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

**39° Cycle**

**Project proposal for a PhD scholarship (with no financial support from Sapienza)**

**Title of the research:**

**Comprehensive genomic analysis and bacterial virulence factors affecting antibiotic resistance of *Klebsiella pneumoniae* lineages in onco-hematological patients**

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**Summary**

*Klebsiella pneumoniae* is a leading cause of healthcare-associated infections worldwide due to the rapid acquisition of multidrug resistance and virulence traits [Navon-Venezia et al, 2017]. Specifically, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a significant threat among oncological and onco-hematological patients, with mortality rates reaching 72.7% [Bassetti et al, 2018; Doi et al, 2017]. The spread of CRKP has been reported worldwide; however, Italy, Greece, and Romania are currently considered 'endemic' for CRKP [Cassini et al, 2019]. In recent years, a worrisome convergence of virulence traits and antibiotic resistance has been associated with severe and invasive *K. pneumoniae* infections [Lan et al, 2021]. Alarmingly, hypervirulent (hv) CRKP strains have emerged, creating a new challenge in combating this already dangerous pathogen. The hypervirulence of *K. pneumoniae* was ascribed to the carriage of a plasmid that harbors two capsular polysaccharides regulator genes (*rmpA* and *rmpA2*) and siderophore determinants [Russo et al, 2018]. Phenotypically, hv *K. pneumoniae* isolates have been characterized primarily by their hypermucoviscosity and greater production of siderophores [Choby et al, 2020]. In addition, biofilm production in certain lineages of *K. pneumoniae* is considered a key factor for pathogenicity, representing an additional resistance mechanism, escaping conventional antibiotic susceptibility testing [Di Domenico et al, 2021; Di Domenico et al, 2020]. Considering the increasing threat caused by this microorganism worldwide, the present study aims to determine genetic virulence profiles for CRKP isolates causing infections in hospitalized onco-hematological patients. In addition, this study will also characterize CRKP isolates in terms of antimicrobial resistance, the presence of virulence factors such as hypermucoviscosity, siderophore production, biofilms, and their putative roles in theclinical outcome.

This knowledge can be fundamental to support efforts to control the threat to human health posed by this bacterium and to recognize or understand the emergence of clinically important clones within highly genetically diverse species.

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

Skin dysbiosis and Cutibacterium acnes biofilm in inflammatory acne lesions of adolescents.

Cavallo I, Sivori F, Truglio M, De Maio F, Lucantoni F, Cardinali G, Pontone M, Bernardi T, Sanguinetti M, Capitanio B, Cristaudo A, Ascenzioni F, Morrone A, **Pimpinelli F**, Di Domenico EG. Sci Rep. 2022;12(1):21104. doi: 10.1038/s41598-022-25436-3.

Duration of humoral response to the third dose of BNT162b2 vaccine in patients with solid cancer: Is fourth dose urgently needed? Di Noia V, **Pimpinelli F**, Renna D, Campo F, Cosimati A, Torchia A, Marcozzi B, Massacci A, Pallocca M, Pellini R, Morrone A, Cognetti F. Eur J Cancer. 2022;176:164-167. doi: 10.1016/j.ejca.2022.09.006. Epub 2022 Oct 9.

Homocysteine and Inflammatory Cytokines in the Clinical Assessment of Infection in Venous Leg Ulcers. Cavallo I, Lesnoni La Parola I, Sivori F, Toma L, Koudriavtseva T, Sperduti I, Kovacs D, D'Agosto G, Trento E, Cameli N, Mussi A, Latini A, Morrone A, **Pimpinelli F**, Di Domenico EG. Antibiotics (Basel). 2022 Sep 18;11(9):1268. doi: 10.3390/antibiotics11091268.

Optimizing the Illumina COVIDSeq laboratorial and bioinformatics pipeline on thousands of samples for SARS-CoV-2 Variants of Concern tracking. Donzelli S, Ciuffreda L, Pontone M, Betti M, Massacci A, Mottini C, De Nicola F, Orlandi G, Goeman F, Giuliani E, Sperandio E, Piaggio G; ISG COVID Team; Morrone A, Ciliberto G, Fanciulli M, Blandino G, **Pimpinelli F**, Pallocca M. Comput Struct Biotechnol J. 2022;20:2558-2563. doi: 10.1016/j.csbj.2022.05.033.

Role of Extracellular DNA in Dalbavancin Activity against Methicillin-Resistant Staphylococcus aureus (MRSA) Biofilms in Patients with Skin and Soft Tissue Infections. Sivori F, Cavallo I, Kovacs D, Guembe M, Sperduti I, Truglio M, Pasqua M, Prignano G, Mastrofrancesco A, Toma L, **Pimpinelli F**, Morrone A, Ensoli F, Di Domenico EG. Microbiol Spectr. 2022;10(2):e0035122. doi: 10.1128/spectrum.00351-22.

Rapid decline of humoral response to two doses of BNT162b2 vaccine in patients with solid cancer after six months: The urgent need of the additional dose! Di Noia V, **Pimpinelli F**, Renna D, Maccallini MT, Gariazzo L, Cosimati A, Campo F, Sperandio E, Pellini R, Giannarelli D, Cognetti F. Eur J Cancer. 2022;165:169-173. doi: 10.1016/j.ejca.2022.01.011.

Impact of anti-CD20 monoclonal antibodies on serologic response to BNT162b2 vaccine in B-cell Non-Hodgkin's lymphomas. Marchesi F, **Pimpinelli F**, Giannarelli D, Ronchetti L, Papa E, Falcucci P, Pontone M, Di Domenico EG, di Martino S, Laquintana V, Mandoj C, Conti L, Cordone I, La Malfa A, Viggiani C, Renzi D, Palombi F, Romano A, Pisani F, Gumenyuk S, Di Bella O, Vujovic B, Morrone A, Ciliberto G, Ensoli F, Mengarelli A. Leukemia. 2022;36(2):588-590. doi: 10.1038/s41375-021-01418-8.

Immunogenicity and Safety of COVID-19 Vaccine BNT162b2 for Patients with Solid Cancer: A Large Cohort Prospective Study from a Single Institution. Di Noia V, **Pimpinelli F**, Renna D, Barberi V, Maccallini MT, Gariazzo L, Pontone M, Monti A, Campo F, Taraborelli E, Di Santo M, Petrone F, Mandoj C, Ferraresi V, Ferretti G, Carlini P, Di Bella O, Conti L, La Malfa AM, Pellini R, Bracco D, Giannarelli D, Morrone A, Cognetti F. Clin Cancer Res. 2021;27(24):6815-6823. doi: 10.1158/1078-0432.CCR-21-2439.

The 12-week kinetics of anti-SARS-CoV-2 antibodies in different haematological cancers after vaccination with BNT162b2. Marchesi F, **Pimpinelli F**, Sperandio E, Papa E, Falcucci P, Pontone M, di Martino S, de Latouliere L, Orlandi G, Morrone A, Ciliberto G, Mengarelli A; I.F.O.-COVID-19-Team. Br J Haematol. 2022;196(2):362-367. doi: 10.1111/bjh.17821.

The Impact of Bacterial Biofilms on End-Organ Disease and Mortality in Patients with Hematologic Malignancies Developing a Bloodstream Infection. Di Domenico EG, Marchesi F, Cavallo I, Toma L, Sivori F, Papa E, Spadea A, Cafarella G, Terrenato I, Prignano G, **Pimpinelli F**, Mastrofrancesco A, D'Agosto G, Trento E, Morrone A, Mengarelli A, Ensoli F. Microbiol Spectr. 2021;9:e0055021. doi: 10.1128/Spectrum.00550-21.

Lower response to BNT162b2 vaccine in patients with myelofibrosis compared to polycythemia vera and essential thrombocythemia. **Pimpinelli F**, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, Spadea A, Pontone M, Di Martino S, Laquintana V, La Malfa A, Di Domenico EG, Di Bella O, Falzone G, Ensoli F, Vujovic B, Morrone A, Ciliberto G, Mengarelli A. J Hematol Oncol. 2021; 14:119. doi: 10.1186/s13045-021-01130-1.

Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. **Pimpinelli F**, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, Pontone M, Di Martino S, Laquintana V, La Malfa A, Di Domenico EG, Di Bella O, Falzone G, Ensoli F, Vujovic B, Morrone A, Ciliberto G, Mengarelli A.

J Hematol Oncol. 2021;14(1):81. doi: 10.1186/s13045-021-01090-6.

Biofilm Production by Carbapenem-Resistant Klebsiella pneumoniae Significantly Increases the Risk of Death in Oncological Patients. 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. Front Cell Infect Microbiol. 2020;10:561741. doi: 10.3389/fcimb.2020.561741.

Silver Sulfadiazine Eradicates Antibiotic-Tolerant Staphylococcus aureus and Pseudomonas aeruginosa Biofilms in Patients with Infected Diabetic Foot Ulcers. Di Domenico EG, De Angelis B, Cavallo I, Sivori F, Orlandi F, Fernandes Lopes Morais D'Autilio M, Di Segni C, Gentile P, Scioli MG, Orlandi A, D'Agosto G, Trento E, Kovacs D, Cardinali G, Stefanile A, Koudriavtseva T, Prignano G, **Pimpinelli F**, Lesnoni La Parola I, Toma L, Cervelli V, Ensoli F. J Clin Med. 2020 Nov 25;9(12):3807. doi: 10.3390/jcm9123807.

Staphylococcus aureus and the Cutaneous Microbiota Biofilms in the Pathogenesis of Atopic Dermatitis. Di Domenico EG, Cavallo I, Capitanio B, Ascenzioni F, **Pimpinelli F**, Morrone A, Ensoli F. Microorganisms. 2019 Aug 29;7(9):301. doi: 10.3390/microorganisms7090301.

Association between CMV and Invasive Fungal Infections After Autologous Stem Cell Transplant in Lymphoproliferative Malignancies: Opportunistic Partnership or Cause-Effect Relationship? Marchesi F, **Pimpinelli F**, Di Domenico EG, Renzi D, Gallo MT, Regazzo G, Rizzo MG, Gumenyuk S, Toma L, Marino M, Cordone I, Cantonetti M, Liberati AM, Montanaro M, Ceribelli A, Prignano G, Palombi F, Romano A, Papa E, Pisani F, Spadea A, Arcese W, Ensoli F, Mengarelli A. Int J Mol Sci. 2019 Mar 19;20(6):1373. doi: 10.3390/ijms20061373.

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David, S., Reuter, S., Harris, S.R., Glasner, C., Feltwell, T., Argimon, S., et al. (2019). Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. Nat Microbiol 4: 1919-1929. doi: 10.1038/s41564-019-0492-8.

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