Summary of a Series of Court Decisions relating to Antibody Drug Patents

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Abstract:
The Intellectual Properties (IP) High Court of Japan handed down decisions on December 27, 2018, in lawsuits against trial decisions by the Japan Patent Office (JPO), to accept the validity of Company A (Amgen)'s patents relating to anti-PCSK9 monoclonal antibodies and cholesterol-lowering antibody drugs (Case Nos. 2017 (H29) (Gyo-ke) 10225 & 10226). Subsequently, the Tokyo District Court handed down a decision on January 17, 2019, to grant an injunction to suspend Company B (Sanofi)'s acts of infringing Company A's patents (Case No. 2017 (H29) (Wa) 16468). These court decisions will have a huge impact, since they will provide guidelines for judging the validity and construction of functionally-defined antibody claims. This article summarizes these court judgments.

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I. Background

(1) History

Company A (Amgen Inc.) is a patent holder of Japanese Patent Nos. 5705288B and 5906333B (both derived from the Japanese entry of PCT/US2008/074097), relating to an monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). Company A also developed an anti-PCSK9 monoclonal antibody (Evolocumab) and a cholesterol-lowering drug product using the same (Repatha®). Company A's patents are intended to protect its antibody and drug product.

Company B (Sanofi S.A.) co-developed a different anti-PCSK9 monoclonal antibody (Alirocumab) and a cholesterol-lowering drug product using the same (Praluent®) with Company C (Regeneron Pharmaceuticals, Inc.), and is producing and selling its antibody and drug product.

Company A filed a patent infringement lawsuit before the Tokyo District Court (Case No. 2017 (H29) (Wa) 16468), arguing that Company B's acts of producing and selling its monoclonal antibody and drug product infringe Company A's patents, and seeking for an injunction to suspend Company B's acts.

In response, Company B demanded patent invalidation trials before the JPO, arguing that Company A's patents involve grounds for invalidation due to lack of inventive step and non-compliance with the support and enablement requirements. Company A made post-grant amendments (corrections) to the claims in the trial proceedings. The JPO handed down decisions to maintain Company A's patents based on the amended claims. Company B filed lawsuits before the IP High Court against the JPO's trial decisions (Case Nos. 2017 (H29) (Gyo-ke) 10225 & 10226).

The IP High Court handed down judgments on December 27, 2018, to decide that Company A's patents shall be maintained based on the amended claims, and Company B's appeal shall therefore be dismissed. Subsequently, the Tokyo District Court handed down a judgment on January 17, 2019, to decide that Company B's acts of producing and selling its monoclonal antibody and drug product infringe Company A's patents based on the amended claims, and to grant an injunction to suspend Company B's acts.

(2) Technical Information

PCSK9 binds to low-density lipoprotein (LDL) Receptor (LDLR) and induces decomposition of LDLR by hepatocytes, thereby increasing the blood cholesterol level and causing hypercholesterolemia.

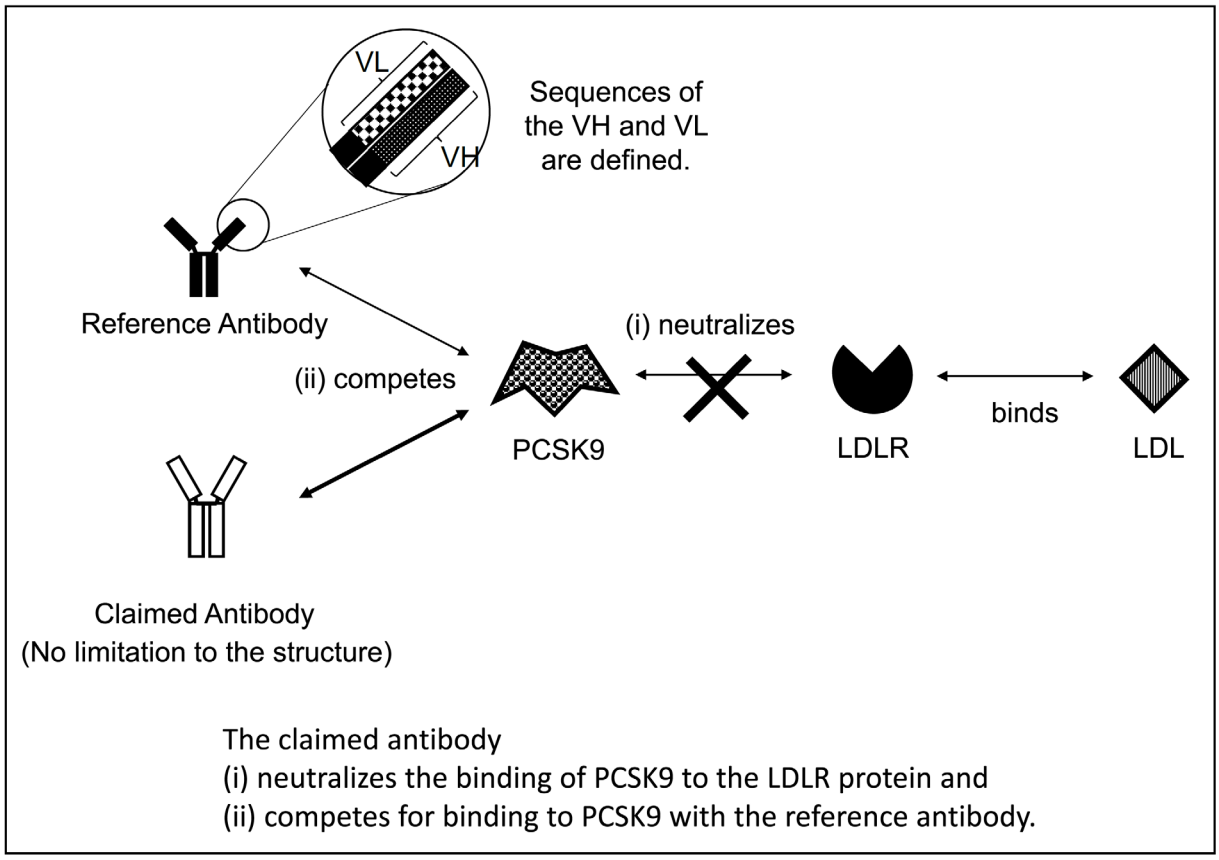
Both Company A' and Company B' antibodies bind to PCSK9 and neutralize the binding of PCSK9 and LDLR to prevent PCSK9-induced decomposition of LDLR, thereby lowering the blood cholesterol level and treating hypercholesterolemia.

(3) Claims

The amended claims of Company A's JP'288 patent read as follows:

1. (Amended) An isolated monoclonal antibody which
(i) is capable to neutralize the binding of PCSK9 to the LDLR protein, and
(ii) competes for binding to PCSK9 with an antibody comprising a heavy chain having a heavy chain variable region consisting of an amino acid sequence defined in SEQ ID NO:49 and a light chain having a light chain variable region consisting of an amino acid sequence defined in SEQ ID NO:23 [Attorney's note: hereinafter called "reference antibody"] (see FIG.1).
2 to 8 (Cancelled)
9. (Amended) A pharmaceutical composition comprising an isolated monoclonal antibody according to claim 1.

FIG.1



The amended claims of Company A's JP'333 patent are the same as those of JP'288 patent except for the amino acid sequences of the reference antibody.

II. IP High Court decisions (validity)

(1) Summary

In the appeal cases before the IP High Court, Company B argued that Company A's patents should be invalid as lacking inventive step over Exhibit 1 (Lagace et al., J. Clin. Invest., (2006), Vol.116, No.11, pp.2995-3005) and not being fully supported or enabled by the original disclosure in view of technical common knowledge. Company B's arguments are mainly directed to the functionally-defined broad language of amended claim 1.

In its decisions, the IP High Court rejected Company B's arguments, and decided that Company A's patents has inventive step over Exhibit 1 and is fully supported or enabled by the original disclosure in view of technical common knowledge, and shall therefore be maintained.

(2) Main issues

(Issue 1) Inventive step

Company B submitted Exhibit 1 (Lagace et al., J. Clin. Invest., (2006), Vol.116, No.11, pp.2995-3005), which describes that an antibody that blocks (neutralizes) the binding of PCSK9 to the LDLR protein can be pursued as an alternative treatment of hypercholesterolemia, and also that a polyclonal (not monoclonal) antibody against human PCSK9 was actually obtained from serum of a rabbit administered the antigen.

Company B also submitted exhibits proving that at the priority date of Company A's patents, at least two means for preparing a monoclonal antibody were known: animal immunization method and phage display method.

Based on these exhibits, Company B argued that Company A's patents could easily have been arrived at from Exhibit 1 in view of technical common knowledge about the animal immunization method and the phage display method.

In response, the IP High Court first judged that a person skilled in the art would have been motivated or suggested by Exhibit 1 to obtain an anti-PCSK9 monoclonal antibody, and could actually have obtained some kind of anti-PCSK9 monoclonal antibody using a prior art technique such as the animal immunization method or the phage display method.

However, the IP High Court further judged that it would have been difficult for a person skilled in the art to arrive at the specific reference antibody as claimed, from Exhibit 1 in view of the technical common knowledge, for the following reasons:

(i) Company A demonstrated, in the Examples of its patents, that the reference antibody strongly neutralizes the binding of PCSK9 to the LDLR protein by specifically blocking the interaction between the EGFa of LDLR and a limited region of the catalytic domain of the PCSK9 (see FIG.2). This specific mechanism of action is neither taught nor suggested by Exhibit 1.

FIG.2

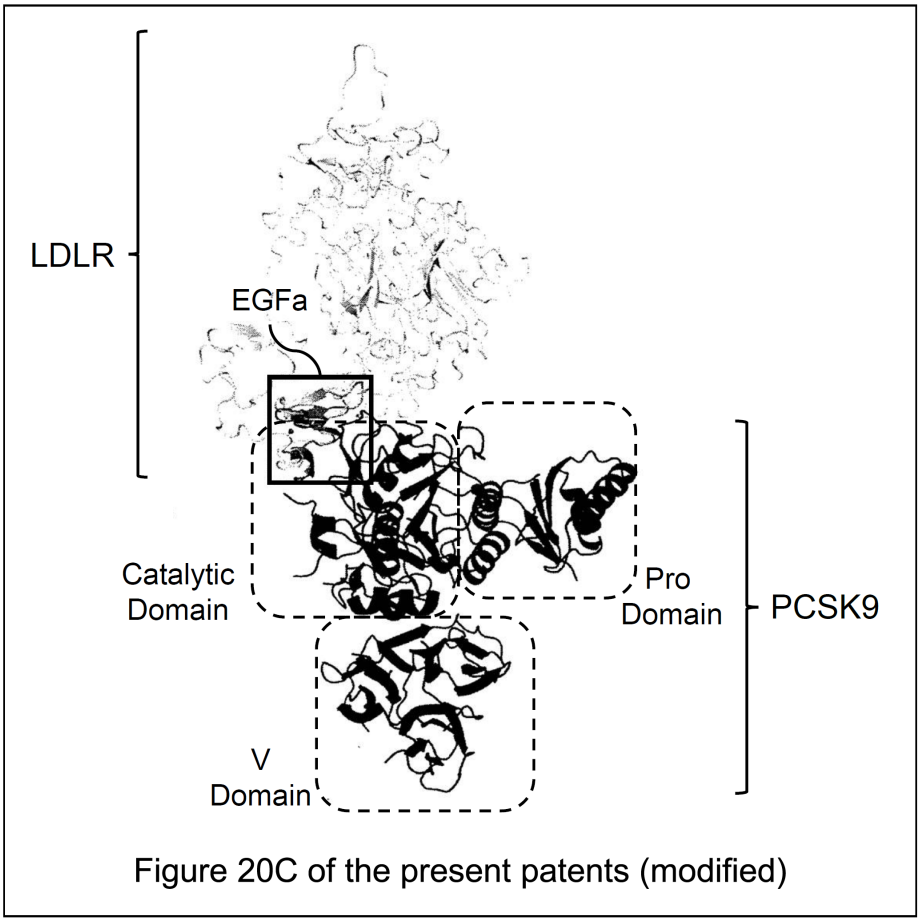


Figure 20C of the present patents (modified)

(ii) Company A obtained the reference antibody not by using a prior art technique such as the animal immunization method or the phage display method, but by using a modified animal immunization method (using a specific adjuvant and a specific immunization schedule) and a series of screening methods (using a specific biotin immobilization method and a specific D374Y-PCSK9 mutant). These methods were optimized for identifying a monoclonal antibody that can block the interaction between the EGFa of LDLR and the catalytic domain of the PCSK9.

The IP High Court further judged that since it would have been difficult to arrive at the specific reference antibody, it would also have been difficult for a person skilled in the art to arrive at the claimed antibody, which competes for binding to PCSK9 with the reference antibody, from Exhibit 1 in view of the technical common knowledge (see FIG.3).

FIG.3

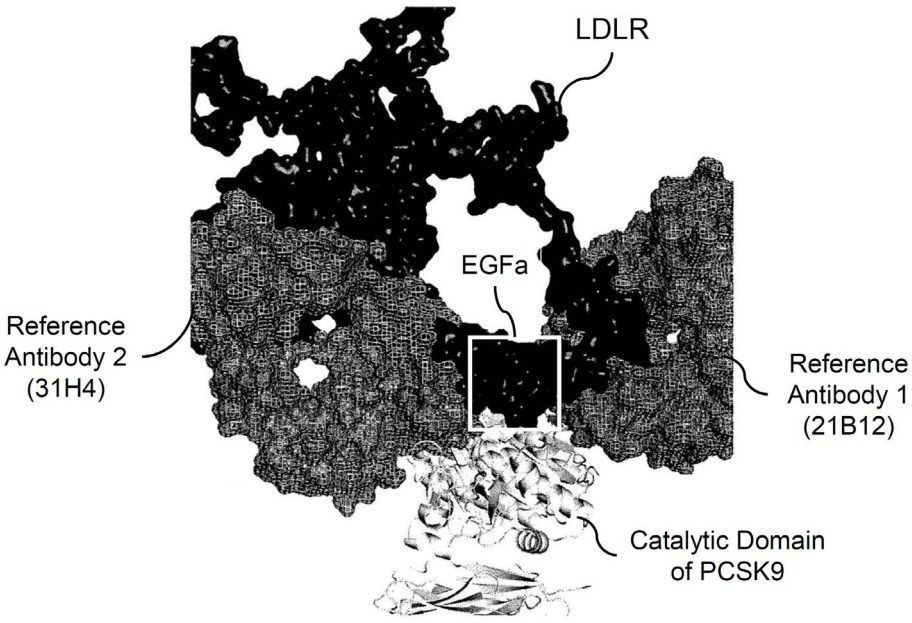


Figure 20D of the present patents (modified)

(Issue 2) Support/Enablement

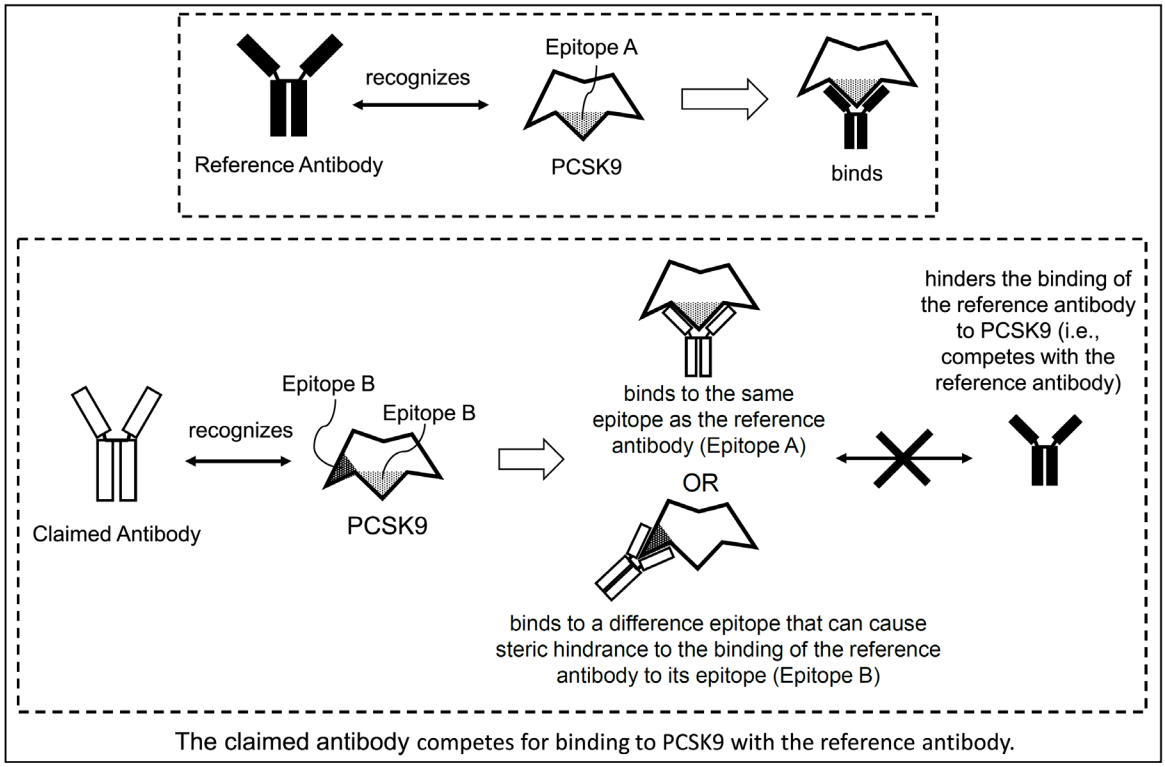
Company B argued that the scope of the claimed antibody is extremely broad and indefinite, since the present invention is not characterized by any structure of the claimed antibody (i.e., the amino acid sequences of the VL/VH or the CDRs of the claimed antibody), but is characterized only by two functions/properties of the claimed antibody. Company B also argued that since one of the claimed functions/properties is a mere recitation of the intended purpose (i.e., capable to neutralize the binding of PCSK9 to the LDLR protein), the claimed antibody is substantially characterized by the only one function, i.e., of competing for binding to PCSK9 with the reference antibody. Company B also argued that the specific antibodies actually obtained in the Examples of the present specification are structurally too limited to support the extremely broad and indefinite claims.

In response, the IP High Court judged that the present invention is fully enabled and supported by the present disclosure, since the present specification describes the process of obtaining the claimed antibody clearly and in details, and in the Examples of the present specification, the present inventors actually obtained a number of monoclonal antibodies that are encompassed by the claimed invention, by following the process described in the present specification. The IP High Court further judged that it is very likely that a person skilled in the art could also obtain monoclonal antibodies of the claimed invention other than those described in the Examples of the present specification, without undue trial-and-error experimentation. The IP High Court also judged that it is not necessary to define the structure of the antibody (e.g., the amino acid sequences of VH/VL or CDRs) in the claims, since it is technical common knowledge that in the process of producing an antibody via the animal immunization method, the structure of the produced antibody is not determined in advance, but is identified in the process of production..

(Additional Issue) Definition of the term "competes"

In the judgments about the above issues, the IP High Court also judged that the term "competes" in the claims shall be interpreted as meaning that the claimed antibody binds to either (i) the same position of PCSK9 to which the reference antibody binds, or (ii) a position of PCSK9 where the claimed antibody sterically hinders the binding of the reference antibody to PCSK9 (see FIG.4).

FIG.4



III. Tokyo District Court decision (infringement)

There was no contest between Companies A and B that Company B's product is encompassed by the literal scope of the claims of Company A's patents.

Company B argued that the scope of the claimed antibodies of Company A's patents should be limited to the specific antibodies actually obtained in the Examples of the present specification as well as their structural analogs (i.e., those derived from the specific antibodies actually obtained in the Examples via substitution, deletion, or addition of one to several amino acid residues), since otherwise the scope of the claimed invention would be unduly broad compared to the Examples of the present specification. Company B further argued that its product is not encompassed by the limitedly-interpreted claims of Company A's patents.

In response, the Tokyo District Court judged that the scope of the claimed antibody should be determined based on the literal meaning of the claims of Company A's patents, generally on the same grounds as those in the IP High Court's judgments about the support/enablement requirements.

Company B also submitted a counterclaim that Company A's patents are invalid, for the same reasons as argued in the IP High Court cases. However, the Tokyo District Court decided that the patent is valid, for the same reasons as those in the IP High Court's decisions.

Consequently, the Tokyo District Court decided that Company B's product infringes Company A's patents, and granted an injunction to suspend Company B's acts of producing and selling its product.

IV. Our comments

With regard to the IP High Court decisions (validity), we believe that the main reason why the IP High Court accepted the validity of Company A's patents is that the technical significance of Company A's inventions are described in details in the specification of these patents. Specifically, Company A demonstrated, in the Examples of its patents, that the reference antibody strongly neutralizes the binding of PCSK9 to the LDLR protein by specifically blocking the interaction between the EGFa of LDLR and a limited region of the catalytic domain of the PCSK9. Company A also actually obtained, in the Examples of its patents, the reference antibodies and a number of specific antibodies competing for binding to PCSK9 with the reference antibodies (i.e., the antibodies of the present

invention), by using a modified animal immunization method (using a specific adjuvant and a specific immunization schedule) and a series of screening methods (using a specific biotin immobilization method and a specific D374Y-PCSK9 mutant), which were optimized for identifying a monoclonal antibody that can block the interaction between the EGFa of LDLR and the catalytic domain of the PCSK9. We believe that such detailed descriptions in Company A's patents favorably affected the IP High Court's opinions.

With regard to the Tokyo District Court decision (infringement), there was one fact that likely affected the court's opinions. Company C (co-developer of Company B's antibody) has a patent covering Company B's monoclonal antibody: JP4695133B, which derives from the Japanese entry of PCT/US2009/068013. Company C's PCT application was filed after the publication of the original PCT application of Company A's patents, and the Examples of Company C's PCT application demonstrate that Company B's antibody competes for binding to PCSK9 with the reference antibodies of Company A's patents. Although this fact is not mentioned either in the IP High Court decisions or in the Tokyo District Court decision, Company A indicated this fact at a later stage of the court proceedings. It is likely that this fact affected not only the Tokyo District Court's opinions but also the IP High Court's opinions.

In any event, these court decisions clearly show that functional claims for antibodies are acceptable and enforceable under specific conditions. However, we believe that the hurdles for obtaining and enforcing such functionally-defined antibody patents are still very high.

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