

Filed on behalf of: Fred Hutchinson Cancer Center

Filed: July 31, 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 SUR-REPLY

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. ARGUMENT	2
A. Singh-2 And Singh-3 Revealed The Cells Of Singh-1 To Be Inherently Inadequate For Immunotherapy	2
1. The Preamble’s “Adoptive Cellular Immunotherapy Composition” Is Limiting	3
2. Singh-1’s Aspirational Statements Are Not Sufficient For Anticipation	3
3. Petitioner’s Characterization Of Singh-3 As Post-Dated Is Unavailing	7
B. Petitioner’s Comparison Of IL-2-Only Cells Across The Singh References Is A Red Herring	7
C. Patent Owner Properly Cited Paugh To Show Copy Number Variability As Of The Filing Date Of The ’308 Patent	9
III. CONCLUSION	10
CERTIFICATE OF SERVICE	

TABLE OF AUTHORITIES

	Page
CASES	
<i>Bd. of Trs. of Leland Stanford Junior Univ. v. Chinese Univ. of H.K.</i> , 860 F.3d 1367 (Fed. Cir. 2017)	7, 9
<i>Cochlear Bone Anchored Sols. AB v. Oticon Med. AB</i> , 958 F.3d 1348 (Fed. Cir. 2020)	3
<i>EMC Corp. v. Intell. Ventures I LLC</i> , IPR2017-00374, Paper 53 (P.T.A.B. June 20, 2018)	3
<i>Ex parte Kao</i> , No. 2008-5150, 2009 WL 1162439 (B.P.A.I. Apr. 29, 2009).....	5, 6
<i>Gilead Scis., Inc. v. Reagents of Univ. of Minn.</i> , IPR2017-01753, Paper 46 (P.T.A.B. Dec. 21, 2020)	9
<i>In re Ciprodex</i> , No. 15-cv-5756 (PGS)(DEA), 2017 WL 2784410 (D.N.J. June 27, 2017)	3
<i>In re Donahue</i> , 766 F.2d 531 (Fed. Cir. 1985)	5, 6
<i>Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.</i> , IPR2020-00040, Paper 91 (P.T.A.B. May 7, 2021)	7
<i>Schering Corp. v. Geneva Pharms., Inc.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	5, 7
<i>Trintec Indus. v. Top-U.S.A. Corp.</i> , 295 F.3d 1292 (Fed. Cir. 2002)	6

TABLE OF ABBREVIATIONS¹

Abbreviation	Description
PO	Patent Owner
POPR	Patent Owner's Preliminary Response, Paper 7
CAR	chimeric antigen receptor
POSA	person of ordinary skill in the art
'308 patent	U.S. Patent No. 9,987,308, Ex. 1001
Singh-1	Singh et al., <i>Redirecting Specificity of T-Cell Populations for CD19 Using the Sleeping Beauty System</i> , CANCER RES. 68(8), 2961-71 (2008), Ex. 1003
Singh-2	Singh et al., <i>Selective Reprogramming of CD19-Specific T Cells with IL-21 and CD28 Signaling for Adoptive Immunotherapy of Acute Lymphoblastic Leukemia</i> , BIOLOGY OF BLOOD & MARROW TRANSPLANTATION 15(2), 61-62, Abstract 164 (2009), Ex. 2003
Singh-3	Singh et al., <i>Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies</i> , CANCER RES. 71(10), 3516-27 (2011), Ex. 2001
Mitsuyasu	Mitsuyasu et al., <i>Prolonged Survival and Tissue Trafficking Following Adoptive Transfer of CD4ζ Gene-Modified Autologous CD4+ and CD8+ T Cells in Human Immunodeficiency Virus-infected Subjects</i> , BLOOD 96(3), 785-93 (2000), Ex. 1004
Paugh	Paugh et al., <i>Reference Standards for Accurate Validation and Optimization of Assays that Determine Integrated Lentiviral Vector Copy Number in Transduced Cells</i> , SCIENTIFIC REPORTS 11(389), 1-9 (2021), Ex. 2014

¹ All emphasis in this brief is added unless otherwise noted.

I. INTRODUCTION

In its POPR, PO exposed two flaws fatal to the Petition. *First*, contrary to Petitioner's assertion that Ex. 1003 (Singh-1) taught cells that were actually used for immunotherapy, PO showed that the Singh-1 authors revealed IL-2-only cells to be inherently deficient for clinical use and not, in fact, pursued in any clinical trial. POPR at 26-33. *Second*, contrary to Petitioner's assertion that Ex. 1004 (Mitsuyasu) discloses the claimed CD62L surface marker positivity, PO showed Petitioner's expert's calculations to be premised on, *inter alia*, an erroneous understanding of transduction efficiency, and hence wrong. *Id.* at 47-51. Nothing in Petitioner's Reply diminishes these points.

With respect to Singh-1, Petitioner focuses on a comparison of *non-clinical* cells made with the IL-2-only protocol described in the three Singh references. This comparison does nothing to resuscitate Petitioner's claim that the IL-2-only cells of Singh-1 have therapeutic efficacy as required by the challenged claims. In fact, Petitioner backs away from this claim entirely, instead re-emphasizing the aspirational statement of potential "clinical application" in Singh-1. Not only is that statement itself insufficient to show anticipation as a matter of law, but Singh-2's (and Singh-3's) revelation of the inherent therapeutic inadequacy of IL-2-only cells

eviscerates any argument that Singh-1 teaches and/or enables the “adoptive cellular immunotherapy composition” of the challenged claims.

With respect to Mitsuyasu, Petitioner employs another diversionary tactic by complaining that Ex. 2014 (Paugh) is a post-priority publication. But it was known well before the priority date and discussed in the '308 patent specification itself that transduction efficiency percentage does not equate to the percentage of transduced cells. Petitioner’s attempt to invoke “other calculations” that ignore transduction efficiency altogether does not fix this problem or salvage Mitsuyasu.

For these reasons, discussed more fully below, the Board should decline to institute the Petition.

II. ARGUMENT

A. Singh-2 And Singh-3 Revealed The Cells Of Singh-1 To Be Inherently Inadequate For Immunotherapy

In support of its anticipation and obviousness arguments based on Singh-1, Petitioner advanced an expert declaration claiming that the manufacturing process of Singh-1 was used in clinical trial NCT00968760. Ex. 1002 at ¶¶ 119-122. PO showed this to be wrong. POPR at 30-31. Petitioner does not attempt to revive this argument, but instead doubles-down on Singh-1’s statement of “anticipated . . . interest” in Singh-1’s “new gene transfer approach for . . . *clinical application*.” Reply at 7 (emphasis in original). This argument fails on both the law and the facts.

1. The Preamble’s “Adoptive Cellular Immunotherapy Composition” Is Limiting

As explained in the POPR, the preamble’s recitation of an “adoptive cellular immunotherapy composition” is limiting and requires therapeutic effect *in vivo*. POPR at 19-26. Contrary to Petitioner’s arguments (Reply at 6), “adoptive cellular immunotherapy” ascribes specific properties to the claimed “composition.” Thus, unlike the preamble phrase at issue in *Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1355 (Fed. Cir. 2020), here, the entire preamble phrase is limiting; the beginning cannot be divorced from its end. Additionally, claim 1’s multiple references to “the composition” refer back to and incorporate the preamble’s “adoptive cellular immunotherapy composition,” using a shorthand “the” to “indicate[] that a new feature is not being introduced in the claim.” *In re Ciprodex*, No. 15-cv-5756 (PGS)(DEA), 2017 WL 2784410, at *8 (D.N.J. June 27, 2017).

2. Singh-1’s Aspirational Statements Are Not Sufficient For Anticipation

As explained in the POPR, the mere hope or desire for clinical efficacy expressed in Singh-1 is insufficient to disclose the immunotherapy limitation of the challenged claims. POPR at 26-28²; *see also EMC Corp. v. Intell. Ventures I LLC*,

² Petitioner’s attack on the POPR for its purported mischaracterization of the law of anticipation (Reply at 8) lacks merit. PO agrees that reasonable expectation of

IPR2017-00374, Paper 53 at 24-25 (P.T.A.B. June 20, 2018) (rejecting anticipation argument based on a statement of “hope[]” in the absence of an enabling disclosure).

As an initial matter, Singh-1’s statement of potential “clinical application” and anticipated interest “for generating clinical grade T cells” (Ex. 1003 at 2970) is unrelated to the efficacy of the T cell milieu which is the subject matter of the challenged claims. Those hopeful statements instead relate to an entirely different aspect of CAR T therapy—the “Sleeping Beauty” process of inserting the CAR into T cells:

In conclusion, we report a new *gene transfer approach* for the clinical application of T cells *with redirected specificity for desired antigens*. It is anticipated that this approach will be of interest not just for generating clinical grade T cells with specificity for CD19, but *for genetically modifying T cells to express CAR with alternative specificities as well as for introducing TCR transgenes*.

Id. For this “new gene transfer approach” to have *true* “clinical application,” it must be used with a T cell milieu that can provide effective therapy. Singh-1 provides no disclosure of such a T cell milieu. And Singh-2 (and later Singh-3) reveals that the T cell milieu of Singh-1 itself is fundamentally *inadequate* for effective therapy.

success is not required for anticipation, but just as for obviousness, aspirational language is also insufficient for anticipation, as discussed herein.

Petitioner glosses over this point in its Reply, citing *Ex parte Kao*, No. 2008-5150, 2009 WL 1162439 (B.P.A.I. Apr. 29, 2009) for the proposition that Singh-1's aspirational reference to "clinical application" is sufficient for anticipation. Reply at 7. Petitioner is wrong.

The quotation from *Kao* on which Petitioner relies is only the first part of a two part sentence in a statement of law from *Schering Corp. v. Geneva Pharmaceuticals, Inc.* That statement reads as follows:

Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; *anticipation requires only an enabling disclosure.*

339 F.3d 1373, 1380 (Fed. Cir. 2003). Indeed, *Kao* turned on the very fact that while the asserted prior art reference (Liao) did not contain *in vivo* data evidencing disease treatment, it was found to teach and enable the claimed treatment. *See* 2009 WL 1162439 at *7.

In this case, Singh-1's disclosure does not and cannot rescue its lack of *in vivo* data because it is not enabling—nothing in Singh-1 would allow a POSA to make and use an "adoptive cellular immunotherapy composition."³ *See In re Donahue*,

³ Petitioner falsely contends that Fig 5B of Singh-3 shows that the cells made by the IL-2-only protocol were therapeutic in mice. Reply at 3. In connection with Fig 5B, Singh-3 itself explains that there was no statistically significant difference between

766 F.2d 531, 533 (Fed. Cir. 1985) (“[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.”). To the contrary, the Singh-1 authors soon understood any hope of clinical application to have been misplaced; they rejected IL-2-only cells for clinical advancement based on the inherent inability of these cells to be used therapeutically. *See* POPR at 30; *Donahue*, 766 F.2d at 533 (“[F]ailures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.”). Unlike the prior art reference in *Kao*, Singh-1 cannot be said to be enabling.⁴

mice receiving the IL-2-only cells and mice receiving no treatment at all, meaning that the IL-2-only cells were *not* therapeutic. Ex. 2001 at 3522 (“Groups of mice receiving no T cells or CAR⁺ T cells grown in the presence of IL-2 showed *similar* rates of tumor growth . . .”).

⁴ The revelation in Singh-2 (and later in Singh-3) of the disqualifying nature of the Singh-1 T cell milieu also means that Singh-1 cannot be said to inherently anticipate the challenged claims. *E.g.*, *Trintec Indus. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (inherent anticipation requires that the missing descriptive material is “necessarily present”).

3. Petitioner's Characterization Of Singh-3 As Post-Dated Is Unavailing

Petitioner's attempt to avoid Singh-3's revelation of inherent inadequacy of the Singh-1 cells is futile. First, Singh-2 is indisputably prior art (that was before the examiner) and reveals the same problems with the Singh-1 composition as does Singh-3. Moreover, it is black letter law that a post-dated reference may be used to show inherency or lack thereof. *Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 91 at 39-40 (P.T.A.B. May 7, 2021) ("Non-prior art evidence can be used to show that certain subject matter is or is not inherent."); *see also Schering*, 339 F.3d at 1380. Petitioner's citation (Reply at 3) to *Board of Trustees of Leland Stanford Junior University v. Chinese University of Hong Kong*, 860 F.3d 1367, 1378 (Fed. Cir. 2017), is of no moment. That case addressed a POSA's reading of a patent specification for purposes of written description, which is not at issue here.

B. Petitioner's Comparison Of IL-2-Only Cells Across The Singh References Is A Red Herring

Petitioner attempts to distract from the teaching of Singh-2 (and Singh-3) that the Singh-1 cells are not immunotherapeutic by arguing that the IL-2-only cells of Singh-1 are different from those of Singh-2 and Singh-3. Reply at 4-5. This argument is a red herring.

As an initial matter, the protocols used by the Singh scientists in the different sets of experiments were highly similar, not different as Petitioner argues. For example, Singh-1 and Singh-2 used the same antigen presenting cells (APCs) and vectors. *Compare* Ex. 2003 at 61, *with* Ex. 1003 at 2962 (both showing γ -irradiated CD19⁺ artificial APCs and a transposon vector). While the Petitioner attempts to draw attention to the 42% vs. 1% CD8⁺ CAR expression in Singh-1 as compared to Singh-2 for IL-2-only cells, this is a distinction without a difference.⁵ It certainly does not reflect that the cells of Singh-1 are “different” from the cells of Singh-2 for purposes of anticipating the immunotherapy claim requirement. Indeed, PO focused on the 1% value because the Singh-1 authors themselves obtained it from a head-to-head comparison of the IL-2-only and IL-2 plus IL-21 protocols.

But even a shift in focus to the 42% does not change the outcome. Well aware of the 42% CD8⁺ CAR expression of Singh-1, the Singh-1 authors nevertheless rejected the Singh-1 cells for therapeutic use due to the problematic outgrowth of CD4⁺ cells that resulted from the IL-2-only protocol. Ex. 2001 at 3519-20 (“We have previously generated CD19⁺CD28⁺ T cells on CD19⁺ aAPC in the presence of

⁵ In fact, Figure 4B of Singh-1 indicates that prior to about day 35 of culturing, CD4⁺CAR⁺ cells predominated, which is consistent with Singh-2’s CD4⁺CAR⁺ outgrowth in IL-2-only media. Ex. 1003 at 2967; Ex. 2003 at 61.

soluble IL-2 which tended to result in a preferential outgrowth of CAR⁺ T cells with a *predominance of CD4⁺ T cells [citing Singh-1].*”). As the Singh-1 authors concluded, the IL-2 protocol—whether resulting in 42% or 1% CD8⁺ T cells—is insufficient to produce adoptive cellular immunotherapeutic T cells; producing such immunotherapeutic cells requires culturing with *both* IL-2 *and* IL-21. Thus, Petitioner’s attempt to distinguish the IL-2-only cells of Singh-1 from those of Singh-2 and Singh-3 has no bearing on the indisputable reality that the Singh-1 composition is inherently flawed for immunotherapy.

C. Patent Owner Properly Cited Paugh To Show Copy Number Variability As Of The Filing Date Of The ’308 Patent

Petitioner’s arguments regarding Ex. 2014 (Paugh) (Reply at 9-10) fare no better. *First*, an expert is not necessary to rebut the assertions of another expert: “[T]he Board is not required to accept every statement made by a petitioner’s expert as established fact simply because the patent owner does not submit contradictory expert testimony.” *Gilead Scis., Inc. v. Reagents of Univ. of Minn.*, IPR2017-01753, Paper 46 at 4 (P.T.A.B. Dec. 21, 2020). The Board is capable of reading Paugh, as well as PO’s citation to the ’308 patent specification, to understand the general principle that viral transduction results in various copy numbers per cell. *See* POPR at 47-48. *Second*, a post-priority paper may be used to establish a scientific fact that existed at an earlier date. *Stanford*, 860 F.3d at 1378. *Third*, Petitioner’s attempt to denigrate Paugh by focusing on the specific cells and transduction goals in Paugh

are irrelevant. Paugh makes clear that copy number variation exists regardless of cell type and transduction goals. Ex. 2014 at 5.

And, *finally*, Petitioner’s general reliance on Dr. Bramson’s “many other calculations” (Reply at 9) is unavailing, as all of his “other calculations” suffer from the same flaw of failing to account for the number of copies of CARs integrated into each T cell. *See* Ex. 1002 at ¶¶ 388-397. In fact, these “other calculations” are even more flawed in that they ignore transduction efficiency and cell copy number entirely. *See id.*

III. CONCLUSION

Petitioner’s Reply does not diminish any of the arguments presented in the POPR. PO respectfully submits that institution should be denied.

Dated: July 31, 2023

Respectfully submitted,

/Sarah A. Geers/

Sarah A. Geers
Reg. No. 69,123
Yi Han Dulkeith, Ph.D.
Reg. No. 70,895
Jones Day
250 Vesey Street
New York, NY 10281
(212) 326-3939
sgeers@jonesday.com
ydulkeith@jonesday.com

Tamera M. Weisser, Ph.D.
Reg. No. 47,856
Anthony M. Insogna
Reg. No. 35,203
Jones Day
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
(858) 314-1200
tweisser@jonesday.com
aminsogna@jonesday.com

Andrea Weiss Jeffries
(to be admitted *pro hac vice*)
Jones Day
555 S. Flower Street
Los Angeles, CA 90071
(213) 243-2176
ajeffries@jonesday.com

Counsel for Patent Owner
Fred Hutchinson Cancer Center

CERTIFICATE OF SERVICE

I hereby certify that on this 31st day of July, a true and correct copy of the foregoing PATENT OWNER'S SUR-REPLY was served by electronic mail upon the following counsel of record for Petitioner Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc.:

Lead Counsel	Backup Counsel
Yite John Lu Reg. No. 63,158 Orrick, Herrington & Sutcliffe LLP 355 S. Grand Ave., Ste. 2700 Los Angeles, CA 90071 Tel. (213) 612-2374 Fax. (213) 612-2499 PTABDocketL2Y7@orrick.com	Gary N. Frischling Reg. No. 35,515 Orrick, Herrington & Sutcliffe LLP 631 Wilshire Boulevard, Suite 2-C Santa Monica, CA 90401 Tel. (310) 633 2841 Fax. (213) 612-2499 PTABDocketG2F1@orrick.com Christopher D. Lynch Reg. No. 68,915 Orrick, Herrington & Sutcliffe LLP 355 S. Grand Ave., Ste. 2700 Los Angeles, CA 90071 Tel. (213) 612-2318 Fax. (213) 612-2499 PTABDocketC3L8@orrick.com Sarah M. Goodman Reg. No. 71,630 Orrick, Herrington & Sutcliffe LLP 2050 Main St. #1100 Irvine, CA 92614 Tel. (949) 852-7748 Fax. (949) 567-6710

Lead Counsel	Backup Counsel
	PTABDocketG3S7@orrick.com David I. Gindler (to be pro hac vice) Orrick, Herrington & Sutcliffe LLP 355 S. Grand Ave., Ste. 2700 Los Angeles, CA 90071 Tel. (213) 612-2370 Fax. (213) 612-2499 PTABDocketG3D7@orrick.com

Dated: July 31, 2023

Respectfully submitted,

/Sarah A. Geers/

Sarah A. Geers Reg. No. 69,123
Jones Day
250 Vesey Street
New York, NY 10281
(212) 326-3939
sgeers@jonesday.com

Counsel for Patent Owner
Fred Hutchinson Cancer Center