Featured Article

Navigating Antibody Patent Strategies in a Global Landscape

——Amgen vs Sanofi's patent battle reflections

Antibodies constitute a staggering $146 billion annual market – an amount projected to almost double by 2027. Consequently, patent covering antibodies are among the most valuable in the patent system[1]. However, the stability of antibody patents seems to be constantly under challenge. On May 18, 2023, the Supreme Court of the United States issued a ruling on the patent dispute between Amgen vs Sanofi concerning PCSK9's antibody drugs, which shocked the global biopharmaceutical industry. The Supreme Court of the United States voted 8 to 1 in favor of Sanofi, upholding the decision of the Federal Circuit (CAFC) that Amgen's patent at issue was invalidated. The ruling declared the death of a genus antibody claim that functionally defined by an antigen or epitope in the United States.

The ruling relates to Amgen's patent US 8,829,165 B2, for example claim 19[2], and patent US 8,859,741B2, for example claim 7[3]. The Supreme Court held that

---

1 The Antibody Patent Paradox, THE YALE LAW JOURNAL, Mark A. Lemley & Jacob S. Sherkow, page 1063

2 1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

19. The isolated monoclonal antibody of claim 1 wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3.

3 1. An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the

Amgen attempted to claim all the antibodies with functional limitation, which included not only 26 antibodies which sequences were determined in the specification of the patents, but also a large number of other unknown antibodies. The description of the two patents does not enable a person skilled in the art to make and use the invention without excessive inventive work or experimentation, and therefore does not comply with the provisions of 35 U.S.C. § 112(a).[4]

I. Status of Chinese Counterparts of Amgen's U.S. Patents

According to the results of searching on Chinese Patent Database, there are eight (8) Chinese applications in the patent family, of which only one application is granted. The antibody claim 1 of the granted patent (CN101932607B) is defined by three (3)

CDRs of the heavy chain variable region and three (3) CDRs of the light chain variable region.[5] The remaining seven applications are divisional applications derived from the granted patent. Three of the divisional applications have been finally rejected and are in a status of lapse. Another three divisional applications are in the substantive examination stage, with the first office action issued in June, July and August of 2023 respectively. The last divisional application was requested to defer the examination for two years.

The following is a detailed analysis of the above three rejected applications to get a glimpse of the examination standards of antibody claims in China.

A. Application CN104311667A:

Reexamination Decision No. 242306, Decision Date of January 4, 2021

Claim 1 directed by the decision is "an isolated monoclonal antibody that neutralizes PCSK9 bound to LDLR and

monoclonal antibody blocks binding of PCSK9 to LDLR.

2. The isolated monoclonal antibody of claim 1, wherein the isolated monoclonal antibody is a neutralizing antibody.

7. The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope.

4 35 U.S.C. § 112(a).....a written description of the invention ... in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same.

5 A separated neutralizing antigen binding protein, with the amidogen acid sequence SEQ ID NO: N0, a 1 of PCSK9 protein, wherein neutralizing antigen binding protein comprises a heavy chain polypeptide, comprises the following complementary determine area (R: as SEQ ID ON: 49 CDRl of heavy chain CDRl HtSSEQ ON ID: 49 heavy chain of CDR2 to CDR2, and as SEQ ID ON 49 in a CDR3 of heavy chain CDR3, and a light chain polypeptide, comprises the following CDRS as SEQ ID ON 23 in a CDRl of light chain CDRl, as SEQ ID ON 23 in a CDR2 light chain of CDR2, and as SEQ ID ON 23 in a CDR3 light chain of CDR3.

competes for binding to PCSK9 with an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 49; and a light chain variable region of the amino acid sequence in SEO ID NO: 23."

The reexamination decision held that the genus antibody claim with functional definitions covers antibodies that could not be obtained by those skilled in the art without inventive labor. Specifically, the panel opined "except for a few reference antibodies (antibody 21B12, which has been claimed in the allowed claims of CN101932607B), the description failed to verify the blocking (neutralizing) effect of other antibodies. ..... Due to the random characteristics of antibody preparation, those skilled in the art cannot expect whether they can obtain other monoclonal antibodies with the same effect as the present application verified and the functions limited by the claims. Neither those skilled in the art get to learn which specific structures of monoclonal antibodies have the technical effect of neutralizing the binding of PCSK9 to LDLR and competing with reference antibodies to bind PCSK9 without inventive labor. "

B. Application CN104311665A:

Reexamination Decision No. 230575, Decision Date of September 21, 2020

Claim 1 directed by the decision is "an isolated monoclonal antibody specifically binding PCSK9, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR; wherein, the monoclonal antibody competes for binding to PCSK9 with(a) an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 49; and a light chain variable region of the amino acid sequence in SEO ID NO: 23; or(b) an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 67; and a light chain variable region of the amino acid sequence in SEQ ID NO: 12. "

The reexamination decision held that the genus antibody claim with functional definitions covers antibodies that could not be obtained by those skilled in the art without inventive labor. The main point of the decision is "claim 1 is defined by functional features, ... Those skilled in the art cannot reasonably expect that the antibody that binds competitively to the reference antibody will necessarily block the binding of PCSK9 to LDLR according to the description of the present application and the prior art, nor can it be reasonably expected which specific monoclonal antibodies can compete with the reference antibody for binding and can block PCSK9 binding to LDLR. ..... Those skilled in the art cannot reasonably expect all the antibodies which binds to any recited site of PCSK9 in the claim and compete binding

to the reference antibody is capable of blocking the binding of PCSK9 to LDLR according to the description of the present application and prior art. Although the method of preparing antibodies is described in the present application, as known in the art, the process for screening antibodies is random and not reproducible, and therefore, those skilled in the art cannot predict whether they can successfully obtain other monoclonal antibodies with the same effect as verified for the reference antibodies in the present application, and thus inventive labor is still required."

C. Application CN104311666A:

Reexamination Decision No. 256958, Decision Date of April 28, 2021

Claim 1 directed by the decision is "an isolated monoclonal antigen, which is capable of binding PCSK9 of SEQ ID NO:1 and neutralizing the binding of PCSK9 to LDLR, said isolated antigen comprises:
a heavy chain variable domain (VH), comprises:
CDRH1 comprising the amino acid residues selected from the group consisting of T28, S30, S31 and Y32 in the specified position of SEQ ID NO:67;
CDRH2: …… ; CDRH3: …… ; and
a light chain variable domain (VL), comprises:
CDRL1 comprising the amino acid residues selected from the group consisting of A31、G32、Y33、D34and H36 in the specified position of SEQ ID NO:12;
CDRL2: …… ; CDRL3: …… ; " [6]

The panel held that "claim 1 defines individual specific residues of the 6 CDRs, rather than the full sequence thereof ..... CDRs with only individual amino acid residues cannot guarantee the defined CDRs recognize and bind to the epitope of the antigen and achieve neutralization. Namely, those skilled in the art cannot determine the binding ability and neutralization ability of the antibody according to the individual residues of CDRs defined in claim 1. Those skilled in the art cannot learn without creative effort which additional amino acid residues are necessary for CDRs to endow the monoclonal antibody with the ability to neutralize the binding of PCSK9 to LDLR. That is, the invention claimed in claim 1 is still in an "unfinished" state, which cannot solve the technical problem to be solved by the present application and cannot achieve the technical effect."

It can be seen that the Chinese current examination standard for antibody claims is:

i. For functional antibody claims

For monoclonal antibody claims characterized by epitopes or antigens to be bound, if the antigen or epitope is novel and not disclosed by prior art, the

6 The three CDRHs and the three CDRLs are defined in the same way.

monoclonal antibody claims are generally considered too broad to be supported by the description. [7]

ii. For structural antibody claims

For a monoclonal antibody claim characterized by structure, if the antibody is defined by 6 CDRs of heavy and light chains, and the CDRs are not disclosed, the inventiveness will generally be recognized and unexpected technical effects are not necessary. However, for antibodies claims covering variants defined by identity percentages of sequences, such claims are generally unacceptable in China.

II. Status of European Counterparts of Amgen's U.S. patents

One of European patent EP2215124B1 renders a genus claim covering functionally limited antibodies [8] which is similar to the claims of CN104311667A. Although the European patent was amended as structural antibody claim defining by sequence thereof with identity percentage in opposition proceedings and was republished as patent EP2215124B2, the amendments were made for the purpose of arguing for involving inventive step. It can be seen that it is acceptable in Europe for a functional antibody claim defined by binding an antigen or epitope thereof.

III. Suggestions on drafting antibody claims of a PCT application

According to the above cases, it is evident that the examination standards for an antibody claim differ from China, the U.S. and Europe. However, for an antibody with therapeutic effects, the patent portfolio is usually a global patent strategy. The antibody is pursued for a patent protection in nations or regions via a PCT application. Being a PCT application document based on which antibodies are pursued for patent protection in worldwide, the PCT application would ideally be universally applicable across different jurisdictions and meet the requirements for allowance. Therefore, when drafting a PCT application, a patent practitioner is recommended to comprehensively consider the examination standards of nations or regions with high economic influence, like China, the United States and Europe, and incorporate diverse claim styles into the application, based on which, proper antibody claims may be selected

7 The provision regarding claims shall be supported by the description in China is similar to the provision of 35 U.S.C. § 112(a).

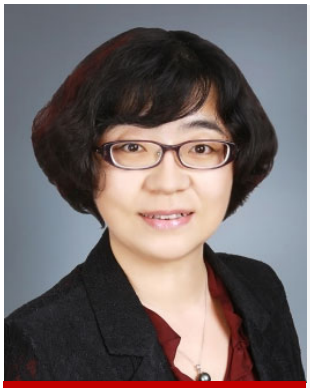
8 A monoclonal antibody or fragment thereof that binds to human PCSK9 and is neutralizing in that an excess of said antibody or fragment thereof is capable of reducing the quantity of PCSK9 bound to LDLR in an in vitro competitive binding assay, wherein said monoclonal antibody or fragment thereof competes for binding to PCSK9 with(a) an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 49; and a light chain variable region of the amino acid sequence in SEO ID NO: 23; or(b) an antibody comprising a heavy chain variable region of the amino acid sequence in SEQ ID NO: 67; and a light chain variable region of the amino acid sequence in SEQ ID NO: 12.

respectively according to the corresponding examination standards at national stages.

First, one may consider including a functional antibody claim in a PCT application. Although the U.S. Supreme Court ruling ended in functional claiming antibody, such claims are acceptable, at least in Europe.

Second, one should include a structural antibody claim which is a universally acceptable claim. The claimed antibody may be defined by CDRs sequences or heavy and light chain variable region sequences or even full sequences thereof. To pursue a broader scope, CDR or variable region variants may be defined by using identity percentages or sites for modification. Antibody claims by such structural definitions in combination with functional definitions are a well-received approach. This approach allows antibody claims, to some extent, to seek a broad protection, covering the antibodies obtained and described in the application as well as the variants which have not yet finished having the recited function. For the purpose of obtaining a patent right, it is advantageous to describe some exemplified variants in the application. Although antibodies defined by identity percentages or modified sites even plus functional definitions are hardly acceptable presently in China, they are still acceptable in Europe and the U.S.. Given that the revised guidelines effective as of January 15, 2021 are less stringent in considering post-filing data than before, it is also possible that China may one day relax the criteria for examining antibody claims.

With the diversified antibody claims described in a PCT application, it becomes widely applicable to different nations or regions, while remaining adaptable to evolving examination standards, so as to achieve a precautionary patent design.



WU, Xiaoying

Partner, Manager, Senior Patent Attorney

Ms. Wu is a partner and senior patent attorney at Lung Tin, and the head of the firm’ s Chemistry & Life Sciences Department, where she focuses on patent matters, primarily on patent application preparation and prosecution in the fields of pharmaceutical and medical science, organic chemistry, material science and biotechnology, as well as on patent reexamination, invalidation, administrative litigation, patent due diligence and freedom to operate investigation, and patent analysis. She is very experienced in advising Chinese individuals and enterprises on expanding their patent portfolios overseas. Ms. Wu also has advised clients on regulatory matters especially those before National Medical Products Administration. Ms. Wu joined Lung Tin in 2002. Prior to joining Lung Tin, Ms. Wu was engaged in research and development in medicinal chemistry and pharmacology.

Ms. Wu is qualified to practice in front of National Intellectual Property Administration, PRC (CNIPA) in China, and United State Patent and Trademark Office (USPTO), and also to practice before court in China.