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Paper 11
Date: October 11, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MILTENYI BIOMEDICINE GmbH and MILTENYI BIOTEC INC.
Petitioner
v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA
Patent Owner

IPR2022-00853
Patent 9,464,140 B2

Before ULRIKE W. JENKS, SUSAN L. C. MITCHELL, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc. (collectively, "Petitioner") filed a Petition for an *inter partes* review of claims 1–19 and 21–28 of U.S. Patent No. 9,464,140 B2 ("the '140 Patent," Ex. 1001). Paper 1 ("Pet."). Trustees of the University of Pennsylvania ("Patent Owner") timely filed a Preliminary Response. Paper 7. ("Prelim. Resp."). Petitioner further filed an authorized Reply to the Preliminary Response (Paper 9, "Reply"); Patent Owner filed a responsive Sur-Reply (Paper 10, "Sur-reply").

For the reasons set forth below, we exercise our discretion, on behalf of the Director, and deny institution of an *inter partes* review because the same or substantially the same prior art or arguments previously were presented to the Office. *See* 35 U.S.C. § 325(d).

B. Real Parties-in-Interest

Petitioner identifies itself, Miltenyi Biomedicine GmbH, and Miltenyi Biotec Inc. as the real parties-in-interest. Pet. 3. Patent Owner, identifies itself, The Trustees of the University of Pennsylvania, and its licensee, Novartis Pharma AG, as real parties-in-interest. Paper 5, 2.

C. Related Matters and Chain of Priority

The '140 patent issued from application No. US 14/996,953, which is a continuation of application No. 13/992,622 ("the '622 parent application"), filed as application No. PCT/US2011/064191 ("the PCT application") on December 9, 2011. The '140 patent further claims benefit of priority to

provisional application No. 61/421,470, filed on December 9, 2010, and provisional application No. 61/502,649, filed on June 29, 2011.

Petitioner reasonably contends that the challenged claims of the ’140 patent are not entitled to benefit of the provisional applications. Pet. 2, 5, 60–64 (citing, e.g., Ex. 1021, 224). Patent Owner does not presently contest this assertion. *See* Prelim. Resp. 41. On the present record, we consider December 9, 2011, filing date of the PCT application, to be the earliest possible priority date for the challenged claims.

Petitioner concurrently challenges claims of related U.S. Patent Nos. 9,518,123 B2 (“the ’123 patent) and 9,540,445 B2 (“the ’445 patent”) in IPR2022-00852 and IPR2022-00855, respectively. The ’123 and ’445 patents similarly issued from continuation applications of the ’622 parent application and, thus, share substantially the same specification. The ’622 parent application issued as U.S. Patent No. 9,499,629 B2 (“the ’629 patent.). The ’140, ’123, ’145, and ’629 patents were Examined by the same Examiner.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 5):

Ground	Claims Challenged	35 U.S.C §[1]	Reference(s)/Basis
1	1–2, 6, 8–9, 11, 16, 21–22, 27–28	§ 103(a)	Campana,[2] CART-19 ClinTrials.gov,[3] Nicholson,[4] Honsik[5]
2	1–2, 6, 8–9, 11, 13, 16, 21–22, 27–28	§ 103(a)	Campana, CART-19 ClinTrials.gov Jensen,[6] Honsik
3	1–19, 21–28	§ 103(a)	Campana, CART-19 ClinTrials.gov, Nicholson, Jensen, Littman,[7] Sadelain,[8] Milone,[9] Honsik
4	1–19, 21–28	§ 103(a)	Campana, Porter,[10] Nicholson, Jensen, Littman, Sadelain, Honsik

[1] The Leahy-Smith America Invents Act ("AIA") included revisions to 35 U.S.C. § 103 that became effective on March 16, 2013. Because the '140 patent issued from an application that is a continuation of an application filed before March 16, 2013, we apply the pre-AIA versions of the statutory bases for unpatentability.
[2] US 2005/0113564, publ. May 26, 2005. *Ex.* 1003.
[3] "*Pilot Study for Patients with Chemotherapy Resistant or Refractory CD19 Leukemia and Lymphoma (CART-19)*," https:/clinicaltrials.gov/ct2/show/NCT00891215. *Ex.* 1006 (includes Declaration of Duncan Hall).
[4] Nicholson et al., "*Construction and Characterisation of a Functional CD19 Specific Single Chain Fv Fragment for Immunotherapy of B Lineage Leukaemia and Lymphoma*," 34 MOL. IMMUNOL. 1157 (1997). *Ex.* 1004).
[5] US 4,844,893, issued July 4, 1989. (*Ex.* 1005.
[6] US 2004/0126363, published July 1, 2004. *Ex.* 1007.
[7] Littman et al., "*The Isolation and Sequence of the Gene Encoding T8: A Molecule Defining Functional Classes of T Lymphocytes*," 40 CELL 237 (1985). *Ex.* 1009.
[8] US 2004/0043401, published March 4, 2004. *Ex.* 1010.

Petitioner further relies on, inter alia, the Declaration of Richard P. Junghans, M.D., Ph.D. Ex. 1002. Patent Owner did not choose to submit testimony of a technical expert at this stage in the proceeding.

E. The '140 Patent

1) Background and Specification

The '140 patent, titled "Compositions and Methods for Treatment of Cancer," issued on October 11, 2016, naming Carl H. June, Bruce L. Levine, David L. Porter, Michael D. Kalos, and Michael C. Milone as inventors. Ex. 1001, code (45), (72). The '140 patent discloses administering immune cells—including T-cells—modified to express a chimeric antigen receptor or CAR construct. *See generally, id*. at code (57), 1:29–42, 2:40–43. The disclosed CARs generally "comprise an extracellular domain having an antigen binding domain fused to an intracellular signaling domain of the T-cell antigen receptor complex [Z]eta chain (e.g., CD3 [Z]eta). The CAR of the invention when expressed in a T-cell is able to redirect antigen recognition based on the antigen binding specificity." *Id.* at 19:6–12.

The '140 patent variously refers to T-cells transduced with CAR constructs as CAR modified T-cells, CART, CAR T, or CAR-T-cells. *Id.* at 3:59–62, 5:23–30, 52:46–48. The CAR modified cells may be autologous T-cells from a patient in need of treatment. *See e.g., id.* at 3:5–15, 9:49–58. Dr. Junghans explains: "When a patient's own T-cells are transduced and

[9] Milone et al., "*Chimeric Receptor Containing CD137 Signal Transduction Domains Mediate Enhanced Survival of T-cells and Increased Antileukemic Efficacy In Vivo*," 17 MOL. THERAPY 1453 (2009). *Ex.* 1008.
[10] Porter et al., "Chimeric Antigen Receptor–Modified T-cells in Chronic Lymphoid Leukemia," 365 N. ENGL J. MED. 725 (2011), (*Ex.* 1012, "Porter")

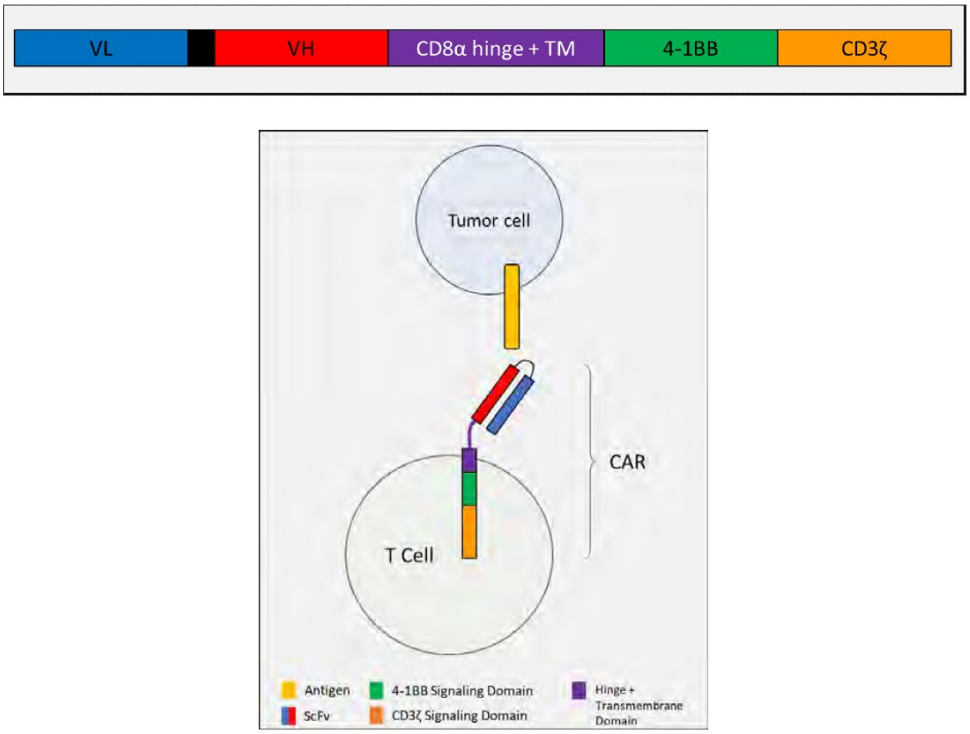
infused into the same patient, the T-cells are identified as 'autologous.' This is in contrast to a cancer patient receiving transduced T-cells from a healthy donor, wherein the T-cells would be considered 'allogeneic.'" Ex. 1002 ¶ 42. The '140 patent discloses that in some embodiments the treatment is directed against a B-cell malignancy, such as Chronic Lymphocytic Leukemia (CLL). Ex. 1001, 18:29–31. 65–67.

According to the '140 patent, "[a]ttempts in using genetically modified cells expressing CARs to treat [patients having B-cell malignancies] have met with very limited success." *Id.* at 1:29–42 (citations omitted). "[A] major impediment to the clinical application of this technology to date has been limited in vivo expansion of CAR+ T-cells, rapid disappearance of the cells after infusion, and disappointing clinical activity." *Id.* at 1:48–54. (citations omitted).

The '140 patent discloses T-cells modified to express a "CAR compris[ing] an antigen binding domain, a transmembrane domain, a costimulatory signaling region, and a CD3 zeta signaling domain." *Id.* at code (57). In a preferred embodiment the CAR comprises an "anti-CD19 scFv[11] derived from FMC63 murine monoclonal antibody, human CD8α hinge and transmembrane domain, and human 4-1BB and CD3zeta signaling domains." *Id.* at 4:37–40 (referencing Figs. 1A–1C). "The CD 19-BB-z transgene (GeMCRIS 0607-793) was designed and constructed as described (Milone et al., 2009, Mol Ther. 17:1453-1464) [Ex. 1008]." *Id.* at 41:5–7.

[11]A "scFV" or "single chain variable fragment" is a recombinant antibody fragment in which Vl and Vh antigen recognition elements are fused with a short peptide linker to form a single polypeptide chain having an antigen recognition moiety derived from the parent antibody. *See Ex.* 1002 ¶ 33.

In the figure below, Dr. Junghans provides "A schematic of the major functional elements of a preferred embodiment of the CAR and an illustration how the CAR could appear when inserted into the T-cell surface." Ex. 1002 ¶ 51.



The above figure illustrates a CAR protein anchored in the T-cell membrane via a CD8α hinge and transmembrane domain with 4-1BB co-stimulatory and CD3ζ signaling domains in the interior of the T-cell, and extracellular VL and VH ScFv domains interacting with CD19 antigen on the surface of a tumor cell. *See id.*

2) Challenged Claims

Petitioner challenges claims 1–19 and 21–28 of the '140 patent, of which only claim 1 is independent. Claim 1 recites:

[(a)] A method of treating cancer in a human patient comprising

> [(b)] administering to the human patient a pharmaceutical composition comprising
>
> [(c)] an anti-tumor effective amount of a population of human T-cells,
>
> [(d)] wherein the T-cells comprise a nucleic acid sequence encoding a chimeric antigen receptor (CAR),
>
> [(e)] wherein the CAR comprises a CD19 antigen binding domain comprising, from the amino to the carboxy terminus, a light chain variable region and a heavy chain variable region of SEQ ID NO:20, [12]
>
> [(f)] wherein the CAR further comprises a transmembrane domain, a 4-1BB costimulatory signaling region, and a CD3 zeta signaling domain.

Ex. 1001, claim 1 (paragraphing and reference letters [a]–[f] as added by Petitioner (*see* Pet. 20–21)).

The challenged dependent claims recite limitations directed to the amount or timing of T-cells administered (claims 2–5); the identity or nucleic acid sequence of the CAR or its components (claims 6–19, 23–26); the source of the T-cells (claim 22); the type of cancer targeted (claim 23); and components of a pharmaceutical composition comprising the CAR construct (claims 27–28).

3) Relevant Prosecution History

The Examiner of the '140 patent issued rejections involving Imai[13] and Milone in related applications. With respect to the former, Petitioner contends that, "[d]uring the prosecution of U.S. Patent Application No.

[12] The '140 patent defines SEQ ID NO: 20 as the amino acid sequence for an anti-CD19scFv. *Ex.* 1001, 61:13.

[13] C. Imai & D. Campana, et al., *Chimeric Receptors with 4-1BB Signaling Capacity Provoke Potent Cytotoxicity Against Acute Lymphoblastic Leukemia*, 18 LEUKEMIA 676 (2004). *Ex.* 1022.

15/353,899 (Ex. 1028), a sister application of the '140 patent with similar claims, the Patent Office rejected claims as anticipated and obvious over Imai [Ex. 1022], which discloses the same anti-CD19-BB-ζ CAR as Campana. Ex. 1028, 613." Pet. 70.[14]

According to the Examiner, "Imai et al teach T-cells from patients with leukemia modified to express a CAR comprising a CD 19-specific scFv, a CD8 transmembrane and hinge domain, a 41BB co-stimulatory region and a CD3zeta signaling domain." Ex. 1028, 5. The parties do not dispute that Applicant abandoned the application without overcoming rejections based on Imai. *See* Pet. 70–71; Prelim. Resp. 52–54.

With respect to Milone, Applicants originally submitted 89 claims in the prosecution of the '622 parent application. Ex. 3002, 94–105. Illustrative of these, originally-filed claim 1 was directed to:

> 1. (original) An isolated nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, a costimulatory signaling region, and a CD3 zeta signaling domain, wherein the CD3 zeta signaling domain comprises the amino acid sequence of SEQ ID NO: 24.

(*id.* at 95); originally-filed claim 47 recited:

> 47. (original) A method of treating a mammal having a disease, disorder or condition associated with an elevated expression of a tumor antigen, the method comprising administering to the mammal an effective amount of a cell genetically modified to express a CAR [comprising the elements set forth in claim 1], thereby treating the animal.

(*id.* at 100); and originally-filed claim 50 was directed to:

[14] Although Petitioner cites to "*Ex.* 1028, 613," the exhibit contains only 15 pages.

> 50. (original) A method of treating a human with chronic lymphocytic leukemia, the method comprising administering to the human a T-cell genetically engineered to express a CAR [comprising the elements set forth in claim 1]."

(*id.*). Originally-filed claim 52 further specified:

> 52. (original) The method of claim 50, wherein the chronic lymphocyteic leukemia is refractory CD19+ leukemia and lymphoma.

Id. at 101,

In a first Office Action, the Examiner rejected the above claims as obvious over Milone (Exhibit 1008) in view of Brentjens and Orentas (not of record). *Id.* at 81. According to the Examiner,

> Milone et al teach nucleic acids, and human T-cells comprising said nucleic acids, encoding a CAR comprising an scFv specific for CD19, a CD8alpha hinge and transmembrane domain, a 4-1BB costimulatory domain, and a TCR/ CD3 zeta signaling domain (CD3zeta is considered to be synonymous with TCRzeta given the prior art of record (e.g. Sadelain et al 2003 [Ex. 1010], Figure 1), applicants specification (e.g. page 27), and priority documents (e.g. 61/421,470, page 48).

Id. The Examiner further found that

> The T-cells of Milone et al were used at "anti-tumor effective amounts", as they could promote tumor regression in mice in a model of human ALL. Since the prior art structure is the same as that recited in the claims, it has the inherent property of being useful as an anti-tumor pharmaceutical as recited. Milone et al teach there is little drop in efficacy between a dose of $2X10^6$ to $5 X 10^5$ cells. Milone et al teach that the T-cells are administered by IV injection (Fig. 5a) could replicate persist in in vivo for > 6 months (abstract, Figs. 6, 7, page 1460).
> To reiterate, since the prior art structure is the same as that recited in the claims, it has the inherent property of being able to persist in a patient of up to three years as recited.

Id.

The Examiner further pointed to Orentas as disclosing a nucleic acid encoding the amino acids of SEQ ID NO: 24, and Brentjens as "teach[ing] the use of human T-cells comprising a nucleic acid encoding a CAR specific for CD19 in the treatment of CLL in human patients." *Id.* at 82. According to the Examiner,

> The claimed methods are essentially disclosed by Milone and Orentas et al with the exception of the limitation of administration to human patients (although this is implied), and the CLL limitation. The ordinary skilled artisan, seeking a method to treat ALL or CLL in human patients, would have been motivated to use the teachings of Brentjens et al with those of Milone et al because both references teach the desirability of treating human patients having ALL or CLL with CD19-specific human T-cells. It would have been obvious for the skilled artisan to do this because of the known benefit of generating an anti-tumor response as taught by both Milone and Brentjens et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Id. at 82. The Examiner maintained the rejection in a subsequent and final Office Action. *See id.* at 43–50 (Further rejection claims in view of Milone, Brentjens, Orentas, and Har-Noy).

Applicants twice addressed rejections involving Milone with argument and amendments. *See id.* at 55–76 (Response dated Dec. 15, 2015); *id.* at 43– 50 (Final OA dated Jan. 5, 2016); *id.* at 26–42 (Response dated July 5, 2016). The Examiner was ultimately persuaded that Orentas (used for its disclosure of disclosure of SEQ ID NO: 24) did not qualify as prior art, and allowed the amended claims on that basis. *Id.* at 12–17 (NOA

dated July 20, 2016). As set forth in The Examiner's Reasons for Allowance:

> All of the pending claims require SEQ ID NO: 24. As explained in previous Office Actions and Applicant's response of 7/5/2016, page 11, the instant claims enjoy a priority date of 12/9/2011, yet the earliest disclosure of SEQ ID NO: 24 by the art of record (Orentas et al) is 10/19/2012. Thus, SEQ ID NO: 24 provides novelty to the instant claims.

Id. at 17.

The '622 parent application subsequently issued as the '629 patent on November 22, 2016. Ex. 3003, code (45). Claim 1 is illustrative:

> 1. A method for stimulating a T-cell-mediated immune response to a targeT-cell population or tissue in a human, the method comprising administering to the human an effective amount of a cell genetically modified to express a CAR wherein the CAR comprises a CD19 antigen binding domain, a transmembrane domain, a costimulatory signaling region comprising 4-1BB, and a CD3 Zeta signaling domain as comprising the amino acid sequence of SEQ ID NO: 24, wherein the CD19 antigen binding domain specifically recognizes CD19 in the targeT-cell population or tissue, wherein the cell is from a human having cancer.

Id. at 91:18–29.

II. ANALYSIS

A. Legal Standards

"In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See*

Dynamic Drinkware, LLC v. Nat'l Graphics, Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

Petitioner challenges claims 1–19 and 21–28 as obvious under 35 U.S.C. § 103. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co*., 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present. *KSR*, 550 U.S. at 406.

"[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *Id.* at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on

obviousness must show that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted). Under the proper inquiry, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

In addressing the level of ordinary skill in the art, Petitioner contends that:

> A POSA is a person skilled in the art of administering CAR T-cell therapies. The person would possess a relatively high level of skill and have at least an MD, together with several years of experience in administering CAR T-cell therapies. The person would also have experience designing CARs. The POSA would have knowledge of the scientific literature pertaining to immunology, including CARs and methods for utilizing CARs before the priority date. A POSA would also be knowledgeable about laboratory techniques related to engineering and testing the function of CAR T-cells. A POSA would also be

> knowledgeable about designing clinical trials, including selecting dose ranges, that evaluate CAR T-cell therapies.

Pet. 10. Patent Owner does not presently contest this definition.

Although Petitioner's definition generally comports with our understanding of the high level of skill in the art, we are not persuaded all of the asserted qualifications must be embodied in a single person. For example, it seems unduly limiting to require that the person of ordinary skill in the art have "at least an MD" degree, and "be knowledgeable about laboratory techniques related to engineering and testing the function of CAR T-cells," as Petitioner suggests. Accordingly, we provisionally adopt Petitioner's definition with the caveat that the asserted qualifications may be shared among multiple individuals working as part of a multidisciplinary team.

C. Claim Construction

We interpret a claim "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 this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.* Moreover, "the specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.'" *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.,* 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)).

1) "treating cancer"

Independent claim 1 is directed to "[a] method of treating cancer in a human patient." Petitioner contends that "[t]he preamble language of 'treating cancer' only states a purpose for the steps articulated in the body of" [claim 1], and should be treated as non-limiting. Pet. 1–13 (*citing e.g.*, *Catalina Mktg. v. Coolsavings.com*, 289 F.3d 801, 808 (Fed. Cir. 2002)); Prelim. Reply 3–4. Patent Owner contends that we should construe the preamble as limiting, and that "treating cancer" should be construed as "reducing the frequency or severity of at least one sign or symptom of cancer." Prelim. Resp. 19; *see* Ex. 1001, 18:18–20 ("To 'treat' a disease . . . means to reduce the frequency or severity of at least one sign or symptom of a disease or disorder experienced by a subject.").

In support of its position, Patent Owner points to *Eli Lilly & Co. v. Teva Pharmaceuticals Int'l GmbH*, 8 F.4th 1331 (Fed. Cir. 2021). Prelim. Resp. 17–19; Prelim. Sur-reply 3–4. The court in *Eli Lily* emphasized that "[w]hether to treat a preamble as a claim limitation is determined on the facts of each case in light of the claim as a whole and the invention described in the patent." *Id.* at 1340 (quoting *Storage Tech. Corp. v. Cisco Sys., Inc.*, 329 F.3d 823, 831 (Fed. Cir. 2003)). But in general, the analysis of "claims directed to apparatuses or compositions . . . often relied on the proposition that '[p]reamble language that merely states the purpose or intended use of an invention is generally not treated as limiting the scope of the claim.'" *Id.* at 1340–1341 (quoting *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006)). Claims to methods of using such apparatuses or compositions, however, typically recite "what a method 'does'" in the preamble. *Id.* at 1341 (collected citations omitted). The court's

analysis of these statements of intended purpose in method claims "has tended to result in a conclusion that such preamble language is limiting." *Id.*

The preamble language found limiting in *Eli Lilly* entailed a preamble to treatment of vasomotor symptoms such as migraine, followed by a single step of administering "an effective amount" of a bioactive composition in the body of each independent claim. *See id.* at 1335–1336, 1340. The court noted that the treatments set forth in the preamble language was "central to the inventions" described in the underlying specification, and "provide the only metric by which one practicing the claim could determine whether the amount administered is an 'effective amount.'" *Id.* at 1342.

Patent Owner points out that the structure of independent claim 1 here is similar to those addressed in *Eli Lilly*. Prelim. Resp. 18. And, as in *Eli Lilly*, the Specification of the '140 patent underscores the centrality of the method recited in the preamble. *Id.* (citing Ex. 1001, codes (54), (57), 1:55–57). Unlike in *Eli Lilly*, however, the body of independent claim 1 does not recite merely "an effective amount" but "an anti-tumor effective amount" of the composition administered. Petitioner argues that whereas the preambles in *Eli Lilly* "provide the only metric by which one practicing the claim could determine whether the amount administered is an 'effective amount,'" the term "anti-tumor effective amount" in independent claim 1 "is well-defined by the specification and provides sufficient guidance for determining effectiveness." Prelim. Reply 3 (citing *Eli Lilly* at 1342).

On balance, Petitioner appears to have the better argument. Nonetheless, even if we were to construe the treatment language of the preamble to mean "reducing the frequency or severity of at least one sign or symptom of cancer" as Patent Owner proposes, this definition is coextensive

with, if not subsumed by, the term "anti-tumor effective amount," discussed below. As such, the outcome of this proceeding does not turn on whether the preamble is limiting.

2) "anti-tumor effective amount"

Claim 1 entails the step of "administering . . . an anti-tumor effective amount of a population of human T-cells." Claim 2 limits the anti-tumor effective amount of T-cells recited in claim 1 to "10^4 to 10^9 cells per kg body weight of a human in need of such cells."[15] Relying on the testimony of Dr. Junghans, Petitioner proposes that "the term "anti-tumor effective amount" should be understood to encompass at least "10^4 to 10^9 cells per kg body weight," and any other amount of CAR T-cells that would have at least one of the biological effects specifically described in the specification, including "a decrease in the number of tumor cells." Pet. 13–15 (citing Ex. 1001, 37:60–64, 12:28–37; Ex. 1002 ¶¶ 56–61); Prelim. Reply 4–5.

In support of this position, Petitioner argues that "[w]hile claim 1 does not expressly state a numerical range for an "anti-tumor effective amount," claim 1 necessarily encompasses at least the numerical range stated in dependent claim 2." Pet. 14. Petitioner further argues that one of ordinary skill in the art would understand that a dose outside the range of 10^4 to 10^9 cells per kg can also satisfy the claim limitation of "anti-tumor effective amount" if it provides at least one "anti-tumor effect" as defined in the Specification. Pet. 14. In this respect, Petitioner points to the '140 patent's express definition of "anti-tumor effect" as

> a biological effect which can be manifested by [(i)] a decrease in tumor volume, [(ii)] ***a decrease in the number of tumor cells***, [(iii)] a decrease in the number of metastases, [(iv)] an

[15] Claim 3 further limits this range to "10^5 to 10^6 cells per kg."

> increase in life expectancy, ***or*** [(v)] amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by [(vi)] the ability of the peptides, polynucleotides, cells and antibodies of the invention in prevention of the occurrence of tumor in the first place.

Id. (quoting Ex. 1001, 12:28–37 (emphasis by Petitioner)).

As we understand it response, Patent Owner does not appear to contest that "anti-tumor effect" can comprise a decrease in the number of tumor cells, but argues that the claim term requires "a palpable therapeutic effect," which is more than "just the death of a single cancer cell or handful of cells." Prelim. Resp. 19–23; Prelim. Sur-reply 4–5. In support, Patent Owner points to the '140 patent's express definition of "[a]n 'effective amount'" as meaning "an amount which provides a therapeutic or prophylactic benefit." Pet. 20 (citing Ex. 1001, 13:53–54). Relatedly, we note that the Specification also teaches that a "'therapeutically effective amount' includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the signs or symptoms of the disorder or disease being treated." Ex. 1001, 18:12–15.

Patent Owner further contends that "[t]he specification teaches that 'an antitumor effective amount' is an amount to be administered that is "determined by a physician" as part of determining '[t]he optimal dosage and treatment regime for a particular patient . . . by monitoring the patient for signs of disease and adjusting the treatment accordingly.'" Prelim. Resp. 22 (citing Ex. 1001, 37:53–38:5).

Considering the argument and evidence of record, we agree with Patent Owner that one of ordinary skill in the art would understand an "anti-

tumor effective amount" as used in claim 1 to require more than the killing of a single tumor cell. Accordingly, we provisionally construe "anti-tumor effective amount" as any amount of CAR T-cells administered to a patient in need of cancer treatment that reduces the frequency or severity of at least one clinically relevant sign or symptom of the disease. To the extent this functional limitation is satisfied, claim 2 indicates that an "anti-tumor effective amount" may be limited to between 10^4 to 10^9 CAR T-cells/kg body weight.

At this stage of the proceeding, no other term requires construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd. v. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Overview of Asserted References[16]

1) Campana (Exhibit 1003)

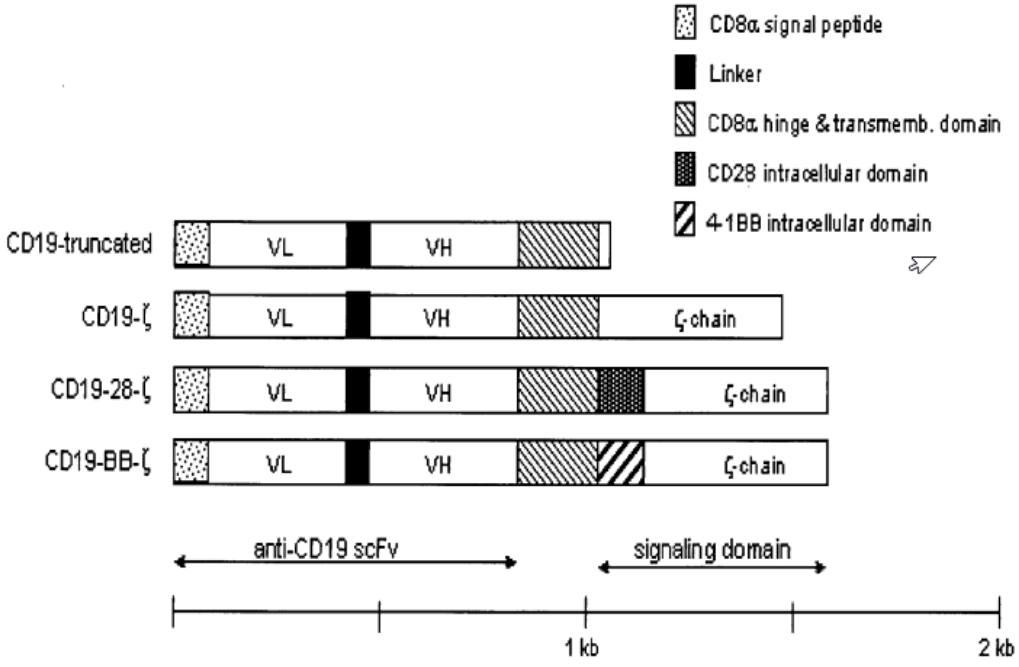
Campana is a US Patent Application Publication, published May 26, 2005, and listing Dario Campana and Chilhaya Imai as inventors. Ex. 1003, codes (43), (75). Campana discloses the results of in vitro studies using an anti-CD19 CAR having the same overall structure as the CAR described in claim 1 of the '140 patent.

[16] Petitioner relies on Nicholson, Jensen Littman, Sadelain (collectively "Sequence Art") as "disclos[ing] amino acid and nucleic acid sequences for components of the Campana CAR are hereinafter referred to as 'Sequence Art.'" Pet. 17.

Campana discloses the use of CARs containing a co-stimulatory 4-1BB signaling domain in T-cells and natural killer (NK) cells. *Id.* at, code (57). With respect to T-cells, Campana states:

> We constructed a chimeric T-cell receptor specific for CD19 that contains a 4-1BB signaling domain. We determined whether T-cells transduced with these receptors could effectively destroy B-lineage ALL cell lines and primary leukemic cells under culture conditions that approximate the in vivo microenvironment where leukemic cells grow. We compared the properties of T-cells expressing the 4-1BB-containing receptor to those of T-cells expressing an equivalent receptor lacking 4-1BB or containing CD28 instead.

Id. ¶ 65. Figure 1 of Campana, reproduced below, is a schematic representation of constructs used in this work.



Id. at Fig. 1, ¶ 20.

Figure 1 discloses representative CAR CD19-BB-ζ comprising a CD8α signal peptide, an anti-CD19 scFv binding region, a CD8α hinge and transmembrane domain, a 4-1BB costimulatory domain, and a CD3-ζ

signaling domain. *Id.* at Fig. 1, ¶ 13; Ex. 1002, ¶ 63. Reflecting its antigen specificity, Campana elsewhere refers to this same construct as "anti-CD19-BB-ζ." *See, e.g., id.* ¶¶ 21, 38, 53.

Campana discloses that primary T-cells were transduced with anti-CD19-BB-ζ, expanded in culture, and tested for activity in vitro. *Id.* ¶¶ 50–51. According to Campana, "[t]hese results show that 4-1BB co-stimulation confers a survival advantage on lymphocytes, which overcomes a major obstacle with current chimeric receptors used in immunotherapy." *Id.* ¶ 51. Subsequent experiments showed that "T-cells expressing the anti-CD19 BB-ζ receptor exhibited cytotoxic activity at the 1:1 and 0.1:1 ratios against all CD19+ cell lines tested." *Id.* ¶ 52. Campana reports that other experiments "show[] that T-cells transduced with the anti-CD19-BB-ζ receptor exhibit cytotoxic activity in an environment critical for B-lineage leukemic cell growth," and that anti-CD19-BB-ζ expression "caused higher levels of TRAIL stimulation" and increased IL-2-mediated T-cell expansion. *Id.* ¶¶ 53, 115, 116 (noting that T-cells require TRAIL for optimal graft-versus-tumor activity).

According to Campana, "[r]esults of this study indicate that anti-CD19-BB-ζ receptors could help achieve effective T-cell immunotherapy of B-lineage ALL." *Id.* ¶ 113; *see also id.* ¶ 54 ("These results further support the use of anti-CD19-BB-ζ receptor for immunotherapy."). Campana concludes that, "[i]n view of the limited effectiveness and the high risk of the currently available treatment options for chemo therapy-refractory B-lineage ALL and other B cell malignancies, the results of our study provide compelling justification for clinical trials using T-cells expressing anti CD19-BB- ζ receptors." *Id.* ¶ 118. For example, "[d]onor-derived T-cells

endowed with chimeric receptors could replace infusion of non-specific lymphocytes post-transplant." *Id.* In addition, "[t]he reinfusion of autologous T-cells collected during clinical remission could also be considered in patients with persistent minimal residual disease." *Id.* Consistent with these assertions, Campana claims

> 17. A method for treating an individual suffering from cancer by introducing into said individual a T lymphocyte or natural killer cell comprising a chimeric receptor wherein said chimeric receptor comprises an extracellular ligand binding domain, a transmembrane domain, and a cytoplasmic domain, wherein said cytoplasmic domain comprises the Signaling domain of 4-1BB.

Id. at claim 17.

2) CART-19 ClinTrials.gov (Exhibit 1006)

CART-19 ClinTrials.gov is a printout of a government website disclosing "Pilot Study for Patients with Chemotherapy Resistant or Refractory CD19 Leukemia and Lymphoma (CART-19)." Ex. 1006, 5; *see also id.* at 1–2 (Declaration of Duncan Hall).

In setting forth the purpose of the study, CART-19 ClinTrials.gov explains that "[t]he subject's T-cells will be modified in one or two different ways that will allow the cells to identify and kill the tumor cells (B cells)." *Id.* at 5. In particular,

> The two types of CART-19 T-cells will be given back to subject's through an infusion. In addition to determining the safety of this approach, the purpose of the study is to determine which way of modifying the T-cells works better in turning them "on" to fight cancer. This is done by monitoring levels of both types of modified cells in the subject's blood stream, and if possible, in the bone marrow and tumor tissue for four weeks after the infusion.

Id.

The reference further discloses that the study, designated NCT00891215, would be conducted at the University of Pennsylvania, Philadelphia, and identifies Dr. Carl H. June and David Porter, MD, as the "Responsible Party" and "Principle Investigator," respectively. Ex. 1006, 6. The reference describes the NCT00891215 as "an open label, single center, pilot study to evaluate the safety and tolerability, and differential persistence and engraftment of autologous T-cells engineered to express a chimeric antigen receptor targeting CD19 which is linked either to the CD3 or CD3:4-1 BB signaling chains in a competitive repopulation setting." *Id.* at 5.

NCT00891215 was expected to enroll 10 patients, each of which would receive three infusions of CART-19 cells for a total dose of ~2xE9 - 5xE10 cells. The reference also discloses an evaluation and monitoring schedule and notes that "[a]nnual follow-up for lentiviral vector safety will be carried out for 15 years in accordance with FDA guidelines for retroviral vectors." *Id.*

3) Nicholson (Exhibit 1004)

Nicholson discloses "a single chain Fv (scFv) fragment from the mouse hybridoma cell line FMC63 which produces monoclonal antibody specific for CD19." Ex. 1004, 1157, 1160 (DNA and amino acid sequence information).

4) Honsik (Exhibit 1005)

Honsik is a United States Patent issued July 4, 1989. Ex. 1005, code (45). Honsik discloses pharmaceuticals compositions for infusing activated leukocytes (including T-cells) using "a physiologically tolerable diluent aqueous medium." *Id.* at 4:45–5:9, 13:58–64; see Ex. 1002 ¶ 116. According to Honsik, "[e]xempary aqueous media include water, normal saline, PBS,

Ringer's solution, lactated Ringer's solution, and the like." Ex. 1005, 13:62–64.

5) Jensen (Ex. 1007)

Jensen is a US Patent Application Publication dated July 1, 2004. Ex. 1007, code (43). Jensen discloses the results of in vitro studies using an anti-CD19 CAR having the general structure as the CAR described in claim 1 of the '140 patent.

Jensen discloses "[g]enetically engineered, CD19-specific redirected immune cells expressing a cell surface protein having an extracellular domain comprising a receptor which is specific for CD19, an intracellular signaling domain, and a transmembrane domain." Ex. 1007, code (57). In preferred embodiments, these cells are CAR T-cells, i.e., "genetically engineered, redirected T-cells" intended for use as "cellular immunotherapy of B-cell malignancies." *Id.* ¶ 36. In one embodiment,

> CD19-specific redirected T-cells express CD19-specific chimeric receptor scFvFc:ζ, where scFv designates the V_H and V_L chains of a single chain monoclonal antibody to CD19, Fc represents at least part of a constant region of a human IgG_1, and ζ represents the intracellular signaling domain of the zeta chain of human CD3. The extracellular domain scFvFc and the intracellular domain ζ are linked by a transmembrane domain such as the transmembrane domain of CD4.

Id. ¶ 38; *see also id.* ¶¶ 67–68 (Example 1, "Construction of a scFvFc:ζ cDNA").

Jensen conducts in vitro studies on scFvFc:ζ CAR T-cells, including chromium release assays that show the killing of tumor lines bearing the CD19 epitope. *Id.* ¶¶ 69–74 (Example 2). Jensen concludes that "[t]hese preclinical studies support the initiation of clinical investigation to explore the safety and anti-tumor activity of adoptive therapy with donor-derived

CD19R:zeta-expressing T-cell clones in patients that relapse following HLA-matched allogeneic bone marrow transplantation." *Id.* ¶ 74. Jensen then presents protocols for the generation, testing, and clinical administration of allogenic scFvFc:ζ CAR T-cells, concluding with the design for a Pilot Phase I clinical trial for the treatment of leukemia. *Id.* ¶¶ 75–82 (Example 2: "Generation and Characterization of T-cell Clones for Therapeutic Use"), 83–116 (Example 4: "Materials for Isolating, Genetically Modifying and Expanding $CD8^+$ T-cell Clones from Healthy Marrow Donors for Therapeutic Use"),117 (Example 6: "Microbiologic Surveillance of T-cell Cultures"), 118 (Example 7: "Quality Control Criteria for Release of Clones for Re-Infusion"), 119 (Example 8: "Quantitative PCR For T-cell Persistence In Vivo"), 120–224 (Example 9: "Pilot Phase I Study").

6) Littman (Ex. 1009)

Littman discloses the DNA and amino acid sequence for human CD8, and predicts its signal peptide and transmembrane region. Ex. 1009, Abstract, 240, 242; *see also* Ex. 1002 ¶¶ 86–88. According to Dr. Junghans, one of ordinary skill in the art reading Littman would further understand that the hinge region would span "48 amino acid residues starting at position 114 and ending at position 161 of the full CD8α sequence displayed in Figure 7A of Littman." Ex. 1002 ¶ 89.

7) Sadelain (Ex. 1010)

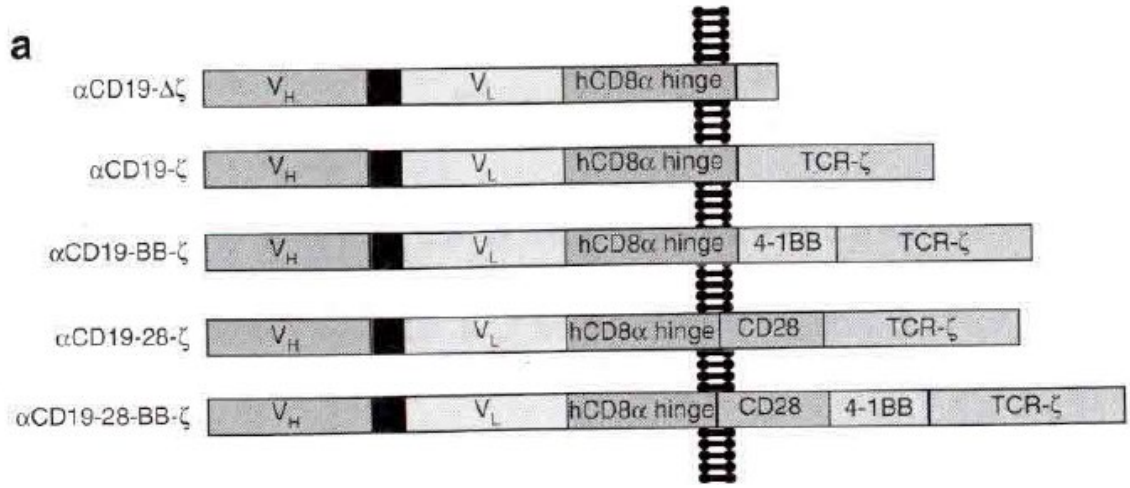
Sadelain describes chimeric T-cell receptors (i.e. CARs) comprising "the intracellular domain of CD3 ζ-chain, a signaling region from a costimulatory protein such as CD28, and a binding element that specifically interacts with a selected target." Ex. 1010, code (57); see id. ¶¶ 52–55, Fig. 2 (exemplary CAR comprising anti-CD19 domain, 4-1BB costimulatory

domain, and the "intracellular domain of the CD3ζ chain"). According to the Petition, Sadelain discloses the amino acid and DNA sequences for a "CD3-zeta signaling domain." Pet. 17, 56; *see* Ex. 1002 ¶¶ 94–96.

8) Milone (Ex. 1008)

Milone is a 2009 scientific publication listing among its authors, Michael Milone and Carl June (the inventors of the '140 patent), and Dario Campana—listed as an inventor in Campana. Ex. 1008, 1453. Milone discloses the results of in vitro and in vivo studies using an anti-CD19 CAR having the general structure as the CAR described in claim 1 of the '140 patent.

Milone discloses "a series of CARs that contain the T-cell receptor-ζ (TCR-ζ) signal transduction domain with the CD28 and/or CDE137(4-1BB) intracellular domains in tandem." *Id.*, Abstract. Milone's constructs are illustrated in Figure 1a, reproduced below.



Id. at 1454 (Fig. 1a). Figure 1a is a schematic diagram showing Milone's CD19-specific CAR constructs. Of these, αCD19-BB-ζ comprises comprising an anti-CD19 scFv binding region, a CD8α hinge and

transmembrane domain, a 4-1BB costimulatory domain, and a TCR-ζ signaling domain. According to Milone, "[t]he cDNA for . . . [αCD19-BB-ζ was] "generated at St Jude's Childrens Research Hospital." *Id.* 1462 (citing Imai).

Milone labels the N-terminal stimulatory domain "TCR-ζ" as opposed to CD3ζ as used in Campana and claim 1. As noted by the Examiner in the '622 parent application, these terms are "considered to be synonymous." Ex. 3003, 81. Milone also does not expressly identify the sequence of the anti-CD19 scFv binding region. Dr. Junghans, however, testifies that Milone's αCD19-BB-ζ is the same construct used in Campana and Imai. *See* Ex. 1002 ¶¶ 97–99, 101. In addition, Milone's αCD19-BB-ζ CAR appears to encode the same polypeptide as used in the '140 patent and in Porter, both of which reference Milone. *See* Ex. 1001, 41:5–7. ("The CD19-BB-z transgene (GeMCRIS 0607-793) was designed and constructed as described (Milone et al., 2009, Mol Ther. 17:1453-1464))"; Ex. 1012, 726 (citing Milone (reference 5) for pre-clinical work on GeMCRIS 0607-79).

Milone discloses that T-cells transduced with αCD19-BB-ζ were effective at killing human CD19+ tumor cells and stimulating T-cell proliferation in vitro. *Id.* at 1455–56, Figures 2 and 3. Milone also conducted whole animal experiments using "an immuno-deficient mouse xenograft model of primary human pre-B-cell acute lymphoblastic leukemia." *Id.* at Abstract. In the animal studies, the infusion of T-cells transduced with αCD19-BB-ζ reduced the number of human CD19+ acute lymphoblastic leukemia cells. *Id.* at 1456–59, Figures 5-7. Milone further teaches that the infused T-cells could persist in the animal for greater than six months. *Id.* Abstract, 1460–1461 ("even animals give the low dose of CARs had a

significant treatment effects on days 57 and 70 . . . . Long-term engraftment of the CAR^+ T-cells was observed in the animals with controlled leukemia, as 3 of 7 mice examined …6 months after T-cell transfer were still engrafted in the spleen. . . and other organs."). Milone concludes that "[t]he antigen-independent signals derived from the [4-1BB] domain within the CAR may be critical to the antileukemic effects observed in our study." *Id.* at 1462; *see also id.* at Abstract ("incorporation of the [4-1BB] signaling domain in CARs should improve the persistence of CARs in the hematologic malignancies and hence maximize their antitumor activity"). *Id.* Abstract.

9) Porter (Ex. 1012, Ex. 1013) [17]

Porter is a New England Journal of Medicine Brief Report authored by David L. Porter, Bruce L. Levine, Michel Kalos, Adam Bagg, and Carl H. June (Ex. 1012) and associated Protocol provided by the authors (Ex. 1013). Porter is a case report on a patient treated in a clinical trial of CART-cells. According to Porter: "The trial (ClinicalTrials.gov number, NCT01029366) was designed to assess the safety and feasibility of infusing autologous CART19 T-cells in patients with relapsed or refractory B-cell neoplasms. The trial was approved by the institutional review board at the University of Pennsylvania." Ex. 1012, 726 (citing Milone (Ex. 1008)), Porter reports that T-cells were transduced with "a self-inactivating lentiviral vector (GeMCRIS 0607-793)," encoding "a chimeric antigen receptor with specificity for the B-cell antigen CD19, coupled with CD137 (a costimulatory receptor in T-cells [4-1BB]) and CD3-zeta (a signal-

[17] In referencing Porter, we understand Petitioner to include the associated "*CD19 Lentiviral T body Protocol, Version 0.3*," (*Ex.* 1013, "Porter Protocol"). *See* Pet. 20.

transduction component of the T-cell antigen receptor) signaling domains." *Id.* at 724 (Summary), 725 (citing reference 5 (Milone, Ex. 1008)); *see also id.* at 728, Fig. 1, Panel A and legend (illustrating lentiviral vector and encoded CAR); Ex. 1013, 7, Figs. 2, 4 (further illustrating structure of CAR αCD19-41BB-CD3ζ).

According to Porter:

> A low dose (approximately $1.5x10^5$ cells per kilogram of body weight) of autologous chimeric antigen receptor-modified T-cells reinfused into a patient with refractory chronic lymphocytic leukemia (CLL) expanded to a level that was more than 1000 times as high as the initial engraftment level in vivo. . . . Engineered cells persisted at high levels for 6 months in the blood and bone marrow and continued to express the chimeric antigen receptor. A specific immune response was detected in the bone marrow, accompanied by loss of normal B cells and leukemia cells that express CD19. Remission was ongoing 10 months after treatment.

Id. at 725 (Summary). Porter notes that "[t]wo other patients with advanced CLL have also received CART19 infusions according to this protocol, and all three have had tumor responses. These findings warrant continued study of CD19-redirected T-cells for B-cell neoplasms." *Id.* at 733 (internal citation number omitted).

E. Ground 4 and the Prior Art Status of Porter[18]

For Ground 4, Petitioner asserts Porter in combination with Campana, Nicholson, Jensen, Littman, Sadelain, and Honsik. Pet. 54–69. Petitioner contends that Porter is prior art under § 102(a). Pet. 19–20. Patent Owner

[18] Petitioner asserts that each of Campana, Nicholson, Littman, Sadelain, Honsik, and CART-19 ClinTrials.gov qualifies as prior art under 35 U.S.C. § 102(b). Pet. 15–19. Patent Owner does not dispute those assertions on the record before us.

contends that Porter is not 102(a) prior art with respect to the challenged claims because the disclosures relied on in the Petition "reflect the inventors' own work." *See* Prelim. Resp. 41–42; Prelim. Sur-reply 1–3; *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982).

As Patent Owner points out, "Porter identifies five authors: Dr. Bruce Levine, Dr. Michael Kalos, Dr. Carl June, and Dr. David Porter, who are all co-inventors of '140 patent, as well as one other individual, Dr. Adam Bagg." Prelim. Resp. 41–42. Patent Owner contends that Dr. Bagg's contribution to Porter "was independent and separate from the invention of the claimed methods of treating cancer and distinct from anything in Porter that is cited by Petitioners." *Id.* at 42. In support, Patent Owner relies on Dr. Bagg's testimony that his role was limited to collecting and analyzing hematopathology samples at the request and direction of the named inventors. *See id.* (citing Ex. 2044).

Dr. Bagg states, for example:

> I assisted in analyzing samples collected in the course of the patients' treatment at the request and at the direction of my coauthors. But I did not come up with the idea for the treatment described in Porter. Also, I was not involved in creating the chimeric antigen receptor modified T-cells used in the study or in formulating them for administration, nor was I involved in developing the dosing schedules or treatment regimens used in the study or in directing the care for any of the patients in the study.

Ex. 2044 ¶ 6.

> As a laboratory-based hematopathologist, I was responsible for analyzing samples collected for this experimental research patient, at the request and direction of my co-authors. From these analyses, I determined the laboratory result indicating remission and Dr. Porter made the clinical determination of

> remission, based on the reported results and the patient's overall clinical/health status.

Id. ¶ 8.

In response, Petitioner argues that "Porter describes Dr. Bagg as evaluating effectiveness by performing 'MRD assessments' after CAR T-cell therapy. Ex. 1013, 36. MRD (or minimal residual disease) assessments refer to the measurement of residual tumor cells remaining in the body after treatment, which is relevant to anti-tumor effectiveness," and that "Dr. Bagg's declaration raises factual questions about whether a portion of Porter, *e.g.*, determination of antitumor effect, was 'by another.'" Prelim. Reply 1–2 (citing Ex. 1013, 36; Pet. 65–66; Ex. 2044 ¶ 8).

On the particular facts of this case, we find it unlikely that Petitioner can demonstrate that Dr. Bagg's contribution to Porter constitutes the work of another. Rather, we find reasonable Patent Owner's assessment that:

> Porter and Dr. Bagg's declaration consistently indicate that Dr. Bagg analyzed samples, determined laboratory results indicating remission, and passed that information on to the inventors. Ex. 2044 at 3; Ex. 1013 at 36, 37; Reply 1–2. In fact, the assays that Miltenyi touts were described in both Porter *and the patent*. *Compare* Ex. 1013, 36 (describing MRD assessments, cited at Reply 1), *with* Ex. 1001, 57:18–26. Dr. Bagg's contribution— performing "assays and testing" at the inventors' instruction, Ex. 2044 at 2–3—may warrant discretionary co-authorship of academic papers, but does not constitute legal inventorship; he is not part of the "common inventive entity" that conceived the work reported in both Porter and the patent. *Katz* at 455; *Riverwood Int'l v. R.A. Jones*, 324 F.3d 1346, 1356 (Fed. Cir. 2003).

Sur-reply 2.

We also do not discern a credible factual dispute as to Dr. Bagg's contribution to Porter. Nor does it appear that the Petition directly relies on

that work. Although Petitioner contends that Dr. Bagg's hematopathological assessments were "relevant to anti-tumor effectiveness," those assessments, as such, are not cited in the Petition. Pet. 65–69. Rather, Dr. Porter appears to have determined "clinical determination of remission" based, in part, on Dr. Bagg's data. *See* Ex. 2044 ¶ 8.

In view of the above, we are not persuaded that Petitioner can establish that Porter qualifies as prior art under §102(a). Petitioner relies on Porter as demonstrating successful clinical results using a CAR T cells within the scope of the challenged claims. *See* Pet. 65–66. Because Petitioner's Ground 4 arguments rely solely on Porter's disclosure for this teaching that Petitioner has not indicated is found in any other reference of record, Petitioner has not established a reasonable likelihood of prevailing in demonstrating the unpatentability of claims 1–19 and 21–28 as obvious under this Ground.

F. Obviousness Based on Combinations including Campana, and CART-19 ClinTrials.gov (Grounds 1–2), and further including Milone (Ground 3)

For Ground 1 Petitioner contends claims 1–2, 6, 8–9, 11, 16, 21–22, 27–28 are obvious in view of Campana, CART-19 ClinTrials.gov, Nicholson, and Honsik. Pet. 20–40. For Ground 2, Petitioner contends claims 1–2, 6, 8–9, 11, 13, 16, 21–22, 27–28 are obvious in view of Campana, CART-19 ClinTrials.gov, Jensen, and Honsik. *Id.* at 40–49. For Ground 3, Petitioner contends claims 1–19, 21–28 are obvious in view of Campana, CART-19 ClinTrials.gov, Nicholson, Jensen, Littman, Sadelain, Honsik, and Milone,, *Id.* at 49–64. Focusing on Campana and CART-19 ClinTrials.gov, Patent Owner addresses Petitioner's Grounds 1–3 collectively. Prelim. Resp. 23–44.

Following the approach set forth in the Petition, we address first the claim elements directed to the CAR T-cell structure (elements [d]–[f]), and then discuss claim elements directed to a method using those cells to treat a patient (elements [a]–[e]).

1. Petitioner's Contentions

a. CAR T Structure: Elements [d]–[f]:

As briefly addressed below, Petitioner relies on Campana as disclosing a CAR T-cell within the scope of elements [d]–[f]. Pet. 22–28.

> [(d)] wherein the T-cells comprise a nucleic acid sequence encoding a chimeric antigen receptor (CAR)
>
> [(e)] wherein the CAR comprises a CD19 antigen binding domain comprising, from the amino to the carboxy terminus, a light chain variable region and a heavy chain variable region of SEQ ID NO:20
>
> [(f)] wherein the CAR further comprises a transmembrane domain, a 4-1BB costimulatory signaling region, and a CD3 zeta signaling domain.

Petitioner relies on Campana as teaching the transduction a viral vector encoding anti-CD19-BB-ζ CAR into T-cells, and the subsequent expression of the encoded CAR. Pet. 22–23 (citing Ex. 1003 ¶¶ 76–83; Ex. 1002 ¶¶ 130–133; *see generally* Section II.D.3, above. Petitioner reasonably contends that the anti-CD19-BB-ζ CAR construct—illustrated in Campana's Figure 1—comprises, from its amino to carboxy terminus: (1) a CD8α signal peptide, (2) an anti-CD19sdFv comprising a light chain region and a heavy chain variable region separated by a linker, (3) a CD8α hinge and transmembrane domain, (4) a 4-1BB costimulatory signaling region, and (5) a CD3 signaling domain. Pet. 22–27 (citations omitted); Ex. 1002 ¶¶ 36–38, 62–68, 130–145; Section II.D.3, above.

With respect to the identity of the CD19 antigen binding domain of element (e), the '140 patent defines SEQ ID NO: 20 as the amino acid sequence for an anti-CD19scFv. Ex. 1001, 61:13. As noted by Petitioner, although "Campana itself does not recite sequences for a VL region and a VH region in an anti-CD19 scFv, it discloses that these can be obtained from Nicholson." Pet. 24 (citing Ex. 1003 ¶ 47; Ex. 1004, 1160). According to Dr. Junghans, SEQ ID NO: 20 corresponds to VH and VL regions of the CD19 antigen binding antibody FMC63 disclosed in Nicholson. *Id.* 25–26; Ex. 1002 ¶¶ 70–73, 138–139 (noting that, as compared to SEQ ID NO: 20, Nicholson discloses an additional 16 amino acids at the end of the VL region).

Patent Owner does not presently contest that the prior art teaches or suggests element [d]–[f].

b. Method of Treatment: Elements [a]–[c]

Petitioner contends that the method of treating cancer recited in elements (a)–(b) would have been obvious in light of Campana and CART-19 ClinicalTrials.gov. Pet. 28–38. Patent Owner opposes. Prelim. Resp. 23–44.

> [(a)] A method of treating cancer in a human patient comprising

To the extent the preamble is limiting, or "imposes clinical efficacy beyond that required by 'anti-tumor effective amount'" in element (c)[19], Petitioner argues that Campana taught that *in-vitro* efficacy '"provides

[19] As noted in Section II.C.1, to the extent the preamble is limiting, we understand it to be coextensive with, or subsumed by, the term "anti-tumor effective amount."

compelling justification for clinical trials'" and [CART-19 ClinicalTrials.gov] disclosed an ongoing clinical study using a dose, 2.5×10^7 to 6.1×10^8 cells per kg, that falls squarely within the specified 'anti-tumor effective amount' dose range in dependent claim 2 of the '140 Patent." Pet. 29 (citing Ex. 1003, ¶ 18; Ex. 1006, 5). Relying on the testimony of Dr. Junghans, Petitioner contends that, a person of ordinary skill in the art "would have been motivated to practice 'a method of treating cancer' with the prior-art CAR and had a reasonable expectation of successfully doing so." Pet. 29; *see also* Junghans ¶¶ 146-47.

> [(b)] administering to the human patient a pharmaceutical composition comprising

Petitioner points to Campana's teaching that "[m]ethods of re-introducing cellular components are known in the art and include procedures such as those exemplified in U.S. Pat. Nos. 4,844,893 and 4,690,915." Pet. 30 (citing Ex. 1003 ¶ 64). As noted by Petitioner, "[t]he former, Honsik, provides exemplar pharmaceutical compositions for administering leucocytes, including T leucocytes (i.e., T-cells)" for therapeutic cellular infusion. *Id.* (citing Ex. 1005, 13:58–64). Honsisk lists the well-known buffer, PBS (phosphate buffered saline), among its preferred diluents. *See id.* (citing Ex. 1005, 13:58–64; Ex. 1001, 28:1, 37:38–39). Accordingly, Petitioner contends that one of ordinary skill in the art would have found element [b] obvious in light of Campana and its citation to Honsik. *Id.* (citing Ex. 1002 ¶¶ 150–153).

> [(c)] an anti-tumor effective amount of a population of human T-cells,

In Section II.C.2, we provisionally construed "anti-tumor effective amount" as any amount of CAR T-cells administered to a patient in need of cancer treatment that reduces the frequency or severity of at least one clinically relevant sign or symptom of the disease, and which may be limited to 10^4 to 10^9 CAR T-cells/kg body weight as set forth in claim 2. Relying on CART-19 ClinicalTrials.gov and the testimony of Dr. Junghans, Petitioner contends that the dose of CART-19 cells administered to patients in the NCT00891215 interventional study satisfies this limitation because it falls within the range of 10^4 to 10^9 CAR T-cells/kg body weight. Pet. 31–32 (citing Ex. 1006, 5; Ex. 1002 ¶¶ 103–105). According to Petitioner, one of ordinary skill in the art would have understood that NCT00891215 used the anti-CD19-BB-ζ CAR described in Campana (*id.* at 32 (citing Ex. 1002 ¶¶ 156–159), or "would have understood that dose disclosed in CART-19 ClinicalTrials.gov could be applied to the Campana anti-CD19-BB-ζ CAR." Pet. 32–33 (citing Ex. 1006; Ex. 1002 ¶¶ 155m 160, 162–164; Ex. 1003 ¶ 119).

c. Motivation and Reasonable Expectation of Success

According to Petitioner, "because the CART-19 ClinicalTrials.gov teaches a dose falling within an express range of "anti-tumor effective amount," this claim limitation does not separately require that a POSA would have had a reasonable expectation of an actual anti-tumor effect in a patient." Pet. 33. Although CART-19 ClinicalTrials.gov may *test* the hypothesis that a dose falling within the range set forth in claim 2 is efficacious, Petitioner has not established sufficiently that one of ordinary

skill in the art would have recognized that dose to be an "anti-tumor effective amount."

In the alternative, Petitioner contends that the skilled artisan "would have reasonably expected, based on Campana and the CART-19 ClinicalTrials.gov, that administering T-cells expressing the anti-CD19-BB-ζ CAR to cancer patients would at least result in a decrease in the number of tumor cells." *Id.* at 34 (citing Ex. 1002 ¶¶ 175, 184). In support of this second theory, Petitioner points to Campana's disclosure that T-cells expressing the anti-CD19-BB-ζ CAR exhibited cytotoxic activity against CD19+ leukemic cells, its conclusions that these results "provide[s] *compelling justification* for clinical trials using T-cells expressing anti-CD19-BB-ζ," and its claims to a method of treating cancer using a CAR of this general structure *Id.* (citing Ex. 1003 ¶¶ 50–54, 118, claims 17–21; Ex. 1002 ¶¶ 166–173).[20] Petitioner contends that Campana's in vitro results and proposed use of anti-CD19-BB-ζ in patients, would have led the skilled artisan to reasonably expect that "administering T-cells transduced with the anti-CD19-BB-ζ CAR to patients with cancer would result in at least a decrease in the number of tumor cells," as required for "an anti-tumor effective amount." *Id.* at 35 (citing Ex. 1002 ¶ 175).

With respect to ClinicalTrials.gov's disclosure of the NCT00891215 study, Petitioner contends that just the "initiation of a clinical trial using

[20] Petitioner further contends that "[t]he Campana inventors also published their results in Imai, a peer-reviewed journal article that also advocated for clinical trials using anti-CD19-BB-ζ." *Id.* (citing *Ex.* 1022, 683 ("[T]he results of our study justify clinical trials using T-cells expressing anti-CD19-BB-ζ receptors."); *Ex.* 1002 ¶¶ 62-67). Petitioner further points to Jensen's in vitro experiments as further supporting "a reasonable expectation of success for CD19 CARs." Prelim. Reply 4.

anti-CD19-BB-ζ is indicative of a reasonable expectation of success." *Id.* at 35–36 (citing Ex. 1002 ¶ 176; M.P.E.P. § 2107.03(IV); 45 C.F.R. §46.111(a)(2)). Petitioner further argues that the ordinarily skilled artisan reading the CART-19 ClinicalTrials.gov would have understood that "several other anti-CD19 CAR T-cells in the art had been used successfully in cancer patients (*id.* at 36 (citing Ex. 1002 ¶¶ 178–184)); that the number of anti-CD19-BB-ζ T-cells administered in NCT00891215 "was within the range of 'therapeutically effective doses' for anti-CD19 CAR T-cells taught by the art (*id.* (citing Ex. 1002 ¶¶ 165, 176–177); and that "the study investigators believed this dose to be safe and effective in the treatment of CD19+ cancers such as "[a]cute lymphoblastic leukemia, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, and diffuse large cell lymphoma" (*id.* at 35–36 (citing ¶¶176–177; Ex. 1006, 5–7)).

In light of the above, Petitioner contends that a person of ordinary skill in the art "would have reasonably expected that the disclosed dose of anti-CD19-BB-ζ CAR T-cells at least would reduce the number of tumor cells in a human patient with cancer, thereby rendering obvious "a method of treating cancer in a human patient comprising administering . . . ***an anti-tumor effective amoun***t' of the claimed CAR T-cells." *Id.* at 37–38 (citing Ex. 1002 ¶¶ 165–184).

For Ground 3, Petitioner asserts that Milone's "preclinical results in tissue culture and animal studies" using that same CAR as Campana "provide[] further support for a reasonable expectation of success." Pet. 50–51 (citing e.g., Ex. 1002 ¶¶ 97–100, 254–276).

Patent Owner argues, inter alia, that Petitioner cannot demonstrate a reasonable expectation of success in light of the unpredictability of cancer therapy and the "uninspiring" results and failures of earlier CAR-T clinical trials. Prelim. Resp. 23–28 (*citing e.g.*, Ex. 2037, 1036; Ex. 2010, 1824–1825; Ex. 2032, 1250–1251). In support, Patent Owner points to *OSI Pharms.* as "directly on-point." *Id.* at 24 (citing *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375 (Fed. Cir. 2019)). The claims at issue in *OSI Pharms.*, were structurally similar to those at issue here and directed to a method of treating non-small cell lung cancer ("NSCLC") in a mammal using a therapeutically effective amount of erlotinib, which had previously been shown to inhibit the epidermal growth factor receptor ("EGFR") in vitro. 939 F.3d at 1378–79. The court stated:

> Cancer treatment is highly unpredictable. Even though the EGFR was identified in some cancers as a drug target, the *in vitro* (i.e., in a test tube) effectiveness of a drug in inhibiting the EGFR turned out to be a poor proxy for how effective that drug actually was in treating cancer *in vivo* (i.e., in the body). Numerous EGFR inhibitors that showed promising *in vitro* activity failed for a variety of reasons.

Id. at 1377; *see also id.* at 1386 ("1,630 other new drug compounds that, like erlotinib, targeted NSCLC and were studied in Phase II trials. The failure rate for these compounds was 99.5%"). Against this backdrop, the court reversed the Board over its unsupported reading of the two cited references, finding that:

> the asserted references do not disclose *any* data or other information about erlotinib's efficacy in treating NSCLC. The record does not contain any clinical (human) data or preclinical (animal) data. It does not even include *in vitro* (test tube) data regarding erlotinib's effect on NSCLC.

Id. at 1384.

Considering the promising in vitro data presented in Campana and Jensen, Petitioner here has a somewhat better position than the Appellees in *OSI Pharms.* At core, Grounds 1 and 2, require us to find a reasonable expectation of success in treating a human cancer based on in vitro experiments, the mere existence of a clinical trial, and absent any of the "clinical (human) data or preclinical (animal) data," highlighted by the court. *See id.* Considering the inherent unpredictability of the field and the history of failures of similar technology documented by Patent Owner, we do not find Petitioner's arguments persuasive. As such, Petitioner has not demonstrated a reasonable likelihood of success in proving that any claim of the '140 patent is unpatentable under Grounds 1 and 2.

Petitioner's argument for a reasonable expectation of success is strengthened by the addition of Milone's preclinical animal data in Ground 3. *See* Pet. 50–51. But because the Examiner extensively discussed Milone in the context of claims similar to those at issue here, we first consider Patent Owner's argument that we should exercise our discretion to deny institution under § 325(d).

G. Discretion Under 35 U.S.C. § 325(d)

A. Legal Principles

Institution of inter partes review is discretionary. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that "the PTO is permitted, but never compelled, to institute an IPR proceeding"). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that "[i]n determining whether to institute or order a proceeding under this chapter, . . . the Director may take into account whether, and reject the petition or request because, the same or

substantially the same prior art or arguments previously were presented to the Office."

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors that may be considered. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("the Becton, Dickinson factors"). Those factors are as follows:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments.

Id.; *see also* The Patent Trial and Appeal Board Consolidated Trial Practice Guide ("Trial Practice Guide") (Nov. 2019) at 62–63 (citing the Becton, Dickinson factors).

As more recently explained in *Advanced Bionics, LLC v. MED-EL Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 8–10 (Feb. 13, 2020) ("*Advanced Bionics*") (precedential), the Board addresses § 325(d)

applying a "two-part framework." In the first part of the framework, we ask whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office. *Advanced Bionics* at 8. Factors (a), (b), and (d) of Becton, Dickinson come into play under this first part of the framework. *Id.* at 8–10. If either condition of the framework's first part is met (e.g., substantially the same art is presented), we move to part two of the framework, asking "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id.* at 8. Factors (c), (e), and (f) of Becton, Dickinson fall within part two of the framework. *Id.* at 10 ("[F]actors (c), (e), and (f) relate to whether the petitioner has demonstrated material error by the Office.").

Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated error. *Advanced Bionics* at 8–10. "If the petitioner fails to show that the Office erred, the Director may exercise his discretion not to institute inter partes review." *Id.* at 8–9. "At bottom, this [§ 325(d)] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9 ("If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.").

B. § 325(d) Framework: Part One

The first part of the *Advanced Bionics* framework requires us to determine whether the Petition advances the same or substantially the same art or arguments previously presented to the Office. *See Advanced Bionics* at

8. For the reasons set forth below, we agree with Patent Owner that the same or substantially the same art was previously presented to the Office, such that part one of the framework is satisfied.

According to Patent Owner, "all of the art cited by Petitioners in Grounds 1–4, including Porter . . . . was either expressly disclosed to the Examiner in an IDS or is substantially the same as art that was disclosed in an IDS." Prelim. Resp. 46. Petitioner, however, argues that denying institution under §325(d) is not warranted because the asserted Grounds rely on Jensen, CART-19 ClinicalTrials.Gov, Honsik, and Littman, which "were not cited by Patent Owner or found by the Examiner." Pet. 69. We do not find Petitioner's argument availing.

At the outset, Petitioner admits that "Jensen claims priority to a PCT application that was submitted in an IDS," and "[a] different Clinicaltrials.gov webpage for NCT00891215 was submitted in an IDS." *Id.* at n.7, 8. Supported by detailed comparisons of these two pairs of references, Patent Owner argues persuasively that there are "no material differences between the versions of the references the applicant disclosed to the Examiner and the versions Petitioners chose to cite in its Petition." Prelim. Resp. 46–48 (citations omitted).

Noting that "Petitioners cite Honsik solely to satisfy the limitation 'a pharmaceutical composition' of T-cells," Patent Owner points to four references cited in the prosecution of the '140 patent, and a further admission in the specification showing that substantially the same information was before the Examiner. *Id.* at 48–49 (citing Pet. 40–41, 49, 60, 68; Ex. 2027, 1; Ex. 2042, 1, Ex. 2026, 8; Ex. 2034, 1326; Ex. 1001, 37:66–38:1).

Patent Owner further argues Littman "is irrelevant to the § 325(d) analysis because "Petitioners rely on Littman only in Grounds 3 and 4 to address certain specific CD8α transmembrane and hinge domain amino acid and nucleic acid sequences specified in dependent claims 7, 10, 14, and 15. PO Resp. 49 (citing Pet. 17, 51–56, 65; Ex. 1009 at 240, 242). Patent Owner reasons that "[b]ecause Littman is not part of Petitioners' obviousness combination as to the independent claim, if the Examiner reasonably concluded that the independent claim would not have been obvious . . . then whether or not Littman discloses the limitations of certain dependent claims would have made no difference to the analysis." *Id.* at 49–50.

Considering the above, we conclude that the record before us is sufficient to satisfy Part One of the *Advanced Bionics* framework. *See Kayak Software Corp. v. IBM*, CBM2016-00075, Paper 16 at 10 (PTAB Dec. 15, 2016) (informative) (holding Petitioners' citation of reference not considered by Examiner solely for "additional subject matter of certain dependent claims[] is insufficient to persuade us that exercising our discretion under 35 U.S.C. § 325(d) is inappropriate").

C. § 325(d) Framework: Part Two

In part two of the framework, we consider "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Advanced Bionics* at 8. In this respect, Petitioner argues that the Examiner erred because a critical portion of the references relied upon in the Grounds were not expressly discussed during prosecution but merely cited in an IDS, "buried among a total of 174 references." Prelim. Resp. 69–70; Prelim. Reply 5. In particular, Petitioner asserts that "the Examiner overlooked Campana, which discloses the claimed CAR. The

Challenged Claims would not have issued if this reference had been considered." Prelim. Resp. 69.

In support of its position, Petitioner points to *Trend Micro* for the proposition that a reference cited among numerous others in an IDS but not applied or discussed in prosecution favors not exercising discretion to deny the Petition. Pet. 70 (citing *Trend Micro v. CUPP Computing AS*, IPR2021-00813, Paper 7 (P.T.A.B. Oct. 25, 2021) ("Citation of a reference in an IDS, without more, does not necessarily equate to evaluation of reference by the Examiner.")). We agree with Petitioner that Campana was not substantively discussed during prosecution. On the facts before us, Petitioner's reliance on *Trend Micro* is unavailing because even if the Examiner had overlooked Campana, the Examiner addressed substantially equivalent disclosure of in vitro results in the context of Milone.

As discussed above, Grounds 1 and 2 rely on Campana for its disclosure of promising in vitro data, which the Campana authors interpreted as warranting clinical testing. *See* generally, sections II.D.1, II.F. We also noted that on the present record, Petitioner's evidence was insufficient to establish a reasonable expectation of success in achieving the outcome promised by the challenged claims. *See supra* section II.F. Petitioner supplements this evidence in Ground 3 by pointing to Milone's preclinical animal data. Pet. 50–51. But unlike Campana, Milone was not merely cited in an IDS, but discussed at length in the prosecution of the '622 parent application. *See* Ex. 3003, 13–20, 45–48, 35–41, 81–84.

As we read the prosecution history, the Examiner understood Milone to disclose successful in vitro and preclinical animal studies using T-cells expressing a CAR substantially the same as that described in the challenged

claims. *See* section I.E.3, above. With respect to at least the in vitro studies, Milone thus teaches substantially the same disclosure that Petitioner argues the Examiner overlooked in Campana.

The same Examiner examined both the '622 parent application and the application leading to the issuance of the '140 patent. *Cf.* cover pages of Ex. 1001 and Ex. 3003. In the examination of '622 parent application, the Examiner lodged rejections based on Milone in office actions dated June 19, 2015 and January 5, 2016, and mailed a Notice of Allowance on July 20, 2016. *See* Ex 3003, 12, 43, 77. Given that the application leading to the issuance of the '140 patent was filed on January 15, 2016 (*see* Ex. 1001, code (22)), it is highly unlikely that the Examiner was unaware of Milone during the prosecution of the '140 patent because Milone was the basis for repeated rejections and responsive amendments in the copending '622 parent application. *See* section I.E.3, above.

We find it particularly relevant that the Examiner, having recently allowed claims over Milone in the '622 parent application, did not lodge a rejection based on this reference in the examination of the related '140 patent. On a clean record, this Panel may have viewed the record differently from the Examiner, but we cannot say that the Examiner overlooked Milone or erred in the issuance of the '140 patent claims. *See Advanced Bionics* at 9 ("If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.").

For the above reasons, we do not find that Part Two of the Framework is satisfied at least with respect to Ground 3. On the particular facts before

us, we exercise our discretion under 35 U.S.C § 325(d) and decline to institute inter partes review.

III. CONCLUSION

For the reasons provided above, we deny the Petition and decline to institute the requested inter partes review.

IV. ORDER

ORDERED, that the Petition is *denied* as to all challenged claims of the '140 patent and no trial is instituted.

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