

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte MARK C. FISHMAN and JOHN MABLY

Appeal 2007-3892
Application 10/467,490
Technology Center 1600

Decided: March 6, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a method of diagnosing risk of heart disease, which the Examiner has rejected for nonenablement and lack of adequate description. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the Examiner's rejections.

BACKGROUND

The Specification discloses that "a mutation (the heart of glass mutation) in a zebrafish gene, designated herein as heart of glass, leads to a

phenotype in zebrafish that is similar to heart failure in mammals” (Spec. 8). The heart of glass (or heg) mutation was identified “[a]s part of a large-scale mutagenesis screen of the zebrafish genome” (Stainier¹ 285 (Summary)). The mutation was found to result in a large, distended heart (*id.* at 286 (Table 1)).

The Specification discloses two forms of the zebrafish heart of glass polypeptide: heg1, “a putative secreted form,” and heg2, which “encodes a potential membrane spanning domain and a highly conserved intracellular domain” (Spec. 8; SEQ ID NOs 2 and 3 (listing the source of the sequences as *Danio rerio*)). The heg1 and heg2 forms are 841 and 977 amino acids long, respectively (Fig. 3; SEQ ID NOs 2 and 3). The “gene is not dominated by any known structural motifs, but does possess two short peptide stretches that have the distinctive six cysteines associated with EGF-repeats (amino acids 580-660), which are found in many different proteins of diverse function” (Spec. 29). The Specification also discloses a putative human heart of glass gene, which encodes a sequence of 652 amino acids (Spec. 4: 1-3; SEQ ID NO: 4).

The Specification discloses that the “mutation in the heart of glass gene is a stop codon resulting from a G to A change at residue 497, switching a tryptophan codon to a stop codon (TGG to TAG). This mutation occurs at amino acid 103, early in the sequence, and would result in a

¹ Stainier et al., “Mutations affecting the formation and function of the cardiovascular system in the zebrafish embryo,” *Development*, Vol. 123, pp. 285-292 (1996) (of record).

dramatic protein truncation.” (*Id.*) The Specification states that the resulting peptide “may not have any physiological function” (*id.*).

The Specification states that a “the heart of glass mutation in zebrafish is characterized by a phenotype that is similar to that of heart failure in mammals, such as humans. Thus, detection of abnormalities in heart of glass genes or in their expression can be used in methods to diagnose . . . human heart disease, such as heart failure” (*id.* at 9).

DISCUSSION

1. CLAIMS

Claims 1-3, 7, and 8 are on appeal. Claims 9-34 are also pending but have been withdrawn from consideration by the Examiner (App. Br. 3). The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative and reads as follows:

1. A method of determining whether a human test subject has or is at risk of developing heart disease, said method comprising comparing the sequence of a nucleic acid molecule encoding a heart of glass protein in a sample from the human test subject to the sequence of SEQ ID NO:4 to determine whether the test subject has a mutation in a gene encoding said protein, wherein the presence of a mutation indicates that said human test subject has or is at risk of developing heart disease.

2. ENABLEMENT

Claims 1-3, 7, and 8 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement (Ans. 3). The Examiner considered the factors set out in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), and found that:

- The claims are broad, because they encompass diagnosing risk of any heart diseases in a patient based on any mutations in a heart of glass

gene, where the Specification defines a “heart of glass” polypeptide as one that “has at least 45% . . . amino acid sequence identity to the sequence of a human (see, e.g., SEQ ID NO: 5) . . . heart of glass polypeptide” (Answer 4-5).

- The prior art does not disclose a human heart of glass gene, and “it is necessary to know the genetic basis of a human disease in order to establish a zebrafish disease model” (*id.* at 5-6, citing Rubinstein² at 222).

- The Specification discloses a single mutation in the zebrafish heart of glass gene and describes results of treating zebrafish embryos with antisense oligonucleotides (Answer 6) but “does not provide sufficient evidence showing that the mutation in the cDNA of SEQ ID NO: 1 is linked to heart failure in zebrafish” (*id.* at 7) and does not disclose if the mutation found in zebrafish also occurs in the human heart of glass gene (*id.*).

- The Specification does not provide guidance or working examples of how to diagnose risk of heart disease by comparing a sample nucleic acid to SEQ ID NO: 4: “It is likely a nucleic acid sequence that differs from the cDNA sequence of SEQ ID NO: 4 is a natural variant of SEQ ID NO: 4, not necessarily a mutation.” (*Id.* at 8.)

- “It is unpredictable whether a mutation in zebrafish with a potential link to heart disease can be extended to determine whether a human test subject has, or is at risk of developing[,] heart disease” (*id.*).

The Examiner concludes that “it would require undue experimentation for one skilled in the art to practice the claimed invention” (*id.* at 9).

² Rubinstein, “Zebrafish: From disease modeling to drug discovery,” *Curr. Opin. Drug Discovery Devel.*, Vol. 6, pp. 218-223 (2003).

We agree. The Specification discloses a single mutation in a zebrafish gene that causes a dramatic truncation of the encoded protein, which is probably nonfunctional (Spec. 29). As a result, the mutant fish embryo's heart develops abnormally: "the walls of the heart are grossly distended" (Stainier 287, right-hand column).

The heart of glass mutation is a "recessive embryonic lethal mutation" (Mably³ 2138, right-hand column); i.e., fish carrying two copies of the mutation die as embryos. Stainier provides evidence that a similar mutation would also be lethal in mammalian embryos: fish embryos are not dependent on blood flow for oxygen delivery during the first few days of life, whereas mammalian embryos are (Stainier 290, right-hand column, and 291, right-hand column). The heart of glass mutation would be expected to be at least as lethal in embryos that are dependent on blood flow for oxygen delivery as it is in embryos that are not.

The lethality of the heart of glass mutation casts doubt on the Specification's assertion that detecting it in human patients would be diagnostic of heart disease or risk thereof. That is, since the heart of glass mutation would be expected to cause death during fetal development, those skilled in the art would not expect to detect it a living human patient, regardless of whether the patient was at risk of heart disease.

The evidence of record also casts doubt on the Specification's description of SEQ ID NO: 4 as the human heart of glass gene. SEQ ID

³ Mably et al., "*heart of glass* regulates the concentric growth of the heart in zebrafish," *Current Biology*, Vol. 13, pp. 2138-2147 (2003). Appellants submitted a copy of Mably along with the Reply Brief dated Feb. 15, 2006.

NO: 4 encodes a polypeptide of 652 amino acids.⁴ The encoded sequence appears to be the same as amino acids 1-591 of the amino acid sequence of the zebrafish heg polypeptide, with an additional 61 amino acids added at the N-terminus (the beginning of the sequence; compare amino acids 62-652 of SEQ ID NO: 4 with amino acids 1-591 of SEQ ID NO: 1). The amino acid sequence encoded by SEQ ID NO: 4 is missing the only part of the protein pointed to in the Specification as potentially important to the function of the zebrafish heart of glass polypeptide. (Spec. 29: “This gene . . . does possess two short peptide stretches that have the distinctive six cysteines associated with EGF-repeats (amino acids 580-660), which are found in many different proteins of diverse function.”)

Mably also provides evidence that SEQ ID NO: 4 is not the human heart of glass gene. Mably was published in 2003 and was co-authored by Appellants. Mably states that the zebrafish heg gene “appears to be the homolog of the human gene KIAA1237, with greatest sequence identity over the 133 amino acids at the C-terminus” (Mably 2141, left-hand column). Mably compares the sequences of zebrafish and human heg proteins (*id.* at Fig. 5C); the sequence given for the human heg protein (“hegB_hs”) is not the same as the sequence in SEQ ID NO: 4 of the instant Specification (among other differences, hegB_hs is much longer and SEQ ID NO: 4 is missing all of the best-aligning sequence at the C-terminus). Thus, the evidence provides a reasonable basis to doubt the Specification’s description of SEQ ID NO: 4 as encoding a human heart of glass protein (Spec. 4: 1-3).

⁴ Some of the “amino acids” encoded by SEQ ID NO: 4 are actually stop codons.

The instant Specification and the prior art of record do not disclose any mutations in the *heg* gene other than the single mutation found to interfere with heart formation in zebrafish. Nor do the Specification or the prior art of record disclose any correlation between a mutation in the putative human *heg* gene and any kind of heart disease or heart failure in humans. Appellants have not provided a reasonable basis for concluding that those skilled in the art would have expected a mutation shown to interfere with heart formation in zebrafish to correlate with increased risk of heart disease in humans. We agree with the Examiner that practicing the claimed method would have required undue experimentation based on the Specification's disclosure.

Appellants argue that comparing the sequence of a nucleic acid encoding a heart of glass protein from a test subject with the sequence of SEQ ID NO: 4 and determining whether the test subject's gene has a mutation involves routine methods (App. Br. 6). Appellants "concede that subjects may contain polymorphisms in SEQ ID NO: 4 that are not harmful," but argue that "one skilled in the art can easily distinguish those polymorphisms . . . from those polymorphisms which would lead to loss of proper functioning of the heart of glass protein (e.g., mutations resulting in a frameshift, a premature stop codon, or a substitution of one amino acid for another amino acid with different properties)." (Reply Br. 12.)

This argument does not persuade us that the Examiner's rejection is in error. First, the Specification provides no support for Appellants' apparent position that the claims are limited to detecting mutations that radically affect the function of the heart of glass protein. The claims are not so

limited; they read on diagnosing heart disease or risk of heart disease (*any* heart disease) by detecting a mutation (*any* mutation) in the heart of glass gene. Also, Appellants have cited no basis in the evidence of record to support their position that those skilled in the art would be able to distinguish easily between mutations that would lead to loss of proper functioning of the heart of glass protein and mutations that would not.

We agree with Appellants that, if and when a mutation in a heart of glass gene has been shown to be associated with heart disease, detecting such a mutation in a subject's DNA would be routine. The experimentation required to practice the claimed method requires more than detecting a particular mutation, however. Practicing the claimed method also requires identifying heart of glass mutations and determining which, if any, of them are diagnostic of heart disease or risk thereof. Appellants' Specification provides a starting point for the required experimentation, but does not provide sufficient guidance to enable practice of the claimed method without undue experimentation.

Appellants and the Examiner both rely on Rubinstein to support their positions. The Examiner cites Rubinstein's statement that "[d]evelopment of disease-relevant assays and disease models in the zebrafish is still in its infancy. . . . In particular, it will be necessary to show that these models recapitulate the underlying mechanisms of human disease" (Answer 6, quoting Rubinstein at 222). The Examiner finds support in Rubinstein for his position that "it is necessary to know the genetic basis of a human disease in order to establish a zebrafish model" (*id.*).

Appellants, by contrast, interpret Rubinstein as showing that “there is a high level of correlation between characterized zebrafish mutations and human disease genes, which supports the scope of enablement of the present claims” (App. Br. 7). Appellants argue that

the critical point is that [they] have shown that the *heart of glass* gene plays a role in proper functioning of the heart, and that a mutation in this gene leads to a phenotype in zebrafish that is consistent with human heart disease. With this knowledge, and the high level of confidence of those of skill in the art with respect to the relevance of the zebrafish model (as is reflected, for example, in Rubinstein), it certainly can be expected that mutations in the human sequence are predictive of heart disease in humans.

(*Id.* at 9-10.)

We do not agree with Appellants that Rubinstein supports the enablement of the instant claims. First, we disagree with Appellants’ assertion that they “have shown that the *heart of glass* gene plays a role in proper functioning of the heart.” The heart of glass mutation was known in the art to interfere with proper heart *development*, not heart function, in zebrafish embryos. (Mably 2138, left-hand col.: “Conclusions: *heart of glass* encodes a previously uncharacterized endocardial signal that is vital for patterning concentric growth of the heart.”) The Specification provides no additional evidence that the heart of glass gene affects the function, as opposed to formation, of the heart.

In addition, the issue raised by this rejection is *not* whether those skilled in the art would have thought there was a reasonable basis to think that mutations in the heart of glass gene would someday be shown to be correlated to human heart disease. The issue is whether a person of ordinary

skill in the art would have been able, based on what is disclosed in the Specification and what was known in the art, to practice the full scope of the claimed method without undue experimentation. On this question, Rubinstein adds very little of substance. Based on a preponderance of the evidence in the record, we agree with the Examiner that Appellants' disclosure does not enable practice of the method of claim 1 in compliance with 35 U.S.C. § 112, first paragraph. We therefore affirm the rejection of claim 1 for nonenablement. Claims 2, 3, 7, and 8 fall with claim 1.

3. WRITTEN DESCRIPTION

Claims 1-3, 7, and 8 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that “the specification fails to provide adequate written description for the instantly claimed invention. . . . There is no description of any mutations in the cDNA of SEQ ID NO: 4 or any other forms of nucleic acids (a genomic DNA or mRNA) in humans that are linked to a heart disease and can be used for diagnosis and prognosis of a heart disease” (Answer 10). The Examiner finds that the prior art does not compensate for the Specification's deficiency, because “the prior art does not teach any mutations in a nucleic acid molecule encoding a heart of glass protein that are linked to a heart disease in a human” (*id.* at 11).

We agree with the Examiner. The Specification discloses a single mutation in the zebrafish heart of glass gene, a mutation that was known in the art to interfere with proper heart development. The Specification provides no persuasive evidence that this specific mutation correlates with the presence or risk of heart disease in zebrafish, or that the specific mutation occurs in humans, or that this specific mutation correlates with

heart disease in humans. Thus, we agree with the Examiner's finding that Appellants have not described "any mutations . . . in humans that are linked to a heart disease and can be used for diagnosis or prognosis of a heart disease" (Answer 10).

Additionally, the method of claim 1 encompasses using a mutation in the human heart of glass gene to diagnose heart disease or risk thereof. Thus, the claims read on diagnosing heart disease or risk thereof by detecting any mutation in the human heart of glass gene. Since the claims encompass using any of a genus of heart of glass mutations, the Specification must describe that genus. *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.").

"A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). The complete structure of the representative species need not necessarily be described. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (The "written description requirement can be met by 'show[ing] that an invention is

complete by disclosure of sufficiently detailed, relevant identifying characteristics” such as partial structure, physical and chemical properties, or a correlation between function and structure).

Appellants have described a single heart of glass mutation, found in zebrafish, that has not been correlated with heart disease. Thus, Appellants have not described even a single member of the genus of human heart of glass mutations that are required to practice the method of claim 1. We agree with the Examiner that the Specification does not show that Appellants were in possession of the claimed method at the time the instant application was filed.

Appellants argue that the

specification provides a firm basis for concluding that detection of a mutation in a *heart of glass* sequence has a strong correlation with human heart disease, and describes a straightforward method for carrying out such a method, by comparison with a single reference sequence, SEQ ID NO: 4. The application thus clearly provides an adequate written description of the presently claimed invention.

(App. Br. 12.)

For the reasons discussed above, we disagree with both Appellants’ premise (that the *heart of glass* mutation has been shown to correlate with human heart disease) and their conclusion (that the claimed method has been adequately described). The rejection of claim 1 for lack of adequate written description is affirmed. Claims 1, 2, 7, and 8 fall with claim 1.

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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

Ssc:

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