The aim of the project is to determine the impact of copper ions on the regulation of complex molecular mechanisms involved in the control of ferroportin expression in resting and proinflammatory (activated with LPS IFN-γ) mouse bone marrow-derived macrophages. Ferroportin is localized mainly on the cell membrane of enterocytes and macrophages of the liver (Kupffer cells), spleen and bone marrow playing a key role in the transport of iron ions to the extracellular environment. Up to now, it is the only known cellular exporter of iron ions. Ferroportin expression within the cell is tightly regulated. It has been shown, that copper may induce transcription of the ferroportin gene. However, mechanism(s) of this regulation remains unknown. Macrophages play a crucial role in the control of systemic iron homeostasis. They phagocytose aged or damaged erythrocytes and catabolize their hem into CO, bilirubin and ferrous ions (Fe^{2+}), which are then transported outside the cell by ferroportin. Ionic iron released by macrophages during the process of erythrophagocytosis accounts for about 90% of body iron request. Considering the fact that every day 200 billion red blood cells are produced, and that more than 2×10^{15} iron ions every second are required to maintain adequate erythropoiesis, it is obvious that processes involved in the regulation of iron metabolism in macrophages including iron release from these cells is especially important for the whole body. Increased iron retention within macrophages is frequently observed under a variety of inflammatory conditions resulting from both infections and some autoimmune diseases or tumors. This phenomenon is due to a decreased ferroportin expression in macrophages. This iron withholding is thought to be one of the mechanisms of host nonspecific defense, limiting the availability of this element to pathogens which, like most organisms, exhibit a high demand for this element essential for the basic life processes of the cell. Retention of iron in proiflammatory macrophages results, in parallel, in limiting the supply of iron for erythropoiesis and, thus in inducing so called anemia of inflammation – the most frequent type of anemia in hospitalized patients. Currently, new therapies are being sought to prevent iron accumulation in tissue macrophages in inflammation.

The present project will include analysis of the expression of iron metabolism genes (with particular focus on the ferroportin gene) in mouse bone marrow-derived macrophages. Macrophages will be exposed to copper chloride ($CuCl_2$) and proinflammatory factors (LPS/IFN-γ) that trigger defense response of the organism. In addition, intracellular iron metabolism protein localization will be determined. Finally, measurements of intracellular iron level will be performed. The results will allow to answer following questions: whether and by which molecular mechanisms copper ions influence regulation of the expression of iron metabolism genes leading to the enhancement of the iron export from macrophages to the extracellular environment; whether such regulation may also occur in proinflammatory macrophages. This may be of particular importance in alleviating symptoms of anemia of inflammation associated with bacterial infections (just after antibacterial treatment) as well as under chronic inflammatory conditions characteristic for autoimmune diseases and cancers.