Patenting Monoclonal Antibodies in China: Criteria on Novelty and Inventiveness Examination

Featured Article

On November 21, 2020, the U.S. Food and Drug Administration issued an emergency use authorization for casirivimab and imdevimab to be administered together for the treatment of mild to moderate Covid-19 in adults and pediatric patients. Casirvimab and imdevimab are monoclonal antibodies that are specifically directed to target antigens (SARS-CoV-2 spike protein) with high specificity, effectiveness and safety. More, monoclonal antibodies ("mAb") are used to treat other diseases such as malignant tumors and autoimmune diseases, and continue to set off new technology hotspots in drug development, such as antibody-drug conjugates, bispecific antibodies, and immunosuppressive antibodies. Thus, protecting the underlying technology has been and continues to be a priority for pharmaceutical and biotechnology companies. In China, with the gradual relaxation of the requirements for supplementary data, novelty and inventiveness will be the most important evaluation indicators for whether claims covering monoclonal antibody products can be allowed. This article, taking account of a revised Guideline for Patent Examination (effective January 15, 2021), will describe the assessment criteria on novelty and inventiveness of monoclonal antibodies from several drafting ways for protecting monoclonal antibodies.

There are usually the following ways to draft a monoclonal antibody claim:

1. An antibody defined by hybridoma cells;
2. An antibody defined with antigen, epitope and/or function/performance parameters; or
3. An antibody defined by sequences.

I. Novelty

i. Rules

If an antigen known in the prior art and an antigen recited in a claim under examination have the same epitope, it is presumed that the monoclonal antibody of the known antigen can bind to the recited antigen. In such a case, the claim directed to a monoclonal antibody does not possess novelty except where the applicant can verify, according to the disclosure of the application or any knowledge in the art, that the claimed monoclonal antibody is different from that disclosed in the prior art applied in the examination. See, the Guideline for Patent Examination ("Guideline"), Part II, Chapter 10, §9.4.1.

ii. Case A: reexamination decision No. 112980, issued on August 10, 2016

Holding of the 112980 decision: If antigen A recited in a claim has the same amino acid sequence as the known antigen A' in the prior art, and it is impossible to distinguish the two antibodies against antigen A and antigen A' according to the prior art and the present application, it is presumed that the antibody against the known antigen A' can bind to the antigen A. Based on this presumption, the claimed antibody is not novel.

Claim 1 reads as "an antibody that selectively bind to intact procalcitonin 1 to 116 (SBQ ID NO:1)....."

Panel's opinions: D1 discloses a monoclonal antibody or polyclonal antibody that can selectively bind to intact procalcitonin 1-116. D1 has clearly pointed out that the precalcitonin bound by the first monoclonal antibody is a peptide composed of 116 amino acids. None of any counter evidence in the prior art can prove that the peptide composed of 116 amino acid residues is different from the claimed sequence. Meanwhile, according to the preparation of antibody described in the specification of this application, those skilled in the art cannot distinguish the claimed monoclonal antibody from that disclosed in D1. Therefore, the antibody claimed in claim 1 that selectively binds to intact procalcitonin 1 to 116 (SEQ ID NO:1) has been disclosed in D1. Thus, claim 1 is not novel and does not meet the requirements of Article 22, paragraph 2 of the Patent Law.

II . Inventiveness

(I) An antibody defined by hybridoma cells; or an antibody defined with antigen, epitope and/or function/performance parameters

i. Rules

If an antigen has been disclosed and it is clearly known that the antigen has immunogenicity (for example, said antigen clearly has immunogenicity because a polyclonal antibody of the antigen is known), a claim covering a monoclonal antibody of the antigen does not involve inventiveness. However, if the claim is further defined by other features, which accordingly has unexpected technical effects, the claim of that monoclonal antibody is inventive (Guideline, Part II, Chapter 10, §9.4.2.1(5)).

ii. Case B: reexamination decision No. 123037, issued on April 28, 2017

Holding of the 123037 decision: If an antigen is disclosed and it is clearly known that the antigen has immunogenicity, and the claimed monoclonal antibody does not have any unexpected technical effects, the claimed monoclonal antibody does not possess inventiveness.

Claim 1 reads as " A humanized antibody having an amino acid sequence that comprises VL CDR1 and VH CDR1, VL CDR2 and VH CDR2, VL CDR3 and VH CDR3 of monoclonal antibody 1D5, ..., the monoclonal antibody is produced by the hybridoma with the accession number PTA-5958 deposited by the American Type Culture Collection, and the monoclonal antibody specifically binds to native extracellular domain of human FcγRIIB with a greater affinity than said antibody binds to the extracellular domain of natural human FcγRIIA."

Panel's opinions: D1 discloses two murine monoclonal antibodies 2B6 and 3H7, which can specifically bind to the extracellular domain of native human FcγRIIB with greater affinity than the antibody binds to the extracellular domain of native human FcγRIIA, wherein 2B6 is secreted by hybridoma PTA-4591, and 3H7 is secreted by hybridoma PTA-4592. D1 also mentions that the monoclonal antibody can be humanized. The distinguished technical feature of claim 1 from D1 lies in that claim 1 specifically defines a specific humanized anti-FcγRIIB antibody. The

technical problem to be solved is to provide another humanized antibody that specifically binds to the extracellular domain of natural human FcγRIIB with greater affinity than that of natural human FcγRIIA. In view of this distinguishing technical feature, D1 has disclosed humanized anti-FcγRIIB antibodies directing to murine monoclonal antibodies 2B6 and 3H7. The native human FcγRIIB extracellular domain antigen is known in the art, and it is clear that this antigen is immunogenic. Moreover, the monoclonal antibody disclosed in D1 has the same binding characteristics as the humanized antibody of claim 1, that is, the affinity of the antibody specifically binding to the extracellular domain of natural human FcγRIIB is greater than that of the antibody binding to extracellular domain of FcγRIIA. It can be seen that the humanized antibody of claim 1 does not achieve any unexpected technical effects compared with the antibody of D1. On the basis of the monoclonal antibodies 2B6 and 3H7 secreted by the hybridomas disclosed in D1, the conventional hybridoma preparation technology in the antibody field and the humanization technology by donor CDR transplantation disclosed in D1, those skilled in the art can easily prepare different hybridomas that secrete anti-FcγRIIB monoclonal antibodies with the same or similar binding properties and then humanize the antibodies accordingly. The hybridoma secreting monoclonal antibody 1D5 recited in claim 1 is only a conventional choice among many hybridomas that secrete anti-FcγRIIB monoclonal antibodies, and humanized antibodies involving monoclonal antibody 1D5 have not been unexpected. In summary, claim 1 does not have outstanding substantive features and significant progress, and does not have inventiveness accordingly, which does not comply with Article 22, paragraph 3 of the Patent Law.

(II) An antibody defined by a specified sequence

i. Rules

For antibody claims defined by sequences, the "three step methodology" (problem-solution-approach) is generally applied to determine whether the claims are obvious. If, after applying the "three-step methodology," it can be concluded that a monoclonal antibody is not obvious to those skilled in the art, then the monoclonal antibody is inventive. In such a case, it is not required that the monoclonal antibody must have unexpected technical effects. (Monoclonal antibody examination guidance, 2019)

If an antigen is known, a monoclonal antibody of the antigen defined by structural features (for example sequences) is obviously different from the known monoclonal antibody in the key motif that determines the function and use, and the prior art does not provide any motivations to obtain the antibody, and the monoclonal antibody can produce beneficial technical effects, the claimed monoclonal antibody is inventive. (Guideline, Part II, Chapter 10, §9.4.2.1(6), revision version effective as of January 15, 2021)

ii. Case C: reexamination decision No. 236715, issued on December 1, 2020

Holding of the 236715 decision: If a claimed antibody or binding fragment having a specific structure and effect, and the prior art does not give those skilled in the art any technical enlightenment to obtain the specific structure, the claimed antibody or binding fragment is not obvious. The claim is inventive.

Claim 1 reads as "Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin for use as a medicament, wherein said antibody or said fragment or said scaffold binds to amino

acids 1-21 of the N-terminal part of adrenomedullin: YRQSMNNFQGLRSFGCRFGTC, wherein the antibody or fragment or framework is monospecific, and binds the epitope containing the first amino acid at N-terminal part, and the heavy chain contains the following sequence: CDR1 shown in SEQ ID NO:1; CDR2 shown in SEQ ID NO:2; CDR3 shown in SEQ ID NO:3 and the light chain comprises the following sequences: CDR1 shown in SEQ ID NO: 4; CDR2 shown in SEQ ID NO: 5; CDR3 shown in SEQ ID NO: 6."

Panel's opinions: claim 1 distinguishes from D1 in that claim 1 specifically defines an antibody binding to amino acids 1-21 of ADM, and it also defines that the antibody is monospecific and binds to the epitope having first amino acid at N-terminal. Additionally, claim 1 specifically defines the CDR1-3 contained in the heavy chain and the CDR4-6 contained in the light chain. However, the amino acid sequence bound as disclosed in D1 is the N-terminal amino acids 1-12, the obtained antibody is not a monospecific antibody, and it is not disclosed that the obtained antibody is used as a medicine. According to the description of this application, based on the technical effects achieved in this application, it is determined that the technical problem actually solved by this application is to provide a monospecific antibody for the preparation of drugs with a specific structure and effective ADM inhibitory activity. First of all, although it is well known in the art that ADM can improve heart function and blood supply in the liver, spleen, kidney and small intestine, the use of ADM antibodies to prepare drugs has been widely reported in the prior art, but those skilled in the art also know that antibodies by screening is random. Even in combination with D1 and common knowledge/techniques, it is impossible to predict whether the claimed specific mAb can be obtained with specific function. D1 and the prior art have failed to suggest an antibody with the recited CDR 1-3 and CDR 4-6 as defined in claim 1 with specific effect of inhibiting ADM, so those skilled in the art cannot expect to obtain the claimed mAb based on D1. Therefore, the claimed mAb in claim 1 is not obvious over D1 in view of common knowledge, and complies with the provisions on inventiveness prescribed in Article 22, paragraph 3 of the Patent Law.

With the rapid development of protein sequencing technology, applicants have been able to easily sequence monoclonal antibodies in recent years, so that more and more claimed monoclonal antibodies are defined with sequences such as CDR sequences. A revised Guideline, effective as of January 15, 2021, will update the rules on inventiveness assessment on sequence-defined monoclonal antibodies, and provide more guidance in this regard.

The evolution of examination criteria in China has made it a bit clearer for companies to obtain protections for their therapeutic monoclonal antibodies. It is important to partner with experienced counsel to develop the best strategy on a case-by-case basis for drafting a patent application with an appropriate amount of data and for claiming an attainable antibody patent protection scope.

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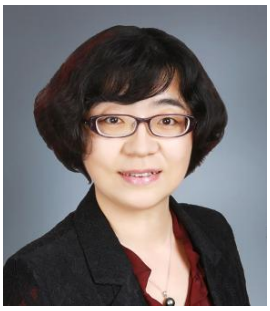

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