FOCUS 1
Evolution of Antibody Engineering Technologies

Maximize the value of drug targets → **Create drugs for undruggable targets and modes of action**

From 1990	From 2005	From 2008	From 2012	From 2018
Humanized antibodies	**Engineering to create best-in-class antibodies** • Stability improvement • Pharmacokinetic improvement • Deimmunization beyond humanization • ADCC[1]/ADCP[2] enhancement	**Engineering to create antibodies with unique modes of action** • Bispecific antibody • Recycling antibody® • Sweeping antibody® • FcγRIIb selective Fc • T cell redirecting antibody (TRAB®)	**Engineering to confer disease tissue/cell specificity** • Switch Antibody™ • Second-generation TRAB® • Others	**Engineering to expand sites of action**

1. Antibody-dependent cellular cytotoxicity 2. Antibody-dependent cellular phagocytosis

Positioning of Antibody Engineering Technologies at Chugai

Chugai has three modalities (therapeutic approaches) in drug discovery research: small molecules and antibodies, in which it has proven strengths and accomplishments, and middle molecules, in which it is focusing on the establishment of new technology. In therapeutic antibodies, we have demonstrated our drug discovery capabilities by creating many innovative medicines and developing proprietary technologies. Now, we are taking these capabilities further.

Innovation of therapeutic antibodies will require an evolution in technologies such as antibody engineering, biology and platforms. "Biology" refers to deep understanding of pathology and the investigation of target molecules and modes of action. "Platforms" are the research infrastructure that we have systematically established. We have clear competitive advantages in platforms in particular, including a high-throughput system for obtaining candidate antibodies; COSMO,[3] a system that enables optimization of candidate antibody molecules ten times faster than was possible just a few years ago; and a deimmunization platform.[4] These platforms allow us to rapidly and efficiently actualize and evaluate drug discovery ideas that utilize our proprietary technologies.

Our antibody engineering technologies have steadily changed and advanced since we began working on creation of humanized antibodies in 1990. In contrast to previous technologies for improving properties such as pharmacological activity and pharmacokinetics, our initiatives in recent years have involved technologies that significantly change our overall approach to drug discovery through unique modes of action and cell specificity, and are expanding the possibilities for using therapeutic antibodies in medicine.

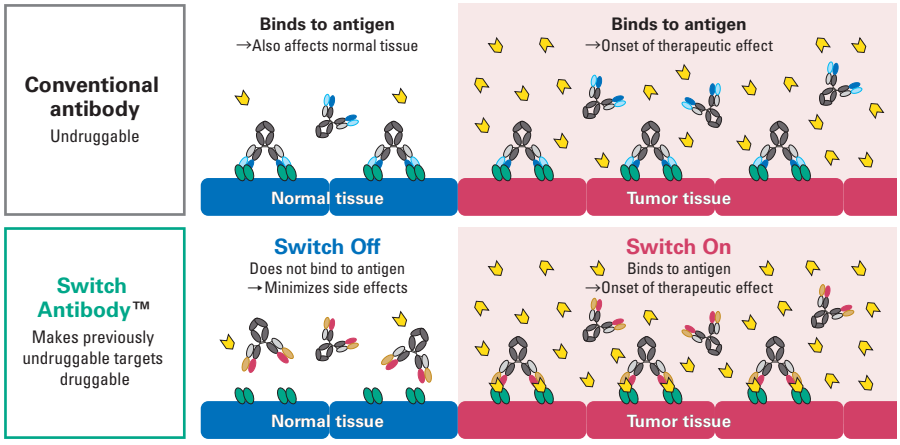
3. Acronym of COmprehensive Substitution for Multidimensional Optimization
4. A research platform technology to evaluate the immunogenicity of proteins containing antibodies in order to minimize the risk of anti-drug antibody production in the clinical setting.

Applications of New Antibody Engineering Technologies

1) Expanding the Scope of Drug Discovery

Chugai's novel antibody engineering technologies open up two promising directions in drug discovery. One direction makes it possible to approach new targets that were previously undruggable with the Recycling antibody, bispecific antibodies and other existing technologies.

Switch Antibody™



: Switch molecule. Expressed in high concentrations in tumor tissue.

Projects Utilizing New Antibody Engineering Technologies

	Discovery	Preclinical	Clinical		Launched
Recycling antibody® Sweeping antibody® Others	2	1	• satralizumab • SKY59 (crovalimab) • GYM329/RG6237	• nemolizumab • AMY109	
Bispecific antibodies (1st, 2nd and 3rd generation)	7		• ERY974	• NXT007	• Hemlibra
Switch antibody™	6	1			
Antibodies applying other new technologies	2	1			

Our Sweeping antibody is a recycling antibody engineering technology that has been further engineered to eliminate, or sweep, target antigens from plasma. By combining the Sweeping antibody with technologies including TwoB-Ig, which selectively increases binding to an Fc receptor called FcγRIIb, we successfully moved in-house project GYM329 into clinical development in 2018.

A noteworthy new technology that we announced in 2019 is the Switch antibody (small molecule-dependent antigen binding). One of the remaining challenges in the development of antibody drugs is on-target toxicity, in which toxicity increases in normal tissue when the antibody binds to the target molecule. Severe toxicity has been observed in projects by many pharmaceutical companies, in some cases resulting in the cancellation of development. Chugai's Switch antibody is a technology that solves this problem. By focusing on a small molecule (the switch molecule) called adenosine triphosphate (ATP), which is present at high extracellular concentrations in tumors, the Switch antibody is designed to "switch on," or bind to the target antigen, only in a tumor microenvironment, where the concentration of extracellular ATP is high, but to "switch off," or not bind to the antigen, in normal tissue, where the concentration of extracellular ATP is low. As a result, target molecules that have been undruggable due to the increase in toxicity can be made druggable, greatly extending the boundaries of drug discovery. We are currently conducting discovery projects utilizing this technology. One project is scheduled to enter clinical development in 2020 and six more are in the discovery stage.

2) Creating Novel Modes of Action

The other promising direction that we want to explore with new antibody engineering technologies is the creation of novel modes of action. By combining technologies such as the next-generation bispecific antibody and the Switch antibody, we will further broaden the possibilities for innovative drug discovery, with our sights set on curing or completely managing diseases.

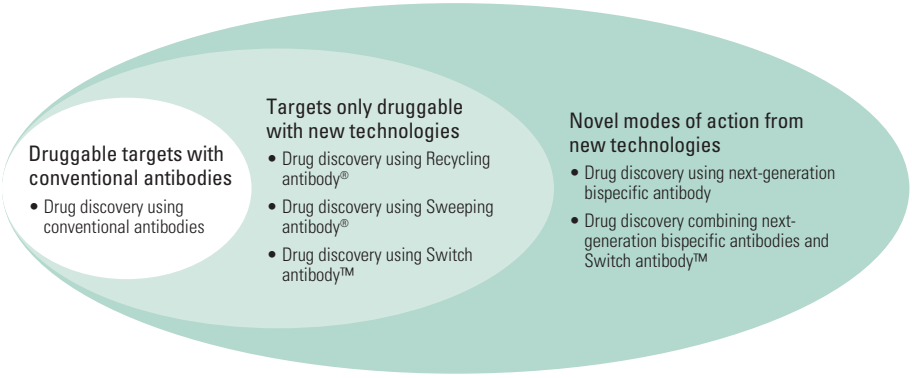
The first-generation bispecific antibody engineering technology used in Hemlibra has common light chains, but the second-generation technology uses different light chains to make more diverse antibody designs possible. The third-generation technology enables antibodies to not only bind to two types of antigens, but also to control the form of bonding with two different antigens. Moreover, while our Switch antibody switches on or off in response to ATP concentration, it can also be engineered to do the same for changes in concentration of other small molecules in specific environments. This will make it possible to target not only cancer, but a wide range of other diseases, and to actualize innovative drug discovery ideas.

When these drug discovery approaches become possible, coming up with ideas will be even more important. In addition to further developing its technologies, Chugai is working to accelerate generation of new ideas through a focus on biology research, TACTICS, and other initiatives. We believe that these initiatives will be essential for maximizing the use of our antibody discovery technologies, for which the possibilities are broadening further.

For details on new antibody technologies, refer to the Information Meeting on Antibody Engineering Technologies (webcast) held on December 9, 2019.

https://www.chugai-pharm.co.jp/english/ir/reports_downloads/presentations.html#sec_85

Application of Antibody Engineering Technologies



The Potential of Antibody Engineering – a Researcher's View

No technology can keep its competitive advantage for very long, no matter how great it is. Technologies must constantly evolve, and that requires utilizing and linking our stock of technologies and expertise. For example, realizing the Switch antibody technology was only possible because we had independently developed the Recycling antibody technology (pH-dependent antigen binding).

Such innovation cannot be achieved without overcoming numerous difficulties, but we are able to do so because we always have the patients in mind. In the creation of Hemlibra, our discovery research was driven by our strong belief that this drug would offer significant value to people with hemophilia and to their families, and that we absolutely had to make it available. Later on, the letters we received from people who had used Hemlibra made us very happy because they confirmed again that our aspirations during research had become a reality.

The purpose of our drug discovery research is to provide medicines that offer true value to patients and society. New antibody engineering technologies can also be expected to lead to the creation of drugs for diseases for which there are currently no treatments, and may lead to new biological discoveries and the innovation of treatment methods. We are striving to be a top innovator in the healthcare industry that contributes to patients and society not only through the innovative medicines we create, but also through the advancement of technology and life science.

Zenjiro Sampei
Head of Discovery Biologics Group 3, Discovery Biologics Dept.