US20070249668 describes a composition containing a PDE inhibitor and a prostacyclin analogue to increase the ATP content in red blood cells.

Presently, no treatments of cystic fibrosis are available that significantly improve quality of life of patients over a longer period. Therefore it is an object of the invention to provide compositions for treatment that can enhance the expression of ΔF508 CFTR and/or chloride channel function in epithelial cells of the lung.

Short description of the disclosure~~invention~~:

In one aspect, there is provided the use of a composition comprising at least one prostacyclin or prostacyclin analogue or a pharmaceutically acceptable salt thereof and at least one phosphodiesterase (PDE) 4 inhibitor in the manufacture of a medicament for treating cystic fibrosis by improving conductance of chloride by cystic fibrosis transmembrane conductance regulator (CFTR).

~~The object of the invention is achieved by providing~~Disclosed is a composition comprising at least one prostacyclin or an analogue, a derivative or a pharmaceutically acceptable salt thereof in combination with at least one PDE 4 inhibitor for use in preventing or treating cystic fibrosis. As an alternative embodiment, said composition can further comprise at least one PDE5 and/or PD7 and/or PDE8 inhibitor.

Specifically, the prostacyclin analogue is selected from the group of Treprostinil, Iloprost, Cicaprost or Beraprost or derivatives or pharmaceutically acceptable salts thereof. In one embodiment of the present disclosure~~invention~~ the Treprostinil derivative is an acid derivative, a prodrug, a polymorph or an isomer of Treprostinil.

According to the disclosure~~invention~~, the PDE4 inhibitor can be specifically selected from the group of Ro 20-1724, Ibudilast, Roflumilast and its N-Oxide, Cilomilast, BAY 19-8004, CC3, AWD 12-281, SCH 351591, Ciclamilast, Piclamilast, CGH2466, Mesembrine, Rolipram, Luteolin and Drotaverine.

According to the disclosure~~invention~~, the PDE5 inhibitor can be specifically selected from Avanafil, Lodenafil, Mirodenafil, Sildenafil citrate, Tadalafil, Vardenafil and Udenafil; the PDE7 and PDE8 inhibitors may be selected from Dipyridamol, BRL-50481 and PF-04957325

According to a specific embodiment of the disciosure~~invention~~, the composition specifically consists of one type of prostacyclin analogue and one type of PDE4 inhibitor.

In one aspect, there is provided a composition comprising~~As a specific embodiment, the composition comprises~~ Treprostinil and a PDE4 inhibitor selected from the group of RO 20-1724, Roflumilast and Ibudilast.

A further embodiment of the disclosure~~invention~~, the composition comprises additional PDE inhibitors selected from PDE5, PDE7 or PDE8 inhibitors.

In another embodiment, the disclosure~~invention~~ provides a composition free of interferon.

Specifically, the inventive composition is formulated as a pharmaceutical composition.

Any known administration forms can be used for administering the inventive combination, for example it can be intravenous or subcutaneous administration or inhalation administration, or in an orally available form selected from the group of sustained release forms, tablets and capsules.

According to a specific embodiment, the effective amount of Treprostinil or a pharmaceutically acceptable salt thereof is preferably of about 1.0 ng/kg of body weight, Ibudilast is preferably up to 5x30 mg, preferably up to 2x30 mg the effective amount of the PDE4 inhibitor is approx. 0.5 mg. Additionally, one or more inhibitors of the group of PDE5 and PDE7 inhibitors may be contained in an effective amount of about 0.5mg of each of the inhibitors.

The present disclosure~~invention~~ also provides an *in vitro* method for increasing the cAMP level in a cell wherein said cell is contacted with at least one prostacyclin or prostacyclin analogue and at least one PDE4 inhibitor or a pharmaceutically acceptable salt thereof. Additionally, a PDE5, PDE7 and/or PDE8 inhibitor may further be used according to said method.

Specifically, the cell is an epithelial cell, more specifically it may be a bronchoepithelial cell.

In one aspect, there is provided a therapeutic combination, comprising at least one prostacyclin or prostacyclin analogue and at least one PDE4 inhibitor and at least one inhibitor selected from the group of or PDE5 inhibitors, PDE7 inhibitors or PDE8 inhibitors, wherein the prostacyclin or prostacyclin analogue and PDE4 inhibitor and at least one inhibitor selected from the group of PDE5 inhibitors, PDE7 inhibitors and PDE8 inhibitors are provided in amounts which together are sufficient to treat and/or prevent at least one symptom associated with cystic fibrosis.

A therapeutic combination is also provided, comprising at least one prostacyclin or prostacyclin analogue and at least one PDE4 inhibitor or a pharmaceutically acceptable salt thereof, wherein the prostacyclin analogue and the PDE4 inhibitor are provided in amounts which together are sufficient to treat and/or

prevent at least one symptom associated with cystic fibrosis. More specifically, the prostacyclin analogue and PDE4 inhibitor are formulated for administration by inhalation.

Said therapeutic composition may, according to an alternative embodiment, contain at least one further inhibitor selected from the group of PDE5, PDE7 and PDE8 inhibitors.

Figures:

Fig. 1: Accumulation of cAMP in IB3-1 cells after incubation with Treprostinil alone or in combination with the PDE 4 inhibitors Ibudilast (100µM) and Cilostazol (100µM).