

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 35

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte NEBOISA JANJIC, and
LARRY GOLD

Appeal No. 2001-0545
Application No. 08/442,423

ON BRIEF

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 20-22. The claims read as follows, with the independent claim appearing first:

22. A method for inhibiting angiogenesis comprising administering a pharmaceutically effective amount of a nucleic acid bFGF ligand.
20. The method of claim 22 wherein said nucleic acid bFGF ligand is identified according to a method comprising the steps of:
 - a) preparing a candidate mixture of nucleic acids;
 - b) contacting the candidate mixture with bFGF, wherein nucleic acids having an increased affinity to bFGF relative to the

total candidate mixture may be partitioned from the remainder of the candidate mixture;

- c) partitioning the increased affinity nucleic acids from the remainder of the nucleic acids in the candidate mixture; and
- d) amplifying the increased affinity nucleic acids to yield a mixture of nucleic acids enriched for sequences with increased affinity to bFGF, whereby said nucleic acid ligand is identified.

21. The method of claim 20 wherein said ligand is a 2'-NH₂-modified ligand selected from the group consisting of SEQ ID NOS: 101-146.

The panel relies upon the following art, which was cited by the examiner in the Examiner's Answer:

Grant et al. (Grant), "Insulin-like growth factor I acts as an angiogenic agent in rabbit cornea and retina: comparative studies with basic fibroblast growth factor," Diabetologia, Vol. 36, pp. 282-91 (1993).

Hayek et al. (Hayek), "An in vivo model for the study of the angiogenic effects of basic fibroblast growth factor," Biochemical and Biophysical Research Communications, Vol. 147, No. 2, pp. 876-80 (1987).

The claims stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. After careful review of the record and consideration of the issue before us, we reverse the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement. We do, however, agree with the examiner that certain of the claims on appeal are unpatentable in view

of the evidence of record, and thus new grounds of rejection are herein set forth under 37 CFR § 1.196(b).

BACKGROUND

The specification teaches a method for identifying “high-affinity RNA ligands to basic fibroblast growth factor (bFGF).” Specification, page 1.

According to the specification:

The present invention is premised on the inventors’ fundamental insight that nucleic acids as chemical compounds can form a virtually limitless array of shapes, sizes and configurations, and are capable of a far broader repertoire of binding and catalytic functions than those displayed in biological systems.

Id. at 5.

Basic fibroblast growth factor stimulates cell proliferation, migration and induction of plasminogen activator and collagenase activities in vitro, and in vivo, it is a potent inducer of neovascularization. Because of its in vivo angiogenic activity, the specification notes that bFGF may not only be involved in wound healing and tissue remodeling, but may also be involved “in some disease states that are characterized by pathological neovascularization such as tumor proliferation, tumor metastasis, diabetic retinopathy and rheumatoid arthritis.” Id. at 12.

DISCUSSION

Claims 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that they contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The rejection analogizes the use of nucleic acid ligands to gene therapy, which, according to the rejection, “the art taught was [] unpredictable without some parameters being taught for achieving effective treatment.” Examiner’s Answer, page 3. The rejection concentrates on the problems of delivery of the nucleic acid, stating that “[t]here is no evidence of record that sufficient ligand could be administered by various routes of delivery in the various target tissues to affect a useful inhibition of angiogenesis.” Id. at 4.

The rejection also discusses anti-sense therapy, which, it is alleged, is also closely related to the claimed methods. According to the examiner, “[t]he art recognized that the major problem to be over come [sic] for antisense therapy to be successful is for the oligonucleotides to reach the target nucleic acid in sufficient quantities to inhibit the disease phenotype.” Id.

The examiner considers the working examples, but questions the results of the assay examining the ability of one of the identified bFGF ligands, 21A, to inhibit bFGF induced neovascularization of the rat cornea. The rejection states that:

[T]his data is not seen as providing sufficient guidance to the artisan so as to enable the methods as claimed for any disclosed use in treating tumor proliferation, tumor metastasis, diabetic retinopathy, rheumatoid arthritis or any other gene therapy type protocols. . . . The rat cornea model as described in example 6 does not naturally become angiogenic unless perturbed to do so. In fact, historically, the model was developed to assay for the angiogenic potential of various compound [sic], especially growth factors. Thus, the rat cornea model of example 6 does not correlate to any naturally occurring disease or condition.

Id. at 5-6. The rejection contends that there “is no evidence that the rat is an art recognized or a correlatable model for the treatment of diseases and conditions that are affected by angiogenesis.” Id. at 7.

In addition, according to the rejection, the specification only provides one example of ligand administration, but does not enable other methods of administration, nor the amounts that would be required to inhibit angiogenesis.

See id. at 6. The examiner concludes:

Therefore, given the unpredictability recognized in the art in the delivery of genes and antisense oligonucleotides for therapies and the lack of evidence in a correlatable animal model, the specification does not provide sufficient guidance to the artisan to implement the claimed invention with a predictable degree of success. The determination of routes of delivery and amounts of ligand to inhibit angiogenesis to a useful degree would require an inventive step on the part of the artisan. Given the arguments presented here, the instant claims are an invitation to invent.

Id., page 8.

Appellants argue that enablement rejection is improper. We agree.

The burden is on the examiner to set forth a prima facie case of unpatentability. See In re Glaug, 283 F.3d 1335, 1338, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002). Facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention 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. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988). In setting forth an enablement rejection under 35 U.S.C. § 112, first paragraph, the examiner should set forth his or her analysis for each of the relevant Wands factors in order to expedite review on appeal.

In this case, the examiner is relying on the state of the art in gene therapy and anti-sense therapy to demonstrate the unpredictability of the instant claims, and thus for the conclusion that the specification does not teach the skilled artisan how to deliver the claimed nucleic acid ligands for bFGF. The examiner acknowledges that gene expression is not a requirement for the claimed method, but does not appear to give that difference much weight. That is, however, a substantial difference, as the instant methods only require the nucleic acid ligand to bind to bFGF, and thus bypass the difficulties of requiring expression. Moreover, as noted by the examiner, the issue with anti-sense therapy is the ability of the anti-sense nucleotide to reach the target nucleic acid in sufficient quantities to inhibit the disease phenotype, which again, is not required by the instantly claimed methods. See Examiner's Answer, page 4. Thus, the discussion of the problems with gene therapy and anti-sense therapy do not support the examiner's proposition that the instant claims are not enabled, as the nucleic acids of the instantly claimed methods act as a binding partner to bFGF, and do not require expression, nor must they bind to a target nucleic acid in order to inhibit the disease phenotype.

Most of the examiner's arguments directed to the use of a nucleic acid ligand for bFGF to inhibit angiogenesis rely on the proposition that there is no evidence that the rat is an art recognized or a correlatable model for the treatment of diseases and conditions that are affected by angiogenesis. The evidence of record, however, does not support that proposition. For example, Hayek states that the rabbit cornea, another rodent model, is a model for the study of in vivo angiogenesis. Similarly, Grant notes that the rabbit cornea is "an established angiogenic model." Grant, page 282, abstract.

Because of the deficiencies noted above, the examiner has not met her burden of setting forth a prima facie case of non-enablement.

REJECTION UNDER 37 CFR § 1.196(b)

New grounds of rejection are entered against claims 20 and 22 under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure fails to provide adequate written description of the claimed subject matter.

Claims 20 and 22 are drawn to methods for inhibiting angiogenesis by administering a pharmaceutically effective amount of a nucleic acid bFGF ligand. The disclosure fails to provide adequate written description of the nucleic acid molecules that are encompassed by the phrase "a nucleic acid bFGF ligand."

The Court of Appeals for the Federal Circuit, our reviewing court, has addressed the issue of what constitutes adequate written description for a claim drawn to a nucleic acid. In Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1602 (Fed. Cir. 2002), the court adopted a portion of the

Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

The written description requirement can be met by “showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics.

Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613 (citations omitted).

The court also addressed the issue of what constitutes adequate written description of a claim to a broad genus of sequences. In The Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998), the court determined that the disclosure of rat cDNA did not provide adequate written description support for claims drawn to mammalian and vertebrate DNA. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. The court stated:

In claims to genetic material, however, a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA,” without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

In Enzo-Biochem, the court refined the approach advanced by Eli Lilly, adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Thus, adequate written description may be present for a genus of nucleic acids based on their hybridization properties, “if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.” Enzo Biochem, 296 F.3d at 1327, 63 USPQ2d at 1615.

Claim 20 is drawn to a method of inhibiting angiogenesis through the administration of “a pharmaceutically effective amount of a nucleic acid bFGF ligand.” Claim 20 further defines the method of identifying the bFGF ligand. The nucleic acid ligand, however, is merely described in terms of function, i.e., the ability to bind to bFGF. Moreover, the specification only discloses a small number of nucleic acid sequences that bind to bFGF, see claim 21, and, as noted by the specification, there are at least two distinct families of nucleic acid ligands that bind to bFGF. See Specification, pages 28-29. Thus, even though the specification discloses several sequences of nucleic acid ligands to bFGF, such a disclosure does not provide an adequate disclosure of the genus as the specification does not present data or evidence that the remaining members of the genus hybridize under highly stringent conditions to the known sequences such that all species within the genus will be structurally similar.

CONCLUSION

This decision contains a new ground of rejection pursuant to 37 CFR § 1.196(b). 37 CFR § 1.196(b) provides that, “A new ground of rejection shall not be considered final for purposes of judicial review.”

37 CFR § 1.196(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .

(2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. .

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REVERSED; 37 CFR § 1.196(b)

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