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for publication and is not binding precedent of the Board.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 STEPHEN ANDERSON and GAETANO MONTELIONE

Appeal No. 2004-2139
Application No. 09/181,601

ON BRIEF

Before ELLIS, SCHEINER and MILLS, Administrative Patent Judges.
ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3-14. Claims 2, 15, 16 and 17 have been canceled.

As a preliminary matter, we note the appellants' statement that the claims stand or fall together. Brief, p. 4. Accordingly, for purposes of this appeal, we consider the issues as they apply to representative claim 1 which reads as follows:

1. A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown three dimensional structure and function comprising:

(A) parsing a target polynucleotide into at least one putative polypeptide domain;

(B) identifying a putative polypeptide domain consisting of 50 to 300 amino acids that properly folds into a stable polypeptide domain consisting of 50 to 300 amino acids;

(C) determining three dimensional structure of the stable polypeptide domain;

(D) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(E) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain.

The references relied upon by the examiner are:

Friedrichs et al. (Friedrichs), "An Automated Procedure for the Assignment of Protein ^{1}HN, ^{15}N, ^{13}C$^{\alpha}$, ^{1}H$^{\alpha}$, ^{13}C^{b} and ^{1}H$^{\beta}$ Resonances*," J. Biomolecular NMR, Vol. 4, pp. 703-726 (1994).

Farber et al. (Farber), "Determination of Eukaryotic Protein Coding Regions Using Neural Networks and Information Theory," J. Mol. Biol., Vol. 226, pp. 471-479 (1992).

Holm et al. (Holm), "Dali: A Network Tool for Protein Structure Comparison," Trends Biotechnol. Vol. 85, pp. 478-480 (1995).

Wallace et al. (Wallace), "Derivation of 3D Coordinate Templates for Searching Structural Databases: Application to Ser-His-Asp Catalytic Triads in the Serine Proteinases and Lipases," Protein Science, Vol. 5, pp. 1001-1013 (June 1996).

Bagby et al. (Bagby), "The Button Test: A Small Scale Method Using Microdialysis Cells for Assessing Protein Solubility at Concentrations Suitable for NMR," J. Biomolecular NMR, Vol. 10, pp. 279-282 (1997).

The claims stand rejected as follows:

I. Claims 1, 5, 6, and 11-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace in view of Holm and Farber.

II. Claims 1, 5-9 and 11-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace in view of Holm, Farber and Friedrichs.

III. Claims 1, 5-14[1] stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace in view of Holm, Farber, Friedrichs and Bagby.

IV. Claims 1-9 [sic, 1, 3-9], 11-14 and 17 [sic][2] stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace in view of Holm, Farber and Friedrichs.

We have carefully considered the respective positions of the appellants and the examiner and find ourselves in substantial agreement with that of the examiner. Accordingly, we affirm.

Background

As indicated by claim 1, above, the present invention is directed to a "high-

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[1] We point out that claim 10 was not included in any of the examiner's rejections; nor has the examiner indicated that said claim is allowable. Given the subject matter of this claim, and that it was included in the rejection of claims 1, 5-9 and 11-14 in the final rejection, it appears that the examiner inadvertently omitted this claim from the § 103 rejection in the Answer. Thus, we have included it with the statement of rejection, above.

[2] We point out that claims 2 and 17 were canceled by amendment filed February 18, 2003.

throughput" method of determining the function of a protein and protein domains by examining their three dimensional (3-D) structure.

It is well known that a protein's tertiary structure is determined by its primary (amino acid) sequence. Specification, p. 2. The tertiary structure or folding of the protein results in one or more autonomous units known as domains. Id., p. 3. Multidomain proteins in higher organisms are said to be encoded by genes containing multiple exons. Id.

The specification discloses that several techniques were known in the art for determining the three dimensional structure of a protein molecule such as X-ray crystallography and Nuclear Magnetic Resonance (NMR). Specification, p. 3. According to the specification, it was rare for prior investigators to determine the three dimensional structure of a protein before its biochemical function was determined by other methods. Id., p. 5. The present invention is said to differ from past research methods because it provides a means of first determining the three dimensional structure of a protein whose function is unknown and using this structure to determine its function. Id.

The first step in the present method is said to involve the use of a computer algorithm to identify (or parse) putative polypeptide domain-encoding regions of a

target polynucleotide. Specification, p. 7, lines 5-7 and lines 22-23; p. 10, lines 23-34. The second step is said to involve identifying polypeptide domains of 50 to 300 amino

acids in length and determining their three dimensional structure using X-ray crystallography or NMR. The protein domain thus identified is compared with others in a publicly-available Protein Data Bank (PDB) to determine whether the unknown protein domain shares homology with any structures recorded therein. Algorithms suitable for such matching studies are said to include the DALI analysis program, the CATH analysis program, VAST analysis program, or similar algorithms for three dimensional structure homology matching. Specification, pp. 24-25. The unknown protein domain can then be analyzed to determine whether its biochemical function correlates with that of a known homologous protein domain.

With respect to the term “high-throughput” the specification states that one skilled in the art is currently able to determine the three dimensional structure of only one protein per year. Specification, p. 26. According to the specification, the claimed invention would “enable a properly equipped laboratory to generate the 3-D structure of one protein per month per NMR machine.” Id. Thus, a “high-throughput” method is said to refer “the ability to determine the 3-D structures of protein domains of unknown function at a rate which is faster than the rate at which a skilled artisan could determine a protein structure using traditional methodologies.” Id.

Discussion

As indicated above, the claims stand or fall with representative claim 1. Since

each of the aforementioned rejections involves the rejection of said claim as being obvious in view of the teachings of Wallace, Holm and Farber, we agree with the appellants that said rejections can be considered together. Brief, p. 13.

To that end, we find that the references disclose the following:

1. Wallace discloses that databases such as PROSITE are well known for identifying the biological function and tertiary (3-D) structure for unknown protein sequences. Wallace, the abstract, p. 1001, col. 1, para. 1. Wallace further discloses that the PROSITE database information, in combination with automatic sequence alignment algorithms, enables swift assessment of an unknown protein sequences. Id.

Wallace still further discloses a method for automatically deriving the 3-D structure of the proteins deposited in the Brookhaven Protein Data Bank (PDB). Wallace, the abstract. Wallace still further discloses that "the development of databases for 3-D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions." Id. Wallace exemplifies its method using the Ser-His-Asp catalytic triad found in serine proteases and triacylglycerol lipases. Id., pp. 1004-1005. To that end, Wallace discloses the generation of 3-D coordinate templates by first extracting all occurrences of interacting

Ser, His and Asp residues, catalytic and noncatalytic, and irrespective of conformation. Id., p. 1004. Wallace further discloses distinguishing those Ser-His-Asp triplets that are

catalytic triads with well-conserved conformations to form the basis for calculating a final 3-D template known as the functional template. Id. Wallace still further discloses that the functional 3-D template was employed to identify other Ser-His-Asp catalytic triads in the PDB as opposed to noncatalytic triads. Id., p. 1009, col. 2. Wallace still further discloses correlating the biochemical function of the newly-identified triads with the biochemical function of the functional consensus Ser-His-Asp template. Id., Figure 5.

In view of these results, Wallace concludes that "[a]s the number of known protein structures increases, so the need for a 3D equivalent of PROSITE grows with it-especially for identifying likely functions of proteins whose biological role is unknown and, equally usefully, for locating the functional regions and residues involved." Wallace, p. 1001, cols. 1-2.

2. Holm discloses that recent growth in the information of 3-D protein structures using X-ray crystallography and NMR has resulted in making structure-structure comparisons in order to elucidate evolutionary relationships between proteins. Holm, p. 478, cols. 2-3. Holmes further discloses that to determine whether a particular structure is unique or similar to known proteins, those skilled in the art can turn to the European Molecular Biology Laboratory which is providing Internet access to the DALI method of protein structure comparison which includes "a database of pre-calculated structural neighbours for all public structures." Id. Holm still further discloses that the

DALI server is capable of performing a database search with a new structure against all structures in the PDB. Id., col. 3. Holm still further discloses that co-ordinates of new structures can be submitted electronically to the PDB and "a list of all structural neighbors of the query structure in protein fold space and optimal structural alignment with each neighbour is returned." Id.

In addition, Holm lists several web servers "related to 3-D protein structure" which include, inter alia, the DALI server- a database search by comparison of 3-D structures, CATH- which provides a structural classification of proteins, PDB- which retrieves 3-D co-ordinates. Id., p. 480, Table II. Holm exemplifies a comparison between the 3-D structure of urease and adenosine deaminase. Id., p. 479, Figure 1.

3. Farber discloses using computational procedures (algorithms) to analyze raw nucleotide sequence data such as that provided by the Human Genome project, to predict coding regions within DNA. Farber, pp. 471-472 and p. 478, col. 1.

The examiner argues that in view of the teachings of Wallace with respect to the use of databases of 3-D templates to identify the functions of new protein structures as they are elucidated (the abstract), and the teachings of Holm with respect to the use of (i) NMR and X-ray crystallography to elucidate new protein structures; and (ii) the DALI server to perform a search which compares a new protein structure with known protein structures in the Protein Data Base, it would have been obvious to one of ordinary skill in the art to combine the teachings of Wallace with respect to the 3-D structural

alignment and functional determination of a protein with the NMR and X-ray crystallography methods and the 3-D database search information taught by Holm to determine whether a protein structure is unique or similar to other known proteins by comparison with structures in the Protein Data Bank. That is, given the teachings of Wallace and Holm, it would have been obvious to one of ordinary skill in the art to determine the biochemical function of an unknown 3-D protein structure by comparing with known 3-D protein structures. Answer, p. 6. The examiner argues that it would have been further obvious to said persons to use domains of 50-300 amino acids because Holm teaches screening domains in this size range. Id. The examiner argues that it would have been still further obvious to combine the methods of Wallace and Holm with the teachings of Farber to predict coding regions in an unknown DNA sequence "in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins." Id., p. 7.

In response, the appellants contend that the art does not suggest two of the limitations set forth in representative claim 1; viz., the use of putative polypeptide domains of 50 to 300 amino acids and the prestep of parsing the target polypeptide. Brief, p. 14. The appellants contend that Wallace teaches neither of these limitations and that even though Holm taught one comparison of 195 amino acid domains, it did

not teach that size is an important factor. Id. Thus, the appellants contend that the applied prior art does not teach or suggest the claimed method. Id., p. 15. According to

the appellants, the examiner used hindsight in combining these two references.

With respect to the teachings of Farber, the appellants argue that the publication is non-analogous art. Id., p. 16. According to the appellants, Faber "is from the art area of information theory." Id. Thus, the appellants urge that one of ordinary skill in the art of protein biochemistry would not use art disclosing the prediction of exon boundaries to identify protein domains. Id.

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). It is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has done.

First, we agree with the examiner that the claimed method is directed to a series of steps routinely performed in biotechnology. Answer, p. 10. DNA sequences are routinely isolated and analyzed to identify those regions therein which encode proteins. See, Farber and the specification, pp. 10-11. Once a protein coding region is identified, it is then analyzed to determine its 3-D conformation and biochemical function. Wallace, the abstract.

Second, with respect to whether the applied prior art would have suggested the analysis of polypeptide domains 50-300 amino acids in length, we point out that the specification discloses that this information was known in the art. That is, the specification states that

> . . . Known domain families generally involve 50-300 amino-acid long segments that are observed as portions of many different proteins. Bioinformatics algorithms capable of identifying these conserved segments, or gene-fragment clusters, in the data base of gene sequences has been reported. These algorithms can be used to identify candidate domain-encoding regions in novel gene sequences. Gouzey et al., Trends Biochem. Sci. 21:493(1994), herein incorporated by reference. Specification, pp. 11-12.

Thus, since it was known in the art that protein domains are generally 50-300 amino acids in length, we find that representative claim 1 is simply reciting an established fact. See, In re Nomiya, 509 F.2d 566, 571, 184 USPQ 604, 611 (CCPA 1975).

Third, we agree with the examiner that Wallace and Holm disclose determining the biochemical function of protein domains between 50-300 amino acids. Wallace discloses the use of the Ser-His-Asp catalytic triad of the serine proteases. See, e.g., Wallace, p. 1001, col. 2, first complete para. The term “triad” refers to three amino acids which “occur far apart in the amino acid sequence of the enzyme and come together in a specific conformation in the active site to perform the hydrolytic cleavage of the appropriate bond in the substrate.” Id., col. 2, second para. Wallace discloses that the “seed triad” was Ser 195-His 57-Asp 102. Id., p. 1004, col. 1, last para; see

also, Table 3. Thus, we find that the "triad" is a protein domain which extends, at a minimum, from amino acid 57 to amino acid 195. Accordingly, contrary to the appellants' argument, Wallace discloses the use of a "functional domain" which is at a minimum, and most likely greater than, 138 amino acids in length.

With respect to Holm, the appellants concur with the examiner that Holm discloses the analysis (structural alignment) of a 196 amino-acid domain (the knob domain of adenovirus type 5 fiber protein) with another known 3-D protein structure. Reply Brief, p. 5.

Thus, we find that Wallace and Holm disclose the 3-D analysis of a range of protein domain sizes within the range set forth in representative claim 1. To that end, we point out that our appellate reviewing court has consistently held that even a slight overlap in a range establishes a prima facie case of obviousness. In re Peterson, 315 F.3d 1325, 1329, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003); In re Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990) ("the applicant must show that the claimed range achieves unexpected results relative to the prior art range"). See also, Titanium Metals Corp v. Banner, 778 F2d 775, 783, 227 USPQ 773, 779 (Fed. Cir. 1985) (a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties). Accordingly, we hold that the examiner has established a prima facie case of obviousness

We disagree with the appellants' contention that Farber is non-analogous art. We point out that analogous art refers to a reference which is either in the field of the applicant's endeavor or, if not, then reasonably pertinent to the particular problem with which the inventor was concerned. See, In re GPAC, 57 F.3d 1573, 1578, 35 USPQ2d 1116, 1120 (Fed.Cir. 1995); In re Deminski, 796 F.2d 436, 442, 230 USPQ 313, 315 (Fed. Cir. 1986); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983); In re Wood, 599 F.2d 1032, 1036, 202 USPQ 171, 174 (CCPA 1979)). Thus, the prior art relevant to an obviousness determination necessarily encompasses not only the field of the inventor's endeavor, but also any analogous arts. See, In re Wood, 599 F.2d at 1036, 202 USPQ at 174; Heidelberger Druckmaschinen v. Hantscho Commercial, 21 F.3d 1068, 1071, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("References that are not within the field of the inventor's endeavor may also be relied on in patentability determinations, and thus are described as 'analogous art', when a person of ordinary skill would reasonably have consulted those references and applied their teachings in seeking a solution to the problem that the inventor was attempting to solve"). Here, we agree with the examiner

that the Farber publication is within the appellants' field of endeavor and it relates to the same problem as that which was addressed by the claimed invention. That is, those in field of molecular biology now sequence megabases of isolated DNA, such as the human or other genomes, identify which segments (i.e., parse the polynucleotide)

therein encode proteins and determine the biochemical function of said proteins. Although Farber discloses this sequence of events for megabases of DNA sequences, the same procedure is applied to the analysis of any unknown DNA sequence. That is, simply isolating a DNA sequence is meaningless unless one skilled in the art can determine (1) whether said DNA encodes a functional product; i.e., a protein; and (2) the function of said protein. In any event, Farber discloses a method of analyzing sequence information and predicting protein coding regions therein using logrithmic methods. Since Farber demonstrates that one of ordinary skill in the art would routinely parse polynucleotide sequence data to identify protein coding regions, we find it [the publication] relates to the same problem as that addressed by the claimed invention. Thus, we find the examiner's use of Farber in the obviousness rejection to be appropriate since the inventors would have been motivated to consider this reference when making their invention. In re Clay, 966 F.2d 656, 659, 23 USPQ2d 1058, 1061 (Fed. Cir. 1992).

The appellants' further arguments with respect to the examiner's failure to consider the invention as a whole, the examiner's use of hindsight to combine the

references, and that there was no reasonable expectation of success, all focus on the issue of whether it would have been obvious to identify polypeptide domains 50 to 300 amino acids in length. We have addressed this issue and, therefore, these arguments above.

In view of the foregoing the decision of the examiner is affirmed.

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

AFFIRMED

JOAN ELLIS Administrative Patent Judge	)
TONI R. SCHEINER Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)

JE/ki

Jane Massey Licata, Esq.
Law Offices of Jane Massey Licata
66 E. Main Street
Marlton, NJ 08053