PROJECT 1

DoS: Daniela Maria Cirillo

Title: How different TB lineages influence tuberculosis picture and outcome and show different susceptibility to new drugs

Curriculum: Experimental and Clinical Medicine

Link to OSR/UniSR personal page:

https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/emerging-bacterial-pathogens/daniela-maria-cirillo.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Tuberculosis (TB) is caused by the intracellular bacterial pathogen *Mycobacterium tuberculosis* (Mtb) and represents a leading cause of morbidity and mortality worldwide. For many years Mtb has been consider a clonal group of microorganisms in term of pathology, clinical picture and outcomes and drug resistance development. An increasing body of evidence is showing that some Mtb lineages appear more likely to produce a particular clinical phenotype than others (2,3). Phenotypes include cavities on chest x-ray and time to culture conversion, as well as TB meningitis vs pulmonary TB. In addition, some lineage shows a decrease sensitivity to newly introduced drugs.

This project aims at:

1) Revising the association of clinical manifestation in term of outcome, clinical picture, Xray score of the TB cases followed at the Lombardia regional center TB (3 years) with Mtb lineage and additional genomic determinants

2) Assessing the efficacy of new anti-tubercular compounds in in vitro/ex vivo models to determine the epidemiological cut-off value (ECOFF) in the different Mtb complex lineages to develop standardized drug susceptibility testing assays and evaluate differences to be used to guide a lineage dependent dosage of the drug (2).

3) Addressing synergisms on new drugs against the different lineages. Anti-mycobacterial efficacy will be also tested in macrophage infection models. Since TB regimens contain multiple drugs, we will analyze synergistic and antagonistic effects between new anti-tubercular compounds and other drugs pillar of current anti-TB treatment therapy. Beside this phenotypic characterization, we will define the mechanism of action and of resistance by developing in vitro-selected mutants that will be analyzed by whole genome sequencing.

Feasibility of the project:

A collaborative agreement is already in place between EBPU and Centro Regionale di Riferimento per il controllo della Tubercolosi. The center evaluates approximately 300 TB cases per year. We are currently performing WGS of all the Mtb strains isolated in Lombardia under the RF RF-2016-02361757 (ending 2/123) and all the MDR-TB strains isolated in Italy for the Italian MoH. UniSR is starting a 7-year IMI grant (United4TB) and we will have access to the new most promising compounds to be tested on clinical trials. We will need to identify the distribution of MIC across the different lineages, to generate in vitro mutants and study the drug resistance mechanisms.

Skills to be acquired by the student:

- scientific independence, critical thinking, problem solving
- Interaction with the TB international community and stakeholders (WHO, pharma companies)
- learning and generating scientific knowledge on tuberculosis pathogenesis
- technical know-how on in vitro models of PBMC infection and antimicrobial testing
- methodological knowledge on immunological/molecular biology/microbiological techniques (E.g. Next generation sequencing, Real Time and Luminex technology, RNA-s. Use of CAT developed for TB imaging)
- Data analysis and interpretation

References (max. 3)

- Temesgen Z et al Precision medicine and public health interventions: tuberculosis as a model? Lancet Public Health. 2019 Aug;4(8):e374. ISSN 2468-2667, doi: 10.1016/S2468-2667(19)30130-6.
- Battaglia S,et al .Characterization of genomic variants associated with resistance to bedaquiline and delamanid in naïve Mycobacterium tuberculosis clinical strains. J Clin Microbiol. 2020 Sep 9:JCM.01304-20. ISSN: 0095-1137, doi: 10.1128/JCM.01304-20
- Coscolla, M Gagneux S Consequences of genomic diversity In M.tuberculosis Sem in Immunology 2014, 26,6 431-444