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Project: **ROLE OF NATURAL PRODUCTS IN OVERCOMING DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS*.**

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The goal of the project is determination of the synergistic mode of action of antibiotics and natural products(adjuvants) in *Mycobacterium tuberculosis* through the combination of metabolomics, transcriptomics and bioinformatics and validation of selected combinations in *in vivo* zebrafish embryo model of tuberculosis. The proposed research project is a response to the growing problem of drug resistance in tuberculosis (TB) treatment in Poland and in the world. Tuberculosis is caused by *Mycobacterium tuberculosis* having specific waxy outer envelope, which is impermeable to drugs and other compounds. Rifampicin, the basic drug used in sensitive TB treatment was introduced more than 70 years ago. The standard therapy regimens are long and often not effective because of an increase in extensively drug-resistant TB (XDR-TB), defined as multidrug-resistant-TB (MDR-TB) with additional resistance to at least one of the fluoroquinolones and one of the injectable agents. The therapy of XDR-TB takes 5 years and often fails to successfully eradicate the bacteria or ends with patient's death. In the age of global population movements, the emergence of MDR-TB and XDR-TB makes the treatment of TB an on-going challenge. An increasing number of economic refugees crossing the borders changed the epidemiological condition in many countries and increased the possibility of spreading infectious diseases. At the same time, the only licensed vaccine [Bacillus Calmette-Guérin (BCG)] for the prevention of TB, which was introduced almost 100 years ago, can prevent the development of severe TB forms in children but is not effective in adults. In this light, the characterization of bacterial metabolic changes under the influence of synergistic action of antibiotics and natural adjuvants will be useful for the understanding of their mode of action and for the development of new or validation of existing adjuvant therapies to combat tuberculosis.

In the project, we the use integration of transcriptomics and metabolomics. Transcriptomics provides the information about functional elements of the genome and reveals the global gene expression profiles in bacterial cells. It describes the association between genes, transcripts and the phenotype, which is depicted by metabolic state of the cells. Metabolomics reflects the end-products of transcriptional, translational and enzymatic activity of the cell and thus reveals the information about the metabolic state of bacteria in physiological and stress conditions. The combination of both strategies reveals functional correlations between differentially expressed genes and cellular metabolic perturbations to identify metabolic pathways that are affected by the action of antimicrobial compounds. The next step is the validation of the activity *in vivo* in zebrafish embryo model of tuberculosis. The results may be useful for the development of new or validation of existing adjuvant therapies to combat tuberculosis.