

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.

IPR2023-00760
Patent 9,987,308 B2

Before ULRIKE W. JENKS, ZHENYU YANG, and DAVID COTTA,
Administrative Patent Judges.

YANG, *Administrative Patent Judge.*

DECISION
Denying Petitioner's Request on Rehearing of
Decision Denying Institution
37 C.F.R. § 42.71(d)

I. INTRODUCTION

Miltenyi Biomedicine GmbH and Miltenyi Biotec Inc. (collectively, “Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking an *inter partes* review of claims 1–16 and 18–31 of U.S. Patent No. 9,987,308 B2 (Ex. 1001, “the ’308 patent”). Fred Hutchinson Cancer Center (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 7 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply (Paper 8) and Patent Owner filed a Sur-reply (Paper 9). We denied the Petition and did not institute *inter partes* review. Paper 10 (“Decision” or “Dec.”). Petitioner filed a Request for Rehearing of the Decision. Paper 11 (“Req. Reh’g”).

For the reasons explained below, we deny the Request for Rehearing.

II. STANDARD OF REVIEW

The party challenging a decision in a request for rehearing bears the burden of showing the decision should be modified. 37 C.F.R. § 42.71(d). A request for rehearing “must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed.” *Id.* When rehearing a decision on institution, the Board reviews the decision for an abuse of discretion. *Id.* § 42.71(c).

It is not an abuse of discretion to have made an analysis or conclusion with which a party disagrees. Instead, an abuse of discretion occurs if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors. *Arnold P’ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004).

III. ANALYSIS

Petitioner contended that Singh-1¹ anticipates claims 1–7, 14, 16, 21, and 26–28 of the '308 patent. Pet. 31–48. Petitioner also argued that claims 1–16 and 18–31 are unpatentable as obvious over Singh-1 and other prior art. *Id.* at 48–77. We determined that Petitioner has not demonstrated a reasonable likelihood that it would prevail in any of its challenges. Dec. 19–36. Petitioner requests rehearing of our Decision on the anticipation ground only. Req. Reh'g 1.

In our Decision, we focused our analysis on the preamble of claim 1. Dec. 10–17, 19–25. Finding the preamble “adoptive cellular immunotherapy composition” limiting, we construed it to mean “a composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response.” *Id.* at 10–17. In its Request for Rehearing, Petitioner does not dispute this construction. *See generally* Req. Reh'g.

Under this construction, we determined that it is not enough that Singh-1's authors “intended to use their compositions in clinical trials.” Dec. 20–22 (quoting Pet. 33). We stated that, to anticipate, Singh-1 must disclose a cellular immunotherapy composition that has therapeutic effect *in vivo*, or include other, enabling disclosure for a composition with therapeutic effect *in vivo*. *Id.* We found that Singh-1 fails to meet either of these criteria. *Id.* In addition, we found that other evidence, including Singh-2,² a prior art reference published after Singh-1, supports Patent

¹ Singh et al., *Redirecting specificity of T-Cell populations for CD19 using the sleeping beauty system*, 68(8) CANCER RES. 2961–71 (2008) (Ex. 1003, “Singh-1”).

² Singh et al., *Selective reprogramming of CD19-specific T cells with IL-21 and CD28 signaling for adoptive immunotherapy of acute lymphoblastic*

Owner's argument that cells cultured in Singh-1's medium would not exhibit therapeutic efficacy. *Id.* at 22–25. Thus, we concluded Petitioner did not demonstrate a reasonable likelihood of prevailing in its anticipation challenge. *Id.* at 25–26.

In its Request for Rehearing, Petitioner contends that we relied on an erroneous interpretation of law concerning enablement for purposes of anticipation. Reh'g Req. 1–11. Petitioner also argues that Singh-2 does not negate Singh-1's conclusion that its composition had clinically meaningful numbers of CD4⁺ and CD8⁺ CAR⁺ T cells. *Id.* at 3–5, 11–15. We address each argument below.

A. Alleged Issues in Our Factual Analysis

In its Rehearing Request, Petitioner takes issue with our reliance of Singh-2. Req. Reh'g 11–15. Petitioner argues Singh-2 does not negate Singh-1's conclusion that its composition had CD4⁺ and CD8⁺ CAR⁺ T cells of clinically meaningful numbers. *Id.* According to Petitioner, it

cited as anticipatory the Singh-1 CAR T composition generated at week five of the culturing process, which had CD4⁺ and CD8⁺ CAR⁺ T cells in clinically meaningful numbers after five weeks of *ex vivo* expansion and the immunophenotype characteristics within scope of claim 1 of the '308 patent. Petition at 21–22, 37. This CAR T composition did not have an outgrowth of CD4⁺ CAR⁺ T cells to the detriment of CD8⁺ CAR⁺ T cells.

Id. at 11–12 (quotation marks and brackets omitted).

We acknowledge that, when rendering the Decision, we did not appreciate Petitioner relied not on the entire disclosure of Singh-1, but rather

leukemia, 15(2) BIOL. OF BLOOD AND MARROW TRANSPLANTATION 61–62 (2009) (Ex. 2003, “Singh-2”).

on the limited teaching of cells after five weeks of the culturing process.³ As such, we agree with Petitioner that Singh-2 does not negate the fact that, after five weeks of expansion, Singh-1 had CD4+ and CD8+ CAR+ T cells of clinically meaningful numbers. This, however, does not change the outcome of this case.

Clinically meaningful numbers of CD4+ and CD8+ CAR+ T cells *in vitro* is not a claim limitation; “[a]n adoptive cellular immunotherapy composition” is. Thus, properly framed, the issue we must address is whether Singh-1 discloses and enables the making of “a composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response.” We find that Singh-1 does not.

As a preliminary matter, in its Request for Rehearing, Petitioner asserts that the “amounts of CAR T cells [in Singh-1] fall squarely within the ’308 patent’s disclosure of a ‘treatment-effective amount of cells,’ which . . . ‘includ[es] 10⁸ or 10⁹ cells.’” Req. Reh’g 4 (quoting Ex. 1001, 18:36–40). Petitioner also points to Singh-1 for showing that “its CAR T cells ‘were able to lyse CD19+ targets’ with *in vitro* efficacy data.” *Id.* (quoting Ex. 1003, 29:68–69, Fig. 5). Neither these arguments, nor the evidence relied on to support them, were presented in the Petition or the Reply. Thus, we could not have erred in not considering them when rendering the Decision.

³ The Petition did not mention Singh-1’s cells at the five-week time point when analyzing claim 1’s preamble. Pet. 32–34. It, however, did discuss Singh-1’s cells at five weeks when summarizing Singh-1’s disclosures and when addressing the limitations directed to phenotypic surface marker positivity. *Id.* at 21–22, 36–40.

Even if these arguments were properly before us, they would not be persuasive because adoptive cellular immunotherapy requires adoptively transferred cells to “persist sufficiently long *in vivo*” to reach therapeutic effect. Ex. 1011, 524 (“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.”). It was known, however, “*in vitro* isolation and expansion of T cells,” as Singh-1 discloses, “may render them less fit to survive and function *in vivo*.” *Id.* at 525. Citing scientific literature, the ’308 patent confirms that “it is apparent from clinical studies 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, 1:45–48.

Singh-1 agreed. In fact, despite touting that its CAR⁺ T cells reached “clinically meaningful numbers,” which Petitioner repeatedly emphasizes, Singh-1 explained that

[c]linical 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, 2970. In other words, Singh-1 does not support Petitioner’s argument that “this five-week CAR T composition was used for successful *in vitro* experiments and would be expected to be successful *in vivo* as well.” Req. Reh’g 12.

In sum, although no actual reduction to practice is required, the anticipatory reference must disclose all of the claim limitations and enable

the subject matter that falls within the scope of the claims-at-issue. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). Petitioner did not present sufficient evidence in the Petition and the Reply to show that Singh-1 discloses a cellular immunotherapy composition that has therapeutic effect *in vivo*, a limitation required under our claim construction of the preamble. Accordingly, Petitioner did not demonstrate a reasonable likelihood of prevailing in its anticipation challenge.

B. Alleged Erroneous Interpretation of Law

Petitioner also contends our Decision “was legally incorrect in holding that Singh-1 was not enabled for purposes of anticipation because Singh-1 did not disclose *in vivo* data or other teachings demonstrating *in vivo* utility, i.e., efficacy.” Req. Reh’g 3. According to Petitioner, “enablement for purposes of anticipation does not require proof of efficacy or a reasonable expectation of successful efficacy.” *Id.* at 2. As support, Petitioner cites “a long line of Federal Circuit decisions” holding that “the enablement requirement for prior art to anticipate under section 102 does not require utility.” *Id.* at 1–3, 6–9 (citing *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366 (Fed. Cir. 2006); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005); *In re Schoenwald*, 964 F.2d 1122 (Fed. Cir. 1992); *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990); *In re Donohue*, 632 F.2d 123 (CCPA 1980) (brackets and emphasis removed)).

Petitioner is correct that in the cases cited, the Federal Circuit stated that “a section 102 prior art reference does not have to be ‘effective’ to be enabling and thus anticipating.” *Impax*, 468 F.3d at 1383 (quoting *Rasmusson*, 413 F.3d at 1326). The facts in those cases, however, are distinguishable from the facts in this proceeding.

In *Impax* and *Rasmusson*, each claim-at-issue recited a method of treating a disease using a known drug. *Impax*, 468 F.3d at 1372; *Rasmusson*, 413 F.3d at 1322. In each of those cases, the prior art disclosed the known drug, and stated that the drug may be used to treat the disease. *Impax*, 468 F.3d at 1382–83 (explaining that the prior art compounds “possess advantageous pharmacological properties and are active with respect to glutamate induced convulsions, and are hence useful in the treatment and prevention of neurological conditions in which glutamate may be implicated, such as ALS” (quotation marks, ellipses, and brackets omitted)); *Rasmusson*, 413 F.3d at 1321–22 (observing that the prior art disclosed a “method of treating prostatic carcinoma in animals including humans which comprises administering a therapeutically effective amount of the compound 17 β -(N-tertbutylcarbamoyl)-4-aza-5 α -androst-1-en-3-one”).⁴ In other words, the prior art disclosed the same method for administering the same drug as recited in the challenged claim. Under those circumstances, the Federal Circuit stated that “proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation.” *Rasmusson*, 413 F.3d at 1326. That is because, the court explained, “[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.” *Id.* (citing *Bristol–Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001)).

⁴ The Federal Circuit did not explicitly cite the disclosure of the prior art reference “EP ’383.” *Rasmusson*, 413 F.3d at 1325. It, however, discussed in detail the disclosure of “Rasmusson’s ’296 application.” *Id.* at 1321–22. It then noted that “EP ’383 and the ’296 application appear to share the same disclosure.” *Id.* at 1327.

Unlike the method claims in *Impax* and *Rasmusson*, the invention in our case, under the undisputed claim construction, is “a composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response.” Unlike the prior art in those cases, which disclosed the same method for administering the same drug as recited in the challenged claim, Singh-1 does not disclose that its composition has therapeutic effect *in vivo*.

Indeed, Singh-1 never discusses the therapeutic effect of its CAR+ T cells generated at week five of the culturing process that Petitioner alleges is anticipatory. *See* Ex. 1003, 2970 (explaining that clinical trials are needed to determine “whether these cells, despite being maintained for weeks in culture, will differentiate after infusion into effector T cells with limited *in vivo* survival”). Rather, Singh-1 broadly discloses a “new gene transfer approach” that it anticipates “will be of interest.” *Id.*

And unlike the cases Petitioner relies on, where the results of the known methods directed to the same purpose were inherent (*see Rasmusson*, 413 F.3d at 1326), Petitioner does not contend that Singh-1’s composition inherently has therapeutic effect *in vivo*. It could not have done so because there is no such inherency. Indeed, as explained above, Singh-1 itself acknowledges that further research is needed to determine *if* its composition has effect *in vivo*. *See supra* Section III.A (citing Ex. 1003, 2970).

It is worth emphasizing that even in *Impax* and *Rasmusson*, the court did not dispense with the requirement that a patent challenger show that the prior art meets the enablement requirement. *See Rasmusson*, 413 F.3d at 1325 (“A patent claim cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.”)

(quotation marks omitted)). Instead, it stated that “[i]n order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art.” *Impax*, 468 F.3d at 1381. “Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention.” *Id.*

Thus, under the Federal Circuit’s instruction in *Impax* and *Rasmusson*, Petitioner bears the burden to show that Singh-1 enables an ordinarily skilled artisan to *make the claimed invention*, that is, a composition that has therapeutic effect *in vivo*. That is what we stated in our Decision. *See* Dec. 22 (“[I]t is Petitioner’s burden to show that Singh-1 has provided other, enabling disclosure for a composition with therapeutic effect *in vivo*.”). We see no error in this statement under *Impax* and *Rasmusson*.

Our statement in the Decision is not inconsistent with *Schoenwald* and *Donohue* either. In *Schoenwald*, the claim-at-issue recited the structure of a compound, and no other limitation. 964 F.2d at 1122. The prior art disclosed the claimed compound but did not disclose a utility for the compound. *Id.* at 1122–23. The Federal Circuit explained that “no utility need be disclosed for a reference to be anticipatory of a claim to an old compound.” *Id.* at 1124. In addition, in *Schoenwald*, it was undisputed that the prior art “adequately described and enabled” the claimed compound. *Id.* at 1122; *see also id.* at 1123 (stating that “a reference which describes and enables [a compound] has been held sufficient” to anticipate the compound).

Similarly, each claim-at-issue in *Donohue* recited the structure of a compound, and no other limitation. 632 F.2d at 124. The court emphasized that a prior art reference “must be capable, when taken in conjunction with the knowledge of those skilled in the art to which it pertains, of placing that

invention in the possession of the public.” *Id.* at 125. Because the claimed compounds were in the possession of the public, the court upheld the anticipation rejection, stating “proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. 102(b).” *Id.* at 126 & n.6.

In contrast, as explained above, Petitioner has not persuasively established that the claimed composition, which under our claim construction, is required to have therapeutic effect *in vivo*, is an old composition. *See supra* Section III.A. In addition, the claims here do not recite just compositions comprising cells; instead, they require that the cells are “adoptively transferred” so that the composition has “therapeutic effect *in vivo*.” Under *Schoenwald* and *Donohue*, thus, we must determine whether Singh-1 adequately describes and enables such compositions, placing them in the possession of the public. We see no error in endeavoring to do just so in the Decision.

Finally, Petitioner relies on *Spada* in support of its argument that “one cannot obtain a new composition patent by claiming a pre-existing composition, regardless of ‘discovery of an unobvious property’ and ‘including the assertedly different properties in the claims.’” Req. Reh’g 7 (quoting *Spada*, 911 F.2d at 709). In *Spada*, the claim-at-issue was directed to a “pressure sensitive adhesive composition” comprising certain polymer latex. 911 F.2d at 706. The prior art disclosed the claimed polymers but did “not show or suggest that [the] polymer latexes can form a normally tacky pressure-sensitive adhesive.” *Id.* at 707. In affirming an anticipation rejection, the Federal Circuit stated that “the discovery of a new property or use of a previously known composition, even when that property and use are

unobvious from the prior art, can not impart patentability to claims to the known composition.” *Id.* at 708.

Here, again, under our claim construction, which Petitioner does not challenge in its Request for Rehearing, the claimed composition is required to have therapeutic effect *in vivo*. As explained above, Petitioner has not persuasively shown that Singh-1’s composition meets this required function. *See supra* Section III.A. In other words, Petitioner has not shown that the claimed composition is a previously known composition.

There is another critical difference between *Spada* and our case here. In *Spada*, the Federal Circuit explained that “it was reasonable for the PTO to infer that the polymerization by both [the prior art] and [the claim-at-issue] of identical monomers, employing the same or similar polymerization techniques, would produce polymers having the identical composition. Products of identical chemical composition can not have mutually exclusive properties.” *Id.*; *see also In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) (stating the PTO may infer that claimed and prior art products that are substantially identical inherently have the same characteristics due to the “fairness,” which is “evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products”). The court suggested that the applicant could have “overcome, with argument or evidence, the apparent chemical identity of his polymers and those of” the prior art. *Spada*, 911 F.2d at 709.

Unlike *Spada*, an appeal from an *ex parte* proceeding, our case is an *inter partes* review, an adversarial proceeding involving two private entities. *See PPC Broadband, Inc. v. Corning Optical Commc’ns RF, LLC*, 815 F.3d 734, 741 (Fed. Cir. 2016) (“One hallmark of these proceedings is their

adversarial nature.”). As a result, we cannot merely “infer” that Singh-1’s composition is the same as the claimed “composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response,” especially in view of Patent Owner’s arguments to the contrary.

In sum, none of the cases Petitioner relies on changes the law that an anticipatory reference must disclose each and every element of the claimed invention, either explicitly or inherently, and must “enable one of ordinary skill in the art to make the invention without undue experimentation.” *Gleave*, 560 F.3d at 1334. It is true that “where the claims themselves do not require a particular activity” the court does not “require something more from the anticipating reference.” *Id.* at 1336. That, however, is not our case. Under our claim construction, which Petitioner does not challenge in its Request for Rehearing, the challenged claims require “a composition comprising adoptively transferred cells that has therapeutic effect *in vivo* by causing or mediating an immune response.” Therefore, we see no error in our Decision requiring Petitioner to show that Singh-1 discloses and enables an ordinarily skilled in the art to make such a composition.

IV. CONCLUSION

For the foregoing reasons, Petitioner has not demonstrated that we misapprehended and/or overlooked the facts and misapplied the law. As a result, we deny Petitioner’s Request for Rehearing.

V. ORDER

Accordingly, it is

ORDERED that Petitioner's Request for Rehearing is *denied*.

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