

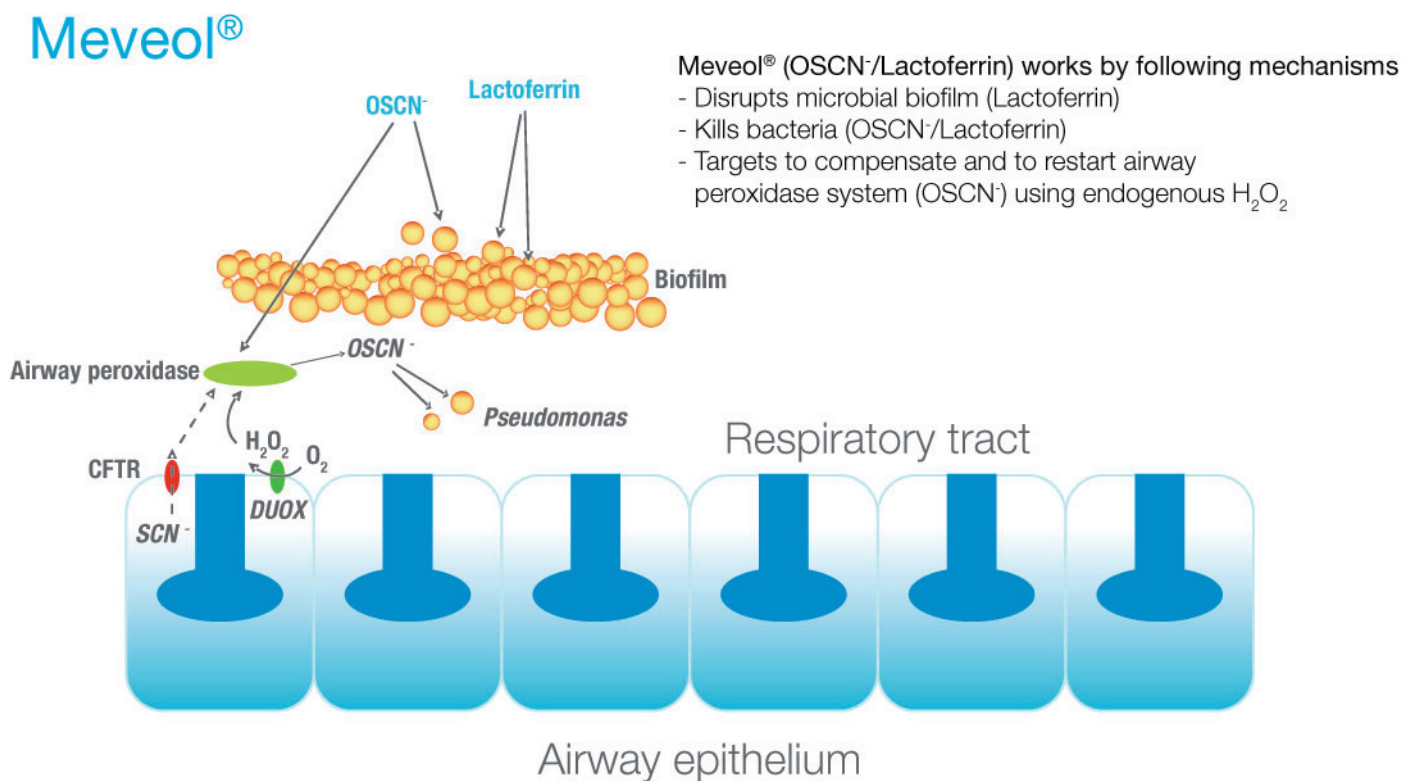
Hypothiocyanite and Lactoferrin use for the treatment of *Pseudomonas aeruginosa*, *Burkholderia cepacia* and MRSA in Cystic Fibrosis cases

SANDRE-BALLESTER C.¹, FICHANT E.², STORDEUR Ph.², BORDEAU Ph.¹, DELAHAUT, Ph.², PERRAUDIN JP.³

¹ALAXIA, 3-11 rue de la Perlerie F-69120 Vaulx-En-Velin, ²CER, 8 rue du Point du jour B-69000 Marloie, ³TARADON Laboratory, 2 avenue Léon Champagne B-1480 Tubize

BACKGROUND :

The CFTR gene is responsible for the production of a protein regulating outflow of water and salts (like chloride Cl⁻ but also rhodanide SCN⁻ and other halides) from cells that cover internal and external surfaces of the body, the so-called epithelial cells. Inactivation of CFTR is likely to cause multiple defects in the airway that together alter local innate immunity (Childers M, 2007). As shown in recent publications, hypothiocyanite (OSCN⁻) antimicrobial molecule (Moskwa P, 2007 and Conner GE) and lactoferrin (Rogan MP, 2004) are deficient in Cystic Fibrosis condition.



RESULTS:

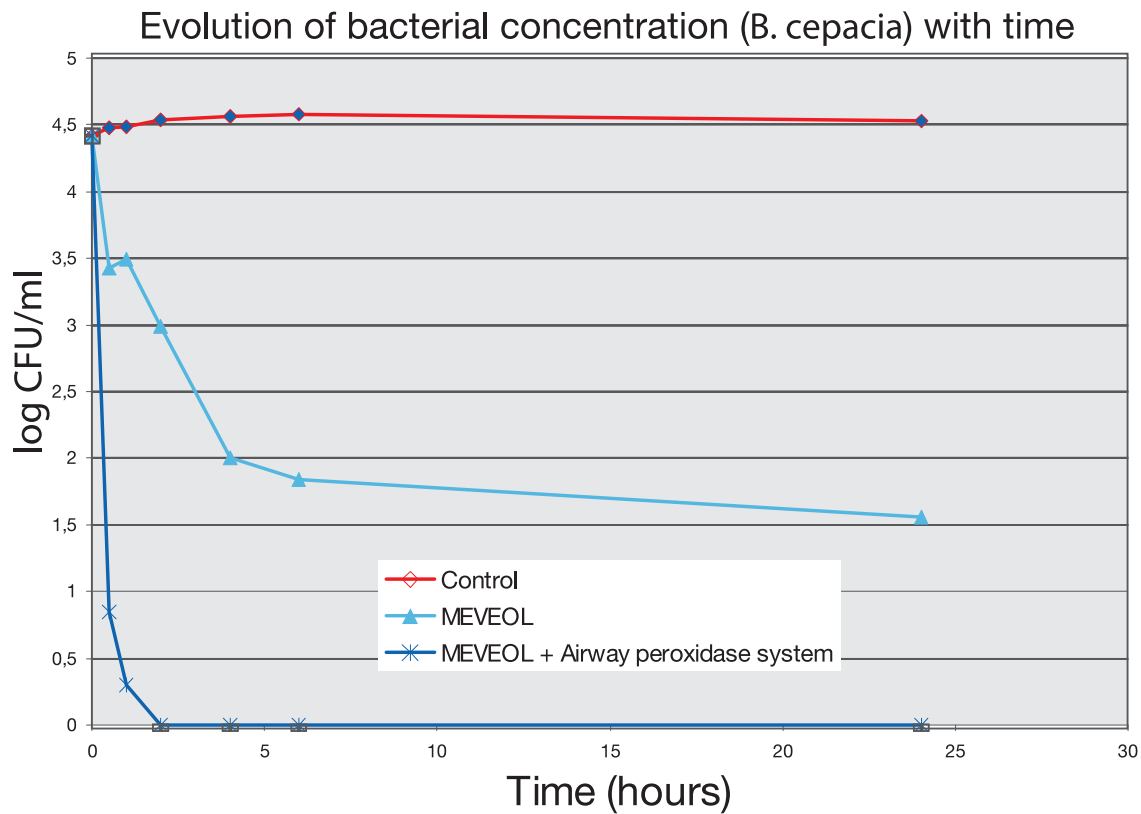
OSCN⁻ molecule is well known by ALAXIA scientists who demonstrated with European appointed experts during MEVEOL® development its antimicrobial efficacy on various strains including MRSA, Burkholderia cepacia, and mucoid Pseudomonas aeruginosa.

MEVEOL® tackles a wide range of micro-organisms including biofilm due to its composition associating naturally linked compounds. Hypothiocyanite and lactoferrin, main bio molecules, are normally present in human body and especially in human airways suggesting low risk of bacterial resistance.

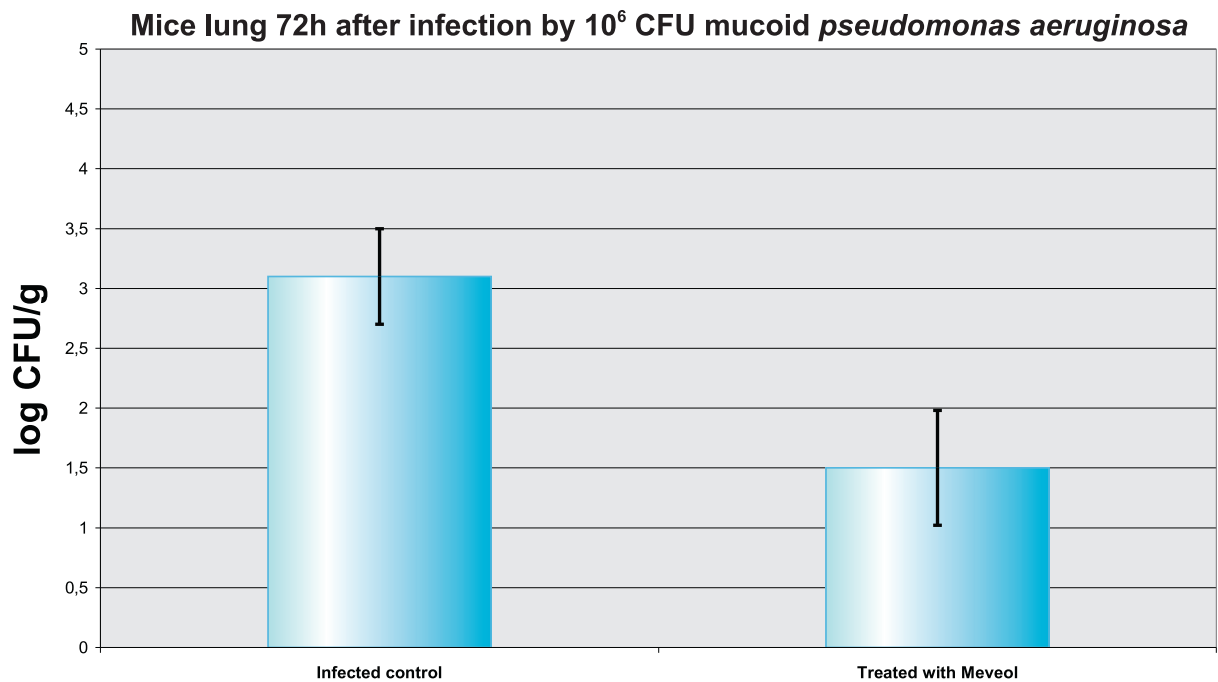
The effects of MEVEOL® have been evaluated both In Vitro (Fig 1) and In Vivo (Fig 2).

In Vitro

Efficacy vs *Burkholderia cepacia* (Strain ATCC BAA-245 : tobramycin and colistin resistant)
(Same kind of results on MRSA, mucoid *Pseudomonas aeruginosa*, not shown here)



In Vivo



In Vivo

Demonstration of efficacy on mice, previously infected with mucoid *Pseudomonas aeruginosa* strain isolated from CF Patients.

CONCLUSION :

MEVEOL® (inhalation use) is of potential significant benefit for the treatment of lung micro-organisms proliferation in Cystic Fibrosis condition thanks to its combined antimicrobial and local mechanism of action. It can be inhaled also in combination with other treatments.

MEVEOL® MAIN BENEFITS

Due to its composition associating OSCN⁻/Lactoferrin
 Acts on super bugs including biofilm and mucoid protection forms
 Acts on MRSA, no antibiotic resistance risk
 Compensates compounds missing in CF lung
 Also anti inflammatory product
 Low risk of side effects due to compounds naturally present in non CF cases
 Easy to breathe

ESSENTIAL BIBLIOGRAPHY

- Childers M, *et al.* A new model of cystic fibrosis pathology: lack of transport of glutathione and its thiocyanate conjugates. *Med Hypotheses.* **2007**;68(1):101-12.
SCN⁻ doesn't cross CFTR
- Moskwa P, *et al.* A novel host defense system of airways is defective in cystic fibrosis. *Am J Respir Crit Care Med.* **2007**;175(2):174-83
OSCN⁻ natural antimicrobial compound misses in CF
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Lactoperoxidase innate host defense system can't work in CF
- Xu Y, *et al.* The antioxidant role of thiocyanate in the pathogenesis of cystic fibrosis and other inflammation-related diseases. *PNAS.* **2009**;106(48):20515-9.
SCN⁻ , Lactoperoxidase, Duox, major importance
- Rogan MP, *et al.* Loss of microbicidal activity and increased formation of biofilm due to decreased lactoferrin activity in patients with cystic fibrosis. *J. Inf. Dis.* **2004**; **190**:1245-53
Lactoferrin activity is decreased in CF

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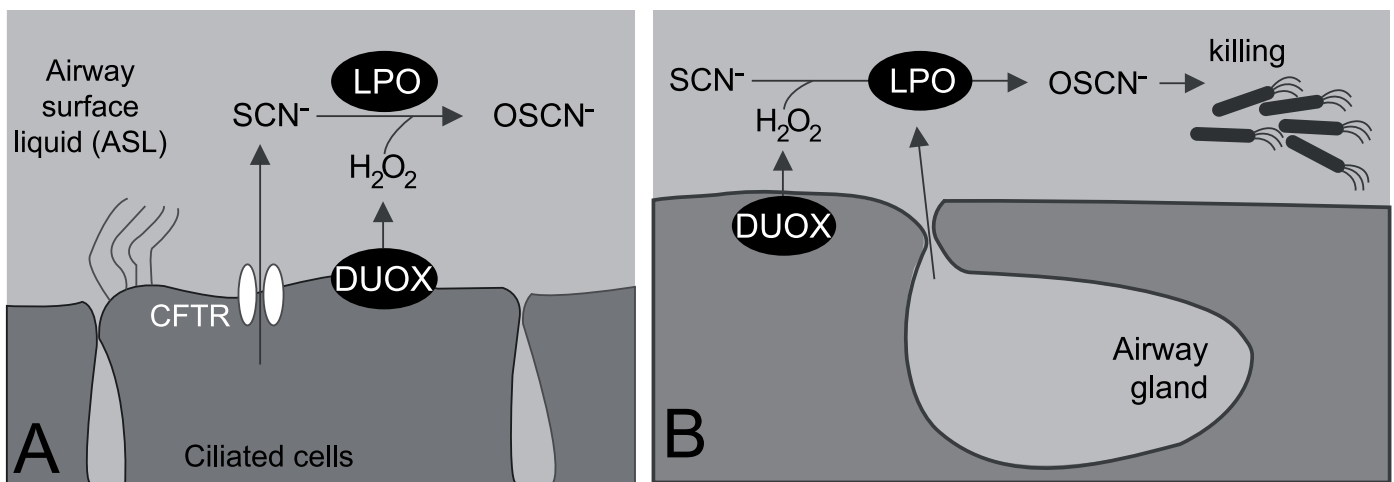


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ANNEX 1 : CFTR, an halogen channel

A model for an antibacterial mechanism based on the Duox/Lactoperoxidase system is based on the observations that normal, uninfamed airways continuously release H_2O_2 into the Airway Surface Liquid where Lactoperoxidase generates antibacterial $OSCN^-$ from H_2O_2 and SCN^- . Thus, in the airways, Duox of the surface epithelium releases H_2O_2 into the airway surface liquid and lactoperoxidase, secreted mainly by submucosal glands (but also by surface goblet cells), produces bactericidal $OSCN^-$. SCN^- transport was stimulated by CFTR activation or blocked by CFTR inhibition and thus is greatly diminished in CF airways. At the same time, bacterial killing by airways in presence of Lactoperoxidase was shown to be directly related to the availability of SCN^- . These investigations gave strong support for the role of the Duox/Lactoperoxidase system as a defense mechanism of the airways that requires normal CFTR function. Thus, this mechanism links CFTR function immediately to innate defense (Fischer H, 2009).

Airway surface liquid



Fischer H. Mechanism and function of DUOX in epithelia of the lung.

Antioxid Redox Signal. 2009;11(10):1-13.

CFTR, Also a SCN^- Channel

In CF patients, never forget SCN^- doesn't cross CFTR and Duox can be inhibited by pyocyanin.

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