Active Motif, Inc. v. EpiCypher, Inc. Doc. 61

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ACTIVE MOTIF, INC.	:	
Plaintiff	:	**CIVIL ACTION**
	:	
v.	:	
	:	**NO. 1:20-cv-01568-MSG**
EPICYPHER, INC.,	:	
	:	
Defendant.	:	

MEMORANDUM OPINION

Goldberg, J. **April 5, 2022**

Before me is a patent infringement case wherein Plaintiff Active Motif, Inc. ("Plaintiff") alleges that Defendant EpiCypher, Inc. ("Defendant") has infringed U.S. Patent No. 10,689,643 through the development and marketing of Defendant's CUTANA™ CUT&Tag Assays and CUTANA™ Direct-to-PCR CUT&Tag Protocols.[1] The parties currently seek construction of six of the patent's terms pursuant to Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996).

I. FACTUAL BACKGROUND

A. Epigenetics

DNA is a biological molecule, made up of sequences of nucleotides, that carries genetic instructions for the development, functioning, growth, and reproduction of organisms. (Joint Claim Construction Br. ("JCCB") at 1.) Epigenetics is the "study of how [one's] behaviors and environment can cause changes that affect the way [one's] genes work." *Genomics & Precision*

[1] On May 18, 2017, then Chief Judge D. Brooks Smith of the U.S. Court of Appeals for the Third Circuit designated me as a visiting judge for the District of Delaware, pursuant to 28 U.S.C. § 292(b), to handle this matter and other Delaware cases.

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Health: What Is Epigenetics?, CDC, https://www.cdc.gov/genomics/disease/epigenetics.htm (last visited Feb. 22, 2022). Epigenetic changes are "reversible and do not change [one's] DNA sequence, but they can change how [one's] body reads a DNA sequence." (Id.) One type of epigenetic changes is "histone modifications." (Id.; JCCB at 2.)

Inside a cell, DNA is stored in the form of chromatin—a combination of DNA and particular proteins (histones). (JCCB at 2.) These histones act as a spool around which the DNA can wind, providing a mechanism by which chromatin is organized. (Id.) When histones are modified, they can influence how chromatin is arranged and, thereby, whether genes in the DNA are turned on or off. (Id.) Proteins called transcription factors bind to specific DNA sequences in the chromatin, turning the genes associated with those DNA sequences on and off. (Id.)

B. The '643 Patent

U.S. Patent No. 10,689,643 (the "'643 Patent") reflects the development of a method to allow researchers to investigate epigenetic changes and transcription factor binding. (JCCB at 2.) The '643 Patent describes the advantages of the claimed invention over existing techniques, including the investigation of multiple histone modifications or the binding of multiple transcription factors in a single experiment. (Id. at 2-3.) Plaintiff sought protection for its employees' inventions in a provisional patent application filed November 22, 2011. (Id. at 3.)[2] The '643 Patent was ultimately issued on June 23, 2020. (Id.)

The invention claimed in the '643 Patent enables investigation of particular locations of chromatin (e.g., histones, DNA-binding sites, and proteins that bind at those chromatin locations

[2] The inventors then filed U.S. Application No. 14/359,877 on November 23, 2012 ("the parent application"), which issued on April 10, 2018, as U.S. Patent No. 9,938,524. (Id. at 3.) A second provisional patent application followed on May 22, 2013. (Id.) U.S. Application No. 14/892,911, a continuation-in-part of the parent application, was filed May 22, 2014. (Id.) U.S. Application No. 14/892,911 issued as the '643 Patent on June 23, 2020. (Id.)

(such as transcription factors)). (Id.) The claimed method uses a targeting protein to deliver another protein ("transposase enzyme") to a location in the chromatin. (Id.) This transposase enzyme works according to a "cut and paste mechanism" by cutting a DNA sequence in the chromatin and inserting a new DNA sequence ("transposon cassette"). (Id.) The '643 Patent's transposon cassette includes a "unique barcode sequence" that corresponds to the targeting antibody (i.e., targeting protein). (Id. at 5-6.) The inclusion of this barcode "enables simultaneous use of multiple antibodies [i.e., targeting proteins] in the same sample and experiment." (Id. at 6.) The '643 Patent's transposon cassette also includes "transposase recognition sequences" and "primer sites." (Id. at 5.)

The transposase enzyme is bound to the transposon cassette, forming a complex ("transposome"). (Id. at 3.) The targeting protein delivers the transposome to a target protein or DNA binding site (location in chromatin). (Id.) The transposase enzyme inserts a DNA sequence from the transposon cassette into a DNA sequence of the chromatin, thereby "tagging" the DNA sequence of the chromatin (marking a location in the chromatin near the targeted protein or DNA-binding site). (Id.) The tagged DNA sequence is subsequently copied many times over, using a process called PCR amplification. (Id. at 4.) DNA libraries can be created via this process; this process is sometimes referred to as "tagmentation." (Id. at 5.)[3] Plaintiff's tagmentation process described in the '643 Patent is referred to as "Transposase-Assisted Multi-analyte Chromatin Immunoprecipitation" or "TAM-ChIP." (Id.) In TAM-ChIP, chromatin is extracted from cells and

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[3] "Tagmentation is the initial step in library prep where unfragmented DNA is cleaved and tagged for analysis." *Reduce Your Library Prep Time with On-Bead Tagmentation*, ILLUMINA, https://www.illumina.com/techniques/sequencing/ngs-library-prep/tagmentation.html (last visited Feb. 22, 2022).

then contacted with a transposome that has been conjugated to a targeting antibody (i.e., targeting protein) that binds to a target protein in the chromatin. (Id.)

Claim 1 of the '643 Patent, the only independent claim, recites in its entirety:

> A method of making a nucleic acid sequence library comprising:
> a. **extracting chromatin from cells** to provide a sample containing chromatin;
> b. adding to said sample containing chromatin at least one assembled conjugate comprising a **targeting protein** covalently conjugated to a stable transposase:transposon complex containing a transposase complexed with a transposon cassette, wherein:
> (i) the **targeting protein** binds a **target protein** or a target DNA-binding site; and
> (ii) the transposon cassette comprises:
> (1) **transposase recognition sequences required for catalysis of a DNA integration reaction**;
> (2) **one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein**; and
> (3) **primer sites for DNA amplification**;
> c. allowing said at least one conjugate to locate at its/their **target proteins** and/or target DNA-binding sites in said chromatin;
> d. tagging nucleic acid in said chromatin with said conjugate by inducing an intermolecular reaction between said transposase recognition sequences and said nucleic acid; and
> e. performing PCR amplification of the tagged nucleic acid using the primer sites.

('643 Patent, col. 41, ll. 1-27 (Ex. A) (emphasis added).)

II. LEGAL STANDARD

The first step in a patent infringement analysis is to define the meaning and scope of the claims of the patent. Markman, 52 F.3d at 976. Claim construction, which serves this purpose, is a matter of law exclusively for the court. Id. at 979.

The words of a patent claim "are generally given their ordinary and customary meaning." Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)). The "ordinary and customary" meaning of a claim term is the "meaning that the term would have to a person of ordinary skill in the art

[PHOSITA] in question at the time of the invention, i.e., as of the effective filing date of the patent application." Id. at 1313. The PHOSITA "is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id.

In some situations, the ordinary meaning of claim language as understood by a PHOSITA may be readily apparent, and "claim construction . . . involves little more than the application of the widely accepted meaning of commonly understood words." Id. at 1314. A determination that a claim term has the "plain and ordinary meaning" may be inadequate when a term has more than one "ordinary" meaning or when reliance on a term's "ordinary" meaning does not resolve the parties' dispute. O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., 521 F.3d 1351, 1361 (Fed. Cir. 2008). It is not appropriate to leave to the jury the task of resolving claim construction disputes. Cobalt Boats, LLC v. Brunswick Corp., 773 F. App'x 611, 614 (Fed. Cir. 2019).

When the ordinary meaning is not readily apparent, the court looks to "the words of the claims . . . , the . . . specification, the prosecution history, and extrinsic evidence." Phillips, 415 F.3d at 1314 (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)). The context in which a term is used in the claim can be highly instructive; the usage of a term in one claim can illuminate the meaning of the same term in other claims. Id. Where a claim lists elements separately, "the clear implication of the claim language" is that those elements are "distinct component[s]" of the patented invention. Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (citing Gaus v. Conair Corp., 363 F.3d 1284, 1288 (Fed. Cir. 2004)). The doctrine of claim differentiation counsels against constructions that render claim language superfluous. Atlas IP, LLC v. Medtronic, Inc., 809 F.3d 599, 607 (Fed. Cir. 2015).

Claims are read in view of the specification. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). Usually, the specification is "dispositive; it is the single best guide to the meaning of a disputed term." Vitronics, 90 F.3d at 1582. A party "may not read a limitation into a claim from the written description" but it "may look to the written description to define a term already in a claim limitation, for a claim must be read in view of the specification of which it is a part." Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed. Cir. 1998). The specification may divulge a "special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." Phillips, 415 F.3d at 1316. Although the specification often describes specific embodiments of the invention, the Federal Circuit has repeatedly warned against confining the claims to those embodiments. Id. at 1323. When a specification reveals "an intentional disclaimer, or disavowal, of claim scope by the inventor," then that inventor "has dictated the correct claim scope, and the inventor's intention, as expressed in the specification, is regarded as dispositive." Phillips, 415 F.3d at 1316.

The court should also consider the patent's prosecution history. Markman, 52 F.3d at 980; Phillips, 415 F.3d at 1317. The prosecution history "consists of the complete record of the proceedings before the [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317. Because the prosecution history "represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." Id.

If ambiguity still exists after considering all the intrinsic evidence, the court may rely on extrinsic evidence, which "consists of all evidence external to the patent and prosecution history,

including expert and inventor testimony, dictionaries, and learned treatises." Id. at 1317-18 (quoting Markman, 52 F.3d at 980) (noting that "conclusory, unsupported assertions by experts . . . are not useful" and that courts should discount expert testimony that is at odds with the construction mandated by the claims, the specification, and prosecution history). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" Phillips, 415 F.3d at 1317 (quoting C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 (Fed. Cir. 2004)).

A construction that "stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." Renishaw, 158 F.3d at 1250.

III. DISCUSSION

Six claim terms of the '643 patent are in dispute: (1) "extracting chromatin from cells"; (2) "target protein"; (3) "targeting protein"; (4) "transposase recognition sequences required for catalysis of a DNA integration reaction"; (5) "primer sites for DNA amplification"; and (6) "one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein."[4] I address each claim term below.

A. "Extracting chromatin from cells" ('643 Patent claim 1)

The first disputed claim term is the phrase "extracting chromatin from cells," which appears in claim 1 of the '643 Patent. ('643 Patent, col. 41, ll. 4-5.) The parties' proposed constructions are below. (JCCB 11, 16.)

Active Motif's Proposed Construction	EpiCypher's Proposed Construction
separating chromatin from at least some cellular components	extracting chromatin from cells to generate isolated chromatin

[4] Construction of these claim terms applies to the entirety of the '643 patent.

Plaintiff Active Motif's proposed construction requires chromatin that is "separated from *at least some* cellular components," whereas EpiCypher's proposed construction requires "chromatin that is *isolated*." (Id. at 22.) The '643 Patent does not expressly define "extracting chromatin from cells." (Id. at 11.) Nor does it define the term "isolated chromatin," used by EpiCypher in its proposed construction. (Id.) Considering the various sources identified by the parties and for the following reasons, I will adopt Plaintiff's proposed definition.

1. Claim Language

The words of a patent claim "are generally given their ordinary and customary meaning." Phillips, 415 F.3d at 1312 (quoting Vitronics, 90 F.3d at 1582). The "ordinary and customary" meaning of a claim term is the "meaning that the term would have to a [PHOSITA] in question at the time of the invention, i.e., as of the effective filing date of the patent application." Id. at 1313. The PHOSITA "is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id.

In claim 1 of the '643 Patent, the step "extracting chromatin from cells" is performed "to provide a sample containing chromatin." ('643 Patent, col. 41, ll. 4-5.) Claim 1 recites the extraction of chromatin from cells, not—as Defendant suggests—from nuclei. (See id.) Consistent with the claim language, so long as the chromatin is removed from cellular components to a degree sufficient to make it accessible to the transposase enzyme, the chromatin has been "extracted," and a sample containing chromatin has been provided.

2. Specification

The specification is often "dispositive; it is the single best guide to the meaning of a disputed term." Vitronics, 90 F.3d at 1582. A party "may not read a limitation into a claim from

the written description" but it "may look to the written description to define a term already in a claim limitation, for a claim must be read in view of the specification of which it is a part." Renishaw, 158 F.3d at 1248.

The Summary of the Invention section explains that part of the invention covered by the '643 Patent is "methods involv[ing] extracting and optionally fragmenting chromatin from a prepared [cell] sample." ('643 Patent, col. 4, ll. 19-20.) The Detailed Description of the Embodiments section describes "*chromatin fragments extracted from isolated cells*, tissue, or whole organs (or other cell-containing biological samples) to allow specific antibody-protein binding." (Id. at col. 12, ll. 58-61 (emphasis added).) This language echoes the claim language above, which requires that chromatin is removed (or taken away) from cellular (as opposed to solely nuclear) components.

Example 1 of the Methods and Representative Examples section of the specification provides that "*chromatin [was] extracted from . . . cells* (a human breast cancer cell line) following established protocols, and *isolated DNA was then purified*." (Id. at col. 17, ll. 16-18 (emphasis added).) This verbiage demonstrates not only that chromatin is required to be taken from cells, as opposed to nuclei, but also that isolation and purification are different concepts.

Example 9 provides that a "*lysis* buffer [is] used to *extract chromatin from cells*." (Id. at col. 24, l. 17 (emphasis added).) "The use of cell lysates, in which the cell membrane is broken down and some cellular components are dispersed, is also consistent with the plain and ordinary meaning, namely, separating chromatin from at least some cellular components." (JCCB at

14-15.)[5] Thus, the removal (or, "breaking down") of the cell membrane meets the definition of "extracting chromatin from cells."

Unlike other examples in the specification, Example 11 expressly contemplates the "extract[ion of] chromatin *from the nuclei* of mammalian cells." ('643 Patent, col. 27, ll. 32-33 (emphasis added).) The patentee knew the difference between extraction from cells and extraction from nuclei—and chose when to use each phrase. That same example, Example 11, provides that "crude *cell lysates containing chromatin, rather than isolated chromatin* could be used as transposase substrates." (Id. at col. 27, ll. 47-49 (emphasis added).) Thus, both isolated chromatin *and* cell lysates could be used as transposase substrates—the substance on which an enzyme acts.

In total, the specification reflects that chromatin is required to be removed from cells, not necessarily from nuclei, as defendant suggests, to "generate isolated chromatin."

3. Prosecution History

The court should also consider the patent's prosecution history. Markman, 52 F.3d at 980; Phillips, 415 F.3d at 1317. United States Patent No. 6,846,622 ("Heffron et al.") was cited during prosecution of the parent application[6] and defines "[a]n 'isolated' biological component" as one that has been "substantially separated, produced apart from, or purified away from other biological components in the cell of the organism in which the component naturally occurs." (Heffron et al., col. 7, ll. 1-5 (Ex. D).) Thus, Heffron et al. shows that a PHOSITA would understand chromatin that has been "isolated" to mean that chromatin has been "produced apart from" other cellular components. While chromatin that has been "purified away from" cellular components would also certainly meet the definition of chromatin that has been "isolated," purification is not required.

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[5] "A cell lysate is a cell in which the outer wall of the cell . . . has been broken down." (Markman Hr'g Tr. 53:7-8.)

[6] *See supra* note 3.

United States Patent Application Publication No. US 2016/0060691 ("Giresi et al."), which was submitted during prosecution of the '643 Patent, defined the term "chromatin isolated from a population of cells" as "a source of chromatin that is caused to be made available." (Giresi et al. ¶ [0076] (Ex. E).) Thus, a PHOSITA would understand chromatin that has been "isolated" to mean chromatin that is "available," as Plaintiff proposes. Further isolation of the chromatin, as proposed by Defendant, is not required. Giresi et al. also provided that "[i]solated nuclei . . . as well as isolated chromatin . . . are both considered types of chromatin isolated from a population of cells." (Id.)

The "ordinary and customary" meaning of a claim term is the "meaning that the term would have to a person of ordinary skill in the art [PHOSITA] in question at the time of the invention, i.e., as of the effective filing date of the patent application." Phillips, 415 F.3d at 1313. Heffron et al. and Giresi et al. show that Plaintiff's construction of "extracting chromatin from cells" ("separating chromatin from at least some cellular components") aligns with what a PHOSITA understands chromatin that has been "isolated" to mean. The '643 Patent does not require that the chromatin be removed from the nucleus (as Defendant proposes); the product of a lysed cell, for example, would be sufficient. As explained by Plaintiff's counsel at the Markman hearing, the "targeting protein . . . can access the chromatin while it's still in the nucleus." (Markman Hr'g Tr. 60:2-3.) "Permeabilized cells, cell lysates, isolated nuclei, these are all examples in which the cells have been treated in some way to make the chromatin more available." (Id. at 60:7-10.)

4. Extrinsic Evidence

I decline to consider the extrinsic evidence offered. "In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence." Vitronics, 90 F.3d at 1583. Here, the

proper construction of "extracting chromatin from cells" is abundantly clear from the '643 Patent's claim language, specification, and prosecution history. Accordingly, reference to extrinsic evidence is improper.

5. Conclusion as to "extracting chromatin from cells"

For all of the foregoing reasons, I adopt the construction proposed by Plaintiff and construe the term "extracting chromatin from cells" as "**separating chromatin from at least some cellular components**."

B. "Target protein" ('643 Patent claims 1, 6, 10, 20)

The second disputed claim term is the phrase "target protein," which appears in claims 1, 6, 10, and 20 of the '643 Patent. ('643 Patent, col. 41, ll. 11, 20, 37; Id. at col. 42, ll. 8, 33.) Plaintiff's and Defendant's proposed constructions are below. (JCCB 46-47.)

Active Motif's Proposed Construction	EpiCypher's Proposed Construction
a protein that is located and bound by the targeting protein	a protein in the chromatin that the targeting protein binds to

The parties' dispute centers on whether the target proteins "must be in the chromatin to begin with," as proposed by Defendant, or whether the target proteins could also be "antibodies that are added to the reaction that merely bind to the chromatin." (Markman Hr'g Tr. 102:2-3, 103:1-2.) For the following reasons, I will adopt Plaintiff's proposed definition.

1. Claim Language

As noted above, the first point of reference in claim construction involves review of the claim language and the surrounding specification. In claim 1 of the '643 Patent, the "targeting protein binds a target protein or a target DNA-binding site" and "at least one conjugate [locates] at its/their target proteins . . . in said chromatin." ('643 Patent, col. 41, ll. 11-12, 19-21.)

This language seems to reflect that the target protein exists "in said chromatin." But the claim language alone does not resolve the parties' dispute here—whether the protein must be "native" to the chromatin. Therefore, review of the specification is required.

2. Specification

The Overview of Epigenetic Mechanisms section (within the Background of the Disclosure of the specification) describes "proteins, such as RNA polymerase II or histone modifications." (Id. at col. 3, ll. 2-3.)) Example 2 of the Methods and Representative Examples section of the specification describes "*chromatin associated protein* (RNA polymerase II) and a *structural chromatin protein*, a histone." (Id. at col. 18, ll. 57-58 (emphasis added).)

This specification information, read in conjunction with the language of dependent Claim 10 ("the target protein is a histone or a polymerase") (Id. at col. 42, ll. 8-9), reflects that the "target protein" can be "a histone or polymerase" and that RNA polymerase II is a "chromatin associated protein" rather than a "structural chromatin protein." Thus, the target protein does not have to "be in the chromatin to begin with," as proposed by Defendant.

The Federal Circuit has repeatedly warned against confining the claims to specific embodiments of the invention. Phillips, 415 F.3d at 1323. Furthermore, a party "may not read a limitation into a claim from the written description." Renishaw, 158 F.3d at 1248. The patentee chose when to use the terms "native target within the chromatin" and "structural chromatin protein." ('643 Patent, col. 3, 11. 44-45; Id. at col. 16, 11. 36-37). The patentee also chose when to use the term "chromatin associated protein." The phrase "in said chromatin" in claim 1 is therefore *not* limited to "native target[s] within the chromatin," because the claims cover target proteins (e.g., RNA polymerase II) that are *associated* with the chromatin, not necessarily structurally part of the chromatin.

Lastly, the doctrine of claim differentiation counsels against constructions that render claim language superfluous. Atlas IP, 809 F.3d at 607. Claim 1 of the ’643 Patent provides that “at least one conjugate [locates] at its/their target proteins . . . *in said chromatin*.” (’643 Patent, col. 41, ll. 19-21 (emphasis added).) Defendant’s proposed construction of “a protein in the chromatin that the targeting protein binds to” would render the “in said chromatin” language of claim 1 superfluous and therefore is improper. Moreover, Defendant’s proposed construction is not supported by the additional claim language and specification sections discussed above.

3. Conclusion as to “target protein”

For all of the foregoing reasons, I adopt the construction proposed by Plaintiff and construe the term “target protein” as “**a protein that is located and bound by the targeting protein**.”

C. “Targeting protein” (’643 Patent claims 1, 6, 7, 8, 9, 10, 20, 21)

The third disputed claim term is the phrase “targeting protein,” which appears in claims 1, 6, 7, 8, 9, 10, 20, and 21 of the ’643 Patent. (’643 Patent, col. 41, ll. 7, 11, 36, 38, 40; Id. at col. 42, ll. 5, 7, 35, 40.) Plaintiff’s and Defendant’s proposed constructions are below. (JCCB 37, 39.)

Active Motif’s Proposed Construction	EpiCypher’s Proposed Construction
a protein that locates and binds to a target	a protein that binds to its target protein or target DNA site in the chromatin

The parties agree that the subject matter claimed in the ’643 patent includes a targeting protein that binds to a target protein. (Id. at 39.) They dispute only whether this *target protein*, bound by the targeting protein, can be outside of the chromatin or whether it must be in the chromatin. (Id. at 39-40.) In other words, the parties’ disagreement concerns the *target protein*, not the *targeting protein*.

This dispute is resolved by the "target protein" analysis above in Part III.B. Accordingly, I adopt the construction proposed by Plaintiff—and construe the term "targeting protein" as "**a protein that locates and binds to a target**."

D. "Transposase recognition sequences required for catalysis of a DNA integration reaction" ('643 Patent claim 1)

The fourth disputed claim term is the phrase "transposase recognition sequences required for catalysis of a DNA integration reaction," which appears in claim 1 of the '643 Patent. ('643 Patent, col. 41, ll. 14-15.) Plaintiff's and Defendant's proposed constructions are below. (JCCB 47-48, 49.)

Active Motif's Proposed Construction	EpiCypher's Proposed Construction
nucleotide sequences capable of recognition by the transposase that must be present for the DNA integration reaction to occur	sequences in the transposon cassette that are recognized by the transposase and that are required for catalysis of a DNA integration reaction

The dispute is whether this limitation requires an explicit construction that such sequences are located "in the transposon cassette," as Defendant proposes. (Id. at 48-49.) Considering the various sources identified by the parties and for the following reasons, I will adopt Defendant's proposed definition.

1. Claim Language

As noted above, the first point of reference in claim construction involves review of the claim language and the surrounding specification. Claim 1 of the '643 Patent provides that "the *transposon cassette comprises* . . . transposase recognition sequences required for catalysis of a DNA integration reaction." ('643 Patent, col. 41, ll. 13-15 (emphasis added).) In other words, the transposon cassette is made up of (or, includes) transposase recognition sequences. This claim language supports Defendant's proposed construction. Plaintiff even acknowledges that "a

transposon cassette *contains* certain features including '[t]ransposase recognition sequences.'" (JCCB at 48 (emphasis added) (quoting '643 Patent, col. 12, ll. 15-27).)

2. Specification

The Field of the Invention section provides that "[t]he present invention is in the field of epigenetics. More specifically, . . . epigenetic analysis based on the *use of transposons* to specifically target specific regions of chromatin." ('643 Patent, col. 1, ll. 30-34 (emphasis added).) Thus, the description of the invention expressly contemplates the use of transposon cassettes.

The Summary of the Invention section of the specification also provides that "antibody-transposome complexes . . . comprise an antibody that binds a [target protein] conjugated to a *transposome that comprises a transposase and a transposon cassette*." (Id. at col. 4, ll. 57-61 (emphasis added).) Again, the transposon cassette is a key part of this invention. The same specification section describes "contacting a . . . chromatin sample with an antibody-oligonucleotide . . . , wherein the *oligonucleotide* is double stranded and *comprises* at least two *recognition [sequences]* . . . , primer sites for amplification, at least one bar code sequence," among other things. (Id. at col. 5, ll. 22-30 (emphasis added).)

The Detailed Description of the Embodiments section provides that a "transposase:transposon complex . . . [is] charged with synthetic *oligonucleotide*(s) that *comprise* a *transposon cassette*." (Id. at col. 12, ll. 22-24 (emphasis added).) A "*transposon cassette contain[s]* the following feature[] . . . [t]ransposase recognition sequences required by the for catalysis of the DNA integration reaction." (Id. at col. 12, ll. 24-27 (emphasis added).) Thus, the oligonucleotide (which is contacted with the chromatin sample) comprises the transposon cassette, which in turn contains the transposase recognition sequences. The specification, which makes clear

that the transposase recognition sequences are housed within the transposon cassette, supports Defendant's proposed construction.

3. Prosecution History

During prosecution, an article published in *Science Magazine* titled "Three-Dimensional Structure of the Tn5 Synaptic Complex Transposition Intermediate" ("Davies et al.") was submitted as non-patent literature for consideration by the PTO examiner. (Ex. B at ACTM00001455; Ex. K at ACTM00000856.) Davies et al. provides that "[o]ne class of transposable elements is a DNA sequence that has the capacity, in the presence of the transposase protein specific for its end sequences, of moving (transposing) from one site in the genome (donor DNA) to a second site (target DNA). DNA transposable elements include simple insertion sequences [and] transposons," among other things.

Plaintiff argues that this "Davies reference does not require transposase end sequences be located in a 'transposon cassette.' Rather, [Davies et al.] explains that such sequences can appear in a variety of 'DNA transposable elements.'" (JCCB at 49.) However, Plaintiff fails to connect the language relied on from Davies et al. to its conclusion that transposase end sequences need not be located in the transposon cassette. Indeed, in Plaintiff's Opening Position statement, the term "transposable element" is not used once. (Id. at 1-4.) Instead, Plaintiff provides that "[i]n the *context of the present invention*, this transposase enzyme works according to a 'cut and paste mechanism' by cutting a DNA sequence in the chromatin at the location of interest, and *inserting a new sequence*, called a '*transposon cassette*.'" (Id. at 3 (emphasis added).) In its Opening Position, Plaintiff describes how the "the transposase enzyme inserts a DNA *sequence from the transposon cassette* into a DNA sequence of the chromatin at the target location." (Id.) Plaintiff actively emphasizes the fact that the transposon cassette contains the DNA sequences to be

inserted. As such, Plaintiff has failed to show that transposase end sequences need not be located in the transposon cassette.

4. Extrinsic Evidence

District courts may rely on extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Phillips, 415 F.3d at 1317–18 (quoting Markman, 52 F.3d at 980). Here, Plaintiff's expert Jeremy Edwards agreed in his deposition that "transposase recognition sequences . . . are in the transposon cassette." (Ex. P at 46:4-8.)

While the doctrine of claim differentiation counsels against constructions that render claim language superfluous, Atlas IP, 809 F.3d at 607, I agree with Defendant, who points out that "Active Motif has not explained why it maintains its objection to EpiCypher's proposed construction, which provides helpful guidance to the jury regarding the scope of the claims." (JCCB at 51.)

5. Conclusion as to "transposase recognition sequences required for catalysis of a DNA integration reaction"

For all of the foregoing reasons, I adopt the construction proposed by Defendant and construe the term "transposase recognition sequences required for catalysis of a DNA integration reaction" as "**sequences in the transposon cassette that are recognized by the transposase and that are required for catalysis of a DNA integration reaction**."

E. "Primer sites for DNA amplification" ('643 Patent claim 1)

The fifth disputed claim term is the phrase "primer sites for DNA amplification," which appears in claim 1 of the '643 Patent. ('643 Patent, col. 41, l. 18.) Plaintiff's and Defendant's proposed constructions are below. (JCCB 79.)

Active Motif's Proposed Construction	EpiCypher's Proposed Construction
regions of a nucleotide sequence where at least one primer can bind to enable DNA amplification	sequences in the transposon cassette to which primers bind during PCR amplification

The primary dispute with respect to this term is whether the sites are located in the transposon cassette, as Defendant proposes. (Id.) Considering the various sources identified by the parties and for the following reasons (and in alignment with my analysis above in Part III.D), I will adopt Defendant's proposed definition.

1. Claim Language

As noted above, the first point of reference in claim construction involves review of the claim language and the surrounding specification. Claim 1 of the '643 Patent provides that "the *transposon cassette comprises* . . . primer sites for DNA amplification." ('643 Patent, col. 41, ll. 13-18 (emphasis added).) In other words, the transposon cassette is made up of (or, includes) primer sites for DNA amplification. As such, the claim language supports Defendant's proposed construction. Plaintiff even acknowledges that "primer sites for DNA amplification" are "a feature of the transposon cassette." (JCCB at 81.)

2. Specification

The Summary of the Invention section provides that "antibody-transposome complexes . . . comprise an antibody that binds a [target protein] conjugated to a *transposome that comprises a transposase and a transposon cassette*." ('643 Patent, col. 4, ll. 57-61 (emphasis added).) The transposon cassette is a key part of this invention. The same specification section describes "contacting a . . . chromatin sample with an antibody-oligonucleotide . . . , wherein the *oligonucleotide* is double stranded and *comprises* at least two recognition [sequences] . . . , *primer sites for amplification*, at least one bar code sequence," among other things. (Id. at col. 5, ll. 22-30 (emphasis added).)

The Detailed Description of the Embodiments section provides that a "transposase:transposon complex . . . [is] charged with synthetic *oligonucleotide*(s) that *comprise* a *transposon cassette*." (Id. at col. 12, ll. 22-24 (emphasis added).) This section also includes "the insertion of the *transposon cassette containing* bar-code sequences and . . . *primer sites*." ('643 Patent, col. 14, ll. 4-6.) As is true for the transposase recognition sequences, the oligonucleotide (which is contacted with the chromatin sample) comprises the transposon cassette, which in turn contains the primer sites for amplification. The specification, which makes clear that the primer sites for amplification are housed within the transposon cassette, supports Defendant's proposed construction.

3. Extrinsic Evidence

Here, Plaintiff's expert Jeremy Edwards agreed in his deposition that "the primer sites for DNA amplification [are] also in the transposon cassette." (Ex. P at 46:15-19.)

While the doctrine of claim differentiation counsels against constructions that render claim language superfluous, Atlas IP, 809 F.3d at 607, I agree with Defendant, who points out that "Active Motif has offered no explanation for its objections to EpiCypher's proposed construction, which provides helpful guidance to the jury regarding the scope of the claims." (JCCB at 81.)

4. Conclusion as to "primer sites for DNA amplification"

For all of the foregoing reasons, I adopt the construction proposed by Defendant and construe the term "primer sites for DNA amplification" as "**sequences in the transposon cassette to which primers bind during PCR amplification**."

F. "One or more oligonucleotide bar code sequences to uniquely identify the conjugated protein" ('643 Patent claim 1)

The sixth disputed claim term is the phrase "one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein," which appears in claim 1 of the '643

Patent. ('643 Patent, col. 41, ll. 16-17.) Plaintiff's and Defendant's proposed constructions are below. (JCCB 51, 56.)

Active Motif's Proposed Construction	EpiCypher's Proposed Construction
one or more short, known nucleotide sequences that uniquely identify the conjugated protein	one or more oligonucleotide sequences in the transposon cassette that are separate from the transposase recognition sequences and the primer sites and that uniquely identify the conjugated targeting protein to distinguish it from other conjugated targeting proteins

Defendant EpiCypher seeks to require that the "oligonucleotide bar code sequences" (1) distinguish the conjugated targeting protein from other conjugated targeting proteins, and (2) be "separate" from the transposase recognition sequences and primer sites. (Id. at 51.) Considering the various sources identified by the parties and for the following reasons, I will partially adopt Defendant's proposed definition.

1. Claim Language

As noted above, the first point of reference in claim construction involves review of the claim language and the surrounding specification. Claim 1 of the '643 Patent provides that "the transposon cassette comprises . . . one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein." ('643 Patent, col. 41, ll. 13-17.) Claim 20 of the '643 Patent recites the following:

> The method of claim 1, comprising adding to said provided sample containing chromatin a plurality of the complexes, wherein each complex comprises a targeting protein that targets a different target protein or target DNA binding site and each complex comprises a different bar code sequence to uniquely identify the targeting protein of the complex.

(Id. at col. 42, ll. 30-36.) Unlike claim 1, claim 20 requires "a plurality" of transposase:transposon complexes to be added to the sample containing chromatin.

Under claim 20, each transposase:transposon complex has a targeting protein that targets a different target protein and a different barcode sequence to uniquely identify the targeting protein of the complex. Claim 20 expressly contemplates "multiplex analysis of different chromatin proteins in a single sample." (JCCB 6-7.)

What claim 20 covers is different from what claim 1 covers: adding to the chromatin at least *one transposase:transposon complex* that contains *one* or more *oligonucleotide barcode sequences* to uniquely identify the conjugated protein. Claim 1 shows that "[t]he invention encompasses methods that use a single targeting protein-transposase conjugate, as well as multiple targeting protein-transposase conjugates." (Id. at 52-53.) Defendant acknowledges that "claim 1 is drafted to cover both single-plexing and multiplexing methods." (Id. at 64.) Because claim 1 covers single-plexing,[7] it does not require that the bar code distinguish the conjugated targeting protein from other conjugated targeting proteins. Thus, claim 1 in light of claim 20 does not support Defendant's contention with respect to distinguishing the targeting protein.

2. Specification

Although it appears in claims 1 and 20 of the '643 Patent, the term "uniquely identify" does not appear in the surrounding specification. In the Summary of the Invention section of the specification, the phrase "at least one bar code sequence to identify the conjugated antibody" is used twice. ('643 Patent, col. 5, ll. 30-31, 42-43.)

In the Detailed Description of the Embodiments section, the specification provides the following:

> [A] transposon cassette containing the following features . . . unique bar code *sequences* (i.e., short nucleotide sequences . . .) that *uniquely label* an oligonucleotide species so that it can be *distinguished from other oligonucleotide*

[7] A "singleplex method" is one in which "you only can look at a single target protein at a time." (Markman Hr'g Tr. 72:3-5.)

> *species* in the reaction, and which correspond to a particular antibody . . . for antibody identification in *multi-analyte applications* in which multiple antibodies are used simultaneously with the same sample material.

(Id. at col. 12, ll. 24-42.) The (one and) only time that the phrase "uniquely label" is used in the specification is to describe multi-analyte applications. Both parties agree that claim 1 covers single-analyte applications ("single-plexing"). Moreover, although the specification often describes specific embodiments of the invention (e.g., multi-analyte applications), the Federal Circuit has repeatedly warned against confining the claims to those embodiments. Phillips, 415 F.3d at 1323.

Example 5 of the Methods and Representative Examples section of the specification describes various embodiments, one being "TAM-ChIPs wherein antibody-transposase conjugates are . . . used singly or simultaneously, and with different degrees of complexity (two-plex, three-plex, etc.), including versions with each conjugate bearing a unique bar-code sequence for antibody identification." ('643 Patent, col. 21, ll. 48-52.) This example does *not* require that the barcodes "uniquely label an oligonucleotide species so that it can be distinguished from other oligonucleotide species in the reaction, and which correspond to a particular antibody." (Cf. id. at col. 12, ll. 24-42.) For these reasons, I do not accept Defendant's argument that the "oligonucleotide bar code sequences" must distinguish the conjugated targeting protein from other conjugated targeting proteins.

Where a claim lists elements separately, "the clear implication of the claim language" is that those elements are "distinct component[s]" of the patented invention. Becton, 616 F.3d at 1254 (citing Gaus, 363 F.3d at 1288). The Summary of the Invention section of the specification also provides that the "oligonucleotide . . . comprises at least two recognition sites . . . , primer sites for amplification, at least one bar code sequence to identify the conjugated antibody." ('643

Patent, col. 5, ll. 22-30, 40-43.) Again, the Detailed Description of the Embodiments section provides the following:

> [A] transposon cassette containing the following features . . . *[t]ransposase recognition sequences* required by the for catalysis of the DNA integration reaction; a[n extraction moiety] conjugated to an oligonucleotide, . . . *unique bar code sequences* (i.e., short nucleotide sequences . . .) . . . ; for whole genome sequencing applications, *platform-specific [sequences, i.e., primer sites] required for next generation sequencing* (NGS).

(Id. at col. 12, ll. 24-42 (emphasis added).) This section also describes the method using Illumina's platform: "the transposon is loaded with oligonucleotides containing both the transpose recognition sequences and sequences for sequencing on the Illumina platform." (Id. at col. 14, ll. 12-15.) The transposon cassette here does *not* contain barcode sequences. Indeed, "[t]he Illumina sequencing platform requires the addition of index primers containing bar-code sequences . . . to the tagmentation reaction products." (Id. at col. 25, ll. 45-48.)

In the Markman hearing, Defendant explained that "nowhere in the specification are bar code sequences ever described as overlapping with other parts of the [transposon] cassette." (Markman Hr'g Tr. 81:11-14.) Because the specification does not expressly contemplate the bar code sequences overlapping with other parts of the transposon cassette, it favors Defendant's position that the bar codes are separate from the transposase recognition sequences and primer sites.

3. Prosecution History

Plaintiff argues that U.S. Patent Application Publication No. US 2010/0240101 ("Lieberman et al."), which was provided to the PTO examiner during prosecution of the '643 Patent, provides that a barcode need not be separate from, but can overlap with, a primer site. (JCCB at 55; Ex. H.) "The[] molecular barcodes serve as primer sites, of which some are universal for all protein analytes, whereas others are target-specific." (Lieberman et al. ¶ [0125] (Ex. H).)

For the reasons explained below, Liberman et al. cannot make up for the fact that the specification does not expressly contemplate that the bar code sequences might overlap with other parts of the transposon cassette.

4. Extrinsic Evidence

Here, Plaintiff's expert Jeremy Edwards agreed in his deposition that "the Lieberman reference . . . doesn't disclose barcodes that are present in transposon cassettes . . . . [Lieberman et al.] just discloses the idea that a barcode could also be used as a primer site." (Ex. P at 178:16-21.) As such, and pursuant to Becton, Plaintiff's reliance on Lieberman et al. does not compensate for the fact that "nowhere in the specification are bar code sequences ever described as overlapping with other parts of the [transposon] cassette." (Markman Hr'g Tr. 81:11-14.) For these reasons, I agree with Defendant that the barcode sequences are "separate" from the transposase recognition sequences and primer sites.

5. Conclusion as to "one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein"

For all of the foregoing reasons, I will partially adopt the construction proposed by Defendant and construe the term "one or more oligonucleotide bar code sequences to uniquely identify the conjugated protein" as "**one or more oligonucleotide sequences in the transposon cassette that are separate from the transposase recognition sequences and the primer sites and that uniquely identify the conjugated protein**."

IV. CONCLUSION

The claims shall be construed as set forth above and in the Claim Construction Order that follows.