PROGETTO

Supervisore: Daniela Maria Cirillo

Titolo/*Title:* Improving the prediction of new regimens efficacy in drug resistant tuberculosis

Curriculum: Cellular and molecular biology

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: _____

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Tuberculosis (TB) is an infectious disease sustained by *Mycobacterium tuberculosis* complex (Mtb) that cause more than 1.5 million deaths per year (WHO. 2023). TB treatment is complicated by the need to use a regimen of at least 3 drugs to successfully clear the infection. In the case of TB caused by Mtb resistant to first line drugs, the treatment success rate is still low (less than 70%) (WHO. 2023). The recent introduction of the new, short regimen for drug resistant TB treatment based on bedaquiline, pretomanid, linezolid with or without moxifloxacin (BPaLM) has partially addressed this problem (WHO. 2022). Nonetheless resistance to these drugs, particularly bedaquiline (BDQ), is rapidly increasing worldwide. Several of the new antitubercular drugs currently in Phase 2B trials shared BDQ resistance pathways involving the impaired expression and/or functionality of efflux pumps (Sonnenkalb et al. 2023; Miotto et al. 2022).

Rationale and hypothesis

The current approach to predict TB treatment efficacy assesses only the role of individual drugs, overlooking crucial parameters characterizing the regimen-based treatment such as drugs synergism, cross-targeting inhibition and shared resistance mechanisms.

A new strategy is needed to overcome these limitations, evaluating drugs synergism, assessing the resistance pathways, and considering the role of the host microenvironment on treatment efficacy.

Objectives and specific aims

Our project has the overarching objective of developing a comprehensive new strategy for assessing the efficacy of new combination regimens for TB before introduction in clinical practice posing the basis for a personalized medicine approach.

Specific objectives:

1) Implement an enhanced minimal inhibitory concentration protocol based on EUCAST standards.

2) Assess the role of efflux pumps on drugs synergism and resistance development.

3) Develop granuloma bio printed 3D models to assess the role of the host microenvironment the combination treatment efficacy (Huang et al. 2023).

Expected outcomes

This project will provide a new strategy comprising 3 different tools for the evaluation of combination treatment efficacy of TB new drugs. Moreover, it aims for the first time to develop a 3D bio printed model that can allow the study of drug pathogen interactions in a granuloma-like micro environment, posing the basis for TB personalized treatment.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

- *Microbiology techniques*: mycobacterial cultivation, (in a BSL.3 facility), MIC (EUCAST based), cells infection, viability assays

- *Molecular biology techniques*: 3D bio-printing, flow cytometry, immunological assays, CRISPR based diagnostic and qRT-PCR and "-omics" analysis.

- *Technical know-how* on data elaboration, statistical analysis and dissemination.

Bibliografia (max. 15)

Global tuberculosis report 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Huang Z, Zhang G, Lyon CJ, Hu TY, Lu S. Outlook for CRISPR-based tuberculosis assays now in their infancy. Front Immunol. 2023 Aug 3;14:1172035. doi: 10.3389/fimmu.2023.1172035. PMID: 37600797; PMCID: PMC10436990.

Miotto P, Sorrentino R, De Giorgi S, Provvedi R, Cirillo DM, Manganelli R. Transcriptional regulation and drug resistance in Mycobacterium tuberculosis. Front Cell Infect Microbiol. 2022 Sep 2;12:990312. doi: 10.3389/fcimb.2022.990312. PMID: 36118045; PMCID: PMC9480834.

Sonnenkalb L, Carter JJ, Spitaleri A, Iqbal Z, Hunt M, Malone KM, Utpatel C, Cirillo DM, Rodrigues C, Nilgiriwala KS, Fowler PW, Merker M, Niemann S; Comprehensive Resistance Prediction for Tuberculosis: an International Consortium. Bedaquiline and clofazimine resistance in Mycobacterium tuberculosis: an in-vitro and in-silico data analysis. Lancet Microbe. 2023 May;4(5):e358-e368. doi: 10.1016/S2666-5247(23)00002-2. Epub 2023 Mar 29. PMID: 37003285; PMCID: PMC10156607.