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for publication and is not binding precedent of the Board.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. 44

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BRIAN C. CUNNINGHAM, and
JAMES A. WELLS

Appeal No. 2003-1469
Application No. 08/479,886

ON BRIEF

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

GRIMES, 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 49-52, 57-60, and 65-67. Claims 41-48 and 53-56 are also pending but have been withdrawn from consideration. See Paper No. 38, mailed April 22, 2002. Claims 57 and 65 are representative and read as follows:

57. A nucleic acid encoding a variant of a wild type, monomeric polypeptide ligand having four amphipathic alpha helices, wherein said native ligand binds to a first receptor polypeptide through a first ligand site and then binds to a second receptor polypeptide through a second ligand site, thereby forming a ternary complex, said variant having a non-naturally occurring amino acid sequence or a covalent modification comprising:

(a) a first mutation including an amino acid substitution in a portion of said first ligand site selected from the group consisting of (i) amino acid residue L15, R16, R19 and Q22, (ii) the C-terminal 2/3 of the loop linking helices 1 and 2, and (iii) the C-terminal ½ of helix 4; and

(b) a second mutation in a portion of said second ligand site selected from the group consisting of (i) the first third of helix 1 and (ii) the middle half of helix 3.

65. A nucleic acid encoding a variant of a wild type growth hormone having a first binding ligand site and a second ligand binding site, said variant having non-naturally occurring amino acid sequences comprising:

(a) a first mutation including an amino acid substitution in a portion of said first ligand binding site selected from the group consisting of:
(i) amino acid residue L15, R16, R19 and Q22;
(ii) amino acids 46-71; and
(iii) amino acids 169-184, and

(b) a second mutation including an amino acid substitution in a portion of said second ligand binding site selected from the group consisting of:
(i) amino acids 1-15; and
(ii) amino acids 106-128.

The examiner does not rely on any references.

Claims 49-52, 57-60, and 65-67 stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled.

We reverse.

Background

"Ligand induced receptor oligomerization has been proposed as a mechanism of signal transduction for the large family of tyrosine kinase receptors that contain an extracellular ligand binding domain." Specification, page 1. The specification discloses that "growth hormones and the class of conformational ligands to which they belong are capable of forming 1:2 complexes with their receptor in which a first ligand site, site 1, binds to one receptor and then a second ligand site, site 2, binds to another molecule of receptor, thereby yielding a 1:2 complex." Page 3.[1]

In "growth hormone and the homologous ligands prolactin and placental lactogen . . . site 2 for this group of quaternary-alpha helical cytokines and hormones principally is comprised by (a) the sequence extending from the N-terminus to about the first 3-4 turns of helix A and (b) about the middle 4-5 turns of helix C." Page 9. "Site 1 also is a discontinuous site. It consists of three segments located (a) in the middle 40% of helix A (perhaps overlapping with the C-terminus of site 2 in helix A), (b) the C-terminal 2/3rds (preferably C-terminal 1/2) of the loop linking helices A and B, and (c) the C-terminal 1/2 (preferably 1/3) of helix D." Page 10.

The specification discloses that identification of the site 1 and site 2 amino acids makes it possible "to efficiently design agonist or antagonist amino acid sequence variants . . . by introducing amino acid sequence variation into sites 1

[1] Conformationally related ligands include prolactin, placental lactogen, erythropoietin, α and β interferon, GM-CSF, G-CSF, and interleukins 2, 3, 4, 6, and 7. See page 8.

and/or 2." Page 3. "[T]he residues falling within the site 1 domains remain unmodified (in the case of antagonists, in which only site 2 is disabled by mutation) or, if modified, the changes to site 1 are selected so as to not disrupt binding. The reason is that it is not desirable in most embodiments to disable site 1. Instead the objective is to increase site 1 affinity by about 10% to greater than 2 fold." Id.

The specification states that the reason site 1 binding should not be disrupted is that "the receptors have been found to bind to these two sites in sequential order, first one site (site 1) and then the other (site 2). The reverse order has not been found to occur. This understanding is especially important for the preparation of antagonist ligands. It is important to preserve, if not enhance, the affinity of the ligand for the first site. Otherwise, the ligand analogue never binds receptor at all. On the other hand effective destruction or inhibition of the second site binding is predicate for antagonist activity." Page 8. Contrariwise, to function as an agonist, a ligand analogue should have "mutations at sites 1 and/or 2 which increase the ligand affinity for one or both sites." Page 4.

The specification provides a table showing candidate substitutions for naturally occurring amino acids, including specified amino acids that are preferred for the formation of agonists or antagonists. See page 11. The specification also provides working examples of growth hormone mutants showing the effect on receptor dimerization of substituting alanine for the naturally occurring amino acid at various positions. See Table 3.

Discussion

Claim 57, the broadest claim on appeal, is directed to a nucleic acid encoding a variant of the class of proteins that includes growth hormone, prolactin, etc. The variant encoded by the claimed nucleic acid has at least two mutations compared to the wild-type protein: one in a portion of the protein corresponding to receptor-interacting "site 2" and one in a portion of the protein corresponding to receptor-interacting "site 1".

The examiner acknowledged that the claims were enabled for nucleic acids "encoding those exemplified human growth hormone (hGH) variants in which specified amino acids are replaced by alanine or by other exemplified amino acids (such as D26E or Q29S)" but rejected the claims on the basis that practicing their full scope (specifically "nucleic acids encoding hGH variants in which any amino acid in a particular domain is replaced by any other amino acid") would have required undue experimentation. See the Examiner's Answer, page 3.

The examiner's main concern seemed to be with the experimentation required to use the claimed products rather than that required to make them. See the Examiner's Answer, page 7: "It can be said that the skilled artisan could make nucleic acids encoding molecules which meet the structural limitations of the claims but the molecules could not be used without a knowledge of whether the molecules have an increased or decreased affinity for the receptor (i.e. antagonistic or agonistic properties)."

The examiner considered the factors set out in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and concluded that "the breadth of the instant claims is not commensurate in scope with the specification." Examiner's Answer, pages 8-9. The examiner summed up her position as follows: "Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims." Examiner's Answer, page 10.

Appellants argue that the Wands factors do not support the examiner's conclusion. See the Appeal Brief, pages 5-6. In particular, Appellants argue that no more than routine experimentation would have been required to make the claimed protein variants and to assay their binding properties. See id., pages 7-8. Appellants argue that the examiner's requirement for sufficient guidance to predict the properties of variants within the scope of the claims is contrary to case law, citing In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). See the Appeal Brief, pages 9-10.

The examiner bears the initial burden of showing nonenablement. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). That some experimentation is required does not suffice to show nonenablement; "the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

"It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the art how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445 (footnote omitted). Whether the amount of experimentation required is "undue" is determined in reference to the well-known Wands factors. See Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

In this case, we agree with Appellants that the examiner has not shown that practicing the full scope of the claims would have required undue experimentation. First, the scope of the claims is not inordinately broad: as the examiner acknowledged, the claims require a mutation in one of 44 amino acids and a second mutation in one of 22 positions. Examiner's Answer page 8. The examiner asserts that each of these mutations could substitute any of 19 amino acids for the naturally occurring one at each position, id., but this assertion ignores the guidance provided by the specification. The specification states that the mutation in the amino acids corresponding to site 1 should at least preserve, if not enhance, binding with the variant's receptor. See page 10. Thus, the

specification states that substitutions in site 1 should be with amino acids that are closely related to the naturally occurring amino acid. See id.

With site 2 mutations, again, the examiner's position ignores the specification's guidance. The specification states that site 2 should be mutated in such a way as to disrupt receptor binding; thus, site 2 mutations should be selected so as to change the characteristics of the naturally occurring amino acid as much as possible. See Table 1a, page 11. While this may entail a greater number of possible substitutions compared to site 1, it evidences a correspondingly higher degree of predictability in achieving the desired result. That is, it is much easier to make an amino acid substitution that destroys a given function than it is to make a substitution that preserves or enhances it.

Thus, while the scope of the claims as written may encompass variants that have any of 19 possible substitutions at any of a variety of positions, the specification guides those of skill in the art toward subsets of potential mutations that are more likely (than others) to have the desired biological activity. This guidance considerably reduces the amount of experimentation that would be expected to be necessary to practice the claimed invention.

In addition, the examiner has conceded that "the level of skill in the art is known to be high," Examiner's Answer, page 8, and does not dispute that the specification provides the methods and assays needed to practice the invention. See id., page 11:

> Appellant [sic] asserts that "the specification also provides considerable direction and guidance on how to practice the claimed invention" in that tools for practicing the invention and assays are

> provided for assessing affinity (top of page 6 of the Brief). It is not disputed that the instant specification provides these elements, however, this is not the type of guidance that is lacking and which is necessary for practicing the invention as claimed.

The examiner's main concern seems to be that the effect of a given mutation, or set of mutations, on the biological activity of a given protein is not predictable. Thus, making and using the full range of variants encompassed by the claims will require those skilled in the art to make such variants and to test them to see which have the desired properties.

This concern, however, does not support the instant rejection. Appellants have disclosed those parts of the growth hormone molecule that are relevant for receptor binding, have identified structurally related proteins that would be expected to behave similarly, have suggested which types of mutations in which sites would be expected to provide the desired function, and have made exemplary mutations to support these disclosures. Thus, while practicing the invention will undoubtedly require some experimentation, that experimentation appears to be of a routine nature and Appellants have provided those skilled in the art with substantial guidance regarding the direction in which the experimentation should proceed. Such experimentation would not appear to be undue. See, e.g., PPG Indus. Inc. v. Guardian Indus. Corp, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996): "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed" (quoting Ex parte Jackson, 217 USPQ 804, 807 (1982)).

Other Issues

This appeal is being decided concurrently with appeal 2003-1668 (application serial no. 08/479,883). According to Appellants, both applications are divisionals of application 08/122,548.

Claims 66 and 67 of the instant application read as follows:

66. A variant of a wild type growth hormone comprising:
(a) a first mutation in an amino acid sequence of a first receptor binding site selected from the group consisting of:
(i) amino acid residue L15, R16, R19 and Q22;
(ii) amino acids 46-71; and
(iii) amino acids 169-184, and
(b) a second mutation in an amino acid sequence of a second receptor binding site selected from the group consisting of:
(i) amino acids 1-15; and
(ii) amino acids 106-128.

67. The variant of claim 66 wherein said variant is covalently attached to a polyethylene glycol molecule.

Claims 54 and 74 of the '883 application read as follows:

54. A variant of a native mature mammalian growth hormone comprising, said variant having a non-naturally occurring amino acid sequence or a covalent modification, comprising:
(a) a first mutation in a first region selected from the group consisting of (i) amino acid residue L15, R16, R19 and Q22, (ii) the C-terminal 2/3 of the loop linking helices 1 and 2, and (iii) the C-terminal 1/2 of helix 4; and
(b) a second mutation in a second region selected from the group consisting of (i) a region corresponding to residue 1 to residue 15 of mammalian growth hormone and (ii) a region corresponding to residue 106 to residue 128 of mammalian growth hormone, numbered from the N-terminus.

74. The variant of claim 54 wherein said variant is covalently attached to a polyethylene glycol molecule.

The instant specification discloses that the helices 1 and 2 of human growth hormone span amino acids 6-33 and 72-92, respectively. See page 15. Thus, the loop linking helices 1 and 2 apparently is made up of amino acids 34-71; the C-terminal 2/3 of that loop would therefore correspond to amino acids 46-71. The specification also discloses that helix 4 of human growth hormone spans amino acids 155-184. See page 15. Thus, the C-terminal 1/2 of that helix would correspond to amino acids 169-184. In other words, the claims in the two applications appear to define substantially similar products, albeit in different terms. Of course, the claims of the '883 application are limited to <u>mammalian</u> growth hormone variants, while the instant claims are not; the claims therefore do not appear to be directed to identical subject matter.

Upon return of this case, the examiner should consider whether the claims of this application and application 08/479,883 are unpatentable for obviousness-type double patenting. If so, a provisional rejection on that basis should be made in both applications.

The examiner should also note that a restriction requirement precludes a double patenting rejection only if the claims in the respective applications are maintained consonant with the restriction requirement. "Consonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction requirement be maintained. Though the claims may be amended, they must not be so amended as to bring them back over the line

imposed in the restriction requirement. Where that line is crossed the prohibition of the third sentence of [35 U.S.C. §] 121 does not apply." Gerber Garment Technology Inc. v. Lectra Systems Inc., 916 F.2d 683, 688, 16 USPQ2d 1436, 1440 (Fed. Cir. 1990).

Summary

The examiner has not established, by a preponderance of the evidence, that practicing the full scope of the claimed invention would have required undue experimentation. The rejection for nonenablement is therefore reversed.

REVERSED

Sherman D. Winters	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Eric Grimes	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
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Lora M. Green	)
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