

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BRADFORD E. WINDLE

Appeal No. 1997-4145
Application No. 08/361,328¹

ON BRIEF

Before WINTERS, SPIEGEL, and MILLS, Administrative Patent Judges.
SPIEGEL, 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 1 through 5, 10, 26 through 29 and 33 through 40. Claims 6 through 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims (see e.g., advisory action mailed December 6, 1996

¹ Application for patent filed December 21, 1994. According to appellant, this application is a continuation-in-part of application 08/264,802 filed June 23, 1994, which issued as U.S. Patent No. 5,707,797 on January 13, 1998, which is a continuation-in-part of application 08/002,781 filed January 8, 1993, now abandoned.

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(Paper No. 12)). Claims 11 through 25 and 30 through 32, the only other claims pending in the application, have been withdrawn from consideration under 37 C.F.R.

§ 1.142(b) as not readable on the elected invention.

Claims 1, 26, 29 and 33 are illustrative and read as follows.

1. A method of producing super-extended DNA, comprising the steps:
streaming a DNA sample over a supporting surface to provide a DNA extended to an interkilobase pair distance that exceeds 0.34 μm .

26. A super-extended DNA that has an interkilobase pair distance greater than 0.34 μm .

29. An extended DNA prepared by gravitationally streaming the DNA over a supporting surface wherein the DNA is stretched to an interkilobase pair distance of about 0.34 μm .

33. The super-extended DNA of claim 26 that has an interkilobase pair distance of between about 0.50 μm and about 60 μm .

The references relied on by the examiner are:

ALBERT L. LEHNINGER (Lehninger), *BIOCHEMISTRY*, 635-658 (1970).

Matsumoto et al. (Matsumoto), "Light Microscopic Structure of DNA in Solution Studied by the 4', 6-Diamidino-2-phenylindole Staining Method," Journal of Molecular Biology, Vol. 152, 501-516 (1981).

Kanda et al. (Kanda), "Isolation of amplified DNA sequences from IMR-32 human neuroblastoma cells: Facilitation by fluorescence-activated flow sorting of metaphase chromosomes," Proceedings of the National Academy of Sciences, USA, Vol. 80, 4069-4073 (1983).

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ISSUES²

Claims 33-40 stand rejected under 35 U.S.C. § 112, first paragraph.³ Claims 1, 2, 4, 5 and 10 stand rejected under 35 U.S.C. § 102(b) as clearly anticipated by Matsumoto. Claims 1-5 and 10 stand rejected under 35 U.S.C. § 103 as unpatentable over Matsumoto in view of Kanda. Claims 26-29 stand rejected under 35 U.S.C. § 103 as unpatentable over Matsumoto in view of Lehninger.

We AFFIRM the rejection under § 112, first paragraph, and REVERSE the rejections under §§ 102(b) and 103.

In reaching our decision in this appeal we have given careful consideration to the appellant's specification and claims and to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's answer (Paper No. 16, mailed May 28, 1997) for the examiner's reasoning in support of the rejections and to the appellant's brief (Paper No. 14, filed April 11, 1997) for the appellant's arguments thereagainst.

² "[T]he rejection of claims 1, 2, 4, 5, and 8-10 under 35 U.S.C. § 103 as unpatentable over Matsumoto ... in view of Pinkel ... has been overcome and therefore withdrawn as stated in the Advisory Action, mailed 12/6/96" (answer, p. 2).

³ "The NEW MATTER rejection of claims 26 and 29 is hereby withdrawn as written basis has been found as filed for these claims" (answer, p. 3).

BACKGROUND

The claimed invention is directed to methods for stretching DNA (claims 1-10) and to intact stretched or "(super)extended" DNA (claims 26-29 and 33-40), which can be combined with fluorescent hybridization procedures as a means for physically mapping DNA sequences or gene clusters (specification, pp. 6 and 7).

The method provides extended and super-extended forms of DNA, the latter stretched to a length beyond the calculated "unwound" length of native DNA. By comparison, the DNA from typical "spreads" (Lehninger, ...) is two-dimensional in the sense of exhibiting two directions in a single plane (including curves and winding). The form of DNA disclosed in the present invention is virtually straight (linear), has no contour and little, if any, randomness. It is thus visualized as extending in only one direction in a single plane. The invention therefore provides a procedure to stretch DNA into novel, linear, one-dimensional forms up to and beyond 0.34 μm per kilobase pair. The DNA can be used as a target for hybridization of labelled probes to visually observe a high resolution map of probes along a single strand of DNA. Mapping resolutions as high as 1 kb are possible with the extended DNA. Super-extended DNA allows even further increases in resolution to at least 0.4 kb, although the extended form is practical for many applications.

Extended DNA is DNA stretched to a substantially one-dimensional form up to about 0.34 μm per kilobase pair. Super-extended DNA is an essentially one-dimensional form stretched beyond what is commonly held to be the maximal length of fully extended DNA (0.34 μm per kilobase pair). [Specification, p. 6, ll. 12-35.]

The specification (p. 23, ll. 4-17) exemplifies stretching duplex DNA

by placing individual cells (100-5000) in two μl of PBS on one end of a glass slide and letting the drop dry. Immediately after drying, 5 μl of 0.5% SDS\50 mM EDTA\200 mM Tris, pH 7.4 solution was placed on the dried spot to dissolve the cells and release the DNA. After 5 minutes of dissolving, the slide was tilted to allow the drop of SDS and DNA to run down the slide. This resulted in a DNA stream extending down the slide

(FIG. 2A). The DNA stream was allowed to air dry and was then fixed to the slide by flooding the slide with a 75% methanol/25% acetic acid fixative. The DNA was fixed to the slide for 1-5 minutes, the excess fixative drained, and the slide air-dried. Slides were used immediately or stored in slide boxes under N₂ with drierite, at -20°C until used for hybridization.

OPINION

I. Rejection of claims 33-40 under § 112, first paragraph

The DNAs of claims 33-40 are "stretched" to various kilobase pair lengths, i.e., "between about 0.50 μm and about 60 μm " (claim 33), "between about 0.55 μm and about 0.65 μm " (claim 34), "between about 0.40 μm and 0.65 μm " (claim 35), "between about 0.60 μm and about 0.70 μm " (claim 36), "between about 0.40 μm and 0.45 μm " (claim 37), "between about 0.45 μm and about 0.60 μm " (claim 38), "about 0.47 μm " (claim 39) and "about 0.1 μm " (claim 40). Appellant admits that these "exact numbers are not recited in the specification," but argues that there is inherent support for kilobase pair stretch lengths between 0.34 μm and 0.65 μm (brief, p. 9). Appellant also disagrees with the examiner that some of these stretch lengths "are unreasonably large or small" (brief, p. 9; answer, pp. 3 and 7). (Compare the 0.34 μm theoretical unfolded length of a kilobase pair of helical DNA with the upper stretch length limit of 60 μm recited in claim 33 and the stretch length of about 0.1 μm recited in claim 40.) According to appellant, "the written description is submitted to satisfy the enablement

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requirement" (brief, p. 9). It is unclear whether the rejection and rebuttal are based on lack of written descriptive support and/or lack of enablement.

"Satisfaction of the description requirement insures that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (quoting In re Smith, 481 F.2d 910, 914, 178 USPQ 620, 623-24 (CCPA 1973)). "[L]ack of literal support ... is not enough ... to support a rejection under § 112." See In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976). The test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985).

In Ralston Purina Co., the Federal Circuit stressed that compliance with the description requirement "must be determined on a case-by-case basis" and rejected the argument of the accused infringer that "several range cases [support the proposition] that ranges found in the applicant's claim language must correspond exactly to ranges disclosed in the parent."

The facts in these cases precluded a determination that one skilled in the art could derive the claim limitations from the parent, due to a number of different factors, e.g. the unpredictable nature of the art, In re Sichert, 566

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F.2d 1154, 196 USPQ 209 (CCPA 1977); failure to distinguish one process from another, In re MacLean, 454 F.2d 756, 172 USPQ 494 (CCPA 1972); the addition of a critical limitation, In re Blaser, 556 F.2d 534, 194 USPQ 122 (CCPA 1977); failure to define a critical term, In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971); and use of a list that did not contain the claimed substance. In re Ahlbrecht, 435 F.2d 908, 168 USPQ 293 (CCPA 1971).

Appellant relies on the following disclosures in the specification to satisfy both the written description and enablement requirement (brief, p. 9):

"super-extension of DNA up to at least 0.6 μm per kilobase pair with no evidence of bond disruption" (p. 7, ll. 1-2);

"a method of extending DNA as a straight line ... reaching at least 0.65 μm per kilobase pair" (sentence, bridging pp. 8-9);

"[l]esser degrees of stretching, e.g., linearization to a kilobase pair distance of about 0.34 μm " (p. 9, ll. 23-25);

"the DNA in these two DIRVISH [i.e., direct visual hybridization] DNA maps is stretched to approximately twice the theoretical maximum of 0.34 μm , i.e., >0.6 μm " (p. 26, ll. 28-30); and,

"the examples showing both super-extended DNA (at least 0.65 μm) and extended forms of DNA results (see Example 7 and reference to FIGs 12 and 13)".

Assuming arguendo that the above disclosure inherently supported DNA stretched to the claimed lengths without breakage, the linchpin question appears to be whether one skilled in the art could reasonably derive these claim limitations based

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upon the disclosure in the specification, i.e., whether it would take undue experimentation to reasonably and predictably obtain stretched DNAs of the specifically claimed lengths.

The enablement requirement of 35 U.S.C. § 112, first paragraph, requires that the patent specification enable “those skilled in the art to make and use the full scope of the claimed invention without ‘undue experimentation.’” Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); see also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (“[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.”). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Here, the specification fails to provide direction or working examples for controlling and/or varying the amount of stretching of a DNA molecule within defined limits, e.g., "between about 0.40 μm and 0.45 μm " as required by claim 37. According to the specification "a fluid should be added to create a suspension in order to affectively stretch out the DNA" and these fluids, including mixtures of organic solvents and aqueous media, "would be expected to have the effect of altering the rate and amount of extension" (p. 10, last para.). However, the specification provides no further guidance as to how to tailor a specific fluid to obtain a specific amount of DNA extension in a reasonable and predictable manner. The specification also notes that "[d]ifferences in surface material and surface tension of the DNA solution may affect the rate of streaming and the ultimate extension of the DNA molecule" (p. 11, ll. 11-13) but gives little, if any, further guidance as to the relationship between different support surfaces, different chemical coatings or other modifications of the support surface or surface tension vis-a-vis the stretching of the DNA molecule within controlled limits without breakage. Moreover, the specification states, on the one hand, that "[t]he gravitational streaming method involves tilting the supporting surface at an angle which will efficiently extend the DNA" (p. 11, ll. 6-8) and, on the other hand, that "[t]he effect of the angle [of tilt] on the DNA stretching process had an insignificant effect on maps <40 kb" (p. 23, ll. 19-20). Finally, the prior art, i.e., Matsumoto, indicate that fluid selection, sample volume, and shear stress significantly affected morphology of DNA

adhered to a glass surface (see e.g., p. 508, § (b) and sentence bridging pp. 510-511, "Thus DNA in the presence of 10 mM-MgCl₂ revealed different orders of unfolding as the sample volume and the shear stress were varied."). Matsumoto also indicates that DNA may be significantly broken during its isolation from cells (sentence bridging pp. 504-505).

Therefore, upon consideration of the record as a whole, we conclude that it would require undue experimentation to derive the invention of claims 33-40, which require controlled stretching of DNA to specific lengths. Consequently, we affirm the rejection for lack of enablement.

II. Rejection of claims 1, 2, 4, 5 and 10 under § 102(b) as anticipated by Matsumoto

Matsumoto studied the structure of DNA in solution using fluorescent microscopy.

Individual DNA molecules in solution can be visualized under a fluorescence microscope by using the DNA binding dye 4',6-diamidino-2-phenylindole and can be recorded on video as mobile structures (Morikawa & Yanagida, 1981). DNA in the presence of 10 mM MgCl₂ was found to adhere to the glass surface, so that 4',6-diamidino-2-phenylindole-stained DNA can be filmed as still images. Fluorescence micrographs of DNA (bacteriophages T4, T3 and λ, yeast and chicken erythrocyte) taken by the present procedure are better in resolution than those obtained by video, showing structural details of DNA molecules hitherto not observed in solution. In the specimens prepared at the reduced shear stress, the folded particles and the short thick filaments were abundant. The shear stream extended them into the wavy and the straight thin filaments. The lengths of the thin filaments seen in viral DNA correlated well with those determined by electron microscopy. Our results

suggest that a DNA molecule in solution forms a certain kind of supercoil of its own accord. [Abstract]

According to the examiner,

[t]he observation that straight thin filaments were produced is discussed on page 514, second full paragraph which reads on the extended or super-extended DNA production of claim 1. ... The instant DNA obtaining step is clearly set forth on page 502 under "Experimental Procedures", part (b). The proteinase K digestion in said part (b) reads on the enzymatic degradation limitation of instant claim 4. The phenol extraction in said part (b) reads on instant claim 10 in that phenol is well known in the art as being a protein denaturant. [Answer, p. 4.]

"To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). Claims 1, 2, 4, 5 and 10 all require a process which produces "a DNA extended to an interkilobase pair distance that exceeds 0.34 μm ." The examiner's apparent position is that since Matsumoto discloses stretching a DNA filament to its maximum length and beyond such that it is broken, such a length and, therefore, the claimed method, is clearly disclosed (answer, p. 8).

However, characterizing a filament as thin and straight does not necessarily mean that the filament has an interkilobase pair distance that exceeds 0.34 μm . Further, the claimed process produces an ultimate DNA which is not broken, i.e., a super-extended DNA (see e.g., specification, para. bridging pp. 6-7). Moreover, Matsumoto discloses that "DNA appears to be significantly broken during the isolation

procedures" (p. 504). Thus, breakage is not necessarily due to stretching beyond a maximum length. The mere possibility that the method of Matsumoto may produce a super-extended DNA having an interkilobase pair distance that exceeds 0.34 μm does not legally suffice to show anticipation. In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). Occasional results are not inherent. Thus, without an inherent teaching about interkilobase pair distances in thin, straight filaments, Matsumoto does not anticipate the claimed invention. Accordingly, the rejection of claims 1, 2, 4, 5 and 10 under \S 102 as clearly anticipated by Matsumoto is reversed.

III. Rejection of claims 1-5 and 10 under \S 103 as obvious over Matsumoto and Kanda

The examiner relies on Kanda to "disclose detergent usage as well as the functional equivalent of mechanical cell disruption [used in Matsumoto] to release DNA" (answer, p. 5). According to the examiner,

it would have been obvious to someone of ordinary skill in art at the time of the instant invention to prepare DNA for in situ hybridization analysis utilizing either the Matsumoto et al. guidance or a functional equivalent that is reasonably expected to perform as well as given by Kanda et al. thus resulting in the hereinunder rejected embodiments (answer, p. 5).

However, Kanda fails to remedy the deficiencies of Matsumoto, in particular by failing to disclose or suggest stretched DNA molecules having an interkilobase pair distance that exceeds 0.34 μm as required by the claimed invention for the reasons discussed above. Therefore, the rejection of claims 1-5 and 10 under \S 103 as obvious over Matsumoto and Kanda is reversed.

IV. Rejection of claims 26-29 under § 103 as obvious over Matsumoto and Lehninger

According to the examiner (answer, p. 6), "Lehninger at page 656 discloses DNA as being of a form where 0.34 μm per kilobase is its length" and concludes that

it would have been obvious at the time of the instant invention to practice a DNA form of instant claims 26-29 because Matsumoto et al. discloses stretched DNA inclusive of various lengths even up to and beyond the theoretical maximum (that is, beyond breakage), such as given in claims 26-28

However, Lehninger fails to remedy the deficiencies of Matsumoto, in particular by failing to disclose or suggest stretched DNA molecules having an interkilobase pair distance that exceeds 0.34 μm as required by the claimed invention for the reasons discussed above. Therefore, the rejection of claims 26-28 under § 103 as obvious over Matsumoto and Lehninger is reversed.

OTHER MATTERS

Appellant and the examiner should review the claims for proper antecedent basis, typographical errors and any other apparent inconsistencies. For example, claims 8 and 9, which depend from claim 1, recite "wherein the fixing is with ..." but claim 1 does not recite a fixing step. Recitation of "about 60 μm ", as opposed to about 0.60 μm , in claim 33 may or may not be a typographical error (depending upon if and where the specification provides support therefore). Claim 40 recites an "extended DNA" having an interkilobase pair distance of about 0.1 μm . Since the calculated

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interkilobase pair distance of an unfolded, i.e., linear, DNA is 0.34 μm , does claim 40 recite an "extended DNA" or only a partially extended DNA.

Secondly, an article by Washizu et al., "Electrostatic Manipulation of DNA in Microfabricated Structures, IEEE Transactions on Industry Applications, Vol. 26, No. 6, November/December 1990, was found in the file. It does not appear to have been made of record by either the examiner or appellant. However, in the event of further prosecution, both appellant and the examiner should review this article and determine its relevance to the claimed invention. Please note that Washizu describes stretched molecules of λ DNA having 48.5 kb and measured to be about 17 μm at p. 1168.

CONCLUSION

To summarize, the decision of the examiner (I) to reject claims 33-40 under 35 U.S.C. § 112, first paragraph, is affirmed, (II) to reject claims 1, 2, 4, 5 and 10 under 35 U.S.C. § 102(b) as clearly anticipated by Matsumoto is reversed, (III) to reject claims 1-5 and 10 under 35 U.S.C. § 103 as unpatentable over Matsumoto in view of Kanda is reversed, and (IV) to reject claims 26-29 under 35 U.S.C. § 103 as unpatentable over Matsumoto in view of Lehninger is reversed.

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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

SHERMAN D. WINTERS)	
Administrative Patent Judge)	
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)	BOARD OF PATENT
CAROL A. SPIEGEL)	APPEALS
Administrative Patent Judge)	AND
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