There are several thousand already known genetic diseases, defined as disorders caused by any changes in the genetic material. The majority of these diseases are the inherited ones. Among them, there is a large proportion of such with severe neurological symptoms which expression starts in childhood. It is estimated that although each particular genetic disease occurs with low frequency in various human populations (for most of these disorders, prevalence is between 1:2,000 and 1:200,000), when considered as a group, the number of affected people is estimated at about 30 million in Europe and another 30 million in the USA. Unfortunately, only very few of these diseases can be effectively treated. Moreover, in vast majority of genetic diseases, neurological symptoms, and particularly cognitive and communicative deficiencies, cannot be treated at all. This leads not only to serious medical difficulties, but also to drastic social problems, since inherited neurodegenerative diseases are so severe that not only patients but also whole families are excluded from normal functions in the society and require intensive help. All these problems concern also lysosomal storage diseases (LSD) which will be investigated in this project. Although patients suffering from LSD constitute only - roughly estimating – about 0.1% of all patients with genetic diseases, enormous severity of vast majority of LSD, requirement for constant care on patients and extremely high costs of management made them a serious medical and social problem. On the other hand, LSD can be considered as model genetic disorders as their primary causes, specific mutations in particular genes, are relatively well understood.

The aim of this project is to determine molecular changes in cellular processes occurring in mucopolysaccharidoses (MPS), inherited metabolic diseases. Mucopolysaccharidoses are a group of genetic disorders belonging to lysosomal storage diseases (LSD). They are caused by genetic defects leading to a lack of severe deficiency of activity of one of lysosomal hydrolases involved in degradation of glycosaminoglycans (GAGs). Partially degraded GAGs accumulate in lysosomes which results in dysfunctions of cells, tissues and organs. Until recently, it was assumed that GAG accumulation in cells is the major, if not the only, mechanism of pathogenesis in MPS, as GAGs may be a physical ballast for lysosomes causing inefficiency of cells due to a large amount of a stored material. However, recent reports suggest that in MPS cells there are changes in many different processes which might be even more important for pathogenesis than lysosomal accumulation of GAGs *per se*. Moreover, there are many recently published results indicating that lysosomes are not only responsible for degradation of various macromolecules, but also they play crucial roles in the regulation of cellular metabolism. Therefore, it appears plausible that previous failures in treatment of MPS (i.e. possibility to correct only some symptoms and slowing down of the disease rather than fully effective management of MPS) might be caused by underestimation of changes in cellular processes and concentration solely on decreasing GAG levels in cells.

In the light of the above facts, in this project we aim to perform complex studies on changes in cellular processes occurring in cells of various types of MPS. The main novelty of this project will be comprehensive determination of cellular dysfunctions in MPS cells, and indication their specificity (i.e. what changes are characteristic to all MPS types and what changes are specific to one or a few types or subtypes). Transcriptomic studies will give results that should be the basis for further experimental studies on molecular mechanisms of the cellular dysfunctions. Finally, the use of recombinant enzymes (which are deficient in MPS cells) and genistein in cell cultures will indicate which processes can be, and which cannot be, corrected by these compounds. This should provide an indication for further studies (not planned in this project) on development of effective therapies for MPS.