**DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO**

**Proposta di progetto per una borsa Dottorato Sapienza**
**Linea di ricerca principale**

**Titolo della ricerca:**
**Looking at bacterial efflux pumps as valuable targets for challenging MDR bloodstream infections in cancer patients and as potential virulence factors**

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**Summary**
Efflux pumps (EPs) are membrane protein complexes conserved in all living organisms. The importance of bacterial EPs has long been associated mainly to their ability to extrude a wide range of antibiotics resulting in the emergence of multidrug resistance (MDR) in many bacteria, including pathogens. Recently, several reports have outlined the great versatility of MDR EPs in exporting a large variety of compounds other than antibiotics, thus contributing to bacterial adaptation to a wide range of habitats. An interesting aspect concerns the involvement of EPs in pathogen-host interaction. As responsible for the emergence of MDR, bacterial EPs will be considered as possible targets for fighting antibiotic resistant bloodstream infections, a leading cause of mortality in cancer patients. In order to impair EP functioning, we plan to identify inhibitors targeting the regulatory systems controlling EP expression rather than the EPs themselves, as the latter approach proved unsuccessful in most cases because of the redundancy of different EPs. The identification of such inhibitors would be the base for developing combination therapies to prevent the occurrence of infections with antibiotic-resistant pathogens in cancer patients. The project also deals with the role that EPs play in the infection process of *Shigella,* the etiological agent of bacillary dysentery. In particular, by gain and loss of function, we plan to study in more detail the contribution to bacterial survival of those EPs we previously identified as modulated in a cell specific manner during infection of macrophages and epithelial cells. Moreover, attempts will be made to establish whether EPs upregulated in response to any cellular environment might be implicated in the release of compounds, such as polyamines, functional to a successful *Shigella* infection.

**Pertinent Publications of the proponent (last 5 years)**

- Pasqua M, Zennaro A, Trirocco R, Fanelli G, Micheli G, Grossi M, Colonna B, Prosseda G. Modulation of OMV Production by the Lysis Module of the DLP12 Defective Prophage of Escherichia coli K12. (2021) Microorganisms. 9:369.
- Fanelli G, Pasqua M, Colonna B, Prosseda G, Grossi M. Expression Profile of Multidrug Resistance Efflux Pumps During Intracellular Life of Adherent-Invasive *Escherichia coli* AIEC Strain LF82. (2020) Front Microbiol;11:1935. DOI:10.3389/fmicb.2020.01935.
- Pasqua M, Grossi M, Zennaro A, Fanelli G, Micheli G, Barras F, Colonna B, Prosseda G. The Varied Role of Efflux Pumps of the MFS Family in the Interplay of

Bacteria with Animal and Plant Cells. (2019). Microorganisms;7(9):285. DOI: 10.3390/microorganisms7090285.

- Pasqua M., Grossi M., Scinicariello S., Aussel L, Barras F., Colonna B., Prosseda G**.** The MFS efflux pump EmrKY contributes to the survival of *Shigella* within macrophages (2019), Scientific Reports, 9:2906 DOI: 10.1038/s41598-019-39749-3
- Pasqua, M., Michelacci, V., Di Martino, M.L., Tozzoli, R., Grossi, M., Colonna, B., Morabito, S., Prosseda, G**.** The intriguing evolutionary journey of enteroinvasive *E. coli* (EIEC) toward pathogenicity (2017) Front. Microbiol., 8, 2390. DOI: 10.3389/fmicb.2017.02390
- Leuzzi, A., Grossi, M., Di Martino, M.L., Pasqua, M., Micheli, G., Colonna, B., Prosseda**, G.** Role of the SRRz/Rz1 lambdoid lysis cassette in the pathoadaptive evolution of *Shigella*. (2017) Int. J. Med. Microbiol., 307 (4-5), 268-275. DOI: 10.1016/j.ijmm.2017.03.002

**References (other citations, if appropriate)**

• Pasqua M., et al**.** (2019) The MFS efflux pump EmrKY contributes to the survival of *Shigella* within macrophages, Scientific Reports, 9:2906
• Gudiol C., et al. (2014) Antibiotic resistance in cancer patients. Expert Rev Anti Infect Ther. 12:1003-16
• Leuzzi, A., et al**.** (2015) Multifactor regulation of the MdtJI polyamine transporter in *Shigella*. PLoS ONE, 10, 0136744.
• Campilongo et al. (2014). Molecular and functional profiling of the polyamine content in enteroinvasive E. coli : looking into the gap between commensal E. coli and harmful Shigella. PLoS One. 9:e106589
• Di Martino ML et al. (2013) Polyamines: emerging players in bacteria-host interactions. Int J Med Microbiol. 303:484-91