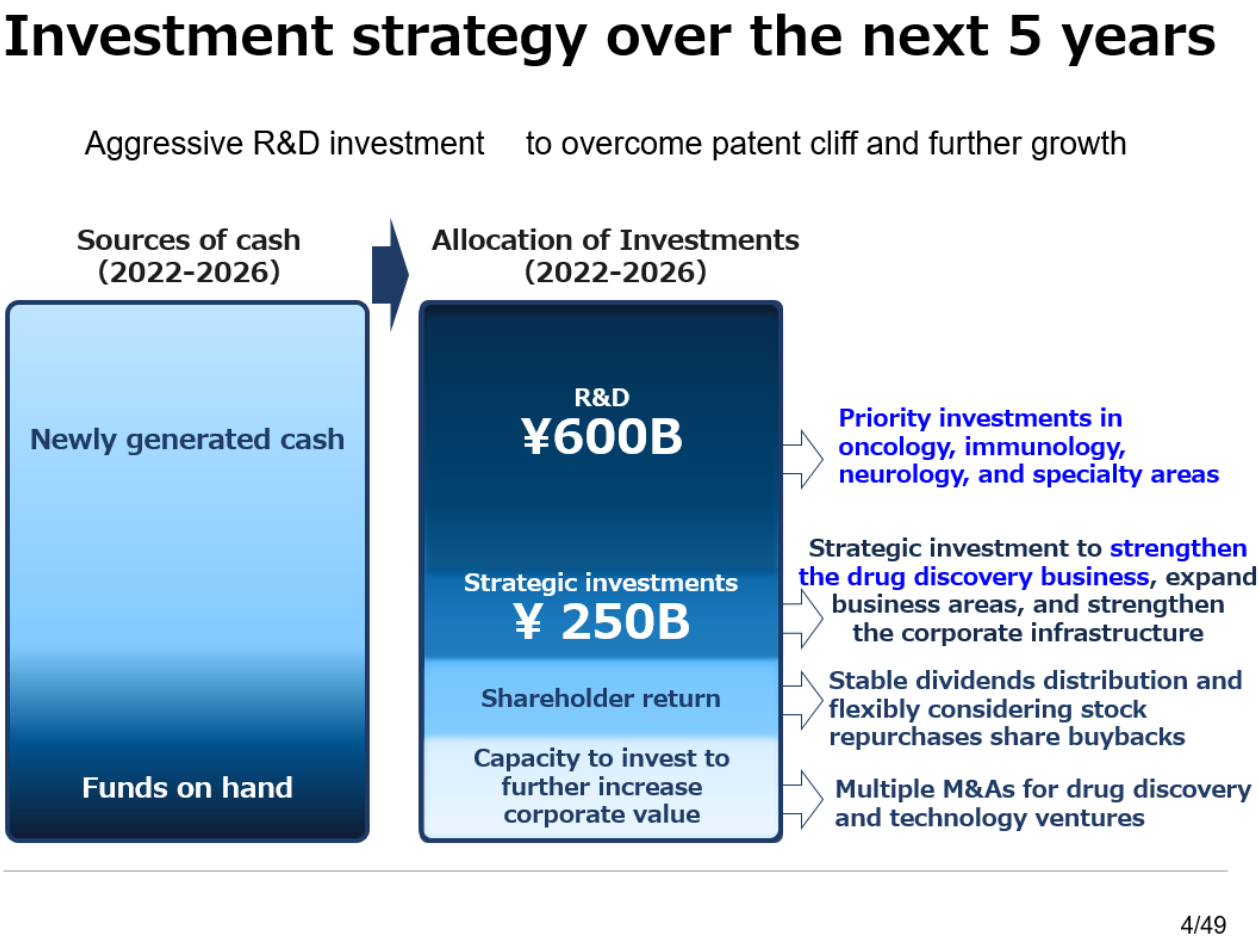
ONO PHARMACEUTICAL CO., LTD.

R&D Presentation Meeting

February 24, 2023

[Number of Speakers]	4	
	Gyo Sagara	President, Representative Director, and Chief Executive Officer
	Toichi Takino	Member of the Board of Directors, Senior Executive Officer, Executive Director of Discovery and Research
	Kiyoaki Idemitsu	Member of the Board of Directors, Executive Officer, Executive Director of Clinical Development
	Yukio Tani	Corporate Executive Officer, Head of Corporate Communications

Presentation

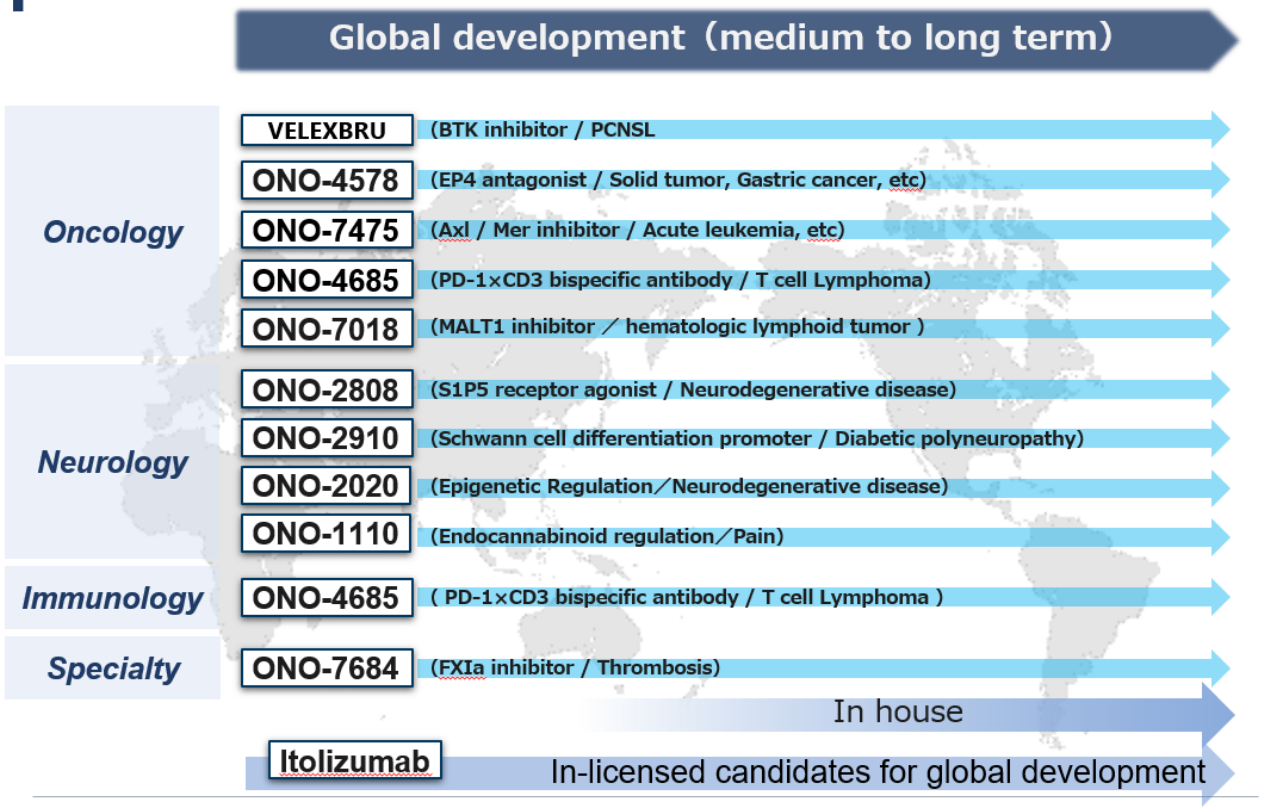


Sagara: When we announced our financial results last May, we talked about our investment policy in our five-year mid-term plan. Specifically, we will invest JPY600 billion in R&D over the five-year period from FY2022 to FY2026.

In addition, JPY250 billion in strategic investments will be made to strengthen the drug discovery business, expand business domains, and the management base. These two are our R&D and related business investments.

Currently, we have been already making investments to strengthen our drug discovery business, such as through alliances with research platforms, acquisition of compounds for expansion of our pipeline, especially those that can be marketed globally, and investments in venture companies. The investment is proceeding steadily. I am not going to explain each individual investment in detail, but we are making steady progress on the strategic investment JPY250 billion.

Global pipeline expansion



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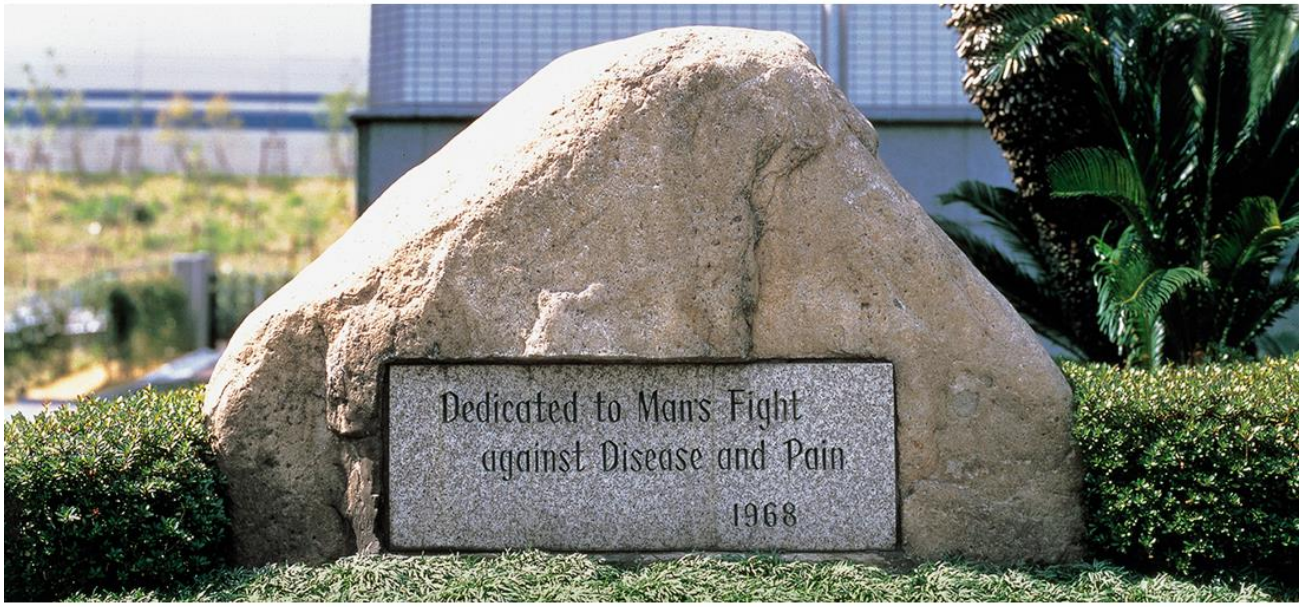
Currently, we have started global development with the pipeline, as you can see, focusing on drugs discovered in-house. In total, we have 10 compounds and 11 clinical trials, and we have one compound with which two indications have been investigated.

While pursuing unique products moving out from our drug discovery policy for Compound Orient approach, we will also focus on oncology, immunology, and neurology. We are following a policy of drug discovery that is to try out any interesting and unique drug that comes our way. As you can see, we have started trials mainly in the areas of oncology, neurology, and immunology.

We are now working diligently to successfully conduct two or three trials in the future and obtain global approval, so that we can supplement Opdivo's cliffs and grow further.

Corporate Philosophy

” Dedicated to the Fight against Disease and Pain”



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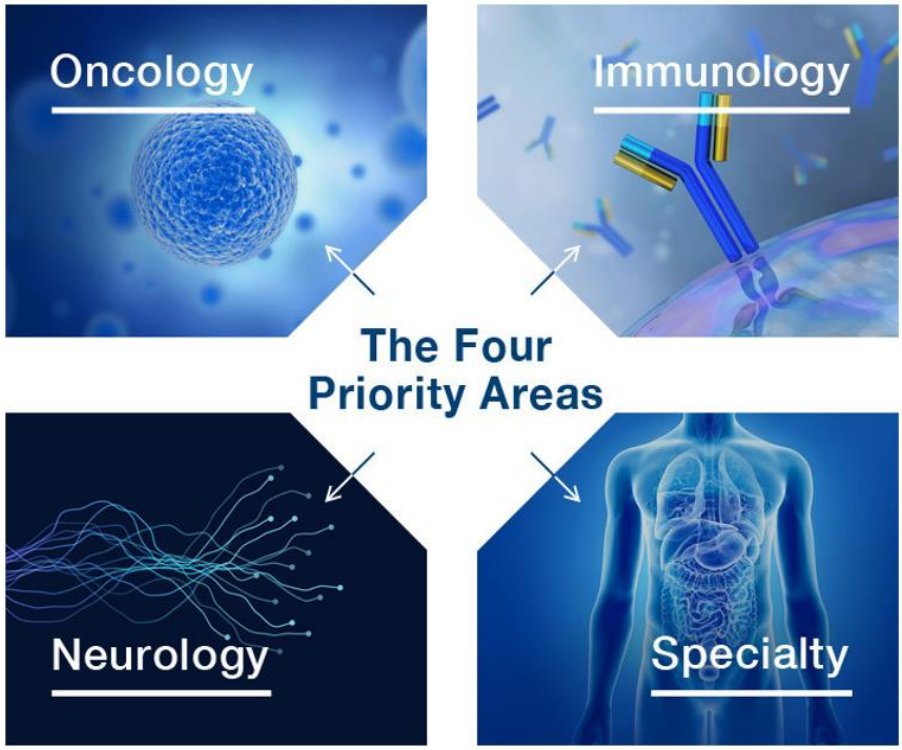
Takino: This is a stone monument that describes our corporate philosophy at our main laboratory, the Minase Research Institute. With the philosophy of Dedicated to the Fight against Disease and Pain, we are dedicated to delivering innovative new drugs.

Focused Areas of Drug Discovery Research



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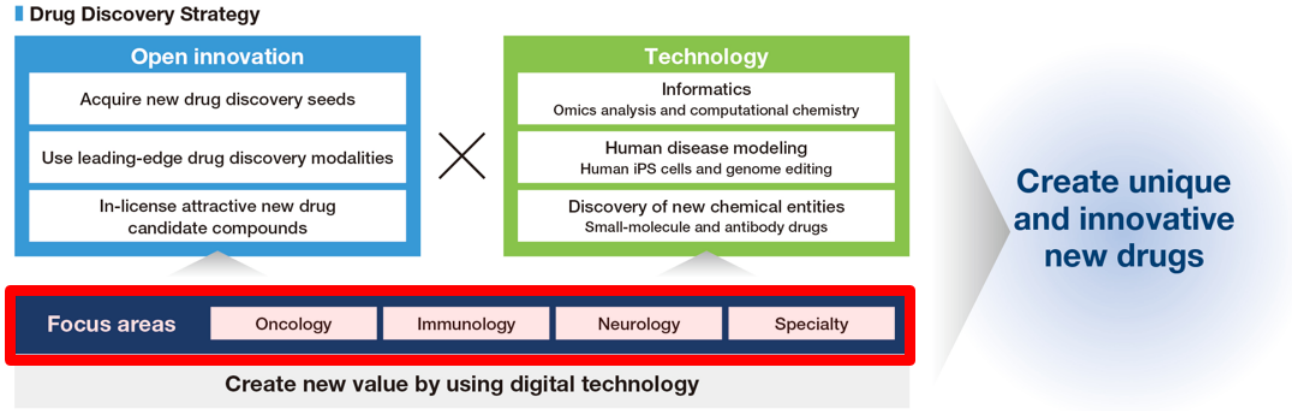
Our approach to R&D has also undergone some transition, as the president mentioned at the beginning of this presentation, we would like to continue to fight for the patients in areas where many of their medical needs remain, which are oncology, immunology, and neurology, and to create drugs in these three areas. However, we do not want to limit our opportunities in those three areas only, but rather, we have designated specialty as our fourth priority.

Drug Discovery Strategy

「Open Innovation」×「Technology」
allows us create unique & innovative new drugs



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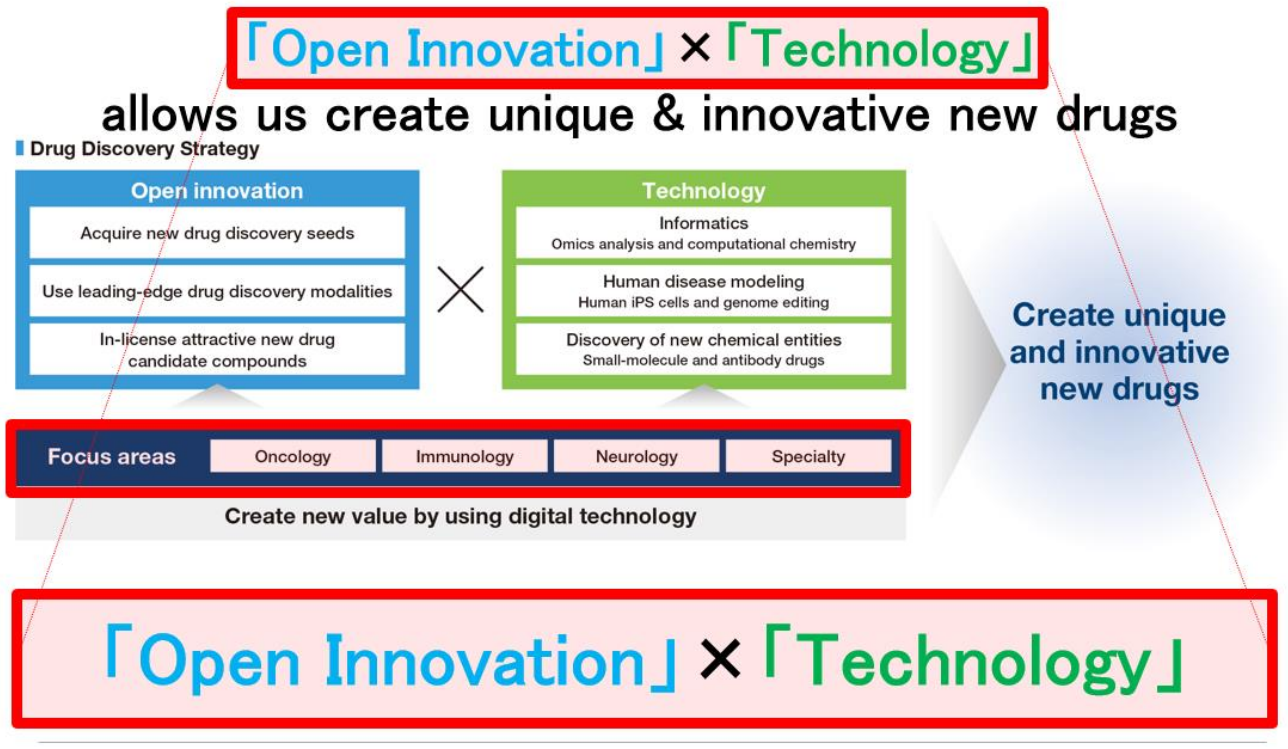
This slide represents our drug discovery policy that we use in our explanation for external parties, but I think it is also difficult to understand with this slide only. Therefore, I would like to talk about Ono's drug discovery by explaining from a view of open innovation with examples.

Drug Discovery Strategy



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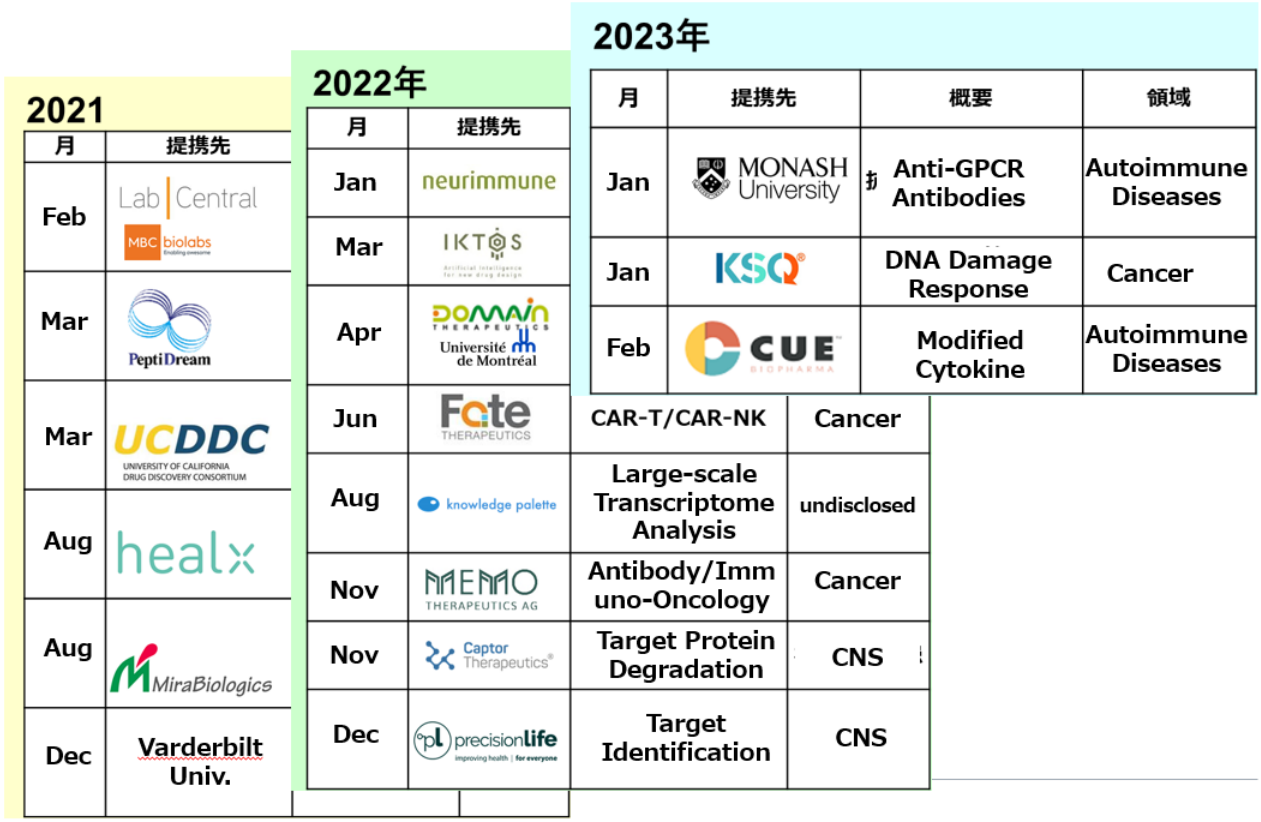
Open innovation is an extremely important initiative, that it would not be an exaggeration to say that it is a lifeline for Ono. We would like to create innovative drugs that other companies cannot do, by actually experimenting with open innovation.

Recent Updates of Discovery Alliances (2021～)



2021

月	提携先
Feb	Lab Central / MBC biolabs
Mar	PeptiDream
Mar	UCDDC UNIVERSITY OF CALIFORNIA DRUG DISCOVERY CONSORTIUM
Aug	healx
Aug	MiraBiologics
Dec	Varderbilt Univ.

2022年

月	提携先	概要	領域
Jan	neurimmune	Anti-GPCR Antibodies	Autoimmune Diseases
Mar	IKTOS		
Apr	Domain Therapeutics / Université de Montréal		
Jun	Fate Therapeutics	CAR-T/CAR-NK	Cancer
Aug	knowledge palette	Large-scale Transcriptome Analysis	undisclosed
Nov	MEMO Therapeutics AG	Antibody/Immuno-Oncology	Cancer
Nov	Captor Therapeutics	Target Protein Degradation	CNS
Dec	precisionlife	Target Identification	CNS

2023年

月	提携先	概要	領域
Jan	MONASH University	Anti-GPCR Antibodies	Autoimmune Diseases
Jan	KSQ	DNA Damage Response	Cancer
Feb	CUE BIOPHARMA	Modified Cytokine	Autoimmune Diseases

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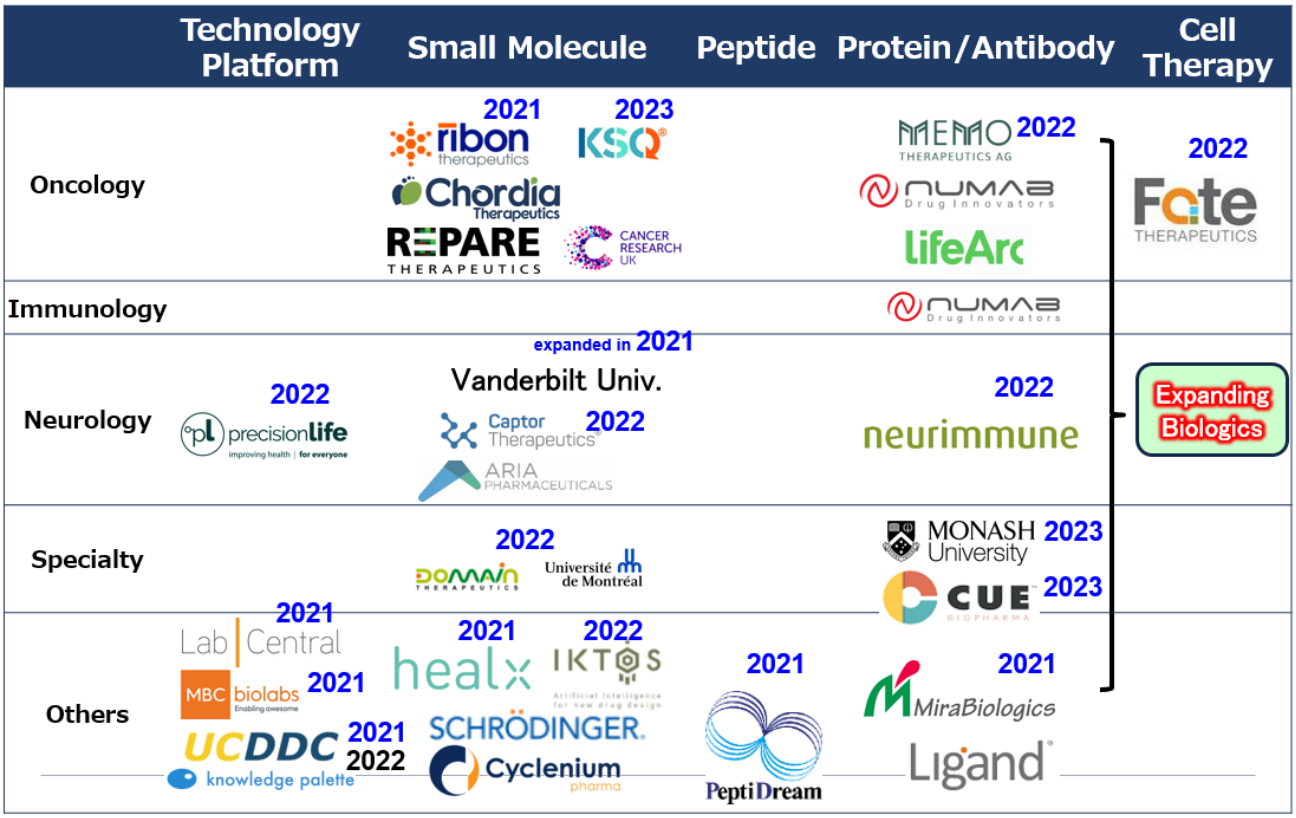
In fact, if we look back at examples in the last two years, in terms of open innovation, and collaborations with other companies, there are doing more than 10 times as many examples as shown here, but we have omitted basic joint research with academia and other alliances with CROs, and limited the list to, that have been released to the press.

We are expanding our drug discovery and research collaboration in terms of number of alliances, for example, in 2021 and 2023, including this week's collaboration with Cue Biopharma.

As the president mentioned at the beginning of this presentation, we are committed to investing in research, not only in terms of cost and funding, but also building a structure and system to actually carry out this work. We will continue to strengthen our own drug discovery activities while looking outside of the Company.

Our Focus on Drug Discovery Platform and Modalities



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This shows the summary by disease area or modality. The point is I can tell you that we're working on a lot of different areas. Another thing is that, as you can see on the right-hand side of the page, biologics initiatives are increasing in Ono.

Drug Discovery Strategy

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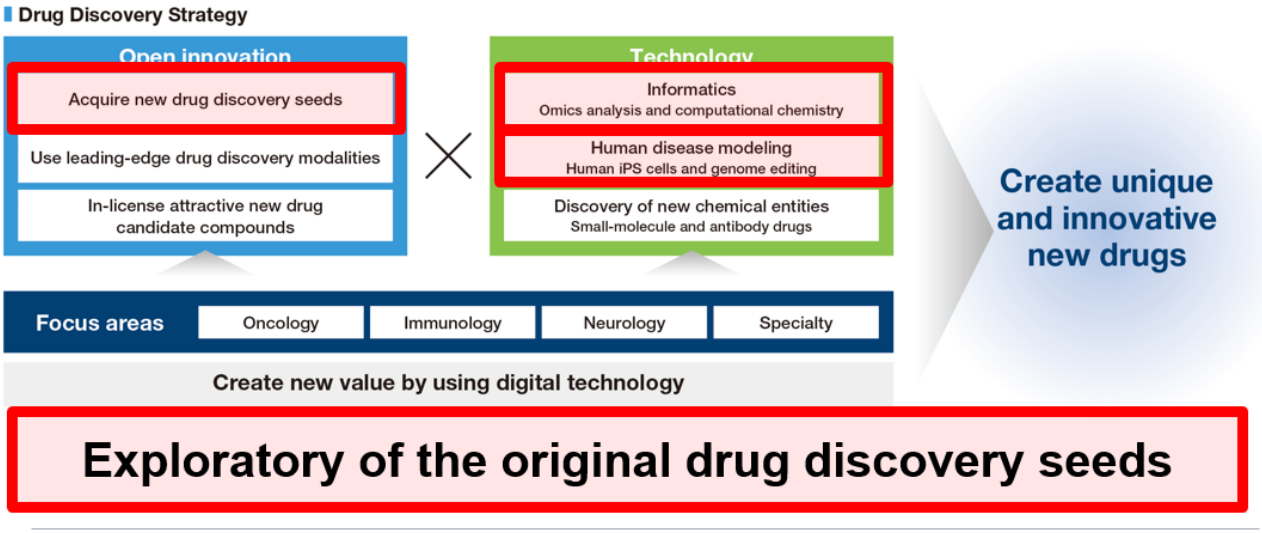

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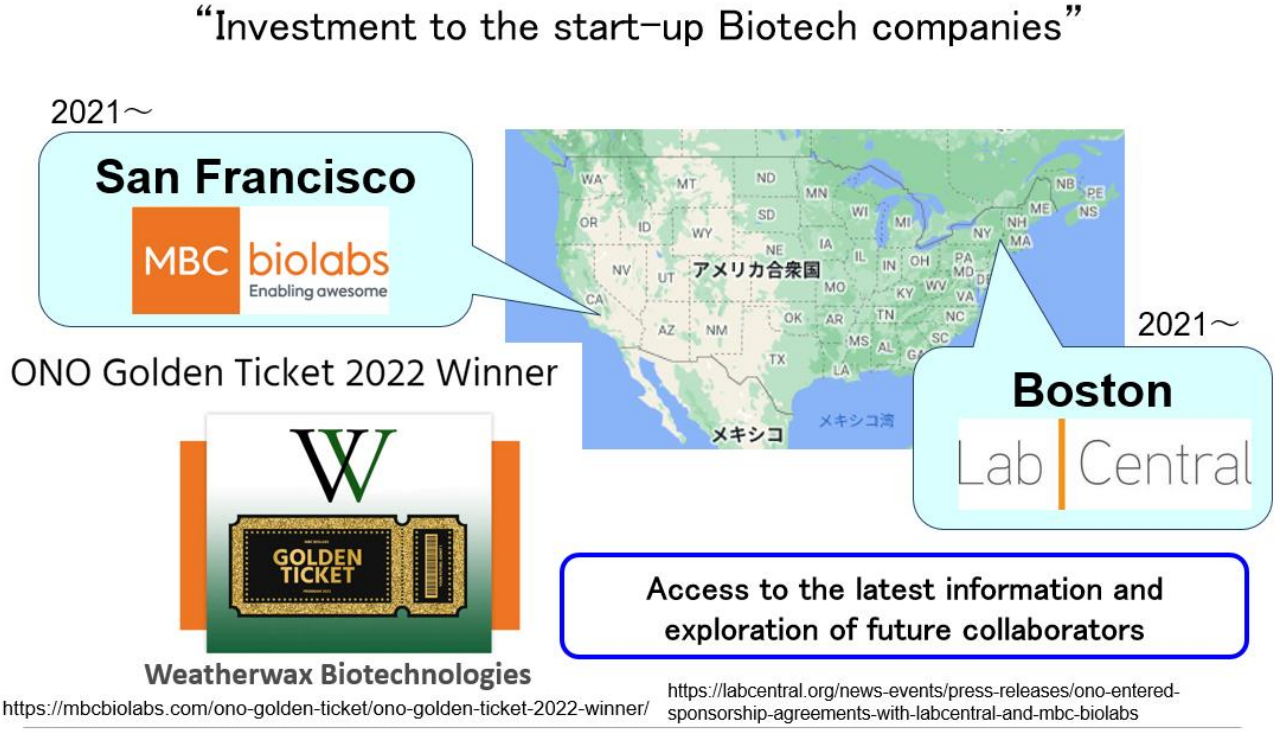
I would like to talk about each of these initiatives. At first, I would like to talk about the seeds of drug discovery and the exploration for drug target.

Sponsorship Agreements with LabCentral and MBC BioLabs
(2021.02.26)



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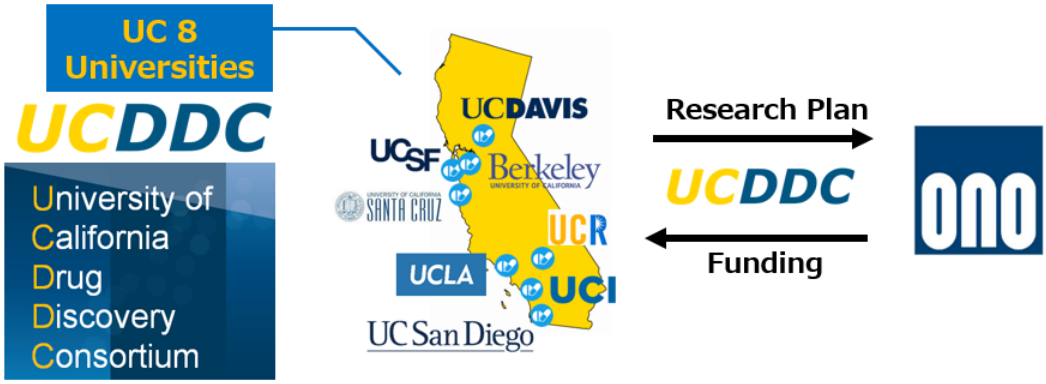
There are incubation labs in the US, one is LabCentral on the east coast, and the other is MBC BioLabs on the west coast. We have a sponsorship agreement with them and we will continue to provide financial support to startup ventures that wish to enter their incubation labs, so that we can catch up with new drug discovery ideas and trends, access them, and link them to future seeds for drug discovery alliances. With that expectation, we are sponsoring an initiative entitled ONO Golden Ticket.

Joins the University of California Drug Discovery Consortium
(2021.03.16)

- Access to undiscovered top scientists
- Explore collaboration opportunities based on unverified and unpublished ideas
- Bridging academia's drug discovery seeds to pharma



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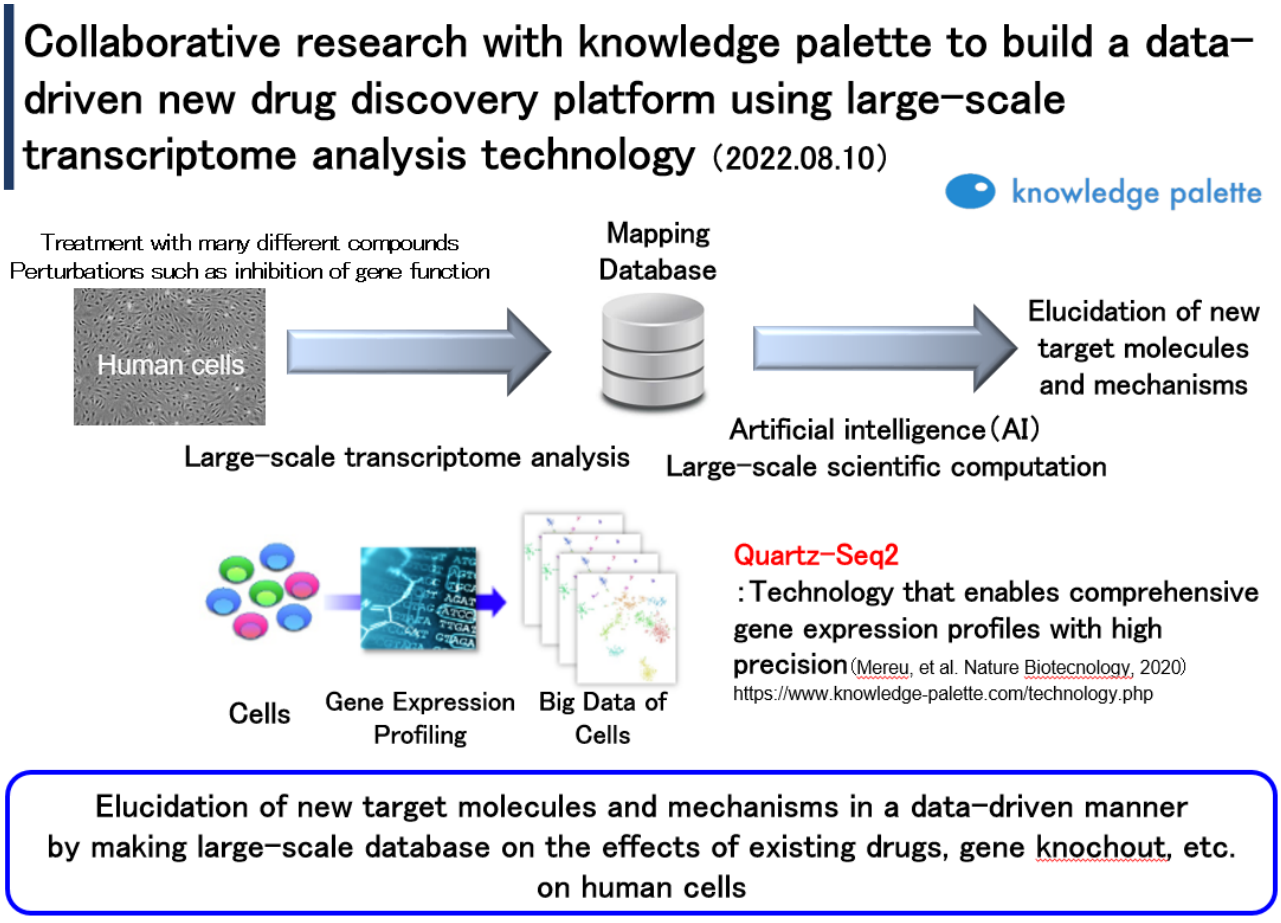
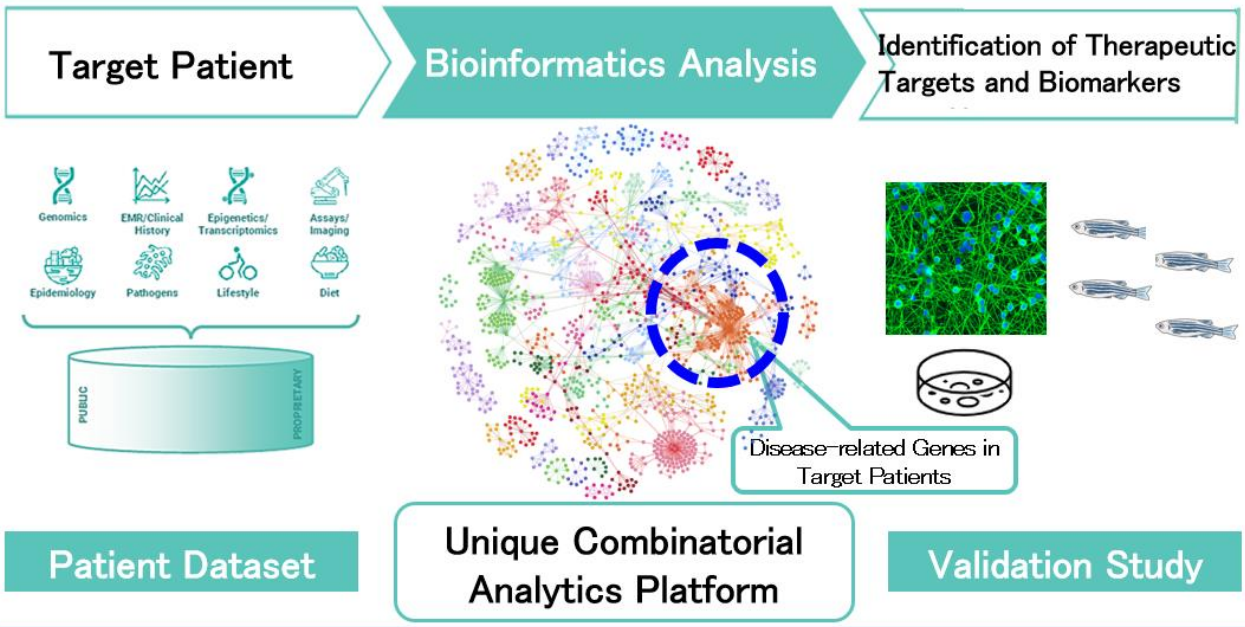
We are also participating in the UC Drug Discovery Consortium, UC DDC, at the University of California in the US. This is a framework for us to explore collaborative research opportunities with UCSF, UC Berkeley, UC Davis, the UC group with eight life sciences faculty or UC universities that are trying to advance research with new ideas.



Also, Knowledge Palette, Inc., which is a domestic venture, has quite outstanding technology in the analysis of large-scale transcriptomes. By partnering with this company, we are now trying to build a foundation in preparation for the future data-driven drug discovery, from the conventional drug discovery, which is often expressed in vague terms, such as researchers' intuition or discernment. We are also trying to establish a foundation that can be used to discover and verify new target molecules and mechanisms of action.

Multi Target R&D Collaboration Agreement with PrecisionLife to identify novel therapeutic targets in CNS disorders

(2022.12.14)

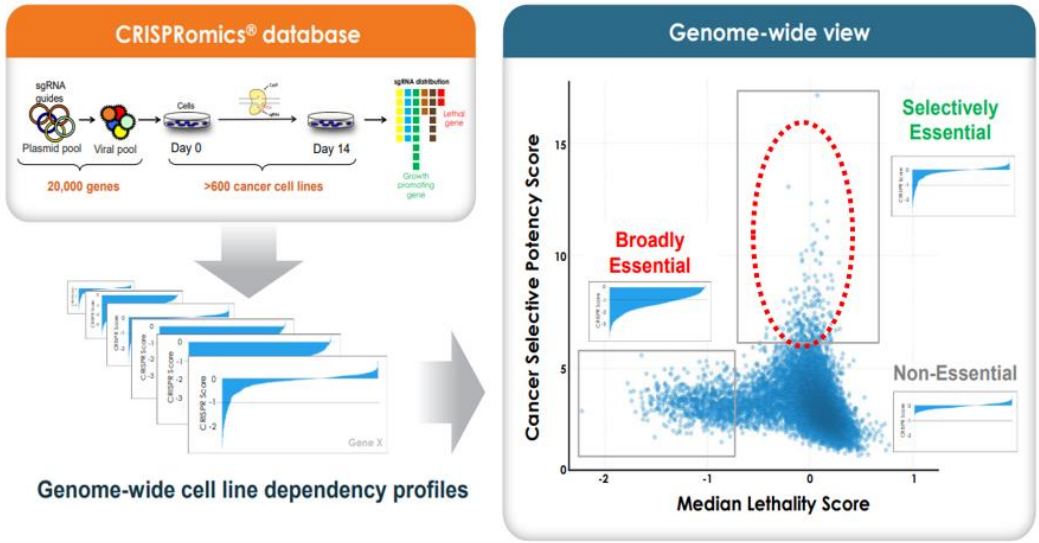


Identification of Novel Therapeutic Targets and Patient Stratification Biomarkers through Unique Combinatorial Analytics Platform to Datasets of Treatment-resistant Patients

Apart from establishing these systems and network, PrecisionLife in the UK is looking for new specific seeds in the area of central nervous system.

Recently, bioinformatics has become very useful, and this company has its own composite analysis platform as well as its own unique patient data assets available. By partnering with this company, we hope to detect and analyze the genetic background and fluctuations of certain patients with central nervous system diseases who are resistant or refractory to certain drugs, even if they continue to use them for a long time. By doing so, we are expecting to discover new drugs, and we have begun to work on this project.

Acquisition of Multiple Research-Stage Oncology Programs from KSQ Therapeutics (2023.01.25)



Acquisition of multiple research-stage DNA damage response programs identified by KSQ's CRISPRomics® platform technology

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This is a new theme in oncology and an oncology drug discovery program with KSQ Therapeutics in the US. This company is a venture company started from a unique drug target discovery technology by a prominent professor from the Broad Institute.

While they were working to find new targets using CRISPR, which is named CRISPRomics, and they have an interesting project on the DNA damage response and PARP inhibitors, which I think will lead to synthetic lethal drugs. we have decided to take over this project.

As described above, we are taking a variety of approaches at different levels to search for the seeds of drug discovery.

Drug Discovery Strategy

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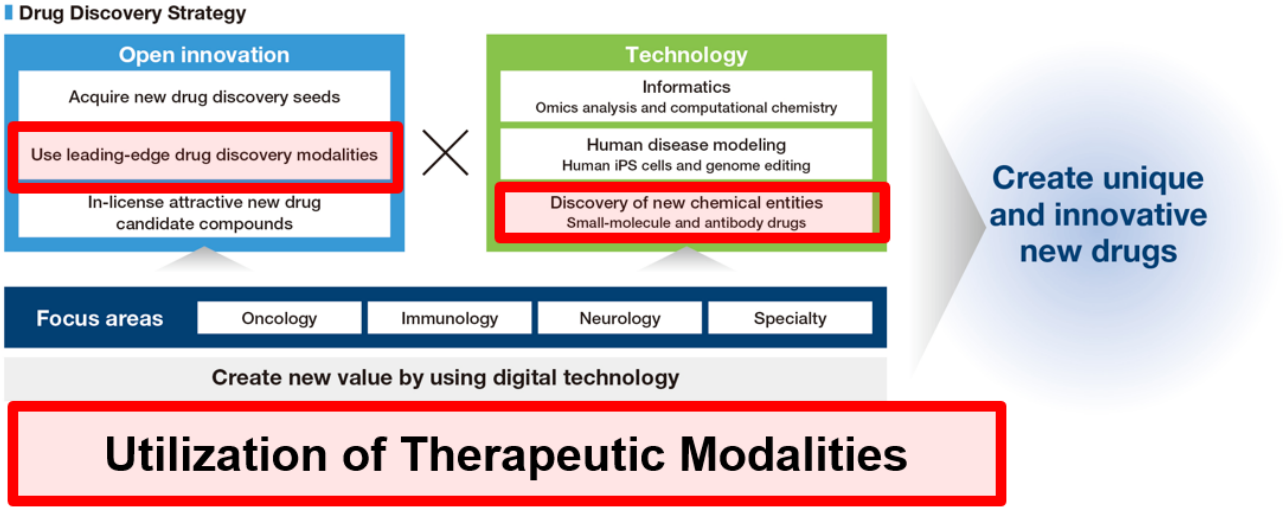

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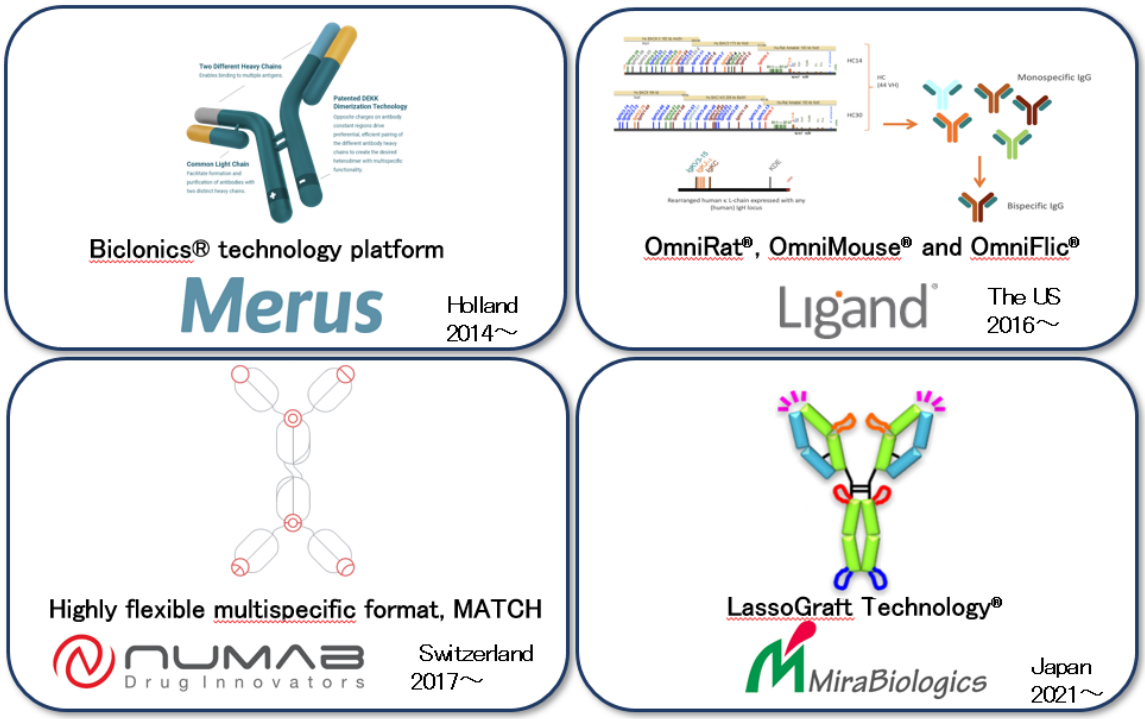
Next, I would like to talk a little bit about what we are doing as a drug discovery modality when attractive drug targets emerge from the search for such drug discovery seeds.

Alliances on Multispecific Antibodies



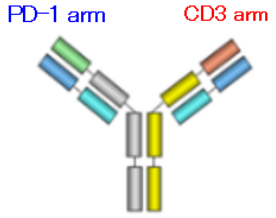
This is our partner's venture in the field of multi-specific antibodies, which we have been working on for some time.

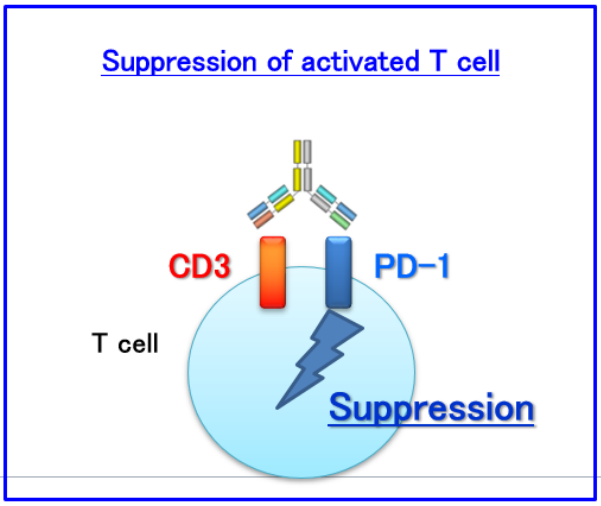
ONO-4685：PD-1 × CD3 Bispecific Antibody

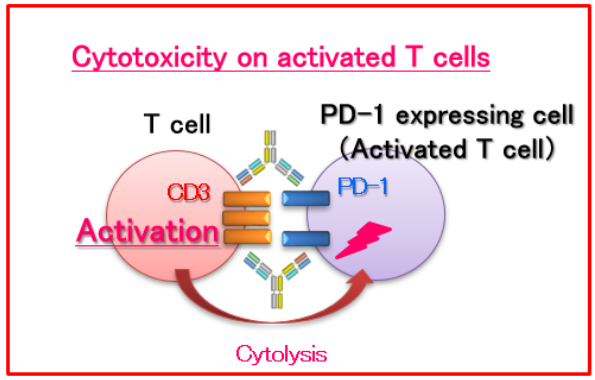
Merus

- PD-1 × CD3 Bispecific Antibody generated by Biclonics® Discovery Platform

  T cell lymphoma（USA, Phase 1）
  Autoimmune Diseases（Japan・EU, Phase1）







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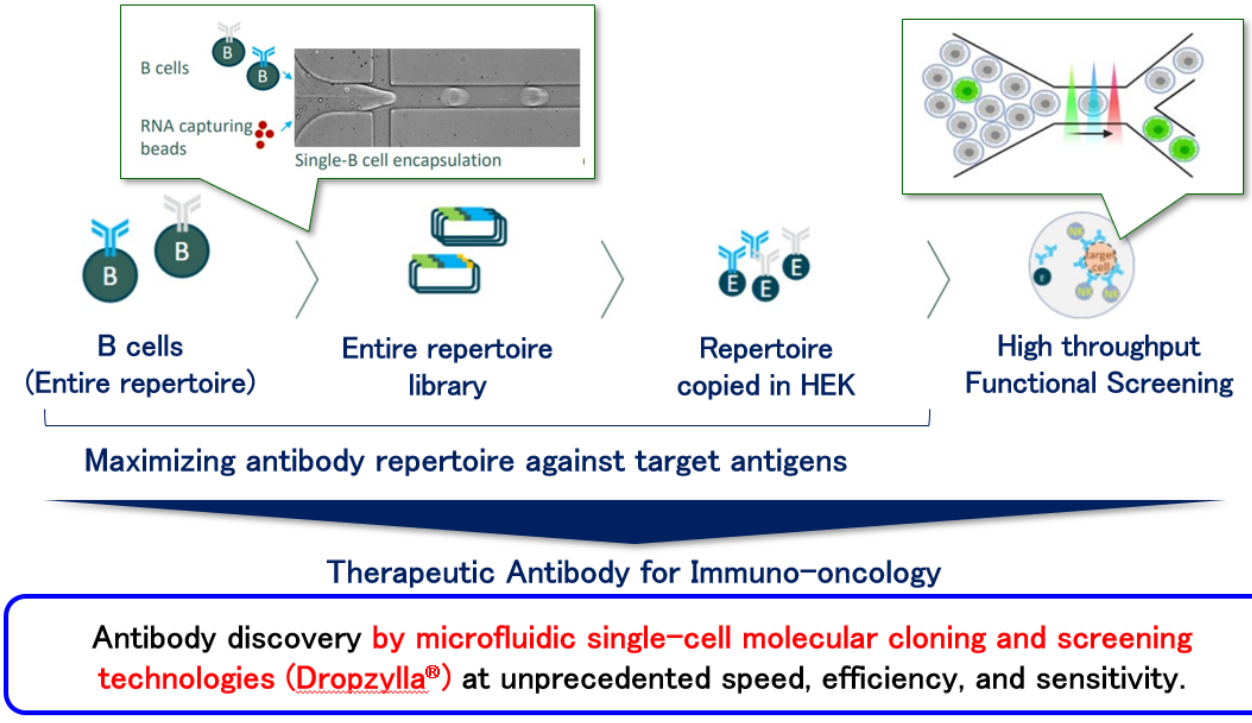
In particular, in our collaboration with Merus, ONO-4685 is currently in the Phase I stage as our clinical project.

TAs expected reactions of the PD-1 and CD3 bispecific antibodies, as shown in the blue box on the left, it suppresses activated T cell and as shown in the red box on the right, it has a trans-acting or engager like effect, which means that activated T cells are injured. We are currently developing it for autoimmune diseases and T-cell lymphoma, assuming both of these effects.

Antibody Discovering Partnership for Immuno-oncology with MEMO Therapeutics (2022.11.01)



Antibody discovery by microfluidic single-cell molecular cloning and screening technologies (Dropzylla®) at unprecedented speed, efficiency, and sensitivity.

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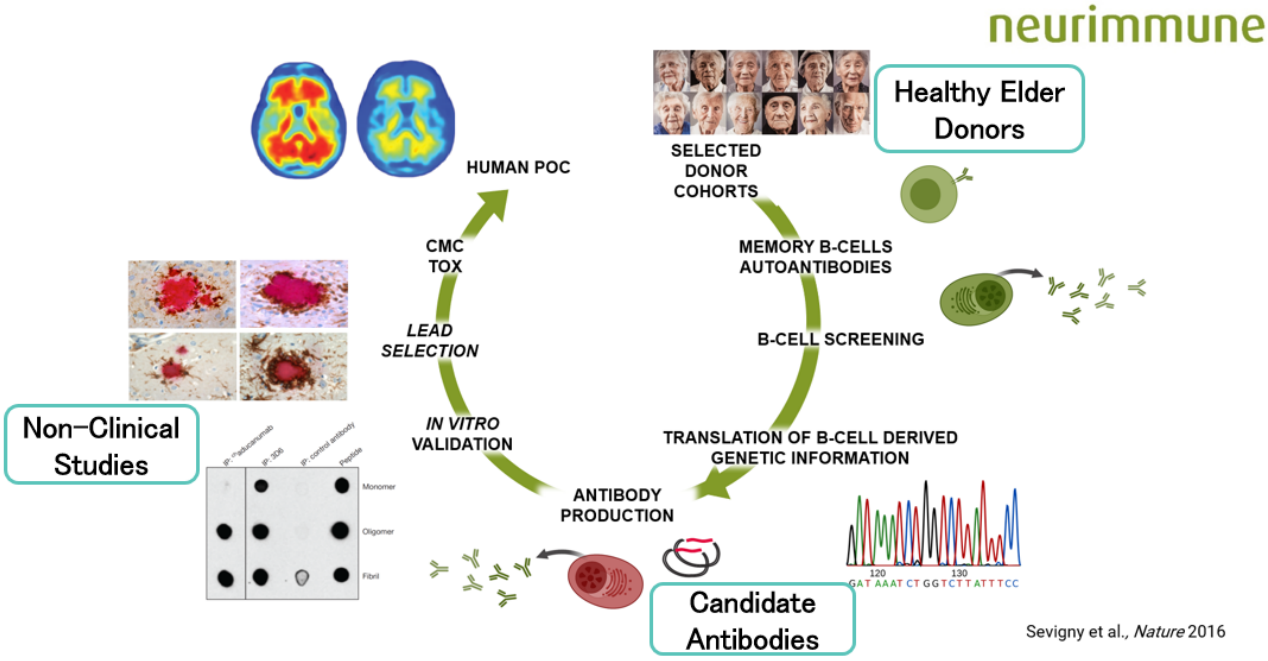
We are not only working on bispecific or multi-specific antibodies. As for ordinary antibodies, I think the technology to create antibodies has been dramatically accelerated in the development of the COVID-19 treatment drugs. We are working with Memo Therapeutics to create antibodies against immune-oncology new targets.

Antibody Drug Discovery Collaboration with Neurimmune AG in the Field of Neurodegenerative Diseases (2022.01.17)



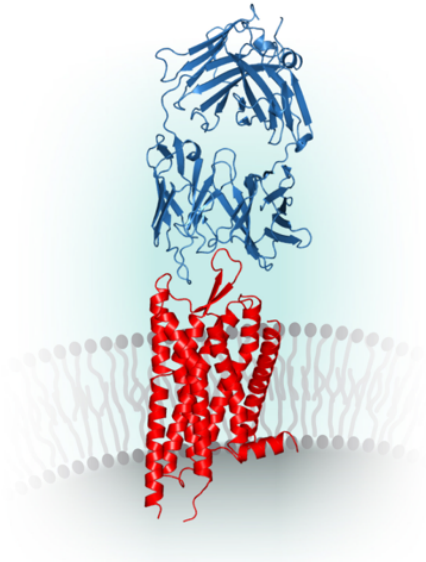
Creating Selective High Affinity Antibodies Using the Reverse Translational Medicine™ Technology Platform Based on Immune Responses to Disease-related Proteins in Healthy Elderly

Our approach to antibody drug discovery is not limited to oncology. We also have been working in the area of central nervous system with several projects of Neurimmune in Switzerland. In fact, as shown in this slide, Neurimmune is a venture company, which is expected to have an advantage in the generation of useful antibodies, by adding a library of B-cell clones from healthy elderly, based on the assumption that healthy individuals have lived a long and healthy life, while probably overcoming various types of diseases.

Neurimmune's track record includes a project on the Aβ antibody Aduhelm with Biogen, and we are also working with them on several projects targeting new drug discovery targets for neurodegenerative diseases.

Research Collaboration with Monash University in the Autoimmune and Inflammatory Diseases (2023.01.13)

MONASH University



- Monash University's sophisticated technologies for antibody discovery which enables the creation of therapeutic antibodies using monoclonal antibodies against two GPCRs traditionally hard to target.
- We expect to increase the efficiency of finding new drug candidates that fulfil unmet medical needs in autoimmune and inflammatory diseases.

Biochem Pharmacol. 2013 Jan 15; 85 (2): 147–52

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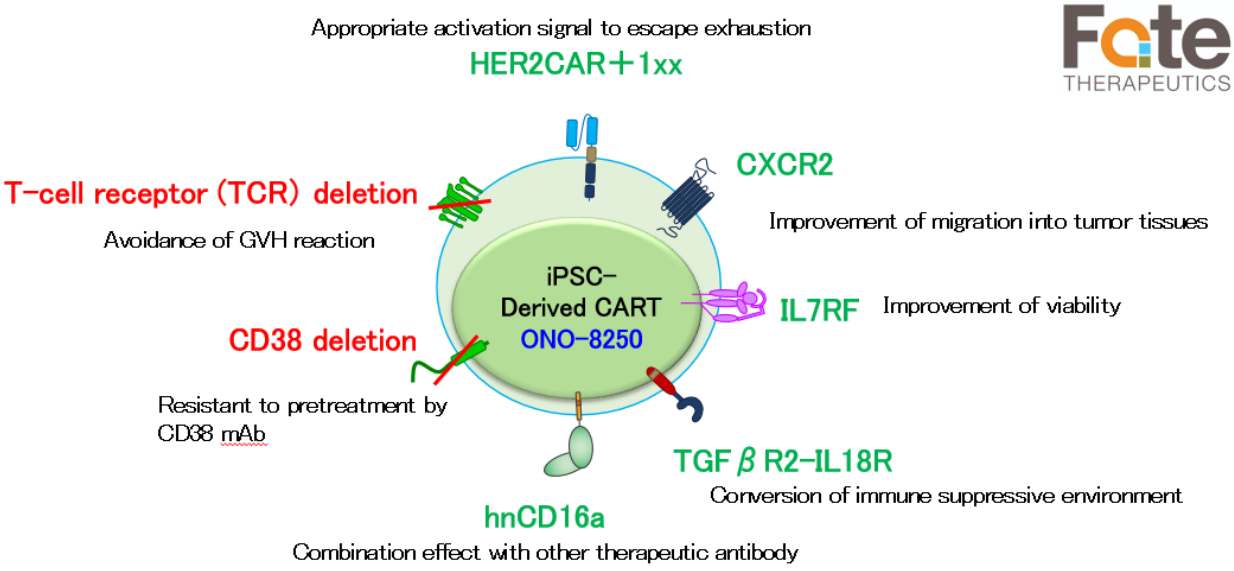
In the field of autoimmune and inflammatory diseases, we are of course also engaged in antibody research collaboration. This is a partnership with academia. We have started a research collaboration with Monash University, where Dr. Robert is an outstanding professor in the field of GPCR, where there are many cases that the antibody creation is not always easya field where antibody creation is not always straightforward.

Strategic Collaboration with Fate Therapeutics to Develop iPSC-derived CAR-T (2018.09.18)

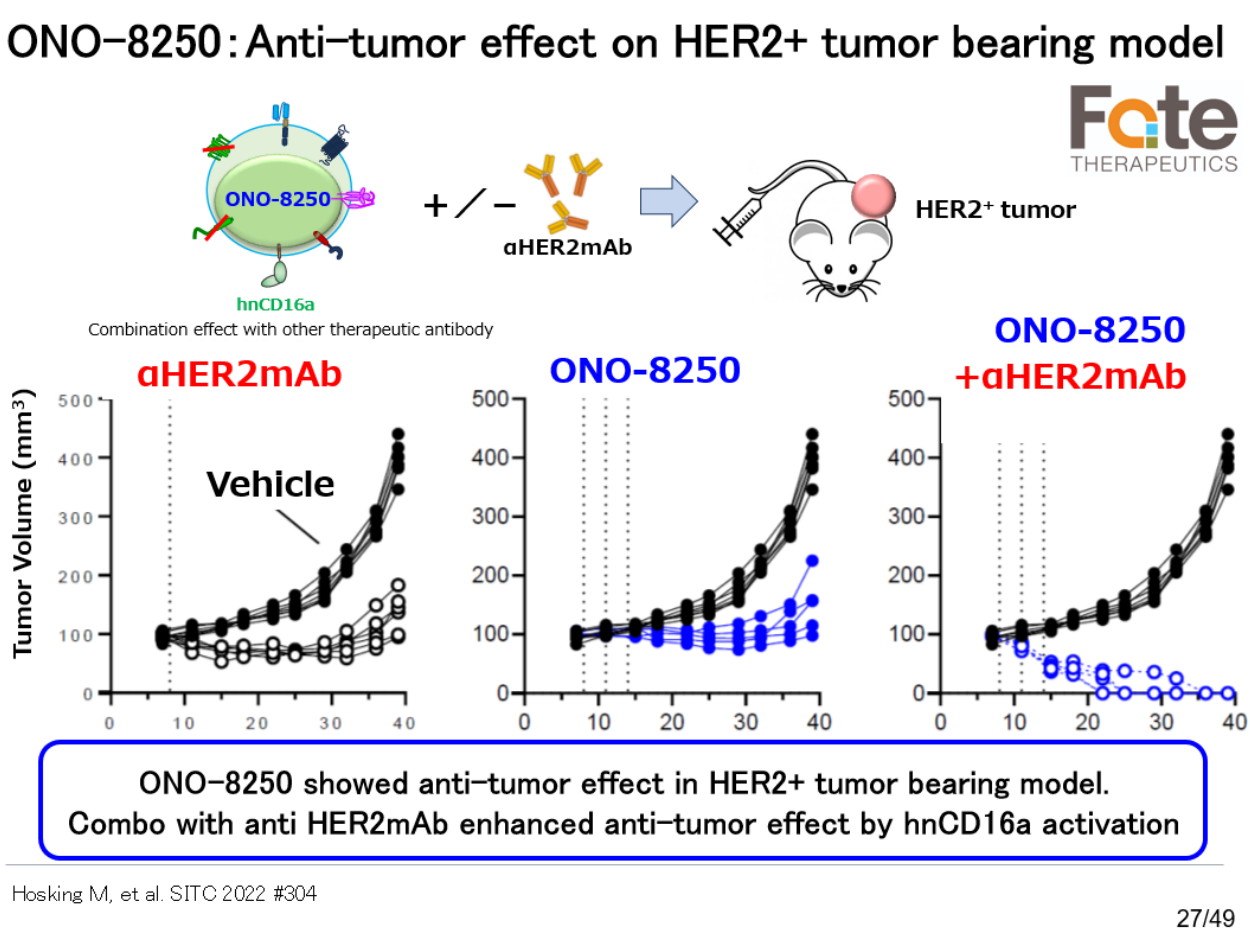
Exercise Option to HER2-targeted CAR T-Cell Product Candidate for Solid Tumors (2022.11.07)



This is all about antibodies. Another example of a biologics project is, that we are currently working on an alliance with Fate Therapeutics. As you know, we are working on iPSC-derived CAR-T. The level of technology of CAR-T and gene editing technology is also very high, and we are now in the process of arming CAR-T to its strongest state by making various modifications that are possible with current science and challenging solid tumors that have been difficult to be effective so far.

Currently, it takes about one month in preparation in the treatment with autologous CAR-T. The preparation process has imposed a burden on medical institutions. By using iPS cell-derived products, we expect that it will be possible to create CAR-T products that can be handled off-the-shelf, similar to the distribution of ordinary pharmaceuticals.

Specifically, as already announced by Fate at last year's ASH meeting, that seven gene-edited, HER2-targeted, iPSC-derived CAR-T cell product platform, which, of course, avoids host attacks and improves tumor migration while increasing CAR-T activity so that it does not get fatigued. This is to arm CAR-T as much as possible.

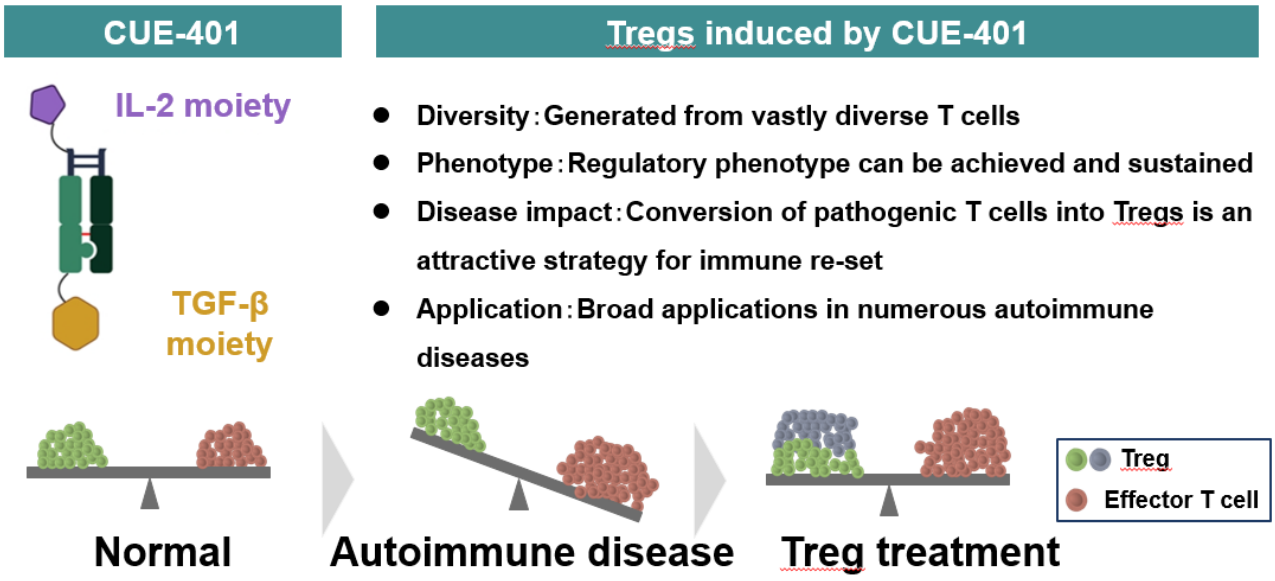


Ordinally, we disclose the ONO number at the stage of entering the clinical stage, but this time, due to circumstances with our partner, we have announced the development code of ONO-8250. We expect to move it to a clinical phase within a year or so.

This is an example of basic data showing that when used in combination with other antibody drugs, the efficacy can be further enhanced in a synergistic manner.

The basic data has shown that ONO-8250 is almost equally effective in killing the cell due to HER2 antibodies. When used in combination, we have seen exciting data that has been shown to be so effective enough to cause cancer regression.

Collaboration and Option Agreement with Cue Biopharma for CUE-401, a Bispecific Protein (2023.02.22)



Efficient induction of Tregs from diverse repertoire is expected to restore the balance of immune cells to help patients suffering from autoimmune and inflammatory diseases.

https://cuebiopharma.gcs-web.com/node/8111/html revised

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As for modalities other than CAR-T, the approach of modifying cytokines to extract only the good parts of their effects is gaining renewed attention through engineering technology and biological elucidation.

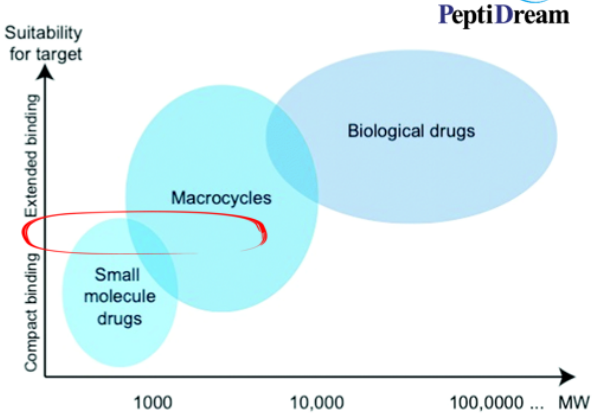
We have also signed an option agreement for CUE-401, which Cue Biopharma is working on, since we are interested in its potential of dual-specificity fusion protein to both IL-2 and TGF-beta.

This is an approach focusing on regulatory T cells, or Treg. I think it is well known recently that Tregs play a role in tumor immunity by suppressing the immune response to attack cancer in the tumor microenvironment.

In the case of autoimmune diseases, on the other hand, if the regulatory T cells are more active both quantitatively and qualitatively, the excessive autoimmune response will be suppressed. We are hoping to induce Tregs efficiently with a wide range of repertoires to treat the inflammatory T cells in autoimmune diseases that tend to be rich.

License agreement with PeptiDream Inc. on automated Peptide Discovery Platform System (2021.03.01)

Characteristics of Specialty Cyclicpeptide Drug Discovery			
	Small molecule	Specialty Cyclic peptide (Middle molecule)	Antibody (Large molecule)
MW	<500	500 – 2000	150000
Specificity	Low	High	High
Oral administration	Available	Available	Not available
Intracellular targets	Available	Available	Difficult
Off-target toxicity	Low – mid	Low	Low
Cost of goods	Low	Low	High



RSC Chem. Biol., 2022, 3, 7-17

Expansion of modality options suitable for tough targets by utilizing the original Peptide Discovery Platform System (PDPS)

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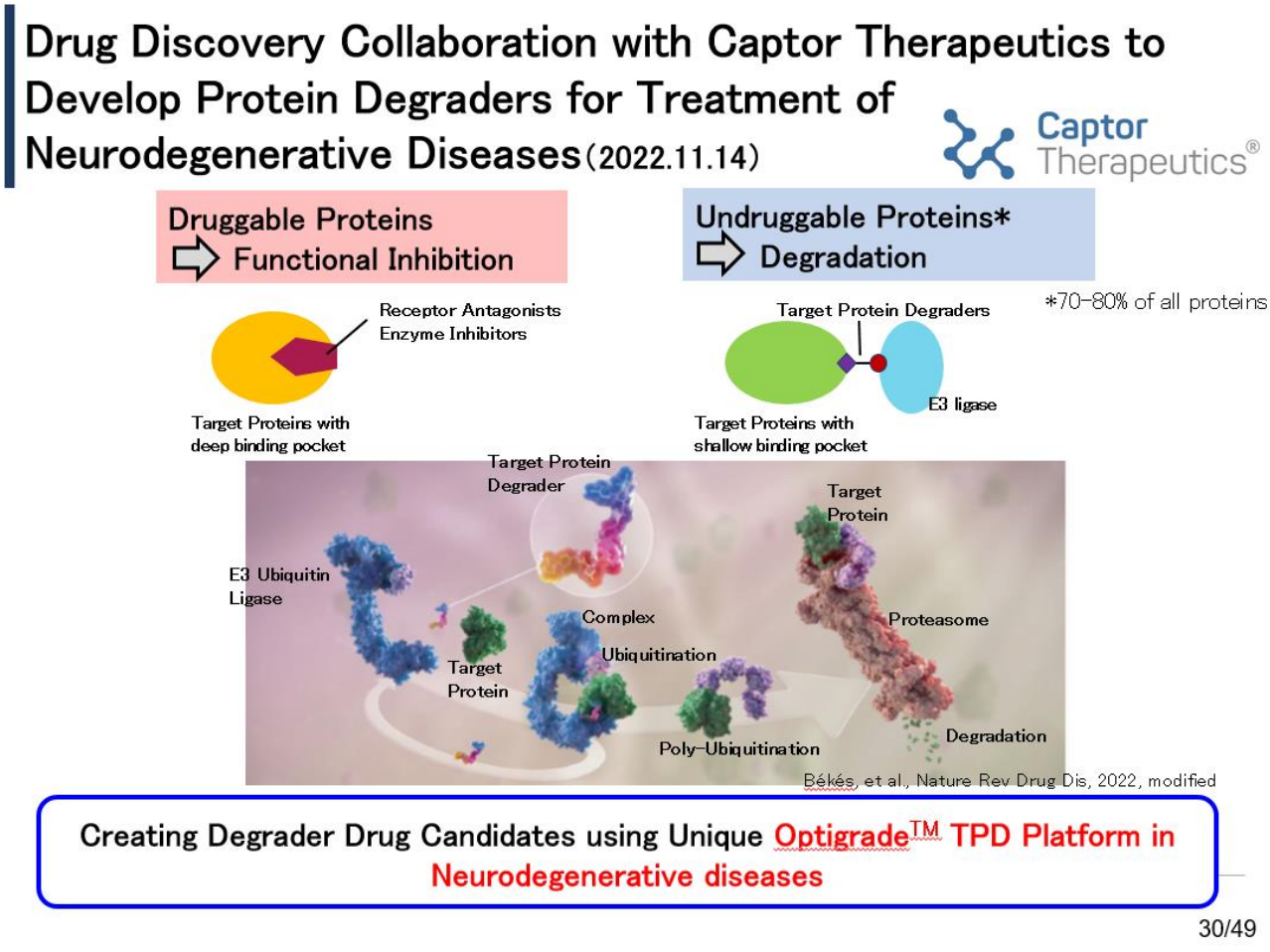
As for cyclic peptide, we are working on as a modality option, in cooperation with PeptiDream Inc.



We are also working with Captor Therapeutics in Poland to apply this approach to targeted protein degradation, TPD.

These are the open innovations we are working on regarding drug discovery modalities.

Drug Discovery Strategy

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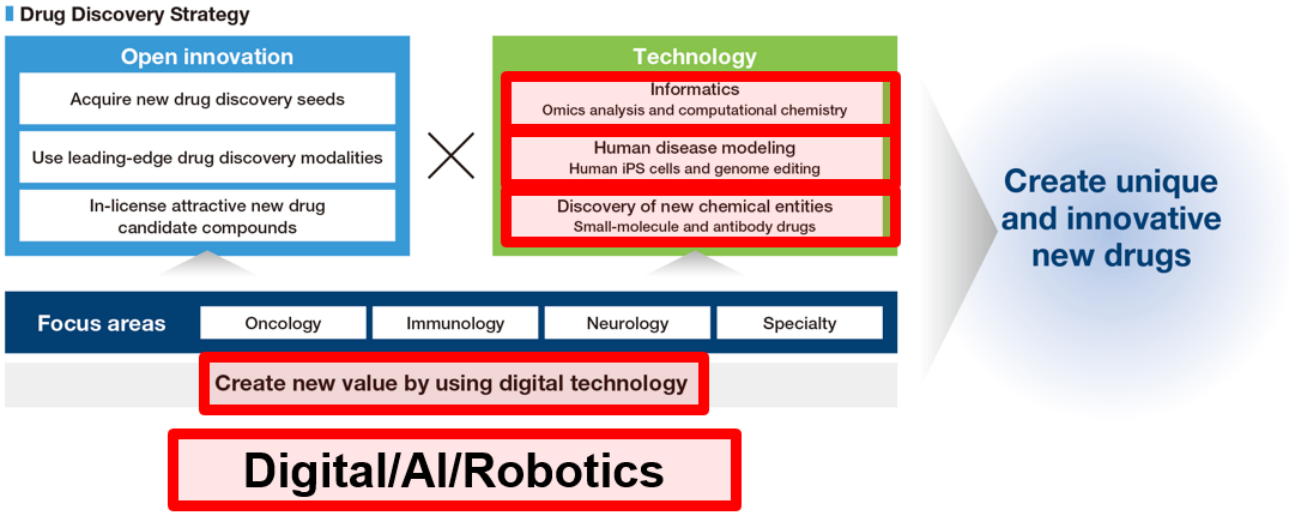

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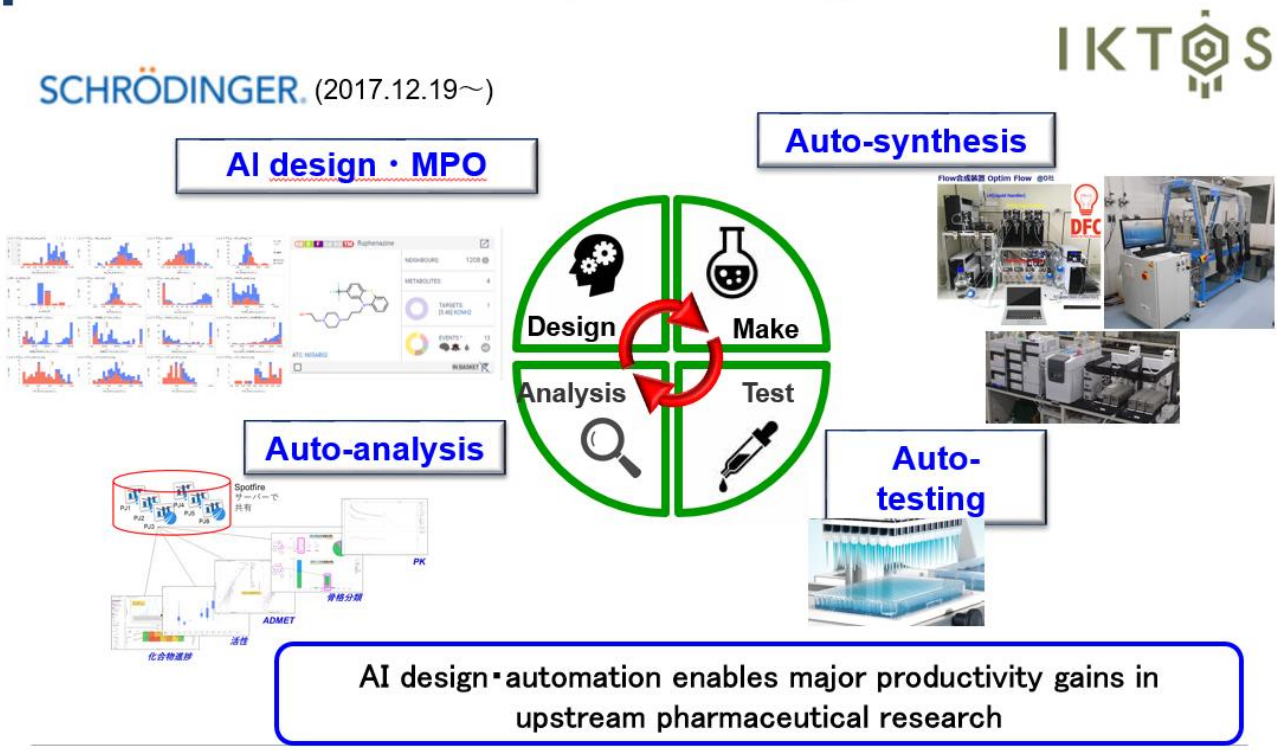
I have talked about drug discovery seeds and drug discovery modalities. I would like to finish with a little update on what we are doing in other technologies, such as digital, AI, and robotics.

Collaboration agreement with Iktos to discover and develop a novel small molecule using AI technology.(2022.03.30)



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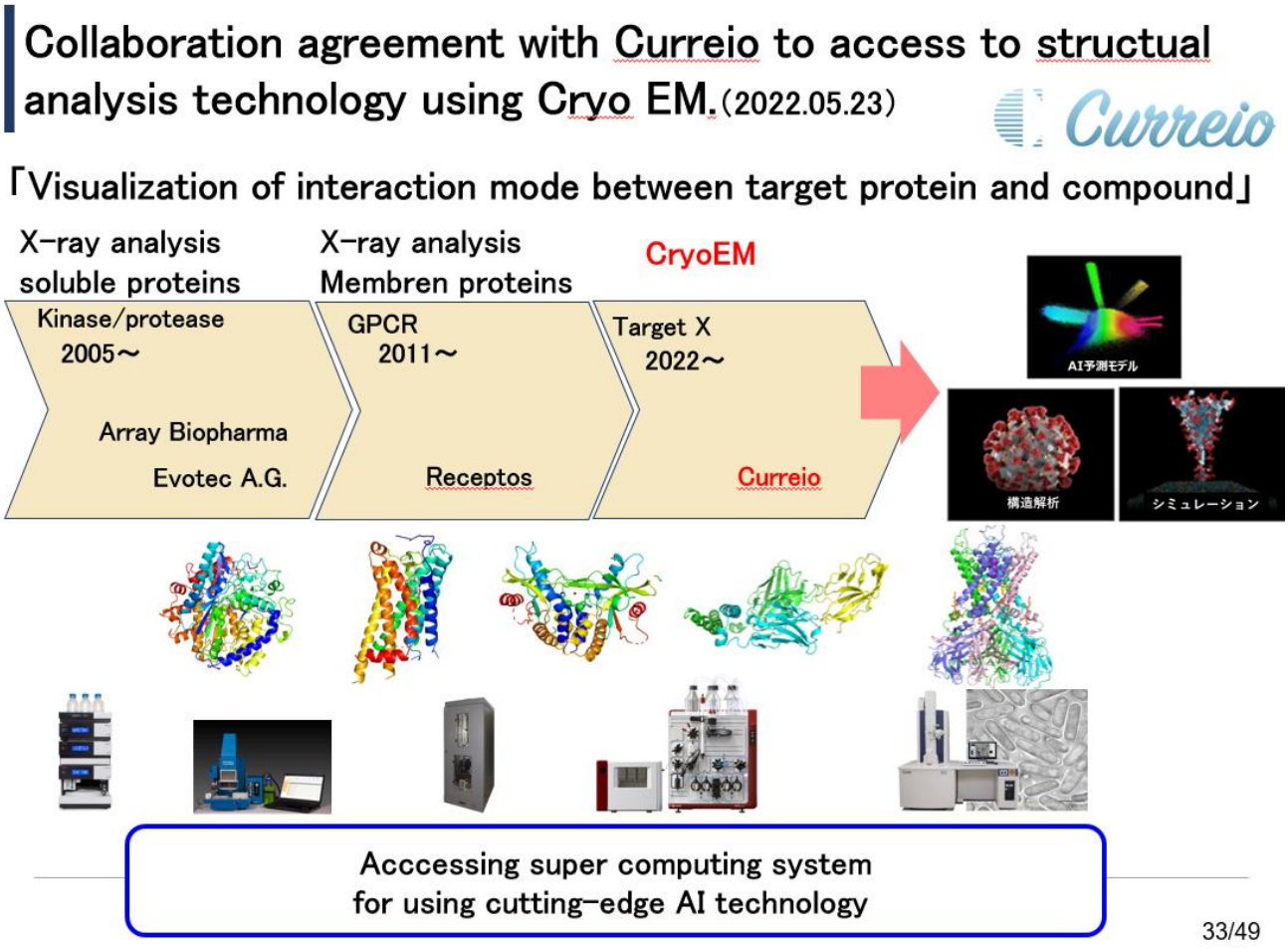
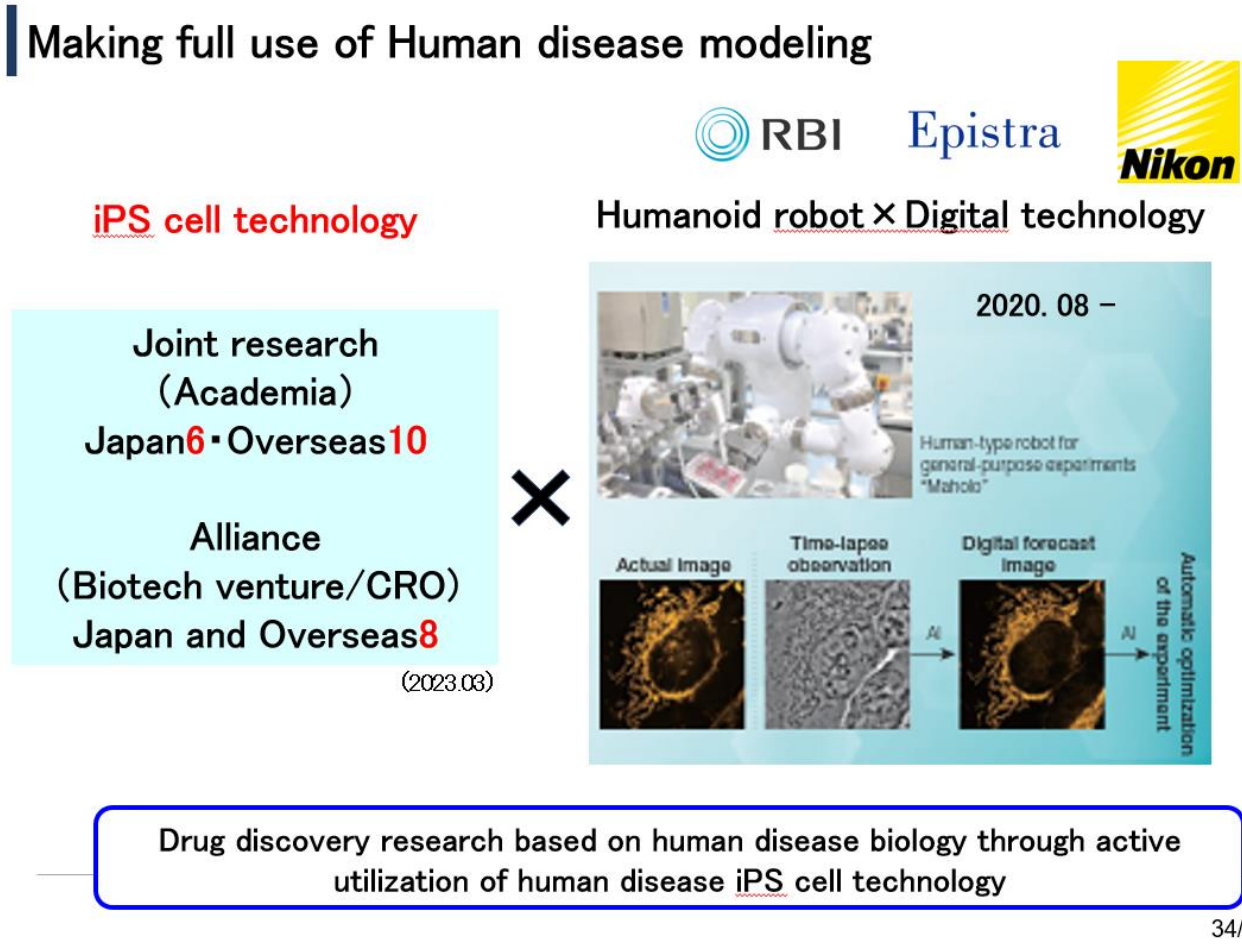
As you can see here, we have introduced automated robots in our company for the small-molecule creation cycle that can be automated. We are also working to make the synthesis cycle as efficient as possible by using the AI design in the upper left corner to make predictions, and we are refining the technology here by incorporating the AI design of Iktos.



In addition, with regard to the visualization of target proteins, it is no longer necessary for me to mention that the level of electron microscopy has been improved as well as X-ray structural analysis. We are now conducting joint research with Curreio, Inc. and working to improve these visualization technologies and link them to drug discovery.

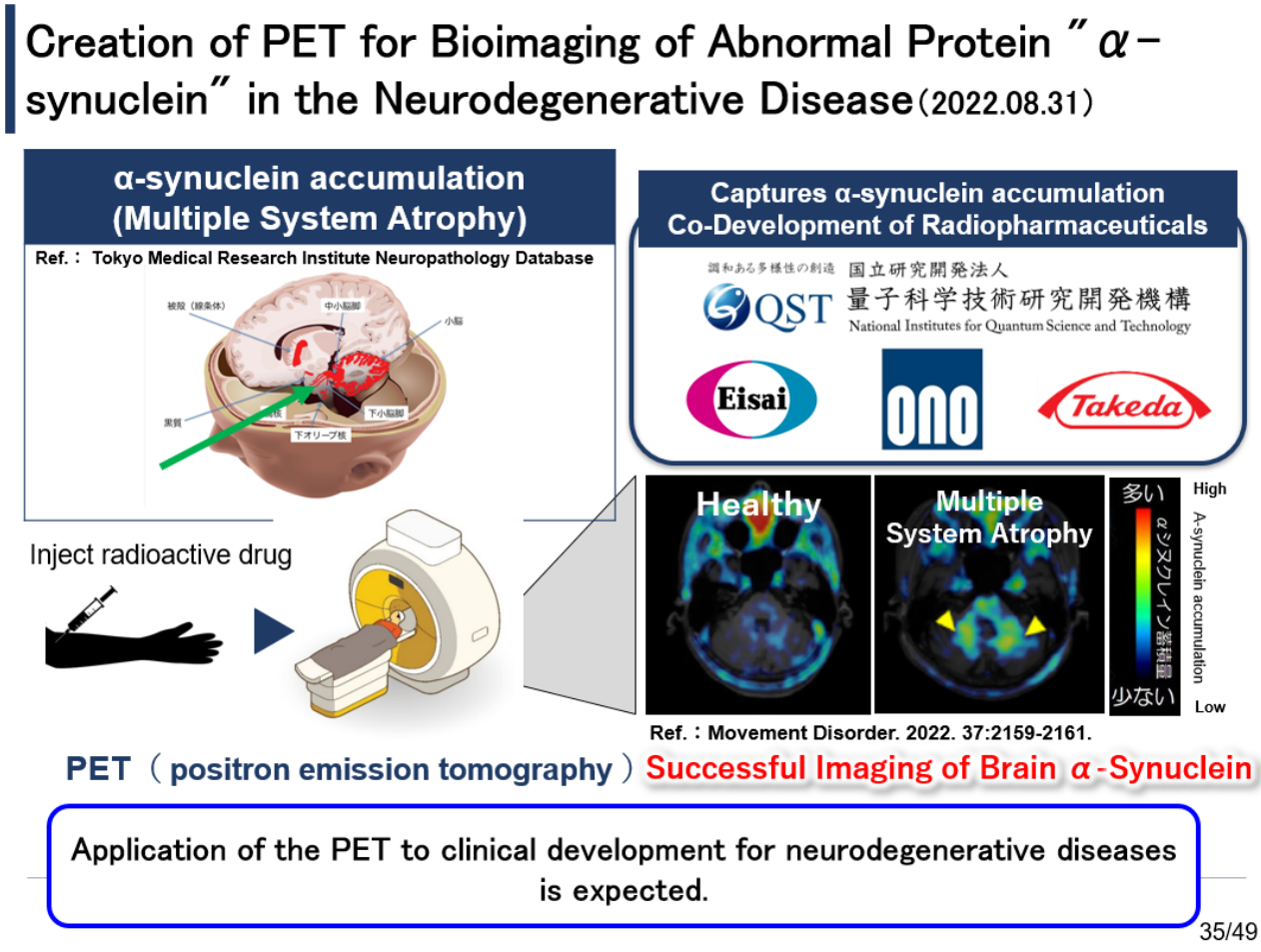
We may announce this at a later time in the future, but we are planning to use supercomputers to further accelerate and enhance the process while making full use of the latest AI technology.



I would like to mention one thing about iPS. iPS is very important not only for direct therapeutic applications, as in the case of CAR-T mentioned earlier, but also as a tool for drug discovery evaluation.

It has been nearly three years since we introduced Mahoro, a humanoid dual-armed robot, and we are steadily establishing an evaluation system to overcome the difficulty of reproducibility, which is the challenges of using iPS cell.

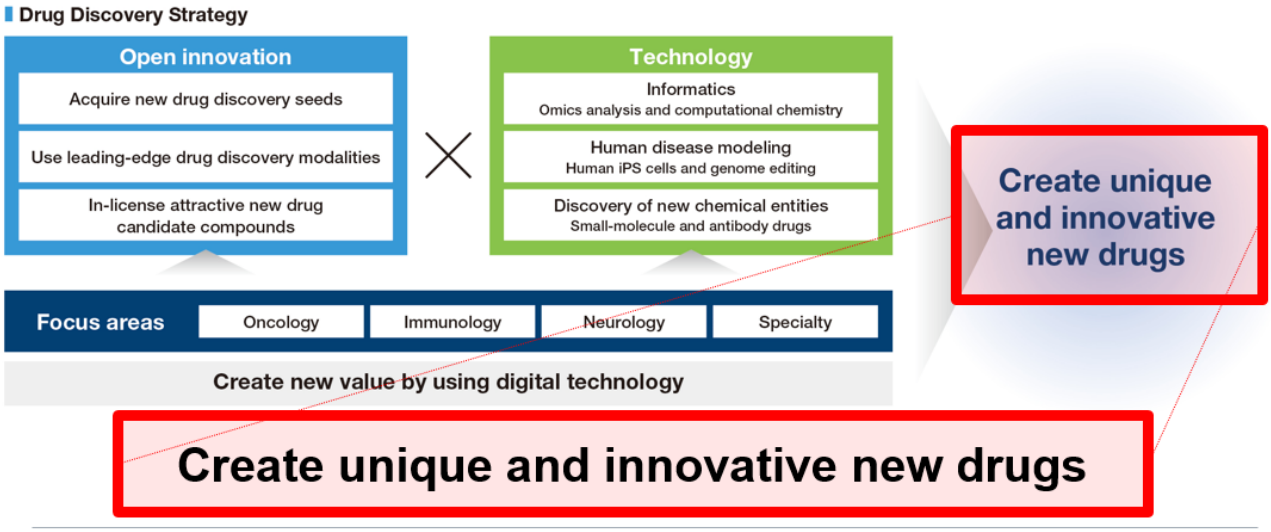
Based on this, we are working with various partners in Japan and overseas to create a variety of systems. We would like to continue to use iPS as a valuable evaluation system that reflects human biology and disease biology in a robotic form, and we would like to develop it into image analysis.



In the area of image analysis, we are working with National Institutes for Quantum Science and Technology, QST. The importance of synuclein as one of the protein aggregations in neurodegenerative diseases is becoming increasingly clear, and we have finally succeeded in developing PET ligand. I hope that we will be able to link the drug discovery to clinical development in this area of disease in the future.

Drug Discovery Strategy

「Open Innovation」×「Technology」
allows us create unique & innovative new drugs



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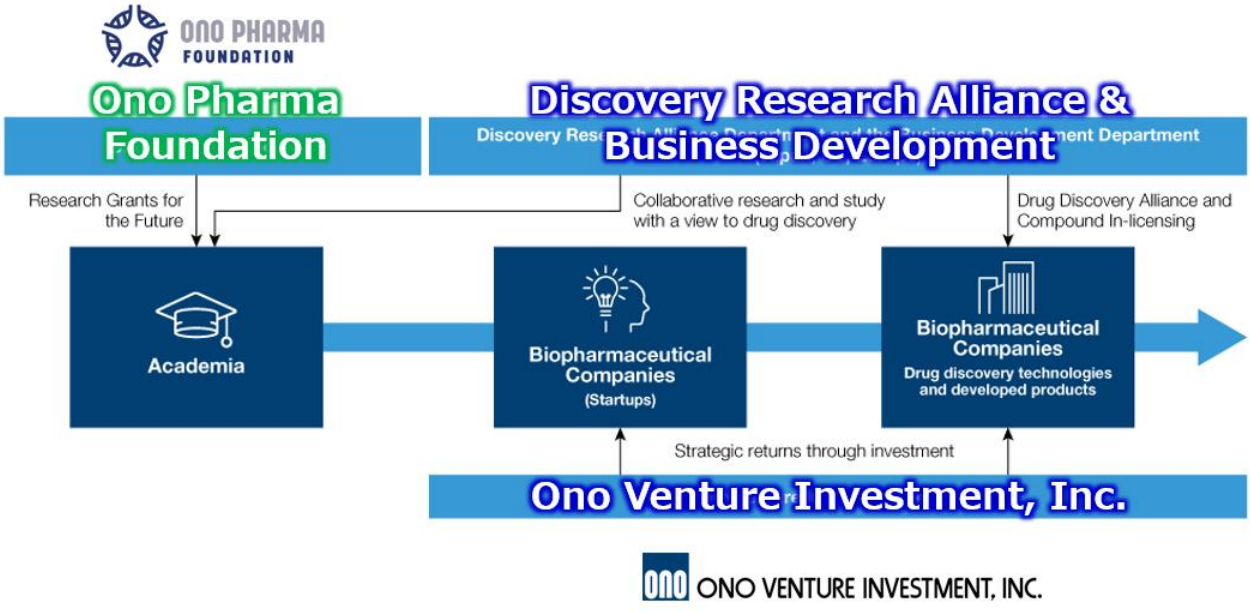
We are confident that this kind of open innovation will eventually lead to the creation of unique and innovative new drugs by actively promoting open innovation, while incorporating seeds and technologies of drug discovery, including modalities. I would like to briefly touch on how we have created a system to support this open innovation itself.

Promotion System to Support Open Innovation Driven Drug Discovery



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We have Ono Pharma Foundation, which promotes research grants to top academics in the US, and Ono Venture Investment, which focuses on start-up ventures. We also have the discovery research alliance department, which promotes research with ventures and discovery in alliances with academia, and the business development department that aims at partnering for the projects on clinical stage. We work on with these three pillars in this system, and in particular, the business development department and the discovery research alliance department are committed not only for financial investment but also for human resources, with a total of about 100 people working in these divisions.

I think it is unusual for a company of our size to be committed to external alliances, and that we are actually starting to gradually see the output of this commitment.

Investment to the start-up Bio-Venture

ONO VENTURE INVESTMENT, INC.

Start-up		Outline
Mediar Therapeutics	Cambridge, MA, USA	• Bio-Venture for development of new drugs for the treatment of fibrosis
Curreio	Tokyo, Japan	• Bio-venture for drug discovery based on detailed protein structure information by cryo-electron microscopy
Immunitas Therapeutics	Waltham, MA, USA	• Bio-Venture Committed to the Creation and Development of Novel Therapies for Cancer Patients
arbor	Cambridge, MA, USA	• Bio-Venture for New Gene Editing Therapy with a Unique DNA/RNA Degrading Enzyme • Established based on the achievements of the Broad Institute and Harvard University
casma therapeutics	Cambridge, MA, USA	• Bio-Venture for Development of New Therapeutic Drugs through Targeted Degradation by Autophagy

https://www.onoventure.com/news

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As for Ono Venture Investment (OVI), these are our current portfolio. While I will not mention about the portfolio companies, we invest in ventures that excel in a variety of technologies, including fibrosis, electron microscopy, oncology, gene editing, and AUTAC technology.

Research Grant Activities by the Ono Pharma Foundation in the United States

ONO PHARMA FOUNDATION

Ono Pharma Breakthrough Science Initiative Awards Program:

is the embodiment of the Foundation's commitment to focus on and accelerate researcher-driven open innovation by supporting high-risk and high-reward science research projects which have potential to lead to science discoveries/solutions and, possibly, based on further research, to breakthrough treatments for patients.

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Prof. Carolyn R. Bertozzi
Stanford University
2022 Nobel Prize Winner in Chemistry

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Ono Pharma Foundation in the US has world-renowned scientific advisory board professors on board. We have one bright and happy news. Among one of them, Dr. Bertozzi of Stanford University was awarded the Nobel Prize in Chemistry last year for click synthesis. Looking back on our history, we believe that we have been able to work together at such a high level of high science, and we would like to lead to the creation of new epoch-making drugs. We believe that there is the groundwork to do so.

This is all from me, and I summarized our efforts through open innovation extensively. I think I could explain how we value open innovation very highly and are striving for drug discovery in a way that is driven by it.

We will continue to take on challenges that other companies cannot, and we will continue to create more and more materials for our company's growth.

That is all from me.

Itolizumab

Ono and Equillium Announce Exclusive Option and Asset Purchase Agreement for the Development and Commercialization of Itolizumab (5 Dec, 2022)

Partner	Equillium, Inc (CA, USA)
Compound Name	Itolizumab
Mechanism	Anti-CD6 antibody
Characteristics	Highly safe FIC drug that change T-cell status to treat autoimmune diseases
Indications and stages	Acute graft-versus-host disease* (aGvHD) : Phase 3 Lupus nephritis : P1b study
Formulation	i.v.(aGvHD) ／ s.c.(Lupus nephritis)
Rights acquisition region	US/Canada/Australia/New Zealand, (Biocon／CIM** reserve rights in all other Region)

- aGvHD : Complications after hematopoietic stem cell transplantation, a treatment for hematologic cancer
- CIM : Centro de Inmunologia Molecular

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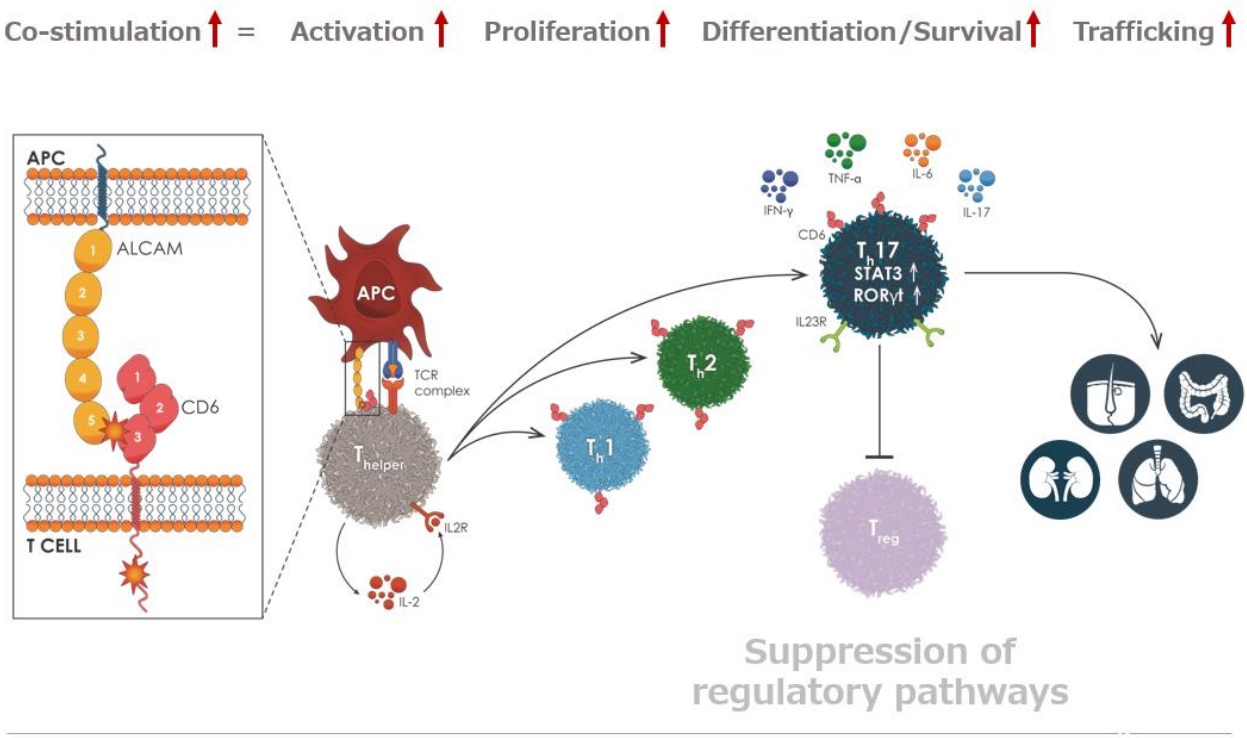
Idemitsu: I would like to introduce Itolizumab.

In addition to our own research, we are also actively engaged in the acquisition of external assets. Itolizumab is a compound for which we obtained an exclusive option rights from Equillium in the US last December for development and commercialization in the US and countries around.

It is an antibody product targeting at CD6 and is intended for acute graft-versus-host disease, acute GVHD, and lupus nephritis. It is a compound that will contribute to the expansion of our pipeline in the immunology area, one of our priority franchises.

CD6 Drives Pathogenic T Cell Activity & Trafficking



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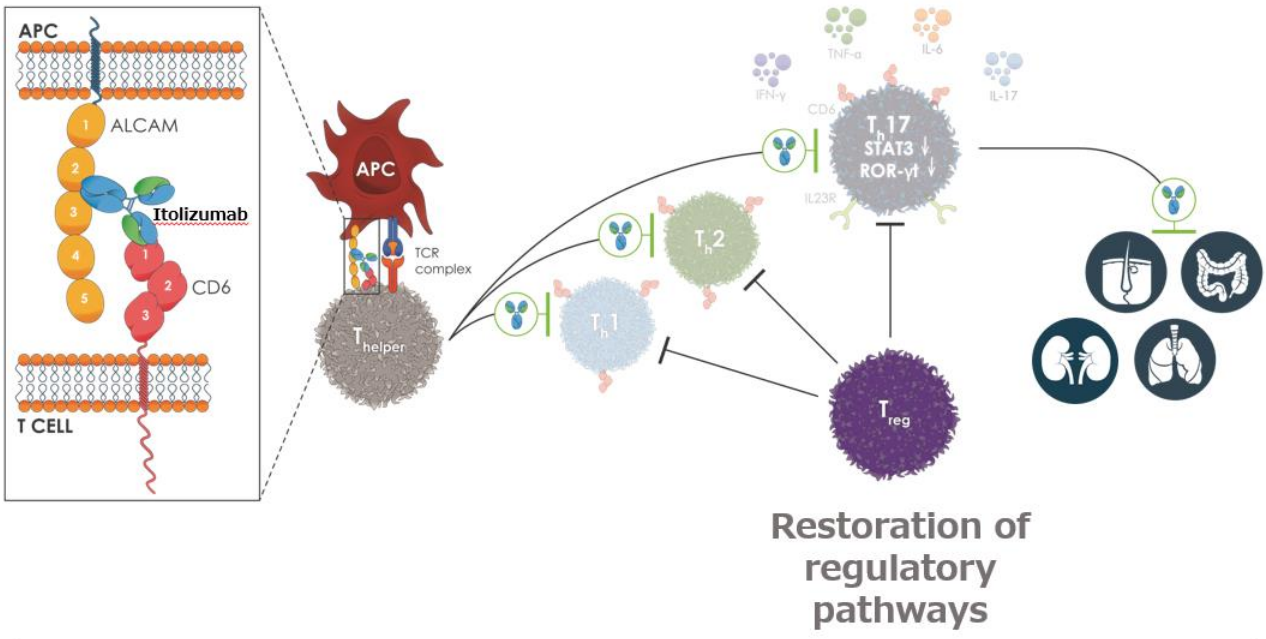
CD6 is expressed on T cells and involved in adhesion. T cells are activated by attaching to various cells to produce an immune response. For example, cells adhere to each other by binding CD6 on T cells and ALCAM expressed on APC, antigen-presenting cells.

T cells become activated, proliferated, and differentiated. Autoimmune disease occurs when activated T cells cause an abnormal immune response in various organs.

Itolizumab inhibits pathogenic T Cell Activity & Trafficking

Co-stimulation = Activation | Proliferation | Differentiation/Survival | Trafficking



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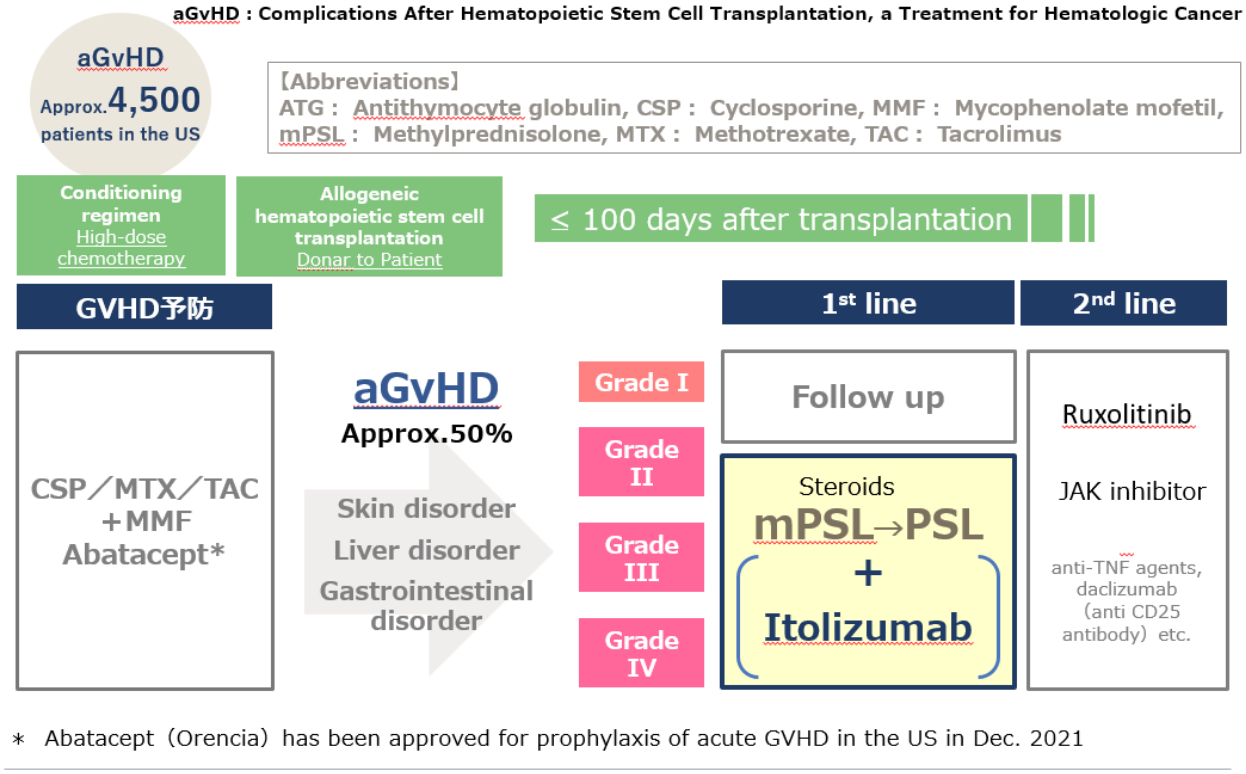
Itolizumab suppresses abnormal activation, proliferation and differentiation of T cells by inhibiting the binding of CD6 and ALCAM, thereby controls autoimmune diseases.

aGvHD treatment guideline in the US



＊ Abatacept（Orencia）has been approved for prophylaxis of acute GVHD in the US in Dec. 2021

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First, I will explain GVHD, one of the target indications. Hematopoietic stem cell transplantation (HSCT) is one of the treatments for blood cancers such as leukemia. When hematopoietic stem cell transplant is performed, GVHD is caused when immune cells of the transplanted donor attacks the cells of patient, recipient side.

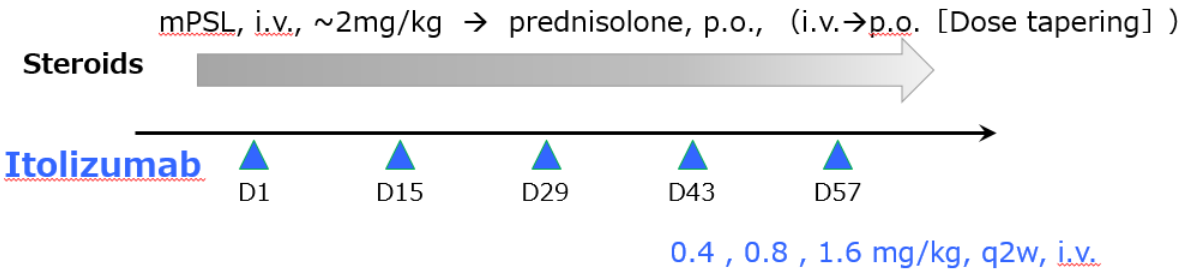
GVHD develops in less than 50% of transplant patients. According to the literature, depending on the severity of the disease, in patients of Grade 3 and 4, classified into high risk, more than 40% patients will die within six months. This is a very serious disease.

In addition, in patients of Grade 1 and 2, classified into standard risk, more than 20% patients will die within six months.

GVHD is a very serious disease. Steroid has been used for the treatment. First, methylprednisolone, an injectable steroid is administered, followed by oral steroids. By adding Itolizumab to this, we expect additional effects.

Phase 1b study - EQUATE study

Evaluate the clinical activity and safety of Itolizumab on top of steroids, as 1st line treatment for aGvHD



- **Scoring of skin, liver, and gastrointestinal symptoms were evaluated**

at D15 and D29.

- **CR (Complete Response) : Disappearance of all symptoms.**

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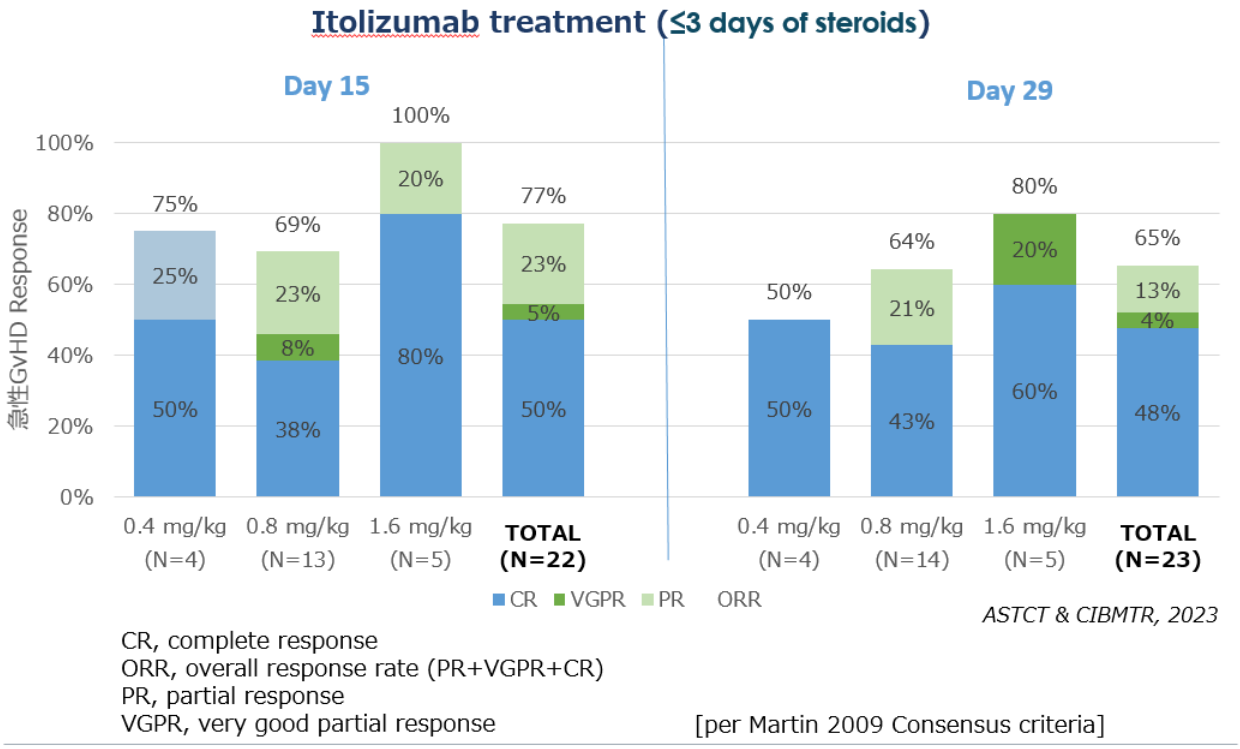
In Phase I, Itolizumab is administered every two weeks for five doses with steroids. In three dose regimens of 0.4, 0.8, and 1.6 mg/kg, it is evaluated for complete response rate on disappearance of all organ lesions.

High Response Rates to Itolizumab + Steroids



CR, complete response
ORR, overall response rate (PR+VGPR+CR)
PR, partial response
VGPR, very good partial response

[per Martin 2009 Consensus criteria]

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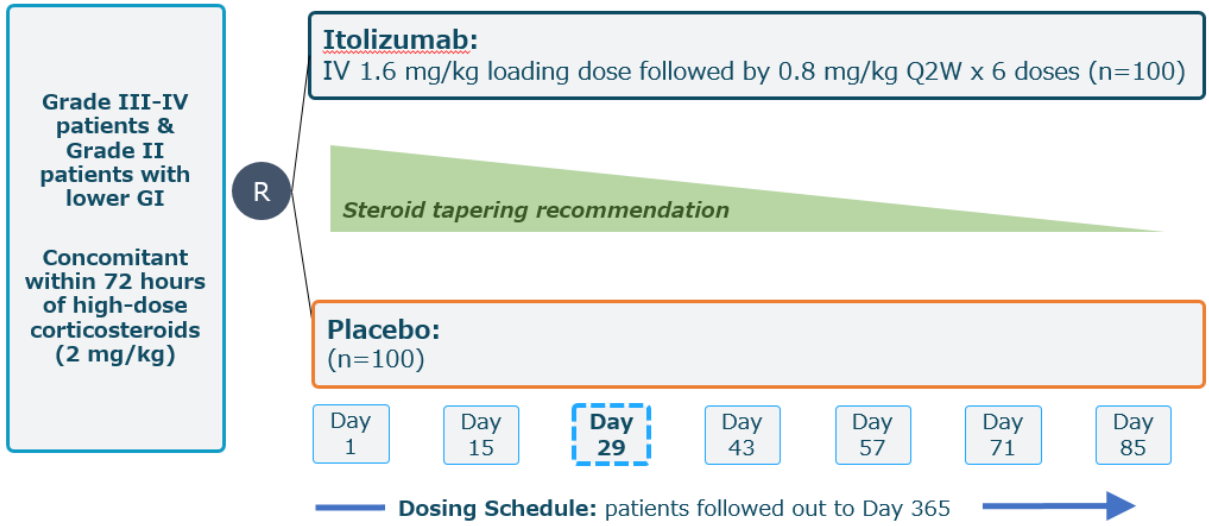
Here are the results. As you can see, the high dose of 1.6 mg produced 60% complete response. Generally, the response rate for standard therapy, so-called steroid therapy, is 30% to 40%. We consider that the additional effect was suggested.

Phase 3 Study for aGvHD （EQUATOR study）



- Primary Outcome : Complete Response Rate at Day 29
- Secondary Outcome : Durability of Complete Response Rate from Day 29 through Day 99

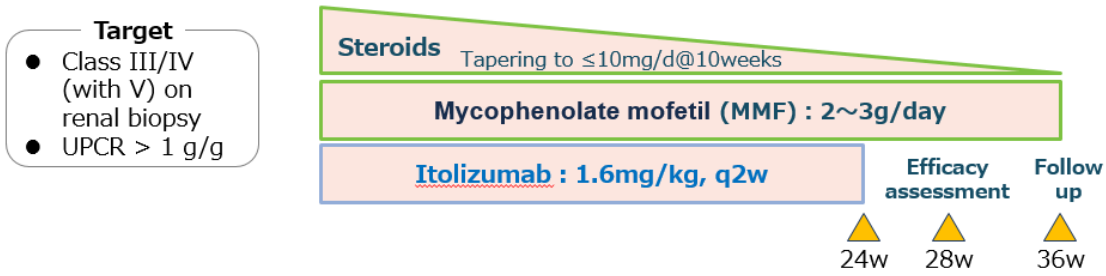
(Interim DSMC Review @ 100 patients) 47/49

Phase III is currently underway. In Phase III, Itolizumab (n=100) is evaluated versus placebo (n=100) in high risk patients Grade 3 and 4, as well as Grade 2 having the lesion of lower gastrointestinal tract. The primary endpoint is complete response rate at day 29.

We will decide whether to exercise the option rights based on the results of this interim analysis.

P1b Study for Lupus Nephritis (EQUALISE study)

Evaluate the efficacy and safety of Itolizumab as an add-on to Steroids + Mycophenolate mofetil



Complete Renal Response

- **UPCR : ≤0.5 g/g**
  (urine protein/creatinine ratio)
- **eGFR : Not less than 20% below baseline**
  (estimated glomerular filtration rate)

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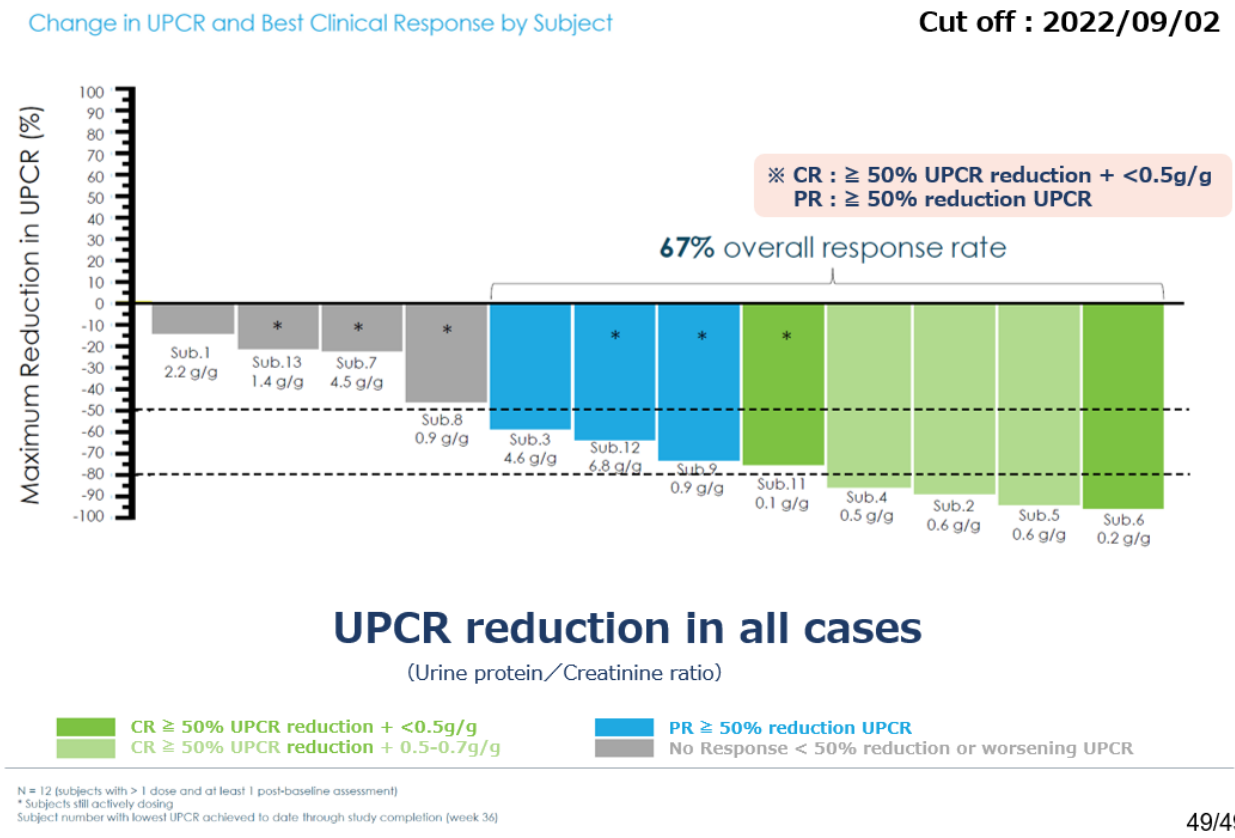
Next, I will explain another indication of lupus nephritis. Lupus nephritis is a disease where the development is very difficult, although the therapeutic agents have recently been approved gradually.

Generally, the combination of steroids and an immunosuppressive agent, Cellcept (mycophenolate mofetil) is used for the treatment of lupus nephritis. Phase 1 is ongoing with Itolizumab by adding this combination therapy. The primary endpoint is complete renal response.

P1b Study for Lupus Nephritis



Here are the results of the ongoing Phase I, still in 12 patients. The dark green color is the complete response. It is still in progress, and the primary evaluation will be conducted at week 28. More than half of the patients have not yet reached week 28. The UPCR, which is an index in all cases, is downward, indicating that a response has been obtained in the previous cases, and the complete response has already been observed in some cases. Although it is still immature result, we believe that this suggests a response on the efficacy.

In addition to the GVHD mentioned earlier, we plan to determine option rights by evaluating the top line data from this lupus nephritis study.

That concludes my introduction for Itolizumab.

Question & Answer

Questioner 1: As for Itolizumab that you just explained, can you tell me when you expect the results of GVHD, lupus nephritis, and LN will be available?

Idemitsu: We have not disclosed a definite time frame, but we do not expect it to take that long.

Questioner 1: Is it correct to imagine that each of them will appear sometime in 2023?

Idemitsu: I believe it will be out by 2024 when we will decide if we will exercise the option.

Questioner 1: I understand. This Itolizumab, I think there was some talk during the last Q3, that if this is the first of the US development or Velexbru. I think these two are not overlapping in terms of business and separate from each other. Is my understanding correct?

Idemitsu: Do you mean timing or franchise?

Questioner 1: I mean the way of sales or commercial platform.

Idemitsu: Both are covered by hematology, so we believe there is a synergistic effect.

Questioner 1: I understand. May I assume that you are still putting in or acquiring from the outside some of these products for the launch of Velexbru, targeting about 2025 or 2026? Is that correct?

Idemitsu: We are always willing to actively acquire assets, not limited to this area.

Questioner 1: I understand. Thank you very much. I think there was a modality chart somewhere showing various projects with various modalities. Looking at that chart, of course, you are doing a lot of biologics. There is only one peptide in terms of the number of projects. After trying various ways of doing this, do you think that you are very satisfied with the current form of the alliance, or do you think that it is difficult to increase the number of peptide project or the priority is declining?

Takino: That is starting as a technique, and we have not yet seen the budding of this technology in any particular area, so we are keeping it in this form.

I think we will be able to develop the project in the future, perhaps in the form of drug discovery alliances, rather than just general technology licensing. However, the current implication is that we have secured one of the modalities as a technical license.

Questioner 1: What is the progress so far, as expected or rather faster or slower than expected?

Takino: It's 50-50. It is also true that this is an area that requires much more know-how than expected. On the other hand, I believe that the potential of cyclic peptides is high, and I know that some other companies are actively explaining this to the public.

Questioner 2: At the beginning of the presentation, I think the president mentioned something that you changed the idea a bit from the "Compound Orient" approach. When I started covering your company, the first impressive word I heard was Compound Orient. I wonder whether this method worked or not in the end. If it worked well, I would like to know a little bit about what came out of it. This is my first question.

Takino: Looking back at the history so far, I think it is appropriate to describe our attitude of pursuing interesting compounds as the Compound Orient approach, such as prostaglandins and PD-1.

However, as the time passes, I think it is natural that the drug discovery approach itself evolves as various biological mechanisms are being elucidated, which could be called translational research. Various technologies and information such as gene editing and informatics are becoming available.

In today's presentation, I think that various ventures are delving into biology using various proprietary technologies.

We believe that it is now essential to catch up with those as the importance of the expertise, knowledge, and know-how of the disease is increasing. We have been conducting research on CNS, along with cancer and immunology for many years, but have had no drugs for CNS. Therefore, we have decided to raise a sign and work on these areas as a franchise in these four priority disease areas, while the fourth is all-around.

It is also true that the commitment to the central nervous system has contributed to the acceleration of iPS research and infrastructure. I believe that we are now entering an era that commitment to the biology side is extremely important. I hope I answered your question.

Questioner 2: In relation to this, I would like to ask you about your company's concept of a drug discovery platform, or to put it another way, a technology platform. I think it will be difficult to develop this platform if it is based on this approach or research approach.

Takino: In general terms, I think that argument will come up. However, I think it is worth mentioning that all the researchers are consciously working to strengthen the inside by using the outside.

In other words, what kind of things will be created as a result of the inward-looking thinking of inside, I think such an approach is highly questionable in this day and age. We believe that our strengths will ultimately grow as a result of our efforts to incorporate a variety of things through trial and error, and if we find a great fit, we will expand and explore it.

Questioner 2: Finally, about Itolizumab, are they the only indications? If only those, I'm not sure if it is enough to draw much attention to it. What do you think?

Idemitsu: I think these two indications alone are interesting, but other indications besides them are under investigation. We cannot say anything, as the data has not yet been available, but we are conducting or preparing clinical trials for other diseases as well.

Questioner 2: Is it an inflammatory system?

Idemitsu: It is an autoimmune disease.

Questioner 1: Now that we are talking about other indications of Itolizumab, isn't this the one that it has been approved and is marketed for psoriasis in India by Biocon, I believe? Based on that, do you think psoriasis is not so interesting?

Idemitsu: Biocon, an Indian company, has launched it for psoriasis, as you mentioned. It has an excellent safety profile and a significant difference in efficacy compared to placebo, but we have not yet decided whether we will develop it for psoriasis because we need to compare to existing drugs in terms of efficacy.

Questioner 1: If I subtract out everything except psoriasis, with my thin imagination, the only thing left is UC/CD, which is the most competitive and difficult. Is it the wrong way to look at it?

Idemitsu: I think it's not too far off the mark in the sense that there is unmet need. I have to refrain from stating it here because of the other company. However, in the sense that unmet needs remain, we think that colon is one candidate indication.

Questioner 1: There are, of course, other possibilities besides the ones just discussed.

Idemitsu: If T cells are involved in all autoimmune diseases, I think there is a possibility to control them by suppressing T cell adhesion

Questioner 3: First of all, there were questions about Itolizumab, so I would like to continue with that. I would like to consider the GVHD potential of this drug and would like to know a few things first.

In terms of this first line treatment of GVHD, you mentioned steroids earlier, but should we only consider steroids as a competitive agent? Since it is an add-on, I don't think steroids are basically a contender, but I would like to know if there are any new drugs that could be a contender in the first-line treatment.

Also, you have given us the number of target patients as 4,500. I think the target patients are between grade 2 and 4, but approximately what percentage of them each?

Also, you said that you will consider options during 2023 in that development plan, so maybe Phase III will be finished during 2023, but I think there is a little bit of time blank between the time and the market launch in 2026. I think it would be possible to get it on the market a little earlier, as I feel that this type of thing would come with priority review and such, but could you tell me more about that?

Idemitsu: We are thinking of going first for the first-line treatment.

We are not disclosing the timing when the result will be available. We will have the interim result in 2024. Based on the interim result, we will decide whether or not to exercise the option, and then the trial will continue for a little longer.

Of the 4,500 patients in the US, we estimate that the number of patients with grade 3, 4 and grade 2 lower gastrointestinal disorders, which are currently the target of Phase III, is roughly about half of the total number.

Questioner 3: Secondly, and lastly, I understand your current approach to fundamental technologies and modalities from the slide on page 10, but could you tell me about your company's structure for managing these projects? How does your company respond to each of these companies? For example, I would like to know if there is a group for small-molecule oncology and if staff of the group is handling this or how your company manages this.

I also think that since you are running so many projects, some of them will be able to enter into clinical trials more and more as they work out. When it comes to reality, I think that the organization of your company to implement Phase I will become an issue, or rather, a point that needs to be further strengthened. Could you please tell us about your current status in that area, the first-in-human clinical trial system? That is all.

Takino: The way we work together in the drug discovery phase varies considerably depending on the project and the partner. However, if the medicinal chemistry or synthesis part is the main collaboration, for example, that is where each concerned division will work together directly. Depending on the tasks, the partner may do all the work, or they may work with us on a 50-50 basis. It varies depending on cases. All projects are carried out in close cooperation with the respective sites, as I mentioned the medicinal chemistry as an example.

Questioner 3: Is this being adequately handled on-site? I think you are affiliated with quite a few now.

Takino: Yes, that's right. I think it has been working well and will continue to do so.

Idemitsu: Next is regarding Phase I. We have a system in place in Japan to implement Phase I without any problems, and we also have experience in implementing many Phase I trials even in Europe, so we can do so without any problems.

In addition, we have recently implemented Phase I in the US, and by further focusing on this, we have established a system that enables us to implement Phase I as quickly as possible in any area without problems. We have almost established a system where we can conduct Phase I studies in any regions as firmly as possible, taking into consideration the next phase, and are now in the process of further strengthening the system.

Questioner 3: Then I understood that you have a system in place that can manifest in the number of pieces that you have given us on the 10th slide.

Questioner 4: Let me confirm about Itolizumab, although it overlaps a little bit with what you mentioned earlier. In the Phase III EQUATOR study, the primary completion date is December 2023 according to the clinical trials. Does it mean an interim analysis? Also, I believe you have got first track and orphan drug designations. Can you tell me if the application is possible depending on the results of the interim analysis, or does the interim mean that the decision is only for the futility?

Idemitsu: The details are confidential, so I am sorry I cannot disclose. However, the interim analysis for our judgement is the result from 100 cases. After that, we will basically apply for approval after obtaining the final results after conducting the study in the rest of 100 cases.

Questioner 4: By the way, do you have any information about the current recruiting state?

Idemitsu: We have just started, so it is a bit difficult to say.

Questioner 4: Looking at Equillium's slides, there are about three different dates for the exercise of option rights. Will you make a decision based on the top line of lupus nephritis and the interim analysis of the EQUATOR trial?

Idemitsu: We plan to make a decision on both together.

Questioner 5: First of all, you introduced the various modalities that your company is currently working on. In the field of oncology, in my opinion, the most exciting things in the field of oncology are the undruggable target and cold to hot. In short, you would like to make PD-1 work more effective in patients in whom PD-1 is ineffective. These two things are still very exciting for us as a person involved in the market.

Looking at the current list of modalities, I see that undruggable is probably the case with Captor Therapeutics. I think that attaching to something that is difficult to attach in the first place, then degrading and inducing it, is a high hurdle in its own. Also, looking at the pipeline in the US, everyone is going to bispecifics rather than ADCs. I think that this multi-specific antibody is probably the main thing.

That being said, the CD3s and such are pretty much filled up. I'm vaguely thinking that maybe you need to do something different. I'd appreciate any feedback on my thoughts if I'm wrong.

Also, ONO-4578 was my personal, one of the most promising stocks that Japanese companies are doing among the cold to hot. You didn't say anything on it, so I wonder what happened there. It has the most clinical programs. Could you please explain that first?

Takino: You are wondering what I think about the idea of drug targets or drug discovery trends in oncology that you just mentioned. However, it is presumptuous for me to say something about it.

I think it's not always a promising oncology drug discovery target for Cold to Hot or hard targets.

It is true that the number of hard targets is increasing, but recently I am positively thinking to some extent that the width of drug discovery targets such as non-coding will spread more and more in the future. I would like to emphasize that we are not pessimistic about the future of drug discovery targets.

Having said that, I think it is true that each one is still becoming more difficult and complicated. Therefore, I think that the risk of limiting to one modality, as well as the point made earlier, are a double-edged sword. I believe that if we keep our windows open widely and are able to use modalities with agility and master them, it will be a great advantage. It is a bit off topic.

I would like Mr. Idemitsu to comment on ONO-4578 later, but this time, we are here to talk about the efforts and directions of new drug discovery in terms of open innovation. As we have compiled the information from the press releases, I would like to omit the issues related to ONO-4578 this time. I am sorry.

Idemitsu: Thank you very much for your attention on ONO-4578. We are in the middle of a PoC trial for various cancer types. Please wait a little longer for the results.

We are hypothesizing that resistance to I-O can be lifted by antagonizing EP4. We hope you can wait a little longer.

Questioner 5: Is it ok to assume that you will have some update on this around 2023 to 2024?

Idemitsu: About the timing of the result, I will be able to tell you when it is clear.

Questioner 5: Lastly, Itolizumab. If I look at GVHD, I think that Ruxolitinib or JAK2 are probably the most recently approved for acute GVHD. As you said, the complete response rate of these products is probably around 30%, your data shows as it is. However, the number of patients is still small in your company, so this is not enough to make a difference. Also, the dose response is not very clear, so I wonder if acute GVHD is a bit risky.

Also, as for lupus nephritis, belimumab is proceeding, so yours is certainly much more effective comparing to it. I think the definition of partial response and complete response is a little different over there, but I think it’s about 40% in terms of partial response. Your compound will probably get about 70% if you do it with them.

What I don’t understand well is I guess the UPCR was about 3.3. I think you need to set the same baseline as used in the belimumab trial. Can I understand that yours is on the same baseline as in the trial of belimumab? This is my last question.

Idemitsu: First of all, as for GVHD, the JAK inhibitor is now approved for second-line treatment, but not for first-line treatment. It is true that the n number is less. For that reason, we now secure the option right to wait for the results. Regarding lupus nephritis, I am not able to reply to your question because I have no base line data on the UPCR at hand right now.

[END]