

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MILTENYI BIOMEDICINE GMBH and MILTENYI BIOTEC INC.,
Petitioner,

v.
FRED HUTCHINSON CANCER CENTER,
Patent Owner.

IPR2023-00760
Patent 9,987,308 B2

Before ULRIKE W. JENKS, ZHENYU YANG, and DAVID COTTA,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

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

I. INTRODUCTION

Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc. (collectively, “Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking an *inter partes* review of claims 1–16 and 18–31 of U.S. Patent No. 9,987,308 B2 (Ex. 1001, “the ’308 patent”). Fred Hutchinson Cancer Center (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 7 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply (Paper 8) and Patent Owner filed a Sur-reply (Paper 9).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

For the reasons provided below, we determine Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Accordingly, we deny institution of an *inter partes* review.

A. Related Matters

According to the parties, there are no matters related to this proceeding. Pet. 4; Paper 5, 1.

B. The ’308 Patent and Related Technology

Before reviewing the purported invention of the ’308 patent, we first explain the background of the technology. T cells are a type of lymphocyte. T cells include helper T cells, which express the CD4 membrane glycoprotein, and cytotoxic T cells (CTL), also known as killer T cells, which express the CD8 membrane glycoprotein. Ex. 1001, 7:7–9; Pet. 7 (citing Ex. 1002 ¶ 20); Prelim. Resp. 7.

T cells can be categorized into several subpopulations. A naïve T cell (T_N) is “a non antigen experienced T lymphocyte that expresses CD62L and CD45RA, and does not express or has decreased expression of CD45RO— as compared to central memory cells.” *Id.* at 7:30–33. A central memory cell (T_{CM}) is a subset of the antigen experienced memory T cells (T_M). *Id.* at 1:51–52. A T_{CM} is an antigen experienced CTL that expresses CD62L and CD45RO, and does not express or has decreased expression of CD45RA as compared to T_N cells. *Id.* at 7:14–17. Another subset of T_M is effector memory cells (T_{EM}). *Id.* at 1:51–53. A T_{EM} is an antigen experienced CTL that does not express or has decreased expression of CD62L on the surface thereof as compared to T_{CM} cells, and does not express or has decreased expression of CD45RA as compared to T_N cells. *Id.* at 7:21–26. In response to antigen stimulation, $CD8^+$ T_{CM} and T_{EM} both differentiate into short-lived cytolytic effector T cells (T_E). *Id.* at 1:59–62. A T_E is an antigen experienced CTL that does not express or have decreased expression of CD62L, CCR7, CD28, and are positive for granzyme B and perforin as compared to T_{CM} . *Id.* at 7:38–42.

The '308 patent relates to adoptive cellular immunotherapy. *Id.* at 2:3–4:3. “Adoptive cellular immunotherapy uses genetically modified cells originally isolated from a patient or a donor to treat disease.” Prelim. Resp. 8; *see also* Pet. 13 (similar explanation). CAR-T therapy is a type of adoptive cellular immunotherapy whereby T cells are genetically modified to express a chimeric antigen receptor (CAR). Prelim. Resp. 8. A CAR comprises “an extracellular variable domain of an antibody specific for an antigen associated with the disease or disorder and an intracellular signaling

domain of a T cell or other receptors, such as a costimulatory domain.”

Ex. 1001, 7:56–60; Pet. 14; Prelim. Resp. 8 n.4.

The ’308 patent explains that for clinical applications of the adoptive immunotherapy, “it is necessary to isolate T cells of a desired antigen specificity or to engineer T cells to express receptors that target infected or transformed cells, and then expand these cells in culture.” *Id.* at 1:34–38. These cells, which can target pathogens or malignant cells, are then transferred to recipients to treat cancer and infections. *Id.* at 1:31–34; 38–45.

According to the ’308 patent, “it is apparent from clinical studies that the efficacy of cultured T cells, particularly cloned CD8⁺ T cells, is frequently limited by their failure to persist after adoptive transfer.” 1:45–48. Thus, the ’308 patent states “[t]here is a need to identify cell populations and methods that provide enhanced survival of adoptively transferred T cells in vivo.” *Id.* at 1:65–67.

The purported invention of the ’308 patent relates to methods and compositions to “confer and/or augment immune responses mediated by cellular immunotherapy, such as by adoptively transferring tumor-specific, subset specific genetically modified CD4⁺ T cells, wherein the CD4⁺ T cells confer and/or augment the ability of CD8⁺ T cells to sustain anti-tumor reactivity and increase and/or maximize tumor-specific proliferation.” *Id.* at 2:3–10.

C. Illustrative Claim

Among the challenged claims, claim 1 is independent. Claim 1 is illustrative of the claimed subject matter and is reproduced below.

1. An adoptive cellular immunotherapy composition containing chimeric antigen receptor-modified CD4⁺ T lymphocytes and

chimeric antigen receptor-modified CD8⁺ T lymphocytes,
wherein:

(a) the chimeric antigen receptor-modified CD4⁺ T lymphocytes contain a chimeric antigen receptor that specifically binds to an antigen and at least 50% of the chimeric antigen receptor-modified CD4⁺ helper T lymphocytes in the composition are surface positive for CD62L and/or CD45RA, and

(b) the chimeric antigen receptor-modified CD8⁺ T lymphocytes contain a chimeric antigen receptor that specifically binds to the antigen and at least 50% of CD8⁺ cytotoxic T lymphocytes in the composition are surface positive for CD62L and/or CD45RO.

Ex. 1001, 31:45–59.

D. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Claim(s) Challenged	35 U.S.C. § ¹	References
1–7, 14, 16, 21, 26–28	102	Singh-1 ²
1–7, 14, 16, 21, 26–28	103	Singh-1, Jensen ³

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102, 103, effective March 16, 2013. The earliest priority date on the face of the ’308 patent is March 23, 2011. Ex. 1001, code 60. Because Petitioner has not challenged this priority claim (*see* Pet. 6), for this Decision, we apply the pre-AIA version of §§ 102, 103.

² Singh et al., *Redirecting specificity of T-Cell populations for CD19 using the sleeping beauty system*, 68(8) CANCER RES. 2961–71 (2008) (Ex. 1003, “Singh-1”).

³ Jensen et al., US Patent Publication No. 2004/0126363 A1, published July 1, 2004 (Ex. 1018, “Jensen”).

Claim(s) Challenged	35 U.S.C. § ¹	References
1–16, 18–31 ⁴	103	Singh-1, Jensen, Mitsuyasu, ⁵ Cooper ⁶ , Hudecek I, ⁷ Hudecek II, ⁸ Abken, ⁹ Reckamp, ¹⁰ Carpenito, ¹¹ Moeller, ¹² Wang, ¹³ Yang I, ¹⁴ Yang II, ¹⁵ Sallusto, ¹⁶ Sun ¹⁷
1, 6, 9–16	103	Mitsuyasu, Singh-1, Cooper

⁴ Petitioner lists the obviousness challenge of claims 1–16 and 18–31 as a single ground. *See* Pet. 6. However, Petitioner also indicates that “not all references are necessary for each claim” and breaks this ground into four sub-parts: (1) claims 3 and 18–25 as being obvious over Singh, Hudecek I, Abken, Hudecek II, Reckamp, or Carpenito; (2) claims 6 and 9–13 as being obvious over Singh, Wang, and/or Mitsuyasu; (3) claims 14 and 15 as being obvious over Singh, Moeller, and/or Mitsuyasu; and (4) claims 8 and 29–31 as being obvious over Singh, Wang, Hudecek I, Yang I, Yang II, Sallusto, and/or Sun. *Id.* 50–52.

⁵ Mitsuyasu et al., *Prolonged survival and tissue trafficking following adoptive transfer of CD4 ζ gene-modified autologous CD4⁺ and CD8⁺ T cells in human immunodeficiency virus-infected subjects*, 96(3) BLOOD 785–93 (2000) (Ex. 1004, “Mitsuyasu”).

⁶ 1 ENCYCLOPEDIA OF CANCER *Chimeric Antigen Receptor on T Cells* (2009) (Ex. 1010, “Cooper”).

⁷ Hudecek et al., *Adoptive T-cell therapy for B-cell malignancies*, 2(5) EXPERT REV. HEMATOL. 517–32 (2009) (Ex. 1011, “Hudecek I”).

⁸ Hudecek et al., *CD8⁺ T cells engineered to express a ROR1-specific chimeric antigen receptor specifically recognize ROR1 positive B cell tumors*, 114(22) BLOOD 383 (2009) (Ex. 1012, “Hudecek II”).

⁹ 1 ENCYCLOPEDIA OF CANCER *Chimeric T Cell Receptors* (2009) (Ex. 1013, “Abken”).

¹⁰ Reckamp et al., *CE7 epitope of L1CAM is a potential target for tumor specific T cell therapy in lung cancer*, 49 PROC. AACR ANNUAL MEETING 1099 (2008) (Ex. 1014, “Reckamp”).

Petitioner relies on the declaration of Dr. Jonathan Bramson as support for its Petition. Ex. 1002.

II. ANALYSIS

A. *Level of Ordinary Skill*

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

¹¹ Carpenito et al., *Control of large, established tumor xenografts with genetically retargeted human T cells containing CD28 and CD137 domains*, 106(9) PNAS 3360–65 (2009) (Ex. 1015, “Carpenito”).

¹² Moeller et al., *Adoptive transfer of gene-engineered CD4⁺ helper T cells induces potent primary and secondary tumor rejection*, 106(9) BLOOD 2995–3003 (2005) (Ex. 1016, “Moeller”).

¹³ Wang et al., *The CD19 chimeric antigen receptor re-directs CMV specific T cells derived from central memory T cells (bi-specific T cells) against human acute lymphoid leukemia (ALL)*, 31(9) J. IMMUNOTHER. 926–27 (2008) (Ex. 1017, “Wang”).

¹⁴ Yang et al., *In vitro generated anti-tumor T lymphocytes exhibit distinct subsets mimicking in vivo antigen-experienced cells*, 60 CANCER IMMUNOL. IMMUNOTHER. 739–49 (2011) (Ex. 1027, “Yang I”).

¹⁵ Yang et al., *TCR engineered and in vitro expanded T lymphocytes recapitulate the properties of central memory T cells*, 18 MOLECULAR THERAPY S184 (2010) (Ex. 1028, “Yang II”).

¹⁶ Sallusto et al., *Two subsets of memory T lymphocytes with distinct homing potentials and effector functions*, 401 NATURE 708–12 (1999) (Ex. 1029, “Sallusto”).

¹⁷ Sun et al., *Dysfunction of simian immunodeficiency virus/simian human immunodeficiency virus-induced IL-2 expression by central memory CD4⁺ T lymphocytes*, 174(8) J. IMMUNOL. 4753–60 (2005) (Ex. 1032, “Sun”).

Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner argues that an ordinarily skilled artisan “is skilled in developing genetically engineered T-cell therapies” and “would possess a relatively high level of skill and have at least a Ph.D., together with several years of experience in researching and publishing academic articles concerning T-cell therapies.” Pet. 15. Petitioner also contends that a person of ordinary skill in the art “would be knowledgeable about laboratory techniques related to engineering and testing the function of genetically modified T cells.” *Id.* (citing Ex. 1002 ¶ 53).

Patent Owner disagrees with Petitioner’s proposed skill level. Prelim. Resp. 12–16. First, Patent Owner argues that by excluding artisans with M.D., but not Ph.D., degrees, Petitioner’s definition excludes “[a] number of authors or listed inventors from Petitioner’s exhibits” as well as the inventors of the ’308 patent, “which is strongly disfavored.” *Id.* at 13 (citing Exs. 2004–2009). Second, Patent Owner challenges Petitioner’s definition of skill level for requiring experience “publishing academic articles,” because it “would exclude otherwise skilled artisans merely because their work is not yet published, cannot be published for business or other reasons, or is purely clinical.” *Id.* at 14. Third, Patent Owner points out “Petitioner’s proposed POSA definition is inconsistent with the POSA it proposed in other IPR Petitions involving CAR-modified T cells.” *Id.* (footnote omitted).

Patent Owner argues that an ordinarily skilled artisan has:

[a]n M.D. and/or Ph.D. degree in a field related to adoptive immunotherapy (for example, immunology, molecular biology, cell/cellular biology, genetics, biochemistry, biology,

biomedical sciences, or a related field), or an equivalent degree, and 2-4 years of work or research experience involving the manufacture of adoptively transferred T cells, as well as the assessment of the functions of adoptively transferred T cells *in vivo*.

Id. at 16. Alternatively, Patent Owner proposes that “a POSA could have a B.S. or a M.S. degree in a field related to adoptive immunotherapy, or an equivalent degree, and 4-6 years of the experience described above.” *Id.*

We agree with Patent Owner that an ordinarily skilled artisan should encompass the inventor. *See Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256–57 (Fed. Cir. 2007). On this record, we also decline to include publication of academic articles as a requirement.

After reviewing the record, for purposes of this Decision, we adopt Patent Owner’s definition as it is consistent with the prior art’s demonstration of the skill level at the time of the invention.

B. Claim Construction

In an *inter partes* review, we construe a claim term “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b) (2020). Under that standard, 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.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (*en banc*).

Petitioner discusses the preamble “adoptive cellular immunotherapy composition” and proposes the construction for “and/or.” We address these issues in turn.

1. “adoptive cellular immunotherapy composition”

Petitioner argues that the preamble “adoptive cellular immunotherapy composition” is not limiting because it is merely a statement of intended use. Pet. 17–19. According to Petitioner, the ’308 patent’s “specification indicates that the preamble is an intended use” because its title is “Method and Compositions ***For*** Cellular Immunotherapy” and the “Field of the Invention” explains that “embodiments of the invention relate to methods and compositions ***for carrying out*** cellular immunotherapy.” *Id.* at 17–18 (citing Ex. 1001, 1:1–2, 1:25–27, 16:26–46, 18:19–23; Ex. 1002 ¶ 75) (emphasis added by Petitioner).

In addition, Petitioner contends that the body of claim 1 recites a structurally complete invention, and the preamble “does not provide antecedent basis for any other claim element, does not recite essential structure or steps, and is not necessary to give life, meaning, and vitality to any Challenged Claim.” *Id.* at 18 (quotation marks and brackets omitted). Further, Petitioner points out Patent Owner never relied on the preamble to traverse rejections during prosecution. *Id.* at 19.

Petitioner argues that if the Board finds the preamble limiting, “adoptive cellular immunotherapy composition” should mean a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal.” *Id.* (citing Ex. 1002 ¶ 81).

Patent Owner contends that the preamble is limiting because cellular immunotherapy “is not merely a potential intended use of a separate invention. Rather, it *is* the invention.” Prelim. Resp. 19. Patent Owner argues “[a] POSA would understand from the specification of the ’308 patent that inventive compositions are inventive precisely because they afford clinically

relevant *immunotherapeutic* effect.” *Id.* at 20. Pointing to Figures 12 and 13B of the ’308 patent, Patent Owner asserts “the specification emphasizes the dramatic therapeutic effect seen following *in vivo* testing with the claimed compositions.” *Id.* at 20–21. Thus, Patent Owner continues, the ’308 patent is directed to compositions that “actually provide clinically beneficial treatment, rather than mere cells *per se* that may or may not have effect.” *Id.* at 21–22. Patent Owner further argues that the preamble is limiting because it serves as antecedent basis for the term “composition” recited in the body of claim 1. *Id.* at 22–23 (citing Ex. 1001, 31:49–59).

As to how the preamble should be construed if given limiting effect, Patent Owner disagrees with Petitioner’s proposed construction. Instead, Patent Owner contends the preamble “adoptive cellular immunotherapy composition” should be given its plain and ordinary meaning, which is “a composition comprising adoptively transferred cells that has *therapeutic* effect *in vivo* by causing or mediating an immune response.” *Id.* at 24–25.

We start our analysis by first acknowledging that determining whether a preamble is limiting, despite (or perhaps because of) the numerous legal canons on the topic, is not an easy task. “No litmus test defines when a preamble limits claim scope.” *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). Instead, “[w]hether to treat a preamble as a limitation is determined on the facts of each case in light of the overall form of the claim, and the invention as described in the specification and illuminated in the prosecution history.” *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1357 (Fed. Cir. 2012) (quotation marks omitted).

In general, “a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention.” *Catalina*, 289 F.3d at 808 (quotation marks omitted). But even then, “[w]hether a preamble stating the purpose and context of the invention constitutes a limitation of the claimed process is determined on the facts of each case in light of the overall form of the claim, and the invention as described in the specification and illuminated in the prosecution history.” *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1572–73 (Fed. Cir. 1996).

We determine that, read in view of the Specification, the preamble, even though it states an intended purpose, is limiting, because “it is necessary to give life, meaning, and vitality to the claim.” *See Catalina*, 289 F.3d at 808 (quotation marks omitted). The ’308 patent discloses “an adoptive cellular immunotherapy composition comprising a genetically modified helper T lymphocyte cell [*i.e.*, CD4⁺ T cell] preparation that augments the genetically modified cytotoxic T lymphocyte cell [*i.e.*, CD8⁺ T cell] preparation[’]s ability to mediate a cellular immune response.” Ex. 1001, 9:4–8, *see also id.* at 9:36–42 (disclosing that in some embodiments, an adoptive cellular immunotherapy composition “comprises an antigen-reactive chimeric antigen receptor modified naïve CD4⁺ T helper cell that augments the CD8⁺ immune response.”), 9:48–51 (the same). The ’308 patent also discloses that in some embodiments, an adoptive cellular immunotherapy composition further “comprises a chimeric antigen receptor modified tumor-specific CD8⁺ cytotoxic T lymphocyte cell preparation that elicits a cellular immune response.” *Id.* at 9:14–17, 23–26.

Thus, the '308 patent describes the component CAR-modified CD8⁺ T cells in an “adoptive immunotherapy composition” as eliciting a cellular immune response, and the component CAR-modified CD4⁺ T cells as augmenting the CD8⁺ immune response.

The '308 patent discloses that, in an *in vitro* co-culture assay, “the addition of CAR-transduced, but not untransduced CD4⁺ T cells to CD8⁺ CAR CTL significantly increased specific proliferation of the CD8⁺ subset compared to CD8⁺ CAR CTL alone.” *Id.* at 24:57–61, Fig. 7.

The '308 patent also provides *in vitro* data, showing that naïve CD4⁺ T Cells are better helpers than memory CD4⁺ T cells. Specifically, the data demonstrated that

co-culture of CD8⁺ N and CM CAR CTL with CD4⁺ N CAR T cells resulted in significantly higher tumor-specific proliferation of the CD8⁺ subset compared to co-culture with CD4⁺ CM or EM CAR T cells, or the CD8⁺ CAR CTL alone (FIG. 9). Out of all combinations, maximum proliferation of the CD8⁺ CAR CTL in response to stimulation with ROR1-positive tumor cells was observed after co-culture of CD4⁺ N CAR T cells with CD8⁺ CM CAR CTL (FIG. 9).

Id. at 27:17–25, *see also id.* at 29:2–7 (“FIG. 10 shows the superior ability of CD4⁺ CAR T-cell lines derived from the naïve subset to augment tumor-specific proliferation of central memory-derived CD8⁺ CAR CTL in co-culture experiments with CD8⁺ CD19-CAR CTLs and CD4⁺ CD19-CAR T-cell lines, stimulated with the CD19⁺ mantle cell lymphoma tumor line Jeko-1.”).

In addition to the *in vitro* data showing CAR-modified CD4⁺ T cells enhance the proliferation of CAR-modified CD8⁺ T cells, the '308 patent also provides two examples using mouse models to show the adoptive transfer of ROR1-CAR (Example 5) or CD19-CAR modified (Example 6)

CD4⁺ and CD8⁺ T cells confers “potent anti-tumor responses in an in vivo model of aggressive systemic lymphoma and provide evidence for a beneficial and synergistic effect of CD4⁺ CAR T cells on the anti-tumor efficacy of CD8⁺ CAR CTL.” *Id.* at 28:21–26, 29:50–56, *see also id.* at 28:15–19 (“Importantly, the reduction in tumor burden after administration of the CD8⁺/CD4⁺ CAR T cell combination was greater than that of the CD8⁺ CAR CTL and CD4⁺ CAR T cell groups combined suggesting that CD4⁺ CAR T cells and CD8⁺ CAR CTL were working synergistically.”), 29:18–26 (“FIG. 12 shows the augmentation and synergistic effect CD4⁺ ROR1-CAR modified T cells on the anti-tumor efficacy of CD8⁺ ROR1-CAR CTLs in a mouse tumor model of systemic mantle cell lymphoma (NSG/Jeko-1-ffLuc).”), 29:27–48 (“FIG. 13 shows synergy of CD8⁺ and CD4⁺ CD19-CAR T cells in a mouse model of systemic lymphoma (NSG/Raji).”).

Thus, the '308 patent's Specification not only describes in detail that CAR-modified CD4⁺ T cells in an “adoptive immunotherapy composition” augment the CD8⁺ immune response, it provides both *in vitro* and *in vivo* data to demonstrate the enhanced efficacy. These disclosures support Patent Owner's argument that “the essence of the invention is that clinically relevant therapeutic effect is achieved by virtue of the inventive T cell compositions.” *See* Prelim. Resp. 19.

We, of course, recognize that “there is sometimes a fine line between reading a claim in light of the specification, and reading a limitation into the claim from the specification.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005). In this case, we find further support to our conclusion in the Summary of the Invention section of the Specification.

“Although a statement’s location is not “determinative,” the location can signal the likelihood that the statement will support a limiting definition of a claim term.” *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004). Statements in the “Summary of the Invention” portion of the specification are not limited to describing preferred embodiments, but more broadly describe the overall invention, and therefore, are more likely to support a limiting definition of a claim term. *Id.*

In the “Summary of the Invention,” the ’308 patent discloses that its invention

relates to methods and compositions to confer and/or augment immune responses mediated by cellular immunotherapy, such as by adoptively transferring tumor-specific, subset specific genetically modified CD4⁺ T cells, wherein the CD4⁺ T cells confer and/or augment the ability of CD8⁺ T cells to sustain anti-tumor reactivity and increase and/or maximize tumor-specific proliferation.

Ex. 1001, 2:3–10.

It states that “an adoptive cellular immunotherapy composition” includes (1) a genetically modified CD8⁺ T cell preparation that “elicits a cellular immune response;” and (2) a genetically modified CD4⁺ T cell preparation “exhibits a predominant Th1 phenotype as well as produce other cytokines, elicits direct tumor recognition and augments the ability of genetically modified cytotoxic T lymphocyte cell [i.e., CD8⁺ T cell] preparations[’] ability to mediate a cellular immune response.” *Id.* at 2:43–44, 50–55, 64–65, *see also id.* at 2:11–26 (disclosing a method of performing cellular immunotherapy by administering the two cell preparations above), 3:7–14 (disclosing “an adoptive cellular immunotherapy composition having an antigen specific CD8⁺ cytotoxic T lymphocyte cell preparation that elicits a cellular immune response” and

“an antigen-reactive chimeric antigen receptor modified CD4+ T helper cell that elicits a Th1 cytokine response and augments the CD8+ immune response to pathogens”), 3:20–24 (disclosing “an adoptive cellular immunotherapy composition with an antigen-reactive chimeric antigen receptor modified CD4+ T helper cell that elicits direct tumor recognition and augments the CD8+ immune response to pathogens”), 3:30–41 (disclosing “a method of manufacturing an adoptive immunotherapy composition by obtaining a chimeric antigen receptor modified tumor-specific CD8+ cytotoxic T lymphocyte cell preparation that elicits a cellular immune response . . . and obtaining a modified naïve CD4+ T helper cell that elicits a Th1 cytokine response”), 3:47–61 (the same).

In sum, the Summary of the Invention, in describing the invention as a whole, confirms our determination that the ’308 patent is directed to “therapeutically effective, clinically relevant compositions that provide ‘adoptive cellular immunotherapy.’” *See* Prelim. Resp. 21. Thus, on this record, and in view of the Specification’s repeated disclosures of the clinically relevant therapeutic effects of the “adoptive cellular immunotherapy composition,” we agree with Patent Owner that the preamble is limiting, and requires relevant therapeutic effect *in vivo*.¹⁸ Consequently, we also agree with Patent Owner that “Petitioner’s proposed construction would expand the claimed compositions to any composition

¹⁸ The parties dispute whether “adoptive cellular immunotherapy composition” serves as antecedent basis for the term “composition” recited in the body of claim 1, and thus, is limiting. *See* Prelim. Resp. 23; Reply 6–7. We do not need to resolve this issue because Patent Owner has shown sufficiently that, in view of the Specification, the preamble is limiting.

that *could* be delivered to a mammal, irrespective of whether they have any clinically relevant therapeutic effect *in vivo*.” Prelim. Resp. 24.

Patent Owner argues that the plain and ordinary meaning of “adoptive cellular immunotherapy composition” should be “a composition comprising adoptively transferred cells that has *therapeutic* effect *in vivo* by causing or mediating an immune response.” Prelim. Resp. 25. We agree. Indeed, the ’308 patent requires its composition “to confer and/or augment immune responses mediated by cellular immunotherapy.” *See, e.g.*, Ex. 1001, Abstract, 2:3–10. Thus, on this record, and for purposes of this Decision, we adopt Patent Owner’s proposed construction of the preamble “adoptive cellular immunotherapy composition.”

2. “and/or”

Claim 1 recites that at least 50% of the CAR-modified CD4⁺ T cells in the claimed composition are surface positive for “CD62L and/or CD45RA,” and the CAR-modified CD8⁺ T cells are surface positive for “CD62L and/or CD45RO.” Petitioner proposes that the term “and/or” includes “embodiments having the element preceding ‘and/or,’ the element following ‘and/or,’ or both the element preceding ‘and/or’ and the element following ‘and/or’.” Pet. 20 (citing Ex. 1002 ¶ 86).

Under this construction, Petitioner argues, the CD4⁺ T cells recited in claim 1 can be surface positive for CD62L, for CD45RA, or both. *Id.* (citing Ex. 1002 ¶ 87). And because CD62L⁺ can be either T_N or T_{CM} cells, Petitioner contends “claim 1’s CAR-modified CD4⁺ T cells can be either majority T_{CM} or T_N.” *Id.* at 17 (citing Ex. 1002 ¶¶ 62–66). For similar reasons, Petitioner argues that “claim 1’s CD8⁺ T cells can be majority T_N,

T_{CM}, T_{EM}, or T_E.” *Id.* (citing Ex. 1002 ¶¶ 67–70); *Id.* at 20 (citing Ex. 1002 ¶¶ 87–88).

At this stage, Patent Owner does not dispute Petitioner’s proposed construction or provide its own construction of “and/or.” Based on the current record, we agree with Petitioner’s proposed construction because it is supported by the claim language and the Specification of the ’308 patent.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly address any other claim term.

C. Alleged Anticipation by Singh-1

Petitioner asserts that Singh-1 anticipates claims 1–7, 14, 16, 21, and 26–28 of the ’308 patent. Pet. 31–48. Patent Owner disputes Petitioner’s challenge. Prelim. Resp. 17–32. Based on this record, and for at least the following reasons, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

1. Singh-1

Singh-1 reports a new approach that employs the *Sleeping Beauty* (“*SB*”) transposon/transposase system “to efficiently generat[e] T cells with redirected specificity.” Ex.1003, Abstract. According to Singh-1, “[w]hen coupled with numerical expansion on CD19⁺ artificial antigen-presenting cells, this gene transfer method results in rapid outgrowth of CD4⁺ and CD8⁺ T cells expressing CAR to redirect specificity for CD19⁺ tumor cells.” *Id.*

The CAR in Singh-1, designated CD19RCD28, includes an anti-CD19 binding site, a CD28 costimulatory domain, and a CD3 intracellular signaling domain. *Id.* at 2961. Singh-1 used electroporation to introduce the

DNA expression plasmids. *Id.* at 2963. Singh-1 “observed that peripheral blood- and umbilical cord blood-derived electroporated CD4⁺ and CD8⁺ T cells readily expressed the CAR transposon.” *Id.* at 2965 (stating “after 28 to 35 days, the efficiency of two DNA plasmid *SB*-mediated gene transfer improved CAR expression by ~49 to 60-fold, compared with a single plasmid transposon control (Table 1)”). Singh-1 reports “a 20-fold growth of genetically modified T cells at the end of 4 weeks with continued and accelerated expansion thereafter (Fig. 4A).” *Id.* at 2967. According to Singh-1, its approach “results in efficient and stable CAR gene transfer, which can be numerically expanded to clinically meaningful numbers within 4 weeks . . . and with the outgrowth of CD8⁺ and CD4⁺ CM and effector CAR⁺ T-cell subpopulations.” *Id.* at 2962.

Singh-1 touts that its approach “provides for robust antigen-driven expansion of CD4⁺ and CD8⁺ CAR⁺ T cells to clinically meaningful numbers.” *Id.* at 2964, *see also id.* at 2961 (suggesting its approach “shortens the culture time to generate T cells with durably expressed transgene and maintains a desired T-cell immunophenotype”), *id.* at 2962 (“This is predicted to greatly facilitate trial design infusing CD4⁺ and CD8⁺ CAR⁺ T cells that have desired immunophenotype, including T_{CM}.”). Singh-1 states that it has “incorporated *ex vivo* CAR-dependent proliferation to derive genetically modified T cells and will evaluate the CD19-specific T cells, using SB transposition and aAPC, in a next-generation clinical trial.” *Id.* at 2970–71.

2. Analysis

For purposes of this Decision, we focus our analysis on the preamble of claim 1. Petitioner argues that Singh-1 discloses the preamble; Patent

Owner asserts that it does not. *See* Pet. 32–34; Prelim. Resp. 26–33. For at least the reasons below, we agree with Patent Owner.

Petitioner contends the preamble “adoptive cellular immunotherapy composition” is not limiting. Pet. 32. But even if it is, Petitioner continues, Singh-1 discloses a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal.” *Id.* (citing Ex. 1002 ¶¶ 178–79).

Relevant to our analysis, Petitioner argues that “Singh[-1] discloses results from its authors’ successful attempts to develop ‘a clinically feasible approach to the efficient propagation of CAR+ T-cell populations, including T_{CM}.’” *Id.* (quoting Ex. 1003, 2961). According to Petitioner, the cells generated using Singh-1’s approach “were suitable for use in a clinical trial.” *Id.* at 32 (citing Ex. 1003, 2971); Reply 7 (citing Ex. 1003, 2970). Petitioner emphasizes that Singh-1’s manufacturing process resulted in “clinically meaningful” numbers of T cells. Pet. 33 (citing Ex. 1003, 2962). According to Petitioner, “[a] POSA would have understood this to mean that Singh[-1]’s compositions would be suitable for administration to a mammal because, at least, the composition had enough T cells to elicit a clinical effect.” *Id.* at 33–34 (citing Ex. 1002 ¶ 183).

Patent Owner argues that Singh-1 does not disclose an “adoptive cellular immunotherapy composition” because Singh-1’s cells do not have therapeutic efficacy. Prelim. Resp. 17–33. Pointing out that Singh-1 does not provide any *in vivo* data, Patent Owner contends that Singh-1 merely expresses “a wish or future plan to evaluate therapeutic effect of its cells in an early-phase clinical trial.” *Id.* at 27. But, “a future plan to test efficacy in

a clinical trial,” Patent Owner continues, “does not itself suggest efficacy.” *Id.* at 28.

On this record, and under our construction of the preamble, we find Patent Owner’s argument more persuasive. It is undisputed that Singh-1 discusses “a new gene transfer approach for the clinical application of T cells,” a manufacturing process “to be used in proof-of-concept clinical trials,” and a system that “uses technology that is readily accessible and practiced in compliance with cGMP for phase I/II trials.” Ex. 1003, 2969–70). These disclosures support Petitioner’s argument that Singh-1’s authors “intended to use their compositions in clinical trials.” *See* Pet. 33.

Under our construction, however, “adoptive cellular immunotherapy composition” means “a composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response.” *See supra* Section II.B.1. It is undisputed that Singh-1 does not show its cells has therapeutic effect *in vivo*.

Petitioner contends that “[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter.” Reply 7–8 (quoting *Ex parte Kao*, No. 2008-5150, 2009 WL 1162439 (BPAI Apr. 29, 2009)). According to Petitioner, Singh-1’s disclosure that “cells in its CAR T-cell composition are suitable for ‘clinical application’ . . . along with positive *in vitro* results” sufficiently meets the preamble. *Id.* at 7. We are not persuaded.

The quoted portion of *Kao* does not present a complete picture of the law of anticipation. Indeed, elsewhere, *Kao* quotes *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373 (Fed. Cir. 2003) as stating that “[a]nticipation does not require the actual creation or reduction to practice of

the prior art subject matter; *anticipation requires only an enabling disclosure.*” *Kao*, 2009 WL 1162439 at *6 (quoting *Schering*, 339 F.3d at 1380) (emphasis added). The emphasized language is critical because, as Patent Owner correctly points out, “*Kao* turned on the very fact that while the asserted prior art reference (*Liao*) did not contain *in vivo* data evidencing disease treatment, it was found to teach and enable the claimed treatment.” Sur-reply 5 (citing *Kao*, 2009 WL 1162439 at *7).

Although a prior art printed publication enjoys the presumption of enablement (*In Re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012)), that presumption only applies to what the prior art teaches. Here, Petitioner concedes Singh-1 does not provide any *in vivo* data to show therapeutic efficacy of its cells in immunotherapy. Thus, to demonstrate that Singh-1 discloses an “adoptive cellular immunotherapy composition” as we construe the term, it is Petitioner’s burden to show that Singh-1 has provided other, enabling disclosure for a composition with therapeutic effect *in vivo*. This, Petitioner has not done.

Moreover, even if the presumption of enablement applies to Singh-1, Patent Owner has provided sufficient evidence to rebut that presumption. *See Antor*, 689 F.3d at 1288. One piece of such evidence is Singh-2,¹⁹ a prior art reference published after Singh-1.²⁰ Singh-1 and Singh-2 have several authors in common.

¹⁹ Singh et al., *Selective reprogramming of CD19-specific T cells with IL-21 and CD28 signaling for adoptive immunotherapy of acute lymphoblastic leukemia*, 15(2) BIOL. OF BLOOD AND MARROW TRANSPLANTATION 61–62 (2009) (Ex. 2003, “Singh-2”).

²⁰ Patent Owner also relies on another reference “Singh-3.” *See, e.g.*, Prelim. Resp. 2, 18, 27, 29–32 (all citing Ex. 2001). But because Singh-3 was

Singh-2 states that improving *in vivo* persistence is needed “to enhance therapeutic potential of CAR⁺ T cells.” Ex. 2003, 61. One way to do so, according to Singh-2, is to “alter[] the culturing milieu to numerically expand CAR⁺ T cells with a proliferative advantage.” *Id.* Singh-2 reports that “the addition of exogenous IL-21 favors the microenvironment to selectively propagate CAR⁺ CD8⁺ T cells with ability to kill CD 19⁺ tumor targets.” *Id.*

As in Singh-1, Singh-2 used the same transduction vehicle (*Sleeping Beauty*) and the same method (electroporation) to introduce the same CAR (CD19RCD28). *Id.* It also used the process involving co-culture with aAPCs, the same as the process in Singh-1. *Id.* But unlike in Singh-1, where cells were propagated in culture medium only with exogenous IL-2 (Ex. 1003, 2970), Singh-2 propagated cells in two different media: one with IL-2 only, and the other with IL-2 and IL-21 (Ex. 2003, 61). Singh-2 presents the data in the Table reproduced below:

Expression of CAR on CD8⁺ and CD4⁺ T cells propagated on aAPC with IL-2 +/- IL-21

Culture conditions	CD4 ⁺ CAR ⁺	CD8 ⁺ CAR ⁺
IL-2	42%	1%
IL-2 + IL-21	22%	76%

The Table above shows that “[t]here was a selective outgrowth of CAR⁺ CD8⁺ T cells when IL-21 was present in the culture medium, compared with predominant outgrowth of CAR⁺ CD4⁺ T cells when IL-21

published after the apparent priority date of the '308 patent, we do not discuss it in this Decision.

was absent.” *Id.* Relying on this Table, Patent Owner argues “Singh-2 taught that cells cultured with IL-2 alone—*i.e.*, the cells of Singh-1— resulted in expression of CAR on *only one percent* of the CD8⁺ T cells ‘with [the] ability to kill CD19⁺ tumor targets.’” Prelim. Resp. 29–30 (quoting Ex. 2003, 61–62).

Petitioner contends that the compositions in Singh-1 and Singh-2 “were made differently.” Reply 5 (“Because it is just a short abstract, Singh-2 is silent on key parameters in its manufacturing process: for example, the identity of the antigen presenting cells (APCs), and the vector used to express the CAR.”). Patent Owner counters that Singh-1 and Singh-2 disclose the same APCs (γ -irradiated CD19⁺ artificial APCs) and the same vector (a transposon vector). Sur-reply 7–8 (citing Ex. 1003, 2962; Ex. 2003, 61). But even if the compositions in the two references are made differently, it does not discredit Singh-2’s teaching that the culturing milieu can shape the population of CAR⁺ T cells, and that the addition of IL-21 and IL-2, but not IL-2 alone, in the culture medium leads to selective outgrowth of CAR⁺ CD8⁺ T cells. Ex. 2003, 61–62.

In fact, the teaching of Singh-2 is consistent with the disclosure of Singh-1. Singh-2 demonstrates that IL-2 alone in the culture medium leads to predominant outgrowth of CAR⁺ CD4⁺ T cells. *Id.* Similarly, Singh-1 discloses that “[i]nitially, the rates of CD4⁺ and CD8⁺ T-cell growth on aAPC were similar, but after ~8 weeks there was an outgrowth of CD4⁺ CAR⁺ T cells.” Ex. 1003, 2967, Fig. 4B. Singh-2 teaches that only CAR⁺ CD8⁺ T cells have the ability to kill tumor targets. Ex. 2003, 61. Thus, we agree with Patent Owner that the culturing process used in Singh-1, which

led to an outgrowth of CD4⁺ CAR⁺ T cells, “would *not* have exhibited any significant therapeutic efficacy.” Prelim. Resp. 30.

Our understanding of Singh-1 is further supported by Petitioner’s own evidence. Dr. Bramson testifies that “some of Singh[-1]’s authors took Singh[-1]’s manufacturing process to the clinic and used it in NCT00968760 to target CD19-expressing cancers.” Ex. 1002 ¶ 122, *see also id.* ¶ 121 (stating clinical trial NCT00968760 and Singh-1 involved the same CAR, used the same transduction vehicle and used the same manufacturing process) (citing Ex. 1026, 447). But, as Patent Owner points out, “cells used in that clinical trial were generated with IL-2 *and* IL-21, that is, the alternative culturing protocol of Singh-2, *not* the IL-2-only culturing protocol of Singh-1.” Prelim. Resp. 30–31 (citing Ex. 1026, 445). Thus, Petitioner’s evidence supports Patent Owner’s argument that “the desire expressed in Singh-1 to test its cells in a clinical trial was *abandoned* following the results discussed in Singh-2, when the Singh-1 authors concluded that the IL-2-only cultured cells of Singh-1 would *not* be immunotherapeutic and did *not* advance them to any clinical trial.” *See id.* at 30.

3. Summary

In sum, Singh-1 does not disclose its cells has therapeutic effect *in vivo*. In addition, Patent Owner presents competent evidence to suggest cells cultured in Singh-1’s medium would not exhibit therapeutic efficacy and Petitioner’s own evidence demonstrate that those cells were indeed not advanced into clinical trial.

Based on this record, and under our claim construction, we find Singh-1 does not disclose an “adoptive cellular immunotherapy

composition.” Thus, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing Singh-1 anticipates claim 1 or its dependent claims 2–7, 14, 16, 21, and 26–28.

D. Alleged Obviousness over Singh-1 and Jensen

Petitioner asserts that claims 1–7, 14, 16, 21, and 26–28 would have been obvious over the combination of Singh-1 and Jensen. Pet. 48–50.

In this combination, Petitioner relies on Singh-1 for its composition and Jensen for formulating Singh-1’s composition. Pet. 48–49 (“A POSA would have understood that formulating Singh[-1]’s composition to be ‘suitable for administration to a mammal’ would have been as simple as diluting the cells in a saline solution, per Jensen’s teachings.”).

As explained above, we are not persuaded that Singh-1 teaches an “adoptive cellular immunotherapy composition” under our construction. *See supra* Section II.C. Because Jensen’s teaching on formulation does not remedy the deficiency in Singh-1’s composition, we determine Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing combination of Singh-1 and Jensen renders obvious claims 1–7, 14, 16, 21, and 26–28.

E. Alleged Obviousness over Singh-1 and Other References

Petitioner also contends that claims 1–16 and 18–31 would have been obvious over different combinations of Singh-1, Jensen, Mitsuyasu, Cooper, Hudecek I, Hudecek II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I, Yang II, Sallusto, and Sun. Pet. 50–66; *see supra* Section I.D. n.4.

Petitioner relies the additional references for teaching the limitations in the dependent claims, including “antigens to which the CAR specifically binds,” “the percentage of CAR-modified T cells that are surface positive for

various surface markers,” “the ratio of CD4⁺:CD8⁺ T cells in a composition,” and “a comparison between aspects of claim 1’s composition and one of two reference populations.” *Id.* at 51–52.

As explained above, we are not persuaded that Singh-1 teaches an “adoptive cellular immunotherapy composition” under our construction. *See supra* Section II.C. The teachings of the additional references do not remedy the deficiency in Singh-1’s composition. Thus, we determine Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing different combinations of Singh-1 and the other references render obvious the claims challenged under this ground.

F. Alleged Obviousness over Mitsuyasu, Singh-1, and Cooper

Petitioner asserts that claims 1, 6, and 9–16 of the ’308 patent would have been obvious over the combination of Mitsuyasu, Singh-1, and Cooper. Pet. 66–77. Patent Owner disputes Petitioner’s challenge. Prelim. Resp. 44–54. Based on this record, and for at least the following reasons, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

1. Mitsuyasu

Mitsuyasu describes a human clinical trial of a CAR-T cell-based adoptive cellular immunotherapy. Ex. 1004, Abstract, *see also id.* at 786 (reporting “the data from a phase II clinical trial of co-infusion of autologous CD4ζ-modified CD4⁺ and CD8⁺ T cells administered . . . in 24 HIV-infected patients with detectable viral loads”).

In Mitsuyasu, the CAR “CD4ζ is a genetically engineered, MHC-unrestricted, chimeric immune receptor composed of the zeta (ζ) subunit of the CD3 T-cell receptor (the cytoplasmic domain involved in

signal transduction) fused to the transmembrane and extracellular domains of human CD4 (which targets HIV *env* expressed on the surface of infected cells).” *Id.* at 786. Mitsuyasu developed a method to generate large numbers of HIV-specific primary T cells rapidly using retroviral-mediated gene transfer to insert CD4 ζ . *Id.*

Mitsuyasu’s rapid T-cell manufacturing process reliably yielded sufficient gene-modified T cells within 2 weeks. *Id.* at 791. According to Mitsuyasu, “[t]his process was successful in 24 of 25 enrolled patients and yielded a mixed population of CD4⁺ and CD8⁺ T cells with an activated cell phenotype (high expression of CD28, CD25, and CD62L).” *Id.*

Mitsuyasu concludes that “[t]his sustained, high-level persistence of gene-modified T cells demonstrates the feasibility of ex vivo T-cell gene therapy in HIV-infected adults and suggests the importance of providing HIV-specific T-helper function.” *Id.* at Abstract.

2. Cooper

Cooper provides an overview of CARs. Ex. 1010, 645–648. It explains that a CAR

consists of an extracellular antigen-binding exodomain, typically derived from a single-chain antibody fragment (scFv) of a monoclonal antibody (mAb), a spacer (such as an antibody Fc region), a transmembrane region, and one or more intracellular signaling endodomains, which can be genetically introduced into hematopoietic cells, such as T cells, to redirect specificity for a desired cell-surface antigen.

Id. at 645.

Cooper states that “[o]ne of the major advantages of the strategy infusing CAR⁺ T cells lies in the modular composition of the CAR molecule that combines an antigen-binding domain with signaling domains for effector-cell activation.” *Id.* at 648. According to Cooper, “[t]his allows

investigators to swap the CAR exodomain with a scFv or ligand that recognizes or binds to a desired cell-surface antigen.” *Id.*

3. Analysis

For purposes of this Decision, we focus our analysis on the surface marker positivity requirements recited in claim 1.

Claim 1 requires that at least 50% of the CAR-modified CD4⁺ T cells in the claimed composition are surface positive for CD62L and/or CD45RA, and 50% of the CD8⁺ T cells are surface positive for CD62L and/or CD45RO. Petitioner argues that Mitsuyasu discloses CD62L surface positivity within the claimed range of claim 1. Pet. 71–76. Patent Owner disputes that Petitioner has carried its burden. Prelim. Resp. 44–54. For at least the reasons below, we find Patent Owner’s arguments more persuasive.

It is undisputed that “Mitsuyasu does not specifically disclose the percentage CD62L-positivity in its subpopulations of receptor-modified CD4⁺ and CD8⁺ T cells.” Pet. 72. Nonetheless, Petitioner argues that Mitsuyasu’s composition meet the recited range of CD62L positivity. *Id.* at 73 (citing Ex. 1002 ¶ 388).

Specifically, Petitioner contends “[a] POSA would understand that, while the rate of CD62L expression in Mitsuyasu’s compositions could vary between CD4⁺ and CD8⁺ T cells, both populations would be expected to have substantially similar CD62L-positivity.” *Id.* at 74 (citing Ex. 1002 ¶ 392). And CAR expression, Petitioner asserts, would not affect the percentage CD62L-positivity in Mitsuyasu’s compositions. *Id.* (citing Ex. 1002 ¶ 394). Thus, according to Petitioner, “a POSA would have expected that the CD4⁺, CD8⁺, and receptor-modified populations in Mitsuyasu’s compositions would exhibit roughly the same rate of

CD62L-positivity as observed in their respective overall compositions.” *Id.* at 74–75 (citing Ex. 1002 ¶ 395).

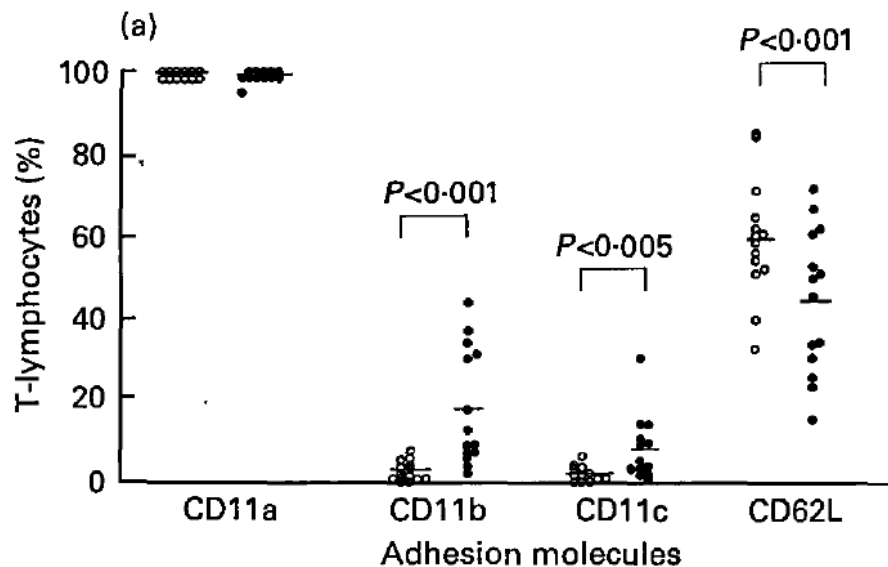
Petitioner points out that in Table 2, Mitsuyasu shows “seventeen tested compositions (a majority) had greater than 80% CD62L-positivity.” *Id.* at 75 (citing Ex. 1002 ¶ 395; Ex. 1004, 788). Based on these data, Petitioner asserts that “a POSA would have expected that the overall CD8⁺ T cells, receptor-modified CD4⁺, and receptor-modified CD8⁺ T cells in those seventeen compositions also would have exhibited greater than 80% CD62L-positivity.” *Id.* (citing Ex. 1002 ¶ 395). Petitioner concludes this would satisfy the “at least 50%” CD62L positivity requirements of claim 1. *Id.* (citing Ex. 1002 ¶ 397).

In addition, Petitioner argues that even if “it was not assumed that CD62L-positivity is substantially similar for CD4⁺ and CD8⁺ T cells,” Mitsuyasu’s compositions still meet the CD62L positivity requirements of claim 1. *Id.* (citing Ex. 1002 ¶ 396). This is because, Petitioner contends, for at least eight of Mitsuyasu’s compositions, the overall CD62L positivity is “so high” that they “must (mathematically) have had CD62L-positivity of >50% for both CD4⁺ and CD8⁺ T cells.” *Id.*

Specifically, Petitioner points to S206 as an example. *Id.* (citing Ex. 1002 ¶ 398). Based on a series of calculations performed by Dr. Bramson, Petitioner argues that “the percent CD62L-positivity of receptor-modified CD4⁺ and CD8⁺ T cells could not mathematically have been below 70% and the overall CD8⁺ T cells could not have been below 80%.” *Id.* at 76 (citing Ex. 1002 ¶¶ 401–412). Thus, according to Petitioner, it is “a mathematical certainty” that the S206 composition meets the CD62L positivity requirements of claim 1. *Id.* (citing Ex. 1002 ¶¶ 413–417).

Patent Owner counters that the calculations Petitioner relies on are based on at least two erroneous assumptions: (1) Petitioner erroneously assumes the same rate of CD62L positivity for CD4⁺ and CD8⁺ T cells; and (2) Petitioner erroneously assumes transduction efficacy percentage equates to percentage of CAR-modified T cells. Prelim. Resp. 46–51. Patent Owner asserts that without these two erroneous assumptions, there is insufficient information in Mitsuyasu to support Dr. Bramson’s calculations and Petitioner’s contentions on surface marker positivity of CD62L. On this record, we find Patent Owner’s arguments more persuasive.

Petitioner and Dr. Bramson rely on Cavers²¹ to show “substantially similar CD62L⁺ for CD4⁺ and CD8⁺ cells.” Pet. 74 (citing Ex. 1002 ¶ 392, Ex. 1020); Ex. 1002 ¶¶ 392–393 (citing Ex. 1020). Specifically, Dr. Bramson relies on Figure 2a of Cavers, which is reproduced below:



²¹ Cavers et al., *Differential expression of β 1 and β 2 integrins and L-selectin on CD4⁺ and CD8⁺ T lymphocytes in human blood: comparative analysis between isolated cells, whole blood samples, and cryopreserved preparations*, 127 CLIN. EXP. IMMUNOL. 60–65 (2002) (Ex. 1020, “Cavers”).

Above is a reproduction of Figure 2a of Cavers. It shows CD62L expression in blood mononuclear cells from 14 subjects, with CD4⁺ cells displayed as open circles (○) and CD8⁺ cells displayed as closed circles (●). Dr. Bramson testifies that “[b]ut for a small minority of outliers, CD4⁺ and CD8⁺ T cells showed substantially similar CD62L-positivity.” Ex. 1002 ¶ 393 (emphasis added). Dr. Bramson, however, does not explain what he considers to be “a small minority of outliers,” which to us, appears to be a subjective assertion without proper support.

More importantly, Dr. Bramson’s testimony is inconsistent with Cavers’ teaching. Indeed, the legend for Figure 2a states that “[w]ithin mononuclear cell isolates CD8⁺ T cells preferentially express CD11b, CD11c and CD49d *in relation to CD4⁺ T cells but less CD62L.*” Ex. 1020, 62 (emphasis added), *see also id.* (stating “the distribution of lymphocytes bearing CD62L was greater in the CD4⁺ subset” than in the CD8⁺ population). Thus, we find Petitioner has not presented sufficient evidence to support its assertion that CD4⁺ and CD8⁺ T cells “would be expected to have substantially similar CD62L-positivity.” *See* Pet. 74.

Without the assumption that CD4⁺ and CD8⁺ T cells have substantially similar CD62L-positivity, Petitioner relies on the individual compositions discussed in Mitsuyasu’s Table 2, and in particular, S206 to meet the recited surface marker positivity of CD62L. *Id.* at 75–76 (citing Ex. 1002 ¶¶ 396, 398–417). Dr. Bramson “reproduced the immunophenotype percentages for patient S206” as follows:

Patient ID	CD4 (%) [*]	CD8 (%) [*]	CD62L (%) [*]	CD28 (%) [*]	CD25 (%) [*]	Culture day [†]	CD4 ζ by PCR [‡]
S206	52	46	93	96	74	17	49

Above is a reproduction of a portion of Mitsuyasu’s Table 2, showing T cell manufacturing data for S206. Ex. 1002 ¶ 402.

“For ease of calculation,” Dr. Bramson “assume[s] that composition S206 includes only 100 T cells.” *Id.* ¶ 403. According to Dr. Bramson, “S206 exhibited CD62L-positivity of 93%. A POSA would thus understand that 93 cells out of 100 would be CD62L⁺ and 7 would be CD62L⁻.” *Id.*

Dr. Bramson also relies on the CD4 ζ transduction efficiency shown in the right-most column of Figure 2. *Id.* ¶ 405. Because the transduction efficiency for S206 is 49%, Dr. Bramson states “the number of chimeric receptor-modified T cells would be 49 out of 100 cells.” *Id.*

Based on his opinion that “93 cells out of 100 would be CD62L⁺” and the number of CAR-modified T cells would be “49 out of 100 cells,” Dr. Bramson calculates CD62L positivity of CD4⁺ and CD8⁺ T cells under numerous scenarios and concludes that “the percentage of chimeric receptor-modified CD4⁺, chimeric receptor-modified CD8⁺, and overall CD8⁺ T cells that were CD62L⁺ was above 50%.” *Id.* ¶ 412 (footnote omitted).

Patent Owner takes issue with Dr. Bramson’s statement that, because the transduction efficiency for S206 is 49%, “the number of chimeric receptor-modified T cells would be 49 out of 100 cells.” Prelim. Resp. 47–51. According to Patent Owner, it is error to assume that “the

transduction efficiency of a pool of cells equates to the percentage of chimeric receptor modified cells.” *Id.* at 47.

Specifically, Patent Owner contends, Petitioner does not dispute, and we agree, that 49% transduction efficiency means 49% of the cells are modified with CAR only when each cell has one copy of the CAR. Prelim. Resp. 49, *see also id.* at 50–51 (explaining “how different copy numbers per cell can all result in the same transduction efficiency”). Neither Petitioner nor Dr. Bramson mentions CAR copy number, let alone pointing to any evidence to show the copy numbers in Mitsuyasu. Thus, Dr. Bramson’s calculations are based on an unsupported premise that, for S206, “the number of chimeric receptor-modified T cells would be 49 out of 100 cells.” *See* Ex. 1002 ¶ 405.

Moreover, as Patent Owner correctly points out, Mitsuyasu teaches transducing T cells with a retroviral vector. Prelim. Resp. 47 (citing Ex. 1004, 786). As the ’308 patent acknowledges, retroviral transduction is “a highly efficient method for gene transfer” and “results in the stable integration of one *or a few copies* of the new genetic information per cell.” Ex. 1001, 13:39–43 (emphasis added).²² Because “retroviral vector transduction can lead to multiple constructs inserted in an individual cell,” we agree with Patent Owner “when the copy number is unknown, it is

²² Patent Owner also relies on a reference published in 2021 (Ex. 2014) to support its argument. Prelim. Resp. 47–48 (citing Ex. 2014, 5). Because the ’308 patent sufficiently supports Patent Owner’s argument that it was known that retroviral vector transduction can lead to multiple constructs inserted in an individual cell, we do not rely on Exhibit 2014 in this Decision.

impossible to calculate the percentage of cells transduced with a construct based only upon the overall transduction efficiency.” Prelim. Resp. 47–48.

In response, Petitioner criticizes Patent Owner for “not includ[ing] expert opinion to rebut the literature relied upon by Petitioner’s expert.” Reply 9 (citing Ex. 1002 ¶ 405). We are not persuaded. Although we appreciate receiving expert opinion from both sides to help us in our analysis, “no expert submissions are required.” *Fanduel, Inc. v. Interactive Games LLC*, 966 F.3d 1334, 1344 (Fed. Cir. 2020). We are not obligated to defer to Dr. Bramson’s opinion just because Patent Owner does not supply an opposing expert opinion. *Id.* Instead, “it is the Board’s duty to independently assess the strength of a petitioner’s argument and evidence.” *Id.*

Here, Patent Owner does not challenge Mitsuyasu, “the literature relied upon by” Dr. Bramson; instead, Patent Owner disagrees with Dr. Bramson’s interpretation of Mitsuyasu, which equates Mitsuyasu’s teaching of 49% transduction efficiency with 49% CAR-modified cells. *See* Ex. 1002 ¶ 405. Patent Owner points to competent evidence to show that Dr. Bramson’s opinion is based on insufficient information, if not a false premise. Prelim. Resp. 48 (citing Ex. 1001, 1339–43). No more is needed.

Petitioner also argues that Dr. Bramson used transduction efficiency only for the calculations of S206, and that he “provided many other calculations showing a POSA would *presume* that Mitsuyasu’s compositions met the claimed ranges.” Reply 9 (citing Ex. 1002 ¶¶ 388–397) (emphasis added). We are not persuaded by this argument either. As an initial matter, a presumption is not competent evidence to support Petitioner’s patentability challenge. Moreover, none of the cited paragraphs from the Bramson

Declaration provides any calculations of CD62L positivity. Instead, Dr. Bramson only provides his opinion, mostly without any support.

Indeed, Dr. Bramson speculates that an ordinarily skilled artisan “viewing the high percentages of CD62L-positivity of the compositions in Table 2 (average of 82% with seventeen compositions >80%) would understand that *it is likely* that a majority of the compositions would have CD4⁺ and CD8⁺ T cell populations in which at least 50% . . . are CD62L⁺.” Ex. 1002 ¶ 396 (emphasis added). Without any explanation or calculation, Dr. Bramson states that, for eight of Mitsuyasu’s compositions, their “rate of CD62L-positivity was so high . . . that the CD4⁺ and CD8⁺ populations must have CD4⁺ and CD8⁺ T cells with more than 50% CD62L positivity.” *Id.* We accord this conclusory and unsupported testimony little weight. *See* 37 C.F.R. § 42.65(a).

Petitioner further asserts that “[e]ven if absolute number of T cells transduced were *slightly lower* in some compositions, it would not change Dr. Bramson’s overall calculations of percent CD62L-positivity.” Reply 9–10 (citing Ex. 1002 ¶¶ 388–397) (emphasis added). Petitioner does not explain what “slightly lower” actually encompasses. Given that Mitsuyasu does not disclose copy numbers, we find this argument unpersuasive.

4. Summary

In sum, “Mitsuyasu does not specifically disclose the percentage CD62L-positivity in its subpopulations of receptor-modified CD4⁺ and CD8⁺ T cells.” Pet. 72. In addition, Petitioner does not sufficiently support its argument that CD4⁺ and CD8⁺ T cells have substantially similar CD62L-positivity. Thus, we are not persuaded that Mitsuyasu’s overall

CD62L positivity of over 80% means the CD62L positivity for CAR-modified CD4⁺ and CD8⁺ T cells would also be over 80%. Furthermore, because Dr. Bramson does not point to evidence to support his conclusion that the transduction efficiency of a pool of cells equates to the percentage of CAR-modified cells, his calculations of Mitsuyasu's S206 are based on insufficient information.

Based on this record, Petitioner has not shown that Mitsuyasu teaches the surface marker positivity requirements recited in claim 1. Petitioner does not rely on Singh-1 or Cooper for these limitations. Thus, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing that claim 1 or its dependent claims 6, and 9–16 would have been obvious over the combination of Mitsuyasu, Singh-1, and Cooper.

III. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. Thus, decline to institute *inter partes* review.²³

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and no trial is instituted.

²³ Patent Owner also argues that we should deny review under § 325(d). *See* Prelim. Resp. 77–79. We do not address this argument because we deny the Petition for reasons explained above.

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