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Paper 92
Entered: July 25, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTELLIGENT BIO-SYSTEMS, INC.,
Petitioner,

v.

ILLUMINA CAMBRIDGE LIMITED,
Patent Owner.

Case IPR2013-00128
U.S. Patent 7,057,026 B2

Before LORA M. GREEN, RICHARD M. LEBOVITZ, and CHRISTOPHER L. CRUMBLEY, *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, Intelligent Bio-Systems, Inc. ("IBS"), filed a Petition (Paper 15, "Pet.") for *inter partes* review of claims 1-8 of U.S. Patent No. 7,057,026 B2 ("the '026 patent") pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1–42.123.

On July 29, 2013, *inter partes* review of claims 1-8 was instituted on five grounds of unpatentability. Decision on Petition ("Dec. Pet.") (Paper 23). After institution of the *inter partes* review, Patent Owner, Illumina Cambridge Limited ("Illumina"), did not file a response under 37 C.F.R. § 42.120 to the decision instituting *inter partes* review.

Illumina filed a Motion to Amend (Paper 61, "Mot. Amend") and a Motion to Exclude Evidence (Paper 70). IBS filed an opposition to Illumina's Motion to Amend (Paper 53) and its own Motion to Exclude Evidence (Paper 67). An oral hearing was held on April 23, 2014. Record of Oral Hearing (Paper 89).

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's Motion to Amend is GRANTED to the extent it requests to cancel claims 1-8; Illumina's Motion to Amend is DENIED to the extent that it requests entry of substitute claims 9-12.

B. The '026 Patent

The '026 patent issued on June 6, 2006. The named inventors are Colin Barnes, Shankar Balasubramanian, Xiaohai Liu, Harold Swerdlow, and John Milton. The '026 patent describes labeled nucleotides and

nucleosides used in "sequencing reactions, polynucleotide synthesis, nucleic acid amplification, nucleic acid hybridization assays, single nucleotide polymorphism studies, and other techniques using enzymes such as polymerases, reverse transcriptases, terminal transferases, or other DNA modifying enzymes." Ex. 1001, col. 2, ll. 10-14. A detectable label (such as a fluorophore) is attached to the base of the nucleotide via a cleavable linker group. *Id.* at col. 2, ll. 6-8. In DNA sequencing by synthesis ("SBS"), nucleotides are added sequentially to a newly synthesized DNA strand complementary to the template DNA in the double-stranded DNA. The detectable label enables the nucleotide to be detected when it is incorporated into the newly synthesized DNA strand. *Id.* at col. 2, ll. 56-64. Once the identity of the nucleotide is determined by detecting the label linked to the base, the detectable label is cleaved from the nucleotide by the cleavable linker. *Id.* at col. 2, ll. 60-64, col. 6, ll. 26-30. The 3′-OH of the sugar residue of the nucleotide contains a protecting group, which can be removed to expose the 3′-OH group for further addition of a nucleotide. *Id.* at col. 2, ll. 30-32, col. 8, ll. 8-15.

C. Related Proceedings

The '026 patent is asserted in the following copending district court case: *Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 1:12-cv-00376-GMS in the United States District Court for the District of Delaware. Pet. 1.

D. The Alleged Grounds of Unpatentability

Inter partes review was instituted on the following five grounds of unpatentability (Dec. Pet. 18):

1. Claims 1-6 under 35 U.S.C. § 102(b) as anticipated by Tsien.[1]

2. Claims 1-6 under 35 U.S.C. §§ 102(a) or 102(e) as anticipated by Ju.[2]

3. Claim 3 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober.[3]

4. Claims 7 and 8 under 35 U.S.C. § 103(a) as obvious in view of Tsien and CEQ.[4]

5. Claims 7 and 8 under 35 U.S.C. § 103(a) as obvious in view of Ju and CEQ.

II. CLAIMS 1-8

Illumina did not file a response to the Decision on Petition instituting *inter partes* review of claims 1-8. Instead, Illumina filed a non-contingent Motion to Amend. Paper 61. "During an inter partes review . . . the patent owner may file 1 motion to amend the patent in 1 or more of the following ways: (A) Cancel any challenged patent claim. (B) For each challenged claim, propose a reasonable number of substitute claims." 35 U.S.C. § 316(d)(1). In the Motion, Illumina requested cancellation of claims 1-8, which request was not contingent on the original claims being determined unpatentable, and proposed substitute claims 9-12 to replace the cancelled claims. Illumina stated that each of the grounds upon which the *inter partes*

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[1] Tsien, WO 91/06678 (published May 16, 1991). Ex. 1012.
[2] Ju, U.S. 6,664,079 B2 (published Dec. 16, 2003). Ex. 1008.
[3] Prober et al., "A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides." 238 SCIENCE 336 (Oct. 16, 1987). Ex. 1013.
[4] CEQ™ User's Guide, Beckman Coulter CEQ™ 2000 DNA Analysis System User's Guide (June 2000). Ex. 1006.

review was instituted "is rendered moot in light of Illumina's proposed substitute claims." Paper 61, 2. We shall GRANT Illumina's Motion to Amend to the extent it requests to cancel claims 1-8.

III. MOTION TO AMEND THE CLAIMS

In the Motion to Amend, Illumina proposed substitute claim 9 to replace claim 1. The claim, as annotated by Illumina to show the differences between original claim 1 and proposed substitute claim 9, is reproduced below:

> 9. A nucleotide triphosphate ~~or nucleoside~~ molecule, having a 7-deazapurine base that is linked to a detectable label via a cleavable linker, wherein the cleavable linker is attached to the 7-position of the 7-deazapurine base and wherein the cleavable linker contains a disulfide linkage, and wherein the nucleotide triphosphate molecule has a ribose or deoxyribose sugar moiety comprising a protecting group attached via the ~~2′ or~~ 3′ oxygen atom, and the disulfide linkage of the cleavable linker and the protecting group are cleavable under identical conditions.

Paper 61, 2.

Proposed substitute claim 9 requires a nucleotide having a 1) triphosphate group; 2) a deazapurine base; 3) a disulfide linkage as a cleavable linker; and 4) a protecting group on the 3′ oxygen. Original claim 3, now canceled, recited that the base of the nucleotide is a deazapurine as recited in proposed substitute claim 9. This limitation, therefore, had been considered in the Decision on Petition. None of the original claims, however, comprised the limitation that the cleavable linker "contains a disulfide linkage." The obviousness of using a disulfide linkage is the main issue to be decided in whether to grant the Motion to Amend.

Proposed substitute dependent claims 10 and 12 replace claims 5 and 8, respectively. Proposed substitute independent claim 11 replaces claim 7, and recites a nucleotide with the same features of claim 9.

Patent Owner bears the burden of proof to establish that it is entitled to the relief requested in the Motion to Amend. 37 C.F.R. § 42.20(c). Patent Owner, therefore, bears the burden of showing the patentability of the amended claims.

Patent Owner must show that the conditions for novelty and non-obviousness are met for the prior art available to one of ordinary skill in the art at the time the invention was filed, not just the prior art cited in the Petition. *See Idle Free Sys., Inc. v. Bergstrom, Inc.*, Case IPR 2012-00027, slip op. at 7 (PTAB June 11, 2013) (Paper 26). Also, a motion to amend "must include a claim listing, show the changes clearly, and set forth: (1) The support in the original disclosure of the patent for each claim that is added or amended." 37 C.F.R. § 42.121(b)(1).

IV. PATENTABILITY OF CLAIMS 9-12

A. Background

The '026 patent relates to labeled nucleotides. For illustrative purposes, an annotated generic nucleotide from Figure 1B of Stemple,[5] one of the prior art publications cited in this *inter partes* review, is reproduced below to show the nucleotide's main parts.

[5] Stemple, WO 00/53805 (published Sep. 14, 2000). Ex. 1002.

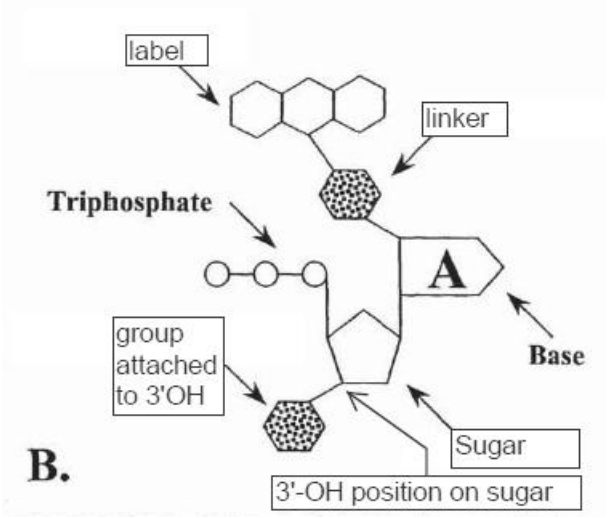


Figure 1B of Stemple shows a generic nucleotide's main parts, including a detectable label ("label"), a linker, and a chemical group attached to the 3′-OH position.

The '026 patent describes its invention as nucleotide molecule "linked to a detectable label via a cleavable linker group attached to the base." Ex. 1001, col. 2, ll. 6-8. The figure reproduced above shows a single ring-like structure, labeled "linker," which links a three-ringed structure, labeled "label," to the base. The '026 patent discloses that the sugar "can include a protecting group attached via the 2' or 3' oxygen atom. The protecting group can be removed to expose a 3′-OH." *Id.* at col. 2, ll. 30-33. The figure shows a protecting group attached to the 3′-OH of the sugar molecule.

Original claim 1 was drawn to a nucleotide or nucleoside with the following features:

1. "a base that is linked to a detectable label via a cleavable linker" (see "label," "linker," and "base" in Figure 1B of Stemple reproduced above);

2. "a ribose or deoxyribose sugar moiety comprising a protecting group attached via the 2′ or 3′ oxygen atom" (the figure shown above shows a protecting group attached to the oxygen of the 3′-OH group); and

3. "the cleavable linker and the protecting group are cleavable under identical conditions."

Proposed substitute claim 9 contains these features, but further recites that the linker comprises a disulfide linkage (two sulfur atoms bonded together) and that the nucleotide base is a deazapurine.

B. Claim Interpretation

Before a claim can be compared to the prior art, it must be interpreted. In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation consistent with the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under the broadest reasonable interpretation standard, claim terms are given their ordinary and customary meaning as they would be understood by one of ordinary skill in the art at the time of the invention. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

1. *deazapurine*

A deazapurine, as recited in proposed substitute claim 9, is interpreted to mean a nitrogen base in which one of the natural nitrogen atoms in the base ring is substituted with a carbon atom. Ex. 1008, col. 8, ll. 4-6.

2. *the cleavable linker and the protecting group are cleavable under identical conditions*

The proposed claim requires a "cleavable linker," which is used to attach the "detectable label" to the 7-position of the deazapurine base. The reason for having a cleavable linker at this position is explained as follows.

In sequencing by synthesis reactions ("SBS"), nucleotides are added sequentially, one at a time. Ex. 1001, col. 2, ll. 56-61. The "identity of each nucleotide incorporated is determined by detection of the label linked to the base, and subsequent removal of the label." *Id.* at col. 2, ll. 61-64. The base is removed by cleaving the disulfide linkage of the cleavable linker ("the disulfide linkage of the cleavable linker [is] . . . cleavable"). *Id.* at Claim 9. The claimed "cleavable linker" is, therefore, necessary to carry out SBS sequencing.

The 3′ oxygen, labeled as the "3′ OH of the sugar" in the figure reproduced above, is recited in proposed substitute claim 9 to comprise a "protecting group." The "protecting group" is described in the '026 patent as "intended to prevent nucleotide incorporation onto a nascent polynucleotide strand." Ex. 1001, col. 8, ll. 11-12. It can be removed by cleavage to allow sequential addition of a nucleotide during SBS sequencing. *Id.* at col. 8, ll. 12-14.

The claims do not specify the type of protecting group. The '026 patent teaches at column 8, lines 28-31, "[s]uitable protecting groups will be apparent to the skilled person, and can be formed from any suitable protecting group disclosed in Green and Wuts, supra. Some examples of such protecting groups are shown in FIG. 3."

Proposed substitute claim 9 recites that "the cleavable linker and the protecting group are cleavable under identical conditions." The '026 patent discloses that the "labile linker may consist of functionality cleavable under identical conditions to the block [the protecting group]. This will make the deprotection process [of the 3′-OH group] more efficient as only a single treatment will be required to cleave both the label and the block." Ex. 1001,

col. 8, ll. 35-44. Thus, "cleavable under the identical conditions," under the broadest reasonable interpretation standard, limits the structure of the protecting group to one which can be cleaved under the same conditions as a disulfide linkage, but does not require a specific structure, such as a disulfide linkage. *See* Paper 61, 6-7.

3. *cleavable linker contains a disulfide linkage*

The main limitation at issue in Illumina's Motion to Amend is the recitation in all the proposed substitute claims that a 7-deazapurine base is linked to a detectable label through a "cleavable linker [which] contains a disulfide linkage." A disulfide linkage is a bond between two sulfur atoms. Ex. 1001, Fig. 2.

C. Illumina's Burden to Show Nonobviousness

The issue in this *inter partes* review is the obviousness of using a cleavable disulfide linker to attach a label to the nucleotide base, where the linker and protecting group of the nucleotide are cleaved under identical conditions.

Because Illumina bears the burden of showing that it is entitled to have its Motion to Amend granted, it must show that one of ordinary skill in the art would not have considered the proposed substitute claims obvious in view of the prior art available before the filing date of the claimed invention. More specifically, the issue is whether it would have been nonobvious at the time of the invention to have attached a detectable label to a deazapurine base using a disulfide linkage, where the base is present in a nucleotide triphosphate having "a ribose or deoxyribose sugar moiety comprising a

protecting group attached via the 2′ or 3′ oxygen atom" and where "the disulfide linkage of the cleavable linker and the protecting group are cleavable under identical conditions." Proposed claim 9.

A patent claim is invalid for obviousness if "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103.

> [The] underlying factual considerations in an obviousness analysis include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations. Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results.

Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286, 1291 (Fed. Cir. 2013).

An important consideration is "whether a person of ordinary skill in the art would, at the relevant time, have had a 'reasonable expectation of success' in pursuing the possibility that turns out to succeed and is claimed." *Institute Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013).

D. Prior Art

Before turning to the specific arguments presented by both parties, we shall summarize some of the prior art of record that was known at the time the application resulting in the '026 patent was filed on August 23, 2002. This discussion is not meant to be exhaustive, but rather provides a brief description of what was known about modified nucleotides prior to the filing date of the '026 patent.

The claimed nucleotides are used in nucleic acid SBS, a process in which 3′-OH protected and detectably labeled nucleotides are added stepwise to a nucleic acid primer during sequencing. In that process, it was known to use a nucleotide labeled at its base with a detectable label in order to identify when the nucleotide is incorporated into the newly synthesized strand. Ex. 1012, p. 27, l. 33-p. 28, l. 2; Ex. 1014,[6] col. 18, l. 64–col. 19, l. 2. It also was known to attach a protecting group to the 3′-OH of the nucleotide. Ex. 1012, p. 9, l. 32-p. 10, l. 3. During DNA synthesis, nucleotides are added sequentially to the 3′-OH group of the nucleotide sugar. The 3′-OH group contains a removable protecting group so the labeled nucleotides can be added one at a time. After each addition, the label is detected and the 3′-OH group is deblocked and new nucleotide (with its own 3′-OH protecting group) is added. *Id.* at 13. In sum, it was not new to employ a nucleotide in sequencing which comprised a detectable label on the nucleotide base and a 3′-OH protecting group.

The prior art also had described attaching a label to the nucleotide base using a cleavable linker as recited in the proposed claims. Ex.1012, p. 28, ll. 20-23; Ex. 1008, Abstract, col. 2, ll. 50-53. Furthermore, as found in the Decision on Petition, Tsien described removing the detectable label and the protecting group simultaneously, as required by the proposed claims. Ex.1012, p. 28, ll. 5-8; Dec. Pet. 8.

The newly added limitation that the cleavable linker is a disulfide bond also is described in the prior art. As discussed in more detail below, Rabani[7] and Church[8] both describe attaching a detectable label to a

[6] Dower, W.J. & Fodor, S.P.A. U.S. 5,547,839, issued Aug. 20. 1996.
[7] Rabani, E. WO 96/27025 (published Sept. 6, 1996). Ex. 2015.

nucleotide base via a disulfide linkage, where the nucleotide is used in nucleic acid sequencing. An example is shown in Figure 5 of Church, reproduced below, which we have annotated to identify specific structures.

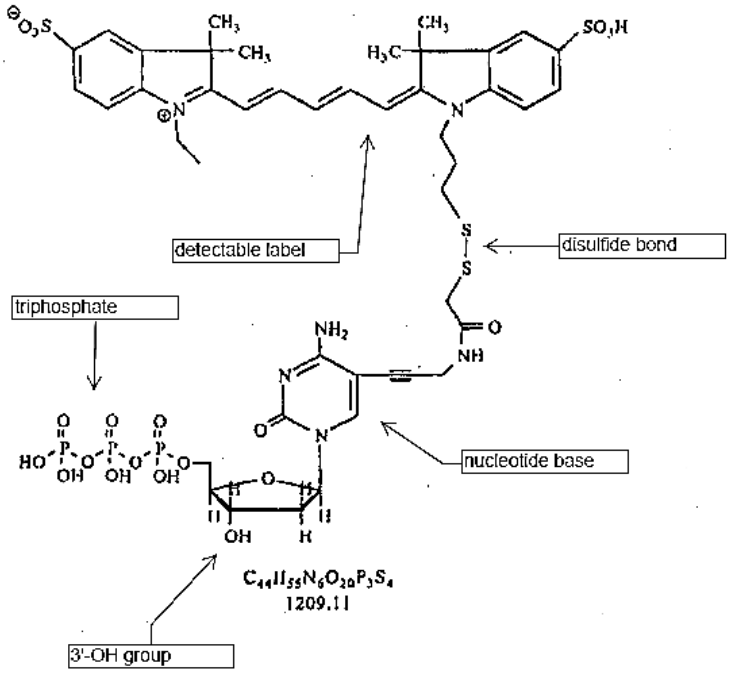
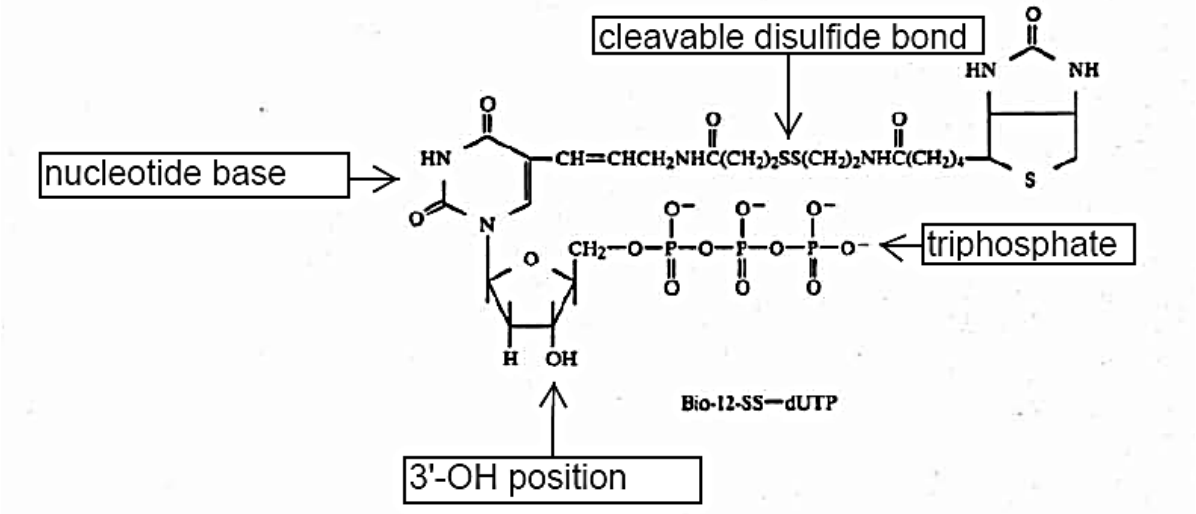


Figure 5 of Church is annotated to identify the specific structures of the nucleotide, including a detectable label, a triphosphate, and a disulfide bond. Ex. 1031, p. 17, ll. 10-11 ("Figure 5 is a schematic drawing of a disulfide-bonded cleavable nucleotide fluorophore complex."). The nucleotide, however, lacks the claimed protecting group on the 3′-OH.

In addition to Church, six additional publications[9] are cited in this *inter partes* review for their description of nucleotides comprising cleavable

[8] Church, G.M. WO 00/53812 (published Sept. 14, 2000). Ex. 1031.
[9] (1) Herman, US Patent No. 4,772, 691, issued Sep. 20, 1988. Ex. 2017.
(2) S.W. Ruby, et al., *Affinity Chromatography with Biotinylated RNAs,* Vol. 181, Methods in Enzymology, 97-121 (1990). Ex. 2016.
(3) Short, WO 99/49082 (published Sep. 30, 1999). Ex. 2018.

linkers with disulfide bonds. One of these publications, Herman, shows a nucleotide with disulfide bond attaching a biotin to a nucleotide base. Exhibit 2017. The orientation of the nucleotide reproduced below is flipped 180 degrees from Church's nucleotide, reproduced above.



Herman's Figure (col. 5) shows a nucleotide with a cleavable linker comprising a disulfide bond joining a biotin ("detectable label") to a nucleotide base. Ex. 2017, col. 7, ll. 24-27. The nucleotide lacks the protecting group on the 3′-OH as required in proposed claim 9.

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(4) Barbara A. Dawson, et al., *Affinity Isolation of Transcriptionally Active Murine Erythroleukemia Cell DNA Using a Cleavable Biotinylated Nucleotide Analog*, Vol. 264, No. 22, The Journal of Biological Chemistry, 12830-37 (1989). Ex. 1030.
(5) Barbara A. Dawson, et al., *Affinity Isolation of Active Murine Erythroleukemia Cell Chromatin: Uniform Distribution of Ubiquitinated Histone H2A Between Active and Inactive Fractions*, Vol. 46, Journal of Cellular Biochemistry, 166-173 (1991). Ex. 2039.
(6) Basil Rigas, et al., *Rapid plasmid library screening using RecA-coated biotinylated probes*, Vol. 83, Proc. Natl. Acad. Sci. USA, 9591-9595 (1986). Ex. 2040.

E. Reason to Use a Disulfide Bond on Nucleotides

In the Decision on Petition, *inter partes* review was authorized for claim 3 (reciting that the nucleotide base is a deazapurine) as anticipated under 35 U.S.C. § 102 in view of Tsien (Ground I) and Ju (Ground II); and as obvious under 35 U.S.C. § 103 in view of Tsien and Prober (Ground IV). Those publications, however, do not describe using a cleavable disulfide linker for attaching the detectable label to a base or the specific deazapurine base recited in the proposed substitute claims. A disulfide bond as a linker is described in the prior art (see pages 12-13 above), along with a reason to have used one.

Rabani

Rabani, in the section titled "Cleavable linkers," teaches that "[l]abeling moieties are favorably in communication with or coupled to nucleotides via a linker of sufficient length to ensure that the presence of said labeling moieties on said nucleotides will not interfere with the action of a polymerase enzyme on said nucleotides." Ex. 2015, p. 32, ll. 10-13. Rabani specifically mentions disulfide linkages as useful when a cleavable linker is desired:

> Linkages comprising disulfide bonds within their length have been developed to provide for cleavability[24]; reagents comprising such linkages are commercially available[25] and have been used to modify nucleotides[26] in a manner which may be conveniently reversed by treatment with mild reducing agents such as dithiothreitol.

Id. at p. 32, ll. 29-33. Footnotes 24 and 26 of the above quoted passage cite to Ruby, S.W. et al. (1990), Methods in Enzymology, 181:97, which is

Exhibit 2016. *Id.* at 49. Footnote 25 references "for example, from Pierce Chemical Co., [ ] of Rockford, IL., U.S.A." *Id.*

Rabani, therefore, would have given a skilled worker reason to have used a cleavable linker with a disulfide bond to ensure that the labeling moieties on the nucleotides will not interfere with the action of a polymerase enzyme during the synthesis reaction.

Church

IBS cited Church as evidence of the obviousness of using a disulfide linker in a sequencing reaction. Paper 53, 2. Church provides another example of the use of a disulfide linker to attach a label to base of a nucleotide, further establishing its conventionality at the time of the invention. Ex. 1031, 17:10-18, 68:12-21. Church describes a working example in which a label was attached to a nucleotide base using a disulfide linker and then cleaving it off with DTT. *Id.* at 86:6-30.

Dr. Bruce P. Branchaud,[10] a declarant for IBS, testified:

> Church teaches a SBS [sequencing by synthesis] method termed fluorescent in situ sequencing extension quantification (FISSEQ). In one embodiment, Church teaches the sequential addition of fluorescently labeled nucleotides in which the label

[10] To support its obviousness challenge, IBS provided two Declarations by Bruce P. Branchaud, Ph.D., Ex. 1015 and Ex. 1035, respectively. Dr. Branchaud is Professor Emeritus in the Department of Chemistry at the University of Oregon. Ex. 1015 ¶ 5. He has a Ph.D. in Organic Chemistry from Harvard University, and has held positions in industry, including as an internal consultant and advisor for DNA sequencing projects. Ex. 1015 ¶¶ 5, 7, 12-15. Dr. Branchaud has the requisite familiarity with DNA sequencing to qualify as one of ordinary skill in the art at the time of the invention. Consequently, we conclude that Dr. Branchaud is qualified to testify on the matters addressed in his Declaration.

> is attached to the base via a "cleavable linkage". Church at p. 67, l. 30 to p. 68, l. 11.

Ex. 1035 ¶ 13.

F. 90% Cleavage Efficiency of the Detectable Label Is Not Required

Illumina contends sequencing by synthesis processes require that the disulfide linker joined to the detectable label be cleaved with 90% efficiency, because of the iterative nature of the process. Paper 61, 11-12. This reasoning is based on Rabani. *Id*. Given Rabani's disclosure, as discussed below, Illumina argues that a person of ordinary skill in the art would not have used a disulfide bond because greater than 90% efficiency in the cleavage reaction could not be achieved.

Rabani disclosed published results "suggest[ing] that the rate of chemical removal of 3'-hydroxy protecting groups (less than 90% removal after 10 minutes of treatment with 0.1M NaOH) will be unacceptably low for such an inherently serial sequencing scheme." Ex. 2015, 3:5-8 (emphasis added). Illumina contends that since Rabani teaches that less than 90% removal of the protecting group from the 3′-OH "will be unacceptably low for . . . [a] serial sequencing scheme," and since "the disulfide linkage of the cleavable linker and the protecting group are cleavable under identical conditions," the disulfide linker joining the detectable label to the nucleotide base must also achieve 90% or more cleavage. Paper 61, 13; Ex. 2015, 3:5-8. Illumina provided evidence that the prior art teaches less than 90% efficiency in cleaving a disulfide linkage at 3′-OH protecting group, leading Illumina to reason "the expectation of unacceptably low 3′-OH protecting group cleavage efficiency when using 'identical conditions' would not lead a skilled artisan to believe that one successfully could use 3′-OH protecting

groups that could be cleaved under identical conditions as a disulfide linkage during SBS [sequencing by synthesis]." Paper 61, 13.

In other words, Illumina's argument is that since 90% efficiency in cleaving the disulfide linkage at the 3′-OH group could not be achieved, there would not have been a reason to use a disulfide linkage to attach the detectable label to the base, because the detectable label must cleaved under identical conditions to the 3′-OH protecting group. Cleavage of the disulfide linkage at the 3′-OH group requires 90% efficiency Illumina argues 90% cleavage efficiency must be achieved at the disulfide bond of the detectable label, as well.

Illumina's argument is flawed. Rabani's disclosure is directed to cleavage of the protecting groups, not the detectable label as claimed. Illumina's arguments are based on the logic that if no better than 90% cleavage of the disulfide bond on the protecting group can be achieved, the skilled worker would not have used it as a cleavable linker for attaching a detectable label to a nucleotide in DNA sequencing, because the proposed substitute claims require it be cleaved under identical conditions to the 3′-OH group, which requires 90% efficiency.

The proposed substitute claims do not require the linkage between the 3′-OH and protecting group to comprise a disulfide bond. We, therefore, discern no reason to apply Rabani's protecting group cleavage efficiency requirement to the disulfide linkage of the proposed substitute claims.

Significantly, Dr. Floyd Romesberg,[11] a declarant for Illumina, conceded that he did not choose a 90% efficiency requirement because of

[11] A declaration by Floyd Romesberg, Ph.D. was submitted by Illumina in support of its Motion to Amend. Ex. 2009. Dr. Romesberg is a professor in

Rabani, but rather because "it was a round number slightly above the values reported by Ruby and Herman." Ex. 1033, 198, ll.11-18.

Illumina has not met its burden to show that cleavage of the disulfide bond, attaching the detectable label to the base, with less than 90% efficiency would be unacceptable for sequencing.

G. Cleavage Efficiency of the Disulfide Bond

Even were we persuaded by Illumina's argument that 90% cleavage of the 3′-OH protecting group is necessary for sequencing, Illumina did not provide adequate evidence that the skilled worker would have been unable to choose conditions and linkages that would achieve 90% cleavage of the 3′-OH group under the same conditions required for cleavage of the label, e.g., using a reducing agent (Ex. 1001, col. 6, ll. 31-35).

The '026 patent suggests that choosing cleavage conditions for the 3′-OH group were conventional to one of ordinary skill in the art:

> Suitable protecting groups will be apparent to the skilled person, and can be formed from any suitable protecting group disclosed in Green and Wuts, supra. Some examples of such protecting groups are shown in FIG. 3. The protecting group should be removable (or modifiable) to produce a 3' OH group. The process used to obtain the 3' OH group can be any suitable chemical or enzymic reaction.

Ex. 1001, col. 8, ll. 28-34.

Dr. Branchaud testified that "even if one of ordinary skill in the art considered the cleavage efficiency of *Ruby* . . . in deciding whether to use

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the Department of Chemistry at The Scripps Research Institute, where he has been a faculty member since 1998. Ex. 2009 ¶ 2. Dr. Romesberg testified that he is an "expert in the field of nucleotide analogue molecules." *Id*. at ¶ 16. Dr. Romesberg's deposition is Exhibit 1033.

such a linker for SBS, one of ordinary skill in the art would know that such cleavage efficiency could be improved by routine experimentation and thus would not be dissuaded from using such a linker." Ex. 1035 ¶ 37. As discussed below, this conclusion is supported by the prior art of record.

Ruby

Ruby is cited expressly by Rabani for its teaching of a disulfide bond that is cleavable with a reducing agent, such as dithiothreitol ("DTT"), and describes attaching a biotin molecule attached to a nucleotide base of a RNA "via a linker containing a disulfide bond." Ex. 2016, 98. The RNA is bound to a column containing avidin, based on the affinity of the biotin for the avidin. *Id.* at 98-99 (Fig. 1). The RNA is "eluted [from the column] by adding dithiothreitol (DTT) to reduce the disulfide bonds linking biotin to the anchor RNA." *Id.* at 98; Ex. 1035 ¶ 31. Relying on testimony by Dr. Romesberg, Illumina states that "Ruby reports that disulfide linkages are cleaved with only ~86% efficiency after more than 100 minutes, which is significantly less than 90% efficient." Paper 61, 12 (citing Ex. 2016, 117-18; Ex. 2009 ¶ 54). The "~86% efficiency" comes from Figure 4 of Ruby, a graph of % RNA eluted using DTT under different conditions. Ex. 2016, 117. Dr. Branchaud did not dispute that Ruby recovered "about 86% of the RNA." Ex. 1035, ¶ 31.

Dr. Romesberg testified that, "[s]ince Ruby's cleavage efficiency under disulfide cleavage conditions is less than 90%, Ruby does not provide an expectation that disulfide cleavage conditions would cleave a 3′-OH protecting group with greater than 90% efficiency." Ex. 2008 ¶ 55.

In response, Dr. Branchaud testified that "even if one of ordinary skill in the art considered the cleavage efficiency of *Ruby* . . . in deciding whether to use such a linker for SBS, one of ordinary skill in the art would know that such cleavage efficiency could be improved by routine experimentation and thus, would not be dissuaded from using such a linker." Ex. 1035 ¶ 37.

Dr. Branchaud's testimony is supported factually. Ruby teaches "[e]lution by reduction of the disulfide bonds on the biotinylated anchor RNA depends on the pH of the buffer, the DTT concentration, and the time of incubation in DTT (Fig. 4) in addition to the type of avidin binding." Ex. 2016, 117-118. Ruby describes manipulating the conditions to alter the elution profile: "By increasing the pH and DTT concentration of the elution buffer slightly, one can effectively elute the RNA during longer incubation times." *Id.* at 118. Thus, Ruby expressly teaches conditions that modify cleavage of the disulfide bond, and that cleavage of the bond can be manipulated by adjusting these conditions. In view of this teaching, one of ordinary skill in the art reasonably would have believed that disulfide bond cleavage could be modified to achieve the desired amount of cleavage.

Dr. Romesberg testified that the 86% value of Ruby could not be exceeded, but did not provide sufficient factual evidence to support this testimony. It is true that Ruby describes an experiment in which, apparently, a maximum of 86% cleavage was obtained, but Ruby did not characterize it as a limit. As Dr. Branchaud testified, it was not critical for Ruby to achieve higher efficiency, so it was not evident why Ruby would have done experimentation to achieve even higher cleavage of the 86% value shown in Figure 4. Ex. 1035 ¶ 37.

Herman

Illumina also cited Herman as evidence that 90% cleavage of a disulfide linkage could not be achieved. Paper 63, 12-13. Herman describes a similar system to Ruby, where RNA is immobilized to a column using a biotin-avidin interaction. Ex. 2017, Abstract, col. 3, ll. 20-25. Herman describes using a biotin attached to a nucleotide base through linker comprising a disulfide bond, as required by the proposed substitute claims. *Id*. at col. 7, ll. 24-34. The disulfide S-S bond is cleaved with a reducing agent, such as DTT or 2-mercaptoethanol. *Id.* at col. 7, l. 47-48; col. 10, ll. 3-19. Herman describes the results of one experiment:

> Bio-SS-DNA with buffer containing 50 mM dithiothreitol resulted in the recovery of a total of 87% of the DNA from the affinity column. Only 7.3% of the 32^{P}-labeled Bio-SS-DNA remained bound to the resin.

Id. at col. 11, ll. 14-17.

Dr. Romesberg makes the same conclusions for Herman that he did for Ruby. That is, since Herman's cleavage was less than 90%, "Herman does not provide an expectation that disulfide cleavage conditions would cleave a 3′-OH protecting group with greater than 90% efficiency." Ex. 2009 ¶ 58. IBS challenged the conclusion that one of ordinary skill in the art reading Herman would have determined the cleavage efficiency to be 87%, providing testimony by Dr. Branchaud that the real efficiency value was above 90% when calculated properly. Ex. 1035 ¶ 36. Dr. Romesberg acknowledged that Herman's values did not "add up," but he testified that there were several possible explanations, of which Dr. Branchaud's was only one. Ex. 2012 (Romesberg Tr.), 193:19–194:13. We are not persuaded,

therefore, that one of ordinary skill in the art would have understood Herman to describe disulfide bond cleavage efficiency above 90%.

The parties cited two additional publications, both co-authored with the same Timothy M. Herman who is listed as inventor of Herman, U.S. Patent No. 4,772, 691: Dawson (1989) (Ex. 1030) (see supra fn. 9), cited by IBS, and Dawson (1991) (Ex. 2039) (see supra fn. 9), cited by Illumina. Dawson (1989) was cited by IBS for its statement in the abstract that "[c]leavage of the disulfide bond in the linker arm of the biotinylated nucleotide resulted in elution of virtually all of the affinity isolated sequences." Ex. 1035 ¶ 37. Dawson (1991) was identified by Illumina for its disclosure that "[r]eduction of the disulfide bond in the biotinylated nucleotide eluted approximately one-half of the affinity isolated chromatin." Ex. 2039, 166.

In other words, the "Herman" publications report varying degrees of cleavage: from "virtually all" in Dawson (1989) (Ex. 1030), to 87% in Herman (Ex. 2017), to approximately 50% in Dawson (1991) (Ex. 2039). It is evident, consistent with Ruby, that the conditions can be routinely varied to achieve a desired level of disulfide bond cleavage.

Moreover, as stated by Dr. Branchaud:

> While it is desirable to achieve a high elution percentage by achieving a high cleavage efficiency of the disulfide linker, unlike SBS, it is not crucial that such elution percentage be greater than 90%. One of ordinary skill in the art would be aware that Ruby and Herman were not necessarily motivated to achieve a high elution percentage and thus a high cleavage efficiency (e.g., greater than 90%). Thus, one of ordinary skill in the art would not be dissuaded from using a disulfide linkage in a modified nucleotide by the cleavage efficiencies shown in Ruby and Herman.

Id. ¶ 35.

In an attempt to rebut this testimony, Illumina cites a 1986 publication by a different group which stated: "Release of the nick-translated probe-plasmid complex from avidin by reduction of the disulfide bond of Bio-19-SS-dUTP gave variable results and was not pursued rigorously." Ex. 2040, 9594. In the ensuing years, however, the Herman group (Exs. 1030, 2017, & 2039) did pursue it and showed that higher cleavage rates could be achieved. Exhibits 1030 & 2017.

Church

Church does not disclose the cleavage efficiency, but shows the results of the experiment in Figure 6. Illumina and IBS dispute the amount of cleavage shown in Figure 6. Because the quality of Figure 6 is so poor, however, the extent of cleavage cannot be determined reliably. A later-filed version of Figure 6 was provided by Illumina to support their claim that cleavage was incomplete, but this Figure was not available until after the August 23, 2002 filing date of the '026 patent. Ex. 2035 (showing that the Figure was not available until October 31, 2002). The later-filed Figure, therefore, does not establish how one of ordinary skill in the art would have interpreted the results of Church at the time the '026 patent was filed. We, therefore, give original filed Figure 6 no weight. Nonetheless, Church suggested disulfide linkers in a sequencing reaction, and carried out an example to show their utility (Ex. 1031, 85-87), providing a reason to have used them in sequencing and a reasonable expectation of success.

Summary

The record contains numerous publications that utilize a disulfide bond linker to join a label to a nucleotide base. Rabani and Church used the linker in the context of DNA sequencing, the primary use for the claimed nucleotides described by Illumina. Ruby, Herman, Dawson (1989), Dawson (1991), Short (referenced in footnote 9), and Rigas, each had used disulfide linkers to attach a label to a base, but not for sequencing purposes. While the prior art reported variability in the disulfide cleavage rates, Illumina has not established by a preponderance of the evidence that efficiency yields above 90% could not be achieved. In particular, Ruby and other publications had no reason to go above whatever cleavage rate was achieved, because it was not critical to their experiments. Herman, in at least one case, described "virtually all" the bond was cleaved. Ex. 1030. Thus, even if 90% efficiency were necessary for a reasonable expectation of success, the ordinary artisan would have expected that such cleavage efficiency of the disulfide bond could be achieved.

Finally, Illumina has not met its burden to show that identical conditions could not be selected in which the disulfide linkage of the cleavable linker is cleavable with less than 90% efficiency and the protecting group is cleavable with greater than 90% efficiency as required by the proposed substitute claims.

H. Objective Evidence of Nonobviousness

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any

relevant secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007); *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute independent evidence of nonobviousness . . . [and] enable [] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks and citations omitted). "This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (internal citations omitted).

In the Motion to Amend, as objective evidence of nonobviousness, Illumina provided a Declaration by Mr. Eric Vermaas, Illumina's Director of Consumables Product Development, describing sequencing experiments utilizing a nucleotide within the scope of proposed substitute claim 9. Ex. 2028 ¶ 4. The sequencing experiments were performed under Mr. Vermaas's supervision while employed by Illumina. *Id*. at ¶ 5. The sequencing experiments used the four nucleotides dATP, dTTP, dGTP, and dCTP, only one of which – dATP – contained a disulfide base linking a fluorophore to the nucleotide base. *Id*. ¶ 6; Ex. 2009 ¶ 61. Each of these nucleotides also contained an azidomethyl group protecting the 3′-OH. Ex. 2009 ¶ 61.

Mr. Vermaas describes sequential sequencing reactions on PhiX Control DNA for over 150 cycles in which nucleotides were added one at a

time. Ex. 2028 ¶¶ 13-17; Ex. 2009 ¶ 63. After each scan for the fluorophore incorporated, a solution comprising 2 mM tris(hydroxymethyl)-phosphine was added. Ex. 2009 ¶ 64. "The 2 mM tris(hydroxymethyl)phosphine reacts with and cleaves the disulfide linkage of the A [adenine of the dATP] nucleobase," but does not cleave the detectable groups on the other nucleotides. *Id*. According to Dr. Romesberg, "[b]ased on the results presented in the Vermaas declaration, a person of skill in the art would recognize that the yield for cleavage of the disulfide linkage was essentially 100%." *Id*. ¶ 74. Dr. Romesberg concluded:

> Therefore, the disulfide cleavage yield achieved by Illumina was essentially 100%. This is a significant and unexpected improvement over the disulfide cleavages of Ruby (~86%) and Herman (87%). Accordingly, Illumina's proposed claims are nonobvious over the prior art for at least this reason.

Id.

To establish unexpected results, the claimed subject matter must be compared with the closest prior art. *In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991). Illumina does not state what references are the closest prior art to the claims. Dr. Romesberg, however, in his declaration, compared the cleavage efficiency reported by Mr. Vermaas with Ruby and Herman. Ex. 2009 ¶ 74.

There are at least two differences between the experiments described in Ruby and Herman, and the experiment described by Mr. Vermaas.

First, while both Ruby and Herman used a nucleotide with a cleavable disulfide bond as did Mr. Vermaas, the references do not use the nucleotide in a sequencing reaction as it has been used in the experiment described by Mr. Vermaas. Ruby involved RNA binding to a column and using the

disulfide linkage to release the bound RNA. Ex. 2016, 98-99. Herman used a system similar to Ruby. Ex. 2017, Abstract, col. 3.

Secondly, the cleavage agents are different. The cleavage agent used in Ruby is DTT (Ex. 2016, 10, "Elution buffer" A and B) and in Herman, the cleavage agent is described as "a reducing agent such as DTT" (Ex. 2017, col. 7, ll. 47-48) with DTT being used in its example (*id*. at col. 10, ll. 47-54, col. 11, ll. 11-22; col. 12, ll. 3-8). Mr. Vermaas describes an experiment that utilized another cleavage agent, 2 mM tris- (hydroxymethyl)phosphine. Ex. 2028 ¶ 10. Illumina did not offer an explanation as to why the phosphine compound was used instead of DTT as used by both Ruby and Herman. Indeed, Church used DTT in a DNA sequencing reaction, similar to the sequencing carried out in the Vermaas experiments, providing an additional reason to have used DTT in Dr. Varmaas's comparison to the prior art. Ex. 1031, Fig. 5; 68, ll. 12-13; 86, ll. 20-23.

There is no testimony that the stated results were due to the claimed nucleotide rather than the reducing agent. Dr. Romesberg testified: "Therefore, the disulfide cleavage yield achieved by Illumina was essentially 100%. This is a significant and unexpected improvement over the disulfide cleavages of Ruby (~86%) and Herman (87%)." Ex. 2009 ¶ 74.

Dr. Romesberg refers to the "disulfide cleavage yield" as being unexpected, but he did not testify that this yield was attributable to the claimed nucleotide configuration, rather than the reducing agent which performs the disulfide bond cleavage.

Illumina has not distinguished the Vermaas results from the prior art by showing that the nucleotide is responsible for the disulfide yield, rather than it being a property of the disulfide bond and the yield being "the mere

recognition" of the bond's "latent properties," which "does not render nonobvious an otherwise known invention." *Baxter*, 952 F.2d at 392; *In re Geisler*, 116 F.3d 1465, 1468 (Fed. Cir. 1997). Absent such evidence, Illumina has not shown that the claimed subject matter possesses "unexpected results relative to the prior art." *Galderma Labs., LP v. Tolmar, Inc*., 737 F3d 731, 738 (Fed. Cir, 2013).

I. Summary

After considering all the evidence as a whole, we conclude that Illumina has not met its burden in showing that the proposed substitute claims are patentable over the prior art considered in this Decision. The Motion to Amend is DENIED to the extent that it requests entry of substitute claims 9-12.

V. MOTIONS TO EXCLUDE EVIDENCE

Both Illumina (Paper 70) and IBS (Paper 67) filed Motions to Exclude Evidence. Illumina's motion is dismissed as moot. IBS's motion is denied in part and dismissed in part as moot.

Illumina's Motion

Illumina requests that Figure 6 from Ex. 1031 (Church), all characterizations of Figure 6 from Ex. 1031, and all arguments based on it be excluded as evidence from this *inter partes* review. Illumina argues that the Figure should be excluded "because it includes poor quality black and white reproductions of images that do not accurately reflect the original underlying data." Paper 70, 1. We agreed with Illumina that the figure of Church is of poor quality and gave it no weight. We, therefore, did not rely

on Figure 6 of Church in reaching our decision. Accordingly, Illumina's motion is dismissed as moot.

IBS's Motion

IBS requests that Illumina's Exhibits 2029, 2030, 2032, 2033, 2035, 2036, and 2039-2042 be excluded as evidence from this *inter partes* review. As we did not rely on Exhibits 2029, 2030, 2032, 2033, and 2042, we dismiss this part of the motion as moot.

Exhibits 2035 and 2036 relate to Figure 6 of Church (Ex. 1031). We did not rely on Figure 6 of Church because it is of such poor quality that the amount disulfide cleavage cannot be determined reliably. To remedy this deficiency, Illumina sought to introduce a substitute Figure 6 from another patent publication by Church. Ex. 2035, 2036. Illumina did not establish that this substitute figure was available prior to the filing date of the '026 patent, however. We, therefore, did not consider it. Consequently, we dismiss this part of the motion as moot.

Exhibits 2039 and 2040 were provided by Illumina as further evidence of the efficacy of disulfide bond cleavage. Paper 64, 3. IBS argues that these Exhibits are not relevant and "without foundation . . . and misleading," because they discuss elution percentages, not cleavage efficiency. Paper 67, 8. We disagree. The Exhibits describe cleavage of a disulfide bond in a nucleotide, the same chemical reaction that is at issue in this *inter partes* review, making them reasonably relevant to the obviousness determination. Nor has IBS explained sufficiently why the documents lack foundation. As to the statement that the Exhibits are "misleading," this argument appears to

go to the weight of the Exhibits, rather than their admissibility. Consequently, we deny IBS's Motion to Exclude Exhibits 2039 and 2040.

VI. ORDER

In consideration of the foregoing, it is

ORDERED that Illumina's Motion to Amend is *denied in part*, to the extent it seeks to add substitute claims 9-12, and *granted in part*, to the extent it seeks to cancel claims 1-8;

FURTHER ORDERED that Illumina's motion to exclude evidence is *dismissed* as moot; and

FURTHER ORDERED that IBS's motion to exclude evidence is *denied in part* with respect to Exhibits 2039 and 2040 and *dismissed in part* as moot with respect to Exhibits 2029, 2030, 2032, 2033, 2035, 2036, and 2042.

IPR2013-00128
Patent 7,057,026 B2

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