines [76], COPD is characterised clinically by cough, hypersecretion and dyspnoea. Cough may be intermittent, progressively becoming present throughout the day, but is seldom entirely nocturnal. Chronic cough is often discounted as it is considered an expected consequence of smoking. Sputum initially occurs in the morning but later will be present all day long. It is usually tenacious and mucoid and in small quantities. Production of sputum for ≥3 months in 2 consecutive years is the epidemiological definition of chronic bronchitis. Dyspnoea is usually progressive and over time it becomes persistent. At the onset it occurs during exercise but as the disease progresses, dyspnoea is elicited even during minimal exertion or at rest.

Although excessive sputum production has been reported in COPD, it is not a is not a hallmark symptom of the condition, appears not to be associated with any specific cause or be predicted by any particular disease phenotype, and must therefore be considered sporadic. When present, it is associated with goblet cell hyperplasia, mucus hypersecretion, and mucus plugging in the airway lumen[77-78]; it is however controversial whether hypersecretion is an independent risk factor for death [79]. Anticholinergics block muscarinic receptors on airway secretory cells and smooth muscle and may reduce vagal tone and mucus secretion and facilitate cough-induced

mucus clearance [80-82], and oxitropium bromide reduces the amount of mucus secretion in patients with COPD [29]; onset of inhibition is however slow. No clinically important improvements in lung function or quality of life have been demonstrated with mucolytic therapy in COPD [83].

**Asthma**

Cough in asthma is usually non-productive and purulent or viscous [84], although bronchorrhoea has been described in bronchial asthma during attack. In contrast to COPD and CF, however, the hypersecretion appears to respond well to corticosteroids or histamine H1-blockers, while anticholinergics and H2-blockers did not alter the sputum volume [85].

**Regulatory Considerations: Endpoints and Registration**

Bronchorrhoea as such is not a recognized indication, but can rather be considered a manifestation of respiratory disease along a continuum of other symptoms. Given the range of aetiologies of bronchorrhoea discussed above, a symptomatic approach that only treats the respiratory hypersecretion would be considered an add-on therapy to other approaches to treating the underlying disease, whether this be COPD, bronchiectasis, asthma or other. An exception to this would be a medically plausible subset of patients where bronchorrhoea is a cardinal symptom (such as BAC) or the main driver for morbidity with known risk factors.

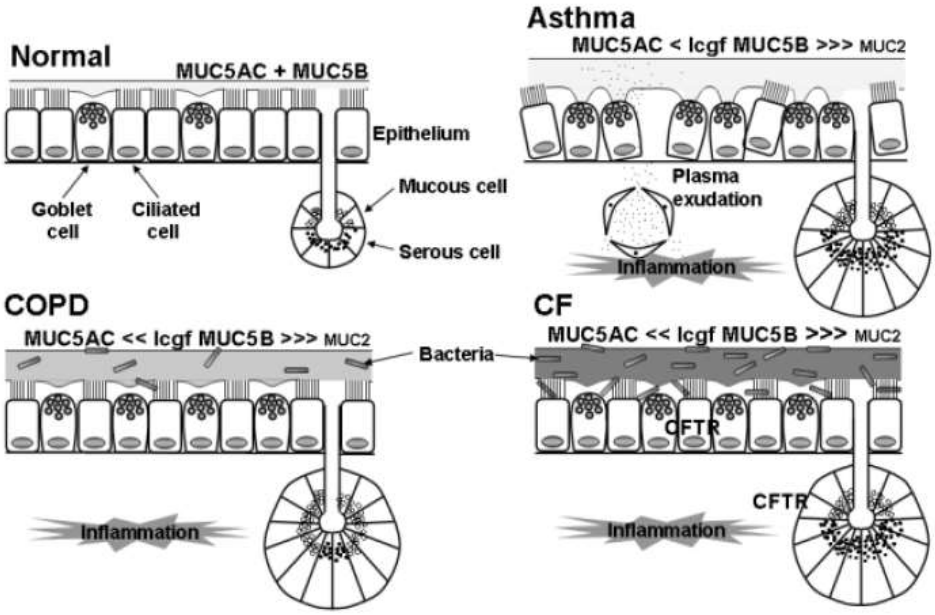
Selection of endpoints merits specific attention; measuring sputum volume is unlikely to be a valid endpoint for most situations, and some means of correlating the reduction of hypersecretion to clinical outcomes or known predictors of outcome of performance status (primarily $FEV_1$ but potentially also the inspiratory capacity, functional residual capacity, residual volume/total lung capacity, forced vital capacity or slow VC and the diffusing capacity of the lung for carbon monoxide, [86] are required to create a scenario for registrational studies.

## SUMMARY AND CONCLUSION

Based on a review of the literature regarding the pathophysiology of hypersecretion across various conditions involving respiratory dysfunction, it would appear there are three main underlying causes for excessive sputum production:

- hypersecretion of mucus glycoprotein and other glandular products from mucus-producing cells;
- increased transepithelial chloride secretion, mediated via $PGE_2$, $PGF_{2\alpha}$, $TxB_2$
- excessive transudation of plasma proteins into the respiratory tract

These factors may operate independently or in combination as summarised graphically in the figure below (from [1]). Asthma is characterised by inflammation, increased luminal mucus, with an increased ratio of MUC5B/MUC5AC and MUC2 present in the mucus, epithelial fragility with loss of ciliated cells, goblet cell hyperplasia, submucosal gland hypertrophy, 'tethering' of mucus to goblet cells and plasma exudation. COPD and CF have a similar




presentation but with a higher MUC5B/MUC5AC ratio and susceptibility to infection.

In contrast with the copious sputum production commonly seen in bronchioalveolar carcinoma, bronchorrhoea is not a common feature of CF, asthma, COPD or other conditions with bronchiectasis, where sputum volumes are lower, and the clinical issue may be related more to the viscosity of mucus than to its quantity. Although dramatic positive effects on the BAC-related bronchorrhoea were seen with octreotide and gefitinib treatment, it is therefore doubtful whether agonism of the SST receptor is of clinical usefulness in these other conditions.

The reduction in sputum production in BAC seen with both octreotide and gefitinib is likely a result of modulation of the EGF receptor, which is known to be involved in goblet cell metaplasia, even if other mechanisms of action cannot be ruled out. As such, the mechanism of action is potentially relevant also for other pathologies, although currently available EGF-R inhibitors (gefitinib, erlotinib) and somatostatin are perhaps less well adapted for chronic therapy.

The business case for developing somatostatin analogues to treat respiratory hypersecretion is likely dependent on a thorough understanding of the tissue specificity of the somatostatin receptors, and some means of achieving subtype selectivity, even in the case of a topical

formulation. The small peptide SST receptor area is crowded from an Intellectual Property perspective [57] and this could be an additional development issue. The main question, however, is whether the unmet medical need in COPD, asthma, non-CF bronchiectasis or chemointoxication for an add-on therapy to treat hypersecretion merits attention.

However, to achieve sufficient exposure in the target tissues without systemic side effects, it is likely an inhaled route will be required, adding additional complexity.

In a conclusion bronchorrhoea appears to be a sporadic rather than characterising manifestation of asthma, COPD, cystic fibrosis and non-CF bronchiectasis. As a therapeutic target, therefore, bronchorrhoea is not perceived as a high value proposition in these indications, considering existing treatment options and the clinical and regulatory complexities inherent in demonstrating a favourable risk/benefit ratio in a medically plausible subset of patients.

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