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Antibodies and the written description requirement of 35 U.S.C.112(a)

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September 17, 2020

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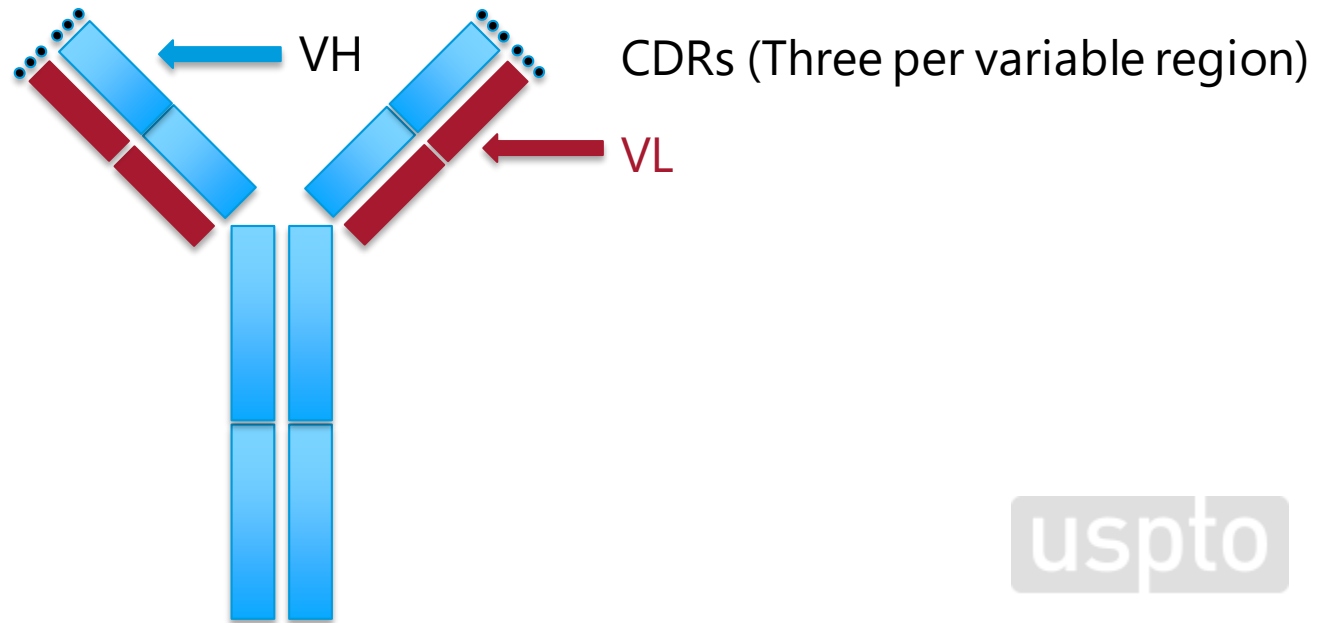


Overview

- Review of antibody structure
- *Amgen Inc., v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017)
- How can claims to antibodies meet the written description requirement?
- Examples

Antibodies – general structure

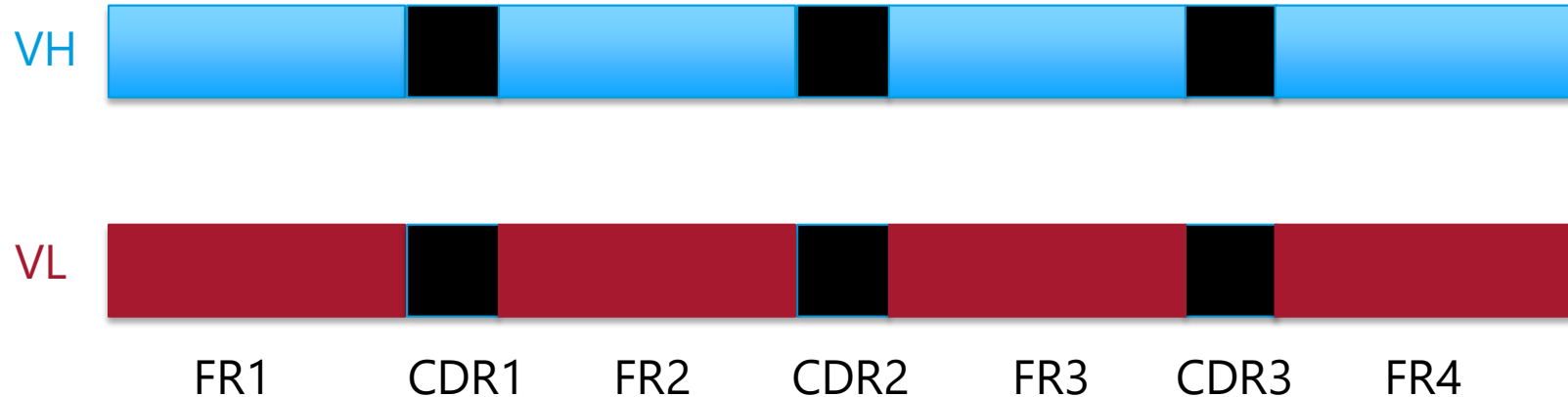
- VH and VL: Heavy and light chain variable regions
- CDRs: Complementarity determining regions



Antibody structure—overview

- Constant regions from a small number of known sequences.
- Highly variable structure in the antigen-binding region.
- Most variability derives from complementarity determining regions (CDRs). Intervening framework sequences less variable by comparison.

Antibody variable domains



VH and VL: heavy and light chain variable regions
CDR1-3: complementarity determining regions
FR1-4: framework regions

CDRs generally control antigen binding

- The CDRs are generally considered to be the region of contact between the antibody and the antigen.^{1, 2}
- While CDRs are necessary for binding, they are highly diverse in structure, and their sequence does not correlate to binding in a predictable fashion.

Antibody structure is highly variable in the CDR regions

- Goel et al. (2004) made three antibodies that bind to the same 12-mer but have very different CDRs.³
- Lloyd et al. (2009) found that on average, about 120 different antibodies in a library can bind to a given antigen.⁴
- Edwards et al. (2003) found that a library contained over 1000 antibodies that bound to a single 51 kDa protein, including 1098 unique VH and 705 VL sequences. There were 568 different CDR3 regions; high diversity.⁵

Reminder: antibody CDRs are highly variable in structure, even when function is conserved

- While the term “antibody” does impart some structure, the structure that is common to antibodies is generally unrelated to antigen-binding function.
- Correlation between structure and function is less likely for antibodies than for other molecules.

Antibody structure cannot be easily predicted

- Given the highly diverse nature of antibodies, particularly in the CDRs, one generally cannot envision the structure of an antibody by knowing its binding characteristics.

Previous USPTO guidelines

- 2008 guidelines indicated that describing an antigen may be sufficient to describe an antibody that binds to that antigen, even if none were produced.
- Those guidelines have been archived in view of recent court decisions.

35 U.S.C. 112(a)

IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

Amgen v. Sanofi

- Amgen had two patents, 8,829,165 and 8,859,741.
- Sanofi made a product which, in Amgen's view, fell within the scope of its patented claims.
- Amgen sued Sanofi for infringement in district court. Sanofi argued the patent specifications did not describe the claimed inventions.

Amgen v. Sanofi

- Claim 1 of the '165 patent is representative:
 - 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 LDL[-]R.

Amgen v. Sanofi

- Amgen made multiple antibodies within the scope of the claim.
- District court judge provided jury instruction:

“In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine.” *Amgen*, F.3d at 1376
- Similar to USPTO 2008 guidelines and practice.

Amgen v. Sanofi

- Court of Appeals for the Federal Circuit (CAFC) remanded the case for consideration by the district court.
- CAFC very clearly stated the test put forth in district court's jury instruction was improper, and one cannot describe an invention by pointing to something else and a method of making the invention.

Amgen v. Sanofi

- Conclusions:
 - Federal Circuit did not reach a conclusion with respect to the facts of this particular case.
 - Federal Circuit indicated that *Ariad* sets forth the test for written description.
 - Federal Circuit did tell us what test not to use.

USPTO memo on written description test for claims drawn to antibodies

- February 22, 2018 memo to Patent Examining Corps
 - www.uspto.gov/sites/default/files/documents/amgen_22feb2018.pdf
- “The *Amgen* court expressly stated that the so-called ‘newly-characterized antigen’ test ... should not be used in determining whether there is adequate written description ... for a claim drawn to an antibody.”

***Amgen v. Sanofi*—where do we go from here?**

- In terms of written description, claims reciting antibodies are to be treated like claims reciting any other molecule.
- Antibody claims often recite at least some structure and some function ("An antibody that binds to antigen X"), therefore MPEP 2163(II)(A)(3)(a)(ii) is informative.

MPEP 2163(II)(A)(3)(a)(ii)

- The written description requirement for a claimed genus may be satisfied through description of:
 - A representative number of species ... or
 - Disclosure of relevant, identifying characteristics ...
 - By functional characteristics coupled with a known or disclosed correlation between function and structure

Example 1

- Claim: An isolated monoclonal antibody or antigen-binding fragment thereof that binds to antigen X, wherein the antibody or antigen-binding fragment comprises the VH as set forth in SEQ ID NO:1 and the VL as set forth in SEQ ID NO:2.
- Facts: Applicant made a single antibody within the scope of the claim. It comprises the recited regions and has a mouse constant region.

Example 1

- Analysis: The claim is drawn to a genus. While the VH and the VL are specified, the constant regions are not specified and can be varied. However, the claim is limited to certain sequences in the VH and the VL, which are the regions known to be responsible for binding.
- Conclusion: The claim complies with the written description requirement, as the function (binding to antigen X) is correlated to a structure recited in the claim (the sequences in the VH and VL).

Example 2

- Claim: An isolated monoclonal antibody that binds to antigen X, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment comprises a VH comprising the CDRs as set forth in SEQ ID NO:1-3 and a VL comprising the CDRs as set forth in SEQ ID NO:4-6.
- Facts: Applicant has made a single antibody with the recited CDRs. Applicant states that a skilled artisan can make other antibodies with these CDRs which retain binding to the antigen. The art recognizes that framework regions and constant regions are generally known. The art recognizes that frameworks can influence binding to some degree, but most of the binding is determined by the CDRs.

Example 2

- Analysis: The claim is drawn to a genus. While the six CDRs are specified, the framework regions and the constant regions are not specified and can be varied. However, the claim is limited to certain sequences in the CDRs, which are the regions known to be responsible for much of the antigen binding. See references on slide 35.
- Conclusion: The claim complies with the description requirement, as the function (binding to antigen X) is correlated to a structure recited in the claim (the sequences in the CDRs). One skilled in the art would be able to immediately envision other antibodies which have different framework and constant regions yet which retain binding as claimed.

Example 3

- Claim: A humanized antibody that binds to antigen X, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment comprises a VH comprising the CDRs as set forth in SEQ ID NO:1-3 and a VL comprising the CDRs as set forth in SEQ ID NO:4-6.
- Facts: Applicant has made a single mouse antibody with the recited CDRs. Applicant has made no humanized antibodies. Applicant states that a skilled artisan can make other antibodies with these CDRs which retain binding to the antigen. The art recognizes that framework regions and constant regions were generally known at the time the application was filed.



Example 3

- Analysis: The claim is drawn to a genus. While the six CDRs are specified, the framework regions and the constant regions are not specified and can be varied. However, the claim is limited to certain sequences in the CDRs, which are the regions known to be responsible for much of the antigen binding. See references on slide 35.
- Conclusion: The claim complies with the description requirement, as the function (binding to antigen X) is correlated to a structure recited in the claim (the sequences in the CDRs). One skilled in the art would be able to immediately envision other antibodies which have different framework and constant regions yet which retain binding as claimed, even though the applicant made no humanized antibodies.

Example 4

- Claim: An isolated antibody that binds to antigen X and which competes for binding with the antibody produced by hybridoma 123 deposited with ATCC.
- Facts: Applicant made a single antibody, and deposited the hybridoma with ATCC. The deposit satisfies all requirements of 37 CFR 1.801 – 1.808. Prophetic assays to screen for antibodies which compete are disclosed in the specification.

Example 4

- Analysis: The claim is drawn to a genus of antibodies that bind a given epitope or otherwise compete for binding. Applicant has disclosed a single member of the genus. One cannot envision the structure of other members of the genus. Even though all members of the genus are antibodies and share certain structure, that structure is unrelated to the claimed function (competing for binding).
- Conclusion: While it is within the skill of the artisan to make and screen for such antibodies, one cannot envision their structure. The claim does not comply with the written description requirement.

Example 5

- Claim: A method of making an antibody comprising administering a peptide consisting of SEQ ID NO:1 to a mammal, and purifying the resultant antibodies.
- Facts: SEQ ID NO:1 is 10 amino acids. Methods of making antibodies to peptides were routine in the art at the time the application was filed. The specification discloses making a single polyclonal antiserum.

Example 5

- Analysis: Each of the claim elements are described, either in the specification or the art. One skilled in the art can immediately envision the starting materials and steps recited in the claim.
- Conclusion: The claim meets the written description requirement. While the products produced by this process may not be fully described, the claim is not drawn to the product itself, but to a process of making the product.

Example 6

- Claim: A method of treating bacterial infection, the method comprising administering an antibody that binds to antigen X.
- Facts: Applicant reduced to practice a single antibody. The antibody was shown to inhibit growth of 50 genera of bacteria from different families. Applicant states that other antibodies can be found by routine techniques. No other antibodies that bind to X are known in the art.

Example 6

- Analysis: The claim encompasses methods of using a genus of antibodies. The totality of the evidence indicates a single species exists. One skilled in the art cannot envision the structure of other antibodies that inhibit bacterial growth and bind to antigen X.
- Conclusion: The claim does not meet the written description requirement and therefore should be rejected.

Example 7

- Claim: A method of decreasing blood pressure in a subject in need thereof, the method comprising administering an antibody that binds to protein X and inhibits its activity.
- Facts: Applicant made a single antibody. The antibody was shown to decrease blood pressure in a relevant animal model. Additional experiments showed that other ways of reducing the level or activity of protein X, including knockouts and small molecule inhibitors, all decrease blood pressure. At the time the application was filed, a genus of antibodies which bind to protein X and inhibit its activity was known and readily available in the art.

Example 7

- Analysis: The claim encompasses methods of using a genus of antibodies. The totality of the evidence indicates a genus of antibodies within the scope of the claim exists. There is scientific reason to believe that any of the antibodies in the art will work in the claimed method.
- Conclusion: The claim meets the written description requirement and therefore should not be rejected.

References

1. Janeway et al. 2001. Immunobiology The Immune System in Health and Disease. 5th edition. New York: Garland Science. See sections 3-6 and 3-7.
2. Almagro 2008. Humanization of antibodies. Frontiers in Bioscience 13: 1619-1633. See introduction and section 4.
3. Goel et al. 2004. Plasticity within the Antigen Combining Site May Manifest as Molecular Mimicry in the Humoral Immune Response. The Journal of Immunology 173(12):7358-7367. See figures 2 and 3 in particular.
4. Lloyd et al. 2009. Modelling the human immune response: performance of a 10^{11} human antibody repertoire against a broad panel of therapeutically relevant antigens. Protein Engineering, Design & Selection 22(3):159-168.
5. Edwards et al. 2003. The remarkable flexibility of the human antibody repertoire; isolation of over one thousand different antibodies to a single protein, BlyS. Journal of Molecular Biology 334:103-118.

Amgen Inc., v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017)



