

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

JANSSEN BIOTECH, INC.,
Petitioner

v.

THE UNITED STATES OF AMERICA,
AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF
HEALTH & HUMAN SERVICES,
Patent Owner.

Case IPR2021-01484
Patent 9,765,342 B2

Before, SHERIDAN K. SNEDDEN, ROBERT A. POLLOCK, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner Janssen Biotech, Inc., (“Janssen”) filed a Petition challenging claims 1–9, 13, 17, and 19 of U.S. Patent No. 9,765,342 (Ex. 1001, “the ’342 patent”). Paper 2 (“Pet.”). Patent Owner, the United States of America, as represented by the Secretary, Department of Health & Human Services (“United States”), timely filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

In Paper 7, we granted Petitioner’s request to file a pre-institution Reply to Patent Owner’s Preliminary Response. Paper 8 (“Prelim. Reply”). We permitted Patent Owner to file a Sur-Reply to Petitioner’s authorized Reply. Paper 9 (“Prelim. 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).

A. Party Identification of Real Parties-in-Interest

Petitioner identifies Janssen Biotech, Inc., Janssen Pharmaceutica NV, Legend Biotech USA, Inc., Legend Biotech Ireland Limited, and Nanjing Legend Biotechnology Co., Ltd. as real parties-in-interest. According to Patent Owner, “[t]he real parties-in-interest are the United States of America, 2seventy bio Inc., and Cartesian Therapeutics, Inc.” Paper 5.

B. Related Patents and Proceedings

The ’342 patent issued from Application Serial No. 14/389,677 (“the ’677 application”), originally filed on March 15, 2013, as PCT application

US2013/032029. Ex. 1001, codes (21), (22). The parties identify 13 other issued patents and two pending applications claiming priority to the '677 Application. Pet. 65–66; Paper 4, 1–2.

Other than the instant IPR, the parties identify no other proceedings related to the '342 patent. *See* Pet. 65–66; Paper 4, 1–2.

C. Asserted Grounds of Unpatentability

Petitioner asserts the following ground of unpatentability (Pet. 7):

Claims Challenged	35 U.S.C. §	Basis
1–9, 13, 17, 19	103	Milone, ¹ Kalled ²

Petitioner also relies, *inter alia*, on the declarations of Hidde Lolke Ploegh, Ph.D., (Ex. 1003) and Abhinav Deol, M.D. (Ex. 1005). Patent Owner similarly relies on the declaration of Djordje Atanackovic, M.D. (Ex. 2001).

D. Overview of Challenged Claims

Claims 2–9, 13, 17, and 19 incorporate the elements of challenged independent claim 1, which recites:

1. A chimeric antigen receptor (CAR) comprising an antigen recognition moiety and a T-cell activation moiety, wherein the T-cell activation moiety comprises a transmembrane domain, wherein the antigen recognition moiety is directed against B-cell Maturation Antigen (BCMA).

¹ Milone et al., “*Chimeric Receptors Containing CD137 Signal Transduction Domains Mediate Enhanced Survival of T Cells and Increased Antileukemic Efficacy In Vivo*,” 17(8) Molec. Therap. 1453–1464 (2009). Ex. 1009.

² WO 2010/104949 A2, publ. Sept. 16, 2010. Ex. 1010.

Among the challenged dependent claims, claims 2–5 limit the antigen recognition moiety to, e.g., “a monoclonal antibody directed against BCMA or an antigen-binding portion thereof” (claim 2), which may be “a single chain variable fragment (scFv) directed against BCMA” (claim 5). Claims 7–9 limit the T-cell activation moiety to, for example, “a T-cell signaling domain of a human 4-1BB protein and a human CD3-zeta protein” (claim 9). Claims 13, 17, and 19, respectively, recite nucleic acids, vectors, or host cells relating to the CAR of claim 1.

E. The ’342 patent and relevant background

The ’342 patent discloses CARs having an antigen recognition moiety directed against B-cell Maturation Antigen (BCMA), and the use of these constructs in CAR-T therapy for treating multiple myeloma (MM). *See, e.g.*, Ex. 1001, 2:26–31, 13:27–38. Multiple myeloma is a hematologic malignancy³ involving clonal expansion of mature or terminally differentiated B cells, known as plasma cells, and often manifests as plasmacytomas in the bone marrow. *Id.* at 1:25–30; Ex. 1003 ¶¶ 18–25 (discussing MM symptoms, etiology, and prior art treatments); Ex. 1005 ¶¶ 18–30 (same). Symptoms of myeloma include bone pain, immunosuppression, and kidney failure. *See, e.g.*, Ex. 1005 ¶¶ 18–19.

With respect to CAR-T immunotherapy, the ’324 patent states that, “[a]doptive transfer of T-cells genetically modified to recognize

³ Petitioner’s experts define hematologic malignancies as “cancers of the blood, bone marrow, or immune system,” categorized as leukemias, lymphomas, and myelomas. Ex. 1003 ¶ 36; Ex. 1005 ¶¶ 16–18.

malignancy-associated antigens is showing promise as a new approach to treating cancer.” Ex. 1001, 1:44–52. In this approach, “T-cells can be genetically modified to express chimeric antigen receptors (CARs), which are fusion proteins comprised of an antigen recognition moiety and T-cell activation domains.” *Id.* at 1:52–55.

The ’324 patent asserts that no clinically effective FDA-approved autologous T cells therapies exist for MM, but “extensive progress has been made in developing adoptive T-cell approaches that utilize anti-CD19 CARs” for treating other B-cell lineage malignancies. *Id.* 1:39–43, 1:58–2:2. In particular, the ’342 patent notes that [a]doptively transferred anti-CD19-CAR-transduced T-cells have cured leukemia and lymphoma in mice,” and early clinical trial data shows that “adoptively transferred T-cells transduced with anti-CD19 CARs eradicated normal and malignant B-cells in patients with leukemia and lymphoma.” *Id.* at 2:2–15. The ’342 patent indicates, however, that this application of CAR-T therapy is unsuited for treatment of MM because CD19 “is only rarely expressed on the malignant plasma cells of multiple myeloma.” *Id.* at 2:16–22. Instead, the ’342 patent discloses “a CAR which comprises an antigen recognition moiety that is directed against B-cell Maturation Antigen (BCMA, also known as CD269).” *Id.* at 4:50–53.

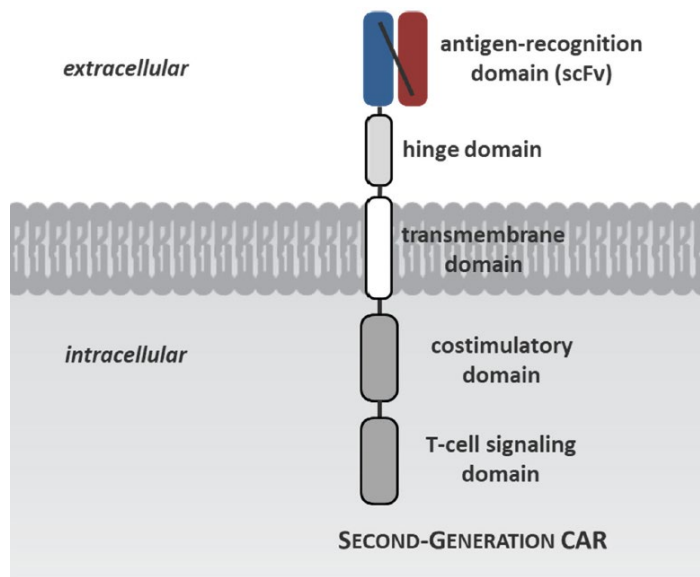
Citing numerous prior art publications, the ’342 patent explains that, “BCMA is a member of the tumor necrosis factor receptor superfamily” known to bind the B-cell activating factor BAFF and the proliferation inducing ligand APRIL. *Id.* at 4:53–59. “BCMA has been reported to be expressed mostly in plasma cells and subsets of mature B-cells.” *Id.* at 4:60–66. “Mice deficient in BCMA are healthy and have normal numbers of B-

cells, but the survival of long-lived plasma cells is impaired.” *Id.* at 4:66–5:4. With respect to malignant cells, “BCMA RNA has been detected universally in multiple myeloma cells, and BCMA protein has been detected on the surface of plasma cells from multiple myeloma patients.” *Id.* at 5:4–11; *see also id.* at 17:58–18:52 (Example 1 “demonstrat[ing] that BCMA is expressed on the surface of multiple myeloma cells, and it has a restricted expression pattern in normal tissues”).

The ’342 patent explains that a CAR

is an artificially constructed hybrid protein or polypeptide containing an antigen binding domain of an antibody (e.g., a single chain variable fragment (scFv)) linked to T-cell signaling or T-cell activation domains. CARs have the ability to redirect T-cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives T-cells expressing CARs the ability to recognize an antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape.

Id. at 4:7–22. The figure below, reproduced from Dr. Plough’s declaration, illustrates basic components of a CAR protein.

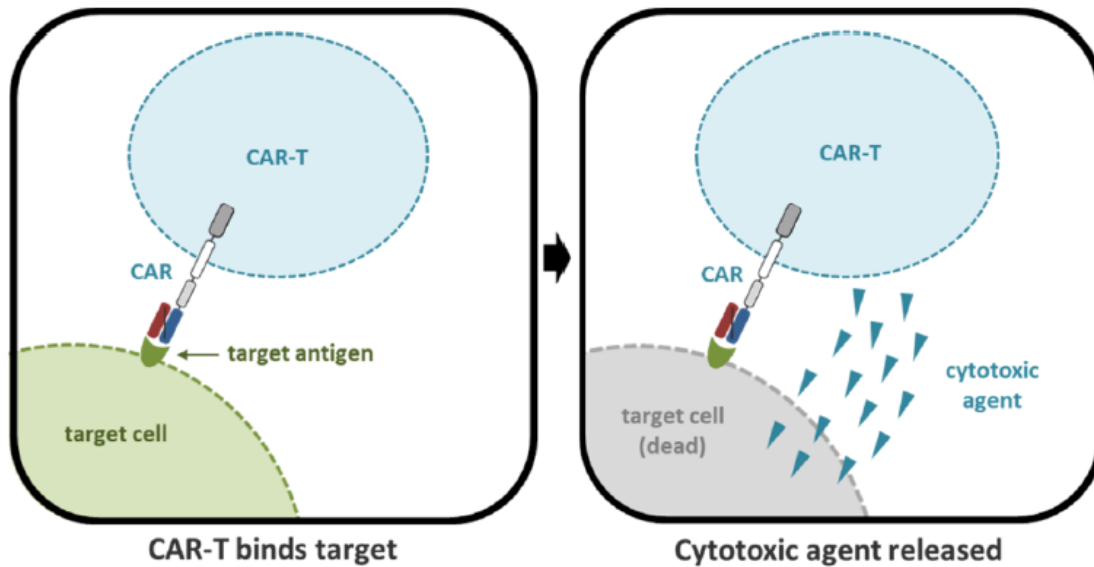


The above figure shows four elements of a “second-generation CAR” comprising an antigen-recognition domain (as illustrated, an scFV)⁴, a hinge domain, a transmembrane domain, an intracellular co-stimulatory domain, and an intracellular T-cell signaling domain. *See* Ex. 1003 ¶ 60; *see also id.* ¶ 49 (describing “first-generation CAR” as lacking an intracellular costimulatory domain).

As explained in detail by Dr. Plough, CAR proteins are critical components of CAR-T immunotherapy, in which a patient’s T cells are modified to express a chimeric antigen receptor (CAR). *See generally id.*

⁴ “scFV” or “single chain variable fragment” refers to an antibody fragment in which V_L and V_H 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 id.* ¶¶ 31–35; Ex. 1001, 4:11–14, 5:39–6:9 (discussing scFv and other suitable antigen recognition moieties).

¶¶ 42–89. The figure below, also reproduced from Dr. Plough’s declaration, illustrates the general principal of CAR-T therapy.



The above figure illustrates the general principle of CAR-T therapy. *See id.* ¶¶ 42–44. T-cells isolated from a patient are programmed to express CAR protein, and then reintroduced into the body. *See id.* ¶ 42. CAR proteins expressed in the patient’s T-cells, become anchored in the T-cell membrane via the transmembrane domain with the antigen recognition domain exposed to the exterior of the cell and the T-cell signaling domain in communication with the cell cytoplasm. *See id.* ¶ 44. Upon binding to a target antigen on the surface of a target cell, signals from the intracellular T-cell signaling domain induce the T-cell to release cytotoxic agents, killing the target cell. *See id.*

According to Dr. Plough, one advantage of this technology is the ability of a small initial population of CAR-transformed T cells to replicate (expand) first *in vitro* and, subsequently, in the patient’s body. *Id.* ¶¶ 42, 47. Dr. Plough further testifies that CAR proteins have a modular design

conducive to swapping antigen recognition moieties using a common framework. *See, e.g., id.* ¶¶ 67–72, 76.

Example 2 of the '342 patent discloses the construction of expression vectors encoding seven CAR constructs summarized in Table 1. *Id.* at 18:55–22:10; *see* Ex. 1003 ¶¶ 156–161. As shown in Table 1 the amino acid sequence of these CARs is identified as SEQ ID NO: 4–12, respectively. *Id.* According to Dr. Plough, the antigen recognition domain in these CARs consists of one of three scFvs derived from mouse-anti-human-BCMA antibody sequences disclosed in Kalled (Ex. 1010) asserted in Ground 1. *See* Ex. 1003 ¶ 159 (citing Ex. 1001 18:60–19:20); *see also* Ex. 1001, 19:3–5, 20:12–15 (referencing a 2003 paper by “Cooper et al.” for the scFv linker sequence). With respect to the remaining CAR elements, the '342 patent discloses that “[t]he sequences used for CD8 α , CD28, CD3 ζ , 4-1BB (CD137), and OX40 (CD134) were obtained from the publicly available National Center for Biotechnology Information (NCBI) database.” Ex. 1001, 19:3–5, 20:12–15. According to the '342 patent, CARs were ligated into lentiviral and/or retroviral vectors and transduced into human T-cells. *Id.* at 20:24–22:9. Examples 4–6 report the results of *in vitro* and *in vivo* (mouse model) testing against MM cells using one of the CARs disclosed in Table 1. *See generally id.* at 25:62–28:20, Figs. 7C, 7D.

F. Prosecution History

1. Restriction Requirement

In the prosecution leading to the issuance of the '484 patent, the Examiner issued a Restriction Requirement requiring election between claims drawn to (I) “a nucleic acid sequence encoding a chimeric antigen

receptor”; (II) “a chimeric antigen receptor”; (III) “a method of destroying cancer cells comprising contacting cancer cells with a nucleic acid sequence encoding a chimeric antigen receptor”; and (IV) “a method of destroying cancer cells comprising contacting cancer cells with a T cell or NK cell producing a chimeric antigen receptor.” Ex. 2005, 582. The Examiner characterized “[t]he technical feature linking Groups I-IV” [a]s “a chimeric antigen receptor which comprises an antigen recognition moiety and a T-cell activation moiety, wherein the antigen recognition moiety is directed against BCMA.” According to the Examiner, this common technical feature was anticipated by Ch’en, as evidenced by Chauhan, for the disclosure of “an antigen recognition moiety directed against BCMA and a T- cell activation moiety.” *Id.*

2. Response to Restriction Requirement and Claim Amendments

Responding to the Restriction Requirement, Applicant argued that

Ch’en fails to disclose a CAR comprising an antigen recognition moiety and a T-cell activation moiety, wherein the antigen recognition moiety is directed against BCMA, as claimed. Ch’en merely discloses anti-BCMA monoclonal antibodies. The antibodies disclosed in Ch’en do not comprise a T-cell activation moiety. That Chauhan may disclose that certain T cells express an Fc receptor which transmits a costimulatory signal upon binding to the Fe domain of IgG does not provide evidence that Ch’en actually discloses a CAR comprising an antigen recognition moiety and a T-cell activation moiety, wherein the antigen recognition moiety is directed against BCMA within the four corners of the Ch’en document. A T-cell activation moiety is missing from the disclosure of Ch’en.

Id. at 593. Applicant also canceled all originally filed claims in favor of new claims 24–43, electing for prosecution of claims 24–36, which it asserted were directed to the chimeric antigen receptor (CAR) of Group II. *Id.* at 591. Each of the newly added claims incorporated the limitations of independent claim 24:

24. (New) A chimeric antigen receptor (CAR) comprising an antigen recognition moiety and a T-cell activation moiety, and wherein the antigen recognition moiety is directed against B-cell Maturation Antigen (BCMA).

Id. at 588.

Among the then-pending claims depending from claim 24, claim 29 stated that “the CAR further comprises a transmembrane domain,” which was further limited in claim 30 to “a CD28 transmembrane domain or a CD8a transmembrane domain.” *Id.* Also depending from claim 24, claim 34 recited a “CAR compris[ing] the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.” *Id.* at 589. Claim 38 was directed to a nucleic acid encoding the same amino acid sequences recited in claim 34. *Id.*

3. Office Action, Responsive Amendment, and Allowance

In the subsequent Office Action, the Examiner rejected claims 24–27, 31–33, 37, 41 and 43 as anticipated by Ch’en, and claims 24–28, 31–33, 35–37 and 39–43 as anticipated by Kalled. *Id.* at 603–605. Referencing the Ch’en rejection, the Examiner found that “*any* anti-BCMA IgG antibody is within the scope of claims 24–27, 31–33, 37, 41 and 43.” *Id.* (emphasis added). As applied to both rejections, the Examiner reasoned that the

claimed “T-cell activation moiety” read on the Fc receptor domain of Ch’en and Kalled’s antibodies. *Id.* at 603, *see id.* at 605 (referencing prior argument). According to the Examiner:

Instant claim 24 is directed to a chimeric antigen receptor (CAR) comprising an antigen recognition moiety directed against BCMA, and a T-cell activation moiety. Since there are no structural or functional limitations on the recited “T-cell activation moiety,” any “moiety” capable of activating any aspect of T cell activity is within the scope of the claim. In particular, an Fc domain of any antibody is a T-cell activation moiety within the scope of the claim, because, as one of skill in the art is aware, IgG antibodies bind to activating Fc receptors on T cells via the Fc domain.

Id. at 603.

With respect to Kalled, in particular, the Examiner stated:

The instant specification admits at page 25 that anti-BCMA monoclonal antibodies “C12A3.2” and “C11 D5.3” were obtained from International Patent Application Publication WO 2010/104949 (Kalled et al.) and the amino acid sequences of the heavy chain variable regions and light chain variable regions of these antibodies were used to design scFvs incorporated into the inventive anti-BCMA CARs as the antigen recognition moieties.

Id. at 604. Further noting the identity between Kalled’s anti-BCMA antibodies C11 D5.3, C12A3.2 and C13F12.1 and scFv portions of SEQ ID Nos: 4–12 of the Specification, the Examiner found that Kalled discloses the same CDRs as claimed in claims 35, 36, 39, and 40, and further teaches that these antibody recognition elements can be in single-chain (scFv) format as required by claim 12. *Id.* at 605.

Notably, the Examiner did not apply Ch'en or Kalled to claims 34 and 38, which recited SEQ IDs encoding complete CARs including transmembrane domains. The Examiner merely objected to the form of claims 29, 30, 34, and 38 as being dependent on a rejected base claim, and indicated that these claims (each of which expressly or implicitly included a transmembrane domain) "would be allowable if rewritten in independent form." *Id.* at 605.

The Applicant amended the claims as indicated in the Office Action. *Id.* at 727–732. The Examiner allowed the '342 patent to issue without substantive comment. *Id.* at 745–749

G. Principles of Law

Petitioner challenges claims 1–9, 13, 17, 19 as obvious under 35 U.S.C. § 103(a). A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence

of nonobviousness, if any.⁵ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

As noted in our Introduction to this Decision, we exercise our discretion to deny institution of an *inter partes* review pursuant to 35 U.S.C. § 325(d). As such, we need not discuss in detail, the merits of Petitioner’s obviousness challenge. Nevertheless, to the extent the definition of a person of ordinary skill in the art or the meaning of certain claim terms is relevant to this proceeding, we address them below. We also note that the parties’ arguments with respect to §325(d) substantially relate to the Milone and Kalled references of the asserted Ground. To provide context for those arguments, we similarly provide an overview of those references.

H. 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) (2019). 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.* “[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Tech., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

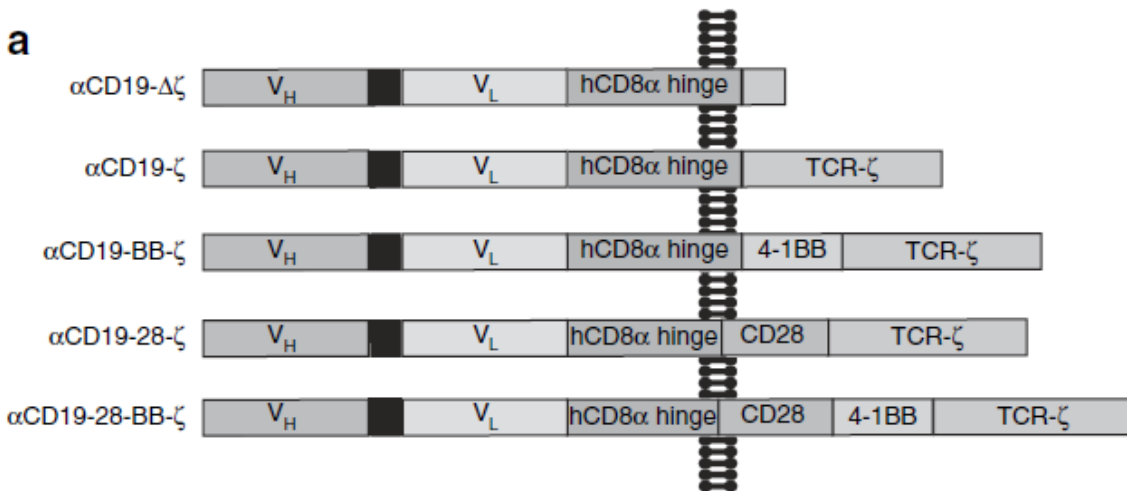
⁵ Patent Owner has not presented evidence of objective indicia of non-obviousness. *See* Prelim. Resp. 64–65; Prelim. Resp.

Relying on the intrinsic record and the testimony of Dr. Plough, Petitioner contends that one of ordinary skill in the art would have understood the “antigen recognition moiety” of claim 1 to “include[] a monoclonal antibody or an antigen-binding portion thereof, such as an scFV.” Pet. 35–36 (citing Ex. 1001, 5:12–15, 6:9–10, claim 1, 2; Ex. 1003 ¶¶ 191–196). Petitioner similarly contends that one of ordinary skill in the art would have understood the “T-cell activation moiety” of claim 1 to “include[] a transmembrane domain and one or more T-cell signaling domains.” Pet. 36 (citing Ex. 1001, 7:4–6, claims 1, 7; Ex. 1003 ¶¶ 197–202). Patent Owner does not dispute Petitioner’s proposed definitions in this proceeding. Prelim. Resp. 43.

Petitioner’s proposed definitions are reasonable in light of the present record and we apply them for clarity.

I. Overview of Milone (Exhibit 1009)

According to Milone, “[p]ersistence of T cells engineered with chimeric antigen receptors (CARs) has been a major barrier to use of these cells for molecularly targeted adoptive immunotherapy.” Ex. 1009, 1453. To



address this issue, Milone investigates CD137 signal transduction domain 4-1 BB as a CAR costimulatory element. Ex. 1009, 1453. Milone's Figure 1a is reproduced below.

Figure 1a depicts a series of CAR and CAR-like constructs embedded in a cell membrane using a common hCD8 α hinge element as a transmembrane domain. *Id.* at Fig. 1a. Four of the constructs contain the TCR- ζ intracellular T-cell receptor domain. *Id.* CAR α CD19-28- ζ further contains a previously-used CD28 costimulatory domain, whereas CARs α CD19-BB- ζ and α CD19-28-BB- ζ contain the 4-1 BB costimulatory domain, with or without CD28, respectively.

Each of Milone's constructs also contains an anti-CD19 scFv antigenic recognition domain as illustrated "VH" and "VL" elements separated by a linker (black box). *Id.* at Figs, 1a, c. With respect to α CD19 target specificity, Milone explains:

We chose the human CD19 antigen as our initial target for several reasons: (i) CD19 displays a pattern of expression that is highly restricted to B cells and B-cell progenitor cells, (ii) CD19 does not appear to be expressed by hematopoietic stem cells permitting the targeting of the B-cell lineage without affecting other hematopoietic lineages, and (iii) CD19 is widely expressed by malignant cells that are derived from the B-cell lineage including most lymphomas and lymphocytic leukemias.

Id. at 1454 (internal citations omitted). Using a lentivirus gene transfer approach, Milone expressed the above constructs in primary human T-cells. *Id.* at 1453. The transfected cells were tested *in vitro* and in a mouse xenograft model of primary human pre-B-cell acute lymphoblastic leukemia. *Id.*

Milone reports that, as expected, “the addition of the CD28 intracellular domain into CARs enhances the *in vitro* proliferation and cytokine production of T cells stimulated through these receptors.” *Id.* at 1461. CARs containing the 4-1BB costimulatory element, however, proved superior in the *in vivo* model. According to Milone, “the α CD19-28- ζ modified T cells failed to show a significant improvement in antileukemic efficacy using our primary pre-B ALL model compared with the α CD19- ζ modified T cells.” *Id.* at 1462. In contrast, cells transfected with CARs containing the 4-1BB element, “could survive for at least 6 months in mice bearing tumor xenografts” and, “many animals had long-term control of leukemia for at least 6 months.” *Id.* at 1457–1461; *see, e.g., id.* at Fig. 6d (enhanced survival of mice treated with T cells expressing α CD19-BB- ζ).

Summarizing their *in vivo* work, Milone states that “CARs containing [the 4-1BB element] exhibited the greatest antileukemic efficacy and prolonged (>6 months) survival *in vivo*, and were significantly more effective than cells expressing CARs containing TCR- ζ alone or CD28- ζ signaling receptors.” *Id.* at 1453. Milone attributes the enhanced persistence and anti-tumor effects of these constructs to antigen-independent proliferative effects conferred by the inclusion of the 4-1BB costimulatory domain. *Id.* at 1453, 1462. Milone concludes that “incorporation of the CD137 signaling domain [4-1BB] in CARs should improve the persistence of CARs in the hematologic malignancies and hence maximize their antitumor activity.” *Id.* at 1453.

J. Overview of Kalled (Exhibit 1010)

Kalled teaches that B cell maturation antigen (BCMA) “has been shown to be expressed on the surface of plasmablasts (i.e., plasma cell precursors) and plasma cells, and is believed to stimulate survival.” Ex. 1010 ¶ 5. And although “[h]uman BCMA protein has been detected on various subtypes of CD38[±] B cells, particularly plasma cells BCMA expression could not be detected on naïve or memory B cells.” *Id.* ¶ 6.

Kalled discloses antibodies, antibody fragments, and CDRs that bind to BCMA, including monoclonal antibodies, chimeric antibodies, Fab fragments and single-chain antibodies.⁶ *Id.* ¶¶ 15–35. Specific embodiments include antibodies A7D1 2.2, C 11D5.3, C12A3.2, and C13F12.1. *See id.* ¶¶ 18–25; *see also* Table 1, Sequence Listing (identification and sequence of anti-BCMA antibodies).

According to Kalled, “expression of BCMA on the surface of some B cells provides a marker by which those cells may be specifically targeted” and provides “a potential target for B cell-related diseases.” *Id.* ¶¶ 5, 8. In this respect, Kalled shows that chimeric variants of anti-BCMA antibodies recognize, and mediate killing of, human plasmacytoma cells⁷ *in vitro*. *Id.*

⁶ On the record before us, we interpret Kalled’s disclosure of single-chain antibodies to encompass, if not equate to, scFv. *See* Ex. 1003 ¶ 224 (citing Ex. 1010 ¶¶ 17, 22).

⁷ Petitioner and Dr. Plough equate Kalled’s plasmacytoma lines with multiple myeloma. *See* Pet. 45; Ex. 1003 ¶ 232. Patent Owner does not object to this characterization. We understand that a multiple myeloma is comprised of multiple plasmacytomas such that Kalled’s use of these cell lines is relevant to the treatment of multiple myeloma. *See* Ex. 1005 ¶ 18.

¶¶ 74–78, Example 8. Kalled further demonstrates that such antibodies mediate the killing of human splenic plasma cells in a humanized mouse model. *Id.* ¶¶ 79–88, Example 8). Kalled expressly claims administration of anti-BCMA antibodies for the treatment of, e.g., “a B cell-related disorder” (claim 19) comprising “a plasma cell malignancy” (claim 22) such as “multiple myeloma” (claim 23).

Kalled further teaches embodiments in which the antibodies or antibody fragments of the invention use BCMA to “target” B cell lymphomas. In essence, such targeting can be generalized as follows: antibodies or antibody fragments of the invention specific to the BCMA surface antigen of B cells are, e.g., injected into a subject and specifically bind to the BCMA cell surface antigen of (ostensibly) both normal and malignant B cells; this binding leads to the destruction and/or depletion of neoplastic B cells. Additionally, chemical agents or radioactive labels having the potential to destroy cancer cells and/or tumors can be conjugated to the antibodies or antibody fragments of the invention such that the agent is specifically “delivered” to the targeted B cells, such as, e.g., neoplastic B cells.

Id. ¶ 45.

K. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the problems encountered in the art, the art’s 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. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner contends a person of ordinary skill in the art at the time of the invention would have had:

at least a Ph.D. (or equivalent experience) in molecular biology, immunology, biochemistry, or a related field, or a medical degree, and also would have been familiar with the design of CAR-Ts and/or the use of CAR-Ts as a therapy for cancers.

Pet. 7–8; *see* Ex. 1003 ¶ 17; Ex. 1005 ¶ 12. Petitioner asserts that “the precise definition of a POSA will not affect the obviousness analysis set forth herein for the Challenged Claims.” Pet. 8.

Patent Owner does not dispute Petitioner’s proposed definition, but states that the person of ordinary skill in the art would “[t]ypically” . . . have had an M.D. or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, or a related discipline, with at least two years of experience in conducting laboratory research on chimeric T cell receptors.” Prelim. Resp. 44 (citing Ex. 2001 ¶ 20). According to Patent Owner, the ordinarily skilled artisan “would have had knowledge of the scientific literature and have skills relating to chimeric T cell receptors and methods of using such receptors” and “may have worked as part of a multidisciplinary team” and been able to draw on the specialized skills of, for example, an immunologist, and/or a clinical oncologist. *See id.* at 43–44.

Considering the record before us, both parties present reasonable definitions of one of ordinary skill in the art. For the purpose of this proceeding, we consider one of ordinary skill in the art as having had an M.D. or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, or a related discipline, with at least two years of experience in conducting laboratory research on chimeric T cell receptors and/or the use of CAR-T immunotherapy. Consistent with Patent Owner’s proposed definition, the ordinarily skilled artisan may have worked as part of a

multidisciplinary team and been able to draw on the specialized skills of, for example, an immunologist, and/or a clinical oncologist.

Considering the background and experience of the parties' technical experts, we find that Drs. Pough, Deol, and Atanackovic meet or substantially exceed those requirements and are qualified to provide testimony as to the understanding of one of ordinary skill in the art in this proceeding. *See, e.g.*, Ex. 1003 ¶¶ 4–14 (Plough); Ex. 1005 ¶¶ 3–9 (Deol); Ex. 2001 ¶¶ 4–14 (Atanackovic).

II. 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).⁸

As more recently explained in *Advanced Bionics, LLC v. MED-EL Electromedizinische 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

⁸ Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

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.

The sole ground of the Petition relies on Milone in combination with Kalled. Pet. 7. In short, Petitioner argues that one of ordinary skill in the art would have found it obvious “to target MM by making Milone’s CARs (and CAR-T cells) using the antigen-recognition domain directed against BCMA taught by Kalled, in place of an anti-CD19 domain.” *Id.* at 46. According to Petitioner,

[t]he ***exact CAR framework claimed in the ’342 patent*** was already known and taught in Milone, for the ***exact purpose*** set forth in the patent—treating blood cancers. The ***only*** difference between Milone and the Challenged Claims was swapping one antigen cancer target (CD19) for another (BCMA). But that was nothing new, for the ***exact anti-BCMA antigen-recognition domain*** in the ’342 patent was already known and taught in Kalled, again for the ***exact purpose*** set forth in the ’342 patent—to bind to BCMA to treat another blood cancer, multiple myeloma.

Id. at 7. Petitioner further argues:

In making the combination of Milone’s CAR framework with Kalled’s anti-BCMA antigen-recognition domain, a POSA would have a reasonable expectation of success for making a functional CAR to BCMA, given that CARs just like Milone’s had been redirected to multiple targets (and had demonstrated efficacy), and that antibodies directed against BCMA were known and already shown to recognize BCMA on MM cells.

Id. at 6.

Patent Owner argues that during prosecution of the ’342 patent, Kalled (WO 2010/104949 A2) was repeatedly presented to the Examiner and formed the basis of an anticipation rejection under 35 U.S.C § 102(b).

See, e.g., Prelim. Resp. 8–9; Ex. 2005, 469 (IPRP⁹ reference D5); 485 (Kalled submitted as IDS document “AN”), 604–605 (anticipation rejection over Kalled). Petitioner does not dispute that Kalled was before the Examiner. *See, e.g.*, Pet. 39–40 (discussing anticipation rejection over Kalled); Prelim. Resp. 8.

There is no evidence that Milone was before the Examiner. Patent Owner and its expert contend, however, that Milone is cumulative to at least fourteen references cited in the prosecution of the ’342 patent. Prelim. Resp. 10–21; Ex. 2001 ¶¶ 28–77 (detailed comparison of Milone’s CAR construct to those used in Kochenderfer (Ex. 1051); Imai (Ex. 2004); Porter (Ex. 1066); Kalos (Ex. 1049); Cartellieri (Ex. 2007); Brentjens (Ex. 2003); Zhao (Ex. 1081); Jensen (Ex. 2008); JP 2012-501180 (Ex. 2006); Cooper (Ex. 2009); Rosenberg (Ex. 2010); Park (Ex. 2032); Sadelain (Ex. 2011); IPRP (Ex. 2005, 462–472)). Upon reviewing the substance of those references, Dr. Atanackovic concludes that “Milone is substantially the same as at least fourteen references cited in the prosecution history of the ’342 Patent” and that Petitioner’s experts “do not—and cannot—identify any material differences between Milone and the references discussed above.” Ex. 2001 ¶¶ 70–71.¹⁰

⁹ The International Searching Authority’s Written Opinion, International Search Report and International Preliminary Report on Patentability (IPRP) for PCT/US2013/032029, are found at pages 462–472 of the ’342 patent prosecution history. *See also* Ex. 2005, 487 (IDS listing IPRP and International Search Report as documents “BP” and “BQ,” respectively).

¹⁰ Dr. Atanackovic points out that six of these references (Jensen,

Petitioner does not contest Dr. Atanackovic's assessment that the above references disclose CARs identical or substantially similar to that taught by Milone. *See, e.g.*, Prelim. Reply 1–3. Rather, Petitioner argues Milone is not cumulative “because it specifically taught that a CAR containing the 4-1BB element would have advantageous persistence and activity against hematologic malignancies” and, as compared to the art cited in prosecution, “[more] clearly links the 4-1BB CAR framework to efficacy in blood cancers.” *Id.* (citing Pet. 42–54; Ex. 1009, 1453, 1461). Petitioner points, for example, to Milone's disclosure that experiments with a CAR having the 4-1BB costimulatory domain demonstrated “long term control of leukemia for at least 6 months” for some animals in a mouse xenograft model of primary human ALL, and “suggest that incorporation of the [4-1BB] CD137 signaling domain in CARs should improve the persistence of CARs in the hematologic malignancies and hence maximize their antitumor activity.” *See id.*; Ex. 1009, 1453, 1461.

We do not find Petitioner's argument persuasive for the reasons set forth at pages 2–3 of Patent Owner's Preliminary Sur-reply. Milone provides data indicating that CAR constructs including the 4-1BB element were superior to those having only a CD28 costimulatory domain in a mouse xenograft model of primary human ALL, and expressly recognizes the benefit using the 4-1BB element in CAR-T therapy. *See* section I.I, above.

Kochenderfer, Porter, Cooper, Brentjens, and Kalos) were cited in the Specification. Ex. 2001 ¶ 80 (referencing Ex. 2001, 1:59–2:2).

Nevertheless, Patent Owner's unopposed evidence that thirteen primary¹¹ prior art references of record in the '342 prosecution history disclosed CAR constructs identical or substantially identical to Milone's indicates that the use of 4-1BB in CARs was well known and appreciated by those of ordinary skill in the art. Kochenderfer, for example, notes as background that "[s]ignaling of the 4-1BB costimulatory molecule has been shown to enhance T cell proliferation and persistence." Ex. 1051, 689 (citation numbers omitted). Moreover, at least Kalos and Porter disclose the use of anti-CD19 CARs containing the 4-1BB element in leukemia patients. *See, e.g.*, Ex. 1049 (Abstract); Ex. 1066 (Summary); Ex. 2001 ¶¶ 38, 41.

Considering the above, we determine that Milone is cumulative to the art of record during prosecution of the '342 patent.

Patent Owner also argues that the Petition advances the same arguments previously presented to the Office. Prelim. Resp. 21–29. According to Patent Owner, the IPRP included in the prosecution history of the '342 patent "lists a combination of references, including Kalled and multiple CAR-T references [including Rosenberg], having substantially the same disclosures as Milone." Prelim. Resp. 24 (citing Ex. 2001 ¶¶ 64–65, 67). Patent Owner interprets the IPRP as finding obviousness in view of

¹¹ In asserting that Milone is cumulative to fourteen references cited in the prosecution, Patent Owner and Dr. Atanackovic arguably double count Rosenberg based on its citation in the IPRP. *See* Ex. 2001 ¶ 28 (summary table identifying where each of the thirteen primary references disclose scFv α CD19, CD8 α hinge/transmembrane, 4-1BB costimulatory, and CD3 ζ signaling domains as used in Milone).

Rosenberg’s CAR framework (IPRP reference D3) combined with Kalled’s anti-BCMA antibodies (IPRP reference D5). *See id.* at 24–25 (citing Ex. 2005, 469, 471). Although we agree that the IPRP lists Rosenberg and Kalled as references D3 and D5, respectively, it does not expressly apply Kalled anywhere in its reasoned statement with regard to novelty, inventive step, or industrial applicability. *See* Ex. 2005, 469–471. Illustrative of its analysis, the IPRP states:

2.1.1 With respect to claims 1-7:

D3 discloses an isolated or purified nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen recognition moiety and a T-cell activation moiety, and wherein the antigen recognition moiety is directed against B-cell Maturation Antigen (BCMA) (claim 8, 9, SEQ ID 10).

Therefore the subject matter of claim 1 is not new in view of D3.

Id. at 469. The above-cited reference D3 (Rosenberg), however, discloses CARs “hav[ing] antigen specificity for vascular endothelial growth factor receptor-2 (VEGFR-2),” but does not mention BCMA. *See, e.g.*, Ex. 2010 ¶ 41; Ex. 2001 ¶¶ 61–63. Although we might infer that the drafter of the IPRP *intended* to cite Kalled (reference D5) for disclosing “antigen recognition moiety directed against B-cell Maturation Antigen (BCMA),” that information is not present in the document as written, nor are we aware of evidence that the Examiner drew this same inference. Ex. 2005, 469. As such, the IPRP does not, on its face, apply the combination of Rosenberg and Kalled, and we do not presume that an argument based on this combination was properly before the Examiner.

Nevertheless, part one of the *Advanced Bionics* framework requires only that the same or substantially the same art *or* substantially the same arguments were previously presented to the Office. *See Advanced Bionics* at 8. Because it is undisputed that Kalled was before the Examiner, and having determined that Milone is cumulative to other art of record during prosecution, we conclude that the art asserted in this proceeding is substantially the same as art previously presented to the Office. Accordingly, we proceed to part two.

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 seems to have fundamentally misunderstood the CAR-T technology.” Pet. 6. Petitioner bases this assertion on the Examiner’s decision to “reject[] the pending claims as ***anticipated by ordinary antibodies,***” but not even discuss, let alone “issue a single obviousness rejection” in view of the CAR-T prior art of record. *See id.* Petitioner surmises that the Examiner did not understand the difference between CAR constructs and antibodies and, thus, “overlooked that CAR frameworks having the same elements as the ’342 patent were known in the prior art and could have been readily modified to target BCMA using the known antibodies of Kalled.” *See generally id.* at 39–41 (citing, *e.g.*, Ex. 2005 ¶¶ 7–74, 84–89, 247–254, 277–287); Prelim. Reply 3–7. In response, Patent Owner presents evidence that the Examiner understood the distinction between CAR constructs and antibodies, and characterizes Petitioner’s

arguments as mere “speculation” reflecting a disagreement with the outcome of prosecution rather than any error on the part of the Examiner. *See* Prelim. Resp. 29–43; Prelim. Sur-Reply 3–7.

Considering the record before us, we agree with Patent Owner that the Examiner adequately understood the relevant art. Petitioner has failed to demonstrate that the Office erred in a manner material to patentability.

Here, the Specification of the ’342 patent begins with a review of CAR-T immunotherapy as applied to diseases other than multiple myeloma. *See* Ex. 1001, 1:44–2:19 (citations omitted); *see also* Ex. 1005 ¶ 100 (Dr. Deol noting that “[t]he ’342 Patent’s description of known CAR-Ts relies on several of the anti-CD19 CAR-T articles . . . including Ex. 1052 (Kochenderfer 2010), Ex. 1049 (Kalos), Ex. 1066 (Porter), and Ex. 1053 (Kochenderfer 2012)’”); Ex. 2001 ¶ 80 (further noting the Specification’s citation to Jensen (Ex. 2008), Cooper (Ex. 2009), and Brentjens (Ex. 2003)).

The Specification makes clear that CARs are non-naturally occurring proteins including at least the antigen binding domain of an antibody. In particular, the ’342 patent expressly defines a CAR as “an artificially constructed hybrid protein or polypeptide containing an antigen binding domain of an antibody (e.g., a single chain variable fragment (scFv)) linked to T-cell signaling or T-cell activation domains.” Ex. 1001, 4:11–15.

The Specification further explains that, by virtue of their antigen binding domain, “CARs have the ability to redirect T-cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies.” *Id.* at 4:15–19. The Specification discloses that the T-cell activation moiety may

comprise a transmembrane domain derived from, for example, human CD8 α or CD28; and may include intracellular T-cell signaling elements comprising or derived from human CD28, CD3 ζ , 4-1BB, OX40, or CD27. *See, e.g., id.* at 6: 53–7:21. Example 2 of the '342 patent discloses construction of expression vectors encoding seven different CARs, each comprising antigen binding, hinge, transmembrane, and intracellular T-cell signaling elements. *See id.* at 18:55–22:10, Table 1; *see* Ex. 1003 ¶¶ 156–161. In addition, Examples 4–6 disclose the results of testing T-cells expressing one of these constructs against human multiple myeloma cells. *See generally id.* at 25:62–28:20, Figs. 7C, 7D.

Petitioner has presented no persuasive evidence that the Examiner did not read and understand the '342 patent Specification including the relevant structural and functional differences between CARs and antibodies. To the contrary, the Examiner expressly referenced page 25 of the Specification and SEQ ID Nos: 4–6 and 8–12 of the '342 patent during prosecution, thus evidencing an understanding of the disclosure. *See* Ex. 2005, 604–605. Petitioner likewise presents no persuasive evidence that the Examiner did not consider and sufficiently understand the primary references regarding CAR-T immunotherapy that were submitted during prosecution, many of which were also discussed in the Background of the Invention. *See* Ex. 1001, 1:44–2:19.

Petitioner points to the Examiner's rejection of then-pending claims as “*anticipated*” by Kalled's disclosure of *antibodies* directed against BCMA” as evidence that the Examiner erred by confusing the then-claimed CAR with an antibody. Pet. 39–41. In short, the independent claim then at issue

recited: “A chimeric antigen receptor (CAR) comprising an antigen recognition moiety and a T-cell activation moiety, and wherein the antigen recognition moiety is directed against B-cell Maturation Antigen (BCMA).” Ex. 2005, 588; *see generally* Section I.F, above. The Examiner rejected most of the claims in view of the α BCMA antibodies taught by Kalled, but stated that dependent claims 29 and 30—which included a transmembrane domain—“would be allowable if rewritten in independent form.” Ex. 2005, 605. Petitioner appears to argue that this rejection shows that the Examiner did not understand that the “chimeric antigen receptor (CAR)” having a “T-Cell activation moiety,” recited in independent claim 24, differed from Kalled’s antibody at least by having the transmembrane domain expressly called out in claims 29 and 30. Pet. 39–40 (citing Ex. 1003 ¶ 187).

We do not find Petitioner’s argument persuasive for the reasons set forth on pages 34–40 of the Preliminary Response. Most particularly, we note that the phrase “[a] chimeric antigen receptor (CAR)” occurs solely in the preamble of independent claim 24. Terms in a preamble, however, are not generally construed as limiting. *See Allen Eng’g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). More specifically, “when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention,” the preamble is not considered a limitation. *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002).

In the present case, we find it plausible—if not likely—that the Examiner gave no weight to the terms in the preamble of claim 24 such that the remaining language did not expressly or implicitly require either a

transmembrane domain, or a “T-cell activation moiety” specific to CAR constructs. The Examiner appears to have recognized, however, that CAR constructs differ from Kalled’s antibodies at least in having a transmembrane domain as expressly recited in claims 29 and 30. *See* Ex. 2005, 605, 745–749 (allowing amended claims). This view is underscored by the Examiner’s decision not to reject claims 34 and 38 as anticipated by Kalled. *See* Ex. 2005, 604. Notably, claims 34 and 38 recite SEQ ID Nos 4–12, each of which encodes a complete CAR construct and, thus, implicitly includes a transmembrane domain. *See id.* at 589 (claiming a CAR comprising the amino acid sequence of SEQ ID Nos: 4–12 (claim 34) or a nucleic acid encoding the same (claim 38)); Ex. 1001, 9:49–53; Ex. 2001 ¶ 92.¹²

Petitioner suggests that in failing to reject any claim as obvious, the Examiner “mistakenly overlooked” at least thirteen prior art references disclosing CARs and CAR framework elements—including six expressly cited in the Specification. *See* Prelim. Resp. 10–21 (citing Pet. 39; Ex. 2001 ¶¶ 28–77); Pet. 38–41; Prelim. Reply 3–6. We do not find Petitioner’s arguments persuasive. As discussed above, the prosecution history indicates that the Examiner read and adequately understood the disclosure of the ’342 patent. Petitioner provides little evidence that the Examiner summarily

¹² We note that then-pending claims 35, 36, 39, 40, and 42 recited only certain elements from SEQ ID Nos: 4–12, not including the transmembrane domain. *See* Ex. 2005, 589–560. Consistent with our interpretation of the prosecution history, the Examiner rejected these claims as anticipated by Kalled. *Id.* at 604.

ignored the prior art of record, including Jensen, Kochenderfer, Porter, Cooper, Brentjens, and Kalos, which are expressly cited and discussed in the Specification. *See* Ex. 2001, 1:59–2:2; Ex. 1005 ¶ 100; Ex. 2001 ¶ 80.

Petitioner also points to the prosecution of the European counterpart to the '342 patent, and further argues that the Declarations of Drs. Plough and Deol in the instant proceeding provide new evidence of Examiner error warranting institution of trial. Pet. 38; Prelim. Reply 2, 7.¹³ The opinions of the European examiner and Petitioner's experts, however, stand in opposition to those of the Examiner of the '342 patent and Dr. Atanackovic.

“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.” *Advanced Bionics* at 9. While it is unfortunate that the Examiner did not discuss the CAR-T art of record or elaborate on the basis for allowing the '342 patent claims, Dr. Atanackovic provides evidence and reasoned argument why one of ordinary skill in the art would not have been motivated to combine an anti-BCMA antibody and a CAR framework with a reasonable expectation of success. *See generally* Ex. 2005 ¶¶ 103–136. Dr. Atanackovic argues, for example, that BCMA was not considered a viable candidate target for treating multiple myeloma (*id.* ¶¶ 110–120); that off-target binding of the BCMA recognition domain could trigger graft vs host disease (*id.* ¶¶ 108); that some therapeutic antibodies

¹³ We agree with Patent Owner that the opinion of the European examiner in the prosecution of the European counterpart is not dispositive here. *See* Prelim. Sur-reply 6 (citing *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006)).

proved toxic when used in CARs (*id.* ¶¶ 106–107); and that the significant impairment in T cell function accompanying multiple myeloma made CAR-T therapy a poor choice for treating this disease (*id.* ¶¶ 126–130, 135–136).

While we do not adopt Dr. Atanacovic’s arguments, they illustrate non-trivial reasons that could have informed the Examiner’s decision. Considering the record before us, we cannot say that the Examiner of the ’342 patent erred in not rejecting the claims as Petitioner contends. Accordingly, part two of the *Advanced Bionics* framework is not satisfied.

III. CONCLUSION

For the reasons provided above, we exercise our discretion under § 325(d) and decline to institute *inter partes* review based on the Ground presented in the Petition.

IV. ORDER

In consideration of the foregoing, it is ORDERED that the Petition is denied, and no trial is instituted.

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