

DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE

Project proposal for a Sapienza PhD scholarship

Main research line

Title: Development of antimicrobials compounds and strategies against critically resistant Gram-negative bacterial pathogens.

Supervisor: Fiorentina Ascenzioni; fiorentina.ascenzioni@uniroma1.it

Website: <https://corsidilaurea.uniroma1.it/it/users/fiorentinaascenzioniuniroma1it>

Summary

Multidrug-resistant (MDR) Gram-negative bacteria pose a significant global health challenge as their infections are associated with high rates of morbidity and mortality, extended hospital stays, and increased healthcare costs. This project aims to develop antimicrobials compounds and strategies, against some of the most critically resistant, in many cases MDR, Gram-negative bacterial pathogens such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*. As Gram-negative bacteria are highly protected from drugs by their outer membrane, which creates a very efficient barrier to drug permeation, we propose different approaches aimed at improving antibiotic activity by modulating OM structure. Additionally, as biofilms are highly antibiotic tolerant, due to efficient protection of the bacteria by the extracellular matrix and possibly low bacterial metabolism, the proposed strategies will be also applied to microbial biofilms, which are recognized as a significant global challenge to healthcare systems.

The project is focused on inhibitors of ArnT, which is a key enzyme that makes Gram-negative bacteria resistant to colistin. Of note, colistin is the last resource drug for treatment of MDR infections. The activity of already isolated compounds will be expanded to other *P. aeruginosa* and *K. pneumoniae* clinical isolates and to biofilms of the same isolates. Additionally, nano delivery vehicles will be addressed for the co-delivery of the adjuvant and antibiotic. Due to the complex structure of the hit compounds, a simplification procedure is undergoing to isolate more easily accessible colistin adjuvant. These compounds will be tested in *P. aeruginosa* and *K. pneumoniae* clinical isolates and to biofilms.

Pertinent Publications of the proponent (last 5 years)

1. Cavallo I, Sivori F, Truglio M, De Maio F, Lucantoni F, Cardinali G, Pontone M, Bernardi T, Sanguinetti M, Capitano B, Cristaudo A, **Ascenzioni F**, Morrone A, Pimpinelli F, Di Domenico EG. Skin dysbiosis and Cutibacterium acnes biofilm in inflammatory acne lesions of adolescents. Sci Rep. 2022 Dec 6;12(1):21104. doi: 10.1038/s41598-022-25436-3. PMID: 36473894; PMCID: PMC9727105. IF_{2y} 4.996; IF_{5y} 5.516 (2021 Journal metrics).
2. Cavinato L, Luly FR, Pastore V, Chiappetta D, Sangiorgi G, Ferrara E, Baiocchi P,

Mandarello G, Cimino G, Del Porto P, **Ascenzioni F***. Elexacaftor/tezacaftor/ivacaftor corrects monocyte microbicidal deficiency in cystic fibrosis. *Eur Respir J*. 2023 Apr 1;61(4):2200725. doi: 10.1183/13993003.00725-2022. IF 33,8; (2023 Journal metrics).

3. **Ascenzioni F**, Cloeckeaert A, Di Domenico EG, Dunyach-Remy C, Guembe M. Editorial: Microbial Biofilms in Chronic and Recurrent Infections. *Front Microbiol*. 2021 Nov 30;12:803324. doi: 10.3389/fmicb.2021.803324. This paper has been reviewed by anonymous evaluators. IF 5,64, IF_{5y} 5.702 (2021 Journal metrics).

4. Di Domenico EG, Cavallo I, Sivori F, Marchesi F, Prignano G, Pimpinelli F, Sperduti I, Pelagalli L, Di Salvo F, Celesti I, Paluzzi S, Pronesti C, Koudriavtseva T, **Ascenzioni F**, Toma L, De Luca A, Mengarelli A, Ensoli F. Biofilm Production by Carbapenem-Resistant *Klebsiella pneumoniae* Significantly Increases the Risk of Death in Oncological Patients. *Front Cell Infect Microbiol*. 2020 Dec 10;10:561741. doi: 10.3389/fcimb.2020.561741. IF 4.83 (2020 Journal metrics).

5. Ghirga F, Stefanelli R, Cavinato L, Lo Sciuto A, Corradi S, Quaglio D, Calcaterra A, Casciaro B, Loffredo MR, Cappiello F, Morelli P, Antonelli A, Rossolini GM, Mangoni M, Mancone C, Botta B, Mori M, **Ascenzioni F***, Imperi F. A novel colistin adjuvant identified by virtual screening for ArnT inhibitors. *J Antimicrob Chemother*. 2020 Sep 1;75(9):2564-2572. doi: 10.1093/jac/dkaa200. IF 5,79, IY_{5y}6.051 (2020 Journal metrics).

6. Quaglio D, Mangoni ML, Stefanelli R, Corradi S, Casciaro B, Vergine V, Lucantoni F, Cavinato L, Cammarone S, Loffredo MR, Cappiello F, Calcaterra A, Erazo S, Ghirga F, Mori M, Imperi F, **Ascenzioni F**, Botta B. *ent*-Beyerane Diterpenes as a Key Platform for the Development of ArnT-Mediated Colistin Resistance Inhibitors. *J Org Chem*. 2020 Aug 21;85(16):10891-10901. doi: 10.1021/acs.joc.0c01459. IF 4,35 (2020 Journal metrics).

7. Cavinato L, Genise E, Luly FR, Di Domenico EG, Del Porto P, **Ascenzioni F***. Escaping the Phagocytic Oxidative Burst: The Role of SODB in the Survival of *Pseudomonas aeruginosa* Within Macrophages. *Front Microbiol*. 2020 Mar 10;11:326. doi: 10.3389/fmicb.2020.00326. IF 5,64 (2020 Journal metrics).

8. Quaglio D, Corradi S, Erazo S, Vergine V, Berardozi S, Sciubba F, Cappiello F, Crestoni ME, **Ascenzioni F**, Imperi F, Delle Monache F, Mori M, Loffredo MR, Ghirga F, Casciaro B, Botta B, Mangoni ML. Structural Elucidation and Antimicrobial Characterization of Novel Diterpenoids from *Fabiana densa* var. *ramulosa*. *ACS Med Chem Lett*. 2020 Jan 30;11(5):760-765. doi: 10.1021/acsmchemlett.9b00605. PMID: 32435382; PMCID: PMC7236223. IF 4,34 (2020 Journal metrics).

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13. Giamarellou H. International J Antimicrobial Agents 2016 doi: 10.1016/j.ijantimicag.2016.09.025.
14. Poirel L, et al., Clin Microbiol Rev. 2017 doi: 10.1128/CMR.00064-16
15. Ghirga F et al., J Antimicrob Chemother. 2020 doi: 10.1093/jac/dkaa200.
16. Inibitori della antibiotico-resistenza mediata da ArnT, 2019 - Imperi, F.; Ascenzioni, F.; Mori, M.; Ghirga, F.; Quaglio, D.; Corradi, S.; Losciuto, A.; Botta, B.; Calcaterra, A.; Stefanelli, R. Patent N 102019000012888
17. Quaglio D et al., J Org Chem. 2020 doi: 10.1021/acs.joc.0c01459.