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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ATUL J. BUTTE and KEIICHI KODAMA[1]

Appeal 2018-004007
Application 13/575,904
Technology Center 1600

Before ERIC B. GRIMES, RYAN H. FLAX, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to methods of reducing insulin resistance, which have been rejected as obvious and lacking adequate written description. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM the rejection for inadequate written description.

STATEMENT OF THE CASE

The Specification discloses that "polymorphisms in the CD44 locus and the CD44 ligand (SPP1, osteopontin) . . . are predictive of a

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[1] Appellant identifies the real party in interest as the Board of Trustees of the Leland Stanford Junior University. Appeal Br. 2. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

susceptibility in an individual to development of type 2 diabetes. Serum levels of CD44 are also diagnostic of insulin resistance." Spec. ¶ 8. "Methods of treatment target the product of these genes, particularly targeting CD44 and/or osteopontin." *Id*.

Claims 1, 2, 4, 5, and 30–32 are on appeal. Claims 1 and 30, reproduced below, are illustrative:

> 1. A method of reducing insulin resistance in an individual having Type 2 diabetes, the method comprising:
>
> administering to said individual an effective dose of an antibody that inhibits CD44.
>
> 30. A method of reducing insulin resistance in an insulin resistant human subject, the method comprising:
>
> administering to said subject an antibody that binds to an extracellular domain of a CD44 splice variant expressed on adipose tissue macrophages, and which antibody blocks interaction between CD44 and a CD44 ligand, in a dose effective to improve glucose homeostasis in said subject.

The claims stand rejected as follows:

Claims 1, 2, 4, 5, and 30–32 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description in the Specification (Final Action[2] 3), and

[2] Office Action mailed March 7, 2017.

Claims 1, 2, 4, 5, and 30–32 under 35 U.S.C. § 103(a) as obvious based on Naor,[3] Hentsch,[4] Chabas,[5] Bingham,[6] Kiefer,[7] Schultz,[8] and Tracey[9] (Final Action 8).

OPINION

Written Description

The Examiner finds that "the instant specification does not describe any particular anti-CD44 antibody, including any particular anti-CD44 antibody having the claimed properties." Final Action 4. According to the Examiner, the "specification does not provide a single particular anti-CD44 antibody having the specificity and the functional properties argued by applicant and disclosed in the specification and recited / encompassed by the claimed methods, including sufficient species representing" the antibodies recited in the claims. *Id*. at 5.

The Examiner also finds that the "specification discloses that the anti-CD44 antibody has certain specificities (a splice variant, exon 3 of CD44, extracellular domain of CD44) and certain functional properties (inhibits ligand binding activity, etc.) (see paragraphs [0054]-[0055]) in order to carry

[3] US 2006/0019340 A1 (publ. Jan. 26, 2006).
[4] EP 1 647 556 A1 (publ. Apr. 19, 2006).
[5] US 2005/0119204 A1 (publ. June 2, 2005).
[6] US 2011/0008328 A1 (publ. Jan. 13, 2011).
[7] Kiefer et al., *Osteopontin deficiency prevents obesity-associated hepatic steatosis and insulin resistance*, Diabetologia 52:S33, abstr. no. 65 (2009).
[8] Schultz et al., *Expression levels and functional aspects of the hyaluronan receptor CD44: Effects of insulin, glucose, IGF-I, or growth hormone on human arterial smooth muscle cells*, Metabolism Clinical and Experimental 54:287–295 (2005).
[9] US 2003/0212104 A1 (publ. Nov. 13, 2003).

out the claimed methods," but "the specification as filed does not provide the correlation between structure and function of anti-CD44 antibodies." *Id*. at 4.

The Examiner concludes that

> the instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of anti-CD44 antibodies . . . encompassed by the claimed invention.

Id. at 6.

We agree with the Examiner that the claims are not supported by a description that satisfies 35 U.S.C. § 112, first paragraph. "[T]he test for sufficiency [of the written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

A "sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or 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." *Id*. at 1350. "[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id*.

"[F]unctional claim language can meet the written description requirement when the art has established a correlation between structure and

function." *Id*. "But merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Id*.

The written description standard set out in *Ariad* applies to antibodies. *See Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1376–79 (Fed. Cir. 2017) (applying the *Ariad* standard to antibodies claimed based on their binding and blocking activities); *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298–1300 (Fed. Cir. 2014) (same).

The claims here are directed to methods of using antibodies, rather than the antibodies themselves, but the same standard applies with regard to the written description requirement. *See University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004):

> Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods.

In *University of Rochester*, the "claimed method depend[ed] upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment." *Id*. (citation omitted). Similarly here, the claimed methods cannot be practiced without antibodies having the inhibiting or blocking activities recited in the claims. Appellant's argument that the claims are adequately described because they are directed to a method, not a composition of matter (Appeal Br. 7), is therefore unpersuasive.

The instant Specification does not describe any specific antibodies that are suitable for use in the claimed methods. The Specification states that one aspect of the invention is "prevention or treatment of type 2 diabetes, by administering to an individual an inhibitor of CD44 activity. . . . Such inhibitors include, without limitation, antibodies, nucleic acid inhibitors . . . ; inhibitory osteopontin peptides, small molecules inhibitors, and the like." Spec. ¶ 9; *see also id*. ¶ 56 ("Representative CD44 inhibitory agents include, but are not limited to: antisense oligonucleotides; antibodies;" etc.).

Because the Specification fails to describe any single antibody having any of the functions recited in the claims, it necessarily fails to describe a representative number of species within the claimed genera. In addition, the Specification fails to describe structural features common to members of the genus that would allow a skilled artisan to distinguish antibodies encompassed by the claim language from other antibodies. Finally, the Specification fails to disclose any correlation between the structure and function of the antibodies encompassed by the claim language. Therefore, the Specification fails to describe the antibodies required to practice the claimed method in a manner that reasonably conveys to those skilled in the art that Appellant was in possession of the claimed method as of the filing date of the instant application.

Appellant argues that "[t]he present invention is based on Appellant[']s surprising finding that CD44 and osteopontin were associated with insulin resistance in a screen of human genome sequences." Appeal Br. 6. Appellant argues that the Specification shows that "a knock-out of the CD44 gene in an animal model for diabetes prone mice was able to improve insulin resistance and glucose homeostasis in these animals." *Id*.

This argument is unpersuasive, because the claimed methods require using antibodies that have specific functional properties. Even if the Specification shows that reducing CD44 activity improves insulin resistance, the claims require using antibodies having specific properties, and the Specification does not describe those antibodies in the manner required by 35 U.S.C. § 112, first paragraph.

Appellant also points to a post-filing publication[10] as evidence that "administering daily injections of anti-CD44 monoclonal antibody (mAb) in a high-fat-diet mouse model . . . reduced fasting blood glucose levels, weight gain, liver steatosis, and insulin resistance to levels comparable to or better than therapy with the drugs metformin and pioglitazone." Appeal Br. 6.

This argument is also unpersuasive. It is unclear which, if any, of the functional limitations in the claims are purportedly met by the antibody described in the post-filing reference but, in any event, written descriptive support depends on "whether the disclosure *of the application* relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter *as of the filing date*." *Ariad*, 598 F.3d at 1351 (emphasis added). Appellant's post-filing evidence does not make up for the Specification's deficiency.

Appellant argues that "many antibodies that bind to human CD44 are known in the art and commercially available, as evidenced by Exhibit C." Appeal Br. 6. Exhibit C is said to "provide[] an example of commercially available monoclonal antibodies reactive with human CD44, from one

[10] Kodama et al., *Anti-CD44 Antibody Treatment Lowers Hyperglycemia and Improves Insulin Resistance, Adipose Inflammation, and Hepatic Steatosis in Diet-Induced Obese Mice*, Diabetes 64:867–875 (2015).

supplier, Novus Biologicals. 36 antibodies are available from this single supplier." *Id*. at 4.

However, Exhibit C lacks any indicia that would indicate that the listed antibodies were commercially available at the time the instant application was filed. In addition, Appellant has not provided evidence that the listed antibodies have the specific inhibiting or blocking properties required by the claims. This argument is therefore unpersuasive.

Finally, Appellant argues that

> [p]roperties of antibodies and methods of generating antibodies are described in the specification at paragraphs 66–73. Paragraph 74 further provides guidance for one of skill in the art to test candidate antibodies for the desired activity. Further, at paragraphs 130–133, assays are provided that allow one of skill in the art to screen available antibodies and determine which are suitable for use in the methods of the invention.

Appeal Br. 6–7.

This argument is unpersuasive. "[T]o satisfy the statutory requirement of a description of the invention, it is not enough for the specification to show how to make and use the invention, *i.e.*, to enable it." *Amgen v. Sanofi*, 872 F.3d at 1377; *see also University of Rochester*, 358 F.3d at 927 (the patent at issue described assays for screening compounds for those having the desired activity, but without disclosure of *which* compounds had that activity, the claimed method had not been described); *AbbVie*, 759 F.3d at 1300 ("One needs to show that one has truly invented the genus, i.e., that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan.").

In summary, we affirm the rejection of claims 1 and 30 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description. Claims 2, 4, 5, 31, and 32 fall with claims 1 and 30. 37 C.F.R. § 41.37(c)(1)(iv) (2016).

Obviousness

Claims 1, 2, 4, 5, and 30–32 stand rejected as obvious based on Naor, Hentsch, Chabas, Bingham, Kiefer, Schultz, and Tracey. Final Action 8. The Examiner finds that Naor teaches "the applicability of anti-CD44 antibodies and antigen binding fragments . . . to treat a variety of inflammatory conditions . . . including diabetes." *Id*. at 11. The Examiner notes that Naor "differs from the claimed methods by not describing treating type 2 diabetes per se with anti-CD44 antibodies and that osteopontin as [sic] another ligand of CD44." *Id*.

The Examiner finds that Hentsch teaches "inhibiting signals via CD44 for the treatment of hyperproliferative disorders, including insulin dependent diabetes and non-insulin dependent diabetes (i.e., type 2 diabetes)." *Id*. The Examiner finds that Chabas teaches "methods of treating various disorders including diabetes / insulin-dependent diabetes . . . with various inhibitors of osteopontin-mediated binding and activity . . . and notes that CD44 was a known ligand for osteopontin as well as the blocking via CD44 binding." *Id*. at 13. The Examiner finds that Bingham teaches "the treatment of insulin-resistance associated with obesity, aging and type 2 diabetes . . . with various osteopontin inhibitors . . . and notes that osteopontin binds to CD44." *Id*.

The Examiner finds that Kiefer teaches "the known role of osteopontin . . . in the pathogenesis of obesity-induced insulin resistance, which, in turn, could be a therapeutic approach to prevent obesity-associated

metabolic disorders, including type 2 diabetes." *Id*. at 14. The Examiner finds that Schultz teaches "the functional consequences of accumulated hyaluronan through binding to CD44 as a feature of diabetic macroangiopathy, where CD44 and its isoform CD44v3 play a role in cell response to metabolic and hormonal disorders of diabetes." *Id*. The Examiner finds that Tracey "teach[es] that treating Type 2 diabetes is associated with various conditions and manifestations, including diabetic macroangiopathy and insulin resistance syndrome." *Id*.

The Examiner concludes that it would have been obvious "to provide CD44 antagonists . . . for the treatment of various diseases / disorders including type 2 diabetes / non-insulin-dependent diabetes with anti-CD44 antibodies, given the teachings of the prior art to target CD44 as well as osteopontin binding . . . to treat various diseases / orders [sic] including type 2 diabetes." *Id*. at 15. The Examiner reasoned that a skilled artisan would have "administer[ed] CD44 antagonists such as anti-CD44 antibodies . . . with an expectation of success, since such properties and advantages are consistent with human therapeutic regimens associated with treating said conditions." *Id*.

Appellant argues that Naor does not teach using anti-CD44 antibodies for "the treatment of Type 2 diabetes, which is a condition distinct from the inflammation and autoimmune responses associated with Type 1 diabetes." Appeal Br. 8. Appellant argues that Hentsch discloses providing "short peptide motifs referred to as CD44v6 peptides, which have the activity of inhibiting complex formation between Met, hepatocyte growth factor and CD44" and provides no reason to "believe that such peptides or CD44 variant are involved in Type 2 diabetes." *Id*. at 10. Appellant notes that

Hentsch discloses non-insulin dependent diabetes as one of a "laundry list" of diseases to be treated, but argues that Hentsch "does not provide any evidence of a common mechanism in the extensive list of disorders" that would lead a skilled artisan to expect that inhibiting CD44 would reduce insulin resistance. *Id*. at 12.

Appellant argues that Chabas discloses a method of inducing an immune response in order to inhibit osteopontin, and that Bingham "fails to teach the use of antibodies to CD44 in the reduction of insulin resistance in a patient with Type 2 diabetes." *Id*. at 13–14. Appellant argues:

> While osteopontin is a ligand for CD44, both of osteopontin and CD44 interact with numerous other molecules including a number of integrins. One of skill in the art would have not have a reasonable expectation that inhibition of osteopontin, and inhibition of CD44, would lead to any similarity of biological results.

Id. at 14.

Finally, Appellant argues that Schultz "relates to effects of insulin and glucose on the behavior of human arterial smooth muscle cells, which cells may be effected by diabetes, but which cells do not have a causative role in insulin resistance"; that Tracey "relates to an entirely unrelated pathway, a sodium-hydrogen exchanger type 1 (NHE-1) inhibitor, for treatment of [certain] disorders"; and that, while Kiefer "is cited for teaching a role for osteopontin in obesity-associated metabolic disorders," and "osteopontin is known to be one ligand of CD44, each of these proteins interacts with numerous other ligands." *Id*. at 15–16.

Appellant concludes that "the combined references fail to provide any motivation or specific teaching that would lead one of skill in the art to treat reduce insulin resistance in an individual having Type 2 diabetes by

administering to the individual an effective dose of an antibody that inhibits CD44." *Id*. at 16.

We agree with Appellant that the Examiner has not shown that the claimed method would have been prima facie obvious to a person of ordinary skill in the art based on the cited references. "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). "[O]bviousness requires . . . showing that a person of ordinary skill at the time of the invention would have selected and combined th[e] prior art elements in the normal course of research and development to yield the claimed invention." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

Naor states that its invention relates to, among other things, "antibodies specific for [a] novel CD44 polypeptide variant, . . . and the use of these antibodies . . . in the diagnosis and treatment of inflammatory diseases such as rheumatoid arthritis." Naor ¶ 3. Naor states that CD44 and variants thereof are known to be involved in autoimmune diseases, and that monoclonal antibodies against various variant CD44 regions have been suggested as treatments of autoimmune diseases. *Id*. ¶¶ 17–18. Naor suggests using antibodies against its CD44 variant (CD44vRA) to treat Type 1 diabetes (*id*. ¶¶ 207–213). However, as the Examiner concedes (Final Action 11), Naor does not describe treating Type 2 diabetes per se with anti-CD44 antibodies, and the Examiner has not pointed to any description of treating insulin resistance.

Hentsch discloses "short peptide motifs, derived from the CD44 v6 region, which are capable of interfering with HGF [hepatocyte growth

factor] signaling via inhibition of the formation of the trimeric complex made up by c-Met, HGF and CD44." Hentsch ¶ 3. Hentsch states that each of these proteins has been associated with tumor metastasis (*id*. ¶ 2), and inhibiting their interaction "might be therapeutically useful for . . . hyperproliferative diseases like cancer or diseases associated with invasive processes of cells." *Id*. ¶ 3.

Hentsch also suggests

> the formation of complexes of CD44 involving other growth factor recetors [sic], such as, but not limited to, FGFR, PDGFR, ErbB2, EGFR, Osteopontin, and integrins, followed by a CD44 mediated signaling of these growth factor receptors, so that an inhibition of the formation of such complexes might be therapeutically benefical [sic] in diseases in which the formation of such complexes contributes to the disease onset, manifestation or progression.

Id. ¶ 55. Hentsch states that such diseases include "insulin dependent diabetes mellitus, non-insulin dependent diabetes [aka Type 2 diabetes]." *Id*.

Chabas discloses a method of treating "a disorder in which expression of osteopontin contributes to the pathogenesis," including autoimmune diseases like Type 1 diabetes, by inducing an immune response that reduces the level of osteopontin in the patient. Chabas ¶ 13. Similarly, Bingham discloses "a method of controlling glucose uptake and/or insulin sensitivity by administration of an inhibitor to OPN [osteopontin]." Bingham ¶ 7. Kiefer likewise relates to targeting osteopontin, not CD44, as a potential treatment for type 2 diabetes. Kiefer, abstract.

However, the Examiner has not pointed to any disclosure in Chabas, Bingham, or Kiefer of inhibiting CD44, as required by the claims. The evidence supports Appellant's position that osteopontin and CD44 both bind to proteins other than each other. *See* Bingham ¶ 5 ("OPN binds to integrins

and CD44"); Hentsch ¶ 55 ("complexes of CD44 involving . . . FGFR, PDGFR, ErbB2, EGFR, Osteopontin, and integrins"). The Examiner has not persuasively explained why a skilled artisan would have been led to administer a CD44-inhibiting antibody based on the disclosure of inhibiting osteopontin in Chabas, Bingham, or Kiefer.

Schultz "investigate[d] the relationship between some of the components in the metabolic disorders of diabetes and the CD44 quantity and function on human[] arterial SMCs [smooth muscle cells]." Schultz 288, left col. Schultz states that its data "support a role of CD44 and its isoform, CD44v3, in the SMC response to the metabolic and hormonal disorders of diabetes." *Id*. at 287, abstract. The Examiner has not explained how Schultz's finding, that CD44 has an effect on arterial smooth muscle cells in diabetic patients, would have suggested inhibiting CD44 to treat Type 2 diabetes or insulin resistance.

Finally, Tracey discloses "methods of treating or preventing type 2 diabetes, . . . and/or insulin resistance syndrome (IRS) in mammals, particularly in humans." Tracey ¶ 2. However, Tracey's method "administer[s] a sodium-hydrogen exchanger type 1 (NHE-1) inhibitor." *Id*. The Examiner has not explained why Tracey's treatment would have provided a reason to administer an anti-CD44 antibody to treat insulin resistance or Type 2 diabetes.

In summary, the disclosure in the cited references that is most relevant to the claimed invention is Hentsch's suggestion that formation of complexes of CD44 and receptors such as FGFR, PDGFR, ErbB2, EGFR, osteopontin, or integrins "might be therapeutically benefical [sic] in diseases

in which the formation of such complexes contributes to the disease onset, manifestation or progression." Hentsch ¶ 55.

In our view, however, Hentsch's disclosure would not have suggested the claimed method without the benefit of hindsight. Hentsch does not suggest inhibiting CD44 complex formation using any compounds other than short peptide motifs derived from CD44 itself, rather than by using an anti-CD44 antibody, as required by the claims. Nor has the Examiner articulated any basis for extrapolating the effect of Hentsch's complex-inhibiting peptides to an effective treatment of Type 2 diabetes via an antibody that inhibits CD44. Thus, although Hentsch includes "non-insulin dependent diabetes" as one of the many diseases in which "inhibition of the formation of such [CD44-containing] complexes might be therapeutically benefical [sic]," we conclude that a skilled artisan would not have been led to modify Hentsch's method by using an anti-CD44 antibody instead of Hentsch's peptides, without the benefit of hindsight gleaned from Appellant's Specification.

We therefore conclude that the cited references do not support a prima facie case of obviousness, and reverse the rejection of claims 1, 2, 4, 5, and 30–32 under 35 U.S.C. § 103(a) based on Naor, Hentsch, Chabas, Bingham, Kiefer, Schultz, and Tracey.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 4, 5, 30–32	112, first paragraph	Written Description	1, 2, 4, 5, 30–32	
1, 2, 4, 5, 30–32	103(a)	Naor, Hentsch, Chabas, Bingham, Kiefer, Schultz, Tracey		1, 2, 4, 5, 30–32
Overall Outcome			1, 2, 4, 5, 30–32	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED