Esculentin and its derivatives for use for treatment of cystic fibrosis.

KEYWORDS

- ❑ CYSTIC FIBROSIS
- ❑ POTENTIATORS OF CFTR CHANNEL
- ❑ THERAPEUTIC AGENTS
- ❑ NTIMICROBIAL PEPTIDES
- ❑ LUNG PATHOLOGY

AREA

- ❑ PHARMACEUTICAL

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Priority Number
n.102019000018938 del 16.10.2019.

Patent Type
Patent for invention.

Co-Ownership
Sapienza Università di Roma 50%, Istituto Giannina Gaslini 25%, Fondazione per la Ricerca sulla Fibrosi Cistica 25%.

Inventors
Maria Luisa Mangoni, Loretta Ferrera.

Industrial & Commercial Reference
Medicine/Pharmaceutics: development of new drugs and their formulation for treatment of lung pathology in cystic fibrosis.

Time to Market
TRL.3-experimental proof of concept-The time required for its placement on the market is not yet predictable.

Availability
Licensing, Research, Development and Experimentation.

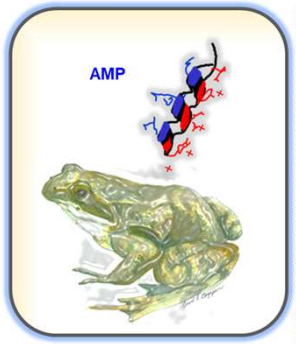

Fig.1 Schematic representation of the antimicrobial peptide (AMP) esculentin-1a, from the green frog's skin secretion.

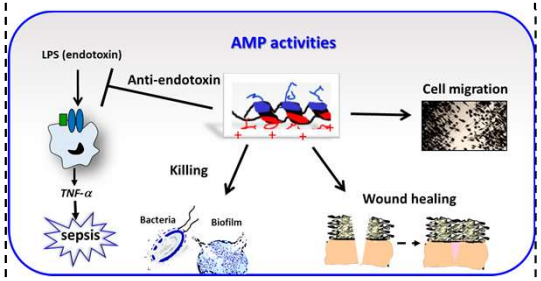

Fig. 2 Schematic representation of the multiple biological functions of the patented frog skin derived AMPs.

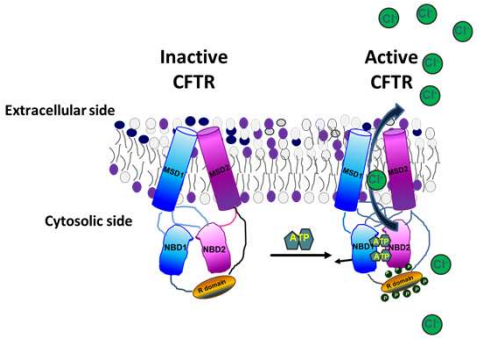

Fig. 3 Schematic representation of closed (inactive) and open (active) CFTR channel in the apical membrane of epithelial cells.

Abstract
The present invention provides the use of synthetic antimicrobial peptides (AMPs) deriving from the frog skin peptide esculentina-1a, to restore the dysregulation of the composition of water and ions of the liquid that bathes the respiratory epithelium, due to mutations in the gene encoding for the ion channel selective for halides, which is defined cystic fibrosis transmembrane conductance regulator (CFTR). More specifically, the invention is directed to the use of these AMPs as modulators of the mutated CFTR channel in patients with cystic fibrosis (CF). It also provides the development of a formulation that includes these AMPs as active ingredient and pharmaceutically acceptable adjuvants and/or vehicles for the treatment of CF lung disease.

Pubblicazioni

- ❖ https://www.fibrosicisticaricerca.it/progetto/ffc-8-2019-peptidi-antimicrobici-da-pelle-di-anfibio-per-il-trattamento-della-patologia-polmonare-nella-fibrosi-cistica-caratterizzazione-funzionale-in-vitro-e-in-vivo/

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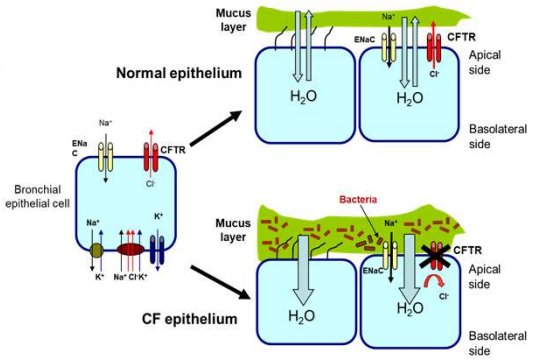
Technical Description

One of the most frequent mutations of CF disease is the loss of phenylalanine 508 in the CFTR channel protein which controls the passage of chloride ions through the membrane of secretory epithelia, including the airway epithelium. This causes the formation of an unfolded (rapidly degraded) protein and with a gating defect. As a result, the secretion of chloride ions is inhibited, causing the formation of a sticky mucus layer on the respiratory epithelium, favouring the development of a chronic lung infection with impaired respiratory functions. AMPs derived from the frog skin esculentina-1a have shown the ability to recover the activity of CFTR with gating mutations, by presumably increasing the open channel probability following their direct interaction with CFTR.



Technologies & Advantages

FC is the most common serious genetic disease in the world. Despite intense efforts to identify small molecules capable of helping the delivery of mutated CFTR to the plasma membrane (correctors) and/or of improving the ion flow through CFTR (potentiators), compounds capable of recovering the complete functionality of the channel are not yet available. Our studies have led to the discovery of peptides with the ability to restore the activity of mutated CFTR, similarly to the current Ivacaftor potentiator. However, unlike traditional CFTR modulators, these peptides have the advantage of having both antimicrobial and immunomodulatory activities. Hence, having the ability to modify the ions flux controlled by CFTR and to act as antibiotics against bacterial lung infections, when administered locally, these molecules represent excellent candidates for the development of new inhalable formulations for treatment of CF lung disease, with greater successful potential compared to already available drugs. Finally, the selected AMPs are made up of short amino acid sequences which reduce production costs.

Fig. 4 Effect of mutated CFTR on the chloride ion current in the lung epithelium of CF compared to normal conditions.

Applications

The selected peptides have a high potential to be developed as future drugs to eradicate bacterial infections, with a reduced risk of inducing resistance, and to recover the activity of the CFTR protein, in patients with CF when applied (either individually or in combination with currently-used modulators) by inhalation. Overall, these peptides are attractive molecules for the generation of new therapeutic agents for treatment of pulmonary pathology of CF, by promoting the restoration of lung function and the integrity of the damaged bronchial epithelium.

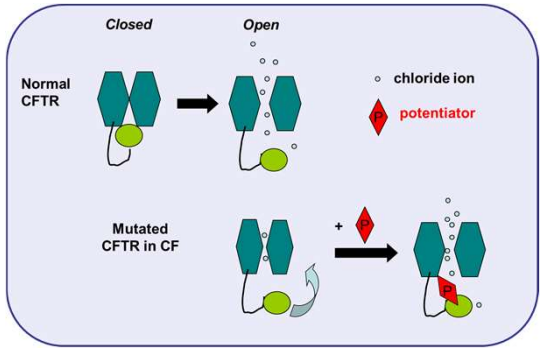


Fig. 5 Schematic representation of the effect of potentiators on CFTR channel.

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