

Chugai's Proprietary Technologies

Through continuous development of advanced technologies, Chugai has built a solid technology platform that gives it powerful advantages. This section introduces some of Chugai's innovative antibody technologies for enabling the generation of antibodies unrivaled by competitors.

SMART-Ig Recycling antibody and sweeping antibody technology

Sequential Monoclonal Antibody Recycling Technology - Immunoglobulin

A conventional antibody derived from known technology, regardless of how high its affinity to a target antigen is, has two limitations: 1) the antibody can bind to the antigen only once; and 2) the antibody can only bind to the antigen and cannot eliminate it from plasma. SMART-Ig, developed by Chugai, is an entirely new

technology that overcomes these two limitations. It enables the targeting of previously untargetable antigens and achieves a product profile that previously could not be realized with a conventional antibody.

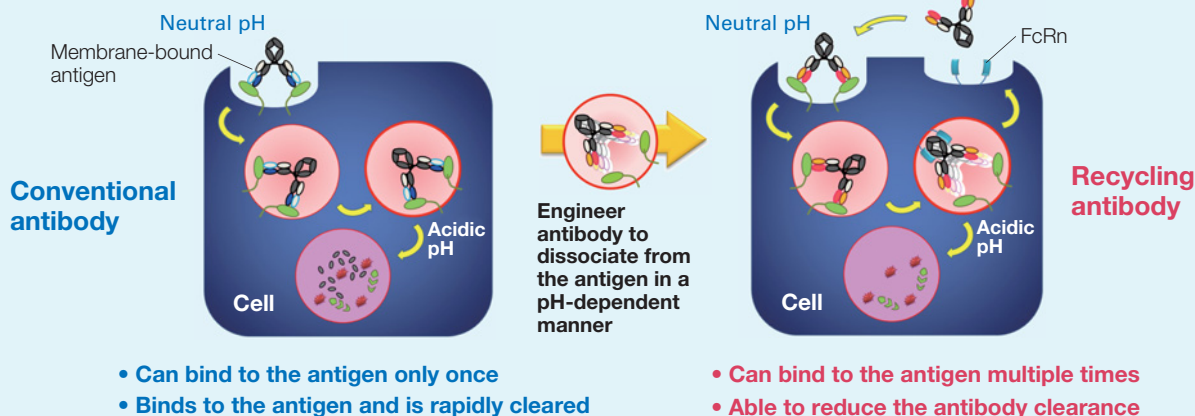
Recycling Antibody

The recycling antibody is engineered so that a single antibody molecule can bind to an antigen multiple times. Binding to the neonatal Fc receptor (FcRn) after being taken up by vascular endothelial cells or other cells contributes to a long half-life for an antibody in plasma compared with other proteins by recycling the antibody back to plasma. However, when a conventional antibody binds to a membrane-bound antigen such as a cytokine receptor, the antibody-antigen complex is transferred to lysosome and degraded by protease. In the case of a soluble antigen such as a cytokine ligand,

the antigen bound to the antibody is recycled back to plasma by FcRn as an antibody-antigen complex. Since antigens would be degraded by lysosome in the absence of the antibody, the antibody would accumulate the antigens in plasma, requiring administration of a large amount of antibodies for long-term blockade of the antigen function.

Conversely, the recycling antibody has been engineered to dissociate from an antigen in acidic conditions within the cell. Since the antibody bound to a membrane-bound antigen dissociates from the antigen

Effect of Recycling Antibody on Membrane-Bound Antigen

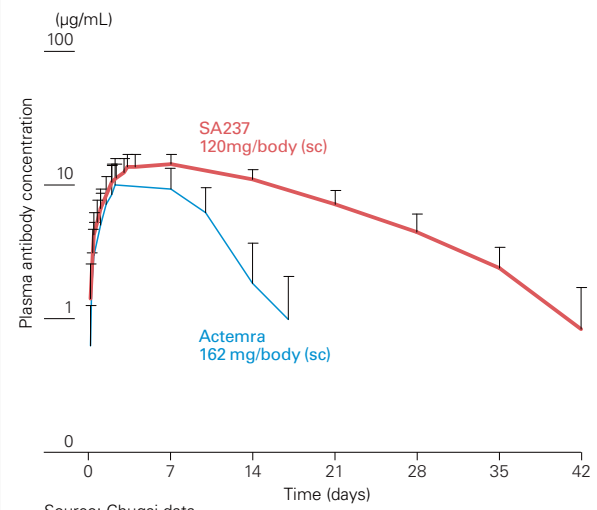


in a pH-dependent manner, a dissociated antibody would be recycled by FcRn while the antigen is transferred to lysosome and degraded, enabling the antibody to bind to other antigens repeatedly in plasma and reducing the antibody clearance.

This antibody technology arose from an idea to prolong the duration of efficacy of Actemra. The engineering of Actemra led to the generation of SA237 (currently in phase III multinational study). In preclinical studies, SA237 exhibited plasma persistence four times that of Actemra, and a phase I clinical trial has demonstrated significant improvement in the effective duration. SA237 is being developed as a subcutaneous formulation with the potential to achieve the convenience of a dosing interval of longer than once a month.*

* Actemra has been approved for the treatment of rheumatoid arthritis in Japan. A drip infusion formulation for once-a-month administration and a subcutaneous formulation for administration every other week were approved in 2008 and 2013, respectively.

Comparison of Plasma Persistence of SA237 and Actemra

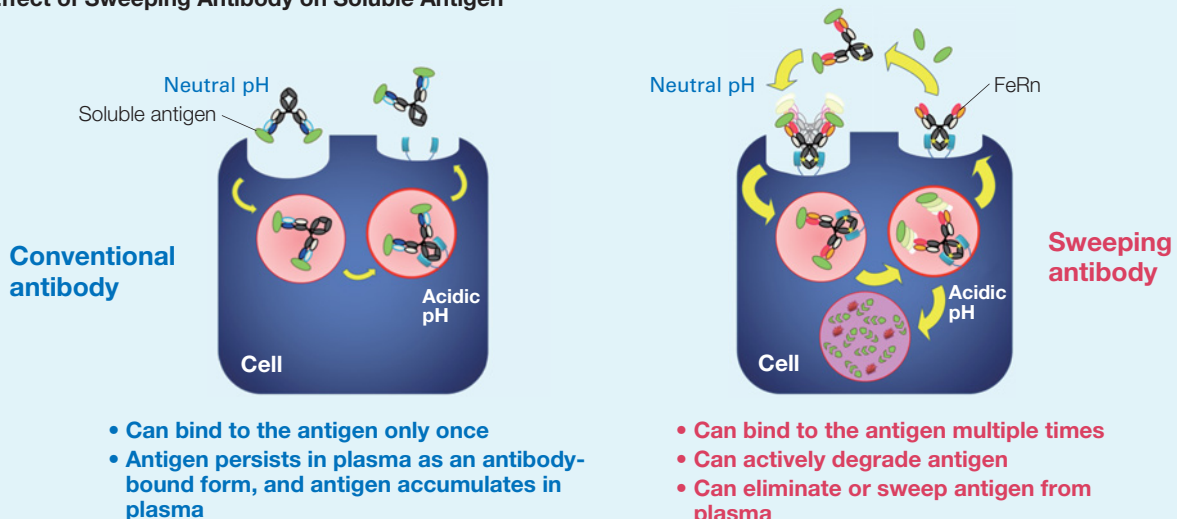


Sweeping Antibody

The sweeping antibody is a recycling antibody that has been further engineered to bind to FcRn at neutral pH. Accordingly, when the target is a soluble antigen present in plasma such as cytokine, the antigen bound to the antibody is actively taken up into the cell by FcRn. This accelerates the turnover rate of antigen degradation, enabling the antibody to eliminate, or sweep, the antigen from plasma. In addition, by modulating the binding affinity for FcRn to modify the turnover rate, the sweeping antibody can be customized with properties appropriate to the antigen or disease it targets.

With these characteristics, a sweeping antibody can be administered in smaller doses with a longer dosing interval that cannot be achieved by conventional antibodies, and it can antagonize antigens present in large amounts in plasma that cannot be antagonized by conventional antibodies. Moreover, even if it does not block an antigen's activity by binding with it, a sweeping antibody can be effective by directly eliminating antigens from plasma, giving it potential for a wide range of applications in medicines.

Effect of Sweeping Antibody on Soluble Antigen



ART-Ig Bispecific antibody manufacturing technology

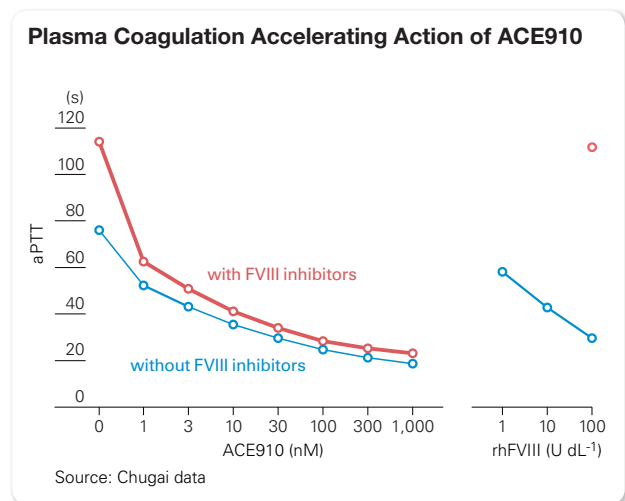
Asymmetric Re-engineering Technology - Immunoglobulin

A conventional IgG antibody has two antigen binding sites that bind to the same antigen. In contrast, a bispecific antibody (BiAb) has two different binding sites consisting of two different heavy chains and two different light chains, which can respectively bind to two different antigens. Due to various issues regarding the manufacturability of BiAb, no recombinant immunoglobulin G (IgG) BiAbs have been approved yet. However, Chugai's antibody engineering technologies have enabled large scale manufacturing of BiAbs, resulting in the generation of a BiAb expected to treat hemophilia A.

With many years of experience and expertise in the field of hematology, including research into erythropoiesis stimulating agent (ESA) and granulocyte-colony stimulating factor (G-CSF), Chugai felt a sense of mission in dealing with hemophilia, an area of high unmet medical needs. Hemophilia A results from an inherited deficiency or a functional abnormality in clotting factor VIII (FVIII) that causes bleeding disorder. Replacement therapy with concentrates of FVIII is the most common treatment, but problems with the therapy include the need for frequent intravenous injections (three times a week) and the creation of antibodies that neutralize FVIII activity. To deal with these issues, Chugai began development of ACE910 (phase I/II clinical trials currently under way in Japan), a BiAb that mimics the cofactor function of FVIII by binding to factor IX (FIX) and factor X (FX). Large-scale manufacturing of BiAbs results in many different antibody species, making the manufacturing of highly pure target BiAb nearly impossible. Chugai overcame this problem with a proprietary technology called ART-Ig. ART-Ig incorporates three antibody

engineering technologies: 1) introduction of a common light chain to reduce the number of combinations of light and heavy chains; 2) introduction of difference in the charges of two heavy chains to facilitate purification of the target BiAb; and 3) use of electrostatic steering of the two heavy chains to facilitate expression of the target BiAb. The application of these three technologies resulted in a process capable of producing a target BiAb on a 2,500-liter scale with productivity and purity similar to conventional antibodies.

The establishment of ART-Ig technology has enabled the use of IgG BiAbs as a practical method for drug discovery. As such, it is expected to lead to the generation of drugs with a new mode of action that enhances efficacy by simultaneously binding with two types of antigen or provides new pharmacology by bridging two antigens.



Differences between Conventional Antibody and Bispecific Antibody

