Antibody Patent Claims: The Past, Present and Future of the Enablement and Written Description Standards

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April 28, 2021

Proskauer

A Proskauer Roundtable
The Business of Litigation

Overview

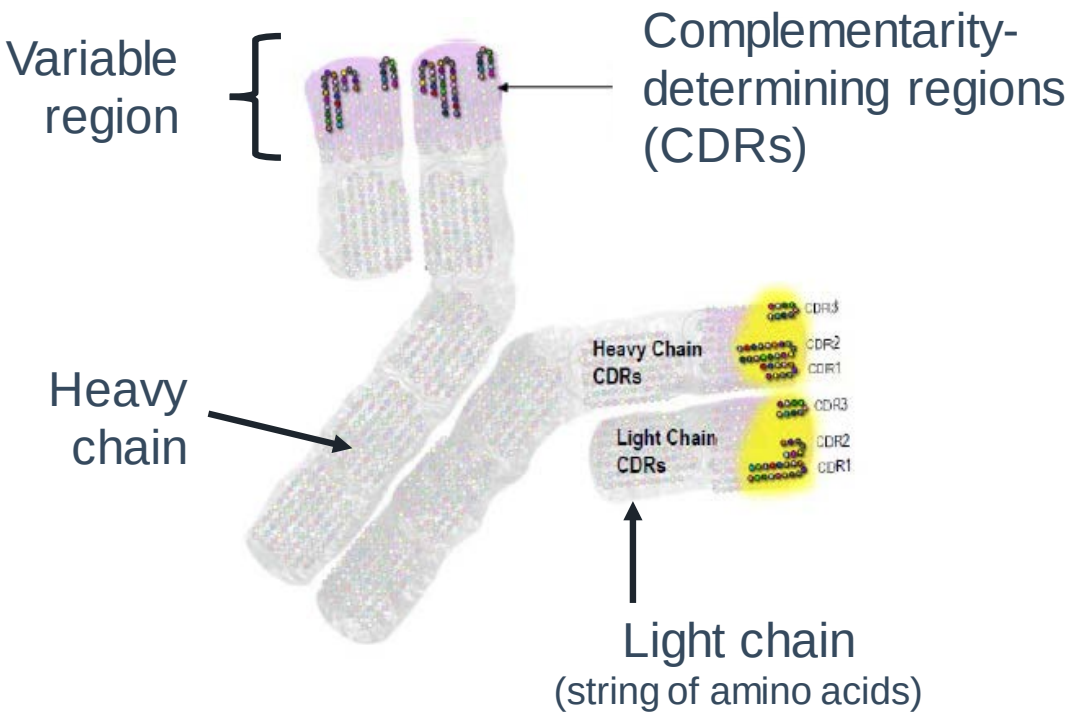
- Antibody Therapeutics
- What is the appropriate antibody claim scope that should result from the identification of a novel antigen or epitope? What are the considerations?
  - Written Description
  - Enablement
- Where are we now — *Amgen v. Sanofi*
- How will the industry respond to the changing enablement and written description landscape

Antibody Therapeutics

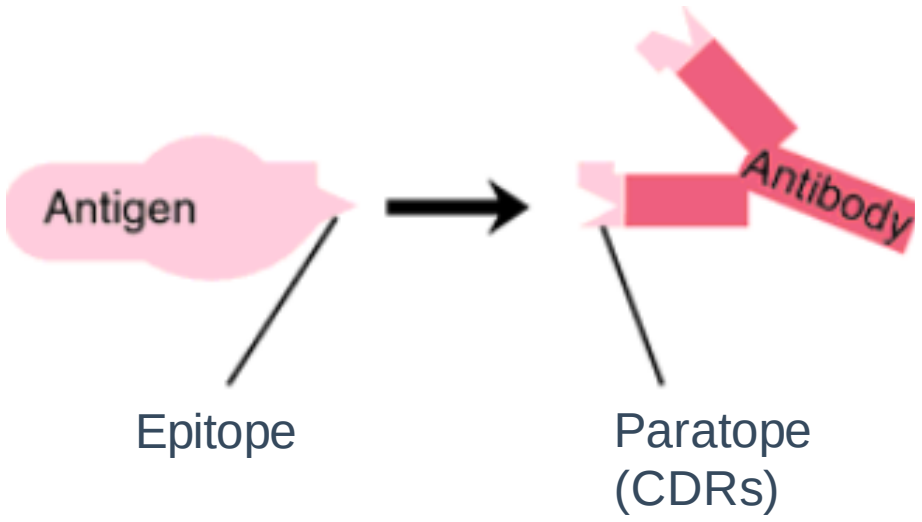
Therapeutic Antibody Market

- The first monoclonal antibody was approved by the FDA in 1986
- The global antibodies market is estimated to be valued at $143.5 billion in 2020 and is forecasted to reach over $350 billion by 2027
- In 2018, the top ten best selling monoclonal antibodies alone generated $73 billion in revenue
- 10 antibody therapeutics were granted the first approval in the U.S. or European Union (EU) in 2020
- As of November 2020, 88 antibody therapeutics were in late-stage clinical studies
- Over 60 companies involved in therapeutic antibodies currently approved in the U.S.

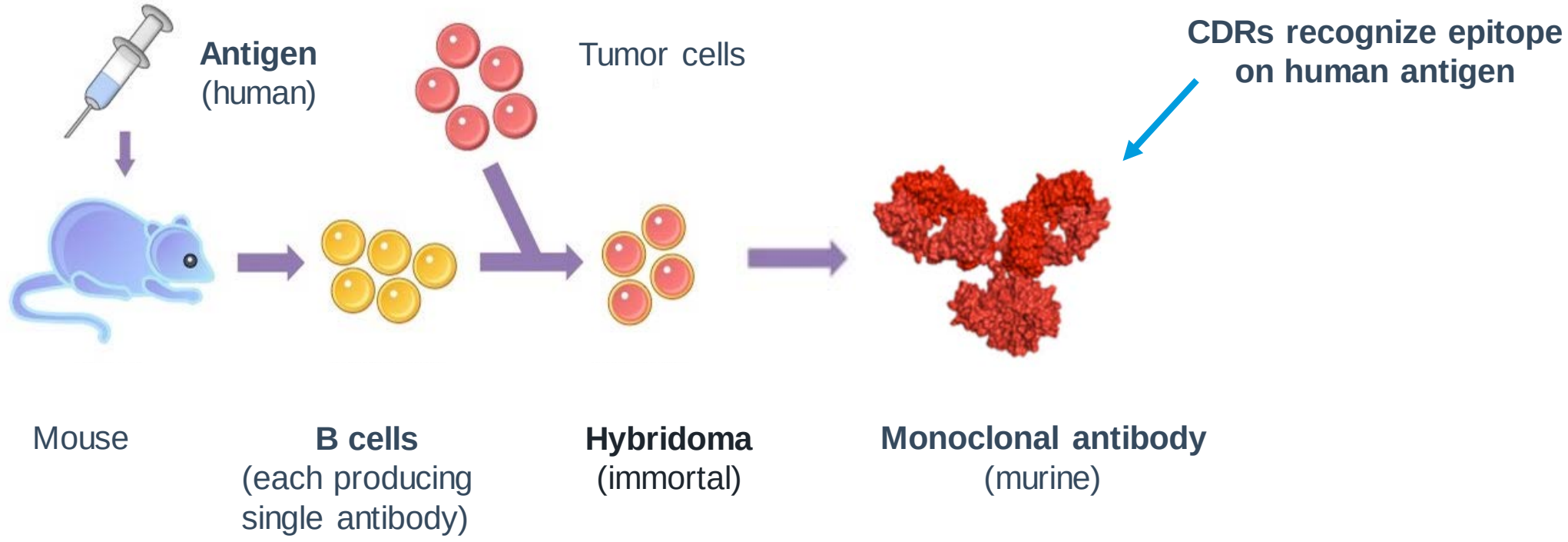
What is an Antibody?



Antibody

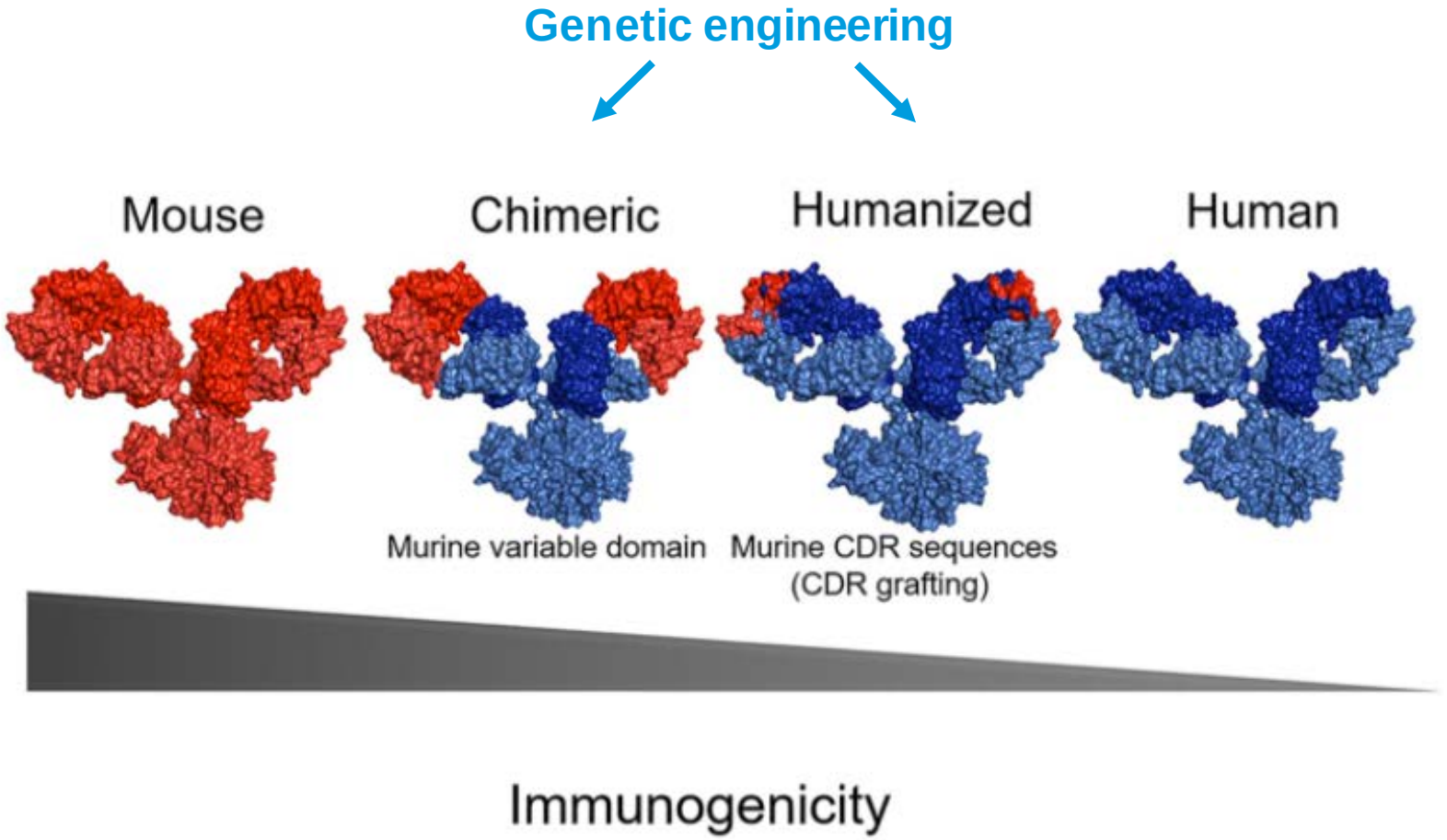


How to Make a Therapeutic Antibody



https://www.mybiosource.com/learn/monoclonal-antibody/

Making Therapeutic Antibodies



Lopes dos Santos et al., 54 BRAZ. J. PHARM. SCI. (2018), Fig. 1

Drug Development: *Antibody vs. Small Molecule*

Antibody:

mAb generation / lead identification
Based on *function*

Lead Optimization
CDR *sequences* and humanization

Small Molecule:

Compound synthesis
Based on *structure*

Lead Identification
Based on *function*

What is the Appropriate Antibody Claim Scope?

- What is the appropriate antibody claim scope that should result from the identification of a novel antigen or epitope?
- What are the considerations?
  - Written Description
  - Enablement

Written Description

35 U.S.C. § 112(a)

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.

Test for Written Description

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had **possession** of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.,* 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 1563, 19 USPQ2d at 1116.

Landmark Cases in the Biopharma Space

- *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (*The mammalian Insulin Case*)
  - A claimed genus fails to satisfy Written Description if it distinguishes itself from other materials only by function.
- *University of Rochester v. G.D. Searl & Co.*, 358 F.3d 916 (Fed. Cir. 2004) (*The Cox-1/Cox-2 Case*)
  - A claim fails to satisfy Written Description even if the specification is enabling but does not describe the structure of compound needed to practice the invention
- *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (*The NF-kB case*)
  - Written Description is separate and distinct from the § 112 enablement requirement
  - **Test:** Does "the disclosure of the application relied upon reasonably convey[ ] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date[?]"

How to show possession of a genus?

- Sufficient description of a genus requires disclosure of either:
  - a representative number of species falling within the scope of the genus; or
  - structural features common to its members so that POSA can "visualize or recognize" members of the genus.

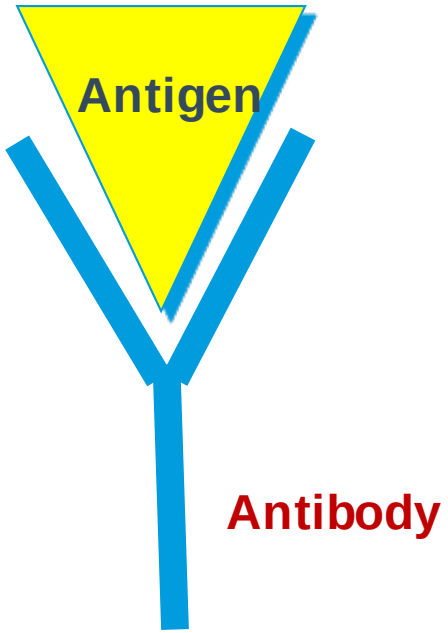
“Antibody Exception” – The Newly Characterized Antigen Test

2000 and 2008 USPTO Written Description Training Materials

- Examples 13 and 14
  - **Claim 1. An isolated antibody capable of binding to antigen X**
  - Specification:
    - Described an isolated antigen X, purifying the antigen, its amino acid sequence, molecular weight, and other characteristics.
    - Did not describe any working or detailed prophetic examples of an antibody that binds to antigen X, a reduction to practice, a complete or partial structure, any physical properties of the antibody, correlation between structure and function or a method of making an antibody that binds antigen X
  - Level of skill and knowledge:
    - Production of antibodies against a well-characterized antigen was conventional
  - **Conclusion**:
    - **The specification satisfies the written description requirement of 35 U.S.C.112, first paragraph, with respect to the full scope of claim 1**

Why "Antibody Exception"?

- Over simplified view of antibody structure
- Antibody is a "Y" shaped bullet



Noelle v. Lederman (Fed. Cir. 2004)

- "Based on our past precedent, as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen."
- **Holding**: The written description requirement was not met where the claims at issue covered antibodies that bound the antigen CD40CR generally, because the patent specification described only the mouse form of CD40CR and did not describe human or other CD40CR antigens.

Centocor v. Abbott (Fed. Cir. 2011)

- "While our precedent suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, that **reasoning applies** to disclosure of newly characterized antigens where creation of the claimed antibodies is routine."
- **Holding**: The written description requirement was not met where the claims recited an anti-TNFα antibody with a "*human variable region*," because the patent specification did not describe those antibodies, and the production of antibodies having the claimed human variable region was not then possible using routine technology, according to the facts adduced in that case.

AbbVie v. Janssen (Fed. Cir. 2014) — A plot of land analogy

- District court — AbbVie sued Janssen and Centocor (referred to collectively as "Centocor" in opinion), alleging Stelara® infringes '128 and '485 patents
  - Jury found claims invalid on written description, enablement, and obviousness grounds
- AbbVie appealed on the issues of written description and enablement (among other issues unrelated to § 112)

AbbVie v. Janssen (Fed. Cir. 2014) — Representative Claim

U.S. Patent No. 6,914,128 Claim 29

- Claim 29. A neutralizing isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and disassociates from human IL-12 with a K_{off} rate constant of $1\times10^{-2}s^{-1}$ or less, as determined by surface plasmon resonance.

IL-12 Antibodies Described in the AbbVie Specification

- Use phage display to identify a lead antibody "**Joe-9**"
- Introduce mutations into the CDRs of Joe-9 to identify antibody with **Y61** mutation with greater binding affinity
- 300 antibodies with amino acid sequences described
  - All derived from Joe-9
  - All within 90% sequence similarity
  - Over 200 differed from Y61 by only one amino acid

Comparison Between Stelara® and Examples in Specification

	AbbVie "Joe-9" + progeny	**Centocor** Stelara®
Development Method	Phage Display	Transgenic mice
Heavy Chain	V_H3	V_H5
Light Chain	Lambda	Kappa
Sequence Similarity	**90%+**	**50%**
CDR Lengths	Same	Different
Epitope	Bottom	Side

Arguments — What Features Matter for Representativeness?

- **AbbVie**
  - Look only to the claimed feature for representativeness
  - The disclosed species are representative because they cover the full range of k_{off} rates (claimed feature)
- **Centocor**
  - Look to the structural diversity of the genus to determine representativeness; k_{off} rate is dependent on the structure
  - Disclosure of a family of closely related and structurally similar antibodies all derived from Joe-9 is not representative of the entire genus

Arguments — Are the Disclosed Species Representative?

- **AbbVie**
  - Claims are limited to a small genus of antibodies
  - Patent was not required to provide written description of an infringing product; all known species aside from that product were disclosed
  - If structure is relevant, a variety of amino acid sequences were disclosed
- **Centocor**
  - All disclosed species are structurally similar and closely related
  - Claims cover antibodies with widely varying structures

Federal Circuit

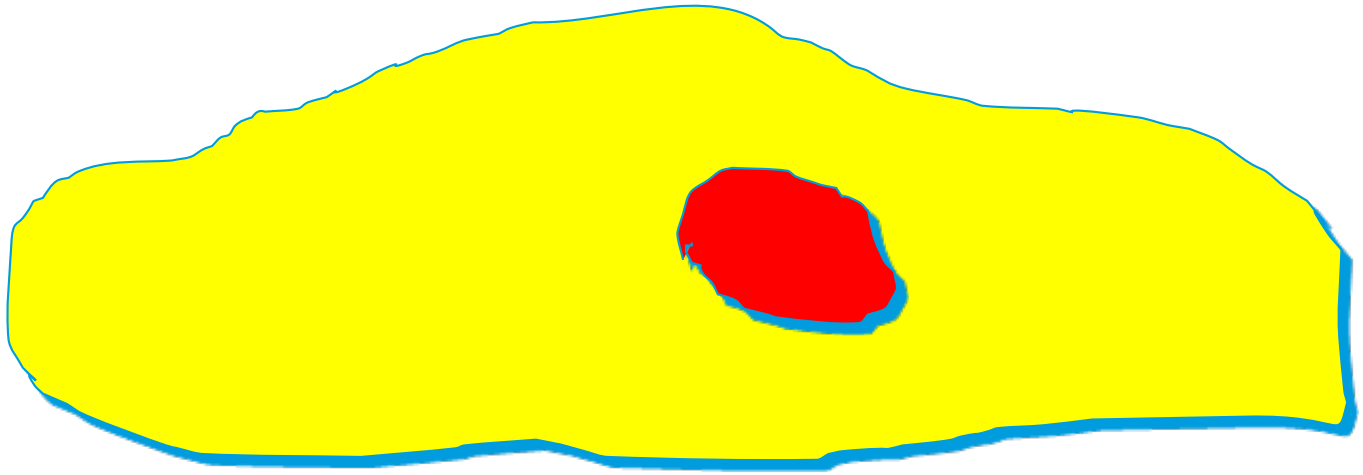
- K_{off} rate is merely a desired result; the structure actually determines the binding characteristics
- Must adequately describe representative antibodies to reflect the structural diversity of the claimed genus

Federal Circuit — Disclosed Species Are Not Representative

- "[J]ury heard ample evidence that AbbVie's patents only describe one type of structurally similar anti-bodies and that those antibodies are not representative of the full variety or scope of the genus."
  - All species derived from Joe-9
  - No examples with heavy chains other than V_H3
  - No examples with light chains other than Lambda
  - All species share 90% sequence similarity, but an antibody with 50% sequence similarity (Stelara®) falls within the claims
    - *Centocor's expert: antibody with 80% similarity could bind completely different antigen*
- "[T]he patents must at least describe some species representative of antibodies that are structurally similar to Stelara."
  - Evidence that predicable changes to disclosed species would produce such a species might have been sufficient

AbbVie v. Janssen (Fed. Cir. 2014) — Key Takeaways

- A large quantity of disclosed species is not necessarily representative
- The court analogized a claimed genus with a plot of land, maintaining that "***if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus***."



Where are we now — *Amgen v. Sanofi*

Amgen v. Sanofi (I) (2017) — Overview

- District court – Amgen sues Sanofi, alleging Praluent® infringes ’165 and ’741 patents
  - Patents found not invalid: Jury found the patents not invalid on written description and enablement grounds; court granted JMOL of non-obviousness
  - Court denied Sanofi’s motions for JMOL and new trial on written description and enablement grounds
- Sanofi Appealed:
  - Exclusion of post-priority date evidence offered for written description purposes;
  - Jury instruction that included the newly-characterized antigen test;
  - Denial of JMOL on written description and enablement; and
  - Other grounds outside the scope of this presentation

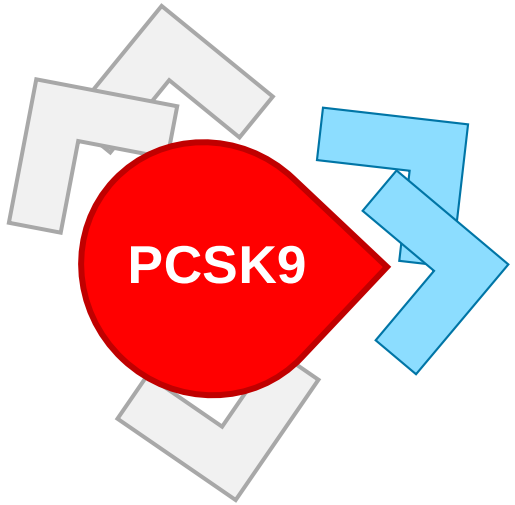
Amgen v. Sanofi (I) (2017) — Representative Claim

U.S Patent No. 8,829,165, claim 1

- Claim 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 LDL[-]R.

PCSK9 Mechanism of Action

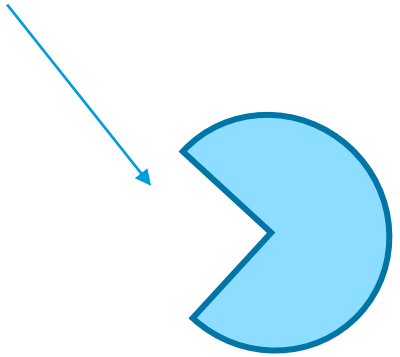
Binds LDL receptor and targets for destruction



High cholesterol

"Sweet Spot"
15 amino acids

EGFa domain



LDL receptor – clears cholesterol from bloodstream

Arguments — Post-Priority-Date Evidence

Question: Can a court rely on post-priority-date evidence for § 112 Issues?

- **Amgen**
  - Post-priority-date evidence may be relevant only if it illuminates the state of the art as of the priority date
  - Antibodies that did not exist until after the priority date can't illuminate the state of the art at the filing date
- **Sanofi**
  - Should be allowed to introduce post-priority-date evidence to establish the scope of the genus which is relevant for both written description and enablement
  - A different rule would undermine the written description requirement's ability to protect against "attempt[s] to preempt the future before it has arrived"

Federal Circuit — Post-Priority-Date Evidence Should Have Been Introduced

- **Written Description**: "Evidence showing that a claimed genus does not disclose a representative number of species may include evidence of species that fall within the claimed genus but are not disclosed by the patent, and evidence of such species is likely to postdate the priority date."
- **Enablement**: Post-priority-date evidence can be used to show that undue experimentation would have been required to enable the claims as of the priority date

Arguments — Newly Characterized Antigen Test Jury Instruction

- Jury Instruction:
  - Uncontested Portion: In order to satisfy the written description requirement, a patentee may disclose either a representative number of species falling within the scope of the genus or disclose structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.
  - Contested Portion: 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.

Arguments — Newly Characterized Antigen Test Jury Instruction

- **Amgen**
  - Instruction simply conveys the law as outlined in previous cases (including *Noelle* and *Centocor*)
- **Sanofi**
  - Disclosing an antigen does not satisfy the written description requirement for a claim to an antibody

Federal Circuit — Newly Characterized Antigen Test Eliminated

- This instruction essentially dispenses with the written description requirement because it allows for a finding that written description is satisfied because antibodies can be easily produced, but the ease with which the antibody can be made and used does not speak to whether the genus of antibodies is described
- Newly characterized antigen instruction would be equivalent to taking judicial notice of a hotly contested factual issue — whether knowledge of the chemical structure of an antigen gives the required kind of structure-identifying information about the corresponding antibodies.
- Written description requires description of the invention; this instruction allows for description to be based on something other than the invention (the antigen)
- Previous mentions of the test were dicta

Federal Circuit — Remand For New Trial on Written Description and Enablement

- "[T]he jury did not hear relevant post-priority-date evidence regarding written description and enablement. This evidence may show, for example, that practicing the invention did not require undue experimentation or that the disclosed species are representative of the claimed genus."
- "Because we are presented with an incomplete record on these issues, the court is unable to determine whether the jury would have a "legally sufficient evidentiary basis" to determine if the patents provide sufficient written description or if the claims are enabled."

Amgen v. Sanofi (I) — Key Takeaways

- **Post-priority-date evidence can be used**:
  - For written description purposes: to show whether a representative number of species has been disclosed
  - For enablement purposes: to show whether undue experimentation would be required to practice the full scope of the claims
- **Newly characterized antigen test cannot be used** to establish written description of a genus of antibody claims

Enablement

35 U.S.C. § 112(a)

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.

Enablement

- **Test:** Does the specification "teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation[?]"

  Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (internal citations and quotations omitted).

- Determining Whether Experimentation is Undue — *Wands* Factors:
  1. the **quantity** of experimentation necessary
  2. the amount of **direction or guidance** presented
  3. the presence or absence of **working examples**
  4. the **nature of the invention**
  5. the state of the **prior art**
  6. the **relative skill** of those in the art
  7. the predictability or **unpredictability of the art**; and
  8. the **breadth** of the claims.

  In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Federal Circuit — Remand For New Trial on Written Description and Enablement

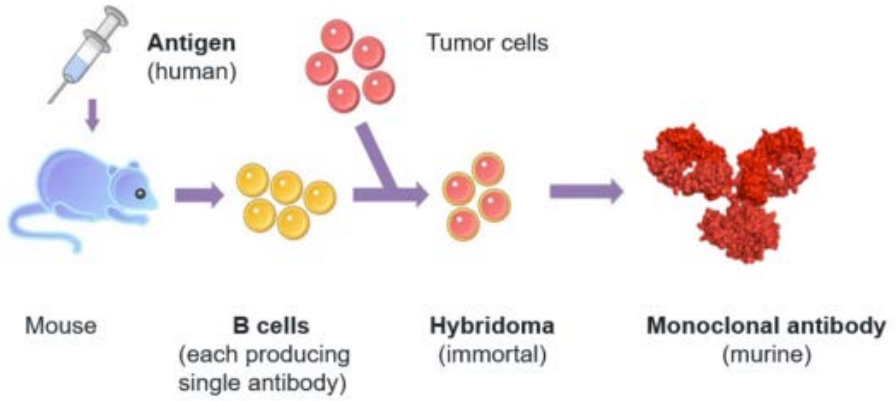
- "[T]he jury did not hear relevant post-priority-date evidence regarding written description and enablement. This evidence may show, for example, that practicing the invention did not require undue experimentation or that the disclosed species are representative of the claimed genus."
- "Because we are presented with an incomplete record on these issues, the court is unable to determine whether the jury would have a "legally sufficient evidentiary basis" to determine if the patents provide sufficient written description or if the claims are enabled."

Enablement — Antibody Cases

In re Wands (Fed. Cir. 1988)

Claim: An immunoassay method utilizing an antibody to assay for a substance . . . wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}

Question: Would it require undue experimentation to produce the high-affinity IgM monoclonal antibodies claimed here?



In re Wands (Fed. Cir. 1988)

- **Holding**: Undue experimentation not required to practice the invention
  - "There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known."
  - "[I]n the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen [including all the steps]. . . Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations."
- **Newman, dissenting in part**:
  - "I would affirm the board's holding that Wands has not complied with 35 U.S.C. § 112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims."

Amgen v. Sanofi (II) (Fed. Cir. 2021) — Overview

- Remand from *Amgen v. Sanofi* (I)- New jury trial on written description and enablement
  - Jury found the claims not invalid again; Sanofi moved for JMOL/ new trial
  - Court denied JMOL on written description and granted JMOL on enablement
- Appeal on enablement decision only

Amgen v. Sanofi (II) (2021) — Representative Claim

U.S Patent No. 8,829,165, claim 1

- Claim 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 LDL[-]R.

Amgen v. Sanofi (II) (Fed. Cir. 2021) — Arguments

- **Amgen**
  - The district court erred by focusing on the effort required to discover and make every embodiment of the claims
  - Disclosed embodiments are structurally representative for written description purposes — this is sufficient to indicate a structure/function correlation establishing enablement
- **Sanofi**
  - The district court correctly determined that undue experimentation would be required under *Wands*
    - Millions of candidates within the scope of the claims
    - Disclosure does not provide sufficient guidance
    - Antibody generation is unpredictable
    - Practicing the full scope of the claims requires substantial trial and error

Federal Circuit — Enablement of Functional Genus Claims

- "While functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language. "
- "We do not hold that the effort required to *exhaust* a genus is dispositive. It is appropriate, however, to look at the amount of effort needed to obtain embodiments outside the scope of the disclosed examples and guidance."
- "[U]ndue experimentation can include undue experimentation in identifying, from among the many concretely identified compounds that meet the structural requirements, the compounds that satisfy the functional requirement."

  (quoting *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 n.2 (Fed. Cir. 2020))

Federal Circuit — Application of *Wands* Factors

- **Breadth**: Claims are broad, particularly when considering functional breadth
- **Predictability**: Field of science is unpredictable with respect to satisfying the full scope of the functional limitations
  - Not possible to translate amino acid sequence into structure
  - Testing required to determine if an amino acid substitution would alter claimed functions (binding and blocking)
  - Lack of nonconclusory evidence that the full scope of the claims can predictably be generated by the described methods
- **Guidance**: Patent did not provide guidance beyond the working examples produced by the patent's "roadmap"
- **Quantity of Experimentation**: Substantial amount of time and effort needed to obtain embodiments outside the scope of the disclosed examples and guidance
- **Overall**: "[T]he evidence showed that the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations."

Amgen v. Sanofi (II) — Key Takeaways

- Functional claims must overcome "high hurdles in fulfilling the enablement requirement"
- Consider amount of experimentation required to *identify* which of the candidates meet the functional limitations
- Consider amount of experimentation required to obtain embodiments outside the scope of the disclosed examples and guidance

Amgen's Petition for Rehearing *En Banc*

Two Questions:

1. Whether the panel's new enablement test for genus claims with functional limitations, which has no basis in § 112's text, conflicts with Supreme Court decisions . . . and decisions of [the Federal Circuit] and its predecessor . . . ?
2. Whether enablement is a question of fact or a question of law?

Amgen's Petition for Rehearing *En Banc*

- Arguments related to the enablement test applied in *Amgen v. Sanofi* (II)
  - The test is inconsistent with the text of §112 and prior precedent
  - Section 112 asks whether POSAs can "make and use" the "invention," not how much work is required to identify all embodiments
  - The full-scope requirement for enablement is focused on whether undue experimentation would be required to practice particular embodiments
  - The test threatens innovation

How will the industry respond to the changing enablement and written description landscape

Thoughts, Questions and Comments?

- What do you think of the *Amgen* decision?
- Are we in the right place?
- Would this decision change companies' strategy around antibody patents?
  - Offensively?
  - Defensively?
- What is the appropriate functional antibody claim scope?
  - Should antibody claims be treated differently than small molecule compound claims?
  - What about antibody claims with "competing with" language?

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A Proskauer Roundtable

The Business of Litigation

Proskauer