UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/782,616	05/18/2010	Lin Chen	374634-000077	5004

73230 7590 03/19/2020

DLA Piper LLP (US)
550 South Hope Street
Suite 2300
Los Angeles, CA 90071-2678

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/19/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

GTDocket@dlapiper.com
joshua.gibbs@dlapiper.com
laccprosecution@dlapiper.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LIN CHEN and REZA KALHOR

Appeal 2019-003807
Application 12/782,616
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review,[2] under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1, 2, 5–18, 21, 22, 24–26, 28, 37, and 41–43.[3] (Appeal Brief filed date ("Appeal Br.") 6.)

We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as the University of Southern California. (*See* Appeal Br. 4.)

[2] We consider the Non-Final Office Action issued January 19, 2018 ("Non-Final Act."), the Appeal Brief filed December 21, 2018 ("Appeal Br."), the Examiner's Answer issued on February 19, 2019 ("Ans."), and the Reply Brief filed April 17, 2019 ("Reply Br.").

[3] Claims 39–36 and 44–51 were withdrawn; claims 3, 4, 19, 20, 23, 27, and 38–40 were cancelled. (Appeal Br. 6.)

INTRODUCTION

Appellant's Specification provides a method for determining the three-dimensional structure of chromatin in eukaryotic cells. (Specification dated May 18, 2010 ("Spec.") ¶ 2.) The Specification describes known chromosome conformation capture (3C) techniques. (Spec. ¶¶ 5–7.) These methods include crosslinking chromatin complexes to maintain existing structural relationships, then ligating DNA loci to identify spatial proximity. (*Id.*) Ligation frequency between DNA loci reveals the spatial arrangement of chromatin at a molecular level. (*Id.*)

The Specification states that prior techniques use low concentrations of crosslinked chromatin complexes in dilute solutions to minimize intermolecular ligation. (*Id.* ¶ 7.) In contrast, the Specification states that the described process promotes intramolecular ligation by immobilizing the crosslinked chromatin complexes. (*Id.* ¶ 12.)

Appellant's claim 1 recites:

> A method of determining structural organization of chromatin, comprising:
>
> cross-linking DNAs of the chromatin with proteins;
>
> cutting the DNAs of the chromatin with restriction enzymes to form cross-linked protein:DNA complexes comprising DNAs with 5′-overhangs;
>
> tethering the cross-linked protein:DNA complexes to at least one support;
>
> blunting the 5 ′-overhangs of the tethered protein:DNA complexes with a biotinylated nucleotide to produce blunt DNA ends;
>
> ligating the blunt DNA ends on the same cross-linked protein:DNA complexes while the complexes are still tethered to the support medium; and

> characterizing the DNA of the protein:DNA complexes to identify structural organization of the chromatin.

(Appeal Br. 45.)

The Examiner rejects the claims as follows:

Claims Rejected	35 U.S.C. §	References/Basis	Non-Final Office Action
1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	112, second paragraph	Indefiniteness	3–5
41–43	112, second paragraph	Indefiniteness	5
1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	103(a)	Cai,[4] Dekker,[5] Lee,[6] Wartiovaara[7]	6–17
8–10, 13, 14	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison,[8] Shiio[9]	17–18
11, 12, 15–17	103(a)	Cai, Dekker, Lee, Wartiovaara,	18–20

[4] Cai, S. et al., *SATB1 packages densely looped, transcriptionally active chromatin for coordinated expression of cytokine genes*, 38 NATURE GENETICS 1278–1288 (2006).
[5] Dekker et al., WO 2008/024473 A2, published February 28, 2008.
[6] Lee, T. I. et al., *Chromatin immunoprecipitation and microarray-based analysis of protein location*, 1 NATURE PROTOCOLS 729–748 (2006).
[7] Wartiovaara et al., US 2007/0277251 A1, published November 29, 2007.
[8] Morrison, A. J. et al., *Retinoblastoma Protein Transcriptional Repression through Histone Deacetylation of a Single Nucleosome*, 22 MOLECULAR CELLULAR BIO. 856–865 (2002).
[9] Shiio, Y. and Aebersold, R., *Quantitative proteome analysis using isotope-coded affinity tags and mass spectrometry*, 1 NATURE PROTOCOLS 139–145 (2006).

Claims Rejected	35 U.S.C. §	References/Basis	Non-Final Office Action
		Morrison, Shiio, Blander,[10] Fujita[11]	
1, 2, 5–7, 18, 21, 22, 24–26, 28, 37, 38, 40, 41	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, GE Healthcare[12]	20–31
8–17	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, GE Healthcare, Blander, Fujita	31–33

ANALYSIS

35 U.S.C. § 112, second paragraph — Indefiniteness

The Examiner rejects claim 1 as indefinite for reciting "characterizing the DNA of the protein:DNA complexes to identify structural organization of the chromatin." (Non-Final Act. 4.) The Examiner finds the Specification does not teach a limiting definition of "characterizing." (*Id.*) The Examiner concludes that Appellant had "the opportunity to limit the claims to sequencing, but wants the breadth of 'characterizing' without a clear written indication of what is required and how it relates to chromatin structure." (Ans. 31–32.)

[10] Blander, G. et al., *SIRT1 Shows No Substrate Specificity in Vitro*, 280 J. BIO. CHEM. 9780–9785 (2005).
[11] Fujita et al., EP 1967582 A1, published September 10, 2008.
[12] GE Healthcare, Instructions 71-7106-00 AF Affinity Media, Activated Thiol Sepharose 4B, Sepharose™ (2008).

Appellant argues that the plain meaning of the claim terms, read in view of the Specification, would be readily understood by one of skill in the art. (Appeal Br. 15.) Appellant argues that the Specification defines characterizing as by "sequencing or other methods suitable to identify structural organization of the chromatin." (*Id.* at 14, citing Spec. ¶¶ 14, 29.)

We are persuaded by Appellant's argument. "A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003). The Specification discloses that ligation frequency of DNAs in protein:DNA complexes, i.e., intramolecular ligation, indicates structural organization of chromatin. (Spec. ¶ 7.) The Specification states that ligation frequency can be measured by various techniques. (*Id*.) These techniques include sequencing or other methods. (*See id.* ¶¶ 14, 30, 55, 59.)

We agree with the Examiner that the claim is broader than the specific sequencing techniques disclosed in the Specification. However, "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971). Because the claim, read in light of the specification, reasonably apprises a person of ordinary skill in the art of the step of "characterizing . . . to identify structural organization of the chromatin," we reverse the Examiner's rejection of claim 1 as indefinite. The rejection of the dependent claims falls with claim 1.

The Examiner also rejects claim 41 as indefinite. (Non-Final Act. 5.) The Examiner determines that the claim and Specification do not provide a standard for ascertaining the requisite degree of separation distance between a majority of individual protein:DNA complexes. (*Id.*)

Appellant argues the claim recites relative terminology defining a distance in which a majority of protein:DNA complexes are less likely to form intermolecular ligation events. (Appeal Br. 20–21, citing Spec. ¶¶ 42–43.) Appellant contends a number of approaches may be used to determine the claimed distance. (*Id.* at 21.) For example, one of skill in the art could predict fragment length based on the particular restriction enzyme and incubation conditions. (*Id.*; *see also* Spec. ¶¶ 98–101.) Likewise, the distance between tethered protein:DNA complexes can be determined by using a support with a well-defined surface area. (*Id.*; *see also* Spec. ¶ 43.) Appellant argues that a person of ordinary skill in the art could determine the distance by "calculating the length of fragments generated by a particular restriction enzyme, the concentration of protein:DNA complexes, and the surface area of the supports used in the method." (*Id.*)

We are persuaded by Appellant's argument. The definiteness requirement is not a demand for unreasonable precision, but rather invokes some standard of reasonable precision in the use of language in the context of the circumstances. *In re Packard*, 751 F.3d 1307, 1313 (Fed. Cir. 2014). Appellant's claim, read in light of the Specification, provides reasonable precision for defining a distance between protein:DNA complexes. Accordingly, we reverse the Examiner's rejection of claim 41 as indefinite. The rejections of dependent claims 42 and 43 fall with claim 41.

35 U.S.C. § 103(a)

Claims 1, 2, 5–18, 21, 22, 24–26, 28 and 37

The Examiner finds Cai teaches using two existing assays, 3C and chromatin immunoprecipitation (ChIP)-loop assay, to determine the

structural organization of chromatin. (Non-Final Act. 7.) The ChIP assay includes the steps of (1) cross-linking DNAs of chromatin with proteins; (2) cutting the DNAs of chromatin with restriction enzymes; (3) tethering cross-linked protein:DNA complexes to at least one support (Sepharose beads); (4) ligating DNA ends on the same cross-linked protein:DNA complexes while the complexes are still tethered to the support; and (5) characterizing the DNA to identify structural organization of chromatin. (*Id.* at 10–11.)

The Examiner finds further that Lee teaches a method of using the ChIP assay including the steps of blunting the 5′-overhangs of the tethered protein:DNA complexes and ligating the blunt DNA ends. (*Id.* at 16.) In addition, the Examiner finds Dekker teaches high-throughput sequencing for identifying and quantifying the structural organization of chromatin. (*Id.* at 13–15.)

The Examiner acknowledges that Cai and Dekker do not teach blunting with biotinylated nucleotides. (*Id.* at 15.) But, because Wartiovaara teaches using biotin-modified nucleotides as polynucelotide labels, the Examiner determines that one of ordinary skill in the art would have been motivated to blunt the sticky ends of the DNAs with a biotinylated nucleotide. (*Id.* at 16.) The Examiner also determines that using biotinylated nucleotides to blunt the 5′-overhangs would have been a mere substitution of one nucleotide for another known in the field. (*Id*.) Accordingly, the Examiner concludes claim 1 would have been *prima facie* obvious over the prior art.

Appellant argues the Examiner failed to provide a "clear articulation of the reasons(s) why the claimed invention would have been obvious." (Appeal Br. 36, citing MPEP § 2143.) Particularly, Appellant objects to the

Examiner's use of block quotes, for example, arguing that the Examiner does not show where Cai teaches the step of tethering. (*Id.* at 37–38.)

We are not persuaded by Appellant's argument. Appellant's own citation to the Examiner's rejection includes the Examiner's description of Cai's teaching that "[t]he use of the protein A sepharose is a method of tethering." (Appeal Br. 38.) The Examiner has positively included the references in the statement of the rejection, *In re Hoch*, 428 F.2d 1341, 1342 n.3 (CCPA 1970), and has articulated "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007). Accordingly, we find that the Examiner has adequately explained the perceived shortcomings of the claims so that Appellant is properly notified and able to respond. *In re Jung*, 637 F.3d 1356, 1362 (Fed. Cir. 2011).

Appellant argues generally that combining Cai with the other references cited by the Examiner would render Cai unsuitable for its intended purpose.[13] (Reply Br. 7.) More specifically, Appellant argues that Cai's intended purpose is the targeted analysis of an individual protein, SATB1, on chromatin structure in response to a stimulus. (Appeal Br. 29.) Thus, Cai specifically analyzes a single chromatin constituent with an antibody and locus-specific PCR. (*Id.* at 30–32.) In contrast, Appellant

[13] Appellant repeatedly emphasizes the number of references cited by the Examiner. (*See* Reply Br. 6–7.) The Examiner's citation of up to nine references does not weigh against a holding of obviousness as "[t]he criterion . . . is not the number of references, but what they would have meant to a person of ordinary skill in the field of the invention. *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991)

argues that combining Cai with Dekker, Wartiovaara, and Lee would negate the specificity of the process taught in Cai. (*See id.* at 30–35.)

For example, Appellant contends that Dekker relates to a high-throughput analysis of the genome, in which information regarding the effect of SATB1 would be lost. (*Id.* at 30.) Appellant contends that "Wartiovaara teaches methods for amplifying or hybridizing the biotinylated DNA that are independent of any proteins bound to the DNA." (*Id.* at 34.) Because Wartiovaara's isolation by biotin is not sequence-specific, Appellant contends that isolation by biotin adds unnecessary complexity and reduces the specificity of Cai's process. (*Id.* at 35.) Appellant contends that Lee's blunting of nucleic acid fragments by adding universal primer binding sites dilutes Cai's desired signal in noise from the rest of the genome. (*Id.* at 36.) Accordingly, Appellant argues "the combination of Lee with Cai renders Cai unsuitable for its intended purpose of specific examination of particular fragments of a specific locus differentially bound by SATB1." (*Id.*)

We are not persuaded by Appellant's argument. We begin with Appellant's argument limiting Cai's teachings to determining the structural organization of chromatin only as it relates to SATB1. When determining obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986).

Cai teaches that, at the time of the invention, there were at least two different known assays, 3C and ChIP, for examining chromatin structure. (*See* Ans. 38–39.) Both Cai and Lee teach using the ChIP assay for determining the structural organization of chromatin. (*See* above.) The combined references teach that the ChIP assay may provide information

about site-specific chromatin structure (Cai), as well as "a whole-genome view of protein-DNA interactions when combined with DNA microarray analysis." (Lee 729.) Nothing in the prior art teaches that the proposed modification of Cai with Lee would result in an inoperable ChIP assay. *See In re Urbanski*, 809 F.3d 1237, 1244 (Fed. Cir. 2016). Therefore, we find that one of ordinary skill in the art would have been motivated to pursue the desirable genome-wide properties taught by Lee, even if that meant foregoing the specificity taught by Cai. *See id.*; *see also Medichem S.A. v. Rolabo S.L.,* 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("The fact that the motivating benefit comes at the expense of another benefit, however, should not nullify its use as a basis to modify the disclosure of one reference with the teachings of another. Instead, the benefits, both lost and gained, should be weighed against one another.")

Likewise, a person of ordinary skill in the art would have been motivated to apply Dekker's genome-wide analysis to the genome-wide ChIP assay taught by Cai and Lee. As for substituting Lee's "universal PCR priming sites" (Appeal Br. 35–36) with Wartiovaara's non-specific biotinylated primers (*id*. at 34), we find that a person of ordinary skill in the art would have made the substitution of known nucleotides given the desire for a non-specific, genome-wide assay. Accordingly, we agree with the Examiner that it would have been obvious to a person of ordinary skill in the art to combine the ChIP assay of Cai with the teachings of Dekker, Lee, and Wartiovaara, and we sustain the rejection of claim 1.

Appellant applies the same argument against the combination of Cai and the additional references cited by the Examiner as to claims 2, 5–18, 21,

22, 24–26, 28, and 37. (*See* Appeal Br. 39–43.) For the reasons set forth above, we sustain the Examiner's rejection of these claims.

Claims 41–43

The Examiner rejects claim 41 as obvious over Cai, Dekker, Lee, Wartiovaara, and Morrison as evidenced by GE Healthcare. (Final Act. 20.) Claim 41 recites:

> The method of claim 1, wherein the crosslinked protein:DNA complexes are tethered such that a majority of the individual protein:DNA complexes are separated from each other by a distance greater than about twice the greatest length from a 5'-overhang on a DNA of the chromatin to the nearest site of the crosslinking event on the DNA.

(Appeal Br. 49.)

The Examiner finds Morrison teaches non-antibody based alternatives to ChIP assays, as well using various beads for these assays. (Final Act. 28–29.) The Examiner cites GE Healthcare as teaching activated thiol Sepharose allows for covalent tethering. (*Id.* at 29.)

Appellant contends the Examiner does not point to any teaching of the elements in claims 41–43. (Appeal Br. 24–25.) Appellant argues that claims 41 recite active steps rather than mere intended results because they recite "observable, structural characteristics of practicing the claimed method." (*Id.* at 25–26.) As such, Appellant argues that the wherein clause of claim 41 is relevant to patentability and must be found in the art before the method of claim 41 is determined to be obvious. *(See id*.)

We are not persuaded by Appellant's argument because even when the wherein clause of claim 41 is given weight, the claimed method would

have been obvious. We begin with interpreting the claims. As discussed above, we agree with Appellant that claims 41–43 are not indefinite. Rather, claim 41 recites a distance between individual protein:DNA complexes that could be readily determined by a person of ordinary skill in the art. (*See* above.) The distance results from the choice of restriction enzyme, concentration of complexes, and surface area of the substrate used in the method. (*Id.*)

Because the distance depends on the restriction enzyme and substrate, we review the Specification's description of each feature. The Specification lists suitable restriction enzymes, including: MboI, which recognizes the sequence 5′-GATC, HindIII which recognizes the sequence 5′-AAGCTT, and BsrGI, which recognizes 5′-TGTACA. (Spec. ¶ 38.) The Specification teaches MboI is expected to produce fragments of 401 bp average size and HindIII is expected to produce fragments of 3461 bp average size. (*Id.* ¶ 99.) The Specification describes the substrate as "media, such as beads, colloids, and matrices with a well-defined surface area." (*Id.* ¶ 43.) The Specification does not describe the appropriate surface area, however, lists DynaBeads MyOne Streptavidin T1 Magnetic Beads as suitable beads for the process. (*Id.* ¶ 48.)

The Examiner cites prior art teaching surface-immobilized conformation capture assays using the same or similar restriction enzymes and supports. For example, Cai teaches performing a ChIP assay by digesting chromatin with *Sau3*AI and tethering to Sepharose 4B beads. (Non-Final Act. 10.) Lee teaches performing a ChIP assay with DNA fragments ranging from 200–600 bp and tethering to Dynabeads. (Lee 732,

745.) Morrison teaches performing a ChIP assay with protein A/G-agarose beads or activated thiol-Sepharose 4B beads. (Morrison 857.)

In sum, the Examiner finds that the combined prior art teaches the claimed process using similar components that would have been expected to give the same results. (Ans. 45.) "Where . . . the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . [The] fairness [of the burden-shifting] is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products." *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Because Appellant fails to direct us to evidence that the actual distances would be different, we sustain the Examiner's rejection of claim 41 over the combined prior art.

Claims 42 and 43 expressly recite the purpose and intended result of the claimed method, i.e., that intramolecular ligation is more frequent than intermolecular ligation (less than 36% of total ligation). (Appeal Br. 49–50.) The Specification discloses that the resulting intramolecular ligation occurs by using the claimed surface-immobilized conformation capture assay as opposed to a solution-based assay (e.g., HiC). (Spec. ¶¶ 95–101, Examples 3 and 4.) Appellant provides no evidence that more frequent intramolecular ligation, as compared to intermolecular ligation, results from variations within the surface-immobilized assay itself. Therefore, the recitations of claims 42 and 43 do not result in a manipulative difference in the steps of the claim. *See Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1375–1376 (Fed. Cir. 2018). Accordingly, we are not persuaded that claims would not have been obvious over the combined prior art

teaching the same method, and we sustain the Examiner's rejection of claims 42 and 43 over the prior art.

CONCLUSION

Upon consideration of the record and for the reasons given, we reverse the Examiner's rejection under 35 U.S.C. § 112, first paragraph.

We affirm the Examiner's rejection under 35 U.S.C. § 103(a).

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	112, second paragraph	Indefiniteness		1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43
41–43	112, second paragraph	Indefiniteness		41–43
1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	103(a)	Cai, Dekker, Lee, Wartiovaara	1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	
8–10, 13, 14	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, Shiio	8–10, 13, 14	
11, 12, 15–17	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, Shiio, Blander, Fujita	11, 12, 15–17	
1, 2, 5–7, 18, 21, 22, 24–26, 28, 37, 38, 40, 41	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, GE Healthcare	1, 2, 5–7, 18, 21, 22, 24–26, 28, 37, 38, 40, 41	

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
8–17	103(a)	Cai, Dekker, Lee, Wartiovaara, Morrison, GE Healthcare, Blander, Fujita	8–17	
Overall Outcome			1, 2, 5–18, 21, 22, 24–26, 28, 37, 41–43	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136.

AFFIRMED