Title: **Metabolomic comparison of *Mycobacterium tuberculosis* and *Mycobacterium marinum* model organisms in response to antimicrobials**

Principal Investigator (PI): Marcin ZIOMEK; Medical University of Lublin

Call Details: PRELUDIUM 23

The aim of the project is to compare the metabolic response to antimicrobials of two species of mycobacteria: *Mycobacterium tuberculosis* and *Mycobacterium marin*um. *M. tuberculosis* is a causative agent of tuberculosis in humans and *M. marinum* causing tuberculosis-like infections in fish (mycobacteriosis). Both species are used in tuberculosis research. Tuberculosis disease can be easily transmitted by airborne aerosols, excreted from people with tuberculosis. *M. tuberculosis* mostly attacks the lungs, causing pulmonary tuberculosis, but it also infects other organs, leading to extrapulmonary tuberculosis. Until the COVID-19 pandemic, tuberculosis was the major cause of death among infectious diseases worldwide. The new incidence of active tuberculosis in 2022 was approximately 7.5 million people and 1.13 million deaths were officially reported because of this disease all over the world. It is estimated that approximately one quarter of the global human population has been infected with *M. tuberculosis*, which represents about two billion people. A small proportion of people with latent tuberculosis (people, who were infected with *M. tuberculosis*, but do not have active tuberculosis) will develop into active tuberculosis. The risk of converting from latent to active tuberculosis is much higher for people infected with HIV and people with chronic disease e. g. diabetes. The mortality rate from tuberculosis disease without treatment is about 50%. The COVID-19 pandemic has escalated the problem and caused limited access to diagnosis and treatment of tuberculosis. Drug resistance of *M. tuberculosis* is recognized as a major global challenge to successful tuberculosis control.

In this light, the research on new substances and new treatment schemes is necessary. Moreover, the alternatives to animal models of research are recently intensively developed. Zebrafish embryo model is a very suitable tuberculosis model from the ethical and economical point of view. However the infection of zebrafish is caused by different pathogenic species than *M. tuberculosis* causing pulmonary tuberculosis in humans. Therefore the comparison of the metabolic response of both organisms to antimicrobials will provide a solid basis about the similarities or differences of *M. tuberculosis* and *M. marinum* in terms of the determination of the drug's mechanism of action, as well as bacterial adaptive strategies that ultimately lead to the development of drug resistance.

To understand the similarities and differences in the metabolic response of both bacterial species to antimicrobials, metabolites (compounds produced by cells) analysis will be used. The response of the bacteria to three different types of antimicrobial agents (1. an antimicrobial antibiotic; 2. a natural molecule with potent antimicrobial activity; 3. an active plant extract) will be monitored to see if possible metabolic changes depend on the species and/or substance used.

The realisation of this research will allow to determine 1) how both bacterial species respond to antimicrobials in terms of the reorganisation/adaptation of cell structure and functions 2) what are specific or common response mechanisms in both species against antimicrobials with unknown targets (natural substances, extracts) 3) what is the difference in general bacterial metabolic response to antibiotics and to natural substances in both bacterial species.