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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOON WON PARK, BONG JIN HONG,
and SUNG HONG KWON[1]

Appeal 2019-000526
Application 12/140,226
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW, and
JAMIE T. WISZ, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Postech Academy-Industry Foundation and Posco as the real parties-in-interest. App. Br. 2.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 23–34 and 42. Specifically, claims 23–26, 29, 31–33, and 42 stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Henderson et al. (US 5,763,768, June 9, 1998) ("Henderson"), Ashby et al. (U.S. 2003/0033863 A1, February 20, 2003) ("Ashby"), B. J. Hong et al., *Nanoscale-Controlled Spacing Provides DNA Microarrays with the SNP Discrimination Efficiency in Solution Phase*, 21 LANGMUIR 4257–261 (2005) ("Hong"), and T. Leskela et al., *Sensitive Genus-Specific Detection* of Legionella by a 16S rRNA *Based Sandwich Hybridization Assay*, 62 J. MICROBIOL. METHODS, 167–79 (2005) ("Leskela").

Claims 23–25, 27–33, and 42 stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Henderson, Ashby, Hong, and Dellinger et al. (US 6,103,474, August 15, 2000) ("Dellinger").

Claim 34 stands rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Henderson, Ashby, Hong, Leskela, and Cai et al. (US 2004/0213910 A1, October 28, 2004) ("Cai").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

NATURE OF THE CLAIMED INVENTION

Appellant's claimed invention is directed to a method for detecting a presence of target ligand in a fluid medium. Abstr.

REPRESENTATIVE CLAIM

Claim 23 is representative of the claims on appeal and recites:

23. A method for determining the identity of a target oligonucleotide in a fluid medium comprising:

(i) contacting the fluid medium with a solid substrate comprising a plurality of different first probe oligonucleotides to form a first probe oligonucleotide-target oligonucleotide complex when the target oligonucleotide is present in the fluid medium, wherein each of the different first probe oligonucleotides is located at a predefined region of the solid substrate, and wherein the nucleotide length of said first probe oligonucleotides is shorter than the length of said target oligonucleotide such that at least a portion of said target oligonucleotide remains uncomplexed in said first probe oligonucleotide-target oligonucleotide complex, and wherein the solid substrate further comprises:

a plurality of dendrons on its surface, wherein each of the dendrons comprises:

a central atom, and

a base portion attached to the central atom and having a plurality of termini that are attached to the surface of the solid substrate, and wherein each of the plurality of different first probe oligonucleotides is attached to the central atom optionally through a linker;

(ii) measuring the binding force between a second probe oligonucleotide that is present on the tip of an atomic force microscope (AFM) and said uncomplexed portion of said target oligonucleotide in said first probe oligonucleotide-target oligonucleotide complex; and

(iii) identifying the target oligonucleotide by analyzing the location of increased binding force within the solid substrate.

App. Br. 12.

ISSUES AND ANALYSES

We agree with, and adopt, the Examiner's findings, reasoning, and conclusion that the claims on appeal are obvious over the combined cited prior art. We address the arguments raised by Appellant below.

Issue

Appellant argues that the Examiner erred in finding that a person of ordinary skill in the art would have used the combined teachings of the references cited by the Examiner to arrive at the claimed invention. App. Br. 10.

Analysis

The Examiner finds that Henderson teaches methods comprising the use of atomic force microscope ("AFM") to detect target ligands present in a solution. Final Act. 6 (citing Henderson Abstr., col. 3, ll. 25–45, Figs. 2, 13). The Examiner finds that Henderson teaches: (1) contacting a fluid medium with a solid substrate upon which a probe that binds to the target ligand is immobilized, and (2) determining the presence of a probe-target ligand complex by measuring the binding force between any target ligand bound to the substrate-immobilized probe and a detection molecule that is immobilized upon an AFM cantilever tip and also binds to the target ligand,

by which an increase in force between the probe-target ligand complex and the detection molecule indicates the presence of the target ligand in the fluid medium. *Id.* (citing Henderson col. 9, ll. 1–23, col. 11, ll. 1–30, cols. 12–13 ll. 45–8, Figs. 2, 10, 13).

The Examiner finds that Henderson further teaches that its methods may be used to detect a target nucleic acid *via* its hybridization to its complement, but also finds that Henderson does not expressly teach that the nucleic acid detection embodiments are conducted in a "sandwich assay" using substrate-immobilized and AFM tip-immobilized oligonucleotides. Final Act. 6–7. The Examiner also finds that Henderson does not teach that the solid substrate upon which the probe is immobilized is coated with an array of dendrons on its surface or immobilizing a plurality of different probes at predetermined locations on the substrate. *Id.* at 7. Furthermore, the Examiner finds, Henderson does not teach an oligonucleotide sandwich assay configuration. *Id.*

The Examiner finds that Ashby teaches a high-throughput AFM method for simultaneously detecting interactions between a plurality of different pairs of biological molecules. Final Act. 7 (citing Ashby ¶ 14). The Examiner finds that the method taught by Ashby comprises contacting a fluid medium with a solid substrate having a plurality of different probes (i.e., test molecules) immobilized upon it at predetermined locations and measuring the binding force between a detection molecule immobilized on an AFM tip and a test molecule. *Id.* (citing Ashby ¶¶ 14, 37–39, 41–48). The Examiner finds that Ashby also teaches that a plurality of different AFM tips, each having a different detection molecule immobilized upon it,

may be used to measure simultaneously interactions between a plurality of different test molecule detection molecule pairs. *Id.* at 7–8.

The Examiner finds that Ashby does not teach using dendrons to attach the probes to the solid substrate, but finds that Hong teaches methods for conducting nucleic acid hybridization reactions on an array comprising a dendron coating. Final Act. 8 (citing Hong Abstr.). Specifically, the Examiner finds that Hong teaches a planar, nonporous solid support coated with an array of cone-shaped dendrons, each of which has a central atom to which an oligonucleotide probe is attached. *Id.* (citing Hong schemes 1–2, 4257–258). The Examiner finds that Hong teaches that the central atom is also attached to a base portion having a plurality of termini that are attached to the solid support. *Id.*

Finally, the Examiner finds that Leskela teaches solid-phase sandwich hybridization assays for detecting a target nucleic acid in a fluid sample. Final Act. 9 (citing Leskela Abstr., 168, 170–71). The Examiner finds that Leskela also teaches that this method is highly sensitive and can provide attomolar sensitivity. *Id.* (citing Leskela Abstract, 173, Table 2).

The Examiner concludes that it would have been *prima facie* obvious to a person of ordinary skill in the art to immobilize a plurality of different probes at predetermined locations on a solid substrate, as taught by Henderson. App. Br. 9. The Examiner finds that a skilled artisan would have been motivated to do so with a reasonable expectation of success in view of the teachings of Ashby, which indicate that this would afford the ability to detect and identify a plurality of different target ligands in the fluid medium in a high-throughput format. *Id.* Furthermore, the Examiner finds, a person of ordinary skill would have understood from the teachings of

Hong that dendron-coated arrays offer an "ideal" array surface with precisely controlled spacing between immobilized molecules, which serves to eliminate non-specific binding to the array surface and also to maximize hybridization efficiency by mimicking solution hybridization conditions. *Id.*

The Examiner further concludes that it would also have been obvious to a skilled artisan to employ the methods suggested by the teachings of Henderson, Ashby, and Hong in a sandwich assay format. Final Act. 9. The Examiner points out that Henderson expressly teaches that its method can be used to detect a target nucleic acid; furthermore, the Examiner finds such an artisan would also have recognized from the above teachings of Leskela that nucleic acid detection using a sandwich assay format would provide a much more sensitive and specific means of detecting nucleic acids than the conventional hybridization methods suggested by Henderson and Hong. *Id.* at 9–10.

Appellant argues that the method taught by Henderson requires: (1) a functionalized particle that is attached to the AFM; and (2) use of two antibodies to detect an antigen. App. Br. 9. Appellant contends that, in contrast to the method recited in Appellant's claims, the method taught by Henderson is similar to an ELISA[2] assay, except that an AFM is used. *Id.*

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[2] The sandwich ELISA (enzyme-linked immunosorbent assay) assay involves attachment of a capture antibody to a microplate. Then, samples containing unknown amount of the target protein or analyte of interest are added and bind to the capture antibody. After washing steps to rid the microplate of unbound substances, an HRP [horseradish peroxidase] conjugate is added for detection. *See* GENERAL SANDWICH ELISA PROTOCOL, available at: https://www.thermofisher.com/us/en/home/

Appellant argues that, unlike hybridization of oligonucleotides where the strength of detection depends on the number of hydrogen bonds between the probe and the target oligonucleotide, binding of an antigen to an antibody generally forms a much stronger bond, and the antibody and antigen are specific to one another. App. Br. 9. Appellant asserts that it is well known to one skilled in the art that binding of an antigen to an antibody is more like a "lock-and-key" interaction in which the antigen is thought to be "inserted" into a pocket of the antibody to provide a strong interaction.

Appellant disputes the Examiner's finding that Henderson teaches detection of a target nucleic acid. App. Br. 9. Appellant asserts, rather, that a close reading of Henderson shows it teaches away from Appellant's claimed method. *Id.* Specifically, Appellant points to columns 3–4, lines 49–8 of Henderson, which teaches that:

> A variety of molecular pairs can be used in the molecular detection system described herein. Some representative examples are listed in Table 1. Some of the molecular pairs listed in Table 1 have been tested by other groups but have not been evaluated using the modified scanning probes and methods described here. They will be useful in comparing reproducibility and reliability of the different systems. Other molecular pairs have not been tested but are important for diagnostic applications. As representative examples of test cases we present data describing molecular force detection using an antibody-antigen system, and supportive data using a protein-DNA system. The antibody system is a "sandwich" type assay in which the antigen is trapped between two antibodies. In our implementation, one antibody is immobilized on a solid surface,

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references/ protocols/cell-and-tissue-analysis/elisa-protocol/general-elisa-protocol.html (last visited October 16, 2019).

> and the second is attached to the probe. When the antigen is introduced, it is trapped between the two antibodies, forming a trimolecular complex. The force necessary to rupture this complex provides the macroscopic signal, in the form of a direct force measurement or, more pertinent to this application, in the form of a change in a resonance property of the probe. The protein DNA system includes a recombinant yeast transcription factor, Gal 4, and its target DNA duplex sequence[.] In this assay, the Gal 4 protein is attached to the probe, and the DNA target is attached to a solid surface. The interaction between the protein and the DNA is detected and measured as described above for the antibody-antigen interaction.

Appellant argues that Henderson does not, therefore, teach detecting oligonucleotide *via* hybridization. App. Br. 10. At most, contends Appellant, Henderson contemplates attaching the DNA target to the solid surface and using the probe that is attached to the cantilever to detect the DNA target. *Id.* Therefore, Appellant asserts, the detection of a DNA target contemplated in Henderson does not involve a sandwich-type assay and, more importantly, the detection of the DNA target taught by Henderson does not involve a three-complex system but a one-to-one hybridization (i.e., two-part) assay. *Id.*

Appellant argues further that Henderson teaches that a detection method using an AFM is sensitive enough to detect interaction between single molecules. App. Br. 10 (citing, e.g., Henderson col. 1, ll. 53–55). According to Appellant, if the AFM method is this sensitive, there would have been no motivation for one skilled in the art to use the sandwich-type three-part assay recited in the claims, because it is more cumbersome and requires more time and cost than a simple two-part assay. *Id.* at 11. Furthermore, Appellant asserts, if a skilled artisan would have been

motivated to obtain a greater sensitivity, such a person would have been motivated to use a higher amount of nucleotide hybridization between the target oligonucleotide and the probe oligonucleotide. *Id.*

Specifically, Appellant argues, in order to achieve a greater sensitivity, one skilled in the art would immobilize the target nucleotide on a solid substrate directly without using a "first probe nucleotide." In this manner, a longer length probe nucleotide on the AFM tip could be used to provide a stronger binding force measurement, and hence a greater sensitivity and selectivity. App. Br. 10. Consequently, Appellant argues, a person of ordinary skill in the art would not have been motivated to use a three-part assay for detecting oligonucleotides.

We are not persuaded by Appellant's argument. Contrary to Appellant's argument, Table 1 of Henderson expressly teaches, in addition to the protein/DNA interaction described by Appellant, DNA/DNA interactions. Table 1 of Henderson is reproduced below:

TABLE 1

Interaction Type	Molecular Pair
DNA/DNA	oligo d(T)/d(C), d(ACTG)n/e(CAGT)n
Protein/DNA	Anti-DNA/DNA
	Protein/DNA
	Gal4/Gal4 binding domain
Receptor/Ligand	NMDA Receptor/conatokin-G
Protein/Protein	antibody-antigen-antibody sandwich
	Anti-streptavidin/streptavidin

Table 1 lists representative examples of molecular pairs that can be used in the detection system of Henderson

Furthermore, Henderson teaches that: "The AFM is extraordinarily sensitive, being capable of detecting force interactions between individual molecules, chemical groups and even single quantized hydrogen bonds.

Specific examples include: avidin/biotin interactions, *DNA-DNA interactions*, antibody-antigen interactions, chemical group interactions, and individual hydrogen bonds." Henderson col. 1, ll. 53–59 (emphasis added, internal references omitted). Therefore, and contrary to Appellant's argument, Henderson teaches that its sandwich assay methods can be used to measure DNA-DNA interactions. Moreover, Henderson suggests an assay in which a test DNA sequence can be bound between first and second DNA hybridizing probes, in a manner similar to the antibody-antigen-antibody assay taught in the quoted passage *supra*.

In short, Henderson expressly teaches a sandwich-type assay, and also teaches that its methods can be used to measure DNA/DNA interactions.

Furthermore, we do not find Appellant's argument with respect to the alleged lack of motivation by a skilled artisan to use the technique taught by Henderson. Appellant argues that:

> [O]ne skilled in the art would immobilize the target nucleotide on a solid substrate directly without using a "first probe nucleotide." In this manner, a longer length probe nucleotide on the AFM tip could be used to provide a stronger binding force measurement, and hence a greater sensitivity and selectivity.

App. Br. 11. Appellant's argument seems to misapprehend the point of Henderson (and of Appellant's claims) which is to detect the presence of an analyte in a solution by first binding it to a probe bound to the substrate. Appellant provides no suggestion as to how the target molecule would be "immobilize[d] on a solid substrate directly," however, such immobilization is directly suggested by both Henderson and Appellant's claims as being performed by a sandwich assay, i.e., binding/hybridizing the test substance to a probe anchored to the substrate. Henderson teaches that the AFM

technique is suitably sensitive for measuring DNA interactions, such that the strength of the hydrogen bond interactions, as Appellant notes, would reflect the amount of hybridization. *See* Henderson col. 1, ll. 53–59; App. Br. 7–8. Indeed, the enhanced sensitivity of the AFM technique permits accurate measurement of DNA/DNA interactions based upon *less*, not more, hybridization between the second probe and the test sequence.

Finally, Appellant argues that Henderson teaches away from Appellant's claimed invention. We disagree. A reference may be said to "teach away" when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Appellant points to no teaching or suggestion of Henderson that would discourage or divert a skilled artisan from arriving at Appellant's claimed invention. To the contrary, and as we have explained, Henderson directly suggests that its method is of sufficient sensitivity such that it can be used to measure DNA-DNA interactions.

Consequently, we affirm the Examiner's rejection of the claims.

CONCLUSION

The Examiner's rejection of claims 23–34 and 42 under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
23–26, 29, 31–33, 42	103(a)	Henderson, Ashby, Hong, Leskela	23–26, 29, 31–33, 42	
23–25, 27–33, 42	103(a)	Henderson, Ashby, Hong, Dellinger	23–25, 27–33, 42	
34	103(a)	Henderson, Ashby, Hong, Leskela, Cai	34	
Overall Outcome			23–34, 42	