United States Court of Appeals for the Federal Circuit

CENTOCOR ORTHO BIOTECH, INC. AND NEW YORK UNIVERSITY,
Plaintiffs-Appellees,

v.

ABBOTT LABORATORIES, ABBOTT BIORESEARCH CENTER, INC., AND ABBOTT BIOTECHNOLOGY LTD.,
Defendants-Appellants.

2010-1144

Appeal from the United States District Court for the Eastern District of Texas in case no. 07-CV-0139, Judge T. John Ward.

Decided: February 23, 2011

DIANNE B. ELDERKIN, Akin Gump Strauss Hauer & Feld LLP, of Philadelphia, Pennsylvania, argued for plaintiffs-appellees. With her on the brief were BARBARA L. MULLIN, STEVEN D. MASLOWSKI, ANGELA VERRECCHIO, and MATTHEW A. PEARSON. Of counsel on the brief were PHILIP S. JOHNSON and ERIC I. HARRIS, Johnson & Johnson, of New Brunswick, New Jersey.

WILLIAM F. LEE, Wilmer Cutler Pickering Hale and Dorr LLP, of Boston, Massachusetts argued for defendants-appellants. With him on the brief were WILLAIM G. MCELWAIN, AMY K. WIGMORE, THOMAS G. SAUNDERS, and ARTHUR W. COVIELLO, of Washington, DC.

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MARK J. STEWART, Eli Lilly and Company, of Indianapolis, Indiana, for amicus curiae Eli Lilly and Company. With him on the brief were ALEJANDRO MARTINEZ, PAUL R. CANTRELL, AMY E. HAMILTON, and ROBERT A. ARMITAGE,

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Before BRYSON, CLEVENGER, and PROST, *Circuit Judges*.

PROST, *Circuit Judge*.

This patent infringement suit involves pharmaceutical antibodies used to treat arthritis. The patent owners, Centocor Ortho Biotech, Inc. and New York University (collectively, "Centocor") sued Abbott Laboratories, Abbott Bioresearch Center, Inc., and Abbott Biotechnology Ltd. (collectively, "Abbott"), alleging that Abbott's Humira® antibody infringes claims 2, 3, 14, and 15 ("the asserted claims") of U.S. Patent No. 7,070,775 ("'775 patent"). After a five-day trial, the jury found Abbott liable for willful infringement. The jury rejected Abbott's argument that the asserted claims were invalid, and awarded Centocor over $1.67 billion in damages.

Abbott moved for judgment as a matter of law ("JMOL") on invalidity, noninfringement, damages, and willfulness. The district court granted Abbott's motion for

JMOL of no willful infringement but denied Abbott's other JMOL motions. Abbott appeals the district court's denial of its JMOL motions. Because the asserted claims of the '775 patent lack written description under 35 U.S.C. § 112, we need not reach Abbott's other invalidity arguments, its infringement arguments, or the question of damages. We reverse the district court's denial of JMOL on this ground and hold the asserted claims invalid for failure to meet the statutory written description requirement.

BACKGROUND

The technology in this case involves antibodies to human tumor necrosis factor α ("TNF-α"). Overproduction of TNF-α can lead to various autoimmune conditions, including arthritis. Although TNF-α antibodies have the potential to reduce the harmful activity caused by excess TNF-α, the human body does not typically make antibodies to human TNF-α. As a result, pharmaceutical companies have been keenly interested in engineering antibodies that can "neutralize" human TNF-α for use as a drug.

TNF-α was identified long before Centocor and Abbott began developing therapeutic antibodies. In fact, by 1985, many researchers had produced antibodies to human TNF-α. These antibodies were typically produced in mice and were not suitable for use in human patients for several reasons. First, many of the antibodies did not have sufficient binding affinity for human TNF-α. Because the antibodies must stick to human TNF-α to work, their binding ability is important. A high affinity antibody sticks better than an antibody that binds with low affinity. If an antibody's affinity is too low, it will not be a viable drug. Second, many of the known antibodies did not have the desired neutralizing activity. While such

antibodies do bind to TNF-α, they do not bind to a place on TNF-α that reduces the harmful TNF-α activity. Since such antibodies do not reduce TNF-α activity, they cannot be used to produce the desired therapeutic effect. In other words, the activity of an antibody is related to both how tightly the antibody sticks as well as the specific location on TNF-α where the antibody binds. Third, human patients frequently have immunological reactions when they are treated with antibodies produced in mice or other non-human species. This is because the human immune system recognizes foreign proteins and attacks them. By engineering foreign antibodies to look more human, scientists try to trick the human immune system and prevent this undesirable immune response. Given these therapeutic limitations of the known TNF-α antibodies, pharmaceutical companies sought to develop an antibody with (1) high affinity, (2) neutralizing activity, and (3) reduced immunogenicity.

In developing their therapeutic TNF-α antibodies, Centocor and Abbott pursued very different strategies. Centocor's path began by identifying a mouse antibody to human TNF-α that had both high affinity and neutralizing activity ("the A2 mouse antibody"). While this antibody had two of the key properties, the mouse antibody was of limited therapeutic use because it would produce an undesirable immune response in humans. To tackle this immunogenicity problem, Centocor decided to use known techniques to modify its mouse antibody to make it look more human. By keeping the parts of the mouse antibody that are responsible for the affinity and the neutralizing activity and changing the less critical portions of the antibody to make these portions more human, scientists sought to preserve the activity of the antibody while reducing its immunogenicity.

For purposes of discussion in this appeal, antibodies basically consist of two regions: a "constant region" and a "variable region." As Centocor's inventor explained to the jury, "the variable regions are really what determines what the antibody is." J.A. 18300, 159:10-12. The variable region is the portion responsible for sticking to TNF-α. The variable region is also the portion of the antibody that determines where on TNF-α the antibody will bind. Making changes in the variable region can thus have a dramatic effect on the affinity and activity of the antibody. Even a small change in the variable region can result in an antibody that does not bind to TNF-α or fails to have neutralizing activity. Centocor avoided the potential pitfalls associated with modifying the variable region by focusing on the constant region. By exchanging the A2 mouse antibody's mouse constant region with a known human constant region, Centocor produced a "chimeric" antibody with a mouse variable region and a human constant region. *See, e.g.*, *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1250-52 (Fed. Cir. 2004) (discussing antibody structure and chimeric antibodies). The resulting chimeric antibody was less immunogenic than the A2 mouse antibody because it contained significantly less mouse protein. At the same time, Centocor's chimeric antibody possessed similar binding and activity to the A2 mouse antibody because they both had the same variable region. Because the chimeric antibody contained a mouse variable region, it was not considered to be "fully human." A chimeric antibody still contains foreign protein, so it is more likely to elicit an immune response than a fully-human antibody.

Centocor filed a patent application disclosing both its A2 mouse antibody and the chimeric antibody in 1991. The application discussed the immunogenicity problem and the difficulties associated with making a fully-human

antibody to a human protein like TNF-α. The application presented chimeric antibodies as the solution to these problems. The 1991 application included eighteen examples detailing methods for making a mouse antibody with high affinity and neutralizing activity and making a corresponding chimeric antibody based on the mouse antibody. The application included claims to Centocor's A2 mouse antibody and chimeric antibodies.

Centocor subsequently filed a series of continuation-in-part ("CIP") applications. In 1993, the U.S. Patent and Trademark Office ("PTO") rejected certain pending claims in a CIP application because they encompassed antibodies with "less than an entire mouse variable region[]." J.A. 38601. The PTO asserted that the specification only enabled antibodies with fully-mouse variable regions. Instead of responding to the rejections, Centocor filed a new CIP application and abandoned the pending application. In due course, the PTO issued the same rejection. Again, instead of responding, Centocor abandoned its application and filed three substantially identical CIP applications in 1994. These 1994 CIP applications added new matter that Centocor now relies on as evidence of written description to support the asserted claims. Although Centocor made these few additions, it did not present claims to human variable regions when it filed the 1994 CIP applications.

While Centocor focused its efforts on making a chimeric antibody, Abbott pursued an alternative path and sought to engineer a fully-human antibody. As discussed above, there is a progression from making a mouse antibody to obtaining the corresponding chimeric antibody. This is because the two antibodies contain the same variable region. In contrast, no corresponding progression exists with respect to making a fully-human antibody.

J.A. 18462 (comparing the process of constructing a chimeric antibody from a mouse antibody with the process of making a human antibody). One of skill in the art cannot look at a mouse variable region and know how to turn it into a human variable region with the same affinity and activity as the mouse antibody.[1]

Abbott decided to work with collaborators to construct a fully-human antibody from scratch. First, Abbott's collaborators created an enormous phage display library containing a spectrum of human variable regions. They searched this library for variable regions that bind to human TNF-α. In the process, they developed a technique known as "guided selection" to help identify variable regions from the library that bind in a specific place so the variable regions have neutralizing activity. After identifying human variable regions that bind to human TNF-α, they used various techniques including "chain shuffling" and "affinity maturation" to improve the binding affinity of the variable regions. These human variable regions were combined with known human constant regions to create fully-human antibodies. By 1995, Abbott had created the therapeutic antibody Humira®. Abbott filed a patent application disclosing this high affinity, neutralizing, fully-human antibody to human TNF-α in 1996. *See* U.S. Patent No. 6,090,382. The PTO granted

[1] The inventor, Dr. John Ghrayeb, testified that "anybody who's experienced would realize that that variable region that we cloned from a mouse could easily have been found in a human, so you could make it." J.A. 18312, 20:11-14. However, Dr. Ghrayeb acknowledged that, in an earlier application that was incorporated by reference in the '775 patent, the inventors had noted the difficulties in developing human monoclonal antibodies, and he admitted that the '775 patent did not offer solutions for those problems. J.A. 18318-19.

the patent in 2000, and Abbott obtained regulatory approval to market Humira® in 2002.

After the grant of Abbott's patent and after regulatory approval of Humira®, Centocor filed its claims to fully-human antibodies. Because the patent family disclosing Centocor's own chimeric antibody was still pending in 2002, Centocor filed the claims as part of a thirteenth application in the family, explicitly claiming human variable regions and fully-human antibodies. Asserted claim 2 and the claim from which it depends are illustrative:

> 1. An isolated recombinant anti-TNF-α antibody or antigen-binding fragment thereof, said antibody or antigen-binding fragment comprising *a human constant region*, wherein said antibody or antigen binding fragment (i) competitively inhibits binding of A2 (ATCC Accession No. PTA-7045) to human TNF-α, and (ii) binds to a neutralizing epitope of human TNF-α in vivo with an affinity of at least $1x10^8$ liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis.
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> 2. The antibody or antigen-binding fragment of claim1, wherein the antibody or antigen binding fragment comprises *a human constant region* and *a human variable region*.

'775 patent col.107 ll.34-46 (emphases added). Independent claim 1, which is not at issue in this appeal, covers antibodies with a human constant region and a variable region from any source. The scope of claim 1 includes, but is not limited to, chimeric antibodies. Asserted claim 2 is limited to antibodies with human constant regions and

human variable regions. Asserted claim 3, which also depends from claim 1, likewise claims antibodies with human variable regions. Asserted claims 14 and 15 similarly include antibodies with human constant regions and human variable regions, although these claims are limited to specific human constant regions. All of the asserted claims cover human variable regions and fully-human antibodies like Abbott's Humira®.

Centocor's application, which contained a priority claim to its earlier applications, issued as the '775 patent in 2006. Shortly thereafter, it filed this action against Abbott, alleging that Abbott's Humira® antibody infringes the asserted claims of the '775 patent. At trial, Abbott argued that the asserted claims were invalid. The jury rejected Abbott's arguments and found willful infringement of the asserted claims. The jury also found that the asserted claims were not invalid for anticipation, lack of enablement, or lack of written description. Abbott moved for JMOL on the issues of infringement, willfulness, and validity. The district court granted Abbott's JMOL motion regarding willfulness and denied the other motions. Abbott now appeals. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

For issues not unique to patent law, we apply the law of the regional circuit in which the appeal would otherwise lie. Thus, we apply Fifth Circuit law when reviewing the district court's denial of Abbott's JMOL motion. *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1328 (Fed. Cir. 2008). The Fifth Circuit reviews denials of JMOL de novo. *Cambridge Toxicology Grp., Inc. v. Exnicios*, 495 F.3d 169, 179 (5th Cir. 2007). JMOL is appropriate only if the court finds that a "'reasonable jury

would not have a legally sufficient evidentiary basis to find for the party on that issue.'" *Id.* (quoting Fed. R. Civ. P. 50(a)(1)).

Patents are presumed to be valid and overcoming this presumption requires clear and convincing evidence. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (en banc). Compliance with the written description requirement of 35 U.S.C. § 112, ¶ 1 is a question of fact, and "'we review a jury's determinations of facts relating to compliance with the written description requirement for substantial evidence.'" *Id.* at 1355 (quoting *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1243 (Fed. Cir. 2002)). A patent also can be held invalid for failure to meet the written description requirement based solely on the face of the patent specification. *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004); *PIN/NIP*, 304 F.3d at 1247-48 (reversing the district court's denial of JMOL because no reasonable juror could have concluded that the asserted claim was supported by adequate written description).

The written description requirement of 35 U.S.C. § 112, ¶ 1 provides, in pertinent part, that:

> 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 of carrying out his invention.

To satisfy the written description requirement, "the applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)). Assessing such "possession as shown in the disclosure" requires "an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. Ultimately, "the specification must describe an invention understandable to [a person of ordinary skill in the art] and show that the inventor actually invented the invention claimed." *Id.* A "mere wish or plan" for obtaining the claimed invention is not adequate written description. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

A

The pivotal issue in this case concerns whether the '775 patent provides adequate written description for the claimed human variable regions. As noted above, Centocor first sought claims to human variable regions and fully-human antibodies in 2002. At that time, Abbott had already discovered and patented a fully-human antibody to TNF-α that had high affinity and neutralizing activity. To ensnare Abbott with later-filed claims, Centocor must use a priority date from an earlier application. Because Abbott's application was filed in 1996, Centocor relies on a priority claim to the 1994 CIP applications. Thus, in order for Centocor to prevail, the asserted claims must be supported by adequate written description in the 1994 CIP applications.

The asserted claims cover fully-human antibodies that possess the same therapeutic properties as Centocor's chimeric antibody, i.e., high affinity, neutralizing activity, and binding at a specific place on human TNF-α. Accordingly, the 1994 CIP applications must provide written description for an antibody to human TNF-α with (1) a human constant region, (2) a human variable region, (3) high affinity for human TNF-α, (4) neutralizing activity, and (5) the ability to bind to TNF-α in the same place as Centocor's A2 mouse antibody ("A2 specificity").

At trial, Abbott's expert, Dr. James Marks, testified about the disclosure in the 1994 CIP applications and explained why a person of ordinary skill in the art would not have understood that Centocor had possession of a high affinity, neutralizing, A2 specific, fully-human antibody. J.A. 18472-75. On appeal, Abbott emphasizes that Dr. Marks provided the only expert testimony that the jury heard about written description. To underscore the inadequacy of Centocor's written description, Abbott points out that the specification does not disclose any fully-human, high affinity, neutralizing, A2 specific antibody. Moreover, the specification does not disclose a single human variable region. Abbott argues that the only described antibody is the chimeric antibody, which has a mouse variable region. Abbott also argues that Centocor has merely disclosed tools that might be used in an attempt to make the claimed invention—essentially, that Centocor's disclosure is no more than a mere wish or plan for how one might search for a fully-human antibody that satisfies the claims. Finally, Abbott points to testimony from Centocor's inventor indicating that the disclosure did not include examples about making a human antibody because "it was never [Centocor's] intention to make a human antibody." J.A. 18312, 18:19-24. Abbott

contends that Centocor is attempting to claim as its own the fruit of Abbott's innovative work.

In response, Centocor points to specific disclosures in the 1994 CIP applications identified by inventor Dr. John Ghrayeb as evidence that the asserted claims are adequately described and enabled. Centocor presented no expert testimony on written description at trial and instead chose to rest on the '775 patent specification and the testimony of its inventors. Without directly relying on the PTO written description guidelines or what it refers to as "dicta" in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), Centocor contends on appeal that the '775 patent "does much more than what the Guidelines and *Noelle* suggest," in that it not only describes the antibodies by their binding affinity for TNF-α, but further describes the antibodies by specifying that they competitively inhibit binding of the A2 mouse antibody to TNF-α. Centocor also argues that the written description requirement demands neither actual reduction to practice nor working examples to claim an invention.

We turn to the four corners of the 1994 CIP applications to assess whether their disclosure provides adequate written description for the asserted claims. Because the pertinent disclosure from the 1994 applications appears in the '775 patent as issued, we refer only to the '775 patent for clarity.

B

Contrary to Centocor's assertions, very little in the '775 patent supports that Centocor possessed a high affinity, neutralizing, A2 specific antibody that also contained a human variable region. The overwhelming majority of the '775 patent describes the A2 mouse anti-

body and the single chimeric antibody that Centocor made based on A2's mouse variable region. The specification describes the structure and characteristics of the chimeric antibody in great detail, indicating that it binds to TNF-α with high affinity, has neutralizing activity, and is A2 specific—characteristics mirrored by the critical claim limitations in the asserted claims. The specification also includes the sequence of the human TNF-α protein, references to cell lines that produce the mouse and chimeric antibodies, and numerous examples describing making and using the chimeric antibody. '775 patent col.15 ll.40–54; col.42 l.60–col.68 l.67; col.99 ll.1–40. As for describing suitable variable regions, the application only provides amino acid sequence information (a molecular description of the antibody) for a single mouse variable region, i.e., the variable region that the mouse A2 antibody and the chimeric antibody have in common. *Id.* at cols.99–103. However, the mouse variable region sequence does not serve as a stepping stone to identifying a human variable region within the scope of the claims.[2]

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[2] Dr. Marks testified at length about the state of the art at the time Centocor's specification was filed and explained that one of skill in the art would not understand from the disclosure of a mouse variable region that Centocor was in possession of an antibody with a fully human variable region. He concluded:

> Q. And how do the protein sequences of the mouse antibody, or the chimeric antibody, compare to a full human antibody?
> A. They're very different.
> Q. And would the disclosure of this sequence information teach of one ordinary skill in the art how to make and use a fully human [antibody]?
> A. No.
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> J.A. 18476, 114:20-115:2.

The undisputed trial testimony indicated that the sequence of Centocor's mouse variable region was "very different" from the sequence of a human variable region like the one in Abbott's fully-human antibody.

In marked contrast to the detailed description of the claimed chimeric antibodies, Dr. Ghrayeb was able to point to only a few sentences sprinkled throughout the '775 patent that mention human antibodies or human variable regions at all. *Id.* at col.5 l.57; col.12 l.29; col.16 l.29; col.18 l.60. Dr. Marks testified that the mere fact that "the words appear" does not reasonably suggest to one of skill in the art that Centocor was in possession of such antibodies. J.A. 18493, 16:8-17:22. Further, while the specification notes that fully-human antibodies can potentially be produced by human B lymphocytes, it does not disclose any B lymphocytes that actually produce a high affinity, neutralizing, A2 specific TNF-α antibody. *Id.* at col.15 ll.1–9.[3]

In addition, Dr. Ghrayeb highlighted a single reference to an article describing using phage display technology to make low affinity, human antibodies. *Id.* at col.18 ll.52–53. Dr. Marks, the author of the article, testified at trial that it teaches low affinity antibodies to red blood cells. He stated that "the antibodies coming out of [these early phage libraries] were very low affinity" and explained that "there's no teaching in this paper about how to make TNF antibodies." J.A. 18475, 110:3-19. Dr. Ghrayeb likewise testified that the article describes using

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[3] Dr. Marks and Dr. Pablo Casali both testified that to this day, the human B lymphocyte method has never been used successfully to make a high-affinity, neutralizing, fully-human, TNF-α antibody. J.A. 18450, 13:1-6; 18464, 69:2-8.

a phage library to identify antibodies that bind to red blood cells. J.A. 18310, 10:10-12. The article does not discuss making fully-human antibodies to human TNF-α, nor does it discuss making antibodies that bind in a specific place like the claimed A2 specific antibodies. Dr. Marks testified that references in the patent addressing phage display "describe[] very general library technologies that could be used to make antibodies, including human antibodies," J.A. 18474, 108:12-14, but they do not teach how to isolate or use such antibodies. The fact that a fully-human antibody could be made does not suffice to show that the inventors of the '775 patent possessed such an antibody.

Besides pointing to these limited references to fully-human antibodies, none of which relate to the specific critical limitations in the asserted claims, Centocor suggests that written description for the asserted claims comes from the limitations described in the claim language itself. However, this specific claim language was not added until 2002 and is not part of the 1994 CIP applications as filed.

Thus, while the patent broadly claims a class of antibodies that contain human variable regions, the specification does not describe a single antibody that satisfies the claim limitations. *See Eli Lilly*, 119 F.3d at 1566-69. It does not disclose any relevant identifying characteristics for such fully-human antibodies or even a single human variable region. *See id.* Nor does it disclose any relationship between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations. *See id.* There is nothing in the specification that conveys to one of skill in the art that Centocor possessed fully-human antibodies or

human variable regions that fall within the boundaries of the asserted claims.

At bottom, the asserted claims constitute a wish list of properties that a fully-human, therapeutic TNF-α antibody should have: high affinity, neutralizing activity, and the ability to bind in the same place as the mouse A2 antibody. The specification at best describes a plan for making fully-human antibodies and then identifying those that satisfy the claim limitations. But a "mere wish or plan" for obtaining the claimed invention is not sufficient. *See id.* at 1566. At the time the 1994 CIP applications were filed, it was entirely possible that that no fully-human antibody existed that satisfied the claims. Because Centocor had not invented a fully-human, high affinity, neutralizing, A2 specific antibody in 1994, a reasonable jury could not conclude that it possessed one.

C

Although it does not fully endorse those positions, Centocor suggests that our decision in *Noelle* and the PTO written description guidelines support the view that fully disclosing the human TNF-α protein provides adequate written description for any antibody that binds to human TNF-α. That suggestion is based on an unduly broad characterization of the guidelines and our precedent.

The current PTO written description guidelines include an antibody example. Referencing only an immunology text published in 1976, the PTO guidelines indicate that a functional claim reciting "an isolated antibody capable of binding to [protein] X" is adequately described where the specification fully characterizes protein X—even if there are no working or detailed prophetic examples of actual antibodies that bind to protein

X. U.S.P.T.O., *Written Description Training Materials Revision 1 March 25, 2008* at 45-46 (available at *http://www.uspto.gov/web/menu/written.pdf*) (hereinafter *PTO guidelines*). The antibody example presumes that the applicant is disclosing a novel protein and then claiming both the protein and an antibody that binds to it. The PTO guidelines characterize "production of antibodies against a well-characterized antigen" as "conventional" and "routine," given "well developed and mature" antibody technology. *Id.* at 46. The PTO guidelines conclude that characterization of the protein alone may be sufficient under circumstances where "one of skill in the art would have recognized that the disclosure of the adequately described [protein] X put the applicant in possession of antibodies which bind to [protein] X."[4] *Id.* In

[4] The PTO guidelines explain why disclosure of a well-characterized protein generally places the possessor of the protein in possession of antibodies to that protein. Basically, producing certain types of antibodies is conventional. *PTO guidelines* at 46. It is routine to raise a spectrum of antibodies to a known protein simply by injecting that protein into a host animal that is a different species. The host generates antibodies to the foreign protein. For this reason, some antibodies to a well-characterized protein may be adequately described even when they are functionally claimed and not actually produced.

Depending on the state of the art, this reasoning might not apply to obtaining *human* antibodies to a *human* protein for several reasons. For example, even if it were ethically possible to use humans as hosts to generate antibodies, proteins like human TNFα are "self" proteins, so a human host might not produce effective antibodies against the antigen. J.A. 18449 (discussing conventional antibody production techniques and the difficulties associated with making human antibodies to self proteins). In fact, the two known high affinity, neutralizing, fully-human antibodies to human TNFα were not produced using this method.

other words, an applicant can claim an antibody to novel protein X without describing the antibody when (1) the applicant fully discloses the novel protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody.

In *Noelle*, we discussed the PTO's antibody example. 355 F.3d at 1349. The case focused on antibodies to a protein called CD40CR. Noelle claimed an antibody that "specifically binds CD40CR." *Id.* at 1346. This broad claim covered antibodies that bind CD40CR from any species. Noelle also claimed an antibody that specifically binds *human* CD40CR, *id.*, yet the specification only disclosed the *mouse* CD40CR protein and an antibody to that protein, *id.* at 1349. The specification did not describe any antibodies to *human* CD40CR or CD40CR from any other species, nor did it describe any CD40CR protein from any species except mouse. *Id.* We concluded that Noelle's specification did not provide adequate written description for such broad claims.

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. Here, both the human TNF-α protein and antibodies to that protein were known in the literature.[5] The claimed "invention" is a class of antibodies containing a human variable region that have particularly desirable therapeutic properties: high affinity, neutralizing activity, and A2 specificity.

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[5] The '775 patent specification describes the existing literature on tumor necrosis factor and the various polyclonal and monoclonal antibodies previously known in the art. '775 patent col.1 l.42–col.3 l.55.

Claiming antibodies with specific properties, e.g., an antibody that binds to human TNF-α with A2 specificity, can result in a claim that does not meet written description even if the human TNF-α protein is disclosed because antibodies with those properties have not been adequately described.

As discussed above, obtaining a high affinity, neutralizing, A2 specific antibody with a human variable region was not possible in 1994 using "conventional," "routine," "well developed and mature" technology. *PTO guidelines* at 46. Centocor highlights Dr. Jochen Salfeld's testimony analogizing the antibody-antigen relationship to "a key in a lock." J.A. 18436, 154:4-5. What Centocor ignores is the remainder of Dr. Salfeld's testimony, which pointed to the challenges of finding an appropriate antibody on "a ring with *a million* keys on it." *Id.*, 154:2-3. Centocor simply failed to support its contention that generating fully-human antibodies with the claimed properties would be straightforward for a person of ordinary skill in the art given the state of human antibody technology in 1994. Unlike the antibody example cited in the PTO guidelines, therefore, simple possession of the known TNF-α protein did not place Centocor in possession of the claimed antibodies.

D

In view of the lack of written description in the specification for fully-human, A2 specific, neutralizing, high affinity antibodies, Centocor's argument that an inventor need not physically make an invention to claim it misses the mark. Indeed, we have repeatedly indicated that the written description requirement does not demand either examples or an actual reduction to practice. *Ariad*, 598 F.3d at 1352. What it does demand is that one of skill in

the art can "visualize or recognize" the claimed antibodies based on the specification's disclosure. *Eli Lilly*, 119 F.3d at 1568. In other words, the specification must demonstrate constructive possession, and the '775 patent's specification fails to do so. *Ariad*, 598 F.3d at 1352. Centocor's asserted claims to fully-human antibodies "merely recite a description of the problem to be solved while claiming all solutions to it." *Ariad*, 598 F.3d at 1353. The actual inventive work of producing a human variable region was left for subsequent inventors to complete.

The scope of Centocor's right to exclude cannot "overreach the scope of [its] contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). Its fully-human antibody claims are beyond the scope of its disclosure. As in *Ariad*, we conclude that the jury lacked substantial evidence for its verdict that the asserted claims were supported by adequate written description. The district court erred when it declined to grant Abbott a JMOL that the asserted claims fail to satisfy the written description requirement of 35 U.S.C. § 112.

CONCLUSION

We hold that claims 2, 3, 14, and 15 of the '775 patent are invalid for lack of written description. The judgment below is reversed.

REVERSED