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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN G. KEIMEL

Appeal 2011-001176
Application 11/124,984
Technology Center 3700

Before DEMETRA J. MILLS, MELANIE L. McCOLLUM, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods of treatment of cardiac disorders. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

Statement of the Case

Background

"The present invention uses an implantable source and catheter to deliver a therapeutic protein formulation containing a protein in a form that is deficient in cardiac cells in a patient with a cardiac disorder. The protein formulation is delivered by the catheter to a pericardial sac region of the heart." (Spec. 4 ¶ 0012.)

The Claims

Claims 18, 23, 25, and 32-36 are on appeal. Claims 18 and 34 are representative and read as follows:

> 18. A method comprising:
>
> diagnosing a patient as having a cardiac disorder caused by a protein deficiency due to a gene mutation, the disorder being selected from the group consisting of glycogen storage disease Type II and Fabry disease;
>
> injecting a therapeutic protein formulation into an implantable source, the therapeutic protein formulation comprising a protein in a form that is deficient in cardiac cells in the patient with the cardiac disorder, the protein being selected from lysosomal acid α-glucosidase and α-galactosidase;
>
> determining a rate for delivering the therapeutic protein formulation based on the genetic sequence of the patient's gene encoding the deficient protein or enzyme level assessment of cardiac tissue; and
>
> delivering the therapeutic protein formulation from the source through an implantable catheter directly to a pericardial sac region of a heart of a patient,
>
> wherein the source is an implantable pump that provides for a programmable delivery rate of the protein formulation, and wherein the protein formulation is delivered at the determined delivery rate.

> 34. The method of claim 18, wherein the rate for delivering the therapeutic protein formulation is based on the genetic sequence of a patient's gene encoding the deficient protein.

The issues

A. The Examiner rejected claims 18, 23, 25, and 32-34 under 35 U.S.C. § 103(a) as obvious over LeBowitz,[1] Struijker-Boudier,[2] and Stafford[3] (Ans. 3-5).

B. The Examiner rejected claims 18, 23, 25, 32, 33, 35, and 36 under 35 U.S.C. § 103(a) as obvious over LeBowitz, Struijker-Boudier, and Martinez[4] (Ans. 5-6).

We begin our analysis with claim interpretation. The "determining" step in claim 18 recites two alternative modes of identifying "a rate for delivering the therapeutic protein formulation". The first mode is through the "genetic sequence of the patient's gene". The second mode is through an "enzyme level assessment of cardiac tissue". The Examiner addressed both alternatives by applying two rejections, the first rejection including Stafford to address the first "genetic sequence" mode and the second rejection including Martinez to address the second "enzyme level" mode. We therefore separately address these rejections consistent with the mode relied upon by the Examiner.

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[1] LeBowitz et al, US 2005/0281805 A1, published Dec. 22, 2005.
[2] Struijker-Boudier et al., US 2003/0009145 A1, published Jan. 9, 2003.
[3] Stafford et al., US 2006/0240440 A1, published Oct. 26, 2006.
[4] Martinez, G., US 6,592,519 B1, issued Jul. 15, 2003.

A. 35 U.S.C. § 103(a) over LeBowitz, Struijker-Boudier, and Stafford

The Examiner finds that "LeBowitz teaches a method of supplying a lyosomal [sic] acid alpha-glucosidase . . . or alpha-galatosidase (Example 12, treatment of Fabry disease) to cells in the body, where the protein formulation includes deficient proteins" (Ans. 4). The Examiner finds that "LeBowitz does not specifically teach delivery to the heart or pericardial sac with a drug pump or determining the drug delivery rate based on the patient's genetic sequence" (*id.*).

The Examiner finds that "Strutjket-Boulder [sic] teaches a method and device for treating a cardiac disorder, such as a cardiodegenerative disease (P0113) using a source (pump, P0166-0184) for supplying a protein formulation (P0185-0197) to the pericardial sac via a catheter" (Ans. 4). The Examiner finds that "Stafford teaches delivering a drug (warfarin) to treat a genetic variation (vitamin K epoxide reductase mutation) by varying the drug delivery dosage and rate based on the patient's specific genetic mutation" (*id.*).

The Examiner finds it obvious to

> use the teachings of Stafford regarding relating treatment of a genetic variation to the patient's genetic mutation to adjust delivery of a protein formulation for treatment of GSD Type II or Fabry disease, since both diseases are genetic disorders. Applying the teachings of Stafford would involve only routine skill in the art since it has been held that improving similar methods (treatment of genetic variation) in the same way is within the skill of an ordinary worker in the art

(*id.* at 4-5).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that LeBowitz, Struijker-Boudier, and Stafford render claim 18 obvious?

Findings of Fact

1. LeBowitz teaches "to evaluate the efficacy of GILT-modified alpha-galactosidase A (α-GAL A) as an enzyme replacement therapy for Fabry's disease" (LeBowitz 21 ¶ 0199).

2. LeBowitz teaches that "Fabry's disease is a lysosomal storage disease resulting from insufficient activity of α-GAL A, the enzyme responsible for removing the terminal galactose from GL-3 and other neutral sphingolipids. The diminished enzymatic activity occurs due to a variety of missense and nonsense mutations in the X-linked gene" (LeBowitz 21 ¶ 0200).

3. LeBowitz teaches that the "glycosylation independent lysosomal targeting (GILT) technology of the present invention directly targets therapeutic proteins to the lysosome via a different interaction with the IGF-II receptor" (LeBowitz 21 ¶ 0203).

4. LeBowitz teaches that the "improved range of tissue distributions could include delivery of GILT-modified α-GAL A across the blood-brain barrier since IGF proteins demonstrably cross the blood-brain barrier" (LeBowitz 21 ¶ 0203).

5. LeBowitz teaches that an "enzyme dose can be about 1 mg/kg body weight administered intravenously, and the enzyme concentration about 1-3 mg/mL. As another example, a dose of about 5 mg/kg body weight of . . . protein treated with periodate and sodium borohydride can be

administered. Injections can, for example, be weekly" (LeBowitz 23 ¶ 0224).

6. Struijker-Boudier teaches that:

> A drug can be administered into the pericardial fluid using any of a number of delivery systems, including sustained release devices. In some embodiments, the drug delivery system will comprise a catheter operably attached to a sustained release drug delivery device. A proximal end of the catheter is operably attached to a sustained release drug delivery device; and a distal end of the catheter may be adapted for transpericardial delivery, or may be adapted for intrapericardial delivery.

(Struijker-Boudier 12 ¶ 0168.)

7. Struijker-Boudier teaches that a "drug delivery device of the invention may release drug in a range of rates of from about 0.01 microgram/hr to about 500 microgram /hr, and which can be delivered at a volume rate of from about 0.01 microliter/day to about 100 microliter/day" (Struijker-Boudier 13 ¶ 0174).

8. Struijker-Boudier teaches that "[d]rug release devices based upon a mechanical or electromechanical infusion pumps can also be suitable for use with the present invention" (Struijker-Boudier 13 ¶ 0177).

9. Struijker-Boudier teaches that "[c]ardiomyopathies include . . . metabolic disorders . . . and idiopathic causes" (Struijker-Boudier 16 ¶ 0219).

10. Stafford teaches "a method of correlating a single nucleotide polymorphism in the VKOR gene of a subject with increased or decreased sensitivity to warfarin" (Stafford 1 ¶ 0013).

11. Stafford teaches "correlating single nucleotide polymorphisms in a subject with an increased or decreased sensitivity to warfarin, thereby allowing for more accurate and rapid determination of therapeutic and maintenance doses of warfarin at reduced risk to the subject" (Stafford 1 ¶ 0006).

12. Stafford teaches that by "direct genomic DNA sequencing and SNP realtime PCR detection, five SNPs were identified in the VKOR gene: one in the 5'-UTR, two in intron 11, one in the coding region and one in the 3'-UTR" (Stafford 8 ¶ 0085).

Principles of Law

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima face case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992).

To establish a prima facie case of obviousness, the Examiner must find "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l. Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007).

Analysis

Lebowitz inherently teaches diagnosis of Fabry disease and teaches treatment of Fabry disease using an injectable therapeutic formulation of α-galactosidase (FF 1-5). Struijker-Boudier teaches delivering the protein drug to the pericardial sac of a patient using a pump that provides for programmed rates of delivery (FF 6-9). Stafford teaches "correlating single nucleotide polymorphisms in a subject with an increased or decreased sensitivity to warfarin, thereby allowing for more accurate and rapid

determination of therapeutic and maintenance doses of warfarin at reduced risk to the subject" (Stafford 1 ¶ 0006; FF 11).

While this evidence might be sufficient to support a *prima facie* case against a generic method of providing a delivery rate of a therapeutic drug based upon single nucleotide polymorphisms, Claim 18 and all the dependent claims are limited to either glycogen storage disease Type II or Fabry disease.

The Examiner has provided no evidence that there are any known mutations, in the prior art, which are associated with either glycogen storage disease Type II or Fabry disease and which correlate with a requirement for treatment with additional amounts of either lysosomal acid α−glucosidase or α-galactosidase. The Specification does not provide any discussion of such mutations nor does the Specification disclose that the prior art was aware of such mutations. In the absence of such evidence, the Examiner has not established a *prima facie* case of obviousness since the prior art does not demonstrate that any rate of protein level can be determined by any SNP or genetic sequence encoding the deficient proteins in either glycogen storage disease Type II or Fabry disease as required by the determining step of claim 18.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that LeBowitz, Struijker-Boudier, and Stafford render claim 18 obvious.

B. 35 U.S.C. § 103(a) over LeBowitz, Struijker-Boudier, and Martinez

The Examiner finds that "LeBowitz teaches a method of supplying a lyosomal [sic] acid alpha-glucosidase . . . or alpha-galatosidase (Example 12, treatment of Fabry disease) to cells in the body, where the protein formulation includes deficient proteins" (Ans. 5). The Examiner finds that "LeBowitz does not specifically teach delivery to the heart or pericardial sac with a drug pump or determining the drug delivery rate based on the patient's genetic sequence" (*id.*). The Examiner finds that "Strutjket-Boulder [sic] teaches a method and device for treating a cardiac disorder, such as a cardiodegenerative disease (P0113) using a source (pump, P0166-0184) for supplying a protein formulation (P0185-0197) to the pericardial sac via a catheter" (Ans. 5).

The Examiner finds that "Martinez teaches delivering a drug based on the local enzyme level assessment of the drug delivery area" (Ans. 6). The Examiner finds it obvious "to use the teachings of Martinez regarding relating treatment using a smart drug delivery pump controlled by a sensor with the pump of Strutijiket-Boulder to more finely control drug delivery (as taught by Martinez)" (Ans. 6).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that LeBowitz, Struijker-Boudier, and Martinez render claim 18 obvious?

Findings of Fact

13. Martinez teaches that sensors "can facilitate the implementation of 'smart' devices that can monitor and control the concentration and amount of drug delivery" (Martinez, col. 7, ll. 21-23).

14. Martinez teaches that "[s]ensors **50** and **53** . . . can monitor the physiological condition **60** of a local area of a patient based on local chemistry, e.g. . . . enzymes, or other optically detectable biological species" (Martinez, col. 7, ll. 29-33).

15. Martinez teaches that the "readings by sensor **53** at a second location **55** can be converted to electrical signals and transmitted to a smart electronics-actuator system **70** that can deliver the required therapy to the patient based on the sensor reading" (Martinez, col. 7, ll. 34-38).

Principles of Law

The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

As noted by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id*. at 421. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id*. at 416.

Analysis

Lebowitz inherently teaches a first step of diagnosis of Fabry disease and explicitly teaches a second step of injecting a protein formulation into patients for treatment of Fabry disease using a therapeutic formulation of α-galactosidase (FF 1-5). Martinez teaches determining a rate for delivery of enzymes by measuring the enzyme level using sensors and transmitting that information to an implantable device (FF 13-15). Struijker-Boudier teaches

delivering the protein drug to the pericardial sac of a patient using a pump that provides for programmed rates of delivery with a drug delivery device (FF 6-9).

Applying the *KSR* standard of obviousness to the findings of fact, we agree with the Examiner that the ordinary artisan would have reasonably found it obvious to diagnose and treat Fabry disease heart damage using the delivery system of Struijker-Boudier as controlled by the enzyme sensors of Martinez. Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

Appellants contend that "[b]ecause the sensors 50 and 53 of Martinez discussed in the Final Action are not at the tissue to which the drug is being delivered, the sensors 50 and 53 do not assess the local enzyme level of the drug delivery area" (App. Br. 9).

We are not persuaded. Martinez teaches that "[s]ensors **50** and **53** . . . can monitor the physiological condition **60** of a local area of a patient based on local chemistry, e.g. . . . enzymes, or other optically detectable biological species" (Martinez, col. 7, ll. 29-33; FF 14). This is an express focus on monitoring enzymes in any specific location of interest.

SUMMARY

In summary, we reverse the rejection of claims 18, 23, 25, and 32-34 under 35 U.S.C. § 103(a) as obvious over LeBowitz, Struijker-Boudier, and Stafford.

We affirm the rejection of claims 18, 23, 25, 32, 33, 35, and 36 under 35 U.S.C. § 103(a) as obvious over LeBowitz, Struijker-Boudier, and Martinez.

AFFIRMED-IN-PART

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