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Asamura NEWS

Special edition for UCB
November 09, 2020

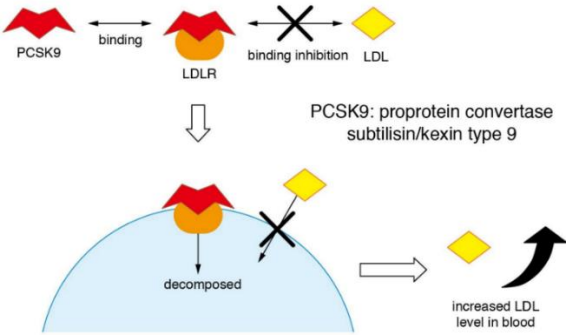
Introduction of antibody patent infringement case

-Heisei 29 (wa) 16468 Tokyo district court decision-

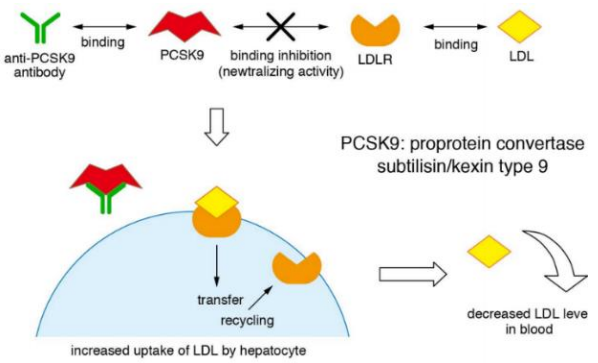
How to effectively use a divisional application and a functional term?

	Plaintiff	Defendant
	AMGEN VS.	SANOFI
Pharmaceutical product	Repatha	Praluent
Active ingredient	Evolocumab	Alirocumab
	✓ Anti-PCSK9 antibodies, but Evolocumab and Alirocumab have different CDRs	
Indication	High blood cholesterol, et	
Patents	1st 5441905 2nd 5705288	5318965 (REGENERON PHARMACEUTICALS)

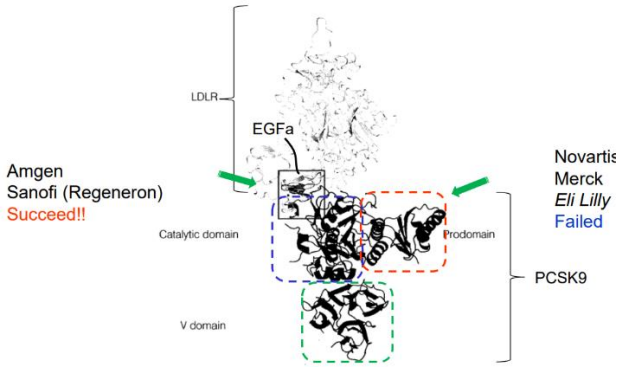
As you know, Amgen and Sanofi are innovative pharmaceutical companies. They have independently developed drugs for the treatment of high blood cholesterol containing anti-PCSK9 antibodies, and they have owned patents to cover their products, respectively. PCSK9 binds to LDLR and inhibits the binding between LDLR and LDL. A complex of PCSK9 and LDLR is internalized and hepatocyte decomposes LDLR. As a result, LDL level in blood increases.



An anti-PCSK9 antibody binds to PCSK9 and inhibits the binding between PCSK9 and LDLR. As a result, the binding between LDLR and LDL is restored, LDLR transfers LDL into hepatocyte, and LDLR is recycled. Finally, LDL level in blood decreases.



Anti-PCSK9 antibodies have attracted many pharmaceutical companies. Actually, not only Amgen and Sanofi but also Novartis, Merck and Eli Lilly tried to develop a drug containing the antibody. Only Amgen and Sanofi succeed to develop the drug, but Novartis, Merck and Eli Lilly failed. In fact, PCSK9 has several domains. Novartis, Merck and Eli Lilly's antibodies were directed to prodomain. On the other hand, Amgen's antibody and Sanofi's antibody were directed to EGFa.

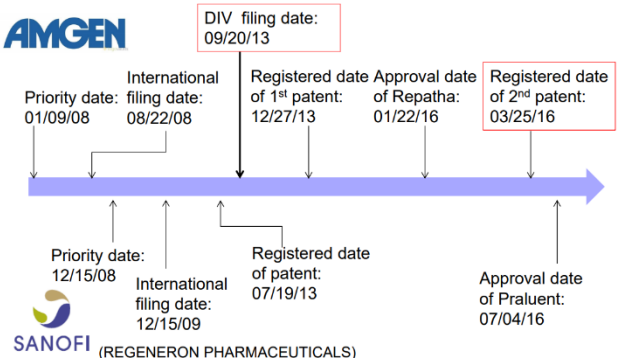


<u>Amgen's antibody and Sanofi's antibody are however different from each other in CDRs and others</u>.

Amgen filed a patent application earlier than Sanofi. About two months after the registration of Sanofi's patent, Amgen filed a divisional application and obtained a 2nd patent from the divisional about three months before the marketing approval of Sanofi's

product.

Timeline of both parties' actions



In this condition, Amgen filed a lawsuit against Sanofi with Tokyo district court to stop selling their products. The 1st patent to Amgen is 5441905, and claim 1 thereof recites:

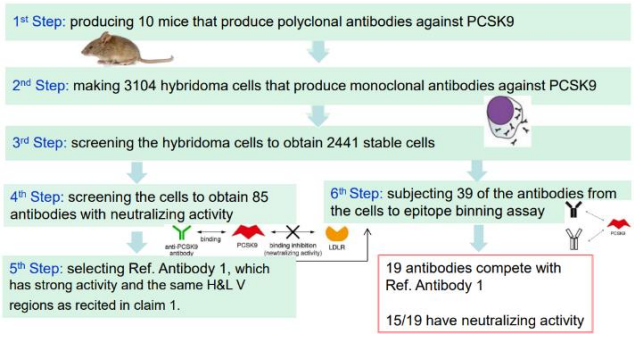
> • An isolated neutralizing human monoclonal antibody that binds to PCSK9 protein comprising:
>
> a heavy chain polypeptide comprising CDR1 represented by SEQ ID NO: 368, CDR2 represented by SEQ ID NO: 175, and CDR3 represented by SEQ ID NO: 180; and
>
> a light chain polypeptide comprising CDR1 represented by SEQ ID NO: 158, CDR2 represented by SEQ ID NO:162, and CDR3 represented by SEQ ID NO: 395.

The claim defines an antibody with **6 CDRs**. This claim covers Amgen's product but does not cover Sanofi's product. On the other hand, the 2nd patent from the divisional application is 5705288, and claim 1 thereof recites:

> An isolated monoclonal antibody that is capable of neutralizing the binding between PCSK9 and LDLR protein and that **competes with** an antibody comprising a heavy chain comprising a heavy variable region consisting of the amino acid sequence of SEQ ID NO: 49, and a light chain comprising a light variable region consisting of the amino acid sequence of SEQ ID NO: 23, for the binding with PCSK9.

The antibody highlighted in blue has the same heavy and light variable regions as those of Amgen's product and an antibody of which strong neutralizing activity against PCSK9 is demonstrated in working examples of the patents, hereinafter referred to as "Ref. Antibody 1". Interestingly, this patent claims a neutralizing antibody that **competes with** the antibody in blue.

The specifications of the patents demonstrate that Ref. Antibody 1 and antibodies competing therewith were obtained by a process comprising the following six steps.



Specifically, in the 1st step, 10 mice producing polyclonal antibodies against PCSK9 were produced. In the 2nd step, about 3000 hybridoma cells producing monoclonal antibodies against PCSK9 were produced. In the 3rd step, the hybridoma cells were screened to obtain stable cells. In the 4th step, the stable cells were screened to obtain 85 antibodies with neutralizing activity against binding between PCSK9 and LDLR. In the 5th step, Ref. Antibody 1 was selected as one of antibodies with the strongest neutralizing activity and it was confirmed that Ref. Antibody 1 has the same heavy and light variable regions as recited in claim 1. In the 6th step, **39 of the 2441 antibodies from the cells obtained in the 3rd step were subjected to an epitope binning assay with Ref. Antibody 1. 19 antibodies competed with Ref. Antibody 1, and 15 of the 19 antibodies had neutralizing activity.** For more details, please review WO2009026558 A1.

The patent also shows to what site of PCSK9 Ref. Antibody 1 binds.

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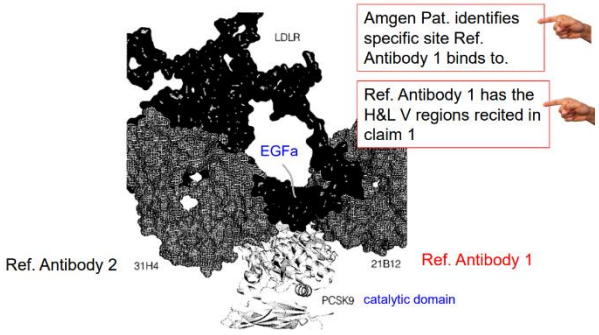

【Court Decision】

Main issues

1. Is the claimed subject-matter fully supported by the original content?
2. Would the claimed antibody be obvious?
3. Should the scope of protection be limited to the specific antibodies demonstrated in Example?

Tokyo district court addressed these issues.

1st Issue: Claimed subject-matter fully supported by original content?

The court identified a problem to be solved by the invention as the provision of a neutralizing monoclonal antibody against PCSK9 based on the specification.

The court then referred to the process for obtaining Ref. Antibody 1 and antibodies competing therewith described above and indicated as follows: 39 of the 2441 antibodies obtained in the 3rd step were subjected to an epitope binning assay, and 19 of the 39 antibodies competed with Ref. Antibody 1. 15 of the 19 antibodies had the neutralizing activity.

Taking into consideration the experimental results in the patent, the court stated that one skilled in the art would reasonably expect that **other neutralizing antibodies that compete with Ref. Antibody 1 could be obtained by subjecting other subgroups of the 2441 antibodies to the epitope binning assay**.

The court then concluded that the claimed subject-matter is fully supported by the original content of the patent.

2nd Issue: Claimed antibody obvious?

The court first found that a closest prior art document describes that PCSK decreases LDLR level; suggests that antibodies capable of blocking the binding between PCSK9 and LDLR protein would be useful for the treatment of high blood cholesterol; and describes that polyclonal antibodies against PCSK9 were obtained.

The court then stated that one skilled in the art would have readily conceived of obtaining a monoclonal neutralizing antibody capable of blocking the binding between PCSK9 and LDLR protein from the closest prior art. The court however showed their view that one skilled in the art could not have readily achieved Ref. Antibody 1 and antibodies competing with it from the closest prior art, because **the closest prior art does not teach or suggest Ref. Antibody 1, which has a specific sequence and binds to a specific site, and therefore antibodies competing with that antibody could not be easily obtained**.

The court concludes the claimed subject-matter would be unobvious over the closest prior art.

3rd Issue: Should scope of protection be limited to specific antibodies obtained in Example?

With regard to this issue, the court ruled that the protection should be extended to **antibodies that one skilled in the art could obtain from the teaching of the specification**.

From this viewpoint, the court decided that one skilled in the art could obtain antibodies competing with Ref. Antibody 1 other than the specific ones actually obtained in Example by the process described above and found that Sanofi's antibody competes with Ref. Antibody 1 for the epitope.

Based on the interpretation of "compete with", the court concluded that Amgen's 2nd patent covers Sanofi's product.

【Some tips for your practice】

- The divisional application and the functional term "compete with" successfully functioned to cover Sanofi's product!! The divisional application is an important tool in patent infringement cases.
- Tokyo District Court ruled the protection should be extended to antibodies that one skilled in the art could obtain from the teaching of the specification.
- Defining an antibody with CDRs is popular in Japan and maybe in other countries, but sometime, it may be insufficient to cover your competitor's product.
- It is to be noted that Amgen patent demonstrates where Ref. Antibody 1 binds and describes how to obtain Ref. Antibody 1 and antibodies competing therewith and demonstrates that some neutralizing antibodies competing with Ref. Antibody 1 were obtained.

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