"Mucopolysccharidosis-plus (MPSPS): the first study on the molecular mechanism of the disease in the light of therapy development"
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Mucopolysaccharidoses (MPS) belong to the group of lysosomal storage disorders (LSDs). They are a progressive hereditary disorder resulting from the complete absence or significant reduction in the activity of specific lysosomal enzymes responsible for the degradation of unbranched polysaccharide chains – glycosaminoglycans (GAGs) [Nagpal et al. 2022]. Undegraded GAGs gradually accumulate in lysosomes, leading to dysfunction of cells, tissues, and eventually entire organs [Freeze et al. 2015]. The activity of individual enzymes, including those in the metabolic pathway, is closely correlated – each enzyme begins to act only after the previous one has completed its reaction. As a result, the lack of activity of even one of them disrupts the entire degradation process [Parenti et al. 2015; Trovão de Queiroz et al. 2016].

MPS inheritance is most often autosomal recessive, with the exception of MPS type II (Hunter syndrome), which is X-linked. The prevalence of individual types varies greatly depending on the region of the world – it is estimated that MPS I occurs at a rate of approximately 1 in 88,000 live births, while MPS VII occurs at a rate of approximately 1 in 2,111,000 births. MPS IX is an extremely rare form – only four cases have been reported worldwide to date [Natowicz et al. 1996; Imundo et al. 2011; Tomatsu et al. 2018; Węgrzyn et al. 2022].

To date, 14 types and subtypes of MPS have been described, classified on the basis of inactive or severely impaired lysosomal enzyme activity or on the basis of GAG accumulation [Zhou et al. 2020]. The clinical picture includes both symptoms common to all forms of the disease and symptoms specific to particular types/subtypes of MPS. Symptoms described in almost all types/subtypes include organomegaly, characteristic facial features, skeletal abnormalities, and, in later stages, changes in the respiratory and cardiovascular systems. In some cases, hearing and vision impairments occur. Cognitive impairment is observed in MPS I, severe forms of MPS II, all types of MPS III, and MPS VII [Muenzer 2011a].

Although individual types/subtypes of MPS are caused by specific mutations in different genes, they lead to the same biochemical effect - the accumulation of GAG in lysosomes [Jakóbkiewicz-Banecka et al. 2009]. Until recently, it was believed that GAG accumulation was the primary and only pathogenic factor [Wraith 2013]. However, recent studies indicate that MPS is also associated with the dysfunction of many cellular processes that are essential for normal cell function. It is therefore possible that molecular disorders, rather than GAG accumulation alone, play a key role in the pathogenesis of the disease. These changes include, among others: apoptosis and autophagy disorders [Tessitore et al. 2009; Brokowska et al. 2021], abnormalities in vesicular transport [Gaffke et al. 2023], proteasome [Pierzynowska et al. 2020], mitochondrial dysfunction [Pshezhetsky 2015], and disorders within the cytoskeleton [Parente et al. 2016] and intracellular signalling [Pierzynowska et al. 2022].

For a long time, therapeutic options for patients with MPS were limited to palliative care. An alternative form of treatment, first introduced in 1980, was bone marrow transplantation [Hobbs et al. 1981]. However, the effectiveness of this method is limited to cases where the disease was diagnosed at a very early stage, before the first clinical symptoms appeared. This therapy does not reverse existing neurological deficits, such as cognitive impairment, hyperactivity, or emotional problems, nor does it correct all structural changes, including common skeletal deformities [Weisstein et al. 2004]. Bone marrow transplantation is considered ineffective in the treatment of MPS types II, III, and IV [Sivakumur and Wraith 1999; Peters and Krivit 2000; Prasad and Kurtzberg 2010].

The introduction of enzyme replacement therapy (ERT), which involves the intravenous administration of the active form of an inactive or partially active enzyme, has led to some restrictions on the use of bone marrow transplants. This decision was justified, among other things, by the high mortality rate after the first transplant in patients with MPS I, amounting to approximately 15% [Boelens et al. 2007]. Over the past dozen or so years, ERT has been developed for MPS I, II, IVA, VI, and VII, with the greatest progress being made in the case of MPS I [Wraith 2005; Wraith and Jones 2014; de Ru et al. 2011; Burton et al. 2025], which is probably due to the highest prevalence of this type of MPS. As with bone marrow transplantation, early diagnosis of the disease and rapid initiation of therapy are crucial [McGill et al. 2010; Schulze-Frenking et al. 2011; Pérez-López et al. 2017; Burton et al. 2025].

The benefits of ERT in patients with MPS include improved joint mobility and, consequently, locomotor ability; improved respiratory function; reduction of hepatomegaly; and a significant decrease in urinary GAG concentration [Wraith et al. 2007; Clarke et al. 2009; Harmatz et al. 2006; Muenzer et al. 2011b; Pérez-López et al. 2017]. Nevertheless, ERT does not eliminate all symptoms of the disease. A particular limitation is the fact that the administered enzyme does not cross the blood-brain barrier, which makes the therapy ineffective in cases involving the central nervous system, as well as the limited effect of the enzyme on bone tissue [Chen et al. 2019; Rossi and Brunetti-Pierri 2024].

Due to the need to develop a therapy for the neuronopathic form, an alternative approach has been proposed – substrate reduction therapy (SRT) [Jakóbkiewicz-Banecka et al. 2009]. This method involves inhibiting GAG biosynthesis when their degradation is impaired, which allows the balance between their formation and removal to be restored. Direct inhibition of GAG-synthesizing enzymes is not feasible because their substrates are simple sugars involved in numerous metabolic processes. Therefore, efforts have been focused on reducing the expression of genes encoding GAG synthetases, which leads to a reduction in their levels and, consequently, a decrease in the rate of synthesis of these compounds. The substance used in this therapeutic approach is trihydroxyisoflavone (genistein) [Jakóbkiewicz-Banecka et al. 2009], a natural compound from the isoflavone group which, due to its broad spectrum of activity, is already used in medicine, among others, as a remedy for menopausal symptoms and for its anti-cancer potential.

Studies conducted using another natural compound, ambroxol (4-((2-amino-3,5-dibromophenyl)methylamino)cyclohexan-1-ol), has shown that it has a positive effect on cellular functions by improving the activity of lysosomal enzymes and lysosomal function, and induces autophagy in a cellular model of mucopolysaccharidosis type III (MPS III) [Goker-Alpan et al. 2020]. Experiments using ambroxol as a potential therapeutic agent were also conducted in a model of Gaucher disease, indicating that it may help reduce the accumulation of toxic substances by activating the autophagy-lysosome pathway [McNeill et al. 2014].

In early 2010, several patients with symptoms resembling Hurler syndrome (a severe form of MPS I) were described in the Republic of Sakha (Yakutia, Russia), leading to death before the age of two [Gurinova et al. 2014]. Initially, the condition was classified as an "undifferentiated hereditary metabolic disease" [Vasilev et al. 2020]. In 2017, after detailed characterization of the clinical picture and determination of the etiology, this entity was described as mucopolysaccharidosis plus (MPS-plus, MPSPS). Patients were found to have excessive GAG excretion in their urine, but this was not due to reduced lysosomal enzyme activity. The name indicates that, in addition to the classic symptoms typical of conventional forms of MPS, patients also have other phenotypic features, including congenital heart defects, renal dysfunction, and hematopoietic abnormalities [Faraguna et al. 2022; Sofronova et al. 2022]. To date, the disease has been diagnosed in several dozen patients, but the exact number is difficult to determine because some patients may have been included several times in different publications [Lipiński et al. 2022]. Most of the diagnosed patients come from the Yakut population (Sakha Republic) [Kondo et al. 2017], but cases have also been reported in other regions of the world – in Turkey [Dursun et al. 2017], and one patient each from the Mediterranean region [Pavlova et al. 2022] and Poland [Lipiński et al. 2022]. It is estimated that the prevalence of MPSPS in the Yakut population is approximately 1:12,100 live births [Kondo et al. 2017].

MPSPS is inherited in an autosomal recessive manner, and to date, two homozygous mutations in the *VPS33A* gene have been described as causing the disorder. The c.1492C > T variant (p.Arg498Trp) has been described in all patients from Yakutia and Turkey [Dursun et al. 2017; Kondo et al. 2017; Faraguna et al. 2022], while the c.599G > C (p.Arg200Pro) mutation has been described in patients from the Mediterranean region and Poland [Pavlova et al. 2022; Cyske et al. 2025b - **Article No. 3** included in this PhD thesis]. Comparing the phenotype of all patients with MPSPS, it can be seen that the c.1492C > T (p.Arg498Trp) leads to much more severe symptoms and very early death, while in the case of the c.599G > C (p.Arg200Pro) mutation, the symptoms are much milder [Pavlova et al. 2019; Pavlova et al. 2022; Lipiński et al. 2022].

Despite the identification of the mutation leading to MPSPS, the exact pathomechanism of the disease remains unknown. However, two hypotheses have been proposed that could potentially explain the mechanism of the disease. The first is based on studies confirming excessive acidification of

lysosomes in the p.Arg498Trp variant of MPSPS. Lysosomal enzymes do not function properly in an excessively acidic environment and cannot break down GAGs, which accumulate in lysosomes, causing a number of severe symptoms [Kondo et al. 2017]. The second hypothesis concerns the p.Arg200Pro MPSPS variant and focuses on the function of the *VPS33A* gene protein product *(*VPS33A protein). This protein is a component of two large, multifunctional complexes: the homotypic fusion and protein sorting complex (HOPS) and the class C core-endosomal vacuolar binding complex (CORVET). Both of these complexes are involved in the transport of proteins to lysosomes, as well as in autophagy and endocytosis processes [Wartosch et al. 2015; Sofronova et al. 2022]. Reduced levels of VPS33A protein have been demonstrated in both MPSPS variants described, but in both cases the protein retained its biochemical activity, indicating that the symptoms are caused by a reduced amount of protein due to its excessive degradation in the proteasome, rather than a lack of activity. [Pavlova et al. 2022; Terawaki et al. 2025]. Further studies have indicated that the pathomechanism of MPSPS may be caused by impaired endosomal transport, which is caused by reduced levels of the VPS33A protein, and thus GAGs are not effectively delivered to lysosomes for degradation [Cyske et al. 2024a – **Article No. 2**; Cyske et al. 2025b – **Article No. 3**; Terawaki et al. 2025]. Such studies have already been conducted on cellular (MPS I, II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, VII, IX) and mouse models of MPS I and have indicated significant disturbances in vesicular transport, as well as an improvement in these parameters after the use of genistein [Gaffke et al. 2023]. If the presented hypothesis were true, there should be significant changes in the levels of proteins involved in vesicular transport in MPSPS, as well as in selected cellular organelles.

Due to the lack of knowledge about the exact pathomechanism, very limited knowledge about cellular disorders in MPSPS, and the need to develop an effective drug, it is justified to investigate which cellular processes may be impaired in MPSPS, which may lead to understanding the exact mechanism of disease development and potential drugs for MPSPS.

Therefore, the aim of my doctoral dissertation was:

1) **To determine which cellular processes are impaired in MPSPS and, consequently, to understand the pathomechanism of the disease**
2) **To test two natural compounds, ambroxol and genistein, as potential drugs for patients with MPSPS**

In my work, I used skin cells – fibroblasts - taken from the only Polish patient with MPSPS with the homozygous variant c.599G>C (p.Arg200Pro) of the *VPS33A* gene. I was unable to obtain more MPSPS cell lines due to the extremely small number of patients (only a few dozen worldwide), the great distance and geographical isolation of most of them (patients mainly live in the regions of Yakutia and Siberia), and the extremely short life expectancy of patients (most die before the age of 2). These and many other problems related to rare diseases are discussed in more detail in the article by Cyske et al. 2025 [Cyske

et al. 2025a - **Article No. 1**]. As a control, I chose skin cells taken from a healthy person matching the age and gender of the patient. In some of the experiments, cell lines taken from patients with Sanfilippo syndrome were also used as a comparison to the already described and better understood cellular disorders in MPS.

1) Identifying which cellular processes are disrupted in MPSPS, and thus understanding the pathomechanism of the disease

To test the hypothesis of impaired endosomal GAG transport resulting from reduced VPS33A protein levels and inefficient delivery to lysosomes, I first determined the level of GAGs in MPSPS cells with the p.Arg200Pro variant of the *VPS33A* gene in control cells and in a patient suffering from Sanfilippo syndrome (MPS III). Experiments using the dot-blotting method showed significantly elevated levels of heparan sulfate (HS) in MPSPS cells compared to control cells. I also visualized the intracellular localization of HS, which proved to be extremely interesting, as the image obtained after staining MPSPS cells differed significantly from that obtained from MPS III cells. Namely, in MPS III, HS was visible in the form of multiple clusters; according to previous literature data, it can be assumed that these are HS aggregates in lysosomes, while in MPSPS, HS was evenly distributed throughout the cell. This image may indicate impaired transport and delivery of GAG to lysosomes.

Previous studies, using both the p.Arg200Pro and p.Arg498Trp variants, indicated a reduced amount of VPS33A protein in MPSPS [Pavlova et al. 2022; Terawaki et al. 2025]. I therefore examined the level of this protein in fibroblasts taken from a Polish patient in comparison with control cells. I found a drastic reduction of more than 80% in the level of VPS33A protein in MPSPS cells compared to control cells. Using fluorescence microscopy, I also demonstrated a reduced fluorescence intensity of this protein. The VPS16 protein, like VPS33A, is one of the subunits of the HOPS and CORVET complexes. These proteins interact closely with each other, which is why I also determined this protein. Similar to the previous experiment determining the level of VPS33A protein, I also found a reduced level of VPS16 protein in MPSPS.

Electron microscopy allows for a broad view of the overall morphology of the cell. For the previously described types/subtypes of MPS, this image is characterized by "onion skin" and "zebra body" structures, which are specific images that can be used to identify lysosomes in which undegraded GAGs are accumulated [Piotrowska et al. 2006]. For a complete view of MPSPS cells, I performed the same test, which showed a significantly increased number of vesicles with altered structure compared to control cells. However, if the theory of impaired vesicular transport is true, it is uncertain whether the vesicles visible in the microscopic image are lysosomes, as in other types of MPS, or endosomes. To answer this question, I stained the lysosomes using LysoTracker dye. The experiments showed a significantly stronger signal in MPSPS cells than in control cells. This may indicate an increased

number of lysosomes, but previous experiments have shown that lysosomes in MPSPS are excessively acidified [Kondo et al. 2017; Pavlova et al. 2022], and it is known that LysoTracker dye has a higher affinity for organelles with lower pH. Therefore, I asked whether lysosomes are more numerous or merely excessively acidified. To obtain the answer, I used the LAMP2 protein, a lysosomal membrane protein and one of the most common markers in lysosome research. Both the level of this protein and the intensity of fluorescence were elevated, on the basis of which it can be concluded that lysosomes are more numerous in MPSPS, regardless of their greater acidification.

Considering the "scattered" image of HS obtained from fluorescence microscopy analyses, I asked whether GAGs are effectively delivered to lysosomes for degradation. Therefore, I determined the colocalization of lysosomes with HS in MPSPS and MPS III and showed that in MPS III, colocalization was at a significantly higher level than in control cells, but in MPSPS, there were no differences. This may indicate that GAGs are not delivered to lysosomes and, although lysosomal enzymes function properly, GAGs cannot be broken down. Another experiment showing the colocalization of HS with LAMP1, another lysosomal membrane protein, proved to be extremely interesting, as the result was the opposite. Namely, HS/LAMP1 colocalization was significantly increased in MPSPS compared to control cells, while in MPS III it was decreased. This might seem contradictory to the previous experiment, but there are studies in the literature describing that the LAMP1 protein is also found in early and late endosomes [Cook et al. 2004]. Therefore, it is likely that GAGs are trapped in endosomes and are not transported to lysosomes for degradation.

Since the VPS33A protein is involved in the maturation of endosomes and their transport to lysosomes [Wartosch et al. 2015; Marwaha et al. 2017; Kümmel et al. 2022], then, according to the tested hypothesis, the level of endosomal markers should be elevated in MPSPS cells. The marker of early endosomes is the EEA1 protein, which is essential for the sorting of early and late endosomes, as well as for sorting at the early endosome stage [Yap and Winckler 2022]. I demonstrated elevated levels of this protein and fluorescence intensity in MPSPS cells compared to control cells, using the western-blotting method and fluorescence microscopy, respectively. In this case, the result also confirms the hypothesis and is consistent with experiments conducted by another team on cells from a patient with the same mutation [Pavlova et al. 2022]. Following this line of reasoning, I checked the level of Rab7 protein, which can be considered a marker of late endosomes, as it is essential for the transport of late endosomes and their delivery to lysosomes. This experiment also showed an increased level of this protein, and microscopic analyses confirmed the increased fluorescence intensity of this protein.

Returning to the above assumption that HS accumulates in endosomes and cannot be transported to lysosomes, I determined the colocalization of HS with the EEA1 protein. Based on the results I obtained, it can be concluded that there is a significantly increased colocalization of HS/EEA1 in MPSPS cells compared to control cells, which confirms the hypothesis. However, it is important to note the level of

HS/EEA1 colocalization in MPS III, which was even higher than in MPSPS, while studies reporting a secondary vesicular transport defect in MPS have already been conducted [Gaffke et al. 2023].

2) Testing of two natural compounds, ambroxol and genistein, as potential drugs for patients with MPSPS

MPSPS is currently an incurable disease, and due to the extremely small number of patients and their very short life expectancy, developing an effective treatment seems to be a huge challenge for modern science. A potential treatment for MPSPS would have to focus on correcting the underlying molecular defects, but it would also have to be safe for long-term use.

I selected two natural compounds that could potentially become drugs for MPSPS: ambroxol (4-((2-amino-3,5-dibromophenyl)methylamino)cyclohexan-1-ol) and genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopiran-4-on). This is because both have been described as inhibitors of protein degradation – endoplasmic reticulum-associated degradation (ERAD) and proteasomal degradation, respectively. Both compounds also have anti-inflammatory and antioxidant properties and induce autophagy [Dhanve et al. 2023; Cyske et al. 2024b; Ponugoti et al. 2024; Borah et al. 2025; Goswami et al. 2025; Pierzynowska et al. 2025], but ambroxol also alleviates endoplasmic stress and inhibits ERAD degradation [Bendikov-Bar et al. 2011; Dhanve et al. 2023], while genistein inhibits proteasomal degradation by modulating protein ubiquitination [Pierzynowska et al. 2020]. As required for drugs that must be taken for life, both compounds have been proven safe for long-term use [Kim et al. 2013; Ghosh et al. 2021; Ponugoti et al. 2024]. Based on the above data, I selected ambroxol and genistein as potential drugs for MPSPS and, in the future, also for other diseases associated with protein instability and endosomal transport disorders. Taking into account other mechanisms of proteolysis inhibition by ambroxol and genistein, I determined whether the use of combination therapy would be more effective than the use of each compound separately.

The first and one of the most important parameters in the search for new drugs is safety. Therefore, this experiment was the first one I performed for ambroxol and genistein as potential drugs for MPSPS, even though both compounds have already been used in medicine for many years. Based on previous literature data, I chose concentrations of 100 μM for ambroxol and 50 μM for genistein, which effectively inhibit proteolysis [Bendikov-Bar et al. 2011; Pierzynowska et al. 2020]. Based on a cell viability test (MTT), I demonstrated that both compounds are safe for MPSPS cells at the concentrations indicated above.

The main problem in MPSPS turned out to be reduced levels of the VPS33A protein, which leads to inefficient vesicular transport and GAG entrapment in endosomes. A potential drug should therefore increase the level of this protein. My research showed a 4-fold reduction in VPS33A protein levels in

MPSPS cells compared to control cells. However, the administration of ambroxol, genistein, or a combination of both resulted in an increase in the level of this protein. The use of a mixture of both compounds proved to be the most effective, and the level of VPS33A protein reached approximately 80% of the control value. I obtained a comparable result for the VPS16 protein, which is closely related to the VPS33A protein. Both of these results indicate that ambroxol and genistein increase the levels of VPS33A and VPS16 proteins by reducing the activity of ERAD (ambroxol) and proteasome (genistein) [Bendikov-Bar et al. 2011; Pierzynowska et al. 2020].

The experiments I conducted confirmed significantly elevated (approximately 3-fold) HS levels in MPSPS cells compared to control cells [Cyske Z et al. 2025b – **Article no. 3**]. However, the use of ambroxol, genistein, and their mixture reduced HS levels, even to the level observed in control cells. To determine whether HS degradation occurs via the lysosomal pathway, I used chloroquine (an inhibitor that blocks the fusion of autophagosomes with lysosomes). The experiments confirmed that after the use of chloroquine at a concentration of 10 μM, very high HS levels can be observed, regardless of the presence of ambroxol and genistein. This result indicates that GAG degradation in MPSPS cells after the use of ambroxol and genistein occurs via the lysosomal pathway.

Since lysosomal disorders occur in MPSPS, I re-determined their number and fluorescence intensity using the LysoTracker dye, but this time I also determined the effect of ambroxol and genistein on these parameters. I showed that the number of lysosomes and the intensity of their fluorescence is significantly increased in MPSPS compared to control cells, and treatment with ambroxol, genistein, and their mixture effectively reduced the number of lysosomes, while the use of a mixture of both compounds most effectively reduced the intensity of fluorescence in MPSPS.

To confirm the normalization of GAG transport to lysosomes, I determined the colocalization of HS with lysosomes (LysoTracker dye). The experiments again showed a significantly reduced level of their colocalization in MPSPS cells compared to control cells, but also an increase in this parameter after the use of ambroxol, genistein, and their mixture, with the use of a mixture of both compounds being the most effective. When examining the colocalization of HS with LAMP2, a lysosomal membrane protein, a reduced level of colocalization can be observed in MPSPS compared to the control, but also an increase to a level comparable to the control after the use of a mixture of ambroxol and genistein. Since my research suggested that in MPSPS, GAGs are trapped in endosomes due to defective endosomal transport [Cyske Z et al. 2025b – **Article no. 3**], I re-determined the level of EEA1 protein and its colocalization with HS, which showed that the level of EEA1 protein is significantly elevated in MPSPS compared to control cells, but the use of ambroxol, genistein, and their mixture resulted in normalization to a level indistinguishable from the control. This result indicates an improvement in vesicular transport efficiency in MPSPS after treatment. This conclusion is further confirmed by the determination of HS colocalization with LAMP1 protein (as mentioned earlier, this protein is found in both lysosomes and

endosomes) [Cook et al. 2024]. This experiment showed, as before, increased HS/LAMP1 colocalization in MPSPS cells compared to the control, but also normalization of this level after the use of a mixture of ambroxol and genistein. Once again, the results confirmed the hypothesis of defective endosomal transport of GAG and an improvement in its efficiency after the use of ambroxol, genistein, and in particular their mixture.

In addition to the level of EEA1 protein (a marker of early endosomes), I also determined the level of late endosome markers – Rab5 and Rab7 proteins. The Rab5 protein is involved in endosome maturation [Nagano et al. 2019], while Rab7 is essential for endosomal transport and the delivery of macromolecules to lysosomes [Marwaha et al. 2017; Mulligan and Winckler 2023]. The levels of both marker proteins for late endosomes were elevated in MPSPS compared to the control, and the use of a mixture of ambroxol and genistein resulted in the normalization of this parameter to the control level (in the case of Rab7) or an improvement in the parameter (in the case of Rab5).

Experiments conducted by other teams [Terawaki et al. 2025] indicated that autophagy is not impaired in the p.Arg498Trp MPSPS variant. However, the results of my research clearly show that this process is impaired in the p.Arg200Pro MPSPS variant [Cyske Z et al. 2025b – **Article no. 3**]. Both ambroxol and genistein are known inducers of autophagy, and I determined their effects on the stimulation of this process in the p.Arg200Pro variant of MPSPS. I determined the level of LC3-II protein (a marker of autophagy) and found that both ambroxol and genistein significantly increase the level of this protein, which indicates effective stimulation of autophagy, and this process is most effective after the use of a mixture of both compounds. The degradation of accumulated protein material is extremely important in the context of potential MPSPS therapy, therefore the induction of autophagy by ambroxol and genistein is extremely helpful in the context of developing a potential therapy using these compounds.

The results of my research described in this chapter were presented in a manuscript article that was submitted to the editors of the journal *Mammalian Genome* and was in peer review at the time of submission of this doctoral dissertation [Cyske et al. – **Article no. 4**].

Conclusions

This dissertation provides experimental evidence supporting the hypothesis of impaired endosomal transport caused by reduced levels of the VPS33A protein, which underlies the molecular mechanism of MPSPS. Therapy with ambroxol and genistein, which I propose as potentially effective in the treatment of MPSPS, results in increased levels of the VPS33A protein, improving almost all impaired parameters or even normalizing them to levels indistinguishable from control. The proposed therapy has the potential to be useful in the future in the treatment of other diseases associated with protein instability and impaired endosomal transport.