JCR Pharmaceuticals Co., Ltd.

R&D Meeting

November 20, 2024

Event Summary

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[Participants]	
[Number of Speakers]	1

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Presentation

Moderator: Thank you very much for watching the R&D meeting of JCR Pharmaceuticals Co., Ltd.

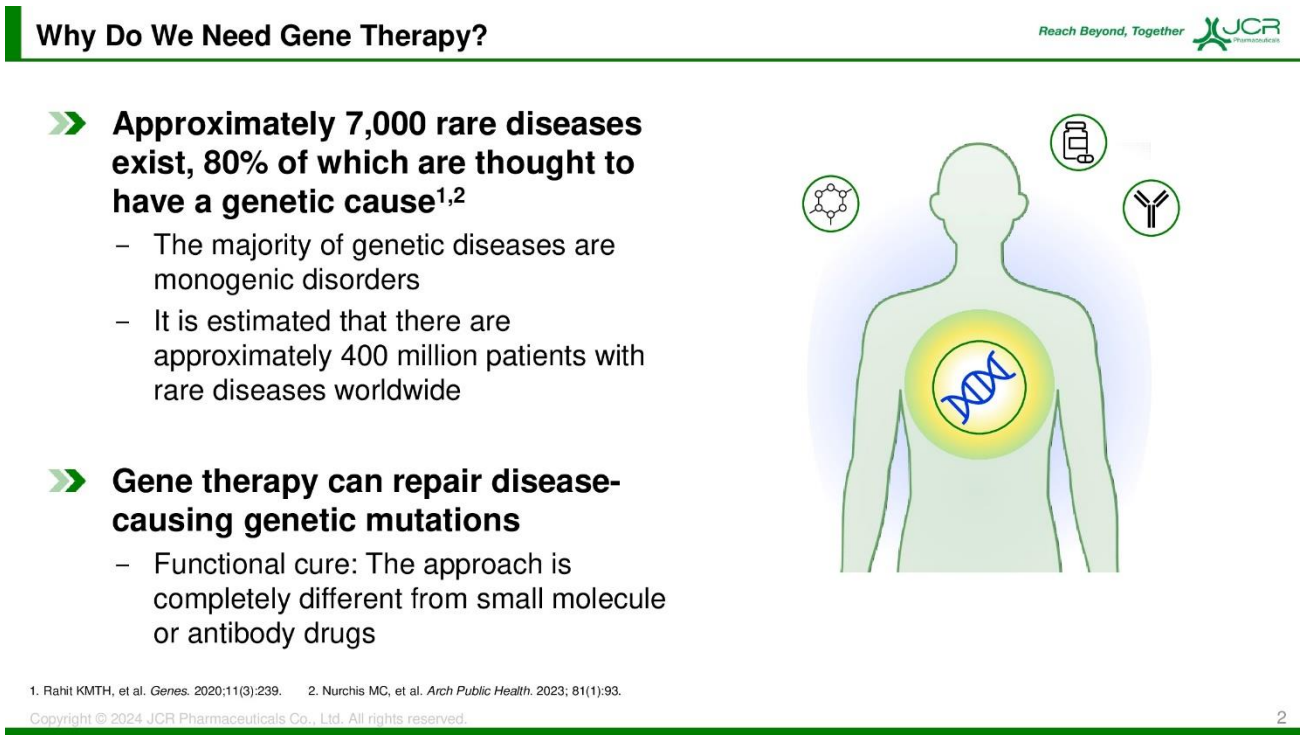
First, let us explain today's language settings. Please select Off, Japanese or English channel by clicking the Interpretation icon at the bottom of your Zoom window. This meeting is being recorded for posting on our website at a later date.

Next, I will explain the flow of today's briefing. Today's session will last approximately one hour and will include a presentation and a Q&A session. Questions will be taken after all presentations have been completed.

Hiroyuki Sonoda, Director, Senior Managing Executive Officer and Executive Director of Research Division, will give an overview of the research and development of gene therapy that we are undertaking today.

Now, Director Sonoda, please go ahead.

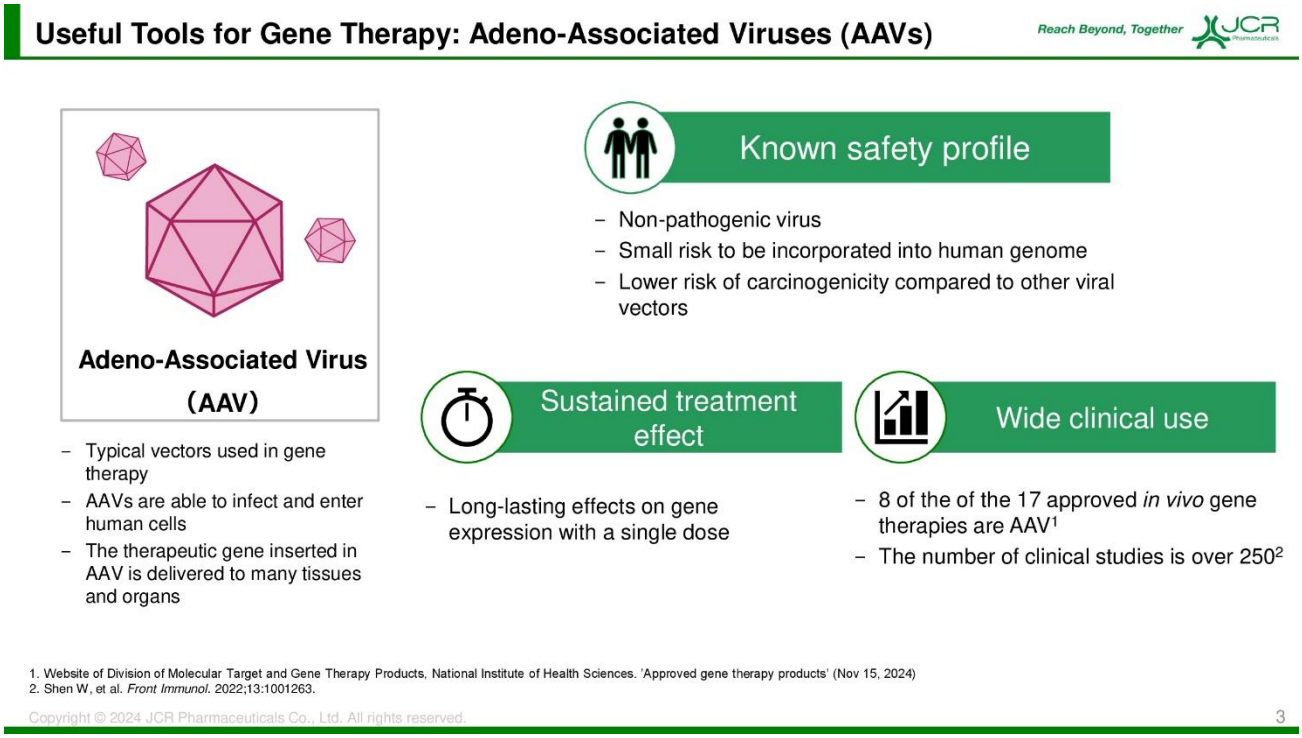
Sonoda: Hello, everyone. My name is Sonoda. Today, I would like to introduce the gene therapy technology that JCR Pharmaceuticals is working on, gene therapy using adeno-associated virus AAV, and our efforts, including our latest data.



First, let me explain why we are developing gene therapy technology. There are approximately 7,000 rare diseases in the world, 80% of which are genetic. Most of these genetic diseases are caused by a single gene defect or abnormality, and in total, approximately 400 million patients worldwide are said to suffer from rare diseases.

This gene therapy is a treatment that can compensate for the genetic abnormality or genetic defect that causes the disease. So it is possible to access the root cause, and then supplement what is missing or repair

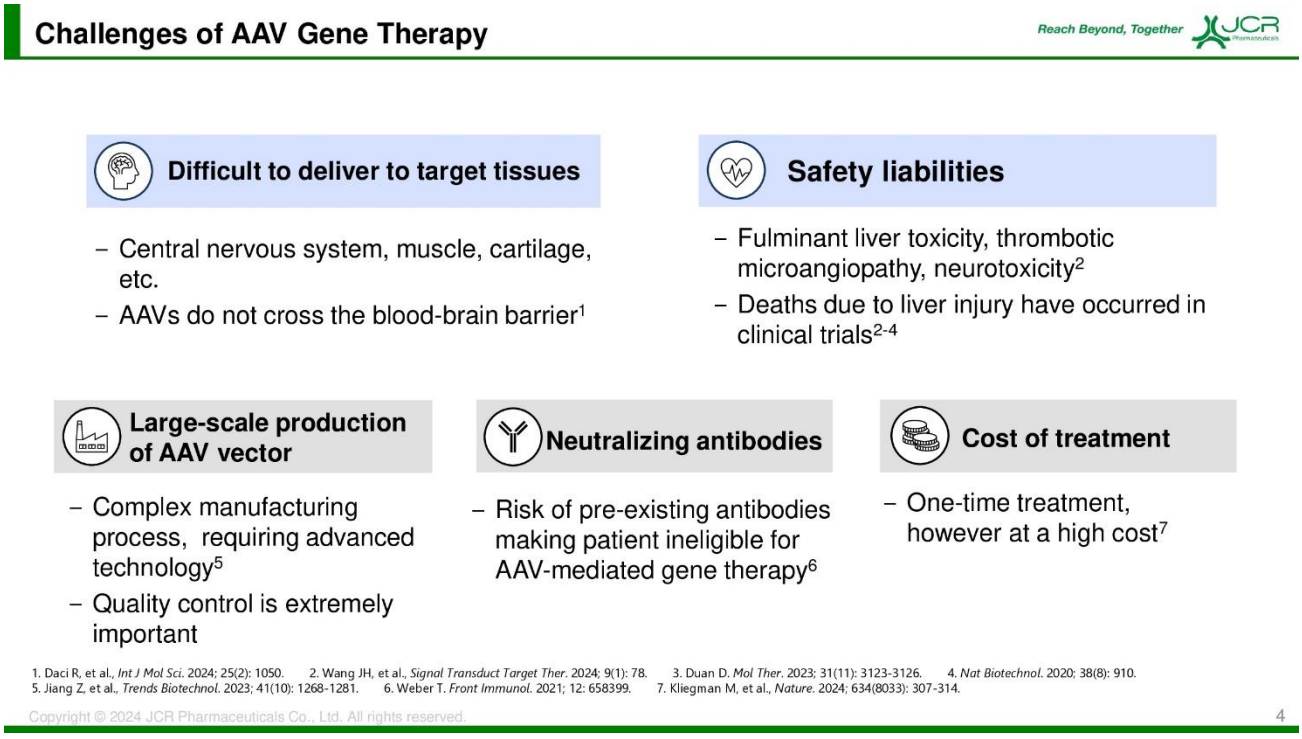
the abnormality, which means that a fundamental treatment can be expected. In this respect, it is a little different from other modalities, such as small-molecular compounds or antibody drugs.



The most useful tool now being used for this gene therapy is this Adeno-Associated Virus, AAV.

There has been considerable research, including clinical studies, and it has been shown that the safety of the drug can be assured and that its expression can reach a therapeutic level and be sustained for a certain period of time. Therefore, various companies and academia have been making practical use of such properties.

In fact, as noted here, AAV is said to be used in eight of the 17 approved in-vivo gene therapies.



On the other hand, however, this gene therapy using AAV is, of course, not a panacea at this point in time. Various problems still remain, and research is being conducted around the world to somehow overcome them. There are some diseases that can be treated with the current AAVs, but there are still many diseases that remain inaccessible and difficult to treat with the current AAVs, and for those, new AAVswhich are more capable and better are being developed by everyone. We are developing the same kind of products.

Here is a description of what the problems are. The first is the difficulty of delivery to the target organ. This is a problem in the central nervous system, including the brain, muscle tissue, and other organs where we want to deliver genes to cure, and where we cannot deliver a sufficient amount of AAV to reach.

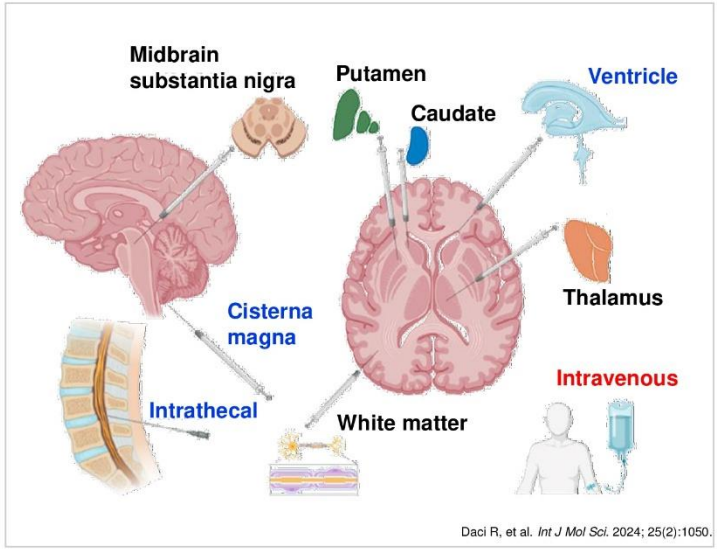
This would lead to raising the dosage, as it is thought that the more amount you give, the more amount of AAV can reach the targets, but this in turn raises the issue of side effects.

In particular, accumulation in the liver and liver damage is now being seen in clinical trials, and some deaths have actually been reported. Therefore, the window between efficacy and toxicity is narrow, which is the biggest problem with AAV treatment today, because the dose has to be increased for lower efficacy, which leads to side effects.

In addition, as shown in the gray area below, it is very difficult to mass produce. I suppose that this was the same problem when antibody drugs were introduced. But it took 20 or 30 years, and now there are no major problems in manufacturing antibody drugs, but AAV is still in its infancy in that sense. The technology for mass production will probably be in place from now on, but at this point, I don't think we can say that we are producing sufficient quantities.

Also, there is the problem of neutralizing antibodies and the very high price of the drug because of the difficulty of manufacturing.

AAV Delivery to Central Nervous System



Intraparenchymal injection Intra-CSF injection Intravenous infusion

There have been attempts to use AAVs to treat diseases of the central nervous system, but it is difficult to deliver AAVs to the target tissues, so there are, and have been, attempts to use AAVs directly to the brain in case of the central nervous system, for example.

It is administered directly into the brain parenchyma or into the cerebrospinal fluid (CSF) that protects the brain. In other words, it is an attempt to deliver the AAV gene into the brain and into brain cells by administering it directly to the brain or a place close to the brain.

The other way is intravenous administration. This is the least damaging to the body, so it is administered intravenously and somehow delivered to the brain. However, this can be quite difficult.

Comparison of Different AAV Brain Delivery Strategies

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	Advantages	Disadvantages
Intraparenchymal	• Direct injection to target site • Low systemic distribution • Avoids neutralizing antibodies	• Highly invasive (risk of infection, hemorrhage, etc.) • Delivery limited to local injection site
Intra-CSF	• Low systemic distribution • Avoids neutralizing antibodies	• Limited access to deep brain regions • Resorption to the body
Intravenous	• Simple, least invasive procedure • Good distribution to peripheral tissues & organs	• Very limited distribution to CNS • Systemic safety issues (liver toxicity) • Delivery to off-target tissues • Pre-existing neutralizing antibodies

Ye D, et al. *Adv Drug Deliv Rev.* 2024; 211:115363. Kang L, et al. *J Control Release.* 2023; 355:458-473.

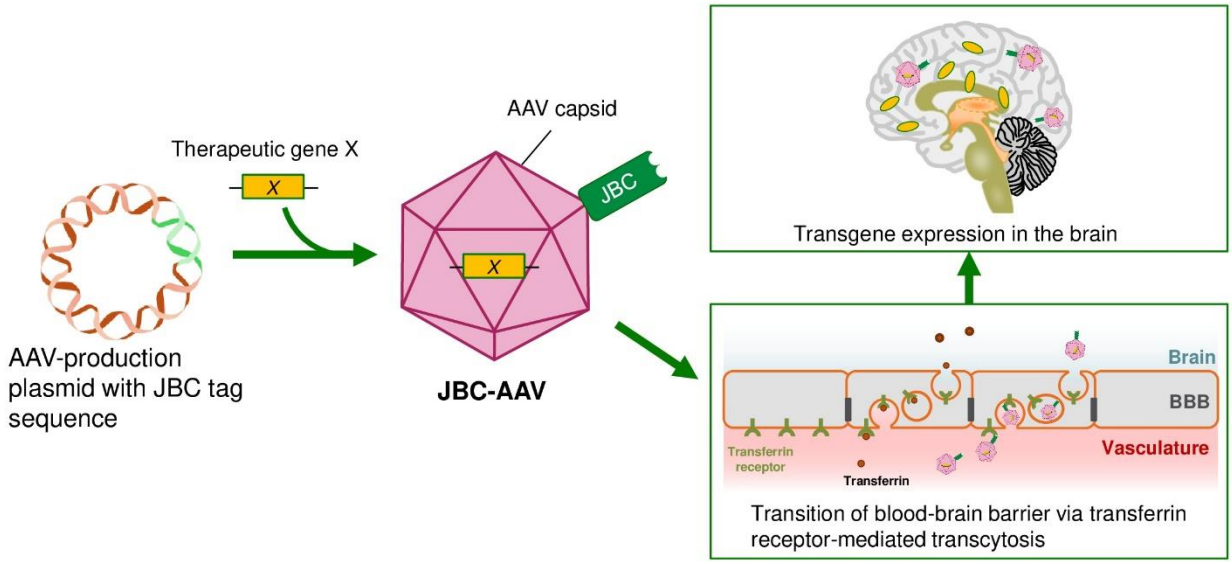
This slide shows the advantages and disadvantages of each.

As for those that are administered directly or in the CSF, they are highly invasive, so the biggest disadvantage is that they are highly invasive. It is highly invasive, because the drug is administered there by inserting a needle directly into the head or into the CSF.

On the other hand, since the desired amount of AAV can be administered to a limited area, it has the advantage of bypassing the blood-brain barrier, which is the most difficult issue in this case, to deliver the drug, in this case AAV.

However, it is still very invasive, and as I will explain later, it is difficult to deliver the drug to the entire brain, even if it is administered directly. The best solution is to administer the drug intravenously, make it go through the blood-brain barrier, and then deliver the AAV and target gene to the entire brain. We believe that this will be the best treatment.

Mechanism of Action of J-Brain Cargo® Applied to AAV



We have a technology called J-Brain Cargo to make the drug pass through the brain-blood barrier. We have been using this to develop protein-based drugs, and some drugs have already been approved in Japan with this technology. In other words, since there are already technologies that have been validated in humans for passing through the blood-brain barrier, we thought that if we applied this to AAV, we could create AAV that could pass through the blood-brain barrier, which we said was a problem, and we have been researching this.

What is shown here is a conceptual diagram. The plasmid is shown on the far left. At the gene stage, we design a capsid protein such that the J-Brain Cargo tag is placed on the surface of the AAV, which is then transfected into mammalian cells to produce the AAV.

At the stage when this AAV is ready, the J-Brain Cargo brain tag, as shown in the middle picture, will be placed on the surface of the AAV, like this. Therefore, there is no need to add this tag after the AAV is produced. This form will be produced from the beginning.

When this is administered intravenously, as shown in the lower picture on the right, it passes through the blood and reaches the capillaries of the brain, where it is transported via the transferrin receptor, which is a mechanism called receptor-mediated transcytosis. This means that the AAV is transported to the parenchymal side of the brain while the BBB is intact.

As you can see in the diagram above, the AAV reaches the brain and is able to express genes in the brain cells.

Advantage of Delivering AAV through Blood-Brain Barrier

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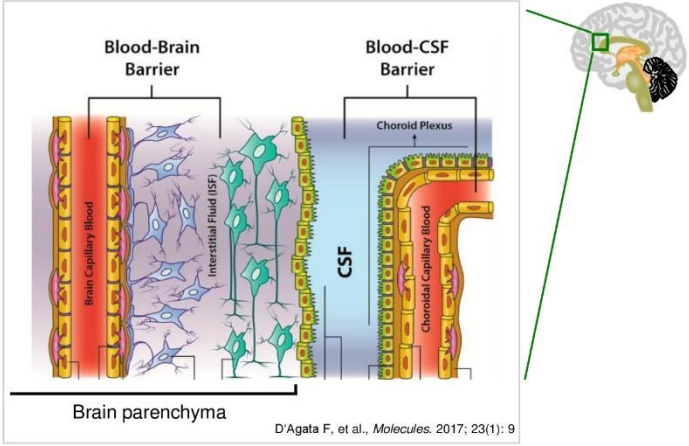
: Cerebrospinal fluid (CSF)

: 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.



D'Agata F, et al., *Molecules.* 2017; 23(1): 9

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

Can deliver therapeutic genes to the entire brain

8

Here is a little schematic of what I said earlier about what the difference is between hitting the brain directly or hitting the CSF with AAV, and AAV reaching the brain cells via blood vessels.

On the right side, this is a picture excerpted from a paper, and it shows that the blood-brain barrier, BBB and the blood-cerebrospinal fluid barrier, BCSFB are two completely different things.

In other words, even if a drug is administered into the CSF, it does not mean that it is going to the brain parenchyma. You can think of the brain as floating in a fluid called cerebrospinal fluid. If the AAV is administered into the floating liquid, and the AAV wants to migrate to the parenchyma side of the brain, it has to pass through the soft membrane and enter the brain parenchyma.

For example, a mouse has a very small brain, 400 mg, so if the drug penetrates to some extent, it can spread throughout the entire brain. However, for organisms with a large brain like ours, it is difficult to spread throughout the entire brain unless the penetration is quite deep and efficient. This can be very difficult, given the nature of the AAV.

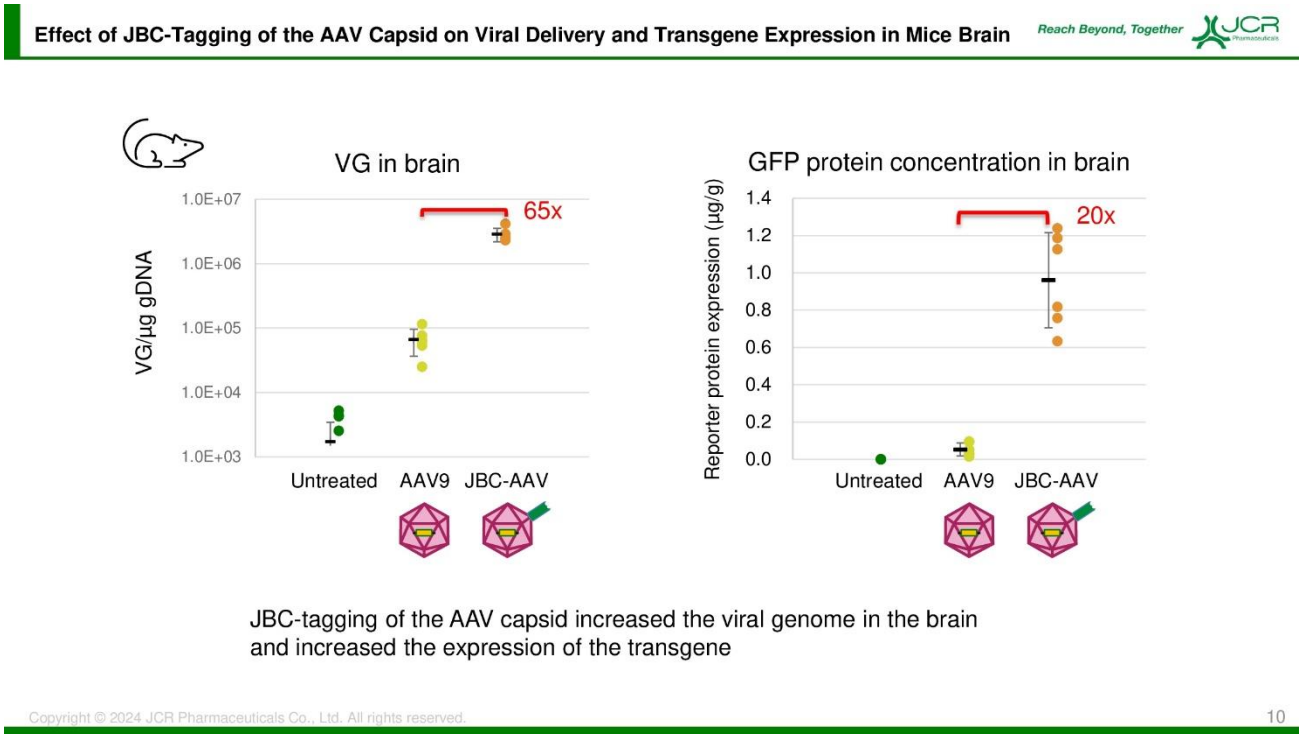
Therefore, when administering to CSF, the brain is floating in a liquid, and the surface of the brain -- the part in contact with the liquid -- has a high chance of being infected by AAV, but the deeper parts of the brain are very difficult to be infected.

If you shot the drug into the brain parenchyma, this is actually shot inside, so it can infect there, but it is still localized to the site where it was shot, so it is difficult to spread it throughout the brain.

On the other hand, it has a chance to reach the brain through this blood-brain barrier in all places where there are blood vessels. Where those blood vessels are located is pictured below on the left side, and as you can see, the blood vessels are very densely packed. According to one report, the distance between blood vessels is approximately 40 micrometers. One cell is 20 micrometers to 30 micrometers in diameter, so if there are two adjacent cells, there is a blood vessel on the other side of the cell, on average.

So, once it passes through the cerebral blood-brain barrier from the cerebral capillaries and enters the parenchymal side of the brain, it is a brain cell, and other particles will come in from the other side without having to open that next door. Therefore, delivering drugs through the blood-brain barrier is a very important point in terms of delivering drugs to the entire brain.

The concept is exactly the same as the one we are developing for our protein products. The same concept is being applied to AAVs.



From here, I would like to introduce the actual data using our new AAV vector, which will be non-clinical data in mice and monkeys.

First of all, this is the data with mice. A single dose of AAV vector is administered through the tail vein of a mouse, and only one dose is given. Then, after a certain amount of time, we remove the mouse brain and see how much of that brain is infected, and how much AAV is able to carry the gene. We then check how much protein is being produced or expressed from the genes carried.

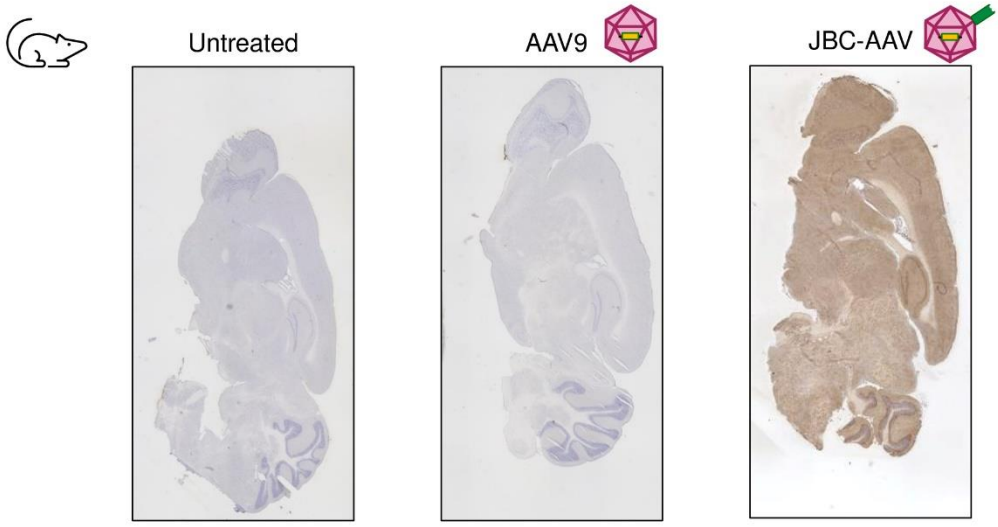
The left side shows how many genes could be carried into the brain, and the right side shows how much protein could be expressed from those genes.

First, the left side. This VG stands for viral genome. So, it shows how much of the gene is in the brain. In this graph, the leftmost one, marked “Untreated,” is unadministered, and the middle one is AAV9. This is the vector that is said to be the most likely to go through the BBB now, and the most likely to be delivered to the brain. On the right is JBC, which stands for J-Brain Cargo, and the JBC-AAV is our new AAV vector.

If you look at this, if you compare AAV9, the middle one, and the other one on the right, you can see that compared to AAV9, 65 times more genes reached the brain of the mice in this test.

As a result, we move on to the next one, on the right side, which is GFP, and we use this protein as a model protein. This is a fluorescent protein. In this case, the expressions of GFP from AAV9 and JBC-AAV were compared on the right side, and the expression level of AAV9 was increased by about 20-fold.

Evaluation of Brain in Mice by Immunohistochemical Staining



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

Next, we use another technique, called immunostaining, to see which parts of the brain express the target protein and how much of it is expressed. The way to look at it is also the same. The leftmost group, Untreated, is mice that have not been treated with anything, and AAV9 in the middle is a group that was treated with commonly used AAV. And on the right is the group that received our new AAV.

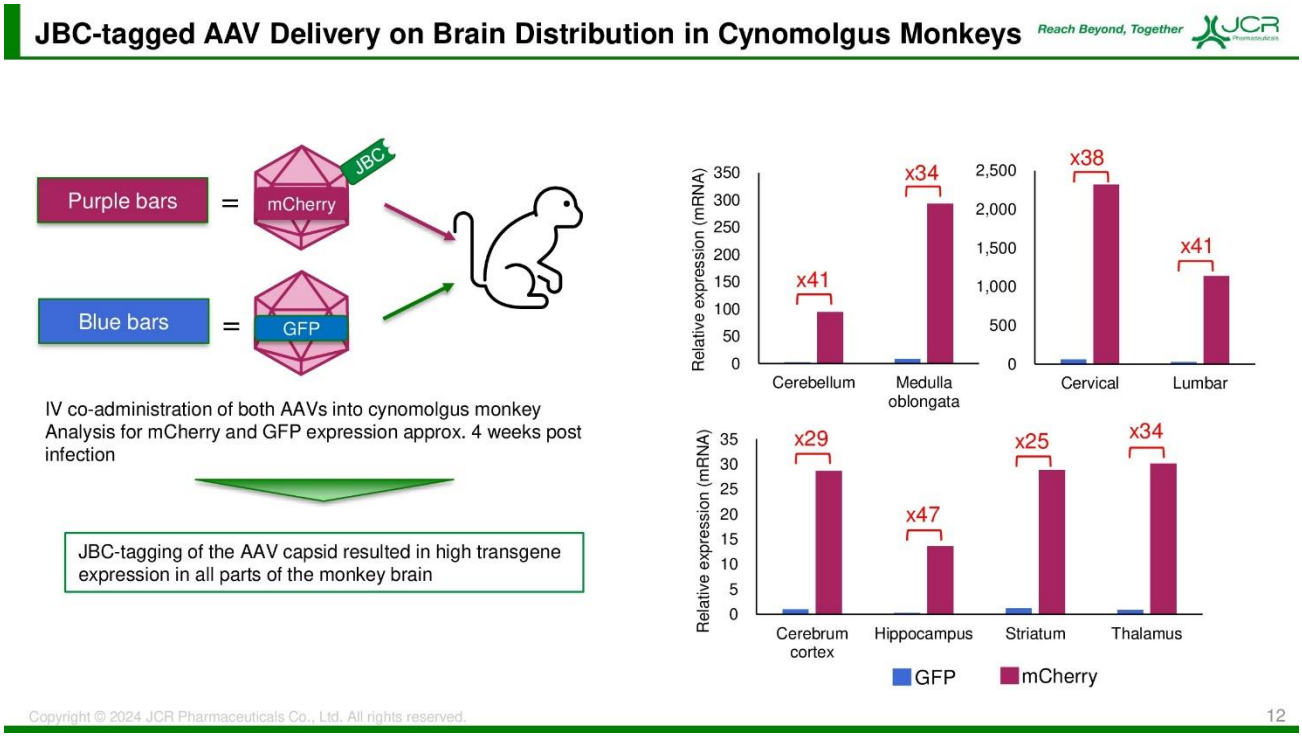
The brownish color is a positive signal, a signal that the protein of interest is expressed and present there.

This is really obvious at a glance. Untreated shows no brown-staining at all. Of course, since we have not been treated with anything, this will be the norm for this data. The AAV9 in the middle is not stained either. There are cases often stained with AAV9 in papers, etc., but when comparing AAV9 and Untreated, this is due to the difference in staining methods, but since the intensity can be increased or decreased, if you keep increasing the intensity, you may be able to see the difference between Untreated and AAV9.

However, in this case, the staining was done in accordance with our new AAV staining, so in that case, there was almost no difference between AAV9 and Untreated.

On the other hand, as for the new JBC-AAV with J-Brain Cargo applied, as you have seen, the brown signal is very darkly tinted, and I think you can see it throughout the brain. This means that the gene is not only expressed in one part of the brain, but in the entire brain.

This is exactly the same pattern of expression of the transferrin receptor. This is consistent with the brain localization patterns we have seen in protein development.



Second, this is the data with monkey.

Testing in primates is very important in the development of gene therapy vectors. It has often been the case that even when we have succeeded in developing very good vectors in mice, they are not applicable in primates equally. We do not mean that this is our case, but rather that such cases have been observed in various studies around the world.

So as soon as we get good results with mice, we want to confirm them with monkeys, so we are conducting experiments on monkeys.

In this case, we put different reporter genes on the previously mentioned AAV9 and our new AAV, and administered both intravenously to the monkeys at the same time, at a single dose, to see how each protein reporter is expressed in different parts of the brain.

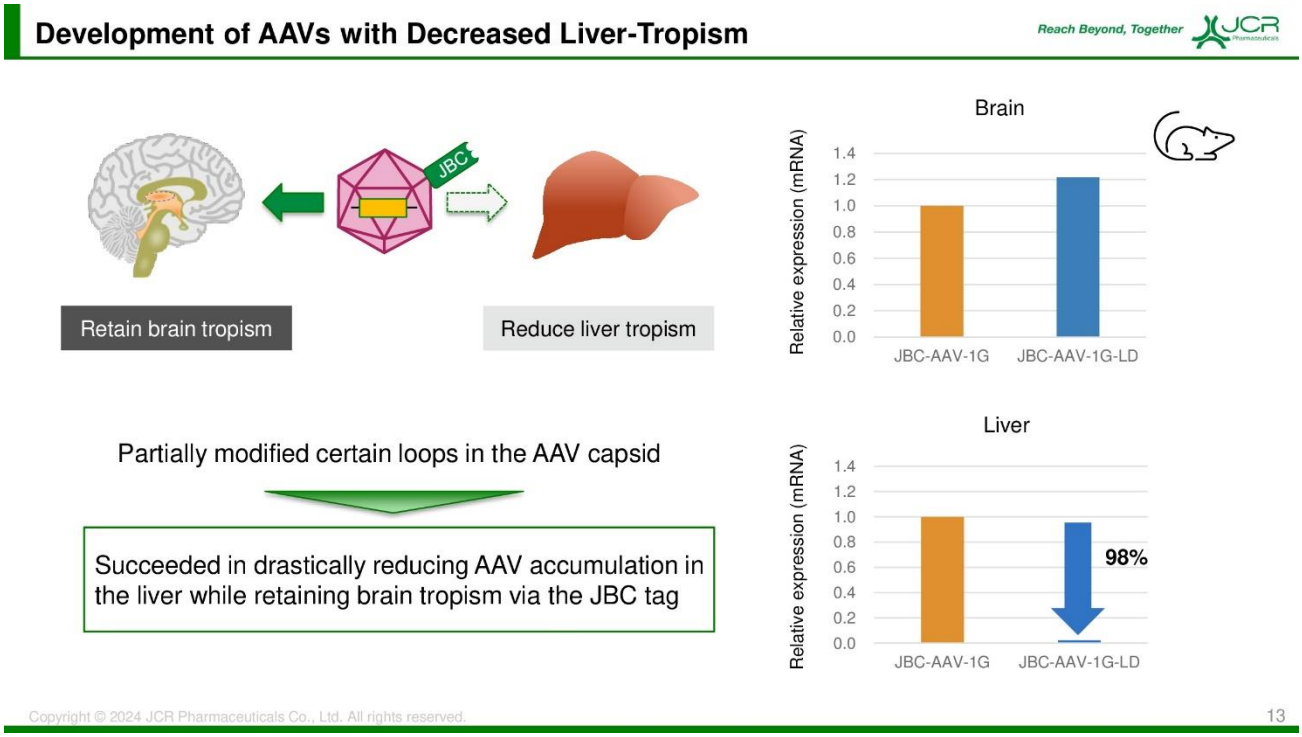
The pink bar, this is our new vector. The blue bar, this is the AAV9 data that has been commonly used. The bar graph on the right, this is a graph with plotting of the actual measurement, and the horizontal axis shows the various regions of the brain.

I think this is also really obvious. The blue bar is almost invisible. The pink bars show very high expressions. So, the newly developed AAV vector is working very well also in monkeys.

This figure shows the difference in expression levels and the ratio of expression compared to AAV9, but what is important here is that the increase seen in mice and the increase seen in monkeys are very similar in terms of the ratio.

This is very important because we have designed AAVs using transferrin receptors and, as I mentioned earlier, using validated platform technology, so to some extent, this was an expected result. We think it is very important that mice and primates, monkeys, show similar directionality to the brain and the transfer rates to the brain.

This means that the results obtained in monkeys would be highly predictive, predictable, that this would be the case in humans, so we think it is a very important point that the same level of expression was observed and seen in mice and in monkeys.



We have succeeded in developing vectors that increase directionality to the brain, and the next step is the side effects I mentioned earlier. We had been working on another research project to somehow solve that problem. That would be to reduce its accumulation in the liver. On the other hand, we want to maintain the directionality to the brain.

Therefore, after intravenous administration, we increase the amount that goes to the organs we want it to go to, which, in our case, is the central nervous system, including the brain, but reduce the concentration in the liver, where side effects can occur. If this can be accomplished, the issues just mentioned will be resolved to a large extent.

The technology that does not make drugs accumulate in the liver was developed as a separate technology from the J-Brain Cargo technology I mentioned earlier for transfer to the brain, and we mixed it in the AAV. The actual data is on the right. This is the data with mice.

The orange bar indicates a vector that has increased its directionality to the brain, but has not taken any action to address the effects on the liver. In case of Brain, in the upper graph, the distribution is of course high. But, in the lower graph, it is indicated as Liver, the drug is also accumulated to some extent in the liver.

Here is the AAV with a modification that prevents it from going to the liver, which is the blue bar, and when this is administered, we are able to maintain the migration to the brain. But below that, we are able to greatly reduce the accumulation to the liver. If we can accomplish this, we can greatly expand the window of drug efficacy and toxicity that I mentioned earlier, so we can increase the transfer and directionality to the brain, and then lower the accumulation in the liver, where side effects are more likely to occur. This is what we are now achieving with mice.

Substrate Reduction in the Brain of GM1-Gangliosidosis mice

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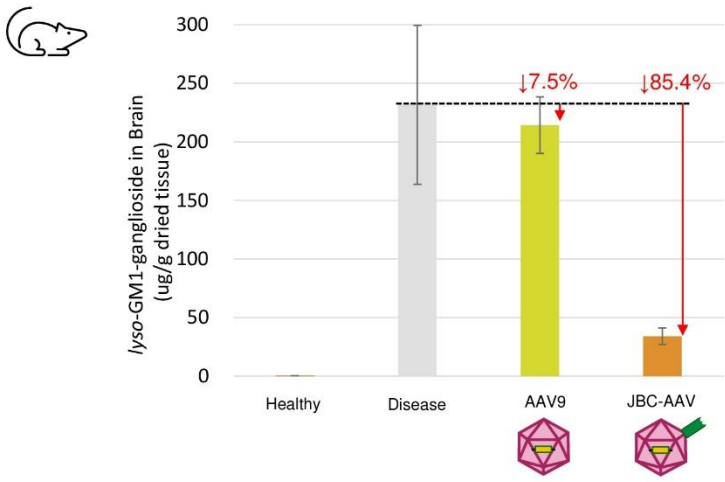


Only JBC-AAV decreased the accumulated substrate in the brain

In fact, using the new AAV vectors we have developed, we have used a mouse model of a certain type of lysosomal storage disease to investigate the efficacy of the drug, since our main target of research and development is lysosomal storage disease.

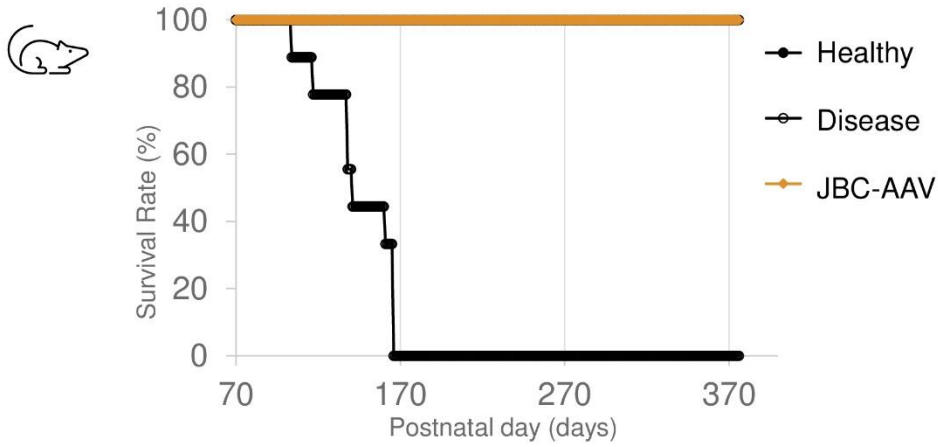
The first case is a disease called GM1 gangliosidosis, which is a lysosomal storage disease that causes a large amount of substrate, a kind of garbage, to accumulate in the brain. The extent to which this waste can be reduced is seen as an indicator of the drug's effectiveness.

The leftmost bar in this graph, this is the data with healthy mice, so the bar is very low because there is no garbage in the head. Next to it, the second from the left, is the disease model, which means that this is how much garbage accumulates in the brain. The third yellow bar from the left is mice with AAV9. This is the group treated with the conventional vector that is commonly used today. And on the far right is the group treated with our new AAV vector.

The amount of waste reduced is indicated there as a percentage, in numbers. I guess this is also very clear data, but it shows a 7.5% decrease in the case of AAV9, and an even larger decrease when using the new AAV. This means that only the new vectors that I showed you earlier are efficiently reaching brain and efficiently expressing proteins from the genes.

The same thing is thought to be happening in this mouse model of GM1 gangliosidosis, which is why we suppose it is showing these drug effects.

Survival in a Mouse Model of a Lysosomal Storage Disease



Gene therapy with JBC-AAV significantly improved life span

Another type of test was conducted using another mouse model of a lysosomal storage disease.

This is yet another model mouse, not the GM1 gangliosidosis mentioned earlier. In this case, we are evaluating survival rates. This model is very severe, with all mice dying in less than six months. We are testing a new AAV that we have developed, in which the causative gene is placed on the AAV and administered intravenously once, to see how the survival rate changes.

The black line shows the disease model, and it says roughly 170, and all the mice will die around there. On the other hand, the yellowish brown color is 100% running, so there is only one straight line at the top, but that is the group treated with our new vectors.

As I mentioned earlier, the reduction of the amount of litter in the mice's brains differs considerably, and this is another model mice group that shows such a difference in life span as a phenotype of the results.

This is very important data, because it shows that the AAV reaches the brain, expresses the gene, shows a therapeutic effect there, and then, as a result, there is a life-extending effect.

Next Generation JBC-AAVs Achieve Higher Gene Expression in the Brain

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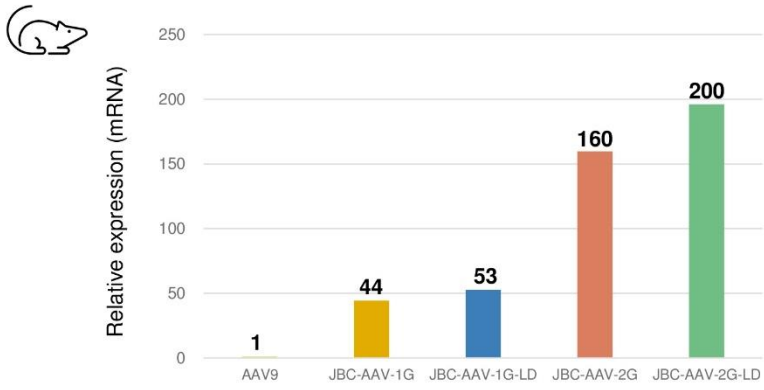


While data disclosed in this deck were obtained with JBC-AAV-1G, next generation capsids already **achieved ~200 fold higher brain expression** in mice than wtAAV9 capsids

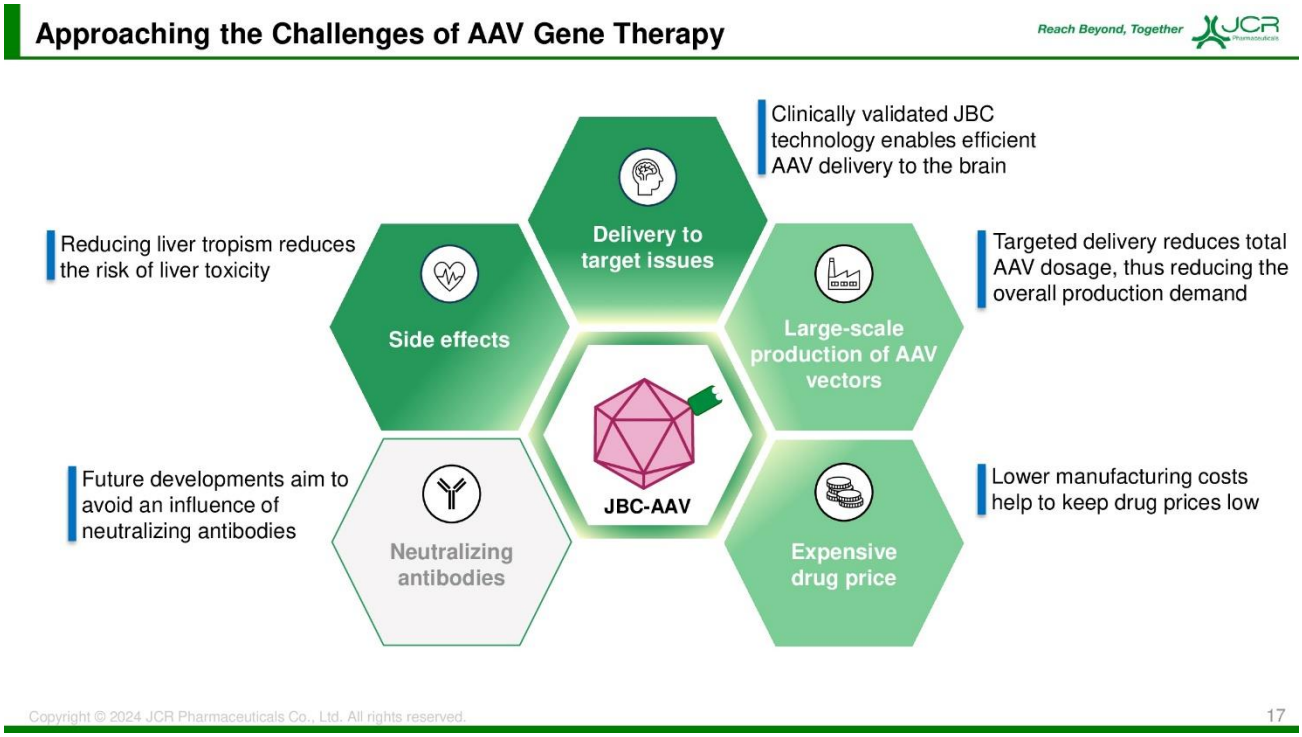
Next, this is the result of model mice, but figures showing further improvement of the now new AAV vector.

The numbers indicate how much is being transferred to the brain, and by what factor, compared with AAV9.

There are many different colored bars, but the first one marked 44 is the first-generation AAV with the J-Brain Cargo, which has enhanced the transferring to the brain. We consider this to be 44 times, or roughly 50 times enhancement. The blue color next to it is the AAV that I mentioned earlier, which includes together the technologies that do not make the drug accumulate in the liver. It means that the transition rate is a little better.

Next to it, in orange, is what we call the second-generation AAV. This is roughly 160 times enhanced. And there, using the technique described earlier that does not allow accumulation in the liver, is about 200 times enhanced, shown in green on the far right.

Therefore, the best mode we have achieved in mice is approximately 200 times more efficient than AAV9 in delivering genes to the brain.

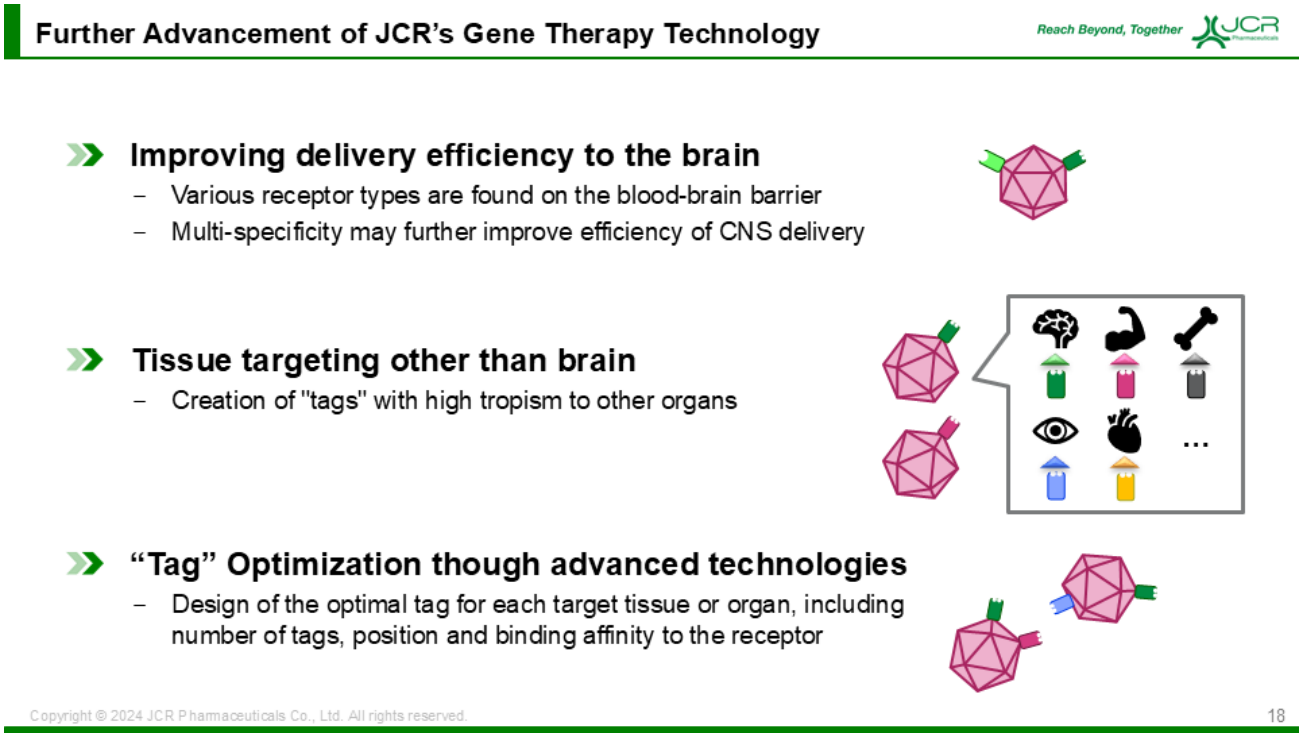


I've shown you some of the problems, and this slide shows you how much we were able to approach each of these problems with the new vector.

Regarding the delivery to target issues, as you saw the data today, we have been able to greatly increase the rate of delivery to the central nervous system. Also, regarding side effects on the left, I think we have been able to greatly reduce the degree of accumulation in the liver, and so greatly reduce concerns about side effects.

Increased delivery rates to target organs means that we may be able to see therapeutic effects at lower doses than previously possible. If this is the case, then even if we do not need to mass-produce so many vectors, we may be able to see therapeutic effects, and I believe that new vectors will make a certain contribution here as well.

If the manufacturing cost can be reduced, it will have a great impact on the price of the drug. We believe that we have succeeded in creating a new vector that can make a significant contribution to more efficient targeting of the central nervous system and lower accumulation in the liver, which is the biggest concern about side effects.



We believe that many more points can be improved, and here is a list of possible ways to do so.

The first is improved targeting efficiency to the brain. As I have already shown, we have achieved efficiencies of up to 200 times, and I believe we can raise this even further.

I believe there are several methods; we are developing a technology that basically uses transferrin receptors, but there are other receptors in the blood-brain barrier. I believe that by making use of such things, we may be able to overcome the efficiency barrier that was not overcome by transferrin receptors.

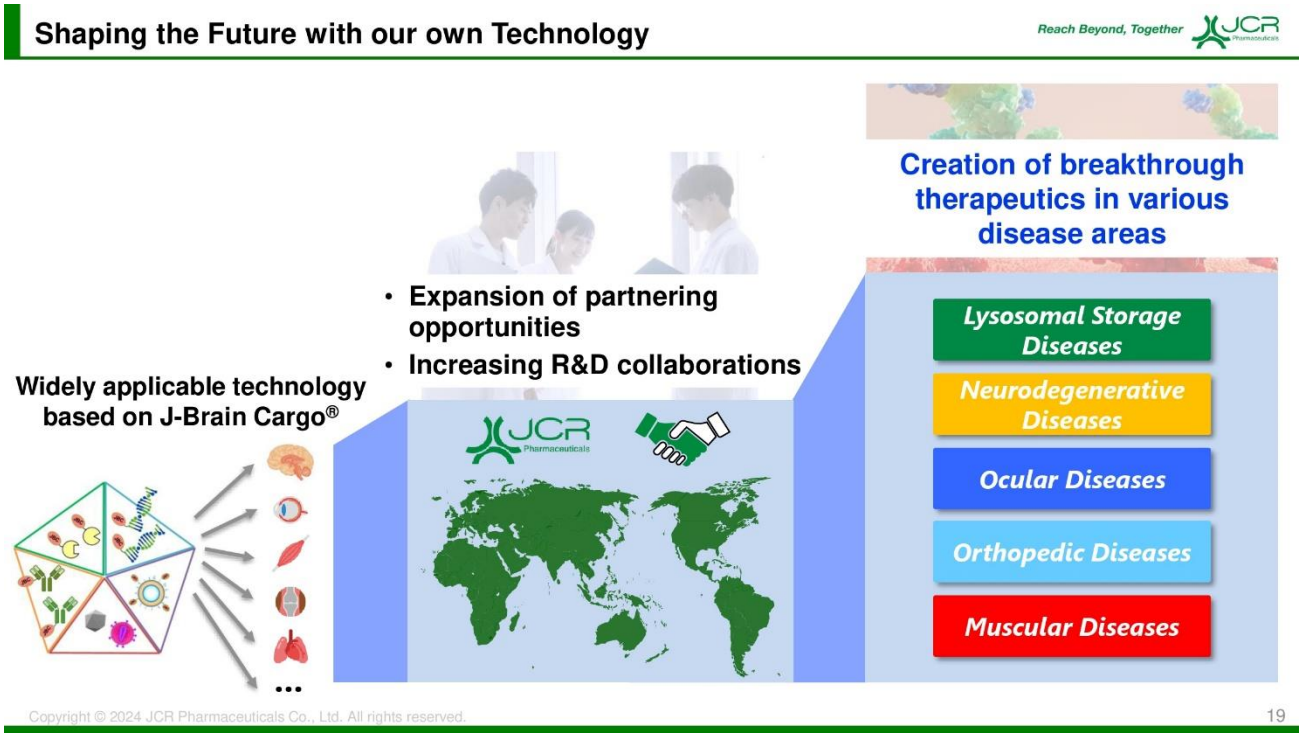
Second, targeting to tissues other than the brain. Of course, the central nervous system is a very important target in gene therapy, and it is the tissue responsible for many diseases, but I believe that other tissues besides the brain will also be important.

We believe that the greatest advantage of our AAVs is that we can design and build it. Instead of using evolutionary engineering, in which mutations are inserted in a treasure hunt-like manner and organs are found afterwards, tags can be created logically and placed on the surface of the AAV while designing the tags, allowing targeting to specific tissues. This means that if the tag is validated, AAV delivery will be much more reliable.

Therefore, I believe that it is possible to create new AAV vectors with targeting ability to tissues other than the brain using this kind of technology.

The third one is a bit similar to what I just mentioned, but it describes the know-how and base technology to optimize each of them. We have been developing technologies for crossing the blood-brain barrier for many years, and I believe that optimization and fine-tuning of these technologies are very important. The same is probably true for AAVs, which will need to be optimized and adjusted to improve the performance of the AAV as a whole.

Simply adding tags is not enough. We think that optimization after adding them is very important. It shows that we have the know-how, experience, and technical capabilities to make such things possible.



This is the last slide.

Today we mainly talked about gene therapy, but we would like to apply J-Brain Cargo and tissue targeting technology to various modalities.

In our clinical pipeline, there are many enzyme drugs that use J-Brain Cargo's technology, but there are also antibody drugs, nucleic acid drugs, and, in the leftmost picture, lipid nanoparticles, LNP. And gene therapy; this platform technology can be applied to a variety of modalities. Today, we have presented data on one of those gene therapies.

Therefore, we would like to establish a technology that can target various tissues to various modalities, and if we can do that, we can cover a wide range of diseases. We will use such technologies to develop rare diseases, and for indications that have a very large scope, we would like to promote partnerships with other companies and link them to drug discovery.

That is all from me. Thank you.

Question & Answer

Moderator [M]: We will now move on to the question-and-answer session. Due to the limited time available, questions will be limited to the one related to this meeting only.

The question method is shown on the screen. When it is your turn to ask a question, I will nominate you. Please state your name and company name first, and then ask your question. Please note that questions will be asked in a question-and-answer format, with a limit of two questions per person, but you may raise your hand as many times as you like.

We will now begin the question-and-answer session. First, Mr. Yamaguchi, please ask your questions.

Yamaguchi [Q]: Thank you very much. I am Yamaguchi from Citi. I have two questions.

First of all, I am afraid this is an amateur's question, but you have developed a technology that does not deliver to the liver, and on the other hand, you have also developed a technology that does deliver to the liver. Is it correct to understand that your company's technology has reached the point where you can basically control AAVs regarding delivering to or not delivering to the liver?

Sonoda [A]: Thank you for your question. I am not sure which technology you mean that delivers to the liver.

Yamaguchi [Q]: Didn't you say at the end that you were targeting the liver?

Sonoda [A]: That is not the liver, but a technology that can target various other tissues. For example, muscle tissue, cartilage, and so on.

Also, maybe that picture of the heart looks like the liver.

Yamaguchi [Q]: I understand. I will change the question. Is the technology that does not deliver the drug to the liver almost ready?

Sonoda [A]: Yes, that's right. As I showed you today, I think we have almost completed the process, and since we have made several AAV vectors, not just one, we will test various combinations to see which one matches best among AAV vectors, such as the first or second generation, as I mentioned earlier, to determine which is the best mode.

Yamaguchi [Q]: I understand. And secondly, you explained about gangliosidosis, and first of all, will you be using this technology for gene therapy against lysosomal storage disease? As an internal pipeline?

Sonoda [A]: Of course, we do not deny the possibility of its use against lysosomal storage disease, and I think the disease is our core, or rather, main target. So there is a significant possibility, I guess.

Lysosomal storage disease is a disease that can be easily cured or treated by the bystander effect, which means that when a gene is inserted into one cell, the product made by that cell, a protein – which, in the case of lysosomal storage disease, is an enzyme -- also contributes to other cells around it. In this sense, I think lysosomal storage disease is an important target.

In some cases, lysosomal storage disease is caused by a deficiency or abnormality of something other than enzymes, such as transporters or cofactors. In these cases, these are no bystander effects as I mentioned earlier, but these diseases could not be treated by conventional methods such as enzyme replacement

therapy, for example. The AAV will be able to cover and treat such diseases, so lysosomal storage disease will be well within our target category.

Yamaguchi [M]: Thank you very much.

Moderator [M]: Thank you. Now for the next question, Mr. Muraoka. Thank you.

Muraoka [Q]: Thank you very much. This is Muraoka from Morgan Stanley. My question is why JBC-AAV is an AAV vector.

I think this is a great technology, but the fundamental problems that AAVs have are that their persistence of effects are doubtful, and they cannot be used for treatment for a second time, or cannot be used for retreatment. I have a question whether these problems can be solved here when it comes to this JBC-AAV.

Furthermore, I imagined that if you use this JBC for another vector, for example, Lenti, or something like that, it would be possible in such a case, or something like that, but what is the background of your choice, AAV? Are there any other vectors you are considering, and do you think you might be able to come up with a better answer? Please tell me about this point.

Sonoda [A]: Thank you for your question. I thought the big question is why AAV, since there are probably other companies using AAV, or various other cases.

We believe that AAV is a very good vector among gene therapy tools. I'm not sure there is a better vector than AAV, at least at this time. Lenti is of course possible, but systemic administration is difficult, and when it comes to vectors that can be administered systemically and have a certain level of persistence, AAVs are inevitably the way to go.

Sustainability, there are certainly cases where sustainability is not seen, or where it is not possible to do a shot twice. This is a problem that will have to be solved in the future, and we do not believe that using J-Brain Cargo at this time will solve this problem.

Therefore, we do not believe that all problems can be solved by this technology. Just that it can solve that part of the many problems we talked about today.

Muraoka [Q]: Thank you. One more thing, this technology, I will be partnering with probably a lot of people at JBC-AAV, but if I were actually on the company side of gene therapy, I would say, no, the case is still mice and monkeys. I was thinking conservatively, "Please show us the results in human beings, otherwise we will think that we don't want to use them ourselves."

I just imagined that the negotiation would be something like, "Please do a clinical trial with JBC-AAV for lysosomal storage disease, and if it works, we'll be on board." Should we consider the possibility that partnering will take time because of such a situation? Or is that just an imaginary story that is totally out of line?

Sonoda [A]: That is a very difficult question to answer because it is not our problem. It is, of course, impossible to say that it is never a possibility, and so it is difficult to say whether there is a high possibility or not.

However, at least in the discussions we are having with our partner now, it's not the case that we have to have human results. However, monkeys are still often required.

Muraoka [Q]: I see. I'm sorry, I repeat, same as Mr. Yamaguchi's question earlier, let's just do a quick clinical trial with JBC-AAV on this lysosomal storage disease, let's do it by ourselves. To have proof of concept, is this idea quite a high priority?

Sonoda [A]: Yes, I think that is quite possible. However, as I mentioned earlier, in the case of lysosomal storage disease, there is a bystander effect. So, if our vector is compared with other vectors head to head, we think we can make a very strong statement. If not, we will need to examine each disease individually. I think that we can talk about safety on the same standpoint, but I don't think that it will be a simple argument to say that because it worked for lysosomal storage disease, it will work for other diseases, such as Alzheimer's disease, or that it will work with this.

Muraoka [M]: I understand. Thank you. That's all.

Moderator [M]: Thank you. Now, the next question, Mr. Mizuno, please.

Mizuno [Q]: Thank you very much. What I didn't understand about the basic point at the very beginning of the presentation, do you mean, regarding to tagged AAV, you produce the AAV itself? Or are you going to tag the AAV? I'm not sure I understand about that point.

Sonoda [A]: Thank you for your question. Sorry, maybe I did not explain it well. This does not mean we add the tag afterward, but rather the AAV itself has been tagged when it is produced. So, for example, AAV9 is generally created in a laboratory by buying vectors and transfection, which is not so difficult.

For example, if you add tags after you've made the AAV, the manufacturing process itself becomes very complicated and difficult. So instead of doing that, what we're doing now is using a technique where we put the designed capsid inside the plasmid, which is a substance that carries genes, when we perform transfection. The design means a protein in the form of this tag on the surface. By putting it and then transfecting it, the cells produce this AAV. The product that is produced is something like shown here in the middle, and the complete product is formed.

Mizuno [Q]: If so, I think this is a very advanced technology, but one of the problems with AAV gene therapy has been the problem of empty capsids, and I wonder if you have been able to prevent, block, or reduce the percentage of empty capsids. Or is it possible?

Sonoda [A]: Thank you for your question. That's correct. As for empty capsids, it's been a problem in terms of quality for AAV, and I think that the current situation is such that various AAVs are being queried by the regulatory side, with more and more demand for higher quality AAVs as the days go by.

We are, of course, focusing on the development of new AAV vectors while also taking care of these issues, so we are able to reduce empty vectors to the same level as commonly used AAVs, and produce products even in terms of quality without any problems.

Mizuno [Q]: Thank you very much. Lastly, CD98 has been mentioned recently in addition to transferrin receptors, but how is this compared to transferrin? Does your company also have it in the library?

Sonoda [A]: This is only an answer based on papers or information that is generally available, but CD98 has often appeared recently, and I think it is being used.

It is a completely different receptor from the transferrin receptor. It is expressed at the blood-brain barrier, and there are reports that this can be used for BBB crossing technology by using the CD98 binder in the same way as the transferrin receptor.

I am sorry, but I cannot tell you whether we are using this or not here.

Mizuno [Q]: I understand. Which is better, or is it up to future development?

Sonoda [A]: Yes. I believe that some papers have found this to be the same level of transferability, and it would be good to use it differently, depending on the modality and purpose.

Mizuno [M]: I understand. Thank you very much.

Moderator [M]: Thank you. Next, Mr. Tsuzuki, please ask your question.

Tsuzuki [Q]: I'm Tsuzuki, Mizuho Securities. Thank you. I, too, have two points. First, I wanted to know how to deal with disease areas with J-Brain Cargo. You also mentioned lysosomal storage disease, but I guess there is a viewpoint that it would be more interesting to go into a different area.

In terms of assay systems, I think there are some diseases that can be established a bit in mice and monkeys, so is this where your company's first priority is? Lysosomal storage disease? Or are you thinking of different areas underfoot as well? I would like to know what it's like around there.

Sonoda [A]: Thank you for your question. As I mentioned earlier, lysosomal storage disease is an area of focus for us, and with model mice and assay systems already in place, it is an easy disease to tackle and evaluate.

So, for example, when a new vector is developed, our researchers can easily access it for evaluation, and if they do, they can obtain some results, and when they see the results, they can develop the vector. That is quite possible to happen, isn't it?

Apart from that, as for lysosomal storage disease, of course, our intention in developing this vector was not to look only at lysosomal storage disease, but to cover diseases that cannot be cured by enzyme replacement therapy because of the technology to deliver the gene. I mentioned earlier that some lysosomal storage diseases cannot be cured by enzyme replacement therapy, but only by gene therapy, especially except for lysosomal storage diseases. Because we believe that the development of this technology is precisely to cover areas other than lysosomal storage disease.

The answer to Mr. Tsuzuki's question is yes and no, but I would say that we are looking at both perspectives, we are conducting research and development.

Tsuzuki [Q]: Thank you very much. One more point: I think there is a point of view that is a little difficult when deriving the technology. With other companies, for example, it says that a mutant of the target AAV was found through random mutation, but I think that your company has been very particular about the number of tags to be incorporated, their positions, and so on, using various kinds of know-how. Including maybe agglomeration and how to pull out the empty capsid, for sure.

If this is the case, when licensing out the technology, it will be necessary to include plasmids or DNA for other diseases, which will also require some technical know-how and accumulation of know-how. So it would be necessary for your company to help a lot, but I wonder if you have a viewpoint of what you can do in this area, or if you are considering licensing out the technology after taking this into account. I hope you could tell us about these points.

Sonoda [A]: Thank you for your question. As for this AAV, when we want to target a different disease, for example, we need to change the genes that are incorporated into it. However, the surrounding outer AAV itself can be the same. As I mentioned earlier, there are, of course, cases of fine-tuning, but even so, the most

significant feature of this gene therapy is that it can be applied to all patients, simply by changing the genes that are included, which is called GOI.

So, I think it is not zero that we have to redo it, but it is not such a big part of it. Once we find the best one, we can try changing genes to it first. If we can achieve sufficient efficacy there, we will go ahead and do it. If that is too difficult, we may try modifying it a little or changing to a different tag, but I do not think that we have to start from scratch every time.

Tsuzuki [Q]: I see. With your company's current technology, the ratio of VP1 and VP2 will not change that much when the genes inside the product are changed, so it is not possible to make any particular difference. That is the level we should understand, right?

Sonoda [A]: Yes. If the gene length fits within the AAV, there is no problem in considering it as such.

Tsuzuki [M]: I understand very well. Thank you.

Moderator [M]: Thank you. We regret to inform you that our time is nearly over and only two more people will be allowed to ask questions.

Now, the next question, Mr. Kawamura, please.

Kawamura [Q]: Thank you for your explanation. I am Kawamura of SBI. I will only ask one more question in short.

I think that it is a very amazing technology. On the other hand, looking at the trend of genome editing, there are groups that are working in a very directed manner with messenger RNA and lipid nanoparticles, and they seem to be making a lot of progress.

I'm wondering how your company's technology compares to these areas, and why, from the outside, it seems that the out-licensing process is a bit stuck, or doesn't seem to be making any progress. I wonder what kind of evidence would make the other side more receptive, and if the industry needs to get excited, and therefore if there are not enough people who can evaluate these things in the first place. If there are any bottlenecks or challenges, from your point of view, would you please inform us about them? That's all.

Sonoda [A]: Thank you for your question. First of all, comparison to LNP. I think this is much stronger for AAVs in terms of their ability to express genes. But as to which is easier to do as a pharmaceutical company, including CMC, I think that really depends on indications.

In the case of LNP, it inevitably depends on the duration of the messenger, and although duration was mentioned earlier, I think AAV is definitely stronger in terms of persistence, and AAV is also stronger in terms of the amount of expression. I just wonder which is better for manufacturing and CMC, so I think it really depends on indication.

Also, you mentioned that the out-licensing part doesn't seem to be very active, but I think that this really takes time, to some extent, regarding technology licensing. When selling assets, I think it is sufficient just to evaluate the asset, but in the case of technology, it is necessary to combine the asset with something else, especially in this case, evaluating it with mice or monkeys, for example, and if it is not in the best mode, then it may go back and forth again.

In this process, we work together to create something that has the desired performance, and that is how we reach out-licensing. It is such a process, and it will inevitably take time.

In fact, there are cases where we are actually doing such tests now, in which we are not open to the public, but inevitably, especially when we incorporate animal tests into that, we cannot roll fast enough to speed up the growth of the animals, so it inevitably takes a long time there.

However, you are right, we will try to speed up the process of out-licensing as soon as possible somehow.

Kawamura [M]: All right, that's all. Thank you.

Moderator [M]: Thank you. Then, the next question will be the last. Mr. Yamakita, please go ahead.

Yamakita [Q]: My name is Yamakita from Jefferies. Thank you. I'll have two questions quickly.

First, regarding your company's entry into Phase I of the in-house process. You mentioned that the second generation has 200 times the brain transferability compared to AAV9. Are you aiming to enter Phase I using second-generation technology? Or have you already been preparing with the first generation, or are you going to create the third generation before entering Phase I? In terms of the technology to use for clinical trials, how do you think about these points?

Sonoda [A]: Thank you for your question. I think this also depends on indication here. For example, if it is determined that the first-generation drug is sufficiently effective, we will probably proceed with the first-generation drug. If not, we need to use the second generation.

In fact, if it is concluded that the second generation is better because the dosage can be lowered, the second generation may be used, even if the first generation is sufficient. We will decide which to use based on the result of animal experimentation. This is true in our case, and I think it will be the same in the case of out-licensing.

I think it is important to have various options like this.

Yamakita [Q]: Thank you very much. The second question, I think there was a point in the mouse study where the transfer to the brain was 65-fold against AAV9 while the expression was 20-fold, but is the expression fold lower than the transfer fold because the tagging may affect the expression fold? Or is this not that much of a difference to be concerned about?

Sonoda [A]: The latter is right. The answer is that there is no need to be concerned. As a vector, this means that once the gene is in, its expression is also highly dependent on the strength of its promoter. We are modifying the AAV itself so that it does not affect the efficiency of infection or the ability to express or do so, so the ability there is the same. We would like to make more and more efforts in the future to further increase that value, but that is not the reason for this difference between 65 and 20.

So, as for 20, the drug is also administered with a promoter or gene inside, and if the sequence is manipulated, this number can be changed.

Yamakita [M]: I understand very well. That is all from me. Thank you.

Moderator [M]: Thank you. I would like to inform you that due to time constraints, this is the end of the Q&A session.

This concludes the R&D meeting of JCR Pharmaceuticals. Thank you very much for your participation today.

[END]

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