Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

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CHUGAI PHARMACEUTICAL CO., LTD.

Chugai Life Science Park Yokohama Laboratory Tour

July 18, 2023

Event Summary

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[Participants]	

[Number of Speakers]	3	
	Dr. Hitoshi Iikura	Vice President Head of Research Div.
	Dr. Atsuhi Ohta	Head of Modality Technology Research Department
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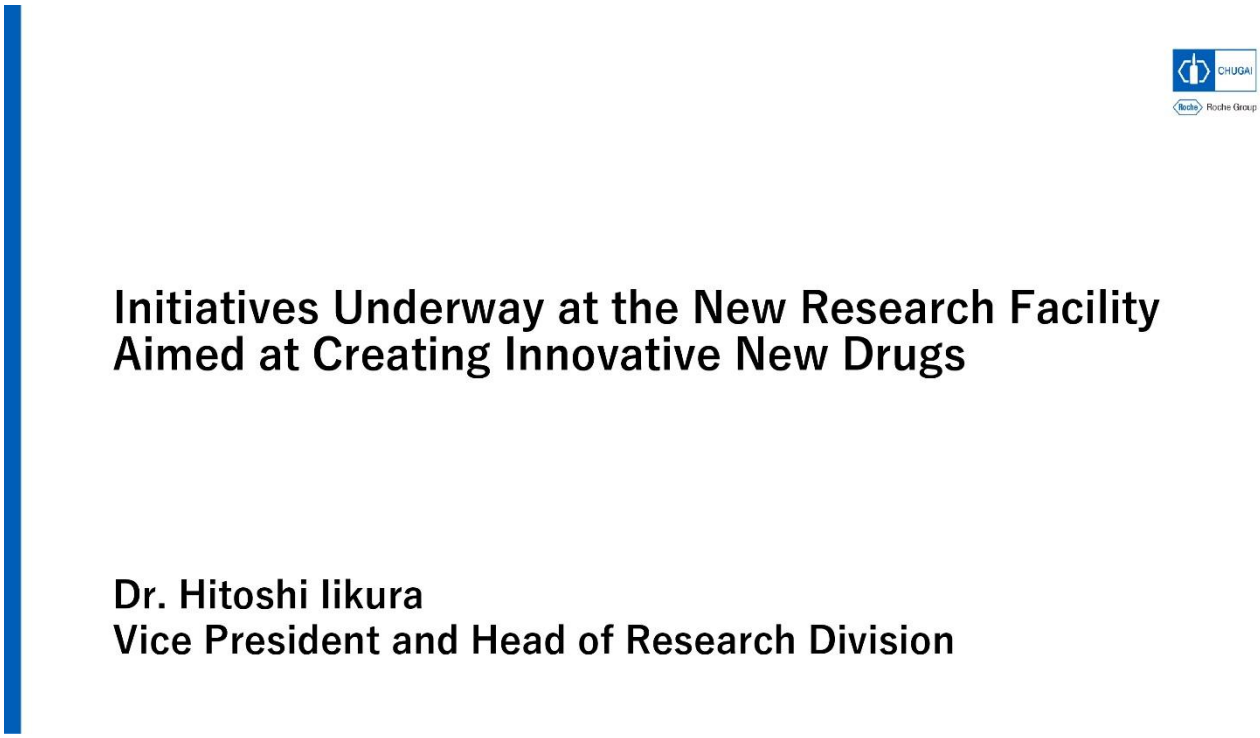
[Analyst Names]*	Miki Sogi	Sanford C. Bernstein
	Seiji Wakao	JPMorgan Securities
	Kazuaki Hashiguchi	Daiwa Securities

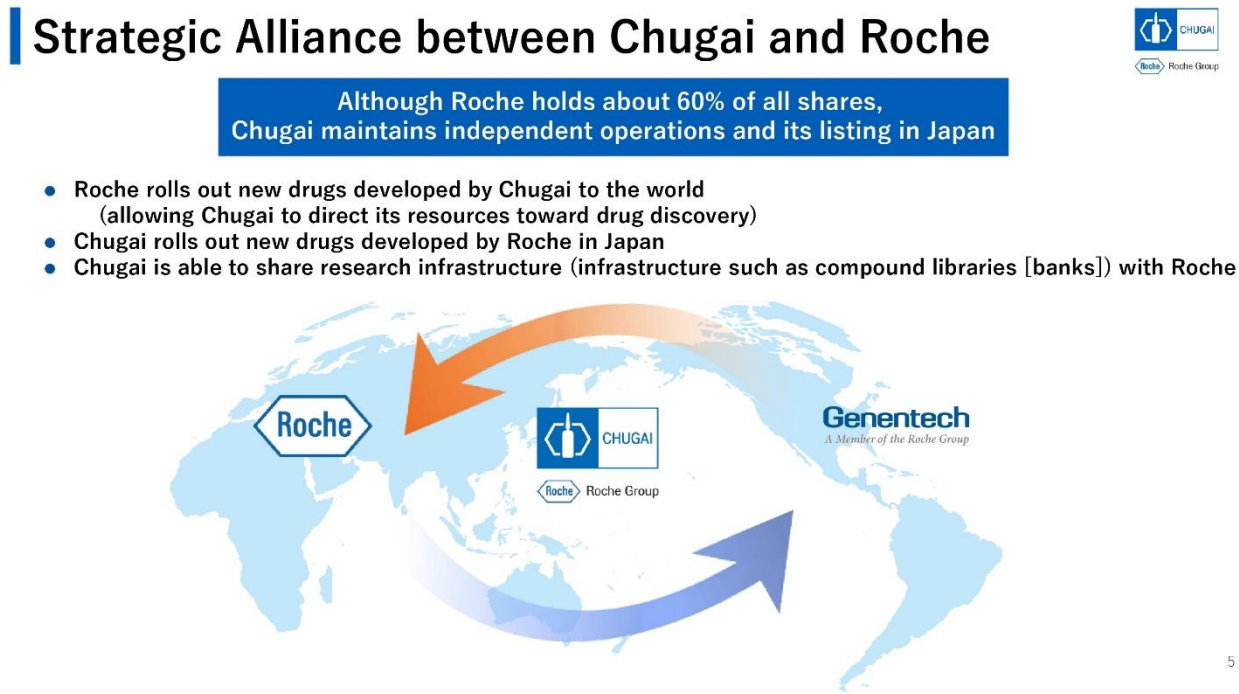
*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A or whose questions were read by moderator/company representatives.

Presentation

Iikura: Hello everyone. Thank you for joining us at our research facility today. My name is Iikura, Vice President, Head of Research Division.



I will begin with a 10-minute presentation on the general framework of our research, titled "Initiatives Underway at the New Research Facility Aimed at Creating Innovative New Drugs." This will be followed by a more detailed explanation of our digital and automation activities.



First, let me briefly touch on CHUGAI's business model. As you are aware, Roche owns approximately 60% of CHUGAI's shares. On the other hand, in the 20 years since this strategic alliance was formed, CHUGAI has continued to operate independently and has continued to list its shares in Japan.

Thanks to this business model, Roche delivers new drugs developed by CHUGAI around the world, and CHUGAI has the rights to develop and market new drugs developed by Roche in Japan. This business model is exactly what the founder, Juzo Ueno, envisioned for CHUGAI. Our business model embodies the concept of bringing new drugs from overseas to Japan, and exporting drugs developed in Japan overseas.

This business model allows us to focus our resources, such as people, money, and equipment, on drug discovery research.

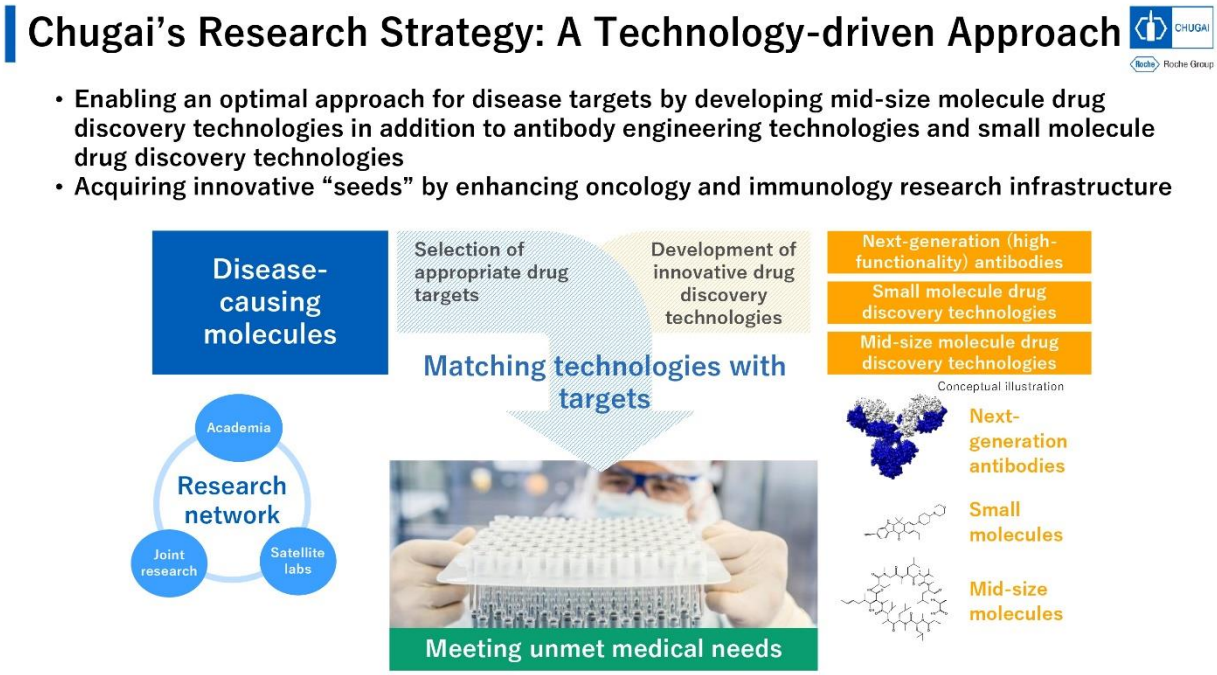
The research division is promoting several initiatives as part of TOP I 2030, under the heading of "global first-class drug discovery."

One of our goals can be summarized as RED SHIFT, in which RED stands for Research and Early Development. We are strengthening our foundation in the area of research and early clinical development.

Regarding the third point, "Open Innovation," I am not sure if it can be said that we have been self-reliant, but we have been rather self-motivated. So, we will actively promote collaboration with external parties.

The fourth point is to fully harness digital technologies in scientific discovery. This is, from our point of view, a completely new fusion with the digital field. This is what we are aiming for.

The Chugai Life Science Park Yokohama is positioned as an important growth engine.

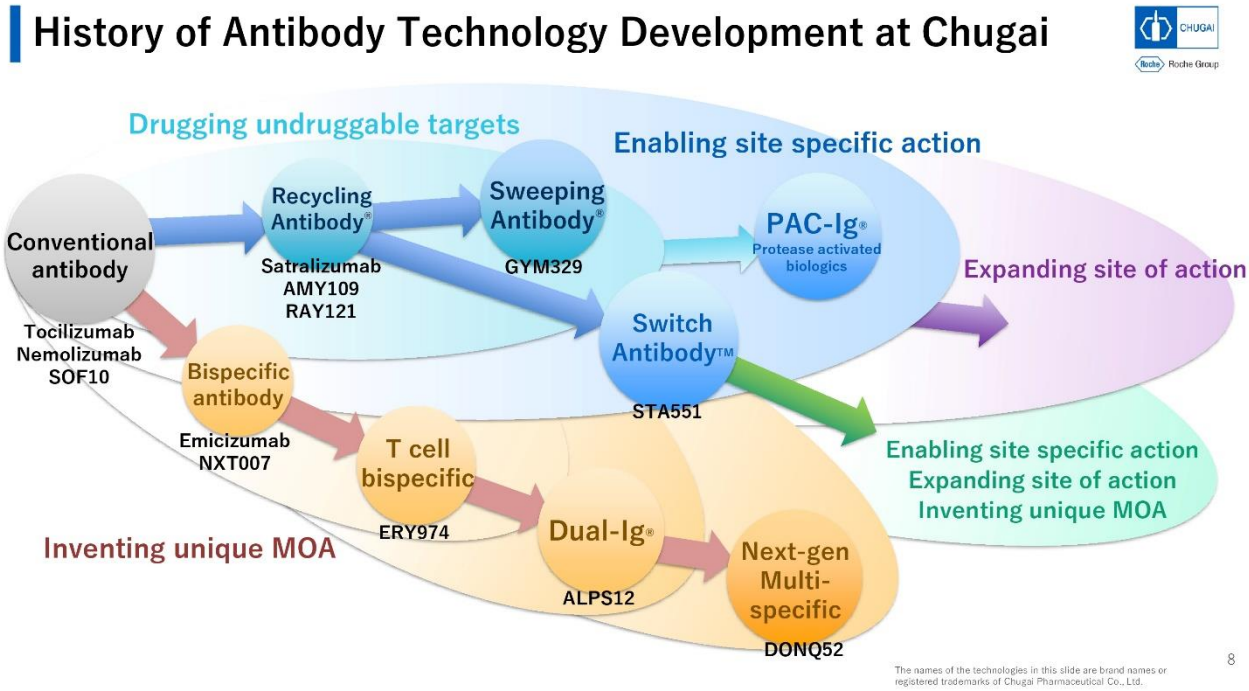


I am sure many of you are aware of this, but let me briefly recap.

What is important in drug discovery is the blue area, such as what disease-causing molecules to target, and identification of the appropriate drug targets. To address this, we have to think about kinds of drug discovery technologies we will use to create the drug candidates. These parts are written in orange. CHUGAI's strength is in this orange area.

CHUGAI's strength lies in its drug discovery technologies that enable drug discovery in ways that were not possible before. As I will show on the next slide, we have a history of realizing new drug discovery, especially with antibodies, by adding functions to them one after another that were not possible before.

Recently, we have been focusing quite a bit on mid-size molecule drug discovery, which is the result of the fusion of chemistry and biotechnology. In the future, we will of course focus on the search for potential drug targets within the Company, but we would also like to strengthen our collaboration with external parties and build on our strengths in this area as well.



To provide an example, I will expound a little about the history of antibody technology development. CHUGAI created and launched Japan's first antibody drugs, such as Actemra. These are so-called conventional antibodies.

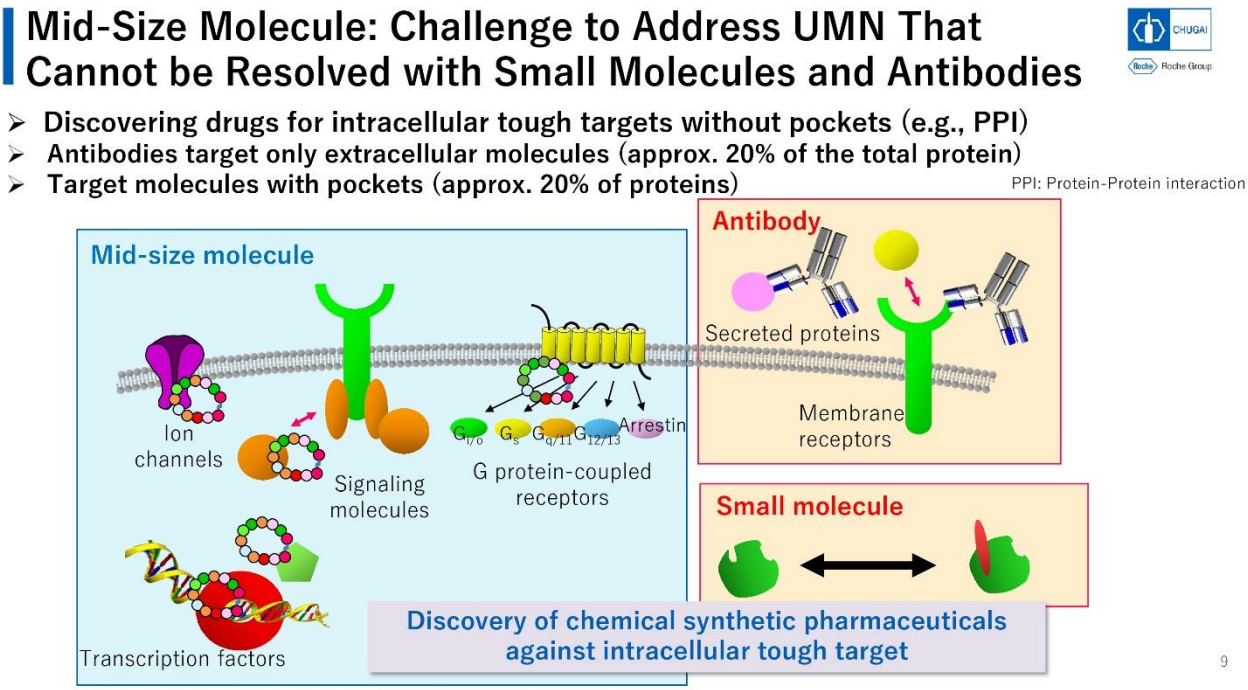
If we go down to the bottom, we have bispecific antibodies, like emicizumab, a drug for hemophilia A. Until then, the conventional wisdom was that a single antibody would bind to a single protein. I am proud to say that this antibody was groundbreaking in that it created a completely new function by recognizing two separate proteins with a single antibody.

From this bispecific antibody, we will continue to develop technology by adding functions one after another in the form of T-cell bispecific, and Dual-Ig.

In this way, we are reaching the point where we can realize drug discovery that we could not achieve before.

Let's turn our attention from conventional antibodies to recycling antibodies, such as Enspryng. While antibodies traditionally bind to a single target protein just once, they are now able to function repeatedly. That is, we made a single antibody possible to bind to the protein many times by this new technology.

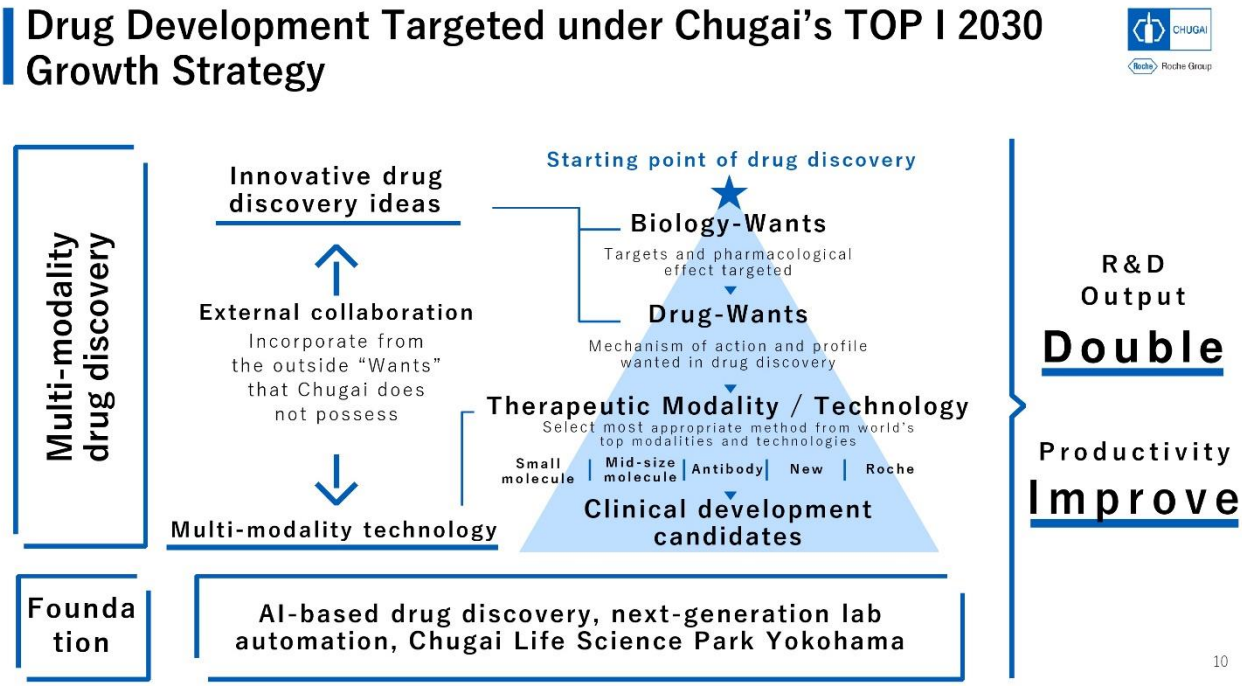
Sweeping antibody and switch antibody are the further development of these concepts. In this way, we have been steadily expanding our drug discovery domain.



That doesn't apply just to antibodies. We have also spent more than 10 years establishing ourselves in mid-size molecule drug discovery. The image in the top right represents antibodies. Antibodies can bind to a variety of proteins, almost any protein, but they are too large to enter cells. The gray area across the two images represents the cell membrane, and the outside of the cell membrane is where antibodies are active. Intracellular proteins are said to account for approximately 80% of the total protein, but antibody technology cannot access these targets.

Small molecules, shown on the bottom right, can enter cells, because they are small. But on the other hand, because they are so small, their ability to bind to proteins is limited to specific situations, such as when a hole is present in the protein. It is said that only about 20% of all proteins have these holes. About 60% of all proteins cannot be targeted by either of the major modalities, antibodies, or small molecules.

Mid-size molecules are a new modality, whose molecular weight is between that of an antibody and a small molecule. They can enter cells and have the potential to target a large range of proteins. We would like to use mid-size molecules to go for targets among the 60% of proteins that are currently out of reach. We can expect a lot from this technology going forward.



This slide is a conceptual summary.

We are focusing on small molecules, mid-size molecules, and antibodies as our strengths, as shown in the third row in the middle of the page. Recently, we are starting new modalities including cell therapy and gene delivery.

In addition to these things, we will make good use of external collaboration. We will make good use of lab automation, AI, and digital technologies, as listed here. Based on these considerations, we will achieve a doubling of R&D output by 2030.

Drug Discovery Research at Chugai Life Science Park Yokohama

Promoting Collaboration among Researchers

- **The 2 research centers at Fuji Gotemba and Kamakura are integrated into Chugai Life Science Park Yokohama to induce innovation through communication among researchers from different fields and the fusion of technologies.**

Digital Transformation (DX)

- **Sophisticated robotics and AI and cutting-edge technologies such as cryo-electron microscopy are used with the goal of achieving better research productivity and quality.**
- **Dry (digital) and wet (biological experiments) are blended to advance drug-discovery research and technology development.**

Acquiring Personnel and Promoting External Collaborations

- **Cutting-edge research environment and equipment will attract skilled personnel and strive to activate collaboration with academia.**

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We have listed here the initiatives in hardware areas such as Chugai Life Science Park Yokohama. Our first expectation is to promote collaboration among researchers. Until now, our company has been divided into two research laboratories, in Gotemba and Kamakura. These have now been completely integrated. We believe that most innovation occurs when researchers with different ideas engage in friendly competition with each other. This can result in the emergence of a new idea, different from the original ideas of researchers.

In this sense, I think it will be of great value for the two laboratories to unite and bring together researchers who have never merged before. I am proud to say that the area of mid-size molecules, as I mentioned earlier, is a drug discovery technology based on a completely new way of thinking. This was created by the fusion of biotechnologists and chemists whose views had never crossed paths before.

It took a long time for biotechnology and chemistry to understand each other, but we know the value of taking the time to integrate them step by step. We would like to continue to realize this kind of collaboration in various fields in the future.

We will aggressively introduce new digital technologies, such as robotics, AI, and cryo-electron microscopy. We will discuss this in more detail later.

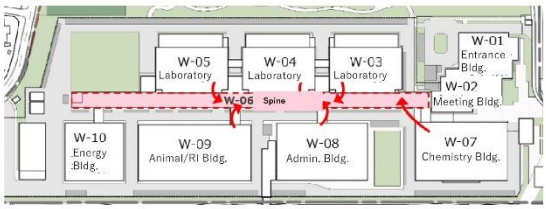
We will continue with the fusion of dry, digital, and wet, biological experiments. I think that the fusion of dry and wet processes is even more challenging than the fusion of biotechnology with chemistry. This is because the fields are so different. However, we believe that when this is achieved, we will be able to demonstrate considerable power, and we intend to move steadily forward with this process.

Facilities and Equipment Designed to Spur Innovation

The Spine

The Spine is the focal point for promoting vigorous communication among researchers from different fields.

- **All functions related to drug-discovery research was integrated to further increase research efficiency and promote collaboration.**
- **The Spine will promote exchange and knowledge integration among a variety of researchers to spur innovation.**

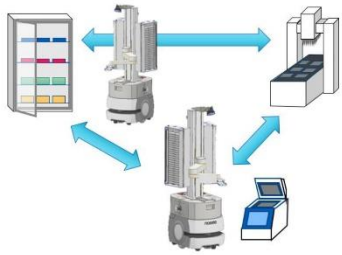


The Spine is a 300-meter corridor that connects the Park's laboratory and administrative buildings. The Spine has features that promote exchange among researchers.

Next-generation laboratory automation

Bringing about next-generation laboratory automation incorporating robotics technology

- **The adoption of self-propelled mobile robots and development of robot technologies will boost productivity in complex processes.**
- **Improvement of productivity will help researchers better work-life balance.**



Mobile robots connect automated instruments.

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Regarding facilities and equipment for innovation, two points are listed here.

One is the spine, which is represented by the line in red on the left. This is a corridor that is approximately 300 meters long. We will tour this later, but this hallway is one of our selling points.

This corridor must be passed through to enter the institute. We can't even get to our office without passing through here. Furthermore, researchers cannot go to their labs without passing through here. The concept is that our researchers will meet in this hallway, and we hope that meeting various people will trigger various discussions.

This morning, I was held up by two people coming from my office to get here, and it took me an extra four minutes to come here. It takes me about three minutes to get here on foot, but I still have to leave about 10 minutes before I want to arrive. That's a good problem to have, because it shows our goal is working.

As a next-generation laboratory automation, the rooms are designed so that the pillars and other parts can be freely replaced. This design is to accommodate machines of different sizes, as well as changes to make paths for robots in the future.

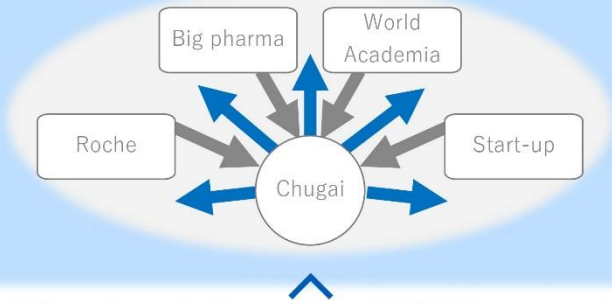
This spine is a great way to enhance our face-to-face communication. We are sometimes asked whether this kind of face-to-face meeting is important in the age of web-based meetings, but we believe it is very important.

As I mentioned earlier, I believe that face-to-face meetings are very important for people from different fields and with different ideas to understand each other and take a new direction. The concept is to promote automation while encouraging communication, so that we are not overly tied down to the research center.

With robotics, researchers will be freed up from having to stay late and wait for their experiments to end. This means that researchers don't have to stay needlessly, and can go home and relax. We believe that this greater freedom in the way we work will lead to a more fulfilling life-work balance.

Breaking Away from Pure Self-reliance

- Become a research base that is more attractive in various aspects, such as activation of exchange with researchers in Japan and overseas, and strive to acquire excellent researchers.
- Accelerate collaboration with academia, leading global players, and high-performing startups to pursue further innovation.
- Establish a corporate venture capital. Accelerate Chugai's proprietary drug discovery engine by combining its strengths with external technologies.



■ External collaboration starting from specific Strategic-Wants

■ Shift from purely self-reliant drug discovery to active collaboration

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Shift from purely self-reliant drug discovery. Many of our previous products have already been accomplished through external collaborations, so it's a bit late to start now. We have remained very much a do-it-yourself company in the development of drug discovery technology. We will continue to be self-reliance. We will continue to innovate by ourselves, but at the same time, we will do this by increasing efficiency through collaboration with outside parties and incorporating capabilities that we have not been able to do ourselves.

Designed with the Environment and Safety in Mind

- Energy-efficient systems and green infrastructure help reduce greenhouse gas emissions and achieve local disaster mitigation
- The facility has been awarded LEED Gold certification.

- Solar panels on the roof of the administrative building reduce CO_2 emissions and the need for externally sourced power.
- The facility has green infrastructure that temporarily pools stormwater in green spaces.
- A stormwater catch basin controls stormwater drainage into the sewer system, reducing the risk of water damage in surrounding areas.

Solar panels have been installed

Green infrastructure

Stormwater management

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Finally, our Company's research facility is designed to be environmentally friendly, safe, and secure. That's all from me. Thank you for your attention.

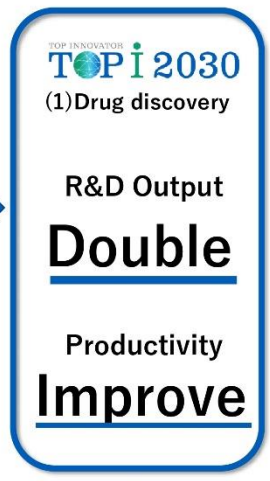
Expansion of Drug Discovery Research that Fuses Dry and Wet Research

Dr. Atsushi Ohta
Head of Modality Technology Research Department

Ohta: I would like to continue with my presentation titled "Expansion of Drug Discovery Research that Fuses Dry and Wet Research." I will also talk about what kind of research we would like to conduct here at the LSP Yokohama.

Accelerating Digital Transformation with the Establishment of the New Research Institute

- **Lab automation systems:** Overhaul equipment and rebuild systems to enable the efficient acquisition of massive amounts of data.
- **Roll out digital infrastructure:** Develop an environment that allows the massive amounts of data acquired to be easily organized and analyzed so that everyone involved is capable of advanced data utilization.
- **Enhance digital personnel skills:** Expand digital personnel skill training to allow wet researchers to make their work more efficient through programming.



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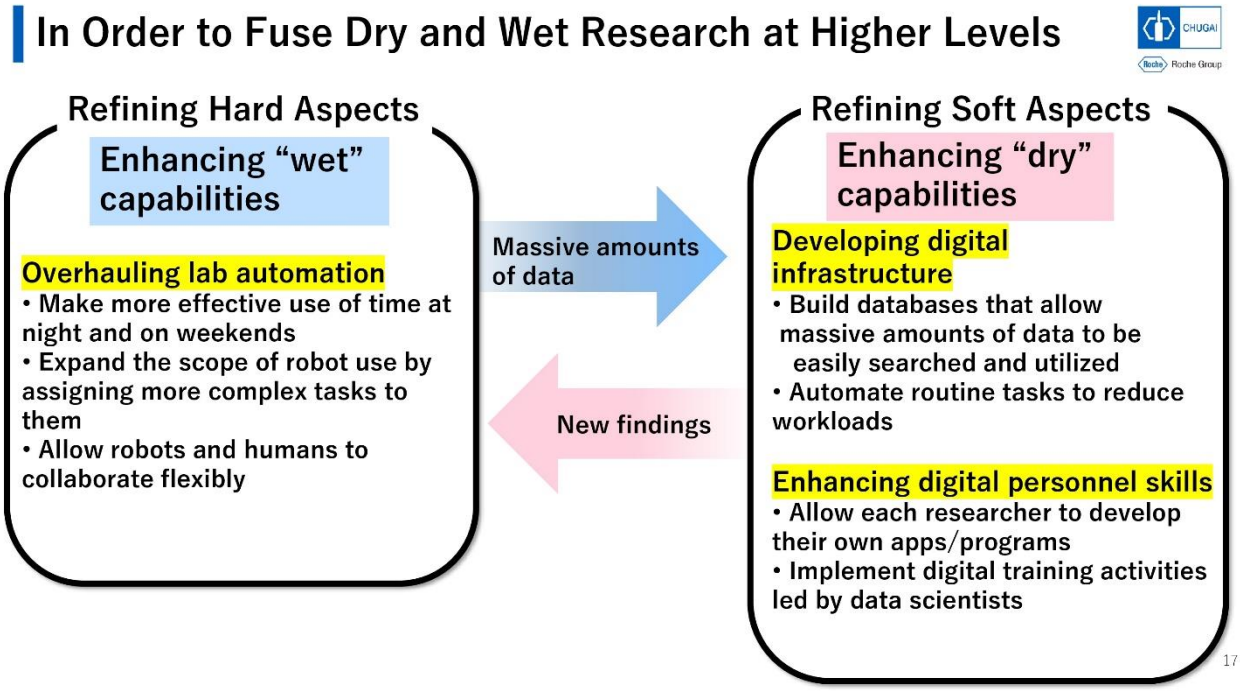
With the relocation of the institute, we decided not only to move, but also to take this opportunity to accelerate our digital transformation.

I would like to focus on three points. The first is lab automation: automation equipment for experiments. Our restructuring in this area allows us to efficiently capture vast amounts of data.

The second is digital infrastructure. There is no point in acquiring a large amount of data if we cannot use it, so we decided to develop a digital infrastructure that would allow everyone to utilize data in a sophisticated way.

The third is digital personnel skills, or people. While it is important to create the infrastructure I mentioned earlier, digital personnel skills are extremely important to be able to use it effectively.

In this way, we would like to contribute to the doubling of R&D output and improvement of productivity, which are the ultimate goals of TOP I 2030, by adding digital technology, such as so-called dry research to the wet research capabilities we have cultivated up to now.



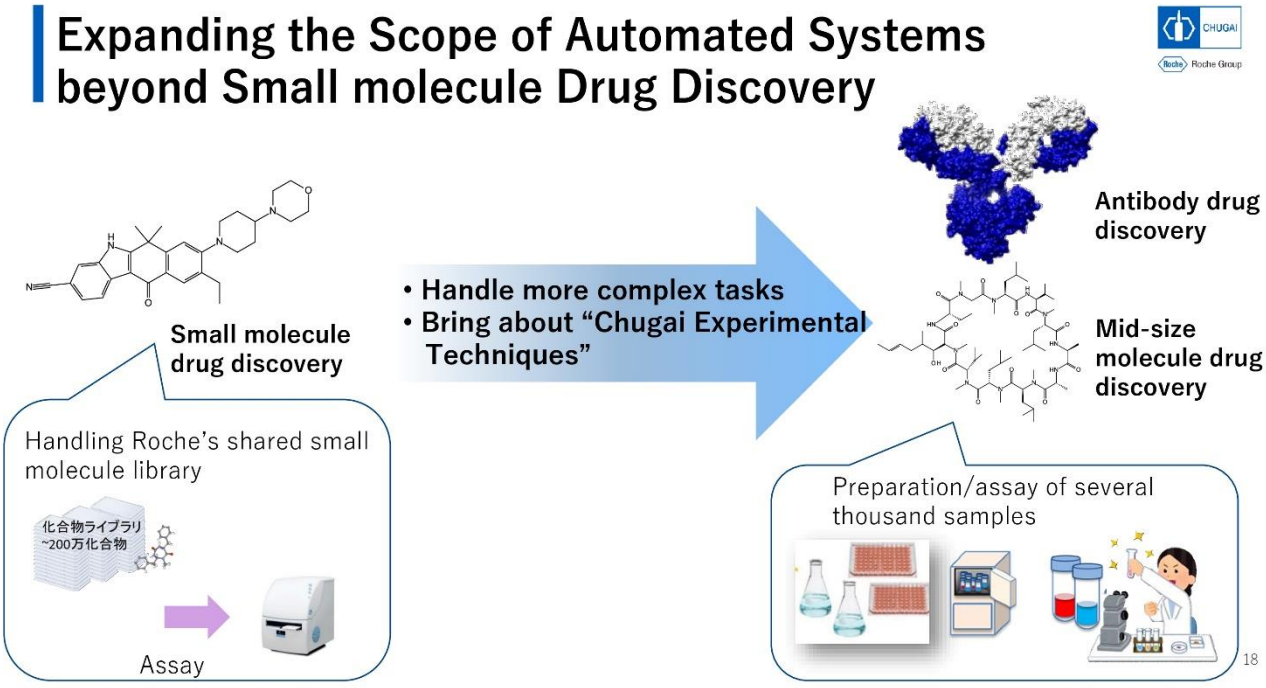
This slide shows in a little more detail how we are going to achieve this.

As for strengthening wet research, our focus here is on the hardware side of lab automation.

We should make more effective use of time that we have not been using, such as nighttime or weekends, and expand the scope of application by having robots perform more complex operations than before. In this way, we thought that we would like to create a large amount of data. On the other hand, as for dry research, in order to use data effectively, it is very important to have a database that can be easily searched and utilized, so we have built a large-scale database. We also considered reducing the burden on the researchers by automating things like routine tasks.

In terms of efficiency, ultimately the work of a research institute is quite individualized, so in addition to incorporating automation as a whole, each researcher can innovate their own research work through the use of applications and programs on their own. That is also important.

By repeating this cycle of generating new knowledge from the large amount of data generated by strengthening our so-called dry abilities, and conducting experiments based on this new knowledge, we will be able to integrate the dry and wet at a higher level than before, and this will lead to innovation. That is our approach.



I will talk about some specific examples of this later.

We have used automated systems in the past, but they were mainly used for screening in small molecule drug discovery and the operations were relatively simple and easy.

We have decided to expand this to other modalities, such as antibodies and mid-size molecules we have. To achieve this, it is necessary to perform more complex operations than before, such as cell cultivation for antibodies, or purification for mid-size molecules to remove impurities from the target product.

In addition, since these modalities are based on experimental techniques that we have studied for many years, it was not possible to simply purchase and use what was available externally. We had to customize them for use at Chugai.

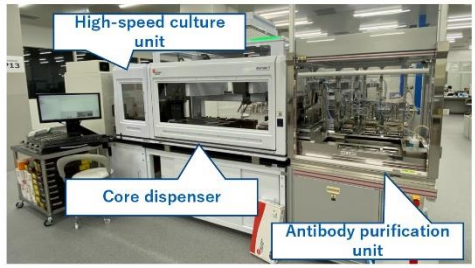
Therefore, we started to build an automated system several years before the relocation.

Succeeded in Making a Robot Perform Complex Operations that Chugai Researcher had Previously Done

Automated gene cloning system

By making use of the night time, which is not usually used, antibody gene preparation work that previously took 5 days was shortened to 3 days.

Automated culturing and antibody purification system



Cell culture (left) and antibody purification (right) experiments are done by one dispenser (middle). This has increased utilization and investment efficiency.

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As a result, automation has been achieved in many research and experimental processes.

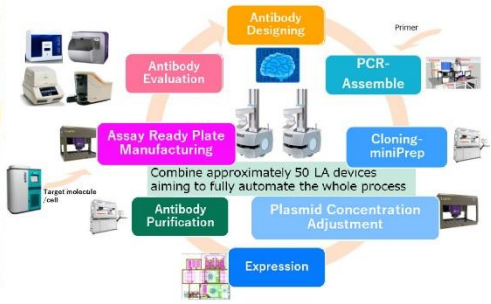
Shown on the left is an automated gene cloning system, mainly used in antibody drug discovery. This enables operations that were previously performed by humans. This also allows experiments to be conducted at night, which was not practical before. Operations that used to take five days can now be completed in three days.

The photo on the right shows an automated purification system. which I mentioned earlier as a little difficult, that can remove impurities from antibody cell cultures. It has become possible to automate such difficult operations.

Equipment are Linked to Each Other by the Mobile Robots, Allowing a Greater Range of Tasks

- Mobile robots transport samples among automated instruments
- This allows continuous and flexible automated tasks

- Humans and robots perform experiments using the same equipment
- At the new research center, the space and operation routes are designed to allow humans and robots to coexist



Automation of the antibody evaluation process using mobile robots is progressing

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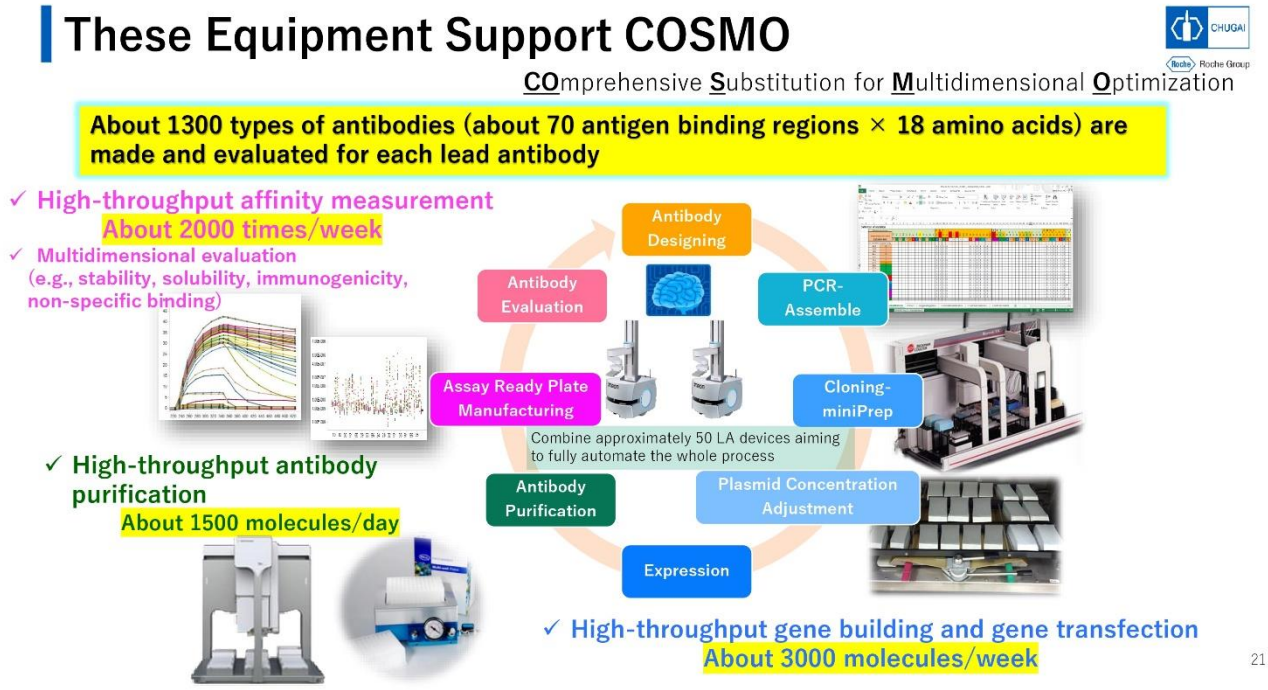
Here at LSP Yokohama, we are taking this automation one step further.

The main player in this process is a device called a mobile robot, which you will see in the photo in the middle of this page. This is a self-propelled robot with an arm that can take samples from research equipment, move them around, and place them on the next piece of experimental equipment, and so on.

Once this is done, each process can now be automated, but when going to the next process, the plates have to be carried by human hands. The process there can also be automated, and the automation equipment can be connected in various combinations, making it very flexible.

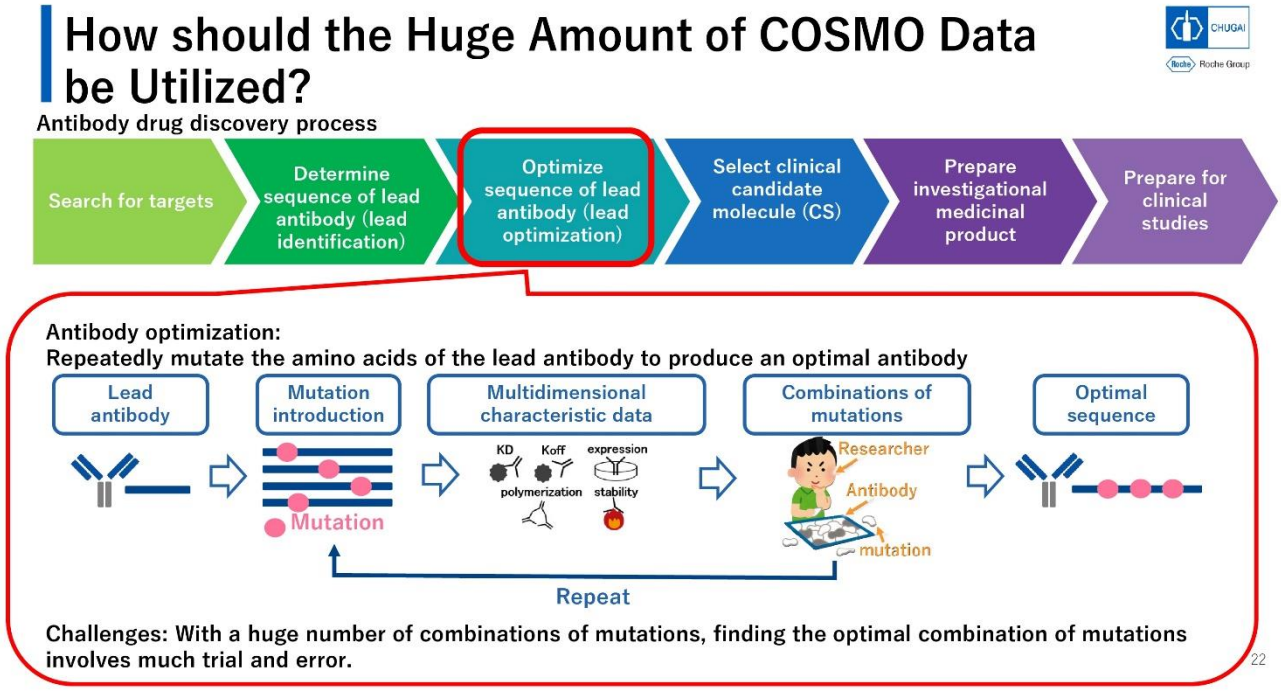
We are currently developing this system so that each automated process of antibody drug discovery can be completed in one continuous operation.



This automation forms the foundation of our company's strength in antibody drug discovery..

In the process of antibody optimization, which we call COSMO, we need to create thousands of antibodies and increase their activity in order to turn a lead antibody into a final drug. The throughput of producing thousands of antibodies and measuring their activity is made possible by the automated equipment I mentioned.

I think we have talked about these slides in the past at such briefings, but there is an automated equipment I just mentioned behind it, which is the point I wanted to talk again.

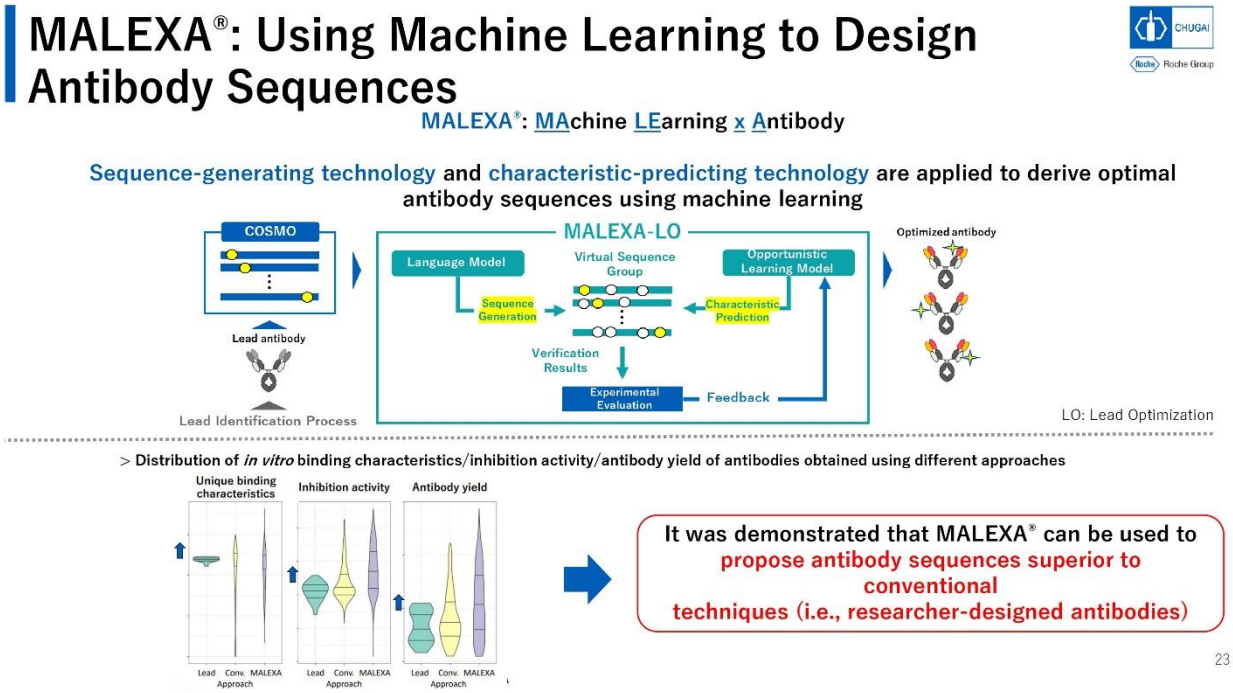


I have talked about how we generate large amounts of data, and now I would like to talk about how we make the most of these large amounts of data.

To elaborate a little more on the antibody sequence optimization I mentioned earlier, for one lead antibody, we are creating about 1,300 different amino acid mutations. Based on the activity, we design antibodies with higher activity by combining mutations that seem to have increased activity, as if we were doing a puzzle. We then make the antibodies again to measure their activity, and combine them with mutations that might increase their activity again.

This cycle is repeated 10 to 20 times to create the antibody that will become the final drug. What becomes very important in this process is the combination of mutations in this antibody.

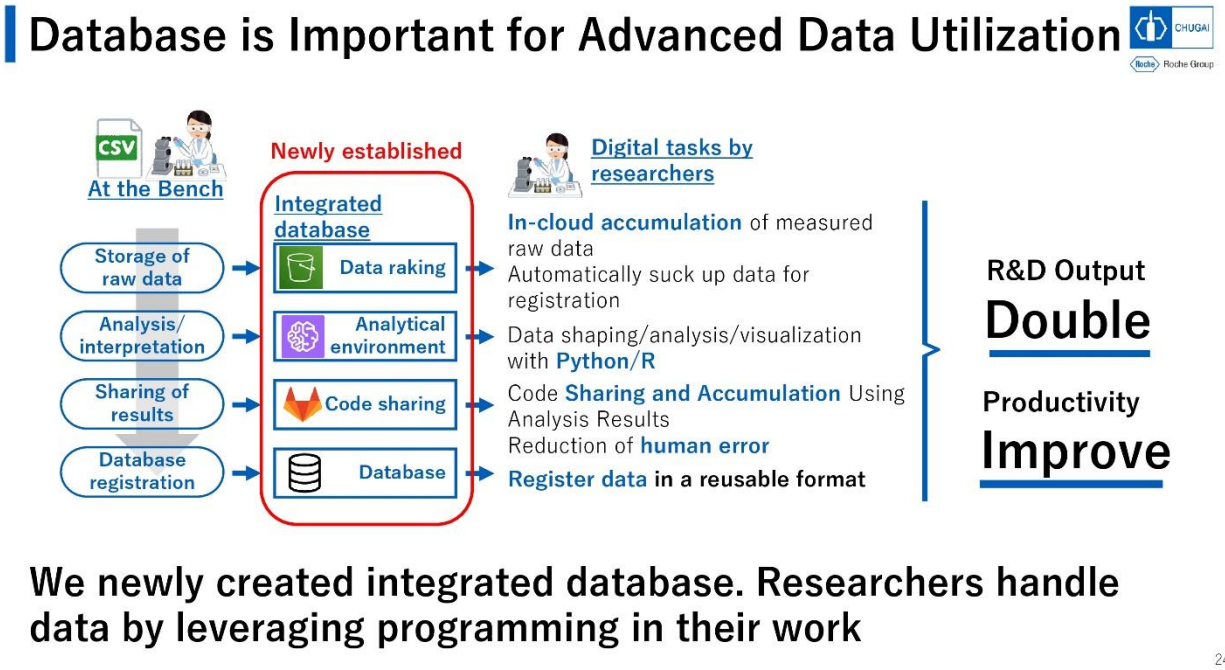
This is a task that until now has been done entirely by people, and I think our scientists have done a very good job of it. Even so, the process was still time-consuming, and even with 1,300 types of data, the range of human thinking was limited to a certain portion of the data. As a result, this was a hit-and-miss, expensive process.



In response, we have developed a technology called MALEXA, which uses machine learning to improve efficiency.

MALEXA will suggest the most active one against the tens of thousands of possible combinations of mutations. In fact, this system has been applied to our project, and although I won't go into details, we have confirmed that it can achieve better antibody sequences than those designed manually by our researchers.

We have already published various press releases and papers on these technologies. The technology itself has evolved since the last presentation, to the point where the final antibody sequence can now be created by machine alone, without the need for human eyes. This is exactly the technology that is now leading the way in our AI drug discovery.



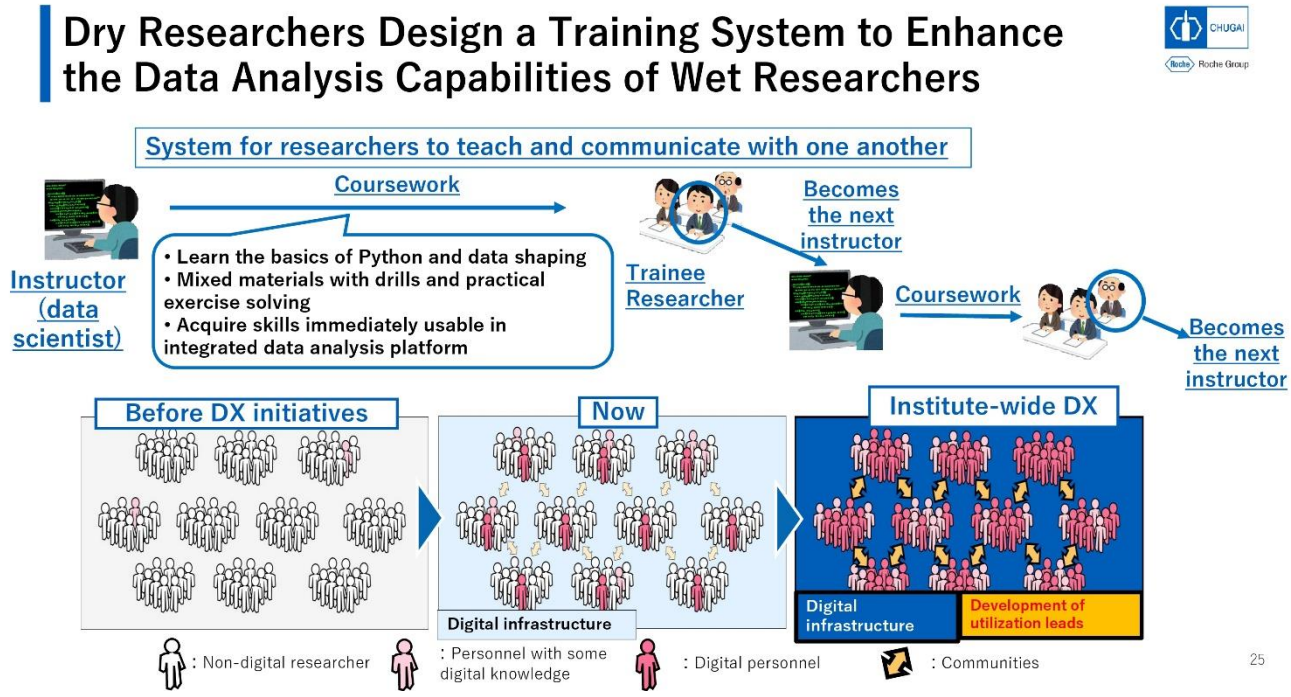
What we learned from this example is that databases are very important for advanced data utilization, such as machine learning. Therefore, with the relocation of the laboratory here at LSP Yokohama, we have created a database that allows us to integrate and analyze all kinds of research data on a large scale, and our researchers have been using it starting this month.

Experimental data taken by each person is stored in a data lake, which is very easy to search, so that research data that was done by someone somewhere, in some department, can be easily analyzed by a third party.

In analysis, as in the past, things such as repeated copy and paste, graphing, and statistical analysis on Excel can be done in one shot with programming. By doing so, everyone will be able to reproduce the analysis equally well.

We also share the program code used in the research, so that when someone performs a sophisticated analysis, other researchers can use it to perform similar code analysis.

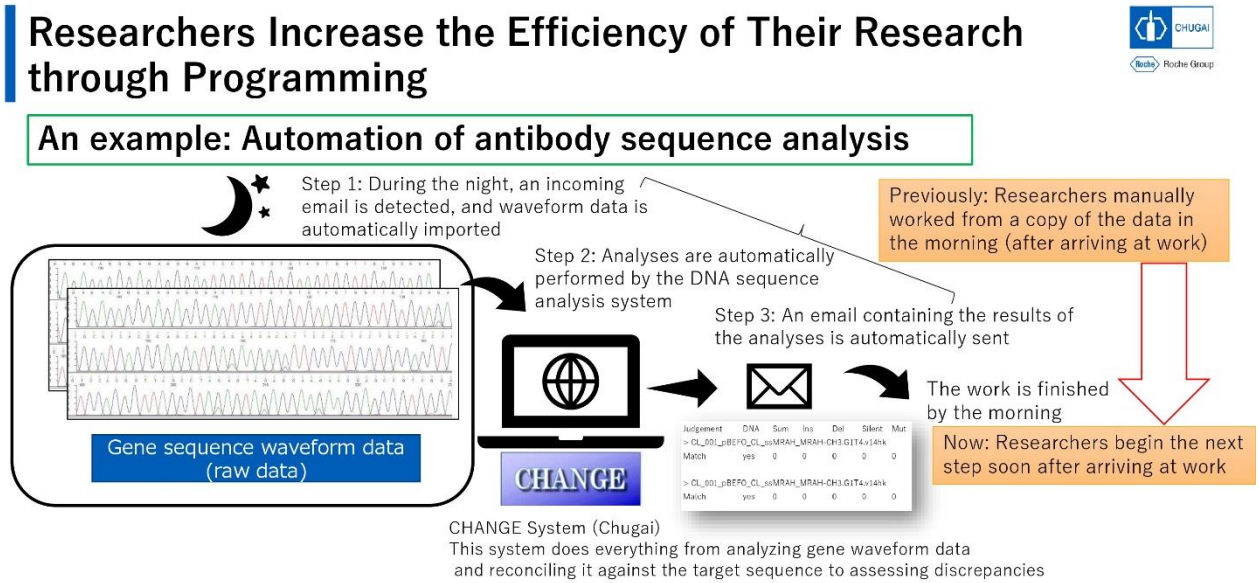
We expect that using such a database will enable us to conduct advanced analysis, or reflect opinions from different perspectives not previously involved in data analysis, thereby producing findings that have never been seen before.



In order to work with the database that I mentioned earlier, it is necessary for researchers to have at least some programming skills, and we started a unique educational program about one or two years ago.

We will spend about six months training wet researchers in Python and data shaping, two skills that data scientists need. The skills gained there can be used immediately in the integrated data infrastructure mentioned earlier.

What is very unique here is that each student will teach the next student that follows them, under the guidance of a data scientist. This will not only multiplicatively increase the number of digital personnel skills, but will also allow digital and wet researchers to communicate with each other and create a unique community.

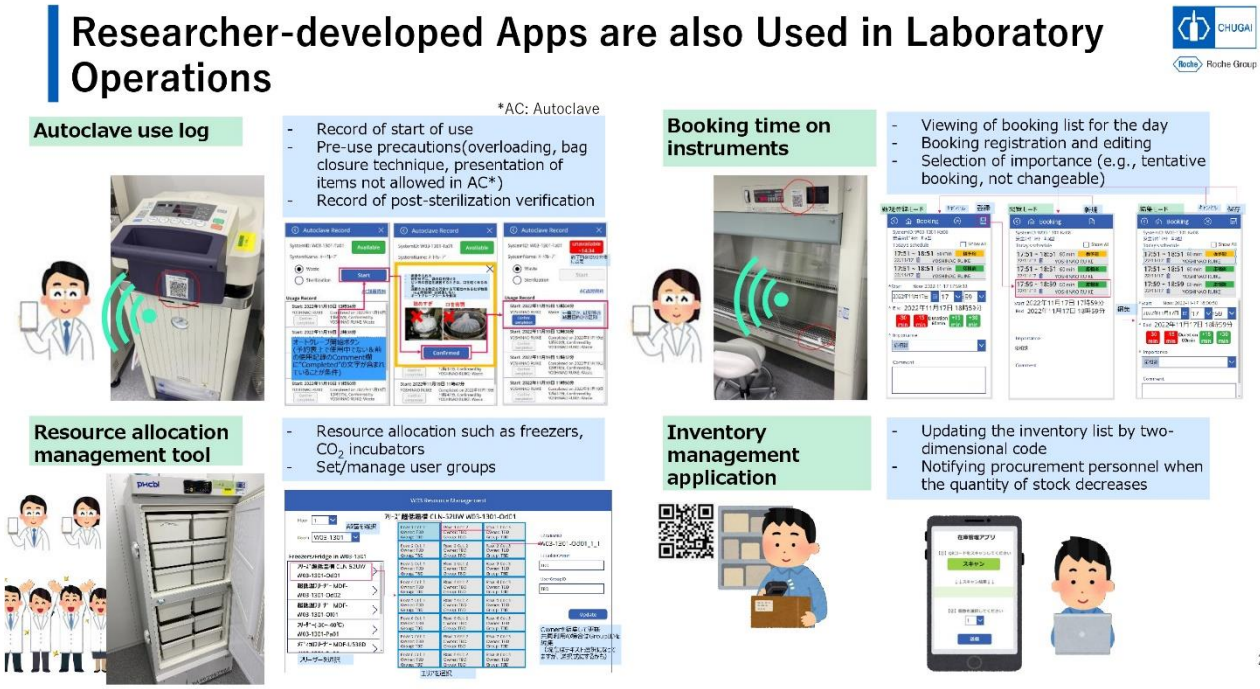


We are seeing more and more examples of researchers actually using programming to improve the efficiency of their own work.

Shown here is a system that automates antibody sequence analysis. Until now, the raw data of experiments generated in nighttime were run through the system the next day when we came to work, and we had to confirm that the genes we wanted to create had been created correctly before moving on to the next experiment. This process can now be automated and completed during the night.

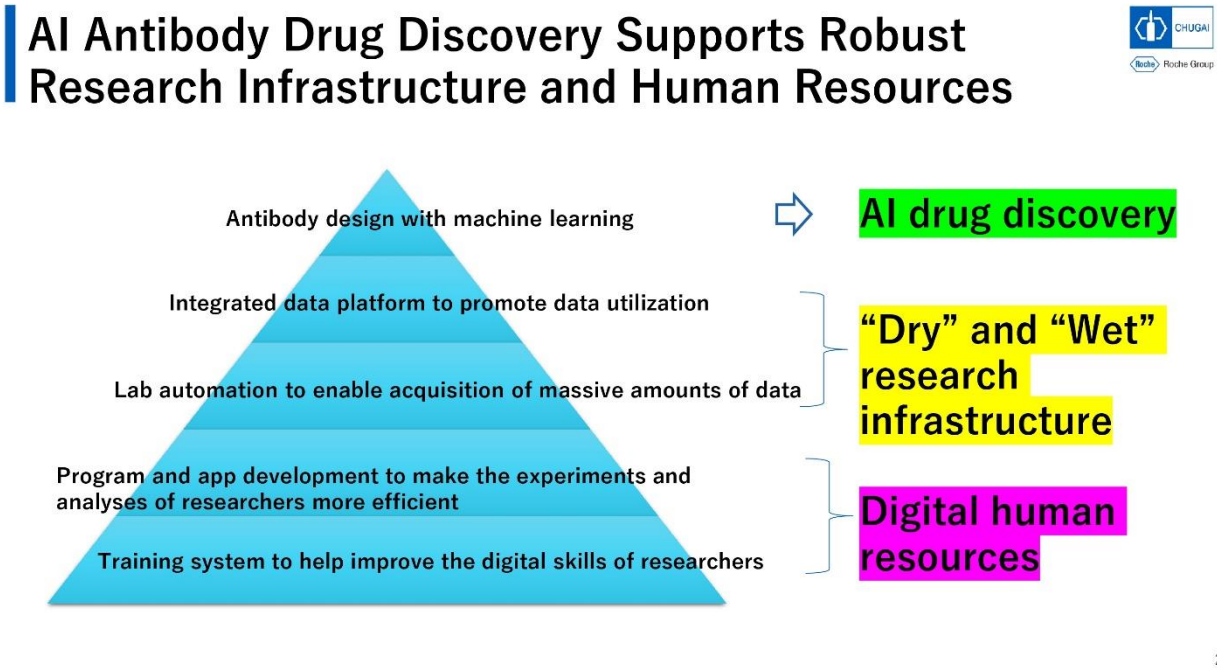
This means that when we come to work in the morning, we can immediately start the next step of the experiment. The process I just described took around eight hours a week, so in effect, this has saved each worker involved 460 hours a year.

The time saved is very important, but I also think it is very important for researchers to be able to look at their results and immediately think about the next process, rather than doing routine tasks just after arriving fresh to work.



This example of what might be called end-user development is also used in, for example, laboratory operations. The example shown here is an application created by a researcher that can be used on a smartphone.

In this context, I would like to talk a little bit about the equipment use reservation shown in the upper right-hand corner in the slide. Some units of experimental equipment are almost fully booked in the laboratory, and waiting for a turn to use them disrupts the experimental schedule and is quite frustrating for the researchers. In order to avoid such a situation, we used to post a paper reservation list, for example, but at our LSP Yokohama, paper reservation lists are not acceptable because mobile robots and other machines as well as humans use the same experimental equipment. In that sense, this mobile application is very useful.

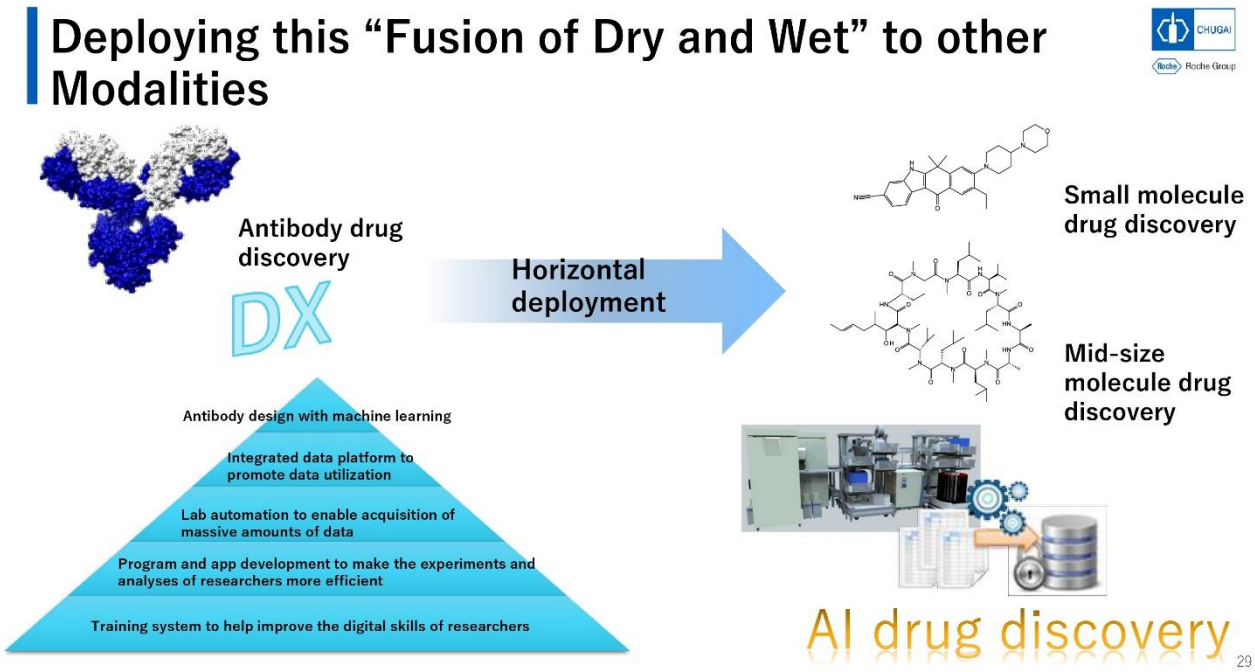


I have spent a few slides talking about examples of automation. What I wanted to convey is that we would like to continue to focus on AI drug discovery, but what is important at this time is the dry and wet research infrastructure, as well as the human resources to support it.

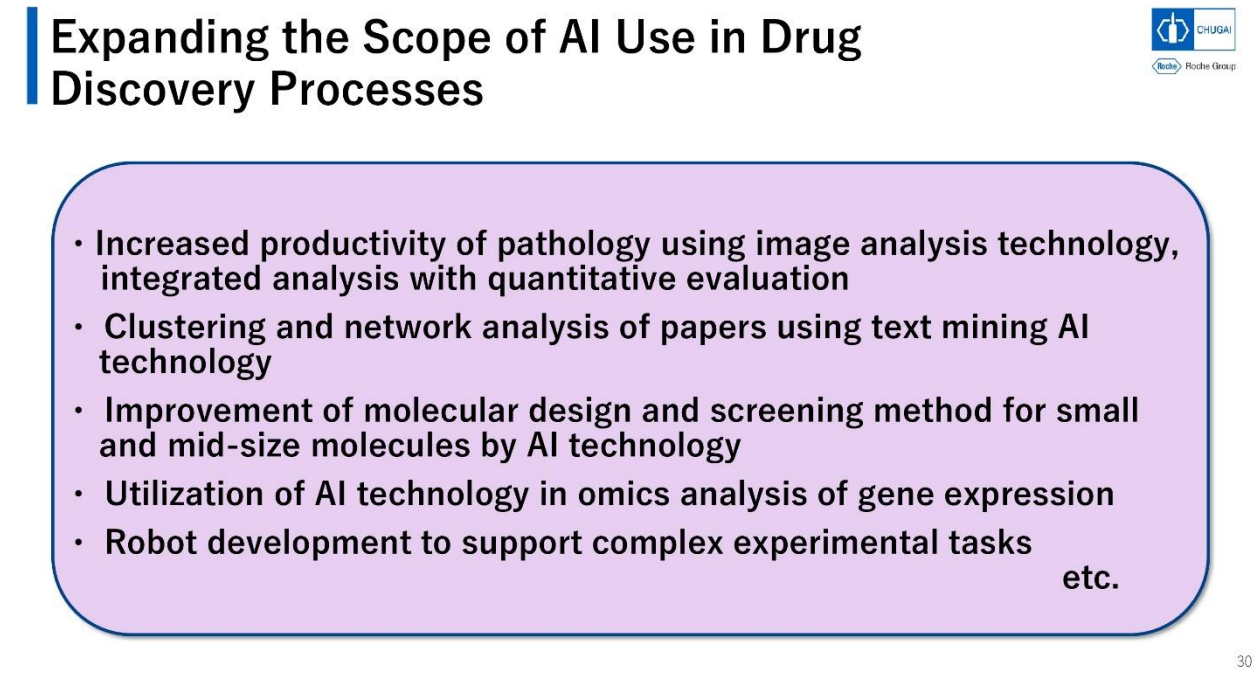
I mentioned earlier about antibody design by machine learning, and this is made possible by databases and lab automation systems that provide databases with large amounts of data.

Behind this is the attitude of researchers who are making efforts to use programs and applications to make their own research more efficient. We have in place an educational system that improves their digital skills.

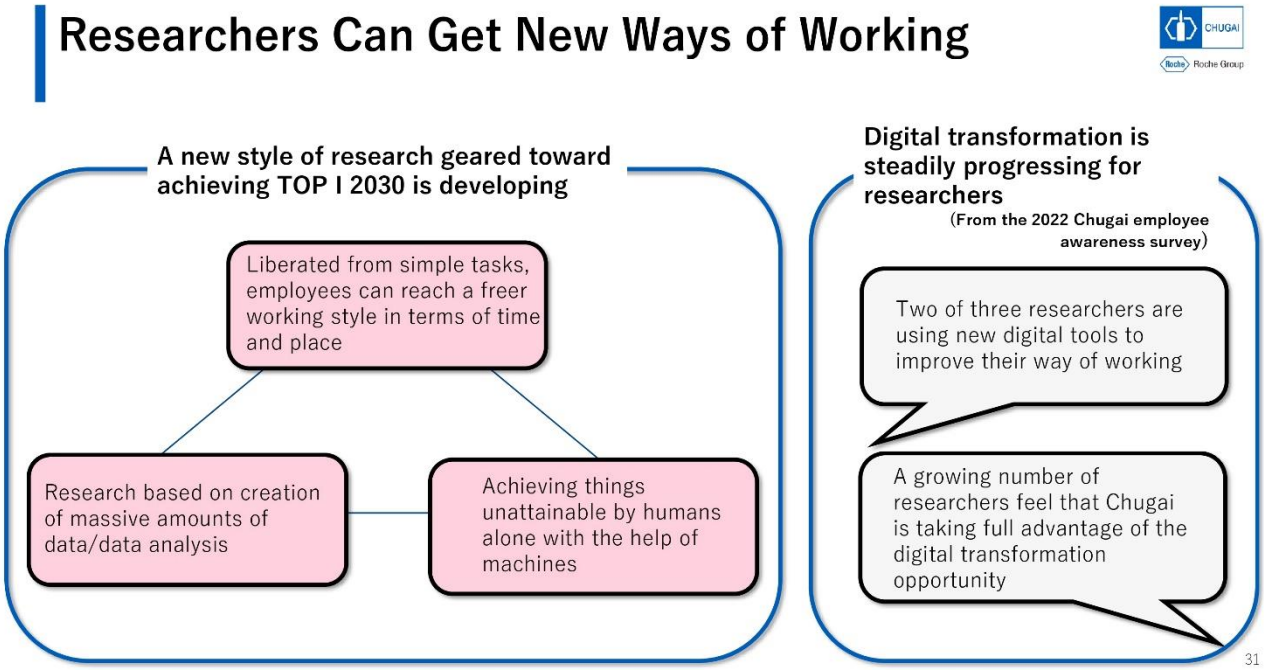
The relocation of the LSP Yokohama was an opportunity for us to strongly leverage research infrastructure and human resources once again.



We are currently expanding our antibody drug discovery system horizontally, using these technologies for our other modalities, such as small and mid-size molecules.



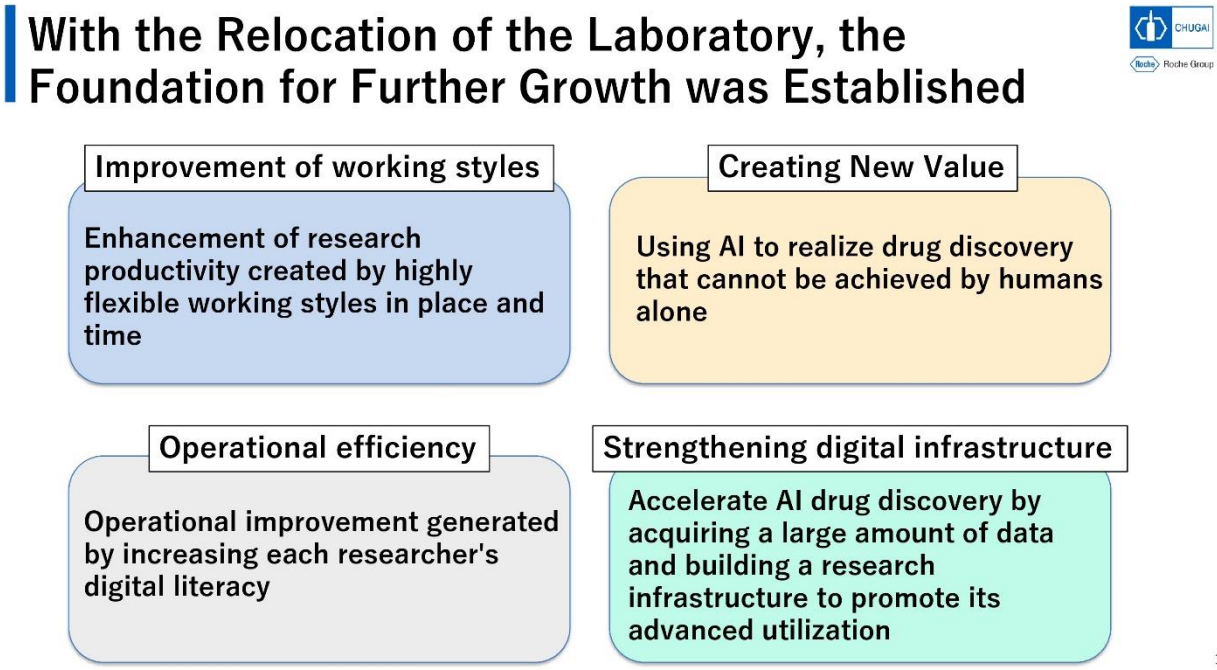
We also use AI technology not only for manufacturing, but also for image analysis of microscopic photographs, for example, or for analysis of papers, which enables accelerated learning, or for analysis to find relationships that humans would not have thought of.



I think this kind of digitalization technology is not limited to data scientists, but is spreading to ordinary researchers as well. We are now beginning to realize that the research style is changing.

Research based on a large amount of data, or a thought process to think about what can be done using a machine if a person finds it difficult, or, and I think this is the most important, the way of working has been liberated from simple tasks and place and time have become more flexible. For example, we have heard that the time required to pick up children from daycare has become less of a concern, making it easier to conduct research while raising children, and that the work-life balance has become more fulfilling.

In addition, according to the results of our employee awareness survey, two out of three employees are using new digital tools, so I feel that the benefits and importance of digitization are becoming more and more apparent to the general research community.



This is the last slide.

With the relocation of the research institute, we have reorganized our facilities as mentioned earlier, and I feel that the foundation for further growth is now in place. I believe that improvements have been made in the way we work and research productivity has improved, and each researcher is becoming very aware of the need to improve efficiency in their work.

We are also gradually seeing an increasing number of cases in which AI is being used to do things that cannot be accomplished by humans. The digital and wet research infrastructures that support this are being renewed and made more powerful.

That concludes my presentation. Thank you very much for your attention.

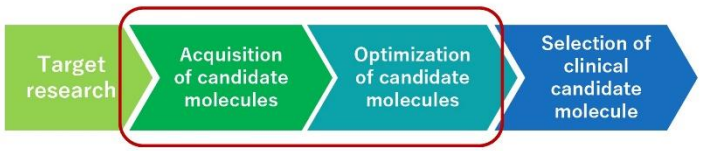
Acceleration of Chugai Drug Discovery with 3D Structures Generated by Cryogenic Electron Microscopy (Cryo-EM)

Dr. Takuya Torizawa
Head of Protein Science Department

Torizawa: I would now like to talk about how creating 3D structures using cryo-EM is accelerating drug discovery in CHUGAI.

3D Structural Analysis is Essential in the Early Stages of the Drug Discovery

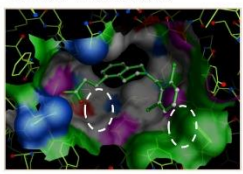
By analyzing the 3D structure of the binding state of the target protein and drug candidate molecules, followed by designing appropriate compounds, it is possible to significantly shorten the time period in the initial stage of drug discovery.



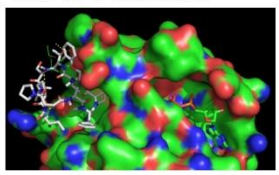
For both small and mid-size molecules drug discovery, the 3D structure information of candidate molecules is utilized in the stage from acquisition to optimization.

The 3D structure is also useful for the design of highly functional antibodies.

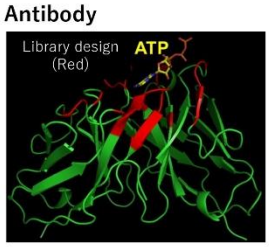
Small molecule



Mid-size molecule



Antibody



Conceptual illustration

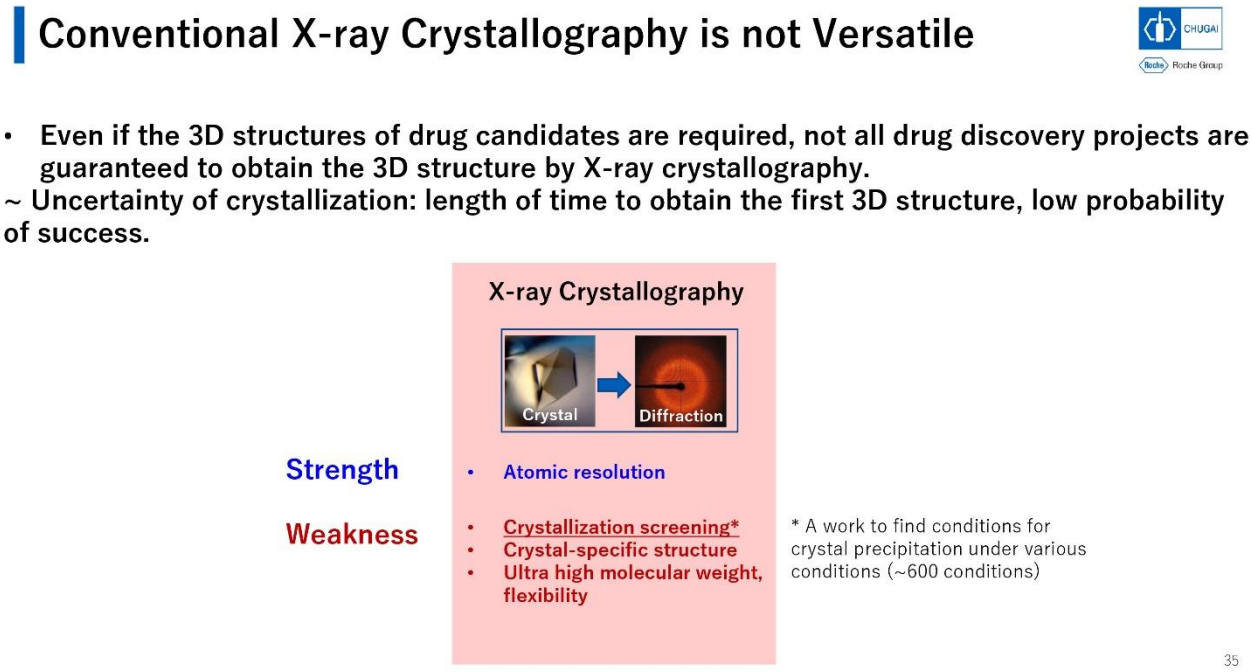
First, I would like to show how knowledge of the 3D structure of a molecule is useful in the drug discovery process.

Shown here is a simple representation of the drug discovery process. Through target research, we will obtain drug candidate molecules that interact with proteins, which are the main target molecules of diseases. The process is to develop these into drugs.

In the portion enclosed in red, it is possible to design a sophisticated candidate molecule by analyzing the structure in space of the target protein molecule bound to the candidate molecule. We conduct this kind of structural analysis not only in small molecule drug discovery, but also in mid-size molecule drug discovery, which is our focus.

Having this 3D structure data shortens the drug discovery process by about 75%. Clearly, structural analysis is very important.

In the design of next-generation antibodies with high functionality, another focus of our company, it is possible to design antibodies with added value by analyzing the 3D structure in this way.



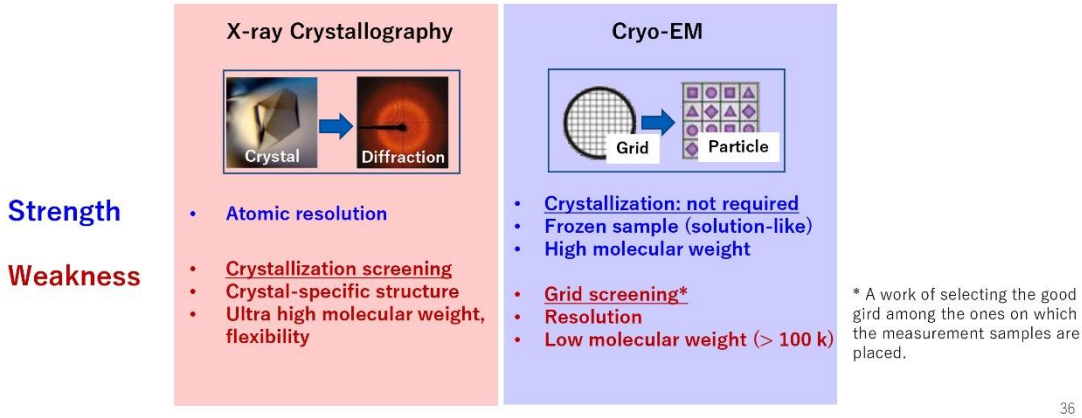
Next, I will talk about how we have obtained these 3D structures so far.

So far, we have been using the X-ray crystallography method to analyze 3D structures. Specifically, we have been working to crystallize proteins in this way. However, we have had a sense that X-ray crystallography is not always able to provide a 3D structure in drug discovery projects.

The reason I say this is that in order to obtain such crystals, we have to try quite a few different kinds of conditions to find the right conditions under which the crystals appear. This can take a very long time and, in some cases, does not even yield a result at all. This leads to delays in drug discovery projects. This has been an issue in 3D structural analysis up to now.

3D Structure Can be Obtained without Crystallization by Cryo-EM

- **Since around 2015, cryo-EM has rapidly developed to the level where molecules can be observed in detail at the atomic level, and is a technique that won the Nobel Prize in Chemistry in 2017.**
- **Since crystallization is not required, it is possible to obtain the 3D structure at an early stage of the drug discovery project, which will play an important role for accelerating drug discovery.**



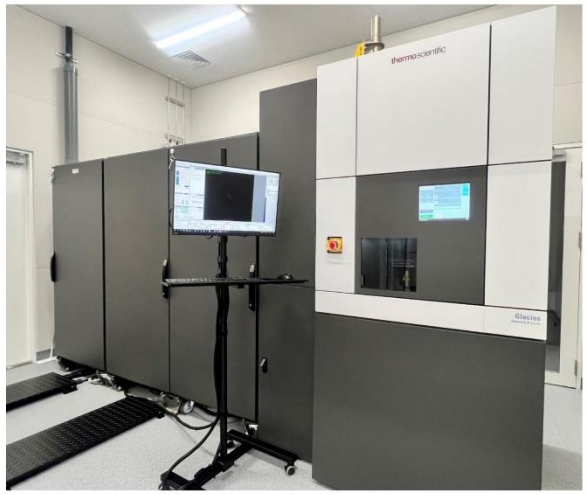
Cryo-electron microscopy is a new method that has emerged in this area. It enables us to obtain 3D structures without going through the crystallization process that I mentioned earlier.

Cryo-EM analysis is a relatively new technique that has been developed since 2015. It can be used to reveal the 3D structure of proteins in great detail. Its creators won the Nobel Prize in Chemistry in 2017 for the discovery.

We will adopt these advanced methods as well. As I mentioned earlier, the advantage is that crystallization is not required. Of course, there are disadvantages too. I will talk about this later in reference to the actual experimental techniques, but we are using the advantages of cryo-EM analysis to compensate for these disadvantages, accelerating drug discovery by visualizing 3D structures.

Introduced Cryo-EM for the First Time among Japanese Peers

- **Chugai installed the cryo-EM in its research laboratory in April 2021.**
- **Since then, thorough continuous investment, the equipment has been updated to the latest version, and the throughput is now more than double compared with the first version.**



Thermo Fisher Scientific
Glacios (200keV)

The photo above was taken at Chugai Life Science Park Yokohama

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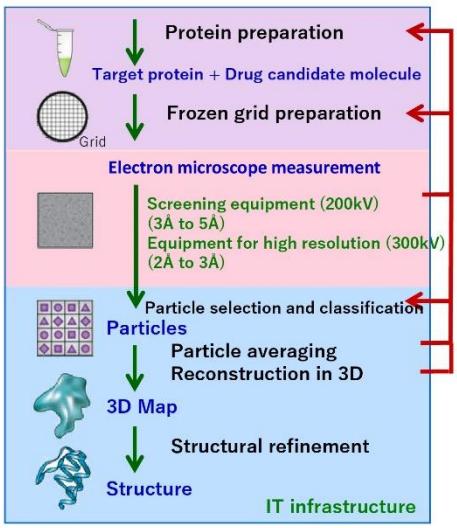
In April 2021, we became the first pharmaceutical company in Japan to introduce cryo-electron microscopy. Continuous investment since then has resulted in equipment with performance that more than doubles throughput from when it was first introduced.

Shown on the right is the actual cryo-electron microscope installed in our laboratory, which I will introduce in a live broadcast later in this presentation.

Long Way to Obtain the 3D Structure by Cryo-EM

(Live Broadcast Scheduled Later)

Experiment flow



- **It is desirable to conduct the subsequent work as quickly as possible to obtain the 3D structure, but if it is not successful at each step, we will have to return to the above work and start over.**

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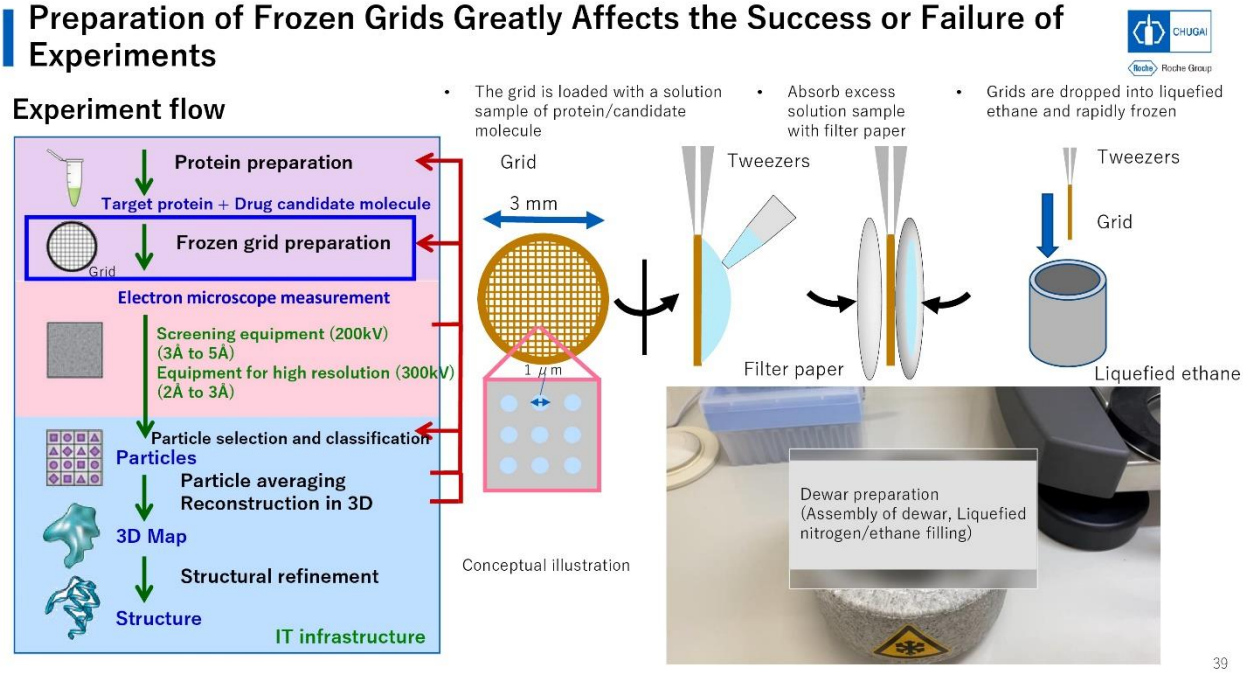
Since cryo-EM is a very advanced technology, I would like to show you what kind of experiments are being conducted today and how new experiments are being conducted to obtain 3D structures.

The experimental flow of cryo-EM is shown on the left. We will conduct the experiment from top to bottom. Ultimately, this 3D structure will be obtained by cryo-EM.

The final 3D structure is created through several steps, but there are hurdles at each step. When a hurdle is encountered, it is necessary to go back to the top and start the cycle over again as quickly as possible.



I will now explain the process in more detail.

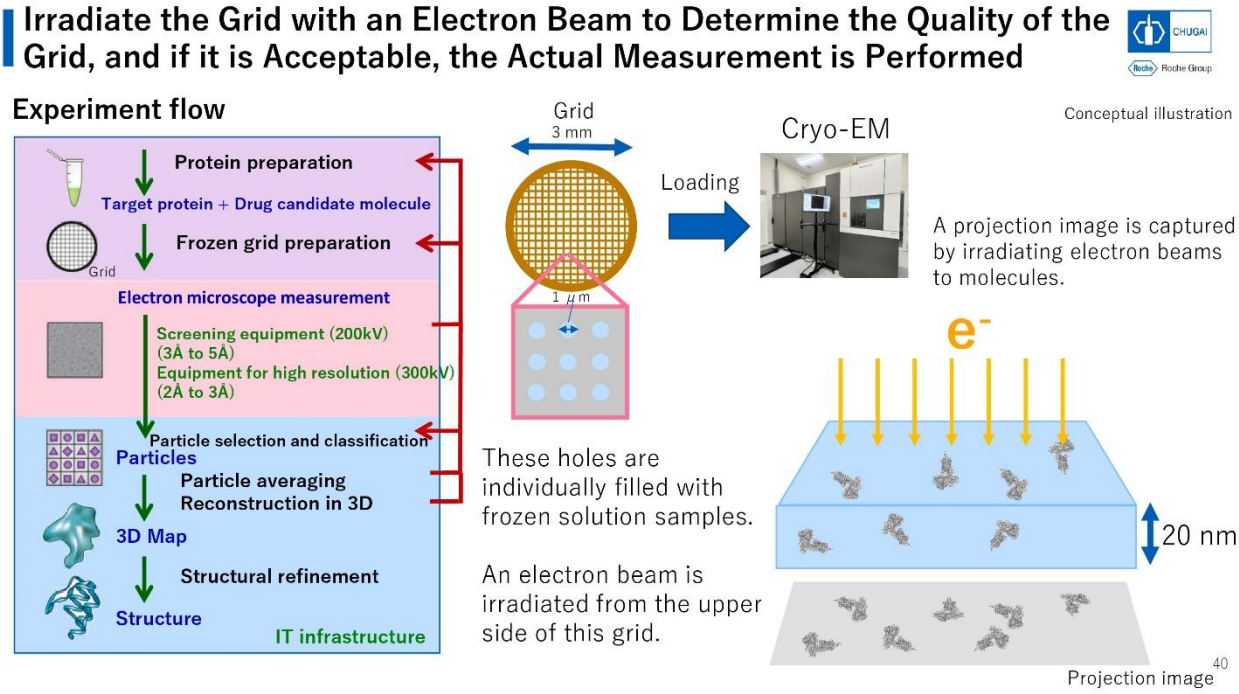
This is the first hurdle. This is the grid on which the sample is placed for analysis. In reality, it is a thin disk of about 3 mm, but it has a grid like this, and if you zoom in on one of the squares, you will find a hole like this.

The protein solution sample is placed here. Viewing the grid from the side, the sample is injected here between the grid and the tweezers. The excess sample is removed with filter paper, and the sample is frozen by placing it in liquefied ethane, a very low-temperature, cryogenic solvent, on the grid. We have a video of this work, which you can view here.

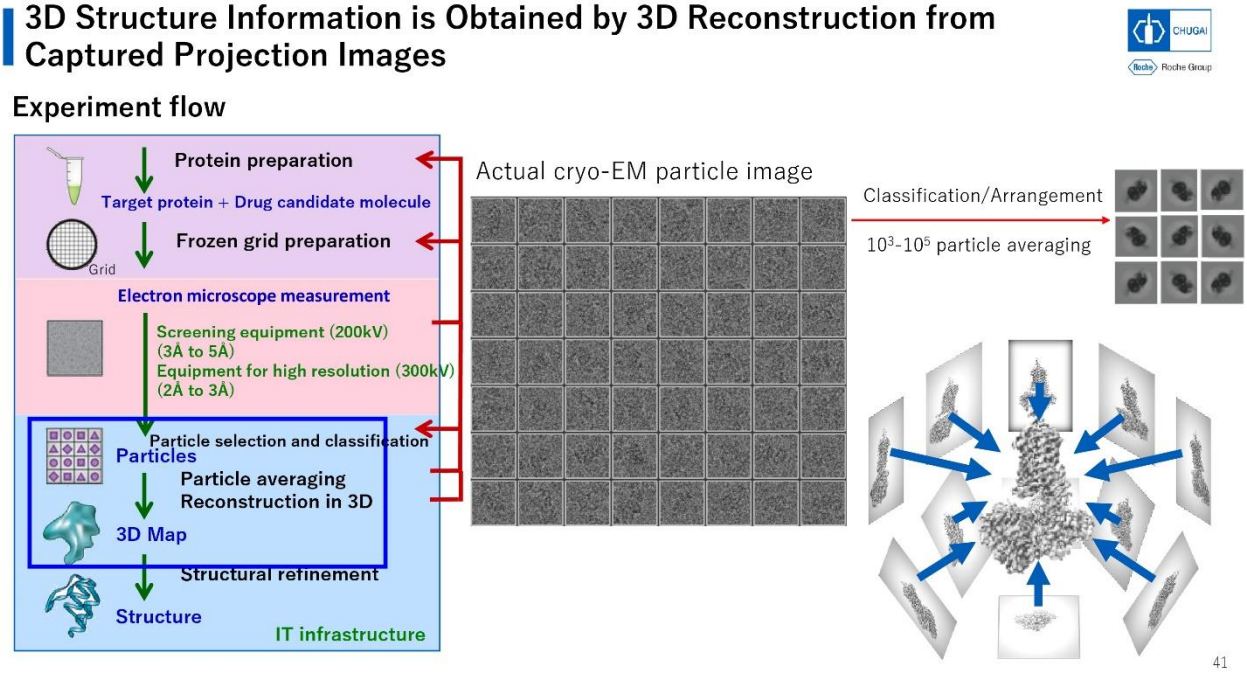
First, we put out two liquefied ethane preparations. The dewar preparation is liquefied by pouring gaseous helium into it. This device fast-freezes the grid. The grid, held by the tweezers, is set into the device.

Next, we show the interior. We set the liquefied ethane here first. This is the interior.

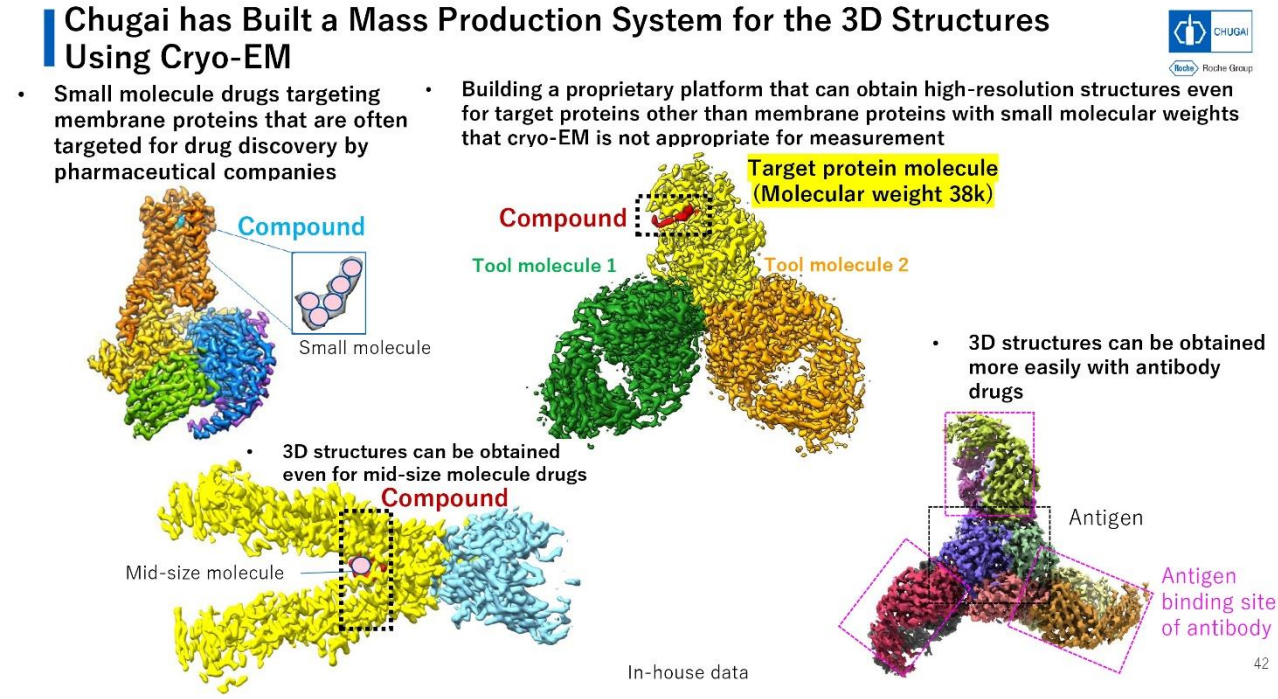
There is a grid here, and the sample is placed here. It is put on the side. Filter paper is available here. We remove excess sample by sandwiching it in filter paper and rapidly freezing it all the way down and toward the liquefied ethane. The sample is frozen, and the grid is now stored in a frozen state.



The frozen sample is placed here on the grid made in this way, and the cryo-electron microscope is used to make measurements by applying an electron beam to it. The molecules to be analyzed are frozen in various orientations in the quick-frozen ice, so that when an electron beam is applied from above, its projected image is recorded by the detector below.



By applying the projected images in various orientations to a computer, a 3D structure can be created. The calculations here require a great deal of data and computational power, so the enhancement of digital infrastructure, which was mentioned earlier in the presentation, is indispensable for cryo-EM analysis.



Using such cryo-EM equipment or processes, I would like to introduce at what level CHUGAI is now producing 3D structures with cryo-EM.

The leftmost figure shows the 3D structure of a membrane protein, which is a common target for small molecule drug discovery. In this regard, we have already been able to see the structure in space of small molecules in their bound state through this kind of conformational analysis. This information can be used in the design of candidate compounds.

In addition to this, cryo-EM has a disadvantage, as I mentioned earlier, that it cannot analyze smaller molecules.

This includes soluble proteins that are not membrane proteins and have a small molecular weight. The one shown here has a molecular weight of 38 kDa. I would say it's a kinase. Since such samples cannot be analyzed by cryo-EM as is, we have developed our own platform that combines tool molecules, which increase the molecular weight of the sample, to increase the molecular weight and bring it into the range of cryo-EM analysis.

If we are able to do this, we will be able to obtain the 3D structure of any target. This will be very useful for accelerating the development of mid-size molecule drugs, which is one of our focus areas.

We are also working on antibody drugs. Cryo-EM analysis for antibody drugs is actually very easy, and we are already able to obtain such data with high efficiency.

Summary of Chugai's Cryo-EM Efforts

- **By 2022, we have realized a robust 3D structure acquisition system using in-house cryo-EM analysis.**
- **At Chugai Life Science Park Yokohama, we aim to establish a system where cryo-EM analysis can contribute to Chugai's diverse drug discovery modalities.**
- **In drug discovery projects where it took time or was impossible to obtain the 3D structure by X-ray crystallography, the use of cryo-EM has made it possible to obtain the 3D structures. Thus, we expect these drug discovery projects can be streamlined significantly going forward.**
- **Acquisition of the 3D structures at the earliest stage of drug discovery has made it possible not only to design candidate molecules, but also to select better candidate molecules at an early stage based on an understanding of their binding mechanisms. As a result, we are now capable of further accelerating drug discovery.**

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In summary, we were able to establish a robust system for acquiring 3D structures by cryo-EM analysis in-house by 2022. Here at Chugai Life Science Park Yokohama, we aim to establish a system in which cryo-EM analysis can contribute to all of the CHUGAI drug discovery modalities.

In drug discovery projects where it took time to obtain 3D structures by X-ray crystallography, or where it was not possible to obtain 3D structures in the past, the use of cryo-EM has made it possible to obtain 3D structures quickly and efficiently. This is expected to significantly improve efficiency in those drug discovery projects.

I have been saying that 3D structures are useful for designing compounds, but now that 3D structures can be obtained at the earliest stages of drug discovery, we can not only design but also screen candidate molecules and obtain compounds with various binding mechanisms.

We are now able to select promising molecules based on their binding mechanisms. This has had an impact in terms of selecting good starting candidate molecules and obtaining their 3D structures at an early stage. We are now building a system that can further accelerate drug discovery.

That is all.

Question & Answer

Moderator [M]: Okay, we will now take your questions for about 10 minutes. In order to take everyone's questions, we would ask that you limit your questions to one per person.

In addition, as we are currently in the silent period prior to the announcement of our Q2 financial results, we are unable to provide any updates on our most recent situation, including the progress of development products. Thank you. The audio of your questions will be posted on our website at a later date, along with the presentation. Thank you.

We will first take questions from those attending on-site, followed by those attending via Zoom.

If anyone in the audience has any questions, please raise your hand. We will bring a microphone, so please state your name and company name, followed by your question.

Sogi [Q]: My name is Sogi from Bernstein. Thank you.

I am very much looking forward to seeing what kind of drug discovery research will be conducted in the future, thanks to your wonderful facilities and technology. I would like to know how much more productive drug discovery research will be with these technologies. In particular, please tell me what KPIs we should be tracking in the future to follow the increases in productivity of your drug discovery research.

Iikura [A]: I will take this question. That is a very important question.

Our goal is to double the output of research by 2030, but it may not always be possible to classify the percentage of increase in research output due to cryo-electron microscopy (cryo-EM), or the percentage due to digital integration, for example.

On the other hand, as Dr. Torizawa mentioned, there is a four-fold difference in hit-to-lead efficiency between a project where the crystal structure could not be obtained until a clinical compound was found, and a project where the crystal structure was obtained at the start of hit-to-lead process.

Then, for example, when a hit is obtained, if we say that in 50% of projects, we can obtain the 3D structure with X-ray crystallography, then in the residual 50% of projects we can't, the project takes four-fold or at least twice as long. I hope you can appreciate that the rest are not so different in that respect.

On the other hand, the digital part, for example, in the case of MALEXA, which was introduced today, the most valuable thing for us is that we can select high-quality antibodies. This was not possible with prior techniques. The value is not so much that the number of compounds obtained increases, but that the quality of each compound improves.

We have not yet reached the point where we can use this technology to produce three candidates in place of the two that we had before. An enormous amount of data is required. However, we are already seeing an increase in quality.

However, we will announce that we are increasing the number of compounds that have enter clinical trials at a certain rate by 2030. That is certainly an index that you could watch. We are currently making steady progress in line with this.

Another thing I would like to mention is that in our company, when we identify an important area, we persistently continue with research and development over a considerable amount of time. Hemlibra, for example, spent more than 10 years in the laboratory alone. Our mid-size molecule work also took more than 10 years, just in the laboratory. After more than 10 years, there is one clinical compound. We are now in the process of establishing a situation where this can be done on a continuous basis.

In this regard, we believe that robotization or the fusion of wet and dry technologies are of great value to us. We are determined to move forward steadily and persistently, step by step. Has this answered your question?

Sogi [M]: Yes, thank you very much.

Wakao [Q]: Thank you. Wakao, JP Morgan.

I would like to know more about cryo-EM. I don't think there are many pharmaceutical companies that have their own cryo-EMs. Therefore, I believe that your company is taking a very innovative approach in Japan. Could you tell us a little more about the impact on your company's development of incorporating cryo-EM? Reading the slides released this time, I think there will be a dramatic change, but I wonder if it has yet materialized. I would be happy if you could give us any quantitative information.

Also, since you have mentioned biology as an issue for your company, I thought that the ability to see the design of candidate molecules with this cryo-EM would strengthen the biology part of your company's research.

Also, I was wondering if it is common for other companies, including global companies, to have their own cryo-EMs for research and development.

Torizawa [A]: Thank you for your question. I will answer.

First of all, as for the quantitative part, as I mentioned verbally during the presentation, the hit-to-lead period can be improved by a factor of four when the 3D structure is in place. That is the first advantage when there is a 3D structure.

Until now, X-ray crystallography has been responsible for that part of the project, but as of 2022, in 58% of projects, the 3D structure could be obtained with X-ray crystallography. With the introduction of cryo-EM, the number of projects for which 3D structures were obtained increased to 80%.

Therefore, we believe that cryo-EM has brought about the measurable effect of shortening the duration of drug discovery projects, and increasing success probability.

Before I go to the second part, let me start with the third part of your question about other companies. As far as I know, when the Nobel Prize in Chemistry was awarded for cryo-EM in 2017, some of the global mega pharmaceutical companies started to introduce cryo-EM. The introduction of cryo-EMs into Japan, including in academia, has been delayed by two to three years, but currently, many mega pharmaceutical companies have cryo-EMs. Chugai was the first in the country to introduce it, so as not to lag behind there. As far as I know, two or three other Japanese companies have recently started to introduce this system.

Iikura [A]: Another point of view is whether biology will become stronger, and I have the feeling that it will be surprisingly strong, especially in the area of mid-size molecules, which I think will be dramatic.

This is because, unlike extracellular proteins, intracellular proteins are pre-designed so that a single protein can bind to a variety of targets. In the extracellular region, one protein is attached to one protein and that is

the end of it, so there is only one place where it can bind. With our mid-size molecules, things can bind into various sites.

Up to now, it was difficult to tell where a mid-size molecule would bind, but now I can tell before I start tinkering with the compound. We can tell which site are related to the main drug effect. This goes back to side effects. We can choose the binding site if we know in advance, and if we don't know we can ascertain through the biology. Therefore, I believe that biology is increasingly a starting point. We can gain insight into the real mechanisms, including those that are not yet understood by mankind.

Sorry. I would like to add one more thing to the earlier question.

I responded that I was hoping that you could look at the number of compounds reaching the clinical stage as an important index. What is also very important in this context is that we will never reduce the quality of our compounds. Quality comes first. The top priority is the quality of the compound. What we value most is still the probability of success, especially in clinical trials. I think it would be best if you could look at whether the output is increasing well while maintaining the probability of clinical success.

Hashiguchi [Q]: Hashiguchi, Daiwa Securities. Thank you for taking my question.

In the upper right corner of slide 31, it is stated that two-thirds of your researchers have used new digital tools to improve their work styles. Conversely, it would appear that one in three respondents had not been able to do so. How much improvement can we expect with the establishment of this new institute? If there are still those who are unable to do these things, what are the reasons for this? I would appreciate your explanation of how further improvements could be made in the future.

Ohta [A]: Thank you very much for your question. I will answer.

As you pointed out, this would be true if one in three did not have a real experience of improvement. However, if you look at these numbers in 2021, they were actually much lower. I'm afraid I don't have the specific numbers to hand. In essence, we have seen a big increase since then, and we anticipate further increases in the future. This is my first thought.

On the other hand, there are some people who are not very good at new fields, such as digital technology. The skills required are a little different from the expertise necessary up to now. We are prepared for the fact that it may take some time to get used to the new skills.

Therefore, we would like to provide such people with the education and other opportunities I mentioned earlier, gradually allowing them to become accustomed to this type of environment and to use digital tools within their own scope.

Iikura [A]: I would like to add something. I recognize that digital technology is very important, but each person has their own strengths and weaknesses. We take the stance that it is fine for some people who have strong wet skills to have difficulty adjusting to digital technology.

I always ask that each of us does not need to be a Superman, and that it is important to help each other. I think it is a matter of great pride that a bottom-up system in the digital field has emerged and has spread, in which strong people teach and educate those who are not so strong. As this number is already at 67%, I would hope that we have already achieved critical mass in terms of impact, when looking at the institution as a whole.

[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.*
2. *This document has been translated by SCRIPTS Asia.*

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