SUMMARY

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease of unclear etiology. The treatment of this disorder is still a therapeutic challenge, due to the ineffectiveness of currently used therapy in many cases. An inflammatory process, which occurs in the liver leads to its cells damage and the development of the organ injury. Inefficiency in AIH treatment leads to development of liver failure and premature death. Therefore, it is extremely important to search for the new therapeutic strategies that will improve the AIH outcome.

Recent studies highlight the significant role of the mitochondria, which are the cellular organelles responsible for energy generation, in activating the death of liver cells, and consequently in progression to this organ failure. In experimental studies, protecting mitochondria against damage significantly inhibited the development of liver injury. Therefore, in AIH therapy both inhibiting the inflammatory process and protecting mitochondria against damage, appears to be beneficial. In recent years, the role of hydrogen sulfide, which is endogenously produced by body cells, in regulating many processes, including inflammation and mitochondrial function, is frequently emphasized. It has been shown that changes in its tissue level are associated with many diseases (including the liver disorders), and regulation of its concentration can have a therapeutic effect. Because hydrogen sulfide has a toxic properties at high concentrations, uncontrolled increasing of its amount in the body should be avoided. In experimental models, sodium sulfides are generally used as compounds which fast release hydrogen sulfide. Unfortunately, due to their chemical instability and uncontrolled release of this gas molecule, they are not suitable for medical usage. Therefore, in recent years, some new compounds have been created that slowly and in a controlled manner release this gaseous particle from its structure. One of them is AP39, which additionally has the ability to attach to the mitochondrial membrane and increase the concentration of hydrogen sulfide within these organelles.

The aim of this project is to evaluate whether AP39 has a protective effect on liver in AIH model in mice by inhibition of inflammation and cell damage. In this project two AP39 administration schemes are planned: before and after induction of hepatitis to, for the first time, verify the effectiveness of hydrogen sulfide donor therapy in the developed stage of the disease. The evaluation of AP39 activity will be made by comparing: the severity of the inflammatory process, the integrity of the liver mitochondria and the extent of liver damage between the experimental groups of animals (two groups of treated mice with the group of untreated and healthy animals). Furthermore, a pharmacokinetic analysis will be performed that will allow to describe the fate of this compound in the body of healthy and diseased mice. To date, there is no such data in the literature, despite the fact that pharmacokinetics is an important element in assessing the efficacy of a compound.

The experiments planned in this project will answer the important question of whether AP39, a new hydrogen sulfide donor, has anti-inflammatory properties and inhibits liver cell damage in a model of AIH in mice, and therefore, whether it has a therapeutic potential in this disease. In addition, the obtained data will significantly increase knowledge about this compound and will provide valuable information that may useful for the preparation of further research on AIH, which, in long term, should result in improvements of existing therapies.