Chugai Life Science Park Yokohama Laboratory Tour

CHUGAI PHARMACEUTICAL CO., LTD.

18 July 2023

Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

Agenda

01

Initiatives Underway at the New Research Facility Aimed at Creating Innovative New Drugs

Dr. Hitoshi Iikura

Vice President and Head of Research Division

02

Expansion of Drug Discovery Research that Fuses Dry and Wet Research

Dr. Atsushi Ohta

Head of Modality Technology Research Department

03

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

Dr. Takuya Torizawa

Head of Protein Science Department

Initiatives Underway at the New Research Facility Aimed at Creating Innovative New Drugs

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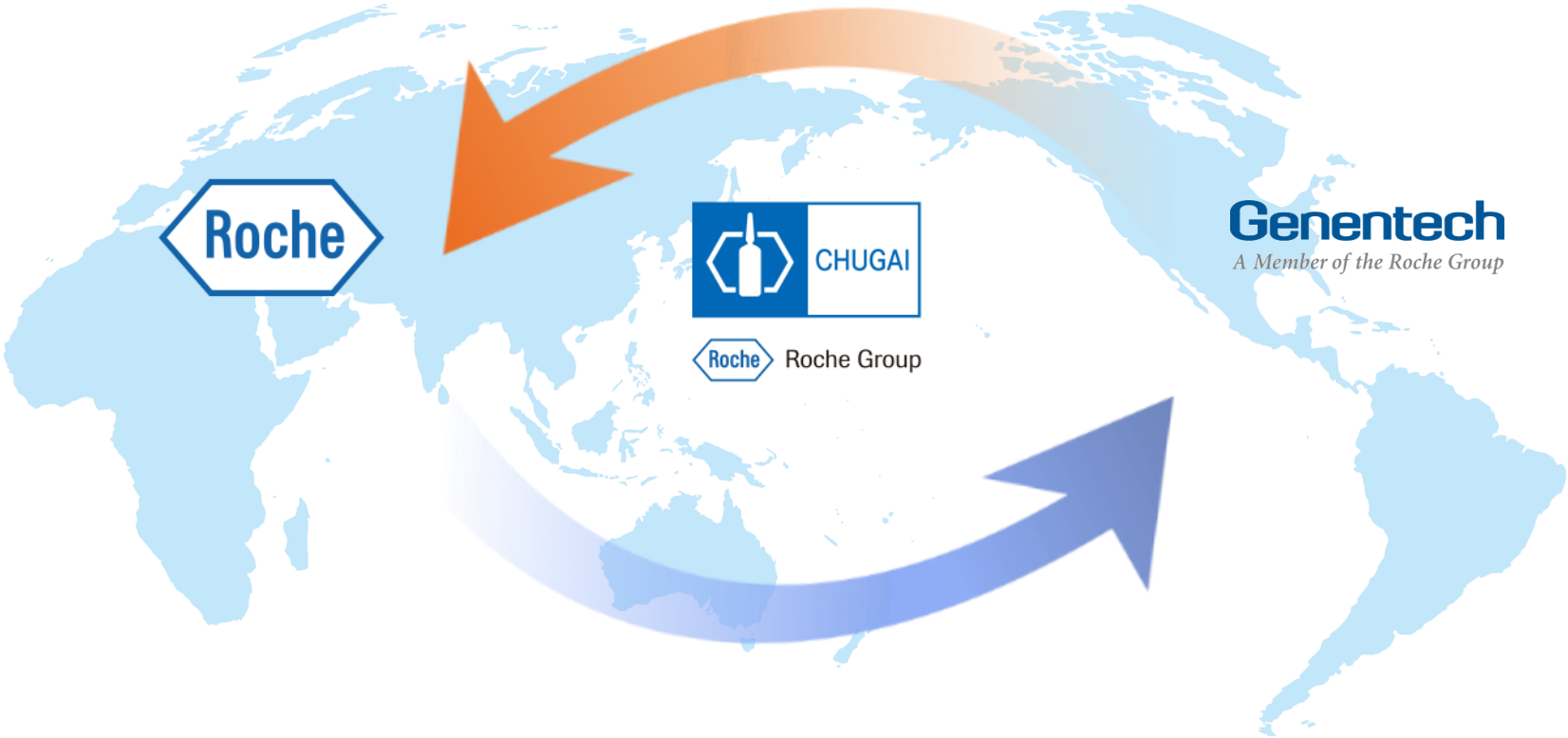
Strategic Alliance between Chugai and Roche

**Although Roche holds about 60% of all shares,
Chugai maintains independent operations and its listing in Japan**

- Roche rolls out new drugs developed by Chugai to the world
  (allowing Chugai to direct its resources toward drug discovery)
- Chugai rolls out new drugs developed by Roche in Japan
- Chugai is able to share research infrastructure (infrastructure such as compound libraries [banks]) with Roche



Drug Discovery Research Targeted by Chugai

Global first-class drug discovery

- Expansion of existing technological bases and building a new technological foundation (RED SHIFT)
- Materialization unique drug discovery ideas
- Collaboration with leading global players (Open Innovation)
- Leveraging digital technologies (Digital Transformation)

Chugai Life Science Park Yokohama is a key growth engine for Chugai Pharmaceutical in its capacity as an R&D-oriented pharma company

Chugai's Research Strategy: A Technology-driven Approach

- Enabling an optimal approach for disease targets by developing mid-size molecule drug discovery technologies in addition to antibody engineering technologies and small molecule drug discovery technologies
- Acquiring innovative "seeds" by enhancing oncology and immunology research infrastructure

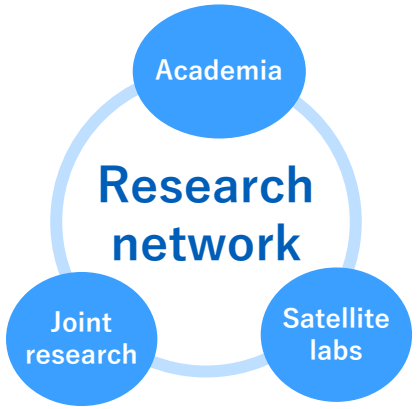
Disease-causing molecules

Selection of appropriate drug targets

Development of innovative drug discovery technologies

Matching technologies with targets

Meeting unmet medical needs

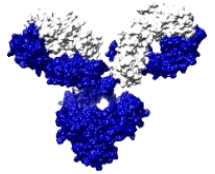


Next-generation (high-functionality) antibodies

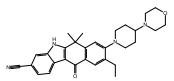
Small molecule drug discovery technologies

Mid-size molecule drug discovery technologies

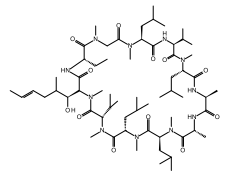
Conceptual illustration



Next-generation antibodies

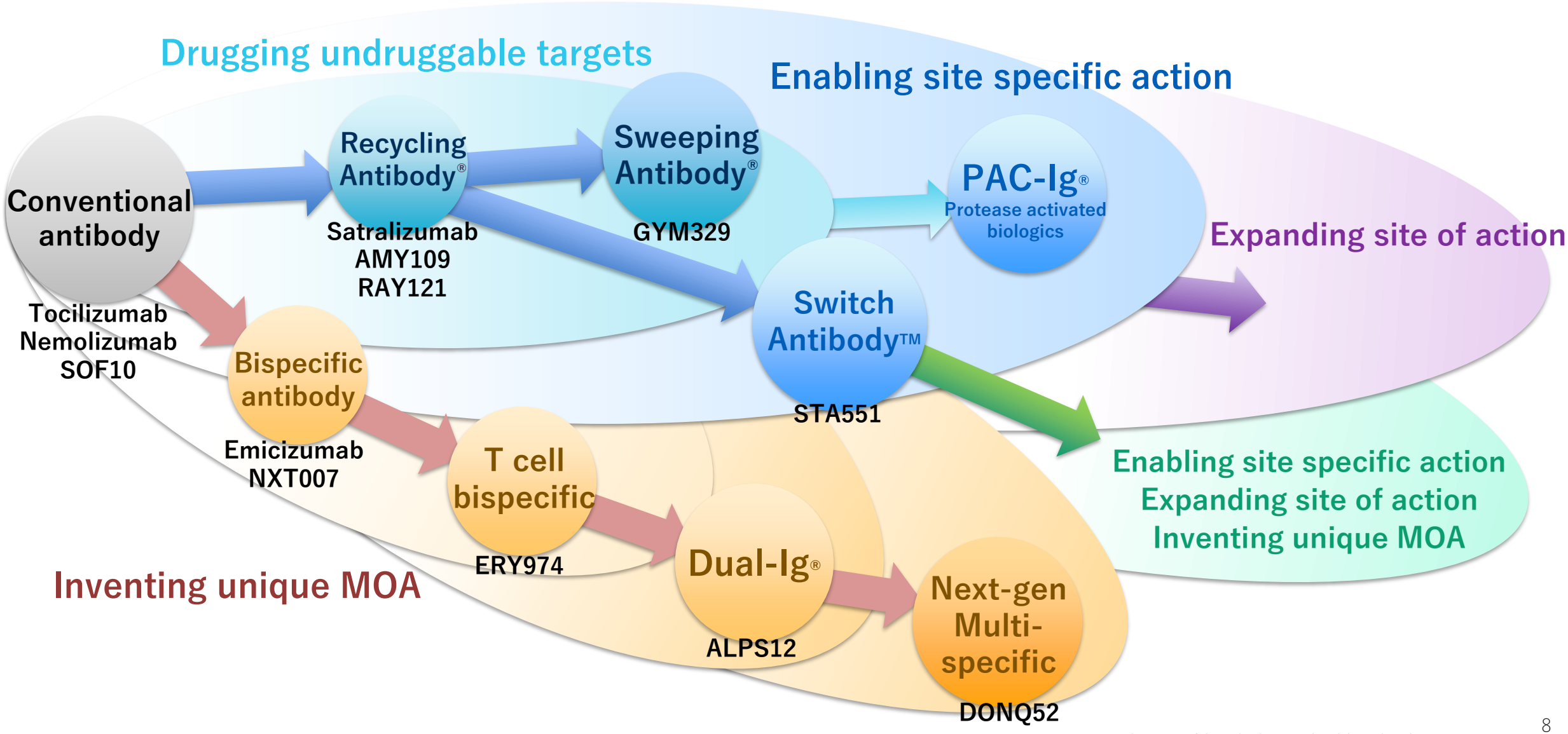


Small molecules



Mid-size molecules

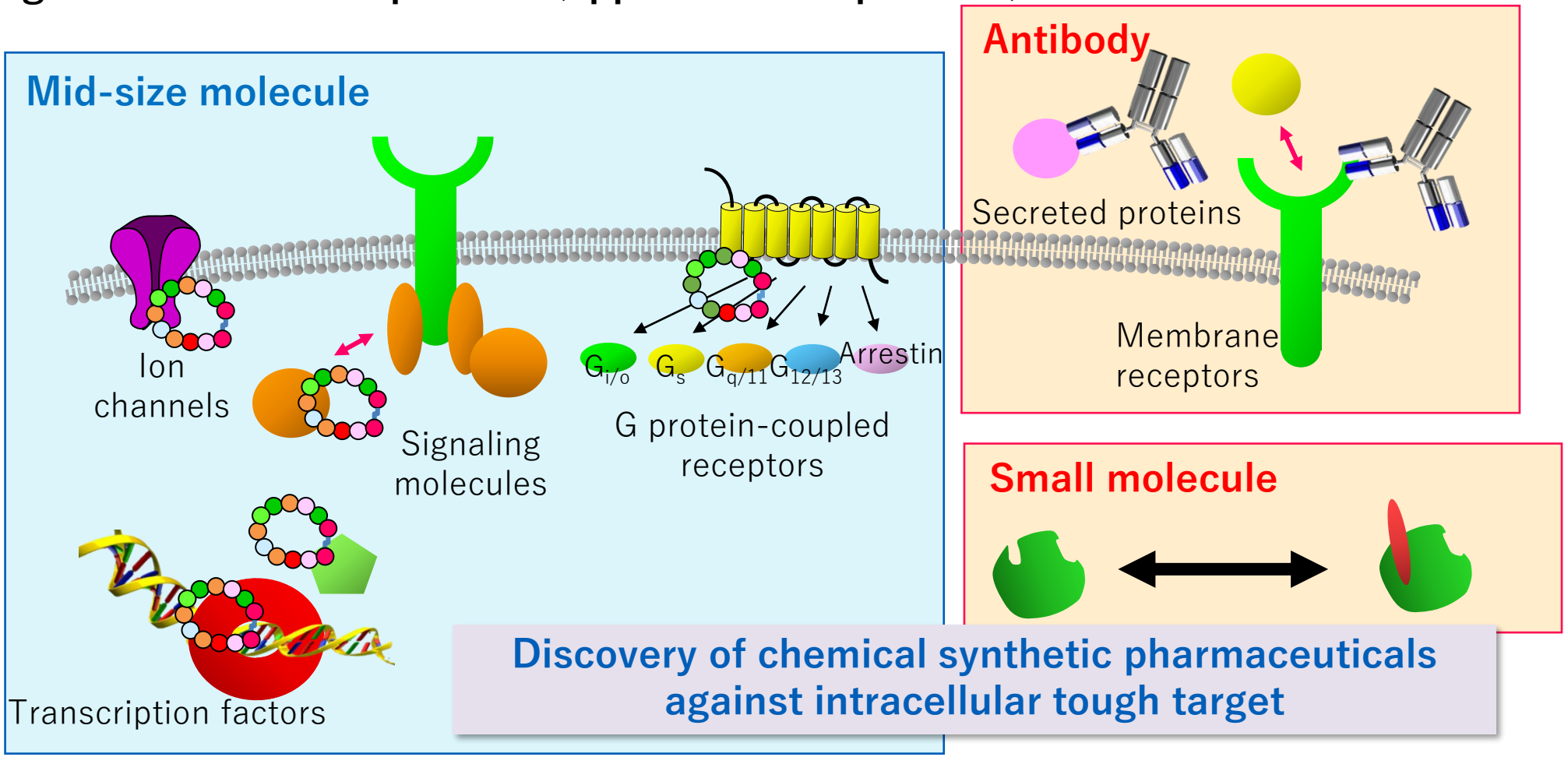
History of Antibody Technology Development at Chugai



Mid-Size Molecule: Challenge to Address UMN That Cannot be Resolved with Small Molecules and Antibodies

- Discovering drugs for intracellular tough targets without pockets (e.g., PPI)
- Antibodies target only extracellular molecules (approx. 20% of the total protein)
- Target molecules with pockets (approx. 20% of proteins)

PPI: Protein-Protein interaction



Drug Development Targeted under Chugai's TOP I 2030 Growth Strategy

Multi-modality drug discovery

Innovative drug discovery ideas

External collaboration

Incorporate from the outside "Wants" that Chugai does not possess

Multi-modality technology

Starting point of drug discovery

Biology-Wants

Targets and pharmacological effect targeted

Drug-Wants

Mechanism of action and profile wanted in drug discovery

Therapeutic Modality / Technology

Select most appropriate method from world's top modalities and technologies

Small molecule | Mid-size molecule | Antibody | New | Roche

Clinical development candidates

Foundation

AI-based drug discovery, next-generation lab automation, Chugai Life Science Park Yokohama

R&D Output **Double**

Productivity **Improve**

Drug Discovery Research at Chugai Life Science Park Yokohama

Promoting Collaboration among Researchers

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

Digital Transformation (DX)

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

Acquiring Personnel and Promoting External Collaborations

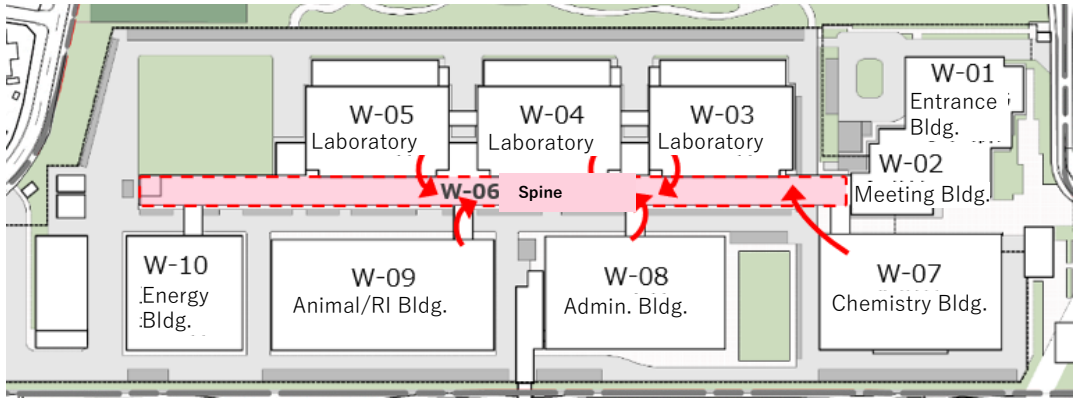
- Cutting-edge research environment and equipment will attract skilled personnel and strive to activate collaboration with academia.

Facilities and Equipment Designed to Spur Innovation

The Spine

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

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

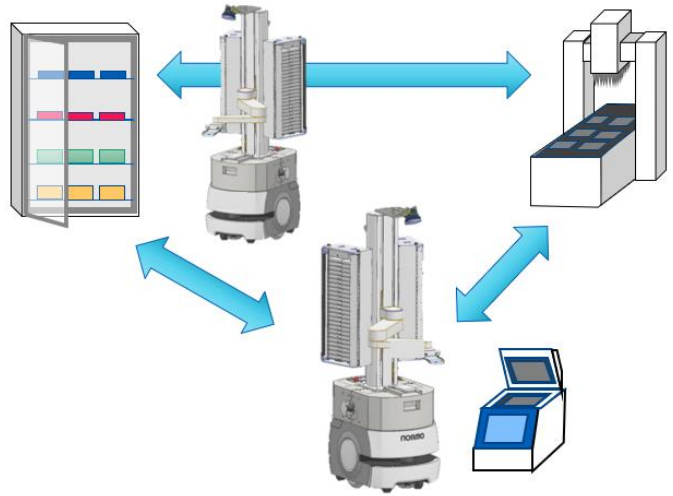


The Spine is a 300-meter corridor that connects the Park's laboratory and administrative buildings. The Spine has features that promote exchange among researchers.

Next-generation laboratory automation

Bringing about next-generation laboratory automation incorporating robotics technology

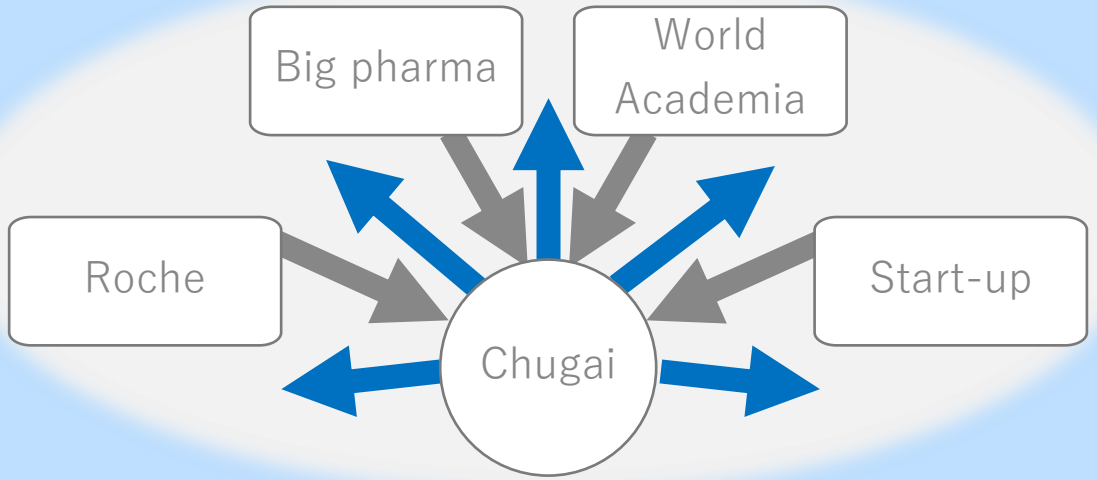
- **The adoption of self-propelled mobile robots and development of robot technologies will boost productivity in complex processes.**
- **Improvement of productivity will help researchers better work-life balance.**



Mobile robots connect automated instruments.

Breaking Away from Pure Self-reliance

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



■ External collaboration starting from specific Strategic-Wants

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

Designed with the Environment and Safety in Mind

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

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

Solar panels have been installed

Green infrastructure

Stormwater management

Expansion of Drug Discovery Research that Fuses Dry and Wet Research

Dr. Atsushi Ohta
Head of Modality Technology Research Department

Accelerating Digital Transformation with the Establishment of the New Research Institute

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

TOP INNOVATOR TOP i 2030

(1)Drug discovery

R&D Output

Double

Productivity

Improve

In Order to Fuse Dry and Wet Research at Higher Levels

Refining Hard Aspects

Enhancing “wet” capabilities

Overhauling lab automation

- Make more effective use of time at night and on weekends
- Expand the scope of robot use by assigning more complex tasks to them
- Allow robots and humans to collaborate flexibly

Massive amounts of data

New findings

Refining Soft Aspects

Enhancing “dry” capabilities

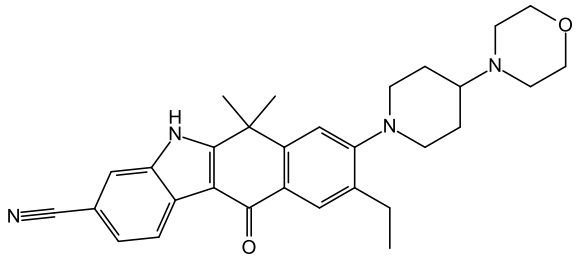
Developing digital infrastructure

- Build databases that allow massive amounts of data to be easily searched and utilized
- Automate routine tasks to reduce workloads

Enhancing digital personnel skills

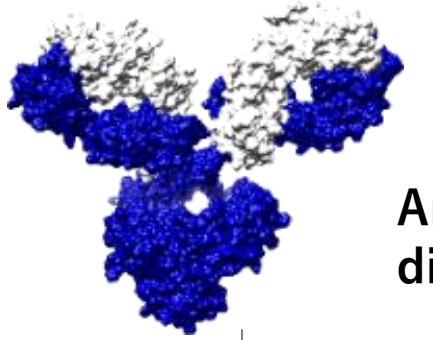
- Allow each researcher to develop their own apps/programs
- Implement digital training activities led by data scientists

Expanding the Scope of Automated Systems beyond Small molecule Drug Discovery

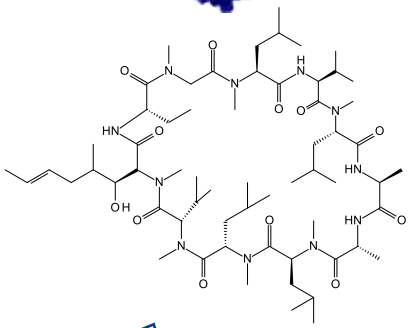


Small molecule drug discovery

- **Handle more complex tasks**
- **Bring about “Chugai Experimental Techniques”**

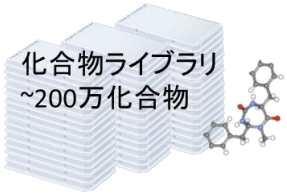


Antibody drug discovery



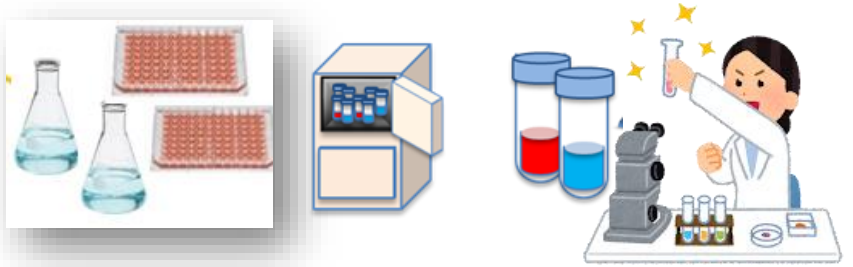
Mid-size molecule drug discovery

Handling Roche’s shared small molecule library



Assay

Preparation/assay of several thousand samples

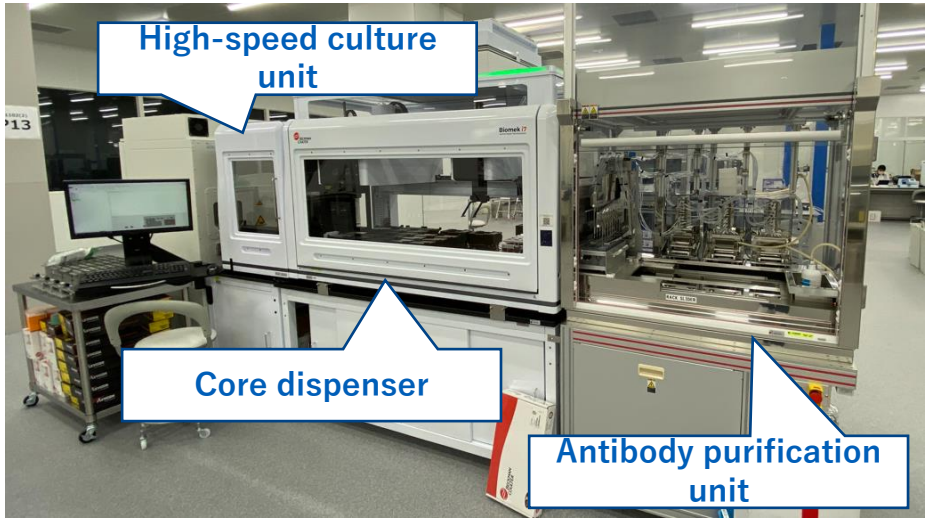


Succeeded in Making a Robot Perform Complex Operations that Chugai Researcher had Previously Done

Automated gene cloning system

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

Automated culturing and antibody purification system

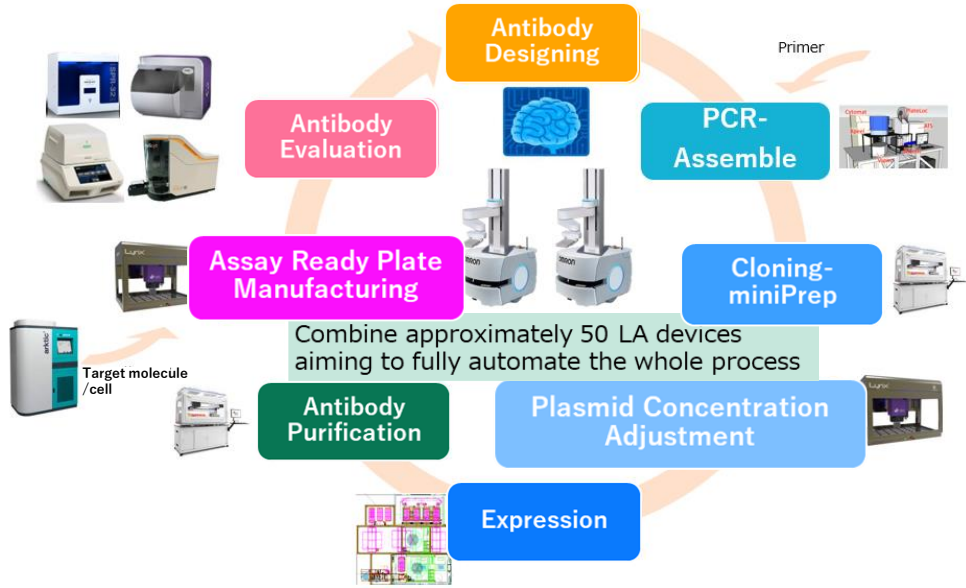


Cell culture (left) and antibody purification (right) experiments are done by one dispenser (middle). This has increased utilization and investment efficiency.

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

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

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



Automation of the antibody evaluation process using mobile robots is progressing

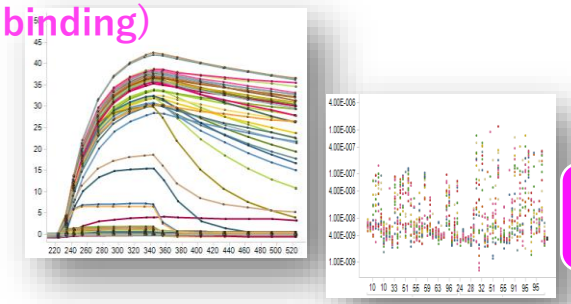
These Equipment Support COSMO

COmprehensive **S**ubstitution for **M**ultidimensional **O**ptimization

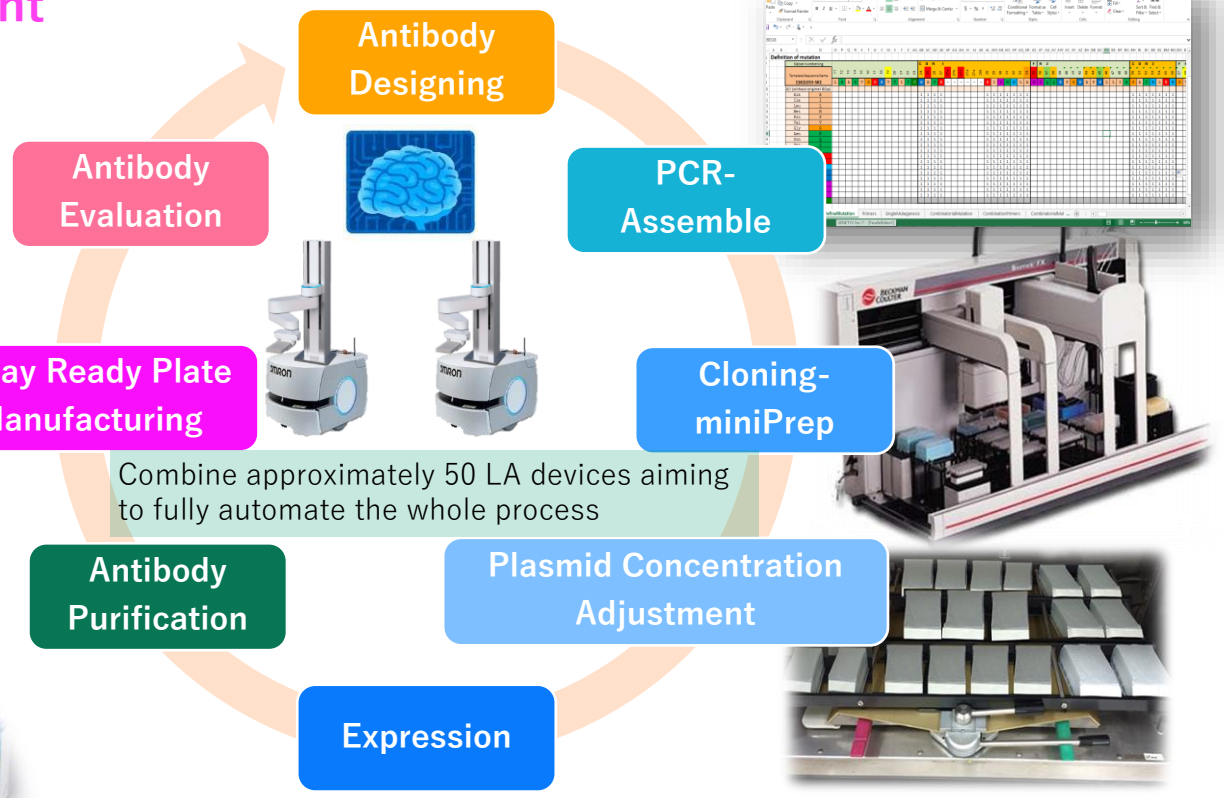
About 1300 types of antibodies (about 70 antigen binding regions × 18 amino acids) are made and evaluated for each lead antibody

✓ High-throughput affinity measurement
About 2000 times/week

✓ Multidimensional evaluation
(e.g., stability, solubility, immunogenicity, non-specific binding)



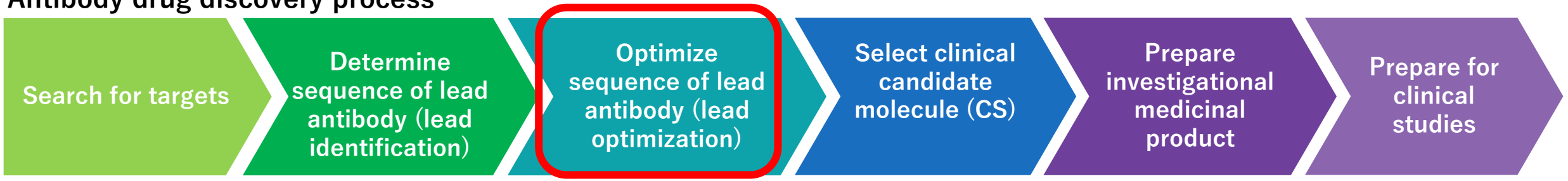
✓ High-throughput antibody purification
About 1500 molecules/day



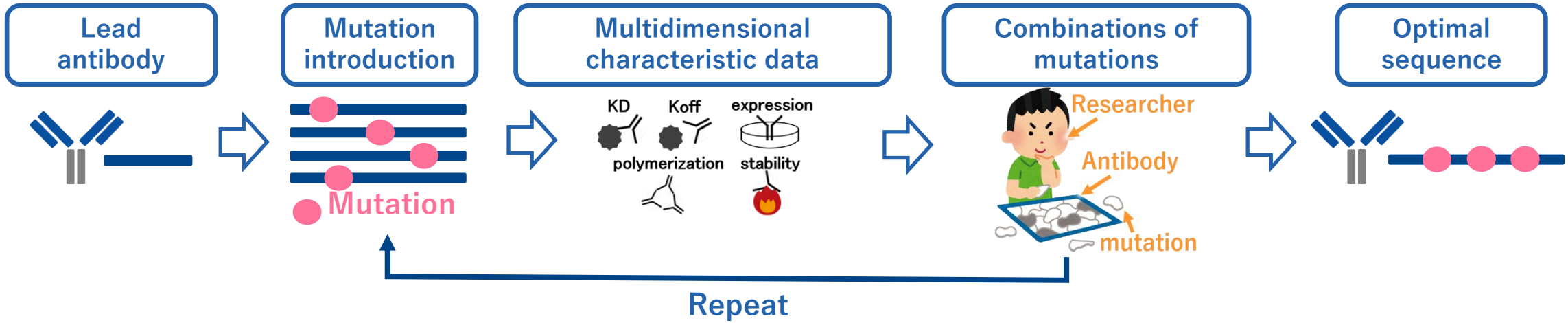
✓ High-throughput gene building and gene transfection
About 3000 molecules/week

How should the Huge Amount of COSMO Data be Utilized?

Antibody drug discovery process



Antibody optimization:
Repeatedly mutate the amino acids of the lead antibody to produce an optimal antibody

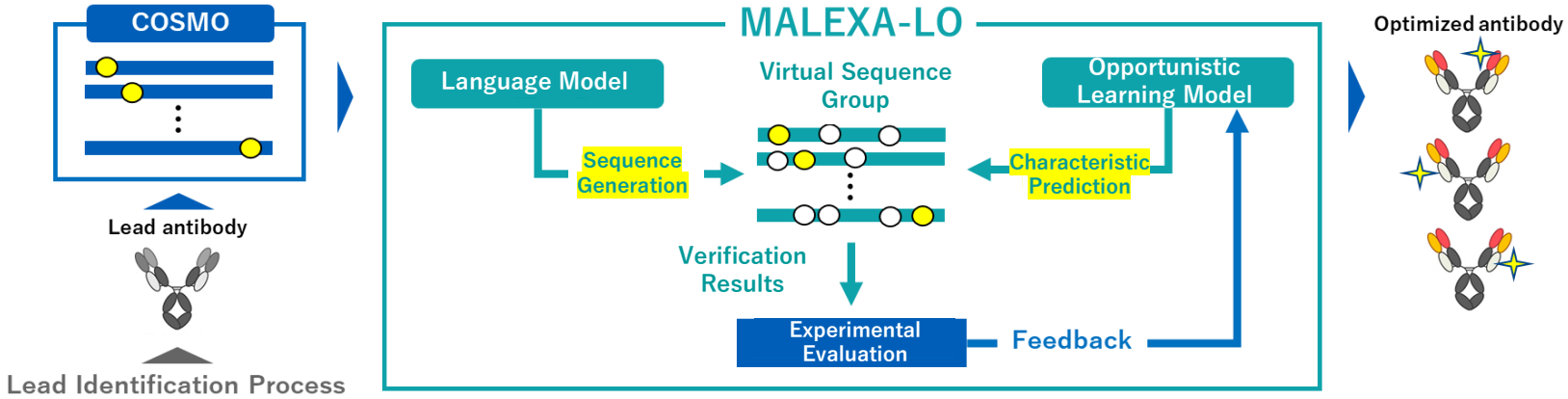


Challenges: With a huge number of combinations of mutations, finding the optimal combination of mutations involves much trial and error.

MALEXA®: Using Machine Learning to Design Antibody Sequences

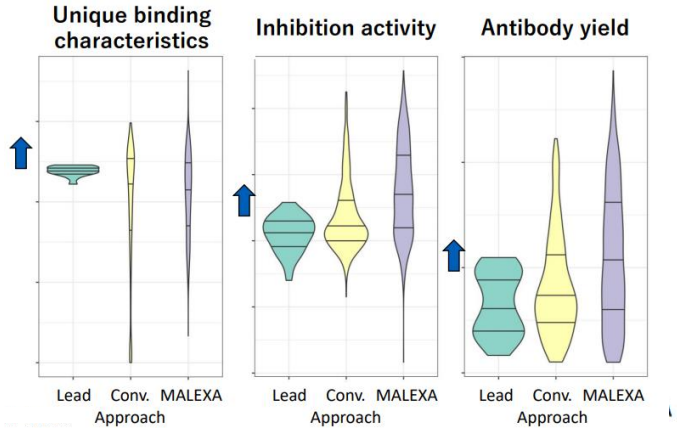
MALEXA®: MAchine LEarning x Antibody

Sequence-generating technology and characteristic-predicting technology are applied to derive optimal antibody sequences using machine learning



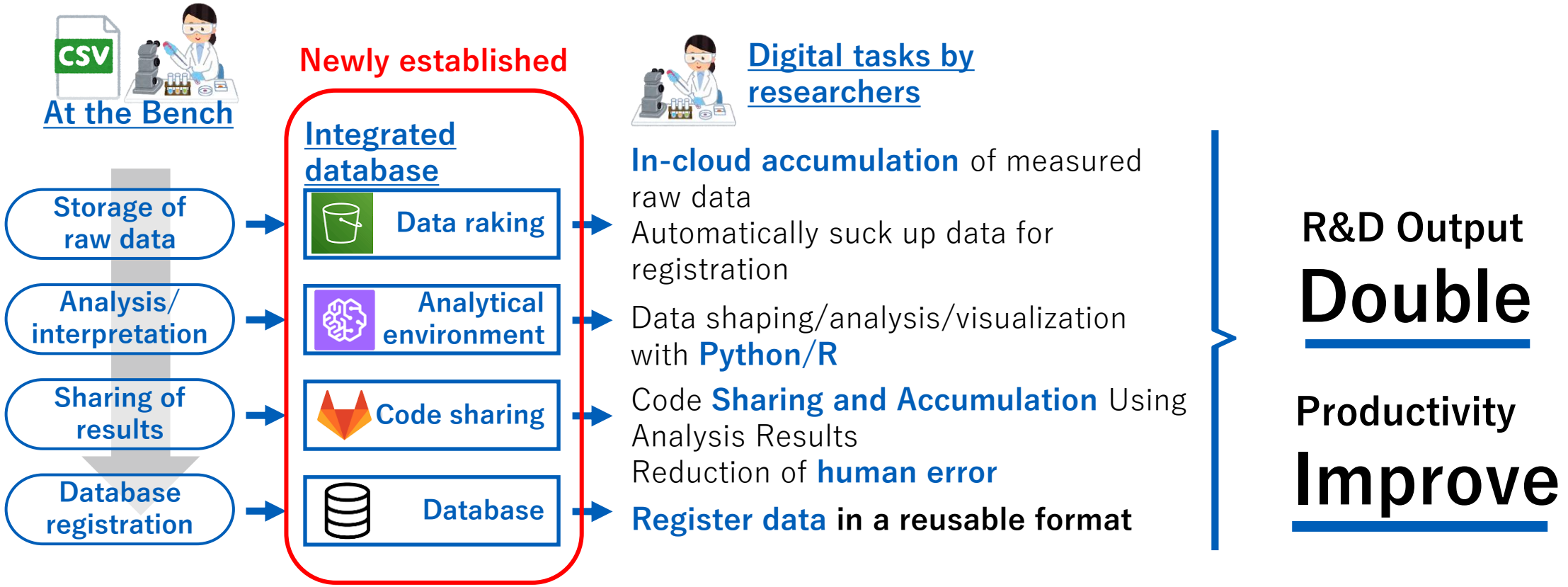
LO: Lead Optimization

> Distribution of *in vitro* binding characteristics/inhibition activity/antibody yield of antibodies obtained using different approaches



It was demonstrated that MALEXA® can be used to propose antibody sequences superior to conventional techniques (i.e., researcher-designed antibodies)

Database is Important for Advanced Data Utilization



We newly created integrated database. Researchers handle data by leveraging programming in their work

Dry Researchers Design a Training System to Enhance the Data Analysis Capabilities of Wet Researchers

CHUGAI
Roche Roche Group

System for researchers to teach and communicate with one another

Instructor (data scientist)

Coursework

- Learn the basics of Python and data shaping
- Mixed materials with drills and practical exercise solving
- Acquire skills immediately usable in integrated data analysis platform

Trainee Researcher

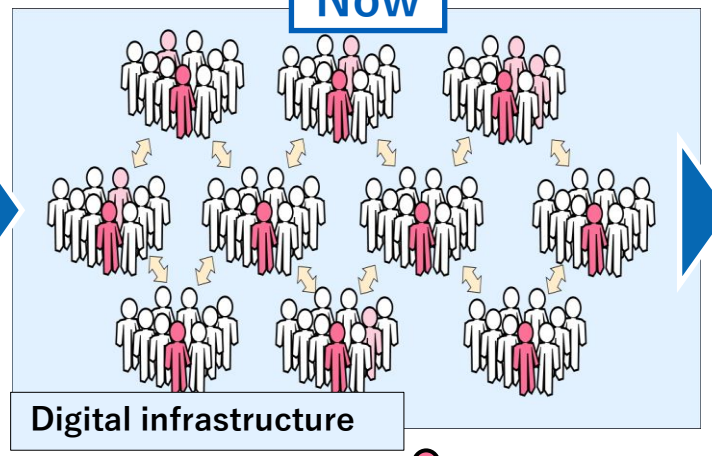
Becomes the next instructor

Coursework

Becomes the next instructor

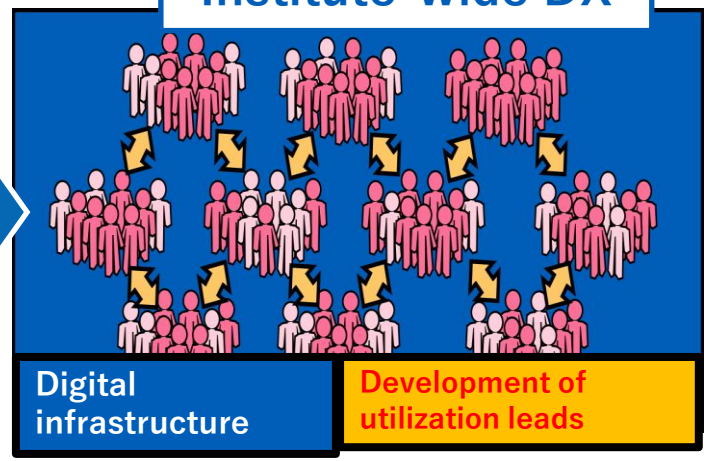
Before DX initiatives

Now



Digital infrastructure

Institute-wide DX



: Non-digital researcher

: Personnel with some digital knowledge

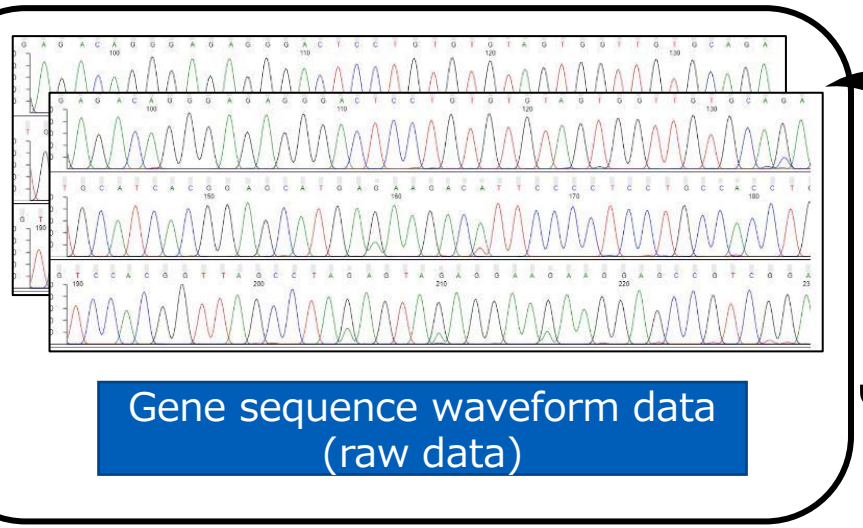
: Digital personnel

: Communities

Researchers Increase the Efficiency of Their Research through Programming

An example: Automation of antibody sequence analysis

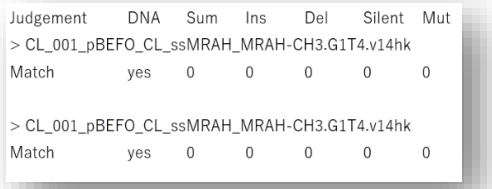
Step 1: During the night, an incoming email is detected, and waveform data is automatically imported



Gene sequence waveform data (raw data)

Step 2: Analyses are automatically performed by the DNA sequence analysis system

Step 3: An email containing the results of the analyses is automatically sent



Judgement	DNA	Sum	Ins	Del	Silent	Mut
> CL_001_pBEFO_CL_ssMRAH_MRAH-CH3.G1T4.v14hk						
Match	yes	0	0	0	0	0
> CL_001_pBEFO_CL_ssMRAH_MRAH-CH3.G1T4.v14hk						
Match	yes	0	0	0	0	0

The work is finished by the morning

Previously: Researchers manually worked from a copy of the data in the morning (after arriving at work)

Now: Researchers begin the next step soon after arriving at work

CHANGE System (Chugai)
This system does everything from analyzing gene waveform data and reconciling it against the target sequence to assessing discrepancies

The system saves 460 hours/year. It finishes these analyses at night so that researchers can work with the results in the morning.

Researcher-developed Apps are also Used in Laboratory Operations

*AC: Autoclave

Autoclave use log

- Record of start of use
- Pre-use precautions(overloading, bag closure technique, presentation of items not allowed in AC*)
- Record of post-sterilization verification

Booking time on instruments

- Viewing of booking list for the day
- Booking registration and editing
- Selection of importance (e.g., tentative booking, not changeable)

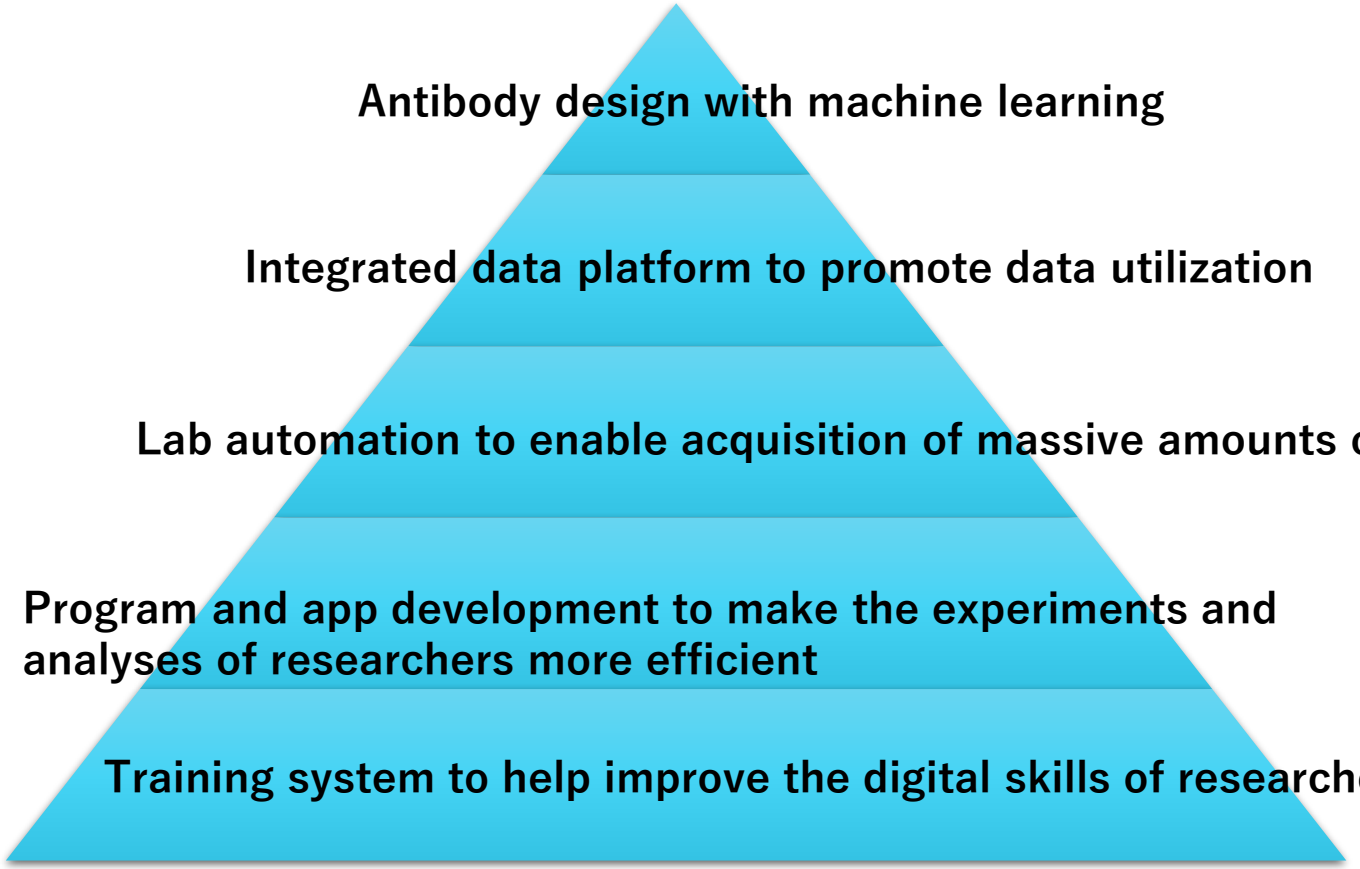
Resource allocation management tool

- Resource allocation such as freezers, CO_2 incubators
- Set/manage user groups

Inventory management application

- Updating the inventory list by two-dimensional code
- Notifying procurement personnel when the quantity of stock decreases

AI Antibody Drug Discovery Supports Robust Research Infrastructure and Human Resources

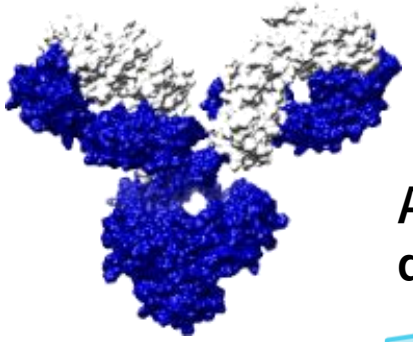


AI drug discovery

"Dry" and "Wet" research infrastructure

Digital human resources

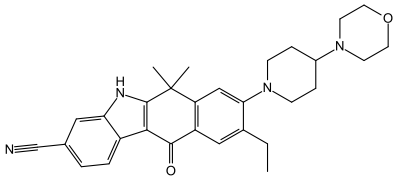
Deploying this “Fusion of Dry and Wet” to other Modalities



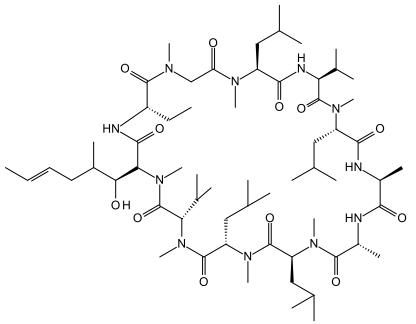
Antibody drug discovery

DX

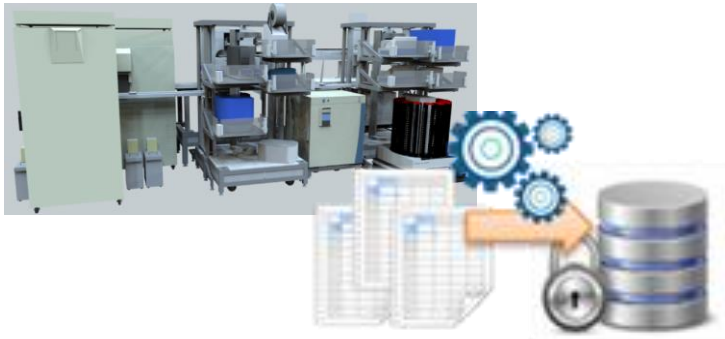
Horizontal deployment



Small molecule drug discovery



Mid-size molecule drug discovery



AI drug discovery

Antibody design with machine learning

Integrated data platform to promote data utilization

Lab automation to enable acquisition of massive amounts of data

Program and app development to make the experiments and analyses of researchers more efficient

Training system to help improve the digital skills of researchers

Expanding the Scope of AI Use in Drug Discovery Processes

- Increased productivity of pathology using image analysis technology, integrated analysis with quantitative evaluation
- Clustering and network analysis of papers using text mining AI technology
- Improvement of molecular design and screening method for small and mid-size molecules by AI technology
- Utilization of AI technology in omics analysis of gene expression
- Robot development to support complex experimental tasks

etc.

Researchers Can Get New Ways of Working

A new style of research geared toward achieving TOP I 2030 is developing

Liberated from simple tasks, employees can reach a freer working style in terms of time and place

Research based on creation of massive amounts of data/data analysis

Achieving things unattainable by humans alone with the help of machines

Digital transformation is steadily progressing for researchers

(From the 2022 Chugai employee awareness survey)

Two of three researchers are using new digital tools to improve their way of working

A growing number of researchers feel that Chugai is taking full advantage of the digital transformation opportunity

With the Relocation of the Laboratory, the Foundation for Further Growth was Established

Improvement of working styles

Enhancement of research productivity created by highly flexible working styles in place and time

Creating New Value

Using AI to realize drug discovery that cannot be achieved by humans alone

Operational efficiency

Operational improvement generated by increasing each researcher's digital literacy

Strengthening digital infrastructure

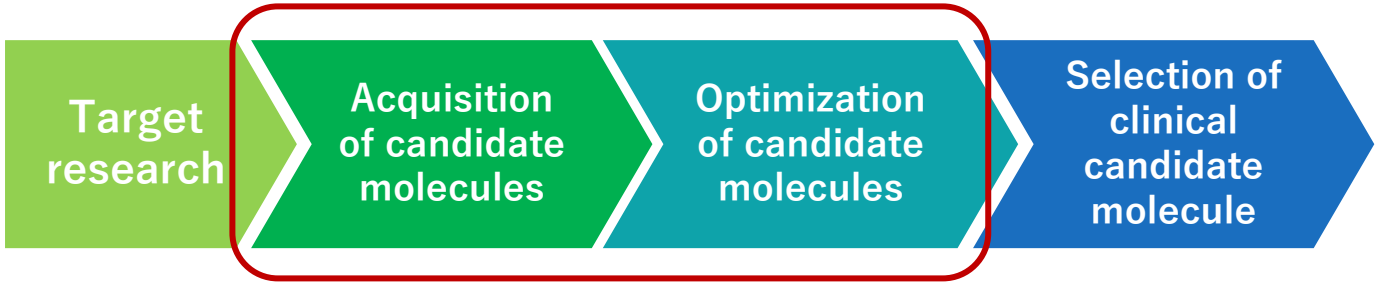
Accelerate AI drug discovery by acquiring a large amount of data and building a research infrastructure to promote its advanced utilization

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

Dr. Takuya Torizawa
Head of Protein Science Department

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

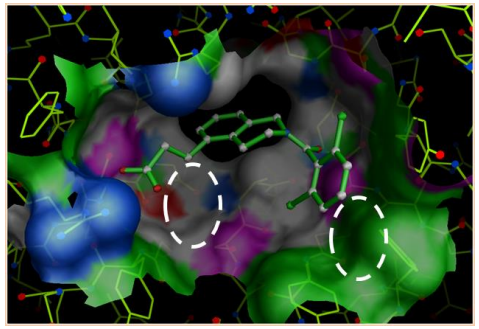
By analyzing the 3D structure of the binding state of the target protein and drug candidate molecules, followed by designing appropriate compounds, it is possible to significantly shorten the time period in the initial stage of drug discovery.



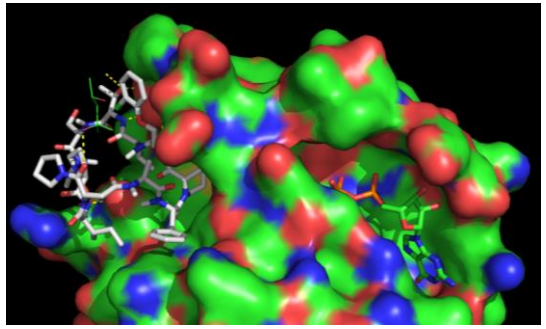
For both small and mid-size molecules drug discovery, the 3D structure information of candidate molecules is utilized in the stage from acquisition to optimization.

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

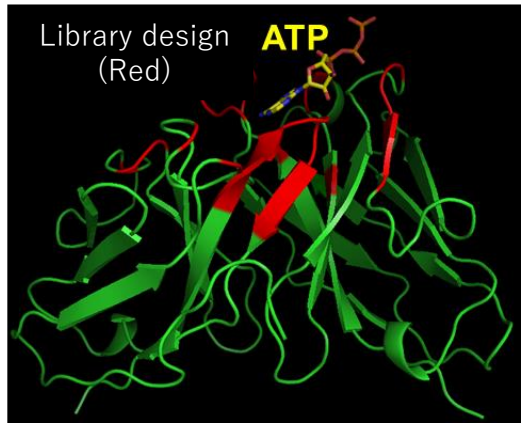
Small molecule



Mid-size molecule



Antibody



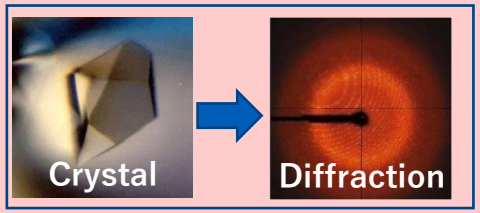
Conceptual illustration

Conventional X-ray Crystallography is not Versatile

- Even if the 3D structures of drug candidates are required, not all drug discovery projects are guaranteed to obtain the 3D structure by X-ray crystallography.

~ Uncertainty of crystallization: length of time to obtain the first 3D structure, low probability of success.

X-ray Crystallography



Strength

- Atomic resolution

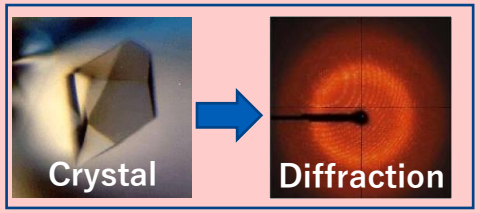
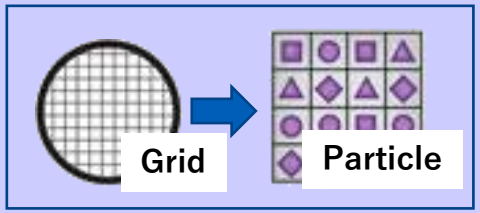
Weakness

- Crystallization screening*
- Crystal-specific structure
- Ultra high molecular weight, flexibility

* A work to find conditions for crystal precipitation under various conditions (~600 conditions)

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

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

	X-ray Crystallography	Cryo-EM
		
Strength	• Atomic resolution	• Crystallization: not required • Frozen sample (solution-like) • High molecular weight
Weakness	• Crystallization screening • Crystal-specific structure • Ultra high molecular weight, flexibility	• Grid screening* • Resolution • Low molecular weight (> 100 k)

* A work of selecting the good gird among the ones on which the measurement samples are placed.

Introduced Cryo-EM for the First Time among Japanese Peers

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

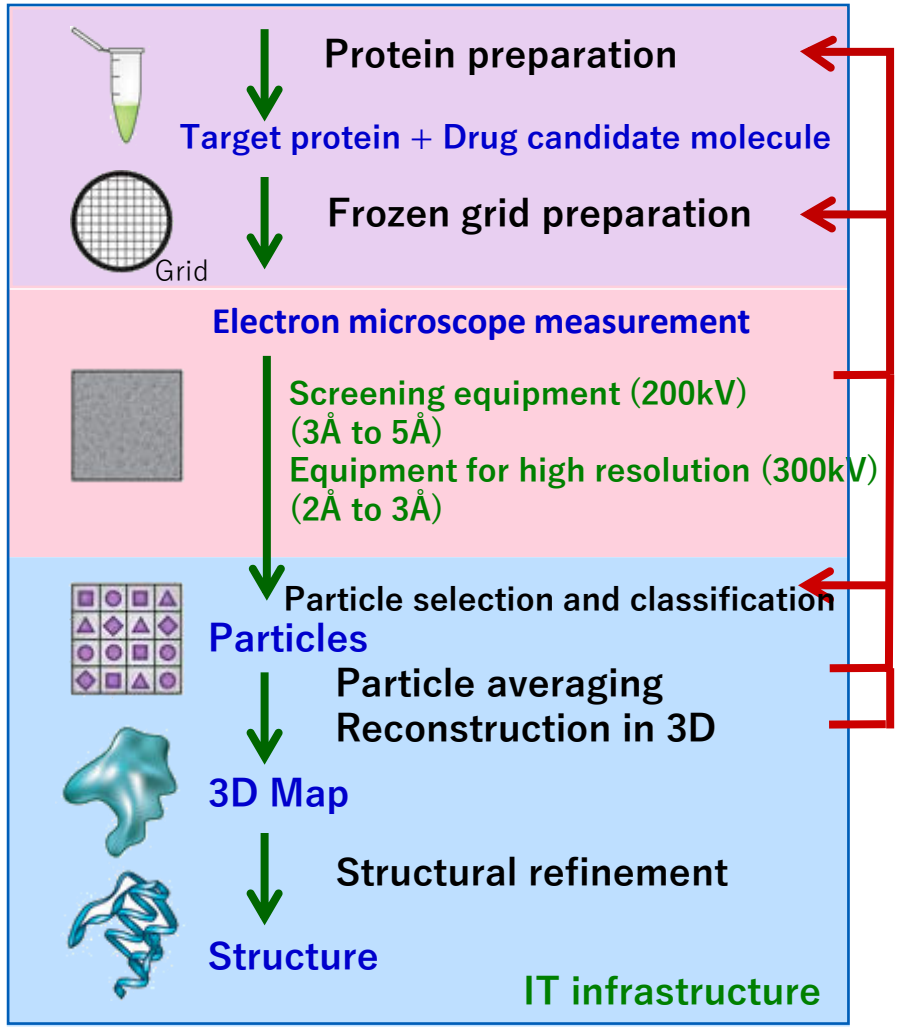
Thermo Fisher Scientific
Glacios (200keV)

The photo above was taken at Chugai Life Science Park Yokohama

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

(Live Broadcast Scheduled Later)

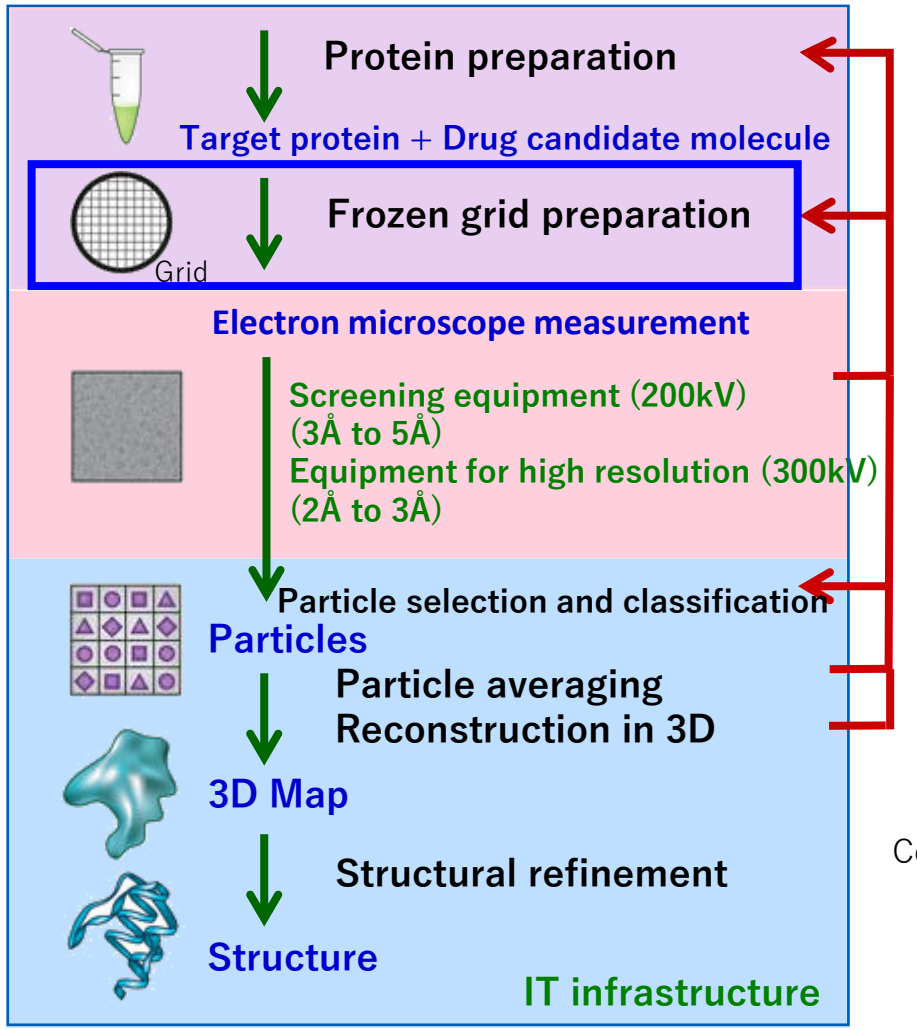
Experiment flow



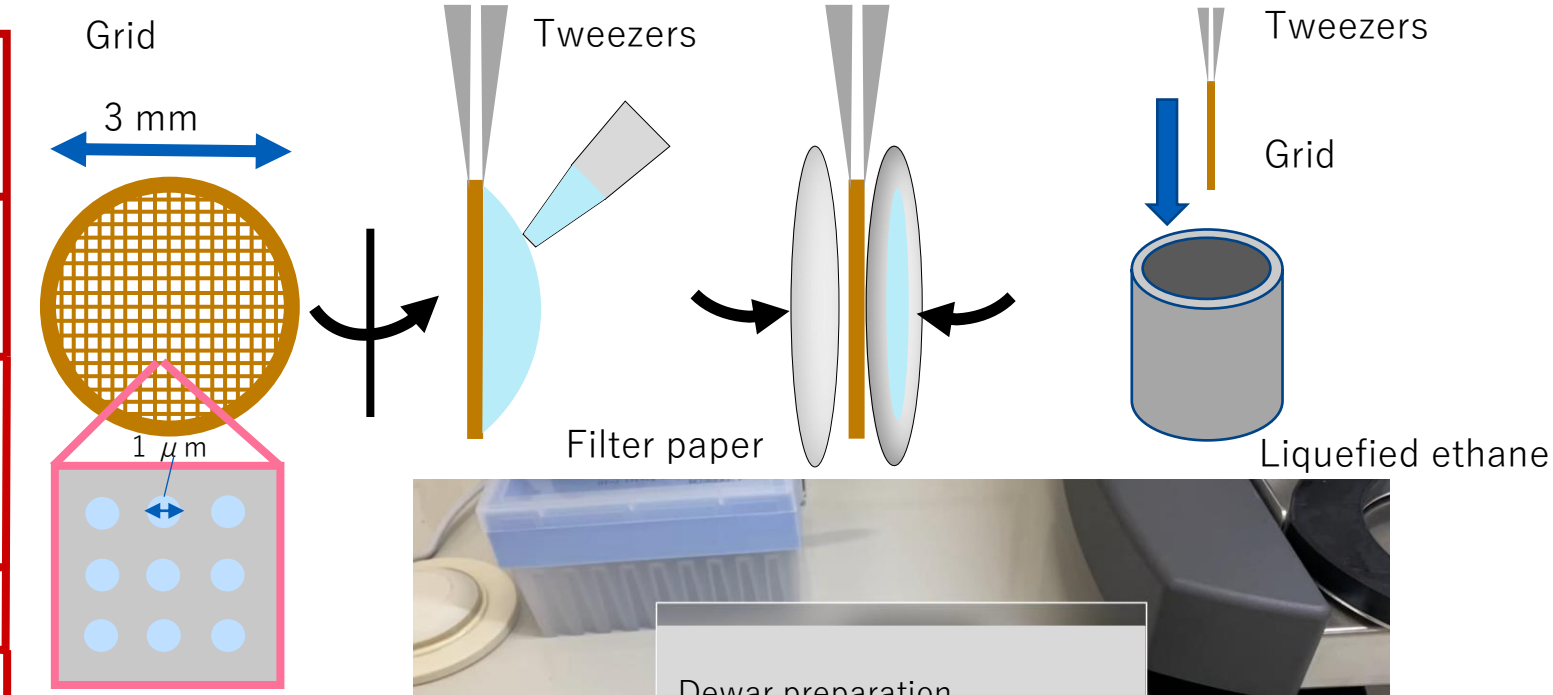
- It is desirable to conduct the subsequent work as quickly as possible to obtain the 3D structure, but if it is not successful at each step, we will have to return to the above work and start over.

Preparation of Frozen Grids Greatly Affects the Success or Failure of Experiments

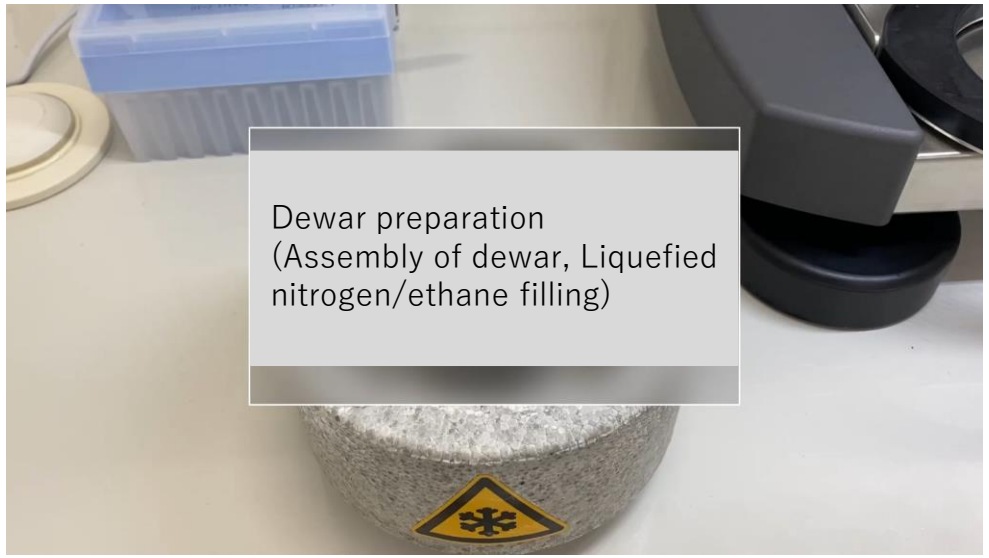
Experiment flow



- The grid is loaded with a solution sample of protein/candidate molecule
- Absorb excess solution sample with filter paper
- Grids are dropped into liquefied ethane and rapidly frozen

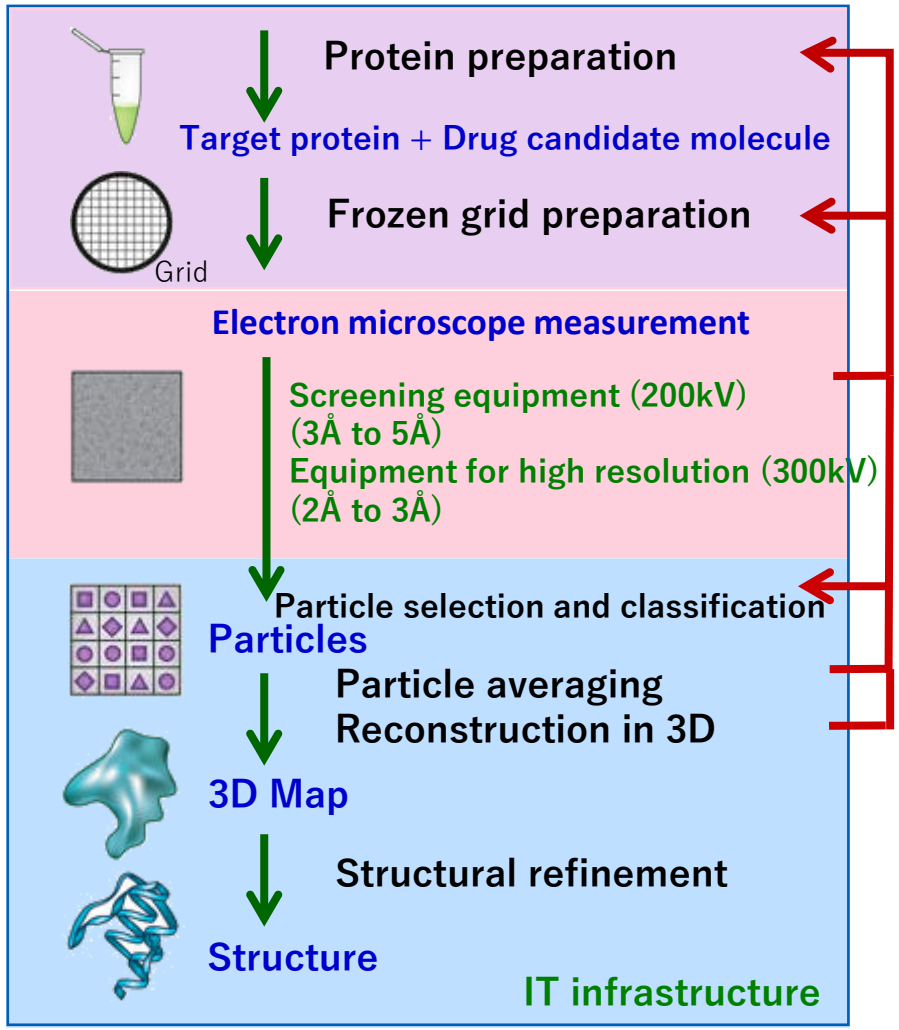


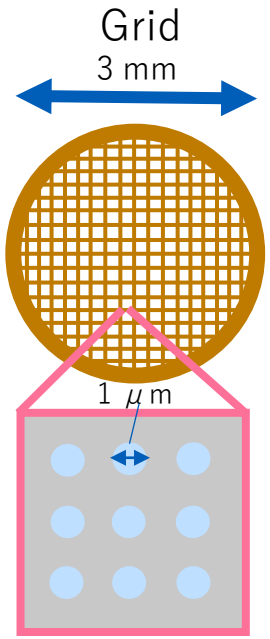
Conceptual illustration



Irradiate the Grid with an Electron Beam to Determine the Quality of the Grid, and if it is Acceptable, the Actual Measurement is Performed

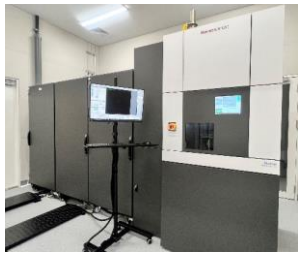
Experiment flow





Loading

Cryo-EM

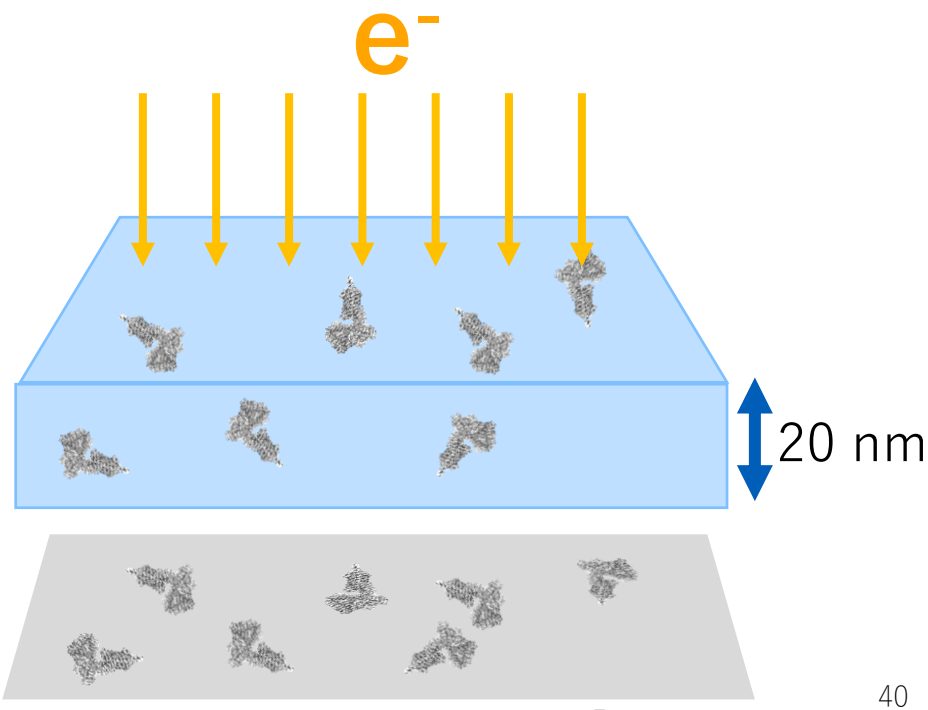


These holes are individually filled with frozen solution samples.

An electron beam is irradiated from the upper side of this grid.

Conceptual illustration

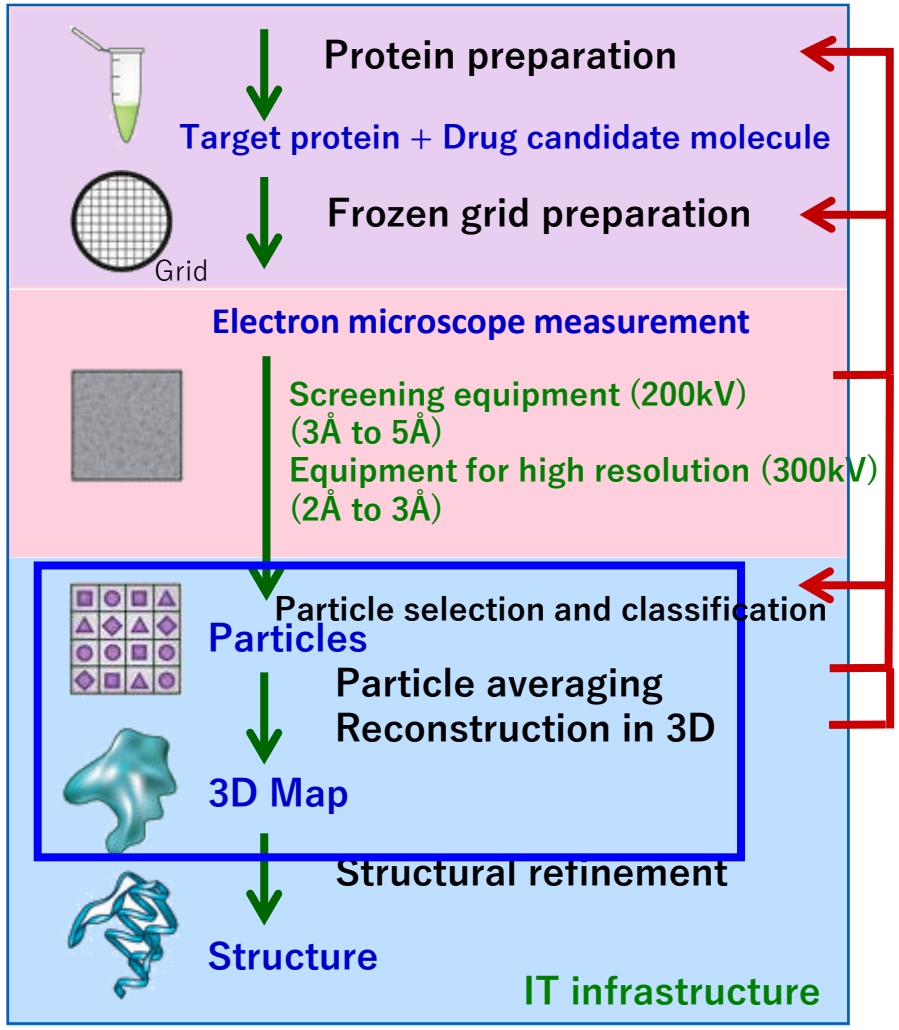
A projection image is captured by irradiating electron beams to molecules.



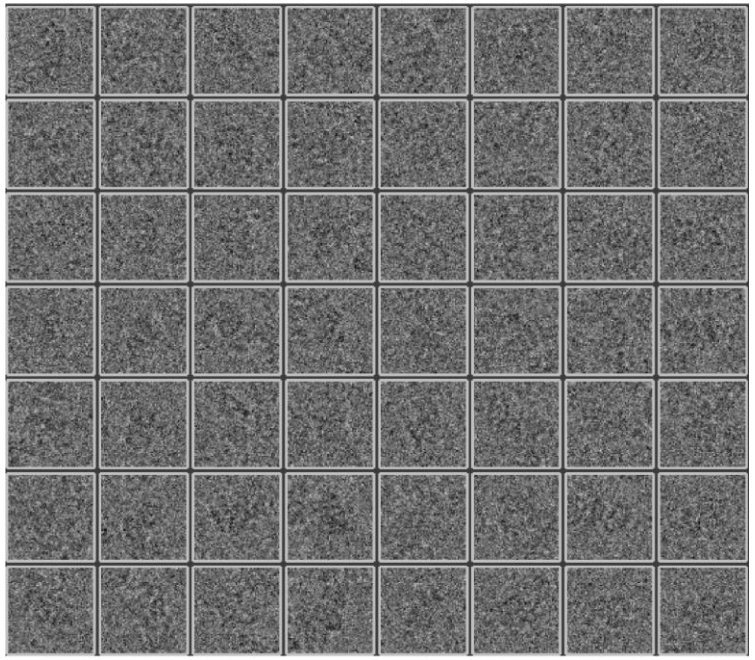
Projection image

3D Structure Information is Obtained by 3D Reconstruction from Captured Projection Images

Experiment flow

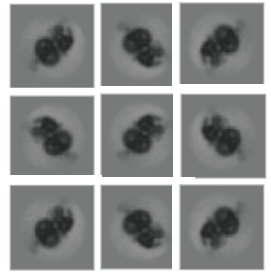


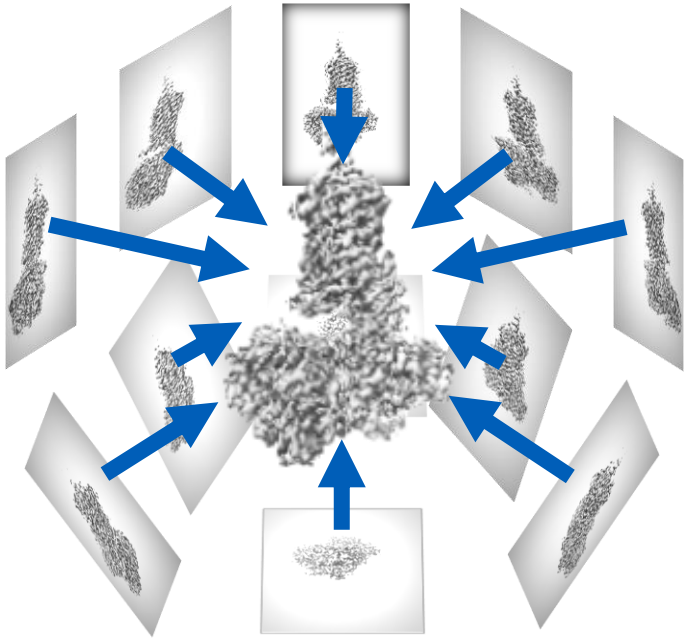
Actual cryo-EM particle image



Classification/Arrangement

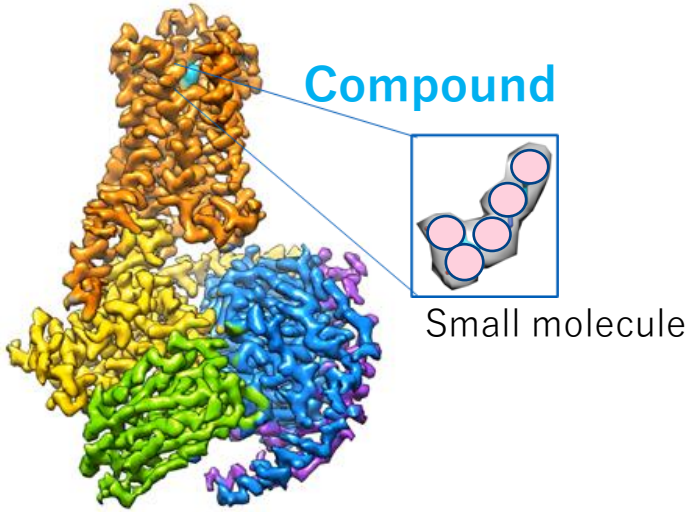
10^3-10^5 particle averaging



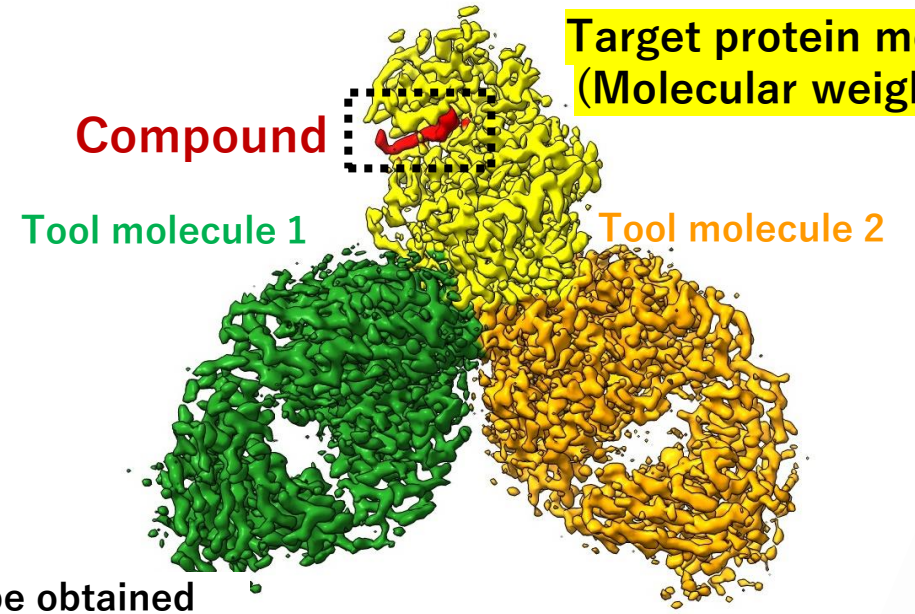


Chugai has Built a Mass Production System for the 3D Structures Using Cryo-EM

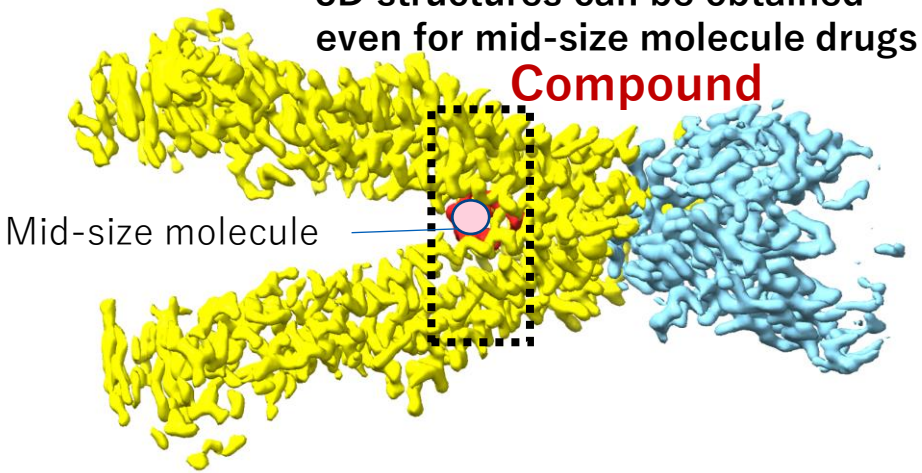
- Small molecule drugs targeting membrane proteins that are often targeted for drug discovery by pharmaceutical companies



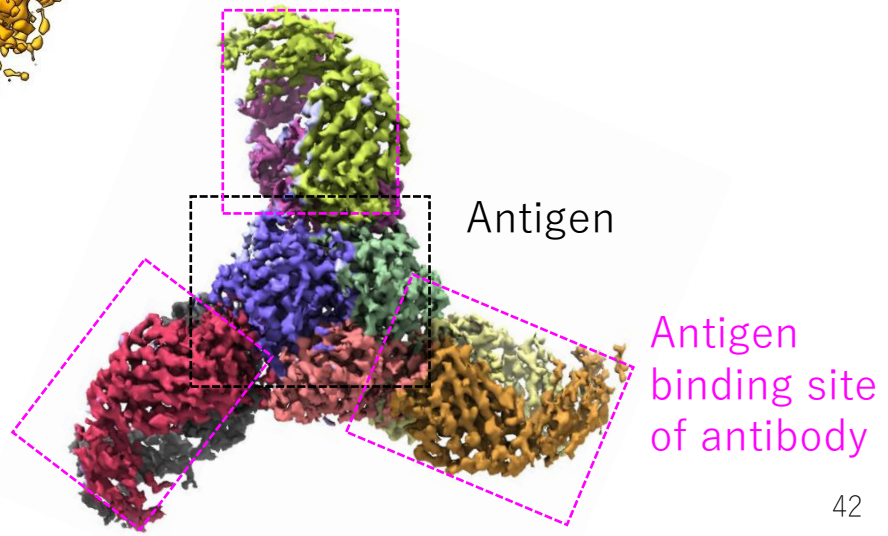
- Building a proprietary platform that can obtain high-resolution structures even for target proteins other than membrane proteins with small molecular weights that cryo-EM is not appropriate for measurement



- 3D structures can be obtained even for mid-size molecule drugs



- 3D structures can be obtained more easily with antibody drugs



In-house data

Summary of Chugai's Cryo-EM Efforts

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

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INNOVATION BEYOND IMAGINATION