

Reduction of Heparan Sulfate in the Brain by Pabinafusp Alfa Results in Prevention of Neurodegeneration and Neurocognitive Impairment in a Mouse Model of Mucopolysaccharidosis II.

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Introduction

- Mucopolysaccharidosis type II (MPS-II) is caused by mutation in the gene encoding iduronate 2-sulfatase (IDS), leading to accumulation of glycosaminoglycan (GAG) including heparan sulfate (HS) throughout the body. Patients with MPS-II are treated with enzyme replacement therapy (ERT) using recombinant human IDS (rhIDS). However, ERT with rhIDS does not treat the brain manifestation, because the enzyme is a large molecule drug that does not cross the BBB. To enable BBB penetration from blood. We have developed a BBB-penetrable IDS designated pabinafusp alfa, which is a genetically engineered fusion protein consisting of an anti-human TfR (hTfR) antibody and human IDS (Figure 1, 2).
- Pabinafusp alfa was administered intravenously to hTfR KI/Ids KO mice, an animal model of MPS-II, at a dose of 2 mg/kg once a week (2 mg/kg EW) or 4 mg/kg once every other week (4 mg/kg EOW) for 36 weeks. IDS was used as a control. The effects of long-term treatment with pabinafusp alfa was evaluated on tissue GAG accumulation, histopathological changings in the brain, and learning disabilities observed in the hTfR KI/Ids KO mice.

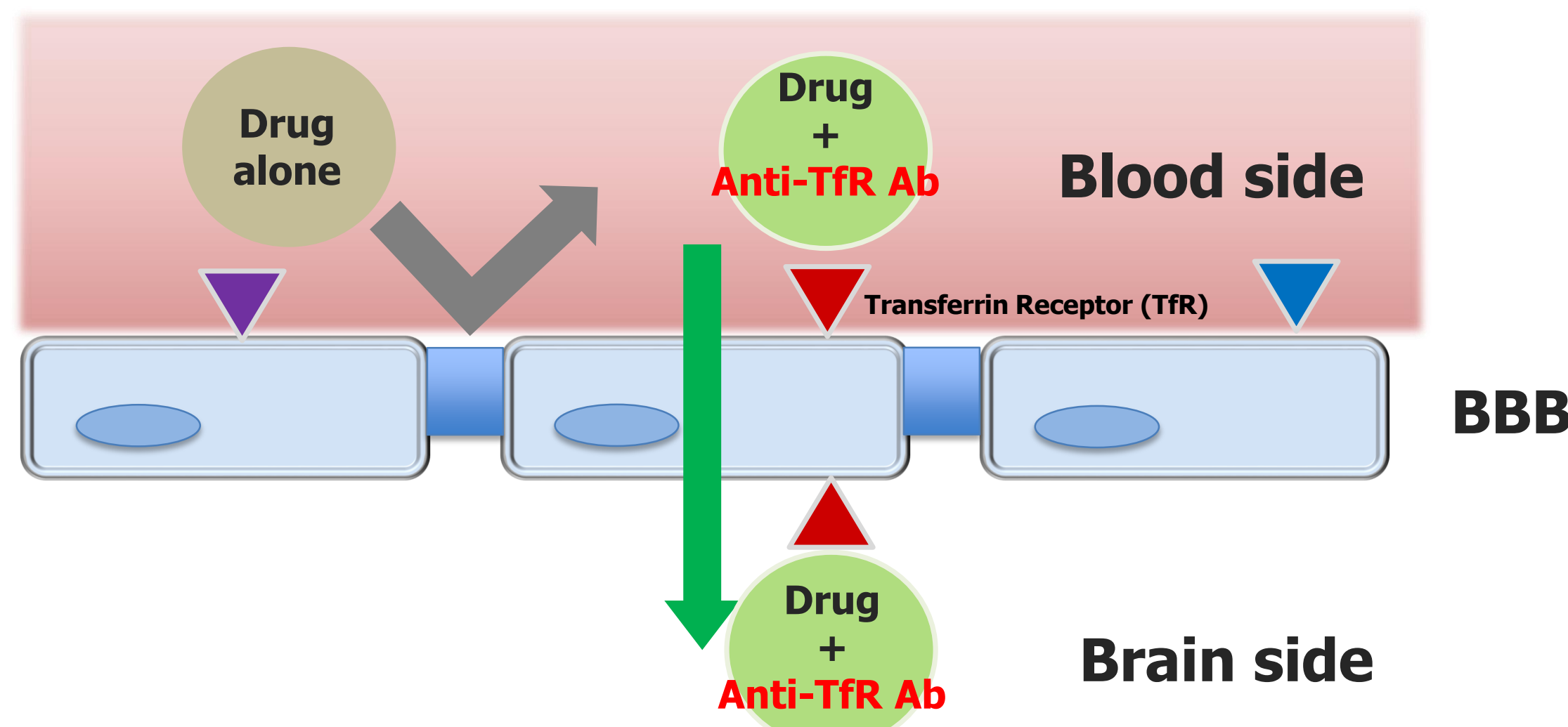


Figure 1. Mechanism of BBB penetration

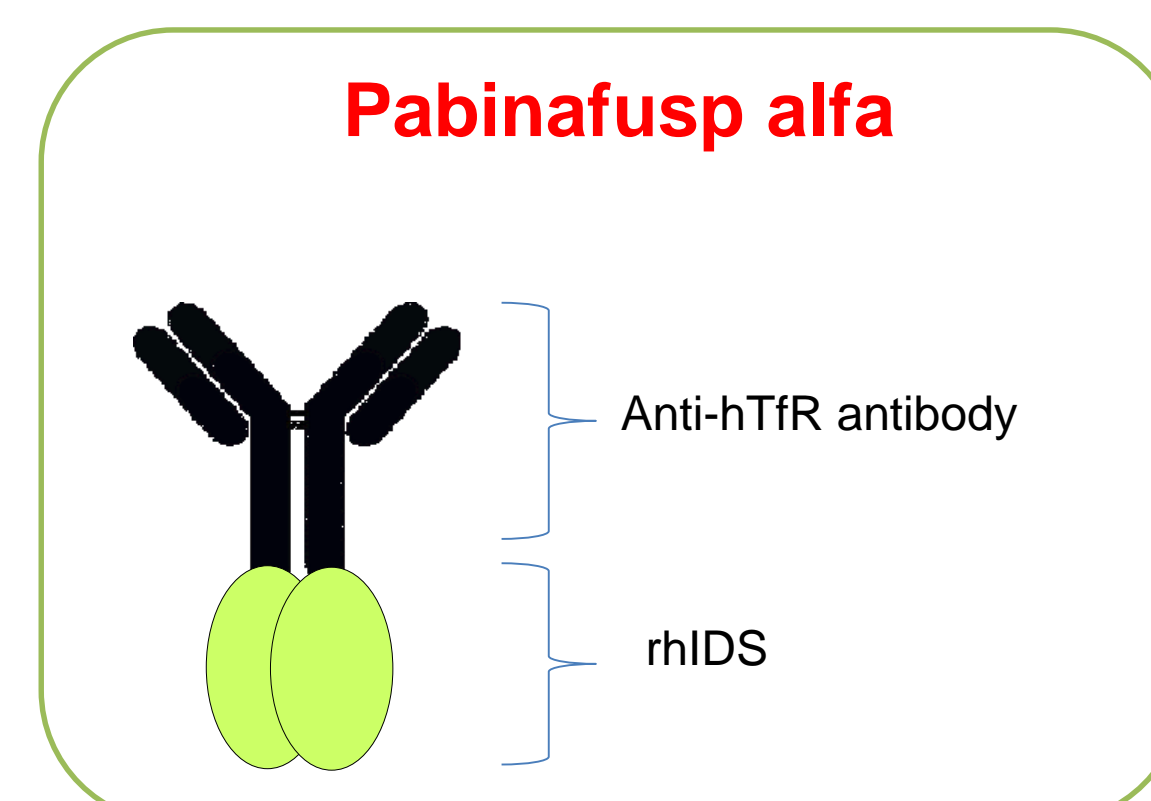


Figure 2. Structure of pabinafusp alfa

Effect of Pabinafusp Alfa on HS Accumulations

- Pabinafusp alfa decreased the brain HS concentration to the level comparable to that of the wild type control. A significant HS reduction in the peripheral tissues were also observed in pabinafusp alfa-treated group at a similar level to that in IDS-treated group (Figure 3, 4). HS concentration in the CSF but not in the serum were correlated well with HS concentration in the brain (Figure 5).

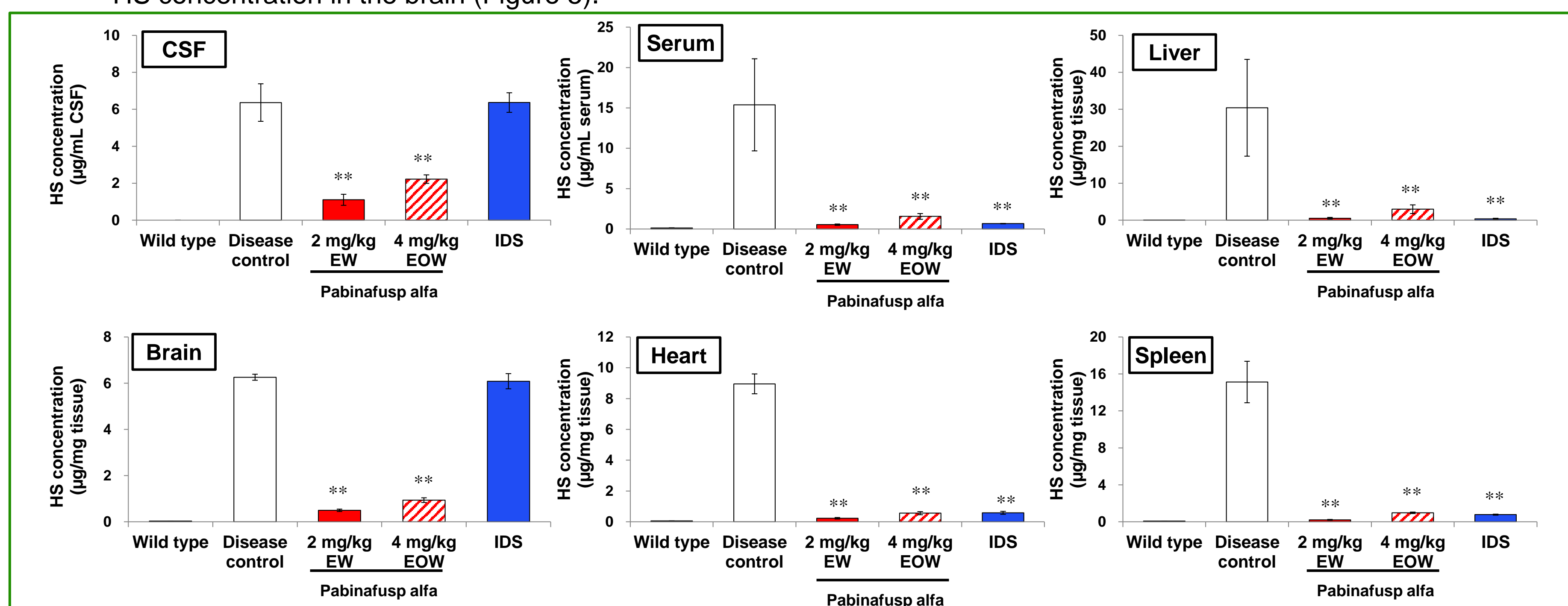


Figure 3. Effect of JR-141 on GAG accumulation

n = 5/group, mean +/- S.D.
**: p<0.01 Tukey-kramer test (vs disease control group)

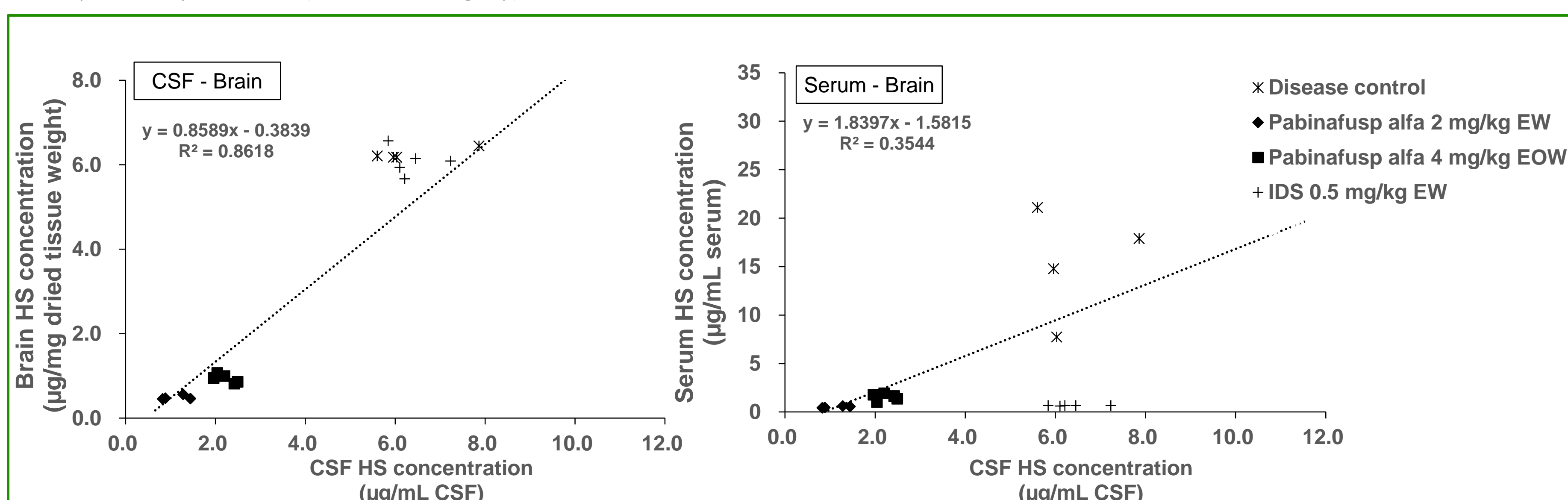


Figure 4. Correlation between HS concentrations in the brain and CSF or serum

Effect of Pabinafusp Alfa on Pathological Changes

- Vacuolization and swelling were observed both in the brain and peripheral tissues of disease control mice.
- In pabinafusp alfa treatment groups, these histopathological abnormalities were suppressed both in the brain and peripheral tissues. By contrast, in IDS treatment group, histopathological abnormalities were suppressed only in peripheral tissues but not in the brain (Table 1. and Figure 5.).

Organ	Findings	Wild type					Disease control					Pabinafusp alfa 2mg/kg EW					Pabinafusp alfa 4mg/kg EOW					IDS				
		-	±	+	++	+++	-	±	+	++	+++	-	±	+	++	+++	-	±	+	++	+++	-	±	+	++	+++
Liver	Swelling, macrophage	10	0	0	0	0	0	5	3	0	0	10	0	0	0	0	10	0	0	0	0	6	1	0	0	0
	Fatty change, centrilobular	0	0	1	9	0	4	2	1	0	1	2	2	3	3	0	3	2	1	4	0	2	2	2	1	0
	Infiltration, mononuclear	7	0	3	0	0	3	3	0	2	0	6	2	1	1	0	4	3	1	2	0	4	0	1	2	0
Spleen	Swelling, macrophage, red pulp	10	0	0	0	0	0	0	0	8	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Hematopoiesis, extramedullary, increased	9	0	1	0	0	8	0	0	0	0	10	0	0	0	0	10	0	0	0	0	6	1	0	0	0
	Vacuolization, Purkinje cell, cerebellum	10	0	0	0	0	0	0	0	8	0	5	5	0	0	0	3	7	0	0	0	0	0	0	0	7
Brain	Deposition, eosinophilic material, medulla oblongata	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	10	0	0	0	0	6	1	0	0	0
	Mineralization	9	1	0	0	0	8	0	0	0	0	9	1	0	0	0	9	1	0	0	0	7	0	0	0	0
	Vacuolization, myocardium, atrium	10	0	0	0	0	0	0	0	8	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
Heart	Vacuolization, myocardium, ventricle	10	0	0	0	0	7	1	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Infiltration, foamy cell	10	0	0	0	0	2	5	1	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Infiltration, inflammatory cell	10	0	0	0	0	7	1	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Fibrosis	10	0	0	0	0	5	2	1	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Swelling, interstitial cell, aortic valve	10	0	0	0	0	8	0	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Swelling, interstitial cell, pulmonary valve	10	0	0	0	0	2	6	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
	Swelling, interstitial cell, tricuspid (right atrioventricular) valve	10	0	0	0	0	6	2	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0
Swelling, interstitial cell, mitral (left atrioventricular) valve	10	0	0	0	0	6	2	0	0	0	10	0	0	0	0	10	0	0	0	0	7	0	0	0	0	

Legend: -: negative +/-: minimal +: mild 2+: moderate 3+: marked

Table 1. Histopathological Changes

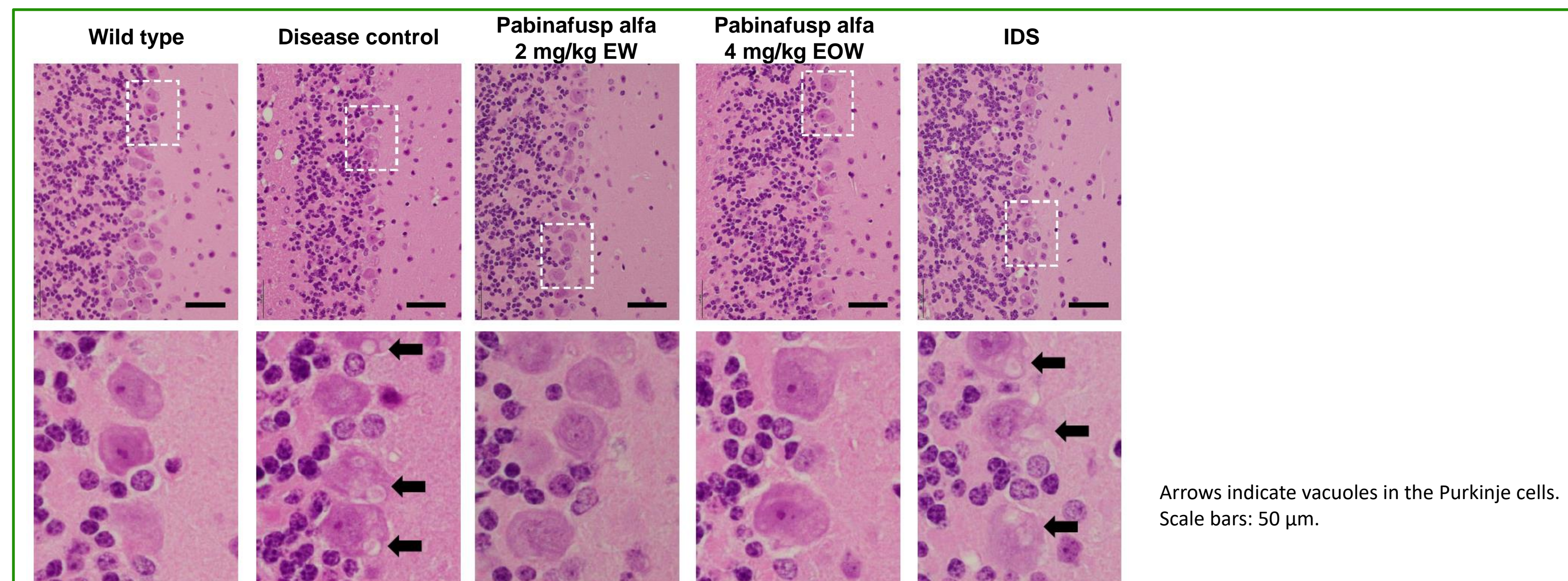


Figure 5. Histopathological changes in the cerebellum

Effect of Pabinafusp Alfa on Neurocognitive Impairment

- Effects of pabinafusp alfa on the CNS dysfunction was assessed using the Morris water maze test. The latency to escape onto the platform was not shortened after repeated trials in disease control, indicating loss of special learning abilities in the mouse model of MPS II (Figure 6.). A shortening of the latency was observed in pabinafusp alfa-treated groups as seen in wild type group. In contrast, IDS had no effect. These results demonstrate that long-term dosing of pabinafusp alfa suppresses the impairment of spatial learning ability in the MPS II mice.

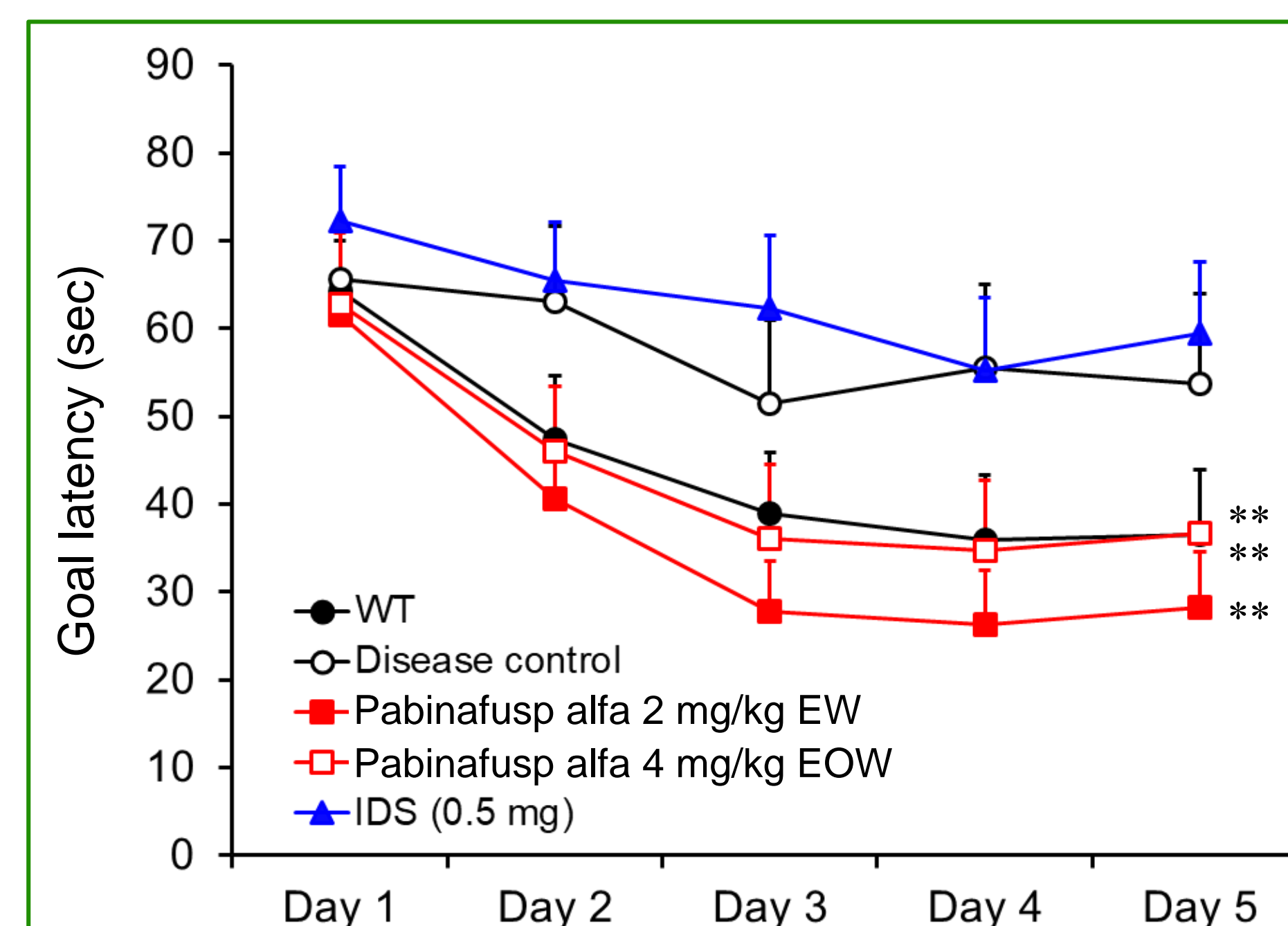


Figure 6. Morris water maze test

n = 13-15/group, mean +/- S.E.
**: p<0.01 paired t test (Day 1 vs Day 5)

Conclusions

- Pabinafusp alfa markedly decreased the HS levels and suppressed histopathological changes in both peripheral and CNS tissues, resulting in maintenance of spatial learning ability.
- HS concentrations in the CSF were correlated with the brain HS concentrations, indicating that HS in the CSF serves as a biomarker reflecting treatment response of the CNS disease in MPS II.

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