NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK,
Appellant

v.

ILLUMINA, INC.,
Appellee

2014-1547

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2012-00006.

TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK,
Appellant

v.

ILLUMINA, INC.,
Appellee

2014-1548

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2012-00007.

TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK,
Appellant

v.

ILLUMINA, INC.,
Appellee

2014-1550

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2013-00011.

Decided: July 17, 2015

PAUL REINHERZ WOLFSON, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for appellant. Also represented by MATTHEW GUARNIERI; DONALD J. CURRY, ROBERT SETH SCHWARTZ, ANTHONY M. ZUPCIC, Fitzpatrick, Cella, Harper & Scinto, New York, NY; JOHN P. WHITE, Cooper & Dunham, LLP, New York, NY.

EDWARD R. REINES, Weil, Gotshal & Manges LLP, Redwood Shores, CA, argued for appellee. Also represented by DEREK C. WALTER, MICHELE GAUGER, MARION MCLANE READ, Redwood Shores, CA; AUDREY LYNN MANESS, Houston, TX.

Before PROST, *Chief Judge*, SCHALL and WALLACH, *Circuit Judges*.

WALLACH, *Circuit Judge*.

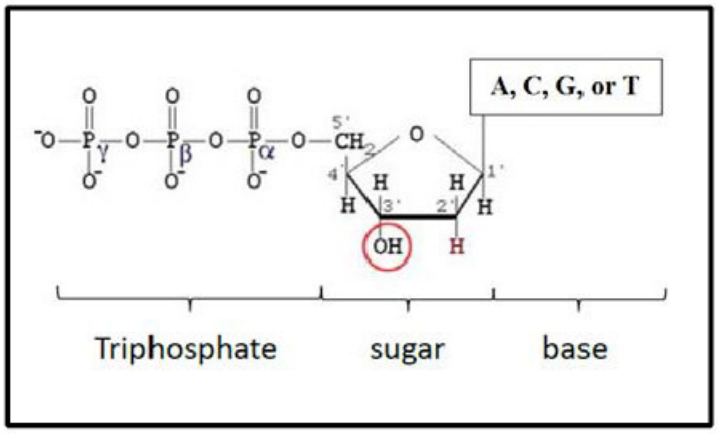
This opinion addresses companion appeals from the inter partes reviews of three patents before the Patent Trial and Appeal Board ("PTAB") of the United States Patent and Trademark Office, with Illumina, Inc. ("Illumina"), as petitioner and the Trustees of Columbia University in the City of New York ("Columbia University") as patent owner. The patents are generally directed to sequencing (i.e., determining the nucleotide sequence of) deoxyribonucleic acid ("DNA"), and include U.S. Patent Nos. 7,713,698 (the "'698 patent") (Appeal No. 2014-1547), 8,088,575 (the "'575 patent") (Appeal No. 2014-1548), and 7,790,869 (the "'869 patent") (Appeal No. 2014-1550). The PTAB found all challenged claims anticipated or obvious over the prior art. For the reasons set forth below, this court affirms.

BACKGROUND

I. The Science of DNA as It Relates to These Appeals

DNA is a double-stranded molecule that encodes the genetic information of living organisms. Each strand consists of a series of chemical structures called nucleotides, the particular order of which determines the heritable characteristics of living organisms. DNA sequencing is useful in a variety of fields, especially medicine, where it can help researchers uncover the genetic bases of diseases and in turn design targeted therapies.

Each nucleotide within the DNA molecule consists of three distinct parts, including a sugar, a base, and one or more phosphate groups:



Appellant's Br. 4.[1]

Four bases exist in naturally-occurring DNA, including adenine ("A"), guanine ("G"), cytosine ("C"), or thymine ("T"). A and G are known as "purines," while C and T are known as "pyrimidines." The sugar component of each nucleotide is comprised of five carbon atoms, conventionally numbered 1' ("one prime") through 5' ("five prime") and represented by the vertices of the pentagonal sugar structure, as illustrated. Nucleotides not incorporated into a DNA strand contain a hydroxyl group (oxygen bonded to hydrogen, or "OH") at the 3' position ("3'-OH group"). When nucleotides join together to form DNA, a single oxygen atom ("O") links the phosphate group with the sugar at the 3'-OH position:

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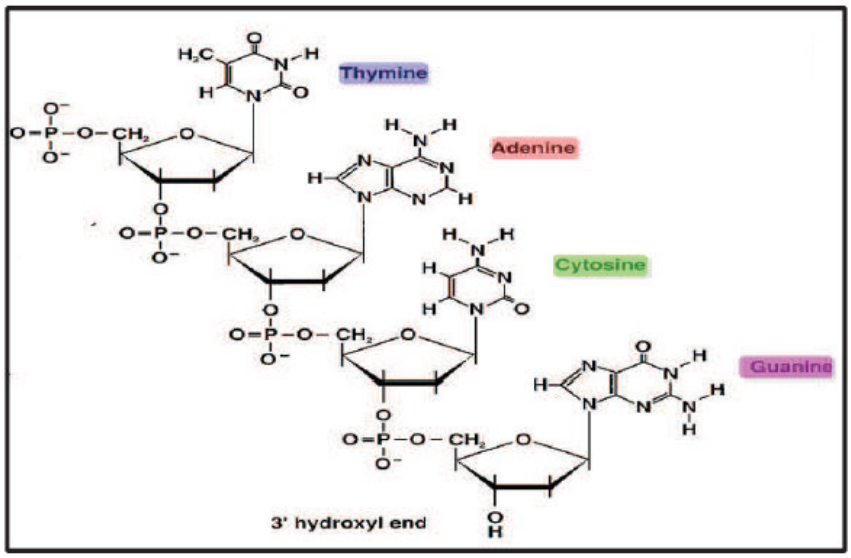
[1] All references to the briefs and Joint Appendix ("J.A.") are to Appeal No. 2014-1547 unless otherwise indicated.



Appellant's Br. 4.

In living organisms, DNA exists as a double-stranded helical structure held together by hydrogen bonds between "complementary" base pairs. A and T are complementary, and thus pair with each other, and G and C are complementary, and thus pair with each other. During DNA replication (such as during sequencing), the two strands are separated and a short chain of nucleotides known as a "primer" binds to a portion of the single-stranded DNA where copying will begin. Polymerase, an enzyme, causes the primer to be extended in a manner complementary to the chain being copied (i.e., matching A to T, and G to C). Important to the present matter, the phosphate group of each new nucleotide added to the lengthening DNA strand bonds to the 3'-OH group of the last nucleotide already in the strand.

In the 1970s, British biochemist Frederick Sanger and Alan Coulson invented a sequencing method that relies on modified nucleotides called dideoxynucleotides ("ddNTPs"), which have a hydrogen atom ("H") rather

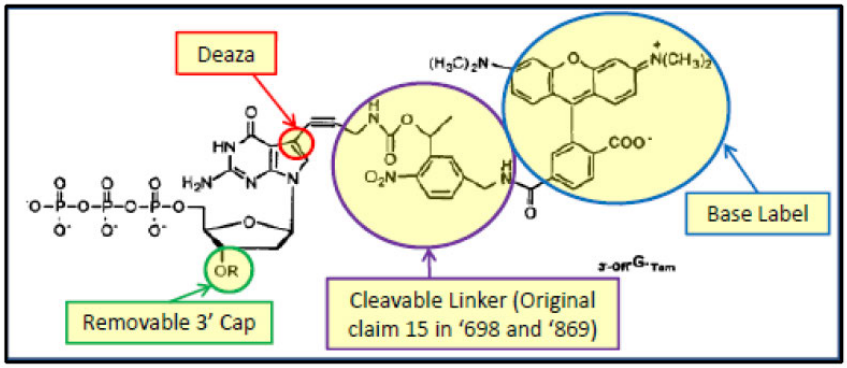
than OH at the 3' position. *See* Frederick Sanger et al., *DNA Sequencing with Chain-Termination Inhibitors*, 74 Proc. Nat'l Acad. Scis. 5463 (1977). In the original version of Sanger sequencing, the DNA template molecule is mixed with polymerase, a primer, isolated nucleotides ("dNTPs"), and a small amount of ddNTPs. When a ddNTP is randomly incorporated into the nucleotide chain, elongation of the new strand cannot continue because there is no 3'-OH group to which the next nucleotide would otherwise bond. This chain termination cannot be reversed, and the result is an array of fragments of different lengths, each containing a single ddNTP.

Each ddNTP, and therefore each fragment, contains a radioactive label (or, in subsequently developed versions of Sanger sequencing, a fluorescent label) that can be detected. After the fragments are sorted by size using a process called electrophoresis, the length information can be combined with the label information to determine the sequence of the DNA. One challenge of Sanger sequencing is ensuring the fluorescent labels remain attached to the base. It was discovered that increased stability can be achieved if the label is attached to a carbon atom at the 7' position of a purine base (A or G) rather than to a nitrogen atom, which normally occupies the 7' position. Purines in which the nitrogen atom at the 7' position has been replaced by a carbon atom are known as "deazapurines."

Due to the electrophoresis step, Sanger sequencing was too slow to efficiently sequence entire genomes, which may contain billions of nucleotides. A new type of process called sequencing by synthesis ("SBS") avoided the need for electrophoresis by placing *removable*, label-bearing "caps" at the 3'-OH group, which would block synthesis long enough to detect the label (and thereby identify the nucleotide) but would then be removed to allow synthesis to continue. Unfortunately, this type of SBS worked

poorly because the "caps" were located near the "active site" of the polymerase and thereby interfered with its operation.

According to Columbia University, Dr. Jingyue Ju and his colleagues avoided the problem caused by the bulky caps by placing an unlabeled removable cap on the 3'-OH group and attaching the label instead to a cleavable linker attached to the deazapurine base:



Appellant's Br. 10. Dr. Ju's method is the subject of the three patents at issue in this suit, each of which is titled "Massive Parallel Method for Decoding DNA and RNA."

II. Procedural Background

In March 2012, Columbia University sued Illumina for infringement of five DNA sequencing patents, including the three at issue in these appeals. Illumina petitioned for inter partes review of the '698, '869, and '575 patents in September and October 2012. The PTAB found most of the challenged claims of the three patents obvious over one or more of the following prior art references: (1) Roger Tsien et al., WO 91/06678 (May 16, 1991) ("Tsien"); (2) James Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 Science 336 (1987) ("Prober"); (3) Rabani et al., WO 96/27025 (Sept. 6, 1996)

("Rabani") (J.A. 3095–3154); (4) U.S. Patent No. 4,804,748 (issued Feb. 14, 1989) ("Seela") (J.A. 3155–58); (5) U.S. Patent No. 5,547,839 (issued Aug. 20, 1996) ("Dower"); (6) U.S. Patent No. 7,270,951 B1 (issued Sept. 18, 2007) ("Stemple"); (7) Takeshi Anazawa et al., WO 98/33939 (Aug. 6, 1998) ("Anazawa"). In addition, the PTAB found a number of claims anticipated by Tsien, Stemple, or Dower. Columbia University timely appealed. This court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A) (2012) and 35 U.S.C. § 141(c) (2012).

DISCUSSION

I. Standards of Review and the Legal Standard for Obviousness

This court reviews the PTAB's factual findings for substantial evidence and its legal conclusions de novo. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1251–52 (Fed. Cir. 2013). "A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding." *K/S Himpp v. Hear-Wear Techs., LLC*, 751 F.3d 1362, 1364 (Fed. Cir. 2014). "Substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000) (internal quotation marks and citation omitted).

A patent is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art [("PHOSITA")] to which said subject matter pertains." 35 U.S.C. § 103(a) (2006).[2] Whether an invention would

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[2] Section 103 has since been amended. *See* Leahy Smith America Invents Act, Pub. L. No. 112-29, § 3(c), 125

have been obvious at the time it was made is a question of law, which this court reviews de novo, based on underlying facts. *Gartside*, 203 F.3d at 1316. Underlying factual inquiries include: (1) "the scope and content of the prior art"; (2) "differences between the prior art and the claims at issue"; (3) "the level of ordinary skill in the pertinent art"; and (4) "secondary considerations [such] as commercial success, long felt but unsolved needs, [and] failure of others." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

II. Certain Challenged Claims Were Obvious at the Time of Invention

A. The PTAB's Failure to Resolve the Dispute Regarding the PHOSITA's Qualifications Was Not Error

Columbia University asserts the PTAB erred in "fail[ing] to resolve the parties' dispute regarding the qualifications of the [PHOSITA]." Appellant's Br. 36. It argues its expert, Dr. Trainor, possessed the qualifications of a PHOSITA while Illumina's expert, Dr. Weinstock, did not. According to Columbia University, a PHOSITA would be skilled in "*both* biology and synthetic nucleotide chemistry" and hold "a graduate degree in chemistry or chemical biology or a related discipline." *Id.* (internal quotation marks and citation omitted). Columbia University asserts that because Dr. Weinstock had not worked in the area of nucleotide synthesis, he was unqualified to opine on matters of synthetic nucleotide chemistry.

Stat. 284, 287–88 (2011) ("AIA"). However, because the applications that led to the '698, '869, and '575 patents were filed before March 16, 2013, the pre-AIA § 103(a) applies. *See* AIA, 125 Stat. at 293.

This court has explained that the failure to make explicit findings regarding the level of skill in the art does not necessarily constitute reversible error:

> While it is always preferable for the factfinder below to specify the level of skill it has found to apply to the invention at issue, the absence of specific findings on the level of skill in the art does not give rise to reversible error "where the prior art itself reflects an appropriate level and a need for testimony is not shown."

Okajima v. Bourdeau, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). However, where the fact finder has failed to make a finding or has made an incorrect finding with respect to the level of ordinary skill in the art in a manner that impacts the ultimate conclusion of obviousness, the failure or incorrect finding could constitute reversible error. *Custom Accessories, Inc. v. Jeffrey–Allan Indus., Inc.*, 807 F.2d 955, 963 (Fed. Cir. 1986).

Here, Illumina's expert Dr. Weinstock asserted the PHOSITA need only have been skilled in molecular biology or associated sciences, but made no mention of chemistry. Columbia University proposes the level of ordinary skill should have additionally included skill in chemistry. *See* Appellant's Br. 36. That is, Columbia University argues the PTAB should have explicitly stated a PHOSITA would have possessed a higher level of skill than that advocated by Illumina. In general, the higher the PHOSITA's skill level, the more likely the PHOSITA would find an invention obvious. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1366 (Fed. Cir. 2012) ("[I]t is generally easier to establish obviousness under a higher level of ordinary skill in the art."). Because the PTAB found the claims would have been obvious to a PHOSITA not necessarily possessing the

additional skill Columbia University proposed, the claims would have also been obvious to a PHOSITA with a higher level of knowledge and ability.

With respect to Columbia University's argument that Dr. Weinstock was "unqualified to opine on matters of synthetic nucleotide chemistry," Appellant's Br. 36, the PTAB found Dr. Weinstock had "experience in DNA sequencing" and was "qualif[ied] to testify on the issues discussed in his declaration," J.A. 3. The PTAB was entitled to weigh the credibility of the witnesses in light of their qualifications and evaluate their assertions accordingly. *See Inwood Labs., Inc. v. Ives Labs., Inc.*, 456 U.S. 844, 856 (1982) ("Determining the weight and credibility of the evidence is the special province of the trier of fact."); *Anchor Sav. Bank, FSB v. United States*, 597 F.3d 1356, 1367 (Fed. Cir. 2010).

B. Prior Art Disclosure of Base Labeling, Cleavable Linkers, and Deazapurine

All of the claims at issue in case number 14-1547 involve modified nucleotides that contain: (1) a labeled base; (2) a removable 3'-OH cap; and (3) a deaza-substituted base. Columbia University first asserts it would not have been obvious at the time of invention to use "a reversible chain-terminating nucleotide with a label attached to the *base*, rather than to the cap on the *3'-OH group of the sugar*." Appellant's Br. 37. Second, it asserts using "a cleavable linker (as required by claim 15 [of the '698 patent]) would not have been obvious." *Id.* at 41. The PTAB made factual findings related to these arguments, which address the state of the art prior to October 2000, i.e., the date U.S. Patent Application No. 09/684,670 was filed, to which each of the three patents-in-suit claims priority.

Although Columbia University concedes that "[d]uring the 1990s [there was] some interest in base-labeled nucleotide analogues," J.A. 5, it argues the most

relevant reference, Tsien, contains a "marked preference" for labeling the 3'-OH caps as opposed to the base, Appellant's Br. 37–38. Illumina responds that "a labeled base and 3'-OH cap were preferred by the late 1990s." Appellee's Br. 5 (capitalization omitted).

The PTAB addressed this factual issue, concluding "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." J.A. 5. This finding was supported by substantial evidence, as is apparent from an examination of the prior art references considered by the PTAB. Tsien, for example, which bears an international publication date of 1991, noted the label could be attached to the base, and cautioned its nomenclature should not be read to "imply that this is the sole place where labeling can occur." J.A. 3011. Tsien described base labeling in some detail:

> While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of alternatives—particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a *remote position such as the base*. . . .
>
> One method involves the use of a *fluorescent tag attached to the base moiety*. *The tag may be chemically cleaved* (either separately from or simultaneously with the *deblocking* step) . . . . This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. . . .
>
> In another type of remote labeling the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The *tether can be cleavable* if desired . . . . There are several cleavable tethers that permit removing the

> fluorescent group before the next successive nucleotide is added . . . . Long tethers may be used . . . . Typical tethers are from about 2 to about 20 . . . atoms in length.

J.A. 3028–30 (emphases added). Tsien thus discloses a reversible chain-terminating nucleotide and a label attached to the base via a cleavable tether.

Columbia University argues that although Tsien describes both (1) cleavable tethers and (2) cleavable labels attached to the base, it does not explicitly disclose the combination of these two elements (i.e., a label attached to the base via a cleavable tether). *See* J.A. 3029 (Tsien) (describing a "fluorescent tag attached to the base moiety" and noting "[t]he tag may be chemically cleaved"). Although Tsien does not expressly disclose a cleavable tether attached to the base, the excerpted portions above, which describe both base labeling and the use of cleavable tethers, are derived from two adjacent paragraphs of Tsien, supporting the PTAB's finding that "[a PHOSITA] reading Tsien would have recognized that its teaching of a cleavable tether to release the label would have been useful when the label is attached to the base." J.A. 15; *see also* J.A. 3029 ("Long tethers may be used so that the large fluorescent groups are spaced sufficiently far away from the base and triphosphate moieties . . . .").

The PTAB also cited Dower and Stemple as reflecting "recognition within the prior art that such nucleotides [i.e., those that are base-labeled and contain removable 3'-OH moieties] were useful and effective in SBS methods." J.A. 6. Dower states:

> One important functional property of the monomers is that the label be *removable*. . . . The label position may be *anywhere on the molecule* compatible with appropriate polymerization. . . . Nucleotide analogs used as chain-terminating reagents will typically have *both a labeling moiety*

> *and a blocking agent* while remaining compatible with the elongation enzymology. As the blocking agent will usually be on the 3' hydroxyl position of the sugar on a nucleotide, it would be most convenient to incorporate the label and the blocking agent at the same site providing for a single reaction for simultaneous removal of the label and blocking agent. However, *it is also possible to put a label on another portion of the nucleotide* analog than the 3' hydroxyl position of the sugar, thereby requiring a two-step reaction cycle for removing the blocking and labeling groups. . . .
>
> There are several suitable labeled, terminator structures as follows: . . . (b) The fluorophore is placed in a position *other than the 3'OH* of the nucleoside,[3] and a different group placed on the 3'OH of the dNTPs to function as the chain terminator. The fluorphore and the 3' blocking group are removed [in a single step or separate steps].

Dower col. 15 l. 52–col. 16 l. 6; col. 25 ll. 23–37 (emphases added). Figure 1B of Stemple illustrates a fluorochrome attached to the base via a photolabile (i.e., cleavable by light) linker:

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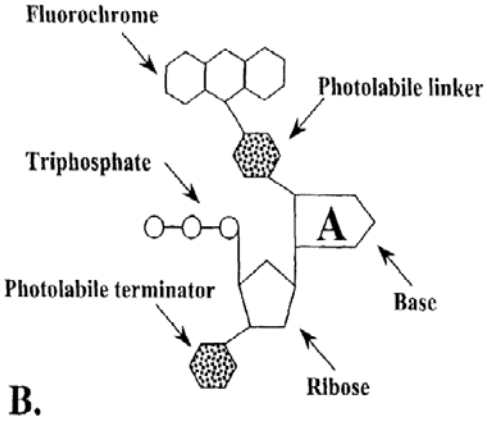
[3] "A 'nucleoside,' unlike a nucleotide, contains only a sugar and a base. Nucleotides can be equivalently referred to as nucleosides with added phosphate groups (hence, 'deoxyribonucleoside triphosphate')." Appellant's Br. 3 n.1.



Stemple, fig.1B. Stemple explains: "Panel B depicts an alternative configuration in which the fluorochrome is attached to the base of the nucleotide by way of a photolabile linker. The 3'-OH is blocked by a separate photolabile group . . . ." *Id.* col. 10 ll. 44–47. This arrangement is described by Stemple as a "preferred embodiment." *Id.* col. 3 l. 31. These disclosures constitute substantial evidence supporting the PTAB's findings that the prior art disclosed "nucleotides with a label on the nucleotide base with a removable 3'-OH group," J.A. 6, and "a cleavable tether to release the label" from the base moiety, J.A. 15.[4]

C. Motivation to Combine

As discussed above, the prior art discloses labels attached to the base, cleavable tethers, and reversibly capped 3'-OH groups. There does not appear to be any dispute that the prior art discloses deazapurines. *See, e.g.*, Natalya Ramzaeva et al., *7-Deazaguanine DNA*, 80

[4] The PTAB found neither Stemple nor its predecessor PCT application was anticipatory because neither disclosed a deaza-substituted base. *See* J.A. 76–77.

Helvetica Chimica Acta 1809 (1997) (J.A. 5257–59); F. Seela et al., *Duplex Stability of Oligonucleotides Containing 7-Substituted 7-Deaza and 8-Aza-7-Deazapurine Nucleosides*, 16 Nucleosides & Nucleotides 963 (1997) (J.A. 5271–72). Columbia University argues, however, that "the [PTAB] erred in concluding that a skilled artisan would have *combined* the prior art to achieve Dr. Ju's invention." Appellant's Br. 34 (emphasis added) (capitalization omitted).

The obviousness of an invention is not established "merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). In addition, the court must determine "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.*; *see also Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1374–75 (Fed. Cir. 2011) ("[E]ven when all claim limitations are found in prior art references, the fact-finder must not only determine what the prior art teaches, but whether prior art teaches away from the claimed invention and whether there is a motivation to combine teachings from separate references."). "[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

Columbia University asserts that if "Tsien disclosed such nucleotides in 1991," then it is difficult to explain the "decade-long SBS research efforts that followed."[5] Reply

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[5] Although this argument might appropriately have been raised in support of the secondary consideration of long-felt need, Columbia University did not assert long-felt need.

Br. 29; *see also* Appellant's Br. 61. However, Illumina points out that Dr. Ju's invention "was not reduced to practice *until six years later* using important changes not disclosed in the patents at issue." Appellee's Br. 53; *see also* J.A. 4130–31. Although the record does not provide a conclusive explanation for either of these long lags, some testimony suggests large capital investments may provide a partial answer. *See* J.A. 3581. With these principles and considerations in mind, the language of the claims of each patent at issue will be considered.

Claims 1 and 11 are the only independent claims of the '698 patent reviewed by the PTAB, and recite:

> 1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:
>
> a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template;
>
> b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a *base labeled* with a unique label and contains a *removable chemical moiety capping the 3'-OH group* of the sugar of the nucleotide analogue, and wherein at least one of the four nucleotide analogues within (i) or (ii) is *deaza-substituted*; and
>
> c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue

> incorporated into the nucleic acid primer extension strand.

'698 patent col. 35 ll. 2–23 (emphases added).

> 11. A plurality of nucleic acid templates immobilized on a solid surface, wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue, at least one of which is *deaza-substituted*, wherein each labeled nucleotide analogue comprises a *base labeled* with a unique label and contains a *removable chemical moiety capping the 3'-OH group* of the sugar of the nucleotide analogue.

Id. col. 36 ll. 24–31 (emphases added).

The only challenged independent claim of the '869 patent is claim 12, which recites:

> 12. A nucleotide having a *base* that is attached to a *detectable label* through a *cleavable linker*, wherein the nucleotide has a deoxyribose comprising a *cleavable chemical group capping the 3' OH group*, wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.

'869 patent col. 33 ll. 40–50 (emphases added). In addition, claim 15 of the '869 patent recites: "15. The nucleotide of claim 12, wherein the base is a *deazapurine*." *Id.* col. 33 ll. 10–11 (emphasis added).

The only challenged independent claim of the '575 patent is claim 1, which recites:

> 1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising: a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template; b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a *base labeled* with a unique label and contains a small *removable chemical moiety capping the 3'-OH group* of the sugar of the nucleotide analogue, wherein said small *cleavable* chemical group does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate; and c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.

'575 patent col. 33 ll. 30–45 (emphases added). In addition, claim 6 of the '575 patent recites: "6. The method of claim 1, wherein said base of at least one of said nucleotide analogues is a *deazapurine*." *Id.* col. 34 ll. 42–43 (emphasis added).

Inter partes review of independent claims 1 and 11 of the '698 patent was instituted on grounds of anticipation by Dower, and obviousness over Tsien, Prober, and Seela. Inter partes review of claim 12 of the '869 patent was instituted on grounds of anticipation by Tsien and

Stemple, and claim 15 on grounds of obviousness over Tsien, Prober, Stemple, and Anazawa. Inter partes review of claim 1 of the '575 patent was instituted on grounds of anticipation by Dower and Tsien, and of claim 6 on grounds of obviousness over Tsien, Prober, and Seela.

The PTAB evaluated the content of the prior art, finding Tsien disclosed an SBS method that used "a fluorescent tag attached to the base moiety," and a removable 3'-OH blocking group. J.A. 10–11. The PTAB noted "Tsien does not disclose a deaza-substituted base, but references Prober I, which does." J.A. 12.

Columbia University argues Tsien's citation to Prober does not render obvious its invention because "Tsien does *not* cite Prober for labeling purines," but only for labeling pyrimidines. Appellant's Br. 43. However, Tsien explicitly invites the PHOSITA to consider Prober in a paragraph discussing both purines and pyrimidines. Although Tsien asserts "[t]he C-8 position of the purine structure presents an ideal position for the attachment of a label," J.A. 3030, it also states:

> While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of alternatives—particularly the formation of a *3'-blocked dNTP analogue* containing a label such as a fluorescent group coupled to a remote position such as the base. This dNTP can be incorporated and the fluorescence measured and removed according to the methods described below. . . . One method involves the use of a fluorescent tag attached to the base moiety. The tag may be chemically cleaved. . . . This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. . . . *Prober et al. (1987) show enzymatic incorporation of fluorescent*

> *ddNTPs* by reverse transcriptase and Sequenase™.

J.A. 3028–29 (emphases added). Tsien thus invites use of the "method[] described [in Prober]" in combination with a "3'-blocked dNTP analogue" and a fluorescent label "coupled to a remote position such as the base." *Id*. Prober's method includes the use of a fluorescent dye "attached . . . to the 7 position in the 7-deazapurines" and explains "the 7-deazapurines were used to facilitate stable linker attachment at that site." J.A. 3063.

A PHOSITA may find reason to combine references to achieve a claimed invention even absent an explicit mention in one reference of the other. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). Here, the express invitation to incorporate a 3'-blocked dNTP having a fluorescent base label using the method disclosed in Prober provides a motivation to combine Tsien with the 7-deazapurine of Prober.

Seela, issued in 1989, also helps to provide a motivation by teaching, according to the PTAB, that deazapurine nucleotides "can advantageously be used . . . in polymerase-based sequencing methods," such as SBS. J.A. 80. In addition, Dr. Weinstock testified that a PHOSITA would be motivated to use the 7-deazapurines of Prober "to improve similar Tsien systems and methods." J.A. 3181. When asked whether "[t]he use of ddNTP that . . . had fluorescent labels attached to the 7-deazapurine position . . . was common by the year 2000 [for Sanger sequencing]," Columbia University's witness, Dr. Trainer, conceded that it was. J.A. 4250. Taken together, the testimony and references provide substantial evidence to support the PTAB's finding that a

PHOSITA would combine the two references to achieve the claimed invention.

Columbia University argues the PTAB "never identified any affirmative motivation that would have led a skilled artisan to abandon the 'ideal,' natural C-8 position taught by Tsien." Appellant's Br. (-1550) 44. However, Tsien itself specifically references Prober as "show[ing] enzymatic incorporation of fluorescent ddNTP's by reverse transcriptase and Sequenase™," J.A. 3029, and Prober discloses attaching a fluorescent label via a linker only at the 7-deaza position, J.A. 4335 (Question: "[Attaching a label to the 7-deaza position is] the only way that you [Trainer] disclose in this particular article [i.e., Prober]?" Answer: "Yes."); *see also* J.A. 3063. Although Tsien described the C-8 position as "ideal," J.A. 3030, this court has previously explained that "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes," *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *see also In re Mills*, 470 F.2d 649, 651 (CCPA 1972) ("We find no merit in appellants' contention that the disclosure of propylene is so submerged in Cooper, and the teaching of the use of ethylene so predominant, that Cooper cannot be said to place foams composed of the claimed ingredients in the possession of the public. All the disclosures in a reference must be evaluated . . . .").

Columbia University further argues there was no motivation for a PHOSITA to use deazapurines with SBS because "the need for 'stable' linkers was unique to Sanger sequencing, with its harsh conditions" associated with electrophoresis. Appellant's Br. (-1550) 44. However, although Prober was concerned only with Sanger sequencing, Tsien's explicit reference to Prober combined with the wide use of deazapurines with prior art sequencing techniques, *see* J.A. 4335 (use of deazapurines was part of a "preferred embodiment" in Prober that was

"commercialized by Applied Bio-Systems"), 3401 (deazapurines were "wide[ly] availab[le]" and "widely used"), provides substantial evidence supporting the PTAB's finding of motivation to combine, *see* J.A. (-1550) 21–24.

D. Reasonable Expectation of Success

To render a claim obvious, a PHOSITA must have had not only a "reason to combine the teaching of the prior art references to achieve the claimed invention," but also "a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal quotation marks and citation omitted). Columbia University challenges the PTAB's finding that a PHOSITA "would have had a reasonable expectation of success in combining Tsien with Prober or with Seela to synthesize a 3'-OH-capped nucleotide with a label attached to a deazapurine base (via a cleavable linker, for claim 15)." Appellant's Br. 45. Specifically, it cites Dr. Trainor's testimony that the chemistry for creating a nucleotide analogue with the claimed features was complex, and a PHOSITA could not have reasonably expected to be successful in devising an appropriate chemical procedure. *Id.* at 45–46; *see also* J.A. 3827.

Illumina responds "that every step of the synthetic process would have been understood to be within the level of ordinary skill [in the art]," and that Dr. Trainer conceded this to be the case. Appellee's Br. 39. It cites the testimony of Dr. Trainer in which he admits to be within the PHOSITA's skill level: the use of "a starting deazaguanine with a 7-iodide for linker attachment;" "attaching a cleavable alkynylamino linker to the 7-iodo position;" and "attaching a fluorescent label to the alkynylamino linker." *Id.* at 39–40. Tsien references Prober as disclosing a method that would be applicable to the synthesis of both ddNTPs and dNTPs. J.A. 3029–30.

Most significantly, the '869 patent explains a "7 deaza-alkynylamino-dGTP[6] is prepared using *well-established* procedures," and does not provide additional guidance with respect to chemical procedures. '869 patent col. 23 ll. 37–38 (emphasis added). Taken together, these disclosures constitute substantial evidence supporting the PTAB's finding that a PHOSITA would have had a reasonable expectation of success in achieving the claimed invention.

III. Secondary Considerations Do Not Weigh Strongly in Favor of Nonobviousness

Both parties present arguments with respect to secondary considerations. Illumina argues simultaneous invention supports its position that the claimed invention was obvious. Columbia University asserts copying, attempted licensing, commercial success, and unexpected results support the nonobviousness of the claimed invention.

A. Simultaneous Invention Weighs Modestly in Favor of Obviousness

"Independently made, simultaneous inventions, made within a comparatively short space of time, are persuasive evidence that the claimed apparatus was the product only of ordinary mechanical or engineering skill." *George M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (internal quotation marks and citation omitted). Illumina asserts two entities, Solexa and Amersham, each separately conceived of an SBS approach as early as December 2001, i.e., before Dr. Ju's patent applications were published, containing the novel features of Dr. Ju's patent claims." Appellee's Br. 47.

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[6] The notation "dGTP" refers to a deoxyribonucleoside triphosphate in which guanine is the base.

Columbia University first responds that the activities of Solexa and Amersham "are not prior art." Reply Br. 6. This response reflects confusion over the difference between simultaneous invention on the one hand and anticipation and obviousness on the other. If simultaneous invention were only relevant where the object of the simultaneous invention constituted prior art, it would be analyzed under 35 U.S.C. § 102 and as part of the second *Graham* factor (i.e., as part of a determination of the "differences between the prior art and the claims at issue") under 35 U.S.C. § 103. *Graham*, 383 U.S. at 17. As a secondary consideration, however—which falls under the fourth *Graham* factor—simultaneous invention is relevant when it occurs within a short space of time from the date of invention, and "is strong evidence of what constitutes the level of ordinary skill in the art." *Ecolochem v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000). Unlike the ultimate determination of obviousness, which requires courts to answer the hypothetical question of whether an invention "would have been obvious," 35 U.S.C. § 103, simultaneous invention demonstrates what others in the field *actually accomplished*.

The tendency of simultaneous invention to weigh in favor of obviousness would, of course, be negated if the purported simultaneous invention was not made independently of the claimed invention. Perhaps with this in mind, Columbia University asserts the Solexa patent was filed "months after features of Dr. Ju's SBS method were disclosed in a public National Science Foundation Grant Announcement." Reply Br. 6–7. However, Columbia University asserts that at the time of Solexa's disclosure, "Solexa . . . thought that a nucleotide with the requisite combination of features was patentable." *Id.* It makes a similar assertion with respect to Amersham. *Id.* In so asserting, Columbia University undermines its own argument: If Solexa and Amersham

had copied their purported simultaneous inventions from the grant announcement, they would have had no basis to believe their simultaneous inventions were patentable.

Columbia University also argues Amersham's activities did not constitute simultaneous invention because the chemical configuration it described was "useless as a chain terminator." Reply Br. 7. It points out that Illumina did not present its simultaneous invention argument to the PTAB. Because the record is not fully developed, the evidence of simultaneous invention as a whole weighs only modestly in favor of obviousness.

B. Copying Does Not Favor Nonobviousness

Columbia University asserts "Manteia, a company whose intellectual property was later acquired by Illumina's predecessor-in-interest Solexa, copied Dr. Ju's invention" as reflected in a 2003 presentation. Appellant's Br. 12. The 2003 presentation cites Dr. Ju's publication. *See* J.A. 3894. Illumina responds that the asserted copying is irrelevant because the only elements shown to be copied were disclosed in Tsien, Dower, and Stemple, and that the presentation does not disclose a deazapurine and therefore does not reflect copying of the *claimed* invention. Appellee's Br. 57.

Illumina further responds that Solexa did not copy Dr. Ju's invention, citing a December 2001 patent application filed by Solexa that discloses "a base that is linked to a detectable label via a cleavable linker," and a removable "protecting group" at the 3' position that "is intended to prevent nucleotide incorporation." J.A. 3750, 3755; *see also* Appellee's Br. 11–14, 58. The PTAB considered Columbia University's evidence of copying and did not find it persuasive. J.A. 29. Because the record is inconclusive as to whether any party in fact copied Dr. Ju's invention, because the PTAB did not make an explicit factual finding in this regard, and because it is unclear whether the asserted actions represent copying or

independent invention, the asserted copying does not weigh in favor of nonobviousness.

C. Attempted Licensing Weighs Modestly in Favor of Nonobviousness

Columbia University cites several emails from Illumina showing an interest in "collaborating with Dr. Ju from Columbia University on his reversible terminators," and stating "Professor Jingyue Ju purportedly has solved the reversible terminator cleavable dye label issue." J.A. 3993–95. Although these emails demonstrate an interest in Dr. Ju's work, none of the emails mentions the '698, '575, or '869 patents or clearly indicates the subject matter sought to be licensed fell within the claims of those patents. *In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("Because, in affidavits reciting the licensing history of the '111 patent, GPAC did not establish which claim(s) of the patent the licensing program incorporates, GPAC has not shown that licensing . . . arose out of recognition and acceptance of the subject matter claimed in the '111 patent."). This factor therefore provides only modest evidence of nonobviousness.

D. Commercial Success Does Not Favor Nonobviousness

Commercial success of a product embodying an invention tends to show nonobviousness when "the commercial success . . . results from the claimed invention" and is "due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *Id.*

Columbia University asserts Illumina's sales were significant and embody the claims of the '698, '869, and '575 patents. Appellant's Br. 59 (citing J.A. 3879–85); Appellant's Br. (-1548) 57; Appellant's Br. (-1550) 57. Illumina responds that "the very features proclaimed by Columbia [University] to be the reason for Illumina's commercial success (attachment of the label to the base via a cleavable linker) were already known in Tsien, Dower, and Stemple," and that Columbia University did not assert the deazapurine contributed to commercial success. Appellee's Br. 54.

Commercial success does not favor nonobviousness. "[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Here, each of the features claimed to be responsible for the commercial success of the invention was disclosed in a single prior art reference, Tsien.

In addition, Columbia University does not itself sell its patented invention. Although reliance on a defendant's or third party's sale of a patented invention to demonstrate commercial success may be probative of nonobviousness in some cases, it is not particularly helpful in the present matter because it is unclear whether any success was attributable to developments in the field that led to simultaneous invention (which would tend to show the invention was obvious) or to copying (which would tend to show the invention was nonobvious).

E. Unexpected Results Do Not Favor Nonobviousness

Evidence of "some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" tends to indicate nonobviousness. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Columbia University asserts, as evidence of unexpected results, Dr. Trainor's testimony that the claimed nucleotides are unexpectedly better than

pyrosequencing. Appellant's Br. 53; *see also* J.A. 30. According to the '698 patent, pyrosequencing is a "widely used" process that "employs four natural nucleotides . . . for sequencing DNA by synthesis" and "is based on the pyrophosphate (PPi) released during the DNA polymerase reaction, the quantitative conversion of pyrophosphate to adenosine triphosphate (ATP) by sulfurylase, and the subsequent production of visible light by firefly luciferase." '698 patent col. 2 ll. 19–28.

Unexpected results "'must be shown to be unexpected compared with the closest prior art.'" *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). The PTAB found pyrosequencing was not the closest prior art. Columbia University argues pyrosequencing was the closest prior art because it was "the only commercial embodiment of SBS at the time of Dr. Ju's invention." Appellant's Br. 63. However, there is no requirement that the closest prior art be commercialized. *See In re Merchant*, 575 F.2d 865, 869 (CCPA 1978) ("In *In re Wright* . . . , failure of a particular reference to constitute the commercial standard did not diminish its position as the closest prior art.") (internal quotation marks and citation omitted); *see also In re Chupp*, 816 F.2d 643, 644 (Fed. Cir. 1987) ("To rebut the prima facie case of obviousness, Chupp submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the *closest prior art* compounds *and* with *two commercial herbicides* . . . . It is undisputed that the claimed compound gave superior results . . . .") (emphases added). Evidence of unexpected results in comparison to pyrosequencing is therefore not probative of nonobviousness.

IV. The PTAB Did Not Err in Determining Certain Challenged Claims Were Anticipated

"Anticipation is a question of fact that we review for clear error . . . ." *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007). In Appeal 2014-1548, Columbia University argues the PTAB erred in rejecting claims 12, 13, 17, 20–26, 28, 29, 31, and 33 as anticipated because "the references are non-enabling" and do not "'disclose all elements of the claim within the four corners of the document . . . *arranged as in the claim*.'" Appellant's Br. (-1548) 64 (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008)). (Columbia University makes a similar argument with respect to claims 1–3 of the '575 patent. *See* Appellant's Br. (-1550) 64.) Specifically, it identifies as elements common to the listed claims, "a [1] 3'-OH-capped nucleotide, [2] base-label, and [3] cleavable linker." Appellant's Br. (-1548) 64. Tsien explains an approach in which:

> a [1] *3'-blocked dNTP* analogue containing a [2] *label* such as a fluorescent group [is] coupled to a remote position such as the *base*. This dNTP can be incorporated . . . according to the methods described below.
>
> One method involves the use of a *fluorescent tag attached to the base moiety*. . . .
>
> In another type of remote labeling the . . . label can be attached to the dNTP through a spacer or tether. The [3] *tether* can be *cleavable* if desired . . . .

J.A. 3028–29 (emphases added).

It is true Tsien provides that elements 1 and 2 may be combined with either a label that is directly attached to the base or one that is attached via a cleavable or non-

cleavable tether. However, "when a genus is so limited that a person of ordinary skill in the art can at once envisage each member of this limited class, . . . a reference describing the genus anticipates every species within the genus." *Abbvie Inc. v. Mathilda & Terrence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1379 (Fed. Cir. 2014) (internal quotation marks and citation omitted). This court agrees with the PTAB that an embodiment comprising a 3'-OH-capped nucleotide, base-label, and cleavable linker could be "envisaged clearly by one of ordinary skill in the art upon reading the Tsien disclosure." J.A. (-1548) 10.

Columbia University also argues Tsien does not "enable[] a skilled artisan to make a base-labeled, 3'-OH-capped nucleotide without undue experimentation," because "[t]he references do not teach the necessary synthetic chemistry." Appellant's Br. (-1548) 64–65. In Appeal 2014-1550, Columbia University similarly argues "Tsien does not enable a skilled artisan to make a base-labeled, 3'-OH-capped nucleotide [as claimed in claims 1–3 of the '575 patent] without undue experimentation." Appellant's Br. (-1550) 67. However, as already explained, if novel and nonobvious chemistry was needed to practice the claimed inventions, Dr. Ju would have been obligated to disclose this chemistry in the patent. *See* 35 U.S.C. § 112(1) (2000).[7]

The PTAB's denial of a procedural motion is reviewed for abuse of discretion. *See Bilstad v. Wakalopulos*, 386 F. 3d 1116, 1121 (Fed. Cir. 2004). The PTAB abuses its discretion when its decision: "(1) is clearly unreasonable,

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[7] Section 112 has since been amended. *See* AIA § 4(c), 125 Stat. at 296. However, because the applications that led to the '698, '869, and '575 patents were filed before Sept. 16, 2012, the pre-AIA § 112 applies. *See* AIA § 4(e), 125 Stat. at 297.

arbitrary, or fanciful; (2) is based on an erroneous conclusion of law; (3) rests on clearly erroneous fact finding; or (4) involves a record that contains no evidence on which the [PTAB] could rationally base its decision." *Id*.

In Appeal 2014-1548, Columbia University argues the PTAB's denial of its motion to amend its claims was erroneous, and that the error was not harmless:

> Columbia's amendments would have rewritten claim 15 in independent form and added the deazapurine limitation to the other challenged claims. . . .
>
> The [PTAB's] failure to enter Columbia's amendment led it to address the critical dispute over the scope of Tsien's and Stemple's disclosures first in the context of anticipation, where the issues were (in the [PTAB's] mistaken view) uncontested. When the [PTAB] turned to the obviousness of claims 15 and 16, it had already decided that Tsien and Stemple disclosed a nucleotide with a 3'-OH cap and a label attached to the base by a cleavable linker, and it asked whether adding a deazapurine was obvious.

Appellant's Br. (-1548) 62–63. Columbia University makes a similar argument with respect to claims 1–3 of the '575 patent. *See* Appellant's Br. (-1550) 60–63. Because the PTAB did not clearly err in its determination of what Tsien teaches, Columbia University's argument based on its contrary assertion does not establish patentability over the prior art, and is therefore rejected. *See Microsoft Corp. v. Proxyconn, Inc.*, No. 2014-1542, 2015 WL 3747257, at *13 (Fed. Cir. June 16, 2015) (explaining that motions to amend may properly be denied where the patentee has failed to establish patentability over the prior art of record).

CONCLUSION

For these reasons, the decisions of the PTAB are

AFFIRMED