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for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN GLEAVE and HIDEAKI MIYAKE

Appeal No. 2005-2447
Application No. 09/619,908

HEARD: October 18, 2005

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 1-23 and 26-40. Claims 24 and 25, also pending in the application, have been allowed.

BACKGROUND

> Insulin-like growth factor (IGF)-I and IGF-II are potent mitogens for many normal and malignant cells. Accumulating evidence suggests that IGFs play an important role in the pathophysiology of prostatic disease and breast cancer. . . .
>
> The biological response to [IGFs] is regulated by various factors, including IGFBPs [(insulin-like growth factor binding proteins)]. To date, six IGFBPs have been identified whose function is believed to involve modulation of the biological actions of the IGFs through high affinity interactions . . . However, some evidence suggests biological activity for IGFBPs that are independent of IGFs, . . . and both stimulatory and inhibitory effects of IGFBPs on cell proliferation have been reported under various experimental conditions. . . .

Specification, pages 1-2.

"[P]rostate cancer is an androgen-sensitive tumor, [thus,] androgen withdrawal . . . is utilized in some therapeutic regimens . . . [and] leads to extensive apoptosis in the prostate tumor, and hence to a regression of the disease. However, . . . apoptosis is not complete, and a progression of surviving tumor cells to androgen-independence ultimately occurs." Id., page 1. The present invention is concerned with delaying the ultimate progression of tumor cells to androgen-independence.

Appellants "initially characterized the changes [in] IGFBPs expression in the Shionogi tumor model[1] after castration and during [progression to androgen-independence]" (Specification, page 5). "Of the IGBFPs expressed in Shionogi tumors, the most dramatic changes in expression were observed with IGFBP-5. Despite undetectable levels in [androgen-dependent] intact tumors, IGFBP-5 expression is highly upregulated after castration, and remains highly expressed in [androgen-independent] tumors." Id., pages 5-6. Moreover, "[t]he pattern of IGFBP-5 upregulation in the Shionogi tumor model during [progression to

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[1] "The Shionogi tumor model is a xenograft of an androgen-dependent mouse mammary carcinoma that grows subcutaneously in male syngenic hosts." Specification, pages 4-5. Shionogi tumor cells "are highly tumorigenic and locally invasive . . . [and] have been shown to respond to androgen withdrawal in a manner which mimics the observed behavior of prostatic tumor cells," that is, "androgen withdrawal precipitates apoptosis and tumor regression in a highly reproducible manner" (id., page 5). "Further, changes in expression of peptides . . . in human prostate cancer following castration and during progression to androgen-independence are similar to those observed in Shionogi tumor cells. Because of these similarities, the Shionogi tumor model mimics human prostate cancer and provides a very useful model for the evaluation of the ability of compounds to delay the onset of androgen-independence. Despite complete tumor regression after castration, rapidly growing androgen-independent Shionogi tumors invariably recur after one month, which provides a reliable end point to evaluate agents which can delay the progression to androgen-independence." Id.

androgen-independence] . . . is similar to that in rat prostate . . . and human prostate" (id., page 6).

According to appellants, antisense oligodeoxynucleotides (ODNs) complementary to portions of the gene encoding IGFBP-5 "inhibit[ ] cell proliferation and induce[ ] cell cycle arrest in Shionogi tumor cells in a time- and dose-dependent manner . . . [and do] not appear to induce apoptosis either in vitro or in vivo, . . . suggest[ing] that antisense IGFBP-5 activity occurs via inhibition of cell proliferation rather than induction of apoptosis." Id. Appellants "hypothesized that targeting upregulation precipitated by androgen using [an] antisense strategy might inhibit progression to androgen-independence." Id., page 7. In appellants' "in vivo experiments, administration of antisense IGFBP-5 after castration delayed time to [androgen-independence] . . . and inhibited [androgen-independent] recurrent tumor growth." Id.

THE CLAIMS

The present invention is directed to "a method for delaying the progression of hormone-regulated (prostatic or breast) tumor cells to hormone (e.g. androgen or estrogen) independence, a therapeutic method for the treatment of individuals . . . suffering from hormone regulated cancers, such as breast or prostate cancer, and therapeutic agents effective for use in such methods." Specification, page 4. In addition, the present invention is directed to a method of inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal. We note that the claims on appeal require an antisense oligonucleotide that inhibits expression of IGFBP-5, with the exception of method claims 8, 12, 15, 19, 39 and 40, which merely

require "a composition effective to inhibit expression of IGFBP-5."

Claims 1, 8, 15 and 22 are representative of the subject matter on appeal:

1. A method for delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, comprising treating hormone-sensitive mammalian tumor cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells.

8. A method for treating a hormone-responsive cancer in a mammalian individual suffering from hormone-responsive cancer, comprising the steps of initiating hormone-withdrawal to induce apoptotic cell death of hormone-responsive cancer cells in the individual, and administering to the individual a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby delaying the progression of hormone-responsive cancer cells to a hormone-independent state in the individual.

15. A method for inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal, comprising the step of administering to the mammal a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby inhibiting or delaying metastatic boney progression of the tumor.

22. A composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells.

THE REJECTIONS

The claims stand rejected as follows:

I. Claims 1, 5, 22 and 36-38[2] under 35 U.S.C. § 102 (b) as anticipated by Huynh.[3]

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[2] Claims 36-38 were subject to this ground of rejection in the final rejection (paper no. 14, January 24, 2003), but were omitted from the examiner's statement of the rejection in the Answer. The omission of these claims appears to have been a typographical error, as they are specifically discussed in the examiner's response to appellants' arguments (see, e.g., page 16 of the Answer).

[3] Huynh et al., "A Role for Insulin-like Growth Factor Binding Protein 5 in the Antiproliferative Action of the Antiestrogen ICI 182780," Cell Growth & Differentiation, Vol. 7, pp. 1501-1506 (November 1996)

II. Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38[4] under 35 U.S.C. § 103 (a) as unpatentable over Huynh in view of Kiefer,[5] Baracchini[6] and Nickerson.[7]

III. Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 under the first paragraph of 35 U.S.C. § 112, written description.

IV. Claims 1-23 and 26-40 under the first paragraph of 35 U.S.C. § 112, enablement.

DISCUSSION

I. Anticipation

Claims 1, 5, 22 and 36-38 stand rejected under 35 U.S.C. § 102 (b) as anticipated by Huynh. Claims 1, 5 and 38 are method claims, while claims 22, 36 and 37 are composition claims. Appellants argue that the method and composition claims do not stand or fall together because "anticipation of a method claim requires a different content of the reference than a composition claim, which need only disclose the same composition, rather than the same method steps." Brief, page 3. Accordingly, we will consider claim 1 to be representative of the method claims, and claim 22 to be representative of the composition claims – claims 5 and 38 will stand or fall with claim 1, while claims 36 and 37 will stand or fall with claim 22.

Claim 1 is directed to a method of delaying progression of hormone-regulated

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[4] Claim 40 was included in this rejection in the final rejection, but the rejection was withdrawn with respect to claim 40 in the Examiner's Answer (page 17).

[5] Kiefer et al., "Molecular Cloning of a New Human Insulin-like Growth Factor Binding Protein," Biochem. Biophys. Res. Commun., Vol. 176, No. 1, pp. 219-225 (1991).

[6] U.S. Patent No. 5,801,154, issued to Baracchini et al. on September 1, 1998.

[7] Nickerson et al., "Castration-Induced Apoptosis in the Rat Ventral Prostate is Associated with Increased Expression of Genes Encoding Insulin-Like Growth Factor Binding Proteins 2, 3, 4 and 5," Endocrinology, Vol. 139, No. 2, pp. 807-810 (1998).

mammalian tumor cells to an androgen-independent state by treating the cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells. According to the examiner, "a key limitation is that the method steps are carried out in hormone sensitive mammalian tumor cells" (Answer, page 14), and "Huynh discloses administering an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 to breast cancer cells" (id., page 5). The examiner acknowledges that Huynh says nothing about delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, but argues that "any recited outcome such as that is merely considered to be an inherent feature, since all the structural and manipulative features of the claim are present in Huynh" (id.).

It is well settled that a prior art reference may anticipate even when claim limitations are not expressly found in that reference, but are nonetheless inherent in it. See, e.g., Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). However, it is also the case that "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Here, Huynh teaches that "IGFBP-5 can either stimulate or inhibit cellular proliferation in different experimental systems . . . suggest[ing] that there are poorly characterized complexities in IGFBP-5 action" (Huynh, pages 1503-1504). Indeed, on this record, there is no dispute that "Huynh [ ] actually teach[es] that antisense to IGFBP-5 stimulates cell proliferation in the [MCF-7] breast cancer cell line used" (Answer, page 14), while it inhibits proliferation in the Shionogi tumor cells used by

appellants. According to the examiner, this variation in the effects of antisense IGFBP-5 is irrelevant "because cellular proliferation (or inhibition thereof) is not recited as a claim limitation" (id.). In our view, however, this variation is relevant because it shows that in the only directly comparable parameter of record, the two cell lines react differently to inhibition of IGFBP-5. While Huynh says nothing about delayed progression to androgen-independence, it is not unreasonable to expect that the two cell lines might react differently to inhibition of IGFBP-5 in this respect as well, especially in light of Huynh's suggestion that the actions of IGFBP-5 are poorly characterized. In our view, the examiner has established that inhibition of IGFBP-5 in Huynh's MCF-7 cells might delay progression to androgen-independence, but has not established that it will. As discussed above, this is not sufficient to establish a prima facie case of anticipation based on inherency.

Accordingly, the rejection of claims 1, 5 and 38 as anticipated by Huynh is reversed.

Claim 22, however, stands on a different footing. Claim 22 is directed to "a composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells." Huynh plainly describes an IGFBP-5 antisense oligodeoxynucleotide which reduces expression of IGFBP-5 in human breast cancer cells. Appellants argue that "the phrase 'for treatment of hormone-regulated cancer' is more than a statement of intended use and deserves to be given weight in assessing the scope of the claims." Brief, page 7. According to appellants, "Huhnh's antisense is not used in the treatment of any animal or human . . . [thus,] [t]here is no teaching of a composition suitable for

administration in the treatment of cancer." Id. Nevertheless, appellants have not pointed out anything which makes Huynh's IGFBP-5 antisense oligonucleotide composition unsuitable for administration to an animal, or which distinguishes it from the claimed IGFBP-5 antisense oligonucleotide composition in any way.

Accordingly, the rejection of claim 1 as anticipated by Huynh is affirmed. As discussed above, claims 36 and 37 stand or fall with claim 22, thus the rejection of claims 36 and 36 as anticipated by Huynh is affirmed as well.

II. Obviousness

Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38 stand rejected under 35 U.S.C. § 103 (a) as unpatentable over Huynh in view of Kiefer, Baracchini and Nickerson. Having already determined that Huynh anticipates the subject matter of claims 22, 36 and 37, we affirm the rejection under 35 U.S.C. § 103 (a) with respect to those claims. "[A]nticipation is the epitome of obviousness." Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983).

Claims 1-3, 5, 6, 23, 26-28 and 38, on the other hand, are directed to methods of delaying the progression of hormone-regulated tumor cells to an androgen-independent state; to treating a hormone-responsive cancer; and to delaying metastatic boney progression of IGF-1 sensitive tumors by inhibiting IGFBP-5.

The examiner relies on Huynh for disclosure of "an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 that was administered to breast cancer cells" (Answer, page 6); on Kiefer for disclosure of the translation initiation and termination regions of IGFBP-5 (id.); and on Baracchini for "teach[ing] that the translation initiation and termination regions are preferred regions for targeting with

antisense oligos" (id.). According to the examiner, these references provide motivation for targeting particular regions of IGFBP-5 in order to inhibit its effects. Id., pages 6-7.

Nevertheless, in our view, the dispositive issue here is the examiner's proposed rationale for inhibiting IGFBP-5 in tumor cells in the first place. The underlying premise of the examiner's rejection is that "Nickerson teaches that prostatic tumor cells over-express IGFBP-5 and [that IGFBP-5] is involved in tumorigenesis" (id., page 6), and that, therefore, it would have been obvious for one skilled in the art to inhibit IGFBP-5 expression in prostatic tumor cells (id., page 7).

We see no factual basis for the examiner's expansive interpretation of Nickerson's teachings. Nickerson's experiments were designed "to study the gene expression of IGFBPs during involution of the rat ventral prostate after castration." Nickerson, page 807. The experiments demonstrated that "IGFBP-5 mRNA increases in the ventral prostate 2-fold by 24 h and 5-fold by 72 h [ ] in keeping with the hypothesis that IGFBP-5 may be involved in apoptosis resulting from steroid hormone deprivation." Id., page 809, left-hand column. According to Nickerson, the experimental system could not determine "whether IGFBPs cause apoptosis in the ventral prostate or are upregulated as a result of apoptosis." Id., right-hand column. Either way, the examiner has not explained how Nickerson's observations suggest that IGFBP-5 is involved in tumorigenesis, or why one skilled in the art would have wanted to inhibit its effects.

The examiner bears the initial burden of establishing prima facie obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a prima facie conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See In re Lowry, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). In addition, the record must provide evidence

that those of skill in the art would have had a reasonable expectation of success in doing so. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

We agree with appellants that the examiner's rejection "fails to state a prima facie case of obviousness." Brief, page 8. The rejection of claims 1-3, 5, 6, 23, 26-28 and 38 under 35 U.S.C. § 103 is reversed.

III. Written Description

Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 stand rejected under the first paragraph of 35 U.S.C. § 112, as lacking adequate written descriptive support.

"The 'written description' requirement serves a teaching function, . . . in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is . . . [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [ ], [the applicant] was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See also Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." University of Rochester, 358 F.3d at 928, 69 USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question

of fact, which must be resolved on a case-by-case basis (Vas-Cath, 935 F.2d at 1562-63, 19 USPQ2d at 1116), and it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)).

With respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38, we disagree with the examiner's rationale and conclusion. These claims require antisense oligonucleotides, of varying scope, which inhibit expression of IGFBP-5 in hormone-regulated mammalian tumor cells. The examiner argues that "[t]he specification . . . only describes two target IGFBP-5 sequences, [mouse and human] . . . , and does not describe any additional sequences that can be targeted via antisense oligos. Without such a description, the skilled artisan would not be able to envision any other target sequences and thus would not be able to synthesize an antisense oligo specific for the sequence" (Answer, page 8), and moreover, would be "required to undertake de novo experimentation to isolate and identify IGFBP-5 encoding nucleic acids" (id.).

Nevertheless, "applicants have some flexibility in the 'mode selected for compliance' with the written description requirement" (University of Rochester, 358 F.3d at 928, 69 USPQ2d at 1896), and it is well settled that actual reduction to practice is not necessary to satisfy the requirement (id. at 926, 69 USPQ2d at 1894). On the other hand, "[i]n claims to genetic material . . . [a] definition by function . . . does not suffice to to define [a] genus because it is only an indication of what the [material] does, rather than what it is." University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court explained that "[a]n adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula,

chemical name, or physical properties,'" (id. at 1566, 43 USPQ2d at 1404) while "[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" (id. at 1568, 43 USPQ2d at 1406). Subsequently, the court clarified that "the written description requirement would be met for [a claim] . . . if [a] functional characteristic . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Enzo Biochem, 296 F.3d at 1324-25, 63 USPQ2d at 1613.

Here, the specification sets forth the sequences of DNA molecules encoding the mouse and human IGFBP-5s, as well as a number of antisense sequences targeting specific regions of the mouse and human IGFBP-5 DNAs. The examiner's rationale would seem to limit the claimed genus to only those antisense oligonucleotides explicitly recited, without explaining why one skilled in the art would not have expected the mouse and human DNAs to be representative of, or have considerable structural similarity to, DNA encoding IGFBP-5 in other mammals. Again, it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (Wertheim, 541 F.2d at 263, 191 USPQ at 97). We find that the examiner has not done so.

Accordingly, the rejection of claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38 as lacking adequate written descriptive support under 35 U.S.C. § 112, first paragraph, is reversed.

With respect to claims 8, 12, 15, 19, 39 and 40, however, we agree with the examiner that adequate written descriptive support is lacking. We note that these

claims merely require “a composition” effective to inhibit expression of IGFBP-5. The only such compositions disclosed in the specification are the afore mentioned antisense oligonucleotides. The examiner’s position is essentially that the specification does not provide “any description, structural[ ] or otherwise, of IGFBP-5 inhibitors other than the instantly described antisense oligo[nucleotides]” and that the instantly described antisense oligonucleotides are “not representative of the breadth of inhibitors sought in the instant claims” (Answer, page 8).

Appellants argue that “the invention is based on the discovery . . . that reducing the expression of IGFBP-5 in hormone-responsive cancer cells has therapeutic benefits” (Brief, page 12), and “antisense inhibitors of IGFBP-5 expression [are] examples of a methodology that can be used in practicing the methods” (id., page 13). Appellants argue that the invention “is not antisense technology per se. It is also not the identification of IGFBP-5, nor any and all inhibitors of IGFBP-5 expression” (id., page 12).

These arguments are not persuasive. The Federal Circuit has recently held that the written description standard discussed in Eli Lilly applies to methods as well as products. See University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (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.”

The facts in Rochester are similar to those of the instant application. Rochester involved a “method for selectively inhibiting PGHS-2 activity in a human host,

comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment." Id. at 920, 69 USPQ2d at 1888 (emphasis added). The court noted that the relevant patent described the cells needed to screen for compounds having the recited property, as well as "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product." Id. At 927, 69 USPQ2d at 1895. Nevertheless, the court concluded that the patent's disclosure was inadequate to enable the claimed method because the patent "[did] not disclose just which peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2." Id. (emphasis in original, internal quotations omitted). "Without such disclosure, the claimed methods cannot be said to have been described." Id.

In this case, as in Rochester, the claims are directed to a process for accomplishing a desired result (in Rochester, selectively inhibiting PGHS-2 activity in a human host; here, "inhibiting expression of IGFBP-5 in hormone-responsive cells") using a composition having a specified functional property (in Rochester, a "non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product"; here, "a composition effective to inhibit expression of IGFBP-5"). And in this case, as in Rochester, the specification provides no description whatsoever of just which compositions have the functional property recited in the claims - the genus recited in the claims is defined exclusively in functional terms, i.e., in terms of what the members of the genus do, rather than what they are.

As discussed above, "[a] definition by function . . . does not suffice to define [a] genus because it is only an indication of what the [material] does, rather than what it is."

Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. To paraphrase Eli Lilly, naming a type of material, which may or may not exist, in the absence of knowledge as to what that material consists of, is not a description of that material. See id. Accordingly, the rejection of claims 8, 12, 15, 19, 39 and 40 as lacking adequate written descriptive support under 35 U.S.C. § 112, first paragraph, is affirmed.

IV. Enablement

Claims 1-23 and 26-40, all the claims on appeal, stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. According to the examiner, the claims are drawn to "antisense oligo[nucleotides] targeted to any transcript of IGFBP-5 as well as methods of treatment using said antisense oligo[nucleotides]" (Answer, page 9), but the specification "is only enabling for antisense oligos of SEQ ID NO:1 targeted to the IGFBP-5 transcripts of [murine] SEQ ID NO:13, and for the use of SEQ ID NOS; 2, 3 and 9 in the inhibition of SEQ ID NO:14 in vitro, and does not provide guidance on the in vivo inhibition of [human] SEQ ID NO:14" (id.).

With respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, all of which require an antisense oligonucleotide capable of inhibiting expression of IGFBP-5, we do not agree with the examiner's rationale or conclusion, for the reasons that follow. Initially, however, we note that the examiner has focused exclusively on the therapeutic use of antisense oligonucleotides, and has not separately addressed the enablement of those claims that do not require antisense oligonucleotides (as was done in the written description rejection above). Nevertheless, our affirmance of the written description rejection for claims 8, 12, 15, 19, 39 and 40 constitutes a disposition of these broader claims, so we need not reach the merits of the enablement rejection with respect to these claims.

Returning to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, then, we find that the reasons cited in support of the examiner's rejection are insufficient to support the examiner's conclusion that these claims are not enabled by the specification.

"The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[8] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510,

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> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (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 (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1513 (Fed. Cir. 1993).

According to the examiner, "the clinical application of antisense therapy is a highly unpredictable art due to obstacles that still face antisense therapy" (Answer, page 9). The obstacles enumerated by the examiner are essentially: the identification of an appropriate target in the disease process; the identification of a molecule that can interfere with the disease process through specific recognition and affinity; the complexity of cellular uptake of oligonucleotides; and physical barriers due to internal structures of target RNAs and associations with cellular proteins. Id., pages 9-10. In addition, the examiner relies on Gewirtz[9] and Branch[10] as evidence that "'the antisense approach has generated controversy [among those of skill in the art] with regard to mechanism of action, reliability, and ultimate therapeutic utility'" (id., page 10), and the sense in the art is that "'efforts should be increased . . . to learn how they may be used successfully in the clinic'" (id.).

We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the field of antisense therapy is indeed recognized as highly unpredictable by those of skill in the art. Nevertheless, appellants point out, and the examiner appears to acknowledge, that appellants have identified the murine and human IGFBP-5s as appropriate targets in treating androgen-dependent cancers like prostate cancer and breast cancer, and that appellants have identified antisense IGFBP-5 molecules that can delay progression to androgen independence in the Shionogi tumor model (asserted to be a useful model of human prostate cancer)

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[9] Giwirtz et al., "Facilitating Oligonucleotide Delivery: Helping Antisense Deliver on Its Promise," Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 3161-3163 (April, 1996).

[10] Branch, A.D., "A Good Antisense Molecule is Hard to Find," TIBS, Vol. 23, pp. 50 (February, 1998).

and/or inhibit expression of IGFBP-5 in human prostate cancer cell lines. See page 17 of the substitute Brief for Appellant (submitted June 10, 2004), and page 9 of the Answer. This concrete guidance, in the form of working examples, would seem to address a number of the examiner's specific concerns, and weigh in favor of finding the specification enabling for claims directed to antisense inhibition of IGFBP-5. In any case, the examiner has not explained why the specific guidance in the specification would not, at least to some extent, mitigate or counterbalance any remaining factors (e.g., the generally unpredictable nature of the field) tending to weigh against a finding of enablement. In other words, the examiner has not explained why identifying other antisense IGFBP-5 molecules capable of delaying progression of hormone-regulated tumor cells to androgen-independence, either in vivo or in vitro would have required undue experimentation, given the specific guidance provided by appellants in their working examples.

Accordingly, the rejection of claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48 as lacking enablement under the first paragraph of 35 U.S.C. § 112 is reversed.

SUMMARY

I. The rejection of the claims under 35 U.S.C. § 102 (b) as anticipated by Huynh is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1, 5 and 38.

II. The rejection of the claims under 35 U.S.C. § 103 (a) as unpatentable over Huynh, Kiefer, Baracchini and Nickerson is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1-3, 5, 6, 23, 26-28 and 38.

III. The rejection of the claims under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support is affirmed with respect to claims 8, 12, 15, 19, 39

and 40, and reversed with respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38.

IV. The rejection of the claims under 35 U.S.C. § 112, first paragraph, as lacking enablement is reversed with respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48. We do not reach the merits of this rejection with respect to claims 8, 12, 15, 19, 39 and 40.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136 (a).

AFFIRMED-IN-PART

	)
Toni R. Scheiner	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
	)
Donald E. Adams	) APPEALS AND
Administrative Patent Judge	)
	) INTERFERENCES
	)
	)
	)
Demetra J. Mills	)
Administrative Patent Judge	)

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