Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

A member of the Roche group

# CHUGAI PHARMACEUTICAL CO., LTD.

Company Briefing for Individual Investors (Antibody Engineering Technologies)

June 30, 2023

# Event Summary

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| **[Participants]** | |
| **[Number of Speakers]** | 2<br>Dr. Osamu Okuda President and CEO<br>Dr. Tomoyuki Igawa Head of Translational Research Division |

## Presentation

**Moderator:** Good evening. Thank you for joining us for today's online information session for CHUGAI PHARMACEUTICAL CO., LTD.

Today's speakers are Dr. Osamu Okuda, President and CEO, and Dr. Tomoyuki Igawa, Head of Translational Research Division. Thank you.

**Okuda:** Thank you.

**Igawa:** Thank you.

**Moderator:** Dr. Okuda, I understand that in today's briefing, you are going to talk about CHUGAI's strength in the field of antibody therapy.

**Okuda:** Yes, that is correct. We have previously given briefings where we present an overall picture of CHUGAI's strengths to individual investors.

Today, we would like to take a closer look at antibodies. This area is a unique attraction and strength of CHUGAI. We have spent the past 20 years developing our antibody technology. Today, Dr. Igawa, who leads our development of antibody technology, is going to give an easy-to-understand explanation about our work in the area.

**Moderator:** Dr. Igawa, we are looking forward to your talk. Thank you.

**Igawa:** Thank you. Today, I would like to explain this complex antibody technology for a non-scientific audience.

**Moderator:** We will come back to you a little later.

First, Dr. Okuda will give an overview of CHUGAI for those who are unfamiliar with the Company. Next, Dr. Igawa will introduce the antibody technologies that CHUGAI has developed as one of its strengths. Afterwards, we will hold a real-time Q&A session to answer any questions you may have. The entire briefing is scheduled to last 45 minutes.

Dr. Okuda, over to you.

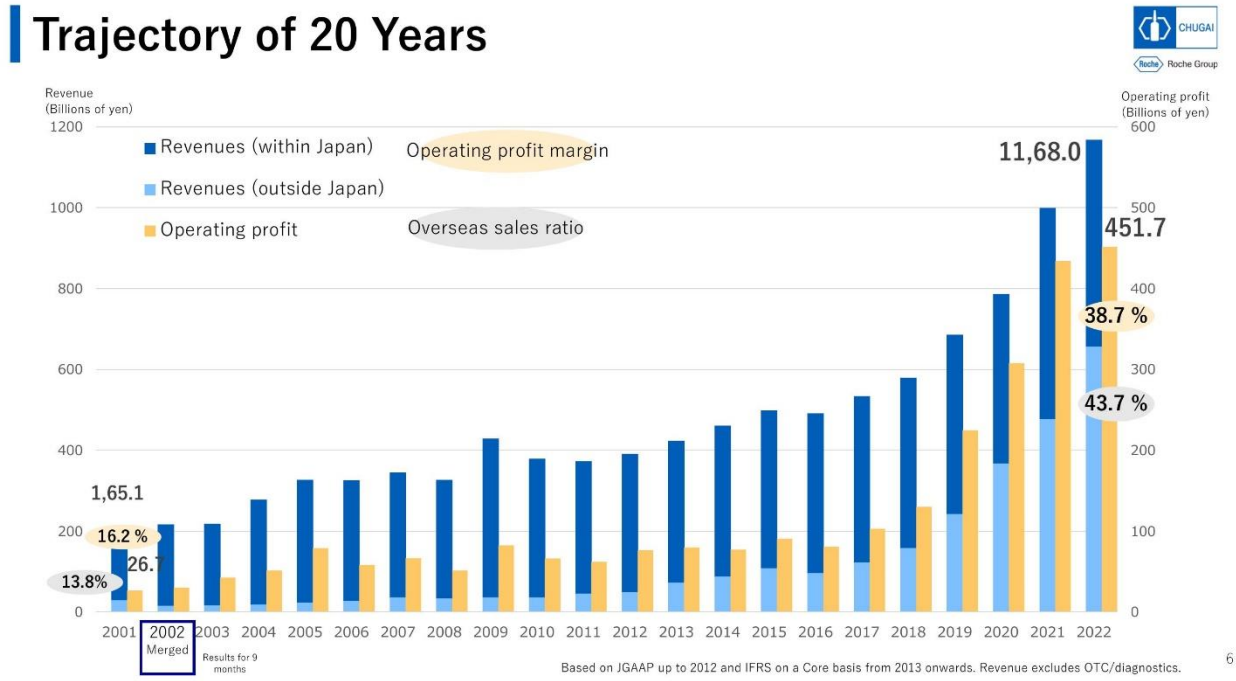

**Okuda:** Thank you.

First, an overview of CHUGAI. CHUGAI is an R&D-driven pharmaceutical company, with strengths in oncology and biotechnology. In Japan, we have maintained the number one position in the field of oncology and in the market share of antibody drugs for many years. We have formed a strategic alliance with Roche, a global pharmaceutical company. We have a unique business model based on this. We will discuss this a little later.

Our company is proud of its strength in drug discovery technologies, including antibodies.

**Moderator:** Thank you for the overview.

I understand that CHUGAI has achieved dramatic growth in recent years.

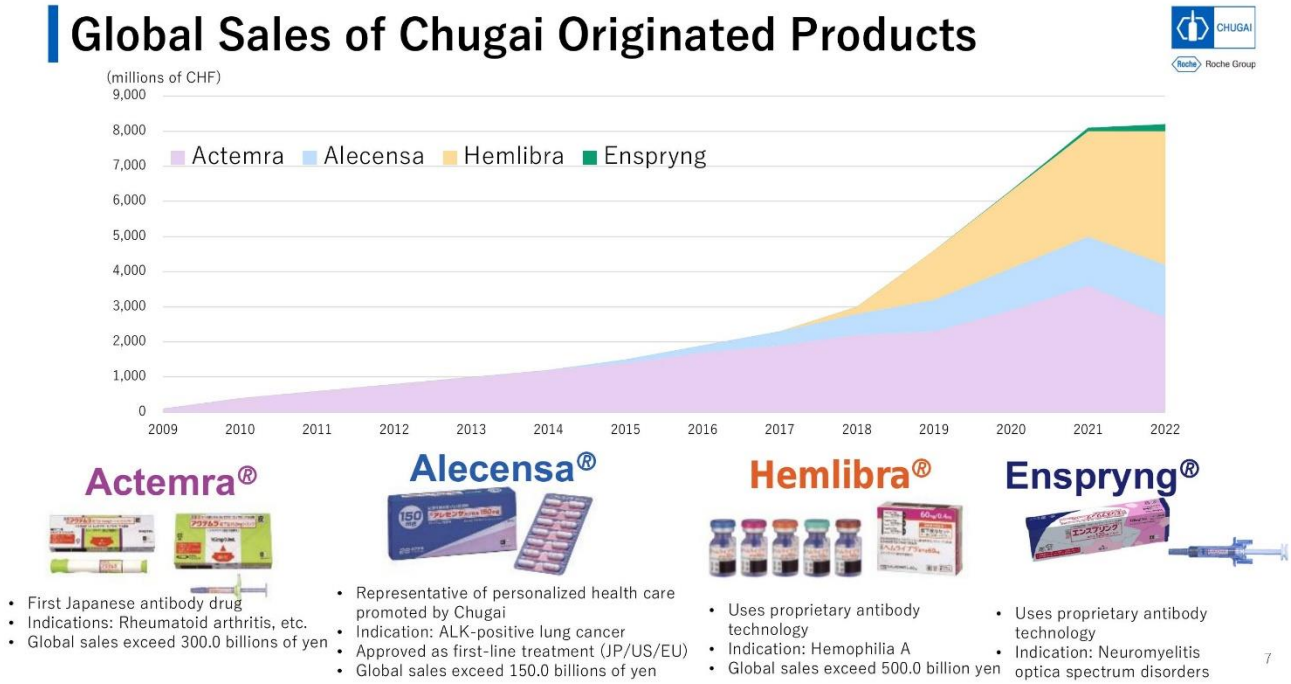



**Okuda:** Yes. Please take a look at this graph.

In 2002, we entered into a strategic alliance with Roche. Since then, sales have steadily grown and revenue have increased. Since 2018, operating profit has increased dramatically.

Looking back over the past 20 years, revenue has increased approximately sevenfold and operating profit has increased approximately 17-fold.

**Moderator:** Looking at the graph, we can indeed see a constant, steady increase. During the period when business in Japan was struggling, the so-called "lost 30 years," why were you able to achieve such growth like this?

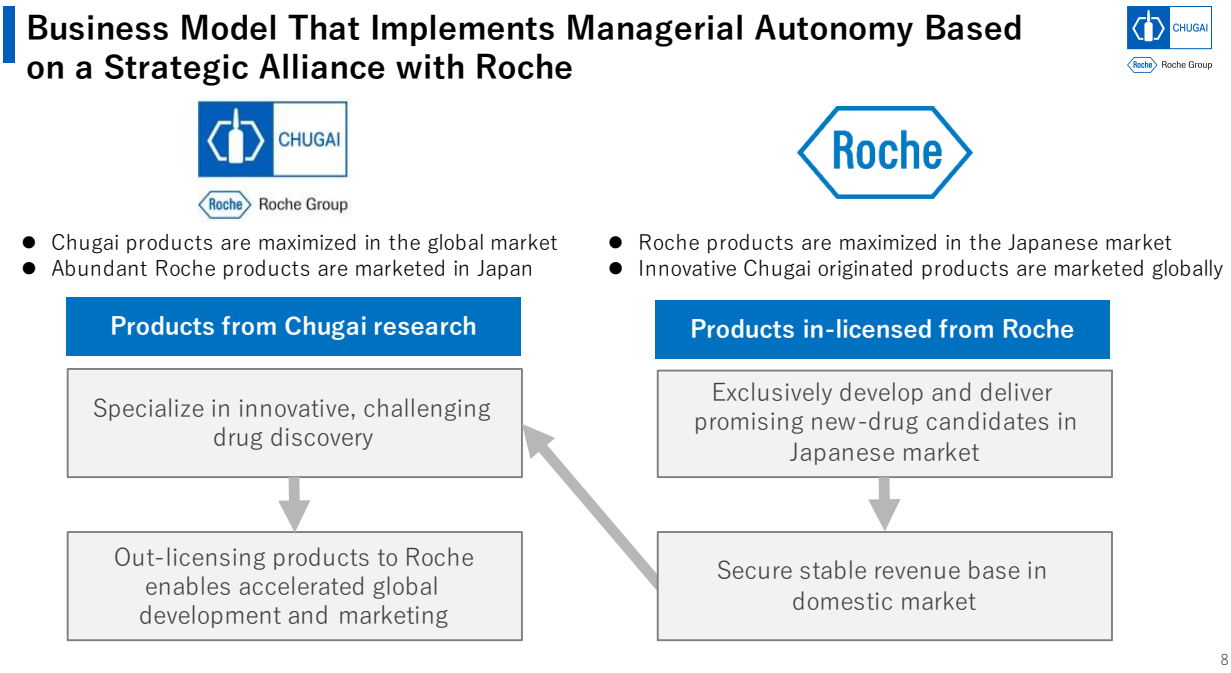



**Okuda:** As you can see from the next slide, the biggest driving force was the development of breakthrough drugs by CHUGAI, which drove global growth. We now have four in-house-developed pharmaceutical products that are sold around the world, as shown here.

The Company sells its products worldwide through Roche, with annual sales exceeding JPY1 trillion. Hemlibra, in particular, the second product from the right, has worldwide sales of over JPY500 billion. It is CHUGAI's largest growth driver.

Together with Actemra and Enspryng, which are shown here, these three are the antibody drugs that are the subject of today's discussion.

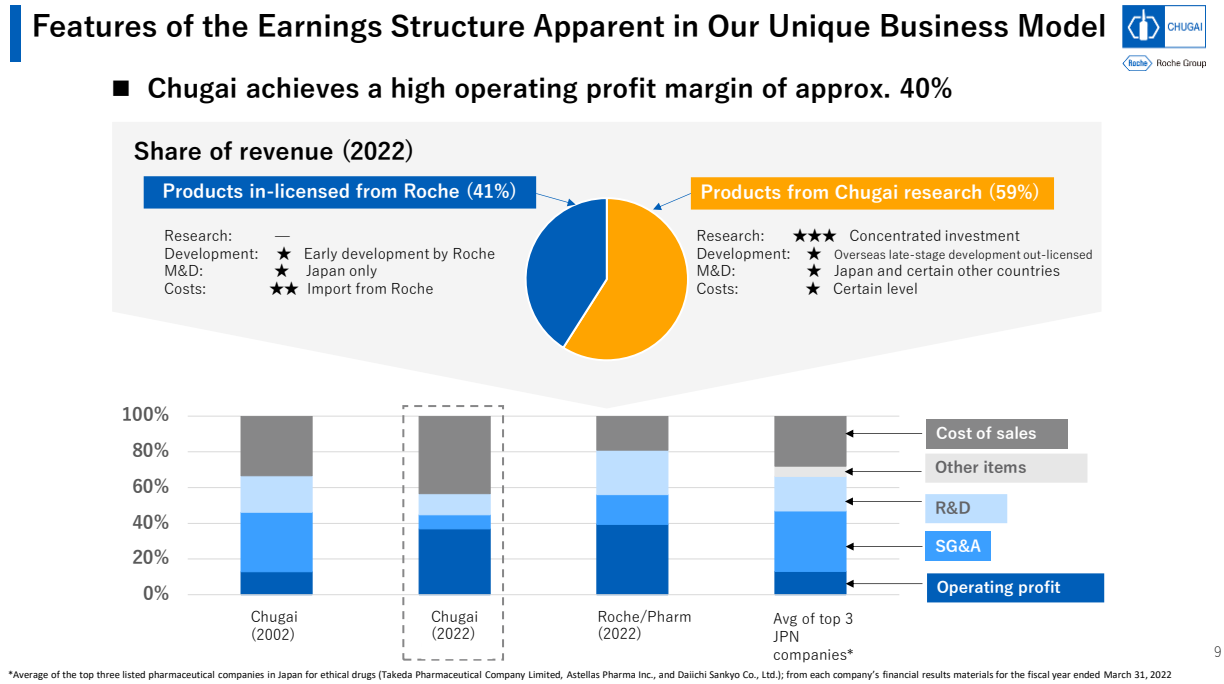
**Moderator:** Now that you have explained, I am sure that many individual investors who are watching have questions about how you were able to continuously create your own products and achieve high growth.




**Okuda:** Supporting all this is our unique business model, which you can see on this slide. Products developed by Roche can be marketed exclusively in Japan by CHUGAI. This allows CHUGAI to secure a stable revenue base in Japan. CHUGAI can then focus on innovative and challenging drug discovery.

Thanks to our business model, we can create innovative technologies and products based on those technologies, which in turn are delivered to patients around the world using Roche's global development and sales network.

**Moderator:** Looking at the operating profit margin, I believe that CHUGAI's operating profit margin has been extremely high in recent years, at around 40%. Could you explain the reason?




**Okuda:** Please take a look at the next slide.

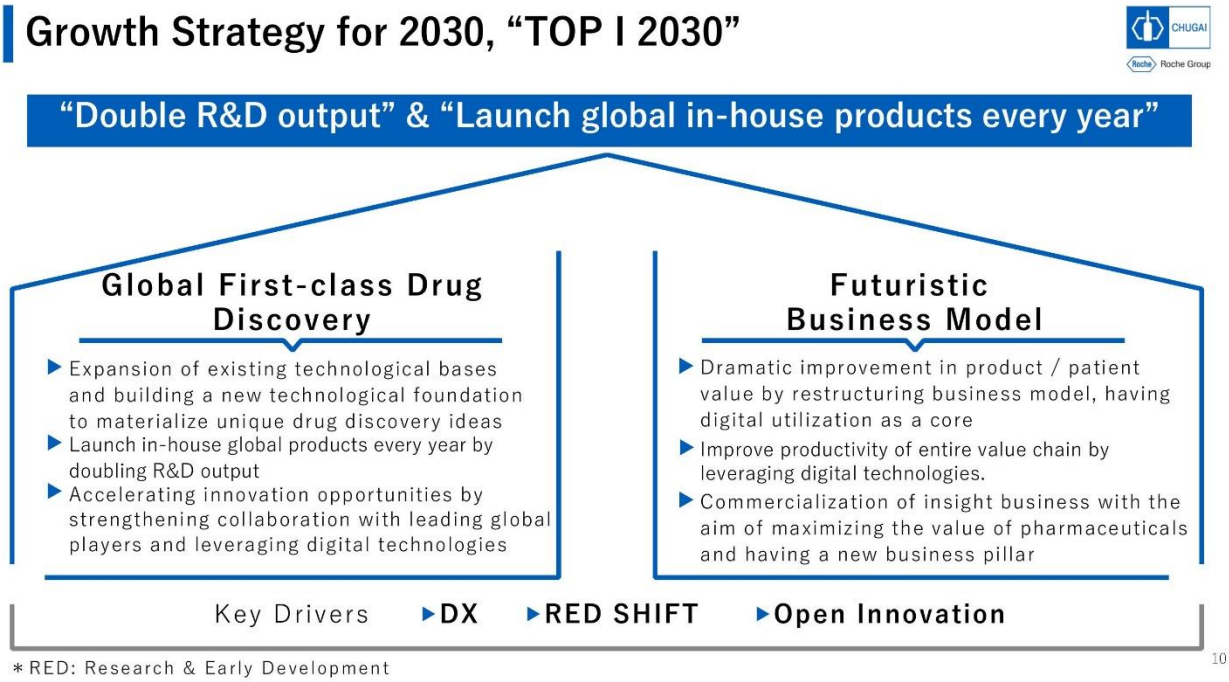
In the pharmaceutical business, stages of development that incur very high costs include the so-called late-stage clinical development part and the marketing and sales part. Through our strategic alliance with Roche, roles are split. Roche takes care of the most expensive overseas development, late-stage development, and marketing and sales.

Although the cost of products introduced from Roche into Japan is a little high, the business model is extremely cost-efficient even after deducting this cost. That is why the operating profit margin is close to 40%.

**Moderator:** The roles are well divided. It seems like a very efficient system.

**Okuda:** I would certainly say so.

**Moderator:** Indeed. You have been able to achieve such a high level of profitability. What do you think are the priorities for CHUGAI in the future?




**Okuda:** We have formulated a new growth strategy, TOP I 2030, and have begun to implement it. In this context, our goal is to become a top innovator in the healthcare industry, not just in Japan, but worldwide.

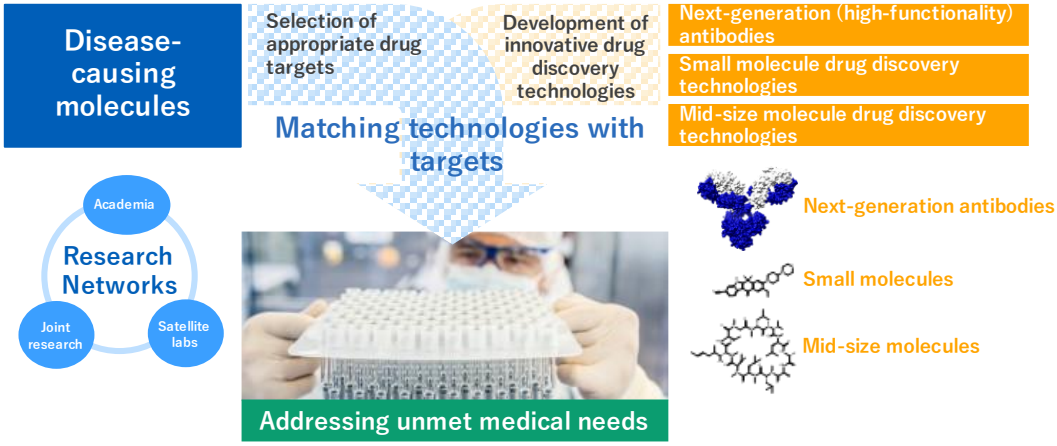
Our goal for 2030 is to double our R&D output. We have set a lofty target of launching one global product created in-house every year.

**Moderator:** I think that is a very lofty goal, but what would be the key to achieving it?

**Okuda:** Well, in a nutshell, it is the pursuit of innovation. The key will be how we can continue to produce innovative drugs. I would like to discuss our research strategy and our approach to what we call technology-driven drug discovery.

## Chugai Research Strategy: A technology-driven approach

- Enabling an optimal approach for disease targets by developing mid-size molecule drug discovery technologies in addition to antibody engineering technologies and small molecule drug discovery technologies
- Acquiring innovative “seeds” by enhancing oncology and immunology research infrastructure

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The next slide shows that, in general, drugs are made by matching disease-related or disease-causing molecules, on the left, with drug discovery technologies.

CHUGAI's strength is in the drug discovery technologies on the right side, such as with small molecules, mid-size molecules, and antibodies. Our strategy is to create a one-of-a-kind technology, in other words, a technology that differentiates us from our competitors. We aim to create innovative drugs by identifying the most appropriate disease-related or causative molecules. We call this a technology-driven drug discovery strategy. We have developed this technique in several contexts, including antibodies, small- and mid-size molecules.

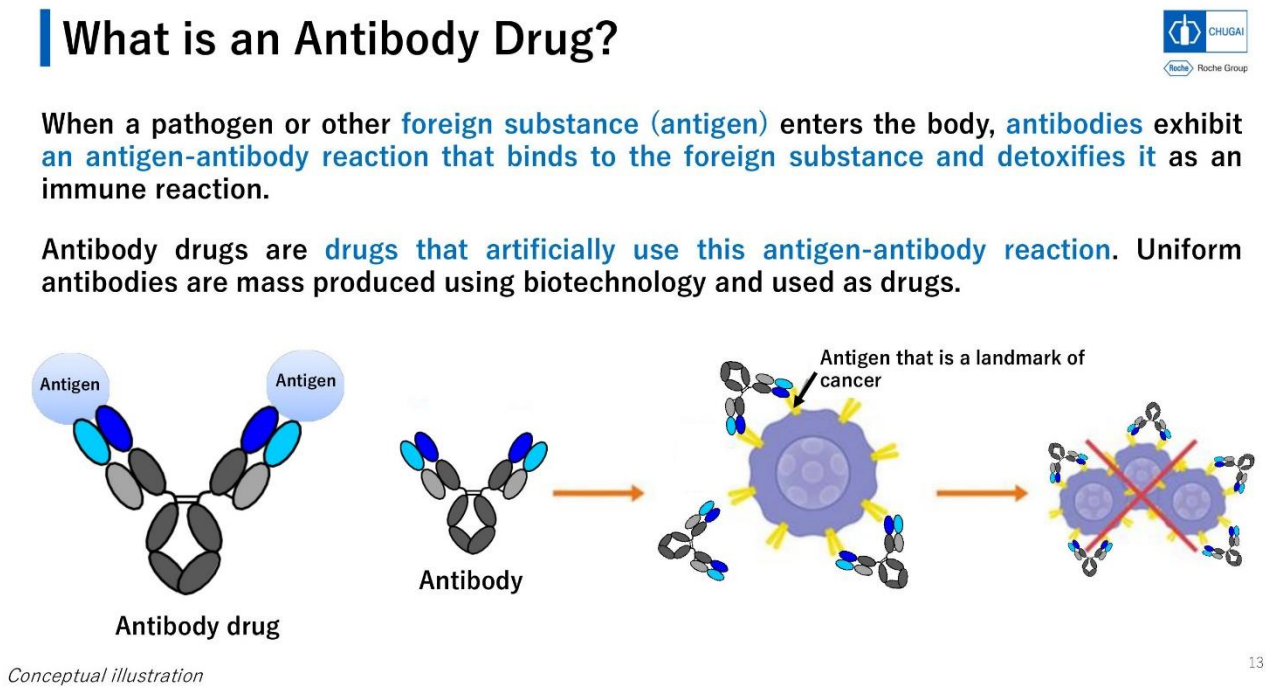
Today, Dr. Igawa will explain our greatest strength, antibodies.

**Moderator:** Thank you, Dr. Okuda.

I'm sure our viewers will agree that this was a useful overview of the background behind CHUGAI's dramatic growth to date, the characteristics of its business model, and its research strategy. Thank you very much.

Next, we will hear from Dr. Igawa.

Dr. Igawa has long been a leader in antibody engineering technology development at CHUGAI. Today, he will be explaining about antibody engineering technologies. Thank you.




**Igawa:** Thank you.

Let me begin by briefly explaining what antibody therapy is.

With the coronavirus pandemic, the word "antibody" appeared in the news a lot, but what is an antibody? When foreign substances, such as pathogens and viruses, enter the body, antibodies recognize them and neutralize them. That's what antibodies do.

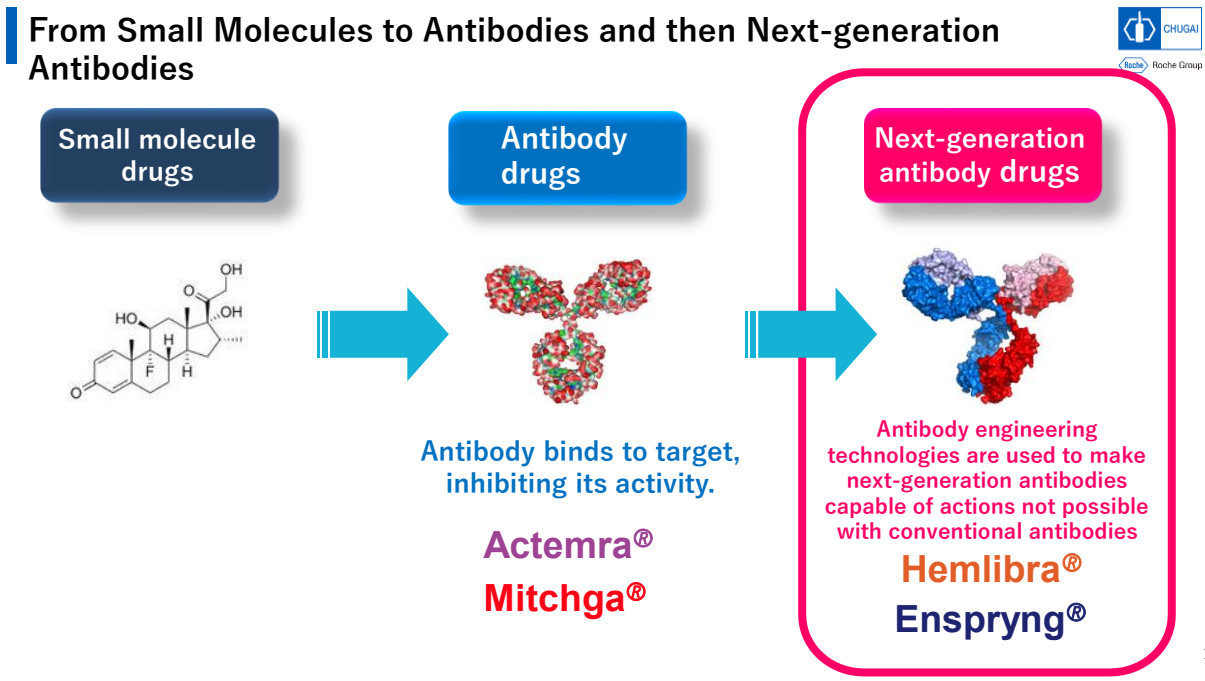
The foreign body, the thing that an antibody binds to, is called the antigen. The binding of the antibody to the antigen is called the antibody-antigen reaction. When an antibody is artificially created and mass-produced using biotechnology, it is called an antibody drug. As you can see on this slide, antibodies are often shaped like the letter "Y" and can bind to their antigen with the tips of both arms.

For example, the antibody binds to the yellow antigen, which is a marker of tumor cells, and thereby kills the tumor cells. The antibody drug is used as an anticancer drug.

**Moderator:** In other words, antibody drugs supplement the capabilities of the body's immune system.

**Igawa:** Yes, that's right.

**Moderator:** We learned earlier that antibody technology is strength of CHUGAI. Could you tell us more about that?




**Igawa:** Originally, "pharmaceuticals" referred only to small molecule drugs, as shown on the far left. Around 1980, antibody drugs started being developed, using biotechnology.

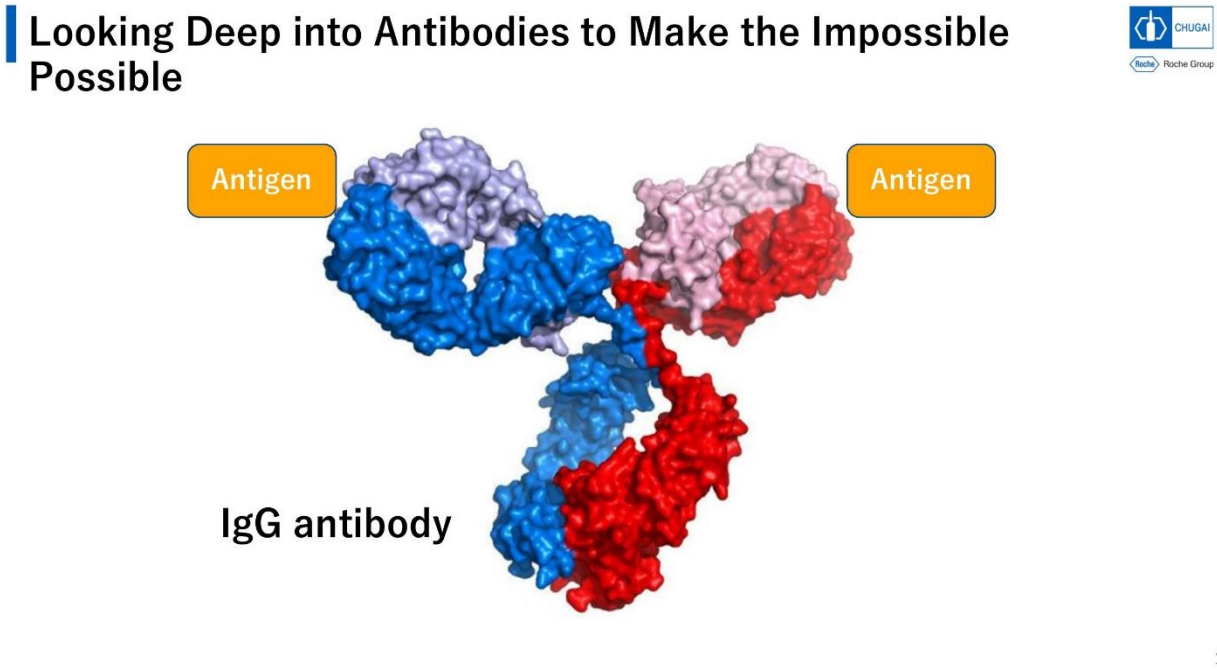
At that time, our company was among the first to research antibody drugs. Back then, the antibody drugs being developed would simply bind to the target, the causative agent of the disease, and inhibit or block it from being involved in a disease.

One of these antibody drugs is Actemra. Actemra binds to interleukin-6, a molecule that triggers inflammation, and blocks its action. As a result, it stops inflammation. These are conventional antibody drugs.

Because of our experience with conventional antibody drugs, we have long recognized the potential to do much more with antibodies, or to put it another way, we know that there are limits to what conventional antibody drugs can do.

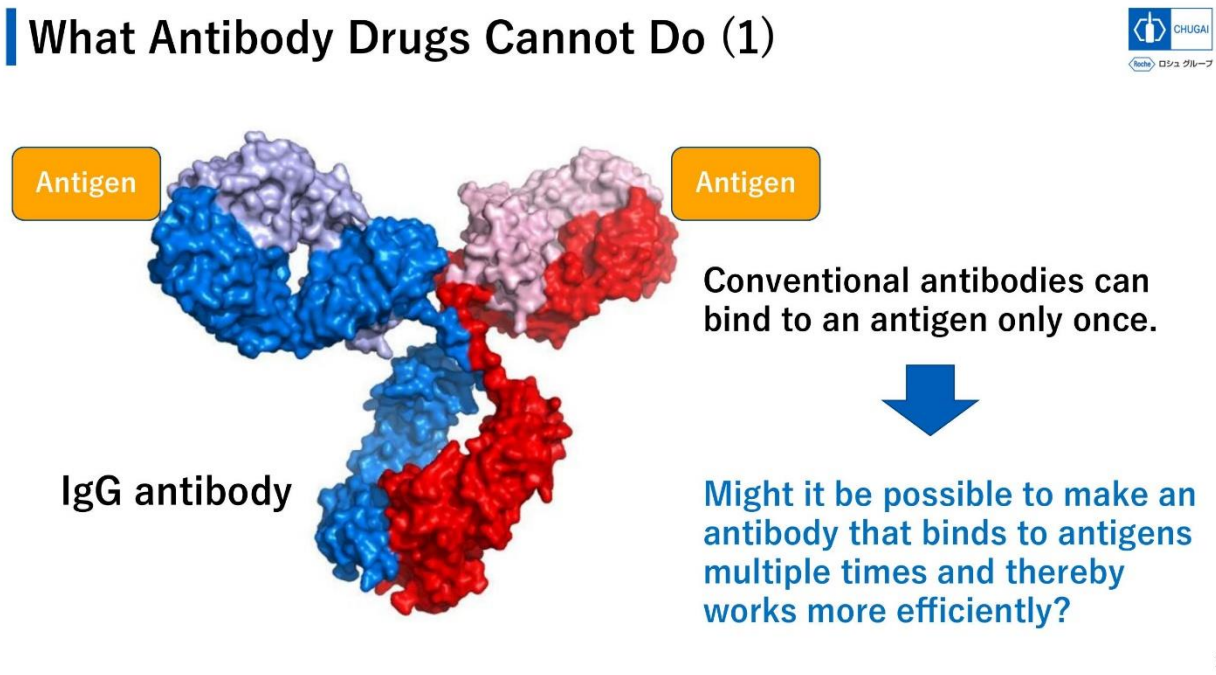
Therefore, we have been developing new technologies, which we call antibody engineering technologies, to create new antibody drugs. These technologies allow these new next-generation antibody drugs to do things that are impossible with conventional antibodies.

**Moderator:** This slide has a diagram. Can you explain this to me?




**Igawa:** Of course. As I mentioned earlier, a typical antibody binds to an antigen with both arms. This seems very simple if it only binds. We have been thinking about various things that can be done by facing this antibody molecule thoroughly.

**Moderator:** Could you tell us about the challenges you overcame in developing this technology?



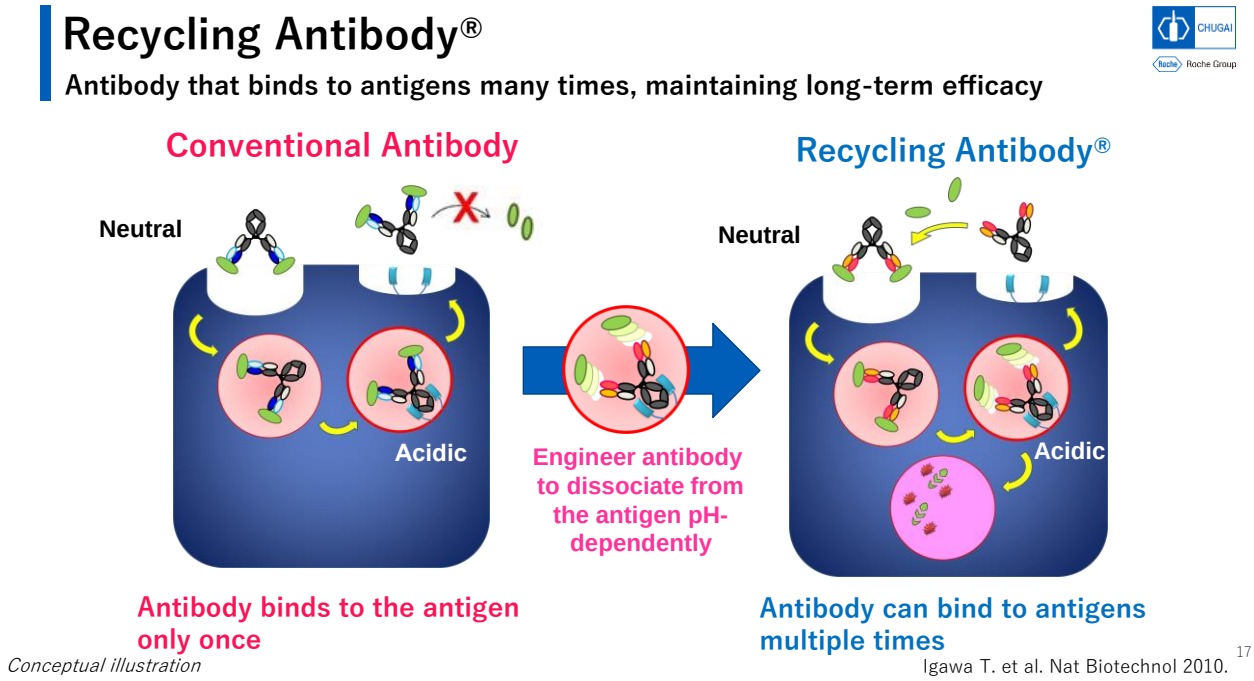
**Igawa:** Of course. Here, I will describe how we have cleared some of the hurdles associated with antibody drugs.

First, what can't we do with antibody drugs?

Conventionally, an antibody can bind to its antigen once. An antibody with two arms like this can only bind two antigens, and that's it.

If there are a lot of antigens in the body, a lot of antibodies must be administered. In some diseases, you can end up with a lot of antigens in the body. This would require a lot of antibody shots, which is not very practical.

Our idea was to create an antibody that could bind to its antigen repeatedly. The next slide shows the idea of the Recycling Antibody.




**Igawa:** We call them Recycling Antibody because they are recycled, and I would like to briefly explain this concept.

As you can see on the left, conventional antibodies, as I mentioned earlier, can bind to an antigen only once on each arm. In other words, as you can see in the picture here, the green blobs on both arms are antigens. The antibody binds to the green blobs, and that's it.

In fact, antibodies, when administered, bind to antigens in the blood, and this area depicted in blue is a cell in the body. Antibodies are going in and out of these cells.

With conventional antibodies, the antigen remains bound to the antibody all the time, whether it is outside or inside the cell, so once they bind, that's it, and you can't do anything about it. It can no longer bind to the next antigen.

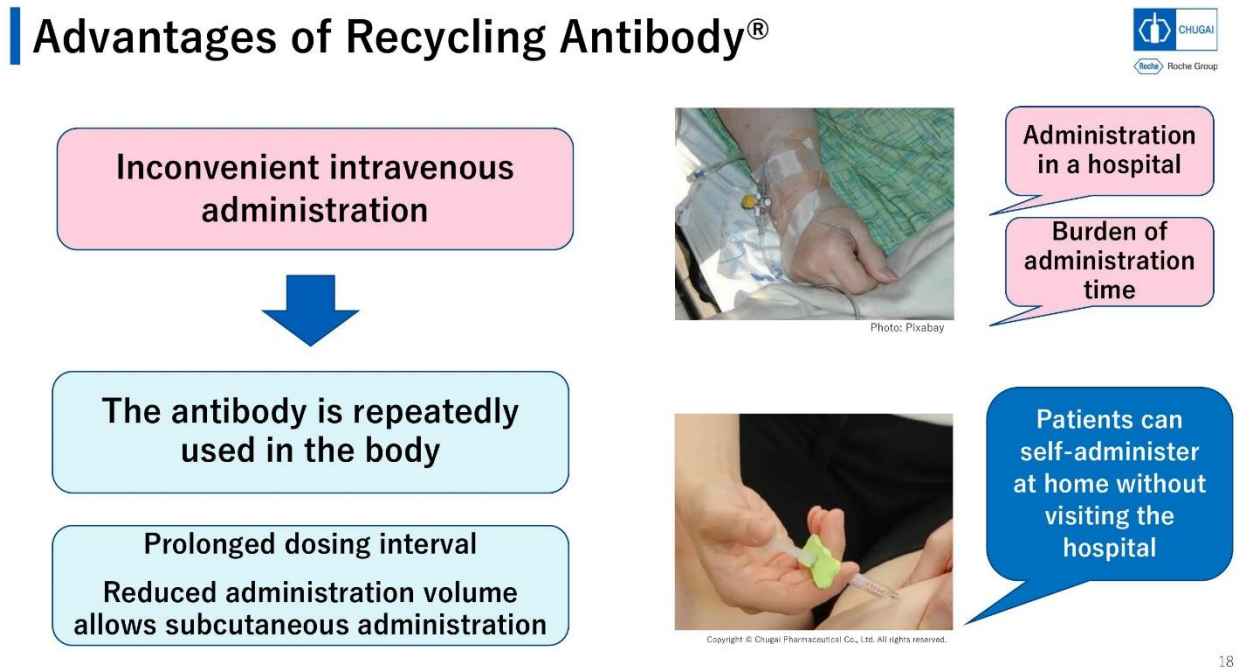
Now, the pH within parts of a cell, represented by this red circle, is acidic. The pH is neutral in the blood, but it is acidic in the cell, so the environment is a little different.

Taking advantage of this difference in environment, we designed the antibody so that the antigen leaves the antibody when it becomes acidic.

The image on the right shows the action of the Recycling Antibody. It binds to the antigen in the blood and firmly blocks its disease-causing action. When the bound antibody enters the cell, it releases the antigen due to the acidic environment. When released, the separated antigen is broken down and destroyed by the cell, since the cell originally has the ability to break down many things.

Afterwards, these antibodies, whose binding arms are now free, can return to the bloodstream and bind to the next antigen. By repeating this process, the antibodies bind to the antigen in the blood. The antigen is released in the cell and the antigen is degraded. The antibody can then go and bind to the next antigen. By repeating this process over and over again, one antibody can bind repeatedly to a number of antigens. This is the Recycling Antibody technology.

**Moderator:** In effect, you have created an antibody technology that truly breaks with conventional wisdom. What kind of benefits does this have for patients? Could you elaborate on this?




**Igawa:** Of course. Antibodies have to be introduced into the body. If you want to administer a large amount of medicine, say 100 milliliters, you have to use an intravenous infusion, as you can see in the picture here. Because it is an intravenous infusion, the patient has to go to the hospital, lie in bed, and receive an intravenous infusion for one or two hours.

The patient would have to go to the hospital to receive the medication. For someone who works, going to the hospital every week or even once a month to receive injections can be a major burden.

**Moderator:** Yes, I can imagine.

**Igawa:** With our Recycling Antibody, a single antibody can act over and over again, so a small amount can be effective.

That allows us to reduce a 100-milliliter injection to 1 milliliter, which can be administered subcutaneously under the skin. It can be administered by inserting a needle under the skin rather than directly into a blood vessel. That way, you don't have to go to the hospital, you can just inject yourself.

**Moderator:** The decrease in volume will allow you to do it on your own without having to go to the hospital.

**Igawa:** Yes, that's right. You administer it under the skin, so you can easily do it yourself. This eliminates the need for hospital visits, which is very beneficial to the patient.

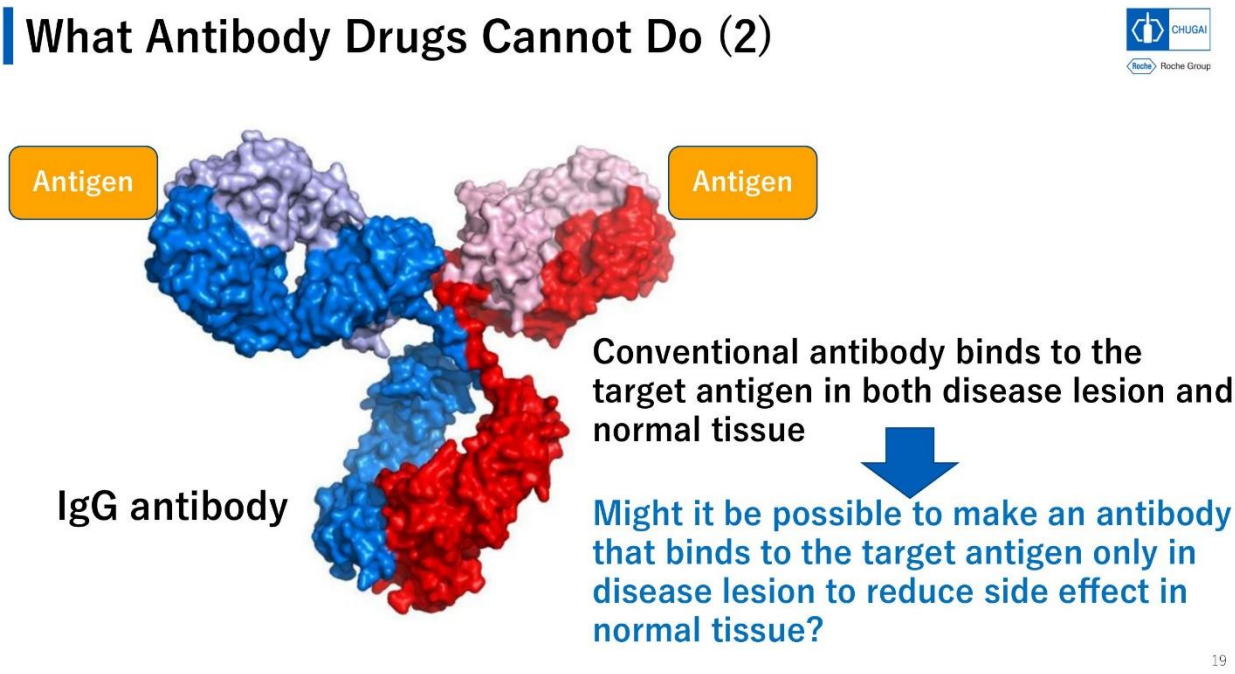
Also, one antibody binds over and over again, so the antibody's action lasts longer. In this way, for example, what used to require once-a-week injections for ordinary antibodies will now require only monthly or every three months injections. Injection is a bit of a burden, even if it is administered subcutaneously under the skin.

**Moderator:** Yes, it's something I'd rather avoid.

**Igawa:** Yes, indeed. If the administration interval could be reduced to monthly or every three -months, it would be much easier for the patient. That is another benefit of the Recycling Antibody.

**Moderator:** I think it's good to see this type of patient-oriented approach.

What challenges have you faced so far?



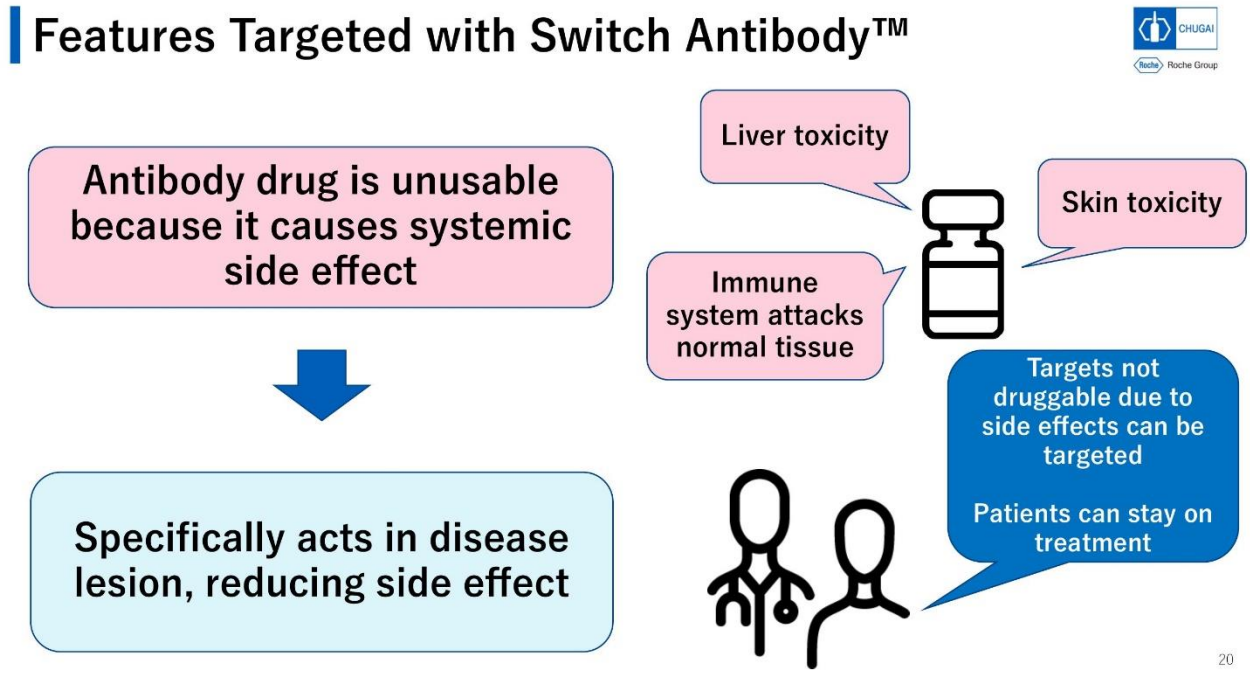

**Igawa:** Well, there's another hurdle I'd like to talk about.

As I mentioned earlier, antibody drugs can bind to antigens. One benefit of antibody drugs is that an antibody binds well to a specific antigen. This is a double-edged sword in the body, however, as it means that the antibody will bind to the antigen wherever it is in the body. In some cases, you want the antibody to bind to the antigen only in disease lesion of the body.

In some diseases, such as cancer, for example, it is better for antibodies to work only in the area where the cancer is located.

We wondered if it would be possible to make such antibodies, which bind anywhere, work only in the disease lesion with pinpoint accuracy. This offers the potential to reduce side effects of treatment, by preventing antibodies from acting outside the disease lesion.

**Moderator:** Now, can you tell us a little more about the benefits that these antibodies bring?



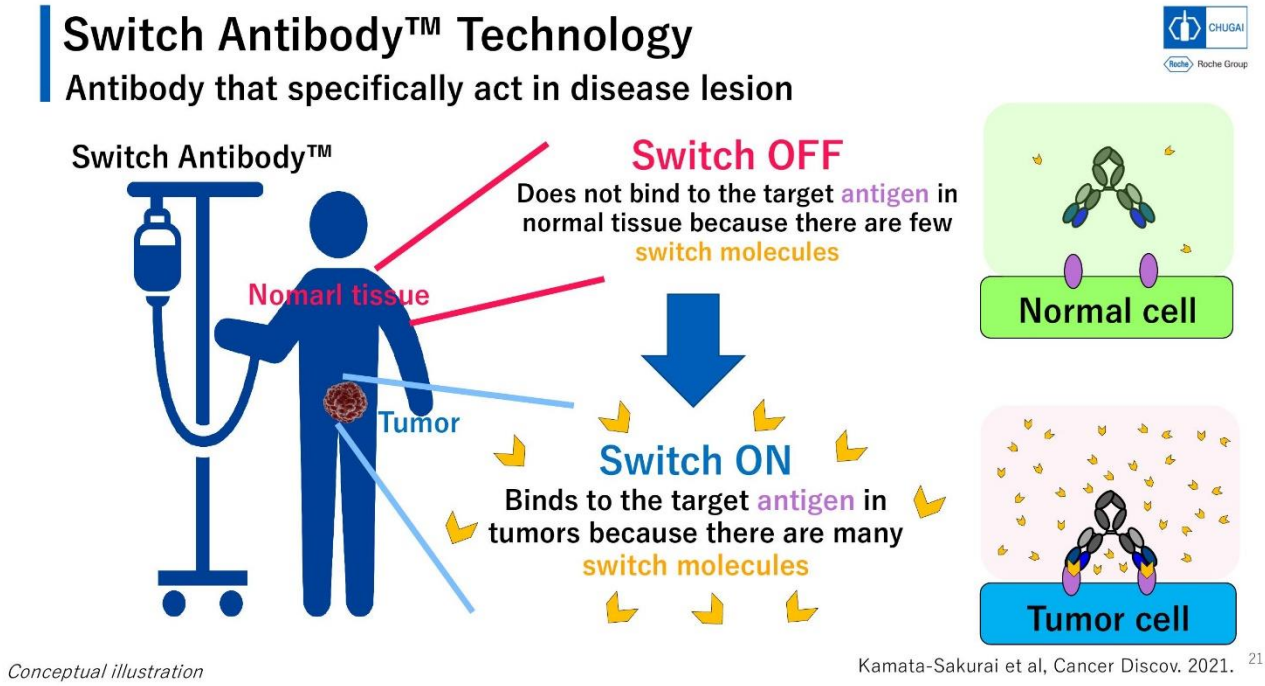

**Igawa:** Of course. This is what we are aiming for with our Switch Antibody technology.

In some cases, normal antibody drugs can have the kind of side effects written here in pink. Depending on the antibody drug, the target you are aiming for, or the antigen, when administered, it will act as I mentioned earlier throughout the body. That may prevent you from using the antibody drug.

For example, imagine if an antibody supplements the immune system to attack cancer. However, if it acts in the liver, it becomes toxic in the liver, or if it acts in the skin, it becomes toxic in the skin. It may be good to strengthen the immune system in attacking cancer, but on the other hand, the immune system can also attack the body. This would naturally lead to these side effects.

In order to solve this problem, as described here, if antibodies can be produced that specifically act in the disease lesion of the body, then we can develop antibody drugs with reduced side effects. Some targets are very attractive, but not druggable with conventional antibodies, ordinary antibodies, because side effects occur if they are used normally, but we can make it druggable. We believe that by reducing side effects, we can turn drugs that are difficult to use due to side effects into antibody drugs that can be used continuously for a long period of time.

**Moderator:** Are there any proprietary technologies that CHUGAI has developed to reduce these side effects?




**Igawa:** Yes, that is our Switch Antibody technology. I will explain on the next slide.

The reason why we named it "Switch Antibody" is, simply put, we have attached a switch function to the antibody molecule. In other words, in this figure, there is a patient who has tumor and the antibodies are switched on only in close proximity to the tumor.

In otherwise normal, disease-free areas, the switch is turned off. As shown in the figure on the right, the antibody does not bind to these normal green cells. You don't want these cells to be attacked by antibodies. We want the antibodies to attack the tumor cells shown below.

Both the normal cells and the tumor cells have this purple antigen. Ordinary antibodies would attack both the normal cells and the tumor cells. This is not useful as a drug.

We have developed this Switch Antibody, which has a molecular switch associated with it. This switch molecule is present in high concentration around the tumor cells, but not around normal cells.

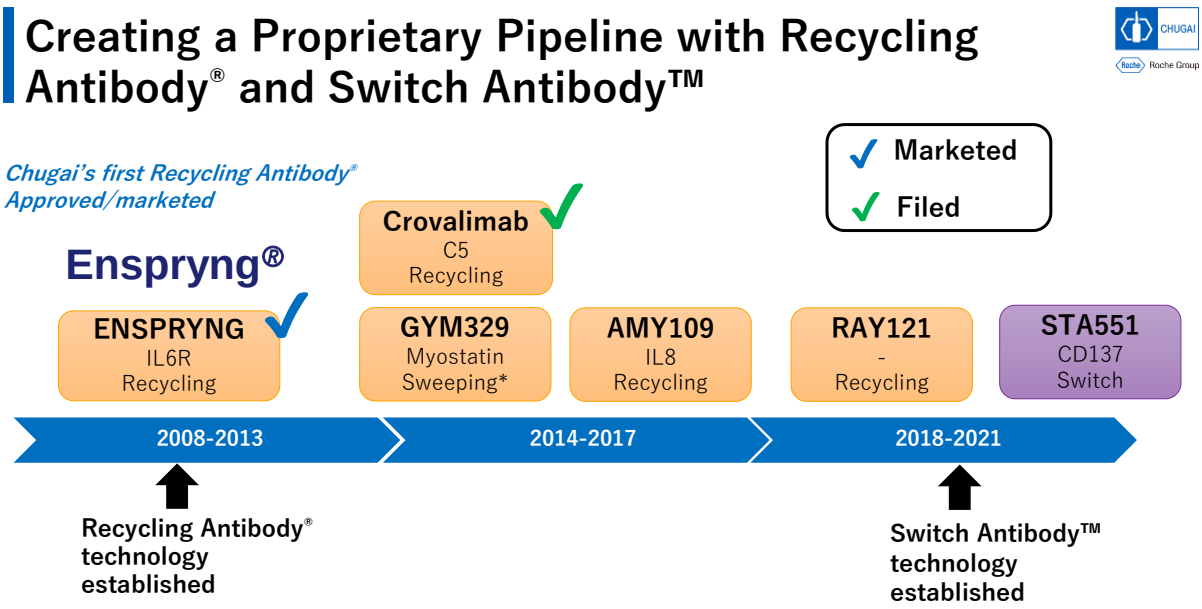
**Moderator:** You can see it in the diagram. There are a lot more around the tumor cells.

**Igawa:** Yes, indeed. This yellow molecule is the switch molecule, and when there are a lot of switch molecules around, the antibody turns on and can bind to this purple antigen.

There are very few switch molecules in the presence of this normal cell, so the switch is not turned on, and the antibody does not bind to normal cells. This is the Switch Antibody technology.

**Moderator:** Now you've told us about the Recycling Antibody and the Switch Antibody.

How are you making the most of these technologies in your development pipeline?




**Igawa:** Of course. This figure shows CHUGAI's unique pipeline of products using the Recycling Antibody and Switch Antibody technologies.

We established this Recycling Antibody technology in 2008. The first product using this technology, Enspryng, was recently approved and launched.

Subsequently, projects, such as crovalimab, GYM329, and AMY109, have been steadily progressing. These all use Recycling Antibody technology or Sweeping Antibody technology, which is a further evolution of the Recycling Antibody technology.

Crovalimab is a Recycling Antibody against C5 complement, another molecule involved in autoimmune diseases. We are now in the process of submitting an application to the health authorities.

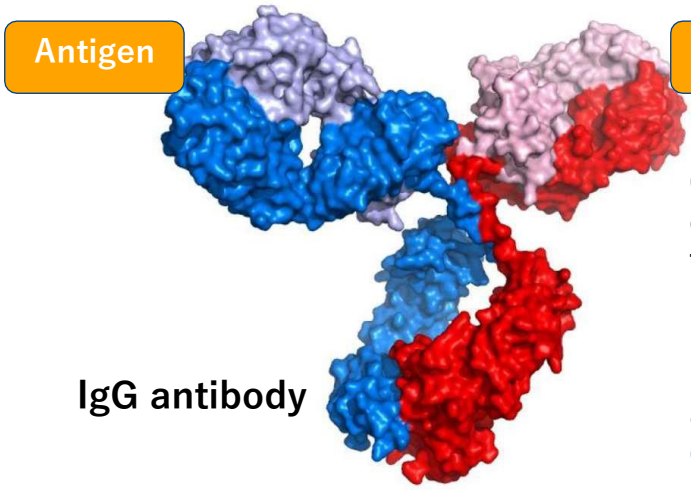
RAY121, another Recycling Antibody for autoimmune diseases, is now in clinical trials.

We have established the Switch Antibody technology and are now in the process of applying this new Switch Antibody technology to more and more projects.

Right now, the first Switch Antibody, STA551, is in Phase I clinical trials testing its effectiveness.

**Moderator:** Are you working on any other new technologies? Please tell us about them.

## What Antibody Drugs Cannot Do (3)




**Conventional antibody binds to only one type of antigen and the function is limited to inhibition.**

**Might it be possible to make an antibody whose arms bind to different antigens to bring those antigens into proximity, and exhibit a new action not previously seen?**

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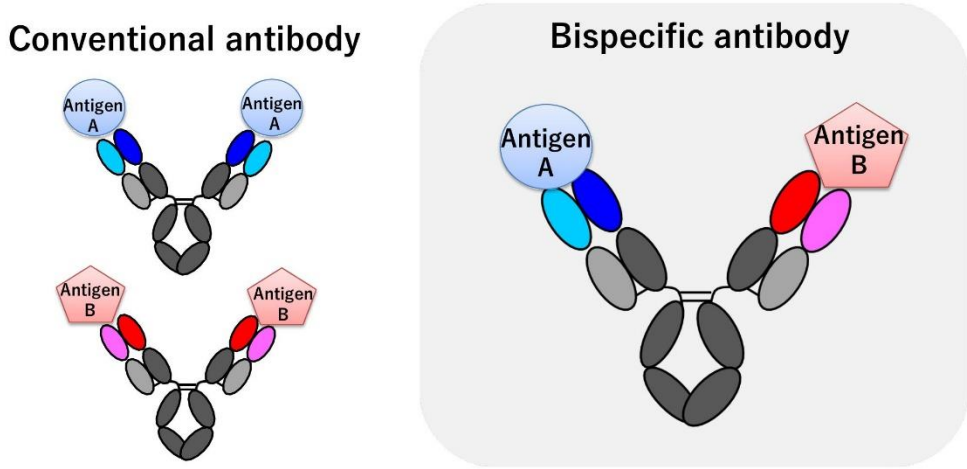
**Igawa:** Of course. Let's talk about another antibody challenge that we're working on.

In the figure here, we can see that the antibody is binding to the same orange antigen on both arms. As I mentioned earlier, the main use of antibodies is to block or inhibit the action of disease-causing molecules.

We wondered what else we could do. Suppose an antibody does not bind to the same antigen with both arms, but binds to one antigen with the left arm and another antigen with the right arm. It could then be as if the two antigens have been joined together by the antibody.

## Bispecific Antibodies Capable of Binding to Two Different Antigens

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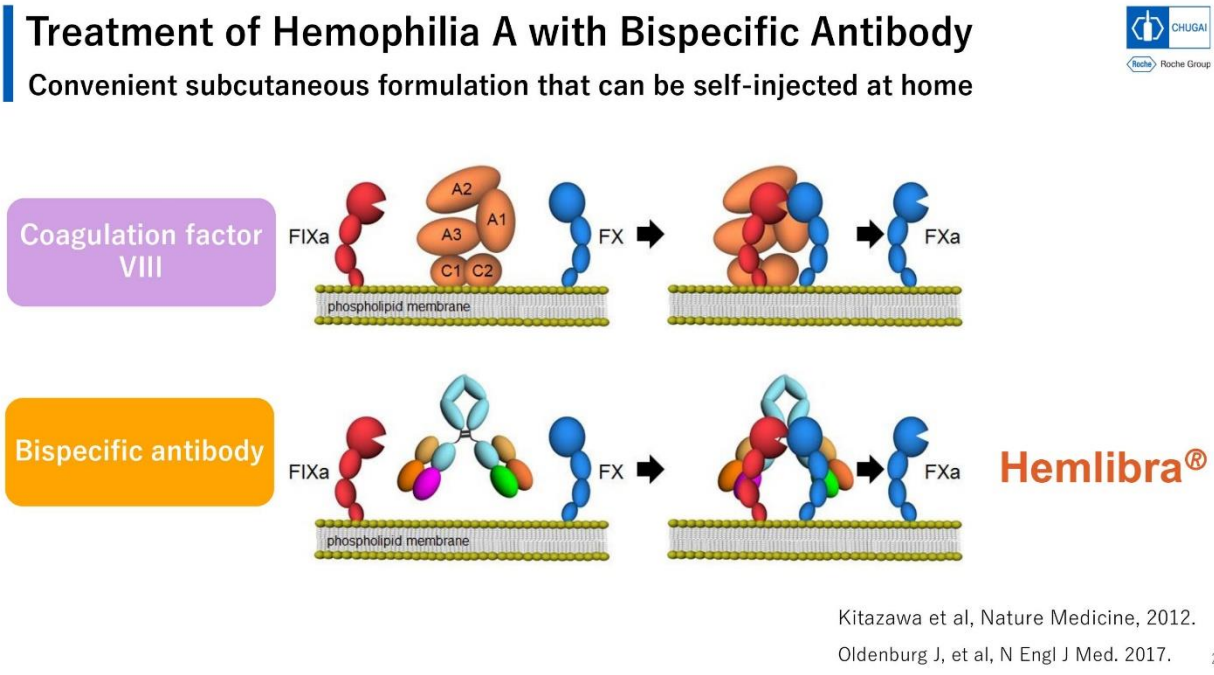
With this in mind, we created a bispecific antibody, as shown on the next slide.

As you can see in the figure, conventional antibodies bind to the same antigen on both arms.

In contrast, a bispecific antibody binds to two antigens. In this case, the blue left arm binds to antigen A and the red right arm binds to antigen B. This is a bispecific antibody.

The following slide shows our first drug discovery project using a bispecific antibody.




As you can see here, we have used this bispecific antibody to create a treatment for hemophilia A, a blood disease.

The cause of hemophilia A is dysfunction of blood coagulation factor VIII, a molecule essential for blood clotting. As a result, the blood does not clot properly. This results in the disease called hemophilia A.

As you can see in the figure above, factor VIII is flanked by red factor IX and blue factor X. Factor IX and factor X are attached to factor VIII in the middle. Factor VIII is responsible for bringing factor IX and factor X together. Patients with hemophilia A have a dysfunction of factor VIII.

When we thought about how we could make this into a therapeutic drug, we came up with the idea of creating a bispecific antibody, which binds to factor IX with the right hand and factor X with the left hand. This would bring factor IX and factor X closer together. Depending on the shape of the antibody, it could be used to bridge the gap.

This project was undertaken in the hope of creating a drug that would act exactly like factor VIII. The resulting product, Hemlibra, is now providing significant value to patients.

**Moderator:** Indeed. Now, I would like to ask you, Dr. Okuda, could you please explain, from a management perspective, how Hemlibra, which you just mentioned, is positioned for CHUGAI?

**Okuda:** In a word, it is our most important product. The drug has already been approved in more than 110 countries around the world and has played a central role in CHUGAI's dramatic growth in recent years.

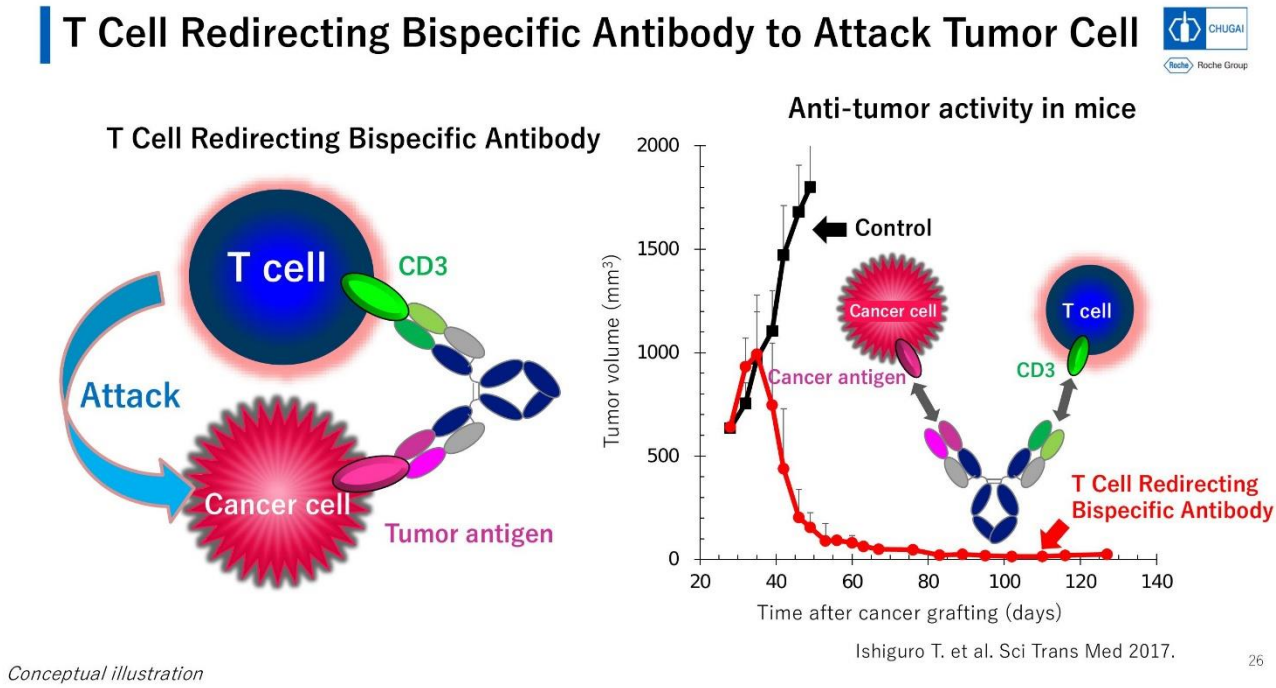
This drug has had quite an impact on society, by truly changing the lives of many hemophilia sufferers.

Conventional treatment has to be injected intravenously. This is given about one to three times a week. For small children, in particular, it can be quite difficult to find a vein for injection. There are also patients for whom the old conventional treatment gradually becomes ineffective.

Hemlibra, made by CHUGAI, is also effective in patients for whom conventional therapy has stopped working. It can be administered weekly, biweekly, or monthly.

It is a subcutaneous injection, which has the advantage of being highly convenient and easy for patients to use. The drug is changing the way this disease is treated because of its convenience and ability to prevent bleeding.

**Moderator:** Indeed. Dr. Igawa, can this treatment be applied to other conditions besides hemophilia?




*Conceptual illustration*

**Igawa:** Of course. Our success with Hemlibra gave us confidence that we could actually use bispecific antibodies therapeutically, as well as clear production-related challenges.

The next idea we thought up is called a T Cell Redirecting Bispecific Antibody. I will briefly explain what that means.

Tumor cells are usually attacked to some extent by the human immune system to prevent the growth of cancer. Depending on the patient's condition, the immune system may become weakened and the balance may tip in favor of cancer cell growth.

We thought it might be possible to use these antibodies to attack tumor cells by enlisting the help of the body's immune system. These cells in blue are T cells. These T cells are the most important immune cells in the human immune system and originally function to kill cancer or virus-infected cells.

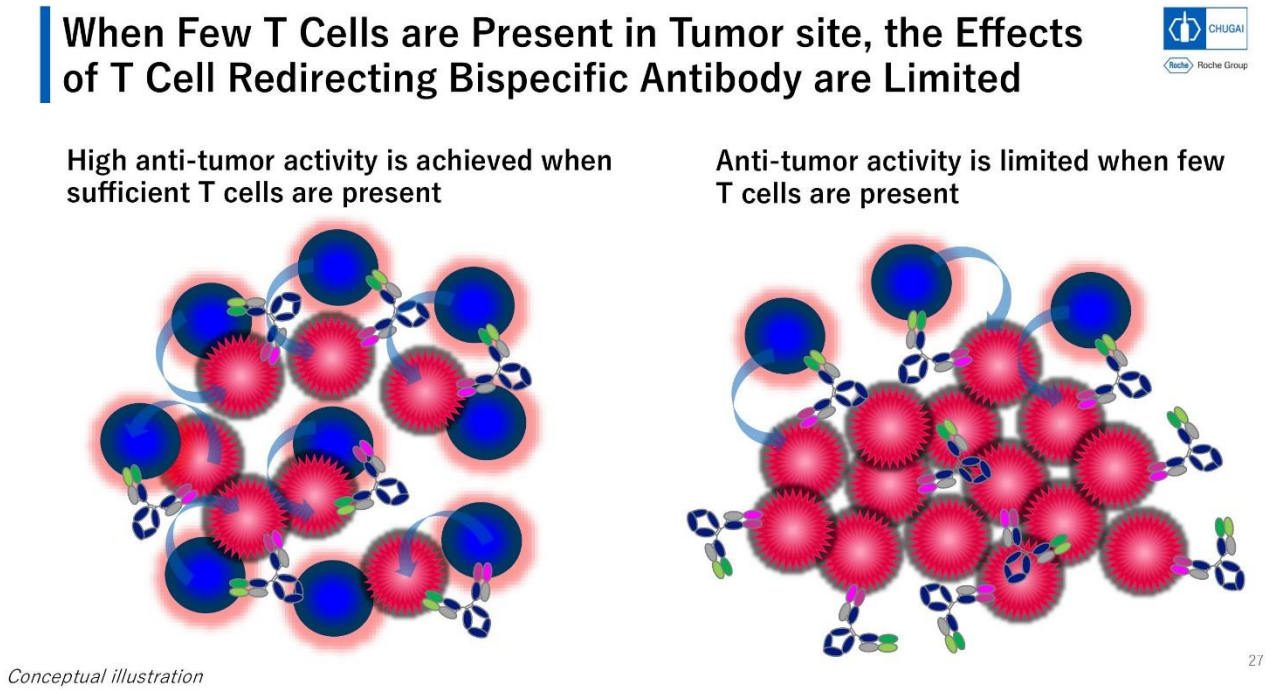
However, these T cells are not capable of attacking any and all tumor cells. Since T cells have this limitation, we wondered if we could support their activity by using bispecific antibodies.

Specifically, as you can see on this slide, we created a bispecific antibody with two arms, a pink arm that binds to the antigen on the surface of tumor cells, which is a tumor antigen, and an arm that binds to the green molecule, called CD3, on the surface of T cells.

In effect, these bispecific antibodies can attach the T cells to tumor cells. These T cells are then able to attack the tumor cells, thanks to the support of our antibodies.

The experiment on the right shows the effect of the antibodies in shrinking tumors in mice. The red line shows the change in tumor size over time in mice treated with bispecific antibody, with the y axis representing tumor volume. After administering the antibody, you can see that the size of the tumor is rapidly decreasing.

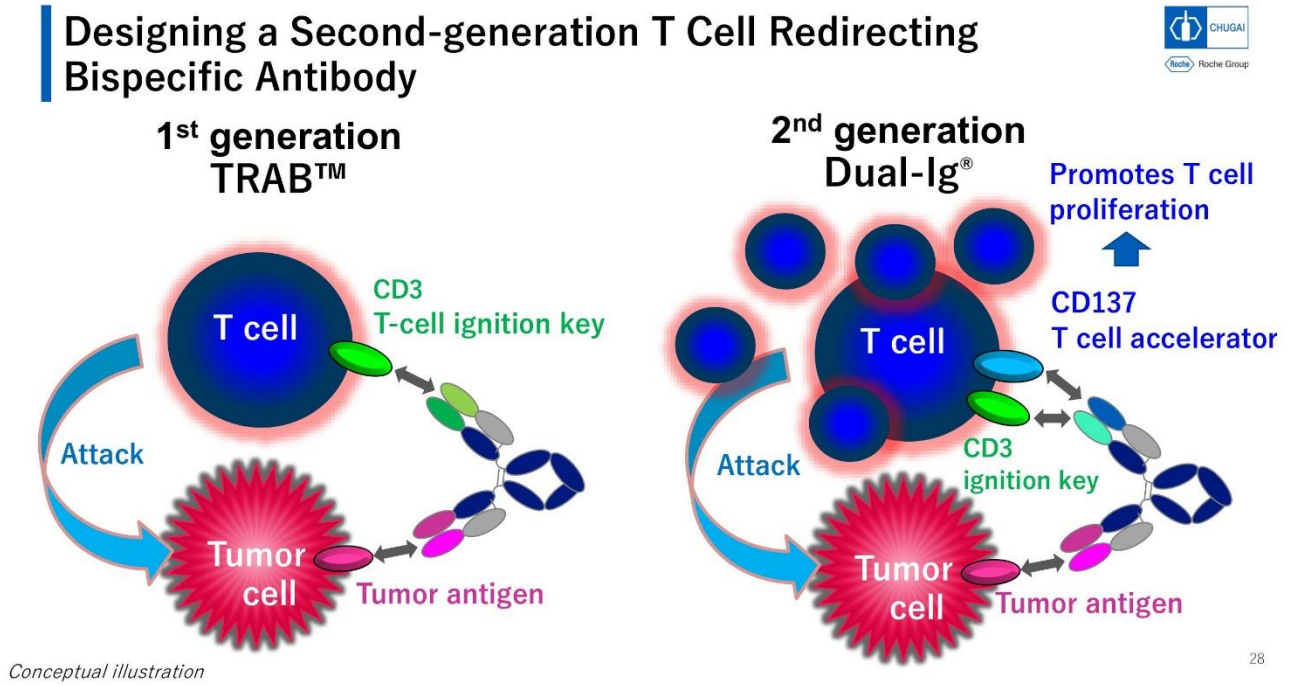
At 100 days after administration, the tumor had practically disappeared. The T Cell Redirecting Bispecific Antibody was shown to have a very strong anticancer effect.




We are continuing to work on how we can make this even better. However, this modality also has a weakness, it kills tumor cells using T cells, so it cannot kill a large number of tumor cells unless there are many T cells.

As shown in the figure on the left, the blue cells are T cells and the pinkish ones are tumor cells. However, in some types of cancer, patients may have very few T cells.

In that case, you end up with this situation on the right. With low numbers of T cells, the antitumor effect is still limited. In this case, the tumor cells are too numerous, and we just can't compete. There simply aren't enough T cells.




We set out to overcome this challenge. We designed a second generation of antibody, which we called Dual-Ig.

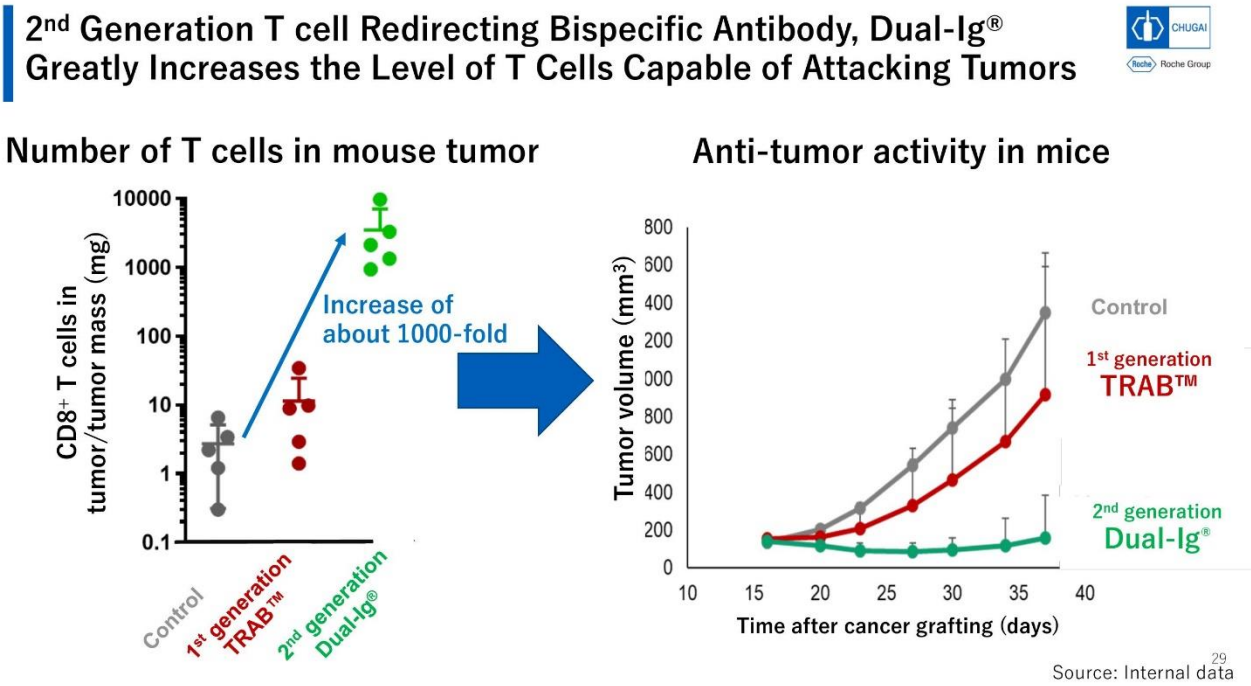
The first generation, named TRAB, bind to these green and pink areas, as shown earlier. The green part represents CD3, which is present on the surface of T cells, and acts like an ignition key. When it binds here, it engages the T cells. As a result, the T cells start attacking the cancer, but this is only the engine.

If you just ignite the engine, the car will run a little. In the left figure, the green arm of the TRAB antibody binds only to the green CD3, but in the second generation, Dual-Ig, one arm binds to CD3, the ignition key, and the same arm binds to CD137, which acts like the accelerator for T cells.

**Moderator:** Are you saying that the accelerating force is there?

**Igawa:** Yes, indeed. When T cells are accelerated, they divide and increase in number. As the number of T cells increases, we will be able to solve the issues that were mentioned earlier.

In the case of ordinary antibodies, one antibody can only bind to CD3, but we have created a technology that can also bind to CD137.




The left figure shows the result of counting the number of T cells in the tumor of a mouse treated with these antibodies. The grey points represent the control, and as you can see, there are very few T cells. With administration of the second-generation antibody, the number of T cells increases 1,000-fold.

**Moderator:** That's a huge difference.

**Igawa:** Indeed. We see only a small increase with the first-generation antibodies, but the effect of the accelerator produces this 1,000-fold difference with the second-generation antibody. The figure on the right shows that this can exert an antitumor effect even on cancers with low T cell counts. While the first generation of the drug did not show much effect, the second generation has been able to markedly suppress the growth of cancer.

**Moderator:** Indeed. At first, I thought it might be a little difficult to understand the content, but after listening to your presentation, it has started to make sense.

Is it correct to say that this Dual-Ig technology has allowed your company to make steady progress toward overcoming challenges in cancer treatment?

**Igawa:** Yes, certainly.

**Moderator:** Now, I would like to ask you, Dr. Okuda, what does it mean, from a management perspective, to develop this Dual-Ig technology?

**Okuda:** This is related to the technology-driven drug discovery strategy I explained earlier, but there are two major points I would like to make here.

One is that it can ensure a competitive advantage. We are developing highly unique and proprietary technologies that no other company can imitate. This allows us to significantly differentiate ourselves from our competitors. That's one point.

Also, this technology is what we call a versatile technology. You can think of it as a technology platform. We have applied this technology to a specific target molecule. If we apply this to other target molecules, it can be used in the treatment of other diseases. That is the process we are engaged in. This way, we can create a continuous pharmaceutical project.

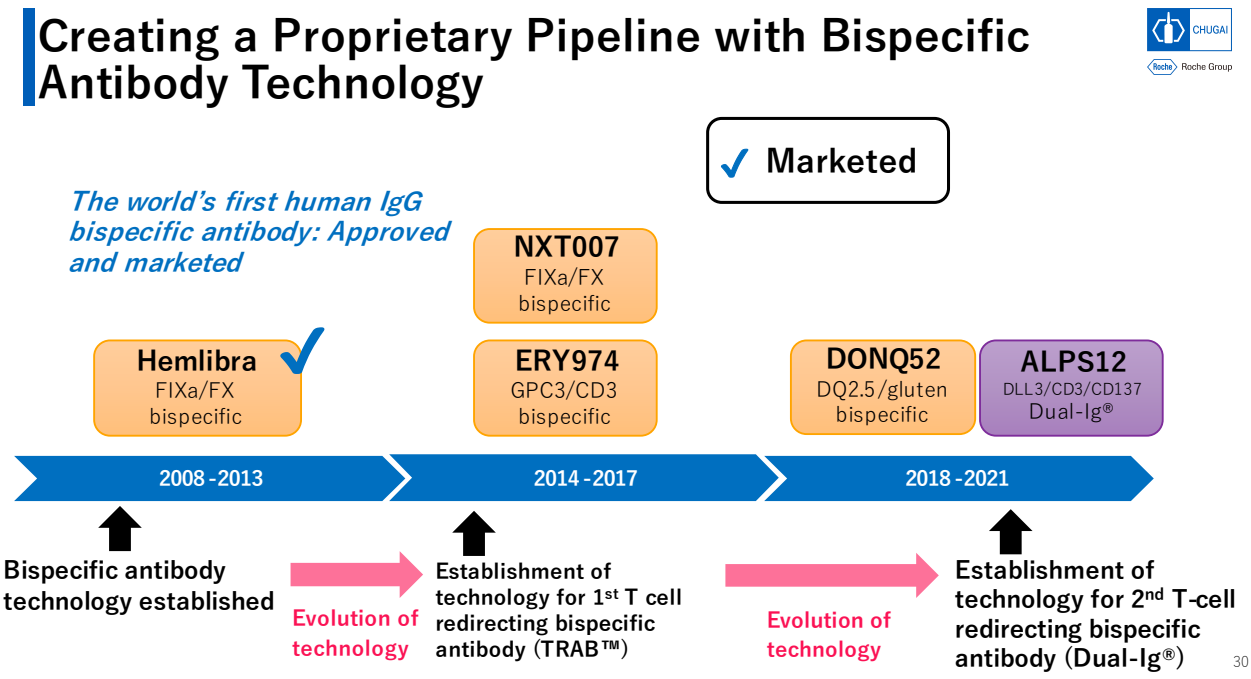
For example, if we can prove the concept of Dual-Ig in clinical trials for one cancer, we can then apply it to various other types of cancer. By doing so, we can create many more breakthrough drugs. This means that research productivity can be very high.

**Moderator:** It's not just about developing the technology, but also about applying it to develop new products.

**Okuda:** That's exactly right.

**Moderator:** Thank you very much.

Now, Dr. Igawa, could you please say a few words about how you are using this technology in your current development pipeline?



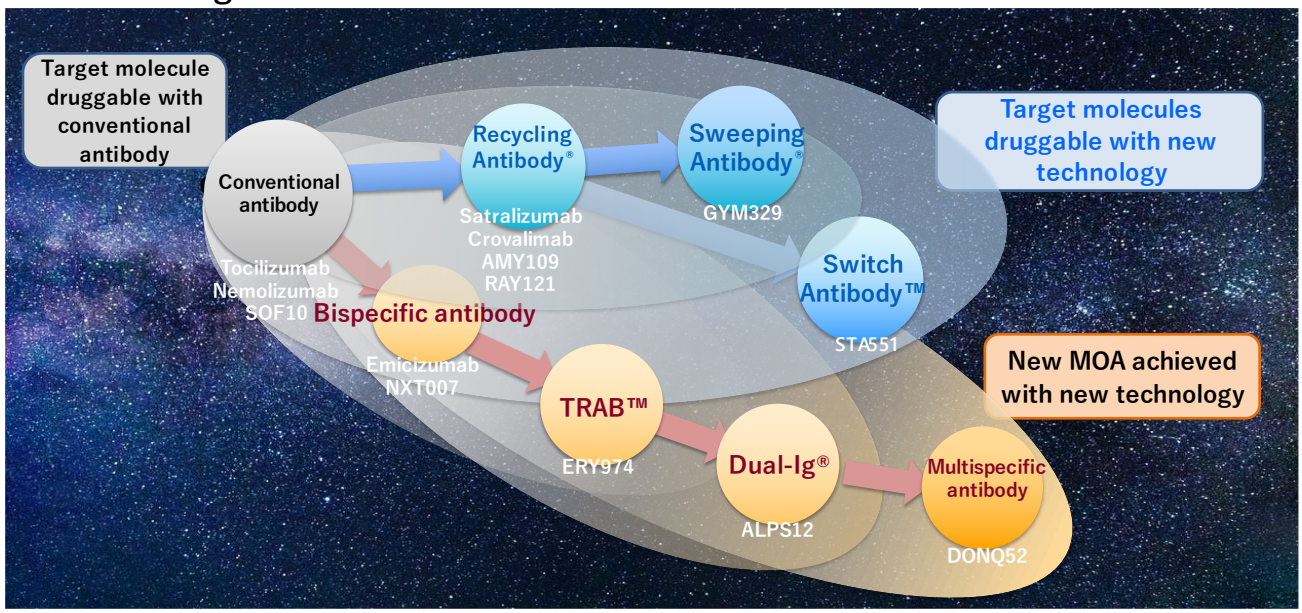

**Igawa:** Of course. This is the pipeline utilizing bispecific antibody technology. Hemlibra, which I mentioned earlier, has been approved and launched as the world's first human IgG-type bispecific antibody.

By further developing our bispecific antibody technology and identifying new areas where it can be applied, we are in the process of developing new treatments using TRAB and Dual-Ig antibodies. To date, this process has brought about the development pipeline you see here.

**Moderator:** Thank you very much for your clear and concise explanation. It has been fascinating to hear about CHUGAI's innovative and groundbreaking technology today.

Dr. Igawa, could you please give us a final summary to wrap up your presentation?

## Expanding Drug Space with Proprietary Innovative Antibody Technologies




**Igawa:** Of course. This is my last slide. There are countless types of diseases, target molecules, and antigens that can be targeted.

However, conventional antibodies are still limited in what they can do, and the molecules they can target are also very limited.

With conventional antibodies, we could only target certain areas, but by creating new technologies, such as Recycling Antibody, Sweeping Antibody, and Switch Antibody, we can fix our sights on new molecules that can be targeted for the first time. This means that there are more and more possibilities to develop new antibody drugs.

Also, the creation of bispecific antibodies opens the door to new mechanisms of action. These antibodies let us do things that would have been unthinkable with ordinary antibodies.

CHUGAI has been and will continue to be involved in highly innovative drug discovery that was not possible in the past. We will do this by creating new antibody technologies that put previously unattainable targets within reach.

**Moderator:** Thank you very much.

## Question & Answer

**Moderator [M]:** We will now move to the Q&A session.

We have already received many questions today, and many of them seem to be about the main theme, antibody technology.

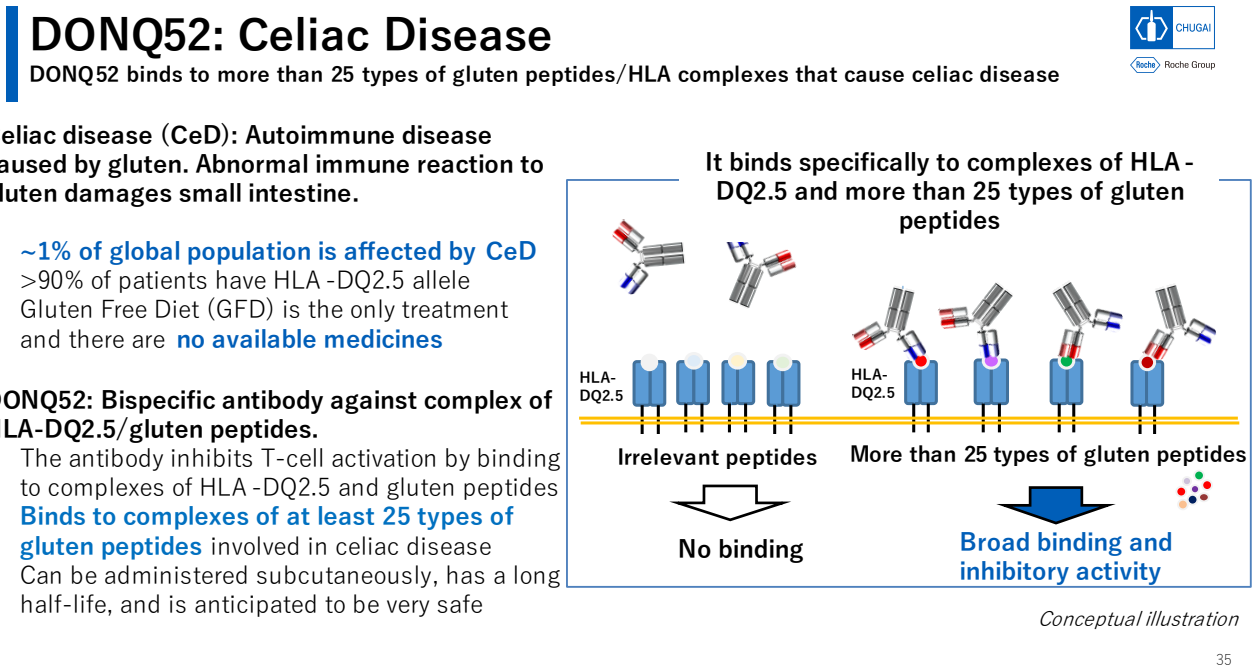
Let me read the first question.

**[Q1]** You have introduced many technologies today, but I am wondering if any of the breakthrough technologies that could be game changers, if successfully developed for pharmaceuticals, are included in your explanation.

**Igawa [A]:** Thank you very much.

I believe that if any of the antibody technologies under development I have introduced today become pharmaceuticals, they will all be game changers. In other words, these could be drugs that will change current systems of treatment.

Since we are here, I would like to introduce another potential game changer that we were not able to introduce today. I would like to show one more slide, about a treatment for celiac disease.




This is DONQ52, and it is a treatment for celiac disease. Celiac disease is an autoimmune disease caused by an abnormal immune response to gluten, which is found, for example, in wheat. About 1% of the global population has this condition.

There is currently no cure for this disease. The only symptomatic treatment for celiac disease is a gluten-free diet, which means a gluten-free diet without things like wheat.

We are currently working on a project to develop a treatment for celiac disease. That is DONQ52. Now, there are actually many different types of gluten. There are more than 20 known types, and all of these can cause disease. As a result, blocking just one of them is not an option.

As shown in the figure on the right, we have created a multi-specific antibody that binds to more than 25 different gluten peptides.

We believe that this will result in a drug that can be administered subcutaneously to patients with celiac disease, with long dosing intervals, to impair the onset of celiac disease. Since there is no medicine to treat, we believe that this development could be a game changer if it works.

**Moderator [M]:** It would be a breakthrough drug that could change current treatment.

The next question is also about antibody technology.

**[Q2]** You mentioned that you have continuously developed the technology to make the impossible possible. Where do you see the development of antibody technology going in the future? Can we expect this unique, one-of-a-kind technology development to continue to evolve in the future?

**Igawa [A]:** Thank you very much.

We have increased what we can do with antibodies by creating these various technologies, but even so, there is still a lot that can't be done. If there is something that cannot be done, and it would be better to solve this problem with antibodies, we are working on solving it by creating new technologies.

One example relates to the brain. Antibodies cannot enter the brain. As a result, it is very difficult to make a therapeutic drug for the central nervous system. How can we make antibodies that can enter the brain? We are working on developing technologies that will solve these problems.

**Moderator [M]:** You would say that there are still more technologies that can be developed.

**Igawa [M]:** Yes, that's right. I believe there are still many more.

**Moderator [M]:** Thank you very much.

Next, the question is about the organizational climate.

**[Q3]** I hear that it takes a very long time to develop a drug. How do you feel about CHUGAI's organizational culture and mindset? It seems that your company allows for highly original technology development and drug discovery.

**Igawa [A]:** I think there are three things that are characteristic of CHUGAI's organizational climate and mindset.

The first point is that ideas for drug discovery come almost exclusively from the bottom up. Rather than a top-down approach, each researcher thinks of various ideas and proposes what he or she would like to do. Proposals are made, worked on, and if they fail, that's okay. I think that is the first point, the mindset of our company is a bit like that of a start-up or venture company.

Secondly, with Hemlibra, for example, if you believe that a product is going to be a game changer, it gives you the tenacity to keep working on it, even if it takes 10 years. Sometimes, after a few years of work, someone may decide to give up on a project, but CHUGAI has the tenacity to see these things through, even if it takes a long time.

**Moderator [M]:** There is a culture of solidly supporting research to the end.

**Igawa [A]:** Yes, that's right. Management provides very good support. If the researchers are giving it their all, management will support them.

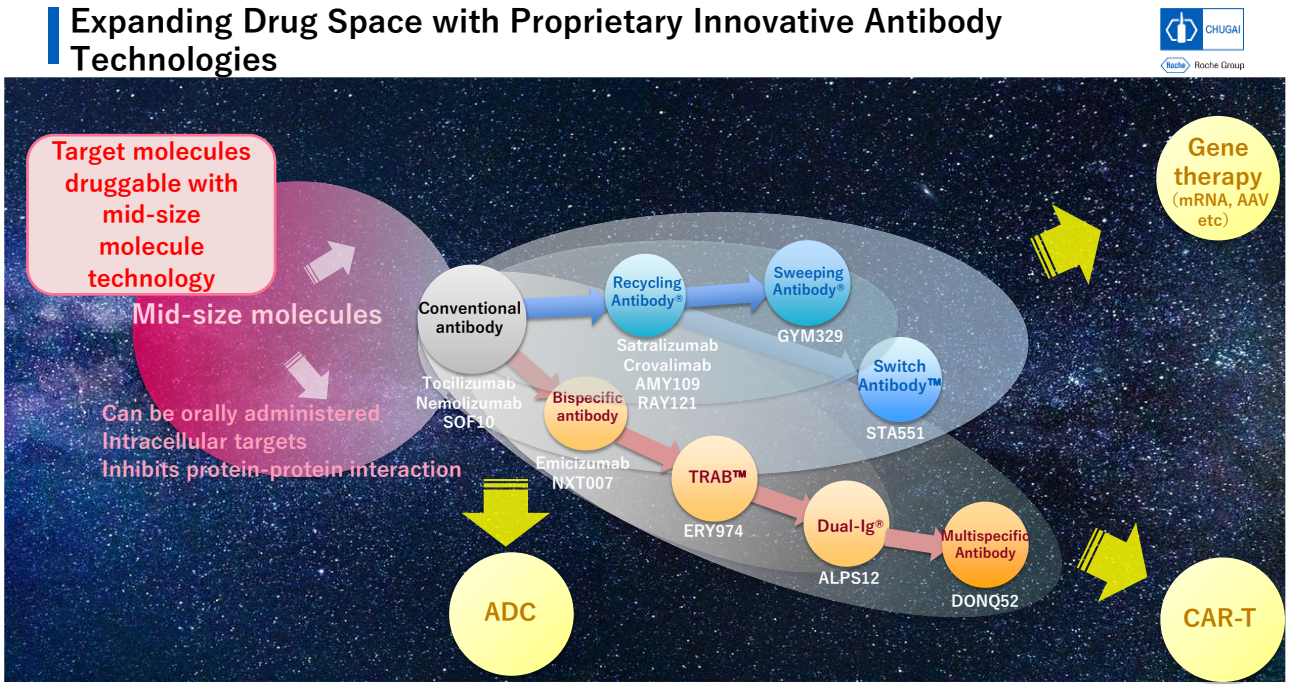
Thirdly, as a pharmaceutical company, we create molecules to be used in clinical trials. We never compromise on the perfection and quality of the molecules we create in our research.

**Moderator [M]:** You think that the three factors you have just mentioned are essential for the creation of new drugs. Thank you very much.

Now, as a follow-up, we have received questions about technologies other than antibodies.

**[Q4]** I understand that you have cultivated a strength with respect to antibodies. Does CHUGAI possess proprietary technologies other than antibodies? Please let us know about other innovative technologies.

**Igawa [A]:** Indeed. Could you open the slide covering mid-size molecule drugs?




This is a diagram about using technology to expand the molecules that can be targeted, as I explained earlier, with antibodies. Of course, there are still things that cannot be done with antibodies. Issues include entry into cells and oral administration. Inevitably, antibodies need to be injected. This means they can't be made into a orally available drugs.

We have been researching the use of mid-size molecules as a technology to solve these problems and to do things that antibodies cannot do. We have been developing the technology for more than 10 years now. These mid-size molecules can be administered orally. It is possible to target targets inside cells that cannot be targeted by antibody drugs.

We at CHUGAI believe that this will expand the target space overwhelmingly. In 2021, we started Phase I clinical trials for the first product using this mid-size molecule technology. We expect to see more drug discovery projects and pipeline items using mid-size molecule technology in the future.

**Moderator [M]:** You are not only focusing on antibodies, but are also moving into the field of mid-size molecules. Dr. Okuda, could you also comment on this?

**Okuda [M]:** Of course. As I explained a little at the beginning, CHUGAI has set the lofty goal of becoming a top innovator in the global healthcare industry by 2030. In this context, our goal is to double our R&D output and launch one in-house product per year on a global basis. Antibody technology is, of course, very important in achieving this goal, but in addition to this, mid-size molecules are indispensable. They will be very important to make this a success.

We have our first mid-size molecule project, LUNA18, which has entered clinical trials. If we can build a platform for mid-size molecule drug discovery, there will be many more projects to follow, offering great potential for new drug development.

I have very high expectations for CHUGAI from the sustainable growth perspective, as well as from the social perspective of fulfilling unmet medical needs and achieving a high level of sustainable patient-centered medical care. We are also investing significant management resources to ensure our success in this area.

**Moderator [M]:** It sounds like an exciting time. Thank you.

We have received many more questions, but we are now out of time, so we will conclude the Q&A session here. Thank you very much for your questions.

Dr. Okuda, would you like to say a few words to finish?

**Okuda [M]:** Thank you very much for staying with us to the end of this late session.

Today, we spoke to you specifically about our greatest strength, our antibody technology. Although some of the details may have been a bit difficult to understand, I hope that these technologies will spark your interest in CHUGAI, even if just a little. We would like to thank you again for your continued understanding and support.

Thank you very much for your time today.

**Moderator [M]:** Thank you very much.

**Igawa [M]:** Thank you.

[END]

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***Document Notes***

1. *Speaker speech is classified based on whether it [Q] asks a question to the Company, [A] provides an answer from the Company, or [M] neither asks nor answers a question.*
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