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Paper 130
Mailed: March 6, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.
Petitioner

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2013-00011
Patent 8,088,575 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. BACKGROUND

A. Introduction

Petitioner, Illumina, Inc. ("Illumina"), filed a petition on October 3, 2012, for *inter partes* review of claims 1-3 and 6 of U.S. Patent 8,088,575 B2 ("the '575 Patent") pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1 - 42.123. On March 12, 2013, the Board instituted *inter partes* review of claims 1-3 and 6 on four grounds of unpatentability (Paper 26, Decision on Petition ("Dec. Pet.")). Illumina requested rehearing on two of the grounds of unpatentability (Paper 29), which had been denied in the Decision on Petition. Upon reconsideration, the Board instituted *inter partes* review of one of these grounds of unpatentability as to claim 6 (Paper 44, Decision on Rehearing ("Dec. Reh'g")). This corresponded to one of the same grounds of unpatentability authorized for claims 1-3.

After institution of the *inter partes* review, Patent Owner, The Trustees of Columbia University in the City of New York ("Columbia"), filed a response under 37 C.F.R. § 42.120 to the decision instituting *inter partes* review (Paper 70, "PO Resp."). Columbia also filed a Motion to Amend Claims (Paper 56) and a Motion to Exclude Evidence (Paper 93). Illumina filed a reply to Columbia's response under 37 C.F.R. § 42.120 (Paper 76, "Pet'r" Reply) and a Motion to Exclude Evidence (Paper 90). An oral hearing was held on December 17, 2013 with both parties in attendance. (Record of Oral Hearing, Paper 126.)

Among the evidence cited in this proceeding are declarations by George L. Trainor, Ph.D. (Ex. 2033, Trainor Decl.) on behalf of Columbia, and by George Weinstock, Ph.D. (Ex. 1021, Weinstock Decl.) on behalf of Illumina. Dr. Trainor has a Ph.D in Organic Chemistry and experience in

DNA sequencing (Exhibit 2033, Trainor Decl. ¶¶ 3 and 6-8), qualifying him to testify on the prior art issues discussed in his declaration. Dr. Weinstock has a Ph.D. in Microbiology and experience in DNA sequencing, including as a director of large-scale genome centers (Ex. 1021, Weinstock Decl. ¶¶ 4, 6, 8, and 9), qualifying him to testify on the prior art issues discussed in his declaration.

The Board has jurisdiction under 35 U.S.C. § 6(c). This final written decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Illumina has shown by a preponderance of the evidence that claims 1-3 and 6 are unpatentable.

B. The '575 Patent

The '575 Patent issued January 3, 2012. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the '575 Patent involves sequencing DNA by incorporating a base-labeled nucleotide analogue into primer DNA strand, and then determining the identity of the incorporated analogue by detecting a label attached to the base of the nucleotide. A polymerase is used to incorporate the nucleotide analogue into the strand of DNA ('575 Patent, col. 3, ll. 2-3). The method is generally referred to as "sequencing DNA by synthesis" or "SBS" because the sequence of the DNA is determined by identifying the successive additions of labeled nucleotides to a strand of DNA as it is synthesized using a complimentary DNA strand as a template (*id.* at col. 2, ll. 9-13).

Columbia does not argue the novelty of the steps utilized in the claimed method of "determining the identity of a nucleotide analogue

incorporated into a nucleic acid primer extension strand," but rather focuses its arguments on the novelty and unobviousness of the nucleotide utilized in the sequencing method. Nucleotides, which are the building blocks of DNA, comprise a sugar (ribose or deoxyribose), phosphates attached to the 5'-position of the sugar, and a nitrogen base on the 1'-position of the sugar. During DNA synthesis, the 5'-position in the sugar of a new incoming nucleotide is linked by DNA polymerase to the 3'-OH group in the sugar of a preexisting nucleotide in the strand under synthesis. In order to identify the newly incorporated nucleotide, one approach described in the prior art is to attach a detectable label to the nucleotide at its 3'-OH group ('575 Patent, col. 2, ll. 35-39). For reference, the 3'-OH corresponds to 3'-position of the deoxyribose sugar of the nucleotide and serves as the site where a new nucleotide is added during DNA synthesis.

The approach described in the '575 Patent is to make nucleotide analogues by linking a unique label, such as fluorescent dye, through a cleavable linker to the nucleotide base or to an analogue of the nucleotide base and to use a small removable chemical moiety to cap the 3'-OH group of the deoxyribose to make it reversibly nonreactive (*id*. at col. 2, ll. 59-65). The reason the 3'-OH group is made reversibly nonreactive is to allow the sequencing reaction to be terminated after each nucleotide is added in order to determine its identity (*id.* at col. 3, ll. 1-4). According to the '575 Patent, the prior art teaches attaching the label to the 3'-OH group. The '575 Patent, in contrast, puts the label on the nucleotide base and the removable chemical moiety on the 3'-OH group. These latter features are at the center of the patentability challenges.

Claims 1-3 in this *inter partes* review involve a nucleotide analogue that comprises: 1) a base labeled with a unique label; and 2) a removable chemical moiety capping the 3'-OH group. Claim 6 further requires a base that is deaza-substituted. A deaza-substituted nucleotide is a nucleotide analogue that includes a deazabase as the nitrogen base (*id.* at col. 7, ll. 46-65). A deazabase is a nitrogen base in which one of the natural nitrogen atoms in the base ring is substituted with a carbon atom (*id.*). For example, in a 7-deazapurine, the natural 7-position nitrogen in the base ring is replaced with a carbon atom (*id.*).

In summarizing the state of the art in Columbia's Patent Owner Response, Columbia states that, "[d]uring the 1990s, despite some interest in base-labeled nucleotide analogues, efforts focused on including a label on the 3'OH group on the sugar in a nucleotide analogue and on the design and synthesis of new nucleotide analogues that could be incorporated by a polymerase into a primer extension strand." (Paper 70, PO Resp. 8). Columbia cites paragraphs 30-35 of Dr. Trainor's Declaration as evidence that "[r]esults were mixed and it was recognized that new nucleotide analogues were needed [for use in] BASS [sequencing by synthesis; also known as SBS] sequencing." (*Id.*)

As discussed in more detail below, Columbia's characterization of the prior art as having "some interest in base-labeled nucleotide analogues" understates the interest level shown in the prior art. Tsien[1] and Dower,[2]

[1] Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002 ("Tsien").
[2] William Dower et al., US 5,547,839 (August 20, 1996), Exhibit 1005 ("Dower").

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