



*Reach Beyond, Together*

# R&D meeting

Nov 20, 2024  
JCR Pharmaceuticals Co., Ltd.

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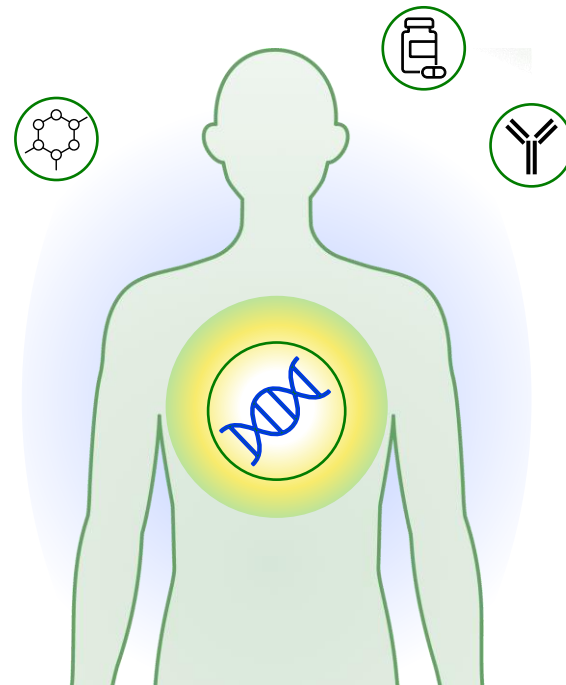
# Introduction

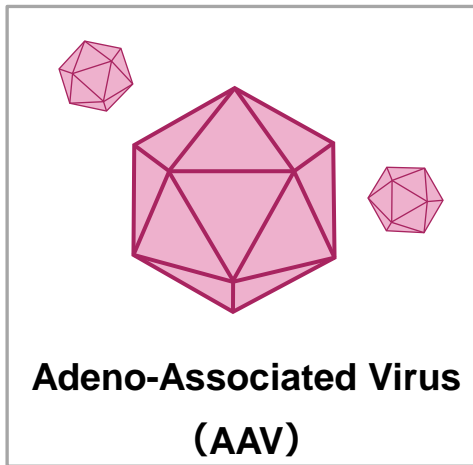
## ➤ Approximately 7,000 rare diseases exist, 80% of which are thought to have a genetic cause<sup>1,2</sup>

- The majority of genetic diseases are monogenic disorders
- It is estimated that there are approximately 400 million patients with rare diseases worldwide

## ➤ Gene therapy can repair disease-causing genetic mutations

- Functional cure: The approach is completely different from small molecule or antibody drugs





- Typical vectors used in gene therapy
- AAVs are able to infect and enter human cells
- The therapeutic gene inserted in AAV is delivered to many tissues and organs



## Known safety profile

- Non-pathogenic virus
- Small risk to be incorporated into human genome
- Lower risk of carcinogenicity compared to other viral vectors



## Sustained treatment effect

- Long-lasting effects on gene expression with a single dose



## Wide clinical use

- 8 of the of the 17 approved *in vivo* gene therapies are AAV<sup>1</sup>
- The number of clinical studies is over 250<sup>2</sup>

1. Website of Division of Molecular Target and Gene Therapy Products, National Institute of Health Sciences. 'Approved gene therapy products' (Nov 15, 2024)

2. Shen W, et al. *Front Immunol.* 2022;13:1001263.



## Difficult to deliver to target tissues

- Central nervous system, muscle, cartilage, etc.
- AAVs do not cross the blood-brain barrier<sup>1</sup>



## Safety liabilities

- Fulminant liver toxicity, thrombotic microangiopathy, neurotoxicity<sup>2</sup>
- Deaths due to liver injury have occurred in clinical trials<sup>2-4</sup>



## Large-scale production of AAV vector

- Complex manufacturing process, requiring advanced technology<sup>5</sup>
- Quality control is extremely important



## Neutralizing antibodies

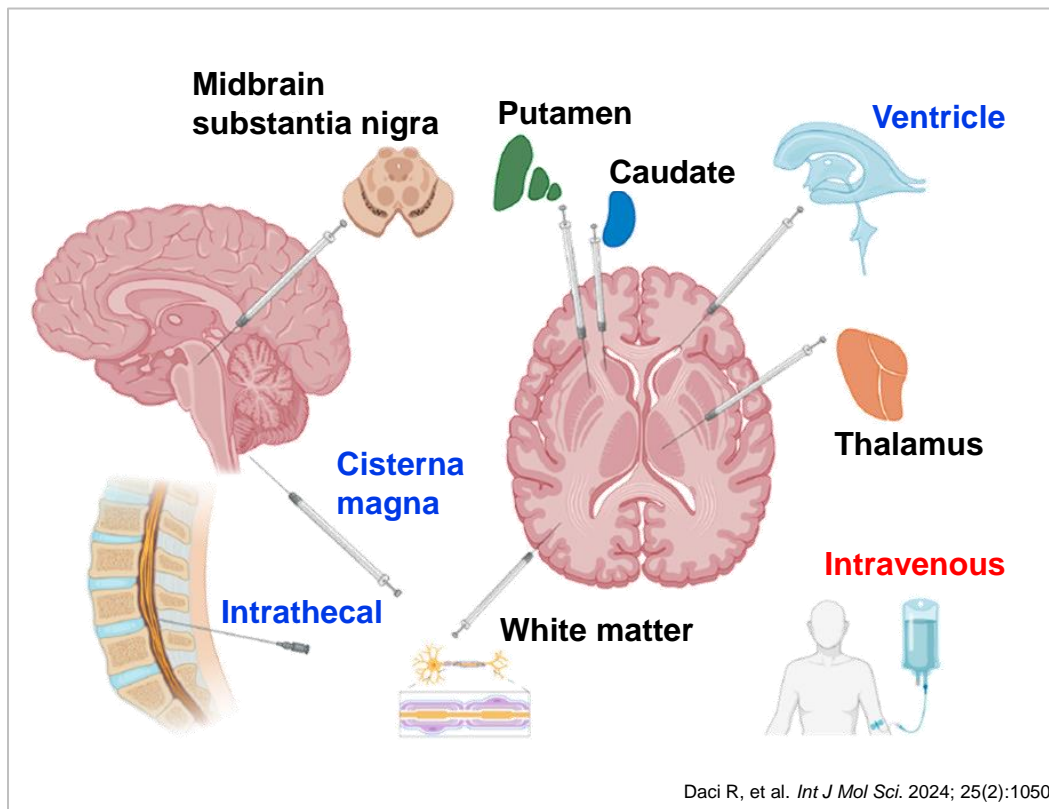
- Risk of pre-existing antibodies making patient ineligible for AAV-mediated gene therapy<sup>6</sup>



## Cost of treatment


- One-time treatment, however at a high cost<sup>7</sup>

1. Daci R, et al., *Int J Mol Sci.* 2024; 25(2): 1050.    2. Wang JH, et al., *Signal Transduct Target Ther.* 2024; 9(1): 78.    3. Duan D. *Mol Ther.* 2023; 31(11): 3123-3126.    4. *Nat Biotechnol.* 2020; 38(8): 910.  
5. Jiang Z, et al., *Trends Biotechnol.* 2023; 41(10): 1268-1281.    6. Weber T. *Front Immunol.* 2021; 12: 658399.    7. Kliegman M, et al., *Nature.* 2024; 634(8033): 307-314.

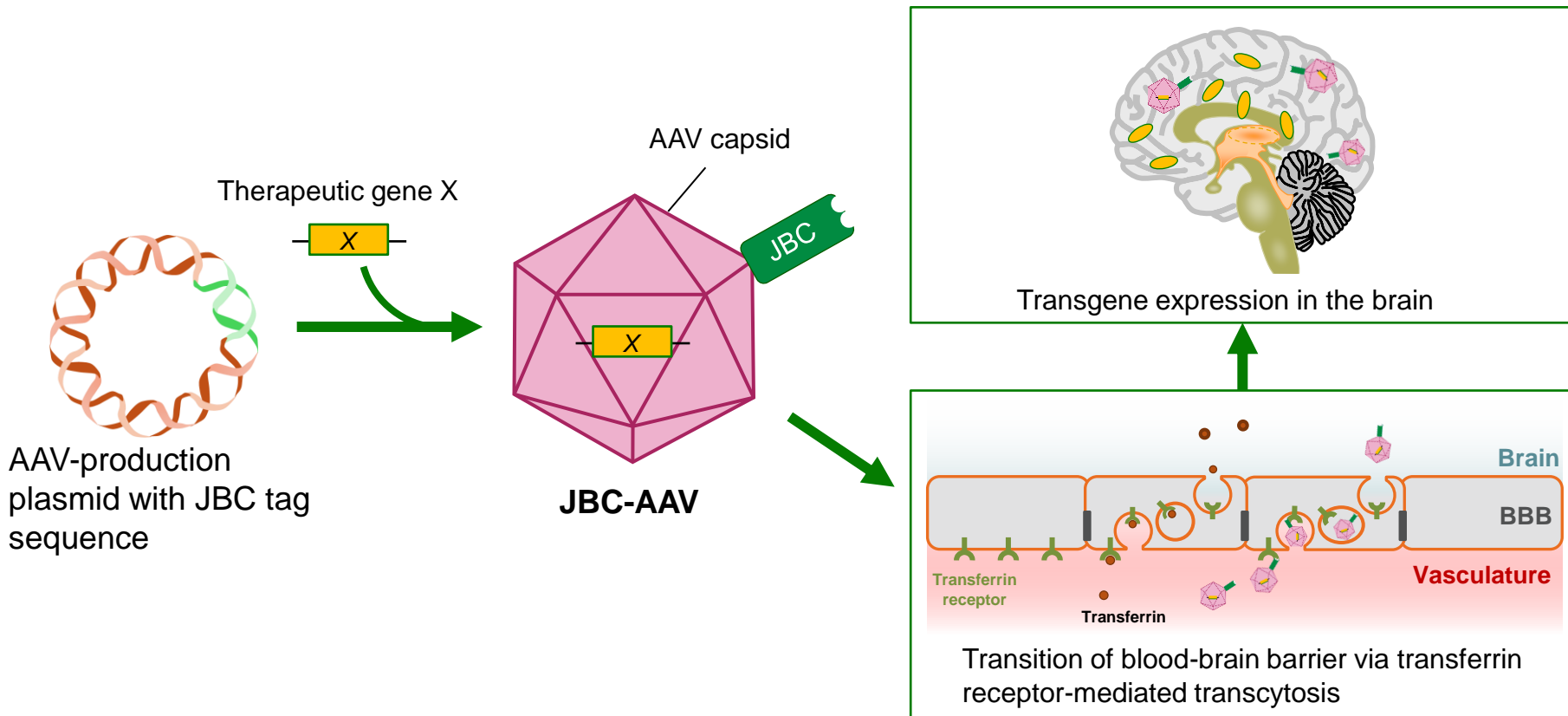


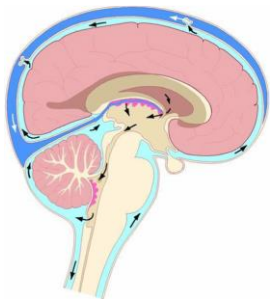
 Intraparenchymal injection



 Intra-CSF injection

 Intravenous infusion


	Advantages	Disadvantages
<b>Intraparenchymal</b>	<ul style="list-style-type: none"><li>• Direct injection to target site</li><li>• Low systemic distribution</li><li>• Avoids neutralizing antibodies</li></ul>	<ul style="list-style-type: none"><li>• Highly invasive (risk of infection, hemorrhage, etc.)</li><li>• Delivery limited to local injection site</li></ul>
<b>Intra-CSF</b>	<ul style="list-style-type: none"><li>• Low systemic distribution</li><li>• Avoids neutralizing antibodies</li></ul>	<ul style="list-style-type: none"><li>• Limited access to deep brain regions</li><li>• Resorption to the body</li></ul>
<b>Intravenous</b>	<ul style="list-style-type: none"><li>• Simple, least invasive procedure</li><li>• Good distribution to peripheral tissues &amp; organs</li></ul>	<ul style="list-style-type: none"><li>• Very limited distribution to CNS</li><li>• Systemic safety issues (liver toxicity)</li><li>• Delivery to off-target tissues</li><li>• Pre-existing neutralizing antibodies</li></ul>





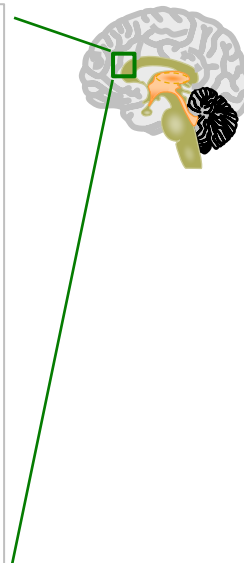
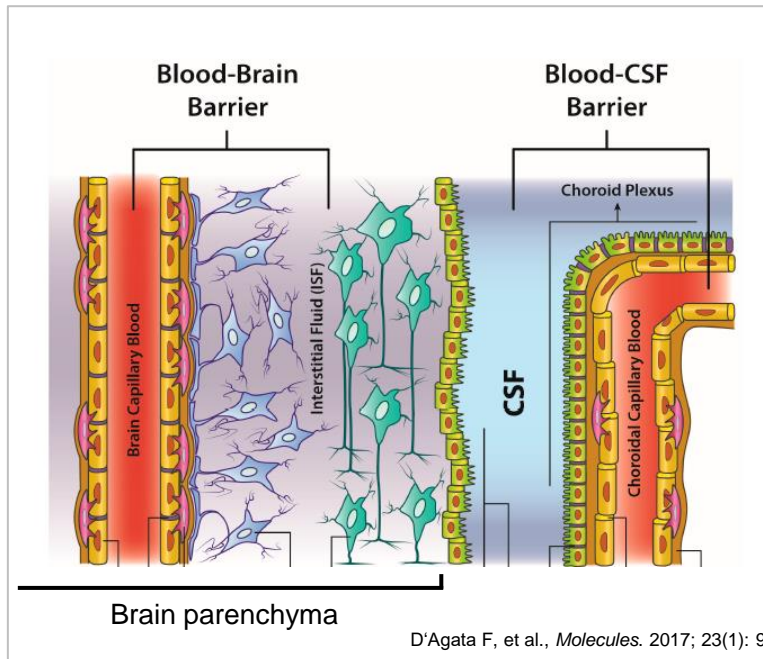
 : Cerebrospinal fluid (CSF)  
 : CSF flow

The CSF provides protection to the brain and the spinal cord from physical injury



Dense network of capillaries in the brain ensures supply of cells with oxygen and nutrients.

Sato Y, et al., *Metab Brain Dis.* 2022; 37(6): 1745-1756.

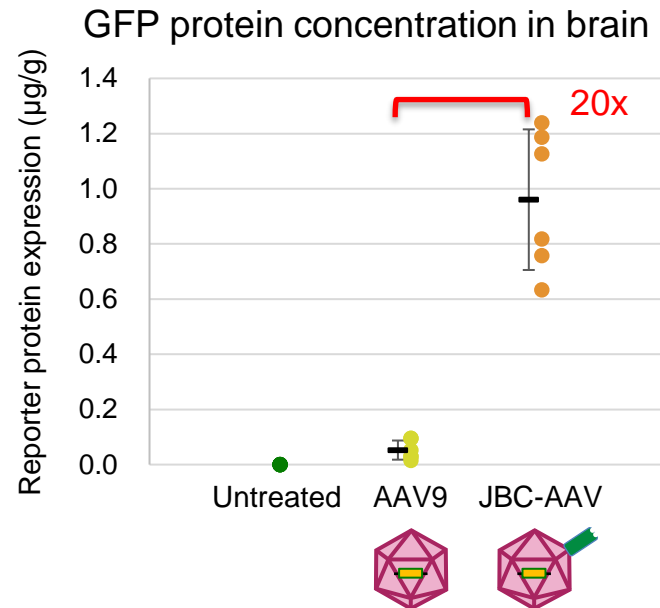
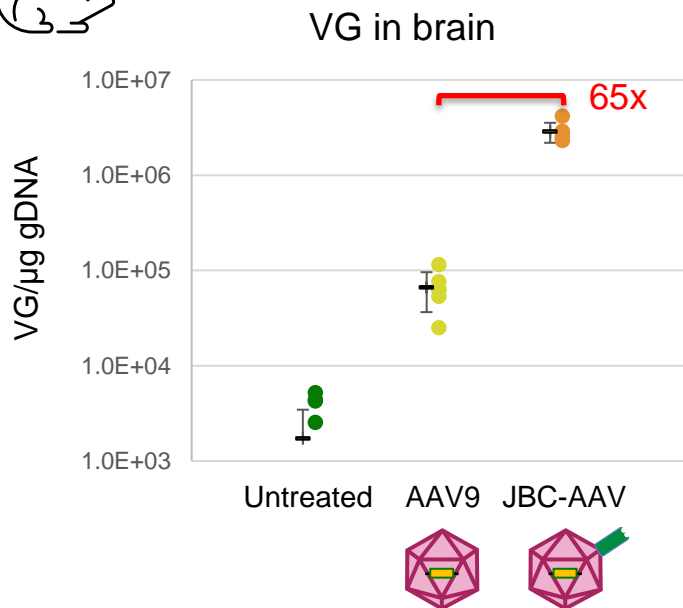


**Delivering AAV to the brain parenchyma via a route that cross the blood-brain barrier**



Can deliver therapeutic genes to the entire brain

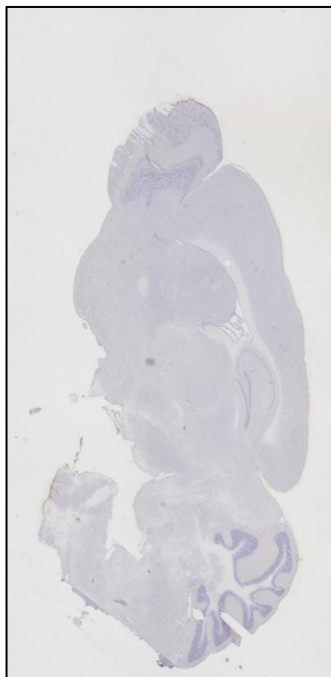
# Non-clinical Data



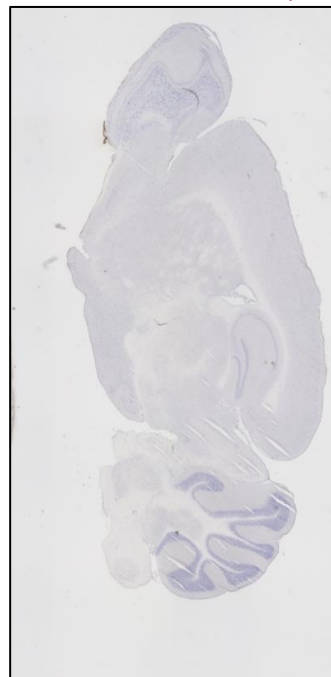
JBC-tagging of the AAV capsid increased the viral genome in the brain and increased the expression of the transgene



Untreated



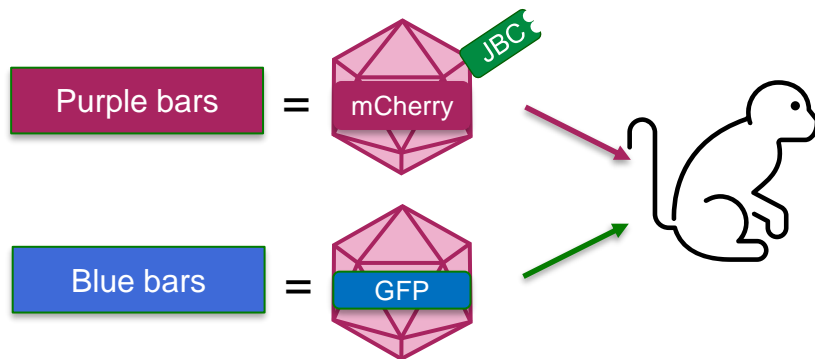
AAV9



JBC-AAV



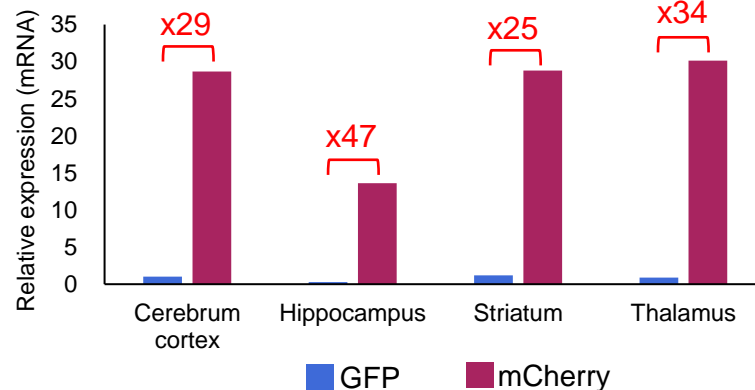
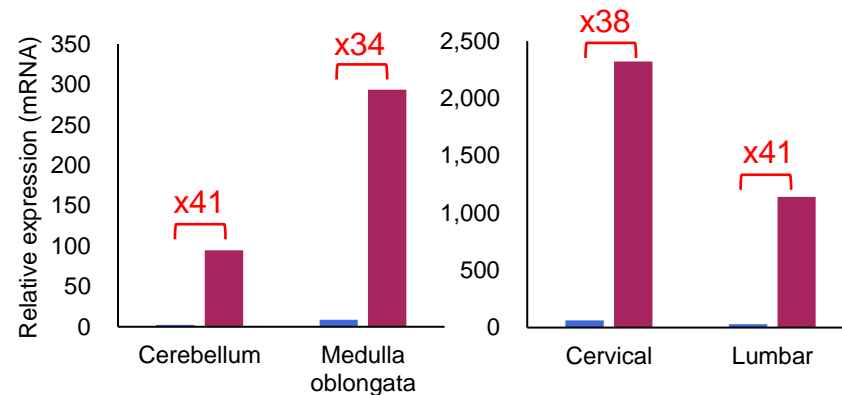
Inserting J-Brain Cargo® tags into AAVs enables efficient gene delivery to the brain

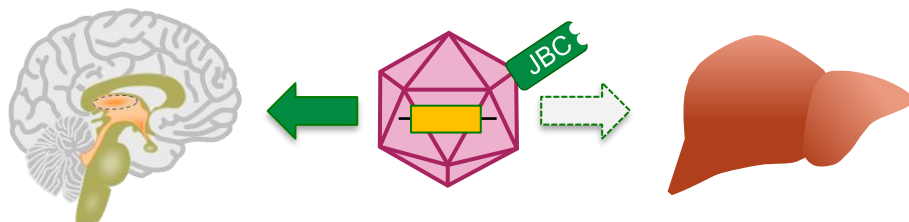


IV co-administration of both AAVs into cynomolgus monkey  
 Analysis for mCherry and GFP expression approx. 4 weeks post infection



JBC-tagging of the AAV capsid resulted in high transgene expression in all parts of the monkey brain



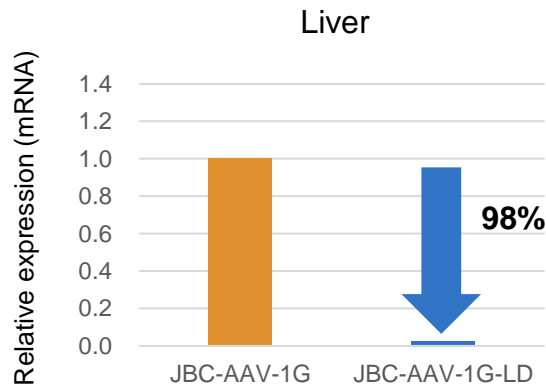
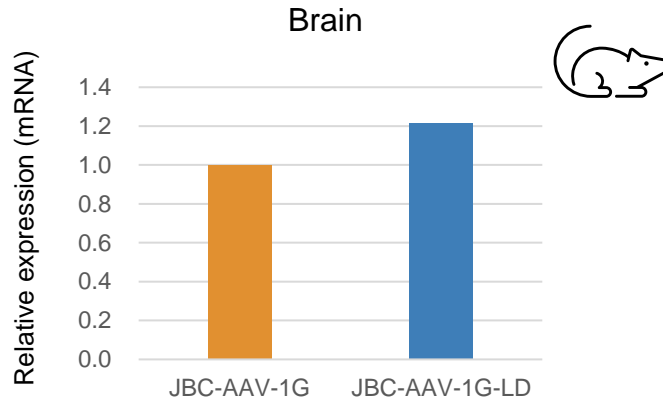


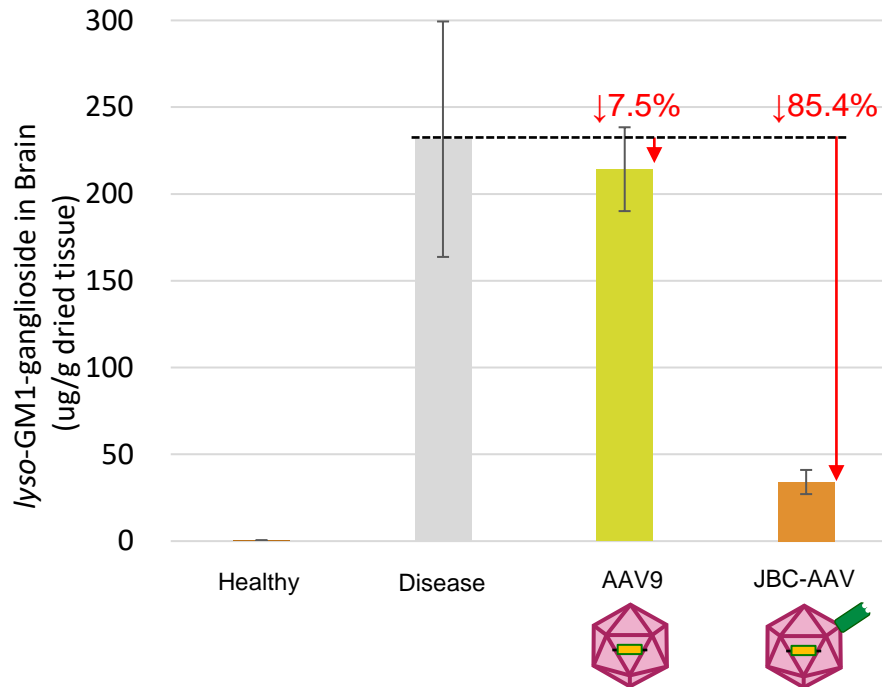
Retain brain tropism

Reduce liver tropism

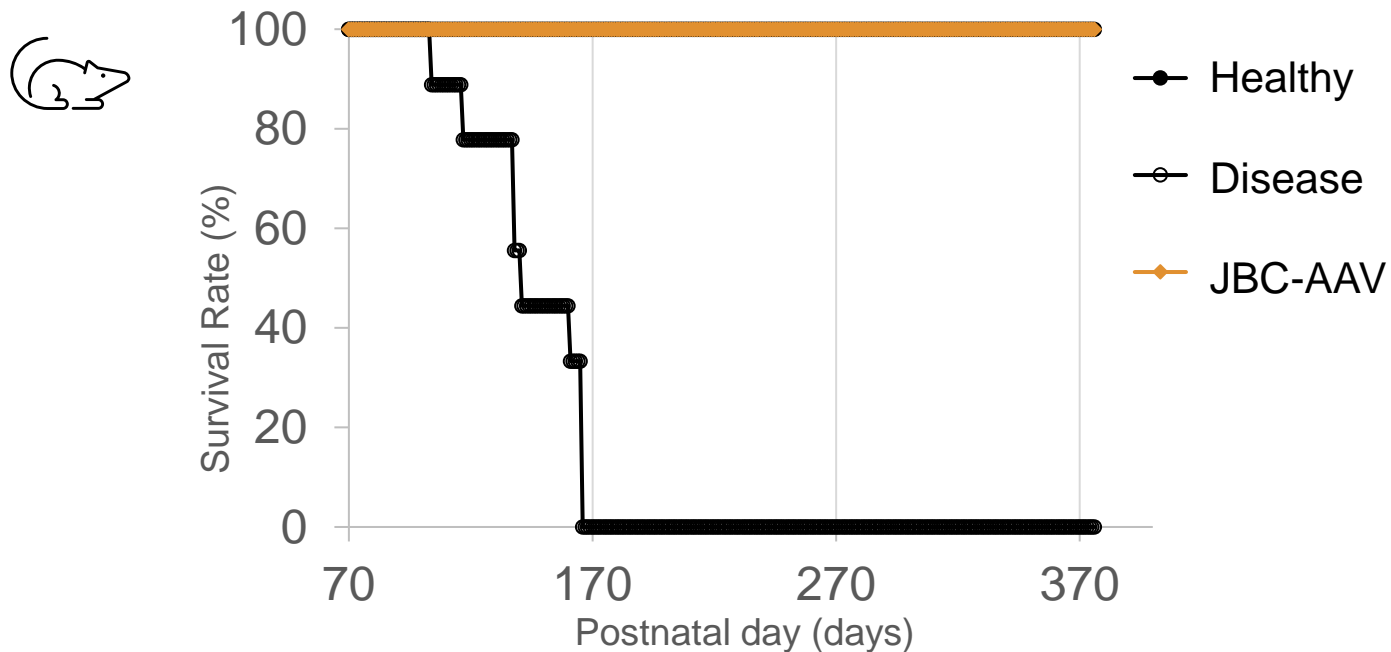
Partially modified certain loops in the AAV capsid

Succeeded in drastically reducing AAV accumulation in the liver while retaining brain tropism via the JBC tag

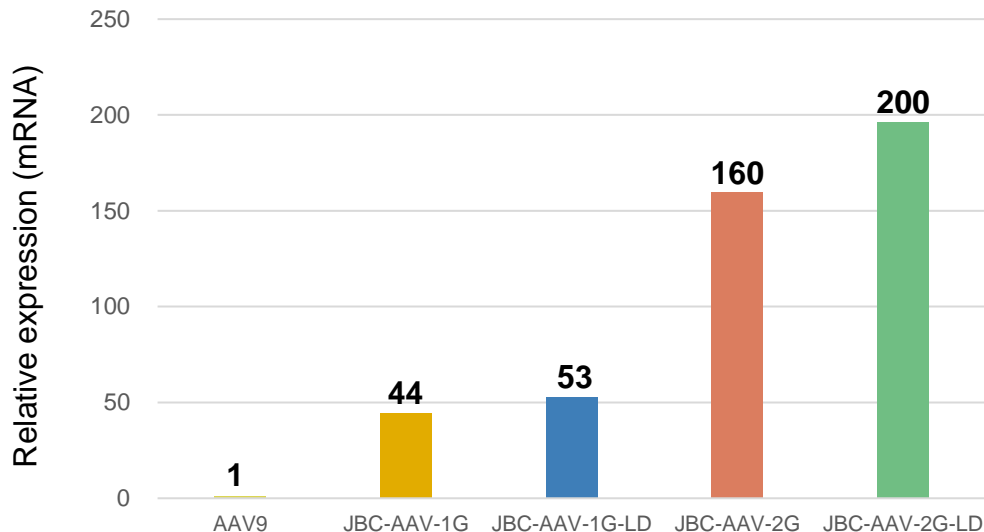




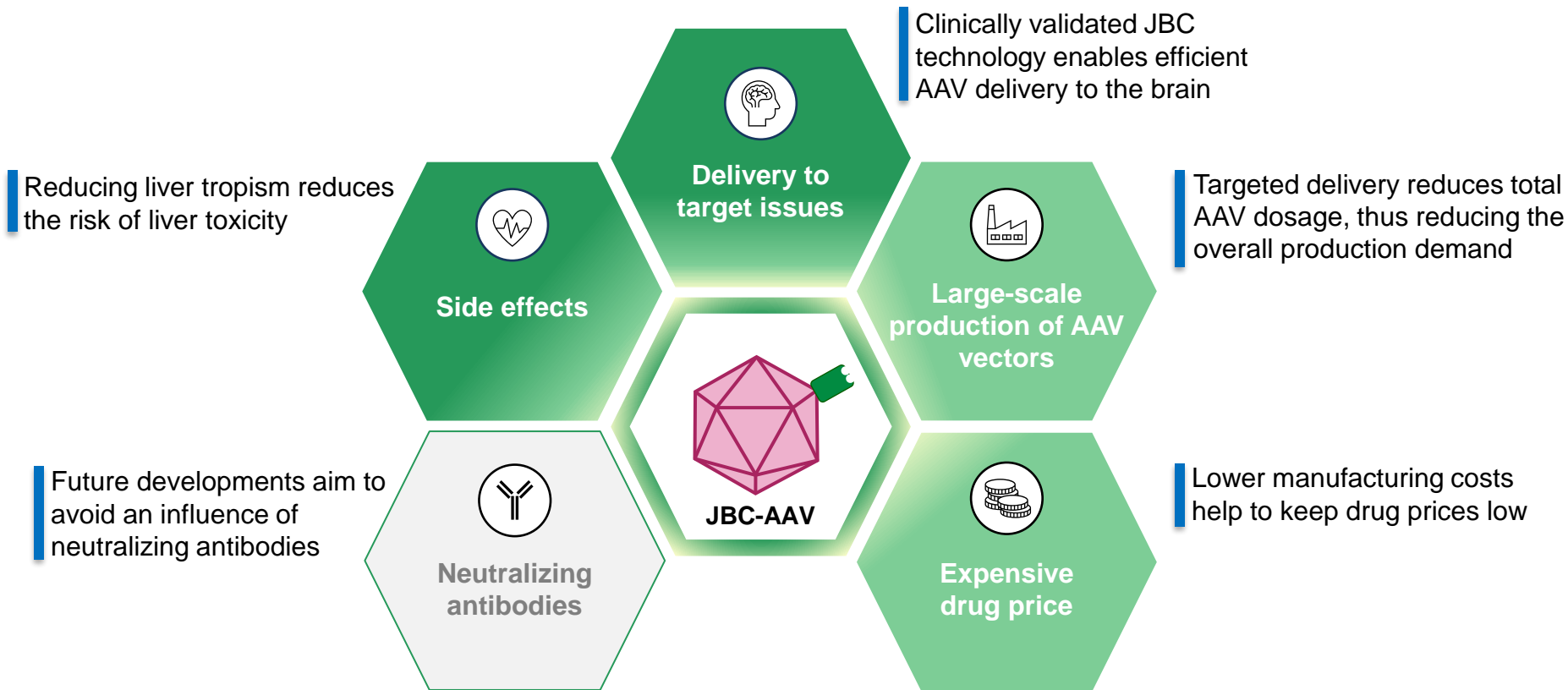
Only JBC-AAV decreased the accumulated substrate in the brain



Gene therapy with JBC-AAV significantly improved life span



While data disclosed in this deck were obtained with JBC-AAV-1G, next generation capsids already **achieved ~200 fold higher brain expression** in mice than wtAAV9 capsids



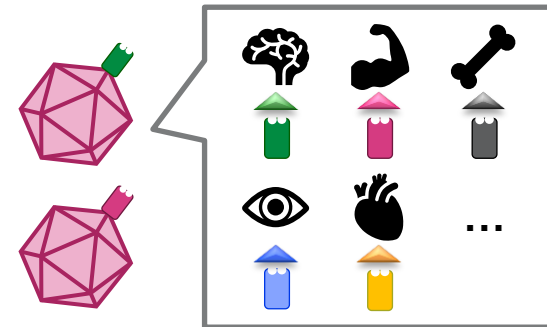
## ➤ Improving delivery efficiency to the brain

- Various receptor types are found on the blood-brain barrier
- Multi-specificity may further improve efficiency of CNS delivery



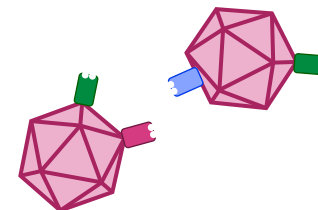
## ➤ Tissue targeting other than brain

- Creation of "tags" with high tropism to other organs



## ➤ “Tag” Optimization through advanced technologies

- Design of the optimal tag for each target tissue or organ, including number of tags, position and binding affinity to the receptor





- Expansion of partnering opportunities
- Increasing R&D collaborations

## Creation of breakthrough therapeutics in various disease areas

*Lysosomal Storage Diseases*

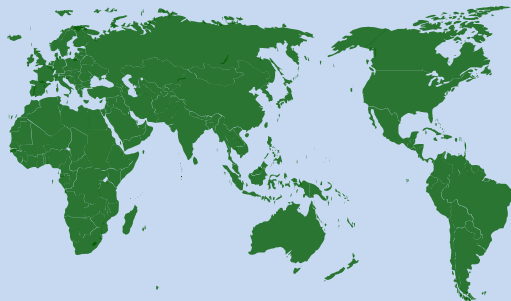
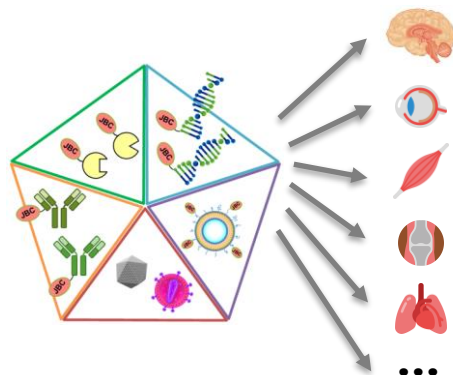
*Neurodegenerative Diseases*

*Ocular Diseases*

*Orthopedic Diseases*

*Muscular Diseases*

Widely applicable technology based on J-Brain Cargo®



***Reach Beyond, Together***



# Appendix

## Enzymes and Protein Delivery

to the brain and muscle

to replace deficient or missing enzymes and proteins

## Antibody Delivery

to the brain

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

## Oligonucleotide (ASO, siRNA) Delivery

to the brain and muscle

to modify gene expression

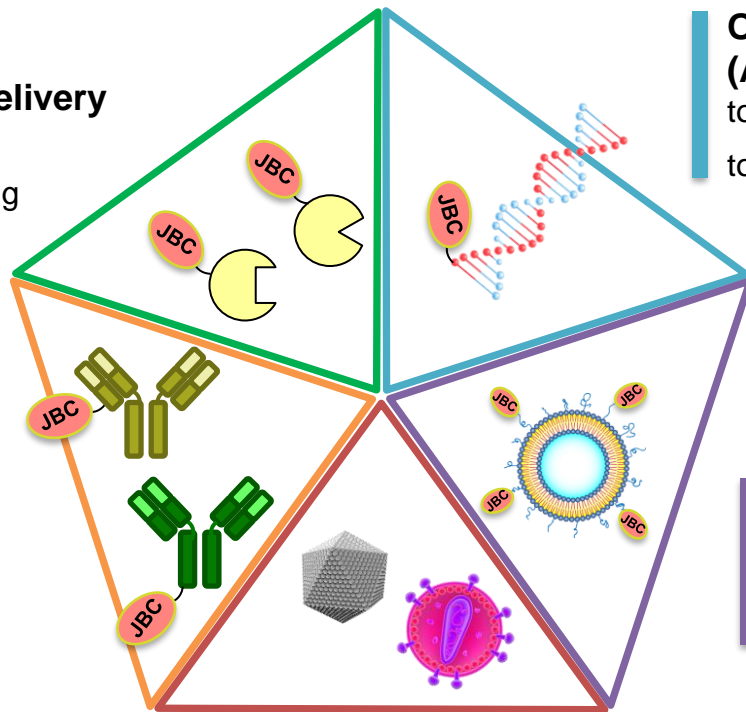
## LNP (mRNA, low-molecular compound) Delivery

to the brain and muscle

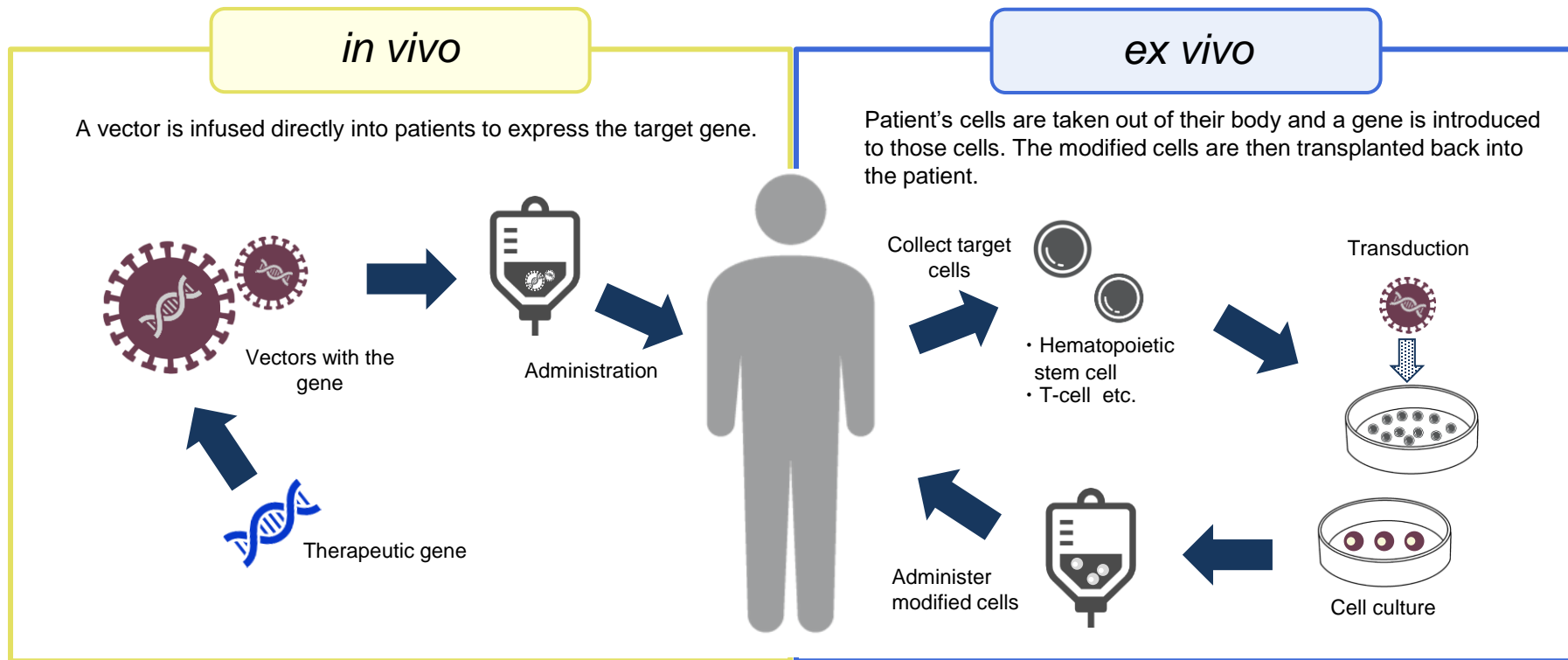
to replace deficient or missing proteins

## Gene/Cell therapy

combined with J-Brain Cargo® technology to pave  
the way towards functional cure of CNS pathologies



- Gene therapy can be classified into two types: ***in vivo*** gene therapy and ***ex vivo*** gene therapy
- Vectors (adeno-associated virus, adenovirus, lentivirus, plasmid, etc.) are used to deliver genes (therapeutic genes)



AAV	Adeno-associated virus	アデノ随伴ウイルス
ASO	Antisense oligonucleotides	アンチセンス核酸
BBB	Blood-brain barrier	血液脳関門
CNS	Central nervous system	中枢神経系
CSF	Cerebrospinal fluid	脳脊髄液
GFP	Green fluorescent protein	緑色蛍光タンパク質
JBC	J-Brain Cargo®	-
LNP	Lipid nanoparticle	脂質ナノ粒子
mRNA	messenger RNA	伝令RNA
siRNA	small interfering RNA	短鎖干渉RNA
VG	Viral genome	ウイルスゲノム

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