NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

NANTKWEST, INC., FORMERLY CONKWEST, INC.,
Plaintiff-Appellant

v.

MICHELLE K. LEE, DIRECTOR, U.S. PATENT AND TRADEMARK OFFICE, DEPUTY UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DEPUTY DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Defendant-Appellee

2015-2095

Appeal from the United States District Court for the Eastern District of Virginia in No. 1:13-cv-01566-GBL-TCB, Judge Gerald Bruce Lee.

Decided: May 3, 2017

ALAN J. HEINRICH, Irell & Manella LLP, Los Angeles, CA, argued for plaintiff-appellant. Also represented by MORGAN CHU, GARY N. FRISCHLING, LAUREN NICOLE DRAKE; SANDRA HABERNY, Newport Beach, CA.

MARY L. KELLY, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for defendant-appellee. Also represented by THOMAS W. KRAUSE, SARAH E. CRAVEN, SCOTT WEIDENFELLER.

Before PROST, *Chief Judge,* DYK, and STOLL, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* DYK, in which PROST, *Chief Judge*, joins.

Dissenting Opinion filed by *Circuit Judge* STOLL.

DYK, *Circuit Judge.*

The United States Patent and Trademark Office ("USPTO") rejected claims 20, 26, and 27 of U.S. Patent Application No. 10/008,955 ("'955 patent application") on the ground that the claims would have been obvious. NantKwest sought review in district court, pursuant to 35 U.S.C. § 145, asserting that claims 20, 26, and 27 of the application were nonobvious. The district court granted the USPTO's motion for summary judgment of obviousness. NantKwest appeals. We *affirm*.

BACKGROUND

NantKwest is the assignee of the patent application at issue, filed by Hans Klingemann ("patent applicant"), directed to the use of a specific type of immune cells for treating cancer.

The immune system can be divided into its innate and adaptive responses. The innate immune response—which is the first line of defense—comprises immune cells like natural killer ("NK") cells that rapidly attack anything that they sense as foreign. NK cells generally have limited target-recognition specificity and attack rather indiscriminately. The adaptive immune response—which is the second line of defense—comprises immune cells like

T cells that attack specific foreign antigens that they have been trained to recognize. The adaptive immune response is thus slower but more target-specific. NK cells and T cells have different cell surface proteins and respond to certain target cell receptors differently. The patent application here concerns the use of a particular cell line[1] of NK cells—NK-92.

Despite these differences between NK cells and T cells, throughout the 1980s and 1990s, various prior art references taught that both T cells and NK cells were capable of lysing (destroying) cancer cells. These references described *in vitro*, *ex vivo* and *in vivo* experiments demonstrating this ability. By 1997, NK cells and T cells were the only two types of immune cells known "to recognize and lyse tumor cells *in vivo* in mammals." J.A. 779–80.

Two specific prior art references are involved here. First, U.S. Patent No. 5,272,082, by Santoli *et al.* ("Santoli"), taught that a specific cell line of T cells, TALL-104, can be used *in vivo* to treat cancer. Second, Gong, Maki, and Klingemann (the '955 patent applicant) published a study ("Gong") that taught that a specific NK cell line, NK-92, can lyse cancer cells *in vitro* with high efficacy. The question here is whether these references rendered the '955 application's claims obvious.

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[1] Immune cells harvested in the laboratory are derived from "cell lines," which refer to cancerous cells that continue reproducing more of their own cell type. For example, tumor cells that produce T cells or NK cells nonstop (and hence cause cancer) can be removed from a patient and nourished in the laboratory to reproduce more T cells or NK cells for subsequent experimental use.

On December 7, 2001, the patent application was filed with a priority date of April 30, 1997. Claim 20, an independent claim on appeal here, provides

> A method of treating a cancer *in vivo* in a mammal comprising the step of administering to the mammal a medium comprising an NK-92 cell line ATCC Deposit No. CRL-2407, wherein said cancer is recognized and lysed by said NK-92 cell line.

J.A. 5. Also on appeal are two dependent claims. Claim 26 teaches that "[t]he method of treating a cancer described in claim 20 wherein the route of administration of the cells to the mammal is intravenous and the mammal is human." *Id.* Claim 27 teaches that "[t]he method of treating a cancer described in claim 20 further comprising the step of administering to said mammal a cytokine that promotes the growth of said NK-92 cell line." *Id.*

The USPTO Examiner rejected the claims at issue and found that "it would have been *prima facie* obvious to a person of ordinary skill in the art . . . in April 1997 to combine the teachings of Santoli and Gong to arrive at the claimed method because Gong . . . teaches use of NK-92 cells to lyse tumor cells, while Santoli . . . teaches *in vivo* use of cytotoxic cell lines." J.A. 8 (internal quotation marks omitted).

The applicant then appealed to the Board of Patent Appeals and Interferences ("Board"). The Board affirmed the Examiner's rejection on the ground that a person of ordinary skill in the art "would have been motivated to replace the TALL-104 cells in Santoli's method with NK-92 cells based on Gong's disclosure that NK-92 cells spontaneously kill [leukemia and lymphoma cancer] cells with high efficiency." J.A. 10 (internal quotation marks omitted).

Pursuant to 35 U.S.C. § 145, NantKwest then filed a complaint in district court, seeking judgment that claims

20, 26, and 27 of the patent application were nonobvious. The USPTO moved for summary judgment. In response, NantKwest argued that this case involves disputes of factual issues that cannot be resolved on summary judgment, relying on expert reports from Dr. Miller ("Miller") and new references submitted for the § 145 proceeding. The district court granted summary judgment "because there is no genuine material factual dispute as to whether the invention claimed in the [patent application] was obvious over the prior art, as found by both the Examiner and the Board." J.A. 15.

NantKwest appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I

This court reviews the district court's grant or denial of summary judgment *de novo*. *MicroStrategy Inc. v. Bus. Objects, S.A.*, 429 F.3d 1344, 1349 (Fed. Cir. 2005) (citations omitted). Summary judgment may be granted only "if the movant shows that there is no genuine dispute as to any material fact." Fed. R. Civ. P. 56(a). Claim construction is an issue of law that we review *de novo* where, as here, there is no relevant extrinsic evidence. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015).

A patent is obvious if "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation marks omitted).

II

NantKwest contends that we should reverse the grant of summary judgment because the district court used an incorrect claim construction. Initially, the district court construed "cancer" to mean a "plurality or multiple cancer cells." J.A. 16. However, in addressing the reasonable expectation of success, the court appeared to consider "cancer" as meaning "one or more cancer cells." J.A. 22. We agree with NantKwest that this is an incorrect construction of "cancer." The correct construction of the claim term "treating a cancer" "require[s] lysis of many cells, in order to accomplish the goal of treating cancer," and not merely lysing one or a few cancer cells. J.A. 722.

However, the district court's erroneous claim construction creates no basis for reversal. First, we review the district court's decision *de novo*. In addressing the issue of obviousness, we will use the correct construction, which renders the district court's erroneous construction harmless error. Second, there is no assertion here that the relevant prior art references taught methods that only lysed one cancer cell or otherwise lysed insufficient numbers of cells for treating cancer.

III

a

Under 35 U.S.C. § 145,

> [a]n applicant dissatisfied with the decision of the [Board] . . . may . . . have remedy by civil action against the Director in [district court] . . . . The court may adjudge that such applicant is entitled to receive a patent for his invention, as specified in any of his claims involved in the decision of the [Board], as the facts in the case may appear . . . .

In § 145 proceedings, "the district court may consider new evidence" presented by the applicant that was not before the Board. *Kappos v. Hyatt*, 132 S. Ct. 1690, 1696 (2012). If there are genuine issues of material fact, "the district court must make *de novo* factual findings that take account of both the new evidence and the administrative record before the PTO." *Id.* at 1701.

We agree with the district court that there is no material dispute that the combination of Santoli and Gong used here produced the invention and that persons of ordinary skill in the art would have been motivated to combine Santoli and Gong.

Santoli was an important advance because it showed that T cells from a cell line, not belonging to a patient, can be administered into a patient to produce *in vivo* therapeutic effects. Such an approach is called "allogeneic" or "adoptive immunotherapy." Santoli specifically taught that the TALL-104 cell line can be used in adoptive immunotherapy *in vivo* for lysing cancer cells.[2]

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[2] We reject NantKwest's argument that Santoli does not "disclose a successful *in vivo* therapy for TALL-104." Appellant Br. 32. A study of TALL-104 *in vivo* therapy in dogs showed clinical responses in eight out of nineteen dogs tested. Another study showed that mice treated with TALL-104 cells remained cancer-free for at least 2 months, while untreated mice all died within 10 to 20 days. In fact, the patent application itself acknowledged that prior TALL-104 studies demonstrated "antitumor activity *in vivo* . . . to induce remissions of spontaneous lymphomas in dogs." J.A. 53; Cesano, J.A. 947, tbl. 3. The alleged post-filing failure of TALL-104 therapy in human clinical trials—not known at the time of the application—is irrelevant. *See In re Vaeck*, 947 F.2d

Gong taught that the NK-92 cell line showed *in vitro* efficacy in lysing cancer cells. In fact, NK-92 was found to have "high efficiency" in lysing the same leukemia tumor cell type as TALL-104 did. *See* J.A. 128, 142. Both TALL-104 and NK-92 lysed cancer cells via the same mechanism, *i.e.*, in a "non-MHC-restricted" manner, in which they do not require presentation of antigens on the MHC cell surface proteins of the tumor cells. J.A. 131, 145.

Prior art publications by the patent applicant himself indicated that there was a motivation to seek clinical applications for the NK-92 cell line. For example, Gong noted that "[b]ecause of their ability to lyse malignant cells, NK . . . cells have been utilized in several clinical trials in cancer patients." J.A. 140. In a separate publication, Klingemann et al. cited to the fact that because "NK-92 cells . . . can lyse [tumor cells] *in vitro*," the authors wanted "[t]o test the suitability NK-92 cells for *ex vivo* purging."[3] J.A. 344. While the appellant is correct that these experiments are different from allogeneic *in vivo* therapy, in that they used the patient's own NK cells, they indisputably indicate that skilled artisans were motivated to pursue clinical applications for NK cells and the NK-92 cell line.

Indeed, the '955 patent application itself referred to Gong to describe the superior qualities of the NK-92 cell line. *See, e.g.*, '955 patent application, ¶ 50 ("The NK-92 cell line has been described by Gong et al. (1994)"); *id.* at ¶ 74 ("NK-92 cells (Gong et al. (1994)) were derived from

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488, 493 (Fed. Cir. 1991) ("[E]xpectation of success must be founded in the *prior* art." (emphasis added)).

[3] *Ex vivo* purging entails removing "a patient's [own] blood . . . cells . . . from the body, activat[ing them] . . . , and then return[ing them] back to the patient" for therapy, with the effects stemming from the activated cells. J.A. 7.

cells obtained from a patient suffering from non-Hodgkin's lymphoma."). The patent application highlighted NK-92's "superior" *in vitro* efficacy (as well as the later-determined *in vivo* efficacy), compared against other immune cells, as "activities [that] are . . . unexpected by a worker in the field of tumor cytotherapy." *Id.* at ¶ 121. The patent application also teaches that NK-92's *in vitro* efficacy was "superior to those activities manifested by the known preparations of cytolytic cells normally present in humans," which suggests NK-92's therapeutic utility based on *in vitro* data. *Id.* In fact, the '955 patent application concluded from *in vitro* data that "the NK-92 cells of the invention are surprisingly and significantly more effective in lysing patient-derived tumor cells . . . than . . . the cells from [the TALL-104] cell line[] known in the field." *Id.* at ¶ 104.

Santoli taught that "[t]here remains a need in the art for therapeutic methods . . . for cancers which can utilize cytotoxic T cell lines and avoid the present need . . . for patient's own killer cells." J.A. 130, col. 2, ll. 33–37. Santoli thus provided an explicit suggestion to use cell lines (allogeneic therapy) in cancer treatments because of their greater availability. In fact, the '955 patent application itself recognized that prior investigators turned to allogeneic therapy in preference to using a patient's own cells. *See* '955 patent application, ¶ 9 (To overcome the "major obstacle" of "expand[ing] NK cells . . . *in vivo*" for clinical use, "many investigators have turned to the use of established NK-like cell lines."). Thus, prior art references on successful *in vivo* therapy using non-allogeneic NK cells taught toward using cell lines.

Finally, there were specific studies undertaken to determine whether the NK-92 cell line would be useful for *in vivo* therapy. Yan et al. ("Yan") is a prior art reference relied on by the Board, in which investigators compared the *in vitro* efficacies between TALL-104 and NK-92 cell lines against various tumors, in order to study the poten-

tial of using these cell lines for *in vivo* therapy. J.A. 226 ("To study the potential of using biological reagents in adoptive immunotherapy, we tested the tumoricidal capacity of T104 [and] NK92."). Yan concluded that the *in vitro* efficacy of NK-92 was even greater than the *in vitro* efficacy of TALL-104, which had already been used for *in vivo* therapy. Through this head-to-head comparison, Yan taught persons skilled in the art to combine the teachings of Santoli—using a cell line in adoptive immunotherapy—with the teachings of Gong—the use of the NK-92 cell line.

b

We also find that it would have been at least obvious for skilled artisans to try to combine the teachings of Santoli and Gong.

> When there is a . . . problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options . . . . If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). Generally, the only situations where this does not apply is where "the inventor would have had to try all possibilities in a field unreduced by direction of the prior art . . . [or] where vague prior art does not guide an inventor toward a particular solution." *Bayer Schering Pharma AG v. Barr Lab., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

Even NantKwest's expert conceded that in 1997, skilled artisans knew that NK cells and T cells were the only two types of immune cells known to have antitumor efficacy. Moreover, both Santoli and Gong recognized that TALL-104 and NK-92 cells attack cancer cells via the

same mechanism, which induced skilled artisans like Yan to compare the efficacies of these two cell lines. Thus, TALL-104 and NK-92 were known to be similar and were among a very limited number of immune cells for use in anticancer therapy. Given the limited number of possibilities in the prior art and the many explicit suggestions "toward a particular solution," *Bayer*, 575 F.3d at 1347, we conclude that combining the teachings of Santoli and Gong would have been at least obvious to try.

IV

NantKwest claims that expert reports by Dr. Miller submitted for the first time in the district court proceeding and new prior art references also submitted for the § 145 proceeding raise genuine disputes of material fact about the reasonable likelihood of success for combining Gong with Santoli. We disagree.

Our cases recognize that there is no general rule that a skilled artisan cannot reasonably extrapolate *in vivo* success from *in vitro* results. "Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). "[P]roviding proof sufficient to justify conducting *in vivo* procedures on humans, while useful, is not a test of patentability." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007).

Rather, our cases hold that whether the skilled artisan can extrapolate *in vivo* success from *in vitro* results is highly fact-specific. *See In re Gangadharam*, 889 F.2d 1101, 1989 WL 127023 (Fed. Cir. 1989) ("The issue . . . is *not* whether *in vitro* results can be used to predict *in vivo* success; rather it's simply whether the [USPTO], in this case, carried its burden of proving a *prima facie* case of obviousness of the claimed invention." (emphasis in original)); *In re Carroll*, 601 F.2d 1184, 1186 (C.C.P.A.

1979) (holding that there was teaching away because a witness had stated that *in vitro* testing was unreliable for *in vivo* effectiveness in a specific context).

The fact that *in vitro* success does not always translate into *in vivo* success cannot defeat summary judgment. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Indeed, NantKwest itself simply argues that "[p]ositive results *in vitro* do not *necessarily* establish a reasonable probability of success for therapeutic use of that drug *in vivo*." Appellant Br. 43 (emphasis added). But here, as we have discussed above, there is overwhelming specific evidence that a skilled artisan could reasonably extrapolate from the *in vitro* data with respect to TALL-104 and NK-92 that would reasonably teach their successful substitution *in vivo*.[4]

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[4] NantKwest argues that the Vujanovic et al. reference ("Vujanovic") teaches that "although the A-NK and NA-NK cells used for therapy showed similar levels of cytotoxicity against HR [gastric cancer] cells tested [*in vitro*] (Table I), A-NK cells demonstrated dramatically and significantly greater antitumor activity than NA-NK cells *in vivo* (Table V, Fig. 4)." J.A. 960. From this, NantKwest concludes that there is "difficulty [in] predicting efficacious *in vivo* cancer treatments from *in vitro* assays," in particular for NK cells. Appellant Rep. Br. 5. We reject this out-of-context reading. Vujanovic indeed teaches that A-NK and NA-NK have similar *in vitro* efficacy against gastric cancer cells. J.A. 957, tbl. I. Vujanovic also teaches that against gastric cancer cells *in vivo*, mice undergoing NA-NK treatment develop only 20% of the cancer metastases that would develop in untreated mice, while mice undergoing A-NK treatment develop

However, the appellant asserts five specific material disputes as to whether *in vitro* success here would translate into *in vivo* success.

First, NantKwest argues that Miller shows that there is a teaching away from using unmodified NK-92 cells *in vivo* because Santoli used TALL-104 cells modified to contain a "suicide gene." Appellant Br. 38. Santoli thus "strongly discourages the skilled artisan from attempting to introduce unmodified [immune] cells into a new host" without this genetic modification, because such cells may cause cancer. J.A. 392.

NantKwest conceded during oral argument that the claim language here does not require administering "unmodified" NK-92 cells; that is, administering modified NK-92 cells is encompassed by the claimed invention. Oral Arg. 33:40–56. Therefore, whether Santoli teaches away from using unmodified NK-92 cells is irrelevant. Furthermore, the prior art had disclosed that TALL-104 cells could be "lethally irradiated," so that they became "non-proliferating," without sacrificing TALL-104's ability to lyse cancer cells. J.A. 183. There is no dispute that there would be motivation to irradiate cell lines to ad-

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only 6% of the cancer metastases that would develop in untreated mice. J.A. 960, tbl. V. To be sure, this is a statistically significant difference between the NA-NK and A-NK treatments. However, what NantKwest fails to highlight is that despite this difference, both NA-NK and A-NK treatments produced very statistically significant reductions in cancer metastases as compared to untreated mice. Vujanovic thus does not support the argument that NK cells' *in vitro* efficacy in antitumor activity cannot be extrapolated to *in vivo* success; at most, it only suggests that the exact magnitude of that success may not be predictable.

dress this problem if it arose.[5] Thus, safely using a genetically unmodified immune cell line was already taught in the prior art.

Second, NantKwest argues that Miller shows that there is a teaching away from using allogeneic NK-92 therapy because "[i]t was not well understood at the time of the invention whether allogeneic NK cells would be subject to [attack by the] foreign host or whether [the administered NK cells would] indiscriminate[ly] kill[] . . . host cells." J.A. 411.

This was a broad and general concern known to skilled artisans. In fact, USPTO expert Dr. Lanier agreed that the "use of foreign immune cells in allogeneic therapies may be associated with" reactions from the host and the foreign cells against each other. J.A. 573. It would be necessary "to test immune cells for reactivity and cytotoxicity against allogeneic normal host cells *in vitro* prior to developing treatments . . . *in vivo*." *Id.* There was no testimony here that such an adverse reaction was likely in this context, and there was no testimony that this well-known, general phenomenon (that administering foreign cells into a host could cause untoward reactions) would prevent a skilled artisan from trying NK-92 cells *in vivo* while undertaking the necessary and known precautions. If the need for such pre-administration trials could prevent securing a patent, then no patent on *in vivo* therapy would ever issue before clinical trials were complete. While that appears to have been Dr. Miller's own view,[6]

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[5] It was ultimately determined that NK-92 cells did not present this risk because they "do not need to be modified or irradiated to prevent uncontrolled proliferation." Appellant Rep. Br. 17 n.2.

[6] Dr. Miller stated the following during deposition:

that view does not correspond to the existing standard for patentability. *See PharmaStem*, 491 F.3d at 1364; *Pfizer*, 480 F.3d at 1364 ("[A] rule of law equating unpredictability to patentability . . . would mean that any new [drug] . . . would be separately patentable . . . [after its] properties . . . [are] verified through testing.").

Third, NantKwest argues that Yan taught away from substituting NK-92 for TALL-104 because it showed that TALL-104 and NK-92 "differed in cytolytic activity against" the tumors tested. Appellant Br. 34 n.6. However, the appellant failed to mention that this difference was actually the fact that "[t]he NK92 [cell line] was highly cytotoxic towards all" of the tumors tested, while TALL-104 only lysed four out of the thirteen tumors tested. J.A. 226. Therefore, NK-92 was much more efficacious than TALL-104, which would teach a skilled artisan *toward* the substitution.

Fourth, NantKwest argues that Yan does not provide a motivation to combine because it cautioned that extrapolating immunotherapy results from one context to another may be unpredictable. Specifically, Yan stated that "our studies suggest that [immune cells'] cytotoxic activity towards [cancer cells derived from laboratory] cell lines cannot be extrapolated to [cancer] cells derived directly

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> Q. Is there anything less than an *in vivo* study in mammals using NK-92 cells that could provide a reasonable expectation of success for the claimed method?
>
> A. . . . I'm not sure that there's any predictability that I would be comfortable with, short of doing those types of experiments with the NK-92 cell line.

J.A. 776–77.

from patients. . . . [S]uch . . . immunotherapy . . . must be accompanied by careful study of the unique patterns of activity" of the antitumor immune cells used. J.A. 226. Contrary to Miller's assertion that this caveat "admonishes against relying on *in vitro* tests to predict *in vivo* activity," J.A. 439, Yan is not in fact comparing *in vitro* and *in vivo* efficacies. In fact, Yan contains no *in vivo* experiments. Rather, Yan is cautioning against extrapolating lysis results against tumors derived from cell lines to tumors derived directly from patients.

And as the data shows, this caveat applies only to TALL-104, but not NK-92.[7] As discussed above, TALL-104 lysed three out of four types of cancer cells derived from laboratory cell lines, but only one out of nine types of cancer cells derived directly from patients. In the same comparison, NK-92 lysed all of the four types of cancers derived from cell lines and all of the nine types of cancers derived directly from patients. In other words, NK-92 showed no difference in lysis efficacy against laboratory cell line cancers and patient-derived cancers. Therefore, unlike TALL-104, which lyses cancer cells differently depending on their source, NK-92's efficacy appears to not be context-dependent. *See* Yan, J.A. 226.

Fifth, NantKwest makes much of the differences between T cells' and NK cells' cell-surface receptors, to argue that these differences would have made it difficult to extrapolate NK-92 behavior from TALL-104's. However, while Miller indeed highlights these differences, he conceded that "NK-92 killing and T-ALL killing [of cancer cells] has not, to my knowledge, in [1997], been associated with the[ir] specific receptor pattern." Miller Deposition,

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[7] NantKwest also points out that a similar caveat is found in two other publications. *See* Appellant Br. 46–47; J.A. 953; J.A. 961. Those caveats, like Yan's, also apply only to TALL-104.

ECF 59-1, at 34. Therefore, these cell-surface receptor differences are not material for the two cell lines' similar ability to lyse cancer cells.

V

NantKwest argues that even against a *prima facie* case of obviousness, it had presented secondary considerations of nonobviousness that "may raise a genuine issue of material fact that precludes summary judgment." Appellant Br. 61. "[E]vidence . . . of . . . secondary considerations must always when present be considered en route to a determination of obviousness." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (quotation marks and citation omitted). However, "[f]or . . . secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention. . . . Moreover, secondary considerations . . . cannot overcome a strong prima facie case of obviousness." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quotation marks and citation omitted).

For secondary considerations of nonobviousness, NantKwest presents a news article announcing a $48 million investment in NantKwest as evidence of commercial success, and some results from NK-92's Phase I clinical trials as evidence of unexpected results.

With respect to the investment, we agree with the district court that there is no direct nexus between the $48 million stock purchase and the merits of the claimed invention to demonstrate commercial success. The report indicates that the stock purchase was made for corporate control purposes.

NantKwest also contends that it "presented evidence of the clinical success of NK-92 *in vivo* therapy . . . [that] has demonstrated unexpected, superior results in two

recent . . . Phase I" clinical trials. Appellant Br. 57. There is no evidence that the efficacy results were unexpected compared to what was expected based on the *in vitro* data. Indeed, as discussed above, the *in vitro* data suggested that the *in vivo* trials would be successful. With respect to the Phase I trials' safety results, there was no support for the conclusion that the NK-92 cell line was surprisingly safer than the TALL-104 cell line therapy. *See* Miller, J.A. 393–94 ¶ 48, J.A. 396 ¶ 53.

We conclude that the district court properly granted summary judgment that claims 20, 26, and 27 were invalid as obvious.

VI

The dissent appears to agree that there is substantial evidence supporting the district court's finding of obviousness. However, the dissent concludes that NantKwest submitted contrary evidence that raises genuine issues of material fact.

The two cases cited by the dissent for the proposition that "lesser evidence [than what is presented here was] sufficient to reverse rejections by the PTO in the past" are clearly distinguishable. Dissent Op. 5. As discussed above, both *Carroll*'s and *Gandadharam*'s holdings are highly fact-specific. In *Carroll*, the court held that the prior art on the *in vitro* use of an antibiotic did not render its *in vivo* use obvious because there was a teaching away from *in vivo* extrapolation for that specific antibiotic. *In re Carroll*, 601 F.2d at 1186. *Carroll* does not discuss *in vivo* extrapolation generally. In *Gandadharam*, the court simply found that "in this case," the USPTO failed to "carr[y] its burden of proving a *prima facie* case of obviousness" because the sole prior art only made "general reference . . . [to] positive results that were obtained . . . in an entirely different context, . . . and [made only] precatory, encouraging statements relating to uncertain future investigations" of *in vivo* applications. 1989 WL 127023,

at *1–2. Here, in contrast, there is in fact teaching *towards* the invention.

The dissent also reads Vujanovic, Yan, and Cesano—as well as Miller's testimony concerning these studies—as creating genuine issues of material fact. The cited passages do not show what Miller argues.

First, the dissent cites Vujanovic for the teaching that "[w]e suggest that standard in vitro cytotoxicity *assays* with target cells in suspensions have little relevance in predicting the in vivo antitumor activity of effector cells." J.A. 962 (emphasis added). This is merely stating that a certain type of experiment setup ("cells in suspension" assay) is not suitable for predicting *in vivo* results. Indeed, the very next sentence addresses spheroids assays and concludes that "[o]ur results further imply that in vitro *assessment* of effector cell functions with multicellular CA spheroids [assays] instead of CA cell suspensions [assays] or monolayers [assays] might be of greater relevance in predicting the in vivo therapeutic antitumor potential of immune effector cells." *Id*; *see also* J.A. 956. Therefore, this passage does not support Miller's testimony that Vujanovic "caution[s] against relying on *in vitro* cytotoxicity *results*." J.A. 458 (emphasis added).

Second, the dissent cites Yan for the teaching that "our studies suggest that cytotoxic activity towards leukemic cell lines cannot be extrapolated to cells derived directly from patients. The use of such biologic reagents *in vitro* or *in vivo* for immunotherapy or purging must be accompanied by careful study of the[ir] unique patterns of activity . . . ." J.A. 226. From this, Miller concludes that "Yan admonishes against relying on *in vitro* tests to predict *in vivo* activity." J.A. 439–40. However, as discussed above, the cited passage from Yan is speaking about the differences in lysis efficacy against tumors from cell lines versus against tumors derived directly from patients. All of the experiments presented in Yan were

performed *in vitro* (albeit for the *purpose* of studying the potential of using NK-92 and TALL-104 *in vivo*). This Yan passage therefore cannot provide support for Miller's warning against *in vivo* extrapolation.

Third, the dissent cites Cesano for the teaching that "the sensitivity of the dogs' tumors to TALL-104 cell lysis *in vitro* did not appear to be a good indicator of clinical responses." J.A. 953. This sentence does not address NK-92 and, as discussed above, NK-92 was shown to be more efficacious than TALL-104. Therefore, this would actually teach a skilled artisan toward substituting NK-92 for TALL-104 (as Yan suggested to do).

"When opposing parties tell two different stories, one of which is blatantly contradicted by the record, . . . a court should not adopt that version of the facts for purposes of ruling on a motion for summary judgment." *Scott v. Harris*, 550 U.S. 372, 380 (2007). That is the situation here. Miller's reading of the prior art is contradicted by the art itself. Miller's testimony thus does not raise genuine issues of material fact.

AFFIRMED

NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

NANTKWEST, INC., FORMERLY CONKWEST, INC.,
Plaintiff-Appellant

v.

MICHELLE K. LEE, DIRECTOR, U.S. PATENT AND TRADEMARK OFFICE, DEPUTY UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DEPUTY DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE,
Defendant-Appellee

2015-2095

Appeal from the United States District Court for the Eastern District of Virginia in No. 1:13-cv-01566-GBL-TCB, Judge Gerald Bruce Lee.

STOLL, *Circuit Judge*, dissenting.

Absent the procedural safeguards provided to the non-moving party at the summary judgment stage, I might very well agree with the majority that the PTO demonstrated the obviousness of these claims. When evaluating a case on appeal from summary judgment, however, "[t]he evidence of the non-movant is to be believed, and all

justifiable inferences are to be drawn in his favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). NantKwest submitted evidence and accompanying expert testimony showing that an ordinarily skilled artisan at the time of the invention would not have had a reasonable expectation of success in combining Santoli's *in vivo* results for TALL-104 cells with Gong's *in vitro* experiments for NK-92 cells. Drawing all reasonable inferences in favor of NantKwest, as we must, this evidence creates a genuine dispute of material fact that bars the grant of summary judgment. Because the majority explains away NantKwest's evidence instead of giving it the weight required by law, I respectfully dissent.

I.

As an initial matter, the difference between *in vitro* and *in vivo* testing is critical to understanding the difficulty in using results from the former to predict efficacy in the latter. *In vitro* experiments typically occur in the controlled environment of a petri dish or test tube; *in vivo* experiments are performed in a living organism. J.A. 886. Experiments *in vitro* cannot account for the variable environment of a living organism and cannot replicate a cell line's interaction with the host's immune system, among other things. J.A. 384, ¶ 24; J.A. 886. This disparity in testing environments can lead to unpredicted *in vivo* results. For example, cell lines with encouraging cytotoxic activity *in vitro* can unexpectedly lose all activity *in vivo*. J.A. 414, ¶ 93. The host's immune system can even destroy the cell line, rendering it ineffective *in vivo*. *Id.* It is also possible for the cell line to trigger severe immune reactions in the host that produce serious complications. J.A. 393, ¶ 47. Therefore, demonstrated cytotoxic activity *in vitro* does not always translate to success *in vivo*.

II.

The presence of each claimed element in the prior art is insufficient to render a claim obvious. Rather, there also must be a motivation to combine the prior art and an ordinarily skilled artisan must have had a reasonable expectation of success in doing so. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) (internal quotation marks and citations omitted). Whether a skilled artisan would have had a reasonable expectation of success is a question of fact, *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1222 (Fed. Cir. 2017), and contemporaneous evidence of what skilled artisans thought at the time of the invention can help inform our inquiry into whether the expectation of success was reasonable. *In re Carroll*, 601 F.2d 1184, 1186–87 (C.C.P.A. 1979). When determining whether a person of ordinary skill possessed a reasonable expectation of success in predicting *in vivo* efficacy based on *in vitro* results, we have recognized that "simply because a drug gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of that drug *in vivo*." *In re Gangadharam*, 889 F.2d 1101, 1989 WL 127023, at *3 (Fed. Cir. 1989) (non-precedential) (citing *Carroll*, 601 F.2d at 1186).

The majority concludes that a person of ordinary skill in the art would have been motivated to combine Santoli with Gong because Santoli demonstrated *in vivo* efficacy for TALL-104 cells, Gong detailed NK-92's *in vitro* ability to lyse cancer cells, and the prior art indicated a desire to seek clinical applications for the NK-92 cell line. Maj. Op. 7–9. NantKwest's arguments that a person of ordinary skill in the art would not have had a reasonable expectation of success in combining Santoli with Gong were not persuasive to the majority in light of the "overwhelming specific evidence that a skilled artisan could reasonably extrapolate from the *in vitro* data with respect

to TALL-104 and NK-92 that would reasonably teach their successful substitution *in vivo*." Maj. Op. 12. In reaching its conclusion, the majority failed to give NantKwest's evidence the weight it deserved and declined to draw all reasonable inferences in NantKwest's favor.

Numerous contemporaneous references identified by NantKwest warned that *in vitro* results were not predictive of *in vivo* efficacy in this field. For example, the Vujanovic reference questioned the correlation between *in vitro* studies and *in vivo* behavior for the NK-92 cell line: "We suggest that standard *in vitro* cytotoxicity assays with target cells in suspensions have *little relevance* in predicting the *in vivo* antitumor activity of effector cells." J.A. 962 (emphasis added). As confirmed by Dr. Miller, this passage from Vujanovic "caution[s] against relying on *in vitro* cytotoxicity results, such as those in Gong, to predict *in vivo* behavior." J.A. 458, ¶ 94. Yan contains similar warnings. Yan concluded his comparison of NK-92 and TALL-104 cells by noting: "[O]ur studies suggest that cytotoxic activity towards leukemic cell lines *cannot be extrapolated* to cells derived directly from patients. The use of such biologic reagents *in vitro* or *in vivo* for immunotherapy or purging must be accompanied by careful study of the unique patterns of activity . . . ." J.A. 226 (emphasis added). Dr. Miller reiterated that "Yan admonishes against relying on *in vitro* tests to predict *in vivo* activity," which was consistent with "the common understanding in the art." J.A. 439–40, ¶ 48. Finally, in Cesano's article describing a Phase I Clinical Trial for TALL-104 in dogs, the authors acknowledged that, "[s]urprisingly, the sensitivity of the dogs' tumors to TALL-104 cell lysis *in vitro did not appear to be a good indicator* of clinical responses." J.A. 953 (emphasis added).

NantKwest's evidence and supporting expert testimony laid bare the uncertainty in this complex field. As Dr. Miller explained, the authors in the above references did

not feel confident in predicting *in vivo* activity based on *in vitro* experiments at the time of the invention. J.A. 439–40, ¶ 48; J.A. 458, ¶ 94. This creates a dispute of material fact regarding the reasonable expectation of success. In my view, the majority's willingness to discredit Dr. Miller's understanding of the disclosures in Vujanovic and Yan does not dispose of the genuine dispute of material fact. Although the majority believes its view of the prior art references is superior to Dr. Miller's, its analysis is not supported by citations to the USPTO's expert report or the district court opinion. *See* Maj. Op. 19–20. Dr. Miller's opinion, on the other hand, is illuminated by the background knowledge of a skilled artisan in this field, and I am not convinced that his opinion lacks support in the record. The result is a genuine dispute of material fact that I believe is not suited for resolution at the summary judgment stage.

Indeed, we have found lesser evidence sufficient to reverse rejections by the PTO in the past. In *Carroll*, for example, the PTO's Board of Appeals rejected as obvious claims of a patent for treating M. paratuberculosis with lauric acid based on the patentee's master's thesis. The thesis disclosed two types of studies: 1) *in vitro* studies, from which the patentee reported that lauric acid completely inhibited the growth of three strains of M. paratuberculosis, and 2) *in vivo* studies, from which the patentee reported the suitability of a certain strain of C57 black mice as laboratory animals for studying the diseases caused by M. paratuberculosis. *Carroll*, 601 F.2d at 1185. An expert in the field, Dr. Merkal, discounted the patentee's thesis at the time of its publication because, among other reasons, "*in vitro* testing was an unreliable indicator for the *in vivo* effectiveness." *Id.* at 1186. When the patentee sought a patent for his later discovery that mammals can be treated with lauric acid orally to treat M. paratuberculosis, the PTO argued that the claims were obvious because his earlier thesis disclosed lauric acid's

activity *in vitro* and that mice were suitable animals for studying the disease. *Id.* at 1185–86. Our predecessor court disagreed with the PTO, relying principally on Dr. Merkal's "*contemporaneous* evaluation of appellant's thesis[] that one skilled in this art would have given no weight to the findings reported therein." *Id.* at 1186–87 (emphasis added).

Similarly, in *Gangadharam*, we held that the Board of Patent Appeals and Interferences erred in finding a reasonable expectation of success for using CQQ to treat tuberculosis in mammals (*in vivo*) based on *in vitro* results. *Gangadharam*, 1989 WL 127023, at *3 (non-precedential). The Board relied on a single reference authored in part by the applicant to reject the claims. It found that the Gangadharam reference's disclosure of "very positive *in vitro* bactericidal activity of CQQ against the [pertinent] bacteria reported by Gangadharam certainly favors the *in vivo* use of said compound in the treatment of tuberculosis in mammals." *Id.* at *1. But simply "[r]emarking that the positive *in vitro* results 'favored' use *in vivo* does not meet the statutory standard," we explained, and therefore the PTO "fell woefully short of its burden" to establish a reasonable expectation of success. *Id.* at *2. Importantly, the Gangadharam reference contained a proviso that further studies were needed "before CQQ can be suggested as a possible antimycobacterial drug for treating humans with [tuberculosis]," and a contemporaneous article warned that *in vitro* tests were neither equivalent to, nor a substitute for, *in vivo* experiments. *Id.* at *2–3. Because "there [wa]s evidence in this record . . . regarding the noncorrelation of *in vivo* from *in vitro* efficacy generally and with respect to tuberculosis," we found that the PTO failed to demonstrate a reasonable expectation of success. *Id.* at *3; *see also Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1350–52 (Fed. Cir. 2008) (affirming non-obviousness in context of district court's grant of preliminary injunction because,

inter alia, the patentee's evidence demonstrated that "it was not predictable" how an antibiotic would perform *in vivo* based on *in vitro* experiments using a closely related antibiotic).

As was the case with both *Carroll* and *Gangadharam*, the record here contains ample evidence that persons of ordinary skill in the art were skeptical about the ability of *in vitro* tests to predict *in vivo* efficacy for the two relevant cell lines. Vujanovic, Yan, and Cesano—in the very same articles where they discussed the promising *in vitro* results for the NK-92 and TALL-104 cell lines—proceeded to expressly caution against inferring efficacy *in vivo* based on these outcomes. A reasonable reading of these references supports the conclusion that one skilled in the art would not have had a reasonable expectation of success in combining Santoli's *in vivo* testing for TALL-104 with Gong's NK-92 cell line. Because NantKwest is the non-movant at the summary judgment stage, it is a reasonable inference that we must draw in its favor. *See Anderson*, 477 U.S. at 255.

III.

Our standard of review for the grant of summary judgment requires us to believe the evidence of the non-movant and to draw all reasonable inferences in its favor. The majority did neither in finding the claims in NantKwest's patent application obvious. Accordingly, I respectfully dissent.