CHUGAI PHARMACEUTICAL CO., LTD.

Chugai R&D Meeting

December 13, 2021

Event Summary

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[Participants]	

[Number of Speakers]	3	
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	Tomoyuki Igawa Ph.D.	Head of Translational Research Division
	Toshiya Sasai	Head of Corporate Communications Department
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	Hidemaru Yamaguchi	Citigroup Global Markets Japan Inc.
	Kazuaki Hashiguchi	Daiwa Securities Co., Ltd.
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	Shinichiro Muraoka	Morgan Stanley MUFG Securities Co., Ltd.

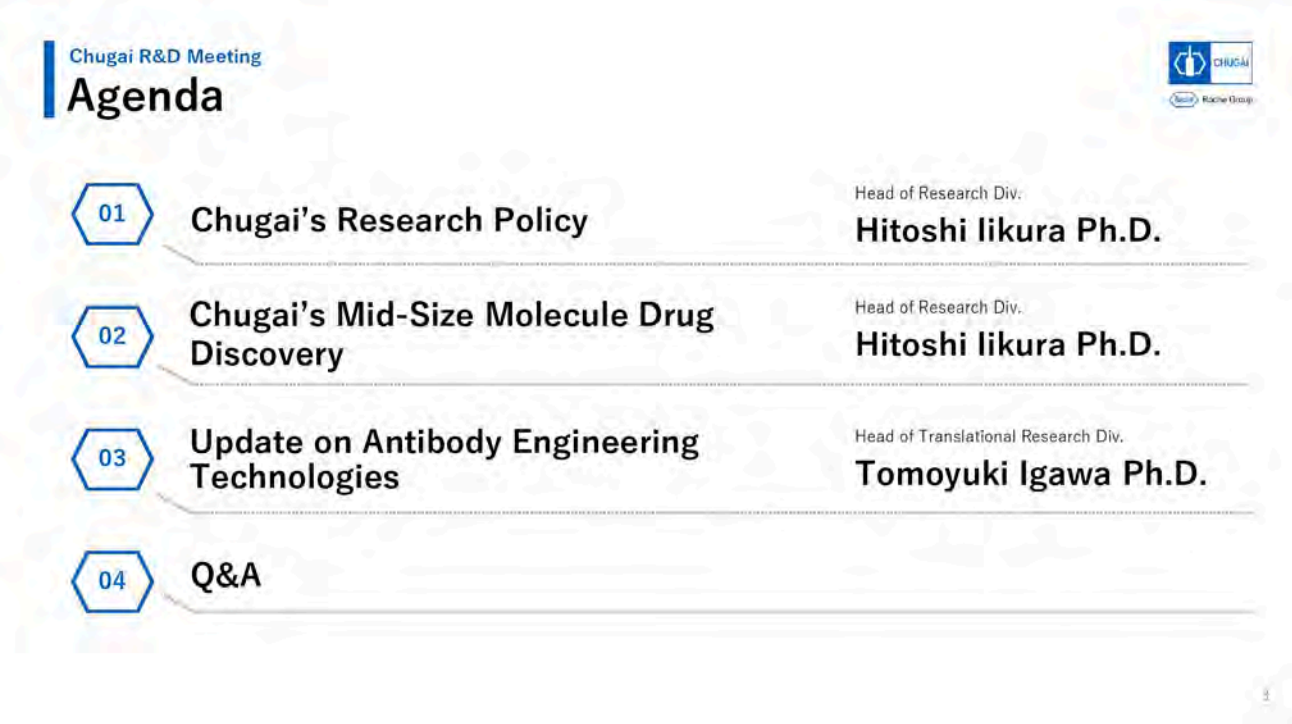
*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

Presentation

Sasai: Hello, everyone. Thank you very much for taking time out of your busy schedule to attend the Chugai R&D meeting today.

My name is Sasai from Chugai's Corporate Communications Department, and I will be moderating today's session. Thank you for your cooperation.

Today's session will be conducted by both on-site lecture and conference call. If you are participating via conference call, please access the URL and link to the webcast at the bottom of the conference call invitation email to view the presentation materials and video along with audio.



The agenda for today's meeting is shown on the screen. Please follow the instructions in this section. Questions will be taken after all presentations have been completed. The Q&A session is expected to last about 30 minutes.

Dr. Iikura, Head of Chugai's Research Division, will now discuss Chugai's research policy and mid-size molecule drug discovery.

Iikura: Hello, everyone. My name is Iikura, Head of Research Div. Thank you for your cooperation today.

I will now give a presentation on Chugai's research policy and current mid-size molecule drug discovery.

This year, our company has announced a long-term strategy and policy to the year 2030 called TOP I 2030. Let me briefly review this: the Company's mission is to be a top innovator globally, not just in Japan, especially in the healthcare field.

The "I" between "TOP" and "2030" has 2 meanings: the "I" of innovator and the "I" of each and every employee.

In line with this company-wide policy, the research division will focus on drug discovery, especially in the healthcare field. This will continue to be our policy. In drug discovery, our mission is to improve patient satisfaction with their treatment.

Here are 4 keywords that will help us achieve this.

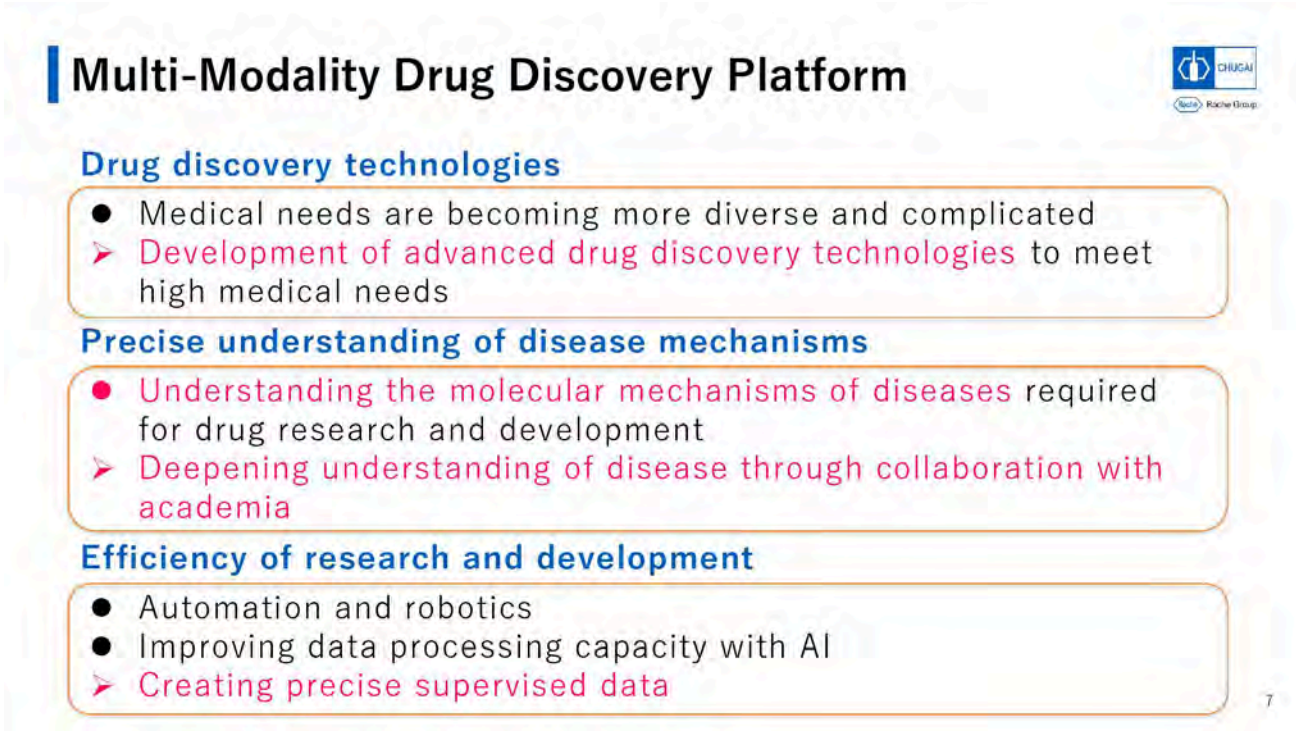
At the top of the list is our technology platform, which is the lifeline of our company. Our policy is to build on our current strengths while also creating new ones.

We would like to continue working to realize the original drug discovery ideas that we have been developing.

In order to realize these goals, I have listed here 2 keywords that we need to further strengthen.

One is to collaborate with global advanced players, and this is written as open innovation. This includes innovation using digital technology.

We will proceed with our research in accordance with these 4 major policies.

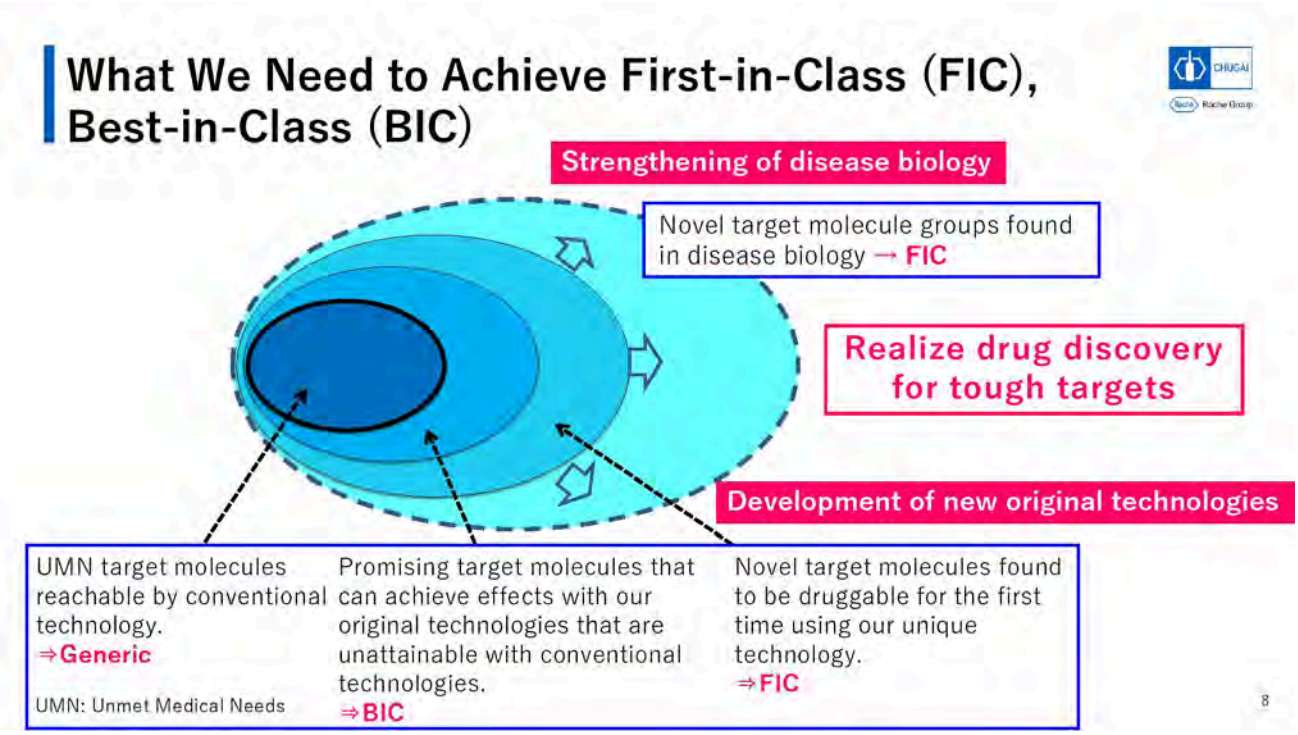


A more detailed description can be found in this slide.

Drug discovery technology will require even more advanced technology development as medical needs become more sophisticated and diverse.

Since a large number of drugs are already on the market, it is necessary to understand the mechanisms of disease more precisely in order to create drugs that are even more effective and enhance quality of life. Naturally, we will continue to do this. Additionally, we aim to work even more closely with academia. In this sense, Open Innovation will be one of the keys to success.

Drug development takes a great deal of time, and improving the efficiency of the process is essential. We recognize that digital technology will play a central role in this. Automation, robotics, and AI will become keywords in the future, but I believe that precise experimental data must not be left out. If you don't have a strong sense of this, you won't be able to use this kind of digital technology very well. As such, we will continue to focus on actual laboratory-based 'wet' research.



These drug discovery technologies are the lifeline of our company, and this slide shows a conceptual diagram of how we see them.

This is one of the guiding principles for our first in class and best in class drug discovery.

The dark blue area on the left is a group of target molecules for which unmet medical needs have already been met by conventional technologies. These are covered by generic drugs, but this is not our strategic area.

On the other hand, the second area, where the blue is a little lighter, is where new technologies can achieve effects that cannot be achieved with existing technologies. Since these targets are already being used, the goal is positioned as best in class, meaning that they are the most effective among the targets. One of the things we need to do is to apply our unique technology to these targets.

The next, paler blue area is the area where we want to do drug discovery. However, this is difficult to realize with current drug discovery technology, so we aim to develop and apply new techniques. This is why this part is positioned as first in class. This is where we want to focus our efforts the most.

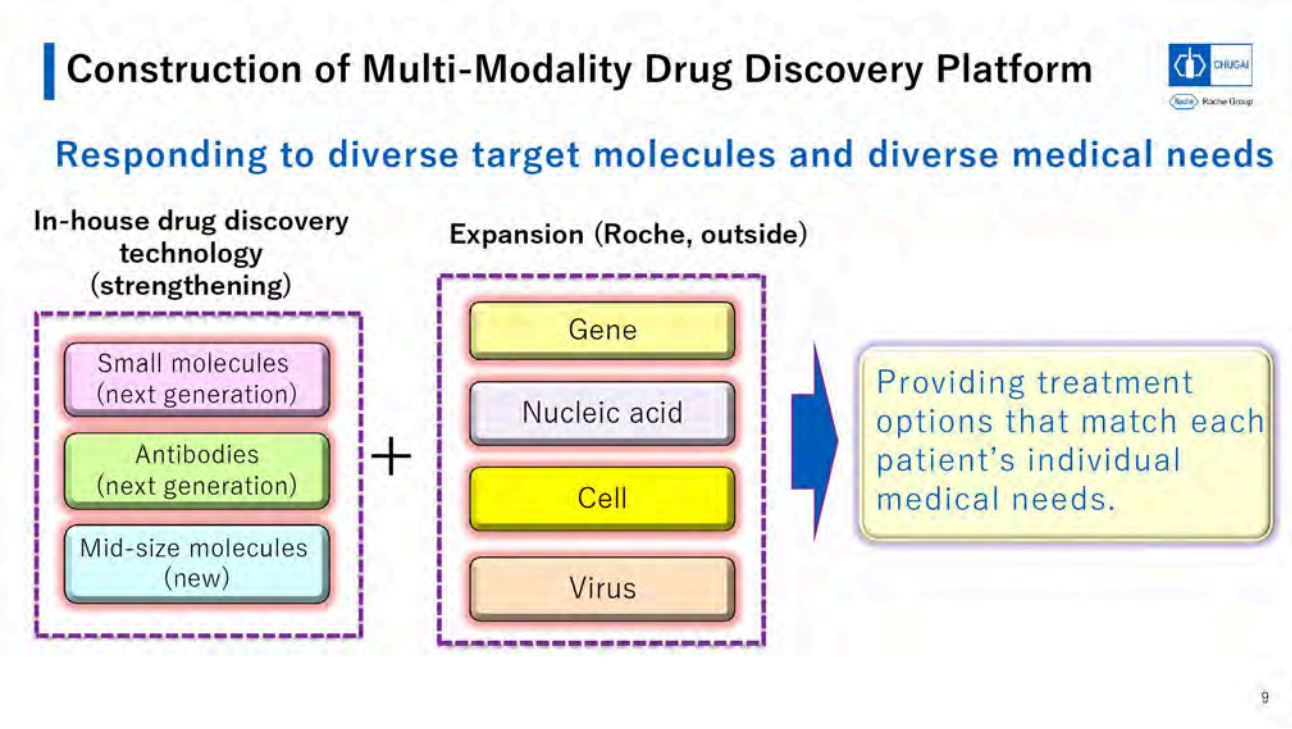
In this way, our most definitive approach is to create first in class and best in class products by developing new technologies.

On the other hand, it is not at all clear that this is the only way to achieve first in class or best in class. For example, suppose that we find a new drug target that is not currently known. Of the approximately 30,000 proteins, only about 2,000 are known to be associated with disease.

In this context, from the 1970s onwards, about 50 drugs have been developed from new targets every 10 years. There are still some that have not yet become drugs. On the other hand, there are still targets that have not yet been identified. Of course, our interest is not limited to proteins. There is a possibility that nucleic acids will also be targeted in the future. If we want to research such areas, we need an even more detailed understanding of disease biology.

This is something we would like to help in developing ourselves. This is the equivalent of the idea of biology that I mentioned earlier, and this is where we want to put special emphasis on external collaboration.

First, let me be a little more specific about the technology here.



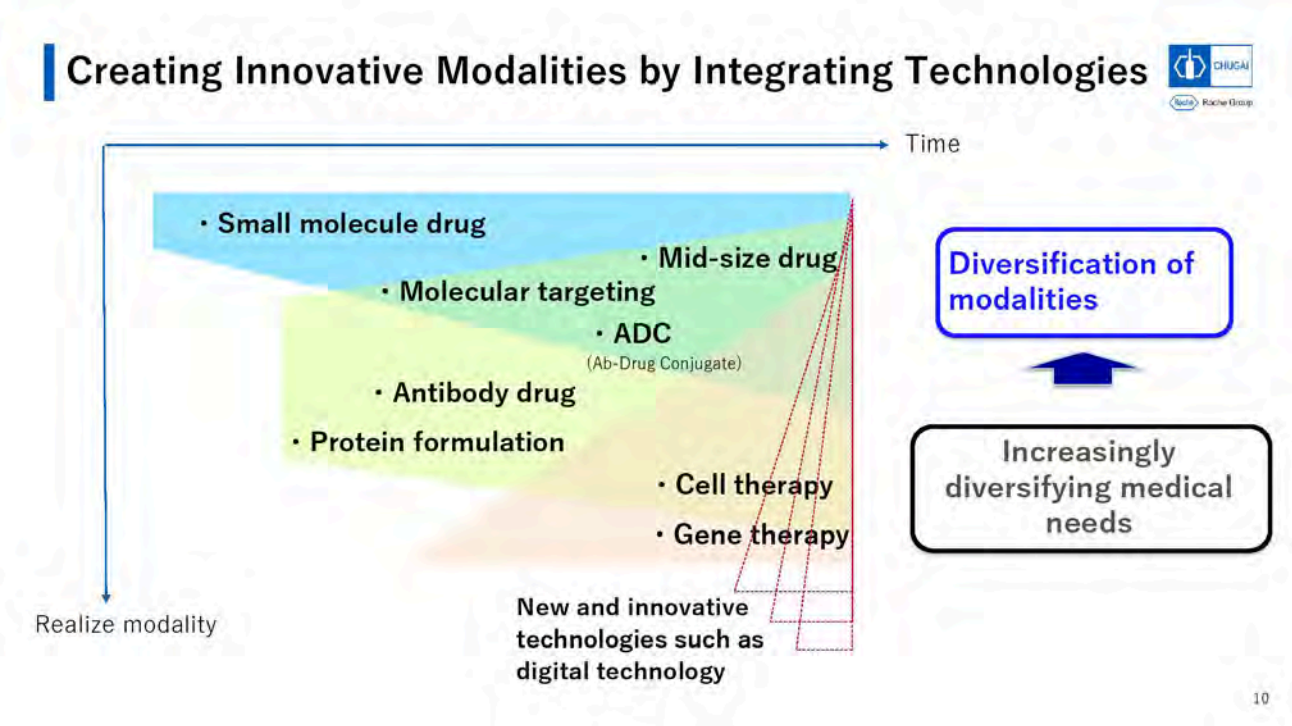
Chugai will strengthen our own technology in three modalities or fields. In addition to small molecules, which have been the mainstay of drug discovery for a long time, we also have a strong track record with antibody therapy. We also aim to highlight the area of mid-size molecules as our new core technology.

I will not cover small molecules in a separate slide today, but we believe that this is another area where we have the potential to do things that have not yet been done. This will also be an area of focus for our company.

In the 1970s, the focus was almost exclusively small molecules. Then biotechnology became big from around 1980, and we started developing into the area of mid-size molecules more than 10 years ago. Recently, the number of new modalities has been increasing rapidly.

This includes genes, nucleic acids, cells, and viruses. As part of our future strategy, we are considering what we can do in each of these modalities.

Of course, it may be difficult for Chugai to place equal focus on all of these areas on our scale. Perhaps, in some areas, our involvement will be a little more limited. In any case, we aim to add to what has come out so far and increase the treatment options for patients with a multi-modality approach.



This slide is a key discussion for how to deal with these 4 modalities.

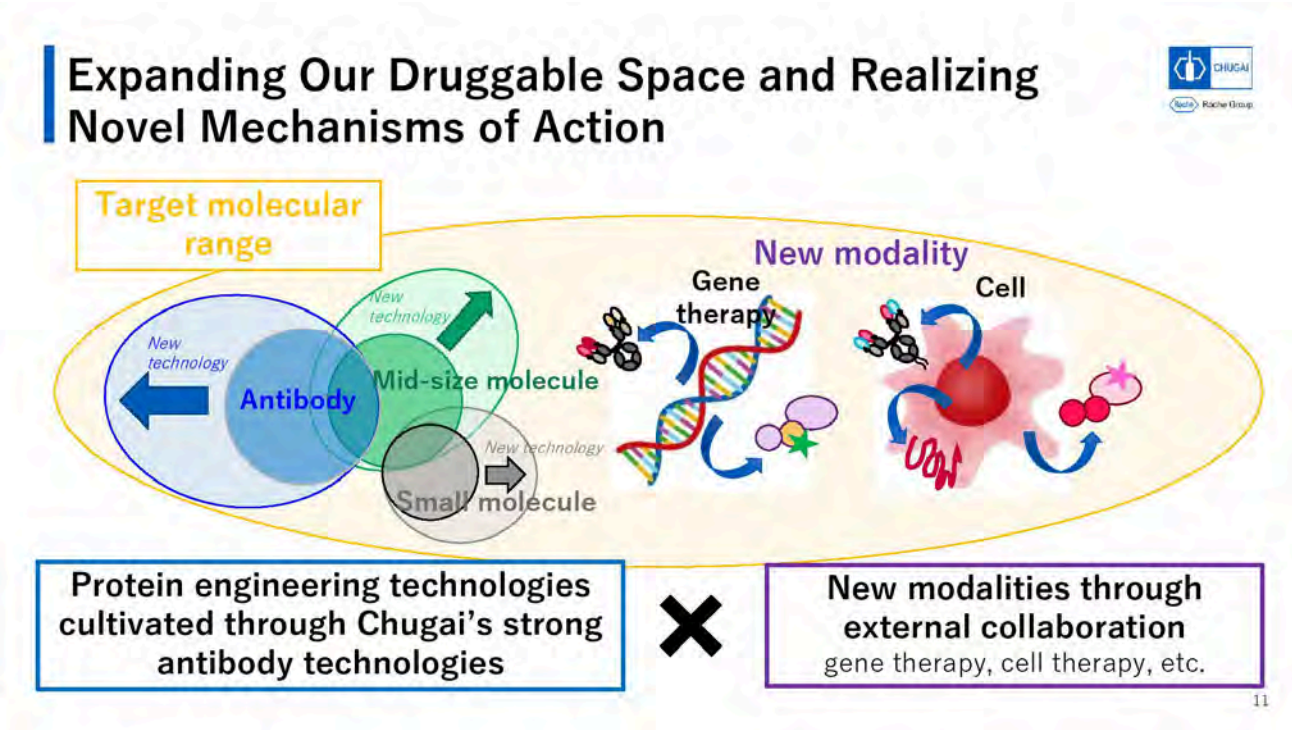
Here, our message will be in the word fusion. Small molecule drugs have been around for a long time, but with the emergence of protein drugs and antibody drugs, a borderline area has emerged. As you all know, ADC, antibody-drug complexes, can only be created by combining the power of chemistry and biotechnology. Where that happens, this kind of boundary area will be born.

Our contention is that most innovation comes from these boundary and fusion domains. Mid-size molecules, which I will explain later today, is just such a fusion domain. It was created by combining the power of chemistry with the power of biotechnology.

As I mentioned above, we are working on small molecules, mid-size molecules, and antibodies. If we continue to work on these alone, we will not be able to deal with the new fusion fields that are emerging.

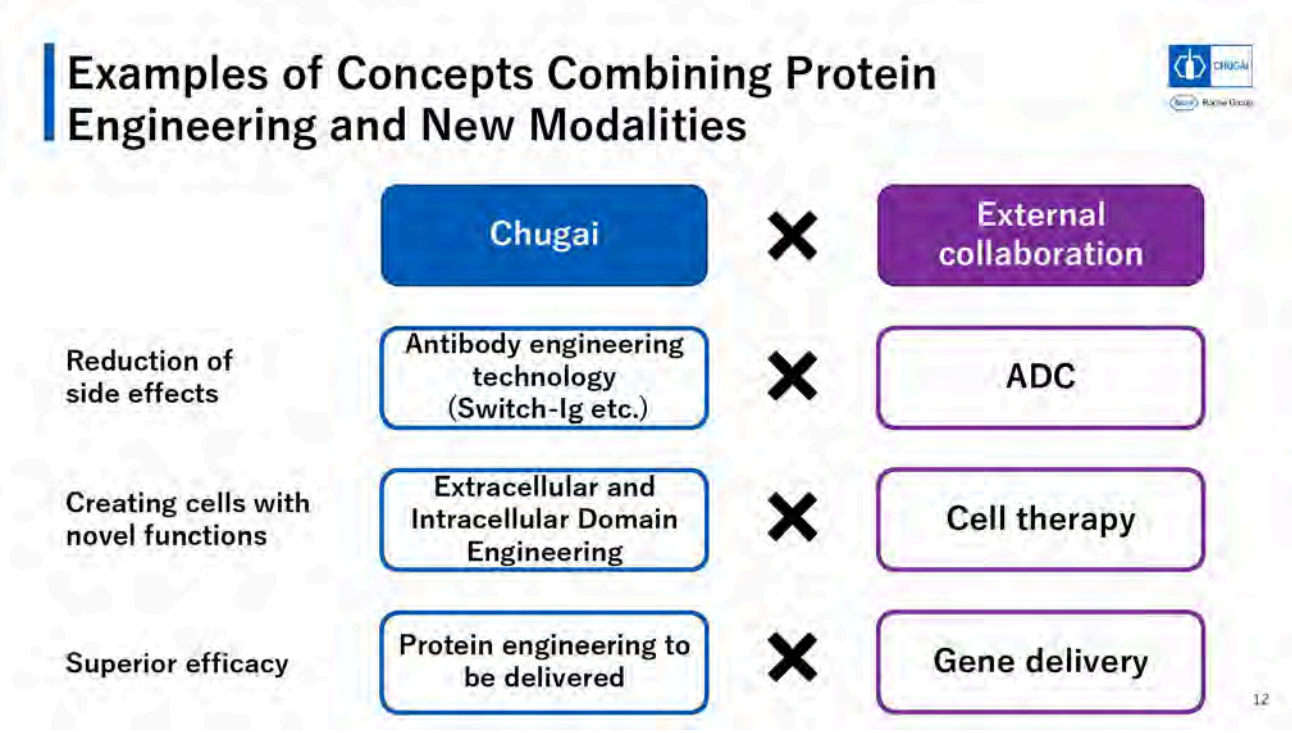
Furthermore, we were able to clarify what we should do because our company has a deep knowledge of both antibody and small molecule technologies. We have been able to identify the scope and limitations of both to some extent. Therefore, our current stance is that we should not leave these new fields unattended in order to grasp the current scope and limitations of drug discovery.

The next slide shows how our company, with its limited resources, will adopt such a strategy.



In other words, we will use our strengths in technology as leverage to enter new areas through external collaboration. Here, we use protein engineering technology as an example to illustrate the concept. In other words, our strength is the protein engineering technology we have cultivated through our antibody technology.

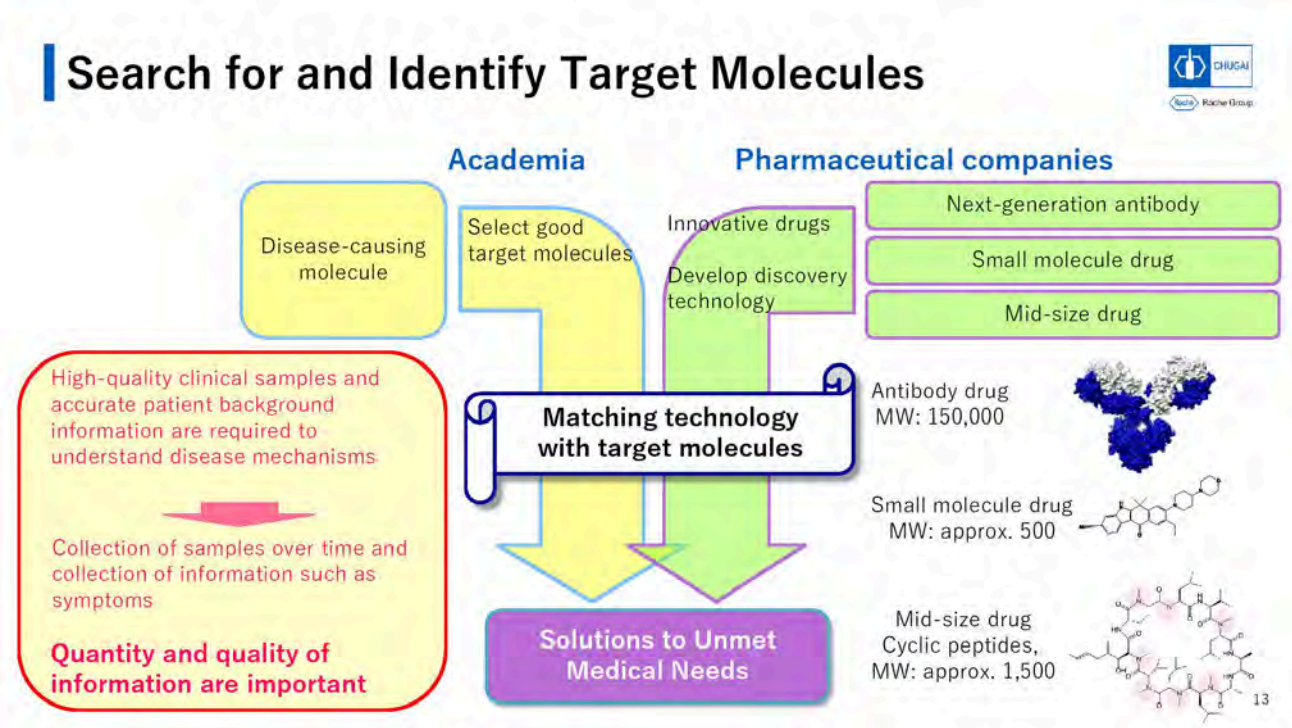
In order to move into areas such as gene therapy and cell therapy, for example, fusion areas must be created, and new value will be created from these areas. Our new strategy is not to do this all by ourselves, but to utilize external collaboration and open innovation.



For example, by combining ADCs from external parties and Chugai's antibody engineering technologies, such as switch antibodies, the side effects can be reduced.

Next, the field of cell therapy. By collaborating with external parties and using our strengths and engineering of extracellular and intracellular domains, we will be able to create cells with new functions.

Since we are almost running out of time, I will skip the third one and move on to the next slide.

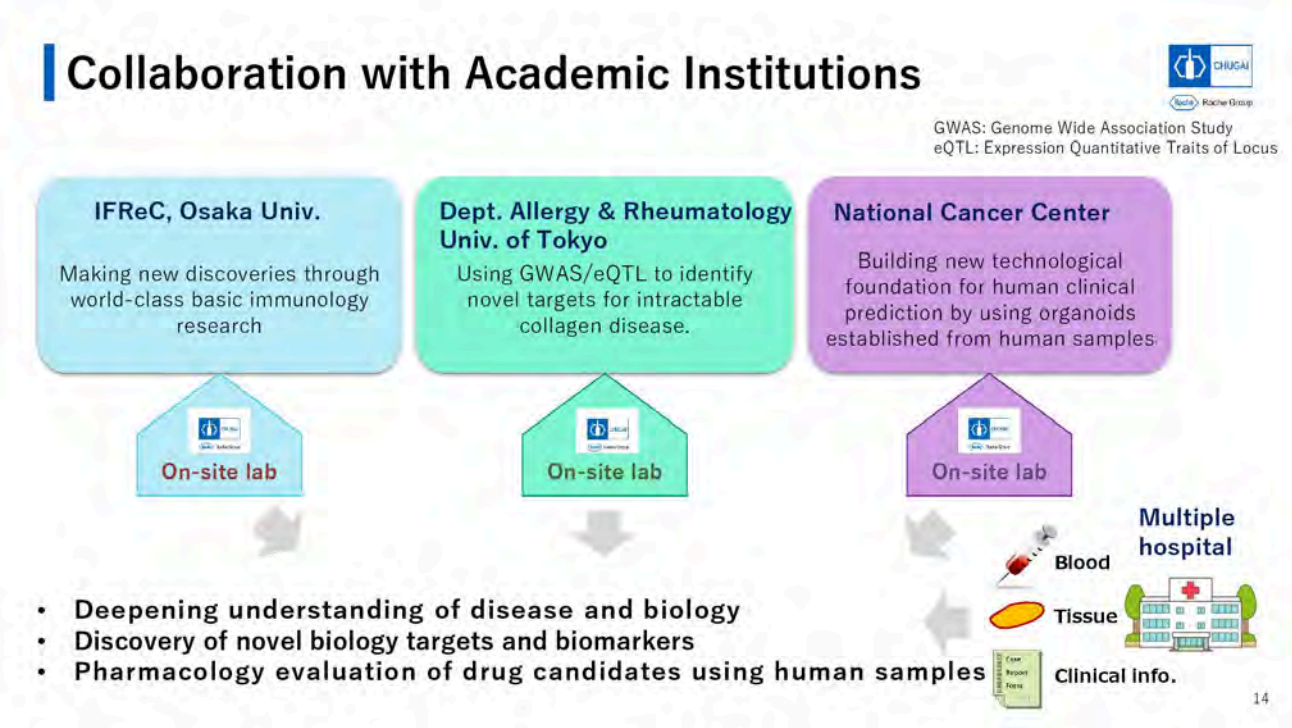


I have just briefly talked about the direction of technological development. Additionally, I would like to discuss how to determine the target and how to clarify the relationship between the target and the disease if it has not yet been clarified.

If this does not match, the potential for our technology to become a highly valuable pharmaceutical product may decline in the future. Of course, there are areas where we want to make drugs now but can't. Even if we do that, we will need to actively search for new targets ourselves.

We can't do this on our own either, so of course we will do it, but we will also adopt a strategy of more active collaboration with academia. This is because, compared to the past, much more accurate information is needed to elucidate mechanisms. We believe that high quality clinical specimens and accurate patient background information will also be essential.

I will be more specific about the search for targets here.

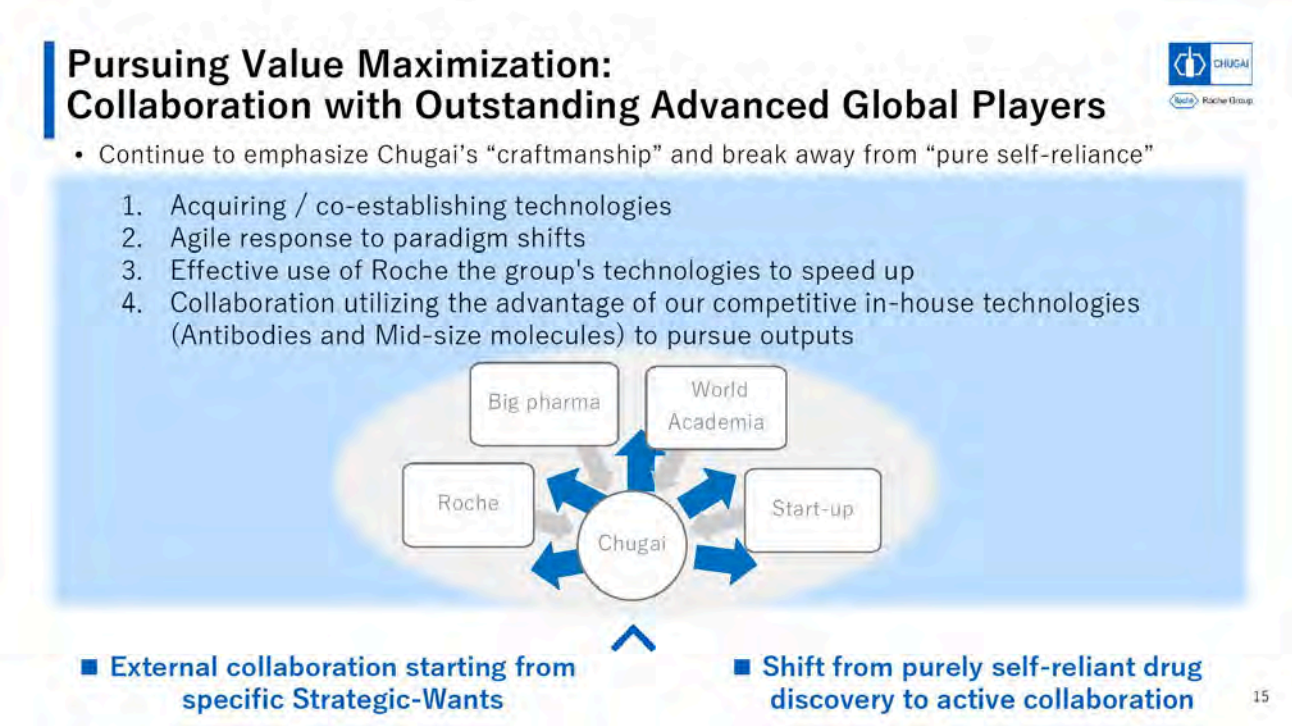


As for academia, I have listed 3 representative examples.

One is Osaka University, IFReC, another is the Department of Allergy and Rheumatology, School of Medicine, University of Tokyo, and the third is the National Cancer Center. There are a number of other collaborative research projects, but I have only mentioned 3 here.

What makes any of these somewhat different from conventional collaborations is that we have our own on-site laboratory at each location. This is based on the idea that if we really want to integrate beyond the boundaries of collaboration and create new value, we need to strengthen that collaboration. If we don't do that, it will be difficult to create something new.

We will continue to set up on-site laboratories to deepen our understanding of pathology and biology.



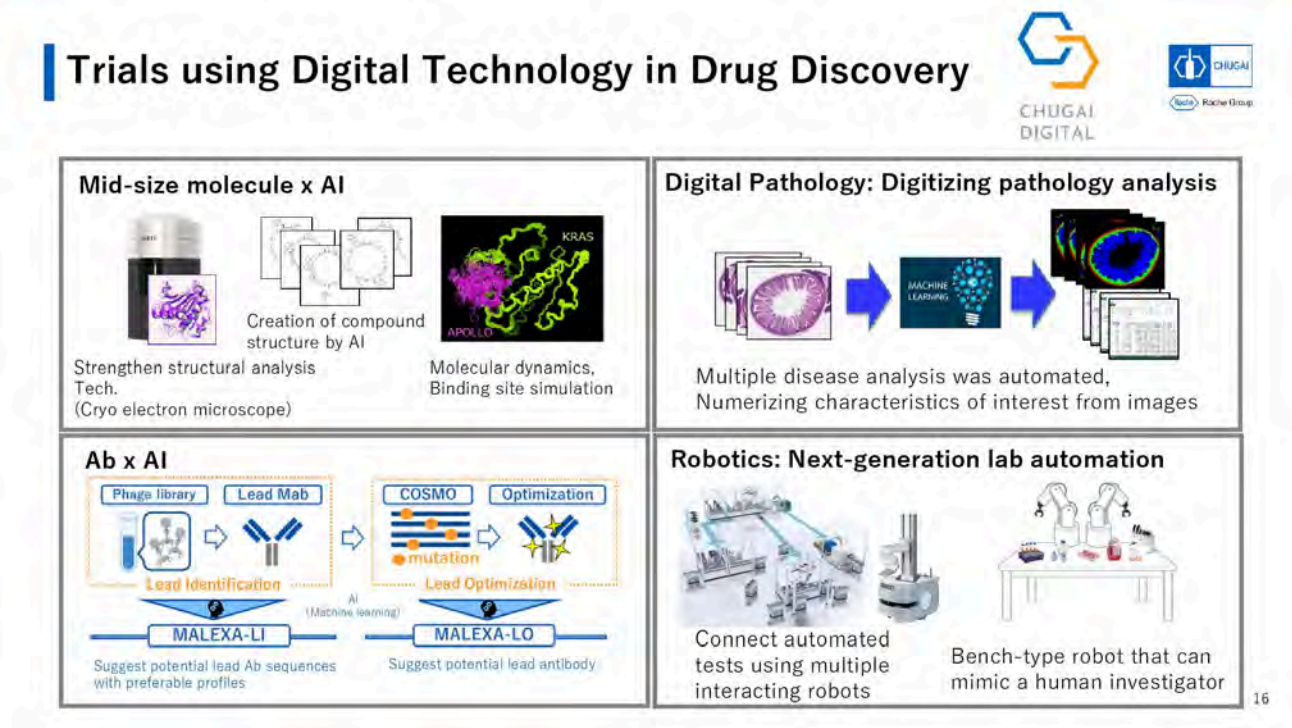
I have described the general strategy here, and I have mentioned open innovation and collaboration with external parties as keywords. I would like to reiterate the external collaboration.

Our company has long been engaged in pure self-reliant drug discovery. Self-reliance is the concept of creating the necessary competitive advantage on our own. We have no intention of abandoning this concept in the future. This is a very important concept for us, and we will maintain this concept.

At the same time, however, we are moving away from purely self-reliant drug discovery. The message is that we are shifting to a direction of delivering greater value by creating a collaborative system with a wider range of external parties.

In terms of acquiring technology, we will consider licensing technology from outside if necessary. In this way, as I mentioned earlier, we can clarify the scope and limitations of new modalities, and make a paradigm shift and increase the possibility of creating new value through integration. We will also further strengthen cooperation with the Roche Group.

We will devise ways to enable others to make use of our areas of competitive advantage. This is the policy we will pursue in our research.



The last part of my presentation on research is about the use of digital technology.

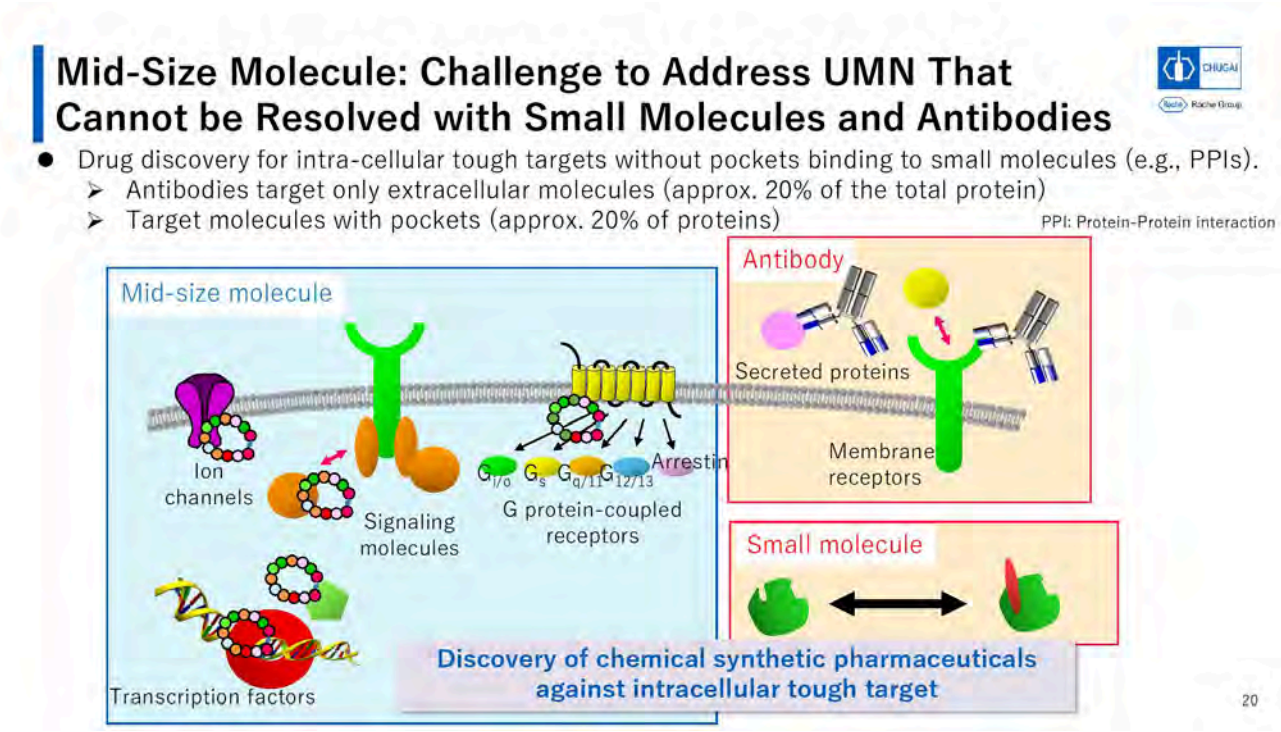
The ones on the left are areas where we want to have a competitive advantage of our own.

In other words, we will improve the efficiency of drug discovery by combining mid-size molecules and AI. This is an effort to improve the efficiency of drug discovery by combining antibodies and AI. Dr. Igawa will explain the antibody part in more detail later.

The parts on the right are areas where we would like to collaborate with external parties to create a system for more effective drug discovery.

For example, it is often said that areas such as digital pathology and image analysis can be applied most quickly to drug discovery. For these areas, we are collaborating with external parties and are making progress in some extent. Furthermore, we would like to strongly promote robotics. It is my understanding that the more we can do this, the more areas we can handle on our own.

That has been a description of the research section.



Next is an explanation of mid-size molecule drug discovery.

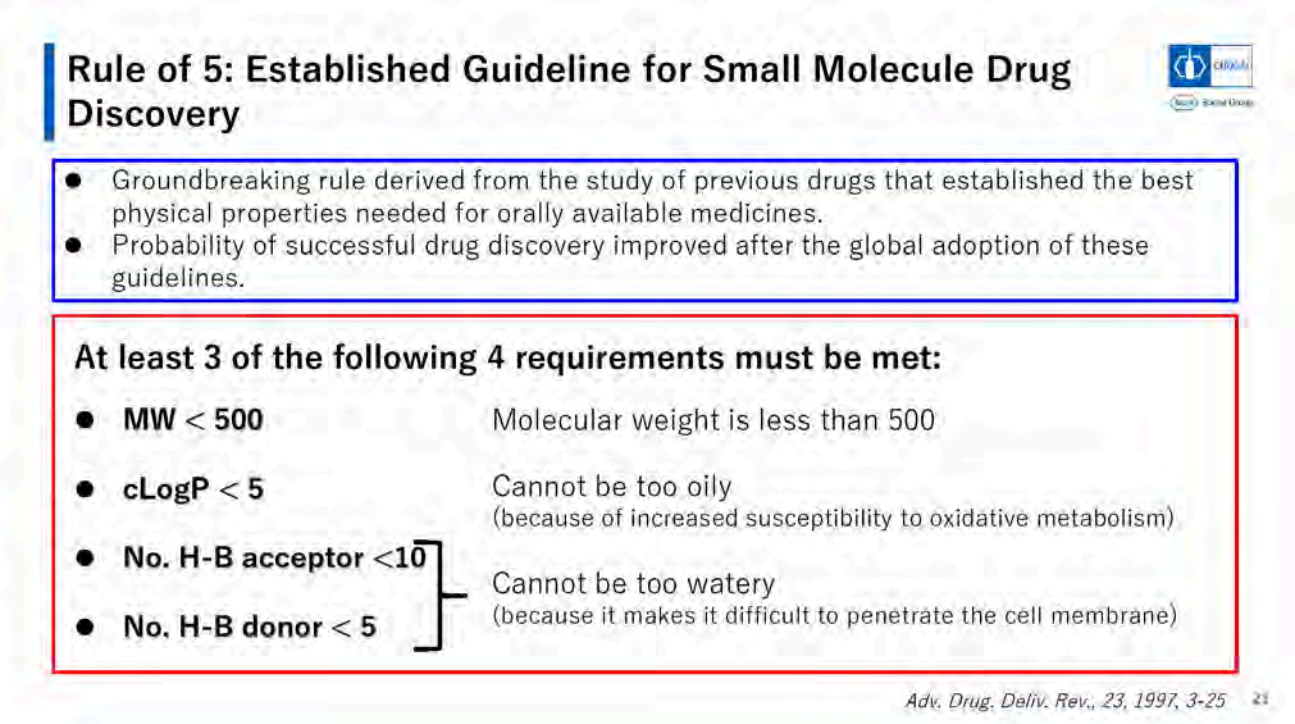
Here is what we hope to accomplish in what is called mid-size molecule drug discovery. Our goal is to achieve things that cannot be done with existing modalities such as antibodies or small molecules. We have been developing technology to do this.

Antibodies are not able to enter cells at the moment.

Drug discovery for antibodies is limited to the area outside the cell, but it is said that only about 20% of proteins are found here. This means that 80% of protein targets are inaccessible to antibodies.

Small molecules, on the other hand, can enter cells. But, it is well known that these small molecules need deep holes, or pockets, in order to stick together. It is said that only about 20% of all proteins have these so-called pockets.

Therefore, no matter how much we want to, there are many areas where conventional modalities such as small molecules and antibodies cannot be used for drug discovery. In particular, proteins that are located inside cells and do not have clear pockets are difficult to approach with existing drug discovery methods. Chugai's mid-size molecule drug discovery and technology development program aims to address this.



An important thing to keep in mind when talking about mid-size molecule is a rule that applies to small molecules, the so-called rule of 5.

Prior to today's presentation, I saw a record of communication between our company and analysts and investors, and one of their comments was from an individual with the impression that mid-size molecules are similar to small molecules. I thought that was a very astute point.

In drug discovery, we generally consider small molecules to be those with a molecular weight of 500 or less. Antibodies, on the other hand, have a molecular weight of roughly 150,000. While on the contrary, mid-size molecules have a molecular weight of about 1,000 or 1,500, so they are 2 or 3 times the size of small molecules. They are about 1/300 the size of the antibody, so if you ask me which molecule is closer to which, of course I would say that mid-size molecules are closer to small molecules.

With that in mind, I would like to talk a little about small molecule drug discovery.

This Rule of 5 is a truism for small molecule and synthetic drug discovery researchers. I have been engaged in chemistry for a long time, and I have been following this rule in drug discovery for a long time.

Why? Anything that meets this rule can maintain its medicinal quality. Medicinal properties include excellent metabolic stability, the ability to penetrate cell membranes, and the ability to dissolve in water.

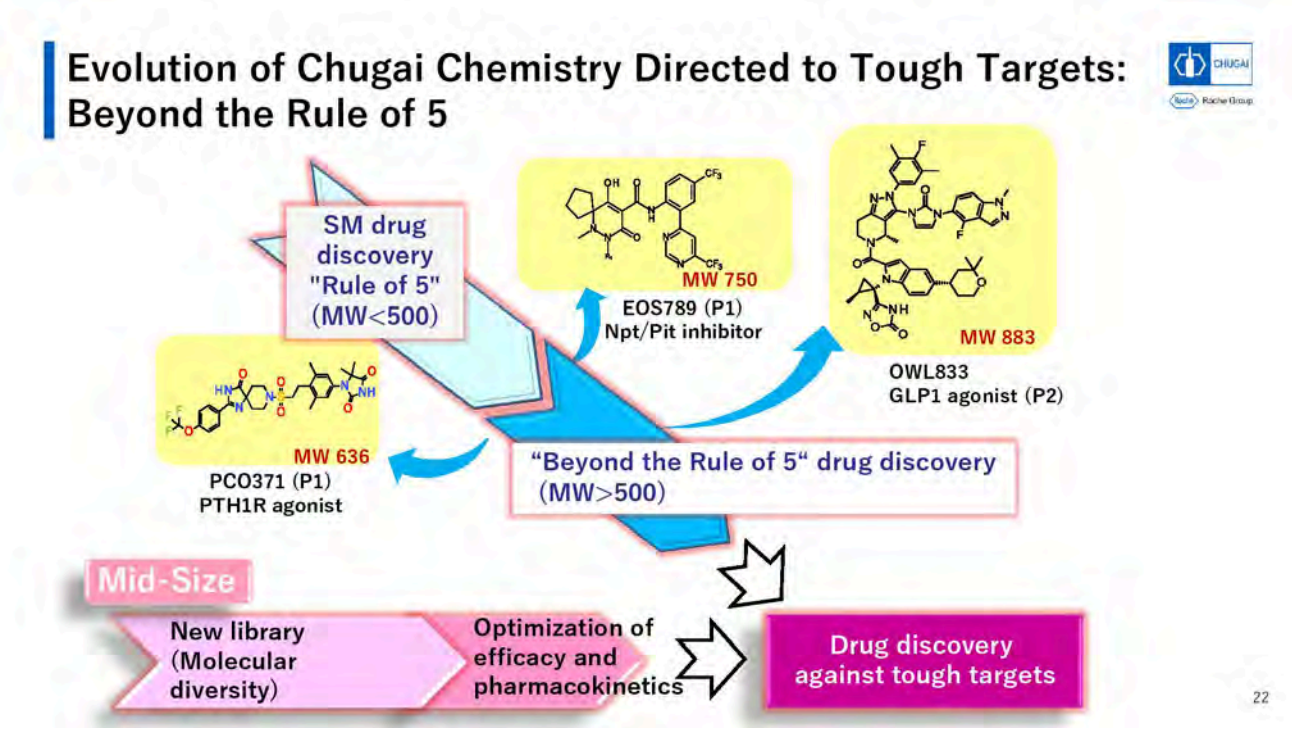
If the basic properties of a molecule are drug-like, then if it can selectively bind to a protein, it has a lot of potential as a drug. Conversely, without these properties, it is difficult to make it into a drug, no matter how strongly it binds to proteins.

This is a crucial rule, as it shows that a very important property on the compound side is likely to be satisfied if this property is satisfied.

The 5 in the Rule of 5 is the 5 in 500, and cLogP 5. The No. H-B acceptor is 10. This is a multiple of 5. It is also said that it is important that 3 out of the 4 are satisfied.

The molecular weight should be less than 500. The cLogP is a measure of oiliness, so it should not be too oily. This is because it undergoes oxidative metabolism.

These bottom 2 things also look like code to many people, but they are saying that it should not be too watery. If it is too watery, the compound has trouble penetrating the cell membrane. Therefore, the basic rule for small molecules is that they should be neither too oily nor too watery, and their molecular weight should be less than 500.



Essentially the entire human history of drug discovery has been based on these rules, so it has been difficult to grasp the properties of drugs other than those satisfying the rule of 5.

We have been focusing on the world outside of the Rule of 5 for about 20 years now. The result of this is we have 3 Rule of 5 drugs with molecular weights of over 500 now in clinical trials. These are not peptides. In particular, this OWL, which was mentioned recently, is now moving smoothly into Phase 2.

What we found out in this drug discovery was that we could indeed make it drug-like even if it exceeds the molecular weight limit of 500 defined by the rule. However, it would take a huge amount of time to do so. This is because the route of progress wasn't clear to us.

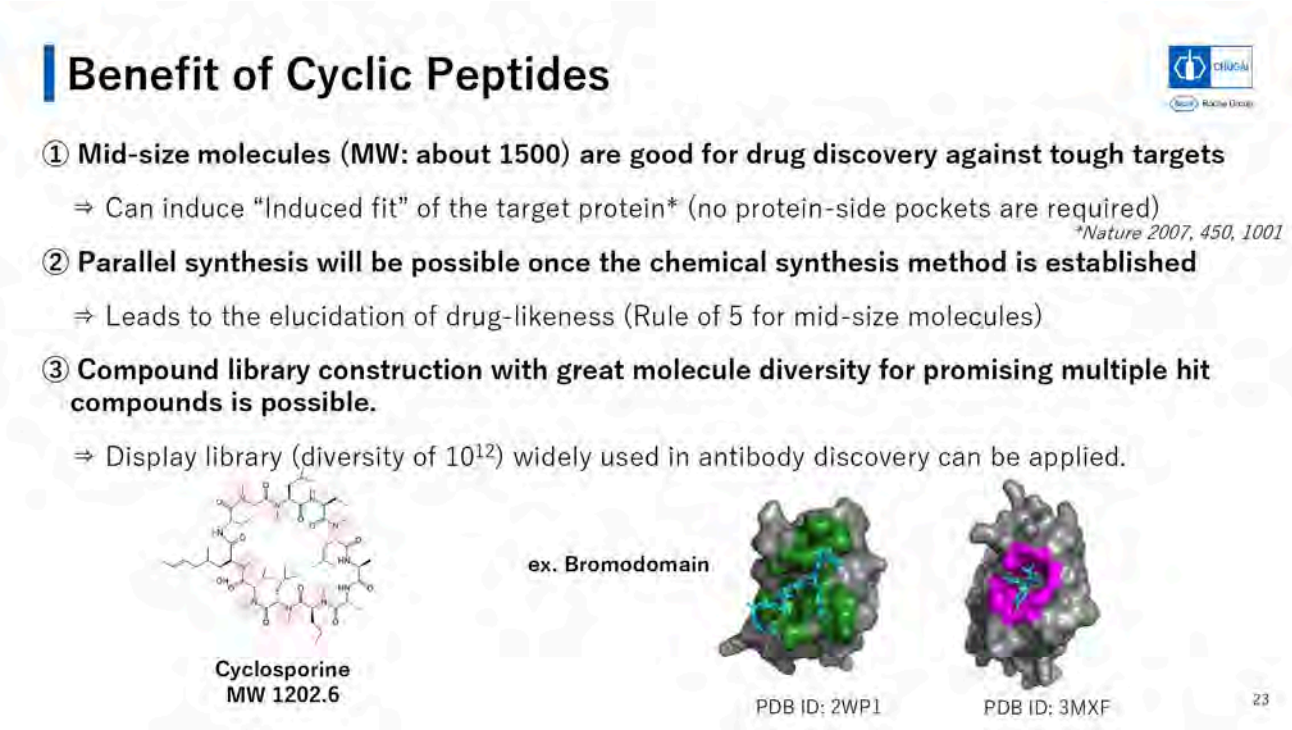
It took a lot of time and resources to do this. For example, it took about 20% of our medicinal chemists, and about 7 or 10 years, to accomplish. It requires a huge number of rules. This also illustrates what's so great about the rule of 5.

If we had a similar rule we could use for mid-size molecules, it wouldn't take as many personnel or as much time. Since there were no such rules, it was difficult to make such a drug. Even so, we are proud of the fact that we have persevered and produced these valuable products. At the same time, we still need to improve the process.

We have previously received questions about whether our mid-size molecules have really entered cells.

While we can't release any specific data, I would like to show as much information on this as possible. We have a lot of experience in making drugs according to the rule of 5, and we thought we could do it. But the difficult part was that we didn't know what to do because we didn't have those rules, so we could only create drugs very inefficiently.

As a result, we started activities to create a new platform for drug discovery for mid-size molecules.



We have chosen cyclic peptides, and here we have shown why we chose cyclic peptides.

First of all, tough targets, as I mentioned earlier, are those that are inside cells and do not have clear pockets. It has become clear that mid-size molecules, those with a molecular weight between roughly 1,000 or 1,500 or 2,000, are likely to be effective against these targets.

For example, as published in Nature in 2007, what this means is that the surface of these proteins was generally thought to interact loosely in this green region before, so they were said to require a molecular weight of 3,000 or so. With a molecular weight of 3,000, it would indeed be difficult to pass through the cell membrane. What we have learned is that if appropriate molecules are taken, it is possible to interact sufficiently in the region shown in red.

In this way, the shape of the protein changes depending on the molecule, making it look like a hole. This is called induced fit, and a number of examples have shown that induced fit can occur. Considering this, we thought that if we could develop drugs with a molecular weight in the range of 1,500, this would be enough to pass through the cell membrane.

For example, cyclosporine, which you know is a cyclic peptide drug, has a molecular weight of 1,200, is orally absorbable, has a bioavailability of 40%, and has an effect on intracellular tough targets. It's a very commonly used drug. There are other examples too.

The next thing is that parallel synthesis is possible once the chemical synthesis method is established.

For instance, as I mentioned earlier in the example of our drug, OWL, it would be amazing if 1 researcher could create 40 compounds in 1 year for such a complex molecule. We made 4,000 compounds to get it into clinical trials.

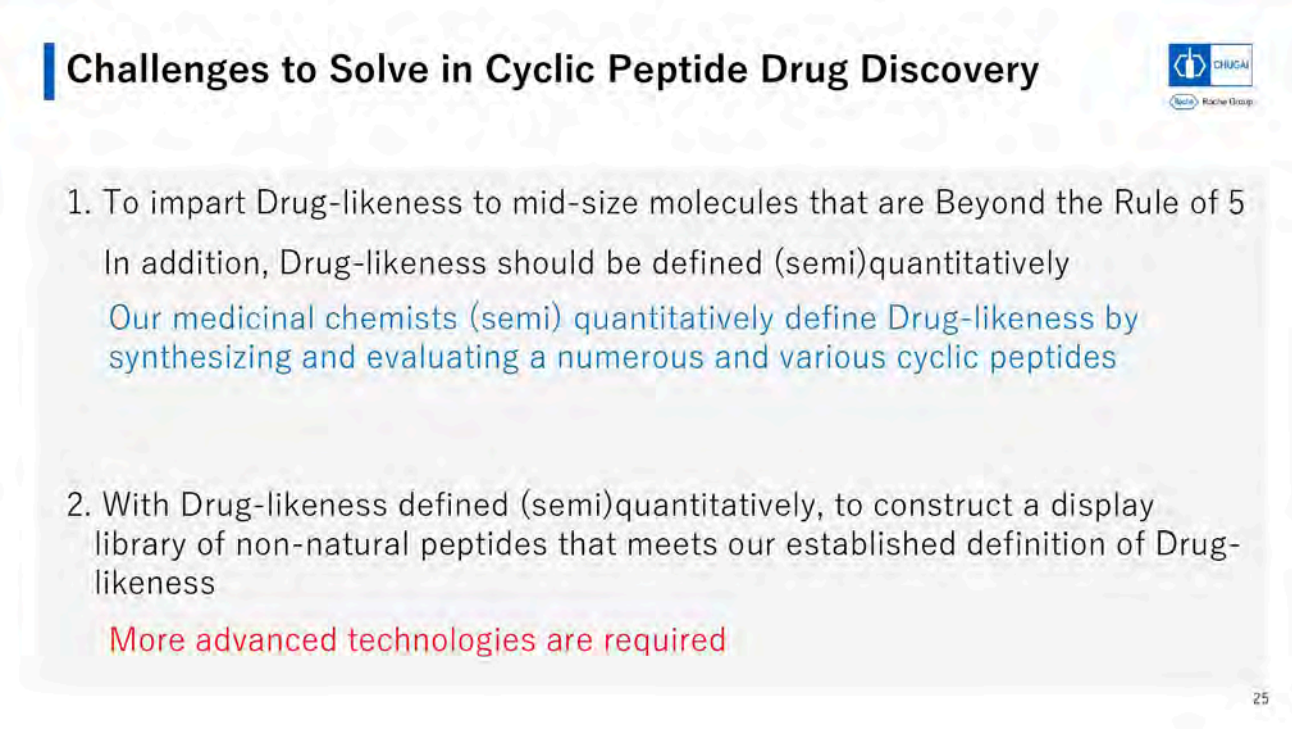
This means that it is necessary to know how much effort was put into the project, but also that it was important to be able to develop a certain amount of compounds to explore unknown areas. In the case of peptides, parallel synthesis is possible once a chemical synthesis method is established.

We now have a stable output of more than 10 times the output of small molecules with a single researcher. With this, the Hit to Lead would be higher, but at the same time, we wanted to elucidate the drug-like properties of mid-size molecules. Without this, even if it binds strongly to proteins, it would be very difficult to make it drug-like.

Third, we can create a library with a large molecular diversity in order to get multiple promising hits. When it comes to peptides, we can use biotechnology, and one of the strengths of biotechnology is that it works at 10 to the 12th power. Using the Display Library technology, we can obtain such diversity.

Incidentally, high-throughput screening with compounds is said to be 1 million compounds, which is 10 to the 6th power. With biotechnology, the variety is so different that that 10 to the power of 6 is multiplied by another 10 to the power of 6. We thought that this diversity, this ability to use biotechnology, was also a very big advantage.

For these reasons, we have selected cyclic peptides as the focus of the next generation of technology.



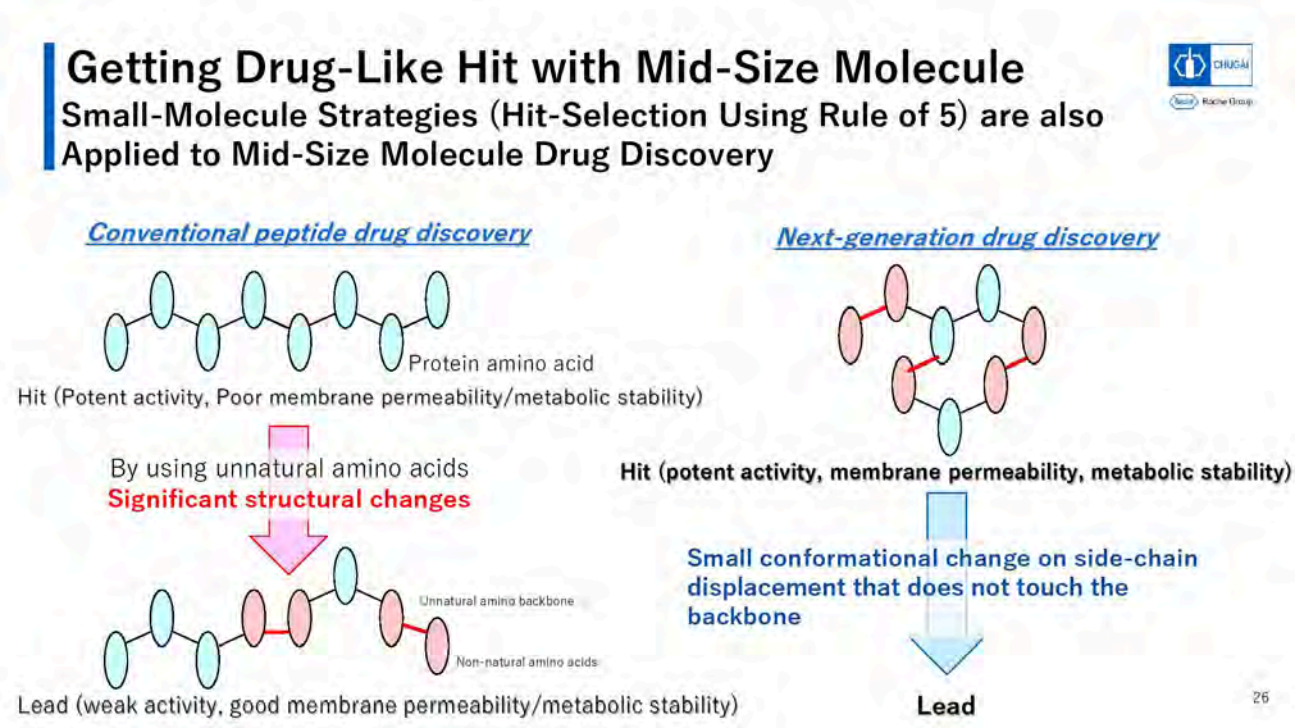
As I mentioned at the beginning, there were several examples of drug-like substances outside the rule of 5, but there was no knowledge of what characteristics would make a substance drug-like. The first thing we did was to collect this data by ourselves.

In other words, we used our skills in medicinal chemistry to synthesize and evaluate a huge number and variety of cyclic peptides to identify, semi-quantitatively, those that looked like drugs.

The fact that these compounds can enter the cells was something that we knew they could do. After that comes the next challenge. Assuming that this can be done, the question is whether it is possible to construct a display library of non-natural peptides that meet these requirements.

This was more advanced than expected. In fact, when we first found out what was required, we thought it was hopeless. This is because it requires very advanced technology. When we showed this to our biotechnology experts, however, they said they could handle it. So we started to build this kind of Display Library.

Today, I can't tell you what kind of technology was used to make this happen, but I can give you an overview of the concept.



I'd like to go back to the question of why this is necessary.

Conventional peptide drug discovery so far has been based on the idea that the first hit compounds, for example, whether you look at GLP or PTH, have very potent activity, but are not membrane permeable or metabolically stable.

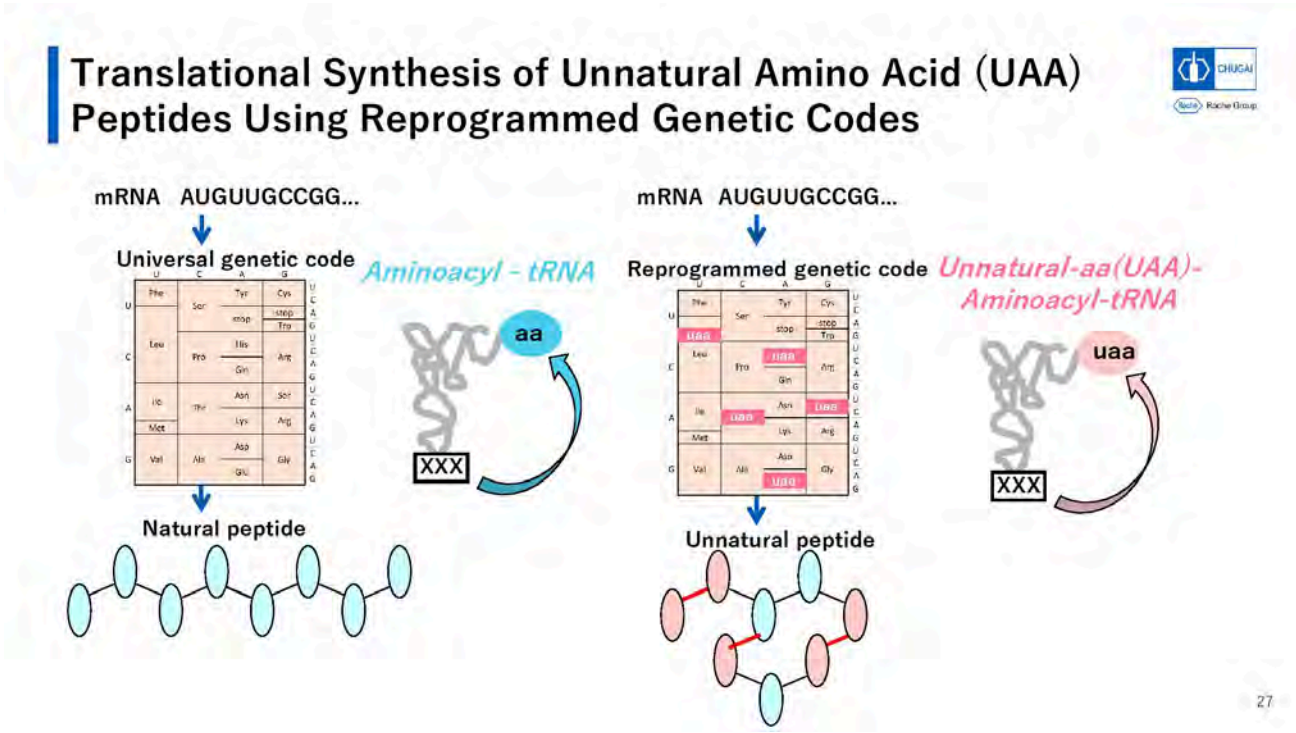
In order to add these properties, a great many transformations have to be added, and as a result of the many transformations, the form completely changes from the original form. In other words, by the time it has achieved metabolic stability and membrane permeability, it is no longer active at all. This is one of the challenges that peptide drug discovery has been facing for decades.

In contrast, our approach is to obtain a drug-like hit in advance. That's why we defined properties of a medicine first. It is difficult to achieve this with biotechnology, but this is what we have focused on achieving.

Once this is done, no major structural changes are needed to achieve membrane permeability or metabolic stability, so small structural changes can be linked to drugs. This is exactly how small molecule drug discovery has blossomed. With something like the rule of 5, we can be sure that almost anything that is in high-throughput screening will be applicable. As a result, the hit compound is drug-like, so we were able to bring

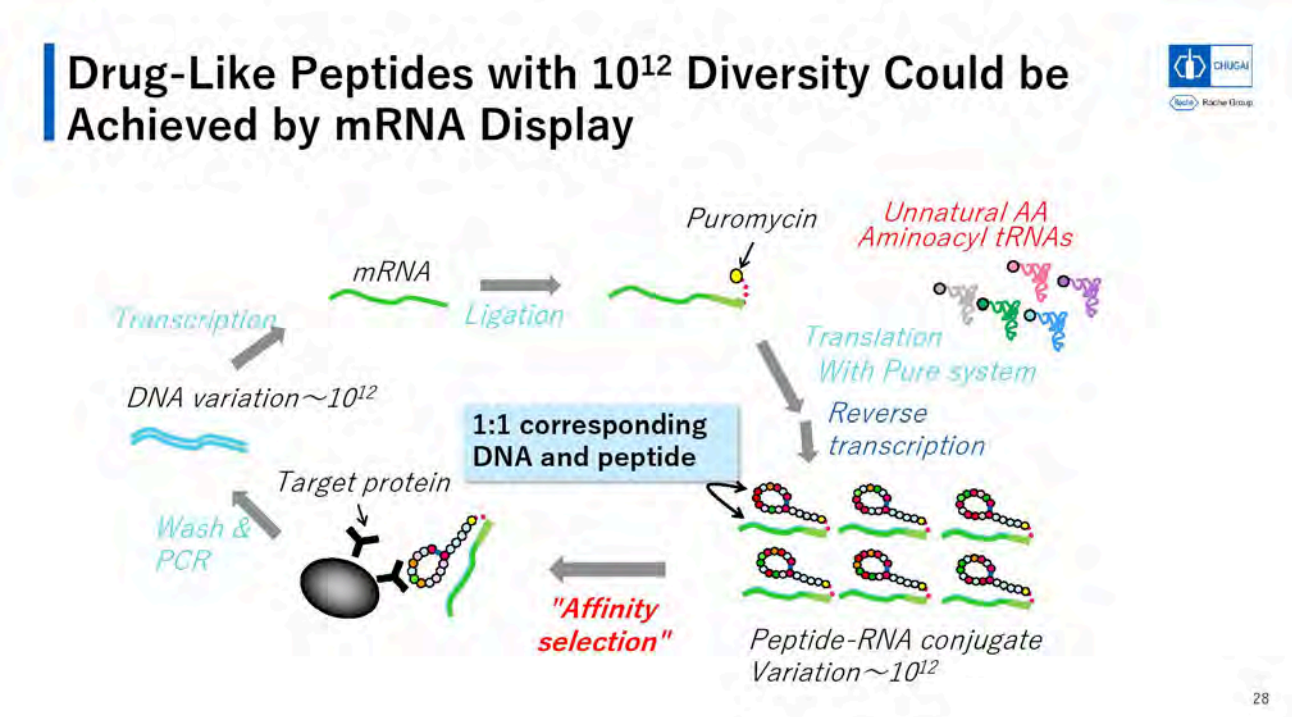
it to medicine without major structural changes. This means that the efficiency of the system has been increasing.

We have been studying the application of this same approach to mid-size molecules.

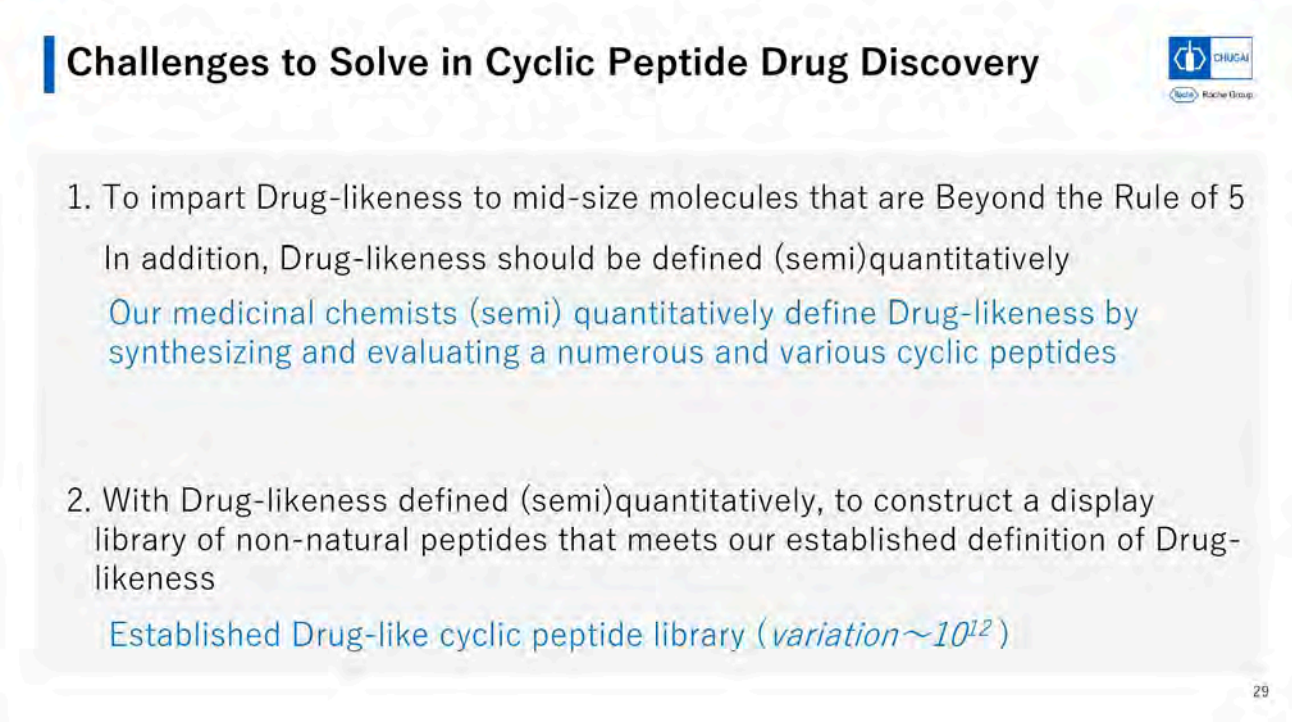


As for the specific methodology of how to do this, if you have mRNA here and you use an ordinary codon table, this codon table has codons that recognize the 3 residues of the mRNA and amino acids attached to it, and this kind of molecule becomes aminoacyl-tRNA. The combination of these 3 is translated 3 at a time to form natural peptides, and the codon table can be rewritten.

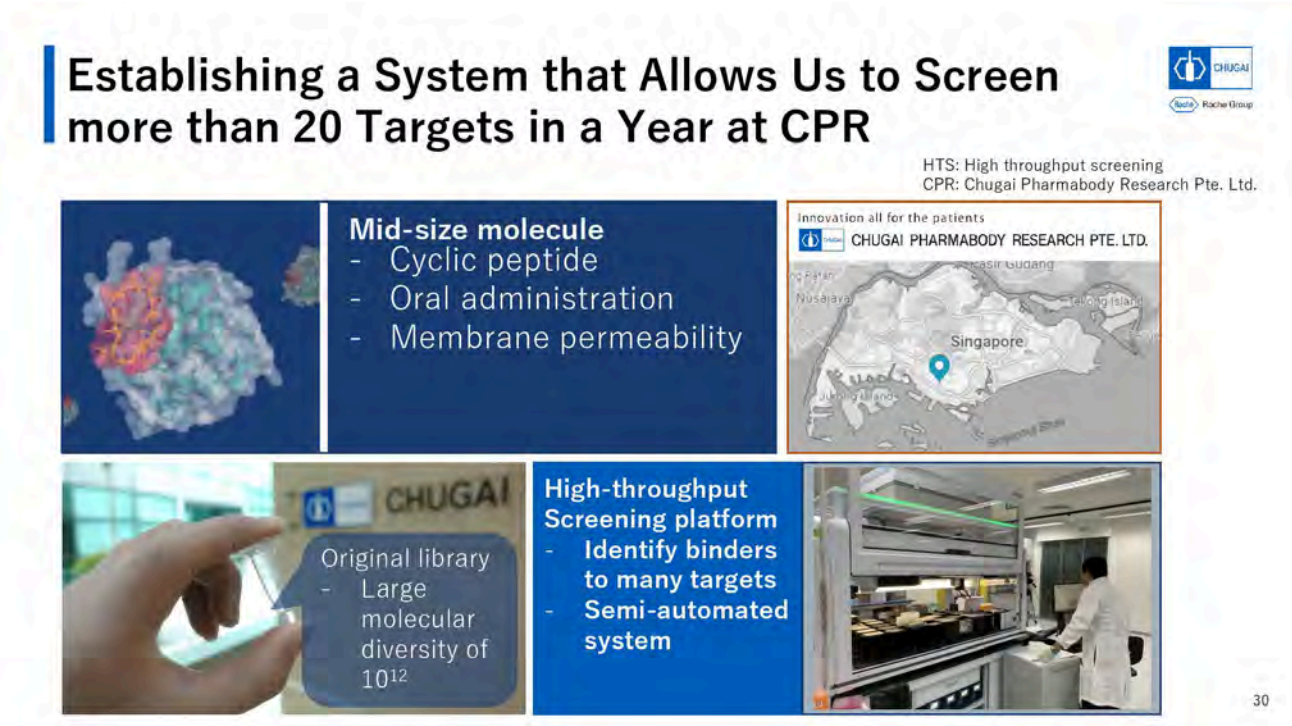
In other words, by changing this combination, it is possible to develop unnatural amino acids. Basically, it is possible to translate peptides with unnatural amino acids through biotechnology. This is where we had to do a lot of work.



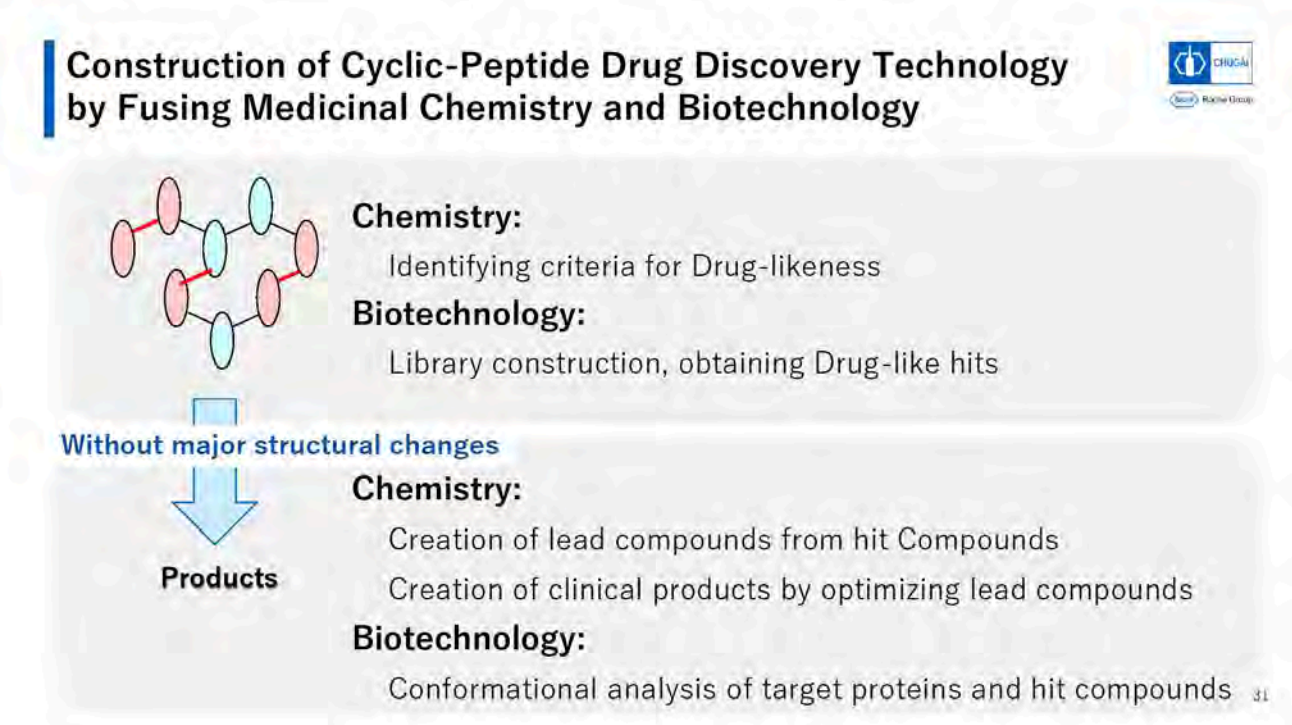
Another method, mRNA Display, was used to achieve diversity at the level of 10 to the 12th power. This technology is commonly used in antibodies, but if you use it, you can attain this level of diversity. I've been going on about this today, so I'll skip this part, but this is something we can do.



As a result, we were able to create something that was adequate for both tasks. In other words, as for the question of whether it is possible to construct drug-like peptides and non-natural display libraries, we have succeeded in doing so.



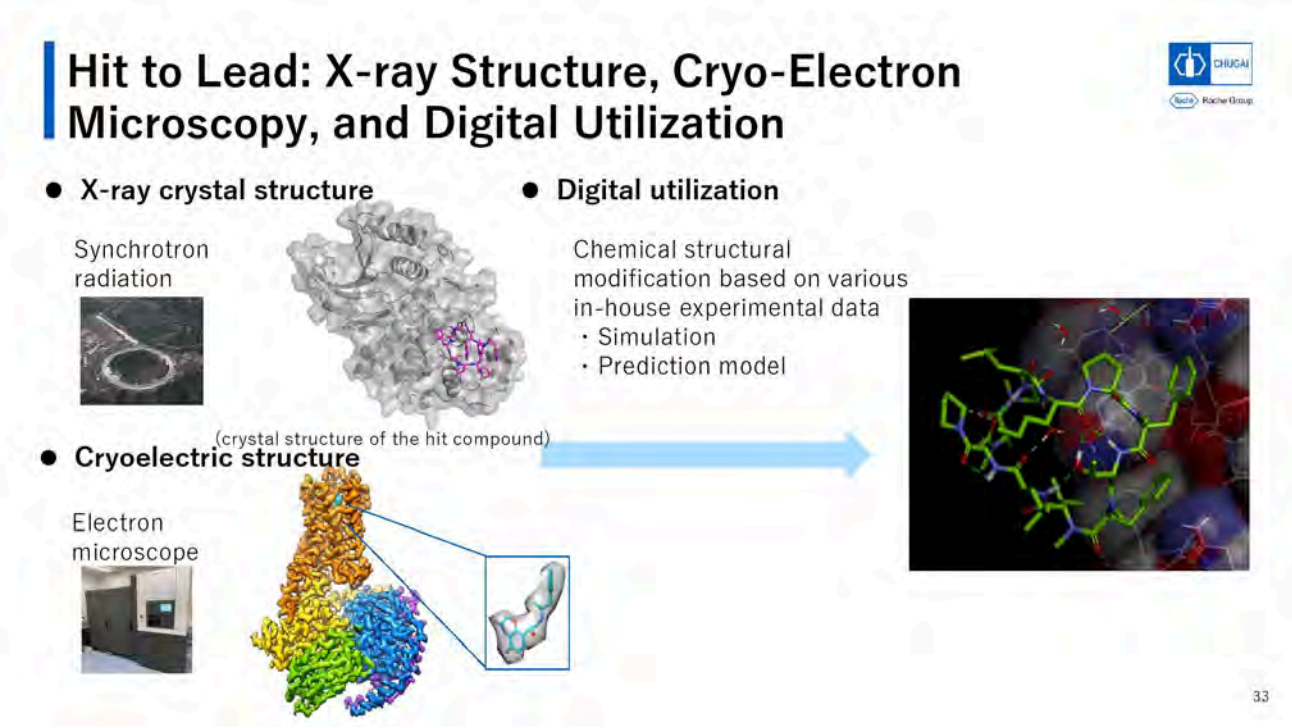
CPR has a laboratory in Singapore, where we can screen more than 20 targets in a year. In these tests, there will be 10 to the power 12 different molecules in a tube like this. This is the beauty of biotechnology, I think.



I'll give a quick summary.

The first step is chemistry, to identify what is drug-like. Then we use biotechnology to build the technology to obtain hits. These can then be made into drugs without major structural changes. Since this is a hit to lead project, chemistry will be responsible for this part, and biotechnology will be responsible for providing structural information to facilitate the process. This is where I think one of the keys to efficiency will be.

In this way, I think we have been able to make use of our strengths in both medicinal chemistry and biotechnology. We call this fusion, and one of our policies is to do this from other resources as well, and in the future, to use external resources as well.



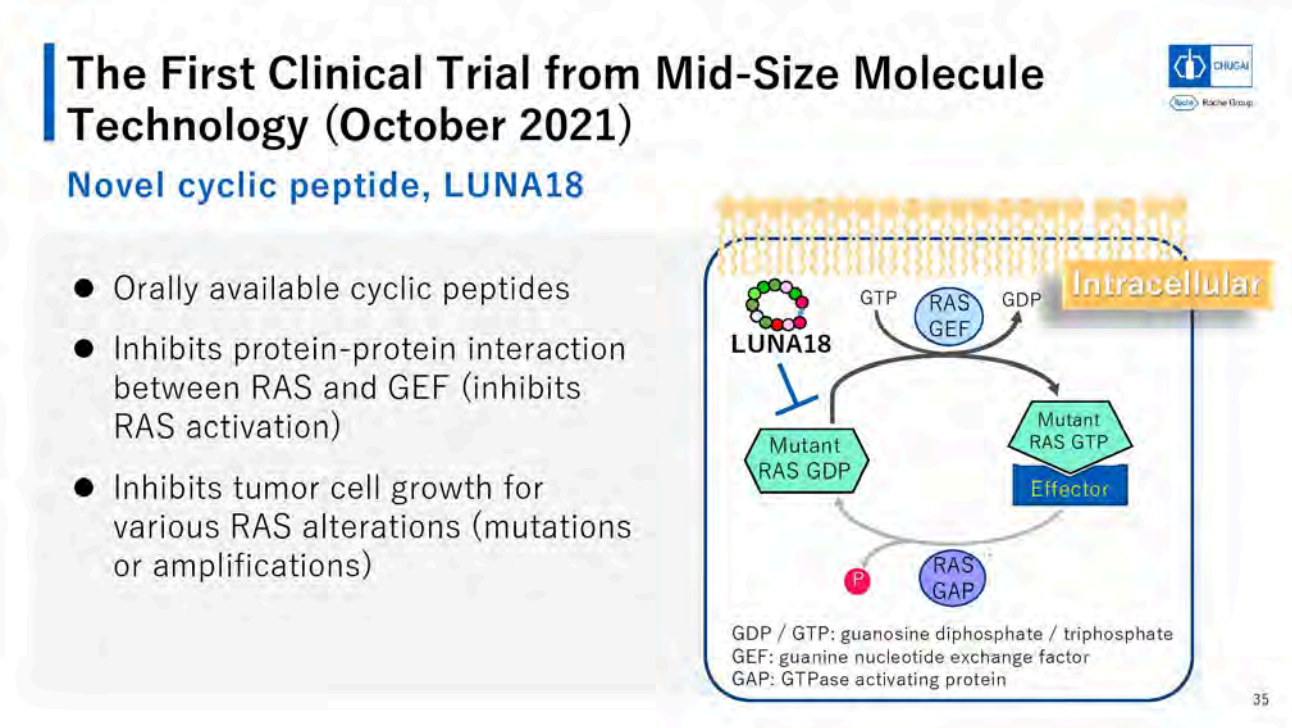
The foundation that supports mid-size molecule drug discovery is the X-ray structure. This shows how exactly protein binds to the mid-size and small molecules. In addition to this, we have recently introduced cryo-electric microscopy, which is a very good tool for us to know what we need to change to increase activity.

This will be a revolutionary technology because it will allow us to obtain this kind of information even without crystallized cells. At present, X-ray assessment requires crystallized cells. As I mentioned at the beginning of this presentation, we are now building such a system to increase the speed of our research by utilizing digital technology.

Next, we decided to make a very large investment in the construction of production facilities, and built a system that can supply compounds up to the initial commercial production by ourselves.

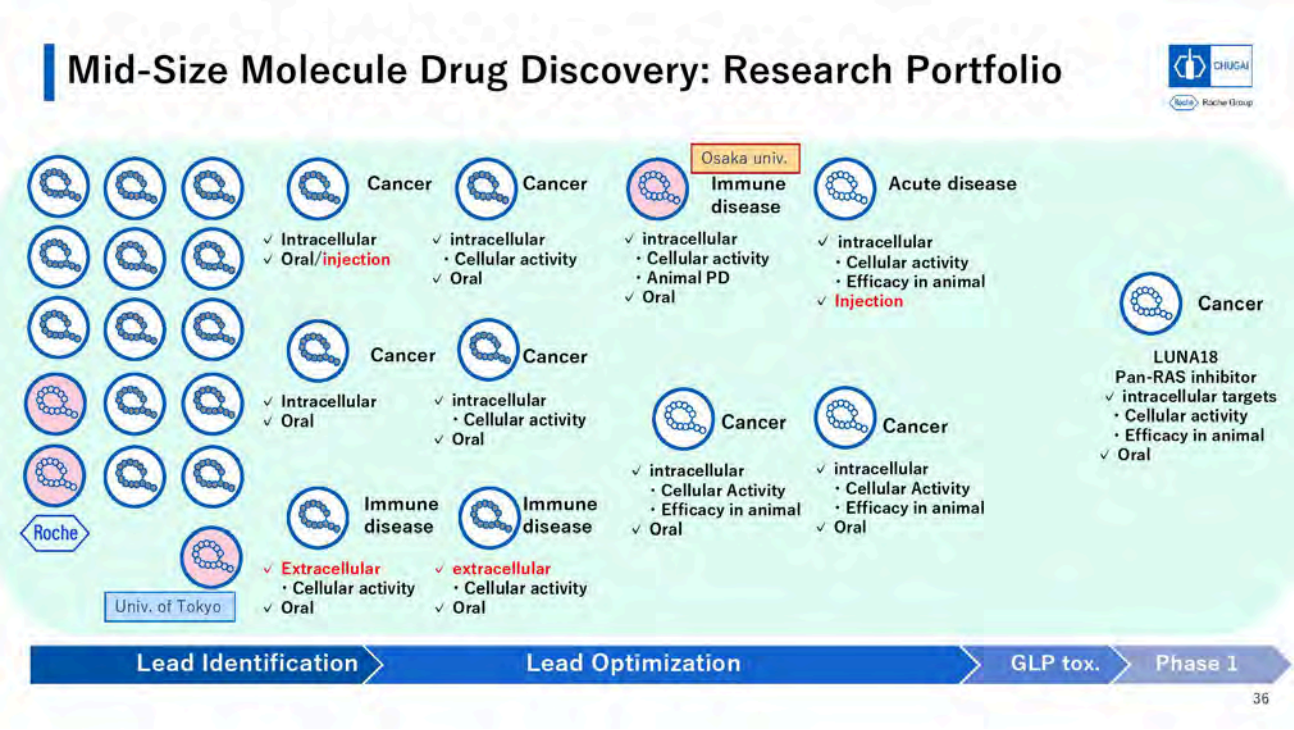
Returning to slide 31, one of the messages here is that chemistry and biotechnology are merging to create mid-size molecule, and after Hit to Lead, it is all chemistry. Biotechnology is suitable for the preparation for the screening of a wide variety of molecules at the 10 to the 12 level, but it is not so suitable for the mass production of such compounds. That part requires chemistry.

We are in the process of establishing such a facility.



This is about LUNA18, which we have just announced.

LUNA18 is such a novel cyclic peptide, and it binds to the RAS protein. I think it was Nomura Securities who showed this the other day, and I thought that they had done a thorough investigation of what we were trying to say. RAS has always been a target that we wanted to discover, but it has been difficult to do so. We have selected RAS as the first target, the first tough target, and we are working on it. The target is intracellular, and this is being developed as an oral drug.



Lastly, as I mentioned at the beginning of this presentation, we are unable to provide specific experimental data, so I will present it in the form of a portfolio.

There is one drug that are already in Phase 1, LUNA18 for cancer, which is for an intracellular target. We have already confirmed its cellular activity and drug efficacy in animal experiments, and we have also confirmed its oral absorption.

As I mentioned at the beginning of this presentation, this is a big improvement from the situation we had in the past with such as OWL, where a project could not proceed unless 20% of the workforce was used.

In other words, for example, in these 2 cancer projects, both are tough intracellular targets, but we have confirmed their activity in cells, and we have also confirmed their oral efficacy in animals.

For example, this project is for acute diseases, and we have confirmed both cellular activity and drug efficacy in animals with intracellular targets. This is an injection. This technology is based on oral formulations, but of course it can be made into injectable form.

In addition, Osaka University, which I mentioned here, is one of the places where we will continue to collaborate with outside organizations. This is related to immunity, and is an intracellular target. We have already confirmed activity in cells, and we have already confirmed that the target is suppressed with oral administration in animals.

The targets shown here have not yet been confirmed in animals, but we have confirmed that they can enter cells and are active.

In addition, of course, this can be used for extracellular targets as an oral drug, so we are working on these projects as well.

The reason why we initially concentrated on cancer is because we believe that it is very important to provide the latest technology with high efficacy and really strong drug effects in areas that are related to patients'

lives. However, in the course of various safety evaluations, we have found that it is possible to apply the technology to areas that are not life-threatening, so we are now starting to work on these areas as well.

In this section, the items shown in red are for collaboration with external parties.

This is my last slide. From 2023, we will be moving to a new research center in the Chugai Life Science Park in Totsuka, Yokohama, which is currently under construction.

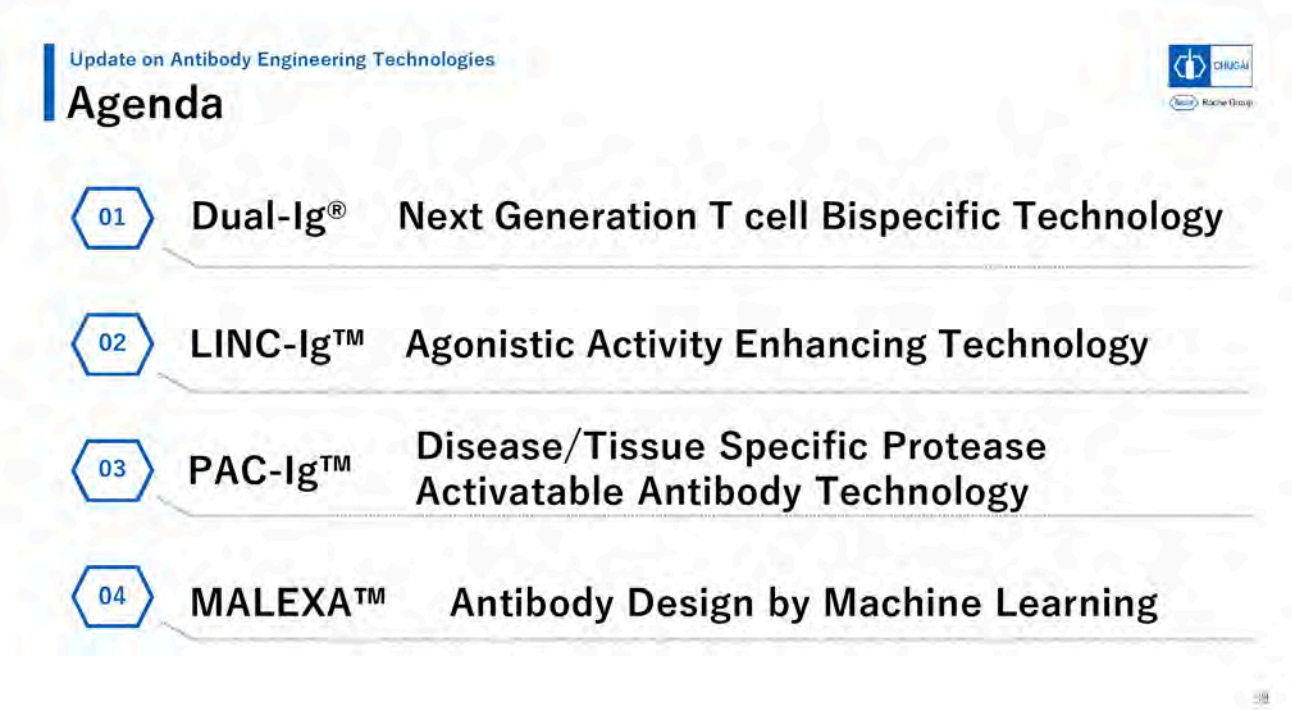
I am very much looking forward to more active discussions among researchers and people from different fields, since the 2 research institutes will now be united.

In addition, we believe that this is a unique opportunity to promote robotization and automation, so we will also promote such activities.

In the area of mid-size molecule, special formulations will be important. We will be constructing new facilities for such products.

Thank you very much for your attention. That's all from me.

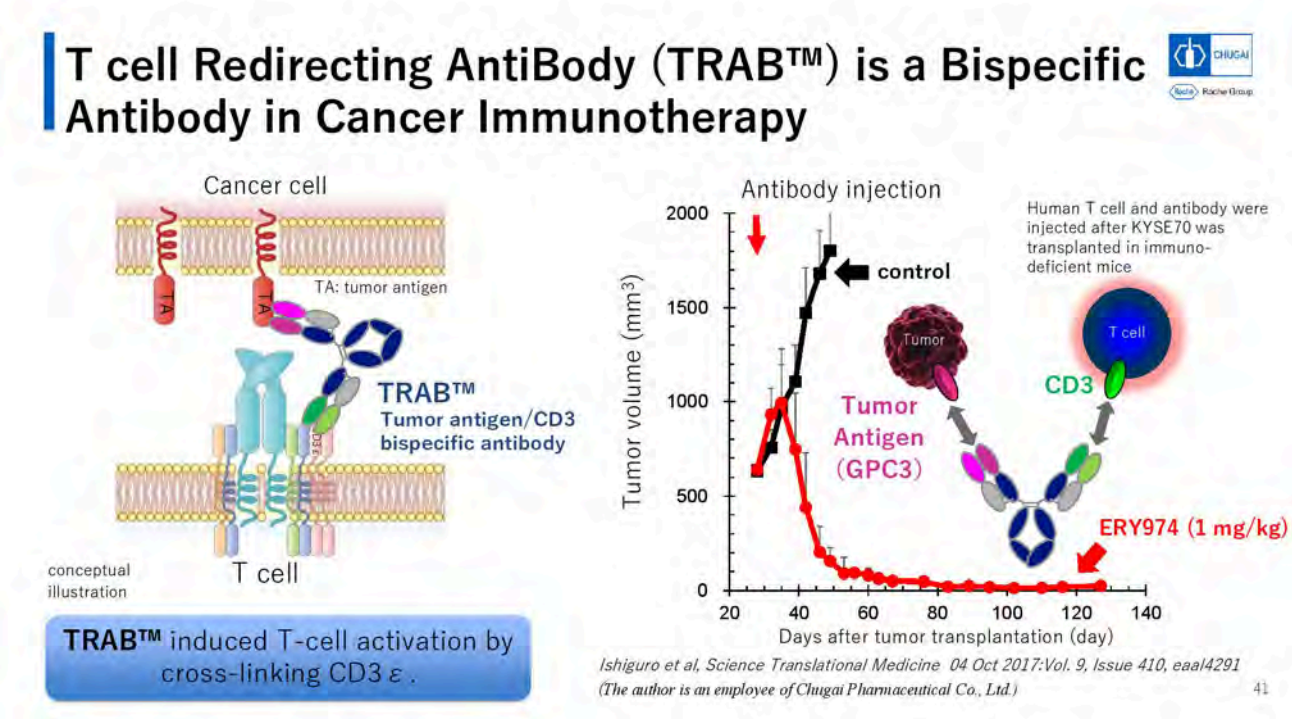
Sasai: Next, Dr. Igawa, Head of Translational Research, will give an update on antibody engineering technologies.



Igawa: I'm Igawa, Head of Translational Research. Thank you.

I would like to give you an update on antibody engineering technologies.

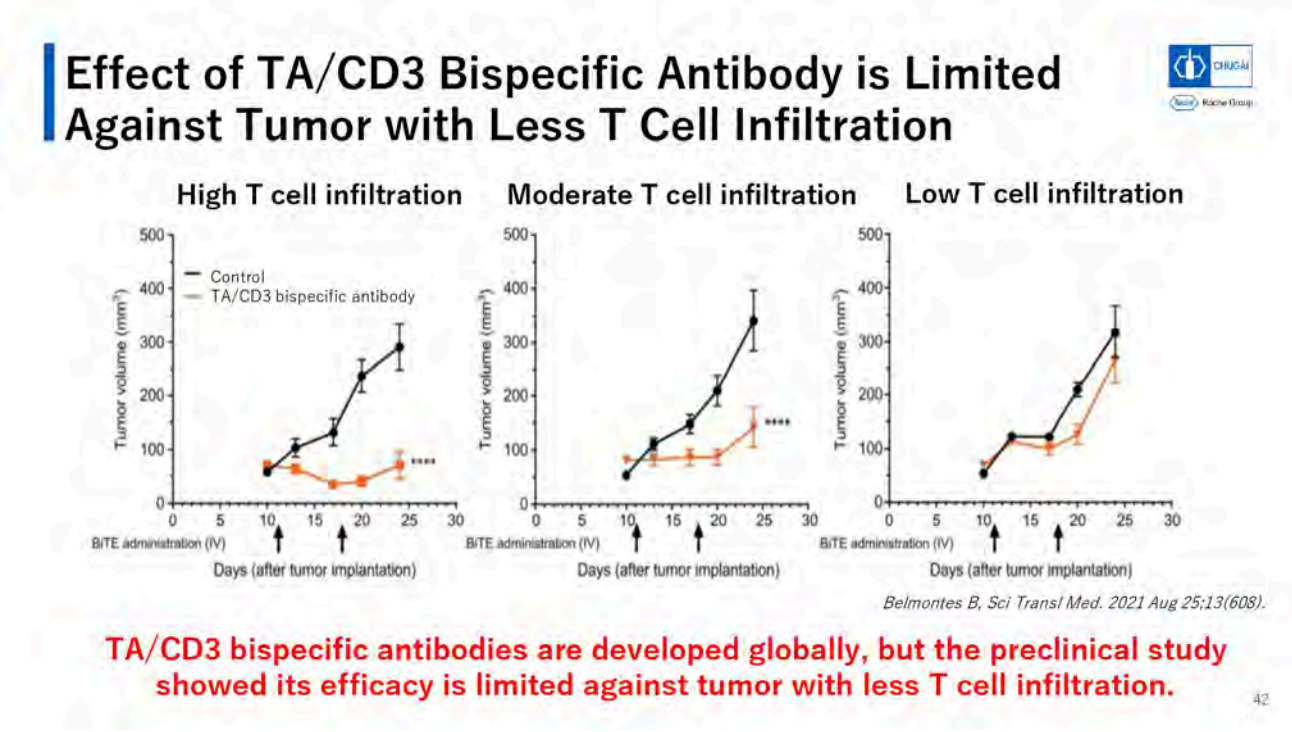
Today, I would like to update you on these 4 technologies. I will mainly focus on the Dual-Ig technology at the top. This Dual-Ig is the next generation of T-cell bispecific antibody technology.



First of all, as an introduction, I would like to introduce TRAB, T-cell Redirecting AntiBody, which we have been working on.

As you can see here, this technology is a bispecific antibody that binds to tumor antigens expressed in cancer with the left side, and binds to CD3 expressed in T-cells with the right side. This bispecific antibody activates T-cells by clustering CD3, a molecule important for T-cell signaling, only when cancer cells are present. The T-cells then kill the cancer cells.

The administration of TRAB, which is specific to these T-cells, can have a very strong effect on regression of these large tumors in a non-clinical setting.



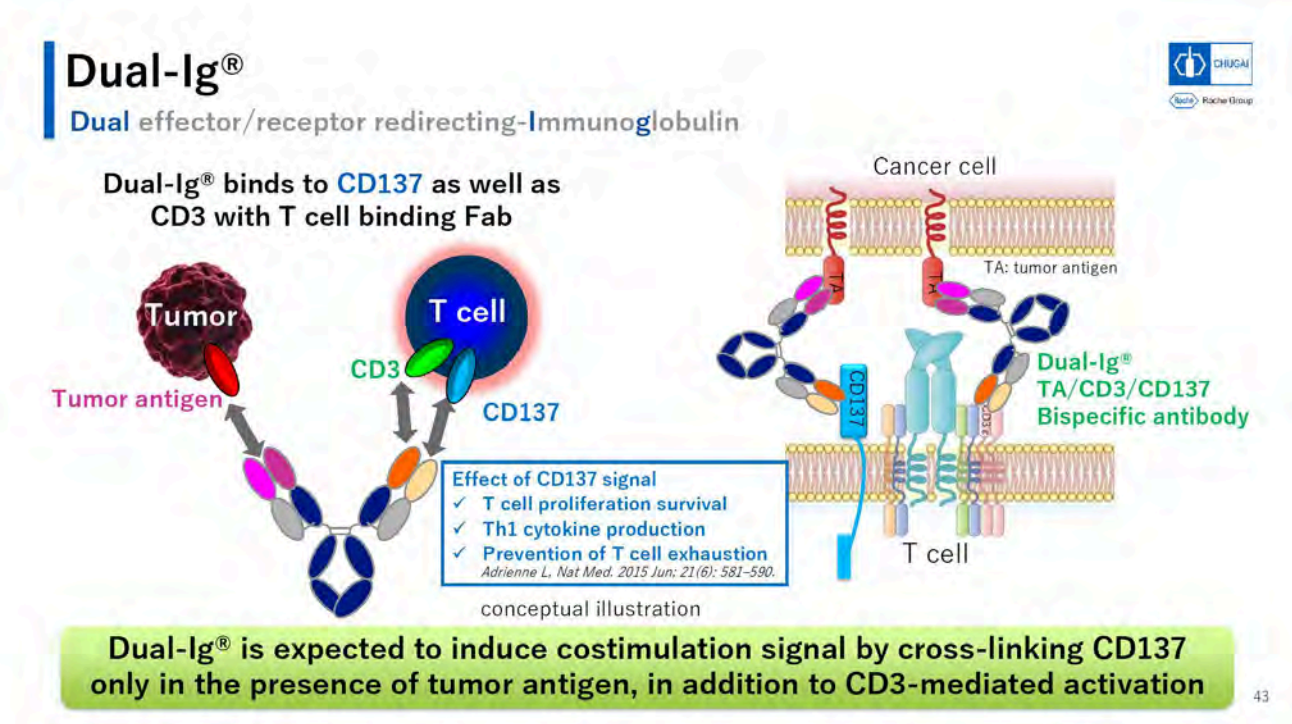
However, there are still issues to be resolved in the development of T-cell and CD3 bispecific antibodies.

Here are 3 different models of cancer. What is different is that the number of T-cells needed to kill this cancer, which is a solid cancer in mice, is high, intermediate, or low.

In this way, CD3 bispecific antibodies have a very strong effect on cancer models that are originally filled with T-cells. However, in models where there are few or no T-cells in the tumor, T-cells and CD3 bispecific antibodies have little effect.

Thus, bispecific antibodies for tumor antigens and CD3 are being developed clinically all over the world, including by our company. It has been shown here that they cannot be fully effective if the number of T-cells in the tumor is low in non-clinical studies.

And most importantly, cancers with low numbers of T-cells are still an area where there remains a very high unmet medical need. Therefore, we wanted to create a new technology to create an antibody drug that could work against cancers that have almost no T-cells in them.

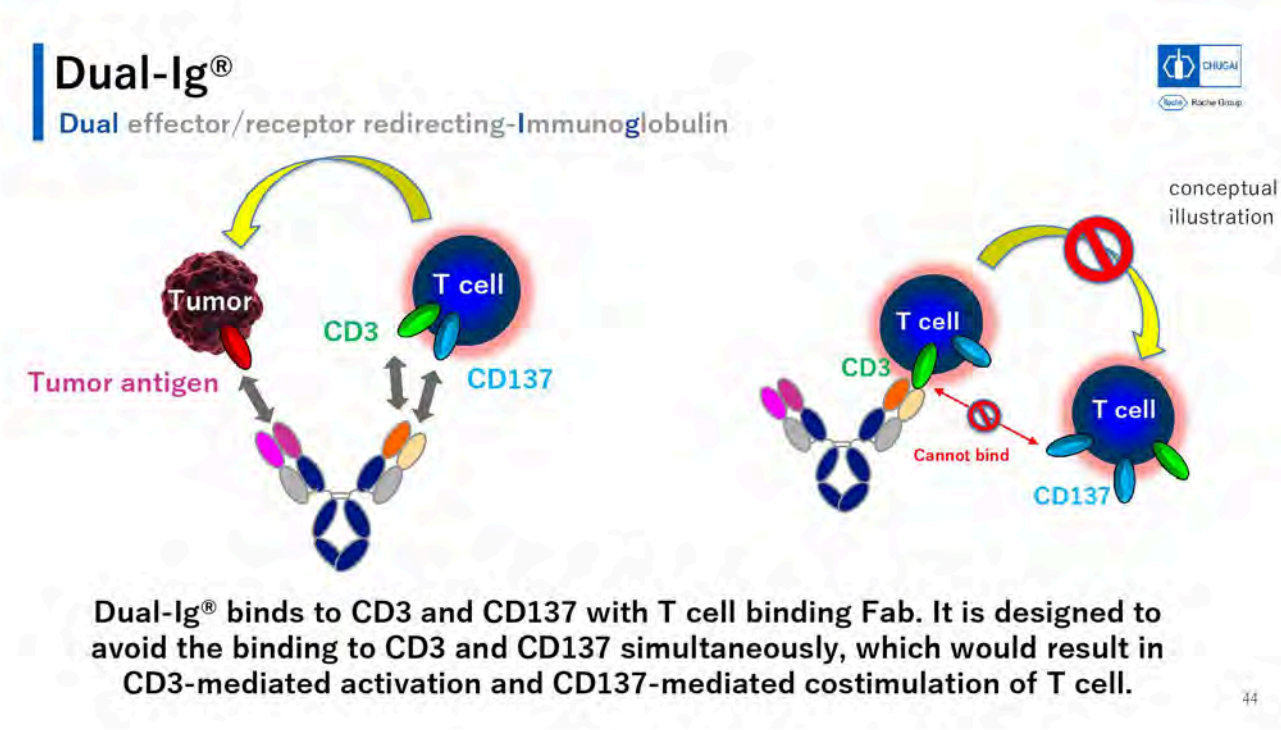


This is why we created the Dual-Ig technology.

The arm that recognizes the cancer is the same as before. The arm that recognizes T-cells is different. This Dual-Ig can bind not only to CD3, but also to CD137.

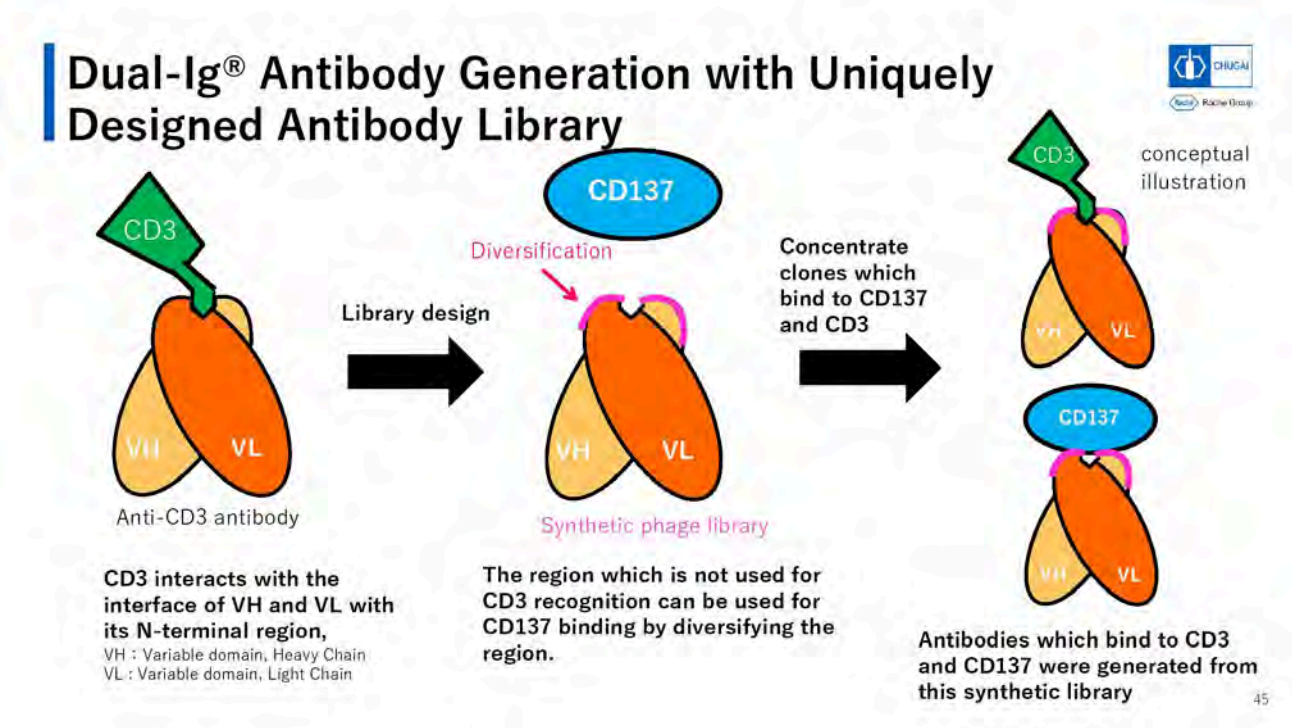
The reason why we focused on the molecule CD137 is that ,as described in this paper, CD137 is a receptor that can co-stimulate T-cells. It is capable of transmitting co-stimulation signals in addition to CD3 stimulation. In other words, CD137 signals can promote T-cell proliferation and survival. It can also stimulate the production of Th1 cytokines, which are important for anti-tumor effects. And it can also prevent the phenomenon of T-cells becoming exhausted.

Since these effects are expected, we thought that by adding CD137 signaling in addition to CD3 signaling, we could expect more powerful anti-tumor effects. In other words, it is a technology that aims to kill cancer cells by activating T-cells more strongly and continuously by adding CD137 signals in addition to CD3 signals when cancer cells are present.



The first thing that is important here is the fact that the arm that binds to T-cells here binds not only to CD3 but also to CD137. This alone is difficult, but what is also very important is the fact that this arm can bind to both, but not at the same time.

The reason is that if this arm binds to CD3 and CD137 at the same time, the T-cells will kill other T-cells. In other words, whether cancer is present or not, a reaction occurs in which T-cells kill T-cells throughout the body. The key was in the design of these antibodies.

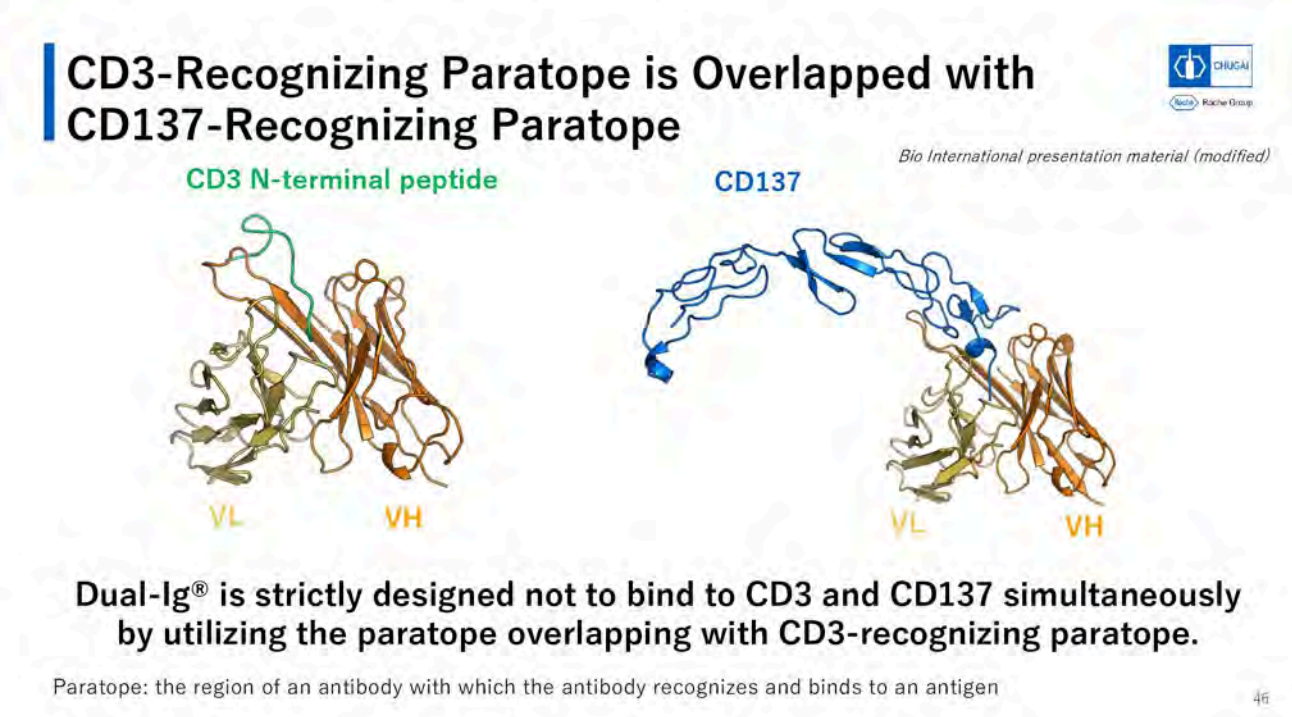


Here we used the library method that was mentioned earlier. Although we are using a phage library here, we originally had a bispecific antibody that binds to the CD3 of first-generation T-cells, and this antibody was brought in first.

If you look at it, you can see that it recognizes CD3 in this way, but it makes a library of regions that are not involved in CD3 recognition. In other words, we designed a synthetic phage antibody library in which various amino acids appear in this region.

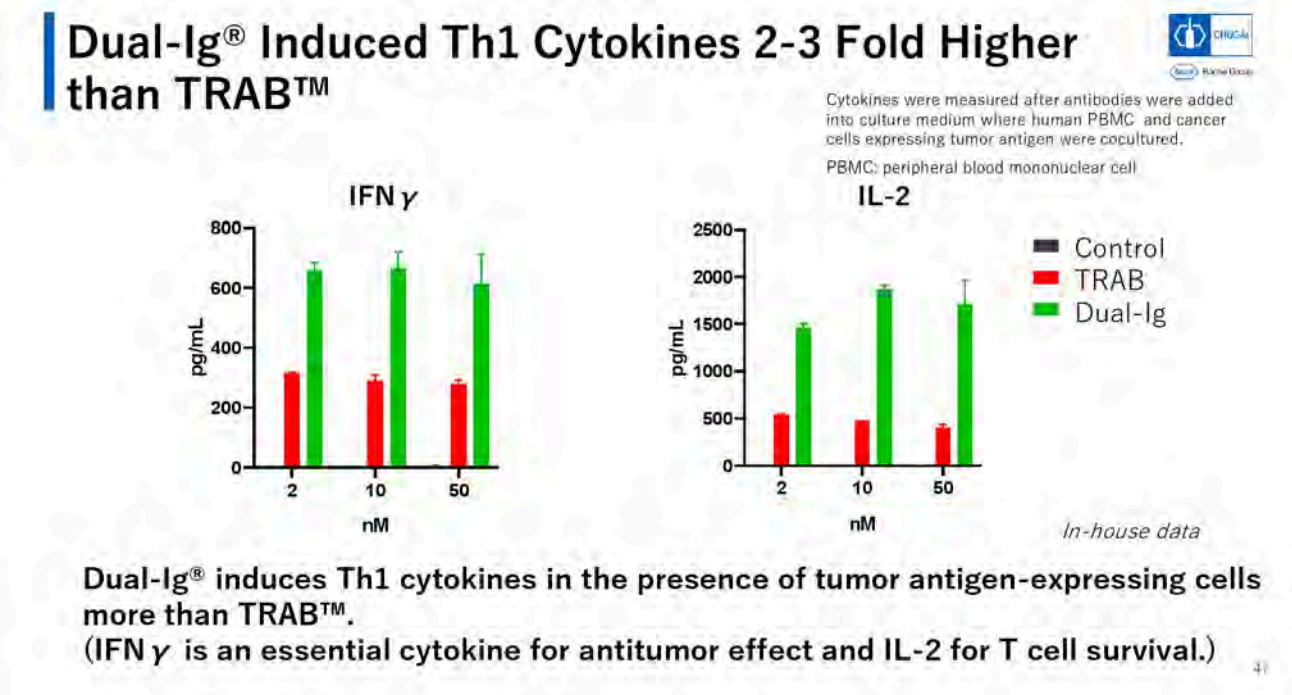
The population of this library can bind to CD3 because this is where it is maintained. This library can be used to screen the phage library for binding to CD137.

By doing this, we were able to obtain antibodies that could bind to both CD3 and CD137.



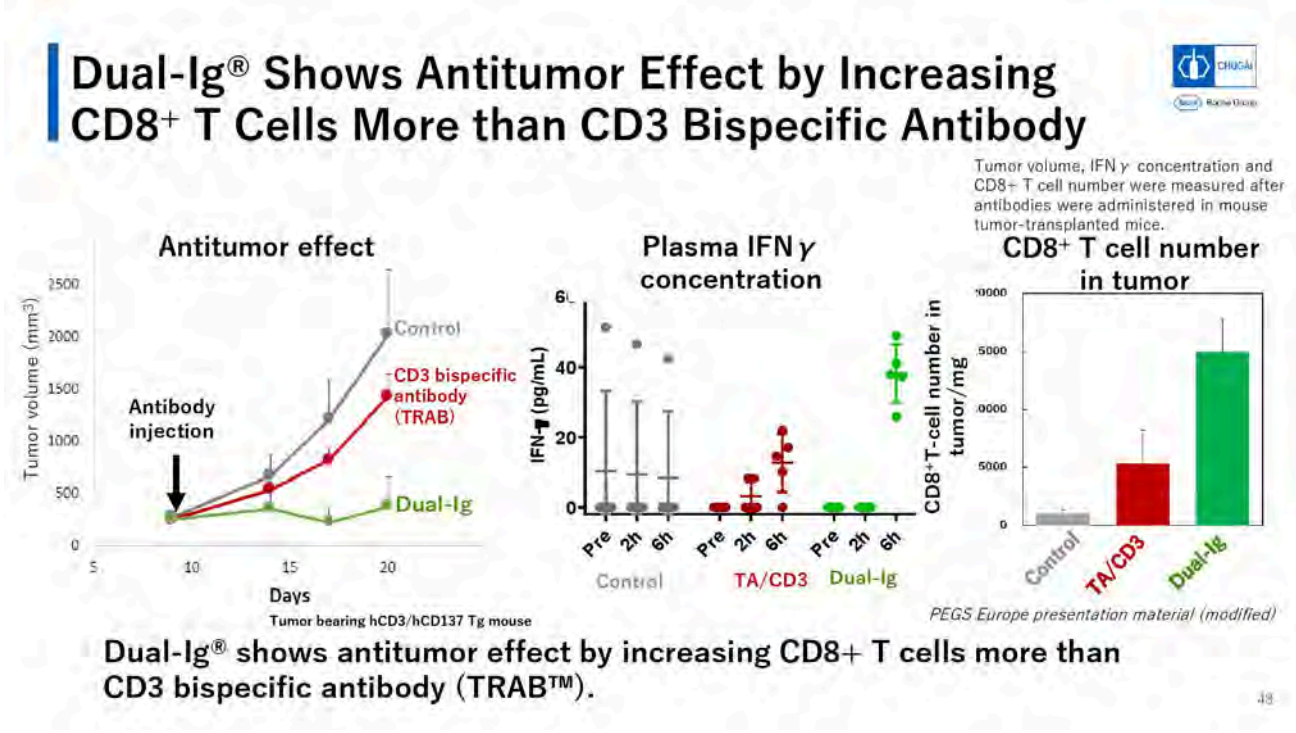
As shown in the X-ray structural data, the antibody that recognizes CD3 in this way also recognizes CD137 using the exact same spot that recognizes CD3. In other words, since there is overlap and duplication here, we have been able to create antibodies that are rigorously designed so that they can never bind to CD137 if CD3 is bound.

From the next slide, I would like to show you some non-clinical data using this Dual-Ig antibody.



This is an in vitro cell assay system, and the data shows that Th1 cytokines are produced in large quantities by the effect of CD137 as I mentioned earlier.

In red is the first generation of T-cell bispecific antibodies. The green one is using Dual-Ig. It was confirmed in vitro that the production of Th1 cytokines such as interferon gamma and IL-2 could be increased in this way.

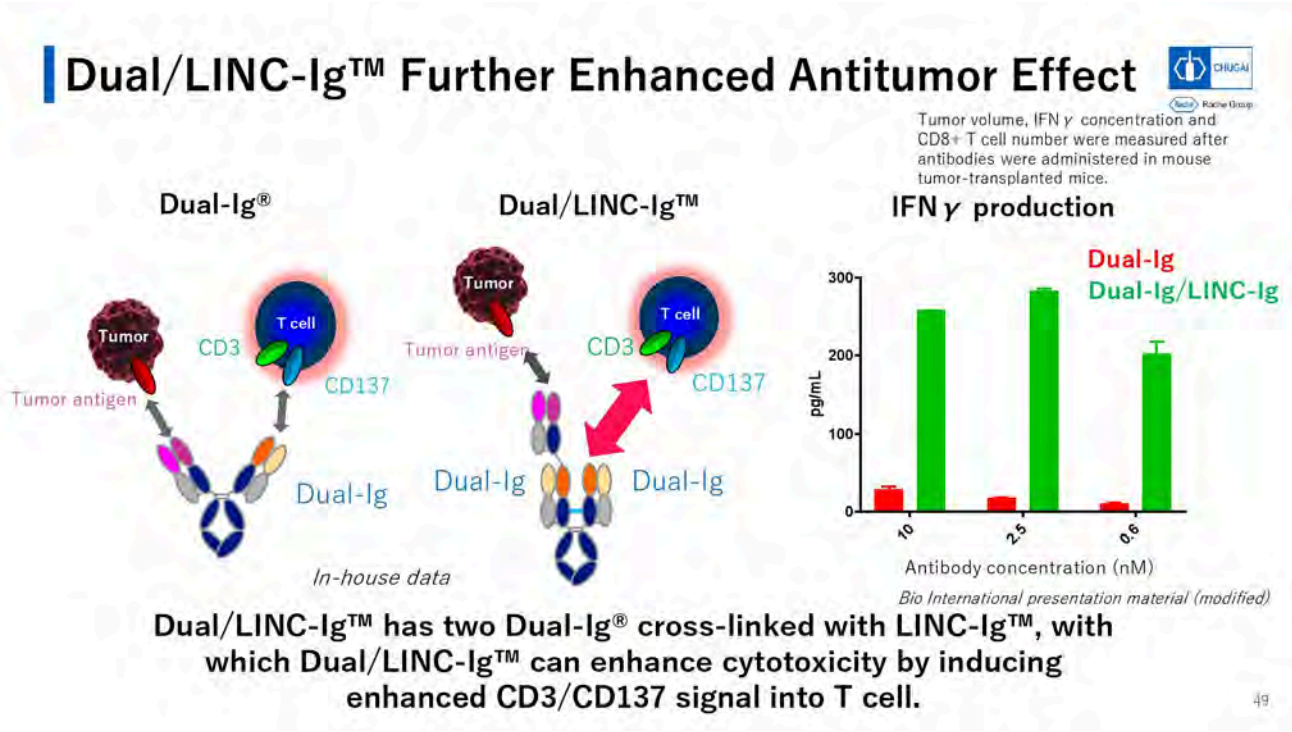


Next, in vivo. I will explain how it worked in a mouse model of cancer.

First of all, the model used here shows that the first generation of CD3 bispecific antibodies, TRAB, has a slight effect, but it is a very weak model. The reason why this doesn't work is due to the number of CD8+ T-cells present in the tumor, which you can see in the figure on the right. In this model, there are only about 1,000 T-cells per milligram of tumor, as you can see in the control. 1 milligram of tumor is roughly a few hundred thousand cancer cells. In a model with hundreds of thousands of cancer cells, but only 1,000 T-cells, the usual first generation TRABs have little effect.

In contrast, as mentioned earlier, Dual-Ig increased the production of Th1 cytokine called interferon gamma and increased the number of T-cells in the tumor from about 1,000 to 15,000. The Dual-Ig showed a strong anti-tumor effect even in such a model where the first generation T-cell bispecific did not work.

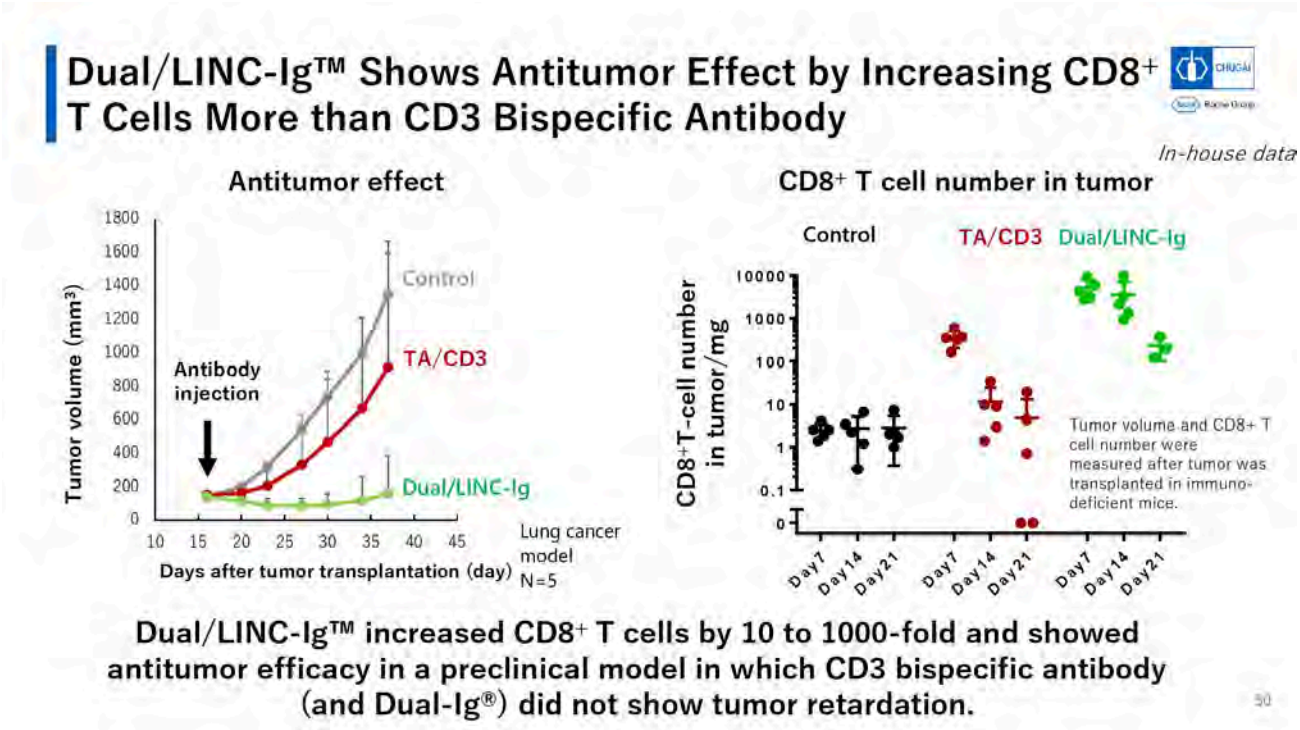
However, we were not satisfied with this. In fact, the number of T-cells in the tumor, 1,000, is still too high. We wanted to create a Dual-Ig technology that would be effective even in models with fewer T-cells, so we worked on the development of the next generation of Dual-Ig technology.



As shown in the figure on the left, the Dual-Ig technology binds to both CD3 and CD137 on the right arm. By using the LINC-Ig technology, which I will discuss later, we were able to create a molecule with 2 Dual-Ig arms in parallel by cross-linking the 2 arms here. Without going into the details of the molecule, we have created a next-generation of Dual-Ig, called Dual/LINC-Ig, in this way.

First of all, in vitro evaluation showed that the production of interferon gamma was enhanced by about 10 times.

In the next slide, I will explain the in vivo effects of these next-generation molecules.

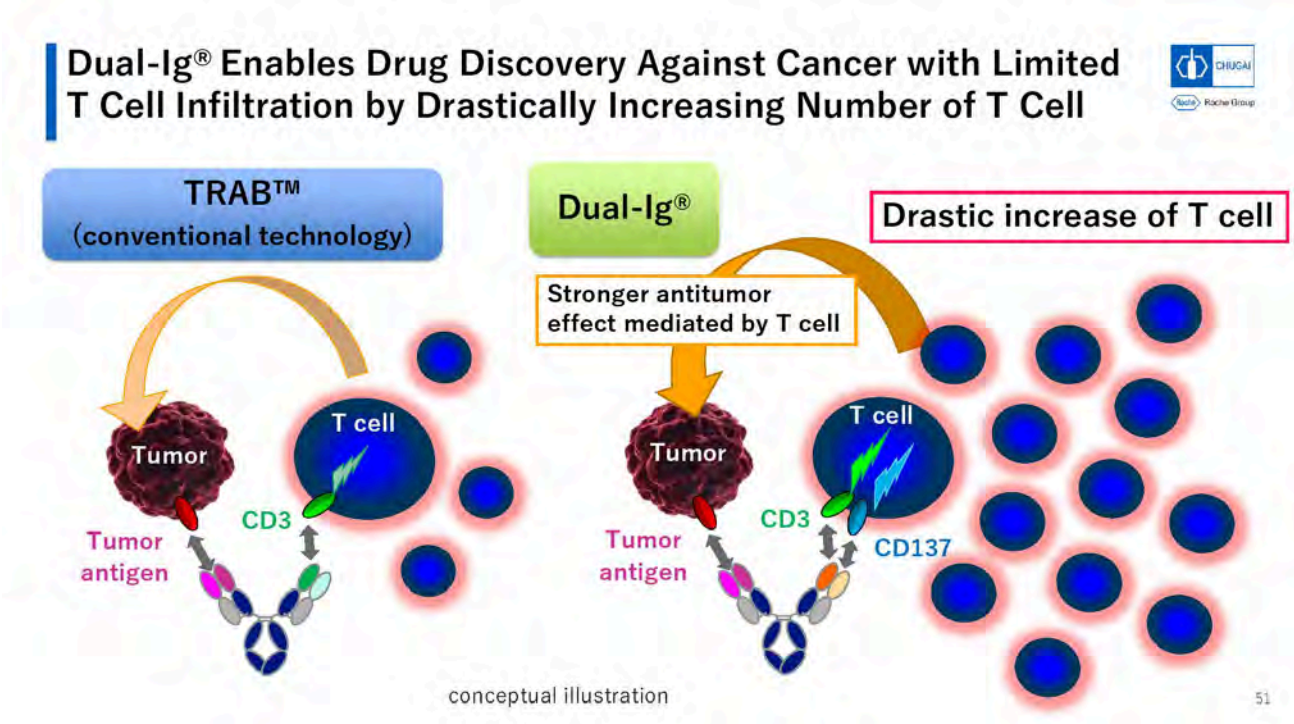


As you can see in the vertical axis, the number of CD8+ T-cells in the tumor is only a few per milligram of tumor. In other words, in 1 milligram of tumor, there will only be a few T-cells for hundreds of thousands of cancer cells.

In this model of cancer with very high unmet medical needs, the first generation TRAB is thus not effective. Although not shown here, the first generation Dual-Ig also shows no effect in this model.

In contrast, Dual/LINC-Ig has shown very strong anti-tumor effects after only 1 administration. This is due to the fact that the number of T-cells increased tens to thousands of times when Dual/LINC-Ig was used. As shown here, you can see that the number of T-cells has increased to about 10,000.

Dual/LINC-Ig is able to exert such a strong anti-tumor effect by increasing the number of T-cells to thousands or even about 10,000. This occurs even for models that contain only a few T-cells.



In other words, although only the first generation of Dual-Ig molecules is described here, we believe that Dual-Ig, including the next generation, will make it possible to create drugs for refractory cancers with low T-cell counts that cannot be effectively treated with conventional TRAB.

The Current Status of Dual-Ig® Application

- Currently have two projects applying Dual-Ig® at GLP-TOX stage.
- Several projects in combination with Switch-Ig™ at research stage.

Project	Technology	Cancer type	Stage
A	Dual-Ig®	Lung cancer etc	GLP-TOX
B	Dual/LINC-Ig™	Lung cancer etc	GLP-TOX
C	Dual-Ig® etc	Lung cancer etc	Lead Optimization
D	TRAB/Dual-Ig	Colorectal cancer etc	Lead Optimization
E	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification
F	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification
G	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification

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- Another project, different from Dual-Ig® at GLP-TOX stage, utilizing the nature of antibody binding to multiple antigens with a single Fab.

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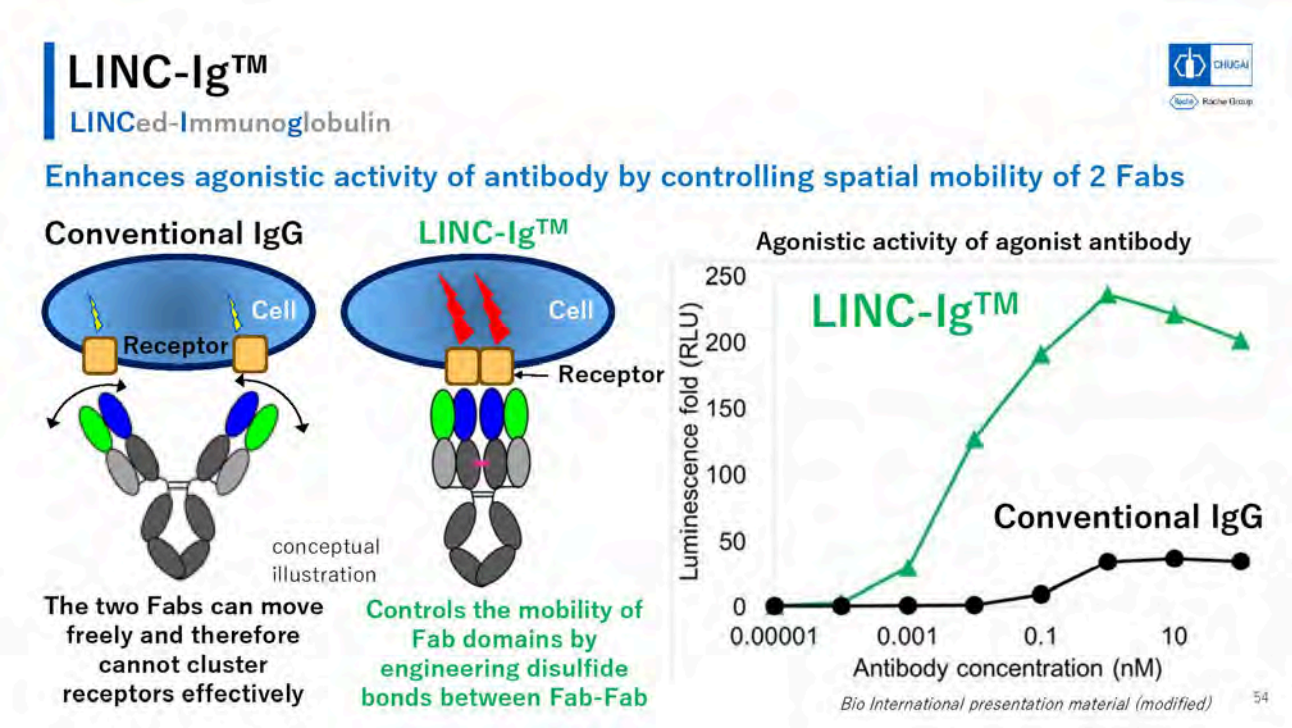
In fact, we are currently running a number of projects using Dual-Ig technology.

Currently, we are working on 2 projects using Dual-Ig for lung cancer. Those are in the GLP-TOX stage. In addition, at the drug discovery stage, by combining Dual-Ig technology and the switch antibody mentioned in

the previous presentation, we are moving forward with a project for antibody drug discovery targeting a wider range of cancer types.

Also, in the process of drug discovery, we have found that a single Fab antibody can bind to multiple targets. We learned that the same paratope can bind to different antigens. There is another completely different project in the GLP-TOX stage that takes advantage of this property.



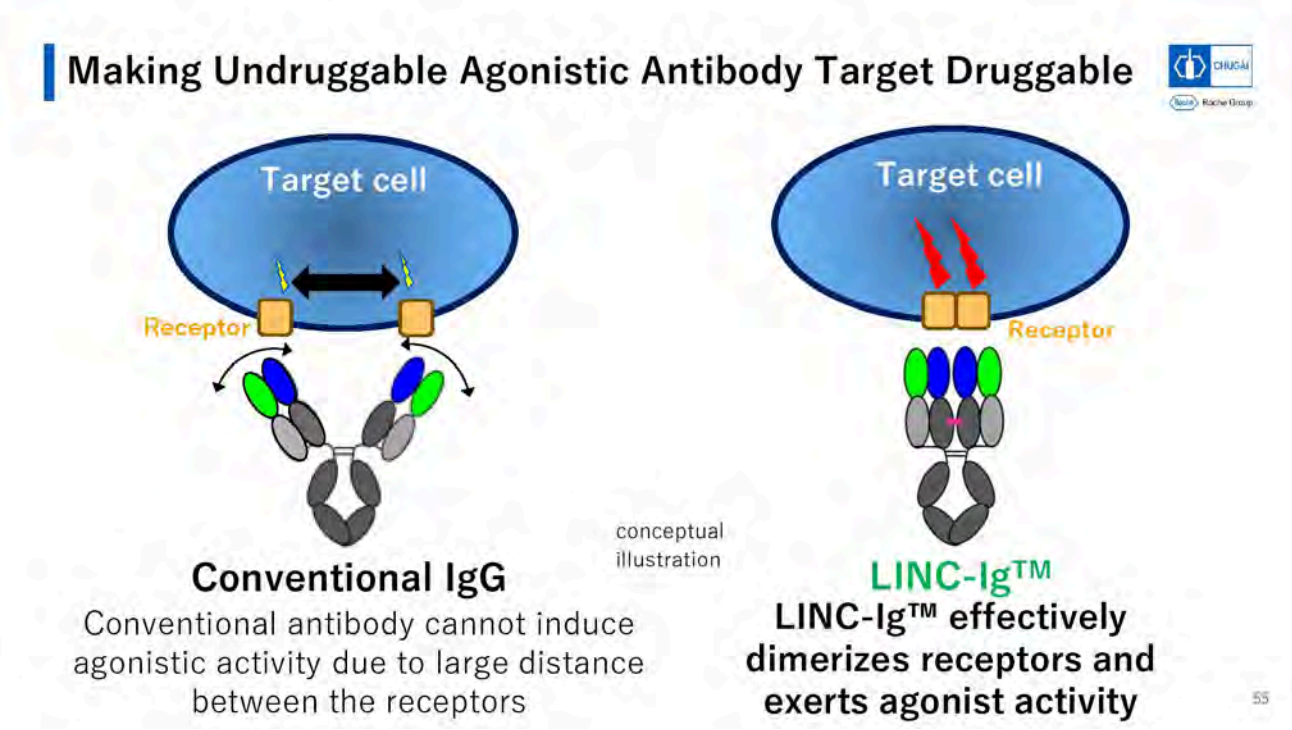
Now, on to the next technology. I would like to talk about LINC-Ig, an agonist activity enhancement technology that I mentioned earlier.

Agonist antibodies are a type that has been known for about 20 years in the field of antibody drugs. However, if you look at the antibody drugs currently on the market, or those that have been confirmed to be effective in Phase 3, agonist antibodies have had little success. We believe that this is because normal IgG antibodies are still unable to induce sufficient agonist activity in cells.

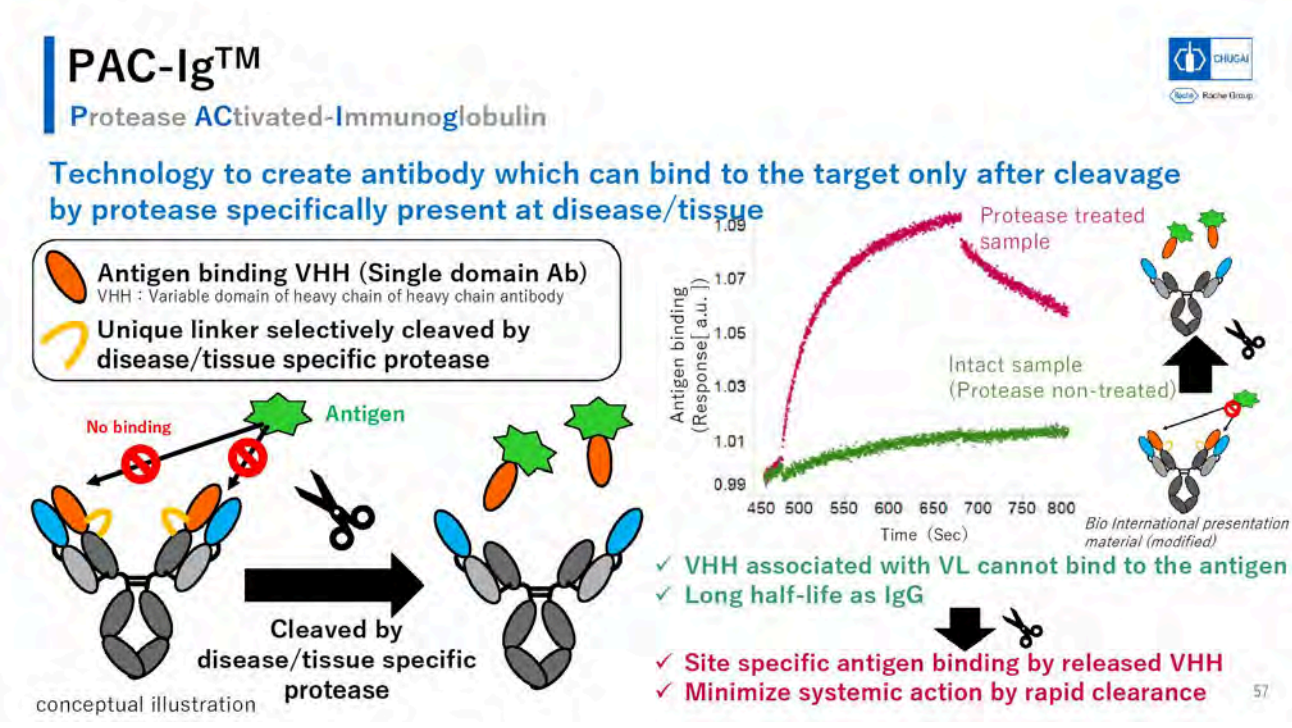
The reason is that agonist antibodies usually signal by dimerizing or multimerizing the receptors to which the antibody binds, the 2 receptors. However, although normal antibodies have a Y shape like this, these arms can move very freely. It's very flexible. Naturally, this flexibility allows the antibody to bind to a variety of antigens because of the flexibility of the biological response, but when applied to agonist antibodies, this works to the disadvantage of the antibody. In other words, because they move freely, they cannot dimerize or multimerize receptors efficiently.

So, we thought, why not fix these freely moving arms? After screening various antibodies, we found that by artificially introducing a disulfide bond at a specific site, we could fix the freedom of both arms.

This is just 1 example, but we found that the activity of antibodies that only show agonist activity with ordinary IgG, so-called normal IgG, can be dramatically increased by introducing a single disulfide bond. By using LINC-Ig, we have created the next generation of Dual-Ig technology, Dual/LINC-Ig.



Thus, we believe that LINC-Ig technology will enable us to create agonist antibodies that are impossible to create with conventional antibodies.



Next, I would like to explain the PAC-Ig technology.

This technology is based on proteases, which are enzymes that break down proteins and are known to be involved in maintaining homeostasis in various organisms and in various diseases.

By utilizing the mechanism of action of proteases to degrade proteins, we thought it would be possible to create antibodies that would work only in certain pathological sites or tissues.

As described here, antibodies can only bind to their target antigens when they are cleaved or degraded by proteases that are specifically expressed in the disease state or specific organ. We have created a technology that allows us to do this.

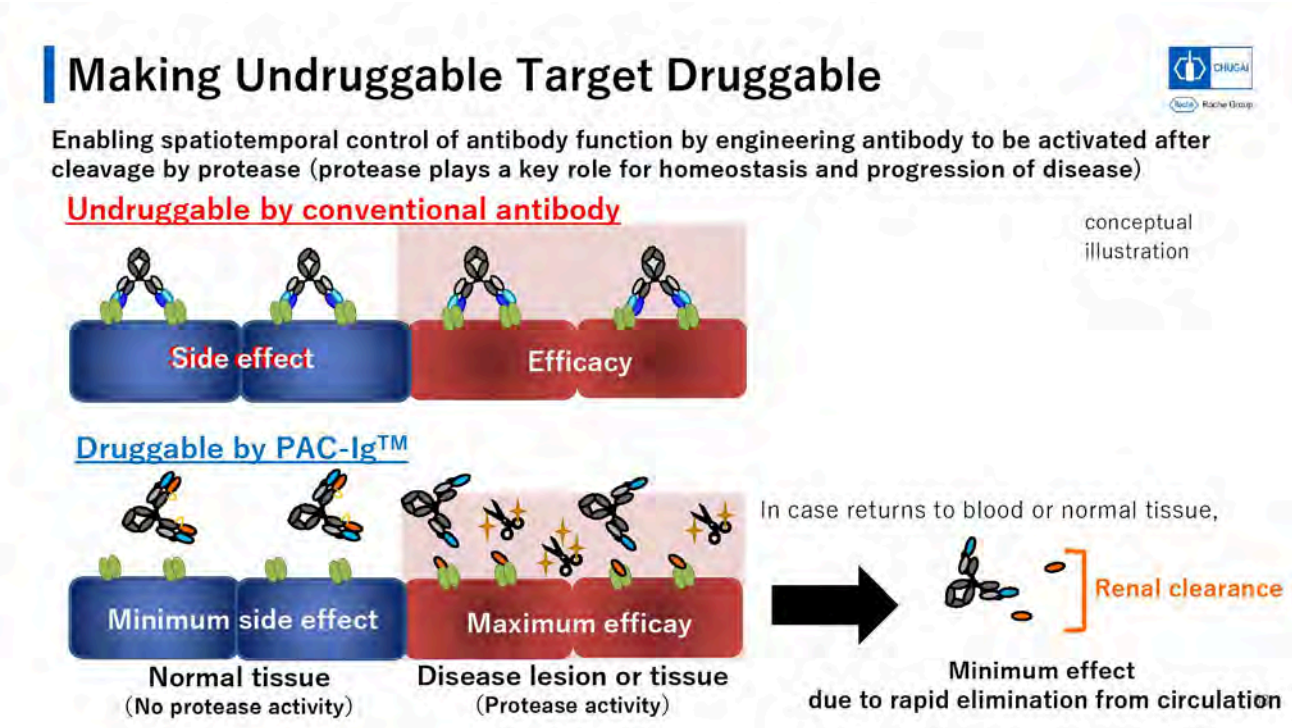
Specifically, we utilized a technology called VHH, a single-domain antibody that can bind strongly to antigens using only the orange part. This is an ordinary amino acid sequence, but by designing this linker well, we were able to create a linker that can be cut only by a specific protease. That is, a protease that is expressed only in a specific organ, such as the liver, lung, or colon, where a certain condition or disease is occurring.

The linker would be embedded here in the antibody. Then, this VHH, a single domain antibody, cannot bind to this antigen because the light blue light chain is in the way when it is bound to the light chain in the IgG format.

However, when the IgG antibody migrates to the pathological site and the yellow linker is cleaved, the orange VHH is released. Then this VHH is able to bind to the antigen.

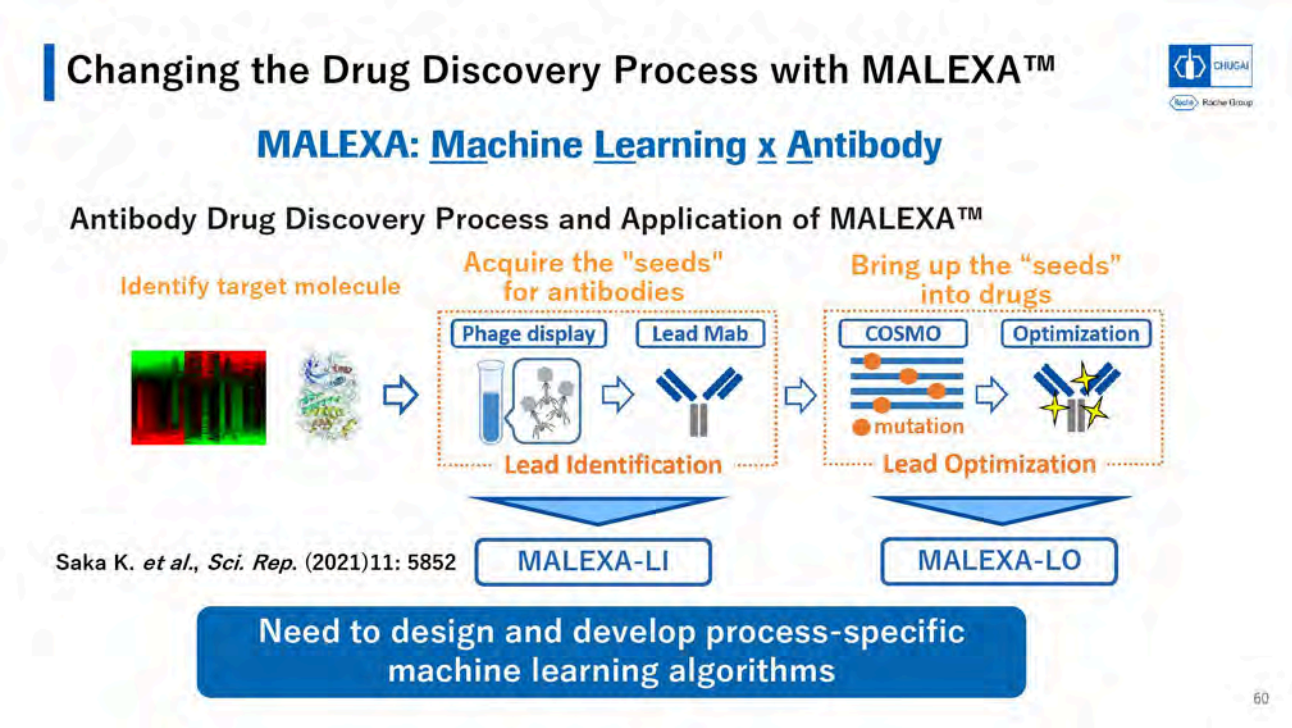
Here is the actual confirmation of this. In this state, it has almost no antigen binding, but when it is cleaved and comes out, it can bind to antigens.

What is even more interesting about this technology is that although the released VHH can bind to the antigen at the targeted site, such as the pathological site, in reality, the produced VHH leaks out throughout the body. However, even if it leaks out, the molecular weight of this VHH is very small, so it is discharged from the kidneys and disappears from the body instantly. In other words, it binds to the antigen only locally, at the site of the condition or in the organ. When it leaks out to the rest of the body, it is excreted in no time, which also avoids systemic effects.



We believe that this technology will enable drug discovery for targets that cannot be targeted by conventional antibodies.

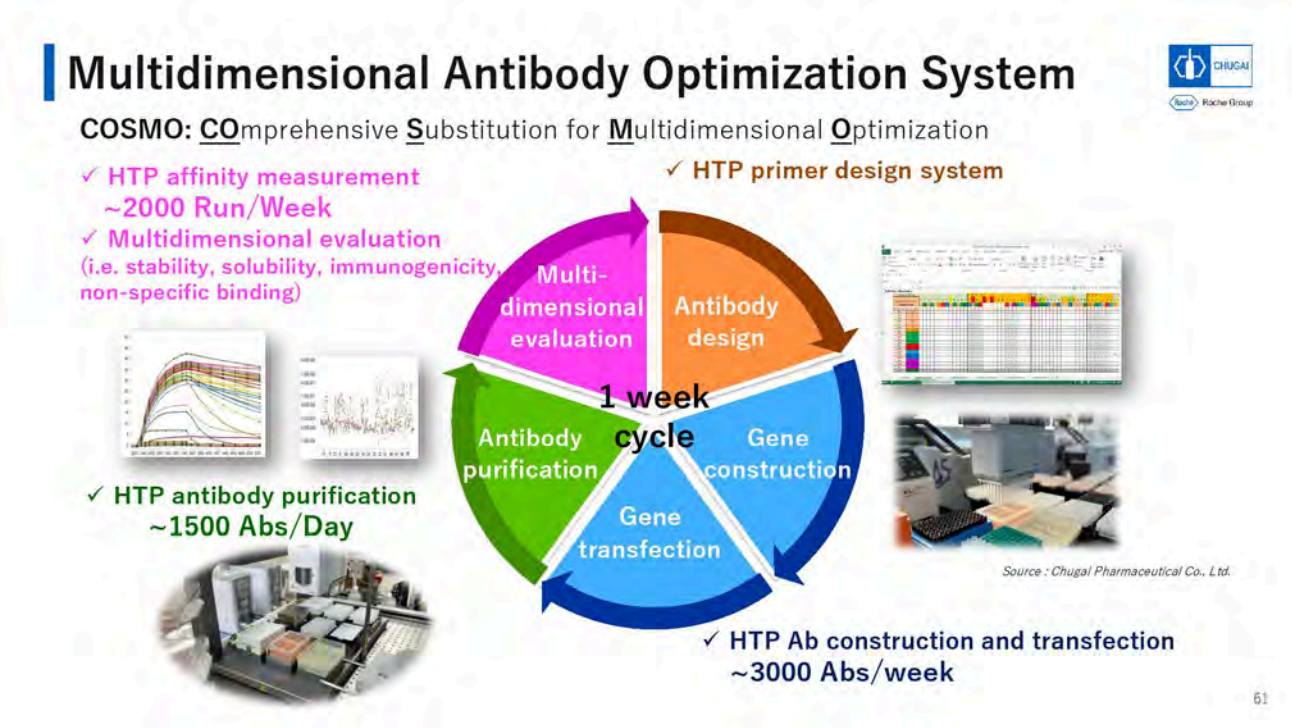
What is important here is that while switch antibodies use small molecules such as ATP as switches, here the activity of antibodies can be controlled depending on protease activity, which will enable drug discovery in new areas that switch antibodies could not target.



Lastly, I would like to talk about MALEXA, antibody design using machine learning.

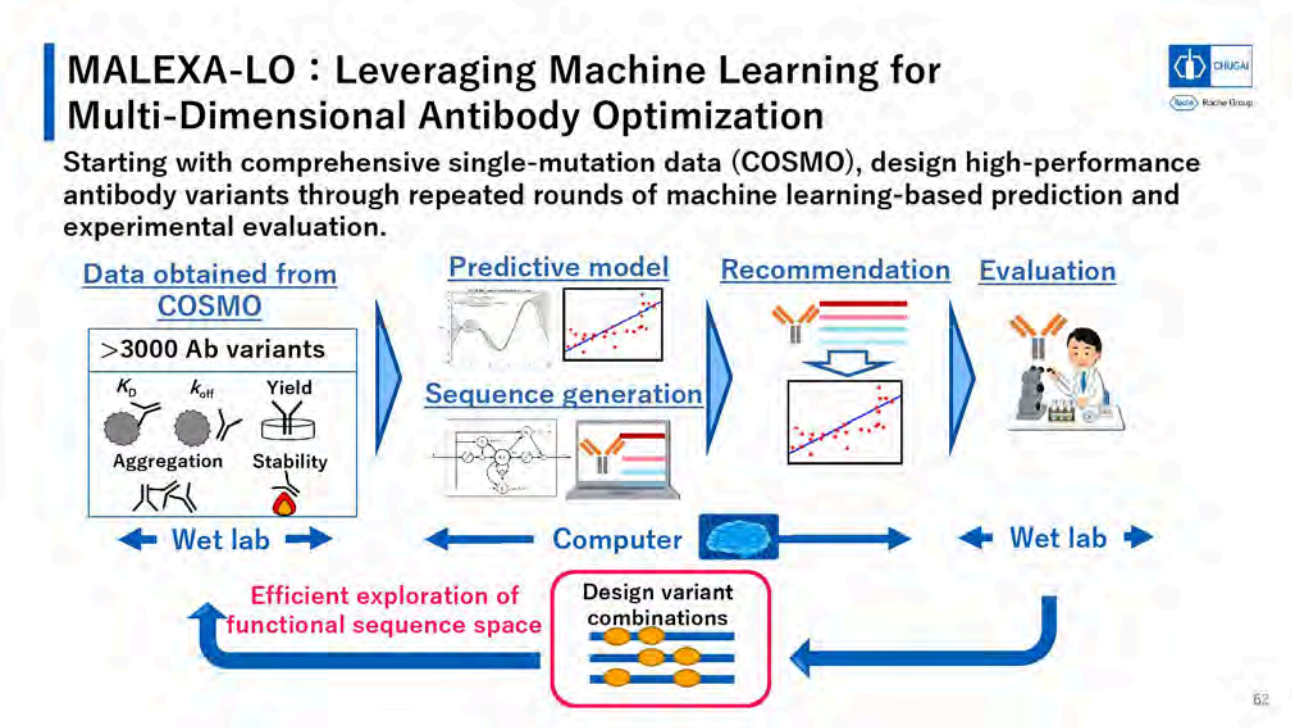
As we have already announced, MALEXA is a system that uses machine learning to obtain antibody leads and optimize antibodies.

Today, I would like to talk about the optimization of antibodies using MALEXA.



One of our strengths in antibody engineering and optimization is our COSMO platform. Using this platform, COSMO, we can design and evaluate thousands of antibodies in a week.

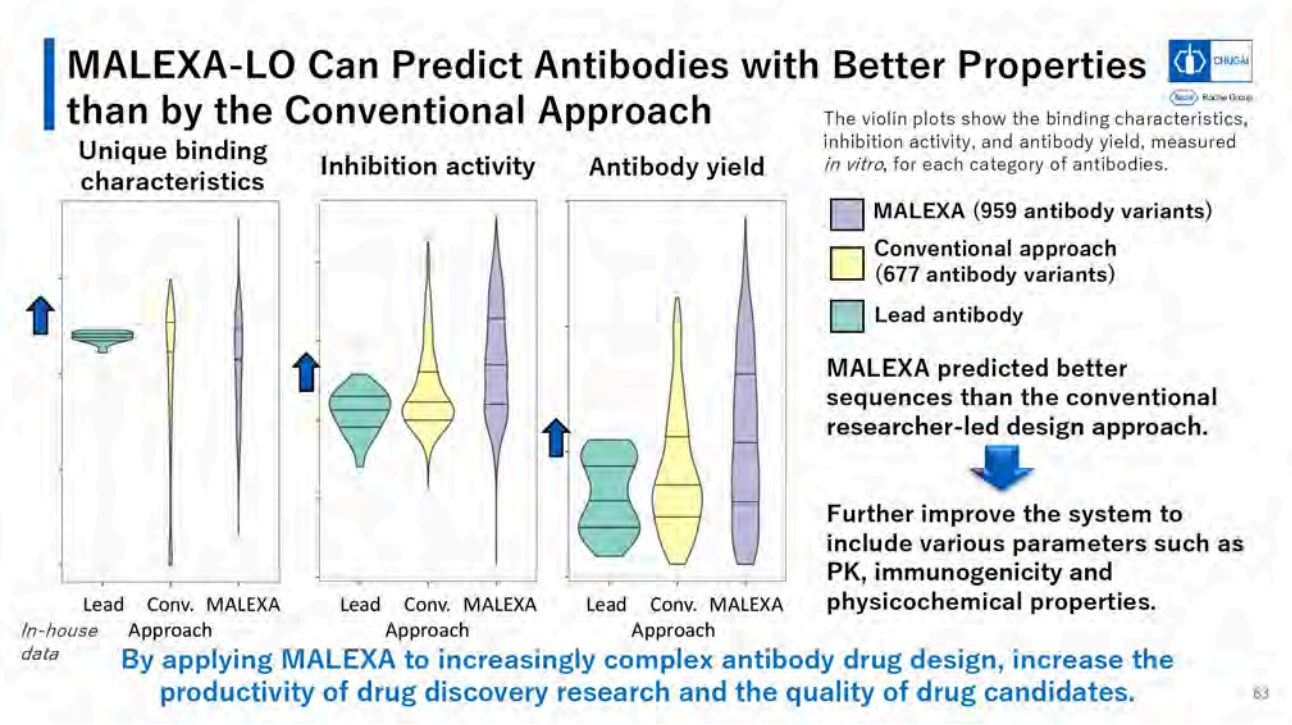
This is just 1 project, and we have the capacity to run multiple projects. In other words, one of Chugai's strengths is its ability to produce a lot of this kind of wet experimental data, and I think there is no other company with this kind of throughput.



This is where machine learning comes into play, as we look at how to use this data for the next step or project.

Since we have such a large amount of data, thousands or tens of thousands of units, we can use this data to create a model, and then let the machine suggest how to design antibodies based on the model. The proposed antibodies will be made and evaluated, and this cycle will go round and round again. In addition to the cycle of producing many antibodies at COSMO, the cycle of machine learning will also go round and round.

In this way, antibodies that could not be designed by human power alone can now actually be created.



Here's an example.

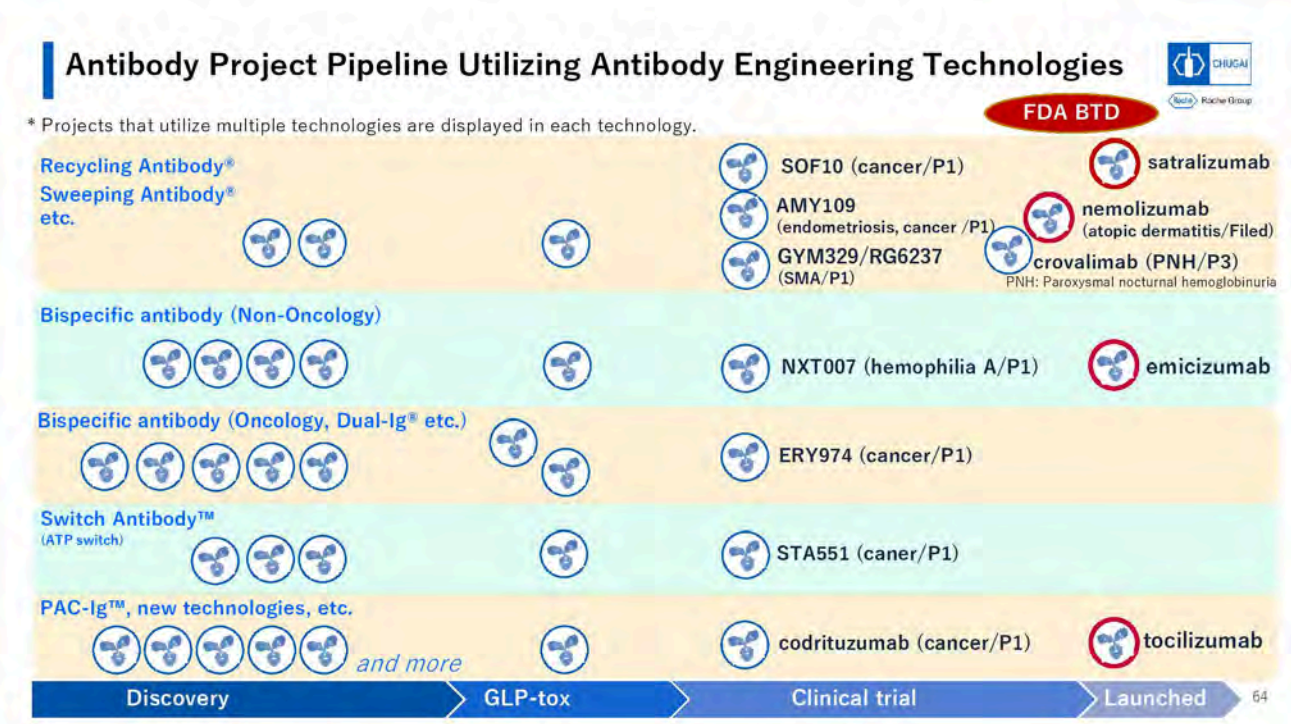
This one is the conventional method when there is an antibody for a certain lead. This means that the researcher thought of and designed the antibody. The one on the right will be the one designed for antibodies using MALEXA.

On the vertical axis, although it is not written, the higher the value, the better the antibody. For example, it is very important to design antibodies that have special binding activity for the target, or inhibitory activity against the target. Another issue is the amount of antibody produced, as the more antibodies are produced, the cheaper the manufacturing cost will be in the future.

In this way, although it is certainly possible to produce excellent antibodies from lead antibodies using conventional methods, as you can see, it is possible to design antibodies with even better properties using MALEXA. In other words, machine learning will be used to propose antibodies that could not have been created by human power or researchers alone. These things are now possible.

We are currently talking about binding and antibody production, but we would like to use this machine learning method to learn about physical properties such as immunogenicity, pharmacokinetics, and stability, so that we can design superior antibodies more comprehensively by using MALEXA.

Also, for antibody drugs, which will become more complex and difficult to design in the future, we would like to use MALEXA to maintain high productivity in drug discovery or to create superior molecules.



Last but not least, here is the pipeline of antibody projects utilizing each antibody technology.

The bottom one is a new technology. I can't go into details today, but we have a number of drug discovery projects using new technologies, and at the same time, we have 2 oncology projects using the new Dual-Ig technology in GLP-TOX.

That's all from me. Thank you very much.

Question & Answer

Sasai [M]: We will now move on to the question-and-answer session.

Please note that in order to allow as many people as possible to ask questions, we would like to limit questions to 2 per person. Please note that the audio of your questions, along with the presentation, will be posted on our website at a later date.

First, we will take questions from the audience, and then we will take questions from the participants in the conference call system.

If you have any questions, please raise your hand and tell us your company name and name.

Yamaguchi [Q]: My name is Yamaguchi from Citi.

The first question is about mid-size molecules. It may be difficult to compare with other companies, but I'm having trouble understanding the similarities and differences between your company's technology and that of PeptiDream.

Listening to what you said today, I felt that the first part of the library was different from the Suga Library, but how does it look from your point of view? I would be grateful if you could explain what the differences are or let me know if they are the same. That's the first question.

Iikura [A]: Thank you for your question, Mr. Yamaguchi.

We thought that Dr. Suga's technique was wonderful, and we are naturally paying close attention to his work. I would like to refrain from commenting on the current situation of PeptiDream, because of course we are not able to grasp the entire situation.

After all, we have been focusing on drug discovery for intracellular tough targets.

Yamaguchi [Q]: I understand.

Secondly, I would like to ask you about Dual-Ig. First of all, there are a variety of existing CD3 systems that have worked well or not so well, but do you think that your company's approach has the potential to replace most of them?

The second part of the question is also about Dual-Ig. It seems to bind both CD137 and CD3, but I wonder what ratio it binds to each of the receptors? Let’s say fifty-fifty or 70:30 roughly. The time when T-cells need to be increased and the time when they need to be activated are probably different, so I was thinking that if they aren't controlled well, the antibody might not work as well as expected.

Igawa [A]: First of all, the so-called first-generation T-cell bispecific therapy has been successful in hematological cancers. Why is that? In our opinion, it is because there are a lot of T-cells in the blood. These T-cells are used to kill B-cells and other cells, so it works properly.

On the other hand, in a solid cancer, the ratio of the number of T-cells to cancer cells is overwhelmingly different. We already know that antibodies can be applied to solid tumors. Various antibodies reach cancer cells. Therefore, although antibodies reach cancer cells, the number of T-cells must be insufficient for the tumor to shrink sufficiently.

Another reason is that even if T-cells are present to a certain extent, if strong signals are continuously applied to T-cells, the T-cells may gradually become exhausted.

In order to solve these 2 problems, we came up with the idea of introducing the CD137 signal. I didn't talk about this today, but we made the decision based on a variety of data.

We believe that the use of this technology in solid tumors will be effective in solving the problem of T-cell numbers or T-cells losing their vitality in the process. We believe that a clinical trial of antibody with Dual-Ig will initiate in next year.

When we design antibodies that bind to both CD3 and CD137, we need to design antibodies that bind to and release from CD3 and CD137 at a precise rate. We discovered that this is very important.

In other words, it cannot bind to CD137 if it remains strongly bound to CD3 all the time, so when it attaches, it leaves and binds to CD137. CD137 is only expressed after a solid, sustained CD3 signal. Normal T-cells do not express CD137. T-cells that have received a CD3 signal then express CD137, so in order to successfully activate both here, we have to bind to both with optimal binding kinetics. This is the molecule that we designed with those things in mind.

Yamaguchi [M]: Thank you very much.

Kohtani [Q]: My name is Kohtani from Nomura Securities. Thank you for your explanation. I think I have to push my way in because I am limited to 2 questions.

First of all, I would like to confirm the high barriers to entry in mid-size molecule drug discovery. As described on page 29, the first step is to semi-quantitatively define whether a mid-size molecule has drug-like properties. Specifically, I think there are probably less than 11 amino acids. Some amino acids are not included, ionic side chains are not included, and so on. Maybe it's not that difficult here.

The next step is to construct a Display Library containing non-natural amino acids that meet these requirements. I think it was said this is difficult. I'm not sure how difficult this was, so I'm not sure how long it took you. I think this can be done by identifying unnatural amino acids and putting them on the mRNA platform, but I don't think it will be that easy. Please tell us about the difficulties there.

However, in the comment, since manufacturing cannot be done by biotechnology, if it is done by chemistry, the manufacturing of mid-size molecules is more like existing peptide synthesis. That is, Merrifield solid-phase synthesis using Fmoc protecting groups. Am I correct in understanding that it is not that difficult there?

I really think that other companies will probably follow suit in the future, and there is a company in the US that has already entered clinical trials with a medium molecule, so please let me know your thoughts on this. This is the first question.

Iikura [A]: Thank you very much for your question.

It was difficult. In my opinion, it is quite difficult to build up a number of innovations in, say, 3 years. It was in the biotechnology part. For example, is it easy to define drug-like properties? Considering the fact that it is still difficult to find such papers in the world, I am aware that there is a considerable gap in the information we currently have.

Regarding production, this is the chemistry part. As you pointed out, it is not a big deal, but we have reached a level where we think it is achievable. I think it depends on the situation.

Kohtani [Q]: If that's the case, is it correct to say that it would typically take other companies 5 years to catch up to where your company is, if they start from scratch?

Iikura [A]: Of course, it depends on the situation of other companies, but for us, it is becoming a platform, and we have a number of projects like the one I showed you at the end. We hope to deliver the medicine to the patients as soon as possible.

Kohtani [Q]: Secondly, I would like to ask about LUNA18.

At the last financial results meeting, it was explained that the drug is a pan-RAS inhibitor, which in essence means that it also inhibits the wild-type RAS found in normal cells. Although you mentioned that it is possible to secure a therapeutic concentration range in animal experiments, the current RAS inhibitors show remarkable effects by binding only to mutations, so there is still a concern that inhibiting even the wild type would be scary.

Now, looking at the research, there are 2 ways to look at it. One is that in normal cancers, wild-type RAS actually works in a suppressive manner against mutant RAS. If this is correct, then inhibiting the normal RAS will cause the cancer to grow, right? Another way to look at it is that, on the contrary, mutant RAS alone cannot drive cancer. I have heard that mutant RAS proteins are too dependent on certain signaling pathways, and that they cannot become cancerous unless they also utilize wild-type RAS proteins.

It would be very helpful if you could explain your company's view about why it is permissible to inhibit wild-type RAS. Thank you.

Iikura [A]: As mentioned earlier, RAS has long been known as a target for which drugs cannot be developed. In recent years, the G12C mutant has already been put on the market, and it is advancing at a very fast pace. After all, one of the mechanisms of drug resistance is that the wild-type RAS becomes more and more functional.

This is fundamentally different from, for example, ALK, which is an allosteric protein. For example, ALK causes cancer at the stage when ALK is mutated, but in RAS, even though it is the same driver, it is said that cancer develops after a number of genes, 5 to 10, are mutated. So it is quite a complex mechanism.

If one of them is a mechanism that uses the wild-type RAS, then, for example, in general terms, we can expect that the effect of G12C inhibitor will be enhanced when used in combination with pan-RAS inhibitor. Since the mechanism is so complex, we don't know if G12C and G12D have the same mechanism of resistance.

Since there are a lot of things we don't know about many different types of cancers, I think this will be the first time that the world will be able to understand which cancers can be treated effectively with a drug that inhibits these proteins. RAS is really a huge area, said to account for 15% of all cancers. We would like to make sure that it can be used where appropriate, and at the same time, of course, we would like to also consider selective ones.

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

Hashiguchi [Q]: My name is Hashiguchi from Daiwa Securities. I have 1 question each about mid-size molecules and Dual-Ig.

On page 30 of the mid-size molecule part, it was mentioned that your company is currently able to produce 20 hits. As you mentioned on the right side of page 26, can we say that we are talking about 20 next-generation quality products? Considering the probability of success from the lead onward, how much of an impact will

this have on the entire Chugai pipeline in the near future? In other words, how many compounds per year can be expected to enter clinical phase?

Can you tell us what defines this number of about 20 and how much it is likely to change when the Totsuka Research Center is built?

Iikura [A]: Thank you for your question, Mr. Hashiguchi. I'm sorry, please tell me if I miss any part of your question.

First of all, the 20 targets per year on page 30 is simply based on the number of personnel. CPR can increase the number of personnel, for example, so if we increase the number of personnel, we can increase the scale of screening by that amount. The quality of the product is already built into the platform, so it can be maintained.

Also, it is very difficult to say how many can reach the clinical trial phase, but page 36 may be useful for reference here.

This number is about 3 times as many as our current number of small molecule themes, and we are planning to release about that many at this point, and possibly more as the maturity increases.

Is that alright? Did I cover everything?

Hashiguchi [Q]: How about when Totsuka is built? The laboratory in Totsuka.

Iikura [A]: We are currently implementing what we call the RED shift, which will allow us to concentrate more personnel on research. When Totsuka is built, it will contribute to that shift in personnel.

Hashiguchi [Q]: Thank you very much.

Also, with regard to Dual-Ig, although it is a very amateurish idea, I thought that it would be a good idea to use 2 types of antibodies in combination, but what is the difference between antigen and CD3 bispecific antibodies and antigen and CD137, and also how much do you think the concept of 1 Fab being able to bind to 2 targets can be protected by intellectual property?

Igawa [M]: You are talking about the concept of Dual-Ig here, that is, if we can administer 2 bispecific antibodies at the same time, right?

Hashiguchi [M]: Simultaneously or sequentially.

Igawa [A]: We tested that approach in principle. One difficulty is that if 2 antibodies that bind to cancer antigens are mixed together, and the 2 antibodies compete in binding to the cancer, only 1 of them can bind to the cancer, so there is an advantage to having only 1 antibody.

One more thing, and this is the biggest one, is that it is very difficult to develop a combination of 2 drugs. When there is a first drug and a second drug, the safety of the first drug and a certain level of efficacy must be confirmed before the second drug can be added.

Third, the balance between CD3 and CD137 signals is very important, as mentioned in the first question earlier. As a simple example, even if the CD3 signal is weak, if the CD137 signal is strong, a very high anti-tumor effect can be achieved.

However, if we consider the development of 2 drugs, only 1 of which has a weak CD3 signal, the patient doesn't respond to anything if the molecule with a weak CD3 signal is administered in 1 drug. In that case, we

will not be able to develop the two agents separately and combine them later. Therefore, it is very important to develop a single molecule with a well-designed balance between CD3 and CD137 signals.

Hashiguchi [Q]: How about exclusivity to other companies?

Igawa [A]: Regarding exclusivity, the basic technology that allows 1 Fab to bind to 2 antigens was developed a long time ago by Genentech, although I have forgotten the name. Therefore, I think that the technology itself, which allows 1 Fab to bind to 2 antigens, is no longer patentable.

However, we have issued a patent for combining CD3 and CD137 at a specific rate or constant as I mentioned earlier, so there is a possibility of exclusivity here depending on the situation.

Hashiguchi [M]: Thank you very much.

Sakai [Q]: My name is Sakai from Credit Suisse.

I was surprised, in a good way, when I saw the table on page 36, but with so many products coming out, I was concerned about future R&D costs. It seems to cost more compared to antibodies or small molecules. What kind of image should we have? I would like to know what you think about that first.

Iikura [A]: Thank you very much for your question, Mr. Sakai.

We have only developed 1 drug for clinical use, so this is completely my personal prediction, but I believe that the development speed is at least faster than that of small molecules.

As I mentioned earlier about the number of compounds synthesized, we can proceed at least 10 times faster. Regarding the complexity of compounds, they are basically peptides, so in a sense, the optimization of antibodies is relatively smooth because there is a common platform of antibodies. In this sense, I imagine that it is easier to create such a platform for mid-size molecules than for small molecules.

The number of personnel required are still not as enough as the number required for antibodies, and we are still discussing how to improve the numbers. After all, antibodies require a small number of people, and even though the time it takes can be reasonable, the number of people it takes to complete a single project is still nowhere near that of antibodies.

Sakai [Q]: I understand. Thank you.

As for antibodies, I think you mentioned at the last R&D briefing that unless we can solve the problem of on-target toxicity of antibodies, we will not be able to expand the market. I think this is where the switch antibody came from.

Considering this problem, I believe that the Dual-Ig concept is more powerful in terms of penetrating the target. Would it be correct to say that you've clear the potential hurdles relating to toxicity?

Igawa [A]: Thank you for your question.

In the case of Dual-Ig, toxicity is very important. This toxicity is determined by how cancer-specific the tumor antigen is, so it all depends on how the tumor antigen is chosen.

For the 2 projects that are currently in the GLP-TOX stage, we conduct preliminary toxicity tests before GLP-TOX, and we select those that have completely passed the tests. Therefore, it is very important to select tumor antigens that are cancer-selective.

On the other hand, as I mentioned earlier, the ability to fine-tune the signals of CD3 and CD137 is a very big advantage of this technology. Even if some tumor antigens are expressed in normal tissues, by fine-tuning the CD3 and CD137 signals, the system can be programmed not to attack unless there is some level of expression.

The other is the combination of Dual-Ig technology and switch antibody technology, as you may have seen in the previous table. Even if it is difficult to make fine adjustments when so much antigen is present in normal tissues, we are thinking of using switch antibody technology to improve tumor selectivity and use Dual-Ig.

Sakai [M]: Thank you very much.

Sasai [M]: We would now like to take questions from the online participants. When it is your turn to ask a question, we will call your name. Please let us know your name and company name.

Your first question. Morgan Stanley Securities, Mr. Muraoka, please go ahead.

Muraoka [Q]: Hello. This is Muraoka from Morgan Stanley. Thank you.

The first question is about peptides. I thought it was a very interesting technology and I was impressed with it, but I wondered myself if I could compare it to ACE910. For example, ACE910 had the interesting characteristic of being long acting compared to existing drugs. I understand that peptide technology can be used orally, and that it is productive, but are you thinking of doing something like long-acting therapies to provide a completely different value? Is that something that is even possible? Please tell us about that.

Iikura [M]: Thank you for your question, Mr. Muraoka. I'm sorry, I didn't quite catch that, so let me check the question.

Are you asking about creating mid-size molecule drug discovery or cyclic peptide drug discovery that will be effective for a long period of time, for example, 1 or 2 months after a single administration?

Muraoka [M]: That's generally what I meant.

Iikura [A]: I think it is conceptually possible for amid-size molecule drug to be effective for 1 or 2 months after a single administration, but we are currently focusing more on oral drugs, so our focus is on intracellular tough targets treated with oral therapies. This is where we believe there is the greatest unmet medical need.

Muraoka [Q]: I understand. Thank you.

One more thing, you said earlier that Dual-Ig will enter Phase 1 next year. Is this referring to the Dual-Ig for glypican 3? Could you also tell us why your company is so focused on glypican 3?

Igawa [M]: Just to clarify. Are you asking if glypican-3 is the target of one of the 2 Dual-Ig projects that will be in Phase 1 next year?

Muraoka [M]: Yes, that's right.

Igawa [A]: Please appreciate that we cannot disclose the targets.

We are using normal IgG antibodies against glypican-3 as well as the first generation, TRAB, antibodies. This is because we believe that glypican-3 is a very promising target. We are continuing to work on drug discovery for glypican-3, but we are unable to disclose the Dual-Ig targets at this time.

Muraoka [M]: I understand. Thank you. I'm sorry my voice wasn't clear. That's all. Thank you.

Sasai [M]: Thank you very much.

Next, Mr. Wakao from JPMorgan Securities, please go ahead.

Wakao [Q]: This is Wakao of JPMorgan. Thank you.

Please tell me about the mid-size molecules research portfolio on page 36. Targets include intracellular and extracellular targets, but many are the so-called tough targets as posited in the concept put forward for mid-size molecules. In other words, am I correct in understanding that you are targeting known protein targets that are not currently targeted by any medications?

Also, the next one after LUNA18 is in the lead optimization section, so can we expect the next one to enter the clinical phase in 2 to 3 years?

In addition, where it says "extracellular" target, I believe that antibodies can also be used for targeting, but what are the advantages of using mid-size molecules instead of antibodies?

Iikura [A]: Thank you for your question, Mr. Wakao.

First of all, I would like to answer the question of whether all the intracellular targets listed here are first in class, that is, there are no drugs that have been commercialized so far. Most are first in class, but a few are best in class. The goal of best in class is targets for which drugs exist, but by changing the binding position to a position where small molecules cannot bind, the drug effect can be enhanced or the effect can be changed. That answers the first part of the question.

The second question is whether the next one will be ready in 2 or 3 years. We would like to aim for around that time.

Next, what are the advantages of extracellular targeting? Basically, our stance is to do with antibodies what can be done with antibodies, and to do with small molecules what can be done with small molecules. After all, each scaffold is quite excellent, so in such a situation, the basic stance is to use mid-size molecules for things that neither antibodies nor small molecules can do.

This includes replacing existing antibody therapies with oral mid-size molecule therapies. We can't disclose today what we are doing with them, but some of the targets will be extracellular, as listed here.

Wakao [Q]: Thank you very much.

Secondly, on page 35, please tell us about LUNA18. I think it was explained earlier, but my impression was that it was targeting a different area than the RAS G12C and other mutations. I understood it to be effective in a wide range of areas.

I think there are some types that contain various mutations, such as G12C, but I wonder if your basic research shows that any of the mutated strains are effective or not. Has that been confirmed? I would like to know how effective it is. Also, it says GEF here, but is it correct to understand that guanine nucleotide exchange factor is SOS? Looking at the patent information, it says that it inhibits the binding of SOS and RAS, is that correct? In that case, I think Boehringer is doing SOS inhibition as well. If possible, please let me know if there is any difference with what Boehringer is doing.

Iikura [A]: The first question is how many mutations does it work on? For example, G12C is now on the market and is being talked about. G12C is only one of the RAS mutations, and it is very important to have drugs that are effective for other mutations, such as G12D and G12V.

Depending on the location of the mutation, it may not be effective for all patients, but as far as we are concerned, it is generally effective.

As for your next question, as you said, this is SOS. What is the difference compared to SOS inhibition? We intend to elucidate this through clinical trials, but I will share my personal opinion on this.

The reason why we wanted to develop drugs for intracellular tough targets is that there have been many cases in the past where the drugs have been effective by suppressing the target itself. For example, because it was difficult to find a drug targeting RAS, people initially tried to suppress EGFR on the cell surface. However, the data showed that suppressing EGFR did not work for patients with RAS, but only for those with EGFR mutations.

In the same way, people tried to create an inhibitor of RAF, but it worked only in patients with RAF mutations. We are starting from the point where there is a high value in suppressing the protein itself that causes the disease, and I understand that in clinical trials, we will have to clarify the difference between inhibiting the protein that causes the disease and the protein that does not cause the disease.

Mr. Wakao, is that alright?

Wakao [M]: Thank you very much. Understood. That's all.

Sasai [M]: Due to time constraints, I would like to conclude with the next question. Thank you.

Mr. Osakabe of Jiho, please go ahead.

Osakabe [Q]: Thank you. This is Osakabe from the Nikkan Yakugyo.

I would like to know about the future position of mid-size molecular compounds. For example, do you envision a 2-pronged approach with antibodies in the future, or will the business be centered on med-sized molecules?

Iikura [A]: We consider small molecules, antibodies, and mid-size molecules to be the 3 pillars of our technology. For example, we are currently engaged in technology-driven drug discovery, which means that we identify areas that we want to turn into drugs but cannot yet, and create technologies to achieve these goals and turn them into drugs.

We call it drug discovery starting from Drug-Wants, and we will continue to deepen this concept, but in the future we would like to change it to drug discovery starting from Biology-Wants. Biology-Wants is the concept of first identifying what you want to do biologically, the mode of action, the target, and then selecting the best modality to use to apply it.

In such a situation, having small molecules, mid-size molecules, and antibodies will be an advantage, and biotechnology will be a foothold to expand into genes and cells. From there, we can choose the most appropriate modality. By taking such an approach, we are able to consider the scope and limitations of each modality and take a stance that allows us to develop the appropriate next technology.

Is that alright? Does that answer your question?

Osakabe [Q]: Thank you very much.

The second point is that you started clinical trials for LUNA18 in October 2021. Do you have a timeline for further development, or for when you plan to launch the product?

Iikura [A]: I'm sorry, but this area is still undisclosed.

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

Sasai [M]: Thank you very much.

This concludes the Chugai R&D meeting.

If you have any additional questions, please contact the Corporate Communications Department. Contact information can be found at the end of the presentation materials.

Thank you very much for taking time out of your busy schedule to join us today. Thank you for your time.

[END]

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