

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JIZHONG ZHOU,
DOROTHEA KATHLEEN THOMPSON, and LIYOU WU

Appeal 2007-2726
Application 10/112,636
Technology Center 1600

Decided: April 29, 2008

Before DONALD E. ADAMS, ERIC GRIMES, and LORA M. GREEN,
Administrative Patent Judges.

ADAMS, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-19, 23-25, and 41-44. The remaining claims, claims 26-40, were withdrawn from consideration (App. Br. 2). We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

The claims are directed to a method for determining the presence or absence of a microorganism in a sample. Claims 1 and 15 are illustrative:

1. A method for determining the presence or absence of a microorganism in a sample comprising the steps of:

providing a nucleic acid microarray wherein the microarray comprises one or more probes for the microorganism wherein the one or more probes comprise at least 90% of the whole genomic DNA or RNA of the microorganism and wherein the one or more probes form one element on the microarray;

providing a labeled DNA or RNA preparation derived from the sample, wherein the DNA or RNA preparation represents at least 90% of the whole genomic DNA, whole genomic RNA, whole cDNA, or whole mRNA of microorganisms in the sample;

hybridizing the labeled DNA or RNA preparation to the microarray;
washing the microarray; and

observing the presence or absence of a hybridization signal at the element to determine the presence or absence of the microorganism in the sample.

15. The method of claim 1, wherein the hybridization is conducted in a buffer containing about 5% to about 70% formamide.

The Examiner relies on the following prior art references to show unpatentability¹:

| | | |
|---------------|-----------------|---------------|
| Slater et al. | US 6,448,387 B1 | Sep. 10, 2002 |
| Gray et al. | US 6,465,182 B1 | Oct. 15, 2002 |

(Sambrook) Molecular Cloning a Laboratory Manual 1.101-1.104 (2nd ed., Sambrook et al. eds.) (1989).

¹ We recognize the Examiner's reliance on Slater, Gray, Sambrook, Krutzman, and Lashkari. We note however, that these references were not included in the listing of "Evidence Relied Upon" at page 3 of the Answer. In the future, the Examiner should ensure that all evidence relied upon is properly cited in the "Evidence Relied Upon" section of the Answer.

Appeal 2007-2726
Application 10/112,636

Kurtzman, "DNA-DNA Hybridization Approaches to Species Identification in Small Genome Organisms" 224 *Methods in Enzymology* 335-348 (1993).

Deval A. Lashkari et al., "Yeast microarrays for genome wide parallel genetic and gene expression analysis," 94 *Proc. Natl. Acad. Sci. USA*, 13057-62 (1997).

(Schena '98) Mark Schena et al, "Microarrays: biotechnology's discovery platform for functional genomics," 16 *TIBTECH* 301-306 (1998).

(Schena '03) Schena, *Introduction to Microarray Analysis in Microarray Analysis 1* (John Wiley & Sons, Hoboken, NJ) (2003).

Gitika Panicker et al., "Detection of Pathogenic *Vibrio* spp. In Shellfish by Using Multiplex PCR and DNA microarrays," 70(12) *Applied and Environmental Microbiology* 7436-44 (2004).

The rejections as presented by the Examiner are as follows:

1. Claims 1-19, 23-25, and 41-44 stand rejected under 35 U.S.C. § 112, second paragraph.
2. Claims 1-19, 23-25, and 41-44 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.
3. Claims 1-5, 8, 10, 13, 18, 19 and 23-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lashkari.
4. Claims 1-14, 18, 19, 23, and 41-44 stand rejected under 35 U.S.C § 102(e) as anticipated by Gray.
5. Claims 15-17 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Gray and Sambrook.

We reverse.

DISCUSSION

Definiteness:

Claims 1-19, 23-25, and 41-44 stand rejected under 35 U.S.C. § 112, second paragraph.

The Examiner finds that “[t]he specification has no definition of [the term] ‘element’” (Ans. 3). According to the Examiner “[t]here is no fixed definition in the art for what constitutes ‘one element’” (Ans. 4). In this regard the Examiner finds that Schena ‘03 defines the term microarray “as an ordered array of microscopic elements on a planar substrate” which “does not require nor define the term element as a single position or location on a microarray” (Ans. 16). According to the Examiner Schena ‘98 “describes the array elements printed as adjacent 9 x 12 subgrids (smaller areas within the array) correspond to cDNA which does not define the term ‘element’ to include only one position on an array” (*id.*). We are not persuaded.

The Examiner’s rationale confuses the plural term “elements” with the singular term “element”. While Schena ‘98 describes an array of elements laid out in adjacent 9 x 12 subgrids, each “element” of this array represents a single position or location (Schena ‘98 305: Fig. 3). Schena ‘03’s definition of a microarray as “an ordered array of microscopic elements on a planar substrate that allows the specific binding of genes or gene products” is consistent with this interpretation of the term element (Schena ’03 1). It is also consistent with Zhou’s interpretation of the term element (Zhou Declaration 2:¶ 3 – 4:¶ 7). Accordingly, we are not persuaded by the Examiner’s reliance on Schena ’98 and ‘03.

We are also not persuaded by the Examiner's reliance on Slater. According to the Examiner, Slater teaches "that an element within the context of DNA microarray technology can have several meaning[s] including encompassing a target molecule (target element) or subarray of the substrate (grid element)" (Ans. 16).

Slater defines the term "array" to mean "rows and columns of spotted molecule elements located on a membrane including rows and columns of subarrays; e.g., a useful array can comprise 16x24 rows/columns of a sub array of spotted molecule elements" (Slater, col. 3, ll. 10-14). Slater defines the term "spotted element" to mean "an amount of target molecule, e.g., polynucleotide or polypeptide in a grid position on an array" (Slater, col. 3, ll. 5-7). Thus, according to Slater each "spotted molecule element" (e.g., polynucleotide) is placed at a particular "grid position" (e.g., a particular row and column number) on the array.

The Examiner's confusion arises when the Examiner considers Slater's definition of the term "sub array". As Slater explains an array may include subarrays (Slater, col. 3, ll. 10-14). Slater defines the term "sub array" to mean "rows and columns of grid positions within a grid element, e.g., a 16x16 . . . rows/columns of spotted molecule elements" (Slater, col. 3, ll. 15-17). Slater does not define the term "grid element".

Therefore, we are left with Slater's reference to two types of "elements": (1) a grid element; and (2) a spotted molecule element. From the foregoing discussion, a grid element includes a number of grid positions, whereas a spotted molecule element is located at one specific grid position. Appellants' claims use the term "element". Thus, in the context of Slater,

the issue is whether Appellants use the term “element” to refer to a grid element or a spotted molecule element.

As set forth in *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997), the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant’s specification.

According to Appellants’ Specification “[t]he whole or a substantial portion of the whole genomic DNA or RNA of a microorganism can be represented by one or more probes” (Spec. 5: ¶ 21). Further, Appellants disclose that “[r]egardless how many probes are used to represent the whole or a substantial portion of the whole genomic DNA or RNA of a microorganism, these probes are spotted within an area of a microarray substrate that is considered to be one single position on the microarray” (*id.*). In addition, Appellants disclose an exemplary array that has 15 rows and 4 columns (Spec. 10: ¶ 37). Appellants disclose that 59 probes were arranged on this array (*id.*). Appellants disclose that “[t]he exact location of each DNA element in the array matrix is listed in Table 1” (*id.*; Spec. 16-19). As illustrated in Table 1, each DNA element is identified by row and column number in the array (Spec. 16-19). Thus, the exact location of each element (e.g., DNA element or probe) of the microarray can be identified (or addressed) by a specific column and row number.

Therefore, in the context of Slater, Appellants’ use of the term “element” corresponds to Slater’s term “spotted molecule element”. Thus, contrary to the Examiner’s intimation, we find that a person of ordinary skill

in the art would understand claim 1 to read on a nucleic acid microarray that comprises one or more probes for a microorganism that are spotted (or located) at one element (e.g., identified by a single column and row number) on the microarray. Claims 2-19, 23-25, and 41-44 depend directly or indirectly from claim 1.

Claims are in compliance with 35 U.S.C. § 112, second paragraph, if “the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits.”

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385 (Fed. Cir. 1987). Accordingly, we reverse the rejection of claims 1-19, 23-25, and 41-44 under 35 U.S.C. § 112, second paragraph.

Enablement:

Claims 1-19, 23-25, and 41-44 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

The Examiner finds that “[t]he claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention” (Ans. 4). More specifically, the Examiner asserts that this rejection is based on the interpretation of the term “one element” as reading on the attachment of an entire chromosome or genome to a microarray element “through a single linker to a single spot/element on an array” (*id.*). In this regard, the Examiner finds that Appellants’ Specification fails to teach “how the single attachment point for the chromosome would avoid the portion of the sequences not attached from folding back on itself, or interacting with other chromosomal DNA” (Ans. 5-

6). In addition, the Examiner finds that “it is unpredictable how an entire genome, or a whole, unsheared chromosome is attached to the microarray for hybridization methods (Ans. 6). Further, the Examiner finds that Kurtzman “teaches that ‘once the DNA has been purified, it is used unsheared when attached to membranes; for free solution reactions and for membrane probes, however, it must be sheared to satisfy reaction kinetics and to maintain specificity’” (Ans. 6). We are not persuaded.

Kurtzman’s discussion of the use of sheared DNA for free solution reactions is off point. The claimed invention is not directed to a “free solution reaction” but instead involves the use of a microarray and does not involve free solution reactions. Further, Kurtzman teaches that unsheared DNA can be used for attachment to membranes. There is no doubt that a membrane can be spotted with nucleic acid to form an array. Kurtzman teaches that unsheared DNA can be used when attached to membranes. Accordingly, the Examiner’s reasoning appears to be off point.

As to Kurtzman’s teaching of sheared DNA – this DNA is used as a probe for the membrane. In the context of Appellants’ claimed invention this represents the labeled DNA or RNA preparation that is hybridized to the microarray (e.g., the unsheared nucleic acid spotted in an array on a membrane or other support)². Therefore, Kurtzman does not support the Examiner’s intimation that whole genomic DNA or RNA cannot be spotted on a microarray. Accordingly, we are not persuaded by the Examiner’s arguments.

² As Appellants explain “the DNA deposited on the glass slides [(e.g., the microarray)] is referred to as the probe, whereas the fluorescently labeled DNA is designated as the target” (Spec. 10: ¶ 0036).

Contrary to the Examiner's assertion, the evidence relied upon by the Examiner supports a conclusion that those of ordinary skill in this art would recognize that unsheared nucleic acid may be used on an array. Appellants' Specification supports this conclusion by asserting that "[o]btaining genomic DNA or RNA from microorganisms and spotting the obtained DNA or RNA onto a nucleic acid microarray substrate are well within the capability of one of ordinary skill in the art" (Spec. 5: 0021). In addition, Appellants disclose "a method for isolating genomic DNA and building a DNA microarray with the isolated genomic DNA" and indicate that "[o]ther methods known in the art can also be used" (*id.*).

In addition, there is no requirement in the claimed invention that a single linker is used to attach a particular nucleic acid to the microarray. As Appellants explain "[e]ven for a detection position or element that contains only one type of probe, there are multiple molecules of the probe attached to the microarray substrate at multiple attachment sites within the area (see section 3 and Fig. 1 of Dr. Zhou's declaration)" (Reply Br. 5; Zhou Declaration 2:¶ 3).

We recognize the Examiner's assertion that "the algae *Laminaria* . . . [is a microorganism which] has 62 chromosomes and the Specification does not teach how to provide a microarray that contains at least 99% of the entire genome of *Laminaria* to form one element of the array" (Ans. 17). We also recognize the Examiner's assertion that "[t]he Specification does not teach how to isolate a genomic DNA as one intact element, and that remains in tact [sic] within 99% of the entire genome in addition to attaching the entire genome to one location on the array, as is encompassed by the claims" (*id.*).

The Examiner has not, however, provided any persuasive reasoning or evidence to rebut Appellants' assertion that the techniques for "[o]btaining genomic DNA or RNA from microorganisms and spotting the obtained DNA or RNA onto a nucleic acid microarray substrate are well within the capability of one of ordinary skill in the art" (Spec. 5: ¶ 0021). In this regard, we note that it

“is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.”

In re Marzocchi, 439 F.2d 220, 224 (CCPA 1971).

On reflection, we find that the Examiner has failed to provide the evidence or reasoning to rebut Appellants' presumptively accurate disclosure. Accordingly, we reverse the rejection of claims 1-19, 23-25, and 41-44 under the enablement provision of 35 U.S.C. § 112, first paragraph.

Anticipation:

Lashkari:

Claims 1-5, 8, 10, 13, 18, 19 and 23-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lashkari.

The Examiner finds that Lashkari teaches, *inter alia*, the isolation of yeast genomic DNA (pg. 13057) and the subsequent amplification and printing onto glass slides of “over 6,000 elements in an area less than 1.8 cm. Given that the yeast genome consists of approximately 6,100 ORFs, the entire set of yeast genes can be spotted onto a single glass slide” (Pg. 13058 right side).

(Ans. 9.) However, as Appellants point out Lashkari's microarray is formed by spotting the open reading frames (ORFs) of an organism on a glass slide to form multiple elements, typically with each ORF as one element. As described in Lashkari . . . approximately 6,100 ORFs of the yeast genome were spotted on a glass slide that could accommodate over 6,000 elements.

(App. Br. 14.) Stated differently, each element of Lashkari's microarray contains a distinct ORF corresponding to the yeast genome.

The Examiner disagrees with Appellants' assertion that Lashkari is distinct from the claimed invention because the Examiner interprets the term "element" as a "subarray". For the reasons set forth above, we disagree with this interpretation of the term "element" as it appears in Appellants' claimed invention.

Accordingly, we reverse the rejection of claims 1-5, 8, 10, 13, 18, 19 and 23-25 under 35 U.S.C. § 102(b) as being anticipated by Lashkari.

Gray:

Claims 1-14, 18, 19, 23, and 41-44 stand rejected under 35 U.S.C § 102(e) as anticipated by Gray.

The Examiner finds that Gray teaches the limitations of the claimed invention including "a nucleic acid microarray or nucleic acid array that is a plurality of target elements, each comprising a target oligonucleotide immobilized on a solid surface to which labeled nucleic acids are hybridized" (Ans. 11). In this regard, the Examiner finds that Gray teaches "that the target element may comprise nucleic acid sequences at 'any desired portion of a genome, including . . . an entire genome" (*id.*).

Appellants disagree. According to Appellants, when read under the context (Column 5, lines 35-41), [Gray] reveals that it was “an array of such elements,” not a single element, that represents any desired portion of a genome (including the whole genome). The microarray recited in claim 1, however, contains at least 90% of the whole genomic DNA or RNA of a microorganism in each element.

(App. Br. 18.) In response, the Examiner directs attention to Slater’s use of the term “element” as including a “grid element” e.g., a subarray (Ans. 20). We agree with the Examiner and Appellants that Gray’s use of the plural term “elements” refers to a subarray that includes a number of individual elements that together account for any desired portion of a genome, including the whole genome of an organism. However, as Appellants point out, this is not what is set forth in their claimed invention. To the contrary, the claimed invention requires that “at least 90% of the whole genomic DNA or RNA of the microorganism . . . form[s] one [singular] element on the microarray.” As Gray does not teach an array that fulfills this requirement it does not anticipate the claimed invention. “Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim.” *Gechter v. Davidson*, 116 F.3d 1454, 1457 (Fed. Cir. 1997). “Every element of the claimed invention must be literally present, arranged as in the claim.” *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Accordingly, we reverse the rejection of claims 1-14, 18, 19, 23, and 41-44 stand rejected under 35 U.S.C § 102(e) as anticipated by Gray.

Obviousness:

Claims 15-17 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Gray and Sambrook.

The Examiner relies on Gray as discussed above (Ans. 13). The Examiner finds that Gray “does not teach a hybridization solution consisting of 50% formamide” (*id.*). To make up for this deficiency in Gray the Examiner relies on Sambrook to teach a hybridization solution containing 50% formamide (*id.*). Based on this evidence the Examiner concludes that

It would have been prima facie obvious to one skilled in the art at the time the invention was made to have used a hybridization solution containing 50% formamide in the hybridization step of Gray because Sambrook et al. teach using 50% formamide and Gray et al. teach the use of the conditions taught by Sambrook.

(Ans 14.)

Claims 15-17 depend directly from claim 1. As discussed above Gray fails to teach the limitations of claim 1. Specifically, Gray fails to teach a microarray wherein “at least 90% of the whole genomic DNA or RNA of the microorganism . . . form[s] one [singular] element on the microarray.” The Examiner failed to identify, and we do not find, a teaching in Sambrook that would make up for this deficiency in the teachings of Gray. Accordingly, we reverse the rejection of claims 15-17 under 35 U.S.C. § 103 as being unpatentable over the combination of Gray and Sambrook.

CONCLUSION

In summary, we reverse the rejections of record.

Appeal 2007-2726
Application 10/112,636

REVERSED

Ssc:

ZHIBIN REN
QUARLES & BRADLEY LLP
1 SOUTH PINCKNEY STREET
P.O. BOX 2113
MADISON, WI 53701-2113