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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/423,927	04/28/2003	David Wallach	WALLACH=12C	1478
1444	7590	01/17/2013	EXAMINER	
Browdy and Neimark, PLLC 1625 K Street, N.W. Suite 1100 Washington, DC 20006			GAMBEL, PHILLIP	
			ART UNIT	PAPER NUMBER
			1644	
			MAIL DATE	DELIVERY MODE
			01/17/2013	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID WALLACH, JACEK BIGDA, IGOR BELETSKY,
IGOR METT, and HARTMUT ENGELMANN

Appeal 2011-005314
Application 10/423,927
Technology Center 1600

Before LORA M. GREEN, JEFFREY N. FREDMAN, and
SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

Opinion for the Board filed by SNEDDEN,
Administrative Patent Judge.

Opinion Concurring filed by FREDMAN,
Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a DNA molecule. The Examiner has rejected the claims as lacking adequate written description and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

STATEMENT OF THE CASE

“Tumor necrosis factor (TNF) is a pleiotropic cytokine, produced by a number of cell types, mainly by activated macrophages.” (Spec., ¶ [0003].) The various effects of TNF are all signaled by the binding of TNF to TNF receptors (TNF-Rs). (*Id.*, ¶ [0003].) There are two forms of TNF-Rs, a 55-kilodalton TNF-R and a 75-kilodalton TNF-R, referred to as p55 (or TBP-I¹) and p75 TNF-R (or TBP-II), respectively. (*Id.*, ¶ [0005].) “The cell-killing activity of TNF is thought to be induced by the p55 receptor,” although “this p55 receptor activity can be assisted by the p75 receptor.” (*Id.*, ¶ [0007].)

Appellants’ invention relates to DNA molecules encoding the antigen binding portion of “[a]ntibodies to [TNF-Rs] which inhibit the cytotoxic effect of TNF but not its binding to the TNF-Rs.” (*Id.*, Abst.) Claim 1, the sole independent claim on appeal, reads as follows:

1. A DNA molecule comprising a DNA sequence encoding a peptide which inhibits the cytotoxic effect of TNF but does not block TNF binding to the p75 TNF receptor,
said peptide comprising the antigen binding portion of a monoclonal antibody that binds to the fourth cysteine rich domain of the p75 TNF receptor, which domain consists of the sequence of amino acid residues 163 to 185 of SEQ ID NO:2, or to the region between said fourth cysteine rich domain of the p75 TNF receptor and the cell membrane, which region consists of the sequence of amino acid residues 201-257 of SEQ ID NO:2.

¹ Terlizese et al., *In vitro comparison of inhibiting ability of soluble TNF receptor p75 (TBP II) vs. soluble TNF receptor p55 (TBP I) against TNF-alpha and TNF-beta*, 16 J INTERFERON CYTOKINE RES. 1047-53 (1996); available at <http://www.ncbi.nlm.nih.gov/pubmed/8974008>.

The claims stand rejected as follows:

- I. Claims 1-4 and 6-10 under 35 U.S.C. § 103(a) as obvious over the combination of Wallach² and Queen.³
- II. Claims 1-3 and 6-10 under 35 U.S.C. § 112, first paragraph, written description.

The Examiner withdrew, on appeal, the rejection of claims 1-4 and 6-10 under 35 U.S.C. § 103(a) in view of Bigda.⁴ (Ans. 3).

I.

Issue

The Examiner has rejected claims 1-4 and 6-10 under 35 U.S.C. § 103(a) as obvious over the combination of Wallach and Queen. The Examiner finds that Wallach discloses “a variety of antibodies that bind the human p75 TNF receptor, including antibodies with blocking and non-blocking properties, as well as their use in immunoassays, affinity purification and as pharmaceutical compositions, including antibody 67.” (Ans. 10.) The Examiner finds that Wallach “differs from the claimed invention by not disclosing the identification or isolation of nucleic acids encoding antibodies of interest at the time the invention was made.” (*Id.*)

The Examiner relies on the teaching of Queen and finds as follows:

Queen et al. teach that at the time the invention was made methods of producing recombinant antibodies starting from hybridoma and antibody producing cells (see entire document).

² Wallach et al., EP 0 398 327 A1, published Nov. 22, 1990.

³ Queen et al., US 5,530,101, issued Jun. 25, 1996.

⁴ Bigda et al., *Dual Role of the p75 Tumor Necrosis Factor (TNF) Receptor in TNF Cytotoxicity*, 180 J. EXP. MED. 445-460 (1994).

Queen et al. teach that immunoglobulin gene structure and organization were well understood in the art at the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs comprising expression vectors containing DNAs encoding immunoglobulin variable regions. The determination and manipulation of the nucleic acid sequences encoding antibodies of interest was an outcome and product(s) of such engineering.

(Ans. 11.)

In reaching a conclusion of obviousness, the Examiner finds “[i]t would have [been] prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to employ the methods of Queen et al. to obtain nucleic acids encoding the anti-TNF p75 receptors antibodies of interest, including the antibody 67 specificity, taught by Wallach.” (Ans. 12.)

Appellants contend that antibody 67 is described by Wallach merely as an “arbitrary name.” (*Id.* at 28.) Appellants further contend that “[a]ntibody 67 is the name of one antibody among the large list of antibodies disclosed in ... [Wallach] that bind to the TNF p75 receptor” and that “[t]his name would mean nothing to one of ordinary skill the art” reading Wallach because Wallach does not refer “to any deposit of a hybridoma by this name and no sequence information or even epitope specificity is disclosed for it.” (*Id.*)

The issue presented is: Does the evidence of record support the Examiner’s conclusion that cited prior art renders claim 1 obvious?

Findings of Fact

FF1. Wallach discloses monoclonal antibodies to TBP-II identified by hybridoma clone numbers. (*See e.g.*, Wallach, pp. 12-14 and 16-17.)

FF2. Wallach discloses that TBP-II or an unspecified fragment may be used for the production of antibodies. (*See e.g.*, Wallach, p. 6. ll. 57-58 and p. 11, ll. 20-45.)

Principles of Law

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993).

Analysis

In the present case, Wallach provides names for antibodies where the names are arbitrary (FF1) and completely devoid of any structural meaning sufficient to inform a person of ordinary skill in the art as to which region of p75 TNF receptor the antibodies bind (FF2). The claims require binding either to the region including amino acids 163 to 185 of SEQ ID NO:2, or to the region which consists of amino acids 201-257 of SEQ ID NO:2. Thus, while Wallach provides evidence that p75 TNF receptor antibodies exist, a person of ordinary skill in the art would not have necessarily produced DNA encoding an antibody capable of binding to the specific regions of p75 TNF receptor recited in the claims using the techniques disclosed by Queen. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (“Inherency, however, may not be established by probabilities or

possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”) We therefore find that the Examiner has not established that the ordinary artisan would have inherently and predictably selected the recited regions of p75 TNF receptor in order to produce DNA encompassed by the claim.

Conclusion of Law

The evidence of record does not support the Examiner’s conclusion that cited prior art renders claim 1 or dependent claims thereto obvious.

II.

Issue

The Examiner finds that claims 1-3 and 6-10 fail to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner concedes that DNA encoding the monoclonal antibody produced from the deposited CNCM No. 1-1368 hybridoma could have been derived using “known procedures of selecting, isolating and linking the particular DNAs from this particular hybridoma/cell line at the time the invention was made.” (Ans. 16.) As such, claim 4, which is directed to DNA derived from the CNCM No. 1-1368 hybridoma, is not subject to this written description rejection. (*See* Ans. 16.) However, the Examiner finds that “the specification is insufficiently representative to provide adequate written descriptive support for the genus of such diverse DNA molecules required to practice the claimed invention.” (*Id.*)

Appellants contend that Example 13 of the Written Description Training Materials⁵ supports a finding that

there is written description for the entire genus of antibodies that are capable of binding to “antigen X,” even if the specification does not describe an actual reduction to practice of an antibody that binds to antigen X, by description of a method of making such an antibody or by deposit, and even if the specification does not describe any physical or chemical properties of the claimed antibody, and even if the specification does not disclose a correlation between the function of binding to antigen X and the structure of the claimed antibody.

(App. Br. 16.) And if “one is in possession of a monoclonal antibody against antigen X, one is also in possession of the hybridoma that produces such a monoclonal antibody, as one cannot produce such a monoclonal antibody by the conventional method without a hybridoma that encodes and expresses it.” (*Id.* at 17.) One is also in possession of the DNA encoding the antibody because the “hybridoma includes DNA encoding the amino acid sequence of the antibody.” (*Id.*)

Appellants further contend that, in the present case, the specification discloses how to make all hybridomas that produce monoclonal antibodies binding to an antigen whose sequence is specifically disclosed and having the desired properties; one such hybridoma has been deposited and the sequence is thus effectively available as part of the written description of the present specification. Applicants were as much in possession of the undeposited hybridomas as they were of the antibodies produced thereby.

⁵ Example 13, “Antibodies to a Single Protein,” Written Description Training Materials, Revision 1, March 25, 2008, available at <http://www.uspto.gov/web/menu/written.pdf>.

(*Id.* at 17-18, citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed Cir. 2002).)

The issue presented is:

Does Appellants' Specification contain a written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed?

Additional Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

FF3. The Specification discloses the deduced amino acid sequence of the p75 receptor as SEQ ID NO: 2. (Spec. 15, ¶ [0045], and Figures 2A-C.)

FF4. The Specification identifies protein regions corresponding to residues 163-201 of SEQ ID NO: 2 and residues 202-257 of SEQ ID NO: 2 as recognized by the claimed antibodies. (*See e.g., Id.* 4, ¶¶ [0009]-[0010].)

FF5. The "67 epitope" refers to a region of the p75 TNF-R that "may extend between about amino acids pro-141 and thr-179 in the p75 TNF-R (residues 163-201 of SEQ ID NO:2) or a corresponding region in another member of the TNF/NGF family." (*Id.*)

FF6. The Specification discloses a general method for the production of monoclonal antibodies using hybridomas. (*Id.*, ¶¶ [0061]-[0062].)

FF7. Hybridoma "TBP-II 67" was deposited with the Collection National de Cultures de Microorganismes (CNCM), Institut Pasteur, 25, rue du Docteur Roux, 75724 Paris Cedex 15, France, on October 11, 1993 and assigned Nos. I-1368. (*Id.*, ¶ [0076].)

FF8. The Specification discloses a “stalk” region of p75 TNF-R (*id.* at 5, ¶ [0014]), where a “stalk-antibody” recognizes a region downstream of the fourth cysteine rich domain, more particularly the region extending from about amino acid 181 to about amino acid 235” of SEQ ID NO:2 (*id.* at 17, ¶ [0055]).

Principles of Law

[W]hether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. For generic claims, [the court has] set forth a number of factors for evaluating the adequacy of the disclosure, including “the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.”

Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357-59 (Fed. Cir. 2005)).

“[S]equences are representative of the scope of the genus claims, *i.e.*, if they indicate that the patentee has invented species sufficient to constitute the genera, they may be representative of the scope of those claims.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 967 (Fed. Cir. 2002).

Disclosure of an amino acid sequence effectively puts those of skill in the art in possession of the entire genus of DNA sequences that encode the amino acid sequence. *See In re Wallach*, 378 F.3d 1330, 1333 (Fed. Cir. 2004).

A functional description is inadequate because “[o]ne skilled in the art ... cannot, as one can do with a fully described genus, visualize or recognize

the identity of the members of the genus. A definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.” *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Analysis

Claim 1 is directed to DNA encoding the antigen binding portion of the recited p75 TNF-R antibodies. The Examiner does not dispute that Appellants were in possession of DNA encoding antibodies produced by the CNCM No. I-1368 hybridoma by virtue of a biological deposit made under the Budapest Treaty (FF5-FF6; Ans. 16). *See, Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d at 965 (“[R]eference in the specification to a deposit [of a nucleotide sequence] in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.”). What is disputed is whether the DNA of CNCM No. I-1368 hybridoma is representative of a genus of DNA molecules encompassed by claim 1.

Claim 1 encompasses a genus of DNA molecules that includes DNA encoding the antigen binding portion of monoclonal antibodies that bind to two domains of the p75 TNF receptor: the first domain defined by amino acid residues 163 to 185 of SEQ ID NO: 2; and the second domain defined by amino acid residues 201-257 of SEQ ID NO: 2. However, there is no evidence of record that supports a finding that hybridomas capable of producing antibodies that bind to residues 202-257 of SEQ ID NO: 2 have been deposited. (*See e.g.*, FF3-FF8.) Appellants have also not adequately

explained how possession of antibodies binding to one domain of the p75 TNF receptor (*i.e.*, the “67 epitope”; FF5-FF8) shows possession of DNA molecules encoding antibodies that bind to each domain recited by the claims (*i.e.*, residues 202-257 of SEQ ID NO: 2). In view of the above, we find that the genus of DNA molecules encoding antibodies that bind to residues 202-257 of SEQ ID NO: 2 are defined solely by function. In the absence of a correlation between structure and function, a description that defines a claimed genus only by function does not satisfy § 112. *Eli Lilly*, 119 F.3d at 1568; *Wallach*, 378 F.3d at 1335 (A “functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art.”).

Conclusion of Law

Appellants have not shown that the Examiner erred in finding that the Specification does not adequately describe the claimed genus of DNA molecules in order to show possession to a skilled worker at the time the application was filed.

SUMMARY

We reverse the rejection of claims 1-4 and 6-10 under 35 U.S.C. § 103(a) as obvious over the combination of Wallach and Queen.

We affirm the rejection of claims 1-3 and 6-10 under 35 U.S.C. § 112, first paragraph, written description.

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TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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CONCURRING OPINION

FREDMAN, *Administrative Patent Judge*.

I fully concur with the opinion of the Majority regarding the reversal of the prior art rejection. I concur with the Majority's result affirming the written description rejection, but I differ with the Majority's analysis of the written description issue. In my opinion, the Examiner's rejection is consistent with the reasoning of *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, 636 F.3d 1341, 1351 (Fed. Cir. 2011).

Principles of Law

“[T]he 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.” *Centocor*, 636 F.3d at 1351. “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.” *Id.*

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. ... Claiming antibodies with specific properties ... can result in a claim that does not meet written description even if the [target] protein is disclosed because antibodies with those properties have not been adequately described.

Id. at 1352.

Analysis

In my view, the central issue in this written description requirement is the functional requirement in claim 1 that the peptide, encoded by the DNA, comprise “the antigen binding portion of a monoclonal antibody that binds . . . amino acid residues 163 to 185 of SEQ ID NO: 2” and also functions to inhibit “the cytotoxic effect of TNF but does not block TNF binding to the p75 TNF receptor.” I do not dispute that an antibody and therefore a peptide portion of an antibody which binds to amino acids 163 to 185 of SEQ ID NO: 2 is described.

However, I conclude that the functional requirement that this peptide also inhibits the cytotoxic effect of TNF without blocking TNF binding to the p75 TNF receptor is the sort of wish list of properties which fails to satisfy the written description requirement since 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.” *Centocor*, 636 F.3d at 1352.

The absence of description in the Specification of a routine method for obtaining antibodies with the functional properties of claim 1 is evidenced by Example 8, where anti-p75 antibodies alone as well as other antibodies (67, 32, and 318) result in continued cell viability (i.e. inhibit cytotoxic effect of TNF), while anti-p55 antibodies reduce cell viability (*see* Spec. 29, ll. 1-16; Fig. 4, 6). There is, however, no disclosure in the Specification of what antibody structures, antigens, or other information is

necessary to obtain the functional result inhibiting TNF without blocking TNF binding to the p75 TNF receptor. Consequently, the instant

claims merely recite a description of the problem to be solved while claiming all solutions to it and, as in *Eli Lilly and Ariad's* claims, cover any compound later actually invented and determined to fall within the claim's functional boundaries—leaving it to the pharmaceutical industry to complete an unfinished invention.

Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1353 (Fed. Cir. 2010).

The Specification provides no information on how the function of “inhibit[ing] the cytotoxic effect of TNF” operates without “block[ing] TNF binding to the p75 TNF receptor” (Claim 1). While such allosteric effects are known to exist, the Specification fails to provide any structural or functional relationships for reliably, routinely or even rarely generating peptides and antibodies which have the functional property of inhibiting TNF’s cytotoxic effects without blocking TNF binding to the p75 receptor.

Appellants contend that “possession of one such hybridoma was sufficient to obviate the present written description rejection for claim 4” (App. Br. 21).

Where a single specific inhibitor, $\text{Ik}\beta$, was taught by the Specification, *Ariad* finds that “a vague functional description and an invitation for further research does not constitute written disclosure of a specific inhibitor” insufficient to satisfy the written description requirement. *Ariad*, 598 F.3d at 1356. Similarly, in the instant case, the possession of a single species of antibody, without any structure or reliable methodology to produce other

antibodies which necessarily share the functional property of “inhibit[ing] the cytotoxic effect of TNF” without “block[ing] TNF binding to the p75 TNF receptor” lacks written description.

This is precisely the sort of situation where Appellants have expressed a wish. A wish for an antibody with certain functional properties. It is a fine, useful and desirable wish, but a wish nonetheless. There is no description of the antigen necessary to obtain this antibody. There is, at best, a single example of such an antibody with no structural description of the antibody itself. There is no description in the Specification of any method which could be reliably used to obtain this antibody. *Centocor* mandates that a “‘mere wish or plan’ for obtaining the claimed invention is not sufficient.” *Centocor*, 636 F.3d at 1351. Here, Appellants’ Specification lacks even a plan, retaining only the wish.

For these reasons, I concur with the result of the Majority in affirming the written description rejection.