UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MILTENYI BIOMEDICINE GmbH and MILTENYI BIOTEC INC.
Petitioner

v.

FRED HUTCHINSON CANCER CENTER
Patent Owner

IPR Trial No. IPR2023-00760
U.S. Patent No. 9,987,308
Issue Date: June 5, 2018

Title: Method and Compositions for Cellular Immunotherapy

PETITIONERS' REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

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As authorized by the Board, Petitioner submits this Reply to address three issues raised by Patent Owner's Preliminary Response.

First, Patent Owner relies principally on a non-prior-art paper, Ex. 2001 ("Singh-3"), and its earlier short abstract Ex. 2003 ("Singh-2"), to argue the composition taught by Singh 2008 (Ex. 1003 and referred to as "Singh-1" in the POPR) was not anticipatory. In doing so, Patent Owner mischaracterizes the Singh-2 and Singh-3 compositions as the same as Singh 2008's composition. They are not. Notably, Singh 2008's percentage of CAR-positive CD8+ T cells was ***42%*** (and 34% of the overall composition) whereas the percentage was only ***1%*** in Singh-2 (the later post-priority Singh-3 did not repeat this percentage). Patent Owner heavily relies on this 1% to make its arguments against Singh 2008 (*see* POPR, 4-5, 26-30), without mentioning the materially higher percentage in Singh 2008.

Second, Patent Owner argues Singh 2008's teaching that its CAR T-cell composition was for "clinical application" does not anticipate the preamble phrase of "adoptive cellular immunotherapy" because no *in vivo* results were reported. But Patent Owner's reliance on a reasonable expectation of success requirement (and one that must be supported by *in vivo* results) is contrary to anticipation case law.

Third, using only attorney argument, Patent Owner mischaracterizes the scientific teachings of a post-priority publication (Ex. 2014) to rebut Petitioner's expert opinion regarding T-cell transduction rate. Petitioner's expert opinion is

supported by prior-art journal articles and not undermined by Exhibit 2014, which provided an artificial transduction rate in a different cell line.

I. EXHIBIT 2001 ("SINGH-3") AND EXHIBIT 2003 ("SINGH-2") DO NOT UNDERMINE THE TEACHINGS OF SINGH 2008

The challenged claims cover a composition of CAR-modified CD4+ and CD8+ T cells with certain percentages of CD62L, CD45RA and/or CD45RO surface markers. Patent Owner does not dispute that Singh 2008 taught a composition with percentages that fall within the claimed scope. Nor does Patent Owner dispute Singh 2008 states its composition is for "clinical application." Ex.1003, 2970. Instead, Patent Owner argues Singh 2008 does not disclose the preamble phrase "adoptive cellular immunotherapy" because it reports no *in vivo* data and therefore a POSA would not expect the composition to be therapeutically successful.[1]

In support of that contention, Patent Owner argues "Singh-3" (Ex.2001, a post-priority date article) and "Singh-2" (Ex.2003, a short abstract) show negative *in vivo* results that nullified the positive teachings of Singh 2008. POPR, 34. That argument is wrong for at least two reasons. First, Patent Owner relies on *in vivo* results published after the priority date, *see* POPR, 31 (admitting Singh-3 was published "[a] couple of months after the filing of the '308 patent application"),

[1] As discussed *infra*, the preamble phrase "adoptive cellular immunotherapy" is not limiting, and also expectation of success is not necessary for anticipation.

whereas prior-art Singh-2 abstract contains no *in vivo* results. Second, compositions discussed in Singh-2 and Singh-3 are not the same as taught by Singh 2008.

First, the POPR intermixes discussion of Exhibits 2001 (Singh-3) and 2003 (Singh-2) to obscure that *in vivo* results in Exhibit 2001 were published post-priority and therefore could not have been considered by a POSA. *E.g.*, POPR, 2 (repeatedly string citing Exhibits 2001 and 2003 together), *see Bd. of Trs. of the Leland Stanford Junior Univ. v. Chinese Univ. of H.K.*, 860 F.3d 1367, 1378 (Fed. Cir. 2017) (explaining "[t]he Board may not, however, use post-dated references as a source for 'later knowledge about later art-related facts . . . which did not exist on the filing date.'"). Singh-2 is a short abstract that does not contain any *in vivo* data. The POPR heavily relies on Singh-3's purportedly negative *in vivo* data (*e.g.*, POPR, 2, 27, 31-32), but none of that data was published before the priority date.[2]

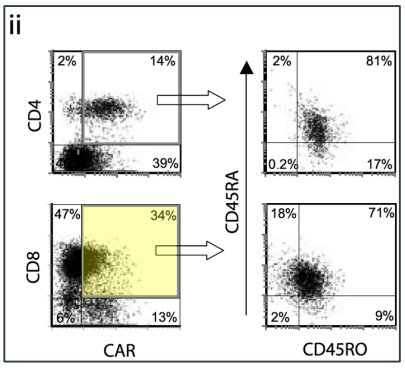
[2] Even if post-priority-date Singh-3 *in vivo* data were considered, Patent Owner incorrectly characterizes Singh-3's IL-2-grown cells as a failure. T cells grown in IL-2 slowed tumor growth relative to control (Ex.2001, Fig. 5B, open squares). Cells cultured in IL-2 + IL-21 fared better than IL-2 alone, but both products were therapeutic in mice. *See id*. (showing tumor reduction at day 17 for both).

Second, neither Singh-2 nor Singh-3 discusses the same composition as Singh 2008. The POPR relies on the "just 1%" CAR+ CD8+ expression in Singh-2's table to argue that this low percentage would lack therapeutic effect:

> 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.

POPR at 4-5; *see also id.* at 29-30 ("Singh-2…only one percent").

But Patent Owner's "just 1%" argument is disingenuous. Omitted is any mention that the anticipatory Singh 2008 composition had a CAR expression percentage of ***42%*** in CD8+ T cells, not "just 1%," and CAR+ CD8+ cells were ***34%*** of total T cells, both substantial amounts. This can be readily seen in the upper-right quadrant of the left-bottom dot plot (yellow shading added) of Ex.1003, Figure 3.B.ii:



The two dot plots on the left show a first gating step in which the authors grouped T cells by CAR expression (x-axes) and CD8 expression (bottom y-axis). Pet., 37, Bramson, ¶¶105,189,202-03 ("The lower-left panel shows that 34% of cells in the sample were CAR-modified, CD8+ T cells"). The percentage of CD8+ cells in the composition is approximately 81% (34% CD8+CAR+ in upper-right quadrant and 47% CD8+CAR- in upper-left quadrant). Therefore, 42% of CD8 cells were CAR+ (34% / 81%) in the Singh 2008 composition.

It is not surprising that the Singh 2008 composition was different than the Singh-2 composition. They were made differently. Because it is just a short abstract, Singh-2 is silent on key parameters in its manufacturing process: for example, the identity of the antigen presenting cells (APCs), and the vector used to express the CAR. But the POPR presumes that the Singh-2 and Singh-3 manufacturing process was the same. POPR, 2. And Singh-3 had many material differences in the manufacturing process compared to Singh 2008: for example, Singh-3 uses a different vector, a different promoter, and different APCs.

In sum, nothing in Singh-2 (or post-priority Singh-3) nullifies the Singh 2008 authors' conclusion that its compositions, which had significant amounts of CAR+ CD8+ cells, would be suitable for "clinical application" or Dr. Bramson's agreement with that conclusion. Ex.1003, 2970; Bramson, ¶¶102,175-184,250, 295-96.

II. ANTICIPATION BY SINGH 2008 DOES NOT REQUIRE *IN VITRO* DATA

The preamble phrase "adoptive cellular immunotherapy" is not limiting because it is a statement of intended use. Pet., 17-19. If the Board agrees, it is unnecessary to reach the question of whether Singh 2008 adequately discloses "adoptive cellular immunotherapy." If limiting, Singh 2008 nonetheless anticipates "adoptive cellular immunotherapy" despite the absence of *in vivo* data.

A. The Preamble Phrase Is Not Limiting

Patent Owner argues the preamble is limiting because deleting it would impact the invention's operation, and because it provides antecedent basis. But the claims' operation is unimpacted if "adoptive cellular immunotherapy" was not limiting. The phrase does not provide antecedent basis and is not repeated outside of the preamble. Patent Owner's district court decision, *In re Ciprodex*, is distinguishable. No. 15-cv-5756 (PGS)(DEA), 2017 WL 2784410, at 6 (D.N.J. June 27, 2017). The preamble in *Ciprodex* included a structural limitation, "a suspension composition," *id.*, 8, that required the composition to include dispersed, but undissolved solid particles. *Id.*, 9. Here, "adoptive cellular immunotherapy" is just an intended use that does not provide any structural limitations to the claimed composition.

Nor does recitation of "the composition" in the claim body provide antecedent basis for the preamble phrase "adoptive cellular immunotherapy." The Federal Circuit has explained that antecedent basis for one word in the preamble does not

provide antecedent basis for the entire preamble. *Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1355 (Fed. Cir. 2020) (holding the emphasized part of this preamble, "***for rehabilitation of unilateral hearing loss*** in a patient," was not limiting even though there was antecedent basis for "a patient").

B. Singh 2008 Discloses an Adoptive Cellular Immunotherapy

Singh 2008 teaches that cells in its CAR T-cell composition are suitable for "clinical application." Pet., 32-33, Bramson, ¶¶176-183, Ex.1003, 2970 ("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…"). This disclosure, along with positive *in vitro* results, sufficiently discloses "[a]n adoptive cellular immunotherapy composition." Pet. 32-34, Bramson, ¶¶183-84.

Given that Singh 2008 expressly says its composition can be used for "clinical application," *in vivo* experimental data are not required for anticipation. For example, in *Ex parte Kao*, No. 2008-5150, 2009 WL 1162439 (B.P.A.I. Apr. 29, 2009), prior art "Liao" predicted an HMG-CoA reductase inhibitor could treat primary pulmonary hypertension based on reported *in vitro* data. The Board held that Liao, which did not contain any *in vivo* data, nonetheless anticipated a claimed "method of treating a lung proliferative vascular disorder":

> [W]e do not agree that Liao needs to provide *in vivo* data showing the treatment of primary pulmonary hypertension

> in order to anticipate… '[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter.'

Id., 8 (quoting *Schering v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed Cir. 2003).)

Patent Owner argues that Singh 2008, because it does not have *in vivo* data, does not anticipate because a POSA allegedly would not have had an "expectation of success" in achieving therapeutic efficacy. *See* POPR, 27-28 (arguments against Ground 1 anticipation).

Patent Owner's position, however, mischaracterizes case law as holding that expectation of success is required for anticipation, when it is not. The cited case holdings were in the context of obviousness, not anticipation. *See, e.g.*, POPR, 28 (citing *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) ("obviousness determination"); *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, IPR2016-00712, Paper 112, 12, 19 (P.T.A.B. Oct. 22, 2019) ("obviousness"); *Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, IPR2015-01136, Paper 23, 10-14 (P.T.A.B. Sept. 2, 2015) ("§ 103(a) obviousness evaluation"). While a reasonable expectation of success is required for obviousness, it is not required for anticipation. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012) (holding while "obviousness under §103…requires…a reasonable expectation of success," it is not for "anticipat[ion]…under §102"); *id.* ("For anticipation, of course, motivation in the prior art is unimportant.").

III. PAUGH DOES NOT NEGATE MITSUYASU'S CD62L SURFACE POSITIVITY

The POPR mischaracterizes a post-priority-date reference (Ex. 2014, "Paugh") to rebut Petitioner expert's opinion that transduction efficiency would be similar to the percentage of chimeric receptor-modified T-cells. Patent Owner does not include expert opinion to rebut the literature relied upon by Petitioner's expert. Bramson, ¶405. Here, "[u]nsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005).

Prior-art reference Mitsuyasu (Ex. 1004) discloses a composition with overall CD62L-positivity within claimed ranges. Bramson, ¶386. As explained by Dr. Bramson, CD62L-positivity is similar for CD4+ and CD8+ T cells regardless of CAR transduction rate. Bramson, ¶¶392-94 (citing Ex.1020). Patent Owner argues Dr. Bramson's explanation is erroneous because there can be more than one construct in each transduced cell, allegedly rendering the percentage of transduced CAR-T cells lower than the overall rate. As a threshold matter, Dr. Bramson provided many other calculations showing a POSA would presume that Mitsuyasu's compositions met the claimed ranges (*see id*., ¶¶388-397), while using transduction efficiency only to argue that the S206 composition necessarily did. *See id.,* ¶405. Even if absolute number of T cells transduced were slightly lower in some compositions, it would not change Dr. Bramson's overall calculations of percent

CD62L-positivity, which is what matters for the '308 patent claim 1. *See id*., ¶¶388-397. Nonetheless, in making this attorney argument about an isolated analysis of Dr. Bramson's opinion, Patent Owner relies on a post-priority reference and mischaracterizes it.

First, a POSA would not consider Paugh because it is a post-priority paper published in 2021. Second, the POPR mischaracterizes Paugh. Patent Owner cites Paugh's statement referencing "from one to five integration events per cell" to argue that some cells will be transduced with multiple constructs. Ex.2014, 5. But far from supporting Patent Owner's assertion that cells "will" be transduced with multiple constructs, Paugh indicates that it "sought" to obtain certain transduction numbers, and thus manufactured a system that yielded its desired results. *See id*., 2 (stating that the authors "selected" a vector "to limit the mean number of integration events to values ranging from one to five"). Simply, a contrived result in Paugh does not indicate anything about Mitsuyasu's transduction efficacy.

Furthermore, although Paugh attempted to obtain integration events of one to five, nowhere does Paugh teach "typically 'one to five integration events per cell,'" as Patent Owner contends. Finally, Paugh is directed at different cells, Jurkat cells (*see* Ex.2014, 1), than Dr. Bramson's opinion, which focused on Mitsuyasu and its use of peripheral blood mononuclear cells from patients.

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Certificate of Service

I hereby certify, pursuant to 37 C.F.R. §§42.6 and 42.105, that a complete copy of the attached **Petitioners' Reply to Patent Owner's Preliminary Response**, is being served on the seventeenth day of July, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the patent owner by serving via electronic mail to the following:

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