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Future perspectives of therapeutic monoclonal antibodies

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Attention to therapeutic monoclonal antibodies has been dramatically increasing year by year. Their highly specific targeting of antigens can provide very effective medical treatment, and the advent of molecular-targeting medicine is allowing development of a new generation of therapeutic agents. However, there is one critical obstacle to overcome. Most of the established therapeutic monoclonal antibodies have specificity for the primary structures of target antigens, although all proteins harbor original native intact structures for their own specific functions. Stereo-specific monoclonal antibodies recognizing conformational structures of target antigens may thus offer a markedly more versatile approach. Their application may change the very concepts underlying use of therapeutic antibodies.

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Therapeutic monoclonal antibodies

The biopharmaceutical market, like the global pharmaceutical market, has been expanding every year and is expected to reach approximately 230 billion dollars in 2018, twice the sum in 2010 [1]. It is forecasted to be >380 billion dollars in 2024 [1]. Recombinant proteins, followed by therapeutic antibodies, have been the main contributors to the biopharmaceutical market in the past. However, in 2017 [2] the sales of antibody-based medicines took on the leading position, with expected sales of 172.8 billion dollars in 2022, about 20% of the global pharmaceutical market [2].

It is noteworthy that the range of therapeutic monoclonal antibodies has been remarkably increasing since the late 1990s, the total number approved by the US FDA reaching 64 in 2018 [2,3] (see [Table 1](#) list for those from 2015 to 2017). In 2017, a total of 11 therapeutic monoclonal antibodies were approved. There are interesting changes in the characteristics of the antibodies attracting attention. As shown in [Figure 1](#), the percentage of human and humanized antibodies in the total has dramatically increased. The reasons for continuous expansion of the market for therapeutic antibodies include an increase in the number of approvals, efforts to explore other target diseases for the already approved therapeutic antibodies, as well as improvements in formulations and dosage forms. Finding new target antigens will be of critical importance for further development of antibody-based medicines in the future.

Bispecific antibodies [6–10], antibody–drug conjugates [11], sugar chain-modified antibodies [12–15] and low molecular weight antibodies [6,16] are now being emphasized as next-generation products. Some bispecific antibodies and antibody–drug conjugates are already on the market, with emicizumab [17] as an example of the former, and gemtuzumab ozogamicin [18], inotuzumab ozogamicin [19] and brentuximab vedotin [20] featuring in the latter.

Advantages of stereo-specific monoclonal antibodies

There is another important point regarding further development of therapeutic monoclonal antibodies. A critical reason for their employment is their high specificity and affinity for targeted antigens. It is known that monoclonal antibodies can specifically recognize two types of epitopes ([Figure 2](#)). One is linear in the primary structures of

Table 1. The US FDA-approved therapeutic monoclonal antibodies from 2015 to 2017. 27 therapeutic monoclonal antibodies were approved by the US FDA from 2015 to 2017. The number has been increasing year by year.

Name of antibody	Brand name	Approved year	Target antigen	Target disease
Dinutuximab	Unituxin®	2015	GD2	Pediatric high-risk neuroblastoma
Idarucizumab	Praxbind®	2015	Dabigatran	Emergency reversal of anticoagulant dabigatran
Mepolizumab	Nucala®	2015	IL-5	Severe asthma
Elotuzumab	Empliciti®	2015	SLAMF7	Multiple myeloma
Nivolumab	Opdivo®	2015	PD-1	Metastatic melanoma
Secukinumab	Cosentyx®	2015	IL-17A	Plaque psoriasis
Evolocumab	Repatha®	2015	PCSK9	Heterozygous familial hypercholesterolemia, Refractory hypercholesterolemia
Alirocumab	Praluent®	2015	PCSK9	Heterozygous familial hypercholesterolemia, Refractory hypercholesterolemia
Necitumumab	Portrazza®	2015	EGFR	Metastatic squamous non-small-cell lung carcinoma
Daratumumab	Darzalex®	2015	CD38	Multiple myeloma
Obiltoxaximab	Anthim®	2016	<i>Bacillus anthracis</i> toxin	Inhalational anthrax
Ixekizumab	Taltz®	2016	IL-17A	Plaque psoriasis
Reslizumab	Cinqair®	2016	IL-5	Severe asthma
Atezolizumab	Tecentriq®	2016	PD-L1	Urothelial carcinoma
Olaratumab	Lartruvo®	2016	PDGFR	Soft tissue sarcoma
Bezlotoxumab	Zinplava®	2016	<i>Clostridium difficile</i> toxin B	Prevent recurrence of <i>C. difficile</i> infection
Gemtuzumab ozogamicin	Mylotarg®	2017	CD33	Acute myeloid leukemia
Ocrelizumab	Ocrevus®	2017	CD20	Multiple sclerosis
Inotuzumab ozogamicin	Besponsa®	2017	CD22	Precursor B-cell acute lymphoblastic leukemia
Emicizumab	Hemlibra®	2017	FIXa, FX	Hemophilia A (congenital Factor VIII deficiency) with Factor VIII inhibitors
Benralizumab	Fasenra®	2017	IL-5R α subunit	Severe asthma, eosinophilic phenotype
Brodalumab	Lumicef®, Siliq™, Kyntheum®	2017	IL17R	Plaque psoriasis
Avelumab	Bavencio®	2017	PD-L1	Metastatic Merkel cell carcinoma
Durvalumab	Imfinzi®	2017	PD-L1	Urothelial carcinoma
Dupilumab	Dupixent®	2017	IL-4R α	Atopic dermatitis
Guselkumab	Tremfya®	2017	IL-23	Plaque psoriasis
Sarilumab	Kevzara®	2017	IL-6R α subunit	Rheumatoid arthritis

The data are based on [3–5].

proteins. The other is conformational, dependent on secondary and tertiary structures. In addition to their primary, secondary and tertiary structures, proteins may also exhibit quaternary structures formed by hetero- or homosubunits, which provide unique interfacial geometries on their complexes. Intact native proteins mainly feature secondary and tertiary structures, but various kinds of monoclonal antibodies do not necessarily have specificity for conformational structures, although they have been raised against a large number of proteinous antigens.

Such specific recognition of conformational structures of proteins would be expected to give more strict selectivity and affinity for therapeutic purposes. Notably, stereo-specific monoclonal antibodies recognizing 3D configurations of molecules, offer advantages over linear epitope-specific monoclonal antibodies, which only recognize 2D configuration. Again we should stress that target antigens for therapy predominantly feature secondary and tertiary structures. Monoclonal antibodies recognizing primary structures can have affinity for only restricted regions in intact antigens, because linear epitopes can be masked by conformational folding. Thus, the employment of stereo-specific monoclonal antibodies should be our goal.

Figure 1. The US FDA-approved therapeutic monoclonal antibodies. 64 therapeutic monoclonal antibodies have been approved by the US FDA. The ratio of human and humanized monoclonal antibodies to the total sum of therapeutic monoclonal antibodies is increasing year by year.

Production of stereo-specific monoclonal antibodies against different proteins

The next point is how to produce stereo-specific monoclonal antibodies. Until very recently, no practical technologies have been available for their generation, because of difficulties like how to immunize a mouse maintaining the structure of the antigen intact in the presence of adjuvant. While adjuvants generally allow more effective sensitization, they usually disrupt the original protein native structure. If an adjuvant is not used, immunization efficiency may be very low. Another difficulty is strict selection of sensitized B lymphocytes secreting stereo-specific monoclonal antibodies. Even when immunization is successful with a native intact antigen, the number of desired sensitized B lymphocytes is usually extremely small, accounting for only a few percent of the total spleen cells after repeated immunization.

However, we have now established an original stereo-specific targeting (SST) technique [21–25]. The protocol promises efficient generation of stereo-specific monoclonal antibodies on the basis of hybridoma technology, as illustrated in [Figure 3](#). One of the critical points is strict selection of the required sensitized B lymphocytes by intact antigens expressed on myeloma cells through B-cell receptors (BCRs). This precise selection also enables efficient formation of B-cell and myeloma-cell complexes for generating hybridoma cells secreting the aimed for antibodies.

In general, proteins are divided into two categories, membrane associated and nonassociated. The former include receptors, membrane-anchored proteins and so on, whereas the latter are mainly soluble proteins present in intra- and intercellular spaces, as shown in [Figure 4](#). Regardless of which types of proteins are used, the important point for raising stereo-specific monoclonal antibodies is that the target antigens have to be recognized by the immune system while retaining native structures. For this purpose, the best method is DNA immunization to maintain intact conformational structures. It is recommended that target antigens be expressed on the surface of cells, because this location facilitates stable exhibition of intact conformational structures to the immune system. With soluble proteins, they can be tethered to membranes to mimic membrane proteins. Appropriate signal peptide and a membrane-penetrating domains are genetically attached in frame as nucleic acid sequences to the 5'- and 3'-terminals, respectively, of the genes for the desired soluble proteins so that they are expressed together.

The next point is the selection of sensitized B lymphocytes, where use of antigen-expressing myeloma cells seems to be the best option. There are several advantages. DNA-immunized B lymphocytes can be efficiently selected by a target intact antigen expressed on myeloma cells by harnessing strong and specific interactions between intact

Figure 2. Two types of epitopes. Epitope recognition by antibodies is generally divided into two types. One is linear epitope-specific recognition and the other is conformational or discontinuous epitope specific.

antigen and antibody (BCR). The antigens expressed on the myeloma cells must clearly keep their original intact structures. In this step, only B lymphocytes secreting stereo-specific monoclonal antibodies directed to the target antigens can be preferentially selected. Moreover, selected B lymphocytes combined together with myeloma cells have another advantage, since they can be selectively fused by electrical pulses to generate hybridoma cells secreting the desired stereo-specific monoclonal antibodies. Indeed, fusion by electric field is very specific, due to the fact that only attached cells can be selectively fused. B lymphocytes selected by antigen-expressing myeloma cells are preferentially fused without causing any undesired fusion among other unattached cells. Thus, successful generation of stereo-specific monoclonal antibodies is based on DNA immunization, selection of sensitized B lymphocytes by antigen-expressing myeloma cells and selective fusion of the B cell–myeloma cell complexes by electrical pulses.

As already noted, the SST technique features selective generation of stereo-specific monoclonal antibodies against various kinds of proteins for not only membranous antigens, but also nonmembranous soluble ones (Figure 4). Recently, Morshed *et al.* have shown that a stereo-specific monoclonal antibody was effective for activating the G-protein coupled receptor, which harbors seven transmembrane domains [26].

Conclusion

Critical points for employing monoclonal antibodies as therapeutic agents are their strict specificity and strong affinity for target antigens. From this viewpoint, conformational epitope-specific monoclonal antibodies offer clear advantages over conventional linear epitope-specific examples, since they maintain the original secondary and

Figure 3. Flowchart of stereo-specific targeting. DNA-immunized B lymphocytes are selected by antigen-expressing myeloma cells, followed by selective fusion by electrical pulses to generate hybridoma cells that can secrete stereo-specific monoclonal antibodies.

tertiary structures, which intrinsically determine their biological functions. Our new technology termed ‘SST’ features selective generation of conformation-specific monoclonal antibodies with high specificity and affinity. Characteristic is the use of strong and specific interactions between BCRs and intact antigens on myeloma cells. SST may also be applicable for new types of bispecific as well as catalytic antibodies. The new technology could greatly contribute to next-generation therapeutic medicine.

Future perspective

New types of bispecific antibody

Bispecific antibodies can recognize two distinct antigens, and have already been developed and used as therapeutic agents for carcinomas, leukemia and hemophilia [27–29]. To develop novel therapeutic bispecific antibodies, it is crucial to identify combinations of target molecules, which are appropriate for producing high-potency antibodies. The enzyme-mediated activation of radical source (EMARS) method reported by Kotani *et al.* is a technology to analyze bi-molecular complexes (hetero-protein complexes) formed on cell membranes under physiological conditions [30] and is also applicable to identifying cancer cell-specific bi-molecular complexes for preparing therapeutic bispecific antibodies against cancer cells. Since combinations of molecules are theoretically almost infinite, this might help overcome the current difficulty of finding candidate antigens in exploring novel therapeutic approaches.

Figure 4. Generation of stereo-specific monoclonal antibodies against all kinds of native proteins. Theoretically, the stereo-specific targeting technique is applicable to generating stereo-specific monoclonal antibodies against all kinds of native proteins. There are three critical steps: DNA immunization; selection of sensitized B lymphocytes by antigen-expressing myeloma cells; and selective fusion of B-cell and myeloma-cell complexes to generate hybridoma cells secreting stereo-specific monoclonal antibodies.

Bispecific monoclonal antibodies harboring stereo-specific recognition may be particularly effective for detecting membranous antigens on cancer cells, which are not easily recognized with conventional linear-specific monoclonal antibodies. Another potential advantage could be recognition of unique conformational structures lying in hetero-protein complexes, in addition to possible individual reactions with pairs of heteroantigens. Thus, detection of bi-molecular complexes as single molecular elements is conceivable, as shown in [Figure 5](#).

New catalytic antibodies

Another application of stereo-specific monoclonal antibody might be as catalytic agents. Recent extensive studies on catalytic antibodies have advanced so that practical applications are now on the horizon. As catalytic antibodies possess the ability not only to recognize but also to degrade antigens, they may exhibit unique characteristics superior to monoclonal antibody drugs. The Uda/Hifumi group has already demonstrated that the mouse-type catalytic antibody light chain could eradicate *Helicobacter pylori* infection in the mouse stomach [31]. The same group also succeeded in suppression of infection with the rabies virus [32] and the influenza virus [33] *in vitro* and *in vivo* using human antibody light chains. On the other hand, Paul's group reported very interesting catalytic antibody capable of reducing the β -amyloid accumulated in the mice brain [34,35]. The catalytic antibody specifically hydrolyzes the target antigen at site-specific recognition. We would also propose that recognition of stereo-specific epitopes by stereo-specific monoclonal antibodies may provide more specific and effective hydrolysis of aimed intact antigens on the cell membranes for new therapeutic medicine ([Figure 5](#)), if catalytic activity can be introduced thereto.

Figure 5. Advantages for conformational recognition. Recognizing conformational structures of intact proteins confers several advantages, promising therapeutic approaches to new regulation of functions of both mono- and multi-mer receptors, as well as novel bispecific and catalytic monoclonal antibodies.

New type of specificity

It is generally accepted that it is difficult to produce monoclonal antibodies against mouse antigens due to immune tolerance when mice are employed as immunization animals. This hampers analysis of disease-related important antigens in the mouse, a very good candidate model animal for many diseases. From the viewpoint of stereo-specific recognition, however, it is possible to cross-react with antigen in other species by recognizing common conformational structures. This has never been reported with linear epitope-specific monoclonal antibodies.

Executive summary

Therapeutic monoclonal antibodies

- The market for therapeutic monoclonal antibodies is increasing year by year.
- Characteristics of therapeutic stereo-specific monoclonal antibodies are high specificity and affinity for target antigens.

Recognition of conformational epitopes

- General monoclonal antibodies show specific affinity to primary structures of target antigens through 2D recognition.
- Stereo-specific monoclonal antibodies show strict specificity to secondary and tertiary structures of target antigens by 3D recognition.

Future therapeutic medicines

- Stereo-specific targeting may contribute to selective production of stereo-specific monoclonal antibodies.
- Stereo-specific recognition of target antigens may provide novel therapeutic approaches, since proteins retain intact conformational structures in nature.
- Stereo-specific targeting may also be applicable to new types of bispecific and catalytic antibodies.

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Ethical conduct of research

All experiments were conducted according to Mie University's guidelines for the care and treatment of experimental animals.

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