Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

A member of the Roche group

CHUGAI PHARMACEUTICAL CO., LTD.

R&D Meeting

December 12, 2023

Event Summary

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[Participants]	

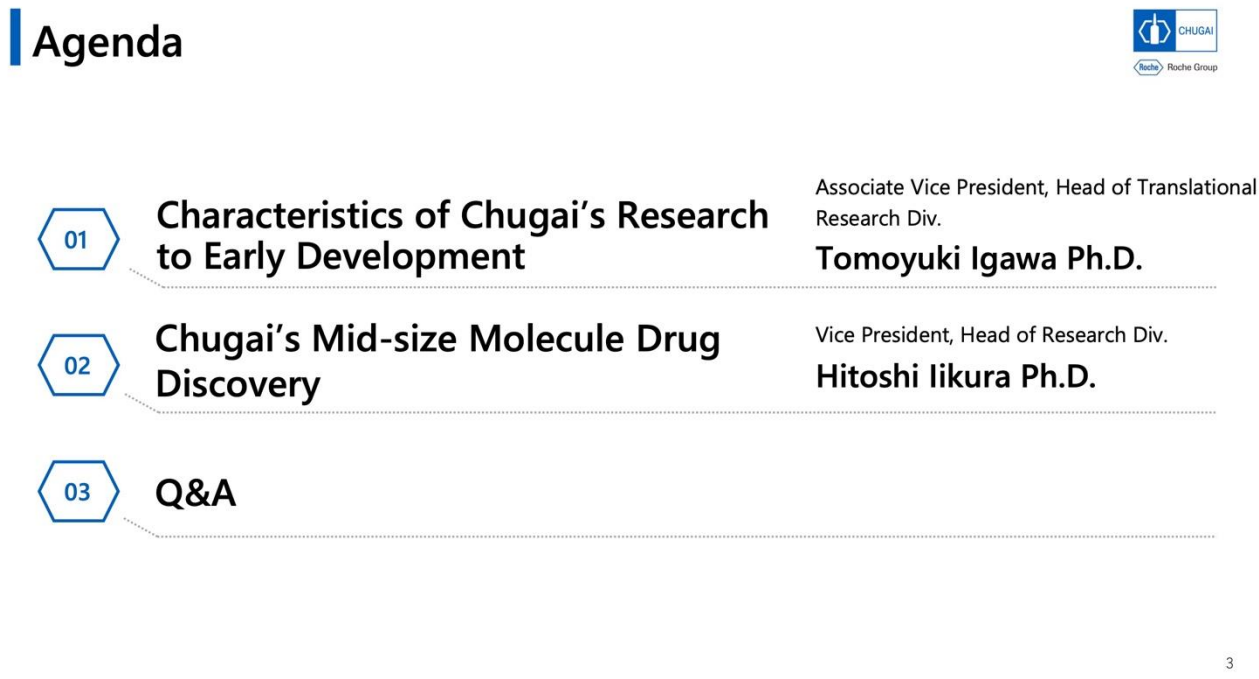
[Number of Speakers]	3	
	Dr. Hitoshi Iikura	Vice President, Head of Research Division
	Dr. Tomoyuki Igawa	Associate Vice President, Head of Translational Research Division
	Kae Miyata	Head of Corporate Communications Department
[Analyst Names]*	Shinichiro Muraoka	Morgan Stanley MUFG Securities
	Kazuaki Hashiguchi	Daiwa Securities
	Hiroyuki Matsubara	Nomura Securities
	Seiji Wakao	JPMorgan Securities
	Miki Sogi	AllianceBernstein Japan
	Hiroshi Wada	SMBC Nikko Securities
	Stephen Barker	Jefferies

*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

Miyata: Thank you very much for joining us today amidst your busy schedules for the CHUGAI PHARMACEUTICAL CO., LTD., R&D Meeting. I am Miyata from the Corporate Communications Department, and I will be moderating today's session. Your cooperation is much appreciated.

Today's session will be conducted both as an in-person event and via a Zoom webinar.



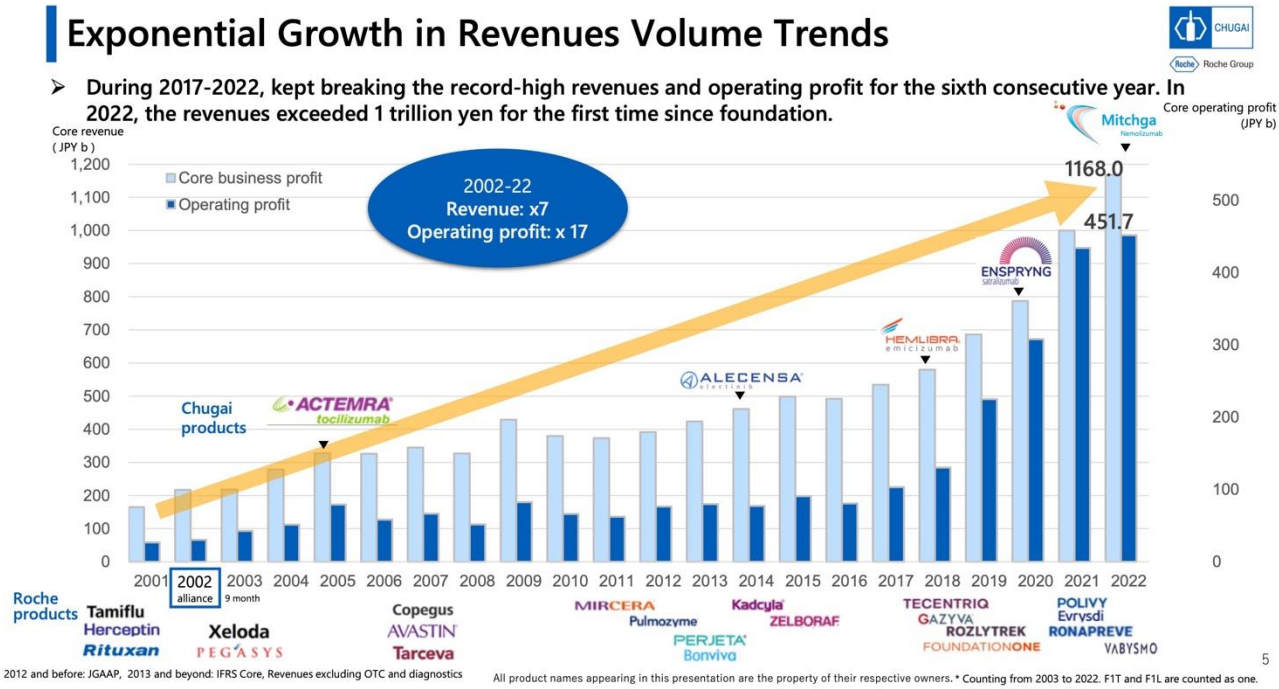
The agenda for today's meeting is displayed on the screen at the venue, the web interface, and on page three of the presentation materials. We will proceed according to the details outlined there.

I regret to inform you that, due to health reasons, Igawa is having difficulty speaking today. Therefore, Iikura will handle Igawa's presentation. Igawa is participating online and will do his best to respond to questions during the Q&A session.

We will take questions after all presentations have concluded. The Q&A session is scheduled to last for 30 minutes, and we encourage you to actively participate with your questions.

Now, Iikura will provide characteristics of Chugai's research and early development , as well as Chugai's mid-size molecule drug discovery .

Iikura: Thank you for taking the time to join us today. I am Iikura, the head of the Research Division, and I look forward to our discussion. Firstly, I will spend about 20 minutes discussing the unique aspects of Chugai Pharmaceutical's research and early development.



Starting with the first slide, it depicts Chugai Pharmaceutical's revenue and operating profit over the past 20 years. In 2022, our revenue exceeded JPY1 trillion, marking an approximately sevenfold increase in revenue over these two decades.

As you may know, Chugai Pharmaceutical established a strategic alliance with Roche in 2002. We believe this alliance has been instrumental in our stable growth.

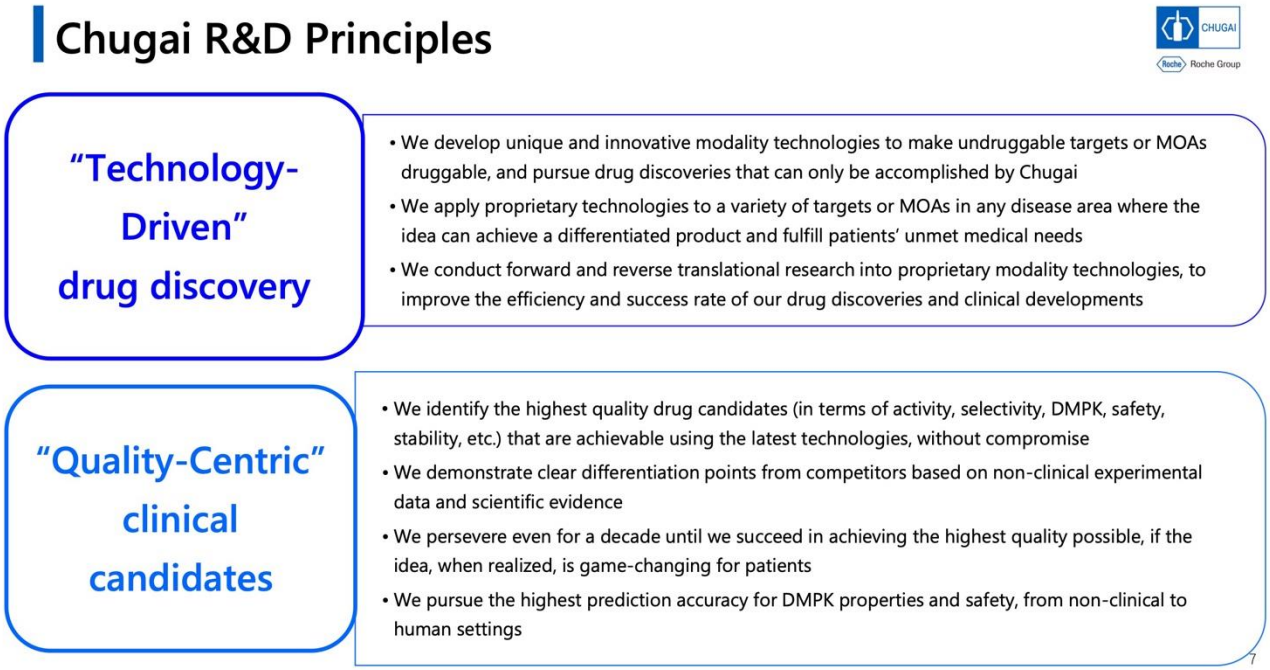
Below the graph, there are several names written. These are the names of drugs that Roche has developed and subsequently launched in Japan. The names at the top are drugs that our company has developed and launched independently.

We hold exclusive distribution rights in Japan for the drugs developed by Roche, which ensures stable revenue. This allows us to focus more on research, particularly in the early stages. Our business model is such that Roche takes over the development during the latter, more costly stages of clinical development.

Chugai Pharmaceutical's revenues have reached JPY1 trillion, and together with the revenues of our developed drugs, Actemra, Alecensa, Hemlibra, and Enspryng, we are currently maintaining approximately JPY1 trillion in global revenues.

This favorable situation has enabled Chugai Pharmaceutical to develop a unique R&D culture. This culture, although it has roots from over 20 years ago, even before our alliance with Roche during Yamazaki's tenure, has been largely informal. However, this year, Igawa has successfully formalized what was previously an unwritten aspect of Chugai's culture. Though we had hoped Igawa could present this himself today, I will cover it in the next three slides.

Our approach can be broadly divided into four key areas. First, we are technology-driven in our drug discovery. Second, we focus on achieving the highest quality. Third, we do not limit ourselves to specific disease areas; our focus is determined based on mechanisms of action and biology. Fourth, our clinical development aims to explore methods that maximize the product value.



We refer to our approach as technology-driven drug discovery, exemplified by our work with antibody technologies. This approach primarily involves transforming what were once considered undruggable targets into druggable ones.

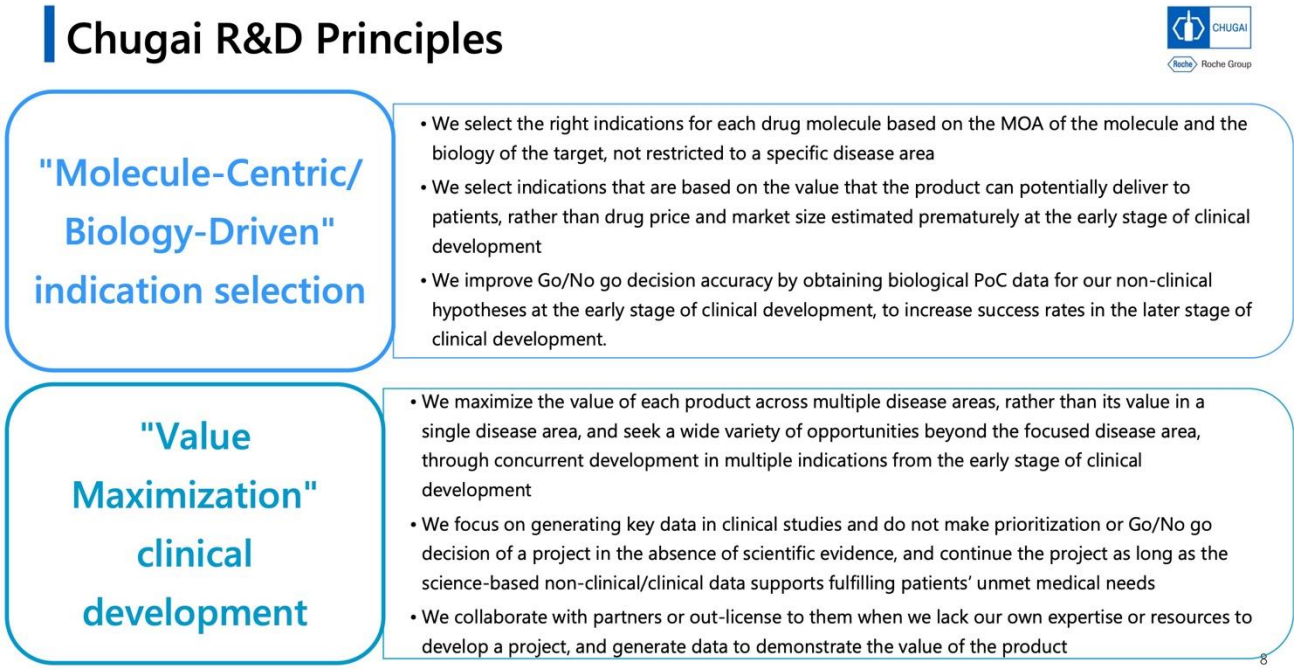
As mentioned at the top of the slide, our goal is to create unprecedented therapeutic drugs that change treatment paradigms, utilizing unique modalities that are characteristic of Chugai.

Moreover, we have been intensifying our efforts, especially over the past three years, to strengthen the connection between clinical and preclinical stages. We rapidly back-translate clinical results into preclinical stages to inform the development of new modalities.

Regarding our second point, the development of molecules with the highest quality, we have an unwavering commitment to quality. This includes aspects such as activity, selectivity, pharmacokinetics, safety, and stability. We aim to produce development candidates of the highest quality possible with current technology, a commitment we have maintained over the past 20 years and plan to continue into the future.

This focus on quality often leads us to scientifically demonstrate differentiating factors from competitors even at the preclinical stage. It also fosters a culture of perseverance, where we persistently pursue game-changing ideas, even if it requires significant time and effort.

The development of this culture has been significantly influenced by our strategic alliance with Roche, which I believe has played a major role in shaping our unique approach.



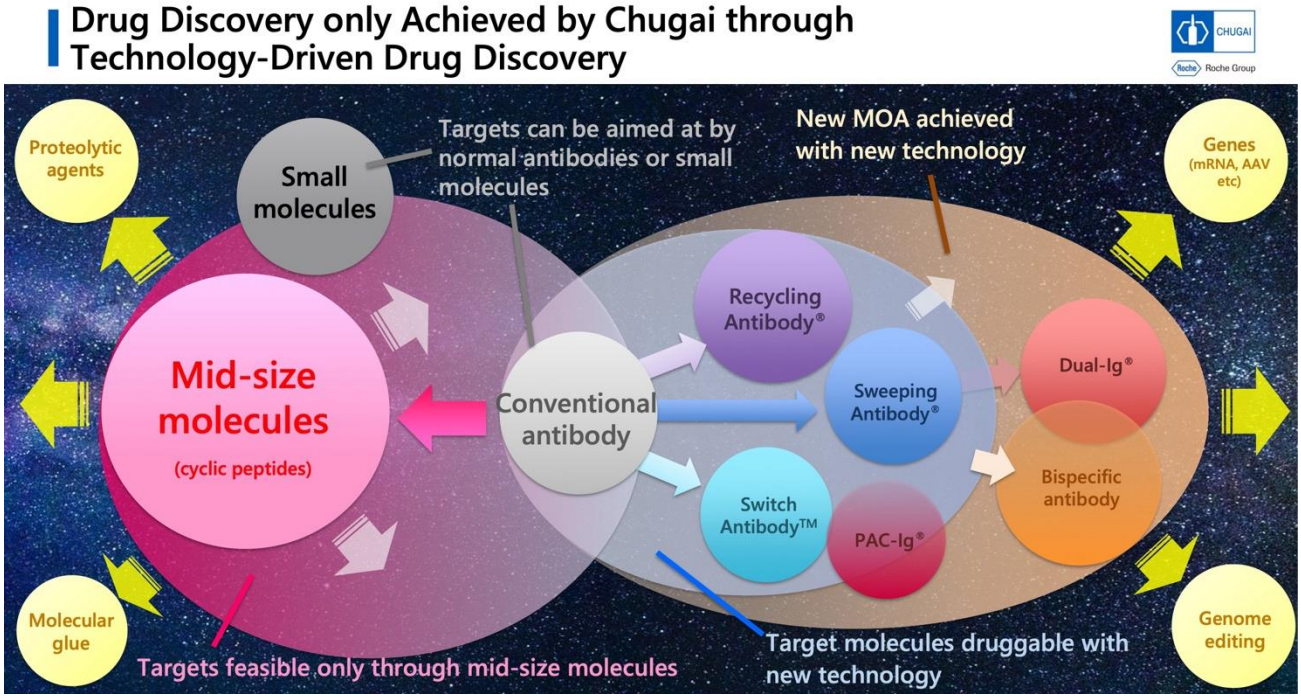
Thirdly, we follow a target disease strategy based on mechanisms of action and biology. As I mentioned earlier, we are technology-driven and do not confine ourselves to specific disease areas. While many of our projects are in oncology or immunology, we do not rule out any areas. We are open to exploring any fields where our new technologies can be effectively applied, as stated at the beginning.

However, while this approach is beneficial for research, it presents significant challenges, particularly in the early stages of clinical development, which are currently overseen by Igawa's Translational Research (TR) division. Clinical development demands specialized knowledge in various areas, and entering fields where we lack expertise can be quite demanding for the TR team. Nevertheless, we view this positively and hope it fosters a culture of learning and versatility, making us a company capable of handling diverse diseases.

Lastly, we focus on maximizing product value in clinical development. This intersects with our emphasis on mechanisms of action, and we do not limit ourselves to specific clinical diseases. Recently, we have been working on simultaneously developing treatments for various diseases right from the early stages of development. This is undoubtedly a challenging task for our translational research team, but it stems from our desire to deliver effective medicines to as many patients as possible as quickly as we can.

Our approach to clinical no-go decisions is quite unique. We don't base these decisions solely on market size or similar factors. Instead, we focus on the potential benefits to patients and the empirical data obtained from clinical trials. This thorough approach to decision-making is something we pride ourselves on.

In conclusion, our partnership with Roche is immensely important. We engage in early and detailed discussions with Roche to maximize product value. However, we are also open to partnering with third parties other than Roche, depending on the situation. Generally, we prefer not to conduct Phase III trials in-house.



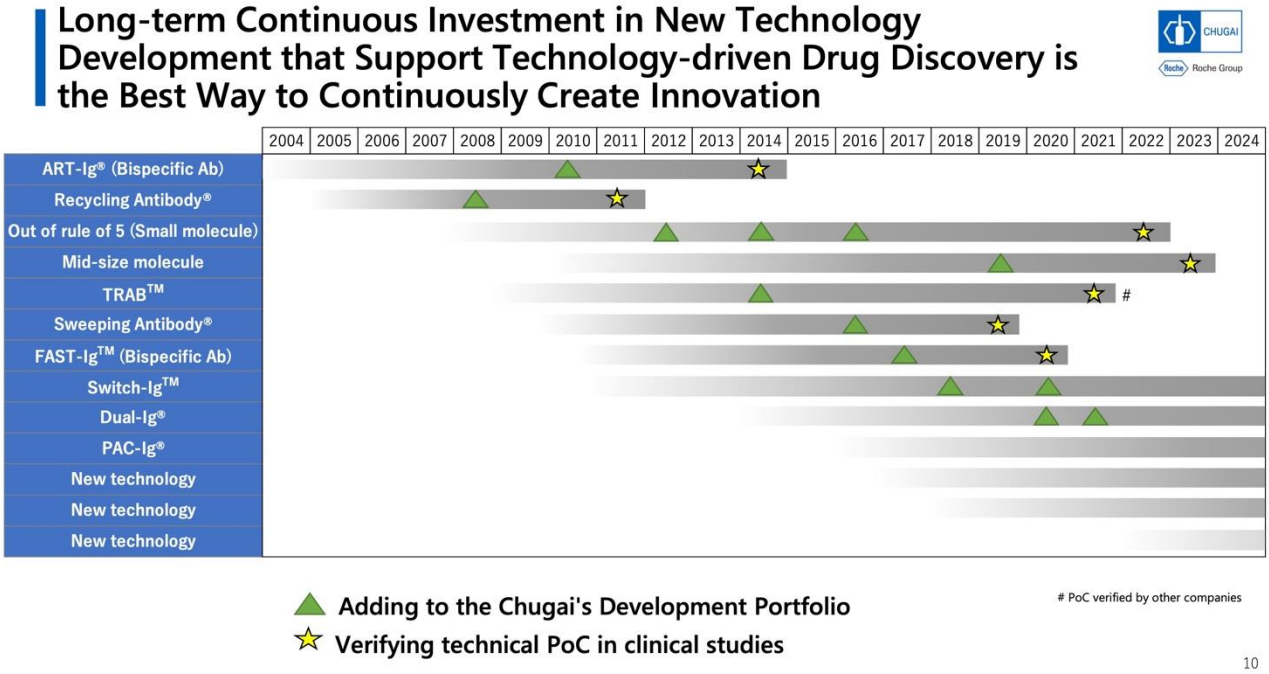
The cornerstone of our competitive edge in R&D, as I believe, lies in our technology-driven approach to drug discovery.

As mentioned in the middle of the presentation, our focus is not just on conventional antibodies. For instance, Igawa has been leading the development of bispecific antibodies, which enable us to accomplish previously unachievable feats. This includes recycling antibodies, sweeping antibodies, switch antibodies, and PAC-Ig. Each of these possesses unique characteristics distinct from traditional antibodies, allowing us to do what was once impossible.

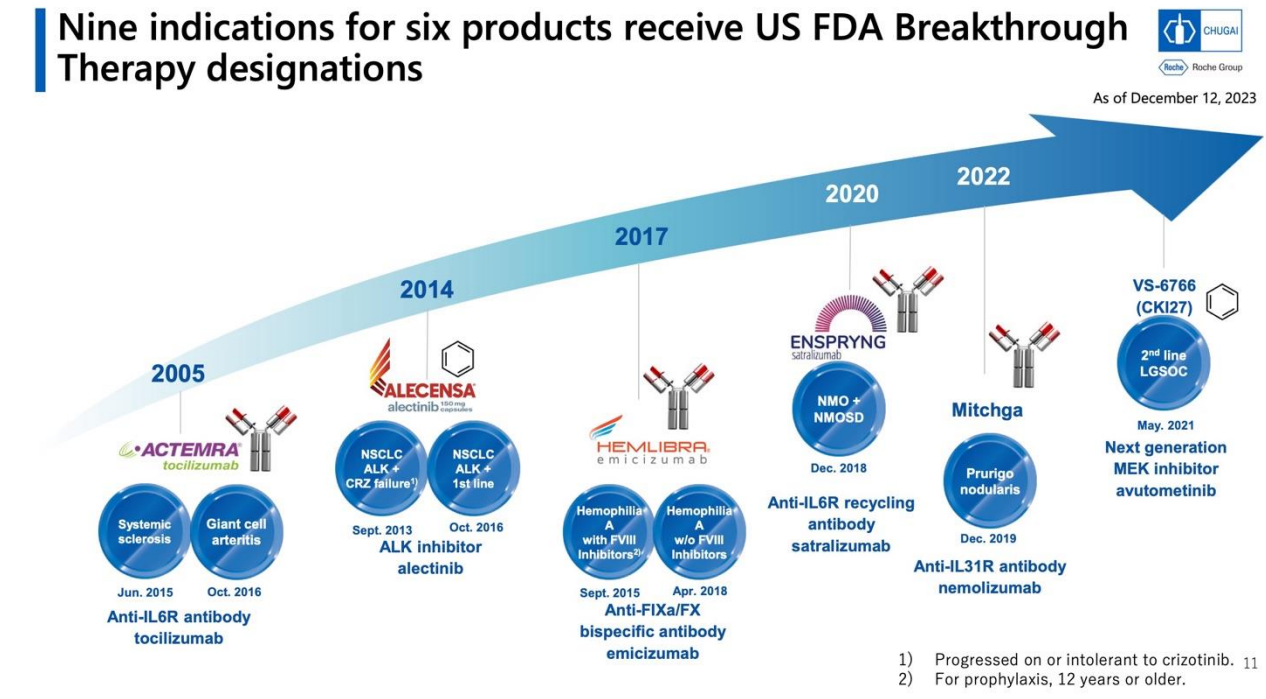
On the other hand, one of today's key topics is mid-size molecules, a modality we are very excited about. Mid-size molecules can achieve things that neither antibodies nor small molecules can. The experimental data we've accumulated over the past two years is quite promising and supports this expectation.

Mid-size molecules have the potential to be applied in areas currently generating a lot of interest, such as Proteolytic agents s and molecular glues. We believe there is ample scope for their application in these areas.

Thus, our fundamental stance is to pursue drug discovery that is uniquely possible because of Chugai's capabilities.

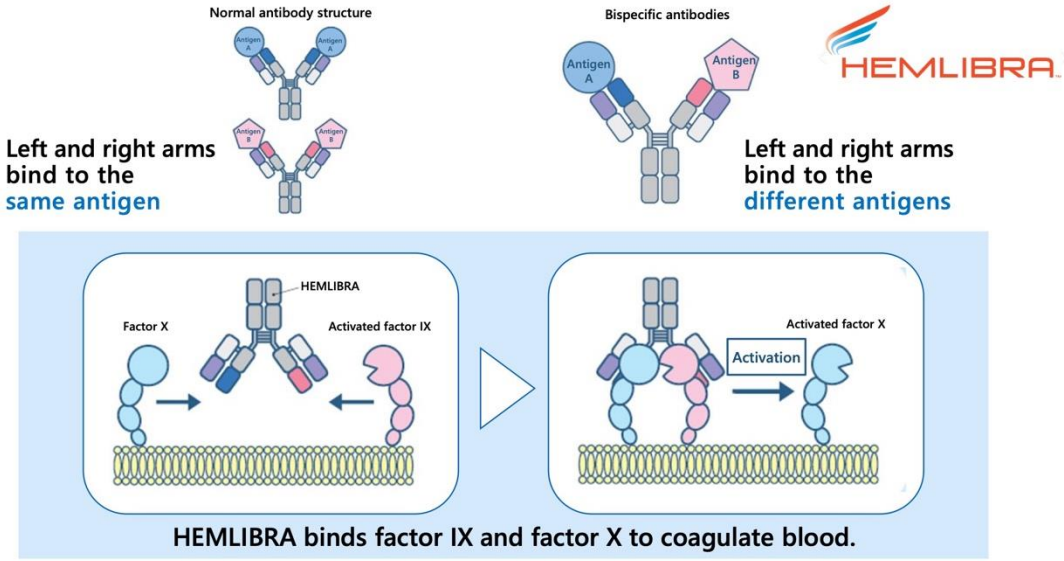


Regarding the time invested in our drug discovery technologies, some take over a decade. As indicated on the slide, this duration has become somewhat standard for us.



Since 2005, six of our products across nine projects have been designated as Breakthrough Therapies by the FDA. This is a source of great pride for us and motivates our ongoing commitment to developing high-quality pharmaceuticals.

HEMLIBRA® Was Created through Chugai's Unique Mindset, Barrier-free Handling of Disease Areas



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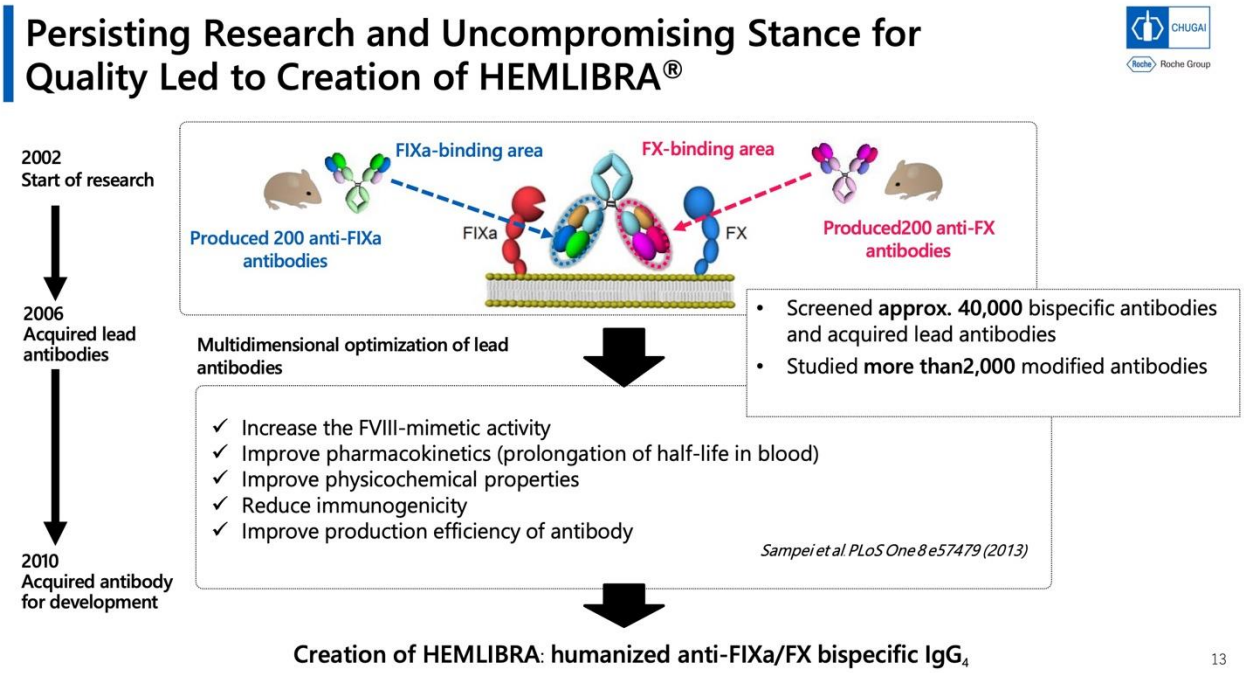
Now, I would like to introduce Hemlibra, one of our flagship products, over the next few slides.

Hemlibra has had a significant impact on Chugai and has been a focus for all our researchers for over a decade. It has played a crucial role in shaping our mindset.

As you may know, Hemlibra is a bispecific antibody. This means that its two arms can recognize different antigens.

While conventional antibodies bind to a single antigen, both arms to antigen A or B, bispecific antibodies has a novel characteristic to be able to bind to two different proteins simultaneously.

This unique characteristic allows Hemlibra to bind to both Factor X and Factor IX, bringing them closer together and activating them. This dual binding capability is a key feature that has been effectively utilized in Hemlibra's therapeutic function.

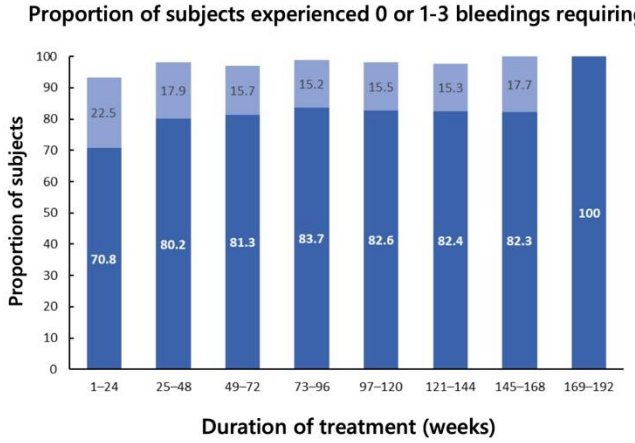


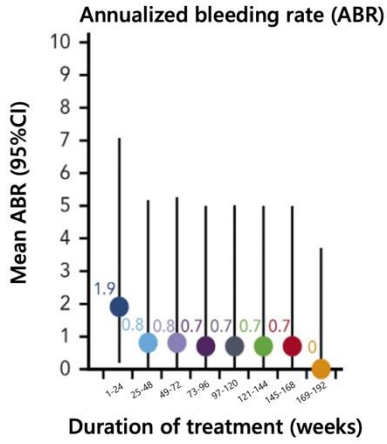
The development of this antibody, initiated in 2002, spanned over eight years before we obtained the development-ready antibody. Notably, there was a point where we had identified a clinical candidate compound, but unexpected toxicity led to its discontinuation, prompting us to start over. This perseverance, not giving up despite setbacks, has become a symbol of our approach, and the development of Hemlibra is an excellent example of this.

We screened approximately 40,000 bispecific antibodies, which is a significant number even by today's standards. This extensive screening was done before 2010 to find the optimal candidate, adhering to our commitment to quality and selecting the one with the least toxicity concerns based on the technology available at the time. This rigorous process led to the creation of Hemlibra.

HEMLIBRA® Creates New Value in Hemophilia Treatment

Long-term administration of HEMLIBRA data showed that as the administration went longer, bleeding requiring treatment were getting to zero.





Collaghan et al, *Blood 2021; 137(16): 2231*

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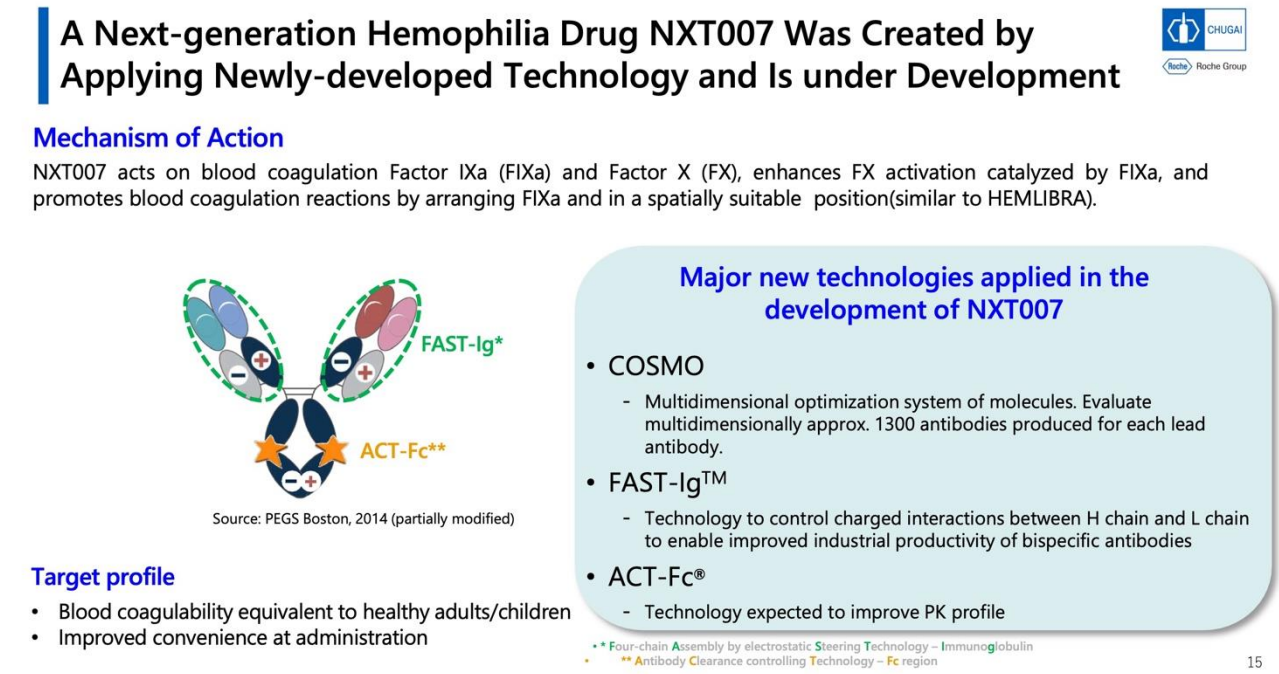
As for the results, which I believe are well-known to you, I will keep it brief. Hemlibra has demonstrated significantly high efficacy.



Furthermore, we are currently engaged in the clinical development of Hemlibra's next-generation drug, which we refer to as NXT007.

Our commitment to continuous technological advancement means that even what we considered the highest quality a decade ago may not hold the same status today. That's why, as highlighted at the beginning of our R&D principles, we emphasize the highest quality with current technology. The word "current" reflects this evolving standard.

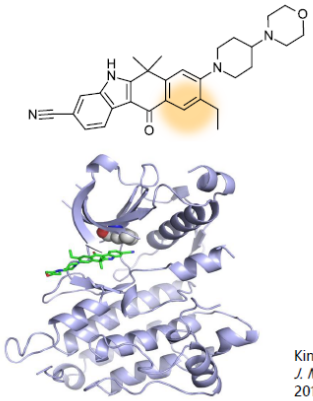
NXT007 incorporates three additional technologies into the antibody. These technologies, known as COSMO, FAST-Ig, and ACT-Fc. COSMO have significantly increased the number of compounds we can assay. FAST-Ig and ACT-Fc have enhanced the functionality of the antibody. Above is successful at least in preclinical stages.

Our goal with this project is to achieve blood coagulability equivalent to healthy adults/children. Dr. Igawa has been leading this initiative, and from what I've observed and heard discussed within the Company, one of the aspirations has been to enable individuals with hemophilia to confidently play basketball, as an example. While we're not certain if we can reach that exact goal, our aim is to obtain blood coagulation ability to the level of healthy individuals.

To add further detail, achieving healthy adult-level blood coagulation ability is incredibly challenging. As mentioned in the previous slide, even though Hemlibra binds and brings together two proteins, if the manner of bringing them together differs from the body's natural process, it cannot achieve 100% activity. Hemlibra was unable to reach this 100% effectiveness. However, NXT007 represents a more successful approach in correctly aligning Factors X and IX. As a result, at least in preclinical stages, we have observed higher efficacy with NXT007. This project is currently in clinical development.

Alectinib (ALECENSA®) Is the Result of Our Commitment to Quality

- Chugai-created ALK inhibitor
- Approved for the treatment of ALK fusion gene-positive non-small cell lung cancer in more than 70 countries including Japan, the United States, and Europe
- Added high selectivity by design based on target structure information



Kinoshita et al. *J. Med. Chem.* 2011, *54*, 6286.

In vitro Enzyme Inhibition Activity

Tyr kinase	IC_{50} (nM)	Ser/Thr Kinase	IC_{50} (nM)
ALK	1.9	AKT1	>5,000
ALK F1174L*	1.0	AKT2	>5,000
ALK R1275Q*	3.5	AKT3	>5,000
INSR	550	AuroraA	>5,000
KDR	1,400	CDK1	>5,000
ABL	>5,000	CDK2	>5,000
EGFR	>5,000	MEK1	>5,000
FGFR2	>5,000	PKA	>5,000
HER2	>5,000	PKCα	>5,000
IGF1R	>5,000	PKCβ1	>5,000
JAK1	>5,000	PKCβ2	>5,000
KIT	>5,000	Raf-1	>5,000
MET	>5,000		
PDGFRβ	>5,000		
SRC	>5,000		

* Hotspot activating point mutations in neuroblastoma

Sakamoto et al. *Cancer Cell* 2011, 19, 679.

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As for small molecules, we have Alecensa, a drug developed for lung cancer patients. Unfortunately, Alecensa is applicable to only about 5% of lung cancer patients, making it more suited for what might be considered a rare cancer. Nonetheless, it was developed with the intention of creating a highly effective treatment for this specific group.

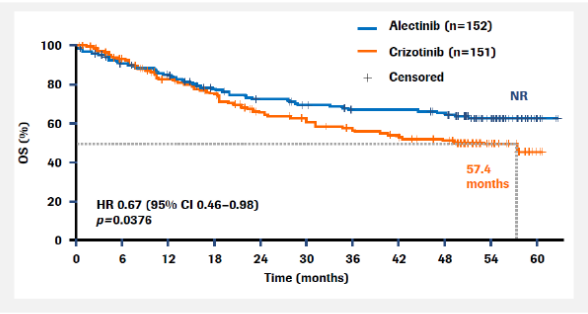
Alecensa has been recognized for its value worldwide and has become the first-choice treatment in many places. Its key feature is its high selectivity for its target. ALK is a type of kinase, and among the approximately 500 similar kinases, Alecensa successfully binds selectively almost only to ALK.

This approach of selectively targeting kinases was a significant endeavor in the past decade globally. Many tried to achieve high efficacy in drugs by enhancing kinase selectivity, but we are so proud that Alecensa stands out as one of the first in a group of compounds that successfully managed this.

ALECENSA® Is Expected to Further Contribute to Treatment of ALK-positive Lung Cancer

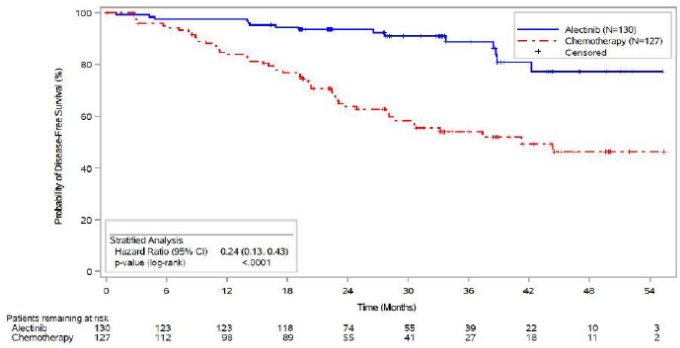
P3 ALEX Study

- Alectinib demonstrated OS superiority and good tolerability over crizotinib
- Five-year survival rate exceeded 60%



P3 ALINA Study

- As an adjuvant postoperative treatment for patients with completely resected Stage IB-IIIA ALK-positive NSCLC, ALECENSA reduced the risk of recurrence or death by 76% compared to chemotherapy



Data cutoff: November 29, 2019; OS: overall survival; ASCO: American Society of Clinical Oncology; NR: not reached.
Dose in ALEX study: 600 mg of alectinib twice daily
Approved dose in Japan: 300 mg of alectinib twice daily

Source: ASCO20 Virtual Roche Analyst Event (partially modified)

Source: FYE DEC 2023 3Q Financial Results Briefing (October 24, 2023)

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As you are aware, the results have shown that Alecensa is considerably more effective than its predecessors. Moreover, the latest results have also demonstrated its effectiveness as an adjuvant therapy.

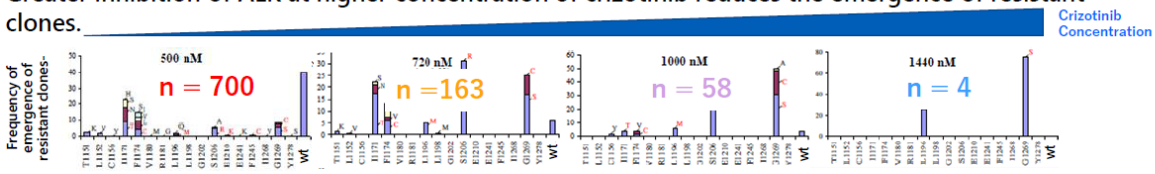
Possibility of Reduced Frequency of Acquired Resistance by Higher Target Inhibition

✓ The *in vitro* efficacy and clinical exposure ratio of alectinib is 6.8 fold higher than that of crizotinib, and the high selectivity of alectinib results in stronger inhibition of ALK.

ALK Inhibitors	Cell-growth inhibition H2228[1]	Clinical Pharmacokinetics			Ratio
	(1) IC_{50} (nM)	$AUC_{0-\tau}$ (ng.h/ml)	Clinical dose (mg)	(2) Mean concentration calculated from $AUC_{0-\tau}$ (nM)	(2)/(1)
Crizotinib	*170*	4608[2]	250, b.i.d.	853	5.02
Alectinib	*30*	4970[3]	300, b.i.d.	1031	34.4

6.8 fold

✓ Greater inhibition of ALK at higher concentration of crizotinib reduces the emergence of resistant clones.



Resistance Induction Study in Ba/F3 Cells Expressing EML4-ALK by Treatment with N-Ethyl-N-Nitrosourea in the Presence of Various Concentrations of Crizotinib[4]

1) Isozaki et al., *Cancer Res.*, 2016, *76 (6)*, 1506
2) Xalkori PMDA interview form
3) alectinib interview form
4) Zhang et al., *Chem. Biol. Drug. Des.* 2011, *78*, 999

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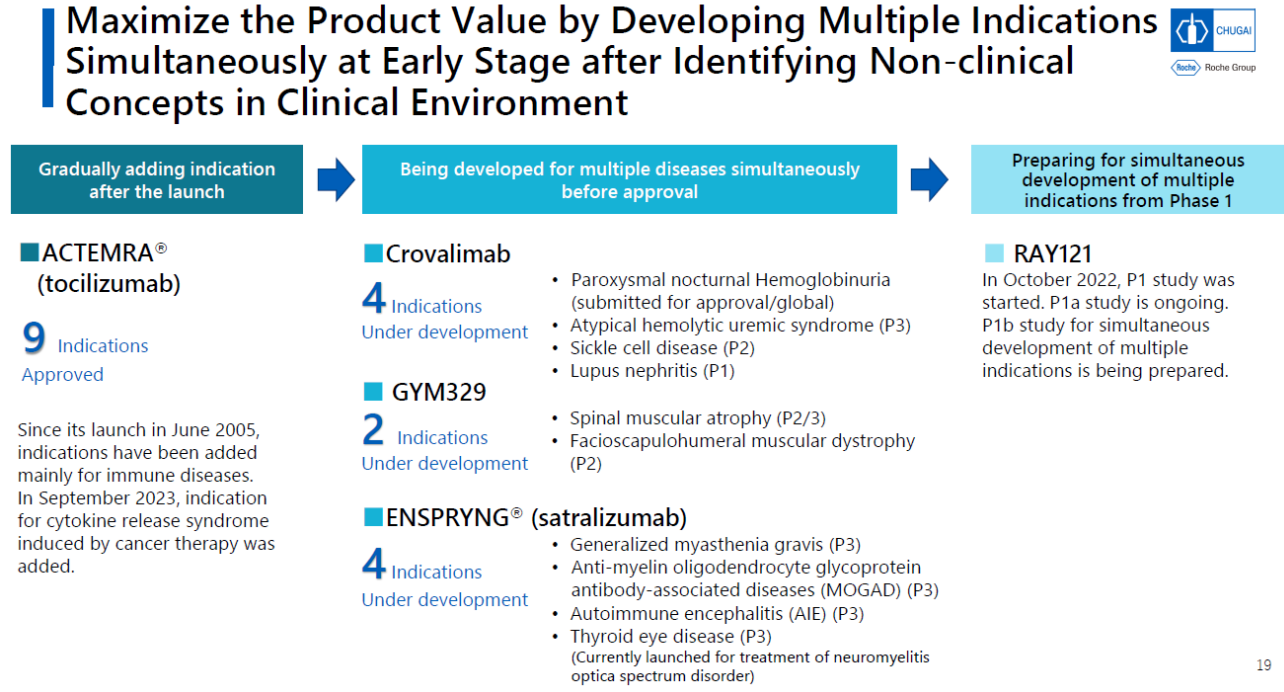
Regarding why Alecensa performs so well compared to its predecessors, our analysis, though speculative on our part, highlights a few key points. The drug concentration in humans is similar to that of the preceding products, but the concentration required to achieve efficacy is about five to six times higher.

This leads to what we call a therapeutic window, where Alecensa can maintain a significantly high concentration without compromising safety. This is a manifestation of our commitment to quality, ensuring both high activity and safety.

To illustrate the effect of this, let's consider a comparison with crizotinib, a predecessor. Data from other companies show that at a concentration of 500nM, crizotinib led to the emergence of around 700 resistant cancer cells in vitro. However, when the concentration was tripled, the number of resistant cells reduced to just four. This indicates that administering a high-concentration drug can significantly counteract cancer resistance, a finding mirrored in clinical trials.

In the case of ALK inhibitors, the toxicity related to on-target effects is minimal, as ALK is not expressed in adults. Therefore, the limit for the maximum concentration is determined by off-target toxicity and drug-induced toxicity. Focusing on this allows us to enhance resistance significantly. Our emphasis on safety has enabled us to develop a high-efficacy and high-safety profile for Alecensa.

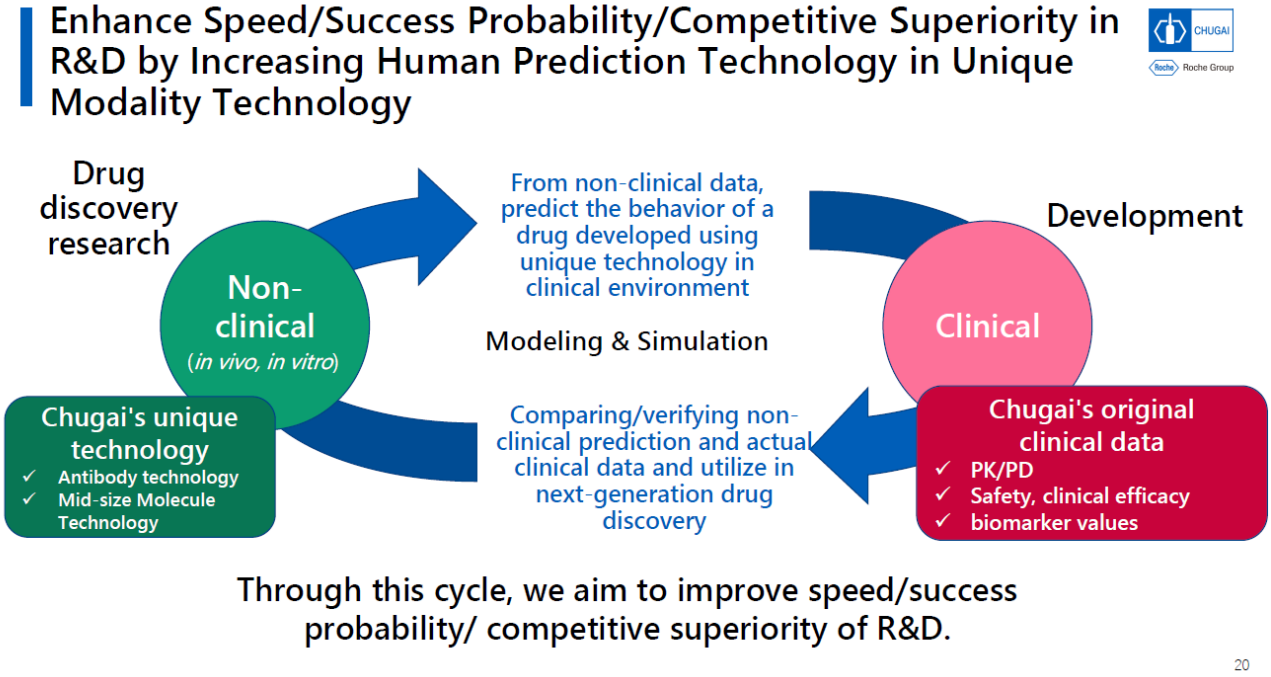
OWL833, a diabetes treatment drug we've licensed to Eli Lilly, is also a product of our dedication. This drug, too, was developed over a period of approximately seven to eight years, with a strong focus on these principles.



Regarding the development of these compounds, one key concept we've been actively pursuing over the past three years, under Dr. Igawa's leadership, is the simultaneous development of treatments for multiple diseases in early stages. As I mentioned earlier, this is extremely challenging, especially when venturing into disease areas where we haven't established a franchise. I understand that our Translational Research (TR) team members have been working tirelessly on this.

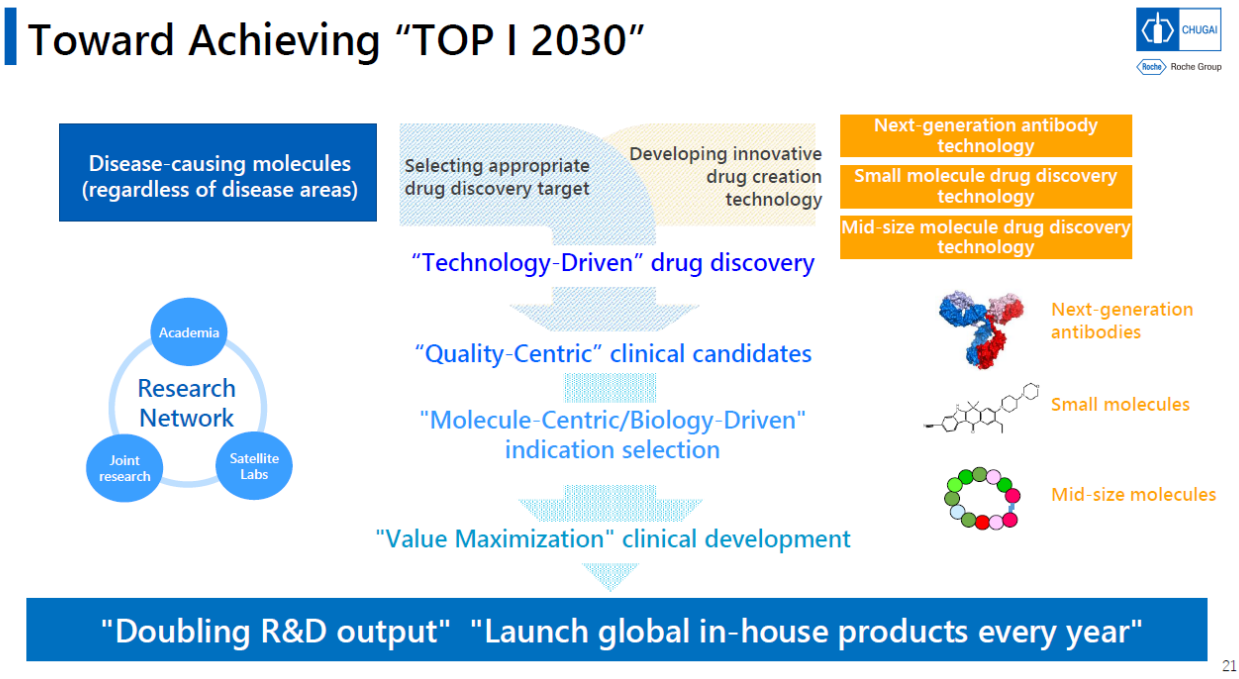
Take Actemra, for instance, which has nine indications. These were approved and added to the lineup gradually. On the other hand, as for crovalimab and GYM, we are currently considering expanding its indications even during clinical trials.

A symbol of this approach that we'd like to highlight is RAY121. We are planning to develop this for a vast array of diseases, starting from Phase I with basket trials.



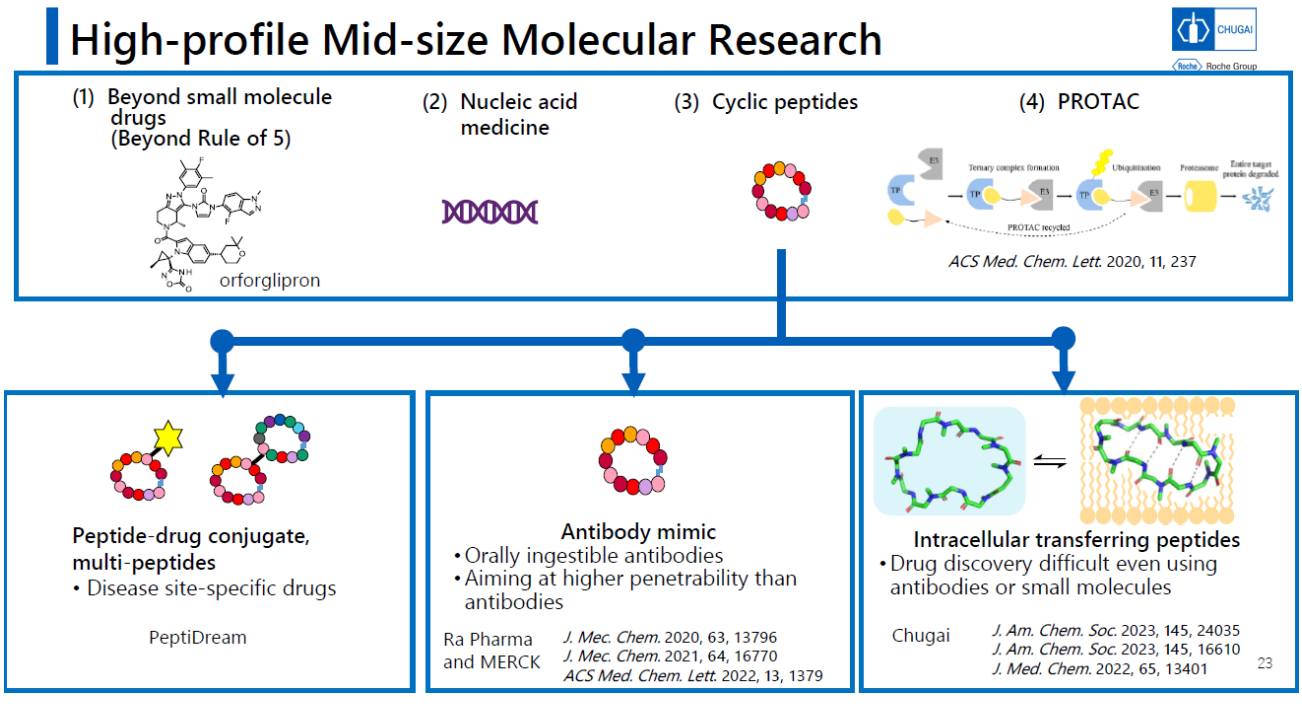
As for the final slide of the first half of our presentation, a crucial factor is how clinical and non-clinical development interact. This has been a significant focus for Dr. Igawa in the past three years. The data obtained from clinical trials is invaluable to us, and figuring out how to leverage this data for future developments is essential.

Similarly, there is room for more innovation in gathering non-clinical data that can be utilized effectively in clinical settings. By improving the precision of this process, we can increase the likelihood of clinical success or choose the more optimal compounds as clinical candidates. We're proud to have initiated a cycle where these factors are being addressed and improved upon significantly.



In our TOP I 2030, we have set ambitious goals to double our R&D output and, launch global in-house products every year. We intend to achieve these objectives by adhering to our current R&D principles.

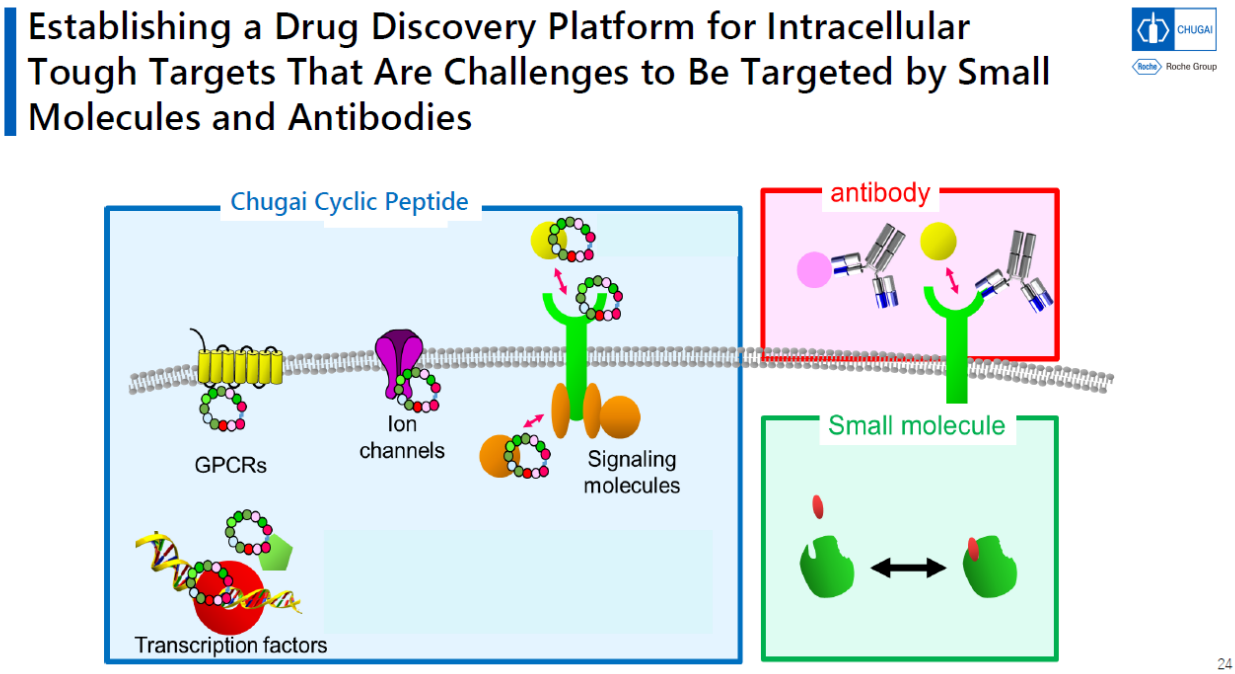
Next, I'd like to talk about Chugai's approach to mid-size molecule drug discovery.



As you may know, the realm of mid-size molecules encompasses various entities, such as nucleic acids, cyclic peptides, and recently, molecules like PROTACs, or it may be considered an extension of small molecule drugs. At Chugai, when we refer to mid-size molecules, we specifically mean cyclic peptides.

We're also engaged in what is termed Out of Rule of 5, and OWL833 is an example in this category. Currently, our focus is particularly on cyclic peptides, a field that's garnering significant attention globally, with many companies exploring various aspects.

Our approach differs notably from others, especially in our focus on peptides that can penetrate cells. While companies like PeptiDream are pursuing a wide range of applications and forming partnerships with major firms, their focus seems to be on peptide drug conjugates. Recent reports, like the collaboration between Ra Pharma and Merck on PCSK9 involving an oral peptide mimic that competes with antibody products, primarily target extracellular entities. In contrast, our technology is specialized in targeting intracellular entities.



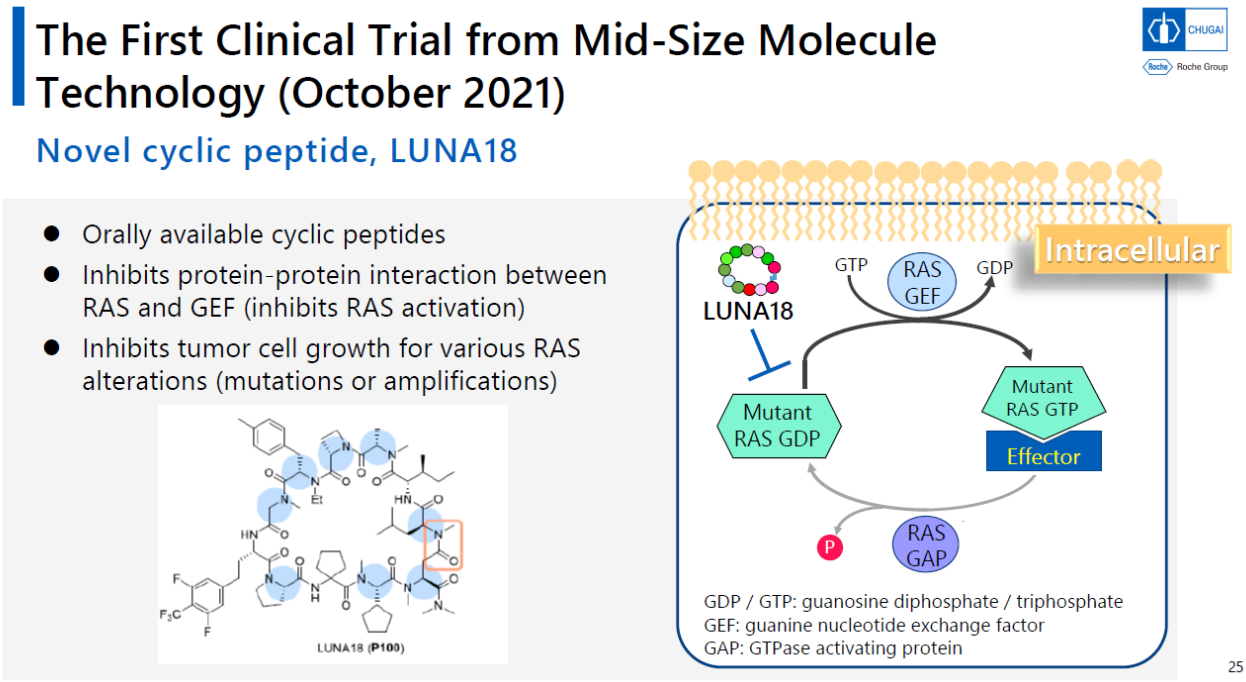
This slide illustrates why we are particularly focused on targeting intracellular entities. Antibodies, in which we have a strong expertise, can bind powerfully to a wide range of proteins, including those we specifically target. However, with current technology, introducing antibodies into cells remains a significant challenge.

It is said that about 80% of all proteins are located within cells. Therefore, the potential targets accessible to antibodies represent only about 20% of all proteins.

On the other hand, small molecules, due to their size, can enter cells, but they require deep pockets in the protein targets to bind effectively.

Such proteins with deep pockets also constitute approximately 20% of all proteins, meaning small molecules can theoretically target only about 20% of all proteins. This leaves about 60% of potential targets, those that are intracellular and lack deep cavities, difficult to address with the major modalities of small molecules and antibodies.

Given our experience with antibodies and small molecules, we sought to address this gap. In our search for a solution, we identified cyclic peptides as a potential modality that could effectively target this significant portion of the proteome that has been challenging to drug.



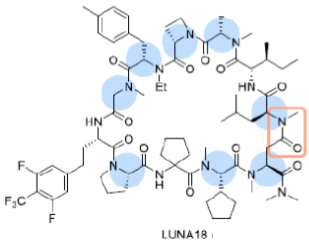
In this context, as you know our first clinical trial using mid-size molecule technology has already commenced. This trial represents a significant step forward in targeting RAS, a challenging protein that has remained largely inaccessible to drug development efforts for over 40 years.

Currently, there are two approved drugs against KRAS G12C mutations, and several other novel therapies based on protein degraders and covalent inhibitors have been developed to target RAS with new technologies. This field has become highly competitive and challenging, but most of the edge docking technologies are still focused on this specific target of RAS. However, LUNA18 offers a novel approach by using cyclic peptides that uniquely act.

LUNA18: Orally Available pan-RAS(GDP) Inhibitor (Phase 1 Study on-going)

J. Am. Chem. Soc. 2023, **145**, 24035

In vitro efficacy



Binding affinity to N-, H-, K-Ras: around 50 pM

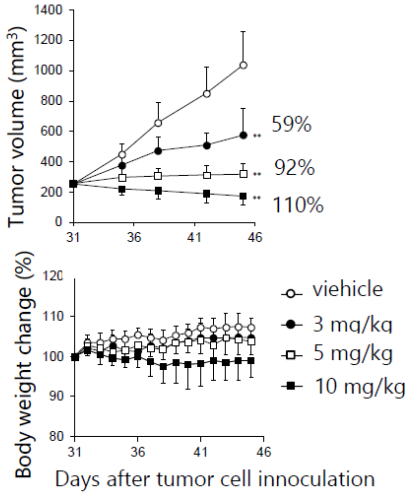
Cell line	Genetic alterations	Cell IC50 (nM) (n = 6)
NCI-H2122	KRAS-G12C	1.4 ± 0.28
NCI-H441	KRAS-G12V	2.9 ± 0.73
GSU	KRAS-G12D	0.17 ± 0.015
A-375	RAS-WT	> 1,000

Animals PK

	LUNA18
Mouse BA	21%
Rat BA	22%
Monkey BA	26%
Dog BA	47%

In vivo efficacy

NCI-H441 (NSCLC)



This is the first time we are introducing the profile of this compound. We have recently been able to publish our findings, showing that LUNA18 demonstrates a strong affinity towards RAS, specifically NRAS, HRAS, and KRAS, at approximately 50pM, which is exceptionally strong. In our analysis, this affinity is comparable to that of antibodies and is tens of times stronger than that of small molecules.

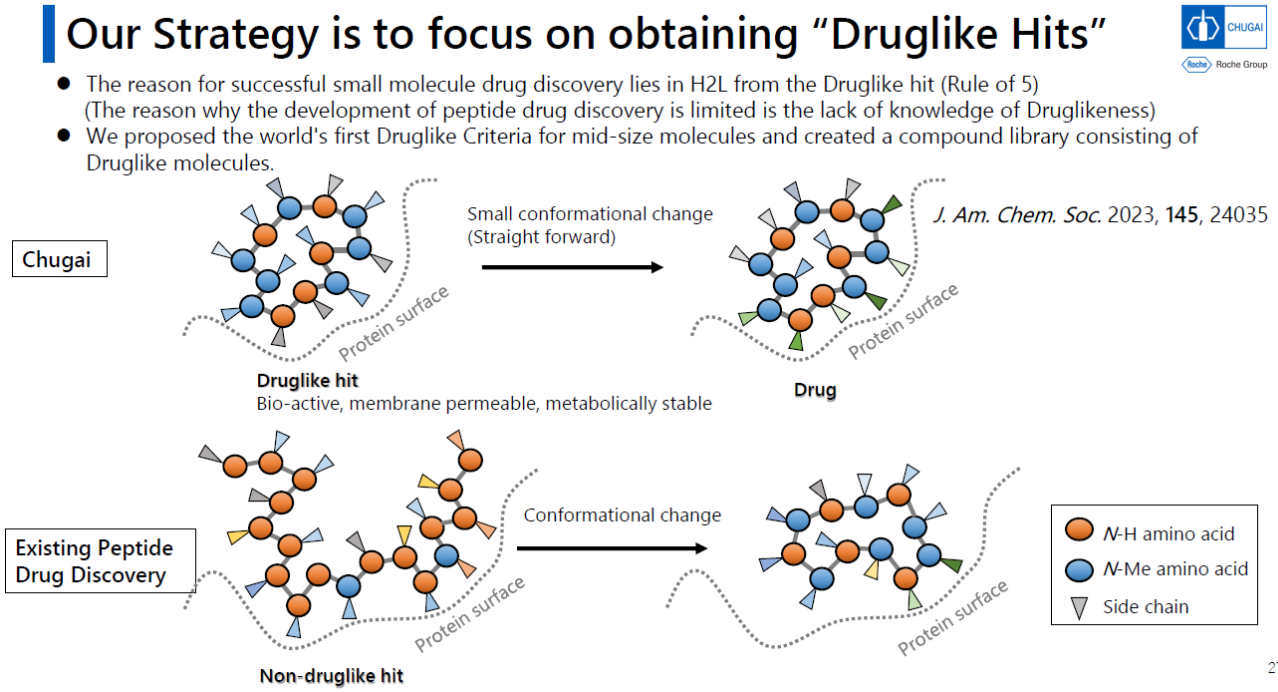
Even with tough intracellular targets like RAS, LUNA18 maintains this level of affinity. Its cellular activity is also robust, showing activity at 1nM and, in some cell lines, even as low as 0.1nM.

On the other hand, for cell lines contains the wild-type of KRAS known to have low RAS dependency, LUNA18 shows a therapeutic window of over 1,000-fold, at 1µM.

In terms of bioavailability in animals, cyclic peptides exhibit over 20% bioavailability across the four animal species we typically use in our studies, indicating its availability for development.

While we've recently announced that LUNA18 achieved sufficient pharmacokinetics (PK) in humans, further details beyond this are not yet available for disclosure.

This slide shows the efficacy confirmed in vivo, using a mouse xenograft model. We observed tumor reduction with once-daily oral administration at a dose of 10mg/kg. These results demonstrate that mid-size molecules indeed possess strong affinity, can penetrate cells, and show a reasonable rate of oral administration utilization, at least in preclinical settings. This promising outcome has led us to proceed with clinical trials.



Regarding our unique strategy, I'd like to explain a bit about it.

We have been particularly focused on achieving what are known as druglike hits. The illustration here depicts the conventional approach to peptide drug discovery. Traditionally, peptides have large molecular weights and are not cyclized. While this approach can yield strong hits, these molecules typically lack membrane permeability and metabolic stability. Many efforts have been made to oralize peptides like GTP and GLP, but these have largely been unsuccessful, primarily due to these limitations.

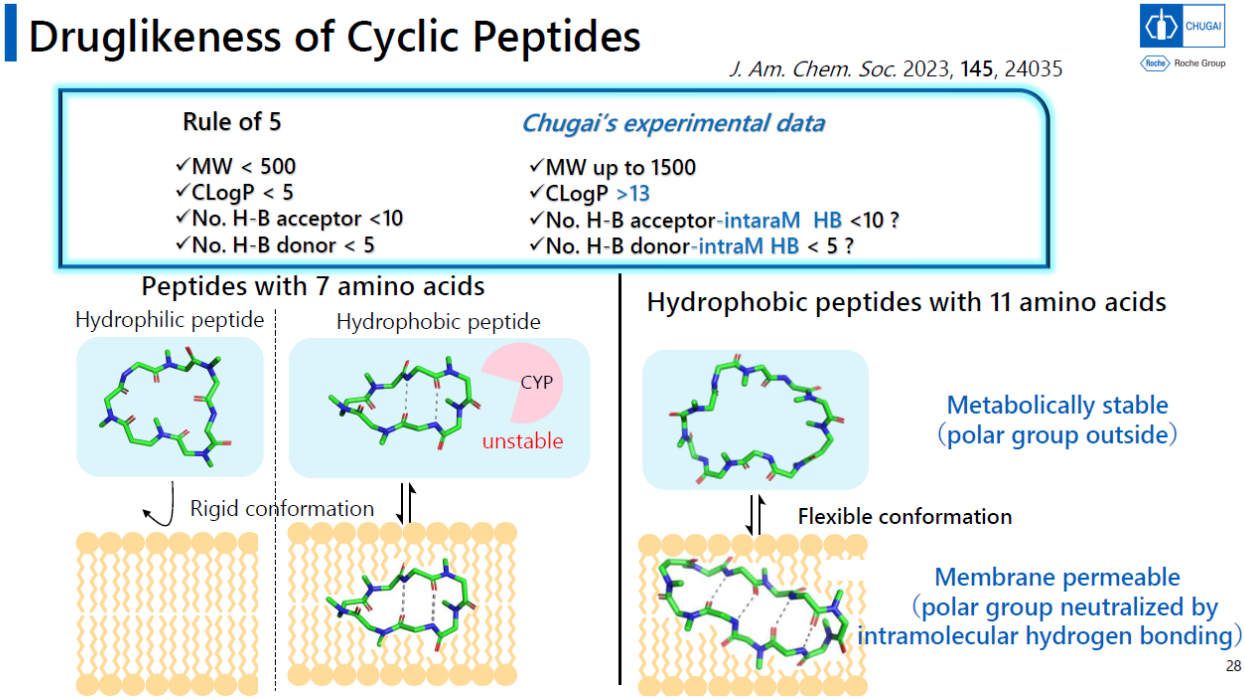
To transform these molecules into drugs, it's essential for them to possess metabolic stability and membrane permeability. However, achieving these properties requires significant alterations to the molecular structure. Such extensive modifications often result in a near-total loss of bioactivity, a challenge that has persisted for decades. This has led to the prevailing belief that developing oral peptide-based drugs is inherently difficult.

Our approach differs in that we don't see the difficulty as inherent to peptides, but rather due to the lack of druglike hits. In small molecule drug discovery, hits from high-throughput screening often already possess some degree of membrane permeability and metabolic stability, even if their bioactivity is not particularly strong. This makes the transition from hit to lead more seamless. The boom in small molecule drugs since the 1990s can be attributed to this.

This relates to Lipinski's Rule of 5, which suggests that compounds fitting within these rules are very likely to possess drug-like properties, specifically in terms of membrane permeability and metabolic stability. Consequently, in small molecule drug development, most hit compounds already exhibit these drug-like characteristics, facilitating a smoother transition from hit to lead without major structural changes.

We aimed to apply this approach to mid-size molecules, particularly peptides. As you might be aware, drug discovery for molecules with a molecular weight exceeding 500 was scarcely undertaken. There was a lack of information on what characteristics make a compound in this category drug-like, so we began by gathering this information ourselves.

Starting from this point, I believe, has been significantly influenced by our alliance with Roche.



What we discovered was quite insightful. For instance, we managed to achieve membrane permeability with peptides with 7 amino acids by making it more lipophilic. While this increased its ability to penetrate lipid membranes, the lipophilic nature also made it more susceptible to oxidative metabolism by cytochrome P450 (CYP), thus compromising its metabolic stability.

When we tried to enhance its stability against oxidative metabolism by CYP by making it more hydrophilic, it became too water-soluble to permeate the membrane effectively. In other words, we could achieve either membrane permeability or metabolic stability, but finding a balance between the two proved extremely challenging.

However, when we expanded the peptide with 11 residues, we found that both goals could be achieved. With 11 residues, the peptide becomes somewhat flexible. It likely forms numerous hydrogen bonds within the molecule, adopting a lipophilic structure to cross the membrane, essentially mimicking a lipophilic nature.

Conversely, when in water, its polar groups face outward, asserting a hydrophilic character which reduces oxidation by CYP. Thus, we found that peptides around with 11 residues, unlike those with 7, can exhibit significantly more drug-like properties. This was a new and valuable insight for us.

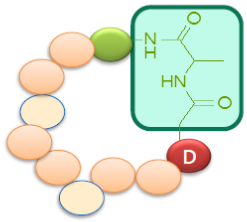
This challenges the long-held belief among many chemists, myself included, that smaller molecular weight equates to being more drug-like. It turns out this was merely a misconception, not reflecting reality. Researchers have traditionally focused on creating drugs with five or six residues, finding it difficult to develop drugs with these smaller molecules and rarely considering larger molecular weights. However, our results indicate that the sweet spot for drug development might actually lie in these larger structures.

This is exemplified by the compound Cyclosporine. Cyclosporine, with its 11 amino acid residues, perfectly fits this sweet spot. In the world of drug discovery, Cyclosporine has long been viewed as an exception. However, our experimental evidence suggests that Cyclosporine is not just an outlier but an indication that there is a significant rationale behind its structure. This has led to the establishment of certain rules in drug development, a development that has recently been reported in Journal of the American Chemical Society (JACS).

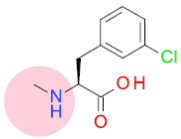
Defining "Druglike" Cyclic Peptide

J. Am. Chem. Soc. 2023, **145**, 24035

Cyclic peptides with 9-11 amino acids,
more than half should be *N*-alkylated, etc,.

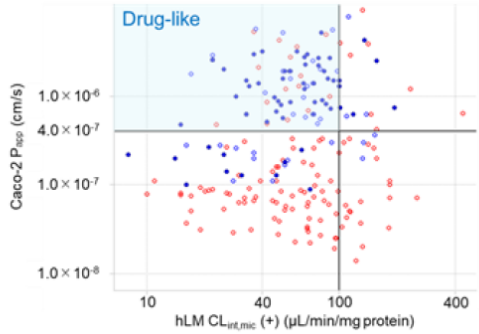


✓ *N*-alkylated amino acids (unnatural amino acids)



✓ Acceptable metabolic stability by appropriate ring size, and our cyclization methodology

✓ Compatibility of membrane permeability and metabolic stability is a key for "drug-like" peptides



	1st campaign ClogP < 12.9 or *N*-alkyl < 6 ○	1st + 2nd campaign ClogP ≥ 12.9 & *N*-alkyl ≥ 6 ○ + ●
drug-like (hLM-Caco-2)	15/116 13%	63/95 66%

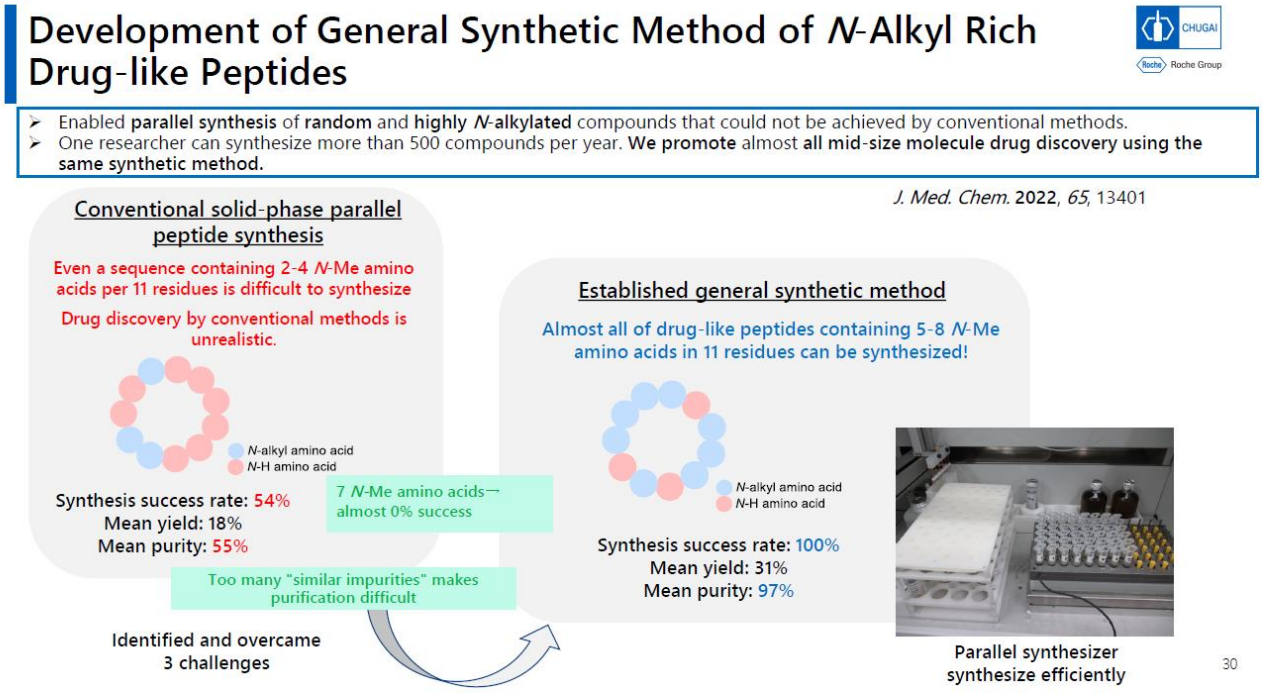
29

Broadly speaking, we've determined that for cyclic peptides to be considered drug-like, they should consist of 9 to 11 residues, with more than half of these being N-alkylated. N-alkylation refers to the modification of the amino group in amino acids, typically NH_2, as shown here with methylation. This alkyl substitution is crucial.

One of the challenges we've identified is the susceptibility of these compounds to oxidative metabolism by cytochrome P450 (CYP) due to their oily nature. This necessitates the development of cyclization methods that avoid oxidative metabolism.

Our extensive experimental data illustrates this point. The horizontal axis represents metabolic stability, while the vertical axis indicates membrane permeability. The compounds that fall into this specific region are considered drug-like. In the blue section, which represents the rules we've established for drug-likeness, out of 95 compounds, 63, or 66%, were assessed as drug-like based on these criteria.

Conversely, 13% of the compounds that did not meet our criteria still fell into the drug-like category. This suggests that while not all compounds that are drug-like fit these rules, a high probability of achieving drug-likeness is associated with possessing these characteristics. Consequently, we have decided to pursue drug discovery in this particular direction, focusing on these identified criteria.



While this part can be gone over quickly, we have faced considerable challenges in synthesizing peptides. The process of peptide synthesis has its advantages, such as parallel synthesis and automation using machines, which might lead one to think that a vast number of peptides can be produced. However, when applied, we find that it hardly produces what we really want.

For instance, the synthesis becomes exceedingly difficult with the presence of N-methyl in 11-residues. Even when attempting to synthesize sequences with two to four N-methyl groups, the results were far from satisfactory. Out of about 30 sequences attempted, only 54% were successfully synthesized, meaning nearly half couldn't be synthesized at all.

The yield was also low at 18%, and the most concerning issue was the purity, which was only 55%. With such low purity, it's impossible to determine what you're analyzing in an assay, rendering the peptides unusable. This is the state of peptide drug discovery, even in areas that are considered well-researched. The synthesis of peptides with numerous N-alkyl groups had not been optimized before our research.

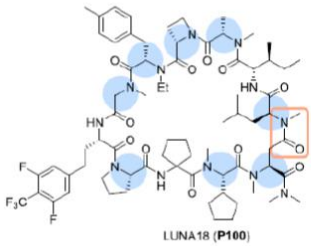
The average purity of 55%, with too many similar impurities, led us to conclude that efficient production was highly unlikely.

For peptides with more than half consisting of N-methyl groups, 6, 7, 8, 9 residues, synthesis was almost entirely unfeasible. Therefore, we began with the development of a new synthesis method. This method, reported in the Journal of Medicinal Chemistry (JMC) in 2020, has now achieved a synthesis success rate of 100% with an average purity of 97%. With this advancement, a single chemist can now synthesize over 500 compounds per year. In comparison, in small molecule synthesis, a chemist producing 50 compounds per year is considered highly productive. This significant increase in our productivity is a powerful asset in our research endeavors.

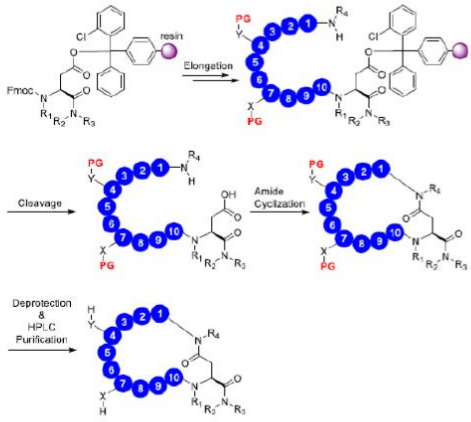
Development of General Synthetic Method of *N*-Alkyl Rich Drug-like Peptides

J. Med. Chem. 2022, 65, 13401

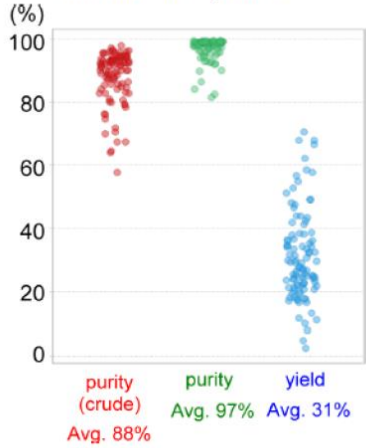
N-alkyl rich cyclic peptides



Solid phase synthesis method



Yield and purity of 100 peptides with various sequences



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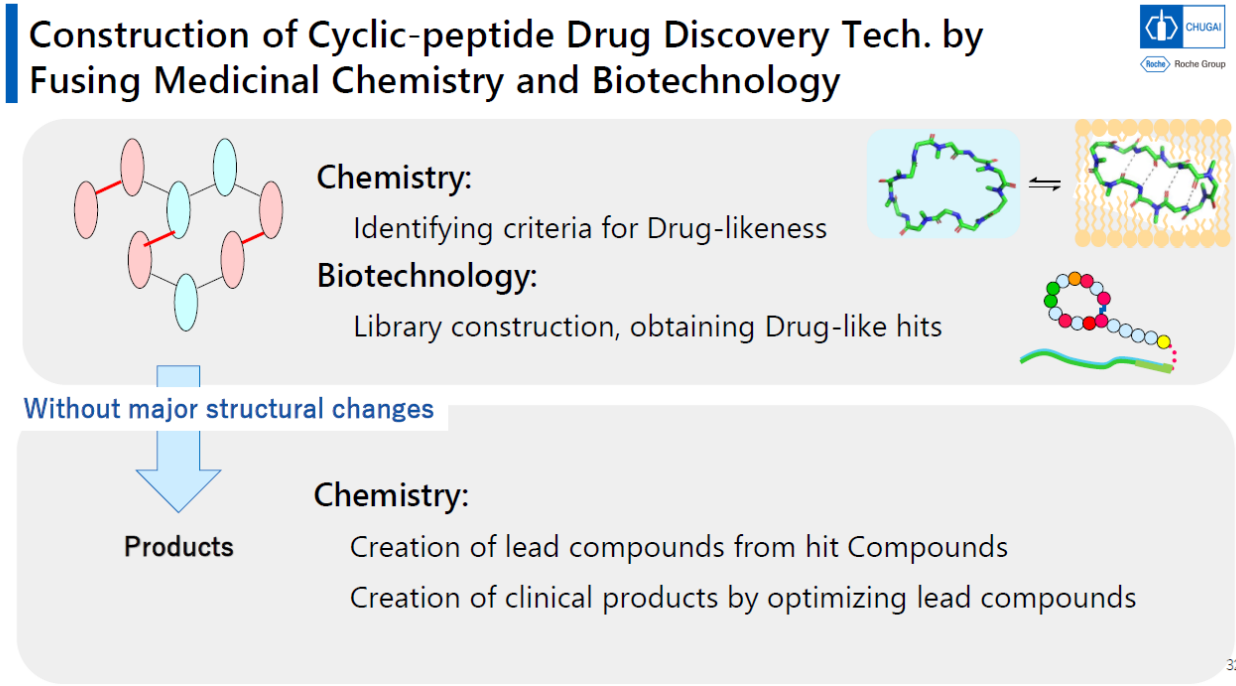
The experimental data show significant progress in the synthesis of cyclic peptides. Even with crude purity levels as low as 60%, after purification, which is a straightforward process and could be further optimized with more detailed work, we achieve much higher purities. This means that even at a production rate of 72 compounds overnight, we can attain such levels of purity, indicating a high degree of refinement in our current processes.

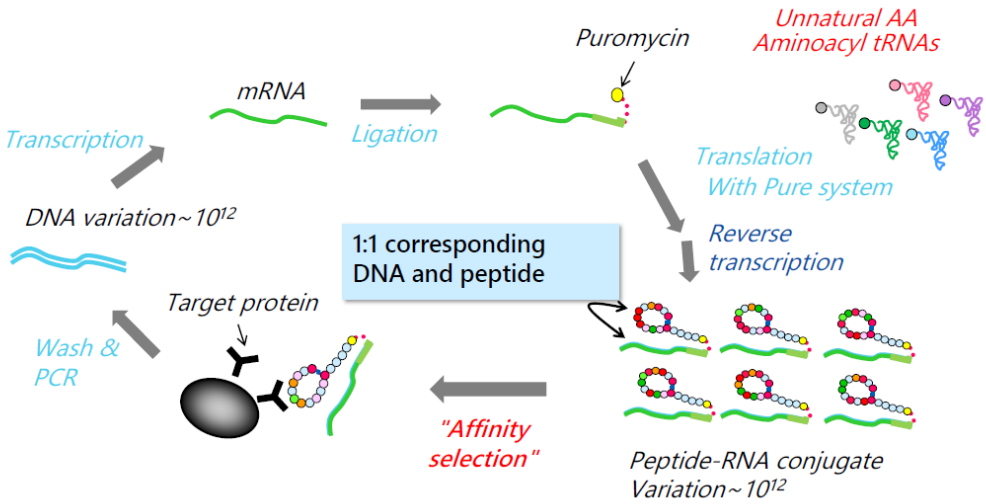


So far, I've discussed our strategy and chemistry for developing cyclic peptides and mid-size molecules. Our approach has been to identify drug-like hits and carry them through to clinical compounds without significant structural changes. Key to this strategy is a blend of flexibility and precise modification in manufacturing, ensuring the drug-like qualities of our products.

While this covers the production side, the next question is how we identify these hits. Here, we utilize biotechnology, including antibody technology. We possess strong capabilities in biotechnology, which we've integrated with our chemical sciences, a fusion we refer to as the synergy of bio and science. Through this fusion, we've developed new technologies and methodologies in drug discovery.

Biotechnology

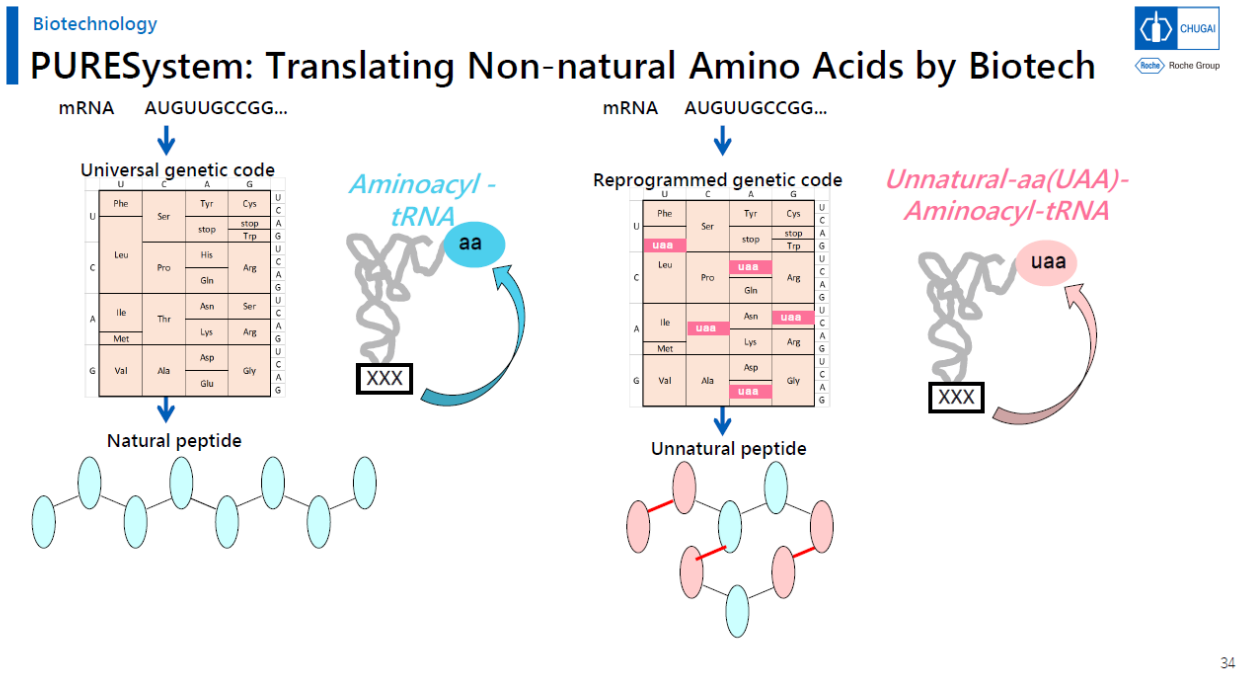
Drug-like Peptides with 10^{12} Diversity Could Be Achieved by mRNA Display



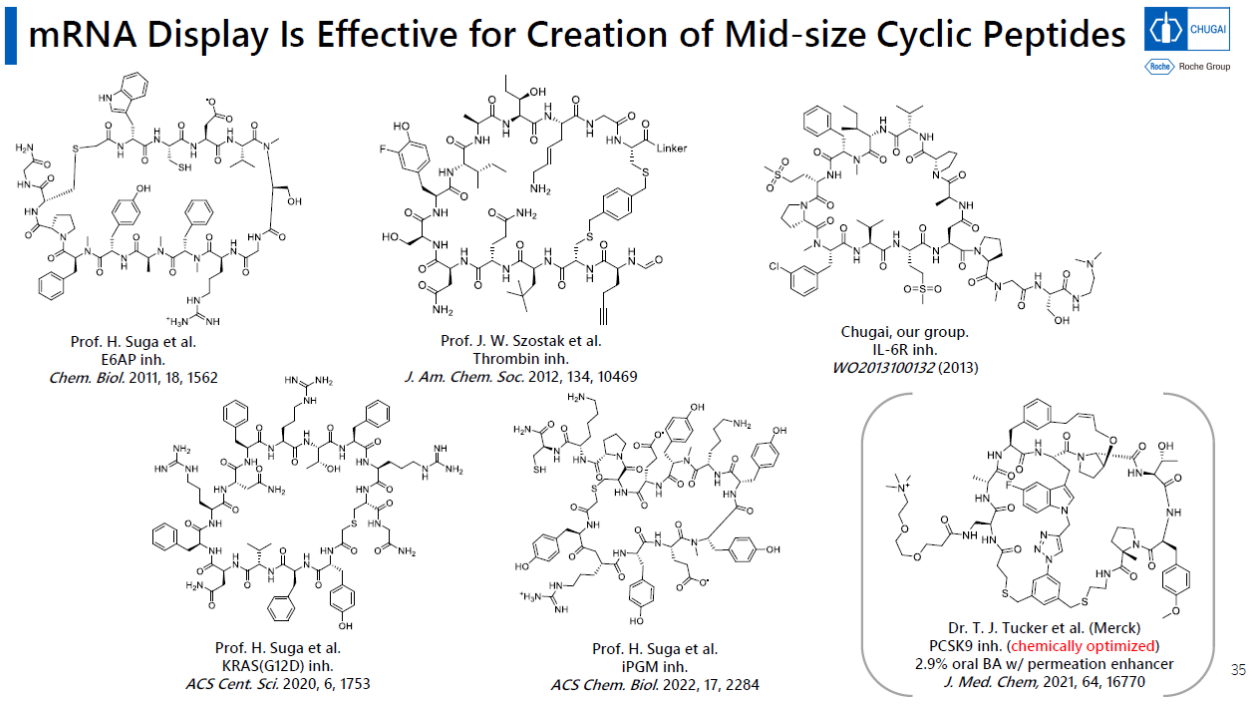
In our biotechnological approach, we employed a technique known as mRNA display. mRNA display is a well-known biotechnology method that involves chemically synthesizing 10^12 different DNA sequences. These sequences are processed through various stages to create a strong one-to-one binding between each peptide and its corresponding sequence, resulting in 10^12 unique peptide-DNA pairs.

Using this technology, we can evaluate 10^12 different peptides in a single flask. This massive parallel screening allows us to select peptides that bind to our target proteins, thus generating potential hits for further development.

A critical aspect of this process involves using an mRNA template to transcribe non-natural amino acids, thereby increasing the diversity of the peptides. A key system in this process is the PURESystem.



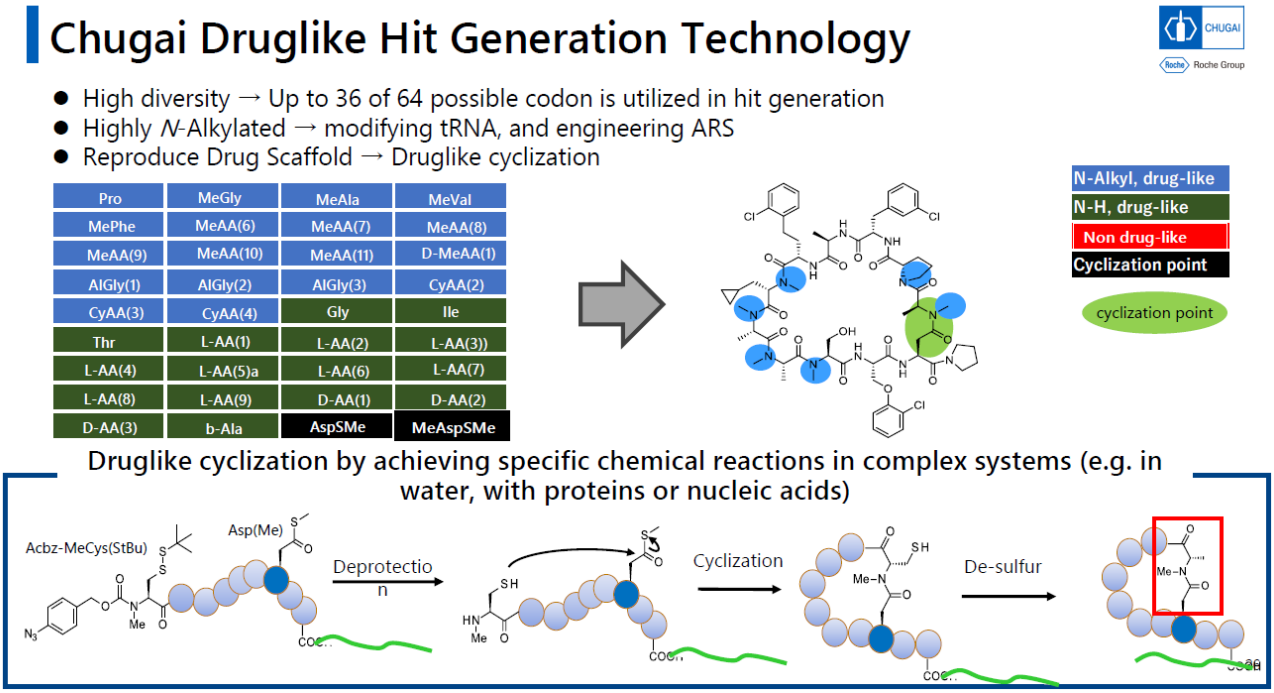
By utilizing the PURESystem, we have been able to expand the codon table to include non-natural amino acids.



Libraries using non-natural amino acids have proven effective for identifying hits in mid-size cyclic peptides. This has been progressively reported, with Suga in 2011, Szostak in 2012, and our own patent in 2013.

As I mentioned earlier, our methodology is characterized by its focus on drug-likeness. For example, our unique method of amidation in the presence of various proteins, RNA, and other impurities allows us to

establish a metabolically stable cyclization process. Additionally, out of the 64 codons available, we have now made it possible to use 32 of these for incorporating non-natural amino acids into our peptides.

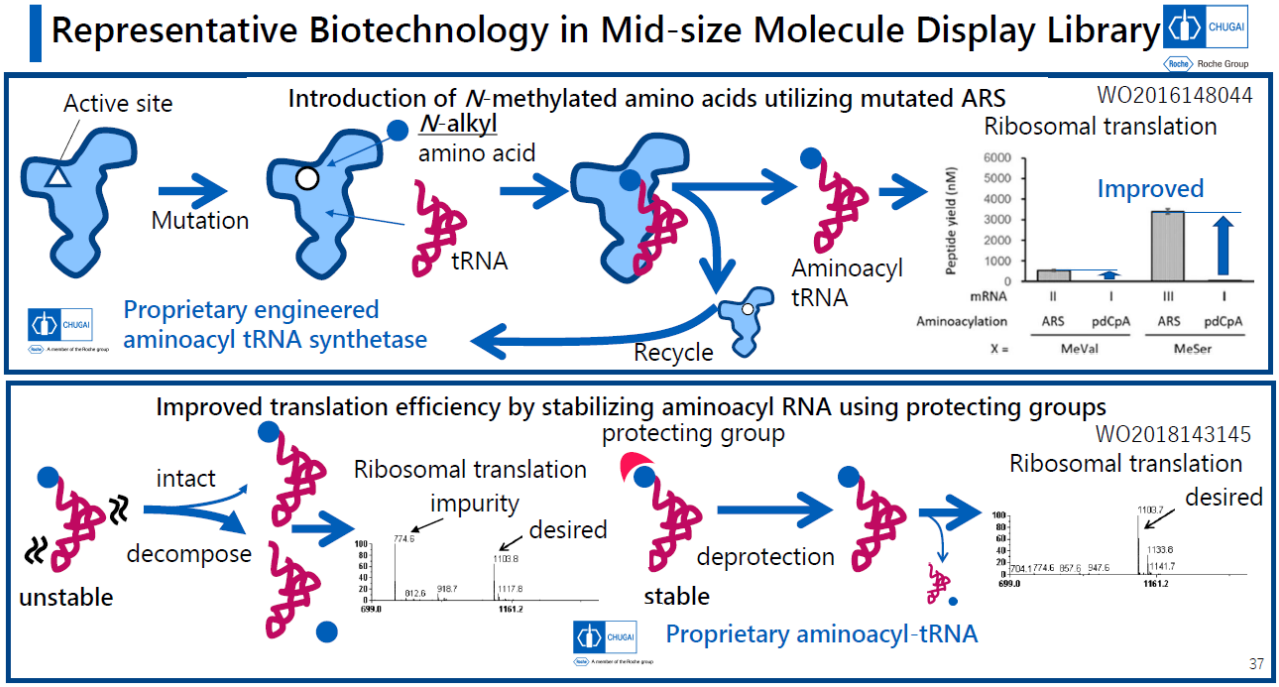


Understanding that there are typically only 20 kinds of amino acids in proteins, the role of expanding this number beyond 20 using biotechnology is immensely important. We recognize that being able to work with as many as 32 different amino acids is a significant achievement. While we haven't yet reported on finding more than 20, we have successfully expanded to 32.

The reason for this expansion to 32 amino acids is largely due to the limitations imposed by the natural variety of amino acids. While increasing the number of amino acid residues to 20 or 30 can make it easier to find hits, our understanding is that peptides with 20 to 30 residues tend not to be drug-like in the sense that they do not easily enter cells. Therefore, to achieve cell permeability, we focus on keeping peptides within a limit of 11 residues.

Adhering to this 11-residue limit increases the complexity of the task, necessitating an expansion in the variety of amino acids we use. Furthermore, more than half of these amino acids need to be N-alkylated. We persistently pursue this approach, using peptides where more than half of the amino acids are N-alkylated.

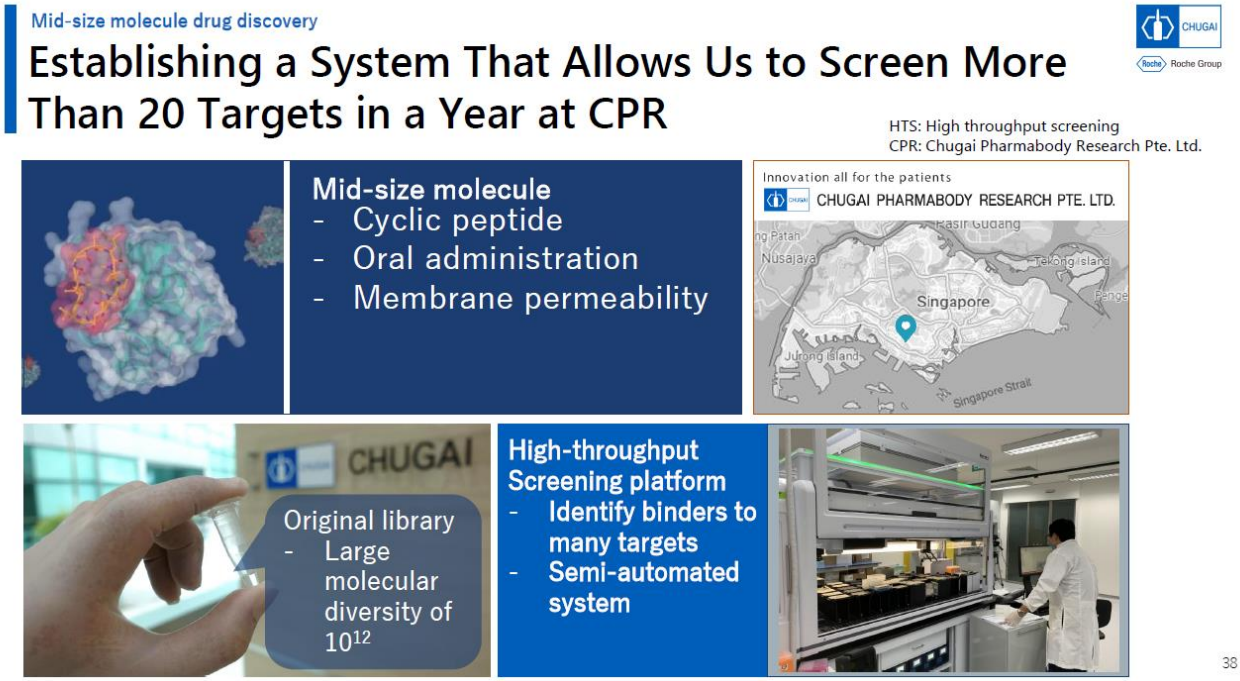
Translating peptides with N-alkylated amino acids into a form that is biologically recognized is extremely challenging. Moreover, to make this process practical on a large scale, we have had to develop various new technologies.



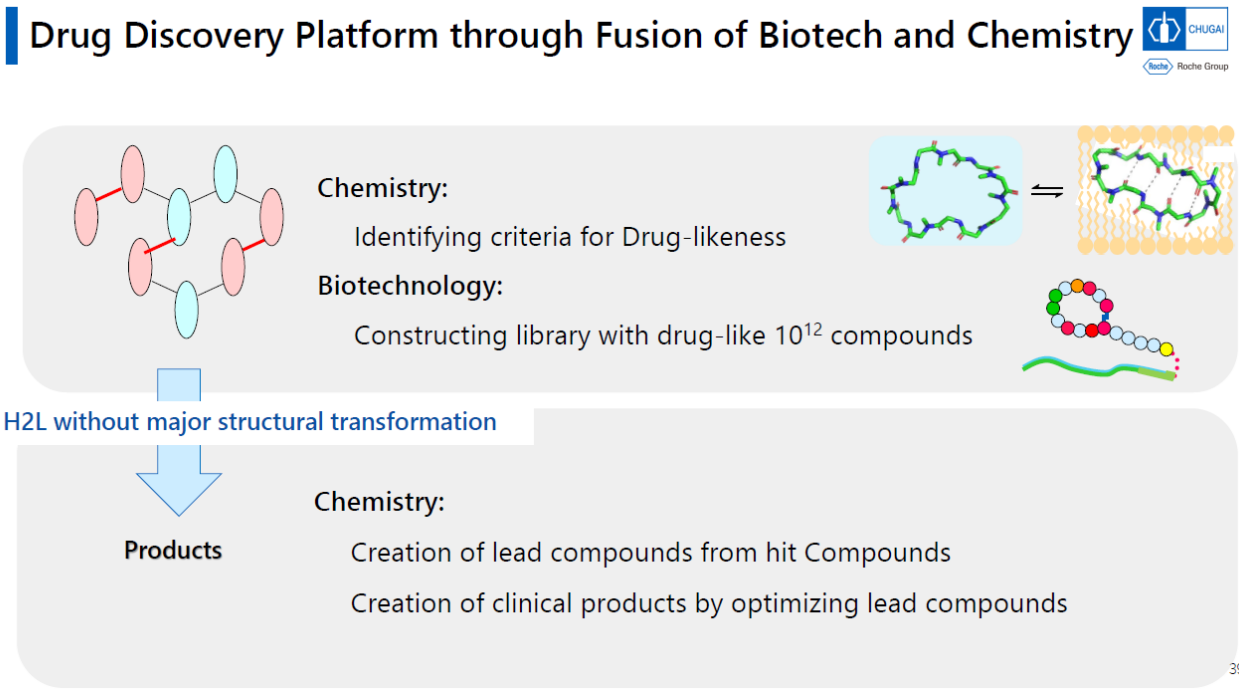
I'll present two representative examples. The first is aminoacyl tRNA synthetase, which plays a role in attaching amino acids to tRNA. When this enzyme is used in translational synthesis, it reattaches these dispersed amino acids. We have mutated this protein, which naturally recognizes only natural amino acids, to enable it to recognize N-alkylated amino acids. As shown here, this allows for translational synthesis using ARS.

The second development concerns the stability of the aminoacyl tRNA-amino acid complex, which is crucial for translation. Under normal conditions, this complex tends to degrade rapidly. Given our desire to incorporate a wide variety of amino acids, degradation would lead to extremely low translation efficiency. To address this, we've applied protective groups to the amino acids chemically. These groups are gradually deprotected in the reaction system, enabling us to establish a highly efficient translation system.

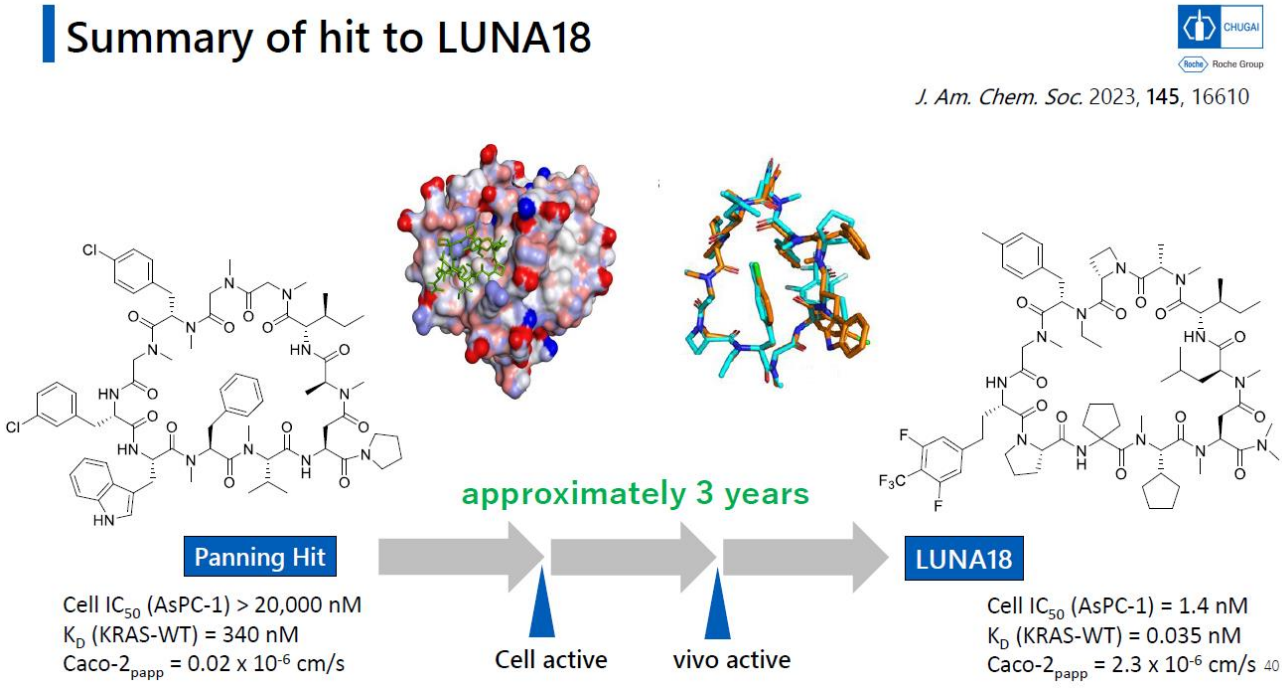
As I've mentioned, achieving drug-likeness is a significant challenge in biotechnology. We've taken pride in identifying the essential elements needed to realize this goal and systematically addressing each challenge to evolve our technology into a practical and effective tool for drug discovery.



We are currently utilizing our advanced technology at CPR, our research subsidiary based in Singapore. This has enabled us to set up a system capable of generating hits for over 20 targets annually.



As I have mentioned earlier, the fusion of chemistry and biotechnology has been pivotal. We've established drug-like criteria through chemistry and generated hits using biotechnology. These hits, by our definition, are drug-like and can be advanced to clinical candidates without significant structural changes. The transition from hit to lead and then to industrial production has been primarily managed by our chemistry team.



The accompanying diagram illustrates our hit to lead process, particularly with a RAS inhibitor. On the left, we have the initial hit, and on the right, the clinical compound. When overlaid, you can see a high degree of alignment in the peptide backbone.

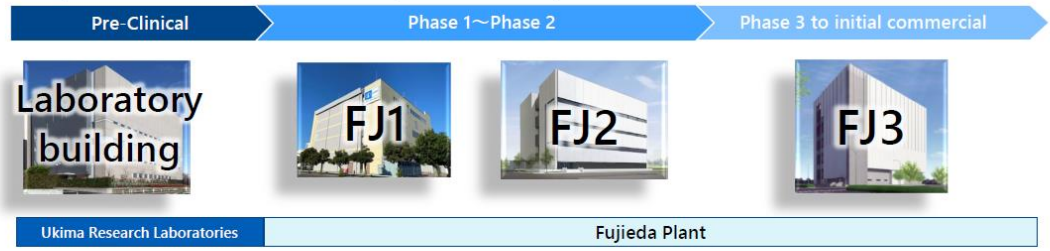
This exemplifies the success of our concept: retaining the original scaffold while optimizing through minor modifications.

For instance, a compound that initially showed almost no cell activity improved to 1.4 nM, and its affinity improved from 340 nM to 0.035 nM, a substantial improvement by any measure.

This process took approximately three years, a period during which our synthetic methods have significantly improved, contributing greatly to these advancements.

Set up of Production Facilities

- Acquired advanced technologies for EHS as well as small-and mid-size molecule with high pharmacological activity
- Build a consistent in-house supply system from manufacturing process development and early clinical development to initial commercial production by 2025



Start of Operation	2020	2003	Dec. 2022	Scheduled in Mar. 2025
Total floor area	4,925 m^2	5,417 m^2	6,190 m^2	10,250 m^2
Total investment	4.5 billion yen	7 billion yen	19.1 billion yen	55.5 billion yen

EHS: Environment, Health and Safety 41

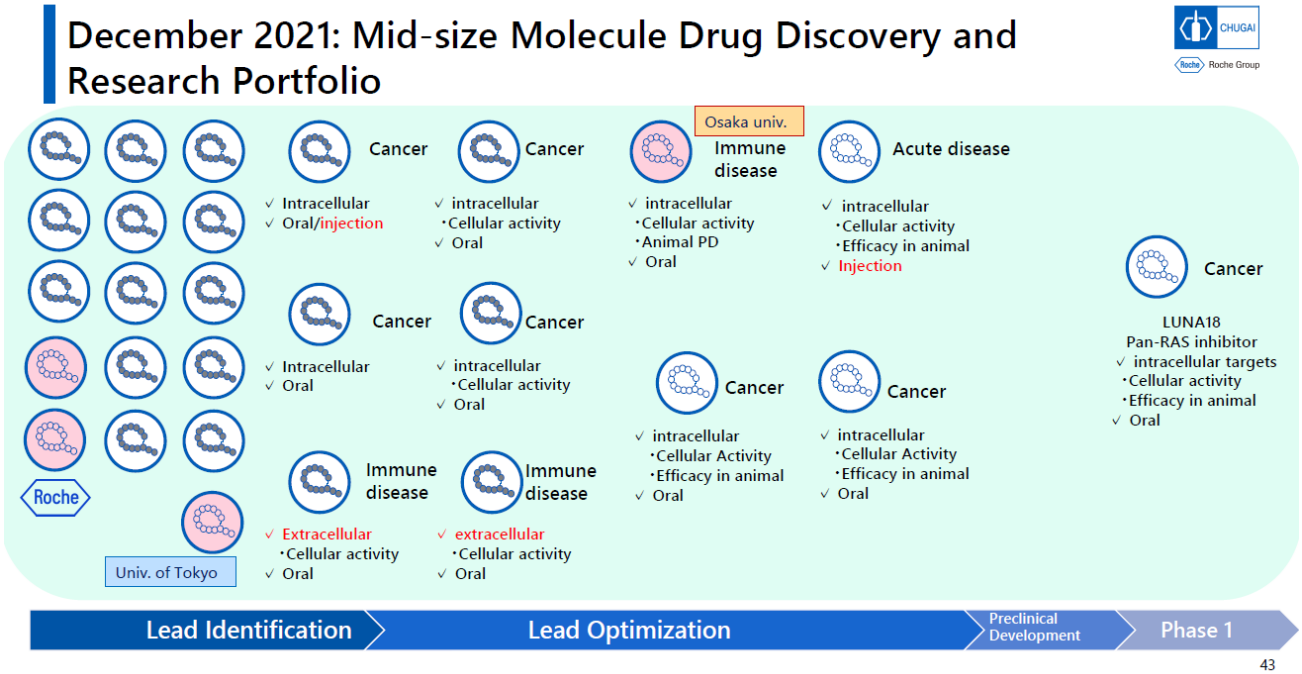
Moving on to manufacturing, due to the need for precise synthesis, we have invested approximately JPY90 billion in setting up new facilities.

Our recently inaugurated facility, FJ2, operational since December 2022, has been awarded a prestigious honor, the Facility of the Year Awards by the International Society for Pharmaceutical Engineering.

The award was given for our advanced containment measures. Containment refers to preventing any contamination of the compounds, both to the external environment and to the workers.

We have placed significant emphasis on this aspect. As I mentioned earlier with the Alecensa example, we are committed to achieving high potency in our compounds and ensuring a high therapeutic window to minimize off-target effects. This principle applies across both small and large molecules in our drug discovery efforts.

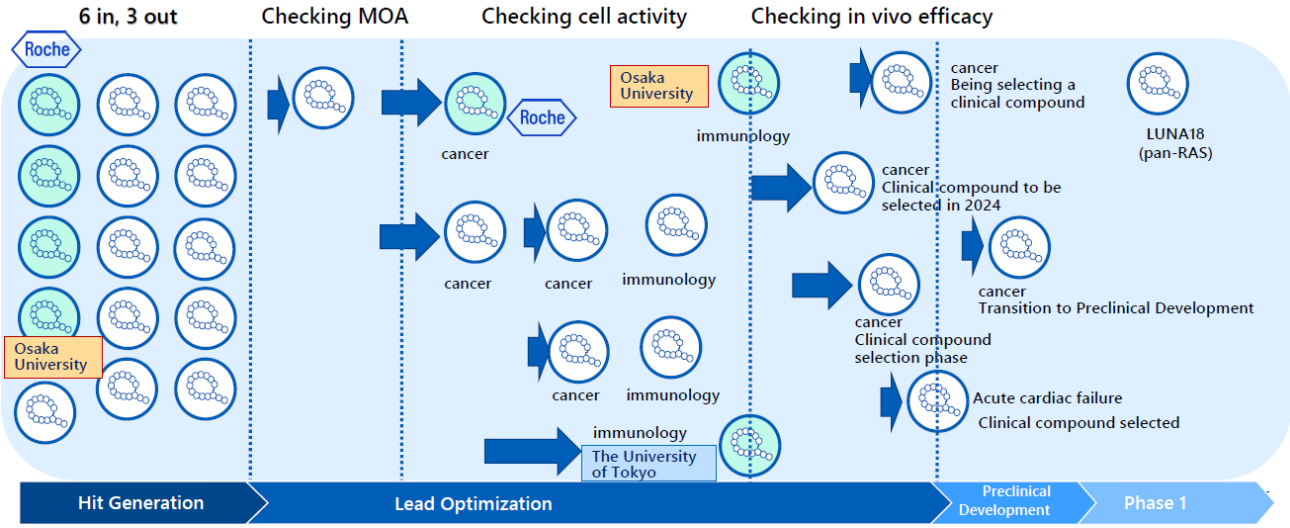
This focus on high potency was a request from our research team. We needed facilities capable of handling highly active compounds. Initially, our request was met with resistance from our manufacturing team, with claims that such technology did not exist and the task was impossible. However, we clarified that our goal wasn't profit-driven or about reducing cost of goods. Instead, it was about the quality of the pharmaceuticals, to enhance efficacy and reduce side effects. After we made this point, there were no further objections, and they proceeded to construct the facility. This achievement, I believe, is a testament to Chugai's strength. Please excuse my pride in sharing this.



This slide presents an update to our mid-sized molecule portfolio, which was originally introduced two years ago.

December 2023: Mid-size Molecule Platform Update

Aim for a consecutive portfolio in from 2023



Firstly, LUNA18, a pan-RAS inhibitor, is currently in Phase I clinical trials. Our second oncology compound is now transitioning into preclinical development and is close to entering clinical trials, with GLP-Toxicology Studies underway.

The third compound targets acute cardiac failure. The clinical candidate has been selected, and we are currently gathering final data to decide whether to proceed with GLP-Tox Studies.

The short arrows on the diagram indicate progress over the previous two years, crossing one step as represented by the dotted line. The medium-length arrows signify two steps of progress, while the longest arrows represent three steps of advancement.

As shown, there are three other compounds where in vivo efficacy has been confirmed, and clinical candidates are being selected. Each of these has progressed by one or two steps.

Seven compounds, including tough targets that have demonstrated cell activity and cell penetration, have made critical advancements in the past two years.

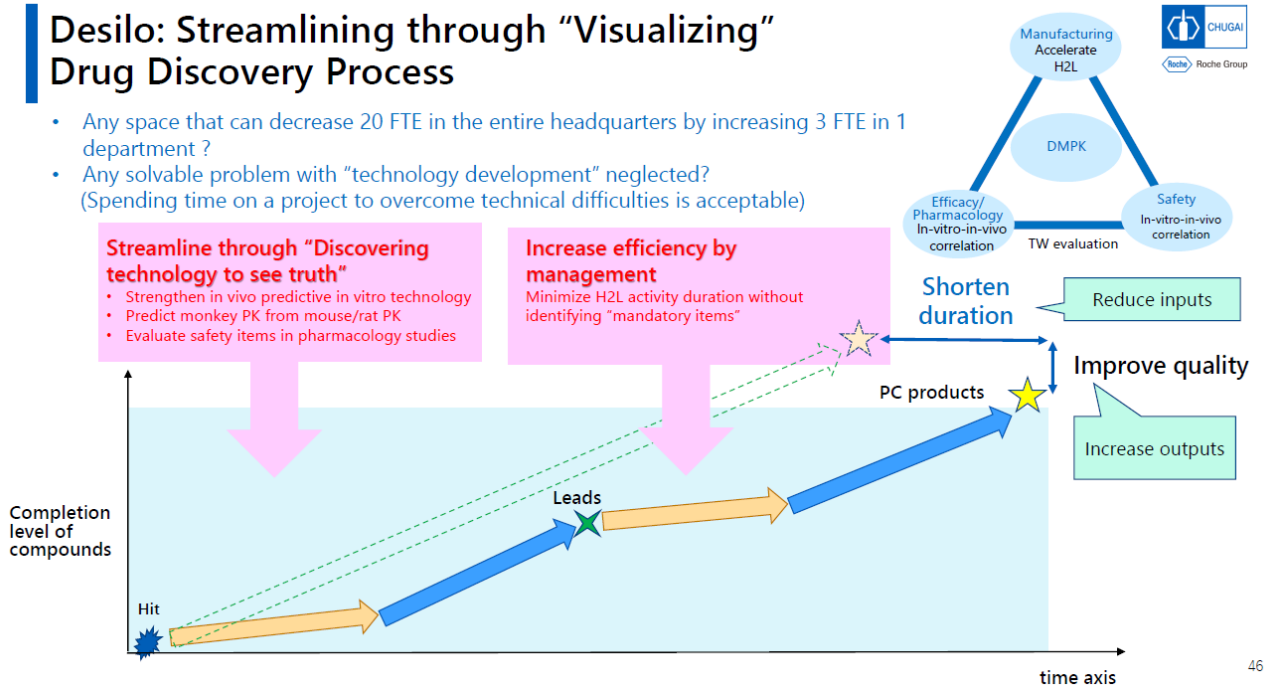
Among these, there's a compound from our joint research with Roche, which has advanced two steps in two years, showing cellular activity. We have four ongoing joint research projects with Roche. Similarly, our collaboration with the University of Tokyo has advanced by three steps, showing the beginning of in vivo efficacy.

However, one project in collaboration with Osaka University hasn't progressed as expected over the past two years, presenting challenges with its mode of action. We had to re-initiate the hit generation process, but we are making steady progress.

Overall, our portfolio has significantly expanded, and our understanding of our approach has solidified. We are confident that we are moving closer to a sustained environment for drug discovery.

I'd like to shift focus from the technical aspects to other initiatives, primarily concerning our mid-sized molecule efforts.

As already announced, the Chugai Life Science Park Yokohama commenced full-scale operations in April this year. This has consolidated our research functions, previously split between Gotemba and Kamakura, into a single hub to enhance communication.



However, it's important to note that having a building alone isn't sufficient. While the facility is crucial, it's the systems and processes within that drive innovation.

For example, we've successfully integrated biology and chemistry, and our next goal is to fuse dry and wet lab approaches. Before this, we've worked extensively on breaking down silos within the organization.

Drug discovery research at Chugai Pharmaceutical, particularly in preclinical stages, typically spans over a decade. Communication between early and late-stage researchers isn't always as smooth as it could be. It's not uncommon for many individuals to lack a comprehensive understanding of the entire drug discovery process, a situation that might be true for many companies, including ours.

When there's no common foundation, each department tends to follow its own set of values, which can lead to misalignments in discussions and decision-making.

I often use an analogy within the Company, comparing this to Mitoma's one millimeter in soccer. Whether the ball is in or out of the line depends on the angle you're viewing it from. Similarly, perspectives in drug discovery can vary greatly depending on one's viewpoint and position within the process. This highlights the complexity and subjective nature of our work.

This siloed perspective in drug discovery is akin to different viewpoints on a single situation. What seems off from an early-stage perspective might appear on target from another angle.

Each perspective is valid in its own right, but aligning these into a cohesive whole is challenging. This is the essence of siloization. To address this, we have been working on visualizing the drug discovery process to create a common understanding. This approach is aimed at improving productivity by fostering better collaboration between early and late-stage research teams.

Creating an environment where communication flows smoothly is crucial. The Yokohama platform, with its setup, promotes more active and efficient communication.

In this graph, the horizontal axis represents time, while the vertical axis indicates the degree of compound completion, specifically the completion level required for clinical trials. In the drug discovery process, there are periods where the quality of compounds increases effectively from the point of hit identification, and periods where there is no improvement at all. Antibody researchers and chemists are quite aware of this, but many in the evaluation departments have not been conscious of this reality.

When I first showed this slide, people from the evaluation departments were quite surprised. The reason this reaction occurs is due to the current evaluation systems not accurately reflecting clinical or in vivo conditions, leading to struggles and uncertainties about what should be done next. Even our established assay systems are, in fact, far from complete. If these systems were improved, it would significantly increase the success rate of drug discovery. The low success rate in drug discovery indicates that these systems are still unfinished, and there's substantial room for improvement and action.

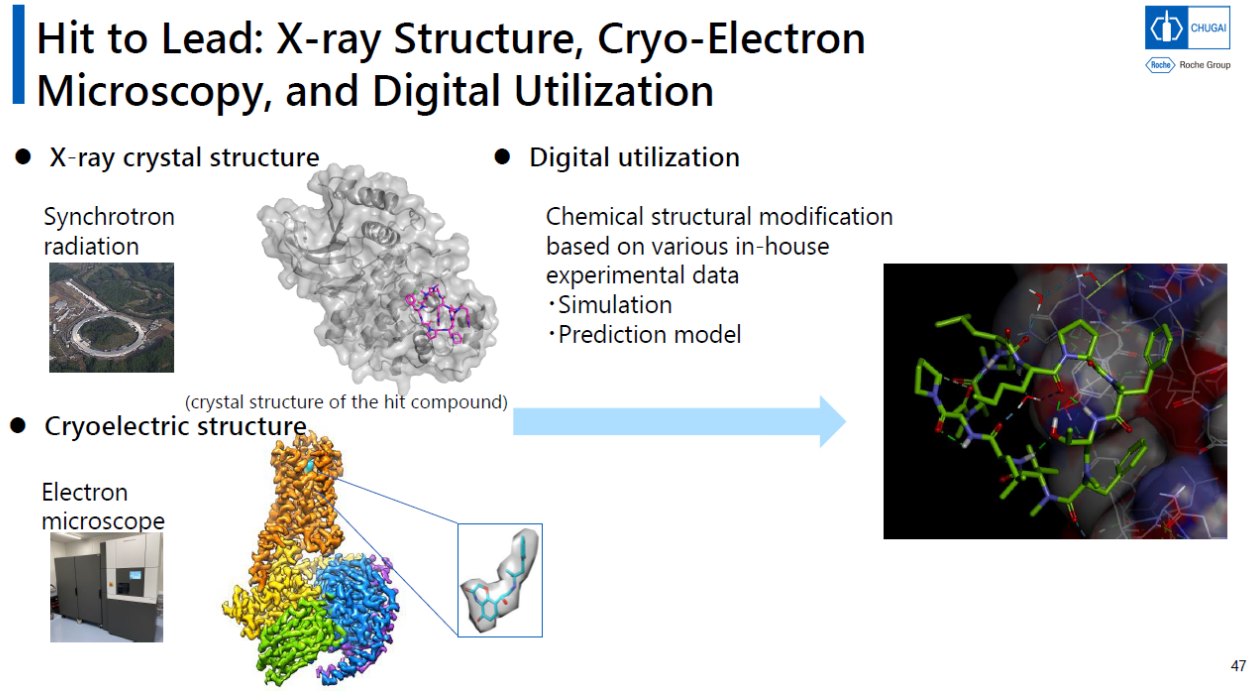
This recognition led us to explore areas where technological development could provide solutions yet had not been addressed. When it comes to accelerating a single project, there's a paradox: focusing on technological development can slow down the process, so often, nobody undertakes it. However, at Chugai, speeding up means collective acceleration. We encourage investing time in technological development for a project, with the understanding that the benefits will be reaped in subsequent projects. This is our value proposition.

Given these considerations, platforms like mid-sized molecules or antibodies, which are more standardized, can greatly benefit from such a focused approach.

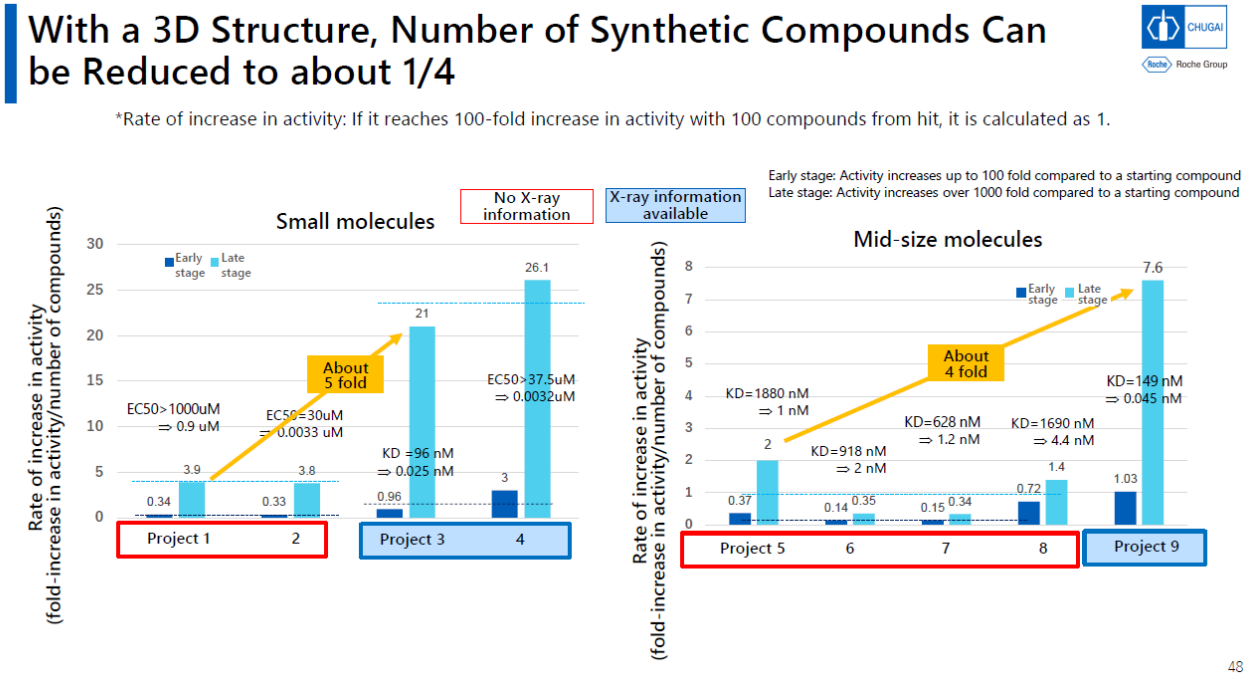
In reality, our ability to continuously refine and evaluate our techniques has become a recognized strength. We are moving towards an era where not only our drug candidates creation but also our evaluation systems will be considered a key strength of Chugai.

Furthermore, the progress in breaking down silos has led to some interesting insights. For instance, adding three people to one department can effectively save the equivalent of twenty people's effort across the entire drug discovery process. This understanding enables us to strategically allocate resources to departments that, though seemingly taking work away, actually enhance overall efficiency in drug discovery. As we eliminate these yellow areas or inefficiencies, we not only shorten the overall time for drug development but also hope to achieve higher quality outputs. We believe this approach is already beginning to show its effectiveness.

Hit to Lead: X-ray Structure, Cryo-Electron Microscopy, and Digital Utilization



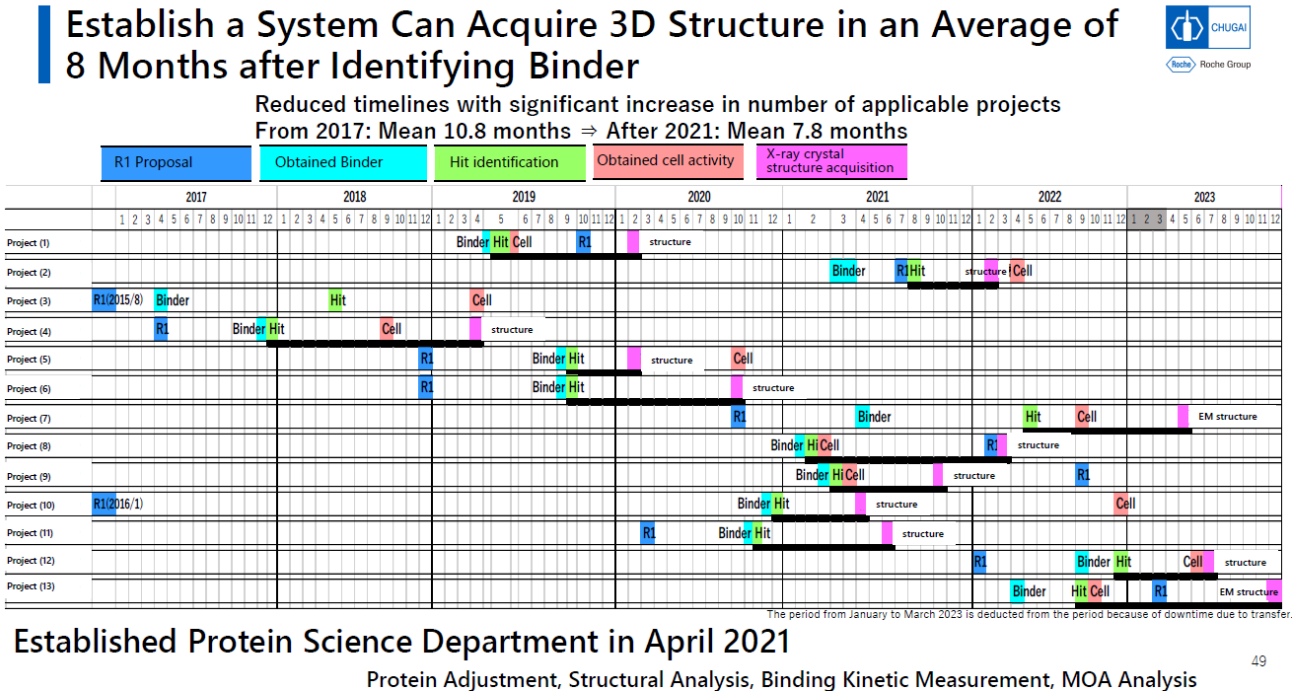
This is one example, but we have introduced cryo-electron microscopy (cryo-EM). It has been two years since its implementation, and it has brought about significant changes. It's not just the introduction of cryo-EM, but also its integration with digital technologies. This integration has led to several developments.



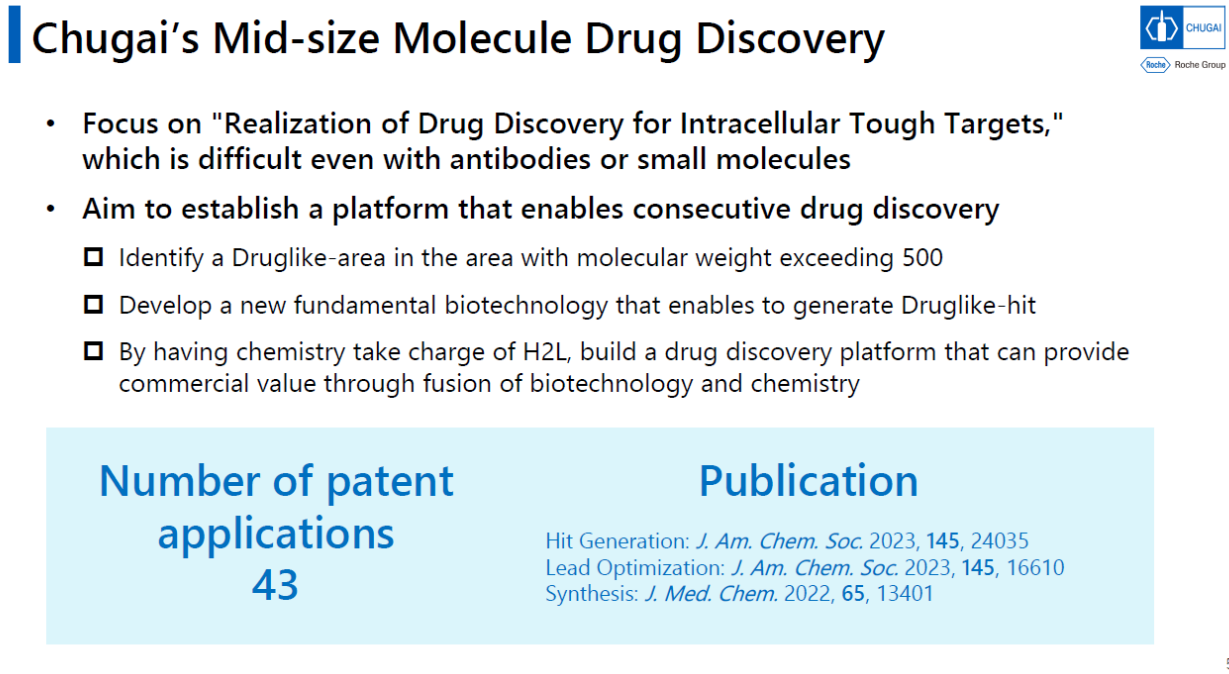
With cryo-EM, we can view the three-dimensional structure of how a protein binds with a compound. This capability greatly enhances the precision of compound design. We systematically evaluated the difference this technology makes in productivity, as shown in this figure. Whether in small or mid-sized molecule development, we observed that the process could be up to four times faster.

Traditionally, crystal structures were mainly utilized in the final stages of the hit to lead process. It usually took about three to four years to reach a stage where a compound was decided upon, and only then would the crystal structure confirm our hypotheses or provide new insights.

However, if we could obtain this structural information in the early stages of hit to lead, the process, which typically takes four years, could be significantly shortened. Even if it's not reduced to a quarter of the time, halving it would still have a tremendous impact.



The implementation of this value-driven approach has led to significant progress. Now, just eight months after binder identification, which is about 20% of the typical four-year hit to lead phase, we are able to obtain crystal structures. This advancement has considerably shortened the subsequent stages of hit to lead.



In summary, Chugai Pharmaceutical's mid-sized molecule drug discovery focuses on addressing intracellular tough targets, which have been challenging for both antibody and small molecule drug discovery. We are committed to establishing a platform capable of continuous drug discovery, not just one or two successes, but a system that allows for sustained innovation.

We have identified a drug-like area in the molecular weight range exceeding 500. New foundational biotechnologies have been developed to capture these drug-like hits.

By having chemistry handle the hit to lead phase, we've created a drug discovery platform that merges biology and chemistry, offering commercial value.

To date, we have published three papers on these topics and have filed 43 patent applications.

Thank you for your attention.

Miyata: Thank you.

Question & Answer

Miyata [M]: We will now begin the question-and-answer session. To allow as many participants as possible to ask questions, we request that each person limit themselves to two questions.

Muraoka [Q]: My name is Muraoka from Morgan Stanley. Thank you for the passionate presentation. Your enthusiasm for the future of peptide products was clearly conveyed, and I'm genuinely excited about what's to come. Unfortunately, I must admit that I may not have fully grasped even a tenth of the chemical aspects of today's presentation, so my question might be quite basic.

I would like to ask about LUNA and RAY121. If I remember correctly, you are taking time to detect toxicity in LUNA, leading to delays in Phase I results. With all the efforts your company is making to improve predictability, can we expect fewer unexpected delays in your future pipeline, similar to what happened with LUNA? I understand that there are no guarantees, but if it's possible to think along these lines, could you explain what efforts are being made in this regard?

Iikura [A]: I'll respond to that. Regarding LUNA, I can't provide specific details about the current clinical trials. However, during the clinical development of LUNA, we gained significant insights. These learnings are being actively applied to our subsequent projects, as per the third principle I mentioned earlier, involving back-translation and the development of new technologies.

In that sense, we hope to reduce unexpected events, as failing to do so would delay delivering medications to patients. As LUNA is one of our initial mid-size molecule projects, we are proceeding with considerable caution. The first three or four projects may progress cautiously, but as we continue, I believe we will become more adept at handling these compounds. Did that answer your question?

Muraoka [Q]: Could you delve deeper and share specific improvements or details about what exactly happened?

Iikura [A]: At this stage, no, it's difficult to share more specific details.

Muraoka [Q]: Understood, thank you. My second question might also be difficult to answer, but I'll ask about RAY121. I remember it was introduced last year. I recall that it was being developed simultaneously for six different indications. Is this approach feasible because the target, which has not been publicly disclosed, is validated in various ways, making it possible to progress all at once? Or is it because RAY121 is targeting a first-in-class pathway, but due to your company's experience, you can develop it simultaneously? Could you provide some background on why RAY121 is so interesting?

Igawa [A]: Regarding RAY121, while I cannot disclose the specific target, it is an antibody drug targeting a very important pathway. Currently, Phase Ia is underway. If we get positive results here, meaning if the antibody functions as we anticipated non-clinically, then we will proceed with simultaneous development for six diseases linked to this pathway. The diseases have already been identified.

Among these six, some have a higher probability of success, while others might be less certain but have a high unmet medical need. We selected these six diseases based on these criteria and are progressing with parallel development.

Muraoka [Q]: Is this a situation where more information will make things clearer, like "Ah, I see how it's progressing," or is it more like "So this is how it turned out"? Which possibility seems more likely?

Igawa [A]: I think it's more of a "Ah, I see" kind of situation.

Muraoka [M]: I see. Understood. Thank you. That's all from me.

Hashiguchi [Q]: I am Hashiguchi from Daiwa Securities. I'd like to start with a basic question. You mentioned that among the various applications of mid-size molecules, your company is focusing on cell-penetrating peptides.

Could you elaborate on why you chose this focus? Is it because cell-penetrating peptides are more likely to lead to innovative, unprecedented drugs compared to other methods, or is there a technical reason behind this choice? Conversely, does this mean that once you've developed cell-penetrating peptides, other technologies become relatively manageable, or is it that each technology has its own challenges, and you've chosen to focus on this area? I'm particularly interested in the technical aspects.

Iikura [A]: In the global context, the technical challenge of transporting mid-size molecules into cells is quite high. Our systematic investigation in this area is a first-of-its-kind endeavor.

The reason for focusing on intracellular targets is that, amidst the vast array of proteins, only about 20% can be targeted by antibodies and another 20% by small molecules. Considering the numerous effective drugs developed for these targets, the remaining 60% of untapped potential offers significant opportunities for new drug discoveries, despite the high technical barriers.

For instance, regarding antibody mimics in the middle of the slide, we are indeed capable of developing such mimics using our technology and are currently working on some in our platform.

Hashiguchi [Q]: Thank you. For my second question, related to page 46, you mentioned Chugai's strengths in evaluation and future prospects. When it comes to moving beyond the lead stage, I believe the assessment methods need to be individualized for each disease.

I had some difficulty understanding how this fits with the technology-driven approach you mentioned at the beginning, without a particular focus on diseases. Could you clarify what differentiates your approach from others in this respect?

Iikura [A]: Thank you for your question. Let me clarify.

While we say we're not focused on specific diseases, creating pharmacological in vivo models and acquiring expertise in all areas internally is quite challenging. Therefore, we believe collaboration with external partners is crucial in certain aspects.

On the other hand, there are many foundational elements common to all pharmaceuticals, such as safety, pharmacokinetics, and formulation. These are universal issues across all drug development areas. In these aspects, there is still much room for human advancement, and we are actively working on developing technologies that can effectively bridge preclinical and clinical studies.

One thing we've learned from working with antibodies is that once we establish a system for one, it can often be applied to other projects, leading to increased efficiency. We're beginning to see that cyclic peptides can also be treated as a sort of scaffold, given their relatively similar properties. By developing technologies in this way, we aim to enhance the effectiveness and value of our pharmaceutical products.

Of course, we apply this approach to pharmacology as well. In areas like oncology, where we have considerable expertise, we'll continue our efforts, but for all-encompassing areas, we're choosing to leverage external collaborations.

Hashiguchi [M]: Thank you very much.

Hashimoto [Q]: I'm Hashimoto from Nikkei BP. Thank you in advance. First, I want to ask about the mid-size molecule platform. I understand that it enables us to target the remaining 60% of proteins, but compared to the typical small molecule drug discovery platform, can the hit to lead time be shortened? Also, regarding hit generation to successful development, is the probability of success using this mid-size molecule platform higher than with small molecules, or is it comparable to small molecule drug discovery? How do you view this?

Iikura [A]: First, I'd like to correct something in my earlier explanation. While I believe it's true that about 60% of protein targets are inaccessible to both small molecules and antibodies, it's not yet clear what percentage of this 60% can be targeted by mid-size molecules.

If we could target even 20%, it would be a significant leap, equal to the current impact of antibodies and small molecules. Gradually expanding into this area is something we should pursue.

Regarding the success rate of this approach, first of all, I think it's fair to say that as a platform, this methodology is quite new. However, regarding the potential of cyclic peptides becoming pharmaceuticals, there is already precedence with drugs like Cyclosporine, which has been used safely for 30 to 40 years, especially in organ transplantation. Recently, there's also Voclosporin. So, I don't think it's unlikely that this modality can lead to viable drugs.

From the results of our animal studies, I believe that this modality has the potential to yield effective drugs.

Comparing it to small molecules, based on our preclinical data, I don't see this modality as being inferior. When it comes to the platform, another factor to consider is that, like antibodies, when pioneers in this field emerge, they tend to choose promising targets for drug discovery, which in turn might increase the probability of success.

With mid-size molecules, we're targeting areas that have long been challenging to drug, so many of the targets we're working on are first-in-class. This gives a certain degree of confidence in the targets, so I hope the success rate will be good, perhaps even better than current small molecules. However, we can't say for certain until this is proven in clinical trials, so we're proceeding with that mindset.

Hashimoto [Q]: What about the speed aspect?

Iikura [A]: I believe it's faster. As I mentioned earlier, a chemist in our company might typically produce about 50 new compounds a year, but now, with our platform, they can produce around 500. Regarding the LUNA case, I mentioned that the hit to lead phase took about three years. As we continue to develop higher quality compounds, I don't necessarily expect this timeframe to shorten significantly.

We currently estimate about four years for small molecules, and we hope to achieve it in three years for mid-size molecules. As we better understand the characteristics of these as a Scaffold, I anticipate we will be able to increase efficiency in various areas.

Hashimoto [Q]: So, do you expect the efficiency of drug discovery to increase further?

Iikura [A]: Yes, I expect it to increase.

Hashimoto [Q]: Earlier, there was a mention of targeting multiple diseases from an early stage, which hasn't been done before. What changes or approaches have you made to realize this strategy of targeting multiple diseases from the early stages?

Igawa [A]: Thank you for the question. In the past, like during the era of Actemra, the primary focus was on obtaining approval, and all efforts were concentrated there.

After getting approval, the expansion of indications was mainly based on reports from doctors using the drug in practice and noting its effectiveness in certain diseases. We would then gradually expand its indications based on such information from the medical community. A recent example of this approach is with COVID-19.

However, with RAY121, we changed our strategy. While we decidedRAY121's primary disease target, we also proactively gather evidence and data to target additional diseases that we believe the drug could be effective against. Previously, we expanded indications using available data, but now we actively collect our own data to support the expansion into new diseases. This is a fundamental change in our approach.

Of course, this means that more resources are required in the initial stages of development due to the various consideration we conduct. However, if the project justifies the investment, we are willing to allocate these resources from the early stages to maximize the value and develop the drug for multiple diseases. Does this answer your question?

Hashimoto [M]: Yes, thank you very much for your explanation.

Watanabe [Q]: I'm Watanabe from The Chemical Daily. Thank you for today. On slide 44, the pipeline update, there were introductions to two compounds for cancer and acute heart failure following LUNA18. Although it may be premature, could you explain if these two compounds possess any clinical potential, especially something that antibodies and small molecules haven't achieved yet?

Iikura [A]: We believe in their potential, which is why we want to proceed to clinical trials.

Watanabe [Q]: Can you specify what kind of potential they have, something that hasn't been seen before?

Iikura [A]: I apologize, but we are not yet in a position to disclose even the disease targets, so I ask for your patience a little longer. I'm sorry.

Watanabe [Q]: Understood. Just to confirm, these targets are the truly novel intracellular targets you mentioned earlier, which couldn't be targeted by antibodies or small molecules, correct?

Iikura [A]: Yes, that's correct.

Watanabe [Q]: Understood. Regarding these targets, have you observed any anti-tumor effects or similar outcomes in specialized mouse models, like PDX mice?

Iikura [A]: In our pipeline, under the second dotted line, there's a section titled in vivo efficacy confirmation. Everything listed there has shown clear efficacy in animal models. We believe the efficacy is strong enough to warrant advancing these compounds to clinical trials.

So, at this stage, our focus is on ensuring that these candidates meet the highest quality standards possible with current technology.

Watanabe [M]: Understood, thank you for your response.

Matsubara [Q]: I'm Matsubara from Nomura Securities. Thank you for the presentation. I was looking at pages 31 and 32 about the synthesis of alkylated peptides. I understand that the manufacturing process is challenging, but the yield is shown as an average of 31%. There are often papers suggesting that using both solid-phase and flow synthesis methods can improve efficiency. What measures is your company taking to improve this, and how are you addressing these challenges?

Iikura [A]: Thank you for your question. The data you're referring to is from a paper we reported in 2022, and we have made improvements since then.

Regarding the yield of 31% at the hit to lead stage, I actually think that's quite high, especially considering there are 24 steps in the process. If each step had a 90% yield over 10 steps, the overall yield would only be about 9%, so achieving 31% over 24 steps suggests that the yield per step is probably around 97% to 98%. That's quite efficient.

Could you please show the next slide? There are some yields less than 10 here, but if a compound shows promise and we synthesize it individually, we can significantly improve the yield.

So, this 31% yield is more indicative of a standard protocol used for random synthesis during initial screening. When we decide that a compound is worth further evaluation and optimization, we tailor the synthesis method for each compound, which significantly improves the yield.

Furthermore, when we scale up to industrial manufacturing, we use a different synthesis method, which is even more efficient. For example, with LUNA18, we employed a different method, and it's significantly better than this one.

Matsubara [Q]: Thank you for the explanation. I understand that your company's peptides are stabilized and have high membrane permeability. Like PeptiDream, which is working on Peptide-Drug Conjugates (PDCs) that might expand target diseases and enhance efficacy, is your company considering anything similar?

Iikura [A]: At present, given that our resources are still quite limited, we are focusing on areas where we can create competitive advantages and deliver valuable pharmaceuticals. We are strategically concentrating on these areas, and currently, we do not plan to venture into the direction of PDCs.

Matsubara [M]: I understand, thank you very much.

Miyata [M]: We will take a question from a participant joining via the Zoom webinar. Mr. Wakao from JPMorgan Securities, please go ahead.

Wakao [Q]: I'm Wakao from JPMorgan. Thank you for the presentation. I have two questions. First, I understand the background and development of your company's technology. I'm interested in knowing how your platform compares to other companies' platforms in terms of superiority.

For instance, if both your company and PeptiDream were to develop mid-size molecules targeting the same protein, would your product be significantly superior? In what aspects does your platform excel compared to others? Is it in terms of speed, or are the outcomes fundamentally different?

Iikura [A]: It's quite challenging for me to compare our platform with others, as I don't have complete knowledge of what other companies are doing. However, based on the information available, I believe we have been the ones to elucidate what kind of properties a compound must have to penetrate cells. This has been published in our papers.

When it comes to creating a technology for generating drug-like hits, it has taken us nearly a decade. We have developed a library that includes compounds with many N-alkyl groups or those stable against oxidative metabolism and focused on hitting targets with a limited range of about 11 residues. It took us about ten years from understanding what makes a compound drug-like to achieving this. That's our history in this field.

Wakao [Q]: Thank you. My second question is about slide 44. From your explanations, it seems like the throughput of compounds has significantly increased from 50 to 500, which is very efficient. However, when

comparing slides 43 and 44, it doesn't seem like the number of projects has increased proportionally. Is there a bottleneck? Or should we expect that the improvements you described will contribute to a significant leap in the number of projects in the next 1-2 years? Can you elaborate on this aspect?

Iikura [A]: When asked if we can continue to increase the number of projects indefinitely, I believe there is still some room for growth. However, rather than endlessly increasing the number, I think it will stabilize to a level where we add more as we advance projects to clinical stages. I think the current number of projects is quite substantial.

For example, over the past 20 years, the portfolio of small molecules at Chugai was probably about a quarter or a fifth of this size, which indicates the efficiency with which we are now able to handle multiple projects simultaneously.

Wakao [Q]: What's the reasoning behind the current number of projects? Is it because you are targeting the most promising candidates in order of priority?

Iikura [A]: It's not quite like that. For example, we currently have four joint projects with Roche, and we can continue to add more. I don't really have the impression that we are limiting the number of projects. In both antibody and small molecule projects, researchers continuously come up with ideas about how they could develop effective drugs. These ideas don't all emerge at once but develop over time, with different people thinking about various aspects. We continually evaluate these proposals and select the ones that seem most promising.

In this sense, there is a considerable number of proposals being made for mid-size molecules, and I believe we are currently running an unusually large number of projects simultaneously.

Wakao [Q]: I see, thank you. Lastly, about the preclinical development cancer projects, when is the earliest they might enter clinical trials? What's the best-case scenario for timing?

Iikura [A]: For preclinical development projects, the typical timeline is about one to two years, I would say. However, this can vary significantly as we need to ensure there are no toxicity issues in the preclinical trials and to confirm other conditions are prepared. So, the standard would be around one to two years.

Wakao [M]: Thank you very much for the clarification. That's all from me.

Miyata [M]: Now, I'd like to invite Ms. Sogi from AllianceBernstein to ask her question.

Sogi [Q]: Hello, Mr. Iikura, and thank you for today. I have two questions. First, regarding the target selection for mid-size molecules: Your company conducts research and drug discovery without limiting the disease area. Moreover, with your mid-size molecule platform, you have the potential to develop drugs for a wider range of intracellular targets. How do you select these targets?

Iikura [A]: Target candidates are sometimes chosen top-down and sometimes bottom-up, but it's mostly bottom-up, about 70% to 80%. Amidst various emerging ideas, we assess which targets truly have value and are technically accessible with our current technology. We evaluate targets based on their potential to deliver real value to patients and choose them accordingly.

Sogi [Q]: I understand. When you are selecting these targets, do you conduct any commercial assessments?

Iikura [A]: No, we do not.

Sogi [Q]: Thank you. My second question is about the synthesis of mid-size molecules. As you mentioned earlier, the synthesis method for a library in solid-phase and the method for actual development at the clinical level are different.

When these products are commercialized, you briefly mentioned 24 steps earlier, do you anticipate that the COGS will be significantly higher compared to current products? What are your thoughts on this?

Iikura [A]: I'm considering how much to disclose about this. Of course, the numbers won't be astronomically high. The 24 steps are for the hit to lead stage, but we expect to significantly reduce the number of steps in the near future.

In that sense, since the compounds are highly active, they won't require large quantities, which makes them commercially viable. As I mentioned on the slide, when I say commercially viable, it includes estimates on these aspects. That's how I would like you to interpret it.

Sogi [M]: Understood, thank you very much for your explanation.

Miyata [M]: Now, I would like to invite Mr. Wada from SMBC Nikko Securities to ask his question.

Wada [Q]: I'm Wada from SMBC Nikko Securities. Thank you. I have two questions regarding the technology patents mentioned on page 50 and their business applications.

First, of the 43 patents mentioned, I'd like to know how many relate to non-peptide compounds. The reason for asking is, compounds like orforglipron seem to exceed a molecular weight of 500 and deviate from the Rule of 5. I believe the advantage of compounds like OWL833, orforglipron, lies in their ability to create high molecular weight compounds that can still enter cells. When thinking about applying this to other non-peptide compounds, I'm curious about any entry barriers that might exist. That's my first question.

If that's feasible, my second question is about the potential application of your technology to PROTAC. PROTAC typically involves attaching two molecules with a molecular weight of around 500, leading to a total molecular weight of about 1,000, which I think is a current bottleneck in the technology.

If your technology could overcome this issue, I'm wondering if you have considered commercializing it, possibly through partnerships or technology licensing.

Iikura [A]: Thank you, Mr. Wada, for your questions. First, regarding the number of patent applications, these do not include OWL833. The current count of 43 is solely for patents related to cyclic peptide technology.

In the area of compounds with a molecular weight over 500, we've been engaged in this well before our focus on cyclic peptides, with projects like OWL833, PCO371, and EOS789. PCO371's clinical development was discontinued partway, but EOS789 is still ongoing.

We have a considerable experience with compounds exceeding a molecular weight of 500 and have come to understand some of the difficulties involved. One major challenge is the control of safety and toxicity, which is not an easy task. Fortunately, our OWL833 project has so far shown a favorable toxicity profile in clinical trials, which is reassuring. However, the challenge of managing these aspects is a bottleneck we face.

In this context, one advantage of creating cyclic peptides, as I mentioned earlier, is that they can be seen as having similar properties as scaffolds. This means that what we learn about controlling toxicity in one project can often be applied to many others. This antibody-like characteristic is something we find quite effective. However, with non-peptide compounds, our experience has shown that each compound is entirely different.

Regarding the application of our technology to PROTAC, we see PROTAC as a very promising new mode of action and are naturally interested in it. However, as for how we might strategize its application, I am not prepared to disclose that today.

Wada [M]: Thank you. I understand.

Barker [Q]: I'm Stephen Barker from Jefferies. I have a question. I would like to ask about the PK of mid-size molecules. Based on page 29, my understanding is that, like small molecules, they can pass through cell membranes. In a broader sense, do they exhibit similar PK properties to small molecules?

Iikura [A]: Could you please turn to the LUNA18 slide? This slide shows the oral PK data in animals. This refers to oral absorption. An oral absorption rate of 21% is within an acceptable range even for small molecules. So, in that sense, I believe it's fair to say they are similar to small molecules.

In other aspects, such as *in vivo* half-life or volume of distribution, the main DMPK parameters are almost all showing values comparable to those of small molecules. It seems that while we humans differentiate between small and mid-size molecules, the biological system does not make such a distinction as strongly as we do.

Barker [M]: Yes, thank you. That's all from me.

Miyata [M]: With that, we will conclude the Q&A session. This also marks the end of Chugai's R&D Meeting.

For questions we couldn't address due to time constraints, please contact our Corporate Communications Department separately. The telephone number and email address are listed on the last page of the presentation materials.

Thank you very much for participating despite your busy schedules. We appreciate your attendance and now close this briefing.

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