CASE NO.: 2:17-cv-07639 SJO (RAOx) **DATE:** October 9, 2018

TITLE: Juno Therapeutics, Inc., et al. v. Kite Pharma, Inc.

==========

PRESENT: THE HONORABLE S. JAMES OTERO, UNITED STATES DISTRICT JUDGE

Victor Paul Cruz Courtroom Clerk	Not Present Court Reporter
COUNSEL PRESENT FOR PLAINTIFF:	**COUNSEL PRESENT FOR DEFENDANT:**
Not Present	Not Present

==========

PROCEEDINGS (in chambers): CLAIM CONSTRUCTION ORDER

Plaintiffs and Counter-defendants Juno Therapeutics, Inc. ("Juno"), Memorial Sloan Kettering Cancer Center, and Sloan Kettering Institute for Cancer Research (together, "MSKCC") (collectively, "Plaintiffs") and Defendant and Counter-claimant Kite Pharma, Inc. ("Kite" or "Defendant") have filed claim construction briefs in which they ask the Court to construe two (2) disputed phrases found in the sole patent asserted in this litigation, U.S. Patent No. 7,446,190 ("the '190 Patent"). Plaintiffs filed their Opening Claim Construction Brief ("Pl.'s Brief") on August 13, 2018. Defendant filed its Responsive Claim Construction Brief ("Def.'s Brief") on August 27, 2018. Plaintiffs filed a reply ("Pl.'s Reply") on September 3, 2018. The Court heard argument from counsel on September 18, 2018.

I. FACTUAL AND PROCEDURAL BACKGROUND

Plaintiffs initiated the instant action on October 18, 2017, alleging that Defendant infringes the '190 Patent through the use, sale, offer for sale, or importation of one of Kite's immunotherapy treatments, Yescarta. Yescarta is described as a "therapy in which a patient's T cells are engineered to express a chimeric antigen receptor (CAR) to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias, and redirect the T cells to kill cancer cells." (Compl. ¶ 18.) Plaintiffs assert that Yescarta infringes on the '190 Patent by utilizing nucleic acid polymers encoding chimeric TCRs within the scope of the '190 Patent claims. (Compl. ¶ 24.) Defendant, in turn, filed counterclaims seeking declaratory judgments of non-infringement and invalidity of the '190 Patent. (*See generally*, Amended Answer and Counterclaims, ECF No. 66.) On March 2, 2018, the Court held a scheduling conference in which it ordered that the Northern District of California's Patent Local Rules will govern the case and set a claim construction ("Markman") hearing for September 17, 2018. (Minutes of Sched. Conf., ECF No. 71.)

///

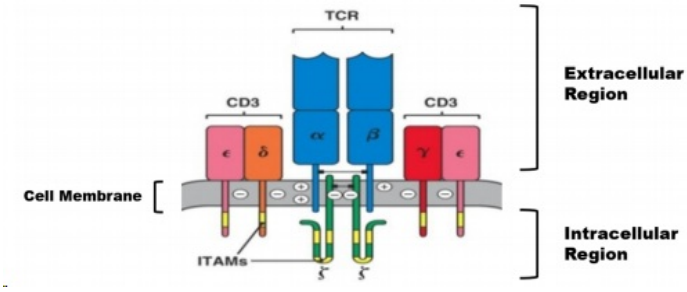
///

II. TECHNOLOGICAL SUMMARY

The '190 Patent issued on November 4, 2008 and incorporates a provisional application filed on May 28, 2002. ('190 Patent Caption.) The claimed invention provides a "nucleic acid polymer encoding [] chimeric TCR's [T Cell Receptors]." ('190 Patent, col. 2:11-14.) The chimeric TCRs encoded by the claimed invention "combine, in a single chimeric species, the intracellular domain of CD3 ζ-chain ('zeta chain portion'), a signaling region from a costimulatory protein such as CD28 with a binding element that specifically interacts with a selected target." ('190 Patent, col. 2:14-18.) These TCRs are designed to "specifically interact[] with a cellular marker associated with target cells," resulting in the stimulation of a T cell immune response to the target cells. ('190 Patent, col. 2:30-36.)

A. T-Cell and Targeted Immune Response

T cells, also known as T lymphocytes, are a form of white blood cell that plays a critical role in the body's cell-mediated immunity. (Declaration of Dr. Richard P Junghans, Ph.D., M.D. ("Junghans Decl.") ¶ 40, ECF No. 87-1; Declaration of Dr. Thomas Brocker, Ph.D. ("Brocker Decl.") ¶ 46, ECF No. 85-2.) The primary role of T cells is to detect and respond to "antigens"—molecules capable of producing an immune response. (Junghans Decl. ¶ 40.) They detect the presence of antigens through the use of T cell receptors ("TCRs"), which are polypeptide chains appearing on the surface of the T cell. (Junghans Decl. ¶ 40; Brocker Decl. ¶ 47.) Within the cell, TCRs typically form a complex with another protein, CD3ζ, and the two work together to create an immune activation signal upon encountering an antigen. (Junghans Decl. ¶ 40; Brocker Decl. ¶ 47.) An illustration of this TCR/CD3ζ complex can be seen below:



(Junghans Decl., Fig. 5.) TCRs are able to detect antigens by binding to particular, identifying protein fragments that appear on the surface of each antigen. (Brocker Decl. ¶ 49.) This is accomplished through the TCR's "variable" region, which allows it to bind with specificity to a particular antigen. (Brocker Decl. ¶ 22.) Because there are a diverse range of TCRs that appear on a given T cell, each cell is able to recognize and respond to a number of antigens. (Brocker Decl. ¶ 50.) Once a TCR binds with a known antigen, it prompts an immune response from the T cell that is specifically targeted at cells displaying that particular antigen. (Brocker Decl. ¶ 50.)

It is the distinct, variable antigen binding domain that permits a TCR to recognize a particular antigen. (Brocker Decl. ¶ 54.) Recognizing that the binding domain presented an opportunity to harness the body's immune response, researchers developed ways of creating "chimeric" TCRs, that is, TCRs that are made by fusing different protein chains together to create a single receptor. (Junghans Decl. ¶ 43.) One of the ways this was accomplished was by linking the variable regions of an antibody—another naturally occurring antigen-receptive element—into a single chain. (Brocker Decl. ¶ 55.) The resulting antigen-specific "single chain antibody fragment" ("scFv") can then be grafted onto other signaling proteins, such as TCRs, permitting those proteins to recognize and respond to the target antigen. (Brocker Decl. ¶ 55.) This is accomplished through the use of recombinent DNA—a process discussed in more detail below.

T Cells utilize a dual-signaling system that combines the initial TCR signal with a second, co-stimulatory signal, reducing the likelihood of erroneous immune response. (Brocker ¶ 57.) When a TCR encounters an antigen that corresponds to its antigen-specific binding domain, it sends a "first signal" to the T Cell. (Brocker ¶ 57.) This first signal is sufficient to trigger an initial immune response. (Brocker ¶ 57.) If the antigen also interacts with the complex's costimulatory receptors, creating a "second signal," the immune response is augmented and/or prolonged. (Brocker ¶ 58.) One such costimulatory domain is CD28. (Junghans ¶ 51.)

The invention claimed in the '190 patent is a nucleotide sequence which encodes a molecule comprising three separate proteins fused into a single chimeric TCR. Specifically, Claim 1 of the '190 Patent recites in full:

> A nucleic acid polymer encoding a chimeric T cell receptor, said chimeric T cell receptor comprising:
>
> (a) a zeta chain portion comprising the intracellular domain of human CD3 ζ chain,
>
> (b) a costimulatory signaling region, and
>
> (c) a **binding element that specifically interacts with a selected target**, wherein the costimulatory signaling region comprises **the amino acid sequence encoded by SEQ ID NO:6**.

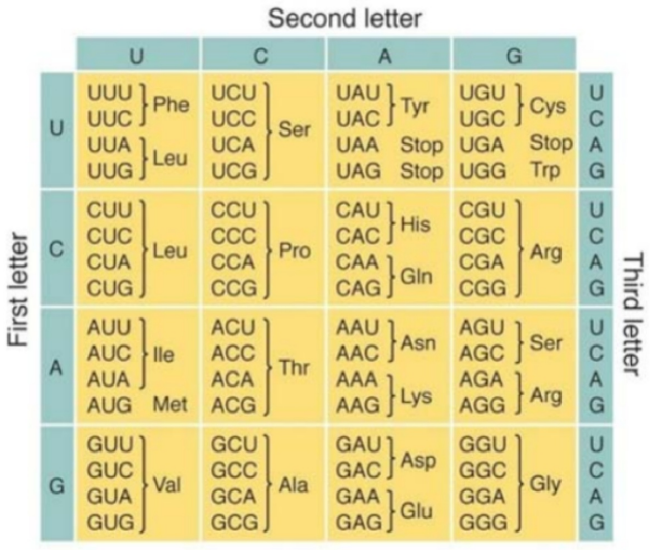
('190 Patent col. 25:30-38 [disputed claim terms in bold].) Such a molecule would theoretically be able to initiate a prolonged immune response upon encountering a specifically targeted antigen triggering both a first and second signal. The target antigen could be chosen by the researcher through the selection of the binding element.

B. Molecular Biology and the Construction of Chimeric TCRs

Because the '190 Patent claims only the nucleic acid polymer that encodes a chimeric T cell receptor, it is important to also understand how such a polymer relates to the creation of a TCR.

Deoxyribonucleic acids ("DNA") are molecules that contain the genetic information necessary to create the proteins that make up each of the components of chimeric TCRs. (Brocker Decl. ¶ 27; Junghans Decl. ¶ 29.) DNA is chain molecule made up of interlinking nucleotides. (Brocker Decl. ¶¶ 28-29; Junghans Decl. ¶ 29.) DNA nucleotides come in one of four flavors: adenine (A), thymine (T), cytosine (C), and guanine (G). (Brocker Decl. ¶ 28; Junghans Decl. ¶ 29.) Each nucleotide is able to form a pair with its complementary base—A with T and G with C. (Brocker Decl. ¶ 29; Junghans Decl. ¶ 29.) In DNA, nucleotides are organized into two complementary chains of nucleotides forming a double helix. (Brocker Decl. ¶ 29; Junghans Decl. ¶ 29.)

Proteins are manufactured from DNA using a two-step process: transcription and translation. During transcription, the DNA is used as a template to produce a strand of messenger ribonucleic acid ("mRNA"). (Brocker Decl. ¶ 31; Junghans Decl. ¶ 31.) This is accomplished by splitting apart or "denaturing" the DNA double helix and allowing a naturally-occuring enzyme, RNA polymerase, to create a complementary mRNA strand from the denatured DNA. mRNA is very similar to single strand DNA, but substitutes uracil (U) in place of thymine (T). (Brocker Decl. ¶ 31; Junghans Decl. ¶ 31.) Following the transcription process, the mRNA strand undergoes translation, whereby the mRNA is used to synthesize proteins from amino acids. (Brocker Decl. ¶ 32; Junghans Decl. ¶ 31.) This is accomplished by translating the sequence of nucleotides contained in the mRNA into a corresponding sequence of amino acids. (Brocker Decl. ¶ 32; Junghans Decl. ¶ 34.) Each group of three nucleotides, referred to as "codons," correlates to one of approximately 20 amino acids. (Brocker Decl. ¶¶ 32-33; Junghans Decl. ¶ 34.) For example, the nucleotide sequence "GCA" is the codon that results in the amino acid alanine, while "GGC" would code for glycine. (Brocker Decl. ¶ 33.) A full chart of RNA codons and their corresponding amino acids is reproduced below:



(Brocker Decl. ¶ 33.)

Thus, the DNA sequence CAAAACCGATGG would translate to glutamine, asparagine, arginine, and tryptophan. In addition to codons that correspond to amino acids, there are several codons that indicate when to stop or start a coding sequence. (Brocker Decl. ¶ 34; Junghans Decl. ¶ 35.) The starting codon is "ATG" and the stop codons are "TGA," "TAA," and "TAG." (Brocker Decl. ¶ 34; Junghans Decl. ¶ 35.) Using this two-step transcription and translation process, a polymeric strand of nucleotides can encode entire complex protein structures.

Using these principles, researchers are able to create chimeric or "recombinant" proteins by fusing together two or more nucleotide sequences that originally coded for wholly separate proteins. (Brocker Decl. ¶ 35; Junghans Decl. ¶ 39.) One method of creating such a protein is through the use of "restriction enzyme cloning." (Brocker Decl. ¶ 36; Junghans Decl. ¶ 39.) This process uses a set of specialized proteins, or "primers," to target and amplify a particular portion of a longer DNA sequence. (Brocker Decl. ¶¶ 36, 38; Junghans Decl. ¶ 38.) Primers are short single-strand nucleotide sequences (typically 18-22 nucleotides in length) that are complementary to the nucleotides found at a specific site ("restriction site") of the target DNA sequence. (Brocker Decl. ¶ 36; Junghans Decl. ¶ 38.) The primer that is complementary to the front end of the target sequence is known as the "upstream" primer. (Junghans Decl. ¶ 38.) The primer that is complementary to the rear end of the DNA sequence is known as the "downstream" primer. (Junghans Decl. ¶ 38.) Once the primers have attached to each of the targeted restriction cites, a "restriction enzyme" is used to cut or "cleave" the target sequence from the larger DNA chain. (Brocker Decl. ¶ 36.) One example of restriction enzyme is Not1, which is used to cleave DNA segments at the sequence GCGGCCGC:

(Junghans Decl., Fig. 4.) The process of cleaving a DNA sequence creates a "sticky end" or a complementary overhang which can be used to join DNA segments to one another. (Brocker Decl. ¶ 37; Junghans Decl. ¶ 39.) In this manner, researchers are able to target particular portions of a longer DNA chain using primers, cut them using restriction enzymes, and attach them to one another using the resulting complementary overhangs, creating a combined DNA sequence encoding a chimeric protein.

III. LEGAL STANDARDS

A. Principles of Claim Construction

Before a jury can determine if any of the asserted claims are invalid or if the defendant's technology infringes one or more asserted claims, the court must determine the meaning and scope of the asserted claims through the process of "claim construction." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370, 116 S. Ct. 1384 (1996). Only after the claims have been construed can the jury compare the allegedly infringing device against the claims. *Id.*

In *Phillips v. AWH Corp.*, 415 F.3d 1303, 1311-24 (Fed. Cir. 2005) (en banc), the en banc Federal Circuit set forth a number of principles to guide lower courts through the claim construction process. The general rule is that the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application" *Id.* 1312-13 (citations omitted). "[T]he person of ordinary skill in the art 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.* at 1313.

"In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314. "In such circumstances, general purpose dictionaries may be helpful." *Id.* Where, however, "determining the ordinary and customary meaning of the claim requires examination of terms that have a particular meaning in a field of art," courts look to other sources, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

Moreover, "[t]he claims themselves provide substantial guidance as to the meaning of particular claim terms," for example by observing "the context in which a term is used in the asserted claim." *Id.* Comparing the usage of a term across different claims and examining difference among claims can also provide valuable insight into the meaning of claim terms. *Id.*

"The claims, of course, do not stand alone," and the specification provides "the single best guide to the meaning of a disputed term." *Id.* at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). One reason the specification is of paramount importance is that it "may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess." *Id.* at 1316; *see also Markman*, 52 F.3d at 980 ("[A]

patentee is free to be his own lexicographer"). That said, "[t]hough understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim, limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." *Superguide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004). Moreover, the prosecution history, which consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent, may also shed "decisive light" on the proper construction of a claim term, particularly where an applicant limits her invention to overcome prior art. *Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1372-73 (Fed. Cir. 2008); *Phillips*, 415 F.3d at 1316-17; *N. Am. Container, Inc. v. Plastipak Packaging, Inc.*, 415 F.3d 1335, 1345 (Fed. Cir. 2005); *Seachange Int'l, Inc. v. C-Cor Inc.*, 413 F.3d 1361, 1372-73 (Fed. Cir. 2005).

District courts may also 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," in construing claims, although such evidence is afforded less significance than the intrinsic record. *Phillips*, 415 F.3d at 1317 (citations omitted). "[W]hile extrinsic evidence 'can shed useful light on the relevant art,' we have explained that it is 'less significant than the intrinsic record in determining "the legally operative meaning of claim language."'" *Id.* (citations omitted).

In summation, although "there is no magic formula or catechism for conducting claim construction . . . . certain types of evidence are more valuable than others," and "what matters is for the court to attach the appropriate weight" to each piece of evidence. *Phillips*, 415 F.3d at 1324.

B. Means-Plus-Function Claiming

In its opinion in *Williamson v. Citrix Online, LLC*, 792 F.3d 1339 (Fed. Cir. 2015), the Federal Circuit modified the standard for determining whether a claim element is governed by 35 U.S.C. § 112, para. 6, which provides that

> [a]n element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

35 U.S.C. § 112(f). The Federal Circuit majority began by observing that its "precedent has long recognized the importance of the presence or absence of the word 'means'" in determining whether § 112, para. 6 applies, and that a "strong" but rebuttable presumption had arisen that was tethered to the inclusion of the word "means." 792 F.3d at 1348-49. The majority found this "heightened burden [to be] unjustified," and accordingly "abandon[ed] characterizing as 'strong' the presumption that a limitation lacking the word 'means' is not subject to § 112, para.

6." *Id.* at 1349. The majority clarified that "[t]he standard is whether the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for structure." *Id.* (citing *Greenberg v. Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1583 (Fed. Cir. 1996)). Thus, "[w]hen a claim term lacks the word 'means,' the presumption can be overcome and § 112, para. 6 will apply if the challenger demonstrates that the claim term fails to 'recite sufficiently definite structure' or else recites 'function without reciting sufficient structure for performing that function.'" *Id.* (quoting *Watts v. XL Sys., Inc.*, 232 F.3d 877, 880 (Fed. Cir. 2000)).

In applying these principles to the claims before it, the majority held that "[g]eneric terms such as 'mechanism,' 'element,' 'device,' and other nonce words that reflect nothing more than verbal constructs may be used in a claim in a manner that is tantamount to using the word 'means' because they 'typically do not connote sufficiently definite structure' and therefore may invoke § 112, para. 6." *Id.* at 1350 (quoting *Mass. Inst. of Tech. & Elecs. for Imaging, Inc. v. Abacus Software*, 462 F.3d 1344, 1354 (Fed. Cir. 2006)). The majority then concluded that the term "distributed learning control module" was subject to the provisions § 112, para. 6, notwithstanding the absence of the term "means." In particular, the majority noted that "[w]hile portions of the claim do describe certain inputs and outputs at a very high level (e.g., communications between the presenter and audience member computer systems), the claim does not describe how the 'distributed learning control module' interacts with other components in the distributed learning control server in a way that might inform the structural character of the limitation-in-question or otherwise impart structure to the 'distributed learning control module' as recited in the claim." *Id.* at 1351.

Where a claim element is subject to application § 112, para. 6, the court must then determine "whether the specification discloses sufficient structure that corresponds to the claimed function." *Id.* If the patentee fails to disclose adequate corresponding structure to perform all of the claimed functions, the claim is indefinite. *Id.* at 1351-52 (citing *Noah Sys., Inc. v. Intuit Inc.*, 675 F.3d 1302, 1311-12 (Fed. Cir. 2012)).

IV. ANALYSIS

A. Definition of "Person of Ordinary Skill in the Art" at the Time of the Invention

Defendant asserts that a person of ordinary skill in the art ("POSITA") at the relevant time would have had a Ph.D. or an M.D. in "immunology, biochemistry, cell biology, molecular biology, or a related discipline and at least two years of experience in conducting laboratory research on chimeric TCR therapies, TCRs, T cells or other types of immune cells, chimeric TCRs or related work." (Junghans Decl. ¶ 28.) Plaintiff generally agrees with the educational requirements (albeit considering a M.Sc. sufficient), but would only require that the POSITA have "knowledge of the scientific literature relating to T cell biology, as well as laboratory techniques and strategies in designing recombinant DNA." (Brocker Decl. ¶ 21.) The Court

does not find that there is any material dispute between the parties on the definition of a POSITA, and therefore adopts a definition that incorporates the characteristics proposed by both parties.

B. "the amino acid sequence encoded by SEQ ID NO:6"

The parties' first dispute centers on the meaning of the term "the amino acid sequence encoded by SEQ ID NO:6," which is recited in independent claim 1 of the '190 Patent as "the costimulatory signaling region comprising the amino acid sequence encoded by SEQ ID NO:6." ('190 Patent col. 25:36-38.) The parties' positions are provided below:

Plaintiff's Proposed Construction	Defendants' Proposed Construction
"Amino Acids 114-220 of CD28 (starting with isoleucine (I))"	**Before the Certificate of Correction:** "Amino Acids 113-220 of CD28 (starting with lysine (K))**"** **After the Certificate of Correction:** Kite agrees with Juno's proposed construction

The parties disagreement is straightforward. Juno contends that "the amino acid sequence encoded by SEQ ID NO:6," as defined in the originally-issued patent, should be construed as beginning with Isoleucine and comprising the amino acids **114**-220 (corresponding to nucleotides **340-**660) of the CD28 protein. Kite, on the other hand, contends that the original patent defined the term as a sequence beginning with Lysine and comprising the amino acids **113**-220 (corresponding to nucleotides **337**-660) of the CD28 protein.

At the center of the parties' dispute is the 2012 Certificate of Correction to the '190 Patent. In the specification as issued in 2008, SEQ ID NO:6 is described as having a length of 328 nucleotides and beginning with nucleotide 336 of the CD28 protein. ('190 Patent col. 15.) The Certificate of Correction alters the definition of this sequence, such that it has a length of 321 nucleotides and begins with nucleotide 340 of the CD28 protein. ('190 Patent, Certificate of Correction.) Defendant claims that this alteration materially changes the scope of the claim terms and intends to challenge the issuance of the Certificate of Correction on these grounds.

Plaintiff first argues that there is no reason to separately assess the scope of the original claim term as the Certificate of Correction supplants the original patent and "shall have the same effect and operation in law on the trial of actions for causes thereafter arising as if the same had been originally issue in such corrected form." 35 U.S.C. § 255. As Defendant notes, however, the

very validity of the CoC is at issue and "[i]nvalidating a certificate of correction for impermissible broadening [] requires proof of two elements: (1) the corrected claims are broader than the original claims; and (2) the presence of the clerical or typographical error, or how to correct that error, is not clearly evident to one of skill in the art." *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1353 (Fed. Cir. 2007). Therefore, while the Court will not rule on the ultimate issue of the CoC's validity at this time, it must nevertheless interpret both the original and amended claims to determine whether they do indeed differ in scope. *Id.*

In determining the scope of a claim term, the Court ordinarily begins with the plain meaning of a claim term. However, because neither party argues that "SEQ ID NO:6" has any plain meaning, it turns instead to the specification, which provides "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). In the specification of the '190 Patent, there are both explicit and implicit definitions of "the amino acid sequence encoded by SEQ ID NO:6." The Court finds that the explicit definition of SEQ ID NO: 6 is provided in the sequence list and describes a sequence beginning with the nucleotide sequence "CAAAATTGAA . . . ," corresponding to the CD28 sequence spanning nucleotides 336-660.

Plaintiffs dispute that this is an express definition, arguing that a person of skill in the art would look beyond the sequence listing to determine the definition, examining primers and other less direct clues in the specification to determine where the sequence begins and ends. (Pl.'s Brief, at 9.) The Court finds, however, that the sequence listing provides, at least in this particular instance, the explicit definition of "the amino acid sequence **encoded by SEQ ID NO:6**" because the claim term expressly points a reader—not to the other potential means of defining the sequence—but directly to the sequence listing itself. The claim term is not, for instance, "the amino acid sequence encoded by the nucleotide sequence **defined by primers SEQ ID NO:4 and SEQ ID NO:5**." Nor is it "the amino acid sequence **corresponding to amino acids 114-220 of CD28**."

While the express definition ordinarily governs the construction of a claim term, the Court nevertheless considers the remainder of the intrinsic record to determine if this definition is rebutted by conflicting definitions. Plaintiffs focus on various information contained in the specification that they assert would indicate to a personal of ordinary skill in the art that the amino acid sequence begins, not at position 113, but rather at the isoleucine found at position 114. In particular, they focus on (1) the provisional application, (2) the specification, (3) the prosecution history, and (4) Defendant's positions taken during IPR. The Court will address each in turn.

///

///

1. Provisional Application

On May 28, 2002, provisional Application No 60/383,872 was filed with the USPTO. (Heinrich Decl., Exh 4 ("Provisional Appl.").) The invention claimed in this Provisional Application was described in a journal article, written by the inventors of the '190 Patent, which was incorporated by reference. In this article, the inventors identified the set of PCR primers used to isolate and amplify the portion of the CD 28 used to construct the costimulatory region of the claimed T-Cell Receptor. The article states that "nucleotides 336-660 of CD28 were amplified using primers 1 (5'-GGCGGCCGCAATTGAAGTTATGTATC-3') and 2 (5'-TGCGCTCTCCTGCTGAACTTCACTCTGGAGCGATAGGCTGCGAAGTCGCG-3')." (Provisional Appl., at 7.) Plaintiffs contend that these primers correspond to a CD 28 domain beginning with isoleucine, and argue that a POSITA "would know to align these primers to the publicly-known sequence of CD28, and in so doing would have readily seen that the CD 28 domain of the construct begins with the isoleucine at amino acid 114 of CD28." (Pl.'s Brief, at 7.) While it is true that these definitions, one by nucleotide number and one by primer, differ from one another, there is nothing in the provisional application that would clarify which of the two definitions is correct. The Court therefore concludes that nothing in the Provisional Application rebuts the explicit definition provided in the sequence listing.

2. Specification

In arguing that the specification defines the claim term differently than does the sequence list, Plaintiffs point to the following passage from column 4 of the '190 Patent.

> In one embodiment, where CD 28 is between the zeta chain portion and csFv, the CD28 portion suitably includes the transmembrane and signaling domains of CD28,i.e., the portion of CD28 cDNA spanning nucleotides 340 to 663, including the stop codon (amino acids 114-220 of Seq. ID No. 10). This portion of CD28 can be amplified by PCR using the primers of Seq ID No. 4 and 5. The full sequence of this region is set forth in Seq ID No: 6.

('190 Patent, col. 4:21-28.) This section defines the given sequence in three ways. The first is its reference to the explicit definition in the sequence list. As discussed previously, this definition clearly defines the sequence as nucleotides 336-660 of the CD28 protein. The second definition directly contradicts this by identifying "the portion of CD28 cDNA spanning nucleotides 340 to 663, including the stop codon (amino acids 114-220 of Seq. ID No. 10)." (190 Patent, col. 4:24-26.) As provided in the sequence listing, SEQ ID NO:10 provides the amino acid sequence of CD28 wherein amino acid 114 is isoleucine, consistent with Juno's current position. Defendant notes, however, that the particular language used in this section is open-ended, stating merely that "the CD28 portion **suitably includes** . . . the portion of CD28 spanning nucleotides 340 to 663"—implying that it could encompass more than this portion. While this is admittedly a

somewhat unnatural interpretation, it is not entirely unreasonable and a POSITA might arrive at this understanding in an attempt to read the specification consistently and bring column 4 in line with the express definition found in the sequence listing.

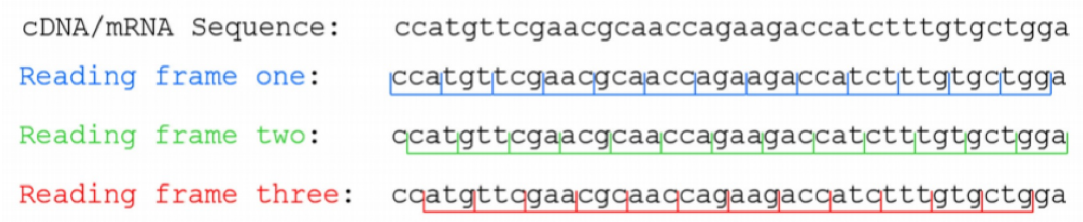
The final definition provided in column 4—the "portion of CD 28 [that] can be amplified by PCR using the primers of Seq ID No. 4 and 5"—is also somewhat unclear. ('190 Patent, col. 4:26-27.) SEQ ID NO:4 is defined twice in the specification, once in the sequence listing and once in column 7. These definitions differ from one another in both the number of nucleotides they contain and the portion of CD28 that they amplify. (Junghans Decl. ¶ 88.) Furthermore, Defendant's expert claims, neither version of the primer would result in the sequence claimed by Plaintiffs in their CoC. (Junghans Decl. ¶ 89.) The first would amplify a nucleotide sequence beginning with nucleotide 339 of the CD28 protein,[1] while the second would amplify the sequence beginning with nucleotide 342. (Junghans Decl. ¶ 89.)

In addition to column 4, Defendant draws the Court's attention to two other portions of the specification. First is SEQ. ID NO:11, which Defendant asserts corresponds directly to the amino acid sequence encoded by SEQ. ID NO:6 and begins, not with isoleucine, but with lysine. This, it claims, is further evidence that Plaintiffs intended to claim the amino acid sequence that appeared in the original issued patent. While this is admittedly an intriguing correlation, it carries little weight as SEQ ID NO:11 is never specifically referenced in the written description and is, it seems, vestigial. The second portion of the specification to which Defendant cites is column 7, where the patent appears to pull language from the Provisional Application and states that "nucleotides 336-660 of CD28 were amplified using primers . . ." ('190 Patent, col. 7:52-53.) This nucleotide sequence maps directly onto the original SEQ. ID NO:6—including the allegedly extraneous leading cytosine. Plaintiffs contend that this is yet another clerical error and points to the fact that this same language was corrected in column 4 during the prosecution of the '190 Patent. (Pl.'s Brief, at 8-9.) "A POSA," they claim, "would clearly recognize that column 7 was merely an oversight to be corrected in the same manner." (Pl.'s Brief, at 9.) Column 7's description is, however, consistent with original SEQ ID NO:6, and could just as easily lead a POSITA to the opposite conclusion: that column 7's description is correct and that it is column 4 that is the outlier.

Plaintiffs' final contention is that a POSITA would know that the nucleotide sequence originally identified as SEQ. ID NO:6 was incorrect because the number of nucleotides was not divisible by three. Defendant offers two convincing arguments why this is not the case. First, it notes that the CD28 portion does not exist on its own, but as a single component of a three part chimeric TCR. Because the entire TCR is made up of amino acids, it is the nucleotide sequence of the entire

[1] An argument made less persuasive by Dr. Abken's position during IPR that the primer disclosed in the post-CoC SEQ ID NO:4 "align[s] perfectly with the start of SEQ ID NO: 6." (Abken Decl. ¶ 100)

TCR chain that must be divisible by three—not the individual components, which may contain additional nucleotides utilized during ligation. Secondly, Defendant's expert contends that a POSITA would have easily been able to determine the correct amino acid sequence by applying the correct "reading frame." (Junghans Decl. ¶ 79.) He explains that a given sequence of nucleotides can be read in one of three "frames." (Junghans Decl. ¶ 79.) The first frame assumes that a given sequence begins with a complete codon, the second that there is a single, leading nucleotide before the first codon, and the third frame includes two leading nucleotides. (Junghans Decl. ¶ 79.) Dr. Junghans provides the following example in his declaration:



(Junghans Decl., Fig 2.) In order to determine which reading frame is correct, Junghans explains, a POSITA would likely look for the longest "open reading frame"; that is, the longest amino acid sequence uninterrupted by a stop codon ("TGA", "TAA", or "TAG").[2] (Junghans Decl. ¶ 37.)

Dr. Junghans opines that examining SEQ ID NO:6 using each of the three reading frames makes readily apparent that frame 2 is the appropriate approach:

> [A] POSA would generally look for a reading frame with the longest uninterrupted sequence useful for encoding an amino acid sequence. The first reading frame includes a stop codon after just six nucleotides, followed by five other stop codons within the chain. The third reading frame begins with a slightly longer sequence, however, it still includes just 32 nucleotides prior to the initial stop codon, followed by six other stop codons within the chain. Unlike the first and third, the second reading frame includes a single stop codon at the very end of the sequence and provides the longest open reading frame.

(Junghans Decl. ¶ 79.)

In light of the above, the specification is, at best, ambiguous regarding the nucleotide sequence comprising SEQ. ID NO:6. The sequence described in column 7 and the explicit definition contained in the sequence list would indicate to a POSITA that the patent is claiming nucleotides

[2] Alternatively, a researcher could make use of the Basic Local Assignment Search Tool ("BLAST"), a free and publicly available software tool that uses a database of known DNA sequences to properly align the sequence. (Junghans Decl. ¶ 36.)

336-660 of CD28, a sequence that, correctly framed, would result in a leading lysine, consistent with Defendant's proposed construction. The information found in column 4 may also be interpreted in a manner consistent with this understanding due to its use of open-ended language. It is only the primers disclosed in column seven and the sequence list that would produce a sequence potentially consistent with Plaintiffs' proposed definition. Yet even here, the specification is unclear, providing two conflicting definitions for SEQ ID NO: 4.

In this way, the present case differs from *Cubist Pharms., Inc. v. Hospira, Inc.*, in which the Federal Circuit found that a claimed compound was not expressly defined by the chemical diagram in the specification. 805 F.3d 1112, 1118 (Fed. Cir. 2015). There, the inventor was granted a certificate of correction altering the structural diagram of a compound labeled "Formula 3." *Id.* at 1116. The court found that, while the alteration was material, the diagram was only one definition of the claim term and was in direct conflict with several other definitions found in the original specification, including references to compounds that were well-known in the art. *Id.* at 1115. Furthermore, the diagram represented the universal understanding of the known compound's structure at the time of filing and it was only years later that researchers discovered that this universal understanding was incorrect. *Id.* at 1116. Here, however, there is no evidence that the specific portion of CD28 referenced in the specification was well-known in the art, nor was the correction related to any new understanding on the part of the scientific community as a whole. Because the sequence listing is supported by numerous other statements found in the specification, the Court finds the disclosure of specific primers, without more, insufficient to rebut the express definition in the sequence listing.

3. Prosecution History

As an initial matter, the Court notes that, while "the prosecution history provides evidence of how the PTO and the inventor understood the patent," it "represents an ongoing negotiation between the PTO and the application, rather than the final product of that negotiation, [and] often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Phillips*, 415 F.3d at 1317. "The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution.'" *Id.* (quoting *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005)).

Plaintiffs contend that the following events that occurred during the prosecution of the '190 Patent would indicate to a POSITA its intent to claim amino acids 114-220. On September 4, 2007, the applicants filed a Request for Continued Examination ("RCE") claiming that:

> In preparing to pay the issue fee for this application, it was determined that an error occurred in the presentation of Seq. ID No. 6, which is recited in the previously allowed claims. In addition, a discrepancy was noted between the bases of Seq ID No. 4 in the specification [] and the sequence listing. Finally, it was noted that the

> Seq ID No. 10 was not referenced in the specification and that the amino acids of the CD28 Sequence (144-220 contained a typographical error and should have been 114-220). This RCE application and amendment are filed to correct these errors.

(RCE, Sept. 4, 2007.)

Along with this request, the applicants submitted a sequence listing which amended (1) SEQ ID NO:4—the nucleotide sequence of the upstream primer—to add a single Thymine, bringing it into agreement with the primer sequence disclosed in column 7 of the specification, and (2) SEQ ID NO:6, removing the first four nucleotides, such that the first codon corresponds to isoleucine, amino acid 114 of CD28, rather than lysine, amino acid 113. This amended listing was rejected by the Patent Office as "damaged and/or unreadable," prompting the applicants to provide a new copy. This copy, too, reflected the amendments requested in the RCE. The Patent Office again rejected the filing, this time for failure to comply with the USPTO formatting requirements. The applicants reformatted the listing and, for the third time, filed an amended sequence listing with the Patent Office. This time, however, they included the original sequence listing that did not reflect the amendments originally requested in the RCE. It was this unaltered listing that was ultimately included in the patent as it was finally issued.

Plaintiffs contend that "any reasonable reader of the prosecution history would understand that the applicants inadvertently submitted the original, incorrect sequence listing in their April 16, 2008 submission." (Pl.'s Brief, at 12.) While it is true that this is one possible interpretation of the events, it is also possible for a POSITA to conclude that the applicants intentionally submitted the original sequence listing.[3] Ultimately, the ambiguity of the prosecution history would require a POSITA to guess at the applicants' intent. Such a level of uncertainty is insufficient to overcome the express definition as provided in the sequence listing and supported by numerous portions of the specification.

4. IPR History

Plaintiffs' final argument is that there are contradictions between the testimony of Dr. Junghans in this action and Kite's expert during the IPR, Dr. Abken. Specifically, they point to the fact that, during the IPR, both parties and their experts agreed that a certain prior art publication (the "Krause Paper") disclosed the same amino acid sequence as the amino acid sequence encoded by SEQ ID NO:6. (Pl.'s Brief, at 13-14.) In reaching this conclusion, Dr. Abken observed that "[b]oth Krause's forward primer and the '190 Patent's forward primer (SEQ ID NO: 4) align

[3] Or, more cynically, that the ambiguity was intentional, calculated to permit the patent-holder to determine at a later date which of the two positions was more advantageous.

perfectly with the start of SEQ ID NO: 6 (*i.e.*, ATTGA . . .)." (Heinrich Decl., Exh. 8 ("Abken Decl.") ¶ 100.) Plaintiffs also point to a diagram prepared by Dr. Abken which depicts SEQ ID NO:6 beginning with ATT—the codon for isoleucine. (Pl.'s Brief, at 14.) These disclosures, they claim, demonstrate that Kite's expert recognized and accepted that SEQ ID NO:6 encoded an amino acid sequence beginning at amino acid 114.

Defendant correctly observes, however, that a petitioner cannot challenge the validity of the certificate of correction during an IPR proceeding and therefore argues that Dr. Abkens statements did not relate to his understanding of SEQ ID NO:6 as disclosed in the original issuance of the '190 Patent, but rather reflected his views on the '190 Patent after the USPTO issued its Certificate of Correction. The Court finds this argument persuasive. Because a patent can only be challenged during IPR on grounds of anticipation or obviousness, Dr. Abkens statements have no bearing on the meaning of the patent as it initially appeared upon issuance. 35 U.S.C. § 311.

5. Conclusion

In a sense, this dispute strikes at the heart of the policy undergirding patent law. Patents are, at their core, a "carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology." *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 63 (1998). They "grant[] inventors 'the right to exclude others from making, using, offering for sale, selling, or importing the patented invention,' in exchange for full disclosure of [the] invention." *Markman,* 517 U.S. at 373 quoting H. Schwartz, Patent Law and Practice 1, 33 (2d ed. 1995). In order to serve this function, "it has long been understood that a patent must describe the exact scope of an invention and its manufacture to 'secure to [the patentee] all to which he is entitled, [and] to apprise the public of what is still open to them.'" *Markman,* 517 U.S. at 373 (quoting *McClain v. Ortmayer*, 141 U.S. 419, 424 (1891)). For this reason, claim terms are interpreted—not based on the intent of the patentee—but based on the understanding of POSITA as members of the public.

In order for a POSITA to arrive at Plaintiffs' proposed construction, she must first determine that (1) the provisional application incorrectly identified the claimed sequence, (2) the originally submitted patent application incorrectly identified the claimed sequence in three separate locations, (3) the applicants attempted to correct the mistakes in column 4, but failed to do so in column 7, and (4) in their attempt to correct the sequence listing, the applicants accidentally submitted the incorrect sequence listing on their third attempt to file corrections. While it is possible that each of these mistakes did occur and that the patentee's intent was to claim the sequence beginning with nucleotide 340 of the CD28 protein, it is unreasonable to expect a POSITA to make each of these assumptions despite (1) the '190 Patent's express definition of SEQ ID NO:6 in the sequence listing, (2) the support for this definition within the specification, and (3) the fact that the other purported definition as provided in the amended column 4 is open-

ended and may be read in a manner consistent with the sequence listing. Accordingly, the Court concludes that the '190 Patent explicitly defined the claim term "the amino acid encoded by SEQ ID NO:6" by way of the sequence listing and that nothing in the intrinsic record is sufficient to overcome this express definition.

For this reason, the Court finds that a POSITA encountering the '190 Patent prior to the CoC would have understood SEQ ID NO:6 to begin with nucleotide 336 of the CD28 protein. It further finds that, when SEQ ID NO:6 is proper framed, it encodes an amino acid sequence corresponding to "amino acids 113-220 of CD28 (starting with lysine (K))." For this reason, the Court construes the term as follows:

Claim Term	Court's Construction
"the amino acid sequence encoded by SEQ ID NO:6"	**Before the Certificate of Correction:** Amino Acids 113-220 of CD28 (starting with lysine (K)) **After the Certificate of Correction:** Amino Acids 114-220 of CD28 (starting with isoleucine (I))

C. "nucleic acid polymer encoding . . . a binding element that specifically interacts with a selected target"

The parties next dispute whether the term "nucleic acid polymer encoding . . . a binding element that specifically interacts with a selected target," found in claim 1, is a means plus function term governed by 35 U.S.C. § 112(6). The parties' positions are provided below:

Plaintiff's Proposed Construction	Defendants' Proposed Construction
Plain and ordinary meaning	Term "binding element" is governed by 35 U.S.C. § 112(6).

When a limitation "recit[es] a function be performed rather than . . . reciting structure for performing that function," the scope of the claim is limited "to only the structure, materials, or acts described in the specification as corresponding to the claimed function and equivalents." *Williamson v. Citrix Online LLC,* 792 F.3d 1339, 1347-48 (Fed. Cir. 2015). While this restriction ordinarily applies only to those claim terms utilizing the word "means," 35 U.S.C. § 112(6) may also apply to certain "nonce words" if "the claim term fails to 'recite sufficiently definite structure' or else recites 'function without reciting sufficient structure for performing that function.'" *Williamson*, 792 F.3d at 1349. Claims that do not explicitly use the term "means" are entitled to

a rebuttable presumption that they are not implicated by § 112(6). *Id.* at 1348; *EnOcean GbH v. Face Int'l Corp.*, 742 F.3d 955, 959 (Fed. Cir. 2014).

Here, Defendant contends that the use of the term "binding element" in Claim 1 of the '190 Patent is just such a nonce word and that the scope of the claim term should therefore be limited only to SJ25C1-derived scFv and J591-derived scFv—the specific embodiments disclosed in the specification. (Def.'s Brief, at 17-20.) Plaintiffs respond that (1) "binding element" is not a nonce word, and (2) the preamble defines the binding element as part of a CAR-T encoded by a nucleic acid polymer and must therefore be a polypeptide. (Pl.'s Brief, at 15-19.) Before determining whether the specification provides sufficient structure, the Court must first decide whether "binding element" is, in fact, a word that is "tantamount to using the word 'means.'" *Williamson*, 792 F.3d at 1350.

Defendant's expert claims that "a POSA would have understood the term [binding element] to convey a purely functional meaning, *i.e.*, a means for binding and specifically interacting with a selected target." (Junghans Decl. ¶ 100.) This very statement, however, undermines his argument that the term is a nonce word; the fact that he reads the term to describe an element that binds to and specifically interacts with a selected target reveals that he does have an understanding of the term's scope. Constrained by the biochemistry required to "bind" to a potential antigen, there is a limited universe of appropriate "binding element[s] that specifically interact[] with a particular target." Defendant admits as much in its invalidity contentions, stating that "[a] person of ordinary skill in the art would understand that the term 'binding element' could include any polypeptide, including for example, receptors, receptor ligands, antibodies, and single chain antibodies." (Heinrich Decl., Exh. 11 ("Invalidity Contentions"), ECF No. 85-11; Abken Decl. ¶ 45 (Defendant's IPR expert stating that researchers were aware of the use of "binding elements" to target antigens at the time of invention of the '190 Patent and that "[t]ypically, the binding element was an antibody or an antibody fragment, with single chain antibody fragments ("scFv") being preferred . . .")).

The disagreement between the parties, then, is not whether a POSITA would have known the class of elements being claimed, but whether narrowing the possible choices to a particular set of polypeptides is sufficient. On this, the Federal Circuit has been clear. A claim term "need not connote a single specific structure; rather it may describe a class of structures." *Apple v. Motorola, Inc.*, 757 F.3d 1286, 1301 (Fed. Cir. 2014), *overruled on other grounds by Williamson*, 792 F.3d at 1349. "To determine whether a claim recites sufficient structure, 'it is sufficient if the claim term is used in common parlance or by persons of skill in the pertinent art to designate structure, even if the term covers a broad class of structures and even if the term identifies the structures by their function.'" *Skyy, Inc. v. MINDGEEK, S.A.R.L.*, 859 F.3d 1014, 1019 (Fed. Cir. 2017) (quoting *TecSec, Inc. v. Int'l Bus. Machs. Corp.*, 731 F.3d 1336, 1347 (Fed. Cir. 2013)). Such is the case here. As evidenced by Defendant's own expert witnesses, a POSITA encountering the disputed claim term would understand it to denote

a particular class of structures—namely polypeptides capable of specifically interacting (*i.e.*, binding) with a particular antigen target. For this reason, the Court finds that § 112(6) is not implicated in this instance. To the extent that Defendant argues that the patent claims too wide a range of species, this is not an argument properly grounded in §112(6), but rather in written description or enablement—claims properly brought upon summary judgment, not at claim construction.

Claim Term	Court's Construction
"nucleic acid polymer encoding . . . a binding element that specifically interacts with a selected target"	Plain and ordinary meaning

V. CONCLUSION

For the foregoing reasons, the Court construes the disputed claim terms as follows:

1. **"the amino acid sequence encoded by SEQ ID NO:6"** before the Certificate of Correction means **"Amino Acids 113-220 of CD28 (starting with lysine (K))"** and after the Certificate of Correction means **"Amino Acids 114-220 of CD28 (starting with isoleucine (I))"**
2. **"nucleic acid polymer encoding . . . a binding element that specifically interacts with a selected target"** is given its **plain and ordinary meaning**.

IT IS SO ORDERED.