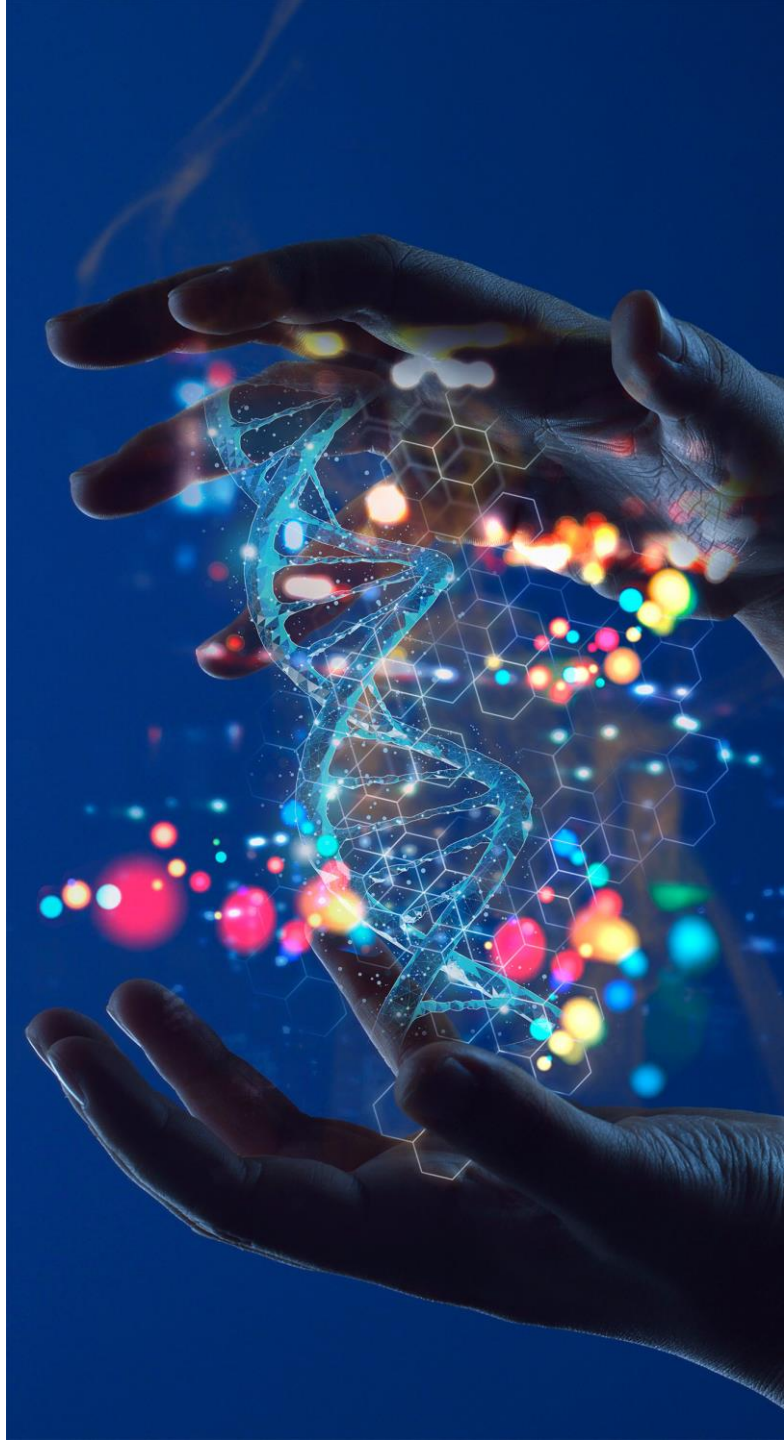
Chugai R&D Meeting



CHUGAI PHARMACEUTICAL CO., LTD.

13 December, 2021

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.

Chugai R&D Meeting

Agenda

01	Chugai's Research Policy	Head of Research Div. Hitoshi Iikura Ph.D.
02	Chugai's Mid-Size Molecule Drug Discovery	Head of Research Div. Hitoshi Iikura Ph.D.
03	Update on Antibody Engineering Technologies	Head of Translational Research Div. Tomoyuki Igawa Ph.D.
04	Q&A	

Chugai's Research Policy

Hitoshi Iikura Ph.D.
Head of Research Div.

Chugai's Growth Strategy Logo

Name of our growth strategy to become a Top Innovator in 2030

"TOP" expresses our aspiration to become the leading innovator globally, not just in Japan.

The "I" has two meanings: "Innovator" and I as in "I" or "me"

"I" of the Innovator

Become a top-class innovator in the global healthcare space

"I" as I or Me

Each one of us plays a leading role in Chugai's pursuit of TOP I 2030.

Drug Discovery to Achieve TOP I 2030

Achieving the world's most advanced drug discovery

- Realize totally original drug discovery ideas
- Expand existing technologies and building new technological foundations
- Adopt digital technology (Digital Transformation)
- Collaborate with leading global players (Open Innovation)

Dramatically Improve Treatment Satisfaction

Multi-Modality Drug Discovery Platform

Drug discovery technologies

- Medical needs are becoming more diverse and complicated
- ➢ Development of advanced drug discovery technologies to meet high medical needs

Precise understanding of disease mechanisms

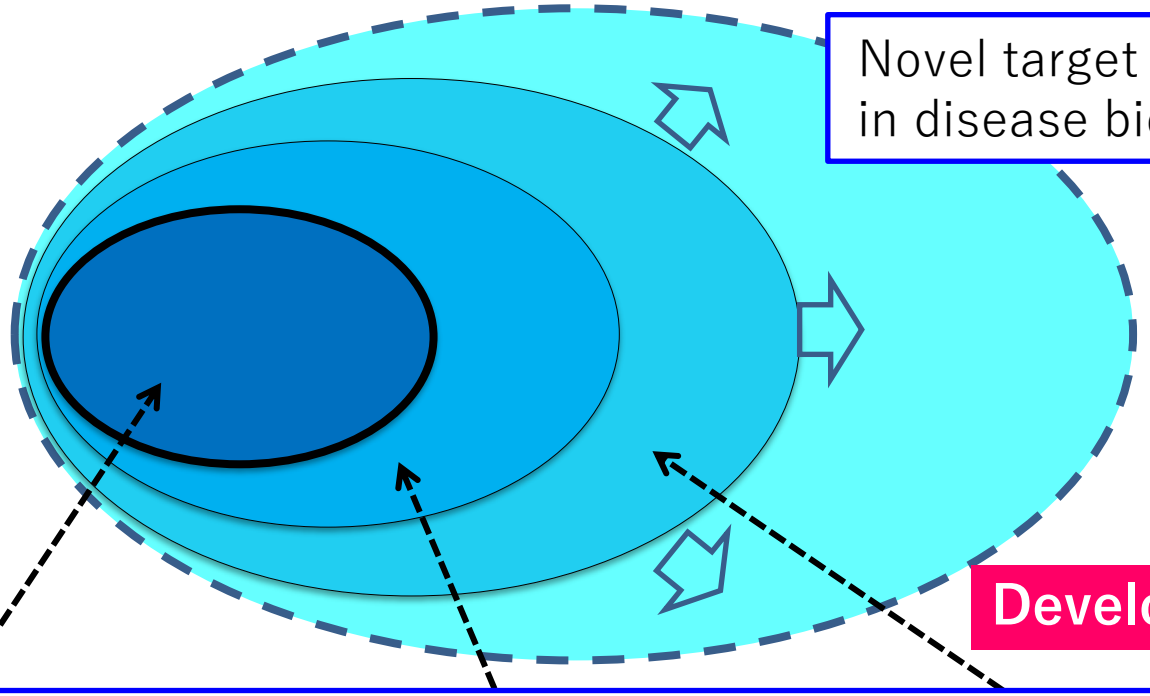
- Understanding the molecular mechanisms of diseases required for drug research and development
- ➢ Deepening understanding of disease through collaboration with academia

Efficiency of research and development

- Automation and robotics
- Improving data processing capacity with AI
- ➢ Creating precise supervised data

What We Need to Achieve First-in-Class (FIC), Best-in-Class (BIC)

Strengthening of disease biology



Novel target molecule groups found in disease biology → **FIC**

Realize drug discovery for tough targets

Development of new original technologies

UMN target molecules reachable by conventional technology.
⇒**Generic**

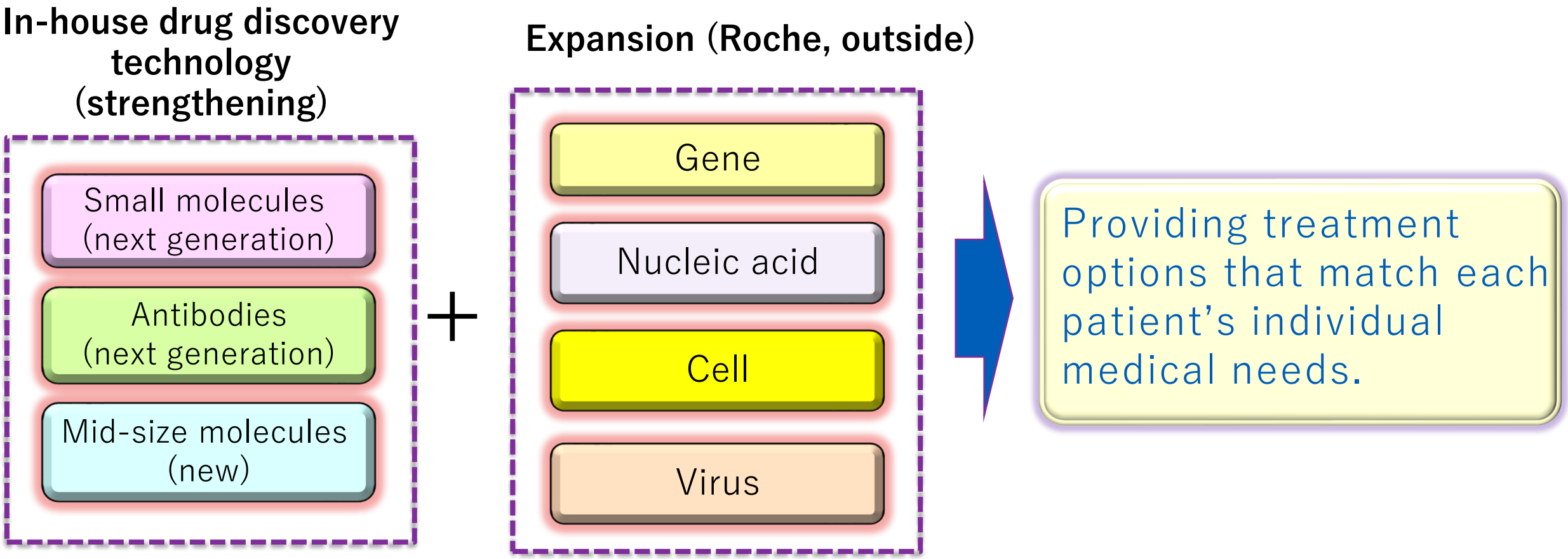
Promising target molecules that can achieve effects with our original technologies that are unattainable with conventional technologies.
⇒**BIC**

Novel target molecules found to be druggable for the first time using our unique technology.
⇒**FIC**

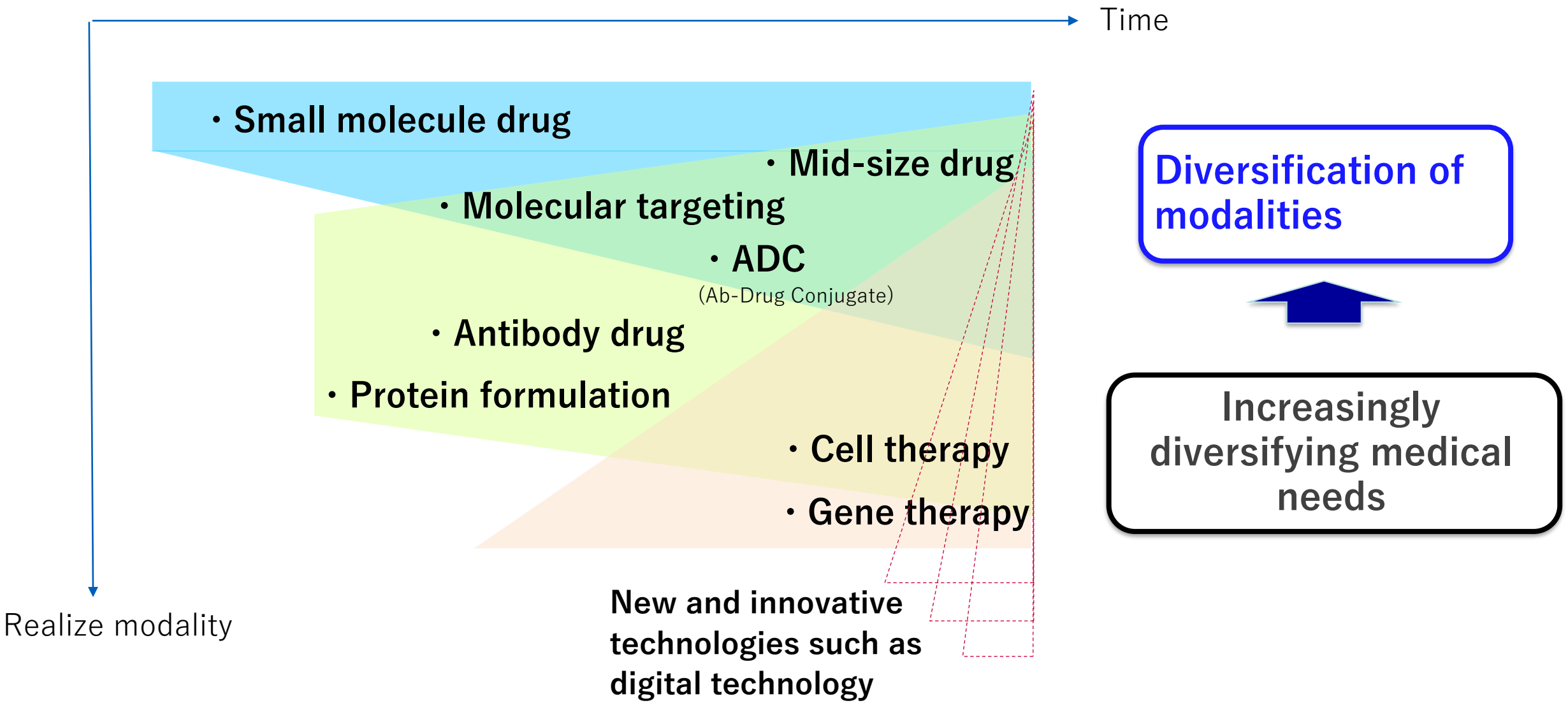
UMN: Unmet Medical Needs

Construction of Multi-Modality Drug Discovery Platform

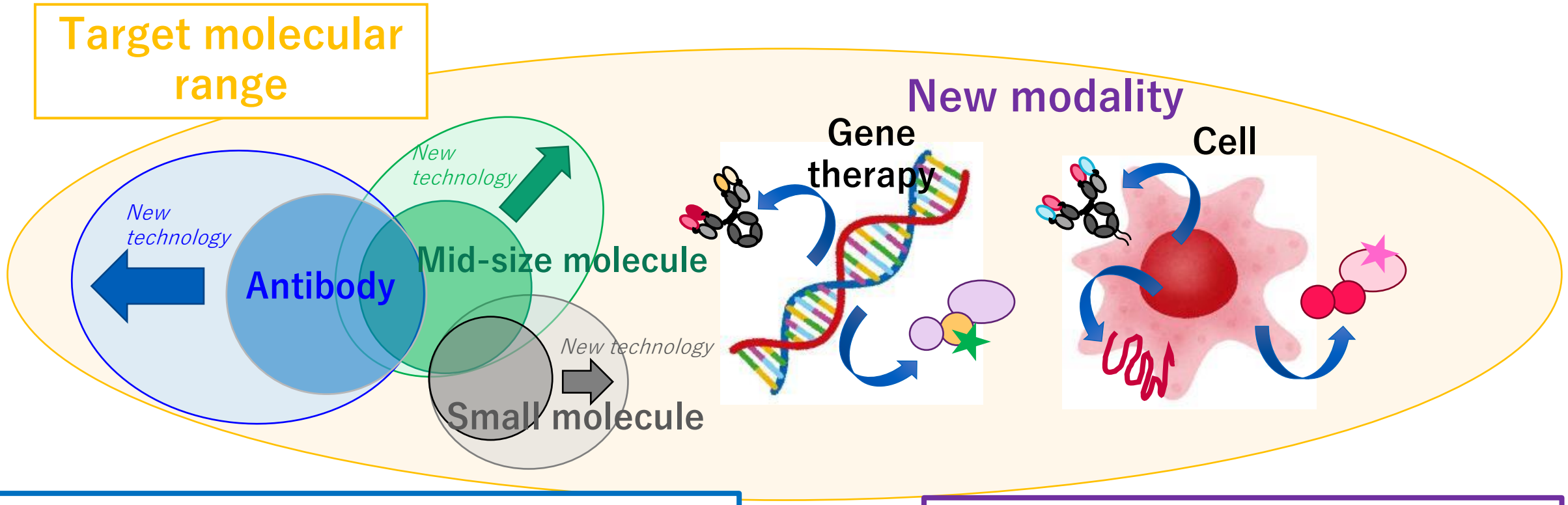
Responding to diverse target molecules and diverse medical needs



Creating Innovative Modalities by Integrating Technologies



Expanding Our Druggable Space and Realizing Novel Mechanisms of Action



Protein engineering technologies cultivated through Chugai's strong antibody technologies

×

New modalities through external collaboration
gene therapy, cell therapy, etc.

Examples of Concepts Combining Protein Engineering and New Modalities

	Chugai		External collaboration
Reduction of side effects	Antibody engineering technology (Switch-Ig etc.)	×	ADC
Creating cells with novel functions	Extracellular and Intracellular Domain Engineering	×	Cell therapy
Superior efficacy	Protein engineering to be delivered	×	Gene delivery

Search for and Identify Target Molecules

CHUGAI
Roche Roche Group

Academia

Disease-causing molecule

Select good target molecules

High-quality clinical samples and accurate patient background information are required to understand disease mechanisms

Collection of samples over time and collection of information such as symptoms

Quantity and quality of information are important

Pharmaceutical companies

Innovative drugs

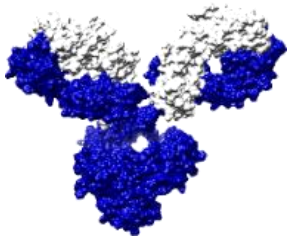
Develop discovery technology

- Next-generation antibody
- Small molecule drug
- Mid-size drug

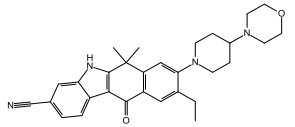
Matching technology with target molecules

Solutions to Unmet Medical Needs

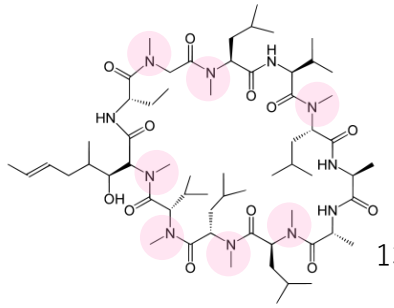
Antibody drug
MW: 150,000



Small molecule drug
MW: approx. 500



Mid-size drug
Cyclic peptides,
MW: approx. 1,500



Collaboration with Academic Institutions

GWAS: Genome Wide Association Study
eQTL: Expression Quantitative Traits of Locus

IFReC, Osaka Univ.

Making new discoveries through world-class basic immunology research

On-site lab

Dept. Allergy & Rheumatology Univ. of Tokyo

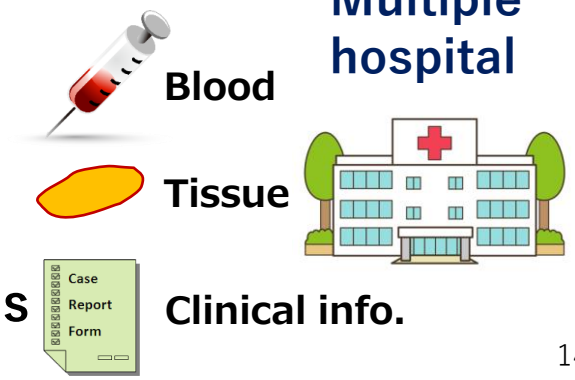
Using GWAS/eQTL to identify novel targets for intractable collagen disease.

On-site lab

National Cancer Center

Building new technological foundation for human clinical prediction by using organoids established from human samples

On-site lab

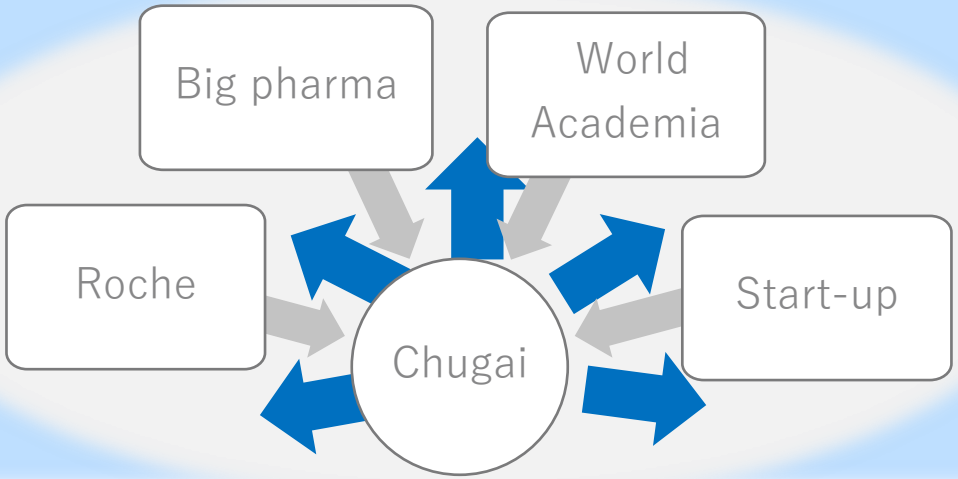


- Deepening understanding of disease and biology
- Discovery of novel biology targets and biomarkers
- Pharmacology evaluation of drug candidates using human samples

Pursuing Value Maximization: Collaboration with Outstanding Advanced Global Players

- Continue to emphasize Chugai's "craftmanship" and break away from "pure self-reliance"

1. Acquiring / co-establishing technologies
2. Agile response to paradigm shifts
3. Effective use of Roche the group's technologies to speed up
4. Collaboration utilizing the advantage of our competitive in-house technologies (Antibodies and Mid-size molecules) to pursue outputs



■ **External collaboration starting from specific Strategic-Wants**

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

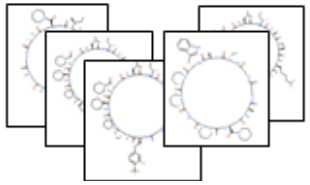
Trials using Digital Technology in Drug Discovery

CHUGAI DIGITAL

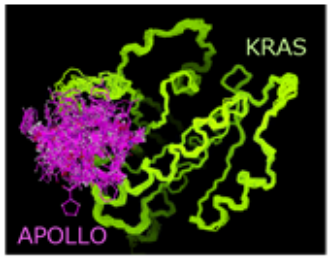
CHUGAI
Roche Roche Group

Mid-size molecule x AI

Strengthen structural analysis Tech.
(Cryo electron microscope)

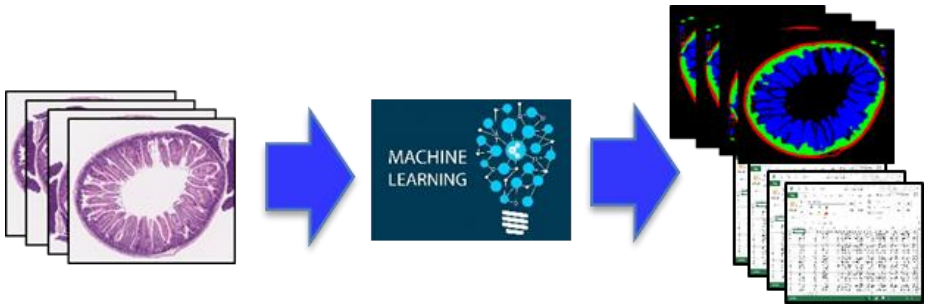


Creation of compound structure by AI



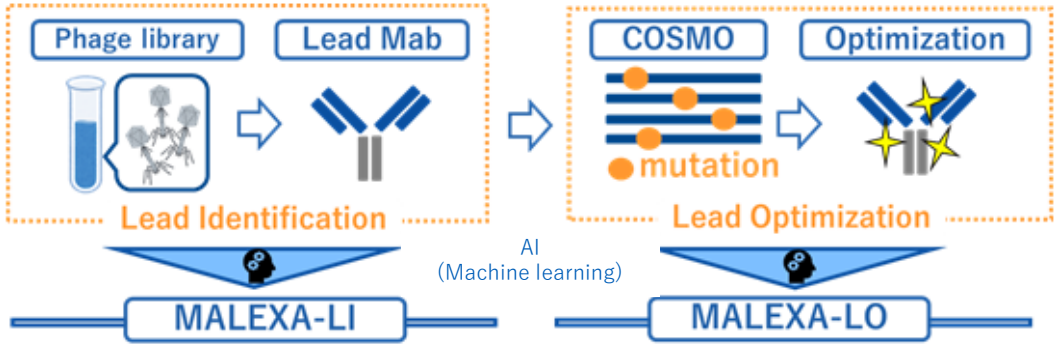
Molecular dynamics, Binding site simulation

Digital Pathology: Digitizing pathology analysis



Multiple disease analysis was automated,
Numerizing characteristics of interest from images

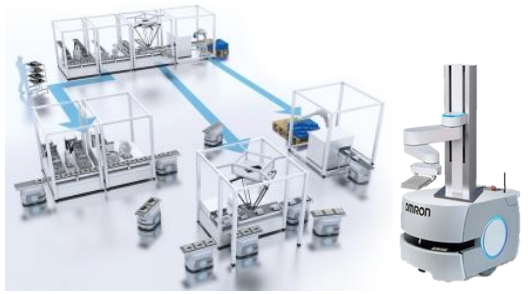
Ab x AI



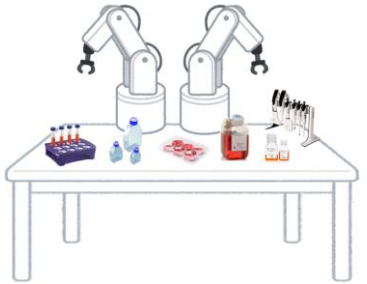
Suggest potential lead Ab sequences with preferable profiles

Suggest potential lead antibody

Robotics: Next-generation lab automation



Connect automated tests using multiple interacting robots



Bench-type robot that can mimic a human investigator

Chugai's Mid-Size Molecule Drug Discovery

Hitoshi Iikura Ph.D.
Head of Research Div.

Agenda

01 Challenge to Mid-Size Molecule Drug Discovery

02 Challenge to Solve in Cyclic Peptide Drug Discovery

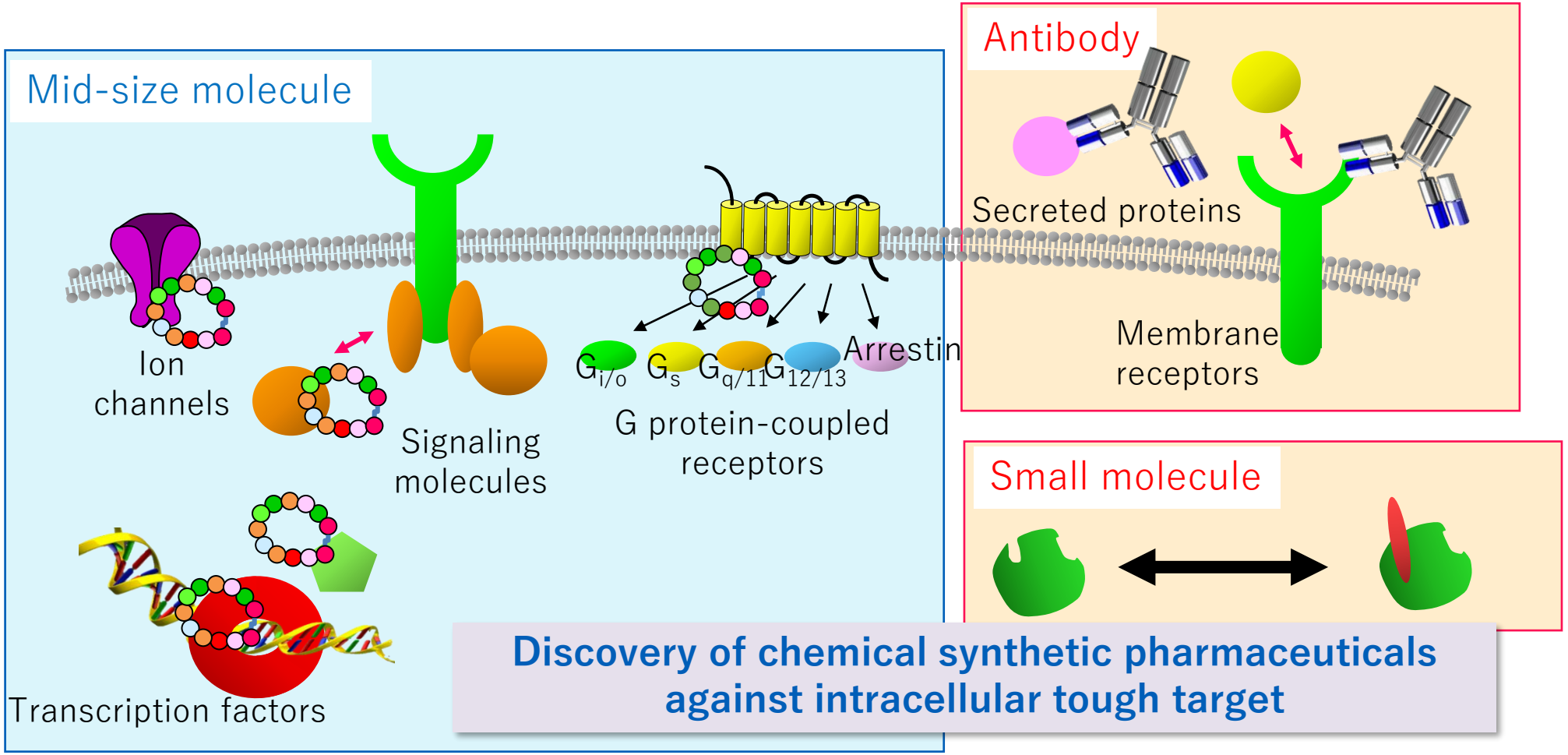
03 Foundation to Support Mid-Size Molecule Drug Discovery

Agenda

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

- Drug discovery for intra-cellular tough targets without pockets binding to small molecules (e.g., PPIs).
  - Antibodies target only extracellular molecules (approx. 20% of the total protein)
  - Target molecules with pockets (approx. 20% of proteins)

PPI: Protein-Protein interaction



Rule of 5: Established Guideline for Small Molecule Drug Discovery

- Groundbreaking rule derived from the study of previous drugs that established the best physical properties needed for orally available medicines.
- Probability of successful drug discovery improved after the global adoption of these guidelines.

At least 3 of the following 4 requirements must be met:

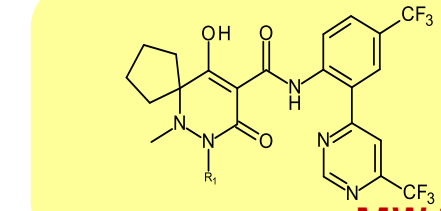
- **MW < 500** — Molecular weight is less than 500
- **cLogP < 5** — Cannot be too oily (because of increased susceptibility to oxidative metabolism)
- **No. H-B acceptor <10**
- **No. H-B donor < 5**

Cannot be too watery (because it makes it difficult to penetrate the cell membrane)

Adv. Drug. Deliv. Rev., 23, 1997, 3-25

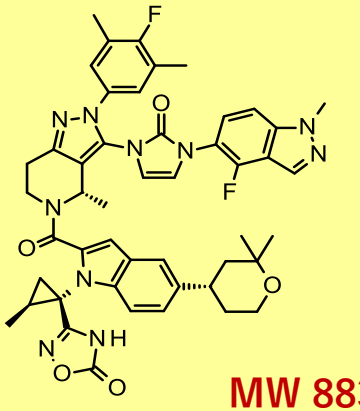
Evolution of Chugai Chemistry Directed to Tough Targets: Beyond the Rule of 5

SM drug discovery "Rule of 5" (MW<500)



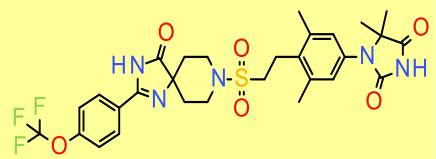
MW 750

EOS789 (P1)
Npt/Pit inhibitor



MW 883

OWL833
GLP1 agonist (P2)



MW 636

PCO371 (P1)
PTH1R agonist

"Beyond the Rule of 5" drug discovery (MW>500)

Mid-Size

New library (Molecular diversity)

Optimization of efficacy and pharmacokinetics

Drug discovery against tough targets

Benefit of Cyclic Peptides

① Mid-size molecules (MW: about 1500) are good for drug discovery against tough targets

⇒ Can induce “Induced fit” of the target protein* (no protein-side pockets are required)

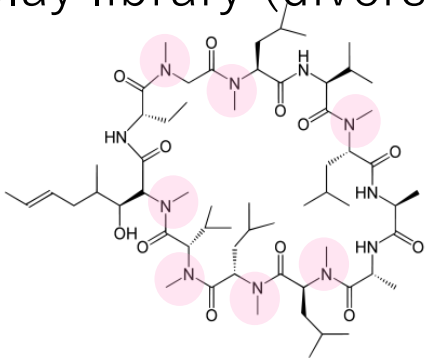
**Nature 2007, 450, 1001*

② Parallel synthesis will be possible once the chemical synthesis method is established

⇒ Leads to the elucidation of drug-likeness (Rule of 5 for mid-size molecules)

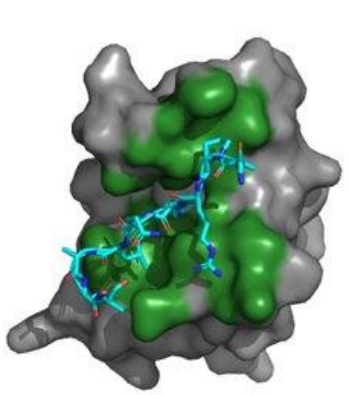
③ Compound library construction with great molecule diversity for promising multiple hit compounds is possible.

⇒ Display library (diversity of 10^{12}) widely used in antibody discovery can be applied.



Cyclosporine
MW 1202.6

ex. Bromodomain



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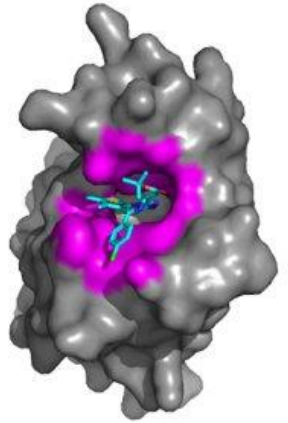

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Agenda

01 Challenge to Mid-Size Molecule Drug Discovery

02 **Challenge to Solve in Cyclic Peptide Drug Discovery**

03 Foundation to Support Mid-Size Molecule Drug Discovery

Challenges to Solve in Cyclic Peptide Drug Discovery

1. To impart Drug-likeness to mid-size molecules that are Beyond the Rule of 5

   In addition, Drug-likeness should be defined (semi)quantitatively

   Our medicinal chemists (semi) quantitatively define Drug-likeness by synthesizing and evaluating a numerous and various cyclic peptides

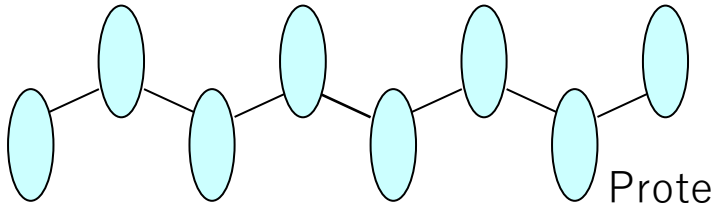
2. With Drug-likeness defined (semi)quantitatively, to construct a display library of non-natural peptides that meets our established definition of Drug-likeness

   More advanced technologies are required

Getting Drug-Like Hit with Mid-Size Molecule

Small-Molecule Strategies (Hit-Selection Using Rule of 5) are also Applied to Mid-Size Molecule Drug Discovery

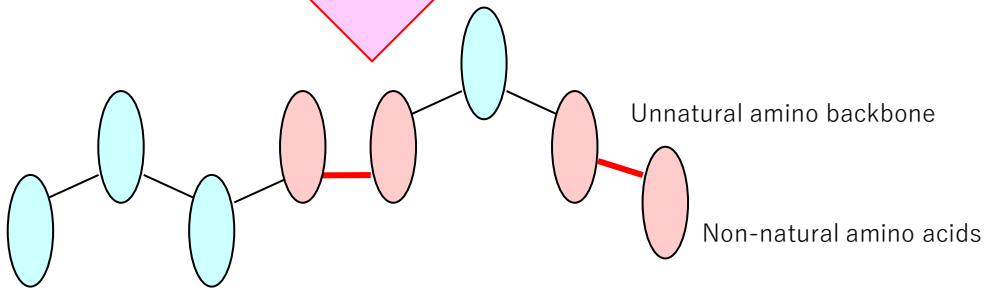
Conventional peptide drug discovery



Protein amino acid

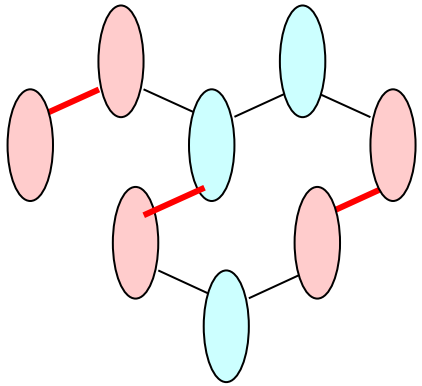
Hit (Potent activity, Poor membrane permeability/metabolic stability)

By using unnatural amino acids
Significant structural changes



Lead (weak activity, good membrane permeability/metabolic stability)

Next-generation drug discovery



Hit (potent activity, membrane permeability, metabolic stability)

Small conformational change on side-chain displacement that does not touch the backbone

Lead

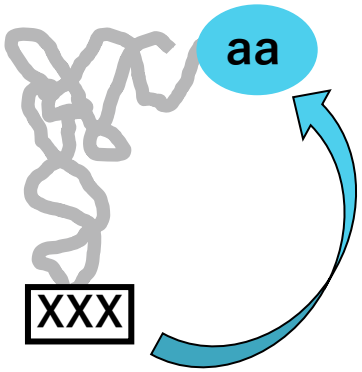
Translational Synthesis of Unnatural Amino Acid (UAA) Peptides Using Reprogrammed Genetic Codes

mRNA AUGUUGCCGG...

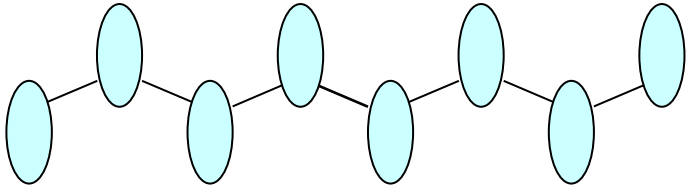
Universal genetic code

	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
			stop	stop	C
	Leu			Trp	A
		Pro	His	Arg	G
C			Gln		U
					C
					A
					G
A	Ile	Thr	Asn	Ser	U
					C
	Met		Lys	Arg	A
					G
G	Val	Ala	Asp	Gly	U
					C
			Glu		A
					G

Aminoacyl - tRNA



Natural peptide

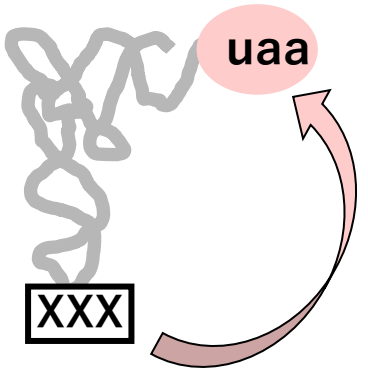


mRNA AUGUUGCCGG...

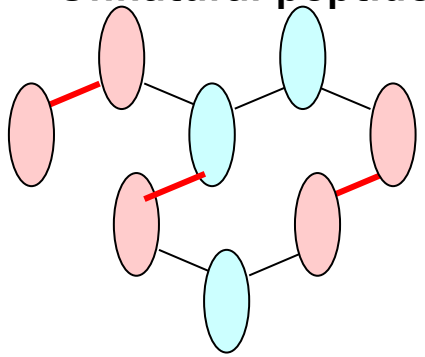
Reprogrammed genetic code

	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	uaa		stop	stop	C
	Leu			Trp	A
		Pro	uaa	Arg	G
C			Gln		U
					C
					A
					G
A	Ile	uaa	Asn	uaa	U
					C
	Met		Lys	Arg	A
					G
G	Val	Ala	Asp	Gly	U
			uaa		C
					A
					G

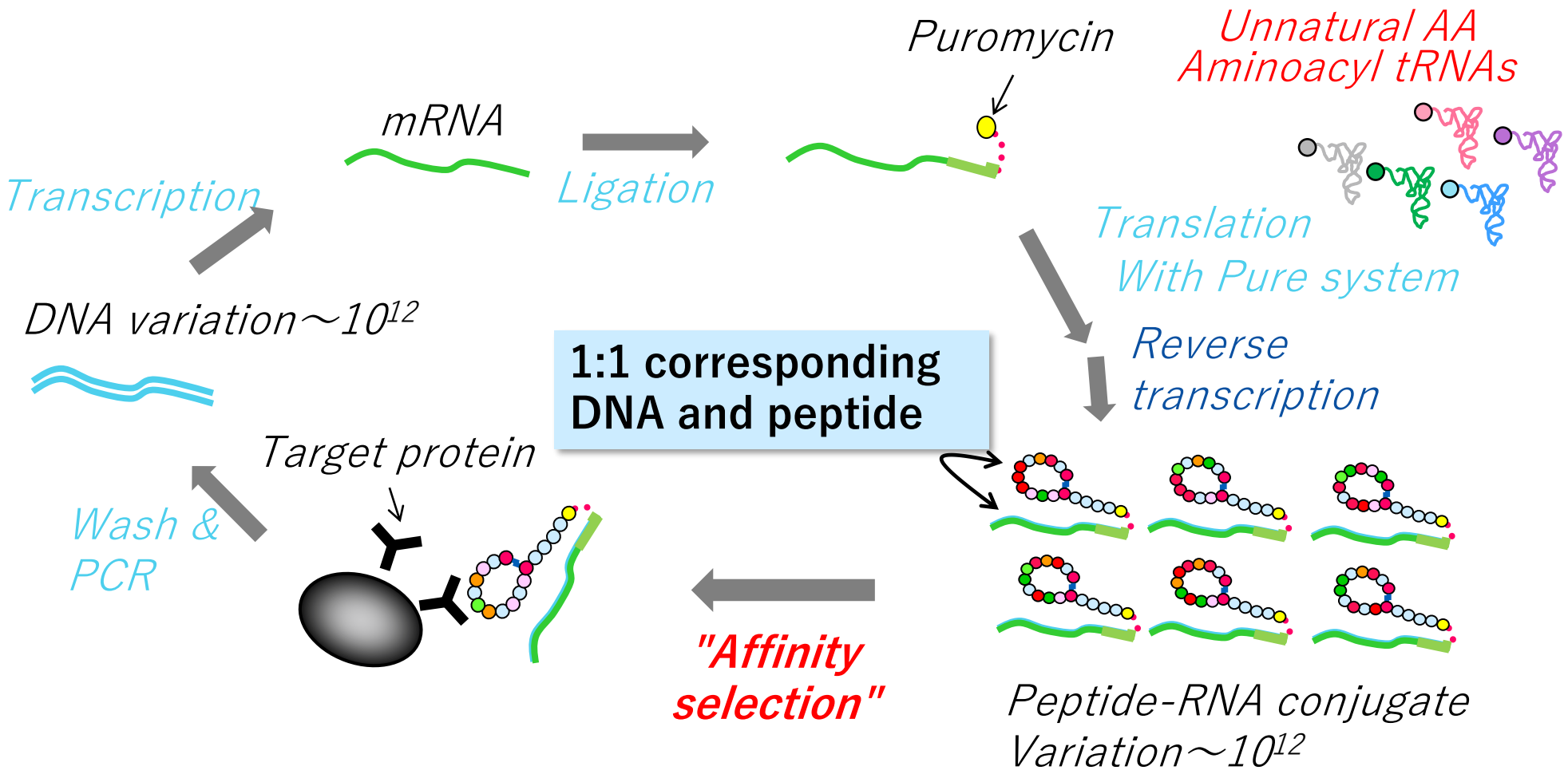
Unnatural-aa(UAA)-Aminoacyl-tRNA



Unnatural peptide



Drug-Like Peptides with 10^{12} Diversity Could be Achieved by mRNA Display



Challenges to Solve in Cyclic Peptide Drug Discovery

1. To impart Drug-likeness to mid-size molecules that are Beyond the Rule of 5

   In addition, Drug-likeness should be defined (semi)quantitatively

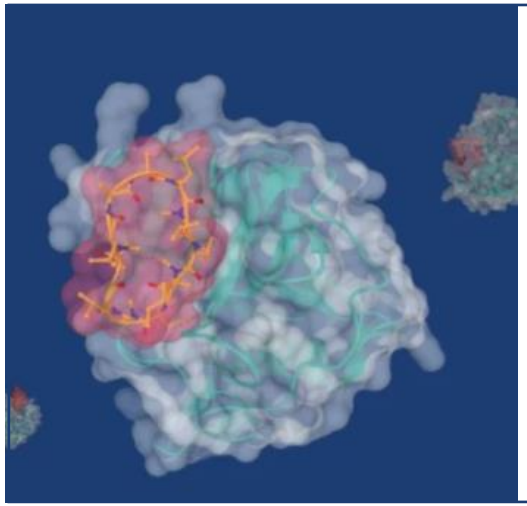
   Our medicinal chemists (semi) quantitatively define Drug-likeness by synthesizing and evaluating a numerous and various cyclic peptides

2. With Drug-likeness defined (semi)quantitatively, to construct a display library of non-natural peptides that meets our established definition of Drug-likeness

   Established Drug-like cyclic peptide library (*variation*～10^{12})

Establishing a System that Allows Us to Screen more than 20 Targets in a Year at CPR

HTS: High throughput screening
CPR: Chugai Pharmabody Research Pte. Ltd.

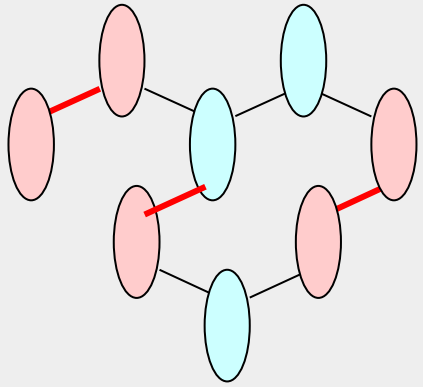


Mid-size molecule
- Cyclic peptide
- Oral administration
- Membrane permeability

Original library
- Large molecular diversity of 10^{12}

High-throughput Screening platform
- **Identify binders to many targets**
- **Semi-automated system**

Construction of Cyclic-Peptide Drug Discovery Technology by Fusing Medicinal Chemistry and Biotechnology



Chemistry:

Identifying criteria for Drug-likeness

Biotechnology:

Library construction, obtaining Drug-like hits

Without major structural changes

Products

Chemistry:

Creation of lead compounds from hit Compounds

Creation of clinical products by optimizing lead compounds

Biotechnology:

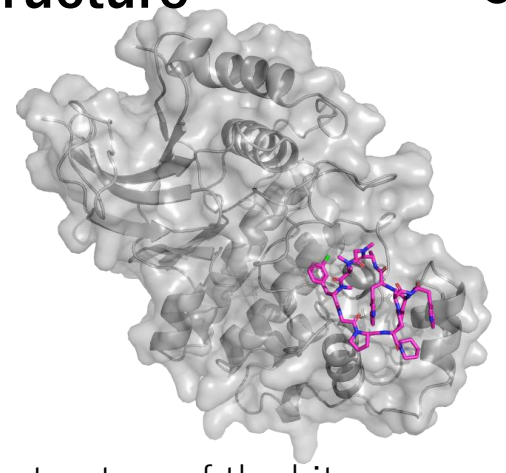
Conformational analysis of target proteins and hit compounds

Agenda

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

- **X-ray crystal structure**

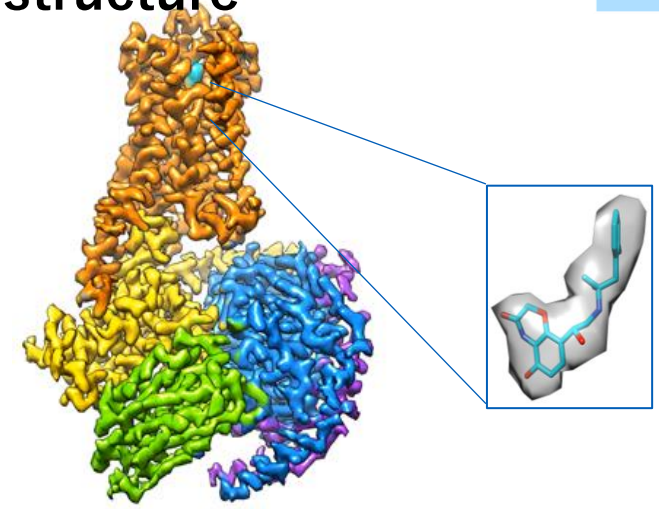
Synchrotron radiation



(crystal structure of the hit compound)

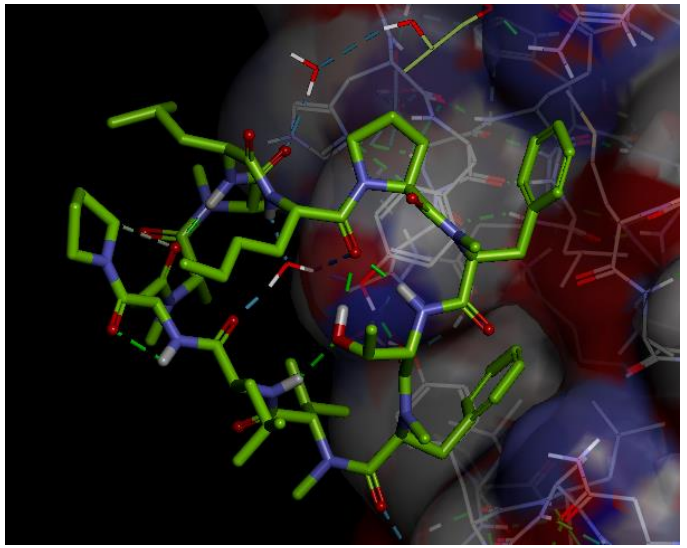
- **Cryoelectric structure**

Electron microscope



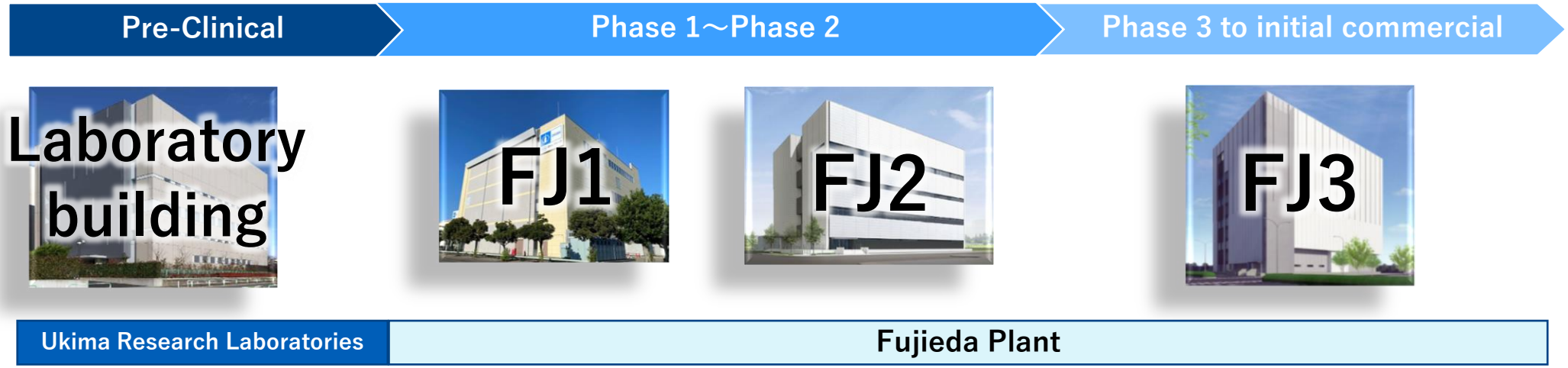
- **Digital utilization**

Chemical structural modification based on various in-house experimental data
- Simulation
- Prediction model



Set up of Production Facilities

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



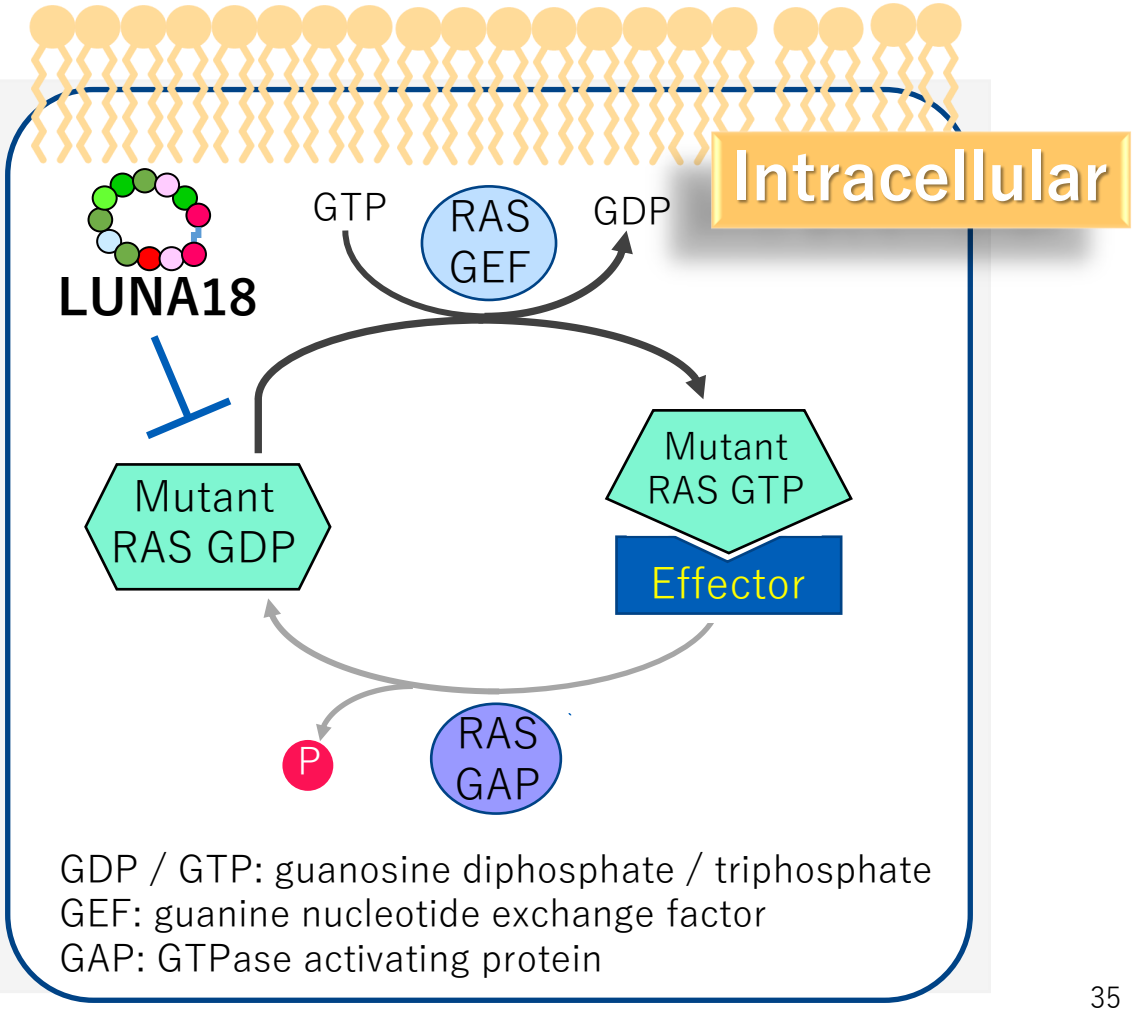
Start of Operation	2020	2003	Scheduled in Dec. 2022	Scheduled in Mar. 2025
Total floor area	4,925 m^2	5,417 m^2	6,190 m^2	10,250 m^2
Total investment	4.5 billion yen	7 billion yen	19.1 billion yen	55.5 billion yen

EHS: Environment, Health and Safety

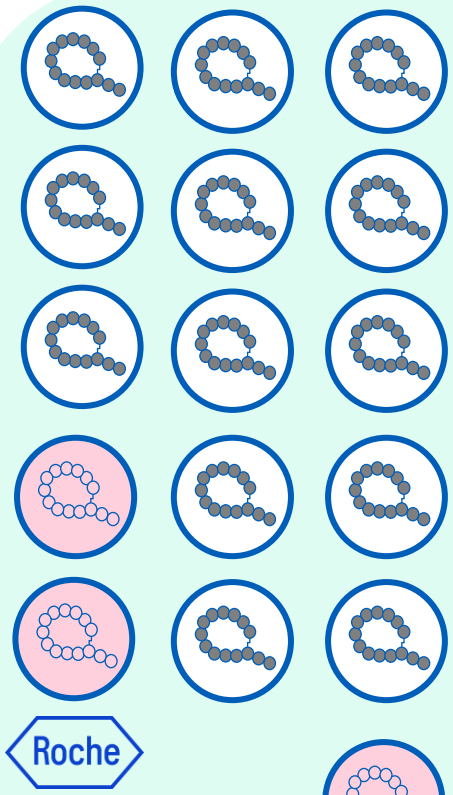
The First Clinical Trial from Mid-Size Molecule Technology (October 2021)

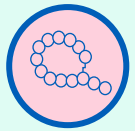
Novel cyclic peptide, LUNA18

- Orally available cyclic peptides
- Inhibits protein-protein interaction between RAS and GEF (inhibits RAS activation)
- Inhibits tumor cell growth for various RAS alterations (mutations or amplifications)

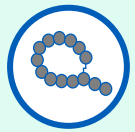


Mid-Size Molecule Drug Discovery: Research Portfolio



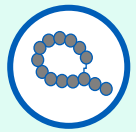


Univ. of Tokyo



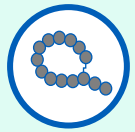
Cancer

- ✓ Intracellular
- ✓ Oral/injection



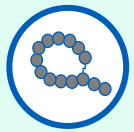
Cancer

- ✓ intracellular
  - Cellular activity
- ✓ Oral



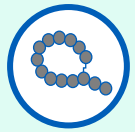
Cancer

- ✓ Intracellular
- ✓ Oral



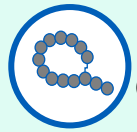
Cancer

- ✓ intracellular
  - Cellular activity
- ✓ Oral



Immune disease

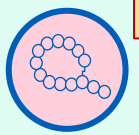
- ✓ Extracellular
  - Cellular activity
- ✓ Oral



Immune disease

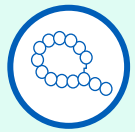
- ✓ extracellular
  - Cellular activity
- ✓ Oral

Osaka univ.



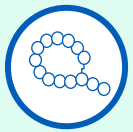
Immune disease

- ✓ intracellular
  - Cellular activity
  - Animal PD
- ✓ Oral



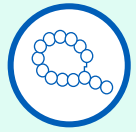
Acute disease

- ✓ intracellular
  - Cellular activity
  - Efficacy in animal
- ✓ Injection



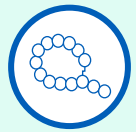
Cancer

- ✓ intracellular
  - Cellular Activity
  - Efficacy in animal
- ✓ Oral



Cancer

- ✓ intracellular
  - Cellular Activity
  - Efficacy in animal
- ✓ Oral



Cancer

LUNA18
Pan-RAS inhibitor

- ✓ intracellular targets
  - Cellular activity
  - Efficacy in animal
- ✓ Oral

Lead Identification | **Lead Optimization** | **GLP tox.** | **Phase 1**

Chugai Life Science Park Yokohama

Overview

Core research laboratory constructing in Totsuka-ku, Yokohama city, Kanagawa (Scheduled for completion in 2022)
- Building area: 35,210m^2
- Total floor area: 119,960m^2

Focusing on global warming countermeasures, regional disaster prevention, and biodiversity conservation, aiming for environmental performance certification

In addition to making environmental agreements with Yokohama City, we emphasize coexistence with the local community

- **By integrating all functions involved in drug discovery research, we will increase the efficiency of research and promote closer cooperation among our researchers.**
- **Promote more intensive integration of biology and technology**
- **Promote technology development of specialized formulation that is important for Mid-size drug production: Construction of a dedicated building**
- **Improve research productivity by utilizing cryo electron microscopy, automatic robots, and digital foundation such as AI**

Update on Antibody Engineering Technologies

Tomoyuki Igawa Ph.D.
Head of Translational Research Div.

Agenda

01 **Dual-Ig®** Next Generation T cell Bispecific Technology

02 **LINC-Ig™** Agonistic Activity Enhancing Technology

03 **PAC-Ig™** Disease/Tissue Specific Protease Activatable Antibody Technology

04 **MALEXA™** Antibody Design by Machine Learning

Agenda

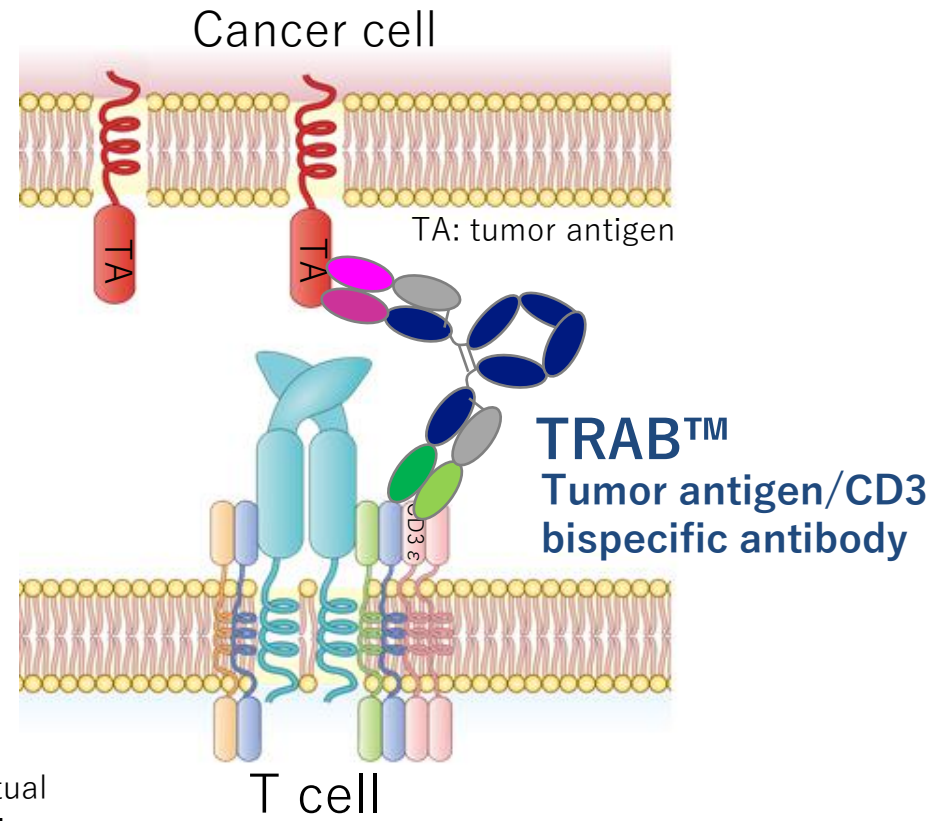
01 **Dual-Ig®** Next Generation T cell Bispecific Technology

02 LINC-Ig™ Agonistic Activity Enhancing Technology

03 PAC-Ig™ Disease/Tissue Specific Protease Activatable Antibody Technology

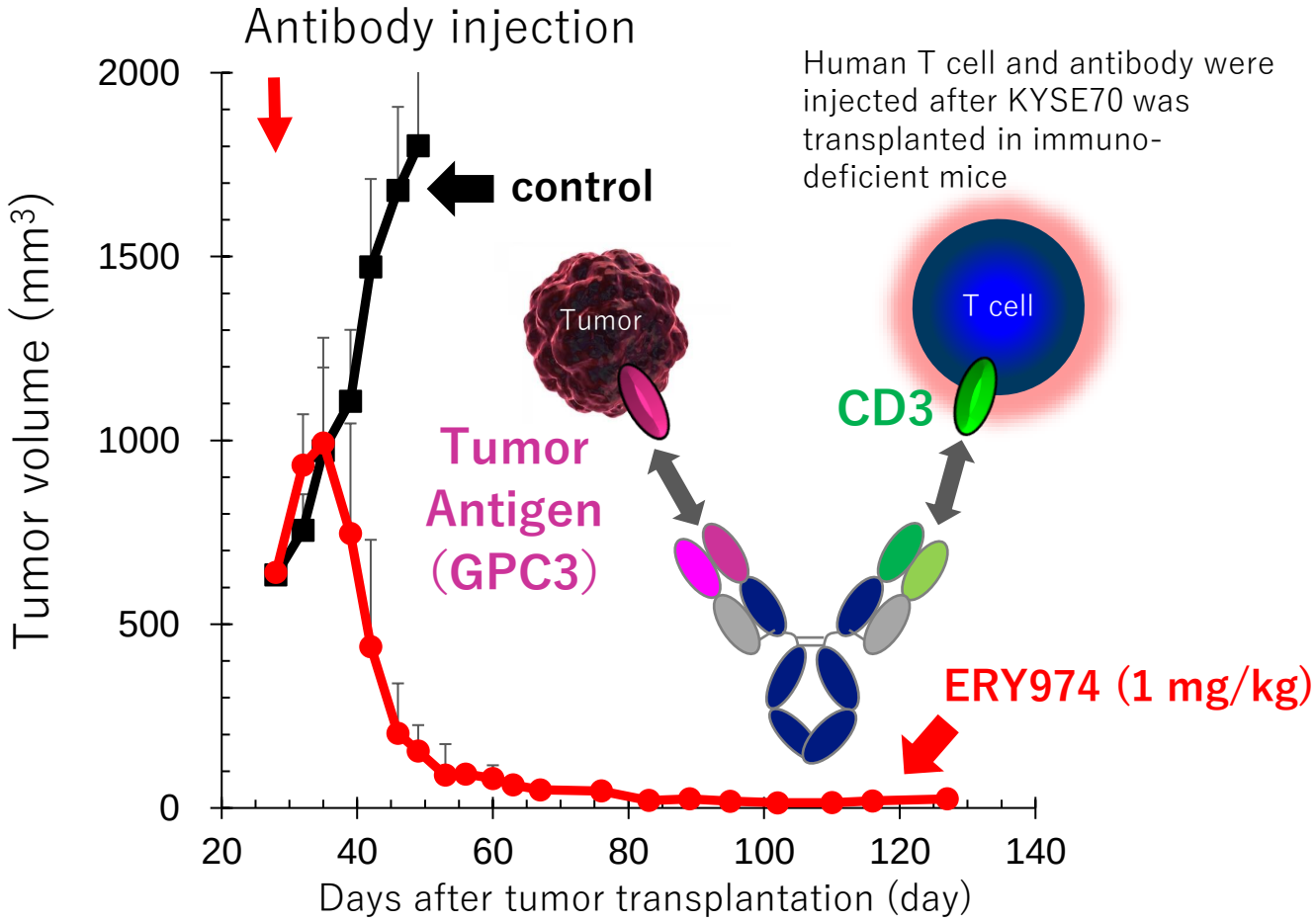
04 MALEXA™ Antibody Design by Machine Learning

T cell Redirecting AntiBody (TRAB™) is a Bispecific Antibody in Cancer Immunotherapy



conceptual illustration

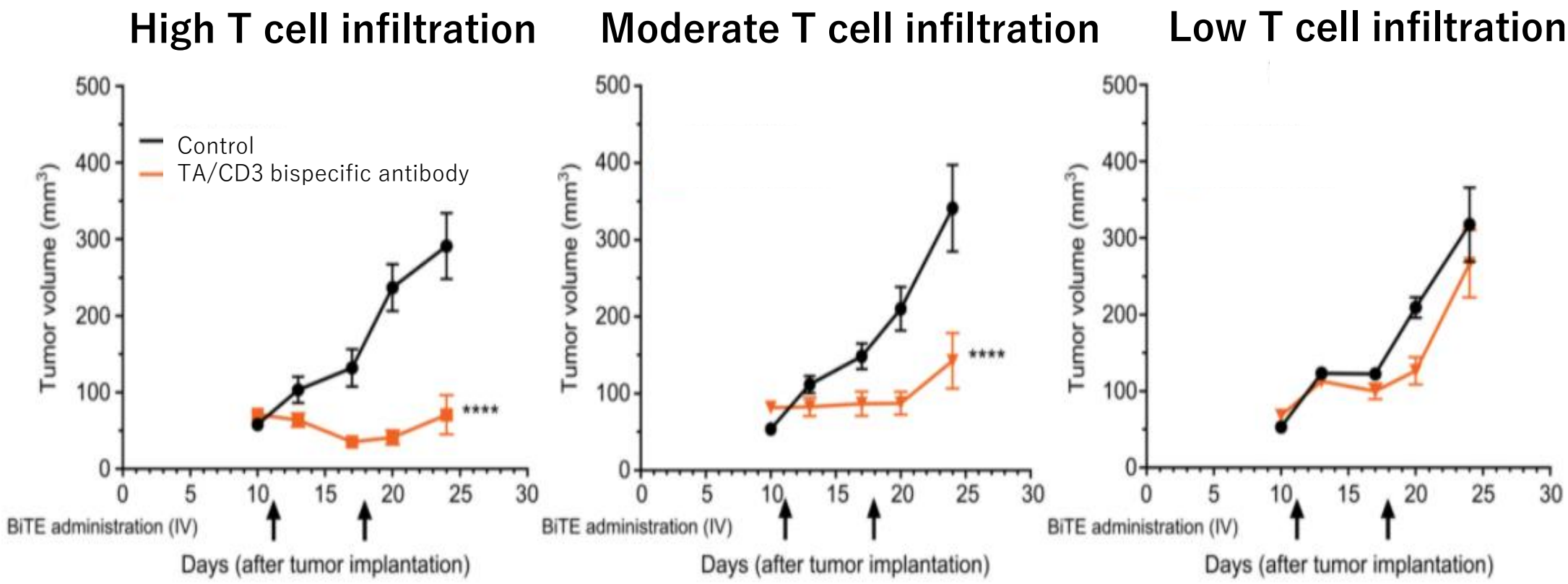
TRAB™ induced T-cell activation by cross-linking CD3 ε .



Ishiguro et al, Science Translational Medicine 04 Oct 2017:Vol. 9, Issue 410, eaal4291

(The author is an employee of Chugai Pharmaceutical Co., Ltd.)

Effect of TA/CD3 Bispecific Antibody is Limited Against Tumor with Less T Cell Infiltration



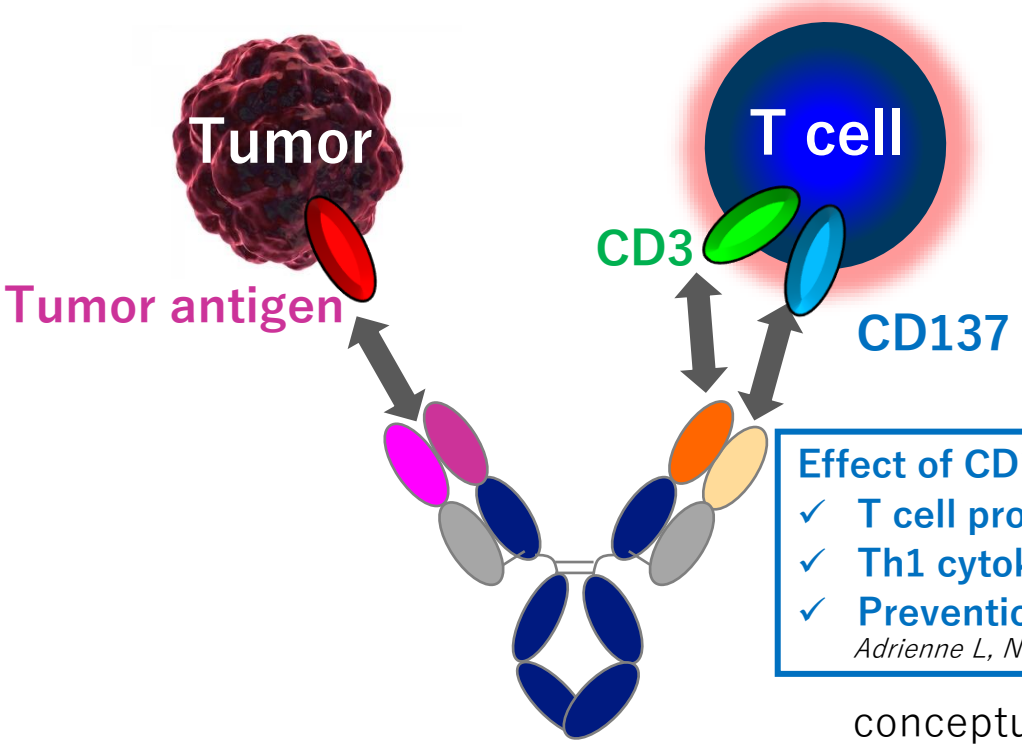
Belmontes B, Sci Transl Med. 2021 Aug 25;13(608).

TA/CD3 bispecific antibodies are developed globally, but the preclinical study showed its efficacy is limited against tumor with less T cell infiltration.

Dual-Ig®

Dual effector/receptor redirecting-Immunoglobulin

Dual-Ig® binds to CD137 as well as CD3 with T cell binding Fab

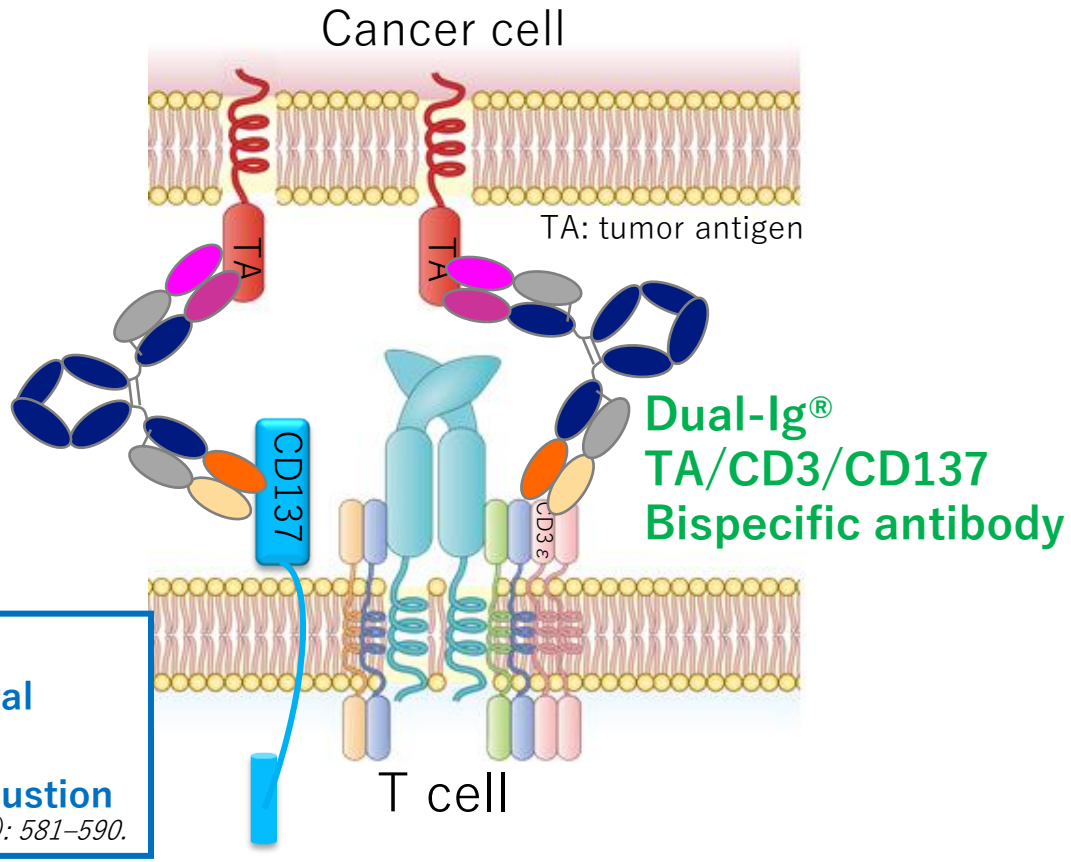


Effect of CD137 signal

- ✓ T cell proliferation survival
- ✓ Th1 cytokine production
- ✓ Prevention of T cell exhaustion

Adrienne L, Nat Med. 2015 Jun; 21(6): 581–590.

conceptual illustration

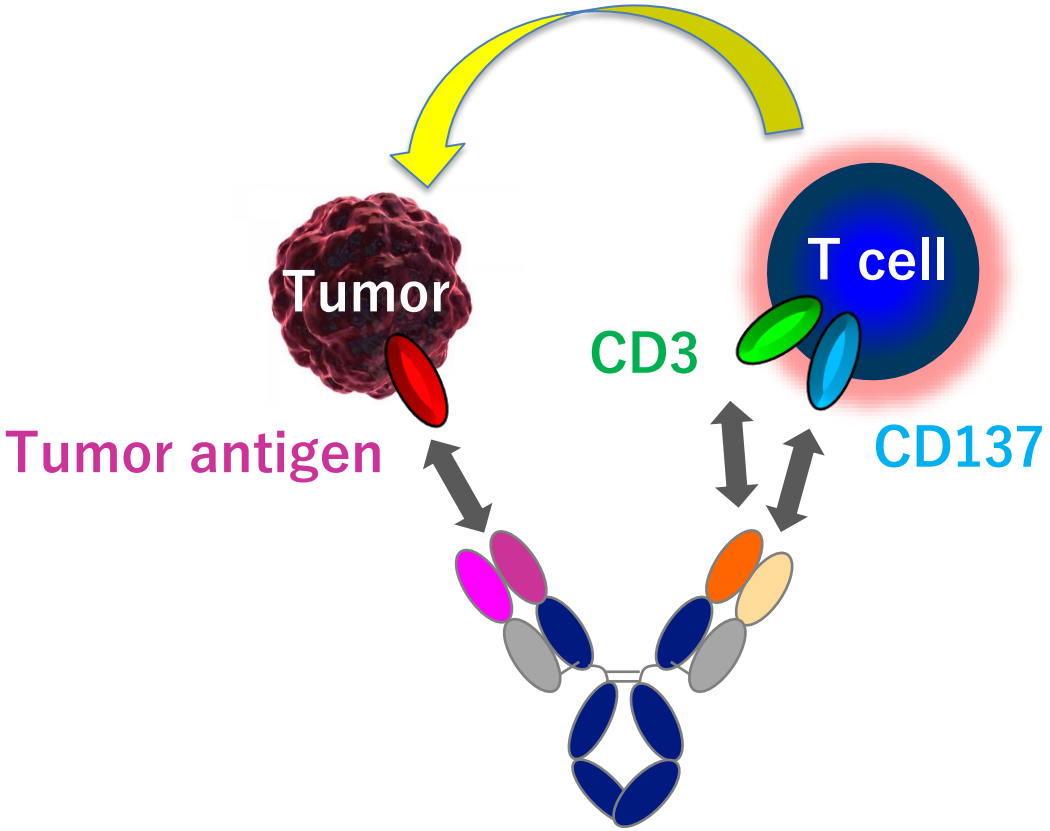


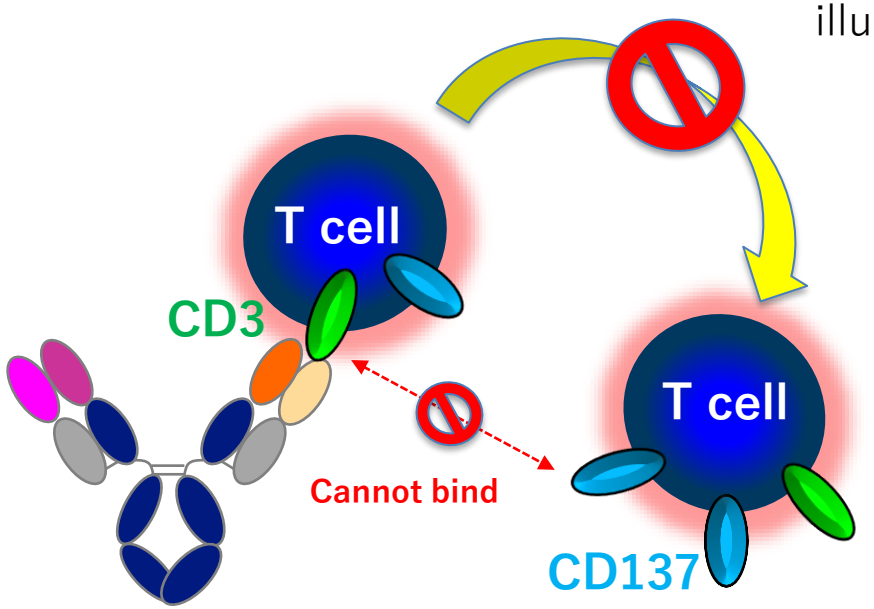
Dual-Ig® is expected to induce costimulation signal by cross-linking CD137 only in the presence of tumor antigen, in addition to CD3-mediated activation

Dual-Ig®

Dual effector/receptor redirecting-Immunoglobulin

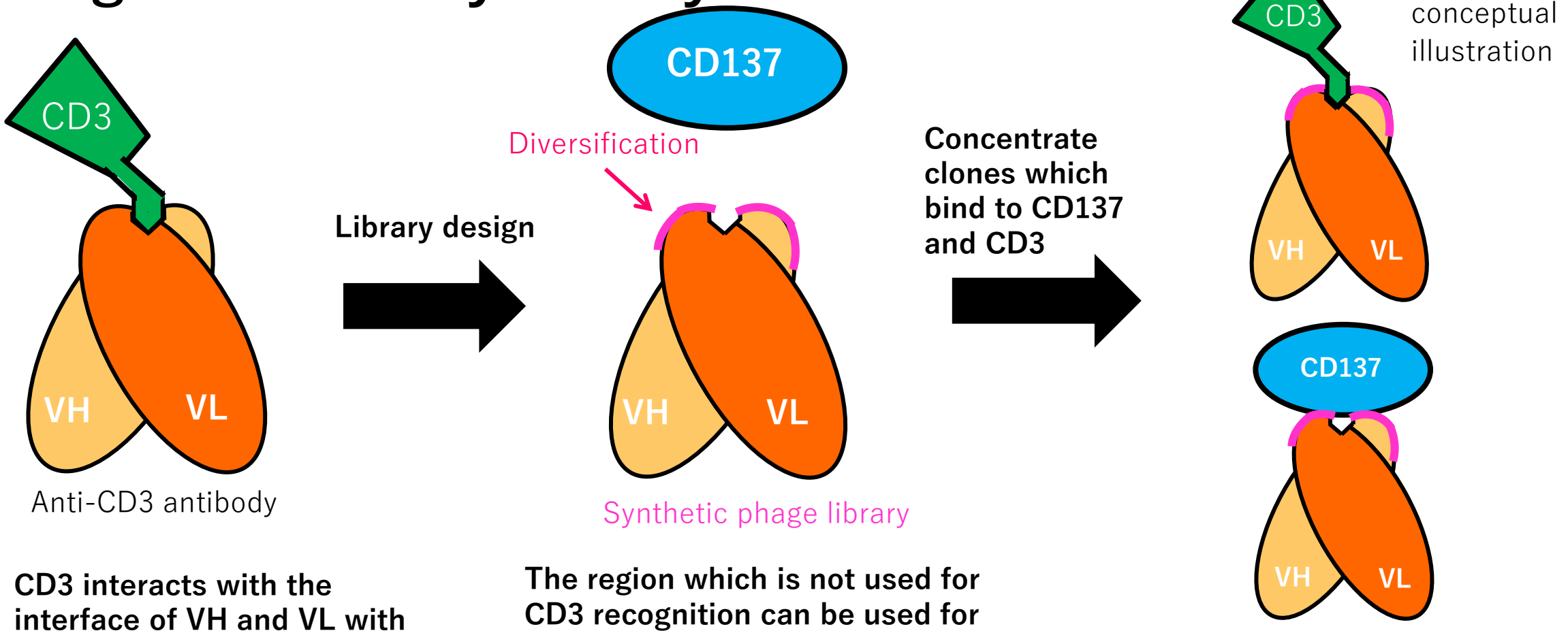
conceptual illustration





Dual-Ig® binds to CD3 and CD137 with T cell binding Fab. It is designed to avoid the binding to CD3 and CD137 simultaneously, which would result in CD3-mediated activation and CD137-mediated costimulation of T cell.

Dual-Ig® Antibody Generation with Uniquely Designed Antibody Library



conceptual illustration

CD3 interacts with the interface of VH and VL with its N-terminal region,

VH : Variable domain, Heavy Chain
VL : Variable domain, Light Chain

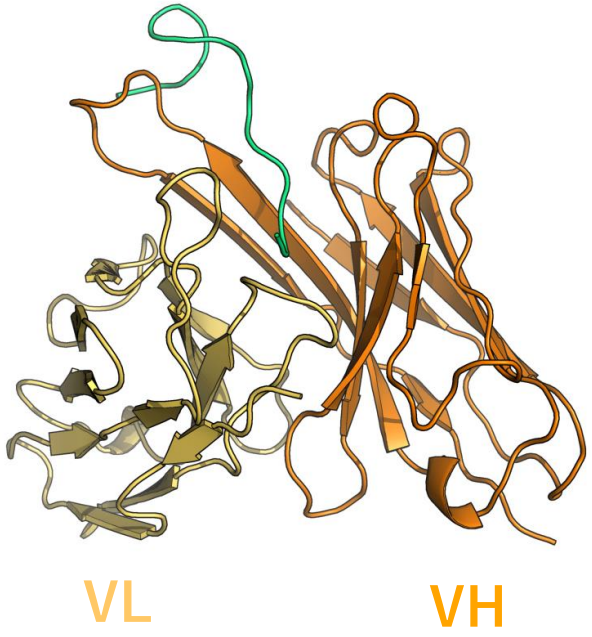
The region which is not used for CD3 recognition can be used for CD137 binding by diversifying the region.

Antibodies which bind to CD3 and CD137 were generated from this synthetic library

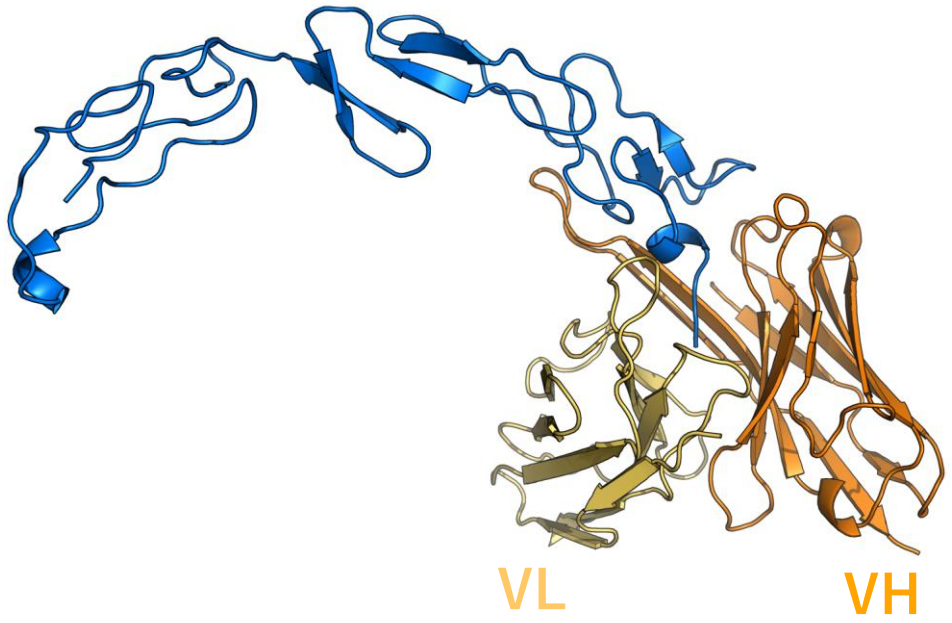
CD3-Recognizing Paratope is Overlapped with CD137-Recognizing Paratope

Bio International presentation material (modified)

CD3 N-terminal peptide



CD137



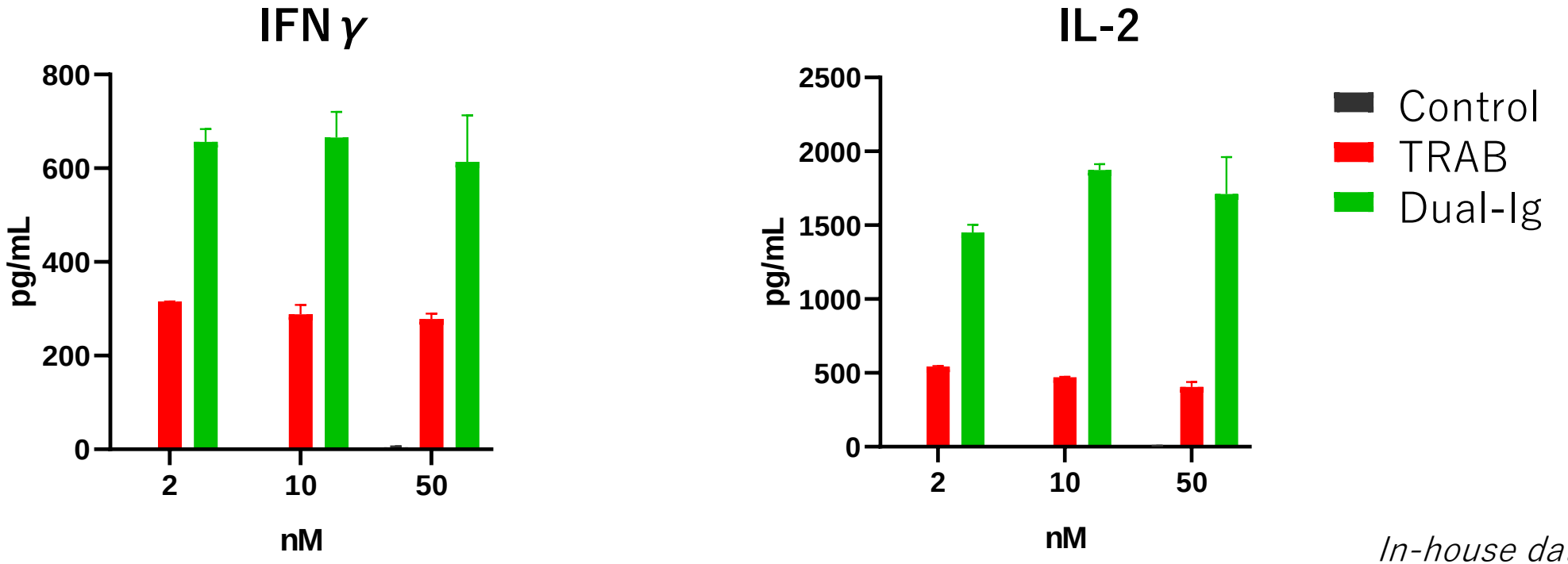
Dual-Ig® is strictly designed not to bind to CD3 and CD137 simultaneously by utilizing the paratope overlapping with CD3-recognizing paratope.

Paratope: the region of an antibody with which the antibody recognizes and binds to an antigen

Dual-Ig® Induced Th1 Cytokines 2-3 Fold Higher than TRAB™

Cytokines were measured after antibodies were added into culture medium where human PBMC and cancer cells expressing tumor antigen were cocultured.

PBMC: peripheral blood mononuclear cell

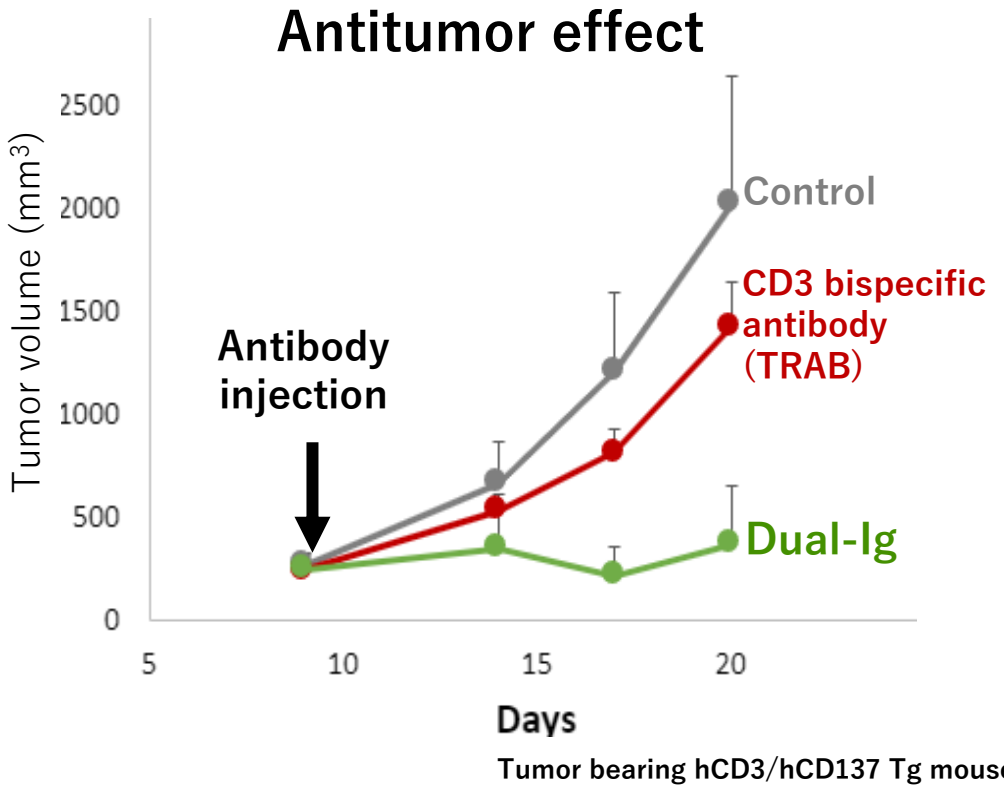


In-house data

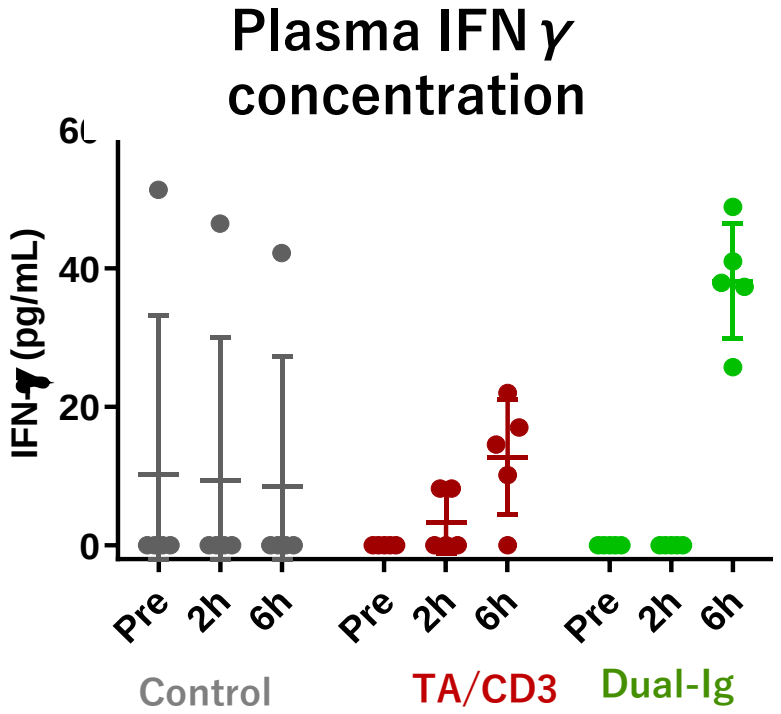
Dual-Ig® induces Th1 cytokines in the presence of tumor antigen-expressing cells more than TRAB™.
(IFNγ is an essential cytokine for antitumor effect and IL-2 for T cell survival.)

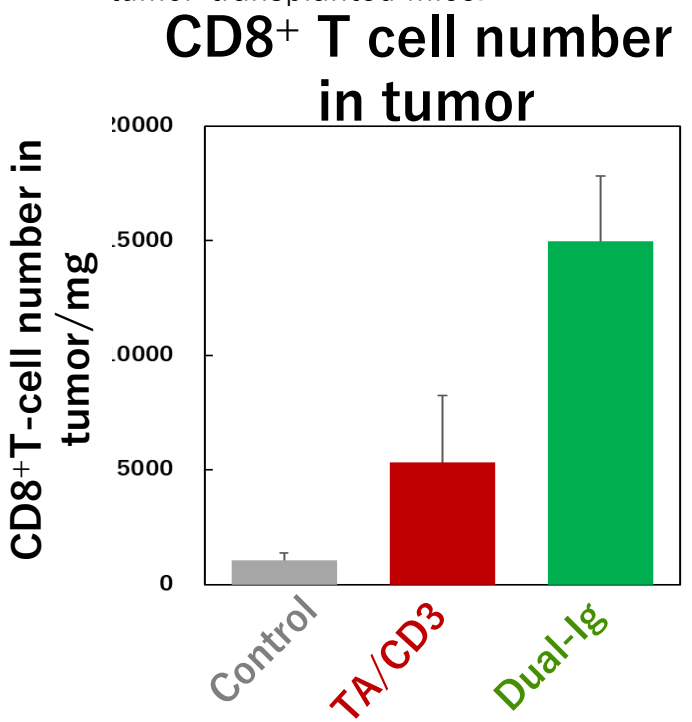
Dual-Ig® Shows Antitumor Effect by Increasing CD8+ T Cells More than CD3 Bispecific Antibody

Tumor volume, IFNγ concentration and CD8+ T cell number were measured after antibodies were administered in mouse tumor-transplanted mice.



Tumor bearing hCD3/hCD137 Tg mouse





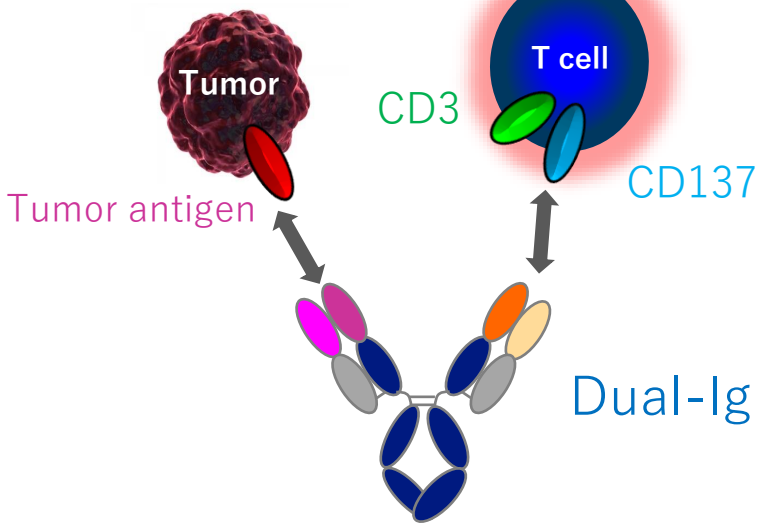
PEGS Europe presentation material (modified)

Dual-Ig® shows antitumor effect by increasing CD8+ T cells more than CD3 bispecific antibody (TRAB™).

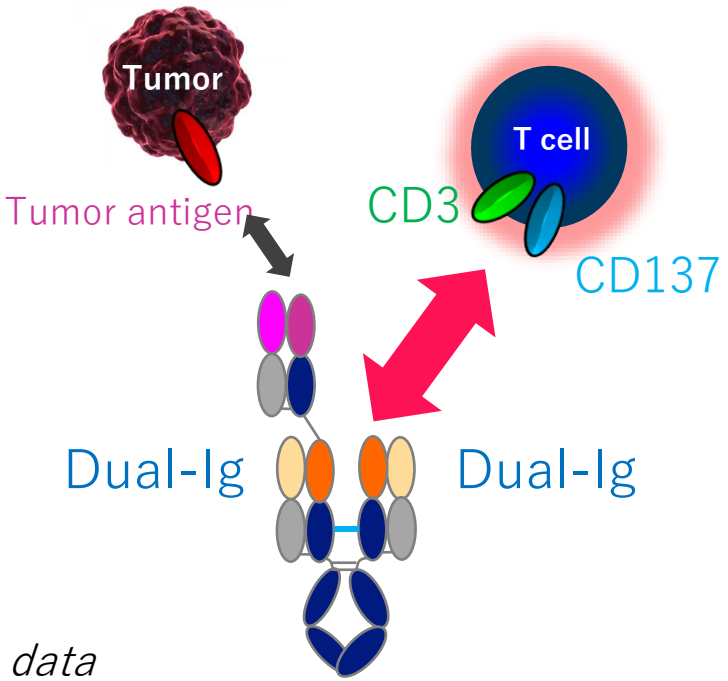
Dual/LINC-Ig™ Further Enhanced Antitumor Effect

Tumor volume, IFNγ concentration and CD8+ T cell number were measured after antibodies were administered in mouse tumor-transplanted mice.

Dual-Ig®

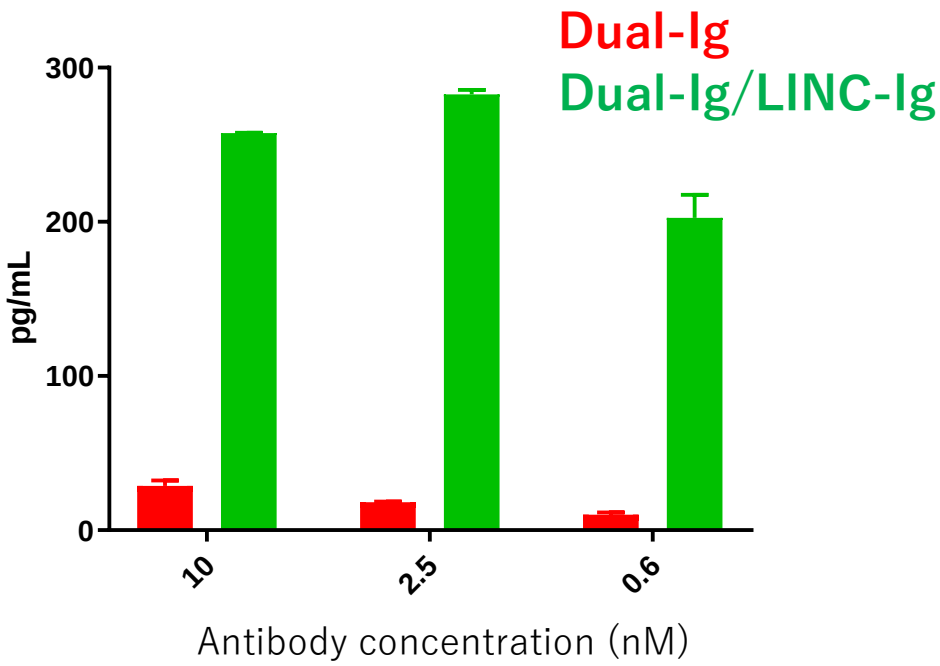


Dual/LINC-Ig™



In-house data

IFNγ production



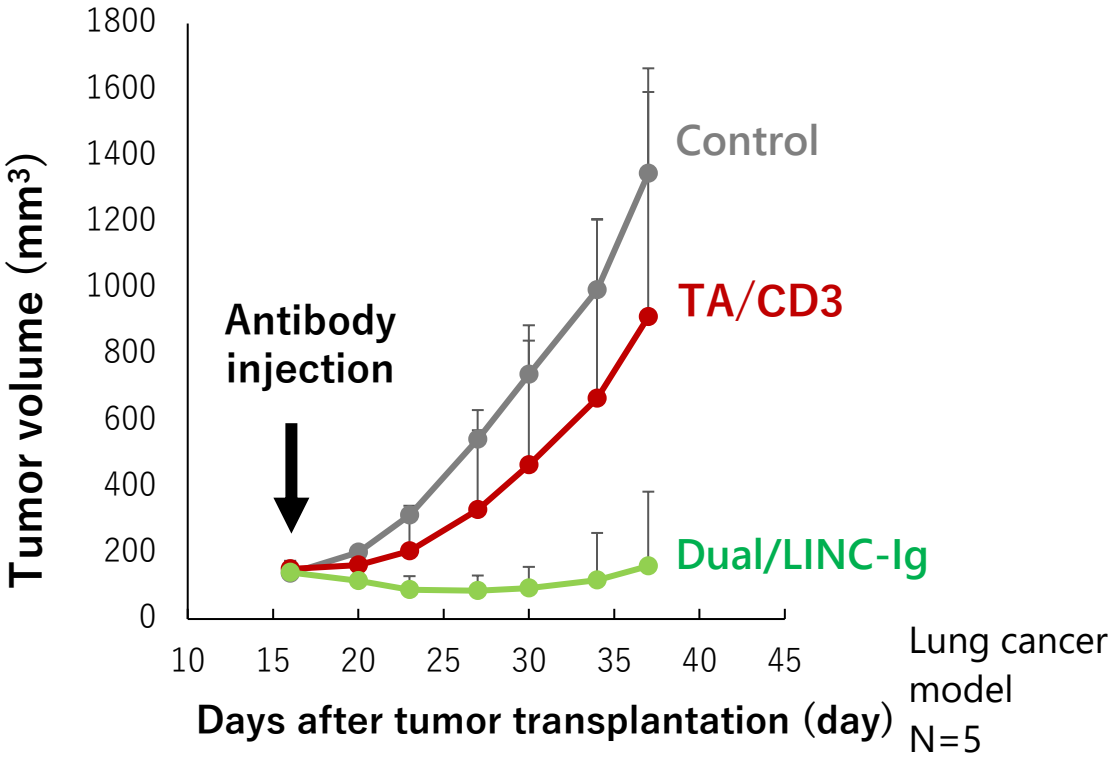
Bio International presentation material (modified)

Dual/LINC-Ig™ has two Dual-Ig® cross-linked with LINC-Ig™, with which Dual/LINC-Ig™ can enhance cytotoxicity by inducing enhanced CD3/CD137 signal into T cell.

Dual/LINC-Ig™ Shows Antitumor Effect by Increasing CD8+ T Cells More than CD3 Bispecific Antibody

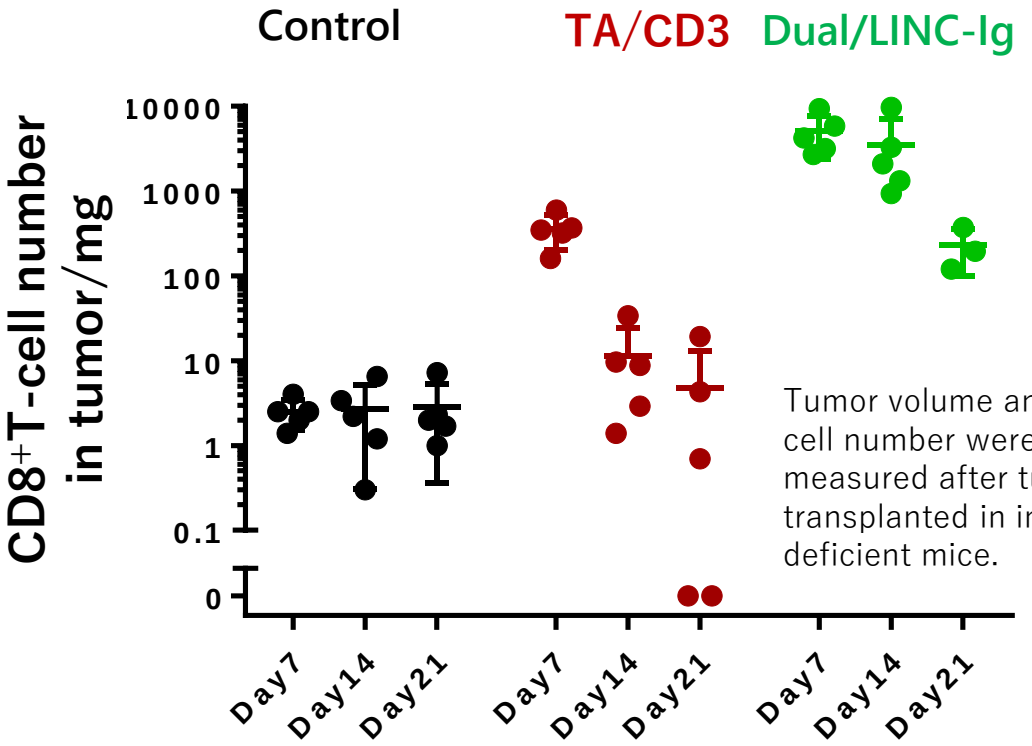
In-house data

Antitumor effect



Lung cancer model
N=5

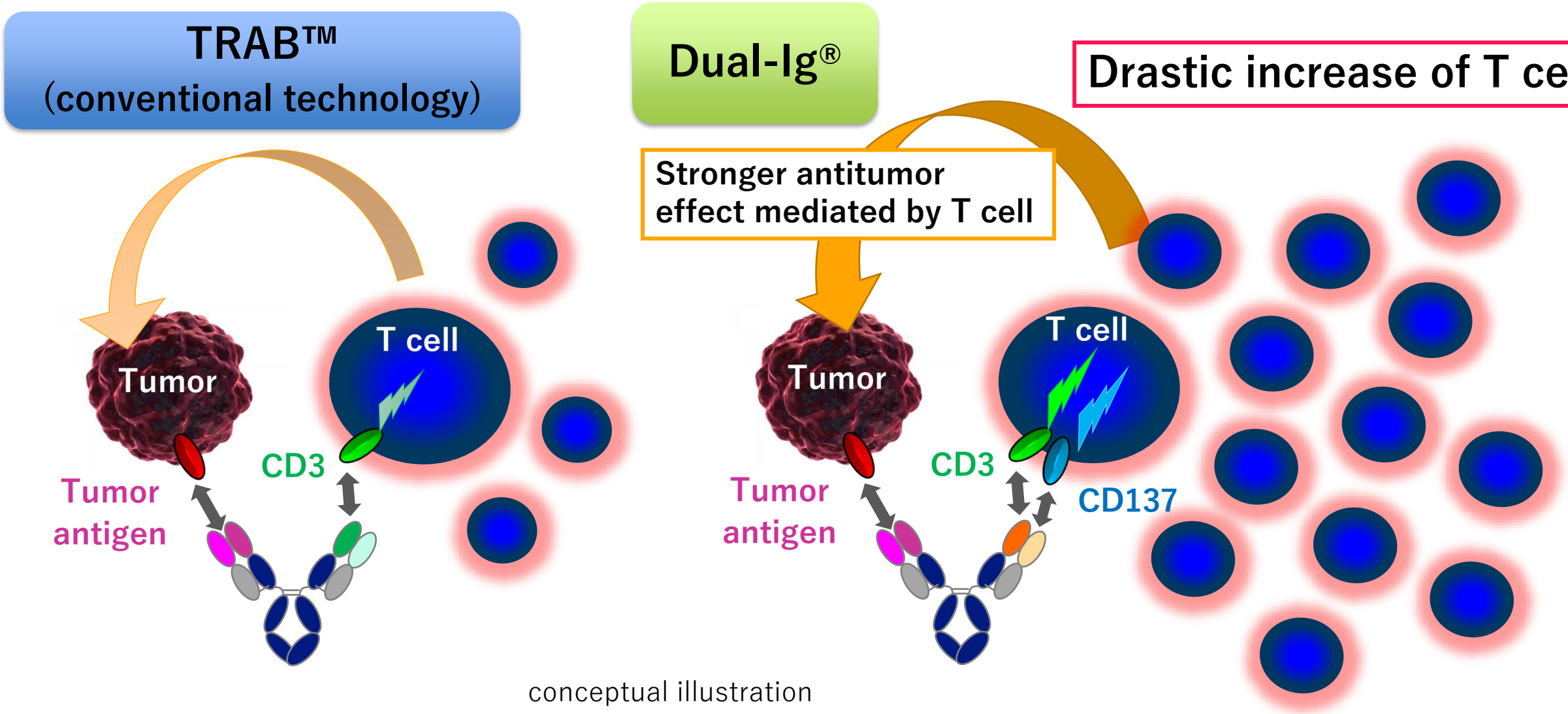
CD8+ T cell number in tumor



Tumor volume and CD8+ T cell number were measured after tumor was transplanted in immuno-deficient mice.

Dual/LINC-Ig™ increased CD8+ T cells by 10 to 1000-fold and showed antitumor efficacy in a preclinical model in which CD3 bispecific antibody (and Dual-Ig®) did not show tumor retardation.

Dual-Ig® Enables Drug Discovery Against Cancer with Limited T Cell Infiltration by Drastically Increasing Number of T Cell



conceptual illustration

The Current Status of Dual-Ig® Application

- **Currently have two projects applying Dual-Ig® at GLP-TOX stage.**
- **Several projects in combination with Switch-Ig™ at research stage.**

Project	Technology	Cancer type	Stage
A	Dual-Ig®	Lung cancer etc	GLP-TOX
B	Dual/LINC-Ig™	Lung cancer etc	GLP-TOX
C	Dual-Ig® etc	Lung cancer etc	Lead Optimization
D	TRAB/Dual-Ig	Colorectal cancer etc	Lead Optimization
E	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification
F	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification
G	TRAB/Dual-Ig & Switch-Ig™	Various cancer types	Lead Identification

- **Another project, different from Dual-Ig® at GLP-TOX stage, utilizing the nature of antibody binding to multiple antigens with a single Fab.**

Agenda

01 Dual-Ig® Next Generation T cell Bispecific Technology

02 **LINC-Ig™ Agonistic Activity Enhancing Technology**

03 PAC-Ig™ Disease/Tissue Specific Protease Activatable Antibody Technology

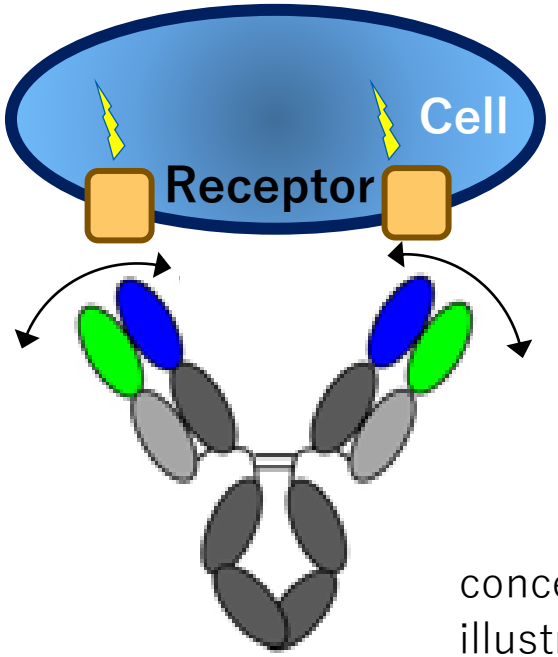
04 MALEXA™ Antibody Design by Machine Learning

LINC-Ig™

LINCed-Immunoglobulin

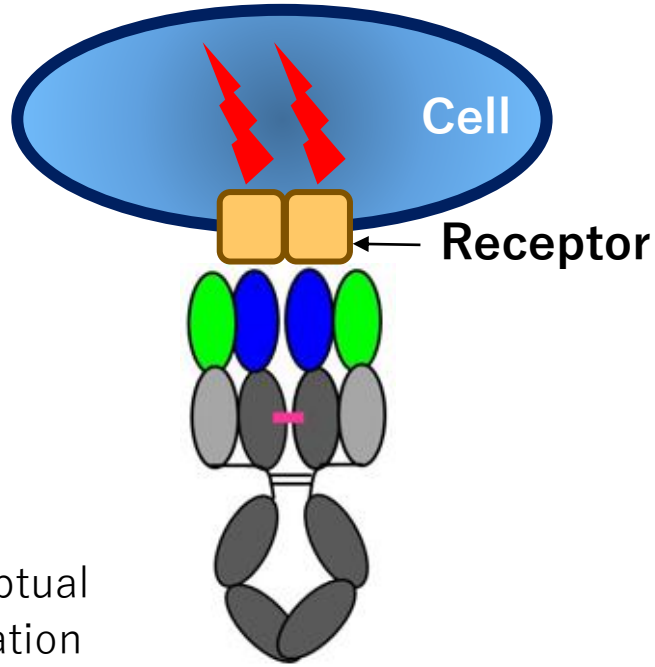
Enhances agonistic activity of antibody by controlling spatial mobility of 2 Fabs

Conventional IgG



The two Fabs can move freely and therefore cannot cluster receptors effectively

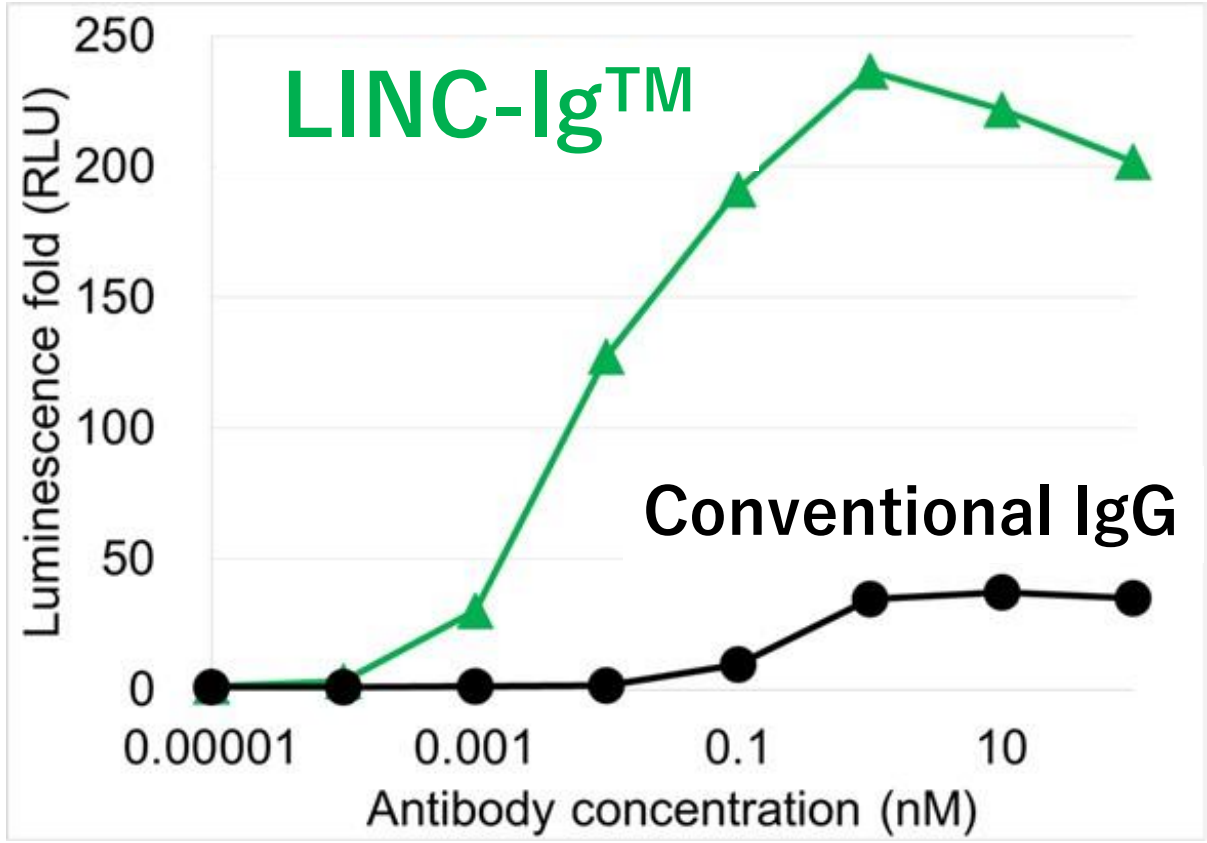
LINC-Ig™



conceptual illustration

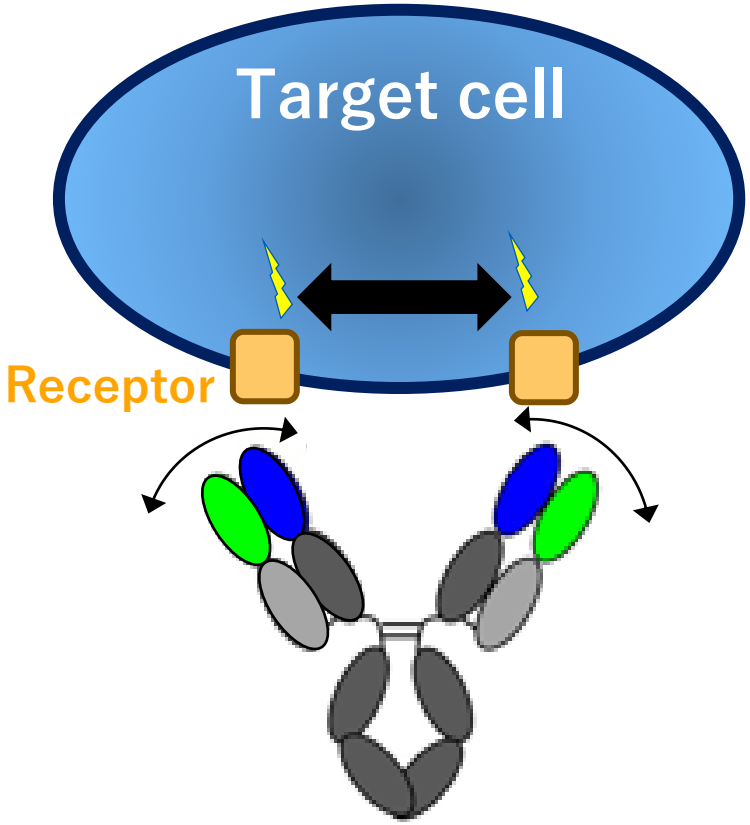
Controls the mobility of Fab domains by engineering disulfide bonds between Fab-Fab

Agonistic activity of agonist antibody



Bio International presentation material (modified)

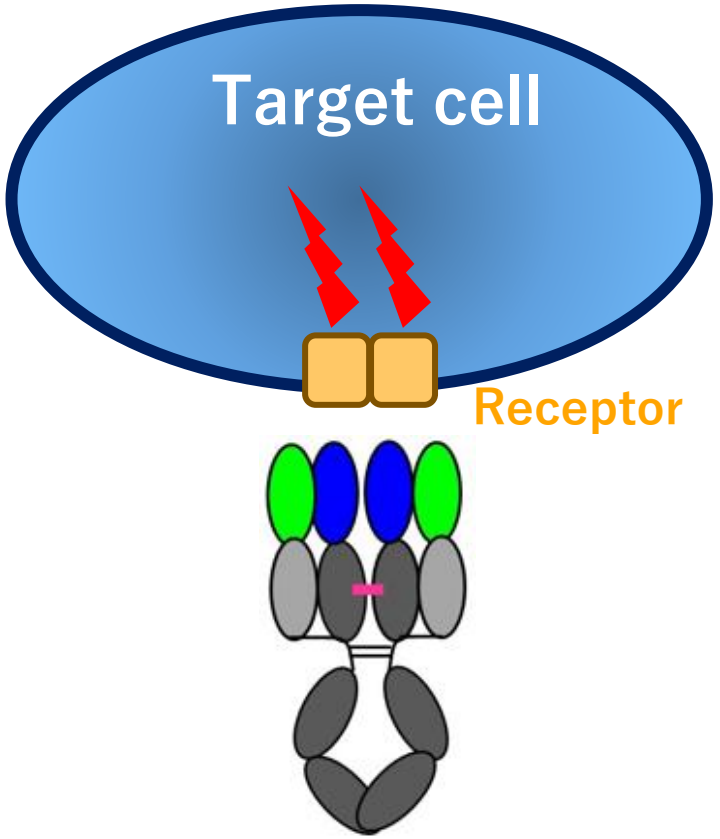
Making Undruggable Agonistic Antibody Target Druggable



Conventional IgG

Conventional antibody cannot induce agonistic activity due to large distance between the receptors

conceptual illustration



LINC-Ig™

LINC-Ig™ effectively dimerizes receptors and exerts agonist activity

Agenda

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02 LINC-Ig™ Agonistic Activity Enhancing Technology

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04 MALEXA™ Antibody Design by Machine Learning

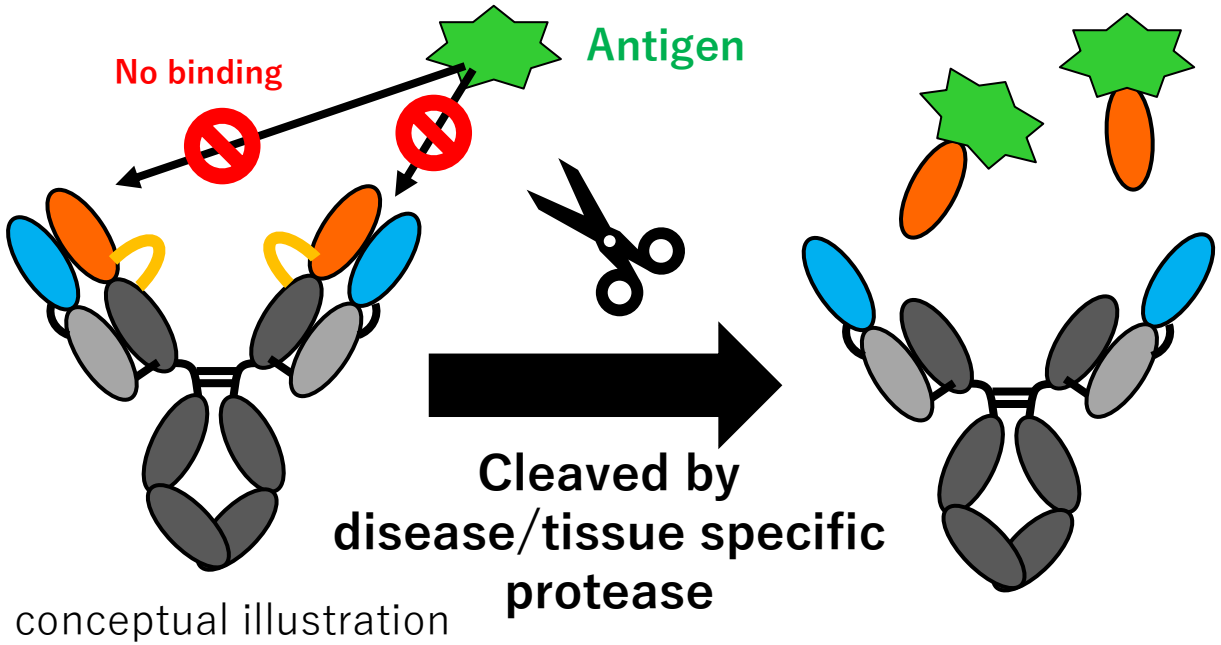
PAC-Ig™

Protease ACtivated-Immunoglobulin

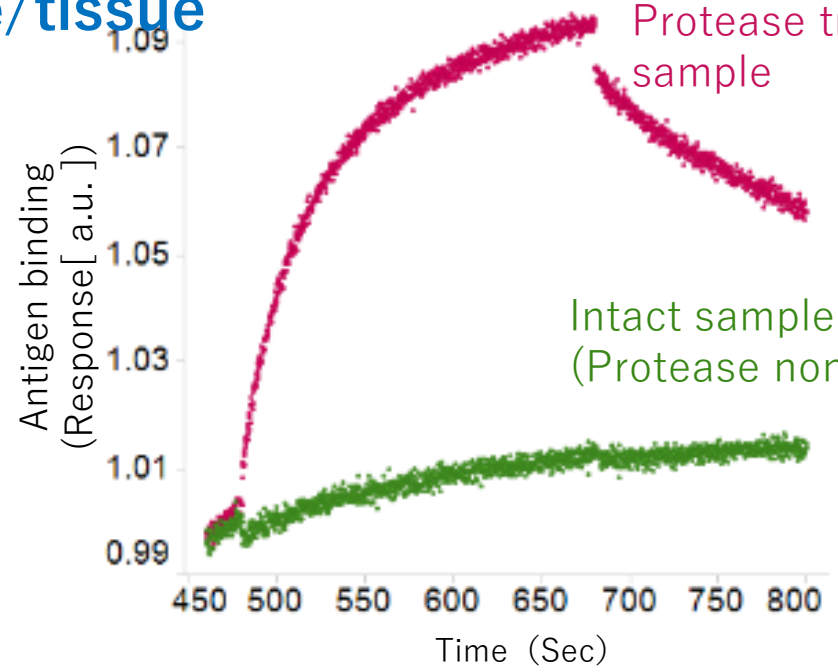
Technology to create antibody which can bind to the target only after cleavage by protease specifically present at disease/tissue

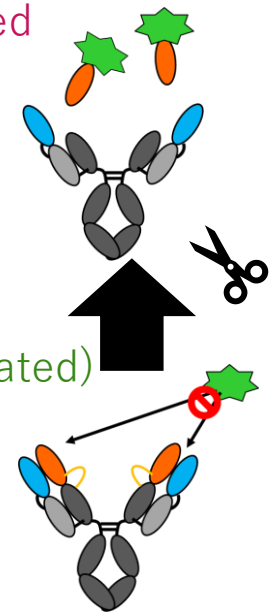
Antigen binding VHH (Single domain Ab)
VHH：Variable domain of heavy chain of heavy chain antibody

Unique linker selectively cleaved by disease/tissue specific protease



conceptual illustration





Bio International presentation material (modified)

- ✓ **VHH associated with VL cannot bind to the antigen**
- ✓ **Long half-life as IgG**

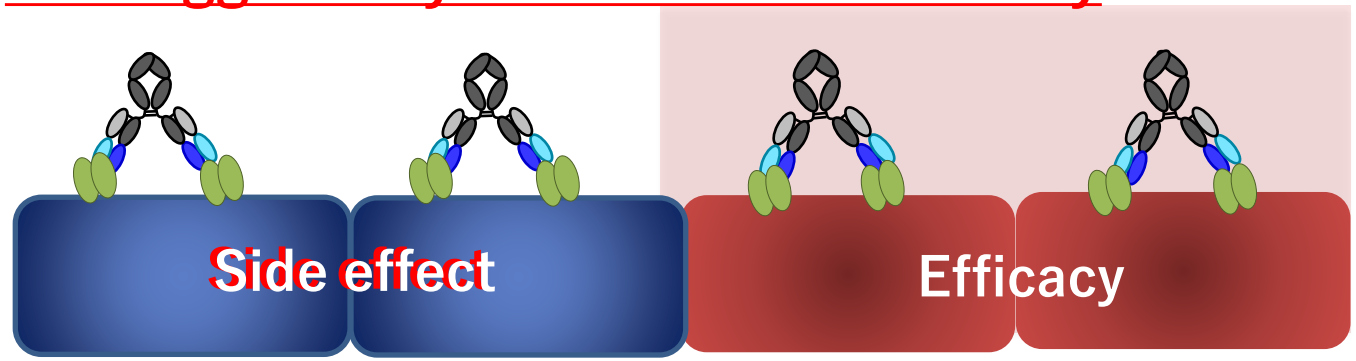
- ✓ **Site specific antigen binding by released VHH**
- ✓ **Minimize systemic action by rapid clearance**

Making Undruggable Target Druggable

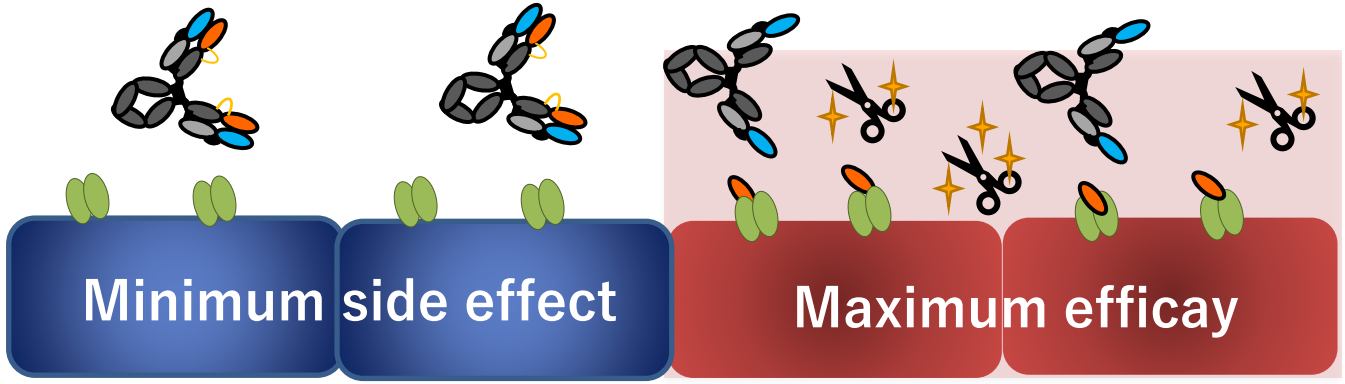
Enabling spatiotemporal control of antibody function by engineering antibody to be activated after cleavage by protease (protease plays a key role for homeostasis and progression of disease)

Undruggable by conventional antibody

conceptual illustration



Druggable by PAC-Ig™



Normal tissue
(No protease activity)

Disease lesion or tissue
(Protease activity)

In case returns to blood or normal tissue,

Minimum effect due to rapid elimination from circulation

Agenda

01 Dual-Ig® Next Generation T cell Bispecific Technology

02 LINC-Ig™ Agonistic Activity Enhancing Technology

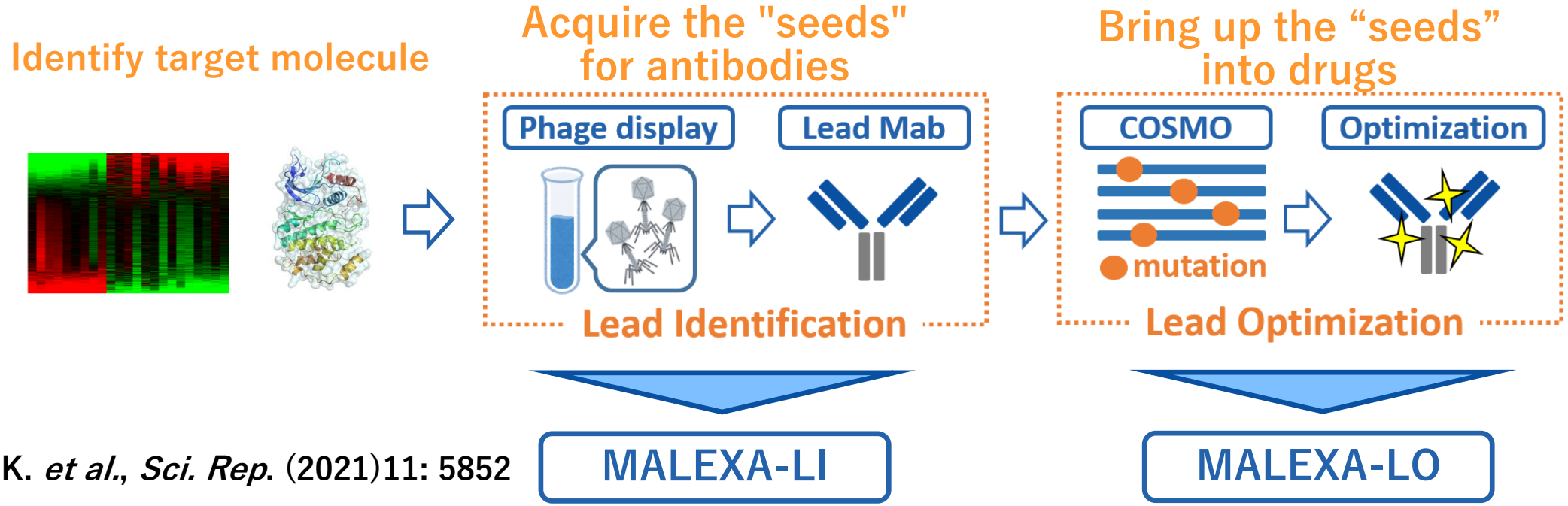
03 PAC-Ig™ Disease/Tissue Specific Protease Activatable Antibody Technology

04 **MALEXA™ Antibody Design by Machine Learning**

Changing the Drug Discovery Process with MALEXA™

MALEXA: Machine Learning x Antibody

Antibody Drug Discovery Process and Application of MALEXA™



Saka K. *et al.*, *Sci. Rep.* (2021)11: 5852

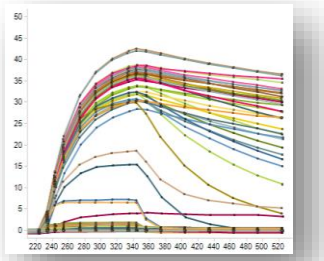
Need to design and develop process-specific machine learning algorithms

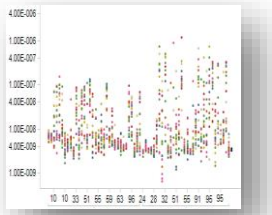
Multidimensional Antibody Optimization System

COSMO: COmprehensive Substitution for Multidimensional Optimization

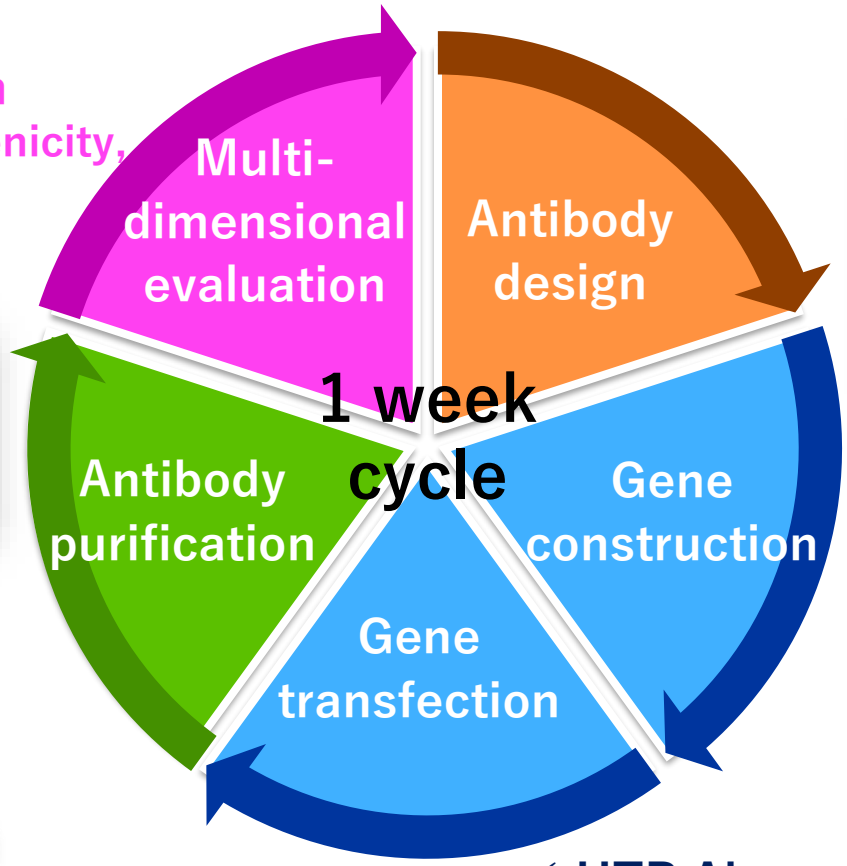
✓ HTP affinity measurement
~2000 Run/Week

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

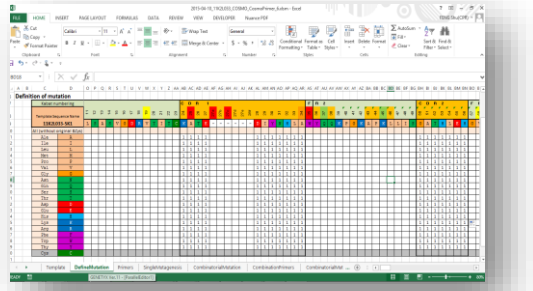




✓ HTP antibody purification
~1500 Abs/Day



✓ HTP primer design system

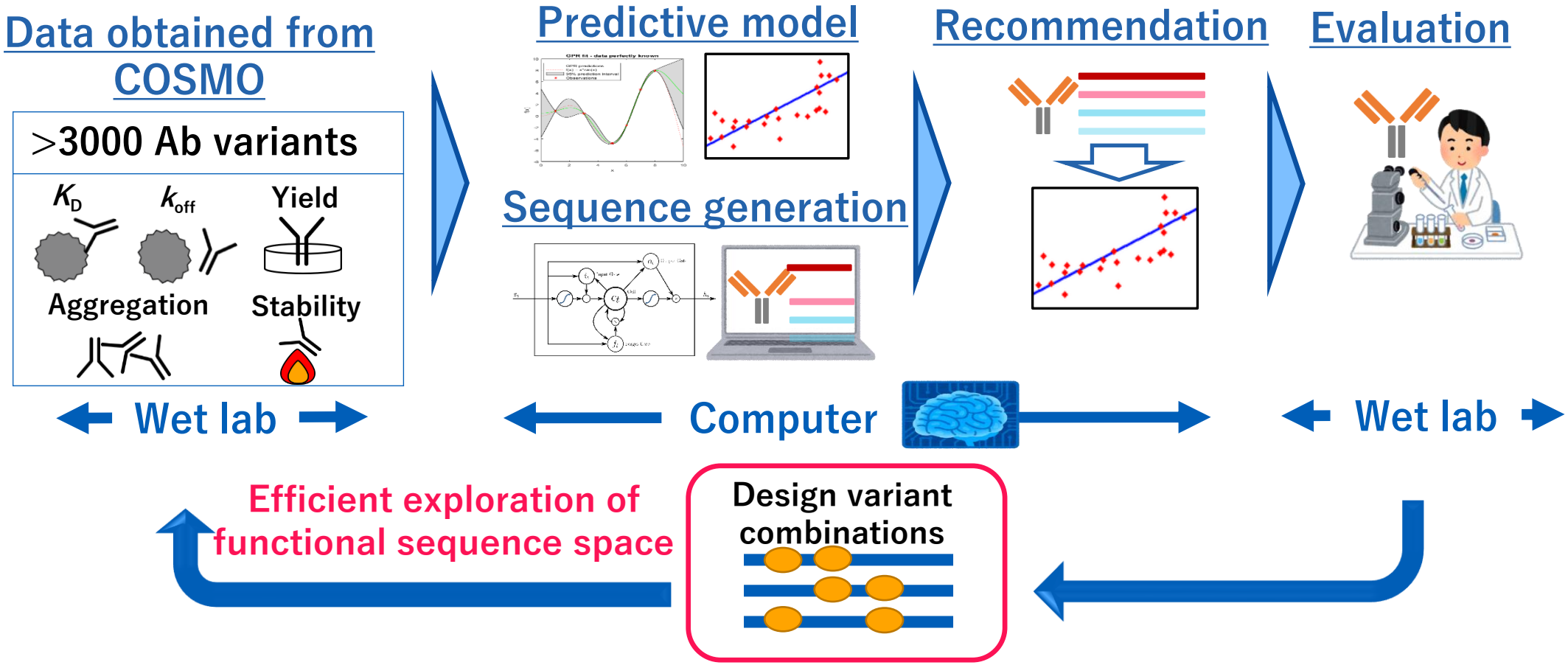


✓ HTP Ab construction and transfection
~3000 Abs/week

Source : Chugai Pharmaceutical Co., Ltd.

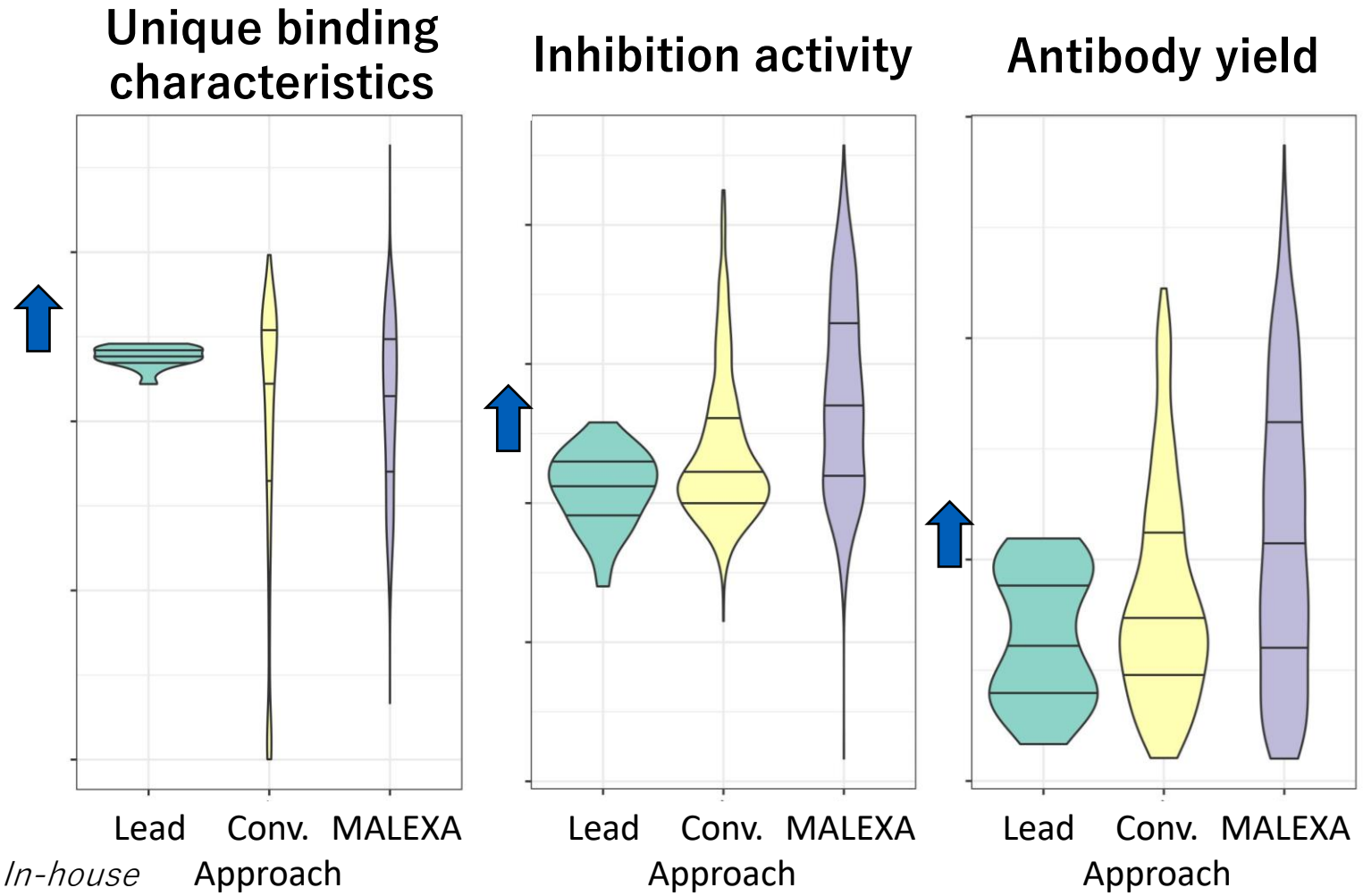
MALEXA-LO：Leveraging Machine Learning for Multi-Dimensional Antibody Optimization

Starting with comprehensive single-mutation data (COSMO), design high-performance antibody variants through repeated rounds of machine learning-based prediction and experimental evaluation.



MALEXA-LO Can Predict Antibodies with Better Properties than by the Conventional Approach

The violin plots show the binding characteristics, inhibition activity, and antibody yield, measured *in vitro*, for each category of antibodies.



In-house data

- MALEXA (959 antibody variants)
- Conventional approach (677 antibody variants)
- Lead antibody

MALEXA predicted better sequences than the conventional researcher-led design approach.

Further improve the system to include various parameters such as PK, immunogenicity and physicochemical properties.

By applying MALEXA to increasingly complex antibody drug design, increase the productivity of drug discovery research and the quality of drug candidates.

Antibody Project Pipeline Utilizing Antibody Engineering Technologies

CHUGAI
Roche Roche Group

FDA BTD

* Projects that utilize multiple technologies are displayed in each technology.

Recycling Antibody®
Sweeping Antibody®
etc.

- SOF10 (cancer/P1)
- AMY109 (endometriosis, cancer /P1)
- GYM329/RG6237 (SMA/P1)
- satralizumab
- nemolizumab (atopic dermatitis/Filed)
- crovalimab (PNH/P3)

PNH: Paroxysmal nocturnal hemoglobinuria

Bispecific antibody (Non-Oncology)

- NXT007 (hemophilia A/P1)
- emicizumab

Bispecific antibody (Oncology, Dual-Ig® etc.)

- ERY974 (cancer/P1)

Switch Antibody™
(ATP switch)

- STA551 (cancer/P1)

PAC-Ig™, new technologies, etc.

and more

- codrituzumab (cancer/P1)
- tocilizumab

Discovery	GLP-tox	Clinical trial	Launched

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INNOVATION BEYOND IMAGINATION