

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 45

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte JAMES A. WELLS and BRIAN C. CUNNINGHAM

Appeal No. 2002-0091
Application No. 08/479,884

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 88, 91, 93, 94, 97, 99, 100, 103, 105, 110, 113, 115, 116, 118-123, 125-129, 132, 133, 139, 151, 153, and 156-177, all of the claims remaining.

Claim 88 is representative and reads as follows:

88. A DNA molecule comprising a nucleic acid sequence encoding a variant of a human growth hormone that binds to a target with an affinity different from the affinity of said human growth hormone for said target, wherein the amino acid sequence of said variant is not found in nature, and said variant comprises an amino acid substitution at an amino acid residue selected from the group consisting of P2, T3, P5, S7, L9, N12, L15, R16, R19, E30, E33, S43, F44, Q46, N47, P48, Q49, T50, F54, S55, E56, S57, I58, P59, S62, N63, E66, Q68, K70, S71, L73, R77, L80, F97, A98, N99, S100, L101, V102, Y103, G104, D169, T175, R178, Q181, C182, R183, S184, V185, E186, G187, S188, and F191, numbered

from the N-terminus of 191-amino acid human growth hormone, wherein said variant is not hGH-V.

The examiner does not rely on any references.

All of the pending claims stand rejected under 35 U.S.C. § 112, first paragraph, as nonenabled.

We reverse.

Background

“Human growth hormone (hGH) . . . exhibits a multitude of biological effects including linear growth (somatogenesis), lactation, activation of macrophages, insulin-like effects and diabetagenic effects.” Specification, page 5. “The three-dimensional structure of hGH is not available.” Id., page 6. Attempts have been made to map the receptor-binding site in hGH using either peptide fragments or monoclonal antibodies, but these techniques have not produced acceptable results. See id., pages 6-7.

The specification discloses a method for identifying active domains in proteins by systematically replacing amino acid residues of the wild-type protein to create protein variants, and comparing the activity of the variants to that of the wild-type protein. See, e.g., pages 13-14. The method is exemplified with hGH, among other proteins. See pages 44-57.

The specification provides numerous exemplary hGH variants,¹ most having an amino acid substitution in a single position. See, e.g., pages 76-79. Other

¹ Appellants put the number at “over 150”, page 6 of the Appeal Brief, which the examiner does not dispute. Not all of these embodiments are encompassed by claim 88, however.

exemplified variants have multiple substitutions. See, e.g., pages 46-47. For some of the mutated positions, the specification provides a list of the amino acid substitutions that are preferred. See, e.g., pages 52 and 56.

Some of the exemplified variants have substitutions in amino acids that are not listed in claim 88. Among the exemplified embodiments that are within the scope of the present claims, however, nearly all have a binding affinity that differs from that of wild-type hGH. The relative binding affinity of the variants is shown in the specification by the ratio $K_d(\text{variant})/K_d(\text{wt})$. A higher K_d value corresponds to lower binding affinity, so a variant that binds worse than wild-type hGH will have a $K_d(\text{variant})/K_d(\text{wt})$ value greater than 1, while a variant that binds better than wild-type hGH will have a $K_d(\text{variant})/K_d(\text{wt})$ of less than 1.

The specification discloses at least 41 single-substitution variants and at least 13 multiple-substitution variants that fall within the scope of claim 88. Of the single-position variants, 31 (about 75%) had a $K_d(\text{variant})/K_d(\text{wt})$ value greater than 1; i.e., they bound the relevant target with less affinity than wild-type hGH. The worst of the lot was variant I58A, which had a $K_d(\text{variant})/K_d(\text{wt})$ value of 17. See page 78. Of the multiple-position variants, 12 (about 92%) had a $K_d(\text{variant})/K_d(\text{wt})$ value greater than 1; the worst of them was a variant having 13 substitutions including Q181K, which had a $K_d(\text{variant})/K_d(\text{wt})$ value of greater than 100. See page 47.

On the other hand, some of the exemplified variants encompassed by claim 88 had a $K_d(\text{variant})/K_d(\text{wt})$ value of less than 1, meaning that they bound the relevant target better than wild-type hGH. Eight of the single-position variants and

one of the multiple-position variants fell into this category; the F191A variant (page 79) bound best, with a $K_d(\text{variant})/K_d(\text{wt})$ value of 0.6.

Two of the exemplified variants within the scope of claim 88 had a $K_d(\text{variant})/K_d(\text{wt})$ value of 1, meaning that they bound the relevant target with the same affinity as wild-type hGH. See page 54. Thus, among the exemplified single- and multiple-position variants that are encompassed by claim 88, 43 out of 54 bound the target worse than wild-type hGH, while 9 out of 54 bound better and 2 out of 54 bound with the same affinity as wild-type hGH. In other words, 52 out of 54 (about 96%) of the exemplified variants bound the target with an affinity different from the affinity of wild-type hGH.

Discussion

Claim 88 is the broadest claim on appeal, and is directed to DNA encoding an hGH variant having at least one amino acid substitution compared to the wild-type protein; the substitution can be at any one of fifty-three specified sites in the protein. The claim also requires that the variant encoded by the claimed DNA must bind “to a target with an affinity different from the affinity of [wild-type] human growth hormone.” Finally, the claim excludes DNA encoding naturally occurring variants and a variant known as hGH-V.

The examiner acknowledged that the specification is “enabling for those exemplified human growth hormone (hGH) variants in which specified amino acids are replaced by alanine or by other amino acids.” Examiner’s Answer, page 3. She concluded, however, that the claims are nonenabled because the specification

does not provide adequate guidance to allow those skilled in the art to use the invention commensurate in scope with the claims. See id.

The examiner reasoned that “[i]n order for one of ordinary skill in the art to use the claimed variants, the skilled artisan must know if the variant is going to bind to the receptor with increased or decreased affinity.” Id., page 4. The examiner acknowledged that the specification’s working examples showing increased or decreased binding affinity, see id., but concluded that the exemplified variants would not be predictive of other hGH variants, because:

- (1) substitution of the same amino acid residue (e.g., alanine) into different positions can have different effects on binding affinity (Examiner’s Answer, pages 4-5); and
- (2) substitution of different amino acids into the same position can have different effects on binding affinity (id., page 5).

The examiner concluded that the effect of amino acid substitution(s) on hGH receptor binding is highly unpredictable and therefore “the specification can provide no guidance regarding which other amino acid substitutions would be likely to result in a hGH variant with a desired biological activity.” Id., page 6.

Appellants argue that there is a reasonable expectation that hGH variants having amino acid substitutions at the specified positions will have altered binding affinities compared to wild-type hGH. Appeal Brief, pages 8-9. Appellants also argue that the amount of experimentation needed to make and screen other variants is not undue. See id., pages 6 and 9-11. Appellants conclude that

practicing the full scope of the claims would not have required undue experimentation.

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).

“[E]nablement requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ . . . 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, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Some experimentation, even a considerable amount, is not “undue” if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In this case, the examiner has not adequately shown that practicing the full scope of the claims would have required undue experimentation. The examiner correctly notes that the open claim language of claim 88 encompasses a vast number of potential hGH variants. See the Examiner’s Answer, page 7.² We also agree with the examiner’s position that the effect of any single amino acid substitution cannot be precisely predicted in advance.

² The examiner’s calculation of 53^{19} single-position substitutions alone, however, is incorrect. The actual number of single-substitution variants is 1007: each of 53 positions can be substituted with any of 19 amino acids; $53 \times 19 = 1007$. Since we’re only counting single-position mutants, only one position can be changed in any given variant. The examiner’s calculation appears to be more in line with the number of mutants having mutations in any or all of the recited positions, but even there, the correct number would be 19^{53} , not 53^{19} .

Thus, we would agree with the examiner that the claims could not be practiced without undue experimentation, if the claims were directed to hGH variants having a binding affinity the same as that of wild-type hGH. But that is precisely what the claims are not directed to: claim 88 requires that the claimed hGH variants have a binding affinity different from the affinity of wild-type human growth hormone. The claimed variants can thus bind a target better or worse than wild-type hGH, but any variants that bind with the same affinity are outside the scope of the claims.

The examiner has conceded that the specification is enabling with respect to the exemplified variants. The examiner has apparently concluded, therefore, that the specification enables those skilled in the art to use hGH variants that bind their target worse than, as well as better than, wild-type hGH. The exemplified variants have $K_d(\text{variant})/K_d(\text{wt})$ ratios varying from 0.6 to over 100. Since the examiner has concluded that those skilled in the art could make and use any of these variants, it follows that they could use other variants having similar binding affinities. The evidence of record suggests that most hGH variants will have a $K_d(\text{variant})/K_d(\text{wt})$ ratio within this range, i.e., from somewhat better binding than wild-type to much worse binding.

The examiner's analysis also seems to assume that an enabling disclosure must allow those skilled in the art to predict what binding affinity will result from a given amino acid substitution. We disagree; enablement does not necessarily require predictability. In the instant case, for example, the specification shows that 96% of the exemplified variants have binding affinities that put them within the

scope of claim 88, and the examiner has conceded that a person of ordinary skill in the art knows how to use all of the exemplified variants. Based on this evidence, those skilled in the art would reasonably expect that other variants would be about 96% likely to have a binding affinity different from wild-type hGH, and person of ordinary skill in the art would know how to use those, too. Whether a given variant would be expected to have a $K_d(\text{variant})/K_d(\text{wt})$ ratio of 2 or 20 makes no difference, if those skilled in the art would know how to use it regardless.

In view of the apparently high likelihood that any given hGH variant will be within the scope of the claims, and given the examiner's concession that even the exemplified variants with very poor binding affinity are enabled, we cannot agree with the examiner that practicing the full scope of the claims would require undue experimentation. The rejection for nonenablement is reversed.

Summary

Those skilled in the art would expect that the vast majority of hGH variants would have binding affinities different from that of wild-type hGH. The examiner has conceded that those skilled in the art would know how to use hGH variants with a wide range of binding affinities. The evidence of record therefore does not support the examiner's position that undue experimentation would have been required to practice the full scope of the claims. The rejection for nonenablement is reversed.

REVERSED

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