

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

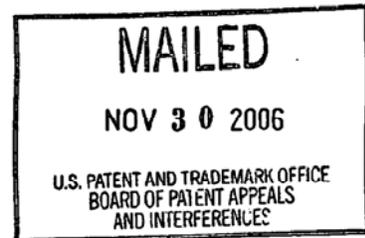
UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte DAVID TYVOLL and WINTHROP D. CHILDERS

Appeal No. 2006-0820
Application No. 10/286,104

ON BRIEF



Before ADAMS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, 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 1-31. Claims 1, 16, 22, and 28 are the independent claims on appeal, and read as follows:

1. A method of analyzing a nucleic acid target in a nucleic acid mixture of the target and non-target nucleic acids, the method comprising:
 - attracting the nucleic acid mixture in fluid to an electrode included in electronics formed on a substrate;
 - retaining the target selectively by binding the target to a receptor disposed near the electrode;
 - locally heating a portion of the fluid near the receptor to adjust a stringency under which the target binds to the receptor;

enriching the mixture for the target by removing unretained nucleic acids; and

amplifying the target from the enriched mixture.

16. A microfluidic device for analyzing a nucleic acid target in a nucleic acid mixture that includes the target, comprising:

a substrate portion at least partially defining a chamber, the substrate portion including a substrate and electronics formed on the substrate, the electronics including at least first and second electrodes and a plurality of heating devices, each electrode being operable to form an electric field in the chamber, the plurality of heating devices being operable to adjust binding stringency locally in the chamber; and

first and second receptors for specifically binding the target, the first and second receptors being distinct and connected to the first and second electrodes, respectively.

22. A microfluidic device for analyzing a nucleic acid target in a nucleic acid mixture of the target and non-target nucleic acids, comprising:

a substrate portion at least partially defining fluidically connected first and second chambers, the substrate portion including a substrate and electronics formed on the substrate, the electronics including a first electrode operable to form an electric field in the first chamber and a second electrode operable to form an electric field in the second chamber, the electronics also including a plurality of heating devices operable to adjust binding stringency locally in at least one of the first and second chambers; and

first and second receptors for specifically binding the target, the first and second receptors being connected to the first and second electrodes, respectively.

28. A microfluidic device for analyzing a nucleic acid target in a nucleic acid mixture of the target and non-target nucleic acids, comprising:

a substrate portion at least partially defining a chamber, the portion including a substrate and electronics formed on the substrate, the electronics including an electrode configured to attract the nucleic acid mixture in the chamber, the electronics also including a plurality of heating devices operable to adjust binding stringency locally in the chamber;

a receptor connected to the electrode and configured to selectively bind the target from the attracted mixture; and

a fluid-handling portion connected to the substrate portion and configured to remove unbound non-target nucleic acids from the chamber and to deliver amplification reagents to the chamber.

Claims 1-31 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Heller¹ and O'Connor.² In addition, claims 1-3 and 5-31 stand rejected under 35 U.S.C. § 102(a) or § 102(e) as being anticipated by Cheng,³ and claim 4 stands rejected under 35 U.S.C. § 103(a) as being obvious over Cheng. After careful review of the record and consideration of the issues before us, we affirm the rejection over Cheng as to claims 16-21 and 28-31, but reverse as to claims 1-3, 5-15, and 22-27. We also reverse the rejection of claim 4 as being obvious over Cheng, and the rejection of claims 1-31 over the combination of Heller and O'Connor.

DISCUSSION

Claims 1-3 and 5-31 stand rejected under 35 U.S.C. §102(a) or 102(e) as being anticipated by Cheng.

According to the rejection,

Cheng [] disclose[s] a microfluidic device comprising a substrate portion comprising electronics formed therein, the electronics including at least a first and second electrodes (Figure 6, elements 32 and 31(a) or 31(b); column 7, lines 49-52); a plurality of heating devices (elements 12, Figure 6; column 7, lines 52-53); at least a first and second nucleic acid probes connected to the first and second electrodes (column 5, lines 60-67; column 6, lines 14-15).

Examiner's Answer, page 20.

The examiner asserts "[w]ith regard to the method claims, Cheng [] disclose[s] that electronically addressable microchip of chamber 31(a) would isolate

¹ Heller et al. (Heller), US Patent No. 6,238,624 B1, issued May 29, 2001.

² O'Connor et al. (O'Connor), U.S. Patent No. 6,729,352 B2, issued May 4, 2004.

³ Cheng et al. (Cheng), US Patent No. 6,403,367 B1, issued June 11, 2002.

and amplify the target nucleic acids (column 11, lines 8-20), wherein electronic stringency involves the well-known steps of attracting the nucleic acid and retaining the target nucleic acids selectively.” Id. at 21. Thus, according to the examiner, “the invention as claimed is anticipated by Cheng [].” Id.

We recognize that in order for a prior art reference to serve as an anticipatory reference; it must disclose every limitation of the claimed invention, either explicitly or inherently. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997). We find that the examiner has met his burden of setting forth a prima facie case as to the apparatus of claims 16-21 and 28-31, but not as to the method of claims 1-15, nor as to the apparatus of claims 22-27.

The examiner relies on Figure 6 of the Cheng patent in rejecting the apparatus claims. See Examiner’s Answer, page 20. Figure 6 of Cheng is reproduced below:

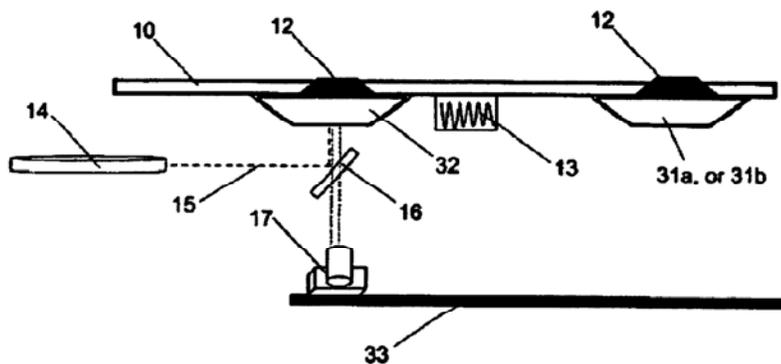


Fig. 6

Figure 6 of Cheng is a schematic showing an embodiment of the invention having two flow cells. See Cheng, col. 7, lines 45-46. Each flow cell (31) and (32) can comprise an electronically addressable microchip (31a), and each flow cell has a heating element (12) attached to it. See id. col. 7, lines 50-55. Moreover, the flow cell is covered by a quartz window and has at least two inlet ports. See id. at col. 7, lines 39-45. The electronically addressable microchip is attached to a substrate (10). See id. at Col. 10, lines 26-30. Cheng teaches that the microarray comprises a grid of individual electrodes, see id. at col. 5, lines 30-32, on which probes for capture/hybridization of molecules of interest are immobilized, see id. at col. 6, lines 7-15. In a preferred embodiment, nucleic acids of interest bind to probes anchored to the microarray. See id., col. 6, lines 46-53. In one of the examples, the amplification products of the spa Q and inv A genes from *Salmonella enterica* are addressed to specific pads of the electrodes which contain gene specific probes attached to the permeation layer overlaying the electrodes. See id. at Col. 15, lines 36-44.

Thus, Cheng anticipates the apparatus of claim 16, as it teaches a substrate (10) at least partially defining a chamber, wherein electronics are formed on the substrate and comprise at least first and second electrodes. As can be seen from Figure 6, when two flow cells are used, the flow cells are formed on the same substrate, thus the substrate also comprises a plurality of heating devices. In addition, the gene specific probes for the spa Q and inv A genes read on the first and second receptors for specifically binding the target, wherein the target is nucleic acid isolated from *Salmonella enterica*.

Cheng also anticipates the apparatus of claim 28, as Figure 6 has a substrate portion (10) that at least partially defines a chamber, the substrate having electronics formed thereon, wherein the electronics include an electrode configured to attract the nucleic acid mixture in the chamber. The electrode also has a receptor connected to it which selectively binds the target. Moreover, as seen in Figure 6, the substrate includes a plurality of heating devices (two), and the flow chamber has at least two inlet ports, which reads on the fluid handling portion connected to the substrate portion.

As to claims 16-21, appellants argue that “Cheng does not teach or suggest distinct first and second receptors for specifically binding the target.” Appeal Brief, page 18.

As noted by the examiner, the term “target” may be broadly interpreted to include different sequences from the same target, such as the same pathogen. See Examiner’s Answer, page 37. Thus, as discussed above, Cheng teaches the use of the gene specific probes for the spa Q and inv A genes, which read on the first and second receptors for specifically binding the target, wherein the target is nucleic acid isolated from the pathogen *Salmonella enterica*. See, e.g., In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (noting that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification).

As to claims 28-31, appellants argue that “Cheng does not teach or suggest a

plurality of heating devices to adjust binding stringency locally in a chamber.”
Appeal Brief, page 19. Cheng, according to appellants, “discloses a single heating device for each chamber.” Id. Appellants’ arguments are not convincing, however, because they are not commensurate in scope with the claimed subject matter. Claim 28 requires a substrate portion at least partially defining a chamber, the portion including electronics formed on the substrate, the electronics including a plurality of heating devices. The claim just requires that the substrate have a plurality of heating elements, and does not exclude an embodiment wherein the heating elements are in separate chambers. Thus, we find that Cheng anticipates the apparatus of claims 28-31.

As to the method of claims 1-3 and 5-15, appellants argue that “Cheng does not teach or suggest ‘retaining the target selectively by binding the target to a receptor disposed near the electrode,’ as required by claim 1. Appeal Brief, page 16. We agree, and the rejection as to claims 1-3 and 5-15 is reversed.

Cheng specifically teaches a method in which total nucleic acid was isolated from bacterial cells by lysing the cells, and amplification primer is added to the isolated nucleic acid in the first chamber. See Cheng, col. 14, line 32-col. 15, line 5. For detection, target nucleic acids are hybridized to oligonucleotide probes that are immobilized on the microarray in either the first (if only a single chamber is used), or the secondary chamber. See id., col. 15, lines 19-35. Thus, Cheng fails to teach the step of “retaining the target selectively by binding the target to a receptor disposed near the electrode” before amplification of the nucleic acids.

The examiner asserts that Cheng teaches that SDA was conducted by introducing primers for spa Q and inv A gene sequences, meeting the limitation of “retaining the target selectively by binding the target to a receptor near the electrode.” See Appeal Brief, page 36. However, the amplification method of Cheng is performed in solution phase, and the examiner has not explained how such solution phase amplification reads on “retaining the target.” Thus, the examiner has failed to set forth a prima facie case of anticipation as claims 1-15, and the rejection of those claims as being anticipated by Cheng need be reversed.

As to claims 22-27, appellants argue that:

Cheng does not teach or suggest first and second receptors for specifically binding a target and connected to electrodes of respective first and second chambers. In particular, . . . Cheng discloses electronically addressable microchips in two chambers, but only discloses a receptor for binding a target in one of the chambers.

Appeal Brief, page 19. We agree, and the rejection of claims 22-27 over Cheng is reversed.

As set forth above, Cheng teaches that for detection, target nucleic acids are hybridized to oligonucleotide probes that are immobilized on the microarray in either the first (if only a single chamber is used), or the secondary chamber. Thus, Cheng only teaches that the first and second receptors are connected to electrodes in a single chamber, not in respective first and second chambers. Thus, the anticipation rejection as to claims 22-27 must also be reversed.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being obvious over Cheng.

Cheng is relied upon as above. According to the examiner, Cheng does not “explicitly disclose that the attracting and retaining of the target nucleic acids be conducted in a first compartment while the amplification reaction be conducted in the second compartment.” Examiner’s Answer, page 22. The examiner concludes, however, that it would have been prima facie obvious to modify the teachings of Cheng to arrive at the claimed invention because:

Cheng [] clearly disclose[s] an apparatus and method of using microfluidics device which allows for prehybridization, amplification, hybridization detection. Whether the pre-hybridization is conducted in a first compartment while the amplification is done in another reflects mere design preference of an ordinarily skilled artisan and given the disclosure of Cheng [], one of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success in modules employed by Cheng [] to arrive at the claimed invention.

Id.

Appellants argue that the rejection is improper for the same reasons set forth above as to claim 1. See Appeal Brief, page 17. We agree, and the rejection is reversed for the same reasons as set forth in the discussion of claims 1-3 and 5-15 as being anticipated by Cheng.

Claims 1-31 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Heller and O’Connor.

According to the examiner, Heller teaches a method of analyzing a nucleic acid target using an electronically addressable microchip, in which a nucleic acid mixture is attracted to an electrode formed on a substrate, selectively retaining the target by binding the target to a receptor disposed near the electrode and enriching the mixture by electronic stringency control. See Examiner's Answer, page 3. The examiner notes that Heller does not "explicitly disclose the method employing heating the receptor to adjust stringency under which target binds to the receptor." Id. at 5.

O'Connor is cited for disclosing "a microfluidic system which comprises different modules connected by fluidics for conducting different reactions . . . , wherein one of the modules are disclosed as comprising heating devices for reactions such as PCR, which necessarily requires the heating element" Id. at 5-6.

The examiner concludes:

With regard to the heating the receptor to adjust a stringency under which the target binds to the receptor, one of ordinary skill in the art would have been motivated to modify the teachings of Heller [] for the following reasons.

While Heller [] disclose[s] that it is "unnecessary to change temperatures," for stringency control (column 6, lines 27-29), Heller [] disclose[s] a well-known nucleic acid hybridization stringency control method which employs temperature fluctuations (column 1, lines 45-48; column 2, lines 28-29; column 7, lines 1-6). In addition, Heller [] also employs [its] microfluidic device to the temperature of 90°C when denaturing the hybridization complex (column 36, lines 38-40).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Heller [] and O'Connor [] which employ microfluidic device comprising a heating device for reactions such as PCR or for stringency control. One of ordinary skill in the art would have a reasonable expectation at modifying the teachings of Heller []

because . . . the microfluidic device of Heller [] was employed in a reaction involving buffer temperature of at least 90°C for stringency control, fully demonstrating that the microfluidic device of Heller [] was capable of performing at such extreme temperature

Id. at 7.

Appellants argue that there is no teaching or suggestion in the prior art to combine Heller with O'Connor. We agree, and the rejection is reversed.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (citations omitted). Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997).

As noted by appellants, Appeal Brief, page 6, Heller teaches that “it is unnecessary to change temperatures” using the device of its invention. Heller, col. 6, lines 27-28. Specifically, Heller teaches:

The active devices of this invention allow each micro-location to function as a completely independent test or analysis site (i.e. they form the equivalent of a "test tube" at each location). Multiple hybridization reactions can be carried out with minimal outside physical manipulations. Additionally, it is unnecessary to change temperatures, to exchange buffers, and the need for multiple washing procedures is eliminated.

Id. at col. 6, lines 22-29.

Heller teaches further that the device "provides complete electronic control over all aspects of the DNA hybridization" through electronic stringency control, and can resolve one base mis-matches. Id. at col. 22, lines 11-13 and lines 57-60. Moreover, Heller teaches that electronic stringency control allows both shorter and longer oligonucleotides to be used with very high discrimination ratios. Id. at col. 23, lines 46-60. Thus, Heller teaches the advantages of electronic stringency control over the use of heat, and one of ordinary skill in the art would not have looked to O'Connor to utilize a microfluidic device that comprises a heating device to perform the method of claim 1 or arrive at the apparatus of claims 16, 22 or 28.

The examiner asserts that Heller does not teach away from the invention because Heller describes the use of temperature as a way to achieve stringency control, citing column 1, lines 44-48 of the Heller patent. See Examiner's Answer, page 25. The examiner cites column 36, lines 38-40, in which the microfluidic device is heated to 90°C to denature the hybridization complex. See id. at 7.

Heller at column 1, lines 44-48, is merely providing the background of the invention, and describes ways in which stringency control has been achieved in the art. That portion of Heller, however, has to be read in the context of the reference as a whole, and as set forth above, Heller teaches the advantages of using electronic

stringency control, and thus the ordinary artisan, when reading the background of the invention in the context of the whole reference, would not be motivated to look to the use of heat to achieve stringency control using the method and device of Heller, given Heller's stated advantages of electronic stringency control.

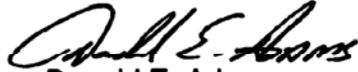
As to column 36, lines 38-40 of Heller, Heller looks at the performance of the device under denaturing conditions to determine if the device is reusable. Again, the fact that the device is stable under denaturation conditions, given the teachings of Heller as to the advantages of electronic stringency control, would not have led the skilled worker to look to the use of heat to obtain stringency control. Thus, the examiner has not set forth a prima facie case of obviousness, and the rejection under 35 U.S.C. § 103(a) over the combination of Heller and O'Connor of claims 1-31 must be reversed.

CONCLUSION

As the examiner has set forth a prima facie case of anticipation as to claims 16-21 and 28-31 over Cheng, the rejection of those claims is affirmed. Because the examiner has not set forth a prima facie case of unpatentability as to claims 1-15 and 22-27, the rejections as to those claims are reversed.

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



Donald E. Adams
Administrative Patent Judge



Eric Grimes
Administrative Patent Judge



Lora M. Green
Administrative Patent Judge

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LG/dym
HEWLETT-PACKARD COMPANY
Intellectual Property Administration
P.O. Box 272400
Fort Collins CO 80527-2400