ALX-109 potentiates the effect of inhaled antibiotics at killing *Pseudomonas aeruginosa* biofilms on human airway cells

Sophie Moreau-Marquis, Ph.D.

Department of Microbiology and Immunology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
PRESENTER DISCLOSURE

Sophie Moreau-Marquis, Ph.D.

No Relationships to Disclose
Permanent eradication of *P. aeruginosa* in CF airways is currently impossible

- About 80% of adults with CF have chronic *P. aeruginosa* infection.
- Able to persist for several decades in the respiratory tract of CF patients in spite of intensive antibiotic therapy.
- Linked to the ability of *P. aeruginosa* to form biofilms.
Permanent eradication of *P. aeruginosa* in CF airways is currently impossible

Intermittent inhalation of Cayston® or TOBI® reduces CFUs by 0.6 – 1.5 logs but:

- Sputum *P. aeruginosa* density increases back up at the end of treatment

- MIC increases in some patients (resistance)

WS 17.2 Moreau-Marquis S. et al. (ECFS 2013)
Goal

Because neither TOBI® nor Cayston® eradicate chronic airway infections in CF, our goal is to identify new drugs that potentiates the killing effect of inhaled antibiotics and abolishes bacterial biofilms grown on CF airway epithelial cells.
Methods: Co-Culture Biofilm Model on Human Airway Epithelial Cells

Previously, we showed that P. aeruginosa biofilms grown at the apical surface of human CF bronchial epithelial cells develop an increased resistance to killing by antibiotics

TOBRAMYCIN
AZTREONAM

ALX-109

PAO1
Clinical Isolates

WS 17.2 Moreau-Marquis S. et al. (ECFS 2013)
ALX-109 (Alaxia, France)

- Composed of Lactoferrin [8 g/L] and hypothiocyanite (OSCN⁻) [100 µM].
- Airway levels of Lactoferrin and OSCN⁻ are reduced in CF.
- A combination of both compounds was granted Orphan Drug designation by the FDA and the EMA.
- The final formulation is scheduled to be administered by inhalation.
P. aeruginosa
BIOFILM PREVENTION
ASSAY

WS 17.2 Moreau-Marquis S. et al. (ECFS 2013)
P. aeruginosa BIOFILM DISRUPTION ASSAY
Additivity in Disrupting Biofilms Formed by *P. aeruginosa* Clinical Isolates

WS 17.2 Moreau-Marquis S. et al. (ECFS 2013)
Tobramycin Concentration Rapidly Declines in Airway Surface Liquid

Pharmacokinetics data from 2004 Prescribing Information TOBI® Novartis

Extrapolated
Dose Dependent Effect of Tb + ALX-109 on Disrupting *P. aeruginosa* Biofilms

**SMC1587**

**SMC1595**

**SMC1596**

**SMC5450 mucoid**

Moreau-Marquis S. et al. (ECFS 2013)
Conclusion

- ALX-109 potentiates the effect of Tobramycin and Aztreonam at disrupting *P. aeruginosa* biofilms by several log units.

- Combined treatment is efficacious against mucoid and non-mucoid clinical isolates of *P. aeruginosa*.

- Additivity between Tb and ALX-109 was observed even at very low concentrations of Tobramycin.
Inhalation therapy combining OSCN-/Lactoferrin with TOBI® or Cayston® may be beneficial to CF patients by decreasing the airway bacterial burden in patients infected with *P. aeruginosa*.

*Phase I clinical trials with an improved formulation of OSCN-/Lactoferrin are planned.*
Acknowledgments

Bruce Stanton
Jocelyn Drexinger
Roxanna Barnaby
Bonnie Coutermarsh

George O’Toole

Philippe Bordeaux
Victor Juarez Perez
Sandrine Perrotto