Description for the general public

All living cells eventually will die. Ferroptosis is a recently (2012) discovered form of cell death, different from better known apoptosis or necrosis. Ferroptosis characteristic feature is increasing level of lipid peroxides. Therefore, free radicals take electrons from the lipids causing the cell damage. Although, a lot of interest of that process can be seen among scientists, the explanation of its bots and nuts **still remains unclear**. This is not good since this gap of knowledge prevents us from controlling this process on molecular level. Ferroptosis was identified as the mechanism of cell death in Parkinson and Huntington's diseases, and sepsis. It plays a critical role in the treatment of **cancers**, and may contribute to the degradation of tissue in brain trauma, kidney diseases and **asthma**. Asthma is a common, long-term, inflammatory condition characterized by periodic attacks of airway obstruction marked by coughing, wheezing, and shortness of breath. In 1990, **183 million people globally were affected by asthma**. Now, this number increased to over **365 million. These people suffer, since** currently, there are only possibilities to minimize the symptoms of this incurable disease, but there is **no effective prevention** for asthma.

In this project we will attempt to alleviate this problem and solve some puzzles related to ferroptosis. Our plan is to investigate computationally molecular mechanisms of ferroptosis processes in order to **bring novel chemical compounds against the ferroptotic cell death**. Our recent studies showed that when two proteins, PEBP1 and 15LOX, combine they will initiate lipid peroxidation i.e. ferroptotic cell death signal. **Therefore, the objective to this research proposal is to develop new medications** which will protect against ferroptosis and therefore improve the quality of life people with asthma and other diseases. Measurements, mainly biochemical, performed by the **US collaborators** of this project – will offer additional information that might be **used in anti-asthma drugs discovery** in clinical tests.

The research plan is divided into **three specific parts, namely**:

1) We will characterize the regulatory mechanisms which initiate the activity of the PEBP1-15LOX complex.
2) We will search systematically for high affinity blockers of 15LOX and PEBP1-15LOX proteins.
3) We will identify and characterize small chemical compounds diffusion (transport) pathways in isolated 15LOX and in a complex with PEBP1 using novel enhanced sampling computational methods.

The project realization will move us closer to in-depth understanding of the fundamental biological process which is ferroptosis. That may help to provide **new intervention methods in asthma** and other diseases.