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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MITCHELL A. LAZAR

Appeal 2011-011217
Application 11/590,736
Technology Center 1600

Before TONI R. SCHEINER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 4-19 and 21, directed to a method of treating type 2 diabetes or Syndrome X. The claims have been rejected for lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Claims 4-19 and 21 are pending and on appeal. Claims 1-3 and 20 have been canceled (App. Br. 6).

Claims 4 and 12 are representative of the subject matter on appeal:

4. A method of treating or alleviating type 2 diabetes, said method comprising administering to a patient afflicted with type 2 diabetes a composition comprising an antibody that specifically binds a resistin polypeptide selected from the group consisting of a resistin polypeptide having the amino acid sequence of SEQ ID NO: 2 and a resistin polypeptide having the amino acid sequence of SEQ ID NO: 4.

12. A method of treating or alleviating Syndrome X, said method comprising administering to a patient afflicted with Syndrome X a glucose uptake-enhancing amount of a composition comprising an antibody that specifically binds a resistin polypeptide.

Claims 4-19 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

The Examiner relies, in relevant part, on the following evidence:

Jennifer H. Lee et al., *Circulating Resistin Levels Are Not Associated with Obesity or Insulin Resistance in Humans and Are Not Regulated by Fasting or Leptin Administration: Cross-Sectional and Interventional Studies in Normal, Insulin-Resistant, and Diabetic Subjects*, 88 J. CLIN. ENDOCRINOL.. METAB. 4848-4856 (2003).

N. Iqbal et al., *Serum resistin is not associated with obesity or insulin resistance in humans*, 9 EUR. REV. MED. PHARM. SCI. 161-165 (2005).

Ivan Nagaev et al., *Human Resistin Is a Systemic Immune-Derived Proinflammatory Cytokine Targeting both Leukocytes and Adipocytes*, 1 PLOS ONE 1-9 (2006).

In addition, Appellant relies on the following evidence:

Haruhiko Osawa et al., *Plasma Resistin, Associated With Single Nucleotide Polymorphism -420, Is Correlated with Insulin Resistance, Lower HDL Cholesterol, and High-Sensitivity C-Reactive Protein in the Japanese General Population*, 30 DIABETES CARE 1501-1506 (2007).

ISSUE

Following an analysis of the *Wands* factors,[1] the Examiner found that the Specification "does not reasonably provide enablement for, a method of treating or alleviating type II diabetes or Syndrome X" in humans by administering an antibody that binds mouse resistin or human resistin-like molecule A (Ans. 5), and that "[t]he specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation" (*id.* at 6).

Appellant contends that the Specification demonstrates that "neutralization of resistin via administration of resistin antibodies enhances glucose uptake in 3T3-L1 adipocytes" (App. Br. 13), and "administration of purified resistin to mice raised glucose tolerance levels to diabetic levels" (*id.*). In addition, Appellant contends that "the human and mouse polypeptides share ~56% identity over the full length, [and] . . . a 72% identity in the C-terminus region and additional conservation of amino acid type over the entire polypeptide in non-identical residues" (*id.*), and "'an immunoblot analysis of <u>human serum</u> using antiserum raised against mouse resistin revealed a band migrating identically with mouse resistin'" (*id.*).

Appellant further contends that the Specification "describe[s] how reducing the amount of resistin in a cell, *e.g.*, by antibody binding, can be

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[1] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Factors to be weighed in determining whether a disclosure is in compliance with the enablement requirement include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

used to treat a disorder such as type 2 diabetes" (*id.* at 12-13), and that "one of skill in the art, given the information provided in the specification, and the knowledge that murine models are commonly used in predicting human outcomes, would have no reason to doubt that administration of resistin antibodies in a human would have a similar effect to that shown in mice" (*id.* at 14).

Finally, Appellant contends that the Examiner improperly relied on post-filing date publications as evidence of non-enablement, and that even if the publications "are relevant to an enablement analysis, they fail to show that Applicant's claims do not work for their intended purpose" (*id.* at 16-17), and that "several additional studies [are of record] . . . which support the pending claims" (*id.* at 17).

The issue raised by this rejection is whether the evidence of record supports the Examiner's position that undue experimentation would have been required to treat or alleviate type II diabetes or Syndrome X in humans using the claimed method.

FACT FINDINGS

1. Claims 4 and 12 encompass treating type 2 diabetes in humans and Syndrome X in humans, respectively.

2. SEQ ID NO:2 is the amino acid sequence of mouse resistin, while SEQ ID NO:4 is the deduced amino acid sequence of human resistin, "which is also referred to herein as human Resistin-like molecule A (hRELM-A)" (Spec. 13: 4-6; 65: 8).

3. According to the Specification, "[t]he overall amino acid identity between mouse and human resistin is 55.6%, with even greater

identity in the C-terminus region where the identity is about 72%" (Spec. 66: 10-12).

4. The Specification demonstrates that addition of anti-resistin antiserum to 3T3-L1 adipocytes (i.e., mouse cells) "increased insulin-stimulated glucose uptake approximately 250-300%" (Spec. 66: 31-36). In addition, the Specification "demonstrate[s] that the blood glucose levels of mice dosed with [concentrated conditioned cell medium containing] resistin increased to diabetic levels" (*id.* at 63, ll. 19-27; 67: 5-6), i.e., administration of resistin to mice results in a "reduction in glucose tolerance" (*id.* at 67: 3).

5. There are no working examples involving human cells or human resistin, other than "[a]n immunoblot analysis of human serum using antiserum raised against mouse resistin [which] revealed a band migrating identically with mouse resistin . . . suggest[ing] that human resistin, like mouse resistin, circulates in blood" (Spec. 66: 18-20).

6. According to the Specification,

> The data disclosed herein identify a novel gene, resistin, as a potential link between obesity, diabetes, and the mechanism of action of antidiabetic drugs (e.g., TZDs). The data disclosed herein demonstrate that resistin is a new signaling molecule that is induced during adipogenesis and secreted by 3T3-L1 cells. Resistin gene expression and protein secretion are markedly reduced by antidiabetic drugs, TZDs. Moreover, resistin expression in vivo is specific to white adipose tissue, where protein levels are regulated by fasting and dietary fat. The protein is also found in the serum of normal mice. These data indicate that resistin is a candidate adipocyte-derived factor that contributes to insulin resistance in vivo. Thus, resistin is a target for the antidiabetic actions of TZDs. The ability of resistin antibodies to enhance basal and insulin-stimulated glucose uptake further supports that resistin is an important therapeutic target for diabetes treatments.

> Resistin is the prototype of a novel family of potential signaling molecules, the RELMs. However, although human resistin (alternatively referred to herein as "hRELM-A") is highly homologous to mouse resistin, the divergence between the mouse and human sequences suggest[s] . . . that human resistin disclosed herein . . . may not be a true homolog of mouse resistin.

(Spec. 67: 18-30.)

7. Further according to the Specification,

> One skilled in the art would understand, based upon the disclosure provided herein, that since reduced resistin expression mediates a beneficial effect, including increased glucose uptake by a cell, that methods of decreasing expression of resistin, decreasing the level of resistin polypeptide present in the cell, and/or decreasing the activity of resistin in a cell (using, e.g., antisense nucleic acids, ribozymes, antibodies, and the like), can be used to treat and/or alleviate a disease, disorder or condition associated with altered glucose uptake where a higher level of uptake would provide a benefit. Thus, whether an antisense nucleic acid or a blocking antibody is administered, the crucial feature of the present invention is that the expression of resistin be reduced in a cell.

(Spec. 50: 6-13.)

8. The Examiner provided several post-filing date references as evidence that it would have required undue experimentation to practice the claimed invention as of the application's filing date, and that "[n]umerous studies . . . have shown that resistin levels in humans do not correlate with insulin resistance, and thus, serum glucose" (Ans. 7).

For example, Lee found "no evidence supporting a role for serum resistin in mediating insulin resistance or reflecting obesity in humans" (Lee 4853, col. 1) and concluded that "the relevance and physiological role of resistin in humans remain unknown. Given the incomplete homology (59%)

between human and mouse resistin . . . . and the absence in humans of one of the three murine resistin isoforms, resistin in humans may have a different physiological role than that in mice" (*id.* at 4848).

Similarly, Iqbal concluded that "[t]he physiologic role of resistin in humans remains unknown" (Iqbal, Abstract), and "that resistin does not play a central role in obesity related insulin resistance. Given the newness of the ELISA assay, . . . and the unknown kinetics of resistin, more studies are needed before the role of resistin in insulin sensitivity and obesity can fully be defined" (*id.* at 164, col. 2).

Likewise, Nagaev concluded that "[t]he characteristics of human resistin . . . are unclear and controversial despite intensive adipose-focused research" (Nagaev, Abstract).

DISCUSSION

The evidence of record supports the Examiner's position that undue experimentation would have been required to treat or alleviate type II diabetes or Syndrome X in humans.

Working examples are not a requirement for enablement. However, in this case, the absence of working examples involving human cells or hRELM-A weighs heavily against the enablement of the claims, given the Specification's assessment that "the divergence between the mouse and human sequences suggest[s] . . . that human resistin disclosed herein . . . may not be a true homolog of mouse resistin" (FF6). Moreover, while it may be true that animal models are commonly used in predicting human outcomes, it is also true that not just any model will do. The animals administered mouse resistin in the present working examples are simply identified as "[m]ale and female mice, 9 weeks of age" (Spec. 63: 22).

There is nothing to indicate whether the animals used were recognized in the art as a model of type 2 diabetes, or whether administering anti-resistin antibodies to the mice could treat or alleviate diabetes. Thus, we agree with the Examiner that the Specification does not establish that the mouse model used was "representative of humans" (Ans. 11).

Essentially the only other relevant guidance provided by the Specification is the assertion that "[o]ne skilled in the art would understand, based upon the disclosure provided herein, that . . . decreasing the activity of resistin in a cell (using, e.g., . . . antibodies, and the like), can be used to treat and/or alleviate a disease, disorder or condition . . . where a higher level of [glucose] uptake would provide a benefit" (Spec. 50: 6-11). Given the relative lack of relevant working examples, the divergence between the mouse and human sequences, and the Specification's acknowledgement that hRELM-A might not be a true homolog of mouse resistin, this assertion weighs very little in favor of enablement.

Moreover, we disagree with Appellant's assertion that the Examiner used post-filing date evidence inappropriately in determining that the claims were not enabled as of the filling date. The prohibition against post-filing date art applies to "the impermissible application of later knowledge about later art-related facts . . . which did not exist on the filing date." *In re Hogan*, 559 F.2d 595, 605 (CCPA 1977).[2] However, it is well settled that

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[2] *Hogan* involved claims directed to a solid polymer of propylene. The Specification disclosed only crystalline forms. The Examiner and the Board took the position that the claims encompassed both crystalline and amorphous forms of polypropylene, cited post-filing date references disclosing the production of amorphous forms, and found that the full breadth of the claims was not enabled. However, it was undisputed that

the "use of later publications as evidence of the state of art existing on the filing date of an application" is permissible (*id.*). *See Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) ("Report of a first success after 1987 indicates failure or difficulty in or before 1987. Thus the district court properly used later reports as evidence of the state of the art existing in 1987."). That is the case here. The post-filing date publications cited by the Examiner collectively show that several years of post-filing date experimentation, with a number of different animal models and experimental designs, failed to clarify the relevance and physiological role of resistin in humans (FF8).

Nor are we persuaded by Appellant's reliance on Osawa, as the study described therein demonstrated that plasma resistin was associated with a single nucleotide polymorphism (SNP -420) in the Japanese general population, and that plasma resistin was correlated with insulin resistance (Osawa 1501). However, there is no mention of SNP -420 in the present Specification. Moreover, Osawa states that, even in 2007, "[i]t remains controversial whether circulating resistin levels are associated with insulin resistance, type 2 diabetes, or adiposity in humans" (*id.* at 1501-02).

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amorphous forms did not exist at the time of filing, and the methods disclosed in the Specification would not have produced amorphous forms. The CCPA held that it was impermissible to test the claims' scope of enablement against "later knowledge about later art-related facts (here, amorphous polymers) which did not exist on the filing date." *Hogan*, 559 F.2d at 605.

SUMMARY

The rejection of claims 4 and 12 as lacking enablement under 35 U.S.C. § 112, first paragraph, is affirmed as the evidence of record supports the Examiner's position that undue experimentation would have been required to treat or alleviate type II diabetes or Syndrome X in humans. Claims 5-11, 13-19 and 21 were not separately argued and therefore fall with claims 4 and 12 and the rejection is affirmed with respect to these claims as well. *See* 37 C.F.R. § 41.37(c)(1)(vii).

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

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