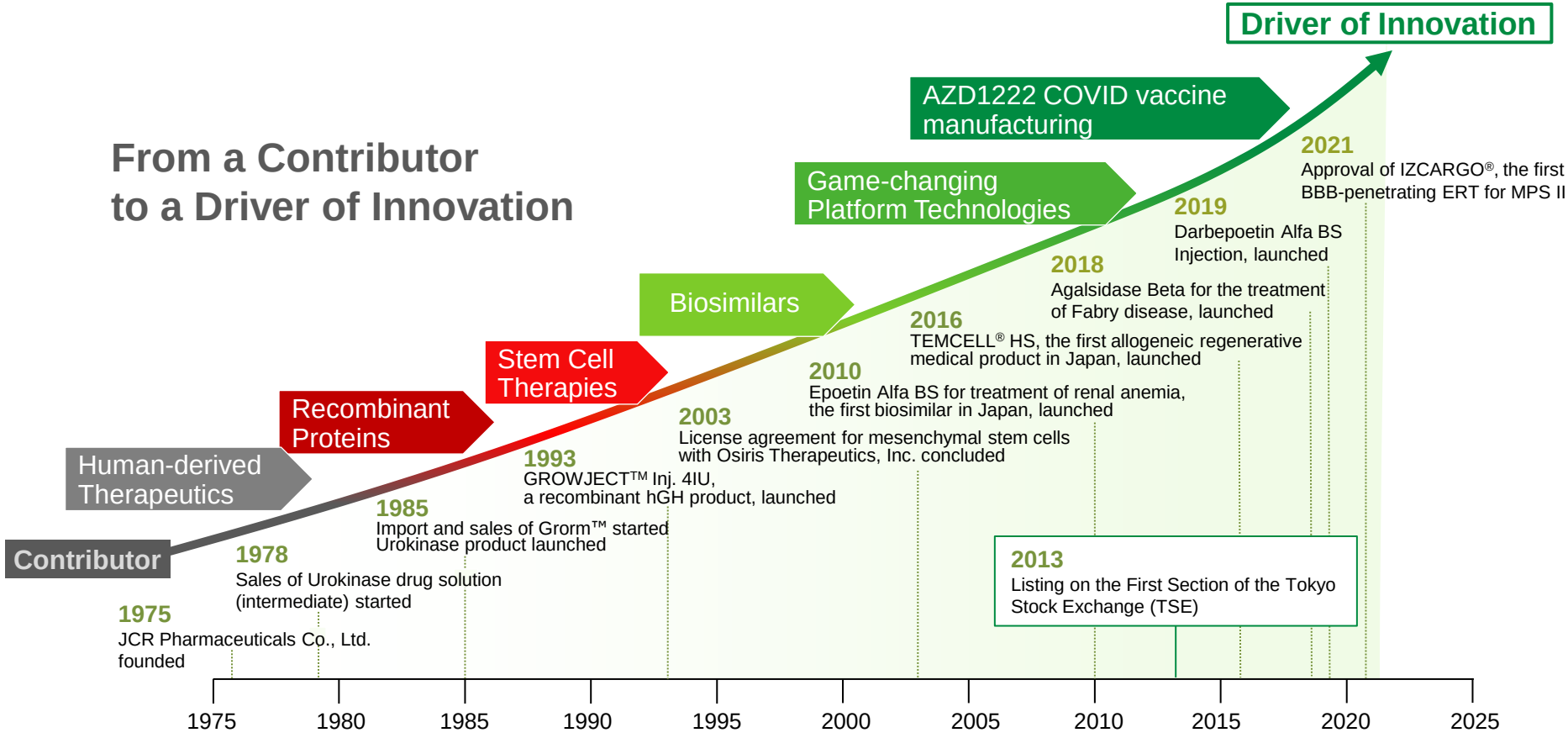
JCR Pharmaceuticals R&D Meeting

Mar. 29, 2022

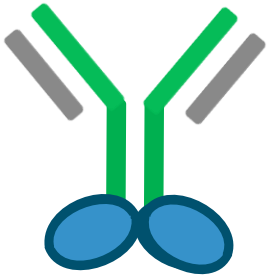
JCR Pharmaceuticals - Our History

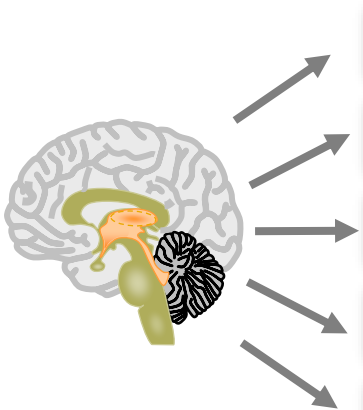


hGH: human Grwoth Hormone

ERT: Enzyme replacement therapy
MPS: Mucopolysaccharidosis

The Approval of IZCARGO® in Japan marked a New Chapter in the History of JCR Pharmaceuticals





- Lysosomal storage diseases
- Alzheimer's disease
- Parkinson's disease
- Neuro-Oncology
- Neuro-Inflammation

J-Brain Cargo®
TfR-targeting antibody
+
Target molecules

As a medicine:

Redefining how we treat MPS II and other LSDs

As a Technology:

Redefining how we address CNS diseases

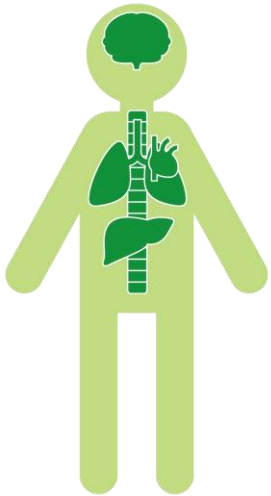
LSD: Lysosomal storage disease

TfR: Transferrin receptor

CNS: Central nervous system

Pathology and Therapy of Lysosomal Storage Diseases

Physiology

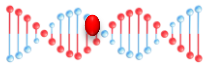


Healthy individual

Pathophysiology

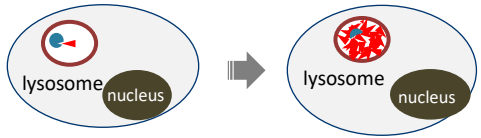
Molecular cause

Defined mutation



Biochemical consequence

Enzyme dysfunction



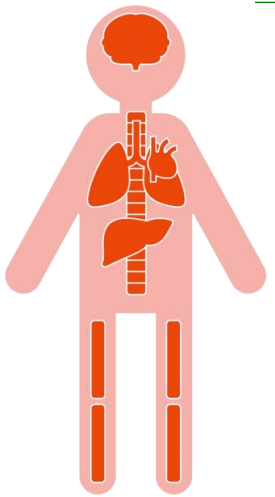
Lysosome dysfunction

Disease Burden

CNS burden

Somatic burden

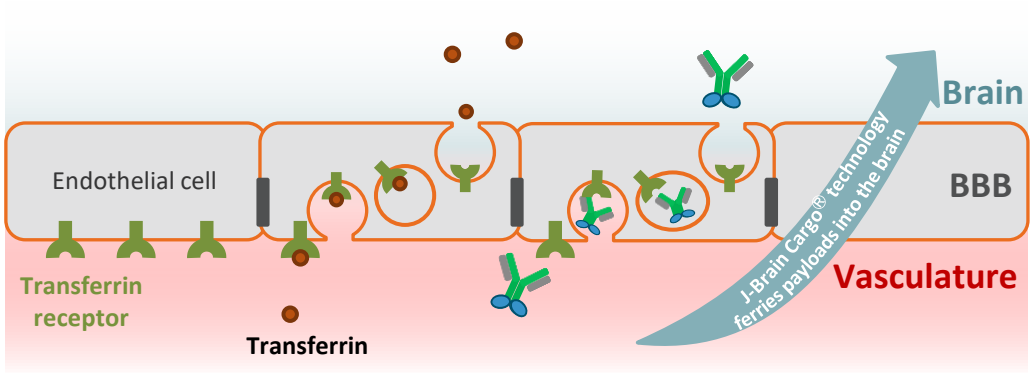
(Standard ERT)

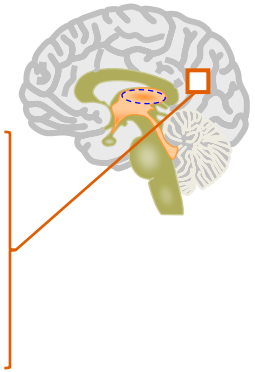


JCR J-Brain Cargo® Asset

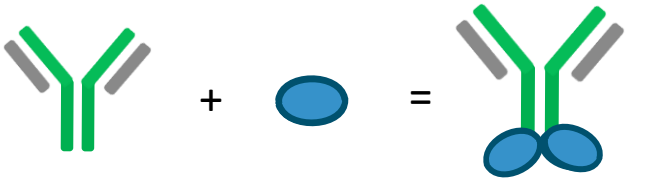
Therapeutic intervention

Mechanism of Action of J-Brain Cargo® Technology to bring Protein Therapeutics across the Blood-Brain-Barrier





BBB: Blood-Brain-Barrier



TfR-targeting mAb + **Effector (enzyme)** = **J-Brain Cargo®**

Antibody-enzyme fusion protein

Clinical Validation:

2021

IZCARGO® for I.V. infusion 10mg for treatment of MPS II, launched in Japan

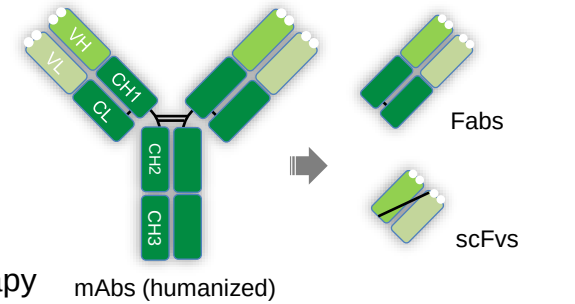
Multi-Modality of the J-Brain Cargo® Technology

A highly modular platform allowing tailoring to different therapeutic purposes

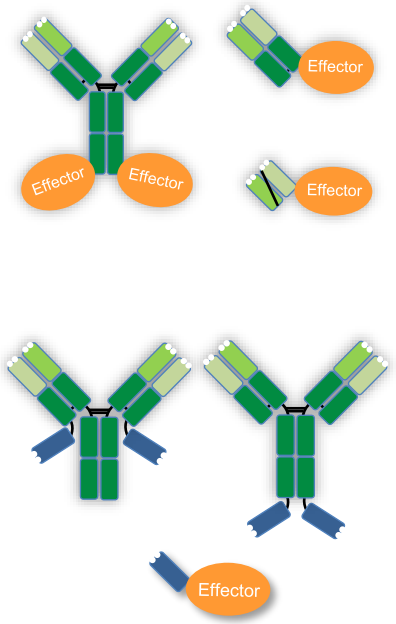
- Coverage of a broad range of epitopes, affinity range from 10^{-8} to 10^{-12} M
- Targeted libraries from immunized Camelid species optimal for vectorization in gene therapy
- Bispecific antibody format applicable to neurodegenerative diseases
- Flexibility for therapeutic effectors and fusion site(s)
- Patents* = 32 filed, 15 issued
  Publications* = 9 original, 1 review

*As of March 2022

BBB-Targeting Molecules



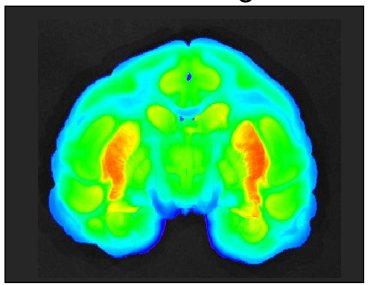
Therapeutic Effector Proteins



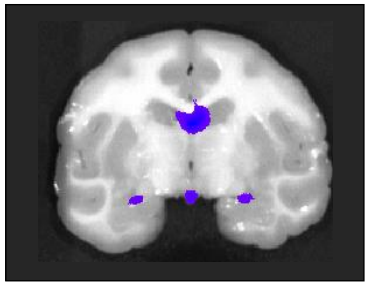
Validation of Brain Passage to the Molecular Level

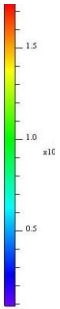
Bioimaging in Monkeys

J-Brain Cargo®



Control

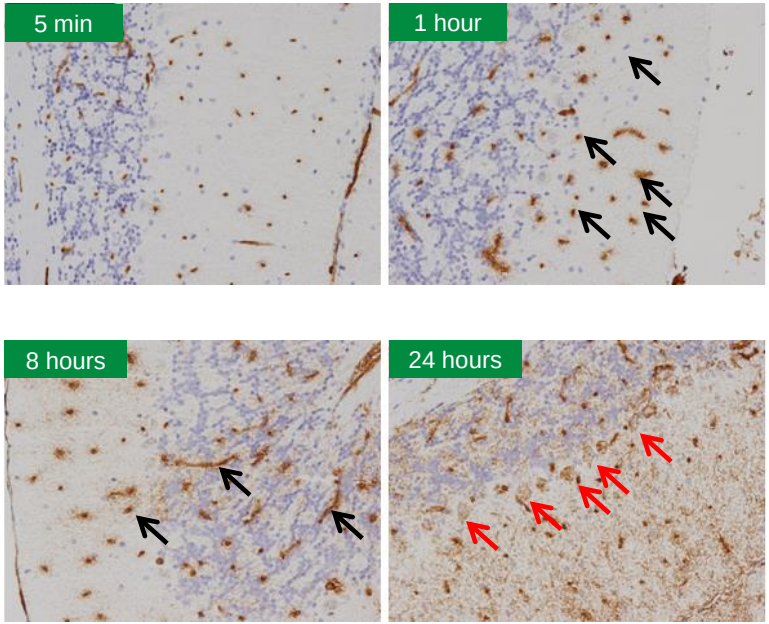




4 mg/kg, 24 hours post iv bolus infusion

iv: Intravenous

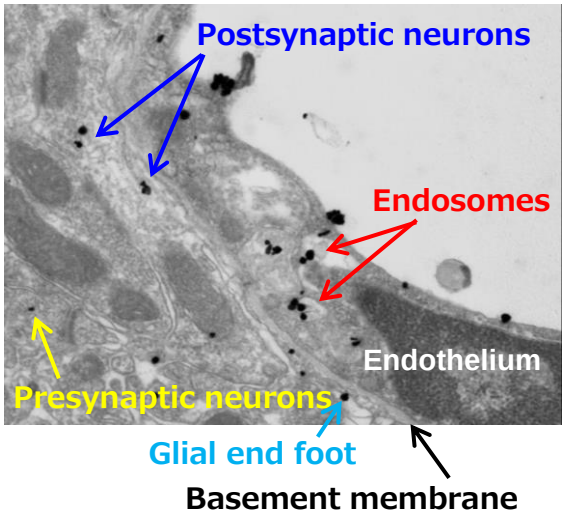
Time Course in Mice



→ vascular endothelium → neuronal cells

Drug + J-Brain Cargo® 6 mg/kg, iv

Immunoelectron microscopy in Mice



JCR Internal Data

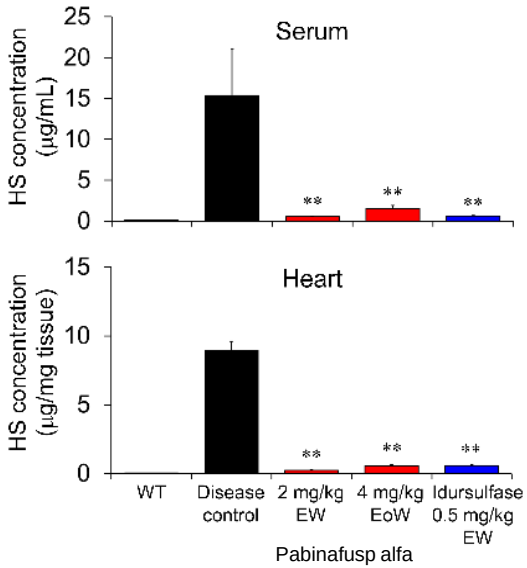
IZCAGRO® (pabinafusp alfa)

The First J-Brain Cargo® Product Approved in Japan for the Treatment of MPS II

Preclinical Validation of pabinafusp alfa

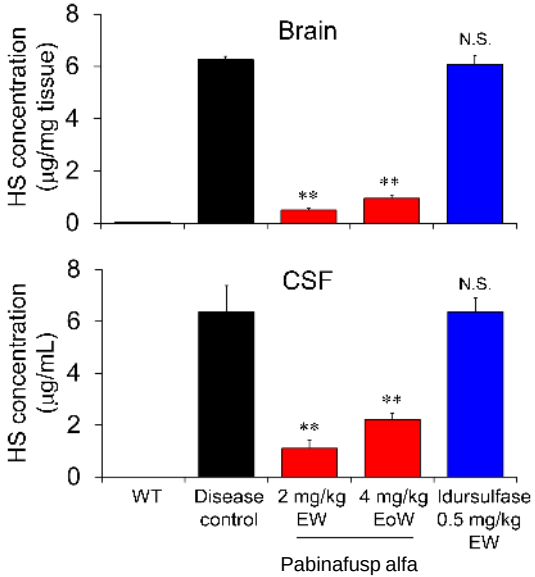
Experiments conducted in IDS KO / hTfR KI mice

Peripheral Organs



**P < 0.01 (vs. Disease control group), Tukey-Kramer test (n = 4-5).

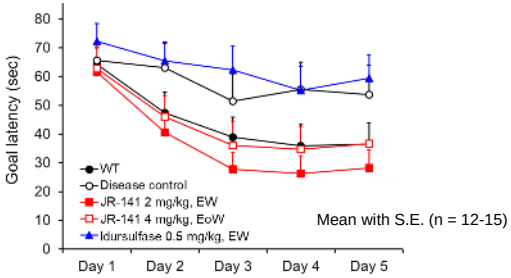
Central Organs



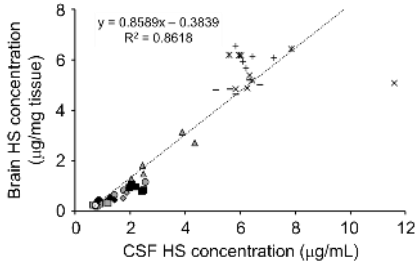
**P < 0.01 (vs. Disease control group), Tukey-Kramer test (n = 4-5).

Functional Outcome

Preservation of spatial learning



Correlation between HS Reduction in Brain and CSF

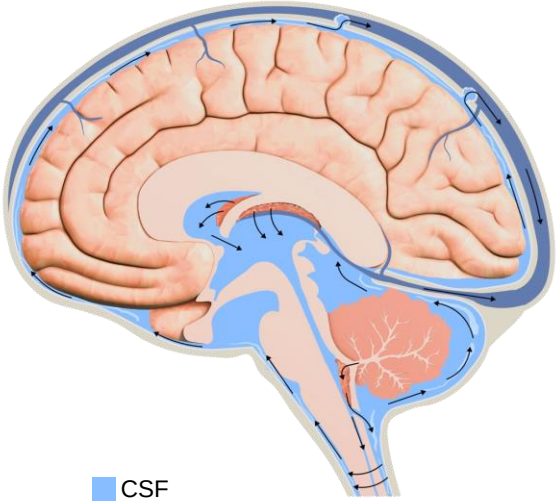


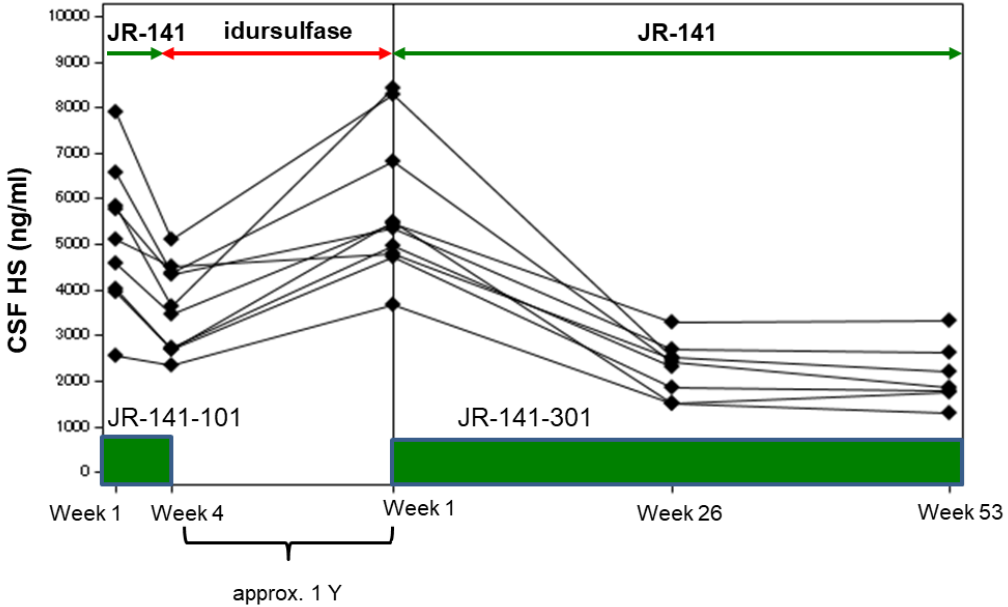
HS: Heparan sulfate

Hideto Morimoto et al., Molecular Therapy, 29(5), 2021, 1853-1861

Reduction of CSF HS Levels by pabinafusp alfa

Changes in CSF Heparan Sulfate levels in JR-141-101 (Ph I/II) through JR-141-301 (Ph III) Studies[1]

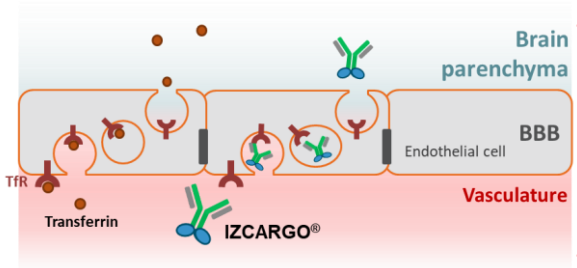




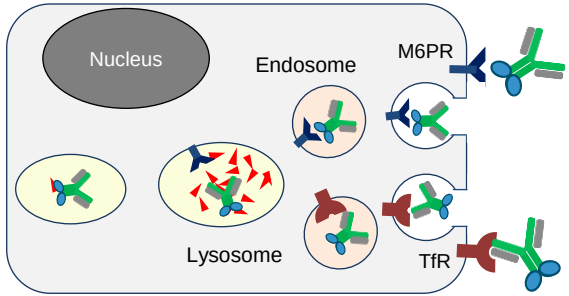
1. JCR Pharmaceuticals Evaluation document at the time of approval: Clinical Overview of JR-141: CTD 2.5.4.3

Mode of Uptake of pabinafusp alfa and Postulated Therapeutic Benefit

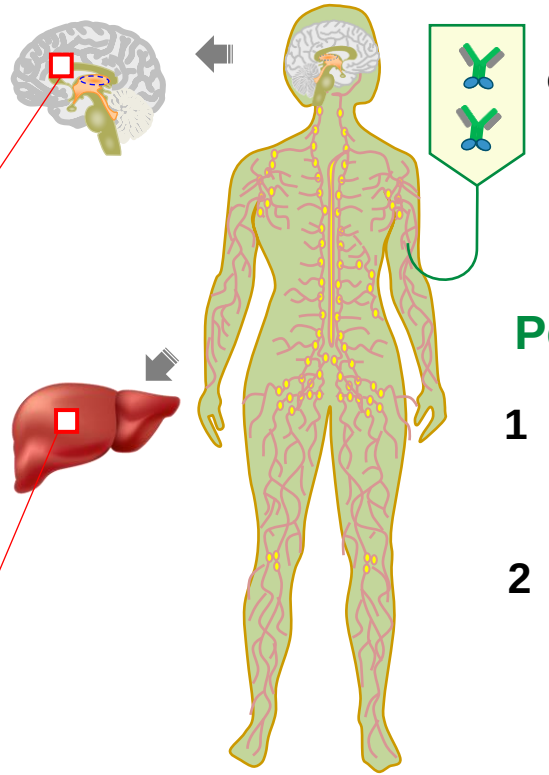
Uptake into the brain



Uptake into somatic organs



M6PR: Mannose-6-phosphate receptor



Intravenous administration of pabinafusp alfa

Postulated therapeutic benefit

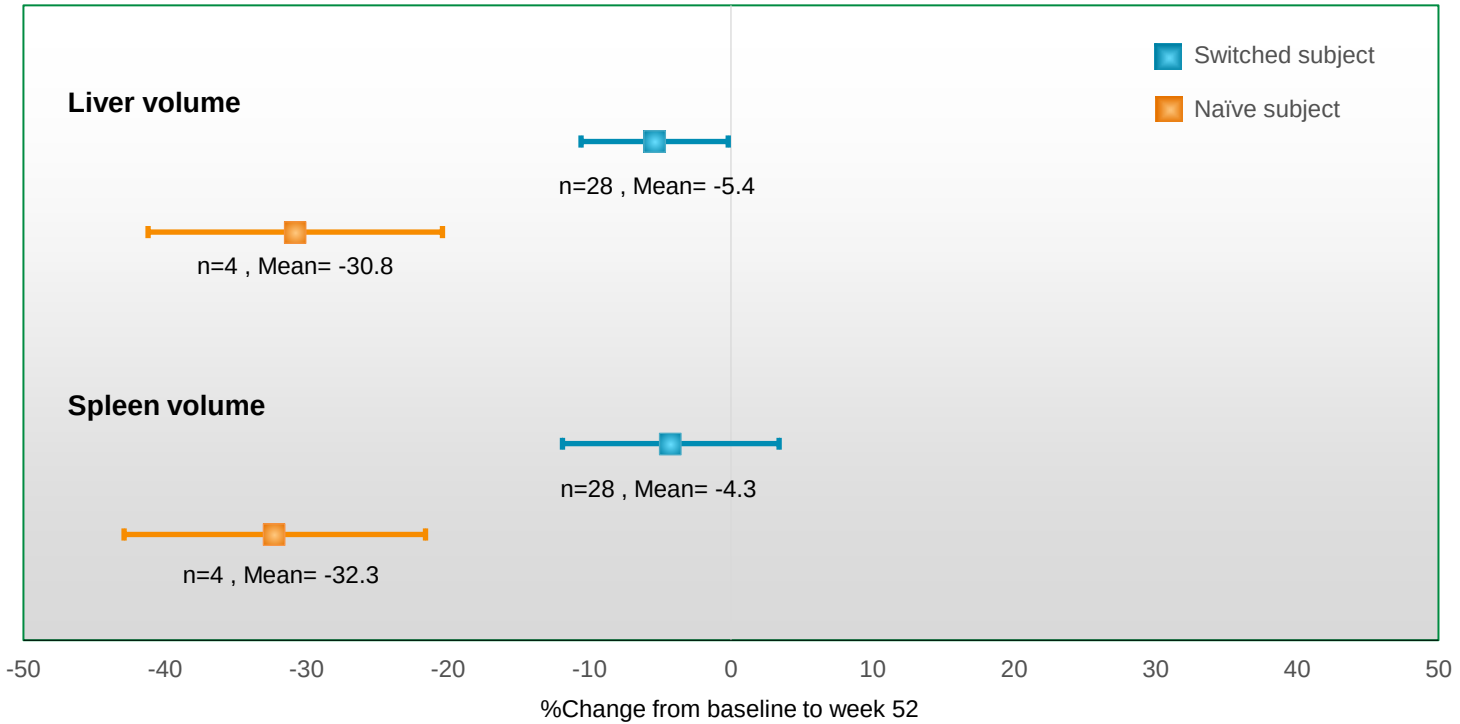
1. Potential therapeutic effect on **central nervous system symptoms** [1].
2. **Somatic disease** control by pabinafusp alfa that is comparable to ERT[1].

1. Based on Roberto Giugliani et al., International Journal of Molecular Sciences, 22(20), 2021, 1-16

Somatic Disease Control in MPS II by pabinafusp alfa

Relative Changes in Organ Volumes [1]

(Baseline vs week 52 in JR-141-301/302, JR-141-BR21/22 Studies)

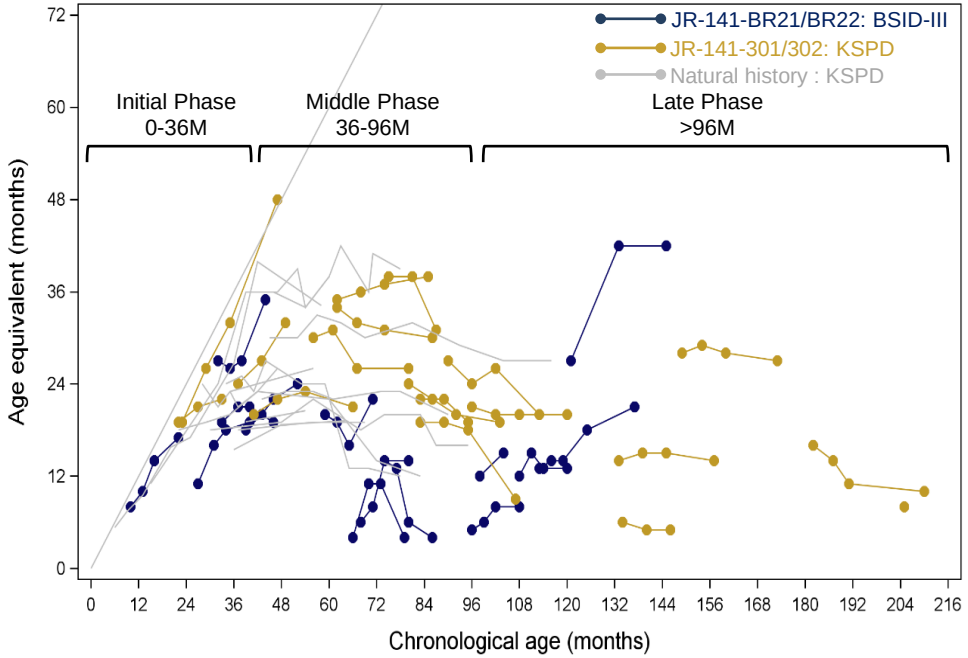


1. Based on Roberto Giugliani et al., International Journal of Molecular Sciences, 22(20), 2021, 1-16

Neurocognitive Benefit of pabinafusp alfa

Merged Age Equivalent Score in severe patients overlayed with natural history[1]

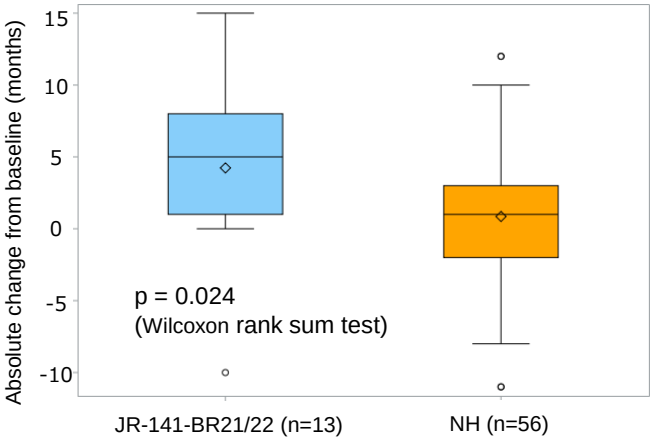
(JR-141-BR21/BR22: BSID-III, JR-141-301/302: KSPD)



Statistical Analysis of BSID-III AES compared to Natural History (1 year)[2]

(BR21/22 Studies)

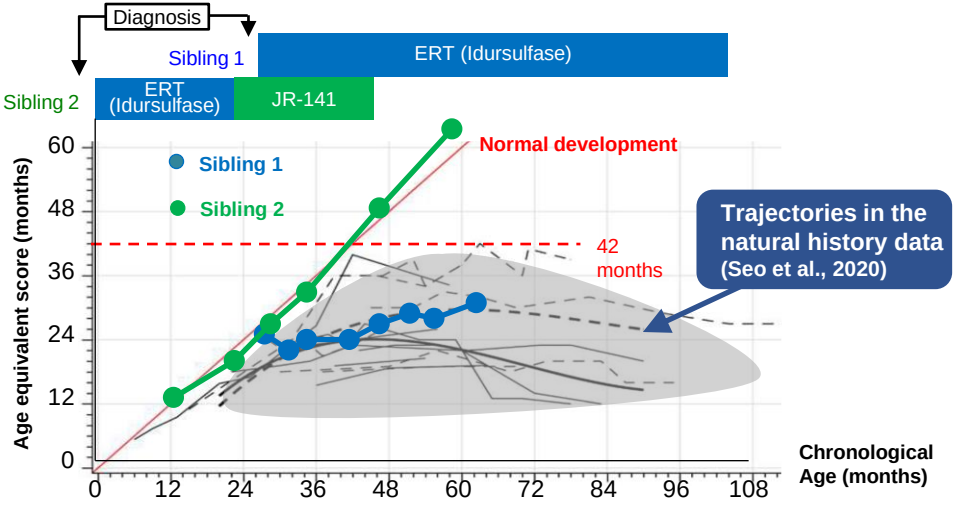
AES: Age equivalent score



1. Based on Roberto Giugliani et al., International Journal of Molecular Sciences, 22(20), 2021, 1-16
2. JCR Internal Data

Case Study: Two siblings with the same genetic variant undergoing different treatments

Neurocognitive developmental trajectories of both siblings[1]



Hepatomegaly	Sib1	++ +
	Sib2	− −
Skeletal deformity	Sib1	+
	Sib2	− −
Joint stiffness	Sib1	+ +
	Sib2	− −

Tomita K et al., JIMD Reports, 2021

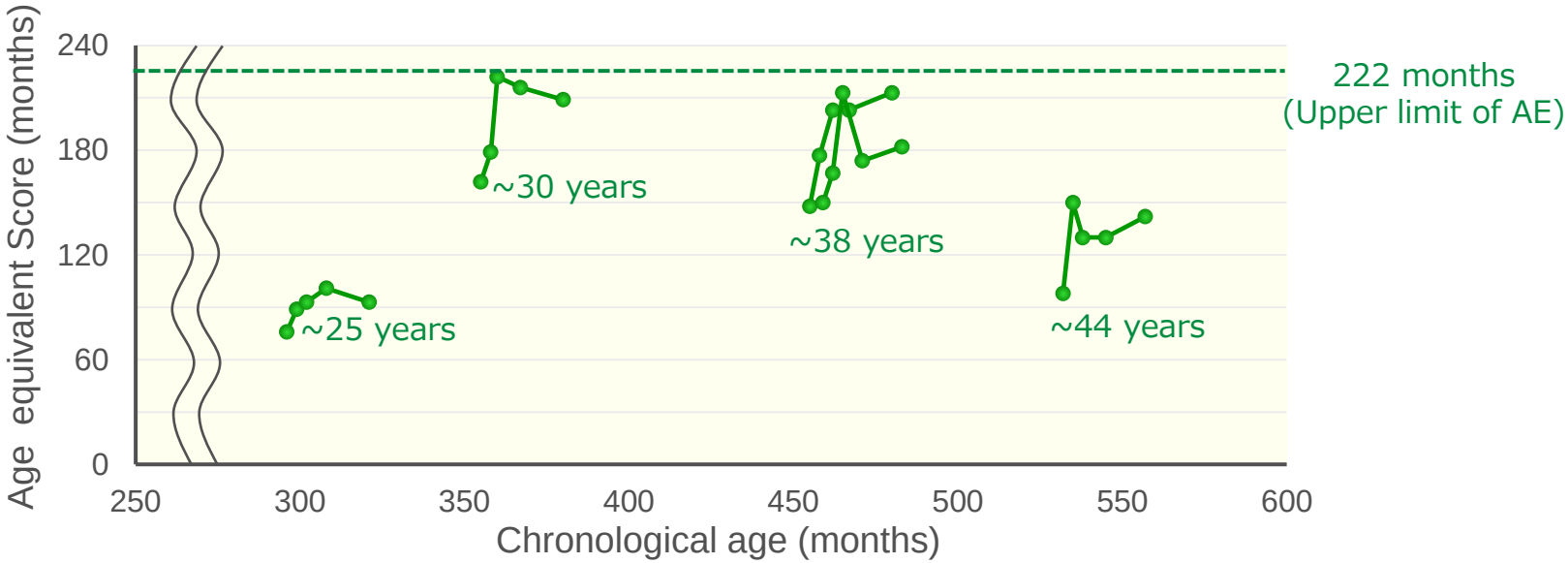
- Older sibling 1 with ERT had AES course similar to natural history.
- Sibling 2 has an above normal developmental AES after 42 months of age.
- An ASE usually declines by age 5 in patients with severe neuronopathic MPSII[2].

1. Based on Tomita K et al., JIMD Reports, 2021, 1-6
2. Based on Seo J.-H et al., MGM Reports, vol.24, 2020, 100630

Neurological Improvement in Older Attenuated MPS II Subjects

Kaufman (KABC II) Assessment in attenuated Subjects[1]

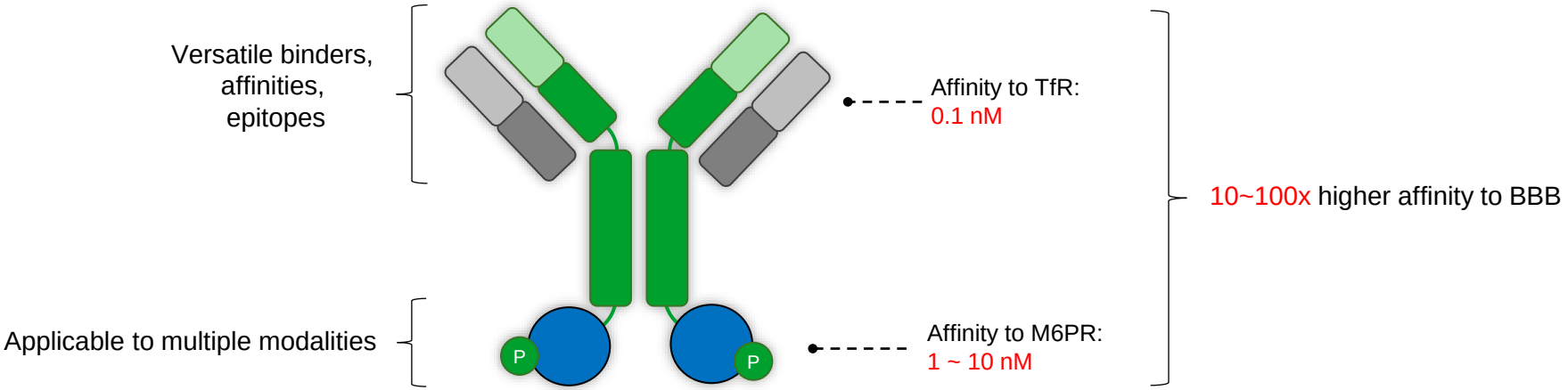
(JR-141-BR21/22 study)



1. Based on Roberto Giugliani et al., Molecular Therapy, 29(7), 2021, 2378-2386

Differentiation of the J-Brain Cargo® Technology

Design Uniqueness of the J-Brain Cargo® Technology



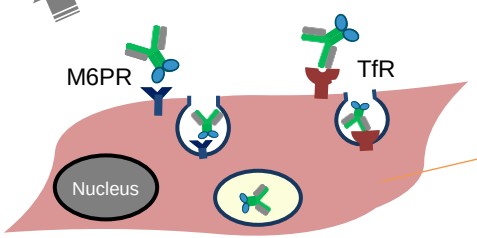
Differentiator	Why does it matter?
Preferential BBB targeting	• Higher uptake to brain compared to somatic tissue
High affinity	• Lower doses resulting in shorter infusion times, manageable infusion reactions
Versatility in binders, affinities, epitopes, modalities	• Customizable to different diseases and modalities
Safety	• Best characterized safety profile in the industry

Applicability of the J-Brain Cargo® Technology and Future Growth Strategy

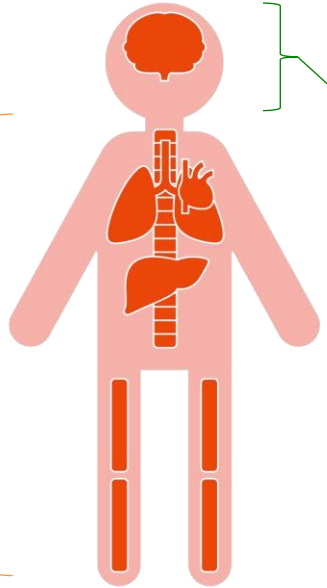
Disease Applicability of J-Brain Cargo® Technology

Somatic Delivery

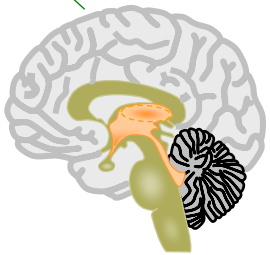
Neuro-muscular Diseases



Liver Diseases



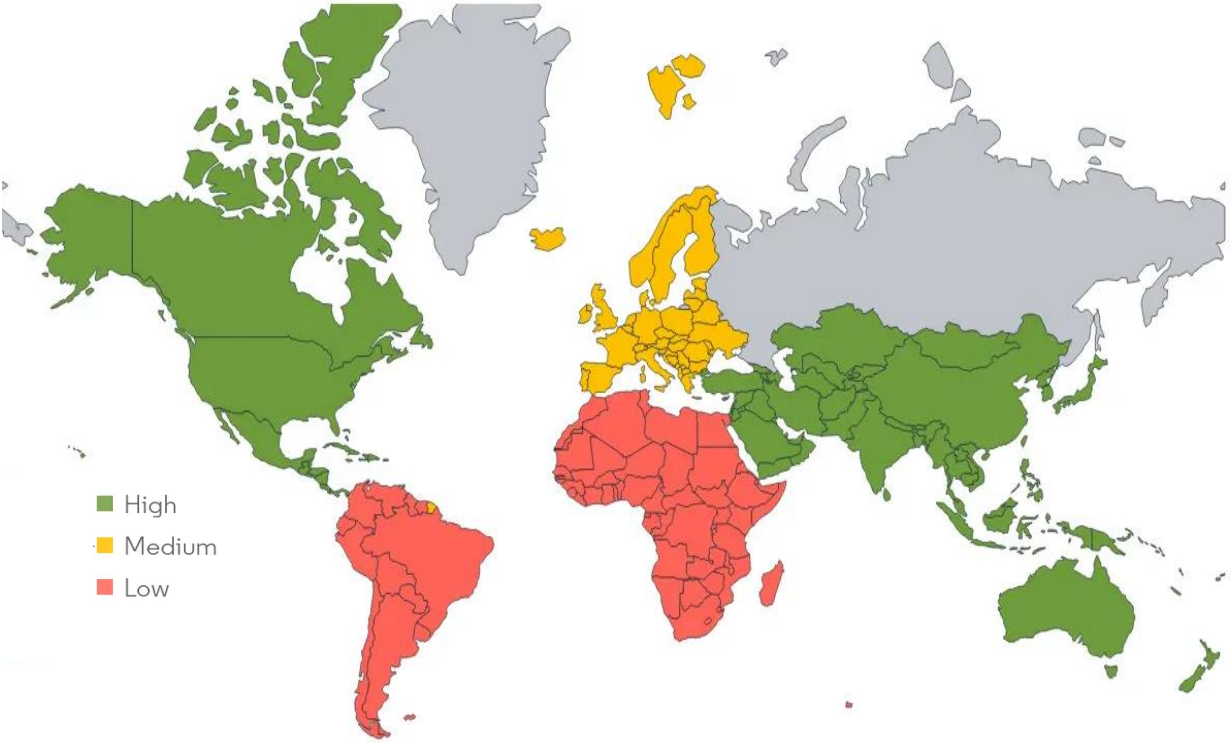
CNS Delivery



- Lysosomal storage diseases
- Alzheimer's disease
- Parkinson's disease
- Neuro-Oncology
- Neuro-Inflammation

The Lysosomal Storage Disease Market

Lysosomal Storage Disease treatment Market – Growth Rate by Region



Source:Mordor Intelligence

- ~$10 BN current Worldwide Market
- 10 % est. CAGR between 2020 and 2027
- Prevalence 7.6 – 25 per 100,000 live births (industrialized nations)
- Diagnosis increasing due to implementation of newborn screening
- >80% of all LSD without treatment option
- Replacement proteins: highest development success rate in industry
- Highest unmet need on CNS manifestations
- Game-changing innovation through brain delivery

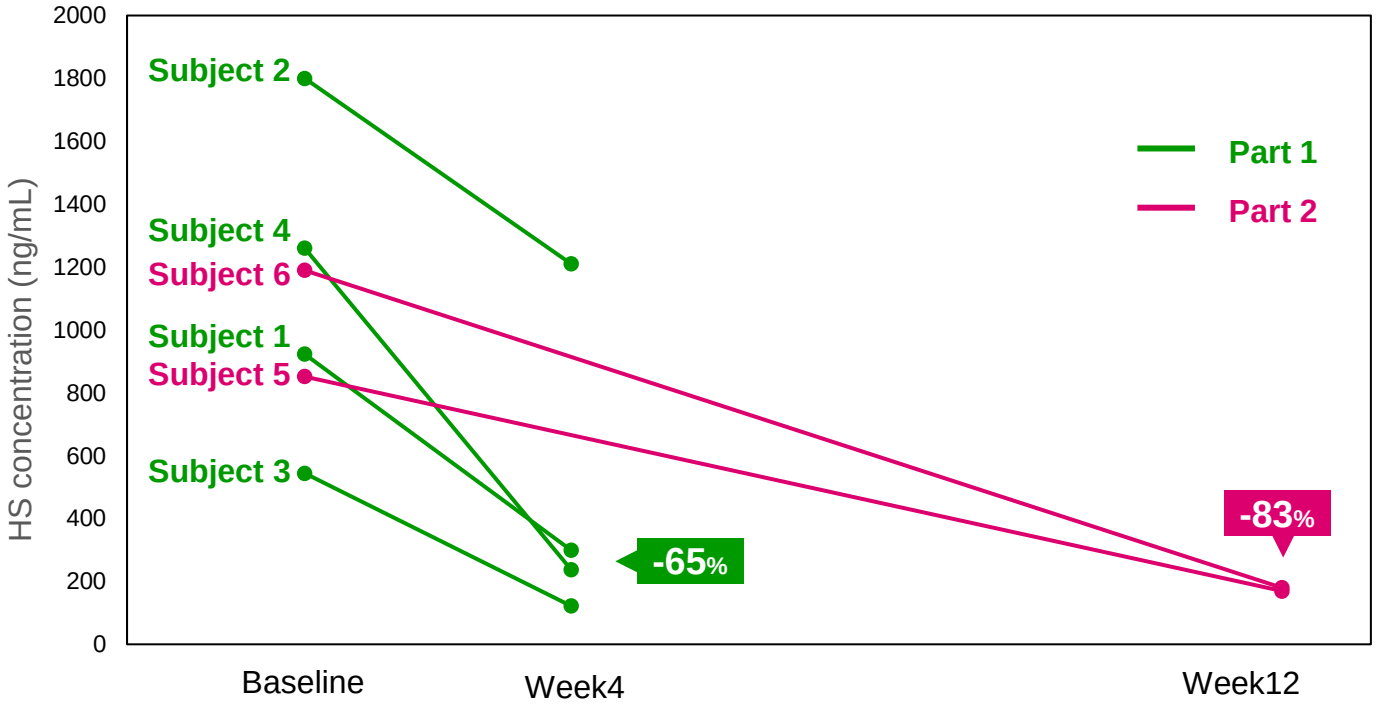
CAGR: Compound annual growth rate

JCR Development Pipeline in Lysosomal Storage Diseases

Assets approved, in clinical development or entering trials within the next 18-24 months

Code	Indication	Preclinical	Clinical trials	Filed	Approved	Time to next value inflection point
JR-141	MPS type II (Hunter Syndrome)	Approved / Filed / Phase 3				~FY2026 (Approval in US, EU)
JR-171	MPS type I (Hurler Syndrome etc.)	Phase 1/2				FY2023 (pivotal trial)
JR-162	Pompe disease	Preclin.				TBD
JR-441	MPS type III A (Sanfilippo A Syndrome)	Preclin.				FY2022 (phase I)
JR-446	MPS type III B (Sanfilippo B Syndrome)	Preclin.				FY2023 (phase I)
JR-443	MPS type VII (Sly syndrome)	Preclin.				TBD
JR-479	GM2 Gangliosidosis (Tay-Sachs, Sandhoff disease)	Preclin.				~FY2025

Ph I/II Interim Results with JR-171: Biomarker Reduction in all Patients [1]



Key upcoming events:

- April 2022: Parallel Scientific Advice with EMA and FDA on pivotal trial strategy
- 2023: Initiation of pivotal trial

EMA: European Medicines Agency
FDA: US Food and Drug Administration

1. Based on Takashi Hamazaki et al., Molecular Genetics and Metabolism, 135(2), 2021, 52-53

JCR Development Pipeline in Lysosomal Storage Diseases

Assets in earlier Research Phases

Indication	Basic Research	In vivo PoC	Process Development	Remarks	Time to next value inflection point
Fucosidosis				• Fucosidase enzyme	FY2024 (phase I)
Batten's Disease Type I (CLN1)				• Palmitoyl-protein thioesterase 1 enzyme	In compassionate use
Krabbe Disease				• galactocerebrosidase (GALC) enzyme	FY2024 (phase I)
GM1 Gangliosiosis				• Beta-galactosidase-1 enzyme	FY2025 (phase I)
Batten's Disease Type II (CLN2)				• Tripeptidyl peptidase 1enzyme	TBD
Gaucher disease				• Glucocerebrosidase enzyme	TBD
α-Mannosidosis				• Alpha-mannosidase enzyme	TBD
Niemann-Pick				• Acid sphingomyelinase enzyme	TBD
Metachromatic leukodystrophy				• Arylsulfatase A enzyme	TBD
Galactosialidosis				• Cathepsin A enzyme	TBD

Treatment Landscape for the Most Prevalent Lysosomal Storage Diseases

Indications with no established treatment

- Galactosialidosis
- α-Mannosidosis
- CLN1
- MPS IIIA
- MPS IIIC
- Fucosidosis
- Niemann-Pick type C
- MPS IIIB
- MPS IIID
- Metachromatic leukodystrophy
- GM1 gangliosidosis
- GM2 gangliosidosis
- Krabbe

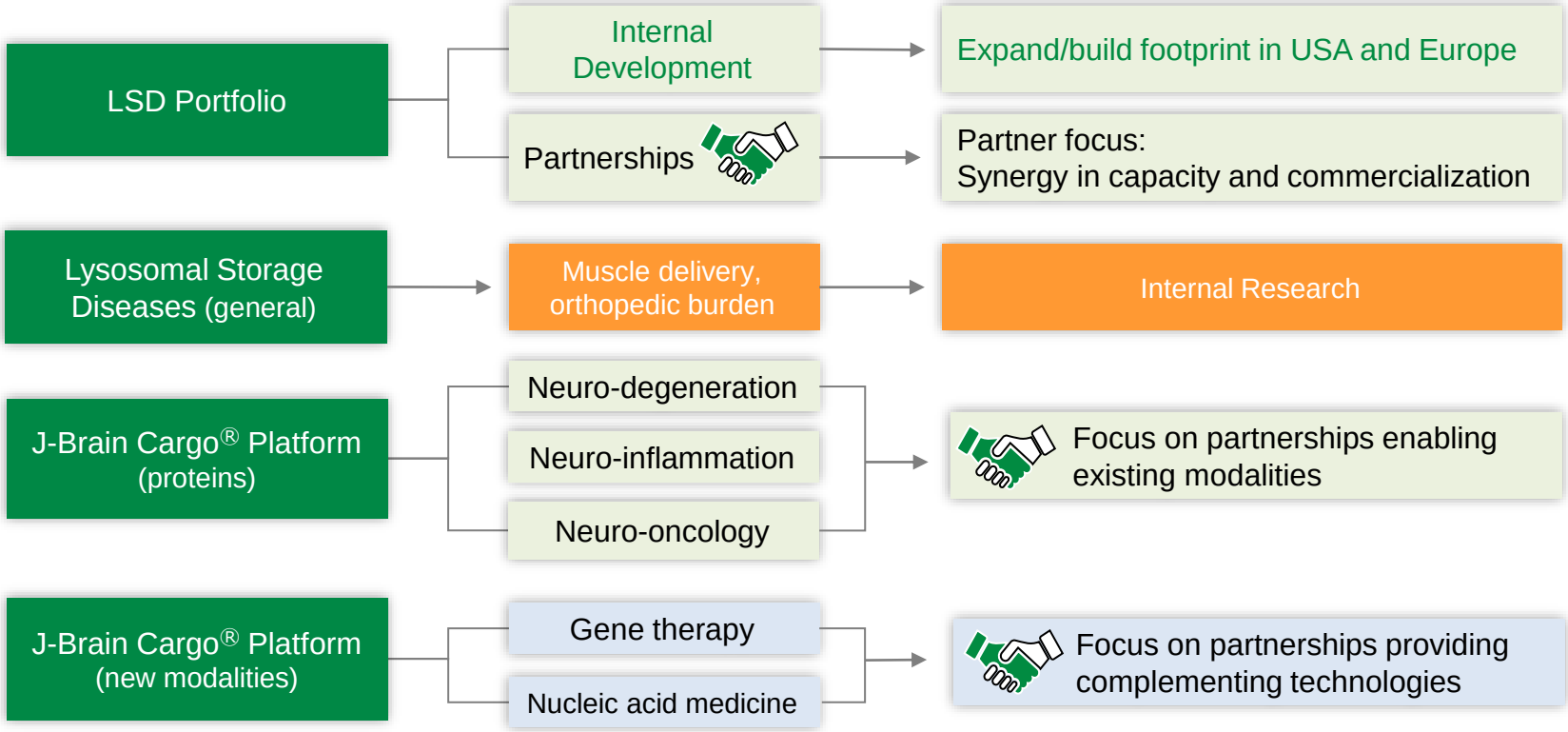
Indications with somatic ERT

- Gaucher
- CLN2
- Fabry
- MPS I
- MPSVI
- Niemann-Pick type A, B
- Pompe
- MPS II
- MPS IV
- MPS VII

Indications with active JCR programs

Future Growth Strategies

Partnerships are at the core of JCR's growth and acceleration strategy



The Partnership with Takeda preserves JCR's DNA

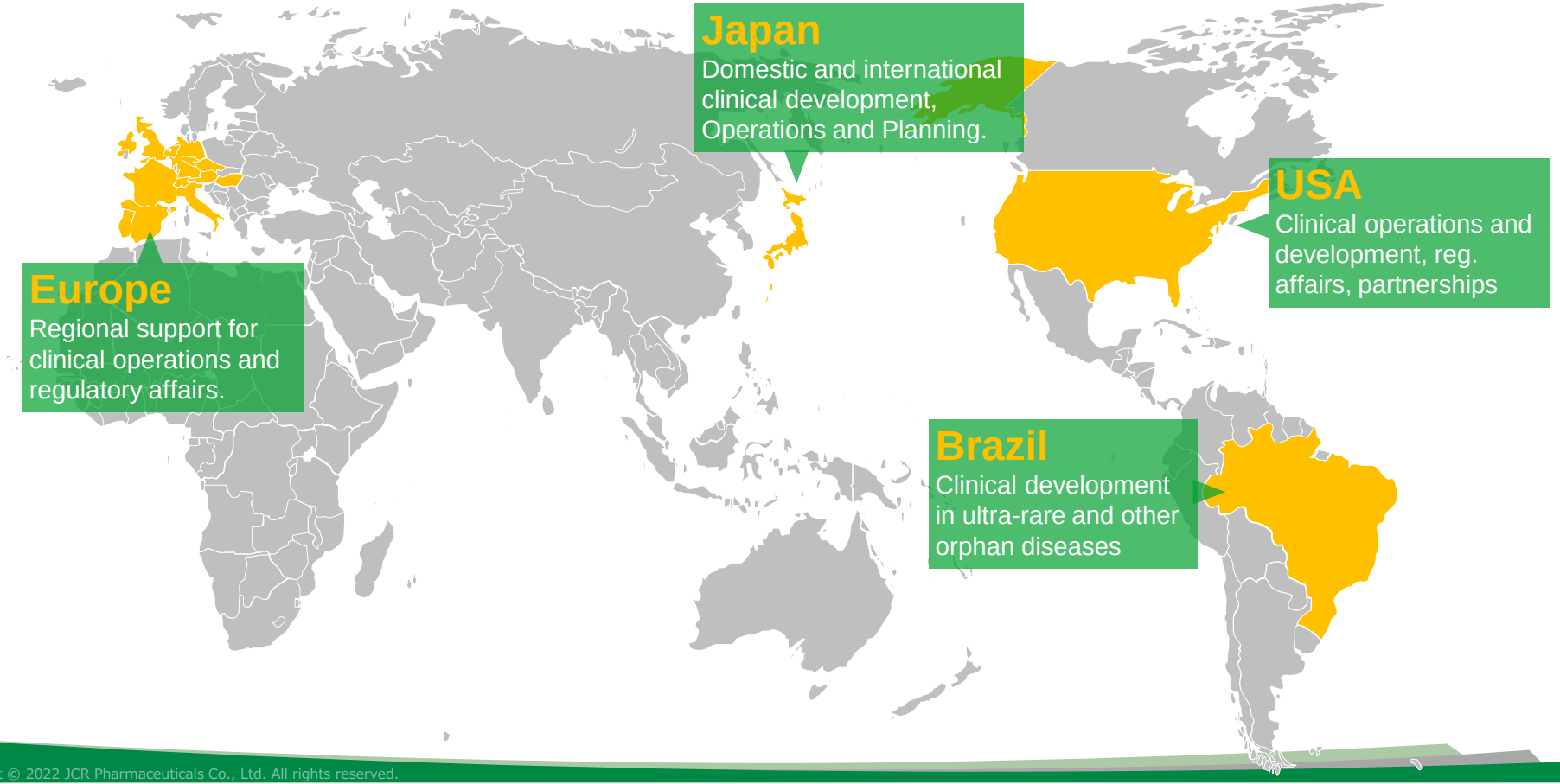
Pillars of strength

- Discovery and development of game-changing orphan drugs
- Manufacturing of our portfolio drugs
- Commercialization in Japan

→ IZCARGO® Approval in Japan

- → Partnership with Takeda → **Maintain our basis of strength**
  - Focus on developing the next J-Brain Cargo® assets and game-changing medicines
- → Global marketing by JCR → **Leave our basis of strength**
  - Move JCR from an R&D driven company and shift resources to global commercialization

Geographies with Planned Increased Future Presence of JCR



JR-441 for MPS IIIA
JR-446 for MPS IIIB

Non-clinical data

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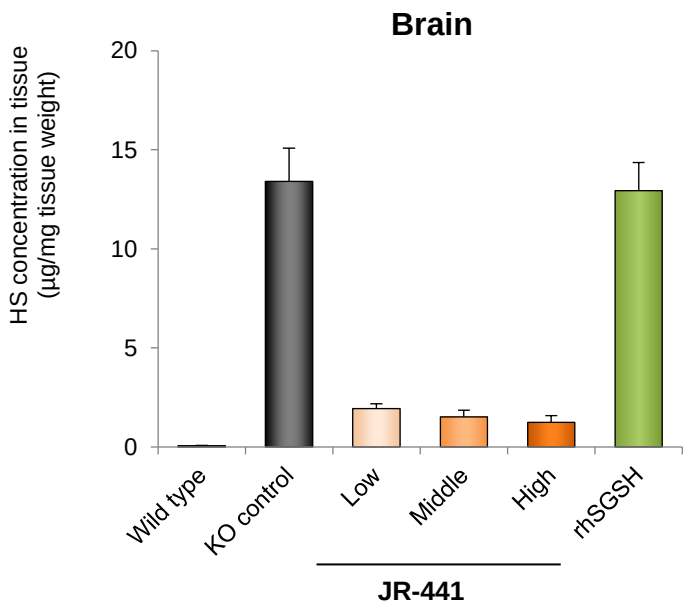
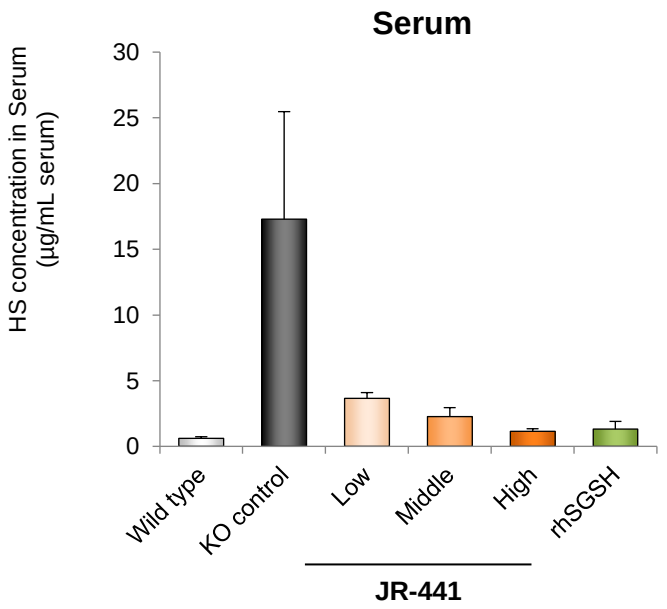
JR-171	MPS type I (Hurler Syndrome etc.)	Phase 1/2				FY2023 (pivotal trial)
JR-162	Pompe disease	Preclin.				TBD
JR-441	MPS type III A (Sanfilippo A Syndrome)	Preclin.				FY2022 (phase I)
JR-446	MPS type III B (Sanfilippo B Syndrome)	Preclin.				FY2023 (phase I)
JR-443	MPS type VII (Sly syndrome)	Preclin.				TBD
JR-479	GM2 Gangliosidosis (Tay-Sachs, Sandohoff disease)	Preclin.				~FY2025

Efficacy of JR-441 in a Mouse Model of MPS IIIA

HS concentrations in tissues after iv administration of JR-441





- JR-441 is a fusion protein consisting of anti-human transferrin receptor antibody (J-Brain Cargo®) and hSGSH.
- JR-441 dose-dependently decreased HS concentrations in the brain, in which rhSGSH failed to affect the concentration. Both JR-441 and rhSGSH decreased HS concentrations in the serum.

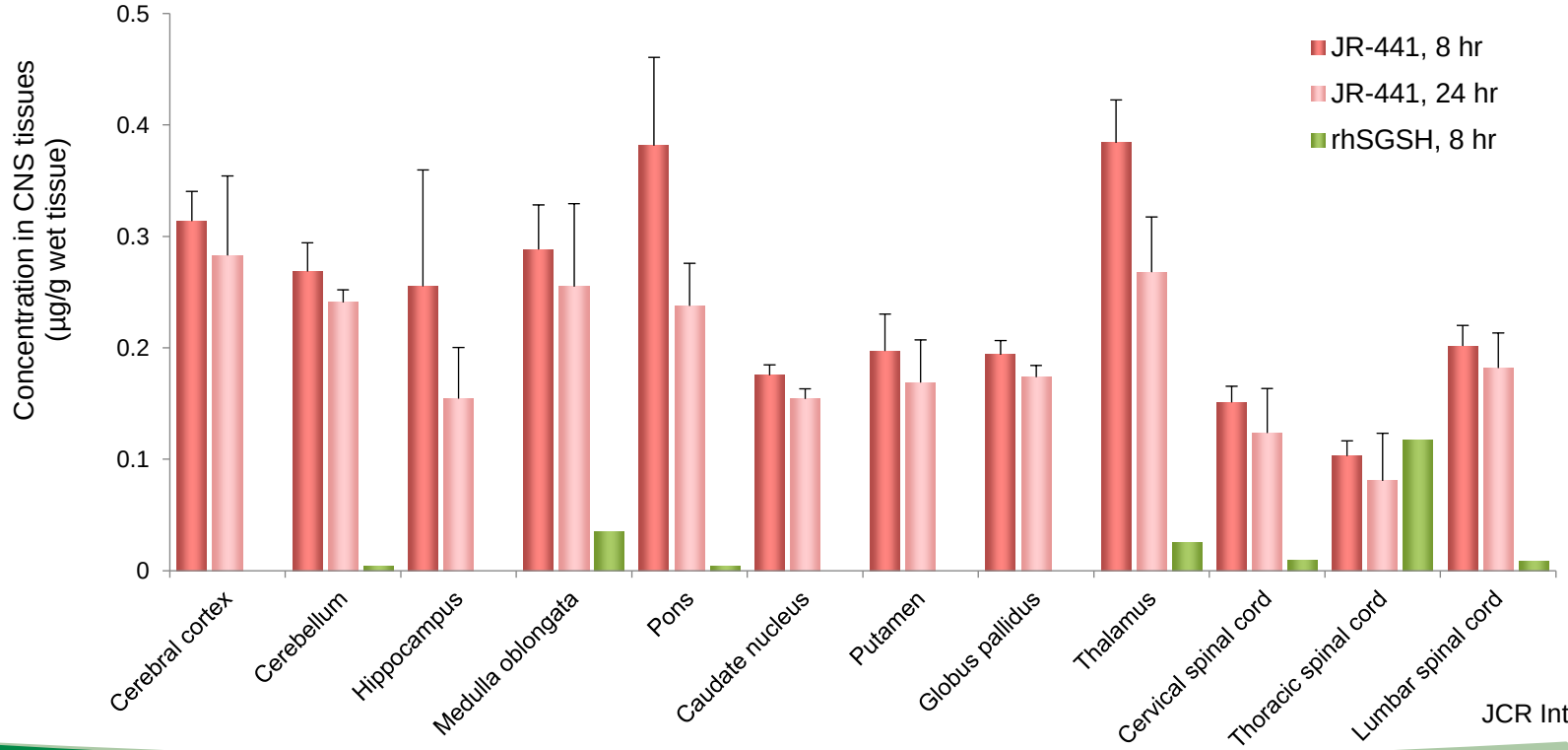
JCR Internal Data

hSGSH: human N-sulfoglucosamine sulfohydrolase

Biodistribution to CNS of JR-441 in Cynomolgus Monkeys

Biodistribution of JR-441 and rhSGSH in the CNS tissues after iv administration

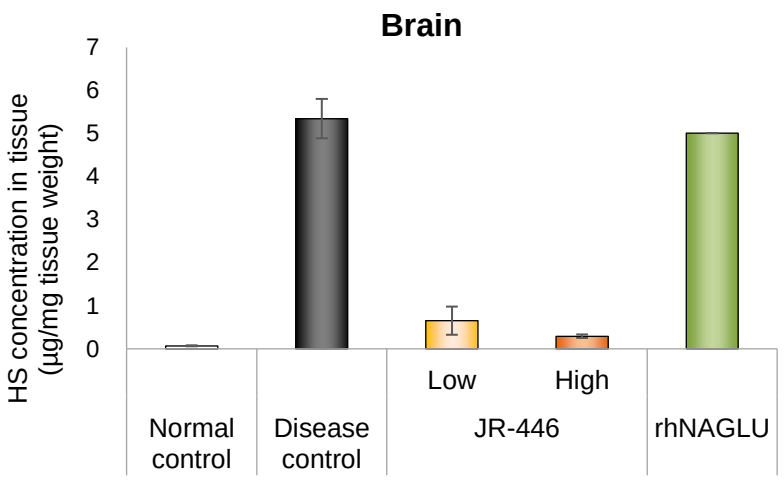
Concentration of drugs in the CNS tissues of cynomolgus monkeys.

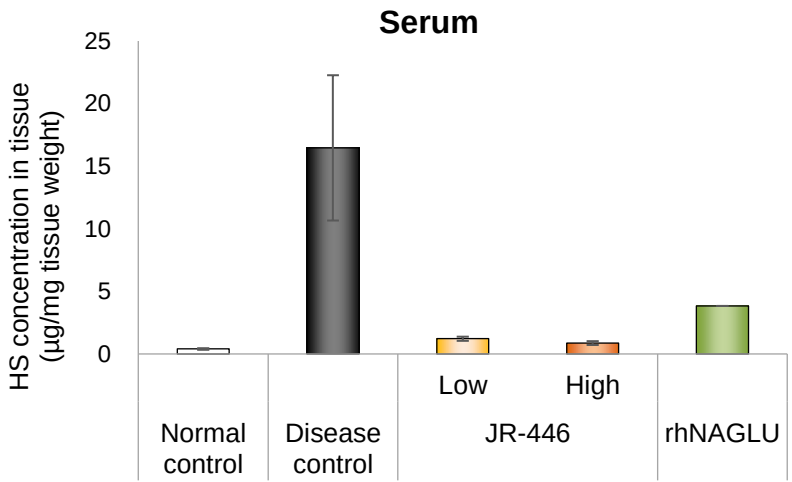


JCR Internal Data

Efficacy of JR-446 in a Mouse Model of MPS IIIB

HS concentrations in tissues after iv administration of JR-446





- JR-446 is a fusion protein consisting of anti-human transferrin receptor antibody (J-Brain Cargo®) and hNAGLU.
- JR-446 reduced concentrations of HS in the brain, in which rhNAGLU failed to affect the concentration.
  In the serum, JR-446 reduced HS concentrations more efficiently than rhNAGLU.

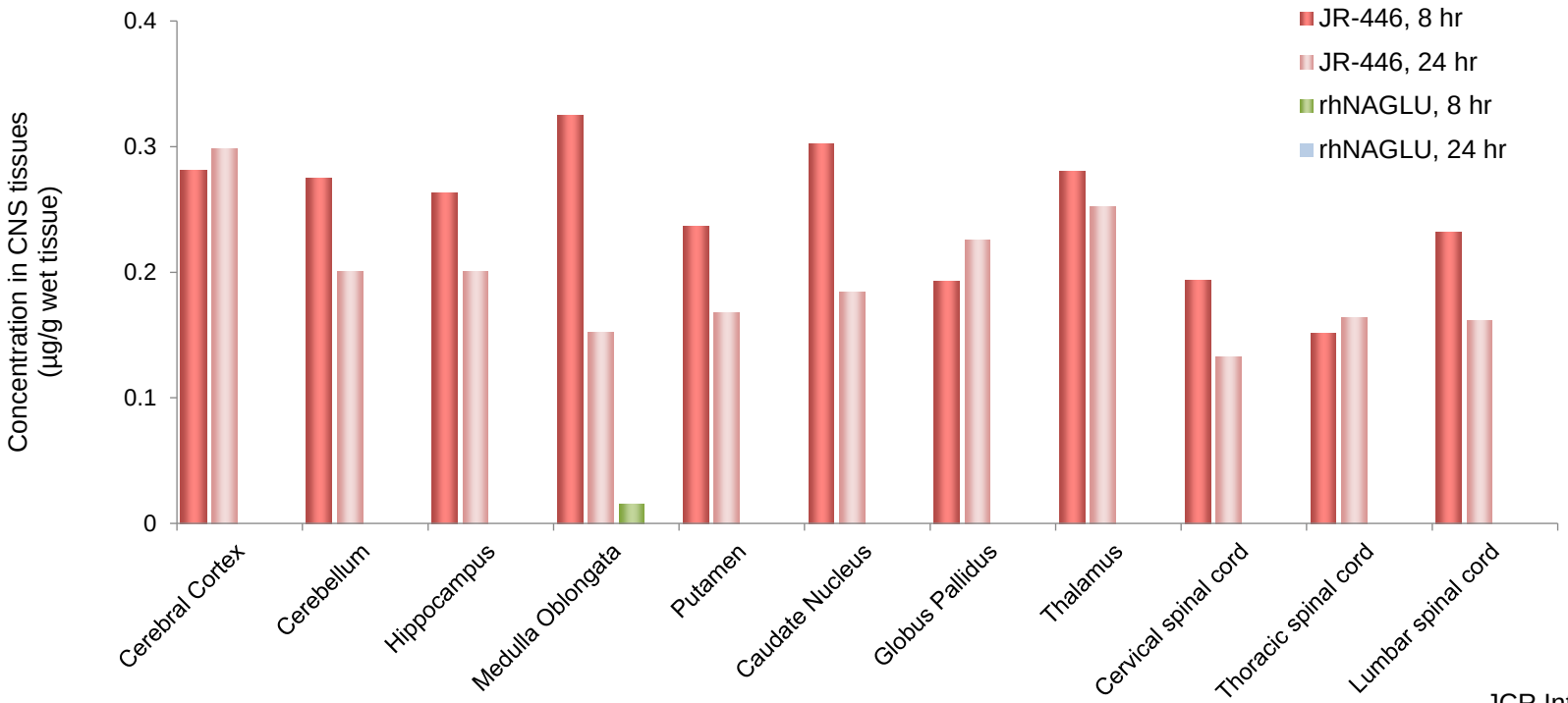
JCR Internal Data

hNAGLU: human a-N-acetylglucosaminidase

Biodistribution to CNS of JR-446 in Cynomolgus Monkeys

Biodistribution of JR-446 and rhNAGLU in the CNS tissues after iv administration

Concentration of drugs in the CNS tissues of cynomolgus monkeys.



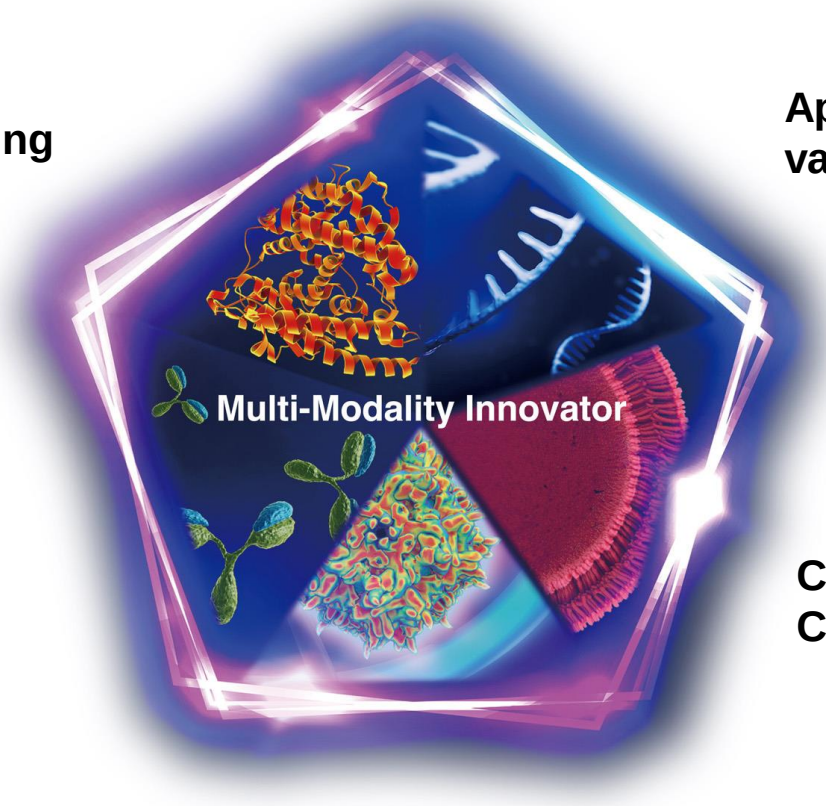
JCR Internal Data

J-Brain Cargo® Platform Applicability to different Modalities

Applicability of J-Brain Cargo® Technology to Various Modalities

Protein Engineering

Applicability to various modalities



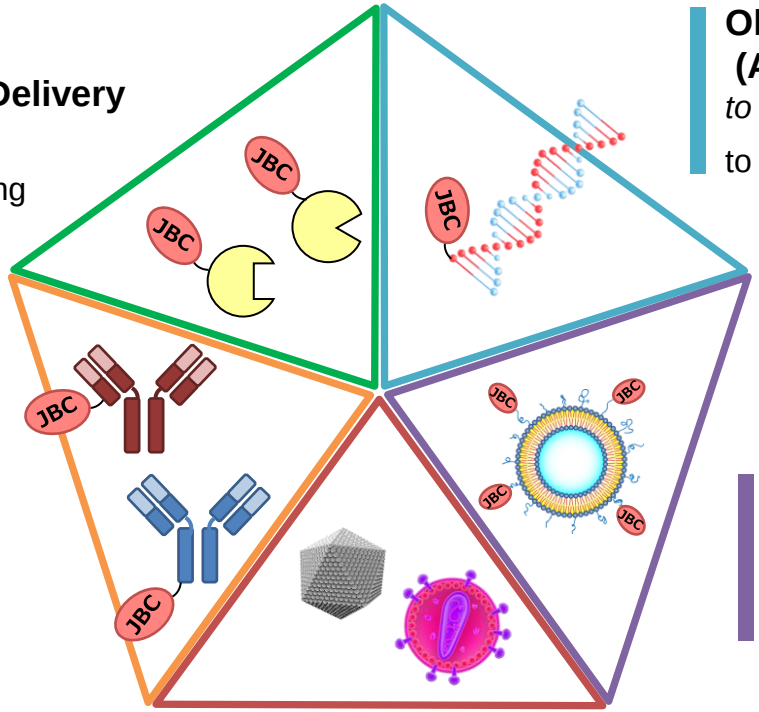
Antibody Engineering

Combination with Cutting Edge Technologies

Applicability of J-Brain Cargo® Technology to different Modalities

Enzymes and **Proteins Delivery**
to the brain and muscle

to replace deficient or missing enzymes and proteins



Oligonucleotide (ASO, siRNA) Delivery
to the brain and muscle

to modify gene expression

Antibody Delivery
to the brain

in various formats (bi-specific, tri-specific)

LNP (mRNA, low-molecular compound) Delivery
to the brain and muscle

to replace deficient or missing proteins

JBC: J-Brain Cargo®

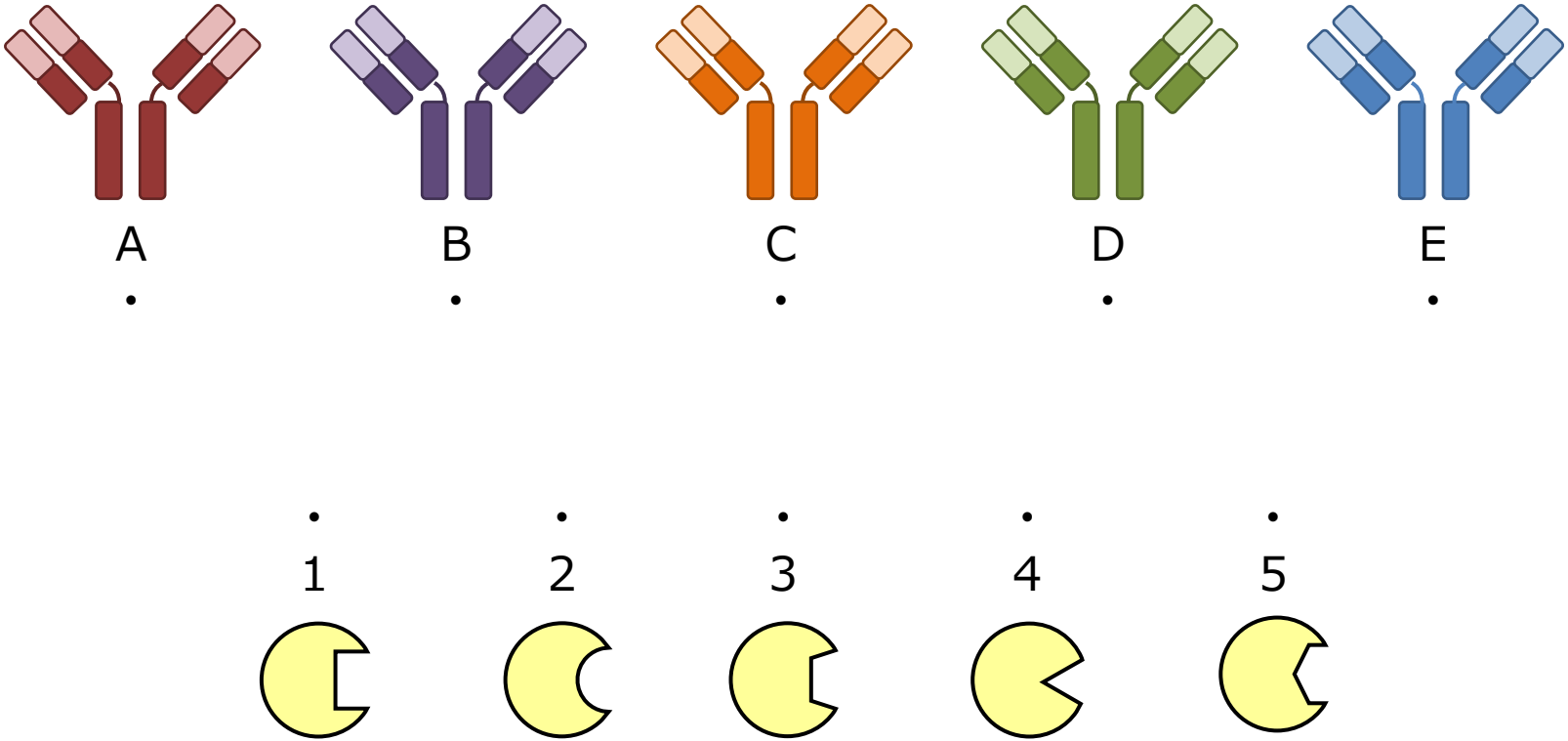
Gene/Cell therapy
combined with J-BrainCargo® technology pave the way to treat CNS pathologies

JCR's strength in development process

Development process

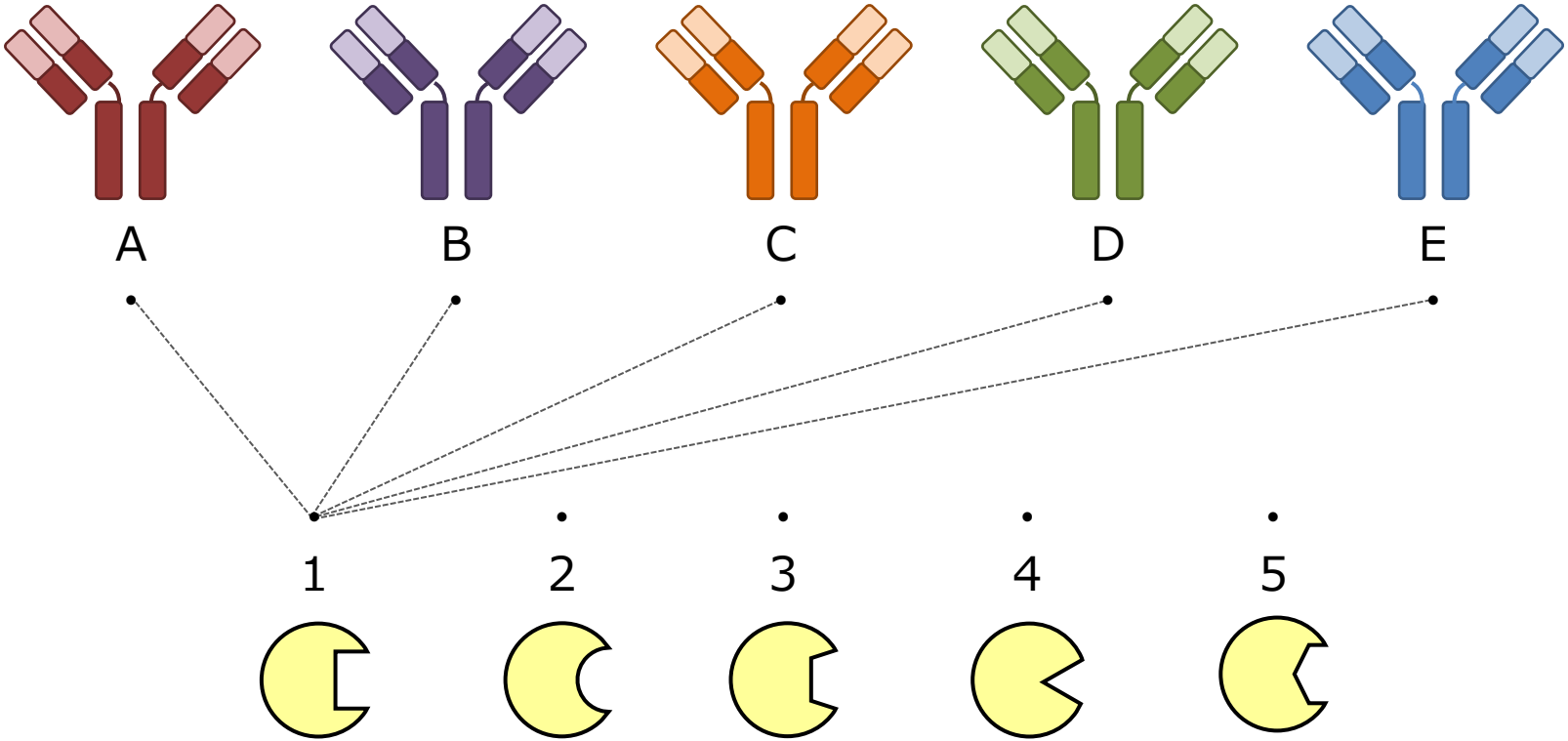
1. Molecular Design	New J-Brain Cargo® Platform enables molecular design without limitation. Knowledge and data accumulated through experience in the field.
2. Prepare Recombinant Protein (cultivation / purification)	JCR's core technology since establishment. Wide experience in producing fusion protein.
3. Evaluation with model animal	JCR developed more than 10 types of model mouse as a result of long devotion in LSD research.
4. Analysis	JCR determined the biomarkers corresponding to each indication, and also established their measurement methods.
5. Trial & Error	JCR has a team structure that can follow this cycle speedy and accurate.

Candidate Optimization



Investigate the optimum combination of antibody and enzyme.

Candidate Optimization



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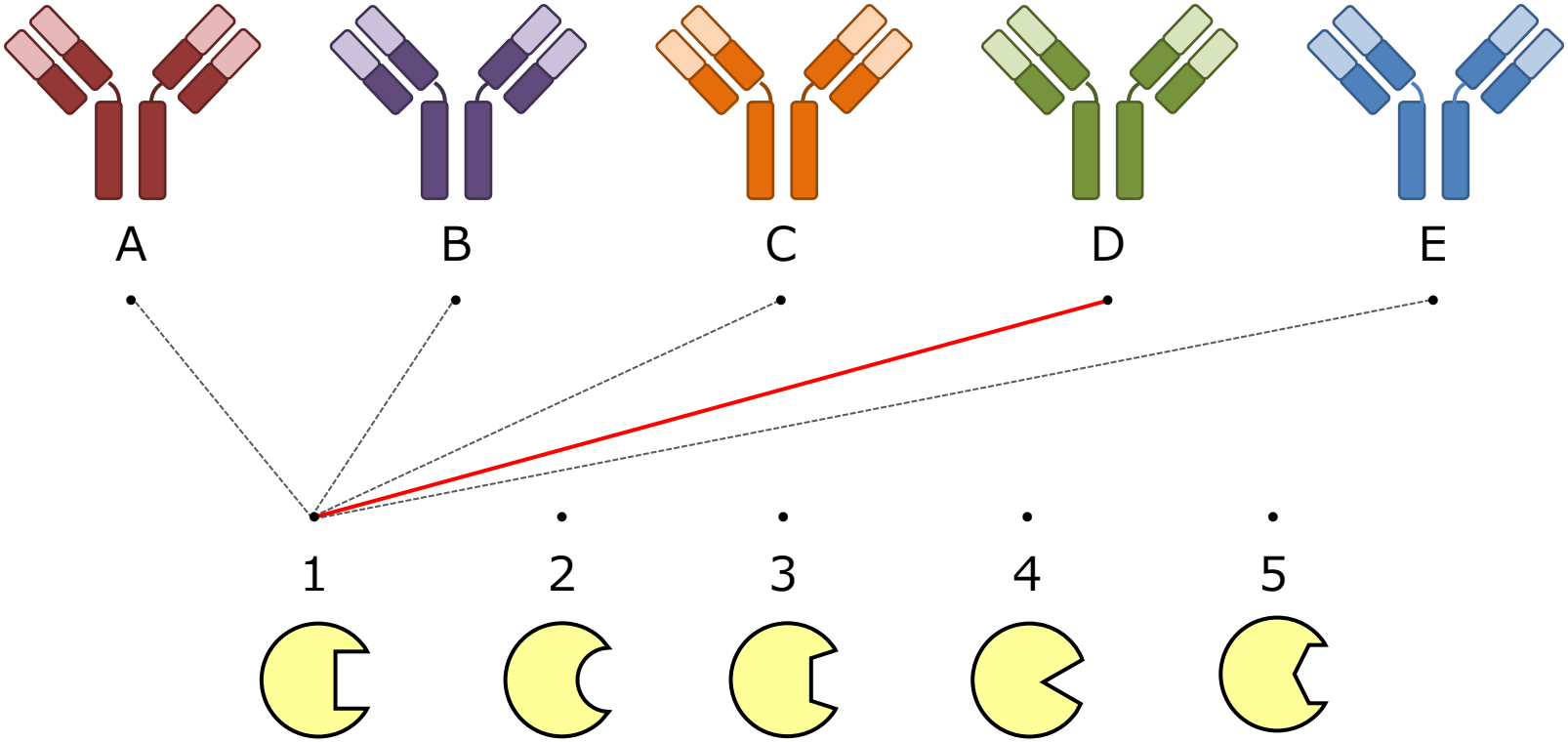
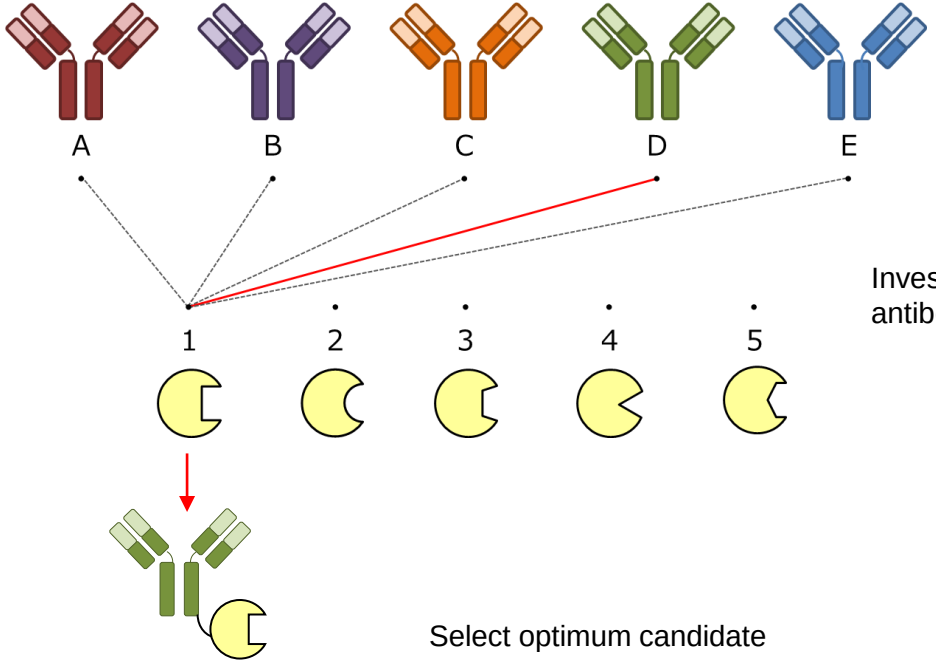


Investigate the optimum combination of antibody and enzyme.

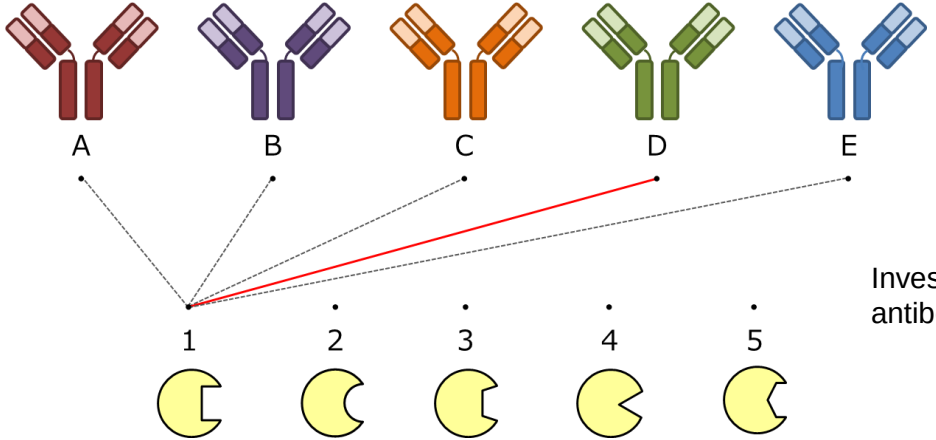
Candidate Optimization



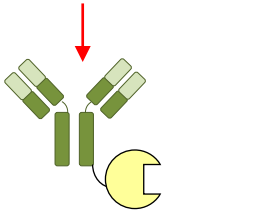
Investigate the optimum combination of antibody and enzyme.

Select optimum candidate

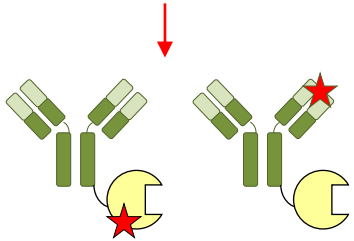
Candidate Optimization



Investigate the optimum combination of antibody and enzyme.

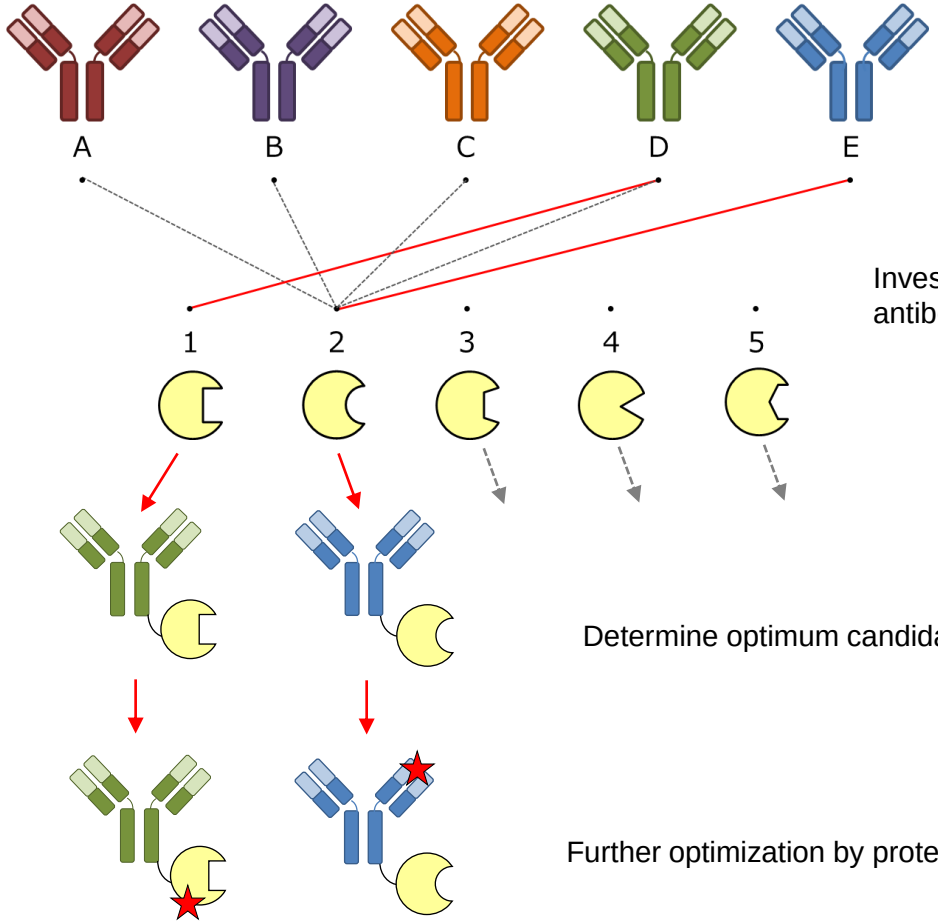


Determine optimum candidate



Further optimization by protein engineering

Candidate Optimization

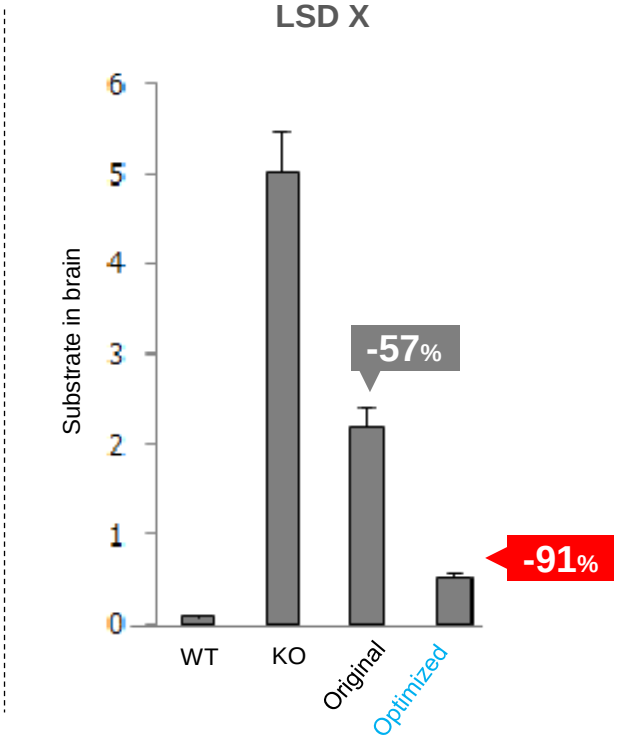


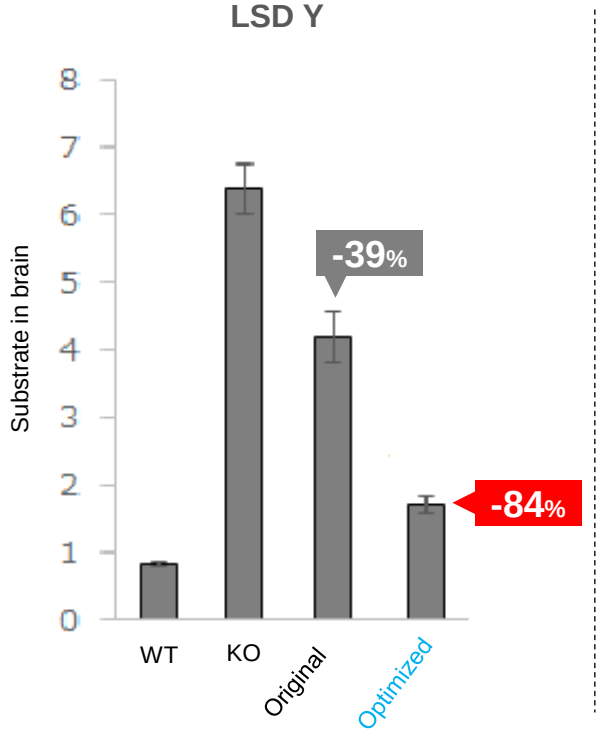
Investigate the optimum combination of antibody and enzyme.

Determine optimum candidate

Further optimization by protein engineering

Modified J-Brain Cargo® Technology with Even Higher Efficiency



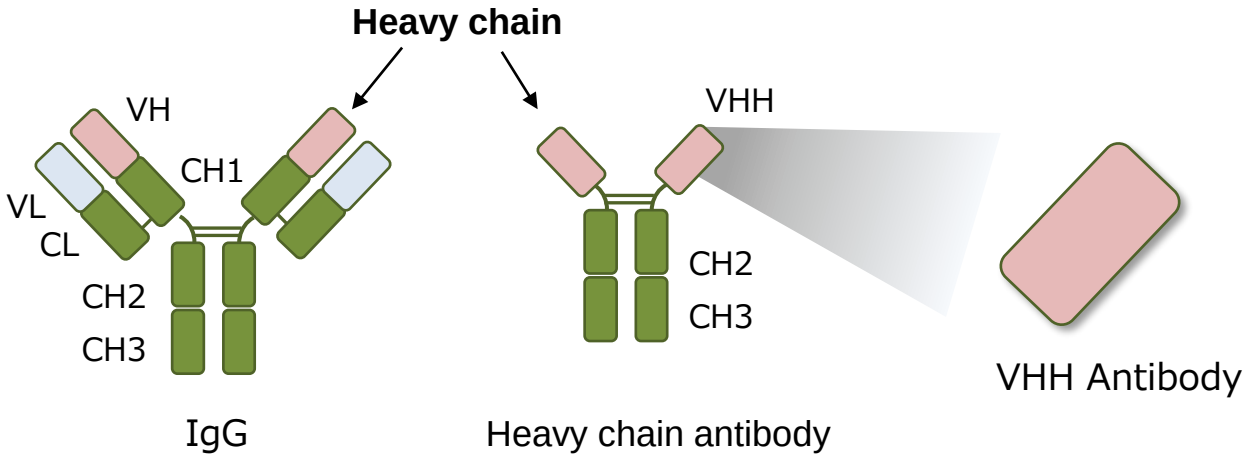


Key results

- ✓ Have successfully developed the evolved version-J-Brain Cargo® technologies
- ✓ Able to tune-up the affinity, valency, fusion design (N or C-terminal), etc.
- ✓ Able to optimize BBB-crossing ability for each molecule

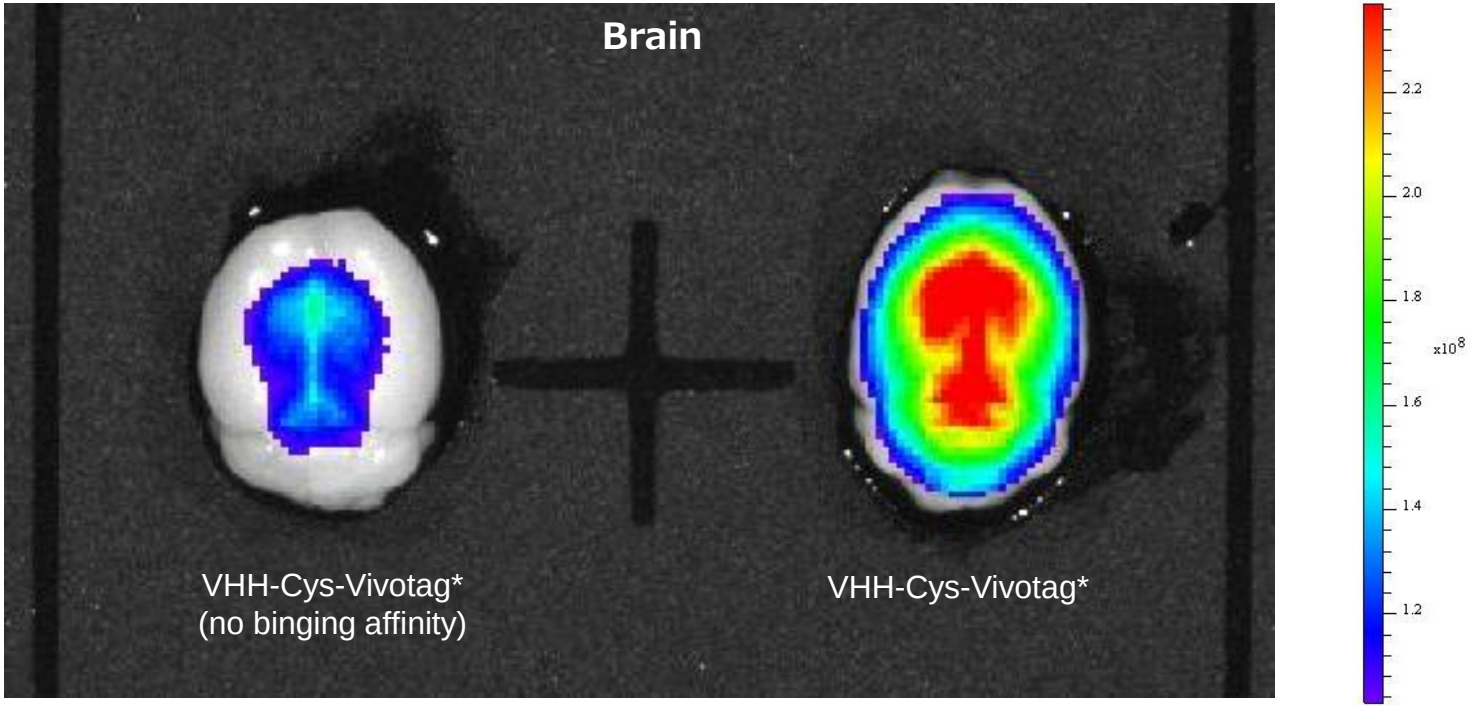
JCR Internal Data

Advantage of VHH over IgG



- The affinity is at the same level as normal antibody.
- Hidden epitope can be detected.
- Higher stability (high temperature, organic solvent, pH)
- Can be bulk produced at low cost by Escherichia coli or Yeast.
- Can be easily modified to bispecific or tri-specific forms.

IVIS ex vivo Imaging

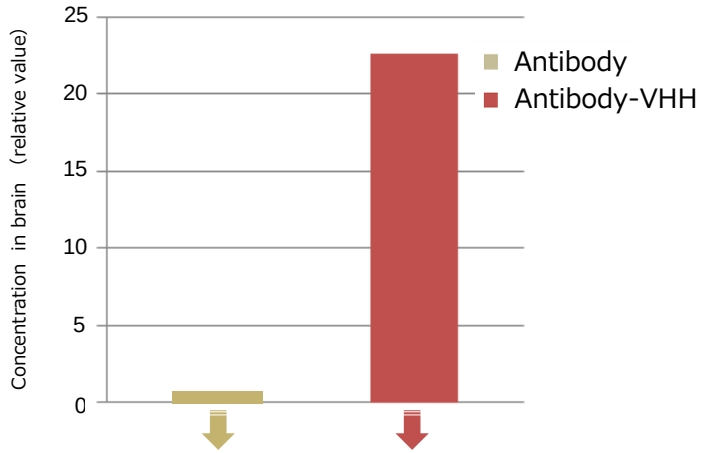


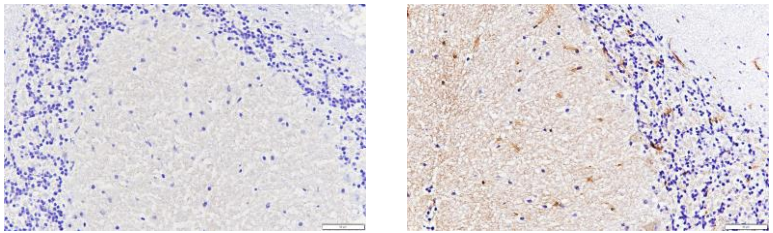
*VivoTag (fluorescent tag) is a registered trademark of Schott AG.

JCR Internal Data

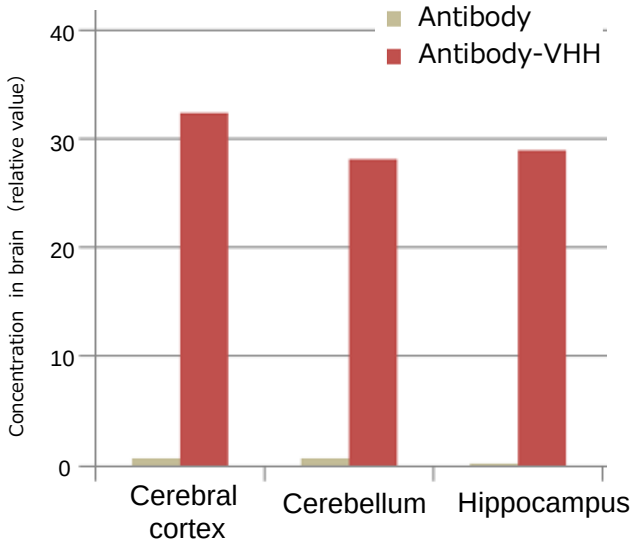
Delivery of Antibody Drug X to the Brain

Mouse (hTfR-KI)





Cynomolgus monkey

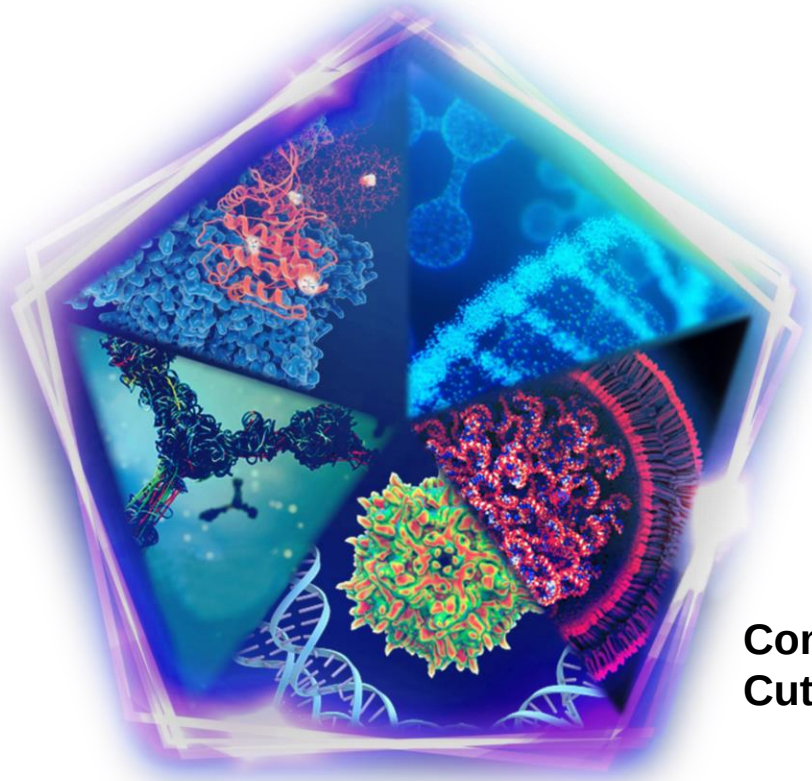


JCR Internal Data

Applicability of J-Brain Cargo® Technology to Proteins and Enzymes

Protein Engineering

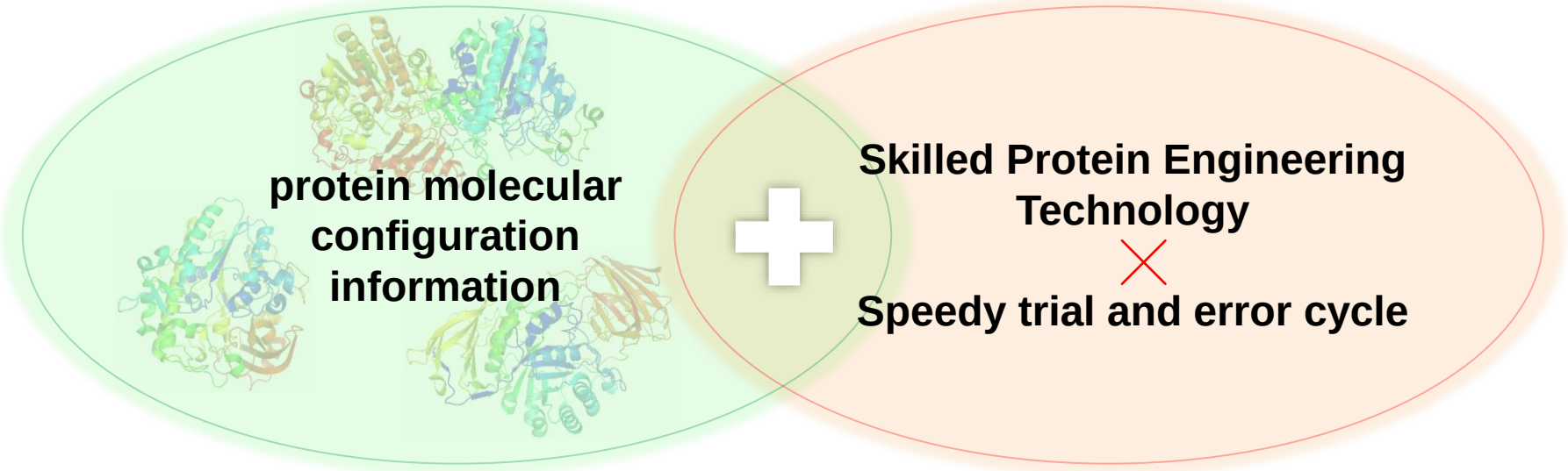
Applicability to various modalities



Antibody Engineering

Combination with Cutting Edge Technologies

Optimizing complex molecular configuration by protein engineering



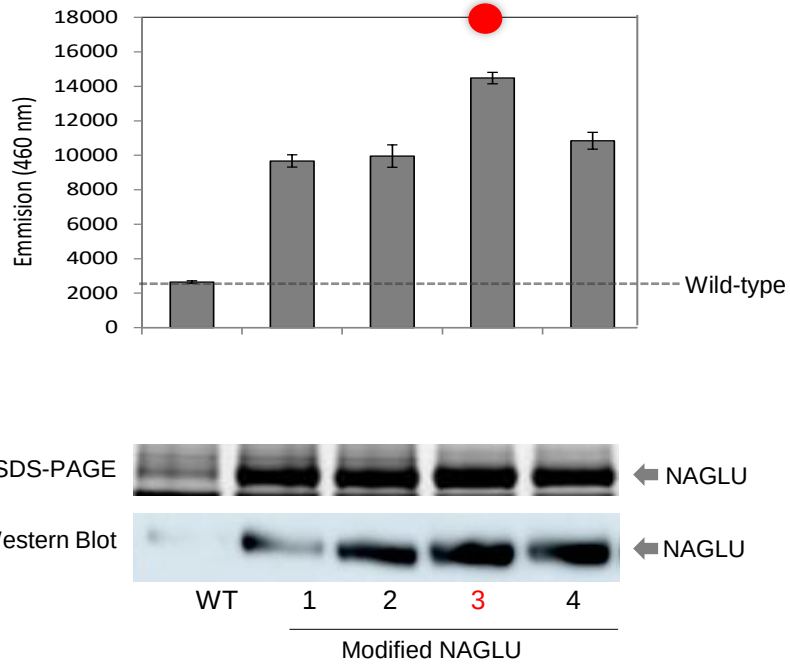
Overcome obstacles (ex. expression level and stability)
by optimizing the target protein in various approaches.

JR-446 Expression Optimization

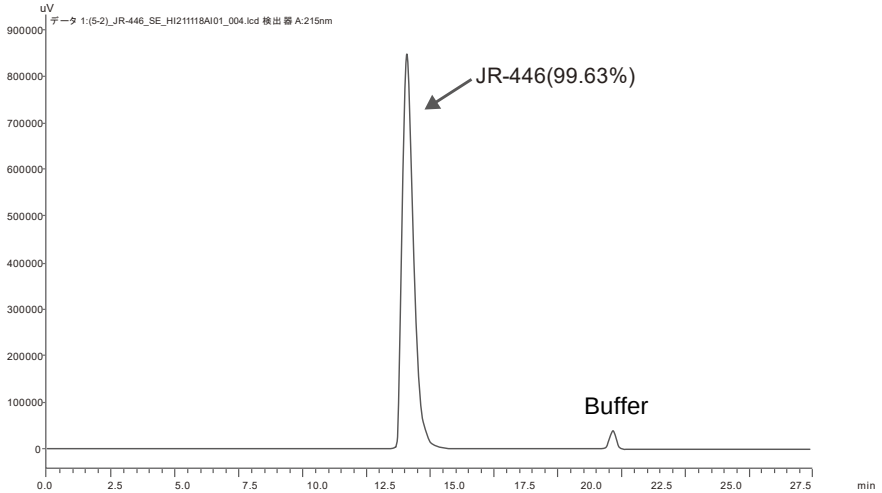
Background:

- Commercially viable expression of NAGLU has been a major bottleneck for the development of any ERT in the treatment of MPS IIIB

Expression levels



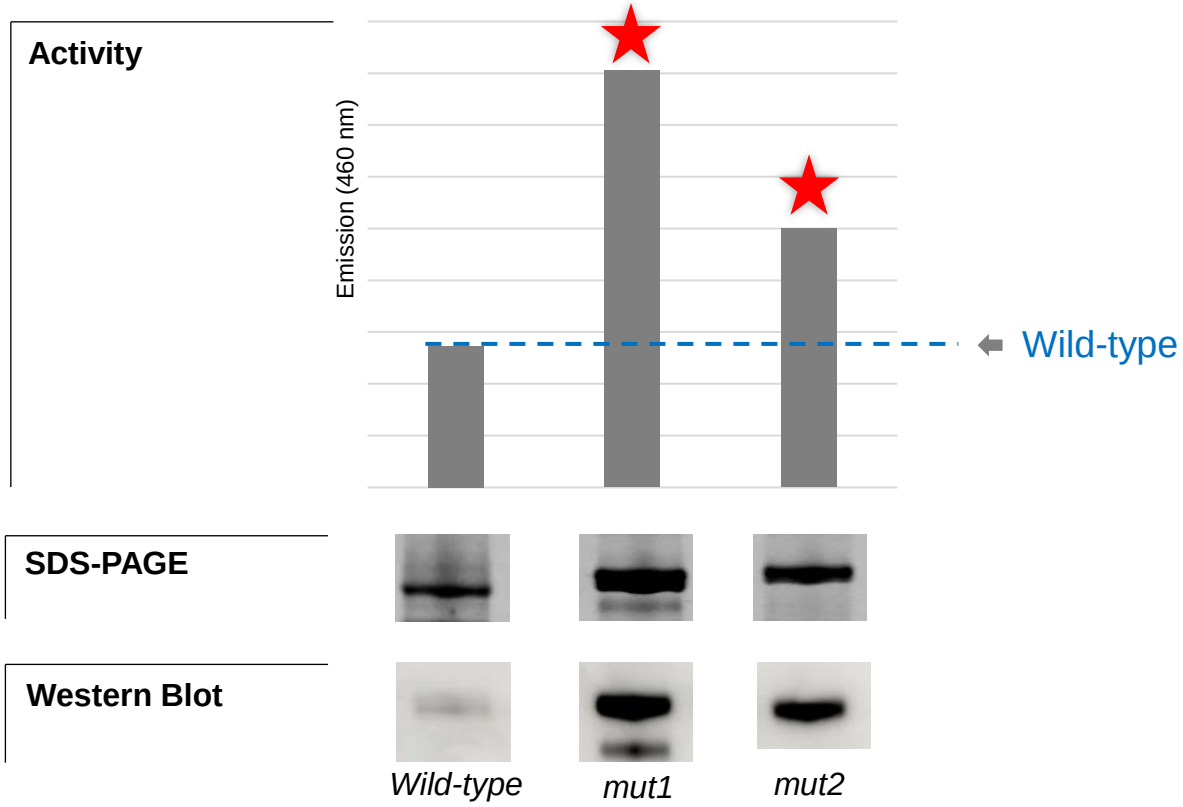
Size exclusion chromatography



Modified NAGLU #3 is expressed at commercially viable titers and exerts significantly higher enzyme activity than wildtype NAGLU

JCR Internal Data

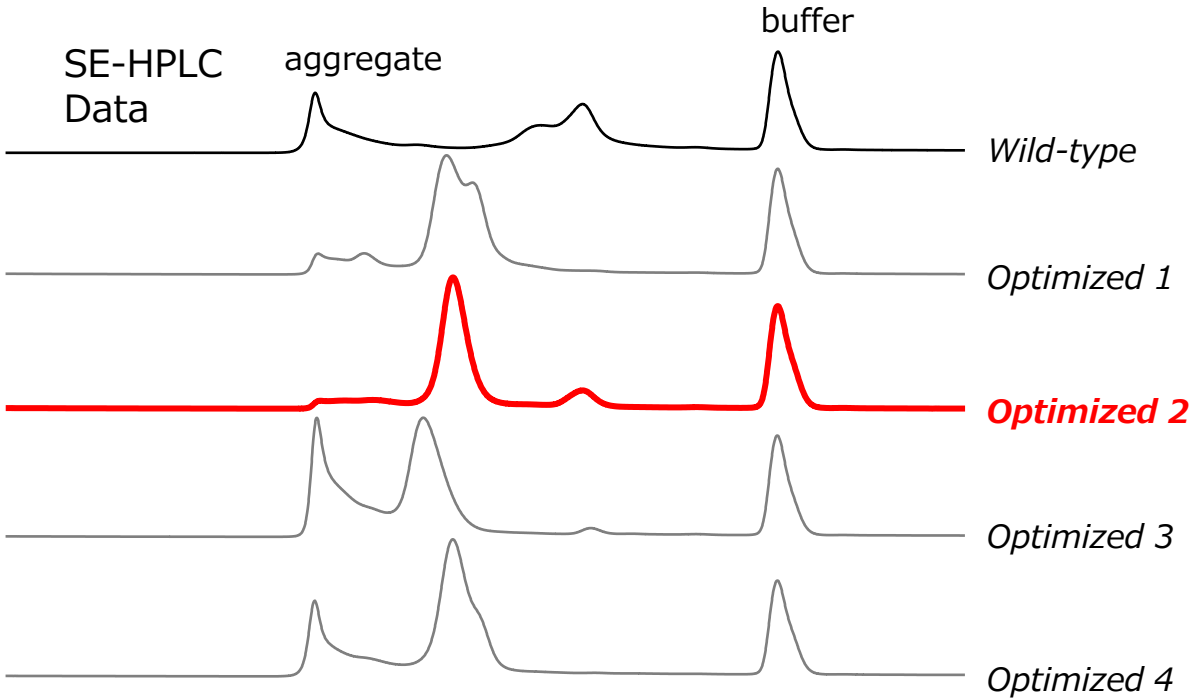
Example of optimized enzyme: Improvements in expression level and stability of Enzyme Y



JCR Internal Data

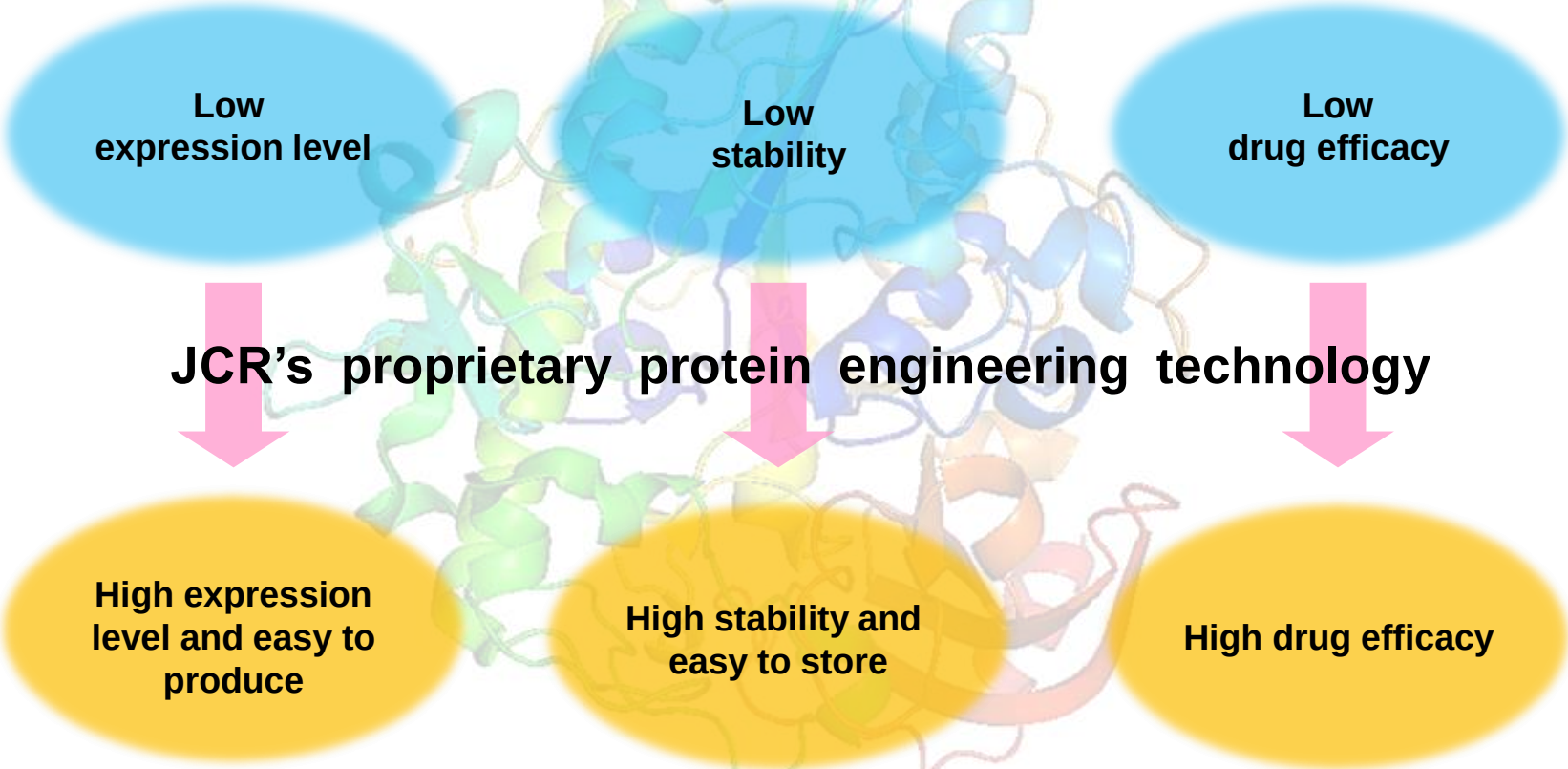
Example of optimized enzyme: Improvements in expression level and stability of Enzyme Y

Improved stability in molecular configuration.



JCR Internal Data

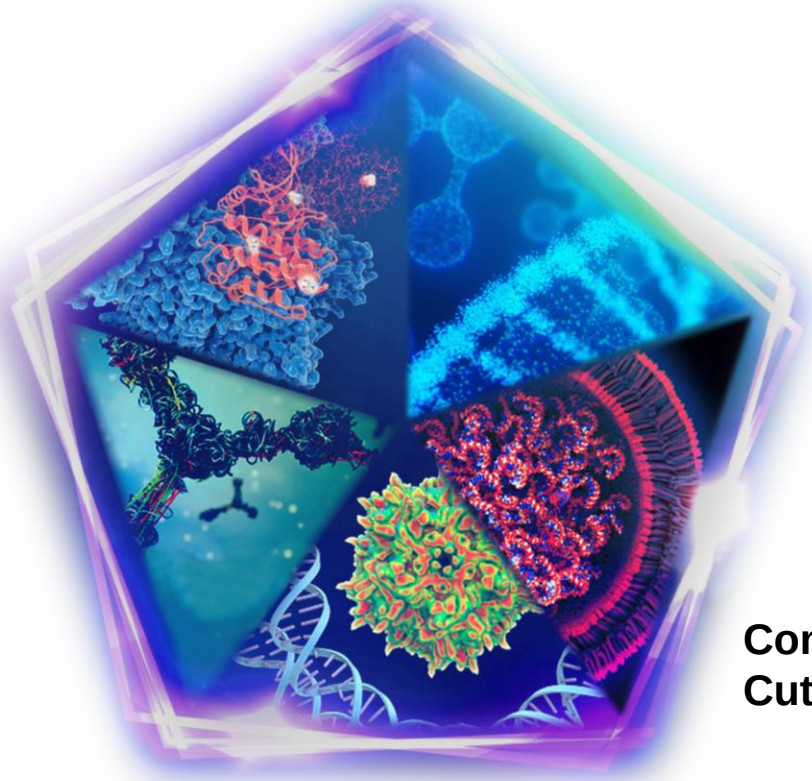
Optimization by JCR's protein engineering technology.



Applicability of J-Brain Cargo® Technology to Proteins and Enzymes

Protein Engineering

Applicability to various modalities



Antibody Engineering

Combination with Cutting Edge Technologies

Targeting Technology

Targeting Technology

Wide Ranged Modalities

Targeting Technology

Wide Ranged Modalities

Expertise in RD field

Targeting Technology

Flexible and Speedy Decision Making

Wide Ranged Modalities

Expertise in RD field

Multi-Modality Innovator


Multi-Modality Innovator

FORWARD-LOOKING STATEMENT

This presentation contains forward-looking statements that are subject to a number of risks and uncertainties, many of which are outside our control. All forward-looking statements regarding our plans, outlook, strategy and future performance are based on judgments derived from the information available to us at this time.

All forward-looking statements speak only as of the date of this presentation.
Except as required by law, we assume no obligation to update these forward-looking statements publicly or to update the factors that could cause actual results to differ materially, even if new information becomes available in the future.

The clinical development data mentioned in this document do not guarantee future results, nor do they guarantee the efficacy or effects of products under development.
This document is not intended to guarantee or advertise the efficacy of the product under development.
The clinical development data mentioned in this document include data not yet published in peer-reviewed academic journals or not yet presented at academic conferences. We will make them public in the future.
In accordance with the Fair Disclosure Rules, data other than those listed in this document will not be disclosed in questions and answers. We appreciate your understanding.
The progress of clinical development may be affected by the pandemic of novel coronavirus infection (COVID-19) in the future .