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Paper 72
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KITE PHARMA, INC.,
Petitioner,

v.

SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH,
Patent Owner.

Case IPR2015-01719
Patent 7,446,190 B2

Before RAMA G. ELLURU, TINA E. HULSE, and
ELIZABETH A. LAVIER, *Administrative Patent Judges.*

LAVIER, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Petitioner, Kite Pharma, Inc. ("Kite"), filed a Petition requesting an *inter partes* review of claims 1–13 of U.S. Patent No. 7,446,190 B2 ("the '190 patent"; Ex. 1001), all the claims in the patent. Paper 2 ("Pet."). Patent Owner, Sloan Kettering Institute for Cancer Research ("Sloan"), filed a Preliminary Response. Paper 7 ("Prelim. Resp."). We instituted an *inter partes* review of the challenged claims, on the three grounds of unpatentability set forth in the Petition. Paper 8 ("Dec. Inst."). Sloan filed a Response to the Petition. Paper 20 ("PO Resp."). Kite filed a Reply to the Response. Paper 31 ("Pet. Reply").

Both parties filed motions to exclude certain exhibits and testimony. Paper 46 (Kite); Paper 52 (Sloan). Both parties opposed the other's motion to exclude. Paper 56 (Kite); Paper 57 (Sloan). And both parties filed reply briefs in support of their motions to exclude. Paper 58 (Sloan); Paper 59 (Kite). Sloan also filed Motions for Observation on certain cross-examination testimony of Kite's declarants (Papers 47–49), to which Kite filed Responses (Papers 60–62).

An oral hearing occurred on October 20, 2016, a transcript of which has been entered in the record.[1] Paper 71 ("Tr.").

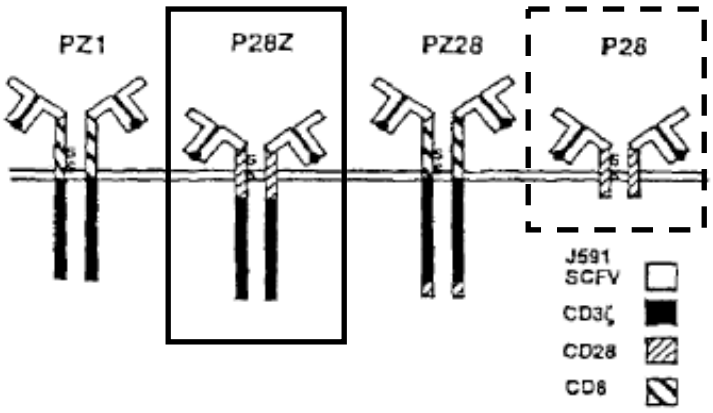
[1] Kite filed Objections to Sloan's Demonstrative Exhibits. Paper 70. In this Final Written Decision, we rely directly on the arguments presented properly in the parties' briefs and the evidence of record. The demonstrative exhibits are considered only to the extent they are consistent with those arguments and evidence.

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Kite has not shown by a preponderance of the evidence that claims 1–13 of the '190 patent are unpatentable.

A. The '190 patent

The '190 patent is titled "Nucleic Acids Encoding Chimeric T Cell Receptors." Ex. 1001, at [54]. The '190 patent explains that genetic engineering of T lymphocytes "to express artificial TCRs [(T cell receptors)] that direct cytotoxicity toward tumor cells" is a promising approach for "enhanc[ing] immune recognition and elimination of cancer cells." Ex. 1001, 1:29–33. Specifically, the '190 patent describes engineered (i.e., chimeric) TCRs that are formed by combining, in a single molecule, an activation signaling region (from CD3ζ (also known as the TCR ζ-chain)), a costimulatory signaling region (from, e.g., CD28), and a binding element for specific interaction with a selected target. *See id.* at 2:14–18. The '190 patent identifies P28Z as a chimeric TCR "in accordance with the invention." *Id.* at 5:28–29. P28Z is the second chimeric TCR from the left depicted in Figure 2 (annotated to highlight P28Z (solid line) and P28 (dotted line)), shown below:



Annotated Figure 2 of the ’190 patent diagrams “a series of chimeric TCRs.”[2] *Id.* at 2:42. P28, a control species, includes “the intracellular, transmembrane and much of the extracellular portions of CD28.” *Id.* at 5:26–28. The CD28 portion of P28 can be amplified from nucleotides 336–660 of human CD28 cDNA using primers listed in the ’190 patent as SEQ ID NO: 4 and 5, to produce the full sequence SEQ ID NO: 6. *See id.* at 4:21–28, 7:51–56; *see also id.*, Certificate of Correction (correcting SEQ ID NO: 6). The ’190 patent states that its “most important finding” is that the “expression of P28z enables T cells to undergo repeated rounds of antigen-dependent stimulation and expansion.” Ex. 1001, 5:58–61.

[2] For reference, each of the four chimeric TCRs depicted in Figure 2 includes an scFV (single-chain variable fragment) specific for PSMA (prostate-specific membrane antigen). *See* Ex. 1001, 5:21–23, 7:43–45.

B. Illustrative Claim

Claim 1 is the only independent claim of the challenged claims, and is illustrative of the claimed subject matter:

> 1. 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.

Ex. 1001, 25:30–38 (some formatting added).

C. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

Ground	Claims	Basis	References
1	1–3, 6–9, 12, 13	§ 103(a)[3]	Krause,[4] Finney,[5] and Aruffo[6]
2	4, 10	§ 103(a)	Krause, Finney, Aruffo, and Gong[7]
3	5, 11	§ 103(a)	Krause, Finney, Aruffo, and Bejcek[8]

[3] The relevant sections of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, took effect on March 16, 2013. Because the application from which the '190 patent issued was filed before that date, our citations to Title 35 are to its pre-AIA version.

[4] Krause et al., *Antigen-dependent CD28 Signaling Selectively Enhances Survival and Proliferation in Genetically Modified Activated Human Primary T Lymphocytes*, 188 J. EXP. MED. 619–26 (1998) (Ex. 1002).

[5] Finney et al., *Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product*, 161 J. IMMUNOL. 2791–97 (1998) (Ex. 1003).

[6] Aruffo & Seed, *Molecular Cloning of a CD28 cDNA by a High-Efficiency COS Cell Expression System*, 84 PNAS USA IMMUNOL. 8573–88 (1987) (Ex. 1012).

[7] Gong et al., *Cancer Patient T Cells Genetically Targeted to Prostate-Specific Membrane Antigen Specifically Lyse Prostate Cancer Cells and Release Cytokines in Response to Prostate-Specific Membrane Antigen*, 1 NEOPLASIA 123–27 (1999) (Ex. 1004).

[8] Bejcek et al., *Development and Characterization of Three Recombinant Single Chain Antibody Fragments (scFvs) Directed against the CD19 Antigen*, 55 CANCER RES. 2346–51 (1995) (Ex. 1016).

II. CLAIM CONSTRUCTION

In our decision instituting *inter partes* review, we determined it was not necessary to construe expressly any of the claim terms. Dec. Inst. 6. Upon consideration of the full record, express construction remains unnecessary. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting claim terms require construction "only to the extent necessary to resolve the controversy"). Indeed, neither the Response nor the Reply directly addresses claim construction, and the parties did not focus on claim construction issues during the oral hearing.

III. OBVIOUSNESS

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

If all the claimed elements are present in the prior art references, the obviousness inquiry turns to the combination of those references:

> [P]roper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to

> those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

Par Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1196 (Fed. Cir. 2014) (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)).

A. Level of Ordinary Skill in the Art

The parties generally agree[9] that one of ordinary skill in the art at the time of the invention[10] would have had an advanced degree in immunology, cell biology, biochemistry, molecular biology, or a related discipline, along with knowledge and experience in the field of T cell research, including laboratory techniques. *See* Pet. 33–34 (citing Ex. 1008[11] ¶ 12); PO Resp. 9 (citing Ex. 2022[12] ¶ 25; Ex. 1008 ¶ 12). In light of the parties' general agreement on this point, we adopt that description of the level of ordinary

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[9] However, Sloan disputes (*see* PO Resp. 9) Kite's assertion that one of ordinary skill in the art would have "taken advantage of certain specialized skills" while working as part of a team (Pet. 34). As these specialties (*see* Pet. 34 ("[f]or example, an immunologist, a cell biologist, and a clinical oncologist")) are in disciplines within the ambit of the relevant art of T cell research, we discern no meaningful distinction in the parties' positions on this issue.

[10] The application leading to the '190 patent was filed on May 28, 2003. Ex. 1001, at [22].

[11] Declaration of Professor Hinrich Abken, M.D. (Ex. 1008).

[12] Declaration of Professor Thomas Brocker, Ph.D. (Ex. 2022).

skill in the art. In our analysis, we consider the applied prior art as representative of the level of ordinary skill. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Overview of Cited Art

Each of the three grounds of unpatentability upon which we instituted this review relies on a combination of Krause, Finney, and Aruffo. *See* Pet. 16. Kite adds Gong and Bejcek for Grounds 2 and 3, respectively. *See id.*

1. Krause

Krause describes a chimeric CD28 construct specific for G_{D2}, a molecule overexpressed on the surface neuroblastoma and other human tumor cells. Ex. 1002, 619. Krause shows that this construct, called 3G6-CD28, "provides CD28 signaling upon specific recognition of the G_{D2} antigen on tumor cells," and further demonstrates selective expansion of $CD8^+$ lymphocytes expressing 3G6-CD28 "when cultured with cells expressing allogeneic major histocompatibility complex [(MHC)] class I together with G_{D2}." *Id.* Thus, Krause focuses on inducing the CD28-mediated costimulatory signal. *See id.* at 619–620, 624. Krause does not indicate that the 3G6-CD28 construct contains CD3ζ specifically, or any other TCR complex-related sequence. Rather, for the primary T-cell activation signal, Krause relies on co-culturing its 3G6-CD28-expressing cells with "cells expressing MHC class I together with G_{D2}." *Id.* at 620.

For its construct, Krause uses "the portion of the CD28 comprising part of the extracellular, the transmembrane, and the cytoplasmic domains."

Id. at 620. More specifically, Krause provides primers for amplifying the CD28 coding sequence from isolated RNA using reverse transcription PCR, and states that the amplified region runs from nucleotides 336 to 663 of human CD28. *See id.* Notably, the '190 patent cites Krause (as well as another paper with the same primary author) as describing the portion of CD28 used in the P28 and P28Z constructs. *See* Ex. 1001, 7:51–56.

2. Finney

Finney describes chimeric receptors that feature "intracellular sequences comprising the signaling region of CD28 in series with the signaling region of the ζ-chain[13] from the TCR complex." Ex. 1003, 2792. Finney states that "[t]hese constructs represent the first of a new generation of single gene multidomain chimeric receptors capable of mediating both primary and costimulatory signaling specifically from a single extracellular recognition event." *Id.* at 2791. Finney's experimental constructs feature sequences derived from an scFv extracellular antibody binding site, followed by one of two "spacer" sequences ("h.28" and "G1"), followed by a "linker," followed by sequences derived from the intracellular domain of CD3ζ and the intracellular and transmembrane domains of CD28. *Id.* at 2792. In some constructs, the CD28 sequence is proximal to the cell membrane; in others, the CD3ζ sequence is proximal. *See id.*

[13] Unless quoting from Finney or another source, we use the "CD3ζ" nomenclature for consistency. The terms are interchangeable, as noted above.

Finney further reports that constructs containing the "h.28" spacer are more efficient than constructs with the "G1" spacer in mediating IL-2 production in the same assays. *See id.* at 2791 (Abstract), 2794–95 (discussing Figure 3). Both spacers include sequences from human IgG1 hinge, but h.28 also includes "part of the extracellular region of human CD28." *Id.* at 2793. In contrast, G1 includes human IgG1 as well as CH2 and CH3 sequences (but not any sequence from CD28).[14] *Id.*

3. Aruffo

Aruffo reports the successful cloning of human CD28 cDNA, and provides the nucleotide sequence. Ex. 1012 (*see especially* Fig. 2).

4. Gong

Gong discloses a chimeric TCR with a binding region specific for prostate-specific membrane antigen (PSMA), a glycoprotein expressed on prostate cancer cells and other tumor cells. Ex. 1004, 123 (Abstract). Gong reports that T cells transduced with Gong's construct successfully lyse prostate cancer cells. *Id.*

5. Bejcek

Bejcek demonstrates cloning, expression, and binding of anti-CD19 single chain antibody fragments. Ex. 1016, 2346 (Abstract).

[14] Immunoglobulin G1 (IgG1) is a subclass of antibodies found in humans. CH2 and CH3 are constant domains of the heavy chain of the antibody.

C. Ground 1

Kite asserts that claims 1–3, 6–9, 12, and 13 are unpatentable because they would have been obvious over the combination of Krause, Finney, and Aruffo. Pet. 34–51. Sloan does not appear to dispute that the combination of cited references teaches each of the claim elements. Rather, Sloan argues Kite has not sufficiently established a rationale for combining the references, or that one of ordinary skill in the art would have had a reasonable expectation of success in doing so. *See* PO Resp. 9–43. Sloan also argues that the objective evidence of nonobviousness in this case is "overwhelming." *See id.* at 48–61.

Kite offers three alternative rationales for combining Krause, Finney, and Aruffo: (1) starting with Krause's construct (with the CD28 sequence as provided in Aruffo), and adding Finney's CD3ζ to it (*see* Pet. 38–40); (2) starting with Finney's chimeric TCR, and replacing its CD28 region with Krause's CD28 region (with the CD28 sequence as provided in Aruffo) (*see id.* at 40–45); and (3) routine optimization of Finney, with guidance from Krause and Aruffo (*see id.* at 45–46).

As explained below, we find none of these rationales to be persuasive. Accordingly, we conclude that Kite has not carried its burden to prove, by a preponderance of the evidence, that claims 1–3, 6–9, 12, and 13 are unpatentable as obvious over Krause, Finney, and Aruffo.

1. Rationale 1: Add Finney's CD3ζ to Krause's Chimeric T Cell Receptor

Kite first argues that an ordinarily skilled artisan focused on the G_{D2} cancer target in Krause "would have been motivated to make a chimeric TCR that included the CD3ζ domain disclosed in Finney together with the binding element and CD28 region Krause teaches, to achieve a chimeric TCR with *both* a primary and a costimulatory domain in a single chimeric receptor." Pet. 38 (citing Ex. 1008 ¶¶ 93–102). However, the purported advantages Kite asserts (*see id.* at 38–40) are all advantages taught by Finney alone (i.e., the advantages of a dual-signaling chimeric T cell receptor over using two separate constructs), as applied to a G_{D2} target. That is, Kite does not proffer any rationale for using Krause's CD28 sequence rather than Finney's. Using either CD28 sequence would yield the general advantages of a dual-signaling chimeric TCR noted in rationale (1) by Kite, but only the combination including Krause's CD28 sequence, not Finney's, would be within the scope of the challenged claims of the '190 patent.

Central to any allegation of obviousness is that the proponent must establish that the prior art renders the invention obvious *as claimed*. *Cf. KSR*, 550 U.S. at 418 (discussing various considerations important in determining "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). Here, Kite's rationale (1), as presented in the Petition, does not distinguish expressly between the advantages of Krause's CD28 sequence versus Finney's, or explain why one of ordinary skill in the art, in developing a dual-signaling chimeric TCR to target G_{D2}, would have been motivated to retain Krause's

CD28 sequence over Finney's when combining the two references. Accordingly, rationale (1) is deficient on its face. However, if we impute the alleged advantages of Krause's CD28 sequence as discussed with respect to rationales (2) and (3) to rationale (1),[15] then rationale (1) rises or falls with rationale (2).[16]

2. Rationale 2: Replacement of Finney's CD28 Sequence with Krause's CD28 Sequence

Second, Kite argues that an ordinarily skilled artisan focused on Finney's CD33 cancer target "would have had a reason to replace Finney's CD28 region[[17]] in Finney's chimeric TCR with Krause's CD28 region, which is longer than Finney's," specifically because they "would have expected Krause's CD28 region to offer advantages with respect to signal transduction and cell surface expression levels." Pet. 40 (citing Ex. 1003, 2793, Fig. 2, 2794, Fig. 3A; Ex. 1008, ¶¶ 103–108). And although Kite's proposed combination uses the CD28 region from Krause, not Finney, Kite

[15] Kite appears to take this approach in its Reply, discussing these advantages in the context of rationale (1). *See* Pet. Reply 11–14.
[16] As we discuss below, rationale (3) is not meaningfully distinct from rationale (2).
[17] The phrase "Finney's CD28 region" is somewhat vague absent additional context because, as discussed above, Finney discloses constructs with one of two spacer sequences, only one of which (h.28) includes extracellular CD28 sequence. By "Finney's CD28 region," we understand Kite to mean the extracellular CD28 sequence from the h.28 spacer plus the transmembrane and intracellular CD28 sequence from the CD28 cassette. *See* Ex. 1002, 2793; Pet. 22; Pet. Reply 18 (Figure 4); Tr. 28:19–25.

argues that Finney itself shows "the benefits of including additional extracellular CD28 sequence in a chimeric TCR," because Finney's construct with a "longer" CD28 region resulted in more cell surface expression and IL-2 production as compared to the construct with "less CD28 sequence." *Id.* at 42.

Further, Kite asserts (*see* Pet. 40–42; *see also* Pet. Reply 15–20) that the extracellular CD28 sequence of Krause includes particularly advantageous features: the "MYPPPY" motif,[18] and the adjacent "LDN" motif,[19] neither of which is present in Finney's extracellular CD28 sequence (*see* Ex. 1008 ¶¶ 74–75). Kite cites a study by Kariv et al.[20] discussing the significance of the MYPPPY and LDN motifs to CD28 expression and IL-2

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[18] "MYPPPY" is the sequence of single-letter amino acid codes representing Methionine-Tyrosine-Proline-Proline-Proline-Tyrosine. *See* Ex. 1010, 390. As Krause does not include full sequence data, Krause does not expressly mention the MYPPPY motif. Rather, Dr. Abken deduces the inclusion of the MYPPPY motif in Krause from Krause's primers and the full CD28 sequence disclosed in Aruffo. *See* Ex. 1008 ¶ 74. Sloan does not dispute that Krause's CD28 region includes the MYPPPY motif.

[19] "LDN" is the sequence of single-letter amino acid codes representing Leucine-Aspartic acid-Asparagine. *Cf.* Ex. 1006, 32. As with the MYPPPY motif, Krause does not expressly mention the LDN motif, but Dr. Abken deduces its inclusion in Krause's extracellular CD28 sequence from Krause's primers and Aruffo's sequence. *See* Ex. 1008 ¶ 74. Sloan does not dispute that Krause's CD28 region includes the LDN motif adjacent to the MYPPPY motif.

[20] Kariv et al., *Analysis of the Site of Interaction of CD28 with Its Counter-receptors CD80 and CD86 and Correlation with Function*, 157 J. IMMUNOL. 29–38 (1996) (Ex. 1006).

production. *See* Pet. 29–30 (citing Ex. 1006); *see also id.* at 40–42 (same). According to Kite, "the MYPPPY motif of CD28 was known to be highly conserved across many species, i.e., 'virtually identical when compared among human, mouse, rat, and even chicken, indicating that it may have an important role in ligand binding and/or *signal transduction*.'" *Id.* at 29 (quoting Ex. 1010,[21] 390 (emphasis added in Petition)). Kite notes that amino acids immediately adjacent to the MYPPPY motif, i.e., the LDN motif, were thought to be required for full surface-level expression of CD28. *Id.* at 30 (citing Ex. 1006, 36, Fig. 6; Ex. 1008 ¶ 75). Accordingly, Kite argues that one of ordinary skill in the art would have been motivated to replace Finney's CD28 region with Krause's (which has a longer extracellular domain, including the MYPPPY and LDN motifs) to improve both signal transduction and cell surface expression. *Id.* at 40–41; *see also id.* at 42 (discussing the benefit of "longer" CD28 regions).

We do not find Kite's analysis to be persuasive, for the reasons outlined below.

a. Finney Does Not Teach or Suggest that "Longer" CD28 Sequences Are Better than "Shorter" Ones

Kite's thesis that "longer" CD28 regions would be considered advantageous over "shorter" ones is not supported by the cited prior art. Although Kite is correct that Finney's chimeric TCR containing a "longer

[21] Greenfield et al., *CD28/B7 Costimulation: A Review*, 18 CRITICAL REVIEWS IN IMMUNOLOGY 389, 390 (1998) (Ex. 1010).

region of CD28" performed better than the chimeric TCR with "less CD28 sequence" (Pet. 42), this statement ignores other differences between Finney's constructs. As discussed above, Finney teaches constructs containing one of two spacers, h.28 or G1. Only the h.28 spacer includes extracellular CD28 sequence; the G1 spacer itself contains no CD28 sequence at all. *See* Ex. 1003, 2792. However, the two spacers further differ from each other insofar as the G1 spacer includes human IgG1, CH2 and CH3 sequences, but the h.28 spacer does not. *Id.* Ultimately, as Sloan points out, the G1 spacer is "218 amino acids *longer* than the h.28 spacer." PO Resp. 13 (citing Ex. 1003, 2793; Ex. 2022 ¶¶ 114, 194; Ex. 2021, 188:10–13).

Kite does not acknowledge these other differences between Finney's spacers in the Petition, and this omission undercuts the persuasiveness of Kite's argument. In its Reply, Kite includes a substantive discussion of the h.28 and G1 spacers, but relies almost exclusively on its experts' analyses to brush aside the other distinctions, concluding that "a POSA would have viewed Finney's constructs as differing essentially in only one way: *the length of the CD28 sequence*." Pet. Reply 19 (citing Ex. 1032[22] ¶ 56; Ex. 1033[23] ¶ 46). Also, Kite characterizes Sloan as allegedly "conced[ing] that the G1 spacer was '*inert, [and] non-signaling*.'" Pet. Reply 18 (quoting PO Resp. 23). But this misses Sloan's point, which is that *neither* the h.28 nor

[22] Second Declaration of Dr. Abken (Ex. 1032).
[23] Declaration of Professor Jürgen Bajorath, Ph.D. (Ex. 1033).

the G1 spacer contains binding domains. Kite's incomplete representation of Sloan's position is clear when the quoted passage is considered in context:

> Skilled artisans also used spacer domains derived from CD8, CD7, and CD4, also found on T cells. *See* KIT1004, 124; Ex. 2015, 102; Ex. 2030, 183; Ex. 2031, 1669; Ex. 2032, 720; Ex. 2033, 412-413; Ex. 2023, 4319. None of these spacers contained the ligand-binding domain of the protein from which it derived, but rather comprised the inert, non-signaling portions of the protein's *constant*-like domain. Ex. 2022, ¶160. Finney's h.28 and G1 spacers likewise contained no portion of the specific binding domains of CD28 or the IgG1, respectively. Ex. 1003, 2792-93; Ex. 2022, ¶161. The CH2 and CH3 domains are inert *constant* regions within the immunoglobulin. Ex. 2022, ¶42.

PO Resp. 23. In other words, Sloan argues that Finney's spacers, like other spacers known in the art, were meant to be non-signaling and otherwise inert. Accordingly, Sloan's argument is consistent with Finney's stated purpose for its spacer sequences: "[s]pacers are used to distance the extracellular binding domain from the membrane" (Ex. 1003, 2792).

To be sure, Finney reports superior results for constructs with the h.28 spacer instead of the G1 spacer. *See, e.g., id.* at 2793 ("The presence of the CD28 extracellular spacer resulted in greater expression of the CD28-ζ signaling sequence than did the G1 spacer."), 2795 ("Again the h.28 spacer was more efficient than the G2 spacer at mediating IL-2 production."). However, as Sloan notes, Finney never "compar[es] the relative 'lengths' of CD28 regions or suggest[s] advantages of 'longer' CD28 regions." PO Resp. 3. Thus, the ordinarily skilled artisan, reading Finney, would

appreciate that the h.28 spacer was superior to the G1 spacer, but would not have attributed that superiority to the presence of extracellular CD28 sequence in the h.28 spacer. Further, we agree with Sloan (*see* PO Resp. 15–16) that even if the ordinarily skilled artisan had attributed some value to the extracellular CD28 sequence in the h.28 spacer, there would have been no reason to expect that *even more* extracellular CD28 sequence would yield further improvements. As Finney includes only one spacer (h.28) comprising extracellular CD28 sequence, there is no trend from which one could extrapolate the relative value of differing extracellular CD28 lengths. Furthermore, to add more extracellular CD28 sequence would risk adding binding domains (as discussed further below), contrary to Finney's stated purpose of the spacer to simply provide "distance" between the construct's intended extracellular binding domain and the cell membrane.

b. The Prior Art Does Not Teach or Suggest that Inclusion of the MYPPPY and/or LDN Motifs Would Have Been Advantageous

We are also not persuaded that one of ordinary skill in the art would have considered the inclusion of more extracellular CD28 sequence, particularly the MYPPPY and LDN motifs, to be advantageous in designing a chimeric TCR.

As discussed above, none of Finney's constructs includes the MYPPPY or LDN motifs. Krause's construct does, but Krause does not emphasize (or even acknowledge) this fact. As Sloan points out, "[n]either Krause nor Finney even suggested a signaling role for *any* extracellular CD28 portion." PO Resp. 18 (citing Ex. 1003, 2792; Ex. 1002, 623).

Rather, Krause characterizes its data as "strongly suggest[ing]" that the costimulatory signal is "dependent on the cytoplasmic domain of CD28" (Ex. 1002, 623), i.e., not the extracellular domain.

Kariv, on which Kite relies, calls the MYPPPY motif a "key site of common and selective recognition" for CD28. Ex. 1006, Abstract. More specifically, Kariv reports that "the majority of substitutions and deletions in the MYPPPY motif abrogate binding to both receptors, while retaining cell surface reception," and also notes that the adjacent LDN residues "also contribute to this site of interaction." Ex. 1006, 35. Kite argues that Kariv supports the motivation to include the MYPPPY and LDN motifs in a chimeric TCR construct because Kariv's studies show that mutations in the MYPPPY motif "dramatically reduced the CD28 protein's ability to signal the release of IL-2 by T cells" and that mutations in the LDN motif "decreased CD28 expression on the cell surface of T cells, indicating that this adjacent region is required for full protein expression." Pet. 29–30 (citing Ex. 1006, 36–37, Figs. 6, 7; Ex. 1008 ¶¶ 74–75). But these arguments only serve to support the general importance of the MYPPPY motif to CD28 function; they do not provide specific support for the proposition that the MYPPPY motif is important in signal transduction. Put differently, we agree with Sloan and credit the testimony of Dr. Brocker that Kariv's mutational analyses do not indicate whether the MYPPPY and/or LDN motifs would have been important for signal transduction decoupled from binding to a natural ligand, i.e., in the case of a chimeric TCR with an

artificial binding domain not reliant on natural ligand binding to CD28. *See* PO Resp. 20; Ex. 2022 ¶¶ 82, 134–44.

Kite's reliance on Greenfield suffers from the same problem, insofar as Greenfield addresses the importance of the MYPPPY motif "in ligand binding and/or *signal transduction*" (Pet. 29 (quoting Ex. 1010, 390 (emphasis added in Petition))), and its cross-species conservation (*id.*). The "and/or" in Greenfield's sentence indicates that the MYPPPY motif was thought to have been important for ligand binding *or* signal transduction *or* both. Greenfield thus stands for the proposition that the MYPPPY motif is important for endogenous CD28 function; it is silent as to the potential role, if any, of the MYPPPY motif in the absence of natural ligand binding to CD28.

In sum, the prior art references cited by Kite in the Petition that expressly address the MYPPPY and/or LDN motifs, i.e., Kariv and Greenfield, show that these sequences are important to CD28 function generally. Further, Kariv provides evidence that the MYPPPY and LDN motifs are important for ligand binding. However, these references shed no light upon what role the MYPPPY and/or LDN motifs would play if natural CD28 ligand binding is bypassed, as would be the case in a dual-signaling chimeric TCR. Accordingly, Kite's argument, that one of ordinary skill in the art would have been motivated to include more extracellular CD28 sequence including the MYPPPY and LDN motifs in designing a chimeric TCR, is not supported sufficiently by Kariv or Greenfield.

c. The Prior Art Teaches Away from Inclusion of the MYPPPY Motif in a Chimeric TCR

The foregoing subsections provide a sufficient basis on which to conclude that Kite has not carried its burden of persuasion as to Ground 1. However, there is an additional, related reason that further supports this conclusion, namely that the prior art teaches away from the claimed combination. More specifically, not only does the prior art fail to provide a motivation to include the MYPPPY motif in a dual-signaling chimeric TCR (as discussed above), we find that the prior art would have discouraged the ordinarily skilled artisan from doing so.

Sloan argues that adding the MYPPPY motif to Finney's dual-signaling chimeric T cell receptor would have been expected to add additional binding specificity for CD28's natural ligands, thus risking so-called "off-target" binding and/or activation. *See* PO Resp. 29 (citing Ex. 1006, Abs.; Ex. 2022 ¶¶ 146, 185–187; Ex. 2087, 10:25–57; Ex. 2016, 1210). Sloan argues that this off-target activation could "induc[e] the engineered T cell to target and kill other activated T cells, or to at least become distracted—in either case, significantly limiting any immune response initiated by the chimeric TCRs or presenting a safety risk." *Id.* at 29–30 (citing Ex. 2022 ¶¶ 144–146). Sloan avers that Krause itself would not have presented this problem, because Krause's construct provides only the costimulatory (CD28) signal, not the primary (CD3ζ) signal, and thus could not have activated an engineered T cell on its own. *Id.* at 30 (citing Ex. 2036, 217; Ex. 1005, 2:31–33; Ex. 2022 ¶ 61).

Although, as Kite notes, Sloan cites no prior art evidence about off-target binding concerns *specifically* in regard to the MYPPPY motif (*see* Pet. Reply 11), Sloan's teach-away argument is nonetheless persuasive. Sloan's argument is based on a reasonable inference from the understanding in the art at the time of the invention that (1) the MYPPPY motif of CD28's extracellular sequence played a key role in ligand binding (as discussed above), and (2) possible ligand binding other than to the scFv, i.e., off-target binding, was a known, problematic design concern for chimeric TCRs.

Kite replies that Krause's data contradict Sloan's position. Kite argues that when Krause tested its construct's ability to signal in response to cross-linking antibodies, including antibody OKT3 (which provided the primary signal), the results showed no evidence of off-target binding to endogenous B7. *Id.* at 11–12 (discussing Krause Table 2) (citing Ex. 1032 ¶¶ 37–40). Further, Kite cites to the opinion of one of its experts, Dr. Bajorath, for the proposition that while the MYPPPY motif is required for B7 binding, "the binding interaction requires other conserved motifs of CD28, and they must all be present in a particular conformation for binding to B7 to occur." *Id.* at 14 (citing Ex. 1033 ¶¶ 48–55; Ex. 1032 ¶¶ 41–42).

Kite's attempts to minimize the off-target binding problem are not persuasive. As to Krause, we disagree with Kite that the data in Krause conclusively show no evidence of off-target binding to endogenous B7. As Kite's expert Dr. Abken admits, all of Krause's transduced T cells also express endogenous CD28 molecules. Ex. 2162, 40:19–41:1, 43:3–7. This endogenous CD28 could bind to B7 on neighboring cells. *Id.* at 43:22–44:6.

Further, Dr. Abken admits that Krause's T cells could receive the co-stimulatory signal through endogenous CD28. *Id.* at 44:16–22 ("That's not proven, but it could be."). Ultimately, then, it is impossible to discern from Krause whether the costimulatory signaling is from endogenous CD28 alone, or from both endogenous CD28 and the MYPPPY motif from the construct.

Kite also argues that Sloan's concerns about off-target binding to the MYPPPY motif are speculative, relying solely on the "unsubstantiated" opinion of Sloan's expert, Dr. Brocker. Pet. Reply 11. However, Dr. Brocker's statement that "[s]cientists in the field, both before and after the filing date, expressed concerns with the potential for this type of off-target binding" is well-supported, as the citing references attest. *See* Ex. 2022 ¶ 146 (citing Ex. 2087,[24] 10:25–27; Ex. 2016,[25] 1210; Ex. 2027,[26] 11002;

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[24] Capon et al., US 6,319,494 B1 (issued Nov. 20, 2001) (Ex. 2087). Capon claims methods for treatment of viral diseases or malignancies using modified T cells, *see* Ex. 2087, 51:50–52:57, and states that its chimeric proteins "will be designed so as to avoid their interaction with other surface membrane proteins native to the target host," *id.* at 10:25–27.

[25] Hombach et al., *Adoptive Immunotherapy with Genetically Engineered T Cells: Modification of the IgG1 Fc 'Spacer' Domain in the Extracellular Moiety of Chimeric Antigen Receptors Avoids 'Off-Target' Activation and Unintended Initiation of an Innate Immune Response*, 17 GENE THERAPY 1206 (2010) (Ex. 2016).

[26] Kowolik et al., *CD28 Costimulation Provided through a CD19-Specific Chimeric Antigen Receptor Enhances* In Vivo *Persistence and Antitumor Efficacy of Adoptively Transferred T Cells*, 66 CANCER RES. 10995 (2008) (Ex. 2027). Kowolik cautions that chimeric T cell receptors including "extracellular CD28 domain that apparently contains the binding site for

Ex. 2025,[27] 699). As Dr. Brocker notes (*see id.* at ¶ 147), one of these post-filing-date references, Hombach (Ex. 2016), was co-authored by one of Kite's experts, Dr. Abken. Hombach reports that the IgG1 CH2CH3 extracellular spacer, which is "commonly used" for chimeric T cell receptors, causes an "off-target" T-cell immune response, i.e., one "mediated independently of scFv-mediated CAR[28] binding to cognate target antigen." Ex. 2016, 1209–10. Although "not expected to have severe clinical consequences," Hombach explains that "'off-target' activation of engineered T cell may result in rapid loss of anti-tumour activity because of activation-induced cell death." *Id.* at 1211. Accordingly, Hombach advises that "[i]n the long term, therefore, adoptive immunotherapy with engineered T cells will substantially benefit from modification of the IgG1 Fc spacer domain" to minimize the risks associated with off-target activation. *Id.*

As Hombach and the other references cited by Dr. Brocker indicate, off-target binding was considered problematic, and best avoided, in the design of chimeric TCRs, both before and after the filing date of the '190 patent.

CD80/CD86, in series with chimeric CD3 ζ, may have the potential for unwanted CD28 mediated activation of the genetically modified T cells." *Id.* at 11002 (citing, *inter alia*, Kariv (Ex. 1006)). Accordingly, Kowolik "does not include the CD28 ectodomain" in its construct. *Id.*

[27] Kochenderfer et al., *Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor*, 32 IMMUNOTHERAPY 689 (2009) (Ex. 2025).

[28] Chimeric Antigen Receptor. This term is interchangeable with "chimeric T cell receptor" or "chimeric TCR." Pet. Reply 3 n.2.

Further, Kite frames Kochenderfer (Ex. 2025) as supportive of its position regarding off-target MYPPPY binding. *See* Pet. Reply 14. However, discussing its own chimeric TCR (FMC63 28Z, which includes the MYPPPY motif in its CD28 sequence), Kochenderfer states:

> The CD28 sequence contained in FMC63 28Z includes the sequence (MYPPPY) that is predicted to form the binding site for the B7 family molecules. Of course, just because the sequence is present does not mean that it is folded in a way to give the 3 dimensional structure necessary for binding to the B7 molecules. We accumulated data that assured us that FMC63 28Z transduced T cells do not recognize B7 molecules.

Ex. 2025, 699 (footnote omitted). We are not persuaded that Kochenderfer, writing years after the '190 patent was filed, supports Kite's position that the ordinarily skilled artisan, at the time of the invention, would have "appreciated that additional CD28 regions not contained in the Krause construct are required for B7 binding" (Pet. Reply 14). To the contrary, Kochenderfer indicates that there was a concern in the art that the MYPPPY motif, when used in a chimeric TCR, could bind to endogenous B7, and that the authors needed to undertake various experiments (*see* Ex. 2025, 699–700), to convince themselves that their particular MYPPPY-containing construct did not do so.

After reviewing the arguments and evidence presented by both sides, we conclude that, at the time of the invention, the ordinarily skilled artisan would have been generally concerned about off-target binding as presenting efficacy and safety risks for chimeric TCRs. Indeed, as Hombach (Ex. 2016) and Kochenderfer (Ex. 2025) attest, off-target binding remained a

concern in the art long after the filing of the ’190 patent. To avoid risking off-target binding, we are persuaded that the ordinarily skilled artisan would have been dissuaded from including sequences that were known to be important for ligand binding, such as the MYPPPY motif in CD28, in designing a dual-signaling chimeric TCR with an artificial binding domain. *See In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.”).

3. Rationale 3: Routine Optimization of Finney’s CD28 Sequence

Kite’s third proffered rationale is that one of ordinary skill in the art would have arrived at the invention “by using routine optimization to vary the length of the extracellular CD28 domain of Finney’s chimeric receptor.” Pet. 45 (citing Ex. 1008 ¶¶ 113–117); *see also* Reply Br. 20–22. As with rationale (2), rationale (3) relies on the premise that Finney “teaches that different lengths of CD28 domains can affect signaling of the chimeric receptor” (Pet. 45 (citing Ex. 1003, 2794, Fig. 3A; Ex. 1008 ¶¶ 68–69, ¶ 114)), such that “the length of the extracellular CD28 domain was known to be a results-effective variable” (*id.* (citing Ex. 1008 ¶¶ 68–69, ¶ 114)).

Accordingly, rationale (2) and rationale (3) are not truly distinct from one another. Thus our analysis of rationale (2) forecloses rationale (3), because we are unpersuaded that Finney’s data can bear the weight of Kite’s arguments.

4. Conclusion

In considering the arguments and evidence presented for Ground 1, we do not find persuasive any of Kite's three rationales for combining the references. Accordingly, we find that Kite has not proven, by a preponderance of the evidence, that claims 1–3, 6–9, 12, and 13 are unpatentable as obvious over Krause, Finney, and Aruffo.

D. Grounds 2 and 3

As Grounds 2 and 3 rely on the same primary combination of Krause, Finney, and Aruffo as does Ground 1, we find that Sloan has not carried its burden of persuasion with respect to Grounds 2 and 3 for essentially the same reasons as with respect to Ground 1.

E. Objective Evidence of Nonobviousness

In light of our determination that Kite has not shown by a preponderance of the evidence that any of the challenged claims is unpatentable as obvious, we need not reach the merits of Sloan's arguments regarding objective evidence of nonobviousness.

IV. MOTIONS TO EXCLUDE EVIDENCE

Both parties filed motions to exclude evidence offered by the opposing side. The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

A. Kite's Motion to Exclude Evidence

Kite moves to exclude Exhibit 2079, a "Market Capitalization" table, as inadmissible hearsay not supported by underlying data as required by 37 C.F.R. § 42.65(b). Paper 46. Because we did not rely on this exhibit or any testimony associated with it in reaching our Decision, we dismiss Kite's motion as moot.

B. Sloan's Motion to Exclude Evidence

Sloan moves to exclude paragraphs 84–97 of Exhibit 1032, Dr. Abken's Second Declaration, which cover Dr. Abken's opinions as to certain objective indicia of nonobviousness, as based on erroneous legal standards and thus irrelevant and unreliable under FRE 402 and 702. Paper 52. Because we did not rely on the testimony contained within these paragraphs, we dismiss Sloan's motion as moot.

V. CONCLUSION

We conclude that Kite has not shown by a preponderance of the evidence that claims 1–13 of the '190 patent are unpatentable under 35 U.S.C. § 103.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–13 of the '190 patent are not held unpatentable;

FURTHER ORDERED that Kite's Motion to Exclude Evidence is *dismissed*;

FURTHER ORDERED that Sloan's Motion to Exclude Evidence is *dismissed*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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