

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 51

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte
TAKESHI SANO, ALEXANDER N. GLAZER
and CHARLES R. CANTOR

Appeal No. 2000-0630¹
Application No. 07/780,717

ON BRIEF

Before WINTERS, ROBINSON, and SCHEINER, 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 39 through 45, 47 through 54, 56 through 58, 60 through 65 and 68.²

¹ Application for patent filed October 21, 1991.

² The final rejection of claims 66 and 67, also pending in the application, was not carried through to the Examiner's Answer, thus claims 66 and 67 are not the subject of this appeal.

Claims 39, 58 and 68 are representative of the claims on appeal and read as follows:

39. A method of making a recombinant bifunctional streptavidin-metallothionein chimeric protein, said method comprising steps:

- (a) introducing into a host cell a nucleic acid encoding a bifunctional fusion protein comprising a streptavidin moiety and a metallothionein moiety, wherein said streptavidin moiety consists of residues 16 to 133 (SEQ ID N0:7) of mature streptavidin;
- (b) incubating said cell under conditions sufficient to express said fusion protein;
- (c) isolating said fusion protein.

58. A bifunctional recombinant streptavidin-metallothionein chimeric protein, wherein said protein comprises a streptavidin moiety and a metallothionein moiety, and said streptavidin moiety consists of residues 16 to 133 (SEQ ID N0:7) of mature streptavidin.

68. A functional streptavidin consisting of residues 16 to 133 (SEQ ID N0:7) of mature streptavidin.

The examiner relies on the following references:

Tolman	4,732,864	Mar 22, 1988
Rodwell et al. (Rodwell)	5,196,510	Mar. 23, 1993
Meade et al. (Meade)	WO 8,602,077	Apr. 10, 1986
Kenten et al. (Kenten)	WO 8,909,393	Oct. 5, 1989
Shoemaker et al. (Shoemaker)	WO 9,006,323	Jun. 14, 1990

Hendrickson et al. (Hendrickson), "Crystal structure of core streptavidin determined from multiwavelength anomalous diffraction of synchrotron radiation," Proc. Natl. Acad. Sci. USA, Vol. 86, pp. 2190-2194 (April 1989)

Lowenadler et al. (Lowenadler), "A gene fusion system for generating antibodies against short peptides," Gene, Vol. 58, pp. 87-97 (1987)

Sano et al. (Sano), "Expression of a cloned streptavidin gene in Escherichia coli," Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 142-146 (January 1990)

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Appellant relies upon the following additional reference:

Pähler et al. (Pähler), "Characterization and Crystallization of Core Streptavidin," J. Biol. Chem., Vol. 262, No. 29, pp. 13933-13937 (October 1987)

PROCEDURAL MATTERS

There is some confusion regarding the issues before us for consideration. The Examiner's Answer refers (improperly) to two previous office actions for the statement of the rejection (paper no. 44, the final rejection; and paper no. 42, a non-final rejection).

In paper no. 42, claims 39 through 45, 47 through 54, 56 through 58 and 60 through 65 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade; in addition, claims 39 through 45, 47 through 54, 56 through 58 and 60 through 65 were rejected under 35 U.S.C. § 103(a) as unpatentable over Rodwell, Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade.

In their response to paper no. 42, appellants submitted new claims 66 through 68 (paper no. 43).

In paper no. 44, the examiner maintained "[a]ll the rejections set forth in the last office action." In addition, new claims 66 and 67 were included in the rejection based on the combined teachings of Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade. Finally, new claim 68 was rejected under 35 U.S.C. § 103(a) as unpatentable over Hendrickson and Sano.

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Appellants' Brief on Appeal (paper no. 45), however, addressed only two issues: (1) the rejection of claims 39 through 45, 47 through 54, 56 through 58, and 60 through 67 as unpatentable over Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade; and (2) the rejection of claim 68 as unpatentable over Hendrickson and Sano.

As set forth in MPEP § 1206, "[a]n appellant's brief must be responsive to every ground of rejection stated by the examiner." "Where an appeal brief fails to address any ground of rejection, appellant shall be notified by the examiner that he or she must correct the defect by filing a brief . . . in compliance with 37 CFR § 1.192(c)."

The examiner did not notify appellants of any deficiency in the Brief on Appeal. Instead, the examiner agreed with appellants' statement of the issues in the Brief (Examiner's Answer, paper no. 48, page 2), but nevertheless maintained all three rejections from the final in the body of the Answer (except that claims 66 and 67 were no longer included in any rejection).

Appellants submitted a Reply Brief (paper no. 49) in response to the Examiner's Answer, but did not address the rejection of claims 39 through 45, 47 through 54, 56 through 58 and 60 through 65 over Rodwell, Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade.

Despite the confusion, we shall decide all three of the rejections set forth in the Examiner's Answer because we view the examiner's proposed combination of Hendrickson and Sano as dispositive in each of the rejections, and because appellants

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have addressed the propriety of this combination. As matters now stand, the issues before us for review are as follows:

(I) The rejection of claims 39 through 45, 47 through 54, 56 through 58 and 60 through 65 under 35 U.S.C. § 103(a) as unpatentable over Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade.

(II) The rejection of claims 39 through 45, 47 through 54, 56 through 58 and 60 through 65 under 35 U.S.C. § 103(a) as unpatentable over Rodwell, Hendrickson, Sano, Kenten, Shoemaker, Tolman, Lowenadler and Meade.

(III) The rejection of claim 68 under 35 U.S.C. § 103(a) as unpatentable over Hendrickson and Sano.

For the reasons discussed in the body of this opinion, we reverse all three of the examiner's rejections.

BACKGROUND

Streptavidin is a protein which binds rapidly and with high affinity to any molecule which contains unhindered biotin (specification, page 2), and streptavidin-containing chimeric proteins can be specifically detected and isolated by their ability to bind biotin (specification, pages 13-14). Native streptavidin has 159 amino acid residues, but, according to the specification, most commercial preparations contain "core" streptavidin with a total of 125 to 127 residues (page 11). Core streptavidin has a much higher solubility in water than native streptavidin (Id.).

DISCUSSION

Claim 68, drawn to “[a] functional streptavidin consisting of residues 16 to 133 (SEQ ID NO:7) of mature streptavidin,” is representative of the claimed invention.

According to the examiner (paper no. 42, page 3):

[Hendrickson] disclose[s] that streptavidin (SA) is a tetramer and each protomer is a simple β -barrel structure (page 2190, Abstract). [Hendrickson] also disclose[s] that residues 16-133 of SA are sufficient to complete the β -barrel structure (page 2194, column 1, full paragraph 1).

[Sano] teach[es] the recombinant expression of a cloned streptavidin gene in E. Coli. [Sano] suggest[s] truncating SA at both the N- and C-termini in order to solve any aggregation problems (page 146, paragraph bridging columns 1-2). It would have been obvious to one of ordinary skill in the art . . . to recombinantly produce SA having residues 16-133, using the guidance of Hendrickson and [Sano], with a reasonable expectation of success.

Appellants disagree with the examiner’s interpretation of Hendrickson. Appellants cite Pähler, published in 1987, as background to Henderson. According to appellants, Pähler describes crystallographic analysis of streptavidin “processed to a minimal sized core streptavidin . . . that still retains full biotin-binding activity,” wherein it was determined that “this minimum size core streptavidin was in fact a mixture of four cleavage products representing residues 14-138, 13-138, 14-139 and 13-139.” Brief, page 3.

Further according to appellants (Brief, page 3):

Hendrickson et al. . . . describe further crystallographic studies of the same core streptavidin. In tracing the alpha carbons of their image, the investigators report that the density of the terminal residues was too weak to include in their drawings; hence, their backbone stick models of their core streptavidin included only residues 14-136 and 16-133 of the 13-139

possible residues. Their stick models suggest that the polypeptide backbone of the core streptavidin runs up and down in eight β -strands forming a barrel structure.

Hendrickson et al. teach nothing about a 16-133 core streptavidin - there was no such polypeptide in existence or contemplated at the time. All Hendrickson et al. say is that their picture of their 13-139 protein was too faint to include the terminal residues. While their models showing residues 14-136 and 16-133 of their 13-139 core show that these residues suffice to complete the β -barrel structure, the same can be said of a 15-135 residue model or a 17 to 132 residue model, or any of numerous other arbitrarily truncated cores that nevertheless retain a β -barrel model structure.

Appellants argue that Sano provides no suggestion to truncate the 13-139 core, as “such a suggestion would fly in the face of the only evidence that (1) the core did not present an aggregation problem and (2) the core was already at a minimum size necessary to retain activity.” Brief, page 4.

We disagree with both the examiner’s and appellants’ interpretations of the prior art. Pähler states that the streptavidin referred to in the reference is a commercial product, and that “the Apcel product has been processed by an undisclosed protocol to a minimal size that still retains full activity” (page 13934, column 1, citing a personal communication). Thus, Pähler provides no direct evidence regarding the minimal functional size of streptavidin. Pähler also notes that this particular commercial product is highly soluble, in contrast to previous experience, but does not suggest any reason for the high solubility (page 13933, last paragraph). Even if one of ordinary skill would have understood Pähler to teach a minimal active core of residues 14-138 or 13-139, Sano provides evidence that

the minimal active core must be smaller, because the active streptavidin fusion protein made by Sano lacks residues 13 and 14 (see Figure 1, part B).

We also disagree with the examiner's statement that "[Sano] suggest[s] truncating SA at both the N- and C-termini in order to solve any aggregation problems." Sano actually states that "the N-terminal region has been truncated in our streptavidin preparation by the deletion of the corresponding coding region, [thus,] it is likely that the C-terminal region of the mature streptavidin is responsible for the aggregation, although participation of the N-terminal region cannot be excluded." Page 146. In any case, Sano suggests that "hydrophilic amino acid residues . . . might be responsible for the intermolecular interactions" leading to aggregation. Id.

Hendrickson outlines two objectives: to examine the biophysical and biotechnological properties of streptavidin in refined crystallographic detail, and to provide a test of multiwavelength anomalous diffraction (MAD) methodology; the focus of the reference is on methodology. Hendrickson describes the "elegantly simple β -barrel structure" of the streptavidin protomer and also describes the assembly of the protomers into the known tetramer, and pinpoints the location of biotin in the structure. Page 2193. Hendrickson further explains (page 2194) that

The initial C" trace included positions 14-136 from the possible 13-139 sequence of the core streptavidin chain. Density for the terminal residues was weak, and thus the initial fitting for the molecule was restricted to residues 14-133. Only residues 16-133 are included in our most recent model. These suffice to complete the β -barrel and leave the cleaved termini

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near one another at the end of the barrel opposite the biotin site and at corners of the tetramer. There is ample space for the terminal peptides in the holo molecule, but we have no information about their disposition if indeed they are ordered. (Citations omitted)

We understand Hendrickson to teach that the C- and N-terminal sequences beyond residues 16-133 are flexible and not organized into the barrel structure, but we do not see any statement in Hendrickson regarding functionality or lack of functionality for the residues beyond 16- 133.

As set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316

(Fed. Cir. 2000) (citations omitted):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. [] Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one “to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.

. . . [T]o establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

We have no doubt that the prior art could be modified in a manner consistent with appellants’ specification and claims, but the fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the

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desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

We agree with the examiner that Sano reasonably suggests truncating recombinant streptavidin to solve aggregation problems. Nevertheless, we do not agree that the evidence suggests truncation at exactly residue 16 - we see no nexus between the teachings of Sano and those of Hendrickson, despite the statement in Hendrickson that "residues 16-133 are sufficient to complete the β -barrel structure." Hendrickson does not discuss solubility of streptavidin. Sano, on the other hand, suggests that hydrophilic amino acid residues in the C-terminal region, and possibly in the N-terminal region, are responsible for unwanted aggregation. The aggregating recombinant streptavidin shown in Figure 1 of Sano contained seven foreign amino acids fused to streptavidin downstream of residue 15; streptavidin residue 15 is alanine. If, as the examiner suggests, the motivation for truncating streptavidin is to remove residues responsible for aggregation - and Sano suggests that hydrophilic amino acids are involved in aggregation - then the reference provides no particular motivation to remove alanine residue 15, because it is not hydrophilic. Without a reason to remove residue 15, one would not arrive at applicant's claimed product consisting of residues 16-133.

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In our judgment, the only reason or suggestion to modify the references in the manner proposed by the examiner comes from appellants' specification. Accordingly, we find that the examiner's initial burden of establishing a prima facie case of obviousness has not been met, and all three of the rejections of the claims under 35 U.S.C. § 103 are reversed.

REVERSED

Sherman D. Winters
Administrative Patent Judge

Douglas W. Robinson
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

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Richard Aron Osman
Science & Technology Law Group
75 Denise Drive
Hillsborough, CA 94104