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Paper 140
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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 IPR2012-00007
Patent 7,790,869 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 September 16, 2012 (Pet.), for *inter partes* review of claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 ("the '869 Patent") pursuant to 35 U.S.C. §§ 311-319. The owner of the '869 Patent is The Trustees of Columbia University in the City of New York ("Columbia"). On March 12, 2013, the Board instituted *inter partes* review as to claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 on four grounds of unpatentability (Paper 38, Decision on Petition ("Dec. Pet." 2)). In a subsequent Decision on Illumina's Request for Rehearing (Paper 40), the Board modified two of the grounds of unpatentability by substituting a different patent publication for one of the cited patent publications, where both publications had the same inventors and shared specifications and disclosures (Paper 54, Dec. Pet. Reh'g 18).

After institution of the *inter partes* review, Columbia filed a response under 37 C.F.R. § 42.120 to the decision instituting *inter partes* review (Paper 78, "PO Resp.). Columbia also filed a Motion to Amend Claims (Paper 79) and a Motion to Exclude Evidence (Paper 122). Illumina filed a reply to Columbia's response under 37 C.F.R. § 42.120 (Paper 83, Pet'r Reply and a Motion to Exclude Evidence (Paper 119 (redacted); Paper 100 (unredacted)). An oral hearing was held on December 17, 2013, with both parties in attendance. (Record of Oral Hearing, Paper 124.)

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 (Ex. 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 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of the '869 Patent are unpatentable.

B. The '869 Patent

The '869 Patent issued September 7, 2010. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the '869 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 ('869 Patent, col. 3, ll. 1-3). 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. 8-12).

All the claims at issue in this *inter partes* review are drawn to a nucleotide analogue, which comprises: 1) a base that is attached to a

detectable label through a cleavable linker; and 2) a cleavable chemical moiety capping the 3'-OH group. 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 ('869 Patent, col. 2, ll. 34-38). 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 '869 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 ('869 Patent, col. 2, ll. 58-66). 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. 2, l. 67 to col. 3, l. 3). According to the '869 Patent, the prior art teaches attaching the label to the 3'-OH group. The '869 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.

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 78, PO Resp. 9.) 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 Stemple III,[2] cited in this *inter partes* review, and Dower,[3] which is cited in related proceedings, describe SBS methods which use base-label nucleotides and nucleotides containing a removable chemical moiety at the 3'-OH position (Ex. 2033, Trainor Decl. ¶¶ 24 and 26-29). Columbia acknowledges that base-labeled nucleotides were described in the prior art (*id.* at 28). We understand it to be Columbia's position that because there is no single example in the cited prior art of a nucleotide with the base-label and removable 3'OH blocking group being used in a DNA sequencing reaction, the disclosure of such a nucleotide is somehow diminished and amounts only to "some interest." Columbia, however, has not identified disclosure in the prior art where a nucleotide analogue with a label on the base and removable

[1] Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002 ("Tsien").
[2] Derek Stemple et al., U.S. Patent 7,270,951 B1 (September 18, 2007), Exhibit 1008 ("Stemple III").
[3] William Dower et al., U.S. Pat. No. 5,547,839 (August 20, 1996), Exhibit 1005 ("Dower").

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