

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MILTENYI BIOMEDICINE GmbH and MILTENYI BIOTEC INC.
Petitioner

v.

FRED HUTCHINSON CANCER CENTER
Patent Owner

IPR Trial No. IPR2023-
U.S. Patent No. 9,987,308
Issue Date: June 5, 2018

Title: Method and Compositions for Cellular Immunotherapy

**PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 9,987,308**

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I. INTRODUCTION

Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc. (collectively, “Petitioner”) respectfully request that the Board institute inter partes review (“IPR”) and cancel claims 1-16 and 18-31 (“Challenged Claims”) of U.S. Patent 9,987,308 (the “’308 patent,” Ex.1001). The ’308 patent is owned by Fred Hutchinson Cancer Center (“Patent Owner”). The Challenged Claims should be found unpatentable as anticipated and obvious under pre-AIA 35 U.S.C. §§102 and 103.

Claim 1 of the ’308 patent—the only independent claim—describes a composition of chimeric antigen receptor (“CAR”) T cells wherein (1) at least half of the helper-T cells have a “CD62L and/or CD45RA” surface marker and (2) at least half of the cytotoxic-T cells have a “CD62L and/or CD45RO” surface marker. The dependent claims narrow the specified percentages of surface markers and add insignificant limitations that do not change the conclusion of anticipation or obviousness.

The claims are much broader than what is taught by the specification. The specification focuses making a composition enriched for two T-cell subpopulations: naïve helper T cells (T_N) and central-memory cytotoxic T cells (T_{CM}). A “naïve” T cell is one “that expresses CD62L *and* CD45RA”¹ surface markers, while a

¹ In quotes, all emphasis added unless otherwise noted.

“central-memory” T cell is one “that expresses CD62L *and* CD45RO” surface markers. Ex.1001, 7:13-20, 7:31-37, 15:25-31. The ’308 patent claims, however, are much broader because they cover T cells with “CD62L *and/or* CD45RA” and “CD62L *and/or* CD45RO” surface markers. The Challenged Claims are, therefore, not limited to a composition with majority helper T_N cells and majority cytotoxic T_{CM} cells. Instead, most claims cover compositions with a majority of other T-cell subpopulations, such as effector-memory-T cells (T_{EM}) and effector-T cells (T_E)—which are CD62L-negative according to the patent. Most claims also cover compositions where all cells are either T_N or T_{CM} (as opposed to mix of both), since both subpopulations are CD62L-positive.

Because the Challenged Claims were drafted so broadly, many are anticipated. A journal article (Singh) published years before the priority date teaches CAR-T-cell composition surface-marker percentages that fall squarely within the scope of many Challenged Claims. Singh teaches CAR-T-cell compositions for treating blood cancers by targeting the CD19 antigen. During prosecution, Singh was not submitted in an information disclosure statement (“IDS”) nor evaluated by the Examiner. Ground 1 explains that Singh is anticipatory. In the alternative, Ground 2 explains that Singh in combination with another reference (Jensen) renders obvious the same subset of Challenged Claims.

Ground 3 combines Singh with no more than a few other references for each Challenged Claim to render them all obvious. The dependent claims not addressed in Grounds 1 and 2 add trivial limitations well known in the prior art. For example, numerous dependent claims simply specify the antigen targeted by the claimed CAR. These claims recite well-known CAR-T-cell targets. Other dependent claims specify the disease associated with the target. These associations between antigen target and disease state likewise were well-known. Still other dependent claims narrow the surface-marker percentages. But these percentages too are taught in prior-art references. The remaining dependent claims recite that claim 1's T-cell composition proliferates or otherwise performs better than a reference population of T cells. These claims, too, are obvious. It was well known that enrichment of some subpopulations, such as T_{CM} , in a CAR-T-cell composition resulted in better performance.

Ground 4 relies on another article, Mitsuyasu, instead of Singh as the primary reference. Mitsuyasu discloses a clinical study where twenty-four HIV-positive patients had their T cells drawn, which were then genetically modified to target the HIV virus, cultured to grow, and injected back into the patients. Of the twenty-four genetically engineered T-cell compositions, all but one had a majority of T cells that were surface-positive for CD62L and therefore fall within claim 1's scope.

All Challenged Claims should be found anticipated and/or obvious.

II. MANDATORY NOTICES

A. Notice of Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc. are real parties-in-interest.

B. Notice of Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is not aware of any related matters involving the '308 patent.

C. Designation of Lead and Back-up Counsel (37 C.F.R. §42.8(b)(3))

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D. Service Information (37 C.F.R. §42.8(b)(4))

A copy of this Petition, in its entirety, including all Exhibits and a Power of Attorney, is being served by Priority Mail Express, costs prepaid, to the address of the agent of record for the '308 patent: David Carlson, John A. Morgan, and Patent Docket Clerk, Seed IP Law Group LLP, 701 Fifth Ave., Suite 5400, Seattle, WA 98104. Petitioner may be served at the addresses provided above in Section II.C for lead and back-up counsel, and Petitioner consents to electronic service at the above e-mail addresses.

E. Power of Attorney

Power of Attorney is filed concurrently with this petition.

III. PAYMENT OF FEES (37 C.F.R. §42.103)

The required fees are submitted per 37 C.F.R. §§42.103(a) and 42.15(a). The Office is authorized to charge any additional fee due or required to the deposit account of Orrick, Herrington & Sutcliffe LLP: 15-0665.

IV. REQUIREMENTS UNDER §§42.104 AND 42.108

A. Grounds for Standing (§42.104(a))

Petitioner certifies that the '308 patent is available for IPR by Petitioner.

B. Grounds of Challenge (§42.104(b))

Petitioner requests institution and a holding that the identified claims are not patentable:

Ground	Claims	Basis
1	1-7, 14, 16, 21, 26-28	Anticipated under §102 by Singh
2	1-7, 14, 16, 21, 26-28	Obvious under §103 over Singh in view of Jensen
3	1-16, 18-31	Obvious under §103 over Singh in view of Jensen, Mitsuyasu, Cooper, Hudecek I & II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I & II, Sallusto, and Sun (not all references are necessary for each claim)
4	1, 6, 9-16	Obvious under §103 over Mitsuyasu in view of Singh and Cooper

This Petition is supported by the Declaration of Dr. Jonathan Bramson (Ex.1002)(“Bramson”), an expert in the field of CAR-T-cell therapy.

C. Requirements for IPR (§42.108(c))

The Board should institute IPR because this Petition establishes a reasonable likelihood of prevailing with respect to at least one Challenged Claim.

V. PRIORITY DATE

The '308 patent is a national stage entry of PCT/US2012/030388 (Ex.1005), filed on March 23, 2012. The patent claims priority from U.S. Provisional Patent Application No. 61/466,552 (Ex.1006), filed on March 23, 2011. Although this Petition assumes that the '308 patent's priority date is March 23, 2011 (the “Priority Date”), Petitioner reserves the right to challenge the patent's priority claims.

VI. TECHNOLOGY BACKGROUND

A. T Cells

T cells are a type of lymphocyte. T cells detect foreign invaders and secrete helpful cytokines (protein-based molecules). Bramson, ¶19.

T cells include helper-T cells which express the CD4 membrane glycoprotein (“CD4”), and cytotoxic-T cells which express the CD8 membrane glycoprotein (“CD8”). A glycoprotein is a protein with an attached carbohydrate group. *Id.*, ¶20.

Cells that express a high level of a membrane protein can be described with a “+” sign. Immunologists use a “-” sign if a cell expresses a low level of a protein or complete absence thereof. *Id.*

B. T-Cell Subpopulations

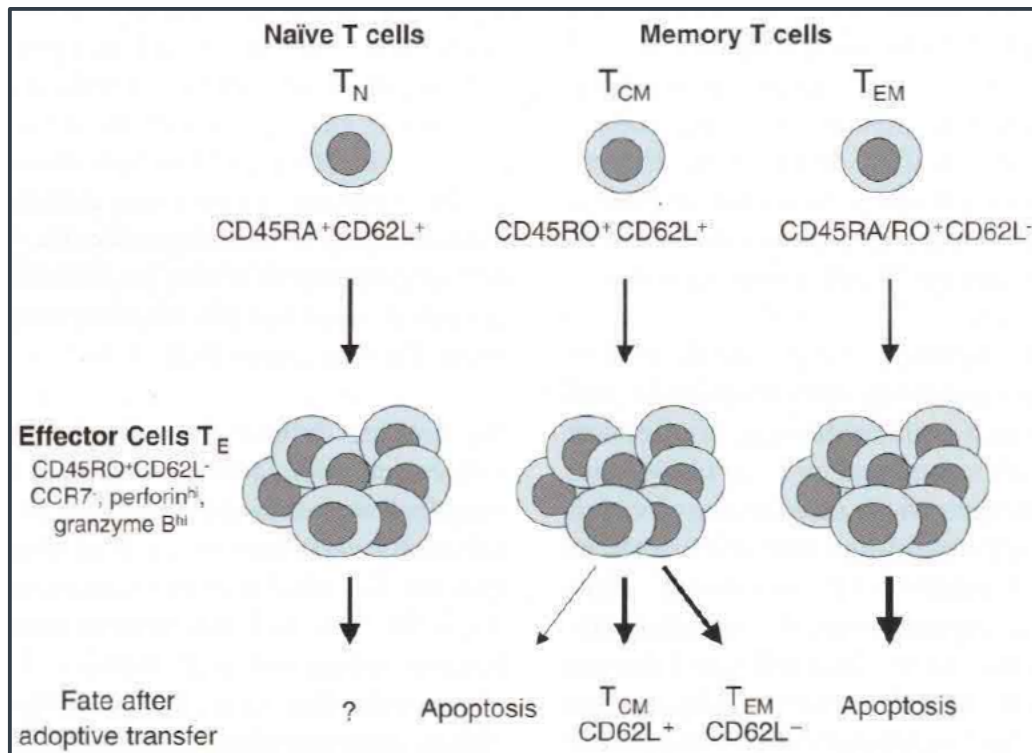
T cells include several categories of T-cell subpopulations. *Id.*, ¶21. T_N have not encountered the antigen to which they can bind. *Id.*, ¶22. Once stimulated by their respective antigenic material, T_N cells activate, proliferate, and produce cytokines. *Id.* Upon activation, T_N cells may differentiate into antigen-specific T_{CM}, T_{EM}, or T_E cells. *Id.*, ¶23. T_E cells are primarily responsible for eliminating infected cells from the body. *Id.*, ¶24. Whereas T_E cells typically die after their target antigen clears from the body, T_{CM} and T_{EM} cells linger, and can respond upon re-exposure to the antigen. *Id.* One way T_{CM} and T_{EM} respond to antigen re-exposure is to differentiate into T_E cells. *Id.* T cells derived from T_{CM} are more capable of persisting long term than those from T_{EM}. *Id.*, ¶¶24-25.

A T cell's persistence refers to its ability to survive. Greater persistence allows a T cell to continue to perform immune system functions and proliferate (*i.e.*, multiply) continually for a longer period. For example, T_{CM} cells persist longer than T_E cells. *Id.*, ¶25.

C. T-Cell Markers

The '308 patent claims recite T-cell subpopulations by their expression of cell surface proteins. *Id.*, ¶26. These proteins, called "T-cell markers," are used to understand which T-cell subpopulations comprise a given composition. *Id.* A T cell's collection of markers is referred to as the T cell's immunophenotype. *Id.*

The claims recite three T-cell markers relevant to this petition: CD45RA, CD45RO, and CD62L. *Id.*, ¶27. As of March 23, 2011, researchers understood those markers could be used to identify T-cell subpopulations: "CD45RA⁺ CD62L⁺ naïve (T_N), CD45RO⁺ CD62L⁺ central memory (T_{CM}), and CD62L⁻ effector memory (T_{EM}).” Bramson, ¶¶27-28, citing Ex.1007, 227. Researchers knew CD45RA⁺ CD62L⁺ indicated a T_N cell, CD45RO⁺ CD62L⁺ indicated a T_{CM} cell, and CD62L⁻ indicated a T_{EM} or T_E cell, as depicted below:



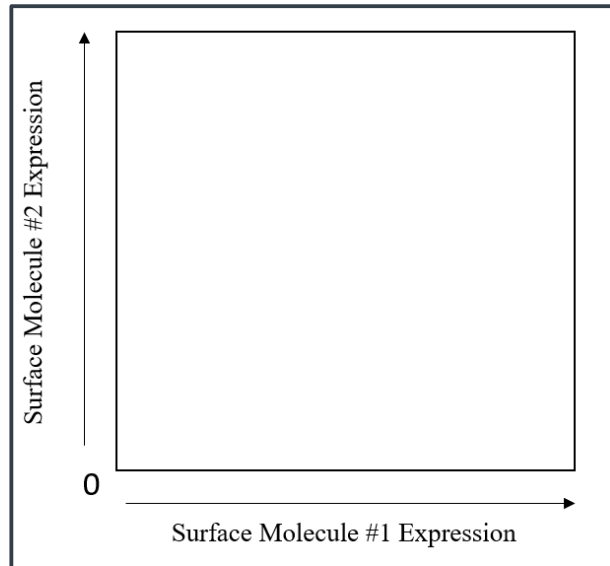
Ex.1007, 228; Bramson, ¶¶29-30.

D. Fluorescence-Activated Cell Sorting (“FACS”)

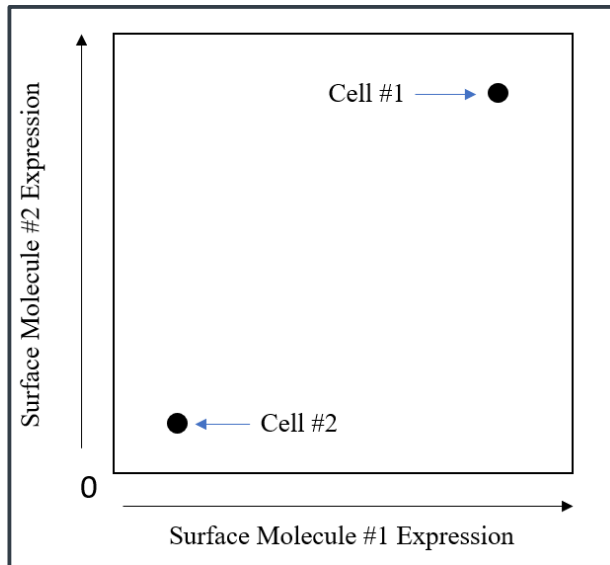
Fluorescence-activated cell sorting (“FACS”) is a technique for sorting cells into subpopulations using fluorescent tags that bind to cell surface markers. *Id.*, ¶¶31-32.

To analyze the number of $CD62L^+$ cells, for example, a scientist would combine the T-cell population with a tag that binds to $CD62L$. *Id.*, ¶33. A flow cytometer would use a laser to detect T cells with the tag attached. *Id.* Those T cells would be counted and separated from T cells that do not express $CD62L$. *Id.* Scientists routinely use flow cytometry to quantify T cell subpopulations. *Id.*, ¶¶34-35,104.

A typical two-dimensional plot of flow cytometry data is shown below. The x- and y-axes each represent expression of a cell surface molecule; here, Surface Molecules #1 and #2:

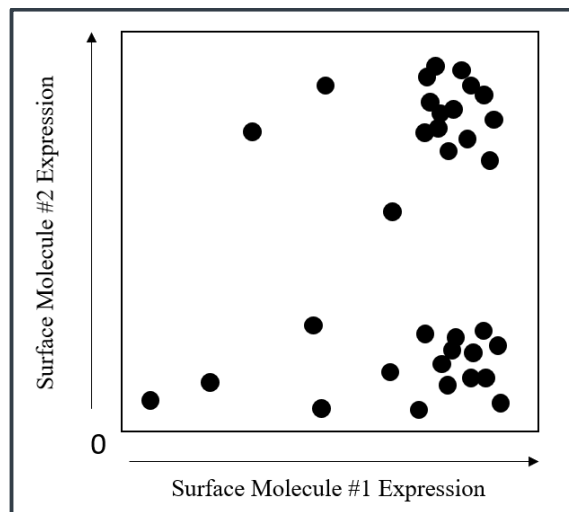


Id., ¶36. In this plot, each dot represents a cell. *Id.*, ¶37. The dot position shows relatively how much of each marker is expressed. *Id.* Here, Cell #1 exhibits relatively high expression of Surface Molecules #1 and #2, whereas Cell #2 expresses those molecules at a low level:



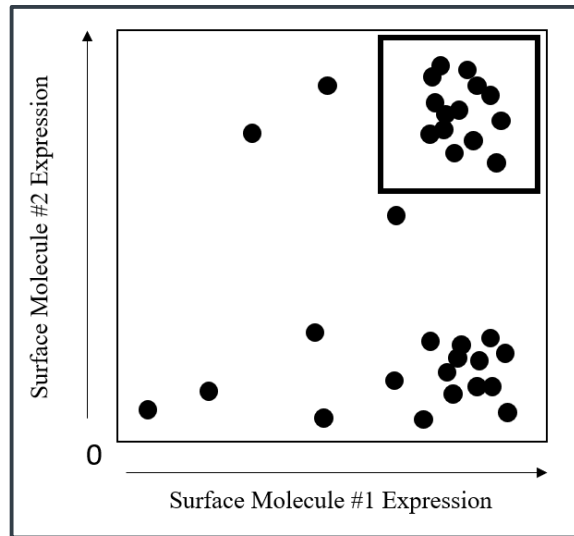
Id., ¶¶37-38.

The following plot shows a population in which most cells express both Surface Molecules #1 and #2 at a high level, or express only Surface Molecule #1:



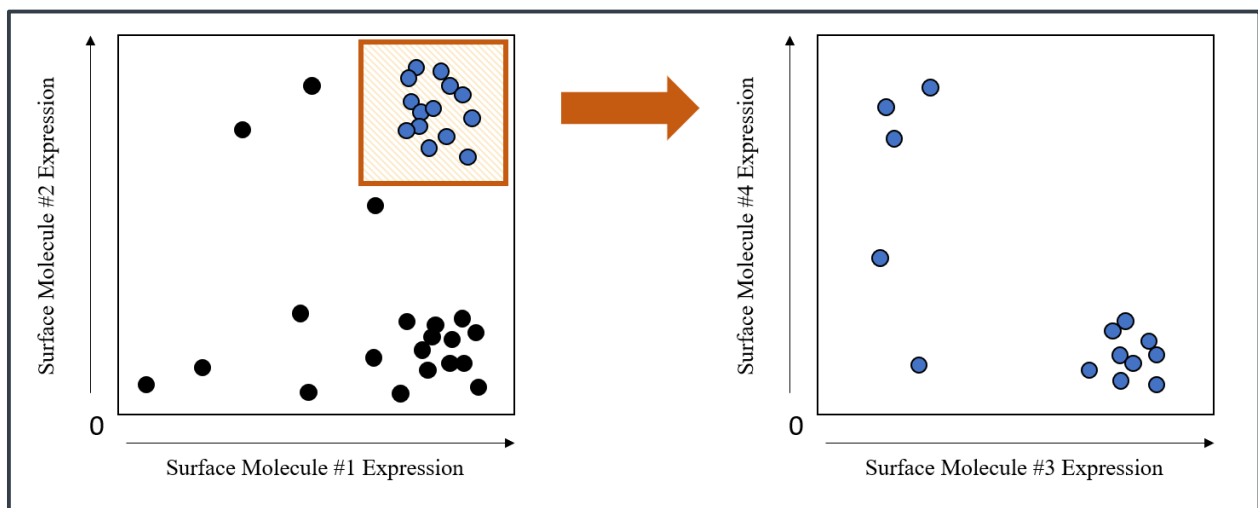
Id., ¶¶39-40.

Flow cytometers enable a user to draw a boundary around a subpopulation:



Id., ¶41.

The user can instruct software to isolate cells within the boundary for further analysis (a process called “gating”), including additional analysis of other molecules, as depicted below:



Id., ¶42. In the example above, most cells expressing high levels of Surface Molecules #1 and #2 are selected, as shown by the box on the left-hand plot. *Id.*, ¶43. The right-hand plot shows that, of these selected cells, most also express a high

level of Surface Molecule #3, but a low level of Surface Molecule #4. *Id.* The arrow from left to right indicates that the right-hand plot is a further analysis of the selected (boxed) cells. *Id.*, ¶¶42-43.

A flow cytometer thus allows researchers to measure expression of multiple surface molecules-of-interest in a cell population, and sort cells into subpopulations. *Id.*, ¶¶44,104; Ex.1001, Figs.1,3,6-7,8A-8B.

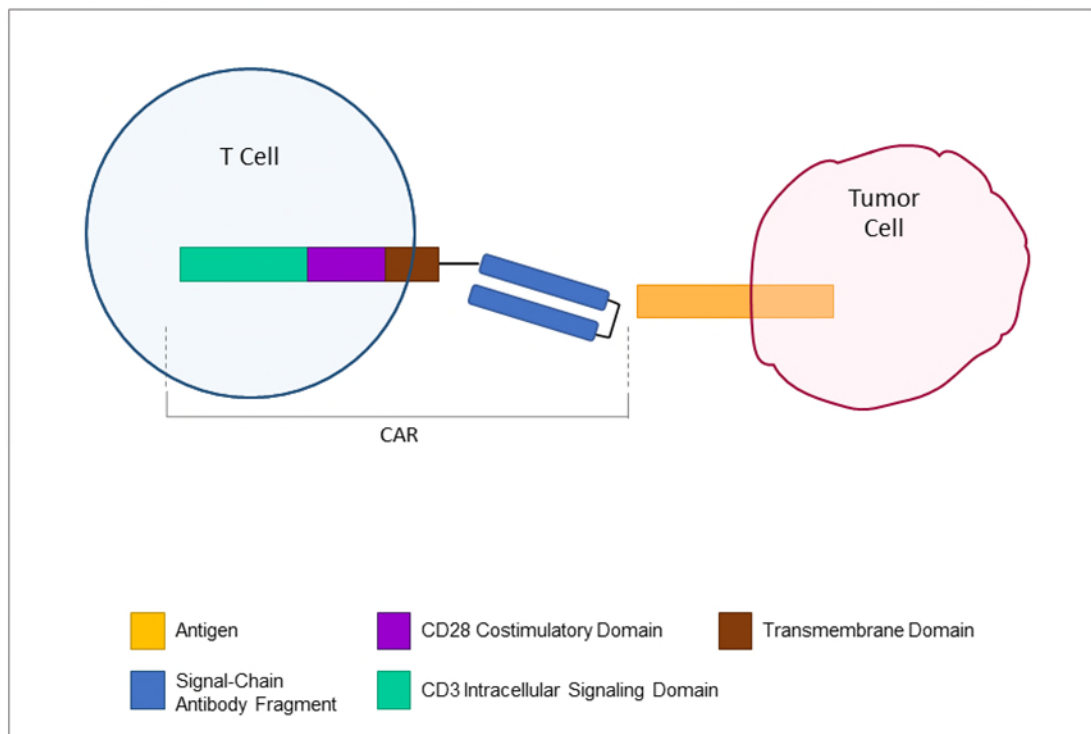
E. Adoptive Immunotherapy

By the 2000s, researchers were developing therapeutic compositions of T cells genetically modified to express receptors targeting an antigen associated with a disorder, such as cancer. Bramson, ¶45. Manufacturing these compositions involved collecting a subject's T cells, modifying them to target a specific antigen-of-interest, and propagating, *i.e.*, growing, those cells to therapeutically acceptable numbers. These compositions are administered to the subject, a technique known as adoptive immunotherapy. *Id.*

By at least March 23, 2011, researchers understood that T cells with certain immunophenotypes, and in certain combinations, performed better than others in adoptive immunotherapy compositions. *Id.*, ¶46. For example, “[c]entral memory T cells (TCM) have a unique ability to self-renew, proliferate, and differentiate into effector TCM, which suggests that [TCM] will be most effective and persistent upon adoptive transfer.” Ex.1017, 926; Bramson, ¶¶46-47.

F. Chimeric Antigen Receptors

Naturally occurring transmembrane receptors on a T cell comprise an extracellular ligand-binding domain, a transmembrane domain, and at least one intracellular signaling domain. Bramson, ¶¶48,137. In the 2000s, scientists developed CARs. *Id.*, ¶¶49-50. A CAR is a genetically modified receptor that includes ligand-binding (*e.g.*, antigen-binding), transmembrane, and signaling domains from two or more proteins. Ex.1010, 645; Bramson, ¶¶48,137-38. In the below example, the ligand-binding domain is a single-chain variable-fragment of an antibody (“scFv”) and the signaling domains are from CD3- ζ and CD28:



Bramson, ¶49.

Scientists have developed CAR-T-cell therapies targeting infections (e.g., HIV) and cancers (e.g., B-cell malignancies). *Id.*, ¶51. B-cell malignancies include leukemias, which affect bone marrow and blood, and lymphomas, which affect the lymphatic system. *Id.*, ¶¶51-52.

VII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) is skilled in developing genetically engineered T-cell therapies. The person would possess a relatively high level of skill and have at least a Ph.D., together with several years of experience in researching and publishing academic articles concerning T-cell therapies. A POSA would be knowledgeable about laboratory techniques related to engineering and testing the function of genetically modified T cells. *Id.*, ¶53.

VIII. THE ’308 PATENT

The ’308 patent claims an adoptive cellular immunotherapy composition containing CAR-modified, CD4⁺ and CD8⁺, T lymphocytes, where a percentage of the T lymphocytes are surface-positive for specific phenotypic markers. *Id.*, ¶54-55. The dependent claims specify, *inter alia*, well-known antigens to which the CAR binds, diseases associated with those antigens, commonly used CAR components, and percentages of surface positivity for phenotypic markers. *Id.*, ¶56.

The specification repeatedly calls out one particular T-cell composition: CD4⁺ T_N cells combined with CD8⁺ T_{CM} cells. Ex.1001, 17:37-39 (“[T]he CD8⁺ cytotoxic

T lymphocyte cell is a central memory T cell and the CD4⁺ helper T lymphocyte cell is a naïve CD4⁺ T cell.”); Bramson, ¶¶57-59. This is consistent with the specification’s examples, which state “maximum proliferation of the CD8⁺ CAR CTL [cytotoxic-T lymphocytes] in response to stimulation...was observed after co-culture of CD4⁺ N [naïve] CAR T cells with CD8⁺ CM [central-memory] CAR CTL.” *Id.*, 27:21-25; 27:29-31 (“sort purified N, rather than CM, EM or bulk CD4⁺ T cells may be best suited to augment the effector function of CD8⁺ CTL”). Bramson, ¶¶60-61.

The claims, however, cover more than just a combination of CD8⁺ T_{CM} cells and CD4⁺ T_N cells. *Id.*, ¶62. Claim 1 recites:

An adoptive cellular immunotherapy composition containing chimeric antigen receptor-modified CD4⁺ T lymphocytes and chimeric antigen receptor-modified CD8⁺ T lymphocytes, wherein:

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

(b) the chimeric antigen receptor-modified CD8⁺ T lymphocytes contain a chimeric antigen receptor that specifically binds to the antigen and at least 50% of CD8⁺ cytotoxic T lymphocytes in the composition are surface positive for CD62L *and/or* CD45RO.²

² A Challenged Claims list is provided as Ex.1022.

Claim 1's CD4⁺ T cells can be majority surface positive for CD62L, CD45RA, or both. Bramson, ¶62. The specification states that CD62L⁺ can be either T_N or T_{CM} cells. *Id.*, ¶63-64. Therefore, claim 1's CAR-modified CD4⁺ T cells can be either majority T_{CM} or T_N. *Id.*, ¶65-66.

Claim 1's CD8⁺ T cells can be majority surface positive for CD62L, CD45RO, or both. *Id.*, ¶67. The specification states that CD62L⁺ can be either T_N or T_{CM} cells. *Id.*, ¶68. Additionally, a POSA would have understood that CD45RO⁺ T cells include T_{EM} and T_E cells. *Id.*, ¶70. Therefore, claim 1's CD8⁺ T cells can be majority T_N, T_{CM}, T_{EM}, or T_E. *Id.*, ¶¶69-70.

IX. CLAIM CONSTRUCTION

A. “adoptive cellular immunotherapy composition”

The preamble “adoptive cellular immunotherapy composition” is merely a statement of intended use for the claimed compositions and not limiting. *Arctic Cat v. GEP Power Prods.*, 919 F.3d 1320, 1327 (Fed. Cir. 2019)(“[generally,] preamble language is not ... limiting.”), 1329 (“a preamble is not limiting ‘where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use’”).

The specification indicates that the preamble is an intended use. Bramson, ¶75. The '308 patent's title is: “Method and Compositions *For* Cellular Immunotherapy.” Ex.1001, 1:1-2; 18:19-23. Bramson, ¶75. The “Field of the

Invention” explains that “embodiments of the invention relate to methods and compositions *for carrying out* cellular immunotherapy.” Ex.1001, 1:25-27; 16:26-46. Bramson, ¶75.

The ’308 patent claim body recites a structurally complete invention—a composition with specific characteristics. *Id.*, ¶76. “[A]doptive cellular immunotherapy” does not provide antecedent basis for any other claim element, does not “recite[] essential structure or steps,” and is not “necessary to give life, meaning, and vitality” to any Challenged Claim. *Arctic Cat*, 919 F.3d at 1327; Bramson, ¶76. The preamble phrase does not change the structure of the compositions. *Id.* The claimed compositions would be no different if “adoptive cellular immunotherapy” were deleted and the claim began, “a composition comprising...” *Arctic Cat*, 919 F.3d at 1329 (a preamble was non-limiting where “deletion of the disputed phrase from the preamble would not affect the structural definition or operation of the invention”)(cleaned up); Bramson, ¶76.

The claims are similar to those in *Application of Craige*, 188 F.2d 505 (C.C.P.A. 1951). There, the preamble specifying a composition for a veterinary use was not deemed limiting because the use did not “add[] nor detract[] from what the composition actually is.” *Id.*, 509. Likewise, here, the preamble merely states the intended use of the composition. Bramson, ¶75.

Additionally, the Patent Owner never relied on the preamble to traverse Examiner rejections, which supports a finding that the preamble is not limiting. *Catalina Mktg. Int'l v. Coolsavings.com*, 289 F.3d 801, 808 (Fed. Cir. 2002). Ex.1008, 17-32, 43-53, 59-68; Bramson, ¶¶77-79.

To the extent the Board finds the preamble to be limiting, “adoptive cellular immunotherapy composition” should be construed as a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal.” Bramson, ¶81. Although the specification does not recite a formal definition of “adoptive cellular immunotherapy composition” (*Id.*, ¶80), Petitioner’s construction is supported by the specification:

In some embodiments, the cells are ***formulated*** by first harvesting them from their culture medium, and then washing and concentrating the cells in a medium and container system ***suitable for administration*** (a “pharmaceutically acceptable” carrier) in a treatment-effective amount.

Ex.1001, 18:26-30; Bramson, ¶82. Moreover, the specification teaches that T cells of the invention “may be from any mammalian, preferably primate, species, including monkeys, dogs, and humans.” *Id.*, 6:66-7:1. Bramson, ¶¶83-84.

Therefore, to the extent that the preamble is limiting, “adoptive cellular immunotherapy composition” should be construed to mean “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal.” Bramson, ¶85.

B. “and/or”

A POSA would understand the term “and/or,” as it appears in the Challenged Claims, to cover embodiments having the element preceding “and/or,” the element following “and/or,” or both the element preceding “and/or” and the element following “and/or”. *Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1359 (Fed. Cir. 2020)(holding “and/or” in a claim created “three alternative subsets of claim coverage—a directivity dependent microphone only; signal processing means only; and a directivity dependent microphone together with signal processing means”); Bramson, ¶86.

For example, claim 1 recites that the composition’s CD4⁺ T cells “are surface positive for CD62L and/or CD45RA.” Bramson, ¶87. Under the proper construction of “and/or,” the CD4⁺ T cells would satisfy this limitation if surface positive for CD62L, for CD45RA, or for both. *Id.* Claim 1 also recites that the composition’s CD8⁺ T cells “are surface positive for CD62L and/or CD45RO.” *Id.*, ¶88. The CD8⁺ T cells would satisfy this limitation if surface positive for CD62L, for CD45RO, or for both. *Id.*

X. PRIOR ART

A. Adoptive Cellular Immunotherapy Compositions With CD45RA⁺, CD45RO⁺, and/or CD62L⁺ Immunophenotypes Were Known

1. Singh

Singh et al., “Redirecting Specificity of T-cell Populations for CD19 Using the Sleeping Beauty System,” *Cancer Res.* 68(8):2961-71(2008) (Ex.1003)(“Singh”) is a research article that published in 2008 and is §102(b) prior art. *Id.*, ¶89.

Singh’s authors developed a process for manufacturing CAR-T adoptive cellular immunotherapy compositions that “maintain[] a desired T-cell immunophenotype.” Ex.1003, 2961. Bramson, ¶90. Singh reported the immunophenotype for a composition of CD19-specific CAR T cells. Ex.1003, 2963; Bramson, ¶¶90,102. Singh’s process “greatly facilitate[s] trial design infusing CD4⁺ and CD8⁺ CAR⁺ T cells that have desired immunophenotype, including T_{CM}.” Ex.1003, 2962. Bramson, ¶102. It “provides for robust antigen-driven expansion of CD4⁺ and CD8⁺ CAR⁺ T cells to clinically meaningful numbers.” Ex.1003, 2964. Bramson, ¶¶102. Specifically, “after 28 to 35 days, the efficiency of...gene transfer improved CAR expression by ~49 to 60-fold.” Ex.1003, 2965; Bramson, ¶¶102.

Singh’s CAR had an anti-CD19 binding site, a CD28 costimulatory domain, and a CD3 intracellular signaling domain. Ex.1003, 2961; Bramson, ¶¶95-96; Ex.1009, 10996.

After CAR transduction and five weeks of *ex vivo* expansion, Singh's authors analyzed immunophenotypes of the resulting T-cell compositions using FACS analysis. Bramson, ¶¶103-104. The results showed that 83% of Singh's CAR-modified CD4⁺ T cells were CD45RA⁺, 80% of the CAR-modified CD8⁺ T cells were CD45RO⁺, and nearly 99% of the overall CD8⁺ T cells were CD45RO⁺. *Id.*, ¶¶106-108.

Singh also discussed the importance of maintaining CD62L expression and the T_{CM} immunophenotype in adoptive cellular immunotherapies: "CD28⁺CD95⁺CD62L⁺ T_{CM} resulted in longer in vivo persistence...." Ex.1003, 2970. Bramson, ¶¶111-113. Singh's process "supports the outgrowth of T cells with these desired phenotypes [T_{CM}] as our CAR⁺ T cells maintain expression of CD27, CD28, CD45RO, CD95, and CD62L." Ex.1003, 2970; Bramson, ¶112-123.

2. Mitsuyasu

Mitsuyasu et al., "Prolonged Survival and Tissue Trafficking Following Adoptive Transfer of CD4ζ Gene-modified Autologous CD4⁺ and CD8⁺ T Cells in Human Immunodeficiency Virus-infected Subjects," BLOOD 96:785-93(2000) (Ex.1004)("Mitsuyasu") is a research article that published in 2000 and is §102(b) prior art. Mitsuyasu was cited in an IDS during prosecution, but the Examiner did not discuss it in office actions. Ex.1008, 3,10-16, 33-42, 54-58; Bramson, ¶¶124-25.

Mitsuyasu described a clinical trial involving engineered T-cell adoptive cellular immunotherapy. Ex.1004, 786. Bramson, ¶126-127. The authors isolated patients' T cells and transduced them with a “chimeric immune receptor,” which a POSA would understand to be equivalent to a CAR. Section XIV.A.1.b; Bramson, ¶128-30.

The authors analyzed the immunophenotype of the T-cell immunotherapy compositions, including for CD4, CD8, and CD62L, Ex.1004, 786. Bramson, ¶131-32, as shown below:

Patient ID	CD4 (%) [*]	CD8 (%) [*]	CD62L (%) [*]	CD28 (%) [*]	CD25 (%) [*]	Culture days [†]	CD4ζ by PCR [‡]
N215	24	73	83	88	—	13	11
H202	62	38	96	98	88	12	17
C211	17	80	84	91	42	12	12
F209	13	83	—	85	45	12	18
S201	26	72	—	89	36	12	9
Q202	22	77	94	98	77	12	5
S206	52	46	93	96	74	17	49
S212	20	79	95	98	43	12	10
P217	31	68	94	93	39	12	13
G251	22	86	82	87	41	12	17
E207	28	69	73	94	60	12	17
T253	24	77	82	88	55	12	18
L218	13	86	85	94	36	12	15
R255	60	37	79	90	27	12	15
Y254	22	76	94	98	59	12	13
U213	7	92	84	96	43	10	9
D282	23	78	82	95	50	13	16
D212	3	96	44	90	64	14	15
T232	28	70	87	88	34	14	11
D256	12	88	59	74	58	15	15
J233	7	90	81	90	43	14	18
Y292	37	61	96	99	28	12	28
X214	8	90	64	79	49	16	38
C298	26	73	83	63	36	12	57
Mean	24	74	82	90	49	13	19
SD	15	16	13	8	16	2	13

^{*}Percentage of CD3⁺ T cells expressing marker by FACS analysis.
[†]Total number of days in culture for each T-cell lot.
[‡]Transduction efficiency as measured by DNA PCR for CD4ζ.

Id., 788. Bramson, ¶133. The compositions had high levels of CD62L⁺ immunophenotype (an average of 82%). Bramson, ¶¶134-36.

B. The Modularity of Chimeric Antigen Receptors Was Known

1. Cooper

Cooper *et al.*, “Chimeric Antigen Receptor on T Cells,” *ENCYCLOPEDIA OF CANCER*, 2ND EDITION:644-48(2009) (Ex.1010)(“Cooper”) is an entry in a reference text that published in 2009 and is §102(b) prior art. Bramson, ¶137. Cooper provides an overview of CARs. Cooper discloses that, because CARs have a modular structure, investigators can “swap [a] CAR[’s] exodomain with a scFv or ligand that recognizes or binds to a desired cell-surface antigen.” Ex.1010, 648; Bramson, ¶138.

C. CARs Targeting CD19, CD20, CD22, ROR1, CEA, Her2, L1-CAM, and Mesothelin Were Known

1. Hudecek I

Hudecek *et al.*, “Adoptive T-cell Therapy for B-cell Malignancies,” *EXPERT REV. HEMATOL.* 2(5):517-32(2009) (Ex.1011)(“Hudecek I”) is an article that published in 2009 and is §102(b) prior art. Bramson, ¶139-140.

Hudecek I disclosed that “[o]ther surface molecules that are expressed on B-cell tumors have been targeted with CAR-modified T cells in preclinical studies, including CD19 and CD22.” Ex.1011, 524. Bramson, ¶141. Hudecek I also reported on data from a recent study: “T-cell clones derived from T_{CM}, but not those derived from T_{EM} cells were capable of persisting long term, reacquiring the phenotype of

memory cells and populating memory T-cell niches *in vivo* after adoptive transfer.”
Ex.1011, 525; Bramson, ¶142.

2. Hudecek II

Hudecek *et al.*, “CD8⁺ T Cells Engineered to Express a ROR1-Specific Chimeric Antigen Receptor Specifically Recognize ROR1 Positive B-Cell Tumors,” BLOOD 114(22):930(2009) (Ex.1012)(“Hudecek II”) is a conference abstract published in 2009 and is §102(b) prior art. Bramson, ¶143.

Hudecek II presented a rationale for targeting ROR1 for treating B-cell malignancies. Ex.1012, 383 (“Analysis of ROR1 protein expression...revealed...expression on B-CLL, suggesting this molecule is a candidate for targeted immunotherapy of B cell malignancies.”); Bramson, ¶144. The authors “constructed a lentiviral vector that encodes a chimeric antigen receptor...specific for ROR1.” Ex.1012, 383. Bramson, ¶144.

3. Abken

Abken, “Chimeric T Cell Receptors,” in ENCYCLOPEDIA OF CANCER, 2ND EDITION, 649-52(2009) (Ex.1013)(“Abken”) is an entry in a reference text that published in 2009 and is §102(b) prior art. Bramson, ¶145.

Abken explained that “patient’s T cells...can be redirected in vitro toward the autologous tumor cells.” Ex.1013, 651. Bramson, ¶148. Abken observed that this “approach is universal since by inserting the appropriate binding domain...chimeric

TCR, T cells can be redirected toward a broad variety of tumor associated antigens expressed on tumor cells of different entities, including...CEA...Her2...[and] CD20”). Ex.1013, 651; Bramson, ¶¶146-48.

4. Reckamp

Reckamp *et al.*, “CE7 Epitope of L1CAM is a Potential Target for Tumor Specific T Cell Therapy in Lung Cancer,” PROCEEDINGS AMERICAN ASSOCIATION CANCER RESEARCH 49:1099(2008) (Ex.1014)(“Reckamp”) is a conference abstract that published in 2008 and is § 102(b) prior art. Bramson, ¶149.

Reckamp discloses that its authors developed a L1-CAM-targeting CAR. Ex.1014, 1099 (discussing “a L1-CAM specific chimeric antigen receptor...(CE7R).”); Bramson, ¶150. “L1CAM has been shown to be overexpressed in multiple tumors and associated with invasive/metastatic tumor biology.” Ex.1014, 1099; Bramson, ¶150. Reckamp concludes that “[t]he data and future murine modeling will further validate L1-CAM as a target on human lung cancer and potential target for novel T cell therapies.” Ex.1014, 1099; Bramson, ¶150.

5. Carpenito

Carpenito *et al.*, “Control of Large, Established Tumor Xenografts with Genetically Retargeted Human T Cells Containing CD28 and CD137 Domains,”

PNAS 106(9):3360-65(2009) (Ex.1015)(“Carpenito”) is a research article that was published in 2009 and is §102(b) art. Bramson, ¶151.

Carpenito explains that “[m]esothelin is a cell-surface molecule over-expressed on a large fraction of carcinomas, and thus is an attractive target of immunotherapy.” Ex.1015, 3360. Bramson, ¶152. Carpenito’s authors used “[l]entiviral vectors...to express a single-chain variable fragment that binds mesothelin and that is fused to signaling domains derived from T-cell receptor zeta, CD28, and CD137 (4-1BB).” Ex.1015, 3360. Bramson, ¶152. Carpenito disclosed that “[m]esothelin proved to be an attractive target as the retargeted T cells efficiently and specifically killed a variety of tumors that express mesothelin.” *Id.*, 3363-3364; Bramson, ¶152.

D. Using Equivalent Numbers of CD4⁺ and CD8⁺ T Cells in Adoptive Cellular Immunotherapy Compositions Was Known

1. Moeller

Moeller *et al.*, “Adoptive Transfer of Gene-engineered CD4⁺ Helper T Cells Induces Potent Primary and Secondary Tumor Rejection,” BLOOD 106:2995-3003(2005) (Ex.1016)(“Moeller”) is a research article that published in 2005 and is §102(b) prior art. Bramson, ¶153. Moeller was cited in an IDS during prosecution of the ‘308 patent, but the Examiner did not discuss or analyze it in his office actions. Ex.1008, 7, 10-16, 33-42, 54-58. Bramson, ¶154.

Moeller's authors reported that "coinfusing equivalent numbers of engineered CD8⁺ and CD4⁺ T cells led to complete eradication of established tumor in mice, whereas transfer of mainly CD8⁺ T cell was less effective." Ex.1016, 2995. Bramson, ¶155. Moeller states that "[o]ptimal antitumor efficacy was achieved with the addition of equivalent numbers of engineered CD4⁺ and CD8⁺ T cells." Ex.1016, 3001; Bramson, ¶155.

E. Benefits of T_{CM}, which are CD62L⁺ T Cells, Was Known

1. Wang

Wang *et al.*, "The CD19 Chimeric Antigen Receptor Re-directs CMV Specific T Cells Derived from Central Memory T Cells Against Human Acute Lymphoid Leukemia," JIMMUNOTHER. 31(9):926-27(2008) (Ex.1017)("Wang") is a conference abstract published in 2008 and is §102(b) prior art. Bramson, ¶156.

Wang discloses that "[c]entral memory T cells (T_{cm}) have a unique ability to self-renew, proliferate, and differentiate into effector T_{cm}, which suggests that this T-cell subset will be most effective and persistent upon adoptive transfer." Ex.1017, 926-927; Bramson, ¶157. Wang selected for T_{CM} by selecting for T cells that express CD62L using an anti-CD62L antibody. Ex.1017, 927 ("we first selected T_{cm} using the Dreg56 (anti-CD62L) biotinylated antibody and CliniMacs selection."). *Id.* The resulting population would have been 100% CD62L⁺. Bramson, ¶158. Wang's authors transduced their CD62L⁺ T_{CM} with a CD19-specific CAR

named “CD19R.” Ex.1017, 927 (“T cells were...genetically redirected to target CD19 on acute lymphoid leukemia through lentiviral transduction with a CD19-specific chimeric antigen receptor, CD19R.”); Bramson, ¶158.

2. Yang I & II

Yang and co-authors published an article and abstract before the March 2011, respectively, captioned Yang et al., “In Vitro Generated Anti-Tumor T Lymphocytes Exhibit Distinct Subsets Mimicking In Vivo Antigen-Experienced Cells,” *CANCER IMMUNOL IMMUNOTHER* 60:739-49(2011)(Ex.1027)(“Yang I”) and Yang et al., “TCR Engineered and In Vitro Expanded T Lymphocytes Recapitulate the Properties of Central Memory T Cells,” *MOLECULAR THERAPY* 18(Supp.1):S184(2010)(Ex.1028)(“Yang II”). Both are §102(a) prior art. In both, Yang taught T_{CM} cells were an optimal subpopulation for immunotherapy, in part, because they were CD62L⁺ and secreted more IL-2, a cytokine that would cause greater proliferation of cytolytic T cells. Bramson, ¶¶159-63. Yang also manufactured T-cell immunotherapy compositions that had high levels of T_{CM} and >80% CD62L-positivity. *Id.*

3. Sallusto

Sallusto et al., “Two subsets of memory T lymphocytes with distinct homing potentials and effector functions,” *NATURE* 401:708–712(1999) (Ex.1029)(“Sallusto”) was published in November 1999 and is §102(b) prior art.

Sallusto taught that central memory CD4⁺ T cells (CD45RA-CCR7⁺) produce more IL-2 than effector memory CD4⁺ T cells (CD45RA-CCR7⁻), and reported experimental data in support. *Id.*, 709. Bramson, ¶164.

4. Sun

Sun, et al. “Dysfunction of Simian Immunodeficiency Virus/Simian Human Immunodeficiency Virus-Induced IL-2 Expression by Central Memory CD4⁺ T Lymphocytes,” *JIMMUNOL.* 174(8):4753–4760(2005) (Ex.1032)(“Sun”) was published in February 2005 and is §102(b) prior art. Sun taught that a greater percentage of central-memory T cells produce IL-2 as compared to effector-memory T cells, and reported experimental data in support. *Id.*, 4756-4758 (Figure 3, Figure 5, Figure 7); Bramson, ¶165.

F. Formulations for Adoptive Cellular Immunotherapy Compositions Were Known

1. Jensen

Jensen *et al.*, U.S. Patent Application 2004/0126363A1 (Ex.1018)(“Jensen”) published on July 1, 2004, and therefore is §102(b) prior art. Bramson, ¶166.

Jensen discloses a clinical trial protocol that involved CD19-specific CAR-expressing T cells. Ex.1018, [0159]; Bramson, ¶167. Jensen discloses a method for processing T cells into a finished dosage form for patient infusion. Ex.1018, [0162](“Processed cells are resuspended in...0.9% NaCl with 2% human serum albumin in a bag for [sic] suitable for clinical re-infusion.”); Bramson, ¶167.

XI. GROUND 1: INDEPENDENT CLAIM 1 AND DEPENDENT CLAIMS 2-7, 14, 16, 21, AND 26-28 ARE ANTICIPATED BY SINGH

Singh is §102(b) prior art. Bramson, ¶89, 172.

A. Independent Claim 1

Independent Claim 1 reads:

[a] “An adoptive cellular immunotherapy composition”

[b] “containing chimeric antigen receptor-modified CD4⁺ T lymphocytes and chimeric antigen receptor-modified CD8⁺ T lymphocytes,”

[c] “wherein: (a) the chimeric antigen receptor-modified CD4⁺ T lymphocytes contain a chimeric antigen receptor that specifically binds to an antigen”

[d] “and at least 50% of the chimeric antigen receptor-modified CD4⁺ helper T lymphocytes in the composition are surface positive for CD62L and/or CD45RA,

[e] “and (b) the chimeric antigen receptor-modified CD8⁺ T lymphocytes contain a chimeric antigen receptor that specifically binds to the antigen”

[f] “and at least 50% of CD8⁺ cytotoxic T lymphocytes in the composition are surface positive for CD62L and/or CD45RO.”

Bramson, ¶173.

The elements of claim 1, to which reference letters [a]-[f] have been added, are addressed below. The first section demonstrates the prior art disclosed the composition components (elements [a]-[c],[e]). The second section demonstrates the prior art disclosed the percent surface positivity of phenotypic markers (elements [d], [f]). Bramson, ¶174.

1. Limitations Directed to Components of the Claimed Composition

Singh discloses an adoptive cellular immunotherapy composition containing CD4⁺ and CD8⁺ T cells modified with a CD19-antigen-specific CAR (claim elements [a]-[c],[e]). Bramson, ¶175.

Singh discloses results from its authors' successful attempts to develop “a clinically feasible approach to the efficient propagation of CAR⁺ T-cell populations, including T_{CM}.” Ex.1003, 2961. Bramson, ¶176. Singh taught that cells generated using its approach were suitable for use in a clinical trial. Ex.1003, 2971 (“We...will evaluate the CD19-specific T cells...in a next-generation clinical trial.”); Bramson, ¶¶176-177.

a. [a] “[a]n adoptive cellular immunotherapy composition”

As discussed in Section IX.A, the preamble is not limiting because it merely describes the intended use of the claimed composition. Even if it were limiting, Singh discloses this limitation. Bramson, ¶178.

A POSA would have understood Singh disclosed a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal” for several reasons. Bramson, ¶179.

First, a POSA would have known Singh's compositions included T cells from mammals—human subjects. Ex.1003, 2963 (“**Human** T cells were isolated...after

consent”); Bramson, ¶179. *Second*, Singh designed its manufacturing process for the mammalian genome. Ex.1003, 2962 (“The *SB* transposase mediates transposition by...inserting the transposon into...sites in a **mammalian** genome.”). Bramson, ¶180. *Third*, Singh’s CAR, CD19RCD28, was codon optimized for use in humans. Ex.1003, 2962 (“The second-generation CD19RCD28 CAR was **human** codon optimized (CoOp)”); Bramson, ¶181. A POSA would understand “human codon optimization” describes a process of making synonymous changes to a DNA sequence to boost expression of the protein it encodes. Bramson, ¶181. *Fourth*, a POSA would understand a composition intended for use in clinical trials would be suitable for administration to a mammal (*e.g.*, human subject), and that Singh’s authors intended to use their compositions in clinical trials. Ex.1003, 2970 (reporting “a new gene transfer approach for the **clinical** application of T cells”), 2969 (describing manufacturing process “to be used in proof-of-concept **clinical trials**.”); Bramson, ¶182. Singh explains its technology “is readily accessible and practiced in compliance with cGMP for **phase I/II trials**” Ex.1003, 2970; Bramson, ¶182.

Fifth, Singh’s manufacturing process resulted in “clinically meaningful” numbers of T cells. Ex.1003, 2962 (explaining its cells “can be numerically expanded to **clinically meaningful** numbers”); Bramson, ¶183. A POSA would have understood this to mean that Singh’s compositions would be suitable for

administration to a mammal because, at least, the composition had enough T cells to elicit a clinical effect. Bramson, ¶183.

Therefore, Singh discloses “[a]n adoptive cellular immunotherapy composition.” *Id.*, ¶184.

b. [b] “containing chimeric antigen receptor-modified CD4⁺ T lymphocytes and chimeric antigen receptor-modified CD8⁺ T lymphocytes,”

Singh recognized the importance of infusing patients with both CD4⁺ and CD8⁺ T cells. Ex.1003, 2970 (“the presence of CD4⁺ T-helper cells improves the persistence of CD8⁺ antigen-specific T cells.”); Bramson, ¶185. Singh’s authors expected future clinical trials would involve infusion of both CD4⁺ and CD8⁺ T cells. Ex.1003, 2970 (“Next-generation clinical trials...are expected to infuse...both CD4⁺ and CD8⁺ T cells”). Bramson, ¶186.

As a result, Singh’s authors designed their manufacturing process to facilitate infusion of CD4⁺ and CD8⁺ T cells. Ex.1003, 2962 (“[Singh’s process] is predicted to greatly facilitate trial design infusing CD4⁺ and CD8⁺ CAR⁺ T cells”); Bramson, ¶187. And Singh confirmed its compositions contained a combination of CD4⁺ and CD8⁺ T cells, both with subsets that had been modified with a CAR. Ex.1003, 2965 (“CD4⁺ and CD8⁺ T cells readily expressed the CAR”); Bramson, ¶188-189. From this, a POSA would have understood Singh satisfies limitation [b]. Bramson, ¶190.

- c. [c] & [e] “wherein: (a) the chimeric antigen receptor-modified CD4⁺ T lymphocytes [and (b) the chimeric antigen receptor-modified CD8⁺ T lymphocytes] contain a chimeric antigen receptor that specifically binds to an antigen”

The CAR in Singh’s CD4⁺ and CD8⁺ T cells (“CD19RCD28”) specifically binds to the CD19 antigen. Ex.1003, 2961 (describing expression of “a *CD19-specific CAR* in memory and effector T cells”); Bramson, ¶191. Singh confirmed CD19RCD28 confers CD19-dependent signaling to Singh’s T cells, rendering the cells capable of specifically binding CD19 on CD19⁺ tumor cells. Ex.1003, 2961 (“CD19RCD28...provides CD19-dependent signaling”); *Id.* (explaining Singh’s method “results in rapid outgrowth of *CD4⁺ and CD8⁺ T cells expressing CAR* to redirect specificity for CD19⁺ tumor cells.”); Bramson, ¶192. This satisfies limitations [c] and [e]. Bramson, ¶193.

2. Limitations Directed to Phenotypic Marker Surface Positivity

Claim 1 recites that at least 50% of its CAR-modified CD4⁺ T cells “are surface positive for CD62L and/or CD45RA,” and that at least 50% of its CD8⁺ T cells “are surface positive for CD62L and/or CD45RO.” Bramson, ¶194. As discussed in Section IX.B, “and/or,” as it appears in the Challenged Claims is broad: covering embodiments having the element preceding “and/or,” the element following “and/or,” or both the element preceding “and/or” and the element following “and/or.” *Id.*, ¶194. Therefore, prior art that discloses a composition with

at least 50% of its CAR-modified CD4⁺ T cells being CD45RA⁺ and at least 50% of its overall CD8⁺ T cells being CD45RO⁺ meets these claim limitations. *Id.*, ¶195-196. To the extent that Patent Owner argues the CD8⁺-related percentage in claim 1 is meant to be only the **CAR-modified** CD8⁺ subpopulation, this would also be disclosed by the prior art. *Id.*, ¶195.

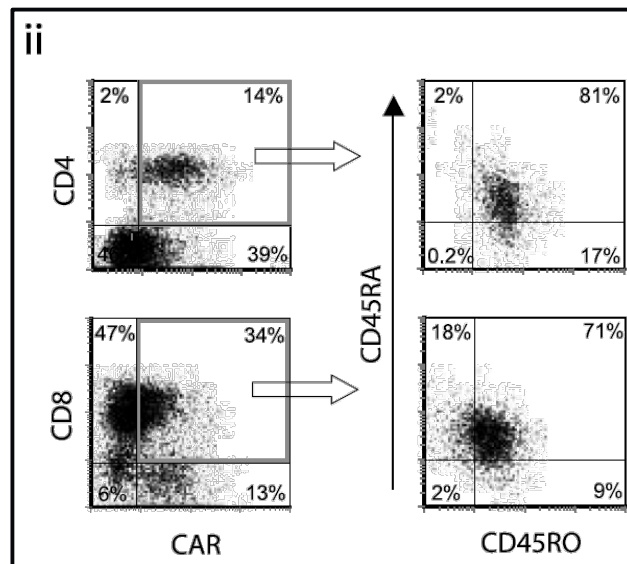
Singh discloses that, of the CAR-modified CD4⁺ T cells in its compositions, at least 50% are surface positive for CD45RA (element [d]). *Id.*, ¶196. Similarly, at least 50% of the overall CD8⁺ T cells, (or the CAR-modified CD8⁺ T cells, if the claim is so-interpreted) in Singh's compositions are surface positive for CD45RO (element [f]). *Id.*, ¶196.

- a. **[d] & [f] “at least 50% of the chimeric antigen receptor-modified CD4⁺ helper T lymphocytes in the composition are surface positive for CD62L and/or CD45RA,” and “at least 50% of CD8⁺ cytotoxic T lymphocytes in the composition are surface positive for CD62L and/or CD45RO”**

As detailed below, 83% of Singh's CAR-modified CD4⁺ helper T cells were surface positive for CD45RA, 80% of its CAR-modified CD8⁺ cytotoxic T cells, and at least 50% of its overall CD8⁺ cytotoxic T cells, were surface positive for CD45RO, thereby satisfying limitations [d] and [f]. *Id.*, ¶197.

Singh details a process for transforming, expanding, and maintaining T cell immunophenotypes involving culturing its CAR-modified T cells. Ex.1003, 2962-2963, 2966 (describing culture on CD19⁺ aAPCs); Bramson, ¶198. After culture and

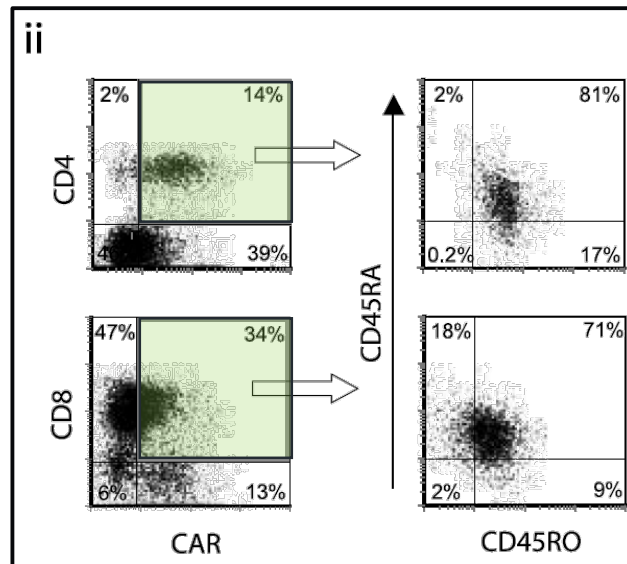
expansion to clinically meaningful numbers at five weeks, Singh's authors assessed CD45RO and CD45RA expression in its T-cell composition using FACS. Singh explains CD45RA and CD45RO are markers of memory cells and that T_{CM} persist longer *in vivo*. Ex.1003, 2968 ("CD45RA and CD45RO...markers are presumably also present on memory cells"); *Id.* (" T_{CM} are associated with long-term persistence after adoptive transfer."); Bramson, ¶199-200. Singh's FACS data for CD4, CD8, CD45RA, and CD45RO expression is shown below:



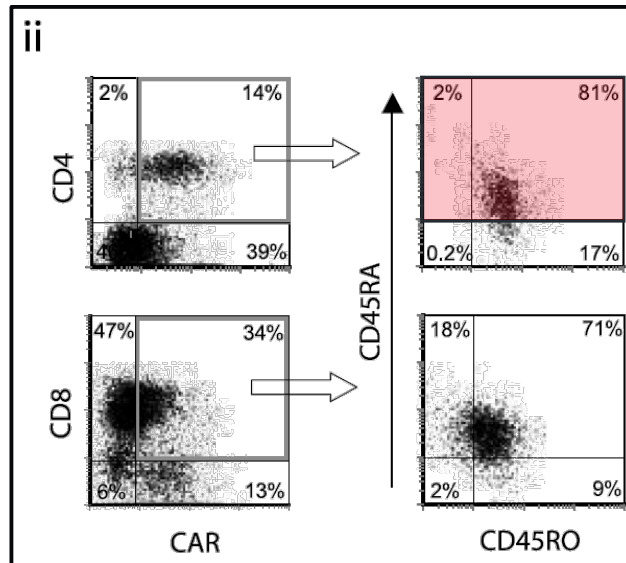
Ex.1003, 2966 (Figure 3.B.ii); Bramson, ¶201.

Singh's Figure 3.B.ii shows FACS results on four dot plots, with each dot representing a single T cell. The two dot plots on the left show a first gating step in which the authors grouped T cells by CAR expression (x-axes), and CD4 (top y-axis) or CD8 expression (bottom y-axis). Bramson, ¶202.

In the first gating step, Singh reports 14% of cells were CAR-modified CD4⁺ and 34% were CAR-modified CD8⁺ in its composition, as shown by the upper-right quadrant of the leftmost dot plots in Figure 3.B.ii (green shading added, below):

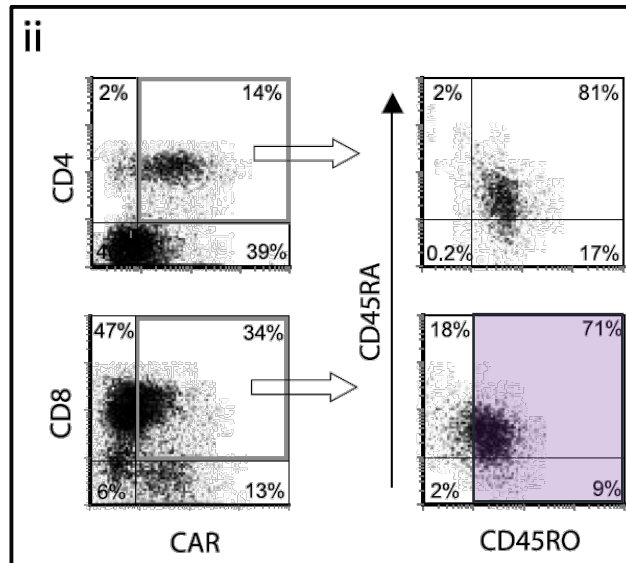


Ex.1003, 2966 (Figure 3.B.ii)(annotated); Bramson, ¶203. As shown on the right side of Fig. 3.B.ii, the Singh authors then used a second gating step to isolate the CAR-modified CD4⁺ and CAR-modified CD8⁺ T cells and assessed their CD45RA (y-axis) and CD45RO (x-axis) expression. Bramson, ¶204. As depicted below, the top quadrants of the upper-right dot plot indicated that of the CD4⁺ T cells that contained the CAR modification, 83% were CD45RA⁺ (red, 2%+81%=83%):



Ex.1003, 2966 (Figure 3.B.ii)(annotated); Bramson, ¶205. It is appropriate to add the subpopulation representing two percent of the composition's cells to the subpopulation representing eighty-one percent of the population because the horizontal line in the dot plot indicates that all cells above that line are CD45RA⁺. Bramson, ¶206.

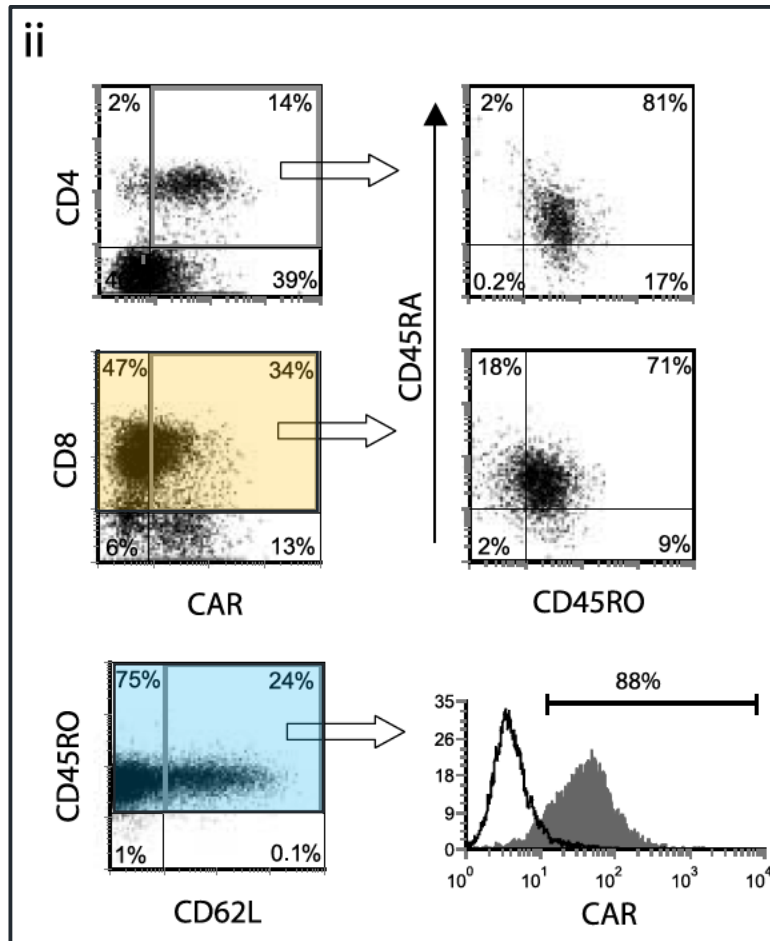
Similarly, Fig.3.B.ii in Singh shows 80% of the CAR-modified CD8⁺ T cells were CD45RO⁺ (purple shading added, 9%+71%=80%):



Id., 2966 (Figure 3.B.ii)(annotated); Bramson, ¶207-208.

Singh thus discloses 83% of its CAR-modified CD4⁺ T cells were CD45RA⁺ and 80% of its CAR-modified CD8⁺ T cells were CD45RO⁺. Bramson, ¶209.

Singh also discloses at least 50% of the overall CD8⁺ T cells in its composition are surface positive for CD62L and/or CD45RO. Fig. 3.B.ii includes a third FACS plot, which is shown below with the other plots discussed above:



Id., 2966 (Figure 3.B.ii)(annotated); Bramson, ¶210.³ As annotated in orange, Singh shows 81% (47%+34%) of cells in its composition were CD8⁺. Bramson, ¶211. As annotated in blue, Singh also shows 99% of its cells (CD4⁺ and CD8⁺) were CD45RO⁺. *Id.*, ¶212. Given this, it is necessary true (mathematically) that the overall CD8⁺ population to comprise at least 50% as CD8⁺ CD45RO⁺ cells in Singh's composition. *Id.*, ¶213.

³ The lower-right panel in Fig. 3.B.ii represents further analysis not relevant to this discussion.

Therefore, Singh discloses an adoptive cellular immunotherapy composition wherein “at least 50% of the chimeric antigen receptor-modified CD4⁺ helper T lymphocytes in the compositions are surface positive for...CD45RA.” Singh’s composition also includes “at least 50% of CD8⁺ cytotoxic T lymphocytes [that] are surface positive for...CD45RO.” Because the claim limitations are written using “and/or,” this data is sufficient to satisfy limitations [d] and [f]. *Id.*, ¶214.

B. Dependent Antigen Claims

1. Claims 2 and 26-28: “wherein the antigen is associated with a disease or disorder”

Claim 2 recites “a disease or disorder selected from a solid tumor, hematologic malignancy,....” Claim 26 depends from claim 2 and recites “the disease or disorder is a solid tumor, hematologic malignancy, or melanoma.” *Id.*, ¶215. Claim 27 also depends from claim 2 and recites “the disease or disorder is a hematologic malignancy.” *Id.*, ¶215. Claim 28 depends from claim 1 and recites “the antigen is a

tumor associated antigen associated with a cancer selected from the group consisting of...B cell lymphoma,...and leukemia.”⁴ *Id.*, ¶218.

As explained in Section XI.A.1.c, Singh’s CAR binds to the CD19 antigen. Singh teaches that CD19 is expressed on B-cell malignancies. Ex.1003, 2961 (describing CD19 as “a molecule constitutively expressed on B-cell malignancies.”). A POSA would have known a B-cell malignancy is a type of hematologic malignancy. Bramson, ¶216 (citing Ex.1011, 517). Singh’s disclosure thus satisfies claims 2 and 26-27. Bramson, ¶¶217,220.

As for claim 28, Singh discloses that CD19 is a tumor associated antigen associated with a cancer because Singh teaches it is expressed by malignant B-cells. Ex.1003, 2961; Bramson, ¶¶217. Moreover, a POSA understood B-cell malignancies encompass B-cell lymphoma and leukemia. Bramson, ¶219 (citing Ex.1011, 518). Singh thus satisfies claim 28 as well. Bramson, ¶220.

⁴ These elements appear to be drafted as Markush groups, and thus are satisfied by a prior-art disclosure of any one of the respective listed diseases or disorders. *Fresenius USA, v. Baxter Int’l*, 582 F.3d 1288, 1297-98 (Fed. Cir. 2009)(“the entire element is disclosed by the prior art if one alternative in the Markush group is in the prior art.”).

Therefore, Singh discloses an adoptive cellular immunotherapy composition wherein the antigen is associated with a hematologic malignancy, including B-cell lymphoma and leukemia. Bramson, ¶219.

2. Claims 3 and 21: “wherein the antigen is selected from ROR1, tEGFR, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, and CEA”

Claim 3 specifies “wherein the antigen is selected from ROR1, tEGFR, Her2, L1-CAM, CD19, CD20, CD22, mesothelin, and CEA,” while claim 21 is limited to “CD19.” Bramson, ¶221. As described in Section XI.A.1.c, Singh teaches this limitation by disclosing a CD19-specific CAR. Bramson, ¶222.

Therefore, Singh satisfies claims 3 and 21. Bramson, ¶223.

C. Dependent CAR Component Claims

1. Claims 4 and 5: “extracellular antibody variable domain or single-chain antibody fragment and an intracellular signaling module”

Claim 4 specifies “wherein the chimeric antigen receptor of (a) and/or (b) comprises an extracellular antibody variable domain or single-chain antibody fragment specific for the antigen and an intracellular signaling module.” Bramson, ¶¶224-25.

Singh discloses that its CAR, designated “CD19RCD28,” includes a single-chain antibody fragment specific for CD19. Ex.1003, 2961 (“CD19RCD28 ... provides CD19-dependent signaling”); Bramson, ¶226. A POSA would have understood CD19RCD28 includes a CD19-specific scFv. Bramson, ¶¶225,227.

Indeed, Singh discloses that the CAR from which CD19RCD28 was derived, designated “CD19R,” “recognizes CD19 via the scFv of a murine CD19-specific monoclonal antibody.” *Id.*, ¶227.

Singh also indicates that its CAR includes an intracellular signaling module. Ex.1003, 2961 (“CD19RCD28 ... provides CD19-dependent signaling through chimeric CD3-ζ and CD28”); Bramson, ¶228. The ’308 patent indicates that an “intracellular signaling molecule” can include CD3 and CD28 intracellular domains. ’308 patent, 17:12-15 (“the intracellular signaling molecule comprises the CD3 intracellular domain, a CD28 domain, [or] a CD28 transmembrane and signaling domain linked to a CD3 intracellular domain”); Bramson, ¶228. A POSA would have understood that CD3-ζ is a CD3 intracellular domain. Bramson, ¶229.

Claim 5 depends from claim 4, and specifies that the CAR in the modified CD4+ and CD8+ T cells includes an intracellular signaling module including “(a) a CD28 costimulatory domain and a CD3 intracellular signaling domain, or (b) a 4-1BB costimulatory domain and a CD3 intracellular signaling domain.” *Id.*, ¶230.

As discussed in relation to claim 4, Singh’s CAR includes a CD28 costimulatory domain and a CD3 intracellular signaling domain. *Id.*, ¶231.

Therefore, Singh discloses a CAR that comprises a single-chain antibody fragment specific for CD19 and an intracellular signaling module. Moreover,

Singh’s intracellular signaling module comprises a CD28 costimulatory domain and a CD3 intracellular signaling domain. *Id.*, ¶¶229,232.

2. Claims 7 and 16: Claims Related to Whether the CAR is the Same in the CD4⁺ and CD8⁺ T Cells

Claims 7 and 16 specify that the CD8⁺ T-cells and CD4⁺ T cells have the same CAR intracellular signaling domain or the same CAR, respectively. *Id.*, ¶¶233,236.

Singh transfected the same CAR—CD19RCD28—into the CD8⁺ and CD4⁺ T cells via a plasmid. Ex.1003, 2963; 2965 (“[W]e observed that peripheral blood- and umbilical cord blood-derived electroporated CD4⁺ and CD8⁺ T cells readily expressed the CAR transposon.”); Bramson, ¶234.

Therefore, Singh satisfies claims 7 and 16. Bramson, ¶¶235,237.

D. Dependent Claims Related to Percentage Surface Positivity of T-Cell Markers

Claim 6 details higher percentage bars for surface positivity of phenotypic markers. Bramson, ¶238. Claim 6 requires an increased positivity percentage of 60% or 80% for CD62L or CD45RA for CD4⁺ T cells or of CD62L or CD45RA for CD8⁺ T cells. *Id.*

Claim 6 recites four claim elements (a)-(d) connected by an “and/or.” Bramson, ¶239. The “and/or” in claim 6 indicates the prior art need only meet one of these four elements. Section IX.B. *Id.*, ¶239. Nonetheless, Singh satisfies all four. Bramson, ¶241. As explained in Section XI.A.2.a, 83% of Singh’s CAR-modified

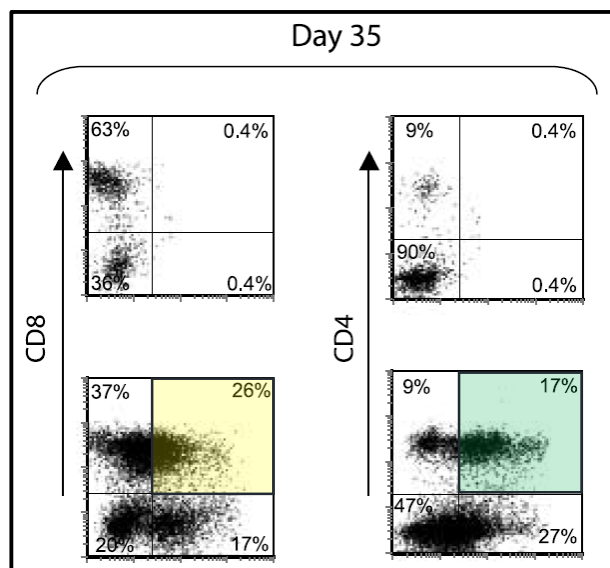
CD4⁺ T cells were CD45RA⁺ (satisfying (a) and (c)), and 80% of the CAR-modified CD8⁺ cells were CD45RO⁺ (satisfying (b) and (d)). *Id.*, ¶240.

Therefore, Singh satisfies claim 6. *Id.*, ¶241.

E. Dependent Ratio Claim

Claim 14 depends from claim 1 and specifies that the CAR⁺ CD4⁺ T cells and CAR⁺ CD8⁺ T cells are present at a ratio of between about 2:1 to about 1:2. Bramson, ¶242.

A 1:2 ratio equals 0.5 and a 2:1 ratio equals 2.0. Bramson, ¶243. Singh's composition comprised 17% CAR-modified CD4⁺ T cells and 26% CAR-modified CD8⁺ T cells, as evidenced by a FACS analysis performed after culture expansion⁵:



⁵ Expansion takes place *ex vivo* after the subject's cells are CAR-modified, before they are re-infused, to ensure clinically useful quantities. Bramson, ¶¶45,101,197.

Ex.1003, 2966 (Fig. 3A)(annotated, x-axes indicate CAR expression); Bramson, ¶244. Seventeen percent divided by twenty-six percent equals 0.65, falling within the scope of the claimed 0.5–2.0 (1:2 to 2:1) range. Bramson, ¶245. Singh thus discloses all elements of claim 14. Bramson, ¶246.

XII. GROUND 2: INDEPENDENT CLAIM 1 AND DEPENDENT CLAIMS 2-7, 14, 16, 21, AND 26-28 ARE RENDERED OBVIOUS BY SINGH IN VIEW OF JENSEN

Ground 2 differs from Ground 1 with the addition of Jensen. Each reference in this Ground was published at least one year prior to March 23, 2011, and is therefore §102(b) prior art. Bramson, ¶247.

A. Independent Claim 1

Ground 1 demonstrates that Singh discloses every element of claims 1-7, 14, 16, 21, and 26-28. *Id.*, ¶247. To the extent Patent Owner argues that Singh does not anticipate each claim element, a POSA would have found any differences to be non-material and obvious.

The Board should not construe the preamble of claim 1 as limiting. Section IX.A; Bramson, ¶248. However, if the Board determines that the preamble is limiting, claim 1 still is obvious. Bramson, ¶249.

A POSA would understand that Singh's authors believed they developed a clinically useful composition. They proposed its use in clinical trials. Ex.1003, 2969

(“here, is a cost-effective gene transfer system...to be used in proof-of-concept clinical trials”). *Id.*, ¶250.

A POSA would have understood that formulating Singh’s composition to be “suitable for administration to a mammal” would have been as simple as diluting the cells in a saline solution, per Jensen’s teachings. *Id.*, ¶¶251-252. Jensen discloses a clinical trial protocol utilizing CD19-specific, CAR-modified T cells. Section X.F.1; Bramson, ¶252. Jensen teaches that, before infusing a T-cell composition into patients, “[p]rocessed cells are resuspended in 100 ml of 0.9% NaCl with 2% human serum albumin in a bag for [sic] suitable for clinical re-infusion.” Ex.1018, [0162]. Bramson, ¶252.

A POSA would have been motivated to combine Singh with Jensen because both references relate to CD19-specific CAR T cell compositions for adoptive cellular immunotherapy. Ex.1003, 2970-71 (“We...will evaluate the CD19-specific T cells...in a next-generation clinical trial.”); Ex.1018, [0159] (“The phase I pilot study determines the safety and toxicity of intravenously infused donor-derived CD8⁺ CTL clones genetically modified to express the CD19R scFvFc:ζ chimeric immunoreceptor”); Bramson, ¶253. Furthermore, Singh explains that its compositions use then-available technologies and already comply with good manufacturing practices (“GMP”) for clinical “phase I/II trials.” Ex.1003, 2970 (asserting that Singh’s process is “accessible” and complies with “cGMP for phase

I/II trials”); Bramson, ¶254. Jensen describes a clinical trial protocol with instructions for formulating a CAR T-cell composition suitable for administration. Ex.1018, [0162]; Bramson, ¶252.

A POSA would have had a reasonable expectation of success in formulating Singh’s compositions to be “suitable for administration to a mammal” according to Jensen’s instructions. Bramson, ¶255. A POSA would have understood that such formulation would have been a simple, routine matter of mixing the cells with a solution of NaCl and human serum albumin in a bag for infusion. Ex.1018, [0162]. Bramson, ¶255.

B. Claims 2-7, 14, 16, 21, and 26-28

As explained in Section XI above, Singh teaches all elements of claims 2-7, 14, 16, 21, and 26-28. Bramson, ¶257.

XIII. GROUND 3: ALL CHALLENGED CLAIMS ARE RENDERED OBVIOUS BY SINGH IN VIEW OF JENSEN, MITSUYASU, COOPER, HUDECEK I & II, ABKEN, RECKAMP, CARPENITO, MOELLER, WANG, YANG I & II, SALLUSTO, AND SUN

Ground 3 differs from Grounds 1 and 2 with the addition of Mitsuyasu, Cooper, Hudecek I & II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I & II, Sallusto, and Sun. Ground 1 demonstrates that Singh discloses all elements of claims 1-7, 14, 16, 21, and 26-28. *Id.*, ¶258. Ground 2 shows that if the claims require a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal,” a POSA would have known that

formulating such a dosage form would be a routine matter of adding the cells to an infusion solution, per Jensen. *Id.*

To be clear, not all additional references in Ground 3 are necessary to teach the elements of any particular Challenged Claim. *Id.*, ¶259. Rather, Singh⁶ plus a few other references are sufficient for any claim, but the sets of references vary. *Id.* ¶260.

- Claims 3 and 18-25 identify antigens to which the CAR specifically binds. These claims are taught by Singh in combination with either Hudecek I, Abken, Hudecek II, Reckamp, or Carpenito;
- Claims 6 and 9-13 concern the percentage of CAR-modified T cells that are surface positive for various surface markers. Singh in combination with Wang and/or Mitsuyasu teaches these claims;
- Claims 14-15 recite limitations concerning the ratio of CD4⁺:CD8⁺ T cells in a composition. Singh in combination with Moeller and/or Mitsuyasu teaches these claims; and,
- Claims 8 and 29-31 require a comparison between aspects of claim 1's composition and one of two reference populations. Singh in

⁶ If the preamble is limiting, Jensen can also be added.

combination with Wang, Hudecek I, Yang I & II, Sallusto and/or Sun teaches the elements of these claims. *Id.*, ¶260-64.

A. Independent Claim 1

Singh, and optionally Jensen, render obvious claim 1 for reasons discussed in Grounds 1 and 2. *See* Sections XI and XII. *Id.*, ¶266. Additionally, Mitsuyasu renders obvious the “adoptive cellular immunotherapy” limitation because the authors successfully administered genetically engineered T-cell compositions to patients. *Id.*

B. Dependent Antigen Claims

1. Claims 3 and 18-25

Singh discloses a CD19-specific CAR, which meets claims 3 and 21. Section XI.B.2; Bramson, ¶267.

Claims 18-20 and 22-25 recite “wherein the antigen is” a specific antigen: ROR1, Her2, L1-CAM, CD20, CD22, mesothelin, or CEA. The prior art rendered obvious targeting each antigen with a CAR-modified T cell. Bramson, ¶268.

A POSA would have been motivated to use CARs targeting other antigens in Singh’s compositions and would have had a reasonable expectation of success in doing so because Singh teaches that its approach is generalizable. Ex.1003, 2970 (“[T]his approach will be of interest . . . for genetically modifying T cells to express *CAR with alternative specificities*”); Bramson, ¶269.

Claim 18 requires the antigen to be ROR1. Bramson, ¶270. Hudecek II teaches targeting ROR1 with a CAR. Ex.1012, 383 (describing “a chimeric antigen receptor...specific for ROR1”); Bramson, ¶271. A POSA would have been motivated to target ROR1, and had a reasonable expectation of success for doing so, because Hudecek II taught that ROR1 is a “uniform, stable, and restricted” candidate for targeting B-cell malignancies. Ex.1012, 383 (“Analysis of ROR1 protein expression...revealed uniform, stable, and restricted cell surface expression on B-CLL, suggesting this molecule is a candidate for targeted immunotherapy of B cell malignancies.”); Bramson, ¶¶272-273.

Claim 19 requires the antigen to be Her2, while claims 22 and 25 require the antigen to be CD20 and CEA, respectively. Bramson, ¶274. Abken teaches targeting these antigens with a CAR. Ex.1013, 651 (“The approach is universal...[because] T cells can be redirected toward a broad variety of tumor associated antigens...including...CEA...Her2...[and] CD20”); Bramson, ¶275. A POSA would have been motivated to target each antigen with CARs because Abken (as does Singh) teaches that its CAR approach is “universal.” Bramson, ¶276-277. A POSA would have had a reasonable expectation of success because Abken suggests targeting each antigen, and explains that clinical trials involving such CARs were already initiated. Ex.1013, 651 (describing “[c]linical trials...using engineered T cells”). Bramson, ¶278.

Claim 20 requires the antigen to be L1-CAM. Bramson, ¶279. Reckamp teaches targeting L1-CAM with a CAR. Ex.1014, 1099 (describing “a L1-CAM specific chimeric antigen receptor...(CE7R)”); Bramson, ¶280. A POSA would have been motivated to target L1-CAM because Reckamp teaches that it is expressed on cancers. Ex.1014, 1099 (“L1CAM has been shown to be overexpressed in multiple tumors.”); Bramson, ¶280-281. There would have been a reasonable expectation of success because Reckamp taught that its CAR can kill cancer cells and Singh taught a generalizable approach. Ex.1014, 1099; Bramson, ¶282.

Claim 23 requires the antigen to be CD22. Bramson, ¶283. Hudecek I teaches that “[o]ther surface molecules that are expressed on B-cell tumors have been targeted with CAR-modified T cells in preclinical studies, including...CD22.” Ex.1011, 524; Bramson, ¶284. A POSA would have been motivated to target CD22 because Hudecek I’s disclosure explained that CD22 was a promising target for B-cell tumors. Bramson, ¶285. There would have been a reasonable expectation of success for the reasons discussed above and because researchers already used CD22 CARs in preclinical studies. Ex.1011, 524; Bramson, ¶286.

Claim 24 requires the antigen to be mesothelin. Bramson, ¶287. Carpenito teaches a mesothelin-targeting CAR. Ex.1015, 3360 (describing “a single-chain variable fragment that binds mesothelin and that is fused to signaling domains”); Bramson, ¶288. A POSA would have been motivated to target mesothelin because

Carpenito explains that mesothelin is expressed on carcinomas. *Id.* (“Mesothelin...over-expressed on...carcinomas”); Bramson, ¶289. There would have been a reasonable expectation of success because Carpenito reported that “the retargeted T cells...killed a variety of tumors that express mesothelin.” Ex.1015, 3363-64; Bramson, ¶290.

In sum, the prior art teaches claims 3 and 18-25. Bramson, ¶291. Singh taught claim 1 and further expressly taught that its approach was generalizable. *Id.*, ¶289. These antigens related to the same subject matter—cancer—and the CARs would have been similar. *Id.* A POSA thus would have been motivated to use Singh’s approach and expected it to succeed with any of these alternative antigens. *Id.*, ¶291.

C. Claims to Marker Positivity Percentages

1. Claims 1, 6 and 9-13

Claim 1 requires at least 50% surface positivity for various surface markers. Claims 6 and 9-13 include additional limitations concerning the percentages. Singh anticipates claim 6 for reasons discussed in Ground 1 (Section XI.A.2.a). Bramson, ¶292-293.

As explained in Section XI.A.2, 83% of Singh’s CAR-modified CD4+ helper T lymphocytes were surface positive for CD45RA, 80% of Singh’s CAR+ CD8+ T cells were surface positive for CD45RO, and at least 50% of Singh’s overall CD8+

T cells were surface positive for CD45RO. These values establish that Singh discloses all elements of claims 1 and 6.

Claims 9-13 recite surface positivity percentages for CD62L instead of CD45RA and CD45RO. A POSA would understand that Singh in view of Wang and/or Mitsuyasu discloses all elements of claims 9-13, and also claims 1 and 6 on the basis of percentage CD62L⁺. *Id.*, ¶¶294-95.

Singh and Wang encouraged using T_{CM} cells and Wang sought to obtain a high percentage of T_{CM} by using a starting population of 100% CD62L⁺ cells. Mitsuyasu shows that a POSA could easily achieve >80% CD62L⁺ composition.

Singh encouraged testing CD62L⁺ cells in clinical trials. Ex.1003, 2970 (“Clinical experience will also be needed to assess whether the presence of CD62L...enables CAR⁺ T cells to traffic to sites...”); Bramson, ¶¶295-96. A POSA would understand that Singh’s authors saw CD62L as beneficial because T_{CM} were desired. Ex.1003, 2961 (“We anticipated that the therapeutic efficacy of adoptive transfer of CD19-specific T cells would be improved by . . . introducing the CAR into central memory (CM) T cells.”); 2962 (describing T_{CM} as a “desired” phenotype); Bramson, ¶297-98.

Wang concerns the same subject matter as Singh (*i.e.*, CD19-specific, CAR-T immunotherapy compositions) *Id.*, ¶299. Wang generated CD19-specific adoptive cellular immunotherapies comprised of a high percentage of T_{CM}, which are

CD62L⁺. *Id.* Wang recognized that T_{CM} “have a unique ability to self-renew, proliferate, and differentiate into effector Tcm, which suggests that this T-cell subset will be most effective and persistent upon adoptive transfer.” Ex.1017, 926. Bramson, ¶300. Other researchers in the field shared this view as well. *Id.*, ¶301 (listing other prior-art references that describe benefits of T_{CM} in immunotherapy compositions).

Wang selected for T_{CM} by using CD62L positivity as a marker. Ex.1017, 927 (“we first selected Tcm using the Dreg56 (anti-CD62L) biotinylated antibody”). As a result of Wang’s selection process, Wang’s starting T-cell population was 100% CD62L⁺. Bramson, ¶302. Wang’s authors expanded this 100% CD62L⁺ population and transduced it with a CD19-specific CAR. Ex.1017, 927; Bramson, ¶303. While the Wang abstract does not expressly report the percentage of CD62L⁺ T cells after expansion and transduction, a POSA would have understood the goal was to maintain up to 100% CD62L⁺ T cells. *Id.*, ¶304.

Singh’s method of generating CAR-modified T cell compositions could be used to maintain a desired immunophenotype, including CD62L-positivity. Ex.1003, 2970 (“our CAR⁺ T cells maintain expression of...CD62L.”); Bramson, ¶305,307. All that would have been required to obtain the claimed percentage of CD62L⁺ cells is to use Singh’s manufacturing process to maintain a high percentage of CD62L⁺ T cells—up to 100%—as encouraged by Wang. Bramson, ¶306.

A POSA would have known from Mitsuyasu that one could easily achieve compositions with $>80\%$ CD62L⁺, as encouraged by Wang. *Id.*, ¶308. Mitsuyasu's authors isolated T cells from HIV-positive patients, transduced the cells with a chimeric receptor named "CD4ζ," and expanded them. *Id.*, ¶309. There was no selection step for CD62L. *Id.*, ¶310. Mitsuyasu's authors determined expression of T-cell markers, including CD4, CD8, and CD62L, in the final adoptive immunotherapy compositions and infused them into patients. *Id.*

Mitsuyasu shows that, even without selecting for CD62L expression, most of the compositions made were $>80\%$ CD62L⁺, with two compositions being $>95\%$ CD62L⁺. *Id.*, ¶310. Human T cells can include a high percentage of CD62L⁺ cells. *Id.* As discussed in Section XIV.A.2 *infra*, Mitsuyasu not only shows that most of its compositions had more than 80% CD62L-positivity in its overall T-cell populations, but also in its CAR-modified CD4⁺ and CD8⁺ populations. *Id.*, ¶¶311-315.

A POSA would have been motivated to combine Singh, Wang, and Mitsuyasu, with an expectation of success, for several reasons. *Id.*, ¶316. All references concern adoptive immunotherapies with chimeric receptors. *Id.* Additionally, Singh and Wang teach that T_{CM} cells, which are CD62L⁺ cells, are optimal for adoptive immunotherapy compositions and should be present at a high percentage. Bramson, ¶¶316-17. A POSA would have understood from Mitsuyasu

that a high percentage of CD62L⁺ T_{CM} would optimize a composition's persistence and it was easily achievable. Ex.1004, 16 (“CD4ζ-modified CD4⁺ and CD8⁺ T cells persisted in the blood of all patients for...at least 1 year”); Bramson, ¶¶316,320. There was nothing preventing a POSA from combining teachings of Singh, Wang, and Mitsuyasu because at the time, researchers could modify cells with CARs and select cells for a desired immunophenotype at the end of the manufacturing period. *Id.*, ¶318-19.

Moreover, the claimed CD62L⁺ percentages are obvious through routine optimization. *Id.* A POSA could have used FACS to isolate populations having the claimed CD62L-positivity levels. *Id.* As discussed, many prior-art references, including Wang, taught the benefits of CD62L positivity for adoptive cellular immunotherapy compositions. *Id.*, ¶321. Wang selected for CD62L⁺ and targeted 100% positivity for all T-cell populations; Mitsuyasu reported CD62L⁺ up to 96% in the final T-cell immunotherapy compositions. Bramson, ¶320. The claims, therefore, are *prima facie* obvious. *E.I. DuPont de Nemours v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018)(“where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence...indicating that the overlapping range would not have been obvious in light of that prior art”).

Therefore, the prior-art compositions with at least 80% CAR-modified CD4⁺ helper T lymphocytes, at least 80% CAR-modified CD8⁺ cytotoxic T lymphocytes, and at least 50% of CD8⁺ cytotoxic T lymphocytes surface positive for CD62L. This renders obvious Claims 1, 6, and 9-13. Bramson, ¶ 321.

D. Dependent Ratio Claims

Claims 14 and 15 specify that the CAR-modified CD4⁺ helper-T lymphocytes and the CAR-modified CD8⁺ cytotoxic-T lymphocytes are present at a ratio of between about 2:1 to about 1:2 (claim 14) or about 2:1, 1:1, or 1:2 (claim 15). Bramson, ¶322.

It was known by at least 2005 that “[o]ptimal antitumor efficacy [could be] achieved with the addition of equivalent numbers of engineered CD4⁺ and CD8⁺ T cells.” Ex.1016, 3001; Bramson, ¶323. From Moeller alone, a POSA would have been motivated to modify Singh’s compositions to include equal numbers of CD4⁺ T cells and CD8⁺ T cells, *i.e.*, a 1:1 ratio that is within the range of claims 14 and 15. Bramson, ¶323.

A POSA would have been motivated to combine Singh with Moeller because both references relate to adoptive cellular immunotherapy, and Moeller teaches a way to optimize Singh’s compositions. *Id.*, ¶324. There would have been a reasonable expectation of success because Singh disclosed an ability, through FACS, to isolate T cells with desired immunophenotypes. *Id.*, ¶325.

Alternatively, Singh and Mitsuyasu teach these claims. Singh discloses a composition with a ratio (0.65) that falls within claim 14's scope (0.5—2.0). Section XI.E; Bramson, ¶326. Mitsuyasu discloses a composition, P217, with a ratio of about 1:2, and another composition, S206, with a ratio of about 1:1 as recited in claim 15. Section XIV.B; Bramson, ¶326.

Therefore, Singh in combination with Moeller or Mitsuyasu render also obvious claims 14-15. Bramson, ¶324,327.

E. Dependent Claims Requiring Comparison to Other Populations

Claims 8 and 29-31 include limitations that require a comparison between prior-art compositions and one of two reference T-cell populations. Bramson, ¶328-329.

1. Claim 8

Claim 8 requires that the CD4⁺ and CD8⁺ T cells be derived from a subject. Singh teaches deriving these cells from a subject. Ex.1003, 2963 (“Human T cells were isolated...after consent”); Bramson, ¶330-31.

Claim 8 further requires that the CD4⁺ T cells “secrete a greater amount of IL-2 and/or exhibit a greater degree of proliferation when cultured in the presence of the antigen as compared to” one of two reference populations. Bramson, ¶332. One reference population is CD4⁺ T cells that have been expanded in vitro from an *effector memory* T cell-enriched CD4⁺ T-cell population. *Id.*, ¶333. A POSA would

have expected the CD4⁺ T cells resulting from the combination of Singh and Wang (which satisfies claim 1, see Section XIII.C, to both secrete more IL-2 and exhibit greater proliferation.

As discussed in Section XIII.C, Singh and Wang combination would be primarily CD62L⁺ because the investigators recognized the benefits of T_{CM} cells. A POSA would have known that Singh and Wang T_{CM} cells secrete more IL-2 than cells expanded from a T_{EM} population. Bramson, ¶¶338-42, citing Ex.1029, Fig.1 (showing CD4⁺ T_{CM} produce more IL-2 than CD4⁺ T_{EM} and CD8⁺ T_{CM} produce more IL-2 than T_{EM}); Ex.1032 (“Central memory T lymphocytes...produce predominantly IL-2.”); *Id.*, Fig. 3 (showing greater IL-2 secretion for central memory as compared to effector memory cells).

A POSA would have also known that this T-cell subtype persist and exhibit a greater degree of proliferation than cells expanded from a T_{EM} population. Bramson, ¶¶335-337, citing Ex.1011, 525 (“T-cell clones derived from T_{CM}, but not those derived from T_{EM} cells were capable of persisting long term”); Ex.1027, 748 (“The Tcm sub-population showed significant engraftment and persistence *in vivo* compared to the Tem sub-population.”); Ex.1032, 4753(“Central memory T lymphocytes...have a high capacity to proliferate. In contrast, effector memory T lymphocytes...lack significant proliferative capacity.”).

Lastly, claim 8's reference population does not expressly require the presence of an antigen. Singh's CD4⁺ T cells exhibit a greater degree of proliferation when cultured in the presence of an antigen compared to cells not exposed to antigen. Bramson, ¶¶343-46, citing Ex.1003, 2970 ("we are yet to observe evidence of antigen-independent proliferation."). Therefore, the cells in Singh's composition proliferate to a greater degree in presence of an antigen than a claimed reference population, rendering claim 8 obvious.

2. Claim 29

Claim 29 requires that "a greater percentage of the chimeric antigen receptor-modified CD4⁺ helper T lymphocytes are surface positive for CD62L and/or CD45RA as compared to" the same reference populations recited in claim 8. Bramson, ¶¶347-348.

As discussed in Section XIII.C, Wang would have motivated a POSA to start with a 100% CD62L⁺ T-cell population and the POSA would have used Singh's process to maintain **high** CD62L-positivity throughout expansion. *Id.*, ¶349. By contrast, claim 29's reference population of "CD4⁺ T cells that has been expanded in vitro from an effector memory-enriched CD4⁺ T cell population" would express **low** levels of CD62L. Bramson, ¶350, citing Ex.1028, S184 (T_{EM} cells are CD62L-negative); Ex.1027, 739 (same); Ex.1001, 11:12-13 ("effector T_E are negative for CD62L"), 25:42-43 (listing the immunophenotype of CD4⁺ T_{EM} as CD45RA⁻

CD45RO⁺**CD62L**⁻). Therefore, a POSA would understand the composition generated by combining Wang and Singh (with high CD62L-positivity) would render claim 29 obvious. Bramson, ¶351-52.

3. Claim 30

Claim 30 requires that a greater percentage of the CAR-modified CD8⁺ cytotoxic T lymphocytes are surface positive for CD62L, CD45RO and/or CCR7 as compared to one of two reference populations. Bramson, ¶353-354. One population is CD8⁺ T cells that have been expanded in vitro from a T_{EM}-enriched CD8⁺ T-cell population. *Id.*, ¶354.

Claim 30 is obvious for similar reasons as claim 29. As discussed, Wang taught a 100% CD62L⁺ T-cell population and Singh's process would maintain that **high** CD62L-positivity throughout expansion. *Id.*, ¶355. By contrast, claim 30's reference population of T_{EM}-enriched CD8⁺ would be of CD62L⁻ immunophenotype. *Id.*, ¶355, citing Ex.1028, S184 (T_{EM} cells are CD62L-negative); Ex.1027, 739 (same); ; Ex.1001, 7:21-27, 7:38-40 (T_{EM} and T_E "[do] not express or [have] decreased expression of CD62L."). Therefore, a POSA would understand the composition generated by combining Wang and Singh (with high CD62L-positivity) would render claim 30 obvious. *Id.*, ¶356.

4. Claim 31

Claim 31 is rendered obvious by the Wang and Singh composition (i.e., a composition with high T_{CM} , which are $CD62L^+$), wherein $CD8^+$ T cells proliferate more when cultured with $CD4^+$ T_{CM} cells as compared to the reference population of $CD4^+$ T cells expanded in vitro from an effector memory-enriched $CD4^+$ T cell population. *Id.*, ¶358-359.

As explained in connection with claim 8, the composition resulting from Singh and Wang would include $CD4^+$ T subpopulation of cells (T_{CM}) that secrete a greater amount of IL-2 and exhibit a greater degree of proliferation as compared to the reference T_{EM} -enriched population. *See* Section XIII.E.1. A POSA would expect both to cause a greater degree of proliferation of $CD8^+$ T cells, rendering claim 31 obvious.

First, increased IL-2 secretion causes a greater degree of proliferation of $CD8^+$ T cells. *Id.*, ¶¶362-64, citing Ex.1030 (IL-2 is the “critical...growth factor” for $CD8^+$ T-cells); Ex.1031 (“demonstrated a correlation between the ability to secrete IL-2 and the proliferation capacity of $CD8^+$ T cells.”); Ex.1018, [0159] (IL-2 supports “in vivo persistence” of $CD8^+$ T-cells). *Second*, a higher level of $CD4^+$ T cells to provide more help for $CD8^+$ T cells to proliferate to a greater degree over time. *Id.*, ¶361, citing Ex.1003, 2970 (“the presence of $CD4^+$ T-helper cells improves the persistence of $CD8^+$ antigen-specific T cells.”).

F. Remaining Challenged Claims

Claims 2, 4-5, 7, 16, and 26-28 are obvious for the same reasons discussed in Grounds 1 and 2. Sections XI-XII; Bramson, ¶356.

XIV. GROUND 4: INDEPENDENT CLAIM 1 AND DEPENDENT CLAIMS 6 AND 9-16 ARE RENDERED OBVIOUS BY MITSUYASU IN VIEW OF SINGH AND COOPER

Ground 4 differs from Grounds 1-3 by presenting Mitsuyasu (instead of Singh) as the primary reference for the obviousness allegations against claims 1, 6, and 9-16. Bramson, ¶366.

A. Independent Claim 1 and Dependent Claims 6 and 9-13

Claim 1's elements, to which reference letters [a]-[f] were added in Section XI.A, are addressed in two sections below. The first section demonstrates that the components of the claimed composition (elements [a]-[c], [e]) were disclosed in the prior art. The second section demonstrates that the claimed surface positivity of phenotypic markers (elements [d] and [f]) was also disclosed in the prior art. *Id.*, ¶367.

1. Claim Limitations Directed to Components of the Claimed Composition

Mitsuyasu, in combination with Singh in view of Cooper, discloses claim elements [a]-[c] and [e]. *Id.*, ¶368. Mitsuyasu describes an adoptive cellular immunotherapy composition of CD4⁺ and CD8⁺ T cells modified with a CIR that

targets the HIV *env* protein. *Id.* A POSA would have understood from Cooper that a CAR, such as that taught by Singh, is easily interchangeable with a CIR. *Id.*

a. [a] “[a]n adoptive cellular immunotherapy composition”

As discussed in Section IX.A, this element of the preamble is not limiting because it merely describes the intended use of the claimed composition. *Id.*, ¶369. To the extent the preamble is limiting, Mitsuyasu discloses a “composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal.” *Id.*, ¶370.

Mitsuyasu discloses results from infusions of engineered T-cell compositions. Ex.1004, 786 (“subjects received a single infusion of...autologous CD4 ζ -modified CD4⁺ and CD8⁺ T cells”); Bramson, ¶371. Mitsuyasu’s compositions were “adoptive cellular immunotherapy[ies] formulated to be suitable for administration to a mammal” because, prior to infusion, the authors diluted the cells in a solution meant to mimic human plasma supplemented with human serum albumin. Ex.1004, 786 (describing a solution used to infuse the cells into subjects); Bramson, ¶371.

Therefore, Mitsuyasu discloses an “adoptive cellular immunotherapy composition.” *Id.*, ¶372.

b. [b] “containing chimeric antigen receptor-modified CD4⁺ T lymphocytes and chimeric antigen receptor-modified CD8⁺ T lymphocytes,”

Mitsuyasu discloses receptor-modified CD4⁺ and CD8⁺ T cells that bind to an antigen, and it would have been obvious to use Singh’s CAR in place of Mitsuyasu’s engineered receptor. *Id.*, ¶373.

Mitsuyasu’s subjects received CD4⁺ and CD8⁺ T cells, and both cell types expressed an engineered receptor known as CD4ζ. Ex.1004, 786 (“subjects received ... autologous CD4ζ-modified CD4⁺ and CD8⁺ T cells”); Bramson, ¶374. CD4ζ is a chimeric receptor that includes the transmembrane and extracellular domains of human CD4 fused to CD3ζ as an intracellular signaling domain. Ex.1004, 786; Bramson, ¶374. Human CD4 targets the HIV *env* protein, which is expressed on the surface of HIV-infected cells. Ex.1004, 786; Bramson, ¶374.

A POSA would have understood that a “CIR” (as the term is used by Mitsuyasu) is the same as a CAR and the different terms reflected the preferences of the researchers. Bramson, ¶375. The prior art described a CIR as an “artificial receptor” that has “an extracellular antigen-binding domain linked through a transmembrane motif to a cytoplasmic lymphocyte-signaling moiety.” Bramson, ¶375, quoting Ex. 1019, 4067. The prior art defined a CAR similarly, as having “an extracellular antigen-binding exodomain...a spacer, a transmembrane region, and one or more intracellular signaling domains.” Ex.1010, 645 (internal parenthetical

omitted); Bramson, ¶375. Although the field has moved toward using the acronym “CAR” instead of “CIR,” scientific publications published prior to the Priority Date largely used the terms interchangeably. Bramson, ¶376.

Mitsuyasu describes the benefit of its manufacturing process—T cells that exhibit “sustained, high level persistence [that] demonstrates the feasibility of ex vivo T-cell gene therapy.” Ex.1004, 785; Bramson, ¶377. This benefit would have motivated a POSA to use Mitsuyasu’s method with CARs targeting other disorders, such as B-cell cancers by targeting the CD19 antigen. Bramson, ¶377-378.

As explained in Sections XI.A.1.b-XI.A.1.c, Singh discloses CD19-specific CAR-modified T cells that bind to CD19. Bramson, ¶379. A POSA would have been motivated to use Singh’s CAR as a substitute for Mitsuyasu’s CD4ζ receptor in order to treat CD19-expressing B-cell malignancies. *Id.* Thus, a POSA would have been motivated to use Singh’s CAR in Mitsuyasu’s system to obtain successful clinical results, but for a different disorder, such as a cancer. *Id.*

Given the successful results described in both Mitsuyasu and Singh, a POSA would have a reasonable expectation of success in using Mitsuyasu’s system with Singh’s CAR. *Id.*, ¶380. Cooper is an entry from an encyclopedia that provides an overview of CARs from the perspective of a POSA and provides further support of a reasonable expectation of success. *Id.*, ¶¶380-381.

Cooper explains that modifying a genetically engineered T cell to include a different binding receptor was simple substitution. Ex.1010, 648 (“One of the major advantages...lies in the modular composition of the CAR molecule...This allows investigators to *swap the CAR exodomain with a scFv or ligand* that recognizes or binds to a desired cell-surface antigen.”); Bramson, ¶381. A POSA would have understood that Mitsuyasu’s receptor had an exodomain that was a ligand—CD4—and that Singh’s CAR utilized an exodomain comprising a scFv. Section XI.C.1; Bramson, ¶382. Therefore, from Cooper, a POSA would have had a reasonable expectation of success swapping Mitsuyasu’s CD4 ligand for Singh’s CD19-targeting scFv. Bramson, ¶382.

The prior art thus renders obvious claim element [b]. *Id.*, ¶382-383.

- c. [c] & [e] “wherein: (a) the chimeric antigen receptor-modified CD4⁺ T lymphocytes [and (b) the chimeric antigen receptor-modified CD8⁺ T lymphocytes] contain a chimeric antigen receptor that specifically binds to an antigen”

Mitsuyasu’s compositions included CD4⁺ and CD8⁺ T cells that expressed a HIV(*env*)-targeting receptor. *Id.*, ¶384. Singh’s compositions included CD4⁺ and CD8⁺ T cells that expressed a CD19-targeting CAR. *Id.* Mitsuyasu’s receptor and Singh’s CAR both specifically bind to an antigen: HIV(*env*) and CD19, respectively. *Id.* As discussed in Section XIV.A.1.b, it would have been obvious to use Singh’s CAR with Mitsuyasu’s manufacturing process. *Id.*

Therefore, the prior art renders obvious claim elements [c] and [e]. *Id.*, ¶385.

2. Claim Limitations Directed to Phenotypic Marker Surface Positivity

Mitsuyasu discloses a composition with the claimed phenotypic marker expression because it discloses CD62L surface positivity within the claimed ranges of claims 1, 6, and 9-13. *Id.*, ¶386. As discussed in prior Grounds, these claims encompass varying percentages of CD62L+ ($\geq 50\%$ in claims 1 and 9-11, $\geq 60\%$ in claims 6 and 12, and $\geq 80\%$ in claim 13) in one or more subpopulations.

Mitsuyasu discloses that its compositions had, on average, 82% CD62L positivity, with seventeen of the tested compositions (a majority) having greater than 80% CD62L positivity. *Id.*, ¶388. Mitsuyasu's Table 2 shows the immunophenotypes of its T-cell compositions:

Patient ID	CD4 (%) [*]	CD8 (%) [*]	CD62L (%) [*]	CD28 (%) [*]	CD25 (%) [*]	Culture days [†]	CD4 ζ by PCR [‡]
N215	24	73	83	88	—	13	11
H202	62	38	96	98	88	12	17
C211	17	80	84	91	42	12	12
F209	13	83	—	85	45	12	18
S201	26	72	—	89	36	12	9
Q202	22	77	94	98	77	12	5
S206	52	46	93	96	74	17	49
S212	20	79	95	98	43	12	10
P217	31	68	94	93	39	12	13
G251	22	86	82	87	41	12	17
E207	28	69	73	94	60	12	17
T253	24	77	82	88	55	12	18
L218	13	86	85	94	36	12	15
R255	60	37	79	90	27	12	15
Y254	22	76	94	98	59	12	13
U213	7	92	84	96	43	10	9
D282	23	78	82	95	50	13	16
D212	3	96	44	90	64	14	15
T232	28	70	87	88	34	14	11
D256	12	88	59	74	58	15	15
J233	7	90	81	90	43	14	18
Y292	37	61	96	99	28	12	28
X214	8	90	64	79	49	16	38
C298	26	73	83	63	36	12	57
Mean	24	74	82	90	49	13	19
SD	15	16	13	8	16	2	13

^{*}Percentage of CD3⁺ T cells expressing marker by FACS analysis.
[†]Total number of days in culture for each T-cell lot.
[‡]Transduction efficiency as measured by DNA PCR for CD4 ζ .

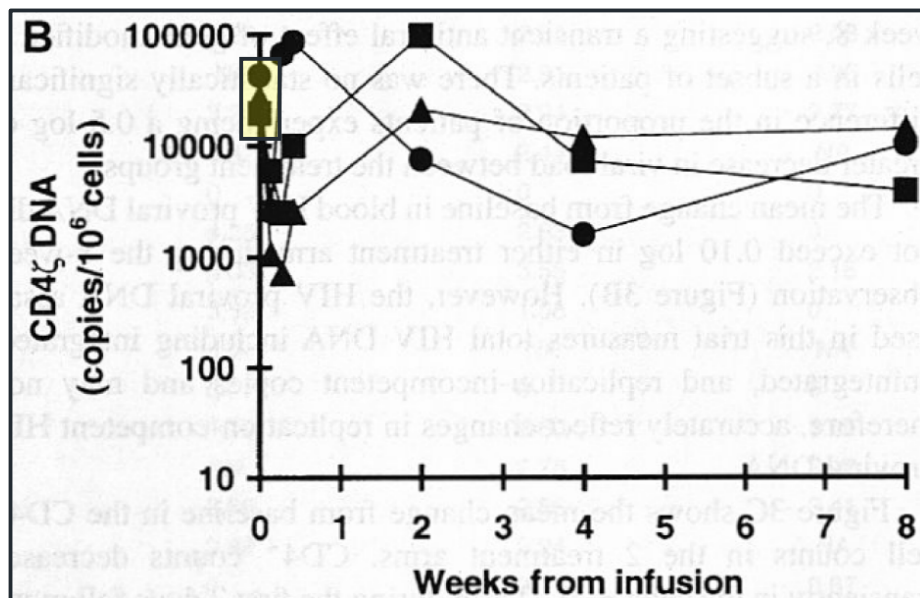
Ex.1004, 788 (annotated); Bramson, ¶¶387-388. Table 2 has been annotated to show the percentages of CD4⁺, CD8⁺, CD62L⁺, and receptor-modified T cells in blue, green, yellow, and red, respectively. Bramson, ¶387.

Mitsuyasu does not specifically disclose the percentage CD62L-positivity in its subpopulations of receptor-modified CD4⁺ and CD8⁺ T cells. Nonetheless, a

POSA would have recognized that Mitsuyasu's compositions met the claimed ranges. *Id.*, ¶388.

(1) Mitsuyasu's Compositions Included Receptor-Modified, CD4⁺ and CD8⁺, T Cells

Mitsuyasu's compositions included receptor-modified CD4⁺ and CD8⁺ T cells. Bramson, *Id.*, ¶389. Mitsuyasu reported that CD4ζ-encoding DNA was present in CD4⁺ and CD8⁺ T cells at the time of infusion, as shown below:



Ex.1004, 789 (annotated); Bramson, ¶390. CD4ζ DNA in CD4⁺ and CD8⁺ T cells is represented by squares (■) and circles (●), respectively. The yellow shading above indicates that at the time of infusion (*i.e.*, 0 weeks from infusion), CD4ζ DNA was present at the same order of magnitude in CD4⁺ and CD8⁺ T cells. Bramson, ¶390-91.

(2) Percentage CD62L-Positivity Is Not Impacted by CD4 Versus CD8, and CIR, Expression

A POSA would understand that, while the rate of CD62L expression in Mitsuyasu's compositions could vary between CD4⁺ and CD8⁺ T cells, both populations would be expected to have substantially similar CD62L-positivity. Bramson, ¶392 (citing Ex.1020, showing substantially similar CD62L⁺ for CD4⁺ and CD8⁺ cells). Therefore, a POSA would recognize that the percentage of CD62L⁺ reported for overall T cells would be informative of the percentage of CD62L⁺ for the CD4⁺ and CD8⁺ subpopulations. *Id.*, ¶393.

Likewise, a POSA would expect that the percentage CD62L-positivity in Mitsuyasu's compositions would not be affected by chimeric receptor expression. A POSA would not have thought that CD62L-positivity affects CAR transduction rate, nor that CAR-positivity would impact CD62L expression. *Id.*, ¶394. The rate of CD62L expression would be roughly equivalent in receptor-modified and receptor-unmodified cells, and thus a POSA would understand that those populations would show similar rates of CD62L-positivity as their respective overall T-cell composition. *Id.*

(3) Most of Mitsuyasu's Compositions Fall Within Scope of the Claimed Percentages of CD62L⁺

As discussed above, a POSA would have expected that the CD4⁺, CD8⁺, and receptor-modified populations in Mitsuyasu's compositions would exhibit roughly

the same rate of CD62L-positivity as observed in their respective overall compositions. *Id.*, ¶395. In Mitsuyasu's Table 2, seventeen tested compositions (a majority) had greater than 80% CD62L-positivity. Ex.1004, 788; Bramson, ¶395. Therefore, a POSA would have expected that the overall CD8⁺ T cells, receptor-modified CD4⁺, and receptor-modified CD8⁺ T cells in those seventeen compositions also would have exhibited greater than 80% CD62L-positivity. Bramson, ¶395. This would satisfy the CD62L⁺ percentage limitations in claims 1, 6, 9-13. *Id.*, ¶397.

Even if it was not assumed that CD62L-positivity is substantially similar for CD4⁺ and CD8⁺ T cells, the POSA would understand that at least eight of Mitsuyasu's compositions must (mathematically) have had CD62L-positivity of >50% for both CD4⁺ and CD8⁺ T cells. *Id.*, ¶396. This is because overall CD62L⁺ was so high: seven of the compositions had CD62L-positivity was >90%, seventeen had >80%, and the overall average of all twenty-two compositions was 82%. *Id.*, ¶396.

One example composition reported by Mitsuyasu—identified as S206—is noteworthy. *Id.*, ¶398. This composition had an overall CD62L⁺ of 93% for all T cells, meaning only 7% of T cells did not have CD62L. *Id.*, ¶398-399. As discussed above, Mitsuyasu showed a similar rate of receptor-modification between CD4⁺ and CD8⁺ cells; and this would have been the expectation of a POSA. *Id.*, ¶400 (citing

Ex.1021, reporting similar transduction rates for CD4⁺ and CD8⁺ cells). Given this, the percent CD62L-positivity of receptor-modified CD4⁺ and CD8⁺ T cells could not mathematically have been below 70% and the overall CD8⁺ T cells could not have been below 80%, even if all the CD62L-negative cells were in a claimed subpopulation (which would, in any event, be an incorrect scientific assumption). *Id.*, ¶¶401-12. This satisfies the percentage CD62L⁺ limitations in claims 1, 6, 9-12. *Id.*, ¶¶413-17. It also would have been mathematically necessary for either the receptor-modified CD4⁺, the receptor-modified CD8⁺ T cells, or both to be >80% CD62L⁺. *Id.*, ¶412. This satisfies the percentage CD62L⁺ limitations in claim 13. *Id.*, ¶¶413-17.

It is, therefore, a mathematical certainty that the S206 composition met the percentage CD62L⁺ limitations in claims 1, 6, 9-13. *Id.*, ¶¶401,417.

B. Dependent Ratio Claims

Claims 14 and 15 recite additional composition ratio limitations. Mitsuyasu and Singh teach all elements of these claims. Sections XI.E, XIII.D; Bramson, ¶418.

Assuming a relatively equivalent rate of chimeric receptor transduction, Mitsuyasu's Table 2 shows at least two compositions, S206 and P217, that meet the elements of these claims. Bramson, ¶419. S206 exhibited a ratio of receptor-

modified CD4⁺ T cells to receptor-modified CD8⁺ T cells of about 1:1.⁷ P217 had a ratio of about 1:2.⁸ Bramson, ¶¶420-421.

Therefore, Mitsuyasu in view of Singh and/or Cooper render obvious claims 14-15. Bramson, ¶422.

C. Dependent CAR Component Claim

Claim 16 specifies that the CAR in the CD8⁺ and CD4⁺ T cells is the same. Mitsuyasu and Singh used their CIR and CAR, respectively, in both CD4⁺ T cells and CD8⁺ T cells. Sections XI.C.2, XIV.A.1.b-XIV.A.1.c. Bramson, ¶¶423-424.

Therefore, Mitsuyasu in view of Singh and Cooper renders obvious claim 16. Bramson, ¶¶425-26.

XV. 35 U.S.C. §325(D) SHOULD NOT BAR THE PETITION

Four Grounds demonstrate that the Challenged Claims are unpatentable. Each Ground relies on prior-art references that were not cited during prosecution—Singh, Jensen, Hudecek I, Wang, Abken, Hudecek II, Reckamp, Carpenito, Cooper, Sun, Sallusto, and Yang I & II were not cited during prosecution.

⁷ Composition S206 had 52% CD4⁺ and 46% CD8⁺ T cells; equaling 1.13 (about 1:1).

⁸ Composition P217 had 31% CD4⁺ and 68% CD8⁺ T cells; equaling 0.46 (about 1:2).

Grounds 1 and 2 are new references—Singh and Jensen—containing teachings that were never considered by the Office. Only two references in Grounds 3 and 4 were cited in IDSs by the applicant, but the Examiner did not discuss them during prosecution.

The Board should not exercise its discretion to deny institution of Grounds 1-4 under *Advanced Bionics v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8 (P.T.A.B. 2020).

The Board should not exercise its discretion to deny institution of Ground 1 or Ground 2 because Singh and Jensen were not before the Examiner. These references also are not substantially the same as, or cumulative of, any art considered during prosecution.

The Examiner did not see prior art that taught “the use of CD4⁺ T cells that are the required % positive for CD62L or CD45RA.” Ex.1008, 74. The Examiner believed that the prior art instead taught “preparing CAR cells from CD8⁺ cells only.” *Id.* But Singh teaches CAR-modified CD4⁺ and CD8⁺ T cell compositions with the claimed percent CD45RA-positivity. Section XI.A.2.

Although the applicant IDS’ed Mitsuyasu and Moeller, the Board should not exercise its discretion to deny institution of Grounds 3 or 4.

“[T]he extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection,” favors not exercising the

Board’s discretion to deny institution. *Becton, Dickinson v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017). Although Mitsuyasu and Moeller were cited in IDSs, the Examiner did not discuss them. *Trend Micro v. CUPP Computing AS*, IPR2021-00813, Paper 7, 23 (P.T.A.B. Oct. 25, 2021)(“[C]itation of a reference in an IDS, without more, does not necessarily equate to evaluation of reference by the Examiner.”); *In re Vivint*, 14 F.4th 1342, 1349-50 (Fed. Cir. 2021)(holding that the Board’s “discretion [under 35 U.S.C. §325(d)] would be meaningless if a question of patentability was not new simply because it had been previously presented to the Patent Office...the Patent Office must have considered and decided that question on the merits.”).

This Petition sufficiently explains how the Examiner erred by failing to evaluate Moeller and Mitsuyasu. For example, the Examiner stated that prior art taught “preparing CAR cells from CD8⁺ cells only.” Ex.1008, 74. However, Moeller discloses optimal antitumor efficacy using an equivalent number of CD4⁺ and CD8⁺ T cells. Ex.1016, 3001 (“Optimal antitumor efficacy was achieved with the addition of equivalent numbers of engineered CD4⁺ and CD8⁺ T cells.”). Moreover, the Examiner overlooked Mitsuyasu, which teaches preparing CAR⁺ cells from CD4⁺ T cells. Sections X.A.2,XIV.A.1.b-XIV.A.1.c.

XVI. CONCLUSION

The Board should institute IPR of all Challenged Claims pursuant to the Grounds and find the Challenged Claims unpatentable.

Certificate of Compliance with Word Count

Pursuant to 37 C.F.R. §42.24(d), I certify that this petition complies with the type-volume limits of 37 C.F.R. 42.24(a)(1)(i) because it contains 13,939 words, according to the word-processing system used to prepare this petition, excluding the parts of this petition that are exempted by 37 C.F.R. §42.24(a).

DATED: March 22, 2023

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Certificate of Service

I hereby certify, pursuant to 37 C.F.R. §§42.6 and 42.105, that a complete copy of the attached **Petition and Accompanying Exhibits**, including related documents, are being served via Priority Mail Express on the twenty-second day of March, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent owner by serving the correspondence address of record with the USPTO as follows:

David Carlson & Patent Docket Clerk
Seed Intellectual Property Law Group LLP
701 Fifth Ave, Suite 5400
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DATED: March 22, 2023

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