CHUGAI
Antibody Engineering Technology

INNOVATION BEYOND IMAGINATION



Application of Chugai Antibody Technology

Type of Engineered Antibody	Description	Component Technologies
Recycling antibody	Antibody that binds to the antigen multiple times and has long-lasting efficacy	SMART-Ig, ACT-Ig
Sweeping antibody	Antibody that can enhance elimination of the antigen from plasma	SMART-Ig, SMART-Fc, TwoB-Ig, pI-Fc, ACT-Ig
Bispecific antibody	Bispecific antibody with controlled heavy and light chain pairing and improved manufacturability	ART-Ig, FAST-Ig
T cell bispecific antibody	Bispecific IgG antibody targeting tumor-associated antigen and TCR complex with reduced FcγR binding or modified CD3/CD137 binding	TRAB, ART-Ig, FAST-Ig, Dual-Ig
FcγRIIb enhanced antibody	Antibody Fc region with enhanced or selective binding to inhibitory FcγRIIb	TwoB-Ig
ADCC/ADCP enhanced antibody	Antibody Fc region with enhanced binding to activating FcγRIIa and FcγRIIIa	ART-Fc, ART-Ig
Half-life extended antibody	Antibody with reduced nonspecific clearance	ACT-Ig
Heavy chain C-terminal homogeneous antibody	Antibody with C-terminal GK deleted heavy chain for minimizing heterogeneity	ΔGK
Tissue environment targeting antibody	Antibody that binds to antigen tissue-environment specifically	Switch-Ig, Pac-Ig VHH
Fab linked antibody	Antibody having modified agonistic activity	LINC-Ig

Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

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SMART-Ig® (Sequential Monoclonal Antibody Recycling Technology - Immunoglobulin)

Stage: Launched

SMART-Ig® is a technology for isolating antibody capable of dissociating the antigen in endosomes with improved antibody pharmacokinetics or increased antigen clearance by means of introducing mutations into the antigen binding domain of an antibody so as to have pH or calcium ion dependent antigen binding and/or by means of identifying and selecting an antibody with pH or calcium ion dependent antigen binding from antibody display library or animal immunization.

In general, an antibody taken up by cells can be captured by FcRn in the endosome and recycled back to plasma, which allows the antibody to have a long plasma half-life. However, a conventional antibody binding to a membrane-associated antigen is transferred to lysosome and degraded with the antigen, leading to a short plasma half-life of the antibody, and a conventional antibody binding to a soluble antigen can be recycled back to plasma by FcRn as an antibody-antigen complex, which would accumulate the antigens in plasma and require a large amount of antibodies for long-term antigen neutralization.

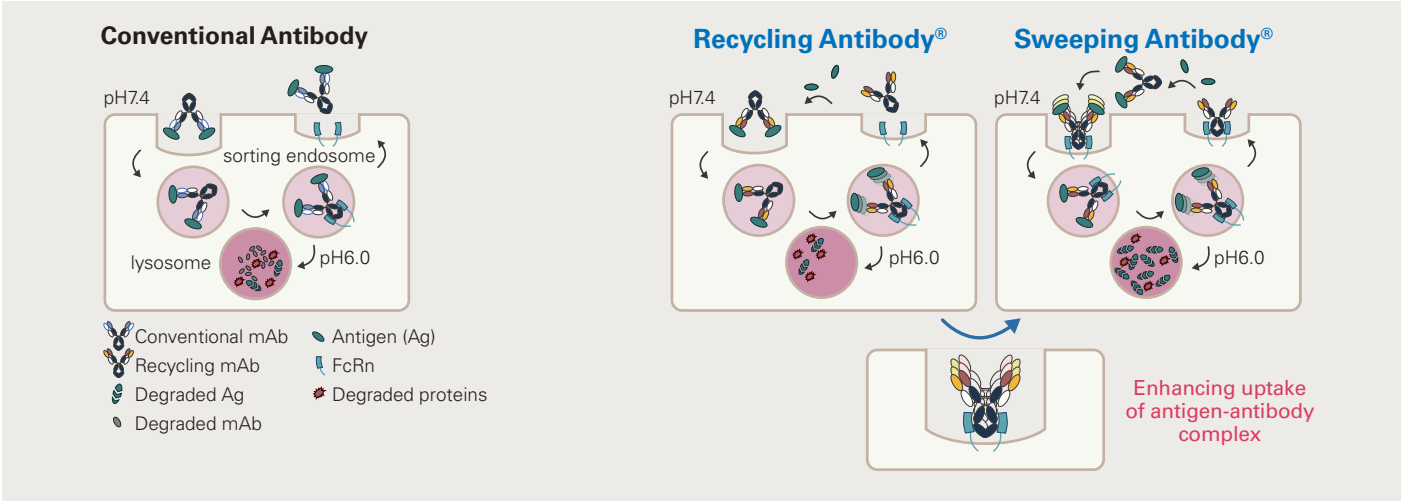
SMART-Ig® is a key technology for creating a Recycling Antibody®, which binds to its target antigens multiple times and has longer-lasting efficacy, by allowing the antibody to dissociate from the antigens in the endosome, leading to efficient FcRn-mediated salvage of the antigen-free antibody back to plasma and lysosomal degradation of the dissociated antigens.

SMART-Fc® (Sequential Monoclonal Antibody Recycling Technology - Fc region)

Stage: Clinical

SMART-Fc® is a technology for enhancing the uptake of antibody-antigen immune complex into the cell to increase the rate of antigen degradation by means of Fc engineering to increase binding affinity to FcRn or FcγR and/or by means of identifying and selecting for one or more antibodies which can form antibody-antigen immune complex containing two or more such antibodies and/or by means of antibody engineering to increase binding affinity to saccharide chain receptor. SMART-Ig® and SMART-Fc® are key technologies for creating a Sweeping Antibody®, which can eliminate or sweep its soluble antigens present in plasma.

A Sweeping Antibody® has a higher capacity for antigen neutralization and can achieve a smaller dose with a longer dosing interval that cannot be achieved by conventional antibodies. Moreover, even if bioactivity of the antigen cannot be neutralized by antibody's binding, a Sweeping Antibody® can be effective by directly eliminating antigens from plasma, giving it potential for a wide range of applications in medicines.

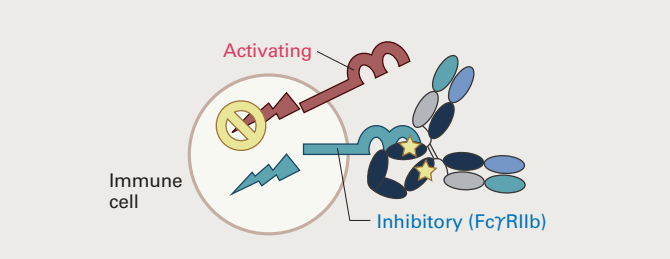


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TwoB-Ig® (FcγRIIb Selective Binding Technology - Immunoglobulin)

Stage: Clinical

TwoB-Ig® is a technology for providing various therapeutic applications through FcγRIIb binding. This technology selectively increases binding affinity of the Fc region to inhibitory FcγRIIb over activating Fcγ receptors including FcγRIIa, FcγRI, and FcγRIIIa by introducing mutations in the Fc region to prevent a risk of inducing platelet activation and aggregation caused by enhanced FcγRIIa binding. FcγRIIb is the only inhibitory Fcγ receptor, and contains an immune-receptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic domain. TwoB-Ig® provides various therapeutic applications such as enhancing agonistic activity or improving efficiency of soluble antigen elimination from plasma using SMART-Ig® /SMART-Fc®.



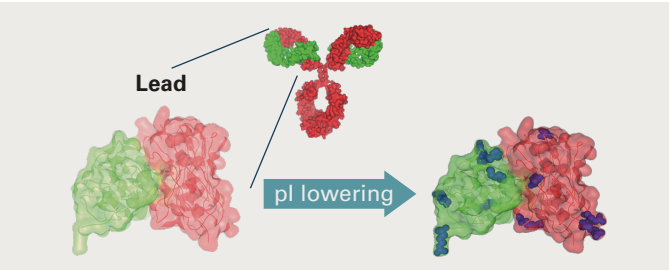
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ACT-Ig® (Antibody Clearance controlling Technology – Immunoglobulin)

Stage: Launched

ACT-Ig® is a technology for controlling antibody pharmacokinetics. This technology modify pI and/or charge characteristics of the antibody and/or optimize FcRn binding by introducing mutations into the antibody. Lowering or increasing the pI makes an antibody become more negatively or positively charged, so as to decrease or increase its nonspecific uptake into a cell through pinocytosis, respectively. Our Fc engineering moderately enhances FcRn binding for improved efficiency of antibody salvage from endosomes without increasing binding to rheumatoid factor autoantibodies.

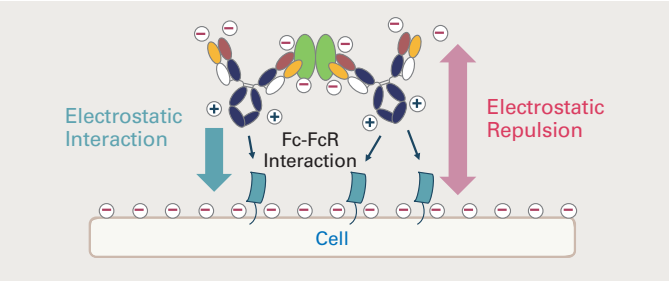


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- *Maeda A, Iwayanagi Y, et al. Mabs 9: 844-853 (2017)*
- *Sampei Z, Igawa T, et al. PLoS One 8: e57479 (2013)*
- *Sampei Z, Haraya K, et al. PLoS One 13: e0209509 (2018)*

pI-Fc® (pI modified Fc region)

Stage: Clinical

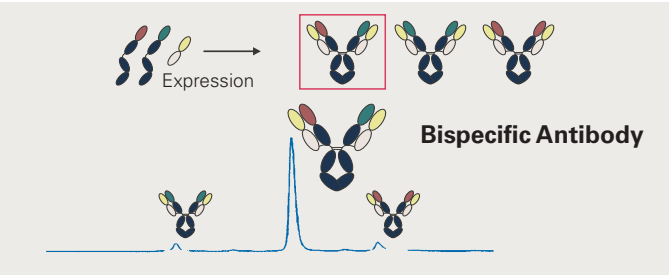
pI-Fc® is a technology for improving agonistic activity or efficiency of soluble antigen elimination from plasma. This technology modifies pI and/or charge characteristics of the Fc region by introducing mutations. The pI-increased Fc region can help the interaction between the antibody and cell membrane-associated molecules including FcγRs and thus improve agonistic activity or antigen sweeping efficacy when combined with TwoB-Ig® or SMART-Ig® /SMART-Fc®.



ART-Ig® (Asymmetric Re-engineering Technology - Immunoglobulin)

Stage: Launched

ART-Ig® is a technology for enabling purification and manufacturing of an asymmetric IgG antibody including a bispecific IgG antibody, which includes three antibody engineering technologies: 1) identifying a common light chain by framework/CDR shuffling to reduce the number of combinations of the heavy and light chains; 2) creating pI or charge characteristic difference between the target asymmetric antibody and the symmetric byproducts by introducing mutations in the two heavy chains to facilitate purification of the target asymmetric IgG antibody; and 3) facilitating heavy-chain heterodimerization by introducing electrostatic steering mutations in the two heavy chains to achieve preferential expression of the target asymmetric IgG antibody with high manufacturing productivity. The application of these three technologies enabled efficient and high-quality production of the bispecific IgG antibody.

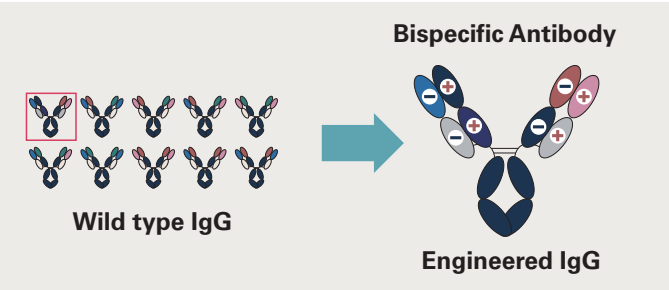


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FAST-Ig™ (Four-chain Assembly by electrostatic Steering Technology - Immunoglobulin)

Stage: Preclinical

FAST-Ig™ is a technology for enabling purification and manufacturing of a four-chain asymmetric IgG antibody including a four-chain bispecific IgG antibody with non-common light chains. This technology facilitates precise assembly of the two heavy and two light chains by introducing electrostatic steering mutations in the heavy and light chains, which can be widely applicable to asymmetric IgG antibody manufacturing without identifying a common light chain.



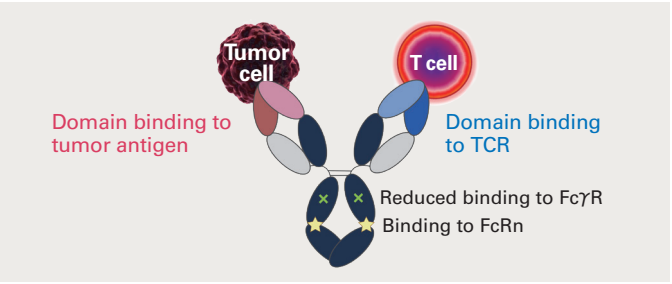
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TRAB™ (T cell Redirecting Antibody)

Stage: Clinical

TRAB™ is a technology for a bispecific IgG antibody that redirects T cells to cancer cells to activate T cells in a tumor antigen-dependent manner and kill cancer without causing FcγR-dependent T cell activation. This technology creates a bispecific IgG antibody targeting a tumor antigen and TCR complex having mutations in its Fc region to reduce the FcγR-binding activity. Presence of an Fc domain with reduced FcγR binding allows convenient dosing without cancer antigen independent T cell activation. This technology can be widely applicable to T cell bispecific antibody drug discovery.

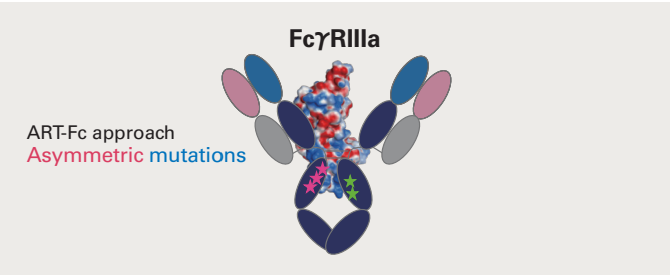


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ART-Fc® (Asymmetric Re-engineering Technology - Fc region)

Stage: Preclinical

ART-Fc® is a technology for enhancing the antibody-dependent cellular cytotoxicity (ADCC) activity and/or antibody-dependent cellular phagocytosis (ADCP) activity. This technology enhances the binding activity of the antibody to FcγRIIIa and/or FcγRIIa and creates an antibody having superior effector function by introducing "asymmetric" mutations in the Fc region of the antibody. "Asymmetric" mutations in the Fc region, the unique feature of the technology, allow superior FcγR-binding profile compared with previously reported symmetric mutations or Fc glycosylation engineering.

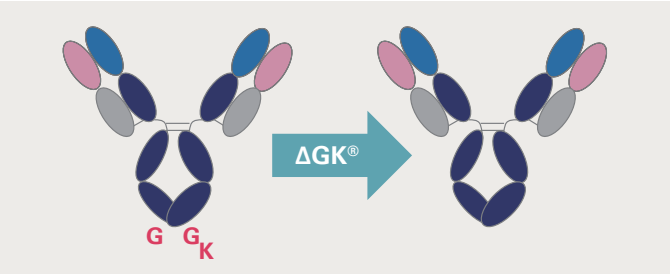


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ΔGK® Technology (IgG antibody with C-terminal glycine-lysine deleted)

Stage: Launched

ΔGK® is a technology for making quality control in manufacturing process less complex. The C-terminal sequence of the antibody heavy chain, -SLSLSPGK or -SLSLSLGK can be digested and amidated by endogenous enzymes in the course of cell culture and antibody production. This technology reduces heterogeneity of an IgG antibody by genetically deleting the C-terminal "GK (Gly-Lys)" sequence, and enables the detection or capture of the antibody using an anti-ΔGK® antibody. This technology can be widely applicable to IgG antibodies and is especially effective when the manufacturing process is complex or assessing the purity is challenging.

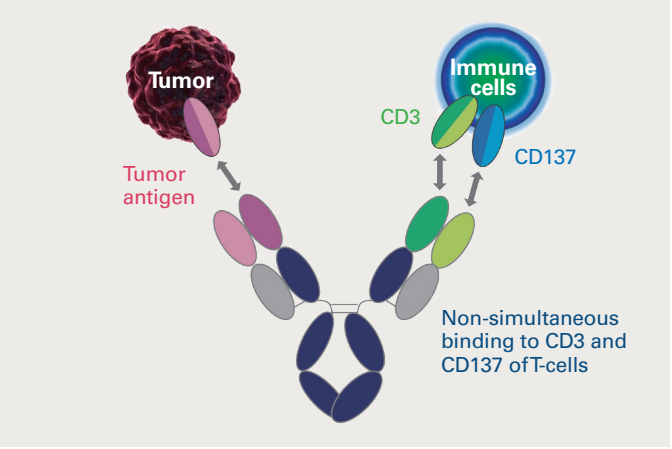


- *Sampei Z, Haraya K, et al. PLoS One 13: e0209509 (2018)*
- *Shiraiwa H, Narita A, et al. Methods 154: 10-20 (2019)*

Dual-Ig® (Dual effector/receptor redirecting-Immunoglobulin)

Stage: Preclinical

Dual-Ig® is the second generation of T cell recruiting antibody. It recognizes both a cancer antigen and the T cell antigens CD3 and CD137, which can activate T cells in an antigen-dependent manner to specifically kill cancer cells. Compared to the conventional CD3 based T cell recruiting antibodies, the additional CD137 agonist activity could further enhance and maintain the cytotoxic activity towards cancer cells and resulting in sustained patient response. The binding activity of the Dual-Ig® antibody towards CD3 and CD137 is designed in a single Fab. This Dual Fab is able to bind and activate either CD3 or CD137 non-simultaneously, which prevents tumor antigen independent T cell activation through crosslinking of two immune cells. The simple design of the Dual Fab allows easy conversion of conventional T cell recruiting antibodies into Dual-Ig antibodies.

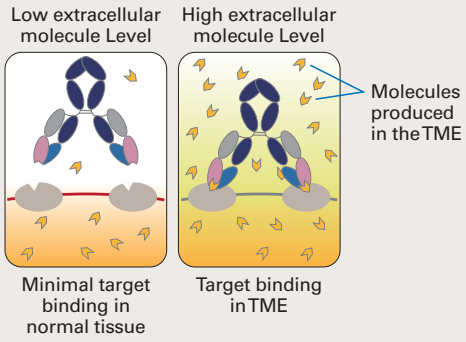


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Switch-Ig™ (SamII molecule dependent antigen binding antibody)

Stage: Clinical

Switch-Ig™ enables binding of antibody to target antigen selectively in tumor microenvironment (TME), leading to a larger therapeutic window, while conventional antibody binds to target antigen in both tumor and normal tissues. The property of Switch-Ig™ is achieved by our proprietary antibody engineering technology that allows antibody to bind to the target antigen only in the presence of extracellular molecules(e.g. ATP) which is selectively present in TME.

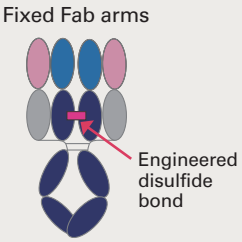


• *Mimoto et al. Cell Reports 33: 108542, (2020)*

LINC-Ig® (Ligating receptors through Interconnected Fab empowers New Connectivity to Immunoglobulin)

Stage: Preclinical

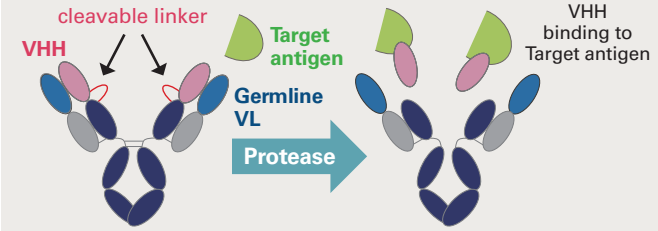
LINC-Ig® is a technology that improves antibody activity by introducing mutations into the constant region of Fab to control Fab mobility. By reducing the mobility between Fabs, the antibody becomes more fixed form and alter the distance between antigens. This technology will be especially effective for an agonistic antibody for which it is difficult to improve activity. In addition, this technology can be easily combined with other technology like Dual-Ig®, and improve the selectivity against antigens on cell surface.



PAC-Ig® VHH (Protease activated-Immunoglobulin, VHH release)

Stage: Preclinical

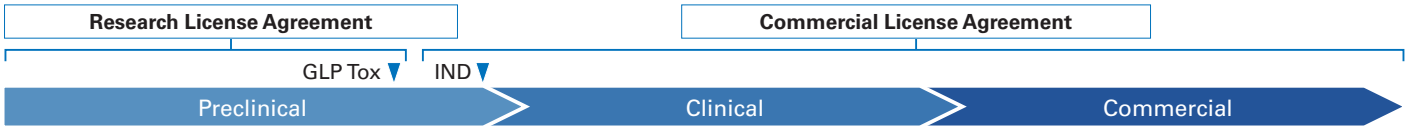
PAC-Ig® VHH is a technology that releases VHH disease site-specifically. VHH domains are fused to antibody domain via protease cleavable linkers and VHH domains do not bind to target antigen due to steric hindrance by antibody domain before cleavage. When this molecule enters disease site, proteases, which are expressed around disease site, cleave the linkers so that VHH domains are released from antibody domain and can bind to target antigen. Even when released VHH leaks out from disease site to circulation, it is subjected to renal clearance due to its small molecular size and thus systemic exposure can be minimized.



Licensing Process



Licensing Scheme



Feasibility Study Agreement

- Non-exclusive use for research before entering into GLP Tox.
- Target registration to secure future patent license, through third-party gatekeeper if requested.
- Annual fee for technology access.

Commercial License Agreement

- Worldwide non-exclusive right on a product-by-product basis.
- For several technologies, certain targets are excluded for licensing, which can be confirmed through third-party gatekeeper.
- Upfront, development milestones, royalty.

Contact us

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Chugai Partnering

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Type of Engineered Antibody	Reference No.
Recycling antibody	1, 2, 3
Sweeping antibody	4, 5
Bispecific antibody	6, 7, 8
T cell bispecific antibody	7, 8, 9
FcγRIIb enhanced antibody	10, 11, 12
ADCC/ADCP enhanced antibody	6, 13, 14
Half-life extended antibody	15, 16
Heavy chain C-terminal homogeneous antibody	6, 7
Tissue environment targeting antibody	17, 18
Fab linked antibody	None

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