Abstract for the general public

Computational deciphering of pro-ferroptotic cell death protein machinery as a fundamental step in the search for therapeutic targets in pneumonia and cystic fibrosis

The human body is composed of quadrillion cells. Cells live and die and their lifetime is limited and controlled by regulated cell death mechanisms which serve to support the organism's life. Ferroptosis is a recently discovered form of regulated cell death program, different from better-known apoptosis. Ferroptosis characteristic feature is increasing level of lipid peroxides where free radicals take electrons from the lipids causing membrane damage and cell failure. Although a lot of interest of that process can be seen among scientists, the explanation of its nuts and bolts still remains unclear. It is not good since this gap of this knowledge prevents us from controlling this process on the molecular level.

Ferroptosis is very important process since it was identified as the mechanism of cell death in Parkinson's and Alzheimer's diseases, and sepsis. It plays a promising role in the treatment of cancers, and may contribute to the degradation of tissue in brain trauma, kidney diseases and asthma. We showed that bacteria *P. aeruginosa* induces ferroptosis in the pathology of pneumonia and cystic fibrosis. Therefore, our plan is to extend our understanding of ferroptosis mechanism at the molecular level to find novel chemical compounds against the ferroptotic cell death signal generated in human cells by bacteria called *P. aeruginosa*. This particular bacteria is considered by the World Health Organization as a pathogen with high medical importance because its infecting abilities and multidrug resistance result in long-term chronic airways infections in patients with cystic fibrosis. These people suffer since currently, there are only possibilities to minimize the symptoms of infections, but there is no effective long-term prevention for their condition. In this project, we will attempt to alleviate this problem and solve some puzzles related to ferroptosis mechanisms initiated by *P. aeruginosa* in humans to improve the quality of life people with cystic fibrosis and other *P. aeruginosa*-associated diseases.

We will use computational methods, such as molecular dynamics and molecular docking simulations, together with bioinformatics and programming abilities to uncover the mechanisms that are used to initiate ferroptosis by *P. aeruginosa* in human cells to finally provide new chemical compounds that will serve as a means for potential medications in the pathology of pneumonia and cystic fibrosis. During the project realization, we plan to develop a new computational tool that will be available for other scientists as a part of a program called *ProDy* (*Python package*) which is used by scientists since 2011. Measurements, mainly biochemical, performed by the US collaborators of this project – will offer additional information that might be used in drug discovery. The project realization will move us closer to the in-depth understanding of the fundamental biological process which is ferroptotic cell death program. That may help to provide new intervention methods for long-term infections of patients with cystic fibrosis and other *P. aeruginosa*-associated diseases.