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CHUGAI PHARMACEUTICAL CO., LTD.

Lasker-DeBakey Clinical Medical Research Award Press Conference

September 10, 2026

Event Summary

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[Venue]	Webcast
[Venue Size]	
[Participants]	
[Number of Speakers]	5

Kunihiro Hattori	Former Senior Fellow
Takehisa Kitazawa	Deputy Head of Research Division
Tomoyuki Igawa	Head of Research Division
Meiri Kawazoe	Hemlibra Lifecycle Leader
Kae Miyata	Head of Corporate Communications Dept.

Presentation

Hattori: Hello, everyone. My name is Hattori. I am deeply honored that together with Dr. Kitazawa and Dr. Igawa, I am receiving the Lasker-DeBakey Clinical Medical Research Award for the creation of emicizumab, Chugai Pharmaceutical's antibody therapeutics for hemophilia A.

My principal role in this project was conceiving the drug discovery concept for emicizumab in 2000. Then by 2004, I had become head of the antibody research department, and so from that position, I worked to create an environment where the whole research team could work effectively while overseeing the research as a whole.

The concept behind emicizumab is often described as far-fetched, but honestly, I never thought the chances of success were low. Even so, we were fortunate, too. Over everything else, the greatest fortune was being able to assemble a wonderful research team of highly talented scientists and engineers, including Dr. Kitazawa and Dr. Igawa. Emicizumab is a crystallization of nearly a decade of researchers' blood, sweat, and tireless effort, guided by our shared motto for the world, for the patients. We also received powerful support and guidance from a clinical perspective from professors Yoshioka, Shima, and Nogami of Nara Medical University. I believe this stands as a leading example of a successful industry-academia collaboration.

When the drug was approved and came into actual clinical use and prescribing doctors in the field told us that patients' lives have improved, I felt there could be no greater joy for a drug discovery researcher, and I was moved to tears. Receiving such a great honor now has reaffirmed for me just how rewarding drug discovery is as a career. Beyond the difficulties we overcame together with our colleagues, there are the smiles of patients waiting for us. I truly hope that young aspiring scientists will take up the challenge of drug discovery. I hope that encouraged by this award, Chugai Pharmaceutical will continue to pursue research that leads to new treatments.

Thank you very much today.

Kitazawa: Hello. I am Kitazawa.

When I heard the news that I would be receiving the Lasker Award together with doctors Hattori and Igawa, my first reaction was that of sheer astonishment. Frankly, I could find no word other than surprise to describe how I felt. Drug discovery is something that can only be achieved when the strength of many colleagues comes together. I am deeply proud that the emicizumab research we all worked so hard to advance has served our goal of helping patients with hemophilia A and their families, and that through this award, scientific significance is now being recognized around the world.

In the emicizumab project, I led biology and pharmacology research. Together with my colleagues, we investigated, one step at a time, whether a bispecific antibody could substitute the function of factor VIII and what properties it would need in order to demonstrate sufficient hemostatic effect in practice. This was an original, unprecedented, and extremely challenging drug discovery effort. The path was never smooth. There were setbacks and failures along the way. But by confronting each one of them, we made new discoveries that allowed us to keep moving the project forward.

I want to convey this to the researchers who will shape the future. Turning failure into fuel is precisely what leads to success. This award does not belong to only the three of us here today. I understand it as the result of the combined efforts of many people who contributed to the research and development of emicizumab. As Dr. Hattori has mentioned, the achievement reflects the combined strength of many professors at Nara

Medical University who worked with us and joined research and drove our clinical trials forward over many years. The staff of Sysmex Corporation who collaborated with us in biomarker research, the healthcare professionals who dedicated themselves to clinical development, the trial participants and their families, and our colleagues at Chugai and across Roche Group; I would like to take this opportunity to express my heartfelt gratitude to all of them.

Igawa: Hello. I am Igawa.

I am deeply honored to be receiving the highly prestigious Lasker Award together with Dr. Hattori and Dr. Kitazawa. I feel that this is way beyond what I deserve as a drug discovery researcher. I am only now coming to terms with the fact that I have received this, receiving so many comments and postings of congratulations.

Drug discovery is research that requires many years and carries an extremely low probability of success. You may be devoting your entire career, but you are never guaranteed that the work will become a medicine that reaches patients. From that point of view, I consider myself truly fortunate.

On top of that, against that backdrop, when I received the news of this global recognition through the Lasker Award, I felt enormous surprise and joy along with a deep gratitude and great sense of responsibility. I joined this research in 2004. At the time, I was in my fourth year with the Company, and I took on two roles, establishing antibody engineering technology to stably manufacture bispecific antibody with high quality and large scale and thoroughly refining and honing the antibody obtained from screening to design the molecule that became emicizumab.

I am deeply grateful not only to my colleagues at the Research Institute, as there were so many of them who worked on the drug discovery research for emicizumab, but also the many employees at Chugai, Roche, and Genentech who worked tirelessly to deliver the molecule we created for patients.

Since emicizumab became available to patients, we received many letters from patients and their families describing how the treatment has changed their lives. Reading them and thinking that we may have been able to answer even in some small way the medical challenge we had wanted to solve for 10 years brings tears to my eyes without even realizing it. I am deeply grateful as a drug discovery researcher to have been blessed with such an opportunity.

While I feel deeply honored by this award, I am also mindful that around the world, there are still countless patients without adequate treatment options waiting for new medicines. As a drug discovery researcher and as someone responsible for research at Chugai Pharmaceutical, I carry a strong sense of mission to continue creating innovative medicines that follow in emicizumab's footsteps, and I intend to keep taking on the challenge of developing new medicines together with all of my colleagues.

Thank you very much today.

A Challenge Born in Japan that Transformed Hemophilia A Treatment Worldwide

The Creation of Emicizumab (Hemlibra) -A journey inspired by the desire to transform the lives of people with hemophilia A-

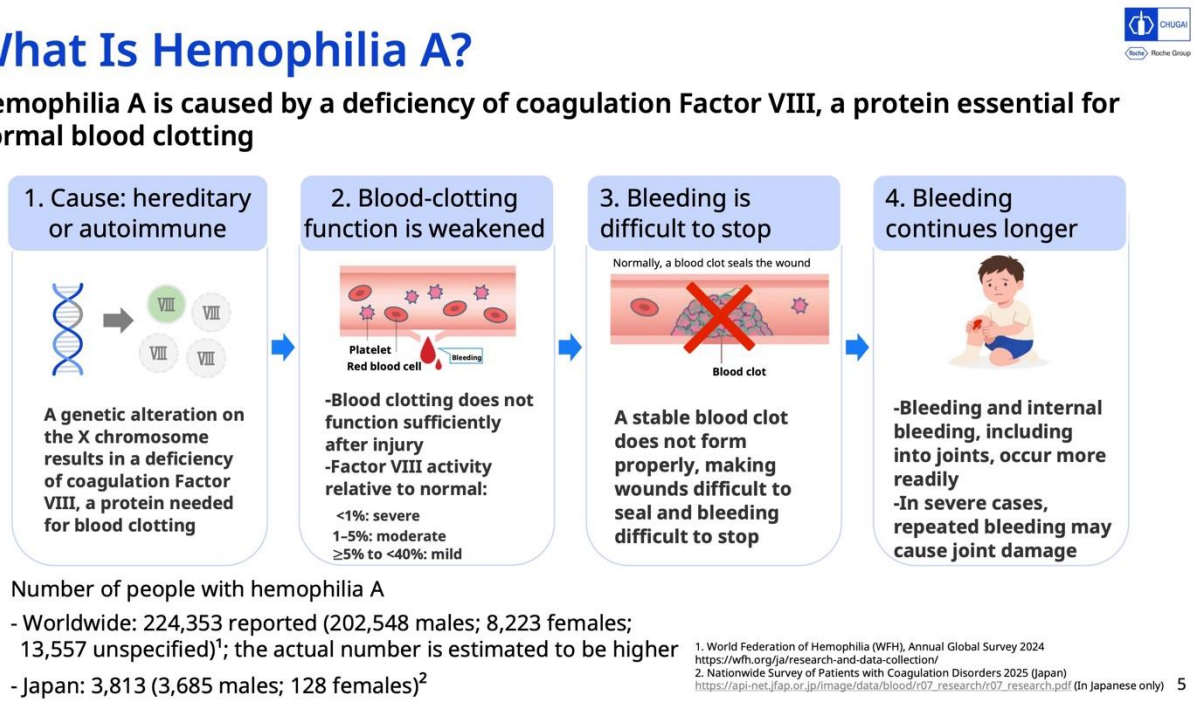
September 10, 2026

Chugai Pharmaceutical Co., Ltd.

Dr. Kunihiro Hattori, Dr. Takehisa Kitazawa, Dr. Tomoyuki Igawa

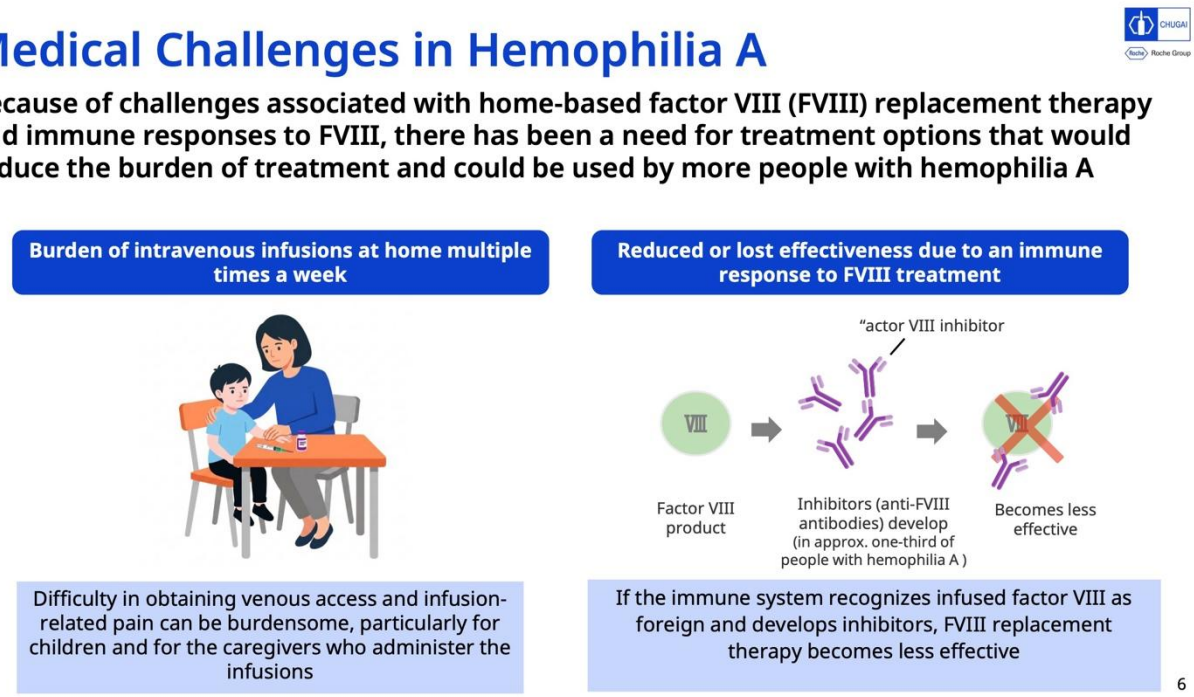
Hattori: Now, I would like to explain how emicizumab known by its brand name, Hemlibra, which won the Lasker Award came to be and how it has transformed the treatment of hemophilia A.

Our starting point was a very simple desire. We wanted to improve the lives of people with hemophilia A, even if only a little. The research that began with this passion after numerous failures and trial and error led to a new treatment. Today, I'd like to share the story of that research and development in a way as easy to follow as possible.



First, let me briefly explain hemophilia A.

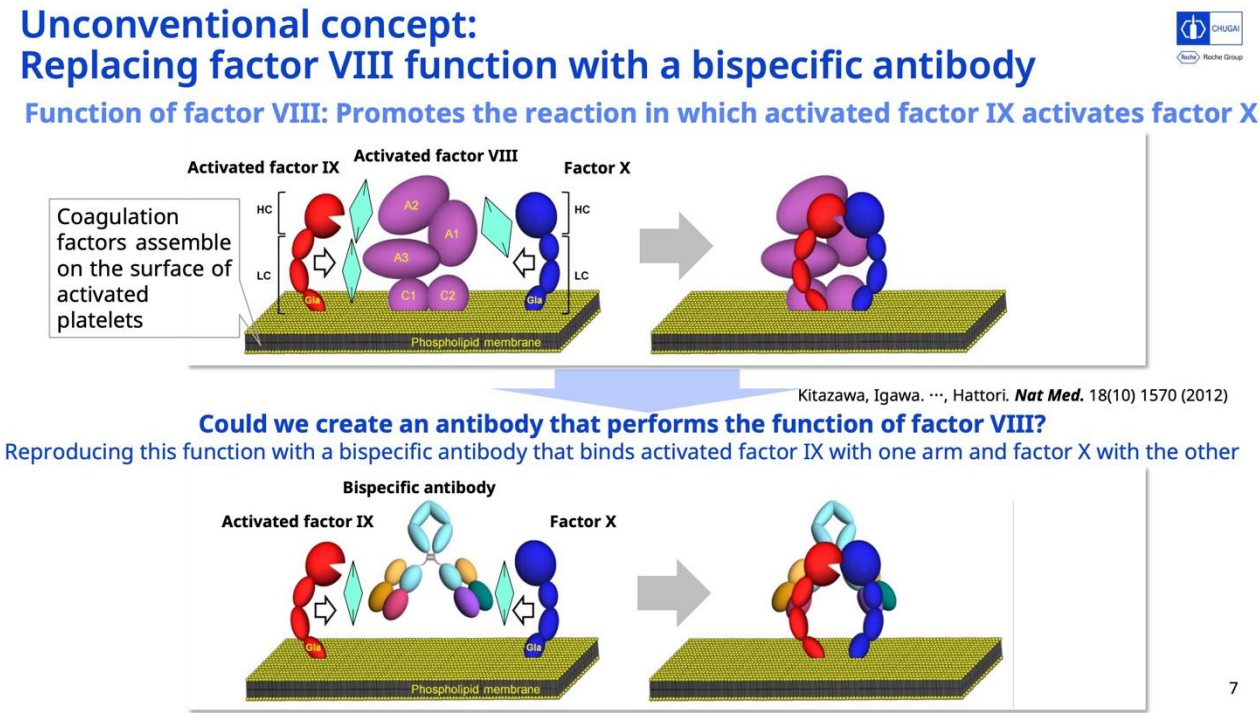
When you get injured, your blood clots to stop the bleeding. For this to happen, various proteins in the blood must work together, passing the baton from one to the next. In hemophilia A, there is a congenital deficiency of a protein called blood coagulation factor VIII, which weakens the blood's ability to clot. As a result, bleeding can occur not only when injured, but also inside joints. In particularly severe cases, repeated bleeding can lead to permanent joint damage. In Japan, about 3,800 people are diagnosed with hemophilia A.



So how has this condition been treated up until now?

The basic approach involves replacing the deficient factor VIII with medication. This has been a highly effective treatment. However, several challenges remain. Factor VIII drugs are typically administered via intravenous injection. Therefore, when treatment is performed at home, the patient or family member must locate the vein and administer the injection. This is not easy particularly in the case of young children.

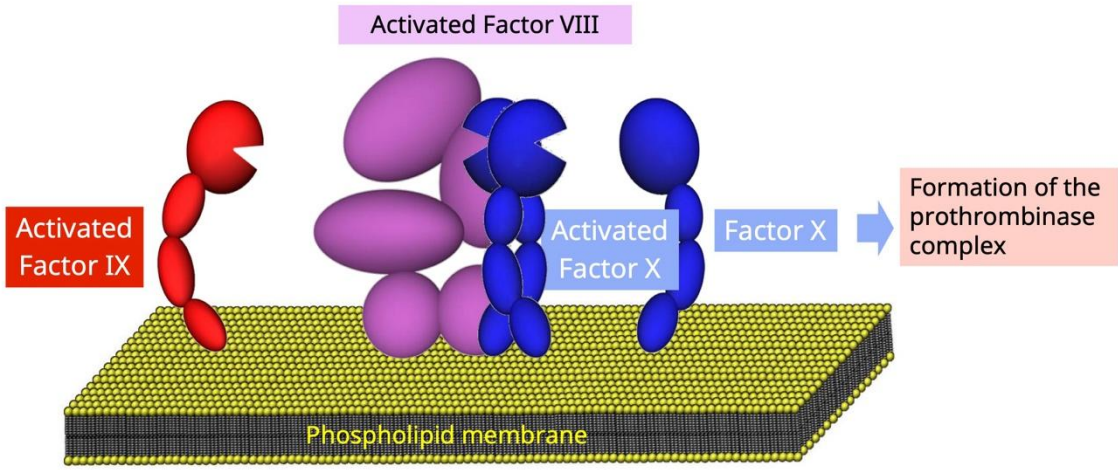
There was another challenge as well. Some patients recognize factor VIII as a foreign substance and develop an immune response known as an inhibitor against it. When this happens, factor VIII drugs become less effective. In other words, perhaps a different approach was needed, one that went beyond simply replacing factor VIII, as has been the case previously, and this is where our new line of thought began.



This schematic shows how activated factor IX activates factor X with the help of factor VIII.

I thought that something else might be able to substitute for the function of factor VIII. Factor VIII works as a cofactor that brings activated factor IX and factor X into close proximity when activated factor IX activates factor X. This is where the idea of a bispecific antibody came in. An antibody has two arms, each of which can bind to a target molecule. Normally, both arms bind to the same target, but in this case, we designed a bispecific antibody in which one arm recognizes activated factor IX and the other arm recognizes factor X. We thought that if we created a large number of such bispecific antibodies, we might find one among them that could substitute for factor VIII.

Unconventional Concept:
A Bispecific Antibody Substitutes for Factor VIII Function



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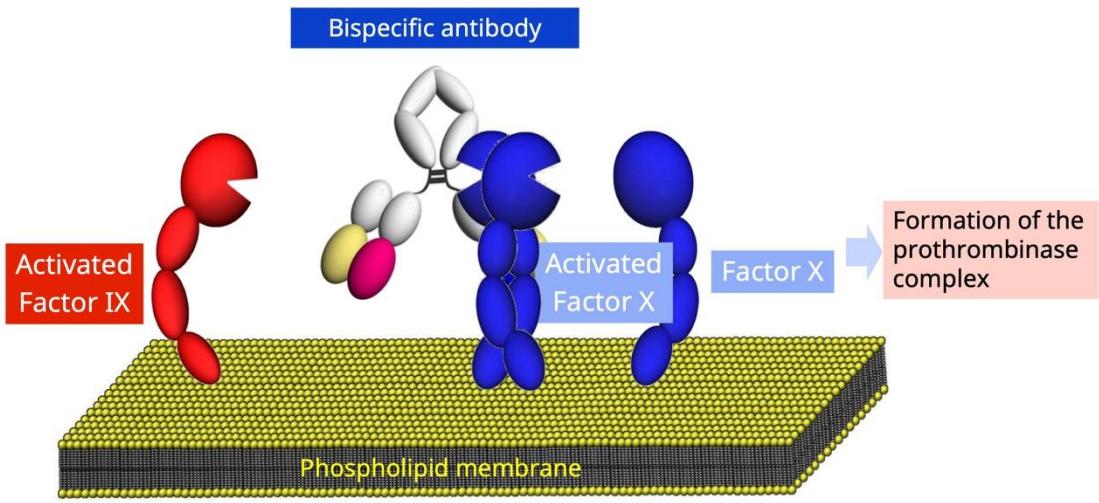
This is an image of how activated factor IX activates factor X with the help of factor VIII.

Unconventional Concept:
A Bispecific Antibody Substitutes for Factor VIII Function



Kitazawa, Igawa, ···. Hattori.
Nature Medicine 18(10) 1570 (2012)

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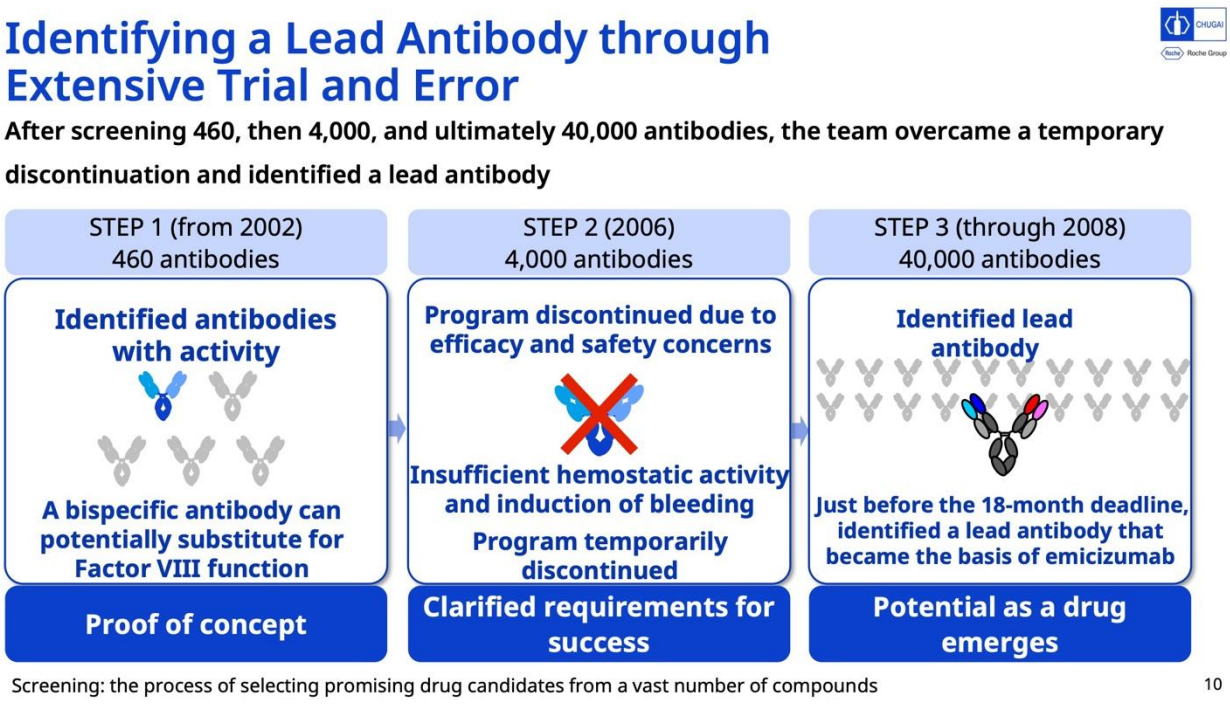
This is an image of the bispecific antibody acting as a substitute for factor VIII.

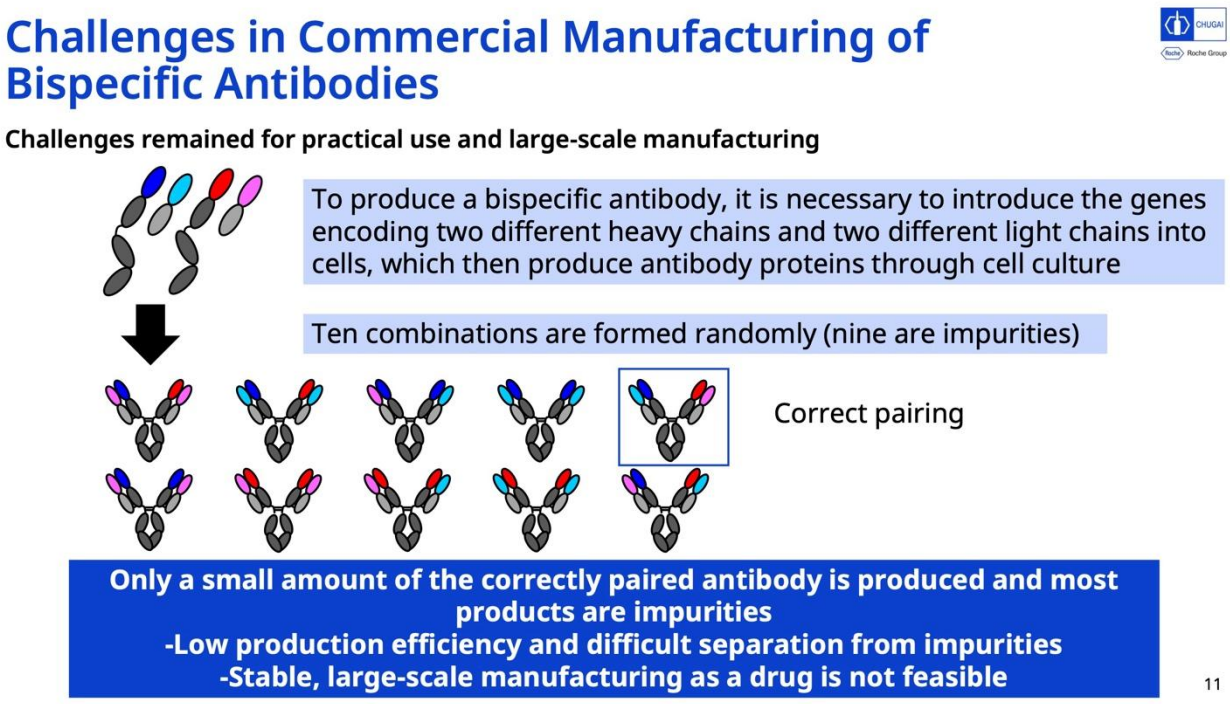


The idea was conceived but a drug couldn't be developed immediately. Rather, this marked the beginning of a long process of trial and error.

First, we produced 460 types of bispecific antibodies to test whether they could substitute for factor VIII. Ultimately, we found one that was active, although it was weak. If we hadn't found anything at that point, I believe this project would have ended there.

Since we had proven that bispecific antibodies could substitute for factor VIII, we next screened about 4,000 different types, improved the resulting antibodies, and created candidate antibodies for development. However, they didn't demonstrate the sufficient hemostatic effects and it induced bleeding so the decision was made to halt the development. However, this data provided us with crucial information on what needed to be improved so we decided to try again.

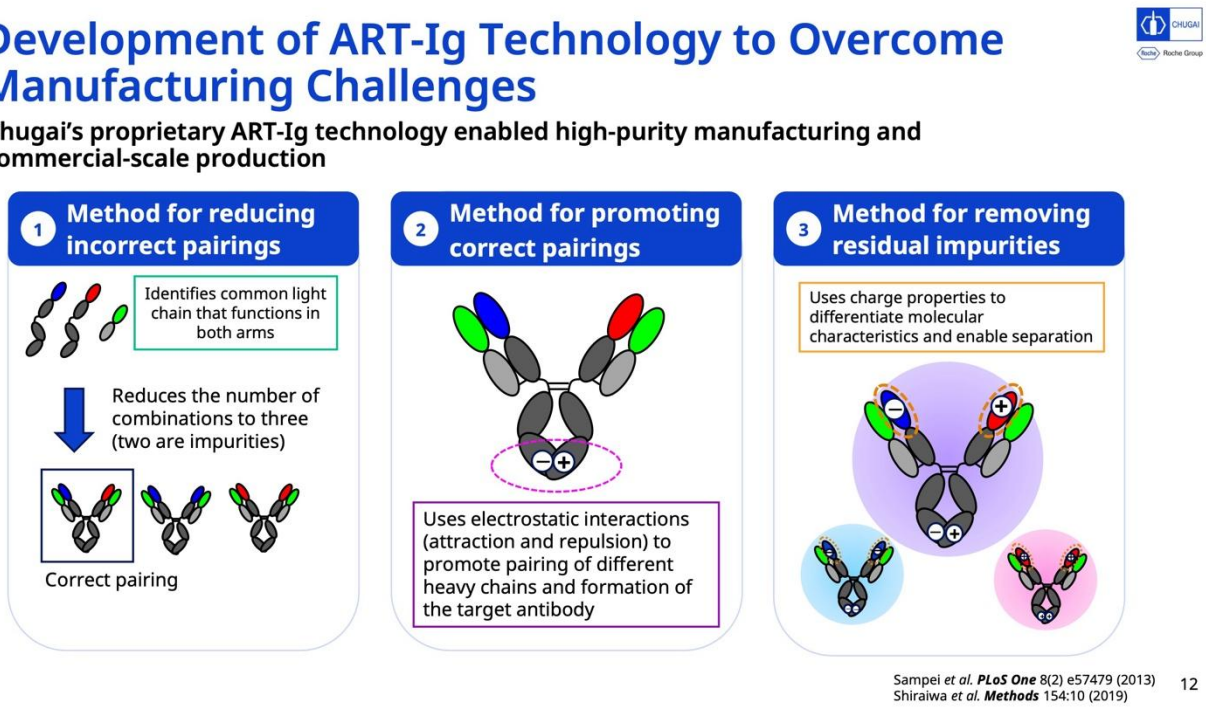
Next, we screened about 40,000 bispecific antibodies, examining, refining, and reevaluating each one individually. Through this iterative process for the limited period of one year and a half, we finally identified a lead antibody with the potential to become a drug.



Now, there are significant manufacturing challenges to overcome in order to commercialize a bispecific antibody as a drug.

Bispecific antibodies are created by combining two types of heavy chains and two types of light chains. When cells produce those, they do not just produce the specific combination that we want, which is shown here. In fact, as many as ten different combinations can be produced. Everything other than the one we want is an impurity. Moreover, since these impurities are very similar in both structure and properties, they are very difficult to separate. Therefore, even if we obtained a good drug candidate, stably producing a bispecific antibody in large quantities was a very difficult challenge.

We also developed technologies to produce the antibody correctly and to purify (extract) it correctly.



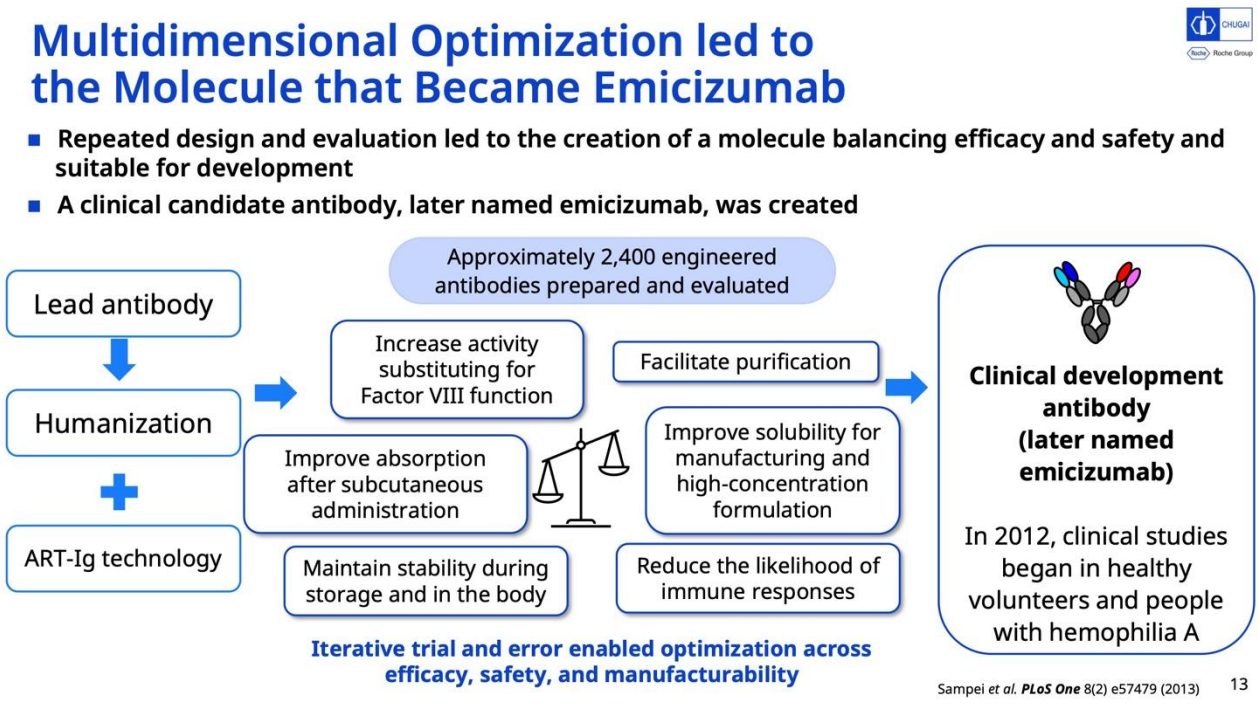
That is our proprietary ART-Ig technology.

This incorporates three main innovations. First, we make it less likely for incorrect combinations to form. We established a method to identify a light chain (L chain) that can be shared by both types of heavy chains. This reduces the number of combinations from 10 to 3.

Second, we make it easier for the correct combinations to form. By slightly altering the amino acids on the surface of the antibody, we give one side a positive charge and the other a negative charge. Plus and plus repel each other, and minus and minus repel as well, so that the plus-minus (correct) combination forms preferentially.

Third, we properly separate the impurities that still form despite these measures. By exploiting differences in the electrical properties of the molecules — namely, their isoelectric points — we made it easier to separate the target antibody from the impurities.

By accumulating these innovations, we became able to manufacture a bispecific antibody on the same platform used for standard antibody production.



Two slides ago, I mentioned that we had obtained a lead antibody. Since the antigen-binding sites of the lead antibody were obtained in rodents, we humanized them by substituting them with human amino acids, and applied the ART-Ig technology I described earlier.

However, that alone does not make a drug. We needed to enhance its activity; make it readily absorbed even by subcutaneous administration; ensure it is stable during storage and in the body; make sure it does not trigger an immune response to the formulation; keep it easy to dissolve even when formulated at high concentrations; and make it easy to purify with sufficiently high production yields. To create an antibody that satisfied all of these requirements simultaneously, we produced 2,400 engineered antibody variants, and the one we selected from among them was emicizumab.

And clinical trials began in 2012.

Bleed Prevention with Emicizumab Demonstrated in Clinical Studies

Clinical studies in people with hemophilia A demonstrated the bleed-prevention efficacy and tolerability of emicizumab regardless of Factor VIII inhibitor status, disease severity, or age

Integrated Analysis of the HAVEN 1–4 Studies

Objective	To evaluate the long-term safety, efficacy, and pharmacokinetics of Hemlibra in people with hemophilia A through an integrated analysis of the HAVEN 1–4 studies
Subjects	HAVEN 1[1]: 113 people aged ≥12 years with inhibitors HAVEN 2[2]: 88 children aged <12 years with inhibitors HAVEN 3[3]: 152 people aged ≥12 years with severe hemophilia A without inhibitors HAVEN 4[4]: 48 people aged ≥12 years with or without inhibitors
Analysis population	Enrolled: 401 Efficacy analysis population (ITT): 400 Safety analysis population: 399
Results	[Efficacy] The primary endpoint, annualized bleeding rate (ABR) for treated bleeds over 24-week intervals throughout the study, was 1.4 events/year. For the secondary endpoint, 70.8% (277/391) had zero treated bleeds during Weeks 1–24, increasing to 82.4% (140/170) during Weeks 121–144. [Safety] No new safety signals were identified. The most common adverse event was injection-site reactions (27.8%).

1.Oldenburg J, et al: N Engl J Med. 377(9): 809-18, 2017
2.Young G, et al: Blood. 134(24): 2127-38, 2019
3.Mahlangu J, et al: N Engl J Med. 379(9): 811-22, 2018
4.Pipe SW, et al: Lancet Haematol. 6(6): e295-e305, 2019

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Beginning with a small-scale Phase I trial and continuing through larger-scale Phase III trials, the bleeding-prevention efficacy and tolerability were consistently confirmed. Importantly, the bleeding-prevention efficacy was confirmed regardless of the presence or absence of factor VIII inhibitors, disease severity, or whether patients were adults or children.

How Emicizumab Changed Hemophilia A Treatment

- **Approved and launched under the product name Hemlibra**
- **Approved in the United States in 2017 and in Japan and Europe in 2018; now approved in more than 120 countries and regions, used by more than 30,000 people with hemophilia A**
- **A treatment that reduces bleeding frequency and treatment burden, expanding possibilities in daily life**

1 Reduced burden of home treatment

- Convenient at-home administration with a subcutaneous formulation
- Choice of dosing interval: once weekly, every 2 weeks, or every 4 weeks
- Psychological and time-related benefits for children and their families

2 Treatment option for people with Factor VIII inhibitors

- Bleed-prevention efficacy comparable to that in people without inhibitors
- Suggested effect on quality of life

3 Bleeding prevention and effects on joint health

- Demonstrated reductions in treated bleeds and bleeding frates
- Beyond bleeding control, a suggested benefit for joint health

Sato et al. The Japanese Journal of Pediatric Hematology/Oncology. 59(1) 19 (2022)
Fletcher et al. Health Expect. . 25(1) 443 (2022)
Shima et al. Haemophilia. 25(6)979 (2019)
Shima et al. Haemophilia. 27(1)81 (2021)
Shimozawa et al. J. Nihon Univ. Med. Ass. 82(1) 23 (2023)
Callaghan et al. Blood. 137(16) 2231 (2021)
Oldenburg et al. Haemophilia. 25(1) 33 (2019)
Mancuso et al. Haemophilia. 26(6) 1009 (2020)
Mahlangu et al. N Engl J Med. 379(9) 811 (2018)
Shima et al. Res Pract Thromb Haemost. 9(8)103228 (2025)
Astermark et al. Haemophilia. 31(6) 1271 (2025)

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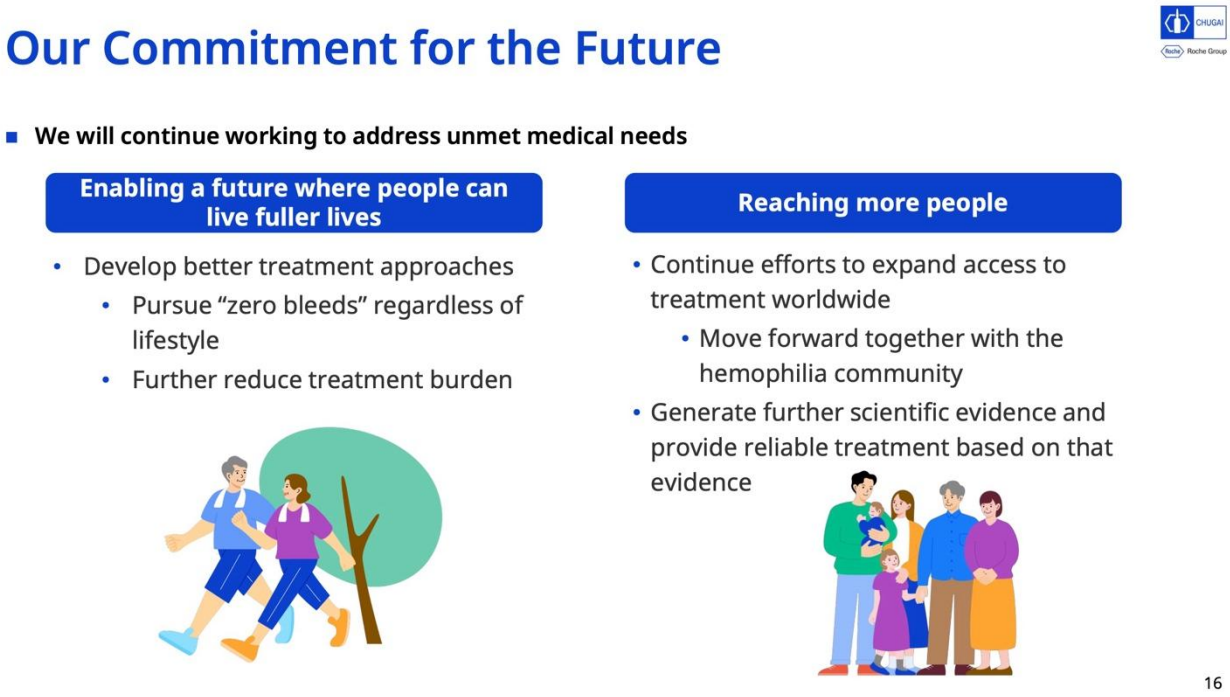
Emicizumab was approved under the brand name Hemlibra in the United States in 2017 and in Japan and Europe in 2018. It's now approved in more than 120 countries and regions.

With emicizumab treatment, administration became simple through subcutaneous injection, and the dosing intervals also became longer. It also made it possible to offer a new treatment option to patients with inhibitors. As a result, the frequency of bleeding was reduced, and the progression of joint damage could also be suppressed.

By even slightly reducing the time spent on treatment, the anxiety around intravenous injections, and the burden borne by patients' families, patients' lives change and the range of what they can do expands. This was exactly what we were aiming for in our research. I believe we have achieved this to a certain extent. There is no greater reward for a drug discovery researcher.



Of course, we don't consider our work finished.

Unmet medical needs remain in hemophilia. We're aiming for zero bleeding regardless of lifestyle and for further reduction in treatment burden. Reaching every patient who needs this therapy worldwide remains equally important.

We intend to keep generating scientific evidence and to work hand-in-hand with healthcare providers, patients, their families, and the broader hemophilia community to expand access to treatment.

Lastly, but not least, this treatment was never the achievement of researchers alone.

It was made possible by the patients with hemophilia A and their families who bravely took part in our clinical trials; by the healthcare professionals—led by those at Nara Medical University—who cooperated with and guided us in clinical settings; and by our colleagues at Roche and Genentech who supported the global development and supply. Thanks to the contributions of so many people, we were able to deliver a single idea born in a Chugai laboratory to people with hemophilia A around the world.

We are deeply honored to have received such great recognition as the Lasker Award. Yet for us, this award is not the goal. Without forgetting our original wish to change patients' lives, we will continue to take on the challenge of addressing the medical needs that remain unmet.

Thank you for your kind attention.

Question & Answer

Ozaki [Q]: I am Ozaki from Nikkei. Congratulations on your award this time.

Following the creation of Actemra, Japan's first domestically developed antibody drug, your achievement this time seems to demonstrate Chugai's strengths in antibody drug discovery. Antibody pharmaceutical is your strength, and that has been demonstrated. How do the three of you view Chugai's strengths in antibody drug discovery?

Hattori [A]: Let me answer the question first.

The idea for emicizumab was conceived around 2000. Back then, there were very few antibody drugs. Actemra was launched by Chugai in 2005, and at the time emicizumab was still in the research stage. In 2004, I became the head of the antibody drug research division, and ACTEMRA was launched around that time. The technology at Chugai was humanization of antibody drug.

In 2002, we became under the umbrella of Roche Group as an alliance. There was Genentech that was quite prominent in biopharmaceutical. There were two giants, Genentech and Amgen, back then in biopharmaceutical. We struggled with how Chugai could demonstrate its own raison d'être within the Roche Group. There was a challenge. We had to come up with something unique following ACTEMRA. Also, in order to produce these on a continuous basis, we thought we should have some proprietary technologies.

Then emicizumab was conceived, and the research on emicizumab was started around that time. This is a genetic disease. Because hemophilia A is a genetic disease, treatment may be needed from infancy and throughout life. We wanted to create a product with the highest possible quality in terms of efficacy, safety, and convenience. We have been refining our technologies, and there are many different researchers that have come up with different ideas. We have made it possible in our environment to try using those. With the advance of emicizumab development, we have been able to accumulate these success experience stories, and that culture has actually sunk into our company.

Kitazawa [A]: Let me also take that up.

As in the presentation by Hattori, we generated 4,000 bispecific antibodies, and then went on to generate 40,000 more. Even if the number has been increased, if the quality has degraded, then there's no point. While maintaining the quality, we had to increase the number of antibodies that we tried. That was the foundation of our research activities. In addition to the corporate culture, we had this practical experience and track record of going through trial and error to pursue both quantity and quality without compromising quality. That was the background for this achievement.

I'd like to ask Igawa-san to add more.

Igawa [A]: Well, everything that I wanted to say was mostly said. But for the research of emicizumab, using this as a trigger, Chugai's unique antibody drug discovery method has been established. At the moment, not just the antibody, as for the research as a whole, something that only Chugai can do in terms of drug discovery is something that we are aiming for. Rather than doing something that can be done by other pharmaceutical companies in the world, why not come up with something that only we can produce and provide as a value for patients? With the technologies, we will do something that only we can do and use. By producing those technologies, we can go into some areas such as hemophilia where we have not been active back then.

Not just this particular disease that we are focusing on, with the technologies that we have produced, if there are any other diseases that we can address with the technologies, then we would try attempting this drug discovery. This is true for emicizumab, but we would go through clinical studies starting from healthy adults and then going on to patients and deliver the product to the patients ultimately. We wanted to come up with the best molecule as a researcher. Of course, timeline is important as a company, but rather than focusing on a timeline, we just make sure that our molecule will be used by the patients in practice. We have to come up with something that would be the best available at that time. This is what we call quality-centric drug discovery. We would make the quality of the pharmaceutical products the best. That is what we value.

In summary, the three strengths of Chugai's antibody research are: technology-driven drug discovery; pursuing drug discovery without being limited to specific disease areas; and quality-centric creation of the best possible molecule.

Ozaki [M]: Thank you.

Orita [Q]: Thank you very much. My name is Orita of Nikkan Yakugyo. Congratulations on the award. I have two questions.

The first question, and I apologize for asking this question right after the award receiving. You did talk about challenges though that still remain. What are some of the challenges which still remain even with emicizumab more specifically, and how does Chugai intend to tackle those?

Kitazawa [A]: Yes, let me start. Emicizumab has addressed past challenges of treating hemophilia and has been quite effective. But when we treat patients with emicizumab, we do achieve good results. More than 80% of patients experience no bleeding requiring treatment, but it's not 100% yet. Even with emicizumab treatment, some people still bleed, and we do need to treat them using other factor replacement therapy. That requires intravenous administration. One important goal is to make sure that there will be zero bleeding that requires treatment.

The second point I would like to mention is because this is subcutaneously injected, emicizumab can now be given once every four weeks maximally. Emicizumab is approved for subcutaneous administration once weekly, once every two weeks, or once every four weeks. We are now also thinking about even less frequent administration or even without injection. One of our current initiatives is NXT007, a bispecific antibody therapeutic for hemophilia A that is currently in Phase III clinical development. It is designed to have higher activity than emicizumab, and it can be maintained at that level for a more extended period of time. We'd like to eventually make zero bleeding in patients.

Igawa [A]: I would like to add about the emicizumab molecule. We learned that a bispecific antibody could mimic the function of factor VIII by binding to two specific targets. We know that. In the 2000s, we knew that that was the best molecule. We were not able to do anything better. But since emicizumab was introduced into the clinic, we began to see excellent data. At the same time, in the labs, we now have more advanced technology of generating antibodies. As was just mentioned by Dr. Kitazawa, we do still have unaddressed challenges. We have established MOA with emicizumab, and we want to improve this so that we can enhance our factor VIII activity to create molecules that can target zero bleeding with longer half-life in vivo. We believe that that is NXT007 which we are working on. We feel that we can create something that's better, and we always want to come up with better and better drugs.

Orita [Q]: Thank you. I have another question.

Many Lasker Award recipients went on to receive the Nobel Prize. I would like to hear from you about that possibility.

Hattori [A]: We are not thinking about that at all.

Participant [M]: Thank you.

Ando [Q]: Ando from Nikkei. Congratulations.

Earlier, you talked about development process, and that you failed in animal experiments. Development work was halted and suspended once. But those who made a success would also say that they experienced failures, and often, they say they continued quietly on a small scale in a corner of the laboratory. But in drug discovery, it costs money so that may not work. How were you able to manage to secure the budget for the research effort?

Hattori [A]: The hemostatic effect was not enough, and there was an induction of bleeding. Those were the things that we found. That was a reason for the suspension or cancellation of the project, but we analyzed what happened and then what sort of molecule we should come up with to avoid that. We learned from that failure. Incorporating the lessons that we've learned, we came up with the proposal and asked for a second chance. Then there was a time limit of one year and a half, and we were given a limited period of 18 months, and the necessary budget for that work was allocated.

Kitazawa [A]: Exactly, but to add more, we tried once and failed and we were disappointed. But even with the failure, we had realized that what we had thought would be true was not true. Because of that failure, the strategy that we wouldn't have thought about now could be pursued, and that was important. This is something that we thought nobody else would do in other companies. But with this, the impact on patients with hemophilia A and their families would be enormous. That was what we were convinced of. If we gave this up at that time, then there would be no drug that would be delivered to the patient, and nobody would do that. We were really serious and intense, but we were able to convince our management to give us the money.

Igawa [A]: Four thousand antibodies were tried and we chose one, but that unfortunately failed. After the antibody selected from the 4,000 candidates unfortunately failed, we proposed screening 40,000 antibodies next. If that was a simple idea, then the management wouldn't have said yes because just by increasing the number simply, we would be more successful. That was not the case. We had made a deep analysis of why it didn't work. This was the reason why there was insufficient hemostatic effect and there was a bleeding event. That's how we explained it. This is the method that we would think would work, and that was the hypothesis that we came up with and screening in line with that was proposed. That was convincing enough. The research team back then had this great passion, and that actually sold the senior management on our ideas.

Ando [Q]: Thank you. How much budget was assigned to you or were you able to manage to secure?

Hattori [A]: We did not allocate budgets by individual project in that way. For early-stage themes, budgets were managed in aggregate, so there was no specific amount assigned to this particular theme.

Ando [Q]: But the proposal was approved in one go?

Hattori[A]: Yes, it was approved after one proposal.

Igawa [A]: However, we had to identify a candidate within 18 months.

Kitazawa [A]: The reagents used in the assays were not inexpensive. Screening 40,000 antibodies at the usual scale would have been very costly for Chugai at the time, so we reduced the assay scale from the usual 100 microliters to about one-tenth of that and used the reagents efficiently.

Igawa [A]: In other words, we were being frugal.

Kitazawa [A]: We did not put it that way, though.

Ando [Q]: Another question. You mentioned that the industry-academia collaboration with Nara Medical University worked well. The industry-academia collaboration may work sometimes but sometimes get halted. Sometimes it doesn't work immediately, then a university may drop out. Why did this particular partnership work?

Hattori [A]: Well, the roles and responsibilities are clearly defined. We generated and evaluated candidate molecules, but the professors at the university had this clinical perspective. Based on their expertise from their clinical practice, they have evaluated our products. There were clearly defined roles and responsibilities. They know how the patients are. Once this product is successful, they knew that this would definitely improve the quality of life of patients. That was the same understanding and we're on the same page, and that's why we're able to pursue the same goal. Even if things didn't go well along the way, that partnership didn't collapse.

When there was some failure, we were not able to supply anything to try to the professors for some time. The professors were quite disappointed, but they were patiently waiting for us to come up with the next one. When we identified the molecule that would become emicizumab and presented it to them, enabling the collaboration to resume, the professors were truly pleased. It's not just the pleasure, but the Phase I study was done in Japan. The Phase I study included both a healthy-volunteer part and a patient part. From the scientific point of view, they had very good understanding about our product, and they were quite helpful in proceeding with the clinical trial for patients. The effect of emicizumab was demonstrated at an early stage, and this was because of the help of the professors.

Suganuma [Q]: My name is Suganuma, Mainichi Newspapers. Congratulations.

Now, I had some questions related to the initial start of the research. This was a very original idea. Bispecific antibody actually was known, I believe, but how did you arrive at this original idea?

Hattori [A]: It's not that we had bispecific antibody and we wanted to use that. For this project to work, it had to be bispecific antibody. The concept of bispecific antibody was present, but technologically, as we have talked about today, there were many important challenges that we needed to overcome. Technology-wise, I thought that we have excellent engineers and we thought they would find a way. I felt that substituting factor VIII with an antibody was important in improving the QOL of patients. That was why we deliberately chose to take on the challenge.

Suganuma [Q]: Thank you. My second question is, you have identified one out of 4,000, but that was a failure and you learned from the failure. Can you give me more details about what the failure actually was?

Kitazawa [A]: Yes, allow me to describe. You draw blood from patients, and you separate the cells from the plasma. The plasma part, if you just leave it, then it would start to clot. You treat the plasma so that it doesn't clot, and then you take it out and in the test tube, introduce stimuli that will coagulate blood again, and you measure how many seconds it takes before the clotting takes place. This is APTT assay.

Now, hemophilia A patients will require more than 100 seconds for the clotting to take place, whereas in healthy individuals, it's only about 30 seconds. When we initially screened 4,000 antibodies, we selected candidates based on their ability to shorten the clotting time of hemophilia A plasma. Now of the 4,000 whereas the patient plasma requires more than 100 seconds to clot, that particular antibody reduced that to very close to 30 seconds. The antibody we identified from those 4,000 candidates could reduce the clotting time of plasma from hemophilia A patients from over 100 seconds to around 30 seconds, comparable to

healthy individuals. Conceptually, shortening clotting time aligned very well with improving coagulation, so we genuinely believed we had found something promising and pursued it with great optimism. But when we introduced the product into an animal model, we found that the shortening of clotting time wasn't as much as what the assay had led us to believe.

For one, we knew that the assay does not tell us how active the product is in terms of hemostatic activity. Also, in order to move on to clinical study in drug development, we have to undergo GLP toxicity testing. In other words, we test this in healthy animals. When we introduced the antibody from the 4000 candidates, we found that it would lead to more bleeding, not the other way around. Again, we learned that to inhibit the coagulation requires care.

From this experience, we learned two major lessons. First, optimizing antibodies solely based on clotting-time measurements could lead us in the wrong direction. Second, we needed to pay much closer attention to potential inhibitory effects on blood coagulation. We applied these lessons when we later screened 40,000 antibodies.

Suganuma [Q]: So you devised the assay system and changed the design?

Kitazawa [A]: Yes. That led to a different set of candidate antibodies. We went to 40,000 different antibodies, and we were able to identify one. The activity itself was not so different from the previous antibody that we were able to achieve, but we were able to get something that is very good in terms of less inhibition and coagulation.

Nakanishi [Q]: Congratulations. Nakanishi from Nikkei Business. This is a similar question to the previous one.

The development was discontinued in 2006, and there were ups and downs that you experienced. But during the six years of research, when was the point that you thought it would never work, and how did you overcome this obstacle? I would like to ask each one of you to answer the question.

Hattori [A]: Well, putting aside the decision to hold the project, which Kitazawa-san can discuss, I came up with this idea in 2000. I explained this idea to people around me, and many of them said that it would never work and very few actually volunteered to work with me. But then I spent the next year to reach the formal proposal, and that was in autumn 2001. Then the proposal was approved. But it was said that the bispecific antibody would be very rare and there wouldn't be so many bispecific antibodies that can substitute for factor VIII. I would have preferred to have broader options to choose from. I had a different theme to pursue in our team. I asked for other personnel to work on this because this project was approved, but no other teams actually assigned any of their team members for this type of project because they had doubts that this would work. But then the theme that we have been working on as the original one was not going well, and so we had to slow down our work for this particular topic. That made us have some spare resource to work on this. That's how we started with 460. I wanted to have a much larger pool of antibodies, but we were able to find the one antibody. That was really fortunate. If we had not found any, then we wouldn't have continued on. Finding one out of this 460 was really a big hurdle.

Kitazawa [A]: Yes, that was really fortunate for us. Maybe that was the biggest milestone. We failed from among 4,000 antibodies, and that was really a big bump. But then we went on to 40,000 antibodies to screen, and we have thought that some of them would work if we try 40,000. But actually, the criteria that we set for ourselves, none of them had satisfied the criteria. The limitation was one year and a half and there was only one month left, and then there we were. Even though the criteria was not met, there were some that were close, and those were 100. Then we modified them, improved them, and then we managed to find one antibody that can satisfy our criteria that was set initially. It almost sounds like a TV show, *Project X*, but we

were able to find one out of this 40,000. That was really fortunate, but then it was never a smooth sailing from then on.

I'd like to ask Igawa-san to explain.

Igawa [A]: The one that we managed to find out of 40,000 was handed over to me to finish this up as a product. First, we were able to have one antibody, but the activity was really weak. We had to increase the activity by 100-fold or 1,000-fold, which was almost impossible. When you talk about the pharmaceutical products or drug, they bind with the pathogenic molecule and inhibit the bad effect. You have to have a strong bonding, and that is the clear direction that we always head for. But in the case of emicizumab, you have to bind with the molecule and then get separated. We were not sure how we can increase the activity so we had to come up with many hypotheses to try them out. Then we gradually managed to increase the activity to 100-fold and we were really happy, but then the antibody with greater activity was not dissolved into buffer. There's no solution that we are able to make.

Then we encountered another problem. The more active antibody would not dissolve properly in solution. One important concept of emicizumab is that it had to be subcutaneously injected rather than intravenously injected so that self-injection will be possible. But when we administered the antibody subcutaneously in animals, it was not absorbed into the bloodstream. The activity was really increased, but it was not dissolved and not absorbed, and we were wondering why. We analyzed and we were able to make it dissolvable and absorbable, but then the activity went down. There was always a trade-off between these two. This was a dilemma that we were in, and that was the biggest hurdle that we faced. Eventually we discovered a way to achieve both activity and developability, but when we were in this dilemma, I honestly felt the project might be impossible.

Nakanishi [Q]: Thank you. When you started the research in 2002, you went into alliance with Roche, and there was help from Genentech. That's what you said. What was the role that Genentech played in this particular research?

Hattori [A]: At the initial stage, there was no involvement. There's no information exchange at all between the two parties. After the Phase I clinical trial was over, Roche, Genentech started to get involved.

Kitazawa [A]: The Phase III study started in 2015. Exactly speaking, that was when they got involved. Roche had a worldwide competency. For emicizumab in the global development, they were of great help to us.

Igawa [A]: Directly, as far as drug discovery and emicizumab is concerned, Roche and Genentech were not involved, but they were involved in clinical studies. But indirectly, for drug discovery, there was an impact from them. Firstly, this is the world's first bispecific antibody that could be produced, and that's the paper that Genentech had come up with. When researchers read this paper, we had thought that it could work even though there were some issues.

But then in 2002, we went into the Roche Group. When you compare the antibody capabilities of Genentech and Chugai, there was a huge difference. There's a big brother, Genentech, that has a huge capability, and we came in as a very small younger brother. We had to catch up, or even not catching up but maybe we should try something else, different from what Genentech was doing. We had Genentech in mind, and Genentech was always at the back of our mind so we had to do something. Otherwise, there is no point for Chugai to do research and development. Alliance with Roche and Genentech actually worked well for this discovery and the creation of emicizumab.

Hashimoto [M]: Hello. I am Hashimoto with Nikkei BP. Congratulations.

We have seen recipients come from Japanese businesses. It is said that, however, the drug discovery capability capacity of pharmaceuticals in Japan is coming down. What do you think is the significance of you working in corporations, in businesses, having won the award?

Hattori [A]: That's a tough one. I believe that Japanese scientists and research teams have the strength of being very focused and meticulous. It's the same for emicizumab research. As was mentioned by Igawa-san and Kitazawa-san, very high granular screening is done. Once the goal is established, you will continue without failing, without giving up. I think there is some strength in Japanese scientists keeping or hanging in there. We improve this one at a time. The assessment of antibody, for example, we design many and we evaluate, and we turn the cycle every day. When I talked about this at the PDL or Protein Design Laboratory, the president said that he was not aware of any research institute or laboratories that do that kind of thing, a very mundane thing day in and day out. That is what we, Japanese, are strong in. It's not just Chugai, but I hope other organizations in Japan will know the strength and continue it.

Igawa [A]: What I'm going to say is quite similar to what Dr. Hattori said. Others have asked the same or similar question. What is different about Chugai? How do we differ from Western pharmaceutical companies? Why could Chugai do this, whereas others couldn't? I always try to say, and this, I believe, is the nature of Chugai, Western pharma tend to follow a top-down decision approach, whereas Chugai tends to be very much bottom-up. Dr. Hattori was not the head of a department when he came up with the idea. He called on his peers and began these bottom-up activities. I think the organizational culture of Chugai allows that kind of proposal and let people start. That kind of frontier spirit is very much part of Chugai Pharmaceutical's culture. Now, start-ups in Western countries probably share the same mindset, but when the organization becomes larger, you tend to lose that kind of spirit, I believe.

Now, emicizumab also, we kept at it for a decade without giving up. Not just pharmaceutical companies, but any businesses require management to draw a timeline. You have to meet KPIs, and if you don't achieve that, you have to discontinue. At Chugai, even when the initial idea is to do research for two years and you cannot achieve this, it could go on for three, four years, and they allow us to continue. In the end, it took a decade, but they allowed us to continue doing this. I don't know if this applies to every Japanese pharmaceutical company, but Chugai did have that environment.

Hattori [A]: Through this award, you have shed light on what drug discovery research is. I hope this is a wonderful opportunity for aspiring scientists to become interested in drug discovery. We have high hopes for that.

Hashimoto [M]: Thank you.

[END]

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