called regulated-intramembrane-proteolysis (RIP). (Kreft, AF, Martone, R, and Porte, A, Recent Advances in the Identification of gamma Secretase Inhibitors To Clinically Test the Ab Oligomer Hypothesis of Alzheimer's Disease, *J. Med. Chem* 2009, 52:6169-6188). While gamma secretase has been of interest as a therapeutic target for several years, due to its complexity, obtaining a detailed understanding of its structure and an understanding of structure activity relationships has been challenging. Nevertheless, significant progress has been made in elucidating certain structure activity relationships. (See Wolfe, MS, Gamma-Secretase Inhibition and Modulation for Alzheimer's Disease, *Curr Alzheimer Res.* 2008; 5(2): 158-164).

GSIs can be classified into three general types based on where they bind to gamma secretase: (1) active-site binding GSIs, (2) substrate docking-site-binding GSIs, and (3) alternate binding site GSIs. The latter category can be further subdivided into carboxamide- and arylsufonamide-containing GSIs. (Kreft et al, at 6171).

Alzheimer's disease clinical trials have revealed toxicities believed to be associated with gamma secretase inhibition. (David B. Henley, Karen L. Sundell, Gopalan Sethuraman, Sherie A. Dowsett & Patrick C. May (2014) Safety profile of semagacestat, a gamma-secretase inhibitor: IDENTITY trial findings, *Current Medical Research and Opinion*, 30:10, 2021-2032).

Additional GSIs have been investigated for potential cancer therapeutics, and generally exhibit toxicities at high doses.

Summary of the ~~Invention~~Disclosure

It has now been surprisingly found that a low dose of gamma secretase inhibitors (GSIs), is effective in reverting the cellular abnormalities seen in association with respiratory diseases characterized by mucus hypersecretion, and is effective at doses allowing therapeutic activity and expected to avoid or minimize the adverse effects previously associated with this class of molecules. It has further been found that GSIs administered in combination with a CFTR modulator is effective in correcting epithelial cell dysfunction in cystic fibrosis cell-based model systems (primary cells from patients), in contrast to certain prevailing concepts, and indeed the combination may be synergistic in improving CFTR ion channel function and epithelial cell correction.

In one aspect, there is provided a use of a low dose of gamma secretase inhibitor (GSI) in the manufacture of a medicament for the treatment of a respiratory disease characterized by mucus hyper-secretion in a human patient in need of such treatment; and

wherein the mucus in such patient's lungs is reduced or mucus accumulation in such patient's lungs is substantially ameliorated or prevented upon administration of the GSI.

The ~~invention~~ disclosure therefore provides methods of treating a respiratory disease characterized by mucus hyper-secretion comprising administering to a human patient in need of such treatment a GSI, wherein the administration of low dose GSI is effective in reducing mucus in such patient's lungs or inhibiting mucus accumulation in said patient's lungs. In some ~~embodiments~~examples, the methods of the ~~invention~~ disclosure are effective in treating a respiratory disease selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease, primary ciliary dyskinesis, chronic bronchitis, asthma, idiopathic and secondary

bronchiectasis, bronchiolitis obliterans, idiopathic pulmonary fibrosis and other fibrotic lung disorders, respiratory infection including exacerbations in chronic respiratory disorders, and mucus accumulation in response to acute infection.

In some ~~embodiments~~examples, the GSI is selected from the group consisting of semagacestat, avagacestat, GS-1, DBZ, L-685,458, BMS-906024, crenigascestat, MRK 560, nirogacestat, RO-4929097, MK-0752, itanapraced, LY-3056480, fosciclopirox, tarenflurbil, and begacestat.

In some ~~embodiments~~examples, the GSI is selected from the group consisting of semagacestat, nirogacestat, MK-0752, RO-492907, or crenigacestat. In some ~~embodiments~~examples, the GSI is a carboxamide based GSI.

In another aspect, there is provided a use of a therapeutically effective amount of semagacestat in the manufacture of a medicament for the treatment of a respiratory disease characterized by mucus hyper-secretion in a human patient in need of such treatment, wherein the medicament is to be systemically administered, and wherein said patient's semagacestat plasma concentration at steady state following multiple dose administration comprises an AUC less than 1220 ng•hr/mL, and

wherein the administration of semagacestat is effective in reducing mucus in such patient's lungs or inhibiting mucus accumulation in such patient's lungs~~-~~.

In some ~~embodiments~~examples, methods are provided for treating respiratory diseases characterized by mucus hypersecretion comprising systemically administering semagacestat in an amount of from about 0.1mg to about 50mg daily, wherein the administration of semagacestat is effective in reducing mucus in such patient's lungs or inhibiting mucus accumulation in such patient's lungs. In some ~~embodiments~~examples, semagacestat is administered in an amount of from about 0.5mg to about 40mg daily. In some ~~embodiments~~examples, semagacestat is administered in an amount of from about 0.5mg to about 30mg daily, or from about 0.5mg to about 20mg daily, or from about 0.5mg to about 10mg daily. For example, semagacestat may be administered in about 0.1mg, 0.25mg, 0.5mg, 1mg, 2.5mg, 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg daily. Preferably, semagacestat is administered orally. In an ~~embodiment~~ example of the ~~invention~~disclosure, a method is provided for treating a respiratory disease characterized by mucus hyper-secretion comprising systemically administering to a human patient in need of such treatment a therapeutically effective amount of semagacestat, wherein said patient's semagacestat plasma concentration at steady state following multiple dose administration comprises an AUC (area under the curve) less than 2100 ng•hr/mL, such as less than 1220 ng•hr/mL, wherein the systemic administration of semagacestat is effective in reducing mucus in such patient's lungs or preventing mucus accumulation in such patient's lungs. In some ~~embodiments~~examples, upon multiple dose administration, said patient's steady state semagacestat

plasma concentration comprises an AUC less than 1500 ng•hr/mL, less than 1200 ng•hr/mL, or less than 900 ng•hr/mL, such as an AUC less than 1220 ng•hr/mL, less than 600 ng•hr/mL, or less than 250 ng•hr/mL.

In another aspect, there is provided a use of an effective amount of GSI in the manufacture of a medicament for the treatment of cystic fibrosis in a human patient in need of a CFTR modulator,

wherein the mucus in such patient's lungs is reduced or mucus accumulation in such patient's lungs is inhibited.

In further ~~embodiments~~ examples of the ~~invention~~disclosure, methods are provided for treating cystic fibrosis comprising administering an effective amount of a GSI to a human patient taking a CFTR modulator, wherein the mucus in such patient's lungs is reduced or mucus accumulation in such patient's lungs is inhibited. In some ~~embodiments~~examples, the GSI is selected from the group consisting of semagacestat, nirogacestat, MK-0752, RO-492907, or crenigacestat. In some ~~embodiments~~examples, the GSI is semagacestat.

In certain of these ~~embodiments~~examples, the CFTR modulator is selected from the group consisting of a CFTR potentiator, a CFTR corrector, a CFTR premature stop codon inhibitor, a CFTR amplifier and combinations thereof. In some ~~embodiments~~examples, the CFTR modulator is selected from the group consisting of ivacaftor, lumacaftor, tezacaftor, elexacaftor and combinations thereof.

Brief Description of the Drawings

Figure 1 shows dose response data of semagacestat in primary human nasal epithelial cells (HNECs) compared to untreated cells and DAPT positive control. MCCs are labeled in green (acetylated tubulin) and cell junctions are labeled in red (ECAD). The percentage of MCCs increases from its baseline at 15.625 nM semagacestat to its maximum at around 125 nM. Toxicity is observed at micromolar doses.

Figure 2 shows the ratio of MCCs to total luminal cells in HNECs treated with DAPT and various doses of semagacestat.

Figure 3 shows method of scoring the ratio of MCCs to non-ciliated cells in airway epithelia in mice treated systemically in vivo by intraperitoneal (IP) dosing of semagacestat. Airways from lung sections of similar size were labeled for all nuclei (red; DAPI) and MCC cell fate (green; FoxJ1 and blue; acetylated tubulin). Cells were scored and the percentage of MCCs determined prior to unblinding treatment condition. Otherwise wildtype mice carried FoxJ1::GFP to facilitate scoring of MCCs.

Figure 4 shows the body weight at days 9, 24 and 30 with daily systemic (IP) administration of semagacestat and vehicle control.

Figure 5 shows the ratio of MCCs to total cells at day 7 following a three-day treatment with DAPT and low and high doses of semagacestat, with vehicle control.

Figure 6 shows the ratio of MCCs to total cells at day 31 following a three-week treatment with semagacestat, with vehicle control.

Figure 7 shows the effect of GSI treatment during proliferation (prior to differentiation) and during differentiation of HNECs.

Figure 8 shows the quantitation of MCCs per total luminal cells of the data of Figure 7.

Figure 9 shows the effects of GSI treatment duration on mature (ALI+30d) HNECs, treated with DAPT and semagacestat for one (ALI+30 to +37d) or two weeks (ALI+30 to +44d).

Figure 10 shows the quantitation of MCCs per total luminal cells of the data of Figure 9.

Figure 11 shows the results of HNECs treated with DAPT and semagacestat during differentiation only (ALI+0 to +21d) from either the apical or basal surface.

Figure 12 shows the quantitation of MCCs per total luminal cells of the data of Figure 11.

Claims

1. Use of a low dose of gamma secretase inhibitor (GSI) in the manufacture of a medicament for the treatment of ~~A method of treating~~ a respiratory disease characterized by mucus hyper-secretion ~~comprising:~~

~~administering a low dose of a GSI to~~ in a human patient in need of such treatment; and

wherein the mucus in such patient's lungs is reduced or mucus accumulation in such patient's lungs is substantially ameliorated or prevented upon administration of the GSI.

2. The ~~method~~ use of Claim 1, wherein the low dose is an effective amount to treat the respiratory disease characterized by mucus hyper-secretion and is a lower dose as compared to a dose of the GSI suitable for administering to a patient suffering from a neurodegenerative disorder, an oncology disorder, or a respiratory disease not characterized by mucus hyper-secretion.

3. The ~~method~~ use of Claim 2 wherein the low dose of a GSI yields a peak plasma level in the submicromolar range.

4. The ~~method~~ use of Claim 1 wherein the respiratory disease is selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease, primary ciliary dyskinesis, chronic bronchitis, asthma, idiopathic and secondary bronchiectasis, bronchiolitis obliterans, idiopathic pulmonary fibrosis and other fibrotic lung disorders and respiratory infection, including exacerbations in chronic respiratory disorders and mucus accumulation in response to acute infection.

5. The ~~method~~ use of any of the preceding claims wherein the GSI is selected from the group consisting of semagacestat, avagacestat, GS-1, DBZ, L-685,458, BMS-906024, crenigascestat, MRK 560, nirogacestat, RO-4929097, MK-0752, itanapraced, LY-3056480, fosciclopirox, tarenflurbil, and begacestat.

6. The ~~method~~ use of Claim 5 wherein said GSI is selected from the group consisting of semagacestat, nirogacestat, MK-0752, RO-492907, or crenigacestat.

7. The ~~method~~ use of Claim 6 wherein the GSI is semagacestat.

8. The ~~method~~ use of Claim 6 wherein the GSI is MK-0752.

9. The ~~method~~ use of Claim 6 wherein the GSI is nirogacestat.

10. The ~~method~~ use of Claim 6 wherein the GSI is RO-492907.

11. The ~~method~~ use of Claim 6 wherein the GSI is crenigacestat.

12. The ~~method~~ use of any of the preceding claims wherein ~~said administration of~~the GSI is to be administered by oral administration.

13. The ~~method~~ use of any of the preceding claims wherein the respiratory disease is cystic fibrosis or chronic obstructive pulmonary disease.

14. Use of a therapeutically effective amount of semagacestat in the manufacture of a medicament for the treatment of~~A method of treating~~ a respiratory disease characterized by mucus hyper-secretion ~~comprising:~~

~~systemically administering~~ ~~to~~in a human patient in need of such treatment ~~a therapeutically effective amount of semagacestat~~, wherein the medicament is to be systemically administered, and wherein said patient's semagacestat plasma concentration at steady state following multiple dose administration comprises an AUC less than 1220 ng•hr/mL, and

wherein the administration of semagacestat is effective in reducing mucus in such patient's lungs or inhibiting mucus accumulation in such patient's lungs.

15. The ~~method~~ use of Claim 14 wherein the respiratory disease is selected from the group consisting of cystic fibrosis, chronic obstructive pulmonary disease, primary ciliary dyskinesis, chronic bronchitis, asthma, idiopathic and secondary bronchiectasis, bronchiolitis obliterans, idiopathic pulmonary fibrosis and other fibrotic lung disorders and respiratory infection, including exacerbations in chronic respiratory disorders and mucus accumulation in response to acute infection.

16. The ~~method~~ use of Claim 15 wherein the respiratory disease is cystic fibrosis or chronic obstructive pulmonary disease.

17. The ~~method~~ use of Claim 14, Claim 15 or Claim 16 wherein the semagacestat is to be administered in an amount of from about 0.1mg to about 50mg daily.

18. The ~~method~~ use of Claim 17 wherein about 0.5mg to about 40mg of semagacestat is to be administered daily.

19. The ~~method~~ use of Claim 18 wherein about 0.5mg to about 40mg of semagacestat is to be administered daily.

20. The ~~method~~ use of Claim 19 wherein about 0.5mg to about 30mg of semagacestat is to be administered daily.

21. The ~~method~~ use of Claim 20 wherein about 0.5mg to about 20mg of semagacestat is to be administered daily.

22. Use of an effective amount of GSI in the manufacture of a medicament for the treatment of ~~A method of treating~~ cystic fibrosis ~~comprising:~~

~~administering an effective amount of a GSI to~~ in a human patient ~~being administered or~~ in need of a CFTR modulator,

wherein the mucus in such patient's lungs is reduced or mucus accumulation in such patient's lungs is inhibited.

23. The ~~method~~ use of Claim 17 wherein the GSI is selected from the group consisting of semagacestat, avagacestat, GS-1, DBZ, L-685,458, BMS-906024, crenigascestat, MRK 560, nirogacestat, RO-4929097, MK-0752, itanapraced, LY-3056480, fosciclopirox, tarenflurbil, and begacestat.

24. The ~~method~~ use of Claim 18 wherein the GSI is selected from the group consisting of semagacestat, nirogacestat, MK-0752, RO-492907, or crenigacestat.