Cilastatin as a repurposed treatment for *P. aeruginosa* respiratory infections

THE INVENTION

We propose to repurpose Cilastatin as a stand-alone antimicrobial against *Pseudomonas aeruginosa* growth for patients at risk of chronic or opportunistic infections, offering potent antimicrobial control without toxicity and in multidrug resistant strains (MDR).

Innovative aspects and advantages

- **A novel antivirulence mechanism**: by disrupting essential iron acquisition, cilastatin effectively combats MDR and imepenem-resistant strains, focusing on virulence rather than cellular damage and thus the risk of developing resistance and exacerbations.
- **Significantly reduces bacterial colonization**: cilastatin curbs *P. aeruginosa* bacterial burden up to ~99.9% in preclinical models.
- **Drug repositioning:** leveraging 505(b)(2) regulatory route and equivalents.

IP Rights

Priority patent EP26382262.9 filed on March 2nd 2026

Summary

Chronic respiratory conditions, including cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease (COPD), are frequently complicated by persistent bacterial infections. *Pseudomonas aeruginosa* is a primary opportunistic pathogen in these diseases, driving frequent hospitalizations and is a major contributor to morbidity and mortality in cystic fibrosis patients.

Current clinical approaches rely heavily on traditional antibiotics, including inhaled and systemic anti-pseudomonal agents, to manage these respiratory infections. However, these conventional treatments face severe limitations, as they exert evolutionary selection pressure on bacterial populations, driving resistance, and often fail to eradicate chronic colonization. Consequently, existing treatments frequently fall short in eradicating chronic colonization, leaving patients susceptible to recurrent exacerbations and ongoing pulmonary deterioration.

UAB researches have repurposed cilastatin, traditionally a renal protective agent co-administered with other therapeutic compounds, as a direct, novel antivirulence approach against *Pseudomonas aeruginosa* that circumvents traditional antibiotic pathways.

To survive and establish chronic colonization, *P. aeruginosa* relies on specialized iron-scavenging mechanisms critical for its growth, virulence, and biofilm maturation. Cilastatin binds to a protein essential in the bacterium's mechanism for this process, interfering with iron acquisition, a pathway required for efficient colonisation and persistence.

Additionally, because it targets virulence rather than conventional bacterial growth pathways, it may help reduce the selective pressure that drives antibiotic resistance.

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Current state of development

- **TRL 3. In vivo Proof of Concept**
- **Target identified and validated**: dual proteomics identified PvdM protein as a key infection-associated target in *P. aeruginosa*, with genetic inactivation confirming a major reduction in bacterial colonisation in CF airway models.
- **Mechanism demonstrated**: PvdM inhibition blocks pyoverdine-mediated iron acquisition, an essential virulence pathway for bacterial growth. Consistent effects were also observed in clinical CF isolates.
- **Repurposed lead identified**: the approved drug cilastatin was shown to inhibit PvdM function, reduce pyoverdine production, and significantly impair *P. aeruginosa* growth and infection in differentiated human bronchial epithelial models, including cystic fibrosis-derived cells.
- **In vivo proof of concept achieved**: efficacy has been demonstrated in two mouse lung infection models (wild-type and CF), with cilastatin reducing bacterial burden by up to 3 three orders of magnitude in WT and up to 2 in the CF model (see Fig.1) .

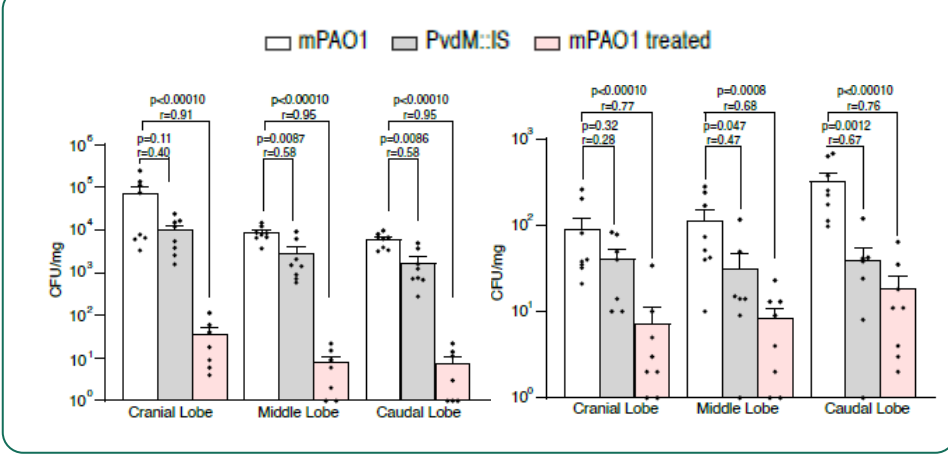

Fig. 1. Cilastatin reduces *P. aeruginosa* bacterial burden in the WT (left) and CF (right) mouse lung infection model. Bacterial loads (CFU; logarithmic scale) were measured in pulmonary lobes after infection, without treatment (mPAO1), with a PvdM knock-out (PvdM::IS) and with cilastatine treatment..

Next steps

- Broaden validation in clinical isolates, generate PK/PD data, and optimize formulation.

Scientific Team

- Led by Marc Torrent, PhD - Professor in Biochemistry and Molecular Biology – Autonomous University of Barcelona.

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