Filed on behalf of: Fred Hutchinson Cancer Center

Filed: June 28, 2023

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

Case IPR2023-00760
U.S. Patent No. 9,987,308

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
Ex. 2001	Singh et al., "Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies," *Cancer Res. 71*(10), 3516-27 (2011) ("Singh-3")
Ex. 2002	Hinrichs et al., "Adoptively Transferred Effector Cells Derived from Naïve Rather than Central Memory $CD8^+$ T Cells Mediate Superior Antitumor Immunity," *PNAS 106*(41), 17469-74 (2009) ("Hinrichs")
Ex. 2003	Singh et al., "Selective Reprogramming of CD19-Specific T Cells with IL-21 and CD28 Signaling for Adoptive Immunotherapy of Acute Lymphoblastic Leukemia," *Biology of Blood and Marrow Transplantation 15*(2), 61-62, Abstract No. 164 (2009) ("Singh-2")
Ex. 2004	Biographical information for Ronald Mitsuyasu, downloaded from https://people.healthsciences.ucla.edu/institution/personnel?personnel_id=8352 ("Mitsuyasu's Bio")
Ex. 2005	Biographical information for Kristen M. Hege, downloaded from https://www.ucsfhealth.org/providers/dr-kristen-hege ("Hege's Bio")
Ex. 2006	Biographical information for Michael Claus V Jensen, downloaded from https://www.seattlechildrens.org/directory/michael-claus-v-jensen/ ("Jensen's Bio")
Ex. 2007	Biographical information for Stephen J. Forman, downloaded from https://www.cityofhope.org/stephen-forman ("Forman's Bio")
Ex. 2008	Biographical information for Stanley Riddell, downloaded from https://www.fredhutch.org/en/faculty-lab-directory/riddell-stanley.html ("Riddell's Bio")
Ex. 2009	Biographical information for Michael Hudecek, downloaded from https://www.vjhemonc.com/speaker/michael-hudecek/ ("Hudecek's Bio")
Ex. 2010	Reserved
Ex. 2011	Reserved
Ex. 2012	U.S. Patent Application No. US 2003/0170238A1 to Gruenberg et al. ("Gruenberg")
Ex. 2013	Jena et al., "Redirecting T-Cell Specificity by Introducing a Tumor-Specific Chimeric Antigen Receptor," *Blood 116*(7), 1035-44 (2010) ("Jena")

Exhibit No.	Description
Ex. 2014	Paugh et al., *"*Reference Standards for Accurate Validation and Optimization of Assays that Determine Integrated Lentiviral Vector Copy Number in Transduced Cells," *Scientific Reports 11:*389, 1-9 (2021) ("Paugh")
Ex. 2015	Sallusto et al., "Central Memory and Effector Memory T Cell Subsets: Function, Generation, and Maintenance," *Annu. Rev. Immunol. 22*, 745-63 (2004) ("Sallusto 2004")
Ex. 2016	Excerpt From the File History of U.S. Patent No. 9,987,308 that Contains the March 10, 2014 Information Disclosure Statement (IDS) that was Initialed by the Examiner on May, 2, 2016
Ex. 2017	Declaration of Sarah A. Geers Under 37 C.F.R. § 1.68 dated June 28, 2023

I. INTRODUCTION

The inventors of U.S. Patent No. 9,987,308 ("the '308 patent") (Ex. 1001) disclosed and claimed adoptive cellular immunotherapy compositions using modified T cells to target and augment the body's anti-tumor immune response. The challenged claims cover an "adoptive cellular immunotherapy composition" comprising a mixture of specific types of T cells that have been modified to include a chimeric antigen receptor ("CAR"), *i.e.*, CAR-T cells, prepared with a specific mixture of $CD4^+$ and $CD8^+$ T cells. The '308 patent demonstrates the superior anti-tumor activity of the claimed compositions of $CD4^+/CD8^+$ CAR-T cells, both *in vitro* and *in vivo*, including in a tumor challenge study in mice.

Petitioner challenges the novelty and non-obviousness of the '308 patent claims under pre-AIA 35 U.S.C. §§ 102 and 103 on four grounds. Petitioner relies on two primary references—Singh (Ex. 1003) (hereinafter "Singh-1") and Mitsuyasu (Ex. 1004)—for its four grounds, but each reference suffers from significant deficiencies that are apparent on its face.

Singh-1. Petitioner's cornerstone reference—figuring into each of the four grounds of the Petition (including anticipation)—does not disclose the "adoptive cellular immunotherapy composition" required by the challenged claims. Singh-1 discloses a CAR-T composition without any *in vivo* data, whereas the claims of

the ’308 patent are all directed to immuno*therapeutic* compositions. Indeed, Singh-1 explicitly warned that further study of its cells would be necessary to determine whether they could have any therapeutic value.

Petitioner’s expert Dr. Bramson attempts to circumvent this problem by asserting that the T cells of Singh-1 were used in a clinical trial. But this is demonstrably false. As can be seen from a side-by-side comparison of Singh-1 and Ex. 1026, the cells described in Singh-1 are *not* the same cells that were used in the clinical trial. Rather, the cells of Singh-1 were prepared with a cell culturing process that used IL-2 alone, whereas the cells used in clinical trial NCT00968760 were prepared with a cell culturing process that used IL-21 in addition to IL-2. *See infra* Section IV.A.1.c.

Later publications by the Singh-1 authors, Singh-2 (Ex. 2003) and Singh-3 (Ex. 2001)—conspicuously not cited by Petitioner—showed that the cells cultured in IL-2 alone had *no* therapeutic effect when tested *in vivo* in mice, and were therefore *never* advanced to *any* clinical trial. Ex. 2003; Ex. 2001. In fact, the tumor burden in mice treated with CAR-T cells cultured in IL-2 alone, as in Singh-1, was no different than the tumor burden in the mice who received no CAR-T cells at all.

Mitsuyasu. Petitioner and its expert similarly misread Petitioner’s second key reference—the primary reference in Ground 4 and a secondary reference in Ground 3—by employing erroneous assumptions fatal to Petitioner’s argument that

Mitsuyasu discloses the claimed percentage of CD62L-positive $CD4^+$ and $CD8^+$ T cells. For example, they wrongly equate the percentage of *individual T cells* transduced with Mitsuyasu's chimeric receptor (CD4ζ or "construct") with the transduction efficiency for the construct in the *entire pool of T cells,* notwithstanding the absence of information regarding the number of constructs contained in each transduced T-cell.[1]

In any transduction process, some cells will be transduced with multiple constructs and others will not be transduced at all. *See, e.g.*, Ex. 2014 at 5[2] (typically

[1] This is like equating the percentage of assigned books read by an entire class of students with the percentage of individual students who did the reading. Knowing that the class as a whole read 60% of the assigned books does not tell us anything about the number of books read by any particular student; it certainly does not tell us that 60% of the students read one or more of the assigned books. It is certainly possible, and perhaps even likely, that of 20 students in the class, 5 students read 50% of the assigned books, 5 students read 10% of the assigned books, and 10 students read zero books. If that were the case, it would be 50% not 60% of the students who read at least one book.

[2] All citations herein refer to the exhibit's native page numbers, except IPR page numbers are used where the exhibits do not include native page numbers.

"one to five integration events per cell"). Accordingly, information about the amount of construct detected in the pool overall is insufficient to determine how many of the individual cells have been transduced. Yet, Petitioner's obviousness argument premised on Mitsuyasu involves precisely this leap of logic. That is, Mitsuyasu discloses only transduction efficiency across the entire pool of T cells, and Petitioner and Dr. Bramson assume—wrongly—that this disclosed pool transduction efficiency equates to the individual T cell transduction rate. (Specifically, they assume that a 49% pool efficiency means that 49% of the individual cells have been transduced.)

Petitioner's Combinations. The deficiencies of each of Singh-1 and Mitsuyasu are significant and cannot be addressed simply by combining Singh-1 and Mitsuyasu with each other, as Petitioner asserts in Grounds 3 and 4, or with additional references, as Petitioner asserts in Grounds 2, 3, and 4.

As an initial matter, there is no motivation for any of Petitioner's combinations. First, as just discussed, the cells of Singh-1 cultured in IL-2 alone were not therapeutically effective, and thus a POSA would not have been motivated to use the cells of Singh-1 in any adoptive cellular immunotherapy composition with any reasonable expectation of success. Specifically, Singh-2 discloses that the CAR expression of "killer" $CD8^+$ T cells is critical for therapeutic effect, and that the cell culturing process used to obtain the Singh-1 CAR-T cells resulted in virtually no

CAR expression (just 1%) of the "killer" $CD8^+$ T cells. Accordingly, a POSA would recognize that the cells of Singh-1 would not be useful for immunotherapy.

Further, even if a POSA would, for some inexplicable reason, look to use the Singh-1 cells, the POSA would not look further to Mitsuyasu because each reference discloses a co-infusion of $CD4^+$ and $CD8^+$ T cells that is specific to a particular type of targeted treatment with different disease biology—tumor (Singh-1) and HIV (Mitsuyasu). A POSA would not have been motivated to place the tumor-specific receptor of Singh-1 into cells that were designed by Mitsuyasu to treat a viral infection.

Petitioner's other thirteen secondary references likewise discourage the combinations and modifications Petitioner relies on. For example, Singh-1 cautions against using $CD62L^+$ central memory T (T_{CM}) cells in an adoptive immunotherapy, thereby dissuading a POSA from combining Singh-1 with Wang (Ex. 1017), which uses $CD62L^+$ T_{CM}-enriched cells. Petitioner misreads or cherry-picks portions of many of its other secondary references as well.

Finally, the asserted combinations offer no reasonable expectation of success. For instance, given the lack of *in vivo* data for the cells of Singh-1, compounded by the disclosure in Singh-2 that the Singh-1 cells lack "CAR^+ $CD8^+$ T cells with ability to kill $CD19^+$ tumor targets," a POSA would not have had any reasonable expectation of successfully combining these *therapeutically ineffective* cells with the

construct of Mitsuyasu—or any other reference(s)—to create the claimed compositions, which are immuno*therapeutic*. Additionally, there would be no reasonable expectation of therapeutic success in targeting tumors (Singh-1) using a system tailored for viral infections (Mitsuyasu) in the context of an adoptive immunotherapy. *See* Cooper (Ex. 1010) at 645 ("infusion of tumor-specific T cells has only been partially successful in clinical oncology trials . . . In contrast, infusing viral-specific T cells has successfully treated and protected patients from opportunistic diseases . . . .").[3]

PTO Examination. Independent of the foregoing, 35 U.S.C. § 325(d) is reason alone to deny institution. Petitioner identifies no material error by the Examiner and omits key pieces of the prosecution history record. Further, Petitioner's asserted art is the same or substantially the same as the art considered by the Examiner.

Petitioner has not established a reasonable likelihood of prevailing on any of the challenged claims, and the Board should deny institution.

[3] Cooper's first author is a co-author of Singh-1.

II. THE '308 PATENT INVENTION

A. The State Of The Art

1. T Cells

T cells, which are also referred to as "T lymphocytes," are a type of lymphocyte (white blood cell) in the immune system. *See* Ex. 1001 at 6:66-67. T cells play a vital role in the adaptive immune response, *e.g.*, protecting the body from infection and helping fight tumors. T cells originate in the bone marrow and mature in the thymus into different types of T cells, including "helper" T cells, "regulatory" T cells, and "cytotoxic" (or "killer") T cells. As defined in the '308 patent, "[c]ytotoxic T lymphocyte (CTL) . . . refers to a T lymphocyte that expresses CD8 on the surface thereof (i.e., a $CD8^+$ T cell)." *Id.* at 7:7-9. A helper T cell refers to a T cell that express CD4 on its surface (*i.e.*, a $CD4^+$ cell). Pet. at 7.

2. T Cell Subsets

T cells can be categorized into several subsets that differ in phenotype and function. The subsets of T cells include naïve T (T_N) cells, effector T (T_E) cells, and memory T (T_M) cells; T_M cells can be divided further into T_{CM} and effector memory (T_{EM}) cells. Ex. 1001 at 1:49-54. Upon T cell activation, T_N cells "undergo proliferation and programmed differentiation, resulting in the generation of large numbers of T_E cells." Hudecek I (Ex. 1011) at 525. Upon antigen re-exposure, both T_{CM} and T_{EM} cells can differentiate into T_E cells. Ex. 1001 at 1:59-62; *see also* Ex. 1011 at 525.

3. T Cell Markers

The subsets of T cells express certain antigens on their surface, which can be useful as markers for T cell type. These T cell markers include those recited in the claims of the '308 patent, *i.e.*, CD62L, CD45RA, and CD45RO. For example, T_{CM} cells express CD62L and CD45RO on the cell surface. Ex. 1001 at 7:12-16. T_N cells express CD62L and CD45RA on the cell surface. *Id.* at 7:30-33. T_{EM} cells do not express or have decreased expression of CD62L on the cell surface as compared to T_{CM} cells. *Id.* at 7:21-26.

4. Adoptive Cellular Immunotherapy

Adoptive cellular immunotherapy uses genetically modified cells originally isolated from a patient or a donor to treat disease. CAR-T therapy is a type of adoptive cellular immunotherapy whereby T cells are genetically modified to express a CAR[4]. Adoptive cellular immunotherapy involves cell isolation, modification (*e.g.*, to express a CAR), *in vitro* propagation to clinically relevant

[4] A CAR is composed of several elements (or domains) that are fused together into a single protein, including an extracellular antigen-binding domain fused to a transmembrane domain followed by one or more intracellular signaling domains. Ex. 1009 at 10995; *see also* Ex. 1001 at 7:56-60. The extracellular antigen-binding domain targets one or more specific antigens.

numbers, and reinfusion of the cells (*e.g.*, T cells) into patients to treat their disease. Ex. 1011 at 517.

Adoptive cellular immunotherapy was still in its infancy at the time of the invention and questions remained as to whether effective adoptive immunotherapy could even be achieved at all. Among other things, it was recognized that therapeutic efficacy would require the adoptively transferred cells to "persist sufficiently long *in vivo* to eradicate the majority or even all of the [target] cells." *Id.* at 524. Clinical studies showed that "the efficacy of cultured T cells, particularly cloned $CD8^+$ T cells, is frequently limited by their failure to persist after adoptive transfer." Ex. 1001 at 1:45-48; *see also* Ex. 1011 at 525.

Scientists have long been searching for ways to improve *in vivo* persistence, particularly of adoptively transferred $CD8^+$ T cells. One area of focus has been the identification of a particular subset or a mixture of subsets of T cells that would provide greater persistence, but the literature at the time of the invention was contradictory and incomplete. For example, some studies showed that tumor-specific $CD8^+$ T cells derived from T_N cells possessed favorable traits for use in an adoptive immunotherapy. *See, e.g.*, Hinrichs (Ex. 2002) at 17471, 17473 (Adoptively transferred $CD8^+$ T_E derived from T_N cells exhibited superior *in vivo* expansion, persistence, and antitumor efficacy relative to T_{CM}-derived T_E cells). In contrast, other studies showed that T_{CM}-derived $CD8^+$ T cells were preferred for

adoptive immunotherapy because they persisted longer after adoptive transfer. Ex. 1011 at 525. The literature regarding enhancing persistence was confusing at best.

5. Generating CAR-T Cells

At the time of the invention, viral transduction was the commonly used technique for introducing and expressing genetic material in a cell. Ex. 1001 at 13:22-31. In the context of making CAR-T cells, this gene transfer technique includes contacting T cells with a viral vector, such as a retroviral vector, encoding a CAR. *Id.* at 13:26-43.

A typical process of generating CAR-T cells via a viral vector includes isolating T cells from a donor, followed by activating the isolated T cells (*e.g.*, by contacting the cells with an anti-CD3 antibody). *Id.* at 20:34-39. Next, the activated T cells are transduced with the viral vector encoding a desired CAR. The CAR-transduced T cells are then expanded *in vitro* in a cell culture medium to greater numbers. *Id.* at 20:36-45. The cell culture medium is usually supplemented with one or more cytokines to stimulate the growth and differentiation of the T cells. *Id.* at 20:39-43; *see also* Ex. 2003 at 61-62. Cytokines can also impact the phenotypes of the generated CAR-T cells. Ex. 2003 at 61-62.

B. The Invention Claimed In The ’308 Patent

Recognizing the unmet need to obtain CAR-modified T cells having enhanced efficacy for use in adoptive cellular immunotherapies, the inventors of the ’308

patent investigated methods and compositions to provide improved *in vivo* persistence of adoptively transferred T cells, including CAR-modified $CD8^+$ T cells. The inventors surprisingly discovered that CAR-modified $CD4^+$ T cells enhanced the *in vitro* proliferation of CAR-modified $CD8^+$ T cells. *See* Ex. 1001 at 24:57-61, FIG. 7. In particular, they discovered that certain subsets of CAR-modified $CD4^+$ T cells enhanced the proliferation of certain subsets of CAR-modified $CD8^+$ T cells. *Id.* at 27:16-21, 29:2-7, FIGs. 9 & 10. These cell compositions thus provided enhanced efficacy, and were claimed in the '308 patent.

For example, claim 1 of the '308 patent 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.

The dependent claims of the ’308 patent recite additional features, such as the antigen, CAR construct, IL-2 secretion, and the ratios of the CAR-modified $CD4^+$ T cells to the CAR-modified $CD8^+$ T cells.

Critically, in addition to providing promising *in vitro* data, the ’308 patent shows synergistic efficacy of the compositions *in vivo*. That is, mice treated with a composition comprising CAR-modified $CD4^+$ and $CD8^+$ T cells experienced significantly greater reduction of tumor burden as compared to mice receiving either CAR-modified $CD4^+$ or $CD8^+$ T cells alone. *Id.* at FIGs. 12 & 13B.

III. LEVEL OF ORDINARY SKILL IN THE ART

As the above discussion indicates, the level of ordinary skill in the art of the ’308 patent involves knowledge of adoptive immunotherapy and the manufacturing of adoptively transferred T cells, as well as experience assessing the functions of adoptively transferred T cells *in vivo*.

Petitioner proposes that the POSA possess “a relatively high level of skill” and have “at least a Ph.D., together with several years of experience in researching and publishing academic articles concerning T-cell therapies.” Pet. at 15. Neither Petitioner nor its expert Dr. Bramson provide any justification for any portion of this definition, including narrowly restricting the POSA to a particular post-graduate degree category to the exclusion of others, and requiring the publication of academic articles. Petitioner’s lack of reasoning alone provides ample reason to reject

Petitioner's proposed POSA definition. *See Apple, Inc. v. Samsung Elecs. Co.*, No. 11-CV-01846-LHK, 2012 WL 1123752, at *3 n.2 (N.D. Cal. Apr. 4, 2012) (rejecting POSA proposal of a party that "has not supported its more narrow definition of a [POSA] with evidence or argument as to why more specialized skills are necessary").

One significant concern with Petitioner's definition is its exclusion of physicians having only Doctor of Medicine (M.D.) degrees (not Ph.D.s) given that many M.D.s perform clinical research and have the required knowledge, skills, and experience to understand and evaluate the claims of the '308 patent, which are directed to an adoptive cellular immuno*therapy*. A number of authors or listed inventors from Petitioner's exhibits hold M.D. degrees but not Ph.D. degrees. This is true of both the first and last authors of Mitsuyasu (Ex. 2004; Ex. 2005) and the first and second inventors of Jensen (Ex. 1018) (Ex. 2006; Ex. 2007). Petitioner provides no basis for excluding active participants in the relevant field—including main authors and inventors from references cited in their own Petition—from the definition of the POSA, merely because they have one degree and not another.

Indeed, Petitioner's proposed POSA definition excludes the inventors of the '308 patent, Drs. Riddell and Hudecek, who have M.D.s, (Ex. 2008; Ex. 2009), which is strongly disfavored by both the Federal Circuit and the PTAB because the "starting point [for how a POSA understands a claim term] is based on the well-settled understanding that inventors are typically persons skilled in the field of the

invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc); *see also Boehringer Ingelheim Int'l GMBH v. Barr Lab'ys, Inc.*, 562 F. Supp. 2d 619, 637 (D. Del. June 26, 2008) ("[T]he Court is not persuaded that the '086 patent is directed solely to medical doctors. Indeed, such a conclusion would exclude at least some of the inventors of the patent from the definition of one of ordinary skill in the art."), *rev'd on other grounds*, 592 F.3d 1340 (Fed. Cir. 2010); *see also, e.g.*, *Reckitt Benckiser LLC v. Gemak Trust,* IPR2020-00186, Paper 8 at 6 (P.T.A.B. May 15, 2020) ("[The POSA] should include the inventor.").

Petitioner's requirement that the POSA has experience "publishing academic articles" also lacks support and defies common sense. There is no requirement that CAR-T work be limited to the academic field or published in academic literature, as academic publishing does not correlate to the knowledge, skills, and experience of a skilled artisan in this field. Petitioner's proposed POSA definition would exclude otherwise skilled artisans merely because their work is not yet published, cannot be published for business or other reasons, or is purely clinical.

Tellingly, Petitioner's proposed POSA definition is inconsistent with the POSA it proposed in other IPR Petitions[5] involving CAR-modified T cells. For

[5] *See Miltenyi Biomedicine GmbH v. Trs. of Univ. of Pa.*, IPR2022-00852, Paper 1 (P.T.A.B. Apr. 12, 2022), ("Miltenyi '852 IPR"); *Miltenyi Biomedicine*

example, Petitioner previously argued that a POSA in the art of constructing CAR-T cells would possess:

> [A] relatively high level of skill, such as having at least *an MD or a PhD degree*[6] in the field of molecular or cellular biology, immunology, or a related discipline, together with several years of experience in evaluating CAR T cells. The POSA would have knowledge of the scientific literature pertaining to immunology, including CARs, before the priority date. A POSA would also have knowledge of laboratory techniques related to engineering CAR T cells.

Miltenyi '852 IPR; *see also* Miltenyi '855 IPR.

As can be seen here, Petitioner's prior POSA definition(s) included skilled artisans without a having an M.D. degree without a Ph.D. degree, and did not require publication of scientific articles. Petitioner offers no rational basis to change those requirements here.

To address the problems with Petitioner's proposed definition, and to acknowledge the proper qualifications of a POSA in the field of the '308 patent, Patent Owner instead proposes the following definition:

GmbH v. Trs. of Univ. of Pa., IPR2022-00855, Paper 1 (P.T.A.B. Apr. 12, 2022) ("Miltenyi '855 IPR"), (collectively, the "prior Miltenyi IPRs").

[6] In this paper, all emphases are added unless otherwise indicated.

> An M.D. and/or Ph.D. degree in a field related to adoptive immunotherapy (for example, immunology, molecular biology, cell/cellular biology, genetics, biochemistry, biology, biomedical sciences, or a related field), or an equivalent degree, and 2-4 years of work or research experience involving the manufacture of adoptively transferred T cells, as well as the assessment of the functions of adoptively transferred T cells *in vivo*.

Alternatively, a POSA could have a B.S. or a M.S. degree in a field related to adoptive immunotherapy, or an equivalent degree, and 4-6 years of the experience described above.

In contrast to Petitioner's proposal, Patent Owner's definition includes the inventors of the '308 patent and correctly identifies—and does not artificially restrict—the level of ordinary skill relevant to the claims of the '308 patent. The Board should adopt Patent Owner's proposed definition of a POSA.

IV. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

The Petition must show "that there is a reasonable likelihood that [it] would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). The Board should deny the Petition and refuse to institute trial because Petitioner has failed to satisfy its burden.

A. Grounds 1-3 Fail Because Petitioner Mischaracterizes Singh-1 As Disclosing Cells With *In Vivo* Efficacy When It Does Not

Singh-1 is the only reference cited in Ground 1, and the primary reference relied upon in Grounds 2 and 3. Grounds 1-3 all fail at least because Singh-1 does not disclose *any* adoptive cellular immuno*therapy* composition. Rather, the authors of Singh-1 later confirmed that the Singh-1 composition resulted in virtually non-existent proliferation of $CD8^+$ cells, had *no* anti-tumor effect in mice, and was *not* actually used in any clinical trial (Ex. 2001; Ex. 2003). In Grounds 2-3, Petitioner relies upon fourteen secondary references in addition to Singh-1 to attack the challenged claims. However, because a POSA would have understood that the composition of Singh-1 lacked *in vivo* efficacy, there would have been no motivation to combine Singh-1 with any of these references for any reason, much less to do so with any expectation of success.

1. Ground 1 Fails Because Singh-1 Does Not Disclose An Immunotherapy Composition

In Ground 1, Petitioner argues claims 1-7, 14, 16, 21, and 26-28 of the '308 patent are anticipated by Singh-1. Pet. at 31. Petitioner's argument rests on its assertions that (i) the claim preamble "adoptive cellular immunotherapy composition" is non-limiting, and (ii) even if "[the preamble] were limiting," Singh-1 discloses this limitation because it discloses a "composition for adoptive cellular

immunotherapy formulated to be suitable for administration to a mammal." Pet. at 32. Both of Petitioner's assertions are wrong.

First, as discussed below, the "adoptive cellular immunotherapy composition" language of the preamble is limiting as it is "necessary to give life, meaning, and vitality" to the claim, and serves as an antecedent basis for limitations in the body of the claims. In limiting the claim, the "adoptive cellular immuno*therapy* composition" of the preamble necessarily requires the composition comprising adoptively transferred cells to have *therapeutic* effect, consistent with the plain and ordinary meaning of this phrase, and the way it is used throughout the '308 patent specification.

Second, Petitioner's contention that Singh-1 discloses a "composition" that is "suitable for administration to a mammal" is beside the point, as it ignores the portion of the preamble requiring an "immuno*therapy* composition." The '308 patent is about therapeutic efficacy, not mere "suitability" for administration. Moreover, the requirement of therapeutic efficacy dooms Petitioner's argument because additional prior art *not cited* by Petitioner and authored one year later by the Singh-1 authors (Singh-2, Patent Owner's Ex. 2003) shows that the cells of Singh-1 did not include significant quantities of the "CAR^+ $CD8^+$ T cells with ability to kill $CD19^+$ tumor targets." Further still, those authors later reported in another publication, Singh-3 (Patent Owner's Ex. 2001), that the Singh-1 cells were

unsuccessful for treating cancer *in vivo* (in mice) and *not* "clinically feasible." *See* Section IV.A.1.c, *infra*.

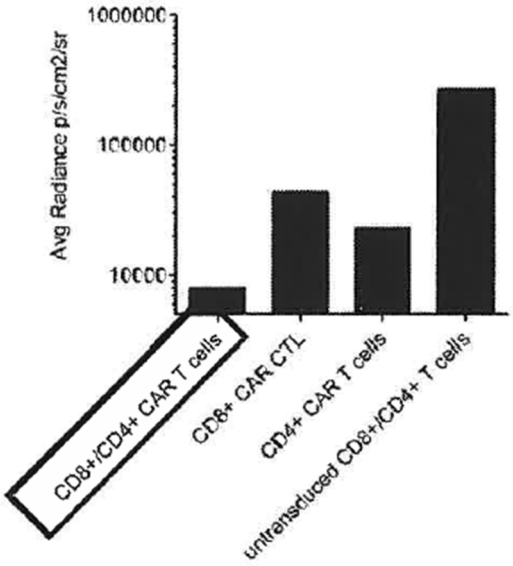
a. The Preamble Of The Challenged Claims Is Limiting

As an initial matter, Petitioner's attempt to dismiss the claim preamble as "merely a statement of intended use for the claimed compositions and not limiting" (Pet. at 17) is flawed. It is true that the claimed compositions are "for" carrying out cellular immunotherapy (*id*. at 17-18), but that is not merely a potential intended use of a separate invention. Rather, it *is* the invention. Here, when the claims are read in view of the entire specification, as is required when construing claim language (*see, e.g.*, *Allergan Sales, LLC v. Sandoz, Inc*., 935 F.3d 1370, 1374 (Fed. Cir. 2019)) it is evident that the essence of the invention is that clinically relevant therapeutic effect is achieved by virtue of the inventive T cell compositions as compared to the non-therapeutic effects of the prior art T cell compositions.

Petitioner also argues that the '308 patent claim preamble is non-limiting because deleting it "does not change the structure of the compositions." Pet. at 18 (citing *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1329 (Fed. Cir. 2019)). This argument ignores *Arctic Cat*'s directive to consider the impact of the preamble on the *operation* of the invention. Deleting the "adoptive cellular immunotherapy" preamble would have a significant impact on the very essence of the invention: the effective treatment of disease.

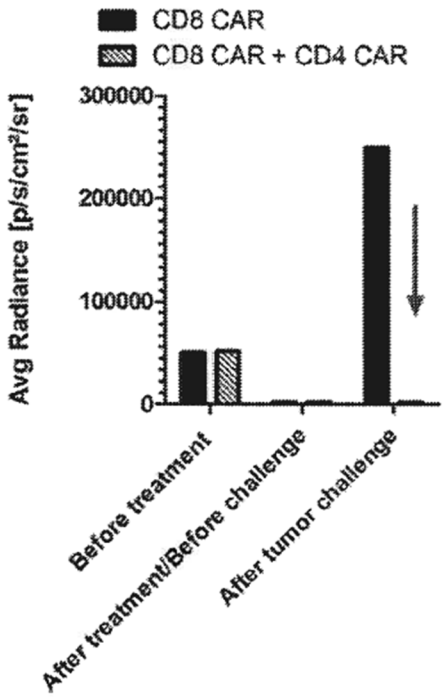
For these same reasons, the preamble is necessary to give life, meaning, and vitality to the challenged claims. *See, e.g.*, *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999); *Bio-Rad Labs., Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1369 (Fed. Cir. 2020). A POSA would understand from the specification of the '308 patent that inventive compositions are inventive precisely because they afford clinically relevant *immunotherapeutic* effect.

For example, the specification emphasizes the dramatic therapeutic effect seen following *in vivo* testing with the claimed compositions. For example, FIG. 12, reproduced below, illustrates that the reduction in tumor burden in mice receiving a combination of CAR-modified $CD4^+$ and $CD8^+$ T cells was synergistic as compared to that seen in mice receiving only one type of CAR-modified T cells.



Id. at FIG. 12.

In addition, FIG. 13B, reproduced below, illustrates that after the second inoculum of Raji tumor cells, there was a drastic difference between the two groups: complete eradication of tumors in mice treated with a combination of CAR-modified $CD4^+$ and $CD8^+$ T cells, whereas mice treated with only CAR-modified $CD8^+$ T cells developed tumors.



Id. at FIG. 13B.

Throughout, the '308 patent is dedicated to therapeutically effective, clinically relevant compositions that provide "adoptive cellular immunotherapy." There is no indication that the inventors were targeting a composition comprising CAR-modified T cells that were merely "suitable" for administration to a mammal, as Petitioner suggests. The specification is unequivocally directed to compositions that

actually provide clinically beneficial treatment, rather than mere cells *per se* that may or may not have effect. There is no legitimate way to read the patent other than to understand that "adoptive cellular immunotherapy" is a "fundamental characteristic of the invention." *See UCB, Inc. v. Accord Healthcare, Inc.*, No. 13-1206-LPS, 2015 WL 2345492, at *4 (D. Del. May 14, 2015) (the "repeated, extended discussions of use of the invented compounds for long-term (potentially lifelong) treatment of conditions including epilepsy mean that the 'therapeutic composition' claimed in claim 10 must at least be capable of providing safe and effective chronic treatment" and therefore "it follows that the term 'therapeutic composition' is a claim limitation, as it states a fundamental characteristic of the invention"). Accordingly, the "adoptive cellular immunotherapy composition" preamble language gives life, meaning, and vitality to the claims of the '308 patent.

The preamble is limiting also because it serves as an antecedent basis for limitations in the body of the claims. *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003) ("When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention."); *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) ("[D]ependence on a particular disputed preamble phrase for antecedent basis may limit claim scope because it indicates a reliance on both the preamble and claim body to define the

claimed invention."). Specifically, the preamble phrase "adoptive cellular immunotherapy composition" provides antecedent basis for the term "composition" recited in the body of the claims. For example, in claim 1, the body of the claim refers to "at least 50% of the chimeric antigen receptor-modified CD4+ helper T lymphocytes in *the composition*" and "at least 50% of CD8+ cytotoxic T lymphocytes in *the composition*." Ex. 1001 at 31:49-59. "The composition" as recited in the claim body is merely shorthand for the "adoptive cellular immunotherapy composition" recited in the preamble.

The courts have applied these legal canons to find preambles limiting in the context of therapeutic compositions similar to the context here. For example, the preamble "[a] topically administrable suspension composition intended for application to the eye, ear or nose" was previously found limiting. *In re Ciprodex*, No. 15-cv-5756 (PGS)(DEA), 2017 WL 2784410, at *6 (D.N.J. June 27, 2017). After noting that "one way for a preamble to 'give meaning' to a claim is provide an antecedent basis for a term in the body of the claim," the court highlighted that "[t]he word 'composition' is recited twice in the body of the claim as '*the* composition.'" *Id*. at *8. "[B]y reciting 'the composition' in the body of the claim, it is evident that it is referring to the 'suspension composition,' recited in the preamble of the claim" and therefore the court found "that 'the composition' in the body of the claim depends on the preamble phrase (suspension composition) as an antecedent basis."

Id. The preamble was "'necessary to give life, meaning, and vitality' to the [] claims, and thereby carry patentable weight that are to be construed as claim limitations." *Id.* The same should be found here.

b. The Preamble Should Be Given Its Plain And Ordinary Meaning

As discussed above, Petitioner's assertion that "to the extent that the preamble is limiting," the preamble "should be construed to mean 'composition for adoptive cellular immunotherapy formulated to be suitable for administration to a mammal,'" (Pet. at 19) is belied by the '308 patent specification. Petitioner's proposed construction would expand the claimed compositions to any composition that *could* be delivered to a mammal, irrespective of whether they have any clinically relevant therapeutic effect *in vivo*. But that is wholly inconsistent with the intrinsic record, which shows the "adoptive cellular immunotherapy composition" of the invention improves on prior compositions that did not have any significant efficacy *in vivo*.

Patent Owner proposes that the "adoptive cellular immunotherapy composition" should be construed in accordance with its plain meaning such that the composition provides therapeutic effect *in vivo*. "[T]he words of a claim 'are generally given their ordinary and customary meaning.'" *See Phillips,* 415 F.3d at 1312 (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)); *see also W.E. Hall Co. v. Atlanta Corrugating, LLC*, 370 F.3d 1343, 1350

(Fed. Cir. 2004) ("We indulge a 'heavy presumption' that the claim terms carry their ordinary and customary meaning.").

"[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1313. A POSA would understand that the plain meaning of an "adoptive cellular immuno*therapy* composition" in the '308 patent as "a composition comprising adoptively transferred cells that has *therapeutic* effect *in vivo* by causing or mediating an immune response."

This meaning is consistent with how the phrase was used in the art:

> Immunotherapy is an emerging treatment modality that seeks to harness the power of the human immune system *to treat disease.* Immunotherapy seeks *to either enhance the immune response in diseases* characterized by immunosuppression or *suppress the immune response in subjects with diseases* characterized by an overactive immune response.

Ex. 2012 at ¶ [0004]. This also accords with how the phrase is used throughout the '308 patent, for example:

> In one aspect, the present invention relates to methods and compositions *to confer and/or augment immune responses* mediated by cellular immunotherapy, such as by adoptively transferring tumor-specific, subset specific genetically modified CD4+ T cells, wherein the CD4+ T

> cells *confer and/or augment the ability of CD8+ T cells to sustain anti-tumor reactivity and increase and/or maximize tumor-specific proliferation*.

Ex. 1001 at 2:3-10.

The '308 patent repeatedly emphasizes the *in vivo* therapeutic effect for its adoptive cellular immunotherapy compositions. And indeed, "[a POSA] is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313. For these reasons, the plain meaning of "adoptive cellular immunotherapy composition" should be adopted and applied as a limitation of the challenged claims.

c. Singh-1's Cells Have No Therapeutic Effect As Admitted By The Singh-1 Authors

Petitioner's main arguments for anticipation and obviousness are based on its interpretation of Singh-1. But that interpretation is wrong.

Petitioner incorrectly alleges that "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}.'" Pet. at 32. However, the words of Singh-1 upon which Petitioner relies involve nothing more than a mere "desire" for clinical success. As Singh-1 states:

> [W]e *desired* a clinically feasible approach to the efficient propagation of CAR^+ T-cell populations, including T_{CM} . . . .

Ex. 1003 at 2961.

While the Singh-1 authors may have "desired" an approach that could be "clinically relevant," the reference does not actually disclose any such approach or provide any *in vivo* data. It contains no support whatsoever for Petitioner's assertion that the cultured cells of Singh-1 have been (or could be) used in an adoptive cellular immunotherapy composition. Indeed, the opposite is true. As discussed in detail below, the Singh-1 authors explained in their own later publications that the Singh-1 composition failed to proliferate the $CD8^+$ cells required by the claims, was *not effective* against tumors, and was *not advanced* to clinical trials. *See* Singh-2 (Ex. 2003) at 61-62; Singh-3 (Ex. 2001) at 3519-22, 3524, 3526, FIG. 5D; Ex. 1026 at 445.

Even without these later fatal disclosures by the authors, Singh-1 could not be read as disclosing anything more than a wish or future plan to evaluate therapeutic effect of its cells in an early-phase clinical trial. Petitioner recognizes this when quotes the language of future plans from Singh-1:

> Singh taught that cells generated using its approach were suitable for use in a clinical trial. Ex.1003 [Singh-1], 2971

("We . . . ***will*** evaluate the CD19-specific T cells . . . in a next-generation clinical trial.")

Pet at 32.

Mere hope for success is insufficient in an anticipation or obviousness analysis, as a hope or desire does not establish a reasonable expectation of success. *E.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (finding that the mere "hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success"). In *Mylan Laboratories Limited*, the PTAB concluded "the fact that a person of ordinary skill in the art would have *hoped* that the method recited in the proposed claims would increase survival does not support a conclusion that that person also would have *expected* such a result." *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 112 at 19 (P.T.A.B. Oct. 22, 2019) (emphasis in original). Similarly, in *Biogen*, the PTAB determined because "a 'hope' may or may not come to pass," the existence of a *hope* that a drug "will turn out to be useful for treating [a particular condition]" does *not* support finding a reasonable expectation of success. *Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, IPR2015-01136, Paper 23 at 10-14 (P.T.A.B. Sept. 2, 2015).

Similarly, a future plan to test efficacy in a clinical trial does not itself suggest efficacy. A POSA was well aware of the high failure rates of CAR-T therapies in

early-stage clinical trials. *See, e.g.*, Ex. 2013 at Table 1 (only four of the 25 early-stage CAR-T clinical trials (16%) reported any reduction in tumor size). The disclosures of Singh-1 do nothing to suggest that its composition would beat these low odds since their cells showed a propensity to result in a "an outgrowth of $CD4^+CAR^+$ T cells" (Ex. 1003 at 2967) and this $CD4^+$ outgrowth was later shown by the authors to have a detrimental impact on "killer" $CD8^+$ T cells. Ex. 2003 at 61. In their later publication, the authors discussed the need to "improv[e] *in vivo* persistence" beyond what was seen in Singh-1 in order to "enhance the therapeutic potential" of CAR-T cells. *Id.* Recognizing that the undesired outgrowth of the $CD4^+$ CAR-T cells was caused by the IL-2 culturing process used in Singh-1, they evaluated various different approaches including "altering the culturing milieu to numerically expand CAR^+ T cells with a proliferative advantage." *Id*. They found that by using IL-21 in conjunction with IL-2, the more desirable outgrowth of $CD8^+$ CAR-T cells was achievable. *Id*. ("*the addition of exogenous IL-21* favors the microenvironment to selectively propagate *CAR^+ $CD8^+$ T cells with ability to kill $CD19^+$ tumor targets* . . . . The propagated CAR^+ T cells produced more IFN-γ in response to $CD19^+$ stimulator cells compared to cells cultured in parallel only on IL-2, and . . . retain[ed] an ability to exhibit CD19-dependent *cytolysis*.").

As compared to these superior cells created with the combination of IL-21 and IL-2, Singh-2 taught that cells cultured with IL-2 alone—*i.e*., the cells of Singh-1—

resulted in expression of CAR on *only one percent* of the $CD8^+$ T cells "with [the] ability to kill $CD19^+$ tumor targets":

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

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

Id. at 61-62. Thus, Singh-2 teaches that the culturing process used in Singh-1 led to CAR-T cells that would *not* have exhibited any significant therapeutic efficacy because they lacked killing ability, and thus teaches away from the composition disclosed by Singh-1. *See id.* at 61. Accordingly, the desire expressed in Singh-1 to test its cells in a clinical trial was *abandoned* following the results discussed in Singh-2, when the Singh-1 authors concluded that the IL-2-only cultured cells of Singh-1 would *not* be immunotherapeutic and did *not* advance them to any clinical trial.

Notwithstanding the disclosures of the Singh references, Petitioner's expert Dr. Bramson relies on Exhibit 1026 to contend that "some of Singh's authors took Singh's manufacturing process to the clinic and used it in NCT00968760 to target CD19-expressing cancers." Ex. 1002 at ¶¶ 119-122. Dr. Bramson got it wrong. The cells used in that clinical trial were generated with IL-2 *and IL-21*, that is, the alternative culturing protocol of Singh-2, *not* the IL-2-only culturing protocol of

Singh-1. Ex. 1026 at 445. As Singh-2 teaches, the culturing milieu is critical to the resulting cell population and properties, and the cells used in the clinical trial were therefore very different from the cells of Singh-1. Petitioner and Dr. Bramson either do not understand or choose to ignore this critical issue.

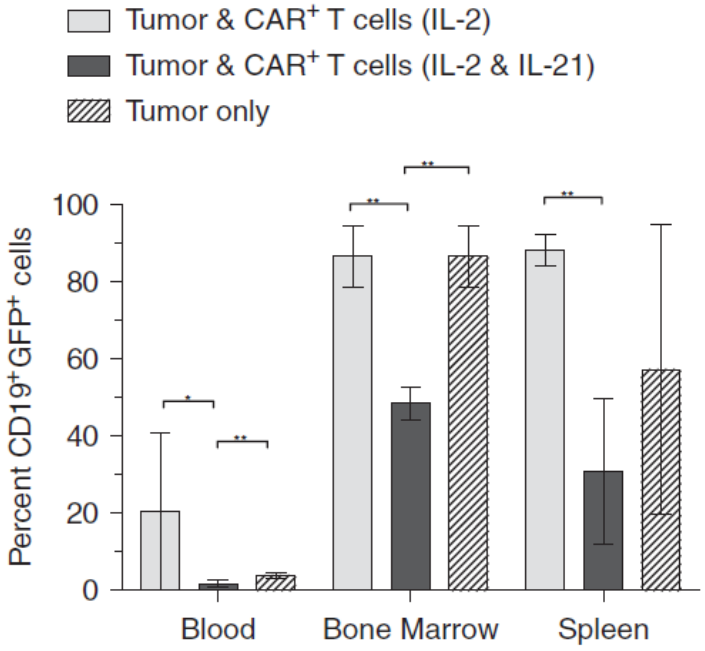
A couple of months after the filing of the '308 patent application, in March 2011, the Singh-1 authors again confirmed the lack of therapeutic effect of the cells of Singh-1 in Singh-3. Singh-3 showed once again that the cells of Singh-1 possessed no *in vivo* efficacy for treating malignancies due to their phenotypes and outgrowth of $CD4^+$ T cells compromising their therapeutic potential, just as previously found by Singh-2. Ex. 2001 at 3519-20.

Like Singh-2, Singh-3 again compared two culturing processes—using IL-2 alone vs. using IL-2 with IL-21. Ex. 2001 at 3521-22. The authors confirmed that these different processes resulted in different mixtures of cell phenotype subpopulations with different propagation of $CD8^+$ CAR-T cells, and that the cells prepared using the IL-2-only process of Singh-1 were inferior and had no therapeutic effect to reduce tumor growth *in vivo*. For example, Singh-3 discloses that the tumor-killing activity of T cells generated by the IL-2-only protocol of Singh-1 were equivalent to having received no T cells at all:

> Groups of mice receiving no T cells or CAR^+ T cells grown in the presence of IL-2 showed *similar rates of tumor growth* . . . . The *tumor burden was similar* in the

blood ($P = 0.07$) and bone marrow ($P = 0.49$) between the mice that received *no T cells and mice that received CAR$^+$ T cells cultured with IL-2*.

Ex. 2001 at 3522. And, while "similar," the reported data showed that the IL-2-cultured CAR$^+$ T cells actually resulted in higher tumor cell burden than *untreated* cells in 2 out of 3 tumor locations tested:



Id. at FIG. 5D.

In other words, the cells of Singh-1 had no therapeutic effect whatsoever *in vivo*, and were thus not moved to future clinical development. *Id.* at 3525 ("from the perspective of manufacturing CAR$^+$ T cells *for clinical application* it appears *beneficial to include IL-21 in the culturing process*"); *see also id*. at 3524 ("the *addition of IL-21* to the culture milieu . . . results in *improved effector function* and

preservation of naïve/memory phenotype of CAR$^+$ T cells which predicts for *improved therapeutic effect in clinical trials*"); *id*. at 3526 (further explaining that the use of IL-21 results in generation of CAR$^+$ T cells "that have desired properties for use in clinical trials").

Thus, the authors of Singh-1 explain conclusively that the Singh-1 cells were not therapeutically effective and not an adoptive cellular immunotherapy composition. Indeed, neither the cells nor the manufacturing process of Singh-1 were advanced to the clinic, contrary to Petitioner's and Dr. Bramson's assertions. Accordingly, Singh-1 fails to disclose an adoptive cellular immunotherapy composition having immunotherapeutic effect, as required by the claims of the '308 patent. Singh-1 does not and cannot anticipate the claims of the '308 patent, and the Petition's Ground 1 fails.

2. Ground 2 Fails Because The Challenged Claims Are Nonobvious Over Singh-1 And Jensen

In Ground 2, Petitioner argues that the challenged claims would have been obvious because "[a] POSA would have understood that formulating Singh[-1]'s composition to be 'suitable for administration to a mammal' would have been as simple as diluting the cells in a saline solution, per Jensen's teachings." Pet. at 49. Petitioner relies upon Jensen for disclosing "a clinical trial protocol that involved CD19-specific CAR-expressing T cells." *Id.* at 30. In view of the non-clinical feasibility of the Singh-1 cells discussed above, Petitioner's argument fails.

As presented in Section IV.A.1, a POSA would have understood that (i) Singh-1 did not show any *in vivo* results, (ii) neither the cells of nor the manufacturing process of Singh-1 was used in the clinical trial (Ex. 1026); and (iii) the Singh-1 cells were therapeutically ineffective (Ex. 2001; Ex. 2003). That is, the prior art taught away from using the cells of Singh-1 in the clinic. Thus, a POSA would not have been motivated to use the cells of Singh-1 in the clinical trial protocol of Jensen, much less with any reasonable expectation of success. *See Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) ("Prior art teaches away when 'a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.'").

A POSA also would not have been motivated to combine Singh-1 with Jensen because, as acknowledged by Petitioner, the composition used in Jensen's clinical trial protocol did not include any $CD4^+$ T cells and instead contained only $CD8^+$ cytotoxic T lymphocytes (CTLs). *See* Pet. at 49 (quoting Ex. 1018 at ¶ [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 . . . ."); *see also* Ex 1018 at ¶ [0109] ("*Criteria for selection of clones for clinical use* include uniform TCR $\alpha\beta^+$, *CD4*$^-$, $CD8^+$ as compared to isotype control FITC-conjugated antibody."). By contrast, and as

acknowledged by Petitioner, Singh-1 encourages infusing *both* CAR-modified $CD4^+$ and $CD8^+$ T cells, because $CD4^+$ T cells were needed to improve persistence of $CD8^+$ T cells:

> Singh recognized the importance of infusing patients with *both $CD4^+$ and $CD8^+$ T cells*. Ex.1003 [Singh-1], 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.

Pet. at 34. A POSA would have recognized that Singh-1 and Jensen would be particularly mismatched because Singh-1 emphasizes that its cells include both $CD4^+$ and $CD8^+$ CAR-T cells, not just $CD8^+$ CAR-T cells as in Jensen. *See* Ex. 1003 at Table 1.

Singh-1 goes even further to report that the majority of its cells are $CD4^+$ CAR-T cells with continued culturing, which caused an "*outgrowth of $CD4^+CAR^+$* T cells." *Id.* at 2967; *see also id*. at FIG. 4B. In view of the emphasis of Singh-1 on infusing both $CD4^+$ and $CD8^+$ T cells and the fact that its cells were actually predominantly $CD4^+$ CAR-T cells, a POSA would not have been motivated to use these cells in the clinical formulation of Jensen which lacked $CD4^+$ CAR-T cells entirely.

In addition, even if there were motivation to combine Singh-1 with Jensen, there would still be no reasonable expectation of success to arrive at the claimed adoptive cellular immunotherapy compositions: Singh-1 notes the important role of $CD4^+$ T cells on the persistence of $CD8^+$ T cells to provide an effective adoptive immunotherapy (*Id.* at 2970), while Jensen's formulation lacks $CD4^+$ CAR-T cells. In addition, there is no reasonable expectation of success because Jensen's teachings of "diluting the cells in a saline solution" fail to rectify Singh-1's lack of therapeutic efficacy, particularly in the context of the very low success rate for CAR-T cell therapies at the time.

For at least these reasons, the claims of the '308 patent are nonobvious over Singh-1 and Jensen and Petitioner's Ground 2 fails.

3. Ground 3 Fails Because The Challenged Claims Are Nonobvious Over Singh-1 In View Of Jensen, Mitsuyasu, Cooper, Hudecek I & II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I & II, Sallusto, And/Or Sun

In Ground 3, Petitioner argues that claims 3 and 18-25 would have been obvious over Singh-1 in view of either Hudecek I (Ex. 1011), Abken (Ex. 1013), Hudecek II (Ex. 1012), Reckamp (Ex. 1014), or Carpenito (Ex. 1015); claims 6 and 9-13 would have been obvious over Singh-1 in view of Wang (Ex. 1017) and/or Mitsuyasu (Ex. 1004); claims 14 and 15 would have been obvious over Singh-1 in view of Moeller (Ex. 1016) and/or Mitsuyasu; and claims 8 and 29-31 would have been obvious over Singh-1 in view of Wang, Hudecek I, Yang I (Ex. 1027), Yang II

(Ex. 1028), Sallusto (Ex. 1029), and/or Sun (Ex. 1032). *See* Pet. at 51-52. Regarding Jensen, Petitioner asserts it can be added, if the "adoptive cellular immunotherapy composition" preamble is limiting. *See id.* at 51 n.6.[7]

As an initial matter, it is difficult to ascertain Petitioner's arguments in view of the number of references and the use of the disjunctive "or" to create numerous different combinations. Having said that, Petitioner's arguments all fail in any event, because a POSA would not have been motivated to combine Singh-1 with any of the secondary references cited in Ground 3.

As with Grounds 1 and 2 discussed above, a POSA would not have been motivated to use the cells of Singh-1 in combination with any other asserted reference, because the POSA would have recognized that the cells of Singh-1 have no therapeutic effect and cannot carry out adoptive cellular immunotherapy, as required by the claims. *See* Section IV.A.1, *supra*. Even if a POSA could modify the cells of Singh-1 with other features disclosed by Jensen, Mitsuyasu, Cooper,

[7] While Cooper is included in the header of Ground 3 and the Table summarizing the Grounds of challenges at Page 6 of the Petition, Section XIII directed to Ground 3 does not discuss Cooper at all. Petitioner thus does not appear to rely on Cooper in Ground 3, and will not be discussed further with respect to Ground 3.

Hudecek I or II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I or II, Sallusto, or Sun, there would still be no reasonable expectation of success that such modification would arrive at the claimed adoptive cellular immunotherapy having therapeutic effect, because none of the secondary references rectify Singh-1's lack of therapeutic efficacy. *See* Section IV.A.1-2, *supra*.

Additionally, as discussed below, many of these secondary references suffer other deficiencies with respect to motivation to combine with Singh-1 and/or reasonable expectation of success of such a combination.

Singh-1 and Jensen

For essentially the same reasons as discussed above with respect to Grounds 1 and 2, a POSA would not have been motivated to use the cells of Singh-1 comprising $CD4^+$ and $CD8^+$ CAR-T cells in the clinical composition of Jensen that omitted $CD4^+$ CAR-T cells altogether, and even if there were motivation, there would still be no reasonable expectation of success to arrive at the claimed adoptive cellular immunotherapy having therapeutic effect.

Singh-1 and Wang

Petitioner alleges "Singh and Wang encouraged using T_{CM} cells" and "teach that T_{CM} cells, which are $CD62L^+$ cells, are optimal for adoptive immunotherapy compositions and should be present at a high percentage." Pet. at 56, 58. Petitioner further argues Wang teaches using a starting population of 100% $CD62L^+$ cells and

highlights the benefit of T_{CM}. *Id.* at 59. However, Singh-1 does *not* encourage using $CD62L^+$ T_{CM} cells, as alleged by Petitioner. On the contrary, Singh-1 expresses concerns about using $CD62L^+$ T_{CM} cells for immunotherapy due to limited *in vivo* survival:

> *Clinical trials will be needed* to determine whether adoptive transfer of these CAR^+ T cells with an apparent central memory immunophenotype ($CD28^+CD95^+$ $CD62L^+$) results in long-term *in vivo* persistence of genetically modified T cells or whether these cells, despite being maintained for weeks in culture, will differentiate after infusion into effector T cells *with limited in vivo survival*.

Ex. 1003 at 2970.

A POSA would therefore not have been motivated to combine Singh-1 with Wang, which expresses a preference for $CD62L^+$ T_{CM} cells. Even if there were motivation, a POSA would have had no reasonable expectation of success due to this mismatch of cell phenotype preferences.

Singh-1 and Hudecek I

Petitioner relies upon Hudecek I in combination with Singh-1 to challenge claim 23, arguing that "Hudecek I's disclosure explained that CD22 was a promising target for B-cell tumors." Pet. at 54. But there would be no motivation to combine

Singh-1 with Hudecek I at least because Hudecek I teaches away from using the cells of Singh-1.

Hudecek I is an earlier publication by the '308 patent inventors. Hudecek I discusses the qualitative properties of T cells required for effective adoptive therapy, and one of the requirements is *in vivo* long-term persistence:

> *The efficacy of adoptive T-cell therapy requires* that the transferred tumor-reactive T cells home to sites of tumor, mediate effector functions in the tumor environment, and *persist sufficiently long in vivo to eradicate* the majority or even all of the malignant cells.

Ex. 1011 at 524.

Hudecek I further discloses tumor-specific T cells generated from unselected T cells showed "inconsistent persistence" because T_N, T_{CM}, and T_{EM} subsets did not persist similarly *in vivo* after adoptive transfer. *Id.* at 525. In particular, T_E derived from T_{CM} (and not T_{EM}) were capable of persisting long term *in vivo* after adoptive transfer. *Id.* As such, Hudecek I promotes using T_{CM} cells, and *not unselected* T cells, as the source to generate CAR-T cells to ensure consistent persistence after cell transfer:

> T-cell clones *derived from TCM*, but not those derived from TEM cells were capable of *persisting long term . . . in vivo* after adoptive transfer. These results . . . provide an explanation for the *inconsistent persistence* of transferred

> T cells when *unselected T cells* are used as the source to generate tumor-specific T cells for adoptive immunotherapy .

Id.

The CAR-T cells described in Singh-1, however, were generated from unselected T cells, namely T cells isolated from umbilical cord blood or peripheral blood mononuclear cells. Ex. 1003 at 2963. Because the cells of Singh-1 are actually *discouraged* by Hudecek I for use in an adoptive cellular immunotherapy, a POSA would not have been motivated to combine Singh-1 with Hudecek I. Even if there were motivation, there would have been no reasonable expectation of success to arrive at an adoptive immunotherapy composition given the teaching of Hudecek I that the CAR-T cells of Singh-1 have undesired *in vivo* persistence.

Singh-1 and Mitsuyasu

Contrary to Petitioner's assertions, a POSA would not have been motivated to combine Singh-1 with Mitsuyasu, based on Mitsuyasu's teaching of CD62L-positivity, to arrive at claims 9-15 of the '308 patent. Pet. at 51. A POSA reading Singh-1 and Mitsuyasu would understand that each reference is specific to treatment of a disease with a particular disease biology—tumor versus HIV, respectively. Mitsuyasu explains the HIV-specific rationale for co-infusion of $CD4^+$ and $CD8^+$ T cells. Ex. 1004 at 785 ("The most direct evidence of *the role of $CD8^+$ T cells in HIV infection* comes from recent studies of $CD8^+$ T-cell depletion in acute and

chronically infected macaques with simian immunodeficiency virus . . . ."); *see also id.* ("Most studies have shown *HIV-specific CD4$^+$ T-cell proliferative responses to be absent or low in patients with chronic, progressive HIV infection*."). In contrast, as recognized by Petitioner, Singh-1 focuses solely on possible treatment of CD19$^+$ tumor cells. Ex. 1003 at Abstract ("this gene transfer method results in rapid outgrowth of CD4$^+$ and CD8$^+$ T cells expressing CAR to redirect specificity for *CD19$^+$ tumor* cells.").

The POSA understood the distinction between adoptive transfer of viral-specific versus tumor-specific T cells. For example, it was well-known (*see, e.g.*, Cooper (Ex. 1010) that the former had a higher success rate in treating patients suffering from viral infections and that adoptive transfer of tumor-specific T cells was more challenging:

> Yet, infusion of *tumor-specific T cells has only been partially successful in clinical oncology trials*. Indeed, most of these trials demonstrate the safety and feasibility of infusing T cells, but . . . only occasionally show a sustained anti-tumor effect. In contrast, infusing *viral-specific T cells has successfully treated and protected patients* from opportunistic diseases associated with adenovirus, CMV, and EBV. Why is it that augmenting an immune response against neoplasms by infusing tumor-specific T cells has proven *more challenging* than engendering an effective anti-viral response?

Ex. 1010 at 645.

Because of the specificity of, and disparity between, these disclosures, a POSA would not have been motivated to apply the HIV-targeted cells of Mitsuyasu to the Singh-1 system for making tumor-specific cells. *See Lassen Therapeutics 1, Inc. v. Singapore Health Servs. Pte Ltd.*, PGR2019-00053, Paper 10 at 33 (P.T.A.B. Feb. 6, 2020) ("Petitioner fail[ed] to . . . sufficiently show why Edwards' disclosure of treatment of a different organ (the lungs) for a different disease (asthma), would render obvious treatment of fibrosis in the heart, liver, kidney, or eye").

Furthermore, even if there were motivation, there would have been no reasonable expectation of success to arrive at an operable system or treatment, because of the lack of therapeutic success against one disease using a system tailored to a different disease, especially in the context of mixing adoptive transfer of viral-specific T cells with adoptive transfer of tumor-specific T cells, as suggested by Petitioner.

Petitioner's Ground 3 fails as the claims of the '308 patent are nonobvious over Singh-1 either alone or in any combination with any of the other fourteen references cited by the Petitioner: Jensen, Mitsuyasu, Cooper, Hudecek I & II, Abken, Reckamp, Carpenito, Moeller, Wang, Yang I & II, Sallusto, and/or Sun.

B. Ground 4 Fails Because The Challenged Claims Are Nonobvious Over Mitsuyasu In View Of Singh-1 And Cooper

Claims 1, 6, and 9-16 would not have been obvious over Mitsuyasu in view of Singh-1 and Cooper as Petitioner alleges in Ground 4, because Mitsuyasu fails to disclose the claimed CD62L surface marker positivity.

1. Mitsuyasu Does Not Disclose The Claimed CD62L Surface Marker Positivity

Despite Petitioner's assertions, Mitsuyasu does not disclose the claimed composition comprising CAR-modified $CD4^+$ and $CD8^+$ T cells, wherein "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 required by the challenged claims.

As an initial matter, Petitioner and its expert Dr. Bramson admit that surface marker positivity is not explicitly disclosed in Mitsuyasu. Pet. at 72 ("Mitsuyasu *does not specifically disclose* the percentage CD62L-positivity in its subpopulations of receptor-modified $CD4^+$ and $CD8^+$ T cells."). The percentage of CD62L-positivity actually disclosed in Mitsuyasu is the percentage of $CD62L^+$ cells *in the entire pool* of all T cells, which includes $CD4^+$ and $CD8^+$ T cells, for each of the 24 HIV-seropositive individuals, as shown in Table 2 of Mitsuyasu, reproduced below.

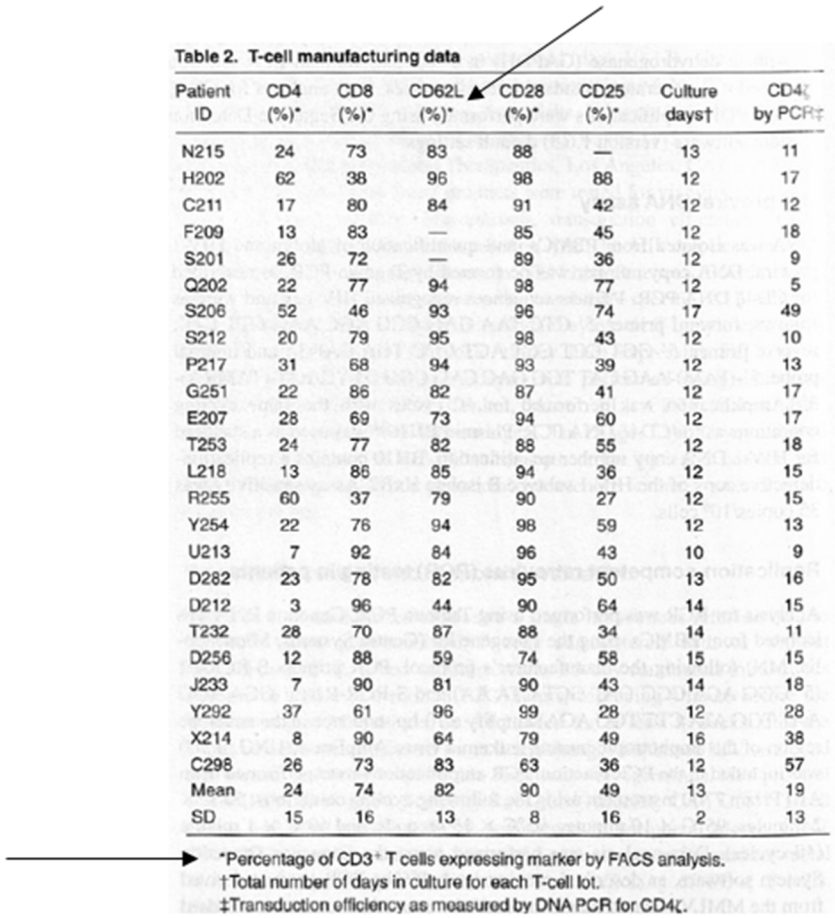


Table 2. T-cell manufacturing data

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.

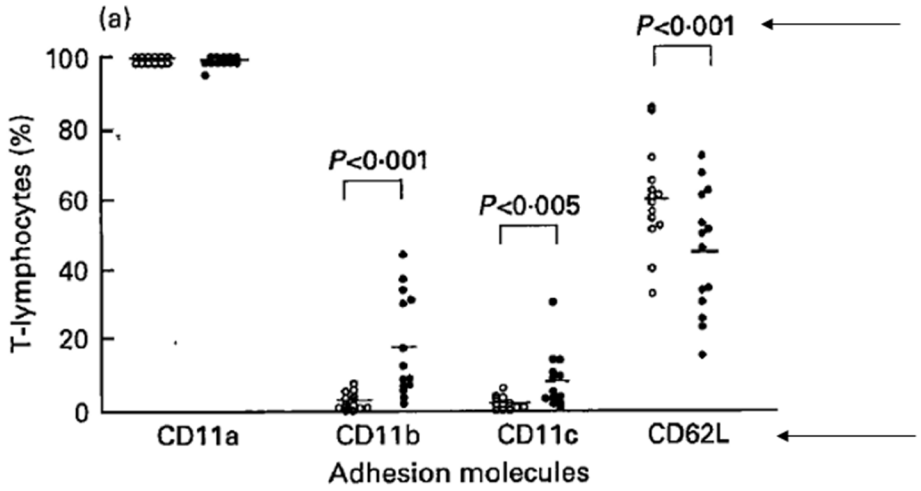
Ex. 1004 at Table 2 n.1.

To arrive at what they contend to be the percentage of CD62L-positivity in claim 1 of the '308 patent from the percentage of $CD62L^+$ cells in the cell population disclosed in Table 2 of Mitsuyasu, Petitioner and its expert Dr. Bramson perform a series of calculations. As discussed below, those calculations are based on at least two erroneous assumptions.

a. Petitioner Erroneous Assumption # 1—Same Rate Of CD62L Positivity Between $CD4^+$ And $CD8^+$ Cells

First, Petitioner and Dr. Bramson rely on Cavers (Ex. 1020) for the proposition that $CD4^+$ and $CD8^+$ cells in a population will have the same rate of CD62L positivity. They allege that Cavers shows "substantially similar $CD62L^+$ for $CD4^+$ and $CD8^+$ cells . . . ." Pet. at 74; *see also* Ex. 1002 at ¶ 392-93 This is an inaccurate reading of Cavers.

Rather, Cavers shows that $CD4^+$ T cells express CD62L at a significantly higher level than $CD8^+$ T cells, as shown in Figure 2a of Cavers:



When explaining the data in Figure 2a, Cavers confirms that "$CD8^+$ T cells . . . in relation to $CD4^+$ T cells [express] . . . less CD62L" and "the distribution of lymphocytes bearing CD62L was greater in the $CD4^+$ subset . . . than in the $CD8^+$ population." *Id*. at 62. Contrary to the assertions of Petitioner's expert Dr. Bramson, nowhere does Cavers disclose that $CD4^+$ T cells have a "slightly higher proportion"

of CD62L-positive cells, let alone "substantially similar" CD62L-positivity between $CD4^+$ T cells and $CD8^+$ T cells.

b. Petitioner Erroneous Assumption # 2—Transduction Efficacy Percentage Equates To Percentage Of Chimeric Receptor-Modified T Cells

Second, Petitioner and its expert perform several complicated mathematical calculations spanning nearly a dozen paragraphs to arrive at their assertion that the cell composition of patient S206 meets the limitations of the '308 patent. *See* Pet. at 75-76; Ex. 1002 at ¶¶ 405-412. But each of those calculations is based on the false premise that the transduction efficiency of a pool of cells equates to the percentage of chimeric receptor modified cells. This is that erroneous equivalence of the percentage of assigned books read by the entire class and the percentage of students who read at least one assigned book, discussed in footnote 1, *supra*.

Mitsuyasu discloses transducing T cells with a CD4ζ retroviral vector. Ex. 1004 at 786. It was well known by the time of the '308 patented invention that retroviral vector transduction can lead to multiple constructs inserted in an individual cell. *See, e.g.*, Ex. 2014 at 5 (referencing "from one to five integration events per

cell).[8] Indeed, the '308 patent inventors expressly recognized that, for the transduction of retroviral vectors, the copy number can be "one or a few copies" per cell. Ex. 1001 at 13:39-43 ("retroviral integration takes place in a controlled fashion and results in the stable integration of *one or a few copies of the new genetic information per cell*."). Thus, when the copy number is unknown, it is impossible to calculate the percentage of cells transduced with a construct based only upon the overall transduction efficiency. Returning to the classroom analogy, it is just not possible to derive the percentage of students who read at least one book from the overall percentage of assigned books read by the class as a whole.

It is undisputed that Mitsuyasu does not disclose copy numbers. Mitsuyasu discloses only two things about the insertion of the DNA construct into the cells: (i) that the cells were transduced with CD4ζ twice (*i.e.*, days 5 and 7) at a MOI (multiplicity of infection) of 2 viral particles per cell (Ex. 1004 at 786); and (ii) with respect to patient S206 on whom petitioner relies, there was a 49% "bulk" transduction efficiency, as measured by DNA PCR, of the *entire pool of cells* received by patient S206. *See id.* at 791; *see also* Ex. 1002 at ¶ 405; Ex. 1004 at 787

[8] Petitioner should be aware of this because, among other reasons, the first author is affiliated with Lentigen, a Miltenyi Biotec Company. *See* Ex. 2014 at 1 n.1.

(reporting assay sensitivity of 117 copies/10^6 cells). Nevertheless, Petitioner and its expert take this 49% *bulk* transduction efficiency number and argue it to mean that 49% of the *individual cells* received by patient S206 were transduced:

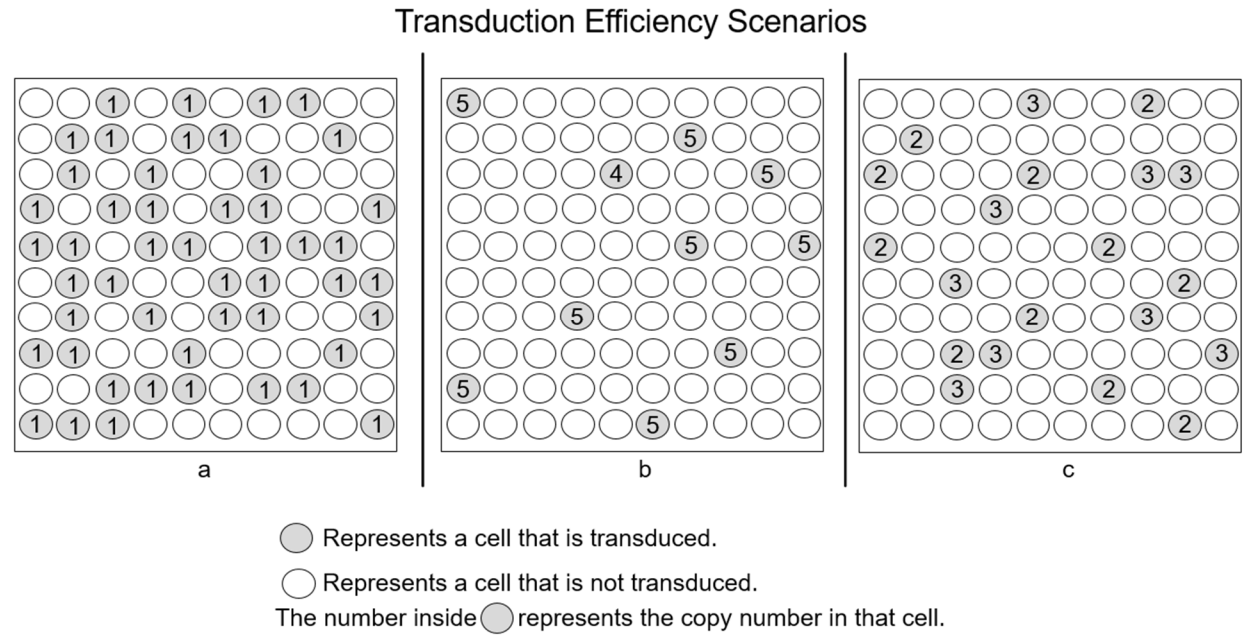
> A POSA would recognize that the right-most column of Figure 2 corresponds to CD4ζ transduction efficiency (here, 49%). . . . Therefore, in S206, the number of chimeric receptor-modified T cells would be *49 out of 100 cells*."

Ex. 1002 at ¶ 405.

That is, Petitioner and its expert erroneously assume that 49% transduction efficiency means that 49% of the individual cells that were modified by CD4ζ. But that calculation only works if the copy number per cell is *one* (*i.e.*, with only one construct per transduced cell), which is both unknown and highly unlikely. Mitsuyasu does *not* provide *any* copy number information, and it was well known that the copy number could be "one or a few" per cell, as discussed above. Petitioner's argument is akin to knowing that 49% of the assigned books were read by the class, and interpreting that to mean that 49% of the students read at least one book, without having information about any individual student and knowing it is more likely that some students read multiple books and others read none. In reality, the 49% transduction efficiency for the pool of cells could correspond to any number

of individual transduced (CD4ζ-modified) cells, depending on the copy number per cell.

The depiction below illustrates how different copy numbers per cell can all result in the same transduction efficiency.



Each box of the figure depicts 100 cells. In (a), the copy number for each cell is 1—one copy per cell. In that case, 49% transduction efficiency would result in transduction of 49% of the cells (49 transduced cells out of 100 cells). This is what Petitioner and its expert assume and focus on. However, there are other possibilities. For example, in (b), where 9 cells have 5 copies and 1 has 4 copies, a transduction efficiency of 49% would mean that just 10% of the cells have been transduced (10 transduced cells out of 100 cells). In (c), where each transduced cell has two or three copies, a transduction efficiency of 49% would mean that 20% of the cells were

transduced (20 transduced cells out of 100 cells). Thus, the same transduction efficiency can equate to very different numbers of individual transduced cells, depending on the number of copies per cell. Because Mitsuyasu does not disclose the copy number per cell, a POSA would not equate the 49% transduced efficiency to be 49% of CD4ζ-modified T cells, as Petitioner and its expert erroneously assert.

In response, Petitioner may attempt to rescue its argument by contending that Mitsuyasu discloses an MOI (multiplicity of infection) of 2. *See* Ex. 1004 at 786. However, even that tactic would not fix Petitioner's error because MOI and copy number per cell are different concepts—MOI refers to the operation of viral infection, whereas copy number per cell refers to the resulting features of the infected cells following the viral infection operation. Stated differently, MOI represents the number of viral vectors used per cell during infection (*e.g.*, 2 viral vectors per target cell), not the number of viral vectors that *actually enter each cell* by virtue of the infection.

In sum, there is insufficient information in Mitsuyasu to support Petitioner and Dr. Bramson's calculations and contentions about the percentage of transduced cells, which, in turn, defeats their arguments about the surface marker positivity of CD62L. Accordingly, Petitioner's Ground 4 should be rejected.

2. There Is No Motivation To Swap Mitsuyasu's CAR With Singh-1's CAR And No Reasonable Expectation Of Success, As Supported By Cooper

Petitioner's Ground 4 also fails for another reason: Contrary to Petitioner's argument, a POSA would not have been motivated to swap Mitsuyasu's HIV-specific CAR with Singh-1's tumor-specific CAR in Mitsuyasu's HIV treatment. As presented in Section VI.A.3, a POSA reading Singh-1 and Mitsuyasu would understand each reference to be specific to a distinct targeted treatment, tumor and HIV, respectively, each with a different disease biology. Mitsuyasu's rationale for co-infusion of $CD4^+$ and $CD8^+$ T cells is specific for HIV treatment. It is known that HIV virus infects and depletes $CD4^+$ T cells, and $CD4^+$ T cell proliferative responses are "absent or low" in HIV-infected patients. Ex. 1004 at 785. Therefore, as described in Mitsuyasu, there would be particular motivation to augment $CD4^+$ T cells for treating HIV.

By contrast, no such relationship exists in cancer patients, and thus there is no rationale for including $CD4^+$ T cells in a system directed to cancer treatment. *See id*. at 785-86. Given that Singh-1 is directed to evaluation of possible tumor (cancer) treatment (*e.g.*, Ex. 1003 at 2961), a POSA would not have been motivated to replace the HIV-specific chimeric receptor of Mitsuyasu with the tumor-specific CAR of Singh-1, as suggested by Petitioner. Furthermore, even if there were motivation to perform such replacement as suggested by Petitioner, there would still be no

reasonable expectation of success to arrive at an operable system or treatment, because of the known lack of success in targeting tumors (Ex. 2013 at Table 1), much less using a system tailored to an entirely different disease (HIV) having a different biology.

In fact, the very reference relied upon by Petitioner to support its reasonable expectation of success argument—Cooper—indicates that swapping viral-specific T cells with tumor-specific T cells in an adoptive immunotherapy for treating a viral infection *would not succeed*. Cooper acknowledges the distinction between adoptive transfer of tumor-specific T cells versus viral-specific T cells, indicating the higher success rate of the latter and the greater challenges facing the former. Ex. 1010 at 645; *see also* Section VI.A.3 above.

Indeed, Cooper goes on to focus exclusively on tumor-specific T cells. *See, e.g.*, Ex. 1010 at 645 ("a *CAR* consists of an extracellular domain composed of a *single chain variable fragment (scFv)* derived from a monoclonal antibody (mAb) against a cell-surface *tumor*-antigen . . . ."). Contrary to Petitioner's assertion, Cooper *never* discloses or suggests swapping a viral-specific CAR with a tumor-specific CAR, or *vice versa*. At most, Cooper suggests swapping one cell surface tumor antigen for another:

> This allows investigators to swap the CAR exodomain with a scFv or ligand that recognizes or binds to a desired cell-surface antigen. Future experiments will build on the

> catalog of antigen-targeting receptors to evaluate . . . affinity of the binding domain for antigen *in the context of tumor targets* with varying antigen density.

Id. at 648.

* * *

In summary, Mitsuyasu does not disclose the claimed CD62L surface marker positivity, and thus does not disclose or render obvious the claimed composition. Furthermore, contrary to Petitioner's assertions, Cooper would discourage a POSA from replacing the HIV-specific receptor of Mitsuyasu with the tumor-specific CAR of Singh-1, and even if there would have been motivation to do so, there still would have been no reasonable expectation of success of using a cell system designed to target HIV with a cancer-targeted CAR. Therefore, Petitioner's Ground 4 fails as the claims of the '308 patent are nonobvious over Mitsuyasu in view of Singh-1 and Cooper.

V. THE BOARD SHOULD DECLINE INSTITUTION PURSUANT TO 35 U.S.C. § 325(d) TO AVOID RETREADING GROUND ALREADY COVERED BY THE EXAMINER

Finally, despite the above reasons why the Petition should fail on the merits, institution should also be denied on Section 325(d) grounds. Under Section 325(d), the Board has clear authority to decline institution of *inter partes* review when "the same or substantially the same prior art or arguments previously were presented to the Office." The Board regularly employs a two-part framework in analyzing

Section 325(d) issues: (1) whether the same or substantially the same prior art or arguments were presented to the Patent Office; and if so, (2) whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential). This framework arises out of the non-exclusive factors set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).[9]

[9] *Becton*, *Dickinson* identifies the following key factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art; (e) whether petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *See Becton*, *Dickinson*, Paper 8 at 17-18 (§ III.C.5, first paragraph).

A. Petition Identifies No Material Error By The Patent Office

First, in attempting to show "material error" on the part of the Examiner, the Petitioner misleadingly quotes and takes the Examiner's statements in the Reasons for Allowance out of context. For example, Petitioner asserts the Examiner failed to acknowledge that the prior art teaches $CD4^+$ T cells or $CD4^+$ CAR-T cells, because the Examiner's Reasons for Allowance "only" describes that the prior art teaches preparing CAR cells from $CD8^+$ cells, not $CD4^+$ cells. Pet. at 79. But Petitioner omitted half of the sentence, in which the Examiner acknowledged $CD4^+$ T cells or $CD4^+$ CAR-T cells in the art. Ex. 1008 at 74 (Examiner stating that "many prior art references teach preparing CAR cells from CD8+ cells only . . . *or that the subset of CD4+ cells to be used was unknown at the time of the invention* . . . ."). Petitioner's misstatement of the record does not constitute a material error on the part of the Examiner.

Second, the Examiner properly evaluated Mitsuyasu and one of Petitioner's secondary references here, Moeller, to find that they failed to disclose the claimed $CD4^+$ CAR-modified T cells, contrary to Petitioner's assertion that the Examiner erred by failing to acknowledge the disclosure of these references. Pet. at 79. The claims of the '308 patent are not directed to just any $CD4^+$ T cells or $CD4^+$ CAR-T cells, but to a specific population of $CD4^+$ CAR-T cells that are surface positive for certain marker(s) (*i.e.*, CD45RA and/or CD62L). With diligent searching and

examination, the Examiner concluded that "the use of CD4+ T cells that are the required % positive for CD62L or CD45RA *is not taught*" by Mitsuyasu or Moeller. Ex. 1008 at 74. That is, neither Mitsuyasu nor Moeller teach the claimed $CD4^+$ CAR-T cells subtypes, which the Examiner properly concluded.

B. Petitioner's Asserted Art Is The Same Or Substantially The Same As The Art Considered By The Examiner

Singh-1 is cumulative of the art considered by the Examiner. Singh-1 discloses methods of making CD19-targeted T cells using the Sleeping Beauty (SB) System. Singh-2 (Ex. 2003) was submitted in an Information Disclosure Statement (IDS) and was considered by the Examiner. Ex. 2016 at 3. Singh-2 includes the majority of the authors of Singh-1, in particular, the first and last authors (usually the principal investigator).

While Singh-2 does not disclose the percentages of $CD62L^+$, $CD45RA^+$, and/or $CD45RO^+$ in the CD19-CAR-modified $CD4^+$ and $CD8^+$ T cells, it reports that the generated cells "displayed a central memory surface phenotype." Ex. 2003 at 61.

The Examiner relied upon his understanding that any T_{CM} cells inherently express CD62L and CD45RO. For example, the Examiner cited Berger (Ex. 1007) and Sallusto 2004 (Ex. 2015) for teaching T_{CM} cells express CD26L and CD45RO. Ex. 1008 at 16, 40. Thus, the Examiner understood that Singh-2 included both CD62L-positive and CD45RO-positive cells. For this reason, Petitioner's primary reference for Ground 1-3 (Singh-1) is cumulative of at least Singh-2 and Berger

and/or Sallusto considered by the Examiner. *See Gardner Denver, Inc. v. Utex Indus.*, IPR2020-00333, Paper 12 at 14 (P.T.A.B. Aug. 5, 2020) (concluding that "that the information disclosed in Hjelsand was already presented to the Office in the rejections of the claims for anticipation and obviousness over the information contained in Roach and Wheeler [two references before the examiner during prosecution]").

Mitsuyasu was also submitted in an IDS and considered by the Examiner during prosecution. Ex. 2016 at 2. As the Board has previously recognized, cumulative references include art cited in an IDS but not applied by the Examiner. For example, in *Biocon Pharma*, the PTAB held that "[i]n light of the Board's precedential *Advanced Bionics* decision, we reject Petitioner's contention that, even though EP '072 appears on an IDS, we should decline to exercise discretion under § 325(d) because EP '072 was 'not applied by the Examiner.'" *See also Biocon Pharma Ltd. v. Novartis Pharms. Corp.*, IPR2020-01263, Paper 12 at 9 (P.T.A.B. Feb. 16, 2021) (noting that "[a]s explained in *Advanced Bionics*, 'previously presented art includes art made of record . . . such as on an Information Disclosure Statement (IDS)'").

In summary, Petitioner has not provided any basis to overturn this determination by the Examiner.

VI. CONCLUSION

The Board should deny institution of the Petition because the asserted grounds are fundamentally deficient. The Petition fails to show that any challenged claim is anticipated or obvious, including failing to present any motivation to combine references, and failing to set forth any reasonable expectation of success in doing so. For all of these reasons, the Petition fails to raise a reasonable likelihood that even one challenged claim is unpatentable.

Dated: June 28, 2023

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that, based upon the word count of the word-processing system used to prepare this preliminary response, the number of words in this preliminary response is 12695, as counted by the word count function of Microsoft Word. Pursuant to 37 C.F.R. § 42.24(a), this word count is less than the limit of 14,000 words and does not include "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

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CERTIFICATE OF SERVICE

I hereby certify that on this 28th day of June, true and correct copies of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE AND EXHIBITS THERETO were served by electronic mail upon the following counsel of record for Petitioner Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc.:

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Respectfully submitted,

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