Chugai's Strategy for Drug Discovery Research

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CHUGAI PHARMACEUTICAL CO., LTD.

December 9, 2019

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

New Mid-Term Business Plan: 5 Strategies

Create global growth drivers and maximize value

Strategy 1
Value Creation
Realize innovative drug discovery
to cure and manage diseases

Strategy 2
Value Delivery
Deliver patient-centric solution
to maximize value of growth drivers

Strategy 3
Promote advances in personalized healthcare
Realize the further advancement of PHC and innovate R&D process
by utilizing digital technology and data

Strengthen HR and infrastructure that support Chugai's business

Strategy 4
Human capital and structural reform
Develop high-caliber HR talent that support
innovation, and drastically reform costs,
systems and processes

Strategy 5
Strengthen sustainable platforms
Simultaneously realize company growth
and sustainable social development

Basic Policy of Chugai Drug Discovery Strategy

Strengths in biology

- Antibody engineering technology
- Middle molecules (cyclic peptides)
- Small molecules (beyond the Rule of 5)

The fusion of biology and technology generates innovations in drug discovery

Create unprecedented and overwhelming patient value

The Fusion of Biology and Technology Generates Innovations in Drug Discover

Biology	Technology	Innovation
Discovery of erythrocyte growth factor Erythropoietin	Recombinant DNA technology	エポジン®
Discovery of neutrophil growth factor G-CSF	Manufacturing biologics using CHO	ノイトロジン®
Discovery of key immune regulator IL-6	Humanization of antibody	アクテムラ®
Discovery of strong driver oncogene ALK	Kinase inhibitor with high selectivity	アレセンサ®
Invention of MOA to mimic Factor VIII	Bispecific antibody	ヘムライブラ®

Measures to Establish Strength in Biology

CHUGAI
Roche Roche Group

Collaboration with Academia

- IFReC (Osaka Univ.)
- Center of Innovation, The University of Tokyo
- National Cancer Center

Cultivation of a deep in-house understanding of human disease biology

- Deep understanding of targets and MoA
- Integrated disease database
- Fresh samples derived from human patients

TACTICS

***T**he **A**utonomous and **C**onstitutive **T**arget **I**dea **C**reating **S**ystem*

- Activities organized across the research division to create drug discovery ideas
  - ✓ Promotion of unique biological discoveries
  - ✓ Sublimation to "invention" that leads to highly effective products

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Collaboration with Academia

IFReC
Osaka Univ.

Acquisition of new findings based on world's top basic immunology

COI
Univ. of Tokyo

Search for new targets in rheumatic diseases through GWAS/eQTL analysis

NCC
National Cancer Center

Search for new CIT targets through immune cell profiling of tumors

On-site Lab.

On-site Lab.

On-site Lab.

Discovery of new biology insights/targets

Measures to Establish Strength in Biology

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Cultivation of a Deep in-house Understanding of Human Disease Biology

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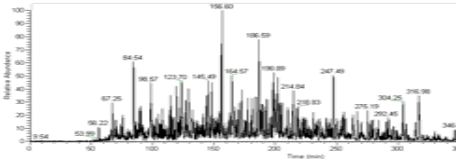
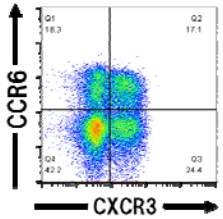
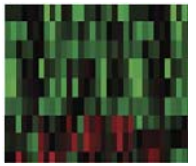
Roche Roche Group

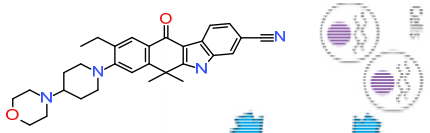
Collection of human disease samples

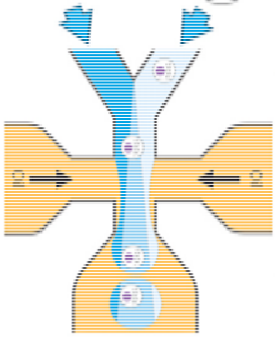






Conceptual illustration





Integrated disease DB

Evaluation of compound activity using fresh samples
Target validation

Acquisition and integration of comprehensive and multifaceted analysis data on various diseases

Measures to Establish Strength in Biology

CHUGAI
Roche Group

Collaboration with Academia

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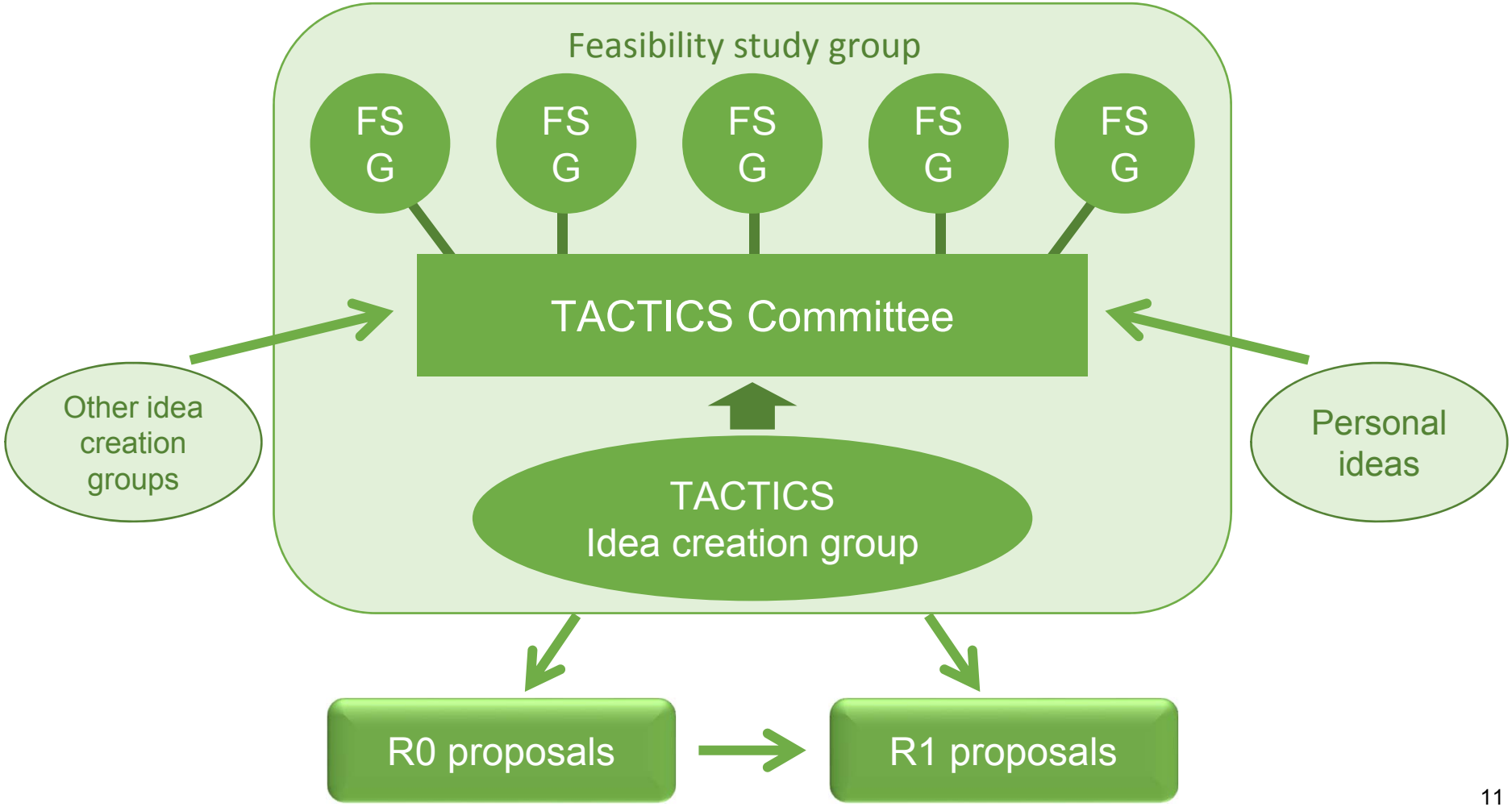
TACTICS: System for Creating Drug Discovery Ideas Across the Research Division



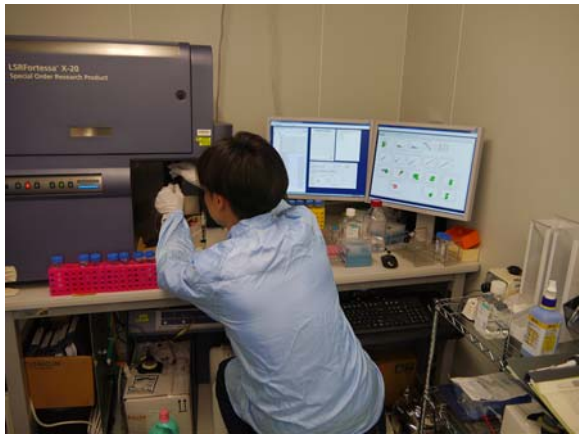
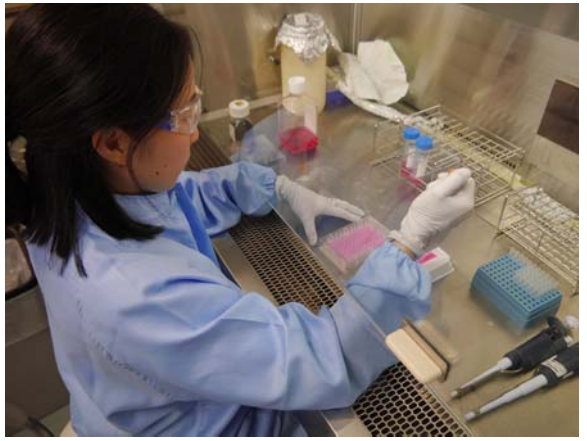
Promote Unique Discoveries and Inventions through TACTICS





Ideas
Hypothesis

Experiments
Discovery

Systematic promotion of unique inventions based on unique discoveries

Paradigm Shift in Drug Discovery
"Era of Discovery → Era of Invention"

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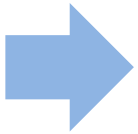
Roche Roche Group

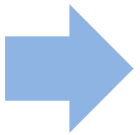
Era of Discovery

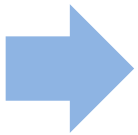
Biological discovery



Drug

Era of Invention

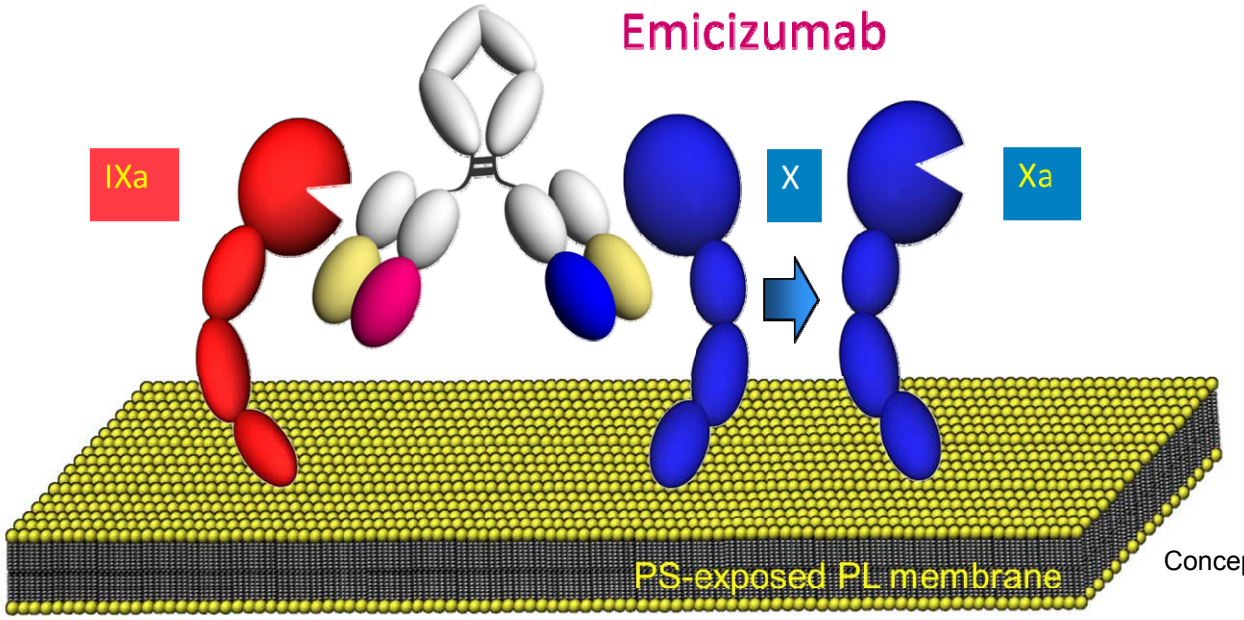




- Invention of drug discovery idea (MoA)
- Invention of modality technology

Create medical value

HEMLIBRA: Brought by Original Invention



Conceptual illustration

Blood coagulation mechanism by Factor IXa/X	→	Generally known
Bispecific antibody	→	Concept: known **Manufacturing: Invention**
Mimic Factor VIII function with a bispecific antibody	→	**Invention**

Chugai Life Science Park Yokohama (New Research Laboratory)

Summary

A core research facility to be built in Yokohama, Kanagawa Prefecture (planned completion in 2022)
・Building area: 35,210m^2
・Total floor area: 119,960m^2

Emphasizing climate change countermeasures, local disaster preparedness, and biodiversity preservation; aiming to acquire LEED Gold certification for environmental performance

Will reduce our overall environmental footprint (including the consolidation of existing facilities)

Signed environmental agreement with city of Yokohama, emphasizing coexistence with the local community

- The integration of all functions related to drug discovery research is expected to promote further research efficiency and collaboration.
- Enhanced efforts to promote the fusion of biology and technology

Chugai Pharmabody Research Pte. Ltd. (Singapore)

- Creation of antibody drugs using Chugai's antibody engineering technologies
- Development of new antibody engineering technologies

Opened in 2012, Fully-owned by Chugai

Chugai's Mission Statement

~Innovation all for the patients~

Mission

Dedicate ourselves to adding value by creating and delivering innovative products and services for the medical community and human health around the world

Core Values

1. Patient Centric	Make each patient's wellbeing our highest priority
2. Pioneering Spirit	Pursue innovation by improving ourselves and thinking differently
3. Integrity	Maintain the highest standards in all we do to create shared value with society

Envisioned Future

Become a top innovator for advanced and sustainable patient-centric healthcare, powered by our unique strength in science and technology and the alliance with Roche

Basic Policy of Chugai Drug Discovery Strategy

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Strengths in biology

- Antibody engineering technology
- Middle molecules (cyclic peptides)
- Small molecules (beyond the Rule of 5)

The fusion of biology and technology generates innovations in drug discovery

Create unprecedented and overwhelming patient value

Appendix: Characteristics of Each Modality

- In addition to antibodies and small molecules, the addition of middle molecules as a drug discovery modality greatly expands the potential for drug discovery.

	Small molecule	Middle molecule	Antibody
Molecular weight	**MW <500**	**700 < MW <1600**	**MW 15000**
Oral administration	**Available**	**Available**	**Not available**
Effects on intracellular targets	**Available**	**Available**	**Difficult**
Inhibition of protein-protein interaction	**Difficult**	**Available**	**Available**
Specificity	**Low**	**Mid - High**	**High**
Dosage interval	**Short (daily)**	**Short (daily)**	**Long (Every 2 weeks)**

Chugai's Antibody Engineering Technologies for Innovative Drug Discovery

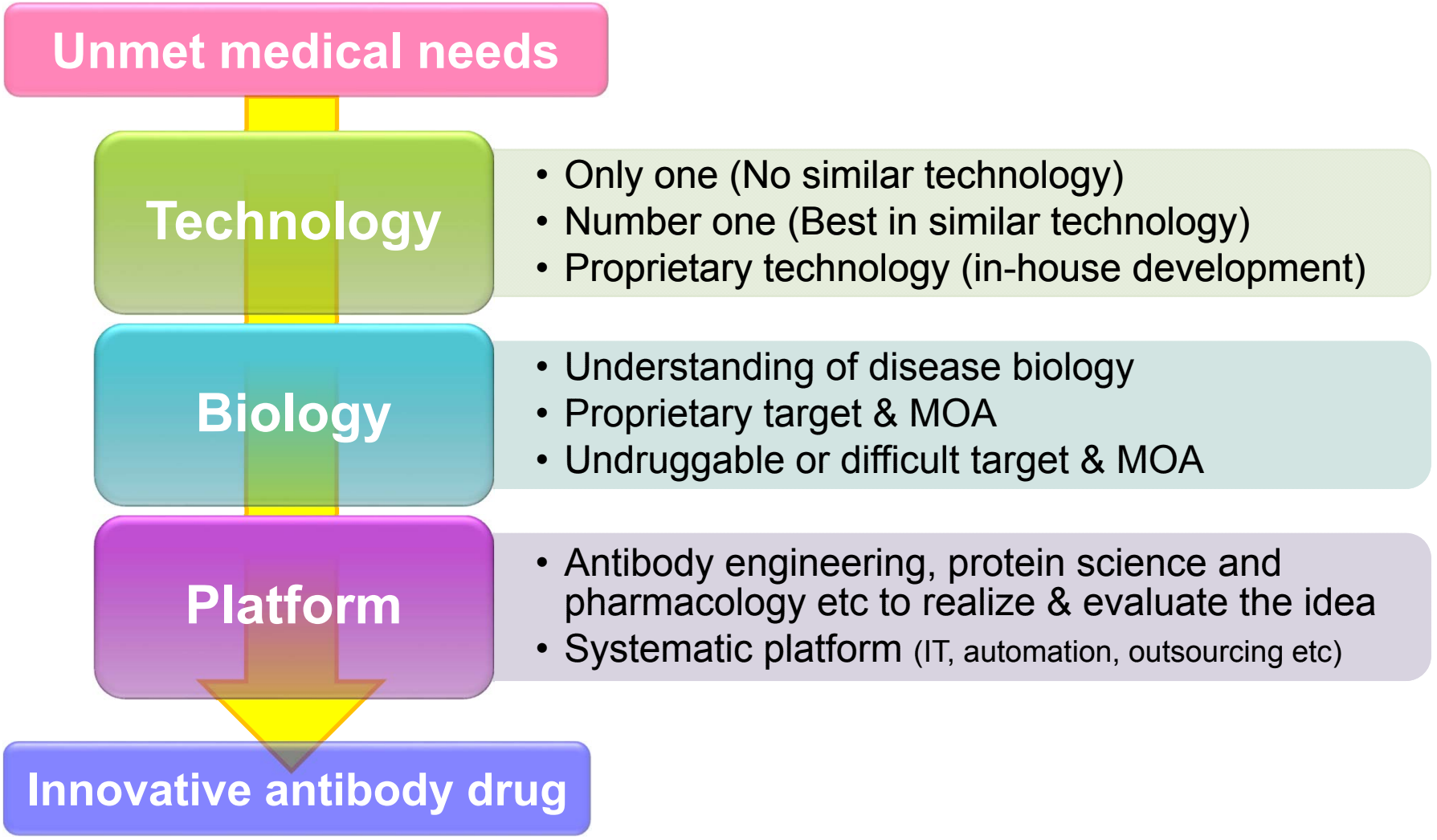
Tomoyuki Igawa Ph.D.
CEO and Research Head
Chugai Pharmabody Research Pte. Ltd.
Singapore

December 9, 2019

Agenda

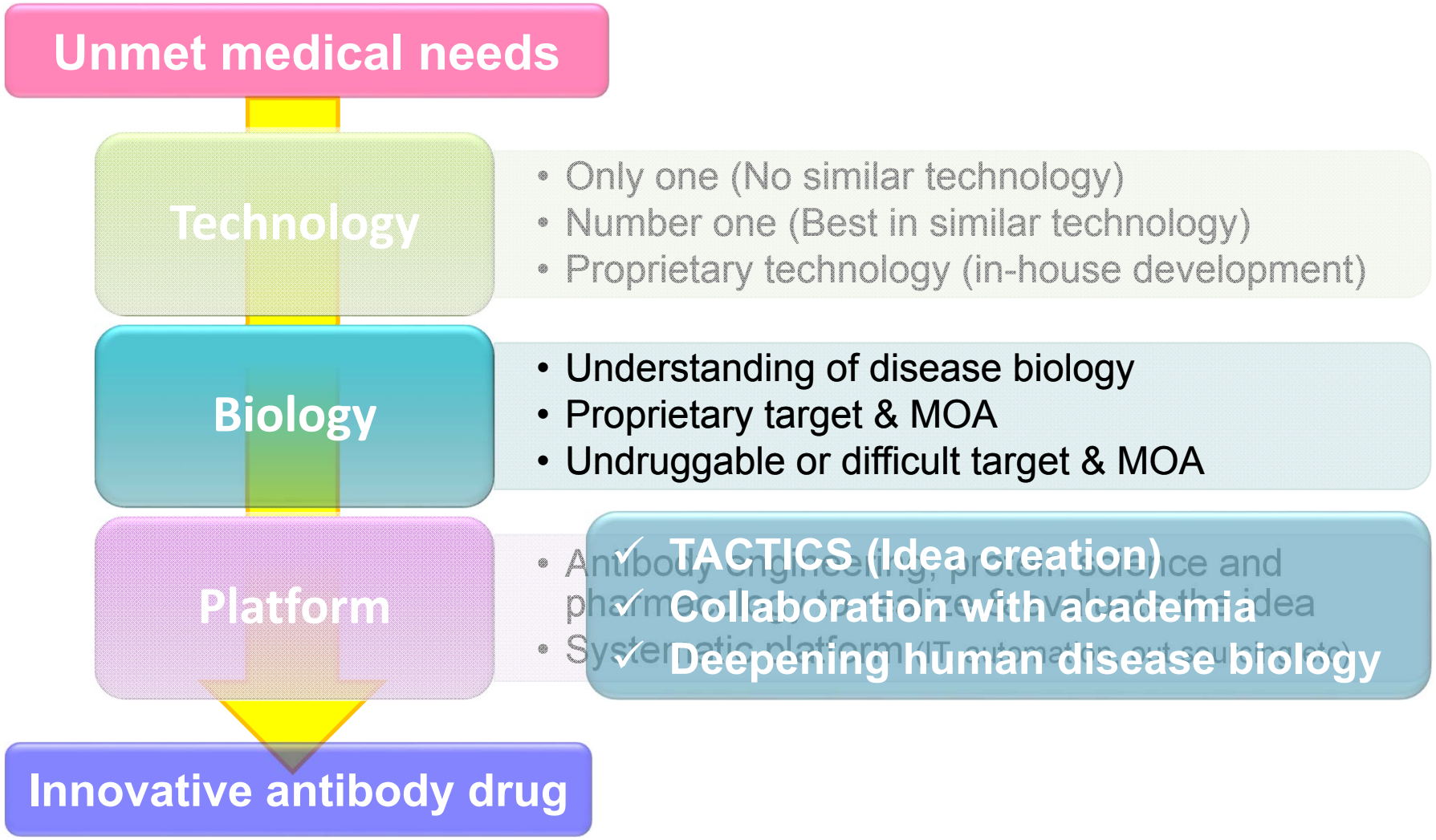
1. Antibody Drug Discovery Strategy and Platforms
2. Recycling antibody® and Sweeping antibody® Technology
3. Switch Antibody™ Technology
4. Next Generation Bispecific Antibody Technology
5. Summary

From Unmet Medical Needs to Discovery of Innovative Antibody Drug



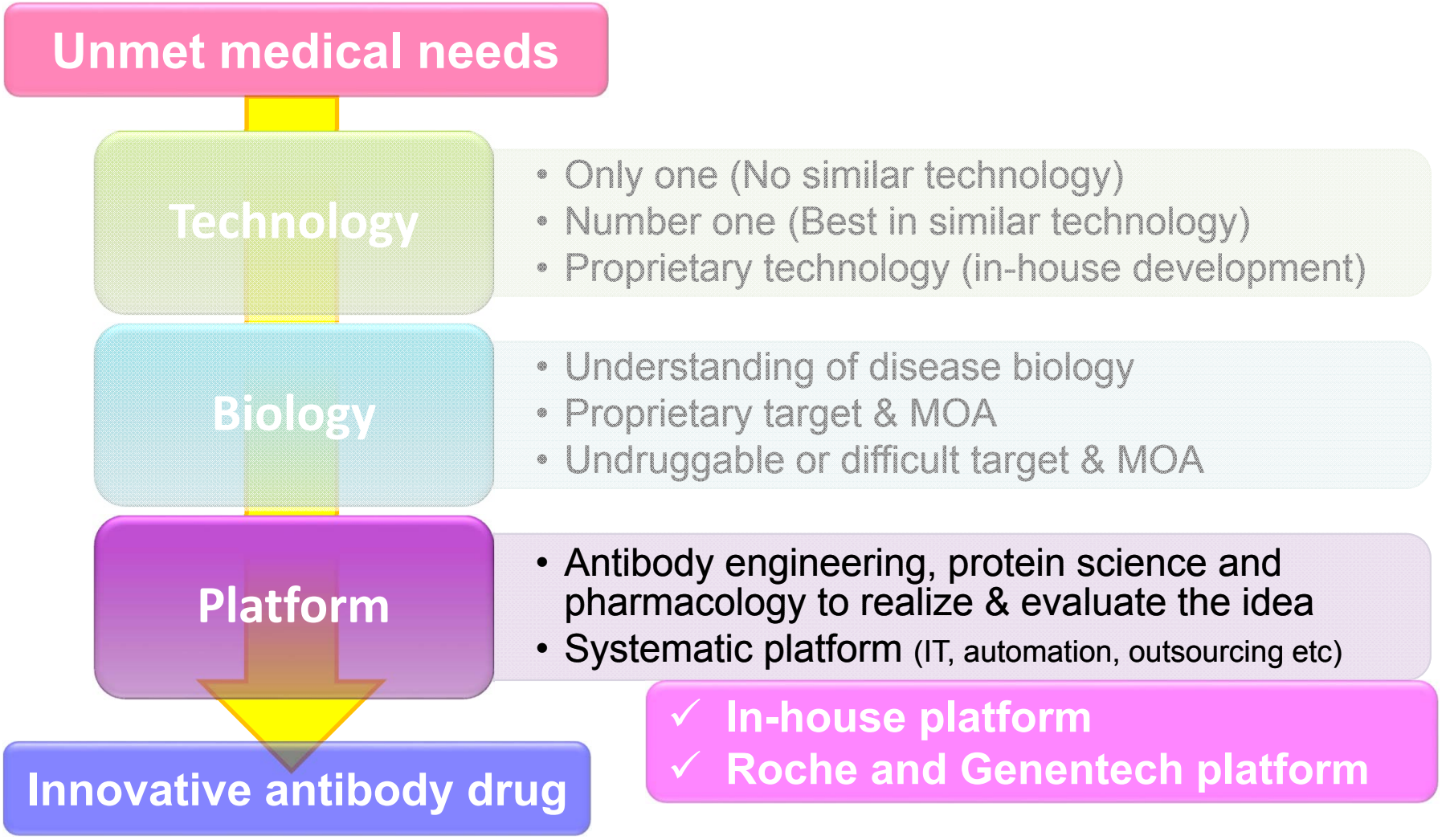
Discovery of Innovative Antibody Drug

Target & MOA



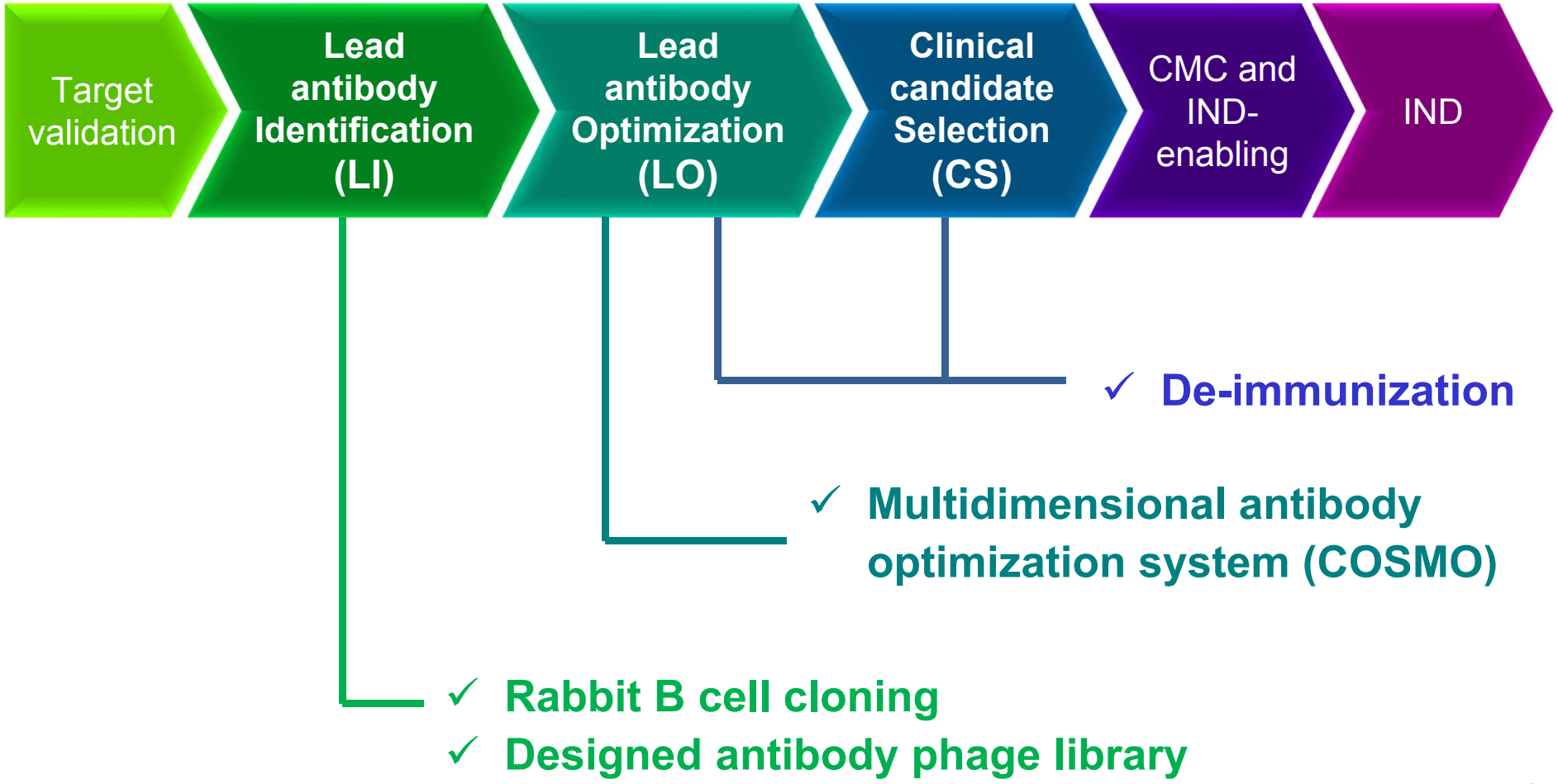
Discovery of Innovative Antibody Drug

Platform



Chugai's Four Competitive Platforms Supporting Antibody Drug Discovery

Antibody drug discovery process



Lead Antibody Identification (LI) Platform

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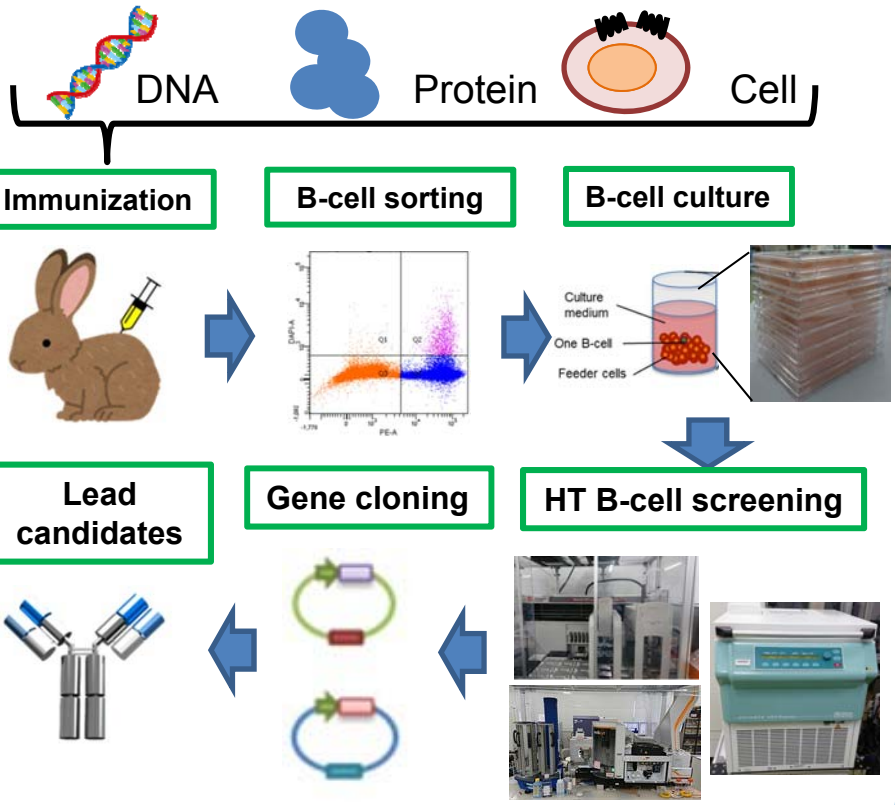
Roche Group

Rabbit B-cell cloning

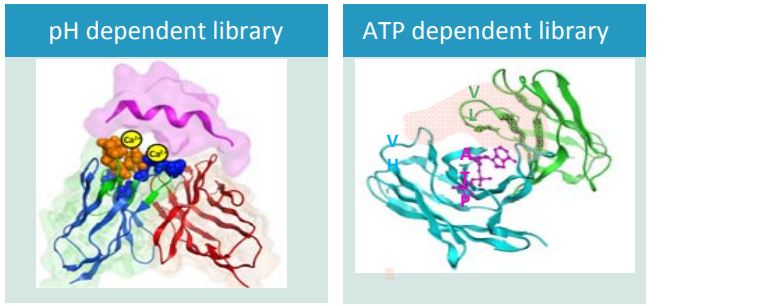
mAb with high affinity binding against the right epitope

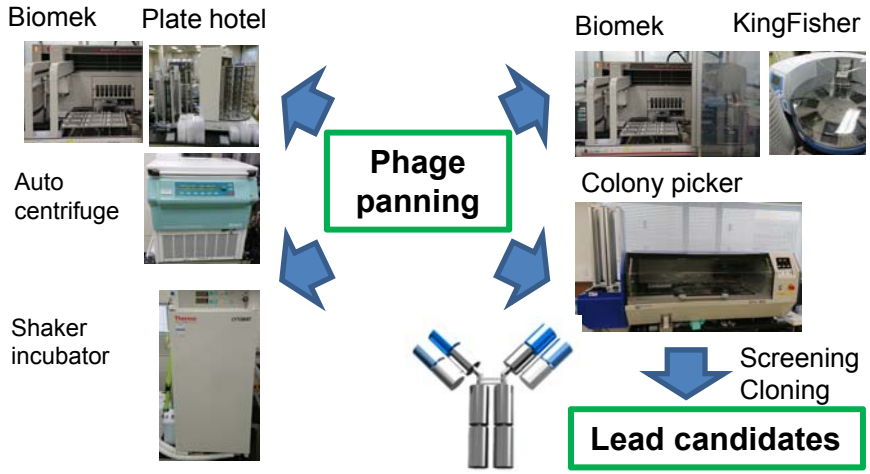


Animal immunization with DNA, protein or cell followed by automated high-throughput screening system

Designed phage library

mAb with unique function which is impossible by animal immunization





Designing library and phage panning (antibody screening) against target protein or cell in automated high-throughput system

Source : Chugai Pharmaceutical Co., Ltd.

Lead Antibody Optimization (LO) Platform

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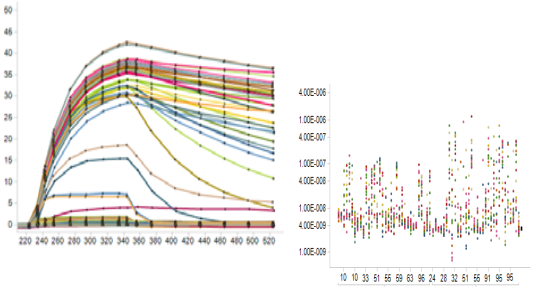
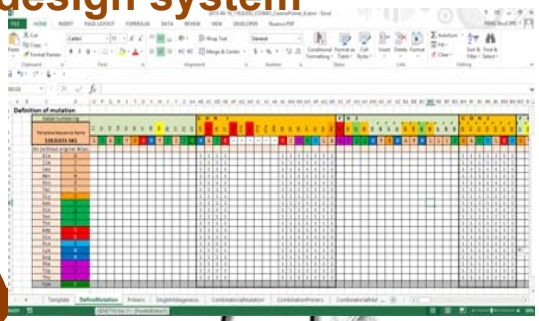
COSMO : COmprehensive Substitution for Multidimensional Optimization

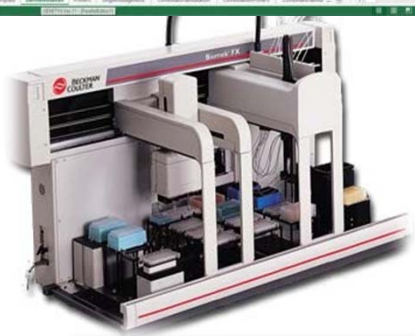
✓ **HTP affinity measurement**
~2000 Run/Week

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



✓ **HTP primer design system**





Multi-dimensional evaluation
Antibody design
Gene construction
Gene transfection
Antibody purification
1 week cycle

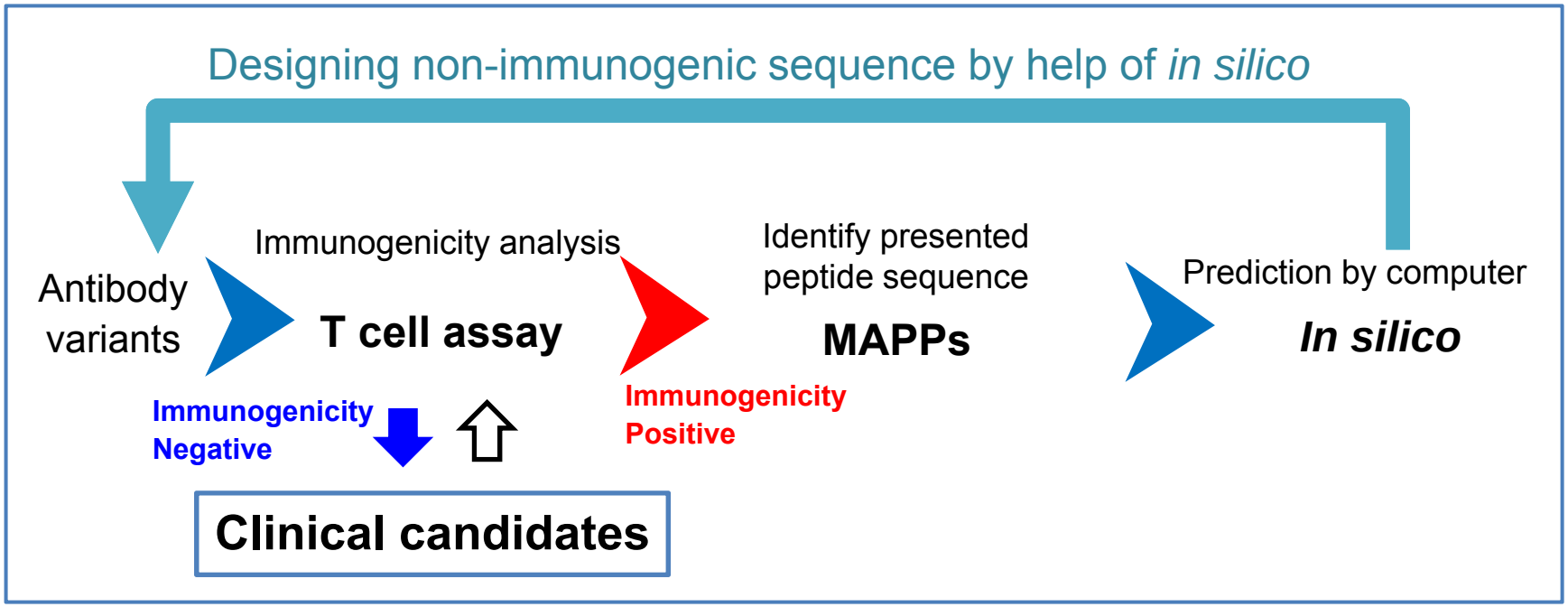
✓ **HTP antibody purification**
~1500 Abs/Day

✓ **HTP Ab construction and transfection**
~3000 Abs/week

Source : Chugai Pharmaceutical Co., Ltd.

De-immunization Platform

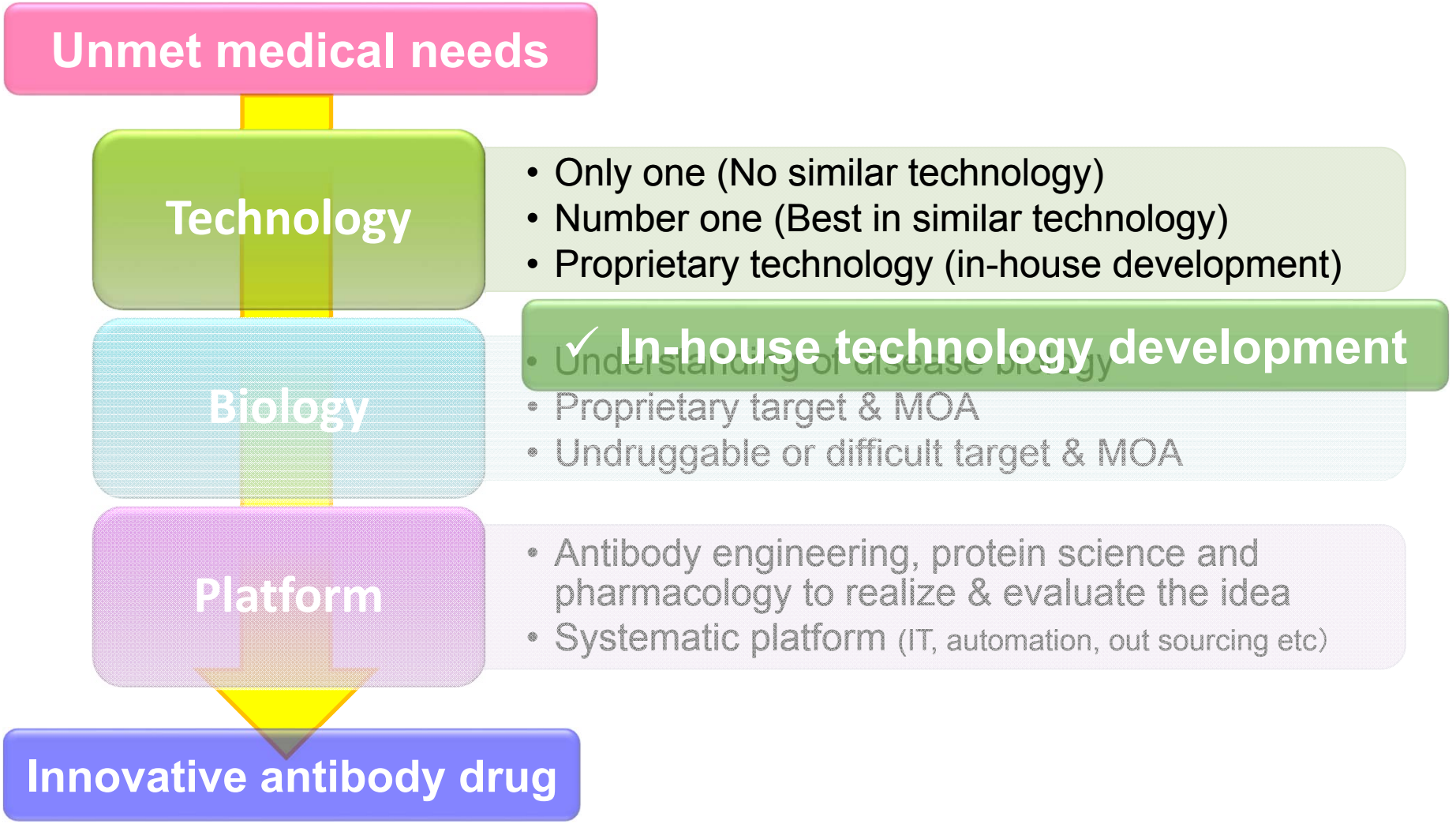
- Challenge: Increased immunogenicity was the main concern when we “engineer” humanized antibody or human IgG1 sequence.
- Solution: We have established de-immunization platform to minimize immunogenicity risk of our highly engineered antibodies.



T cell assay: In vitro method to predict immunogenicity using human CD4+ T cell
MAPPs: Mass spectrometry method to identify the sequence of peptide presented on MHC class II by dendritic cells
In silico: Prediction of binding affinity of peptide to MHC class II

Discovery of Innovative Antibody Drug

In-house technology development



Continuous Evolution of Proprietary Antibody Engineering Technologies

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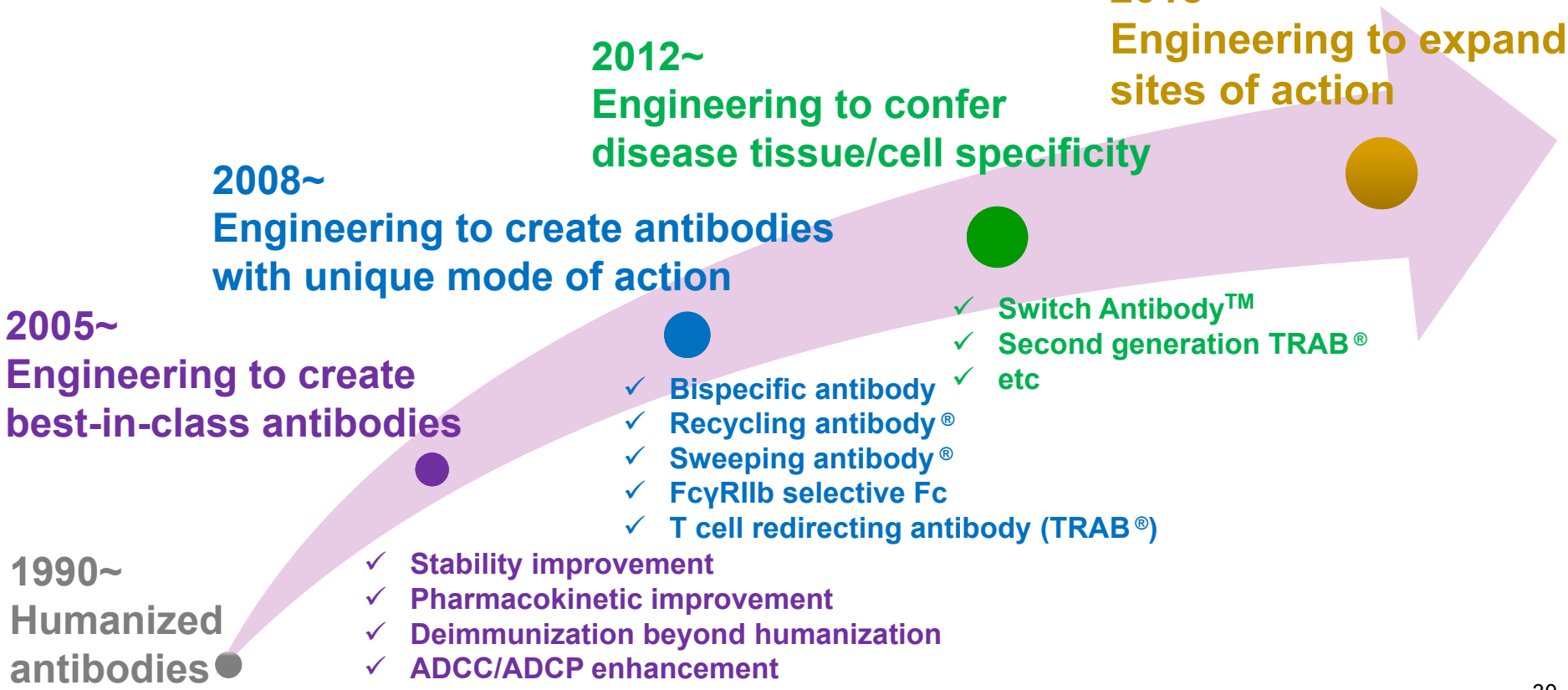
Maximize the value of drug target → **Create drug against undruggable target and MOA**

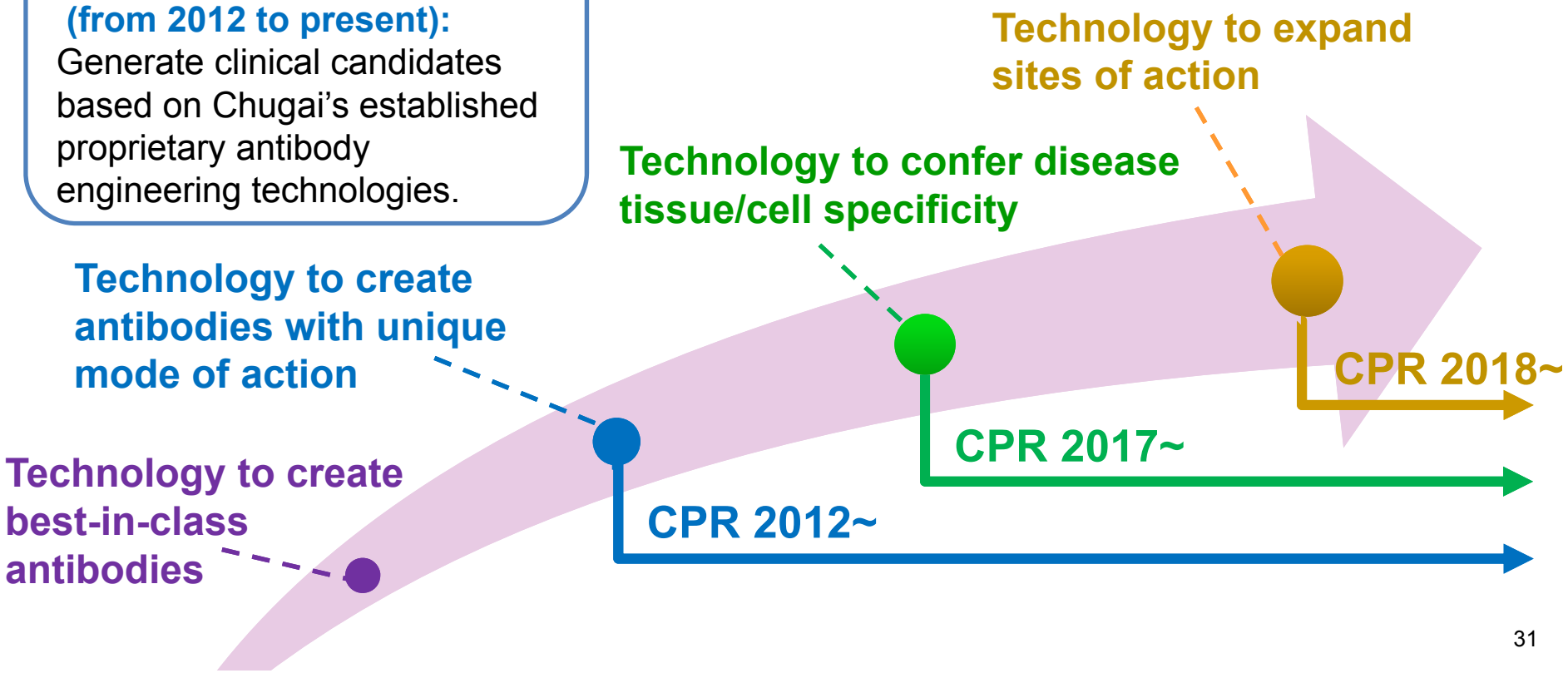


Mission of Chugai Pharmabody Research

Maximize the value of Chugai's antibody engineering capability

Technology development
(from 2017 to present):
Establish novel antibody engineering technologies to create drug against undruggable target and MOA.

Drug discovery
(from 2012 to present):
Generate clinical candidates based on Chugai's established proprietary antibody engineering technologies.



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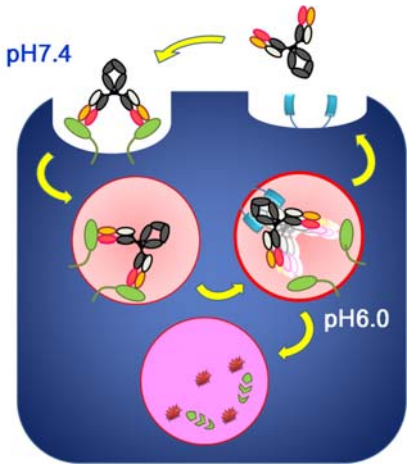
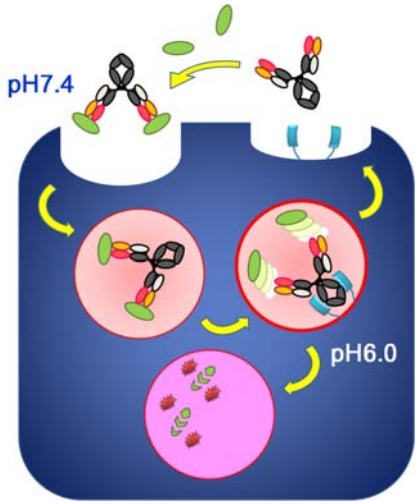
Recycling antibody®
and Sweeping antibody® Technology

Recycling antibody®

Enables antibody to bind to target multiple times





Conceptual illustration

- Satralizumab (anti-IL6R Recycling antibody®)
  - Confirmed recycling effect against **membrane** antigen in human
  - Positive phase 3 data in NMOSD patients

SAkuraSky Study

Yamamura et al, N Engl J Med 2019; 381:2114-2124

- Crovalimab (anti-C5 Recycling antibody®)
  - Confirmed recycling effect against **soluble** antigen in human
  - Positive phase 1/2 data in PNH patients

COMPOSER Study interim report at ASH2018

- AMY109 (Recycling antibody®)
  - Phase 1 study in endometriosis patients

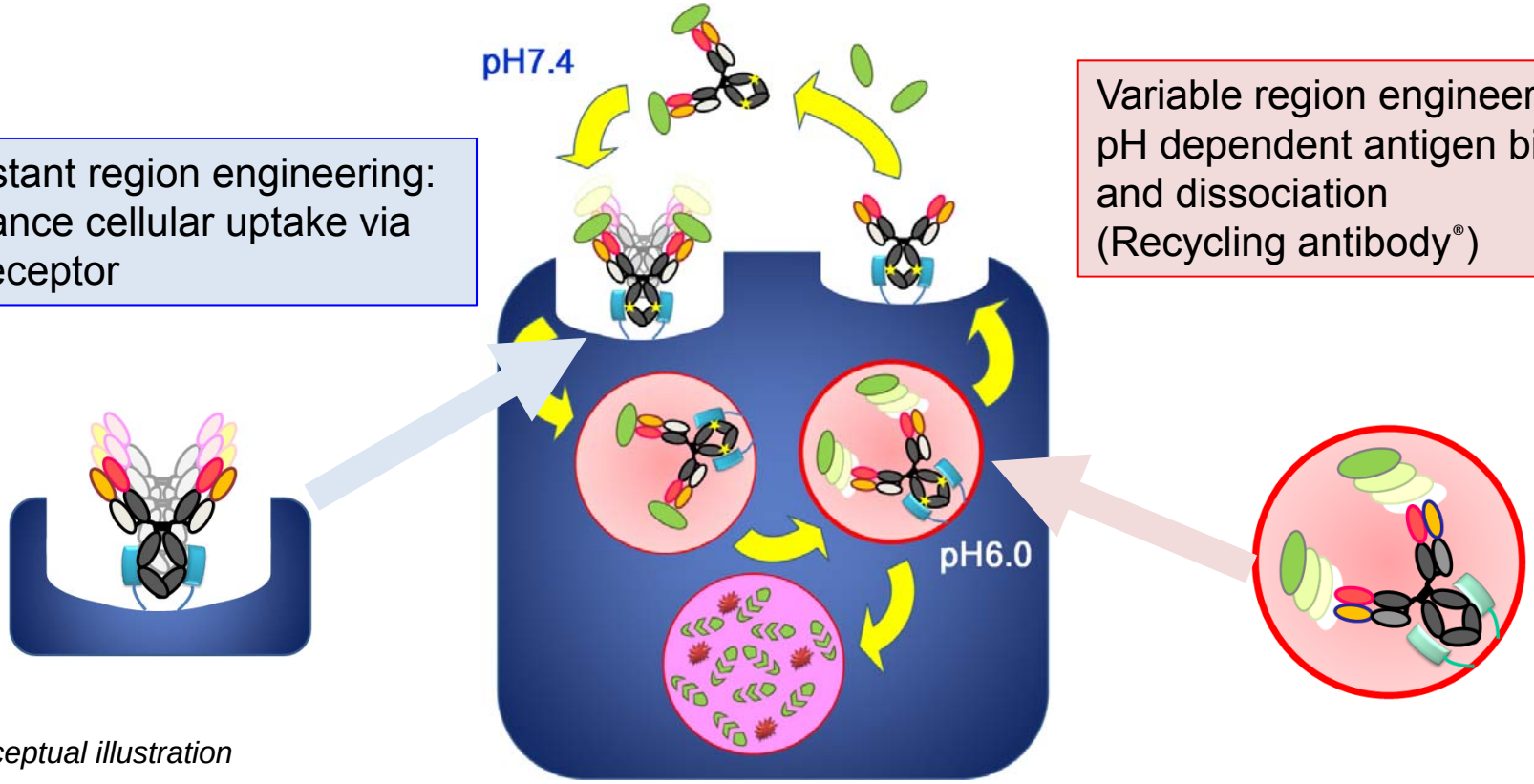
JapicCTI183841

Sweeping antibody®

Eliminates soluble antigen from plasma

Constant region engineering:
Enhance cellular uptake via
Fc receptor

Variable region engineering:
pH dependent antigen binding
and dissociation
(Recycling antibody®)



Conceptual illustration

Elimination of soluble antigen from plasma by accelerated endosomal delivery and lysosomal degradation of the antigen can be expected.

Nature Biotechnology, 2010, Igawa et al

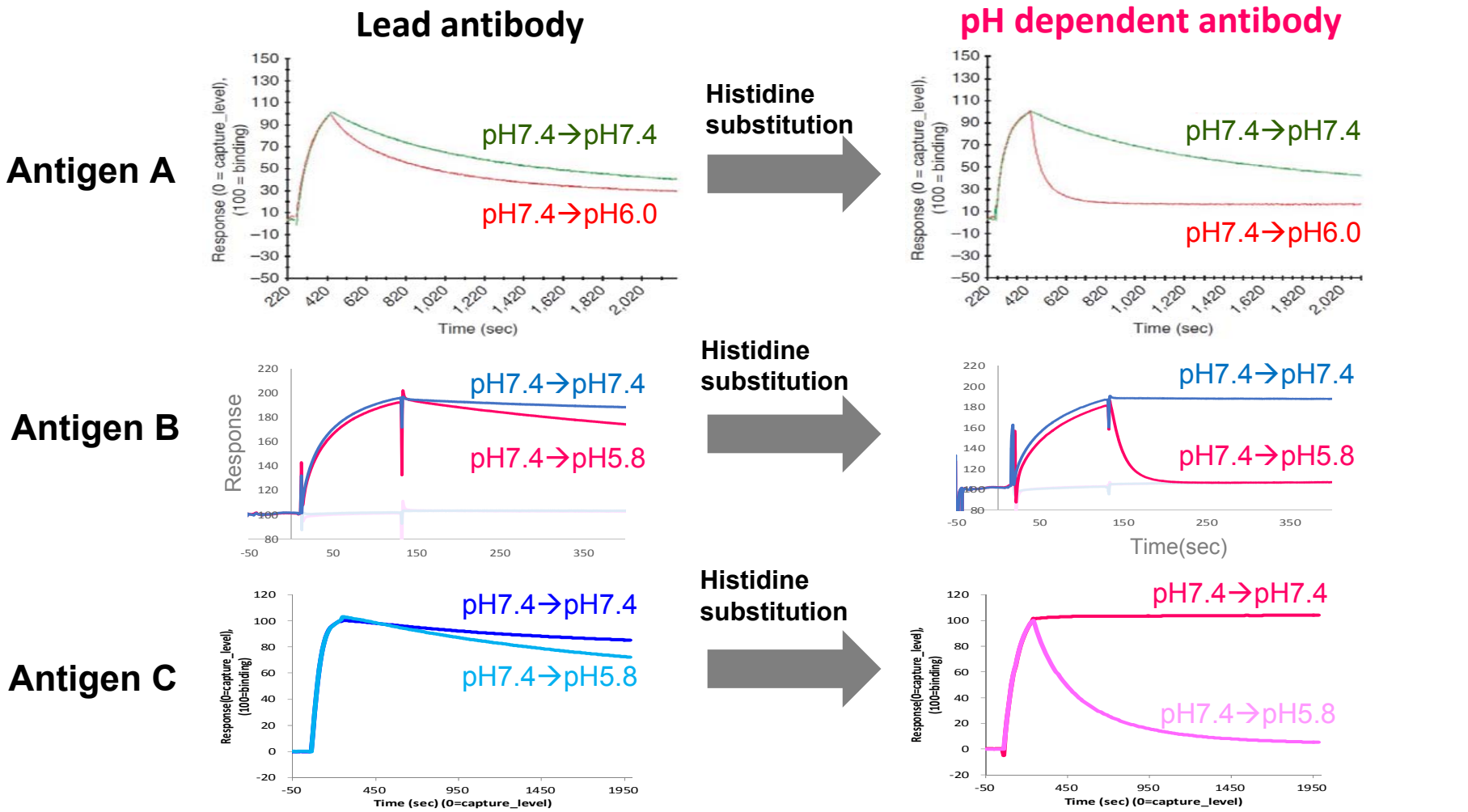
PLOS One, 2013, Igawa et al

Biochim Biophys Acta, 2014, Igawa et al

(All of the above, author is an employee of Chugai Pharmaceutical Co., Ltd.)

pH Dependent Antibody Can be Generated from Any Lead Antibody by COSMO

Binding analysis by surface plasmon resonance



COSMO : **CO**mprehensive **S**ubstitution for **M**ultidimensional **O**ptimization

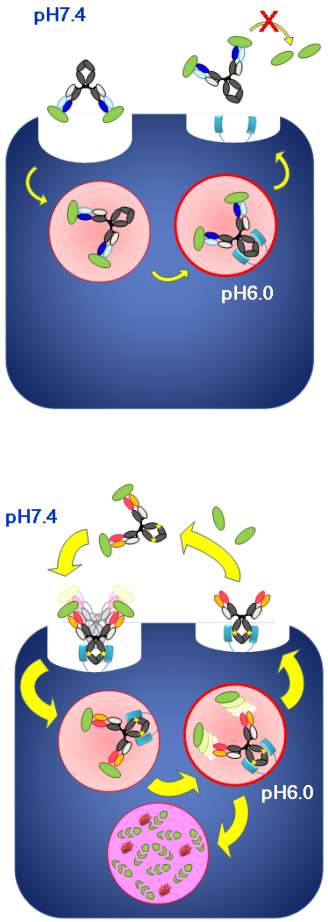
In-house data

pH Dependent Antigen Binding Antibody Release the Soluble Antigen in Endosome

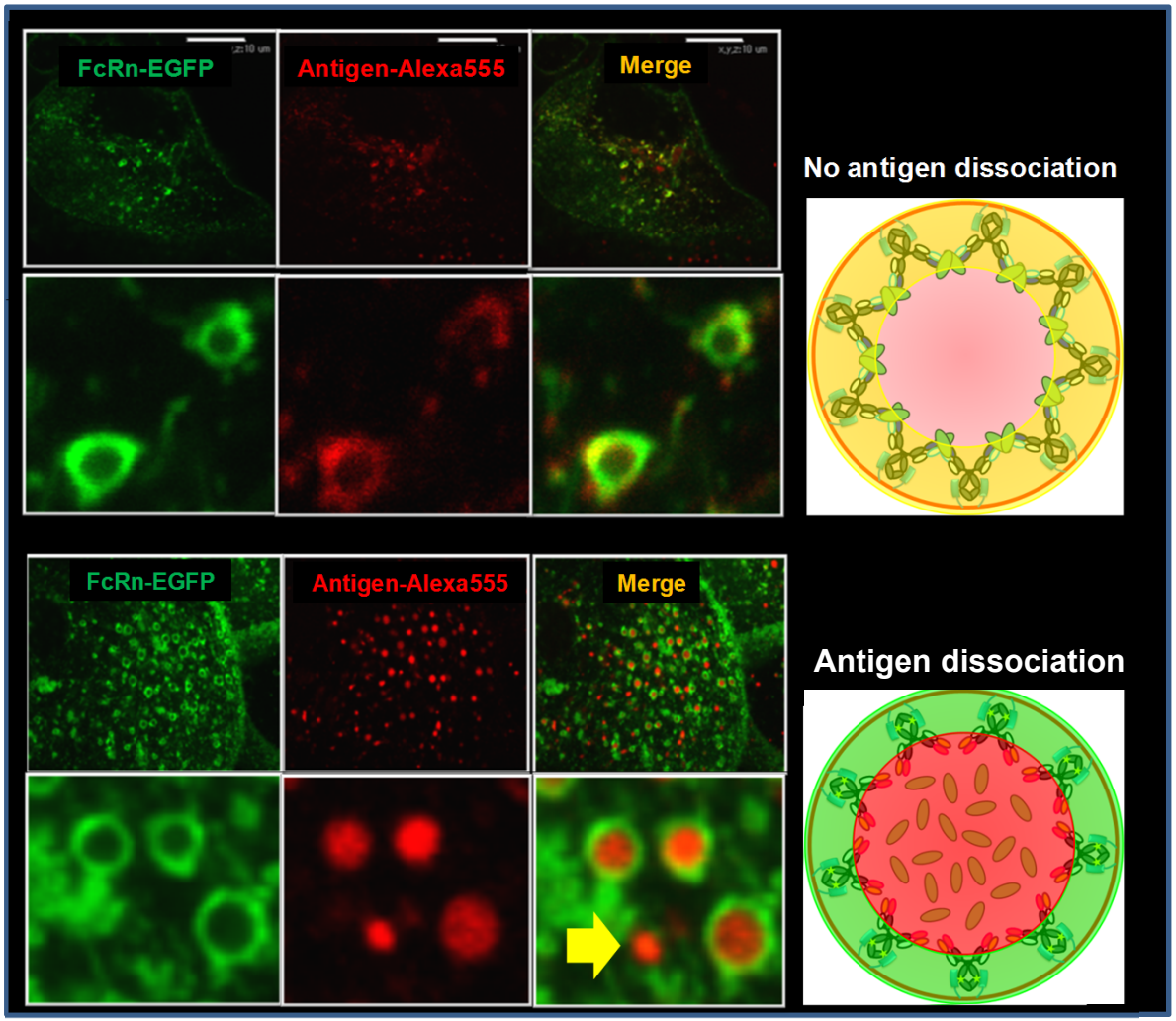
In vitro confocal microscope

Conventional antibody

pH dependent antigen binding antibody



Conceptual illustration

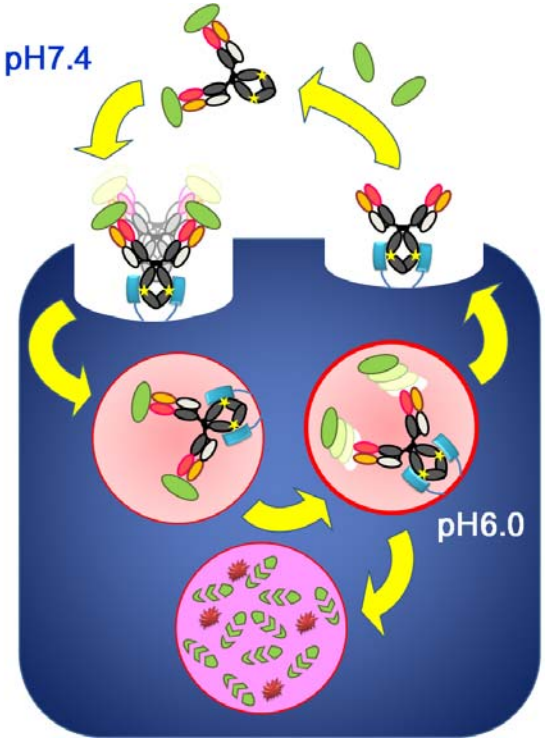


Biochim Biophys Acta, 2014, Igawa et al

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

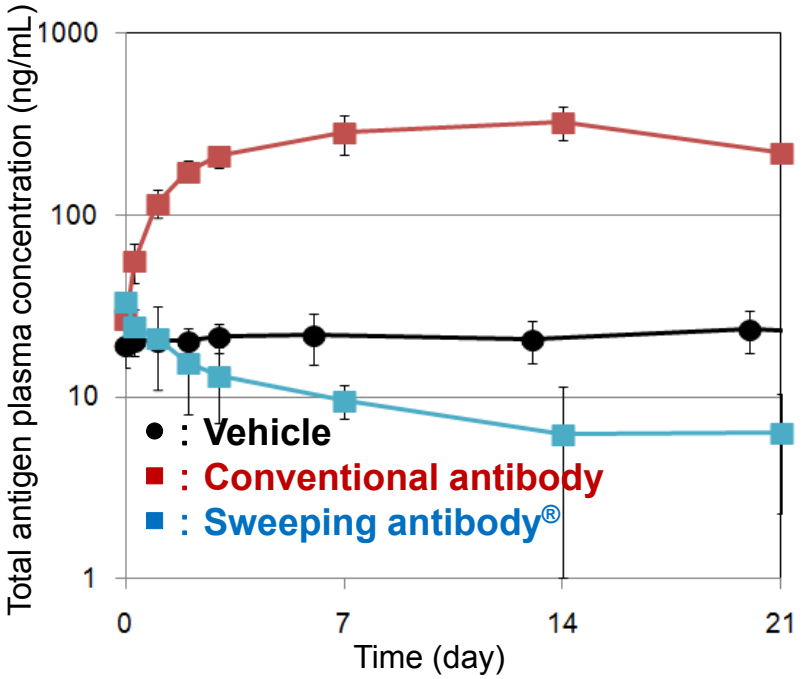
Challenges in First Generation FcRn Mediated Sweeping antibody® Technology

- **FcRn** mediated first generation Sweeping antibody® showed modest sweeping in mouse (~50-fold reduction of antigen)



Conceptual illustration

Mouse *in vivo* study



PLOS One, 2013, Igawa et al
(Author is an employee of Chugai Pharmaceutical Co., Ltd.)

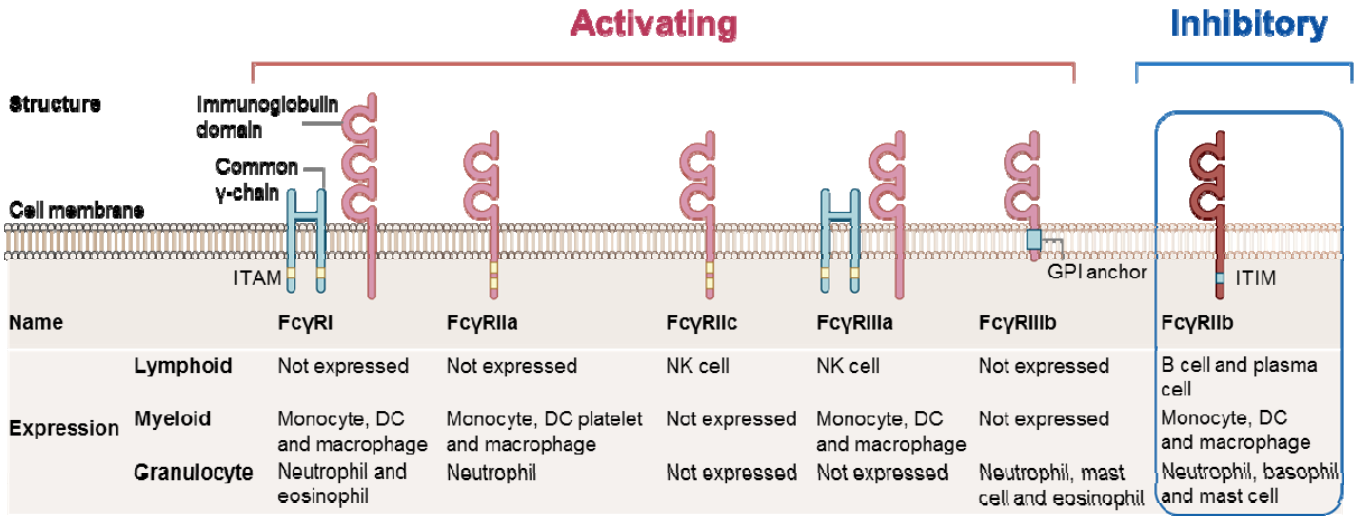
- However, sweeping was inefficient in cynomolgous monkey
  - Effective sweeping in monkey is required for human translatability

TwoB-Ig® : Enhancing FcγRIIb Mediated Uptake of Antibody-Antigen Complex

- FcγRIIb plays a major role in clearing antibody-antigen complexes from body through liver sinusoidal endothelial cells (LSEC)
- TwoB-Ig® variant is applied to selectively increase FcγRIIb binding
  - Enhance FcγRIIb-mediated uptake of antibody-antigen complex by LSEC
  - Reduced FcγRIIa/IIIa binding to prevent platelet activation and ADCC activity

FcγR type	TwoB-Ig®*
FcγRI	0.061
FcγRIIa (H)	0.068
FcγRIIa (R)	2.0
FcγRIIb	**217**
FcγRIIIa (V)	N.D.

*relative binding compared with normal IgG1



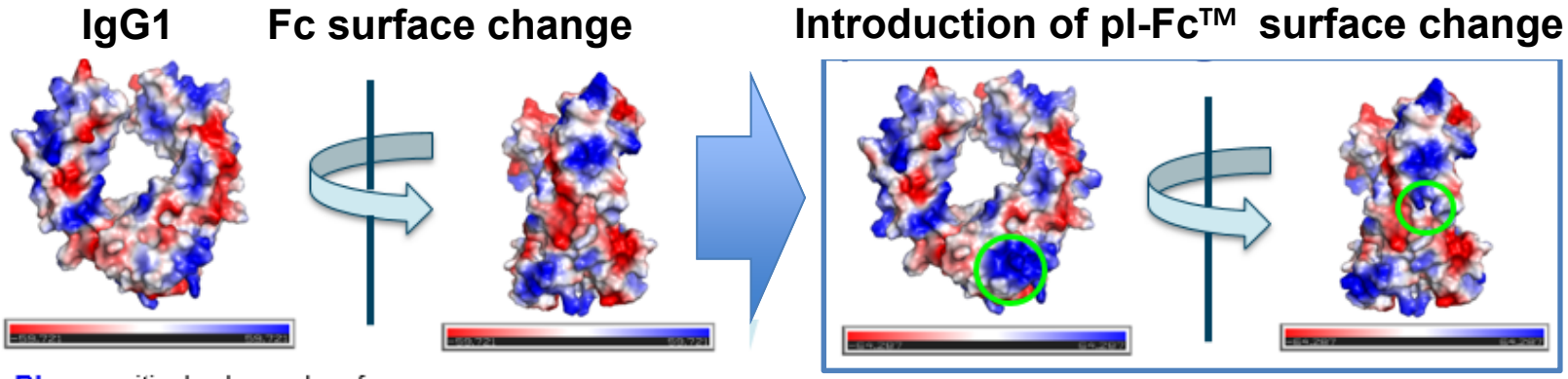
Name		FcγRI	FcγRIIa	FcγRIIc	FcγRIIIa	FcγRIIIb	FcγRIIb
Expression	Lymphoid	Not expressed	Not expressed	NK cell	NK cell	Not expressed	B cell and plasma cell
	Myeloid	Monocyte, DC and macrophage	Monocyte, DC platelet and macrophage	Not expressed	Monocyte, DC and macrophage	Not expressed	Monocyte, DC and macrophage
	Granulocyte	Neutrophil and eosinophil	Neutrophil	Not expressed	Not expressed	Neutrophil, mast cell and eosinophil	Neutrophil, basophil and mast cell

Protein Eng Des Sel, 2013, Mimoto et al
(Author is an employee of Chugai Pharmaceutical Co., Ltd.)

Nat Rev Immunol. 2010, 10, 328-343.

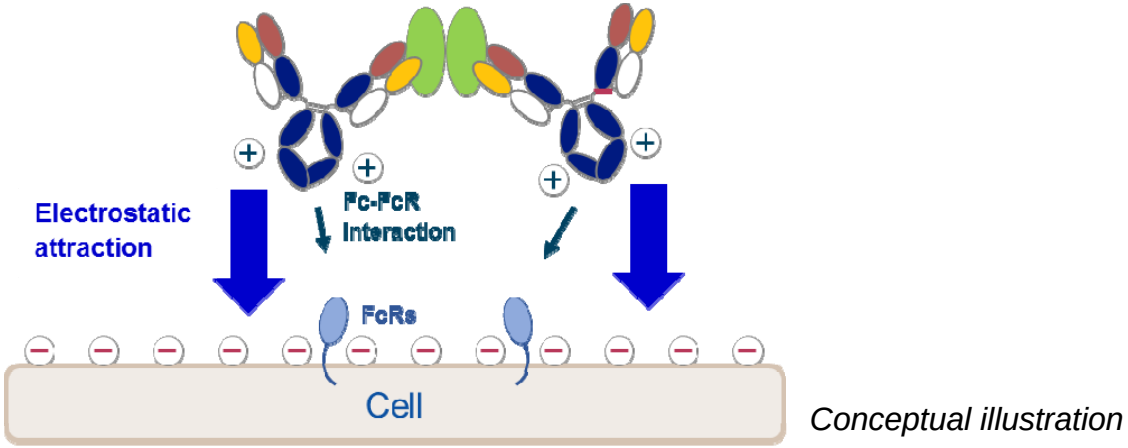
pI-Fc™: Positively Charged Fc to Enhance the Uptake of Antibody–Antigen Complex

- Introducing positive charge to the Fc domain



In-house data

- Positively charged Fc enhance cellular uptake of the complex



Conceptual illustration

Combination of TwoB-Ig® and pI-Fc™ Achieved Strong Antigen Sweeping in Monkey

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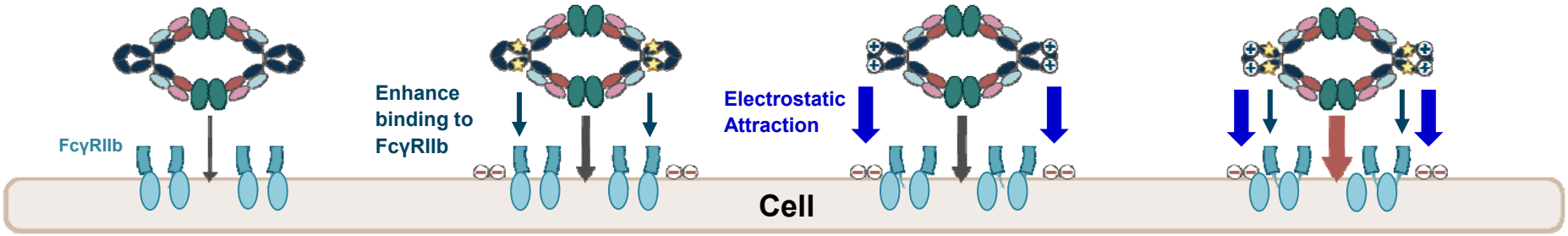
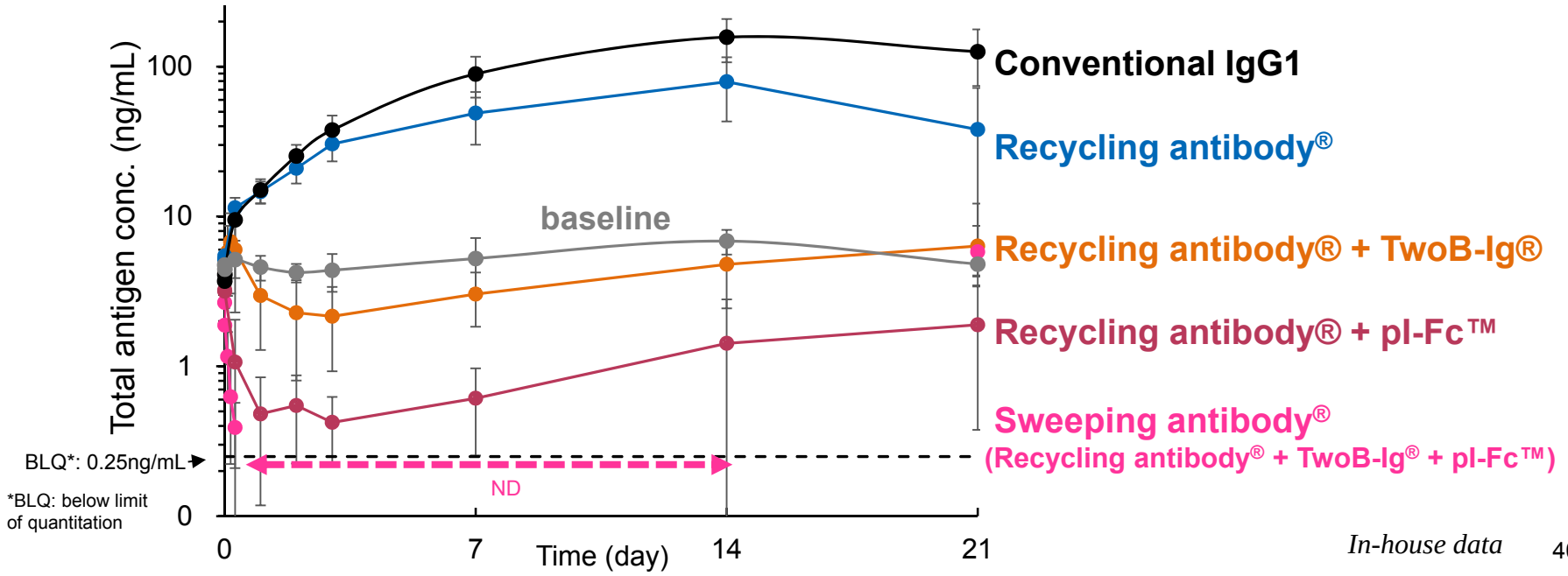
Roche Roche Group



Conceptual illustration

Antigen Sweeping effect in Cynomolgus monkey

Cyno *in vivo* study

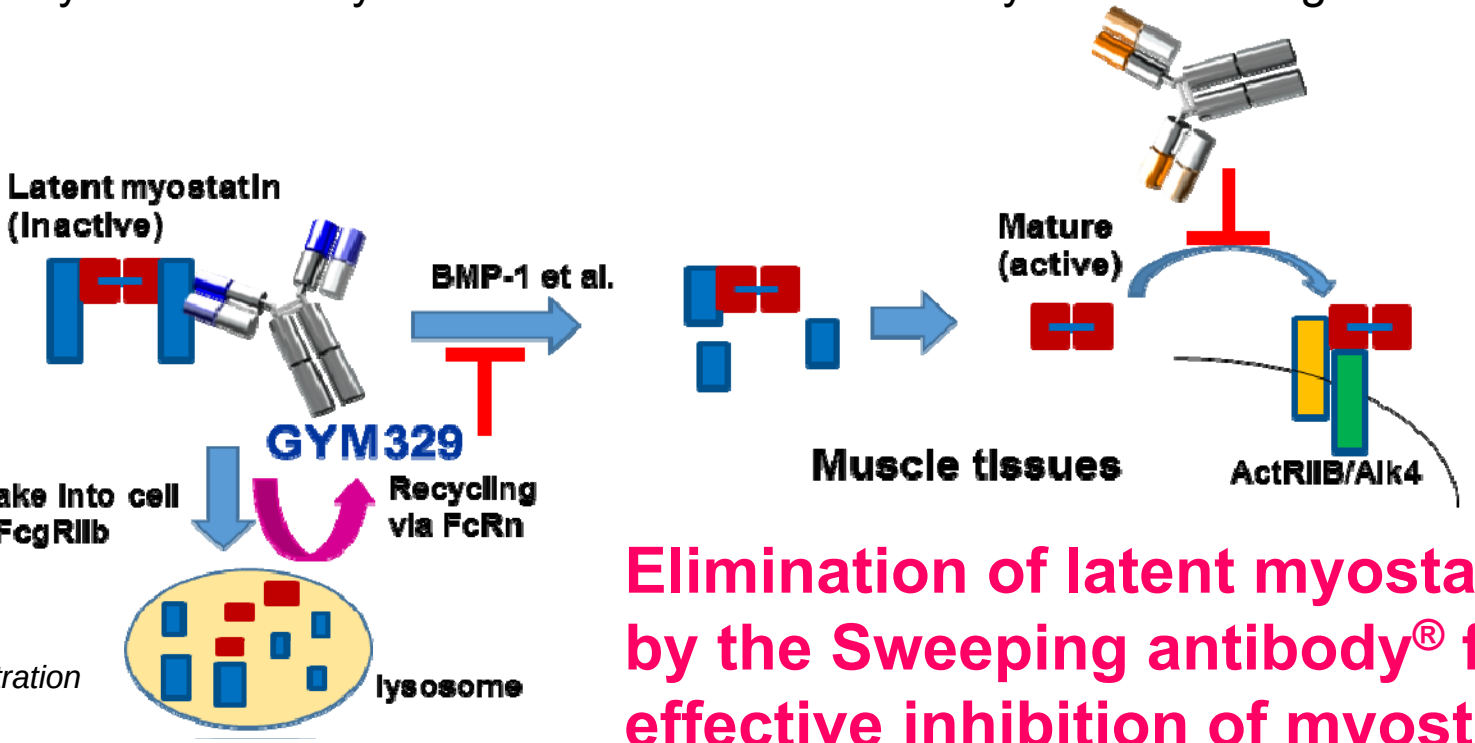


In-house data

GYM329/RG6237

Anti-latent myostatin Sweeping antibody®

- Control progression of loss in muscle strength by latent myostatin inhibition for neuromuscular disease
  - Myostatin is autocrine/paracrine protein secreted from skeletal muscles as an inactive form (latent and pro-myostatin) and complete inhibition of biological activity of mature myostatin is understood as a very hard challenge.



Conceptual illustration

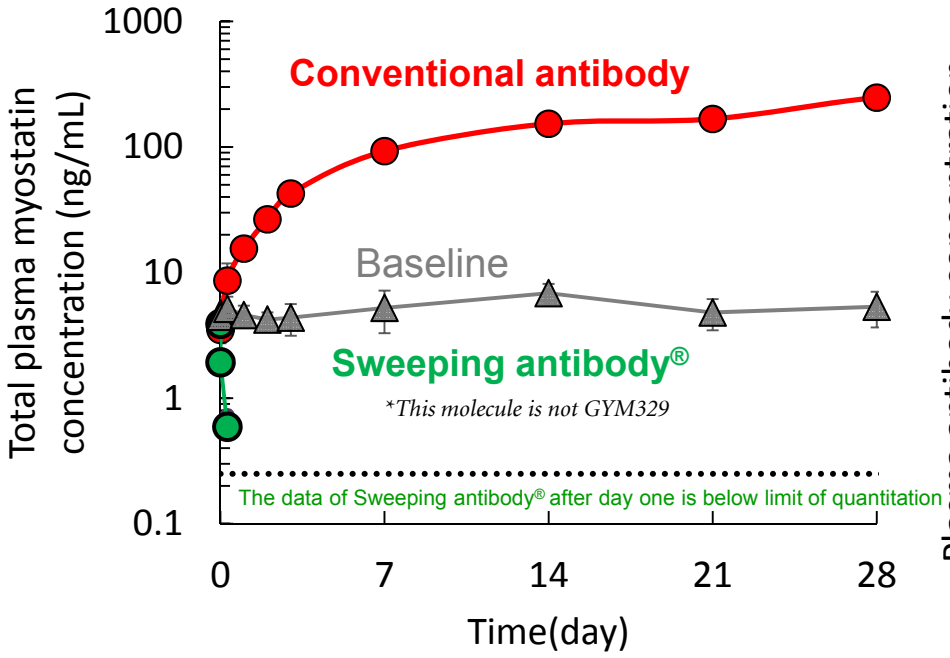
Sweeping latent myostatin (elimination from plasma)

Elimination of latent myostatin by the Sweeping antibody® for effective inhibition of myostatin

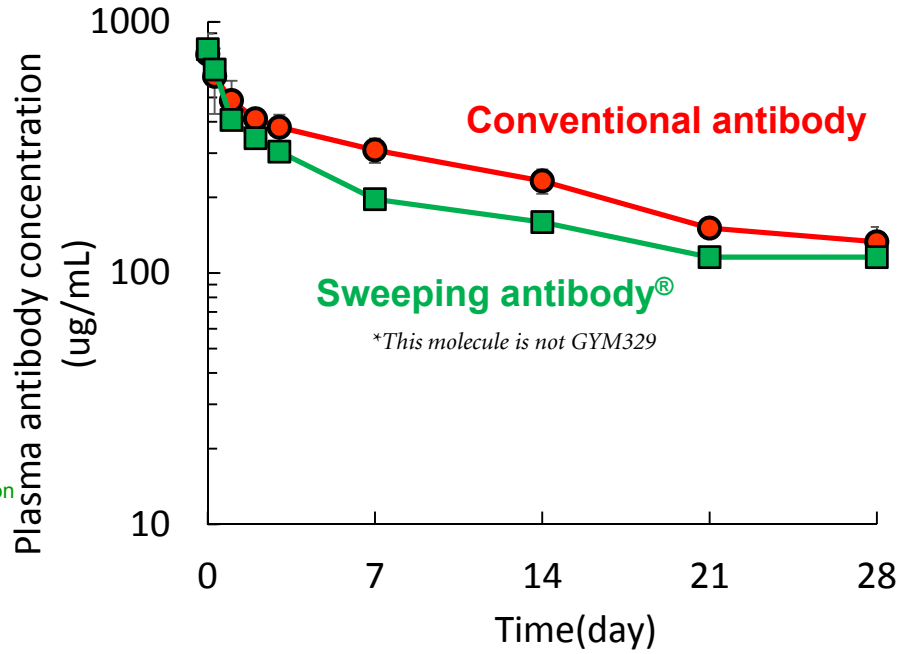
Sweeping antibody® Reduced Plasma Latent Myostatin by >1000-fold

Cyno *in vivo* study

Total latent myostatin concentration



Antibody concentration

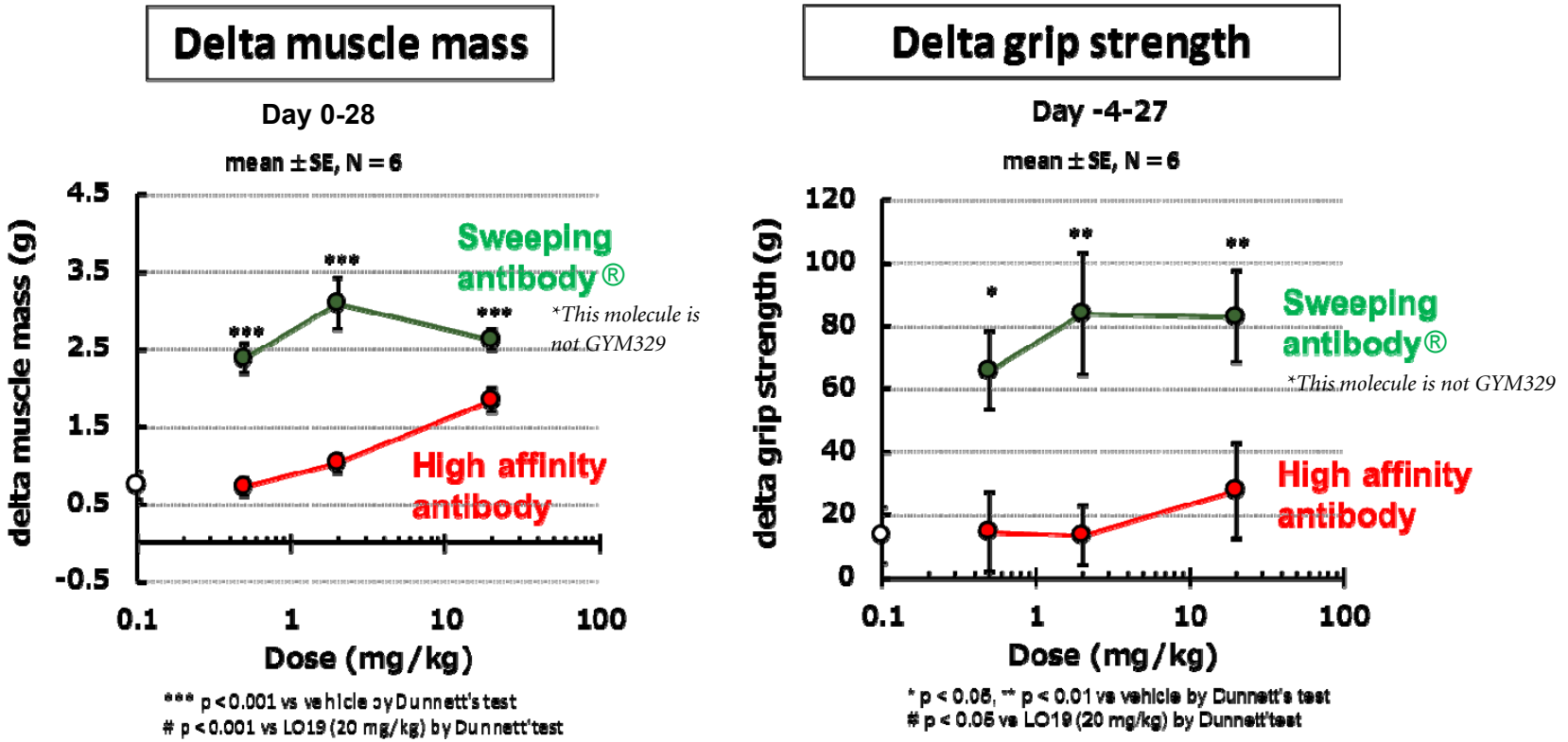


Sweeping antibody® eliminated latent myostatin from plasma while antibody pharmacokinetics was similar to conventional antibody.

In-house data

Sweeping antibody® against latent myostatin is Superior to High Affinity Neutralizing Antibody in Mouse

Mouse *in vivo* study



Sweeping antibody® against latent myostatin is highly effective in increasing both muscle mass and muscle function of SCID mouse.

In-house data

Recycling antibody® and Sweeping antibody® Summary

- ❑ Recycling antibody® technology was validated clinically.
- ❑ Sweeping antibody® technology was established by combination of TwoB-Ig® and pI-Fc™ technology.
  - Confirmed sweeping effect in cynomolgous monkey
- ❑ Sweeping antibody® against latent myostatin reduced total antigen concentration by >1000-fold and improved maximum pharmacological efficacy.

- ❑ **4** project utilizing these technologies in clinical development.
  - Satralizumab (anti-IL6R Recycling antibody®)
  - Crovalimab (anti-C5 Recycling antibody®)
  - GYM329/RG6237 (anti-latent myostatin Sweeping antibody®)
  - AMY109 (Recycling antibody®)
- ❑ **2** project utilizing these technologies in discovery stage.

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Switch-Ig® / Switch Antibody™ Technology

On-target Toxicity is One of the Remaining Challenges of Antibody Therapeutics

Anti-CD44v6 antibody drug conjugate

Systemic killing of CD44v6+ cells

↓

Kill CD44v6 positive cancer cell

Fatal skin toxicity as side effect (clinical development terminated)

Anti-4-1BB agonist antibody

Systemic activation of 4-1BB+ immune cells

↓

Activate tumor infiltrating 4-1BB+ T cells

Fatal hepatic toxicity as side effect (clinical development terminated)

Anti-EGFR Ab for colorectal cancer

Systemic neutralization of EGFR

↓

Kill EGFR dependent cancer cell

Severe skin toxicity as side effect

Engineered T cell (CAR-T etc) therapy

Systemic killing of antigen expressing cells

↓

Kill antigen positive cancer cell

Severe side effect by attacking normal cells expressing the target antigen

Anti-CTLA4 antibody for melanoma

Systemic neutralization of CTLA4

↓

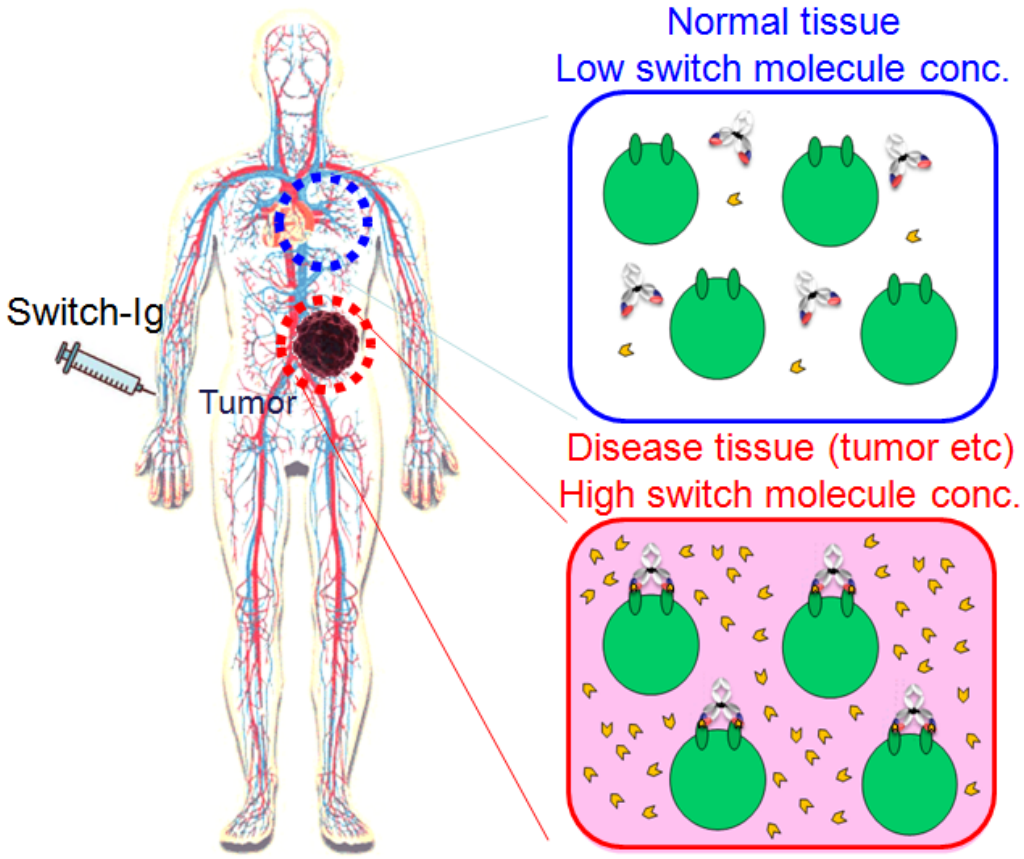
Activate tumor infiltrating CTLs

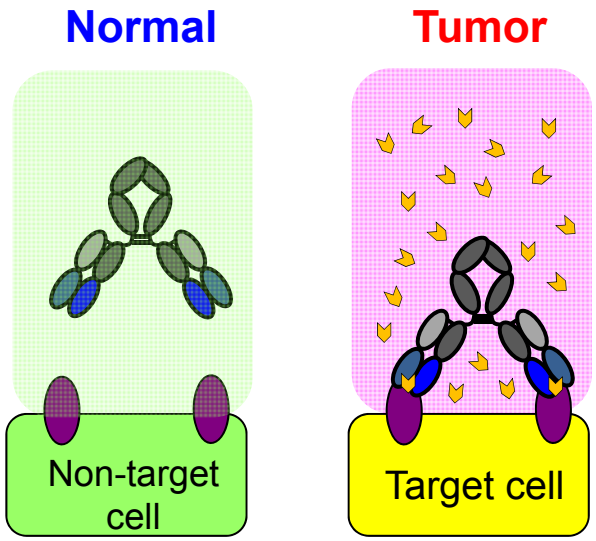
Severe autoimmune as side effect

Switch-Ig®

Disease microenvironment Switch Antibody™ technology

"Switch Antibody™" binds to the antigen only in the presence of tumor specific small molecule metabolite (switch molecule).





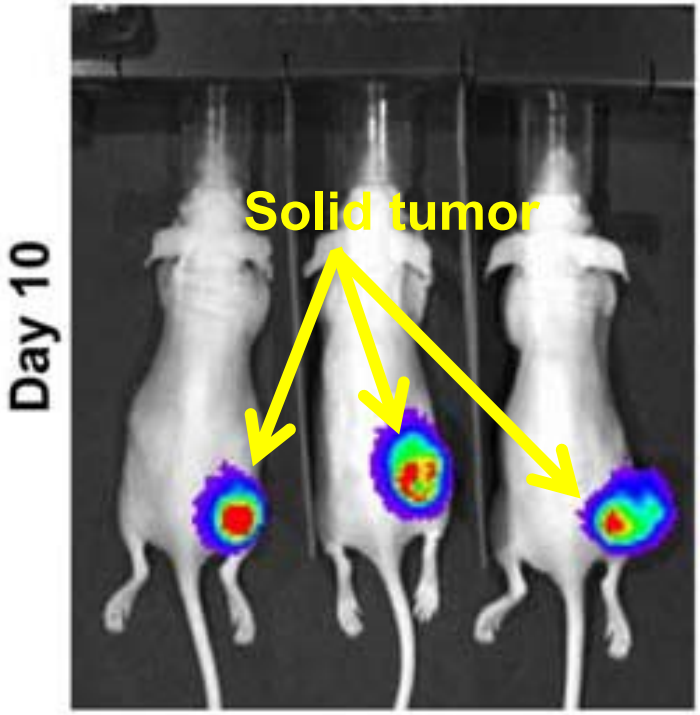
No side effect (**Switch OFF**)

Active in local disease tissue (**Switch ON**)

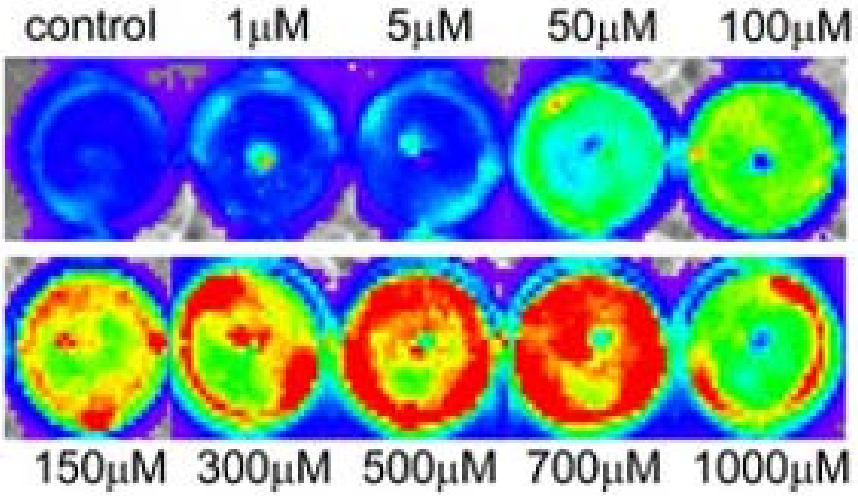
Conceptual illustration

Extracellular ATP Selectively Elevated in Tumor Microenvironment as Switch Molecule

- Intracellular ATP (adenosine triphosphage) is 5-8 mM, and extracellular ATP in **normal tissue and plasma** is tightly regulated at around **~30 nM**.
- Within solid tumor microenvironment, intracellular ATP is released from necrotic, apoptotic and stressed cancer cells.
- **>100 µM** extracellular ATP is accumulated in **solid tumor** in mice tumor.

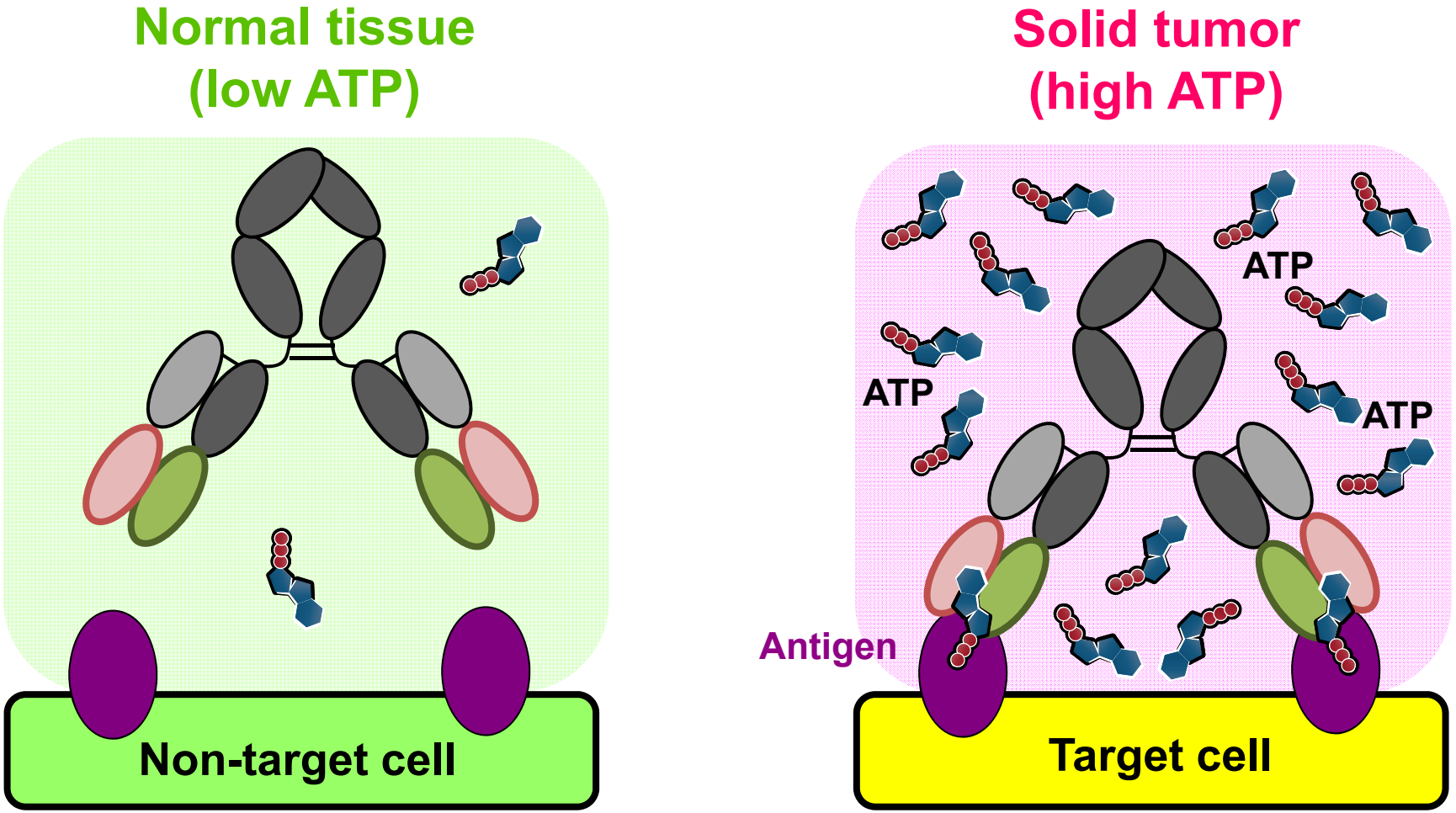


Mouse *in vivo* study



Pellegatti et al, 2008, PLoS ONE3(7): e2599.

Switch Antibody™ Binds to the Target Antigen Only under the Presence of ATP



Conceptual illustration

Designed Phage Library with ATP-binding Motif for ATP Switch Antibody™ Generation

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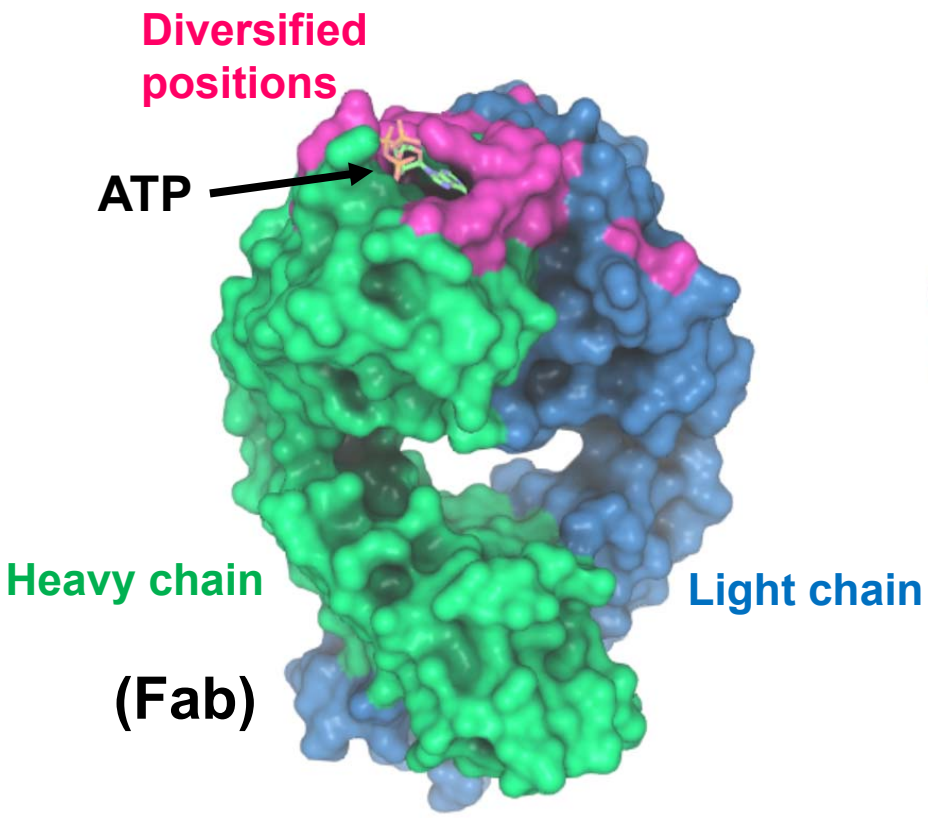
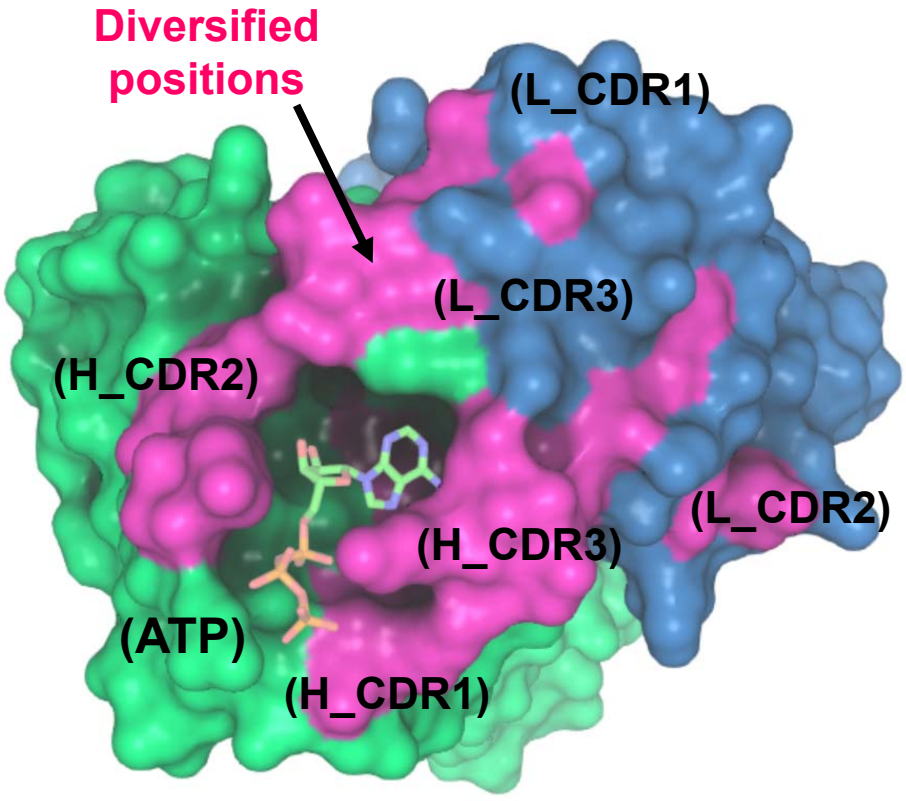
Roche Roche Group

X-ray crystal structure

Side view



Top view



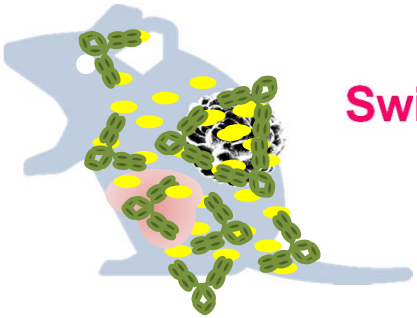
The Fab library is displayed on phage for ATP-dependent binding antibody selection

In-house data

Demonstrating the Concept of Switch Antibody™ Using Model Antigen and Animal

- Model antigen
  - Antigen: Human IL-6 receptor (hIL-6R)
  - Goal: **Generate ATP dependent anti-hIL-6R Switch Antibody™**
- Mouse model
  - Mouse: Transgenic mouse systemically overexpressing hIL-6R in normal tissues, and bearing hIL-6R expressing solid tumor
  - Goal: **Switch Antibody™ does not bind to hIL-6R in normal tissue, but bind to hIL-6R expressed on cancer cell and exert anti-tumor activity**

Non-switch Antibody (=Conventional Ab)



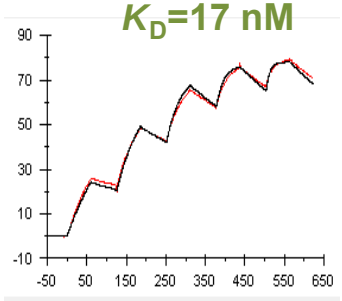
Switch Antibody™

Conceptual illustration

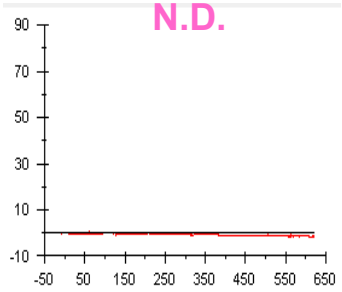
Switch Antibody™ Demonstrates ATP Dependent hIL-6R Binding and ADCC Activity

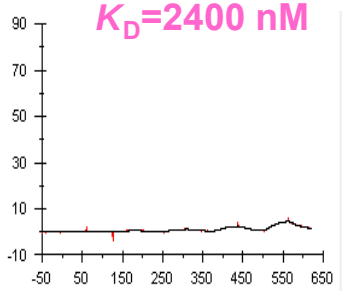
Binding analysis by surface plasmon resonance in vitro study

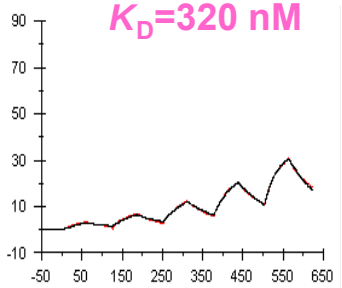
Non-switch Antibody

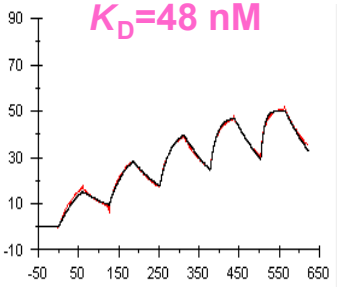


Switch Antibody™

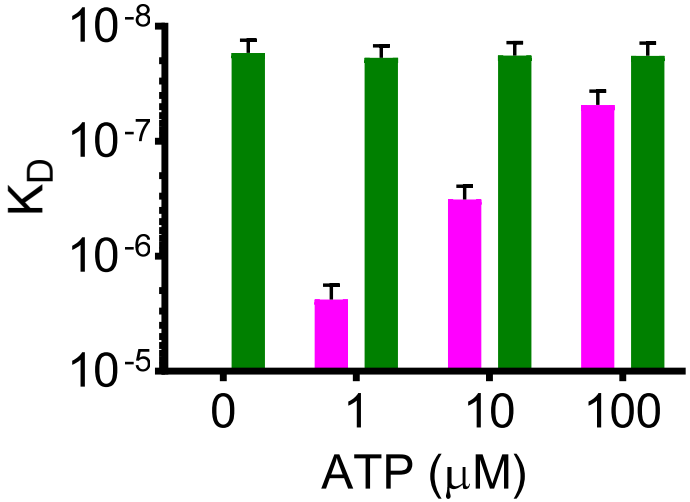




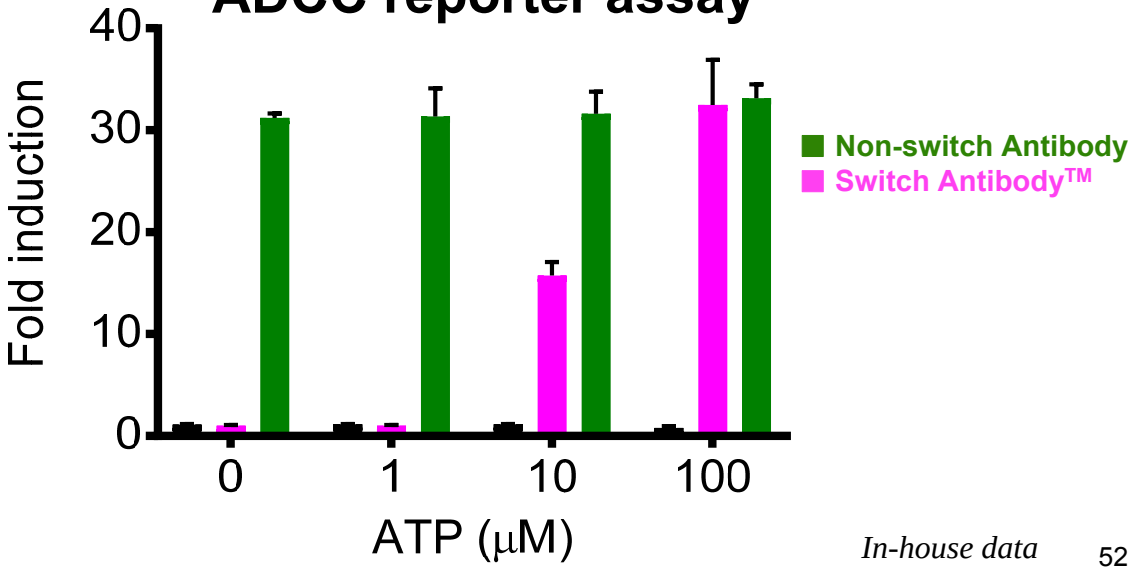




Binding affinity (K_D)



ADCC reporter assay

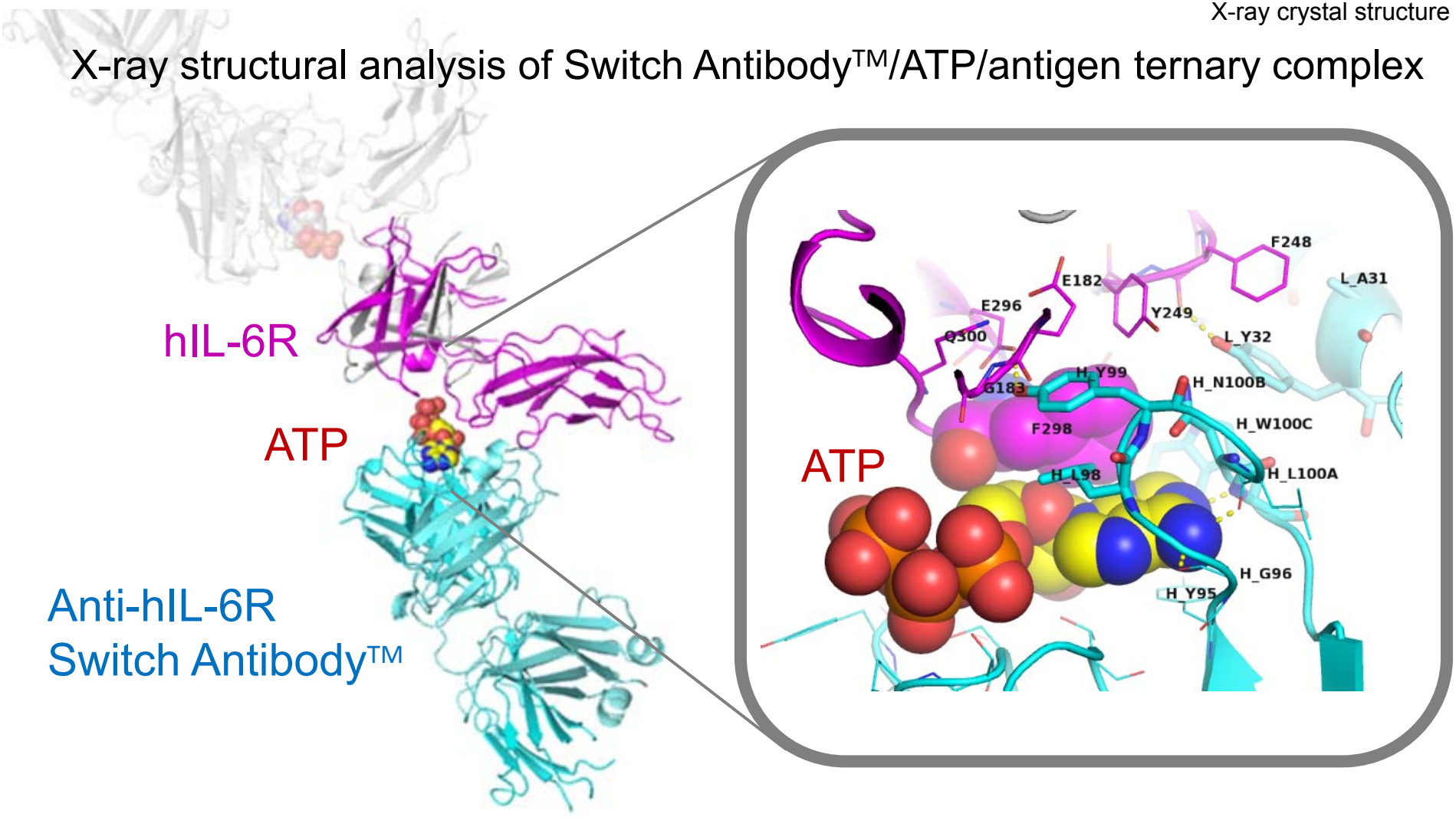


In-house data

ATP Located in Between Switch Antibody™ and the Antigen Serving as a Switch

X-ray crystal structure

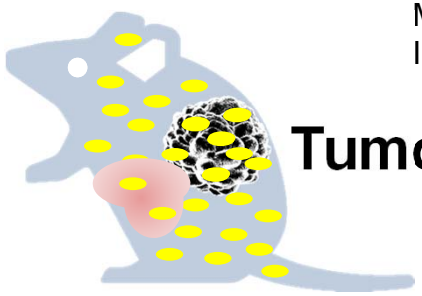
X-ray structural analysis of Switch Antibody™/ATP/antigen ternary complex



In-house data

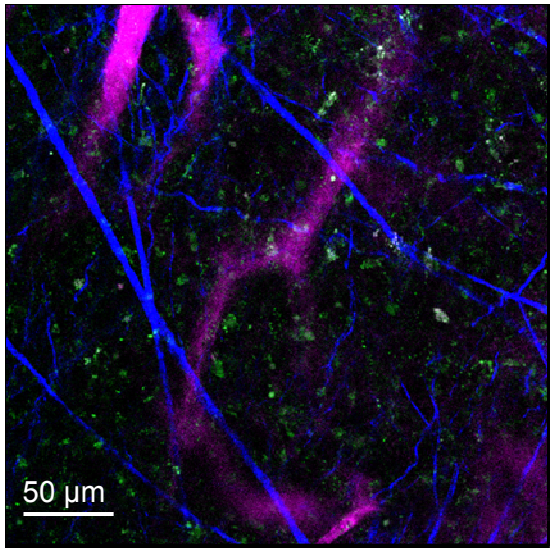
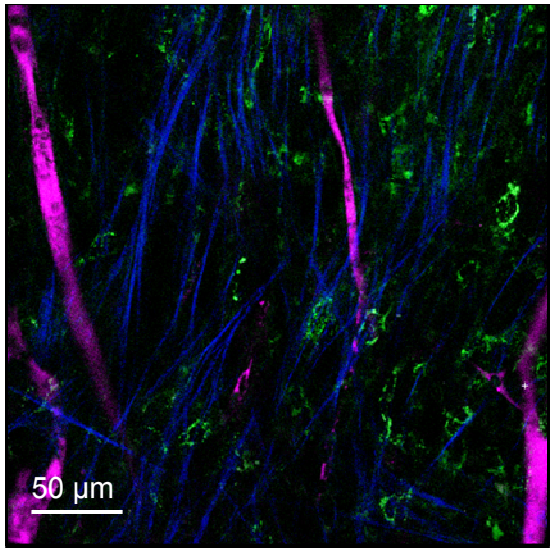
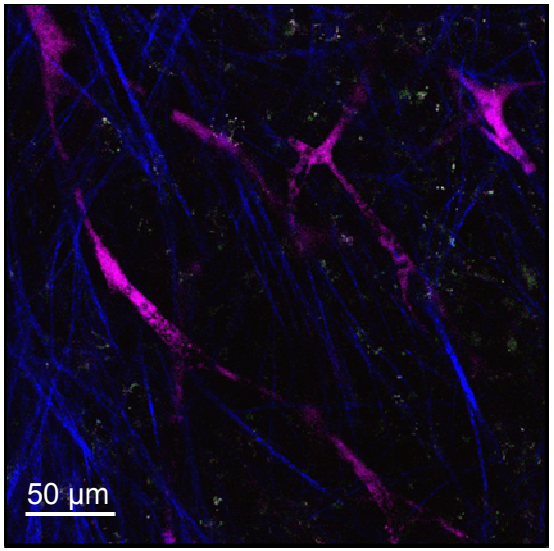
Switch Antibody™ was Similarly Distributed to hIL-6R Expressing Tumor as Non-switch Antibody

hIL-6R transgenic mouse with
hIL-6R expressing Hepa 1-6 mouse tumor
(all three antibodies were labelled in green)



Mouse *in vivo* study
Intravital imaging

Conceptual illustration

Non-switch Antibody	Switch Antibody™	Isotype control
		

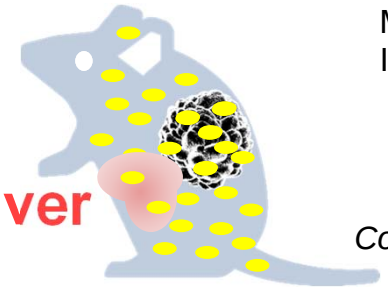
Collaboration with Department of Immunology and Cell Biology, Graduate School of Medicine, Osaka university

Green signal : Antibody
Pink signal : Blood vessel
Blue signal : collagen

In-house data

Switch Antibody™ was not Distributed to hIL-6R Overexpressing Liver

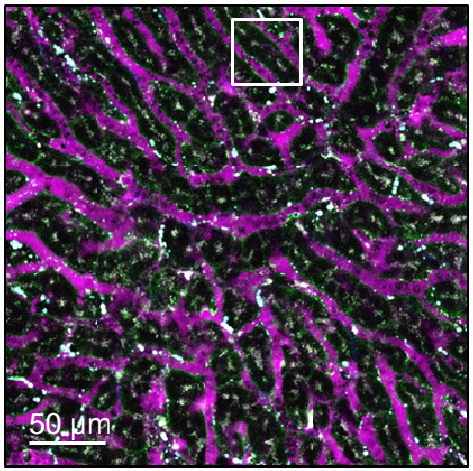
hIL-6R transgenic mouse with
hIL-6R expressing Hepa 1-6 mouse tumor
(all three antibodies were labelled in green)

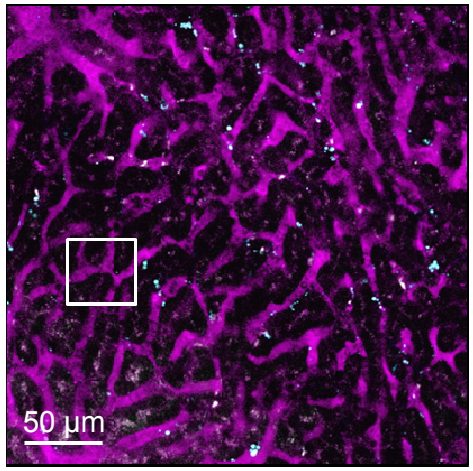


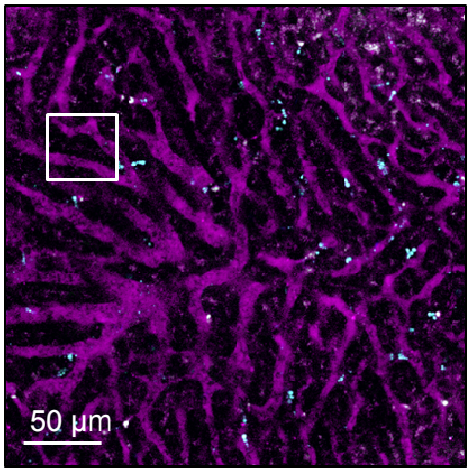
Mouse *in vivo* study
Intravital imaging

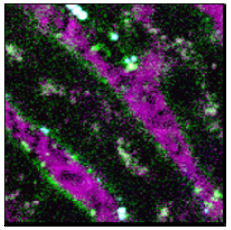
Conceptual illustration

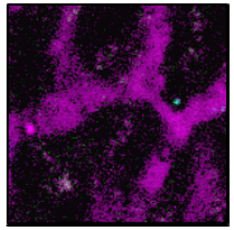
Non-switch Antibody | **Switch Antibody™** | **Isotype control**

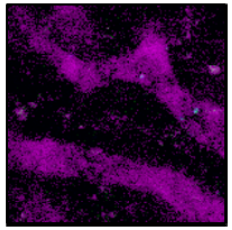












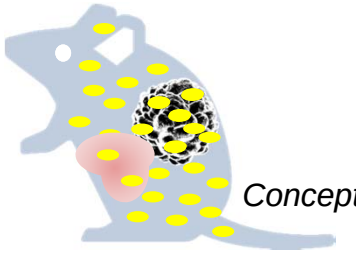
Green signal : Antibody
Pink signal : Blood vessel
Blue signal : collagen

Collaboration with Osaka university

In-house data

Switch Antibody™ was Selectively Distributed to Tumor but not to Liver

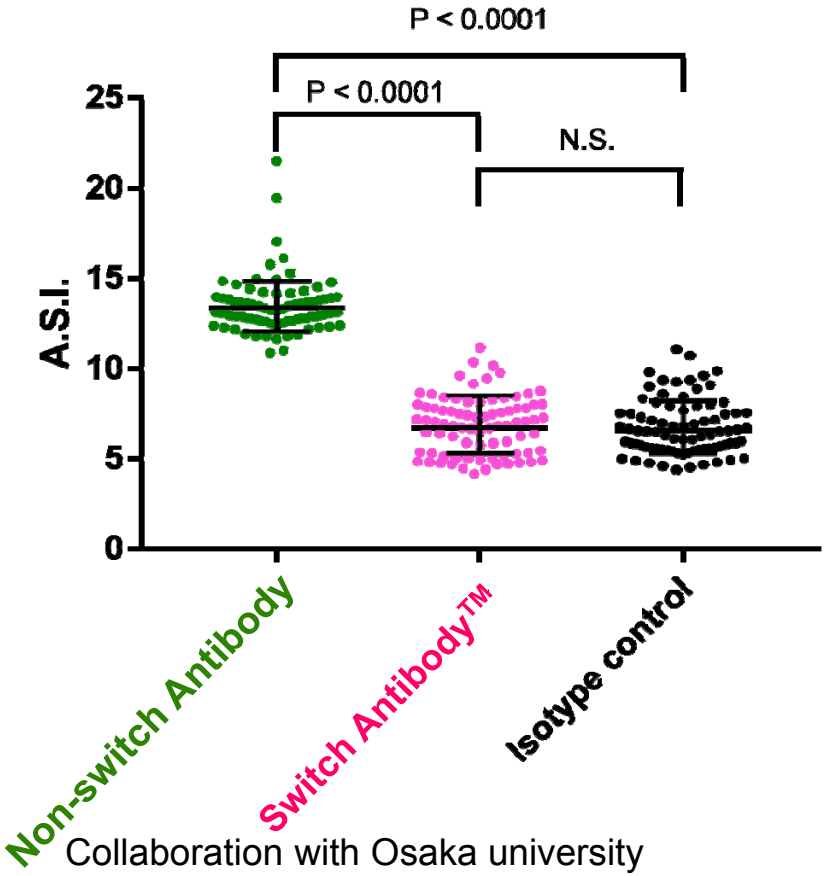
hIL-6R transgenic mouse with
hIL-6R expressing Hepa 1-6 mouse tumor



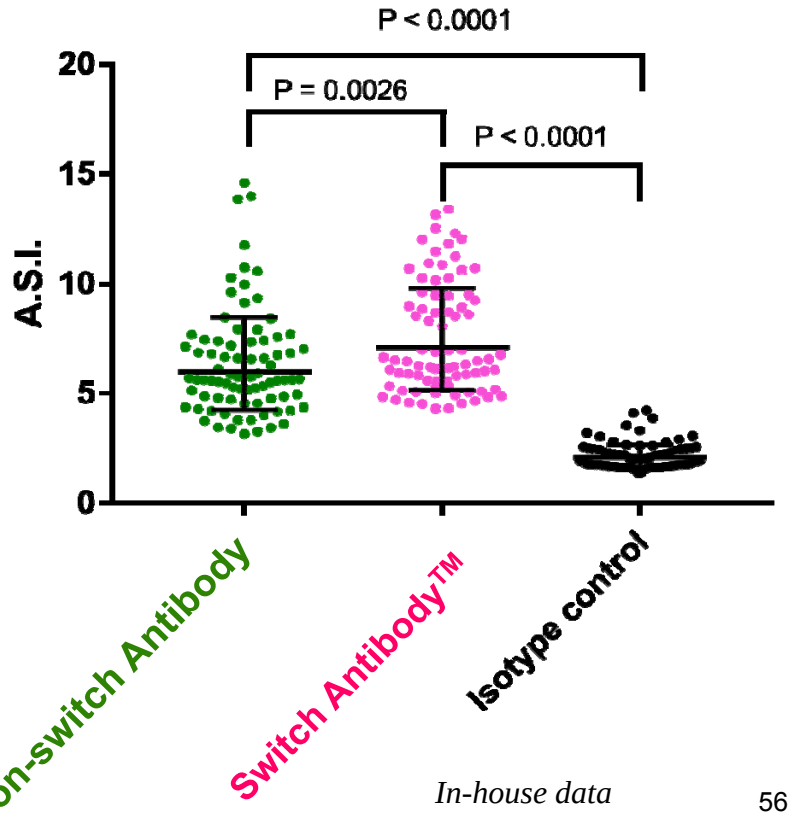
Conceptual illustration

Mouse *in vivo* study
Intravital imaging
Tukey's multiple comparison test

Liver



Tumor



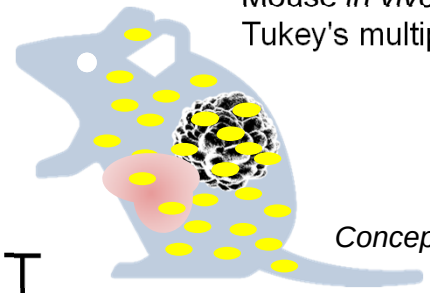
Collaboration with Osaka university

In-house data

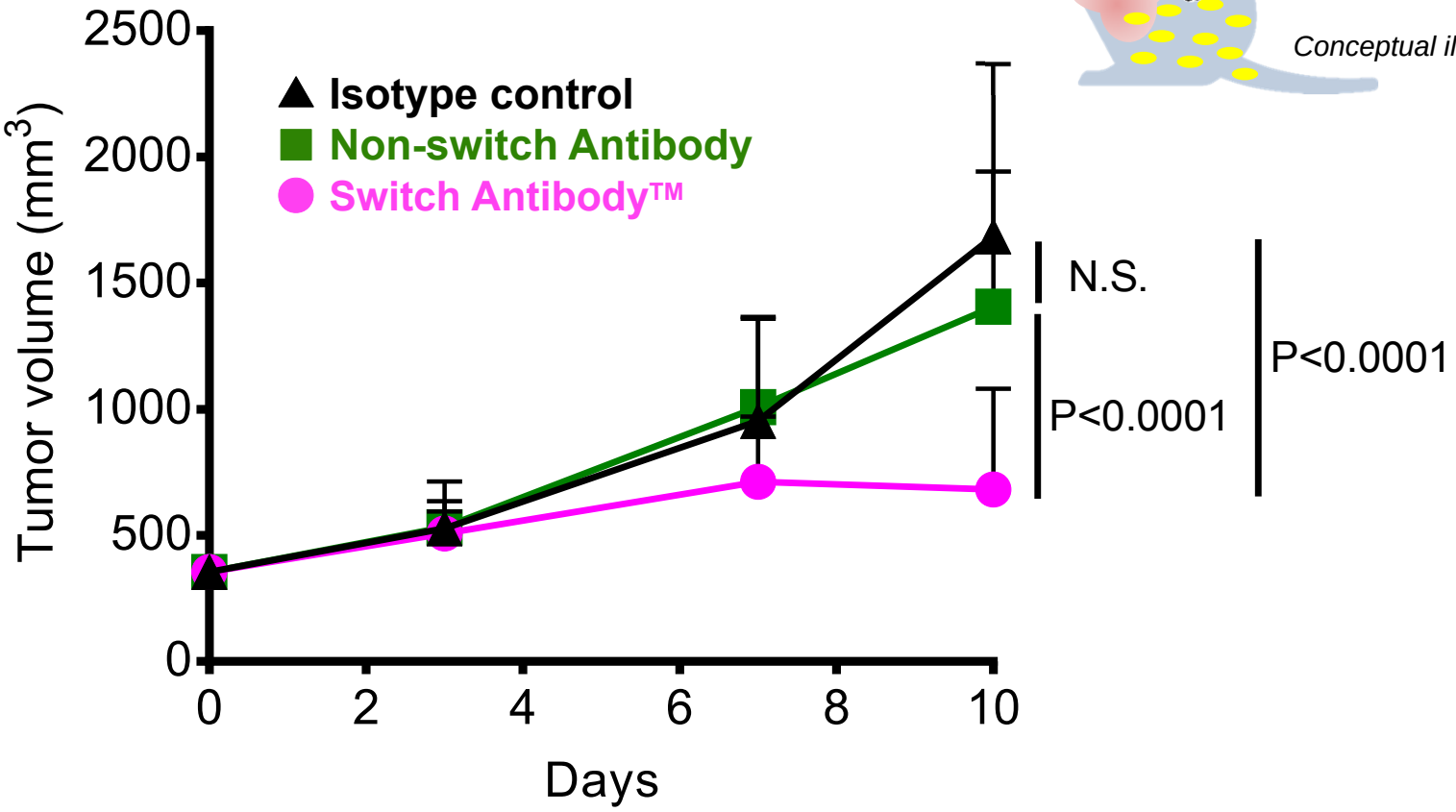
Switch Antibody™ Demonstrated Tumor Growth Inhibition

hIL-6R transgenic mouse with
hIL-6R expressing Hepa 1-6 mouse tumor

Mouse *in vivo* study
Tukey's multiple comparison test



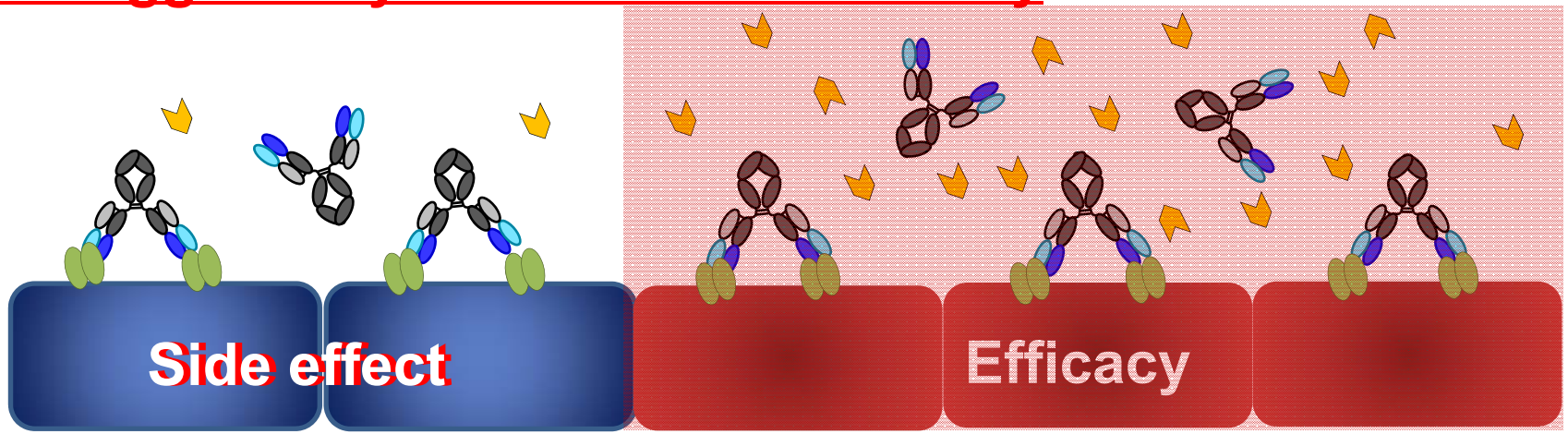
Conceptual illustration



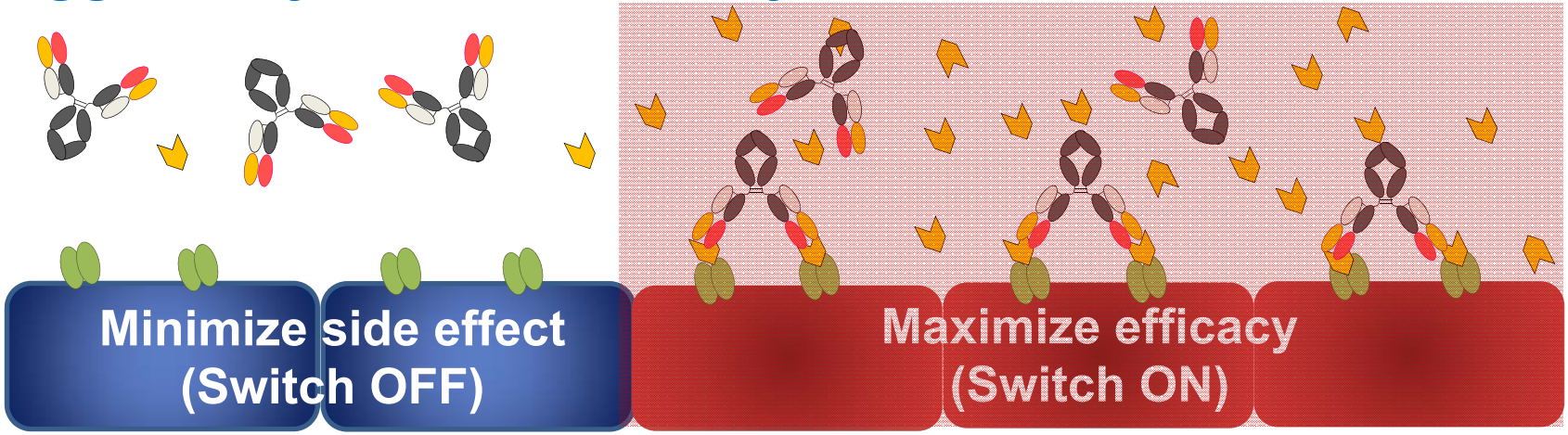
In-house data

Making Undruggable Target Druggable

Undruggable by conventional antibody



Druggable by Switch Antibody™



Normal tissue **Disease lesion with high switch molecule**

Conceptual illustration

Switch Antibody™ Summary

- Switch-Ig® specifically binds to the target antigen in the tumor microenvironment without detectable binding to the antigen in plasma and normal tissue.
- Switch-Ig® technology transforms undruggable target into druggable target, and enables more effective and safer antibody therapeutics in oncology field.

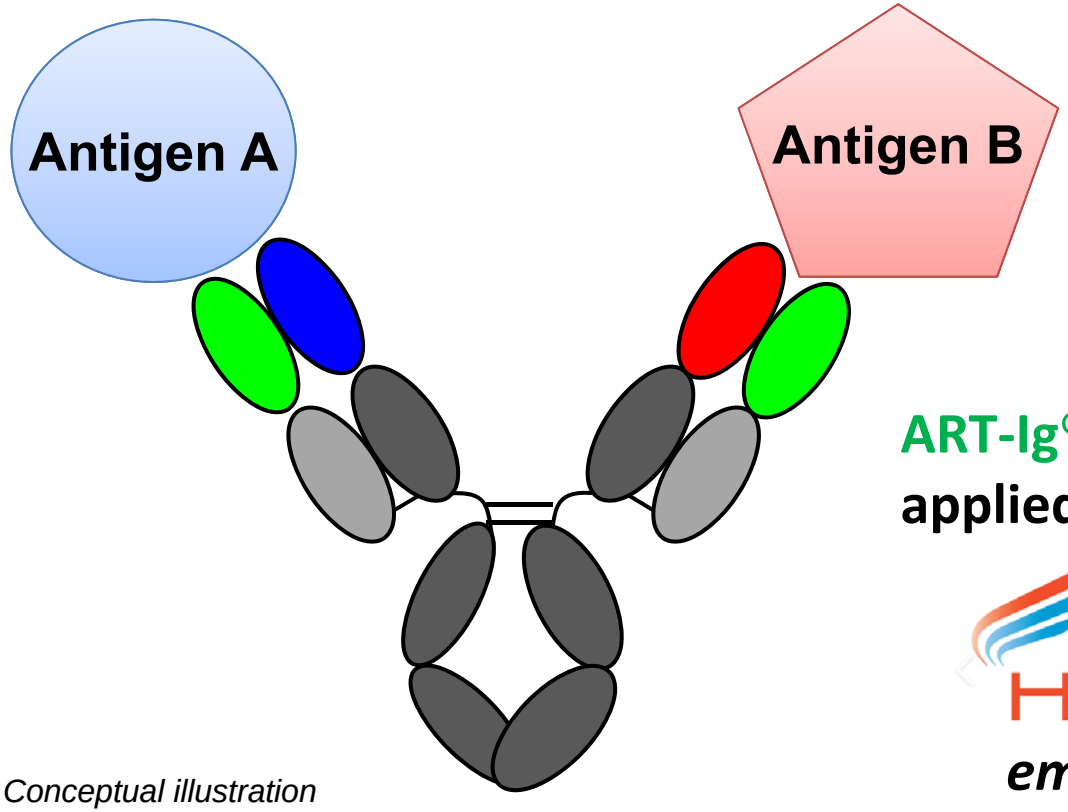
  - **1** project utilizing Switch-Ig® planned to enter into clinical development next year.
  - **6** projects utilizing Switch-Ig® in discovery stage.

CHUGAI
Roche Roche Group

Next Generation
Bispecific Antibody Technology

First Generation Bispecific Antibody

Asymmetric bispecific IgG antibody with common light chain



Conceptual illustration

ART-Ig® technology successfully applied to create Hemlibra®

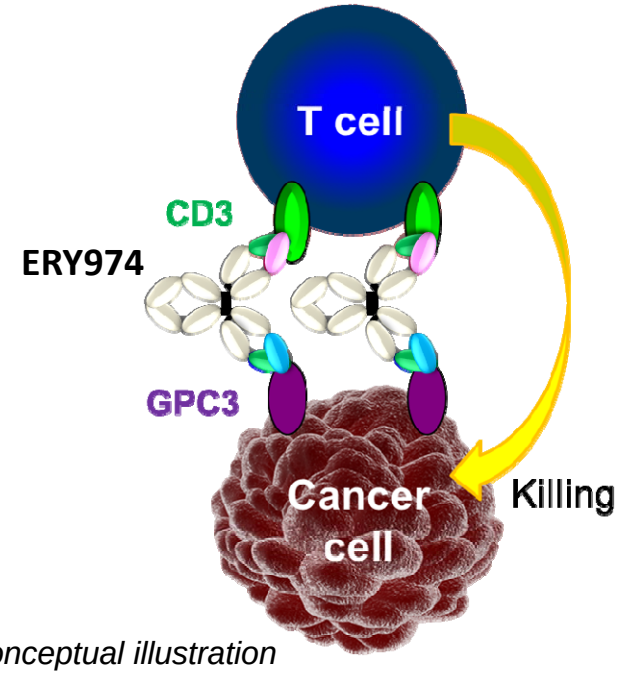
HEMLIBRA™

emicizumab

ERY974: T cell Redirecting AntiBody (TRAB®)

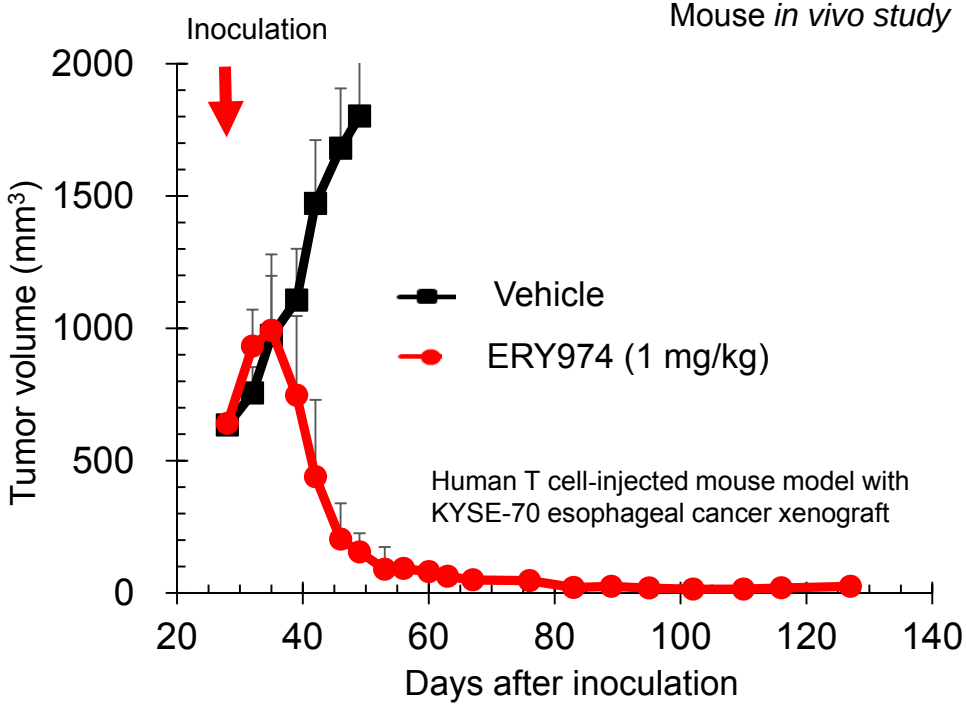
Anti-GPC3/CD3 bispecific antibody

- **TRAB®** is Chugai's proprietary platform with TA(tumor antigen)/CD3 bispecific IgG antibody engineered not to bind to FcγR.
- ERY974 is Chugai's first TRAB® being tested in phase 1 study.



Conceptual illustration

Mouse *in vivo study*



Applied **ART-Ig®** with common light chain for bispecific antibody manufacturing.

Science Trans Med, 2017, Ishiguro et al

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

Next Generation Bispecific Antibody

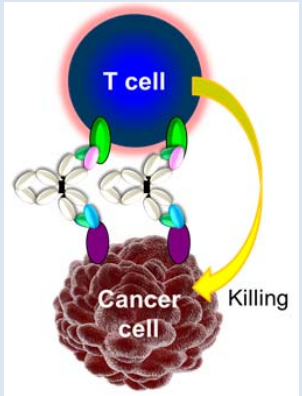
CHUGAI
Roche Roche Group

❑ Second generation

HEMLIBRA™

NXT007
Second generation emicizumab

TRAB®



1. **Expand to other tumor antigens**
2. **Enhance efficacy**
3. **Improve safety**

Conceptual illustration

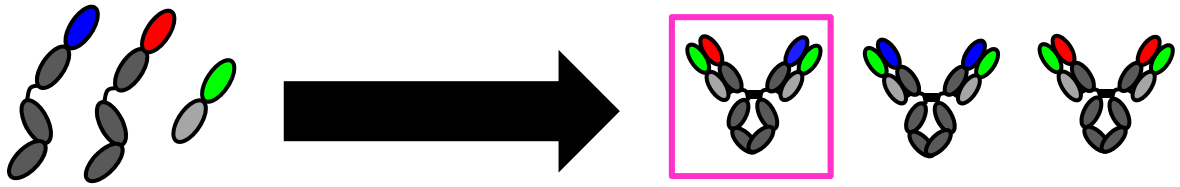
❑ Third generation

Novel mode of action by <u>controlled</u> binding to two antigens (not just binding to two different antigens)

Second Generation Bispecific Antibody

Non-common Lch asymmetric bispecific antibody

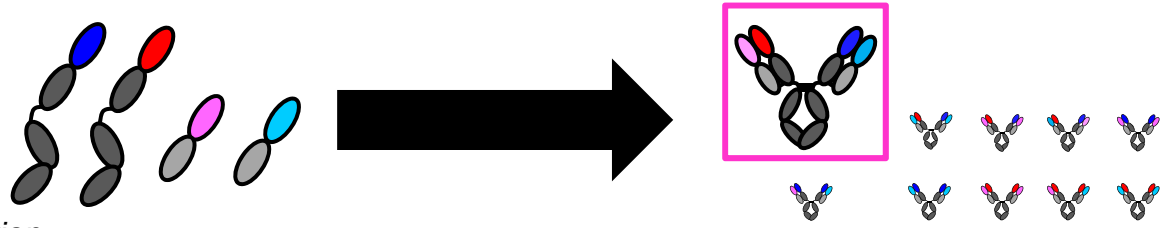
- First generation: **ART-Ig®** using common light chain



Advantage Easiness for manufacturing

Conceptual illustration *Disadvantage* Engineering freedom is limited

- Second generation: **FAST-Ig™** with non-common light chain



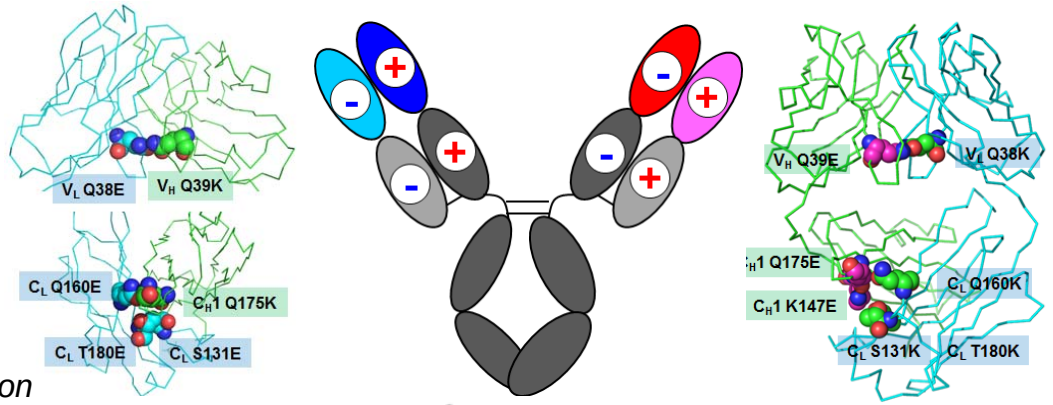
Conceptual illustration

Freedom to engineer two light chains independently, and allows design of bispecific antibody with complex mode of action

FAST-Ig™

Four-chain Assembly by electrostatic Steering Technology

- Controlled heavy and light chain assembly by charge engineering

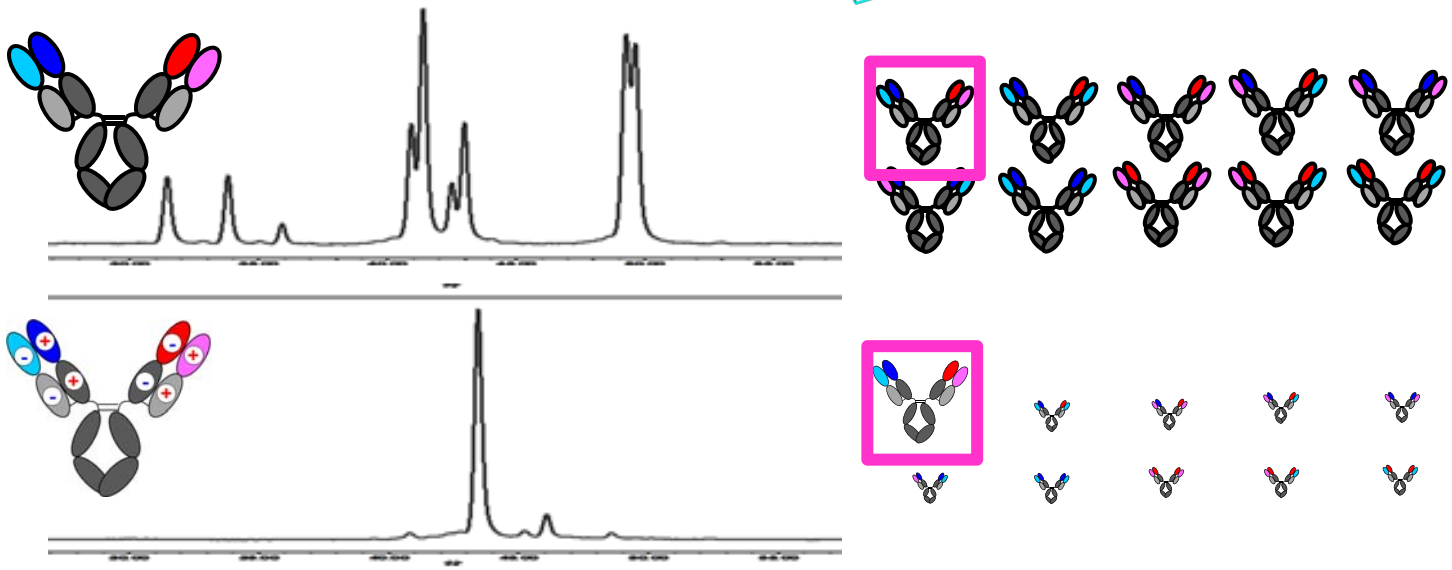


X-ray crystal structure

Conceptual illustration

Wild type IgG1 (HHLL)

FAST-Ig™ (HHLL)



Ion exchange chromatography analysis of protein A purified samples

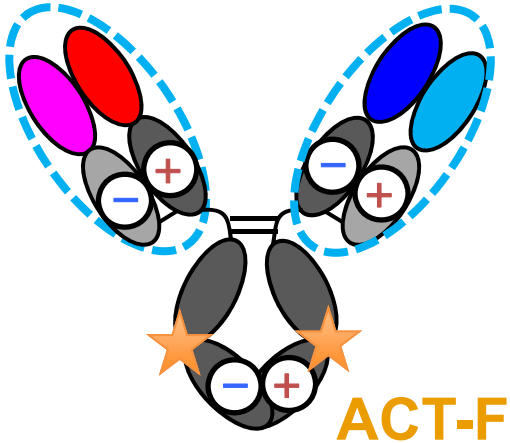
In-house data

NXT007

Anti-FIXa/FX bispecific antibody

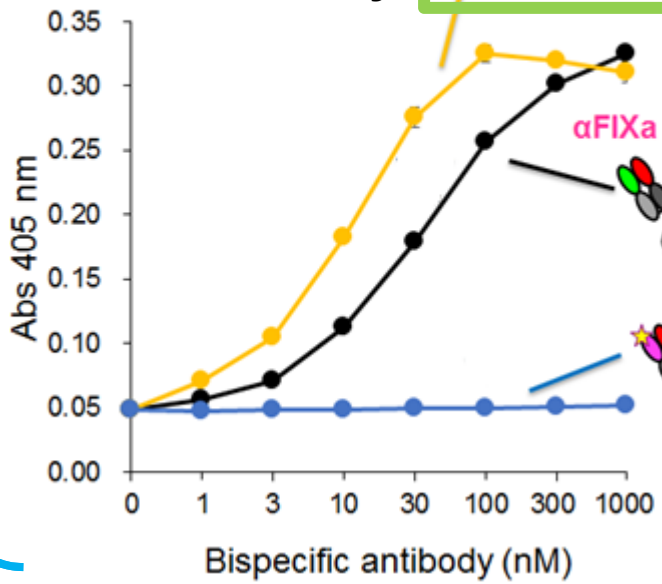
Example of enhancing activity with non-common Lch

FAST-Ig™



Conceptual illustration

FVIII-like activity



Mutations in FX arm Lch only
(Non-common Lch)
**This molecule is not NXT007*

in vitro study

αFIXa αFX

emicizumb
(Common Lch)

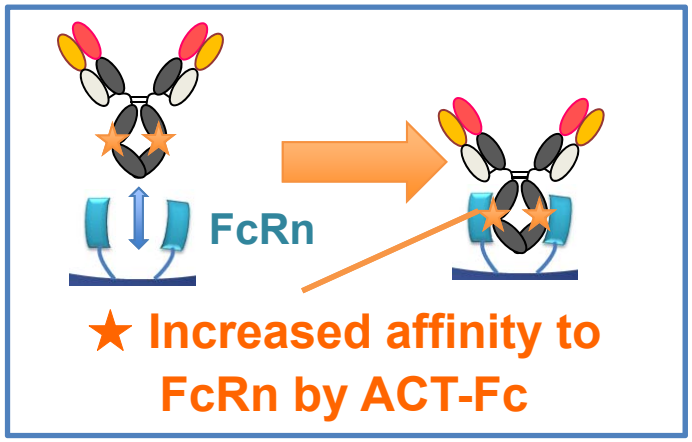
Same mutations in both Lch
(Common Lch)

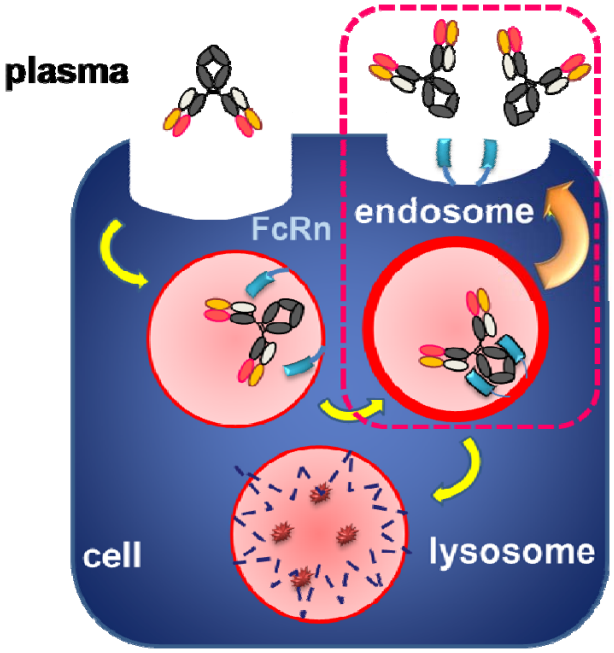
In-house data

NXT007 Target Profile

- ❑ Achieve normal level of hemostatic ability
  - ✓ Further optimization of emicizumab variable region enabled by **FAST-Ig™**
- ❑ Improved convenience in administration
  - ✓ Achieved by **ACT-Fc** and application of administration device etc

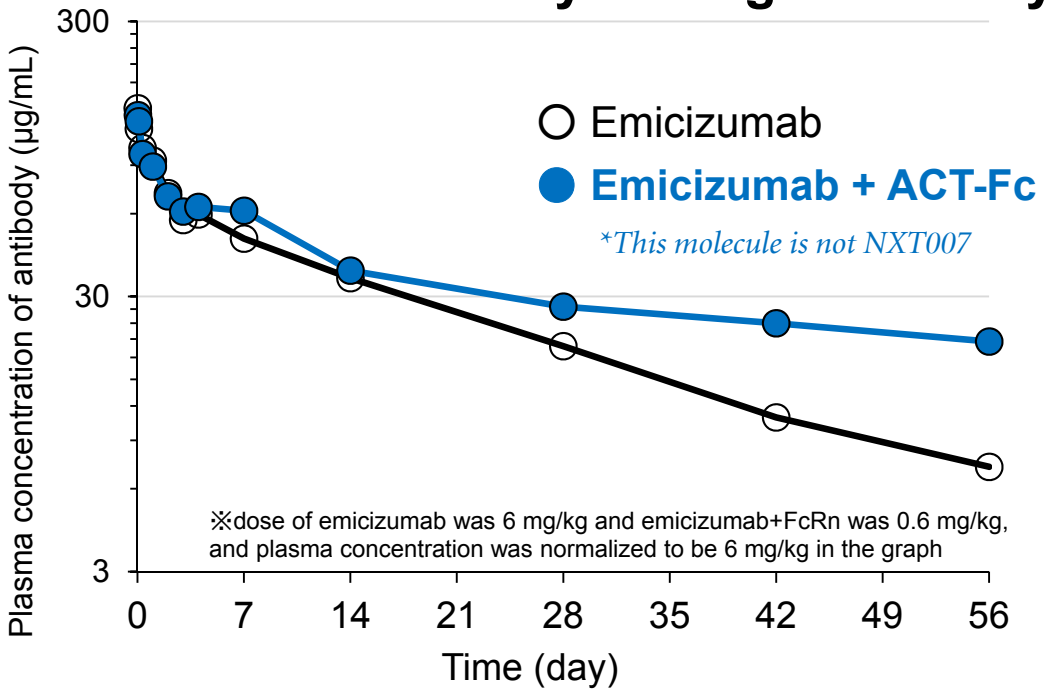
ACT-Fc: FcRn Binding Enhancing Mutation Improves the Pharmacokinetics of Emicizumab





Conceptual illustration

Pharmacokinetics in cynomolgus monkey



	$T_{1/2}$ (day)	CL (mL/day/kg)
Emicizumab	19.4	3.69
Emicizumab + ACT-Fc	**54.5**	**1.70**

ACT-Fc is also applied to crovalimab, AMY109 and GYM329

T cell Redirecting AntiBody (TRAB®) Drug Discovery Strategy

1. Bringing multiple TRAB® projects targeting various tumor antigens (TAs) into discovery research pipeline
   - CD3 bispecific antibodies against novel tumor antigens
   - **FAST-Ig™** with non-common light chain accelerates the research

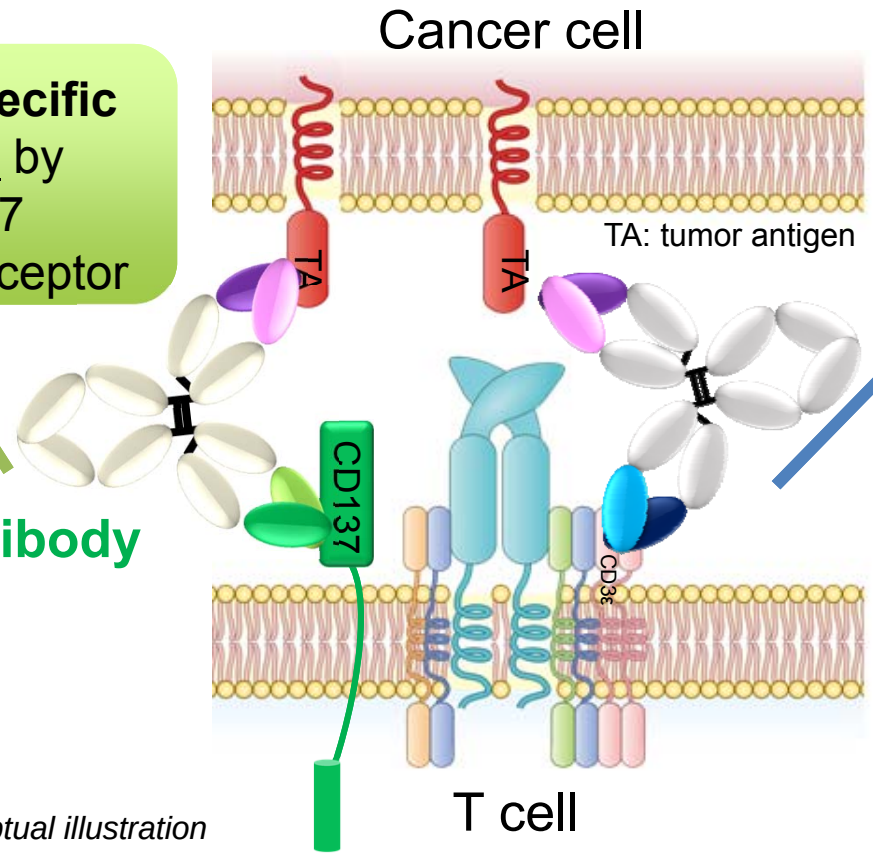
2. Combining **costimulatory signal** to improve anti-tumor efficacy of TRAB®
   - Combination of costimulatory signal with TA/CD137 bispecific

3. Incorporating **Switch Antibody™** technology to improve the safety profile of TRAB®
   - Tumor antigen expressed in normal tissue leads to toxicity
   - ATP dependent tumor antigen binding to avoid normal tissue toxicity

TA(tumor antigen)/CD137 Bispecific Antibody to Induce Costimulatory Signal to T cell

TA/CD137 bispecific induces signal 2 by clustering CD137 costimulatory receptor

TRAB® induces signal 1 by clustering CD3ε



TA/CD137 bispecific antibody

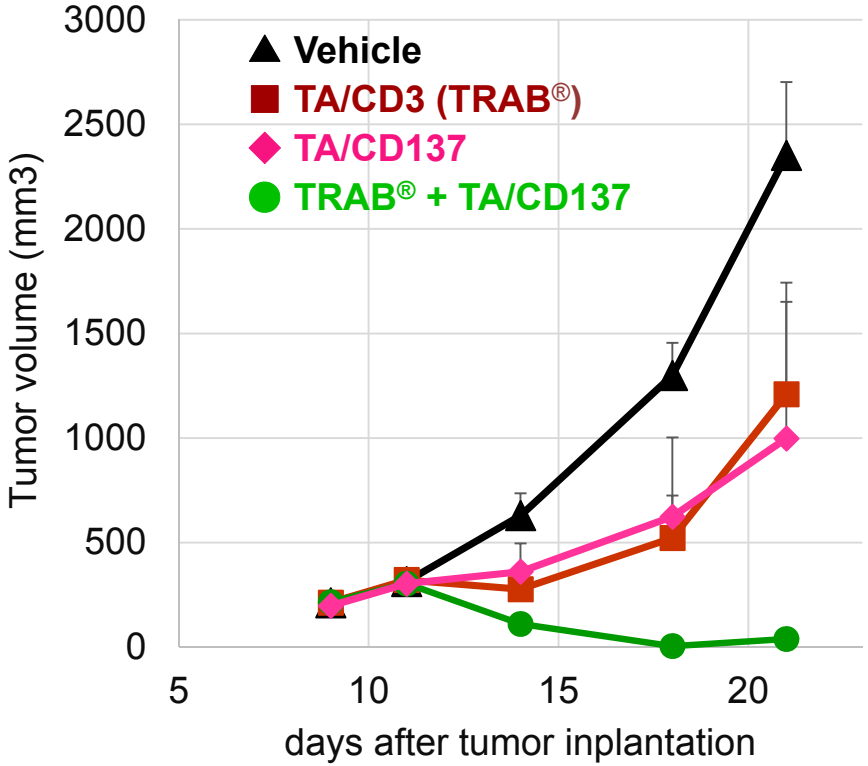
TRAB®
(TA/CD3 bispecific antibody)

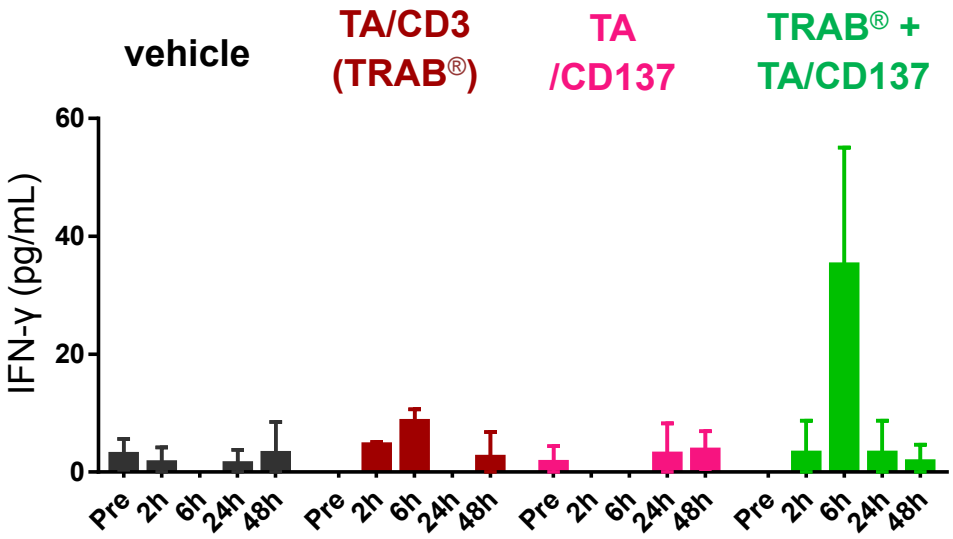
Conceptual illustration

Full activation and improved survival by combining signal 1 and 2 mimics the natural process of T cell activation

Synergistic Anti-tumor Effect by Combining TA/CD3 and TA/CD137 Bispecific Antibodies

Mouse *in vivo* study

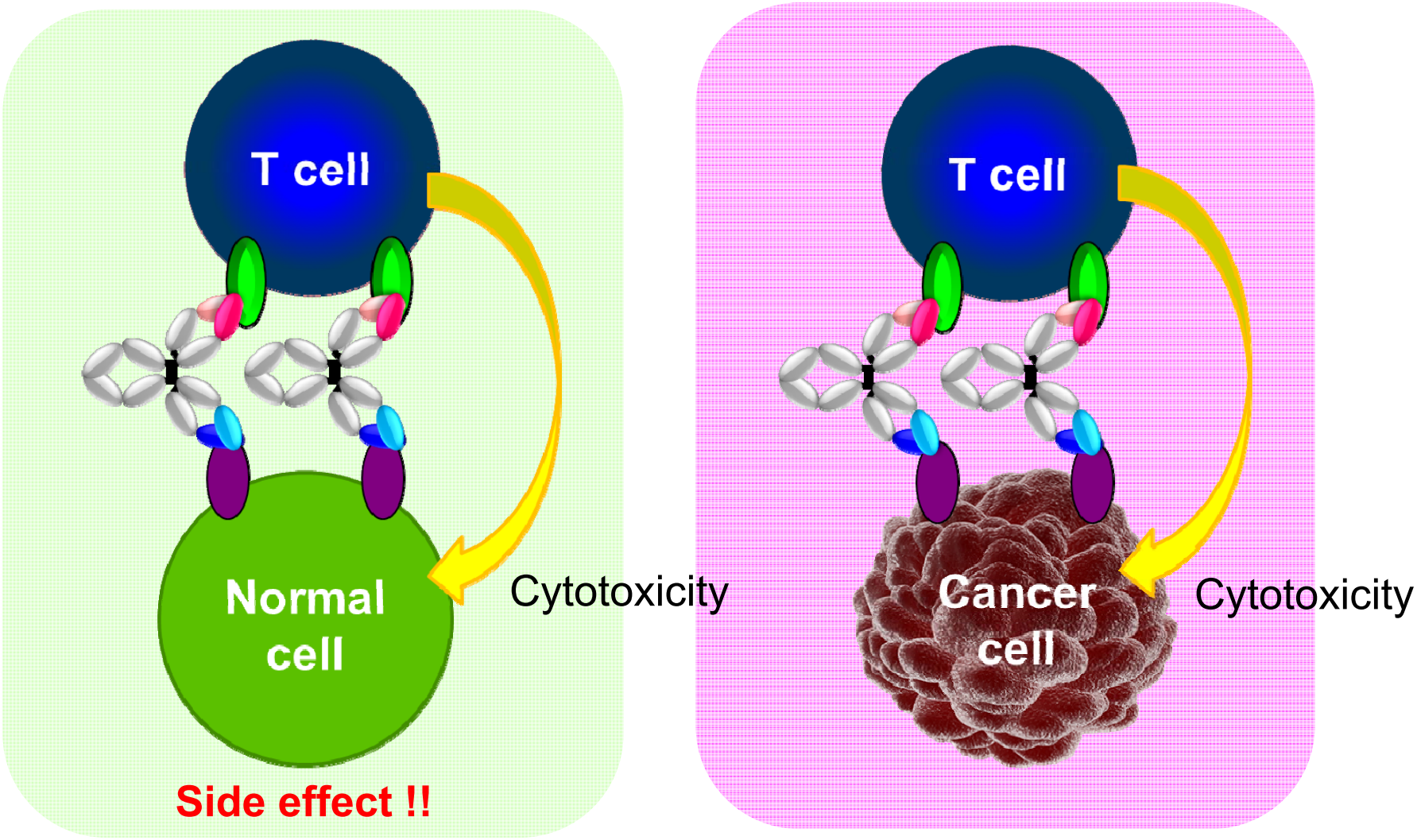




In TRAB resistant mouse tumor model, combination of TA/CD137 bispecific antibody significantly improved anti-tumor efficacy and IFNγ production.

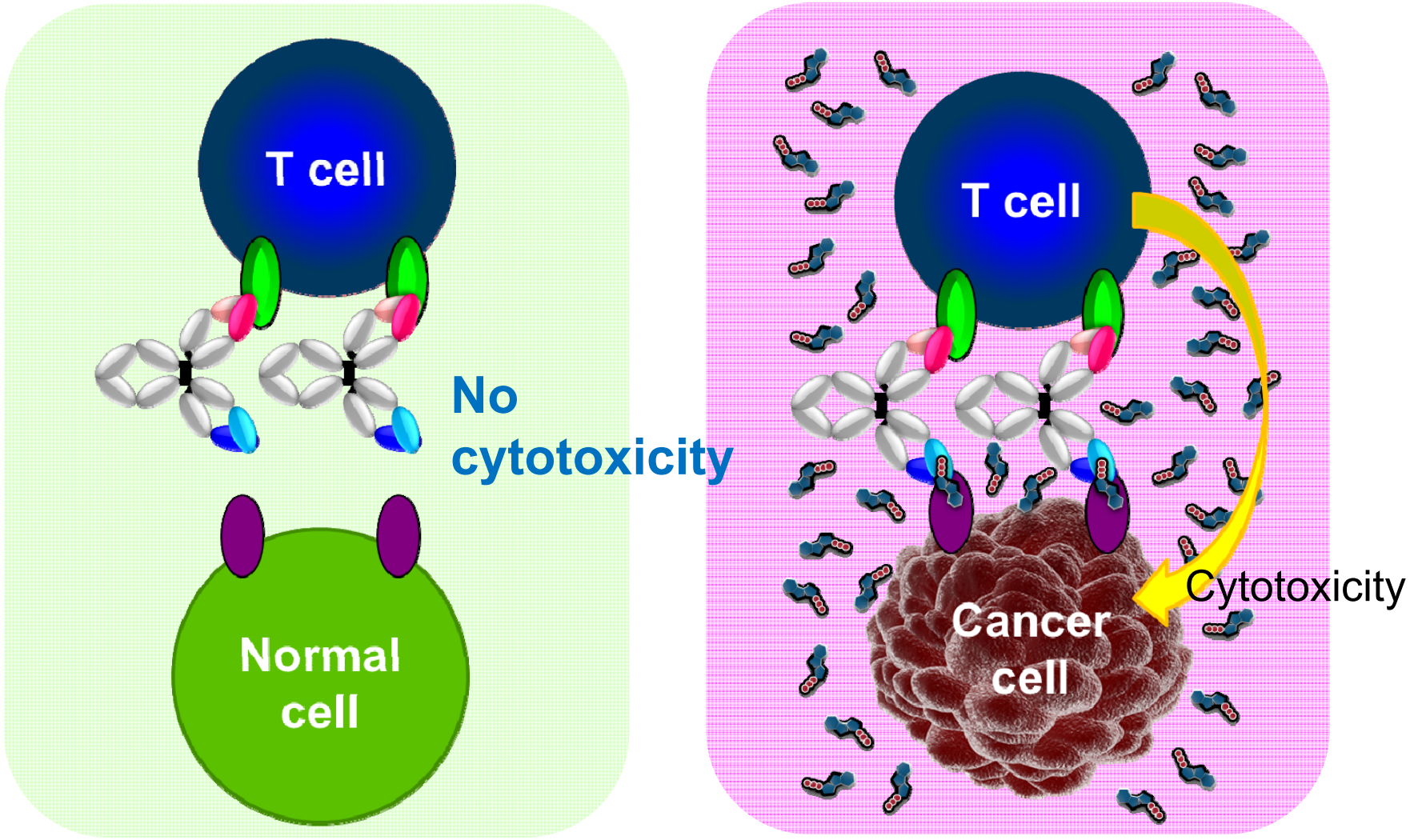
In-house data

ON-target OFF Tumor Side Effect is the Major Challenge of TRAB®



Conceptual illustration

Switch Antibody™ is Applicable to TRAB® and Various Cancer Immunotherapies

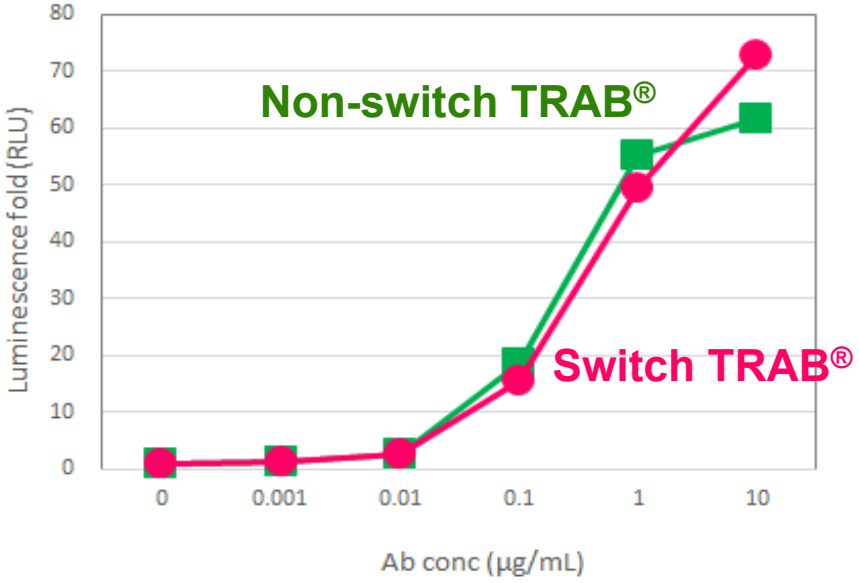


Conceptual illustration

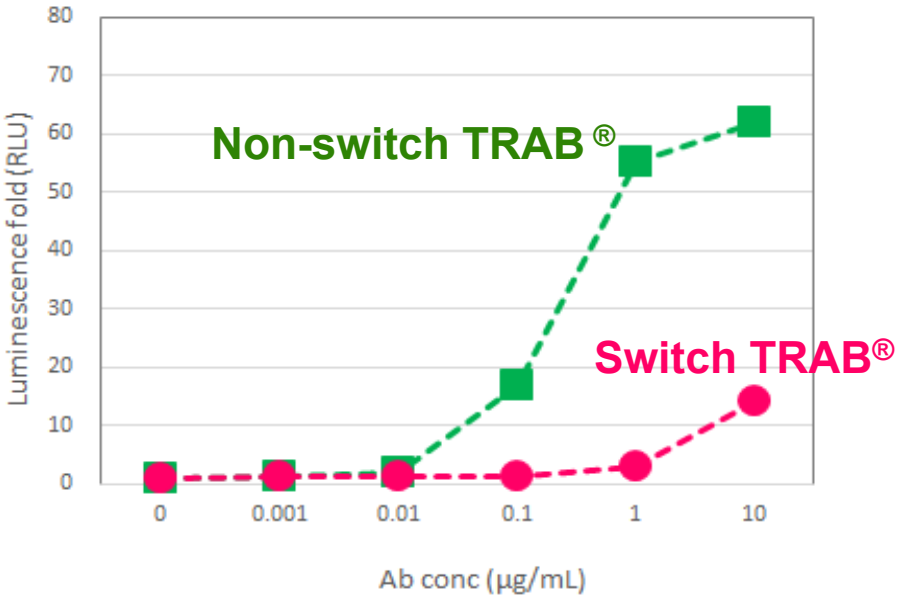
Switch TRAB® Shows Strong T cell Activation Only under the Presence of ATP

In vitro reporter cell assay

100 μM ATP



No ATP

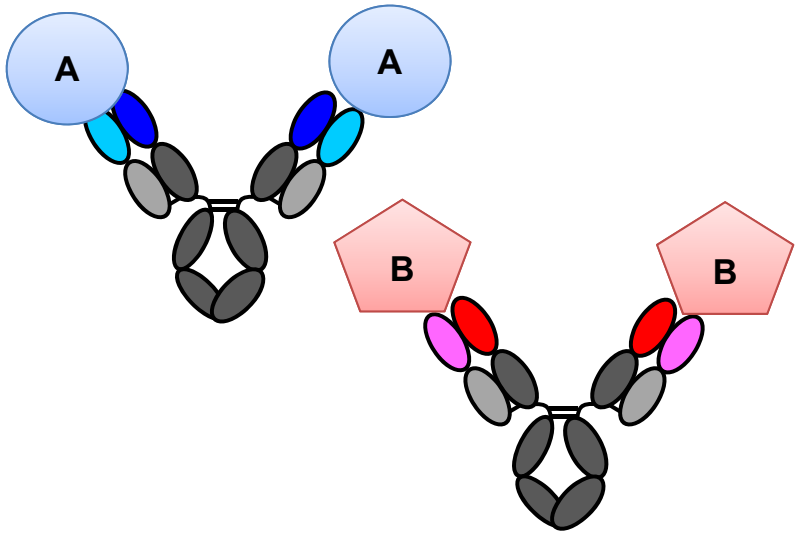


In-house data

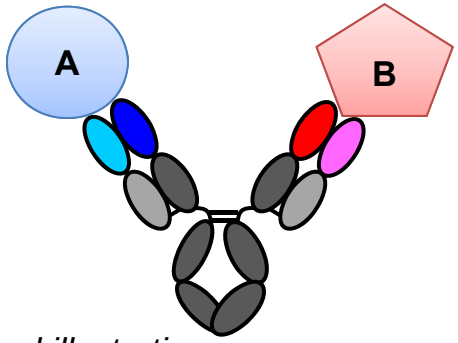
Third Generation Bispecific Antibody

Dual specific mutually competitive bispecific Fab

Conventional IgG antibody

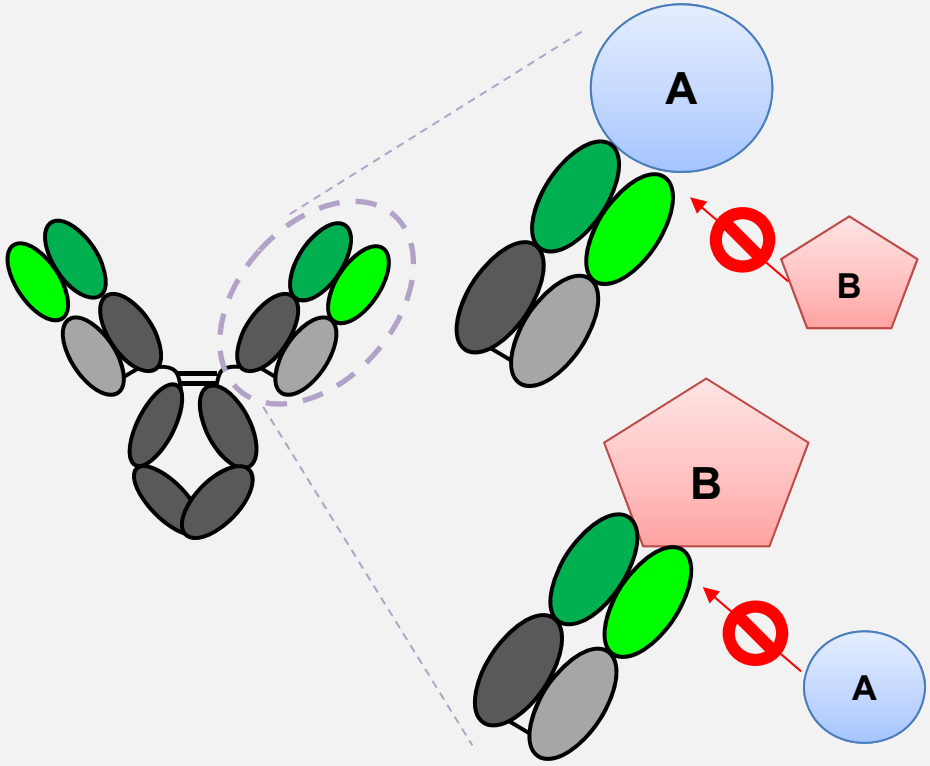


Asymmetric bispecific IgG antibody



Conceptual illustration

Antibody with mutually competitive bispecific Fab



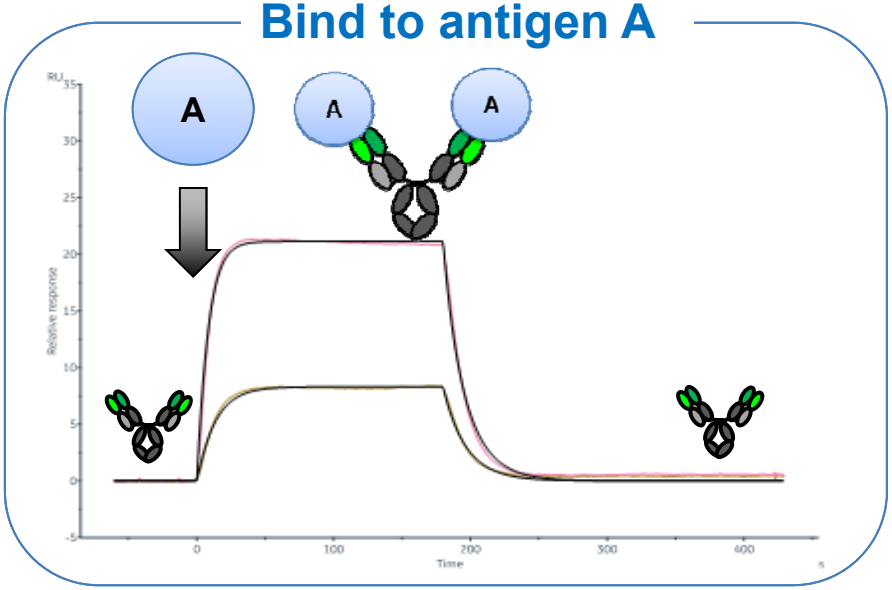
Enables novel mode of action by **controlled** binding to two antigens

Novel Bispecific Antibody Can Bind to Two Different Antigens but not at the Same Time

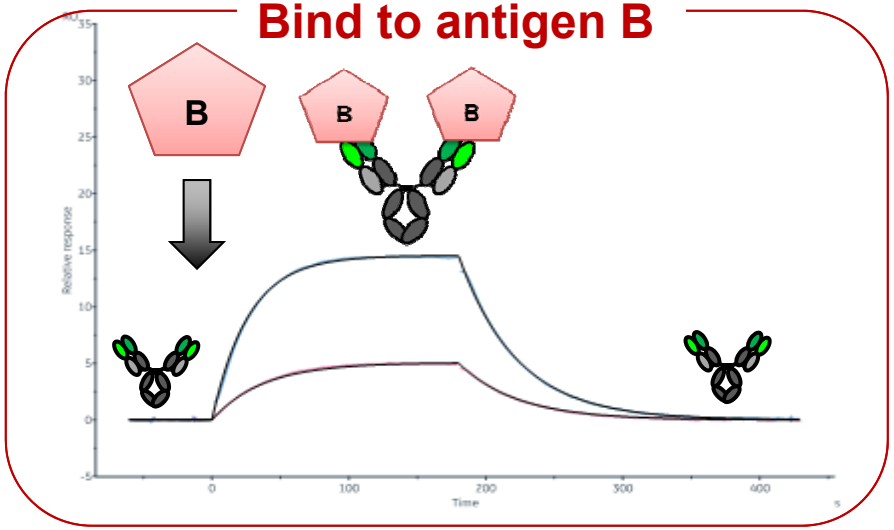
CHUGAI
Roche Roche Group

Binding analysis by surface plasmon resonance

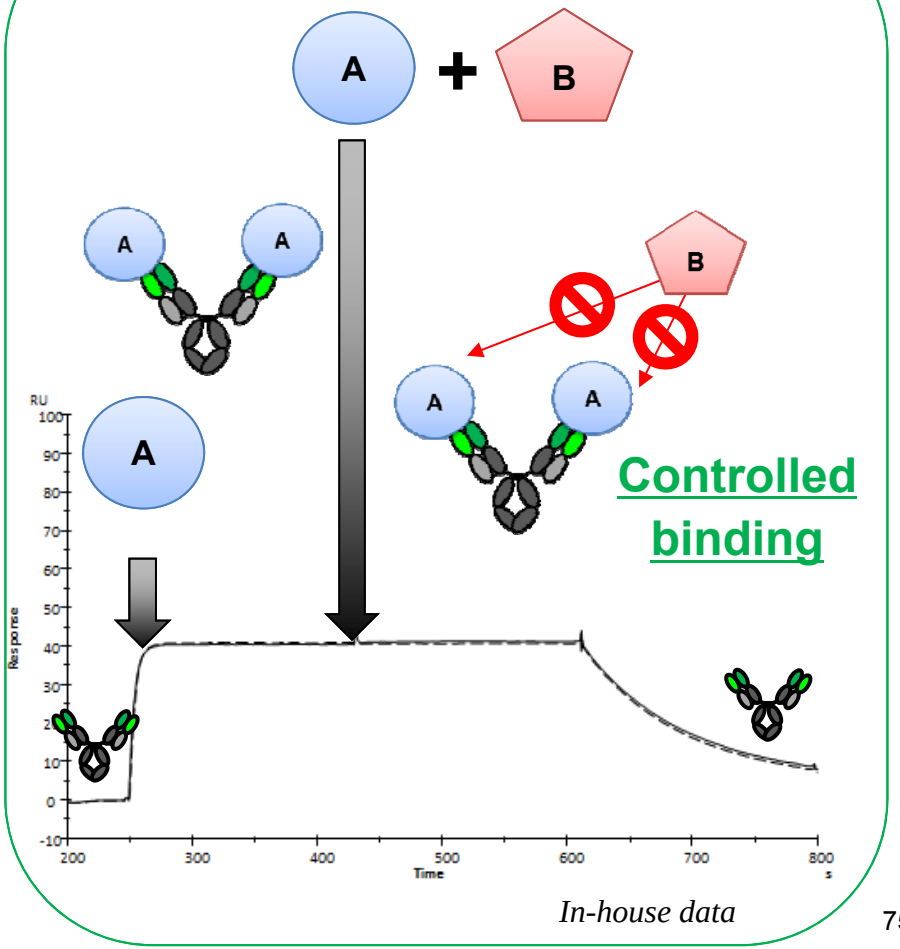
Bind to antigen A



Bind to antigen B



When antigen A is bound, antigen B cannot bind



In-house data

Next Generation Bispecific Summary

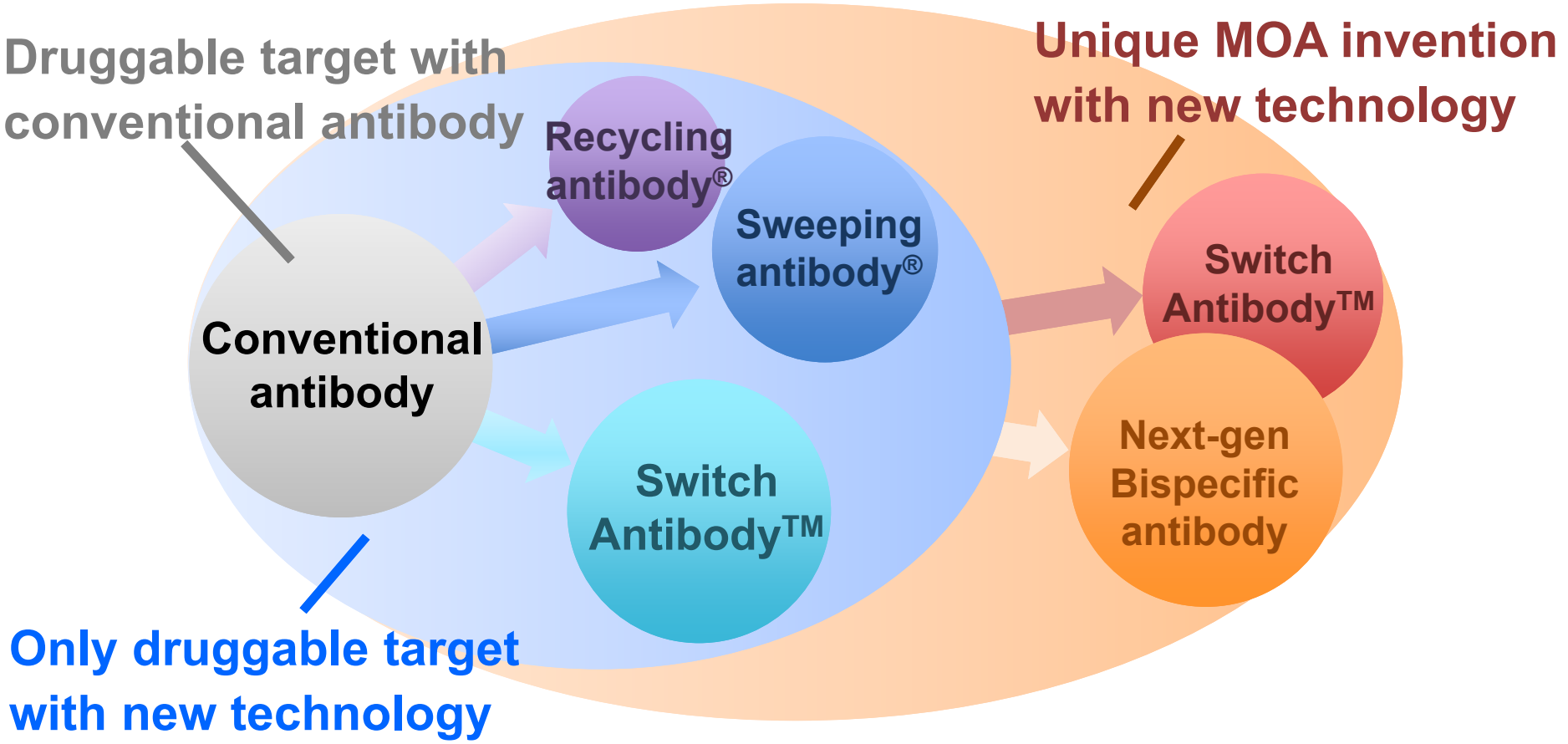
❑ Second generation bispecific antibody

- FAST-Ig™ removes common light chain restriction to manufacture bispecific antibody, and enables complex engineering of two arms of bispecific antibody.
  - **1** project utilizing FAST-Ig™ in clinical development.
    - NXT007 (anti-FIXa/FX bispecific antibody)
  - **4** projects utilizing FAST-Ig™ in discovery stage.

❑ Third generation bispecific antibody

- Mutually competitive bispecific Fab enables novel mode of action by controlled binding to two antigens and antibody with unique mechanism action can be designed.
  - **5** projects utilizing bispecific Fab in discovery stage.

Summary (1)



New antibody engineering technologies enables expansion of druggable target and invention of unique modes of action

Summary (2)

CHUGAI

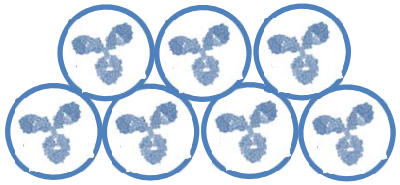
Roche Roche Group

Recycling antibody®
Sweeping antibody®
etc

- Satralizumab
- Nemolizumab
- SKY59 (crovalimab)
- AMY109
- GYM329/RG6237

- ❑ SMART-Ig®
- ❑ ACT-Ig®
- ❑ SMART-Fc®
- ❑ TwoB-Ig®
- ❑ pI-Fc™
- ❑ ACT-Fc
- ❑ ΔGK™

Bispecific antibody (1st, 2nd and 3rd generation)

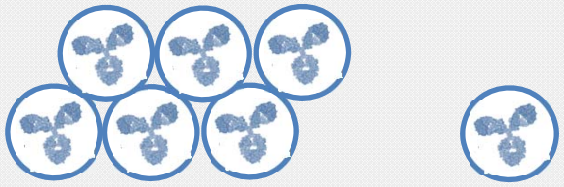


- ERY974
- NXT007

HEMLIBRA

- ❑ ART-Ig®
- ❑ FAST-Ig™
- ❑ TRAB®

Switch Antibody™



- ❑ Switch-Ig®

NEW technology etc

etc

- ❑ XXX
- ❑ YYY
- ❑ ZZZ

Discovery | Preclinical | Clinical | Launched

Licensable Antibody Engineering Technologies

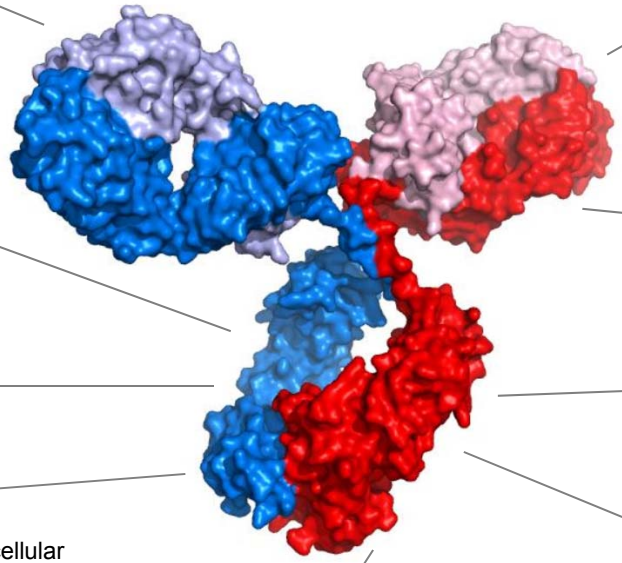
CHUGAI
Roche Roche Group

SMART-Ig®
Creates the Recycling Antibody®, which is designed to achieve a longer duration of action than conventional antibodies by binding to an antigen multiple times.

SMART-Fc®
Creates the Sweeping Antibody®, which eliminates soluble antigens from plasma.

ACT-Ig®
Reduces clearance from plasma.

ART-Fc®
Expected to enhance the antibody-dependent cellular cytotoxicity (ADCC) activity and/or antibody-dependent cellular phagocytosis (ADCP) activity by improving the binding activity of the antibody to specific type of FcγRs. Potential applications in the oncology field.



ΔGK™
Makes manufacturing process less complex. Removes heavy chain C-terminal amino acids (glycine and lysine). This technology reduces the heterogeneity of IgG antibody and can be widely applicable to IgG antibodies.

ART-Ig®/FAST-Ig™
Enable large-scale production of bispecific IgG antibodies which bind to two different antigens. Eliminates complex downstream process and enables highly efficient manufacturing process.

TRAB®
Activates T cells in an antigen-dependent manner to specifically kill cancer cells without non-specific FcγR dependent T cell activation.

TwoB-Ig®
Increases binding selectivity of the Fc region to inhibitory Fcγ receptor IIb. Potential applications in autoimmune diseases and other areas.

pI-Fc™
Improves agonistic activity or efficiency of soluble antigen elimination from plasma through the facilitation of Fc-FcγR interaction. Enhances the potency when used in combination of SMART-Fc®/TwoB-Ig®

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