

Drug repurposing to inhibit *Pseudomonas aeruginosa* adaptation to the cystic fibrosis lung environment

Claudia Ridolfi¹, Marta Mellini¹, Lavinia Renzi¹, Valeria Stornelli¹, Paolo Visca^{1,2,3}, Francesco Imperi^{1,2,3}, Livia Leoni¹, Giordano Rampioni^{1,2}

¹*Department of Science, University Roma Tre, Rome, Italy;* ²*IRCCS Fondazione Santa Lucia, Rome, Italy;* ³*NBFC, National Biodiversity Future Center, Palermo, Italy*

The advent of CFTR modulators has led to remarkable improvements in lung function and overall health in many people with cystic fibrosis (CF). However, these therapies do not eradicate chronic lung infections caused by *Pseudomonas aeruginosa*, which remain a major health threat for people with CF.

Traditional antimicrobial discovery mainly relies on screening compounds in nutrient-rich media that poorly reflect *in vivo* conditions and rarely yields novel therapeutic options. Adapting screening conditions to better mimic the host environment has emerged as a promising strategy to uncover previously unrecognized antimicrobial activities in existing drugs. In particular, repurposed drugs that inhibit *P. aeruginosa* growth or biofilm formation in the synthetic cystic fibrosis medium (SCFM), which closely reproduces the chemical composition of CF sputum, may reduce bacterial burden and pathogenicity in the CF lung.

On this basis, over 3,000 FDA-approved drugs were screened in parallel in SCFM and in a standard rich medium. This approach allowed identifying drugs with potent and previously unrecognized antimicrobial or antibiofilm activity against *P. aeruginosa* specifically in SCFM. The best hits showed robust *in vitro* activity against the reference strain PAO1 and a panel of clinical CF isolates. Ongoing studies aim to identify their specific molecular target(s) and clarify their mechanism of action.

By leveraging drug repurposing in a physiologically relevant context, this study uncovered the antimicrobial potential of safe drugs that could improve the treatment of *P. aeruginosa* lung infections in people with CF.