

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte
H. STEVE ZHANG and LEI ZHANG

Appeal 2008-2455
Application 11/101,095
Technology Center 1600

Decided: September 29, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS, and LORA M. GREEN,
Administrative Patent Judges.

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims 1-3 and 6, directed to a method for increasing cardiac contractility in a subject. The Examiner has rejected the claims as lacking enablement, and as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

BACKGROUND

“Congestive heart failure is a syndrome characterized by left ventricular dysfunction . . . Decreased contractility of the left ventricle leads to reduced cardiac output with consequent systemic arterial and venous vasoconstriction” (Spec. 1: 12-15). “Contractility appears to be regulated primarily by calcium flow” (Spec. 1: 16).

“Phospholamban (PLN) is a regulatory phosphoprotein that modulates the active transport of Ca²⁺ by the cardiac sarcoplasmic reticular Ca(2+)-ATPase enzyme (SERCA2) into the lumen of the sarcoplasmic reticulum” (Spec. 1: 25-28).

The Specification describes several zinc finger proteins (ZFPs) that bind to target sites on the phospholamban gene, as well as fusion proteins wherein the ZFPs are fused to a transcriptional repression domain, e.g., a KOX domain (Spec. 2: 20-24, 3: 25-26).

According to the Specification, “repression of PLN expression can be achieved using the ZFP[] [fusion proteins] described herein, thereby increasing contractility (e.g., by increasing SERCA2a:PLN ratio). Thus, . . . the ZFPs can be used to repress expression of PLN, both *in vitro* and *in vivo*. Such repression can be utilized for example to alter the contractile activity of cardiac muscle and, accordingly, as treatment for congestive heart failure” (Spec. 20: 17-21).

The present invention is directed to a method of increasing cardiac contractility in a subject by administering a fusion protein comprising a phospholamban-targeted ZFP and a repression domain.

DISCUSSION

CLAIMS

Claim 1 is representative and reads as follows:

1. A method for increasing cardiac contractility in a subject, the method comprising:

introducing a nucleic acid into the subject, wherein the nucleic acid encodes a polypeptide, wherein the polypeptide comprises:

(i) a zinc finger DNA-binding domain that is engineered to bind to a target site in the phospholamban gene; and

(ii) a transcriptional repression domain;

such that the nucleic acid is expressed in one or more cardiac cells of the subject, whereby the polypeptide binds to the target site and represses transcription of the phospholamban gene.

Claims 1-3 and 6 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement throughout their scope.

Claims 1 and 6 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Choo,¹ GenBank,² Rebar,³ and del Monte.^{4, 5}

ENABLEMENT

The Examiner rejected claims 1-3 and 6 under 35 U.S.C. § 112, first paragraph, as nonenabled, on the basis that the “nature of the claimed

¹ International Application WO 01/25417 A2 of Choo, published April 12, 2001.

² GenBank Accession No. AF177763 (dated September 21, 1999) (hereinafter “GenBank”).

³ International Application WO 02/057293 A2 of Rebar, published July 25, 2002.

⁴ F. del Monte et al., *Targeting Phospholamban by Gene Transfer in Human Heart Failure*, 105 Circulation 904-7 (2002).

⁵ This ground of rejection has been withdrawn by the Examiner with respect to claims 2-5 (Ans. 29).

invention can be reasonably construed as a gene therapy method” (Ans. 7), “for use in treating heart failure” (*id.*). “However, [the] specification fails to demonstrate . . . modulation of any global cardiac function indicating that exemplified gene transfer would result in . . . functionally meaningful expression for [a] sustained period to achieve any therapeutic response” (Ans. 12).

The Examiner acknowledges that “claims 1-3 and 6 are drawn to a method for increasing cardiac contractility” in a subject (Ans. 5), and that “[t]he specification provide[s] guidance with respect to administering plasmids encoding 6439-KOX . . . directly into adult rat myocardium” and “[t]he data shows 6439-KOX increases Ca²⁺ transients in isolated adult rat cardiomyocytes” “isolated after injection” (Ans. 10). Nevertheless, the Examiner contends that “the claimed invention can be reasonably construed as a gene therapy method” (Ans. 7), thus, the claims have been analyzed accordingly, and “have been also analyzed for their intended use in the treatment of heart failure and other cardiac disorders” (Ans. 5).

In this regard, the Examiner cites a number of references⁶ in support of the assertion that “[t]he state of the art of gene therapy or delivering nucleic acids at the time of the filing of this application was unpredictable wherein any gene was expressed in an individual” (Ans. 9).

Appellants argue “the claims are not drawn to treatment methods or to methods of maintaining a sustained pharmacological response” (Reply Br.

⁶ For example, the Examiner cites Verma & Somia, *Gene Therapy - Promises, problems and Prospects*, 389 Nature 239-242 (1997), and Pfeifer & Verma, *Gene Therapy: Promises and Problems*, 2 Annu. Rev. Genomics Hum. Genet. 177-211 (2001).

4), thus the claims do not “necessitate any showing . . . [of] *in vivo* treatment of heart failure resulting from a sustained ‘pharmacological response.’ All that is required is that the specification teach one of skill in the art how to increase cardiac contractility using PLN-repressing ZFPs” (*id.*). Appellants contend that “[t]he as-filed specification includes working examples showing enablement of the claimed methods both *in vitro* (repression of PLN) and *in vivo* (repression of PLN increases cardiac contractility)” (*id.*). Thus, Appellants argue, “the working examples exemplify and adequately support the claimed methods” (*id.*).

We agree with Appellants that the Examiner has applied an overly stringent standard for enablement in this case. “[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). “That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is ‘undue.’” *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (emphasis in original). Some experimentation, even a considerable amount, is not “undue” if, for example, the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The enablement analysis must be focused on the product or method defined by the claims. “Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.”

CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338 (Fed. Cir. 2003).

See also In re Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims to method of “restoring hair growth” encompassed achieving full head of hair but did not require it).

The claims on appeal are directed to a method of increasing cardiac contractility in a subject, not to a method of treating heart failure. It is true that the Specification contemplates the use of the claimed method to treat heart failure and other cardiac disorders, but practicing the claimed method does not require a therapeutically effective result.

Moreover, the Examiner’s apparent position that the Specification cannot teach how to use the claimed method unless it teaches solutions to all the problems in the field of gene therapy is contrary to controlling case law. *See, e.g., In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

In *Brana*, the claims were directed to compounds disclosed as anti-cancer agents. *Id.* at 1562. The USPTO rejected the claims as nonenabled, *id.* at 1563-64, despite working examples in Brana’s specification showing treatment of cancer in a mouse model. *Id.* at 1562-63. The USPTO argued that the results of the mouse testing “are not reasonably predictive of the success of the claimed compounds for treating cancer in humans.” *Id.* at 1567. The court concluded that this position “confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption.” *Id.* The *Brana* court held that “[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an

invention in this field becomes useful is well before it is ready to be administered to humans.” *Id.* at 1568.

Here, the claims are simply directed to a method for increasing cardiac contractility in a subject, and Appellants’ Specification provides several working examples demonstrating just that in rats. The Examiner has interpreted the claims as being directed to a method of treating heart failure, and has discounted the Specification’s working examples because they do not demonstrate “express[ing] ZFP-KOX *in vivo* for [a] sustained period showing that [the] instant method could be achieved *in vivo* in substantial number[s] of cardiac cells in order to elicit any pharmacological response” (Ans. 9). However, enablement - especially in the context of pharmaceutical inventions - includes an expectation of further research and development. In the pharmaceutical field, an invention can be enabled well before it is ready to be administered to humans. Thus, enablement is not precluded even if the claims encompass methods, such as gene therapy, that have not yet overcome all the obstacles to their clinical use.

The Examiner has not established that undue experimentation would have been required to practice the *claimed* method; specifically, a method of increasing cardiac contractility in a subject. The claims do not require therapeutically effective treatment of any disease, and we do not concur with the Examiner’s conclusion that such an effect is required to satisfy 35 U.S.C. § 112, first paragraph.

The rejection of claims 1-3 and 6 for lack of enablement under the first paragraph of 35 U.S.C. § 112 is reversed.

OBVIOUSNESS

The Examiner rejected claims 1 and 6 under 35 U.S.C. § 103(a) as unpatentable over Choo, GenBank, Rebar, and del Monte.

Choo describes a library of DNA sequences immobilized on a solid support that “allows improved selection for zinc fingers with particular sequence identity” (Choo 5: 20-21). Choo does not disclose ZFPs specific for phospholamdan.

Rebar describes a fusion protein “comprising a modified zinc finger DNA-binding domain and a functional domain . . . for . . . [repressing] endogenous gene expression” (Rebar 21: 1-3), for example, a ZFP DNA-binding domain fused to a KRAB repression domain from the human KOX-1 protein (Rebar 21: 9-11). Rebar does not disclose fusion proteins specific for phospholamdan.

GenBank discloses the sequence of the phospholamdan genes for several species.

del Monte teaches that decreasing the level of phospholamdan using an antisense approach improves contractility in failing cardiomyocytes (del Monte Abstract).

The Examiner contends that “[i]t would have been obvious for one of ordinary skill in the art . . . to modify the method of del Monte by replacing . . . anti-sense-PLN . . . with a nucleic acid encoding polypeptide comprising zinc finger DNA-binding fusion protein specifically designed to target [PLN]” (Ans. 16-17), because “GenBank had already disclosed the . . . sequence of different regions of PLN in different species” (*id.* at 17), while Choo “had disclosed method to design a composition to target a target gene”

(*id.*), and Rebar “had shown that a transcription repressor domain could be fused to ZFP-binding domain comprising plurality of zinc fingers for the inhibition of expression of the target gene” (*id.*). The Examiner contends that “[o]ne who would practice the invention would have had reasonable expectation of success because del Monte et al had already described decreasing phospholamdan expression restores contractility in failing ventricular cells of heart” (*id.*).

Appellants contend that “the cited references do not teach all the elements of appealed claims 1 and 6” (Reply Br. 11). Specifically, “del Monte and GenBank . . . are silent as to ZFPs entirely and Choo does not teach nucleic acids encoding a fusion of a ZFP and a repression domain, let alone a PLN-specific ZFP fused to repression domain as claimed. Rebar also fails to teach or suggest PLN-repressing ZFPs” (*id.*). Appellants contend that “[n]one of these references provide any suggestion of increasing cardiac contractility by repressing PLN expression” rather than destroying phospholamdan mRNA, and moreover, “del Monte’s antisense RNA has not been shown to be interchangeable with ZFP technology” (App. Br. 15).

Appellants have the better argument. Given the complete lack of any teaching regarding PLN-specific ZFPs, the Examiner has not established that one of skill in the art would have had a reasonable expectation of success in essentially “starting from scratch,” and therefore the Examiner has not established a *prima facie* case of obviousness for the claimed invention.

Accordingly, the rejection of claims 1 and 6 as unpatentable over the prior art is reversed.

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SUMMARY

The rejection of claims 1-3 and 6 under 35 U.S.C. § 112, first paragraph, as lacking enablement is reversed. The rejection of claims 1 and 6 under 35 U.S.C. § 103(a) is reversed as well.

REVERSED

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