United States Court of Appeals for the Federal Circuit

2008-1079
(Serial No. 08/469,749)

IN RE KENNETH ALONSO

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Appealed from: United States Patent and Trademark Office
Board of Patent Appeals and Interferences

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Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in Appeal No. 2006-2148.

DECIDED: October 30, 2008

Before MICHEL, Chief Judge, MAYER, Circuit Judge, and STEARNS,* District Judge.

STEARNS, District Judge.

Dr. Kenneth Alonso appeals a decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") sustaining in part the examiner's final rejection of claim 92 of U.S. Patent Application No. 08/469,749 ("'749 Application"). In its decision, the Board reversed the examiner's rejection of claim 92 for lack of enablement and sustained the rejection as invalid for lack of adequate written description. Ex parte Alonso, No. 2006-2148 (B.P.A.I. July 25, 2007) ("Decision"). We affirm.

I. BACKGROUND

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* Honorable Richard G. Stearns, District Judge, United States District Court for the District of Massachusetts, sitting by designation.

An arsenal of antibodies generated by the immune system defends the human body against illnesses caused by bacteria and cancerous cells and other invasive agents. Antibodies are large, Y-shaped molecules secreted by white blood cells known as "B lymphocytes," or "B-cells." Antibodies are capable of binding to the surfaces of foreign cells or other substances known as "antigens." The specific location on the surface of the antigen where the antibody attaches is termed the "epitope." The arms of the Y-shaped molecule bind to the epitope with specificity. Antibodies that bind to the same epitope are said to have the same "idiotype." Monoclonal antibodies ("MAbs") are derived from a single precursor and have a single idiotype. They are produced using "hybridoma" (fusion) technology. A human-to-human hybridoma is created by fusing a human tumor cell to an antibody-producing human B-cell, resulting in secretion by the B-cell of monoclonal antibodies with identical affinity and specificity to a given epitope on the surface of the tumor cell.

On June 6, 1995, Dr. Alonso filed the '749 Application entitled, "Method of Producing Human-Human Hybridomas, The Production of Monoclonal and Polyclonal Antibodies Therefrom, and Therapeutic Use Thereof."[1] The claimed invention recites a method for treating neurofibrosarcoma, a rare cancer of the sheath of a peripheral nerve, that uses human monoclonal antibodies targeted at a patient's tumor. Claim 92 of the '749 Application discloses

> [a] method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.

[1] Alonso claimed priority to an application he filed seven years earlier involving similar subject matter.

In Example 1 of the '749 Specification, Alonso described the preparation of a tumor cell suspension from the sample of a tumor and the subsequent sensitization of human spleen cells. The sensitized spleen cells are fused with an immortalized cell line (e.g., a fetal marrow line, a lymphoblastoid line, or a plasma cell line from myeloma). The resulting cells are screened for hybridomas that secrete antibodies specifically reactive with the sensitizing tumor cells (and non-reactive with a range of other tissues and cell types). Example 2 disclosed the results of an experiment conducted by Alonso in treating Melanie Brown, a patient with neurofibrosarcoma. Adult spleen cells were sensitized with cells from Brown's tumor. The resulting hybridoma secreted monoclonal antibodies, which reacted with a 221 KiloDalton tumor surface antigen. The spleen line (AS-151), the lymphoblast fusion line (BM-95), and the hybridoma (HB983) were deposited with the American Type Culture Collection in September of 1998. The antibody from the hybridoma line was deposited with the Food and Drug Administration.[2]

The examiner rejected claim 92 as lacking adequate written descriptive support for the broad genus of antibodies encompassed by the claim language.

[2] Alonso infused Brown with 100 mg of the antibody, and cancerous lesions in her lungs were cleared within twenty-four hours. In addition, Brown's brain tumor became necrotic within seven days, and she experienced a one-month regression of her cancer.

> Applicant is reminded that the disclosure only describes the preparation of a single Mab produced by the hybridoma cell line HB983. However, the claims are directed toward a much larger genus of molecules (i.e., Mabs that bind to a neurofibrosarcoma), not a specific Mab identified by the deposited hybridoma. . . . The crux of the rejection is whether or not applicant has provided sufficient support for the broadly claimed genus of therapeutic anitbodies. As set forth in the rejection, the skilled artisan would reasonably conclude that applicant was clearly not in possession of the claimed genus of compounds. Applicant should direct the claim language toward the only described embodiment (e.g., a Mab produced by hybridoma HB983).

The Board affirmed the rejection, agreeing that Alonso had not adequately described the claimed invention because the "single antibody described in the Specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed invention." Decision, slip op. at 7.

II. DISCUSSION

Whether an applicant has complied with the written description requirement is a finding of fact, to be analyzed from the perspective of one of ordinary skill in the art as of the date of the filing of the application. Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991). This Court reviews the Board's factual determinations under a substantial evidence standard. In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000). "Substantial evidence" is relevant evidence that "a reasonable mind might accept as adequate to support a conclusion." Id. at 1312 (citation omitted). In making the assessment, we examine "the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." Id. That a fact finder could draw "two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence." Id. (citation omitted). Rather,

the Board's decision must be affirmed if any "reasonable fact finder could have arrived at the [same] decision." Id.

The written description requirement of 35 U.S.C. § 112, ¶ 1, is straightforward: "The specification shall contain a written description of the invention . . . ." To satisfy this requirement, the specification must describe the invention in sufficient detail so "that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997); see also LizardTech, Inc. v. Earth Res. Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005); Eiselstein v. Frank, 52 F.3d 1035, 1039 (Fed. Cir. 1995).

The requirement "serves a teaching function, as a 'quid pro quo' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" Univ. of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922 (Fed. Cir. 2004) (quoting Enzo Biochem, Inc. v. GenProbe Inc., 323 F.3d 956, 970 (Fed. Cir. 2002)).[3] The Board framed the issue raised by the '749 Application as follows.

> [W]hether the single monoclonal antibody described in the Specification is representative of the genus of monoclonal antibodies required to practice the claimed treatment method. That, in turn, depends on whether or not the antibodies (and the antigens they bind) would have been expected to vary substantially within the genus. The greater the variation in the genus, the less representative any particular antibody would be.

Decision, slip op. at 6.

[3] The requirement is rigorous, but not exhaustive: "[I]t is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention." LizardTech, 424 F.3d at 1345.

The Board properly characterized the relevant genus as the "genus of antibodies specific to neurofibrosarcoma cells." Id. A genus can be described by disclosing: (1) a representative number of species in that genus; or (2) its "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Enzo, 323 F.3d at 964.

Relying principally on two scientific articles, including one authored by Alonso himself, the Board determined that

> [t]here is ample evidence of record that the specificities of antibodies falling within the scope of the genus (and the structures of the antigens they bind) would be expected to vary substantially. For example, Osband[4] provides evidence of a recognition in the art that considerable antigenic "heterogeneity of tumors both between patients and metastatic sites within a single patient" is to be expected. In addition, an article authored by [Alonso][5] acknowledges that "[t]he efficacy of antibody therapy is thought to be related to tumor burden as well as to idiotypic change in the original tumor." This acknowledged heterogeneity is reflected in the goal of the claimed method - to raise customized antibodies to possibly unique antigens on a particular patient's tumor.
>
> Finally, as discussed above, for purposes of satisfying the written description requirement, it is not enough merely to disclose a method of making and identifying compounds capable of being used to practice the claimed invention. That is, it is not enough to describe[] the procedure for making a human-human hybridoma from neurofibrosarcoma, and teach how to determine whether a given antibody, specific to a patient's neurofibrosarcoma, will function in the claimed method. We find that the single antibody described in the Specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed invention.

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[4] M.E. Osband and S. Ross, Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy, 11 Immunology Today 193-95 (1990).

[5] Kenneth Alonso, Human-Human Monoclonal Antibody Directed Against Tumor Surface Antigen in the Treatment of Human Malignancy, 14 American Journal of Clinical Oncology 463-71 (1991).

Decision, slip op. at 6-7 (internal quotation marks and citations omitted, footnotes supplemented).

The Board's conclusion is supported by substantial evidence. The articles relied upon by the Board confirm the hypothesis that the antibodies required to perform Alonso's claimed method vary substantially in their composition. We have previously held in a similar context that "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." Noelle v. Lederman, 355 F.3d 1343, 1350 (Fed. Cir. 2004).

In another similar case, we evaluated claims directed to a method of determining whether a drug could selectively inhibit the activity of COX-2, a cyclooxygenase thought to be responsible for inflammation associated with arthritis. See Rochester, 358 F.3d at 917-18. One of the claims at issue was directed to "a method for selectively inhibiting [COX-2] activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the [COX-2] gene product to a human host in need of such treatment." Id. at 918. We found that the specification lacked written descriptive support, agreeing with the district court that

> it is clear from reading the patent that one critical aspect of the method - a compound that selectively inhibits [COX-2] activity - was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound. . . . [T]he claimed method depends upon finding a compound that selectively inhibits [COX-2] activity. Without such a compound, it is impossible to practice the claimed method of treatment.

Id. at 926. We further noted that the specification contained "no disclosure of any method for making even a single 'non-steroidal compound that selectively inhibits

activity of the [COX-2] gene product,'" and failed to "steer the skilled practitioner toward compounds that can be used to carry out the claimed methods." Id. at 928, 929.

Alonso attempts to distinguish his claimed invention from Rochester by emphasizing that he reduced his method to practice and identified the resulting compound. We are not persuaded by the distinction. "[P]roof of a reduction to practice, absent an adequate description in the specification of what is reduced to practice, does not serve to describe or identify the invention for purposes of [the written description requirement]." Enzo, 323 F.3d at 969.[6] Moreover, while it is true that Rochester disclosed no compounds that worked with the claimed method, the one compound disclosed by Alonso cannot be said to be representative of a densely populated genus.

In Rochester, we reasoned that while the specification

> describes what can be done with any compounds that may potentially be identified through those assays, including formulation into pharmaceuticals, routes of administration, estimation of effective dosage, and suitable dosage forms . . . the '850 patent does not disclose just which peptides, polynucleotides, and small organic molecules have the desired characteristics of selectively inhibiting [COX-2]. Without such disclosure the claimed methods cannot be said to have been described.

Rochester, 358 F.3d at 927 (internal citation and quotation marks omitted). We additionally found that Rochester had failed to present any evidence that one skilled in

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6 The reduction-to-practice argument also implicates § 112's enablement requirement. The Board reversed the examiner's rejection of claim 92 for lack of enablement. See Decision, slip op. at 12. Alonso argues that the Board's findings as to sufficiency of description and enablement are at odds with one another. It is true that the written description and enablement requirements "usually rise and fall together. That is, a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa." LizardTech, 424 F.3d at 1345. However, we have been clear that "[a]lthough the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements." Capon v. Eshhar, 418 F.3d 1349, 1360 (Fed. Cir. 2005). "[A]n invention may be enabled even though it has not been described." Rochester, 358 F.3d at 921.

the art would have been able to isolate and identify any given compound based on Rochester's "vague functional description . . . ." Id. at 928. Even more recently, we held that the written disclosure requirement was not met where the claims at issue covered a broad "genus of recombinant plasmids that contain coding sequences for DNA polymerase . . . from any bacterial source, [but] the narrow specifications of the [relevant patents] only disclose[d] the . . . gene coding sequence from one bacterial source . . . ." Carnegie Mellon Univ. v. Hoffman-LaRoche Inc., 541 F.3d 1115, 1125 (Fed. Cir. 2008) (emphasis added).

The same is true here. The specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient.[7] The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language – "a monoclonal antibody idiotypic to the neurofibrosarcoma of said human." This sparse description of antibody structure in the claim stands in stark contrast to the detailed method of making the antibodies found in the specification.

The Eli Lilly decision is also instructive. In Eli Lilly, the University of California laid claim to all vertebrate insulin cDNAs, including the human insulin cDNA, although it had identified only the cDNA for rat insulin. See Eli Lilly, 119 F.3d at 1567.[8] We ruled

[7] It bears mentioning that the examiner encouraged Alonso to amend his claims to cover only the MAb produced by the identified hybridoma.

[8] The claims at issue in Eli Lilly were directed to "a recombinant plasmid

that the written description requirement was not met because "a description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian insulin cDNA." Id. at 1568. As in Eli Lilly, the specification of the '749 Application contains information about only one compound.[9]

Apart from the representative number of species test applied by the Board, we have found adequate written descriptive support for a claimed invention where the disclosure specifies "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Enzo, 323 F.3d at 964 (emphasis in original). Alonso argues that there is a well-known correlation between the structure and function of the neurofibrosarcoma-specific antibodies generated by his disclosed treatment method. He maintains that the members of the genus of antibodies directed to a particular patient's tumor share the same function - they each bind to a patient's neurofibrosarcoma, thereby bolstering the patient's immune mechanism and stimulating an attack on the tumor cells. As for structure, Alonso argues that because monoclonal antibodies are secreted from a hybridoma made from a particular neurofibrosarcoma,

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replicable in [a] procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a *vertebrate*, which mRNA encodes insulin." Eli Lilly, 119 F.3d at 1563 (emphasis in original).

[9] Alonso cites In re Herschler, 591 F.2d 693 (CCPA 1979), where our predecessor court held that the disclosure of a single corticosteroid was sufficient to describe the genus of physiologically active steroids that could be used in practicing the claimed invention. The court based its decision on the fact that the class of implicated compounds was "chemically quite similar." Id. at 701. Alonso argues that the same is true with respect to the antibodies generated by a patient's specific neurofibrosarcoma. However, he points to no evidence in the record corroborating his "similarity" thesis.

the antibodies are necessarily specific. He further argues that there is a "well-known correlation between human antibody structure and antibody function."

Alonso did not raise this structure-function correlation argument in the proceedings before the Board. "Failure to advance legal theories before the [B]oard constitutes a failure to 'make a complete presentation of the issues,' and permitting a party to raise those theories for the first time [after the agency has rendered its final decision] would be both inefficient and 'wasteful of administrative and judicial resources.'" Boston Scientific Scimed, Inc. v. Medtronic Vascular, Inc., 497 F.3d 1293, 1298 (Fed. Cir. 2007). Accordingly, we will not consider this newly minted argument on appeal.[10]

III. CONCLUSION

For the aforementioned reasons, the decision of the Board is affirmed.

AFFIRMED.

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10 Even were we tempted to consider the argument, Alonso would not be entitled to relief. In Noelle, the applicant claimed a human monoclonal antibody (or fragment thereof) secreted from a particular hybridoma that binds to an antigen expressed on activated T-cells. The application did not, however, disclose any structural information about the human antigen. Noelle, 355 F.3d at 1345-46. It described only the mouse antigen. We concluded that the function-structure correlation test was not met.

> If [the applicant] had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. [The applicant] did not describe human CD40CR antigen. Therefore, [the applicant] attempted to define an unknown by its binding affinity to another unknown.

Noelle, 355 F.3d at 1349. As Alonso has not pointed to any structure for his claimed antibodies, there is no structure to which he may correlate the function of his claimed antibodies.