Non-Clinical Evaluation of a Blood-Brain Barrier-Penetrable a-N-acetylglucosaminidase in a Mouse Model of Mucopolysaccharidosis IIIB

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Introduction

- Mucopolysaccharidosis type IIIB (MPS IIIB, also known as Sanfilippo syndrome type B) is caused by mutations in a-N-acetylglucosaminidase (NAGLU) gene, leading to accumulation of glycosaminoglycan heparan sulfate (HS) throughout the body, followed by mild somatic features and severe neurological diseases. There is no definite treatment available for MPS IIIB patients so far.
- Here we report the development of JR-446, a fusion protein consisting of Fab fragment of anti-human transferrin receptor antibody (named J-Brain Cargo®) and rhNAGLU (Figure 1). JR-446 has potential to cross the blood-brain barrier (BBB) through the mechanism of receptor-mediated transcytosis of transferrin, to reach the brain parenchyma (Figure 2).

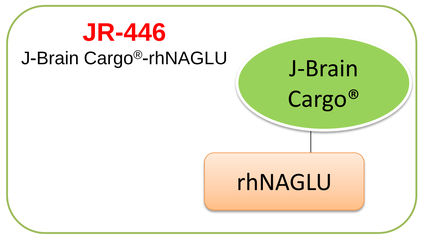


Figure 1. Structure of JR-446

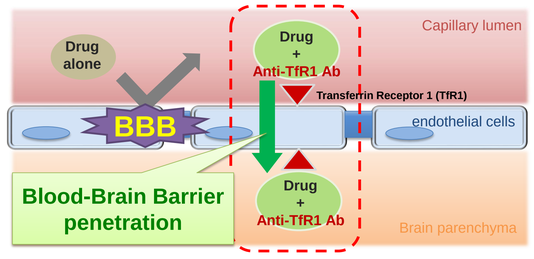


Figure 2. J-Brain Cargo® technology

Biodistribution of JR-446 and rhNAGLU in Cynomolgus Monkeys

- Biodistribution of JR-446 was compared to that of rhNAGLU after intravenous administration to cynomolgus monkeys. Tissues were collected and homogenized to measure drug concentrations. Concentration of each drug was determined by electrochemiluminescence assay using anti NAGLU antibody.
- When administered intravenously, concentrations of JR-446 and rhNAGLU in the plasma and the CSF were higher than those of rhNAGLU (Figure 3).
- JR-446 was detected in all CNS tissues tested, and the concentrations decreased over time (Figure 4). On the other hand, rhNAGLU was hardly detectable in the CNS tissues.
- In cerebral cortex, immunohistochemical analysis showed that JR-446 was delivered to neuronal cells (Figure 4).

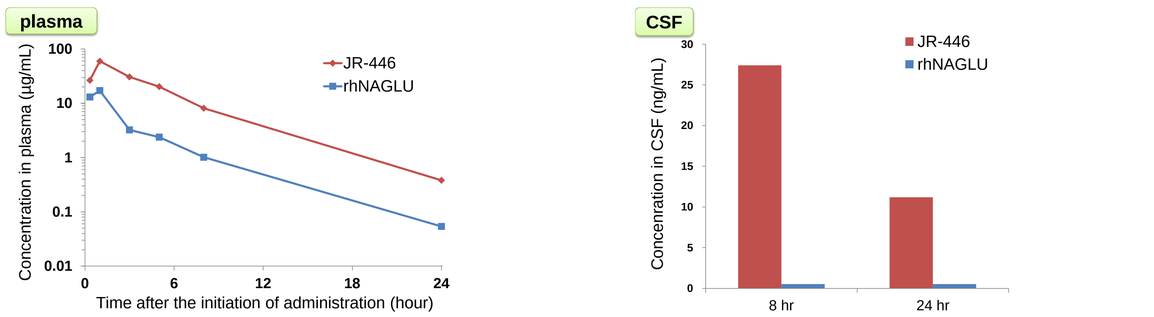


Figure 3. Concentrations of JR-446 and rhNAGLU in plasma and CSF

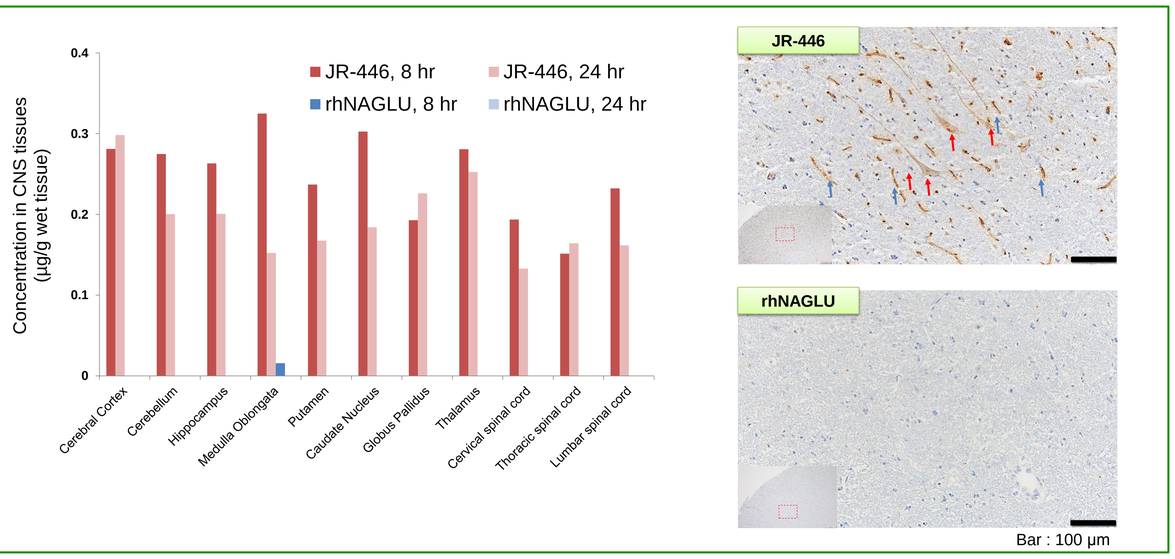
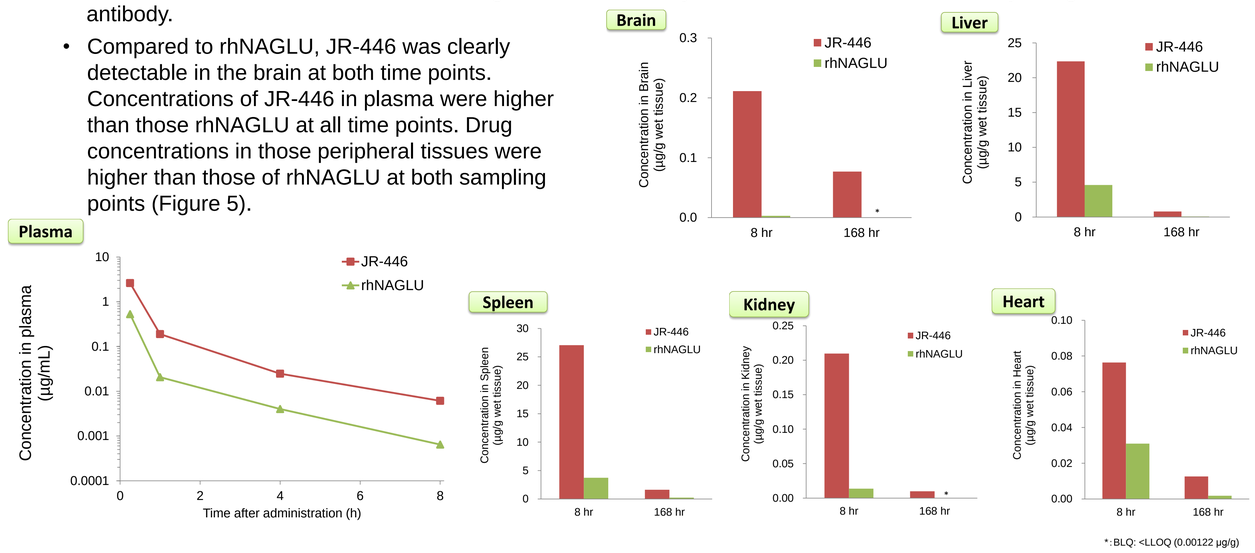


Figure 4. Biodistribution of JR-446 and rhNAGLU in the CNS tissues

- Left) Concentrations of drugs in the CNS tissues.
- All CNS tissues treated with rhNAGLU were BLQ, except for medulla oblongata at 8 hr (<LLOQ：0.00783 μg/g)
- Right) Drug localization assessment by IHC in cerebral cortex. Brains were removed 8 hours after administration.
- Red allows: neuronal cells, Blue allows: blood vessels

Biodistribution of JR-446 and rhNAGLU in hTfR KI Mice

- Biodistribution of JR-446 was compared to that of rhNAGLU after intravenous administration to human transferrin receptor knock–in (hTfR-KI) mice (n=2/group). Tissues were collected and homogenized to measure drug concentrations. Concentration of each drug was determined by electrochemiluminescence assay using anti NAGLU antibody.
- Compared to rhNAGLU, JR-446 was clearly detectable in the brain at both time points. Concentrations of JR-446 in plasma were higher than those rhNAGLU at all time points. Drug concentrations in those peripheral tissues were higher than those of rhNAGLU at both sampling points (Figure 5).



*：BLQ: <LLOQ (0.00122 μg/g)

Figure 5. Concentrations of JR-446 and rhNAGLU in plasma and tissues

Reduction of HS Levels by Administration of JR-446 in MPS IIIB Model Mice

- Efficacy of JR-446, in terms of reduction of accumulated HS, was evaluated in the brain, CSF, serum and heart of hTfR-KI/Naglu-KO mice as a model mice of MPS IIIB. JR-446 or rhNAGLU was intravenously administered to mice for 11 weeks.
- JR-446 reduced concentrations of HS in the brain and CSF, in which rhNAGLU failed to affect the concentration (Figure 6). In the serum and heart, JR-446 reduced HS concentrations more efficiently than rhNAGLU (Figure 6).

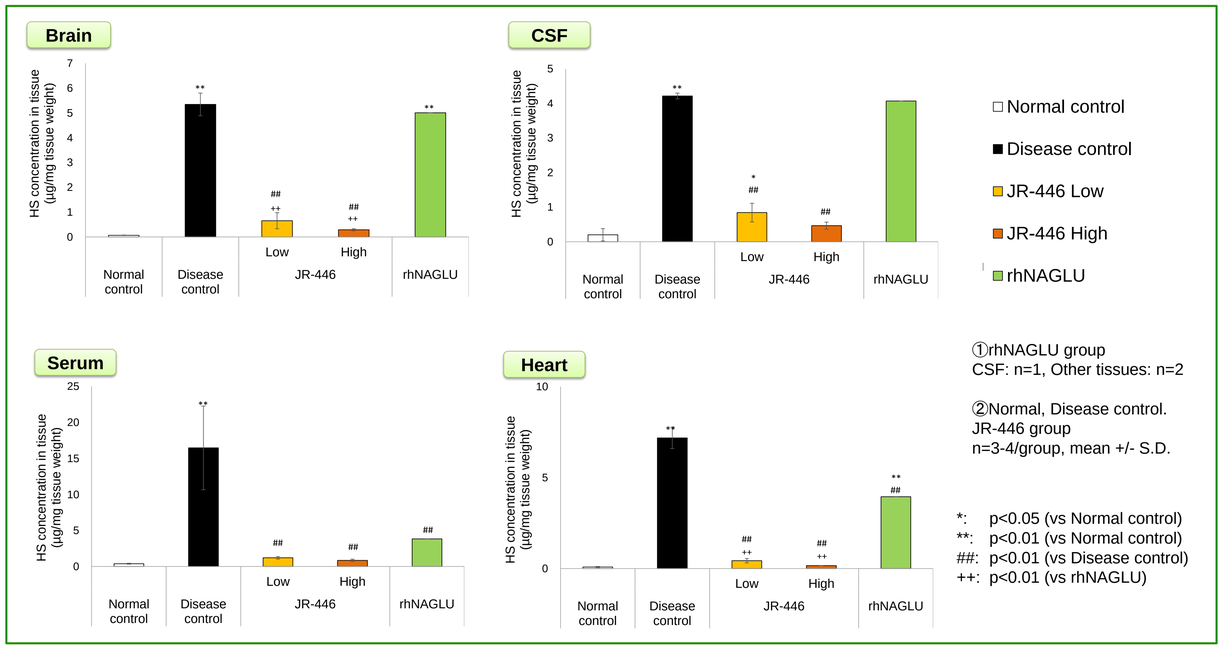


Figure 6. Result of evaluation of drug efficacy of JR-446 on HS reduction

Conclusions

- Anti-hTfR antibody-fused NAGLU (JR-446) was delivered to the brain by crossing the BBB in mice and monkeys.
- JR-446 reduces the accumulated substrate in both CNS and peripheral tissues when administered intravenously to MPS IIIB model mice.
- JR-446 has a potential to exert therapeutic benefit on the severe CNS symptoms in patients with MPS IIIB.

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