

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

MOLECULAR LOOP BIOSCIENCES, INC.,
Patent Owner.

IPR2024-01419
Patent 11,840,730 B1

Before ANNETTE R. REIMERS, SUSAN L. C. MITCHELL, and
ZHENYU YANG, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. *Background and Summary*

Illumina, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking *inter partes* review of claims 1–9 of U.S. Patent No. 11,840, 730 B1 (Ex. 1001, “the ’730 patent”). Molecular Loop Biosciences, Inc. (“Patent Owner”) filed a Preliminary Response in which it raises challenges to the merits of the grounds in the Petition. Paper 6 (“Prelim. Resp.”).

After considering the arguments and evidence presented at this stage of the proceeding, we are persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. *See* 35 U.S.C. § 314(a). Accordingly, we institute *inter partes* review of all challenged claims on all asserted grounds. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a).

B. *Real Parties-in-Interest*

Petitioner identifies Illumina, Inc., as its real party-in-interest. Pet. 10. Patent Owner identifies Molecular Loop Biosciences, Inc. as its real party-in-interest. Paper 3, 1.

C. *Related Matters*

The parties indicate that the ’730 patent is involved in *Molecular Loop Biosciences, Inc. v. Illumina, Inc. et al.*, No. 1:24-cv-00680 (D. Del.), filed June 10, 2024, which is currently pending. Pet. 10–11; Paper 3, 1.

D. *The ’730 Patent (Ex. 1001)*

The ’730 patent is titled “Methods and Compositions for Evaluating Genetic Markers.” Ex. 1001, code (54). The ’730 patent is directed to

methods and compositions for determining genotypes in patient samples. *Id.* at 1:13–14.

The '730 patent discusses solving the problems of systematic and random error that are associated with genome amplification and sequencing library construction techniques. *See e.g.* Ex. 1001, 27:45–30:47.

Specifically, the '730 patent states:

In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules. In some embodiments, the differentiator tag sequence permits the detection of bias based on the frequency with which pairs of differentiator tag and target sequences are observed in a sequencing reaction. In other embodiments, the methods reduce errors caused by bias, or the risk of bias, associated with the capture, amplification and sequencing of genetic loci, e.g. for diagnostic purposes.

Ex. 1001, 28:1–24.

These unique differentiator tag sequences are described in the '730 patent as

useful to distinguish independent target molecules from each other thereby allowing an analysis to be based on a known number of individual target molecules. For example, if each of a plurality of target molecule sequences obtained in an assay is associated with a different differentiator tag, then the target sequences can be considered to be independent of each other and a genotype likelihood can be determined based on this information. In contrast, if each of the plurality of target molecule sequences obtained in the assay is associated with the same differentiator tag, then they probably all originated from the same target molecule due to overrepresentation (e.g., due to biased amplification) of this target molecule in the assay.

Ex. 1001, 28:29–42.

The '730 patent further describes these unique differentiator tag sequences as follows:

As used herein, a “differentiator tag sequence” is a sequence of a nucleic acid (a preparative nucleic acid), which in the context of a plurality of different isolated nucleic acids, identifies a unique, independently isolated nucleic acid. Typically, differentiator tag sequences are used to identify the origin of a target nucleic acid at one or more stages of a nucleic acid preparative method. For example, in the context of a multiplex nucleic acid capture reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, target nucleic acid capture events. Also, in the context of a multiplex nucleic acid amplification reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, for example. Thus, combinations of target nucleic acid and differentiator tag sequence (target:differentiator tag sequences) of an isolated nucleic acid of a preparative methods provide a basis for identifying unique, independently isolated target nucleic acids.

Ex. 1001, 28:53–29:4.

E. The Challenged Claims

Petitioner challenges claims 1–9 of the '730 patent. Pet. 1. Claims 1 and 9 are independent. Claim 1 is representative and is reproduced below:

1. A method for correcting for errors or bias introduced during nucleic acid analysis workflow, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin;

introducing a set of differentiator tags, wherein members of said set of differentiator tags are associated with members of said plurality, such that one or more of said loci of origin are associated with more than one differentiator tag;

amplifying each of the plurality of tagged target nucleic acid molecules to generate amplicons;

sequencing the amplicons, obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and

correcting for error or bias introduced during said workflow by collapsing target: differentiator tag combinations observed more than once into a single count.

Ex. 1001, 131:28–49.

Claim 9 explicitly requires “unique” differentiator tags that “are randomly associated with members of said plurality of target nucleic acid molecules, such that any given tag is uniquely associated with said locus of origin.” Ex. 1001, 132:44–48.

F. Evidence

Petitioner relies upon information that includes the following.

Ex. 1010, Chee, US 9,085,798 B2, issued July 21, 2015 (“Chee”).

Ex. 1015, Gahan et al., *Circulating Nucleic Acids in Plasma and Serum*, ANN. N.Y. ACAD. SCI. 1137:1–6 (2008) (“Gahan”).

Ex. 1013, Bignell et al., US 8,053,192 B2, issued Nov. 8, 2011 (“Bignell”).

Ex. 1012, McCloskey et al., US 2007/0020640 A1, published Jan. 25, 2007 (“McCloskey”).

E. 1017, Bentley, *Whole-genome re-sequencing*, Current Opinion in 16 Genetics & Development 545–552 (2006) (“Bentley”).

Ex. 1033, Chiang et al., *High-resolution mapping of copy-number alterations with massively parallel sequencing*, 6 Nature Methods 99–103 (2009) (“Chiang”).

Petitioner also relies on the Declaration of Stacey Gabriel, Ph.D. (Ex. 1005) to support its contentions.

G. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–9 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1	1–4, 9	102	Chee
2	1–4, 7, 9	103	Chee
3	5–6, 8	103	Chee, Gahan
4	1, 4–6, 9	103	Bignell, McCloskey
5	2–3	103	Bignell, McCloskey, Bentley
6	6, 8	103	Bignell, McCloskey, Gahan
7	7	103	Bignell, McCloskey, Chiang

H. Claim Construction

The challenged claims “should be read in light of the Specification, as it would be interpreted by one of ordinary skill in the art.” *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Thus, we generally give claim terms their ordinary and customary meaning. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (“The ordinary and customary meaning is the meaning that the term would have to a person of ordinary skill in the art in question.” (internal quotation marks omitted)); *see also* 37 C.F.R. § 42.100(b) (stating that claims are construed in IPRs according to the same standard as used in federal court).

Petitioner provides express constructions for three claim phrases: “set of differentiator tags,” “set of unique differentiator tags,” “locus of origin,” and “consensus base call.” *See* Pet. 15–20. We determine on the record

¹ Because the ’730 patent has an earliest possible effective filing date before March 16, 2013, it is not subject to the post-grant review provisions of the America Invents Act. *See* The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (“AIA”) § (3)(n)(1)(A) (2011).

before us that only “set of differentiator tags,” “set of unique differentiator tags,” and “locus of origin” need be addressed at this stage of the proceeding. We determine that no express construction of “consensus base call” is necessary to determine whether to institute *inter partes* review. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

1. “Set of [Unique] Differentiator Tags”

Petitioner asserts that both “set of differentiator tags” as used in claim 1 and “set of unique differentiator tags” as used in claim 9 should be given the same construction—“set of prepared tags where each tag includes a unique sequence as compared to the other tags.” *See* Pet. 16 (citing Ex. 1005 ¶ 89; Ex. 1001, 28:25–29, 28:53–57). Petitioner further asserts that “[t]hese unique differentiator tags are associated with target nucleic acids so that each nucleic acid is uniquely identifiable.” Pet. 16. Petitioner also points to the prosecution history of the ’730 patent in which Petitioner asserts the Patent Owner argued and the Board acknowledged that each differentiator tag is unique. *Id.* at 16–17. Petitioner concludes that “[a]n interpretation of ‘differentiator tags’ to include non-unique tags is not possible, and if it were, Applicant disclaimed any interpretation that would allow non-unique tags.” *Id.* at 17.

Patent Owner does not offer any alternative constructions at this stage of the proceeding. *See* Prelim. Resp. 14.

On the record before us, we agree with Petitioner that both claim phrases, “set of differentiator tags” and “set of unique differentiator tags”

should be construed to mean “set of prepared tags where each tag includes a unique sequence as compared to other tags.” Petitioner has provided sufficient support for such a construction in the Specification of the ’730 patent as set forth below.

For instance, Petitioner points us to an express definition that links uniqueness with “differentiator tag,” which states:

[A] “differentiator tag sequence” is a sequence of a nucleic acid (preparative nucleic acid), which in the context of a plurality of different isolated nucleic acids, identifies a *unique*, independently isolated nucleic acid.

Ex. 1001, 28:53–57 (emphasis added). Petitioner also points us to the statement that “[a]spects of the invention relate to associating *unique* sequence tags (referred to as *differentiator tag* sequences) with individual target molecules that are independently captured and/or analyzed (e.g., prior to amplification or other process that may introduce bias).” Ex. 1001, 28:25–29 (emphasis added).

2. “*Locus of Origin*”

Both independent claims 1 and 9 use the term “locus of origin.” See Ex. 1001, 131, 28–49, 38–59. Petitioner asserts that this term should be construed to mean “the location in a genome where a nucleic acid came from.” Pet. 17 (citing Ex. 1005 ¶¶ 96). Petitioner explains that Patent Owner added this term to clarify “that each molecule in the starting sample was associated with a different unique differentiator tag, even if multiple molecules were from the same genetic locus of origin.” Pet. 18–19 (citing Ex. 1005 ¶¶ 100–101).

Again, Patent Owner does not offer any alternative construction at this stage of the proceeding. See Prelim. Resp. 14.

Dr. Gabriel testifies that “[i]n the field of genetics, a ‘locus’ refers to a fixed location on a chromosome which contains a gene or other genetic marker.” Ex. 1005 ¶ 96. Dr. Gabriel further testifies that “[a] POSA would have understood that the ‘locus of origin’ of a nucleic acid refers to the location on a chromosome which contains the sequence that encodes for a given nucleic acid molecule.” *Id.* ¶ 98.

Dr. Gabriel points to statements in the Specification of the ’730 patent that are consistent with her construction of “locus of origin.” *See* Ex. 1005 ¶¶ 96–97. For instance, the ’730 Specification “describes a genetic loci as a location on the genome that can correspond to heritable disorder,” and “provides examples of genetic loci in Table 1.” *Id.* (citing Ex. 1001, 3:2–20, 3:43–47, 66:3–11, 31:50–42:12 (Table 1)). We also note that the ’730 patent defines a “target nucleic acid” as a genetic locus. *See* Ex. 1001, 24:2–3.

We credit Dr. Gabriel’s testimony on the record before us and determine for purposes of institution that “locus of origin” refers to the location in a genome where a nucleic acid came from.

I. Level of Ordinary Skill in the Art

Petitioner proposes that a person of ordinary skill in the art (“POSA” or “POSITA”) at the time of the invention “would have had (i) a Ph.D. in molecular biology, genetics, bioinformatics, or a related field, and at least two years of experience in high-throughput sequencing technologies, or (ii) a Master’s degree in one of the same fields with at least four years of experience in high-throughput sequencing technologies,” with acknowledged flexibility in the varying combinations of education and practical experience. Pet. 10; Ex. 1005 ¶ 36. Patent Owner does not set forth an alternative level of skill for a POSA. Prelim. Resp. 14.

For this Decision, we adopt and apply Petitioner’s proposal above, which does not appear to be inconsistent with the level of skill reflected in the asserted prior art.

II. ANALYSIS

A. Introduction

“In an *inter partes* review, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Moreover, a petitioner should not “place the burden on [the Board] to sift through information presented by the Petitioners, determine where each element [of the challenged claims] is found in [the cited references], and identify any differences between the claimed subject matter and the teachings of [the cited references.]” *Google Inc. v. EveryMD.com LLC*, IPR2014-00347, Paper 9 at 25 (PTAB May 22, 2014).

1. Anticipation

To show anticipation under § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims in order to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). It is also permissible to take into account not only the literal teachings of the prior art

reference, but also the inferences an ordinarily skilled person would draw from the reference. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). A reference may also anticipate a claim even if it does not expressly teach all the limitations arranged or combined as in the claim, “if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed. Cir. 2017) (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

2. Obviousness

A claim is unpatentable under 35 U.S.C. § 103 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. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish

obviousness. *Id.* Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420.

Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotation marks omitted). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

An obviousness 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; see *In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. “*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than

the predictable use of prior art elements according to their established functions.” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

B. *Summary of the Cited Prior Art*

We will summarize Chee, Bignell, and McCloskey that are applicable to the grounds that we will discuss for purposes of this institution decision.

1. *Chee (Ex. 1010)*

Chee “relates to the field of oligonucleotide selection and synthetic biology and nucleotide determination.” Ex. 1010, 1:11–12. Chee recognizes that constructing multi-kilobase scale DNA molecules is costly because “de-novo chemical synthesis of the DNA building blocks is quite error-prone.” *Id.* at 1:38–41. To solve this problem, Chee asserts that “[t]he present invention addresses this need by providing constructs, sets of constructs, and methods for ensuring accuracy of oligonucleotides having a desired sequence,” which Chee identifies as “regions of interest” or ROI. *Id.* at 1:55–58, 2:5–9.

Chee further describes the invention as providing:

A set of oligonucleotide constructs, where the constructs of the set comprise an ROI and an identifier unique to the individual construct. It is a fundamental element of the invention that the unique identifier is associated with a construct, not the ROI; thus, constructs with ROIs having the correct sequence can be differentiated from constructs having substantially the same ROI but containing errors.

Ex. 1010, 2:21–28, 9:9–12 (“The constructs of the invention have a unique identifier associated with the initial construct, thus giving the ability to differentiate between constructs having substantially the same ROI.”).

Chee further states:

The unique identifiers associated with a particular ROI confirm that the amplification molecules are related, and thus sequence differences between molecules with the same ROI can be identified as technical errors rather than real differences in the sequence (e.g., sequence differences from two copies of a similar sequence in a sample). Furthermore, because molecules that are identical by descent can be identified, a consensus sequence can be determined using data from multiple molecules, thereby achieving a much higher accuracy rate than most conventional high throughput methods.

Ex. 1010, 9:29–39.

Chee concludes that “[t]he use of the uniquely identifiable constructs of the invention to ensure the determination, selection and/or isolation of error-free regions of interest (ROIs) are correct is extremely effective, and allows specific sequences to be selected with high accuracy and high throughput.” Ex. 1010, 2:9–14.

2. McCloskey (Ex. 1012)

McCloskey describes methods for verifying the authenticity of a nucleic acid molecule and its sequence using a molecular barcode and a batch-stamp, as well as authenticating nucleic acid amplification products such as polymerase chain reaction (“PCR”) products. Ex. 1012, Abst., ¶¶ 2–4. More specifically, McCloskey states:

In the practice of the present invention nucleic acid molecules (e.g., genomic DNA fragments) are labeled with distinct sequence tags prior to PCR amplification. These sequence tags authenticate a nucleic acid sequence with information, such as the date of the experiment, and the sample

identity. Thus, the present invention permits identification of valid sequences, and distinguishes the valid sequences from contaminants and redundant sequences arising from template re-cloning. Contaminant sequences can be identified even when multiple control (no DNA) PCR samples are negative. Barcoding permits, for example, quantification of the relative abundance of genomic methylation patterns or polymorphic sequences by correcting for skewing that can arise from PCR amplification or the cloning of the products.

Ex. 1012 ¶ 5.

3. *Bignell (Ex. 1013)*

Bignell describes an invention that “relates to methods for indexing samples during the sequencing of polynucleotide templates, resulting in the attachment of tags specific to the source of each nucleic acid sample such that after a sequencing run, both the source and sequence of each polynucleotide can be determined.” Ex. 1013, Abst., 1:24–28. Bignell noted that it would be advantageous to genotype large populations in a small number of reactions, but be able to identify the source of the individual samples in those reactions to “yield the information content of a full non-pooled population screen in the time and at the cost of a pooled reaction.” *Id.* at 2:3–8. Bignell states that to accomplish this, “DNA from more than one source can be sequenced on an array if each DNA sample is first tagged to enable its identification after it has been sequenced.” *Id.* at 3:3–6. To this end, Bignell describes methods “for sequencing nucleic acid sequences on an array and identifying subsets of nucleic acid sequences on an array, wherein each subset of nucleic acid sequences is isolated from a different source.” *Id.* at 3:60–64.

C. The Chee Grounds (Grounds 1–3)

1. Petitioner’s Contentions

Petitioner asserts that claims 1–4, and 9 are anticipated by Chee; that claims 1–4, 7, and 9 would have been obvious over Chee; and that claims 5, 6, and 8 would have been obvious over Chee and Gahan. Pet. 3. Petitioner asserts that Chee teaches every element of independent claims 1 and 9. *See* Pet. 25–32, 35–38. Petitioner asserts the obvious ground over Chee to rebut any argument from Patent Owner that “Chee does not disclose the claimed ‘*differentiator tags*’ because Chee states that its unique identifiers ‘need not be absolutely unique.’” Pet. 38 (citing Ex. 1010, 11:22–25; also *id.* at 9:60–63). Petitioner posits that “[e]ven if that distinction were accepted, configuring Chee’s technique to use identifiers that were absolutely unique would have been obvious in view of Chee’s own teachings.” *Id.*

As to claim 7, which adds “the step of determining the copy number of genomic region or transcript in a patient from whom the sample is obtained” to claim 1, Petitioner asserts:

A POSA would have recognized that analyzing the DNA sequences generated from Chee’s method to determine a copy number would have been beneficial and important for detecting and diagnosing certain diseases. A POSA would have also known that copy number analysis may be influenced by bias and would have been motivated to use Chee’s methods to identify and correct for bias.

Pet. 42 (citing Ex. 1005 ¶¶ 212–214; Ex. 1033, 101).

As to Ground 3 involving claims 5, 6, and 8, Petitioner adds the teachings of Gahan concerning the additional limitations of samples that include nucleic acids from bacteria or a virus, from a tumor, or from a fetus or placenta, respectively. Pet. 42–45.

Petitioner provides detailed claim analysis for each of these grounds explaining how each claim limitation is disclosed in the asserted references and how its assertions are supported by the testimony of Dr. Gabriel. *See* Pet. 25–37 (Ground 1), 38–42 (Ground 2), 42–45 (Ground 3); Ex. 1005 ¶¶ 113–232.

2. *Patent Owner’s Contentions*

At this point in the proceeding, Patent Owner disputes whether Chee teaches the following limitation of claim 1—“one or more of said loci of origin are associated with more than one differentiator tag”—and the following limitation of claim 9—“any given tag is uniquely associated with said locus of origin.” Prelim. Resp. 15–19. Patent Owner takes issue with Petitioner’s reliance on Chee’s teaching that “its methods can create ‘two constructs with substantially the same ROI and different unique identifiers’” as allegedly teaching these limitations in claims 1 and 9. *See* Prelim. Resp. 16.

Patent Owner further explains:

Chee explains that its methods provide “validated sequences” that correspond to “one or more *desired sequences, i.e., ‘regions of interest.’*” Chee, 2:5–9. In explaining how it obtains constructs having certain desired sequences (that is, the ROIs), Chee explains that one construct having “substantially the same ROI” as another construct means one construct “containing errors” relative to the other ROI. Chee, 2:23–28. In other words, a construct with “substantially the same ROI” is a construct that is almost a desired sequence (i.e., almost the ROI), except for errors in that sequence. Nowhere does Petitioner cite disclosure in Chee tying either the desired sequence (i.e., the ROI) or a sequence having “substantially the same ROI” to a locus of origin. And while Petitioner cites testimony from Dr. Gabriel (Pet., 28), that testimony simply states in a conclusory manner that “substantially the same ROI” means “the same locus of origin on the genome.” Ex. 1005,

¶ 155. But Dr. Gabriel does not provide any support for that purported meaning from Chee, and does not address Chee’s different explanation that “substantially the same ROI” refers to errors, not location, as “***ROIs having the correct sequence*** can be differentiated from ***constructs having substantially the same ROI but containing errors.***” Chee, 2:21–28.

Prelim. Resp. 16–17.

3. Discussion

We will focus our analysis for purposes of institution on Ground 1 and claim 1 involving anticipation by Chee, which address Patent Owner’s assertions that Chee does not teach certain limitations of claims 1 and 9 as described above.

Having considered the parties’ positions and evidence of record, summarized above, we determine that the information presented in the Petition establishes that Petitioner has shown sufficiently a reasonable likelihood of succeeding with respect to at least claim 1 challenged in Ground I. Petitioner provides sufficient support on the record before us to provide a reasonable likelihood of succeeding in showing that claim 1 is anticipated by Chee.

Petitioner shows where Chee teaches that its techniques can be used to correct for amplification bias, thus teaching the preamble of claim 1, which calls for a method for correcting for errors or bias introduced during nucleic acid analysis workflow. *See* Pet. 25 (citing Ex. 1010, 9:29–39, 10:42–46, 10:54–59, 14:39–50, 23:53–64; Ex. 1005 ¶¶ 134–135). Dr. Gabriel points to statements in Chee concerning correcting for sequencing errors. *See* Pet. 25, Ex. 1005 ¶¶ 134–135. Dr. Gabriel testifies that Chee explains that when errors arise during the sequencing step, those errors can be corrected by comparing the sequence reads of multiple molecules with the same unique identifier. Ex. 1005 ¶ 135 (citing Ex. 1010, 9:29–39). By comparing the

sequence reads of multiple molecules with the same unique identifier, Dr. Gabriel points to statements in Chee that a consensus sequence can be determined and any sequencing error can be overcome “by sequencing multiple instances of the same ROI (i.e. identical by descent).” *Id.* (citing Ex. 1010, 14:39–50, 10:54–59). We credit Dr. Gabriel’s testimony on the record before us.

Petitioner also shows sufficiently where Chee teaches “obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin.” *See* Pet. 26–27. Dr. Gabriel testifies that:

Chee also teaches that the sample comprises target nucleic acids from “more than one locus of origin.” For instance, Chee explains that its method “is especially useful for very complex sequencing sets or sequencing of nucleic acids having highly related sequences in different regions.” A person of ordinary skill in the art would have understood that the analysis of nucleic acid molecules “in different regions” refers to nucleic acid molecules at different loci of origin on a genome.

Ex. 1005 ¶ 139 (citing Ex. 1010, 5:24-26, 11:56-60); *see also id.* ¶ 143 (linking Chee’s detection of polymorphisms, mutations, and sequence variants to obtaining and analyzing nucleic acids from multiple loci of origin across the genome).

Contrary to Patent Owner’s assertions, Dr. Gabriel shows in Chee where a desired sequence or ROI is tied to a locus of origin. *See* Prelim. Resp. 17. Dr. Gabriel links these target nucleic acids that are from more than one locus of origin to Chee’s “region of interest” or ROI. *See* Ex. 1005 ¶ 116. Dr. Gabriel testifies that “Chee typically uses the term ROI or region of interest to refer to a specific target nucleic acid (*e.g.*, a DNA fragment)

present in an initial sample.” *Id.* (citing Ex. 1010, 4:1–3); *see also* Ex. 1005 ¶ 153 (stating “[e]ach construct also has one ROI, which is a nucleic acid molecule from the starting sample”).

We also find on the record before us that Petitioner has shown sufficiently that Chee teaches the limitation of claim 1 requiring “introducing a set of differentiator tags wherein members of said set of differentiator tags are associated with members of said plurality, such that one or more of said loci of origin are associated with more than one differentiator tag.” We disagree with Patent Owner’s assertion that Dr. Gabriel has not provided support in Chee for her assertion that “substantially the same ROI” means “the same locus of origin on the genome,” as opposed to Patent Owner’s interpretation that it means a ROI with errors, not a location on the genome.

Dr. Gabriel testifies that Chee teaches that each nucleic acid molecule in a sample “is associated with a different unique identifier.” Ex. 1005 ¶ 153. Dr. Gabriel further states that “[t]he result is that each nucleic acid molecule in a starting sample is part of its own construct and with its own unique identifier.” *Id.* “In other words, no two nucleic acids in the starting sample will be associated with the same unique identifier.” *Id.* ¶ 154 (citing Ex. 1010, 5:27–36). Dr. Gabriel further testifies what this uniqueness means.

Chee explains that the initial sample may include multiple nucleic acids from the same region of a genome. Chee states that its method can create multiple constructs that have “substantially the same ROI” but different unique identifiers. By “substantially the same ROI,” Chee means nucleic acids from the same locus of origin on the genome (*e.g.*, because the sample naturally included multiple copies of the same DNA). These nucleic acids would have the same or overlapping

sequences. Because each nucleic acid molecule is part of its own construct, each one is associated with a different unique identifier. Any copies made of it, to be identified and traced throughout the sequencing process.

Ex. 1005 ¶ 155 (citing Ex. 1010, 2:34–38, 2:38–43, 10:41–46, 24:1–4).

On the record before us, we credit Dr. Gabriel’s explanation set forth above that “substantially the same ROI” refers to nucleic acids from the same locus of original on the genome because a sample may include multiple copies of the same DNA, which would have the same or overlapping sequences.

Finally, we determine that Petitioner has shown sufficiently where Chee teaches the remainder of the limitations of claim 1 involving generating amplicons of the tagged target nucleic acid molecules, sequencing the amplicons, and correcting for error or bias. *See* Pet. 30–32.

4. Conclusion

For the foregoing reasons, we determine that Petitioner has shown a reasonable likelihood of prevailing on showing that at least claim 1 of the ’730 patent is unpatentable as anticipated. Accordingly, we institute an *inter partes* review of claims 1–9 of the ’730 patent. *See SAS*, 138 S. Ct. at 1359–60.

D. The Bignell Grounds (Grounds 4–7)

1. Petitioner’s Contentions

Petitioner presents four grounds that rely on Bignell to teach the majority of the limitations of the asserted claims in Grounds 4 through 7. *See* Pet. 45–70. For Ground 4, Petitioner asserts that claims 1, 4–6, and 9 of the ’730 patent would have been obvious over Bignell and McCloskey. Pet. 45–60. For Ground 5, Petitioner asserts that claims 2 and 3 would have

been obvious over Bignell, McCloskey, and Bentley. Pet. 60–63. For Ground 6, Petitioner asserts that claims 6 and 8 would have been obvious over Bignell, McCloskey, and Gahan. Pet. 63–65. For Ground 7, Petitioner asserts that claim 7 would have been obvious over Bignell, McCloskey, and Chiang. Pet. 65–66.

Petitioner asserts that “McCloskey teaches methods for preparing a sample so that individual nucleic acids can be tracked during a sequencing analysis,” but does not require a specific sequencing technology. Pet. 46–47 (citing Ex. 1012 ¶¶ 2, 106). Petitioner asserts that Bignell teaches such a sequencing technology on next-generation sequencing machines. *Id.* at 47 (citing Ex. 1013, 17:12–27, 41:51–61, 46:45–47:3, 6:36–43). Petitioner also asserts that a “POSA would have recognized that adding McCloskey’s unique barcodes to Bignell’s method, which includes several amplification steps, could improve it,” *see* Prelim. Resp. 47–48 (citing Ex. 1005 ¶ 251), and such a combination would have a reasonable expectation of success, *see* Prelim. Resp. 48 (citing Ex. 1005 ¶¶ 253–257).

Petitioner provides detailed claim analysis for each of Grounds 4–7 explaining how each claim limitation is disclosed in the asserted references and how its assertions are supported by the testimony of Dr. Gabriel. *See* Pet. 51–66; Ex. 1005 ¶¶ 223–344.

2. Patent Owner’s Contentions

Patent Owner asserts that Petitioner has not shown that McCloskey teaches “correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count,” because Petitioner relies on McCloskey for teaching correcting skewing by identifying duplicate *barcodes* in an amplified sample

versus the target:differentiator tag combinations. Prelim. Resp. 20–21. For instance, Patent Owner explains that:

Indeed, in each of McCloskey’s examples redundant sequences were identified by identifying the duplicate barcodes themselves, not a combination of the barcode and target nucleic acid molecule. Petitioner also argues that McCloskey discloses “collapsing target:differentiator tag combinations” because McCloskey’s bar-coded oligonucleotides “allow it ‘to identify . . . redundant sequences and to quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences.’” But Petitioner does not explain how this meets the ’730 Patent’s claimed limitation “collapsing target:differentiator tag combinations observed more than once into a single count.”

Prelim. Resp. 20–21 (citing McCloskey ¶ 53; Pet. 56–57).

As to independent claim 9, Patent Owner asserts that Petitioner has not shown sufficiently that McCloskey teaches a “set of unique differentiator tags [that] are randomly associated with members of said plurality of target nucleic acid molecules” as required by claim 9 of the ’730 patent. Prelim. Resp. 21–22. Patent Owner asserts that McCloskey teaches “bar-coded oligonucleotides that are targeted to specific nucleic acid molecules.” *Id.* at 22 (citing McCloskey ¶ 17).

Patent Owner further explains:

McCloskey’s bar-coded oligonucleotides require three components “a first sequence complementary to the target nucleic acid molecule, a second sequence providing a random barcode, and a third sequence that is not complementary to any sequence in the sample.” [McCloskey ¶ 17.] Because McCloskey’s bar-coded oligonucleotides require “a first sequence complementary to the target nucleic acid molecule,” each random barcode will be associated with the same starting sequence. *Id.* In the examples disclosed in McCloskey, each bar-coded oligonucleotide was specifically associated with a nucleic acid molecule in a targeted region. *See, e.g. id.*, [0052]

(noting the sequences correspond to complementary FMR1 regions). Petitioner does not point to any disclosure in McCloskey where random barcodes are “randomly associated” with nucleic acid molecules. Instead, Petitioner cites instances in McCloskey where random barcodes are specifically associated with a targeted nucleic acid. Pet., 59 (citing McCloskey [0017], [0046]-[0047]).

Prelim. Resp. 22.

We address each of Patent Owner’s arguments in turn.

3. Discussion

Petitioner relies on McCloskey for correcting the skewing effect from PCR amplification by identifying duplicate barcodes in an amplified sample, which indicate multiple amplified sequences derived from a single original molecule. Pet. 56 (citing Ex. 1012 ¶¶ 5, 53, 93; Ex. 1005 ¶ 293). Petitioner shows the similarity between McCloskey’s use of unique barcodes and the ’730 patent’s counting only unique tags to determine how many times a sequence appeared in an original sample. Pet. 57 (citing Ex. 1012 ¶ 93, 16; Ex. 1001, 30:48–51, 72:63–73:2).

We begin our analysis by reviewing what the Specification of the ’730 patent describes as “collapsing target:differentiator tag combinations observed more than once into a single count” to determine if on the record before us, we determine that McCloskey teaches such a step. Figure 5 of the ’730 patent set forth below shows a method for genotyping based on target and 5 differentiator tag sequences. Ex. 1001, 19:35–36.

FIG. 5

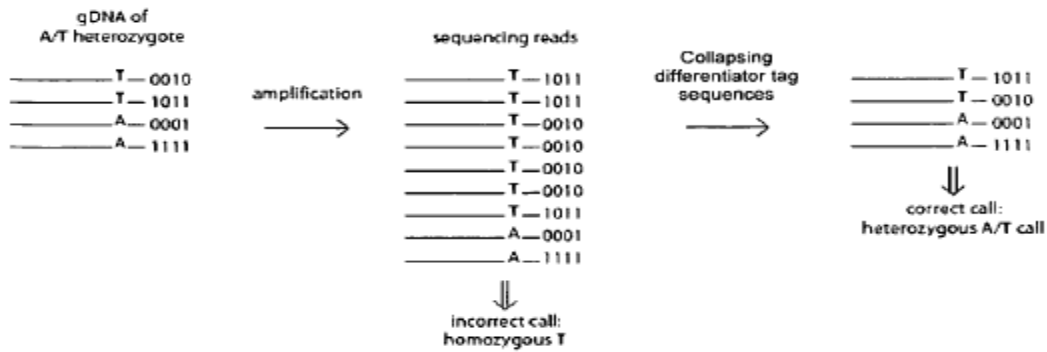


Figure 5 “depicts a method for making diploid genotype calls in which repeat target:differentiator tag combination are collapsed.” Ex. 1001, 73:3–5. It appears from Figure 5, that the unique differentiator tags shown as combinations of 1s and 0s are used to determine which are repeat target:differentiator tag combinations that need to be collapsed to a single count, and not the target DNA.

By the same token, Example 2, titled “Use of Differentiator Tag Sequences to Detect and Correct Bias in a MIP-Capture Reaction of a Set of Exon Targets,” again shows use of the unique differentiator tags to determine the count. *See* Ex. 1001, 71:25–73:5. Example 2 shows the construct of a table of target:differentiator tag abundances from the read data as shown below. *Id.* at 72:50–51. This table appears below.

	Target ID	Differentiator Tag sequence ID	Count
1	1	3547	1
	2	4762	1
	1	9637	1
	1	1078	5
2	3	4762	1
	1	2984	1

Ex. 1001, 72:53–62.

In analyzing the table shown above, the '730 patent states:

All 'count' entries should be '1', since any particular target-differentiator tag mapping will not occur more than once by chance, and therefore will only be observed if bias was present somewhere in the sample preparation process. For any target:differentiator tag combination observed more than once, all such reads are 'collapsed' into a single read before consensus basecalls are determined. This will cancel the effect of bias on consensus basecall accuracy.

Ex. 1001, 72:63–73:3.

There are duplicate target IDs in the table that are included in individual counts because the differentiator tag sequence ID is different for these duplicates. The table shows that the differentiator tag sequence ID is used to determine the count.

Therefore, we agree on the record before us with Petitioner that the '730 patent's step of "collapsing target:differentiator tag combinations observed more than once into a single count" is done in a similar way to McCloskey's use of unique bar codes.

We now turn to Patent Owner's assertion about claim 9 that Petitioner has not shown that McCloskey teaches randomly associating barcodes with nucleic acid molecules.

Petitioner asserts that:

McCloskey's "random barcodes" are "*randomly associated*" with target nucleic acids. The barcodes are separately synthesized oligonucleotides that are added to the sample and attached to the target nucleic acids. A POSA would have understood that the unique barcodes would have been randomly associated with the nucleic acids in the sample. One reason is that McCloskey's barcodes do not have a sequence that is complementary to any [of] the target nucleic acids, and therefore the barcodes are not destined for any particular molecule.

Pet. 59 (citing Ex. 1012 ¶¶ 17, 21, 46–47; Ex. 1005 ¶ 280).

Patent Owner takes issue with Petitioner’s analysis of McCloskey because McCloskey’s bar-coded oligonucleotide has a sequence that is complementary to the target nucleic acid molecule. Therefore, Patent Owner asserts that the barcode that is part of this oligonucleotide cannot be randomly associated with target nucleic acid molecules as required by claim 9. *See* Prelim. Resp. 22 (stating “[i]n the examples disclosed in McCloskey, each bar-coded oligonucleotide was specifically associated with a nucleic acid molecule in a targeted region”).

We determine that Patent Owner’s focus on the bar-coded oligonucleotide of McCloskey as opposed to the random barcodes themselves as described in McCloskey is incorrect. McCloskey states that “random barcode” refers to “an arbitrary sequence that can uniquely identify a target nucleic acid in an experiment, and whose sequence is unknown at the start of the experiment.” Ex. 1012 ¶ 21. McCloskey also states that oligonucleotides with a random sequence “are synthesized by randomly incorporating a nucleotide at each of the positions” of the random barcode. *Id.* Finally, McCloskey states that “[t]he length of the second sequence is sufficient to provide, with high probability, a unique identity to each target nucleic acid molecule in the sample prior to amplification.” *Id.*

We find nothing in McCloskey’s description of the random barcode itself to support Patent Owner’s position that these random barcodes are not “randomly associated” with target nucleic acid molecules. *See* Prelim. Resp. 22 (relying on McCloskey’s bar-coded oligonucleotide to show lack of randomness).

4. *Conclusion*

On the record before us at this point in the proceeding, we do not find Patent Owner's assertions about Ground 4 through 7 to be well-taken.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in showing that at least claim 1 of the '703 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition"); 37 C.F.R. § 42.108(a). At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

IV. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–9 of the '730 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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